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PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: A REVIEW OF CONTEMPORARY GUIDANCE AND LITERATURE

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Abstract:

Cardiovascular disease is a serious and rapidly expanding issue in the worldwide , contributing to about one-third of all fatalities and causing a substantial amount of morbidity. Additionally, it is of urgent concern as developing nations undergo lifestyle changes that bring new cardiovascular disease risk factors, sparking an increase in risk of cardiovascular disease in underdeveloped nations. Since careful risk reduction can lessen the burden of cardiovascular disease, primary prevention should be a top focus for all those who establish health policy. International guidelines are highly consistent about the need to stop smoking, optimise weight, and emphasise the value of exercise. However, guidelines differ slightly about how to treat hypertension and significantly about how to achieve an optimal lipid profile, which is still a concern. While once-popular concepts like the polypill seem to have no in-vivo value, there are still areas of potential future research, such as the advantages of lowering homocysteine and serum urates.

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

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INTRODUCTION:

Coronary heart disease, peripheral artery disease, cerebrovascular disease, rheumatic and congenital heart illnesses, and venous thromboembolism are all included under the general term "cardiovascular disease" (CVD). 31% of deaths worldwide are related to CVD, with the bulk of cases being CHD and cerebrovascular accidents.[1]As the incidence of CVD risk factors rises in previously low-risk countries, the rate of CVD is predicted to climb globally.[2]

As of right now, 80% of deaths from CVD occur in developing countries. In most of these countries, CVD is predicted to surpass infectious diseases as the leading cause of death. Not only is cardiovascular disease (CVD) the world's largest cause of death, but it also accounts for the majority of years of life lost due to disability.[3]Over 75% of premature CVD is thought to be preventable, according to the World Health Organisation (WHO), and lowering risk factors can help lessen the increasing burden of CVD on patients and healthcare professionals.[4] Despite the fact that age is a in later years is not inevitable,[5] thus risk reduction is crucial recognised risk factor for CVD, autopsy data indicates that the disease's development process.

The INTERHEART trial showed the preventive benefits of eating a diet high in fruits and vegetables and engaging in regular physical activity, while also clarifying the impact of several CVD risk factors, such as smoking, diabetes, hypertension, dyslipidemia, and abdominal obesity.These risk variables contributed to the viability of standardised approaches to primary prevention of CVD worldwide since they were consistent across all populations and socioeconomic levels evaluated.[6]

In this review, we examine the key elements of primary CVD prevention as they are covered in the most recent best practice guidelines from Europe and America, and we make an effort to give physicians a concise overview of these guidelines.

METHODS:

Specifically, we examined the most recent NICE (National Institute for Health and Care Excellence) guidelines.[7-9]Guidelines from the American Heart Association (AHA), American College of Cardiologists (ACC)[12–14], and the European Society of Cardiology (ESC) [3–9], as well as those referred to by the ACC in the case of hypertension, are all recommended.16 We conducted a review of recent literature and highlighted the areas that these guidelines are intended to address. The search terms "Primary prevention in cardiovascular disease," "hypertension",‘lipids’, ‘exercise’, ‘smoking’, ‘alcohol’‘polypill’, ‘weight’, ‘blood glucose’ and the term ‘cardiovascular disease prevention", were used to conduct a literature search. Data, guidelines and their scientific underpinning were extracted from the above and compared.

DISCUSSION

Here, we go over the key areas targeted for CVD primary prevention, including current recommendations, the information that backs them up as well as any differences in the guidelines' suggestions.

LIFESTYLE MODIFICATIONS

Exercise: It is widely acknowledged that exercise improves most health outcomes, and cardiovascular disease is no exception. Even at very high levels of exercise, there is very little direct correlation between mortality and morbidity from exercise, and for the vast majority of people, the advantages of exercise outweigh the hazards.[16]

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.[7]The guidline also states that any form of exercise provides CVD risk reduction,with those newly starting exercise achieving greatest benefits and any subsequent increases providing significant but diminishing returns.[17]

Diet: Diet is assumed to be a major factor in CVD risk, however there is conflicting evidence to support this claim, and there is also a lack of overwhelming consensus over recommended practices.

The Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruits, vegetables, and whole grains and low in sweets and saturated fats, is advised by the American Heart Association. This does not aim to demonstrate a direct decrease in the risk of CVD; rather, it has been demonstrated to be a means of lowering blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C), which are independent risk factors for CVD.[12]

NICE advises consuming less saturated fat, more monounsaturated fatty acids, and five servings of fruits and vegetables daily. They also recommend eating two servings of fish per week and a diet high in fibre. Although they concede that there is insufficient evidence to support a direct influence of these adjustments on CVD risk, they do note that other

aspects of health appear to benefit from them.Interestingly, most of the studies cited were conducted before the 1990s, when dietary habits were very different, and nearly all of their findings on the risk of CVD were underpowered.[18]

The ESC suggests moving away from saturated fats and towards polyunsaturated fats, increasing your intake of fibre, fruit, vegetables, and seafood, giving up alcohol, and following a Mediterranean-style diet.It has been demonstrated that all of these significantly lower the risk of CVD.[10]Furthermore, there is convincing evidence linking industrially produced transfats to CHD[19]; as a result, ESC and NICE guidelines specifically prohibit these transfats.The differences between the suggestions are caused by a variety of factors. When it comes to fibre intake, for instance, the NICE guidelines only consider randomised controlled trials (RCTs) from the 1980s; in contrast, the ESC refers to meta-analyses of data up to the 2010s.

Regarding attention to the recommendations for saturated fats, the AHA guidelines make no particular mention of CVD risk, whereas the ESC guidelines employ modelling data—rather than epi-demiological or RCT—to infer a reduction in CVD risk from a decrease in LDL-C. In this domain, NICE guidelines stand to gain from an expansion of their use of prospective or epidemiological data to support recommendations, as well as an updating of their evidence base.

In conclusion, it appears that there is solid data supporting the recommendation of diets low in simple carbohydrates and salt and high in fruit and vegetable intake and fibre.Following a Mediterranean-style diet seems to have additional cardioprotective benefits.

Smoking: The primary risk factor for CVD has long been recognized to be smoking[20].30 percent of CVD deaths are related to smoking, while European data show that smoking doubles the 10-year CVD mortality rate[12]. It is harmful in addition to having no known safe lower limit and being doserelated.[21] A considerable decrease in CVD events is linked to UK public health initiatives, such as smoking bans, and workplace exposure to tobacco smoke raises the risk of CVD by 30%. Therefore, passive smoking is just as dangerous.[10]

The most economical measure for preventing CVD is quitting smoking, and there are some immediate advantages.[10, 12] All standards recommend quitting, and regardless of the duration or severity of a smoker's habit, there are both short- and long-term benefits. It is generally accepted that buproprion, a norepinephrine dopamine reuptake inhibitor, and especially varenicline, a partial nicotine receptor agonist, should be used in conjunction with nicotine replacement therapy (NRT). Although varenicline doubles abstinence, the two former both increase rates of abstinence by 50–70%.[22,23]
Patient-led medication selection is recommended, with special attention to side-effect profiles. Although evidence suggests that quitting smoking has more advantages than disadvantages, NRT has already issued warnings about its usage in people with CVD.[24]Physician intervention is also suggested as an economical means of quitting smoking,[25]especially useful for secondary prevention following myocardial infarction (MI).[14]

Concerns about the danger of CVD remain with e-cigarettes. Even if the amount of harmful substances in cigarette smoke has decreased, animal models of nicotine exposure still show impacts on CVD, with mice models showing higher levels of atherosclerotic plaques.[26] We are awaiting long-term data to investigate the impact on humans.

Weight: Although the lowest all-cause mortality is observed at BMI [19–24], having a body mass index (BMI) > 25 is a risk factor for CVD. Reductions below this level are not commonly advised due to the increased all-cause mortality with BMI < 20.[27]Maintaining a healthy weight is advised to lower the risk of CVD, but no specific weight management is recommended by the guidelines.Although visceral adiposity and liver fat are significant risk factors at all BMI levels, BMI is an excellent predictor of CVD risk, especially at higher levels.[28] The heterogeneity in the CVD risk profile observed in overweight individuals, which changes based on the location of adipose deposition, is explained by this. There are indications that lowering waist circumference, which serves as a stand-in for lowering visceral fat, should be prioritized in addition to lowering BMI in order to lower the risk of CVD.

Alcohol: Because frequent and excessive alcohol use have known consequences, alcohol intake is a contentious topic. The challenge arises from the historical evidence of a J-shaped curve for risk, where low alcohol intake is linked to a lower level of CHD and abstinence is associated with an increase in CVD compared to light drinkers.[29] In addition to the well-known physiological consequences of alcohol, such as its interference with platelet aggregation, evidence from the INTERHEART trial would seem to support

these statements, demonstrating lower risk for individuals who drink alcohol moderately or lightly.[30]On the other hand, a recent large mendelian investigation by Holmes et al.[31] has demonstrated that drinking less alcohol is linked to a lower risk of cardiovascular disease (CVD) across a genetic subgroup for alcohol dehydrogenase. This implies a lower risk of CVD is linked to reducing alcohol use, especially for individuals who drink in moderation. Accordingly, there is no safe threshold of alcohol consumption, according to the ESC standards.[10].NICE guidelines[7] 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.[32]As yet there does not seem to be a consensus of opinion regarding safe levels, but high levels are evi-dentlydeleterious. Prior to the release of this data, NICE guidelines[7] were developed. They maintain their recommendations for moderate intake, recommending no more than four units per day for men and three for women, even though these are arbitrary numbers. Along similar lines, the ACC recommends moderation as well: one drink for women and two for men each day.[32] Although there does not appear to be agreement on acceptable amounts just yet, excessive doses are clearly harmful.

MEDICAL TREATMENT

Lipid-Lowering Therapy: Primary prevention strategies that aim to lower cholesterol levels have been around for a while, and research has been done to distinguish between the various impacts of serum lipid subfractions on the risk profile for CVD. With a high association between LDL-C levels and CVD risk, LDL-C is the most well-understood atherogenic subfraction. Reducing LDL-C by 1.0 mmol/L results in a commensurate 20–25% risk reduction in CVD mortality and nonfatal MI.[9]Although the causal relationship between elevated high-density lipoprotein cholesterol (HDL-C) and cardioprotection has not been shown, the idea has been supported. This debate is supported by the unfavorable CVD profile of HDL-raising medications like torcetrapib and a recent mendelian randomization research that indicates there is no inherent advantage to naturally elevated HDL-C levels.[10]

While blood triglycerides may not have the same statistical power as LDL, they are nevertheless a significant risk factor for CVD. Apolipoprotein B (ApoB) appears to be a similar predictor of CVD risk to LDL.[10]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.[33]The ESC recommends statins in high-risk individuals or those whose cholesterol levels have increased to > 4.9 mmol/L, while the AHA recommends statins for primary prevention in all patients with a serum LDL-C > 4.9 mmol/L regardless of risk profile.[13] While they are more cautious when it comes to their overall application, they do propose them as the best first-line monotherapy without offering dosage recommendations. Cancer prevention in individuals under 85 years old with a QRISK2 score greater than 10%. Despite a dearth of supporting evidence, it also mentions that individuals older than 85 years old are probably going to gain from a similar CVD risk decrease. NICE suggests consulting a specialist if total lipid levels exceed 9 mmol/L or non-HDL exceed 7.5 mmol/L, however it does not consider specific cholesterol levels or ratios as individual risk signals. There are no recommendations defining a normal range, therefore satisfactory lipid levels continue to be a contentious issue.[7]Since statins are among the most often prescribed drugs in the world, there is a wealth of data supporting their usage. Of the many risk profiles, atorvastatin has been demonstrated to be the most cost-effective and to dramatically lower LDL-C. According to NICE, therapy is still cost-effective for patients with a QRISK2 < 10%; however, because of the side-effect profile that has been shown, NICE recommends that statins be used as primary preventive if there is a 10% risk of CVD.[7]There are two sides to the aforementioned controversy. First off, a 2013 study by Abramson et al. asserted that their reanalysis of the data revealed no decrease in low-risk population mortality or morbidity[34], leading to iatrogenic harm in the form of unacceptable side effects that were recorded in 5–10% of patients. Second, the practically universal prescription of statins in otherwise healthy people would be the consequence of this recommendation. Even with an ideal BMI, excellent cholesterol, and no comorbidities, a 65-year-old male would have a 10% risk; the same would apply to a 70-year-old female.[35] The medical community is reluctant to use blanket therapy on a population-wide scale for theoretical gains because of the present side-effect recommendations. However, a reanalysis by Collins et al. revealed that there is a significant underreporting of the side-effect profile, which causes the riskbenefit ratio to swing back in favor of statins.[36]During the course of five years of statin therapy, their study

identifies a 1% risk of diabetes, 1% risk of muscle soreness or weakness, 0.1% risk of hemorrhagic stroke, and 0.05% risk of myopathy. This is a considerable reduction in the rate of adverse effects. Although there is still debate, the data strongly suggests using it in people with high risk of CVD and may also be suitable for people with more moderate risk profiles; however, prescriptions should be carefully customized for each patient. Table 1 presents an overview of the guidelines' suggestions for lowering LDL levels.

TABLE 1.
Guidelines for LDL reduction.

Guideline	**NICE[8]**	**ACC[13]**	**ESC[11]**
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.

When statin monotherapy is unable to optimize a patient's lipid profile, non-statin treatments are frequently employed. Bile acid sequestrants, fibrates, and nicotinic acid are commonly used medications; however, because of adverse effects and a lack of reduction in CVD events, these medications are not advised as monotherapy.[10]Combination treatments can lower serum LDL levels even further. While no specific combination is advised by guidelines, in circumstances where a patient is resistant to a statin or is not tolerant of them, they do propose combining them with additional lipid-lowering medications. Phase III findings from proprotein convertase subtilisin–kexin type 9 (PCSK9) monoclonal antibodies, including alirocumab, indicate that new treatments for decreasing cholesterol levels are on the horizon. They have a major effect on CVD events and can be administered as monotherapies or as supplements to statins.[37]Recently, NICE approved evolocumab and alirocumab for the prevention of CVD in people with mixed dyslipidemia, primary hypercholesterolemia, or in cases when statins are insufficient to manage cholesterol.[38] With additional phase III and IV clinical trial data and a potential cost reduction, their use is probably going to spread.

Anti-Hypertensive Therapies: A major predictor for the onset of cardiovascular disease is hypertension. A continuous and exponential effect happens when blood pressure is raised over 115/75 mmHg; for every 20 mmHg increase in systolic blood pressure, also known as SBP, or every 10 mmHg increase in diastolic blood pressure (BP), the risk of a cardiovascular event doubles.[39]

Previous meta-analyses have demonstrated a decrease in CVD risk throughout a broader range of BPs, indicating that the benefits of BP reduction are not restricted and that there is no clear threshold beyond which further reductions are detrimental.[40,41]

According to recent systematic reviews, there may be conflicting or even harmful effects from reducing blood pressure from a baseline of less than 140.[42] Combining these data would imply that lowering blood pressure in hypertensives lowers mortality; however, there is minimal support for early intervention in normotensive or pre-hypertensive individuals.Most people agree that treating hypertension in people at risk of CVD should start at a lower threshold because it works both independently and in concert with other risk factors to increase the risk of CVD.[43]

There is some variation within guidelines with regard to the timing of action and specific goal ranges, which is mainly evident in Table 2.

TABLE 2.
Guidelines for commencement of anti-hypertensives and target BP.

Guideline	NICE[8]	ACC recommended guidelines[15]	ESC[11]
Commencement of treatment – no comorbidities	>160/100 mmHg	>150/90 mmHg if ≥60 yrs >140/90 mmHg if <60 yrs	>160/100 mmHg – after lifestyle modification attempted
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

DM:Diabetes Mellitus; CKD:Chronic Kidney Disease; CVD:Cardiovascular Disease
The preponderance of data indicated that people with blood pressure readings over 160/100 mmHg improved the most, and although there may be benefits at lower levels as well, the evidence was deemed insufficient to make firm recommendations, according to the ESC and NICE guidelines.[11]

Most persons with hypertension need more than one antihypertensive medication for adequate control, which further supports the strong evidence that the reduction in blood pressure matters more than the specific drug type taken.[46]Table 3 shows the prescribed pharmacotherapy.

TABLE 3.
Recommended anti-hypertensive therapy.

Guideline	NICE[8]	ACC recommended guidelines[15]	ESC[11]
First line anti-hypertensive therapy	If <55 yrs – ACEi/ARB If > 55 yrs/Afrocaribbean descent – CCB or thiazide	ACEI/ARB, thiazide, CCBs If black – thiazide or CCB	ACEi, thiazide, CCB, ARB, beta blocker
Additional notes		Use 2 drugs if goal BP not reached within one month	

BP:Blood Pressure; ARB:Angiotension Receptor Blocker; ACEi:Angiotension Converting Enzyme Inhibitor; CCB:Calcium Channel Blocker
NICE justifies the modifications to Afro-Caribbean patients' treatment plans because of variations in plasma renin concentrations among ethnic groups and a propensity for Afro-Caribbean hypertensives to have reduced cardiac output and higher peripheral resistance.[47] The ALLHAT trial shown better results for Afro-Caribbean patients treated with thiazides, while calcium channel blockers (CCBs) improved all outcomes except heart failure, according to the ACC recommended guidelines.[48]

There is a little inconsistency with the ESC recommendations. The ESC acknowledges conflicting data that implies inferiority and a greater side-effect profile, but their use of beta blockers is based on a meta-analysis that suggests the class causes an equivalent reduction in CVD mortality.[11]

Although blood pressure raises the risk of cardiovascular disease (CVD), most population events fall within the greater range of normal. Accordingly, NICE public health guidelines[9] indicate that a considerable decrease in blood pressure across the population would result in a decrease in CVD events. Since this group is not receiving antihypertensive medication, they advise the public to cut back on salt consumption. There is a strong causal relationship between an increase in salt intake and a rise in blood pressure. The opposite is also true: research on

lowering salt intake demonstrates steady drops in blood pressure, especially in hypertensive people[49], as well as indications of a decrease in CVD events.[50] In light of the aforementioned, all three recommendations suggest lowering salt intake on a population- and individual-level, independent of blood pressure.

Due in significant part to the responsibilities of each organization, the specific daily targets are as follows: AHA 2.4 g, ESC 5–6 g, and NICE 6 g, which will decrease to 3 g by 2025.[9,10,12] NICE also has a broader focus on public health than the ESC and AHA, and to help reduce salt intake, it suggests national-level initiatives like population education, price adjustments for higher-salt goods, and national legislation where needed (NICE PH25). Everyone does agree, though, that consuming less salt lowers blood pressure and thereby lowers the risk of CVD.[51]

Blood Glucose: Although it is not a substantial risk factor for CVD in non-diabetics, glucose management is important in the diabetic population. While people with impaired fasting glucose (IFG) are known to be at considerable risk of both CVD and the progression to diabetes mellitus (DM), people with diabetes mellitus (DM) have an average risk of CVD.[52] With the lowest risk at normal blood sugar levels, DM serum glucose lowering has been demonstrated to lower CVD.[53]More drastic glucose reductions were harmful, and dipeptidyl peptidase-4 inhibitors and certain thiazolidinediones in particular increased the risk of CVD.[54] Recent studies have demonstrated that, when compared to conventional therapy, oral hypoglycemics like empagliflozin, which belong to the sodium/glucose transporter 2 inhibitor class, significantly lower all-cause mortality by 32%, CVD death by 28%, and heart failure by 35%.Although it seems that cardio-renal hemodynamic effects rather than a decrease in glucose were the mechanism underlying these outcomes, the significant advantages seen would suggest starting it early in diabetic patients. Further information about these drugs is required to update the current guidelines.

Anti-Platelet Therapy: Anti-platelet therapy is a major factor in secondary avoidance, but it shouldn't be used for primary prevention in those without comorbidities because it increases the risk of bleeding and shows no signs of lowering the risk of CVD. There is conflicting advice for DM patients: Aspirin medication is advised for patients with diabetes mellitus who have a 10-year CVD event risk of ≥10%, according to the American College of Chest Physicians, but ESC recommendations maintain that the bleeding risk outweighs the advantages of aspiration therapy.[56]

Further Investigation Areas: Homocysteine, uric acid, and the polypill are some more areas. Although polypills, or combination pills, have outstanding theoretical benefits for reducing CVD risk, meta-analyses of in-vivo data have not shown a statistically significant improvement in CVD risk.[57]

Since patients with gout or hyperuricaemia receiving urate-lowering therapies have improved CVD and all cause mortality, lowering serum uric acid levels may reduce CVD risk. More research is necessary to determine whether these benefits translate to a reduction in risk across the population. Although homocysteine is recognized to be an atherogen, reducing treatments have not shown a decrease in CVD.[60]

CONCLUSION:

Preventing CVD aims to lower the frequency of significant cardiovascular events, which will decrease early morbidity and disability while increasing longevity and standard of existence.

While there is broad agreement regarding smoking and exercise as ways to lower the risk profile for CVD, the specifics of other factors may cause variations in the advice from the United States, Europe, and the United Kingdom. While lifestyle advice hasn't changed much over the years, pharmaceutical choices have.

Primary prevention is still changing, and as long-term data becomes more widely available, our knowledge of the best ways to lower the risk of CVD improves as well. If we are to lessen the burden of a preventable disease, we must keep up this endeavor.

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REFERENCES:

1. WHO. Cardiovascular diseases (CVDs). 2016. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/ (accessed 10 October 2016).
2. Nichols M, Townsend N, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics. *European Cardiovascular Disease Statistics 2012 edition*, Brussels, Belgium: European Heart Network AISBL, 2012.

3. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701
4. WHO. The challenge of cardiovascular disease – quick statistics, 2016. Available at: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics (accessed 10 October 2016).
5. Kannel WB, Doyle JT, Shephard RJ, et al. Prevention of cardiovascular disease in the elderly. *J Am Coll Cardiol* 1987; 10: 25A–28A.
6. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *The Lancet* 2004; 364: 937–952.
7. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE Guideline CG181, 2016.
8. NICE. NICE Guideline CG127. NICE Guidelines, 2011.
9. NICE. Cardiovascular disease prevention. NICE Guideline PH25, 2010.
10. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
11. Council ES, Redon J, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J* 2013; 34: 2159–2219.
12. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013. 2014: 63(25_PA).
13. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2889–2934.
14. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. *Circulation* 1997; 96: 3243–3247.
15. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520
16. Marijon E, Tafflet M, Celermajer DS, et al. Sports-related sudden death in the general population. *Circulation* 2011; 124: 672–681.
17. Sattelmair J, Pertman J, Ding EL, et al. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; 124: 789–795.
18. MODIFICATION L. *Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*, London: NICE, 2008, 2008.
19. de Souza RJ, Mente A, Maroleanu A, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* 2015; 351: h3978–h3978.
20. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; 109: 1101–1107.
21. Law MR, Wald NJ. Environmental tobacco smoke and ischemic heart disease. *Prog Cardiovasc Dis* 2003; 46: 31–38
22. Fiore MC, Smith SS, Jorenby DE, et al. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. *JAMA* 1994; 271: 1940–1947.
23. Kottke TE, Battista RN, DeFriese GH, et al. Attributes of successful smoking cessation interventions in medical practice: a meta-analysis of 39 controlled trials. *JAMA* 1988; 259: 2882–2889.
24. Tzivoni D, Keren A, Meyler S, et al. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovasc Drugs Ther* 1998; 12: 239–244.
25. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Health Education Authority. *Thorax* 2000; 55: 987–999.
26. Bhatnagar A. E-Cigarettes and cardiovascular disease risk: evaluation of evidence, policy

implications, and recommendations. *Curr Cardiovasc Risk Rep* 2016; 10: 1–10.
27. Khosravi A, Akhavan Tabib A, Golshadi I, et al. The relationship between weight and CVD risk factors in a sample population from central Iran (based on IHHP). *ARYA Atheroscler* 2012; 8: 82–89.
28. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012; 126: 1301–1313.
29. Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol* 1990; 66: 1237–1242.
30. Leong DP, Smyth A, Teo KK, et al. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case-control study. *Circulation* 2014; 130: 390–398.
31. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* 2014; 349: g4164–g4164.
32. Garcia S. Alcohol Consumption and CVD: The case for moderation, 2015. Available at: http://www.acc.org/latest-in-cardiology/articles/2015/01/05/13/06/alcohol-consumption-and-cvd-the-case-for-moderation (accessed 25 October 2016).
33. Liberty Pharmaceuticals. Atorvastatin, 2016. Available at: https://www.drugs.com/pro/atorvastatin.html (accessed 10 October 2016).
34. Abramson JD, Rosenberg HG, Jewell N, et al. Should people at low risk of cardiovascular disease take a statin? *BMJ* 2013; 347 f6123.
35. ClinRisk. QRISK®2-2016 cardiovascular disease risk calculator, 2016. Available at: https://qrisk.org/2016/ (accessed 10 October 2016).
36. Interpretation of the evidence for the efficacy and safety of statin therapy Collins, Rory et al. *The Lancet* 2016; 388: 2532–2561.
37. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372: 1489–1499.
38. NICE. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. NICE Guideline TA393 2016 05/05.
39. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet* 2002; 360: 1903–1913.
40. MacMahon S, Peto R, Collins R, et al. Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *The Lancet* 1990; 335: 765–774.
41. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338: b1665–b1665.
42. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016; 352: i717–i717.
43. Chobanian A. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206–1252.
44. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *The Lancet* 1998; 351: 1755–1762.
45. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338: b1665–b1665.
46. Cushman W, Ford C, Cutler J, et al. ALLHAT Collaborative Research Group: success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens* 2002; 4: 393–404.
47. Khan JM, Beevers DG. Management of hypertension in ethnic minorities. *Heart* 2005; 91: 1105–1109.
48. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic:

the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997.
49. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens* 2006; 24: 215–233.
50. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007; 334: 885–888.
51. Obarzanek E, Proschan MA, Vollmer WM, et al. Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* 2003; 42: 459–467.
52. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet* 2010; 375: 2215–2222.
53. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405–412.
54. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545–2559.
55. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
56. Halvorsen S, Andreotti F, Jurriën M, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014; 64: 319–327.
57. Hughes A. One pill, four questions: what we still need to know about reducing cardiovascular risk with combination therapy. *Cochrane Database Syst Rev* 2014; (4): ED000079.
58. Chen J, Lan J, Cheng C, et al. Effect of urate-lowering therapy on all-cause and cardiovascular mortality in hyperuricemia patients without Gout: a case-matched cohort study. *PloS One* 2015; 10: e0145193–e0145193.
59. Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. *J Rheumatol* 2015; 42: 1694–1701.
60. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J* 2015; 14: 1.