Update on Cardiovascular Prevention in Clinical Practice

A Position Paper of the European Association of Preventive Cardiology of the European Society of Cardiology

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1.INTRODUCTION

The 2016 European Guidelines on cardiovascular disease prevention (CVD) represented an evidence-based consensus of the Sixth European Joint Task Force (JTF) involving 10 professional societies, where the evidence and knowledge gaps in managing CVD prevention were revised. In addition, the guidelines provided tools for healthcare professionals to promote population-based strategies and integrate these into national or regional prevention frameworks and to translate these in locally delivered healthcare services, in line with the recommendations of the World Health Organization (WHO) global status report on non-communicable diseases 2010 [1].

For the present document, components from the 6th JTF and experts from the European Association of Preventive Cardiology (EAPC) of the European Society of Cardiology (ESC) were invited to provide a summary and critical review of the most important new studies and evidence since the 2016 Guidelines were published.

The structure of the document follows that of the previous Guidelines and has four parts: 1. Introduction (epidemiology and cost effectiveness); 2. Cardiovascular (CV) risk; 3. How to intervene? (at population level, at individual level, and in specific diseases); 4. The settings: where to intervene?

In keeping with the 2016 Guidelines, greater emphasis has been put on a population-based approach, and on disease-specific interventions. Finally, the presence several gaps in knowledge is highlighted.

1.1 Epidemiology

According to the latest (2017) European data from the ESC Atlas, CVD accounts for 45% of all deaths in Europe and 37% of all deaths in the European Union (EU) and thus remains one of the most common disorders[2]. There were ~83.5 million people living with CVD in ESC member countries in 2015. The prevalence was driven predominantly by peripheral vascular disease (~35.7 million), followed by ischemic heart disease (IHD) (~29.4 million), other CVD such as pericardial disease, valvular heart disease (~13.3 million), atrial fibrillation (AF) (~9.5 million) and stroke (~7.5 million). Moreover, the economic status with the differences in gross domestic product (GDP) in each country plays a critical role. Age-standardized prevalent cases of CVD per 100 000 people in high- and middle- income countries were 5093 and 6570 for women compared with 6563 and 8358 for men. IHD was less prevalent in high-income compared with middle-income countries in women (1212 vs. 2212) and men (2267 vs. 3788). Stroke prevalence showed similar inequality between high- and middle-income countries in women (448 vs. 843) and men (497 vs. 863). This reflects not only population growth and ageing, because age-standardized data for men and women show consistent declines in CVD prevalence across high-income ESC member countries during the last 25 years. Instead half of the middle-income countries recorded an increase in disease prevalence, with the inequalities in disease burden being further emphasized by a greater than two-fold excess of disability-adjusted life years (DALY) lost to IHD in middle-income

compared with high-income ESC member countries: in women and men, there were a mean of 1004 and 2407 age-standardized DALYs per 100 000 people lost during 2015 in high-income member countries compared with 2715 and 5977 in middle-income member countries.

Similarly for incidence, out of more than 11 million new cases of CVD in the 47 ESC member countries in 2015, larger increases were observed in middle-income countries in both women and men (by 17% and 26% respectively) vs high-income countries (by 11% and 22% respectively).
Higher prevalence of CVD risk factors, such as obesity, diabetes mellitus (DM), age-standardized raised blood pressure (BP), and smoking in middle-income countries are likely to have contributed to the higher CV mortality [2]. For example, the average prevalence of age-standardized raised BP in women and men was 18.3% and 27.3% in high-income ESC member countries and 23.5% and 30.3% in middle-income countries.
This presents the middle-income member countries of the ESC with a clear economic imperative to develop policies to protect their populations against the development and progression of CVD. Prevalence statistics are not always closely associated with GDP. Thus, the commitment to the cause of tackling CVD is not simply a question of resources but also requires sound health policies that are backed up by implementation strategies.

1.2 Cost effectiveness

How to reduce CVD costs is an increasingly pressing question for low- and middle-income countries. In primary prevention, across all age ranges, targeted case finding using a prior estimate of CVD risk is more efficient than universal case finding in healthy adults, which supports the implementation of validated risk scores.[3] A small case-based training program for general practitioners in the Stockholm County, aimed to implement evidence-based care of patients at very high risk of coronary death, was associated with decreased mortality and showed long-term cost-effectiveness[4].
In an extra European country (India) a microsimulation model of myocardial infarction (MI) and stroke has demonstrated the efficacy and the cost-effectiveness of expanding national insurance to cover primary prevention, secondary prevention, and tertiary treatment for CVD[5].

2. CARDIOVASCULAR RISK

2.1 Risk stratification and scores

2.1.1 Non-traditional CVD risk factors.

Non-traditional risk factors are considered potentially useful if 1) improve risk classification, 2) there was no evidence of substantial publication bias and 3) their measurement is likely to be cost-effective. Consequently, socio-economic status, family history, (central) obesity, coronary artery calcium scoring (CAC), carotid plaque, abnormal ankle-brachial index (ABI)

have been considered potentially useful risk modifiers of the SCORE [1]. In 2018, the US Preventive Services Task Force updated its 2009 and 2013 recommendations by providing a novel evidence report and systematic review.[6] They concluded that ABI, CAC, and high-sensitivity C-reactive protein (hsCRP) can improve discrimination and reclassification with respect to conventional risk score, but that such improvements were generally small and that the literature was insufficient to draw firm conclusions on their added value [6].

The 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Primary Prevention of CVD, which considers 10-year risk estimation, takes a relatively liberal position, in that many 'risk enhancing factors' are recommended (Class IIa) to guide decision making in borderline (5% to <7.5%) and intermediate (7.5% to <20%) risk groups [7]. These include, amongst others, family history, ethnicity, metabolic syndrome criteria, renal function, hsCRP, lipoprotein(a) (Lp(a)), apolipoprotein B (apoB), ABI, history of pregnancy-associated conditions or premature menopause, and chronic inflammatory disease. The US guideline apparently fails to account for the substantial level of publication bias in this field [8] and does not make explicit that a *favourable* profile of these 'risk enhancers' would *lower* an individual's risk considerably. A separate class IIa recommendation was issued regarding the use of CAC in some patients at borderline and all patients at intermediate risk. This approach seems more aggressive than the 2016 ESC guideline, which only has a class IIb recommendation to consider CAC around decisional thresholds [1]. Taken together, relatively little new evidence has emerged regarding the added value of many suggested biomarkers and other risk modifiers. Key questions regarding evidence, cost-effectiveness and potential harm of larger-scale use of CAC scoring for refinement of risk stratification remain.

Future interest in the wider use of cardiac biomarkers (i.e. natriuretic peptide and cardiac troponin blood concentration) is rising due to emerging promising data [9,10] but further work is needed.

2.1.2 Which Risk Score?

There is debate about the optimum algorithm for CVD risk estimation. Although the Systematic COronary Risk Evaluation (SCORE) risk engine is generally recommended in the current ESC guideline, the use of any risk score is encouraged, if such risk score was developed in a methodologically sound manner and are optimally calibrated for use in particular countries or geographical regions [11], such as Q-RISK/JBS3 of people in the United Kingdom [12].

However, the need for a revaluation with recalibration of the current risk scores has been underlined. A head-to-head comparison of four algorithms (Framingham risk score, SCORE, pooled cohort equations, and Reynolds risk score) recommended by primary prevention guidelines have shown wide differences in clinical performances. These differences were reduced after 'recalibration', using the risk factor profile and CVD incidence of target populations. It was estimated that to prevent one CVD event, it would be necessary to initiate statin therapy in 44–51 such individuals using original algorithms, in contrast to 37–39 individuals with recalibrated algorithms [11].

Furthermore, two other important issues regarding risk assessment are subject to current debate.

First, the question of whether risk stratification for people with previous CVD events may be appropriate remains unanswered. Risk among such persons is heterogeneous and with the introduction of very costly interventions (such as proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors), further risk stratification in secondary prevention may become necessary. Some models have already been developed, and suggest that predictors of risk may be quite different from primary prevention[13,14].

A second interesting development is to adopt a lifetime perspective on CVD risk assessment. Although this was already touched upon in the 2016 ESC guideline, and is also part of the 2019 US guideline [7], there is no consensus as to which level of lifetime risk and at which particular age this risk is calculated should trigger treatment recommendations. An extension of this lifetime risk perspective is to calculate lifetime benefit from the initiation of CV preventive drugs. This perspective may be more intuitive to patients facing a decision whether or not to start preventive drug treatment. Models have been developed to calculate (disease-free) life-years gained for both for populations of people with and without DM [15,16]. For the time being, such alternative perspectives primarily facilitate communication with patients about treatment decisions, but if further studies validate this approach, life-time *(disease-free)* gained could become a more central criterion in formal treatment recommendations and in supporting the importance of even moderate reduction in CV risk.

2.2 Other risk markers

2.2.1 Genetics and Epigenetics

There has been a significant increase in the number of epidemiological studies investigating CV risk factors and outcomes in relation to DNA methylation, histone modifications, RNA-based mechanisms but many gaps remain in our understanding of the underlying cause and biological implications. An association between coronary artery disease (CAD) presence and characteristics and selected circulating transcriptional and epigenetic-sensitive biomarkers linked to cholesterol pathway has been observed [17].

A polygenic risk score derived from up to 57 common DNA sequence variants previously associated with CAD [18] has allowed to identify individuals with a greater burden of subclinical atherosclerosis and would derive a greater relative and absolute benefit from statin therapy to prevent a first CAD event [19].

It is noteworthy that there is still no evidence of cost-effectiveness of application of CV genetic risk score testing in clinical practice, such as targeting statin therapy in individuals at low-to-moderate CV risk [20].

2.2.2 Psychosocial

The EUROASPIRE IV survey[21] confirmed the high prevalence of symptoms of depression and anxiety in patients with CAD (22,4% and 26,3%, respectively). Both symptoms were more prevalent in women than men (30,6% vs. 19,8%, and 39,4% vs. 22,1%, respectively), and

were associated with lower educational level and more sedentary lifestyle. Furthermore, depression was associated with current smoking, central obesity and DM.
The ESC position paper on depression and CAD [22] confirmed the relevance of depressive symptoms for CAD incidence and prognosis, and summarized pathophysiological mechanisms like poor and sedentary lifestyles, neurohumoral activation, inflammation and endothelial dysfunction, that promote coronary atherosclerosis and microvascular remodeling. Thus, depression may trigger more intensive efforts to detect and manage risk factors. Whether treating depression per se improves outlook remains unclear.
With respect to the ESC guideline regarding the clinical interview [1], a validation study has shown only moderate to fair correlations of the screening items with established psychometric questionnaires [23]. Hence, refinement of the screening items is required.
As adverse experiences in childhood and adolescence, such as psychological, physical, or sexual abuse in the child and substance abuse of family members, are associated with worse cardiometabolic outcomes in adults, a position statement of the AHA [24] recommended the development of early interventions to ameliorate these harmful exposures.

In the recent update on QRISK score [https://qrisk.org/three] having severe mental illnesses (i.e. schizophrenia, bipolar disorder and moderate/severe depression) leads to meaningful risk reclassification[25].

2.2.3 Imaging Methods

In patients with intermediate or borderline cardiovascular risk, CAC measurement based on computed tomography (CT) can reclassify risk upward (particularly if the score is ≥100 Agatston units or ≥75th age/sex/race percentile) or downward (if CAC is zero and it is now a IIa recommendation in the ACC/AHA guidelines) in risk stratification[7].

However, while the amount of CAC roughly correlates with the total amount of atherosclerosis present in the coronary arteries, it correlates poorly with the degree of luminal narrowing. Furthermore, it does not provide direct information about the total plaque burden or stenosis severity and can be absent in middle-aged patients with soft non-calcified plaque.

In the randomized open-label, SCOT-HEART trial [26] in patients with stable chest pain, the use of CT coronary angiography on top of standard of care (with consequent changes in treatment) reduced the rate of death from CAD or nonfatal MI (hazard ratio [HR] 0.59; 95% confidence interval [CI], 0.41 to 0.84; P=0.004), compared with standard care alone. This difference was driven primarily by a lower rate of nonfatal MI. The reductions in coronary events were the same irrespective of symptoms, independent of baseline statin use or cardiovascular risk score. These findings suggest that using a cardiovascular risk score both over and under treats individuals, and that CT coronary angiography appears to be associated with better reductions in coronary events irrespective of the risk score. The reasons for the benefits of CT coronary angiography might be related to better targeted secondary prevention, closer adherence to lifestyle modifications and preventative therapies, and coronary revascularisation in those with prognostically significant disease.

Currently, the use of CT coronary angiography as a risk stratification tool in asymptomatic individuals is not supported by data since no prospective, randomized intervention studies have been performed.

2.3 Clinical conditions affecting CV risk

2.3.1 Diabetes Mellitus

One group that can benefit from earlier identification are subjects with undiagnosed DM. Screening for DM in individuals identified as high risk by validated DM risk scores applied to electronic primary care data is feasible and can result in more intensive treatment of CVD risk factors and reduction in CVD risk[27,28]. Patients who lost $\geq$ 5% body weight at one year after diagnosis of DM had a 48% lower 10 year adjusted hazard of CVD incidence compared to maintained weight[27]. Weight loss can also result in remission of DM as shown in the DIRECT trial in primary care randomising people with overweight/obesity and type 2 DM diagnosed in the last 6 years to a diet replacement programme or usual care. In the intervention group, 24% achieved a weight loss of ≥ 15 kg, 46% had DM remission, compared to 0% and 4% of the usual care group at one year. The amount of weight loss was associated with DM remission, as 86% of those who lost $\geq$ 15 kg achieved remission in the first year compared to 34% of those with 5 – 10 kg weight loss[29].

Whilst most guidelines prioritize the use of intensive risk factor management in people with type 2 DM above the age of 40, as do the 2016 ESC CVD prevention guidelines[1], recent research has better highlighted the importance of age of onset as a predictor of life years lost from DM. There is now clear evidence that younger onset type 2 DM leads to considerably greater losses and excess CVD outcomes, such that those developing Type 2 under the age of 20 can lose well over a decade in life years whereas there may be negligible loss of life when DM develops after the age of 80 years of age [30]. These findings should help to better focus on CVD risk factor management in those developing DM under the age of 40, though caution with the use of statins and some antihypertensive agents remains important for women of childbearing age. Similarly, recent evidence suggests that age of onset also matters to those with Type 1 DM because associated with greater loss of life expectancy [31]. There is some evidence that people with type 1 DM have greater excess and absolute risks for CAD and heart failure (HF) than those with type 2 DM [32] and thus there may be longer-term benefits from more aggressive use of statins and BP control.

2.3.2 Chronic kidney disease

Chronic kidney disease is a recognized as a marker for future CVD events. In the recent update on QRISK score [https://qrisk.org/three] having chronic kidney disease (stage 3-4-5) leads to meaningful risk reclassification[25].

2.3.3 Influenza

An association between acute respiratory infections, especially those occurring at times of peak influenza virus circulation, and acute MI has been reported by observational studies. [33,34]

A self-controlled case-series design to evaluate the association between laboratory-confirmed influenza infection and hospitalization for MI showed that the incidence of admissions for MI was six times as high during the 7 days after laboratory confirmation of influenza infection vs. control interval (20.0 admissions per week vs. 3.3 admissions per week). The incidence ratio point estimates were highest for older adults, for patients with influenza B infection, and for patients who had their first MI. [35]

The recommendation on influenza vaccination on secondary prevention in patients with CVD is supported by new evidences. A Cochrane review of 8 randomized clinical trials in 12,029 patients with CVD [36] reported a significant reduction in CV mortality among patients vaccinated against influenza (RR 0.44, 95% CI 0.26-0.76).

Strong evidences of the effectiveness of influenza vaccination in primary prevention of CVD are still lacking.

2.3.4 Periodontitis

Most published studies have found a positive association between periodontitis and CVD [37]. A cross-sectional analysis of a cohort of 60,174 participants [38] showed that periodontitis was independently associated with atherosclerotic CVD (OR 1.59 ,95% CI 1.39-1.81). A nationwide cohort of 17,691 patients who received a hospital diagnosis of periodontitis within a 15-year period and matched them with 83,003 controls from the general population found an increased risk for CV death (OR 2.02; 95% CI 1.87 to 2.18) and for all-cause mortality (OR 2.70; 95% CI 2.60 to 2.81). [39] A meta-analysis of observational studies including 22 observational studies including 129,630 participants showed that patients with periodontitis have increased risk of MI (OR 2.02; 95% CI 1.59-2.57). [40]

A systematic review to investigate the effects of periodontal therapy in preventing the occurrence of, and management or recurrence of, CVD in patients with chronic periodontitis [41] found very low quality evidence that was insufficient to support or refute whether periodontal therapy can prevent the recurrence of CVD in the long term in patients with chronic periodontitis. No evidence on primary prevention was found.

2.3.5 Cancer

Several systemic review and meta-analyses are available on the benefit of exercise training program in attenuating the reductions in exercise tolerance[42] and in improving outcome[43].

Regarding early detection of cardiac injury, exercise cardiac magnetic resonance imaging has been shown to be a more sensitive marker of cardiotoxicity than the current standard of care tools to assess resting left ventricular ejection fraction in breast cancer patients.[44] Also, the use of biomarkers has emerged as a valuable tool for the early identification and monitoring of cardiotoxicity. In particular, cardiac troponin and B-type natriuretic peptide (BNP) elevation during chemotherapy allows identification of patients more prone to develop myocardial dysfunction and cardiac events [45].

2.3.6 Autoimmune disease

The assessment of risk factor profile is warranted in adults with inflammatory autoimmune disorders. The current guideline[1] draws attention to increased CVD risk in auto-immune disease, particularly rheumatoid arthritis (RA), but potentially all auto-immune diseases are associated with systemic inflammation increased risk: e.g. there is emerging evidence that connective tissue disease and, to a somewhat lesser degree, inflammatory bowel disease are associated with increased CV risk.[46]

In 2017, the European League Against Rheumatism (EULAR) updated its CVD risk management guideline,[47] but this is now being updated again. The evidence supporting increased CVD risk has strengthened, and related to both traditional and non-traditional risk factors, the latter including inflammatory activity, clinical disease phenotype, and serum antibody profile. Based on recent evidence, EULAR has widened their recommendation for CVD risk management to all types of inflammatory joint disease, although the evidence remains strongest for RA. Their recommendation is to use CVD risk prediction models in these patients and multiply risk estimates by 1.5, even though this multiplication factor is uncertain and critically depends on disease phenotype and activity.

That noted, RA was associated with a higher independent HR for CVD outcomes in QRISK3 of around 1.2 to 1.3, but this may be because oral steroids was also a strong independent risk factor for incident CVD, suggesting (though not providing) some of the risk previously associated with CVD in RA, may have been mediated by steroids, or else steroids may reflect disease severity[25].

2.3.7 Sleep apnoea

Epidemiological research indicates that obstructive sleep apnoea (OSA) is associated with increases in the incidence and progression of CAD, heart failure (HF), stroke and AF. [48] Central sleep apnea associated with Cheyne-Stokes Respiration (CSA-CSR) predicts incident HF and AF; among patients with HF, CSA-CSR strongly predicts mortality. Thus, OSA and CSA-CSR are potentially modifiable risk factors for CVD. Treatment of OSA is generally reserved for those individuals with an apnoea–hypopnea index (AHI; the number of apnoeas and hypopnoeas observed per hour) ≥5 in patients with either signs/symptoms of sleep apnoea or associated medical conditions (including hypertension, HF, CAD, significant arrhythmias, and other forms of CVD). Alternatively, an AHI ≥15 is treated as OSA, even in the absence of signs, symptoms, or associated medical conditions [49].

Treatment of OSA with continuous positive airway pressure (CPAP) may improve patient-reported outcomes such as sleepiness, quality of life and mood, but evidences in primary prevention of CV disease with CPAP is limited to small studies, with surrogate endpoints, combined endpoints and observational data [48]. Furthermore, adherence to CPAP seems a critical issue, and a potential role for oral appliances (mandibular advancement devices) has been put forward [50].

2.3.8 Erectile dysfunction

Erectile dysfunction (ED) is often associated with CAD.[51] The third Princeton Consensus Conference [52] recommends assessing CV risk in all patients with ED and CVD to estimating the risk of mortality and morbidity, associated with sexual activity and advocates lifestyle changes [53]: these measures are likely to reduce CV risk and improve erectile function. Notably ED features as a new independent risk factor for CVD in QRISK3.[25]

2.3.9 Migraine

Migraine headache, especially migraine with aura, has been linked to cerebral hypoperfusion, systemic vasculopathy, endothelial dysfunction and a hypercoagulable state: these factors may increase the risk of various adverse CV and cerebrovascular events [54]. A meta-analysis of 16 cohort studies, which included 394,942 migraineurs and 757,465 non-migraineurs has shown that migraine was associated with a higher risk of major adverse CV and cerebrovascular event (adjusted HR 1.42, P<0.001), driven by a higher risk of stroke and MI. There was no difference in the risk of all-cause mortality [55].

2.4 Other relevant groups

2.4.3 Young

A large body of data suggests that younger adults (i.e. <40 years of age) tend to develop an increasingly unhealthy CV risk profile, especially in terms of an increased prevalence of being overweight or obese, increasing rates of DM, substance abuse, and electronic cigarette (e-cig) smoking over the past two decades.[56]

Obesity has been identified as the major risk factor to address for the successful prevention of CVD and associated mortality. Substance abuse such as opioids, cocaine and anabolic steroids has increased among young adults in the past decades that is likely to carry adverse risks of future CV events, particularly among those from a low socioeconomic background. [56]

In young adults, very high levels of circulating LDL cholesterol are often attributable to familial hypercholesterolemia. By use of the modified Dutch Lipid Clinic Network criteria, which are based on nongenetic data, familial hypercholesterolemia is predicted to affect approximately 1 in 130–250 individuals worldwide; however, this condition is thought to be severely underdiagnosed in most countries [57].

The continuous relationship between BP and risk of events has been shown at all ages and in all ethnic groups. Diastolic BP appears to be a better predictor of events than systolic BP in younger (<50 years) vs. older patients. Diastolic BP tends to decline from midlife as a consequence of arterial stiffening; consequently, systolic BP assumes even greater importance as a risk factor from midlife [58].

Masked hypertension is associated with higher CV risk[59] and is more common in younger people than in older ones, associated with male sex, smoking habit, and higher levels of alcohol consumption, anxiety, physical and job stress[58].

On the other side, physical activity 'per se' in young athletes play an hypotensive role with respect to normal control [60,61].

The presence of organ damage in younger hypertensive patients with grade 1 hypertension classified as low risk according to the SCORE system provides unequivocal evidence of hypertension-mediated damage and indicates a clear need for BP lowering treatment [58]. The recent ESC Guidelines recommend that in younger patients with hypertension treated with BP-lowering medication, office BP should be reduced to ≤ 130/80 mmHg if treatment is well tolerated [58].

Further studies are warranted to improve our understanding of the magnitude of the problem of CVD in young adults and to elucidate treatable risk factors that underlie the observed increasing rates of CVDs in this population.

2.4.1 Aging

Management of CV risk factors in the elderly (>65 years of age) should be followed with caution and common sense, adverse effects should be monitored closely, and treatment should be reconsidered periodically. Moreover, individuals older than 75 years are biologically a very heterogeneous group with frequent frailty, comorbid conditions, and multiple concomitant drugs. All these, as well as personal preferences, must be taken into account in treatment decisions.

A prospective cohort study of subjects aged 80 years and older [62] found that CV risk factors were not associated with mortality (such as body mass index [BMI], levels of total cholesterol and LDLc, current or prior smoking habit), while the presence of frailty was a strong risk factor for all-cause mortality (HR: 2.5, 95% CI 1.9–3.2), and for CV mortality (HR: 2.2, 95% CI 1.4–3.4). The optimal target BP may be higher among older treated hypertensive patients than among middle-aged. In addition, among frail or multimorbid older individuals, a relatively low BP may be associated with worse outcomes, and antihypertensive treatment may cause more harm than benefit [63].

Care should be individualized in older diabetic adults, and glycaemic targets suggested by guidelines are considered too tight for frail older individuals [64]. Management of DM in older adults should be adjusted for frailty status, with the intention of reducing complications and improving quality of life [65].

The decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly on randomised clinical trials evidence [66].

A meta-analysis of data from all large statin trials to compare the effects of statin therapy at different ages showed significant reductions in major vascular events irrespective of age, but there is less direct evidence of benefit among patients older than 75 years who do not already have evidence of occlusive vascular disease [67]. Thus, limited evidence is available on therapy for primary prevention of CVDs in very elderly and frail individuals.

2.4.4 Women

It is generally held that women are at lower risk of CVD than men, but this is misleading. Ultimately more women than men die of CVD in Europe, but at an older age. Inspection of the SCORE charts suggests that risk is deferred by about 10 years. The ESC guideline[1] emphasises the increased risk of the development of sustained hypertension and/or DM in women who have had obstetric complications including pre-eclampsia, pregnancy-related

hypertension, and gestational DM. The degree to which CVD risk is elevated independent from these risk factors was less certain. Moreover, pregnancy complications, such pre-eclampsia, also increases the CV risk of the offspring, and not only of the mother [68].
Lifestyle (before conception) of the future mother and father can (by epigenetic mechanisms) influence the possibility to have an healthy child [69].
Although the evidence has been strengthened and now extends to miscarriage and stillbirth[70], it remains unclear if obstetric conditions predict CVD independent from classical risk factors. Awareness of the risk of, in particular, future hypertension and DM remains as relevant as before for women with the aforementioned pregnancy-related disorders.
As for non-obstetric conditions, few new data on the association of polycystic ovary syndrome have emerged. Premature menopause, particularly if associated with early oophorectomy, remains an important risk factor[70] .
Gender disparities in CVD prevention are age dependent, as shown by an analysis of the Treatment of CV Risk in Primary care using Electronic Decision suppOrt (TORPEDO) study [71]. Women attending primary healthcare services in Australia were less likely than men to have risk factors measured and recorded such that absolute CVD risk can be assessed. For those with, or at high risk of, CVD, the prescription of appropriate preventive medications was more frequent in older women, but less frequent in younger women, compared with their male counterpart [71].

Although the percentage of women smokers is lower than men, a recent meta-analysis of 75 cohort studies (approximately 2.4 million individuals) showed a 25% greater risk of CAD in women smokers compared with male smokers (RR, 1.25; 95% CI, 1.12–1.39) [72].

2.4.2 Ethnicity

CV risk varies considerably according to ethnicity[1]. In the recent update on QRISK score ethnicity (Indian, Pakistani, Bangladeshi, Chinese, Black African Black Caribbean, Other Ethnic group) leads to meaningful risk reclassification[25].

3 HOW TO INTERVENE AT POPULATION LEVEL

3.1 Healthy Diet

3.1.1 Governmental restrictions and mandates

Providing a growing global population with healthy diets from sustainable food systems is an immediate challenge. Although global food production of calories has kept pace with population growth, more than 820 million people worldwide have insufficient food and many more consume low-quality diets that cause micronutrient deficiencies and contribute to a substantial rise in the incidence of diet-related obesity and diet-related non-communicable diseases, including CAD, stroke, and DM. Unhealthy diets pose a greater risk to morbidity and mortality than do unsafe sex, and alcohol, drug, and tobacco use combined[73,74].
It is predicted that the current generation of children may have a shorter life expectancy than their parents due to the high prevalence of obesity and its health consequences. According to

the UNICEF and WHO, in Europe 800,000 children suffer from obesity, due to children's exposure to unhealthy food marketing[75].
A global transformation of the food system is urgently needed.[73] Dietary changes from current diets to healthy diets are likely to substantially benefit human health, averting about 10.8 – 11.6 million deaths per year, a reduction of 19.0–23.6%.
Healthy diets have an appropriate caloric intake and consist of a diversity of plant-based foods (including plant protein, i.e. peas, lentils), low amounts of animal source foods, unsaturated rather than saturated fats, and small amounts of refined grains, highly processed foods, and added sugars[73].
A reduction of intake of sugars and sweeteners and progressive elimination of industrially produced trans-fats is recommended [1].
On 24 April 2019, the European Union Commission adopted a regulation setting a maximum limit of trans fat in industrially produced trans fats of 2 grams per 100 grams of fat[76]. This regulation is in line with the Danish regulation and corresponds to what European Heart Network (EHN) and other organizations called for. However, the two-year transition period till 1 April 2021 is considered too long.
Evidence-based recommendations on the control of marketing of foods and calorie-rich beverages to children which requires governments to protect children's health have been set up[77]. On June 2019, the European Commission's science and knowledge service updated the document on "Health Promotion and Disease Prevention" highlighted the need for policy recommendations to reduce intake of sugars, with a special focus on recommendations for children: these recommendation included provision of information to the consumers, to make healthy choice more available and to implement financial (dis)incentives such as taxes on products with high sugars [78].

3.1.2 Labelling and information

Independently and coherently formulated criteria for nutrient profiles, nutrition claims and front-of-pack logos (e.g. traffic lights, healthy choices, keyholes and Nutriscore) have been promoted [79]. In particular, since 2017, the logo Nutriscore has been implemented comprising negative components (energy, sugar, saturated fat, salt) as well as positive components (vegetables, fruits, nuts, fibre and protein) leading to an end score from A "best nutritional quality" to E for the "least good nutritional quality"[80]. This logo has been introduced in France and recently in Belgium[81]. Countries like Spain and Portugal are considering this logo. European Consumer organization (BEUC) supports this system, while the EHN continues to recommend the traffic light system. In the Netherlands firstly a survey into the consumer understanding of different logo's will be conducted.

3.2 Physical Activity Promotion

Physical activity (PA) promotion should be integrated into the settings in which people live, work and play, to increase participation. There are multiple policy opportunities across different sectors: schools, business and industry, community recreation, fitness and parks, faith based settings, health care, mass media, public health and sports [82].

A population-based policy approaches can contribute to reducing inequalities by age, sex and socioeconomic status, geographic location and domains of PA, targeting less active in PA and should be interconnected with policies actions focused on individually centred intervention. The WHO indicates four strategic objectives to create 1) active societies, 2) active environments, 3) active people and 4) active systems. Each objective is an important effective component of a population-based response to increasing PA and reducing sedentary behaviour, and are achievable through 20 policy actions [83].

3.2.1 Community-wide campaign.

Community-wide campaigns that use intensive contact with the majority of the target population over time, can increase PA across the population [84]. It should involve educational, recreational, worksite, primary care and faith-based settings, offering convenient locations for reaching different target groups with different strategies. Multicomponent kindergarden and school intervention are effective in promoting increased school-based PA [82], [83].

3.2.2 Environment and Policy Level

Longer occupational sitting time are significantly associated with higher mortality, while higher levels of PA are associated with a reduced risk of cancer and CV death [85]. Strong evidence shows that point of decision prompts to encourage individuals to make an active choice and can increase the use of stairs.[84,86] Moderate evidence shows that: 1) built environment characteristics and infrastructure that support pedestrian or bicycling transport positively affect PA levels among children, adults and older adults; 2) readily usable and safe walking and cycling infrastructure and related built environment features are also associated with greater amounts of recreational PA among children and adults; 3) access to indoor (gym or fitness centres) or outdoor facilities (parks, trails and other green spaces) are associated with grater PA among children and adults. To decrease sedentary behaviours, moderate evidence suggests that school-based interventions targeting reduction in television viewing and other screen-time activities; and worksite interventions including modifications to the workstation can have a positive impact.[84,86]

3.3 Smoking Bans

Tobacco consumption has been confirmed to be the leading cause of preventable death worldwide[87]. The risk is high also in never smokers, but who are exposed to exposed to second hand smoke: in Greece these individuals exhibited a two-fold elevated 10-year CVD risk [88].

Despite several population-based anti-smoking policies, 28% of the total population across Europe is still smoking [89].

Only high-income European countries showed accelerated decreases in consumption since the action plan by the WHO Framework Convention on Tobacco Control (FCTC) on global cigarette consumption was ratified by 181 countries. In contrast, low and middle-income countries showed increased consumption [90]. The difference in effect between the countries might be because low and middle-income countries have limited resources to regulate the tobacco industry. This should motivate stronger implementation of proven tobacco control policies and more forceful responses to the activities of the tobacco industry[90]. There is very

strong scientific evidence about the measures that successfully reduce and prevent tobacco use. The most effective strategy is to increase the price of tobacco products[87]. In addition, there are smoke free legislation and policies, marketing restrictions, advertising bans and hard-hitting media campaigns, and access to smoking cessation services[91]. These measures should be regulated through robust legislation and rigorous enforcement and have resulted in substantial prevalence declines of tobacco use in high-income countries[92]. A sign towards the opposite direction has been given in Austria: the smoking ban which was scheduled to begin in May 2018 in all bars and restaurants, was recently overturned by lawmakers from a new ruling coalition in the government [93].

3.3 Air pollution

Exposure to PM2.5 has been linked to premature mortality, in 70% of the cases due to CV causes [94], [95]. Even brief exposures to polluted air are associated with MI, stroke, arrhythmias, AF, and hospitalization for exacerbation of HF in susceptible individuals [96]. There is equally strong evidence suggesting that chronic and persistent exposure to air pollution increases the progression of atherosclerotic lesions and has adverse effects on BP regulation, peripheral thrombosis, endothelial function, and insulin sensitivity. In addition to individual susceptibility factors, vulnerability to ambient air pollution is also moderated by environmental factors, such as the built environment, noise, ambient temperature, neighborhood greenspaces, and proximity to major roadways or co-exposure to other pollutants and toxins.[97] [98]

4 HOW TO INTERVENE AT INDIVIDUAL LEVEL

4.1 Behaviour

In addition to face-to-face communication, media-based (e.g. telephone, internet, mass media) interventions have gained increased attention for CVD prevention. A randomized controlled trail on telephone coaching for behaviour change in patients after acute coronary syndrome (ACS) has shown significant though modest effects on BMI, waist circumference, physical activity, and daily intake of vegetables[99]. A randomized clinical trial showed the effectiveness of a Web-based health behaviour change support system and group lifestyle counselling on body weight loss in overweight and obese subjects [100].
A systematic review on internet-delivered interventions in patients with CAD has shown that personalized, concrete support for behaviour change may have favourable outcomes, however, a considerable heterogeneity between studies with respect to the design and quality hinder sound conclusions [101].

4.2 Adherence

CV fixed-dose combination pills, or polypills, may help address the widespread lack of access and adherence to proven medicines. Adherence benefits from switching to a polypill

resulted in risk factor changes that were at least as good as usual care across a wide variety of treatment patterns, including equally potent or more potent regimens [102].
In addition to face-to-face interventions, there were increasing efforts to evaluate the effects of mobile phone-based interventions. With respect to CVD primary prevention, a Cochrane systematic review and meta-analysis [103] concluded that there is low-quality and inconclusive evidence that mobile phone-based interventions might improve medication adherence and/or have favourable effects on outcomes like BP or LDL-cholesterol [103].
With respect to secondary prevention, a Cochrane Systematic Review[104] evaluated mobile phone text messaging for patients after acute cardiac events. Due to the heterogeneity of methods, populations and outcomes, the authors were unable to perform a meta-analysis. Although the authors found favourable effects on medication adherence in 6 out of 7 trials, they concluded that there is insufficient evidence to draw conclusions on the effectiveness of mobile phone-based interventions in CVD secondary prevention [104]. Similar conclusions were derived by a systematic review and meta-synthesis of quantitative and qualitative data on mobile applications for CVD patients [105]. Patients holding implanted device (such as Implantable Cardioverter Defibrillator or Cardiac Resynchronisation Sytems) showed little interest in receiving dedicated information on the overall management of their disease, underlying the insufficient awareness of patients towards the key role of self-control health status and the promotion of a healthy lifestyle [106].

4.3 Physical activity and sedentary behaviour.

PA is associated with beneficial health outcomes. There is an inverse dose-response relationship between moderate-vigorous aerobic PA and all-cause and CV mortality and incident CVD: CAD, ischaemic stroke and HF [107]. Benefit start to accumulate from moving to being inactive to perform PA at lower amount, and increases with higher amount of PA [108]. In healthy adults 150 to 300 minutes a week of moderate-intensity PA or 75 to 150 min of vigorous-intensity PA or an equivalent combination thereof (a volume of 500-1000 MET-minutes per week), reduces the risk of all cause of mortality[109]. Higher volumes of PA through higher intensity, greater frequency or longer duration contributes to risk reduction, but greater increases in PA is required to obtain a modest gain in benefit. PA amounts up to three to five times the recommendation shows no evidence in mortality risk [107]. There is now evidence that bouts of any duration, even less than 10 minutes, are effective and counts for the daily/weekly volume target of PA[84,110].
There is moderate evidence that high intensity interval training can improve insulin sensitivity, BP and body composition similarly to aerobic continuous PA training, especially in overweight or obese adult [111]. The improvement in risk factors control are more likely to occur in adult at greater risk of CVD and DM. There are no universally accepted lengths for high intensity period, recovery period or ratio of the two, no universally accepted relative intensity at which the high intensity component should be performed.
There is a strong evidence of a dose-response association between sedentary behavior and all cause of mortality, CVD mortality and incident CVD, and type 2 DM[84]. Individuals who sit the most and perform the least of moderate to vigorous PA have the greatest risk of mortality, while individual who sit the least and perform the most of moderate to vigorous

PA have the lowest risk[84,112]. Strong evidence for sedentary behavior's guideline is still lacking.
The most effective interventions to increase activity are based on theories of behaviour change, teaching people skills to incorporate PA in their daily routine and attain an active lifestyle. Strong evidence demonstrates that counselling participants to set PA goals and self-monitoring their progress increase PA in the adult population [110,113].
Technologies that use computerized information or communication interfaces-based approaches can provide virtual coaching and deliver behavioural changes, "just in time" personalized advice and support to the users. Wearable activity monitors such as pedometer and accelerometers in combination with goals-setting and other behavioural strategies provide direct PA feedback and can increase PA levels in general and type 2 DM population [114]. Telephone assisted, web based on internet-based intervention, with educational component provide effective remotely guidance to individuals to increase PA. Smartphone applications increase PA in children and adolescent [115,116].

4.4 Smoking Cessation: role of electronic cigarette.

E-cigarettes (electronic cigarettes) are a rapidly changing product class, and are known by many different names, including "e-cigs," "e-hookahs," "mods," and "vape pens"[117]. Most e-cigs contain nicotine whose exposure can harm the developing brain and nicotine exposure during adolescence can impact learning, memory, and attention [117]. In addition to nicotine, the aerosol that users inhale and exhale from e-cig can potentially expose both themselves and bystanders to other harmful substances, including heavy metals, volatile organic compounds, and ultrafine particles that can be inhaled deeply into the lungs [117]. To making e-cig more appealing to young people, some of the chemicals used to create certain flavors may also have health risks [117]. Recently, a new type of e-cig (JUUL) has become increasingly popular due to its minimal exhaled aerosol, reduced odor, and small size, making it easy to conceal [118], but with a high level of nicotine [119].
E-cig can be used to deliver other drugs, including marijuana: in 2016, one-third of U.S. middle and high school students who ever used e-cig had used marijuana in e-cigarettes [120]. It may be that e-cigarettes are more effective in promoting nicotine dependence than as an aid to smoking cessation.

4.5 Body weight

There is increasing evidences on the beneficial effect of body weight reduction with caloric restriction. A meta-analysis of sixty-three studies showed that each additional kilogram loss induced by life-style intervention was associated with 43% lower type 2 DM odds[121].
Caloric restriction without malnutrition leads on increased longevity and delayed onset of age-associated disorders in rhesus monkeys [122].

4.6 Nutrition

4.6.1 Fatty acids and carbohydrate intake

Novel finding have challenged the current guidelines recommendation which restricts saturated fat to <10% total fat[1]. The PURE study of dietary habits in 135,000 people from 18 countries around the world for 7 years observed that high carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality[123]. These findings should be considered cautiously since about 85% of the fat intake in EU countries is within the highest fat quintile of PURE, where the high carbohydrate intake may have been just a proxy for poverty and saturated fat consumption was generally low. Finally the negative relationship goes against multiple studies[1].

The PURE findings are only partially confirmed by other reports studying the association between saturated fats and risk of CAD where the importance of which nutrients saturated fats are replaced by is considered: poly unsaturated fats (-25%), mono unsaturated fats (-15%) and to a lesser extent carbohydrates from whole grains (-9%) reduce CVD risk with isocaloric substitution of dietary saturated fat[124,125]. Also the replacement of animal fats, including dairy fat, with vegetable sources of fats and PUFAs may reduce risk of CVD[126,127]. Whether the food matrix may modify the effect of dairy fat on health outcomes warrants further investigation.

4.6.2 Fruit and vegetables

The PURE study also observed the beneficial effect of increasing consumption of fruit, vegetables, and legumes on total and CV mortality: the maximum benefit was seen at three to four servings a day (equivalent to 375–500 g/day), with no additional benefit with higher intakes[123]. The benefit from some fruits, vegetables, or legumes was greater if they were eaten raw rather than cooked [128].

4.6.3 Meats

From both a health point of view as well as environmentally sustainable food production, a lower consumption of red meat, especially processed meat, has been usually recommended.

However, evidences are still controversial. A meta-analysis of 24 RCTs concluded that ≥0.5 serving/day of red meat did not influence blood lipids, lipoproteins, or BP in comparison with <0.5 serving/day [129]. A subsequent meta-analysis which included 36 RCTs, only when red meat was substituted with high-quality plant foods (i.e. nuts, soy, and legumes) more favourable LDL-cholesterol concentrations (-0,2 mmol/l) was observed [130]. By reducing processed meats, salt intake will be reduced as well.

4.6.4 Functional foods

Red yeast rice (RYR) (white rice with the yeast Monascus purpureus) contains monacolins, which is chemically identical to lovastatin. Although RYR supplementation is effective in reducing LDL-cholesterol, long-term safety and possible adverse effects are not determined. Most supplements also contain other ingredients, with unknown effects and interactions[131,76]. The formulation and dosage of RYR is also variable[132] rising concerns regarding their medical prescription.

4.6.5 Minerals

The relation between salt intake and CVD is debated. A U-shape association has been recently observed in a pooled analysis, which included 133,118 individuals (63,559 with hypertension and 69,559 without hypertension), from 49 countries with estimated 24-h urinary sodium excretion, from a single morning fasting urine sample[133]. This finding should be confirmed by a more rigorous methodology (eg by 24-hours urine samples complete, preferably in several days).

4.6.6 Alcoholic beverages

The relation between alcohol consumption and CVD is still controversial, even though the evidence base for overall harm is increasing.

There have been multiple systematic reviews and meta-analyses of the association between consumption and aggregated CVD: most have shown that, compared with non-drinking, moderate levels of alcohol intake are associated with a lower risk of morbidity and mortality from CVD, as well as more favourable CV health profiles in general[134]. A large-scale study of 1.93 million adults without CVD at baseline showed that in the group of non-drinkers there is an increased risk of CAD, CVD, and all-cause mortality [135].

There is, however, a growing skepticism around this observation, with recent commentary pieces pointing out several methodological shortcomings in the evidence on which the U shape is based [136]. In a large analysis involving 599,912 current drinkers without previous CVD from 19 high-income countries, the threshold for lowest risk of all-cause mortality was about 100 g per week. For CVD subtypes, alcohol consumption was roughly linearly associated with a higher risk of stroke, CAD excluding MI, HF, fatal hypertensive disease and fatal aortic aneurysm. By contrast, increased alcohol consumption was log linearly associated with a lower risk of MI [137]. These data support adoption of lower limits of alcohol consumption than are recommended in most current guidelines, for example to a maximum of 1 glass/portion per day for both men and women.

4.7 Lipid control

4.7.1 Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition

The FOURIER trial tested the effect of evolocumab on 27,564 patients with atherosclerotic CVD and LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on a background of statin therapy [138]. Following treatment with evolocumab, at 48 weeks LDL-C was reduced by 59% compared with placebo. After a median follow-up of 2.2 years, evolocumab reduced the risk of the primary end point (a composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% (p<0.001) and secondary end point (a composite of CV death, MI, or stroke) by 20% (p<0.001)[138]. The effectiveness of evolocumab was independent of the baseline LDL-C levels [139].

The ODYSSEY OUTCOMES study assessed the effect of alirocumab in 18,924 patients with a recent ACS, having LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) and receiving statin therapy at a high-intensity dose or at the maximum tolerated dose[140]. At 48 weeks, alirocumab reduced LDL-C levels by 54.7%; after a median follow-up of 2.8 years, the risk of a composite primary end-point event (death from CAD, nonfatal MI, fatal or nonfatal, ischemic stroke, or unstable

angina requiring hospitalization) was reduced by 15% (p<0.001), with a greater absolute benefit among patients with higher baseline LDL-C levels[140].
In both studies no increase in new-onset DM nor worsening of glycaemic parameters were observed, nor was there evidence of an adverse effect on cognitive function or risk of cancer. The results of these two trials support a clinical benefit from LDL-C lowering beyond that obtained with statin therapy in high and very high risk patients and lower LDL-C targets adopted by the 2019 ESC guidelines [64]. However data on long term safety and total survival are still awaited.
Cost-effectiveness can be a critical issue in the context of prescription of PCSK9-inhibitors[141] and a selective adoption to very high-risk CVD patients to reduce the overall budgetary impact of PCSK9i treatment has been advised [142],[143].

4.7.2 Omega-3 Fatty Acids

Patients with elevated triglyceride (TG) levels are at increased risk for ischaemic events; the REDUCE-IT trial evaluated the effect of icosapent ethyl (a highly purified eicosapentaenoic acid ethyl ester, 4 g daily) in 8,179 patients with established CVD, under statin therapy and with high fasting TG levels (135-499 mg/dL) [144]. After a mean follow-up of 4.9 years, the risk of primary endpoint (a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) was reduced by 25% and secondary endpoint (a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke) by 26%[144].
These results should be contrasted against the background of other recent findings. A meta-analysis of 10 randomized trials involving 78,000 patients did not show that the groups that received n–3 fatty acids had a lower risk of major adverse CV events than those receiving placebo [145], although most trials were not confined to subjects with raised triglyceride levels, nor did ASCEND (A Study of Cardiovascular Events in Diabetes), which tested 1-g capsules containing 840 mg of marine n–3 fatty acids daily in patients with type 2 DM[146]. In addition, the results of the Vitamin D and Omega-3 Trial (VITAL), a primary-prevention trial involving more than 25,000 participants, did not show a lower incidence of the primary CV composite outcome of MI, stroke, or CV death in either arm [147].
More data are needed to clarify the benefit of this class of drugs. also in higher dosage in CV event reduction.

4.8 Diabetes Mellitus

Multiple positive trials demonstrating superiority of novel class of DM agents for either CV or renal outcomes have emerged. In some cases, total or CV mortality was reduced, and positive results were also seen for the prevention of HF. Such positive trials come either from the Sodium-glucose co-transporter-2 (SGLT2) inhibitor class (empagliflozin, dapagliflozin or canagliflozin), as recently summarized in a meta-analysis [148], or the glucagon-like peptide 1 (GLP-1) receptor agonist class of drugs (liraglutide, semaglutide, albiglutide, dulglutide) likewise recently summarised for drugs [149]. The outcome benefits for most of the drugs in each class outweigh potential harms and side effects and both classes cause weight loss and reductions in BP without increasing hypoglycaemia rates. Consequently, the use of such agents in those with existing CVD has been promoted in many

guidelines, although uptake has been modest[150]. Notably, the prevention of HF or prevention of meaningful renal outcomes seems to occur to broadly similar extents with SGLT2 inhibitors whether patients have existing CVD or multiple risk factors [148]. Thus, those without existing CVD but at elevated risk of HF or renal progression would stand to benefit from earlier SGLT2 inhibitor use. Such guidance fits with an increasing focus on prevention of HF in DM. The outcome benefits of both classes seem to be largely independent of their effects on glucose levels per se. This is in keeping with the recent findings from the DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) trail: among patients with HF and a reduced ejection fraction, the risk of worsening HF or death from CV causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes [151].

4.9 Hypertension

The SPRINT trial introduced the "unobserved" BP measurement, a method that it is recommended in the Canadian Guidelines [152], but that it is difficult to apply in many healthcare facilities and produces BP levels that are lower than office measures on which many epidemiological studies and previous intervention trials have been based. Furthermore, some SPRINT participants had medication reduced to allow them to participate, which complicates interpretation. Out-of office BP measurement is upgraded as the best method to diagnose and control hypertension. Wider use of out-of-office BP measurement with ambulatory monitoring (ABPM) and/or Home BP measurement (HBPM) are considered an option to confirm the diagnosis of hypertension, detect white coat and masked hypertension, and monitor BP control is today recommended[58].

The second recommendation includes a change in the strategy to improve BP control. Two drug combination therapy for the initial treatment of most people with hypertension, preferred in single pill, is today recommended. Simplified drug-treatment algorithms are recommended with the preferred use of an angiotensin-converting enzyme inhibitor (ACE) inhibitor or angiotensin receptor blocker (ARB) combined with a calcium channel blocker or/and a thiazide/thiazide-like diuretic as the core treatment strategy for most patients, with beta-blockers used for specific indications. Monotherapy is recommended for subjects with stage 1 hypertension with low risk (particularly if SBP <150 mmHg) or in very old (>80 years) or frailer subjects [58].

The third recommendation corresponds to when to treat and goals to be achieved. Overall there is a less conservative treatment of BP and the newly introduced target *BP ranges* for treated patients, to better identify the recommended BP target and lower safety boundaries for treated BP, according to a patient's age and specific comorbidities. Lower BP thresholds and treatment targets for older patients are recommended with emphasis on considerations of biological rather than chronological age (i.e. the importance of frailty, independence, and the tolerability of treatment). In this regard, treatment should never be denied or withdrawn on the basis of age, provided that treatment is tolerated[58].

Guidelines also recommended drug treatment: a) to subjects with white-coat hypertension if evidence of hypertension multi organ damage or in whom CV risk is high or very high is present; b) to subjects in high-normal BP when their CV risk is very high due to established CVD, mainly coronary heart disease[58].

Finally, strong emphasis on the importance of evaluating treatment adherence as a major cause of poor BP control is today a key issue, as well as the key role for dieticians, nurses and pharmacists in the longer-term management of hypertension. Their role in the education, support, and follow-up of treated hypertensive patients is relevant as part of the overall strategy to improve BP control[58].

Unfortunately, not all the gaps pointed out in the ESC CVD prevention guidelines are solved today. What still unanswered is the optimal out-of-office (home and ambulatory) BP targets, and does treatment strategies based on control of out-of-office BP provide an advantage over strategies based on conventional (office) BP control?

4.10 Antiplatelet therapy

New evidence supports the current recommendation against aspirin use in primary prevention[1]. Recent meta-analyses including respectively 11 and 15 trials with >155,000 individuals each without history of atherosclerotic disease demonstrated that aspirin did not affect all-cause mortality or CV death or no CV death in the primary prevention setting[153]. This was further confirmed by sequential analysis, which also suggested the futility of conducting further trials to assess a benefit of aspirin on all-cause mortality[154].

The lack of benefit was evident even in people with DM and patients with high CV risk (i.e. 10-year risk >7.5%). The use of aspirin for primary prevention in patients with DM increases the risk of total bleeding without reducing the risk of major adverse CV outcomes [155].

4.11 Psychosocial factor

The current Guideline [1] recommends treatment of psychosocial risk factors via multimodal behavioral interventions, psychotherapy, medication or collaborative care, in order to counteract psychosocial stress, depression and anxiety, to facilitate behaviour change and to improve quality of life and prognosis in patients with established CVD and patients at high CVD risk, when the psychosocial risk factor worsens classical risk factors.

A recent meta-analysis on psychological interventions in addition to exercise-based CR compared to exercise-based CR alone in patients with CAD[156] has shown a trend for a reduction of depressive symptoms and cardiac morbidity, but no additional impact on anxiety, quality of life and CV or total mortality [156]. Hence, considering the low to moderate quality and high methodological heterogeneity of available studies, there is considerable uncertainty under which conditions psychological interventions in addition to exercise-based CR exert their optimal effects [156].

Another meta-analysis showed the efficacy of cognitive psychotherapy for reducing psychological symptoms in patients with CVD and significant symptoms of depression and anxiety [157], but there was no effect on CV events [157]. But, a recent trial, for the first time, has shown a favorable effect of antidepressant medication on long-term cardiac outcomes [158]. In patients with ACS and minor/major depression, the effectiveness of therapy with a Selective Serotonin Reuptake Inhibitors (SSRI, escitalopram) on depression and anxiety resulted in a significant reduction of major adverse cardiac events (MACE) after 8.1 years (HR 0.68, 95%

CI, 0.49-0.96; p=0.03)[158]. Thus, treatment with SSRIs may improve subjective wellbeing and prognosis in depressed patients with CAD, but confirmation by additional trials is needed.

5 DISEASE SPECIFIC INTERVENTION

5.1 Atrial fibrillation

The focused update on CV prevention in patients with AF is mainly based on the topic of anticoagulation, because of the approval of new medications and the emerge of new strategies after ACS.

Based on the four major randomized clinical trials comparing non–vitamin K oral anticoagulants (NOACs) with warfarin (vitamin K antagonist, VKA)[159,160,161,162], there is now consistent evidence of at least noninferiority for the combined endpoint of stroke or systemic embolism. When combined with a superior safety profile, NOAC are now recommended as first line therapy for eligible patients.

In patients with AF and ACS managed by percutaneous coronary intervention (PCI), recommended strategies need to incorporate recent evidence from PIONEER AF-PCI (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) [163] and RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) [164], considering rivaroxaban and dabigatran options for anticoagulants in this patient population. PIONEER AF-PCI randomized patients to low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months; very-low-dose rivaroxaban (2.5 mg twice daily) plus dual anti-platelet therapy (DAPT) for 1, 6, or 12 months; or standard therapy with a dose-adjusted VKA (once daily) plus DAPT for 1, 6, or 12 months. The rates of thromboembolic events (death from CV causes, ACS, or stroke) were similar in the three groups, while significant bleeding was lower in the two rivaroxaban groups. RE-DUAL PCI randomized patients to receive double therapy with dabigatran (110 mg twice daily) plus either clopidogrel or ticagrelor, double therapy with dabigatran (150 mg twice daily) plus either clopidogrel or ticagrelor, or triple therapy with warfarin plus aspirin (≤100 mg daily) and either clopidogrel or ticagrelor. With respect to the composite efficacy end point of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization dabigatran-based dual therapy was non-inferior to VKA-based triple therapy. Dual therapy with dabigatran also reduced bleeding complications as compared to conventional triple therapy. Also a non inferiority for bleeding of an edoxaban-based regimen compared with the VKA-based regimen, without significant differences in ischaemic events in patients with AF who had PCI was observed in the ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial [165].

Taken together, these two studies seem to orient clinical practice towards an increasing use of dual therapy (consisting of a NOAC plus clopidogrel, which was the most common P2Y12

inhibitor used), even though current recommendations consider NOAC-based dual therapy in only a subset of patients at increased risk of bleeding [166].

5.2 Coronary Artery Disease

In CAD patients, secondary prevention should start as soon as possible, and physicians in general practice are the key person to initiate and coordinate intervention and provide long-term follow-up. A systematic approach is recommended to risk assessment. Specialized prevention programmes should be delivered as cardiac rehabilitation[167] or other structured, physician-led prevention programmes for all patients with CVD or at high risk for CVD. The structure, length and type of programme offered differs widely by country, affected by national guidelines and standards, legislation and payment factors.
Despite significant improvements in the management of patients presenting with ACS, secondary prevention remains challenging [168]. The implementation of pharmacological and non-pharmacological interventions is [169].: Proper utilization of and adherence to evidence-based treatment strategies and interventions has to be the priority after ACS in order to improve long-term outcomes. It is essential to identify health system-related difficulties and weaknesses in the management and support of secondary prevention post-ACS discharge [170].

5.3 Heart Failure

5 3 1 Biomarkers

Plasma biomarkers are useful tools in the diagnosis and prognosis of HF. Whereas cardiac-specific biomarkers, including natriuretic peptides (ANP and BNP) and high sensitivity troponins (hsTn), are widely used in clinical practice, other biomarkers have not yet proven their utility [171]. Thus, some plasma biomarkers have the potential to provide information about specific processes (e.g. cardiac strain, interstitial/replacement fibrosis, endothelial dysfunction, and pathological hypertrophic processes) that drive cardiac dysfunction in the individual HF patient [172] and they could be used to improve and guide medical therapy [173].

5 3 2 Exercise training

New meta-analysis[174] and the Cochrane meta-analysis[175] involved 44 studies that included 5783 people with HFrEF, had findings consistent with those of the previous (2014) version of Cochrane Review: significant reductions of overall hospital admissions, as well as of HF admissions. These findings have been recently confirmed by the CROS-HF meta-analysis and review [176].
Further evidence is needed to better show the effects of exercise rehabilitation among traditionally less represented HF patient groups including older, female, people with HFpEF (currently under investigation) as well as the impact of and alternative delivery settings including home- and using technology-based programmes.

5 3 3 Telemonitoring

Recent Cochrane review identified 25 relevant trials and found that telemonitoring reduced all-cause mortality by about 20% and HF hospitalisation by about 30% [177] The beneficial

effects have been confirmed by the TIM-HF2 trial which demonstrated that remote telemonitoring including home assessment of weight, BP, ECG and general health status in the context of a 24/7 support system, reduced the proportion of days lost due to unplanned CV (mainly HF) hospitalizations or death (p=0.046) [178].

5.4 Cerebrovascular disease

Despite advances in earlier diagnosis, reperfusive strategies, and aggressive management of risk factors, stroke remains a leading cause of death and long-term disability worldwide. Recently, the POINT study[179] compared short-term (three months) DAPT based on aspirin and clopidogrel with a single antiplatelet regimen in patients with minor stroke and high-risk Transient Ischemic Attack, showing a reduction in recurrent stroke in the DAPT group at 90 days and a higher risk of major bleeding than aspirin alone: HR for ischemic events (mostly occurring in the first week after the index event) was 0.75 [95% CI 0.59 to 0.95], while 90 days prevalence of major haemorrhage was 0.9% in the DAPT group versus 0.4% in the aspirin alone group [HR 2.32; 95% CI 1.10 to 4.87]. In this population generally considered as having lower risk (as compared to patients with AF in whom anticoagulation is mandatory, or patients with severe extracranial carotid disease who might benefit from endarterectomy or stenting), novel evidence confirmed the difficulty to obtain clear net benefit by adopting combination antiplatelet therapy.
Recent acquisitions are also targeted on risk reduction of future stroke and dementia in subjects with silent cerebrovascular disease (SCD), a common incidental finding on cerebral brain imaging defined as the presence of silent brain infarcts, magnetic resonance imaging white matter hyperintensities of presumed vascular origin and cerebral microbleeds. In clinical practice, magnetic resonance imaging is preferred to computed tomography (for the diagnosis of SCD, as it allows to detect chronic microbleeds. As in the case of primary and secondary prevention of stroke, patients with SCD also need intensive evaluation and modification of vascular risk factors, including hypertension, DM, dyslipidemia, cigarette smoking, and physical inactivity [180].

5.5 Peripheral artery disease

Patients with peripheral arterial disease (PAD) have heightened risk of CV morbidity and mortality, being unfortunately often under-recognized and under-treated.
Exercise training combined with revascularization procedures, is the cornerstone in the treatment, and prevention of progression in PAD [181,182].

Antithrombotic therapy based on combination therapies may play important role in prevention of death, ischaemic CV and limb events in patients with lower extremities PAD. In the COMPASS trial[183], low dose (2.5 mg twice a day) of NOAC rivaroxaban plus aspirin (100 mg once a day) – as compared to aspirin alone - showed to reduce the composite endpoint of CV death, MI, or stroke (HR 0.72, 95% CI 0.57-0.90, p=0.0047), and major adverse limb events including major amputation (HR 0.54, 95% CI 0.35-0.82, p=0.0037) among patients with previous peripheral bypass surgery or angioplasty, limb or foot amputation,

intermittent claudication, carotid or CAD with an ABI of less than 0.90. However rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (HR 1.61, 95% CI 1.12-2.31, p=0.0089), which was mainly gastrointestinal. The cost-effectiveness of low-dose rivaroxaban and aspirin versus aspirin alone in people with peripheral or carotid artery disease has been assessed by in a high-income country only (Australian).[184]

In the PEGASUS-TIMI 54 randomized trial[185] the addition of ticagrelor (90 mg b.i.d. or 60 mg b.i.d.) to aspirin in a subgroup of PAD patients with a history of MI (one to three years earlier) was associated with reduced risk of CV and limb events at the expense of increased major bleeding. The absolute risk reduction was 4.1% (number needed to treat: 25) and the 60-mg dose had particularly favorable outcomes for CV and all-cause mortality. According to novel evidence, the use of combined antithrombotic therapies could be now advocated for secondary prevention in symptomatic PAD, even though their adoption needs to be tailored according to individual thrombotic and bleeding risk.

The pivotal role of exercise training has been highlighted in systemic reviews of randomized controlled trial where the combination of physical intervention and lower limb revascularization lead to increase in pain-free (mean difference range 38-408 m) and in maximal walking distances (range 82-321 m) [181].

Another meta-analysis confirmed the higher efficacy of the combination of exercise training and revascularisaion in improving total walking distance, ABI, and reducing the risk of future revascularization or amputation [182].

6. SETTINGS AND AUDIT

6.1 Clinical settings

The role of primary care and community services in CV prevention remains essential, both in identification of high-risk individuals and in providing interventions. Population screening via Health Checks in England has shown that the proportion of individuals attending was higher among older people, those with CVD family history and those in economically deprived areas. Data on impact are limited but have shown a small increase in disease detection, statin and anti-hypertensive prescriptions and a small decrease in modelled CVD risk[186]. A systematic review of 31 studies using multiple health behaviour changes in primary care to reduce CV risk in people without established CVD found a modest, statistically significant effect on individual behaviours and overall CV risk [187].

A meta-analysis of prospective controlled cohort studies (pCCS) and retrospective controlled cohort studies (rCCS) published since 1995 confirmed the efficacy of cardiac rehabilitation (CR) on cardiac prognosis even in the era of statin therapy and acute revascularisations[188]. CR after ACS event and coronary artery bypass graft (CABG) intervention was significantly associated with reduced mortality (HR pCCSs 0.37, 95% CI 0.20-0.69; rCCSs 0.64, 95% CI 0.49-0.840.37 – 0.64), but the heterogeneity of study designs and CR programmes highlight the need for defining internationally accepted standards in CR, including lifestyle changes [188].

6.2 E-Health

Engaging CV prevention more widely with at–risk individuals and patients could be enhanced through eHealth interventions. To improve CR uptake and delivery, e-health (telemedicine) technology has been shown to be cost-effective in Belgium [189]. In a systematic review of 30 trials, telehealth as an adjunct or an alternative to rehabilitation or usual care achieved improved outcomes in recurrent cardiac events, total cholesterol, LDL and smoking. [190]

The use of mobile apps continues to grow. A review of 10 studies (n = 607 patients) found that patients found some features appealing: behavioural tracking, self-monitoring, education, managing provider communication, and flexible, customisable options. The studies found variable results in effectiveness in risk factor control and self-management[105]. A major challenge for eHealth interventions is their variability, and need to determine the features, components, frequency and duration of contact that are most effective for changing behavior and decreasing CVD risk.

6.3 How to monitor preventive activities: Standard of performance

The latest 2016 Guidelines[1] recommends to monitor the process of CVD prevention activities delivery and outcomes to improve implementation quality of care in clinical practice. The development of standards of performance involves the identification of a set of measures, targeting a specific patient population observed over a particular time period. These measures should be specifically suitable for public and external reporting, providing an indication of quality. The EAPC of the ESC is undergoing to a Quality of care program aiming to develop and implement an accreditation of clinical centres providing primary prevention, secondary prevention and rehabilitation, and sports cardiology, to be applied in ESC related countries [191].

The ACC/AHA reviewed updated the Clinical Performance and Quality measures for Cardiac Rehabilitation (CR)[192], considering the following CR Performance Measures (PM):

1 CR Patient Referral (Inpatient Setting): Percentage of patients, hospitalized with qualifying event/diagnosis for CR in previous 12 months referred to outpatient CR program.

2 Exercise Training Referral for HF (Inpatient Setting) Percentage of patients, hospitalized with primary diagnosis of HF with reduced ejection fraction (HFrEF) in previous 12 months, referred for exercise training, typically delivered in the setting of outpatient CR program

3 CR Patient Referral (Outpatient Setting) Percentage of patients, in outpatient setting, who in the previous 12 months had a qualifying event/diagnosis for CR and did not participate in CR program, but are to be referred to a program

4 Exercise Training Referral for HF (Outpatient Setting) Percentage of patients, in outpatient setting who in the previous 12 months, had a new HF*r*EF event or exacerbation, and have not participated in an exercise training program, but are to be referred for exercise training.

5a CR Enrolment–Claims Based (Outpatient Provider) Percentage of patients, with qualifying event/diagnosis for CR who attend at least 1 session in a CR program

5b CR Enrolment–Registry/Electronic Health Records Based (Inpatient Provider) Percentage of patients with qualifying event/diagnosis for CR who attend at least 1 session in a CR program.

Every CV Prevention or CR program should formally be submitted to regular audits, which should include the collection of data to meet the purpose of monitoring prevention and rehabilitation service resources[193].

7 GAPS IN KNOWLEDGE

Unfortunately, not all the gaps pointed out in the ESC CVD prevention guidelines are solved today.

- The need for a revaluation and recalibration of the current risk scores
- Evidence, cost-effectiveness and potential harm of larger-scale use of CAC scoring for refinement of risk stratification
- The role of cardiac biomarkers (i.e. natriuretic peptide and cardiac troponin blood concentration) in risk stratification
- There is still no evidence of cost-effectiveness of application of CV genetic risk score testing in clinical practice, such as targeting statin therapy in individuals at low-to-moderate CV risk
- The use of CT coronary angiography as a risk stratification tool in asymptomatic individuals is not supported by data
- Refinement of the screening items with established psychometric questionnaires is required.
- Strong evidences of the effectiveness of influenza vaccination in primary prevention of CVD are still lacking.
- Whether periodontal therapy can prevent the recurrence of CVD in the long term in patients with chronic periodontitis. No evidence on primary prevention was found.
- The magnitude of the problem of CVD in young adults and to elucidate treatable risk factors that underlie the observed increasing rates of CVDs in this population
- The decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly on randomised clinical trials evidence
- Thus limited evidence is available on therapy for primary prevention of CVDs in very elderly and frail individuals.

- E-cigarettes may be more effective in promoting nicotine dependence than as an aid to smoking cessation.
- Evidences on the benefit in terms of increased longevity and delayed onset of age-associated disorders of caloric restriction without malnutrition in humans
- The relation between alcohol consumption and CVD is still controversial, even though the evidence base for overall harm is increasing.
- The U-shape association between salt intake and CVD is debated.
- The clinical benefit from LDL-C lowering beyond that obtained with statin therapy in high and very high risk patients has been put forward, although data on long term safety and total survival are still awaited.
- To clarify the benefit of Omega-3 Fatty Acids also in higher dosage in CV event reduction.
- The optimal out-of-office (home and ambulatory) BP targets, and whether treatment strategies based on control of out-of-office BP provide an advantage over strategies based on conventional (office) BP control
- Cost-effectiveness of low-dose rivaroxaban and aspirin versus aspirin alone in people with peripheral or carotid artery disease has been assessed by in a high-income country only
- Which conditions psychological interventions in addition to exercise-based CR exert their optimal effects
- Treatment with SSRIs may improve subjective wellbeing and prognosis in depressed patients with CAD, but confirmation by additional trials is needed
- The heterogeneity of study designs and CR programmes highlights the need for defining internationally accepted standards in CR, including lifestyle changes
- Further evidence is needed to better show the effects of exercise rehabilitation among traditionally less represented HF patient groups including older, female, people with HFpEF (currently under investigation) as well as the impact of and alternative delivery settings including home- and using technology-based programmes.
- A major challenge for eHealth interventions is their variability, and there need to determine the features, components, frequency and duration of contact that are most effective for changing behavior and decreasing CVD risk.

Abbreviations

ABI	ankle–brachial (blood pressure) index
ABPM	ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE-I	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndromes
AF	atrial fibrillation
AHA	American Heart Association
AHI	apnea–hypopnea index
AMI	acute myocardial infarction
apoA1	apolipoprotein A1
apoB	apolipoprotein B
ARB	angiotensin receptor blocker
BEUC	Bureau Européen des Unions de Consummateurs
BMI	body mass index (weight (kg)/height (m2))
BNP	B-type natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
CI	confidence interval
CKD	chronic kidney disease
CPAP	continuous positive airway pressure
CR	cardiac rehabilitation
CSA	Central sleep apnea
CSR	Cheyne-Stokes Respiration
CT	computed tomography

CV	cardiovascular
CVD	cardiovascular disease
DALYs	disability-adjusted life years
DAPT	dual anti-platelet therapy
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DHA	docosahexaenoic acid
DM	diabetes mellitus
e-cig	E-cigarettes
ED	erectile dysfunction
EHN	European Heart Network
ESC	European Society of Cardiology
EU	European Union
GLP-1	glucagon-like peptide 1
HBPM	home blood pressure measurements
HF	heart failure
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IHD	ischaemic heart disease
JTF	Joint Task Force
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MACE	major adverse cardiac events
MI	myocardial infarction
NOAC	non–vitamin K oral anticoagulants
OSA	obstructive sleep apnoea

OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
RA	rheumatoid arthritis
SCD	silent cerebrovascular disease
SGLT2	Sodium-glucose co-transporter-2
SSRI	Selective Serotonin Reuptake Inhibitors
TG	triglycerides
VKA	vitamin K antagonist
WHO	World Health Organisation

REFERENCES

1. 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(29):2315-2381. doi:10.1093/eurheartj/ehw106

2. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J*. 2018;39(7):508-579. doi:10.1093/eurheartj/ehx628

3. Crossan C, Lord J, Ryan R, Nherera L, Marshall T. Cost effectiveness of case-finding strategies for primary prevention of cardiovascular disease: a modelling study. *Br J Gen Pract J R Coll Gen Pract*. 2017;67(654):e67-e77. doi:10.3399/bjgp16X687973

4. Groot-Jensen S, Kiessling A, Zethraeus N, Björnstedt-Bennermo M, Henriksson P. Cost-effectiveness of case-based training for primary care physicians in evidence-based medicine of patients with coronary heart disease. *Eur J Prev Cardiol*. 2016;23(4):420-427. doi:10.1177/2047487315583798

5. Basu Sanjay, Bendavid Eran, Sood Neeraj. Health and Economic Implications of National Treatment Coverage for Cardiovascular Disease in India. *Circ Cardiovasc Qual Outcomes*. 2015;8(6):541-551. doi:10.1161/CIRCOUTCOMES.115.001994

6. Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2018;320(3):281-297. doi:10.1001/jama.2018.4242

7. Arnett Donna K., Blumenthal Roger S., Albert Michelle A., et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation*. 0(0):CIR.0000000000000678. doi:10.1161/CIR.0000000000000678

8. Tzoulaki I, Siontis KC, Evangelou E, Ioannidis JPA. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med*. 2013;173(8):664-671. doi:10.1001/jamainternmed.2013.3018

9. Natriuretic Peptides Studies Collaboration null, Willeit P, Kaptoge S, et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *Lancet Diabetes Endocrinol*. 2016;4(10):840-849. doi:10.1016/S2213-8587(16)30196-6

10. Willeit P, Welsh P, Evans JDW, et al. High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. *J Am Coll Cardiol*. 2017;70(5):558-568. doi:10.1016/j.jacc.2017.05.062

11. Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J*. 2019;40(7):621-631. doi:10.1093/eurheartj/ehy653

12. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart Br Card Soc*. 2014;100 Suppl 2:ii1-ii67. doi:10.1136/heartjnl-2014-305693

13. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. *Heart Br Card Soc*. 2013;99(12):866-872. doi:10.1136/heartjnl-2013-303640

14. Lindholm D, Lindbäck J, Armstrong PW, et al. Biomarker-Based Risk Model to Predict Cardiovascular Mortality in Patients With Stable Coronary Disease. *J Am Coll Cardiol*. 2017;70(7):813-826. doi:10.1016/j.jacc.2017.06.030

15. Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J*. May 2019. doi:10.1093/eurheartj/ehz239

16. Berkelmans GFN, Gudbjörnsdottir S, Visseren FLJ, et al. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. *Eur Heart J*. January 2019. doi:10.1093/eurheartj/ehy839

17. Infante T, Forte E, Schiano C, et al. Evidence of association of circulating epigenetic-sensitive biomarkers with suspected coronary heart disease evaluated by Cardiac Computed Tomography. *PLOS ONE*. 2019;14(1):e0210909. doi:10.1371/journal.pone.0210909

18. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history | European Heart Journal | Oxford Academic. https://academic.oup.com/eurheartj/article/37/6/561/2466087. Accessed October 17, 2019.

19. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prev... - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/28223407. Accessed October 17, 2019.

20. Cardiovascular Genetic Risk Testing for Targeting Statin Therapy in the Primary Prevention of Atherosclerotic Cardiovascular Disease | Circulation: Cardiovascular Quality and Outcomes. https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.117.004171. Accessed October 17, 2019.

21. Pogosova N, Kotseva K, De Bacquer D, et al. Psychosocial risk factors in relation to other cardiovascular risk factors in coronary heart disease: Results from the EUROASPIRE IV survey. A registry from the European Society of Cardiology. *Eur J Prev Cardiol*. 2017;24(13):1371-1380. doi:10.1177/2047487317711334

22. Vaccarino V, Badimon L, Bremner JD, et al. Depression and coronary heart disease: 2018 ESC position paper of the working group of coronary pathophysiology and microcirculation developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J*. January 2019. doi:10.1093/eurheartj/ehy913

23. van Montfort E, Denollet J, Widdershoven J, Kupper N. Validity of the European Society of Cardiology's Psychosocial Screening Interview in Patients With Coronary Artery Disease-The THORESCI Study. *Psychosom Med*. 2017;79(4):404-415. doi:10.1097/PSY.0000000000000433

24. Suglia Shakira F., Koenen Karestan C., Boynton-Jarrett Renée, et al. Childhood and Adolescent Adversity and Cardiometabolic Outcomes: A Scientific Statement From the American Heart Association. *Circulation*. 2018;137(5):e15-e28. doi:10.1161/CIR.0000000000000536

25. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi:10.1136/bmj.j2099

26. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. *N Engl J Med*. 2018;379(10):924-933. doi:10.1056/NEJMoa1805971

27. Strelitz J, Ahern AL, Long GH, et al. Moderate weight change following diabetes diagnosis and 10 year incidence of cardiovascular disease and mortality. *Diabetologia*. 2019;62(8):1391-1402. doi:10.1007/s00125-019-4886-1

28. Webb D, Dales J, Zaccardi F, et al. Intensive versus standard multifactorial cardiovascular risk factor control in screen-detected type 2 diabetes: 5-year and longer-term modelled outcomes of the ADDITION-Leicester study. *Diabetes Metab Res Rev*. 2019;35(3):e3111. doi:10.1002/dmrr.3111

29. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet Lond Engl*. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1

30. Sattar N, Rawshani A, Franzén S, et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. *Circulation*. 2019;139(19):2228-2237. doi:10.1161/CIRCULATIONAHA.118.037885

31. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet Lond Engl*. 2018;392(10146):477-486. doi:10.1016/S0140-6736(18)31506-X

32. McAllister DA, Read SH, Kerssens J, et al. Incidence of Hospitalization for Heart Failure and Case-Fatality Among 3.25 Million People With and Without Diabetes Mellitus. *Circulation*. 2018;138(24):2774-2786. doi:10.1161/CIRCULATIONAHA.118.034986

33. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart Br Card Soc*. 2015;101(21):1738-1747. doi:10.1136/heartjnl-2015-307691

34. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal Influenza Infections and Cardiovascular Disease Mortality. *JAMA Cardiol*. 2016;1(3):274-281. doi:10.1001/jamacardio.2016.0433

35. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med*. 2018;378(4):345-353. doi:10.1056/NEJMoa1702090

36. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2015;(5):CD005050. doi:10.1002/14651858.CD005050.pub3

37. Berlin-Broner Y, Febbraio M, Levin L. Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature. *Int Endod J*. 2017;50(9):847-859. doi:10.1111/iej.12710

38. Beukers NGFM, van der Heijden GJMG, van Wijk AJ, Loos BG. Periodontitis is an independent risk indicator for atherosclerotic cardiovascular diseases among 60 174 participants in a large dental school in the Netherlands. *J Epidemiol Community Health*. 2017;71(1):37-42. doi:10.1136/jech-2015-206745

39. Hansen GM, Egeberg A, Holmstrup P, Hansen PR. Relation of Periodontitis to Risk of Cardiovascular and All-Cause Mortality (from a Danish Nationwide Cohort Study). *Am J Cardiol*. 2016;118(4):489-493. doi:10.1016/j.amjcard.2016.05.036

40. Xu S, Song M, Xiong Y, Liu X, He Y, Qin Z. The association between periodontal disease and the risk of myocardial infarction: a pooled analysis of observational studies. *BMC Cardiovasc Disord*. 2017;17. doi:10.1186/s12872-017-0480-y

41. Li C, Lv Z, Shi Z, et al. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. *Cochrane Database Syst Rev*. 2014;(8):CD009197. doi:10.1002/14651858.CD009197.pub2

42. Mustian KM, Alfano CM, Heckler C, et al. Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. *JAMA Oncol*. 2017;3(7):961-968. doi:10.1001/jamaoncol.2016.6914

43. Cormie P, Zopf EM, Zhang X, Schmitz KH. The Impact of Exercise on Cancer Mortality, Recurrence, and Treatment-Related Adverse Effects. *Epidemiol Rev*. 2017;39(1):71-92. doi:10.1093/epirev/mxx007

44. Howden EJ, Bigaran A, Beaudry R, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. *Eur J Prev Cardiol*. 2019;26(3):305-315. doi:10.1177/2047487318811181

45. Cardinale D, Biasillo G, Salvatici M, Sandri MT, Cipolla CM. Using biomarkers to predict and to prevent cardiotoxicity of cancer therapy. *Expert Rev Mol Diagn*. 2017;17(3):245-256. doi:10.1080/14737159.2017.1283219

46. Baena-Díez JM, Garcia-Gil M, Comas-Cufí M, et al. Association between chronic immune-mediated inflammatory diseases and cardiovascular risk. *Heart Br Card Soc*. 2018;104(2):119-126. doi:10.1136/heartjnl-2017-311279

47. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of

inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17-28. doi:10.1136/annrheumdis-2016-209775

48. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation*. 2017;136(19):1840-1850. doi:10.1161/CIRCULATIONAHA.117.029400

49. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2017;13(3):479-504. doi:10.5664/jcsm.6506

50. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA*. 2015;314(21):2280-2293. doi:10.1001/jama.2015.16303

51. Raheem OA, Su JJ, Wilson JR, Hsieh T-C. The Association of Erectile Dysfunction and Cardiovascular Disease: A Systematic Critical Review. *Am J Mens Health*. 2017;11(3):552-563. doi:10.1177/1557988316630305

52. Banks E, Joshy G, Abhayaratna WP, et al. Erectile Dysfunction Severity as a Risk Marker for Cardiovascular Disease Hospitalisation and All-Cause Mortality: A Prospective Cohort Study. *PLOS Med*. 2013;10(1):e1001372. doi:10.1371/journal.pmed.1001372

53. Hackett G, Kirby M, Wylie K, et al. British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction in Men—2017. *J Sex Med*. 2018;15(4):430-457. doi:10.1016/j.jsxm.2018.01.023

54. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study | The BMJ. https://www.bmj.com/content/360/bmj.k96. Accessed October 17, 2019.

55. Mahmoud AN, Mentias A, Elgendy AY, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. *BMJ Open*. 2018;8(3):e020498. doi:10.1136/bmjopen-2017-020498

56. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol*. 2018;15(4):230-240. doi:10.1038/nrcardio.2017.154

57. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation*. 2016;133(11):1067-1072. doi:10.1161/CIRCULATIONAHA.115.018791

58. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339

59. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. *N Engl J Med*. 2018;378(16):1509-1520. doi:10.1056/NEJMoa1712231

60. Cardiovascular risk profile in Olympic athletes: an unexpected and underestimated risk scenario. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/30217832. Accessed October 17, 2019.

61. Prevalence and Management of Systemic Hypertension in Athletes - American Journal of Cardiology. https://www.ajconline.org/article/S0002-9149(17)30197-2/fulltext. Accessed October 17, 2019.

62. Vaes B, Depoortere D, Van Pottelbergh G, Matheï C, Neto J, Degryse J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. *BMC Geriatr*. 2017;17(1):234. doi:10.1186/s12877-017-0626-x

63. Anker D, Santos-Eggimann B, Santschi V, et al. Screening and treatment of hypertension in older adults: less is more? *Public Health Rev*. 2018;39:26. doi:10.1186/s40985-018-0101-z

64. Francesco Cosentino, Peter J Grant, Victor Aboyans, Clifford J Bailey, Antonio Ceriello, Victoria Delgado, Massimo Federici, Gerasimos Filippatos, Diederick E Grobbee, Tina Birgitte Hansen. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD).August 31, 2019:00-169.

65. Seidu S, Achana FA, Gray LJ, Davies MJ, Khunti K. Effects of glucose-lowering and multifactorial interventions on cardiovascular and mortality outcomes: a meta-analysis of randomized control trials. *Diabet Med J Br Diabet Assoc*. 2016;33(3):280-289. doi:10.1111/dme.12885

66. Mortensen MB, Falk E. Primary Prevention With Statins in the Elderly. *J Am Coll Cardiol*. 2018;71(1):85-94. doi:10.1016/j.jacc.2017.10.080

67. Armitage J, Baigent C, Barnes E, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *The Lancet*. 2019;393(10170):407-415. doi:10.1016/S0140-6736(18)31942-1

68. T Katrien J Groenhof, Bas B van Rijn, Arie Franx. Preventing cardiovascular disease after hypertensive disorders of pregnancy: Searching for the how and when.16 2017.

69. Judith Stephenson, Nicola Heslehurst, PhD, Jennifer Hall. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health.April 16, 2018.

70. Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. *Heart Br Card Soc*. 2018;104(13):1069-1075. doi:10.1136/heartjnl-2017-312289

71. Hyun KK, Redfern J, Patel A, et al. Gender inequalities in cardiovascular risk factor assessment and management in primary healthcare. *Heart Br Card Soc*. 2017;103(7):492-498. doi:10.1136/heartjnl-2016-310216

72. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485

73. Food in the Anthropocene : the EAT–Lancet Commission on healthy diets from sustainable food systems. https://library.wur.nl/WebQuery/wurpubs/547292. Accessed July 10, 2019.

74. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of ri... - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/27733284. Accessed July 10, 2019.

75. Word Health Organizzation. Mapping the health system response to childhood obesity in the WHO European Region An overview and country perspectives. In: *Investing in Children: The European Child and Adolescent Health Strategy 2015–2020.* ; 2015.

76. Bronzwaer S, Kass G, Robinson T, et al. Food Safety Regulatory Research Needs 2030. *EFSA J.* 2019;17(7):e170622. doi:10.2903/j.efsa.2019.e170622

77. Amandine Garde, Seamus Byrne, Nikhil Gokani and Ben Murphy. A child rights-based approach to food marketing: a giode for policy markers. April 2018.

78. EU science Hubt. The European Commission's science and knowledge service. Health promotion and disease prevention. Sugar and sweetener.January 2019.

79. Objective Understanding of Front-of-Package Nutrition Labels: An International Comparative Experimental Study across 12 Countries. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6213801/. Accessed July 10, 2019.

80. Michel Chauliac. Nutri score. The front of pack nutrition labelling scheme reccomended in France. 2017.

81. Front-of-pack Nutri-Score labelling in France: an evidence-based policy - The Lancet Public Health. https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(18)30009-4/fulltext. Accessed July 10, 2019.

82. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition. 2018.

83. World Health Organization; Geneva 2018. Global action plan on physical activity 2018–2030: more active people for a healthier world. 2018.

84. Washington, DC: U.S. Department of Health and Human Services,. Physical Activity Guidelines Advisory Committee Scientific Report. 2018. https://health.gov/paguidelines/second-edition/report/.

85. Association between physical activity, occupational sitting time and mortality in a general population: An 18-year prospective survey in Tanushimaru, Japan, Akiko Sakaue, Hisashi Adachi, Mika Enomoto. Association between physical activity, occupational sitting time and mortality in a general population: An 18-year prospective survey in Tanushimaru, Japan.2018.

86. The impact of interventions to promote physical activity in urban green space: a systematic review and recommendations for future research. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/25462429. Accessed July 10, 2019.

87. World Health Organization, Geneva, SZ. WHO Report on the Global Tobacco Epidemic, 2015: Raising Taxes on Tobacco. 2015.

88. Exposure to second hand smoke and 10-year (2002–2012) incidence of cardiovascular disease in never smokers: The ATTICA cohort study - International Journal of Cardiology. https://www.internationaljournalofcardiology.com/article/S0167-5273(19)31600-6/abstract. Accessed October 17, 2019.

89. Tobacco control in Europe: a policy review | European Respiratory Society. https://err.ersjournals.com/content/25/140/151. Accessed July 10, 2019.

90. Impact of the WHO Framework Convention on Tobacco Control on global cigarette consumption: quasi-experimental evaluations using interrupted time se... - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/31217191. Accessed July 10, 2019.

91. Global tobacco prevention and control in relation to a cardiovascular health promotion and disease prevention framework: A narrative review. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/27717667. Accessed July 10, 2019.

92. Implementation of key demand-reduction measures of the WHO Framework Convention on Tobacco Control and change in smoking prevalence in 126 countrie... - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/29253448. Accessed July 10, 2019.

93. Austria's Reversal of Smoking Ban in World Spotlight | IASLC Lung Cancer News. http://www.lungcancernews.org/2018/08/28/austrias-reversal-of-smoking-ban-in-world-spotlight/. Accessed July 10, 2019.

94. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2015;12(11):627-642. doi:10.1038/nrcardio.2015.152

95. Cohen G, Levy I, Yuval null, et al. Long-term exposure to traffic-related air pollution and cancer among survivors of myocardial infarction: A 20-year follow-up study. *Eur J Prev Cardiol*. 2017;24(1):92-102. doi:10.1177/2047487316669415

96. Kwon OK, Kim S-H, Kang S-H, et al. Association of short- and long-term exposure to air pollution with atrial fibrillation. *Eur J Prev Cardiol*. 2019;26(11):1208-1216. doi:10.1177/2047487319835984

97. Bhatnagar A. Environmental Determinants of Cardiovascular Disease. *Circ Res*. 2017;121(2):162-180. doi:10.1161/CIRCRESAHA.117.306458

98. Cohen G, Levy I, Yuval null, et al. Chronic exposure to traffic-related air pollution and cancer incidence among 10,000 patients undergoing percutaneous coronary interventions: A historical prospective study. *Eur J Prev Cardiol*. 2018;25(6):659-670. doi:10.1177/2047487318760892

99. Leemrijse CJ, Peters RJ, von Birgelen C, et al. The telephone lifestyle intervention "Hartcoach" has modest impact on coronary risk factors: A randomised multicentre trial. *Eur J Prev Cardiol*. 2016;23(15):1658-1668. doi:10.1177/2047487316639681

100. Teeriniemi A. M., Salonurm T., Jokelainen I. T et al. A randomized clinical trial of the effectiveness of a Web- based health behaviour change support system and group lifestyle counselling on body weight loss in overweight and obese subjects: 2- year outcomes.284: 534–545 2018.

101. Palacios J, Lee GA, Duaso M, et al. Internet-Delivered Self-management Support for Improving Coronary Heart Disease and Self-management-Related Outcomes: A Systematic Review. *J Cardiovasc Nurs*. 2017;32(4):E9-E23. doi:10.1097/JCN.0000000000000392

102. Lafeber M, Spiering W, Visseren FL, et al. Impact of switching from different treatment regimens to a fixed-dose combination pill (polypill) in patients with cardiovascular disease or similarly high risk. *Eur J Prev Cardiol*. 2017;24(9):951-961. doi:10.1177/2047487317695616

103. Palmer MJ, Barnard S, Perel P, Free C. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. *Cochrane Database Syst Rev*. 2018;6:CD012675. doi:10.1002/14651858.CD012675.pub2

104. Adler AJ, Martin N, Mariani J, et al. Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;4:CD011851. doi:10.1002/14651858.CD011851.pub2

105. Coorey GM, Neubeck L, Mulley J, Redfern J. Effectiveness, acceptability and usefulness of mobile applications for cardiovascular disease self-management: Systematic review with meta-synthesis of quantitative and qualitative data. *Eur J Prev Cardiol*. 2018;25(5):505-521. doi:10.1177/2047487317750913

106. Villani GQ, Villani A, Zanni A, et al. Mobile health and implantable cardiac devices: Patients' expectations. *Eur J Prev Cardiol*. 2019;26(9):920-927. doi:10.1177/2047487319830531

107. Kraus WE, Powell KE, Haskell WL, et al. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. *Med Sci Sports Exerc*. 2019;51(6):1270-1281. doi:10.1249/MSS.0000000000001939

108. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*. 2015;175(6):959-967. doi:10.1001/jamainternmed.2015.0533

109. King AC, Whitt-Glover MC, Marquez DX, et al. Physical Activity Promotion: Highlights from the 2018 Physical Activity Guidelines Advisory Committee Systematic Review. *Med Sci Sports Exerc*. 2019;51(6):1340-1353. doi:10.1249/MSS.0000000000001945

110. Gourlan M, Bernard P, Bortolon C, et al. Efficacy of theory-based interventions to promote physical activity. A meta-analysis of randomised controlled trials. *Health Psychol Rev*. 2016;10(1):50-66. doi:10.1080/17437199.2014.981777

111. Campbell WW, Kraus WE, Powell KE, et al. High-Intensity Interval Training for Cardiometabolic Disease Prevention. *Med Sci Sports Exerc*. 2019;51(6):1220-1226. doi:10.1249/MSS.0000000000001934

112. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet Lond Engl*. 2016;388(10051):1302-1310. doi:10.1016/S0140-6736(16)30370-1

113. Best KL, Miller WC, Eng JJ, Routhier F. Systematic Review and Meta-Analysis of Peer-Led Self-Management Programs for Increasing Physical Activity. *Int J Behav Med*. 2016;23(5):527-538. doi:10.1007/s12529-016-9540-4

114. Jakicic JM, Davis KK, Rogers RJ, et al. Effect of Wearable Technology Combined With a Lifestyle Intervention on Long-term Weight Loss: The IDEA Randomized Clinical Trial. *JAMA*. 2016;316(11):1161-1171. doi:10.1001/jama.2016.12858

115. Brannon EE, Cushing CC. A systematic review: is there an app for that? Translational science of pediatric behavior change for physical activity and dietary interventions. *J Pediatr Psychol*. 2015;40(4):373-384. doi:10.1093/jpepsy/jsu108

116. Schoeppe S, Alley S, Van Lippevelde W, et al. Efficacy of interventions that use apps to improve diet, physical activity and sedentary behaviour: a systematic review. *Int J Behav Nutr Phys Act*. 2016;13. doi:10.1186/s12966-016-0454-y

117. Office of the Surgeon General AS for H (ASH). Tobacco Reports And Publications. HHS.gov. https://www.hhs.gov/surgeongeneral/reports-and-publications/tobacco/index.html. Published April 5, 2019. Accessed July 12, 2019.

118. Ramamurthi D, Chau C, Jackler RK. JUUL and other stealth vaporisers: hiding the habit from parents and teachers. *Tob Control*. September 2018:tobaccocontrol-2018-054455. doi:10.1136/tobaccocontrol-2018-054455

119. Willett JG, Bennett M, Hair EC, et al. Recognition, use and perceptions of JUUL among youth and young adults. *Tob Control*. 2019;28(1):115-116. doi:10.1136/tobaccocontrol-2018-054273

120. Trivers KF, Phillips E, Gentzke AS, Tynan MA, Neff LJ. Prevalence of Cannabis Use in Electronic Cigarettes Among US Youth. *JAMA Pediatr*. 2018;172(11):1097-1099. doi:10.1001/jamapediatrics.2018.1920

121. Galaviz KI, Weber MB, Straus A, Haw JS, Narayan KMV, Ali MK. Global Diabetes Prevention Interventions: A Systematic Review and Network Meta-analysis of the Real-World Impact on Incidence, Weight, and Glucose. *Diabetes Care*. 2018;41(7):1526-1534. doi:10.2337/dc17-2222

122. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. *Nat Commun*. 5. doi:10.1038/ncomms4557

123. Mente A, Dehghan M, Rangarajan S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol*. 2017;5(10):774-787. doi:10.1016/S2213-8587(17)30283-8

124. Li Y, Hruby A, Bernstein AM, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A

Prospective Cohort Study. *J Am Coll Cardiol*. 2015;66(14):1538-1548. doi:10.1016/j.jacc.2015.07.055

125. Sacks Frank M., Lichtenstein Alice H., Wu Jason H.Y., et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation*. 2017;136(3):e1-e23. doi:10.1161/CIR.0000000000000510

126. Wang DD, Li Y, Chiuve SE, et al. Association of Specific Dietary Fats With Total and Cause-Specific Mortality. *JAMA Intern Med*. 2016;176(8):1134-1145. doi:10.1001/jamainternmed.2016.2417

127. Chen M, Li Y, Sun Q, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr*. 2016;104(5):1209-1217. doi:10.3945/ajcn.116.134460

128. Miller V, Mente A, Dehghan M, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *The Lancet*. 2017;390(10107):2037-2049. doi:10.1016/S0140-6736(17)32253-5

129. O'Connor LE, Kim JE, Campbell WW. Total red meat intake of ≥0.5 servings/d does not negatively influence cardiovascular disease risk factors: a systemically searched meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2017;105(1):57-69. doi:10.3945/ajcn.116.142521

130. Guasch-Ferré M, Satija A, Blondin SA, et al. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. *Circulation*. 2019;139(15):1828-1845. doi:10.1161/CIRCULATIONAHA.118.035225

131. Peng D, Fong A, Pelt A van. Original Research: The Effects of Red Yeast Rice Supplementation on Cholesterol Levels in Adults. *Am J Nurs*. 2017;117(8):46-54. doi:10.1097/01.NAJ.0000521973.38717.2e

132. Cohen PA, Avula B, Khan IA. Variability in strength of red yeast rice supplements purchased from mainstream retailers. *Eur J Prev Cardiol*. 2017;24(13):1431-1434. doi:10.1177/2047487317715714

133. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *The Lancet*. 2016;388(10043):465-475. doi:10.1016/S0140-6736(16)30467-6

134. Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. *Nat Rev Cardiol*. 2015;12(10):576-587. doi:10.1038/nrcardio.2015.91

135. Bell S, Daskalopoulou M, Rapsomaniki E, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ*. 2017;356:j909. doi:10.1136/bmj.j909

136. Chikritzhs T, Stockwell T, Naimi T, Andreasson S, Dangardt F, Liang W. Has the leaning tower of presumed health benefits from 'moderate' alcohol use finally collapsed? *Addiction*. 2015;110(5):726-727. doi:10.1111/add.12828

137. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *The Lancet*. 2018;391(10129):1513-1523. doi:10.1016/S0140-6736(18)30134-X

138. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664

139. Giugliano RP, Keech A, Murphy SA, et al. Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial. *JAMA Cardiol*. 2017;2(12):1385-1391. doi:10.1001/jamacardio.2017.3944

140. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379(22):2097-2107. doi:10.1056/NEJMoa1801174

141. Kazi DS, Penko J, Coxson PG, et al. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. *JAMA*. 2017;318(8):748-750. doi:10.1001/jama.2017.9924

142. Ko DT, Khan AM, Kotrri G, et al. Eligibility, Clinical Outcomes, and Budget Impact of PCSK9 Inhibitor Adoption: The CANHEART PCSK9 Study. *J Am Heart Assoc*. 2018;7(21):e010007. doi:10.1161/JAHA.118.010007

143. Fonarow GC, van Hout B, Villa G, Arellano J, Lindgren P. Updated Cost-effectiveness Analysis of Evolocumab in Patients With Very High-risk Atherosclerotic Cardiovascular Disease. *JAMA Cardiol*. 2019;4(7):691-695. doi:10.1001/jamacardio.2019.1647

144. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

145. Aung T, Halsey J, Kromhout D, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. *JAMA Cardiol*. 2018;3(3):225-233. doi:10.1001/jamacardio.2017.5205

146. Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus. *N Engl J Med*. 2018;379(16):1540-1550. doi:10.1056/NEJMoa1804989

147. Manson JE, Cook NR, Lee I-M, et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*. 2019;380(1):23-32. doi:10.1056/NEJMoa1811403

148. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*. 2019;393(10166):31-39. doi:10.1016/S0140-6736(18)32590-X

149. Zelniker Thomas A., Wiviott Stephen D., Raz Itamar, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. *Circulation*. 2019;139(17):2022-2031. doi:10.1161/CIRCULATIONAHA.118.038868

150. Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010-2017. *Diabetes Obes Metab*. 2019;21(7):1576-1584. doi:10.1111/dom.13687

151. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;0(0):null. doi:10.1056/NEJMoa1911303

152. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*. 2018;34(5):506-525. doi:10.1016/j.cjca.2018.02.022

153. Abdelaziz HK, Saad M, Pothineni NVK, et al. Aspirin for Primary Prevention of Cardiovascular Events. *J Am Coll Cardiol*. 2019;73(23):2915-2929. doi:10.1016/j.jacc.2019.03.501

154. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J*. 2019;40(7):607-617. doi:10.1093/eurheartj/ehy813

155. Khan SU, Ul Abideen Asad Z, Khan MU, et al. Aspirin for primary prevention of cardiovascular outcomes in diabetes mellitus: An updated systematic review and meta-analysis. *Eur J Prev Cardiol*. January 2019:2047487319825510. doi:10.1177/2047487319825510

156. Albus C, Herrmann-Lingen C, Jensen K, et al. Additional effects of psychological interventions on subjective and objective outcomes compared with exercise-based cardiac rehabilitation alone in patients with cardiovascular disease: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2019;26(10):1035-1049. doi:10.1177/2047487319832393

157. Reavell J, Hopkinson M, Clarkesmith D, Lane D. Effectiveness of Cognitive Behavioral Therapy for Depression and Anxiety in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Psychosom Med*. 2018;80(8):742-753. doi:10.1097/PSY.0000000000000626

158. Kim J-M, Stewart R, Lee Y-S, et al. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. *JAMA*. 2018;320(4):350-357. doi:10.1001/jama.2018.9422

159. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561

160. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638

161. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

162. Edoxaban versus Warfarin in Patients with Atrial Fibrillation | NEJM. https://www.nejm.org/doi/10.1056/NEJMoa1310907?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov. Accessed July 17, 2019.

163. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016;375(25):2423-2434. doi:10.1056/NEJMoa1611594

164. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377(16):1513-1524. doi:10.1056/NEJMoa1708454

165. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *The Lancet*. 2019;394(10206):1335-1343. doi:10.1016/S0140-6736(19)31872-0

166. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTSThe Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213-260. doi:10.1093/eurheartj/ehx419

167. Piepoli MF, Corrà U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: A Policy Statement from the Cardiac Rehabilitation Section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol*. 2014;21(6):664-681. doi:10.1177/2047487312449597

168. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol*. 2019;26(8):824-835. doi:10.1177/2047487318825350

169. Kotseva K, Wood D, De Bacquer D, EUROASPIRE investigators. Determinants of participation and risk factor control according to attendance in cardiac rehabilitation programmes in coronary patients in Europe: EUROASPIRE IV survey. *Eur J Prev Cardiol*. 2018;25(12):1242-1251. doi:10.1177/2047487318781359

170. Székely O, Lane DA, Lip GYH. Guideline-adherent secondary prevention post-acute coronary syndromes: the importance of patient uptake and persistence. *Eur Heart J*. 2018;39(25):2365-2367. doi:10.1093/eurheartj/ehy308

171. Piek A, Du W, de Boer RA, Silljé HHW. Novel heart failure biomarkers: why do we fail to exploit their potential? *Crit Rev Clin Lab Sci*. 2018;55(4):246-263. doi:10.1080/10408363.2018.1460576

172. Gajardo AI, Llancaqueo M. Circulating biomarkers of left ventricular diastolic function and dysfunction: filling the research gap under high pressure. *Eur J Prev Cardiol*. 2019;26(1):18-21. doi:10.1177/2047487318810019

173. Miller WL, Jaffe AS. Biomarkers in heart failure: the importance of inconvenient details. *ESC Heart Fail*. 2016;3(1):3-10. doi:10.1002/ehf2.12071

174. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail*. 2018;20(12):1735-1743. doi:10.1002/ejhf.1311

175. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:CD003331. doi:10.1002/14651858.CD003331.pub5

176. Bjarnason-Wehrens B, Nebel R, Jensen K, et al. Exercise-based cardiac rehabilitation in patients with reduced left ventricular ejection fraction: The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF): A systematic review and meta-analysis. *Eur J Prev Cardiol*. June 2019:2047487319854140. doi:10.1177/2047487319854140

177. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JGF. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev*. 2015;(10):CD007228. doi:10.1002/14651858.CD007228.pub3

178. Koehler F, Koehler K, Deckwart O, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet Lond Engl*. 2018;392(10152):1047-1057. doi:10.1016/S0140-6736(18)31880-4

179. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med*. 2018;379(3):215-225. doi:10.1056/NEJMoa1800410

180. Smith EE, Saposnik G, Biessels GJ, et al. Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(2):e44-e71. doi:10.1161/STR.0000000000000116

181. Menêses AL, Ritti-Dias RM, Parmenter B, Golledge J, Askew CD. Combined Lower Limb Revascularisation and Supervised Exercise Training for Patients with Peripheral Arterial Disease: A Systematic Review of Randomised Controlled Trials. *Sports Med Auckl NZ*. 2017;47(5):987-1002. doi:10.1007/s40279-016-0635-5

182. Pandey A, Banerjee S, Ngo C, et al. Comparative Efficacy of Endovascular Revascularization Versus Supervised Exercise Training in Patients With Intermittent Claudication: Meta-Analysis of Randomized Controlled Trials. *JACC Cardiovasc Interv*. 2017;10(7):712-724. doi:10.1016/j.jcin.2017.01.027

183. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet Lond Engl*. 2018;391(10117):219-229. doi:10.1016/S0140-6736(17)32409-1

184. Zomer E, Si S, Hird TR, et al. Cost-effectiveness of low-dose rivaroxaban and aspirin versus aspirin alone in people with peripheral or carotid artery disease: An Australian healthcare perspective. *Eur J Prev Cardiol*. 2019;26(8):858-868. doi:10.1177/2047487318817910

185. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. *J Am Coll Cardiol*. 2016;67(23):2719-2728. doi:10.1016/j.jacc.2016.03.524

186. Martin A, Saunders CL, Harte E, et al. Delivery and impact of the NHS Health Check in the first 8 years: a systematic review. *Br J Gen Pract J R Coll Gen Pract*. 2018;68(672):e449-e459. doi:10.3399/bjgp18X697649

187. Alageel S, Gulliford MC, McDermott L, Wright AJ. Multiple health behaviour change interventions for primary prevention of cardiovascular disease in primary care: systematic review and meta-analysis. *BMJ Open*. 2017;7(6):e015375. doi:10.1136/bmjopen-2016-015375

188. Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). *Eur J Prev Cardiol*. 2016;23(18):1914-1939. doi:10.1177/2047487316671181

189. Frederix I, Vandijck D, Hens N, De Sutter J, Dendale P. Economic and social impact of increased cardiac rehabilitation uptake and cardiac telerehabilitation in Belgium - a cost-benefit analysis. *Acta Cardiol*. 2018;73(3):222-229. doi:10.1080/00015385.2017.1361892

190. Jin K, Khonsari S, Gallagher R, et al. Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review and meta-analysis. *Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol*. 2019;18(4):260-271. doi:10.1177/1474515119826510

191. Janssen A, Wagenaar KP, Dendale P, Grobbee DE. Accreditation of clinical centres providing primary prevention, secondary prevention and rehabilitation, and sports cardiology: A step towards optimizing quality. *Eur J Prev Cardiol*. July 2019:2047487319867503. doi:10.1177/2047487319867503

192. Thomas RJ, Balady G, Banka G, et al. 2018 ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2018;71(16):1814-1837. doi:10.1016/j.jacc.2018.01.004

193. John Buckley; Patrick Doherty, Gill Furze, Jenni Jones, Sally Hinton, Jo Hayward, Joe Mills, Linda Speck. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation 2017 (3d edition). 2017.