The year in cardiology 2016: prevention

Massimo F. Piepoli¹, Stefano Taddei², and Ulrich Laufs³

¹Heart Failure Unit, Cardiology, G da Saliceto Hospital, AUSL Piacenza, 29121, Piacenza, Italy
²Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy
³Klinik für Innere Medizin III, IMED 41.1; UdS; Universität des Saarlandes, 66421, Homburg, Germany

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Corresponding author: Massimo F. Piepoli, Tel. +390 523 303217, Fax: +390 523 303220
E-mail: m.piepoli@imperial.ac.uk; m.piepoli@ausl.pc.it; article-lifecyclePAP

Preamble

Cardiovascular disease (CVD) accounts for most of the deaths from non-communicable diseases, or 17.5 million people annually in Europe (1). The new 2016 European Society of Cardiology (ESC) European Guidelines on CVD prevention in clinical practice, (developed by the Sixth Joint Task Force of the ESC and nine other societies) emphasize, for the first time in an European Guidelines, not only an individual-based approach but also a population-based intervention, focusing on smoking cessation, a healthy diet, physical activity, alcohol abuse prevention, and a healthy environment promotion (2). Also new aspect of the 2016 Guidelines is the presentation of preventive measures targeted at specific groups (e.g. younger and older persons; women; ethnic minorities; patients with inflammatory diseases or under cancer therapy). In the present article, we summarize some of the interesting novel insights in the field of CVD prevention published in the year 2016.

Lifestyle

A sedentary behaviour, such as prolonged sitting time viewing TV or a computer display has been associated with increased risks for morbidity and mortality. A crucial question is if the individual is active enough, will this attenuate or even eliminate the detrimental association of daily sedentary habit with mortality? Some good news comes from a systematic review and meta-analysis which has documented that about 60–75 min per day of vigorous intensity physical activity (>35.5 METs·h/week) seems to reduce the increased risk of death associated with high sitting time. However, this high activity level does not eliminate completely the increased risk associated with extremely high TV-viewing time (≥5 h/day) (3). These results support the new ESC prevention Guidelines recommendation on the added benefit of high intensity physical activity, although prospective interventional studies are still missing (2).

The importance of income and healthy behaviour in longer survival was confirmed in a large analysis that included all US individuals with a valid social security number between the years 1999 and 2014. Life expectancy increased continuously with income. At the age of 40 years, the gap in life expectancy between subjects in the top and bottom 1% of the income distribution was 15 years for men and 10 years for women. These changes varied significantly across different regions, due to differences in health behaviours, including smoking, obesity, and exercise (4).

Diet

Guidelines promote the consumption of fruit (≥200 g of per day, 2–3 servings) and vegetables (≥200 g of per day, 2–3 servings). A global population analysis of high-risk patients with stable coronary artery disease confirmed that a 'Mediterranean' dietary pattern, assessed using a simple self-administered food frequency questionnaire, was associated with better outcomes and lower all-cause mortality. Subjects with higher Mediterranean dietary pattern were also less likely to be current smokers, took slightly more physical activity, had lower body mass index (BMI), and lower white blood cell count, C-reactive protein, and fasting blood glucose levels (5). A study using data from 2 large US cohort studies with
repeated measures of diet and up to 32 years of follow-up prospectively observed that high intake of animal protein was positively associated with mortality, with the inverse true for high intake of plant protein, among individuals with at least 1 lifestyle risk factor (i.e. smoking, heavy alcohol intake, overweight or obesity, and physical inactivity). This was not evident among those without any of these risk factors. Protein intake from processed red meat was strongly associated with mortality, whereas no association was found for protein from fish or poultry (6).

The effect of changes in overall diet quality on later occurrence of Type 2 diabetes has been highlighted in a large US cohort study, involving around 120,000 subjects, free of diabetes at baseline observed for more than 20 years. To assess overall diet quality changes, changes in Alternate Healthy Eating Index (AHEI) scores every 4 years were calculated. AHEI 2010 score consisted of 11 components, which included higher intakes of vegetables, fruits, whole grains, nuts and legumes, long-chain n-3 fatty acids, and polyunsaturated fatty acids (excluding long-chain n-3 fatty acids); lower intakes of red/processed meat, sugar-sweetened beverages and fruit juice, transfat, and sodium; and moderate alcohol consumption, as being adherence to healthy eating. The results showed that greater improvement in diet quality was associated with lower diabetes risk across different baseline diet quality status and baseline BMI. The association was not affected by changes in body weight or physical activity, but these data were only based on questionnaires (7).

High sucrose intake (>15% of total energy intake) was associated with an increased risk of coronary event, based on a prospective analysis on 26 190 individuals (62% women) free from diabetes and without a history of CVD from the Swedish population-based Malmö Diet and Cancer cohort, over an average of 17 years of follow-up. Sucrose intake was obtained from an interview-based diet history method, including 7-d records of prepared meals and cold beverages and a 168-item diet questionnaire covering other foods (8).

However, since all the above results are derived from not randomized studies, it remains unclear whether certain dietary habits are protective or whether they simply identify individuals with a healthy lifestyle, higher education and income.

Use of dietary supplements, often at high doses, is commonplace, despite the absence of convincing evidence for health benefits. Many supplements have been evaluated in observational studies and controlled trials as potential therapies to prevent CVD or other conditions. Evaluated doses in such trials have often exceeded usual or even recommended dietary intakes, often under the assumptions that higher levels would produce greater benefits, and that there was little risk of harm. Evidence has accrued that most of these supplements have little CVD benefit, and that certain supplements including β-carotene, calcium, and vitamin E may even be harmful (9).

Smoking habit
The new ESC Guidelines recommend reducing the density of retail tobacco outlets in residential areas, schools and hospitals (2). A pooled analysis of two prospective Finnish cohorts has provided further evidences to support this. Each 500-m increase in distance from home to the nearest tobacco outlet was associated with a 20–60% increase in odds of quitting smoking (10). This finding was robust to adjustments for a range of potential confounding factors such as marital status, work status, chronic diseases, and recent death or severe illness in the family. The authors discussed two plausible mechanisms. First, having a tobacco outlet closer to home decreases the time and travel costs related to purchasing tobacco. Second, higher density of tobacco outlets may promote smoking by increasing environmental cues to smoke. Increase in distance to tobacco outlet was not associated with the odds of smoking relapse among ex-smokers.

Obesity
During the past decades, the prevalence of overweight and obesity in the Western world has increased by 30–50%, leading to what has been described as a global epidemic. The significance of obesity involves the associated risks of diabetes, CVD, stroke, and death (11). However the rates of death and myocardial infarction (MI) are decreasing while the prevalence of obesity increases. This suggests that the association between obesity and CVD and death are more complex. Genetic confounding has been proposed as another important source of bias. To assess this factor, the risk of MI, Type 2 diabetes, and death was compared in monozygotic twin pairs discordant for BMI: during a mean 12.4-year follow-up period, the heavier twin had a higher risk of incident diabetes but did not exhibit a higher risk for MI or death than the leaner twin. The results revealed a significant association between obesity and diabetes after accounting for genetic factors (12).

Overweight and obesity have increased substantially in recent decades and affect a third of the adolescent population in some developed countries. Obesity early in life is considered to be a risk factor for death from CVD and from all causes in adulthood. These data have been confirmed by a nationwide population-based study (13) of 2.3 million Israeli adolescents, where obesity during adolescence was associated with a substantially increased risk of CV outcomes in middle age, particularly death from coronary heart disease and all-cause mortality during 40 years of follow-up. Also high-normal
BMI range (75–84th percentiles) was associated with hazard ratios (HRs) of 2.2 for coronary heart disease and 1.8 for total CV causes (Figure 1). There is a need to focus preventive strategies on obesity also in young individuals.

Diabetes

The ‘year in prevention’ was characterized by several landmark studies in patients with diabetes mellitus. Previous state of the art concept was that glucose control failed to significantly affect the rates of CV events and death (14). Three recent important outcome trials have challenged this.

The EMPA-REG trial evaluated the selective inhibitor of sodium glucose cotransporter 2 (SGLT2) empagliflozin (15). Seven thousand and twenty patients with Type 2 diabetes at high-CV risk received empagliflozin or placebo for 3.1 years. The primary outcome (death from CV causes, non-fatal MI, or non-fatal stroke) was reduced by 1.6% [HR 0.86; 95.02% confidence interval (CI), 0.74–0.99; P = 0.04 for superiority]. There was no significant effect on MI but the SGLT2-inhibitor prevented death from CV causes (38% relative risk reduction), and death from any cause (32% relative risk reduction). Importantly, empagliflozin reduced heart failure endpoints such as hospitalization for heart failure (35% relative risk reduction) with consistent benefit in patients with and without baseline heart failure (16). Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events (17). As side effect, SGLT2 inhibition increased glucose urine concentrations, causing an increased rate of genital infections (15).

The LEADER trial (18) examined the CV effects of liraglutide, a glucagon-like peptide 1 (GLP1) analogue, in patients 9340 with Type 2 diabetes followed for 3.8 years. The primary outcome (first occurrence of CV death, non-fatal MI, or non-fatal stroke) was reduced by 1.9% in the liraglutide group (HR 0.87; 95% CI 0.78–0.97; P = 0.01 for superiority). Liraglutide also prevented CV and total death (22% and 15% relative risk reduction). The rates of non-fatal MI, non-fatal stroke, and hospitalization for heart failure were non-significantly lower in the treated group compared to placebo. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events.

In the pre-approval SUSTAIN-6 trial (19), the GLP1 analogue semaglutide was compared to placebo in 3297 patients with Type 2 diabetes for a relatively short duration of 2.1 years. The drug has an extended half-life of approximately 1 week. The mean glycated haemoglobin level in the treated groups was reduced by 0.7–1.0%. The GLP1-analogue reduced the primary outcome (first occurrence of CV death, non-fatal MI, or non-fatal stroke) by 2.3% (HR 0.74; 95% CI 0.58–0.95; P < 0.001 for non-inferiority).

These three well-designed trials have shown for the first time that CV events can be reduced by agents used to treat elevated glucose levels in patients with diabetes mellitus. The effect was observed on top of current

![Figure 1](https://example.com/fig1.png)

**Figure 1.** Body-mass index (BMI) during adolescence and subsequent cardiovascular mortality. Shown are rates of death from cardiovascular causes during up to 44 years of follow-up according to BMI. Grey shading denotes 95% confidence intervals. The model was adjusted for sex, age at examination, birth year, education, residential socioeconomic status, country of origin, and height. Adapted from Twig et al. (2016) (13)
therapies including statins. In all three studies, the lowering of glucose and glycated haemoglobin was only moderate. Some observations were unexpected, e.g. the positive effect of the SGLT2-inhibitor empagliflozin on heart failure and renal outcomes. Therefore, the studies have triggered important new research projects that are needed to reproduce, to characterize and to mechanistically understand these findings. Clearly, the results will have profound impact on the clinical care of patients with Type 2 diabetes.

Lipids

New lipid guidelines

The new ESC/EAS Guidelines for the Management of Dyslipidaemias (20) are consistent with the ESC Guidelines on CVD Prevention (2). Important practical information relates to the measurement of lipid and lipoprotein analysis. Non-fasting blood samples should be routinely used for the assessment of plasma lipid profiles, based on extensive observational data indicating that the maximal mean lipid changes at 1–6h after habitual meals are not clinically significant (21). In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of CVD. However, fasting sampling may be considered when non-fasting triglycerides are >5mmol/L (440mg/dL).

The primary target of treatment remains LDL-cholesterol (LDL-C), since all trials have used it, and LDL-C has been established in recommendations around the world. However, non-HDL-C is recommended as a secondary target when the LDL-C goal is reached. Non-HDL-C (=total cholesterol minus HDL-C) and apolipoprotein B (ApoB) are helpful to estimate of the total amount of atherogenic lipoproteins in plasma [VLDL, VLDL remnants, intermediate-density lipoprotein (IDL), LDL, Lp(a)]. Compared to LDL-C, non-HDL-C and ApoB provide additional risk prediction, especially in patients with high triglycerides and low HDL, such as in diabetic dyslipidaemia.

The ESC/EAS experts acknowledge that continuous nature of the relationship between LDL-C reduction and reduction in risk. They base their recommendations of treatment targets on the individual variability in the LDL-C response to dietary and drug treatments. A goals approach serves the concept of individualized total CV risk reduction, helps communication and may facilitate adherence to treatment. The new guidelines maintain the LDL-C goal of <1.8mmol/L (70mg/dL) for patients at VERY HIGH CV risk. A new recommendation is that alternatively or a reduction of at least 50% is advised if the baseline LDL-C is between 1.8 and 3.5mmol/L (70 and 135mg/dL). In patients at HIGH CV risk, an LDL-C goal of <2.6mmol/L (100mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2mmol/L (100 and 200mg/dL) is recommended. In subjects at LOW or MODERATE risk an LDL-C goal of <3.0mmol/L (<115mg/dL) should be considered. Goals for non-HDL-C can be calculated as LDL-C goals plus 0.8mmol/L (30mg/dL).

Statins revisited

In addition to lifestyle, statins are recommended as the primary treatment of hypercholesterolemia. A meta-analysis of the Oxford Group summarizes the available evidence from randomized trials (22) showing that statins reduce the risk of a major CV outcome by 24% for each mmol/L reduction in LDL-C during each year (after the first) that it continues to be taken. These benefits continue long term (Figure 2) (23). The absolute benefits of LDL-C lowering depend on the individual’s global CV risk, baseline LDL-C and extent of LDL-C reduction. The authors report that treatment of 10 000 patients for 5 years with an effective regimen (e.g., atorvastatin 40mg daily) would cause about 5 cases of myopathy with large increases of creatine kinase (one of which might progress, if the statin therapy is not stopped, to the more severe condition of rhabdomyolysis), 50–100 new cases of diabetes, and 5–10 haemorrhagic strokes.

In contrast to randomised controlled trials, registries suggest that >10% of patients complain of statin-associated muscle symptoms (SAMS), which are the major cause of discontinuation of a life-saving treatment. This discontinuation may impair clinical outcomes in high-risk individuals and therefore deserves careful consideration: the clinical diagnosis of SAMS requires time and
re-exposure to different statins at low doses because the majority of patients with SAMS exhibit normal CK concentrations. For review of the topic, please refer to the recent consensus document of the European Atherosclerosis Society on statin associates muscle symptoms (24).

Recent randomized studies, using PCSK9-inhibitors (PCSK9i), found an higher prevalence of statin-associated muscle symptoms compared to the Cholesterol Treatment Trialists (CTT) analysis; but the majority of the so called ‘statin-intolerant’ patients were still able to tolerate a substantial dose of a statin (e.g. atorvastatin 20 mg) (25–27).

**LDL-C lowering in individuals with low or intermediate risk and average cholesterol levels**

In the HOPE 3 trial (2-factorial design), 12,705 participants at intermediate risk who did not have CVD received rosuvastatin 10 mg or placebo for 5.6 years (28). Baseline LDL-C was 128 mg/dL. LDL-C was 26.5% lower in the statin group. Rosuvastatin reduced the composite of death from CV causes, non-fatal MI, or non-fatal stroke by 1.1% (HR 0.76; 95% CI 0.64–0.91; P = 0.002). The results were consistent in subgroups defined according to CV risk at baseline, lipid level, C-reactive protein level, BP, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% vs. 3.1% in the placebo group; P = 0.02) and muscle symptoms (5.8% vs. 4.7% in the placebo group; P = 0.005).

In a hotline presentation at the ESC congress, Ference highlighted the effect of long-term LDL-C lowering (29). From 102,773 individuals, genetic scores for each patient were computed based on genetic polymorphisms known to be associated with LDL or systolic BP (SBP). A combined effect of genetically low-LDL and low-SBP levels “had independent, multiplicative and cumulative effects on the risk of CVD.” Ference calculated that long-term exposure to the combination of 1 mmol/L (38 mg/dL) lower LDL-C and 10 mm Hg lower SBP was associated with a 86% lower risk of major vascular events suggesting that the majority of CV events may be potentially preventable (Figure 3).

Taken together, recent studies point out the potential of early and long-term LDL-C lowering to reduce CV events, even for low-risk individuals based on average cholesterol levels.

![Figure 3](https://example.com/figure3.png)

**FIGURE 3.** A combined effect of genetically lower LDL and lower SBP had independent, multiplicative and cumulative effects on the risk of CV disease. CHD, chronic heart disease; LDL-C, LDL cholesterol; MI, myocardial infarction; revasc, cardiac revascularization; SBP=systolic blood pressure. Adapted from Ference (2016) (29)

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Update on PCSK9 inhibitors

PCSK9i was the main topic of the “The year in cardiology 2015” (30). The potent LDL-C reduction (by 50–60% on top of oral lipid lowering therapy) of the two approved fully human anti-PCSK9 antibodies, alirocumab and evolocumab, was well documented in clinical practice and their bi-weekly injections well tolerated (31). However, on 1 November, Pfizer has announced that the global development program for the PCSK9i bococizumab will be discontinued, because of “an emerging clinical profile that includes an unanticipated attenuation of the LDL-C lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions” with bococizumab compared to alirocumab and evolocumab (32). Bococizumab is a humanized antibody that may cause more anti-drug antibodies (ADA) compared to the approved two fully human antibodies. Inhibiting ADA may cause a loss of efficacy and may contribute to injection site reactions. Therefore the topic of ADA will remain important for the future surveillance of the class (33). On the positive side, the PCSK9i evolocumab met its primary end point of change in percent atheroma volume (PAV) from baseline to week 78 compared with placebo, as determined by intravascular ultrasound, in the GLAGOV trial involving 968 patients with coronary artery disease (34). LDL-C was 36.6 mg/dL in the statin+evolocumab group vs. 93.0 mg/dL in the statin group. This was associated with a reduction in percent atheroma volume for evolocumab (~0.95%) but not placebo (~0.05%) and a greater percentage of patients demonstrating plaque regression (64.3% vs. 47.3%). Post hoc analysis examining the relationship between achieved LDL-C level and change in percent atheroma volume showed a linear reduction down to very low-LDL-C levels of 20 mg/dL. No safety signals were observed in the GLAGOV study. The two most important open questions with regards to PCSK9i relate to their effects on clinical outcomes and the long-term safety. Two very large outcome trials, FOURIER (~27,000 patients with a history of CVD and at high risk of recurrent events, NCT01764633) and ODYSSEY OUTCOMES (~18,000 patients re-
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Environmental stressors
An emerging and dramatic problem facing increasing urbanization is the impact of environment on CVD. This topic has been addressed by a comprehensive and exhaustive review from Münzel and coworkers (39). In particular, particulate matter in the air together with traffic noise pollution contribute to > 75% of environment attributable diseases, and their effects may be additive. However the mechanism and quantity of this interaction are still to be investigated. In addition, air pollution and traffic may enhance classical CV risk factors, including hypertension and Type 2 diabetes. Mechanisms involved in the pathogenic effects of environmental stressors are low-grade inflammation, oxidative stress and the consequent vascular dysfunction, especially at the level of NO pathway. In addition, these factors can lead to a derangement of sympathetic nervous system activity. Taken together these mechanisms may potentially independently accelerate the pathogenesis of atherosclerosis and susceptibility to cardiovascular events (Figure 6). Importantly, the negative effects of air pollution and noise are observed for values below the thresholds considered to be safe. Since exposure to noise and pollution are highly correlated with income, education and life style (e.g. smoking), randomized prospect-

Hypertension
The most relevant topic was the discussion about which BP targets should be reached with antihypertensive treatment. 2016 ESC guidelines (2) recommend that pharmacological treatment should lower BP values under 140–90 mmHg, considering higher targets in frail elderly, or lower in most patients with DM and in some (very) high-risk patients without DM who can tolerate multiple blood pressure lowering drugs. These recommendations took into consideration also the results of SPRINT trial (36) demonstrating that lowering SBP values to 120 mmHg produced a significant effect as compared to less tight BP control (SBP at 130 mmHg), in 9361 at increased CV risk (≥15%, according to Framingham score). Few months after SPRINT, BP lowering results of HOPE-3 trial (37) demonstrated no effect of antihypertensive treatment (the combination of candesartan 16 mg with hydrochlorothiazide 12.5 mg) versus placebo in 12,705 patients at intermediate CV risk and no CV risk, whose baseline BP values at baseline were 138–82 mmHg. Thus in the same range of BP reduction, but in patients with different clinical characteristics, HOPE-3 trial does not demonstrate a beneficial effect of an aggressive treatment.

However, the difference in the degree of CV risk of patients enrolled in SPRINT or HOPE-3 cannot be considered a totally convincing explanation, especially considering the results of an interesting post-hoc analysis of the large database provided by the VALUE study (38). The aim of this analysis was to compare the incidence of CV events (MI, heart failure, and stroke) and all-cause mortality in the high-risk patients participating in the VALUE study whose BP values were reduced to <140–90 mmHg as compared to those who reached <130–80 mmHg. Results demonstrated that in the high risk patients of the VALUE trial the greater beneficial effect was obtained by targeting BP values to lower that 140–90 mmHg while the more aggressive treatment to lower than 130–80 mmHg led only to some possible further benefit on stroke (Figure 4).

Other explanations of the differences between HOPE-3 and SPRINT include the method of BP measurements with systematically lower values in the SPRINT study due to a protocol of automated measurements. Thus, BP targets in hypertension remain a not well-defined issue. While no doubt exists about the beneficial effect of reducing BP values under 140–90 mmHg, lower targets might be beneficial in some patients, but controlled clinical trials cannot identify the clinical characteristic of patients. This topic clearly underlines the lack of knowledge of the physiopathology of most cases of hypertension and therefore treatment is not tailored to the single patient but it derives from the results of pharmacological intervention performed in thousands of patients and analysed as a mean effect. Our opinion is that, increasing the number of trials can only lead to an increase in the scientific discussion but not in a real advancement in the daily clinical practice. Figure 5 presents a summary with blood pressure goals recommended by 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2).
Conclusions

Novel data published in the last year strongly support the importance of life style as the basis of CV prevention. The reduction of environmental stressors such as particulate matter air and noise pollution may represent an important novel area of investigation: future studies need to better differentiate the effects of environmental stressors and life style from social factors such as income that remain highly significant predictors of CV outcomes. In hypertension, the main academic discussions of the year 2016 have focused on treatment strategies rather than novel agents and a further refinement of the BP goals. Clearly, the general goal of 140/90 mmHg was strongly supported. Further analyses are needed to define sub-populations that may need less intensive intervention (e.g. frail individuals) or more stringent BP control.

In lipid lowering, statins have been confirmed as the mainstay of therapy. The newly approved PCSK9-inhibiting antibodies show impressive additional lipid lowering. The termination of the bococizumab program highlights the need for additional data on their safety and their efficacy on clinical event reduction that will be provided in the near future by large outcome trials.

In the field of diabetes, the last year has seen a revolution as three well-designed trials have shown for the first time that CV events can be reduced by agents used to treat elevated glucose levels. Many important research projects have been triggered by these results to further elucidate the underlying mechanism(s) that are likely to go beyond the lowering of glucose, also in different clinical conditions such as heart failure and kidney diseases.

Conflict of interest: None declared.
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