The year in cardiology 2014: prevention

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Preamble
This overview of key studies, published in 2014, regarding epidemiology and prevention of cardiovascular disease (CVD) illustrates the great potential of CVD prevention as summarized in recent guidelines. New insights became available in the complex interaction between CV risk factors; surveillance of the CVD epidemic remains crucial and should allow better CVD risk estimations at the national level. Intervention studies are needed to examine effectiveness and safety of preventive strategies; new approaches to better control dyslipidaemias are promising in this respect.

This overview demonstrates how fast CV epidemiology and prevention is moving ahead serving by this the mission of the European Society of Cardiology: ‘to reduce the burden of cardiovascular disease in Europe’.

Introduction
Knowledge alone is futile without implementation.

This was the last sentence of the abstract of ‘The year in cardiology 2013: cardiovascular disease prevention’. Fortunately, 2014 has been a year during which great efforts were made to reduce the gap between evidence-based recommendations on the prevention of cardiovascular disease (CVD) and daily practice. Practitioners require clear and practical guidance, applicable to the patients seen in their practice, and in accordance with national, cultural, and socio-economic aspects of their societies. In recent years and particularly during the past few months, new guidelines related to the prevention of CVD have been presented in Europe2–5 and in the USA6–10 A debate has emerged that focuses on the differences between these guidelines,11–13 differences that are mainly related to strategies and implementation, not to the scientific evidence. Insufficient attention has been given to the similarities between these guidelines (see Table 1).

In this overview, we report on additional developments in the field of cardiovascular (CV) epidemiology and prevention published in the past year.

Cardiovascular risk estimation and epidemiological studies of novel risk markers

Estimation of total cardiovascular risk
In guidelines on CVD prevention it is a strong recommendation to adapt the intensity of intervention to the overall CV risk of the patient. In otherwise healthy individuals, CV risk estimation requires adequate algorithms. Different models have been developed over the past years; in Europe the SCORE model, based on 12 large European cohorts, is in widespread use. SCORE provides two risk charts, one for high-risk countries and another for low-risk countries. Vikhireva et al.14 tested the SCORE model in cohorts from the MONICA project and from the HAPIEE study in the Czech republic, Poland, Lithuania and Russia. The results show that one size does not fit all. The high-risk SCORE model underestimated the risk of a fatal CV event in the Russian MONICA centre but performed well in most other MONICA cohorts and in the Russian HAPIEE centre; however, it overestimated risk in the more contemporary Czech and Polish cohorts. So, once a model has been developed it will overestimate CV risk in a country where CV mortality has declined. Cardiovascular disease mortality is very dynamic; it changes rapidly over time as societies change lifestyles on the basis of socio-economic developments. In Figure 1, age-standardized CHD mortality rates are presented from 1970 to 2006 for men from Lithuania, the Russian Federation, Poland, Czech republic, former Czechoslovakia, Scandinavian-, Eastern European-, and Southern European countries; these time trends are more related to changes in lifestyle than to improvements in therapies.

Several attempts have been made to improve risk estimation models; Ian Graham and MT Cooney elegantly summarized the vulnerability of the performance of all models.15 In addition, numerous novel biomarkers have been proposed to improve existing risk estimation models but in only a few the incremental predictive value was of clinical importance.16 One could improve risk stratification at the population level by detecting sub-clinical atherosclerosis and identifying patients at high or very high CV risk; this has been proposed using the ankle brachial index
which seems to carry incremental predictive value in people at intermediate CV risk.\textsuperscript{17}

The SCORE model also has the advantage that it can be recalibrated using national statistics and this has already been undertaken in several European countries.

The Joint British Societies’ consensus recommendations for the prevention of CVD (JBS3)\textsuperscript{18} has chosen QRISK lifetime as the basis for guiding preventive strategies. However, questions remain as to how this risk estimate was derived, validated, and presented.

One should use these models with caution especially in countries where the actual CV risk is different from that of the cohort from which the model was derived. This also indicates the need for new cohort studies in Europe that could be used to develop current and precise algorithms to estimate total CV risk at the level of the asymptomatic population.

**Psychological symptoms and cardiovascular disease risk**

The association between psychological symptoms such as anxiety and depression and CVD remains an intense subject of debate. Different mechanisms have been put forward to explain these associations. In a large population-based cohort of 57,953 Norwegians, followed for 11.4 years, self-reported symptoms of depression and anxiety were associated with an increased risk of an acute myocardial infarction (AMI). But further analyses suggest that this association partly reflects reverse causation and confounding by co-morbidities;\textsuperscript{19} in a review by Hare et al.\textsuperscript{20} depression was also a major determinant of quality of life in patients with CVD; in another systematic review of 53 studies on depression and adverse medical outcomes after an acute coronary syndrome consistent associations were found;\textsuperscript{21} so, it seems that the debate is not closed as of yet.

**Air pollution, noise, and cardiovascular disease risk**

Environmental factors such as the exposure to excessive noise and to air pollution have been associated with CVD for many years but

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**Table 1** Similarities between European and US guidelines on evidence-based cardiovascular disease prevention

- The potential of CVD prevention has been repeatedly demonstrated.
- The basic elements of all CVD prevention strategies constitute lifestyle changes such as no exposure to tobacco, taking regular physical exercise, and healthy eating habits.
- The multifactorial origin of CVD is recognized and therefore the focus should be on the total cardiovascular risk and its modifiable components such as blood pressure, LDL- and non-HDL-cholesterol, diabetes mellitus, smoking, physical exercise, body weight, and nutritional habits.
have gained little attention. More recently, better exposure measurements and increasing levels of exposure in certain areas of Europe have re-activated this interest.

In a population-based cohort study of 4814 participants in the German Heinz Nixdorf Recall study, exposure to air pollution and to road traffic noise were measured and related to thoracic aorta calcification; both exposures were independently associated with subclinical atherosclerosis.22 In the prospective Nurses’ Health Study, roadway proximity was studied as a proxy for air pollution and for road traffic noise; it was associated with a significant increased risk of sudden cardiac death and of fatal coronary heart disease (CHD), even after controlling for other CV risk factors.23

The CV consequences of excessive noise exposure were reviewed by Münzl et al.24 and it was concluded that noise contributes to the incidence of arterial hypertension and CVD. The relative risk of these exposures might be limited but the population attributable risk may be much larger when a large proportion of the population is exposed, such as certain social classes that are more exposed to noise at home and at work. Part of the large inequalities in CV health may be related to differences in exposure to these environmental factors.

**Intervention studies**

1. Prevention of CHD through LDL-cholesterol (LDL-C) reduction with statins has received overwhelming attention during the past decades; results from numerous RCTs have demonstrated the efficacy of statins in preventing ‘hard’ CV events. There is more controversy about possible adverse effects. Indeed, results from RCTs are in sharp contrast to observational studies regarding the incidence of muscle-related side effects. The true incidence of ‘statin intolerance’ is therefore poorly understood. There is a need for a validated scale to diagnose statin-associated myalgia. All this received more attention recently by the Statin Muscle Safety Task Force in the USA25 and in meta-analyses and systematic reviews.26–27

2. High-intensity statins induce a greater LDL-C decline and have also a more potent effect on plaque regression. In the IBIS-4 study, it was found that a high dose of rosuvastatin (40 mg/day) also had favourable effects on coronary plaque regression in patients after an AMI.28

3. Results from a meta-analysis using individual data from eight RCTs focused the attention on the large inter-individual variation in response to a given dose of a statin;29 the causes of that need to be examined in more detail.

4. The potential of CVD prevention by raising HDL-C levels is still under discussion; both genetic studies and results from RCTs have been disappointing. Altered vascular effects of HDL in patients with CVD when compared with healthy subjects have suggested ‘HDL dysfunction’ in these patients.30

5. There is some renewed interest in elevated triglycerides (TGs) as a CV risk factor but also as a possible target for therapy; non-fasting TG levels could contain as much or even more predictive information than fasting levels.31 Whether lowering TG reduces CV risk needs further studies in large-scale trials.

6. While statins are most effective in CVD prevention, additional lipid lowering drugs are needed for patients with true statin intolerance and for those who cannot reach the LDL-C goal on a maximally tolerable dose of statin. Studies of human monoclonal antibodies, gene therapy, RNA-based targets, and atherogenic lipoproteins other than LDL might bear fruit in the very near future.32

7. With ezetimibe, a drug that lowers LDL-C by inhibiting the activity of the Niemann-Pick C1-like 1 protein, two interesting findings became recently available. Naturally occurring mutations that disrupt the function of NPC1L1 were identified; carriers of these mutations had a mean LDL-C that was 12 mg/dl lower than in non-carriers and had a 53% lower risk of CHD.33 At the AHA meeting in Chicago in November 2014 results were presented of the IMPROVE-IT trial; the addition of ezetimibe to background simvastatin therapy was studied in 18 144 patients stabilized following an acute coronary syndrome. The primary endpoint was CV death, myocardial infarction, hospitalization for unstable angina, coronary revascularization or stroke; 5314 primary endpoint events were observed over a 5.68 years period; LDL-C was reduced to a median time average of 69.5 and 53.7 mg/dl, in respectively, the simvastatin and the simvastatin/ezetimibe group. The primary endpoint was reached in 34.7% of the simvastatin group and in 32.7% of the simvastatin/ezetimibe group resulting in a hazard ratio of 0.936 (95% confidence level 0.881–0.988) P = 0.016, number needed to treat = 50.34 The study shows that an incremental LDL-C lowering with ezetimibe on top of simvastatin, provides an incremental outcomes benefit; the risk reduction was what could be expected from the LDL reduction based on previous trials; a lower boundary of the benefit of lowering LDL-C in secondary prevention of CVD has not yet been established.

8. But it should also be mentioned that a number of drugs that targeted specific proteins in lipid and lipoprotein metabolism have failed such as Varespladib in the VISTA 16 trial,35 Darapladib in the SOLID and the STABILITY trials,36,37 and Aligitazar in the ALECARDIO trial.38

9. A promising development comes from proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition. Several monoclonal antibodies are in clinical development programs; initial results are very hopeful, efficacious with respect to LDL-C lowering on top of maximal tolerated statin therapy as well as safe. In 2014, results from large Phase III RCT’s with evolocumab and with alirocumab have either been published or presented; they are summarized in Table 2.39–48 In all these RCT’s, these PCSK9 inhibitors resulted in strong reductions of LDL-C and were well tolerated.

Large ongoing trials with these new agents (ODYSSEY Outcomes, FOURIER, and SPIRE) will provide information on the long-term safety and efficacy in preventing CV events.

10. Changes in lifestyle were examined in the Coronary Artery Risk Development in Young Adults Study. Over a period of 20 years, an improvement of a composite healthy lifestyle factor (based on smoking habits, diet, and physical exercise) was associated with a reduced odds of coronary artery calcification and of a smaller carotid intima-media thickness.49
An elevated heart rate is accepted as an independent CV risk marker. In the SIGNIFY RCT in patients with stable CHD without heart failure and a heart rate of 70 bpm or more, the addition of ivabradine to standard therapy reduced heart rate to 61 vs. 71 bpm in those on placebo but had no effect on the incidence of CVD. 50

The blood pressure level is a central and crucial haemodynamic marker of the risk of developing CVD and other organ damage. The management of arterial hypertension has recently been updated in guidelines in Europe 5 and the USA. 10 Remaining gaps have received attention in 2014; in a review of intervention trials on the effect of blood pressure reduction in the very elderly (80 + years), it has been demonstrated that a treatment strategy aiming at a goal of <150/80 mmHg resulted in benefits both in terms of CVD event reduction and in quality-of-life outcomes. 51 results from the INVEST study suggest that in patients with CHD, aged ≥60, reaching a target of <140 mmHg systolic results in more CVD protection than a target of 140 – <150 mmHg as recommended in the JNC8. 52 Another remaining problem is patients with ‘resistant’ hypertension. Renal denervation ablation is an interesting novel approach in them; results from the SYMPLICITY HTN-3 trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal artery denervation when compared with a sham control. 53 Long-term registry data have suggested a continued blood pressure lowering effect; however, more studies are clearly needed in this field. 54 The technique used to achieve renal denervation may play an important role, and measures to monitor the efficacy of renal denervation are clearly needed; it could also be that not all blood pressure reducing mechanisms have a similar effect on CVD outcomes.

Future perspectives

In an update for 2014 on the burden of CVD across Europe, it was shown that the differing trends in CV mortality and case fatality have led to increasing inequalities between European countries. 55 Cardiovascular disease caused by atherosclerosis remains an important challenge to prevention; this is even more important because in some European countries such as France the decline in CHD mortality was not observed in younger subjects, 56 there is also an emerging need to prevent a decline in quality of life particularly in the elderly with heart failure. In that respect, the publication in 2014 of a new validated Health-Related Quality-of-Life questionnaire for patients with CHD, developed with the support of the ESC and the EACPR 57 is very welcome.

Smoking of tobacco remains a major cause of concern both in primary and secondary prevention of CVD. In the hospital arm of the EUROASPIRE IV survey, conducted in 24 European countries, it was found that only half of the coronary patients who smoked before hospitalization had stopped smoking 1.35 years later. Results from a large European study regarding determinants and prevalence of e-cigarette use in 27 countries illustrate the need to rapidly evaluate the health effects of e-cigarettes and the need for EU-based regulations. 58 The AHA also released a policy statement supporting effective regulations that addresses marketing, labelling, quality control of manufacturing, and standards for contaminants of e-cigarettes. 59 Levels of physical activity have been found to be associated with CVD in the general population. In a large observational study of patients with type-2 diabetes, low physical activity was associated with 25–70% increased risk of CVD and mortality over a 5-year period. 60 The importance of physical exercise has further been
documented and explained in recent European and US guidelines on lifestyle and CVD prevention.3,7

(4) Compliance with multiple drug therapies in secondary prevention of CVD is a major source of concern. Intervention studies are ongoing to test the efficacy of strategies using a polypill formula that may improve long-term adherence.51,62

(5) We need more studies in the field of preventive cardiology. Results from a survey of the European cardiovascular research landscape and recommendations for future research strategy (CardioScape, EU 7th Framework programme), delivered in September 2014 (www.cardioscape.eu), indicate that in 2010–2012 research spend on CVD was highest for the area of human/clinical research and lowest for research in prevention/population/public health; EU funding for prevention/population/public health was negligible.

(6) Finally, it should be mentioned that hard work has been performed in 2014 to have the new EACPR Textbook on Preventive Cardiology in Clinical Practice ready and we can look forward to its publication in 2015.

Conflict of interest: G.D.B. is a consultant on an advisory panel of MSD and consulted with Amgen. J.J.P.K. declares that he has acted as a consultant and received honoraria from the following companies: Aegerion, Amgen, AstraZeneca, Athero Nova, Boehringer Ingelheim, Catabasis, Cerenis, CSL Behring, Dezima Pharmaceuticals, Eli Lilly, Esperion, Genzyme, Isis, Merck, Novartis, Omthera, Pronova, Regen,eron, Sanofi, The Medicines Company, UniQure, Vascular Biogenics and VivaS.U.L. has acted as a consultant or received lecture honoraria from Amgen, MSD, Sanofi, Pfizer, Roche, Berlin Chemie.

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