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REVIEW

The Year in Cardiology

The Year in Cardiology 2012: focus on cardiovascular disease prevention

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Current data suggest that advances in cardiovascular (CV) treatment have resulted in significant reduction in CV mortality but also in prolongation of life with disability. Focus on CV prevention is likely to reverse this unfavourable trend. In this review we provide information on the new European guidelines on CV prevention and discuss biomarkers and vascular imaging techniques which can assist in refining CV risk prediction. Finally, we provide new information on lifestyle and pharmacological advances which are likely to result in significant CV risk reduction.

Keywords Guidelines • Prevention • Biomarkers • Intervention

Introduction

Despite emerging trends for mortality in developed countries cardiovascular (CV) disease remains the major cause of premature death in Europe with most clinical events due to complications of atherosclerosis.[1,2] Much of the success in reducing mortality has resulted from better treatment of disease. However, this approach is expensive and the increasing risk factor burden in the population threatens to reverse current favourable trend in the CV outcome. A recent study using data pooled from 18 US cohort studies, including 257 384 participants, reported that among the total population aged 55 years, only ~3% of subjects were optimally managed for all key CV risk factors.[3] Furthermore, in the NHANES III population, <7.5% of the population met six or more of the seven CV health metrics (i.e. not smoking, being physically active, having normal weight and blood pressure, glucose and total cholesterol levels; eating a healthy diet) which were recently published by the American Heart Association (AHA) for CV prevention.[4] Similar findings have been described in Europe. The EUROASPIRE III economic project emphasized the economical and societal value of optimizing CV disease prevention, with an average cost-effective ratio per quality-adjusted life (QUALY) years up to €12.484 in data from eight countries.[5]

Guidelines

The new European guidelines on CV disease prevention were published in 2012.[1] They reported a number of advances, including recommendations for more aggressive therapy and identification of populations at a high risk of CV disease (e.g. patients with chronic inflammatory, kidney disease, and diabetes). These guidelines refined the traditional algorithms which base recommendations for interventions on 10-year CV risk. However, as this approach is known to disenfranchise many women and young people from effective CV risk management, it was suggested that relative risk should be considered in young people.[1]

An alternative approach has been recommended by Berry *et al.*[3] By estimating the lifetime CV risk, they demonstrated that even a relatively low burden of CV risk factors at a young age is associated with a significant increase in later CV mortality.[3] This relatively easy concept may permit better communication of risk, justify lifestyle interventions in the young, and support aggressive early lowering of CV risk factors in high-risk populations.

Biomarkers and vascular imaging

There is increasing interest in the development of novel biomarkers and imaging methods to refine CV risk prediction. The

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Emerging Risk Factors Collaboration investigated the predictive value of adding C-reactive protein or fibrinogen levels to conventional risk factors.[6] In a meta-analysis of 52 prospective studies of 246 669 participants without a history of CV disease, the assessment of C-reactive protein or fibrinogen levels yielded only a modest reclassification improvement for those at intermediate risk compared with models which included only age, sex smoking status, blood pressure, history of diabetes, and total cholesterol levels.[6] It was estimated that 13 199 participants at intermediate risk who did not meet recommendations for the initiation of statin therapy by ATPIII guidelines would become eligible after an additional assessment of C-reactive protein and this might result in prevention of 30 additional CV events over a 10-year period.[6] These results, however, have been challenged by the ASCOT investigators.[7] In this large study of hypertensive patients, there was no improvement in CV event prediction when C-reactive protein was added to the Framingham risk score. Importantly, reduction in C-reactive protein associated with statin therapy was not a predictor of CV benefit.[7]

The Emerging Risk Factors Collaboration has also explored the benefit of including lipid-related markers [i.e. apolipoprotein B, apolipoprotein A-I, lipoprotein(a), or lipoprotein-associated phospholipase A_2] in prognostic models for CV disease risk prediction.[8] They demonstrated that these improve discrimination capacity but that the net reclassification improvement was $<1\%$.[8] This highlights the difficulty of CV risk prediction using multi-marker combinations and the opportunities for the identification of novel biomarkers which ideally are on the causal pathway for CV disease.

At the AHA, Ganz[9] presented novel data on proteomics from blood sample in stable coronary artery disease patients, which considerably refined risk prediction. This promising approach needs to be evaluated in both higher and lower risk populations.

Imaging techniques, such as carotid intima media thickness (cIMT) and coronary artery calcium (CAC) score, have attracted considerable interest as adjuncts for CV risk stratification. In the IMPROVE trial, a 12.1% reclassification improvement of patients at increased CV risk was found when information derived from a single cIMT was combined with classical risk factors (*Figure 1*).[10] However, the MESA investigators showed that the addition of CAC, rather than cIMT to the Framingham risk score resulted in a net reclassification index of 0.659.[11] This is not surprising as CAC represents a cumulative burden of disease rather than a 'snapshot' of current CV risk factors.[11] Currently, the European and American guidelines include cIMT and CAC measurement as a class IIa recommendation for asymptomatic adults at moderate CV risk.[1,12] New imaging modalities, such as MRI, are likely to improve further ability to characterize functional and structural arterial wall changes. It is important to note, however, that there is currently no evidence to support the use of these imaging methods to monitor the evolution of disease in relation to the overall risk.

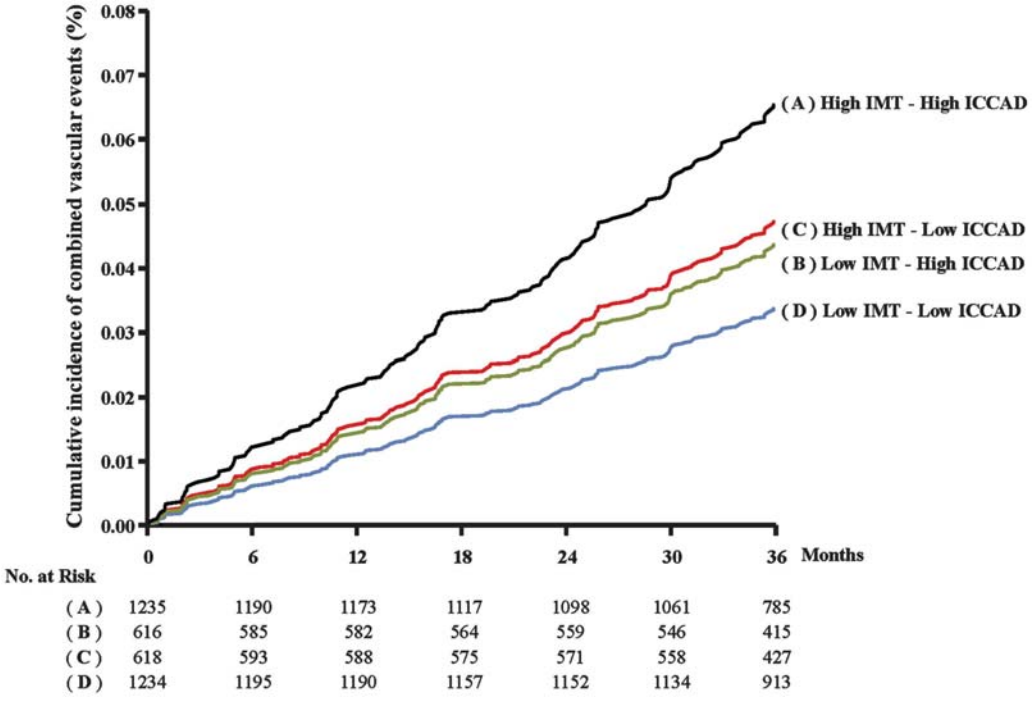

Figure 1 Framingham risk score-adjusted Kaplan–Meier incidence curves. The study population was stratified according to intima media thickness (measured as average of maximal intima media thickness measured in eight segments including common carotid, bifurcation, and internal in left and right carotid arteries) and inter-adventitia common carotid artery diameter values above or below their respective medians (1.34 and 7.74 mm, respectively). Curves were computed for the mean value of FRS (22.6%). Reproduced with permission from Baldassarre *et al.*[10]

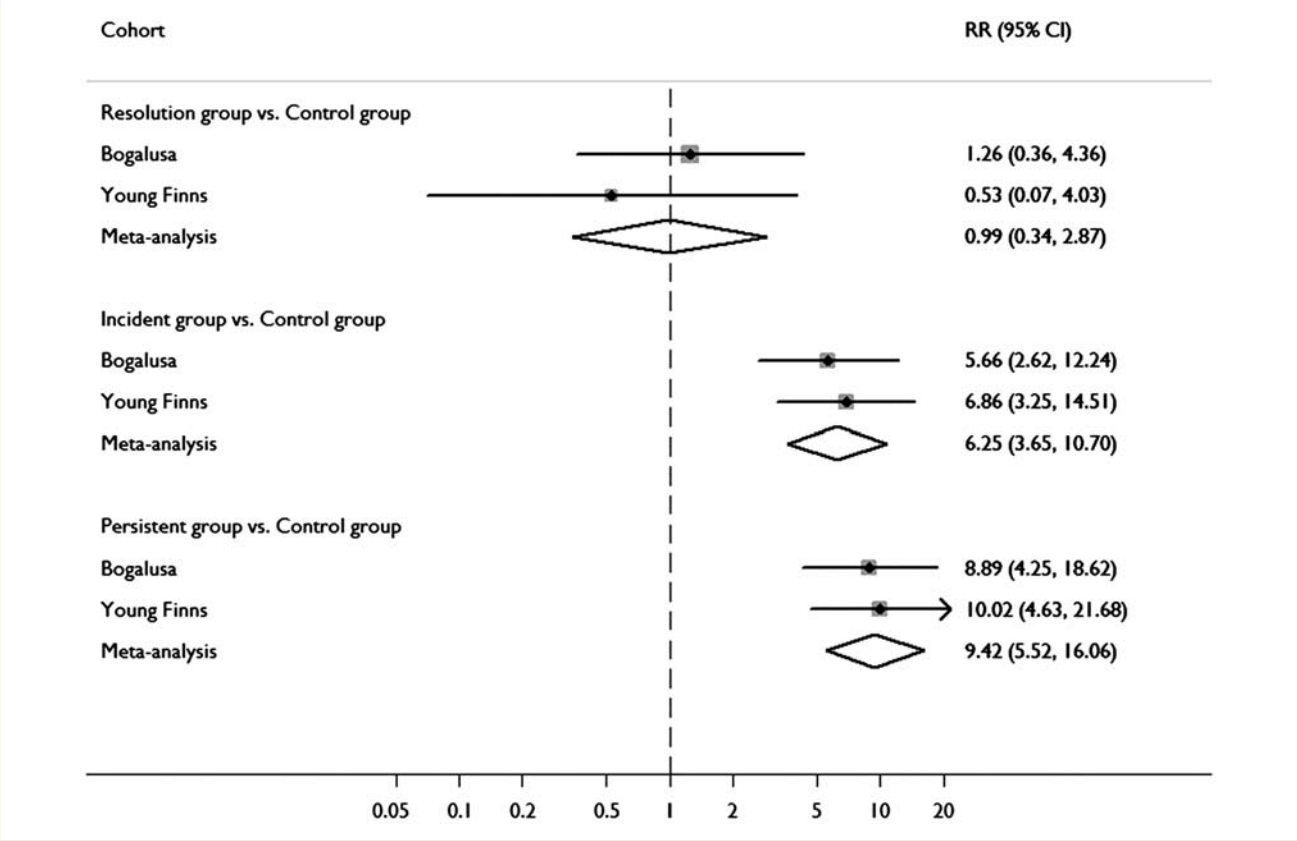

Figure 2 Impact of metabolic syndrome on carotid intima media thickness by the length of exposure. Metabolic syndrome in youth but not in adulthood is associated with normalization of carotid intima media thickness compared with increased carotid intima media thickness noted in participants with persistent metabolic syndrome (youth to adulthood) or those with metabolic syndrome when emerged in adulthood. The size of each box is directly proportional to the weight of the cohort in the meta-analysis. The diamonds represent the relative risks estimated from the meta-analysis, with the lateral points indicating the 95% confidence intervals. The *P*-values for heterogeneity were 0.97 for the comparison of Group II with Group I, 0.89 for the comparison of Group III with Group I, and 0.15 for the comparison of Group IV with Group I, suggesting that there was no dissimilarity between cohorts. Reproduced with permission from Magnussen *et al.* J Am Coll Cardiol. 2012;**60**(17):1631-9.[16]

Early intervention for optimal cardiovascular prevention

Atherosclerosis is known to begin in childhood, with evidence of prenatal, epigenetic, and childhood risk factor impact on the initiation and progression of early arterial disease. Four studies published this year from the Young Finns cohort examined determinants and outcomes of CV risk factors in childhood. They reported that the AHA CV health metrics in childhood predicted subsequent cardiometabolic changes in adulthood.[13] Furthermore, they demonstrated that physical, environmental childhood risk factors, family history of hypertension, and genetic variants were associated with the development of hypertension in adulthood.[14] A childhood risk factor burden was associated with increased cIMT and CAC in adulthood,[13,15] while resolution of an unfavourable cardiometabolic profile from youth to adult life resulted in normalization of both increased cIMT and risk of type 2 diabetes (*Figure 2*).[16] These data suggest that CV prevention strategies in the young might be the best investment for future population health. Further studies are needed to establish the time course of the evolution of arterial wall changes as well as the response to therapy.

New frontiers in cardiovascular disease treatment

Several studies in 2012 addressed strategies for reduction in CV risk factors. The statins have been the cornerstone of therapy to lower LDL cholesterol. The recent report from the Cholesterol Treatment Trialists' Collaborators, which included 27 randomized trials demonstrated a substantial benefit from statin use even in individuals with relatively low-predicted risk of CV disease (<10% 5-year risk of major CV events).[17] A reduction of 1 mmol/L in LDL cholesterol might prevent 11 major CV events per 1000-treated patients. This benefit greatly exceeded any known hazards of statin therapy, including type 2 diabetes.[17,18] Despite statin use, a considerable residual risk of CV disease remains in many patients and novel approaches to lower LDL cholesterol are warranted in high-risk individuals. The use of a

monoclonal antibody against PCSK9 may represent an important new strategy. PCSK9 is a serine protease which binds to LDL receptor accelerates its degradation and increases LDL plasma levels. In three different phase 1 trials, treatment with this monoclonal antibody resulted in significant reduction in LDL cholesterol levels in healthy volunteers and in patients with familial or non-familial hypercholesterolaemia. Importantly, no discontinuation of treatment was recorded because of adverse events.[19] Three phase II trials in hypercholesterolaemic patients GAUSS, Rutherford and RN316 were also recently reported at AHA meeting.[20–22] They all showed significant reduction in LDL cholesterol within the first 2 weeks of the initiation of PCSK9 antagonists sustained for 12 weeks.

As epidemiological studies have shown an association between low HDL cholesterol and increased CV risk, there has been great interest in the potential benefit of HDL raising therapies. Cholesterol ester transfer protein (CETP) inhibition results in a marked elevation of HDL levels, but the first drug in class (torcetrapib) failed due to off target effects and increased mortality.[23] In a carefully designed programme, the effect of dalcetrapib was evaluated on endothelial function (dal-VESSEL) and carotid plaque (dal-PLAQUE).[24,25] Despite a 30% increase in HDL cholesterol and the lack of adverse vascular effects, the dal-VESSEL trial did not show evidence of improvement in endothelial function. These studies were followed by premature termination of the dal-OUTCOME trial due to the lack of CV benefit.[26] A small increase of 0.6 mmHg in the systolic blood pressure was noted and might have contributed to these disappointing findings. A recent meta-analysis challenged further the benefit of raising HDL, as genetic mechanisms that raise HDL cholesterol did not lower risk of myocardial infarction.[27] There are a number of possible explanations, including of possibility that HDL 'functionality' rather than plasma levels alone may be important. Indeed, accumulating evidence now suggests that while HDL has important anti-inflammatory and anti-thrombotic actions on the vascular endothelium in healthy individuals, these beneficial actions may be reversed in patients with established coronary disease.[26]

Further studies have explored the impact of a range of different interventions in high-risk cohorts. The familial benefit of a renin–angiotensin–aldosterone system blockade on CV mortality has recently been confirmed by two meta-analyses.[28,29] The first involved 158 998 hypertensive patients and reported that the use of ACE inhibitors was associated with 7% reduction in CV mortality.[28] The second included a total of 80 594 patients and both ACE inhibitors and ARB were found to be beneficial for patients with, or at increased risk for, atherosclerotic disease even if their systolic pressure was within normal range.[29] In contrast, the ORIGIN trial reported neutral effects of insulin glargine treatment and n-3 fatty acid supplementation on an incidence of CV disease and CV mortality in 12 536 patients with insulin resistance.[30,31]

In three well-conducted clinical trials, the impact of sugar sweetened beverages consumption on weight gain has been demonstrated. Qi *et al.*[32] reported that genetic risk of obesity has an impact on weight gain following consumption of sugar sweetened beverages. De Ruyter *et al.*[33] demonstrated that this association can be partially modulated as reduced weight gain and fat accumulation in normal weight children can be effectively achieved by the simple substitution of sugar free for sugar sweetened beverages. However, Ebbeling *et al.*[34] showed that, in overweight obese adolescents, differences in BMI achieved after 1 year of a similar intervention could not be maintained at 2-year follow up. Furthermore, in the Interheart study which included 10 043 cases of first myocardial infarction and 14 217 controls, increased leisure time physical activity was associated with reduced risk for myocardial infarction.[35] These findings underscore the importance of behaviour and lifestyle approaches, which may involve legislation for adoption of healthy behaviours, over and above interventions which target individual patients.[36]

Further new insights on the impact of novel treatments emerged at the American Heart Association Congress 2012. Thom *et al.*[37] reported the preliminary results of the UMPIRE Trial, where a fixed-dose combination pill containing aspirin, a statin, and two antihypertensives was administered to patients with or at high risk for CV disease. The use of a single pill (polypill) resulted in 21% increase in the number of patients adherent to medications.[37] This was associated with significantly lower systolic blood pressure and LDL cholesterol recorded in the polypill group compared with patients who received usual care. In contrast, results from the Physicians' Health Study II showed that a daily multivitamin is not useful for reducing CV risk in older men.[38]

Conclusion

It is now clear that a 'disease-based' health care approach, while important for patients, will not prevent the rise in CV disease in the population. An interesting analogy has been drawn to the demise of Kodak Company after 131 years of continuous production due to failure to advance their product.[39] Health maintenance rather than merely care of disease requires an ongoing emphasis on CV prevention.

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