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CURRENT OPINION

The Year in Cardiology

The Year in Cardiology 2013: cardiovascular disease prevention

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The decline in cardiovascular mortality in Europe by nearly 50% over the last three decades resulted in particular from improved risk factor control and prevention interventions in addition to improved treatment. This review provides an overview of key studies in epidemiology, hypertension control, lipidology, diabetology, and lifestyle changes published in 2013. EXAMINE in diabetology and AIM-High and HPS-2-THRIVE in lipidology failed to demonstrate an event reduction. According to EUROASPIRE IV clinical implementation of secondary prevention treatments is still suboptimal. The 2013 study highlights in prevention prove the dynamic progress of knowledge in the field;, however, knowledge alone is futile without implementation.

Keywords Cardiovascular disease prevention • Epidemiology • Intervention • Heart rate • Lifestyle

Introduction

Despite the significant decline in cardiovascular mortality in Europe by nearly 50% over the last three decades[1] cardiovascular diseases remain the primary cause of death accounting for 42% of fatalities in men and 52% of deaths in women.[2] They cause over 4 million deaths in Europe annually (17.3 million worldwide) of which 1.5 million are premature below the age of 75.[3,4] The total financial burden is estimated to be 190 billion Euros per year. It is therefore encouraging to see that prevention is entering a new era not just in scientific knowledge but also in implementation in health-care systems. During the last years the epidemiological, clinical, and experimental data accumulated in research in prevention have finally influenced political decisions at the highest level. In September 2011 representatives from 113 United Nation Member States met at a UN High Level Meeting in New York to sign a common declaration making the fight against non-communicable diseases (NCDs) a top priority in health care. The political goal is to reduce the mortality from NCDs by 25% by the year 2025. However, not all NCDs are equally responsive to preventive interventions. It is estimated that a 40% reduction in cardiovascular disease (CVD) mortality is needed by 2025 in order to come anywhere near the global goal of 25% reduction in total NCD mortality. The rapidly expanding knowledge in prevention research provides the scientific evidence to achieve these ambitious goals. In the present article we summarize some of the interesting novel insights in the field of cardiovascular prevention published in the year 2013.

Epidemiological studies in prevention

Current trends in cardiovascular risk factor control

PURE Study

The PURE Study is one of the few truly global epidemiological studies in CVD prevention. The total number of 154 000 people from 628 communities in 17 countries represent not only the high-income countries in North America and in Europe but also the middle- and low-income contries of the world, including Brazil, Argentina, Malaysia, and China as middle-income countries, and India, Pakistan, Bangladesh, Zimbabwe as low-income contries. Prof. Yusuf and his team aimed to determine the prevalence and mortality of CVD in different socioeconomic environments by long-term follow-up (3.8 years) and regular contacts to ascertain mortality from participants and family

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members. The INTERHEART risk score (IRS) comprising data on age, sex, smoking, diabetes, hypertension, family history of heart disease, waist-hip-ratio, psychosocial status, diet, and physical activity was calculated for each participant. Not surprisingly the IRS was highest in the high-income countries (~13), lower in the middle-income countries (10–11), and lowest in the low-income countries (7–9). However, the gradient for fatal CVD incidence was in the opposite direction, indicating that the low-income countries pay a higher death toll per IRS score because their health systems are not able to treat risk factors and disease manifestations as effectively as in the high-income countries. The authors conclude that the PURE study documents the 'Need for stronger and efficient health-care systems for CVD prevention and treatment globally'.[5–7]

EUROASPIRE-IV

The fourth iteration of this landmark study gives a unique insight into current trends of control of cardiovascular risk factors and the use of drugs in patients with coronary disease in Europe. The study included >100 sites in >25 European countries. Despite a high prevalence of statin, aspirin, and angiotensin-converting enzyme inhibtor use, 75% of patients with coronary disease are not at the goal for LDL cholesterol (<1.8 mmol/L) and 45% of patients are not at the goal for the blood pressure (<140/90 mmHg, for patients with diabetes <140/80 mmHg). These observations suggest further important opportunities in improving cardiovascular preventive measures in these patients in the future, including novel agents to target LDL cholesterol, such as proprotein convertase subtilisin/kexin type 9 (PCSK-9) or cholesterylester transfer protein (CETP) inhibition that are currently examined in large clinical outcome trial programmes. Moreover, in EUROASPIRE-IV the prevalence of obesity and type-2 diabetes is increasing in patients with CAD when compared with the previous EUROASPIRE III study, suggesting that implementation of life style changes needs to be more intensely pursued.

Heart-healthy lifestyle adds years in people without risk factors

Leading a heart-healthy lifestyle is not only important for people with a clear cardiovascular risk profile. In a substudy of the NHANES III follow-up Mortality Survey the authors were able to show that even among adults without common cardiovascular risk factors such as elevated cholesterol (low-density lipoprotein, LDL, cholesterol >130 mg/dl), inflammation (C-reactive protein, CRP, >3.0 mg/L, or hypertension (blood pressure >140/90 mmHg) neglecting healthy lifestyle habits significantly increased all-cause mortality. People who practised 0–1 healthy habits had a nearly five-fold increase in all-cause mortality when compared with those who observed all 5 healthy habits [heart rate (HR) 4.89, 95% confidence interval 1.49–16.0].[8]

Heart rate in the general population: an indicator of cardiovascular risk?

Since the publication of the SHIFT study it is common medical sense that high HRs are predictive of increased mortality in heart failure patients. But is the same true in the general population and does average HR change over time? These two questions were at the heart of a large population-based study led by Plichart who analysed 226 288 consecutive participants (141 533 men and 84 755 women) aged 44.7 ± 12.7 years who had a free standard health check up between 1992 and 2007. During the 15-year study period the crude mean HR decreased from 68.9 ± 10.4 to 63.7 ± 9.0 b.p.m. in men and from 72.2 ± 10.3 to 65.2 ± 9.0 b.p.m. in women; $P < 0.001$ for both) independent from risk factor changes. On multivariate analysis, higher HR (≥80 vs. <60 b.p.m.) was associated with 111% higher 5-year mortality rate in men and a 58% increased 5-year mortality in women. It may be worthwhile to study if elevated resting HR should be included as independent risk factor in cardiovascular risk assessments (*Figures 1* and *2*).[9]

Clinical intervention studies in prevention

Hypertension: obesity and selection of antihypertensive medication

In previous studies of antihypertensive drugs in high-risk patients a paradoxically higher cardiovascular event rate has been observed in normal weight vs. obese patients. This paradox was now resolved in a pre-specified analysis of the *Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension* (ACCOMPLISH) trial, in which the patient cohort was subdivided into three groups: obese [body mass index (BMI) ≥ 30, $n = 5709$], overweight (≥25–<30, $n = 4157$), and normal weight (<25, $n = 1616$) individuals. In patients allocated to a combination of benazepril and hydrochlorothiazide, the primary endpoint (per 1000 patient-years) was 30.7 in normal weight, 21.9 in overweight, and 18.2 in obese patients ($P = 0.0034$). This obesity-related gradient of cardiovascular events was absent in those allocated benazepril and amlodipine. The authors hypothesize that hypertension mechanisms may be different in normal weight and obese patients and therefore thiazide-based treatment provides less cardiovascular protection in normal weight than in obesity but amlodipine-based therapy is equally effective across BMI subgroups and thus may offer superior cardiovascular protection in non-obese hypertension.[10] Three-year follow-up data of an open-label study of renal denervation (RDN) with radiofrequency ablation suggest that in patients with treatment-resistant hypertension RDN may result in persistent changes in blood pressure after 3 years (as observed in 88 patients after 36 months).[11]

Lipidology: high-density lipoprotein cholesterol: not an easy target for cardiovascular preventive therapies?

The cardiovascular preventive efficacy of statin therapy is broadly supported by clinical trials, and a meta-analysis of the cholesterol treatment trialists (CTT) has shown that when compared with less intensive statin regimens, more intensive statin regimens produced a significant 15% further reduction in major vascular events, supporting intensive statin therapy in patients at high cardiovascular risk.[12] Another interesting meta-analysis of this group has now suggested that in individuals with a lower risk of vascular disease (i.e. 5-year risk of major vascular events lower than 10%), each 1 mmol/L reduction in LDL cholesterol by statin therapy produced an absolute

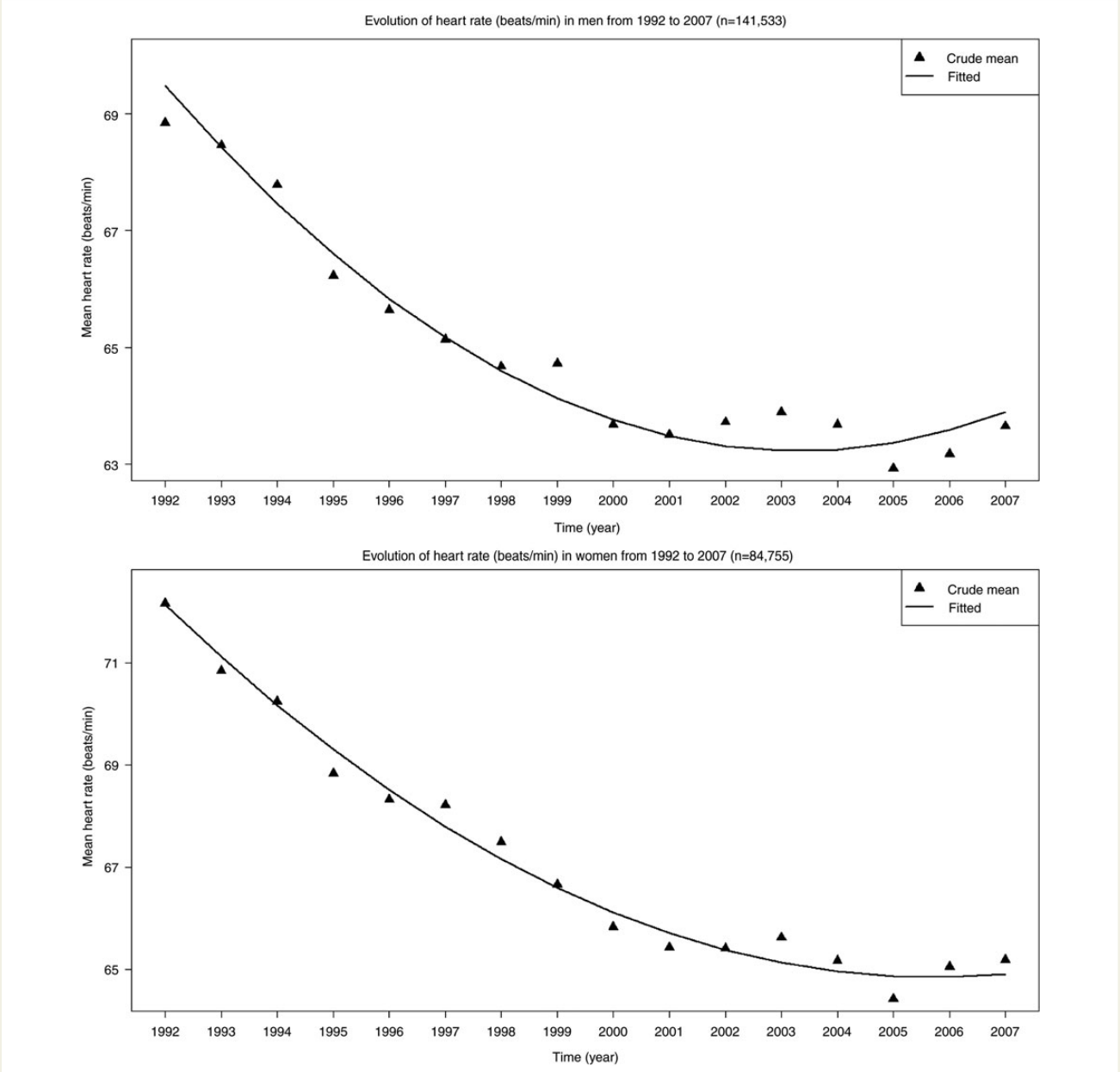

Figure 1 Trends in the mean resting heart rate from 1992 to 2007 in men and women. Fitted curves are adjusted for age, body mass index, blood pressure ≥140/90 mmHg, smoking status, glycaemia ≥7 mmol/L, total serum cholesterol, physical activity, and cardiovascular treatment. Reprinted from ref. 9.

reduction in major vascular events of ~11 per 1000 over 5 years, supporting earlier use of statin therapy in these individuals.[13]

An important question is whether addition of other lipid-modulating agents to statin therapy can further reduce cardiovascular events. Addition of niacin to statin therapy, which can also moderately raise HDL cholesterol serum levels, has now been examined in high-risk patients in the AIM-High and HPS-2-THRIVE study.[14] Both clinical trials failed to demonstrate a further reduction of cardiovascular events by addition of niacin therapy, that, however, caused several adverse effects.[14] Inhibition of the secretory phospholipase A2 by varespladip in addition to statin therapy failed to reduce cardiovascular events in patients with a recent ACS and increased the risk of myocardial infarction.[15] Moreover, CETP-inhibition by dalcetrapib leading to a moderate increase of HDL cholesterol levels did not improve endothelial function[16] and failed to reduce cardiovascular events in patients after an ACS.[17] The difficult search for an effective 'partner' of statins in lipid-targeted prevention of vascular events therefore goes on.[18] The IMPROVE-IT study currently examines the effect of ezetimibe on cardiovascular events in addition to statin

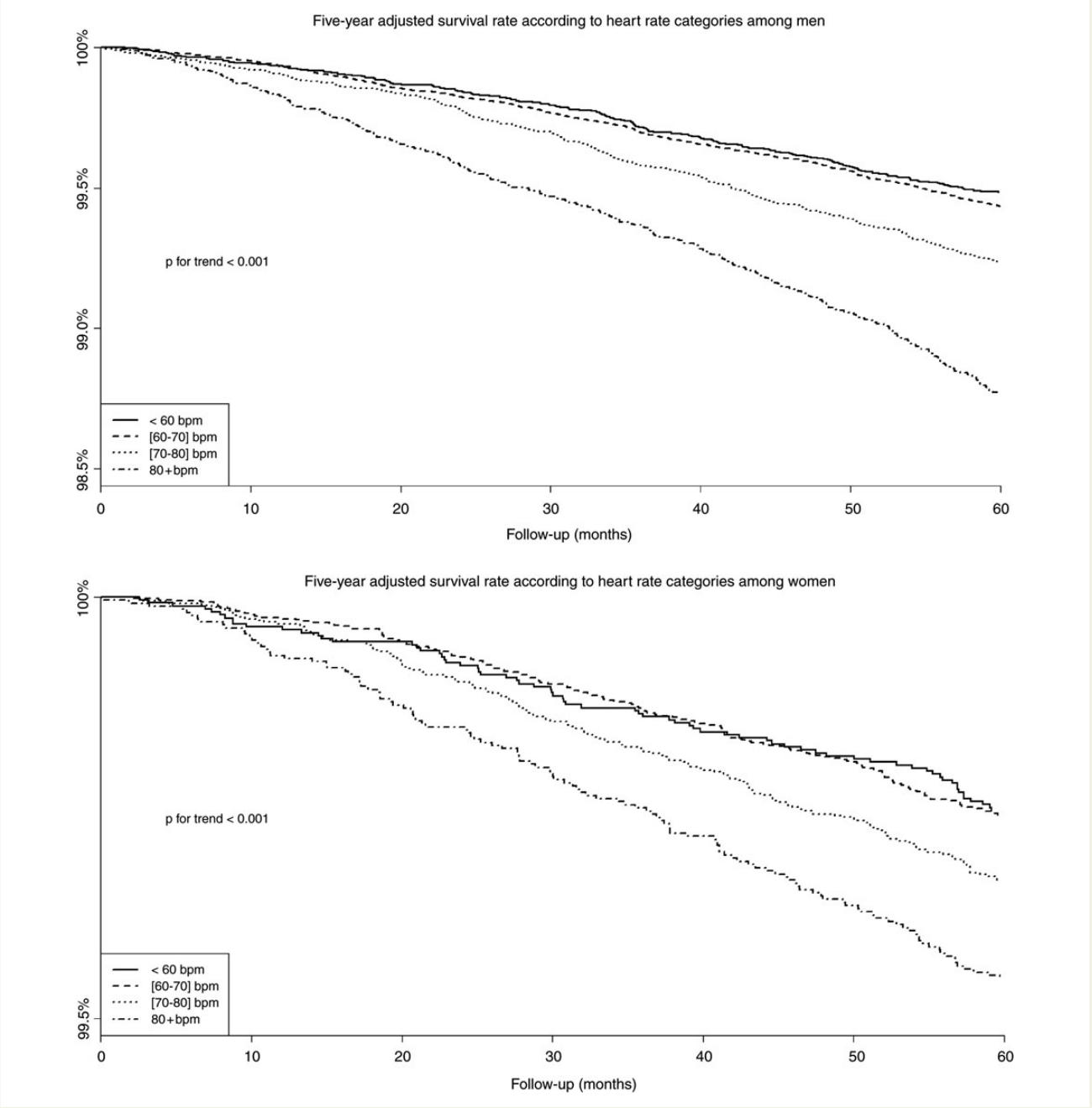

Figure 2 Five-year adjusted survival rates according to heart rate categories in both men and women. Adjustment was made for the same variables as in Figure 1. Reprinted from ref. 9.

therapy. Besides CETP inhibitors with potent LDL cholesterol lowering effects, PCSK9 inhibition by monoclonal antibodies in addition to statin therapy has now entered large-scale clinical trial programmes. Moreover, PCSK9 inhibition by means of RNA interference has recently been shown in a phase-1 study to be a potentially safe mechanism to reduce LDL cholesterol concentration in humans.[19]

The recently published largest genetic association study of blood lipid levels by the Global Lipids Genetics Consortium identified a large number of loci and many candidate genes that may give novel insights into lipid biology. Moreover, it was suggested that in univariate analyses, genetic effects on LDL cholesterol and triglyceride levels predicted an association with coronary disease, but HDL cholesterol levels did not.[20] Furthermore, HDL cholesterol-associated variants had markedly different effects on lipid subphenotypes (such as sphingomyelin), suggesting that functional groupings of HDL cholesterol-associated variants may have to be performed in future studies.[20]

Diabetes and obesity:

First large-scale cardiovascular outcome data for incretine-based treatment of diabetes

Several studies in patients with diabetes mellitus have demonstrated that improved glucose control reduces microvascular complications. However, uncertainty remains whether any glucose-lowering strategy is safe from a CV standpoint or can lower macrovascular complications, such as myocardial infarction, stroke, or CV death. Two large-scale clinical trials have now examined the effects of dipeptidyl peptidase 4 (DPP-4) inhibition by saxagliptin and alogliptin to lower glucose on cardiovascular events. Dipeptidyl peptidase 4 inhibition with saxagliptin did not increase or decrease the rate of ischaemic cardiovascular events, although glycaemic control was improved.[21] In the EXAMINE trial including patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not decreased or increased with the DPP-4 inhibitor alogliptin when compared with placebo.[22] These studies suggest that other approaches are necessary to reduce cardiovascular risk in patients with diabetes.

Lifestyle change difficult to maintain in long-term studies

It is well-established that obesity and diabetes are associated with an increased risk for future cardiovascular events. Intuitively, one would conclude that weight reduction should therefore reduce cardiovascular events in obese diabetics. Surprisingly, the long-term effects of weight loss on CVD remain unknown. In the Look-AHEAD Study the investigators therefore randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). Although weight loss was greater in the intervention group (8.6 vs. 0.7% at 1 year; 6.0 vs. 3.5% at study end) and reduced glycated haemoglobin other cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels the primary outcome (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina) was not significantly reduced (1.83 and 1.92 events per 100 person-years, respectively; HR 0.95; 0.83–1.09; $P = 0.51$).[23] The study reminds us that there are no simple solutions in metabolic syndrome. A key problem in the intervention group was that a large weight reduction after 1 year was followed by weight regain in the remaining study period. Likewise, physical fitness improved significantly at 12 months and deteriorated thereafter. These observations imply that the adherence to the lifestyle intervention was optimal in Year 1 and decreased thereafter. Future lifestyle interventions need to address the long-term intervention compliance as a key problem—possibly using telemedicine or telenursing as tools.

Exercise training: non-responders have impaired chronotropic competence

Endurance training has proven beneficial effects including chronic heart failure patients, such as increase of exercise capacity, quality of life, reduced hospitalization, and most likely reduced mortality (based on meta-analyses[24]). However, rehabilitation specialists all know patients who do not show the expected positive outcomes and the search for predictors for being a non-responder has not yet been very successful. In their article in the *European Journal of Preventive Cardiology* Schmid *et al.* from Berne, Switzerland, assessed 120 consecutive CHF patients with sinus rhythm (peak VO_2 17.3 $\pm$ 5.1 mL/min/kg) who participated in a 3-month outpatient cardiac rehabilitation programme for non-responders (defined as subjects who failed to improve peak VO2 by $>$5%, work load by $>$10%, or VE/VCO_2 slope by $>$5%). Multivariate analysis and receiver operating characteristic (ROC) analysis identified non-reponders with $<$30 b.p.m. for HR reserve, $<$6 b.p.m. for HR recovery, and $<$101 b.p.m. for peak HR. In conclusion, an adequate chronotropic response to exercise seems to be a prerequisite for deriving a clinical benefit from exercise training in chronic heart failure.[25]

Future research perspectives

Research in CVD prevention has traditionally focused on epidemiological research in time trends of risk factor and disease prevalence, on clinical studies in pharmaceutical risk factor control (most notably in diabetes, blood pressure, and lipid control), and experimental research to better understand the vascular biology of atherogenesis. However, by just telling people how to lead a heart-healthy life and by using drugs to control hypertension, diabetes, and hyperlipidaemia we did not succeed in winning the battle against CVD. We know disease mechanisms and have potent drugs, however, patients are too frequently not willing to change their unhealthy lifestyle and their physicians invest more time and money in acute care of complications than in aggressive disease prevention. Several key perspectives for future research in prevention emerge from this situation:

- We need well-designed studies comparing not a single drug treatment but an entire prevention strategy to each other. There is nearly no evidence on how to best educate and motivate patients to change their lifestyle and to maintain regular physical activity and healthy eating habits in the long run. Optimizing communication and motivation is key to influencing lifestyles.
- Efforts in individual prevention education will be futile if not backed up by coherent legislative frameworks which reward healthy lifestyles and make risky lifestyle behaviours unattractive. There is clear evidence from epidemiological studies from which laws and taxation mechanisms work[3]—the challenge is to implement them.
- Physicians follow the priorities of their health-care systems. If reimbursement for preventive activities is not adaequate there may be too little motivation to invest time and effort in prevention. Pilot studies are needed in which reimbursement mechanisms or other incentives work best in motivating physicians to focus on prevention and to shift from a procedure centred to an outcome-focused performance.

In a recent article published simulaneously in the *European Heart Journal*, *Circulation*, *JACC* and the *World Heart Journal* the large cardiovascular societies called for action to achieve the 25 by 25 goal. The title of the article was ‘Our time: a call to save preventable death from

CVD' and timely it is indeed to make prevention of CVD the health priority that it should be.[26]

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