Cardiologia Hungarica
2019; 49: 317–329.

The year in cardiology 2018: prevention

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Introduction

Cardiovascular prevention has been in the focus of important studies in 2018. Several large-scale clinical studies have further supported the strong association of an unhealthy lifestyle with an increased cardiovascular risk.

New data have become available for the novel treatment approaches for dyslipidemia (including large scale clinical outcomes data for PCSK9 inhibition and recommendations for their use in clinical practice) and novel data on the impact of SGLT2 inhibition on the risk of heart- and kidney failure diabetic patients. More-over, new European Guidelines on Arterial Hypertension have been published in 2018 and several moderate-sized randomized trials have investigated the efficacy and safety of advanced renal denervation treatments in hypertension. In the field of antithrombotic therapy it has become clear that the use of aspirin in primary prevention does not have a favorable risk-benefit ratio, whereas in patients with atherosclerotic cardiovascular disease (CVD) at very high risk, the addition of low-dose factor Xa inhibition to aspirin can provide a net clinical benefit. New data on inflammation as a treatment target for CVD prevention have become available.

Lifestyle

Sedentary behaviour has been associated with increased cardiovascular risk. A large prospective registry (PURE) on 130 843 participants without pre-existing ASCVD recorded physical activity during a mean of 6·9 years of follow-up. This large analysis suggests that increasing physical activity may represent a simple, low cost global strategy that could reduce CVD events and deaths irrespective of age, gender or country of origin (1).

Another observational study performed on 17,989 men and women found that physical fitness in middle age is tied not only to a lower risk of CVD death but also to a lower risk of later-life depression. Subjects with higher fitness showed lower rates of inflammation which may contribute to both ASCVD and depression (2).

A recent controlled, randomized, supervised 6 months training study revealed that endurance training compared to baseline and to the control group increased telomerase activity and telomere length which are both important for cellular senescence, regenerative capacity and thus, healthy aging. Interestingly, resistance training did not exert these effects (3). The data support the ESC's current guideline recommendations that resistance exercise should be complimentary to endurance training rather than a substitute. The data identify telomerase activity and telomere length as sensitive cellular parameters to measure preventive effects of exercise interventions. Individual training recommendations guided by measurement of parameters associated with cellular senescence and training response may improve both adherence to and efficacy of exercise training programs in cardiovascular prevention.

Interesting results were obtained in a study performed on 1,307 individuals (1,038 women) with CHD from the HUNT (Nord-Trøndelag Health Study). In this study sustained physical activity was associated with substantial CVD risk reduction while no mortality risk reductions were noted associated with weight loss in individuals

with CHD. Surprisingly, a reduced mortality risk was associated with weight gain in individuals who were normal weight at baseline (4).
„Stress“ is also considered to increase CVD risk. A study was performed based upon data on seven cohort studies initiated between 1985 and 2002 in Finland, France, Sweden, and the UK, to examine the association between work stress and mortality taking into consideration cardiometabolic diseases at baseline (5). Work stress was denoted as job strain or effort-reward imbalance at work. The study was performed on 102,633 subjects with, of whom 3,441 had prevalent cardiometabolic disease at baseline and 3841 died during a mean follow-up of 13.9 years. In men with cardiometabolic disease, age-standardized mortality rates were substantially higher in those with job strain than in those without it and this mortality difference was almost as great as that for current smoking versus former smoking and greater than those due to hypertension, elevated total cholesterol, obesity, physical inactivity, and high alcohol consumption. Excess mortality associated with job strain was also noted in men with cardiometabolic disease who had achieved treatment targets, including those with a healthy lifestyle, with normal blood pressure and no dyslipidaemia. Importantly, in all women and in men without cardiometabolic disease, relative risk estimates for the work stress-mortality association were not significant.
A large analysis of 79,201 working men and women from Sweden and Denmark reveals that bullying and violence at work represents a risk marker for CVD (6). After adjustment for age, sex, country of birth, marital status and educational level, being bullied at work versus not was associated with a hazard ratio of 1.59 (95% CI 1.28–1.98) for CVD. Experiencing workplace violence versus not was associated with a hazard ratio of 1.25 (95% CI 1.12–1.40) for CVD. The population attributable risk was 5.0% for workplace bullying and 2.9% for workplace violence. The analysis shows that bullying and violence are common at workplaces and those exposed to these stressors are at higher risk of CVD.

Obesity

Analysis of 296,535 participants (57.8% women) from the UK biobank shows that in individuals without comorbidities adiposity measures have a near linear association with CVD risk: 1 SD increase in waist circumference was associated with a hazard ratio of 1.16 for women and 1.10 for men with similar magnitude of associations for 1 SD increase in waist-to-hip ratio, waist-to-height ratio, and percentage body fat mass (7).
Identifying an effective diet to reduce the excessive body weight is difficult. This question was addressed by the DIETFITS Randomized Clinical Trial, a 12-month weight loss diet study on 609 participants. It revealed no significant difference in weight change between a healthy low-fat diet vs. a healthy low-carbohydrate diet. Neither genotype pattern nor baseline insulin secretion was associated with the dietary effects on weight loss (8).
Lorcaserin, a selective serotonin 2C receptor agonist that modulates appetite, was studied in the CAMELLIA–TIMI 61 trial on 12,000 overweight or obese patients with atherosclerotic CVD or multiple cardiovascular risk factors. After a median follow-up of 3.3 years the sustained weight difference was approximately 2 kg between lorcaserin (10 mg twice daily) or placebo without a higher rate of major cardiovascular events. The rate of major cardiovascular events was 4.1% and 4.2% per year, respectively. There was a higher rate of serious hypoglycemia in the lorcaserin group (13 vs. 4) (9).

Dietary supplementation with omega-3 fatty acids

Some of the most analyzed aspects of diet influencing CVD were the effects of omega-3 fatty acids, the effects of salt and the effects of coffee consumption. The very large ASCEND study randomized 15,480 patients with diabetes but without evidence of CVD to 1-g capsules containing either omega-3 fatty acids or olive oil as comparator (no placebo), the primary outcome was a first serious CVD event. During a mean follow-up of 7.4 years, a serious CVD event occurred in 8.9% in the omega-3 fatty acid group and in 9.2% of the patients in the placebo group (P=0.55). Death from any cause occurred in 9.7% and 10.2%, respectively. This study did not find any significant difference in the risk of serious CVD events between those who were assigned to receive dietary omega-3 fatty acid supplementation and those who were assigned to receive placebo (10).
The VITAL Research Group used a two-by-two factorial randomization to test the effects of vitamin D_3 (2000 IU per day) and marine n−3 fatty acids (1 g per day) in the primary prevention of CVD and cancer among men ≥50 years and women ≥55 years of age. VITAL included 25,871 individuals with a median follow-up of 5.3 years. The study revealed two important results: Neither supplementation with n−3 fatty acids nor the intake of vitamin D result in a lower incidence of cardiovascular events or invasive cancer compared to placebo (11, 12). These dietary supplements are therefore not associated with benefit.
Similar results were obtained in a Cochrane systematic review that encompassed findings of 79 studies involving more than 112,000 subjects. The results of this analysis suggest that increasing dietary consumption of omega-3 fatty acids (alpha linolenic acid and the long-chain omega-3 fatty acids – eicosapentaenoic acid or docosahexaenoic acid) does not reduce risk for

CVD events, deaths from CHD, strokes, or cardiac arrhythmias (13).
In contrast to the dietary supplementation with omega-3 fatty acids, a large study (REDUCE- IT) that used the high dose 4g of icosapent ethyl, a purified eicosapentaenoic acid ethyl ester, showed positive resuts(14).This strategy is different from the concept of dietary supplementation and is therefore discussed in the section on dyslipidemia below.

Salt

It is well known that excessive dietary salt (sodium) intake increases CVD risk, particularly by influencing blood pressure. This was confirmed in a meta-analysis analyzing the effects of dietary sodium intake on stroke. It included 14 prospective cohort studies, one case-cohort study, and one case-control study (total n=261,732) with 10,150 cases of stroke. Higher sodium intake and higher dietary sodium-to-potassium ratio were associated with a higher risk of stroke. The authors suggest that reducing dietary sodium-to-potassium ratio might be considered as a supplementary approach in parallel with the decrease in sodium intake in order to decrease stroke risk (15). Nevertheless, the results of Prospective Urban Rural Epidemiology (PURE) study suggest that not everyone needs to cut back on salt in order to reduce their CVD risk. In this analysis, 369 communities were assessed for blood pressure and 255 for CVD outcomes over a median of 8.1 years. Participants were adults ages 35–70 years in the general population who had no CVD. The results suggest that for every 1-g increase in sodium intake, people across 18 countries had an overall additional 0.73 CVD events per 1,000 years (P<0.0001). The relationship was non-linear, however, such that each extra gram of sodium's link to CVD event rates on the community level depended on the population's average daily consumption. The highest tertile (mean 5.75 g/day) had a non-significant trend for greater risk (P=0.07). The associations between sodium intake and cardiovascular events did not change when adjusted for age, sex, and blood pressure, suggesting that the effects of sodium intake on CVD events are largely unrelated to the effects of sodium intake on blood pressure but the data clearly indicated that all major CVD outcomes decreased with increasing potassium intake in all communities. The results of this study suggest that a population-specific strategy for sodium reduction targeted at countries or communities with sodium intake greater than 5 g/day would be preferable to a population-wide strategy of sodium reduction to reduce CVD and premature deaths while increasing the consumption of foods that are rich in potassium (e.g., fruits and vegetables) should be stimulated population wide (16). PURE is a large ongoing epidemiology study and it is by some researchers considered controversial since the authors of this study previously published results indicating that diets rich in fats don't increase mortality risk and that eating more than a few servings of fruits, vegetables, and legumes doesn't amount to more cardiovascular benefit, as well as that salt restriction reduced the risk of CHD, stroke, or death only in patients who had high blood pressure, while salt restriction could be harmful if salt intake became too low (17).

Coffee

Coffee consumption and its influence on CVD has been debated for decades. In an observational study performed on 903 subjects drinkers of ≤1 cup of coffee/day and >1 cup/day showed lower CVD mortality than non-drinkers of coffee during 6 years of follow up, respectively (p trend = 0.04). This association of coffee with CVD mortality attenuated after 12 years of follow-up. No significant association was observed with all-cause or cancer mortality, neither for caffeinated and decaffeinated coffee. Coffee consumption was associated with lower CVD mortality in elderly subjects (18). In another study performed on 3042 healthy adults (1514 men) 10-year follow-up was performed in 2583 participants (15% of the participants were lost to follow-up). The multivariate analysis revealed a J-shaped association between daily coffee drinking and the risk for a first CVD event in a 10-year period. Particularly, the odds ratio for low (<150 ml/day), moderate (150-250 ml/day) and heavy coffee consumption (>250 ml/day), compared to abstention were 0.44 (95% CI 0.29–0.68), 0.49 (95% CI 0.27–0.92) and 2.48 (95% CI 1.56–1.93), respectively. This inverse association could not be verified among participants with the metabolic syndrome. The data of this study also support the protective effect of drinking moderate quantities of coffee (equivalent to approximately 1-2 cups daily) on CVD risk (19). Similar results were obtained based upon data of 498 134 middle-aged subjects. 78% were coffee drinkers. Over 10 years of follow-up, 14,225 deaths occurred. Coffee drinking was inversely associated with all-cause mortality. Including among those drinking 8 or more cups per day and those with genetic polymorphisms indicating slower or faster caffeine metabolism. The findings of this study provided further reassurance that coffee drinking can be a part of a healthy diet (20). However, all association studies on nutrition are prone to bias, e.g. by socioeconomic factors, environment or education.

Environmental pollution

Environmental pollution may have detrimental influence on CVD risk. In a meta-analysis the results of 37 studies (348 259 participants), CVD outcomes were analyzed concerning the effects of environmental exposure.

Exposure to arsenic, lead, cadmium, and copper was associated with an increased risk of CVD and CHD while mercury was not associated with CVD risk. The findings of this study reinforce the importance of environmental toxic metals in CVD risk (21).
Another interesting study compared subjects aged 60 years and older with stable ischaemic heart disease or stage 2 Global initiative for Obstructive Lung Disease (GOLD) COPD who had been clinically stable for 6 months with age-matched healthy volunteers. All participants had abstained from smoking for at least 12 months and medications were taken as recommended by participants' doctors during the study. Participants were randomly assigned to do a 2 h walk either along a commercial street in London (Oxford Street) or in an urban park (Hyde Park). Concentrations of black carbon, NO2, PM10, PM2.5, and ultrafine particles were higher on Oxford Street than in Hyde Park. The authors show that short-term exposure to traffic pollution prevents the beneficial cardiopulmonary effects of walking in people with COPD, ischemic heart disease, and those free from chronic cardiopulmonary diseases. They also suggest that medication use might reduce the adverse effects of air pollution in individuals with ischemic heart disease (22).

Smoking

Patient that attempt to quit smoking are worried about putative health risk associated with the possible weight gain. To assess the relationship of smoking cessation and BMI change with CVD risk, more than 100.000 men from a claims database in Korea were grouped into sustained smokers, quitters with BMI gain, quitters without BMI change, quitters with BMI loss, and non-smokers (23). Compared to the sustained smokers, the risk of MI was significantly reduced in both quitters with BMI gain (HR 0.33) and without BMI change (HR 0.55), but no significant association was found in quitters with BMI loss. Non-smokers had lower risk of MI (HR 0.37) compared to the sustained smokers. The data show that post-cessation BMI change does not reduce the protective association of smoking cessation with MI and stroke.
Many patients believe that smoking very few cigarettes is “safe”. A meta-analysis including 141 cohort studies assessed the relation between cigarette consumption and cardiovascular disease to quantify the risk of smoking one to five cigarettes/day (24). The data show that men who smoke about one cigarette per day have a 48% higher risk of heart disease than never smokers and a 25% higher risk of stroke. The estimates are even higher in women: 57% for heart disease and 31% for stroke compared with never smokers. People who smoke about one cigarette each day have about 40-50% of the excess risk associated with smoking 20 per day (CHD and stroke). The authors concluded that smoking only about one cigarette per day carries a risk of CHD and stroke much greater than expected: around half that for people who smoke 20 per day. There is no safe level of smoking exists for CVD. Smokers should aim to quit instead of cutting down to significantly reduce their risk of CVD (24).

Dyslipidemia

High-dose EPA: One of the most discussed studies in 2018 was the Reduction of Cardiovascular Events with icosapent Ethyl–Intervention Trial (REDUCE-IT) (14). N=8179 patients with established ACSVD (70.7% of the population) or with diabetes and other risk factors (29.3%), and who had a fasting triglyceride level of 135 to 499 mg/dl plus a LDL-C < 100 mg/dl were assigned to receive 2 g of icosapent ethyl twice daily or mineral oil as comparator. The median duration of follow-up was 4.9 years (maximum, 6.2 years). The active treatment, 4g of icosapent ethyl baseline, was tested on top of statin therapy. At baseline, the median triglyceride level was 216 mg/dl and LDL-C was 75 mg/dl. Compares to the mineral oil placebo group, triglycerides were 19.7% (44.5 mg/dl) lower and LDL-C 6.6% (5.0 mg/dl) lower in the icosapent ethyl group.
The study reports positive results: the primary MACE end-point was reduced by 25%. Similarly, the key secondary end point of cardiovascular death, myocardial infarction, or stroke was reduced by 26% (11.2% vs 14.8). The rates of additional pre-specified ischemic outcomes were consistently reduced, including cardiovascular death that was reduced by 20% (4.3% vs. 5.2%). Icosapent ethyl treatment was associated with increased hospitalization for atrial fibrillation (3.1% vs. 2.1%, P=0.004) and a trend for increased serious bleeding events (2.7% vs 2.1%, P=0.06). Gastrointestinal symptoms were similar between groups.
The high-dose intervention and the formulation (a highly purified and stable EPA ethyl ester) used in REDUCE-IT is markedly different from the concept of dietary supplementation of n−3 fatty acids that has no effect on ASCVD (e.g. see ASCEND and VITAL data above). A previous positive study in Japan using a similar concept (JELIS) showed that the risk of ischemic events was reduced in the group that received the combination of statin and high dose EPA treatment (25). Plasma EPA levels in JELIS (170 μg/ml) were similar to that attained with a daily dose of 4 g of icosapent ethyl in a Western population (183 μg/ml) 26, 27). The underlying mechanisms responsible for the benefit of icosapent ethyl are not known. Possible explanations may include the lowering of triglycerides, potential beneficial effect on platelets and on cell membranes as well as anti-inflammatory actions, however, none of these potential effects can fully explain the quantitatively

remarkable reduction of ASCVD outcomes reported in REDUCE-IT, therefore additional clinical and mechanistic studies are needed.

PCSK9 inhibition: In 2018 the results of the second large clinical outcome trial of PCSK9 inhibition by a human monoclonal antibody, the ODYSSEY Outcomes study, have been presented. 18,924 patients who had an Acute Coronary Syndrome (ACS) within the previous 12 months and who had residual LDL-C levels ≥70 mg/dL, non–HDL-C ≥100 mg/dL or apolipoprotein B ≥80 mg/dL after two to 16 weeks of intensive or maximally tolerated statin therapy (atorvastatin or rosuvastatin) had been included. After a median follow-up of 2.8 years there was a significant reduction of the primary endpoint of major adverse cardiovascular events (MACE) – the time to first occurrence of CHD death, nonfatal myocardial infarction (MI), unstable angina requiring hospitalization or ischemic stroke –in the patients treated with alirocumab versus placebo (9.5 vs. 11.1 percent) (28).

Practical recommendations for clinical use of PCSK9 inhibition have been published by a joint task force of the European Society of Cardiology (ESC) and the European Atherosclerosis Society in 2018 (29, 30). The molecular reduction of PCSK9 using a siRNA approach (Incliseran) has been further examined. Inclisiran produced a significant and prolonged reduction in atherogenic lipoproteins in 501 patients at high cardiovascular risk with increased LDL-cholesterol levels, suggesting that inhibiting synthesis of PCSK9 through siRNA may be a viable alternative to other approaches which target PCSK9 (31, 32).

HDL cholesterol: A large scale genetic study using the resource of whole-genome sequenced Icelanders indicated that SCARB1 mutations associate with high-density lipoprotein cholesterol levels, but not with coronary artery disease (33). These findings further support the concept that there is not necessarily a causal link between HDL cholesterol plasma levels and the risk of coronary disease (34).

n3-fatty acids/triglycerides: In contrast to the previously mentioned results of ASCEND trial 10, the REDUCE-IT study using a higher dose of n3-fatty acids (4 g/day) resulted in patients with persistent elevated triglycerides (median baseline 216 mg/dL) and either established CVD (secondary prevention cohort) or diabetes mellitus and at least one other CVD risk factor (primary prevention cohort) a significant reduction of the primary endpoint of first occurrence of MACE (including cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization) was observed.

Triglycerides: Elevated triglycerides (TGs) are also a risk factor for CVD but extremely elevated TGs are a risk factor for pancreatitis. Familial chylomicronaemia syndrome (FCS) is a rare, inherited disorder characterized by impaired clearance of triglyceride (TG)-rich lipoproteins from plasma due to the lack of lipoprotein lipase (LPL) leading to severe hypertriglyceridemia (HTG). Pragmatic clinical scoring, by standardizing diagnosis, was developed to help differentiate FCS from multifactorial hypertriglyceridemia. This may alleviate the need for systematic genotyping in patients with severe HTG (35).

Lipoprotein (a): A Mendelian Randomization Analysis has been published that aimed to determine the clinical benefit of lowering of Lp(a) and has suggested that large absolute reductions in Lp(a) of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of coronary disease similar in magnitude to what can be achieved by lowering LDL-C level by 38.67 mg/dL (ie, 1 mmol/L) (36).

Familial hypercholesterolemia (FH): A large survey of 63 countries shows that FH represents an under-diagnosed and under-treated public health concern. Efforts and initiatives to improve FH knowledge and management are underway, but awareness and support are greatly needed (37).

Diabetes

A paradigm shift in the management of type 2 diabetes (T2DM) has been observed with sodium/glucose co-transporter 2 (SGLT2) inhibitors. Empagliflozin was the first glucose-lowering drugs able to reduce cardiovascular mortality and hospitalizations for heart failure (HHF) in T2DM patients at high cardiovascular risk. In this regard, a recent post-hoc analysis of the EMPA-REG OUTCOME trial investigated whether empagliflozin was equally effective on risk of CVD death and HHF across the spectrum of HF risk (38). This study considered patients without HF at baseline. The investigators found that 67% of them had low-to-average (<10%), 24% high (10-20%) and 5% very high (20%) 5-year risk of HF. For the first time, these results suggest that empagliflozin, and perhaps other SGLT2 inhibitors, are effective for the prevention of HF in T2DM. Ongoing trials such as DAPA-HF and EMPEROR-Reduced will help us to appreciate the potential of SGLT2 inhibitors to prevent adverse remodeling and dysfunction in patients without T2DM.

An analysis of the Get With The Guidelines-Stroke registry, enrolling >409 000 patients, found that after an ischemic stroke, patients with diabetes compared to those without experienced higher risk of death and hospitalization for CVD and non-CVD events as well as higher rates of readmission for stroke recurrence (39). Patients in the EMPA-REG OUTCOME and CANVAS trial programme, randomized to empagliflozin and canagliflozin, experienced a lower rate of major adverse cardiovascular events (MACE) than those randomized to placebo. However, no protection from stroke was observed but rather a trend toward increased rates of non-fatal stroke was found in the group treated with

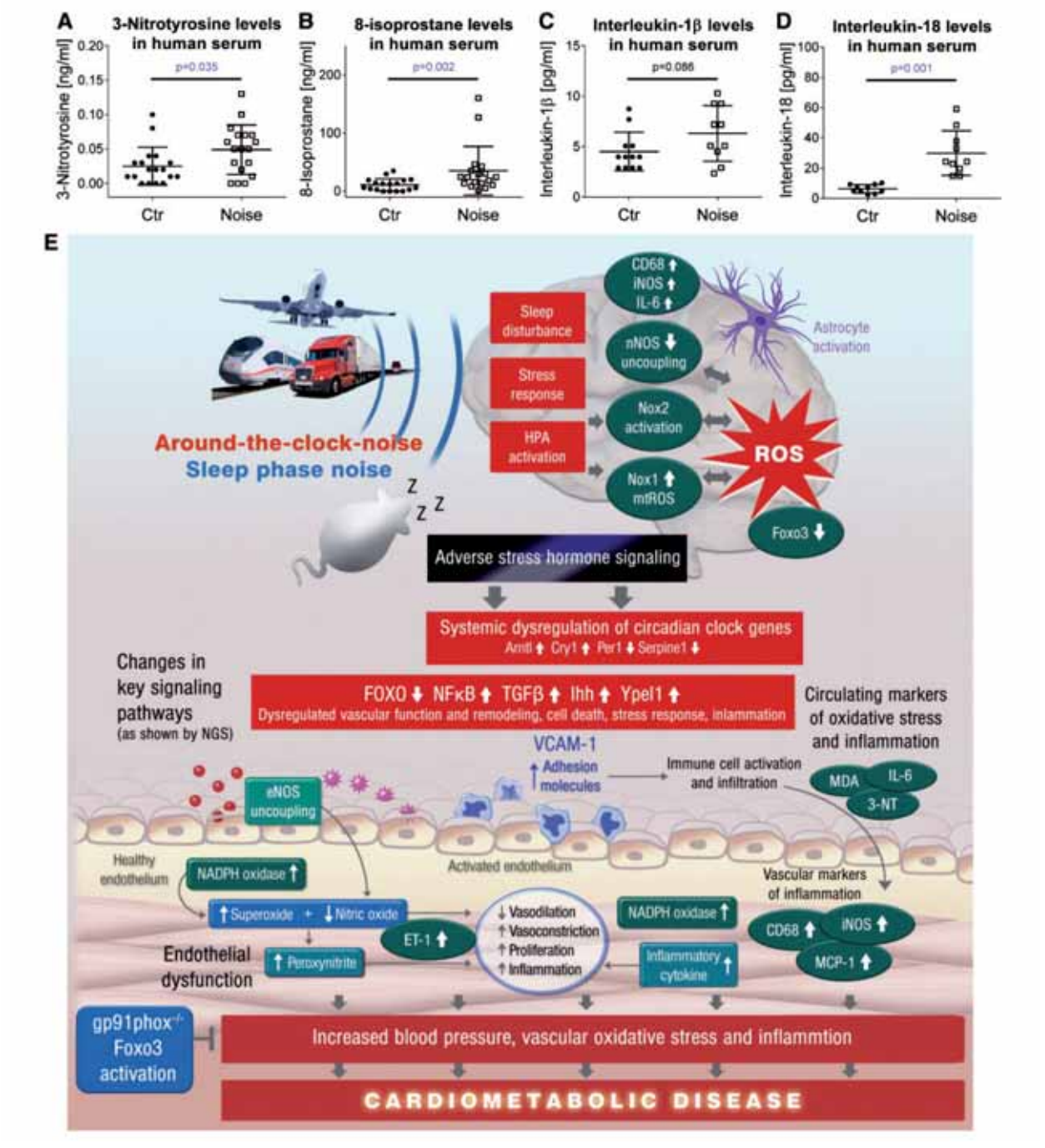

Figure 1. Oxidative stress markers in serum of noise-exposed human subjects. 3-nitrotyrosine (3NT)-positive proteins (A), 8-isoprostane concentrations (B) and markers of inflammation [IL1ß by trend (C), IL-18 significant (D)] are also increased in serum of human subjects. (E) Summarizing central scheme: around the clock and sleep phase noise triggers cerebral oxidative stress and a neuroinflammatory phenotype that translates the adverse effects of noise to the vascular and systemic level. Noise via the neuronal pathways triggers vascular oxidative stress and inflammation with subsequent endothelial dysfunction, and increases in blood pressure, all of which contribute to the development and progression of atherosclerotic CVD. (from KröllerSchön S, Daiber A, Steven S, Oelze M, Frenis K, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. Eur Heart J 2018; 39: 3528–3539).

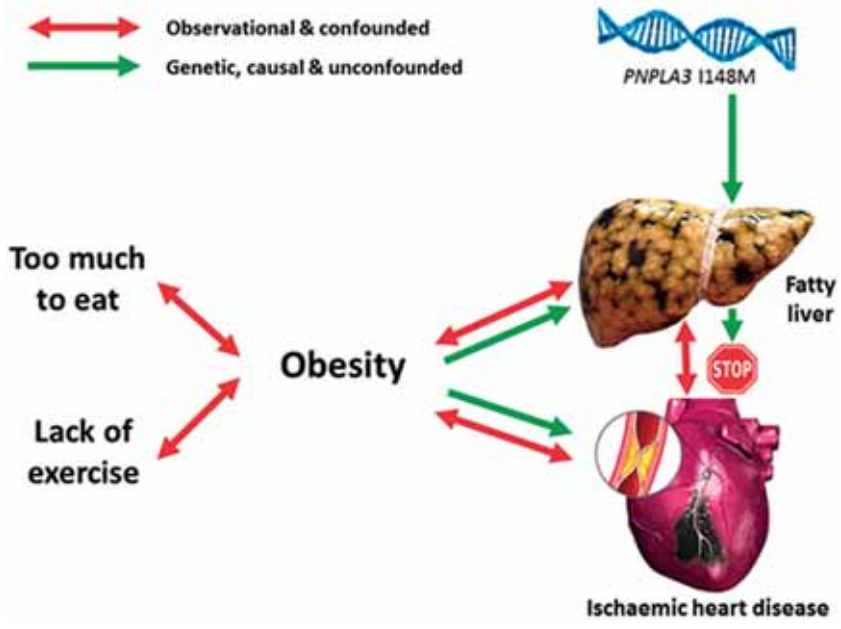

Figure 2. To circumvent confounding and reverse causation between high caloric intake combined with lack of exercise leading to obesity, NAFLD and CHD, a genetic variant in PNPLA3, I148M, as used as a proxy for liver fat content and NAFLD in a Mendelian randomization design. PNPLA3 I148M genotype, a robust and specific cause of NAFLD, seems not to be associated with risk of CHD. (from Lauridsen BK, Stender S, Kristensen TS, Kofoed KF, Køber L, Nordestgaard BG, Tybjærg-Hansen A. Liver fat content, non-alcoholic fatty liver disease, and ischaemic heart disease: Mendelian randomization and meta-analysis of 279013 individuals. Eur Heart J 39: 385–393)

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empagliflozin. In contrast, patients randomized to the long-acting GLP-1 receptor agonist liraglutide in the LEADER trial showed a reduced risk of stroke rates. Moreover, in the SUSTAIN-6 trial with semaglutide the significant reduction in MACE was mainly driven by a reduction in non-fatal stroke. The reported evidence that diabetes worsens the long-term outcome after an ischemic stroke indicates that a comprehensive management of CV disease in diabetes remains a moving target.

The long-term cardiovascular outcome trial, CARMELINA, which studied the impact of linagliptin in patients with type 2 diabetes and high CV risk met its primary endpoint with linagliptin demonstrating a similar cardiovascular safety profile compared to placebo when added to standard of care (40). In contrast to saxagliptin in SAVOR-TIMI 53, linagliptin did not increase hospitalization for heart failure.

Interestingly, results from the Dapagliflozin Effect on CArdiovascular Events-TIMI 58 (DECLARE) (41) show that SGLT-2 inhibitor dapagliflozin may reduce CV death or hospitalizations for heart failure (HHF) in patients with type 2 diabetes. The DECLARE-TIMI 58 is a phase 3, double blind, randomized, cardiovascular outcomes trial in 17.160 patients with type 2 diabetes and multiple risk factors (n=10.186) or established CVD (n=6.974). The trial evaluated the effects of 10 mg dapagliflozin daily versus placebo with a median follow-up of 4.2 years. In the primary safety outcome analysis dapagliflozin was non-inferior to placebo for MACE (CV death, myocardial infarction, or ischemic stroke). In the two primary efficacy analysis, dapagliflozin did not result in a lower rate of MACE (8.8% vs. 9.4% in the placebo group, HR 0.93; p=0.17) but significantly reduced the other prespecified primary efficacy end-point CV death or HHF (4.9% vs. 5.8%; HR 0.83; p<0.005). These results occurred across multiple subgroups showing that dapagliflozin prevent CV event regardless of a history of CVD or HF. Dapagliflozin is safe and generally well tolerated with an increase in genital infections and diabetic ketoacidosis, no difference in amputations, stroke and fracture compared to the placebo. Furthermore, a recent systematic review and meta-analysis of the three CVOTs support this conclusion (42). Compelling evidence suggest that SGLT2i should now be considered in most people with type 2 diabetes even in those without established CVD but with multiple risk factors.

A certain degree of controversy remains regarding the appropriate blood pressure goals for patients with dia-

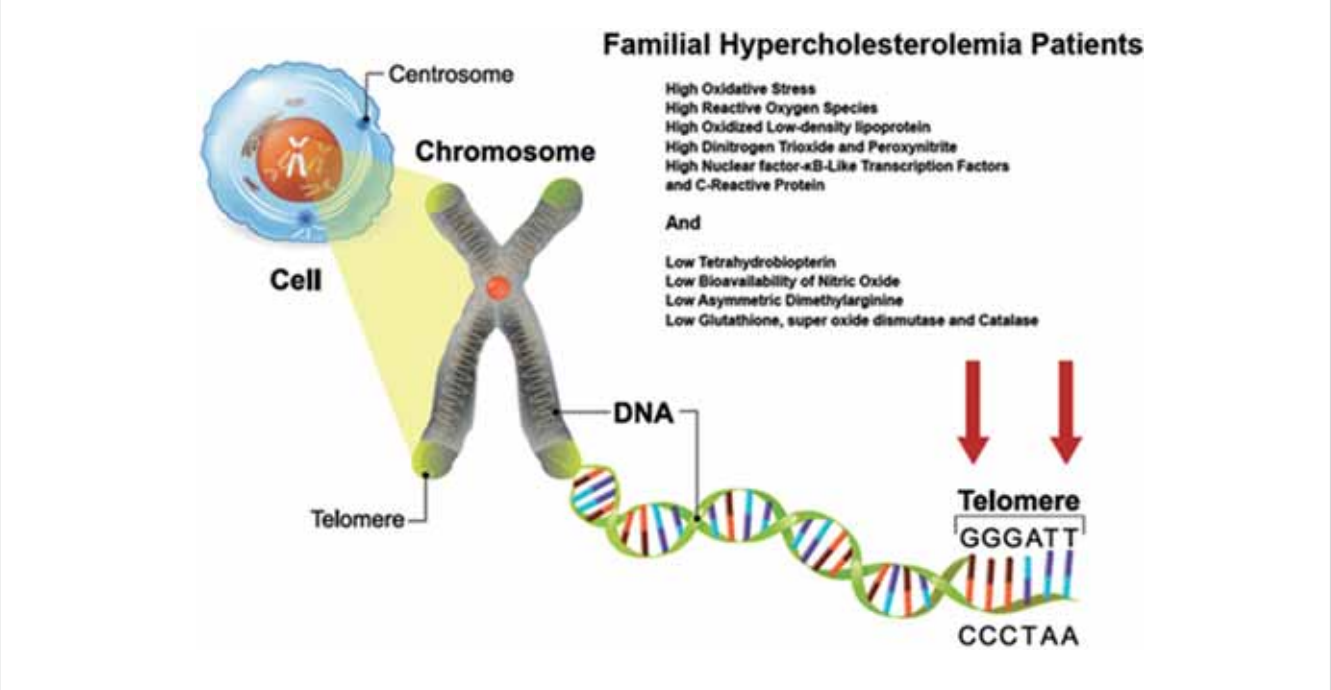

Figure 2. Proposed pathways on how elevated LDL-cholesterol in familial FH patients might accelerate the telomere shortening. (from Banach M, Mazidi M, Mikhailidis DP, Toth PP, Jozwiak J, et al. Association between phenotypic familial hypercholesterolaemia and telomere length in US adults: results from a multi-ethnic survey. Eur Hear J 2018; 39: 3635–3640)

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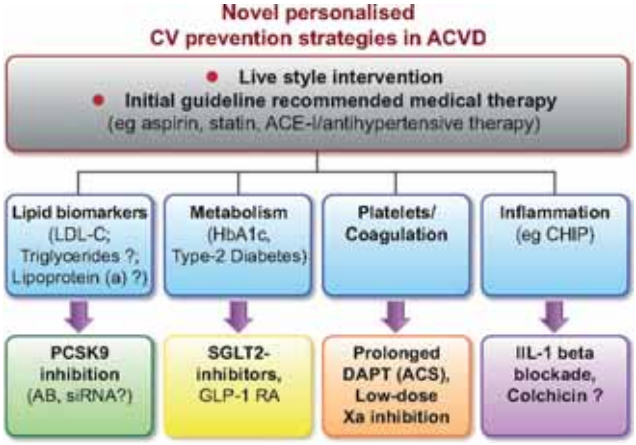
betes, atherosclerotic CVD, advanced age and renal insufficiency (3). In this perspective, a post-hoc analysis of SAVOR-TIMI 53 trial, including a large, well-characterized population of patients with T2DM at elevated CV risk, assessed the optimal blood pressure for prevention of CVD outcomes (44). Adjusted risk of the composite endpoint of CVD death, MI, or ischemic stroke showed U-shaped relationship with baseline systolic (SBP) and diastolic blood pressure (DBP), with nadirs at SBP 130-140 mmHg or DBP 80-90 mmHg. Diastolic blood pressure <60 mmHg was associated with increased risk of MI compared to DBP 80-90 mmHg. Although this observational analysis demonstrates a robust association between DBP and MI, the underlying mechanisms and prognostic implications deserve further investigation.

As a consequence of media reports we are experiencing an exaggerated public perception of the adverse effects of statins. In this regard, a timely systematic review of randomized controlled trials and genetic studies focused on the perception vs evidence of statins-related adverse effects (45). Main results were that statin therapy is associated with a modest increase in risk of new-onset diabetes (about 1/1000 patient-years). This risk is significantly higher in patients with metabolic syndrome or prediabetes. Statins do not adversely affect cognitive function and are not associated with clinically significant deterioration of renal function or development of cataract. Transient increase in liver enzymes occurs in 0.5-2.0% of patients treated with statins. Furthermore, there is no evidence of increased risk of haemorrhagic stroke in patients without cerebrovascular disease and the small increase in risk observed in the setting of a prior stroke by the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study has not been confirmed in randomized controlled trials and observational studies. The authors of this comprehensive literature search covering 2000–2017 concluded that “established CVD benefits of statin therapy far outweigh potential risks”.

The ASCEND (A Study of Cardiovascular Events in Diabetes) (46) trial randomized 15.480 patients with diabetes mellitus and no evident CV disease to aspirin 100 mg/od or placebo (exclusion criteria: clear indication or clear contra-indication to aspirin). Participants were also randomized 1:1 to receive 1g of n-3 fatty acid once daily or matching placebo. The primary efficacy outcome (non-fatal MI, non-fatal stroke transient ischemic attack, death from any cause) occurred in 658 patients (8.5%) on aspirin vs. 743 (9.6%) on placebo (RR: 0.86, 95% CI: 0.79–0.97, P=0.01). Major bleeding (intracranial, sight threatening, gastro-intestinal or other serious bleeding occurred in 314 (4.1%) patients on aspirin vs. 245 (3.2%) on placebo (RR: 1.29, 95% CI: 1.09–1.52, P=0.003). Most excess was due to gastro-intestinal (GI) bleeding. Thus, risk of the prima-



TAKE HOME FIGURE. Over the past year numerous data have suggested that depending on individual patient characteristics novel therapeutic approaches can reduce cardiovascular risk. These novel therapeutic approaches, such as PCSK9 inhibition, SGLT-2 inhibition, low-dose Xa inhibition or Interleukin-1 beta inhibition have been shown to lower cardiovascular risk allowing for a more tailored individual preventive treatment in patients at particular high cardiovascular

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ry efficacy outcomes was significantly reduced by 12% in patients taking aspirin vs. placebo (absolute risk reduction 1.1%). In exploratory analyses, the difference in risk was seen mainly in the first 5 years. Aspirin was also shown to reduce the risk of the secondary outcome (non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, death from any vascular cause or revascularization) by 12% (absolute risk reduction 1.3%). However, patients receiving aspirin showed a 29% higher risk of major bleeding vs those randomized to placebo (4.1% vs. 3.2%, absolute risk reduction 0.9%). Notably, there was no difference in the occurrence of fatal bleeding and of fatal/non-fatal cancer across the study groups. A substantial proportion of the major bleedings were in the upper GI tract, which might have been prevented with a proton pump inhibitor (PPI) as shown by a very large meta-analysis of individual data from randomized control trials demonstrating that PPIs substantially protect from upper GI bleeding with an odd ratio of approximately 0.20 (47). In this regard, it should be emphasized that only one out of four ASCEND patients were being treated with a PPI at the end of the study. Using a two-factorial design, n-3 fatty acids reported neutral results (45). In summary, the findings of the ASCEND trial provides a direct evidence of the balance of benefits and hazards of aspirin use for prevention purpose in contemporary patients with diabetes but without history of cardiovascular disease receiving other cardio-protective treatments such as statins and blood-pressure lowering drugs.

Arterial Hypertension

In 2018 the new joint European Hypertension Guidelines have been presented and published (48). In these guidelines initial antihypertensive combination treatment is recommended preferably in a single pill for most patients, that is also supported by recent analyses suggesting more effective cardiovascular protection by this approach (49). In resistant hypertension the addition of low-dose spironolacton is now recommended. Device-based treatment of hypertension is not recommended as a routine treatment, but rather in the setting of a clinical trial.

Several studies have reported a U-shaped relation between blood pressure lowering and cardiovacular risk in patients with coronary disease, such as the analysis for the STICH trial indicating an increased cardiovascular risk when blood pressure was lowered below 120 mm Hg (50). In the new European hypertension guidelines the lowering of systolic blood pressure below 120 mm Hg is therefore not recommended in patients with coronary disease.

In 2018 the 24-hour ambulatory blood pressure analysis form the SPYRAL HTN OFF-MED study indicated a significant difference in blood pressure reductions between the sham and renal denervation group both at daytime (−3.9 mm Hg; P=0.039) and at nighttime (−4.3 mmHg; P=0.038) diastolic BP (51).

Moreover, several moderate-sized randomized clinical studies have suggested in 2018 the short-term antihypertensive efficacy of advanced approaches of renal denervation (52). Kandzari et all could demonstrate in the SPYRAL HTN-ON MED study that renal denervation in the main renal arteries and branches significantly reduced blood pressure compared with sham control with no major safety events in a study that randomized 80 patients (52). Similarly, in the RADIANCE-HTN SOLO study 146 patients were randomized to a sham procedure or endovascular ultrasound renal denervation and a reduced ambulatory blood pressure at 2 months in patients with combined systolic-diastolic hypertension in the absence of medications was observed compared with the sham procedure (53). These studies are in line with the concept that advanced approaches of renal denervation can lower arterial blood pressure in Grade 1 & 2 hypertension in patients without antihypertensive medication, and this treatment approach could develop into an addition or alternative in treatment of hypertension avoiding the issue of patient compliance. Longer follow-ups will be needed to assess midterm efficacy and safety.

Antithrombotic treatment and cardiovascular prevent-

ion – No indication for aspirin in primary prevention but net benefit of aspirin plus low-dose Xa-Inhibition in very high risk patients with established atherosclerotic CVD. Aspirin reduces CVD risk in patients with established CVD. In primary prevention, the benefit risk ratio was less clear (54). Therefore the current joint European CV prevention guidelines state that aspirin is not recommended in individuals without CVD due to the increased risk of bleeding (55). On this background, three very large randomized trials and a large meta-analysis attempted to better characterized the effects of aspirin in intermediate risk groups and have reported in 2018.

The ARRIVE trial (Aspirin to Reduce Risk of Initial Vascular Events) assessed the efficacy and safety of aspirin in patients at moderate (intermediate) risk (56). ARRIVE randomized 12,546 individuals with a mean follow-up of 5 years (~60.000 patient years) to 100 mg enteric-coated aspirin daily versus placebo. The study included males ≥ 55 years with 2 – 4 risk factors, females ≥ 60 years with ≥ 3 risk factors. Risk factors were high LDL-cholesterol (LDL-C >130 mg/dl), current smoking, HDL-C < 40 mg/dl, hypertension, medication or SBP >140 mmHg, positive family history. The ITT analysis showed no CV risk reduction by aspirin vs placebo (MI, Stroke or CV Death, UA or TIA: 4.3 vs. 4.5%; MI, Stroke, CV death: 3.3 vs. 3.5%). Bleeding was rare and increased by aspirin as expected (0.97 vs. 0.46%). Importantly, the study observed significantly less events then expected (10y ACC/AHA CVD risk 8-9% vs expected 17-18%). Therefore, the population did not represent an intermediate risk category as intended but was at low CVD risk. Medication adherence was poor (<60%) confirming this factor as the key challenge in primary prevention strategies. In addition to non-adherence, dosing may represent an issue. This discussion was fueled by an individual patient data meta-analysis of 10 trials (117,279 participants) by Peter M Rothwell et al (57). The provocative result of the retrospective analysis was that the ability of low-dose aspirin (75-100 mg) to reduce CVD events appeared too decreased with increasing bodyweight (data similar for height). However, there was no heterogeneity for weight reported in other studies such as ASCEND (46). The large ASCEND trial randomized 15,480 persons who had diabetes and no evident CVD (follow-up 7.4 years). Aspirin prevented serious vascular events (8.5% vs. 9.6%) but increased major bleeding events (4.1% vs 3.2%). The main conclusion of the authors was „ the absolute lower rates of serious vascular events were of similar magnitude to the absolute higher rates of major bleeding, even among participants who had a high vascular risk“. To address the important question of the effects of aspirin in primary prevention in the elderly, the ASPREE trial randommized 19,114 community-dwelling persons who were 70 years of age or older without CVD. The risk of death from any cause was 12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group and there was no reduction of cancer (58). The rate of major hemorrhage was 8.6 events and 6.2 events per 1000 person-years, respectively (59, 60). The trial was terminated at a median of 4.7 years because aspirin „did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo” (57). In summary, these three very large randomized trials show that aspirin is not indicated in primary CVD prevention, including individuals with diabetes mellitus without very high CVD risk and the elderly.

However, the benefit-risk ratio of aspirin in patients with established atherosclerotic disease (= secondary prevention) is clearly positive (54). In fact, the COMPASS trial in 27,395 patients with stable coronary artery disease or peripheral artery disease showed that adding low dose rivaroxaban 2×2.5 mg to aspirin reduced the primary outcome of myocardial infarction, stroke, or cardiovascular death more than aspirin alone (4% vs. 6%) (61). Major bleeds increased to 3% vs. 2%. Rivaroxaban plus aspirin reduced mortality when compared with aspirin alone (3% vs. 4%). The COMPASS authors concluded that “there was also a significant net benefit in favour of rivaroxaban plus aspirin and deaths were reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from coronary artery disease worldwide.”

Inflammation – an upcoming treatment target in CV prevention

Further analysis from the CANTOS study that demonstrated for the first time reduced cardiovascular event rates by interleukin-1 beta antibody therapy in patients after an acute coronary syndrome and CRP >2 mg/l have been published (62). These analyses have suggested that modulation of the IL-6 signaling pathway, at least with canakinumab, associates with reduced cardiovascular event rates, independent of lipid lowering (63). Moreover, patients with chronic kidney disease (i.e. baseline eGFR <60 ml/min/1.73 m^2) had an increased absolute cardiovascular risk and a similar relative risk reduction with canakinumab treatment in the CANTOS trial (64). Patients with increased CRP levels have a higher absolute cardiovascular risk, and therefore derive particular benefit from PCSK9 inhibition (65). However, in a post hoc analysis of the SPIRE trials, evidence of residual inflammatory risk persisted among patients treated with both statin therapy and PCSK9 inhibition (66).

Conclusion

New data published in the last year support once again in the importance of lifestyle for CVD prevention. This

does not include only traditional components of lifestyle such as physical activity but also job strain in subjects with cardiometabolic disease and bullying and violence at work. Diet is important as well. It has been confirmed that higher salt intake is associated with stroke. Although there were some controversial results concerning sodium intake and CVD events, a population-wide strategy for sodium reduction is preferable in those populations with excessive salt intake while increasing the consumption of foods rich in potassium such as fruits and vegetables should be stimulated. It has been shown that coffee drinkers have lower CVD mortality, particularly if they drink coffee moderately (equivalent to approximately 1-2 cups daily).

Environmental pollution has also an impact on CVD. It has been shown that environmental exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of CVD and that short-term exposure to traffic pollution prevents the beneficial cardiopulmonary effects of walking in people with COPD, ischaemic heart disease, and those free from chronic cardiopulmonary diseases. Concerning smoking it is interesting that compared to the sustained smokers, the risk of MI was significantly reduced in both quitters with BMI gain and without BMI change, but no significant association was found in quitters with BMI loss. One of the myths has also been unmasked - smoking only about one cigarette per day carries a risk of CHD and stroke much greater than expected: around half that for people who smoke 20 per day. There is no safe level of smoking exists for CVD.

Supplementation with omega-3 fatty acids in doses of 1 g/dan does not decrease the risk of serious CVD events but it seems that 4g/day does decrease the RR of CVD. Particularly interesting are also the results of trials with aspirin indicating that low doses of aspirin (75-100 mg) were only effective in preventing vascular events in patients weighing less than 70 kg with no benefit in the 80% of men and nearly 50% of all women weighing ≥ 70 kg. It has also been shown that addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from CVD.

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