Current opinion

The year in cardiology 2017: prevention

Børge G. Nordestgaard1*, Francesco Cosentino2, Ulf Landmesser3, and Ulrich Laufs4

1Department of Clinical Biochemistry and The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
2Cardiology Unit, Department of Medicine, Karolinska University Hospital, Solna, Stockholm, Sweden
3Department of Cardiology, Charité Universitätsmedizin Berlin, Berlin Institute of Health (BIH), German Center of Cardiovascular Research (DZHK), Hindenburgdamm 30, 12203 Berlin, Germany
4Klinik und Poliklinik für Kardiologie, Department für Innere Medizin, Neurologie und Dermatologie, Universität­sklinikum Leipzig, Leipzig, Germany

Received 26 October 2017; revised 14 November 2017; editorial decision 8 December 2017; accepted 19 December 2017; online publish-ahead-of-print 2 January 2018

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author: Tel: +45 3868 3297, Fax: +45 4488 331, E-mail: boerge.nordestgaard@regionh.dk

Preamble

During 2017 several landmark studies have been published that have practical implications for atherosclerotic cardiovascular disease (ASCVD) prevention and risk factor control, such as lipids and lipoproteins, inflammation, diabetes, hypertension, and healthy lifestyle. We use the term "ASCVD" where relevant to simplify the reading of this article for the non-specialist, although the exact definition as ASCVD differ slightly from study to study. However, in sections where ASCVD clearly is not the relevant endpoint (e.g. in hypertension research) we do not use "ASCVD", but instead of use other words to describe endpoints. All relevant trials have been performed on a background of optimal medical therapy, such as described in the European Society of Cardiology(ESC)/European Atherosclerosis Society(EAS) guidelines on ASCVD prevention and management of dyslipidaemia for lipid-lowering (1, 2). For example, important new evidence for additional risk reduction relates to lipid-lowering [proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition (3), cholesteryl ester transfer protein (CETP) inhibition (4) to the reduction of systemic inflammation (interleukin-1β inhibition) (5) and to anti-thrombotic therapy (low-dose factor Xa antagonism) (6). Since these novel treatments have not yet been tested in combination and because of the practical and economic limitations, an important challenge for the years to come is patient selection. Also, the benefit to risk dimension of any new therapeutic agent needs to be considered. This review article is intended to provide the practicing physician with the information needed to identify patients in secondary prevention that may benefit the most from additional novel treatments (Figure 1), and at the same time give a comprehensive update of novel insights relevant both to primary and secondary prevention of ASCVD. Use and accessibility of novel treatments will depend critically on whether patients live in high income, upper middle-income or lower middle-income countries, as levels of cardiovascular risk factors, cardiovascular mortality rates, and thus the prevention potential differ between such countries (7).

Lifestyle

Observational epidemiology in the field of lifestyle is difficult to trust due to the high-risk of confounding (a third factor influences both disease risk and lifestyle) and reverse causation (diseases will change a person's lifestyle), and therefore only randomized intervention trials and genetic Mendelian randomizations studies can be trusted. However, each of these study designs has limitations (8–10). Importantly, as randomized intervention trials are very difficult to conduct for lifestyle factors, we often are left with observational and genetic studies in this field. Below is what we choose to highlight for 2017.
The concept of “metabolically healthy obesity”, namely that in the absence of metabolic dysfunction, individuals with excess adiposity are not at greater cardiovascular risk, has been controversial. A recent pan-European case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition study (EPIC-CVD), observed higher cardiovascular risk with increasing general and central adiposity (11). Other cohort studies have challenged this concept reporting an excess of cardiovascular risk in metabolically healthy obese as compared to normal weight individuals (12–15). These results highlight the importance of population-wide prevention of obesity with lifestyle intervention targeting eating behaviour and physical activity. Importantly however, steady and sustained weight loss is preferable as in patients with coronary heart disease the highest vs. lowest variation in body weight was associated with 64% more coronary and 124% more mortality events (16).

Coffee consumption is observationally associated with reduced all-cause, cardiovascular and other cause-specific mortality (17–19). However, both reverse causation and confounding by other lifestyle factors may bias such results. Interestingly therefore, Mendelian randomization studies free of confounding found no causal effect of coffee intake on all-cause or cardiovascular mortality, or on cardiovascular disease (19). Likewise, in Mendelian randomization studies milk intake appears not to influence risk of hypertension or cardiovascular disease (20, 21).

Alcohol intake: novel findings include that acute beer alcohol consumption during the Munich Octoberfest was associated with cardiac arrhythmias and sinus tachycardia (22). Large UK and USA cohorts found moderate alcohol intake associated with less of most cardiovascular disease endpoints while heavy and binge drinking or alcohol abuse were associated with more cardiovascular disease or deaths (23–25).

A Mendelian randomization study of genotypes associated with higher education suggested that low education is causally associated with ASCVD events (26). Using UK-Biobank participants, it was observed that the association between physical activity and mortality was strongest in those with lowest strength and lowest cardiorespiratory fitness, suggesting that these subgroups would benefit the most from more physical activity (27); preventing or delaying cardiovascular disease or diabetes seemed to delay cognitive decline and possibly dementia (28).

Adherence to a healthy lifestyle consisting of non-smoking, light to moderate alcohol intake, high physical activity, fruit and vegetables intake, and normal body weight was associated with a substantially lower burden of ASCVD in Chinese (29, like previously observed in Europeans. Interestingly, in Spain skipping breakfast was associated with more non-coronary and generalized atherosclerosis, independent of other cardiovascular risk factors (30). Importantly however, lifestyle can be difficult to change, even for patients with acute coronary syndrome and/or revascularization (31). Further, in the PURE study covering all major parts of the World and recruiting 135,335 individuals between}

For a 2017 optimally treated patient with coronary heart disease

<table>
<thead>
<tr>
<th>Current treatment:</th>
<th>Additional non-optimal risk factors:</th>
<th>You could consider for a patient based on individual decision:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smoking</td>
<td>High LDL cholesterol</td>
<td>Ezetimibe and/or PCSK9 inhibitor</td>
</tr>
<tr>
<td>Exercise</td>
<td>High C-reactive protein</td>
<td>Interleukin-1β inhibitor (if available)</td>
</tr>
<tr>
<td>Low-fat diet</td>
<td>Diabetes</td>
<td>Sodium/glucose cotransporter 2 inhibitor or glucagon like peptide 1 receptor agonist</td>
</tr>
<tr>
<td>Statin max dose</td>
<td>Atherothrombosis risk</td>
<td>Long-term dual antiplatelet therapy or low-dose factor Xa antagonist with aspirin</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Inhibitor +/− Beta-blocker</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 1. A 2017 optimally treated patient with coronary heart disease on statin, aspirin, angiotensin-converting enzyme inhibitor, and beta-blocker. Do new trials suggest that we should add additional drugs or lifestyle modification, and what in whom? PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low-density lipoprotein cholesterol; ACE, angiotensin converting enzyme.**

This Figure has been reprinted by permission of Oxford University Press on behalf of the Society of Cardiology.
2003 and 2013 with follow-up until 2017, higher intake of fruit, vegetables, and legumes was associated with lower non-cardiovascular and total mortality, with a non-significant trend for cardiovascular mortality (32). The findings also included that as little as three servings per day consisting of only 375 g per day were associated with similar benefit. This indicates that optimal health benefits may be achieved with a more modest consumption of fruit, vegetables, and legumes than that recommended in high-income Europe and the USA, an approach that is more likely to be affordable in low-income and middle-income countries. In contrast to popular opinion, higher fat intake was not associated with ASCVD or death.

Finally, air pollution, noise, and other environmental stressors, depending on where a person chooses to live, may influence cardiovascular health and mortality (33, 34). For example, long-term exposure to road traffic noise and ambient air pollution were associated adversely with cardiovascular biochemical risk factors (35) and self-reported hypertension (36). Worldwide ambient air pollution with aerodynamic diameter <2.5 µm was the fifth-ranked mortality factor in 2015, and has increased in importance over 25 years (37).

Low-density lipoprotein cholesterol

The causal role of high LDL cholesterol for ASCVD was clearly documented using large meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized trials including more than 2 million individuals with over 20 million person-years and over 150,000 ASCVD events (38). Notably, this effect increased with duration of exposure to high LDL cholesterol, suggesting that the exposure in genetic Mendelian randomization studies determines the lifetime ASCVD risk (Figure 2). Interestingly, as judged by coronary artery calcification a forager-horticulturalist population of the Bolivian Amazon with LDL cholesterol of only 2.4 mmol/L (91 mg/dL) and despite high infectious inflammatory burden, had five-fold lower coronary atherosclerosis as compared to industrialized populations (39).

The most prescribed drugs for LDL cholesterol lowering at present are statins that reduce endogenous cholesterol synthesis. Using maximal doses, statins can reduce LDL cholesterol levels by up to 50% and in consequence ASCVD events by up to 50%; however, such large effect sizes are not always obtained likely due to poor compliance and inter-individual variability in drug

![FIGURE 2](image_url). Association of change in LDL-C with risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies with lifelong 52 years exposure (=follow-up), prospective epidemiologic cohort studies with 12 years exposure, and randomized trials with 5 years exposure. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL cholesterol has both a causal and a cumulative effect on the risk of cardiovascular disease. CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol. Reproduced with permission from Ference et al (38).

This Figure has been reprinted by permission of Oxford University Press on behalf of the Society of Cardiology.
effects. Working synergistically with statins, PCSK9 inhibitors contribute to preservation of LDL receptors and increase their density at the membrane of liver cells, thus enhancing the reduction of LDL cholesterol. Landmark trials include those with PCSK9 inhibition, currently the most effective approach to lower LDL cholesterol. In the FOURIER trial, 27,564 patients with ASCVD and LDL cholesterol ≥1.8 mmol/L (70 mg/dL) or non-HDL cholesterol >2.6 mmol/L (100 mg/dL) treated with intense statin therapy, were randomized to evolocumab or placebo (3): LDL cholesterol was reduced 59% to 0.8 mmol/L (30 mg/dL), ASCVD events 15% (absolute risk reduction 1.5%), and myocardial infarction was reduced 27% (absolute risk reduction 1.2%). Moreover, a pre-specified secondary analysis of FOURIER suggested reduced ASCVD at achieved LDL cholesterol <0.2 mmol/L (8 mg/dL) (40). Conversely, there were no safety concerns with very low LDL cholesterol over 2.2 years including no change in risk of diabetes; however, lifelong genetically reduced PCSK9 did appear to cause a small increase in risk of diabetes (41). Further, the EBBINGHAUS substudy of FOURIER examining cognitive function did not detect between-group differences over 19 months (42). Similarly, in a Mendelian randomization study involving 111,194 individuals, low LDL cholesterol caused by PCSK9, and HM-GCR genetic variants had no causal effect on the risk of Alzheimer’s disease, vascular dementia, any dementia, or Parkinson’s disease (43). Also, pooling data from 14 phase 2 and 3 studies of alirocumab vs. placebo, LDL cholesterol levels <0.4 mmol/L (15 mg/dL) was not associated with increases in neurocognitive events (44). A similar conclusion came from pooling data from 12 phase 2 and 3 studies of evolocumab vs. placebo (45). Finally, in the IMPROVE-IT trial using ezetimibe patients achieving LDL cholesterol <0.8 mmol/L (30 mg/dL) had a similar safety profile over a 6-year period compared with patients achieving higher LDL cholesterol concentrations (46). Two randomized trials comparing the PCSK9 inhibitor bococizumab with placebo were stopped prematurely due to immunogenic effects of the humanized monoclonal antibody bococizumab (47, 48): this PCSK9 inhibitor lost efficacy with time due to developments of anti-drug autoantibodies. Bococizumab had no benefit with respect to ASCVD events in the trial involving lower-risk patients with a very short follow-up, but did have a significant benefit in the trial involving higher-risk patients with a longer follow-up. The ODYSSEY clinical outcomes study using PCSK9 inhibition with alirocumab in patients after an acute coronary syndrome is still ongoing. Based on the new PCSK9 endpoint trials, an updated ESC/EAS consensus document reported recommendations on the use of PCSK9 inhibition in clinical practice in patients with ASCVD or familial hypercholesterolaemia (FH) (49). Notably, PCSK9 small interfering RNA therapy with inclisiran was found to lower PCSK9 and LDL cholesterol levels in a phase 1 study of healthy volunteers (50) and among patients at high cardiovascular risk in a phase 2 study (51). At day 180, the mean reductions in LDL cholesterol levels were 28–42% after only one single dose of inclisiran and 36–53% after two doses (51). This compound is currently entering a phase 3 clinical study program. RNA interfering therapies lower the PCSK9 protein and their advantage lies to the long-dosing possibility, once every 3 or 6 months. Moreover, in experimental studies in APOE*3Leiden. CETP mice it was shown that PCSK9 immunisation using the AT04A anti-PCSK9 vaccine resulted in a significant reduction of plasma lipids, systemic and vascular inflammation, and atherosclerotic lesions in the aorta (52). A phase 1 study using the vaccine is currently ongoing. Finally, in the HIJ-PROPER study of acute coronary syndrome patients ezetimibe added to pitavastatin did not significantly lower ASCVD events overall; however, the study size was limited with <2000 patients and in those with higher cholesterol absorption a 29% reduced ASCVD event rate was observed (absolute risk reduction 9.7%) (53).

Familial hypercholesterolaemia

One of the biggest potential for preventing ASCVD worldwide is to find and treat individuals with FH early in life. Because of the recognition that FH is found in roughly 1/250 (rather than 1/500) (54–56), because FH is underdiagnosed and undertreated (57–59), and because PCSK9 inhibitors together with statins now offer efficient LDL cholesterol reduction in FH, interest in FH research is increasing. After optimal statin therapy, PCSK9 inhibitors can reduce LDL cholesterol by an additional up to 65% in individuals with heterozygous FH, and up to the same absolute extent in the very rare individuals with homozygous FH but depending critically on the types of mutations involved and thus the ability to up-regulate LDL receptors. A Japanese study documented that classical signs of FH and FH mutations additively added to ASCVD risk above high LDL cholesterol alone (60); importantly however, except for the Netherlands, Norway, a number of other European countries, and Canada, in most countries in the World FH is underdiagnosed and genetic testing is not used (Take home figure) (61); although Japan has a relatively high rate of FH screening, genetic testing is still only used rarely in Japan. The advantage of genetic testing is the use in cascade screening of FH index cases and their family members (62), and such testing in the UK including consequent cholesterol-lowering treatment has an estimated lifetime cost per relative tested of only 1212 Euro (£1092) if 3.2 relatives are tested per mutation-positive index case (63). Thus, can we afford not to screen for FH (64)?
To better select individuals for genetic testing for FH, based on Dutch data with validation in Canada, an online calculator to estimate the probability of an FH mutation in individual patients has been developed (65). Further, among Spanish patients with acute coronary syndrome and LDL cholesterol ≥4.1 mmol/L (160 mg/dL), 9% had an FH mutation (66). Also, using the Dutch Lipid Clinic Network Criteria or simply a high LDL cholesterol alone also improved finding those with FH mutations (55); the most optimal threshold for LDL cholesterol concentration to discriminate between Danish mutation carriers and non-carriers was 4.4 mmol/L (170 mg/dL).

In children with homozygous FH rosuvastatin reduced LDL cholesterol by 22% (67) and in children with heterozygous FH rosuvastatin slowed the progression of carotid intima-media thickness (68), supporting early statin therapy in children with FH. Interestingly, the pro-inflammatory phenotype of monocytes in FH patients was dampened by LDL cholesterol lowering (69).

Further, based on the Spanish SAFEHEART registry, ASCVD risk prediction depended on age, sex, previous ASCVD, blood pressure, body mass index, smoking, LDL cholesterol, and lipoprotein(a) (70); an independent predictive value of lipoprotein(a) in FH for ASCVD agrees with previous findings (71). Finally, based on WOSCOPS trial 20-years follow-up data we can now say definitively that statin treatments of primary prevention patients with LDL-C ≥4.9 mmol/L (190 mg/dL) is safe and leads to significant reductions in ASCVD events and total mortality (72).

Lipoprotein(a)

Genetic evidence documents that lipoprotein(a) is causally related to myocardial infarction, atherosclerotic
steno-sis, and aortic valve stenosis, but not necessarily with development of early atherosclerosis (73, 74). Until now focus has been on genetic variants that increases lipoprotein(a) and increases disease risk, but in 2017 in individuals with small apolipoprotein(a) isoforms a novel genetic variant that reduces lipoprotein(a) and cardiovascular disease risk was documented (75). Another novel genetic approach include the use of genetic variants solely associated with lipoprotein(a) concentrations and not with number of kringle IV-2, or vice versa, to show that the higher diabetes risk observed at low lipoprotein(a) is explained by high kringle IV-2 and not by low lipoprotein(a) per se (76); for future aggressive lipoprotein(a) lowering (74, 77), this is a reassuring finding. Across Europe lipoprotein(a) levels vary; however, high lipoprotein(a) was associated with high ASCVD risk in all regions (78); absolute lipoprotein(a) concentrations were lower in this study than in many others, pointing towards the need for further standardization of lipoprotein(a) measurements. At present, statins are applied to individuals with high lipoprotein(a) to reduce ASCVD risk. Other investigational therapies include apheresis, PCSK9 inhibitors, and most importantly antisense oligonucleotides targeting apolipoprotein(a) production (74, 77). Interestingly and surprisingly, in a study of only 20 patients with refractory angina lipoprotein apheresis improved myocardial perfusion, atheroma burden, exercise capacity and symptoms (79); these findings may initiate studies in similar patients using PCSK9 inhibitors or antisense oligonucleotides (80).

Triglycerides and remnants

Three large randomized double-blind ASCVD endpoint trials of triglyceride-lowering with omega-3 fatty acids or pemafibrate in individuals already on a statin, the REDUCE-IT (NCT01492361), STRENGTH (NCT02104817), and PROMINENT (NCT03071692) trials, are now ongoing. In the meantime, the genetic evidence that triglyceride-rich lipopro- teins and remnant cholesterol represent an independent cause of ASCVD beyond LDL cholesterol is increasing in strength (9); remnant cholesterol is the cholesterol content of all triglyceride-rich lipoproteins and can either be calculated (total minus LDL minus HDL cholesterol) or now also measured directly on standard hospital autoanalysers (81). Individuals with loss-of-function mutations in angiopoietin-like protein 3 (ANGPTL3), a known inhibitor of triglyceride-degrading lipoprotein lipase, had 27% lower triglycerides, 9% lower LDL cholesterol, and 41% lower ASCVD risk (82); similar findings were observed in an independent study (83). Pharmacologically, antibodies against ANGPTL3 reduced triglycerides by up to 76% and LDL cholesterol up to 23%,82 while antisense oligonucleotides against ANGPTL3 messenger RNA reduced triglycerides by up to 63% and LDL cholesterol up to 33% (84). Conversely, loss-of-function mutations in lipoprotein lipase lead to increased triglycerides and increased ASCVD risk (85), supporting earlier findings (86). Another novel observation include that autoantibodies against glycosylphosphatidylinositol-anchored HDL binding protein 1 (GPI-HBP1), a facilitator of lipoprotein lipase, lead to severely elevated triglycerides (87). Together with previous evidence (9), the above mentioned findings from 2017 suggest that pharmacological improved lipoprotein lipase activity, directly or through blocking inhibitors of the enzyme, will lead to lower triglycerides and lower ASCVD risk. Another novel observation is that triglyceride-related genetic variant were associated with mitral annular calcification (88); future studies should examine if lowering of triglycerides will reduce mitral valve disease. Finally, as many guidelines worldwide now recommend non-fasting rather than fasting lipid profiles the average triglyceride levels during most of a 24 h cycle will be obvious for many patients and clinicians in the future (89).

High-density lipoprotein cholesterol

Low HDL cholesterol is considered a risk marker (not a causal factor) for ASCVD. Previously, it was thought that high HDL cholesterol would prevent or help reverse atherosclerosis by mediating transfer of cholesterol from the arterial wall to the liver for excretion. Cholesteryl ester transfer protein inhibitors increase the concentration of HDL cholesterol by blocking cholesterol transfer between HDL and other lipoprotein particles, and not necessarily through cholesterol uptake from the arterial wall. Results of recent trials showed that treatment with CETP inhibitors increased HDL cholesterol in the ACCELERATE trial (90) and in the dal-OUTCOMES study (91), without profound reductions of apolipoprotein B, and had no effect on ASCVD (Figure 3); the Dal-GenE randomized trial is ongoing to examine cardiovascular effects of dalcetrapib in a genetically defined population (92). In the ILLUMINATE trial with 72% higher HDL cholesterol increases in ASCVD and all-cause mortality was observed (93); the negative outcome in ILLUMINATE have been associated with off-target effects. Although the recent REVEAL HPS-3/TIMI-55 study observed 9% less ASCVD (absolute risk reduction 1.0%) coinciding with 104% higher HDL cholesterol, a reduction in apolipoprotein B containing lipoproteins more likely explains the beneficial effects, as also supported by a genetic Mendelian randomization study (94). None of the CETP inhibitors will be available for clinical practice. Importantly, current ESC/EAS dyslipidaemia guidelines do not recommend HDL cholesterol as a treatment target in ASCVD prevention (2).
Importantly, the cardiovascular benefit of anacetrapib should not be compared directly to that of statins, ezetimibe, or PCSK9 inhibitors, all working mainly through up-regulation of LDL receptors to reduce LDL cholesterol. In contrast, CETP inhibition influence levels of cholesterol in LDL, other apolipoprotein B containing lipoproteins and HDL through exchange of cholesterol and triglycerides between lipoprotein particles. Notably, it has previously been suggested that vascular effects of HDL are altered in patients with ASCVD and chronic kidney disease, in part due to alterations of the protein cargo and small molecules such as symmetric dimethylarginine (95). These findings are now further supported by recent data, indicating that in patients with high symmetric dimethylarginine levels increased HDL cholesterol is associated with adverse cardiovascular outcomes (96).

Moreover, in a large-scale analysis from two Copenhagen prospective population-based studies, it was observed that men and women in the general population with extreme high HDL cholesterol paradoxically have high all-cause mortality (97) (Figure 4); this further indicates that high HDL cholesterol levels have to be interpreted with caution and are not necessarily beneficial. Certainly, at high HDL cholesterol concentrations the HDL particle may not be functioning properly.

### Inflammation

Inflammation plays a critical role in atherosclerosis and ASCVD (98), as well as in cancer (99). Intra-arterial accumulated lipoproteins initiate and modulate low grade inflammation and the production of cytokines and C-reactive protein. However, even after aggressive treatment and control of LDL cholesterol with statins, there remains residual risk. This residual inflammation and residual risk was addressed by the recent landmark CANTOS trial. The CANTOS trial enrolled 10,061 patients with previous myocardial infarction and C-reactive protein ≥2 mg/L despite the use of aggressive secondary prevention strategies. Findings of this study include that anti-inflammatory therapy targeting interleukin-1β with canakinumab in the highest dose reduced ASCVD by 14% (absolute risk reduction ≈2%), total cancer mortality by 51% (absolute risk reduction ≈2.5%), and lung cancer mortality by 34% (absolute risk reduction ≈2%).

![Figure 3. Summary of main results from randomized, double-blind, placebo-controlled trials of cholesterol ester transfer protein inhibition in statin treated patients. This figure does not illustrate in detail the contrasting safety profiles of these four cholesterol ester transfer protein inhibitors. ASCVD, atherosclerotic cardiovascular disease; ApoB, apolipoprotein B; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); CETP, cholesterol ester transfer protein](image-url)
incidence by 67% (absolute risk reduction=1.6%) (5, 100). Adverse events included a small absolute increase in fatal infection or sepsis, but also a beneficial effect on osteoarthritis and gout. The cardiovascular benefit obtained at the 150 mg dose of canakinumab came at the expense of an excess of mortality from infection, implying a narrow therapeutic window for such an anti-inflammatory approach.

In a follow-up study, it was suggested that the magnitude of reduction in C-reactive protein following a single dose of canakinumab might provide a simple clinical method to identify individuals most likely to accrue the largest benefit from continued treatment (101). These data further suggested that lower is better for inflammation reduction with canakinumab.

It is yet unclear if and when canakinumab will be available for ASCVD prevention. However, it is also important to recognize the value of clinical trial results like those from CANTOS for mechanistic insight in development of myocardial infarction (102). For example could such data of the vascular impact of targeting inflammation help us better understand the relative role of plaque rupture and plaque erosion in myocardial infarction? Importantly, substantial residual ASCVD risk remains even after optimal lifestyle and medical therapy according to ESC/EAS Guidelines (1, 2), as well as after additional canakinumab therapy (5), lipid-lowering therapy with the cholesterol absorption inhibitors ezetimibe (103), the PCSK9 inhibitors evolocumab (3) and bococizumab (48), bezafibrate (104), or with the CETP inhibitor anacetrapib (4). Therefore, there remain large unmet medical needs for ASCVD prevention.

Diabetes

A paradigm shift in the management of type 2 diabetes (T2D) has been observed with sodium/glucose cotransporter 2 inhibitors (SGLT-2i). This class of agents prevent re-absorption of glucose from the urine, thus resulting in glycosuria and lower blood glucose levels. It seems however that they possess additional, yet not fully identified effects that enhance their protective effect on the cardiovascular system. These drugs reduce the risk of cardiovascular complications, kidney disease, and death beyond glycaemic control (105–107), benefits that recently were confirmed in 10,142 patients with T2D and high cardiovascular risk from CANVAS and CANVAS-Renal trials designed to assess effects on albuminuria (108); canagliflozin also lowered progression of albuminuria and loss of kidney function. In consideration of the increased risk of amputations seen, care is warranted in the use of canagliflozin in patients at such risk (108). Similarly, liraglutide, a glucagon like peptide 1 (GLP1) receptor agonist, reduced not only ASCVD (109) but also development and progression of diabetic kidney disease (110).

Further, CVD-REAL, a large observational study of T2D patients of 15% with and 85% without established ASCVD, found that the SGLT-2i drug class was associated with a lower risk of heart failure and all-cause mortality (111). The CVD-REAL Nordic – thanks to a complete population-level registries in Denmark, Norway, and Sweden – demonstrated that SGLT-2i also were associated with reduced cardiovascular mortality and morbidity (112). These retrospective cohort studies extend the results of EMPA-REG OUTCOME (106) and CANVAS (108) to the unselected T2D population. A putative confirmation of these results by the on-
going trials such as DECLARE-TIMI 58 (dapagliflozin; NCT01730534), due in 2019, would certainly impact clinical practice in primary prevention. In patients with insulin resistance (but not diabetes) and a history of cerebrovascular accidents, the thiazolidinedione drug pioglitazone in the IRIS trial showed a 24% reduction of ASCVD (absolute risk reduction 2.8%) and lower progression to diabetes (113), reinforcing the emerging precision-medicine approaches to vascular disease and that pioglitazone may represent an option for secondary prevention in selected patients with cerebrovascular disease. Furthermore, the TOSCA IT trial showed cardiovascular safety of second-line glucose lowering drugs (114); the study examined effects of add-on pioglitazone vs. sulfonylureas on the incidence of ASCVD events in patients inadequately glucose-controlled with metformin and was stopped early because of futility. The confirmed safety profile in combination with the wide affordability of pioglitazone and sulfonylureas might promote trials comparing outcomes with ‘newer’ glucose-lowering drugs.

The EXSCEL trial recruited the hitherto largest patient population of any cardiovascular outcomes trial of the GLP1 receptor agonist class with more than 14,500 patients across 35 countries (115). In patients with T2D at a wide range of cardiovascular risk, exenatide extended-release once weekly compared with placebo showed cardiovascular safety. Although the primary efficacy objective of ASCVD events missed statistical significance, nominally 11.4% ASCVD events were observed in the exenatide vs. 12.2% in the placebo arm. Additional information from ongoing studies are awaited to define the effects of specific drugs, provide further insights into the mechanisms of cardiovascular benefit and put these results in the perspective of current treatment algorithms and healthcare economy.

In patients with T2D and high ASCVD risk, the long-acting insulin degludec compared with basal insulin glargine caused 40% fewer severe hypoglycaemic events and was non-inferior with respect to ASCVD (116). Further, intensive lifestyle intervention in patients with T2D lead to reduced use of glucose-lowering medication, but not to better glycaemic control (117). Interestingly, although diabetes risk was not increased during short-term therapy with PCSK9 inhibitors (3, 48) lifelong genetically reduced PCSK9 and corresponding lower LDL cholesterol did appear to cause a small increase in risk of diabetes, but only in those with impaired fasting glucose (41). Also, genetic evidence document that overweight and obesity, either through increased body mass index or waist-to-hip ratio, is causally related to increased risk of both diabetes and ASCVD (118–121). Finally, in a healthy Asian population without comorbidities impaired fasting glucose and prehypertension were important risk factors for atrial fibrillation (122).

**Hypertension**

Poor medication adherence and late initiation of blood pressure (BP)-lowering represent important but missed opportunities for cardiovascular prevention. Previous studies had reported BP-lowering following catheter ablation for renal denervation (123). However, the large SYMPLICITY HTN-3 trial did not confirm these findings (124), possibly due to insufficient ablation, adherence to antihypertensive therapy and/or patient selection (125). Therefore, SPYRAL HTN-OFF MED randomized drug-naïve or drug-discontinued hypertensive patients to more extensive and more distal denervation of renal arteries, in a blinded design including a sham procedure in controls and drug testing for patient compliance (125). Office systolic BP decreased by 10 mmHg and 24 h ambulatory BP by 6 mmHg, without major adverse events. Although these new data on renal denervation are interesting, they should be interpreted cautiously in light of the prior failures in this field. Nevertheless, these results with rigorous sham-design set a new standard for future interventional and surgical clinical studies.

Substantial BP-lowering could potentially cause severe side effects, like in the SPRINT trial of individuals who received intensive BP-lowering of 15 mmHg and consequently, benefitted from reduced cardiovascular events and mortality (126); however, these individuals reported similar physical, mental, and depressive outcomes compared with those receiving standard treatment (127). Also, in meta-analyses of hypertensive patients ≥65 years intensive BP-lowering reduced cardiovascular disease, cardiovascular mortality, and heart failure, but increased renal failure (128). Finally, a recent population-based study documented transgenerational risk of hypertension from grandparents through parents to grandchildren (129).

**Arterial and venous thrombosis**

Arterial thrombosis, especially in the coronary arteries, represents the most common precipitant of acute vascular syndromes, such as myocardial infarction and limb ischaemia. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial assigned 27,395 patients with stable atherosclerotic vascular disease to receive rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone (6). The study was prematurely stopped due to 24% fewer ASCVD events (absolute risk reduction 1.3%) and 18% fewer deaths (absolute risk reduction 0.7%) in the rivaroxaban-plus-aspirin group compared with the aspirin-alone group; however, this was at the cost of 70% increased major bleeds (absolute risk increase 1.2%). Younger individuals compared with the elderly showed relatively larger reduction of ASCVD and lower bleeding risk. The
effects of proton pump inhibitors on bleeds that are tested in a partial factorial design are pending. It is unclear how very low dose rivaroxaban + aspirin would compare with dual antiplatelet therapy or to the combination of rivaroxaban + P2Y12 inhibitor. In the COMPASS subgroup of 27% with chronic peripheral arterial disease, rivaroxaban plus aspirin vs. aspirin alone in addition reduced amputations (130). Since evidence-based treatments for patients with peripheral arterial disease are scarce, low-dose rivaroxaban provides an important novel strategy for this high-risk population. In patients with acute coronary syndrome dual antiplatelet therapy of low-dose rivaroxaban or aspirin, in combination with clopidogrel or ticagrelor, lead to similar risk of bleeding in 5% of patients (131). Importantly, discontinuation of any direct oral anticoagulant 3 days prior to elective invasive procedures will secure minimal concentrations pre-procedure in almost all patients (132).

A Danish study randomized >50,000 men aged 65–74 to screening or not for abdominal aortic aneurism, peripheral arterial disease, and hypertension; those diagnosed in the screening group were offered relevant follow-up and treatment including surgery and antihypertensive medication, which was associated with a 7% reduced all-cause mortality (absolute risk reduction 0.6%) primarily linked to initiation of pharmacological therapy (133). Importantly, mortality related to abdominal aortic aneurism may differ from country to country, and can be influenced by rate of surgical repair and aneurysm diameter at repair (134). A low ankle-brachial index help identify patients with abdominal aortic aneurism and peripheral arterial disease and predict ASCVD events, although to a lesser extent than increased coronary artery calcification (135).

Arterial thrombosis depends on atherosclerotic plaque vulnerability, which likely differs in individuals taking statins or not due to reduced lipid-driven plaque inflammation in those on statins (136). Interestingly, new data support that a chronically affected haematopoietic system potentially drive low-grade inflammation in patients with atherosclerosis (137).

For venous thromboembolism, meta-analyses of observational studies found a 27% reduced risk of recurrent venous thromboembolism associated with statin use (138), in accordance with findings in the randomized JUPITER trial (139). Finally, in patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was reduced approximately 70% by rivaroxaban compared with aspirin, without a significant increase in bleeding rates (140); this confirms previous studies with other novel oral anticoagulants.

**Guidelines and consensus statements**

Despite evidence-based recommendation for widespread use of statins in both primary and secondary prevention of ASCVD (1, 2), statin compliance is a major problem worldwide (141, 142), partly due to negative press (143, 144) and in consequence discontinuation of statin use and increased risk of myocardial infarction and cardiovascular mortality (143–146). In support, in the ASCOT-LLA trial muscle-related adverse events were similar in those receiving atorvastatin and placebo during blinding, however, after un-blinding and follow-up for an additional 2.3 years muscle-related adverse events were now 41% higher in those who knew they were receiving atorvastatin (147). Therefore, any patient claiming statin intolerance including muscle symptoms needs careful counselling with his or her physician, including better diagnostics of statin intolerance and advice on how to continue statin therapy despite perceived side effects (141, 142, 148).

Various updates of major guidelines for prevention of cardiovascular disease has occurred lately (1, 149–154), and despite use of the same scientific evidence to guide lifestyle changes and medical intervention advise tend to differ between guidelines. For example, the ACC/AHA guidelines compared with the ESC/EAS guidelines placed higher priority for assigning statins in primary prevention to those who later developed ASCVD (155); this difference was mainly explained by the fact that the American guidelines assigned statin therapy to more individuals that the European guidelines. That said, the European guidelines is limited by using the SCORE algorithm for ASCVD risk assignment based only on ASCVD mortality in cohorts recruited many years ago, and limited to only 40–65 years old (156, 157). Although the risk of ASCVD increases with increasing age above 65 years (156) with age as the most important ASCVD risk predictor, arguments differ with respect to how important age should be in determining statin assignment (158, 159).

Although the American ACC/AHA risk score overestimates ASCVD risk, particularly in Chinese (160), the European ESC/EAS SCORE may in some populations overestimate risk even more (155). Therefore, ideally risk scores for ASCVD needs to be recalibrated to each country and ethnic group before it is used to assign statin therapy. In 2017, exactly that has happened for the UK QRISK3 risk prediction algorithms for the NICE guidelines (149), using current data from 981 general practices and 7.9 million patients aged 25–84 in England to develop new scores and another 328 practices and 2.7 million patients to validate the new score algorithms (161). By 2017, the use of non-fasting rather than fasting lipid profiles is now recommended in many guidelines and consensus statements worldwide (89), including in the UK (149), Europe (1, 2, 162), Canada (150, 150) Brazil (163), and in the USA (153, 164, 165). Finally, new USA guidelines have lowered the threshold for the definition of hypertension to ≥130/80 mmHg systolic/diastolic BP (earlier 140/90 mmHg) (166), placing very large propor-
2017 has been a very exciting year for studies in ASCVD prevention, including landmark clinical trials, genetic Mendelian randomization studies, and observational prospective cohort studies. Figure 1 illustrates some of the new concepts for additional preventive measures in secondary prevention in a patient with coronary heart disease already on statin, aspirin, ACE inhibitor, and beta-blocker. Naturally, many new concepts await confirmation by additional studies and their test in clinical practice. Importantly, considerable inter-individual variability has been noted in the response to a number of the agents discussed in this review. Therefore, for all new (and old) drugs, it is important to monitor response, particularly at a time when economic pressures oblige clinicians to use therapeutic agents in an optimal manner on a personalised basis.

Conflict of interest: none declared.

References


August 2017.


Noordostaer et al.: The year in cardiology 2017: prevention


62. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for fami-
liar hypercholesterolemia and the use of genetic testing. JAMA 2017; 318: 381–382.

63. Kerr M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, Watson M, Humphries SE. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercho-

lolesterolaemia services in the UK. Eur Heart J 2017; 38: 1832–1839.


65. Besseging J, Reitsma JB, Gaudet D, Brisson D, Kastelein JJ, Ho-
vinh GK, Huttten BA. Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the purpose of a prevention campaign using raised lipoprotein(a): a ran-


dov NP, Hu X, Allman CM, Larsson M, Machida T, Murakami M, Kreue K, Tillerson P, Goldberg IJ, Moulpin P, Charrrier E, Fonc LG, Nakajima K, Young SG, Autoimmune S, Floorries against GPIHIiP1 as a cause of hyper-

73. Afshar M, Luk K, Do R, Dufresnes L, Owens DS, Harris TB, Pe-


74. Nordestgaard BG. A test in context: lipid profile, fasting versus


