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REVIEW

Secondary prevention of cardiovascular diseases: current state of the art

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Abstract

Prevention strategies for cardiac events depend of the risk for such an event. A very high risk is defined as a risk > 10% over 10 years. For example, a patient with known coronary artery disease has such a very high risk of death. However, a patient with diabetes and severe hypertension without known coronary artery disease carries the same risk. Here, secondary prevention and primary prevention overlap. Prevention guidelines include a number of general recommendations, such as changes in behaviour, nutrition, body weight, and physical activity as well as smoking intervention strategies. Drug treatment-based prevention strategies address diabetes mellitus, hypercholesterolaemia, platelet aggregation, and arterial hypertension. Following hospitalisation for heart failure or acute coronary syndrome, participation in a centre-based or home-based rehabilitation programme is recommended. There are a number of new treatment options with a promising potential to reduce the rate of events in patients with cardiovascular diseases and in patients with cardiovascular risk factors. Very recent treatment strategies include the PCSK9 inhibitors for hypercholesterolaemia and the SGLT2 inhibitors for reduction of cardiovascular events in patients with diabetes mellitus and increased cardiovascular risk.

Key words: prevention, cardiovascular disease, intervention, treatment

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INTRODUCTION

Secondary prevention of cardiovascular diseases (CVDs) is a major effort of a non-interventional cardiologist or internist. Secondary prevention of CVD means prevention of progression or recurrence of coronary artery disease (CAD) or CVD in general. It is worth highlighting that secondary prevention of CVD also means prevention of endocarditis, sudden cardiac death, rheumatic fever, stroke, and heart failure (HF) or HF decompensation. However, this review is focused on CAD.

SCORE CHARTS

The 2016 European Society of Cardiology (ESC) guidelines on CVD prevention in clinical practice [1] provided a risk score chart showing the 10-year risk of fatal CVD [1]. A very high risk is defined as > 10% risk of fatal CVD over 10 years, while a high risk is defined as 5% to 10% risk of death related to CVD. The chart presents data for women and men divided into smokers and non-smokers [1]. It also includes data on age, which is known to be the most prominent CVD risk factor, as well as blood pressure and cholesterol level. For example, a 55-year-old male smoker who has a systolic blood pressure of 160 mmHg and total cholesterol level of 5.0 mmol/L (200 mg/dL) would be classified as having 11% risk of suffering from a fatal cardiovascular (CV) event over 10 years (a very high-risk patient).

Comparison of the total CV event risk, including stroke, myocardial infarction (MI), peripheral artery disease (PAD), or artery dissection, with the fatal CV risk shows that in general, the total CV event risk is three (in men) or four (in women) times higher than the fatal CV risk. What is interesting, the risk of a fatal CV event differs considerably across countries, and there are also significant differences within Europe [2]. For example, in Poland the CV mortality is higher (> 450/100,000 for male patients and > 350/100,000 for female patients per year) as compared with Germany, which is a low-risk country (> 225/100,000 for men and > 175/100,000 for women per year).

There is a significant overlap between primary prevention and secondary prevention, which can be easily seen in the very high-risk category. A very high risk of a CV event,

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even a fatal CV event, is present in patients who have already experienced a documented CVD or CAD, in patients after MI or acute coronary syndrome (ACS), after stroke or transient ischaemic attack (TIA), with aortic aneurysm or PAD; so, all patients who have a documented atherosclerotic vascular disease are classified into a very high-risk group. However, patients with diabetes mellitus (DM), target organ damage such as proteinuria, or DM with an additional risk factor (tobacco smoking, marked hypercholesterolaemia, or markedly elevated blood pressure) are also included in the very high-risk group, even if they do not have documented CVD. The same is true for patients with severe chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 or those with a calculated risk SCORE ≥ 10% [1]. A low-risk CVD category denotes < 1% risk of fatal CVD events within 10 years. Overall, there is a differentiation between primary and secondary prevention, but both overlap in the very high-risk group. The prevention strategies of CVD are the same for a patient with the presence of atherosclerotic vascular disease or a diabetic patient with marked hypertension, because both have a high risk (same strategies for secondary and primary prevention). This is important because it is highly relevant for the recommended strategies.

GENERAL RECOMMENDATIONS

In the literature there have been a number of general recommendations for primary and secondary prevention of CVD. For example, there is a recommendation for an annual influenza vaccination and the guidelines state that this may be considered in patients with established CVD (class IIb, level of evidence C) [1–6]. This recommendation may be considered; its class and the level of evidence indicate that it is an expert opinion and there are no randomised controlled trials (RCTs) actually showing that this recommendation is associated with a morbidity or mortality benefit.

The guidelines include a number of general recommendations with respect to changes in behaviour, smoking intervention strategies, nutrition, correct body weight and body weight change, or physical activity [1]. There is a strong recommendation to use established cognitive-behavioural strategies (e.g. motivational interviewing) with involvement of multidisciplinary health care professionals (e.g. nurses, dieticians, psychologists), particularly in subjects at very high CVD risk, who require multimodal interventions including education on healthy lifestyle, physical activity, stress management, and psychosocial counselling, to support lifestyle changes (class I, level of evidence A) [7–10]. Regarding smoking of tobacco, all smokers should be identified and advised on quitting using the follow-up support, nicotine replacement therapies, as well as varenicline and bupropion in monotherapy or in combination (class I, level of evidence A) [11–14]. It is recommended that smoking of herbal products like tobacco, both actively and passively, be stopped (class I, level of evidence B) [15–21].

There is consensus that a healthy diet is strongly recommended in CVD prevention (class I, level of evidence B) [22]. This recommendation is related to another stating that overweight and obese individuals should achieve a normal weight or aim for a reduction in weight in order to improve the CV risk profile through a decrease in blood pressure, elevated cholesterol and triglycerides, and risk of developing type 2 DM (class I, level of evidence A) [23, 24].

There is no doubt that these recommendations are important and should be implemented.

CHOLESTEROL-LOWERING AGENTS

Regarding drug-treatment recommendations, the first important strategy is for lipid control treatment, which is recommended in patients at a very high CV risk, i.e. those with CV atherosclerotic disease, or a very high-risk factor, e.g. DM, cigarette smoking, or arterial hypertension. For these patients the low-density lipoprotein cholesterol (LDL-C) goal is < 1.8 mmol/L (< 70 mg/dL), or a reduction of at least 50% if the baseline level is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) [1]. This is a class I recommendation; therefore, this goal should definitely be reached [25–28].

If a patient is in the high-risk category (but not the very high-risk category), the LDL-C level should unquestionably be < 2.5 mmol/L (< 100 mg/dL). For example, this target level of LDL-C refers to a patient without a proven CVD, who has a high blood pressure and suffers from DM as well as chronic kidney disease. Usually the first step to reach the target LDL-C level is to prescribe a statin, but if it is not possible, there are now two options. The first is to administer ezetimibe, and the other is to use one of the antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9), substantially reducing LDL-C levels by 60%, as shown for the monoclonal antibody, evolocumab [29], which was evaluated in a large RCT published in 2017 in the *New England Journal of Medicine* [30]. In the FOURIER study involving 27,564 patients with atherosclerotic vascular disease and LDL-C > 70 mg/dL (> 1.8 mmol/L), evolocumab given subcutaneously every two weeks on a background of statin therapy was assessed in comparison with a statin plus placebo [30]. The mean reduction in LDL-C on evolocumab was 59% compared with placebo. The primary endpoint was the composite of CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation. There was a significant reduction of the risk for the primary endpoint in patients receiving evolocumab vs. placebo (9.8% vs. 11.3%, p < 0.001) with no difference regarding adverse events, including neurocognitive events [30]. However, a disappointing result was no significant reduction in all-cause mortality, which stimulated a discussion on why this might have happened.

The Cochrane Collaboration meta-analysis of 20 RCTs with a follow-up time of at least 24 weeks published up to March 2017 involved data on 67,237 participants aged 52 to 64 years (median 61 years), including trials testing different PCSK9 inhibitors (alirocumab, n = 12; bococizumab, n = 3, RG7652, n = 1, and evolocumab, n = 4) [31]. The authors confirmed a marked LDL-C reduction and demonstrated that "PCSK9 inhibitor use probably leads to little or no difference in mortality. Evidence on relative efficacy and safety when PCSK9 inhibitors were compared with active treatments was of low to very low quality; follow-up times were short, and events were few. Large trials with longer follow-up are needed to evaluate PCSK9 inhibitors versus active treatments as well as placebo. Owing to the predominant inclusion of high-risk patients in these studies, applicability of results to lower-risk groups is limited. Finally, estimated risk differences indicate that PCSK9 inhibitors only modestly change absolute risks (often to less than 1%)" [31].

In March 2018 at the American College of Cardiology scientific sessions, the results of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) study [32] were presented, in which a fully human monoclonal antibody to PCSK9, alirocumab, administered in biweekly injections, was used in 20,000 patients at one to 12 months after ACS, who were followed for four years. The investigators reported that there was a significant (15%) reduction of all-cause death.

In the 2017 ESC guidelines for the management of acute MI in patients presenting with ST-segment elevation myocardial infarction (STEMI) [33] it is stated that additional lipid-lowering therapy is needed if the target LDL-C level of < 1.8 mmol/L (< 70 mg/dL) cannot be reached despite treatment with maximum-tolerated statin dose and ezetimibe (a cholesterol-absorption inhibitor that may reduce LDL levels by about 10%) [34]. PCSK9 inhibitors are also a very important option for all patients who cannot tolerate statins.

ANTIDIABETIC DRUGS

Regarding recommendations for secondary prevention in DM patients, in the 2016 ESC prevention guidelines [1] it is said that the HbA_{1c} level which should be achieved in such patients is < 7% in general (class I, level of evidence A). A target HbA_{1c} level of < 7% (< 53 mmol/mol) for the reduction in risk of CVD and microvascular complications in DM is recommended for most adults with either type 1 or type 2 DM, except for pregnant women (class I, level of evidence A) [35, 36]. Among antidiabetic drugs, metformin is the first-line therapy following renal function evaluation [37].

However, it should be noted that geriatricians usually have a different view, and they generally recommend that in diabetic patients over 70 years old, the HbA_{1c} level should not be < 7%, and in patients above 75 years old with a multimorbid disease it should be above 7.5%. A major adverse event of key importance among elderly DM patients is hypoglycaemia [38]. Of note, diabetic patients including the elderly benefit particularly from statin therapy in terms of reduced CV risk [39, 40].

Another important recommendation, present already in 2016, is that in patients with type 2 DM and CVD the use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor should be considered early in the course of the disease to reduce CV and overall mortality. The SGLT2 inhibitor is an inhibitor of a kidney transporter. It is important for the reabsorption of glucose from the urine into the blood, which causes glucosuria and lower blood glucose. It has been shown in a large number of patients and for a number of different drugs (starting with empagliflozin [41]) that the SGLT2 inhibitors reduce CV morbidity and mortality.

The EMPAgliflozin Removal of Excess Glucose: Cardiovascular OUTCOME Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was the first CV outcome trial investigating a SGLT2 inhibitor, empagliflozin, in patients with type 2 DM. In this trial involving more than 7000 patients with DM and CVD the primary endpoints were CV death, MI, and stroke. Compared with placebo, the primary endpoints were significantly reduced in patients who were on empagliflozin in addition to previous antidiabetic medications. The indication for using empagliflozin was not primarily to reduce glucose. It has also been shown that empagliflozin reduced all-cause mortality [41]. Of note, it was also observed that these drugs reduce rates of hospitalisation for HF. The CANagliflozin CardioVascular Assessment Study (CANVAS) programme investigating another SGLT2 inhibitor, canagliflozin, in patients with type 2 DM and high CV risk, was published in 2017 [42]. This study confirmed the findings of the empagliflozin study. The rate of the primary outcome, involving death from CV causes, nonfatal MI, or nonfatal stroke, was lower with canagliflozin than with placebo (hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.75–0.97). There was also a benefit of canagliflozin regarding the progression of albuminuria (HR 0.73; 95% CI 0.67–0.79). Of note, canagliflozin was associated with an increased risk of amputation (HR 1.97; 95% CI 1.41–2.75), mainly at the level of the toe or the metatarsus [42].

The results of these trials were confirmed by CV data from the retrospective multinational study Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL), in which SGLT2 inhibitors were compared with other classes of glucose-lowering drugs [42]. It has been reported that the use of SGLT2 inhibitors was associated with decreased risk of death and HF [43].

Currently in many institutions patients with DM and CVD, in particular those with HF, are treated with empagliflozin or canagliflozin, regardless of whether there is an additional need to improve glucose levels.

ANTIPLATELET DRUGS

Agents that inhibit platelet function remain the mainstay of secondary prevention of CVD. Lifelong use of low-dose acetylsalicylic acid (ASA) is recommended in all patients with proven atherosclerotic CVD [1]. However, low-dose ASA is not recommended in at-risk patients without proven atherosclerotic CVD (primary prevention). There have been a number of studies showing that if CV atherosclerotic disease is absent, use of ASA in such patients does not confer any benefit with respect to CV risk, but a higher risk of bleeding is observed. ASA should also be administered in patients after ischaemic stroke and after TIA, except for those with any type of atrial fibrillation (AF), who require lifelong oral anticoagulation.

In patients with ACS, ASA should be given to all individuals without contraindications at an initial loading dose of 150 to 300 mg, and a $P2Y_{12}$ inhibitor should be added to ASA as soon as possible. Then ASA should be given at a dose of 75 to 100 mg daily, while the $P2Y_{12}$ inhibitor should be maintained over 12 months, unless there are contraindications (class I, level of evidence A) [44–48].

A proton pump inhibitor (preferably not omeprazole) is strongly recommended in patients receiving dual antiplatelet therapy, who have a history of gastrointestinal bleeding or peptic ulcer, and it should be considered in the case of multiple other risk factors of bleeding, including *Helicobacter pylori* infection, age ≥ 65 years, concurrent oral anticoagulation, or use of corticosteroids (class I, level of evidence A) [49–51]. Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of the initial treatment strategy (class I, level of evidence A) [48], whereas clopidogrel (300-mg loading dose, 75-mg daily dose) is the first-line therapy for patients with contraindications to ticagrelor or prasugrel (class I, level of evidence A) [46, 52, 53].

In the future the treatment of stable CVD may change after the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [54], which was published in the *New England Journal of Medicine* in 2017. In this superiority study, a huge number of patients with stable CAD or PAD, i.e. 27,395 participants (22% women) at a mean age of 68 years from 602 centres in 33 countries, were randomised to a non-vitamin K antagonist oral anticoagulant (NOAC), the direct factor Xa inhibitor, rivaroxaban, at a very low dose (2.5 mg twice a day) plus ASA 100 mg/day as compared to rivaroxaban 5 mg twice a day or ASA alone. The primary endpoints in the COMPASS trial were CV death, stroke, and MI. The highest endpoint rate was found for ASA alone, while ASA plus rivaroxaban 2.5 mg twice a day showed a significant reduction of primary endpoints (HR 0.76) as well as in mortality and ischaemic stroke (Fig. 1). Benefits in terms of CV events were observed despite the fact that 90% of study participants were treated with statins. An increased risk of major bleeding was shown in the rivaroxaban plus ASA group vs. the ASA group (incidence 3.1% vs. 1.9%, HR 1.70; 95% CI 1.40–2.05), but this did not relate to fatal or nonfatal intracranial bleeding (0.2% vs. 0.1% and 0.2% vs. 0.2%, respectively). Limitations of this trial include exclusion of patients with recent stroke, severe HF, or end-stage renal disease, no determination of baseline low-density lipoprotein levels to assess statin therapy, and early termination of the trial (February 2017, a year ahead of time), which may have overestimated the treatment effect.

Recently, the COMPASS investigators have shown that, compared with ASA alone, rivaroxaban 2.5 mg twice a day combined with ASA lowered the incidence of severe limb ischaemia leading to an intervention or major vascular amputation by 43%, total vascular amputations by 58%, peripheral vascular interventions by 24%, and all peripheral vascular outcomes by 24% [55]. This convincingly indicates that the combination of rivaroxaban 2.5 mg twice a day and ASA could be a valuable therapeutic option for patients with PAD. The COMPASS trial supports the concept of combined antithrombotic therapy as an important component of long-lasting effective CV prevention.

It is well established that antiplatelet therapy is needed after ACS [1], and in most patients a combination of low-dose ASA with a $P2Y_{12}$, an ADP receptor inhibitor, for 12 months is used. There are potential deviations from this rule. In ACS patients with a high bleeding risk the duration of dual antiplatelet therapy (DAPT) may be reduced to between three and six months. However, after the results of the PEGASUS trial were published [56], in patients with a very high CV risk and no particular bleeding risk a longer therapy (over three years), precisely a combination of ASA 100 mg/day with ticagrelor 60 mg twice a day, may be considered.

The ESC guidelines on DAPT in CAD were published in September 2017 [57]. After a percutaneous coronary intervention (PCI) the strategies are different depending on whether it was a stable CAD or an ACS. In stable CAD the use of ASA and clopidogrel is recommended for at least six months, regardless of the type of stent that has been implanted, but in patients with high bleeding risk the duration of the combination therapy may be reduced to three months or to one month [57]. In patients with ACS the standard therapy is 12 months of DAPT. Patients with STEMI at high gastrointestinal bleeding risk should receive a proton pump inhibitor together with DAPT [58, 59]. In most European centres ticagrelor or prasugrel are preferred over clopidogrel in combination with ASA. In STEMI patients with a high bleeding risk, DAPT should be recommended for at least six months, and then the $P2Y_{12}$ inhibitor should be discontinued (class IIa, level of evidence B) [60, 61], but in such patients prasugrel should not be used; clopidogrel or ticagrelor are the preferred options. DAPT is also recommended in STEMI patients who did not undergo PCI, and its duration should be 12 months, except for patients with excessive bleeding risk (class IIa, level of evidence C) [33].

STEMI patients in whom left ventricular thrombus was detected should receive anticoagulation for up to six months. Therapy should be guided by repeated imaging [62, 63].

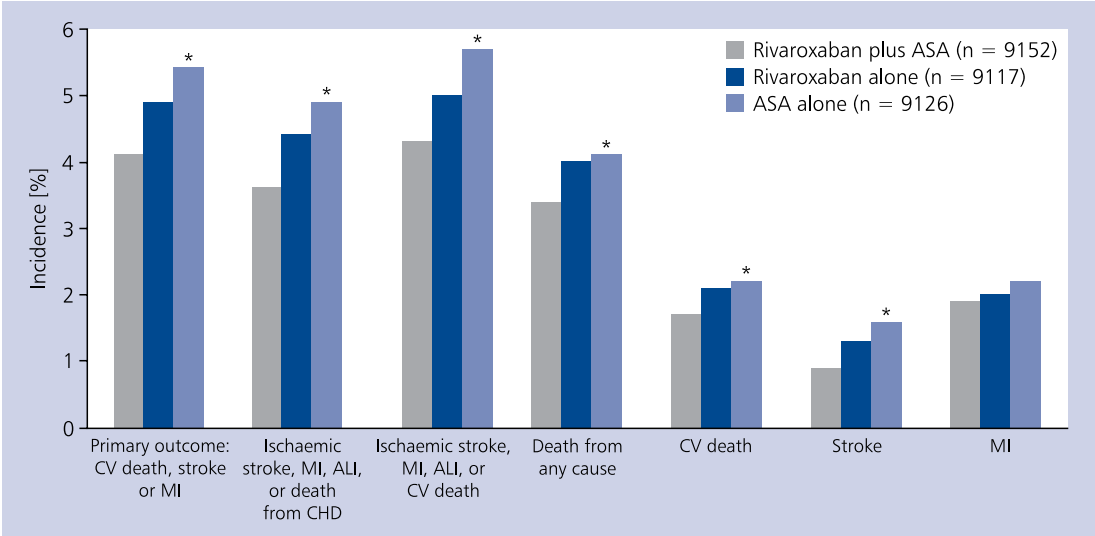

Figure 1. Clinical efficacy outcomes from the COMPASS trial (based on [66]). Patients on rivaroxaban 2.5 mg twice a day combined with acetylsalicylic acid (ASA) 100 mg/day compared with those treated with ASA alone had lower risk of most cardiovascular events, including death; only the risk of myocardial infarction (MI) was similar in both groups; *p < 0.05 for differences between the rivaroxaban-plus-ASA arm and the ASA-alone arm. No significant differences were observed between the rivaroxaban-alone and the ASA-alone arms except for the secondary outcome including ischaemic stroke, MI, acute limb ischaemia (ALI), or cardiovascular (CV) death; CHD — coronary heart disease

In a number of patients, particularly in those with AF, triple antithrombotic therapy, involving two antiplatelet drugs in combination with a vitamin K antagonist (VKA) or a NOAC, is needed following PCI [57, 64]. In patients who require chronic anticoagulation, the therapeutic options are now more complicated. Generally, in triple antithrombotic therapy prasugrel or ticagrelor should not be used. The use of ASA and clopidogrel with an anticoagulant is recommended. The absolute minimum of such a triple-therapy treatment after PCI is one month, and then two drugs should be continued, ASA or clopidogrel plus a NOAC or a VKA for an additional 11 months. In AF patients who experienced ACS the triple therapy should be given for up to six months, and then changed for the dual antithrombotic therapy (ASA/clopidogrel + NOAC/VKA) for an additional six months. Then the AF patients should receive a NOAC or a VKA alone [64].

In a patient with a very high bleeding risk, in order to avoid anticoagulation, one may decide to implant a left atrial appendage occluder in addition to using antiplatelet therapy [64].

ANTIHYPERTENSIVE DRUGS

In hypertensive patients who are at high CV risk, starting from grade 1 or 2 hypertension, drug treatment should be considered (class IIa, level of evidence B) [65]. Experts recommend initiating the therapy of arterial hypertension with a two-drug combination in patients with markedly elevated baseline blood pressure or high CV risk, suggesting also that such a combination in a single pill may be considered because of improved adherence (class IIb, level of evidence C) [66]. Regarding various classes of antihypertensive drugs, the following ESC recommendations were published in 2016 [1]:

- β-blockers in all patients with reduced left ventricular systolic function (left ventricular ejection fraction [LVEF] ≤ 40%) (level of evidence A);
- angiotensin converting enzyme inhibitors (ACEIs) within 24 h in all patients with LVEF ≤ 40% and in patients with HF, DM, hypertension, or chronic kidney disease, unless contraindicated (level of evidence A), to prevent recurrent ischaemic events (level of evidence B);
- angiotensin receptor blockers in patients who are intolerant to ACEI (level of evidence B);
- eplerenone, an aldosterone blocker, in patients with prior MI receiving ACEI and β-blockers, who have an LVEF ≤ 35% and either DM or HF, with serum creatinine < 221 μmol/L (< 2.5 mg/dL) for men and < 177 μmol/L (< 2.0 mg/dL) for women or normokalaemia (level of evidence A).

Pharmacological prophylaxis is supported also by national preventive initiatives [67].

REHABILITATION PROGRAMMES

There is a strong recommendation to encourage patients hospitalised for an ACS or revascularisation to participation in a cardiac rehabilitation programme. The same holds true for patients with HF [68, 69]. Of note, the 2017 updated Cochrane systematic review of 23 RCTs (n = 2890), which

compared centre-based cardiac rehabilitation (including hospitals) with home-based programmes in patients with MI, angina, HF, or a history of revascularisation, indicated that the two interventions provide similar effects in terms of improving clinical and health-related quality of life outcomes [70].

In current guidelines there is consensus that stable patients with CVD should take part in preventive programmes for therapy optimisation, adherence, and risk factor management [71–75]. Implementation of these recommendations in everyday practice is suboptimal worldwide.

ANTI-INFLAMMATORY AGENTS

Lately, a new strategy to treat the residual CVD risk related to inflammation has been successfully tested. This strategy has been shown in the recently published Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial [76]. The study evaluated anti-inflammatory therapy with a fully human monoclonal interleukin-1β antibody, canakinumab, in 10,061 patients with atherosclerotic vascular disease, following previous MI, who were either on statin or on conventional therapy of CVD with elevated highly-sensitive C-reactive protein ≥ 2.0 mg/L. Patients at a mean age of 61 years were randomised to an interleukin-1β antibody, canakinumab, at a dose of 50 mg, 150 mg, or 300 mg, administered subcutaneously every three months, or placebo. The primary endpoints in the CANTOS trial were non-fatal MI, non-fatal stroke, or CV death. As expected, use of all the three doses of canakinumab led to a significant decrease in C-reactive protein concentrations, by 26%, 37%, and 41%, respectively, with no impact on cholesterol levels. The results showed a significant reduction in the primary endpoints for 150-mg and 300-mg doses of canakinumab at a median follow-up of 3.7 years (HR 0.85 and HR 0.86, respectively). Importantly, an increase in the rate of fatal infections was observed among patients receiving canakinumab (incidence rate, 0.31 vs. 0.18 events [for placebo] per 100 person-years; p = 0.02), despite the fact that patients with a history of chronic or recurrent infection, an immunocompromised state, a history or high risk of tuberculosis or disease related to the human immunodeficiency virus, or using other anti-inflammatory treatments, were excluded [76]. The authors concluded that "anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every three months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering" [76].

SUMMARY

Secondary prevention of CVD equals primary prevention in patients with the highest risk. The important drugs in the prevention include antiplatelet drugs, statins, antihypertensive medications, and antidiabetic agents, including some new options, i.e. the SGLT2 inhibitors, the PCSK9 inhibitors, and potentially the combination of low-dose ASA and rivaroxaban 2.5 mg twice a day Now we may look to the future to learn more about the new anti-inflammatory therapies.

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