PREVENTION OF CORONARY ARTERY DISEASE

Assessment of Cardiovascular Risk

Recommendations for the assessment of cardiovascular risk in the adult population is presented in Tables 1 and 2 and Figures 1-6. Several multifactorial risk scores to assess the risk for cardiovascular disease have been used to identify patients at high cardiovascular risk and candidates for preventive therapy. The ESC uses the SCORE (Systematic Coronary Risk Estimation) algorithms (SCORE 2 and SCORE2-OP) (http://www.heartscore.org) .[1,2]
The 2019 ACC/AHA guidelines on primary prevention use the Pooled Cohort Equation to estimate the 10-year ASCVD (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/).[3] These algorithms, as well as those based in the Framingham risk score overestimate the risk.[4] The 2026 ACC/AHA GL on dyslipidemia recommend use the American Heart Association Predicting Risk of cardiovascular disease EVENTs (PREVENT) equations for 10- and 30-year risk assessment to guide lipid-lowering therapy in primary prevention in adults aged 30 to 79 years (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator) . They also recommend use of the "CPR" Model: A) *C*alculate 10-year ASCVD risk; B) *P*ersonalize the estimated risk to the specific patient by considering factors not included in PREVENT-ASCVD equations; and C) possibly *R*eclassify with selective use of coronary artery calcium (CAC) and *R*eassess treatment recommendations.[5] Genetic risk estimate for CAD may also be used to predict sudden cardiac death.[6] Screening for hyperlipidemia is presented in Table 3.

Prevention of Cardiovascular Disease

General recommendations for primary prevention measures are presented in Tables 4 and 5 and Figures 7-12. The four standard modifiable cardiovascular risk factors (SMuRFs) are hypertension, dyslipidaemia, diabetes mellitus, and smoking. These and body-mass index are the most important modifiable risk factors.[7] **Hypertension** is discussed in detail in the relevant Chapters.

Lifestyle

Data from the Framingham and CARDIA studies provide evidence for the importance of healthier lifestyle for the primordial prevention of cardiovascular disease.[8,9] Among persons at high genetic risk, a favorable lifestyle ***(avoiding smoking and obesity, regular physical activity and a healthy diet)*** is associated with a nearly 50% lower relative risk of coronary artery disease than an unfavorable lifestyle.[10-14] Regular ***physical activity*** has a protective

effect, regardless of whether physical activity follows a weekend warrior pattern or is spread more evenly throughout the week,[15] and vigorous physical activity provides greater health benefits per unit time than moderate activity.[16] However, the value of strenuous exercise is debatable. A U-shaped association between all-cause mortality and dose of jogging has been detected with light and moderate joggers having lower mortality than sedentary nonjoggers, whereas strenuous joggers having a mortality rate not statistically different from that of the sedentary group.[17] Lifelong endurance sport participation (ie Marathon runners) is not associated with a more favourable coronary plaque composition compared to a healthy lifestyle.[18] Extremes of physical exertion may trigger myocardial infarction.[19] Thus, moderate-intensity aerobic (endurance) physical activity for a minimum of 30 minutes on 5 days each week, or vigorous-intensity aerobic PA for a minimum of 20 minutes on 3 days each week, or combinations thereof, is generally recommended.[20] ***Smoking*** is associated with a substantially increased risk of myocardial infarction that is reduced but not becoming negligible with electronic cigarettes.[21] ***Dietary*** habits are important although their significance and implementation depend on the social environment. ***Mediterranean diet*** has long-term effects on the gut microbiome composition that modulates the protective association between diet and cardiometabolic risk.[22] Restriction of calories and, probably, intermittent fasting are cardioprotective.[23] Higher ***olive oil*** consumption is associated with lower risk of total and cause-specific mortality.[24] Replacement of ***saturated fat and trans-fats*** (mainly hydrogenated oils) with unsaturated fats reduces mortality.[25-28] The PURE prospective observational study to assess the association of nutrients with cardiovascular disease and mortality collected data on more than 135 000 individuals from 18 countries all over the world, and mainly including middle- and low- income countries, for an average of 7·4 years. Higher fruit, vegetable, and legume consumption (375–500 g/day) was associated with a lower risk of non-cardiovascular, and total mortality.[29] High ***carbohydrate*** intake was associated with higher risk of total mortality, but also higher intake of fats (including saturated fatty acids, monounsaturated fatty acids, and total polyunsaturated fatty acids) and animal protein were each associated with lower mortality.[30] In the mainly low- or middle-income populations studied, total fat and types of fat were not associated with cardiovascular disease, whereas saturated fat had an inverse association with stroke.[30] ***Butter consumption*** was low and associated with an increased, but not significant, risk of cardiovascular disease, whereas dairy products were associated with lower mortality and cardiovascular disease, particularly stroke.[31] Reducing saturated fatty acid intake and replacing it with carbohydrate has an adverse effect on blood lipids.[32] ***Fish (especially oily)*** consumption was beneficial.[33] The results of PURE may not be directly applicable to western countries with a higher rate of saturated fat and protein, since there has been evidence for a direct association between ***red meat*** intake and CVD incidence and mortality, although the magnitude of the association is

less strong than that for ***processed meat***.[27,28] In an individual-level data analysis of 29,682 adult participants in six prospective cohort studies in the USA, higher intake of processed meat, unprocessed red meat, or poultry, but not fish, was significantly associated with a small increased risk of incident CVD, whereas higher intake of processed meat or unprocessed red meat, but not poultry or fish, was significantly associated with a small increased risk of all-cause mortality.[34] In the US Health Professionals Follow-Up Study cohort (1,023,872 person years of follow-up), total, unprocessed, and processed red meat intake were each associated with a modestly higher risk of CHD.[35] In a prospective study from UK Biobank, compared with meat-eaters, fish eaters had a lower risk of several cardiovascular outcomes—incident CVD, IHD, MI, stroke, and HF—independent of confounders. ***Ultraprocessed*** foods (chips, soft drinks, sweets, processed meats, many ready meals, fruit yogurts, many breakfast cereals), are high in saturated fat, added sugars, and sodium, which are already targets for cardiometabolic risk reduction.[36,37] Eating fish rather than meat or poultry was associated with a lower risk of a range of adverse cardiovascular outcomes, and vegetarians showed only lower risk of CVD incidence.[38] The effect of unprocessed meat on the risk of IHD is certainly less than that of processed red meat.[27,34,39,40] It seems that total red meat intake does not differentially influence blood lipids and apolipoproteins, with the exception of triglycerides, when all comparison diets are analyzed together.[41] As discussed in Chapter on Epidemiology, the discrepant results are likely heavily contributed to by residual confounding, since it is difficult to distinguish between the effect of dietary cholesterol per se and the effect of dietary patterns high in cholesterol or ***saturated fat***,[42] and the impact of dietray approaches on clinical outcomes has so far been inconsistent.[43] In a prospective cohort study and updated meta-analysis, greater ***dietary cholesterol*** and ***egg*** consumption were associated with increased risk of overall and CVD mortality. However, the positive association for egg consumption and CVD risk was significant in US cohorts, there was a marginal positive association in European cohorts, and no association in Asian cohorts.[44] Excess ***sodium*** intake is associated with an increased risk of coronary heart disease and cardiovascular mortality.[45,46] Low to moderate amounts of ***alcohol*** (such as no more than 1 to 2 drinks a day), as opposed to heavy drinking, are associated with a reduced risk of coronary artery disease, stroke, sudden death, and possibly heart failure.[47-49] In a large cohort study, even low-risk drinking was associated with higher cancer mortality among older adults with health-related or socioeconomic risk factors. However, an attenuation of mortality was observed for wine preference and drinking only during meals.[50] Moderate wine consumption, 12-35 glasses/month is associated with a significantly reduced cardiovascular risk.[51] ***Caffeine***, studied primarily in the context of coffee, has been shown either to have no relationship or to be associated with a lower risk of coronary artery disease and heart failure.[52,53] Data on relationships between caffeine and diabetes are not consistent, but habitual coffee consumption has been associated with a lower

risk of incident type 2 diabetes.[52] Whereas no clear relationship between caffeine and blood lipids is evident, unfiltered coffee raises low-density lipoprotein cholesterol.[52] Data are fairly consistent that moderate caffeine consumption, again studied primarily in the setting of coffee consumption, was associated with a lower risk of stroke. Data on high doses of caffeine such as that found in energy drinks are limited and generally suggest cardiovascular harm.[52] Exposure to ***preservative food additives*** widely used in industrial foods is associated with a higher incidence of hypertension and CVD.[54]

Aspirin

Although aspirin is necessary for secondary prevention, its value for primary prevention is controversial, because although effective for preventing CAD, it is also associated with excess haemorrhage and the benefit-risk ratio may be small. Aspirin had been found clearly beneficial in high-risk patients as defined by the Million Heart's initiative,[55] in intermediate risk (TIPS-3 trial),[56] and in patients with elevated Lp(a) levels.[57] Discontinuation of low-dose aspirin prescribed for primary prevention in the absence of major surgery or bleeding has been associated with a>30% increased risk of cardiovascular events.[58] However, in other trials (ASCEND, ARRIVE, JAPAD, and, especially, the three ASPREE reports but with several limitations[59]) in both diabetic and nondiabetic patients, produced rather controversial results and a risk of increased gastro-intestinal bleeding.[60-63] In the most recent meta-analyses, aspirin for primary prevention reduced cardiovascular events, but significantly increased the bleeding risk in most,[64-66] although not all of them.[67] The 2019 ACC/AHA (2019 GL on Primary Prevention of CVD) considers aspirin 75-100 mg, for primary prevention among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (IIb A), and discourages its use in persons aged >70 years.[68] Similar recommendations (for patients with a 10-year CV risk >=10% and aged 40-59 years but not for those >=60 year)-old) were provided by the 2021 U.S. Preventive Services Task Force (USPSTF) report.[69] The ESC discourages its use (III A) in patients without cardiovascular disease (ESC 2021 GL on CVD prevention), but gives a IIb A recommendation for high risk patients with diabetes (ESC 2021 GL on CVD Prevention, and 2023v GL on diabetes).[70,71] Diabetics are at increased risk for CVD, and aspirin may be considered in high-risk, and especially young (<70 years) patients.[72,73] Individuals with coronary artery calcium (CAC)≥100 and, in particular, CAC≥400 may be good candidates for aspirin therapy for primary prevention.[74] In adults ≥70 years without overt CVD and with an estimated risk of major CVD events <1% per year, aspiring is not indicated.[75] Of note, aspirin use 3 or more times per week has been associated with a reduction in all-cause cancer, and especially oesophageal, gastro-intestinal, and colorectal cancer, and mortality, [76,77] as well as with a significantly lower risk of hepatocellular carcinoma in patients with chronic viral hepatitis.[78] Thus, an individualized

approach should always be adopted.[60,79] Currently available P2Y12 inhibitors are rather unlikely to replace aspirin, because of unconvincing demonstration of their superiority vs. low-dose aspirin.[59]

Lipid disorders

Screening with a lipid profile should start at the age of 19 years unless if familial hypercholesterolemia is suspected (Table 3). Non-fasting blood samples can be routinely used for the assessment of ***plasma lipid profiles***.[80] Preparative ultracentrifugation represents the gold standard for measuring ***LDL-C***, but it is time-consuming and expensive to perform. Thus LCL-C is traditionally estimated by equations such as the Friedewald, or the Martin/Hopkins and Sampson/NIH equations. The last two are preferred by the ACC/AHA 2026 GL on dyslipidemias, but the most commonly used is the Friedewald equation [LDL-C = total cholesterol - HDL-C – (triglycerides/5)], that underestimates LDL when triglycerides are >=150mg/dl.[81] LDL-C, therefore, depends on triglyceride measurements, and fasting, defined as 10-12 h of no oral intake other than water or medications, may affect its value. Maximal mean changes for random, non-fasting vs fasting levels are +26 mg/dL for triglycerides and -8mg/dL for total cholesterol or LDL.[82] A novel adaptable LDL-C estimation method that uses an adjustable factor instead of 5 in the equation, has been found more accurate in nonfasting individuals by means of approaching direct measures of LDL by rapid ultrcentrifugation.[83] If triglycerides are >200 mg/dl elimination of sugar and trans fats intake as well as weight reduction and regular exercise may achieve reductions of up to 50%. Tests of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 do not add significant improvement in CVD prediction (Table 3).[84] Recommendations for lifestyle changes are provided in Tables 6 and 13, for medical therapy in Tables 6-13 and Figures 13-24. Specfic recommendation for hypertriglyceridemia are presented in tables 10 and 13 and Figures 17-21.

Drugs for Hypercholesterolaemia

Statins

Statin therapy is associated with a relative risk reduction of 24% for CAD, and this raises to 44% among persons at high genetic risk for CAD.[85] Statins inhibit the enzyme HMG-CoA reductase that facilitates the production of cholesterol in the liver, and significantly reduce mortality and cardiovascular events both in patients with established CAD and persons at risk as a primary prevention measure.[86,87] Guidelines on dyslipidemia (2026 ACC/AHA, 2019 and 2025 ESC) a goal of LDL-C <70mg/dL (1.8 mmol/L) for high-risk patients and LDL-C <55 mg/ dL (1.4 mmol/L) for secondary prevention in patients at very high risk of ASCVD events.[1,2,5] Strict LDL-C control with a target of <70 mg/dl has been found to significantly attenuate plaque volume progression based on noninvasive quantitative assessment by

coronary CTA.[88] There has also been evidence that patients who achieve an LDL-C level <50 mg/dl are at lower cardiovascular disease risk than are those achieving an LDL-C level 75 to <100 mg/dl, but clear attribution of this to high-dose statin therapy could not be ascertained.[89] However, the intensity of statin therapy is associated with mortality reduction in patients with cardiovascular disease.[90] Statin therapy in an intermediate-risk, ethnically diverse population without cardiovascular disease has also resulted in a significantly lower risk of cardiovascular events (Hope 3).[91] Thus, cholesterol-lowering therapy is also indicated in patients with diabetes , chronic kidney disease, transplantation, peripheral artery disease, and at risk of stroke. Optimal LDL-C control should be started early in life.[92] Lipid lowering drugs, with the possible exception of bile acid sequestrants that are not absorbed, should not be given in ***pregnancy*** or during the ***breastfeeding*** period.[93]

Low ***HDL-C*** levels can be caused by genetic abnormalities, haematologic malignancies, liver disease, acute inflammatory states and drugs such as anabolic steroids, atypical antipsychotics, antiretroviral therapy, β-blockers, and immunosuppressive agents.[94] They are treated with life-style changes, since *niacin* or *inhibitors of cholesteryl ester transfer* protein did not improve cardiovascular outcomes despite significantly increasing the HDL cholesterol level. [95-97]

Statins may be *lipophilic* (lovastatin, simvastatin, atorvastatin, pitavastatin) or *hydrophilic* (pravastatin, rosuvastatin). Hydrophilic statins may have fewer side effects due to less muscle cell penetration and lower dependence on the cytochrome P450 enzyme but differences between the two groups by means of clinical outcomes are not established.[98] Furthermore, lipophilic statins cross the blood-brain barrier and might be protective against neurogenerative disorders, such as Parkinson disease,[99] and may specifically inhibit aldosterone secretion.[100] Rosuvastatin is twice as potent as atorvastatin, but there is considerable individual variation in the LDL-C reduction at all doses statins.[101] All statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, and may thus produce statin-associated ***myopathy***.[102] [103] Statin-associated muscle symptoms and CK levels cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels (< 4 ULN), with a prevalence of 7–29% in registries and observational studies. All statins may result in elevated CK levels but simvastatin has been particularly associated with myopathy.[104] Additional risk factors for myopathy are age (>80 years), female sex, hypothyroidism, diabetes, renal and hepatic function impairment, preexisting myopathies, major surgery, and vitamin D deficiency that by itself can cause muscoskeletal pain.[105] Interruption of statins for 2-6 weeks and resumption of another statin with lower or intermittent doses and ezetimibe may be needed. When it is difficult to determine whether a patient's symptoms are attributable to statin, the "n-of-1 trial" approach may be used, ie the patient is assigned to statin therapy or placebo, up to three times each, for

up to three weeks.[106] The possibility of "nocebo effect", ie exaggeration of symptoms when the patients and the doctor are aware of statin therapy (as opposed to blinded, randomised trials), should be also considered.[107] Most patients with statin myopathy can continue statin therapy.[108] Myopathy with significant elevation of serum creatine kinase (>10 of upper limit of normal-ULN), is a rare but serious side effect of statins, affecting 1 per 10 000 people on standard statin doses. ***Mild myalgia*** may affect 5-10% of statin users.[103] For ***muscle cramps*** a switch to another statin might be tried, as well as diltiazem, and vitamin B complex with or without magnesium supplements (see also Chapter 33).[109] Statin-associated ***autoimmune myopathy*** is a more serious condition, occurring on 2-3/100,000 patients treated with statins. It is characterized by CK levels >2000 IU/L)ie >10 times the upper normal limit), muscle weakness, evidence of muscle-cell necrosis on biopsy, and the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase that establish diagnosis. In contrast to most patients who have side effects from statin therapy, those with statin-associated autoimmune myopathy may have progressive weakness that must be controlled with immunosuppressive therapy.[110] ***Rabdomyolysis*** with additional renal impairment and/or myoglobinuria is a rare (1/10000) but serious complication of high-dose stating therapy.[111]

Mild elevations in ***serum aminotransferases*** arise in up to 3% of treated patients, usually, but not invariably, without concomitant γGT elevation, but clinically apparent drug-induced liver injury is rare.[112] In the U.S. Drug Induced Liver Injury Network Registry, among 1,188 cases of drug-induced liver injury, 22 cases were attributed to a statin with a latency to onset of 34 days to 10 years (median 155 days) since starting therapy. Nine patients presented with cholestatic hepatitis and 12 patients presented with hepatocellular injury, of which six had an autoimmune phenotype. Nine patients were hospitalized, four developed evidence of hepatic failure, and one with pre-existing alcoholic liver disease died. All commonly used statins were implicated.[113] Statin therapy (as well as niacin) is associated with a slightly increased risk of development of ***diabetes*****,** especially in high doses, but the risk is low, approximately one patient per 1000 per year.[112] Inhibition of HMG-CoA reductase is associated with increased body-mass index leading to increased insulin resistance, and to increased diabetes,[114] and diabetes progression in diabetics.[115] The proposed mechanism is that augmented uptake of cholesterol (caused by statins) in pancreatic β cells lowers insulin production. Patients with familial hypercholesterolemia have *low* incidence of type 2 diabetes mellitus, due to their genetically determined *low* production of the LDL cholesterol receptor.[116] Statins should not be stopped in high-risk primary and secondary prevention patients, but screening of individuals with evidence of metabolic syndrome is reasonable. Pitavastatin has been associated with a lower risk of new-onset diabetes mellitus,[117] but it lacks data on cardiovascular outcomes from large trials in patients with diabetes. Rosuvastatin

(20 mg od) and atorvastatin (40 mg od) have comparable efficacy for reducing cardiovascular risk but rosuvastatin results in lower LDL cholesterol levels and a higher risk of new onset diabetes mellitus and cataract.[118] There is no increased risk of developing cognitive defects such as memory loss.[112,119] In another retrospective observational analysis of databases, an increased risk of acute kidney injury was found with high potency statins (>=10 mg rosuvastatin, >=20 mg atorvastatin, and >=40 mg simvastatin) in the first 120 days after initiation of treatment,[120] but such a relationship was refuted in a subsequent meta-analysis.[121] There is no increased risk of cancer with statins,[122] and these agents may actually reduce the risk of cancer in heart transplant recipients.[123] Statins reduce the risk of ischaemic stroke risk,[124] while an association with intracranial haemorrhage has not been confirmed.[112] particularly those cases with a lobar location.[125] Some worsening in energy and exertional fatigue, especially in women, may be seen.[126] However, the prevalence of statin intolerance, in general, may be overestimated.[127] In the ***elderly*** (>=75 years) current guidelines recommendations are less clearly defined. However recent evidence is clearly in favour of therapy even in patients >80 years.[128-132] Statins have traditionally been contraindicated during ***pregnancy*** and lactation due to concerns about their potential risks. However, in a National Norwegian Registry, no association between statin exposure in pregnancy and congenital malformations was detected.[133]

Metabolism of statins occurs through *cytochrome P450* enzymes subcategories such as CYP3A4 (the most common enzyme involved in drug metabolism), and *CYP2C9*, and several ***drug interactions*** may occur.[134] Simvastatin and lovastatin undergo significant CYP3A4 metabolism, whereas atorvastatin undergoes a much lesser amount. Fluvastatin, rosuvastatin and pitavastatin utilize CYP2C9, and pravastatin (a substrate for P-gp) does not undergo CYP450 metabolism. Thus, CYP3A4 inhibitors *ketoconazole, posaconazole,* and especially *itraconazole, erythromycin, clarithromycin, telithromycin, ciprofloxacin, HIV protease inhibitors (*such as *lopinavir, ritonavir, atazanavir, darunavir*, and *fosampenavir),* and *hepatitis C virus protease inhibitors (*such as *boceprevir and telaprevir)*, may significantly increase statin, and especially lovastatin and simvastatin exposures, and result in rhabdomyolysis. Concomitant administration of lovastatin and simvastatin with HIV protease inhibitors or HCV protease inhibitors, therefore, is contraindicated (see also www.hiv-druginteractions.org). Atorvastatin should be restricted to 20 mg od, rosuvastatin to 10 mg, and pravastatin does not need dosage modification, whereas no data are available for fluvastatin, in patients taking HIV or HCV protease inhibitors. *Calcium channel blockers*, as well as *dronedarone*, *ranolazine* and *conivaptan* (an IV vasopressin receptor antagonist used for the treatment of euvolemic or hypervolemic hyponatremia), may result in moderate increases in statin exposure, and caution is needed for combinations with lovastatin and simvastatin. High atorvastatin doses (80 mg) may increase digoxin toxicity. Combination

therapy of *cyclosporine*, everolimus, tacrolimus or sirolimus with lovastatin, simvastatin and pitavastatin are potentially harmful. Rosuvastatin, fluvastatin, pravastatin, and atorvastatin may be used but at the lowest doses. In patients taking *colchicine*, lovastatin, simvastatin and atorvastatin should be given at lower doses.[134]

Ezetimibe

Several patient groups may need additional medication.[135] Ezetimibe is an inhibitor of NPC1L1, a protein that transports dietary cholesterol from the gut into intestinal enterocytes. Mutations that inactivate NPC1L1 have been associated with a reduced risk of CAD,[136] and compared with atorvastatin monotherapy, the combination of statin plus ezetimibe results in greater coronary plaque regression.[137] In the large IMPROVE-IT trial, adding ezetimibe to statin therapy in patients with an acute coronary event decreased the risk of MI and stroke by 1-2% without affecting cardiovascular mortality,[138] and with a particularly large effect seen in patients with a prior stroke.[139] The clinical benefit following an acute event appears to be enhanced in patients with a prior CABG.[140] In the EWTOPIA 75 trial ezetimibe prevented cardiovascular events in individuals aged ≥75 years with elevated LDL-C levels, supporting the importance of primary prevention in this age group.[141]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Monoclonal antibodies

Alirocumab and evolocumab are monoclonal antibodies that significantly reduce LDL and Lp(a) levels, given alone or in combination with statins. In patients not responding or intolerant to high-intensity statins and ezetimibe, alirocumab 75-150 mg subcutaneously every two weeks, or evolocumab 140 mg subcutaneously every two weeks or 420 mg monthly, reduced the atheroma volume and cardiovascular events by reducing both LDL-C and hsCRP (FOURIER and ODYSSEY trials).[142,143] The addition of alirocumab to high-intensity statin therapy has also resulted in regression of coronary plaque burden and plaque stabilization in patients with familial hypercholesterolemia (PACMAN-AMI and ARCHITECT trials).[144,145] In patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke but with an LDL >= 90 mg/dL, evolocumab led to a lower risk of first cardiovascular events (VESALIUS-CV RCT).[146] The effect of PCSK9 inhibitors depends on residual LDL receptor activity, and side effects are similar to those of statins, without increased risk of diabetes as initially observed. [147] However, when LDL levels <25 mg/dL are achieved there is an increased risk of cataracts and neurocognitive effects,[148,149] although the latter has not been verified in all trials.[150] Concerns have emerged for high immunogenicity with antidrug-antibody formation for agents such as bococizumab,[151] and, to a much lesser degree, alirocumab.[152] The FDA approved alirocumab and evolocuman for secondary prevention in high-risk patients who cannot control their cholesterol with statins in 2015, and both ACC and ESC recommend their use in statin-

treated high-risk patients who cannot achieve a LDL-C<70 mg/dL.[153,154] Other monoclonal antibodies are also effective.[155] Enlicitide is an oral PSK9 inhibitor with a very good efficacy and safety profile in patients with heterozygous familial hypercholesterolaemia.[156] In statin-treated adults with a history of a major ASCVD event or at increased risk for a first event, enlicitide achieved greater reductions in LDL-C, ApoB, and non-HDL-C than ezetimibe or bempedoic acid.[157] Laroprovstat is a small-molecule proprotein convertase subtilisin/kexin type 9 inhibitor that does not block the proprotein convertase subtilisin/kexin type 9–LDL receptor interaction but stabilizes the proprotein convertase subtilisin/kexin type 9 C-terminal domain and prevents lysosomal trafficking and degradation of the LDL receptor. Laroprovast and rosuvastatin treatment lowers LDL levels by 80%.[158]

RNA interference (RNAi) inhibitors

These are nucleic acid therapies that catalytically degrade PCSK9 mRNA.

Inclisiran (also FDA-approved) can be given with an infrequent dosing regiment , ie 300 mg SC injection repeated in 3, 9 and 15 months or just twice a year (ORION trials).[159-161] Main side-effects are injection-site reactions and pain in 10% of patients.[160,162] Antidrug CSK9 inhibitor antibodies in post-treatment samples was seen in up to 2.5% of patients on inlcisiran but were often transient and not associated with changes in any pharmacologic or clinical measurements. Injection-site adverse events occurred in 2-4% of patients but were mild. [159,161] Interestingly, in patients with homozygous familial hypercholesterolemia, inclisiran treatment did not reduce LDL-C levels despite substantial lowering of PCSK9 levels.[163] This finding could be explained, at least in part, by the fact that LDLR is completely lacking or defective in patients with HoFH. In such circumstances, even complete elimination of PCSK9, a target of inclisiran, does not influence the impaired clearance of LDL-C.[164] *Olezarsen*, an antisense oligonucleotide targeting messenger RNA for apolipoprotein C-III (APOC3) has also shown promising results in reducing triglyceride levels and reducing the risk of pancreatitis in patients with fasting triglyceride levels >500 mg /dL.[165,166]

ATP-citrate lyase inhibitors

Bempedoic acid is an oral small molecule that inhibits cholesterol synthesis by inhibiting the action of ATP-citrate lyase, a cytosolic enzyme upstream of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase pathway.[167] Bempedoic acid (single dose 180 mg/day) reduces LDL-C levels by approximately 23% as monotherapy, approximately 18% when given on a background of statin therapy, and by 38% when given in a fixed-dose combination with ezetimibe.[168,169] Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) (CLEAR RCT). The incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo, as were the incidences of small increases in serum

creatinine, uric acid, and hepatic-enzyme levels.[168] In the BempedACS RCT, adding bempedoic acid to statin–ezetimibe therapy in the setting of ACS was safe but failed to improve the percentage of patients achieving the LDL-C goal (<55 mg/dL) at 8 weeks.[170]

Angiopoietin-like 3 (ANGPTL3) inhibitors

ANGPTL3 is a hepatic protein involved in the regulation of lipoprotein metabolism and homeostasis. SHR-1918 is a long-acting, fully-human, monoclonal antibody directed against ANGPTL3 is a new promising approach.[171]

Cholesteryl ester transfer protein inhibitors

Cholesteryl ester transfer protein (CETP) facilitates the exchange of cholesteryl esters and triglycerides between HDL particles and atherogenic particles containing apolipoprotein B in the blood. However, trials of various CETP inhibitors, with one exception studying anacetrapib, [172] have shown neutral or adverse effects on cardiovascular outcomes. In a pooled analysis of trials, obicetrapib a highly selective CETP inhibitor, resulted in reductions in circulating concentrations of Lp(a).[173]

Current tools of human genetics may also be of help by estimating the effects of modifying therapeutic targets. Genetic variants the mimic the effect of ATP citrate lyase inhibitors and statins have been shown to reduce LDL levels and cardiovascular risk by the same mechanism of action.[167] Genetic (polygenic) risk scores are also useful for identifying patients for whom PCSK9 therapy is justified.[174,175]

Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [4.9 mmol/L])

Specific therapy of ***familial hypercholesterolaemia*** is presented in Figure 8, and Table 8. Patients with homozygous familial hypercholesterolemia, and severe forms of heterozygous familial hypercholesterolemia may not respond to conventional therapy, and nucleic acid therapies such as PCSK9 inhibitors and small interfering RNA may be required.[164] Evinacumab, a monoclonal antibody against ANGPTL3, has also shown potential benefit in patients with homozygous familial hypercholesterolemia.[176] Recent advances in DNA- and RNA-based therapeutics are making gene-based therapy for FH an alternative approach for treatment of FH.[164]

Specific recommendations for stating therapy Racial/Ethnic Issues in evaluation, and Treatment of CVD risk in Asian Americans, Hispanic/Latino Americans, and Blacks have been provided by the AHA/ACC 2018 GL on cholesterol.

Drugs for Hypertriglyceridaemia

Fibrates

Fibrates added to statin have not been found to reduce cardiovascular events (ACCORD and PROMINENT RCTs).[177,178] Fibrates reduce triglyceride levels and increase HDL, but by stimulating lipoprotein lipase they result in increased levels of LDL and apolipoprotein B. According to new guidelines by the AHA, treatment with fibrates is indicated only for triglyceride levels >500 mg/dl.[179] The combination (especially with gemfibrosil) increases the risk of myopathy and fibrates increase homocysteine levels that may be prothrombotic; in addition, the ability of fibrates to increase HDL may be attenuated in patients with type-2 diabetes. Combinations of a statin with a fibrate (apart from gemfibrozil) might still be considered in high risk individuals such as diabetics with a high triglyceride/low HDL-C pattern.[180] New fibrates, such as pemafibrate, are in study.[181]

Omega-3 fatty acids

The omega-3 fatty acids (n-3 FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a dose of EPA+DHA or EPA-only at a dose of 3-4 g/d are now recommended by both AHA and ESC for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.[93,182] However, the evidence is to some extent controversial. No established benefit of capsule supplementation of a mixture of omega-3 fatty acids was found in a previous meta-analysis,[183] and three subsequent RCTs (ASCEND, VITAL and STRENGTH trials).[184-186] No reduction in clinical events in elderly patients with recent MI who were treated with 1.8 g n-3 PUFAs daily for 2 years was seen in the OMEMI RCT.[187] In the REDUCE-IT RCT, the EPA icosapent ethyl (2g bd) was shown to reduce the risk of ischaemic events and cardiovascular death in patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level 135 - 499 mg/dl.[188] Risk reduction was observed across a range of Lp(a) levels,[189] and a reduction in plaque volume was also detected.[190] In patients with a history of coronary artery bypass grafting, treatment with icosapent ethyl was associated with significant reductions in first and recurrent ischemic events.[191] In a meta-analysis, triglyceride lowering was associated with a lower risk of major vascular events, even after adjustment for LDL-C lowering, although the effect is less than that for LDL-C and attenuated when REDUCE-IT was excluded.[192] The different results of the STRENGTH and REDUCE-IT have been attributed to the atherogenic mineral oils (STRENGTH) vs the corn oils (REDUCE-IT) that were used as comparator oils.[193] In the RESPECT-EPA RCT, icosapent ethyl treatment resulted in a numerically lower risk of cardiovascular events that did not, however, reach statistical significance in patients with chronic coronary artery disease.[194] Thus, supplementation of EPA should be recommended in these patients,[195] but at

an increased risk of AF, since marine omega-3 fatty acid supplementation (especially >1g/day) is associated with a significant increased risk of AF.[196,197] Recommendations are provided in Table 8.

RNA Interference Targeting ApoC3

Plozasiran, a small interfering RNA targeting *APOC3* messenger RNA, lowers triglyceride levels and potentially mitigates the risk of acute pancreatitis in patients with severe hypertriglyceridemia.[198]

Drugs for *Lp(a)*

High dose statins increase ***Lp(a)*** although they reduce the risk of CVD, but PSK9 inhibitors lower Lp(a).[199] Many Lp(a)-lowering drugs, including monoclonal antibodies, drugs that that block the linkage of apolipoprotein(a) and apolipoprotein B thus reducing assembly of lipoprotein(a) particles, antisense oligonucleotide consisting of single-stranded DNA and double-stranded small interfering RNA therapeutic agents, are at different stages of clinical investigation and show promise for clinical use.[200-203] However, in the Lp(a)HORIZON RCT, the antisense oligonucleotide pelacarsen did not result in a lower risk of major adverse cardiovascular events than placebo at a median follow-up of 4.7 years.[203]

Diabetes Mellitus

Ideally, and especially in young patients, preprandial and postprandial glucose should be maintained at <130 mg/dl and <180 mg/dl, respectively.[204] Intensive glycemic control reduces risk for cardiovascular disease events, although the effect appears modest in comparison to the cardiovascular benefits from lipid and blood pressure management. Along with lifestyle recommendations, the standard initial pharmacologic treatment used in patients with type 2 diabetes is **metformin.** Addition of a glucose-lowering medication with demonstrated cardiovascular benefit, including specific agents from the **glucagon-like peptide-1 (GLP-1) receptor agonist** especially in obese patients or **sodium–glucose cotransporter type 2 (SGLT2) inhibitor** classes especially in patients with heart failure and reduced ejection fraction or kidney disease, is also recommended.[73,205,206] GLP-1RA receptor agonists and SGLT2 inhibitors are now recommended to improve cardiovascular outcomes in patients with high cardiovascular risk, regardless of HbA1c.[73,207,208] SGLT2 inhibitors are most effective if the estimated glomerular filtration rate is more than 60 ml/min/1·73m² at initiation, and should be avoided where there is a risk of diabetic ketoacidosis. GLP-1 receptor agonists are contraindicated in those with a history of medullary thyroid cancer and used with caution in patients with a history of pancreatitis of a known cause.[209]

Metformin (a biguanide) has a low side-effect profile and proven efficacy for cardiovascular risk and total mortality reduction (UKPDS).[210] It is associated with weight loss and fewer hypoglycemic episodes, and decreased mortality compared to sulfonylureas, and is considered first-line therapy.[211-213] There has also been evidence that patients with IHD may benefit from metformin irrespective from diabetic status.[214] In a post hoc analysis of the SAVOR-TIMI 53, metformin use was associated with lower rates of all-cause mortality although not with lower rates of the composite end point of cardiovascular death, MI, or ischemic stroke.[215] A relevant meta-analysis was also inconclusive.[205] It is contraindicated in patients with GFR <=30 mL/min/1.73 m^2, advanced liver disease and any condition that might lead to lactic acidosis.

Inhibitors of sodium-glucose cotransporter 2 (SGLT2-gliflozins), such as ***empagliflozin*** (10 or 25 mg od), ***canagliflozin*** (100-300 mg od), ***dapagliflozin*** (10 mg od), ***ertuglifozin*** (5-15 mg od), and ***sotagliflozin*** (200-400 mg od) reduce filtered glucose reabsorption in the proximal renal tubule, leading to glucosuria. They have been shown to significantly reduce heart failure, progression of kidney disease, and cardiovascular mortality in patients with HFrEF (EMP-REG trials, CANVAS program, DECLARE-TIMI 58, CREDENCE, DAPA-HF, EMPEROR-Reduce, VERTIS CV and SOLOIST-WHF trials), via various mechanisms.[216-223] SGLT2 inhibitors are considered first-choice drugs for patients with CVD, renal disease (but with eGFR>=30 ml/min/1.73 m^2) or heart failure.[213] Dapagliflozin also appears to lower the risk of AF/AFL in patients with type 2 diabetes mellitus, including those with and without coronary artery disease or heart failure.[224] However, a reduction in total and cardiovascular mortality was seen only in the EMP-REG trial.[225] They are FDA-approved agents but due to resultant increased glycosuria they should be used with caution in patients with poor urinary hygiene, especially in those with prior mycotic genital infections.[226] FDA warnings have emerged due to increased risk of renal injury and fractures and leg and foot amputations with the SGLT2 *canagliflozin*,[227] and cases of Fournier gangrene, a rare urologic emergency characterized by necrotizing infection of the external genitalia, perineum, and perianal region with SGLT2 inhibitors in general.[228] These complications are very rare, and although studies have detected reduced bone mineral density at the hip, meta-analyses of clinical trials have not shown increased hip fracture risk with the use of SGLT2 inhibitors.[73] However, the drugs should be avoided in patients with such history, as well as history of diabetic ketoacidosis, or when the patient is considering pregnancy or is breast feeding.

SGLT2 inhibitors with the additional capacity of **SGLT1 inhibition**, such as ***sotagliflozin***, may be even more efficacious in inhibitors in lowering hemoglobin A1C levels in patients with chronic kidney disease and preventing downstream microvascular complications of type 2 diabetes.[229] SGLT2 is of primary importance for glucose reabsorption

from the urinary filtrate, whereas SGLT1 is responsible for glucose absorption in the small intestine and the distal proximal tubule. SGLT1 inhibition reduces glucose and hemoglobin A1C levels in patients with an estimated glomerular filtration rate < 30 mL/(min·1.72 m^2) to a similar degree as in those with an estimated glomerular filtration rate ≥ 30 mL/ (min·1.72 m^2). Thus, a relative increase in SGLT1 inhibition, such as that occurring with sotagliflozin, may have an advantage compared with currently available SGLT2.

Incretin-based therapies potentiate the glucagon-like peptide-1 (GLP-1) action through selective **GLP-1 receptor (GLP-1RA)** agonism or by prevention of enzymatic degradation by inhibition of **dipeptidyl peptidase 4 (DPP-4)**, and thus enhance insulin secretion, inhibit glucagon release, and decrease gastric emptying to slow glucose absorption.[230,231] The **GLP-1 receptor agonists** are administered as daily (***liraglutide, lixisenatide***) or once weekly (***albiglutide, dulaglutide, efpeglenatide, exenatide, and semaglutide***) injections. ***Semaglutide*** is also available for oral administration. They have been shown to lower body weight, and decrease cardiovascular events, adverse renal outcomes, and cardiovascular mortality.[213,232,233] ***Liraglutide,*** in combination with metformin, appears to be the most effective agent (LEADER,[234] and GRADE RCTs[235]). It reduces cardiovascular events significantly higher than other agents such as sitagliptin or glimepiride.[236]

Although tirzepatide benefits patients with HF with preserved ejection fraction,[237] there has been no evidence of clear benefit on HF-related outcomes and there is even uncertainty regarding the safety in those with HF with reduced ejection fraction.[238] They are avoided in persistent nausea, history of gastroparesis, gallbladder disese, history of MEN 2 or proliferative retinopathy (caution with semaglutide or dulaglutide), and pregnancy or breast feeding.[206] Liraglutide (up to 1.8 mg SC daily) is also suitable for patients with a history of NYHA functional class I to III HF.[239] In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was also superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months.[240] Major concerns regarding pancreatitis, pancreatic cancer, and medullary thyroid cancer have not panned out in meta-analyses of clinical trials. Retinopathy occurred at a higher rate with semaglutide.[73] ***Tirzepatide*** is a GLP-1 receptor agonist that is also an analogue of the Gastric Inhibitory Polypeptide (GIP) that stimulates the realease of insulin from the pancreas. It is more effective than semaglutaide for weight loss.[241] The **DPP-4 inhibitors *saxagliptin*, *alogliptin*** and ***sitagliptin*** do not affect adverse cardiovascular events.[213,242] The rate of hospitalization for heart failure may be increased with these agents, mainly saxagliptin, with the magnitude of risk dependent on the method of glucose lowering and, potentially, weight gain,[230,243] although not all reports have verified this finding. [244 245] In a recent real-world study including >30 000 patients with type 2 diabetes, GLP-1RA use was

associated with a lower risk of heart failure compared with DPP-4i and similar risks compared with SGLT-2i in routine clinical care.[246] Glycemic control with ***insulin*** may also reduce cardiovascular risk,[210,235] but early addition of insulin confers no benefit in patients with prediabetes (for definition see Chapter 25) or patients whose type 2 diabetes is well controlled on diet or medication.[207,247] Insulin therapy leads to increased fluid retention, and body weight gain, and is associated with greater hypoglycaemia risks.[242]

Sulfonylureas are associated with increased risk of hypoglycaemia and weight gain, and most of them, especially *chlopropamide* and *tolbutamide*, may increase the risk of cardiovascular events,[242] and in April 2016 the FDA issued a warning regarding this risk. However, the risk is considered low, especially for and *gliclazide* and g*limepiride*,[248] and the American College of Physicians still allows their use. [211] ***Thiazolidinediones*** may increase the risk of heart failure and should not be used in the presence of impaired LV function. *Pioglitazone* is safer than rosiglitazone in this respect,[249,250] and achieves greater increases in HDL and reductions in glycated hemoglobin, and triglycerides, compared to glimepiride with a resultant slower progression of atherosclerosis.[251] Among patients with insulin resistance without diabetes mellitus, pioglitazone has reduced the risk for acute coronary syndromes after a recent cerebrovascular event.[252] Concerns about association with bladder cancer have emerged,[253] although this is debatable.[254] *Rosiglitazone* has also been associated with a significant increase in the risk of myocardial infarction, although not cardiovascular mortality, in patients with type 2 diabetes mellitus.[255] However, an analysis of from BARI 2D trial did not detect an association of rosiglitazone treatment with an increase in major ischemic cardiovascular events among patients with type 2 diabetes and established coronary artery disease.[256] Thiazolidinediones may also increase the risk of long bone fractures and weight gain.[211] ***Acarbose***, an alpha-glucosidase inhibitor that blocks the absorption of carbonhydrate has been demonstrated to delay diabetes mellitus but its effect on major cardiovascular effects is not proven.[257]

Prevention in diabetes mellitus is presented in Tables 14-16, and Figures 25-35.

Chronic Kidney Disease

GFR <60 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio (uACR) ≥3 mg/mmol (≥30 mg/g) are most commonly used as indicators of kidney disease. The simplest method to estimate GFR is using blood creatinine and a validated estimated GFR (eGFR) equation. The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equation without the race coefficient appears to be an optimal compromise for European populations, instead of the newer 2021 equation that was developed for a US population and overestimates GFR in large parts of Europe.[258] Recommendations are presented in Figures 36-38, and Tables 17-20.

Patients on cancer therapy

Recommendations are presented in Tables 8 and 13.

Exercise

Recommendations of exercise in individuals at risk of CAD are presented in Table 21.

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