CORONARY ARTERY DISEASE

Acute coronary syndromes (NSTEMI and STEMI)

Relevant Guidelines

ACC/AHA 2025 guidelines on ACS

2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndroms. J Am Coll Cardiol. 2025

AHA/ACC 2021 guidelines on Chest Pain

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. *Circulation*. 2021

ESC 2023 guidelines on acute coronary syndromes

2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023.

ESC/EACTS 2018 guidelines on revascularization

2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2018.

ESC 2021 guidelines on heart failure

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J

ESC 2021 guidelines on pacing and cardiac resynchronization

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021.

ACC/AHA/ACCP/HRS 2023 guideline on AF

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023

ACCF/AHA/HRS 2018 guideline on bradycardia and conduction delay

2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay

AHA/ACC 2026 Guideline on Cardiovascular-Kidney-Metabolic Syndrome

2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2026;87:e1889-e2007.

ESC 2026 GL on chronic kidney disease

2026 ESC Guidelines for the management of cardiovascular disease and chronic kidney disease, in collaboration with the European Renal Association (ERA). *Eur Heart J*. 2026.

ESC 2024 guilines on AF

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024.

ESC 2022 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022.

ACC/AHA 2019 Guideline on the Primary Prevention of Cardiovascular Disease

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. J Am Coll Cardiol. 2019;74:1376-1414.

ESC 2021 Guidelines on cardiovascular disease prevention

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021

ACC/AHA 2026 Guideline on Management of Dysliidemia

ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2026.

ESC 2023 Guidelines in diabetes

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023.

ESC 2019 Guidelines on Dyslipidaemias

2019 ESC/EAS Guidelines for themanagement of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2019.

ESC 2025 Update of Guidelines on Dyslipidaemias

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2025

ESC 2020 Guidelines on sports

2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020.

ESC 2022 Guidelines on cardio-oncology

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022.

ESC 2026 Guidelines on Rehabilitation

2026 ESC Guidelines on cardiac rehabilitation. *Eur Heart J*. 2026.

ESC 2025 Guidelines on pregnancy.

ESC 2025 Guidelines on the management of cardiovascular diseases and pregnancy. Eur Heart J. 2025.

Relevant Scientific Statements and Important Position Papers

ESC/ACC/AHA/WHF 2018 Fourth universal definition of myocardial infarction

Thygesen K, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2018.

AHA 2016 Scientific Statement on STEMI in women

Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. *Circulation*. 2016;133:916-947

AHA 2018 Statement on Spontaneous Coronary Artery Dissection

Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. *Circulation*. 2018.

AHA 2021 Statement on Cardiogenic Shock

Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143:e815-e829.

AHA 2021 Statement on Practices in the Cardiac Catheterization Laboratory

Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement From the American Heart Association. *Circulation*. 2021:CIR0000000000000996.

AHA 2021 Statement on Mechanical Complications of Acute MI

Mechanical Complications of Acute Myocardial Infarction: A Scientific Statement From the American Heart Association. *Circulation*. 2021:CIR0000000000000985.

AHA 2022 Scientific Statement on ACS in the Elderly

Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement From the American Heart Association. *Circulation*. 2022

AHA 2023 Scientific Statement on Postoperative Ischaemia after CABG

Considerations on the Management of Acute Postoperative Ischaemia After Cardiac Surgery: A Scientific Statement From the American Heart Association. *Circulation*. 2023;148:442-454.

AHA 2024 Scientific Statement on CYP2C19 Genetic Testing

CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association. *Circulation*. 2024;150:e129-e150.

ESC groups 2026 Statement on sex differences in IHD.

Sex and gender differences in coronary pathophysiology and ischaemic heart disease. *Eur Heart J*. 2026;47:2727-2749.

ESC groups 2026 Statement on antithrombotic therapy

Antithrombotic therapy for secondary prevention in patients with acute coronary syndromes treated with percutaneous coronary intervention: options for personalization to reduce bleeding or ischaemic risks. A Clinical Consensus Statement of the ESC Working Group on Thrombosis, the Association for Acute CardioVascular Care of the ESC, the European Association of Percutaneous Cardiovascular Interventions of the ESC, and the ESC Working Group on Cardiovascular Pharmacology. *EuroIntervention*. 2026;22:e653-e677.

ACC 2026 Report on Antiplatelet Therapy

Antiplatelet Therapy in the Management of Atherosclerotic Cardiovascular Disease: 2026 ACC Scientific Statement: A Report of the American College of Cardiology. *J Am Coll Cardiol*. 2026.

AHA 2026 Statement on Antiplatelet management

Multidisciplinary Approach to Antiplatelet Management in Coronary Syndromes: A Scientific Statement From the American Heart Association. *Circulation*. 2026;154:e687-e701.

Stable CAD

Relevant Guidelines

ESC 2024 guidelines on chronic coronary syndromes

2024 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2024.

AHA/ACC 2023 guideline on Chronic Coronary Disease

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation.* 2023

AHA/ACC 2021 guidelines on Chest Pain

2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. *Circulation*. 2021

ACC/AHA/SCAI 2021 guideline on revascularization

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

ESC/EACTS 2018 guidelines on revascularization

2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2018.

ESC 2023 Guidelines in diabetes

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023.

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2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-2962.

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2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023

ACC/AHA 2019 Guideline on the Primary Prevention of Cardiovascular Disease

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. J Am Coll Cardiol. 2019;74:1376-1414.

ACC/AHA 2026 Guideline on Management of Dysliidemia

ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2026.

ESC 2019 Guidelines on Dyslipidaemias

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019.

ESC 2025 Update of Guidelines on Dyslipidaemias

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2025

ESC 2021 Guidelines on cardiovascular disease prevention

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021

ESC 2022 Guidelines on noncardiac surgery

2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022

AHA/ACC 2024 Guideline on noncardiac surgery

2024 AHA/ACC/ACS/ASNC/HRS/ SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular

Management for Noncardiac Surgery. JACC 2024

ESC 2020 Guidelines on sports

Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020.

ESC 2022 Guidelines on cardio-oncology

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022.

ESC 2018 Guidelines on pregnancy.

ESC Guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018.

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AHA 2022 Scientific Statement on CVD Risk Factors in Diabetes.

Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes. A Scientific Statement From the American Heart Association. Circulation. 2022 Jan 10:CIR0000000000001040

ACC 2020 Expert Consensus on Diabetes

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes. JACC 2020; 76: 1117-1145

AHA 2021 statement on obesity and CVD

Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021

AHA 2021 Statement on Practices in the Cardiac Catheterization Laboratory

Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement From the American Heart Association. *Circulation*. 2021:CIR0000000000000996.

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2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy suitable for PCI or CABG. *Eur Heart J*. 2023:ehad476.

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Alcohol Use and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2025.

AHA 2025 Scientific Statement on Intraoperative Transesophageal Echocardiography During Adult Cardiac Surgery. Considerations of Intraoperative Transesophageal Echocardiography During Adult Cardiac Surgery: A Scientific Statement From the American Heart Association. Circulation 2025

AHA 2025 Scientific Statement on "Food is Medicine"

A Systematic Review of "Food Is Medicine" Randomized Controlled Trials for Noncommunicable Disease in the United States: A Scientific Statement From the American Heart Association. *Circulation*. 2025.

AHA 2025 Scientific Statement on Cornary Artery Calcium

Opportunistic Detection of Coronary Artery Calcium on Noncardiac Chest Computed Tomography: An Emerging Tool for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. *Circulation*. 2025;152:e391-e401.

AHA 2025 Scientific Statement on Cardiac Rehabilitation in Women

Cardiac Rehabilitation in Women: A Scientific Statement From the American Heart Association. *Circulation*. 2025;152:e376-e390.

AHA 2026 Scientific Statement on Dietary Guidance

2026 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation*. 2026.

AHA 2026 Scientific Statement on Secondary Prevention After CABG

Secondary Prevention After Coronary Artery Bypass Graft Surgery: 2026 Update: A Scientific Statement From the American Heart Association. *Circulation*. 2026

ESC and EACTS 2026 antithrombotivc therapy after CABG

Antithrombotic therapy after coronary artery bypass graft surgery: a Clinical Consensus Statement of the ESC Working Group on Cardiovascular Surgery, the ESC Working Group on Cardiovascular Pharmacotherapy, and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2026;47:2419-2436.

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Antiplatelet Therapy in the Management of Atherosclerotic Cardiovascular Disease: 2026 ACC Scientific Statement: A Report of the American College of Cardiology. *J Am Coll Cardiol*. 2026.

AHA 2026 Statement on Caffeine

Caffeine and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2026;154:e345-e355.

ESC Working Groups 2026 Statement on Metabolic Risk Factors

Novel cardiovascular metabolic risk factor mechanisms and therapeutic opportunities: A scientific statement of the ESC Council on Basic Cardiovascular Science, the ESC Working Group on Atherosclerosis and Vascular Biology, the ESC Working Group on Cellular Biology of the Heart, the ESC Working Group on Myocardial Function, and the ESC Working Group on Cardiac Cellular Electrophysiology. *Eur Heart J* 2026; 47: 6560–6577.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE

Definitions and Classification

Persons with atherosclerosis of epicardial coronary arteries and/or microcirculation may be asymptomatic or present with angina pectoris on effort or develop an acute coronary syndrome (ACS). ***Stable coronary artery disease*** may be detected following a diagnostic ischaemia test, or get diagnosed after presentation with an acute coronary syndrome. ***Acute Coronary Syndrome (ACS)*** refers to an acute imbalance of myocardial oxygen supply and demand due to progressive or abrupt flow-limiting coronary stenosis, and/or high-output or increased afterload states. ACS include myocardial infarction with ST segment elevation or new LBBB (***STEMI***), and non-ST-elevation myocardial infarction (***NSTEMI***) that is diagnosed by enzyme rise. ***Unstable angina*** is diagnosed when there are new or worsening symptoms of ischaemia, and ischemic ECG changes such as ST-segment depressions and T-wave inversion, with normal biomarkers. It is now evident that a large majority of patients with clinical manifestations of myocardial ischaemia, with rest pain but without elevated troponins by a commercially available assay, and therefore considered to have UA, have an elevation of circulating troponins measured by a high-sensitivity assay and could therefore be classified as NSTEMI.[1]

Epidemiology

The global burden of Cardiovascular Disease (CVD) is increasing, primarily because of the ageing of the population.[2] Atherosclerotic cardiovascular diseases were estimated to be responsible for 21% of all deaths in the third *Lancet* Commission on Investing in Health, Global Health 2050 that estimated crude mortality rates from 1970 to 2019.[3] Silent atherosclerosis is detectable in early adulthood (18 to 29 years), being present in 8.7% of men and 6.7% of the women.[4] Isolated coronary-artery atherosclerosis is uncommon in every age stratum (≤9.3% of men and ≤5.0% of women).[4]

According to NHANES 2021 to 2023 data, the prevalence of CVD, comprising coronary artery disease (CAD), heart failure (HF), stroke, and hypertension) in adults ≥20 years of age was 48.9% overall (130.6 million in 2022) and increases with age in both males and females.[5]

The total CHD prevalence is 5.2% in US adults ≥20 years of age, affecting 15.9 million Americans. CHD prevalence is higher in males (6.9%) than females (3.7%).[5] Epidemiology data are presented in Figures 1 and 2. It is estimated that in the USA by the

year 2060, compared with the year 2025, the number of people with ischemic heart disease will increase by 31.1% (21.9M to 28.7M), heart failure by 33.0% (9.7M to 12.9M), myocardial infarction by 30.1% (12.3M to 16.0M), and stroke by 34.3% (10.8M to 14.5M).[6] CVD remains the most common cause of death in ESC member countries with over 3 million deaths per year.[7] Although the risk-factor burden is lowest in low-income countries, the rates of major cardiovascular disease and death are substantially higher in low-income countries than in high-income countries, probably due to inferior control of risk factors and proper therapy.[8] In the developed world, CVD is the single most common cause of death (WHO Report 2020). According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), in 2019, CVD was the underlying cause of 9.6 million deaths among men and 8.9 million deaths among women, approximately one-third of all deaths globally. Of these deaths, 6.1 million occurred in people between the ages of 30 to 70 years. Despite a 30-year decline in age-standardized CVD mortality rates globally, the GBD 2019 study reveals increasing age-standardized CVD mortality in many locations since 2010 and an overall flattening of the global decline in the past 5 years.[9]

Approximately half of CVD mortality is due to CAD.[10, 11] Atherosclerosis in general can be detected by computed tomography angiography in up to 42% of apparently healthy individuals aged 50-64 years, although significant stenosis (≥50%) is less common (5%).[12] Worldwide, more than 3 million people each year are estimated to have a STEMI and more than 4 million have a NSTEMI.[13] In the USA, the estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks.[5] Hospital mortality is higher in patients with STEMI but in the long-term mortality is higher in patients with NSTEMI.[14] MI that occurs in the community still carries a 25% mortality risk, whereas in-hospital mortality without fibrinolysis approaches 15%. Current pharmacological and mechanical therapeutic approaches have reduced this risk to 3-5%.[13, 15] In-hospital occurring STEMI carries a higher mortality, especially in patients admitted for noncardiac reasons.[16] Silent myocardial infarctions represent >45% of incident myocardial infarctions and are associated with poor prognosis.[17]

The estimated direct and indirect cost of IHD in 2017 to 2018 (average annual) was $228.7 billion. MI ($12.1 billion) and CAD ($9.0 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2013.[18] A study examining public and private health insurer records in the USA from 1996 to 2016 reported an estimated cost of $28.4 billion for IHD out of a total of 3.1 trillion dollars for health care in general.[19] Between 2013 and 2030, medical costs of CAD are projected to increase by approximately 100%.[20] CVD accounts for 11% of the European Union's total healthcare expenditure.[7]

Aetiology

Coronary artery disease is due to a complex interaction of political, social, behavioural, physical, biological, and genetic risk factors.[21] Noncommunicable diseases such as air and noise pollution, chemical contamination, artificial light at night, and climate change effects like heat extremes, floods, wildfires, and desert storms, are the leading cause of mortality globally, accounting for 70% of deaths, with cardiovascular disease constituting 44% of these fatalities.[22] More than 90% of myocardial infarctions are attributable to modifiable risk factors such as ***hypertension, dietary risks, dyslipidaemia, smoking, diabetes, exposure to traffic air pollution*** and ***micro- and nanoplastics***, ***traffic noise, obesity*** (not in the very elderly) and, especially, ***abdominal obesity, insomnia, psychosocial factors, greater nighttime light exposure***, and ***very low socioeconomic status***.[9, 23-34] ***Hypertension*** is the most important modifiable factor (Table 1),[31] and CV risk increases at a lower BP level in females than in males.[35] ***Smoking*** is associated with a substantially increased risk of myocardial infarction that is reduced but not becoming negligible with electronic cigarettes.[36] Noncigarette tobacco use (cigar, pipe, and smokeless tobacco) is associated with increased inflammatory markers markers related to cardiovascular harm, including high-sensitivity C-RP fibrinogen, and measures of carotid vascular disease.[37]

Dietary habits are important. ***Saturated fat and trans-fats*** (mainly hydrogenated oils), high ***carbohydrate intake***, ***processed meat*** and ***ultra-processed foods*** have been associated with increased CVD risk and total mortality. ***Ultraprocessed*** foods and beverages in particular, pose a growing public health challenge.[38, 39] A simplified guide to Nova food classification for clinical use is presented in Table 2. Excess ***sodium*** intake is associated with an increased risk of coronary heart disease and cardiovascular mortality.[40, 41] The data on ***alcohol*** suggest possible risk reduction when alcohol, especially wine, is consumed in low amounts (such as no more than 1 to 2 drinks a day) in regard to coronary artery disease, stroke, sudden death, and possibly heart failure. ***Coffee*** consumption, 2-3 cups a day is most probably associated with a reduced risk of CVD, whereas high doses of caffeine such as that found in energy drinks mat be associated with cardiovascular harm.[42, 43] For a detailed discussion on alcohol and caffeine see the Chapter on Prevention.

However, the limitations of non-randomized, observational trials on human nutrition are well established,[44] and focusing on a single lipid marker such as LDL cholesterol alone, does not capture the net clinical effects of nutrients on cardiovascular risk. The evidence from observational studies examining the relationship between dietary ***cholesterol*** and CVD risk is inconsistent, but 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***.[45] In general, studies on

dietary habits ("Food is Medicine") often positively influence diet quality and food security, but the impact on clinical outcomes has so far been inconsistent and often failed to reach statistical significance.[46]

Coronary artery disease has a multifactorial aetiology, causality on certain occasions is a matter of judgement, and risk factors should be considered within the context of socioeconomic and political factors. In approximately 15% of patients with CAD, no traditional risk factor can be identified.[47]

Lipids

Plasma lipid levels are, to a very large extent, determined by genetic factors. In its more extreme forms this is manifested as familial dyslipidaemias. Patients with extreme hypercholesterolemia have an elevated risk of ischemic events. The ***severe hypercholesterolemia phenotype*** includes all patients with low-density lipoprotein cholesterol levels >190 mg/dl, regardless of cause. There is now unequivocal evidence for a casual effect of LDL-C.[48] Incident CVD event risk depends on cumulative prior exposure to LDL-C. As such, individuals with the same cumulative LDL-C exposure at age 40 years but with a greater fraction of that exposure occurring earlier in life (between 18 and 30 years) have a greater risk of subclinical plaque development and incident CVD event risk after age 40 years.[49] Non-HDL cholesterol concentrations in blood are strongly associated with long-term risk of atherosclerotic cardiovascular disease.[50] Autosomal dominant hypercholesterolemia results from mutations in genes controlling LDL levels (Table 3). This includes familial hypercholesterolemia, as well as other inherited forms of a potential polygenic origin.[51] Rare variations in a gene (APOC3) that encodes for apolipoprotein C3 are associated with reduced triglyceride levels and lower risk for heart disease.[52, 53] There is a causal effect of ***triglycerides*** on CAD risk, but the role for ***HDL-C*** though possible, remains less certain, particularly as far as therapeutic interventions are concerned.[54-58] In a Danish registry, the association between ***HDL cholesterol*** concentrations and all-cause mortality was U-shaped, and men and women from the general population with extreme high HDL cholesterol had high all-cause mortality.[59] However, low-density lipoprotein cholesterol is associated with near-term atherosclerotic cardiovascular disease events in middle-aged patients with presence of coronary atherosclerosis, whereas no association is established for those without coronary atherosclerosis.[60] ***Lipoprotein A Lp(a)***, especially >50 mg/dl (105 mmol/L), is associated with cardiovascular risk continuously and independently of LDL-C level.[61-66] Concentrations are more than 90% genetically determined and 17% higher in post-menopausal women than in men.[67] Blood levels of ***apolipoprotein*** B (apoB) provide additional atherosclerotic risk information beyond LDL-C across the entire range of LDL-C level.[68] ApoB measurement in young adulthood provides a comprehensive measurement since it also captures low-density lipoprotein particle (LDL-P), and triglyceride-rich lipoprotein

particle (TRL-P) that are associated with CVD risk.[69, 70] ***Remnant cholesterol***, ie total cholesterol minus LDL and (HDL, and including the cholesterol content of the triglyceride-rich very-low-density lipoproteins, intermediate-density lipoproteins, and chylomicron remnants in the nonfasting state, is an important risk factor for future cardiovascular events.[71]

Familial hypercholesterolemia (FH) is an autosomal codominant monogenic disorder, characterized by elevated low-density lipoprotein cholesterol (LDL-C) mainly caused by loss-of function mutations in genes related to reduced clearance of LDL particles. It is very rarely recessive, and the phenotype may also be polygenic.[72-74] Heterozygous FH (HeFH) affects around 1 in 300 people worldwide, and homozygous FH (HoFH) affects around 1 in 300 009. The prevalence of heterozygous FH (HeFH) is 1:300 in the general population, with data suggesting that ≈1% of those potentially affected are detected.[75] Homozygous FH (HoFH) affects around 1 in 300 000.[76] Monogenic familial hypercholesterolemia is associated with lower responsiveness to conventional low-density lipoprotein cholesterol lowering therapies and increased preclinical coronary atherosclerosis when compared with hypercholesterolemia of polygenic or unknown genetic cause.[77]

Familial hypercholesterolemia is clinically diagnosed by five major criteria including: presence of early CAD in the index case, elevated LDL-C (>190mg/dl-5 mmol/l), family history of premature CAD (women<60 years, men<55 years), tendon xanthomas or corneal arcus (age<45 years).[78] The 2015 EAS consensus statement on FH in children proposed that any child with an LDL-C ≥5.0 mmol/L (190 mg/dL) measured twice after dietary intervention has a high probability of genetically based FH; this threshold was lowered to ≥4.0 mmol/L (155 mg/dL) if there was a family history of premature ASCVD and/or high baseline cholesterol in one parent, and further lowered to LDL-C ≥3.5 mmol/L (135 mg/dL) if one parent had a genetic diagnosis of FH.[79] However, recent data digest that when using these criteria, early diagnosis in almost half of children with an FH-causing variant would have been missed, and a 1016 a European Atherosclerosis Society consensus statement proposed a modification of these criteria.[76] From 1 year of age, LDL levels discriminate between familial and non-familial hypercholesterolemia in children.[80]

Heterozygous FH is caused by a variant in a single allele of LDLR (LDL receptor), apoB (apolipopro- tein B), or PCSK9 (proprotein convertase subtilisin/kexin type 9), whereas ***homozygous FH*** is produced by variant in 2 alleles of the same or different canonical genes.[81] Patients with heterozygous FH have a total cholesterol 350–550 mg/dL (9–14 mmol/L) and LDL-C values 200–400 mg/dL (5–10 mmol/L) (Table 2). [82] [78] In homozygous FH, plasma LDL-C levels are >10 mmol/L (400 mg/dL).[83] The consequent diminution in LDL receptor activity leads to extreme elevations of LDL cholesterol from birth, accelerated atherosclerosis, and premature death (18 years of age or less) from acute coronary syndromes, often associated with valvar and supravalvar atheroma of the aortic root. The prevalence of

molecularly defined homozygous autosomal dominant familial hypercholesterolaemia is rather high (1/300,000), and the clinical phenotype is more variable than previously assumed, with disease often underdiagetween familial and non-familial hypercholesterolaemia in children.nosed.[84] ***Familial combined hyperlipidaemia*** is a highly prevalent mixed dyslipidaemia (1:100-200) characterized by elevated levels of LDLC, TGs, or both, and is an important cause of premature CAD.[85] In normolipidaemic patients, post-prandial TG values rarely exceed 400 mg/dL (4.6 mmol/L).[55] Extremely high fasting triglyceride levels > 880 mg/dL indicate persistent chylomicronemia that is associated with the risk of recurrent acute pancreatitis.[86] Criteria have been proposed for diagnosis (Table 3) that is confirmed by genetic testing.

Genetic testing is recommended for patients with definite or probable FH, as well as for their at-risk relatives (Table 4).[83] Testing should mainly include the genes encoding the low-density lipoprotein receptor (*LDLR)*, apolipoprotein B (*APOB)*, and proprotein convertase subtilisin/kexin 9 (*PCSK9*).[74, 87] Among participants with LDL cholesterol ≥190 mg/dl, in general, gene sequencing identifies an FH mutation in <2%. However, in patients presenting with an ACS and LDL-C levels ≥160 mg/dl, the prevalence of genetically confirmed FH is high (approximately 9%). [88, 89] Genetic (polygenic) risk scores also appear valuable in predicting recurrent cardiovascular events in patients, and thus identifying patients in whom PSK9 therapy is beneficial.[90, 91]

Comorbidities

Arterial hypertension is the top modifiable risk factor for CVD burden, followed by ***dyslipidaemia (high LDL).***[9, 31] ***Type 2 diabetes mellitus*** is an established risk factor for CVD. CVD is the leading cause of death in adults with diabetes mellitus, and the life expectancy of these patients, especially those with a previous MI, is considerably shorter than non-diabetics.[92] ***Chronic kidney disease*** is one of the strongest risk factors for the development of CVD. Chronic kidney disease mimics an accelerated aging of the cardiovascular system by causing a systemic, chronic proinflammatory state contributing to vascular and myocardial remodeling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and calcification of cardiac valves.[93, 94] ***Polycystic ovarian syndrome*** is associated with increased cardiovascular morbidity and a higher risk of atherosclerotic cardiovascular disease.[95] ***Obesity*** leads to the development of cardiovascular disease independently of other cardiovascular risk factors. However, susceptibility to obesity-related cardiovascular complications is not mediated solely by overall body fat mass and body mass index (BMI), but depends largely on individual differences in regional body fat distribution, such as abdominal obesity and visceral adiposity.[96, 97] In the elderly (>=80 years) both higher BMI and waist circumference are associated with a lower risk of all-cause mortality, but persons with higher BMIs but lower waist circumferences have the lowest

mortality risk.[98] ***Congenital heart disease*** is an independent risk factor for the occurrence and outcome of myocardial infarction.[99] A ***myocardial bridge***, ie muscle overlying the intramyocardial segment of the epicardial coronary artery, usually the LAD, is a usually benign abnormality of multifactorial origin that, however, may lead to ischaemia.[100, 101] The reported prevalence varies widely depending on the imaging modality, appearing in 5%–8% of coronary angiograms and 18%–25% of CCTAs. Autopsy studies, however, suggest an even higher prevalence of 30%–86%, indicating that MB may be more of an anatomical variant than a true anomaly.[101] ***Hyperuricaemia*** may contribute to the development and progression of chronic kidney disease (CKD), and, probably, cerebral and cardiovascular disease, and mortality. However, the clinical utility of uric acid-lowering for the prevention or treatment of hypertension, CVD, or CKD is controversial.[102] ***Non-alcoholic fatty liver disease*** increases the risk of CVD due to systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress, and altered lipid metabolism.[103] Clinically, both ***hyper-*** and ***hypothyroidism*** can affect dyslipidaemia and atherosclerotic vascular disease.[104] Patients with ***cancer*** have a substantially increased short-term risk of arterial thromboembolism.[105] ***Chronic venous insufficiency*** is related to cardiovascular disease and is predictive of all-cause death. [106] Inflammatory and immune mechanisms are implicated in atherosclerosis.[107] ***Chronic inflammation*** is associated with atherosclerosis as expressed by traditional markers such as the neutrophil-lymphocytre ratio (>2.5), CRP, IL01 and IL-6.[64, 108] A hrsCRP >3 mg/L indicates an increased cardiovascular risk in women, even in the absence of traditional risk factors such as hypertension, dyslipidemia, diabetes and smoking.[109] ***Severe infections*** that require hospitalization are associated with increased risks for major cardiovascular disease events.[110] Chronic inflammatory diseases including ***HIV*** infection, ***psoriasis, rheumatoid arthritis***, and ***systemic lupus erythematosus*** predispose to atherosclerotic cardiovascular disease.[111-113] ***Hodgkin lymphoma*** survivors have an increased risk of cardiovascular disease for at least 40 years after diagnosis.[114] ***Ionizing radiation*** induces endothelial dysfunction and accelerated atherosclerosis. Risks are determined both by radiotherapy, including the radiation dose and the proximity of coronary arteries to the radiotherapy field, and by patient-specific factors, such as younger age, higher baseline cardiovascular risk, and concurrent cardiotoxic systemic therapies. Clinical presentation may occur early, within 1 to 2 years, especially in patients with higher cardiac radiation doses (eg, lung or esophageal cancer), or after a latency period of 5 to 20 years with lower cardiac dose radiation exposure (eg, left-sided breast cancer). Patients with ***antiphospholipid syndrome*** are at increased risk for accelerated atherosclerosis, myocardial infarction, stroke, and valvular heart disease.[115] However, factor V Leiden is not associated with increased risk of atherothrombotic events and mortality in patients with established and treated CAD.[116] ***Kawasaki disease*** is an acute

vasculitis of childhood that leads to coronary artery aneurysms in ≈25% of untreated cases.[117] ***Community-acquired bacteremia*** is associated with increased short-term risk of myocardial infarction and stroke.[118] ***Respiratory infection*****s**, especially influenza, are associated with acute myocardial infarction.[119] Patients with ***syphilis*** have a higher risk of cardiovascular events and all-cause mortality.[120] ***COVID-19 pneumonia*** is associated with acute myocardial injury and thrombosis.[121, 122] ***Herpes zoster*** infection is associated with CVD.[123] ***Fibromuscular dysplasia*** involving the coronary arteries is an uncommon but important condition that can present as acute coronary syndrome.[124, 125] ***Endometriosis*** is associated with a higher risk of cardiovascular events including myocardial infarction, arrhythmia, and heart failure.[126] ***Periodontitis*** is more common in patients with a myocardial infarction, and it seems that the relation periodontal disease and CVD is causal.[127] The prevalence of ***obstructive sleep apnoea*** is as high as 40% to 80% in patients with hypertension, heart failure, coronary artery disease, pulmonary hypertension, atrial fibrillation, and stroke.[128] ***Mental and substance addiction disorders***, especially when diagnosed at a young age, are associated with increased risk of cardiovascular disease.[129] ***Pregnancy complications*** such as spontaneous preterm delivery, miscarriages, placenta abruption and still birth are associated with increased rates of future CVD, cerebral infarction, and renovascular hypertension.[130, 131] This has been attributed to either shared etiology or the initiation of pathological processes by a pregnancy loss leading to atherosclerosis.

Drugs

Chemotherapeutic agents for cancer may also cause accelerated atherosclerosis and arterial thrombotic events (see Tables on Risk Assessment). For a detailed discussion see Chapter 92. ***NSAIDs*** (both non-selective and selective COX-2 inhibitors that spare COX-1 in the gut) are associated with an increased thrombotic risk (see Chapter 30.[132] Platelet cyclo-oxygenase (COX)-1 activity results in production of thromboxane A, whereas COX-2 activity results in the production of prostacyclin (PGI_2). Regular acetaminophen has been associated with hypertension,[133] and **s*odium-containing acetaminophen*** (e.g. the effervescent or soluble) is associated with increased risks of CVD and all-cause mortality among individuals with or without hypertension.[134] Women who use ***oral contraceptives containing ethinyl estradiol*** are at dose-dependent increased risk for thrombotic stroke and myocardial infarction compared to women using progesterone only contraception.[135] These cardiovascular risk factors induce oxidative stress that causes endothelial inflammation and damage. Both ***androgen deprivation therapy***, prescribed for prostate cancer, and ***testosterone therapy*** has been associated with increased risk of CVD.[136, 137 132] Long-term ***anabolic-androgenic steroids*** use is associated with increased mortality due to cardiovascular disease.[138, 139] ***Antipsychotic drugs*** use may also be associated with a transient increase in risk for AMI, possibly mediated by dopamine type 3 receptor blockades.[140] ***Clarithromycin*** has been found

to increase cardiovascular mortality in patients with stable coronary heart disease who were not on statin,[141] and in February 2018 the FDA issued a safety communication. However, the evidence is rather inconsistent. ***Opioid*** use has been associated with acute coronary syndromes.[142] ***Cocaine*** has a multitude of pathophysiological pathways by which it affects the cardiovascular system, including coronary vasoconstriction and acute myocardial infraction.[143]

Other conditions

Environmental risk factors are emerging as critical contributors to noncommunicable diseases.[22] ***Traffic air pollution*** (mainly fine particles especially <2.5 μm in diameter-$PM_{2.5}$, as well as PM_{10}, CO, NO_2, and ozone) as well as ***microplastics*** (defined as particles smaller than 5 mm) and ***nanoplastics*** (particles smaller than 1000 nm) that are released by plastics degradation are associated with cardiovascular disease.[144-147] ***Radiation-associated cardiac disease*** is a heterogeneous and complex disease, with cardiac manifestations which range from pericarditis, coronary artery disease, valvular heart disease, nonischemic cardiomyopathy, and conduction abnormalities, and may occur years or even decades following radiation exposure to the chest.[148] Both ***early*** and ***late menarche*** are associated with increased risk of CAD.[149] Self-reported symptoms of ***anxiety*** and ***depression*** as well as outbursts of ***anger and emotional upset*** increase the risk of myocardial infarction.[150] [151] [152] ***Psychological stress*** is a risk factor and prognostic factor for CAD,[153] and psychosocial factors in youth such as the socioeconomic and emotional environments predict development of CAD.[154] ***Short sleep duration*** and deprivation (<6h a day) are associated with increased risk of CVD.[155] [156] ***Compat experience*** is a risk factor for CAD.[157] Cardiovascular disease is a major cause of death among ***homeless*** adults.[28] ***Extreme hot and cold temperatures*** are associated with increased risk of death from any cardiovascular cause, ischemic heart disease, stroke, and heart failure.[158] ***Shorter height*** is associated with increased risk for coronary artery disease.[159] The rate of progression of cellular ***ageing*** in late midlife (reflected by the rate of leucocyte telomere length attrition) relates to vascular damage, independently from contribution of CV risk factor exposure.[160] The possibility of ***deep space radiation*** promoting endothelial dysfunction and atherosclerosis has also been raised.[161] Non-linear Mendelian randomization analyses suggest an association of 25(OH)D with CVD risk, with increased CVD risk largely restricted to individuals with **low vitamin D** status.[162]

Genetic factors

Coronary artery disease is the most studied cardiovascular phenotype for polygenic risk scores.[163] However, apart from genetic disorders of lipoprotein metabolism, distinct morphological characteristics such as left main or proximal disease also display a high heritability.[164] Epidemiological studies have shown that genetic predisposition accounts for

40-60% of the risk for coronary artery disease. Genome-wide association studies have led to the discovery of at least 67 loci associated with the risk of coronary artery disease, explaining approximately 15% of the disease's heritability.[165] Approximately 10 of them are associated with hypertension or hyperlipidemia, and the rest of them mediate their risks through unknown mechanisms. The strongest genetic effect on the risk of coronary artery disease and myocardial infarction is that of single nucleotide polymorphisms at ***chromosome 9p21.3*** (CDKN2A/2B), that is also a significant risk factor for abdominal aortic aneurysm, stroke, and Alzheimer's disease.[166-168] The 9p21.3 risk allele is carried by 75% of the European population and confers risk of coronary atherosclerosis in a dose-dependent way (by means of allele copies). However, in patients with established CAD, variants at the 9p21 locus do not affect risk of recurrent or subsequent events, including mortality, ie cannot be used for risk stratification purposes.[169] The identification of the ***ABO blood group locus*** as a risk factor for myocardial infarction might provide an explanation on why blood group O offers protection from myocardial infarction and thromboembolism compared to blood groups A and B.[170] Common genetic influences appear to affect both height and CAD risk, partly mediated by genetic effects on LDL cholesterol and triglycerides. Genetically predicted short sleep duration is associated with increased risk of CVD.[155] The presence of a common ***Y chromosome variant***, haplogroup I, has been founds found to increase coronary risk by 50%.[171] This might explain the higher prevalence of CAD in men. All these genetic variants are not yet ready for routine testing. Loss of function mutations in ***ANGPTL4***, a protein that inhibits lipoprotein lipase-LPL and thus reduce triglycerides levels and elevate HDL cholesterol, confer lower risk of coronary artery disease.[172, 173] Loss of function variants of ***ANGPTL3***, a LPL inhibitor that reduces triglycerides levels as well as LDL and HDL cholesterol, or treatment antisense oligonucleotides that targeted ANGPTL3 messenger RNA has also retarded the progression of atherosclerosis in mice.[174, 175] Genetic scores, such as the metaGRS, derived from large biobanks have been developed as predictors of CAD.[176] ***TSR1***, a novel gene located in the chromosome 17p13.3 region, has been identified as a potential causal gene of spontaneous coronary artery dissection.[177] ***JCAD*** (Junctional cadherin 5 associated, also known as *KIAA1462)*, also encodes a junctional protein associated with CAD.[178] A locus on chromosome 1p21.3 harbouring choline-like transporter 3 (***SLC44A3***), has been implicated in the pathophysiology of vulnerable plaques and development of MI.[179] Finally, genetic variants known to affect educational attainment may have broad implications for a health-conscious lifestyle later in life and the risk of CAD.[180] The development of large disease-based consortia and biobanks have enabled the discovery of genetic variants associated with CAD. The availability of these large datasets, along with computational advances, has allowed for the easier derivation, calculation, and validation of genetic

(polygenic) risk scores that predict recurrent cardiovascular events in patients with pre-existing CAD.[181]

Pathophysiology

Originally thought to be dominantly a lipid storage disease, our current understanding of the pathogenesis of atherosclerosis implicates endothelial injury and inflammation. Following endothelial injury, smooth muscle cells and monocytes/macrophages migrate into arterial intima in the preatherosclerotic stage and during plaque development, and become foam cells by accumulating cholesterol.[182] Additional chemical and mechanical factors that may trigger endothelial injury are altered sheer stress, high oxidative stress, smoking, and insulin resistance.[183] More than half of men and women with suspected CAD have microvascular dysfunction even with the absence of an abnormal stress test, and this is a major predictor of major adverse events.[184] Coronary microvascular disease may represent an epiphenomenon or contribute to the pathogenesis of cardiovascular disease. The development of atherosclerotic disease may be an age-related asymptomatic process or lead to stable ischemic heart disease or an acute coronary syndrome.

Stable ischemic heart disease

Non-acute myocardial ischaemia syndromes are caused by ischaemia due to epicardial coronary stenosis or by ischaemia with non-obstructive coronary arteries (***INOCA***).[185] The underlying mechanism of chronic CAD is the chronic limited ability to increase oxygen supply to the myocardium in the setting of increased oxygen demand, usually caused by the obstruction of at least one large epicardial coronary artery by atheromatous plaque, microvascular dysfunction, vasoconstriction at the site of dynamic stenosis, or combination of the above. Because myocytes already extract about 75% of the oxygen in coronary blood at rest, a higher demand is primarily met by increasing coronary blood flow. Myocardial ischaemia results in hypoxia that activates cellular anaerobic pathways; produced mediators such as lactate are responsible for the sensation of pain. Thee development of ***collateral circulation*** is an adaptive response to ischemia, and may be partially responsible for the nonlinear relationship between stenosis severity, ischemia, and symptom burden.[186]

Up to 70% of patients presenting to the cardiac catheterization laboratory with angina may have no angiographic evidence of coronary artery disease (***Ischaemia with nonobstructive coronary arteries – INOCA)***, and an increasing number of patients, especially women, develop signs and symptoms of myocardial ischaemia in the absence of obstructive coronary artery disease.[184, 187-189] In the CORONER study on stable CAD outpatients, incident MI occurred at a stable rate of 0.8% annually, and was related to late stent thrombosis in one-fifth of cases.[190]

Acute coronary syndromes

Acute myocardial ischaemia syndromes are caused by coronary plaque rapture or erosion or by myocardial infarction with non-obstructive coronary arteries (***MINOCA***).[185] The most frequent mechanism of an ACS is a reduction of the myocardial oxygen supply usually due to rupture or erosion of a vulnerable atherosclerotic plaque, which results in endothelial injury and associated thrombosis and dynamic vasoconstriction. Vulnerable plaques likely to rupture or erode have evidence of inflammation with macrophages that overproduce matrix-metalloproteinases (MMP) with collagenase activity, and T-cell infiltrates.[191] Histologically, vulnerable plaques have thin fibrous caps (<65 μm) with large lipid cores (thin-cap fibroatheroma-TCFA) [192-195] although statin therapy in the modern era may modify their characteristics. [196] The detection of lipid accumulation within the coronary artery wall predicts cardiovascular outcomes.[197] Usually, atherosclerosis occurs within usually in an environment of low shear stress, but high shear stress may promote plaque rupture.[198] Plaque rupture remains the leading cause of ACS, accounting for approximately 60%–70% of cases.[199] Plaque rupture in non-obstructive lesions of non-infarct related arteries is present in 12% of patients with acute MI. More than half of untreated ruptures transitioned into stable morphologies.[200] Plaque erosion (underlying between 25% to 45% of ACS), intraplaque hemorrhage, calcified nodule, and functional coronary alterations also play an important triggering role.[201 199, 202] Plaque haemorrhage may occur from plaque rupture (fissure) or from neovascularization (angiogenesis). Plaque fissure or rupture exposes the highly thrombogenic subendothelium (collagen and tissue factor) to circulating platelets and white blood cells. Platelets are also activated by vasoconstrictors such as thromboxane A2, and adenosine diphosphate (ADP) that binds to to $P2Y_{12}$ receptors, and cause increased expression of glyocoprotein IIb/IIIa that binds fibrinogen or von Willenbrand factor. Thus, platelet aggregation and creation of the *white clot* occurs. The platelet-derived mediators together with other potent vasoconstrictors such as activated thrombin, oxygen-derived free radicals and endothelin result in dynamic vasoconstriction and transient thrombosis. The coagulation cascade may be activated and factor X leads to generation of thrombin that converts fibrinogen to fibrin (*red clot*).[203] The term 'calcified nodule' indicates calcified coronary atherosclerotic plaque nodules. Fragmentation of the necrotic core of the plaque nodules promotes fibrous cap disruption and luminal thrombosis.[204]

It should be noted that erosion or rupture of the coronary atherosclerotic plaque is typically required for an event to happen, but only when coinciding with a prothrombotic state and subsequent thrombosis at the site of plaque rupture or erosion, it leads to an event. In the majority of cases, plaque ruptures or erosions take place in the absence of symptoms and commonly lead to healing and progression of coronary arterial narrowing.[205] Vulnerable plaques, intact or ruptured, may be found along the coronary tree and the true culprit lesion

can be difficult to define.[206] ACS may also occur without apparent epicardial coronary thrombus or stenosis. Such events may arise from coronary artery spasm, microvascular disease, or other pathways.[191]

If the ischaemia is prolonged and severe enough to cause limited myocardial necrosis the diagnosis of ***NSTEMI*** is put; further damage, usually due to formation of a red thrombus that causes ST elevation, produces the clinical picture of ***myocardial infarction (STEMI)***. Thrombosis and occlusion of the coronary artery is the commonest cause of STEMI.[207 208] Myocardial injury can result from a wide variety of ischemic and nonischemic mechanisms.[209] Angiography at the acute phase reveals an occluded coronary artery in 90% of cases, although the converse is not the case due to the possible presence of collaterals. Intracoronary thrombi are mainly composed of fibrin (increased content with increased ischemic time), platelets, erythrocytes, and few cholesterol crystals and leukocytes.[207] There is a circadian periodicity with most events occurring between 6 am and noon. Platelet hyper-reactivity and pro-coagulant states contribute to the thrombotic process that diminishes microcirculatory perfusion by reduced coronary artery flow through epicardial stenoses, as well as by distal embolization of thrombus. Histochemical stains can identify zones of necrosis 2-3 hours after the onset of necrosis, while gross pathology changes can be identified 6-12 hours following occlusion. Eight to 10 days after infarction the thickness of the affected ventricular wall is reduced as necrotic muscle is removed by mononuclear cells, and over the next 2-3 months the firm scar develops. Infarct expansion (disruption and tissue loss not explained by additional necrosis) and ventricular dilation may also occur and determine ventricular remodeling. The systemic inflammatory reaction to acute myocardial infarction can aggravate inflammation in the plaque, thus resulting in recurrent thrombotic events in the aftermath of an acute coronary syndrome.[183] Following reperfusion, the course of myocardial edema is bimodal. Acute reperfusion is responsible for the initial acute edematous reaction that dissipates at 24 h, and then initiates days after infarction, reaching a plateau at 4-7 days because of tissue healing processes.[210, 211] In the modern era of primary PCI, improved LVEF is detected in 55% of patients one month after the event.[212]

Myocardial infarction is now classified into one of three clinical types: primary, secondary and procedure related (see also Chapter on Diagnosis of ACS). ***Primary myocardial infarction*** is due to spontaneous presentation due to a primary acute coronary pathology. The diagnosis is confirmed and aetiology defined if atherothrombosis or an alternative acute coronary pathology is identified***. Secondary myocardial infarction*** **results** from myocardial oxygen supply–demand imbalance due to another acute condition. However, two-thirds of these patients may have coronary artery disease, and one-third had left ventricular impairment, which were previously unrecognized and untreated in the majority. Thus, investigation with invasive or noninvasive coronary and cardiac imaging should be

considered in patients with secondary infarction.[213] ***Procedure-related myocardial infarction*** occurs as a complication of a percutaneous or surgical cardiac procedure.

Primary myocardial infarctions have been previously shown to frequently occur at sites of mild-to-moderate stenosis.[214-218] Postmortem and older angiographic data, however, have demonstrated that ruptured plaques leading to thrombosis more likely occur within the segment of complex lesions with significant (>50%) stenoses.[219-223] In the PROSPECT trial on patients with acute coronary syndromes treated by coronary intervention, 3-year recurrence rates were 20%. Half of them occurred in angiographically mild (<70% stenosis), non-culprit lesions. However, predictors of recurrent events were both a luminal area ≤ 4 mm^2, and the presence of thin-cap fibroatheroma.[224] An analysis of the data of the COURAGE trial has also shown that MIs are not more likely to occur from mild coronary lesions compared with moderate or severe ones; the number of non-revascularized lesions >=50% was the only angiographic predictor or an acute coronary syndrome.[225] In the ROMICAT trials, lesions with >=50% stenosis were detected in 78% of patients with ACS.[226] Data from a large retrospective cohort study of US veterans undergoing elective coronary angiography, have also demonstrated that obstructive (stenoses>=70%) CAD was associated with worse outcomes such as MI and death. Patients with nonobstructive CAD were at increased risk compared to those with no apparent CAD.[223] In the SCOT-HEART trial, adverse coronary plaque characteristics and overall calcified plaque burden conferred an increased risk of coronary heart disease death or nonfatal myocardial infarction.[227] In a Danish CT angiography study on asymptomatic persons, subclinical, obstructive (>50% diameter stenosis) coronary atherosclerosis was associated with a more than 8-fold elevated risk for myocardial infarction.[228]

Thin-cap fibroatheroma (TCFA) lesions with a large plaque burden as detected by intravascular ultrasound radiofrequency analysis, carry higher risk than small thin-cap fibroatheroma lesions.[229] When intravascular imaging information is available, the lesions with <85μm thick cap and >75% cross-sectional luminal area stenosis are the most probable to rupture.[193] The absolute number of TCFA has been found 3 times greater in nonsevere stenosis than in severe stenosis. It was, however, twice as likely for a lesion to be TCFA in cases of severe stenosis than in nonsevere stenosis, and TCFA in severely-stenotic areas had more features of plaque vulnerability.[230] Nonculprit lesions identified by optical coherence tomography (OCT), as thin-cap atheroma and/or having a minimum luminal area <3.5 mm^2, many of which appear angiographically mild, were also associated with a high risk of future ischemic events.[194] Plaque healing may occur, and the evolution of coronary artery disease appears to be more stable in patients with healed plaques than in patients with unhealed plaques.[231]

Additional causes of UA/NSTEMI are coronary spasm, coronary emboli, coronary arterial inflammation, or spontaneous dissection. Spontaneous ***coronary artery dissection*** is frequent cause of myocardial infarction (up to 35%) in the young, and especially women <50 years of age. Postpartum status, fibromuscular dysplasia, cocaine use, Ehlers-Danlos syndrome, hormonal therapy, connective tissue disorders, systemic inflammatory disease, and extreme physical exertion are conditions that have been associated with spontaneous coronary dissection. [232-236] There has also been some evidence that SCAD may be caused by intramural bleeding (the outside-in mechanism), possibly associated with more potent antiplatelet therapy.[237] Hypertension increases the risk of recurrent dissection, whereas beta-blocker therapy is protective. Pregnancy-related spontaneous coronary artery dissection is the most common cause of pregnancy-associated myocardial infarction.[238] It is estimated that 1 in 16000 pregnancies is complicated by acute myocardial infarctions in the US, and up to one fourth of these are due to spontaneous coronary dissection. [239, 240] It is a rare and potentially lethal complication of pregnancy.

Epicardial or microvascular coronary spasm occurs commonly in the absence of severe coronary disease and can present with or without anginal pain.[241] It may be associated with exogenous or endogenous catecholamines excess.[242] Epicardial coronary spasm is a well-reported cause of cardiac arrest. Identification of non-critical coronary disease in the absence of other causes of cardiac arrest might suggest the diagnosis, particularly in cocaine abusers, as well as in smokers.[243-245]

Coronary embolism occurs in up to 3% of patients with STEMI, and AF is the most frequent cause.[246]

Eosinophilic myocarditis is also a cause of coronary vasculitis and thrombosis.[247]

Myocardial infarction with nonobstructive coronary arteries (MINOCA) occurs in in 5% to 10% of all patients with acute MI and is usually seen in younger patients and women.[248, 249] The most common conditions associated with MINOCA are epicardial coronary artery disease with possible contribution of coronary artery spasm (e.g. plaque rupture with transient thrombosis), imbalance between oxygen supply and demand (e.g. coronary artery spasm and coronary embolism), microvascular dysfunction, hereditary thrombophilia disorders, and secondary to myocardial disorders without involvement of the coronary arteries (e.g. myocarditis or Takotsubo cardiomyopathy).[248-250] Most patients clinically diagnosed with MINOCA have a final diagnosis of myocardial infarction (59%), and an alternate diagnosis mimicking myocardial infarction is present in 20%.[251] Most patients (up to 64%) have a final diagnosis of myocardial infarction.[250] Approximately 20% of patients with MINOCA and age >65 years in a MEDICARE population suffered a major adverse event over the next 12 months.[252] In the CIAO group of the ISCHAEMIA study, half of the patients had resolution of stress-induced wall motion abnormalities on repeat stress echocardiography at 1 year and

symptoms improve in 43%. There was no significant correlation between change in angina and change in ischaemia on stress echocardiography.[253]

Stunned myocardium refers to depressed contractility following transient ischaemia prior to full recovery, and having sustained no irreversible myocyte damage.[254] ***Hibernating myocardium*** is dysfunctional and viable myocardium, but with more severe cellular structural changes, that recovers systolic function following revascularization.[254]

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