Chapter 8
Drug Discovery for Coronary Artery Disease

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Abstract Cardiovascular disease is the number one cause of human morbidity and mortality worldwide. Although cholesterol-lowering drugs, including statins and recently approved PCSK9 inhibitors, together with antithrombotic drugs have been historically successful in reducing the occurrence of coronary artery disease (CAD), the high incidence of CAD remains imposing the largest disease burden on our healthcare systems. We reviewed cardiovascular drugs recently approved or under clinical development, with a particular focus on their pharmacology and limitations. New agents targeting cholesterol/triglyceride lowering bear promise of further cardiovascular risk reduction. Some new antidiabetic agents show cardiovascular benefit in patients with diabetes. Improved antithrombotic agents with diminished bleeding risk are in clinical development. The recent clinical success of the IL-1β antibody in reducing atherothrombosis opens a new era of therapeutic discovery that targets inflammation. Chinese traditional medicine and cardiac regeneration are also discussed. Human genetics studies of CAD and further delineation of key determinants/pathways underlying the residual risk of CAD under current standard therapy will continue to fuel the pipeline of cardiovascular drug discovery.

Keywords Coronary artery disease · Drug discovery · Therapy · Inflammation · Lipid

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Currently available therapeutics for patients with atherosclerotic cardiovascular disease is largely restricted to alleviating hyperlipidemia or preventing thrombotic complications. Discovery of cholesterol-lowering drugs and antithrombotic drugs has been historically successful in reducing the occurrence of coronary artery disease (CAD) and its complications. Despite these progress,cardiovascular disease remains the major cause of human death worldwide. Ischemic heart disease is the number one disease burden to the whole society (Murray et al. 2015). Understanding of new mechanisms of the disease will provide further opportunities to prevent and treat CAD. In this chapter,we mainly overview CAD drugs that are under clinical development or approved recentlywith particular focus on those of new mechanisms of action or being first of class. Their pharmacologyadvantages and limitations will be discussed. Traditional medicine and regenerative medicine for CAD will also be discussed.

8.1 Lipids Modulating Drugs

The discovery that statins reduce cholesterol levels and CAD has promoted searching for new targets to lower cholesterol. This has yielded new drugs, such as PCSK9 inhibitors and cholesterol-absorption blockers, as well as drug candidates.

8.1.1 Proprotein convertase subtilisin/kexin type 9 inhibition

Low-density lipoprotein (LDL) particles receptor (LDLR) binds and initiates the ingestion of LDL-particles, which contains lipid molecules (including cholesterol), from the circulation, thus reducing plasma cholesterol concentrations. Proprotein convertase subtilisin/kexin type 9 (PCSK9) interacts with LDLR and mediates its intracellular degradation. When PCSK9 is blocked, more LDLRs are recycled to remove LDL-particles from the circulation. Thus, PCSK9 inhibition promotes LDLR-mediated liver uptake of circulating LDL, lowering plasma cholesterol levels. A link between PCSK9 and hypercholesterolemia was initially published in 2003, and PCSK9 monoclonal antibodies were approved as a new therapeutic strategy to reduce LDL-C in 2015. The progress from PCSK9 discovery to targeted treatment is unprecedented in terms of scale and speed.

Monoclonal Antibodies

Treatment of patients at high risk for cardiovascular events with antibodies blocking PCSK9 allows further cholesterol lowering by ~60% on top of standard therapy, including statin (Sabatine et al. 2015; Robinson et al. 2015). The first two PCSK9 inhibitors, alirocumab (Praluent, Sanofi/Regeneron) and evolocumab (Repatha, Amgen), were approved as biweekly subcutaneous injections, by the U.S. Food and Drug Administration (FDA) for lowering LDL cholesterol when statins and

other drugs are not sufficiently effective or poorly tolerated. The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial (Nicholls et al. 2016) showed that adding evolocumab to statin therapy produced significant atheroma regression and a continuous benefit with LDL-C levels down to as low as 20 mg/dL. The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial showed that in patients with atherosclerotic cardiovascular disease who were receiving statin therapy, subcutaneous injection of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) reduced LDL cholesterol by 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol/L) to 30 mg per deciliter (0.78 mmol/L), and decreased cardiovascular risk (the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% (Sabatine et al. 2017). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab. No difference in cognitive function was observed between evolocumab and placebo over a median of 19 months (Giugliano et al. 2017). Recent ODYSSEY OUTCOMES trial shows that among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, alirocumab treatment with a target level of LDL cholesterol level of 25–50 mg per deciliter (0.6–1.3 mmol/L) reduces the risk of recurrent ischemic cardiovascular events (Schwartz et al. 2018).

Future use of these PCSK9 antibodies may rely on compliance with injection delivery, safety of prolonged exposure to very low levels of LDL cholesterol and on possibilities of developing anti-drug antibodies, which may curtail cholesterol-lowering efficacy. Cost-effectiveness analysis indicates limitations on the general use of PCSK9 antibody drugs (about $14,000 per year) (Hlatky and Kazi 2017). Their use may particularly be appropriate for those with genetic defects for whom statins are not sufficiently effective, or intolerable (Nissen et al. 2016).

Antisense Oligonucleotide

Suppression of PCSK9 expression by antisense oligonucleotide has been explored for functional inhibition of PCSK9. Inclisiran is a synthetic small interference RNA (siRNA) molecule, inhibits intracellular PCSK9 synthesis by suppressing mRNA translation in hepatocytes. In phase I and II clinical trials (Fitzgerald et al. 2017; Ray et al. 2017), subcutaneous injection of inclisiran results in a dose-dependent, long-term, sustained reduction in LDL-C, with a single or double doses of 300 mg (at a 90 days interval) achieved ~50% reduction at day 180. Inclisiran provides advantages over monoclonal antibodies with an infrequent dosing interval of twice a year to reduce LDL-C by over 50%, similar to that achieved with biweekly or monthly administered antibodies. Inclisiran has been well tolerated and safe, without severe adverse events so far. Serious adverse events (myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, and dizziness) occurred similarly between inclisiran group and placebo group (11% vs. 8%) (Ray et al. 2017). Ongoing studies will establish the long-term safety of inclisiran, which is also important to RNA based therapy in general.

Vaccination
A vaccine that targets PCSK9 has been developed to treat high LDL-particle concentrations. The vaccine uses a virus-like particle (VLP) as an immunogenic carrier of an antigenic PCSK9 peptide. VLP's are viruses that have had their DNA removed so that they retain their external structure for antigen display and can induce an immune response but are unable to cause infection. Mice and macaques vaccinated with bacteriophage VLPs displaying PCSK9-derived peptides developed high-titer IgG antibodies that bound to circulating PCSK9. Vaccination was associated with significant reductions in total cholesterol, free cholesterol, phospholipids, and triglycerides (Crossey et al. 2015).

Small Molecules
Development of small molecular inhibitor for PCSK9 is challenging. This may reflect general difficulty to use small molecules to directly block protein-protein interaction. The plant alkaloid berberine inhibits the transcription of the PCSK9 gene in immortalized human hepatocytes in vitro, and lowers serum PCSK9 in mice and hamsters in vivo (Dong et al. 2015). Given the low bioavailability of berberine, its action on intestinal microbiota has recently emerged as a new mechanism underlying its hypolipidemic effect (See also in the section of Traditional Chinese Medicine).
Cholesterol-lowering drugs with differential mechanisms of action may have complementary clinical applications. For example, PCSK9 inhibitors may be appropriate for patients with statin intolerance, such as those with statin-associated muscle symptoms.

8.1.2 Cholesterol absorption

Blocking the absorption of cholesterol from the small intestine decreases the amount of cholesterol normally available to liver cells, leading them to absorb more from circulation and thus lowering levels of circulating cholesterol. Ezetimibe targets the critical mediator of cholesterol absorption, the Niemann-Pick C1-like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes, thereby reducing the absorption of cholesterol from the intestine. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (Cannon et al. 2015) reports that, in stable patients who had had an acute coronary syndrome within the preceding 10 days, Ezetimibe, when added to statin therapy, resulted in incremental lowering of LDL cholesterol levels (1.4 mM vs. 1.8 mM) and improved cardiovascular outcomes—32.7% versus 34.7% on composite rate of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke, over an median follow-up of 6 years.

8.1.3 Cholesteryl ester transfer protein inhibition

Cholesteryl ester transfer protein (CETP) mediates the transfer of HDL cholesteryl esters for triglyceride (TG) in VLDL/LDL (Millar et al. 2017; Krauss et al. 2015). CETP inhibition increases high-density lipoprotein (HDL) cholesterol (traditionally regarded as good cholesterol) levels and decreases low-density lipoprotein (LDL) cholesterol (traditionally regarded as bad cholesterol) levels. It once bears promise to reduce the risk of atherosclerosis and other cardiovascular diseases by improving blood lipid levels. However, four drugs of this class failed in clinical trials for high-risk patients. Torcetrapib failed due to excess deaths in Phase III clinical trials, likely owing to the off-target effects of the drug. Lacking clinical efficacy, Dalcetrapib, Evacetrapib, and Obicetrapib halted, respectively, in 2012, 2015, and 2017. REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) trial evaluated Anacetrapib, a novel CETP inhibitor, in patients with atherosclerotic vascular disease who were receiving intensive statin therapy (Group et al. 2017). The mean level of HDL cholesterol was higher by 1.12 mM in the anacetrapib group than in the placebo group (a relative difference of 104%), and the mean level of non-HDL cholesterol was lower by 0.44 mM, a relative difference of −18%. The major coronary event occurred in 10.8% of patients in the anacetrapib group versus 11.8% of patients in the placebo group (9% relative risk difference), after 4.1 years of follow-up (Group et al. 2017). Anacetrapib treatment was associated with a slightly higher systolic blood pressure level (0.7 mm/Hg) and an elevated risk for a diminished estimated glomerular filtration rate, with no significant between-group differences in the risk of death, cancer, or other serious adverse events. It is unclear whether the reduction in cardiovascular risk is the consequence of effects on the HDL raising or on CETP inhibitor-mediated reductions in LDL cholesterol, which has been validated with statins. Anacetrapib accumulates in adipose tissue with prolonged administration, and only minimally decline 1 year after cessation of treatment. Merck halted the development of anacetrapib, likely due to relatively modest benefit and safety concerns. It remains unknown whether CETP inhibitors may work better as monotherapy (intensive statin use in the patients of REVEAL trial may actually attenuate the efficacy), and whether certain subgroups with certain genotype may respond better to CETP inhibition in terms of HDL particles taking up cholesterol from the vessel wall. It is necessary to gain insights into the relation between HDL-particle content and beneficial function and to identify alternative targets and drug candidates.

8.1.4 Targeting high-density lipoprotein cholesterol

High-density lipoprotein (HDL) mediates reverse transport of cholesterol from atherosclerotic plaque and thus HDL cholesterol is traditionally believed to be “good cholesterol”, as compared to LDL cholesterol, which increases cardiovascular risk.

However, this notion has been challenged. Niacin lowers the LDL cholesterol level and raises the HDL cholesterol level. Among participants with atherosclerotic vascular disease, the addition of extended-release niacin–laropiprant(a drug itself has no cholesterol-lowering effect, but reduces facial flushes induced by niacin) to statin-based LDL cholesterol-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events (HPS2-THRIVE trial).

Artificial HDL-like apolipoprotein A1 complexes (apoA1-Milano) once held promise in mediating regression of atherosclerosis. The failure to show benefits with MDCO-216 in the MILANO-PILOT trial further challenges the idea of raising HDL for cardiovascular benefit. There are other forms of HDL that continue to undergo clinical trials, as these trials progress we will see how the HDL story ultimately plays out.

8.1.5 Triglyceride lowering drugs

There is compelling epidemiological and genetic evidence indicating that triglyceride lowering may lower cardiovascular risk. Different approaches to lowering triglyceride are being evaluated in cardiovascular outcome trials.

Peroxisome Proliferator-Activated Receptor Alpha Agonist

Peroxisome proliferator-activated receptor alpha (PPARα) is the main target of fibrate drugs, a class of amphipathic carboxylic acids (clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate). They were originally indicated for cholesterol disorders and more recently for disorders of high triglycerides.

Pemafibrate (marketed as Parmodia) is a PPARα agonist. It is approved in July 2017 in Japan, indicated for the treatment of dyslipidaemia. Parmodia is available in 0.1 mg tablets and the recommended dose is 0.1 mg twice daily. In clinical trials (Camejo 2017), pemafibrate as a monotherapy remarkably promotes triglycerides (TG) catabolism by enhancing fatty acid oxidation and inducing lipoprotein lipase gene transcription in liver and muscle. It reduces plasma TG in VLDL and postprandial chylomicrons and also the levels of cholesterol-rich remnants from these two lipoproteins. Pemafibrate as an add-on to statin therapy for managing atherogenic dyslipidaemia reduces TG with a dose–response relationship, remnant cholesterol, Apo B48 and Apo C-III (Fruchart 2017; Arai et al. 2017). Activation of PPARα by pemafibrate has multiple metabolic effects, rendering it difficult to attribute its potential cardiovascular benefit to individual change. For example, pemafibrate elevated levels of FGF21 that can improve plasma lipids, plasma glucose, and insulin resistance, pemafibrate upregulates hepatic ApoA-I synthesis and HDL production, and enhances cholesterol transport to the liver through ApoA-I apolipoprotein (Hennuyer et al. 2016).

PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes) trial is a phase-3 trial to determine whether

pemafibrate administered 0.2 mg tablet twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or cardiovascular death, in patients with type 2 diabetes and dyslipidemia. This trial is estimated to complete in 2022.

Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA) is the main component of fish oil. EPA belongs to the omega-3 series of polyunsaturated fatty acids (PUFA). It is an indispensable essential nutrient that cannot be synthesized by the human body. Therefore, it is called an essential fatty acid. Although linolenic acid can be converted into EPA in the human body, this reaction is very slow in the human body and the amount of conversion is very small, far from meeting the human body's need for EPA, and therefore must be supplemented directly from food. Clinical trials have demonstrated that omega-3 series fatty acids not only can lower cholesterol and triglyceride levels, but inhibit platelet aggregation and inflammatory responses. Its mechanism of action may be that omega-3 PUFA competes with the storage of arachidonic acid to replace it and block the production of pro-inflammatory eicosanoids (Davinelli et al. 2018). Extensive research shows marine-derived omega-3 fatty acids decrease triglycerides with a potential reduction in cardiovascular disease in certain populations.

AMR101 (icosapent ethyl) is ethyl eicosapentaenoic acid, an ethyl ester of eicosapentaenoic acid (EPA, an omega-3 fatty acid). AMR101 is a highly purified ethyl ester of EPA, and is approved by the FDA in 2012 for severe hypertriglyceridemia. REDUCE-IT (Bhatt et al. 2019) (Reduction of Cardiovascular Events With EPA—Intervention Trial) evaluated the cardiovascular effect of 2 g of icosapent ethyl twice daily 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 of 135–499 mg per deciliter (1.52–5.63 mmol/L) and a low-density lipoprotein cholesterol level of 41–100 mg per deciliter (1.06–2.59 mmol/L). Compared with placebo, 4 g/Day AMR101 reduced long-term cardiovascular events (Composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina) (17.2% vs. 22.0%, hazard ratio, 0.75; 95% [CI], 0.68–0.83; $P < 0.001$) in high-risk patients with elevated triglyceride levels despite the use of statins. A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, $P = 0.004$).

The cardiovascular benefit of n–3 fatty acids appears to relate to disease condition and/or dose. In general, populations at usual risk (VITAL trial, a primary prevention trial among men 50 years of age or older and women 55 years of age or older), marine n–3 fatty acids (at a dose of 1 g per day) did not result in a lower incidence of major cardiovascular events (primary endpoint, a composite of myocardial infarction, stroke, or death from cardiovascular causes) (hazard ratio, 0.92; 95% confidence interval [CI], 0.80–1.06; $P = 0.24$), but reduced a key secondary endpoint, total myocardial infarction, 0.72 (95% CI, 0.59–0.90) (Manson et al. 2019). Among patients with diabetes without atherosclerotic cardiovascular disease (ASCEND trial)

(Group et al. 2018) 1 g n – 3 fatty acids daily did not reduce the risk of serious vascular events compared with placebo (olive oil).

Epanova (omega-3 carboxylic acids) is a concentrate of omega-3 free fatty acids, developed from fish oils. STRENGTH (STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) trial is a long-term cardiovascular outcome study to assess Epanova, taken once daily on top of statin, in patients with hypertriglyceridemia and low HDL and high risk for CVD. This phase 3 trial is started in 2014 and estimated to complete in late 2019.

Apolipoprotein C-III Inhibition

Apolipoprotein C-III (APOC3) is a component of TG-rich lipoproteins, known to inhibit lipoprotein lipase-mediated hydrolysis of TG-rich lipoproteins and to negatively affect receptor-mediated hepatic uptake of remnants of TG-rich lipoproteins, thereby regulating plasma TG levels. Elevated APOC3 levels result in accumulation of atherogenic very-low-density lipoproteins (VLDL) and chylomicron remnants, as a consequence of impaired lipolysis and disturbed clearance of TG-rich lipoproteins. Elevated APOC3 levels, especially when present on apolipoprotein E-containing lipoproteins, are an independent risk factor for CVD. Rare mutations that disrupt APOC3 function were associated with lower levels of plasma triglycerides and APOC3 and with a reduced risk of CAD (Tg et al. 2014). People with homozygous loss of function of APOC3 show marked blunting of the usual postprandial rise in plasma triglycerides (Saleheen et al. 2017). Although fibrates, statins and omega-3 fatty acids modestly decrease triglyceride levels (and apoC-III concentrations), there are many patients who still have severe hypertriglyceridemia and are at increased risk for pancreatitis and potentially for CVD.

ISIS 304801 is an antisense oligonucleotide that specifically binds to *APOC3* mRNA and induces its degradation. It robustly decreases both, apoC-III production and triglyceride concentrations. In a phase 2 trial in patients with severe or uncontrolled hypertriglyceridaemia, weekly subcutaneous injections of 100, 200, or 300 mg of ISIS 304801 for 13 weeks ISIS 304801 as monotherapy produced a dose-dependent, prolonged reduction in TG levels (largest decrease with 300 mg: 70.9% vs. 20.1% increase on placebo) and increase in HDL levels (300 mg: 45.7% vs. 0.7% with placebo). A similar effect was observed when the drug was used as an add-on to stable doses of fibrate therapy (Gaudet et al. 2015). It is being currently evaluated in phase 3 trials (Schmitz and Gouni-Berthold 2018). An outcome trial is needed to establish clinical proof-of-concept with therapeutics that inhibit APOC3.

Angiopoietin-Like 3 Inhibition

Angiopoietin-like 3 (ANGPTL3) is a protein that inhibits lipoprotein lipase (LPL) and endothelial lipase (EL), thereby increasing plasma triglyceride, LDL cholesterol, and HDL cholesterol. LPL is a rate-limiting enzyme for the hydrolysis of circulating triglycerides (TG) into free fatty acids that are absorbed by peripheral tissues (Zhang 2016). ANGPTL3 is a novel target to reduce triglyceride-rich lipoproteins (Olkkonen et al. 2018). Evinacumab is an antibody from Regeneron, which blocks the actions of ANGPTL3. An antisense oligonucleotide from Ionis Pharmaceuticals also blocks ANGPTL3 activity. Animal studies, as well as early clinical studies, show that

they can lower triglycerides to unprecedented levels. Further cardiovascular outcome studies are needed before considering these drugs for clinical approval.

8.1.6 Other lipid modulators

ETC-1002 (bempedoic acid) is a small molecule with a unique mechanism of action shown in nonclinical studies to modulate pathways of cholesterol, fatty acid, and carbohydrate metabolism (Nikolic et al. 2014; Bilen and Ballantyne 2016). ETC-1002 lowers LDL cholesterol and other lipids and shows that high-sensitivity C-reactive protein is improved in patients with type 2 diabetes and hypercholesterolemia (Gutierrez et al. 2014). In phase 2 studies, ETC-1002 reduced LDL-C as monotherapy, combined with ezetimibe, and added to statin therapy, with LDL-C lowering most pronounced when ETC-1002 was combined with ezetimibe in patients who cannot tolerate statins (Thompson et al. 2016).

8.2 Targeting Inflammation

Historical success of statins, together with the recent approval of PCSK9 inhibitors, has firmly established the therapeutic principle of lowering LDL-C for treating CAD. However, residual cardiovascular risk following successful LDL-C lowering therapy remains substantial. Inflammation is thought of as an essential pathology for CAD and its acute manifestation, myocardial infarction (MI), which involves cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, and C-reactive protein (CRP, a marker of inflammation) production. In addition to innate immunity, adaptive immunity is also associated with atherosclerosis through antigen-presenting cells, T and B lymphocytes. Statin is known to have anti-inflammatory activity besides LDL-C lowering effects, which may also contribute to its cardiovascular efficacy. Indeed, aggressive lipid lowering by high-dose atorvastatin decreases high-sensitivity CRP (hsCRP) serum levels and entails regression of atheromas. The clinical benefit is extended to primary prevention in patients with LDL-C levels < 130 mg/dl but elevated hsCRP, where rosuvastatin significantly reduces major cardiovascular event rates, with reductions in both LDL-C and hsCRP. In acute coronary syndrome (ACS), aggressive statin therapy also lowered the incidence of primary endpoints including MI, with the most substantial benefit in patients with declines in both LDL-C and CRP. Recent FOURIER Trial reveals that LDL-C and hsCRP are independently associated with the cardiovascular outcome (Bohula et al. 2018). Nevertheless, teasing out the anti-inflammatory effect of statin from its LDL cholesterol-lowering effect in cardiovascular prevention appears practically impossible.

Previous trials exploring treatment that specifically targets inflammation failed to show clinical benefits in CAD patients. The targets involved include p38 MAP

kinase, CRP, secretory phospholipase A2 (sPLA2, an enzyme catalyzes the first step of the arachidonic acid pathway of inflammation), lipoprotein-associated phospholipase A2 (Lp-PLA2, a secreted acetylhydrolase that catalyzes the degradation of platelet-activating factor), IL-1R, the IL-6 receptor, CC2 chemokine receptor, and some immunomodulatory or immunosuppressive therapies, such as cyclosporine and colchicine, CD20 blocker. Recently, the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial provides first clinical evidence that an IL-1β antibody that leads to marked reductions in IL-6 and CRP reduces cardiovascular risk.

- **IL-1β inhibition**

IL-1, a pro-inflammatory cytokine, promotes the development of atherosclerosis and contributes to adverse remodeling and left ventricular dysfunction after acute myocardial infarction (AMI). In phase II studies, IL-1 blockade suppressed the inflammatory response associated with ST-segment elevation AMI and prevented heart failure (HF). Other phase II studies show improved exercise capacity with IL-1 blockade in patients with HF. Several IL-1 blockers are available for clinical use, which differ in mechanism of action, and potentially also efficacy and safety.

Canakinumab (trade name Ilaris) is a human monoclonal antibody that specifically inhibits IL-1β function. IL-1β is synthesized as a precursor form protein only after stimulation, in contrast to IL-1α. Canakinumab was approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) in 2009. CAPS is a spectrum of auto-inflammatory syndromes including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease. In September 2016, FDA approved the use of canakinumab on 3 additional rare and serious auto-inflammatory diseases: TNF receptor-associated periodic syndrome, hyper immunoglobulin D syndrome/mevalonate kinase deficiency and Familial Mediterranean fever.

CANTOS trial shows that, in patients with previous myocardial infarction and persistently elevated hsCRP (>= 2 mg/L), subcutaneous administration of canakinumab every 3 months at 150 mg led to a significantly lower rate of recurrent cardiovascular events (nonfatal MI, nonfatal stroke, or cardiovascular death) than placebo with a hazard ratio (HR) of 0.85 (95% CI, 0.74–0.98), independent of lipid-level lowering (Ridker et al. 2017). Baseline clinical characteristics did not define patient groups with greater or lesser cardiovascular benefits when treated with canakinumab. However, trial participants allocated to canakinumab who achieved hsCRP concentrations less than 2 mg/L had a 25% reduction in major adverse cardiovascular events (HR = 0.75, 95% CI 0.66–0.85), whereas no significant benefit was observed among those with on-treatment hsCRP concentrations of 2 mg/L or above (HR = 0.90, 0.79–1.02, p = 0.11). These data further suggest that lower is better for inflammation reduction with canakinumab (Ridker et al. 2018). This phase 3 trial provides the first clinical proof-of-principle for anti-inflammatory therapy for atherosclerosis. Interestingly, the CANTOS trial also showed a significant reduction in lung cancer incidence and mortality in the canakinumab treated group compared to the placebo. A higher incidence of fatal infection was observed in the canakinumab group than in

the placebo, which is likely due to a blunting of the inflammatory signs of infection leading to delayed presentation and diagnosis. IL-1 blockade was not associated with opportunistic infections and there was no difference in all-cause mortality with the canakinumab treatment. Cost-effectiveness and potential risk of immune suppression determine whether and who might benefit from the use of canakinumab for cardiovascular prevention.

- **Methotrexate and lessons learned**

Methotrexate inhibits dihydrofolate reductase that is essential for DNA synthesis and it also inhibits lymphocyte activation. It is on the World Health Organization's List of Essential Medicines being used as a chemotherapy agent and immune system suppressant. Low-dose methotrexate is an effective anti-inflammatory therapy widely used to treat rheumatoid arthritis. The CIRT (Cardiovascular Inflammation Reduction Trial) evaluates effects of low-dose (15–20 mg per week) methotrexate on rates of MI, stroke, and cardiovascular death among patients with previous MI or multivessel coronary disease who additionally had either type 2 diabetes or metabolic syndrome, conditions associated with an enhanced pro-inflammatory response. However, low-dose methotrexate did not reduce levels of IL-1β, IL-6, or CRP and did not result in fewer cardiovascular events than placebo in these patients with stable atherosclerosis (Ridker et al. 2018), raising questions on the dose and population selected.

Clinical data on inflammatory biomarkers, biological data and recent Mendelian randomization data suggest that inflammatory mediators of atherosclerosis may converge on the central IL-1, tumor necrosis factor (TNF-a), IL-6 signaling pathway. On this basis, emerging anti-inflammatory approaches to vascular protection can be categorized into two broad groups, those that target the central IL-6 inflammatory signaling pathway and those that do not. Both approaches have the potential to benefit patients and reduce vascular events, but may not concord each other. The inflammatory system is redundant, compensatory, and crucial for survival, evaluation of risks, as well as benefits, must drive the development of agents in this class.

8.3 Antiplatelet Drugs

Thrombosis that occludes blood vessels is the direct cause of acute manifestations of CAD. Antiplatelet drugs reduce thrombotic risk by inhibiting platelet activation and aggregation. Thromboxane and ADP activate their corresponding platelet receptors TP and P2Y12, respectively, and result in platelet inside-out signaling and integrin αIIbβ3 (glycoprotein IIb/IIIa) conformation change allowing its binding to fibrinogen to aggregate platelets. Drugs targeting the above pathways have been successfully used in the clinic. Aspirin suppresses thromboxane production and inhibits platelet aggregation. It is a cornerstone therapy for secondary cardiovascular prevention in ACS, a benefit further enhanced by additional P2Y12 antagonism through clopidogrel, or, more recently developed prasugrel or ticagrelor. Platelet integrin αIIbβ3 inhibitors are potent antithrombotic drugs that are used intravenously to treat

ACS, but they also have the life-threatening adverse effect of causing bleeding. Discovery of antiplatelet drugs that can effectively prevent thrombosis while sparing bleeding side effects remains an unmet medical need.

- **Proteinase-activated receptors**

Thrombin activates platelets by cleaving/activating a G–protein-coupled family of proteinase-activated receptors (PARs). The signaling mechanism involves the proteolytic unmasking of an N-terminal receptor sequence that acts as a tethered receptor-activating ligand. The recognized targets of thrombin cleavage and activation for signaling are PAR1 and PAR4, in which thrombin cleaves at a conserved target arginine to reveal a tethered ligand. Unlike anticoagulants, PAR1 inhibitors block downstream of PAR1 without directly impacting thrombin-induced fibrin polymerization. Vorapaxar (Zontivity), a competitive PAR1 antagonist, is effective in treating ACS, however, the severe bleeding associated with this drug has limited its use in the clinic. Due to the efficacy of thrombin acting via PAR1, strategies to selectively inhibit specific PAR1-mediated G protein signaling pathways or to target the second thrombin platelet receptor, PAR4, are being devised (Wong et al. 2017). The rationale behind these alternative approaches is to bias downstream thrombin activity via PARs to allow for inhibition of pro-thrombotic pathways but maintain other pathways that may preserve hemostatic balance and improve bleeding profiles for widespread clinical use.

- **Platelet integrin outside-in signaling**

Activated platelets facilitate coagulation (platelet procoagulant activity, PPA) mainly by exposing the procoagulant phospholipid phosphatidylserine (PS) on the outer membrane surfaces and releasing PS-expressed microvesicles (MVs). Recent studies indicate that selective targeting of integrin outside-in signaling as a new antithrombotic strategy that has the advantage of potently inhibiting occlusive platelet thrombus expansion without causing excessive bleeding (Shen et al. 2013). β3 integrins serve as a shear sensor activating the Gα13-dependent outside-in signaling pathway to facilitate platelet procoagulant function. An inhibitor of outside-in signaling that targets Gα13-integrin interaction was discovered to prevent occlusive thrombosis in vivo by inhibiting both coagulation and platelet thrombus formation (Pang et al. 2018). It is known that partial inhibition of platelet thrombus formation by platelet activation inhibitors or by integrin inhibitors are not effective in inhibiting fibrin clot formation, whereas complete inhibition of integrin ligand-binding function is likely to cause excessive bleeding. Thus, by targeting integrin outside-in signaling without blocking platelet adhesion and primary aggregation, it is possible to diminish platelet-dependent intravascular fibrin clot without causing excessive bleeding. Because the intravascular fibrin clot around the platelet thrombus is associated with thrombus expansion and stabilization, this novel effect of outside-in signaling inhibitors is likely to contribute to the potency and anticlotting effect of these new drugs, and is advantageous over the current antiplatelet drugs. Pharmacological targeting of Gα13-integrin interaction is under preclinical development.

- **Reactive oxygen species**

Reactive oxygen species is known to regulate thrombosis (Pietraforte et al. 2014; Forstermann 2008; Delaney et al. 2016). In a randomized, placebo-controlled clinical trial in patients with antiphospholipid syndrome, treatment with ubiquinol, the reduced equivalent of coenzyme Q10, improved endothelial function, and reduced thrombotic risk markers, likely through reduced platelet activation and endothelial inflammation related to oxidative stress (Perez-Sanchez et al. 2017).

8.4 Anticoagulation Drugs

Activation of coagulation is essential to thrombosis. The coagulation pathway is a protease activation cascade in the blood, leading to the formation of fibrin that stabilizes blood clot (Fig. 8.1). It is classified into the extrinsic pathway and intrinsic pathway, which are initiated by tissue factor and contact activation, respectively. Both pathways share the common pathway of coagulation that generates factor Xa and thrombin, which cleaves fibrinogen to form fibrin.

Heparin and vitamin K antagonists (VKAs) are the first used as anticoagulants in the middle of the twentieth century. Heparin is a naturally occurring anticoagulant produced in the body. It binds to and activates antithrombin III (AT), thus inactivating thrombin and factor Xa. VKAs, such as warfarin, inhibit vitamin K epoxide reductase and thus the formation of vitamin K that is required for the production of certain

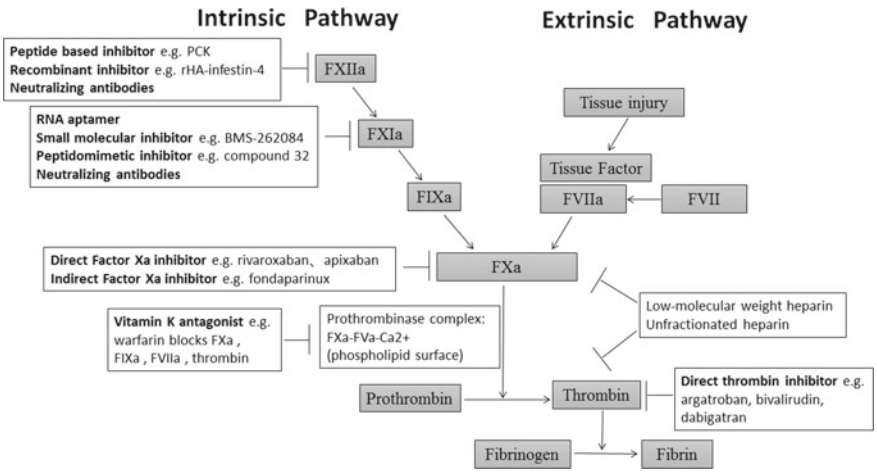

Fig. 8.1 Coagulation pathway and anticoagulant targets. Coagulation cascade is a series of sequential reactions in which zymogens are converted to active serine proteases ultimately resulting in the formation of covalently cross-linked fibrin. Blood coagulation can be triggered via the extrinsic pathway that is initiated by tissue factor following tissue trauma or via an intrinsic pathway that is driven by FXII activation. Anticoagulants targeting FXII, FXI and FIX are in development

clotting proteins, including the carboxylation of prothrombin to form active thrombin. VKAs and heparin have been the gold standard for the treatment and prevention of thromboembolic disease for many years. Unfortunately, they are accompanied by serious bleeding problems, it is necessary to monitor the therapeutic window, and there are various interactions with food and other drugs. A serious side-effect of heparin is heparin-induced thrombocytopenia, caused by an immunological reaction against platelets, resulting in platelet degradation. VKAs are very effective in the prevention and treatment of venous and arterial thrombosis. However, warfarin has many side effects of which bleeding is the most pronounced. It is estimated that, on a yearly basis, 0.5% of patients on VKAs suffer from major bleeding for which medical treatment is necessary, with a death rate of 0.25% due to bleeding. In 1985 and 2001, low-molecular-weight heparin (LMWH) and fondaparinux (chemically related to LMWH) were developed, respectively, which demonstrate better bioavailability after subcutaneous injection than heparin and more predictable anticoagulant responses. They do not need coagulation monitoring, thereby reducing healthcare costs and increasing patient satisfaction.

Coincident with these advances was the development of bivalirudin, a parenteral synthetic peptide inhibitor of thrombin that is derived from the naturally occurring drug hirudin found in the saliva of the medicinal leech. Bivalirudin is a synthetic peptide that directly inhibits thrombin and overcomes many of the limitations seen with indirect thrombin inhibitors. It inhibits both circulating and clot-bound thrombin, and also inhibits thrombin-mediated platelet activation. It does not bind to plasma proteins or to red blood cells and has a half-life of approximately 25 min in patients with normal renal function with a predictable antithrombotic response. It does not activate platelets and has been used in patients with, or at risk of, heparin-induced thrombocytopenia or heparin-induced thrombocytopenia and thrombosis syndrome. Following two large randomized controlled trials, HORIZONS-AMI and ACUITY, which showed a reduced rate of adverse clinical events (primarily driven by lower major bleeding events) with bivalirudin compared with unfractionated heparin (UFH) with glycoprotein IIb/IIIa inhibitors, bivalirudin rapidly gained favor in the United States, surpassing the use of UFH as the anticoagulant of choice during percutaneous coronary interventions (PCI) for NSTEMI and STEMI. Bivalirudin is widely used in place of heparin during PCI (Erlinge et al. 2017).

Efforts in seeking oral anticoagulants that are more convenient to administer than VKAs lead to the discovery of a new generation of drugs, which is known as direct oral anticoagulants (DOACs). DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit factor Xa. These agents are at least as effective as VKAs but are associated with less bleeding, particularly less intracranial bleeding, and are easier to administer because they can be given in fixed doses without routine coagulation monitoring. Because of these attributes, current guidelines give preference to the DOACs over VKAs for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism. Prescriptions for DOACs now surpass those for VKAs in several countries and are likely to increase as new indications are identified.

Currently available coagulants inhibit the common pathway of the coagulation cascade that is also required for hemostasis and, as such, bear an inherent risk for bleeding complications. Despite a similar or even superior effectiveness compared to VKAs, DOACs have different limitations: (1) bleeding is still an important problem; (2) there is no routine, widely available diagnostic test that can safely monitor the therapeutic window; (3) there is no reversal agent available for these anticoagulants, which is particularly undesirable in trauma patients. Therefore, the search for new anticoagulants continues. The goal of anticoagulant therapy is to attenuate thrombosis without compromising hemostasis. Drugs targeting the intrinsic pathway of coagulation (factor XIIa, factor XIa, and factor IXa) bear such potential. This pathway amplifies the clotting cascade but unlike the extrinsic (tissue factor and factor VIIa) and common pathways (factor Xa and thrombin) appears not essential for hemostasis.

- **Coagulation factor XI**

Growing evidence suggests that factor (F) XI plays an important role in thrombosis with a relatively limited contribution to hemostasis. Congenital FXI deficiency defined using an FXI activity assay is protective against venous thromboembolism (VTE), ischemic stroke, and myocardial infarction (Preis et al. 2017). Subjects with higher levels of FXI are more prone to ischemic stroke and VTE, Inhibitors targeting FXI/FXIa (the active form of FXI) have emerged as a new generation of anticoagulants to effectively curtail thromboembolic diseases without potential fatal bleeding. Available inhibitors of FXI/FXIa include polypeptides, active site peptidomimetic inhibitors, allosteric inhibitors, antibodies, aptamers, and antisense oligonucleotides (ASOs), which reduce FXI biosynthesis by blocking its expression. In animal studies, FXI antibodies attenuate platelet and fibrin deposition and FXI ASO reduces thrombosis in a concentration-dependent manner.

Proof-of-concept comes from a small phase 2 study of patients undergoing elective knee arthroplasty (Buller et al. 2015). Subcutaneous injection of an FXI ASO (IONIS-416858, 300 mg) starting 35 days before surgery reduced mean FXI levels to 28% of baseline values, at the time of surgery. Compared with 40-mg enoxaparin (low-molecular-weight heparin) once daily starting after surgery and continued for at least 10 days, IONIS-416858 reduced venous thromboembolism events (asymptomatic or symptomatic deep-vein thrombosis, symptomatic pulmonary embolism, and VTE-related mortality) 4% (3 of 71 patients) versus 30% (21 of 69 patients). The rates of the composite of major and clinically relevant nonmajor bleeding were 3% in the IONIS-416858 group and 8% in the enoxaparin groups. Nevertheless, this encouraging observation needs confirmation in larger trials to show the relative advantage of lowering FXI levels in reducing VTE risk but without increasing bleeding risk, compared with enoxaparin. The addition of low doses of rivaroxaban (FXa inhibitor) to patients with recent ACS reduces the rates of death from cardiovascular causes without increasing fatal bleeding, but increases intracranial hemorrhage. In light of this, reducing FXI levels or inhibition of FXI in patients with a recent ACS might also reduce death rates in a similar manner to treatment with rivaroxaban but without an increase in intracranial hemorrhage. It is likely that inhibition of FXI

prevents the propagation of coagulation by suppressing both intrinsic pathway and its amplification of extrinsic activation. Thus, FXI-directed strategies may be further explored for additional clinical indications. Initial findings have also demonstrated the potential of FXI/FXIa inhibitors in sepsis, listeriosis, and arterial hypertension.

- **Coagulation factor XII**

FXII is a plasma protease that is activated by binding to negatively charged surfaces. The active form of FXII (FXIIa) initiates the intrinsic coagulation pathway. Although there is a lack of human data supporting the relationship between factor XII and thrombosis, FXII deficiency is not associated with bleeding (Key 2014). Preclinical evidence consistently shows that pharmacological inhibition of FXII/FXIIa may be a promising therapeutic anticoagulation treatment strategy with less bleeding risk (Nickel et al. 2017). FXIIa also contributes to inflammation through the activation of the bradykinin-producing kallikrein–kinin system. FXII(a) inhibitors have been developed, including recombinant proteins, synthetic peptides, small molecular inhibitors, antibodies, and ASO. Most of these inhibitors showed antithrombotic effects with additional anti-inflammatory properties.

FXII monoclonal antibody 15H8 inhibited thrombosis formation in baboons (Matafonov et al. 2014). 3F7 is a recombinant fully human FXIIa-neutralizing antibody, which blocked experimental thrombosis in mice and rabbits (Larsson et al. 2014) and inhibited thrombosis as efficiently as heparin in a rabbit model of cardiopulmonary bypass, without the increased bleeding risk seen with heparin. 3F7 was also reported to abolish bradykinin generation in hereditary angioedema (HAE) type III patient plasma and to blunt edema in a mouse model (Bjorkqvist et al. 2015). Suppressing FXII expression with ASO reduced arterial and venous thrombosis in mice (Revenko et al. 2011) and attenuated catheter-induced thrombosis in rabbits (Yau et al. 2014) without increasing bleeding risk. Targeting FXII by ASO has a slow onset of action and requires multiple parenteral ASO administration. Small-molecule inhibitors of FXIIa are still under development.

The FXII-driven coagulation mediates not only thrombosis but also inflammatory life-threatening diseases. These include edema, experimental autoimmune encephalomyelitis, hereditary angioedema and settings where the blood comes in contact with nonphysiological surfaces such as catheters, extracorporeal membrane oxygenation, dialysis membranes, and ventricular assist devices. Although pharmacological inhibition of FXII has been identified as a potent strategy to limit thrombosis in animal models, without increased bleeding tendency, and to treat edema formation and hypotension in mice with possible implications for patients, these promises await confirmation in clinical trials.

8.5 Antidiabetic Agents

Epidemiologic studies show a clear correlation between lower blood sugars and better health outcomes in patients with diabetes mellitus. Every 1% increase in the

hemoglobin A1c was associated with an 18% increase in the risk of cardiovascular (CV) events, 12–14% increase risk of death and a 37% increased risk of eye disease or kidney disease. Most diabetic patients die of cardiovascular disease (CVD). Hyperglycaemia itself contributes to the pathogenesis of atherosclerosis and heart failure (HF) in these patients. Treating blood glucose to current guidelines is safe and very important for reducing microvascular complications like nerve, kidney and eye disease. However, most glucose-lowering drugs studied, as in trials of ADVANCE, ACCORD, VADT, etc., failed to reduce cardiovascular adverse events despite the proven ability to lower blood glucose, especially in patients with a long duration of type 2 diabetes mellitus (T2D) and prevalent CVD. Such drugs include metformin, sulfonylureas, PPAR agonists thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors. No significant long-term efficacy of insulin on any clinical outcome in T2D was observed. Actually, some diabetes drugs, in particular, rosiglitazone, even increase adverse cardiovascular events. As such, regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with T2D in order to rule out excess cardiovascular risk. There is evidence suggesting that earlier treatment in prediabetic patients before disease onset may be effective although its effects are delayed (UKPDS trial). Recent trials show that diabetes drugs targeting SGLT2 or GLP1 may improve cardiovascular outcome in patients with established T2D.

- **Sodium-glucose linked transporter 2 inhibition**

Sodium-glucose linked transporter (SGLT) is a family of glucose transporter, with SGLT1 and SGLT2 being the two most well-known members. SGLT1 is found in the enterocytes of the small intestine and in the proximal straight tubule. SGLT2 is mainly expressed in the proximal convoluted tubule of the nephron. They contribute to renal glucose reabsorption. In a healthy nephron, the filtered glucose in the glomerulus is all reabsorbed along the nephron (at least 90% in the proximal convoluted tubule, via SGLT2). In hyperglycemic condition, glucose is excreted in urine because SGLT is saturated with the filtered glucose. SGLT2 inhibitors increase urinary glucose excretion, thus improving glycemic control independent of insulin.

Empagliflozin (trade name Jardiance) is an SGLT2 inhibitor, approved for the treatment of T2D in adults in 2014. EMPA-REG OUTCOME trial (Zinman et al. 2015) reports that in a population of patients with T2D and established cardiovascular disease on a background of standard care, empagliflozin reduces the combined CV endpoint of CV death, nonfatal MI, and nonfatal stroke compared to placebo (10.5% vs. 12.1%, HR = 0.86). Empagliflozin also significantly and robustly reduced the individual endpoints of CV death (3.7%, vs. 5.9%; 38% relative risk reduction), any cause mortality (5.7% and 8.3%, respectively; 32% relative risk reduction), and hospitalization for HF (2.7% and 4.1%, respectively; 35% relative risk reduction) in this high-risk population. These cardiovascular beneficial effects of empagliflozin may result from an interplay of various factors beyond glucose control such as weight loss, blood pressure lowering and sodium depletion, renal hemodynamic effects, effects on myocardial energetics, and/or neurohormonal effects, etc. Future studies are warranted to clarify the underlying mechanisms, and importantly to assess whether such

beneficial effects are evident across the SGLT2-inhibitor class of medications or unique to empagliflozin. An increased rate of genital infection was observed among patients receiving empagliflozin (Zinman et al. 2015). Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care (Wanner et al. 2016). The risk of developing diabetic ketoacidosis (DKA) among T2D patients initiating an SGLT2 inhibitor is about double that seen among patients starting a DPP-4 inhibitor, but the overall risk is still low (Fralick et al. 2017). Patients are advised to be monitored for signs of DKA after starting on SGLT2 inhibitors.

Canagliflozin is another SGLT2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. Patients with T2D and prior cardiovascular events had higher rates of cardiovascular outcomes compared with the primary prevention patients. Canagliflozin reduced cardiovascular and renal outcomes similarly among both primary and secondary prevention participants (Mahaffey et al. 2018). In two CANVAS trials involving patients with T2D and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal (Neal et al. 2017). Canagliflozin was also associated with a lower rate of progression of albuminuria, however, amputation occurred more frequently. The benefit of canagliflozin may be greater among those with a prior history of heart failure, and did not appear to be modified by baseline renal function (Neuen et al. 2018; Radholm et al. 2018).

- **Glucagon-like peptide-1**

Glucagon-like peptide-1 (GLP-1) is an incretin and has the ability to decrease blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin. GLP-1 is a 30 amino acid long peptide hormone derived from posttranslational processing of the proglucagon peptide. It is produced and secreted by intestinal enteroendocrine L-cells and certain neurons in the brainstem upon food consumption. Endogenous GLP-1 is rapidly degraded primarily by DPP-4, but also neutral endopeptidase 24.11 and renal clearance, resulting in a half-life of approximately 2 min. Consequently, only 10–15% of GLP-1 reaches circulation intact, leading to fasting plasma levels of only 0–15 pmol/L. To overcome this, GLP-1 receptor agonists and DPP-4 inhibitors have been developed to increase GLP-1 activity. As opposed to common treatment agents such as insulin and sulphonylurea, GLP-1-based treatment has been associated with weight loss and a lower risk of hypoglycemia, two important considerations for patients with T2D.

Liraglutide (Victoza, Novo Nordisk) is a once-daily injectable derivative of the human incretin GLP-1, for the treatment of T2D or obesity. It binds to the same receptors as does the endogenous metabolic hormone GLP-1 that stimulates insulin secretion. Liraglutide reduces meal-related hyperglycemia by increasing insulin secretion when required by increasing glucose levels, delaying gastric emptying, and suppressing prandial glucagon secretion. In patients with T2D and high cardiovascular risk(LEADER Trial), liraglutide, when added to standard care, reduces the rate of the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal

stroke (13.0% vs. 14.9%, HR, 0.87; 95% CI, 0.78–0.97). The rate of death from cardiovascular cause (4.7% vs. 6.0%, HR, 0.78, 95% CI, 0.66–0.93) and from any cause (8.2% vs. 9.6%, HR, 0.85; 95% CI, 0.74–0.97) was lower in the liraglutide group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events (Alvarez-Villalobos et al. 2016).

Semaglutide (Ozempic, Novo Nordisk) is a GLP-1 analogue with an extended half-life of approximately 1 week. In a trial (SUSTAIN-6) of 3297 patients with T2D who were at high cardiovascular risk, semaglutide treatment significantly lowered the combined risk for CV death, nonfatal MI or nonfatal stroke compared to placebo (6.6% vs. 8.9%, HR, 0.74). The rates of nonfatal MI and nonfatal stroke, for the semaglutide group as compared to placebo group, were 2.9% versus 3.9% (HR, 0.74; $P = 0.12$) and 1.6% versus 2.7% (HR, 0.61; $P = 0.04$), respectively. Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (HR, 1.76; 95% CI, 1.11–2.78; $P = 0.02$). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal (Marso et al. 2016).

The cardiovascular beneficial effects of empagliflozin and liraglutide may attribute to effects other than their glucose-lowering effect, since both drugs only modestly reduced blood glucose (0.4% in HbA1c). Understanding the underlying mechanism may provide new therapeutic targets for patients with atherosclerotic disease or at risk.

8.6 Emerging Therapeutic Targets from GWAS

The exceptionally rapid development of the new class of cholesterol-lowering drugs targeting PCSK9 exemplifies how the genetic discovery of human diseases may expedite the development of new drugs. In this regard, genome-wide association studies (GWAS) of CAD provide tremendous opportunities for elucidating novel disease mechanisms and potential therapeutic targets (Consortium et al. 2013; Roberts 2014; Yao et al. 2018). Candidate genes of potential mechanistic relevance, such as CDKN2A/B, CXCL12, and LIPA, are under intensive research. Genetic loci of CXCL12, and plasma levels of its chemokine product, also known as SDF1, are associated with CAD. Recent studies of its secondarily discovered receptor, CXCR7, indicate that activation of CXCR7 promotes endothelial repair and angiogenesis, thus restrains injury-induced adverse vascular remodeling, and promotes hear functional recovery after an attack of MI (Hao et al. 2017).

8.7 Traditional Chinese Medicine

Coronary artery disease (CAD), also known as coronary heart diseases or ischemic heart disease, refers to a series of diseases such as stable angina, unstable angina, myocardial infarction and sudden cardiac death that are mainly attributable to coronary artery stenosis due to atherosclerotic plaque. The development of atherosclerosis leads to a decrease or even cessation (in the case of atherothrombosis) of the coronary artery flow, resulting in cardiomyocyte damage and functional loss. Some traditional Chinese medicine (TCM) has been used for CAD, to relieve symptoms. However, there is a lack of clinical outcome trials for most if not all TCM that are already in practice for CAD treatment. Because TCM is an impure natural product, potential multiple active ingredients and their interactions make it challenging to precisely delineate their molecular pharmacology or therapeutic target. Nevertheless, with a modern pharmacological approach, researchers have identified some bioactive components in TCM extractions. Further studies may lead to the discovery of new drugs that demonstrate clear pharmacology, clinical efficacy as well as toxic profile. Listed below are some bioactive ingredients derived from TCM extractions that have published evidence on their potential mechanism of action. It's worth to note that purified ingredients from TCM do not necessarily have a similar profile of efficacy or safety compared with the TCM from which they are isolated.

- **Berberine**

Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in such plants as Berberis. This first recorded use of berberine is described in the ancient Chinese medical book *The Divine Farmer's Herb-Root Classic*. Berberine is considered an antibiotic and has been used to treat gastroenteritis, bacillary dysentery, ocular conjunctivitis, suppurative otitis media. Whether berberine may be used for treating diabetes, hyperlipidemia is under investigation. Berberine might also possess antiaging (gero-suppressive) properties. The bioavailability of berberine is low (Liu et al. 2016). Berberine is reported to inhibit the intestinal absorption of cholesterol and promote the excretion of cholesterol from the liver to the bile in hyperlipidemic hamsters (Li et al. 2015). Berberine may influence microbiota in the intestine, which contributes to the reduced plasma cholesterol levels, a novel mechanism different from statin (Zhu et al. 2018; Feng et al. 2018). Phase II clinical trial of berberine is ongoing.

- **Danshensu**

Radix Salviae miltiorrhizae, danshen root (danshen), is one of the widely used Chinese herbal medicines in clinics, containing rich phenolic compounds. Danshensu (DSS) is the main active compound responsible for the pharmacologic effects of danshen. DSS has various various cardiovascular protective effects, which include coronary artery dilation, platelet inhibition, microcirculation improvement, cardiomyocyte protection from myocardial ischemia-reperfusion injury (Yu et al. 2017). DSS appears to act on mTOR signaling (Fan et al. 2016) and involve in ROS scavenging and boosting endogenous antioxidants, including SOD, CAT, MDA, GSH-PX

and HO-1, via activating nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway (Yu et al. 2015).

Dantonic® (T89-07-CAESA) is a botanical drug that consists of extracts of danshen (Radix Salviae Miltiorrhizae) and sanqi (Radix Notoginseng) with borneol in a capsule form. The drug is currently approved in 26 countries outside the USA for the treatment and prevention of chronic stable angina pectoris and other cardiovascular disease related conditions. A Phase III clinical trial (https://clinicaltrials.gov/ct2/show/NCT01659580) is to confirm the efficacy and safety of the drug at 150 and 225 mg doses in the prevention and treatment of angina pectoris in patients with Chronic Stable Angina. The trial was completed in late 2016, with no results published.

- **Tanshione IIA**

Lipid-soluble extractions of Danshen consist of tanshinone I, IIA, B, cryptotanshinone, dihydrotanshinone I, methylenetanshinone, and isotanshinone IIA. Among the tanshinone, tanshinone IIA is widely used in treatment of various cardiovascular diseases. Tanshinone IIA decreases expression of TLR4, NF-Kb-p65, MyD88, IL-2, IL-6, IL-8, PICP, and PIINP, as well as alleviates macrophage infiltration, cardiomyocyte apoptosis, which might result from inhibition of TLR4/MyD88/NF-KB signaling pathway (Wu et al. 2018). In addition, the cardioprotective effect of tanshinone IIA may also partially mediated via blocking alternative complement pathway (Wang et al. 2011) and by repressing miR-1 level in ischemic and hypoxic cardiomyocytes, which subsequently restored its target Cx43 protein (Zhang et al. 2010).

- **Ligustrazine**

Ligustrazine (4-methyl-pyrazine[tetramethylpyrazine]), a crude herbal drug isolated from the dried root or rhizome of Rhizoma Chuanxiong, has been long used in China to treat CVDs including coronary heart disease, hypertension, arrhythmia, heart failure, dilated cardiomyopathy, dyslipidemia, and myocarditis (Lv et al. 2012; Kwan et al. 1990). Ligustrazine suppresses the development of atherosclerosis and hepatic lipid accumulation via the alleviation of oxidative stress and dyslipidemia (Jiang et al. 2011). Ligustrazine has a protective function on the endothelium via inhibition of immunological reactions, underscores its role in atherosclerotic prevention (Wu et al. 2012).

- **Ginkgolide B**

Ginkgolide B (GB) is the major terpenoid component extracted from G. Biloba leaves. GB exerts an antagonistic activity against the platelet-activating factor (PAF) and thus inhibits PAF-induced inflammatory reactions (Yang et al. 2004; Mahmoud et al. 2000). PAF antagonist GB has a protective effect against IR-induced myocardial dysfunction likely via protecting membrane phospholipids (Pei et al. 2015).

- **Astragaloside**

Astragalus membranaceus is a commonly used traditional Chinese herb that contains flavonoids, saponins, and other active ingredients that have wide pharmacological

actions, including antidiabetic, antihypertensive, anti-inflammatory, and cardioprotective effects as well as the prevention of heart failure. Astragaloside is one of the main components of Astragalus membranaceus, which could modulate the RAAS and inhibit cardiomyocyte hypertrophy and apoptosis to protect the heart (Huang et al. 2016; Li et al. 2017; Zhang et al. 2015). It is also noteworthy that Astragaloside alleviates heart failure via activating PPARα to switch glycolysis to fatty acidβ-oxidation. In this regard, recent research shown that Astragaloside significantly reduced anaerobic glycolysis and increased oxygen consumption ratio that was illustrated in the switch glycolysis to fatty acid β-oxidation in failure heart model. Furthermore, in vitro, Astragaloside increased the level of ATP production, enhanced mitochondrial function to regulate metabolism that attributes to increased oxygen consumption and slightly augmented mitochondrial Ca^{2+}uptake (Dong et al. 2017).

- **Ginsenoside Rg1**

Ginsenoside Rg1, one of the major medicines to treat Qi-deficiency related diseases in traditional Chinese medicine, is an active component derived from herbal medicine Radix ginseng (Renshen). Rg1 is shown to decrease myocardial infarction area (Wang et al. 2010), enhance the myocardial perfusion and preserve left ventricle (LV) function, as well as ameliorate ventricular remodeling in acute or chronic myocardial infarction animal model (Wei et al. 2007; Yin et al. 2011). These cardioprotective effects of Rg1 may reflect the improvement in myocardocyte apoptosis, myocardial blood flow, and restoration of ATP production in the myocardium after I/R (Li 2018).

- **Hydroxy safflower yellow A**

Hydroxy safflower yellow A (HSYA) is the active ingredient and is extracted from the flower of the safflower plant, *Carthamus tinctorius L.* HSYA inhibits platelet-activating factor receptor and is used to treat several ischemic diseases, including coronary heart disease and cerebral thrombosis. Additionally, HSYA may activate PPAR-γ which is a key regulator of lipid metabolism, and insulin sensitivity and endothelial inflammation. HSYA decreased the elevated ST segment and infarct size by augmenting the level of Bcl-2 positive cells in acute myocardial infarction in rat (Zhou et al. 2015).

- **Ginsenoside Rb1**

Ginseng as an important herbal drug has been worldwide used in oriental countries for thousands of years and is also one of the most extensively used botanical products in other areas in the world. Ginsenosides, the triterpene saponins, is one of the major components of ginseng. To date, more than 30 kinds of ginsenosides have been identified. Ginsenoside Rb1 (G-Rb1) possesses a variety of biological activities in the cardiovascular systems including anti-oxidation, anti-inflammation, and antiapoptosis, pro-angiogenesis, antiarrhythmic, suppression of ventricular remodeling after acute MI, and inhibition of hypertrophy and ventricular hypertrophy (Kwok et al. 2015; Lu et al. 2009; Zheng et al. 2017). G-Rb1 binds RhoA and inhibits activation

of the RhoA signaling pathway, and restores the production of ATP during cardiac I/R (Cui 2017).

Use of TCM mainly relies on empirical experience. Confirming the efficacy of TCM with placebo-controlled and randomized clinical trial, and clarification of their molecular pharmacology, will allow identification of new therapy/targets for treating CAD. In this regard, TCM is an enriched resource for new drug discovery.

8.8 Cardiac Regeneration

Coronary artery disease is a leading cause of death worldwide. Heart ischemia, mainly resulted from atherosclerosis, thrombosis, vasospasm or coronary microvascular dysfunction, or oxygen supply/demand imbalance alone, is followed by loss of the damaged cardiomyocytes, which are replaced with fibrotic scar tissue. Loss of normal cardiomyocytes results in decreased cardiac contraction, further pathological cardiac dilatation, and additional cardiomyocyte loss, culminating in heart failure. Many therapies have focused on preventing heart failure. However, after patients have developed end-stage heart failure, intervention is limited to heart transplantation, cardiac assistance device, or even artificial heart. Regenerating an injured heart holds promise for patients suffering from heart diseases. Reparative tools have been engineered to restore damaged heart tissue and function using the body's natural ability to regenerate. The mammalian heart appears to have the capacity to regenerate only for a brief period (~7 days) after birth (Porrello et al. 2011). Adult cardiomyocytes in mammals are terminally differentiated, with only limited regeneration capability (Bergmann et al. 2009, 2015). Substantial progress has been made toward understanding the cellular and molecular mechanisms regulating heart regeneration, offering the potential to control cardiac remodeling and redirect the adult heart to a regenerative state.

$Scar^+$ cardiac progenitor cells mainly differentiate into cardiac endothelial cells and fibroblasts but not cardiomyocytes during cardiac homeostasis and after injuries and non-cardiomyocyte does not differentiate to cardiomyocyte under physiology or post-MI injury (Tang et al. 2018). In adult mammals, new cardiomyocytes are more likely to be derived from preexisting cardiomyocytes that undergo proliferation to minimally regenerate rather than differentiation of cardiac stem cells or progenitor cells (Senyo et al. 2013; Kimura et al. 2015; van Berlo et al. 2014).

Generation of new coronary vasculature during cardiac homeostasis and after injury(such as ischemia) is fundamental in cardiac regeneration in CAD. Cardiac fibroblasts expand substantially after injury, but they do not contribute to the formation of new coronary blood vessels. Essentially all new coronary vessels in the injured heart are derived from preexisting endothelial cells, but not from other cell lineages. Targeting lineage transdifferentiation such as mesenchymal-to-endothelial transition may not be a viable approach to for therapeutic induction of neovascularization. Instead, preexisting endothelial cells appear more likely to be the therapeutic

target for promoting neovascularization and driving heart regeneration after injury (MI) (He et al. 2017).

In the past 2 decades, several strategies to repair the injured heart and improve heart function have been pursued, including cellular and noncellular therapies. Cell therapy is a central issue of regenerative medicine and is raising a growing interest in the scientific community, but its full therapeutic potential in CAD has not been reached yet. Different strategies for the production of cardiomyocytes from human embryonic stem cells or human-induced pluripotent stem cells, by direct reprogramming and induction of cardiomyocyte proliferation have been tried. Transplantation of induced pluripotent stem cell-derived cardiomyocytes for cardiac repair has encountered problems related to safety and low engraftment rates. Cell-free-based approaches for heart repair and regeneration involve cardioprotective secretory factors or direct reprogramming of resident cardiac fibroblasts to cardiomyocyte-like cells. Endogenous cardiomyocyte proliferation can be evoked by modulating cell cycle regulators, the Hippo signaling pathway, and the cardiac microenvironment. Hippo-Yap signaling pathway controls heart regeneration and size in adult mice. Agrin, a component of the extracellular matrix, has been identified to promote cardiomyocyte regeneration by interrupting the interaction between dystrophin glycoprotein complex and YAP (Bassat et al. 2017; Morikawa et al. 2017). In particular, treatment with Agrin after MI promoted cardiac regeneration in adult mice, raising a possibility of its clinical use of Agrin with a novel promising approach. Genome editing can correct underlying mutations causing heart disease in animals and offers a state-of-the-art therapeutic approach for cardiac repair. The therapeutic potential of cardiac regeneration approaches can be improved by optimizing the delivery method of therapeutic factors. Significant clinical efforts have been put forward following the explosion of preclinical research showing the efficacy of stem/progenitor cell therapy in failing heart. However, preclinical outcomes of cardiac regenerative therapy approaches have not translated effectively to clinical trials. A reproducible cell-based therapy or regenerative medicine remains to come.

8.9 Cardiovascular Drugs Under Clinical Development

A brief summary of cardiovascular drugs under clinical development is listed in Table 8.1. Also included are their indication, mechanism of action, development stage, and sponsor.

8.10 Conclusions and Perspectives

The high incidence of CAD imposes an enormous burden on healthcare systems. Atherosclerosis is the main cause of CAD, however, the pathological mechanism is complex. The key determinants/pathways underlying the residual risk of CAD under

Table 8.1 Cardiovascular drugs under clinical development

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
CER-001	Atherosclerosis and ACS and Familial Primary Hypo-Alphalipoproteinemia	An engineered complex of recombinant human apolipoprotein A-1 to increase apoA-I and the number of HDL particles	Phase 2	Cerenis Therapeutics
CER-209	Atherosclerois and of NASH	Oral P2Y13 receptor agonists that acts on the last step of the Reverse Lipid Transport pathway, increasing HDL recognition by the liver and facilitating the elimination of lipids in the feces, leading to a regression of atherosclerotic plaque	Phase 1	Cerenis Therapeutics
Metoprolol Succinate/Bisoprolol	AMI and Non-STEMI and STEMI	Evaluation of Decreased Usage of Beta-blockers After MI in the SWEDEHEART Registry (REDUCE-SWEDEHEART)	Phase 4	Karolinska Institutet
Dutogliptin Tartrate/Filgrastim	AMI and Acute Myocardial Ischemia and STEMI	Study of Dutogliptin in Combination With Filgrastim in Post-MI	Phase 2	Recardio, Inc.
Tocilizumab	MI and CAD	ASSessing the Effect of Anti-IL-6 Treatment in MI: The ASSAIL-MI Trial (ASSAIL-MI)	Phase 2	Oslo University Hospital
Paroxetine	MI and Cardiac Remodeling	Paroxetine-mediated GRK2 Inhibition to Reduce Cardiac Remodeling After AMI	Phase 2	University Hospital Inselspital, Berne

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Beta-Blockers Carvedilol Phosphate	MI	Effect of Beta-blocker on Cardioprotective Effect of Remote Ischemic Conditioning	Phase 4	Seoul National University Hospital
SAR407899	Microvascular CAD	A Dose Titration Study to Assess the Effects of SAR407899 in Patients With MVA and/or Persistent Stable Angina Despite Angiographically Successful PCI	Phase 2	Sanofi
Nicardipine	CAD	Prevention of Coronary Microvascular Dysfunction Post-PCI by Intracoronary Nicardipine	Early Phase 1	Thomas Jefferson University
Hydroxychloroquine Sulfate	CAD	Hydroxychloroquine (Plaquenil) blocks toll-like receptor signaling and reduces the activation of dendritic cells and the inflammatory process. It is a disease-modifying antirheumatic drug (DMARD)	Phase 4	First Affiliated Hospital Xi'an Jiaotong University
AZD5718	CAD	AZD5718 Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of Oral AZD5718 in Patients With Coronary Artery Disease (CAD)	Phase 2	AstraZeneca
PF-06282999	ACS	Irreversible inactivator of myeloperoxidase	Phase 1	Pfizer

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
AZD5718 oral suspension	CAD	A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD5718 After Single and Multiple Ascending Dose Administration to Healthy Japanese Men	Phase 1	AstraZeneca
AZD5718 tablets	CAD	A Study to Assess the Bioavailability of Different Formulations of AZD5718 and the Food Effect on the Selected Formulation of AZD5718 in Healthy Volunteers	Phase 1	AstraZeneca
Sodium Thiosulfate Pentahydrate	ACS	Safety and Tolerability of Sodium Thiosulfate in Patients With an ACS Undergoing CAG Via Trans-radial Approach (SAFE-ACS)	Phase 2	University Medical Center Groningen
ACT-246475	Stable CAD	A Medical Research Study to Evaluate the Effects of ACT-246475 in Adults With CAD	Phase 2	Idorsia Pharmaceuticals Ltd.
Proleukin	IHD	Low-Dose IL-2 in Patients With Stable IHD and ACS (LILACS)	Phase 1	Cambridge University Hospitals NHS Foundation Trust

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Sitagliptin/Saxagliptin	Platelet Aggregation During AMI	DPP-4 Inhibitors and AMI: Effects on Platelet Function	Phase 3	University of Sao Paulo General Hospital
Yangxinshi pill	CHD	A study to evaluate the effects of Yangxinshi pill in improving exercise tolerance of patients with CHD and quality of life or restore social function and mental health	Phase 2	Affiliated Hospital of Changchun University of Chinese Medicine
Danlou Tablets/Tongmai Yangxin Pills	CHD	A study to evaluate the relation between syndrome and disease of Turbid Phlegm and blood stasis for CHD and its biological basis	Not Applicable	Tianjin University of Traditional Chinese Medicine
68 Ga-NODAGA-E[c(RGDyK)]2	Chronic IHD	A study to examine the expression of αvβ3 integrin and investigate if it is a suitable tool for predicting myocardial recovery and thus prognosis after intervention	Phase 2	Rigshospitalet, Denmark
Varenicline	CHD	A study to determine if varenicline for smoking cessation is more effective than the standard nicotine replacement therapy aide currently used, “the patch” among smokers hospitalized with coronary heart disease	Phase 4	Ottawa Heart Institute Research Corporation, Heart and Stroke Foundation of Ontario

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Proleukin	IHD	IL-2 supplementation appears to be an attractive therapeutic option playing a key role in Treg cell development, expansion, survival and suppressive function of post-ischemic immune responses and the promotion of myocardial healing	Phase 1	Cambridge University Hospitals NHS Foundation Trust
Amiloride	CHD	A study to evaluate the pharmacological effects of Amiloride on RBC K-uptake and transport and its impact on reversion of angina, electrocardiographic changes of myocardial ischemia and electrical regeneration of the heart in subjects with coronary artery diseases	Phase 2	University of Carabobo
BI10773 (empagliflozin)	HF	A small molecule that inhibits SGLT 2	Phase 3	Eli Lilly and Boehringer Ingelheim
AMG 986	HF	A small-molecule agonist of the Apelin receptor (APJ)	Phase 1	AMGEN
Omecamtiv mecarbil	Chronic HF	A small-molecule activator of cardiac myosin.	Phase 3	AMGEN

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Anakinra	HF in Patients With Advanced Chronic Kidney Disease (E-HART)	A recombinant human IL-1 receptor antagonist	Phase 2	Virginia Commonwealth University
Vericiguat (MK-1242)	HF	A novel activator of cardiac myosin, the motor protein that powers cardiac muscle contraction	Phase 3	AMGEN and Cytokinetics
Pirfenidone	Cardiac Failure	The Efficacy and Safety of Pirfenidone in Patients With HFpEF	Phase 2	Manchester University NHS Foundation Trust
Metolazone Oral Tablet	HF	Prospective Comparison of Metolazone Versus Chlorothiazide for Acute Decompensated HF With Diuretic Resistance	Phase 4	University of Virginia
Macitentan	HFpEF	A Study to Evaluate Whether Macitentan is an Effective and Safe Treatment for Patients With HFpEF and Pulmonary Vascular Disease	Phase 2	Actelion
Bisoprolol	HF	Efficacy of Oral Bisoprolol on Heart Rate Reduction in Chinese Chronic Heart Failure Subjects	Phase 4	Merck KGaA
Tolvaptan	Pediatric Congestive HF Patients With Volume Overload	Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of Tolvaptan in Pediatric Congestive HF Patients With Volume Overload	Phase 3	Otsuka Pharmaceutical Co., Ltd.

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
OPC-61815	Congestive HF	Phase I Study of OPC-61815	Phase 1	Otsuka Pharmaceutical Co., Ltd.
rhNRG-1	Chronic HF	Study of the Survival of Recombinant Human Neuregulin-1β in Chronic HF Patients	Phase 3	Zensun Sci. & Tech. Co., Ltd.
BMS-986224	HF	A Study of BMS-986224 in Healthy Subjects and HFrEF	Phase 1	Bristol-Myers Squibb
Omecamtiv Mecarbil/AMG423	HF	Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic HFrEF	Phase 3	AMGEN
HNO Donor	HF	Evaluate the Safety and Efficacy of 48 h Infusions of HNO (Nitroxyl) Donor in Hospitalized Patients With HF	Phase 2	Bristol-Myers Squibb
AZD8601	HF	AZD8601 Study in CABG Patients	Phase 2	AstraZeneca
Vericiguat (BAY1021189)	Chronic HFpEF	Patient-reported Outcomes in Vericiguat-treated Patients With HFpEF	Phase 2	Bayer

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Dapagliflozin	Chronic HFrEF	Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening HF or Cardiovascular Death in Patients With Chronic HF	Phase 3	AstraZeneca
Empagliflozin	HF	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced)	Phase 3	Boehringer Ingelheim
Sotagliflozin (SAR439954)	Cardiac Failure Aggravated	Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients With Worsening HF	Phase 2	Sanofi
Sacubitril/Valsartan	HFpEF	A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX)	Phase 3	Novartis Pharmaceuticals
Valsartan/Sacubitril	HF	Differential Vascular and Endocrine Effects of Valsartan/Sacubitril in HFrEF	Phase 4	University of Zurich
Levosimendan	HF	Levosimendan for Cardiac Patients Undergoing Major Abdominal Cancer Surgeries	Phase 2	National Cancer Institute, Egypt
IW-1973	HFpEF	A Study of the Effect of IW-1973 on the Exercise Capacity of Patients With HFpEF (CAPACITY-HFpEF)	Phase 2	Ironwood Pharmaceuticals, Inc.

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
Ivabradine	HF, Cardiogenic Shock and Tachycardia	Effect of Ivabradine in Stage D HF/Cardiogenic Shock Patients on Dobutamine	Phase 4	Loyola University
Neladenoson bialanate (BAY1067197)	HF	A Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients With Chronic HFrEF	Phase 2	Bayer
AMG 986	HF	AMG 986 20150186 Renal Impairment Study	Phase 1	AMGEN
Rilonacept	CVD and Chronic Kidney Disease	An antagonist of the cytokine IL-1	Phase 2	VA Office of Research and Development
AMG 598	CVD and obesity	A human monoclonal antibody being investigated as a treatment for obesity	Phase 1	AMGEN
OPC-269	CVD	NA	Phase 1	Ligand Pharmarceuticals, Inc.
Nitroxyl Donor	CVD	A small molecule inhibits inflammatory by reducing cytokine production and activating the cGMP/PKG/ATP-sensitive K+ channel	Phase 2	Bristol-Myers Squibb
CS-3150/Esaxerenone	CVD	A novel nonsteroidal mineralocorticoid receptor antagonist	Phase 3	Ligand Pharmarceuticals, Inc.
CXL-1427	CVD	A nitric oxide donor and prodrug of CXL-1020	Phase 2	Ligand Pharmarceuticals, Inc.

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
XL652/BMS-779788	CVD	A molecule is potent partial LXR agonist with LXRβ selectivity	Preclinical	Ligand
APJ Agonist	CVD	A small molecule could selective against the AT1 receptor and cell active	Phase 1	Bristol-Myers Squibb
FPR-2 Agonist	CVD	A small molecule could activate formyl peptide receptor 2 (a Gi-protein-coupled receptors that are expressed mainly by mammalian phagocytic leukocytes)	Phase 1	Bristol-Myers Squibb
OPC-108459	CVD	NA	Phase 1	Ligand and Otsuka
GNR-008	CVD	Selexis SURE technology	Phase 1	Ligand and IBC Generium
BMS986231	CVD	A second-generation prodrug that chemically breaks down to produce nitroxyl (HNO) and an inactive byproduct	Phase 2	Ligand and BMS
Sparsentan	Cardiovascular/Kidney disease	Dual mechanism of action combines angiotensin receptor blockade with endothelin receptor blockade	Phase 3	Ligand and Retrophin

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
hCDR1	CVD/Systematic Lupus Erythematosus	A new drug ameliorates autoimmune process by specific upstream immunomodulation through the generation of regulatory T cells	Phase 2	Ligand and XTL Bio
Edoxaban	Cardiac Disease	Edoxaban is an oral anticoagulant drug which acts as a direct factor Xa inhibitor. Edoxaban for Prevention of Blood Vessels Being Blocked by Clots (Thrombotic Events) in Children at Risk Because of Cardiac Disease	Phase 3	Daiichi Sankyo, Inc.
Ralinepag (APD811)	PAH	Prostacyclin receptor agonist	Phase 2	Arena
MRA/RG1569 (RO4877533, tocilizumab, Actemra®)	Large-vessel vasculitis, Giant cell arteritis and Systemic sclerosis	Humanized antihuman IL-6 receptor monoclonal antibody	Phase 3	Chugai Pharma USA, Inc.
DP9	Pectoris	DP9 provides transdermal skin cream progesterone in unit-dose packages that allow reliable achievement of effective exposure levels with optimized pharmacokinetics; DP9 provides transdermal skin cream progesterone in unit-dose packages that allow reliable achievement of effective exposure levels with optimized pharmacokinetics	Phase 2	Dimera

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Table 8.1 (continued)

Drug name	Indication	Mechanism of action	Clinical stage	Sponsor
PF-06427878	Hyperlipidemia	NA	Phase 1	Pfizer
PF-05221304	NASH and Cardiovascular Risks	Acetyl CoA-Carboxylase (ACC) Inhibitor	Phase 1	Pfizer
PF-06835919	NASH and Cardiovascular Risks	Ketohexokinase (KHK) Inhibitor	Phase 1	Pfizer
PF-06865571	NASH and Cardiovascular Risks	Diacylglycerol O-Acyltransferase 2 (DGAT2) Inhibitor	Phase 1	Pfizer

CAD coronary artery disease; *ACS* acute coronary syndrome; *AMI* acute myocardial infarction; *STEMI* ST elevation myocardial infarction; *IHD* ischaemic heart disease; *HF* heart failure; *HFpEF* HF with preserved ejection fraction; *HFrEF* HF with reduced ejection fraction; *CABG* coronary artery bypass grafting; *NA* nonavailable; *CVD* cardiovascular disease; *NASH* nonalcoholic steatohepatitis; *PAH* pulmonary arterial hypertension

current standard therapy remain largely unknown. The atherogenic process as a consequence of hypercholesterolemia, and inflammation has been considerably refined by the appreciation of endothelial injury, the role of myeloid cells, T/B lymphocytes, and dendritic cells in innate and acquired immunity, subendothelial apoB-lipoprotein retention, and the identification of signals, such as chemotactic cytokines, regulating the lesional recruitment and homeostasis of inflammatory cells. Further understanding the mechanistic links among lipid metabolism disorder, inflammation, hypertension, and thrombosis continue to emerge as the pathogenic interface that fuels the therapeutic options for CAD.

Just like the Scandinavian Simvastatin Survival Study in 1994 marked the beginning of the statin era, the Canakinumab Anti-inflammatory Thrombosis Outcome Study in 2017 opens a new era for atherosclerosis prevention focused on inflammation inhibition. Canakinumab is currently the only agent specifically targeting inflammation that is proven to reduce cardiovascular event rates at clinical levels. Inhibition of IL-6 and modulation of upstream determinants of IL-1 activation, such as NLRP3 inflammasome, might be an alternative therapeutic option that is under investigation. Inhibition of other inflammatory pathways might also benefit from vascular disease patients. Future studies are needed for an in-depth understanding of cardiovascular inflammation, delineation of candidate target from the perspective of systems biology, appropriate selection of patients or timing of intervention that allows maximal benefit. New agents with improved safety profiles and favored cost-effectiveness are still in need.

Antihypertensive beta-blockers lower mortality from MI and delay atheroprogression (IVUS trials) (Sipahi et al. 2007). Intensive blood pressure lowering (Group et al. 2015; Chobanian et al. 2003) reduces major adverse cardiovascular events in patient population at high risk. In a population of intermediate-risk (HOPE-3 trial), cholesterol lowering (Yusuf et al. 2016), or combination of cholesterol lowering and blood pressure lowering (Yusuf et al. 2016), but not blood pressure lowering alone (Lonn et al. 2016), reduced the risk of cardiovascular events. Interference with the renin–angiotensin system improves endothelial function and reduces coronary event rates disproportionately to lower blood pressure, supporting direct atheroprotective effects (Investigators et al. 2008). Dyslipidemia and hypertension might contribute to the occurrence of cardiovascular events at different stages of atherosclerosis. Elucidation of the underlying mechanisms may allow new therapeutic intervention.

Human genome-wide association study, transcriptional, proteomic and metabolic profiling of CAD, complemented with animal studies of established and unstable atherosclerosis that faithfully recapitulate human biology, will further delineate molecular mechanism of CAD and pave the way toward discovery of new therapeutic targets and drugs. New strategies are emerging, such as anti-inflammation, triglyceride lowering, chemokine signaling modulation and vaccination against oxidized/pro-inflammatory phospholipids (Que et al. 2018). These strategies will have to overcome translational challenges before further reducing CAD, the main disease burden to mankind.

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References

Alvarez-Villalobos NA, Trevino-Alvarez AM, Gonzalez-Gonzalez JG (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375:1797–1798. https://doi.org/10.1056/NEJMc1611289

Arai H et al (2017) Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMalpha), in combination with statin treatment: Two randomised, double-blind, placebo-controlled clinical trials in patients with dyslipidaemia. Atherosclerosis 261:144–152. https://doi.org/10.1016/j.atherosclerosis.2017.03.032

Bassat E et al (2017) The extracellular matrix protein agrin promotes heart regeneration in mice. Nature 547:179–184. https://doi.org/10.1038/nature22978

Bergmann O et al (2009) Evidence for cardiomyocyte renewal in humans. Science 324:98–102. https://doi.org/10.1126/science.1164680

Bergmann O et al (2015) Dynamics of cell generation and turnover in the human heart. Cell 161:1566–1575. https://doi.org/10.1016/j.cell.2015.05.026

Bhatt DL et al (2019) Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 380:11–22. https://doi.org/10.1056/NEJMoa1812792

Bilen O, Ballantyne CM (2016) Bempedoic acid (ETC-1002): an investigational inhibitor of ATP citrate lyase. Curr Atheroscler Rep 18:61. https://doi.org/10.1007/s11883-016-0611-4

Bjorkqvist J et al (2015) Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. J Clin Investig 125:3132–3146. https://doi.org/10.1172/JCI77139

Bohula EA et al (2018) Inflammatory and cholesterol risk in the FOURIER trial. Circulation 138:131–140. https://doi.org/10.1161/CIRCULATIONAHA.118.034032

Buller HR et al (2015) Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med 372:232–240. https://doi.org/10.1056/NEJMoa1405760

Camejo G (2017) Phase 2 clinical trials with K-877 (pemafibrate): a promising selective PPAR-alpha modulator for treatment of combined dyslipidemia. Atherosclerosis 261:163–164. https://doi.org/10.1016/j.atherosclerosis.2017.04.013

Cannon CP et al (2015) Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 372:2387–2397. https://doi.org/10.1056/NEJMoa1410489

Chobanian AV et al (2003) the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2572. https://doi.org/10.1001/jama.289.19.2560

Consortium CAD et al (2013) Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 45:25–33. https://doi.org/10.1038/ng.2480 (2013)

Crossey E et al (2015) A cholesterol-lowering VLP vaccine that targets PCSK9. Vaccine 33:5747–5755. https://doi.org/10.1016/j.vaccine.2015.09.044

Cui YC et al (2017) Ginsenoside Rb1 protects against ischemia/reperfusion-induced myocardial injury via energy metabolism regulation mediated by RhoA signaling pathway. Sci Rep 7

Murray CJ, GBD et al (2015) Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet 386:2145–2191. https://doi.org/10.1016/s0140-6736(15)61340-x

Davinelli S et al (2018) Cardioprotection by cocoa polyphenols and omega-3 fatty acids: a disease-prevention perspective on aging-associated cardiovascular risk. J Med Food. https://doi.org/10.1089/jmf.2018.0002

Delaney MK et al (2016) Differential roles of the NADPH-Oxidase 1 and 2 in platelet activation and thrombosis. Arterioscler Thromb Vasc Biol 36:846–854. https://doi.org/10.1161/ATVBAHA.116.307308

Dong B, Li H, Singh AB, Cao A, Liu J (2015) Inhibition of PCSK9 transcription by berberine involves down-regulation of hepatic HNF1alpha protein expression through the ubiquitin-proteasome degradation pathway. J Biol Chem 290:4047–4058. https://doi.org/10.1074/jbc.M114.597229

Dong Z et al (2017) Astragaloside IV alleviates heart failure via activating PPARalpha to switch glycolysis to fatty acid beta-oxidation. Sci Rep 7:017–02360

Erlinge D et al (2017) Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med 377:1132–1142. https://doi.org/10.1056/NEJMoa1706443

Fan G et al (2016) Danshensu alleviates cardiac ischaemia/reperfusion injury by inhibiting autophagy and apoptosis via activation of mTOR signalling. J Cell Mol Med 20:1908–1919. https://doi.org/10.1111/jcmm.12883

Feng R et al (2018) Gut microbiota-regulated pharmacokinetics of berberine and active metabolites in beagle dogs after oral administration. Front Pharmacol 9:214. https://doi.org/10.3389/fphar.2018.00214

Fitzgerald K et al (2017) A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med 376:41–51. https://doi.org/10.1056/NEJMoa1609243

Forstermann U (2008) Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. Nat Clin Pract Cardiovasc Med 5:338–349. https://doi.org/10.1038/ncpcardio1211

Fralick M, Schneeweiss S, Patorno E (2017) Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. N Engl J Med 376:2300–2302. https://doi.org/10.1056/NEJMc1701990

Fruchart JC (2017) Pemafibrate (K-877), a novel selective peroxisome proliferator-activated receptor alpha modulator for management of atherogenic dyslipidaemia. Cardiovasc Diabetol 16:124. https://doi.org/10.1186/s12933-017-0602-y

Gaudet D et al (2015) Antisense inhibition of apolipoprotein C-III in patients with hypertriglyceridemia. N Engl J Med 373:438–447. https://doi.org/10.1056/NEJMoa1400283

Giugliano RP et al (2017) Cognitive function in a randomized trial of evolocumab. N Engl J Med 377:633–643. https://doi.org/10.1056/NEJMoa1701131

Group SR et al (2015) A Randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116. https://doi.org/10.1056/nejmoa1511939 (2015)

Group HTRC et al (2017) Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 377:1217–1227. https://doi.org/10.1056/nejmoa1706444

Group ASC et al (2018) Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 379:1540–1550. https://doi.org/10.1056/nejmoa1804989 (2018)

Gutierrez MJ et al (2014) Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 34:676–683. https://doi.org/10.1161/atvbaha.113.302677

Hao H et al (2017) Loss of endothelial CXCR7 impairs vascular homeostasis and cardiac remodeling after myocardial infarction: implications for cardiovascular drug discovery. Circulation 135:1253–1264. https://doi.org/10.1161/CIRCULATIONAHA.116.023027

He L et al (2017) Preexisting endothelial cells mediate cardiac neovascularization after injury. J Clin Investig 127:2968–2981. https://doi.org/10.1172/JCI93868

Hennuyer N et al (2016) The novel selective PPARalpha modulator (SPPARMalpha) pemafibrate improves dyslipidemia, enhances reverse cholesterol transport and decreases inflammation and atherosclerosis. Atherosclerosis 249:200–208. https://doi.org/10.1016/j.atherosclerosis.2016.03.003

Hlatky MA, Kazi DS (2017) PCSK9 inhibitors: economics and policy. J Am Coll Cardiol 70:2677–2687. https://doi.org/10.1016/j.jacc.2017.10.001

Huang H, Lai S, Wan Q, Qi W, Liu J (2016) Astragaloside IV protects cardiomyocytes from anoxia/reoxygenation injury by upregulating the expression of Hes1 protein. Can J Physiol Pharmacol 94:542–553

Investigators O et al (2008) Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 358:1547–1559. https://doi.org/10.1056/NEJMoa0801317

Jiang F, Qian J, Chen S, Zhang W, Liu C (2011) Ligustrazine improves atherosclerosis in rat via attenuation of oxidative stress. Pharm Biol 49:856–863

Key NS (2014) Epidemiologic and clinical data linking factors XI and XII to thrombosis. Hematology Am Soc Hematology Educ Program 2014:66–70. https://doi.org/10.1182/asheducation-2014.1.66 (2014)

Kimura W et al (2015) Hypoxia fate mapping identifies cycling cardiomyocytes in the adult heart. Nature 523:226–230. https://doi.org/10.1038/nature14582

Krauss RM, Pinto CA, Liu Y, Johnson-Levonas AO, Dansky HM (2015) Changes in LDL particle concentrations after treatment with the cholesteryl ester transfer protein inhibitor anacetrapib alone or in combination with atorvastatin. J Clin Lipidol 9:93–102. https://doi.org/10.1016/j.jacl.2014.09.013

Kwan CY, Daniel EE, Chen MC (1990) Inhibition of vasoconstriction by tetramethylpyrazine: does it act by blocking the voltage-dependent Ca channel? J Cardiovasc Pharmacol 15:157–162

Kwok HH, Chan LS, Poon PY, Yue PY, Wong RN (2015) Ginsenoside-Rg1 induces angiogenesis by the inverse regulation of MET tyrosine kinase receptor expression through miR-23a. Toxicol Appl Pharmacol 287:276–283

Larsson M et al (2014) A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. Sci Transl Med 6:222ra217. https://doi.org/10.1126/scitranslmed.3006804

Li L et al (2018) Ginsenoside Rg1 ameliorates rat myocardial ischemia-reperfusion injury by modulating energy metabolism pathways. Front Physiol 9

Li XY et al (2015) Effect of berberine on promoting the excretion of cholesterol in high-fat diet-induced hyperlipidemic hamsters. J Transl Med 13:015–0629

Li L, Hou X, Xu R, Liu C, Tu M (2017) Research review on the pharmacological effects of astragaloside IV. Fundam Clin Pharmacol 31:17–36

Liu CS, Zheng YR, Zhang YF, Long XY (2016) Research progress on berberine with a special focus on its oral bioavailability. Fitoterapia 109:274–282

Lonn EM et al (2016) Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 374:2009–2020. https://doi.org/10.1056/NEJMoa1600175

Lu JM, Yao Q, Chen C (2009) Ginseng compounds: an update on their molecular mechanisms and medical applications. Curr Vasc Pharmacol 7:293–302

Lv L, Jiang SS, Xu J, Gong JB, Cheng Y (2012) Protective effect of ligustrazine against myocardial ischaemia reperfusion in rats: the role of endothelial nitric oxide synthase. Clin Exp Pharmacol Physiol 39:20–27

Mahaffey KW et al (2018) Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 137:323–334. https://doi.org/10.1161/CIRCULATIONAHA.117.032038

Mahmoud F et al (2000) In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A. Jpn J Pharmacol 83:241–245

Manson JE et al (2019) Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med 380:23–32. https://doi.org/10.1056/NEJMoa1811403

Marso SP et al (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375:1834–1844. https://doi.org/10.1056/NEJMoa1607141

Matafonov A et al (2014) Factor XII inhibition reduces thrombus formation in a primate thrombosis model. Blood 123:1739–1746. https://doi.org/10.1182/blood-2013-04-499111

Millar JS et al (2017) Effects of CETP inhibition with anacetrapib on metabolism of VLDL-TG and plasma apolipoproteins C-II, C-III, and E. J Lipid Res 58:1214–1220. https://doi.org/10.1194/jlr.M074880

Morikawa Y, Heallen T, Leach J, Xiao Y, Martin JF (2017) Dystrophin-glycoprotein complex sequesters Yap to inhibit cardiomyocyte proliferation. Nature 547:227–231. https://doi.org/10.1038/nature22979

Neal B et al (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377:644–657. https://doi.org/10.1056/NEJMoa1611925

Neuen BL et al (2018) Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS program. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.118.035901

Nicholls SJ et al (2016) Effect of Evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 316:2373–2384. https://doi.org/10.1001/jama.2016.16951

Nickel KF, Long AT, Fuchs TA, Butler LM, Renne T (2017) Factor XII as a therapeutic target in thromboembolic and inflammatory diseases. Arterioscler Thromb Vasc Biol 37:13–20. https://doi.org/10.1161/ATVBAHA.116.308595

Nikolic D, Mikhailidis DP, Davidson MH, Rizzo M, Banach M (2014) ETC-1002: a future option for lipid disorders? Atherosclerosis 237:705–710. https://doi.org/10.1016/j.atherosclerosis.2014.10.099

Nissen SE et al (2016) Efficacy and tolerability of evolocumab versus ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. JAMA 315:1580–1590. https://doi.org/10.1001/jama.2016.3608

Olkkonen VM, Sinisalo J, Jauhiainen M (2018) New medications targeting triglyceride-rich lipoproteins: Can inhibition of ANGPTL3 or apoC-III reduce the residual cardiovascular risk? Atherosclerosis 272:27–32. https://doi.org/10.1016/j.atherosclerosis.2018.03.019

Pang A et al (2018) Shear-induced integrin signaling in platelet phosphatidylserine exposure, microvesicle release, and coagulation. Blood 132:533–543. https://doi.org/10.1182/blood-2017-05-785253

Pei HX, Hua R, Guan CX, Fang X (2015) Ginkgolide B reduces the degradation of membrane phospholipids to prevent ischemia/reperfusion myocardial injury in rats. Pharmacology 96:233–239

Perez-Sanchez C et al (2017) Ubiquinol effects on antiphospholipid syndrome prothrombotic profile: a randomized, placebo-controlled trial. Arterioscler Thromb Vasc Biol 37:1923–1932. https://doi.org/10.1161/atvbaha.117.309225

Pietraforte D et al (2014) Redox control of platelet functions in physiology and pathophysiology. Antioxid Redox Signal 21:177–193. https://doi.org/10.1089/ars.2013.5532

Porrello ER et al (2011) Transient regenerative potential of the neonatal mouse heart. Science 331:1078–1080. https://doi.org/10.1126/science.1200708

Preis M et al (2017) Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood 129:1210–1215. https://doi.org/10.1182/blood-2016-09-742262

Que X et al (2018) Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. Nature 558:301–306. https://doi.org/10.1038/s41586-018-0198-8

Radholm K et al (2018) Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation. https://doi.org/10.1161/CIRCULATIONAHA.118.034222

Ray KK et al (2017) Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 376:1430–1440. https://doi.org/10.1056/NEJMoa1615758

Revenko AS et al (2011) Selective depletion of plasma prekallikrein or coagulation factor XII inhibits thrombosis in mice without increased risk of bleeding. Blood 118:5302–5311. https://doi.org/10.1182/blood-2011-05-355248

Ridker PM et al (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131. https://doi.org/10.1056/NEJMoa1707914
Ridker PM et al (2018a) Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 391:319–328. https://doi.org/10.1016/S0140-6736(17)32814-3
Ridker PM et al (2018b) Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med. https://doi.org/10.1056/NEJMoa1809798
Roberts R (2014) Genetics of coronary artery disease. Circ Res 114:1890–1903. https://doi.org/10.1161/CIRCRESAHA.114.302692
Robinson JG et al (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 372:1489–1499. https://doi.org/10.1056/NEJMoa1501031
Sabatine MS et al (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 372:1500–1509. https://doi.org/10.1056/NEJMoa1500858
Sabatine MS et al (2017) Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 376:1713–1722. https://doi.org/10.1056/NEJMoa1615664
Saleheen D et al (2017) Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. Nature 544:235–239. https://doi.org/10.1038/nature22034
Schmitz J, Gouni-Berthold I (2018) APOC-III antisense oligonucleotides: a new option for the treatment of hypertriglyceridemia. Curr Med Chem 25:1567–1576. https://doi.org/10.2174/0929867324666170609081612
Schwartz GG et al (2018) Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 379:2097–2107. https://doi.org/10.1056/NEJMoa1801174
Senyo SE et al (2013) Mammalian heart renewal by pre-existing cardiomyocytes. Nature 493:433–436. https://doi.org/10.1038/nature11682
Shen B et al (2013) A directional switch of integrin signalling and a new anti-thrombotic strategy. Nature 503:131–135. https://doi.org/10.1038/nature12613
Sipahi I et al (2007) Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. Ann Intern Med 147:10–18
Tang J et al (2018) Fate mapping of sca1(+) cardiac progenitor cells in the adult mouse heart. Circulation 138:2967–2969. https://doi.org/10.1161/CIRCULATIONAHA.118.036210
Tg et al (2014) Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med 371:22–31. https://doi.org/10.1056/NEJMoa1307095
Thompson PD et al (2016) Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. J Clin Lipidol 10:556–567. https://doi.org/10.1016/j.jacl.2015.12.025
van Berlo JH et al (2014) c-kit + cells minimally contribute cardiomyocytes to the heart. Nature 509:337–341. https://doi.org/10.1038/nature13309
Wang XD, Gu TX, Shi EY, Lu CM, Wang C (2010) Effect and mechanism of panaxoside Rg1 on neovascularization in myocardial infarction rats. Chin J Integr Med 16:162–166
Wang X et al (2011) Differential cardioprotective effects of salvianolic acid and tanshinone on acute myocardial infarction are mediated by unique signaling pathways. J Ethnopharmacol 135:662–671
Wanner C et al (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375:323–334. https://doi.org/10.1056/NEJMoa1515920
Wei HJ et al (2007) Gelatin microspheres encapsulated with a nonpeptide angiogenic agent, ginsenoside Rg1, for intramyocardial injection in a rat model with infarcted myocardium. J Control Release 120:27–34
Wong PC et al (2017) Blockade of protease-activated receptor-4 (PAR4) provides robust antithrombotic activity with low bleeding. Sci Transl Med 9. https://doi.org/10.1126/scitranslmed.aaf5294
Wu HJ, Hao J, Wang SQ, Jin BL, Chen XB (2012) Protective effects of ligustrazine on TNF-alpha-induced endothelial dysfunction. Eur J Pharmacol 674:365–369

Wu DM et al (2018) Tanshinone IIA prevents left ventricular remodelling via the TLR4/MyD88/NF-kappaB signalling pathway in rats with myocardial infarction. J Cell Mol Med 22:3058–3072

Yang Y, Nemoto EM, Harvey SA, Subbotin VM, Gandhi CR (2004) Increased hepatic platelet activating factor (PAF) and PAF receptors in carbon tetrachloride induced liver cirrhosis. Gut 53:877–883

Yao C et al (2018) Genome-wide mapping of plasma protein QTLs identifies putatively causal genes and pathways for cardiovascular disease. Nat Commun 9:3268. https://doi.org/10.1038/s41467-018-05512-x

Yau JW et al (2014) Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. Blood 123:2102–2107. https://doi.org/10.1182/blood-2013-12-540872

Yin H et al (2011) Ginsenoside-Rg1 enhances angiogenesis and ameliorates ventricular remodeling in a rat model of myocardial infarction. J Mol Med 89:363–375

Yu J et al (2015) Danshensu protects isolated heart against ischemia reperfusion injury through activation of Akt/ERK1/2/Nrf2 signaling. Int J Clin Exp Med 8:14793–14804

Yu LJ et al (2017) Salvianolic acid exerts cardioprotection through promoting angiogenesis in animal models of acute myocardial infarction: preclinical evidence. Oxidative Med Cell Longev 2017:8192383. https://doi.org/10.1155/2017/8192383

Yusuf S et al (2016a) Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 374:2021–2031. https://doi.org/10.1056/NEJMoa1600176

Yusuf S et al (2016b) Blood-pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 374:2032–2043. https://doi.org/10.1056/NEJMoa1600177

Zhang S et al (2015) Astragaloside IV protects against isoproterenol-induced cardiac hypertrophy by regulating NF-kappaB/PGC-1alpha signaling mediated energy biosynthesis. PloS one 10

Zhang R (2016) The ANGPTL3-4-8 model, a molecular mechanism for triglyceride trafficking. Open Biol 6:150272. https://doi.org/10.1098/rsob.150272

Zhang Y et al (2010) Tanshinone IIA inhibits miR-1 expression through p38 MAPK signal pathway in post-infarction rat cardiomyocytes. Cell Physiol Biochem 26:991–998

Zheng X et al (2017) Ginsenoside Rb1 improves cardiac function and remodeling in heart failure. Exp Anim 66:217–228

Zhou MX, Fu JH, Zhang Q, Wang JQ (2015) Effect of hydroxy safflower yellow A on myocardial apoptosis after acute myocardial infarction in rats. Genet Mol Res 14:3133–3141. https://doi.org/10.4238/2015

Zhu L et al (2018) Berberine treatment increases Akkermansia in the gut and improves high-fat diet-induced atherosclerosis in Apoe(-/-) mice. Atherosclerosis 268:117–126. https://doi.org/10.1016/j.atherosclerosis.2017.11.023

Zinman B et al (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 373:2117–2128. https://doi.org/10.1056/NEJMoa1504720