New pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2022

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Abstract

Cardiovascular diseases (CVD) remain the leading cause of death worldwide and pharmacotherapy of most of them is suboptimal. Thus, there is a clear unmet clinical need to develop new pharmacological strategies with greater efficacy and better safety profiles. In this review, we summarize the most relevant advances in cardiovascular pharmacology in 2022 including the approval of first-in-class drugs that open new avenues for the treatment of obstructive hypertrophic cardiomyopathy (mavacamten), type 2 diabetes mellitus (tirzepatide), and heart failure (HF) independent of left ventricular ejection fraction (sodium-glucose cotransporter 2 inhibitors). We also dealt with fixed dose combination therapies repurposing different formulations of "old" drugs with well-known efficacy and safety for the treatment of patients with acute decompensated HF (acetazolamide plus loop diuretics), atherosclerotic cardiovascular disease (moderate-dose statin plus ezetimibe), Marfan syndrome (angiotensin receptor blockers plus β-blockers), and secondary cardiovascular prevention (i.e. low-dose aspirin, ramipril and atorvastatin), thereby filling existing gaps in knowledge, and opening new avenues for the treatment of CVD. Clinical trials confirming the role of dapagliflozin in patients with HF and mildly reduced or preserved ejection fraction, long-term evolocumab to reduce the risk of cardiovascular events, vitamin K antagonists for stroke prevention in patients with rheumatic heart disease-associated atrial fibrillation, antibiotic prophylaxis in patients at high risk for infective endocarditis before invasive dental procedures, and vutrisiran for the treatment of hereditary transthyretin-related amyloidosis with polyneuropathy were also reviewed. Finally, we briefly discuss recent clinical trials suggesting that FXIa inhibitors may have the potential to uncouple thrombosis from hemostasis and attenuate/prevent thromboembolic events with minimal disruption of hemostasis.

Key words: cardiovascular, drugs, drug combinations, pharmacological agents, cardiovascular pharmacological strategies

Abbreviations:

ACEIs: angiotensin-converting-enzyme inhibitors
ADHF: acute decompensated HF
ARBs: angiotensin receptor blockers
ASCVD: atherosclerotic cardiovascular disease
ATPase: adenosine triphosphatase
cAMP: cyclic adenosine monophosphate
DRX: disordered state of the myosin globular head
EMA: European Medicines Agency
EPAC2: exchange protein activated by cAMP2
FBN1: fibrillin-1 gene
FDA: U.S. Food and Drug Administration
FDC: fixed dose combinations
GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide-1
HCM: hypertrophic cardiomyopathy
HF: heart failure
HFmrEF: HF with mildly reduced ejection fraction
HFpEF: HF with preserved ejection fraction
HFrEF: HF with reduced ejection fraction
hATTR: hereditary transthyretin-related amyloidosis
LDL-C: low-density lipoprotein-cholesterol
LV: left ventricular
LVEF: LV ejection fraction
MI: myocardial infarction
MRI: magnetic resonance imaging
NAFLD: non-alcoholic fatty liver disease
oHCM: obstructive hypertrophic cardiomyopathy
PKA: protein kinase
RCTs: randomized clinical trials
RHD-AF: rheumatic heart disease-associated atrial fibrillation
SGLT2Is: sodium-glucose cotransporter-2 inhibitors
siRNA: small interfering RNA
SRX: super-relaxed state of the myosin globular head
T2DM: type 2 diabetes mellitus
TGF-β: transforming growth factor beta
TTR: transthyretin gene

Introduction

Cardiovascular diseases remain the leading cause of death worldwide and pharmacotherapy of most cardiovascular diseases is suboptimal and is often associated with potentially harmful effects. Thus, there is a clear unmet clinical need for novel pharmacological agents and therapeutic approaches to improve treatment efficacy and drug safety profiles.

The year 2022 was exciting because important "first-in-class" cardiovascular drugs have been approved and many randomized clinical trials (RCTs) assessing the efficacy and safety of repurposing 'old' drugs in combination were published, thereby filling existing gaps in knowledge, and opening new avenues for the management of cardiovascular diseases. In this review, we highlight the new pharmacological agents and the main advances in cardiovascular pharmacotherapy strategies (**Figure 1**) and discuss the most relevant RCTs **(Table 1**) that have taken place during 2022.

For the selection of the most relevant advances in cardiovascular pharmacology, we reviewed individual drugs or combinations of drugs approved by the European Medicines Agency and the Food and Drug Administration in 2022. We also searched for clinical trials in pre-specified fields published in 2022 using the PubMed and EMBASE databases. The drugs and clinical trials were selected for inclusion in this review mainly from a pharmacological point of view by consensus of the authors.

1. First-in-class drugs

This section includes drugs with "new mechanisms of action", which constitute important advances in current pharmacotherapy options. A summary of their pharmacokinetic properties is provided in **Table 2.**

1.1 Mavacamten for treatment of obstructive hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a complex cardiac disease often caused by mutations in genes encoding proteins responsible for cardiac sarcomere function[1,2]. Albeit phenotypically and clinically variable, it is often characterized by left ventricular (LV) hypertrophy, fibrosis, hypercontractility, and diastolic dysfunction.[2,3] HCM is predominantly an obstructive disease (oHCM) and ~70% of patients present a dynamic LV outflow tract obstruction (LVOTO) at rest or during exercise causing severe symptoms in many cases.[3] Exercise intolerance and arrhythmogenic risk are hallmarks of HCM, partially due to specific alterations in cellular electro-mechanical properties.[4]

For almost 50 years, the pharmacological treatment of HCM was based on the off-label use of non-vasodilator β-blockers and/or non-dihydropyridine L-type Ca^{2+} channel blockers, and add-on therapy with

antiarrhythmic drugs like disopyramide.[2,3] These drugs slow heart rate and decrease cardiac contractility, alleviate symptoms, reduce LVOTO and myocardial stress during systole, improve LV diastolic filling, ventricular relaxation, and quality of life, and prevent cardiac arrhythmias. However, they do not specifically target the underlying cause of the disease or its pathophysiological mechanisms and, therefore, are unable to halt the natural progression of the disease and its complications.[5]

During the chemo-mechanical cycle, the globular head of the myosin molecule bends towards and binds to actin to form cross-bridges. The movement of the myosin head requires the hydrolysis of ATP to release energy, the so-called "power stroke". During this process, the myosin heads can adopt three different conformations: 1) an open-headed state, available for actin cross-bridge formation; 2) a super-relaxed state (SRX) in which both myosin heads are folded-back along the thick-filament backbone and cannot bind actin; and 3) a disordered state (DRX), in which one myosin head adopts a folded state, while the other head is active and able to hydrolyse ATP and bind to actin.[6–8]

HCM-associated sarcomere mutations shift the proportion of myosin heads from the SRX to the DRX state and increase the DRX/SRX ratio, leading to an excessive actin-myosin cross-bridge formation, hypercontractility, impaired relaxation, increased ATP consumption, abnormal Ca^{2+} sensitivity, altered Ca^{2+} handling and cardiac hypertrophy.[6–8] Drugs decreasing the number of cross-bridges by shifting the overall myosin population towards an energy-sparing, recruitable, SRX state may restore the physiological actin-myosin interactions, counteract the hypercontractile state and improve myocardial efficiency in patients with oHCM.[8] This was the rationale for the development of cardiac myosin adenosine triphosphatase (ATPase) inhibitors.

Mavacamten is a first-in-class, small molecule, allosteric and reversible myosin ATPase inhibitor specifically designed to target sarcomeric hypercontractility in patients with oHCM.[9,10] In animal models harbouring MYH7 and MYBPC3 mutations, mavacamten reduces the rate of phosphate release from myosin heads (the rate-limiting step in the electromechanical cycle), shifts overall myosin population towards the SRX state **(Figure 2A),** decreases the number of myosin heads available for cross-bridge formation, cardiac contractility and impaired ventricular filling, and improves ATP consumption and relaxation shortening the time to restore resting sarcomere length.[5,10,11] After 20-26 weeks of treatment, mavacamten reduces/prevents the development of LV hypertrophy, sarcomere hypercontractility, myocyte disarray and cardiac fibrosis, improves active lusitropic function and normalizes profibrotic and mitochondrial gene expression.[10]

In phase 2 (PIONEER-HCM, MAVERICK-HCM, PIONEER-OLE, MAVERICK-LTE) and 3 (PIONEER-OLE, VALOR-HCM, MAVA-LTE, EXPLORER-HCM; EXPLORER-CN) trials mavacamten significantly improves exercise capacity, resting and post-exercise LV outflow tract gradient, functional NYHA class and serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hs-cTroponin-I levels suggesting an improvement

in myocardial wall stress. Mavacamten also shows a favourable effect on cardiac remodeling and reduces LV mass index, maximum LV and left atrial volume index in patients with oHCM.[5,12,13] Based on these results, mavacamten was approved by FDA and EMA for the treatment of adults with symptomatic NYHA class II–III oHCM to improve functional capacity and symptoms.[13] This new therapeutic option validates the potential of targeted molecular approaches for patients with HCM.

Recently, the VALOR-HCM trial demonstrated that in patients with severely symptomatic drug-refractory oHCM who met guideline criteria of eligibility for SRT, mavacamten significantly reduces the need for SRT by ~77% after 16 months of treatment.[14] Nevertheless, larger follow-up clinical trials are required to establish and validate the safety and efficacy of mavacamten as an alternative or add-on option to SRT or alcohol septal ablation in patients with symptomatic oHCM. However, as no direct comparative studies were performed, it remains unclear whether life-long pharmacotherapy using mavacamten with potential side effects and very high costs will be superior to SRT. Furthermore, there is no evidence that "a drug fits all" strategy is equally effective in a disease with high genotypic variability and phenotypic presentation, especially for mutations in the thin filament.

Pharmacologically, the use of mavacamten is challenging because of its long half-life time and extensive metabolism via major CYP2C19, CYP3A4 and CYP2C9 enzyme families (**Table 2**). Thus, mavacamten is contraindicated in patients treated with strong CYP2C19 or CYP3A4 inhibitors that increase drug exposure and the risk of heart failure (HF) or with moderate-strong CYP2C19 or CYP3A4 inducers that decrease mavacamten exposure and potentially reduce its clinical efficacy.[5,13,15] Conversely, since mavacamten is an inducer of CYP3A4, CYP2C9, and CYP2C19, its combination with CYP3A4, CYP2C19, or CYP2C9 substrates may reduce the exposure and activity of these drugs. In such cases close monitoring of the patients is highly recommended.[5,13,15] Because mavacamten reduces cardiac contractility its co-administration with negative inotropic drugs (e.g., disopyramide, verapamil or diltiazem) may cause LV systolic dysfunction and HF symptoms in patients with oHCM and should be avoided. Mavacamten may decrease exposures of ethinyl estradiol and progestin leading to contraceptive failure. Use of contraceptives not affected by CYP450 induction or addition of non-hormonal contraception during treatment and for 4 months after last dose is recommended.

The most frequent adverse reactions of mavacamten include dizziness (>10%), syncope and a dose-dependent decrease in LV ejection fraction (LVEF) due to systolic dysfunction. Thus, regular LVEF and Valsalva left ventricular outflow tract (LVOT) gradient assessment is required. Algorithms for initiation and maintenance dosing, patient monitoring schedules, and guidance for treatment interruption or discontinuation are provided in the prescribing information.[15] Drug initiation is not recommended in patients with LVEF <55% and treatment should be interrupted if LVEF drops <50% or if the patient experiences HF

symptoms or worsening clinical status.[15] In the US mavacamten is available only through a Risk Evaluation and Mitigation Strategy (REMS) called CAMZYOS REMS Program.

Several ongoing trials analyse the effects of mavacamten in patients with HCM [EXPLORER-LTE (NCT03470545), EXPLORER-CN (NCT05174416), PIONEER-OLE (NCT03496168), MAVA-LTE (NCT03723655), VALOR-HCM (NCT04349072] and with HF with preserved ejection fraction (HFpEF) (EMBARK-HFpEF, NCT04766892).

1.2. Tirzepatide for therapy of diabetes and obesity

Tirzepatide (LY329817) is the first dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of type 2 diabetes mellitus (T2DM) approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, particularly associated with obesity/overweight.[16–18] Tirzepatide is a 39-aminoacid synthetic chimeric peptide based on the native GIP that contains 2 aminoisobutyric acid residues at positions 2 and 13, a C-terminal amide, and at position 20 the lysine residue is attached to a 1,20-eicosanedioic acid, which increases binding to albumin and prolongs its half-life allowing for once-a-week administration.[17–19] Tirzepatide is an imbalanced dual GIP/GLP-1 receptor agonist binding to GIP receptors with the same affinity as native GIP, whereas its affinity to GLP-1 receptors (GLP-1R) is about 5-fold weaker than native GLP-1.[16] The main physiological effects of GIP and GLP-1 are summarized in **Figure 2B** and the pharmacokinetic properties of tirzepatide in **Table 2**.

GLP-1 and GIP receptors are expressed on pancreatic β-cells and their activation stimulates insulin secretion and lowers blood glucose in T2DM. The binding of GLP-1 and GIP to their receptors activates the adenylate cyclase/cyclic adenosine monophosphate (cAMP)/protein kinase (PKA) and the exchange protein activated by cAMP2 (EPAC2)/cAMP-guanine nucleotide exchange factor (GEF) signalling pathways (**Figure 2B).** PKA inhibits both voltage-dependent and ATP-sensitive K^+ channels leading to membrane depolarization that activates Ca^{2+} influx through voltage-gated Ca^{2+} channels, along with Ca^{2+} release from intracellular stores.[16,20] The subsequent increase in intracellular [Ca^{2+}] enhances the gene transcription of proinsulin, increases the density of insulin-containing granules near the plasma membrane and promotes the fusion of insulin-vesicles with the plasma membrane, thereby increasing insulin secretion from pancreatic β-cells, preferentially in a glucose-dependent manner after food intake.[16,20]

The effectiveness and safety of once-weekly administration of tirzepatide (5-15 mg given s.c.) compared with placebo and other glucose-lowering drugs to improve glycemic control in adults with T2DM was established in the SURPASS clinical program which comprised 10 clinical trials recruiting >13,000 patients.[17] Tirzepatide significantly reduces glycated hemoglobin (HbA1c) compared to placebo or glucose-

lowering drugs and in comparative trials, at the dose of 15 mg produces a 0.5%, 0.9% and 1.0% greater reduction in HbA1c than semaglutide or insulin-analogs, respectively. Drug efficacy is not influenced by age, gender, race, ethnicity, baseline body mass index or HbA1c, diabetes duration, or renal function.

In patients with T2DM, tirzepatide decreases fasting and postprandial glucose levels more effectively than semaglutide, reduces food intake and body weight, enhances first- and second-phase insulin secretion, and improves insulin sensitivity after 28 weeks of treatment. It also reduces fasting and postprandial glucagon concentrations and delays gastric emptying.[16]

Most importantly, tirzepatide reduces body weight and systolic blood pressure (~5–6 mmHg) in a dose-dependent manner and decreases inflammatory markers (e.g. high-sensitivity C-reactive protein), triglycerides and very low density lipoproteins levels. In a sub-study of the SURPASS-3 trial, using magnetic resonance imaging, tirzepatide significantly reduces liver fat content and the volume of visceral and abdominal subcutaneous adipose tissue.[21] At high doses, tirzepatide significantly decreases biomarkers of non-alcoholic fatty liver disease (NAFLD) and increases adiponectin level in patients with T2DM.[16,22]

In a recent meta-analysis of seven RCTs (4,887 participants treated with tirzepatide, 2,328 controls), each with at least one MACE-4 event, treatment with once weekly tirzepatide (5, 10 and15 mg daily) for up to 24 months does not increase the risk of four-component major adverse cardiac events (cardiovascular death, myocardial infarction (MI), stroke and hospitalized unstable angina) across a spectrum of T2DM duration and cardiovascular risk levels.[23]

Tirzepatide does not inhibit/induce CYP enzymes or block drug transporter proteins, but it delays gastric emptying and may affect the absorption of concomitantly administered oral drugs. Of note, hepatic or renal impairment does not impact the pharmacokinetics of tirzepatide. Most frequent adverse reactions (>10%) are nausea, vomiting, diarrhea, along with decreased appetite. Vomiting, constipation, dyspepsia and abdominal pain are reported in 4-10% of patients and hypersensitivity reactions and injection site reactions (e.g., eczema and urticaria) in 3% of the individuals. Although hypoglycemia is not an intrinsic adverse effect of tirzepatide monotherapy, tirzepatide might increase the risk of hypoglycemia from 2% to 16% when combined with insulin secretagogues or insulin.[24] Like GLP-1R agonists, tirzepatide may cause acute gallbladder disease (0.5%) and acute pancreatitis and should be avoided in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

Tirzepatide represents a promising drug for the treatment of metabolic disorders, including T2DM, obesity/overweight and NAFLD.[17,18] Several ongoing clinical trials analyse its efficacy and safety in patients with T2DM [SURPASS-6 (NCT04537923), SURPASS-PEDS (NCT05260021), SURPASS-CVOT (NCT04255433)], T2DM and obesity/overweight [SURMOUNT-2-4: NCT04184622, NCT04657003 NCT04657016, NCT04660643), SURMOUNT-CN (NCT05024032), SURMOUNT-J (NCT04844918),

SURMOUNT-MM (NCT0555651)], non-alcoholic steato-hepatitis (SYNERGY-NASH, NCT04166773), overweight/obesity and chronic kidney disease with or without T2DM (TREASURE-CKD, NCT05536804) and HFpEF and obesity (SUMMIT, NCT04847557). The recent approval of tirzepatide will certainly foster the development of other dual agonists or tri-agonists, achieving a concurrent activation of GLP-1, GIP, and glucagon receptors, leading to the development of more efficient pharmacological approaches for cardiometabolic diseases.

1.3 Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) for heart failure treatment

The 2022 AHA/ACC/HFSA Guideline for the Management of HF recommend SGLT2Is in adults already on guideline-directed medical therapy with:[25] a) HF and T2DM for the management of hyperglycemia and to reduce HF-related morbidity and mortality (I, A). b) T2DM and either established cardiovascular disease or at high cardiovascular risk to prevent HF hospitalizations (1, A). This benefit predominantly reflects primary prevention of symptomatic HF, because only 10-14% of participants had HF at baseline. c) Symptomatic chronic HF with reduced ejection fraction (HFrEF, LVEF ≤40%, NYHA class II-IV, and elevated natriuretic peptides), to reduce HF hospitalizations and cardiovascular mortality, irrespective of the presence of T2DM (I, A). d) Mildly

reduced (HFmrEF) or HFpEF to reduce HF hospitalizations and cardiovascular mortality (2a, B-R). In 2022, for the first time, the FDA approved an expanded indication of empagliflozin to reduce the risk of cardiovascular death and HF hospitalization in adults with HF, regardless of ejection fraction, which confirmed SGLT2 inhibitors as first-choice drugs for the treatment of HF. A similar statement was made Butler et al.[26] However, SGLT2Is have not been evaluated in patients with severe renal impairment (estimated glomerular filtration rate <25 mL/min/1.73 m^2), T1DM or systolic blood pressure <100 mm Hg.

2. Novel insights filling existing gaps in knowledge in cardiovascular pharmacotherapy

In this section we briefly discuss clinical trials that provided novel insights that fill existing gaps in knowledge in cardiovascular pharmacotherapy.

2.1 Efficacy and safety of SGLT2Is among patients with HFmrEF or HFpEF

Although patients with HFmrEF or HFpEF represent about half of the HF population, current pharmacological options are very limited. SGLT2Is reduce the risk of HF hospitalization and cardiovascular death among patients with HFrEF, but their efficacy has been less frequently assessed in patients with LVEF ≥40%.

The DELIVER trial randomized patients with HF and a LVEF >40% to dapagliflozin or placebo, in addition to usual therapy. The trial also included patients with a previously reduced LVEF that improved to >40% by the time of enrollment, a group that was usually excluded from prior trials.[26] Over a median of 2.3 years, dapagliflozin significantly reduced the composite primary outcome of worsening HF or cardiovascular death and total events and symptom burden as compared to placebo. First statistical significance was reached for worsening HF by day 16 after randomization.[27] Effects on the primary endpoint were consistent among patients with LVEF ≥60% or ≤60%, with recent HF hospitalization (during or within 30 days) or with/without previous LVEF ≤40% that improved to >40% by the time of enrollment, and in other pre-specified subgroups, including patients with/without diabetes.[26,28] Serious adverse events and adverse events leading to discontinuation were similar in both groups.[28]

Thus, among patients with HFmrEF or HFpEF dapagliflozin reduces the risk of worsening HF and cardiovascular deaths, and symptom burden, with no excess of adverse events. These data are complementary to the findings from the EMPEROR-Preserved trial[29] and strongly support the use of SGLT2Is in all patients with HF, irrespective of patient phenotype or care setting.

2.2 Long-term LDL-C lowering with evolocumab reduces the risk of cardiovascular events

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors lead to marked reductions in LDL-C even in patients receiving high-intensity statin therapy, but median treatment durations in major trials was 2-3 years only. Therefore, large-scale, long-term data are lacking. Originally, the FOURIER (parent) trial recruiting 27,564 patients with ASCVD and LDL-C ≥70 mg/dL showed that after a median of 2.2 years evolocumab reduced LDL-C and risk of cardiovascular events, but not cardiovascular mortality. A total of 6635 patients who completed the FOURIER trial (3355 originally randomized to evolocumab, 3280 to placebo) were eligible to receive evolocumab in 2 open-label extension studies (FOURIER-OLE) designed to assess drug safety during a median follow-up of 5.0 years (maximum exposure to evolocumab in parent plus FOURIER-OLE 8.4 years).[30] The primary end point was the incidence of adverse events; lipid values and major adverse cardiovascular events were prospectively collected. After 12 weeks in FOURIER-OLE, the median LDL-C was 30 mg/dL, and 63.2% of patients achieved LDL-C levels <40 mg/d. The incidence of serious adverse events (injection-site reactions, allergic reactions, muscular events, new-onset diabetes, cataracts, hemorrhagic stroke, and neurocognitive events) did not exceed that observed in placebo-treated patients during the FOURIER study and did not increase over time. Importantly, patients originally randomized in the parent trial to evolocumab versus placebo had a 15% lower risk of cardiovascular death, MI, stroke, or hospitalization for unstable angina or coronary revascularization, a 20% lower risk of cardiovascular death, MI, or stroke, and a 23% lower risk of cardiovascular death when compared with placebo-treated patients switched to evolocumab once the parent trial was completed. Thus, despite the

open-label design, long-term LDL-C lowering with evolocumab for more than 8 years is safe and well tolerated and leads to further reductions in cardiovascular events compared with delayed treatment initiation. These findings support current guidelines recommendations, confirm that targeting LDL-C to lower levels for a longer time is likely to yield the best results and suggest to start lipid-lowering therapy as early as possible to reduce the detrimental life-long impact of elevated LDL-C on vessel function and CVD burden.

2.3 Vitamin K antagonists for prevention of cardioembolic events in patients with rheumatic heart disease-associated atrial fibrillation (RHD-AF)

Patients with RHD-AF constitute a unique AF population because they are younger, more often female, present advanced valvular disease, and are at higher risk of stroke. Of note, these patients are usually excluded from trials using direct oral anticoagulants. The INVICTUS trial compared the efficacy and safety of rivaroxaban and dose-adjusted vitamin K antagonist (VKA) therapy, in 4531 patients with RHD-AF (mean age 50.5 years; 72.3% women; about 85% with moderate-severe mitral valve stenosis) and at least one of the following criteria: a CHA_2DS_2VASc score ≥2, mitral stenosis (mitral-valve area <2 cm^2) or echocardiographic evidence of either left atrial spontaneous echo contrast or left atrial thrombus.[31] The primary efficacy outcome (composite of stroke, systemic embolism, MI, or death from vascular or unknown causes) occurred in 560 patients in the rivaroxaban group and in 446 patients in the VKA group (35.0% vs 26.6%, respectively). This significant difference was primarily driven by more deaths (552 vs 442) and ischemic strokes (74 vs 48) in the rivaroxaban group. This difference in mortality was almost entirely due to higher rates of sudden cardiac death (141 vs 94) and of death due to mechanical or pump failure (237 vs 174) in the rivaroxaban group. Drug discontinuation was greater with rivaroxaban than with VKA (23% vs 6%) at all visits, but there were no differences in major bleedings between treatment groups, although the rate of fatal bleeding was lower with rivaroxaban. The higher rates of sudden cardiac death and death from mechanical or pump failure with rivaroxaban were unexpected and were unrelated to heart-valve deterioration or the higher incidence of drug discontinuation, because many patients who discontinued rivaroxaban then received a VKA. These results support current guidelines, which recommend VKA as the standard of care for stroke prevention in patients with RHD-AF.[32]

2.4 Antibiotic prophylaxis of endocarditis before invasive dental procedures

The ESC guidelines recommend antibiotic prophylaxis before invasive dental procedures to prevent infective endocarditis in patients at high risk of endocarditis.[33] However, there are limited data directly supporting the efficacy of antibiotics in endocarditis prevention during invasive dental procedures. Using cohort and case-crossover methodologies in a population of almost 8 million people, Thornhill et al[34] found a significant temporal association between invasive dental procedures and subsequent development of infective endocarditis in high infective endocarditis risk individuals, and between antibiotic prophylaxis and reduced infective endocarditis incidence following invasive dental procedures. Time course studies and case-crossover analysis showed a significant temporal association between occurrence of infective endocarditis and invasive dental procedures in the preceding 4 weeks, with this relationship being

strongest for dental extractions and oral-surgical procedures. Prophylaxis with antibiotics was associated with a 51% reduction in infective endocarditis incidence following invasive dental procedures. The cohort study confirms the association between infective endocarditis and invasive dental procedures in patients and the efficacy of prophylaxis with antibiotics in reducing these associations. These data are consistent with guidelines recommendation that patients at high risk for infective endocarditis should receive antibiotic prophylaxis before invasive dental procedures.[33]

2.5 Vutrisiran for treatment of hereditary transthyretin-mediated amyloidosis

Hereditary transthyretin (TTR)-related amyloidosis (hATTR) is a rare, rapidly progressive malignant disease caused by variants in the *TTR* gene.[35,36] Normal TTR is a tetramer composed of four identical subunits produced primarily in the liver that functions as a transporter for thyroxine and retinol (vitamin A). TTR mutations result in abnormal depolymerization, misfolding and aggregation of TTR into amyloid fibrils that deposits in multiple organs and tissues leading to a heterogeneous clinical presentation including sensory, motor, and autonomic polyneuropathy, along with cardiomyopathy.[36,37] Without treatment, median survival is 4.7 years following diagnosis,[36,38] while median survival for hATTR patients with cardiomyopathy is only 3.4 years.[36,38]

Vutrisiran (ALN-TTRSC02) is a double-stranded small interfering RNA (siRNA) conjugated to a triantennary N-acetylgalactosamine ligand that binds to asialoglycoprotein receptors (ASGPR), which are almost exclusively expressed on hepatocytes, the primary site of TTR synthesis **(Figure 3).**[39]

Based on the results of the HELIOS-A study, vutrisiran administered by subcutaneous injection once every 3 months (Q3M) was approved for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. This study compared vutrisiran with patisiran (another siRNA targeting TTR mRNA) and the placebo arm from the APOLLO phase 3 study of patisiran recruiting a comparable patient population of adults with hATTR and polyneuropathy.[40] Vutrisiran produced a rapid (≤3 weeks) and sustained reduction in serum TTR levels over 18 months across all patient subgroups, like that observed in the patisiran group. Vutrisiran significantly improved signs and symptoms of polyneuropathy in the modified Neuropathy Impairment Score +7 (mNIS+7), Norfolk Quality of Life-Diabetic Neuropathy total score, 10-meter walk test, modified body-mass index, and Rasch-built Overall Disability Scale at 9 and 18 months compared to placebo. Vutrisiran caused a 2.2-point mean decrease (improvement) in mNIS+7 from baseline compared with a 14.8-point mean increase (worsening) in the external placebo group (P<0.0001). After 9 months, 50% of patients treated with vutrisiran experienced improvement in neuropathy signs relative to baseline.

Of importance, no dose adjustment of the drug is required in patients with mild-moderate renal impairment (eGFR ≥30 to <90 mL/min/1.73 m^2) or mild hepatic impairment.[39] Vutrisiran is not a substrate/inhibitor of CYP enzymes, which makes relevant drug-drug interactions less likely. The most common adverse

reactions (≥4%) were arthralgia, dyspnea, and decreased vitamin A levels. Vitamin A supplementation is recommended and patients who develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness) should be referred to an ophthalmologist.

The pharmacokinetic properties of vutrisiran are shown in **Table 2**. A biannual 50 mg dosing regimen is currently being evaluated in the ongoing randomized treatment extension period in the HELIOS-A trial. The ongoing HELIOS-B phase 3 trial (NCT04153149) will assess both the efficacy and safety of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy.

2.6 Factor XI inhibitors: an emerging new class of anticoagulants

Anticoagulants are the mainstream therapy for the prevention and treatment of venous thrombosis and cardioembolic complications, but their use is associated with an increased risk of bleeding despite the better safety profile of direct oral anticoagulants vs. vitamin K antagonists. Therefore, there has been great interest in developing new anticoagulants with a reduced risk of bleeding, while maintaining similar efficacy in treating/preventing thrombosis.

In principle, the bleeding risk of anticoagulants can be avoided if they could selectively target the coagulation factors that are more important for pathological thrombus formation than for physiological hemostasis. Selective inhibition of factor (F)XI or FXIa has been proposed as a possible target for the development of safer anticoagulants.[41,42] FXI is activated by FXIIa, a component of the contact system (so called intrinsic pathway), and thrombin generated during the final phase of the coagulation (**Figure 4**), and contributes to clot formation, growth and stabilization.[43,44] However, some evidence suggests that FXI contributes more to thrombosis with a minor role in physiological hemostasis. Indeed, in animal models, FXI inhibition protect against arterial and venous thrombosis without an increase in bleeding complications. Additionally, patients with congenital FXIa deficiency present with a reduced risk of thrombosis and cardiovascular events, their risk of bleeding is lower compared to other coagulation factor deficiencies with a less clear dose-dependence for bleeding risk. Conversely, patients with elevated FXI levels show prothrombotic phenotypes.[41,45,46]

Several FXI or FXIa inhibitors, including antisense oligonucleotides, monoclonal antibodies, and small molecules are under clinical development (**Table 3**). They have been investigated in phase 2 studies for prevention of venous thromboembolism in patients undergoing total knee arthroplasty or major adverse vascular events in patients with end-stage kidney disease undergoing hemodialysis or as add-on to antiplatelet therapy for prevention of recurrent ischemic events in patients with acute MI, AF or non-cardioembolic stroke. Despite some promising results of these small trials, as all dose-finding phase II trials, they were underpowered to assess drug efficacy on clinical outcomes. Furthermore, for some of them a clear dose-response in terms of bleeding or prolongation of laboratory tests for hemostasis could not be

identified. Ongoing phase III trials will validate the hypothesis of FXI as being a clot factor less important for physiological hemostasis in humans and determine whether FXI inhibitors attenuate thrombosis with little or no disruption of homeostasis.

3. Novel insights regarding fixed dose combinations of cardiovascular drugs

Non-adherence to therapy remains a major obstacle in the primary and secondary prevention of CVD. Fixed dose combinations of drugs (FDC) with diverse and/or complementary mechanisms of action that may allow dose reduction of individual drugs and may lead to synergistic or additive clinical effects. Thus, FDC of drugs could achieve greater efficacy and may overcome potential adverse effects often associated with high doses of individual drugs, by either countering biological compensatory mechanisms, sparing doses on each compound, or acting on multi-target mechanisms. FDC may also improve the poor compliance and drug maintenance associated with polypharmacy and could reduce the total costs of treatment.

3.1 Combination of acetazolamide and loop diuretics in HF patients resistant to loop diuretics alone

Acute decompensated HF (ADHF), usually due to volume overload, is among the most common causes for hospitalization, morbidity, mortality, and health care expenditures.[25,47] Treating the clinical signs and symptoms of HF, while preserving or improving renal function, is a crucial therapeutic goal.

Due to their rapid onset of action and strong diuretic efficacy, intravenous loop diuretics have been, for decades now, the cornerstone of ADHF treatment to alleviate symptoms and signs of fluid overload and congestion, decrease ventricular filling pressures, improve exercise capacity, and reduce HF hospitalization.[47] However, selection of appropriate drug, dosing schedule, and route of administration of diuretics remained uncertain and more than 50% of patients admitted for ADHF are discharged on loop diuretics with residual pulmonary congestion, which is associated with re-hospitalization and death within 6 months after discharge.[48]

Among patients with ADHF, there are no significant differences in patients' global assessment of symptoms or in changes in renal function from baseline to 72 hours when diuretic therapy is administered by means of boluses as compared with continuous infusion or with a low-dose strategy as compared with a high-dose strategy. Although differences in the patient's global assessment of symptoms does not reach statistical significance, the high-dose group has more favorable outcomes with regard to several pre-specified secondary measures, including relief of dyspnea, change in weight, and net fluid loss.[49] However, at high doses both orally or intravenously applied loop diuretics may produce harmful effects, including neurohumoral activation, electrolyte disturbances, ototoxicity (especially in combination with

aminoglycosides) and acute worsening of renal function.[50] Additionally, intermittent bolus dosing may be associated with a higher rate of diuretic resistance due to prolonged periods of subtherapeutic drug levels in the kidney and higher risk of ototoxicity. Continuous infusions result in lower peak plasma levels but more constant delivery of the drug to the tubule, leading to a greater diuresis and better safety profile, but restrict patient mobility.[50]

Since diuretics act at different regions in the nephron, conceptually it would be expected that the combination of loop diuretics with other diuretic drugs acting at distinct nephron sites (*sequential nephron blockade*) will result in a synergistic diuretic effect, leading to faster and stronger decongestion in patients with ADHF treated with loop diuretics alone.

Acetazolamide is a carbonic anhydrase inhibitor that reduces sodium and bicarbonate resorption in the renal proximal tubules, but produces poor diuretic and natriuretic effects, with rapidly emergent diuretic resistance in case of prolonged use.[51] Therefore, acetazolamide was infrequently used in AHF. However, several recent small-size studies with a short follow-up (up to 72 hours) suggest that addition of acetazolamide increases the natriuretic response to loop diuretics compared to an increase in loop diuretic dose in ADHF at high risk for diuretic resistance.[52–54] The potential underlying mechanisms may include: 1) the blockade of sodium reabsorption produced by acetazolamide in the proximal tubules, so that more sodium reaches the Henle's loop, which increases the effect of loop diuretics; and 2) the direct renal vasodilator[55] and protective effects of acetazolamide against ischemia–reperfusion via up-regulating hypoxia-inducible factor-1α (HIF-1α),[56] along with inhibition of pendrin expression in the distal nephron, which may potentiate furosemide-induced diuresis.[57]

The ADVOR trial randomized 519 patients with ADHF, volume overload, and NT-proBNP >1000 pg/mL (or B-type natriuretic peptide levels >250 pg/mL) to either intravenous acetazolamide or placebo added to standardized intravenous loop diuretics (at a dose equivalent to twice the oral maintenance dose).[58] The combination of acetazolamide with loop diuretics increases cumulative urine output and natriuresis, improves the incidence of successful decongestion at day 3 from 30.5% to 42.2%, an effect consistent with a better diuretic efficiency, and shortens length of hospital stay from 9.9 to 8.8 days. However, combination therapy has no significant effect on all-cause death or HF re-hospitalization rate during 3 months of follow-up. The incidence of worsening kidney function, hypokalemia, hypotension, and other adverse events were similar in both groups.

Although these results suggest that addition of acetazolamide to loop diuretics may increase the successful decongestion in ADHF patients, the study has several limitations. Patients with newly diagnosed HF and those being on SGLT2Is were excluded and renin-angiotensin-aldosterone inhibitors were prescribed in only 52% of patients. It was also unclear how many participants with HFrEF were on goal directed therapy at baseline. Although the acetazolamide group had a higher rate of successful decongestion, there were no

differences in the risk of death or re-hospitalization between groups. Subgroup analysis suggested that acetazolamide was not superior among patients with a greater likelihood of diuretic resistance, including females, patients receiving >60 mg of furosemide, with ischemic cardiomyopathy or estimated glomerular filtration rate (eGFR) ≥ 39 mL/min/1.73 m^2. Finally, the trial does not prove superiority of acetazolamide compared to other potential strategies, i.e. the combination of thiazide diuretics (metolazone or hydrochlorothiazide) with loop diuretics, or even a more aggressive loop diuretic therapy in patients with ADHF and refractory volume overload. Thus, further clinical trials are required to demonstrate and validate the therapeutic value of different combinations of diuretic drugs for the treatment of ADHF.

3.2 Combination of statins and ezetimibe in patients with atherosclerotic cardiovascular disease

In patients with atherosclerotic CVD (ASCVD) the extent of low-density lipoprotein-cholesterol (LDL-C) reduction is the strongest independent predictor of major vascular events (coronary death or non-fatal myocardial infarction, coronary revascularization, and ischaemic strokes). In a meta-analysis of 26 RCTs (>170,000 patients), the use of high-intensity statin therapy produces an additional 15% reduction in major vascular events compared to less intense regimens.[59] Thus, clinical guidelines recommend monotherapy with the highest tolerated dose of statin before consideration of additional non-statin therapy to reach LDL-C goals in patients with ASCVD.[60,61] However, high-intensity statin therapy may increase the risk of adverse effects, drug-drug interactions, drug discontinuation, and of non-adherence to therapy in the primary and secondary prevention of ASCVD.[62]

A meta-analysis showed that low-intensity statin plus bile acid sequestrants or ezetimibe decreased LDL-C level to an extent like that obtained with high-intensity statin monotherapy. Thus, such combinations may constitute an alternative to high-intensity statin monotherapy among high-risk patients who are statin-intolerant or who do not achieve lipid-lowering goals on statins alone.[63,64] However, the long-term clinical benefits/harms of a lower-intensity statin-ezetimibe therapy remained uncertain in patients with ASCVD.

The RACING trial compared the efficacy and safety of moderate-intensity statin with ezetimibe (rosuvastatin plus ezetimibe) to high-intensity statin monotherapy in patients with ASCVD who required high-intensity statin therapy to achieve LDL-C levels ≤70 mg/dL.[65] After 3 years, the primary outcome (composite of cardiovascular death, major cardiovascular events, or non-fatal stroke) occurred in 9.1% of patients in the combination therapy group and 9.9% in the monotherapy group. This result met the non-inferiority margin of 2.0%, indicating that the combination therapy was non-inferior to statin monotherapy. At 1, 2 and 3 years, LDL-C levels <70 mg/dL were observed in 72%-75% of patients on combination therapy and in 55%-60% of those treated with high-intensity statin monotherapy. Interestingly, discontinuation or dose reduction of the study drug due to intolerance occurred less frequently in the combination therapy group (4.8% vs. 8.2%). The secondary composite endpoint of all-cause mortality, major cardiovascular event, or nonfatal stroke was similar in both treatment groups.

Thus, combination of moderate-intensity statin therapy with ezetimibe is non-inferior to high-intensity statin monotherapy in patients with ASCVD but is associated with a lower incidence of drug discontinuation or dose reduction due to adverse effects and a higher proportion of patients reaches their LDL-C level target. Thus, combination therapy rather than doubling the statin dose might be considered for patients at high-risk for adverse effects or intolerance to high-intensity statin therapy. However, because of the open-label design of the study further clinical trials are required to validate the non-inferiority and improved tolerability of moderate-intensity statin therapy with ezetimibe compared to high-intensity statin monotherapy in patients with ASCVD.

3.3 Combination of angiotensin receptor blockers and β-blockers in patients with Marfan syndrome

The Marfan syndrome is a rare genetic disorder with autosomal dominant heritage caused by pathological variants in the fibrillin-1 gene (*FBN1*), which leads to increased levels of active transforming growth factor beta (TGF-β), along with abnormal microfibrils formation and connective tissue synthesis. This causes progressive enlargement of the aortic root and increases the risk of aortic complications, mainly aortic dissection, leading to premature death or disability.[66] Beta-blockers and angiotensin receptor blockers (ARBs) reduce TGF-β expression and circulating TGF-β levels and slow aortic root enlargement.[67] Because the effects of their combination remained uncertain, Pitcher et al[68] performed a meta-analysis 10 RCTs including 1836 patients with no previous aortic surgery that compared ARBs versus control or ARBs versus β-blockers, which followed a protocol that was agreed and published before study analyses. The primary endpoint was the annual rate of change of body surface area-adjusted aortic root dimension Z score, measured at the sinuses of Valsalva. During a median follow-up of 3 years, ARB therapy approximately halved the primary endpoint, and the benefits were significantly greater in patients with than in those without pathogenic *FNB1* variants and persisted in those treated with β-blockers. Three trials compared ARBs with β-blockers in 766 patients and showed that during a median follow-up of 3 years, the annual change in the aortic root Z score was similar in the two groups. Assuming additivity, combination therapy with both ARBs and β-blockers from the time of diagnosis would provide even greater reductions in the rate of aortic enlargement than either treatment alone, and if maintained over a number of years, would be expected to delay the need for aortic surgery substantially.

This meta-analysis, however, has several limitations. For instance, not all trial datasets were available for individual data analysis. In addition, all RCTs analysed the effects of losartan or atenolol and only 1 trial studied irbesartan or nebivolol. Why the individual studies used different ACEIs and β-blockers, making an interstudy comparison difficult, is unclear and should be considered when interpreting the study outcomes. Furthermore, only 11% of the patients were older ≥40 years, so that the extrapolation of the present data to older adults with Marfan syndrome is uncertain. Finally, the number of patients who had major clinical

outcomes was too small to provide sufficient statistical power to detect benefit on such outcomes over the relatively short duration of the trials.

3.4 Polypill strategy in secondary cardiovascular prevention revisited

Almost 20 years ago, Wald and Law[69] proposed a FDC of six drugs, so-called "polypill", for the prevention of CVD, suggesting that administration of this polypill to all adults ≥55 years of age would reduce cardiovascular events by over 80%. In recent years, different cardiovascular polypills have been developed to prevent the progressive increase in global CVD burden. These data were further confirmed by more recent trials and a large individual patient's data meta-analysis.[70,71] A FDC that includes drugs with established efficacy to improve cardiovascular outcomes (low-dose aspirin, angiotensin-converting-enzyme inhibitors [ACEIs], and statins) was proposed for the secondary prevention of cardiovascular death and complications post-MI.[72] This polypill simplifies treatment, increases adherence and persistence to therapy and has the potential to improve pharmacological treatment worldwide while reducing direct and indirect costs. However, its efficacy in preventing secondary cardiovascular events remained uncertain.[72,73]

The SECURE trial compared a polypill-based strategy containing low-dose aspirin (100 mg), ramipril (2.5, 5, or 10 mg) and atorvastatin (20 or 40 mg) with usual care in patients with a MI within the previous 6 months.[74] After a follow-up of 3 years the primary composite outcome (cardiovascular death, non-fatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization) decreases significantly by ~25% (9.5% vs 12.7%) in the polypill group. A key secondary composite outcome of cardiovascular death, non-fatal type 1 MI, or non-fatal ischemic stroke is also reduced by ~30% in the polypill group as compared with the usual-care group (8.2% vs 11.7%). The lower risk of cardiovascular events in the absence of substantial differences in blood pressure and LDL-C levels may be related to the pleiotropic effects of statins and ACEIs[75,76] and the greater drug adherence.[77,78] Indeed, in patients with recent MI, cardiovascular risk was 27% lower among the patients with a high degree of adherence than among those with a low degree of adherence[77] and in secondary prevention patients, compared with control groups, those treated with a polypill containing aspirin, ramipril, and atorvastatin showed a 27% lower frequency of recurrent MACE, improved BP and LDL-C control rates, and increased medication persistence.[78]

Future directions

Several new anticoagulants and platelet antiaggregants, cardiac myosin inhibitors, lipid-lowering drugs targeting LDL-C, triglycerides, and apolipoprotein (a), oral dual endothelin receptor antagonists and drugs that may improve cardiac function in patients with HF or MI are under clinical development and are expected to offer new therapeutic opportunities in the near future. These potential advancements, along with the repurposing of approved drugs (i.e. SGLT2is in the treatment of HF, glucagon-like peptide 1

receptor agonists in the treatment of obesity or colchicine in the treatment of coronary artery disease) will create unique opportunities and opened up new avenues in the treatment of cardiovascular diseases.

Conclusions

This review provides a summary of the most recent and relevant advances in cardiovascular pharmacology in 2022 including the approval of first-in-class drugs that open new avenues for pharmacotherapy of oHCM (mavacamten), T2DM (tirzepatide), and HF independent of LVEF (SGLT2Is). Fixed dose combination therapy repurposing different formulations of "old" drugs with well-known efficacy and safety offer new effective options for the treatment of patients with ADHF (acetazolamide plus loop diuretics), ASCVD (moderate-dose statin plus ezetimibe), Marfan syndrome (ARBs plus β-blockers), and secondary cardiovascular prevention (i.e. low-dose aspirin, ramipril and atorvastatin). In addition, some trials have confirmed the role of dapagliflozin in patients with HFmrEF or HFpEF, of long-term evolocumab to reduce the risk of cardiovascular events, vitamin K antagonists for stroke prevention in patients with RHD-AF, the value of antibiotic prophylaxis in patients at high risk for infective endocarditis before invasive dental procedures, and of vutrisiran for the treatment of hATTR with polyneuropathy. Finally, the results from multiple phase 2 trials with FXIa inhibitors suggest that these drugs may have the potential to prevent thromboembolic events which has to be confirmed in large ongoing phase III trials.

Conflicts of interest:

J Tamargo: none

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C. Borghi: has received lecture fees form Menarini Corporate, Servier Pharma, Amarin, Novo Nordisk, Alfasigma, Berlinchemie, Sanofi and is member of advisory board of the same companies.

C Ceconi: none

E. Cerbai: none

G. A Dan: none

P. Ferdinandy: is the founder and CEO of Pharmahungary Group, a group of R&D companies

E. Grove: has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, MundiPharma, Organon and Lundbeck Pharma. He is an investigator in clinical trials sponsored by AstraZeneca, Bayer and Idorsia, and has received unrestricted research grants from Boehringer Ingelheim.

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Data Availability Statement

The data underlying this review were taken from the quoted references.

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Figure legends

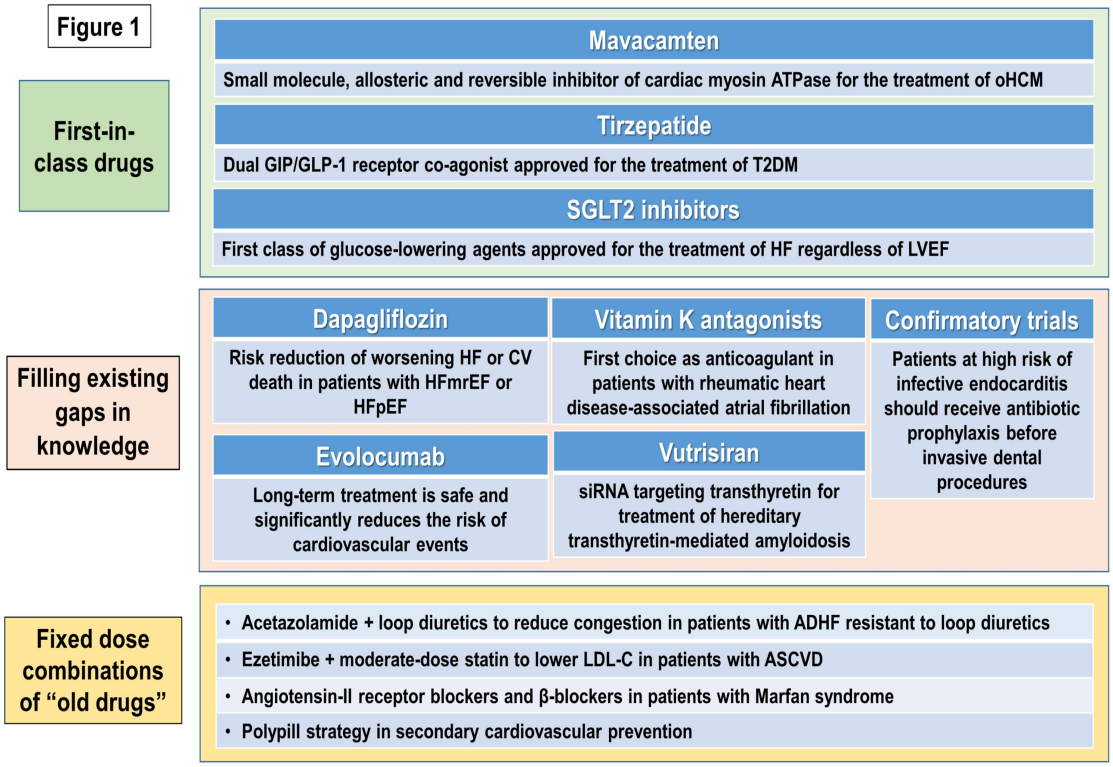

Figure 1. Summary of new pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2022

Abbreviations. ADHF: acute decompensated heart failure. ASCVD: atherosclerotic cardiovascular disease. ATPase: adenosine triphosphatase. GIP: glucose-dependent insulinotropic polypeptide. GLP-1: glucagon-like peptide-1. HF: heart failure. HFmrEF: HF with mildly reduced ejection fraction. HFpEF: HF with preserved ejection fraction. HFpEF: heart failure with preserved ejection fraction. LDL-C: low-density lipoprotein cholesterol. LVEF: left ventricular ejection fraction. oHCM: obstructive hypertrophic cardiomyopathy. SGLT2Is: sodium-glucose cotransporter-2 inhibitors. siRNA: small interfering RNA. T2DM: type 2 diabetes mellitus.

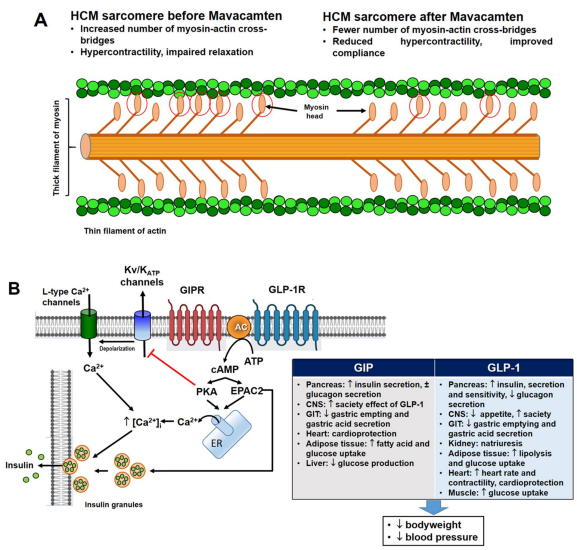

Figure 2. Mechanism of action of (A) mavacamten (red circles indicate myosin-actin cross-bridges) and (B) tirzepatide (A). See the text for further details and explanation.

Abbreviations. cAMP: cyclic adenosine monophosphate. CNS: central nervous system. EPAC2: exchange protein activated by cAMP2. ER: endoplasmic reticulum. GIP: glucose-dependent insulinotropic polypeptide. GIPR: GIP receptor. GIT: gastrointestinal tract. GLP-1: glucagon-like peptide-1. GLP-1R: receptor of GLP-1. HCM: hypertrophic cardiomyopathy. K_V/K_{ATP}: voltage-dependent and ATP-sensitive K^+ channels. PKA: protein kinase. SNC: central nervous system.

Figure 3

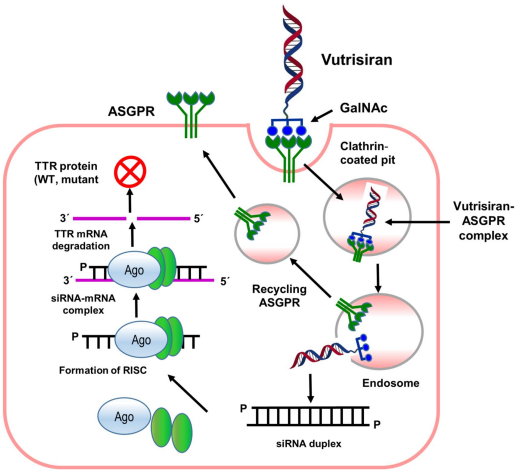

Figure 3. Mechanism of action of vutrisiran. This is a double-stranded siRNA conjugated to a triantennary N-acetylgalactosamine ligand that binds to asialoglycoprotein receptors (ASGPR), which are almost exclusively expressed on hepatocytes. The vutrisiran-ASGPR complex is rapidly taken into hepatocytes by clathrin-mediated endocytosis and binds to the RNA-induced silencing complex (RISC) and the messenger RNA (mRNA) encoding TTR. The siRNA-RISC complex cleaves mutant and wild-type TTR mRNA through RNA interference, reducing serum TTR protein and tissular TTR protein deposits. The ASGPR is recycled to the cell surface to facilitate further siRNA uptake.

Abbreviations. Ago: Argonaut proteins. ASCVD: atherosclerotic cardiovascular disease. ASGPR: asialoglycoprotein receptors. cAMP: cyclic adenosine monophosphate. GalNAc; triantennary *N*-acetylgalactosamine. mRNA: messenger RNA. RISC: RNA-induced silencing complex. siRNA: small interfering RNA. TTR: transthyretin protein.

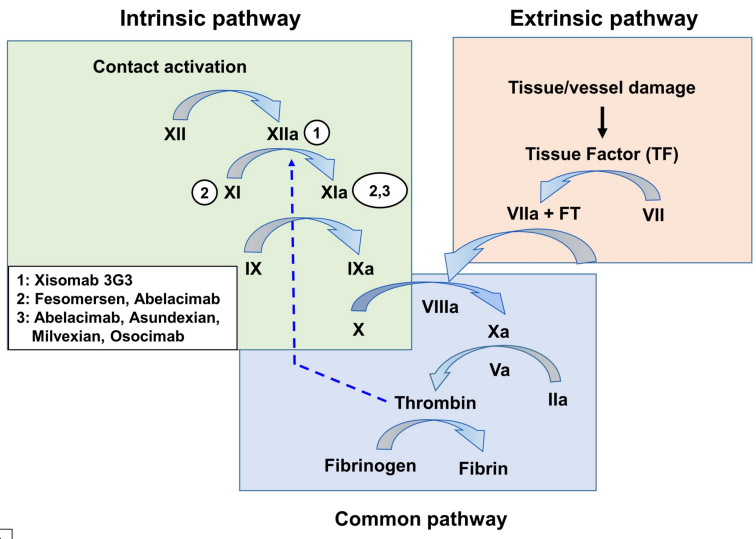

Figure 4

Figure 4. Coagulation cascade and putative mechanism of action of new factor XI inhibitors. Numbers in circles represent the point of action of new FXI, FXIa and FXIIa anticoagulants. Abbreviations. F: coagulation factor.

Table 1. Summary of selected Phase 2 and 3 clinical trials published in 2022

Study (NCT), [Reference]	Trial design	Drug, doses	Primary endpoint	Results
Anticoagulants				
AXIOMATIC-SSP	Phase 2, R, DB, PC, dose-ranging N=2,366 patients with mild-to-moderate acute non-lacunar stroke or TIA with evidence of arterial atherosclerosis on background treatment with open-label aspirin (100 mg) and clopidogrel (75 mg) for 21 days, followed by OL aspirin thereafter FU: 90 days	Milvexian 25 mg QD, 25, 50, 1000 or 200 mg BID or matching placebo	Primary efficacy endpoint: composite of ischaemic stroke during treatment or incident infarct on brain MRI at 90 days. Main safety endpoint: major bleeding, defined as Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding	There was no apparent dose-response. Milvexian numerically reduced the risk of clinical ischaemic stroke (excluding covert brain infarction) in the intention-to-treat population at all doses except 200 mg BID; at 25-100 mg BID milvexian produced an approximately 30% relative risk reduction versus placebo. The rate of major bleeding was similar for milvexian and placebo
PACIFIC-AF (NCT04218266)	Phase 2, R, DB, PC, dose-finding N=862 with AF FU=12 weeks	Asundexian 20 or 50 mg QD vs apixaban, 5 mg QD	Composite of major or clinically relevant non-major bleeding according to ISTHs criteria, assessed in all patients who took at least one dose of study medication	Asundexian at 20 mg and 50 mg daily had lower observed rates of bleeding compared with apixaban. The rate of AEs was similar in the three groups
PACIFIC-AMI Investigators (NCT04304534)	Phase 2, R, DB, PC, PG, dose finding N=1601, within 5 days of their qualifying MI and received dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor. 99% underwent PCI before randomization FU: 368 days	Asundexian 10, 20, or 50 mg or placebo QD	Prespecified main safety outcome: bleeding Academic Research Consortium type 2, 3, or 5 bleeding comparing all pooled asundexian doses with placebo. Prespecified efficacy outcome: composite of CV death, MI, stroke, or stent thrombosis comparing pooled asundexian 20 and 50 mg doses with	Asundexian, added to aspirin plus a P2Y12 inhibitor, resulted in dose-dependent, near-complete inhibition of FXIa activity (>90% inhibition at 50 mg) without a significant increase in bleeding and a low rate of ischemic events. The main safety outcome was similar with asundexian or placebo (HR 0.98; 0.71-1.35). The

			placebo.	efficacy outcome was similar with asundexian (10, 20 or 50 mg) or placebo, respectively (pooled asundexian 20 and 50 mg vs placebo: HR 1.05; 0.69-1.61)
PACIFIC-Stroke (NCT04304508)	Phase 2b, DB, PC, R, dose-finding trial N=1808 with acute (within 48 h) non-cardioembolic ischaemic stroke FU: 26-52 weeks	Asundexian 10, 20 or 50 mg/day or placebo	Efficacy outcome: effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischaemic stroke at or before 26 weeks after randomisation. Safety outcome: major or clinically relevant non-major bleeding	Asundexian did not reduce the composite of covert brain infarction or ischaemic stroke and did not increase the composite of major or clinically relevant non-major bleeding compared with placebo
Cardiac amyloidosis				
HELIOS-A (NCT03759379)	Phase 3, R, PA, OL N=164 adult patients with hATTR amyloidosis with polyneuropathy (vutrisiran, *n* = 122; patisiran reference group, *n* = 42; external placebo, *n* = 77) FU= 16 months	Vutrisiran 25 mg s.c. Q3M) vs patisiran 0.3 mg/kg IV Q3W vs an external placebo group (APOLLO study)	Change from baseline in the modified Neuropathy Impairment Score +7 at 9 months compared with the placebo group of the APOLLO phase 3 study (external placebo group) at month 9	Vutrisiran significantly improved multiple disease-relevant outcomes versus external placebo, with an acceptable safety profile. The 9-month endpoints will be analysed at 18 months with the addition of other secondary endpoints
Diuretics				
ADVOR study (NCT03505788)	Phase 4, R, DB, PA N=519 Acute decompensated HF on ≥40 mg of furosemide, signs of volume overload and BNP>250 pg/mL	Acetazolamide (500 mg OD) or placebo added to standardized i.v. loop diuretics (at a dose equivalent to twice the oral maintenance dose). The	Successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy	The addition of acetazolamide to loop diuretic therapy resulted in a greater incidence of successful decongestion (42.2% vs 30.5%; P<0.001). Acetazolamide treatment was associated with higher cumulative urine output and natriuresis. The incidence of worsening

		intervention continued for 3 days or until the time of decongestion		kidney function, hypokalemia, hypotension, and adverse events was similar in the two groups.
Glucose-lowering drugs				
SURMOUNT-1 (NCT04184622)	Phase 3, DB, R, PC N=2539 with a BMI of ≥30, or ≥27 and at least one weight-related complication, excluding diabetes FU=72 weeks	Tirzepatide 5 mg, 10 mg, or 15 mg once weekly or placebo	Percentage change in weight from baseline and a weight reduction of ≥5%	Tirzepatide provided substantial and sustained reductions in BW vs placebo (-15.0%, -19.5% and -20.9% vs -3.1%, respectively). 50% and 57% of participants in the 10-mg and 15-mg groups had a reduction in body weight ≥20% (3% with placebo; all P<0.001)
SURPASS-3 MRI (NCT03882897)	Phase 3, R, OL, PG N=502 with T2DM, BMI ≥25 kg/m^2, stable weight, insulin-naive, on treatment with metformin alone or in combination with a SGLT2I for at least 3 months before screening FU: 52 weeks	Tirzepatide: 5, 10 0r 15 mg s.c. once weekly or s.c. injection once per day of titrated insulin deglude	Change from baseline in liver fat content (LFC measured by MRI-proton density fat fraction [MRI-PDFF]) at week 52 using pooled data from the tirzepatide 10 and 15 mg groups vs insulin degludec.	The absolute reduction in LFC at week 52 was significantly greater for the pooled tirzepatide 10 and 15 mg groups (-8·09%, SE 0·57) vs the insulin degludec group (-3·38%, 0·83). The reduction in LFC was significantly correlated (P≤0·0006) with baseline LFC, reductions in VAT, ASAT and body weight in the tirzepatide groups.
SURPASS-5 (NCT04039503)	Phase 3, R, DB, PA N=475 with T2DM inadequately controlled on insulin glargine with or without metformin FU=40 weeks	Tirzepatide: 2.5, 5, 10 or 15 mg once weekly or volume-matched placebo	Mean change from baseline in HbA1c at week 40	Higher percentages of patients treated with tirzepatide vs those treated with placebo had HbA_{1c} less than 7% (85%-90% vs 34%; *P* < .001 for all)

SURPASS J-mono (NCT03861052)	Phase 3, DB, R N=615 adults with T2DM who discontinued oral antihyperglycemic monotherapy or were treatment-naïve FU=52 weeks	Tirzepatide 5 mg, 10 mg, or 15 mg once weekly or dulaglutide (0·75 mg once per week)	Mean change in HbA_{1c} from baseline at week 52 measured in the modified intention-to-treat population	Tirzepatide was superior compared with dulaglutide for glycaemic control and reduction in bodyweight.
Hypertrophic cardiomyopathy				
VALOR-HCM (NCT04349072)	Phase 3, R, DB, PC N=112 with symptomatic oHCM (NYHA Class III-IV or NYHA Class II with exertional syncope or near syncope) who meet guideline criteria for septal reduction therapy (SRT)	16-week placebo-controlled period, a 16-week treatment with mavacamten; and a 96-week long-term extension period where all patients will continue to receive mavacamten	Composite of the number of patients who decide to proceed with SRT prior to or at week 16 and the number of patients who remain SRT-guideline eligible (LVOT gradient of ≥50mmHg and NYHA Class III-IV or Class II with syncope) at Week 16 in the mavacamten group compared with the placebo group	In oHCM patients with intractable symptoms, after 32 weeks of treatment with mavacamten showed sustained reduction in the proportion proceeding to SRT or remaining guideline eligible, with similar effects observed in patients crossed over from placebo after 16 weeks.
Lipid-lowering drugs				
FOURIER-OLE (NCT03080935)	Phase 3, R, OL N=6635 patients with ASCVD and LDL-C ≥70 mg/dL completing the FOURIER trial (3355 randomized to evolocumab and 3280 to placebo) FU: 5 years	Evolocumab 120 mg every 2 weeks or 420 mg monthly vs placebo	Incidence of adverse events. Lipid values and major adverse cardiovascular events were prospectively collected.	At 12 weeks, median LDL-C was 30 mg/dL, and 63.2% of patients achieved LDL-C <40 mg/dL on evolocumab. Incidences of serious adverse events, did not exceed those for placebo-treated patients during the parent study and did not increase over time.
RACING (NCT03044665)	OL, R, PA, non-inferiority N= 3780 patients with ASCVD (MI, ACS, coronary revascularization and other arterial revascularization	Rosuvastatin 10 mg QD with ezetimibe 10 mg QD vs high-intensity statin monotherapy (rosuvastatin	3-year composite of CV death, major CV events or nonfatal stroke , in the intention-to-treat population with a non-inferiority margin of 2.0%	The primary endpoint occurred in 9·1% in the combination group (CG) and 9.9% in the high-intensity statin monotherapy group (MG). LDL-C levels <70 mg/dL at

	procedures, ischemic stroke, or PAD FU: 3 years	20 mg QD)		1-3 years were observed in 72-75% of patients in the CG, and 55-60% MG (all p<0·0001). Discontinuation or dose reduction of the study drug by intolerance was observed in 4·8% and 8·2%, respectively (p<0·0001)
Polypill				
SECURE (NCT02596126)	Phase 3, R, PA, OL N=2,499 with previous MI	Cardiovascular polypill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) or usual care for 36 months	CV, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization	Treatment with this polypill within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse CV events than usual care
SGLT2 inhibitors				
DELIVER (NCT03619213)	Phase 3, R, DB, PC N=6263 with HF and LVEF >40% and NT-proBNP ≥300 pg/mL or ≥600 pg/mL FU: 2.3 years	Dapagliflozin (10 mg QD) or matching placebo, in addition to usual therapy	Composite of worsening HF (defined as either an unplanned hospitalization for HF or an urgent visit for HF) or cardiovascular death, as assessed in a time-to-event analysis	The primary outcome occurred less in the dapagliflozin than in the placebo group (16.4% vs 19.5%; P<0.001). Worsening HF (11.8% vs 14.5% HR, 0.79; 0.69-0.91), CV death (7.4% vs 8.3%; HR, 0.88; 0.74-1.05) and total events and symptom burden were lower in the dapagliflozin group than in the placebo group.

References are presented in Supplementary material online, Table S1.

Acronyms. ADVOR: Acetazolamide in Decompensated Heart Failure With Volume OveRload. AXIOMATIC-SSP: Antithrombotic Treatment With Factor XIa Inhibition to Optimize Management of Acute Thromboembolic Events for Secondary Stroke Prevention. DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure. FOURIER: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk. FOURIER-OLE: FOURIER Open-Label Extension. HELIOS.A: HELIOS-A: A Study of Vutrisiran (ALN-TTRSC02) in Patients With Hereditary Transthyretin Amyloidosis. INVICTUS: INVestIgation of rheumatiC AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies. PACIFIC-AF: Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation. PACIFIC-AMI; Study to Gather Information About the Proper Dosing and Safety of the Oral FXIa Inhibitor BAY 2433334 in Patients Following an Acute Heart Attack. PACIFIC-Stroke: Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke. RACING: RAndomised Comparison of Efficacy and Safety of lipid lowerING with statin mono-therapy versus statin–ezetimibe combination for high-risk cardiovascular disease. SECURE: Secondary Prevention of Cardiovascular Disease in the Elderly Trial. SURMOUNT-1; A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight. SURPASS; A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes. VALOR-HCM: A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy.

Abbreviations. AC: active-controlled. ACS: acute coronary syndrome. ASAT: abdominal subcutaneous adipose tissue. BARC: Bleeding Academic Research Consortium. CI: confidence interval. CVD: cardiovascular disease. DB: double-blind. HbA1c: glycated hemoglobin. HR: hazard ratio. MI: myocardial infarction. MRI: magnetic resonance imaging. MRI-PDFF: MRI-proton density fat fraction. OL: open-label. NT-proBNP: N-terminal pro B-type natriuretic peptide. PA: parallel assignment. PAD: peripheral artery disease. PC: placebo-controlled. PCI: Percutaneous coronary intervention. PG: parallel-group. Q3M: every 3 months. R: randomized. TIA: transient ischemic attack. VAT: volume of visceral adipose tissue.

Table 2. Pharmacokinetic properties of mavacamtem, tirzepatide and vutrisiran

Drug (route of administration))	F (%)	T_{max} (h)	PPB (%)	Vd (L/kg)	Drug metabolism	$t_{½}$ (h)	Renal Excretion (%)	Dose (mg)
Mavacamten (oral)	80	1	98	9.5	CYP2C19 (74%), CYP3A4 (18%) and CYP2C9 (8%)	6-9 days*	85	2.5-15 QD
Tirzepatide (s.c.)	80	8-72	99	0.14	Proteolytic cleavage of the peptide backbone, β-oxidation of the C20 fatty acid moiety, and amide hydrolysis	5 days	0*	2.5-15 qWeek
Vutrisiran (s.c)		4 (1-12)	80	0.14	Endo- and exonucleases to short nucleotide fragments	2-6	20*	25 mg once every 3 months

Abbreviations. CYP: cytochrome P450. F: oral bioavailability. H: hours. i.v.; intravenous. PPB: plasma protein binding. s.c.: subcutaneous. $t_{1/2}$: drug half-life.T_{max}: time to peak plasma levels. Vd: volume of distribution. *: renal excretion without biotransformation (up to 23 days in CYP2C19 poor metabolizers)

Table 3. Factor XI inhibitors in phase 2 and 3 clinical trials

Type of drug	Drug	Mechanism of action	Administration route	Population, Comparator (Acronym, NCT)
Antisense oligonucleotides	Fesomersen (IONIS-FXI-L_{Rx}/ISIS 416858/ BAY2306001)	Inhibits FXI mRNA	s.c. (weekly)	• ESKD on chronic hemodyalisis vs placebo (NCT02553889; EMERALD, NCT03358030)** • TKA vs enoxaparin (NCT01713361)**
	FXI-LICA (*BAY2976217*)	Same RNA sequence as IONIS-FXI_{RX} conjugated with GalNAc		• ESRD on hemodialysis (RE-THINc, ESRD (NCT04534114)**
Monoclonal antibodies	Abelacimab (MAA868)	Binds and inhibits FXI and FXIa	s.c. (monthly)	• AF vs rivaroxaban (AZALEA-TIMI 71, NCT04755283)** • CAT vs apixaban (ASTER, NCT05171049)*** or dalteparin (MAGNOLIA, NCT05171075)*** • Postoperative VTE after TKA vs enoxaparin (EudraCT number, 2019-003756-37)**
	Osocimab (BAY 1213790)	Binds and inhibits FXIa	i.v./s.c. (monthly)	• ESKD on chronic hemodyalisis vs placebo (CONVERT, NCT04523220)** • Postoperative VTE after TKA vs enoxaparin or apixaban (FOXTROT, NCT03276143)**
	Xisomab 3G3 (AB023)	Binds FXI and blocks its activation by FXIIa	i.v. (single dose)	• ESKD on chronic hemodyalisis vs placebo (NCT03612856)** • Prevention of CAT in patients with cancer receiving chemotherapy (NCT04465760)**

	MK-2060	Binds and inhibits FXIa	i.v. once a week	• ESRD receiving hemodyalisis (NCT05027074)**
	REGN9933	Binds and inhibits FXIa	i.v.	• TKA vs enoxaparin and apixaban (NCT05618808)**
Small molecules	Asundexian (BAY 2433334)	Binds and inhibits FXIa	Oral, daily	• AF vs apixaban (PACIFIC-AF, NCT04218266)** • Post-AMI vs placebo (PACIFIC-AMI, NCT04304534)** • Brain infarcts and recurrent symptomatic ischemic stroke vs DAPT (PACIFIC-STROKE, NCT04304508)**
	Milvexian (BMS-986177/JNJ-70033093)	Binds and inhibits FXIa	Oral, daily	• TKA vs enoxaparin (AXIOMATIC-TKR, NCT03891524)** • Post-acute ischemic stroke or high-risk transient ischemic attack vs SAPT/DAPT (LIBREXIASTROKE, NCT05702034)*** • Stroke prevention in patients receiving aspirin and clopidogrel (AXIOMATIC-SSP, NCT03766581)**

** Phase 2 clinical development. *** Phase 3 clinical development

Abbreviations. AMI: acute myocardial infarction. AF: atrial fibrillation. CAT: cancer-associated thromboembolism. CRT: catheter-related thrombosis in cancer patients. DAPT: dual antiplatelet therapy (aspirin plus clopidogrel). ESKD: end-stage kidney disease. F: coagulation factor. i.v.: intravenous. mRNA: messenger RNA. SAPT: single antiplatelet therapy. s.c.: subcutaneous. TKA: total knee arthroplasty. VTE: venous thromboembolism