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Review

Exploring the potential of soluble guanylyl cyclase stimulators and activators in heart failure

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ABSTRACT

Heart failure (HF) is a life-threatening disease characterized by substantial morbidity and mortality. Yet despite recent advances, prognosis remains poor. Cyclic guanosine 3′,5′-monophosphate (cGMP) mediates a wide range of physiological processes in various cell types. Its deficiency has been implicated in numerous pathological cardiovascular diseases, including HF, pulmonary hypertension (PH), and kidney disease. Therefore, restoring and enhancing the nitric oxide (NO)–soluble guanylyl cyclase (sGC)–cGMP signalling pathway appears to have far-reaching therapeutic potential.

The discovery of sGC stimulators and activators marked a milestone in the field of NO–sGC–cGMP pharmacology, enabling NO-independent and long-acting enhancement of cGMP signalling without the formation of NO-derived radicals. Over a decade ago, the sGC stimulator riociguat was approved for the treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). More recently, the sGC stimulator vericiguat was approved for symptomatic chronic HF. A number of sGC activators are currently being investigated for the treatment of chronic kidney diseases.

This review summarizes the evidence for NO–sGC–cGMP signalling in the regulation of cardiovascular and cardiac function, focusing on preclinical and clinical evidence for sGC stimulators and sGC activators in HF subtypes. Promising results have been observed in clinical trials of HF with reduced ejection fraction (HFrEF),

Abbreviations: ACF, aortocaval fistula; ACEi, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; AHF, acute heart failure; AHFS, acute heart failure syndromes; ANG II, angiotensin II; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CAD, coronary artery disease; CAS, coronary artery spasm; cGMP, cyclic guanosine 3′,5′-monophosphate; CHD, congenital heart disease; CHF, chronic heart failure; cGK (also PKG), cGMP-dependent protein kinase; CI, confidence interval; CKD, chronic kidney disease; cmfKO, CMF-specific cGKI knockouts; CNG, cyclic nucleotide–gated (cGMP-regulated) cation channel; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; CV, cardiovascular; Dahl SS, Dahl salt-sensitive; dTGR, double transgenic rats; ECM, extracellular matrix; EF, ejection fraction; eNOS, endothelial nitric oxide synthase; ESC, European Society of Cardiology; FCAVS, fibrocalcific aortic valve stenosis; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; GTP, guanosine-5′-triphosphate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HTN, hypertension; IHD, ischaemic heart disease; INOCA, ischaemia with non-obstructive coronary arteries; I/R, ischaemia/reperfusion; LAD, left anterior descending artery; L-NAME, N-nitro-L-arginine methyl ester (NOS inhibitor); LPS, lipopolysaccharide; LV, left ventricle; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; mPAP, mean pulmonary artery pressure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NO, nitric oxide; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension after congenital heart disease correction; PDE, phosphodiesterase; PDEi, phosphodiesterase inhibitor; pGC, particulate guanylyl cyclase; PH, pulmonary hypertension; Postn+ CMF, periostin-positive myofibroblasts; RAAS, renin angiotensin aldosterone system; RBC, red blood cell; ROS, reactive oxygen species; RRR, relative risk reduction; RV, right ventricle; SAC, suprarenal aortic constriction; sGC, soluble guanylyl cyclase; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SHR, spontaneously hypertensive rats; SHR-SP, stroke-prone spontaneously hypertensive rats; SPF, specific pathogen-free; TAC, transverse aortic constriction; TGF-β1, transforming growth factor beta 1; TGR, transgenic rat; VO_2, oxygen consumption; UUO, unilateral ureteral obstruction..

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but not in clinical trials of HF with preserved ejection fraction (HFpEF). Further studies are needed to determine the precise mechanisms of action of sGC agonists in HF and associated cardiorenal diseases to fully leverage their therapeutic potential and address the challenges of implementing these agents in routine clinical practice.

1. Introduction

Heart failure (HF) is a heterogenous clinical syndrome characterized by high morbidity and mortality, and its socioeconomic burden continues to rise worldwide, particularly in ageing populations [1]. HF is categorized into specific phenotypes based on left ventricular ejection fraction (LVEF). Patients with LVEF below 40 % are classified as having heart failure with reduced ejection fraction (HFrEF), whereas those with LVEF above 50 %, who exhibit HF symptoms and signs along with evidence of structural and/or functional cardiac abnormalities and/or elevated natriuretic peptides (NPs), are classified as heart failure with preserved ejection fraction (HFpEF). According to the latest European Society of Cardiology (ESC) guidelines, patients with LVEF between 41 % and 49 % have mildly reduced LV systolic function, defined as heart failure with mildly reduced ejection fraction (HFmrEF), and may benefit from therapies similar to those used in HFrEF [2]. HF can also be categorized by presentation into acute heart failure (AHF) and chronic heart failure (CHF).

Current guideline-directed medical therapy (GDMT) for acute and chronic HF consists of four core classes of drugs: (1) angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or angiotensin receptor–neprilysin inhibitors (ARNIs), (2) mineralocorticoid receptor antagonists (MRAs), (3) beta-blockers, and (4) sodium glucose co-transporter 2 inhibitors (SGLT2i) [3]. Despite these established therapies, a substantial unmet medical need for the prevention and adequate treatment of HF remains, as its prevalence continues to steadily increase worldwide, accompanied by high residual morbidity and mortality [1].

Since the 1998 Nobel Prize was awarded to Furchgott, Murad, and Ignarro for the discovery of nitric oxide (NO) as a signalling molecule, extensive research has highlighted the critical role of NO signalling in maintaining cardiovascular (CV) and renal homeostasis [4]. The classical NO–sGC–cGMP signalling cascade starts in the intact endothelium, where hormonal or physical stimuli activate endothelial nitric oxide synthase (eNOS) to produce NO, which further diffuses to surrounding tissues (Fig. 1). Subsequently, NO binds to soluble guanylyl cyclase (sGC), its receptor, a heterodimeric protein composed of an α-subunit and a β-subunit, the latter carrying the haem group (HNOX domain) [5–7]. NO binding induces a conformational change in sGC, which catalyses the conversion of guanosine-5′-triphosphate (GTP) to cGMP. As a second messenger, cGMP regulates multiple effector molecules, including cGMP-dependent protein kinase (PKG/cGK), cGMP-regulated cation channels (CNGs), and cGMP-regulated phosphodiesterases (PDEs), thereby mediating diverse cellular effects [8] (Fig. 1). Notably, PKG activation lowers intracellular calcium, promoting vasodilation and blood pressure (BP) reduction, improving vascular function, providing renal and neuroprotection, and inhibiting inflammation, fibrosis, and proliferation [5,9–12]. In the heart, cGMP could also influence myocardial contractility and relaxation but does not act as direct inotrope [11,13–16]. NO simultaneously benefits blood vessels and heart muscle performance, working together to reduce the energy the heart needs to pump effectively. By dilating blood vessels and reducing the late-systolic pressure waves that reflect back from the arteries, NO lowers the resistance the left ventricle (LV) must overcome during contraction. At the same time, it enhances the heart's metabolic efficiency by modulating mitochondrial respiration, improving oxygen use, and optimizing energy substrate metabolism [16,17].

Currently several pharmacological strategies for CV disorders aim to

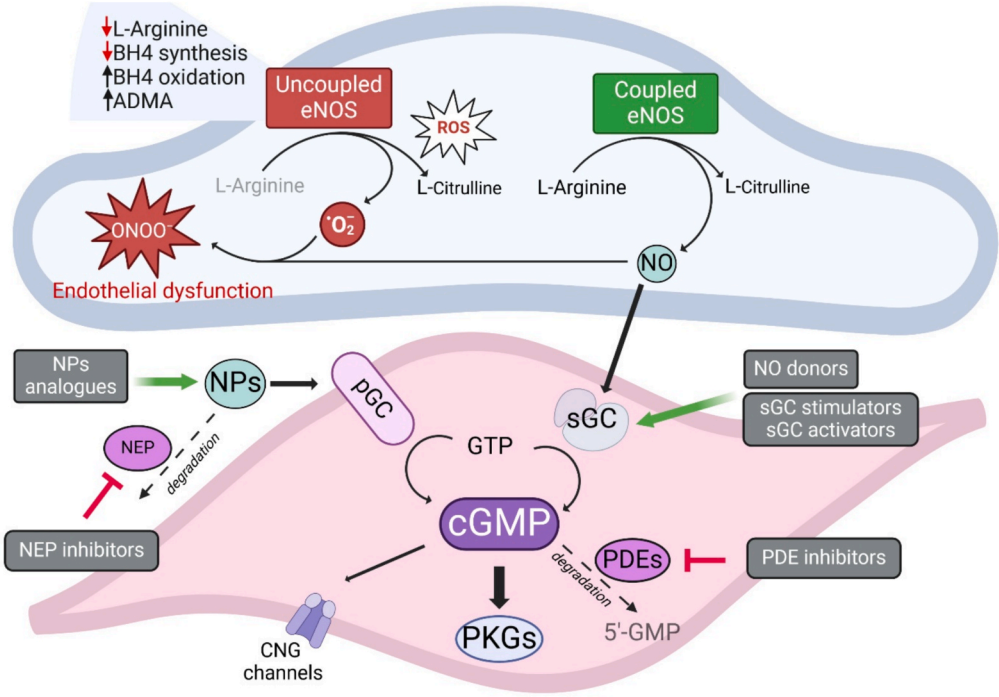

Fig. 1. The classical NO–sGC–cGMP signalling pathway in physiological and pathological contexts, with examples of pharmacological interventions that enhance cGMP production. *Abbreviations: 5′GMP, guanosine monophosphate; ADMA, asymmetric dimethylarginine; BH4, tetrahydrobiopterin; cGMP, cyclic guanosine 3′,5′-monophosphate; CNG, cGMP-regulated cation channels; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate; NEP, neprilysin; NO, nitric oxide; NPs, natriuretic peptides; PDEs, phosphodiesterases; pGC, particulate guanylyl cyclase; PKG, cGMP-dependent protein kinase; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase.*

increase NO and/or cGMP production. The first drug targeting the NO–sGC–cGMP pathway, commonly known as nitroglycerine was used to treat angina pectoris as early as the late 19th century [18]. The class of NO donors is a heterogeneous group of compounds from different chemical classes, each with distinct pharmacodynamic and pharmacokinetic profiles, but sharing the ability to release NO enzymatically or non-enzymatically [4,19–22]. Recently, more attention is given to inorganic nitrates and nitrites (including also dietary sources like beetroot juice), since an alternative pathway for NO generation was discovered [23] and is currently intensively investigated [22,24–26]. Studies show that nitrate and nitrite, regardless of the source, can be recycled in the blood and/or tissues to form NO (and other bioactive nitrogen oxides) complementing the eNOS-dependent pathway [23].

In addition to the NO–sGC pathway, cGMP can be generated by NPs binding to their membrane-bound, particulate guanylyl cyclase (pGC) receptors [27–31]. Finally, phosphodiesterase inhibitors (PDEi) can enhance cGMP signalling, by preventing cGMP degradation. They are used for the management and treatment of erectile dysfunction, pulmonary arterial hypertension (PAH) or lower urinary tract symptoms [32–34].

More recently, the discovery of NO-independent sGC stimulators and sGC activators marked a milestone in the field of NO-sGC-cGMP pharmacology. By directly stimulating sGC, these agents enable cGMP production even under conditions of endothelial dysfunction and low or impaired NO production. Unlike NO donors, sGC stimulators and activators do not trigger the production of reactive oxygen species (ROS) and possess favourable physiochemical properties, allowing stable, chronic oral treatment. Importantly, sGC stimulators and sGC activators increase cGMP production not only independently of NO, but also act synergistically and additively to endogenous NO, respectively [35–37]. These unique mode of actions of sGC stimulators and sGC activators allowed for the first time a non-NO dependent and long-lasting enhancement of cGMP signalling which allow to target diseases like HF.

In this review, we first describe the mechanisms of action of sGC stimulators and sGC activators, followed by a current overview of the steadily growing number of preclinically or clinically used compounds. Consecutively, we summarize available data with sGC stimulators and sGC activators in preclinical models of HF and in clinical studies across different HF populations. Finally, the clinical outcomes and the therapeutic use of sGC stimulators and sGC activators in HF are critically discussed to also address the question for which HF patients sGC stimulators and sGC activators could be beneficial.

2. Overview of sGC stimulators and activators – Mechanism of action and nomenclature

As described above, both sGC stimulators and activators can increase sGC activity and trigger cGMP production independently of NO [5]. sGC stimulators specifically target the native, ferrous (Fe^{2+}) haem-containing form of sGC, binding allosterically to the NO–haem-binding domain. They can therefore be considered positive allosteric modulators of sGC activity. sGC stimulators exhibit a dual mode of action and binding of the sGC stimulator leads to a) an NO-independent increase of cGMP production and b) to a stabilizing of the NO–sGC binding therefore enhancing the activity of endogenous NO in a synergistic manner [5,35,38].

In contrast to sGC stimulators, sGC activators bind to the haem-free (apo) form of sGC at the NO-binding site. They can also activate the oxidized ferric (Fe^{3+}) form of sGC by facilitating haem displacement and mimicking the NO-bound haem entity. Therefore, sGC activators can trigger cGMP production under oxidative stress by targeting NO-unresponsive form of sGC. Like sGC stimulators also sGC activators lead to an NO-independent activation of sGC. In addition, sGC activators increase cGMP in an additive manner to endogenous NO [36]. Since the discovery of sGC stimulators and sGC activators was overlapping and to distinguish these differentiated binding and mode of actions, these two compound classes were historically termed sGC stimulators, which are NO-independent but haem-dependent, whereas sGC activators are NO-independent and haem-independent (Fig. 2).

2.1. Heme-dependent sGC stimulators

The discovery of the first sGC stimulators, a benzyl indazole compound, called **lificiguat (YC-1)** and **BAY 41–2272** was made almost two decades ago within Bayer Pharmaceuticals and in Taiwan at the Taiwan University and Yung Shin Pharmaceuticals [39–43]. However, these early compounds like **BAY 41–2271**, **YC-1** or **BAY 41–8543** were not suitable for further clinical development and intensive research and discovery efforts finally lead to the development of **riociguat (BAY 63–2521)** [44]**. Riociguat** became the first sGC stimulator to enter controlled late-stage clinical trials and was approved for pulmonary hypertension (PAH, CTEPH) [45–47]. However, pharmacokinetics of **riociguat** requires dosing three times daily, which is not favourable for conditions like HF [5]. Therefore, intense research efforts lead to the discovery of other sGC stimulators also with improved kinetic profiles and longer half-life which were or are in clinical development: **nelociguat (BAY 60–4552)**, **vericiguat (BAY 1021189)** [38,48–51], **praliciguat (IW-1973)** [52–54]**, olinciguat (IW-1701)** [55], and **zagociguat (CY6463)** [56–58]. Recently, new generation sGC stimulators, including **BAY 1165747 (BAY 747)** [59], **HEC-95468** [60], and **SGC003F** [61], has been profiled for HF and hypertension (HTN), while **frespaciguat** (**MK-5475)** [62] represents the first sGC stimulator developed for inhalative administration. To date, only **riociguat** (Adempas®) and **vericiguat** (Verquvo®) are approved for the use in patients.

2.2. Heme-independent sGC activators

One of the first identified sGC activators was **cinaciguat (BAY 58–2667)** [63]**,** which was evaluated in a broad variety of preclinical disease models, including chronic renal failure, pulmonary arterial hypertension (PAH), CHF, and myocardial infarction (MI) [64,65] before advancing to clinical trials. In patients with acute decompensated HF, **cinaciguat** demonstrated dose-dependent reductions in preload and afterload, decreased systemic vascular resistance, and increases in cardiac output (CO) and cardiac index. However, further clinical development was halted due to a high incidence of hypotension [66–70].

Other sGC activators, **HMR1766** and **S3448** were identified [71]. **HMR1766** received the INN name **ataciguat (HMR1766)** and after preclinical evaluation including multiple animal models of CV and renal diseases [36,72–75] was also evaluated in several clinical trials. However, none of these initial sGC activators were approved.

Currently, second-generation sGC activators are under extensive preclinical and clinical investigation, including **runcaciguat** (**BAY 1101042**) [76], **avenciguat** (**BI 685509**) [77,78], and **nurandociguat** (**BAY 3283142**; NCT06522997) for CV and renal diseases. **Mosliciguat** (**BAY 1237592**) which could be applied via inhalation is also in clinical development [79,80].

2.3. Preclinical evidence for the use of sGC agonists in HF

Preclinical animal studies have evaluated the use of sGC stimulators and activators in CV and cardiorenal disease models. These models employ various stimuli that mimic, at least in part, the different aetiologies of HF. However, predicting clinical efficacy in HF patient subpopulations – namely HFrEF, HFmrEF, and HFpEF – remains challenging, as animal models typically reflect only selected aspects of these heterogeneous syndromes. In this section, we review key studies categorized according to the underlying pathophysiological mechanisms of HF.

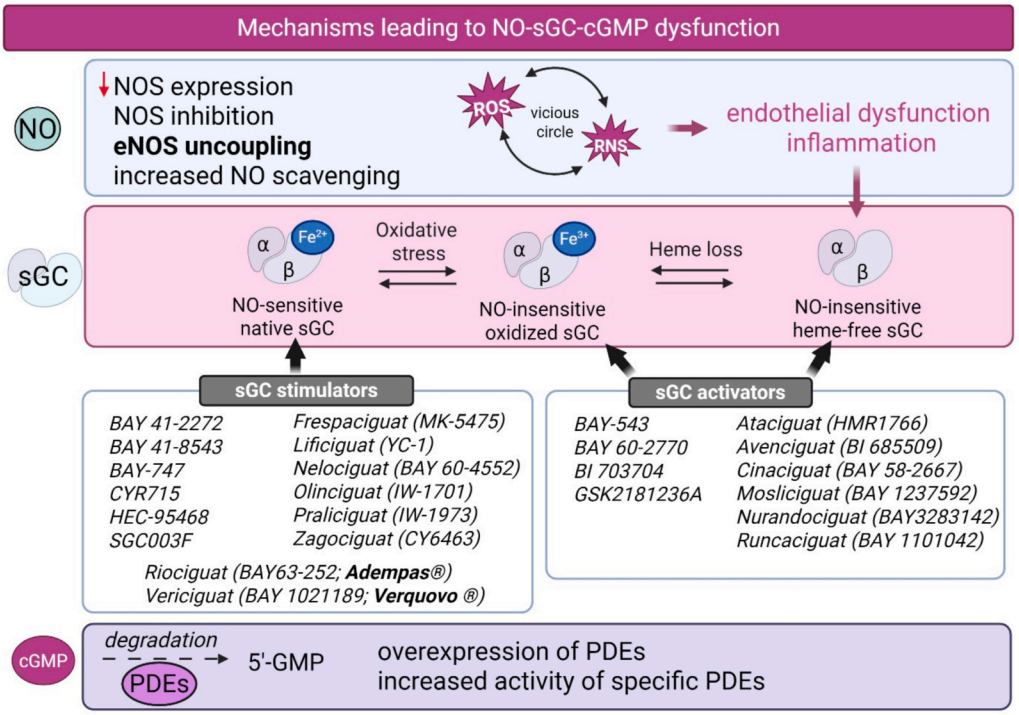

Fig. 2. Dysregulation of the NO–sGC–cGMP signalling pathway and the distinct mechanisms of action of sGC stimulators and activators, with representative examples. *Abbreviations: 5′GMP, guanosine monophosphate; cGMP, cyclic guanosine 3′,5′-monophosphate; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PDEs, phosphodiesterases; RNS, reactive nitrogen species; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase.*

2.3.1. Pressure overload and hypertension-induced HF

Models of pressure overload and HTN-induced HF are used to simulate the haemodynamic stress and pathological remodelling observed in HF patients. Chronic HTN, often driven by neurohormonal dysregulation or vascular alterations, imposes sustained pressure overload on the myocardium, ultimately leading to hypertrophy, fibrosis, and HF [81].

The sGC stimulator BAY 41–2272 attenuated cardiac fibrosis and hypertrophy in L-NAME-treated rats, a model characterized by low NO bioavailability, endothelial dysfunction, and HTN. Similar benefits were observed in angiotensin II (ANG II)-induced hypertensive rats, partly via BP-independent mechanisms [82,83]. In a rat model of hypertensive cardiac disease induced by suprarenal aortic constriction (SAC), **BAY 41–2272** significantly reduced myofibroblast numbers, perivascular and interstitial collagen accumulation, TGF-β1 mRNA, and type 1 collagen in the LV, counteracting the fibrotic remodelling caused by aortic constriction [84]. In spontaneously hypertensive rats (SHR) fed a Western diet – a model reflecting HTN with metabolic syndrome – **BAY 41–2272** prevented HTN development, improved glucose tolerance, restored cardiac inotropy, and improved coronary vasodilation [85].

The sGC stimulator **BAY 41–8543** was tested in heterozygous Ren-2 transgenic rats (RenTGR), bearing an additional renin gene, which were supplemented with L-NAME causing malignant hypertension and endothelial dysfunction. **BAY 41–8543** improved survival and decreased BP [86]. **BAY 41–8543** was also tested in double transgenic rats (dTGRs), an experimental model that partly mimics HFpEF [87]. dTGR, which express human renin and angiotensinogen genes, develop severe HF with diastolic dysfunction and preserved EF, severe systemic HTN, cardiac hypertrophy, fibrosis, inflammation, arrhythmias, cardiac cachexia, pulmonary congestion, and endothelial dysfunction. dTGR are typically characterized by high mortality beginning at 7 to 8 weeks of age. Treatment with the sGC stimulator **BAY 41–8543** strikingly improved survival and cardiac performance of dTGR and also reduced cardiac fibrosis, macrophage infiltration, and gap junction remodelling. Additionally, extensive microarray analysis revealed that **BAY 41–8543** corrected the dysregulated expression of cardiac genes associated with fibrosis, inflammation, apoptosis, oxidative stress, and ion channel function. **BAY 41–8543** also decreased BP and improved endothelium-dependent vasorelaxation of dTGR resistance vessels [87,88].

These results align with a recent study in RenTGR supplemented with L-NAME, where oral **BAY 41–8543** markedly reduced mortality and cardiac damage [89]. Echocardiography revealed significant improvement in LV systolic function and normalization of CO, likely driven by reduced afterload secondary to substantial BP lowering with high-dose **BAY 41–8543** [89]. The effects of lower doses need to be examined in future studies.

The sGC stimulator **nelociguat** (**BAY 60–4552**) was administered to stroke-prone SHR (SHR-SP) fed a high-salt/fat diet [90], a model particularly relevant for therapies targeting HTN alongside metabolic and CV disorders such as HFpEF. **Nelociguat** improved survival even at low doses and offered partial protection against chronic high-salt/fat diet-induced end-organ damage [90]. The CV effects of the sGC stimulator **riociguat** were evaluated in hypertensive RenTGR treated with L-NAME and in rats after 5/6 nephrectomy. In both models, **riociguat** improved survival, normalized BP, and significantly reduced cardiac and renal interstitial fibrosis in the high-renin model [91,92].

In a model of secondary PH due to left heart disease induced by transverse aortic constriction (TAC) in C57BL/6N mice, **riociguat** (10 mg/kg/day) administered for two weeks (after six weeks of TAC) did not reduce LV hypertrophy or improve LV systolic function, despite significantly ameliorating secondary PH and improving RV function [93]. In contrast, Rüdebusch *et al.* demonstrated in the same model that prolonged **riociguat** treatment (five weeks) reversed pathological cardiac remodelling [94]. Specifically, **riociguat** improved LVEF, decreased LV hypertrophy (expressed as the LV-to-body weight ratio), and reduced myocardial fibrosis. RNA sequencing further revealed that **riociguat** downregulated genes responsible for myocardial stress and remodelling, including *Nppa*, *Nppb*, *Myh7*, and collagen [94].

An extensive series of *ex vivo* and *in vivo* studies with the sGC stimulator **praliciguat** demonstrated anti-inflammatory, renoprotective,

and antifibrotic activity across multiple preclinical models, including normotensive and hypertensive rats (SHR), Dahl Salt-Sensitive (Dahl SS) rats, an acute mouse model of lipopolysaccharide (LPS)-induced inflammation, and the rat unilateral ureteral obstruction (UUO) model of renal fibrosis [52]. In addition, **praliciguat** exerted beneficial effects in Dahl SS rats on a high-salt diet [95]. These rats develop systemic HTN, HFpEF, and associated features of chronic renal and liver failure.

Preclinical data also support the efficacy of the novel sGC stimulator **vericiguat**, in models of CV disease and end-organ damage. In RenTGR supplemented with L-NAME, **vericiguat** reduced LV and right ventricle (RV) hypertrophy and decreased mortality, accompanied by lower plasma ANP levels, suggesting improved cardiac function [96]. More recently, **vericiguat** was shown to reduce the aortic augmentation index in dogs with resistant HTN, indicating decreased vascular stiffness – a parameter directly correlated to CV mortality and event rates in patients [97]. In mice infused with ANG II, **vericiguat** attenuated LV hypertrophy and fibrosis through BP-independent mechanisms [98]. The authors suggest that **vericiguat** suppressed myocardial oxidative stress via regulation of ERK 1/2 or p38 MAPK signalling, leading to anti-hypertrophic and antifibrotic effects [98]. These pathways merit further investigation to clarify the BP-independent cardio-protective effects of **vericiguat**, which may enable more targeted treatment approaches for different HF subpopulations in the future.

The sGC stimulator **olinciguat (IW-1701)** was investigated in Dahl SS rats fed a high-salt diet. **Olinciguat** treatment reduced cardiac hypertrophy, lung weight, and NT-proBNP levels, indicating a beneficial effect on cardiac function [99]. sGC activators have also been tested in animal models of HTN-induced HF. **Cinaciguat** improved cardiomyocyte function and reduced inflammation and oxidative stress in Dahl SS rats on a high-salt diet [100]. In SHR-SP fed a high-salt/fat diet, higher doses of the sGC activator **GSK2181236A** improved survival, while even low doses attenuated cardiac hypertrophy [90]. **Runcaciguat** improved survival and renal function in RenTGR supplemented with L-NAME (low-NO/high-renin model) and dose-dependently reduced BP [76]. Collectively, these findings highlight the potential of sGC activators in HF. Future head-to-head studies will be important to directly compare the relative benefits of sGC stimulators and sGC activators.

2.3.2. Volume overload models of HF

Volume overload models are essential for studying HF resulting from chronic increases in cardiac preload. The signalling pathways mediating myocardial adaption to volume overload fundamentally differ from those activated by pressure overload [101]. Conditions such as valve regurgitation or arteriovenous shunting impose sustained volume stress on the myocardium, driving eccentric hypertrophy, ventricular dilation, and progressive systolic dysfunction. These models mimic various aspects of human HFrEF, including secondary atrioventricular valve regurgitation, and provide valuable tools for evaluating therapeutic interventions aimed at preventing maladaptive cardiac remodelling [81,102].

Intravenous administration of the sGC stimulator **BAY 41–2272** was evaluated in a canine model of congestive HF induced by rapid ventricular pacing, in comparison to nitroglycerine [103]. **BAY 41–2272** unloaded the heart, increased CO, and preserved the glomerular filtration rate (GFR) without activating the renin–angiotensin–aldosterone system (RAAS) [103]. More recently, it was shown that the treatment with **BAY 41–8543** improved survival in RenTGR with high-output HF induced by aortocaval fistula (ACF), a model that develops cardiorenal syndrome [104]. After two months of treatment, survival remained 50 % in rats treated with BAY 41–8543 compared with only 8 % in untreated controls, while the treatment had only a transient impact on BP [104].

In a model of chronic mitral regurgitation surgically induced in Sprague-Dawley rats, **vericiguat** preserved cardiac function and structural remodelling [105]. It also improved mitochondrial quality by attenuating ROS production and exhibited antifibrotic properties. All of the above models also result in substantial renal damage and decline in kidney function. Consequently, renal endpoints were also investigated in most of these studies. Overall, treatment with sGC stimulators or sGC activators reduced proteinuria and kidney damage across various chronic kidney disease (CKD) models. Notably, preclinical studies provide widespread evidence for the efficacy of the sGC activator **runcaciguat** in acute and chronic CKD models of various aetiologies [106,107], laying the foundation for clinical testing that yielded positive outcomes in a phase 2 study in CKD patients [108]. However, this review focuses on HF, and a detailed discussion of CKD studies is beyond its scope.

2.3.3. Ischaemic heart disease

Ischaemic heart disease (IHD), also referred to as coronary artery disease (CAD), remains a major global health burden with persistently high mortality and morbidity [109]. Almost 70 % of all HF cases can be attributed to underlying CAD [110]. Therapeutic enhancement of the NO–sGC–cGMP pathway has long been proposed as a promising treatment strategy for ischaemic disorders, including myocardial ischaemia and reperfusion (I/R) injury [111]. Both sGC stimulators and sGC activators could relax coronary arteries ex vivo across different species [112–115]. Beyond its vasodilatory effects, NO is a key regulator of platelet function and vascular homeostasis, exhibiting antiaggregatory properties [116,117].

Ample preclinical evidence points to the therapeutic potential of sGC agonists in IHD. The sGC stimulator **vericiguat** ameliorated myocardial I/R injury in mice by improving microcirculation [118] and showed similar protective effects in a pig model [119]. Consistently, **riociguat** attenuated I/R-induced myocardial damage in rats [120] and improved donor organ function in a rat model of I/R injury following heterotopic transplantation [121]. In a post-MI rat model induced by coronary artery ligation – leading to HFrEF – treatment with the sGC stimulator **olinciguat (IW-1701)** exhibited a trend towards increased EF [99].

Interestingly, sGC stimulation with **CYR715** in red blood cells (RBCs) from patients with type 2 diabetes increased cGMP export from RBCs and activated cardiac PKG, attenuating I/R injury [122]. Additionally, perfusion of isolated hearts subjected to I/R injury with extracellular supernatant from hypoxia-exposed mouse RBCs improved post-ischaemic cardiac function and reduced infarct size [123], suggesting that sGC stimulation could be cardioprotective *via* a paracrine mode of action.

In addition to sGC stimulators, sGC activators also demonstrated cardio-protective effects in animal models of IHD. **Ataciguat** was tested in a coronary ligation-induced MI model in Wistar rats, where it promoted vasorelaxation, improved vasomotor function, and reduced platelet activation [75]. In another study using the same model, **ataciguat** reduced LV diastolic filling pressure and pulmonary congestion, augmented LV contractile function, improved diastolic stiffness (independent of BP), and attenuated cardiac fibrotic remodelling [124].

In mice and rabbits, pre-treatment with **cinaciguat** caused a robust reduction in the infarct size suggesting that it might represents a powerful protection against I/R injury in the heart [70,125]. Frankenreiter *et al.* demonstrated that ischaemic post-conditioning with **cinaciguat** significantly reduced the extent of myocardial infarction in control mice, but not in mice with cardiomyocyte-specific deletion of NO-GC [126]. These findings highlight the critical role of the NO–sGC–cGMP pathway for cardio-protective-mediated signalling following acute MI [127]. In a rat MI model induced by isoproterenol, pre-treatment with **cinaciguat** improved histopathological lesions, cardiac performance, and relaxation, while also reducing oxidative stress and downregulating expression of cyclooxygenase 2, TGF-β, and β-actin genes [128]. The same study further demonstrated cardio-protective effects of post-ischaemic **cinaciguat** treatment in a canine model of global I/R during cardiopulmonary bypass with hypothermic cardiac arrest [128].

Pre-treatment with the sGC activator **BAY 60–2770** protected

against cardiac I/R injury, reduced infarct size, and improved LV function as assessed by echocardiography [129]. **BAY 60–2770** was also tested *ex vivo* and *in vivo* as a potential treatment for ischaemia with non-obstructive coronary arteries (INOCA) caused by coronary artery spasm (CAS) [130]. In experimental models of vasospasm, **BAY 60–2770** exhibited antispastic activity in coronary arteries, suggesting a potential therapeutic role of sGC activators in INOCA [130].

The sGC activator **GSK2181236A** was assessed in SHR-SP rats fed a high-salt/fat diet. Even at low doses, it attenuated cardiac hypertrophy, while higher doses improved survival [90]. However, pre-treatment with **GSK2181236A** did not confer cardio-protection in Sprague-Dawley rats during coronary artery I/R injury [90].

Overall, these preclinical findings indicate that further clinical studies are warranted to explore the effects of sGC modulation during acute myocardial ischaemia and to investigate the therapeutic potential of sGC agonists in this patient population [111].

2.3.4. Chemotherapy-induced cardiotoxicity

Doxorubicin is still among the most effective and widely used anticancer drugs. However, anthracycline-induced cardiotoxicity and the consequent development of HF, still represent a challenge for long term successful outcomes [131,132]. Doxorubicin induces oxidative stress through redox cycling and by increasing iron accumulation, while peroxides in mitochondria react with NO to produce ROS, all of which can reduce NO bioavailability and impair the NO–sGC–cGMP pathway. Restoring NO-cGMP signalling is therefore hypothesized to be cardioprotective and mitigate doxorubicin-induced cardiotoxicity [133–135].

Oral treatment with the sGC stimulator **BAY 41–8543** improved survival and cardiac function of RenTGR with chemotherapy-induced HFrEF and nephrotic syndrome. HFrEF was induced by doxorubicin at a cumulative dose of 10 mg/kg, administered intravenously once per week for five weeks [136]. Pre-treatment with the sGC activator **BAY 60–2770** also attenuated chemotherapy-induced cardiotoxicity in Sprague-Dawley rats treated with a cumulative doxorubicin dose of 20 mg/kg (three times per week for two weeks) [137]. *In vivo* evaluation demonstrated that **BAY 60–2770** decreased mitochondrial ROS formation and alleviated membrane potential loss, autophagy, and subsequent apoptosis [137].

Zeng *et al.* showed that **vericiguat** mitigated doxorubicin-induced cardiac insufficiency in mice, reversed mitochondrial dysfunction in neonatal rat cardiomyocytes, and suppressed the expression of inflammatory factors [138]. Mechanistically, **vericiguat** alleviates mitochondrial dysfunction and reduces mtDNA leakage into the cytoplasm by upregulating PRKG1, which activates PINK1 and subsequently inhibits the STING/IRF3 pathway, thereby alleviating doxorubicin cardiotoxicity [138]. In a recent study, Chen *et al.* tested **vericiguat** in specific pathogen-free (SPF) male Sprague-Dawley rats and found that it reversed doxorubicin-induced cardiac remodelling and augmented systolic function by alleviating oxidative stress and apoptosis [139].

Taken together, these findings support further studies investigating the long-term survival of animals treated with doxorubicin and the efficacy of sGC stimulators and/or activators in treating established HF.

2.3.5. Antifibrotic and antihypertrophic actions of sGC agonists

sGC activators and stimulators exert antifibrotic and antihypertrophic effects that appear largely independent of BP reduction, highlighting a direct cellular mechanism. The exact antifibrotic mechanisms mediated by cGMP are not yet fully understood; however, several common pathways have been described, including modulation of TGF-β-induced fibroblast-to-myofibroblast differentiation, suppression of TGF-β-induced collagen synthesis and extracellular matrix (ECM) deposition, and inhibition of TGF-β-induced cell proliferation [92,140,141].

In various preclinical models, sGC activators and stimulators demonstrated numerous beneficial antifibrotic effects, including reductions in interstitial and perivascular fibrosis, decreased myofibroblast infiltration, and downregulation of pro-fibrotic gene markers such as TGF-β1, type I collagen, and α-SMA [82–84,91,94,98,140–145].

Recent *in vivo* evidence further supports the antifibrotic role of the NO–cGMP pathway. A novel mouse model lacking cGMP-dependent protein kinase I (cGKI) specifically in periostin-positive myofibroblasts (Postn + CMF) was developed [146]. Postn + CMF have been identified as one of the key effector cells contributing to myocardial fibrosis. These CMF-specific cGKI knockouts (cmfKO) were exposed to ANG II, a well-established trigger of myocardial fibrosis. Despite similar BP responses, cmfKO mice developed greater myocardial fibrosis, hypertrophy, and systolic dysfunction compared to controls, underscoring the essential role of cGKI in limiting myofibroblast activation and protecting cardiac structure and function [146].

In a recent study by Zhang *et al.*, the sGC activator **ataciguat** slowed the progression of valve calcification and dysfunction in a mouse model of fibro-calcific aortic valve stenosis (FCAVS), and it is currently being developed for FCAVS in humans [147].

2.3.6. Summary of the preclinical findings

As demonstrated above, sGC stimulators and activators exhibit significant therapeutic potential in multiple preclinical models of CV diseases. Given the role of impaired NO–cGMP signalling in CV diseases, both sGC stimulators and sGC activators represent promising therapeutic classes due to their unique mode of action in restoring cGMP levels independently of NO.

One of the key mechanisms by which sGC stimulators and activators exert beneficial effects is through lowering BP, achieved through vascular smooth muscle relaxation mediated by cGMP-mediated vasodilation. HTN is considered the most common risk factor for the development of hypertensive heart disease and can exacerbate ventricular remodelling, fibrosis, and the progression of both HFrEF and HFpEF [148]. By reducing afterload, these agents improve CO and LV performance, as demonstrated in numerous models of pressure-overload and HTN-induced HF (Table 1). Importantly, this BP-lowering effect also contributes to improved survival in models of malignant hypertension and volume overload, indirectly relieving cardiac stress and preventing adverse remodelling (Table 1). However, while BP reduction is beneficial in the earlier phases of HF progression, there is a risk of hypotension in patients with already established HF, particularly those with compromised cardiac function [149] who are concurrently receiving other therapies (RAAS inhibitors and beta-blockers) with hypotensive effects.

Beyond haemodynamic improvements, sGC activators and stimulators exert potent antifibrotic and antihypertrophic effects (see paragraph 2.3.5). sGC agonists also improve endothelial function and enhance coronary and systemic vascular responsiveness (Table 1) [75,85,87,88,115,118,124,150,151], which is particularly relevant in HFpEF, where microvascular dysfunction is prevalent. In ischaemic models, both sGC stimulators and activators have been shown to preserve myocardial function and reduce infarct size, likely through improved coronary microcirculation and mitigation of I/R injury (Table 1). These protective effects appear to involve both direct myocardial actions and paracrine signalling, as evidenced by studies using RBC-conditioned media [122,123].

In summary, the preclinical evidence highlights the broad therapeutic potential of sGC stimulators and activators in targeting diverse HF aetiologies – ranging from haemodynamic overload and myocardial remodelling to endothelial dysfunction, oxidative stress, and inflammation, which are key drivers of HF progression. These pleiotropic effects further support their clinical investigation in both HFrEF and HFpEF populations (Fig. 3).

2.4. Clinical evidence for the use of sGC agonists in HF (Table 2)

The most relevant clinical trials investigating sGC stimulators and

Table 1
Sgc stimulators and activators – preclinical evidence in experimental models of hf.

Compound	Experimental model	Main results	Key ref.
sGC stimulators			
BAY 41–2272	CHF induced by rapid ventricular pacing (dogs)	Unloaded the heart, increased CO, preserved GFR	[103]
	High-renin, low-NO model of HTN induced by L-NAME (rats)	Decreased cardiac fibrosis and hypertrophy, BP reduction	[82]
	HTN induced by ANG II infusion (rats)	Ameliorated cardiac remodelling	[83]
	HTN induced by suprarenal aortic constriction (rats)	Attenuation of cardiac fibrosis	[84]
	I/R injury in isolated hearts exposed to reversible left coronary artery occlusion (rats)	Reduced MI size, simultaneous treatment with sGC activator BAY 60–2770 did not further improve efficacy	[212]
	HTN with metabolic syndrome (SHR fed cafeteria diet)	Prevention of HTN development and glucose intolerance, restored cardiac inotropy and coronary vasodilation	[85]
BAY 41–8543	Langendorff preparation (rat heart)	Reduced coronary perfusion pressure with no effect on LV pressure and HR	[213]
	High-renin, low-NO model of HTN induced by L-NAME (RenTGR)	Improved survival, BP reduction, renal protection	[86]
	HTN-induced HF (dTGR)	Improved survival and cardiac performance	[88]
	HF induced by aortocaval fistula (RenTGR)	Improved survival, BP-independent	[104]
	Chemotherapy-induced HFrEF with nephrotic syndrome (RenTGR treated with doxorubicin)	Improved survival and cardiac function	[136]
	malignant HTN (RenTGR supplemented with L-NAME)	Improved survival and LV systolic function, normalization of CO, BP reduction	[89]
Nelociguat BAY 60–4552	Coronary artery, I/R injury (SD rats)	No cardio-protection after pre-treatment	[90]
	HTN in SHR-SP fed a high-salt/fat diet	Improved survival, partial protection against chronic high-salt/fat diet-induced end-organ damage	
Riociguat BAY 63–2521	Malignant HTN in Dahl SS on high-salt diet	Improved survival and systolic heart function, attenuated HTN and cardiac and renal fibrosis	[144]
	High-renin, low-NO model of HTN induced by L-NAME (RenTGR)	Improved survival, normalized BP, CV protection	[91]
	MI induced by ligation of coronary artery (C57/BL6 mice)	Reduced infarct size, long-term preservation of LV systolic function	[120]
	Pressure overload-induced HF by transverse aortic constriction (C57BL/6N mice)	No improvement in LV hypertrophy or function, improvement in PH and RV function	[93]
	I/R injury following heterotopic transplantation (rats)	Decreased I/R injury and improved donor organ function	[121]
	Pressure overload-induced HF by transverse aortic constriction (C57BL/6N mice)	Improved EF of LV, attenuated myocardial fibrosis	[94]
Praliciguat IW-1973	SHR, Dahl SS	Reduced BP and inflammatory cytokine levels, renal protection	[52]
	HTN and cardiorenal failure induced in Dahl SS rats on a high-salt diet	Attenuated cardiorenal damage, reduction in inflammation and fibrosis, BP decrease	[95]
Vericiguat BAY 1,021,189 (MK-1242)	HTN induced by L-NAME (RenTGR)	Decreased RV and LV hypertrophy, decreased plasma ANP levels and proteinuria, BP reduction	[96]
	Myocardial I/R injury (mice)	Increased myocardial microcirculation	[118]
	Myocardial I/R injury (pigs)	Reduced myocardial I/R injury	[119]
	Chronic mitral regurgitation (SD rats)	Cardio-protective, BP reduction, antifibrotic preservation of mitochondrial quality	[105]
	Chemotherapy-induced HF (mice, neonatal rat cardiomyocytes)	Improved cardiac insufficiency, prevented mitochondrial dysfunction, anti-inflammatory effect	[138]
	ANG II infusion in mice	Reduced cardiac hypertrophy and fibrosis, suppression of myocardial oxidative stress	[98]
CYR715	Myocardial I/R injury (isolated hearts)	Reduced MI size	[122]
Olinciguat IW-1701	HTN and cardiorenal failure in Dahl SS rats on a high-salt diet, HFrEF model (post-MI induced by ligation of coronary artery in rats)	Reduced cardiac hypertrophy, lung weight and NT-proBNP (Dahl SS rats), trend towards higher EF (not significant in post-MI rat HF)	[99]
sGC activators			
Cinaciguat BAY 58–2667	Anaesthetized Beagle dogs	Reduction of ventricular pre- and afterload, vasodilation	[214]
	Myocardial I/R injury (rat, rabbit)	Reduction in MI size	[125]
	MI induced by isoproterenol (rats), myocardial I/R (dogs)	Improved cardiac function and histopathological lesions, reduced oxidative stress	[128]
	Myocardial I/R injury in isolated coronary arterial rings exposed to peroxynitrite, cardiopulmonary bypass with cardioplegic arrest (dogs)	Pre-conditioning reduced peroxynitrite-induced endothelial dysfunction and restored vasodilatory responses to acetylcholine (*in vitro*), improved LV and RV functional recovery and endothelial function (*in vivo*)	[215]
	Myocardial I/R injury (mice, rabbits)	Reduced infarct size when given before (63 %) and at reperfusion (40 %) in rabbits, pre-treatment in mice caused an 80 % reduction in infarct size vs 63 % reduction when given at reperfusion (preserved cardiac function)	[70]
	Neonatal rat cardiomyocytes incubated with ET_1	Protection of cardiomyocytes	[216]
	HTN in Dahl SS rats fed a high-salt diet	Improved survival, cardiac and renal functions, anti-inflammatory and antifibrotic effects	[217]

(*continued on next page*)

Table 1 (*continued*)

Compound	Experimental model	Main results	Key ref.
	Myocardial I/R injury (mice with a cardiomyocyte-specific deletion of NO-GC)	Reduced cardiac injury in wild-type mice, but not in NO-GC knockout mice	[126]
	HFpEF and HTN model in Dahl SS on a high-salt diet	Improved cardiomyocyte function, reduced inflammation and oxidative stress	[100]
Ataciguat HMR1766	Cultured coronary endothelial monolayers, isolated saline-perfused hearts (rats)	Decrease in endothelial intercellular gap formation, diminished myocardial oedema	[218]
	MI induced by coronary ligation (Wistar rats)	Vasorelaxation, improved vasomotor function and reduced platelet activation	[75]
	MI induced by coronary ligation (Wistar rats)	Reduction in LV diastolic filling pressure and pulmonary oedema, augmented LV contractile function and diastolic stiffness (BP-independent effects), diminished cardiac fibrotic remodelling (superior to ACEi)	[124]
GSK2181236A	Coronary artery I/R (SD rats)	No cardio-protection after pre-treatment	[90]
	HTN in SHR-SP fed a high-salt/fat diet	Improved survival (high dose), protection against end-organ damage	
BAY 60–2770	I/R injury in isolated hearts exposed to reversible left coronary artery occlusion (rats)	Reduced infarct size, simultaneous treatment with sGC stimulator BAY 41–2272 did not further improve efficacy	[212]
	Myocardial I/R injury (LAD ligation in rats)	Decreased myocardial injury, reduced mitochondrial superoxide production	[129]
	Chemotherapy-induced cardiotoxicity (SD rats)	Improved myocardial dysfunction	[137]
	Isolated coronary arteries (pigs, dogs), vasopressin-induced angina (rats)	Antispastic effects on coronary arteries	[130]
Runcaciguat BAY 1101042	HTN induced by L-NAME (RenTGR)	Improved survival and renal function, enhanced heart hypertrophy, dose-dependent BP reduction	[76]
	HTN induced by L-NAME (RenTGR)	Improved survival, attenuated heart injury, reduced cardiac hypertrophy, BP reduction at higher doses	[219]

Abbreviations: **ACEi**, angiotensin-converting enzyme inhibitor; **ANG II**, angiotensin II; **ANP**, atrial natriuretic peptide; **BP**, blood pressure; **CO**, cardiac output; **CHF**, congestive heart failure; **dTGR**, double transgenic rats; **EF**, ejection fraction; **GFR,** glomerular filtration rate; **HF**, heart failure; **HFpEF**, heart failure with preserved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction; **HR**, heart rate; **HTN**, hypertension; **I/R,** ischemia–reperfusion injury; **LAD**, left anterior descending artery; **L-NAME**, Nω-nitro-L-arginine methyl ester; **LV**, left ventricle; **MI**, myocardial infarction; **NT-proBNP**, N-terminal pro B-type natriuretic peptide; **NO**, nitric oxide; **RV**, right ventricle; **sGC**, soluble guanylyl cyclase; **SD**, Sprague-Dawley rats; **SHR**, spontaneously hypertensive rats; **SHR-SP,** stroke-prone spontaneously hypertensive rats; **SS,** salt-sensitive; **RenTGR**, heterozygous Ren-2 transgenic rats.

sGC activators across different heart failure phenotypes and other cardiovascular pathologies are summarized in Table 2. The first sGC agonist tested in clinical trials was the sGC activator **cinaciguat** (**BAY 58–2667**). Its safety, tolerability, and haemodynamic effects were assessed in patients with acute decompensated heart failure (ADHF), demonstrating potent preload- and afterload-reducing effects [67]. Further examination of **cinaciguat** included the COMPOSE trials, comprising three randomized, double-blind, placebo-controlled studies in patients with acute heart failure syndromes (AHFS), with or without an indication for invasive haemodynamic monitoring (COMPOSE 1 and 2, and COMPOSE EARLY) [69]. **Cinaciguat** failed to improve dyspnoea or cardiac index and, even at low doses, caused hypotension; consequently, further development was discontinued [12,68,69]. Most clinical studies testing vasodilator drugs in the setting of acute HF yielded negative results [152], likely because BP reduction in patients with acute HF often worsens systemic perfusion and renal function.

Another compound evaluated in clinical trials was the sGC stimulator **riociguat.** It was tested in the Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial (LEPHT) [153]. **Riociguat** failed to improve mean pulmonary artery pressure (mPAP) in HF patients, regardless of the dose applied; however, several secondary effects were augmented, including improvements in cardiac index and pulmonary and systemic vascular resistance [12]. **Riociguat** was well tolerated in patients with PAH and CTEPH and improved exercise capacity, pulmonary vascular resistance, and clinical stability [45,47]. It is currently approved for the treatment of adults with PAH, inoperable CTEPH, or persistent or recurrent CTEPH after pulmonary endarterectomy, based on the series of PATENT and CHEST clinical trials [45,47,154–160]. The approval of the first sGC stimulator and its favourable safety profile laid the foundation for further investigation of sGC stimulators in other indications, including chronic HF [161].

Rosenkranz *et al.* performed a *post hoc* subgroup analysis of the PATENT clinical trials to explore the efficiency and safety of **riociguat** in patients with persistent or recurrent PAH after correction of congenital heart disease (PAH-CHD) [162]. **Riociguat** was well tolerated by PAH-CHD patients and improved a range of clinical outcomes compared with the placebo group. The authors speculate that **riociguat** could be a promising treatment for adult patients with persistent or recurrent PAH after correction of CHD [162].

Vericiguat was the first sGC stimulator approved for the treatment of patients with HF. In 2013, the pertinent series of SOCRATES trials was launched [163,164]. **Vericiguat** was specifically designed for patients with HF to avoid excessive vasodilation and unfavourable reductions in BP, to minimize drug interactions, and to ensure favourable pharmacokinetics even in patients with advanced kidney disease [96]. In phase 2 dose-finding studies, **vericiguat** was well tolerated by both HFrEF and HFpEF patients. Though it did not improve the primary endpoint, it caused a reduction in N-terminal pro B-type natriuretic peptide (NT-proBNP), as observed in aggregated active treatment groups in HFrEF in the SOCRATES trial [164,165]. **Vericiguat** resulted in a slightly higher incidence of hypotension (15.4 % vs 6.5 %) compared to placebo groups [12,163–165], but overall was well tolerated. These results provided the rationale for additional studies to determine the potential of **vericiguat** in high-risk patients with HFrEF and recent episodes of worsening HF.

The pivotal phase 3 VICTORIA study showed that **vericiguat** lowered the incidence of death from CV causes or hospitalization in patients with HFrEF and a recent history of cardiac decompensation, or "recently worsened HFrEF". Based on these results, **vericiguat** was approved for the treatment of adults with symptomatic worsening of chronic HFrEF in early 2021 in the United States and later in Europe [38,48–51].

Although the primary event reduction may seem modest in amplitude [relative risk reduction (RRR) 10 %, hazard ration, 0.90; 95 % confidence interval (CI, 0.82 to 0.98; P = 0.02)], it was considerable in absolute numbers. The 10 % relative difference between groups in the primary composite outcome in this high-risk population, at a median follow-up of 10.8 months, translated into an absolute event-rate reduction of 4.2 events per 100 patient-years. reflecting the very high event rates in the VICTORIA trial [166].

The *post-hoc* analyses of VICTORIA data showed a particular benefit in a less sick subpopulation, which provided the rationale for testing it in more clinically stable HFrEF patients [167–169]. In 2021 the VICTOR

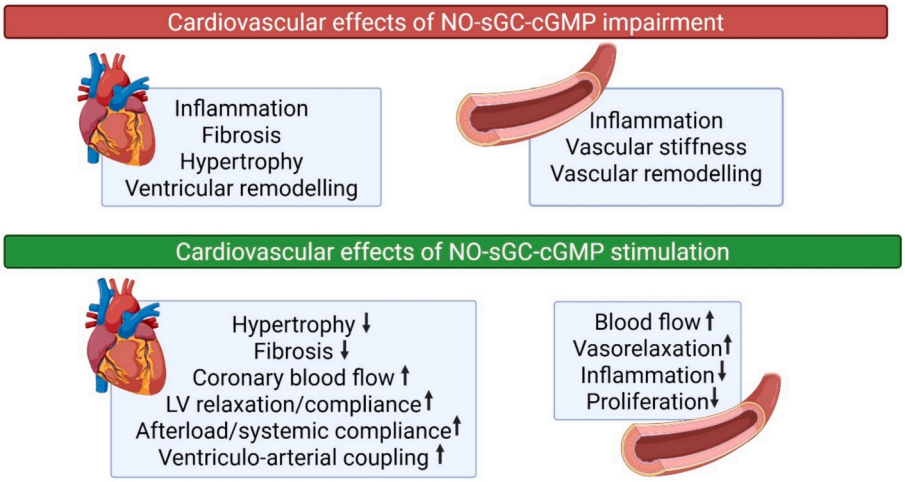

Fig. 3. Cardiovascular effects of NO-sGC-cGMP impairment and stimulation. Abbreviations: cGMP, cyclic guanosine 3′,5′-monophosphate; LV, left ventricle; NO, nitric oxide; sGC, soluble guanylyl cyclase.

study (a double-blind, placebo-controlled, phase 3 trial, conducted across 36 countries) was launched in patients with HFrEF without HF hospitalisation within 6 months or outpatient intravenous diuretic use within 3 months. Patients were treated with oral **vericiguat** (target 10 mg/dose) or matching placebo on top of optimal GDMT [170].

Patients had a median follow-up of 18.5 months. The primary composite endpoint was time to CV death or HF hospitalisation, and the study was designed and powered to address the key secondary endpoint of CV death [171]. Although the primary composite endpoint was not met (hazard ratio [HR] 0.93 [95 % CI 0.83–1.04]; p = 0.22) and HF hospitalizations were marginally reduced (HR 0.95 [95 % CI 0.82–1.10]), patients on **vericiguat** showed fewer events of CV death (HR 0.83 [95 % CI 0.71–0.97]), and the reduction was nominally significant (p < 0.02), driving a reduction in all-cause death (HR 0.84 [95 % CI 0.74–0.97]) [172]. The most common adverse event was symptomatic hypotension, which occurred in 11.3 % of patients in the **vericiguat** group and in 9.2 % of patients in the placebo group. Moreover, the rates of HF hospitalizations in the VICTOR study were lower than expected, and many enrolled patients had never been hospitalized before for HF, perhaps reflecting changing patterns of HF care. If an outpatient escalation of diuretics were used as a surrogate for HF hospitalizations, the study would have been positive for this endpoint.

The study extends the evidence of the VICTORIA trial to a broader, more stable ambulatory population with HFrEF receiving contemporary GDMT, including an unprecedented proportion of ARNI and SGLT2i. The observed reduction in CV mortality suggests that **vericiguat** addresses further the residual risk of CV death and may provide an additional mortality benefit in this population. This is confirmed by a network *meta*-analysis of HFrEF trials, showing that the addition of **vericiguat** to the contemporary standard of care including four HF drug classes reduces the RR of CV death by an additional 10 % [173].

A prespecified, pooled individual participant-level analysis was conducted on data from VICTORIA and VICTOR points at the totality of evidence across the risk spectrum of HFrEF patients, with a significant reduction in the primary composite endpoint of time to CV death or HF hospitalization of 9 % (HR 0.91 [95 % CI 0.85–0.98]; p = 0.0088), with reductions in its individual components of similar magnitude: CV death (HR 0.89 [0.80–0.98]; p = 0.020) and HF hospitalisation (HR 0.92 [0.84–1.00]; p = 0.043) [174]. The benefit of **vericiguat** appeared greater in the large cohort of patients with an NT-proBNP concentration of 6000 pg/mL or lower, as originally shown in secondary analyses of VICTORIA [167].

In addition, a novel liquid formulation of **vericiguat** is being investigated for paediatric HF (NCT05086952).

2.4.1. *Clinical studies of sGC agonists in HFpEF*

Several clinical trials have evaluated the efficacy of sGC agonists in patients with HFpEF, including CAPACITY HFpEF (**praliciguat**), SOCRATES-PRESERVED and VITALITY-HFpEF (**vericiguat**), and the DILATE-1 and DYNAMIC trials (**riociguat**) [175].

The CAPACITY HFpEF randomized clinical trial demonstrated no improvement in peak oxygen consumption (VO_2) in patients with HFpEF after two weeks of treatment with **praliciguat** [54]. **Vericiguat** failed to improve mortality or quality of life in patients with HFpEF [176,177]. In the DILATE-1 clinical trial, **riociguat** was well tolerated in patients with HFpEF and improved some haemodynamic and echocardiographic parameters, but had no significant effect on mPAP and did not improve the clinical symptoms of PH-HFpEF within the study observation period [178]. In the phase 2b DYNAMIC trial, **riociguat** improved haemodynamics in PH-HFpEF and was well tolerated, but did not alter clinical symptoms within the study period [179]. The use of sGC stimulators was associated with an increased incidence of drug-related adverse events in HFpEF patients; therefore, caution is advised when considering sGC agonists for HFpEF treatment [177,180,181].

Based on clinical trial data, sGC stimulators do not appear to be promising in a broad HFpEF population. The reasons for these failures remain unclear, but are likely related to the greater-than-expected heterogeneity of mechanisms underlying clinical HFpEF, only some of which may be responsive to sGC modulation. Other studies testing agonists of the NO–cGMP pathway in HFpEF patients, such as nitrates [182] or PDE5 inhibitors [183], also failed to meet pre-defined efficacy criteria.

Borlaug proposed a classification system distinguishing HFpEF into clinically and pathophysiologically relevant phenotypes, which may exhibit differential responses to pharmacological interventions [184]. Matsuoka *et al.* applied a machine learning approach to large-scale hospitalization data from patients with HFpEF and identified five distinct stable-phase phenotypes. The study demonstrated that specific acute-phase phenotypes often transitioned into defined stable groups, highlighting the potential of data-driven, phenotype-guided treatment strategies in HFpEF [185]. *Post hoc* analysis of the CAPACITY trial [54] suggested that **praliciguat** might have greater efficacy in a HFpEF subgroup of postmenopausal women [186]. Notably, only sGC stimulators were clinically tested in HFpEF.

2.4.2. *Clinical studies demonstrating the value of sGC agonists in IHD*

Despite positive preclinical data, clinical evidence supporting the use of sGC agonists in IHD indications remains scarce. The antiaggregatory effects of **riociguat** and **cinaciguat** in blood collected from three groups

Table 2
Sgc stimulators and activators – key clinical trials related to hf.

Compound	Indication	Key clinical trials	Phase	Main findings	Key ref.
sGC stimulators					
Riociguat BAY 63–2521	PH-sLVD	LEPTH (NCT01065454)	2	Primary endpoint not met, improved cardiac index and pulmonary and systemic vascular resistance, well tolerated	[153,220]
	PH-HFpEF	DILATE-1 (NCT01172756) Terminated	2	No significant effect on mPAP, improved exploratory haemodynamic and echocardiographic parameters, well tolerated	[178]
	PH-HFpEF	DYNAMIC (NCT02744339)	2	Improved haemodynamics, no change in clinical symptoms	[179,221]
	PAH, CTEPH	PATENT-1 (NCT00810693),PATENT-2 (NCT00863681) ,CHEST-1 (NCT00855465) ,CHEST-2 (NCT00910429) ,	3	Improved primary endpoint (6-minute walking distance), improved exercise capacity and pulmonary vascular resistance, approved (Adempas®)	[45,47,154–159,162]
Vericiguat BAY 1,021,189 (MK-1242)	HFrEF	SOCRATES-REDUCED (NCT01951625)	2	No significant effect on NT-proBNP level at 12 weeks, well tolerated	[161,164,222,223]
		VICTORIA (NCT02861534)	3	Reduced incidence of death from CV causes or hospitalization in patients with HFrEF and recent worsening, approved (Verquvo®)	[48,49,51,201,224–228]
		VICTOR (NCT05093933)	3	Primary composite endpoint was not met; significant reduction in the key secondary outcome of CV death and all-cause mortality	[168,170–172,174,229,230]
	HFpEF	SOCRATES-PRESERVED (NCT01951638)	2	No change in NT-proBNP and left atrial volume at 12 weeks, trend towards improved quality of life, well tolerated	[161,176,231]
		VITALITY-PRESERVED (NCT03547583)	2	No improvement KCCQ physical limitation score (24-week treatment)	[177,232]
	CAD	VENICE (NCT02617550),VISOR (NCT03255512) , NCT03504982	1	Co-administration with nitroglycerine (VENICE) or isosorbide mononitrate (VISOR), well tolerated with both drugs	[198–201]
Praliciguat IW-1973	HFpEF	CAPACITY-HFpEF (NCT03254485)	2	No significant improvement in peak Vo2 after 12 weeks	[54,233]
Nelociguat BAY 60–4552	bivHF	NCT00565565	1	Potent vasodilation, improved biventricular pre- and afterload, increase in cardiac index, well tolerated	[234]
sGC activators					
Cinaciguat BAY 58–2667	ADHF	2005–004473-14	2	Preload- and afterload-reducing effects, CO increase	[67]
		NCT00559650	2	Unloaded the heart, high doses associated with hypotension, terminated	[68]
		COMPOSE 1 (NCT01065077), COMPOSE 2 (NCT01067859), COMPOSE EARLY (NCT01064037)	2	Short-term use of intravenous cinaciguat decreased BP without improving dyspnoea or cardiac index, discontinued	[69]

Abbreviations.**ADHF**, acute decompensated heart failure; **bivHF**, biventricular heart failure; **CAD**, coronary artery disease; **CTEPH**, chronic thromboembolic pulmonary hypertension; **CV**, cardiovascular; **HFpEF**, heart failure with preserved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction; **KCCQ**, Kansas City Cardiomyopathy Questionnaire; **mPAP**, mean pulmonary artery pressure; **NT-proBNP,** N-terminal pro B-type natriuretic peptide; **PAH**, pulmonary arterial hypertension**; PH-HFpEF,** pulmonary hypertension with heart failure with preserved ejection fraction; **PH-sLVD**, pulmonary hypertension with significant left ventricular dysfunction; **sGC**, soluble guanylyl cyclase.

of subjects: healthy individuals, patients with myocardial ischaemia, HF and/or atrial fibrillation, and patients in the chronic stage of CAS. In patients with already impaired NO–sGC–cGMP signalling, **riociguat** and **cinaciguat** tended to normalize platelet aggregation, suggesting potential for the treatment of CAS [187]. R**iociguat** was also reported to inhibit epicardial CAS (confirmed with acetylcholine testing) in a clinical case of severe coronary spasms [188].

2.5. Safety of sGC agonists and risk of hypotension in HF patients

In general, sGC stimulators are considered safe and well tolerated, with no serious adverse events reported [12,189]. Many HF drugs, including sGC agonists, carry a risk of hypotension, which is a major limitation in optimizing medical treatment of HF. Low BP is reported in up to 15 % of patients with HF in clinical trials, but in routine clinical practice it is considerably higher [149,190]. Among the four pillars of HFrEF treatment – ACEi/ARBs/ARNIs, beta-blockers, MRAs, and SGLT2i – the first two carry a higher risk of hypotension, whereas MRAs and SGLT2i typically do not cause substantial BP reduction [190,191]. Delayed titration of GDMT often results in poorer prognosis, highlighting the importance of rapid implementation of therapy [192]. Nevertheless, BP should always be monitored during HF treatment [191], and there remains an unmet need for HF drugs that minimize BP-lowering effects.

A recent *meta*-analysis examined clinical trials of sGC agonists for HF management, focusing on safety and the risk of hypotension [193]. The authors evaluated the efficacy and safety of sGC stimulators (**riociguat, vericiguat, praliciguat**) and the sGC activator **cinaciguat**. The analysis covered 10 randomized controlled trials with 7,526 patients across all HF phenotypes and evaluated multiple clinically relevant drug-related adverse events, including hypotension, ventricular tachycardia, syncope, peripheral and pulmonary oedema, and headache. The *meta*-analysis revealed a significant increase in the incidence of hypotension across almost all trials [193]. Early clinical evaluation of **cinaciguat** was discontinued because it failed to improve primary outcomes and caused hypotension, even at low doses [12,68,69].

Another important consideration is the safety of sGC agonists in the setting of life-threatening hypotension due to severe trauma or sepsis. Sepsis can lead to multiple organ failure, including myocardial dysfunction and septic shock, and is associated with profound

vasodilation and hypotension [194]. sGC agonists could theoretically exacerbate hypotension by enhancing vasodilation. Inadequate organ perfusion due to excessive vasodilation could actually worsen outcomes in septic patients. Given the scarce clinical evidence, the use of sGC stimulators in septic patients should be carefully weighed against the potential risks, including exacerbation of hypotension and interactions with inflammatory pathways [195].

sGC stimulators have also been associated with a risk of anaemia. Retrospective analyses highlight the importance of the haematopoietic system for the prognosis and treatment of HF [196,197]. In the PATENT-1 study, **riociguat** was associated with a higher risk of anaemia (8 %). Similarly, the analysis of the safety outcomes in VICTORIA trial revealed that **vericiguat** treatment resulted in 7.6 % cases of anaemia vs 5.7 % in the placebo group, with decreases in haemoglobin occurring more frequently in patients on **vericiguat** than on placebo [48]. However, the pathogenesis of this phenomenon remains unknown and proved unrelated to the primary clinical outcomes [45].

Vericiguat has also been investigated in CAD and was studied in several clinical trials co-administered with nitroglycerine (VENICE) or isosorbide mononitrate (VISOR). The only conclusion (so far) is that there are no clinically relevant pharmacodynamic interactions between **vericiguat** and the tested drugs, and further studies are necessary [198–201].

2.6. Summary and clinical perspective

HF is a chronic disease which, despite decades of research and advances in GDMT and non-pharmacological therapies, remains a significant medical burden worldwide [1,202]. A considerable number of HF patients continue to experience residual symptoms and disease progression, leading to repeated hospitalizations. The sGC stimulator **vericiguat** with its unique mode of action compared to other HF treatments, was expected to address this gap and support patients with symptomatic HFrEF [163].

Following multiple preclinical studies demonstrating the beneficial potential of sGC stimulators, and subsequent successful clinical trials, initial enthusiasm for this form of sGC-cGMP-based therapy has somewhat decreased [12]. Indeed, the positive outcomes of **vericiguat** studies have been overshadowed by the effects of SGLT2i, which demonstrated reductions in HF hospitalization and CV death across the spectrum of LVEF [203–205].

There is a clear need to determine the efficacy of **vericiguat** in combination with the four pillars of GDMT, which have class I recommendations due to their life-prolonging effects [2]. Combined therapies may have additive or synergistic effects, altering the course of HFrEF [203]. The advantages of **vericiguat** in this context include its low tendency to induce hypotension, simple titration scheme, and suitability for use even in HF patients with severely reduced GFR.

The recently completed VICTOR trial extended the evidence from VICTORIA to a broader, more stable ambulatory HFrEF population treated with contemporary GDMT [172]. While the primary endpoint was not met, **vericiguat** significantly reduced CV and all-cause mortality, confirming its potential to address residual risk in stable HFrEF. Moreover, a prespecified pooled analysis of VICTORIA and VICTOR demonstrated consistent benefits across the HFrEF risk spectrum, with significant reductions in CV death and HF hospitalisation [174]. Another important aspect to be clarified is the correct way to initiate and titrate **vericiguat** along with GDMT. Based on the registry data, the compliance with GDMT is still poor among patients, especially for initiating multiple drugs and titrating drugs [12].

With regard to HFpEF, evidence for sGC stimulators remains inconclusive, as all relevant clinical trials failed to demonstrate clinical benefit; caution is therefore advised. Further studies are required to identify patient populations who may benefit from sGC agonists [66,189,206]. One explanation for the limited success in HFpEF is the substantially different underlying pathophysiology compared with HFrEF [207]. In HFrEF, impaired NO–sGC–cGMP signalling contributes to reduced contractility and maladaptive remodelling, making this pathway an attractive therapeutic target [16]. In contrast, HFpEF is a heterogeneous syndrome, often driven by systemic comorbidities (hypertension, obesity, diabetes, ageing) that promote inflammation, fibrosis, and microvascular dysfunction, where cGMP deficiency may not be the predominant driver of disease progression [208]. It is speculated that some recent failures in the search for new HFpEF therapies could be avoided through mechanism-based patient stratification [209]. In addition, the use of sGC activators, which preferentially act under conditions of oxidative stress, may prove particularly effective in HFpEF. This hypothesis merits clinical trials investigating sGC activators in this HF subpopulation.

Successful management of HF remains a major challenge. Appropriate pharmacological therapy is crucial to reduce risk factors, provide haemodynamic support, and confer protective effects [210]. Based on preclinical and clinical evidence, sGC stimulators and sGC activators may play an important role in the prevention or treatment of various CV diseases, particularly because they are not associated with the risks of hyperkalaemia or worsening renal function that can accompany standard GDMT drugs, such as ACEi or ARBs [211]. Future clinical trials should focus on identifying specific subgroups of patients with distinct cardiac and renal phenotypes to determine who is most likely to benefit from treatment with sGC stimulators or activators.

CRediT authorship contribution statement

Olga Gawrys: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Petr Kala:** Writing – review & editing, Writing – original draft, Validation. **Michal Šnorek:** Writing – review & editing, Writing – original draft, Validation. **Vojtěch Melenovský:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Stefano Corda:** Writing – review & editing, Validation, Supervision. **Peter Sandner:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Olga Gawrys, Petr Kala, Michal Šnorek, Vojtěch Melenovský have no competing interests.

Stefano Corda and Peter Sandner are employees of Bayer HealthCare.

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