



Vericiguat for Post-Myocardial Infarction Heart Failure Prevention: From Molecular Mechanisms to Clinical Translation

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Abstract

Myocardial infarction (MI) remains a major cause of morbidity and mortality, largely due to the development of heart failure (HF). More molecular mechanisms should be investigated concerning the pathophysiology of HF after MI since current therapies for reperfusion and clinical guidelines in medicine cannot solve the problem. The regulation of the signalling pathway involving nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate is responsible for the stability of the cardiovascular system. This pathway works properly in healthy individuals but gets disrupted in MI, causing adverse consequences. Vericiguat acts as an orally administered soluble guanylate cyclase stimulator that restores the levels of cyclic guanosine monophosphate to counteract pathological events leading to HF. Numerous pre-clinical and clinical investigations into vericiguat have shown the capacity of early administration to prevent HF following MI, especially in patients who are at risk of having continued myocardial stress. Moreover, combination approaches using vericiguat alongside current cardioprotective modalities have proven to be promising in yielding better outcomes. The current review is therefore designed to give an insight into various aspects relating to heart with special attention being paid to the role of vericiguat as a disease-modifying agent for prevention of post-MI myocardial HF.

Keywords

myocardial infarction, heart failure, vericiguat, soluble guanylate cyclase

Introduction

Myocardial infarction (MI) persists as one of the most prevalent medical conditions, which leads to death and illness across the globe, while ischemic heart diseases result in an overwhelming number of fatalities, creating a worldwide health crisis [1]. Ischemic heart diseases caused 9 million deaths and 250 million prevalent cases in 2021, which shows the global impact of this health issue [2]. The high prevalence of MI in the elderly, as shown in recent global statistics, demonstrates that more people now experience both MI and its related health issues [3]. Age-stratified global data show that older people face a greater risk of developing ischemic heart disease, which proves that this disease burden increases with advancing age [4]. The advancement of MI treatment through reperfusion therapies and medications has not eliminated the disease, since MI still serves as a major pathway, which leads to heart failure (HF), a condition that results in high rates of medical complications leading to death [5]. The process from MI to HF follows a complicated pathophysiological process [6]. The structural and molecular alterations lead to diminished cardiac function, which results in reduced cardiac output that produces the clinical symptoms of HF [7]. Post-MI HF is a significant cause of socioeconomic issues, leading to increased hospitalisations, health expenditure, and an increased strain on the national health infrastructure [8]. At the patient level, post-MI HF results in decreased physical activity, reduced quality of life, and an increased risk of mortality [9]. The current standard of care post-MI HF prevention requires

medical professionals to perform early reperfusion procedures and administer antiplatelet drugs, statins, β -blockers, renin-angiotensin-aldosterone inhibitors, and mineralocorticoid receptor antagonists [10]. Treatment according to guidelines following MI is linked to improved survival rates and increased longevity among Medicare patients, but there is still considerable risk of developing HF [11]. The combination of endothelial dysfunction and oxidative stress, and nitric oxide signalling pathways leads to continuous myocardial damage and heart tissue remodelling in patients following guideline-based medical treatment [12]. The NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signalling pathway controls cardiovascular homeostasis through its effects on vascular function, myocardial function, and inflammatory function, and fibrosis development [13]. The pathway has been demonstrated to play a vital role in the development of ventricular dysfunction and HF that occurs after ischemic injury [14]. Pharmacological stimulation of sGC currently serves as a promising treatment method, which restores cGMP signalling to prevent the development of pathological remodelling [15]. Vericiguat, an oral sGC stimulator, has demonstrated therapeutic effectiveness for patients suffering from worsening HF with reduced EF by decreasing their chances of cardiovascular death and HF hospitalisations thus validating the use of NO-sGC-cGMP pathway targeting for cardiovascular disease treatment [16]. The therapeutic rationale of targeting the NO-sGC-cGMP axis in cardiovascular disease management, however, remains to be established in the context of the prevention of HF following MI, thus underlining an important area of unmet clinical need [16,17]. The burden of post-MI HF remains a challenge in contemporary medicine, with increasing interest in molecularly targeted approaches to complement conventional neurohormonal

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blockade [18]. Hence, a critical synthesis of evidence from basic research and clinical studies is warranted to clarify the therapeutic rationale of targeting the NO-sGC-cGMP axis in the prevention of post-MI HF [19]. This review aims to integrate current knowledge on MI-induced pathophysiology, the pharmacology of vericiguat, and emerging clinical evidence to inform future translational strategies and optimise preventive care.

Pathophysiological mechanisms of post-MI progression to HF

MI triggers a series of complex structural, cellular, and molecular changes that finally lead to the development of adaptive repair responses or to detrimental remodelling and HF [20]. The process of pathophysiological transition from MI to HF occurs through the active interaction between five distinct factors, which include acute ischemic damage, inflammatory responses, neurohormonal activation, endothelial dysfunction, and chronic fibrotic remodelling [21].

1. Phases of MI: from acute injury to chronic remodelling

The initial stage of MI starts when blood circulation in the coronary arteries stops, which results in cardiomyocyte death through necrosis and apoptosis within the affected heart tissue [22]. The process results in a major inflammatory reaction, which brings immune cells to the site while dead cells are removed from the infarcted region [23]. The body produces an excessive inflammatory response, which causes both infarct growth and microvascular impairment that leads to harmful heart tissue changes [24].

The myocardium follows a healing process that starts with its first stage of repair work and lasts until complete recovery through the initiation of fibroblast activity, extracellular matrix production, and scar tissue formation [25]. The processes maintain structural integrity until persistent fibroblast activation leads to pathological changes, which result in ventricular enlargement, wall thinning, and contractility dysfunction [26]. This remodelling, which results in changes in geometry and function of the heart, and contributes to the pathophysiology of HF [27].

2. Pathological cascades driving HF progression

The process of remodelling after MI occurs through various intertwined pathological pathways, involve cell loss, hypertrophy of the surviving cells, disruption of the extracellular matrix, mitochondrial dysfunction, and activation of neurohormonal systems [28]. These pathways, though initially compensatory, eventually become adverse, hastening the process of ventricular dysfunction and progression of HF [29].

Inflammatory pathways maintain their essential functions in this process because of macrophage activation, and together with cytokine signalling, drive scar development, blood vessel formation, and tissue remodelling through fibrosis [30]. Neurohormonal systems, which include the renin-angiotensin-aldosterone system and the sympathetic nervous system, lead to cardiac remodelling by increasing wall tension and causing fibrosis and cardiomyocyte death [31].

Although progress in reperfusion strategies and pharmacological treatments, such as reperfusion therapies, has been made, a significant percentage of MI patients experience detrimental left ventricular remodelling, which is a major mechanistic link to the development of HF [32].

3. Focus on the NO pathway: endothelial dysfunction and oxidative stress

Endothelial dysfunction, which happens after MI causes negative effects on left ventricular remodelling. The study indicates that endothelial dysfunction serves as a significant factor that leads to HF because it disrupts vasodilatory signalling, thereby causing negative cardiovascular changes [33]. The process leads to endothelial nitric oxide synthase impairment, which results in decreased natural nitric oxide production. This effect blocks normal blood vessel operations [34].

The reduced nitric oxide signalling system results in dysfunction of coronary microcirculation and myocardial contractility and anti-fibrotic pathways which together drive negative heart remodelling [35]. The alteration of the NO-sGC-cGMP signalling axis compromises the function of cardiomyocytes, vascular tone, and relaxation [36].

In HF states, reduced endogenous NO production and subsequent cGMP signalling have been causally linked to endothelial dysfunction and progression of HF, emphasising the role of this signalling axis in post-MI pathophysiology [37].

4. Mechanistic cascade triggered by post-MI NO depletion

The body loses nitric oxide after MI, which begins a destructive process that decreases sGC activation and cGMP production while increasing oxidative damage and causing myocardium relaxation and blood flow problems [38]. This particular environment creates conditions that lead to inflammation and fibrosis while causing ventricular stiffness, which collectively drive the transition from compensated remodelling to overt HF (Figure 1) [39].

Mechanistic role of vericiguat in preventing post-MI HF

Patients with MI develop chronic HF because of sustained neurohormonal activation and endothelial impairment and inflammatory response and negative changes to their heart muscle structure [6]. The nitric oxide NO-sGC-cGMP signalling system experiences significant impairment because of these processes which are directly linked to its functioning [40]. Vericiguat functions as an oral sGC stimulator because it enables cGMP signalling restoration through two mechanisms: direct sGC stimulation and NO sensitivity enhancement [41]. The vericiguat drug increases intracellular cGMP levels which activate protein kinase G pathways that protect cells and control blood vessel function and heart structure changes after an ischemic event [42].

Vericiguat demonstrates multiple biological effects which extend beyond its regulation of blood flow because it affects essential biological mechanisms that drive post-MI HF development [43].

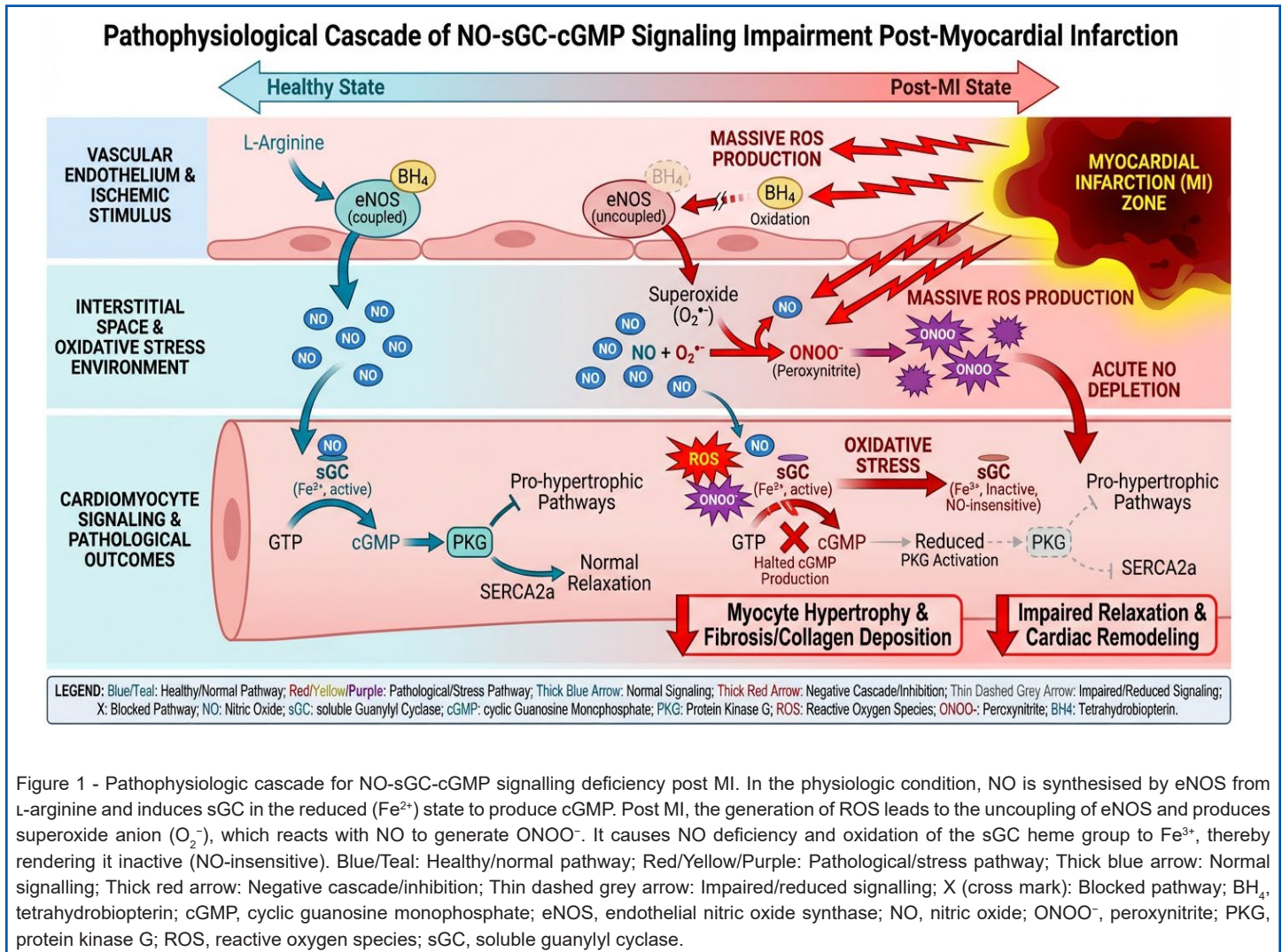


Figure 1 - Pathophysiologic cascade for NO-sGC-cGMP signalling deficiency post MI. In the physiologic condition, NO is synthesised by eNOS from L-arginine and induces sGC in the reduced (Fe^{2+}) state to produce cGMP. Post MI, the generation of ROS leads to the uncoupling of eNOS and produces superoxide anion ($\text{O}_2^{\cdot-}$), which reacts with NO to generate ONOO^- . It causes NO deficiency and oxidation of the sGC heme group to Fe^{3+} , thereby rendering it inactive (NO-insensitive). Blue/Teal: Healthy/normal pathway; Red/Yellow/Purple: Pathological/stress pathway; Thick blue arrow: Normal signalling; Thick red arrow: Negative cascade/inhibition; Thin dashed grey arrow: Impaired/reduced signalling; X (cross mark): Blocked pathway; BH₄, tetrahydrobiopterin; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ONOO⁻, peroxynitrite; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase.

The experimental findings demonstrate that activation of the NO-sGC-cGMP pathway results in two cardiovascular benefits which include protection against oxidative damage and enhancement of endothelial performance while reducing heart muscle damage, thus establishing its mechanisms of cardioprotective effects during post-MI treatment [44].

5. Anti-fibrotic effects

Cardiac fibrosis is a central determinant of adverse ventricular remodelling after MI and it leads to progressive systolic and diastolic dysfunction [45]. The activation of cGMP-dependent signalling pathways prevents fibroblast growth and extracellular matrix production, which leads to decreased collagen buildup in the heart muscle [46]. The preclinical studies demonstrate that vericiguat decreases heart muscle fibrosis while it protects against structural changes that occur through its effects on TGF- β 1/Smad2/3 profibrotic signalling pathways [47].

6. Metabolic optimisation and mitochondrial protection

Mitochondrial impairment together with energy metabolism disruption and heightened oxidative stress damages post-MI

myocardial tissue, which results in cardiomyocyte death and ventricular impairment [48]. The preservation of mitochondrial integrity with vericiguat results from its ability to enhance mitochondrial quality through decreasing oxidative damage and mitochondrial impairment [49]. The research findings show that vericiguat activates the AMPK/Nrf2 pathway, which results in enhanced antioxidant protection together with increased cellular defence against oxidative damage and maintenance of mitochondrial balance in ischemic heart tissue [50]. Nrf2 signalling impairment has created links between oxidative stress and metabolic disruption, which affects HF patients, thus making sGC stimulation pathways vital for treatment development [51].

7. Anti-inflammatory actions

The process of inflammation functions as a key mechanism that drives both post-MI heart remodelling and HF development through its activation of inflammasome pathways, results in damage to heart muscle cells and the formation of scar tissue [52]. Vericiguat demonstrated its ability to block NLRP3 inflammasome activation while it simultaneously reduced pyroptotic signalling in studies examining cardiac damage in experimental models which showed

its direct anti-inflammatory effect that operated independently from its effect [50]. The anti-inflammatory properties of these substances work to decrease unfavourable heart changes while they protect heart tissue from damage that occurs after ischemic events [53].

8. Renoprotective mechanisms

MI to HF progression connects to cardiorenal interactions, which include renal hypoperfusion and neurohormonal activation, and results in the progressive renal dysfunction that defines cardiorenal syndrome [54]. Vericiguat enhances sGC activity and increases cGMP bioavailability, which results in improved vascular function and restoration of endothelial function [41]. The NO-sGC-cGMP pathway controls renal vascular tone and glomerular haemodynamics, so its pathway modulation may help preserve kidney function in HF patients [55]. The research data from experimental and clinical studies demonstrate that sGC stimulation reduces renal inflammation and fibrotic signalling pathways; however, further studies need to investigate both mechanisms and outcomes to confirm vericiguat's direct renoprotective and antifibrotic effects in humans [42,56].

9. Microvascular and endothelial benefits

Coronary microvascular dysfunction represents the key component of post-MI remodelling which leads to persistent ischemia and heart muscle damage and ventricles that do not function properly [57]. Vericiguat restores the NO-sGC-cGMP pathway, which leads to better endothelial function and microvascular blood flow resulting in improved heart muscle oxygen distribution and decreased oxidative damage [58]. The treatments provide microvascular advantages that function as essential components that help prevent localised heart damage from developing into complete HF [59]. The combination of microvascular and endothelial changes together with reductions in myocardial fibrosis and alterations to metabolic and structural remodelling processes demonstrates that vericiguat has the potential to function as a disease-modifying treatment for patients who experience post-MI HF (Figure 2) [60].

Clinical evidence and optimal timing of intervention

1. Trial insights: VICTORIA and SOCRATES

The clinical application of sGC stimulation research finds its basis in the results of the phase II SOCRATES study and the phase III VICTORIA trial, which assessed the effects of vericiguat on patients with HF across different clinical presentations and levels of clinical risk [61]. The SOCRATES-REDUCED trial showed that vericiguat caused changes in myocardial stress indicators, which included NT-proBNP and this connection established its role in the early stages of disease development [62]. The companion SOCRATES-PRESERVED trial suggested that sGC stimulation operates in patients who maintain their ejection fraction, with potential benefits in physical function and health status [63].

The VICTORIA trial provided clinical evidence that vericiguat decreases the risk of combined cardiovascular death and hospital admission for patients who exhibit worsening HF with reduced ejection fraction (HFrEF) [16]. Apart from VICTORIA, another study known as the VICTOR trial (Vericiguat Global Study in Participants with Chronic HF) aims to assess the benefits of vericiguat on patients suffering from HF, thus increasing the evidence base of sGC stimulation therapy among various groups of patients with HF [64]. This study focused on biomarkers for ventricular remodelling after MI, and how these help in determining the patients at risk of undergoing ventricular remodelling leading to HF. [65]. The results suggest that early treatment, which targets damaged NO-sGC-cGMP pathways, can prevent the progression from acute myocardial damage to chronic HF [66].

2. Clinical research synthesis: vericiguat and post-MI HF prevention

The current research framework has established limited large-scale randomised studies. It focuses on preventing HF after MI. Yet, in spite of the existing mechanistic and clinical research findings, it demonstrates that sGC stimulation reduces harmful ventricular remodelling that occurs after ischemic damage [67]. Vericiguat shows therapeutic potential through its ability to improve endothelial function together with its capacity to decrease fibrosis and enhance myocardial blood flow which determines patient outcomes after MI [68]. Observational and biomarker analyses indicate that patients with elevated natriuretic peptide levels constitute a high-risk population suitable for evaluating sGC modulation strategies. [69]. The research findings indicate that vericiguat functions as a preventive treatment because it treats existing HF yet may change the disease progression path which follows MI [70].

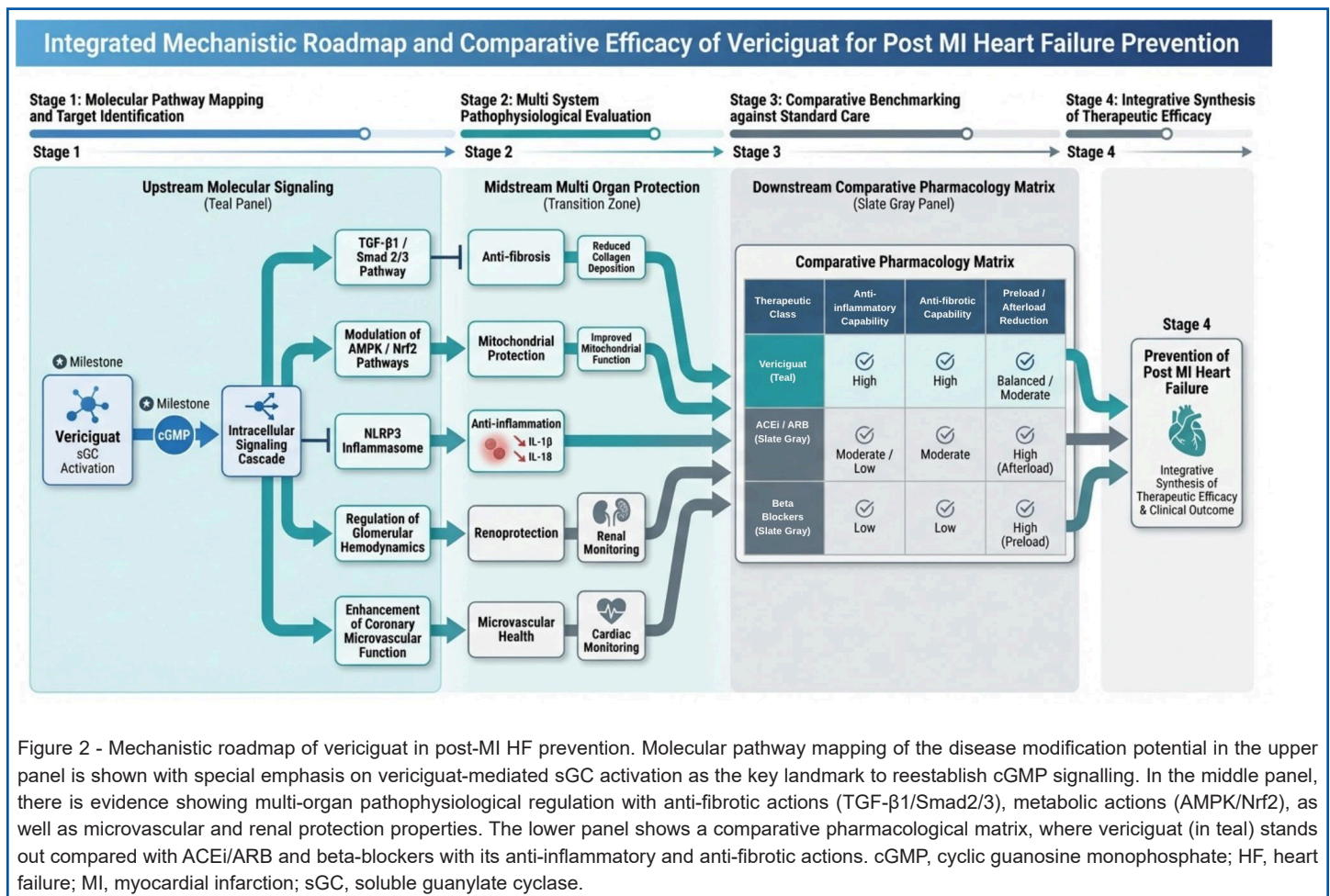
3. Target population stratification

Emerging evidence suggested that the clinical benefit of sGC stimulation may be greatest in specific high-risk subgroups which experience accelerated remodelling and ongoing myocardial stress [71]. Patients who sustain large anterior MIs present a higher risk of negative ventricular remodelling because of their widespread heart tissue damage and increased activation of neurohormonal systems [72].

Diabetes patients constitute a high-risk group because their metabolic dysregulation, endothelial dysfunction, and oxidative stress may worsen post-MI heart damage and HF progression [73]. Patients who show early elevations in natriuretic peptides but maintain their ejection fraction appear to show a transitional phenotype, which develops molecular dysfunction before they experience systolic impairment [74]. The identification of these subgroups may allow for targeted implementation of vericiguat and optimising decision making about benefits and risks [75].

4. Intervention windows: optimal timing ('goldilocks zone')

The timing of pharmacological intervention in patients with MI greatly influences the outcome, as a too early or delayed start of



the treatment reduces its efficacy [76]. The early post-MI period presents an overwhelming inflammatory response, which, along with haemodynamic instability, renders patients unable to respond to vasodilatory agents [77]. The therapeutic efficacy of the drugs to influence the course of the disease is less if the start of the treatment follows the occurrence of structural changes [78].

A therapeutically relevant window might be identified during the transition from acute haemodynamic stabilisation to early remodelling, a time during which progressive endothelial dysfunction, along with impairment in the NO-sGC-cGMP cascade may occur [79]. Experimental and clinical evidence suggest that the impairment in the cGMP cascade precedes the onset of fixed structural fibrosis, leading to adverse remodelling in the heart [80]. Since vericiguat works by stimulating sGC, independently of the availability of NO, the time course at which the drug is active appears to be optimally positioned in an intermediate window [81]. This line of reasoning supports the idea that the initiation of vericiguat in the early remodelling phase, but not in the acute instability and not in the late fibrosis, might define the therapeutic window [82]. This framework aligns with conceptual strategies proposed for targeting specific phases of myocardial remodelling, where intervention is most likely to alter the progression towards chronic HF (Figure 3)[83].

Challenges and future perspectives

The combination of mechanistic studies and clinical trials suggests sGC stimulation leads to promising results but researchers face scientific and translational challenges which remains unclear how vericiguat should be used to prevent HF after MI [84]. The development of future cardiovascular treatments will depend on combination strategies that target multiple maladaptive pathways at the same time [85]. The use of personalised risk assessment together with biomarker-based treatment methods will improve both patient selection processes and treatment effectiveness according to research findings [86]. The development of precision medicine methods that treat patients during active periods of heart muscle remodelling will enable doctors to stop disease progression before patients develop symptoms of HF [87].

1. Synergistic potentials: combination strategies

The current state of HF treatment requires research to study how vericiguat interacts with different therapies that affect multiple biological systems [16]. The combination of vericiguat and sodium glucose cotransporter 2 inhibitors has shown promise, as SGLT2 inhibitors offer cardiovascular and renal protection through their capacity to induce sodium excretion, improve metabolic function, and decrease glomerular pressures [88]. The efficacy of SGLT2i in

Clinical Management Pathway for Early sGC Stimulation to Prevent Post-Myocardial Infarction

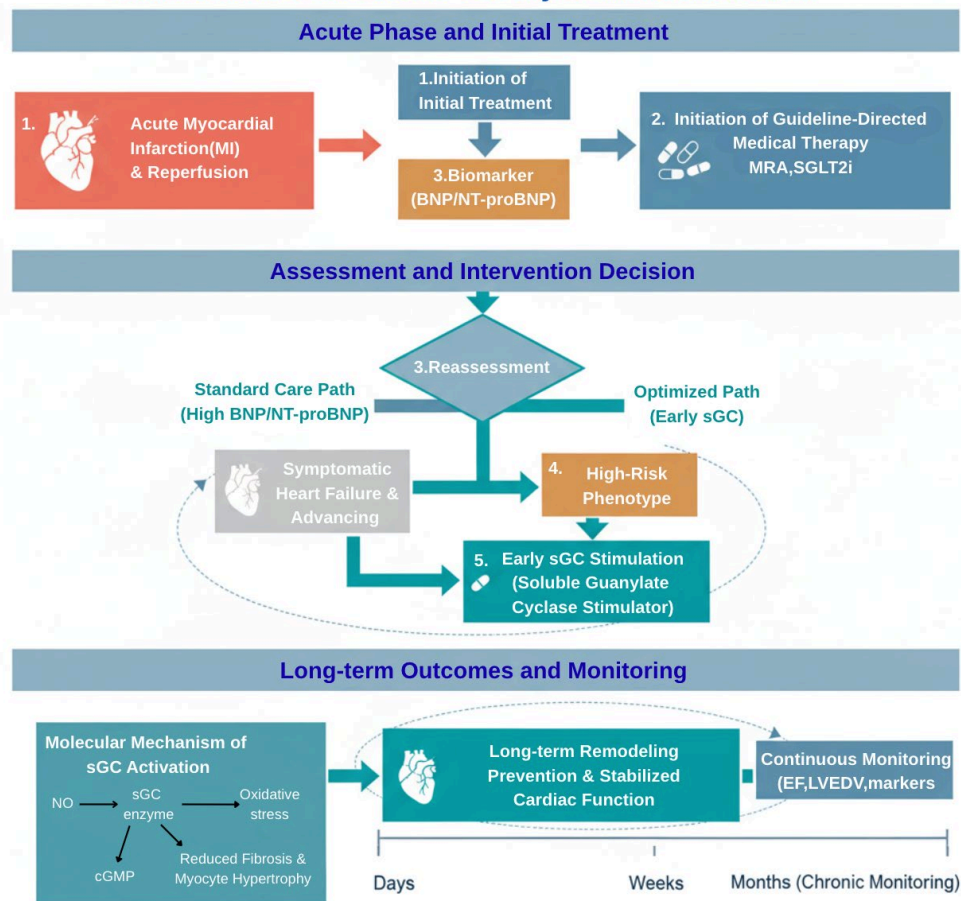


Figure 3 - Early clinical management pathway of sGC stimulation to avoid post-MI HF. After MI with reperfusion, a treatment protocol according to guidelines, including MRA and SGLT2i, is started. For patients with high BNP/NT-proBNP levels (high-risk group), the next step would be early sGC stimulation with vericiguat in the critical phase of cardiac remodelling. The pathway is focused on the restoration of the NO-sGC-cGMP pathway and prevention of oxidative stress, fibrosis, and excessive growth of cardiomyocytes. The timeline shows the shift from the acute stage to the remodelling phase avoidance. cGMP, cyclic guanosine monophosphate; HF, heart failure; MI, myocardial infarction; NO, nitric oxide; sGC, soluble guanylate cyclase.

reducing hospitalisations for HF and cardiovascular death in a broad range of patients, with or without diabetes, has been established, making them a cornerstone of therapy [89].

This dual approach of vericiguat, in combination with an SGLT2 inhibitor, appears to be promising, as indicated by the positive effects of the dual action of vericiguat in combination with an SGLT2 inhibitor on parameters of cardiac function and remodelling in the quadruple combination therapy approach [90]. The combination of vericiguat with ARNI treatment shows potential as a dual treatment method because it produces beneficial clinical outcomes through ARNI treatment, which affects natriuretic peptides, and through vericiguat's impact on cGMP signalling [91]. The cGMP production process of sGC activation, together with the cGMP degradation process through neprilysin inhibition, is activated by vericiguat combined with ARNI, which produces a combined effect on the signalling pathways of vericiguat, including its anti-fibrotic, vasodilatory, and anti-remodelling properties [42]. Multiple mechanism treatments provide their highest value during the early post-MI period because this time period

experiences rapid disease progression through neurohormonal activation, endothelial dysfunction, and oxidative stress [92].

Clinical hurdles

Vericiguat shows therapeutic potential, but several clinical considerations need resolution before its integration into post-MI prevention strategies [93]. The vasodilatory effects of the drug can cause hypotension as an adverse effect, which may restrict its use in patients who have unstable blood pressure or who are taking multiple vasodilators [94]. The process of patient selection should be conducted with precision, and medical professionals must begin treatment with low doses, which they should increase slowly to decrease risk factors and enhance patient compliance with the treatment plan [95].

Another challenge involves differentiating therapeutic effects across HF phenotypes, especially between HFrEF and HF with

preserved ejection fraction (HFpEF), which differ substantially in their disease mechanisms and response to treatment [96]. The research showed that vericiguat provides benefits to HFrEF patients, but its effectiveness for HFpEF prevention remains unclear because there are different ways in which diastolic dysfunction and systemic inflammation develop [63].

Furthermore, the complexity of polypharmacy in contemporary cardiovascular care necessitates careful evaluation of drug interactions, cumulative haemodynamic effects, and patient-specific tolerability when implementing combination therapy [97].

1. Precision medicine and biomarker-guided therapy

The future of post-MI HF prevention might rely on precision medicine approaches to identify patients who are most likely to benefit from molecular-targeted therapies [98]. Biomarkers of myocardial stress, endothelial dysfunction, and cGMP signalling might help to identify maladaptive remodelling before the onset of clinical HF [99]. Among these, biomarkers related to the oxidation status of sGC and the impairment in NO signalling have shown potential as biomarkers in the responsiveness to sGC stimulation, providing a mechanistic basis for stratifying patients [100]. Natriuretic peptides, inflammatory biomarkers, and molecular imaging could further enhance the prediction and therapeutic time course [101].

In the future, new omics technology and systems biology approaches may help to identify which patients are most likely to benefit from vericiguat and other pathway-directed therapies, which might allow for a more individualised therapeutic approach (conceptual) [102]. Such approaches might eventually lead to a paradigm shift in the management of HF from a reactive to a proactive approach [103].

Collectively, addressing these challenges and leveraging combination strategies, biomarker-guided therapy, and precision medicine will be essential to fully realise the potential of vericiguat in preventing post-MI HF and optimising long-term cardiovascular outcomes [104].

Conclusion

HF after MI is a leading long-term outcome and a powerful predictor of death, even in the current therapeutic era with improved reperfusion strategies and guideline-adherent medical therapy. This is a consequence of the inability to halt the process of adverse remodelling, and the current therapeutic strategies only address the downstream effects of neurohormonal activation, not the upstream effects of the initial injury cascade.

In addition, recent understanding of the nitric oxide-sGC-cGMP signalling axis has significantly altered the current understanding of post-MI disease progression, with endothelial signalling, oxidative stress, and decreased bioavailability of cGMP being identified as major contributing factors to the decline in cardiac function and structure. Within this context, vericiguat may be more than a vasodilator; it is a drug with a unique mechanism of action that targets a range of pathophysiological processes, from fibrosis to

inflammation, microvascular function, metabolic disturbances, and cardiorenal syndrome. Thus, a paradigm shift from a second-line adjunctive therapy for advanced HF to a potential first-line therapeutic strategy to prevent the process of remodelling in the early post-MI period, with the ultimate goal of preventing the transition from localised myocardial injury to global HF, appears to be justified. Such a therapeutic strategy would redefine prevention rather than treatment as the goal of vericiguat's therapeutic action. The therapeutic implications of this paradigm shift are substantial. The incorporation of vericiguat into the early post-MI management of patients, especially those with large infarcts, metabolic disturbances, or early signs of remodelling, may provide an opportunity to prevent the process of remodelling before irreversible cardiac damage occurs.

Future research should be aimed at establishing the timing, identifying responder phenotypes, and understanding the role of sGC stimulation in different phenotypes of HF. Randomised trials, which are specifically designed for post-MI prevention, are the next steps required for translating the therapeutic promise into clinical guidelines. Ultimately, the dynamic evolution of the role of vericiguat represents a paradigm shift in the way cardiovascular medicine is practiced, from a reactive response to treating HF after it has developed to a proactive response aimed at preventing remodelling at its earliest stages of occurrence. This review, by integrating the underlying mechanisms, translational information, and emerging clinical data, emphasises the therapeutic opportunity of targeting the NO-sGC-cGMP axis as a novel therapeutic strategy for the prevention of post-MI HF and the ongoing need for innovation in the field of pathway-directed cardioprotection.

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Author contributions

Author 1: Writing original draft, visualisation, and data curation.

Author 2: Conceptualisation, methodology, and validation.

Author 3: Supervision, review, and editing.

Conflict of interest

The authors declare no conflict of interest.

Ethics statement

This article is a narrative review and does not involve any human participants or animal subjects. Therefore, ethical approval and informed consent were not required.

REFERENCES

1. Khan MA, Hashim M. J, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, et al. Global epidemiology of ischemic heart disease: results from the global burden of disease study. *Cureus*. 2020;12(7):e9349. doi:10.7759/cureus.9349.
2. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403(10440):2162–2203. doi:10.1016/S0140-6736(24)00933-4. Erratum in: *Lancet*. 2024 Jul 20;404(10449):244. doi:10.1016/S0140-6736(24)01458-2.
3. Salari N, Morddarvanjoghi F, Abdolmaleki A, Rasoulpoor S, Khaleghi AA, Hezarkhani LA, et al. The global prevalence of myocardial infarction: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2023;23(1):206. doi:10.1186/s12872-023-03231-w.
4. Safiri S, Karamzad N, Singh K, Carson-Chahhoud K, Adams C, Nejadghaderi SA, et al. Burden of ischemic heart disease and its attributable risk factors in 204 countries and territories, 1990-2019. *Eur J Prev Cardiol*. 2022;29(2):420–431. doi:10.1093/eurjpc/zwab213.
5. Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, et al. Heart failure after myocardial infarction: incidence and predictors. *ESC Heart Fail*. 2021;8(1):222–237. doi:10.1002/ehf2.13144.
6. Jiang H, Fang T, Cheng Z. Mechanism of heart failure after myocardial infarction. *J Int Med Res*. 2023;51(10):3000605231202573. doi:10.1177/03000605231202573.
7. Leancă SA, Crișu D, Petriș AO, Afrăsănie I, Genes A, Costache AD, et al. Left ventricular remodeling after myocardial infarction: from physiopathology to treatment. *Life (Basel)*. 2022;12(8):1111. doi:10.3390/life12081111.
8. Darvish M, Shakoor A, Feyz L, et al. Heart failure: assessment of the global economic burden. *Eur Heart J*. 2025;46(31):3069–3078. doi:10.1093/eurheartj/ehaf323.
9. Gerber Y, Weston SA, Enriquez-Sarano M, Berardi C, Chamberlain AM, Manemann SM, et al. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. *Circ Heart Fail*. 2016;9(1):e002460. doi:10.1161/CIRCHEARTFAILURE.115.002460.
10. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720–3826. doi:10.1093/eurheartj/ehad191.
11. Bucholz EM, Butala NM, Normand ST, Wang Y, Krumholz HM. Association of guideline-based admission treatments and life expectancy after myocardial infarction in elderly medicare beneficiaries. *J Am Coll Cardiol*. 2016;67(20):2378–2391. doi:10.1016/j.jacc.2016.03.507.
12. Zodda E, Tura-Ceide O, Mills NL, Tarragó-Celada J, Carini M, Thomson TM, et al. Autonomous metabolic reprogramming and oxidative stress characterize endothelial dysfunction in acute myocardial infarction. *Elife*. 2023;12:e86260. doi:10.7554/eLife.86260.
13. De Feo D, Massari F, Campanella C, Livrieri A, Ciccone MM, Caldarola P, et al. Influence of soluble guanylate cyclase on cardiac, vascular, and renal structure and function: a physiopathological insight. *Int J Mol Sci*. 2025;26(10):4550. doi:10.3390/ijms26104550.
14. Blanton RM. cGMP signaling and modulation in heart failure. *J Cardiovasc Pharmacol*. 2020;75(5):385–398. doi:10.1097/FJC.0000000000000749.
15. Butler J, Usman MS, Anstrom KJ, Blaustein RO, Bonaca MP, Ezekowitz JA, et al. Soluble guanylate cyclase stimulators in patients with heart failure with reduced ejection fraction across the risk spectrum. *Eur J Heart Fail*. 2022;24(11):2029–2036. doi:10.1002/ehfj.2720.
16. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382(20):1883–1893. doi:10.1056/NEJMoa1915928.
17. Cai Y, Zhang B, Shalamu A, Gao T, Ge J. Soluble guanylate cyclase (sGC) stimulator vericiguat alleviates myocardial ischemia-reperfusion injury by improving microcirculation. *Ann Transl Med*. 2022;10(12):662. doi:10.21037/atm-22-2583.
18. Faridi KF, Bhalla N, Atreya N, Venditto J, Khan ND, Wilson T, et al. New heart failure after myocardial infarction (from the National Cardiovascular Data Registries [NCDR] linked With all-payer claims). *Am J Cardiol*. 2021;151:70–77. doi:10.1016/j.amjcard.2021.04.019.
19. Gawrys, O, Kala P, Šnorek M, Melenovský V, Corda S, Sandner. Exploring the potential of soluble guanylyl cyclase stimulators and activators in heart failure. *Biochem pharmacol*. 2025;242(Pt 3):117363. doi:10.1016/j.bcp.2025.117363.
20. Schirone L, Forte M, Palmerio S, Yee D, Nocella C, Angelini F, et al. A review of the molecular mechanisms underlying the development and progression of cardiac remodeling. *Oxid Med Cell Longev*. 2017;2017:3920195. doi:10.1155/2017/3920195.
21. Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. *Eur Heart J*. 2022;43(27):2549–2561. doi:10.1093/eurheartj/ehac223.
22. Marcos-Garcés V, Bertolín-Boronat C, Merenciano-González H, Martínez Mas ML, Climent Alberola JL, López-Bueno L, et al. Left ventricular remodeling after myocardial infarction-pathophysiology, diagnostic approach and management during cardiac rehabilitation. *Int J Mol Sci*. 2025;26(22):10964. doi:10.3390/ijms262210964.
23. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY, Cabrera-Fuentes HA, Hausenloy DJ. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. *Pharmacol Ther*. 2018;186:73–87. doi:10.1016/j.pharmthera.2018.01.001.
24. Yong J, Tao J, Wang K, Li X, Yang Y. Post-myocardial infarction cardiac remodeling: multidimensional mechanisms and clinical prospects of stem cell therapy. *Stem Cell Rev Rep*. 2025;21(5):1369–1427. doi:10.1007/s12015-025-10888-7.
25. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Fail Rev*. 2011;16(1):13–21. doi:10.1007/s10741-010-9181-7.
26. Zhao W, Zhao J, Rong J. Pharmacological modulation of cardiac remodeling after myocardial infarction. *Oxid Med Cell Longev*. 2020;2020:8815349. doi:10.1155/2020/8815349.
27. Janssens KLPM, Kraamer M, Barbarotta L, Bovendeerd PHM. Post-infarct evolution of ventricular and myocardial function. *Biomech Model Mechanobiol*. 2023;22(6):1815–1828. doi:10.1007/s10237-023-01734-1.
28. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation*. 2000;101(25):2981–2988. doi:10.1161/01.cir.101.25.2981.
29. Udelson JE, Konstam MA. Ventricular remodeling fundamental to the progression (and regression) of heart failure. *J Am Coll Cardiol*. 2011;57(13):1477–79. doi:10.1016/j.jacc.2011.01.009.
30. Gombozhapova A, Rogovskaya Y, Shurupov V, Rebenkova M, Kzhyskowska J, Popov SV, et al. Macrophage activation and polarization in post-infarction cardiac remodeling. *J Biomed Sci*. 2017;24(1):13. doi:10.1186/s12929-017-0322-3.
31. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005;111(21):2837–2849. doi:10.1161/CIRCULATIONAHA.104.500546.
32. Galli A, Lombardi F. Postinfarct left ventricular remodeling: a prevailing cause of heart failure. *Cardiol Res Pract*. 2016;2016:2579832. doi:10.1155/2016/2579832.
33. Obata JE, Horikoshi T, Nakamura T, Kugiyama K. Sustained endothelial dysfunction in the infarct-related coronary artery is associated with left ventricular adverse remodeling in survivors of ST-segment elevation myocardial infarction. *J Cardiol*. 2020;75(3):261–269. doi:10.1016/j.jjcc.2019.08.001.
34. Sun Y. Oxidative stress and cardiac repair/remodeling following infarction. *Am J Med Sci*. 2007;334(3):197–205. doi:10.1097/MAJ.0b013e318157388f.
35. Scherrer-Crosbie M, Ullrich R, Bloch KD, Nakajima H, Nasseri B, Aretz HT, et al. Endothelial nitric oxide synthase limits left ventricular remodeling after myocardial infarction in mice. *Circulation*. 2001;104(11):1286–91. doi:10.1161/hc3601.094298.
36. Bajec T, Poglajen G. Targeting the NO-sGC-cGMP pathway: mechanisms of action of vericiguat in chronic heart failure. *Cells*. 2025;14(17):1400. doi:10.3390/cells14171400.
37. Zuchi C, Tritto I, Carluccio E, Mattel C, Cattadori G, Ambrosio G. Role of endothelial dysfunction in heart failure. *Heart Fail Rev*. 2020;25(1):21–30. doi:10.1007/s10741-019-09881-3.
38. Mace EH, Kimlinger MJ, Billings FT 4th, Lopez MG. Targeting soluble guanylyl cyclase during ischemia and reperfusion. *Cells*. 2023;12(14):1903. doi:10.3390/cells12141903.

39. French BA, Kramer CM. Mechanisms of post-infarct left ventricular remodeling. *Drug Discov Today Dis Mech.* 2007;4(3):185–196. doi:10.1016/j.ddmec.2007.12.006.
40. Numata G, Takimoto E. Cyclic GMP and PKG signaling in heart failure. *Front Pharmacol.* 2022;13:792798. doi:10.3389/fphar.2022.792798.
41. Trujillo ME, Ayalasomayajula S, Blaustein RO, Gheyas F. Vericiguat, a novel sGC stimulator: mechanism of action, clinical, and translational science. *Clin Transl Sci.* 2023;16(12):2458–2466. doi:10.1111/cts.13677.
42. Tricarico L, Correale M, Bevere EML, Daniele Brunetti N, Iacoviello M. The role of Vericiguat in heart failure therapy: from clinical trials to clinical practice. *Rev Cardiovasc Med.* 2025;26(8):39886. doi:10.31083/RCM39886.
43. Zhao Y, Li H, Wu Z, Wang H, Zhang L, Zhang Y, et al. Vericiguat attenuates post-myocardial infarction inflammation associated with macrophage polarization and regulation of the Survivin/Caspase-6 pathway. *FASEB J.* 2026;40(6):e71635. doi:10.1096/fj.202501845RRR.
44. Inserte J, Garcia-Dorado D. The cGMP/PKG pathway as a common mediator of cardioprotection: translatability and mechanism. *Br J Pharmacol.* 2015;172(8):1996–2009. doi:10.1111/bph.12959.
45. Talman V, Ruskoaho H. Cardiac fibrosis in myocardial infarction-from repair and remodeling to regeneration. *Cell Tissue Res.* 2016;365(3):563–581. doi:10.1007/s00441-016-2431-9.
46. Werner F, Prentki Santos E, Michel K, Schrader H, Völker K, Potapenko T, et al. Ablation of C-type natriuretic peptide/cGMP signaling in fibroblasts exacerbates adverse cardiac remodeling in mice. *JCI Insight.* 2023;8(13):e160416. doi:10.1172/jci.insight.160416.
47. Sun X, Sheng Y, Xu P, Peng Q, Ruan Z. Vericiguat reduces atrial fibrillation recurrence by alleviating myocardial fibrosis via the TGF- β 1/Smad2/3 pathway. *PLoS One.* 2025;20(7):e0328272. doi:10.1371/journal.pone.0328272.
48. Ide T, Tsutsui H, Hayashidani S, Kang D, Suematsu N, Nakamura K, et al. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts after myocardial infarction. *Circ Res.* 2001;88(5):529–535. doi:10.1161/01.res.88.5.529.
49. Jungtanasomboon P, Nussaro S, Winwan H, Suebthawinkul P, Boonpala P, Dong VNK, et al. Vericiguat preserved cardiac function and mitochondrial quality in a rat model of mitral regurgitation. *Life Sci.* 2023;328:121929. doi:10.1016/j.lfs.2023.121929.
50. Khoumphinith, E, Zhou Y, Yi Z, Li T, Li L. Vericiguat reduces pyroptosis in rats with coronary microembolization by inhibiting the AMPK/Nrf2/NLRP3 signaling pathway. *Korean J Physiol Pharmacol.* 2025;29(6):755–767. doi:10.4196/kjpp.25.008.
51. Fiori E, Davinelli S, Ferrera A, Medoro A, Barsali C, Battistoni A, et al. The emerging role of Nrf2 in heart failure: from cardioprotection to therapeutic approaches. *ESC Heart Fail.* 2025;12(6):4000–4020. doi:10.1002/ehf2.15406.
52. Takahashi M. Role of NLRP3 inflammasome in cardiac inflammation and remodeling after myocardial infarction. *Biol Pharm Bull.* 2019;42(4):518–523. doi:10.1248/bpb.b18-00369.
53. Krishnamurthy P, Rajasingh J, Lambers E, Qin G, Losordo DW, Kishore R. IL-10 inhibits inflammation and attenuates left ventricular remodeling after myocardial infarction via activation of STAT3 and suppression of HuR. *Circ Res.* 2009;104(2):e9–e18. doi:10.1161/CIRCRESAHA.108.188243.
54. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52(19):1527–1539. doi:10.1016/j.jacc.2008.07.051.
55. Krishnan, SM, Kraehling JR, Eitner F, Bénardeau A, Sandner P. The impact of the nitric oxide (NO)/soluble guanylyl cyclase (sGC) signaling cascade on kidney health and disease: a preclinical perspective. *Int J Mol Sci.* 2018;19(6):1712. doi:10.3390/ijms19061712.
56. Liu X, Tang M, Lu J, Kong Y, Shen W, Zhang C, et al. Vericiguat attenuates cyclosporine A-induced nephropathy by targeting the NF- κ B/TGF- β 1 axis: an integrated network pharmacology, Mendelian randomization, and experimental study. *Front Immunol.* 2026;16:1756582. doi:10.3389/fimmu.2025.1756582.
57. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72(21):2625–2641. doi:10.1016/j.jacc.2018.09.042.
58. Vannuccini F, Campora A, Barilli M, Palazzuoli A. Vericiguat in heart failure: characteristics, scientific evidence and potential clinical applications. *Biomedicine.* 2022;10(10):2471. doi:10.3390/biomedicine10102471.
59. Singh A, Ashraf S, Irfan H, Venjhraj F, Verma A, Shaikat A, et al. Heart failure and microvascular dysfunction: an in-depth review of mechanisms, diagnostic strategies, and innovative therapies. *Ann Med Surg (Lond).* 2024;87(2):616–626. doi:10.1097/MS9.0000000000002971.
60. Chen T, Kong B, Shuai W, Gong Y, Zhang J, Huang H. Vericiguat alleviates ventricular remodeling and arrhythmias in mouse models of myocardial infarction via CaMKII signaling. *Life Sci.* 2023;334:122184. doi:10.1016/j.lfs.2023.122184.
61. Kassis-George H, Verlinden NJ, Fu S, Kanwar M. Vericiguat in heart failure with a reduced ejection fraction: patient selection and special considerations. *Ther Clin Risk Manag.* 2022;18:315–22. doi:10.2147/TCRM.S357422.
62. Gheorghiadu M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, et al. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: The SOCRATES-REDUCED randomized trial. *JAMA.* 2015;314(21):2251–2262. doi:10.1001/jama.2015.15734.
63. Pieske B, Maggioni AP, Lam CSP, Pieske-Kraigher E, Filippatos G, Butler J, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate Cyclase stimulator in heart failure patients with PRESERVED EF (SOCRATES-PRESERVED) study. *Eur Heart J.* 2017;38(15):1119–1127. doi:10.1093/eurheartj/ehw593.
64. Reddy YNV, Butler J, Anstrom KJ, Blaustein RO, Bonaca MP, Corda S, et al. Vericiguat global study in participants with chronic heart failure: design of the VICTOR trial. *Eur J Heart Fail.* 2025;27(2):209–218. doi:10.1002/ehf.3501.
65. Bostan MM, Stătescu C, Anghel L, Șerban IL, Cojocaru E, Sascău R. Post-myocardial infarction ventricular remodeling biomarkers-the key link between pathophysiology and clinic. *Biomolecules.* 2020;10(11):1587. doi:10.3390/biom10111587.
66. Fraccarollo D, Galuppo P, Motschenbacher S, Ruetten H, Schäfer A, Bauersachs J. Soluble guanylyl cyclase activation improves progressive cardiac remodeling and failure after myocardial infarction. *Cardioprotection over ACE inhibition. Basic Res Cardiol.* 2014;109(4):421. doi:10.1007/s00395-014-0421-1.
67. Methner C, Buonincontri G, Hu CH, Vujic A, Kretschmer A, Sawiak S, et al. Riociguat reduces infarct size and post-infarct heart failure in mouse hearts: insights from MRI/PET imaging. *PLoS One.* 2013;8(12):e83910. doi:10.1371/journal.pone.0083910.
68. Dempster T, Corker A, Vu K, Troncoso M, Bradley N, Hazzard A, et al. Modulation of macrophage polarization with acute administration of vericiguat after myocardial infarction. *Am J Physiol Heart Circ Physiol.* 2026;330(3):H890–H903. doi:10.1152/ajpheart.00626.2025.
69. Senni M, Lopez-Sendon J, Cohen-Solal A, Ponikowski P, Nkulikeyinka R, Freitas C, et al. Vericiguat and NT-proBNP in patients with heart failure with reduced ejection fraction: analyses from the VICTORIA trial. *ESC Heart Fail.* 2022;9(6):3791–3803. doi:10.1002/ehf2.14050.
70. Chang PC, Lee HL, Wo HT, Liu HT, Wen MS, Chou CC. Vericiguat suppresses ventricular tachyarrhythmias inducibility in a rabbit myocardial infarction model. *PLoS One.* 2024;19(4):e0301970. doi:10.1371/journal.pone.0301970.
71. Rüdebusch J, Benkner A, Nath N, Fleuch L, Kaderali L, Grube K, et al. Stimulation of soluble guanylyl cyclase (sGC) by riociguat attenuates heart failure and pathological cardiac remodelling. *Br J Pharmacol.* 2022;179(11):2430–2442. doi:10.1111/bph.15333.
72. Silveira CFDSMPD, Malagutte KNDS, Nogueira BF, Reis FM, Rodrigues CDSA, Rossi DAA, et al. Clinical and echocardiographic predictors of left ventricular remodeling following anterior acute myocardial infarction. *Clinics (Sao Paulo).* 2021;76:e2732. doi:10.6061/clinics/2021/e2732.
73. Mao S, Chen P, Pan W, Gao L, Zhang M. Exacerbated post-infarct pathological myocardial remodelling in diabetes is associated with impaired autophagy and aggravated NLRP3 inflammasome activation. *ESC Heart Fail.* 2022;9(1):303–317. doi:10.1002/ehf2.13754.
74. Carlsen CM, Bay M, Kirk V, Gøtzte JP, Køber L, Nielsen OW. Prevalence and prognosis of heart failure with preserved ejection fraction and elevated N-terminal pro brain natriuretic peptide: a 10-year analysis from the Copenhagen Hospital Heart Failure Study. *Eur J Heart Fail.* 2012;14(3):240–247. doi:10.1093/eurjhf/hfs003.

75. Yang H, Luo C, Lan WQ, Tang YH. Vericiguat treatment of heart failure: a systematic review and meta-analysis. *World J Clin Cases*. 2023;11(35):8330–8342. doi:10.12998/wjcc.v11.i35.8330.
76. Dudek D, Dziewierz A, Rakowski T, El Masri N, Sorysz D, Zalewski J, et al. Time-to-reperfusion therapy influences outcome of patients with myocardial infarction subjected to facilitated PCI. *EuroIntervention*. 2005;1(3):309–314.
77. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. *Nat Rev Cardiol*. 2014;11(5):255–265. doi:10.1038/nrcardio.2014.28.
78. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990;81(4):1161–1172. doi:10.1161/01.cir.81.4.1161.
79. Drera A, Rodella L, Brangi E, Riccardi M, Vizzardi E. Endothelial dysfunction in heart failure: what is its role? *J Clin Med*. 2024;13(9):2534. doi:10.3390/jcm13092534.
80. Tsai EJ, Kass DA. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. *Pharmacol Ther*. 2009;122(3):216–238. doi:10.1016/j.pharmthera.2009.02.009.
81. Fritsch A, Meyer M, Blaustein RO, Trujillo ME, Kauh E, Roessig L, et al. Clinical pharmacokinetic and pharmacodynamic profile of vericiguat. *Clin Pharmacokinet*. 2024;63(6):751–771. doi:10.1007/s40262-024-01384-1.
82. Yin X, Yin X, Pan X, Zhang J, Fan X, Li J, et al. Post-myocardial infarction fibrosis: pathophysiology, examination, and intervention. *Front Pharmacol*. 2023;14:1070973. doi:10.3389/fphar.2023.1070973.
83. Tarone G, Balligand JL, Bauersachs J, Clerk A, De Windt L, Heymans S, et al. Targeting myocardial remodelling to develop novel therapies for heart failure: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. *Eur J Heart Fail*. 2014;16(5):494–508. doi:10.1002/ehf.62.
84. Correale M, Pelaggi G, Catanoso MC, Micciché S, Teresi L, Bonanno S, et al. Vericiguat in heart failure with reduced ejection fraction: hope or solid reality? *Heart Fail Rev*. 2024;29(5):1135–1143. doi:10.1007/s10741-024-10425-7.
85. Tang H, Germinal K, Milfort A, Chen WH, Chang SH, Huang W, et al. The most effective combination of pharmacological therapy for heart failure with reduced ejection fraction: a network meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2024;24(1):666. doi:10.1186/s12872-024-04339-3.
86. Xia C, Smith AM, Lefebvre B, Jamal FA, Armenian SH, Koropeczyj-Cox D, et al. Biomarker-guided cardioprotection for patients treated with anthracyclines: a randomized clinical trial. *JAMA Netw Open*. 2025;8(12):e2546201. doi:10.1001/jamanetworkopen.2025.46201.
87. Weldy CS, Ashley EA. Towards precision medicine in heart failure. *Nat Rev Cardiol*. 2021;18(11):745–762. doi:10.1038/s41569-021-00566-9.
88. Norre T, Grimm D, Simonsen U. Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat for congestive heart failure therapy. *Basic Clin Pharmacol Toxicol*. 2022;130(4):425–438. doi:10.1111/bcpt.13714.
89. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400(10354):757–767. doi:10.1016/S0140-6736(22)01429-5.
90. Zhao D, Zhang Y, Yong Y, Wang L, Liu J. Vericiguat combined with “new quadruple” therapy enhances cardiac function and life quality in patients with heart failure: a single-center prospective study. *Front Cardiovasc Med*. 2024;11:1476976. doi:10.3389/fcvm.2024.1476976.
91. Falco L, Brescia B, Catapano D, Martucci ML, Valente F, Gravino R, Contaldi C, et al. Vericiguat: the fifth harmony of heart failure with reduced ejection fraction. *J Cardiovasc Dev Dis*. 2023;10(9):388. doi:10.3390/jcdd10090388.
92. Bellis A, Di Gioia G, Mauro C, Mancusi C, Barbato E, Izzo R, et al. Reducing cardiac injury during ST-elevation myocardial infarction: a reasoned approach to a multitarget therapeutic strategy. *J Clin Med*. 2021;10(13):2968. doi:10.3390/jcm10132968.
93. Cacciapuoti F, Mauro C, Capone V, Chianese S, Tarquinio LG, Gottilla R, et al. The role of Vericiguat in early phases of anterior myocardial infarction: a potential game-changer? *Medicina (Kaunas)*. 2024;60(10):1595. doi:10.3390/medicina60101595.
94. Chioncel O, Mebazaa A, Farmakis D, Abdelhamid M, Lund LH, Harjola VP, et al. Pathophysiology and clinical use of agents with vasodilator properties in acute heart failure. A scientific statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2025;27(6):1067–1088. doi:10.1002/ehf.3673.
95. Cowie MR, Schöpe J, Wagenpfeil S, Tavazzi L, Böhm M, Ponikowski P, et al. Patient factors associated with titration of medical therapy in patients with heart failure with reduced ejection fraction: data from the QUALIFY international registry. *ESC Heart Fail*. 2021;8(2):861–871. doi:10.1002/ehf2.13237.
96. Varnado S, Ali HR, Trachtenberg B. Medical therapy for heart failure with preserved ejection fraction. *Methodist Debaque Cardiovasc J*. 2022;18(5):17–26. doi:10.14797/mdcvj.1162.
97. Radu AF, Radu A, Bungau GS, Tit DM, Vesa CM, Jurca T, et al. Polypharmacy and drug-drug interaction architecture in hospitalized cardiovascular patients: insights from real-world analysis. *Biomedicines*. 2026;14(1):218. doi:10.3390/biomedicines14010218.
98. Hernandez AF, Udell JA, Jones WS, Anker SD, Petrie MC, Harrington J, et al. Effect of empagliflozin on heart failure outcomes after acute myocardial infarction: insights from the EMPACT-MI trial. *Circulation*. 2024;149(21):1627–1638. doi:10.1161/CIRCULATIONAHA.124.069217.
99. Cauwenberghs N, Sabovčik F, Magnus A, Haddad F, Kuznetsova T. Proteomic profiling for detection of early-stage heart failure in the community. *ESC Heart Fail*. 2021;8(4):2928–2939. doi:10.1002/ehf2.13375.
100. Evgenov OV, Pacher P, Schmidt PM, Haskó G, Schmidt HH, Stasch JP. NO-independent stimulators and activators of soluble guanylate cyclase: discovery and therapeutic potential. *Nat Rev Drug Discov*. 2006;5(9):755–768. doi:10.1038/nrd2038.
101. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation*. 2017;135(22):e1054–e1091. doi:10.1161/CIR.0000000000000490.
102. Rasooly D, Pereira AC, Joseph J. Drug discovery and development for heart failure using multi-omics approaches. *Int J Mol Sci*. 2025;26(6):2703. doi:10.3390/ijms26062703.
103. Kotta PA, Nambi V, Bozkurt B. Biomarkers for heart failure prediction and prevention. *J Cardiovasc Dev Dis*. 2023;10(12):488. doi:10.3390/jcdd10120488.
104. Dies RM, Jackson CN, Flanagan CJ, Sinnathamby ES, Spillers NJ, Potharaju P, et al. The evolving role of vericiguat in patients with chronic heart failure. *Cureus*. 2023;15(12):e49782. doi:10.7759/cureus.49782.