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Soluble Guanylate Cyclase Stimulators: a Novel Treatment Option for Heart Failure Associated with Cardiorenal Syndromes?

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Abstract Heart failure in the setting of chronic kidney disease (CKD) is an increasingly common scenario and carries a poor prognosis. Clinicians lack tools for primary or secondary heart failure prevention in patients with cardiorenal syndromes. In patients without CKD, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) and statins mitigate cardiovascular risk in large part due to salutary effects on the endothelium. In the setting of CKD, use of these therapies is limited by adverse effects of hyperkalemia in pre-dialysis CKD (ACE-I/ARB), or potential increased risk of stroke in end-stage renal disease (statins). The soluble guanylate cyclase (sGC) stimulators are a novel class of medications that promote endothelial and myocardial function with no known risk of hyperkalemia or stroke. In this review, we discuss the evidence emerging from recent clinical trials of sGC stimulators in pulmonary hypertension and heart failure, the diseased pathways involved in cardiorenal syndromes likely to be restored by sGC stimulators, and several strategies for designing future clinical trials of cardiorenal syndromes that might shorten the timeline for discovery and approval of effective cardiovascular therapies in these high-risk patients.

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Introduction

Heart failure (HF) is the most common cardiovascular event [1] among the 20 million Americans with chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate [eGFR] <60 ml/min/m^2 or albuminuria) [2]. Several investigations have focused on the prevalence and ramifications of reduced eGFR or albuminuria in patients with HF [3], as well as the risks of hyperkalemia and worsening renal function associated with inhibition of the renin angiotensin aldosterone system (RAAS) in these patients [4]. Many of these patients have some form of cardiorenal syndrome, whether type 4 (CKD leading to cardiovascular disease [CVD]) or type 2 (chronic CVD leading to CKD) [5]. In 2008, approximately 10 % of the $200 billion United States Medicare budget was devoted to patients with concomitant CKD and CVD, highlighting the significant economic burden of cardiorenal syndromes [6].

Despite the public health impact of co-existing HF and renal disease, we lack safe and effective preventive or therapeutic options for cardiorenal syndromes, particularly in patients who already have CKD. Contributing factors to this treatment gap include an incomplete understanding of the mechanisms of CVD in patients with advanced CKD; the risks of hyperkalemia and worsening eGFR associated with the use of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) in advanced CKD; exclusion of patients with CKD from most HF trials due to safety issues or high burden of comorbidities; non-specific inclusion criteria for cardiovascular trials in CKD; and

difficulty recruiting and retaining patients with advanced CKD into clinical trials.

The sGC stimulators are a novel class of medications that activate the enzymatic activity of sGC to produce cyclic guanosine monophosphate (cGMP), an important mediator of endothelial function. The endogenous stimulator of sGC, nitric oxide (NO), is generated by vascular endothelium, and diffuses into adjacent target tissues. sGC itself, the "NO receptor" is located intracellularly in all tissues, with highest expression levels in the myocardium. When NO is inactivated or low, sGC stimulation by these new agents occurs directly in target tissues. Importantly, the sGC stimulators could ameliorate endothelial dysfunction without the risk of hyperkalemia, which prevents the use of ACE-I/ARB in up to one third of CKD patients [7]. Here, we review the pathophysiology of the cGMP pathway, discuss the potential advantages of sGC stimulators for patients with HF and cardiorenal syndromes, and propose strategies for efficient trial design of this novel therapy.

Pathways Leading to HF in Patients with Cardiorenal Syndromes

There are several known pathways leading to HF in patients with cardiorenal syndromes. Left ventricular hypertrophy is prevalent in over 50 % of CKD patients; lower eGFR is associated with higher left ventricular mass across all stages of CKD [8]. The elegant work of Wolf and colleagues has identified the phosphaturic hormone fibroblast growth factor (FGF)-23 as a kidney-specific mediator of left ventricular hypertrophy [9] and predictor of HF in CKD [10]. Anemia is an important risk factor, and iron deficiency may be an important link between anemia, bone metabolism, and cardiovascular disease in CKD [11]. At all stages of CKD, deranged mineral metabolism contributes to vascular calcification, leading to accelerated atherosclerotic disease characterized by medial and intimal plaque calcification. Renin-aldosterone activation leads to sympathetic overactivity, volume overload, and cardiac remodeling in patients with CKD.

There are at least two additional aspects of CKD that, while less studied, implicate cGMP deficiency as a modifiable, pathogenic factor in the development of HF in this population. First, endothelial dysfunction is a characteristic of CKD, and lower eGFR is associated with severity endothelial dysfunction across stages of CKD 1–5 [12]. Mechanisms for endothelial dysfunction in CKD include oxidative stress and higher levels of asymmetric dimethylarginine [12], both of which reduce NO bioavailability. NO is the first signal in the NO-cGMP pathway leading up to intracellular cGMP production, which in turn results in beneficial endothelial properties including vasorelaxation, anti-proliferation, anti-platelet, anti-inflammation, and anti-fibrosis (Fig. 1) [13, 14]. Second, right ventricle (RV) dysfunction and pulmonary hypertension are under- appreciated aspects of cardiorenal syndromes. Pulmonary hypertension is common in end-stage renal disease (ESRD) [15]. A recent study extended these findings to study participants with pre-dialysis CKD, in whom 23 % had estimated pulmonary artery systolic pressure (ePASP) >35 mmHg, and ePASP was associated with adverse cardiovascular outcomes independently of eGFR and left ventricular hypertrophy [16]. Pulmonary hypertension in CKD may be due to increased preload from arteriovenous fistula, abnormal LV diastolic function, obstructive sleep apnea, endothelial function causing pulmonary vasoconstriction, or increased pulmonary vascular stiffening [17]. A therapy such as the sGC stimulators that upregulate production of cGMP independently of NO might overcome NO deficiency in CKD and improve pulmonary endothelial function, with subsequent improvement in pulmonary hypertension (pulmonary vascular resistance, pulmonary artery compliance, and right ventricular-pulmonary artery coupling) in these patients.

Mainstays of Primary and Secondary HF Prevention Have Adverse Effects in CKD: ACE-I/ARB, Statins

The need for novel HF therapies for patients with CKD is compounded by the problems associated with the use of ACE-I/ARB in this population. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend these medications in patients with eGFR <60 ml/min/1.73 m^2 or albuminuria >30 mg per 24 h [18].

However, ACE-I/ARB are often avoided in patients with eGFR < 30 ml/min/1.73 m^2 not yet on dialysis, due to the risk of hyperkalemia or worsening eGFR. In a study of renal clinic patients in the Veterans Administration Health System, nearly one third of 279 CKD patients were not on RAAS blockade despite a clinical indication [7]. The problem of hyperkalemia associated with RAAS inhibition in patients with CKD is so widespread that it was recently addressed by a clinical trial of patiromer, a potassium-lowering medication [19]. There may be a lower risk of hyperkalemia with aldosterone antagonists in anuric ESRD patients. Spironolactone was shown to reduce cardiac events in ESRD patients with urine output <200 ml/day; however, there were discontinuations of the drug due to hyperkalemia and other side effects [20]. Whether ACE-I alone benefits patients with ESRD is uncertain [21], although adding an ARB to background ACE-I treatment did improve outcomes for patient on hemodialysis with reduced ejection fraction [22]. As of 2011, 55 % of patients on dialysis with a diagnosis of HF (ejection fraction [EF] not specified) were not on ACE-I or ARB [23]. Furthermore, statins—which form the mainstay of primary and secondary prevention of cardiovascular disease—may be ineffective [24] or associated with increased risk of stroke in ESRD [25].

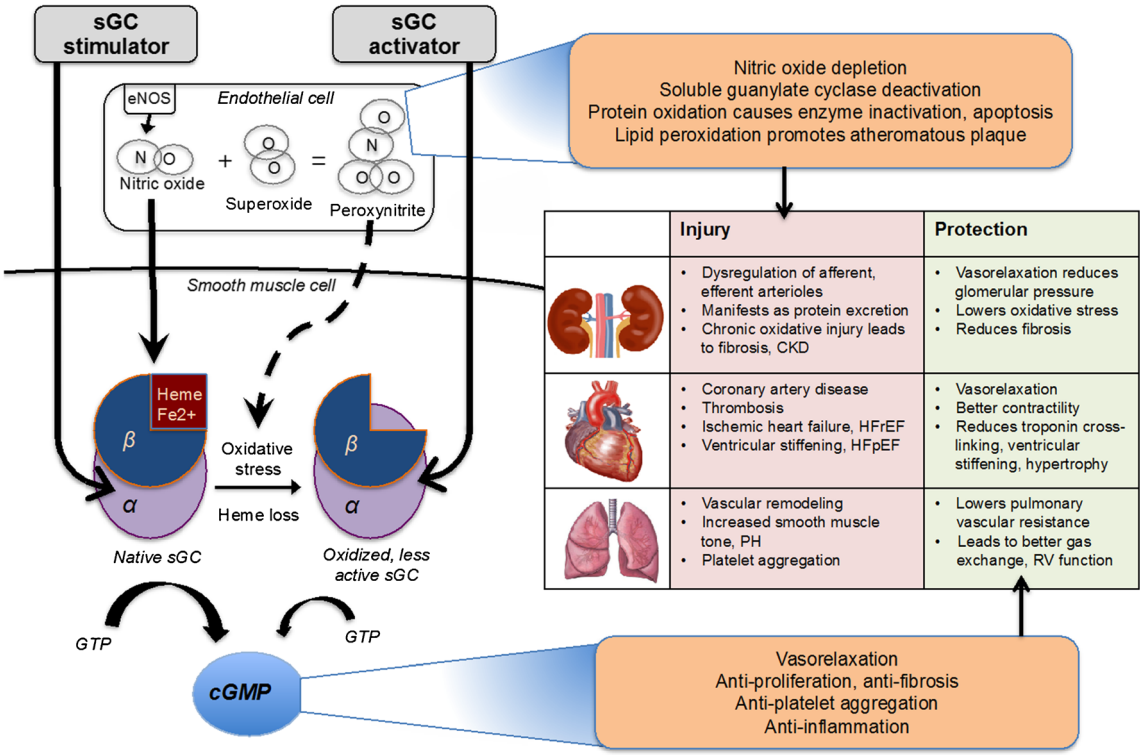

Fig. 1 Actions of the cGMP stimulators on systems involved in cardiorenal syndromes. Starting at the *top left*, this figure illustrates the production of cGMP within the smooth muscle cell via endogenous NO from the endothelium or by exogenous sGC stimulators/activators. The sGC α/β heterodimer is pictured in the native, heme(+) form and the oxidized, heme(−) form. *sGC* soluble guanylate cyclase, *eNOS* endothelial nitric oxide synthase, *GTP* guanosine triphosphate, *cGMP* cyclic guanosine monophosphate

Evidence Base for the Role of the cGMP Pathway in Pulmonary, Cardiac, and Renal Disease

The diverse functions of the endothelium, including vasorelaxation, anti-proliferation, anti-platelet, anti-inflammation, and anti-fibrosis, depend on an intact NO-cGMP pathway (Fig. 1) [13, 14]. NO diffuses into vascular smooth muscle cells and other tissues to stimulate sGC, which converts guanosine triphosphate (GTP) to cGMP, which in turn leads to production of protein kinase-G (PKG) and PKG's downstream effects [13].

Cell culture and animal studies have shed light on organ-specific effects of the NO-cGMP pathway. In the lungs, disruption of the NO-cGMP pathway results in pulmonary vascular remodeling, upregulated smooth muscle tone, and platelet aggregation characteristic of pulmonary hypertension [14]. In the heart, modulation of the NO-cGMP pathway within the cardiomyocyte directly influences ventricular distensibility [26]. Phosphorylation of troponin I by cGMP-dependent kinases prevents troponin cross-linking and myocardial stiffening [27]. Animal studies have shown that titin, a key determinant of diastolic cell length and cardiomyocyte length-tension relationship, is also phosphorylated by cGMP-dependent kinases [28]. When the cGMP-PKG pathway is deficient, titin is hypophosphorylated, leading to cardiomyocyte stiffening. In the coronary vascular smooth muscle, the NO-cGMP pathway permits coronary vasorelaxation, which results in improved perfusion and contractility [29].

In the kidney, impairment of the NO-cGMP pathway leads to interstitial fibrosis and renal tubular apoptosis [30, 31]. NO depletion results in dysregulation of afferent and efferent arterioles and impairs renal medullary flow [14]. A recent review enumerates the large body of preclinical evidence that supports the use of sGC stimulators and activators to mitigate these pro-fibrotic and hemodynamic effects of low NO bioavailability [32]. In rats with sub-total nephrectomy, treatment with the sGC activator cinaciguat slowed progression of kidney disease and left ventricular hypertrophy [33]. Rats with anti-thy-1-induced glomerulosclerosis had reduced glomerular and interstitial inflammation, glomerular proliferation, and matrix deposition, after treatment with the sGC stimulator BAY 41–2272 [34]. In low-renin, high-renin, or salt-sensitive hypertensive rats, the sGC stimulator riociguat reduced cardiac and renal fibrosis and improved cardiac and renal function [35, 36].

Given the importance of the NO-cGMP pathway in the lungs, heart, and kidneys, therapies affecting this pathway may have high potential for preventing or treating HF associated with cardiorenal syndrome [14]. In advanced CKD, NO production is severely impaired by high levels of asymmetric

dimethylarginine and oxidative stress [37]. High oxidative stress negatively impacts the NO-cGMP pathway at several levels. The oxidant peroxynitrite uncouples endothelial NO synthase (eNOS); the uncoupled enzyme shifts from NO to superoxide production, which in turn generates more peroxynitrite. Downstream of NO production, oxidants deactivate NO, and oxidize sGC to its heme-free state, which is less responsive to NO [13]. sGC stimulators sensitize sGC to NO, upregulate sGC production of cGMP independently of NO, and promote the non-oxidized, more active form of sGC by stabilizing the nitrosyl-heme complex [38]. Because the sGC stimulators bypass NO by acting downstream of NO directly on sGC, these agents are potential candidates for treating endothelial dysfunction in severe CKD. Thus, they are effective even in states of low NO bioavailability—in theory, this gives them an advantage over phosphodiesterase type 5 inhibitors, medications that prevent cGMP degradation but have little impact when NO and cGMP levels are low [13].

Clinical Trials of sGC Stimulators

Short- and long-term effects of the sGC stimulator, riociguat, were studied in patients with pulmonary arterial hypertension (Pulmonary Arterial Hypertension sGC- Stimulator Trial [PATENT]-1 and -2) [39, 40] and chronic thromboembolic pulmonary hypertension (Chronic Thromboembolic Pulmonary Hypertension sGC Stimulator Trial [CHEST]-1 and -2) [41, 42]. Six-minute walk distance and World Health Organization functional class improved over a 6-week time period in patients receiving riociguat, and these improvements were sustained after 1 year.

In the Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure (DILATE-1) trial, a single 0.5–2 mg dose of riociguat was given to patients with pulmonary hypertension and heart failure with preserved ejection fraction (HFpEF). While the primary endpoint (reduction in mean pulmonary artery pressure) was not achieved, riociguat did result in higher stroke volume, lower right ventricular end-diastolic volume, and a decrease in systolic blood pressure by 12 mmHg [43]. In the Left Ventricular Systolic Dysfunction Associated with Pulmonary Hypertension Riociguat Trial (LEPHT), 200 patients with pulmonary hypertension due to heart failure with reduced ejection fraction (HFrEF) already on optimal therapy were randomized to placebo or target doses of riociguat 0.5, 1, or 2 mg three times daily over 16 weeks. As in DILATE-1, the primary endpoint, reduction in mean pulmonary artery pressure, was not achieved; however, patients treated in the 2 mg target dose arm had reduced pulmonary and systemic vascular resistance, increased cardiac index, and improved quality of life, without reduction of systolic blood pressure [44]. Notably, DILATE-1 [43] and LEPHT [44] were the only studies to include patients with reduced renal function, and none included patients with eGFR < 30 ml/min/1.73 m2 (Table 1). The parallel-group Soluble Guanylate Cyclase Stimulator in Heart Failure Studies (SOCRATES) trials aimed to study the effects of a once-daily sGC stimulator, vericiguat, in patients recently hospitalized for HFrEF (SOCRATES-Reduced) or HFpEF (SOCRATES-Preserved) [45]. In SOCRATES-Reduced, vericiguat was safe and well-tolerated [46]. The study did not meet its primary endpoint (12-week change in N-terminal pro-B-type natriuretic peptide [NT-proBNP] in the pooled three highest vericiguat dose groups). However, in secondary analyses, there was a dose–response relationship such that NT-proBNP decreased in a step-wise fashion with increasingly higher doses of vericiguat. The SOCRATES-Preserved trial is complete, but the results have not yet been presented. Both SOCRATES studies included patients with moderate CKD (30–59 ml/min/1.73 m^2) and should yield important information on safety and efficacy of sGC stimulation in CKD patients who have concomitant HF. However, it is important to note that both SOCRATES trials involved patients recently hospitalized with worsening HF, a time during which renal function may be quite variable. Thus, determining the true severity of CKD in the enrolled patients may be difficult. In addition, patients with worsening chronic HF (such as those enrolled in the SOCRATES trials) have been notoriously difficult to treat in clinical trials. Thus, in terms of the utility of sGC stimulators in cardiorenal syndromes associated with HF, while the SOCRATES trials will provide some insight, future outpatients studies of cardiorenal patients will likely be able to better inform the long-term benefit of sGC stimulators in this patient population.

Design Considerations for a Trial of sGC Stimulators in Patients with HF and Cardiorenal Syndromes

More efficient testing of HF therapies in patients with cardiorenal syndromes could be accomplished by focusing phase II clinical trials on specific subgroups of patients of similar phenotype, and choosing intermediate endpoints that are most relevant to the disease phenotype (Table 2). For example, in HF patients with mildly reduced eGFR, stabilizing renal function is an important long-term goal. In cardiorenal syndromes, an sGC stimulator could preserve renal function by improving cardiac function; alternatively, sGC stimulators could slow progression of renal disease by direct effects on the kidney. Change in eGFR, endothelial function or left ventricular mass would be appropriate intermediate physiological endpoints. In patients with CKD who do not have HF, in whom preventing HFpEF is an important long-term goal, improving LV diastolic function might be an appropriate intermediate endpoint. sGC stimulators could potentially

Table 1 Previous and ongoing clinical trials of the soluble guanylate cyclase stimulators

Trial	sGC stimulator	Year	Target population; treatment duration	Endpoints primary endpoints = underlined or *italics*	eGFR exclusion criteria	eGFR among participants
PATENT-1 [39]	Riociguat	2013	Symptomatic PAH; 12 weeks	Improved 6-min walk distance, WHO functional class, pulmonary vascular resistance, NT-proBNP	n/a	Not reported
PATENT-2 [40]	Riociguat	2015	Symptomatic PAH; 1 year	Sustained improvements in 6-min walk distance, WHO functional class; *primary endpoint (long-term safety and tolerability) was achieved*	n/a	Not reported
CHEST-1 [41]	Riociguat	2013	CTEPH; 16 weeks	Improved 6-min walk distance, pulmonary vascular resistance, NT-proBNP	n/a	Not reported
CHEST-2 [42]	Riociguat	2015	CTEPH; 1 year	Sustained improvements in 6-min walk distance, WHO functional class; *primary endpoint (long-term safety and tolerability) was achieved*	n/a	Not reported
DILATE-1 [43]	Riociguat	2014	HFpEF with PH; single dose	Improved stroke volume, systolic blood pressure, right ventricular end-diastolic area; *primary endpoint (decrease in mean PAP) was not achieved*	n/a	Serum creatinine range in treatment group: 0.71–1.80
LEPHT [44]	Riociguat	2013	HFrEF with PH; 16 weeks	Improved stroke volume index, cardiac index, pulmonary and systemic vascular resistance, Minnesota Living with Heart Failure score; *primary endpoint (decrease mean PAP) was not achieved*	<30 ml/min/1.73 m^2	Mean eGFR >60 ml/min/1.73 m^2
SOCRATES-Reduced [46]	Vericiguat	2015	WCHF	Dose response relationship whereby higher vericiguat doses were associated with greater reductions in NT-proBNP; primary endpoint (change in NT-proBNP in the pooled three highest-dose vericiguat groups) was not achieved	<30 ml/min/1.73 m^2	58.4 ± 19.5 ml/min/1.73 m2
SOCRATES-Preserved [45]	Vericiguat	*Ongoing*	WCHF	Change in NT-proBNP, left atrial volume index	<30 ml/min/1.73 m^2	*Ongoing*

Clinical trials of the sGC stimulators, riociguat and vericiguat, are shown above with patient population, endpoints, and eGFR exclusion criteria

PAH pulmonary arterial hypertension, *CTEPH* chronic thromboembolic pulmonary hypertension, *PAP* pulmonary artery pressure, *WCHF* worsening chronic heart failure requiring hospitalization or IV diuretics

Table 2 Proposed intermediate cardiovascular endpoints for clinical trials to prevent or treat heart failure associated with cardiorenal syndromes

Patient subgroup	Clinical problem	Potential effect of sGC stimulator	Appropriate short- or intermediate-term endpoints
HF patients with mildly reduced eGFR	Progression of CKD	Slow progression of cardiac and renal disease by improving endothelial function during the pre-dialysis period when most patients are taken off ACE-I/ARB	Left ventricular mass Endothelial function measured by flow mediated dilation Change in eGFR
CKD	Development of HFpEF	Improve diastolic function and cardiac mechanics Decrease LV wall stress	High sensitivity troponin (marker of ongoing myocardial injury) BNP or NT-proBNP Left ventricular mass[a] Diastolic function measured by Doppler and tissue Doppler imaging Indices of cardiac mechanics (e.g., longitudinal strain) measured by speckle-tracking echocardiography
Pre-dialysis or end-stage renal disease undergoing fistula placement	Pulmonary hypertension following fistula placement	Prevent right ventricular dysfunction occurring after fistula placement	Right ventricle function structure and function measured with comprehensive echocardiography (including speckle-tracking analysis of right ventricular free wall strain) and/or cardiac MRI before and after fistula placement Right heart catheterization before and after fistula placement

In future clinical trials of heart failure associated with cardiorenal syndromes, it may be useful to specify inclusion and exclusion criteria according to the clinical problem that the therapy is meant to address, and choosing appropriate short-term physiological endpoints

eGFR estimated glomerular filtration rate, *CKD* chronic kidney disease

[a] Measurements of LV mass with non-contrast MRI, as opposed to echocardiogram, would reduce sample size. These strategies may decrease sample size and yield results that are easier to interpret and to apply clinically

increase cGMP levels, reduce troponin and titin cross-linking and prevent the ventricular stiffening [27, 28, 47] that can lead to HFpEF. Diastolic function, measured by Doppler and tissue Doppler echocardiography, cardiac mechanics measured by speckle-tracking analysis, and left ventricular mass measured by echocardiography or cardiac magnetic resonance (CMR) imaging would be useful intermediate endpoints.

In addition to focusing trials on subgroups of participants with similar cardiac phenotype, a potential strategy for augmenting statistical power, lowering sample size, and shortening trial duration would be to use imaging modalities such as speckle-tracking echocardiography (STE) or CMR imaging. These imaging modalities provide highly reproducible measurements, allowing for a smaller sample size in a clinical trial without sacrificing the power needed to detect a significant change in a given index of cardiac function. STE is sensitive to small decrements of systolic dysfunction among patients with normal EF, and these differences in systolic function predict mortality in patients HFpEF [48] or ESRD [49, 50], providing further support of the utility of STE in this population. CMR provides higher accuracy and reproducibility in measurement of LV mass than either 2D or 3D echocardiography, and unlike cardiac CT, does not require potentially harmful contrast. For example, the sample size needed to detect a 10-g change in LV mass by CMR is only ten patients each in placebo and treatment group; the sample size would need to be six times larger if 2D echo is used instead [51].

A larger sample size, coupled with examination of LV mass by CMR, would allow detection of smaller changes in LV mass, potentially shortening the duration of the clinical trial.

Conclusions

The sGC stimulators may have a particular role in preventing or treating HF in the setting of advanced CKD as they would not be expected to carry the risks of hyperkalemia or worsening renal function that limit the use of ACE-I/ARB in these patients. Focusing future clinical trials on subgroups most likely to benefit and employing sensitive imaging modalities such as STE and cardiac MRI as intermediate physiological endpoints could expedite the evaluation of sGC stimulators and other novel therapies for treatment and prevention of HF associated with cardiorenal syndromes.

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Compliance with Ethical Standards

Conflict of Interest Ruth F. Dubin declares that they have no conflict of interest.

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