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Partial adenosine A1 receptor agonism: a potential new therapeutic strategy for heart failure

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Abstract Heart failure (HF) represents a global public health and economic problem associated with unacceptable rates of death, hospitalization, and healthcare expenditure. Despite available therapy, HF carries a prognosis comparable to many forms of cancer with a 5-year survival rate of ~50 %. The current treatment paradigm for HF with reduced ejection fraction (EF) centers on blocking maladaptive neurohormonal activation and decreasing cardiac workload with therapies that concurrently lower blood pressure and heart rate. Continued development of hemodynamically active medications for stepwise addition to existing therapies carries the risk of limited tolerability and safety. Moreover, this treatment paradigm has thus far failed for HF with preserved EF. Accordingly, development of hemodynamically neutral HF therapies targeting primary cardiac pathologies must be considered. In this context, a partial adenosine A1 receptor (A1R) agonist holds promise as a potentially hemodynamically neutral therapy for HF that could simultaneous improve cardiomyocyte energetics, calcium homeostasis, cardiac structure and function, and long-term clinical outcomes when added to background therapies. In this review, we describe the physiology and pathophysiology of HF as it relates to adenosine agonism, examine the existing body of evidence and biologic rationale for modulation of adenosine A1R activity, and review the current state of drug development of a partial A1R agonist for the treatment of HF.

Keywords Adenosine · Adenosine A1 receptor · Partial agonist · Therapy · Heart failure · Mitochondria

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The global prevalence of heart failure (HF) continues to rise and carry significant mortality, morbidity, and healthcare costs. Despite provision of guideline-recommended therapies, survival for patients with HF is comparable or worse than many cancers [1]. Although multiple early therapeutic breakthroughs have substantially improved outcomes for patient with chronic HF and reduced ejection fraction (EF), with few notable exceptions [2, 3], there have been few successes in the HF clinical trial arena over the past decade [4]. Built on the success of early trials, the current treatment paradigm for patients with HF with reduced EF (HFrEF) centers on systemic blockade of maladaptive neurohormones in efforts to attenuate, halt, or reverse adverse cardiac remodeling and improve clinical

outcomes. However, these therapies may carry significant concurrent hemodynamic effects (i.e., reducing heart rate, preload, and/or afterload) and repeated stepwise addition of such hemodynamically active medications raises tolerability and safety concerns (e.g., hypotension and bradyarrhythmias) [5]. Likewise, the high failure rate of phase III HFrEF trials in recent years suggests that incremental benefit with the addition of such agents may be difficult or unattainable [6], and hemodynamic compromise represents a frequent reason for failed HF drug development [5]. This difficult landscape for HF drug development is particularly troubling considering the complete absence of effective therapy for HF with preserved EF (HFpEF), a condition that accounts for approximately half of all HF diagnoses. Attempts to reproduce benefits of neurohormonal antagonism seen in HFrEF have thus far been unsuccessful in HFpEF populations.

The difficulties encountered in the discovery of novel effective drugs for the treatment of HFrEF and HFpEF have fostered research efforts to develop so-called hemodynamically neutral treatments that directly target intrinsic myocardial pathophysiology, while manipulating central hemodynamics to a much lesser extent [5, 7–11]. Along these lines, partial adenosine A1 receptor (A1R) agonism represents a promising novel approach. Preclinical data using these partial agonists suggest an ability to attenuate or reverse progressive left ventricular (LV) remodeling and favorably influence myocardial energetics without eliciting hemodynamic effects such as hypotension or bradycardia [12]. In this review, we examine the physiology and pathophysiology of HF as it relates to adenosine agonism, review the existing body of evidence and biologic rationale for modulation of adenosine A1R activity in HF, and describe the current state of drug development of a partial A1R agonist for HF.

Adenosine A1 receptor physiology

Adenosine is a purine nucleoside that exerts a variety of physiological actions by binding to adenosine cell surface receptor subtypes, namely A1, A2a, A2b, and A3. Adenosine acts as a cytoprotective modulator linking cardiac function to metabolic demand under physiological and pathophysiologic conditions. The primary physiological undertaking of adenosine is to preclude tissue injury and promote repair in response to stress by different mechanisms [13–15]. The cardio-protective effects of adenosine have been extensively studied and are primarily mediated by activation of the A1R subtype. The adenosine A1R is a G-protein-coupled receptor expressed in multiple body tissues including the heart, brain, adipose tissue, and kidney. In the heart, the highest densities of receptors are found in smooth muscle cells and cardiomyocytes within the atria, with lower expression in the ventricles [16]. Activation of adenosine A1R results in downstream inhibition of adenyl cyclase and reduction in intracellular levels of cyclic adenosine monophosphate (cAMP) [15, 17]. Such adenyl cyclase modulation combats sympathetic over-activation and augments release of atrial natriuretic peptide, thus favoring a cardioprotective state [18–20]. Adenosine A1Rs also influence phospholipase C-mediated processes. The modulation of mitochondrial K_{ATP} channels via A1 receptor activation of protein kinase C results in reduction in mitochondrial protein transition pore opening and thereby improvement of mitochondrial function under hypoxic conditions [21]. Intracardiac calcium currents are also modulated by the A1R, primarily at the atrioventricular node via nitric oxide-dependent mechanisms [22]. Furthermore, the A1R is coupled to pertussis-toxin-sensitive potassium channels and K_{ATP} channels [23].

Collectively, via these processes, A1R activation favors cardiac protection. However, activation of the A1R using *full* agonists, while offering potential therapeutic benefits, is limited by side effects including bradycardia, atrioventricular blocks, vasoconstriction, negative inotropy and dromotropy, sedation, and anti-diuretic effects [15]. These potentially undesirable physiological effects may be overcome with use of a *partial* A1R agonist (Fig. 1) [12, 24].

Adenosine modulation in heart failure

To date, there has been only one published preclinical study exploring the impact of partial adenosine A1R agonism in HF [12]. In contrast, extensive work has explored adenosine A1R *antagonism*, driven primarily by perceived benefits of adenosine blockade on renal function, including prevention of afferent arteriole constriction and proximal tubule sodium reabsorption [25]. This potential for renal benefit with adenosine antagonism led to large-scale drug development programs with adenosine A1R antagonists,

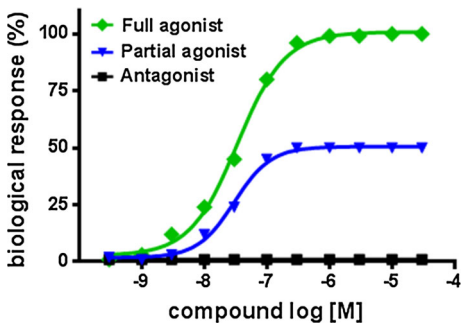

Fig. 1 Adenosine A1 receptor activation by a full or partial agonist or blockade by an antagonist in the presence of adenosine

such as rolofylline, that included multiple phase II and phase III clinical trials. Phase II experiences were generally "positive," suggesting rolofylline could augment urine output while preserving or improving glomerular filtration rate among patients with HFrEF and moderate renal insufficiency [4, 26, 27]. However, the subsequent large phase III study was neutral, demonstrating no benefit on symptoms, renal function, mortality, or rehospitalization [28]. Also, higher rates of persistent renal impairment, seizure, and stroke were noted in the rolofylline group [28, 29]. Indeed, ~1 % of rolofylline patients experienced seizures, a well-recognized risk of adenosine A1R antagonism, as compared to none with placebo [28, 30]. Failure of the rolofylline program provided support, albeit indirect, to continue development of a partial adenosine agonist program for the treatment of HF.

Rationale for partial adenosine A1 receptor agonism for heart failure

The goal of HF therapy is to restore cardiac structure and function, or at least, slow the rate of progression toward a worsening HF state. Ideally, such improvements in intrinsic cardiac structure would be durable and persist for a reasonable period of time even after withdrawal of the therapy (i.e., not related directly to the immediate ingestion of the medication). Therapies proven to improve survival in HFrEF (e.g., beta-blockers, angiotensin-converting enzyme inhibitors) have shown the ability to reverse remodel the failing LV. This benefit, however, may come at a risk of significant hemodynamic effects that can limit tolerability or prevent achievement of target dosing (e.g., in one long-term registry, only 30 % of patients received target dosages of these drugs) [31]. In contrast, positive inotropic agents can improve hemodynamics acutely but at the risk of increased mortality [32].

Accordingly, alternative therapeutic targets with hemodynamically neutral mechanisms (i.e., minimal hypotension and bradycardia) are being increasingly explored. Such agents include those that improve mitochondrial function, energetics, intracellular calcium handling, cardioprotection, and reversal of interstitial fibrosis. Despite potential therapeutic benefits with *full* A1R agonism, undesired effects of this strategy have limited further drug development. Accordingly, efforts have been directed toward development of partial A1R agonists that elicit beneficial effects (e.g., cardioprotection, reverse LV remodeling) while maximizing safety by avoiding off target side effects. Based on pharmacologic and preclinical data, as compared to full agonists, partial agonists exert minimal effects on blood pressure, heart rate, AV conduction, central nervous system, and renal function [12, 24]. Furthermore, no relevant negative inotropy is observed in animal models [12]. Thus, a partial A1R agonist may fulfill many of the characteristics of an ideal hemodynamically neutral HF therapy and exert benefits via multiple mechanisms (Table 1; Fig. 2).

Table 1 Potential mechanisms of benefit from a partial adenosine A1R agonist in heart failure

Improve mitochondrial function
Increase levels of mitochondrial uncoupling proteins
Decrease rate of opening of mitochondrial permeability transition pores leading to reduced apoptosis
Decrease reactive oxygen species production
Improve efficiency of electron transport chain and ATP production
Protection from Ca^{2+} overload and resultant mitochondrial damage
Energy substrate utilization
Increase expression of GLUT-1 and GLUT-4 glucose transporters
Decrease levels of fatty acid oxidation
Reverse ventricular remodeling
Reduce interstitial fibrosis
Prevent myocyte hypertrophy
Preserve myocardial capillary density and oxygen diffusion distances
Anti-ischemic cardioprotective effects
Improved Ca^{2+} handling and protection from Ca^{2+} overload
Attenuate mechanical and metabolic responses to excessive adrenergic stimulation
Decrease catecholamine release

Mitochondrial function

The failing heart is characterized by abnormal mitochondrial structure and function including hyperplasia and reduced organelle size, poor organelle respiration, reduced mitochondrial membrane potential, opening of membrane permeability pores, and reduced rates of adenosine triphosphate (ATP) synthesis [8, 12, 33, 34]. In addition, mitochondrial dysfunction is associated with derangements in the electron transport chain and excessive production of reactive oxygen species (ROS) [8, 34, 35]. Excessive generation of ROS by mitochondria can exert widespread adverse effects on the heart through damage to cellular and subcellular components that include key signaling pathways, membrane lipid sublayers, and the extracellular matrix [8, 36]. Mitochondrial uncoupling proteins, particularly UCP-2 and UCP-3, are necessary for preserving appropriate mitochondrial membrane potential and regulating production of ATP and ROS [37, 38]. Thus, restoring the integrity of mitochondrial membranes and optimizing their number and function represent emerging therapeutic targets.

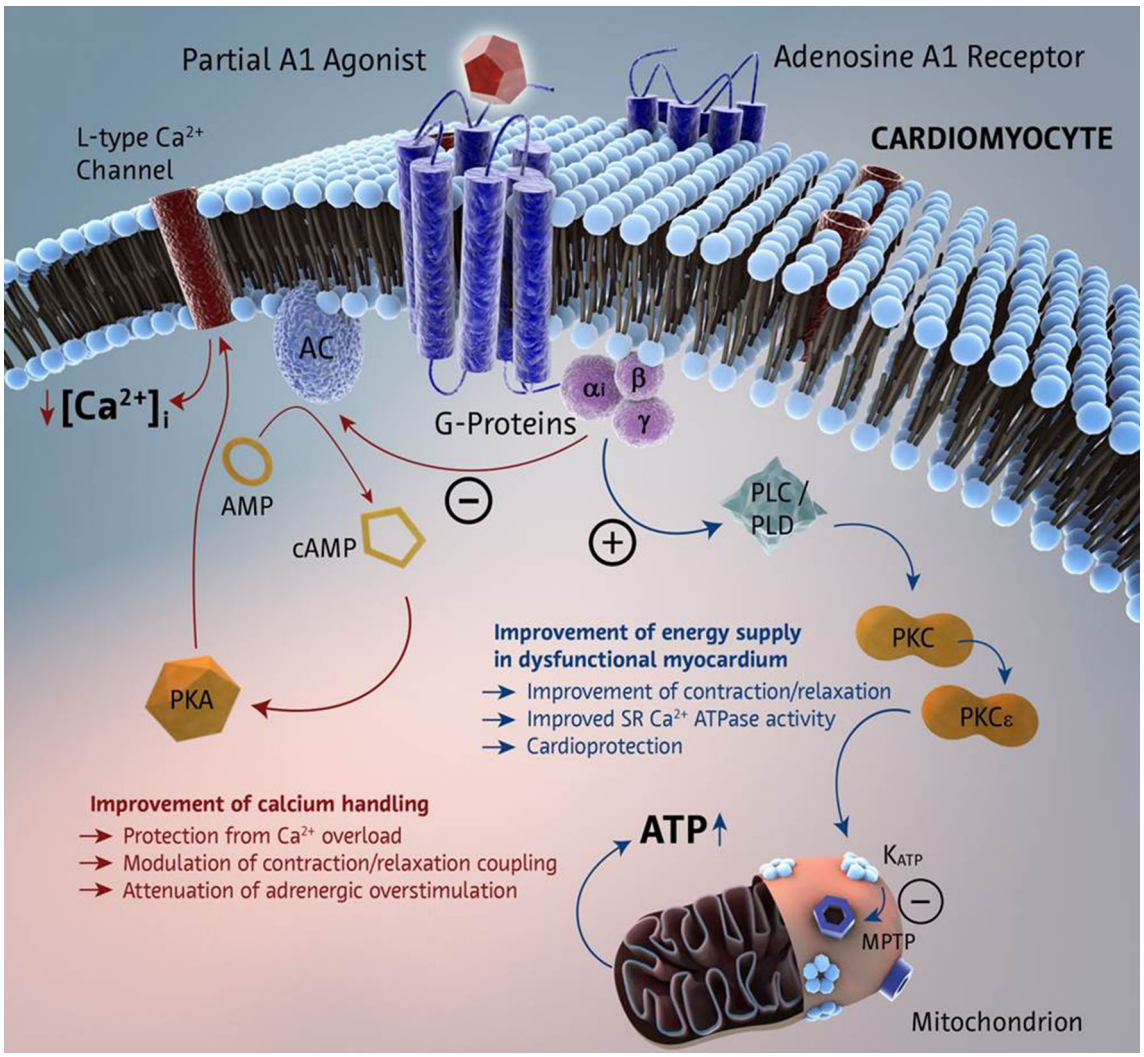

Fig. 2 Adenosine A1 receptor signaling pathways in the failing heart. *AC* adenylate cyclase; K_{ATP} ATP-dependent potassium channel, *MPTP* mitochondrial permeability transition pore, *PKA* phosphokinase A, *PLC* phospholipase C, *PLD* phospholipase D, *SR* sarcoplasmic reticulum

Canine models receiving the partial A1R agonist capadenoson offer strong evidence that modulation of this pathway is a viable strategy for treating mitochondrial dysfunction in HF [12]. In the untreated control HF arm, expression of UCP-2 and UCP-3 was reduced compared to normal, whereas in HF animals treated with capadenoson, a near normalization of UCP-2 and UCP-3 protein levels was observed [12]. Likewise, treatment with capadenoson improved sarcoplasmic reticulum calcium-ATPase (SERCA-2a) activity, leading to decreased intracellular calcium overload (Fig. 3) [12]. Lastly, capadenoson appeared to regulate mitochondrial permeability transition pores (mPTP), a key regulator of cellular apoptosis [12]. In HF, these pores may demonstrate increased opening, facilitating increased rates of apoptosis [39]. Preclinical evidence suggests adenosine agonists are capable of preventing this increased rate of mPTP opening and maintaining mitochondrial and cell viability [21]. These results are consistent with findings from the capadenoson canine study, where adenosine normalized expression of citrate synthase, an established marker of intact mitochondria [12]. In aggregate, these effects of partial adenosine A1R agonism support improvement in the efficiency of mitochondrial electron transport chain and, therefore, a potential for an improvement in the rate of ATP synthesis and attenuation of excessive ROS formation.

Myocardial energy substrate utilization

Besides mitochondrial dysfunction, the failing heart may undergo other separate maladaptive changes in energetics. HF is characterized by an added reliance on fatty acid oxidation, with downregulation of myocardial glucose transporters [40, 41]. These changes characterize the

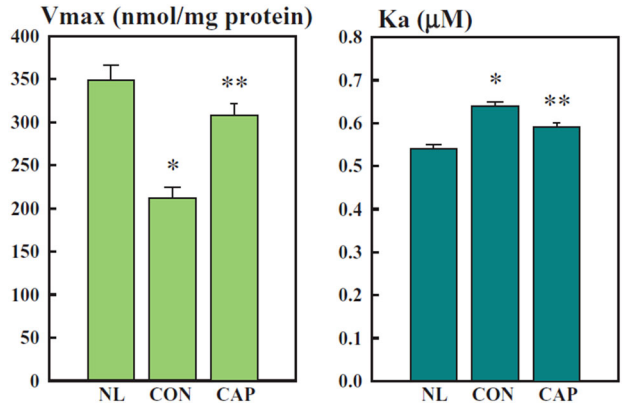

Fig. 3 *Left panel*: *Bar graphs* depicting changes in Ca^{2+}-ATPase activity (Vmax) in left ventricular (LV) myocardium. *Right panel*: *Bar graphs* depicting changes in affinity for calcium (Ka) in LV myocardium. Changes are for normal (NL) dogs, untreated heart failure control dogs (CON), and dogs with heart failure treatment with capadenoson (CAP). Data are shown as mean ± SEM. $*P < 0.05$ versus NL; $**P < 0.05$ versus CON. Reprinted with permission from Sabbah et al. [12]

transition of the failing heart to a fetal metabolic phenotype and gene profile, an adaptation that can further promote HF progression [40–42]. Animal studies suggest that partial A1R agonists can augment expression of the GLUT-1 and GLUT-4 glucose transporters to near-normal levels [12]. Moreover, therapy with a partial A1R agonist has also been associated with normalization of protein levels that mediate fatty acid oxidation and reduction in free fatty acid plasma levels [12, 43]. Thus, A1R agonism appears capable of partially correcting derangements in cardiac substrate utilization and restoring a physiological metabolic profile in HF.

Reverse remodeling

Decreases in ventricular filling pressures and augmentation of cardiac output can be seen acutely with multiple medications and are not uniformly associated with improved outcome [32]. Structural recovery of the failing heart with global reverse ventricular remodeling represents a more elusive goal but one that is more often associated with long-term clinical benefit. Overall, the biology of cardiac structural recovery in HF is not fully understood but has been described as at least partial reversal of cardiomyocyte structure and function and extracellular matrix abnormalities facilitating improved ventricular geometry and contractile performance [44]. The relative proportion of dysfunctional viable myocardium and the nature of the myocardial interstitium are recognized as key factors in this process [7, 9].

Beyond beneficial effects on cardiac myocytes themselves, adenosine A1R agonism may exhibit favorable remodeling by altering the extracellular matrix with a reduction in interstitial fibrosis. Such changes would favor improvements in ventricular compliance and filling, as well as preservation of acceptable cardiac capillary density and oxygen diffusion distances. Twelve-week treatment with capadenoson was associated with a significant increase in EF and decreases in end-diastolic and systolic volumes and natriuretic peptides (Fig. 4) [12]. Moreover, capadenoson treatment mediated improvements in volume fraction of interstitial fibrosis, capillary density, oxygen diffusion distance, and myocyte hypertrophy [12].

Cardioprotection

Adenosine has been shown in animal and human studies to be cardioprotective [45, 46]. The major underlying mechanism appears to be maintenance of intracellular homeostasis and ischemia prevention, potentially mediated by activation of downstream effectors (e.g., protein kinase C, K_{ATP} channels, mitogen-activated protein kinase) and inhibition of adenylate cyclase activation and reduction in cyclic adenosine monophosphate [47, 48]. Among patients with angina pectoris, treatment with capadenoson prolonged total exercise time and time to ischemia [49]. Adenosine carries anti-adrenergic properties that can protect the heart from adverse mechanical and metabolic activation from excessive catecholamine stimulation, thereby limiting ischemia. Activation of the A1R may also inhibit norepinephrine release [50]. Conceivably, these effects may be important for preventing disease progression and further adverse remodeling, particularly in those ongoing or latent ischemia.

Development of a partial A1R agonist for human heart failure

HF is not a disease but a final common syndrome stemming from various admixtures of cardiac and noncardiac abnormalities. As we increasingly recognize the heterogeneity in cardiac substrates, comorbidities, biomarkers, and reasons for HF progression, it has been proposed that future development of novel therapeutics begins with investigation in homogenous HF subsets deemed most likely to benefit from the study drug [51]. Generally speaking, it is felt that patients with large segments of dysfunctional but viable myocardium constitute an ideal platform for testing novel therapies, but other traditional parameters such as EF, natriuretic peptides, and comorbidities (e.g., atrial fibrillation, coronary artery disease, diabetes, renal disease) should continue to be considered in conjunction [4, 7, 11].

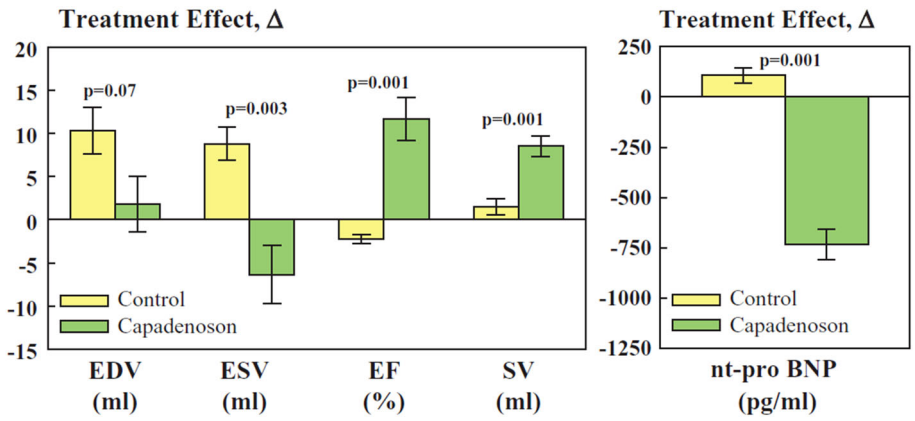

Fig. 4 *Left panel*: Change (treatment effect) between pre-treatment and 12 weeks post-treatment of left ventricular (LV) end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and stroke volume (SV) in untreated control dogs and dogs treated for 3 months with capadenoson. *Right panel*: Change (treatment effect) between pre-treatment and 12 weeks post-treatment in plasma levels of n-terminal pro-brain natriuretic peptide (NT-proBNP). Data are shown as mean ± SEM. Probability values are comparisons between untreated control and capadenoson. Reprinted with permission from Sabbah et al. [12]

Identifying hurdles to successful development of these agents is difficult at this early stage. Obvious attention must be given to monitoring for side effects typical of full adenosine agonists to ensure that the sound preclinical safety profile of partial agonists remains applicable to human subjects. New opportunities are emerging in the area of "eHealth" that offer potentially useful tools for ensuring patient safety. For example, remote telemonitoring devices can continuously monitor and automatically transmit electrocardiogram data to centers for real-time monitoring (e.g., auto-trigger electrocardiogram data upon event onset with notification episode reporting). However, although such novel methods of patient monitoring and selection may be helpful in homogenizing study cohorts in smaller phase II/proof-of-concept studies (e.g., monitoring devices, biomarkers, genomics, cardiac magnetic resonance), the feasibility of these instruments in subsequent large trials remains to be seen.

Conclusions

Heart failure remains a growing public health problem with unacceptable long-term outcomes despite the use of guideline-directed medical and device therapies. Continued development of more potent hemodynamically active medications for stepwise addition or replacement of existing therapy carries an inherent risk of poor tolerability and safety [5]. Moreover, application of this approach in HFpEF has been unsuccessful. It is under this framework where a partial A1R agonist for HF holds promise—a potentially hemodynamically neutral therapy that could simultaneously improve cardiomyocyte energetics, cardiac structure and function, and prevent further tissue injury while being well tolerated when added to background medical therapy. Although drug development of a partial A1R agonist remains at an early stage, compelling biologic rationale and encouraging preclinical evidence support continued attention be given to ongoing and future trials with these agents in HF.

Compliance with ethical standards

Conflict of interest Dr. Greene reports no conflicts. Dr. Sabbah has received research Grants and/or is consultant to Bayer Healthcare AG, Stealth Peptides, Inc., Amgen Corp., Johnson & Johnson, Inc., Novartis Corp., Merck, and Takeda Pharmaceuticals. Dr. Butler reports research support from the National Institutes of Health, European Union, and Health Resources Service Administration and is a consultant to Amgen, Bayer, BG Medicine, Cardiocell, Celladon, Gambro, GE Healthcare, Medtronic, Novartis, Ono Pharma, Takeda, Trevena, and Zensun. Dr Voors received consultancy fees and/or research Grants from: Alere, Amgen, Bayer, Boehringer, Cardio3Biosciences, Celladon, GSK, Merck/MSD, Novartis, Servier, Singulex, Sphingotec, Trevena, Vifor, ZS Pharma, and is supported by a Grant from the European Commission: FP7-242209-BIOSTAT-CHF. Drs. Albrecht-Küpper and Dinh are employees of Bayer Healthcare. Dr. Düngen has received research grants and/or is consultant to Bayer Healthcare AG, Amgen Corp., Novartis, Trevena, Celladon, AstraZeneca and reports research support from German Ministry of Education and Research. Dr. Gheorghiade has been a consultant for Abbott Laboratories, AstraZeneca, Bayer Schering Pharma AG, Cardiocell LLC, Cardiorentis Ltd, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Pharmaceuticals USA, Otsuka Pharmaceuticals, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Stealth BioTherapeutics, Sticares InterACT, Takeda Pharmaceuticals North America, Inc and Trevena Therapeutics.

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