

# New Drugs You are Going to Read About: Serelaxin, Ularitide, TRV027

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**Abstract** Nitrovasodilators have long been used as first-line treatment for hypertensive acute heart failure (AHF). Although effective for BP control and symptom alleviation, this class of agents has never been shown to improve mortality or prevent hospital readmissions. Consequently, there has been tremendous interest in development of newer vasodilators with more beneficial therapeutic profiles. In this review, we focus on three of the most promising agents currently being studied: serelaxin, ularitide, and TRV027. While regulatory approval has yet to be obtained, should they prove beneficial in on-going trials, we are looking at a new era of drug therapy that could supplant more conventional treatments and broaden the horizon for management of patients with AHF.

**Keywords** Drug development · Acute heart failure · Nitrovasodilators · TRV027 · BP control

## Introduction

Nitrovasodilators (isosorbide mono- and dinitrate, nitroglycerin, and nitroprusside) have long been used as first-line treatment for hypertensive acute heart failure (AHF). As a class, nitrovasodilators share a common mechanism of action that involves provision of exogenous nitric oxide (NO), which then binds to soluble guanylate cyclase (sGC), producing cyclic guanosine monophosphate (cGMP) and vascular smooth muscle relaxation [1]. While use of these agents is largely reserved for patients with elevated blood pressure (BP), there are data to suggest that normotensive patients may also derive benefit, particularly when improved forward flow through afterload reduction is needed [2]. As such, the horizon for use of vasodilators in the treatment of AHF may be expanding.

Although effective for BP control and symptom alleviation, nitrovasodilators have never been shown to affect hard outcomes (i.e., readmission or death) [3]. Consequently, there has been tremendous interest in development of newer vasodilators with more beneficial therapeutic profiles. In this review, we focus on three of the most promising agents currently being studied: serelaxin, ularitide, and TRV027 (Table 1).

## Serelaxin

Serelaxin is a pharmaceutical analog of relaxin, a 53 amino acid protein composed of two peptides connected by disulfide bridges, a structure very similar to insulin. Relaxin is a naturally occurring hormone released in pregnancy that helps regulate hemodynamic function by increased arterial compliance, reduction in total peripheral resistance, vasodilation, enhancement of glomerular filtration rate (GFR),

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**Table 1** Comparison of on-going serelaxin, ularitide, and TRV027 clinical trials

| Active drug        | Serelaxin   | Ularitide   | TRV027   |
|--------------------|---|---|--|
| Trial name         | RELAX-AHF 2   | TRUE-AHF  | BLAST-AHF  |
| Study design       | Phase III double-blind RCT  | Phase III double-blind RCT  | Phase II double-blind RCT  |
| Targeted number    | 6375 patients   | 2152 patients   | 500 patients   |
| Active drug dosing | 30 µg/kg/day  | 15 ng/kg/min  | Comparison of 3 doses with placebo   |
| Inclusion criteria | Male or female aged 18–85 years, with body weight ≤160 kg<br>Hospitalized for AHF defined by dyspnea at rest or with minimal exertion with AHF defined by pulmonary congestion on chest radiograph; and BNP ≥ 350 pg/mL or NT-proBNP ≥ 1400 pg/mL<br>Systolic BP ≥ 125 mmHg at the start and at the end of screening<br>Able to be randomized within 16 h from presentation to the hospital, including the emergency department<br>Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation (this includes outpatient clinic, ambulance, or hospital including emergency department) and the start of screening for the study for the treatment of the current acute HF episode                                 | Males and females aged 18–85 years.<br>Unplanned hospitalizations or emergency department visit for AHF with AHF defined by dyspnea at rest in a recumbent sitting position (30–45 degrees), which has worsened within the past week; radiological evidence of HF on a chest X-ray; BNP > 500 pg/mL or NT-pro-BNP > 2000 pg/mL<br>Ability to start infusion of the study drug within 12 h after initial clinical assessment performed by a physician at the emergency room/hospital.<br>Ability to reliably carry out self-assessment of symptoms<br>Systolic blood pressure ≥ 116 mmHg and ≤ 180 mmHg at the time of randomization.<br>Persistent dyspnea at rest despite standard background therapy, which must include IV furosemide (or equivalent diuretic) at ≥ 40 mg (or its equivalent) at any time after start of emergency services (ambulance, emergency department, or hospital) | Men or women aged ≥ 21 and ≤ 85 years<br>Pre-existing diagnosis of heart failure.<br>Systolic blood pressure ≥ 120 mmHg and ≤ 200 mmHg within 30 min of randomization<br>Ventricular rate ≤ 125 bpm. Patients with rate-controlled persistent or permanent atrial fibrillation (aFib) at screening are permitted.<br>Presence of AHF defined by:<br>BNP > 400 pg/mL or NT-proBNP > 1600 pg/mL (For patients with BMI > 30 kg/m <sup>2</sup> : BNP > 200 pg/mL or NT-proBNP > 800 pg/mL. For patients with rate-controlled persistent or permanent aFib: BNP > 600 pg/mL or NT-proBNP > 2400 pg/mL) AND at least two (2) of the following: congestion on chest; rales on chest auscultation; peripheral edema ≥ +1 on a 0–3 + scale; elevated jugular venous pressure<br>Receipt of a IV loop diuretic at a minimum dose 40 mg furosemide (or equivalent loop diuretic) for the treatment of dyspnea due to ADHF at least 1 h prior to anticipated randomization and the initiation of study medication<br>Patient report of dyspnea at rest or upon minimal exertion during screening at least 1 h after administration of IV loop diuretic<br>Women who are pregnant or breast-feeding. |
| Exclusion criteria | Dyspnea primarily due to non-cardiac causes<br>Temperature >38.5 °C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment<br>Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment.<br>AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate <45 beats per minute, or atrial fibrillation/flutter with sustained ventricular response of >130 beats per minute<br>Patients with severe renal impairment defined as pre-randomization eGFR < 25 mL/min/1.73 m <sup>2</sup> calculated using the sMDRD equation, and/or those receiving current or planned dialysis or ultrafiltration | Known as active myocarditis, obstructive hypertrophic cardiomyopathy, congenital heart disease, restrictive cardiomyopathy, constrictive pericarditis, uncorrected clinically significant primary valvular disease<br>Treatment with dobutamine at a dose >5 µg/kg/min or use of drugs for support of BP at the time of randomization<br>Treatment with levosimendan, milrinone, or any other phosphodiesterase inhibitor within 7 days before randomization<br>Treatment with nesiritide within 30 days before randomization<br>Creatinine clearance <30 mL/min/1.73 m <sup>2</sup> (as measured by the MDRD formula) at the time of screening<br>Planned coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting) within 5 days of randomization<br>Clinical diagnosis of acute coronary  | Clinical presentation:<br>ACS in the 3 months prior to screening or planned during current admission.<br>Temperature >38.5 °C<br>Clinically significant anemia<br>Current or planned ultrafiltration, paracentesis, hemofiltration, or dialysis at time of screening<br>Any mechanical ventilation<br>History of primary pulmonary hypertension<br>History or current use of left ventricular assist devices or intra-aortic balloon pumps<br>Intravenous radiographic contrast agent within 72 h prior to screening or presence of acute contrast induced nephropathy at the time of screening  |

Table 1 continued

| Active drug        | Ularitide   | TRV027  |
|--------------------|---|---|
| Serelaxin          | <p>Clinically suspected acute mechanical cause of AHHF (e.g., papillary muscular rupture). The diagnosis need not be confirmed by imaging or cardiac catheterization</p> <p>Anemia (hemoglobin <math>&lt;9</math> g/dL or a hematocrit <math>&lt;25</math> %)</p> <p>Known vasculitis, active infective endocarditis, or suspected infections including pneumonia, acute hepatitis, systemic inflammatory response syndrome, or sepsis</p> <p>Body temperature <math>\geq 38</math> °C just prior to randomization</p> <p>Acute or chronic respiratory disorder (e.g., severe chronic obstructive pulmonary disease) or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret dyspnea assessments or hemodynamic measurements</p> <p>Terminal illness other than congestive heart failure with expected survival <math>&lt;180</math> days.</p> <p>Any previous exposure to Ularitide</p> <p>Known allergy to natriuretic peptides</p> <p>Participation in an investigational clinical drug trial within 30 days prior to randomization</p> <p>Current drug abuse or chronic alcoholism sufficient to impair participation and compliance to the study protocol</p> <p>Women who are breast-feeding</p> <p>Women of child-bearing potential (i.e., pre-menopausal women) without documentation of a negative urine/blood pregnancy assay within 12 h prior to randomization</p> <p>Any condition that, in the Investigator's opinion, makes the patient unsuitable for study participation</p> <p>Legal incapacity or limited legal capacity</p> <p>Patients requiring mechanical circulatory support.</p> <p>Patients with severe hepatic impairment</p> | <p>Presence of clinically significant arrhythmia</p> <p>Medications:</p> <p>Nitroprusside or nesiritide</p> <p>Intravenous nitrates</p> <p>Use of inotropes</p> <p>Use of ARBs within 7 days of prior to randomization</p> <p>Use of any investigational medication within 30 days</p> <p>Clinically significant hypersensitivity or allergy to, or intolerance of, angiotensin receptor blockers</p> <p>Medical history:</p> <p>Major surgery within 8 weeks prior to screening</p> <p>Stroke within 3 months prior to screening</p> <p>eGFR (sMDRD) <math>&lt; 20</math> mL/min/1.73 m<sup>2</sup> or <math>&gt;75</math> mL/min/1.73 m<sup>2</sup> between presentation and randomization</p> <p>Post cardiac or renal transplant</p> <p>Listed for renal transplant or cardiac transplant with anticipated transplant time to transplant <math>&lt;6</math> months</p> <p>History of severe left ventricular outlet obstruction (either valvular or sub-valvular), severe mitral valve stenosis or severe aortic regurgitation</p> <p>Cardiac valvular abnormality that requires surgical correction</p> <p>Complex congenital heart disease</p> <p>Hypertrophic or restrictive cardiomyopathy</p> <p>Significant pulmonary or hepatic disease that could interfere with the evaluation of safety or efficacy of TRV027</p> <p>Life expectancy of less than 6 months</p> <p>Time from randomization to death through day 30</p> <p>Time from randomization to heart failure rehospitalization through day 30</p> <p>Time from randomization to worsening heart failure through day 5</p> <p>Change in dyspnea VAS score (calculated area under the curve) from baseline through day 5.</p> <p>Length of initial hospital stay (in days) from randomization</p> <p>The component outcomes will be combined by deriving an average Z for each patient</p> |
| Primary end-points | Time to confirmed cardiovascular (CV) death during the follow-up period of 180 days   | <p>Improvement in a hierarchical clinical composite comprised elements associated with: patient global assessment using a 7-point scale of symptomatic improvement, lack of improvement, or worsening; persistent or worsening heart failure requiring an intervention (initiation or intensification of IV therapy, circulatory or ventilatory mechanical support, surgical intervention, ultrafiltration, hemofiltration or dialysis);</p> <p>All-cause mortality</p> <p>Assessment of the clinical composite will be performed at 6, 24 and 48 h after start of IV Ularitide infusion</p>  |

**Table 1** continued

| Active drug          | Serelaxin   | Ularitide  | TRV027                |
|----------------------|---|--|-----------------------|
| Secondary end-points | <p>Time to all-cause death through day 180.</p> <p>Time to worsening of heart failure (WHF) through day 5</p> <p>Length of total hospital stay (LOS) during the index AHF hospitalization</p> <p>Time to first occurrence of the composite endpoint of CV death or rehospitalization due to heart failure or renal failure through day 180</p> <p>Length of intensive care unit and/or Coronary care unit stay for the index AHF hospitalization</p> <p>Change from baseline in congestive signs and symptoms of heart failure through day 5</p> <p>Change from baseline in selected biomarkers from baseline through day 14 in a subset</p> <p>Number of patients reported with total adverse events, serious adverse events, and death.</p> <p>To evaluate the safety and tolerability of intravenous serelaxin in AHF patients, number of patients with total adverse events, serious adverse events, and death will be analyzed</p> | <p>Changes of N-terminal pro brain natriuretic peptide (NT-pro-BNP) at 48 h of treatment compared to baseline</p> <p>All-cause mortality and cardiovascular rehospitalization at day 90 after start of the study drug infusion</p> <p>Cardiovascular rehospitalization at day 90</p> | <p>None specified</p> |

and renal blood flow [4]. These effects stem from a combination of increased NO production, vascular endothelial growth factor (VEGF) and matrix metalloproteinase, and inhibition of endogenous vasoconstrictors (i.e., endothelin and angiotensin II) [5].

Relaxin binds to G-protein-coupled receptors known as relaxin family peptide receptor (RXFP) to trigger these effects. Two major receptors, RXFP1 and RXFP2, have been identified in both male and female mice in small renal vessels, mesenteric vessels, and the thoracic aorta [6]. Further evidence has identified receptors in blood vessels and in tissue samples from kidney, brain, and heart [7]. The vasodilatory effects of relaxin appear to be coupled to RXFP activation of adenylyl cyclase and activation of secondary messenger pathways, which modulate the NO system. In this pathway relaxin acts to stimulate endothelial vasodilation by upregulation endothelin (ET) B receptor [8].

Reduction of vascular compliance is a common phenomenon in HF and likely contributes to development of acute decompensation. Relaxin has been implicated as a regulator of fibrotic change by induction of matrix metalloproteinase-9 (MMP-9) [9], a protein involved in tissue remodeling and degradation of type 4 collagen, along with reduction of fibroblast collagen deposition [10]. These effects in mice models have demonstrated the ability to reduce cardiac fibrosis and collagen deposition [11], an effect that could have long-term implications for human health by increasing cardiovascular compliance.

Ischemic injury from an inability to perfuse/oxygenate during AHF may lead to end-organ damage. Increasing flow to organs is one way which relaxin can ameliorate these effects from worsening; however, relaxin has also been shown to improve post ischemia events in multiple animal models [12, 13]. This could owe to antifibrotic effects and ability to modulate tissue remodeling as well as an ability to promote VEGF [14] and subsequent angiogenesis with to revascularization of ischemic areas.

Initial investigations of relaxin in humans began in the 1980, where it was used intravaginally to induce labor and later followed with trials of systemic administration for scleroderma and tolerated without side effects [15]. An early trial of relaxin in 11 healthy humans (six males, five females) to assess renal hemodynamic changes did demonstrate a significant increase in renal plasma flow and natriuresis [16]. However, it did not demonstrate significant change in glomerular filtration as predicted based on animal data and data from scleroderma trials.

A safety trial of relaxin in humans with stable HF ( $n = 16$ ) compared 24 h infusion of relaxin ranging from 10–960  $\mu\text{g}/\text{kg}/\text{day}$  with three groups of escalating dose regimens every 8 h; 10, 30, and 100  $\mu\text{g}/\text{kg}/\text{day}$ ; 240, 480, and 960 and 960  $\mu\text{g}/\text{kg}/\text{day}$ . This study did not find any

significant side effects such as hypotension. Important for its potential role in AHF, a dose-dependent reduction in pulmonary capillary wedge pressure (PCWP) at both lower and higher doses (10–100 and 960  $\mu\text{g}/\text{kg}/\text{day}$ , respectively) and improved cardiac index at moderate to high doses (240–960 and 960  $\mu\text{g}/\text{kg}/\text{day}$ ) were noted. Such data suggest a preferential venodilating effect at lower doses and more vasodilation at moderate to high doses, both of which might be beneficial in the management of AHF patients [17].

Preliminary studies were followed by a dose-finding pilot trial (Pre-RELAX-AHF—Phase II Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Relaxin in Subjects With Acute Heart Failure) of 234 patients. In this trial, relaxin infused at 30  $\mu\text{g}/\text{kg}/\text{day}$  produced greater dyspnea improvement than placebo or other doses with a trend toward a reduction in cardiovascular death or readmission due to heart or renal failure at day 60 (2.6 vs. 17.2 %;  $p = 0.053$ ) [18••]. This led to a follow-up study, the Relaxin in Acute Heart Failure (RELAX-AHF) trial, which enrolled 1161 AHF patients with mild-to-moderate renal insufficiency and a systolic BP > 125 mm Hg (mean BP for the study cohort  $\sim 142/82$  mm Hg with no difference by group). A significant decrease in dyspnea as assessed on a 10-point visual analog scale dyspnea was demonstrated starting at 6 h and extending through day 5 for those who received relaxin ( $n = 581$ ) compared with placebo ( $n = 580$ ) [19••]. Although more hypotensive episodes requiring a study-specified dose reduction were noted in the relaxin group (29 vs. 18 %;  $p = 0.0001$ ), there was no difference in hypotension-related adverse events (5 vs. 4 %;  $p = 0.78$ ). Significant decreases in worsening HF, clinical signs of vascular congestion, adverse events related to renal impairment, and length of initial hospital stay were also seen in the relaxin group, while the total dose of intravenous (IV) loop diuretic administered through day 5 was lower (161 vs. 213 mg;  $p = 0.006$ ). This study demonstrated slight improvement of dyspnea, but did not demonstrate any difference in 60-day all-cause mortality or hospital readmission for renal/cardiovascular reason. However, relaxin was associated with a significant reduction in both all-cause (6.1 vs. 9.6 %;  $p = 0.028$ ) and cardiovascular (7.3 vs. 11.3 %;  $p = 0.02$ ) mortality through 180 days, which no other trial in AHF has shown to date [19••]. It is possible that the vasodilation, antifibrotic, and cardioprotective effects discussed earlier provide for the 180 days reduction in mortality. While biomarker data from RELAX-AHF suggest attenuation of cardiac and renal end-organ damage with relaxin as well [20•], the putative mechanism responsible for the demonstrated mortality benefit has yet to be identified.

Regardless of the mechanism, the identification of a potential therapy that can potentially reduce cardiovascular death in AHF is an important advance [21].

At present, several trials of relaxin (now rebranded as serelaxin) are being conducted to test the treatment in adult AHF (NCT01870778), pediatric AHF (NCT02151383), chronic HF (NCT01982292), and coronary artery disease (NCT01979614). The largest and most important of these studies is a multinational randomized control trial (RELAX-AHF 2), which will include approximately 6800 patients, with the goal to detect a difference in mortality at 180 days and worsening HF through day 5. Enrollment for this trial is on-going with an estimated completion by August 2016.

## Ularitide

Ularitide is a synthetic analog of urodilatin, a 32 amino acid atrial natriuretic peptide. Urodilatin was initially isolated in human urine, and like other natriuretic peptides, production is tissue specific and isolated to the renal tubule cells [22]. In the renal tubule, urodilatin acts as a paracrine signal, interacting with natriuretic peptide receptors (NPR), NPR-A, NPR-B, and NPR-C. NPR-A and NPR-B stimulate sGC and increase intracellular cGMP. Downstream effects lead to natriuresis with reduction of sodium reabsorption in proximal and distal convoluted tubules via modulation of basolateral sodium-ATPase [23] and amiloride-sensitive sodium channels [24], respectively. cGMP also leads to decreased intracellular calcium levels in renal artery smooth muscle cells leading to vasodilation of the afferent limb and vasoconstriction of the efferent limb [25] likely causing improvement of renal perfusion pressure. Antagonism of the renin angiotensin aldosterone system (RAAS) with infusion of urodilatin also occurs in humans as evidenced by decreased plasma concentrations of renin, angiotensin II, and aldosterone [26].

Compared to other exogenous natriuretic peptides, urodilatin has some particularly appealing properties for translation into a viable pharmaceutical drug. There are two known mechanisms to inactivate circulating natriuretic peptides: binding to the clearance receptor, NPR-C and enzymatic degradation by binding to enzymatic neutral peptidases located preferentially on the brush boarder of lung and kidney [24]. Biochemical evidence suggests that urodilatin is more stable against enzymatic degradation leading to longer bioavailability [27]. This is correlated clinically with the demonstration that urodilatin has prolonged activity when compared to atrial natriuretic peptide [28].

Ularitide is similar to nesiritide [a synthetic analog of B-type natriuretic peptide (BNP)], with multiple pharmacologic effects including modulation of fluid and electrolyte balance, arterial smooth muscle relaxation, and

RAAS inhibition [26, 29]. Initial study of ularitide in eight healthy humans demonstrated significant decreases in systolic BP at higher doses with bolus administration and a dose-dependent enhancement of GFR and filtration fraction of sodium and chloride [28]. Later studies in patients with chronic HF showed similar effects with diuresis and natriuresis and a reduction in PCWP along with decreased systemic vascular resistance (SVR) and increased stroke volume index [30]. However, hemodynamic side effects including reflex tachycardia and hypotension among some patients were noted. Further study in a randomized placebo-controlled crossover study in healthy humans demonstrated dose-dependent vasodilation with venodilation occurring at smaller doses followed by arterial dilation at larger doses (20–40 ng/kg/min). The net effect was an initial decrease in cardiac output (CO) with small doses, likely secondary to decreased preload, and no change in CO at higher doses presumably due to afterload reduction [26].

These preliminary studies were followed by SIRIUS I (Safety Intravenous Randomized Infusion Ularitide Study), a phase I randomized double-blinded ascending dose trial designed to evaluate the safety and efficacy of a 24-h ularitide infusion in 24 patients with AHF. Compared to placebo, ularitide significantly decreased PCWP, SVR, and renal artery pressure. Dyspnea was improved compared to placebo, and 24-h change in N-terminal pro-BNP (NT-pro-BNP) was significantly lower with ularitide even though there was no significant difference in urine output between the two groups. At 30 ng/kg/min, 1/3 of treated patients developed hypotensive episodes with a systolic BP < 90 mm Hg; however, the average initial systolic BP for this group was <120 mm Hg. In the 15 ng/kg/min group (average initial systolic BP = 130 mm Hg), no episodes of hypotension were observed, suggesting a better safety profile when used at more modest doses in patients with higher baseline BP [31••].

The hemodynamic effects of ularitide were further defined in SIRIUS II, a phase II randomized controlled trial involving a 24-h infusion of ularitide in 221 patients that showed an increase in cardiac index at 15 and 30 ng/kg/min along with decreased PCWP and SVR, and significant reductions in NT-pro-BNP. Hypotension defined as a systolic BP < 80 mmHg was common and appeared as a dose-dependent side effect [32••]. However, unlike prior studies, no significant beneficial renal effects were noted. This was accounted for by contaminant use of loop diuretics and, as suggested by other studies, a downregulation of NPR-A in the setting of AHF [33] with an upregulation of neutral endopeptidase [34].

Based on SIRIUS I and SIRIUS II, the TRUE-AHF trial (an on-going phase III trial of Ularitide's Efficacy and Safety in Patients with Acute Heart Failure) was launched

in late 2012. This study is an on-going double-blinded randomized clinical trial comparing a 48-h IV infusion of ularitide at 15 ng/kg/min with placebo (NCT01661634). The primary end point is a hierarchic composite with a patient-centered assessment of clinical progress that includes demonstrated the lack of improvement or worsening of HF requiring a prespecified intervention, and cardiovascular mortality. Estimated enrollment is 2152 patients from centers across North America, Europe, and Latin America with a targeted end date of October 2015.

## TRV027

TRV027 is a novel beta-arrestin biased ligand of the angiotensin II type 1 receptor (AT1R) that has recently been developed for potential use in patients with AHF. Completely novel in its pharmacology, TRV027 acts like a conventional angiotensin receptor blocker, inhibiting angiotensin II-mediated vasoconstriction while concurrently enhancing cardiomyocyte contractility through biased, G-protein-independent activation of the beta-arrestin signaling pathway. [35•] In preclinical studies done on tachypaced canine HF model, TRV027 showed a dose-dependent decrease in mean arterial pressure and PCWP with an increase in CO while preserving renal function (even in animals that were administered furosemide) [35•, 36]. Apparent BP effects of TRV027 are rapid in onset and relatively short in duration, providing an ideal hemodynamic profile for use in AHF.

Human experience with TRV027 is currently limited to a single ascending dose study designed to explore tolerability, pharmacokinetics, and pharmacodynamics of the drug in healthy volunteers. In this trial, salt intake was controlled to simulate RAAS activation and TRV027 was safe and well tolerated, with a half-life ranging between 2.4 and 13.2 min. Blood pressure reduction was greater among the subjects with RAAS activation, as measured by elevated plasma renin activity (PRA) level [37••]. Further study in BLAST-AHF (A Study to Explore the Efficacy of TRV027 in Patients Hospitalized for Acute Decompensated Heart Failure), a phase II double-blind, placebo-controlled, dose ranging trial targeting enrollment of approximately 620 patients hospitalized for AHF is currently underway (NCT01966601).

## Conclusions

The role of vasodilators in the management of patients with AHF continues to evolve. With the advent of novel compounds such as serelaxin, ularitide, and TRV027 that have advanced pharmacological profiles, use of vasodilators will

likely grow to include treatment of patients with mild-to-moderate BP elevations. While these agents are still under investigation and none have achieved regulatory approval for clinical use, should they prove beneficial in on-going trials, we are looking at a new era of drug therapy that could supplant more conventional treatments and broaden the horizon for management of patients with AHF.

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#### Compliance with Ethics Guidelines

**Conflict of Interests** Dr. Viau declares no conflict of interests with the paper. Dr. Levy reports receiving consulting fees from Cardiorentis, Novartis, and Trevena, and grants/contracts from Cardiorentis, Novartis, and Trevena.

**Human and Animal Rights and Informed Consent** This article contains no studies with human or animal subjects performed by the author.

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