Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)

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Background
Hospitalizations for acute heart failure syndromes (AHFS) are associated with high post-discharge mortality and readmission rates in spite of available therapies. Renin-angiotensin-alderosterone system (RAAS) antagonists improve outcomes in outpatients with heart failure (HF) and reduced ejection fraction, however these therapies have not been tested in AHFS. Aliskiren is a direct renin inhibitor (DRI) that is known to enhance RAAS inhibition, which may result in improved clinical outcomes in AHFS. The aim of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study is to evaluate the effect of aliskiren on cardiovascular death and HF in AHFS patients.

Methods
ASTRONAUT will be an event-driven trial with an estimated enrolment of 1782 patients hospitalized with worsening chronic HF, a left ventricular ejection fraction ≤40%, and an estimated glomerular filtration rate ≥40 mL/min/1.73 m². Patients will be randomized 1:1 in a double-blind fashion to receive aliskiren or placebo, in addition to standard HF therapy. The primary endpoint will be a composite of time to either cardiovascular death or first occurrence of HF re-hospitalization.

Perspective
Aliskiren is a DRI with a favourable neurohormonal and haemodynamic profile that may benefit patients hospitalized with worsening HF. Given the neurohormonal abnormalities that are present during and after hospitalization for AHFS, it is hypothesized that adding aliskiren to standard therapy will reduce post-discharge mortality and re-hospitalization. NCT00894387.

Keywords
Acute heart failure syndromes • Aliskiren • Direct renin inhibition • Renin-angiotensin-alderosterone system

Introduction
Approximately one million patients per year are admitted with a primary diagnosis of heart failure (HF) in the USA.1 Similar numbers are reported in Europe; however, regional geographic variation exists in rates of in-hospital mortality, re-hospitalization rates, and length of stay.2–5 The number of patients with HF in the USA for 2009 is estimated to be 5.8 million. The estimated healthcare cost of caring for these patients is $39.2 billion representing a significant financial burden on the US health-care system.6

Acute heart failure syndromes (AHFS) have been defined as new-onset or gradual or rapid change in HF signs and symptoms...
necessitating urgent therapy and hospitalization.\textsuperscript{2,7} In spite of significant improvement in HF signs and symptoms that occur during hospitalization and continuation or introduction of evidence-based therapies, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone antagonists, post-discharge mortality and re-hospitalization are as high as 15 and 30\%, respectively within 60 to 90 days.\textsuperscript{8–10} Recent data suggest that early post-discharge death and re-hospitalization are preceded by a worsening neurohormonal profile, in particular an increase in serum aldosterone concentration.\textsuperscript{11}

Since incomplete suppression of the renin–angiotensin–aldosterone system (RAAS) may contribute to high event rates, further neurohormonal modulation during this early post-discharge period, also called the ‘vulnerable phase’, with aliskiren may improve long-term outcomes.\textsuperscript{7,11–15} Aliskiren has a favourable haemodynamic and neurohormonal profile given its ability to reduce blood pressure, enhance renal blood flow, augment natriuresis, and reduce plasma levels of B-type natriuretic peptide (BNP), plasma renin activity (PRA), and urinary aldosterone.\textsuperscript{16–18}

The objective of Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) is to evaluate the effect of in-hospital initiation of aliskiren compared with placebo, both in addition to standard therapy, on post-discharge cardiovascular mortality and HF re-hospitalization in AHFS patients.

\section*{Study design}

\subsection*{Overview}

ASTRONAUT is an international, multicentre, randomized, double-blind, placebo-controlled study to evaluate the 6-month efficacy and safety of aliskiren therapy in addition to standard therapy, on post-discharge mortality and re-hospitalization rates when initiated early after AHFS hospital admission (defined as admission to a hospital or attendance in an acute care setting or any other health-care facility for at least an overnight stay) and before discharge.

\subsection*{Patients}

The study population will consist of patients hospitalized for HF with signs and symptoms of fluid overload and a pre-existing history of chronic HF (NYHA Class II–IV), aged ≥ 18 years, with a left ventricular ejection fraction ≤40\%, and without significant renal insufficiency.

\subsection*{Selected inclusion criteria}

Patients hospitalized with a primary admission diagnosis of worsening HF who meet the following criteria.

- A history of chronic HF (NYHA Class II–IV) on standard therapy defined as requiring treatment for at least 30 days before the current hospitalization.
- Symptoms (dyspnoea or fatigability) and signs of congestion (i.e. jugular venous distension, rales heard on auscultation, oedema, or radiographic pulmonary congestion) at the time of hospitalization.
- Left ventricular ejection fraction ≤40\% (measured by any method such as radionuclide angiography, echocardiography, cardiac magnetic resonance imaging, or invasive left ventriculography within the last 12 months prior to randomization).
- Haemodynamically stable for at least 6 h, defined as a systolic blood pressure (SBP) ≥110mmHg.
- Elevated BNP or NT-proBNP prior to randomization (BNP ≥400 pg/mL or NT-proBNP ≥1600 pg/mL).

\subsection*{Selected exclusion criteria}

- Patients that required any use of IV vasodilators (except nitrates), and/or any IV inotropic therapy from the time of presentation for worsening HF to randomization.
- Treatment within the past 3 months prior to randomization with intravenous inotrope therapy or direct renin inhibitors (DRIs) such as aliskiren.
- Persistent SBP < 110 mmHg prior to the 6 h stabilization period.
- Concomitant use of ACE-I and ARB at randomization.
- Myocardial infarction (MI) or cardiac surgery, including percutaneous coronary intervention (PCI) within the past 3 months.
- Patients with a history of heart transplant or patients who are on a transplant list.
- Primary right-sided HF.
- A diagnosis of post-partum cardiomyopathy.
- End-stage HF defined as requiring left ventricular assist devices, intra-aortic balloon pump (IABP) or any type of mechanical support, or requiring continuous intravenous inotropic therapy.
- A serious life-threatening illness with a life-expectancy of <6 months.
- Acute coronary syndromes likely to require coronary artery bypass graft or PCI before randomization.
- Symptomatic ventricular arrhythmias within the past 3 months.
- Stroke within the past 3 months.
- Severe primary liver disease in the opinion of the investigator.
- Serum potassium > 5.0 mEq/L (5.0 mmol/L).
- Severe hyponatraemia < 130 mEq/L.
- An estimated glomerular filtration rate < 40 mL/min/1.73m\(^2\) (as measured by the MDRD formula).

\section*{Study endpoints}

The primary endpoint in ASTRONAUT will be the time to either cardiovascular death or first HF re-hospitalization within 6 months of hospitalization.

Secondary endpoints include the time to:

- Cardiovascular death or first HF re-hospitalization within 12 months of hospitalization.
- First cardiovascular event (defined as cardiovascular death, HF re-hospitalization, non-fatal MI, non-fatal stroke, or sudden death with resuscitation).
- All cause mortality within 6 months and 12 months of hospitalization.

Additional secondary endpoints include changes in BNP, Quality of Life (Activities of Daily Living assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ)), blood pressure control, and...
biomarkers related to vascular or organ damage known to occur in the acute HF patient at 1, 6, and 12 months.

Protocol

Patients hospitalized with AHFS will initially be treated with standard therapy at the discretion of the treating physician according to guideline-based recommendations (Visit 1) (Figure 1). Stable patients [defined as SBP $\geq$ 110 mmHg for at least 6 h and not requiring IV vasodilators (other than nitrates) or IV inotropic drugs at anytime from presentation to randomization] meeting all other inclusion criteria and none of the exclusion criteria will be randomized (Visit 2). Patients will be randomized in a 1:1 ratio to receive either aliskiren 150 mg or placebo, in addition to standard therapy, prior to discharge. Standard therapy treatment will be left to the discretion of the treating physician but should include diuretics, ACE-Inhibitors or ARBs, beta-blockers, and aldosterone blocking agents, unless contraindicated.

One week after randomization (Visit 3) patients will be assessed for safety and tolerability compared with background standard therapy as necessary. Patients will continue to receive either aliskiren 150 mg or placebo. Two weeks after randomization (Visit 4), the dose will be increased to 300 mg of aliskiren or placebo unless the patient is unable to tolerate (e.g. development of low blood pressure, hyperkalaemia, or worsening renal function) the initial dose. At Visit 5 (Week 4), patients will return to the site to ensure that the 300 mg dose is tolerable with additional study visits to follow at month 2, month 3, month 6, and every 3 months thereafter. Patients unable to tolerate the 300 mg dose increase will have their dose decreased to 150 mg at any time during the study period at the investigator’s discretion.

Statistical considerations

For the primary comparison between aliskiren and placebo, a superiority test will be performed. The primary analysis model will be a Cox proportional hazards model with treatment assignment and with baseline BNP as a covariate. The null hypothesis will be tested at the two-sided significance level alpha 0.0495 (two-sided) ($=0.0495$ for $k = 1$ planned safety interim analysis).

All randomized patients will remain in the trial until 381 cardiovascular deaths and/or HF hospitalizations within the first 6 months after the acute HF event have occurred. It is anticipated that all randomized patients will have a minimal follow-up of 8 weeks, even if the 381 events are reached earlier.

An interim analysis to assess safety will be performed after $\sim$50% of randomized patients have either completed 2 weeks of study treatment or discontinued. The primary efficacy endpoint will also be reviewed as an additional safety parameter at the interim safety assessment, which shows semi-blinded information. To account for this, the overall $\alpha$ will be adjusted for [0.005% (two-sided)]. During the safety looks, there is no intention to stop the study for efficacy.

Statistical power and sample size

The sample size is determined to have 80% power to reject the null hypothesis of equal hazard rates, assuming exponential survival curves, a 25% event rate (according to literature) in the placebo group at 6 months, a hazard ratio of 0.75 (25% reduction for superiority of aliskiren vs. placebo), a common exponential dropout rate of 10% and alpha $= 0.0495$ (two-sided). Based on a maximum likelihood comparison of survival curves at 6 months, approximately 1782 patients (891 per treatment arm) will have to be randomized to reach 381 primary events (defined as either cardiovascular death or HF hospitalization).

Assuming the accrual period is the maximum follow-up period 21 months, with the same assumptions as for the primary variable, the comparison for time to cardiovascular death or HF hospitalization will have power $>80%$.

A blinded analysis will be performed to assess the observed event rate for the primary endpoint and to re-assess the sample size. All events (number of events and time of event) for the primary endpoint will be included in the interim analysis such that the results are available $\sim$1.5 months prior to completion.

Figure 1 Protocol. ADHF, Acute decompensated heart failure.
of the projected recruitment. No other unblinded interim efficacy analyses will be performed for this study.

Adjudication
All potential study endpoints will be adjudicated by a central adjudication committee (CAC, see Appendix 1). Investigators will complete endpoint adjudication forms and submit these along with endpoint-specific source documentation. All potential endpoints will be independently reviewed and adjudicated by two physician reviewers. Most potential endpoints will be subsequently presented in a full committee meeting. When there is disagreement regarding the appropriate adjudication among the two reviewers, events will be mandatorily brought and discussed before the endpoint committee comprising of other physician reviewers and the committee chair and/or co-chair, who will serve as the final arbiter of the appropriate adjudication in the event of inability to achieve consensus. All deaths will be classified as cardiovascular or non-cardiovascular, and cardiovascular death will be subclassified as: fatal MI, pump failure, sudden death, presumed sudden death, fatal stroke, fatal pulmonary embolism, procedure-related death, or presumed cardiovascular death. Non-cardiovascular deaths will also be subclassified.

Sudden death will be defined as death occurring unexpectedly in an otherwise stable subject and will be further subclassified as: death witnessed or subject last seen alive <1 h previously or subject last seen alive between 1 and 24 h previously.

Presumed sudden death will be defined as death occurring unexpectedly in an otherwise stable subject last seen alive 24 h previously, with circumstances suggestive of sudden death. Deaths within 14 days of a cardiovascular procedure due to procedural complications will be classified as cardiovascular deaths. The following non-fatal endpoints will be adjudicated: (i) Unplanned hospitalization for HF, (ii) resuscitated sudden death, (iii) stroke, (iv) doubling of baseline serum creatinine concentration, (v) MI, and (vi) unplanned hospitalization for myocardial ischaemia. A complete list of endpoint definitions is presented in Table 1.

Current status
ASTRONAUT started enrolling patients in May 2009. As of September 2010, it had enrolled in excess of 800 patients in 300 centres and 24 countries distributed over all of the major regions worldwide (see Supplementary material online, Appendix 2).

Discussion
Acute heart failure syndromes: targets and timing
Acute heart failure syndromes represent a major public health problem because of the high post-discharge mortality and morbidity rates and the associated economic burden of patient care. Patients at high risk of death or re-hospitalization at 60 to 90 days following hospitalization for AHFS are likely to experience worsening signs and symptoms of congestion, neurohormonal profile, and renal function during the first few weeks after discharge. Clinical and neurohormonal deterioration occurs not only in those patients receiving standard therapies, but also in those experiencing significant clinical improvement during hospitalization. The early post-discharge period, sometimes referred to as the ‘vulnerable phase’, provides an ideal opportunity to conduct AHFS Stage C trials focused on introducing experimental medications administered before or soon after discharge and continued on an outpatient basis with the objective of reducing post-discharge mortality and morbidity. The recently recommended early post-discharge visit coincides with the ‘vulnerable phase’, thereby allowing for the implementation and/or dosing optimization of evidence-based therapies with a known mortality benefit.

Antagonism of all neurohormonal systems has not proved to be uniformly beneficial in patients with HF. However, targeted attenuation of the RAAS in AHFS appears appropriate given the therapeutic benefit observed in the treatment of patients with chronic HF with reduced ejection fraction and post-MI with left ventricular systolic dysfunction.

Renin–angiotensin–aldosterone system excess in AHFS may have many of the same deleterious effects observed in chronic HF. Control of the RAAS may be of particular importance in patients with AHFS since patients admitted with worsening HF often present with further activation of neurohormones. The majority of these patients have secondary right-sided HF resulting in hepatic congestion and decreased clearance of RAAS effector molecules. Furthermore, the extent of neurohormonal activation in AHFS predicts the development of atrial and ventricular arrhythmias and post-discharge mortality.

Renin in acute heart failure syndromes: potential for therapeutic antagonism
Renin–angiotensin–aldosterone system activity may be exacerbated by common therapies utilized in patients hospitalized with worsening HF, and inadequately suppressed by current neurohormonal antagonists. Despite their undisputable beneficial effects in chronic HF patients, both ACE-Inhibitors and ARBs present some possible shortcomings in inhibiting the RAAS.

The phenomenon of ‘RAAS escape’ occurs when renin, angiotensin I, angiotensin II, and aldosterone accumulate in the setting of ACE-Inhibitor and ARB therapy. The reactive rise in renin concentration and PRA (or RAAS escape) observed in patients treated with ACE-Inhibitors/ARBs and the unacceptably high mortality and readmission rates for patients admitted with AHFS, suggest that the development and investigation of new means of neurohormonal modulation may hold promise. An alternative approach for blockade of the RAAS is to directly inhibit renin, the rate-limiting enzyme for the formation of angiotensin II. Direct renin inhibitors act at the point of activation of the RAAS, thereby reducing circulating levels of angiotensin I and angiotensin II.

Aliskiren is a non-peptide agent with a low-molecular weight, which acts as an oral inhibitor of renin, leading to significant reductions in mean arterial pressure and PRA. Aliskiren is primarily excreted unchanged in the faeces, but ~1.4% of the dose is metabolized and 0.6% of the dose is recovered in the urine. Pharmacokinetic studies show that no dosage adjustment
of aliskiren is required in patients with mild to moderate renal impairment, hepatic impairment or diabetes, or on the basis of gender or race. However, aliskiren has not been studied in patients with severe renal impairment. Furthermore, aliskiren has a low potential for drug interactions as it has no clinically relevant interactions with the cytochrome P450 isoenzymes. 32

Furosemide, a loop diuretic, is often used in patients with AHFS and congestion but may lead to further neurohormonal activation and worsening renal function. 33 Aliskiren, unlike furosemide, has demonstrated the ability to increase renal blood flow in healthy volunteers. The renal vasodilatation observed in healthy individuals treated with aliskiren exceeded the responses previously seen with ACE-Inhibitors and ARBs. The effects were long-lasting and associated with significant natriuresis. These results indicate that aliskiren may provide more complete inhibition of the RAAS and potentially alleviate cardiopulmonary congestion. 19 This is important since the main reason for admission and readmission for worsening HF is related to congestion rather than low cardiac output. 34

### Previous clinical trials of aliskiren

In addition to its efficacy as an antihypertensive, aliskiren may also have a number of potential renal and cardio protective benefits. In the AVOID (Aliskiren in the Evaluation of Protei

<table>
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<th>Endpoint definitions synopsis</th>
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<tr>
<td><strong>Cardiovascular death</strong></td>
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<tr>
<td>Death due to cardiovascular cause, subclassified as myocardial infarction, heart failure, death during a cardiovascular procedure or as a result of procedure-related complications, sudden or presumed sudden death, stroke, pulmonary embolism, or death resulting from a documented cardiovascular cause other than those listed above. Death likely due to a cardiovascular cause in which the available clinical data are insufficient to support a more specific cause of death will also be adjudicated in this category.</td>
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<tr>
<td><strong>Non-cardiovascular death</strong></td>
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<tr>
<td>With an unequivocal and documented non-cardiovascular primary cause of death, these will be further classified as infection, malignancy, pulmonary, gastrointestinal, renal, accidental, suicide, diabetes, or other (which will be specified).</td>
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<tr>
<td><strong>Unknown death</strong></td>
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<tr>
<td>Insufficient data are available to make a reasonable differentiation of cardiovascular or non-cardiovascular cause of death.</td>
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<tr>
<td><strong>Non-fatal endpoints</strong></td>
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<tr>
<td><strong>Myocardial infarction</strong></td>
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<td>Non-procedural: troponin or CKMB ≥ 2 X URL and either ischaemic symptoms or new ischaemic ECG changes. Post-PCI Troponin or CKMB &gt; 3 X URL within 48 h. Post-cardiac surgery: troponin or CKMB ≥ 5 X URL AND new pathological Q waves, left bundle branch block (LBBB), new native or graft vessel occlusion, or imaging evidence of loss of myocardial function.</td>
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<tr>
<td><strong>Unplanned hospitalization for heart failure</strong></td>
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<td>Presentation to an acute care facility requiring an overnight hospitalization (change in calendar day) with an unexpected exacerbation of heart failure (1 or more symptoms and 2 or more signs), requiring treatment with either IV diuretics, vasodilators, inotropes, mechanical fluid removal, or insertion of an intra-aortic balloon pump for haemodynamic compromise, initiation of standing oral diuretics or intensification (doubling) of the maintenance diuretic dose.</td>
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<tr>
<td><strong>Doubling of baseline serum creatinine concentration</strong></td>
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<tr>
<td>A doubling of baseline serum creatinine to a value greater than the upper limit of normal as determined by two central laboratory measurements separated by ≥ 30 days.</td>
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<td><strong>Resuscitated sudden death</strong></td>
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<tr>
<td>Subject experiences sudden death or cardiac arrest and is successfully resuscitated by cardioversion, defibrillation, or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Transient losses of consciousness such as seizures or vasovagal episodes that do not reflect significant cardiac dysfunction are excluded.</td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
</tr>
<tr>
<td>Event meeting one of the following criteria: (1) A focal neurological deficit of central origin lasting &gt; 24 h, with or without imaging confirmation of cerebral infarction or intracerebral haemorrhage. (2) Focal neurological deficit of central origin lasting &lt; 24 h with corresponding imaging evidence of cerebral infarction or intracerebral haemorrhage. (3) A focal neurological deficit of central origin lasting &lt; 24 h that was treated with thrombolytic therapy or directed percutaneous intervention. (4) A non-focal encephalopathy lasting &gt; 24 h with imaging evidence of cerebral infarction or haemorrhage adequate to account for the clinical state. (5) Retinal artery ischaemia or haemorrhage. Further classified as: ischaemic, ischaemic with haemorrhagic conversion, primary intracranial haemorrhage, unknown.</td>
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**URL, upper reference limit.**
ARB) and beta-blocker in patients with stable CHF (NYHA Class II–IV), prior or current hypertension, and B-type BNP >100 pg/mL. Aliskiren was well tolerated in this population of patients when added to standard HF therapy, with no significant increase in worsening renal function, hyperkalaemia, or hypotension compared with placebo. In addition, aliskiren significantly reduced neurohormone levels and improved echocardiographic assessments of LV function. The ALOFT trial demonstrated the safety of multiple RAAS antagonists in patients with stable chronic HF. A reduction in neurohormonal markers, without the increased risk of adverse events, suggests the possible utility of aliskiren in HF patients. To address this hypothesis two morbidity and mortality trials, one in acute decompensated HF (ASTRONAUT) and the other in chronic stable systolic HF (ATMOSPHERE) have been designed.

Summary
To date, no treatment initiated at the time of the hospitalization for AHFS has demonstrated an improvement of clinical outcomes post-discharge. The potential impact of a higher level of RAAS inhibition (when compared with the traditional approach) as well as the early initiation of RAAS therapy has not been evaluated. The higher level of RAAS inhibition provided by aliskiren without an adverse effect on renal function may result in a decreased rate in post-discharge hospitalizations and mortality for patients admitted with AHFS. This is particularly important since post-discharge events continue to be high in spite of available therapies and have not decreased for the last decade.

Supplementary material
Supplementary material is available at European Journal of Heart Failure online.

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Conflict of interest: M.G. is or has been a consultant for and/or received honoraria from Abbott, Astellas, Bayer, AstraZeneca, Corthera, Debiopharm, Errekaappa Therapeuicti, EKR Therapeutics, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Nile, Novartis, Otsuka, PeriCor, PDL BioPharma, Scios, Inc., Solvay Pharmaceutical, and Sigma-Tau. MA has no financial disclosures. F.Z. reports research funding from Novartis for conduction of ASTRONAUT CAC. C.G., S.M., J.B., and H.R. are employees of Novartis. A.M. has received research grants from Novartis and received honoraria for lectures from Novartis. He is a steering committee member in studies sponsored by Novartis, Johnson & Johnson, and Bayer.

Appendix 1

Executive Steering Committee
Chairman: Mihai Gheorghiade, Co-Chair: Aldo Maggioni, Members: Gregg C. Fonarow, Michael Böhm, Faiez Zannad.

Clinical Adjudication Committee
Chairman: Scott Solomon, Co-Chair: Eldrin Lewis, Physician Reviewer: Peter Finn, Howard Hartley, Larry Weinrauch, Ebrahim Barkoudah, Operational Manager: Chau Duong, Research Assistant: Austin Rogers.

Data and Safety Monitoring Investigators

References
the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. 

Am J Cardiol 2008;52:1640–1648.

10. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O’Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. 


