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ORIGINAL RESEARCH ARTICLE

Systolic blood pressure, heart rate, and outcomes in patients with coronary disease and heart failure

Islam Y. Elgendy[1,2]*, James A. Hill[1], Anita D. Szady[1,3], Yan Gong[4], Rhonda M. Cooper-DeHoff[1,4] and Carl J. Pepine[1]

[1]*Division of Cardiovascular Medicine, Department of Medicine, University of Florida, Gainesville, FL, USA;* [2]*Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA;* [3]*Cardiovascular Center of Marin, MarinHealth, Larkspur, CA, USA;* [4]*Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL, USA*

Abstract

Aims Data regarding the optimal systolic blood pressure (SBP) and heart rate (HR) for coronary artery disease (CAD) patients with hypertension and a history of heart failure (HF) are limited. Accordingly, using data from a large clinical trial, we investigated the association between SBP and heart rate and subsequent adverse outcomes in CAD patients with a history of HF, and we aimed to better understand how pre-existing HF impacts outcomes among patients with CAD.

Methods and results Among 22 576 CAD patients enrolled in the INternational VErapamil SR-Trandolapril STudy (INVEST), 1256 were identified with a history of physician-diagnosed HF New York Heart Association (NYHA) Class 1–3 at entry. The primary outcome was the first occurrence of all-cause death, myocardial infarction (MI), or stroke. Cox proportional-hazards models adjusted for pre-specified covariates were constructed to estimate risk among the HF cohort compared with a case-matched sample from the non-HF cohort. At a mean 2.5 years' follow-up, those with prior HF had a higher risk of the primary outcome (hazard ratio (HR) 2.55, 95% confidence interval 2.30–2.83, $P < 0.0001$). Among those with history of HF, a low ($<$120 mmHg) or high ($>$140 mmHg) SBP and heart rate $\geq$ 85 b.p.m. were associated with increased risk for adverse outcomes, which persisted after covariate adjustment.

Conclusions In patients with CAD, a physician diagnosis of HF at baseline portended a higher risk for death, MI, or stroke than in those without an HF history. Achieving SBP of 120–140 mmHg and heart rate $<$ 85 b.p.m. was associated with a better outcome in patients with known HF and CAD.

Keywords Blood pressure; Hypertension; Heart failure; Coronary artery disease

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**Correspondence to: Islam Y. Elgendy, Division of Cardiology, Massachusetts General Hospital/Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA.*
Tel: +1 (617) 643 3238; Fax: +1 (617) 726 7855.
Email: iyelgendy@gmail.com
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Introduction

While it is well known that the majority of patients who develop heart failure (HF) have coronary artery disease (CAD) and antecedent hypertension,[1] knowledge on the interactions with blood pressure (BP) levels and heart rate is limited. Poorly controlled BP exacerbates left ventricular loading and may exacerbate ischaemia with the potential to contribute to adverse outcomes. Many established HF medications [e.g. angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers] have BP-lowering and heart rate-lowering effects as a component of their mechanism for preventing HF and improving outcomes. On the other end of the spectrum, it is established that persistently low BP may limit options to fully deploy medications proven to reduce adverse outcomes and is linked with poor prognosis in HF patients.[2–4] Furthermore, evidence suggests that heart rate is an important prognostic marker in patients with HF.[5] The INternational VErapamil SR-Trandolapril STudy (INVEST) was a randomized trial that evaluated hypertension management in ambulatory patients with chronic CAD.[6] Patients were assigned to either a calcium antagonist (verapamil SR) strategy or a beta-blocker (atenolol) hypertension management strategy. During the trial, very good BP control was achieved (~71% with

<140/90 mmHg) in both treatment strategies, and the adverse outcomes were equivalent among the strategies. These results provide the rationale for combining patients from both treatment strategies to investigate the interrelationships of BP, heart rate, and HF and their associations with adverse outcomes. Therefore, we addressed whether pre-existing HF impacts outcomes in patients with CAD, and we determined the optimal systolic blood pressure (SBP) and heart rate in CAD patients with a history of HF.

Methods

The INVEST protocol and primary outcome results have been described in detail elsewhere.[6] INVEST was conducted according to the principles of the Declaration of Helsinki, the institutional review boards at participating sites approved the protocol, and patients provided written informed consent. Briefly, clinically stable ambulatory patients with chronic CAD requiring therapy for hypertension were randomized to either a calcium antagonist (verapamil SR) strategy or a beta-blocker (atenolol twice daily) strategy. To achieve BP control, ACEI (trandolapril) was pre-specified as add-on therapy in the calcium antagonist strategy, and hydrochlorothiazide (HCTZ) was pre-specified as add-on in the beta-blocker strategy. The addition of trandolapril to the calcium antagonist strategy and HCTZ to the beta-blocker strategy was directed by the on-treatment BP in an attempt to meet the achieved BP goal and not related to the onset of symptoms suggestive of HF. Consistent with clinical practice guidelines, the ACEI trandolapril was recommended for all patients with HF, diabetes, or renal insufficiency. As directed by protocol, BP control gradually improved over follow-up with drug dose titration and addition of new drugs. Goal BP (systolic and diastolic) recommended by the guidelines at the time of the trial was achieved in both treatment groups by 6 months.[7] There was no difference between groups in the degree of BP control or the BP levels achieved.

The diagnosis of HF was clinically determined from the baseline evaluation. Patients with physician-documented New York Heart Association (NYHA) Class 1–3 symptoms at entry were eligible, while those with NYHA Class 4 symptoms, as well as those with recent myocardial infarction (MI) or cardiovascular hospitalization, were excluded. The site physician was asked to use all of the patient's clinical and laboratory findings to support the diagnosis, but data on the left ventricular function were not systematically collected. BP target of ≤130/85 mmHg was recommended for all HF patients, consistent with guidelines at the time of the study.

To determine the independent contribution of a history of HF on the risk for adverse outcome, a comparison of the cohort with HF at entry was made with a propensity score-matched, non-HF cohort (1:1 ratio). The primary outcome was the first occurrence of all-cause death, non-fatal MI, or non-fatal stroke. BP was measured at each clinic visit, and drug use was analysed at baseline and at 6, 12, and 24 months.

Statistical analysis

Data for continuous variables were presented as means and standard deviations, and for categorical variables as percentages. Kaplan–Meier survival curves were plotted for time to first occurrence of all-cause mortality, non-fatal MI, or non-fatal stroke and were compared using the log-rank test. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the use of Cox proportional-hazards models adjusted for pre-specified covariates—treatment strategy, age (decades), sex, race/ethnicity (White, Asian, Black, Hispanic, and multiracial/other), and previous MI—with further adjustments for covariates that were selected by stepwise selection ($P < 0.2$ for entry and $P < 0.05$ for retaining in the model) including US residency, body mass index (5 kg/m^2 increments), renal impairment, peripheral vascular disease, aspirin use, left ventricular hypertrophy, smoking (ever), coronary revascularization, stroke/transient ischaemic attack, angina pectoris, unstable angina, arrhythmia, hypercholesterolaemia, and diabetes. All statistical analyses were performed with SAS software, Version 9.2 (SAS Institute, Cary, NC). All reported P values are two-sided, with $P < 0.05$ considered to indicate statistical significance.

Results

Of the 22 576 patients enrolled in INVEST, 1256 had a history of physician-diagnosed HF (NYHA Class 1–3) at baseline. During follow-up (mean 2.5 years), 3113 patient-years were accumulated for the HF cohort and 57 752 patient-years for the non-HF cohort. Pertinent baseline demographics and medical history are summarized in *Table 1*. At 24 months, the percentage of patients taking study drugs was high (*Table S1*).

As expected, patients with a history of HF tended to be older and more frequently had a history of MI, coronary revascularization, and/or diabetes. The primary outcome occurred more frequently in those with prior HF than in those without HF (HR 2.55, 95% CI 2.30–2.83, $P < 0.0001$). This effect was also observed for the individual components of the primary outcome (*Table 2*). After adjustment of covariates, including on-treatment heart rate, there was no statistical difference for the primary outcome between hypertension treatment strategies (non-calcium antagonist vs. calcium antagonist, HR 0.92, 95% CI 0.73–1.15, $P = 0.48$). In the cohort with HF compared with the matched non-HF cohort, there was a higher incidence of the primary outcome (*Figure 1*). Interestingly, these outcome–time relationships began to

Table 1 Pertinent baseline characteristics[a]

Demographics	Heart failure (n = 1256)	No heart failure (n = 21 320)	P value
Age, mean years (SD)	69 (10)	66 (10)	<0.0001
BMI, mean kg/m^2 (SD)	30 (7)	29 (7)	0.01
Age > 70	45	33	<0.0001
Female	52	52	0.83
Race			<0.0001
White	59	48	
Black	22	13	
Hispanic	18	37	
Medical history			
Myocardial infarction	48	31	<0.0001
Angina pectoris	65	67	0.1
Coronary revascularization	32	27	<0.0001
Transient ischaemic attack or stroke	13	7	<0.0001
Left ventricular hypertrophy	46	21	<0.0001
Unstable angina	17	11	<0.0001
Arrhythmia	18	6	<0.0001
Peripheral vascular disease	22	11	<0.0001
Smoking history	53	46	<0.0001
Diabetes[b]	42	28	<0.0001
Renal dysfunction[c]	7	2	<0.0001
Hypercholesterolaemia[b]	56	56	0.8
Medications at baseline			
Any lipid-lowering agent	35	37	0.2
Nitrates	51	35	<0.0001
Aspirin or other antiplatelet agent	64	56	<0.0001
Other NSAIDS	16.7	17.8	0.3
Potassium supplement	28.7	5.6	<0.0001
Antidiabetic medication	32.8	21.9	<0.0001

BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary interventions.
[a]Values expressed as number (percentage) unless otherwise indicated.
[b]History of or currently taking antidiabetic or lipid-lowering medications.
[c]History of or currently have elevated serum creatinine level but <4 mg/dL (354 μmol/L).

Table 2 Adverse cardiovascular outcomes for patients with (n = 1256) and without history of heart failure (n = 21 320)

Adverse outcome	Patients	No. of event	Event rate (%)	Events per 100 patient-years	P value
Primary outcome	Non-HF	2114	9.92	3.66	
	HF	318	25.32	10.21	<0.0001
All-cause mortality	Non-HF	1660	7.79	2.87	
	HF	286	22.77	9.19	<0.0001
Non-fatal MI	Non-HF	279	1.31	0.48	
	HF	25	1.99	0.80	0.04
Non-fatal stoke	Non-HF	253	1.19	0.44	
	HF	26	2.07	0.84	0.006
Total MI	Non-HF	764	3.58	1.32	
	HF	129	10.27	4.14	<0.0001
Total stroke	Non-HF	341	1.60	0.59	
	HF	36	2.87	1.16	0.0007

HF, heart failure; MI, myocardial infarction.

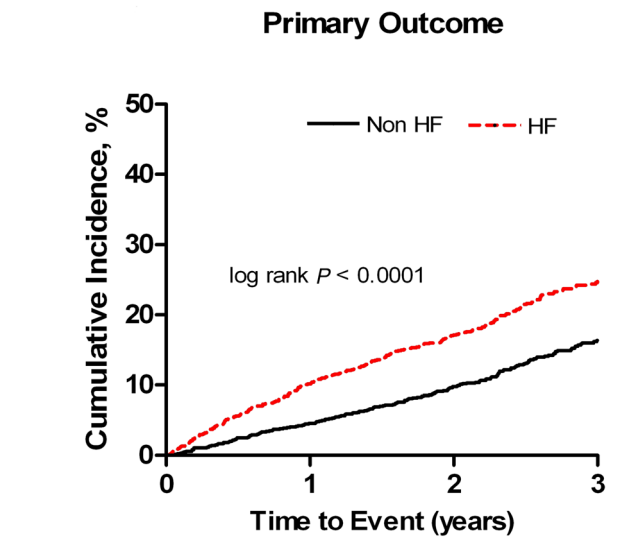
separate within the first month of follow-up. The incidence of the primary outcome remained higher for both treatment strategies among the HF cohort vs. matched non-HF cohort within either strategy (*Figure 2*).

There was, however, a relationship between level of SBP achieved and occurrence of a primary outcome event. The optimum achieved SBP ranged between 120 and 140 mmHg. Both lower-achieved and higher-achieved SBP levels were associated with increased risk for the primary outcome (*Figure 3*). The mean heart rate during the follow-up period was also associated with the primary outcome—increased heart rate (>85 b.p.m.) was associated with a significantly higher risk for the primary outcome (*Figure 4*).

Discussion

In this post hoc analysis of a large randomized trial of hypertensive patients with CAD, we observed that a physician-documented diagnosis of HF at baseline was associated with

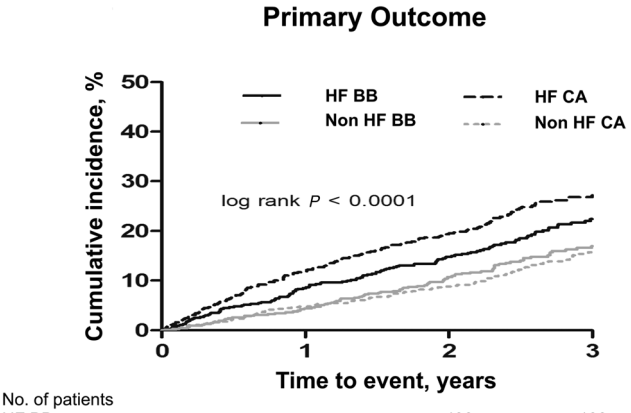
Figure 1 Kaplan–Meier analysis for time to primary outcome (first occurrence of death, myocardial infarction, or stroke) among the heart failure (HF) and propensity score-matched non-HF patients.



No. of patients at risk:

HF	1256	1102	966	393
Non HF	1256	1165	1068	446

Figure 2 Kaplan–Meier analysis for time to primary outcome among heart failure (HF) and propensity score-matched non-HF patients by treatment strategy [CA = calcium antagonist strategy (verapamil SR); BB = beta-blocker strategy (atenolol)]. Log-rank $P < 0.0001$; HF CA vs. HF BB: $P = 0.067$; non-HF CA vs. non-HF BB, $P = 0.29$.

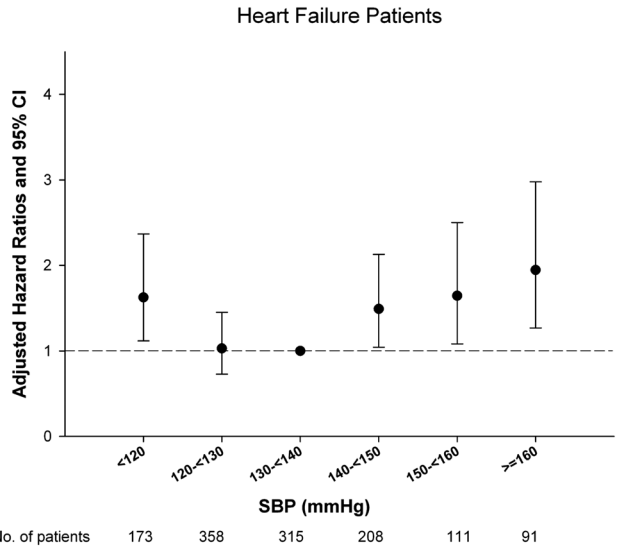


No. of patients

HF BB	629	570	499	199
HF CA	627	532	467	194
Non HF BB	624	570	512	219
Non HF CA	632	595	556	227

a higher incidence of adverse outcome compared with that in those without HF history, despite a similar degree of BP control. This finding was noted in the propensity-matched comparison group and confirms that a history of physician-diagnosed HF (only NYHA Class 1–3) itself carries very important adverse prognostic information beyond other aspects of

Figure 3 On-treatment systolic blood pressure (SBP) and the risk for primary outcome in patients with heart failure.

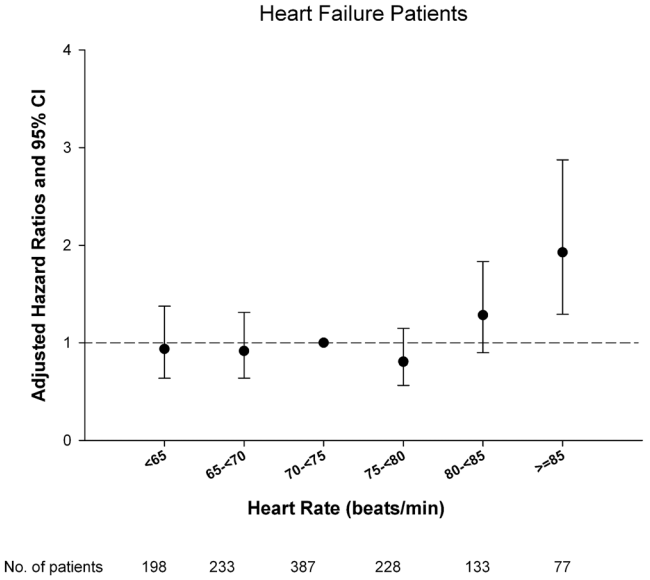


No. of patients	173	358	315	208	111	91

the more high-risk patient profile. This analysis shows that there is a J-shaped relationship between SBP and adverse events among CAD patients with prior HF (i.e. the optimal SBP target is between 120 and 140 mmHg, and there is a higher incidence of events among those with an SBP $<$ 120 as well as those with $>$140 mmHg). Although data regarding systolic left ventricular function were not collected in the INVEST, the fact that all patients had CAD and almost half of the HF patients also had a history of prior MI supports the suggestion that a large proportion of these patients likely had abnormal systolic function at baseline.[8] Nevertheless, more recent studies have suggested that there is no significant difference in mortality (cardiovascular and non-cardiovascular related) between patients with HF and preserved and reduced systolic function.[9] The current analysis confirms that the presence of a history of HF (NYHA Class 1–3) predicts an adverse prognosis in hypertensive patients with known CAD.

This analysis also suggests that the risk of adverse outcome was significantly elevated among those with the lowest and highest SBP levels (i.e. $<$120 and $>$140 mmHg). The optimal BP for a patient with CAD and prior HF remains unknown, as BP trials such as SPRINT did not include patients with HF at baseline.[10] The 2017 American College of Cardiology/American Heart Association Hypertension guidelines recommended an SBP target of $\leq$130 mmHg in patients with HF.[11] However, a secondary analysis of the SPRINT trial demonstrated that intensive BP control (i.e. SBP $<$ 120 mmHg), compared with standard BP control (i.e. SBP $<$ 140 mmHg), was associated with lower incidence of acute decompensated HF events at a median of 3.3 years.[12] But the SPRINT had limited numbers of patients with documented

Figure 4 On-treatment mean resting heart rate and risk for the primary outcome in patients with heart failure



CAD. Further, acute decompensated HF events in that analysis were associated with a higher incidence of future cardiac events. Our data suggest that there is a J-curve for SBP and outcomes in CAD patients with HF (i.e. achieving an SBP target of ~130 mmHg is associated with a lower incidence of adverse events). This difference could be explained by the lack of observer during automated BP measurements at some of the sites in the SPRINT trial, which has been estimated to lower the SBP ~ 10 mmHg[13]; therefore, the optimum SBP might be ~130 mmHg. Similar to our findings, other observational analyses have indicated that an optimum SBP target might be ~120–130 mmHg in the HF population (i.e. secondary to any cause).[14] Our findings extend our knowledge by examining this association in those with documented CAD and hypertension. A secondary analysis of the STICH trial, which enrolled patients with ischaemic cardiomyopathy (mean ejection fraction 28%), has also suggested that the optimal SBP is ~120–130 mmHg.[15] Our findings support this suggestion in those with documented CAD and clinical HF (Class 1–3) at baseline.

In this analysis, we also found that an average heart rate $>$ 85 b.p.m. during follow-up was associated with a higher incidence of adverse events. Previously, we found that baseline heart rate was an important predictor of adverse outcomes in the INVEST (~6% excess risk for every 5 b.p.m. increase) and that the risk appeared even greater for on-treatment heart rate, but we had not previously analysed the influence of heart rate among those with HF.[16] Consistent with the findings of this analysis, a secondary analysis of the SHIFT trial, which included patients with chronic HF (~2/3 with ischaemic cardiomyopathy), showed that the quintile of patients with heart rate $\geq$ 87 b.p.m. had a two-fold increase in the risk of the composite of cardiovascular or HF hospitalizations.[17] Similarly, a post hoc analysis of the EVEREST trial suggested that a higher heart rate ($>$70 b.p.m.) in the early post-discharge period was linked to increased mortality among patients hospitalized with HF with reduced ejection fraction and in sinus rhythm.[18] These findings support the importance of heart rate control in CAD patients with HF.

Although the INVEST compared a calcium antagonist (i.e. verapamil SR) strategy, which is considered contraindicated by many in HF, with a beta-blocker (atenolol) strategy, which is not a commonly used beta-blocker in patients with HF, there were no significant differences in the primary outcome between treatment strategies as reported in the primary outcome results.[19] This provided the rationale to combine both treatment arms for the current analysis. Perhaps the protocol-recommended addition of an ACEI to patients with HF in the calcium antagonist strategy helped to limit adverse outcomes in this group. One small study found that the combination of verapamil and trandolapril in patients with angina and depressed left ventricular function resulted in improved ejection fraction and decreased incidence of angina.[20] Another much larger study showed no effect of the combination on mortality.[21] While atenolol has not been extensively studied for a mortality benefit in patients with HF, two small randomized trials have shown that atenolol, as compared with placebo, is associated with a survival benefit in patients with chronic HF.[22,23] In the present study, the addition of HCTZ may have offset any mortality benefit of atenolol, if any, in the beta-blocker group. Notably, the concern for possible lack of benefit from atenolol in HF patients is partly related to only once-daily dosing,[22] whereas in INVEST, atenolol was given twice daily.

Limitations

As noted, strengths of this analysis are the multicentre design, that these data are from a large number of patients with CAD and hypertension with the goal of BP control, and that outcomes were adjudicated by an events committee masked to treatment assignment. Also, the protocol also recommended sodium restriction, an SBP goal of ≤130 mmHg, and guideline recommendations for secondary atherosclerosis prevention. However, there are several limitations worth noting. First, because of the very large sample size and exclusion of patients with NYHA Class 4 HF, randomization was not stratified for patients with a pre-existing history of HF. As expected, the baseline characteristics known to influence outcomes were well distributed between treatment groups. Second, data on left ventricular function were not collected; thus, we cannot compare patients with various degrees of decreased ejection fraction with those with preserved ejection fraction. However, in a report from the ALLHAT study, long-term follow-up suggested that incident HF carried the same mortality whether ejection fraction was preserved or reduced.[24] Finally, there was no protocol-driven HF management plan other than the requirement for an ACEI, which was repeatedly reinforced by the online data monitoring system.

Conclusions

In this large study of CAD patients and hypertension with a pre-existing history of HF, outcomes were worse than in those without HF. There was a J-shaped relationship between SBP and adverse events in this cohort. Achieving an SBP of 120–140 mmHg and heart rate < 85 b.p.m. appeared to have a significant impact on outcomes in HF patients.

Conflict of interest

RMC reports receiving research funding from Abbott Laboratories while INVEST was being conducted. CJP reports grant support (significant) from Adelphi Values (Qualitative MVA), Amorcyte (PreSERVE), Athersys (MI-NSTEMI), BioCardia (CardiAMP), Brigham and Women's Hospital (INVESTED), Capricor (ALLSTAR), Cytori Therapeutics (ATHENA), Duke University (ADAPTABLE), Gilead Sciences, Inc. (RWISE, University of Florida site), Merck & Co., Inc. (VICTORIA), Mesoblast (TEVA, University of Florida site), NIH/NHLBI (CONCERT), US Department of Defense (WARRIOR), and Ventrix (CV-201); and educational support (modest) for the Vascular Biology Working Group from Amgen Inc., AstraZeneca Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc., Daiichi Sankyo, Ionis, and Relypsa; consultant fees/honoraria (modest) from Amgen Inc., AstraZeneca Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Gilead, Merck and (significant) from Ironwood Pharmaceuticals Inc., and SLACK Inc.; and is a task force member (no compensation) of FACT: Foundation for the Accreditation of Cellular Therapy. IYE, JAH, ADS, and YG report that they have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Study and non-study drug use of the heart failure patients.

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