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Usefulness of *Isosorbide Dinitrate* and *Hydralazine* as Add-on Therapy in Patients Discharged for Advanced Decompensated Heart Failure

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Abstract

Data supporting the use of oral isosorbide dinitrate and/or hydralazine (I/H) as add-on therapy to standard neurohormonal antagonists in advanced decompensated heart failure (ADHF) are limited, especially in the non-African-American population. Our objective was to determine if addition of I/H to standard neurohormonal blockade in patients discharged from the hospital with ADHF is associated with improved hemodynamic profiles and improved clinical outcomes. We reviewed consecutive patients with ADHF admitted from 2003 to 2006 with a cardiac index <2.2 L/min/m² admitted for intensive medical therapy. Patients discharged with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (control group) were compared with those receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers plus I/H (I/H group). The control (n = 97) and I/H (n = 142) groups had similar demographic characteristics, baseline blood pressure, and renal function. Patients in the I/H group had a significantly higher estimated systemic vascular resistance (1,660 vs 1,452 dynes/cm⁵, p <0.001) and a lower cardiac index (1.7 vs 1.9 L/min/m², p <0.001) on admission. The I/H group achieved a similar decrease in intracardiac filling pressures and discharge blood pressures as controls, but had greater improvement in cardiac index and systemic vascular resistance. Use of I/H was associated with a lower rate of all-cause mortality (34% vs 41%, odds ratio 0.65, 95% confidence interval 0.43 to 0.99, p = 0.04) and all-cause mortality/heart failure rehospitalization (70% vs 85%, odds ratio 0.72, 95% confidence interval 0.54 to 0.97, p = 0.03), irrespective of race. In conclusion, the addition of I/H to neurohormonal blockade is associated with a more favorable hemodynamic profile and long-term clinical outcomes in patients discharged with low-output ADHF regardless of race.

Although isosorbide dinitrate and hydralazine (I/H) were considered 1 of the earliest “evidence-based” treatment strategies for systolic heart failure (HF) based on the cardiocirculatory model of HF,^{1,2} its current use is eclipsed by the large volume of evidence supporting the use of neurohormonal antagonists. Recently, the African-American Heart

Failure Trial demonstrated a significant decrease in adverse clinical outcomes in response to therapy with a fixed-dose formulation of I/H on top of neurohormonal blockade in ambulatory African-American patients who were highly symptomatic and had significant cardiac impairment and remodeling.³ As a result, the latest clinical guidelines advocate the use of a combination of I/H as “a reasonable option” as part of the treatment strategy for patients with stable but advanced systolic HF who remain symptomatic despite optimal standard therapy.^{4,5} Perhaps the major benefit of neurohormonal antagonist is to delay the disease progression of HF syndrome. Hence, hemodynamic perturbations may only be delayed (rather than decreased) as the disease progresses, and at advanced stages hemodynamic effects of vasodilators may sustain the failing heart from further deterioration. Because angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) may not provide the same hemodynamic balance of preload and afterload decrease or mechanistic benefits as I/H, the primary aim of this study was to determine if addition of I/H to standard neurohormonal blockade after an episode of advanced decompensated HF (ADHF) would be associated with sustained hemodynamic improvement and better clinical outcomes in patients admitted with ADHF.

Methods

We reviewed consecutive patients ≥ 18 years of age with chronic (>6 months) systolic HF (New York Heart Association class III to IV) who underwent intensive medical therapy guided by pulmonary artery catheter at the Cleveland Clinic (Cleveland, Ohio) in a dedicated HF intensive care unit from January 1, 2003, to December 31, 2006. From this cohort, we narrowed our study population to include only patients discharged from the hospital after therapy. Subjects who met the additional inclusion criteria at the time of admission were enrolled in the study: (1) impaired left ventricular systolic function as defined by a left ventricular ejection fraction $<30\%$ measured by the Simpson method within 2 months before admission; (2) impaired cardiac output, defined by a cardiac index ≤ 2.2 L/min/m²; and (3) evidence of congestion as determined by a pulmonary capillary wedge pressure >18 mm Hg and/or central venous pressure >8 mm Hg. Exclusion criteria included (1) those with congenital heart disease, (2) recipients of a heart transplant, and (3) those with a mean arterial pressure <65 mm Hg. Institutional review board approval of this research project and informed consent were obtained for hospitalization, treatment, and all standard invasive procedures and documented in the medical records, according to protocol and Cleveland Clinic policy.

Systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer and central hemodynamic parameters were derived from pulmonary artery catheter measurements every 15 minutes (except for cardiac index, which was calculated at 4-hour intervals). Complete hemodynamic information was collected in all subjects before starting intensive medical therapy and again before removing the pulmonary artery catheter. Central venous pressure and pulmonary capillary wedge pressure were assessed at end-expiration with a balloon-tipped catheter at steady state with the subject in a supine position. Cardiac index was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. Estimated systemic vascular resistance (SVR) was calculated according to the formula $80 \times (\text{mean arterial pressure} - \text{right atrial pressure}) / \text{cardiac output}$.

The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been described previously.^{6,7} Briefly, optimal hemodynamic response was defined as a decrease in pulmonary capillary wedge pressure to ≤ 18 mm Hg, a decrease in central venous pressure to ≤ 8 mm Hg, and an improvement in cardiac index to ≥ 2.2 L/min/m² while mean

arterial pressure was maintained at >65 to 70 mm Hg and/or systolic blood pressure at >85 mm Hg. To achieve the hemodynamic goals, most patients were treated with parental vasodilators or inotropic agents with or without intravenous loop diuretic therapy. Oral drug regimens including ACE inhibitor or ARB, β blockers, and spironolactone were continued at their admitting doses as tolerated (except in the case of intravenous dobutamine or vasodilator administration, when β blockers or I/H would be stopped, respectively). The duration of infusions of intravenous agents in the intensive care unit was typically 24 to 48 hours.

Upon stabilization, the decision to use I/H in addition to an ACE inhibitor (or ARB) versus further up-titration of ACE inhibitor (or ARB) alone was at the discretion of the physician caring for the patient and no randomization scheme was employed. Regardless, titration of oral drugs was aimed to wean off parental therapy and based on maintaining a target mean arterial pressure of 65 to 70 mm Hg and/or systolic blood pressure >85 mm Hg. Titration of oral vasodilator drugs followed standard protocols established in our HF intensive care unit and was conducted by highly trained nursing staff experienced in the care of patients with advanced HF (Figure 1), but the sequence of drugs was also at the attending cardiologist's discretion. Systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer every 15 minutes. If hypotension occurred during the titration protocol, the previously tolerated dose was administered without further up-titration. Once blood pressure goals were achieved and optimal hemodynamic measurements maintained, patients were discharged from the intensive care unit to a regular nursing floor (usually within 48 to 72 hours). Neurohormonal antagonists and I/H were further titrated, as tolerated, to guideline-recommended therapeutic doses if not already achieved in the HF intensive care unit. Standard HF patient education materials and counseling were given to the patient during the admission, and postdischarge follow-up visits were provided by an HF disease management clinic.

Our objectives were to determine if addition of I/H to an ACE inhibitor or ARB was associated with not only improved hemodynamic profiles at discharge but also improved long-term clinical outcomes. Three long-term clinical end points were analyzed and compared between patients who received an ACE inhibitor or ARB alone (control group) and those who received I/H plus an ACE inhibitor or ARB (I/H group) at discharge, namely all-cause mortality, cardiac transplantation, and first readmission for HF after index hospitalization discharge. A combined end point of event-free survival (time to all-cause mortality and first HF readmission) was also analyzed. Death was determined using data documented in the medical record and confirmed by surveying the Social Security Death Index.

All data are expressed as mean $\pm$ SD (normal distribution) or median (interquartile range, nonparametric) for continuous variables and as a ratio for categorical data. Differences in continuous clinical variables between patient groups were assessed by Student's *t* test or the Kruskal-Wallis (rank-sum) test according to whether or not their distribution was gaussian. Comparisons by chi-square and Fisher's exact test were performed for categorical data. Cox proportional hazards regression model was used to determine which variables were related significantly to the different end points during the follow-up period and Kaplan-Meier survival curves were constructed using SPSS 13.0 for Windows (SPSS, Inc., Chicago, Illinois). Variable selection in multivariable modeling was based on the statistical significance of univariate analysis. Statistical significance was set at a 2-tailed probability level of <0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the report as written.

Results

A total of 266 consecutive patients fulfilled all inclusion and exclusion criteria, including 142 in the I/H group and 97 in the control group. The remaining 27 patients did not receive an ACE inhibitor at discharge, typically because of chronic renal insufficiency as evidenced by a higher serum creatinine level throughout admission and were further excluded from this analysis. No patient received the combination of an ACE inhibitor and an ARB in our study cohort. Baseline clinical characteristics were similar in patients in the 2 study groups except for creatinine level at discharge (Table 1). Mean intensive care and hospital durations were 3.5 ± 1 and 8 ± 7 days, respectively, and were similar between the I/H and control groups.

As presented in Table 2, we observed that the I/H group presented with a higher estimated SVR and demonstrated a lower cardiac output compared with the control group. Compared with baseline hemodynamic assessment, a statistically significant decrease of filling pressures and an increase in cardiac output were achieved in the 2 groups. However, a statistically significant decrease in estimated SVR and systolic blood pressure was documented only in the I/H group and was not as apparent in the control group. In addition, the increase in cardiac output (2.1 ± 1.9 vs 1.4 ± 1.6 L/min, $p = 0.005$) and cardiac index (1.05 ± 0.8 vs 0.65 ± 0.6 L/min/m², $p = 0.005$) was greater in I/H-treated patients, although the overall mean hemodynamic measurements at the time of pulmonary artery catheter removal were similar between the 2 groups. Only estimated SVR at this time was lower in patients treated with ACE inhibitor plus I/H. As presented in Table 3, adherence to optimal pharmacologic therapy was high on admission and discharge and comparable between the 2 groups, with >65% use of β blockers at discharge.

Patients were followed for a median duration of 26.3 months (total of 584 patient-years) after the index hospital admission. No patient was lost to follow-up. There were 104 (39%) deaths and 52 (20%) cardiac transplantations. Primary outcome differences between cohorts are listed in Table 4. Patients in the I/H group had lower all-cause mortality (34% vs 41%, odds ratio [OR] 0.65, 95% confidence interval [CI] 0.43 to 0.99, $p = 0.04$) and lower all-cause mortality/HF rehospitalization (70% vs 85%, OR 0.72, 95% CI 0.54 to 0.97, $p = 0.03$) compared with the control group (Figure 2). The 2 treatment groups did not differ in overall cardiac transplantation or HF rehospitalization rates during the entire study period. The more favorable outcome in the I/H group was irrespective of race, although there was a trend toward more significance for the African-American population (all-cause mortality for whites in the I/H group, OR 0.66, 95% CI 0.4 to 0.98, $p = 0.05$; all-cause mortality for African-Americans in the I/H group, OR 0.44, 95% CI 0.23 to 0.85, $p = 0.01$). Interestingly, early separation of the outcome curves started after 3 months and was mainly driven by a decrease in HF rehospitalizations, whereas a mortality benefit was noted after only 6 months of therapy.

To further validate our findings, we performed a subanalysis to include only those patients with an admission mean arterial pressure of 65 to 85 mm Hg ($n = 141$). In this cohort, use of I/H plus an ACE inhibitor or ARBs was still associated with decreased all-cause mortality (OR 0.55, 95% CI 0.31 to 0.97, $p = 0.03$) and all-cause mortality/HF rehospitalization (OR 0.66, 95% CI 0.44 to 0.97, $p = 0.03$). Addition of I/H to an ACE inhibitor in patients previously not on I/H ($n = 87$) was also associated with decreased all-cause mortality (OR 0.58, 95% CI 0.37 to 0.93, $p = 0.02$) and all-cause mortality/HF rehospitalization (OR 0.61, 95% CI 0.45 to 0.85, $p = 0.003$).

Discussion

The key finding of our nonrandomized, single-center, case-control series of patients with advanced HF is that careful, protocol-driven administration of oral I/H can provide favorable hemodynamic improvements incremental to standard neurohormonal therapy despite similar systemic blood pressure targets. Furthermore, we demonstrated that add-on I/H to standard neurohormonal blockade might be associated with significantly lower all-cause mortality and fewer clinical adverse events at follow-up compared with standard neurohormonal blockade alone. We also found this effect to be independent of race. Therefore, although neurohormonal blockade can effectively delay disease progression in advanced HF, adding oral vasodilators in those with evidence of hemodynamic derangements and adequate systemic blood pressures allows restoration of optimal hemodynamic balance, which can potentially translate into incremental intermediate- and long-term benefits.

With the broad adoption of the neurohormonal hypothesis after the head-to-head comparison between enalapril and I/H,⁸ vasodilator therapy has taken a less prominent role in the armamentarium of pharmacologic therapy in chronic systolic HF. Although add-on aldosterone receptor antagonists and ARBs have been advocated recently, their benefits have largely assumed to be associated with a more comprehensive blockade of the “aldosterone escape” or “angiotensin escape” rather than optimization of hemodynamic derangements.⁹ Also, it is important to emphasize that the profile of our patient population has important differences from clinical trials that tested the combination of I/H in chronic systolic heart failure.^{1,2} Patients analyzed in our study cohort were not stable or ambulatory but were admitted with ADHF and were recently stabilized with parenteral vasoactive therapy. With an average systolic blood pressure of 110 mm Hg and mean left ventricular ejection fraction of 16%, our patient cohort has far more advanced disease and is highly vulnerable to repeat HF hospitalizations. By demonstrating the potential advantages of using add-on vasodilators over up-titration of standard neurohormonal antagonists, we revisited the concept of “hemodynamic dependence” in the setting of progressive pump failure.

There is reluctance of physicians to use vasodilators (parental and/or oral) in addition to neurohormonal blockers in hospitalized patients with advanced HF and low cardiac output. This may stem from the belief that vasodilatation may lead to significant hypotension if SVR is decreased without an ability to provide a compensatory increase in cardiac output. Some even consider ACE inhibitor/ARBs to be effective vasodilators themselves because they are commonly used antihypertensive agents. Our data corroborate the hypothesis that a decrease in afterload or wall stress during vasodilator administration can lead to a marked increase in cardiac output with an effective SVR decrease, preventing the development of significant hypotension. Despite similar systemic blood pressures at discharge, the I/H group had a more favorable hemodynamic profile compared with that achieved in the control group. Furthermore, patients with a mean arterial pressure ≤ 85 mm Hg also demonstrated a better outcome in the I/H-treated group. These observations may imply that there may be differential effects of various oral HF therapies on central hemodynamics even independent of their blood pressure-lowering effects.

Post hoc analyses of several trials have suggested a potential biological difference of lower ambient renin activity in African-American patients to explain the decreased efficacy of ACE inhibitor. Hence, the beneficial effects of I/H may be explained primarily on the basis of a more pronounced blood pressure decrease particularly in African-Americans.^{10–12} Nevertheless, a recent subanalysis of the African-American Heart Failure Trial demonstrated that, although the beneficial effects of I/H were similar in patients with baseline systolic blood pressure above or below the median of 126 mm Hg, I/H did not further decrease systolic blood pressure in patients with a baseline systolic blood pressure below the median.

¹² The lack of a clear difference in hemodynamic profiles or long-term outcomes between African-American and non-African-American patients in our study further supports the concept of a patient responsive to oral vasodilator therapy with advanced HF irrespective of ethnicity.

Although invasive measurements were obtained in our study, it is not our intention to imply the need for invasive monitoring, but rather to illustrate the relative mechanistic contributions of I/H in the improvement of hemodynamic compromise in the setting of ADHF. In this report, we demonstrated that add-on I/H to guideline-recommended ACE inhibitor (100%), β blocker (65%), and spironolactone (52%) may further decrease all-cause mortality and adverse events. Importantly, the benefit of I/H is still apparent at 3 months and is mainly driven by a decrease in HF rehospitalization, whereas a mortality benefit is seen at 6 months of therapy. The short-term benefit of decreased HF rehospitalization likely relates to achieving a more favorable hemodynamic profile (lesser SVR/higher cardiac index).

Previous studies have suggested that the delayed survival benefit can be attributed to further inhibition of left ventricular remodeling.^{2,13–15} Indeed, the fact that this benefit was observed in patients already treated with neurohormonal antagonism lends credence to the suggestion that a combination of direct and indirect vasodilators may provide benefits beyond blockade of the adrenergic and renin–angiotensin–aldosterone systems. Neurohormonal blockers slow the progression of left ventricular dysfunction, retard structural left ventricular remodeling, and decrease the rate of death and complications in patients with HF. Impaired bio-availability of nitric oxide and increased oxidant stress leading to endothelial dysfunction may also contribute to the remodeling process in HF.^{16,17} Therefore, it has been postulated that combining the nitric oxide donor (isosorbide dinitrate) with the antioxidant (hydralazine) may provide an alternative or supplemental approach to slow or reverse progressive HF.¹⁸ Based on our data, we cannot confirm or exclude the potential benefits of incremental I/H benefit beyond their role in hemodynamic optimization. Nevertheless, our patient characteristics were consistent with the clinical profile of “direct vasodilator responders,” particularly in those with dilated ventricles, whereby decrease of left ventricular impedance (or increased systolic ejection) and decrease in regurgitant volume may lead to decreased wall stress.¹⁹ Our observations may encourage future investigations to better understand the mechanistic underpinnings of such a multidrug strategy and further clarify our understanding of the complex role of nitric oxide and oxidative stress in advanced HF.

Obvious limitations inherent to the retrospective study design should be considered when findings are interpreted. Comprehensive follow-up, review of events, and centralized adjudication minimized the potential for missed or misclassified outcomes. However, selection bias probably entered the decision to treat or not treat patients with I/H, which may have trended toward the use of I/H in patients with more deranged hemodynamic measurements. Nevertheless, the decision to use I/H in addition to neurohormonal blockade may have been driven in part because of a higher systemic blood pressure at baseline, a known predictor of better outcomes in the setting of ADHF.²⁰ Accurate estimates about duration of vasoactive therapies administered and medication doses and tolerance to incremental dosing could not be retrieved due to logistic limitations from a chart-review process. It should also be emphasized that our patient population was relatively younger than the overall HF population, perhaps explaining the higher cardiac transplantation rate. Because none of our patients had add-on ARB therapy, the relative differences between add-on I/H and add-on ARB cannot be compared. Patients were hospitalized in a specialized HF intensive care unit, which included medical and nursing staff that was experienced in the use of vasodilator therapies. Hence, our results of this carefully managed patient population may not directly translate into general-practice settings and further studies are warranted.

Recognizing all these limitations, we believe that the information provided represents a well-balanced description of our longstanding and overall positive experience of adding vasodilators to standard therapy in patients with ADHF. These findings await verification in a proper controlled trial before a refined clinical approach using these commonly utilized drugs can be advocated.

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Captopril

Incremental ↑ 6.25→12.5→25→50 mg

Begin at 6.25-12.5 mg orally

After 2 hours, if initial dose tolerated, ↑ incrementally to next dose

After 2 hours, if previous dose tolerated, ↑ incrementally to next dose

After 6 hours, if previous dose tolerated, then 50 mg orally TID*

Isosorbide Dinitrate

Begin 10 mg orally

After 2 hours, if initial dose tolerated, ↑ to 20 mg

After 8 hours, if 20 mg tolerated, ↑ to 40 mg

After 8 hours, if 40 mg tolerated, ↑ to 60 mg

After 8 hours, if 60 mg tolerated, then 60 mg orally TID*

Hydralazine

Begin 25 mg orally (10 mg if systemic blood pressure low or patient in labile condition)

After 2 hours, if initial dose tolerated, ↑ to 50 mg

After 6 hours, if 50 mg tolerated, ↑ to 75 mg

After 6 hours, if 75 mg tolerated, ↑ to 100 mg

After 6 hours, if 100 mg tolerated, then 100 mg orally TID or QID*

* If previous dose is not tolerated, administer highest dose tolerated TID or QID

Figure 1.

Standard oral medication protocols for the Cleveland Clinic HF intensive care unit. ACE-I = ACE inhibitor; QID = 4 times/day; TID = 3 times/day.

Figure 2.

Clinical outcomes according to use of different medication regimens at discharge. Kaplan-Meier curves of all-cause mortality (*top*) and the combined end point of all-cause mortality and HF rehospitalization (*bottom*) between patients who were on an ACE inhibitor or ARB and those on an ACE inhibitor or ARB plus I/H. Abbreviation as in Figure 1.

Table 1

Baseline patient characteristics

Variable	Control Group (n = 97)	I/H Group (n = 142)	p Value (control vs I/H group)
Age (yrs)	55 ± 11	54 ± 12	0.2
Men	80%	80%	0.9
Caucasian	79%	80%	0.9
African-American	21%	20%	0.8
Hypertension (>140/90 mm Hg)	70%	70%	0.9
Hyperlipidemia (LDL >110 mg/dl)	54%	58%	0.6
Diabetes mellitus	28%	33%	0.3
Smoker (current or former)	47%	52%	0.4
Previous coronary bypass surgery	33%	35%	0.5
Implantable cardiac defibrillator	38%	42%	0.4
Cardiac resynchronization therapy with defibrillator	18%	15%	0.7
LV ejection fraction (%)	17 ± 7	16 ± 6	0.4
Ischemic cardiomyopathy	53%	55%	0.7
Idiopathic dilated cardiomyopathy	47%	45%	0.6
Hemoglobin (g/dl)	12.7 ± 2.1	13.0 ± 2.0	0.06
B-type natriuretic peptide (pg/ml)	634 (247–1,200)	740 (422–1,200)	0.43
Sodium (mmol/L)	136 ± 4	137 ± 4	0.1
Creatinine admission (mg/dl)	1.3 ± 0.6	1.4 ± 0.7	0.09
Creatinine peak (mg/dl)	1.4 ± 0.7	1.5 ± 0.8	0.2
Creatinine discharge (mg/dl)	1.2 ± 0.5	1.4 ± 0.5	0.005

Values are means ± SDs, percentages of patients, or medians (interquartile ranges).

LDL = low-density lipoprotein; LV = left ventricular.

Table 2

Baseline and follow-up hemodynamic measurements

Variable	Control Group (n = 97)			I/H Group (n = 142)		
	Admission	Follow-Up	p Value	Admission	Follow-Up	p Value
Systolic blood pressure (mm Hg) [*]	107 ± 15	105 ± 10	0.4	110 ± 17	106 ± 13	0.001
Heart rate (beats/min)	81 ± 15	80 ± 14	0.4	85 ± 13	83 ± 13	0.6
Central venous pressure (mm Hg) [*]	12 ± 6	9 ± 6	<0.001	13 ± 6	9 ± 5	<0.001
Systolic pulmonary artery pressure (mm Hg) [†]	53 ± 17	44 ± 14	<0.001	55 ± 16	43 ± 11	<0.001
Pulmonary capillary wedge pressure (mm Hg) [†]	24 ± 8	18 ± 7	0.01	25 ± 8	17 ± 5	<0.001
Cardiac output (L/min) [‡]	3.9 ± 0.8 [‡]	5.1 ± 1.2	<0.001	3.5 ± 0.9	5.2 ± 1.4	<0.001
Cardiac index (L/min/m ²) [‡]	1.9 ± 0.4 [‡]	2.4 ± 0.4	<0.001	1.7 ± 0.4	2.5 ± 0.5	<0.001
SVR (dynes/cm ⁵) [‡]	1,452 ± 477 [‡]	1,553 ± 249 [‡]	0.7	1,660 ± 571	1,030 ± 339	<0.001

Values are means ± SDs.

^{*} Follow-up occurred at discharge from hospital.[†] Follow-up occurred at the moment of removal of the pulmonary artery catheter.[‡] p <0.001 between the 2 treatment groups at the same time.

Table 3

Use of medication on admission, during hospitalization, and at discharge

Variable	Control Group (n = 97)	I/H Group (n = 142)	p Value
On admission			
Aspirin/clopidogrel	43%	46%	0.6
Coumadin	50%	44%	0.2
ACE inhibitor/ARB	81%	87%	0.2
Digoxin	60%	64%	0.5
β blockers	67%	69%	0.7
Spironolactone	47%	34%	0.03
Loop diuretic	92%	94%	0.4
Hydralazine	4%	20%	<0.001
Isosorbide	8%	34%	<0.001
Statin	44%	45%	0.7
Amiodarone	22%	22%	0.9
During hospitalization			
Lasix	73%	79%	0.2
Nitroprusside	34%	54%	0.002
Dopamine	2%	2%	0.9
Dobutamine or milrinone	41%	42%	0.3
Intra-aortic balloon pump	3%	2%	0.2
On discharge			
Aspirin/clopidogrel	54%	52%	0.8
Warfarin	43%	43%	0.9
ACE inhibitor/ARB	100%	100%	1
Digoxin	58%	62%	0.06
β blockers	66%	65%	0.7
Spironolactone	57%	52%	0.3
Loop diuretic	92%	92%	0.8
Hydralazine	0%	79%	<0.001
Isosorbide	0%	94%	<0.001
Statin	41%	43%	0.8
Amiodarone	27%	30%	0.7
Dobutamine or milrinone	10%	6%	0.5

Table 4

Primary outcomes

Primary Outcome	Control Group (n = 97)	I/H Group (n = 142)	p Value
All-cause mortality	41%	34%	0.04
Cardiac transplant	19%	22%	0.5
HF rehospitalization	64%	59%	0.4
All-cause mortality + HF rehospitalization	85%	70%	0.03