Effectiveness of Isosorbide Dinitrate and Hydralazine in Racial/Ethnic Subgroups With Heart Failure

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Abstract

**Background:** The addition of hydralazine-isosorbide dinitrate (H-ISDN) to standard heart failure therapy in The African-American Heart Failure Trial demonstrated a 43% reduction in mortality. However, the effectiveness of H-ISDN in a community sample of African-Americans and other racial/ethnic groups is unknown.

**Methods:** The objectives of this retrospective cohort study were to assess the associations between treatment with H-ISDN and mortality or heart failure hospitalization in veterans with heart failure. Electronic data on outpatient prescriptions, comorbidity, and other risk factors on 76,828 veterans with heart failure were analyzed using propensity-adjusted Cox regression analyses with exposure to H-ISDN modeled as a time-varying covariate.

**Results:** H-ISDN prescription was not associated with risk of death in five of nine subgroups predefined by race/ethnicity (African-American, White, Hispanic) and time of initiation of H-ISDN (1 - 4, 5 - 12, or > 12 months) following heart failure diagnosis), but was associated with an increased risk of death in the four subgroups with longer times to initiation. H-ISDN was associated with a significantly increased risk of heart failure hospitalization in all but one subgroup. H-ISDN was associated with significantly lower risk for both mortality and hospitalization in African-Americans than in Hispanics or Whites.

Other evidence-based heart failure therapies (e.g., angiotensin converting enzyme inhibitors, beta-blockers, and combinations) had a strong association with reduced mortality.

**Conclusions:** H-ISDN was not associated with significant reduction in mortality or hospitalization for heart failure in any subgroups analyzed. African-Americans had lower risks of adverse outcomes with H-ISDN than Hispanics or Whites.
Introduction

In 1986, the Vasodilator in Heart Failure Trial (V-HeFT-I) demonstrated a survival benefit with the combination of hydralazine and isosorbide dinitrate (H-ISDN) compared to placebo.\(^1\) The V-HeFT-II trial soon demonstrated the superiority of an angiotensin converting enzyme inhibitor (ACEI) over H-ISDN,\(^2\) and subsequent randomized trials of ACEIs in patients with heart failure (HF) and left ventricular systolic dysfunction established this drug class as the cornerstone of HF therapy,\(^3\)-\(^5\) relegating H-ISDN to a secondary role.\(^6\)-\(^8\)

The African American Heart Failure Trial (AHeFT)\(^9\) established the efficacy of a fixed-dose combination of H-ISDN (BiDil\(^,\) NitroMed, Lexington, MA) added to standard HF therapy in patients with New York Association Class III or IV heart failure by reducing mortality (43\%) and hospitalization for heart failure (33\%) in a selected population of self-identified African-American patients. However, the effectiveness of H-ISDN in unselected populations with HF led to the following (null) hypotheses that there is no association between exposure to H-ISDN initiated 0 – 4, 5 – 12, or >12 months following diagnosis and either time to death or first HF hospitalization:

- H\(^0\)(1): In a community-based population with HF;
- H\(^0\)(2): Within African-American, Hispanic, or White racial/ethnic groups; and
- H\(^0\)(3): Within subgroups defined by race/ethnicity and the prescription of the other life-prolonging HF therapies.

We used our clinical judgment and the distribution of the intervals between heart failure diagnosis and the initiation of H-ISDN shown in Figure 1 to define the intervals of 0 – 4, 5 – 12, and >12 months following diagnosis.

Patients and Methods

This retrospective cohort (historical prospective) study was approved by the Colorado Multiple Institutional Review Board.

Patient Population

We used the set of ICD-9 codes proposed for use in performance measures for HF\(^10\) to identify 589,404 veterans receiving VHA inpatient or outpatient care for HF between 10/1/1998 and 9/30/2005. We excluded 366,249 patients (62\% of the total) and took a random sample of 20\% of Whites (excluding 25\% of the total) as described in Figure 1, leaving 32,551 African Americans, 7,729 Hispanics, and 36,548 Whites.

Data Sources/Collection

We obtained ambulatory care prescription data from the VHA’s Pharmacy Benefits Management Strategic Health Group (PBM/SHG).\(^11\) Data on HF diagnosis, comorbidities, demographics, other risk variables, hospitalizations, and clinic visits were obtained from the VHA a hospital discharge abstract and ambulatory care files. Deaths were ascertained from a VHA dataset that has a sensitivity of 98.3\% and a specificity of 99.8\% compared to the National Death Index.\(^12\)
The dependent variables for our analyses were time to death from any cause and time to the first VHA HF hospitalization following diagnosis. Both outcomes were censored on September 30, 2005, and time to first hospitalization was censored at the time of death.

We calculated the span of days for which the patient had prescriptions for both hydralazine and isosorbide dinitrate. Patients prescribed hydralazine, but not ISDN, and vice versa were included in the control group. The fixed-dose combination of hydralazine/isosorbide dinitrate (BiDil®) was not used in the VHA during the period of this study.

Comorbidities were identified in the year prior to HF diagnosis according to groups of ICD-9 codes described by Quan and colleagues13 plus coronary artery disease, tobacco use disorder, history of tobacco use, and 12 social and demographic characteristics (see Table 1). Finally, we included as covariates any use of digoxin, thiazide or thiazide-like diuretic, loop diuretic, ACEI or angiotensin receptor blocker (ARB), beta-blocker, and spironolactone during the period of observation.

Beginning with FY-2003, the VHA changed its method of determining race/ethnicity to include the source of the information (e.g., self-identified), but retained the previous variable. We combined information from the two race variables to identify patients as Black or African-American, White Hispanic or Latino, White non-Hispanic, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, and Unknown. For patients with inconsistent values of racial/ethnic status, we selected self-identified first and then the most recent value.

**Statistical Analysis**

We compared baseline characteristics across subgroups defined by H-ISDN exposure and racial/ethnic status using the chi-square test for categorical variables and the two-sample t-test or one-way ANOVA for continuous variables. Our primary statistical method for testing our hypotheses was the multivariable Cox regression model14 with adjustment for the propensity to receive H-ISDN and with the exposure variable treated as a time-dependent covariate.15-17 Comorbidities and other risk variables described above were included as covariates in the Cox model.

Because of concern that some patients might receive H-ISDN late in their illness as a salvage treatment, we added indicators of the time of initiation of H-ISDN following HF diagnosis. This model assumes that the hazard ratio associated with the H-ISDN combination is constant for a particular individual over time, but may vary depending on when treatment was initiated. The hazard ratio is a function of the time, s, from diagnosis of HF that an individual started H-ISDN:

$$HR(s) = \exp(\hat{\beta}_0 + \hat{\beta}_1 I(s > 0) + \hat{\beta}_2 I(s > 4) + \hat{\beta}_3 I(s > 12))$$

where $$(s > #)$$ is 1 if the start of the H-ISDN combination is greater than # and 0 otherwise. We chose to use three time intervals: 1-4 months, 5-12 months, and >12 months after HF diagnosis.

We created propensity scores for the receipt of H-ISDN using logistic regression with the dependent variable any use of H-ISDN within six months of HF diagnosis and all the independent variables described above. The underlying hazard rate ($$h_0(t)$$) was stratified into quintiles of propensity score.
Results

Baseline Patient Characteristics

Table 1 compares the baseline characteristics of patients receiving the combination of H-ISDN for ≥1 day with those never receiving this combination. Clinically significant comorbidities were more frequent in the group receiving H-ISDN; for example, renal failure was present in 24.8% of the H-ISDN group, but only 8.3% of the no H-ISDN group. Also, the prescription of digoxin, thiazides and related diuretics, and loop diuretics was more frequent in the H-ISDN group.

Exposure to H-ISDN

Overall, 3,829 of 76,828 (5.0%) patients received concurrent prescriptions for hydralazine and isosorbide dinitrate. A greater proportion of African-American HF patients received H-ISDN (6.9%) than Hispanic (5.8%) or White HF patients (3.1%). Among those receiving the combination, the average mean daily dose of hydralazine for African-Americans was 154 mg, Hispanics 137 mg, and Whites 126 mg; similarly, for isosorbide dinitrate: African-Americans 71 mg, Hispanics 66 mg, and Whites 73 mg. Once H-ISDN was initiated, concomitant prescriptions for H-ISDN covered only 41% of the follow-up time to death or censorship.

As shown in Figure 2, it took up to three years after first HF diagnosis before 80% of patients in the H-ISDN group received their first prescription. This contrasts sharply with ACEI/ARB, where about 80% of patients who ever received an ACEI/ARB obtained their initial prescription within 30 days of diagnosis of HF.

Overall, 36% (27,717/76,828) of the patients died during the period of observation. Death occurred more frequently in the H-ISDN group (46.7%) than in the no H-ISDN group (35.5%). However, there was very little difference in unadjusted mortality between African-American (35.3%), Hispanic (37.0%), and White patients (36.6%). One or more VHA hospitalizations for HF occurred in 15,332 patients (20% of the total). Hospitalization(s) for HF occurred much more frequently in the H-ISDN group (48.6%) than in the no H-ISDN group (18.5%). African-American patients were significantly more likely to be hospitalized for HF (25.5%) than White patients (15.1%); Hispanic patients were intermediate (19.9%).

Hypothesis Testing

H0(1): There is no association between exposure to H-ISDN and either time to death or first HF hospitalization in a community-based sample with HF.

There were no significant associations between H-ISDN exposure initiated at 1–4 months and 5–12 months following HF diagnosis and mortality in the sample as a whole. However, when H-ISDN was initiated more than 12 months after diagnosis, the hazard ratio was significantly increased (HR 1.51, 95% C.I. 1.37, 1.67). The hazard ratios for the association between H-ISDN and hospitalization for HF among the population as whole were significantly >1.0 at all three time intervals for the initiation of H-ISDN.
H0(2): There is no association between exposure to H-ISDN and either time to death or first HF hospitalization within the following racial/ethnic subgroups: African-American, Hispanic, and White.

We found no significant association between H-ISDN and mortality within racial/ethnic subgroups with the following exceptions where the hazard ratios were significantly >1.0: African Americans with initiation of H-ISDN >12 months, Hispanics with initiation at 5–12 months and >12 months, and Whites with initiation >12 months (Figure 3). The hazard ratios for the association between H-ISDN and hospitalization for HF within racial/ethnic subgroups were all significantly >1.0, with the exception of Hispanic and African-American patients with initiation of H-ISDN between 1 and 4 months following HF diagnosis where the associations were not significantly different from 1.0.

H0(3): There is no association between exposure to H-ISDN and either risk-adjusted time to death or first HF hospitalization within subgroups based on racial/ethnic status and the prescription of the following other life-prolonging HF therapies: ACEI or ARB only, beta-blocker only, ACEI or ARB plus beta-blocker; and ACEI or ARB plus beta-blocker plus spironolactone.

No mortality hazard ratios were significantly <1.0 in the 15 subgroups defined by racial/ethnic status and concomitant HF therapy. Hazard ratios significantly >1.0 were seen when H-ISDN was initiated >12 months after the diagnosis of HF in all HF therapy subgroups. The findings are similar when these analyses are limited to African-American patients. Ten of 15 hazard ratios for the effect of H-ISDN on hospitalization for HF were significantly >1.0, with the remainder not significantly different from 1.0.

In general, the hazard ratios for the association between H-ISDN and mortality or hospitalization increased with increasing length of time from HF diagnosis to initiation of H-ISDN. Similarly, the time of initiation of H-ISDN was a statistically significant (p = 0.003) predictor of all cause mortality in the propensity score adjusted model.

The tests for interactions between race/ethnicity and H-ISDN effects on both mortality and hospitalization for HF were highly significant (p = 0.001 and <.0001, respectively). Pairwise comparisons of racial/ethnic subgroups showed that the effects of H-ISDN on both mortality and hospitalization for HF were significantly different for African-Americans versus Whites (p = 0.01 for mortality and <.0001 for hospitalization) and African-Americans versus Hispanics (p = 0.0006 for mortality and =0.0002 for hospitalization), but not Whites versus Hispanics (p = 0.12 for mortality and 0.97 for hospitalization). The hazard ratios were lower for African-Americans (mortality 1.11, hospitalization 2.48) than for Hispanics (1.74, 3.83) or Whites (1.42, 3.81).

The Effect of Other HF Therapies

Figure 4 shows the risk-adjusted association between mortality and exposure to other HF therapies previously shown to improve survival; these hazard ratios were derived from the same models used to assess exposure to H-ISDN. In contrast to H-ISDN, ACEI/ARB, beta-blocker, ACEI/ARB plus a beta-blocker, and ACEI/ARB plus a beta-blocker plus spironolactone were all associated with statistically significant and clinically important reductions in mortality in all racial/ethnic groups. The combination of ACEI/ARB and a beta-blocker was associated with the greatest reduction in the hazard ratio – below 0.4 in all racial/ethnic groups, which was lower
than that of either drug alone. Comparable analyses with HF hospitalization as the dependent variable consistently showed hazard ratios significantly >1.0.

**Discussion**

This observational study showed no absolute reduction in mortality or HF hospitalization associated with the prescription of H-ISDN in the population as a whole or any subgroup. Exposure to H-ISDN was associated with a greater risk of mortality and hospitalization if initiated later in the course of HF. These conclusions are tempered by concerns that substantial residual “confounding by indication” might explain some or all of these results.

The absence of data on the clinical severity of HF and left ventricular function, potent predictors of adverse outcomes in HF patients, is, perhaps, the greatest limitation of this study. Patients who are prescribed a drug usually have greater disease severity and higher risk of the adverse outcome than those not receiving the drug. The inability to fully adjust for this confounding by indication would result in falsely elevated hazard ratios for the association of H-ISDN with both mortality and HF hospitalization. Also, this greatly limited our ability to detect and exclude patients with diastolic HF, shown to be present in 31% and 47% of HF admissions. However, we identified and excluded only 0.2% of the original population as having isolated diastolic HF on the basis of ICD-9 codes. No therapy, except hypertension control, has been shown to reduce mortality from diastolic HF.

The significant interactions between race/ethnicity and H-ISDN effects on both mortality and hospitalization for HF suggest that African-Americans respond differently to H-ISDN than Whites or Hispanics.

The equivocal findings for the association between H-ISDN and mortality were overshadowed by the dramatic reduction in risk of death associated with the prescription of ACEI/ARB, beta-blockers, and particularly, the combination of ACEI/ARB and beta-blockers. However, less than 40% of patients had been started on this combination within six months of their HF diagnosis.

**Limitations**

Although ascertainment of death was virtually complete, we were able to include only data on VHA hospitalizations. Thus, the number of hospitalizations for HF was underestimated by an unknown amount. Patients in the H-ISDN group had significantly lower incomes, and were more likely to be uninsured (Table 1). These findings raise the possibility that the patients receiving H-ISDN might have been more likely to seek free inpatient care at the VHA than patients not receiving H-ISDN. If so, this would have resulted in more complete ascertainment of HF hospitalizations in the H-ISDN group and a falsely elevated hazard ratio.

Modeling drug exposure in observational studies is complex. For example, patients in the exposure group must survive until drug therapy is initiated, while patients in the control group are at risk for an outcome at any interval following initiation of follow-up; this “survival bias,” or “immortal time” bias, favors the exposed group. In accordance with the conclusions of a paper by Zhou and colleagues, we modeled exposure with a time-varying covariate. This use of the time varying covariate also accounted for gaps in H-ISDN therapy or cessation of therapy prior to the occurrence of a primary outcome or censorship.

Of patients who eventually received H-ISDN, this combination was not initiated until a year or more after HF diagnosis in about half (Figure 2), suggesting that some patients may have...
received H-ISDN as “last ditch” treatment for very severe HF that had proven refractory to other treatments. This use of H-ISDN as salvage therapy might result in a spurious association between H-ISDN and increased mortality. The increasing hazard ratios for the association of H-ISDN prescription and mortality or hospitalization with increasing time from HF diagnosis support this conclusion. This finding is difficult to fully explain in the absence of information about the severity of HF at the time of H-ISDN initiation.

We stratified the underlying hazard by the propensity score for receipt of H-ISDN to reduce confounding by indication. However, recent reviews\textsuperscript{25} and simulations\textsuperscript{26} have raised questions about the ability of this approach to reduce confounding beyond that provided by traditional regression analyses.\textsuperscript{27,28} We found that the H-ISDN hazard ratios from the models without and with propensity score adjustment were very similar (correlation coefficient for 68 pairs 1.00; mean hazard ratio without propensity analysis 1.88; mean with 1.87; p-value 0.06 with paired t-test), suggesting that the incorporation of the propensity score into our analyses had little or no effect on the confounding by indication.

Another problem in assessing HF severity and other important covariates is that these variables change over time, and inform the decision to initiate or stop medications. We used information in the year prior to the diagnosis of HF to define comorbidities, and thus did not assess the severity of HF or the occurrence of new comorbidities over time that might have influenced the initiation of H-ISDN. As in all observational studies, we were unable to adjust for non-equivalent distribution of unmeasured covariates between individuals unexposed to H-ISDN and those exposed.

Our sample was >98% male, limiting the generalizability of our findings to women. We also excluded approximately 20% of our sample who lacked racial or ethnic identifiers, as well as individuals from other racial/ethnic groups for whom the numbers were too small to allow statistically meaningful analyses. Thus, our findings cannot be applied to any of these subsets of VHA patients.

Tam and colleagues have shown differences in the bioavailability of hydralazine among the three specially-manufactured preparations of H-ISDN used in VHeFT I, VHeFT II, and AHeFT.\textsuperscript{29} We do not know how these findings would influence our results, as we are unaware of any bioavailability studies comparing these preparations with the widely available generic preparations of hydralazine used by the VA.

**Strengths**

Despite these limitations, this study has important strengths. From prescription and outcome data on more than half a million patients with a diagnosis of HF, we selected 76,828 patients with the highest likelihood of definite HF of new onset and with known racial/ethnic status. This large sample allowed us to evaluate outcomes in multiple subgroups.

In contrast to many pharmaco-epidemiologic studies that have relied on inpatient prescription databases, we utilized data on every outpatient prescription dispensed to these patients through the VHA over a seven year period. Without these data, we would not have been able to identify the consistent rise in hazard ratios with increasing time between diagnosis of HF and initiation of H-ISDN.

The VHA system provides a substantial financial incentive for veterans to obtain their medications within the system. During the period of this study, many veterans had no co-pays for their drugs, and the remainder paid $5 to $7 per prescription, which was generally less than
private insurance co-payments. Thus VHA pharmacy data likely provide relatively complete information about prescription drug exposures.

**Conclusions and Implications For Care**

In conclusion, we found no apparent benefit from H-ISDN in the sample as a whole, or within any racial/ethnic subgroup. However, African-Americans had relatively lower hazards for death or hospitalization for HF in association with H-ISDN than Hispanics or Whites. There was some evidence of increased risk for mortality or HF hospitalization among patients receiving the H-ISDN combination, particularly for those receiving these medications for the first time more than 12 months after their diagnosis of HF. However, we suspect that the limitations noted above, most of which bias our results against the exposure group, explain many of these findings.

Perhaps the most important observations for improving the outcomes of care for HF patients are the dramatic reduction in the hazard of death associated with the combination of an ACEI or ARB plus beta-blocker, and the fact that <40% of patients were on this combination at six months after diagnosis.

**References**


Table and Figures
Table 1. Comparison of patient characteristics between individuals not exposed vs. exposed to hydralazine/isosorbide dinitrate (H-ISDN) combination*

<table>
<thead>
<tr>
<th>VARIABLE GROUP</th>
<th>No H-ISDN (72,999 Patients)</th>
<th>H-ISDN &gt;1 Day (3,829 Patients)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% or Mean</td>
<td>% or Mean</td>
<td></td>
</tr>
<tr>
<td><strong>SOCIO-DEMOGRAPHIC DATA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.8%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98%</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Age at first diagnosis of heart failure</td>
<td>69 years</td>
<td>67 years</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Income (less medical care)</td>
<td>$19,477</td>
<td>$15,869</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Insurance coverage</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Major medical, HMO, etc.</td>
<td>12%</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>CHAMPUS, Medicare, etc.</td>
<td>39%</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>0.3%</td>
<td>0.3</td>
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<tr>
<td>No insurance</td>
<td>48%</td>
<td>54</td>
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</tr>
<tr>
<td>Unknown</td>
<td>0.4%</td>
<td>0.4</td>
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</tr>
<tr>
<td>Marital status</td>
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<td>&lt;.0001</td>
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<tr>
<td>Unknown</td>
<td>0.9%</td>
<td>1.1</td>
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</tr>
<tr>
<td>Married</td>
<td>55%</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Never married, divorced</td>
<td>32%</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>12%</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>COMORBIDITY (Quan 13 modification of Elixhauser 30)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>28.1%</td>
<td>24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peripheral vascular disorder</td>
<td>13.6%</td>
<td>20</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension (uncomplicated)</td>
<td>73.7%</td>
<td>84</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension (complicated)</td>
<td>8.5%</td>
<td>18</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes (uncomplicated)</td>
<td>39.7%</td>
<td>54</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes (complicated)</td>
<td>15.3%</td>
<td>27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5.1%</td>
<td>4.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8.3%</td>
<td>25</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peptic ulcer disease excluding bleeding</td>
<td>2.9%</td>
<td>3.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>0.9%</td>
<td>0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.1%</td>
<td>3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Fluid and electrolyte disorder</td>
<td>8.5%</td>
<td>14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Deficiency anemia</td>
<td>5.5%</td>
<td>8.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>6.9%</td>
<td>7.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>4.8%</td>
<td>6.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>15%</td>
<td>14</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>OTHER COMORBIDITY</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>48%</td>
<td>55</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>OTHER HEART FAILURE THERAPY</strong></td>
<td></td>
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</tr>
<tr>
<td>Digoxin</td>
<td>40%</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Thiazides/Related Diuretic</td>
<td>28%</td>
<td>42</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>83%</td>
<td>95</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Life-Prolonging Heart Failure Therapies</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ACEI/ARB only</td>
<td>25%</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Beta-Blocker (B-B) only</td>
<td>8.5</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB + B-B</td>
<td>40%</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB + B-B + spironolactone</td>
<td>8.8%</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>4.6%</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*There was no significant difference (p > 0.05) in the distribution of the following variables by H-ISDN exposure: COMORBIDITY (Quan 13 modification of Elixhauser 30): Valvular heart disease, Pulmonary circulation disorders, Paralysis, Other neurologic disorders, Chronic pulmonary disease, Liver disease, AIDS/HIV, Lymphoma, Solid tumor without metastases, Rheumatoid arthritis/collagen vascular diseases, Coagulopathy, Obesity, Blood loss anemia, Psychoses; Tobacco use disorder, History of tobacco use.

**Abbreviations:** N – number of patients; S.D. – 1 standard deviation; HMO – health maintenance organization; CHAMPUS - Civilian Health and Medical Program Uniformed Services, AIDS/HIV – acquired immune deficiency disorder/ human immunodeficiency virus; ACEI – angiotensin converting enzyme inhibitor, ARB –angiotensin receptor blocker; B-B – beta-blocker
Figure 1. Selection of patient population

PATIENT POPULATION

- ANY IN-OR OUTPATIENT VISIT BETWEEN 10/1/1998 AND 9/30/2005 WITH A HEART FAILURE CODE (N = 569,404)
- EXCLUDE PATIENTS WITH ISOLATED DIASTOLIC HEART FAILURE (N = 588,280)
- SYSTOLIC OR UNSPECIFIED HEART FAILURE (N = 569,404)
- EXCLUDE PATIENTS WITH LIMITED EVIDENCE OF HEART FAILURE (N = 369,859)
- STRONGER EVIDENCE OF HEART FAILURE (N = 298,401)
- EXCLUDE PATIENTS WITH INVALID DEATH DATE OR NO COMORBIDITY DATA (N = 101)
- AFRICAN-AMERICAN, HISPANIC, OR WHITE (N = 223,253)
- TAKE RANDOM 20% SAMPLE
- WHITE (N = 182,911)
  - EXCLUDE 60 PATIENTS WITH INVALID DEATH DATE PRIOR TO SECOND INDEX HEART FAILURE DIAGNOSIS DATE
  - AFRICAN-AMERICAN (N = 32,551)
  - NO H-ID (N = 30,318)
  - H-ID (N = 2,233)
  - HISPANIC (N = 7,729)
  - NO H-ID (N = 7,281)
  - H-ID (N = 448)
  - WHITE (N = 36,548)
  - NO H-ID (N = 35,400)
  - H-ID (N = 1,148)
- LIMITED EVIDENCE OF HEART FAILURE (N = 218,421)
- EXCLUDE PATIENTS WITH ISOLATED DIASTOLIC HEART FAILURE (N = 218,421)
- DIASTOLIC HEART FAILURE ONLY (N = 1,124)
- EXCLUDE PATIENTS WITH ISOLATED DIASTOLIC HEART FAILURE (N = 1,124)
- SYSTOLIC OR UNSPECIFIED HEART FAILURE (N = 218,421)
- EXCLUDE PATIENTS WITH LIMITED EVIDENCE OF HEART FAILURE (N = 1,124)
- STRONGER EVIDENCE OF HEART FAILURE (N = 218,421)
- INCIDENT HEART FAILURE (N = 218,421)
- EXCLUDE PATIENTS WITHUNKNOWN RACIAL/ETHNIC STATUS OR INADEQUATE SAMPLE SIZE (N = 75,047)
- RACIAL/ETHNIC STATUS UNKNOWN OR INADEQUATE SAMPLE SIZE (N = 75,047)
- KNOWN RACIAL/ETHNIC STATUS WITH ADEQUATE SAMPLE SIZE (N = 223,354)
- INVALID DEATH DATE (99) OR NO COMORBIDITY DATA (2) (N = 7,281)
- EXCLUDE PATIENTS WITH INVALID DEATH DATE OR NO COMORBIDITY DATA (N = 7,281)
- AFRICAN-AMERICAN, HISPANIC, OR WHITE (N = 223,253)
- TAKE RANDOM 20% SAMPLE
- WHITE (N = 182,911)
  - EXCLUDE 60 PATIENTS WITH INVALID DEATH DATE PRIOR TO SECOND INDEX HEART FAILURE DIAGNOSIS DATE
  - AFRICAN-AMERICAN (N = 32,551)
  - NO H-ID (N = 30,318)
  - H-ID (N = 2,233)
  - HISPANIC (N = 7,729)
  - NO H-ID (N = 7,281)
  - H-ID (N = 448)
  - WHITE (N = 36,548)
  - NO H-ID (N = 35,400)
  - H-ID (N = 1,148)
Figure 2. Time from heart failure diagnosis to initial hydralazine-isosorbide dinitrate exposure among those ever receiving H-ISDN
Figure 3. Mortality hazard ratios for H-ISDN vs. no H-ISDN by times of initiation following heart failure diagnosis and by race/ethnicity
Figure 4. Mortality hazard ratios for receipt of selected heart failure therapies or combinations versus no therapy by racial/ethnic status.

Mortality Hazard Ratios for "Intermittent" Receipt of Selected Heart Failure Therapies or Combinations Versus No Therapy by Racial/Ethnic Status

- **ALL PATIENTS**
- **AFRICAN-AMERICAN**
- **WHITE - HISPANIC**
- **WHITE - NON-HISPANIC**

Hazard Ratio (95% C.I.)

Heart Failure Therapy:
- ACEI/ARB
- Beta-Blocker
- ACEI/ARB + B-B
- ACEI/ARB + B-B + Spironolactone