Hydralazine–Isosorbide Dinitrate Use in Patients With End-Stage Kidney Disease on Dialysis

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Introduction: The combination of hydralazine–isosorbide dinitrate (H-ISDN) has potential as a heart failure (HF) therapy in the setting of maintenance dialysis.

Methods: In this retrospective study, we analyzed the efficacy of H-ISDN using United States Renal Data System (USRDS) data. We identified all adult patients with a history of HF on maintenance dialysis between January 1, 2011, and December 31, 2016, with at least 1 prescription for H-ISDN. Baseline characteristics, prescriptions, and outcomes were retrieved from institutional and physician claims. The primary outcome was death from any cause. Additional outcomes included cardiovascular death, sudden cardiac death, hospitalization for HF, an inpatient diagnosis of myocardial infarction (MI), or new-onset atrial fibrillation. Stabilized inverse probability weights were estimated using relevant baseline characteristics and were used in Cox proportional hazards regression.

Results: We identified 6306 patients who were treated with H-ISDN and 75,509 patients who did not receive H-ISDN. The crude all-cause mortality rate was lower in patients treated with H-ISDN (16.0 events/100 patient years [PYs]) than in nonusers (27.9/100-PY). H-ISDN use was independently associated with lower mortality: hazard ratio (HR) 0.48 (95% CI 0.43–0.54). Cardiovascular death and sudden cardiac death were less common among H-ISDN users than nonusers, Weighted HR was 0.62 (95% CI 0.53–0.71) and 0.62 (95% CI 0.52–0.73), respectively. In contrast, HF admission and MI were more frequent in patients treated with H-ISDN (195.5 and 18.0 events/100-PY) compared with nonusers (73.4 and 10.2 events/100-PY).

Conclusion: H-ISDN therapy may improve cardiovascular outcomes in maintenance dialysis patients with HF.

M ortality and morbidity due to cardiovascular disease (CVD) in the chronic kidney disease (CKD) and end-stage kidney disease (ESKD) population are high.[1] One of the most common manifestations of CVD in this population is HF. Between 2014 and 2018, the percentage of all patients receiving dialysis with HF of any type increased from 39.2% to 43.0%, the overall prevalence of HF with reduced ejection fraction (HFrEF) in dialysis patients was 17.1%, HF with preserved ejection fraction was 13.5%, whereas 12.4% was of unspecified type.[2] This population presents with unique risk factors compared with individuals with preserved kidney function that have led to exploration of novel treatment options to prevent and reduce the burden of CVD. Combination therapy with H-ISDN is a promising option because ESKD is associated with both oxidative stress and a nitric oxide (NO)-deficient state.[3]

Hydralazine has been studied for its antioxidant properties, and it causes vasodilation of arteries and arterioles, while sparing venous smooth muscle.[4] Isosorbide dinitrate is metabolized to NO, which may induce vascular smooth muscle relaxation in arteries and veins, including the coronary arteries. The synergistic effect of combination H-ISDN should therefore lead to reduction in afterload and preload, augmentation of cardiac output, and reduction in myocardial workload while limiting the downstream adverse effects of oxidative stress and reduced NO bioavailability

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on myocardial remodeling and fibrosis.[5,6] Furthermore, hydralazine has been shown to mitigate nitrate tolerance, a principle drawback to long-term use of nitrates.[7,8] For these reasons, combination therapy might be an attractive option in ESKD patients with HF.

Historically, the combination therapy with H-ISDN was first evaluated for HFrEF in the Veterans affairs Vasodilator—Heart Failure Trial I (V-HeFT I) trial where it showed a trend toward improved survival along with a significant improvement in ejection fraction at 8 weeks and 1 year.[9] The African-American Heart Failure Trial (A-HeFT) trial was conducted on the basis of a *post hoc* analysis of the V-HeFT I trial and showed a 43% reduction in mortality among Black patients with HFrEF with the use of fixed-dose H-ISDN combination in comparison to placebo.[10–12] However, combination therapy has not been well studied in the ESKD population, and it is not known whether its use improves cardiovascular outcomes in this population, which in part might result from nitroso-redox balance that H-ISDN could specifically address. In this retrospective study, we analyzed USRDS data to better understand whether H-ISDN combination therapy can be used in ESKD and its relationship with cardiovascular outcomes.

METHODS

Study Population, Follow-up, and Censoring

This was a retrospective cohort study using data from the USRDS.[13] The USRDS is a "national data system that collects, analyzes, and distributes information about CKD and end-stage renal disease in the United States. The USRDS is funded directly by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)."[2] The USRDS includes information on Medicare part A, B, and D coverage. Medicare part A provides inpatient/hospital coverage. Medicare part B provides outpatient/medical coverage. Medicare part D provides prescription drug coverage.

We identified all adult patients on maintenance dialysis (including both peritoneal dialysis and hemodialysis patients) between January 1, 2011, and December 31, 2016 ($N = 1,096,967$). We next identified all patients with at least one prescription for H-ISDN therapy during this time frame (users $n = 18,817$).

We excluded nonusers who were assigned a starting date (described subsequently) after December 31, 2016 ($n = 214,059$), or who had died before the assigned starting date ($n = 91,802$). We also excluded patients with <6 months of Medicare A and B coverage during the year before starting date ($n = 470,651$), who did not have continuous part D enrolment for at least 6 months before the starting date ($n = 198,682$), or who were

censored (because of kidney transplantation or loss of part D coverage) before the assigned starting date ($n = 91$). We further excluded 39,867 patients without history of HF and restricted our analysis to patients with history of HF at baseline because H-ISDN is primarily prescribed in this population ($n = 81,815$).

All patients were followed until death, kidney transplantation, loss of part D coverage, or December 31, 2016. The final cohort included 75,509 patients with HF who were not treated with H-ISDN and 6306 patients treated with H-ISDN (Figure 1).

The starting date for H-ISDN users was the date of initial H-ISDN prescription. We censored users who had treatment interruption of >90 days on the interruption. Users without treatment interruption were censored at the last available prescription date (including supply days) or on December 31, 2016 (whichever came first). To account for immortal time bias, we used the following method[14]:

We calculated time to prescription from dialysis initiation for each user. For patients who never had a H-ISDN prescription (nonusers), we randomly assigned a time to prescription value from the data set of all users' time to prescription values. The starting date for nonusers was the date of dialysis initiation plus the assigned "time to prescription." Therefore, the time interval between dialysis initiation and starting date was the same in users and nonusers.

Comorbidities

Relevant baseline characteristics and prescriptions were retrieved from each patient from institutional and physician claims (Table 1). For a comorbidity or medication to be considered as present at baseline, the respective claim or prescription had to occur before the starting date. Comorbidities of interest included hypertension, diabetes, coronary artery disease, stroke, peripheral vascular disease, dyslipidemia, and atrial fibrillation (Supplementary Table S1). Medications were obtained by evaluating part D data for filled prescriptions and included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, β-blockers, and statins in addition to H-ISDN.

Outcomes

Outcomes data were extracted on the basis of dates of death or hospitalization and administrative codes. The primary outcome was death from any cause. The key secondary outcome was cardiovascular death. Additional outcomes included sudden cardiac death, an inpatient diagnosis of HF, an inpatient diagnosis of MI, or new-onset atrial fibrillation (for codes, see Supplementary Table S2). Only the primary cause of
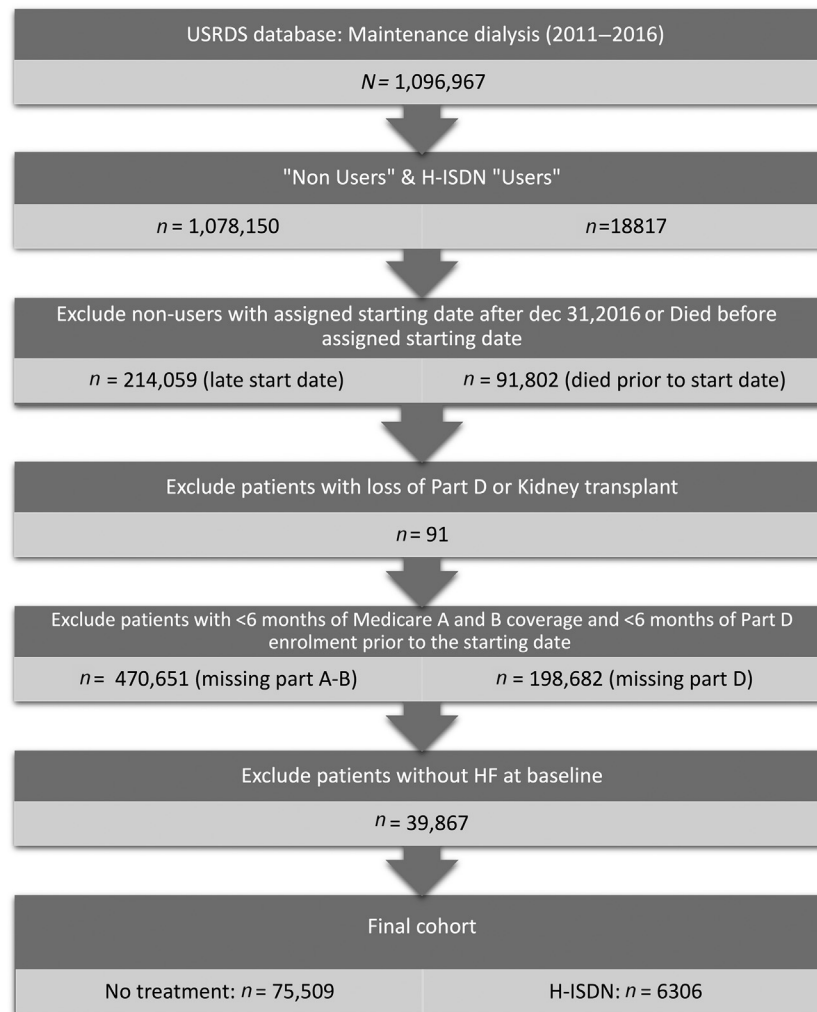
Figure 1. Study flow. H-ISDN, hydralazine–isosorbide dinitrate; HF, heart failure; USRDS, United States Renal Data System.

death was considered for the adjudication of the cause of death. For the outcomes of HF, MI, and new-onset atrial fibrillation, institutional inpatient claims were required and were based on International Classification of Diseases codes 9 and 10. To assess the specificity of our findings and the probability of residual confounding, we in addition evaluated an outcome not expected to be related to H-ISDN use: hip fracture. For this outcome, 1 inpatient claim was required (Supplementary Table S2).

Statistical Analysis

Baseline data are presented as n (%), mean ± SD, or median (25th–75th percentile) according to their distribution. Standardized differences were calculated to assess balance of the treated and nontreated cohorts, with a cutoff of <0.1 considered a negligible difference.[15]

Stabilized inverse probability weights for H-ISDN treatment or for not being censored were estimated using relevant baseline characteristics (Table 1).

Weights were then used in Cox proportional hazards regression. The teffects/tebalance commands in Stata were used to estimate covariate balance over treatment groups. Given that clinical trials have previously demonstrated that combination H-ISDN improves mortality compared with placebo therapy in Black patients with HF,[10–12] we performed subgroup analyses in patients of Black race ($N = 23,696$).

Sensitivity Analyses

In a sensitivity analysis, multivariable logistic regression was used to calculate a propensity score for H-ISDN prescription.[16] The score included 18 baseline parameters (Table 1). H-ISDN users were matched 1:1 without replacement to nonusers using a caliper width of 0.3%. Cox proportional hazard regression models were then used to evaluate association of H-ISDN with clinical outcomes. We also performed the following sensitivity analyses: (i) incident users: we restricted our sample to patients who had not been treated with H-ISDN in the 6 months before treatment initiation; (ii)

Table 1. Baseline characteristics in the final cohort

	H-ISDN	Nonusers	Standardized difference (raw)	Standardized difference (weighted cohort)
Number	6306	75,509		
Demographics				
Age	66 ± 13	69 ± 13	−0.24	0.00
Male sex	3180 (50%)	38,886 (51%)	0.01	0.02
Black race	3244 (51%)	20,452 (27%)	0.51	0.00
Peritoneal dialysis	299 (5%)	3940 (5%)	−0.02	0.02
Dialysis vintage (mo)	25 ± 31	15 ± 19	0.38	−0.07
Comorbidities				
Hypertension	6297 (100%)	75,472 (100%)	0.21	-0.00
Diabetes	5411 (86%)	63,605 (84%)	0.05	0.03
Coronary disease	5499 (87%)	60,263 (80%)	0.20	0.01
Stroke history	2961 (47%)	31,182 (41%)	0.11	0.10
PVD	4063 (64%)	47,982 (63%)	0.02	0.01
Dyslipidemia	5726 (91%)	67,880 (89%)	0.04	0.03
Atrial fibrillation	2173 (34%)	28,909 (38%)	−0.07	−0.02
Medication				
ACEI	686 (11%)	3935 (5%)	0.21	−0.02
ARB	357 (5%)	2424 (3%)	0.12	0.02
MRA	57 (1%)	326 (0.4%)	0.05	−0.00
β-blocker	1466 (23%)	10,595 (14%)	0.24	−0.03
Statin	1008 (16%)	8412 (11%)	0.14	−0.02

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; H-ISDN, hydralazine–isosorbide dinitrate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease.
Standardized differences are shown at baseline (raw data) and for the weighted cohort. The weighted cohort was well-balanced for all baseline characteristics. The teffects/tebalance commands in Stata were used to estimate covariate balance over treatment groups.

incident dialysis: we restricted our analysis to incident dialysis patients; and (iii) subgroups according to dialysis modality (hemodialysis and peritoneal dialysis).

Analyses were performed in SPSS Statistics (version 24.0, IBM Corp., Armonk, NY) or in Stata (version 14 IC, College Station, TX). SPSS was used to set up the data set from individual claims, whereas Stata was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Study Population
Population selection is presented in Figure 1. The final cohort included 6306 patients with HF who were treated with H-ISDN and 75,509 nonusers who did not receive H-ISDN. Baseline characteristics of the final cohort are shown in Table 1. Mean age was similar among H-ISDN users (66 ± 13 years) and nonusers (69 ± 13 years) with 50% and 51% male patients in each group, respectively. A total of 29% of patients were Black. Treatment initiation was on average at 440 days from dialysis initiation (median of 158 days, interquartile range of 31–679 days). Dialysis vintage was longer in H-ISDN users compared with nonusers at 25 versus 15 months, respectively. Although the 2 groups were different at baseline, the weighted cohort was well-balanced for all characteristics (Table 1).

Primary Outcome
The crude all-cause mortality rate was lower in patients treated with H-ISDN (16.0 events/100-PY) than in nonusers (27.9/100-PY). In inverse probability weighted models, H-ISDN use was independently associated with a marked reduction in all-cause mortality: HR 0.48 (95% CI 0.43–0.54) (Table 2 and Figure 2a).

Secondary Outcomes
Cardiovascular death and sudden cardiac death were less common among H-ISDN users than nonusers (Table 2 and Figure 2b and c). In contrast, admission with HF was more frequent in patients treated with H-

Table 2. Clinical outcomes in H-ISDN users and nonusers using an inverse probability weighted model

	Incidence rate (events)		Weighted HR (95% CI)	P value
Outcomes	H-ISDN (n = 6306)	Nonusers (n = 75,509)		
All-cause mortality	16.0 (497)	27.9 (34,371)	0.48 (0.43–0.54)	<0.001
CV death	8.9 (275)	12.4 (15,214)	0.62 (0.53–0.71)	<0.001
SCD	6.7 (207)	9.2 (11,292)	0.62 (0.52–0.73)	<0.001
CHF	195.5 (3352)	73.4 (48,324)	1.51 (1.44–1.57)	<0.001
MI	18.0 (532)	10.2 (11,602)	1.33 (1.20–1.48)	<0.001
New-onset AF	12.5 (257)	13.0 (9789)	0.92 (0.79–1.06)	0.25

AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; H-ISDN, hydralazine–isosorbide dinitrate; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death.
Incidence rates are before inverse probability weighting (crude) and are reported per 100-patient years. Number of events are reported in parenthesis.
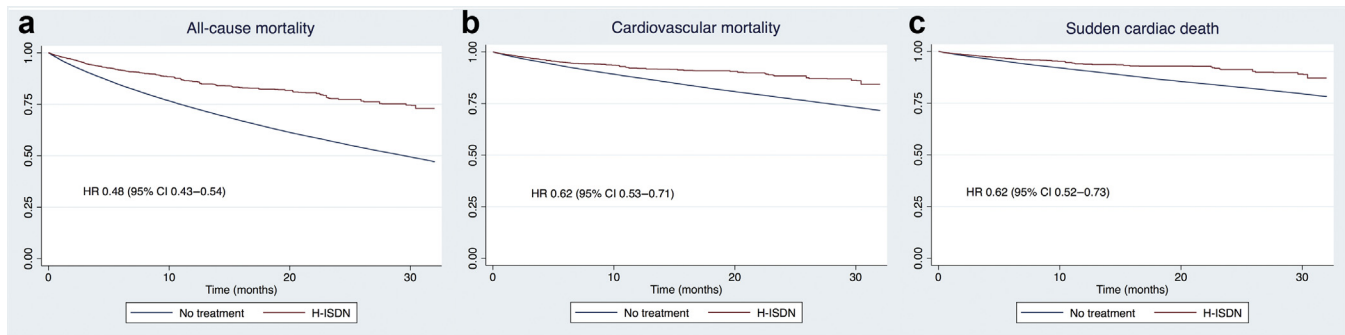
Figure 2. Inverse probability weighting adjusted survival curves for all-cause and cardiovascular mortality, sudden cardiac death H-ISDN users versus nonusers. Adjusted survival estimates for users versus nonusers are shown for (a) all-cause mortality, (b) cardiovascular mortality, and (c) sudden cardiac death. In inverse probability weighted models, H-ISDN use was independently associated with a marked reduction in all-cause mortality, cardiovascular mortality, and sudden cardiac death. H-ISDN, hydralazine–isosorbide dinitrate; HR, hazard ratio.

ISDN (195.5 events/100-PY) compared with nonusers (73.4 events/100-PY). The association with increased risk of HF hospitalization persisted after inverse probability weighting (HR 1.51, 95% CI 1.44–1.57, $P < 0.001$) (Table 2). In addition, H-ISDN use was associated with a higher incidence of MI (18.0 vs. 10.2 events/100-PY) that persisted after inverse probability weighting (HR 1.33, 95% CI 1.20–1.48, $P < 0.001$) (Table 2).

We evaluated an additional outcome, hip fracture, that was not expected to be affected by use of H-ISDN, to evaluate the hypothesis of healthy user bias. The incidence of hip fracture was similar in both groups: 2.1 versus 2.7 events per 100-PY, HR 0.80 (95% CI 0.60–1.06).

Subgroup Analyses

Associations of H-ISDN with outcomes were quantitatively and qualitatively similar for all outcomes in patients of Black race and those of other races (Figure 3). Tests for interaction with race were nonsignificant ($P > 0.05$) for all outcomes. In addition, results were qualitatively and quantitatively similar in patients with HFrEF ($n = 3289$), HF with preserved ejection fraction ($n = 4990$), or unidentified HF ($n = 73,878$) (Figure 4).

Propensity Score-Matched Analysis

In a sensitivity analysis, we matched (1:1) H-ISDN users and nonusers using a propensity score for H-ISDN prescription. This cohort included 6204 patients on H-ISDN and 6204 patients who did not receive H-ISDN. The 2 cohorts were well-matched (standardized difference < 0.1) for all baseline characteristics (Table 3). Overall, the results were qualitatively similar to the primary analysis (Table 4).

Sensitivity Analyses

A total of 17,875 patients had been treated with H-ISDN in the 6 months before current prescription (prior to dialysis initiation). In a sensitivity analysis,

these patients were excluded to include only potentially new users. The results of this analysis were comparable to the main analysis (Table 5).

In our cohort, there were 65,550 incident dialysis patients. Results in this subgroup of patients were comparable with the main analysis (Table 6).

There were 77,587 patients on hemodialysis ($n = 6007$ on H-ISDN) and 4228 patients on peritoneal dialysis (299 on H-ISDN). Results in patients on hemodialysis and on peritoneal dialysis are shown in Supplementary Table S3.

DISCUSSION

Although the combination of H-ISDN has been shown to reduce mortality among patients with HFrEF, particularly those of Black race, to our knowledge, data on the use of this combination in the setting of dialysis-dependent ESKD are limited despite its being routinely prescribed in this population. We analyzed utilization of H-ISDN in patients with ESKD with HF and its relationship with all-cause mortality and cardiovascular outcomes using 2011 to 2016 data from the USRDS. We identified significantly reduced risks of all-cause mortality, cardiovascular death, and sudden cardiac death in H-ISDN users compared with nonusers.

To our knowledge, there are minimal data on the use of nitrates, particularly the combination of isosorbide and hydralazine, in the setting of maintenance dialysis. Two small studies have analyzed the use of nitrates without hydralazine in maintenance dialysis patients. They demonstrated a favorable response for blood pressure reduction in hypertensive patients and significantly reduced left ventricular hypertrophy.[15,17] The first, a prospective trial of 144 patients on hemodialysis in China, demonstrated a reduction in left ventricular hypertrophy and the incidence of acute HF with 24 weeks of isosorbide mononitrate compared with placebo.[15] A subsequent nonblinded study by
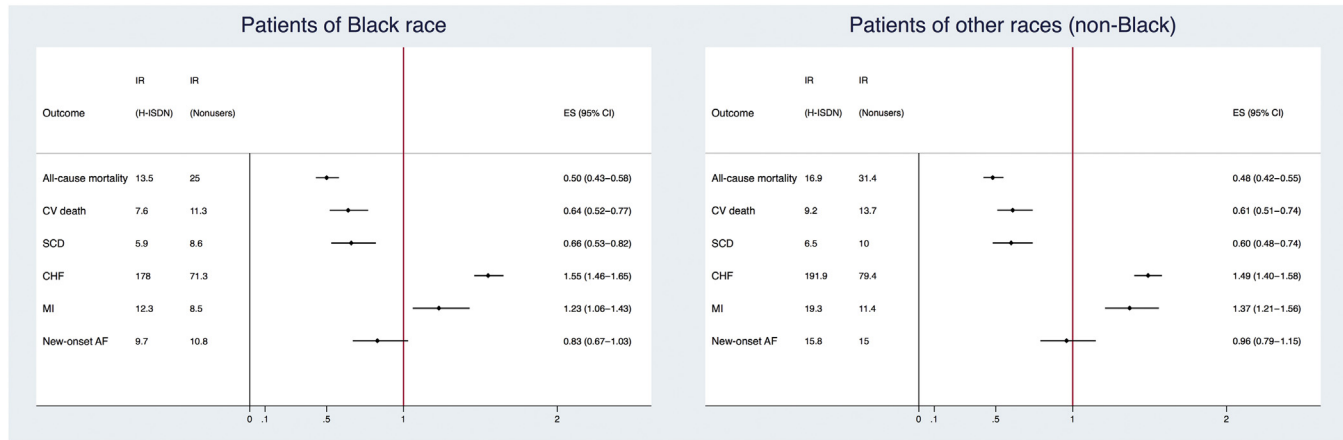
Figure 3. Clinical outcomes in H-ISDN users and nonusers in Black patients and in patients not of Black race, using inverse probability weighted Cox models. The ES is the hazard ratio. *P* values for interaction were >0.05 for all outcomes. AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; ES, effect size; H-ISDN, hydralazine–isosorbide dinitrate; IR, incidence rate (crude incidence rates before inverse probability weighting); MI, myocardial infarction; SCD, sudden cardiac death.

this group demonstrated similar effects on ventricular morphology in 64 peritoneal dialysis patients.[17] Although results of these trials were promising, neither included hydralazine in the tested regimen. Furthermore, there were few fatalities and no significant effect on mortality was reported. To our knowledge, the only prior report on the use of combination H-ISDN in the dialysis population is the Hydralazine and Isosorbide dinitrate in dialysis-dependent end-stage renal disease (HIDE) trial—a pilot randomized placebo-controlled trial that assessed safety and tolerability of combination H-ISDN in patients on maintenance dialysis.[18] This study compared 24 weeks of H-ISDN or placebo therapy in 17 maintenance hemodialysis patients. Although the combination was well tolerated, adverse events were more frequent among H-ISDN patients than placebo-treated patients. Furthermore, although power to detect changes in cardiovascular parameters was limited, no significant effects were observed on myocardial perfusion or diastolic function, and no deaths occurred in either group.

Our findings extend on these studies by providing initial data regarding the effects of H-ISDN on hard outcomes in the dialysis population. There was a significantly lower risk of mortality in the H-ISDN users. In addition, the incidence of cardiovascular death and sudden death was significantly lower in the users compared with nonusers. Notably, the rates of HF hospitalizations and MI were much higher in H-ISDN. This suggests that patients with advanced HF or advanced coronary disease were both more likely to be hospitalized and to be prescribed H-ISDN based on guideline-directed medical therapy. Although this raises the possibility of indication bias in the use of H-ISDN, it suggests that sicker patients were more likely to be prescribed H-ISDN and that residual confounding is unlikely to explain our findings. Thus, our analysis is more likely to have underestimated the effect size than to have overestimated it. In addition, the mechanism of action of the combination with H-ISDN would likely not be expected to impact the incidence of MI as these drugs do not prevent plaque formation or rupture
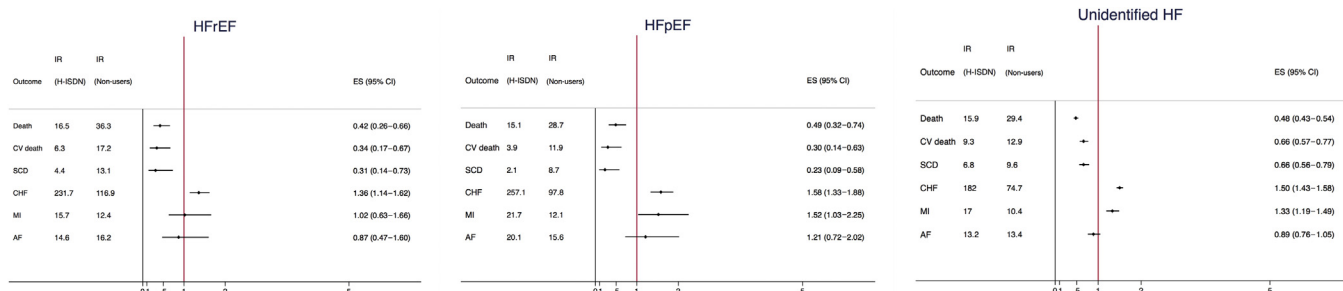
Figure 4. Clinical outcomes in H-ISDN users and nonusers in HFrEF, HFpEF, and unidentified HF, using inverse probability weighted Cox models. The ES is the hazard ratio. *P* values for interaction were >0.05 for all outcomes. AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; ES, effect size; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; H-ISDN, hydralazine–isosorbide dinitrate; IR, incidence rate (crude incidence rates before inverse probability weighting); MI, myocardial infarction; SCD, sudden cardiac death.

Table 3. Baseline characteristics of the cohort after propensity score matching mean $\pm$ SD or n (%)

	H-ISDN	Nonusers	Standardized difference
Number	6204	6204	
Demographics			
Age	66 $\pm$ 13	66 $\pm$ 13	0.01
Male sex	3129 (50%)	3061 (49%)	0.02
Black race	3143 (51%)	3126 (50%)	−0.01
Peritoneal dialysis	296 (5%)	288 (5%)	−0.01
Dialysis vintage (d)	695 $\pm$ 863	702 $\pm$ 786	0.01
Comorbidities			
Hypertension	6195 (99%)	6197 (99%)	0.01
Diabetes	5332 (86%)	5360 (86%)	0.01
Coronary disease	5402 (87%)	5412 (87%)	0.01
Stroke history	2894 (47%)	2815 (45%)	−0.03
PVD	4000 (64%)	3929 (63%)	−0.02
Dyslipidemia	5635 (91%)	5645 (91%)	0.00
Atrial fibrillation	2130 (34%)	2081 (34%)	−0.02
Medication			
ACEI	657 (11%)	640 (10%)	0.01
ARB	340 (5%)	341 (6%)	0.00
MRA	60 (1%)	51 (1%)	0.02
β-blocker	1378 (22%)	1401 (23%)	−0.01
Statin	936 (15%)	978 (16%)	−0.02

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; H-ISDN, hydralazine–isosorbide dinitrate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease.
Standardized differences are shown after matching; the 2 cohorts were well-matched (standardized difference < 0.1) for all baseline characteristics.

but would most likely provide benefit by reducing the left ventricular remodeling and microvascular dysfunction after MI. Notably, despite prior studies suggesting a particular benefit of H-ISDN for Black patients with HF, we did not identify significant effect modification by race.

NO deficiency and the concurrent oxidative stress have been implicated as one of the key pathways involved in evolution of CVD in CKD population.[19,20] NO deficiency has thus been correlated with the vicious cycle of CKD worsening and cardiac remodeling,

Table 4. Clinical outcomes in H-ISDN users and nonusers using a propensity score-matched cohort

	Incidence rate (events)			
Outcomes	H-ISDN (n = 6204)	Nonusers (n = 6204)	HR (95% CI)	P value
All-cause mortality	15.9 (486)	26.7 (2777)	0.56 (0.51–0.62)	<0.001
CV death	8.7 (267)	12.2 (1269)	0.68 (0.59–0.79)	<0.001
SCD	6.5 (199)	9.2 (962)	0.69 (0.59–0.81)	<0.001
CHF	195.5 (3296)	75.9 (4062)	1.59 (1.52–1.67)	<0.001
MI	18.0 (523)	10.3 (986)	1.40 (1.25–1.57)	<0.001
New-onset AF	12.4 (251)	12.5 (826)	0.91 (0.78–1.06)	0.23

AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; H-ISDN, hydralazine–isosorbide dinitrate; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death.
Incidence rates are reported per 100-patient years. Number of events is reported in parenthesis.

Table 5. Clinical outcomes in incident users of H-ISDN and nonusers using an inverse probability weighted model

	Incidence rate (events)			
Outcomes	H-ISDN (N = 3759)	Nonusers (N = 60,181)	Weighted HR (95% CI)	P value
All-cause mortality	16.7 (294)	28.7 (27,323)	0.42 (0.41–0.55)	<0.001
CV death	8.7 (154)	12.6 (11,988)	0.58 (0.48–0.71)	<0.001
SCD	6.5 (115)	9.3 (8842)	0.58 (0.46–0.72)	<0.001
CHF	188.1 (1892)	73.3 (38,069)	1.48 (1.39–1.57)	<0.001
MI	15.4 (261)	10.1 (8918)	1.16 (1.01–1.35)	0.04
New-onset AF	13.1 (150)	13.4 (7605)	0.92 (0.76–1.12)	0.42

AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; H-ISDN, hydralazine–isosorbide dinitrate; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death.
Incidence rates are before inverse probability weighting (crude) and are reported per 100-patient years. Number of events is reported in parenthesis.

fibrosis, hypertension, and atherogenesis.[21,22] Pharmacologic treatments modulating NO production or bioavailability have garnered significant interest over the last few decades. However, there have been numerous challenges in successfully implementing these therapies due to the pleiotropic role of NO.[19,23,24] Nitrate donors might inhibit the cycle of worsening CKD and cardiac remodeling, but tolerance to ISDN, which is attributed to increased production of superoxide anions that react with NO to produce peroxynitrite which causes vasoconstriction, is an impediment to chronic use of nitrate donors. In addition, oxidative stress is implicated as one of the proposed mechanisms of CVD, inflammation, and atherosclerosis.[25] Hydralazine is purported to have antioxidant properties possibly via inhibition of reduced nicotinamide adenine dinucleotide phosphate/superoxide production and by direct free radical scavenging properties. It may thus have a role in mitigating CVD directly and by reducing nitrate tolerance.[19,26]

Hydralazine is not removed during dialysis likely because it undergoes extensive first-pass metabolism,

Table 6. Clinical outcomes in H-ISDN users and nonusers using an inverse probability weighted model in incident dialysis patients

	Incidence rate (events)			
Outcomes	H-ISDN (n = 4351)	Nonusers (n = 61199)	Weighted HR (95% CI)	P value
All-cause mortality	15.1 (330)	27.4 (25,645)	0.46 (0.41–0.52)	<0.001
CV death	8.3 (182)	11.9 (11,182)	0.60 (0.51–0.71)	<0.001
SCD	6.3 (137)	8.8 (8258)	0.60 (0.49–0.72)	<0.001
CHF	194.3 (2339)	75.7 (38,382)	1.44 (1.36–1.51)	<0.001
MI	16.1 (336)	10.2 (8816)	1.22 (1.01–1.38)	0.002
New-onset AF	12.3 (174)	13.0 (7272)	0.92 (0.77–1.09)	0.35

AF, atrial fibrillation; CHF, congestive heart failure; CV, cardiovascular; H-ISDN, hydralazine–isosorbide dinitrate; HR, hazard ratio; MI, myocardial infarction; SCD, sudden cardiac death.
Incidence rates are before inverse probability weighting (crude) and are reported per 100-patient years. Number of events is reported in parenthesis.

especially in fast acetylators, and because it is highly protein bound. ISDN also undergoes hepatic metabolism, but it does not have extensive protein binding and can be removed during dialysis.[27,28] Combination therapy with H-ISDN has been studied at doses up to 40 mg of isosorbide and 75 mg of hydralazine daily and was well tolerated.[18]

The mortality benefits of angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, and mineralocorticoid receptor antagonists in patients with HFrEF are well established.[29] However, these treatments are either underused due to intolerance or hyperkalemia issues in HFrEF patients on dialysis. H-ISDN might be an attractive option in this population, particularly among patients who are intolerant to the other classes of HF medications.

There were several limitations to this study. Data collection using institutional and physician claims may not be perfectly reflective of the clinical diagnosis and could lead to misclassification of baseline characteristics or outcomes. Adjudication of the cause of death is likely best interpreted with caution due to the administrative and observational nature of the data and absence of direct adjudication. Inclusion criteria required prescription of H-ISDN. However, we were unable to gather any information on the actual medication dosage, use, or compliance.

Coronary disease was among the parameters used to calculate the stabilized weights, but it is not possible to discern whether this was a comorbidity versus an indication for H-ISDN treatment. Patients may be continued on H-ISDN until they are too sick, so that the time they accrue on H-ISDN represents times when patients may be healthier. In addition, patients on H-ISDN had longer survival time to accrue other events, such as HF and MI. Moreover, our data were restricted to patients with Medicare eligibility and thus may not be broadly generalizable to young, incident dialysis patients or those outside the United States. Last, we cannot rule out residual confounding, although the increase in HF and MI admission among H-ISDN users and the lack of an impact on hip fracture suggest that this would be unlikely to fully explain the observed effects.

In conclusion, the combination of H-ISDN has not been well studied in the ESKD population, and it is uncertain whether its use improves cardiovascular outcomes in this population, despite being an attractive, targeted therapeutic option. Our retrospective analysis suggests that combination H-ISDN might provide survival benefits to maintenance dialysis patients with HF who suffer from a very high incidence of cardiovascular complications. Our results are only hypothesis generating due to their retrospective nature

and randomized controlled trials testing use of H-ISDN in the ESKD population are needed to assess efficacy, appropriate patient selection, and optimal dosage.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

DMC and TAM designed the study. TAM obtained data and performed the statistical analysis. All authors participated in data interpretation. QHS wrote the first draft, and TAM and DMC critically revised it. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Table S1. Comorbidity diagnostic codes.
Table S2. Outcome diagnostic codes.
Table S3. Outcomes in patients on hemodialysis and on peritoneal dialysis.

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