Combination Hydralazine and Isosorbide Dinitrate in Dialysis-Dependent ESRD (HIDE): A Randomized, Placebo-Controlled, Pilot Trial

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Abstract

Background Combination therapy with isosorbide dinitrate (ISD) and hydralazine (HY) reduces heart failure mortality. The safety and tolerability in individuals requiring maintenance hemodialysis (HD) is unknown.

Methods Single-center, randomized, placebo-controlled, double-blind pilot trial to explore safety and tolerability of ISD/HY in maintenance HD. Participants were randomized to placebo or combination ISD/HY. Dose was escalated over 3 weeks from ISD 10 mg/HY 10 mg to ISD 40 mg/HY 75 mg three times per day with the maximum tolerated dose maintained for the subsequent 21 weeks. Primary endpoints included adverse events, adverse events precluding further treatment with study medication, serious hypotension (i.e., requiring hospitalization or emergency room visit), and recurrent intra-dialytic hypotension. Efficacy signals included change in mitral annular E’ velocity by tissue Doppler echocardiography and change in left ventricular coronary flow reserve on positron emission tomography.

Results A total of 17 individuals were randomized to ISD/HY (N=7) or placebo (N=10). All participants assigned to ISD/HY completed dose escalation to 40/75 mg, but dose reductions were required in two participants. No participants discontinued therapy. There were no serious hypotension events. Recurrent intradialytic hypotension was less frequent with ISD/HY (0.47 events/patient-year) than placebo (1.83 events/patient-year, P=0.04). In contrast, nausea (ISD/HY, 1.90 events/patient-year; placebo, 0.50 events/patient-year, P=0.03) was significantly more frequent, and headache and diarrhea were numerically but not significantly more frequent with ISD/HY. Adverse events were more frequent with ISD/HY (11.4 events/patient-year) than placebo (6.31 events/patient-year). We did not detect between-group differences in the change in E’ (P=0.34); ISD/HY showed a mean increase of 0.6 cm/s (SD 1.1), and placebo showed a mean decrease of 0.04 cm/s (SD 0.9). Changes in coronary flow reserve were minimal, –0.3 (0.2) with ISD/HY and –0.03 (0.5) in the placebo group, P=0.19.

Conclusions ISD/HY appears to be well tolerated in patients being treated with maintenance HD, but headache and gastrointestinal side effects occur more frequently with ISD/HY compared with placebo.

Introduction

The majority of patients with dialysis-dependent ESKD die from cardiovascular disease (1). How to best treat and prevent cardiovascular disease in this setting remains unclear, but several lines of evidence suggest that nitric oxide (NO) bioavailability is impaired in ESKD (2), and that impaired NO homeostasis is a key mechanism underlying the increase in myocardial...
fibrosis and myocardial microvascular rarefraction observed in advanced kidney disease (3–5). Additional data suggest these changes contribute to reduced myocardial perfusion, mechanical dysfunction, and propagation of malignant cardiac arrhythmias, and are likely to at least partly account for the high incidence of cardiovascular death in CKD (6–10).

Agents that improve NO bioavailability thus have the potential to antagonize the pathologic changes occurring in late-stage ESKD and provide a specific means of treating and preventing cardiovascular morbidity and mortality in this setting.

NO homeostasis may be reset with combination therapy with isosorbide dinitrate (ISD), an NO donor, and hydralazine (HY) to prevent tachyphylaxis to the nitrate compound (11,12). This pharmacologic approach has the potential for potent therapeutic effects as suggested by heart failure trials in which the combination reduced mortality and improved left ventricular remodeling (13–15). ISD and HY offer a particularly intriguing possibility for the treatment of individuals with ESKD, given the importance of NO deficiency in the development of cardiovascular disease in this setting. However, neither the optimal dosing regimen for ISD/HY nor the incidence of side effects such as headache, hypotension, or nausea in the setting of ESKD are well understood. We conducted the Safety and Cardiovascular Efficacy of Hydralazine and Isosorbide Dinitrate in Dialysis-Dependent ESRD (HIDE) study to preliminarily assess safety and tolerability and estimate initial signals on the effect on left ventricular function and perfusion with combination ISD/HY compared with placebo in individuals with ESKD requiring maintenance hemodialysis (HD).

HIDE is one of the studies conducted by the Hemodialysis Novel Therapies Consortium established by the National Institute of Diabetes and Digestive and Kidney Diseases to conduct safety and feasibility studies of interventions for patients being treated with maintenance HD.

Materials and Methods

Design

HIDE (NCT02228408) was a double-blind placebo-controlled, dose-escalating trial comparing combination ISD/HY with placebo. The full protocol is provided as Supplemental Data.

Participants

Participants were enrolled from three dialysis units affiliated with Brigham & Women’s Hospital. Data were managed by the Hemodialysis Novel Therapies Data Coordinating Center at the University of Pennsylvania. The Institutional Review Boards at both centers approved the protocol and all participants provided written informed consent. Inclusion criteria were age of 18–85 years, treatment with maintenance HD for ≥90 days, and pre-dialysis systolic BP ≥120 mm Hg for all sessions during the 2 weeks before screening and on the day of randomization. Major exclusion criteria included: (1) unscheduled dialysis for hyperkalemia within 3 months or potassium concentration ≥6.5 mEq/L within 2 months before screening; (2) predialysis systolic BP<100 mm Hg within 4 weeks before screening; (3) three episodes or more during the prior 30 days of intra-dialytic hypotension or intra-dialytic symptoms of hypotension; (4) severe mitral valve disease or mitral valve repair or replacement (these conditions might interfere with assessment of mitral annular E’ velocity); (5) current use of study medications, allergy to study medications, or use of contraindicated medication (sildenafil, vardenafil, tadalafl, monoamine oxidase inhibitors); (6) severe aortic stenosis or left ventricular outflow obstruction; (7) pregnancy or breastfeeding; and (8) anticipated change in renal replacement modality or death within 6 months.

Randomization and Intervention

Participants were randomized to receive ISD/HY or placebo for 24 weeks. Randomization was web based using a random number generator prepared by the data coordinating center using blocks of random sizes with stratification by baseline left-ventricular ejection fraction (≤45% versus >45%). Participants and research personnel were blinded to study assignment.

Participants were evaluated either in person or by telephone weekly during the 4-week dose escalation phase, every 4 weeks between week 4 and 24, then at week 26 and 30 for a total follow-up of 30 weeks to assess BP, dialysis treatment records, symptoms of hypotension adverse events, and medication changes. ISD/HY or matching placebo medication was started at 10/10 mg three times daily, increased if tolerated to 20/35 mg after 1 week, then increased to the maximum dose of 40/75 mg as tolerated after an additional week. Adjustment to dry weight and other anti-hypertensive medications were managed by treating clinicians and were not dictated by the protocol. However, in the event of hypotension, the protocol allowed for an increase in dry weight (in the absence of peripheral or pulmonary edema), ultrafiltration rate, or change to non-study anti-hypertensive medications after consultation with a participant’s clinical providers. Participants were scheduled to continue the maximal tolerated dose from the end of week 4 to week 24 with the dose held and/or reduced as needed in the event of dose-limiting side effects such as hypotension, nausea, or headache. Cardiovascular testing included echocardiography with a measurement of mitral annular (E’) velocities by tissue Doppler imaging and measurement of rest and adenosine-induced stress myocardial perfusion and coronary flow reserve using positron emission tomography (PET) at baseline before randomization and week 24.

Outcomes

The principal objective was to evaluate safety and tolerability of ISD/HY in patients being treated with maintenance HD. The safety endpoints included serious hypotension (hypotension requiring hospitalization or emergency room visit not attributable to sepsis or cardiovascular cause), recurrent intra-dialytic hypotension (systolic BP<80 mm Hg during ≥3 HD sessions per 30-day period, or treatment for intra-dialytic systolic BP<100 mg Hg or symptoms of hypotension, e.g., with intravenous fluids or lowering ultrafiltration rate), adverse events, and adverse events precluding further treatment with study medication. Tolerability events included study drug dose reduction or discontinuation. Given the predicted side-effect profiles of the study medications and the interest in utilizing ISD/HY
as a chronic cardiovascular therapy, the occurrence of headache, nausea, vomiting, diarrhea, recurrent intra-dialytic hypotension, and cardiovascular hospitalization were ascertained as tolerability or safety outcomes through direct querying of participants and/or medical records every week for the first 4 weeks and every 4 weeks thereafter.

Efficacy signals included change from baseline in the following parameters: (1) coronary flow reserve (CFR, the ratio of post-stress myocardial blood flow to resting myocardial blood flow) measured on rest and pharmacologic stress PET, and (2) diastolic function, measured by early (E’) diastolic mitral annulus velocity (average of lateral and septa mitral annulus) on transthoracic tissue Doppler echocardiography. All echocardiographic variables were systematically measured by an echocardiography core laboratory.

Sample Size Determination and Statistical Analyses
This study was designed to explore safety and tolerability, rather than to assess efficacy. We also wished to examine any preliminary signals that might suggest a clinical effect of the study medicines. We calculated that with a sample size of 16 participants there would be 80% power to detect an adverse event rate of 10.4 events per patient-year in ISD/HY assuming an event rate of 6.0 events per patient-year in placebo using a Poisson regression model with a binary exposure of treatment assignment. The study was not powered to detect differences in the individual adverse events of interest.

With eight participants per group we were powered to detect only large changes in cardiovascular function. Power was 80% to detect a change in CFR of 0.75, assuming a common SD for change in CFR of 0.5. Assuming the common SD of 2.0 cm/s and baseline measure of 5.8 ± 1.8 cm/s, power was ≥80% to detect a change ≥3.0 cm/s in E’.

Differences of this magnitude in CFR and E’ were associated with mortality in previous studies (16,17).

Baseline variables are presented as mean (SD), N (%), or median (interquartile range) according to distribution with P<0.05 considered significant. The primary analyses were on the basis of incidence rate in intention-to-treat populations with all participants analyzed on the basis of randomized group assignment. Poisson regression was used for comparison of incident rates, chi-squared or Fisher’s exact test for binary and incidence measures, and two-sample t or Wilcoxon rank sum test for continuous measures. All analyses were performed using SAS version 9.4 (SAS Institute Inc.) and gee pack packages in R version 3.4.3 (https://www.r-project.org). Given the pilot nature of the study with a focus on safety, no corrections were made for multiple comparisons.

Results
Participants
Between August 28, 2017 and August 16, 2018, we enrolled 20 individuals of whom 17 were randomized: seven to ISD/HY and ten to placebo (Figure 1). The median (interquartile range) age was 62 (53–66) years, and the majority of participants were male (71%), Black (77%), and had a history of diabetes (65%) (Table 1). Baseline characteristics were similar across groups with the exception of body mass index, which was lower in the ISD/HY group (25.9 kg/m²) compared with placebo (32.3 kg/m²). In addition, both systolic (141 mm Hg versus 154 mm Hg) and diastolic pressure (72 mm Hg versus 77 mm Hg) at baseline were numerically lower in those assigned to ISD/HY compared with those receiving placebo.

Follow-up ended on May 7, 2019 with a total duration of follow-up of 10.2 patient-years. Total follow-up with ISD/HY was 4.2 patient-years with one participant withdrawing

Figure 1. | Enrollment and follow-up of study participants. ISD/HY, isosorbide dinitrate/hydranalazine.
on day 89 for reasons unrelated to adverse events. All participants in the placebo group completed 28 weeks of follow-up. None of the participants died, underwent kidney transplantation, or transferred to a different dialysis unit during the study. All randomized participants were included in the primary safety analysis. One of the 17 randomized participants (in the ISD/HY arm) did not have the week 24 testing and was therefore not included in the efficacy analysis.

### Safety and Tolerability

All participants assigned to ISD/HY were able to escalate to the target dose of 40/75 mg. Two participants subsequently required dose reduction because of headache and gastrointestinal symptoms in one subject and gastrointestinal symptoms in the other. The final dose was 10/10 mg in one participant and another participant had a last dose of 20/35 mg. In the placebo group, the final dose was the lowest dose in one (10%) participant, the middle dose in one participant and another participant had a last dose of 20/35 mg. In the placebo group, the final dose was the lowest dose in one (10%) participant, the middle dose in one participant and another participant had a last dose of 20/35 mg.

### Table 1. Baseline characteristics

| Characteristic                   | Total (N=17) | ISD/HY (N=7) | Placebo (N=10) |
|----------------------------------|--------------|--------------|----------------|
| Male                             | 12 (70.6%)   | 5 (71.4%)    | 7 (70.0%)      |
| Age (yr)                         | 62.0 (53.0–66.0) | 62.0 (54.0–64.5) | 62.5 (54.5–67.8) |
| Race                             |              |              |                |
| White                            | 2 (11.8%)    | 1 (14.3%)    | 1 (10.0%)      |
| Black                            | 13 (76.5%)   | 5 (71.4%)    | 8 (80.0%)      |
| Prefer not to answer             | 2 (11.8%)    | 1 (14.3%)    | 1 (10.0%)      |
| Hispanic ethnicity               | 5 (29.4%)    | 2 (28.6%)    | 3 (30.0%)      |
| BMI (kg/m²)                      | 29.2 (25.9–32.8) | 25.9 (23.5–27.4) | 32.3 (29.6–38.7) |
| Systolic BP (mm Hg)              | 141.0 (136.0–173.0) | 141.0 (134.0–150.0) | 153.5 (136.2–176.8) |
| Diastolic BP (mm Hg)             | 75.0 (65.0–85.0) | 72.0 (65.0–84.5) | 77.0 (69.8–87.0) |
| Hypertension                     | 17 (100.0%)  | 7 (100.0%)   | 10 (100.0%)    |
| Diabetes mellitus                | 11 (64.7%)   | 4 (57.1%)    | 7 (70.0%)      |
| Coronary artery disease          | 2 (11.8%)    | 0 (0%)       | 2 (20.0%)      |
| Heart failure                    | 6 (35.3%)    | 1 (14.3%)    | 5 (50.0%)      |
| Atrial fibrillation              | 2 (11.8%)    | 0 (0%)       | 2 (20.0%)      |
| Peripheral vascular disease      | 2 (11.8%)    | 0 (0%)       | 2 (20.0%)      |
| Hyperlipidemia                   | 9 (52.9%)    | 3 (42.9%)    | 6 (60.0%)      |
| Current smoking                  | 4 (23.5%)    | 3 (42.9%)    | 1 (10.0%)      |
| Single pool (Kt/V)               | 1.44 (1.29–1.57) | 1.42 (1.27–1.54) | 1.47 (1.31–1.57) |
| Hemoglobin (g/dl)                | 11.1 (10.2–11.5) | 11.3 (10.5–11.8) | 11.0 (10.2–11.5) |
| Potassium (mEq/L)                | 4.3 (4.1–4.9) | 4.3 (4.0–5.0) | 4.3 (4.2–4.7)  |
| Albumin (g/dl)                   | 4.3 (4.0–4.5) | 4.4 (4.1–4.7) | 4.2 (4.0–4.4)  |
| Cardiovascular medications       |              |              |                |
| ACE-I                            | 3 (17.6%)    | 1 (14.3%)    | 2 (20.0%)      |
| ARB                              | 3 (17.6%)    | 1 (14.3%)    | 2 (20.0%)      |
| Alpha blockers                   | 7 (41.2%)    | 1 (14.3%)    | 6 (60.0%)      |
| Beta blockers                    | 11 (64.7%)   | 2 (28.6%)    | 9 (90.0%)      |
| Calcium channel blockers         | 9 (52.9%)    | 3 (42.9%)    | 6 (60.0%)      |
| Diuretics                        | 3 (17.6%)    | 0 (0%)       | 3 (30.0%)      |
| Vasodilators                     | 1 (5.9%)     | 1 (14.3%)    | 0 (0%)         |
| Number of anti-hypertensive medications | 2.0 (1.0–3.0) | 1.0 (0.5–2.0) | 2.5 (2.0–4.0) |
| Dialysis vintage (yr)            | 3.4 (0.9–4.6) | 4.9 (3.5–5.2) | 2.1 (0.7–3.4) |

Values are expressed as number (%) or median, interquartile range. ISD/HY, isosorbide dinitrate/hydralazine; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

*aBaseline potassium was missing in one participant in the placebo group.*

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Figure 2. | Study drug dose reduction and temporary discontinuation by treatment group. Each circle represents a dose reduction. Each square represents a temporary discontinuation of the study drug. There were no permanent discontinuations of the study drug. A closed circle/square represents ISD/HY whereas an open circle/square represents placebo.
(10%), and the highest in the remaining eight participants (80%). Temporary discontinuation of study drug was required in two (29%) participants in the ISD/HY group and three (30%) in the placebo arm (Figure 2). None of the participants in either arm required permanent discontinuation of the study drug. Pill counts demonstrated that ISD/HY participants took 78.9% (46.3%–98.1%) of doses compared with 76.1% (58.7%–90.0%) in the placebo arm (P = 0.77).

Safety outcomes and adverse events of interest are shown in Table 2, and Supplemental Table 1. Recurrent intra-dialytic hypotension was less frequent with ISD/HY (0.47 events/patient-year) compared with placebo (1.83 events/patient-year, P = 0.04). There was one inter-dialytic hypotension event in the ISD/HY group and none in the placebo group (P = 0.18). Change in estimated dry weight from baseline to end of follow-up was similar with ISD/HY (−0.9 ± 3.5 kg) and placebo (0.6 ± 2.9 kg, P = 0.37). The mean pre-dialysis BP and mean nadir intra-dialytic BP were similar in the ISD/HY and placebo groups (Supplemental Figure 1, Table 3). In contrast, nausea appeared to occur more frequently with ISD/HY (1.90 events/patient-year) than placebo (0.50 events/patient-year, P = 0.03).

Overall, adverse events were more frequent with ISD/HY (11.40 events/patient-year) than placebo (6.31 events/patient-year). Differences in the rate of adverse events of interest were NS, although power for individual events was low (Table 2). No adverse events required permanent discontinuation of the study medication. In addition to the prespecified adverse events, there were four events of dizziness with ISD/HY participants and one with placebo (Supplemental Table 1). A similar proportion of adverse events of interest were considered to be related, or possibly related, to the study drug in the ISD/HY (69.6%) and placebo arms (64.0%, Table 4). No participants in either group permanently discontinued study medication because of an adverse event.

The incidence rate of serious adverse events was higher with ISD/HY (3.6 events/patient-year) than placebo (0.7 events/patient-year). As with nonserious events, differences in the rate of serious adverse events of interest were not significantly different between ISD/HY and placebo (Table 2). Additionally, the majority were assessed by the

| Table 2. Safety and tolerability outcomes |
|------------------------------------------|
| **Outcome**                             | ISD/HY (N=7) | Placebo (N=10) | \( P \) Value \( a \) | \( P \) Value \( b \) |
| Number (%) of Participants with Event   | Number of Events Per Patient-yr | Number (%) of Participants with Event | Number of Events Per Patient-yr |
| Safety outcomes                         |             |               |                           |                           |
| Adverse events                          | 7 (100)     | 11.40         | 10 (100)                  | 6.31                      |
| Serious adverse events                  | 5 (71.4)    | 3.56          | 3 (30)                    | 0.67                      |
| Adverse event precluding further treatment with study medication | 0 (0) | 0 | 0 (0) | 0 |
| Adverse events of interest              | 6 (85.7)    | 5.46          | 10 (100)                  | 4.15                      |
| Serious hypotension                     | 2 (28.6)    | 0.71          | 1 (10)                    | 0.17                      |
| Intercylodialytic hypotension           | 0 (0)       | 0             | 0 (0)                     | 0                         |
| Interdialytic SBP<90 mm Hg              | 1 (14.3)    | 0.47          | 6 (60)                    | 1.83                      |
| Requiring medication change, ER visit, or hospitalization | 1 (14.3) | 0.24 | 0 (0) | 0 |
| Cardiovascular hospitalization          | 1 (14.3)    | 0.24          | 0 (0)                     | 0                        |
| Stroke                                 | 0 (0)       | 0             | 0 (0)                     | 0                         |
| Death                                  | 0 (0)       | 0             | 0 (0)                     | 0                         |
| Tolerability outcomes                  |             |               |                           |                           |
| Headache                               | 5 (71.4)    | 1.90          | 7 (70)                    | 1.16                      |
| Nausea                                 | 4 (57.1)    | 1.90          | 3 (30)                    | 0.50                      |
| Vomiting                               | 1 (14.3)    | 0.24          | 1 (10)                    | 0.17                      |
| Diarrhea                               | 2 (28.6)    | 0.48          | 2 (20)                    | 0.33                      |
| Anorexia                               | 0 (0)       | 0             | 0 (0)                     | 0                         |

ISD/HY, isosorbide hydralazine; NA, not applicable; SBP, systolic blood pressure; ER, emergency room.

\( a \)P value for comparing number of patients with event using chi-square or Fisher’s exact tests.

\( b \)P value for comparing number of patients per patient-yr using Poisson regression.
blinded investigators to be unrelated or unlikely related to the study medication. Only a single serious adverse event, which occurred in the ISD/HY group, was assessed as being possibly related to study medication. No serious adverse events were considered definitely related (Supplemental Table 1, Table 4). However, the serious events did include several events in the ISD/HY group such as a fall, nausea, vomiting, and episode of dyspnea that are consistent with previously described adverse event profiles of ISD/HY.

**Preliminary Signals of Efficacy**

As shown in Table 5 there was a nominal increase in mitral annular E’ velocity in the ISD/HY (+0.56±1.10 cm/s) group and no change in the placebo group (−0.04±0.92) but the difference between the groups was not statistically significant (P=0.34). There was similarly no compelling evidence of a difference between treatments in the degree of change over time in the secondary echocardiographic measures of cardiac structure, systolic function, or diastolic function. Changes in coronary flow reserve were marginal in both groups and were similar with ISD/HY (−0.27±0.23) and placebo (−0.03±0.46, P=0.19).

**Discussion**

We randomized patients receiving maintenance HD to 24 weeks of a combination of ISD and HY at doses up to 40 mg of ISD and 75 mg of HY daily or placebo. Overall, ISD/HY was well tolerated. All participants were able to reach the target dose of 40/75 mg. Although two participants did not tolerate the highest dose, none required permanent discontinuation of study medication during follow-up.

A particular concern before this trial was that ISD/HY might result in hypotension with or without symptoms as a result of BP lowering or decreased preload. Although our study was small and excluded individuals with a baseline systolic BP ≤120 mm Hg, the findings are reassuring. Despite BP being lower at baseline and during follow-up in the ISD/HY group, the rate of recurrent intradialytic hypotension events was lower with combination therapy than with placebo. When intradialytic hypotension was evaluated as individual rather than recurrent events, the rate remained lower in the ISD/HY group than in the placebo group. Furthermore, there was only a single episode of interdialytic hypotension over 24 weeks and it did not require changes in medication, visit to an emergency room, or hospitalization. Headaches and nausea occurred more frequently with ISD/HY than with placebo; these are side effects that have been well established in the non-ESKD population.

We detected a significant increase in the rate of adverse events and serious adverse events with ISD/HY compared with placebo. Although few events were assessed by the

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**Table 3. Blood pressure throughout follow-up**

| Outcome                                      | Total | ISD/HY | Placebo | P Value |
|----------------------------------------------|-------|--------|---------|---------|
| N=17                                         |       |        |         |         |
| Mean-per-participant pre-dialysis SBP (mm Hg)| 148.0 (15.4) | 142.0 (13.8) | 152.3 (15.7) | 0.18    |
| Mean-per-participant pre-dialysis DBP (mm Hg)| 78.7 (10.4)  | 77.2 (10.0)  | 79.7 (11.1)  | 0.63    |
| Mean-per-participant nadir intra-dialytic SBP (mm Hg) | 117.0 (15.3) | 115.8 (12.6) | 117.8 (17.6) | 0.79    |

ISD/HY, isosorbide hydralazine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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**Table 4. Relatedness of adverse events**

| Classification     | Adverse Events | Serious Adverse Events |
|--------------------|----------------|------------------------|
|                    | Total (%)      | ISD/HY (%)             | Placebo (%)       | Total (%) | ISD/HY (%) | Placebo (%) |
| Not related        | 7 (14.6)       | 3 (13)                 | 4 (16)            | 3 (75)     | 2 (66.7)   | 1 (100)     |
| Unlikely related   | 9 (18.8)       | 4 (17.4)               | 5 (20)            | 0 (0)      | 0 (0)      | 0 (0)       |
| Possibly related   | 27 (56.2)      | 12 (52.2)              | 15 (60)           | 1 (25)     | 1 (33.3)   | 0 (0)       |
| Related            | 5 (10.4)       | 4 (17.4)               | 1 (4)             | 0 (0)      | 0 (0)      | 0 (0)       |
| Other Adverse Events |               |                        |                    |            |            |             |
| Not related        | 20 (52.6)      | 12 (48)                | 8 (61.5)          | 10 (66.7)  | 9 (75)     | 1 (33.3)    |
| Unlikely related   | 7 (18.4)       | 3 (12)                 | 4 (30.8)          | 5 (33.3)   | 3 (25)     | 2 (66.7)    |
| Possibly related   | 6 (15.8)       | 5 (20)                 | 1 (7.7)           | 0 (0)      | 0 (0)      | 0 (0)       |
| Related            | 5 (13.2)       | 5 (20)                 | 0 (0)             | 0 (0)      | 0 (0)      | 0 (0)       |

ISD/HY, isosorbide hydralazine.

*Protocol specified adverse events of interest include headache, nausea, vomiting, diarrhea, recurrent intra-dialytic hypotension and cardiovascular hospitalization.
Table 5. Results of cardiovascular imaging studies

| Variable | ISD/HY (N=6) | Placebo (N=10) | P Value |
|----------|--------------|----------------|---------|
| Mean (SD) | Pre | Post | Change | Pre | Post | Change |
| **Echocardiography** | | | | | | |
| Mitral annular E’ velocity, cm/s | 6.34 (1.14) | 6.90 (1.13) | 0.56 (1.10) | 6.55 (0.86) | 6.51 (1.37) | −0.04 (0.92) | 0.34 |
| LV end-diastolic diameter, mm | 4.75 (0.42) | 4.57 (0.35) | −0.18 (0.22) | 4.73 (0.52) | 4.62 (0.52) | −0.11 (0.18) | 0.53 |
| LV end-systolic diameter, mm | 3.27 (0.19) | 3.12 (0.20) | −0.14 (0.15) | 3.32 (0.37) | 3.27 (0.54) | −0.05 (0.22) | 0.35 |
| LV end-diastolic volume (BSA adjusted), ml/m² | 52.8 (10.9) | 51.6 (10.4) | −1.2 (2.7) | 47.3 (9.1) | 48.4 (9.9) | 1.1 (5.1) | 0.28 |
| LV end-systolic volume (BSA adjusted), ml/m² | 17.55 (4.64) | 17.60 (3.28) | 0.05 (1.67) | 17.70 (5.04) | 18.29 (5.28) | 0.59 (2.01) | 0.60 |
| LV ejection fraction 2D, % | 67.19 (2.17) | 65.78 (1.66) | −1.41 (2.09) | 62.99 (4.22) | 62.64 (4.13) | −0.35 (2.28) | 0.37 |
| LV mass index (BSA adjusted), g/m² | 124.6 (17.9) | 113.9 (35.9) | −10.6 (8.5) | 105.5 (15.0) | 97.5 (12.5) | −8.0 (11.1) | 0.62 |
| LV global longitudinal strain, % | −14.48 (3.06) | −18.88 (3.88) | −4.40 (3.32) | −13.64 (3.69) | −14.67 (2.84) | −1.02 (3.45) | 0.14 |
| LA diameter, cm | 3.88 (0.19) | 3.72 (0.15) | −0.15 (0.12) | 3.98 (0.44) | 3.72 (0.34) | −0.26 (0.18) | 0.17 |
| LA volume (BSA adjusted), ml/m² | 33.45 (5.99) | 31.28 (8.03) | −2.17 (3.05) | 29.24 (7.33) | 24.73 (7.81) | −4.50 (5.01) | 0.30 |
| **Positron emission tomography** | | | | | | |
| CFR global LV | 2.45 (0.59) | 2.19 (0.65) | −0.27 (0.23) | 1.86 (0.35) | 1.84 (0.53) | −0.03 (0.46) | 0.19 |
| Stress myocardial blood flow global LV, ml/min per gram | 1.97 (0.44) | 1.85 (0.60) | −0.12 (0.37) | 1.78 (0.43) | 1.60 (0.44) | −0.18 (0.25) | 0.76 |
| Rest myocardial blood flow global LV, ml/min per gram | 0.81 (0.13) | 0.84 (0.08) | 0.03 (0.15) | 0.95 (0.14) | 0.89 (0.15) | −0.06 (0.13) | 0.23 |

ISD/HY, isosorbide hydralazine; LV, left ventricle; BSA, body surface area; 2D, two dimensional; CFR, coronary flow reserve.

blinded investigators as related to the study medication, that overall rates of adverse events were higher with the active treatment mandates careful monitoring of adverse events in any future investigations and necessitates caution before expanding use of ISD/HY outside of clinical trials. Furthermore, the overall count of serious and nonserious adverse events included several not obviously consistent with the known profile or biology of ISD/HY, such as episodes of hyperkalemia, gastric hemorrhage, dialysis access procedures, and subconjunctival hemorrhage. Further study is clearly warranted to verify or refute this safety signal in a larger population.

In addition to studying safety, we were also interested in exploring efficacy. Our study was powered only to detect very large changes in microvascular coronary function or echocardiographic parameters of diastolic function, and our main objective was to generate pilot estimates of efficacy. We did not observe any significant differences between ISD/HY and placebo in change from baseline in either the primary parameters of interest—mitral annular E’ velocity on Doppler echocardiography and coronary flow reserve on rest and stress PET—or secondary cardiovascular imaging parameters.

Tissue Doppler echo and PET parameters were chosen as surrogates for changes in myocardial fibrosis (18,19) and myocardial capillary supply (20,21), respectively. Differences in between-group change in flow reserve from baseline to follow-up were marginal whereas numerical differences in E’ (consistent with improved diastolic function) and in measures of strain (consistent with improved systolic function) with ISD/HY compared with placebo were small and did not achieve significance. Given the relatively short duration and small size of the trial, these data provide preliminary estimates of the effect of ISD/HY on these measures that may be useful for the design of definitive studies but do not provide firm evidence in favor or against benefit from ISD/HY. In particular, they suggest a sample size of 26, 36, or 48 patients would be required to provide 80% power to detect a between group difference of 20 in change E’, E/E’, or left ventricle global strain at 6 months, respectively.

Combination ISD/HY is thought to improve NO bioavailability (22) and improves mortality and left ventricle function in Black patients with heart failure (15). It may be a particularly promising therapy for the treatment of cardiovascular function in individuals treated with maintenance HD, given its proven efficacy in heart failure, combined with the role played by altered NO homeostasis in late-stage CKD (2–5). However, despite this promise and
clinical use of this combination in some patients receiving HD, the combination has not been studied in the setting of maintenance HD. We are aware of only two prospective studies examining the use of nitrates in ESKD. In one study from China, 144 patients with hypertension and receiving HD were randomized to isosorbide mononitrate 30–120 mg daily or placebo daily for 24 weeks with dose adjustment to target BP (23). Left ventricular mass index and the proportion of patients with left ventricular hypertrophy decreased more in the isosorbide mononitrate group than in the placebo group. Interestingly, the incidence of heart failure was also lower with isosorbide mononitrate (1%) than placebo (11%). A second open-label study by the same group randomized 64 hypertensive patients on peritoneal dialysis to isosorbide mononitrate 15–60 mg daily or usual care (24). Nitrate dose was adjusted to a target systolic BP <140 mm Hg. At 24 weeks, the left ventricular mass index was lower in the nitrate group, although it is unclear whether the change over time differed between groups. Adverse events were rare in both studies. However, differences in rates between treatment groups were not well reported.

Our study is consistent with these earlier studies, in showing therapy with nitrate donors is well tolerated in ESKD and it advances the field in a few ways. In contrast with the previous studies, we assessed a target dose rather than a target BP. Additionally, our study provides information on the use of nitrate donors in the context of US patients receiving dialysis. To our knowledge, ours is also the first trial conducted in the United States to specifically assess use of ISD in ESKD. In addition, this study reports on the use of a nitrate donor in combination with HY in the setting of maintenance dialysis. This represents an important advance for several reasons. First, the combination of ISD/HY is well studied in other settings, and, as opposed to therapy with a nitrate alone, has been shown to improve mortality, cardiovascular structure and function, and reduce hospitalizations in randomized clinical trials (14,15). The side effects and tolerability of combination therapy, however, are likely to differ from those of monotherapy. Furthermore, although the use of HY in this combination is primarily designed to reduce tachyphylaxis to the nitrate donor (11,12), “off-target” effects on epigenetic DNA methylation (25,26) and BP control may be important contributors to both safety and anticipated cardiovascular effects. Our study thus contributes important new data regarding use of this combination in the setting of HD-dependent ESKD, and suggests use of this combination at doses proven to reduce mortality in other settings is tolerated sufficiently to consider advancing to longer and better powered studies.

Strengths of this study include use of a double-blind placebo-controlled design, recruitment from multiple dialysis units, blinded assessment of echocardiographic parameters by a core laboratory, investigation of multiple aspects of cardiovascular structure and function, and pre-specified definitions of safety. Several limitations should also be acknowledged. We investigated ISD/HY in patients with and without prior heart failure on the basis of evidence implicating NO homeostasis as a key mechanism underlying the cardiovascular sequelae of ESKD (2–5). Although we did not identify compelling evidence of cardiovascular efficacy in the overall maintenance HD population, further investigation in patients receiving dialysis with established heart failure would be of interest given the clinical benefits of ISD/HY previously documented in Black patients with heart failure and preserved kidney function (13–15). The study size was small, and the duration of follow-up was short. As a result, the power for both safety and efficacy outcomes was low. Given the pilot design, we did not correct for multiple comparisons, and the results of significance tests should be interpreted cautiously. Furthermore, the enrolled population included a high proportion of Black and Hispanic HD patients not fully representative of the larger US HD population. Lastly, all three recruitment sites were in a single city and within a short distance of a single academic medical center.

In conclusion, in this trial ISD/HY administered for 24 weeks to individuals receiving maintenance HD was well tolerated compared with placebo, with side effects consistent with the known profile of ISD/HY and not requiring dose discontinuation. The study was underpowered to detect differences in cardiovascular structure and function, and no major differences between treatment groups were observed. The incidence of safety events was higher with ISD/HY. In aggregate, our data suggest ISD/HY is sufficiently tolerated in maintenance HD to justify further study in larger trials with sufficient power to robustly analyze adverse events and changes in cardiovascular function.

Disclosures
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Author Contributions

A. Kliger was responsible for the investigation, methodology, and supervision. D. Charytan was responsible for conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, and writing of the original draft. D. Raj was responsible for the methodology and project administration. F. Mc Causland was responsible for the investigation, project administration, and supervision. H. Skali was responsible for conceptualization, investigation, methodology, resources, supervision, and validation. J. Hsu was responsible for data curation, formal analysis, validation, and the writing of the original draft. J. Landis was responsible for the formal analysis, methodology, project administration, and supervision. L. Dember was responsible for data curation, formal analysis, funding acquisition, methodology, project administration, supervision, and writing of the original draft. M. DiCarli was responsible for conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, and writing of the original draft. M. Williams was responsible for funding acquisition, the investigation, project administration, and supervision. P. Kimmel was responsible for the methodology, and project administration. R. Mehrotra was responsible for funding acquisition and the methodology. S. Waikar was responsible for project administration, resources, and supervision. T. Ikizler was responsible for funding acquisition, the investigation, and the methodology. All authors reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at http://kidney360.annajournals.org/lookup/suppl?doi=10.3406/kid.0004342020/-/DCSupplemental. Supplemental Material. Study Protocol. Supplemental Table 1. Detailed listing of adverse events. Supplemental Figure 1. Blood pressure over time in individual participants according to randomized therapy.

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### Supplementary Table 1. Detailed Listing of Adverse Events

| AE Term                                      | Non-Serious Adverse Events | Serious Adverse Events |
|----------------------------------------------|----------------------------|------------------------|
|                                              | Total | ISD/HY | Placebo | Total | ISD/HY | Placebo |
|                                              |       |        |         |       |        |         |
|                                              | Events of Interest (#)     | Events of Interest (#) |
| Headache                                     | 15    | 8      | 7       | 0     | 0      | 0       |
| Nausea                                       | 11    | 8      | 3       | 1     | 1      | 0       |
| Vomiting                                     | 2     | 1      | 1       | 1     | 1      | 0       |
| Diarrhea                                     | 4     | 2      | 2       | 0     | 0      | 0       |
| Recurrent intra-dialytic hypotension         | 13    | 2      | 11      | 0     | 0      | 0       |
| Inter-dialytic hypotension                   | 1     | 1      | 0       | 0     | 0      | 0       |
| Cardiovascular hospitalization               | 2     | 1      | 1       | 2     | 1      | 1       |
| Overall adverse events of interest           | 48    | 23     | 25      | 4     | 3      | 1       |
|                                              |       |        |         |       |        |         |
|                                              | Other Events (#)           | Other Events (#)       |
| Angioplasty                                  | 1     | 0      | 1       | 1     | 0      | 1       |
| Arteriovenous fistula occlusion              | 1     | 0      | 1       | 0     | 0      | 0       |
| Arteriovenous fistula operation              | 1     | 1      | 0       | 1     | 1      | 0       |
| Chest pain - cardiac                         | 1     | 1      | 0       | 0     | 0      | 0       |
| Confusion                                    | 1     | 1      | 0       | 1     | 1      | 0       |
| Constipation                                 | 2     | 0      | 2       | 0     | 0      | 0       |
| Dizziness                                    | 5     | 4      | 1       | 0     | 0      | 0       |
| Dyspepsia                                    | 1     | 1      | 0       | 0     | 0      | 0       |
| Dyspnea                                      | 2     | 2      | 0       | 2     | 2      | 0       |
| Edema face                                   | 1     | 1      | 0       | 0     | 0      | 0       |
| Fall                                         | 2     | 1      | 1       | 2     | 1      | 1       |
| Ferritin high                                | 1     | 0      | 1       | 0     | 0      | 0       |
| Gastric hemorrhage                           | 1     | 1      | 0       | 1     | 1      | 0       |
| Heartbeats increased                        | 1     | 1      | 0       | 0     | 0      | 0       |
| Hyperkalemia                                 | 2     | 2      | 0       | 2     | 2      | 0       |
| Hypotension                                  | 1     | 1      | 0       | 0     | 0      | 0       |
| Iron overload                                | 2     | 2      | 0       | 2     | 2      | 0       |
| Leukopenia                                   | 1     | 1      | 0       | 0     | 0      | 0       |
| Melaena                                      | 1     | 1      | 0       | 1     | 1      | 0       |
| Musculoskeletal pain                         | 1     | 0      | 1       | 0     | 0      | 0       |
| Non-cardiac chest pain                       | 1     | 0      | 1       | 0     | 0      | 0       |
| Palpitations                                 | 1     | 1      | 0       | 1     | 1      | 0       |
| Subconjunctival hemorrhage                   | 1     | 1      | 0       | 1     | 1      | 0       |
| Thrombectomy                                 | 1     | 0      | 1       | 0     | 0      | 0       |
| Thrombocytopenia                             | 1     | 1      | 0       | 0     | 0      | 0       |
| Transient ischemic attacks                   | 1     | 1      | 0       | 1     | 1      | 0       |
| Vomiting                                     | 1     | 0      | 1       | 0     | 0      | 0       |
| Not coded                                    | 2     | 0      | 2       | 1     | 0      | 1       |
| Overall other events                         | 38    | 25     | 13      | 15    | 12     | 3       |
Supplementary Figure 1.
Blood pressure over time in individual participants according to randomized therapy. SBP-systolic blood pressure. DBP-diastolic blood pressure.
### Supplementary Table 1. Detailed Listing of Adverse Events

| AE Term                                    | Non-Serious Adverse Events |                  | Serious Adverse Events |                  |                  |
|--------------------------------------------|---------------------------|------------------|------------------------|------------------|------------------|
|                                            | Total   | ISD/HY | Placebo | Total   | ISD/HY | Placebo |
| **Events of Interest (#)**                 |         |        |         |         |        |         |
| Headache                                  | 15      | 8      | 7       | 0       | 0      | 0       |
| Nausea                                     | 11      | 8      | 3       | 1       | 1      | 0       |
| Vomiting                                   | 2       | 1      | 1       | 1       | 1      | 0       |
| Diarrhea                                   | 4       | 2      | 2       | 0       | 0      | 0       |
| Recurrent intra-dialytic hypotension       | 13      | 2      | 11      | 0       | 0      | 0       |
| Inter-dialytic hypotension                 | 1       | 1      | 0       | 0       | 0      | 0       |
| Cardiovascular hospitalization             | 2       | 1      | 1       | 2       | 1      | 1       |
| **Overall adverse events of interest**     | 48      | 23     | 25      | 4       | 3      | 1       |
| **Other Events (#)**                       |         |        |         |         |        |         |
| Angioplasty                                | 1       | 0      | 1       | 1       | 0      | 1       |
| Arteriovenous fistula occlusion            | 1       | 0      | 1       | 0       | 0      | 0       |
| Arteriovenous fistula operation            | 1       | 1      | 0       | 1       | 1      | 0       |
| Chest pain - cardiac                       | 1       | 1      | 0       | 0       | 0      | 0       |
| Confusion                                  | 1       | 1      | 0       | 1       | 1      | 0       |
| Constipation                               | 2       | 0      | 2       | 0       | 0      | 0       |
| Dizziness                                  | 5       | 4      | 1       | 0       | 0      | 0       |
| Dyspepsia                                  | 1       | 1      | 0       | 0       | 0      | 0       |
| Dyspnea                                    | 2       | 2      | 0       | 2       | 2      | 0       |
| Edema face                                 | 1       | 1      | 0       | 0       | 0      | 0       |
| Fall                                       | 2       | 1      | 1       | 2       | 1      | 1       |
| Ferritin high                              | 1       | 0      | 1       | 0       | 0      | 0       |
| Gastric hemorrhage                         | 1       | 1      | 0       | 1       | 1      | 0       |
| Heartbeats increased                       | 1       | 1      | 0       | 0       | 0      | 0       |
| Hyperkalemia                               | 2       | 2      | 0       | 2       | 2      | 0       |
| Hypotension                                | 1       | 1      | 0       | 0       | 0      | 0       |
| Iron overload                              | 2       | 2      | 0       | 0       | 0      | 0       |
| Leukopenia                                 | 1       | 1      | 0       | 0       | 0      | 0       |
| Melaena                                    | 1       | 1      | 0       | 1       | 1      | 0       |
| Musculoskeletal pain                       | 1       | 0      | 1       | 0       | 0      | 0       |
| Non-cardiac chest pain                     | 1       | 0      | 1       | 0       | 0      | 0       |
| Palpitations                               | 1       | 1      | 0       | 1       | 1      | 0       |
| Subconjunctival hemorrhage                 | 1       | 1      | 0       | 1       | 1      | 0       |
| Thrombectomy                               | 1       | 0      | 1       | 0       | 0      | 0       |
| Thrombocytopenia                           | 1       | 1      | 0       | 0       | 0      | 0       |
| Transient ischemic attacks                 | 1       | 1      | 0       | 1       | 1      | 0       |
| Vomiting                                   | 1       | 0      | 1       | 0       | 0      | 0       |
| Not coded                                  | 2       | 0      | 2       | 1       | 0      | 1       |
| **Overall other events**                   | 38      | 25     | 13      | 15      | 12     | 3       |
Supplementary Figure 1.
Blood pressure over time in individual participants according to randomized therapy. SBP-systolic blood pressure. DBP-diastolic blood pressure.