Kidney360 Publish Ahead of Print, published on October 15, 2020 as doi:10.34067/KID.0004342020

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

David M. Charytan[1], Jesse Y. Hsu[2], Finnian R. Mc Causland[3], Sushrut S. Waikar[4], T. Alp Ikizler[5], Dominic S. Raj[6], J. Richard Landis[2], Rajnish Mehrotra[7], Mark Williams[8], Marcelo DiCarli[9], Hicham Skali[10], Paul L. Kimmel[11], Alan S. Kliger[12], Laura M. Dember[13], For the Hemodialysis Novel Therapies Consortium*

[1]Division of Nephrology, Department of Medicine, NYU Grossman School of Medicine, New York, NY

[2]Department of Biostatistics, Epidemiology and Informatics, and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[3]Renal Division, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA

[4]Renal Section, Department of Medicine, Boston University Medical Center, Boston, MA

[5]Division of Nephrology and Hypertension, Department of Medicine, and Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, TN

[6]Division of Renal Diseases and Hypertension, George Washington University School of Medicine, Washington, DC

[7]Kidney Research Institute, Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA

[8]Renal Division, Beth Israel Deaconess Medical Center, Boston, MA

[9]Departments of Radiology and Medicine, Brigham and Women's Hospital, Boston, MA

[10]Cardiovascular Division, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA

[11]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

[12]Department of Medicine, Yale School of Medicine, New Haven, CT

[13]Renal, Electrolyte and Hypertension Division, and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Address for Correspondence:
David Charytan, MD MSc
NYU Langone Medical Center
426 1st Avenue C & D 689
New York, NY 10010
Phone: (646) 501-9086
David.charytan@nyulangone.org

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 three weeks from ISD 10 mg/HY 10 mg to ISD 40 mg/HY 75 mg three times/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 (CFR) on positron emission tomography.

Results: 17 individuals were randomized to ISD/HY (7) or placebo (N=10). All participants assigned to ISD/HY completed dose escalation to 40/75 mg, but dose reductions were required in 2 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 (PY)) than placebo (1.83 events/patient-year, P=0.04). In contrast, nausea (ISD/HY1.90 events/PY, placebo 0.50 events/PY, 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/PY) than placebo (6.31 events/PY). We did not detect between-group differences in the change in E' (P=0.34) —ISD/HY—mean increase of 0.6 cm/S (SD 1.1), placebo—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.

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

Introduction

The majority of patients with dialysis-dependent end stage kidney disease (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 rarefaction observed in advanced kidney disease.[3-5] Additional data suggest that 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.

Nitric oxide homeostasis may be reset with combination therapy with isosorbide dinitrate, a nitric oxide donor, and hydralazine 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/HY offers a particularly intriguing possibility for the treatment of individuals with ESKD, given the importance of nitric oxide 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 HD. HIDE is one of the studies conducted by the Hemodialysis Novel Therapies (HDNT) Consortium established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to conduct safety and feasibility studies of interventions for patients being treated with maintenance hemodialysis.

Methods

Design

HIDE (NCT02228408) was a double-blind placebo-controlled, dose-escalating trial comparing combination ISDH/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 HDNT 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 blood pressure ≥120 mm Hg for all sessions during the two weeks prior to screening and on the day of randomization. Major exclusion criteria included: a) unscheduled dialysis for hyperkalemia within 3 months or potassium concentration ≥ 6.5 mEq/L within 2 months prior to screening; b) pre-dialysis systolic blood pressure <100 mm Hg within 4 weeks prior to screening; c) ≥3 episodes during the prior 30 days of intra-dialytic hypotension or intra-dialytic symptoms of hypotension; d) severe mitral valve disease or mitral valve repair or replacement (these conditions might interfere with assessment of mitral annular E' velocity); e) current use of study medications, allergy to study medications, or use of contraindicated medication (sildenafil, vardenafil, tadalafil, monoamine oxidase inhibitors); f) severe aortic stenosis or left ventricular outflow obstruction; g) pregnancy or breastfeeding, and h) 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% vs >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 4-24, and then at week 26 and 30 for a total follow-up of 30 weeks to assess blood pressures, dialysis treatments records, symptoms of hypotension adverse events, and medication changes. ISD/HY or matching placebo medication was started at 10 mg/10mg three times daily, increased if tolerated to 20 mg/35 mg after one week, and then increased to the maximum dose of 40 mg/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 end of week 4 through 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 including 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 prior to randomization and week 24.

Outcomes

The principal objective was to evaluate safety and tolerability of ISDH/HY in maintenance HD patients. 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 blood pressure <80 mm Hg during ≥3 HD sessions per 30-day period, or treatment for intra-dialytic systolic blood pressure <100 mg Hg or symptoms of hypotension-e.g. with intravenous fluids or lower of 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: a) coronary flow reserve (CFR, the ratio of post-stress myocardial blood flow to resting myocardial blood flow) measured on rest and pharmacologic stress positron emission tomography (PET), and b) 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 Analysis

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 8 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 standard deviation for change in CFR of 0.5. Assuming the common standard deviation 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 (standard deviation, SD) or n (%) or median (interquartile range, IQR) according to distribution with $P<0.05$ considered significant. The primary analyses were based on incidence rate in intention-to-treat populations with all participants analyzed based on 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 geepack 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: 7 to ISD/HY and 10 to placebo (Figure 1). Median (IQR) age was 62 (53 – 66) years, and the majority of participants were male (71%), African American (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/m^2) compared with placebo (32.3 kg/m^2). In addition, both systolic (141 mmHg vs. 154 mm Hg) and diastolic pressure (72 vs. 77 mmHg) at baseline were numerically lower in those assigned to ISD/HY compared to 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 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. In the placebo group, the final dose was the lowest dose in one (10%) participant, the middle dose in 1 (10%), and the highest in the remaining 8 participants

(80%). Temporary discontinuation of study drug was required in 2 (29%) participants in the ISD/HY group and 3 (30%) in the placebo arm (Figure 2). None of the participants in either arm required permanent discontinuation of 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 Supplementary 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 kilograms) and placebo (0.6 ± 2.9 kg, P=0.37). The mean pre-dialysis blood pressure and mean nadir intra-dialytic blood pressure were similar in the ISD/HY and placebo groups ((Table 3, supplementary Figure 1). 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 not significant although power for individual events was low (Table 2). No adverse events required permanent discontinuation of the study medication. In addition to the pre-specified adverse events, there were 4 events of dizziness with ISD/HY participants and 1 with placebo (Supplementary Table 1). A similar proportion of adverse events of interest were considered to be related or possibly related to 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 non-serious 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 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 (Table 4, Supplementary Table 1). 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 hemodialysis to 24 weeks of a combination of isosorbide dinitrate and hydralazine at doses up to 40 mg of isosorbide and 75 mg of hydralazine 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 prior to this trial was that ISD/HY might result in hypotension with or without symptoms as a result of blood pressure lowering or decreased preload. Although our study was small, and excluded individuals with baseline systolic blood pressures <120 mm Hg, the findings are reassuring. Despite blood pressure being lower at baseline and during follow-up in the ISD/HY group, the rate of recurrent intradialytic hypotension events was actually 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 inter-dialytic hypotension over 24 weeks and this episode 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-ESRD 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 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 prior to expanding use of ISD/HY outside of clinical trials. Furthermore, the overall count of serious and non-serious 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 that 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 LV global strain at 6 months, respectively.

Combination ISD/HY is thought to improve nitric oxide bioavailability[22] and improves mortality and LV function in African American 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 nitric oxide homeostasis in late stage chronic kidney disease.[2-5] However, despite this promise and clinical use of this combination in some HD patients, 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 HD patients with hypertension were randomized to isosorbide mononitrate 30-120 mg daily or placebo daily for 24 weeks with dose adjustment to target blood pressure.[23] Left ventricular mass index as well as 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 blood pressure <140 mm Hg. At 24 weeks left ventricular mass index was lower in the nitrate group, although it is unclear whether 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 that therapy with nitrate donors is well-tolerated in ESKD and it advances the field in a few ways. In contrast to the previous studies, we assessed a target dose rather than a target blood pressure. Additionally, our study provides information on the use of nitrate donors in the context of United States dialysis patients. To our knowledge, ours is also the first trial conducted in the United States to specifically assess use of isosorbide dinitrate in ESKD. In addition, the current study reports on use of a nitrate donor in combination with hydralazine 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 mono-therapy. Furthermore, while the use of hydralazine 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 blood pressure 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 that 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 nitric oxide 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 dialysis patients 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 duration of follow-up was short. As a result, power for both safety and efficacy outcomes was low. Given the pilot design, we did not correct for multiple comparisons, and results of significance tests should be interpreted cautiously. Furthermore, the enrolled population included a high proportion of black and Hispanic hemodialysis patients not fully representative of the larger US HD population. Lastly, all 3 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 under-powered 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 that 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:

D.M. Charytan received research support from Medtronic Inc, Gilead, NovoNordisk, and Janssen, and consulting fees or fees for service on data safety or clinical events committees from Fresenius, Janssen, Astra Zeneca, Merck, Gilead, Allena Pharmaceuticals, and NovoNordisk.

S.S. Waikar reports Personal fees from Public Health Advocacy Institute, personal fees from CVS, personal fees from Roth Capital Partners, personal fees from Kantum Pharma, personal fees from Mallinckrodt, personal fees from Wolters Kluewer, personal fees from GE Health Care, personal fees from GSK, grants and personal fees from Allena Pharmaceuticals, personal fees from Mass Medical International, personal fees from Barron and Budd (vs. Fresenius), personal fees from JNJ, personal fees from Venbio, personal fees from Strataca, personal fees from Takeda, personal fees from Cerus, personal fees from Pfizer, personal fees from Bunch and James , personal fees from Harvard Clinical Research Institute (aka Baim), outside the submitted work.

T.A. Ikizler reports personal fees from Fresenius Kabi, Abbott Renal Care and International Society of Nephrology during the conduct of the study .

R. Mehrotra has received honoraria from Baxter HealthCare and he is a member of the Board of Trustees of the Northwest Kidney Centers.

M. Di Carli received research grants from SpectrumDynamics and Gilead Sciences, and consulting honoraria from Sanofi and General Electric.

H. Skali-received stock options from OptimizeRx for consulting/advisory roles, outside the submitted work.

L.M. Dember received compensation from the National Kidney Foundation for serving as Deputy Editor of the American Journal of Kidney Diseases, and consulting fees from Merck.

All remaining authors have nothing to disclose.

Funding: This trial was funded by the following cooperative agreements from the National Institute of Diabetes and Digestive and Kidney Diseases: U01 DK096189, U01 DK099923, U01 DK099914, and U01 DK099919. Additional support was provided by R21DK100772, the Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers. Dr Mc Caulsand was additionally supported by NIH grants K23DK102511 and R03DK122240.

Acknowledgements: The opinions expressed in this paper do not reflect those of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, the Department of Health and Human Services, or the Government of the United States.
All Group Members of the Hemodialysis Novel Therapies Consortium are listed in title except for Jonathan Himmelfarb.
Project officers from the National Institute of Diabetes and Digestive and Kidney Diseases worked collaboratively with the investigators in designing the study, monitoring the study performance, interpreting data, and preparing the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers. The authors would like to thank the participating patients, dialysis unit personnel, and dialysis provider organizations for their important contributions to this work.

Author Contributions: D Charytan: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing

J Hsu: Data curation; Formal analysis; Validation; Writing - original draft; Writing - review and editing

F Mc Causland: Investigation; Project administration; Supervision; Writing - review and editing

S Waikar: Project administration; Resources; Supervision; Writing - review and editing

T. Ikizler: Funding acquisition; Investigation; Methodology; Writing - review and editing

D Raj: Methodology; Project administration; Writing - review and editing

J. R. Landis: Formal analysis; Methodology; Project administration; Supervision; Writing - review and editing

R Mehrotra: Funding acquisition; Methodology; Writing - review and editing

M Williams: Funding acquisition; Investigation; Project administration; Supervision; Writing - review and editing

M DiCarli: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing

H Skali: Conceptualization; Investigation; Methodology; Resources; Supervision; Validation; Writing - review and editing

P Kimmel: Methodology; Project administration; Writing - review and editing

A Kliger: Investigation; Methodology; Supervision; Writing - review and editing

L Dember: Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing

References

1. U.S. Renal Data System. USRDS 2018 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2018.

2. Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol* 2008; **294:** F1-9.

3. Aoki J, Ikari Y, Nakajima H*, et al.* Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* 2005; **67:** 333-340.

4. Charytan DM, Padera R, Helfand AM*, et al.* Increased concentration of circulating angiogenesis and nitric oxide inhibitors induces endothelial to mesenchymal transition and myocardial fibrosis in patients with chronic kidney disease. *Int J Cardiol* 2014; **176:** 99-109.

5. Amann K, Breitbach M, Ritz E*, et al.* Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 1998; **9:** 1018-1022.

6. Moreo A, Ambrosio G, De Chiara B*, et al.* Influence of myocardial fibrosis on left ventricular diastolic function: noninvasive assessment by cardiac magnetic resonance and echo. *Circ Cardiovasc Imaging* 2009; **2:** 437-443.

7. In *Empatica E4 Wristband* (vol 2018), Empatica

8. Shimoni S, Frangogiannis NG, Aggeli CJ*, et al.* Microvascular structural correlates of myocardial contrast echocardiography in patients with coronary artery disease and left ventricular dysfunction: implications for the assessment of myocardial hibernation. *Circulation* 2002; **106:** 950-956.

9. Jayaweera AR, Wei K, Coggins M*, et al.* Role of capillaries in determining CBF reserve: new insights using myocardial contrast echocardiography. *Am J Physiol* 1999; **277:** H2363-2372.

10. Charytan DM, Skali H, Shah NR*, et al.* Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. *Kidney Int* 2017.

11. Munzel T, Kurz S, Rajagopalan S*, et al.* Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase. A new action for an old drug. *J Clin Invest* 1996; **98:** 1465-1470.

12. Daiber A, Oelze M, Coldewey M*, et al.* Hydralazine is a powerful inhibitor of peroxynitrite formation as a possible explanation for its beneficial effects on prognosis in patients with congestive heart failure. *Biochem Biophys Res Commun* 2005; **338:** 1865-1874.

13. Cohn JN, Archibald DG, Ziesche S*, et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314:** 1547-1552.

14. Cohn JN, Tam SW, Anand IS*, et al.* Isosorbide dinitrate and hydralazine in a fixed-dose combination produces further regression of left ventricular remodeling in a well-treated black population with heart failure: results from A-HeFT. *J Card Fail* 2007; **13:** 331-339.

15. Taylor AL, Ziesche S, Yancy C*, et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; **351:** 2049-2057.

16. Park SJ, Lee SC, Jang SY*, et al.* E/e' ratio is a strong prognostic predictor of mortality in patients with non-valvular atrial fibrillation with preserved left ventricular systolic function. *Circ J* 2011; **75:** 2350-2356.

17. Murthy VL, Naya M, Foster CR*, et al.* Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. *JACC Cardiovasc Imaging* 2012; **5:** 1025-1034.

18. Shan K, Bick RJ, Poindexter BJ*, et al.* Relation of tissue Doppler derived myocardial velocities to myocardial structure and beta-adrenergic receptor density in humans. *J Am Coll Cardiol* 2000; **36:** 891-896.

19. Weidemann F, Herrmann S, Stork S*, et al.* Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* 2009; **120:** 577-584.

20. Kaul S. The role of capillaries in determining coronary blood flow reserve: Implications for stress-induced reversible perfusion defects. *J Nucl Cardiol* 2001; **8:** 694-700.

21. Tsagalou EP, Anastasiou-Nana M, Agapitos E*, et al.* Depressed coronary flow reserve is associated with decreased myocardial capillary density in patients with heart failure due to idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2008; **52:** 1391-1398.

22. Feelisch M, Brands F, Kelm M. Human endothelial cells bioactivate organic nitrates to nitric oxide: implications for the reinforcement of endothelial defence mechanisms. *Eur J Clin Invest* 1995; **25:** 737-745.

23. Li H, Wang SX. Improvement of hypertension and LVH in maintenance hemodialysis patients treated with sustained-release isosorbide mononitrate. *J Nephrol* 2011; **24:** 236-245.

24. Li H, Wang S. Organic nitrates favor regression of left ventricular hypertrophy in hypertensive patients on chronic peritoneal dialysis. *Int J Mol Sci* 2013; **14:** 1069-1079.

25. Tampe B, Steinle U, Tampe D*, et al.* Low-dose hydralazine prevents fibrosis in a murine model of acute kidney injury-to-chronic kidney disease progression. *Kidney Int* 2017; **91:** 157-176.

26. Tampe B, Tampe D, Zeisberg EM*, et al.* Induction of Tet3-dependent Epigenetic Remodeling by Low-dose Hydralazine Attenuates Progression of Chronic Kidney Disease. *EBioMedicine* 2015; **2:** 19-36.

Table 1. Baseline Characteristics

	Total (n=17)	ISD/HY (n=7)	Placebo (n=10)
Male	12 (70.6%)	5 (71.4%)	7 (70.0%)
Age (years)	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/African American	13 (76.5%)	5 (71.4%)	8 (80.0%)
Prefers 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/m^2)	29.2 (25.9 - 32.8)	25.9 (23.5 - 27.4)	32.3 (29.6 - 38.7)
Systolic BP (mmHg)	141.0 (136.0 - 173.0)	141.0 (134.0 - 150.0)	153.5 (136.2 - 176.8)
Diastolic BP (mmHg)	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 (years)	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, inter-quartile range
Abbreviations: ISD/HY, isosorbide dinitrate/hydralazine; BMI, body mass index;
BP, blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker;
*Baseline potassium was missing in 1 participant in the placebo group.

Table 2. Safety and Tolerability Outcomes

	ISD/HY (n = 7)		Placebo (n = 10)			
	Number (%) of participants with event	Number events per patient-year	Number (%) of participants with event	Number events per patient-year	P-Value*	P-Value†
Safety Outcomes						
Adverse Events	7 (100%)	11.40	10 (100%)	6.31	NA	<0.01
Serious Adverse Events	5 (71.4%)	3.56	3 (30%)	0.67	0.15	<0.01
Adverse Event Precluding Further Treatment with Study Medication	0 (0%)	0	0 (0%)	0	NA	NA
Adverse Events of Interest	6 (85.7%)	5.46	10 (100%)	4.15	0.41	0.34
Serious Hypotension	2 (28.6%)	0.71	1 (10%)	0.17	0.54	0.17
Inter-Dialytic Hypotension	0 (0%)	0	0 (0%)	0	NA	NA
Inter-Dialytic SBP<90 mmHg	1 (14.3%)	0.47	6 (60%)	1.83	0.13	0.04
Requiring medication change, ER visit, or hospitalization	1 (14.3%)	0.24	0 (0%)	0	0.41	0.18
Cardiovascular hospitalization	1 (14.3%)	0.24	0 (0%)	0	0.41	0.18
Stroke	0 (0%)	0	0 (0%)	0	NA	NA
Death	0 (0%)	0	0 (0%)	0	NA	NA
Tolerability Outcomes						
Headache	5 (71.4%)	1.90	7 (70%)	1.16	1.00	0.34
Nausea	4 (57.1%)	1.90	3 (30%)	0.50	0.35	0.03
Vomiting	1 (14.3%)	0.24	1 (10%)	0.17	1.00	0.80
Diarrhea	2 (28.6%)	0.48	2 (20%)	0.33	1.00	0.72
Anorexia	0 (0%)	0	0 (0%)	0	NA	NA

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

*P-value for comparing number of patients with event using chi-square or Fisher's exact tests

†P-value for comparing number of patients per patient-year using Poisson regression

Table 3. Blood Pressure Throughout Follow-Up

	Total n=17	ISD/HY n=7	Placebo n=10	P Value
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

Abbreviations: ISD/HY,isosorbide hydralazine; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation

Table 4. Relatedness of Adverse Events

Protocol Specified 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						
Classification	**Adverse Events**			**Serious Adverse Events**		
	Total	**ISD/HY**	**Placebo**	**Total**	**ISD/HY**	**Placebo**
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%)

*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
E/E'	14.22 (6.99)	12.38 (7.68)	-1.83 (2.01)	12.25 (3.71)	12.61 (3.37)	0.36 (2.95)	0.10
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/m^2	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/m^2	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/m^2	124.6 (17.9)	113.9 (25.9)	-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/m^2	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/g	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/g	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

Abbreviations: ISD/HY,isosorbide hydralazine; LV, left ventricle; BSA-body surface area, 2D, two dimensional; CFR, coronary flow reserve; cm/s, centimeters/second; mm, millimeter; mL/m^2, milliliter/square meter; mL/min/m^2, milliliter per minute per square meter; g/m^2, gram/square meter; | mL/min/g, milliliter per minute per gram.

*Corrected CFR normalizes the resting myocardial blood flow by dividing by the rate-pressure product (an index of cardiac workload), and multiplying by 10,000.

Figure Legends

Figure 1. Enrollment and follow-up of study participants

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 study drug. There were no permanent discontinuations of study drug. A closed circle/square represents ISD/HY whereas an open circle/square represents placebo.

Figure 1.

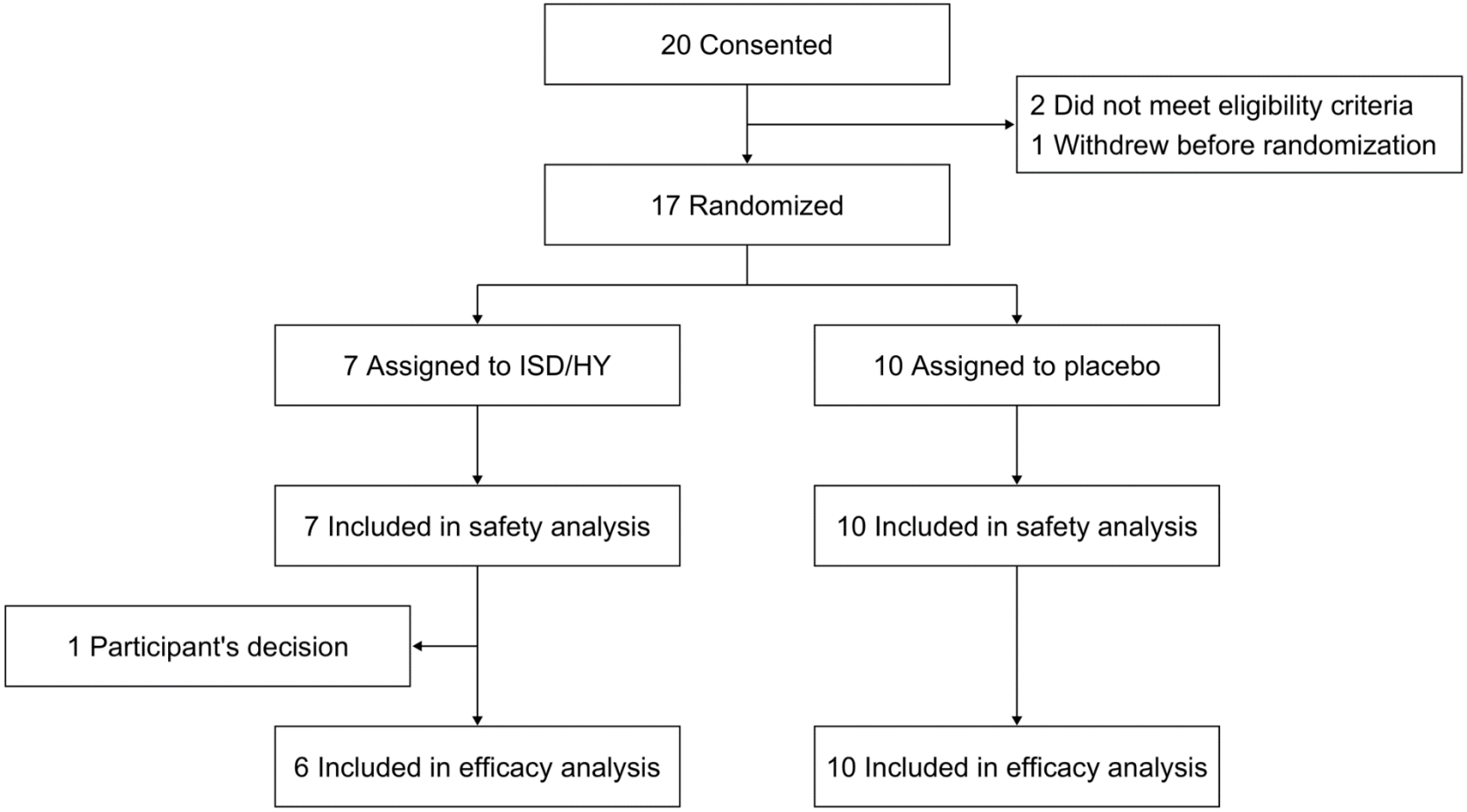
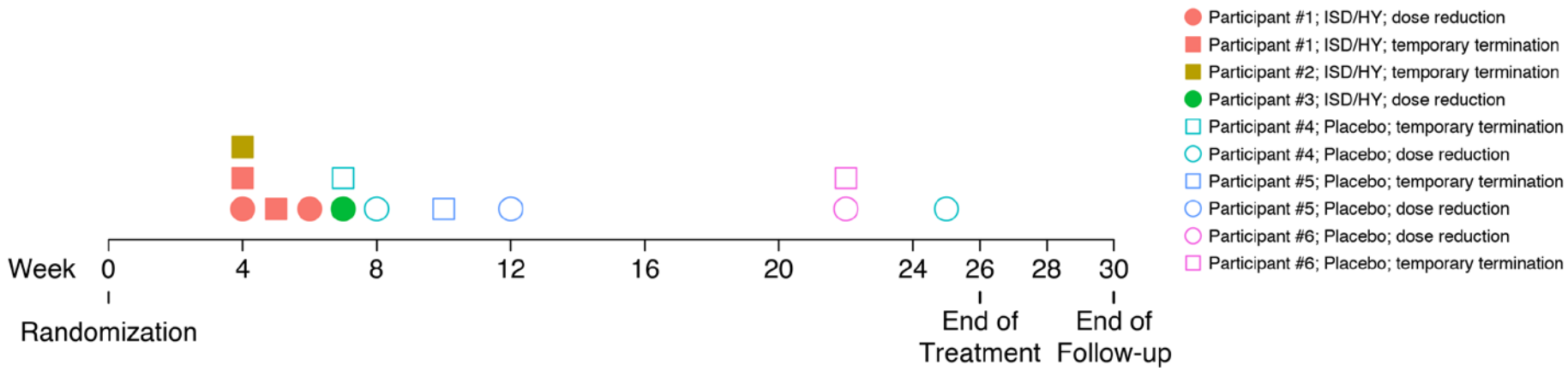

20 Consented
2 Did not meet eligibility criteria
1 Withdrew before randomization
17 Randomized
7 Assigned to ISD/HY
10 Assigned to placebo
7 Included in safety analysis
10 Included in safety analysis
1 Participant's decision
6 Included in efficacy analysis
10 Included in efficacy analysis

Figure 2.


Participant #1; ISD/HY; dose reduction
Participant #1; ISD/HY; temporary termination
Participant #2; ISD/HY; temporary termination
Participant #3; ISD/HY; dose reduction
Participant #4; Placebo; temporary termination
Participant #4; Placebo; dose reduction
Participant #5; Placebo; temporary termination
Participant #5; Placebo; dose reduction
Participant #6; Placebo; dose reduction
Participant #6; Placebo; temporary termination
Week 0 4 8 12 16 20 24 26 28 30
Randomization
End of Treatment
End of Follow-up