Hemodialysis International 2020; **24**:397–405

ORIGINAL ARTICLE

Volume Control

Fluid overload is associated with use of a higher number of antihypertensive drugs in hemodialysis patients

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ABSTRACT

Introduction: Hypertension is multifactorial, highly prevalent in the hemodialysis (HD) population and its adequate control requires, in addition to adequate volume management, often the use of multiple antihypertensive drugs. We aimed to describe the use of antihypertensive agents in a group of HD patients and to evaluate the factors associated with the use of multiple classes (≥3) of antihypertensives.

Methods: We analyzed the baseline data from the HDFit study. Clinically stable patients with HD vintage between 3 and 24 months without any severe mobility limitation were recruited from sites throughout southern Brazil. Fluid status was measured pre-dialysis with the Body Composition Monitor (BCM; Fresenius, Germany). Fluid overload (FO) was considered when the overhydration index (OH) was greater than 7% of extracellular water (OH/ECW > 7%) and overweight was defined as a body mass index (BMI) greater than 25 kg/m^2. Prescriptions of antihypertensive drugs were obtained from participants' reports and medical records. Logistic regression was employed to determine factors associated with excessive use of antihypertensive medication (≥3 classes).

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Conflict of interest: Roberto Pecoits-Filho is employed by Pontifícia Universidade Católica do Paraná, an employed by Arbor Research Collaborative for Health, a recipient of a scholarship from the Brazilian Council for Research (CNPq), and receives research grants, consulting fees, and honoraria from Baxter Healthcare and Fresenius Medical Care. Carlos E Poli-de Figueiredo and Américo L Cuvello Neto receive consulting fees and speaker honorarium from Fresenius Medical Care. Ana B Barra is an employee of Fresenius Medical Care Brazil. Jochen G. Raimann is employee of Fresenius Medical Care North America, or the subsidiary company Renal Research Institute. Maria E. F. Canziani is employed by Federal University of São Paulo, is a recipient of a scholarship from the Brazilian Council for Research (CNPq), and receives research grants, consulting fees, and honoraria from Baxter Healthcare and Fresenius Medical Care. All other authors declare no relevant conflicts of interest.

Disclosure of grants or other funding: This trial is being performed as a multi-center investigator-initiated study, whereby the site investigators and principal investigator are not being monetary funded for the conduct of study activities and are supporting the study with their own time and resources. This project is being supported by: (a) the study investigators, (b) the proponent institution Pontifícia Universidade Católica do Paraná, (c) the outpatient dialysis centers, and (d) the dialysis company Fresenius Medical Care. The steering committee includes nephrologists representing all the institutions and affiliates supporting this trial.

DOI:10.1111/hdi.12829

Findings: Of 195 studied patients, 171 with complete data were included (70% male, 53 ± 15 years old, 57% of them with FO). Pre-dialysis systolic blood pressure (SBP) was 150 ± 24 mmHg and patients used a median of 2 (1–3) antihypertensive drugs. Vasodilators (20%) were of lowest prevalence, use of other classes varied from 40% to 53%. Sixty-two (36%) subjects used ≥3 classes and presented a higher prevalence of diabetes and FO, lower prevalence of overweight, and higher SBP. In a logistic regression model age, BMI <25 kg/m^2, and OH/ECW > 7% were associated with excessive drug use.

Discussion: More than one-third of participants used ≥3 classes of antihypertensive drugs, and it was associated with older age, BMI <25 kg/m^2 and FO. Strategies that better manage FO may aid better blood pressure control and avoid the use of multiple antihypertensive medications.

Keywords: fluid overload, antihypertensive, blood pressure, hemodialysis, chronic kidney disease

INTRODUCTION

Elevated blood pressure (BP) is highly prevalent in the dialysis population affecting more than 80% of patients[1,2] and is a risk factor for cardiovascular outcomes, including ventricular hypertrophy, cardiac insufficiency, and cardiovascular events.[3,4]

The pathophysiology of blood pressure abnormalities is complex and most often pertains three principal factors: cardiac function (resulting in variations of cardiac output), arterial stiffness (affecting mainly large arteries), and intensity of wave reflections (principally vasomotor tone of resistance arterioles). The complex pathogenesis of blood pressure elevation explains the difficulty to determine the optimal treatment, which is even further complicated in the dialysis population due to the high prevalence of fluid overload.[5] Sodium intake retained in the body due to the lack of renal function, consequent thirst-driven fluid intake and volume overload are the main pathogenic mechanisms of blood pressure elevation in this population. However, other factors such as increased arterial stiffness, activation of the renin-angiotensin-aldosterone system, sleep apnea, activation of the sympathetic nervous system and use of recombinant erythropoietin are also be involved further accentuating the complexity.[2]

While volume management is central to control BP in dialysis patients, additionally the prescription of antihypertensive medication is often necessary, which in some cases may even require the combination of several classes of antihypertensive drugs.[6] Studies evaluating the amount of prescribed hypotensive drugs reported a median of open prescriptions ranging from 2 to 2.5 classes per participant.[7–10] While the vast majority of HD patients use these drugs, the pre-dialysis blood pressure is on average greater than 140 mmHg in 55%–75% of patients. This implies that the prescribed antihypertensive drugs do not provide sufficient blood pressure control in a majority of the population.[11]

The pathways by which these drugs lower blood pressure are well established and were recently reviewed by Bakris and colleagues. Common pathways include effects on the renin-angiotensin-aldosterone system (RAAS), blockade of sympathetic receptors and influences on the excretion of fluid and volume in those with residual renal function. However, in the presence of sodium and fluid overload these agents (except for diuretics) are not able to treat the main cause of hypertension in dialysis patients[12] which notably is considered a predictor of mortality in HD patients independent of its effects on the cardiovascular system.[13–16]

Besides fluid overload, other factors have been associated with the difficulty of controlling blood pressure in these patients, such as medical advice of not taking antihypertensive drugs prior to dialysis,[17] lack of adherence to medication prescriptions for different reasons,[18] poorly controlled diabetes.[19] High sodium intake[20] which is associated with excessive water intake and greater interdialytic weight gains, makes it difficult to achieve and maintain optimal post-dialysis target weights.[21]

Thus, the main objectives of the present study were to describe the use of antihypertensives drugs in a multicenter national population and to evaluate the role of fluid overload and other possible factors associated with the use of multiple classes of antihypertensive drugs among HD patients.

METHODS

This is a cross-sectional analysis of baseline data from the "HemoDiaFiltration on Physical Activity and Self-Reported Outcomes: A Randomized Controlled Trial

(HDFIT)", the design of which was described previously.[22] Briefly, HDFit was a multicenter open controlled randomized clinical trial with the primary aim to investigate the effect of high volume online hemodiafiltration (HDF) compared to high flux hemodialysis (HD) on physical activity reflected by the number of steps measured by accelerometer.

All patients from 13 dialysis centers in Brazil were over 18 years old, underwent HD treatment between 3 and 24 months, received adequate dialysis doses (Kt/V ≥ 1.2), an arteriovenous fistula/graft or permanent central-venous catheter with adequate flow and not considered as having limited mobility. Participants gave informed consent for participation. The HDFIT study (registered at clinicaltrials.gov #NCT02787161) was conducted according to the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Pontifícia Universidade Católica do Paraná (central request #54926916.7.1001.0020; approval number 1.538.784).

Data was collected in an electronic case report form (eCRF) in the software REDCap. We collected demographic (gender, age, educational level and race) and clinical data (pre-dialysis weight, pre-dialysis systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI) [calculated by weight (kg)/height (m^2)]. SBP, DBP, and weight were obtained according to the individual clinics' protocols and routine practice at the same time as the bioimpedance evaluation. Although there was no implementation of a standardized protocol, the approach to BP capture, including a 10 minutes rest before measurement, evaluation in the arm without the fistula, and a sitting position was recommended during the initiation visit and the investigator's meetings. Patients with a BMI ≥25 kg/m^2 were considered overweight or obese according to WHO criteria.[23] A bioimpedance measuring the conductance and reactance at different frequencies was used to assess the hydration status (Body Composition Monitor (BCM); Fresenius Medical Care, Bad Homburg, Germany).[24] Different hydration status indexes are provided by this bioimpedance, including extracellular water (ECW), intracellular water (ICW), total body water (TBW), and overhydration index (OH). It was performed before the dialysis session according to the manufacturer recommendations. Volume overload was defined as a relative OH value (OH normalized to ECW or OH/ECW) ≥7%, corresponding to the value of the 90th percentile for the reference cohort.[25] We also calculated the number of participants with greater overhydration (OH/ECW > 15%). One single measure of BCM and BP performed simultaneously was used for this analysis.

Information on the use of antihypertensive drugs (classes) was obtained from the patient medical records and checked with participants. In case of any conflict between two sources, we considered the participants' report. The antihypertensives were classified in the following classes: RAAS [including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB)], beta-blockers (BB); calcium channel antagonist (CCA); vasodilators and diuretics. For the analyses, we compared the participants who used none or up to two classes of antihypertensive drugs to those that used three or more classes.

Statistical analysis was performed using SPSS software, version 22.0 for Windows (SPSS, Inc. Chicago, IL, U.S.A.). The results were expressed as mean and standard deviation, median and interquartile or in percentages, when appropriate. For the correlation analysis, Pearson or Spearman tests were used according to the distribution of the variables. To compare variables between groups, Student's t test or Mann-Whitney U test were used, as appropriate. Categorical variables were compared using chi-square test. A P value less than 5% was considered significant.

Logistic regression analysis was used to assess independent predictors of the use of three or more antihypertensive classes. P value <0.05 was used as criteria for inclusion in the model. Diabetes mellitus (DM) was not included due to its influence on participants' OH/ECW (12.1 ± 7.3% in DM vs. 6.6 ± 8.5% in non-DM; $P < 0.001$).

RESULTS

A total of 195 patients participated in the HDFit study, 171 had complete bioimpedance data and were included in this analysis. The prevalence of antihypertensive drug prescription was demonstrated in Figure 1. Only 16% did not have an open prescription of an antihypertensive

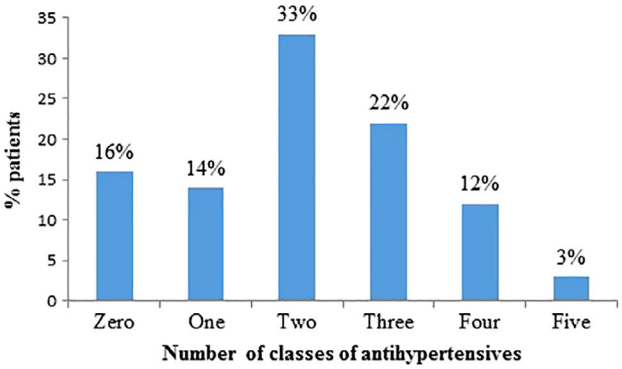

Figure 1 Distribution of participants according to the number of antihypertensive classes prescription. [Color figure can be viewed at wileyonlinelibrary.com]

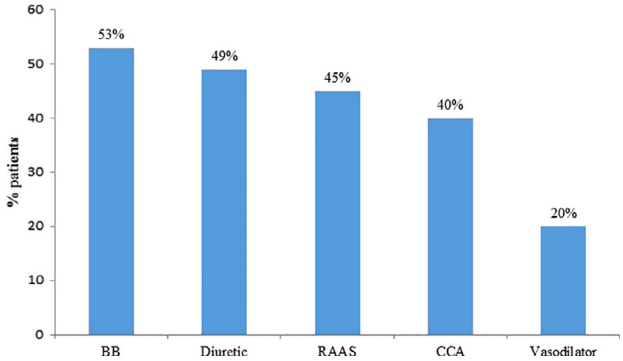

Figure 2 Distribution of participants according to antihypertensive classes. BB = beta blocker; RAAS = inhibitors of the resin anginotensin aldosterone system; CCA = calcium channel antagonist. [Color figure can be viewed at wileyonlinelibrary.com]

drug at all. The lowest prevalence was for vasodilators (20%), whereas of RAAS, BB, CCA, and diuretics, the prescription varied from 40% to 53%. These data are shown in Figure 2.

Regarding chronic kidney disease (CKD) etiology, 28% had diabetic nephropathy, 26% hypertensive nephrosclerosis, 16% chronic glomerulopathy, 6% polycystic kidney disease, 8% undetermined, and 16% other.

Main demographic and clinical data of participants stratified as per the number of antihypertensive classes are reported in Table 1. The study population included more male participants (70%) and 33% had diabetes mellitus (DM). Pre-dialysis SBP was high (150 ± 24 mmHg) and participants used 2 (1–3) classes of antihypertensive drugs. Eighty-one percent had hypertension, 32% some cardiovascular disease [coronary artery disease (17%), heart failure (8%), and arrhythmia (2%)], 2% cancer, 1% lupus, and only 9% had no CKD-associated morbidity.

Sixty-two (36%) used three or more classes of antihypertensives. Compared to the others (who used up to two classes), they were older (56.2 ± 14.4 vs. 50.9 ± 15.3 years old; $P = 0.03$), had a higher prevalence of diabetes (49% vs. 24%, $P < 0.001$), lower body mass index (26.1 ± 4.3 vs. 28.2 ± 5.3 kg/m^2; $P < 0.01$) as well as lower prevalence of overweight or obesity (53% vs. 70%; $P = 0.03$).

Table 1 Clinical and demographic characteristics according to antihypertensive classes groups

Parameters	All patients(n = 171)	Antihypertensive classes 0–2 (n = 109)	≥ 3 (n = 62)	*P*
Age (years)	52.8 ± 15.1	50.9 ± 15.3	56.2 ± 14.4	0.03
Gender				0.31
Male	121 (70%)	80 (73%)	41 (66%)	
Female	50 (30%)	29 (27%)	21 (34%)	
Race				0.20
White	94 (55%)	60 (55%)	34 (55%)	
Brown	57 (10%)	39 (36%)	18 (29%)	
Black	18 (33%)	10 (9%)	8 (13%)	
Yellow	2 (1%)	0 (0%)	2 (3%)	
Years at school				0.93
≤8	57 (33%)	37 (34%)	20 (32%)	
9-11	70 (41%)	45 (41%)	25 (41%)	
>11	44 (26%)	27 (25%)	17 (27%)	
Diabetes mellitus	53 (33%)	26 (24%)	30 (49%)	0.001
BMI				
kg/m^2	27.4 ± 5.0	28.2 ± 5.3	26.1 ± 4.3	0.01
>25 kg/m^2	109 (64%)	76 (70%)	33 (53%)	0.03
SBP				
mmHg	150 ± 24	146 ± 22	157 ± 25	0.002
>140 mmHg	121(71%)	72 (66%)	49 (79%)	0.07
DBP				
mmHg	80 ± 14	81 ± 16	80 ± 13	0.92
>140 mmHg	49 (29%)	32 (29%)	17 (27%)	0.79
OH/ECW				
%	8.52 ± 8.52	7.1 ± 8.3	11.0 ± 8.4	0.003
>7%	98 (57%)	54 (49%)	44 (71%)	0.006
>15%	38 (22%)	19 (17%)	19 (31%)	0.04
Total antihypertensive classes	2 (1–3)	2 (0–2)	3 (3–4)	<0.001

Abbreviations: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; OH = overhydration; ECW = extracellular water.

Table 2 Logistic regression analysis of independent predictors of use of three or more classes of antihypertensives (R^2 = 0.12)

Variables	OR	(95% CI)	*P*
Age (years)	1.02	(1.00–1.04)	0.047
BMI < 25 kg/m^2	2.15	(1.08–4.27)	0.038
OH/ECW > 7%	2.15	(1.09–4.3)	0.028

Abbreviations: BMI = body mass index; OH = overhydration; ECW = extracellular water.

Participants using more hypotensive drugs also had higher SBP (157 ± 25 vs. 146 ± 22 mmHg; *P* = 0.002), OH/ECW (11.0 ± 8.4% vs. 7.1 ± 8.3%; *P* = 0.003) and prevalence of patients with fluid overload (71% vs. 49%; *P* = 0.006). In the correlation analysis, there was a positive association between OH/ECW and systolic blood pressure (*R* = 0.15; *P* = 0.04).

In the logistic regression analysis (Table 2), the factors associated with the use of three or more classes of antihypertensives were age [OR = 1.02 (95% CI 1.00–1.04); *P* = 0.047], BMI < 25 kg/m^2 [OR = 2.15 (95% CI 1.08–4.27); *P* = 0.038], and OH/ECW > 7% [OR = 2.15 (95% CI 1.09–4.30); *P* = 0.028].

DISCUSSION

We found more than one-third of participants using three or more classes of antihypertensive drugs without adequate control of blood pressure. Based on the results of the logistic regression fluid overload, increased age and BMI lower than 25 kg/m^2 were independent predictors of the use of multiple drugs.

Despite the use of antihypertensives, pre-dialysis SBP (150 ± 24 mmHg) was higher than recommended, a result usually consistent with other studies.[7,26–29] These results could be influenced by the fact that patients did not use all the antihypertensive drugs prescribed prior to the HD session (either on their own or by medical advice) to reduce the risk of intradialytic hypotension and to facilitate ultrafiltration.[30] Also, noncompliance with medications is likely a contributor to uncontrolled hypertension in HD patients.[31,32]

Our patients used around 2 (25th and 75th percentile 1–3) classes of antihypertensive drugs. A similar result was found in an investigation that included more than 12,000 American patients who were on dialysis for six months (mean of 2.5 classes).[8] Smaller European studies identified a variation of 1 to 2.5 classes.[9,10]

In this study, at least one type of antihypertensive drug was used by 84% of the participants. In the literature, the frequency of use of hypotensive drugs has varied between 60% and 90% in HD population samples.[33,34] Regarding the antihypertensive class, when comparing our results with DOPPS (Dialysis Outcomes and Practice Patterns Study), which included in phase 5 (2012–2015) almost 9,000 participants from different regions of the world, the prevalence of the use of BBs was similar (53% vs. 50%), as were SRRAs (45% vs. 39%) and CCAs (40% vs. 41%). For diuretics, the use was much higher in our population (49% vs. 28%).[29] Lower HD vintage of our patients (up to 24 months) may be one of the reasons for this finding.

The drugs used by our participants are those usually recommended for the treatment of hypertension in HD patients.[6] However, no current guideline addresses the management of hypertension in HD.[7] A recent survey that included 160 U.S. practicing nephrologists found that the highest percentage of respondents prescribe CCAs (68%) because they consider it to be more effective in treating hypertension in dialysis patients, followed by BB (35%), ACE (32%), BRA (29%), and diuretics (25%).[30] Studies suggest that lower systolic and diastolic blood pressure with the use of antihypertensive drugs results in a 30% lower risk of cardiovascular events and mortality,[2,35,36] but adequately controlled hypertension is observed in only 65% of hypertensive patients.[37]

More than one-third (36%) of participants used three or more classes of antihypertensives. When compared to the other group, they were significantly older, had a higher percentage of people with DM, lower BMI, higher SBP and fluid overload. In the logistic regression analysis, the independent predictors for prescription of three or more classes of antihypertensives were increased age, BMI lower than 25 kg/m^2 and fluid overload.

We found higher age among participants using multiple drugs and according to regression analysis, every year increased by 2% the risk of using more antihypertensive classes. Indeed, age is the main determinant of arterial stiffness. Central arteries stiffen progressively with age and this is accompanied by elevated SBP.[38] Also, elderly patients may have greater fluid overload and poorer nutritional status than young patients in HD,[39] factors that also increase BP. Lee and colleagues did not find significant differences in the prescription of antihypertensives when they divided their sample of 82 patients by age (cut-off age 65 years).[40]

In this sample, patients using three or more classes of antihypertensives also had a higher prevalence of diabetes. Diabetes has been closely correlated with hypertension. Many pathophysiological mechanisms seem to influence this association such as insulin resistance in the nitric oxide pathway;

the stimulatory effect of hyperinsulinemia on sympathetic impulse, smooth muscle growth and sodium retention and the excitatory effect of hyperglycemia in the RAAS.[41] Poor DM control may also increase thirst, leading to increased interdialytic weight gain as shown in a study by Davenport and colleagues. In 175 patients evaluated, the interdialytic weight gain was lower in the group with the best glycemic control (2.8 ± 1.5% vs. 3.3 ± 1.3%; $P < 0.05$).[42] Although we did not evaluate glycemic control participants with DM had twice the OH/ECW than non-DM.

We found lower BMI among patients taking more antihypertensive classes and participants with BMI < 25 kg/m^2 were twice as likely to use three or more classes of antihypertensive drugs. We hypothesize that these findings may be a consequence of the better hemodynamic stability found in patients with greater body volume.[43] Overweight and obese patients may have better resilience against large volumes and faster rates of ultrafiltration during dialysis and a lower likelihood of transient hypotension. This may attenuate sympathetic and RASS activity.[44] In fact, it is believed that hemodynamic stability may play a role in the survival advantage of obesity found in advanced CKD.[45] In addition, there is evidence that patients with lower BMI have a higher percentage of interdialytic weight gain,[46] which may influence the need for a higher prescription of hypotensive agents. A study involving 163,668 Japanese patients comparing the characteristics of those taking or not antihypertensive drugs did not find a difference in BMI between the groups (21.1 ± 1.4 vs. 21.1 ± 1.3 kg/m^2).[47] However, the mean BMI was much lower than in our patients.

In this study, patients that used more classes of antihypertensives had a higher SBP. Besides the possibility of lack of adherence as previously discussed, this finding may be a consequence of the higher fluid overload found in this group (71% vs. 49%).

More than half (57%) of participants had fluid overload (OH/ECW > 7%). There is no diagnostic consensus for fluid overload classification. Some studies use OH cut points (eg, 2 L) and others OH/ECW ratio.[9,48] The prevalence in other studies, with different cut-offs, ranged from 25% to 85%.[49–52] A study that used the same parameter as ours found the same prevalence (58%).[9]

Patients with fluid overload were twice as likely to use multiple classes of antihypertensives. Volume excess is considered the main factor responsible for the increase in BP in the HD population.[12] Therefore, the patient's blood pressure varies during an HD session, as well as between sessions.[53] Dekker et al., in a large cohort of patients on dialysis (MONDO n = 8883) showed that the higher the fluid overload, the higher the pre-dialysis BP.[54] The study by Wizemann et al. which included 269 chronic HD patients, showed that severe volume overload (OH/ECW > 15%) was an independent predictor of mortality.[55] Using the same cut-off point we used (OH/ECW > 7%), Yilmaz et al. showed that fluid overload was an independent predictor of pulmonary arterial hypertension.[56] Volume overload can lead to congestive heart failure and pulmonary edema, so volume control strategies (gradual reduction of post-dialysis body weight and salt-restricted diet) can lead to successful blood pressure control as shown by Ok et al. The authors reported that 90% of patients submitted to these strategies had BP normalized, without the use of antihypertensive drugs.[11] Onifriesco et al. also showed a significant reduction of SBP (145.4-138.9 mmHg) in 131 hemodialysis patients after improvement of fluid overload.[57] Another alternative is performing HD sessions more frequent and more prolonged than conventional.[12]

Since patients treated by three or more antihypertensives also had the highest blood pressure, the results could also be interpreted as that prescribing multiple antihypertensives may have caused both the high blood pressure and fluid overload. This alternative interpretation is possible since antihypertensives are known to interfere with blood volume homeostasis during hemodialysis, making it more challenging to remove fluid by ultrafiltration. Further studies will be necessary to address which of these potential causative pathways is the most critical determinant of fluid overload in hemodialysis patients.

As limitations, we did not evaluate medications doses and prescription adherence, the agreement between patients report and medical records, as well as the interdialytic weight gain. We used only a single measure of predialysis BP. According to KDIGO guidelines, the measure provided by outpatient blood pressure monitoring between dialysis sessions should be considered as the standard to define BP in HD patients.[58] As a strength, we highlight the inclusion of a population of multiple dialysis centers.

In conclusion, in this stable HD population, we found a significant number of patients using multiple classes of antihypertensives, and the associated factors were age, BMI lower than 25 kg/m^2 and fluid overload (OH/ECW > 7%). Nonpharmacological strategies to improve fluid overload may contribute to decreasing the need for multiple antihypertensive drugs, reducing treatment cost and impacting positively in the quality of life of this population.

ACKNOWLEDGMENTS

We would like to acknowledge and thank the participating dialysis centers and staff conducting this trial; the

EPICENTER ACRO staff managing the trial; and the external advisory committee members Bernard Cannaud, MD, PhD, Cristina Marelli, MD, Peter Kotanko, MD, FASN, Len Usvyat, PhD, and Rodrigo S. Reis, PhD, MSc. On Behalf of the HDFIT Study Investigators.

Manuscript received August 2019; revised February 2020; accepted February 2020.

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