KI REPORTS
KIReports.org
CLINICAL RESEARCH

Association of Calcium Channel Blocker Use With Intradialytic Hypotension in Maintenance Hemodialysis

Armida Lefranc Torres[1,2], Simon Correa[3,4] and Finnian R. Mc Causland[1,2]

[1]Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA; [3]Yale New Haven Hospital, New Haven, Connecticut, USA; and [4]Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Introduction: Calcium channel blockers (CCBs) are common antihypertensive agents among patients receiving hemodialysis (HD). Despite this, the association of CCBs with intradialytic hypotension (IDH), an important adverse outcome that is associated with cardiovascular morbidity and mortality, remains largely unexplored.

Methods: Using kinetic modeling sessions data from the Hemodialysis (HEMO) Study, random effects regression models were fit to assess the association of CCB use versus nonuse with IDH (defined as systolic blood pressure [SBP] $<$ 90 mm Hg if pre-HD SBP $<$ 160 mm Hg or $<$ 100 mm Hg if pre-HD SBP $\geq$160 mm Hg). Models were adjusted for age, biological sex (distinguishing between males and females), race, randomized Kt/V and flux assignments, heart failure, ischemic heart disease, peripheral vascular disease, diabetes mellitus, blood urea nitrogen, ultrafiltration rate, access type, pre-HD SBP, and other antihypertensives.

Results: Data were available for 1838 patients and 64,538 sessions. At baseline, 49% of patients were prescribed CCBs. The overall frequency of IDH was 14% with a mean decline from pre- to nadir-SBP of 33 $\pm$ 15 mm Hg. CCB use was associated with lower adjusted risk of IDH, compared with no use (incidence rate ratio [IRR]: 0.84; 95% confidence interval [CI]: 0.78–0.89). The association was most pronounced for those in the pre-HD SBP lowest quartile (IRR: 0.77; 95% CI: 0.70–0.85); compared with the highest quartile (IRR: 0.86; 95% CI: 0.77–0.97; *P*–interaction $<$ 0.001).

Conclusion: Among patients receiving HD, CCB use was associated with a lower risk of developing IDH, independent of pre-HD SBP and other antihypertensives use. Mechanistic studies are needed to better understand the effects of CCB and other antihypertensives on peridialytic blood pressure (BP) parameters among patients receiving HD.

Kidney Int Rep (2024) **9,** 1758–1764; https://doi.org/10.1016/j.ekir.2024.03.024
KEYWORDS: antihypertensives; blood pressure; calcium channel blocker; HEMO study; hemodialysis; intradialytic hypotension

Despite advances in dialysis techniques and general medical care, the mortality of patients with end-stage kidney disease receiving maintenance HD remains unacceptably high. Most patients still succumb to cardiovascular disease, which accounts for about 40% of deaths and substantial morbidity.[1]

One of the main complications of maintenance HD is IDH, which affects ~10% to 50% of HD sessions, depending on the definition considered.[2] The consequences of IDH include end organ hypoperfusion, with associated risks of cardiac arrhythmias, coronary ischemia, cerebral ischemia, vascular access thrombosis, as well as a higher risk of death.[3,4] The optimal BP for patients receiving HD is not clear, and the timing and optimal regimen for antihypertensive use among these patients remains the source of much debate.[5]

CCBs are one of the most commonly prescribed antihypertensives among patients with HD (~45% of adult patients), likely related to once-daily dosing, minimal clearance by HD, and lack of effect of serum potassium concentration.[6–8,9] In a previous observational study of United States patients, compared to no use, CCBs were associated with a lower risk of all cause and cardiovascular mortality,[10] despite similar reported

Correspondence: Finnian R. Mc Causland, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, MRB-4, Boston, Massachusetts 02115, USA. E-mail: fmccausland@bwh.harvard.edu

Received 17 October 2023; revised 26 February 2024; accepted 18 March 2024; published online 27 March 2024

comorbidities between users and nonusers at baseline. In a recent systematic review and meta-analysis, dihydropyridine CCBs were noted to lower predialysis systolic and diastolic BP, compared with placebo or no treatment. A lower risk for IDH was observed for CCB use compared to no use, although this was nonsignificant, perhaps reflective of the limited sample size.[11]

Based on the above reports, we explored the association of CCB use with IDH using the detailed session level data from the HEMO study,[12] hypothesizing that CCB use (vs. no use) would be associated with lower risk of IDH among patients receiving outpatient maintenance HD.

METHODS

Study Design and Population

The design and results of the HEMO study have been reported.[12,13] Briefly, the HEMO study was a 2-by-2 factorial design clinical trial that randomized 1846 patients receiving thrice weekly HD to higher versus standard target Kt/V and higher versus lower membrane flux. Patients were excluded from the study if they had baseline serum albumin <2.6 g/dl, if they were unable to achieve an equilibrated Kt/V ≥ 1.3 within 4.5 hours in 2 of 3 consecutive HD sessions targeting the higher dose goal, if their residual kidney urea clearance was >1.5 ml/min per 35 l of urea distribution volume, or they had end-stage morbid conditions. Baseline exposure and outcome data were available for 1838 individuals who were included in the present analyses. During follow-up, these patients contributed a total of 64,538 sessions.

Table 1. Baseline characteristics according to calcium channel blocker use

Characteristics	Not taking CCB (n = 930)	Taking CCB (n = 908)	P-value
Age, yr	58 ± 14	57 ± 15	0.05
Female, n (%)	518 (56%)	514 (57%)	0.69
Black, n (%)	552 (59%)	598 (66%)	0.004
Diabetes mellitus, n (%)	400 (43%)	420 (46%)	0.16
Ischemic heart disease, n (%)	384 (41%)	338 (37%)	0.07
Heart failure, n (%)	371 (40%)	358 (39%)	0.84
Peripheral vascular disease, n (%)	242 (26%)	228 (25%)	0.65
Pre-HD SBP, mm Hg	147 ± 26	157 ± 25	<0.001
Post-HD SBP, mm Hg	132 ± 24	142 ± 25	<0.001
Ultrafiltration rate, ml/kg/h	11.8 ± 5.5	12.7 ± 5.9	<0.001
Ultrafiltration volume, l	2.9 ± 1.3	2.9 ± 1.3	0.25
Post-HD weight, kg	70.4 ± 15.0	68.1 ± 14.6	<0.001
Access			0.76
Graft	548 (58%)	544 (59%)	
Fistula	317 (34%)	308 (34%)	
Catheter	65 (7%)	56 (6%)	
Pre-HD BUN, mg/dl	57.1 ± 17.3	57.1 ± 17.3	0.96
Hemodialysis vintage, yr	2.3 [1.1, 4.9]	2.3 (1.1, 4.7)	0.84
Angiotensin converting enzyme, n (%)	203 (22%)	257 (28%)	0.001
Beta blockers, n (%)	257 (28%)	296 (33%)	0.02
Alpha-1 blockers, n (%)	42 (4.5%)	83 (9%)	<0.001
Other hypertensives, n (%)	145 (16%)	194 (21%)	0.001
Nitrates, n (%)	152 (16%)	163 (18%)	0.36
Angiotensin II receptor blockers, n (%)	8 (0.9 %)	17 (2%)	0.06
Minoxidil, n (%)	15 (2%)	17 (2%)	0.67
Adrenergic blockers, n (%)	29 (3%)	32 (3%)	0.63
Total number of antihypertensives, n	1 [0, 1]	1 [0, 2]	<0.001
Higher Kt/V assignment, n (%)	464 (50%)	451 (50%)	0.92
Higher flux assignment, n (%)	454 (49%)	463 (51%)	0.35
Serum Albumin, g/dl	3.9 ± 0.3	3.9 ± 0.4	0.39
Serum Phosphorous mg/d	5.7 ± 1.9	5.8 ± 1.9	0.26
Hematocrit, (%)	34 ± 4	33 ± 5	0.25

BUN, blood urea nitrogen; CCB, calcium channel blocker; post-HD, posthemodialysis; pre-HD, prehemodialysis; SBP, systolic blood pressure.

Exposures and Outcomes

The primary exposure of interest was the usage of CCBs. Medication data was collected by dedicated study staff on specific case report forms every 6 months. Subcategories of CCBs were not recorded. The primary outcome was the development of IDH, defined as a nadir intra-HD SBP < 90 mm Hg if pre-HD SBP < 160 mm Hg or < 100 mm Hg if pre-HD SBP ≥160 mm Hg (Nadir 90/100), this definition has been associated with the risk of death in previous analyses from HEMO.[14] In sensitivity analyses, other IDH definitions were considered, including Fall20 (pre-HD SBP − nadir SBP ≥20 mm Hg), Fall30 (pre-HD SBP − nadir SBP ≥30 mm Hg), Fall20Nadir90 (pre-HD SBP − nadir SBP ≥20 mm Hg and nadir SBP <90 mm Hg), Fall30Nadir90 (pre-HD SBP − nadir SBP ≥30 mm Hg and nadir SBP <90 mm Hg), and Nadir90 (intra-HD SBP <90 mm Hg regardless of pre-HD SBP); this definition is also associated with an increased risk of death,[14] and HEMO definition of IDH which was defined as fall in SBP resulting in intervention of ultrafiltration reduction, blood flow reduction, or saline administration.[12] As a secondary outcome, we considered the decline in SBP from pre- to nadir-HD as a continuous variable. Detailed BP data were abstracted from monthly kinetic modeling sessions.

Study Data

Data for the HEMO Study were collected through a variety of methods, including chart review, participant interviews, and self-reported questionnaires. Demographic information such as age, sex, and self-reported race were recorded at baseline. Comorbidities (diabetes, peripheral vascular disease, and heart failure) were recorded annually; HD treatment data were recorded monthly; and general laboratory parameters were recorded every 6 months. Comorbidities were graded using the Index of Co-existing disease scale and were dichotomized for the present analyses.[15]

Table 2. Association of calcium blocker use with alternative definitions of intradialytic hypotension

IDH definition	Not taking CCBs *n/N* (%)	Taking CCB *n/N* (%)	*P*-value
Nadir90/100	5589/34,703 (16%)	3228/29,835 (11%)	<0.001
Fall20	23,601/34,703 (68%)	20,101/29,835 (67%)	0.09
Fall20Nadir90	4142/34,703 (12%)	2301/29,835 (8%)	<0.001
Fall30	17,330/34,703 (50%)	14,961/29,835 (50%)	0.60
Fall30Nadir90	3582/34,703 (10%)	2159/29,835 (7%)	<0.001
Nadir90	4824/34,703 (14%)	2454/29,835 (8%)	<0.001
Nadir100	9294/34,703 (27%)	5134/29,835 (17%)	<0.001
HEMO study defined IDH	6499/34,845 (19%)	4958/29,952 (17%)	<0.001

CCB, calcium channel blocker; IDH, intradialytic hypotension.

Statistical Analysis

Continuous variables were reported as mean (± SD) for normally distributed data, or median (25th–75th percentile) for nonnormally distributed data, with baseline (first kinetic modeling session) comparisons made using *t* tests or Wilcoxon rank sum tests, as appropriate. Categorical variables were examined by frequency distribution, recorded as proportions, and comparisons made using the χ^2 test. Unadjusted and adjusted random effects Poisson regression models were fit to examine the association of CCB use with IDH to account for the repeated measures and nonindependence of data. Model 1 adjusted for age, sex, and race (Black vs. non-Black). Model 2 additionally adjusted for randomized Kt/V assignment, randomized flux assignment, heart failure, peripheral vascular disease, diabetes mellitus, access type (catheter, fistula, or graft), predialysis blood urea nitrogen, ultrafiltration rate, and pre-HD SBP. Model 3 further adjusted for the baseline use of angiotensin converting enzyme inhibitors, beta-blockers, alpha-1 blockers, nitrates, angiotensin II receptor blockers, minoxidil, adrenergic blockers, and other antihypertensives. Model 3b adjusted for the same variable as Model 2, with the addition of the total count of antihypertensive medications. Analogous models using random effects linear regression were used with the pre-HD, nadir intra-HD, and post-HD systolic BP as the outcomes. In exploratory analyses, in an attempt to minimize potential selection bias, we restricted the analyses to patients who did not have any other antihypertensive medications prescribed.

For the present analyses, data recorded less frequently than monthly was carried forward to each HD session until the next update was available. Relevant cross product terms were included in Model 3 to assess if the association of CCB with IDH differed according to prespecified variables (sex, race, pre-HD systolic BP, heart failure, randomized Kt/V assignment, and randomized flux assignments). All analyses were performed using Stata/MP, version 16 (StataCorp), at a 2-sided alpha of 0.05, without correction for multiple hypothesis testing. Missing data was not imputed (<1% for all model variables).

Table 3. Association of CCB use (vs. nonuse) with intra dialytic hypotension

Outcome	Model	Incidence rate ratio (95% CI) for CCB vs. none	*P*-value
Nadir90/100			
	Unadjusted	0.81 (0.76–0.86)	<0.001
	Model 1	0.81 (0.76–0.87)	<0.001
	Model 2	0.84 (0.78–0.89)	<0.001
	Model 3	0.85 (0.79–0.90)	<0.001
	Model 3b	0.84 (0.79–0.90)	<0.001
	Subgroup without other antihypertensives (Model 2)	0.76 (0.67–0.85)	<0.001

CI, confidence interval; CCB, calcium channel blocker.
Model 1 was adjusted for age, sex, and race (Black vs. non Black).
Model 2 was additionally adjusted for randomized Kt/V assignment, randomized flux assignment, heart failure, peripheral vascular disease, diabetes mellitus, access type (catheter, fistula, or graft), predialysis blood urea nitrogen, ultrafiltration rate, and predialysis systolic blood pressure.
Model 3 was additionally adjusted for baseline use of angiotensin converting enzyme inhibitors, beta-blockers, alpha-1 blockers, nitrates, angiotensin II receptor blockers, minoxidil, adrenergic blockers, and other antihypertensives.
Model 3b was adjusted for the same variables as Model 2, as well as the count of antihypertensive medications.

Ethics

The study was approved by the institutional review board at each of 15 clinical centers associated with 72 participating dialysis units, and all patients gave written informed consent. Data from the HEMO study was obtained with the permission of the National Institute of Diabetic and Digestive Kidney Diseases. The full list of participating site and ethics committees can be found at https://www.nejm.org/doi/full/10.1056/NEJMoa021583.

RESULTS

Baseline Characteristics

At baseline, the mean age of participants was 58 ± 14 years, 63% were Black, and 49% were taking CCBs. Patients taking CCBs were more likely to be Black, have higher predialysis SBP and higher ultrafiltration rate, and were more likely to be taking additional antihypertensive agents, than those not taking CCBs (Table 1).

Association of CCB Use With IDH

The Nadir90/100 outcome occurred in 3228 of 29,835 (11%) sessions among those taking CCBs and in 5589 of 34,703 (16%) sessions among those not taking CCBs ($P < 0.001$). The frequency of IDH using alternative definitions according to CCB use is presented in Table 2. With the exception of the Fall20 and Fall30 definitions, the frequency of IDH was lower among those taking CCBs, compared with those who were not.

In patient-level unadjusted analyses, CCB use (vs. nonuse) was associated with 19% lower risk of

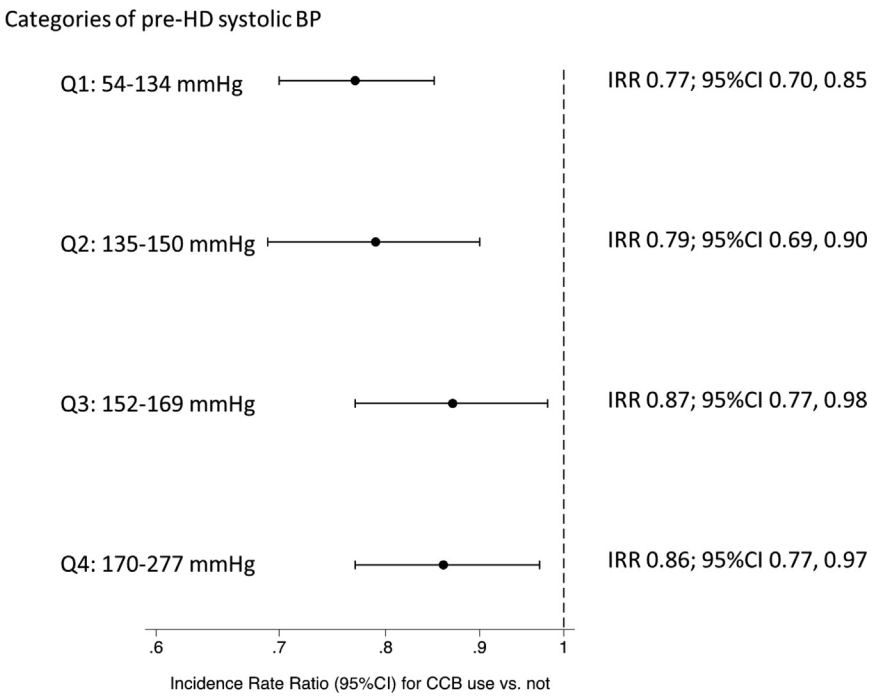

Figure 1. Adjusted association (Model 3) of calcium channel blocker use (vs. nonuse) with intradialytic hypotension according to categories of predialysis systolic blood pressure. BP, blood pressure; CCB, calcium channel blocker; HD, hemodialysis; IRR, incidence rate ratio.

developing Nadir90/100 (IRR: 0.81; 95% CI: 0.76–0.86). In fully adjusted models, this association attenuated marginally, but remained significant (Model 3, IRR: 0.85; 95% CI: 0.79–0.90; Table 3). Similar patterns of association were noted when the count of antihypertensive medications was adjusted for (Model 3b, Table 3) and in sensitivity analyses that considered alternative definitions of IDH (Supplementary Table S1).

Association of CCB Use With IDH in Subgroups

There was no evidence for effect modification according to sex, race, heart failure, randomized Kt/V arm, or randomized flux arm (P–interaction > 0.25 for all). The association of CCB use with IDH appeared to differ according to quartiles of pre-HD systolic BP (P–interaction < 0.001). Specifically, CCB use (vs. nonuse) was associated with a 23% lower risk of Nadir90/100 among those in the lowest quartile of pre-HD systolic BP, whereas CCB use (vs. nonuse) was associated with a 14% lower risk of Nadir90/100 among those in the highest quartile of pre-HD systolic BP (Figure 1).

Similar to the analyses with pre-HD systolic BP, there was some suggestion that the association of CCB use (vs. nonuse) with IDH differed according to the number of other antihypertensive medications used (P–interaction $= 0.16$). In models restricted to patients who did not have any other antihypertensive medications prescribed, the association of CCB use (vs. nonuse) with a lower risk of IDH was accentuated (Model 2, IRR: 0.76; 95% CI: 0.67–0.85). These findings were consistent among the various definitions of IDH considered (Table 3).

Association of CCB Use With Changes in SBP During HD

The mean decline from pre- to nadir intradialytic SBP was 33 ± 15 mm Hg, on a patient level basis. In fully adjusted models, considering the intradialytic decline in systolic BP as a continuous variable, patients using CCBs had less SBP decline (−1.6; 95% CI: −2.1 to −1.2 mm Hg; $P < 0.001$), compared with those who were not taking CCBs. Similar patterns of association were noted in fully adjusted models for the nadir intradialytic SBP and the post-HD SBP, which were 1.6 (95% CI: 1.2–2.1) mm Hg and 1.9 (95% CI: 1.4–2.3) mm Hg higher respectively, among those taking versus those not taking CCBs in the fully adjusted analyses (Figure 2).

DISCUSSION

In this analysis of patients receiving maintenance HD, those taking CCBs had a lower risk of developing IDH, compared with those who were not, independent of pre-HD SBP and other antihypertensive medication use. The association was consistent across various definitions of IDH but appeared to be more pronounced among those with lower pre-HD systolic BP and those who were not prescribed any other antihypertensive medications.

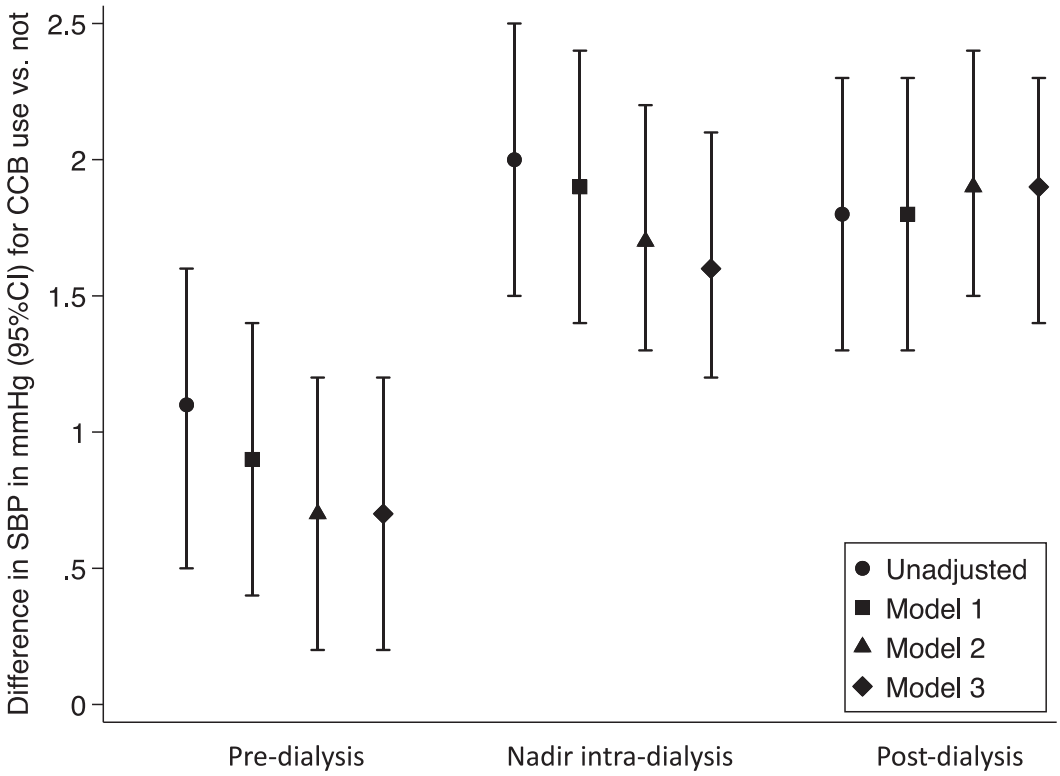

Figure 2. Association of calcium channel blocker use (vs. nonuse) with predialysis, nadir, and postdialysis systolic blood pressure. CCB, calcium channel blocker; SBP, systolic blood pressure.
Model 1 was adjusted for age, sex, and race (Black vs. non-Black).
Model 2 was additionally adjusted for randomized Kt/V assignment, randomized flux assignment, heart failure, peripheral vascular disease, diabetes mellitus, access type (catheter, fistula, or graft), predialysis blood urea nitrogen, ultrafiltration rate, and predialysis systolic blood pressure.
Model 3 was additionally adjusted for baseline use of angiotensin converting enzyme inhibitors, beta-blockers, alpha-1 blockers, nitrates, angiotensin II receptor blockers, minoxidil, adrenergic blockers, and other antihypertensives.

Hypertension is highly prevalent among patients receiving maintenance HD.[1] Although clearly a major risk factor for cardiovascular disease among the non-HD CKD population,[16] observational data in the HD population suggests the presence of a U-shaped association of pre-HD systolic BP with mortality,[17] and the limited trials to date have not defined an optimal BP target or antihypertensive regimen.[18,19] Indeed, some have promoted the idea of permissive hypertension among patients receiving maintenance HD, given the associations of IDH with adverse outcomes, and there is a lack of clarity in relation to the optimal timing of antihypertensive use with respect to the HD session.[5]

CCBs are one of the most commonly prescribed antihypertensive medications among patients receiving maintenance HD, with estimated use in about 45% of patients in the United States in 2020.[1] Previous observational data from Kestenbaum *et al.*[10] reported a lower risk of all cause and cardiovascular mortality with CCB use (vs. nonuse), with some suggestion that the associated risk reductions were more apparent among those with a history of cardiovascular disease. Data from a modest sized trial in 2008 ($N = 251$) reported a nonsignificant lower risk of all-cause mortality among hypertensive patients on HD for those randomized to amlodipine, compared with placebo (hazard ratio: 0.65; 95% CI: 0.34–1.23); though the trial under recruited and was underpowered. Despite lowering pre-HD systolic BP by 10 mm Hg more than placebo, no difference in terms of hypotensive episodes was noted; hypotension was defined as an event of reduction in BP associated with clinical symptoms during the HD treatment.[20] Subsequent data from a meta-analysis was less convincing, with low certainty evidence suggesting that dihydropyridine CCBs may reduce pre-HD systolic BP compared with placebo or no treatment. Although a nonsignificant lower risk of IDH was noted for CCB use versus placebo or no treatment (relative risk: 0.54; 95% CI: 0.25–1.15); this was also deemed as low certainty evidence, coming from only 2 studies with a total of 287 patients.[11]

In our present analyses, we observed a lower risk of IDH for those receiving CCBs versus nonuse, with supportive findings in sensitivity analyses examining differences in nadir and post-HD systolic BP. Several hypotheses have been proposed by which CCBs may be

advantageous among patients receiving maintenance HD. One potential mechanism relates to improved coronary blood flow, with a double blind cross over trial of patients on HD with known coronary artery disease ($N = 196$) reporting that diltiazem reduced the frequency and duration of symptomatic ischemic episodes, as assessed by 48-hour Holter monitoring, compared with placebo.[21] Aslam *et al*[22] examined the effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in a crossover trial of 23 patients with hypertension receiving maintenance HD, and found that both medications reduced asymmetric dimethylarginine (a nitric oxide inhibitor).[22] Another study of 20 hypertensive patients reported less variation in systolic BP for CCB versus ARBs, with higher post-HD systolic BP for CCB (116 vs. 110 mm Hg).[23] This potential reduction in BP variability with CCBs may partially explain why we observed a lower risk of threshold-based definitions of IDH for those with lower pre-HD systolic BP and among those not prescribed other antihypertensive medications in the present analyses. Nevertheless, confirmatory studies and mechanistic studies are needed to better understand the underlying pathophysiology.

There are several strengths to our study, including the availability of HD session-level BP data from a large and well-executed randomized trial, as well as repeated collections of medication and comorbid data. However, there are several limitations that are also important to consider. These include a lack of detail on the subtype of CCBs and other antihypertensive medications, medications that augment BP, adherence, dialyzability, and the timing in relation to the HD session; and the fact that medication regimens were only updated every 6 months during the trial. The potential for residual confounding also remains (despite the use of multivariable adjusted models) because data related to the dialysate prescription, temperature, and other potential confounders were not available. Concerns also exist with respect to generalizability beyond that of the included patients and to contemporary HD populations, although the CCBs in use today are similar to those at the time of the HEMO study and it is unlikely that the pathophysiology of BP responses has changed in the interim.

In summary, our findings demonstrate that the use of CCBs is associated with a lower risk of developing IDH among patients receiving maintenance thrice-weekly HD. Given the associated risks of IDH and the lack of consensus on BP targets for patients on HD, CCBs may represent a reasonable therapeutic choice to balance the optimization of pre-HD BP control with minimizing the risk of IDH. Further interventional trials and mechanistic studies are urgently needed to test these hypotheses in this high risk patient population.

DISCLOSURE

FRM reports funding from NIH, Satellite Healthcare, Novartis, Leixcon, and Fifth Eye paid directly to his institution; expert witness fees from Rubin-Anders Scientific; and consulting fees from GSK and Zydus Therapeutics. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We express our gratitude to the researchers and participants involved in the HEMO study for their valuable contribution of data to this publication.

AUTHOR CONTRIBUTIONS

FRM contributed to project supervision, statistical analysis, interpretation of data, review, editing and approval of current manuscript.

ALT contributed to writing of current manuscript, statistical analysis, and interpretation of the data.

SC contributed to review and editing of manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Association of calcium channel blocker use (vs. nonuse) with various definitions of intradialytic hypotension.

REFERENCES

1. USRDS. Annual data report; 2021. Accessed February 1, 2023. https://usrds-adr.niddk.nih.gov/2021
2. Mc Causland FR, Brunelli SM, Waikar SS. Dialysis dose and intradialytic hypotension: results from the HEMO study. *Am J Nephrol*. 2013;38:388–396. https://doi.org/10.1159/000355958
3. Palmer BF, Henrich WL. Recent advances in the prevention and management of intradialytic hypotension. *J Am Soc Nephrol*. 2008;19:8–11. https://doi.org/10.1681/ASN.2007091006
4. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int*. 2004;66:1212–1220. https://doi.org/10.1111/j.1523-1755.2004.00812.x
5. Chang TI, Tatoian ET, Montez-Rath ME, Chertow GM. Timing of antihypertensive medications on key outcomes in hemodialysis: a cluster randomized trial. *Kidney360*. 2021;2:1752–1760. https://doi.org/10.34067/KID.0001922021
6. Wong A, Hoffman RS, Walsh SJ, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2021;59:361–375. https://doi.org/10.1080/15563650.2020.1870123
7. Elliott WJ, Ram CVS. Calcium channel blockers. *J Clin Hypertens (Greenwich)*. 2011;13:687–689. https://doi.org/10.1111/j.1751-7176.2011.00513.x
8. Luft FC. Calcium-channel-blocking drugs and renal sodium excretion. *Am J Nephrol*. 1987;7:39–43. https://doi.org/10.1159/000167541

9. Inrig JK. Antihypertensive agents in hemodialysis patients: a current perspective. *Semin Dial*. 2010;23:290–297. https://doi.org/10.1111/j.1525-139X.2009.00697.x
10. Kestenbaum B, Gillen DL, Sherrard DJ, Seliger S, Ball A, Stehman-Breen C. Calcium channel blocker use and mortality among patients with end-stage renal disease. *Kidney Int*. 2002;61:2157–2164. https://doi.org/10.1046/j.1523-1755.2002.00355.x
11. Mugendi GA, Mutua FM, Natale P, Esterhuizen TM, Strippoli GF. Calcium channel blockers for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. 2020;10:CD011064. https://doi.org/10.1002/14651858.CD011064.pub2
12. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002;347:2010–2019. https://doi.org/10.1056/NEJMoa021583
13. Greene T, Beck GJ, Gassman JJ, et al. Design and statistical issues of the hemodialysis (HEMO) study. *Control Clin Trials*. 2000;21:502–525. https://doi.org/10.1016/s0197-2456(00)00062-3
14. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26:724–734. https://doi.org/10.1681/ASN.2014020222
15. Miskulin DC, Athienites NV, Yan G, et al. Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. *Kidney Int*. 2001;60:1498–1510. https://doi.org/10.1046/j.1523-1755.2001.00954.x
16. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease Stages 3 to 5: a systematic review and meta-analysis. *JAMA Intern Med*. 2017;177:1498–1505. https://doi.org/10.1001/jamainternmed.2017.4377
17. Park J, Rhee CM, Sim JJ, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int*. 2013;84:795–802. https://doi.org/10.1038/ki.2013.237
18. Miskulin DC, Gassman J, Schrader R, et al. BP in dialysis: results of a pilot study. *J Am Soc Nephrol*. 2018;29:307–316. https://doi.org/10.1681/ASN.2017020135
19. Agarwal R. Blood pressure and mortality among hemodialysis patients. *Hypertension*. 2010;55:762–768. https://doi.org/10.1161/HYPERTENSIONAHA.109.144899
20. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant*. 2008;23:3605–3612. https://doi.org/10.1093/ndt/gfn304
21. Cice G, Di Benedetto A, D'Andrea A, et al. Sustained-release diltiazem reduces myocardial ischemic episodes in end-stage renal disease: a double-blind, randomized, crossover, placebo-controlled trial. *J Am Soc Nephrol*. 2003;14:1006–1011. https://doi.org/10.1097/01.asn.0000059309.66107.fc
22. Aslam S, Santha T, Leone A, Wilcox C. Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis. *Kidney Int*. 2006;70:2109–2115. https://doi.org/10.1038/sj.ki.5001983
23. Takenaka T, Sueyoshi K, Arai J, et al. Calcium channel blockers suppress daily variations of blood pressure in hypertensive patients with end-stage renal diseases. *Clin Exp Hypertens*. 2014;36:78–82. https://doi.org/10.3109/10641963.2014.892116