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Antihypertensive Drug Treatment and the Risk for Intrahemodialysis Hypotension

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Key Points

- Antihypertensive medications are often used by hemodialysis patients, and intradialytic hypotension is a common complication in these patients.
- The study emulates a randomized clinical trial comparing antihypertensive drug treatment for the risk of hemodialysis hypotension in 4072 incident patients.
- Compared with calcium antagonists, β and α - β blockers, angiotensin converting enzyme inhibitors or angiotensin II antagonists, and diuretics may increase the risk of hemodialysis hypotension.

Abstract

Background Antihypertensive medications are often prescribed to manage hypertension in hemodialysis patients, and intradialytic hypotension (IDH) is a common complication in these patients. We investigated the risk of IDH in incident hemodialysis patients who initiated treatment with antihypertensive drugs in monotherapy.

Methods The study was conducted as an emulation of a randomized clinical trial in 4072 incident hemodialysis patients who started antihypertensive drug treatment between January 2016 and December 2019. The primary outcome was the occurrence of IDH during hemodialysis sessions. The generalized estimating equation analysis was adjusted by inverse probability treatment weighting.

Results Calcium channel blocker (CCB) use was associated with an IDH incidence rate of 7.4 events per person-year (95% confidence interval [CI], 6.2 to 8.6). Compared with CCB use, use of β and α - β blockers was strongly associated with a higher likelihood of IDH (odds ratio [OR] [95% CI, 2.27; 1.50 to 3.43]). The use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (OR [95% CI, 1.71; 1.14 to 2.57]) and diuretics (OR [95% CI, 1.52; 1.07 to 2.16]) were also associated with a higher likelihood of IDH compared with CCB use.

Conclusions The study suggests that using β and α - β blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and diuretics may increase the risk of IDH in hemodialysis patients compared with CCB use.

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See related editorial, "Intradialytic Hypotension in the Face of Using Different Antihypertensive Medication Classes," on pages 1227–1229.

Introduction

Intradialytic hypotension (IDH) is a common complication of hemodialysis that can lead to serious adverse outcomes, including cardiovascular events and mortality.¹ Antihypertensive drugs are commonly used in patients with ESKD to manage hypertension, but their impact on the risk of IDH is not well understood.²

In general, observational studies in dialysis patients that investigated the relationship between antihypertensive medication and the risk of cardiovascular events did not report the risk of IDH by these drugs.^{3–9} In a UK-based cohort study of more than two thousand hemodialysis patients, the risk of IDH was higher in patients who met the postdialysis recommended BP target than in those who did not,¹⁰ but paradoxically the frequency of IDH was lower in patients on antihypertensive drugs than in those not taking these drugs. Similarly, randomized clinical trials (RCTs) comparing these drugs in the hemodialysis population have not consistently collected or reported data on IDH²; therefore, only sparse information is available.^{10–13} Kidney Disease Outcome Quality Initiative guidelines recommend withholding antihypertensive medications before dialysis¹⁴ in hypotension-prone patients. However, in observational studies, no evidence exists that these drugs affect IDH.^{10,15} European Best Practice guidelines recommend that antihypertensive agents be given with caution before dialysis depending on pharmacodynamics but should not be routinely withheld on the day of hemodialysis treatment.¹⁶ There is no study head-to-head comparing the main antihypertensive drugs and the risk of incident IDH. The issue is relevant because these drugs interfere with cardiovascular reflex control by different mechanisms.¹⁷

Target trial emulation minimizes the risk of selection bias¹⁸ and immortal time bias and other biases^{19–21} in observational studies, and this approach has already been applied to studies in patients with CKD^{22,23} and dialysis²⁴ patients. Using target trial emulation, we herein compare the risk of incident hypotension among patients with antihypertensive medication-naïve ESKD who started different classes of antihypertensive medications used in monotherapy. By examining the impact of antihypertensive drugs on the incident risk of IDH, we aim to produce novel insights into the risk of IDH in patients with ESKD and inform the design of future RCTs.

Methods

The study was conducted along the principles of the Declaration of Helsinki, and written informed consent was obtained from each participant. We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement for reporting observational studies.

Data Sources

Data were retrieved from the central EuCLiD 5 database, which integrates patient characteristics, day-by-day treatment data, laboratory parameters, and medications. This database contains detailed clinical information including laboratory data, comorbidities, and clinical outcomes. A

detailed description of European clinical database is reported elsewhere.²⁵

Target Trial

Target trial emulation is a framework for designing and analyzing observational studies. It has multiple advantages compared with traditional observational studies, including clear reporting and appropriate emulation of time zero, which prevents immortal time and selection biases and other sources of confounding.²¹ Trial emulation uses inverse probability to adjust for confounding. Informally, the weights create a pseudopopulation where measured confounders no longer predict treatment.²¹

Specification of the target trial protocol on the effect of monotherapy with antihypertensive drugs on IDH and its observational emulation is given in [Supplemental Table 1](#). The target trial would randomize patients to four classes of antihypertensive drugs commonly used in hemodialysis patients, namely calcium channel blockers (CCBs), β blockers and α - β blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), and diuretics.

Eligibility Criteria

As the source population, we considered adult patients (≥ 18 years) who received hemodialysis treatments in Fresenius NephroCare dialysis centers network operating in seven countries (Turkey, Russia, Spain, Portugal, Italy, Slovakia, and the Czech Republic) between January 2016 and December 2019 and followed up until May 2023. Eligibility required incident antihypertensive medication use as monotherapy.

Treatment Strategies

We considered ACE inhibitors, ARBs, β blockers, α - β blockers, CCBs, and diuretics, all used in monotherapy. In the Fresenius Medical Care clinical manual, which is used in all Fresenius Medical Care centers, it is suggested to withhold antihypertensive agents during dialysis treatments in patients with recurrent IDH and, if needed, consider dosing once daily at night (see [Supplemental Information](#), Fresenius Medical Care clinical manual). Diuretics on interdialytic days were suggested in fluid-overloaded patients with residual kidney function who cannot achieve their target weight despite appropriate measures undertaken (*ibidem*). Furthermore, dialyzable rather than nondialyzable β blockers were recommended in this dialysis network.

Start and End of Follow-Up

Follow-up began when each patient started one of the study drugs to avoid immortal time^{26,27} and prevalent users²⁷ biases. The end of the follow-up was May 2023.

Outcome

Our outcome of interest was IDH. Along with the study by Flythe *et al.*²⁸ that found that the nadir BP during the hemodialysis session was the sole definition related to the

risk of death, we defined IDH as a nadir BP of <90 mm Hg during the hemodialysis session. Predialysis fluid excess was quantified by applying bioimpedance analysis (Body Composition Monitor, Fresenius Medical Care).

Causal Estimand

The study aimed to assess the effect of ACE inhibitors or ARBs, β blockers or α - β blockers, CCBs, and diuretics, all used in monotherapy, on repeated episodes of IDH by adjusting for all potential confounders by inverse probability treatment weighting (IPTW). We included patients who initiated treatment with a single antihypertensive drug and did not escalate the number of drugs throughout the follow-up period. Among the treatment groups, we considered as reference category that of patients with the lowest incidence rate of IDH (*i.e.* patients on CCBs).

Statistical analysis is reported in Supplemental Information (statistical analysis and Supplemental Tables 1–3).

Results

The source study population was composed of a cohort of 46,440 hemodialysis patients. Among them, 11,695 patients were excluded because they were never treated with antihypertensive drugs and 23,843 patients because they were prevalent antihypertensive drugs users. Of 10,902 incident users (*i.e.*, patients starting treatment after the study inception), 6680 were excluded because they were receiving therapy with two or more antihypertensive drugs and 150 because they were receiving

monotherapy with antihypertensive drugs not meeting the inclusion criteria (Figure 1). Thus, 4072 hemodialysis patients (mean $\pm$ age: 60.4 $\pm$ 15.6 years; 58.4% male) treated in Turkey ($n=1445$), Russia ($n=863$), Spain ($n=656$), Portugal ($n=445$), Italy ($n=360$), Czech Republic ($n=129$), and Slovakia ($n=174$) were available for the data analysis.

Seven hundred and thirty-seven patients were on monotherapy with ACE inhibitors ($n=438$) or ARBs ($n=299$), 1672 with β blockers ($n=1326$) or α - β blockers ($n=346$), 1112 with CCBs, and the remaining 551 with diuretics (Figure 1 and Supplemental Table 2). The main demographic and clinical characteristics of patients included in the analysis ($n=4072$) are summarized in Supplemental Tables 2 and 3. Overall, average predialysis and postdialysis systolic/diastolic BPs were 139.4 $\pm$ 25.9/72.2 $\pm$ 15.4 mm Hg and 133.6 $\pm$ 26.2/70.0 $\pm$ 14.7 mm Hg, respectively. Fractional urea clearance (Kt/V) was, on average, 1.68 $\pm$ 0.40. Predialysis fluid overload was 2.08 L. Most patients had one or more comorbidities in their clinical history (see Supplemental Table 3). The remaining demographic, clinical, and biochemical characteristics of the whole study population and of patients, as divided according to antihypertensive drug classes, are detailed in Supplemental Tables 2 and 3. Detailed information about the names of antihypertensive drugs prescribed in hemodialysis sessions considered in the study ($n=623,875$) are given in Supplemental Table 4.

The four treatment groups substantially differed for major clinical and hemodynamic factors (see Supplemental

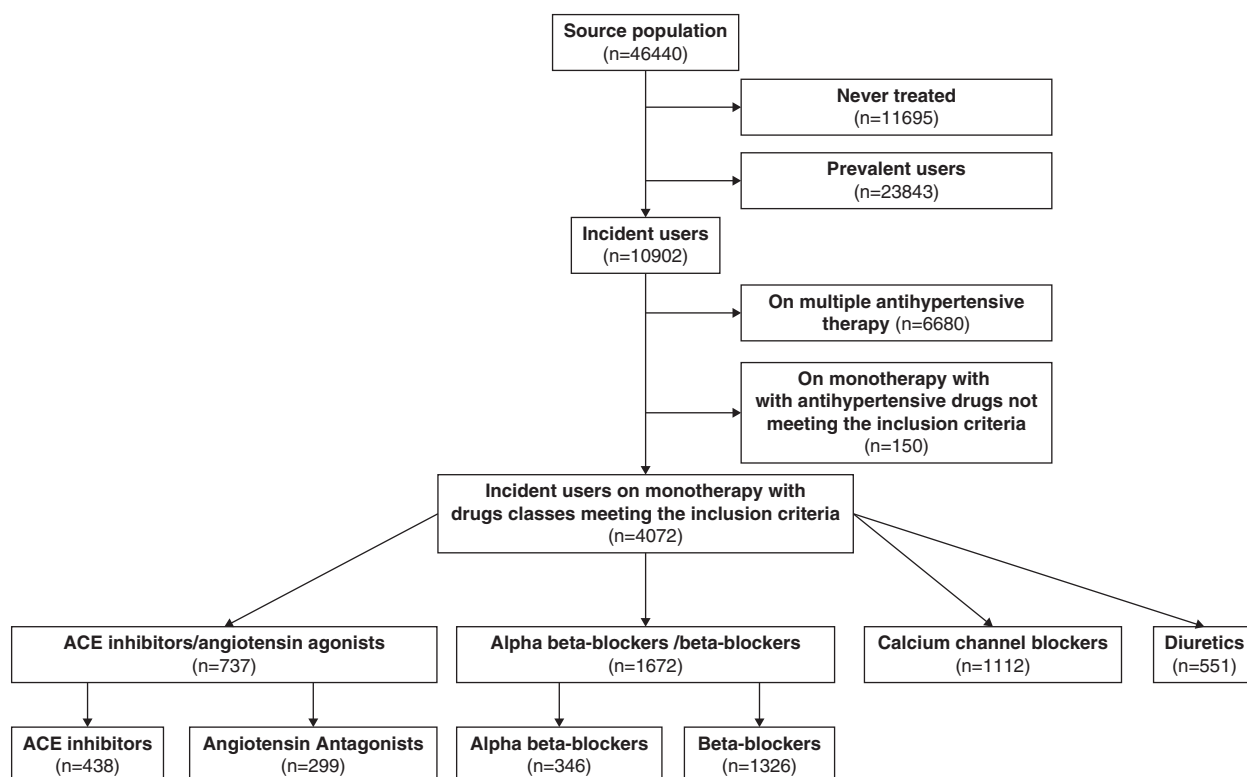


Figure 1. Flow of patients across the study. ACE, angiotensin converting enzyme.

Table 1. Demographic and clinical characteristics of the ^apseudopopulation of patients as divided according to antihypertensive drugs classes

Characteristic	On Monotherapy with			
	ACE Inhibitors or ARBs (n=4131)	α - β Blockers or β Blockers (n=4182)	CCBs (n=4150)	Diuretics (n=3757)
Age, yr	60.5 $\pm$ 15.2	60.0 $\pm$ 15.5	60.5 $\pm$ 15.2	62.2 $\pm$ 15.3
Males, %	2474 (59.9)	2242 (58.4)	2382 (57.4)	2269 (60.4)
Fluid overload prehemodialysis, L	2.03 $\pm$ 3.21	2.10 $\pm$ 1.86	2.08 $\pm$ 1.81	2.15 $\pm$ 1.96
Weight prehemodialysis, kg	74.9 $\pm$ 18.3	74.1 $\pm$ 16.7	73.7 $\pm$ 16.3	73.6 $\pm$ 16.4
Weight posthemodialysis, kg	73.0 $\pm$ 18.1	72.3 $\pm$ 16.4	71.8 $\pm$ 16	71.8 $\pm$ 16
Body mass index, prehemodialysis, kg/m ²	27.6 $\pm$ 6.1	27.5 $\pm$ 8.3	27.4 $\pm$ 6	27.2 $\pm$ 5.8
Systolic BP prehemodialysis, mm Hg	137.8 $\pm$ 27.9	141.0 $\pm$ 27.3	138.0 $\pm$ 27.9	136.7 $\pm$ 24
Systolic BP posthemodialysis, mm Hg	133.6 $\pm$ 26.1	135.1 $\pm$ 27.6	132.5 $\pm$ 28.8	131.3 $\pm$ 25.2
Diastolic BP prehemodialysis, mm Hg	70.3 $\pm$ 17.9	73.7 $\pm$ 16.9	71.9 $\pm$ 15.2	70.7 $\pm$ 14.1
Diastolic BP posthemodialysis, mm Hg	68.4 $\pm$ 17.2	71.6 $\pm$ 16.8	69.7 $\pm$ 14.8	68.6 $\pm$ 13.0
Heart rate prehemodialysis, beats/min	75.6 $\pm$ 12.2	76.3 $\pm$ 14.4	76.6 $\pm$ 13.1	75.3 $\pm$ 11.4
Heart rate posthemodialysis, beats/min	74.6 $\pm$ 14.3	75.8 $\pm$ 14.6	75.8 $\pm$ 12.5	76.1 $\pm$ 12.4
Treatment effective time posthemodialysis, min	241 $\pm$ 26	242 $\pm$ 24	241 $\pm$ 23	240 $\pm$ 30
Ultrafiltration rate posthemodialysis, ml/min	0.91 $\pm$ 0.28	0.91 $\pm$ 0.26	0.91 $\pm$ 0.28	0.90 $\pm$ 0.29
Dialysate temperature prehemodialysis, °C	36.1 $\pm$ 0.42	36.1 $\pm$ 0.38	36.1 $\pm$ 0.37	36.0 $\pm$ 0.35
Hemoglobin, g/dl	10.7 $\pm$ 1.7	10.8 $\pm$ 1.7	10.8 $\pm$ 1.6	10.7 $\pm$ 1.6
Albumin, g/dl	3.82 $\pm$ 0.48	3.85 $\pm$ 0.46	3.84 $\pm$ 0.47	3.82 $\pm$ 0.47
Calcium, mg/dl	8.83 $\pm$ 0.77	8.86 $\pm$ 0.75	8.85 $\pm$ 0.73	8.81 $\pm$ 0.77
Phosphate, mg/dl	4.6 $\pm$ 1.69	4.66 $\pm$ 1.42	4.62 $\pm$ 1.38	4.65 $\pm$ 1.24
Sodium, mEq/L	138 $\pm$ 3.1	138 $\pm$ 3.2	138.1 $\pm$ 3.1	138.0 $\pm$ 3.4
Potassium, mEq/L	5.02 $\pm$ 0.8	4.99 $\pm$ 0.78	4.98 $\pm$ 0.78	4.96 $\pm$ 0.83
C-reactive protein, mg/L	17 $\pm$ 5	16.9 $\pm$ 6.3	17.3 $\pm$ 6.5	21.1 $\pm$ 4.9
Kt/V	1.66 $\pm$ 0.41	1.67 $\pm$ 0.38	1.68 $\pm$ 0.41	1.67 $\pm$ 0.38
Dialysis vintage, mo	6.1 $\pm$ 0.34	5.88 $\pm$ 0.33	6.21 $\pm$ 0.33	5.03 $\pm$ 0.28
Treatment modality	On HDF: 2251 (54.5%) On hemodialysis: 1880 (45.5%)	On HDF: 2108 (50.4%) On hemodialysis: 2074 (49.6%)	On HDF: 2129 (51.3%) On hemodialysis: 2021 (48.7%)	On HDF: 1777 (47.3%) On hemodialysis: 1980 (52.7%)

Data are mean (or geometric mean) and SD or as absolute number and percent frequency, as appropriate. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

^aThe pseudopopulation was created by calculating a propensity score on individual basis. The inverse of the propensity score was used to reweight patients within the original study sample by creating a pseudo-population in which there is no longer an association between potential confounders and treatments under investigation.

Tables 2 and 3). For this reason, by a multinomial logistic regression and a propensity score calculation, we created a pseudopopulation (see Methods-Statistical analysis for more details) in which the distribution of measured confounders were substantially balanced among the four treatment groups (see Tables 1 and 2). The pairwise standardized mean difference (SMD) of demographic data and clinical biomarkers after IPTW between the reference group (CCBs) and the remaining treatment groups and of background comorbidities (Supplemental Tables 5 and 6) was indeed minimal (SMD $\leq$ 0.20). The SMDs of demographic and clinical data after IPTW among treatment groups other than CCBs are given in Supplemental Tables 7 and 8.

The Incidence Rate of IDH by Antihypertensive Drugs Classes

Of 4072 patients followed up for a total person-time of 11,860 years, 1761 deaths were observed (*i.e.*, 15 deaths per 100 persons-year, 95% confidence interval [CI], 14 to 16). The incidence rate of IDH was 15.8 events per person-year (95% CI, 14.8 to 16.9). Patients on monotherapy with β blockers or α - β blockers were those with the highest rate of IDH (25.3 events per person-year, 95% CI, 23.3 to 27.3), followed by those on diuretics (14.9 events per person-year, 95% CI, 12.5 to 17.3), ACE inhibitors or ARBs (7.8 events per person-year, 95% CI, 6.2 to 9.4), and CCBs (7.4 events per person-year, 95% CI, 6.2 to 8.6) (Figure 2). As shown in Figure 2, the incidence rates of IDH in patients on β blockers and α - β

Table 2. Patients' comorbidities of the ^apseudopopulation of patients as divided according to antihypertensive drugs classes

Diseases	On Monotherapy with			
	ACE Inhibitors or ARBs (n=4131)	β or α - β Blockers (n=4182)	CCBs (n=4150)	Diuretics (n=3757)
Hypertension, No. (%)	2528 (61.2)	2530 (60.5)	2407 (58)	2149 (57.2)
Diabetes mellitus, No. (%)	1253 (30.3)	1317 (31.5)	1282 (30.9)	1383 (36.8)
Congestive heart failure, No. (%)	1181 (28.6)	1201 (28.7)	1116 (26.9)	1078 (28.7)
Connective tissue disorders, No. (%)	92 (2.2)	88 (2.1)	112 (2.7)	71 (1.9)
Coronary artery disease, No. (%)	303 (7.3)	343 (8.2)	290 (7)	338 (9)
Atrial fibrillation, No. (%)	318 (7.7)	341 (8.2)	390 (9.4)	471 (11.1)
Ischemic heart disease, No. (%)	971 (23.5)	1030 (24.6)	1025 (24.7)	1018 (27.1)
Other forms of heart disease, No. (%)	1337 (32.4)	688 (31.8)	1345 (32.4)	1262 (33.6)
Cerebrovascular disease, No. (%)	615 (14.9)	570 (13.6)	539 (12.0)	466 (12.4)
Peripheral vascular disease, No. (%)	861 (20.8)	732 (17.5)	639 (15.4)	691 (18.4)
Chronic pulmonary disease, No. (%)	647 (15.6)	547 (13.1)	452 (10.9)	417 (11.1)
Pulmonary hypertension, No. (%)	75 (1.8)	48 (1.1)	50 (1.2)	64 (1.7)
Dementia, No. (%)	80 (1.9)	65 (1.6)	54 (1.3)	53 (1.4)
Hemiplegia, No. (%)	15 (0.4)	29 (0.7)	37 (0.9)	34 (0.9)
Metastatic solid tumor, No. (%)	31 (0.7)	27 (0.7)	29 (0.7)	19 (0.5)
Tumor without metastasis, No. (%)	437 (10.6)	410 (9.8)	544 (13.1)	323 (8.6)
Mild liver disease, No. (%)	437 (10.6)	471 (11.3)	407 (9.8)	394 (10.5)
Moderate/severe liver disease, No. (%)	28 (0.7)	31 (0.7)	29 (0.7)	19 (0.5)
Peptic ulcer disease, No. (%)	239 (5.8)	262 (6.3)	228 (5.5)	218 (5.8)
Chronic rheumatic heart disease, No. (%)	51 (1.2)	65 (1.6)	79 (1.9)	68 (1.8)
AIDS, No. (%)	7 (0.2)	11 (0.3)	17 (0.4)	8 (0.2)
Other unspecified circulatory disorders, No. (%)	73 (1.8)	70 (1.7)	71 (1.7)	34 (0.9)

Data are given as absolute number and percent frequency. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

^aThe pseudopopulation was created by calculating a propensity score on individual basis. The inverse of the propensity score was used to reweight patients within the original study sample by creating a pseud-population in which there is no longer an association between potential confounders and treatments under investigation.

blockers largely overlapped between them, and this was also true for patients on ACE inhibitors and ARBs.

Generalized Estimating Equation Regression Analyses of IDH

The relationship between antihypertensive drugs classes and repeated IDH episodes over time was investigated in unweighted and weighted generalized estimating equation (GEE) models (see [Table 3](#), models 1–2) and by considering patients on monotherapy with CCBs as the reference category (*i.e.*, the group with the lowest incidence rate of IDH). In patients on monotherapy with antihypertensive drugs, only in 362 of 623,875 dialysis sessions considered for treatments comparison, there was a switching from the initial drug to another drug and these changes were taken into account in the GEE analysis. As reported in [Table 3](#), in an unweighted GEE model only including antihypertensive drugs classes ([Table 3](#), model 1), patients on β blockers or α - β blockers were those with the highest odds ratio (OR) of IDH (OR, 3.25; 95% CI, 2.13 to 4.94; $P < 0.001$) versus those on CCBs (OR, 1.00; *i.e.*, the reference category). In a weighted GEE model (see [Table 3](#), model 2 and [Figure 3](#)), patients on β or α - β blockers had an OR of IDH that was 2.27 times higher ($P < 0.001$) than that of those on CCBs (*i.e.*, the reference category). In the same weighted GEE model, compared with CCBs, the ORs for IDH associated with use of ACE inhibitors or ARBs ($P = 0.01$) and diuretics ($P = 0.02$) were similarly elevated but numerically lower than that of β or α - β blockers ([Figure 3](#) and [Table 3](#), model 2). The inclusion of country into the GEE analysis did not materially modify

the OR versus CCBs of β and α - β blockers (OR, 95% CI, 2.49; 1.65 to 3.78, $P < 0.001$), ACE inhibitors/ARBs (OR, 95% CI, 1.81; 1.16 to 2.82, $P < 0.01$), and diuretics (OR [95% CI, 1.40; 1.01 to 1.94], $P = 0.05$). Further data adjustment for baseline predialysis systolic and diastolic BPs and follow-up time did not affect the OR of the link between antihypertensive drugs classes and IDH (see [Supplemental Table 9](#)).

Effect modification analyses are reported as supplemental information and in [Supplemental Figure 1](#).

Discussion

In this observational study emulating a clinical trial, CCBs were the category of antihypertensive drugs associated with the lowest risk of incident IDH, and β and α - β blockers, ACE inhibitors and ARBs, and the use of diuretics emerged as the classes entailing the highest risk of hemodialysis hypotension as compared with CCBs.

Most hemodialysis patients are treated with antihypertensive drugs. These drugs interfere with cardiovascular reflex control by various mechanisms,¹⁷ and the degree of reduction in vascular and humoral responses to selective cardiopulmonary receptor manipulation depends on left ventricular mass. This metric is most frequently altered in hemodialysis patients.²⁹ Therefore, these drugs are commonly considered a risk factor of hemodialysis hypotension.² As discussed in the introduction, only sparse observational studies investigated the problem.^{10–13} As discussed, a study with a very small sample size (ten

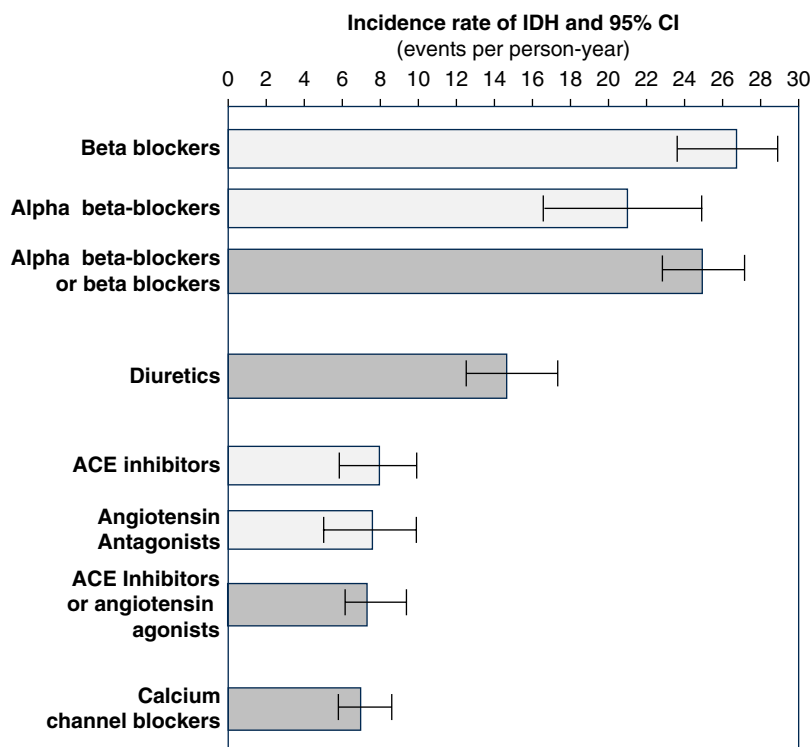


Figure 2. Incidence rate of IDH according to each antihypertensive drug class. Data are events per person-year and 95% CI. Light gray columns represent the incidence rate of IDH in the combined group of patients on α - β blockers or β blockers and of those on ACE inhibitors or ARBs. ARB, angiotensin II receptor blocker; CI, confidence interval; IDH, intradialytic hypotension. Figure 2 can be viewed in color online at www.cjasn.org.

Table 3. Generalized estimated equations models of repeated episodes of intradialytic hypotension

Drugs	Model 1	Model 2
	OR (95% CI), and <i>P</i> Value	OR (95% CI), and <i>P</i> Value
β and α - β blockers (yes/no)	3.25 (2.13 to 4.94), <i>P</i> < 0.001	2.27 (1.50 to 3.43), <i>P</i> < 0.001
Diuretics (yes/no)	2.09 (1.51 to 2.87), <i>P</i> < 0.001	1.52 (1.07 to 2.16), <i>P</i> = 0.02
ACE inhibitors/ARBs (yes/no)	1.52 (1.01 to 2.30), <i>P</i> = 0.04	1.71 (1.14 to 2.57), <i>P</i> = 0.01
CCBs (yes/no)	1 (reference group)	1 (reference group)

Dependent variable: repeated intradialytic hypotension episodes (nadir systolic BP <90 mm Hg during the hemodialysis session). The odds ratios of each drug classes for intradialytic hypotension were calculated by considering patients on calcium channel blockers as the reference group (*i.e.*, the group with the lowest incidence rate of intradialytic hypotension). Model 1: only antihypertensive drugs classes. Model 2: inverse probability treatment weighted generalized estimated equation model. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.

patients) and a very short observation period (2 weeks) testing the effect of verapamil on IDH³⁰ and safety-related analyses in a RCT in 251 hemodialysis patients testing the effect of amlodipine administered 1 hour before hemodialysis on all-cause death lasting found no excess risk for IDH by CCBs over.¹¹ Very scarce information for other drug classes exists. In a series of 21 hypertensive patients, the 1-month incidence of IDH episodes did not increase after antihypertensive drug intensification with one or more drugs, including CCBs (20 patients), β blockers (nine patients), α - β blockers (two patients), ACE inhibitors (17 patients), and ARBs (17 patients).¹³

We aimed to investigate whether antihypertensive medications are associated with an increased risk of IDH by an approach emulating an RCT.^{18,19} This approach has several advantages, including the ability to examine the impact of antihypertensive medications on IDH in a large and diverse patient population and the ability to thoroughly adjust for potential confounding factors and bias by indication, which are the main methodological threats when comparing the effect of medications in observational settings. In this study, β and α - β blockers emerged as the drug class with the highest risk for IDH. This observation contradicts findings in an

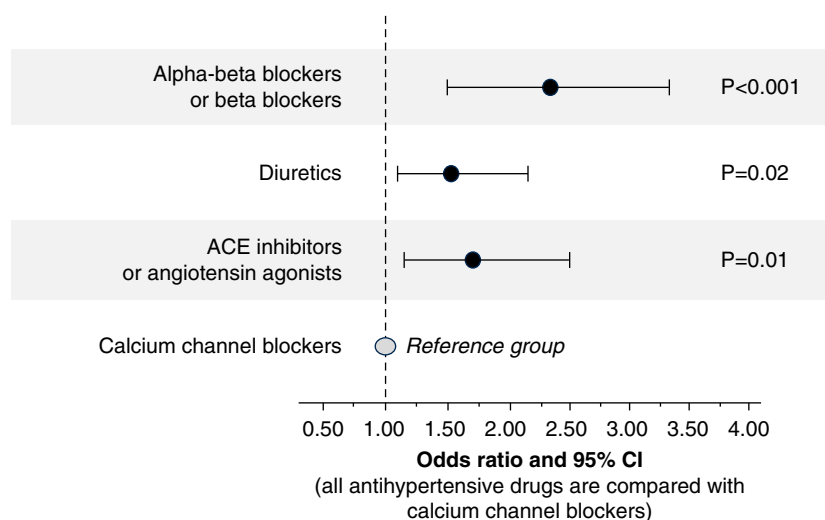


Figure 3. ORs, 95% CIs, and P values for IDH of antihypertensive drugs class versus the common comparator (CCBs). The effect of each drug is derived from the IPTW GEE model given in Table 3—model 2. CCB, calcium channel blocker; GEE, generalized estimating equation; IPTW, inverse probability treatment weighting; OR, odds ratio. Figure 3 can be viewed in color online at www.cjasn.org.

uncontrolled study of eight hypertensive hemodialysis patients.¹² Acute hypotension is an established side effect of β blockers.³¹ A trial testing an α - β blocker in hemodialysis patients had to be discontinued for excessive side effects, including IDH.³² Furthermore, we show that ACE inhibitors and ARBs and diuretics also impinge on IDH. In a meta-analysis testing the effect of ACE inhibitors and ARBs in hemodialysis patients, no excess risk for hypotensive episodes emerged.³³ However, no information on IDH was reported in this meta-analysis. The renin-angiotensin system is a fundamental effector system for arterial pressure control, and pharmacological interference with this system may produce hypotension if coin-terventions on fluid volume status are applied,³⁴ like ultrafiltration during hemodialysis. In the Dialysis Outcomes and Practice Patterns Study, about 11% of patients were on diuretics 2 years after starting hemodialysis,³⁵ a prevalence close to that in our study (13.5%). Theoretically, it has been hypothesized that a larger use of diuretics in hemodialysis patients may reduce the risk for IDH.³⁶ Continuous use of these drugs may predispose to IDH by reducing circulating volume because diuresis' effect adds to ultrafiltration during dialysis.

Our study provides insights into preventing IDH in patients with ESKD and informs the design of future RCTs. We carefully designed the trial emulation (Supplemental Table 1), and our target trial protocol emulated a RCT comparing the risk of IDH among new users of antihypertensive drugs in monotherapy. In our design, eligibility criteria, treatment allocation, and the start of follow-up were all aligned at time zero, thereby preventing immortal time bias, lead time bias, and selection bias. We adjusted the analysis for a set of 41 predefined potential confounders. Furthermore, because we were interested to the risk of continuous, protracted antihypertensive drug treatment, we adjusted the analysis with time-dependent variables, as formally recommended.²¹ By protocol, we adopted the class of drugs showing the lowest risk of

IDH (CCBs) as a comparator. The finding that CCBs in our study are the class with the lowest risk for IDH conforms with findings in a previously discussed randomized trial testing the effect of amlodipine on all-cause death.¹¹ Importantly, for studies like ours focusing on IDH, an unintended harmful effect of drugs, the probability of confounding is less than that in studies focusing on the intended benefits of drugs.³⁷ In addition, we adopted the active comparator, the new user design,³⁸ a face-to-face comparison of drugs, which is less prone to confounding than designs comparing the users of drugs to nonusers. The hypotensive effect of β blockers during hemodialysis was already well documented,³⁹ which depends on a combination of decreased heart rate and contractility in a situation with a risk of reduced blood volume because of fluid removal. In this study, loop diuretics increased the risk of IDH, likely because they can relax the smooth vascular muscle cells, particularly in the venous system.⁴⁰ This can lead to decreased systemic vascular resistance and a drop in BP during hemodialysis-ultrafiltration fluid volume subtraction.

Hemodiafiltration, a treatment that, *per se*, reduces the risk of IDH compared with standard hemodialysis⁴¹ was an effect modifier (an attenuator) of the risk for IDH. In this respect, it must be noted that in isothermic treatments, the impact of hemodiafiltration on IDH was no different from that during hemodialysis.⁴²

Our study has limitations. Trial emulation using observational data can provide valuable insights, especially when randomized trials are impossible. Still, the findings may only sometimes be generalizable to the larger population due to biases and methodological differences inherent to observational research. Concomitant comorbidities and known side effects influence the selection of antihypertensive drugs prescribed to hypertensive patients.⁴³ We tried to minimize this confounding through extensive adjustment for a large series of potential confounders, including classical risk factors and risk factors peculiar to kidney failure. However, we cannot rule out

the possibility that drugs compared in this study may have been prescribed for other indications uncontrolled in our analysis. We used an intention-to-treat approach, and initiated treatment was continued across the observation period, like the continuous treatment in a clinical trial. We adopted an accepted definition of IDH, that is, nadir systolic BP during dialysis, a metric associated with the risk of death. The dialyzability of β blockers could not be examined as a factor affecting the results since the prescriptions were limited primarily to dialyzable agents. Furthermore, other antihypertensive classes (e.g., vasodilators, pure α -blockers, centrally acting alpha agonists) were not studied.

In conclusion, the findings of this large observational study in a large cohort suggest that in hemodialysis patients, CCBs are the antihypertensive drug class with the lowest risk of IDH. At the same time, β and α - β blockers, ACE inhibitors, ARBs, and diuretics have a substantially higher risk of IDH than CCBs. Overall, the findings in this study provide the rationale for pragmatic trials comparing β and α - β blockers with other antihypertensive drugs on IDH in the hemodialysis population.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/CJN/B967>.

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Data Sharing Statement

Partial restrictions to the data and/or materials apply. Upon request to S. Stuard, 6 months after the publication of the study, the study data will be made available for the following 6 months.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/CJN/B966>.

Supplemental Table 1. Specification of the target trial protocol on the effect of monotherapy with antihypertensive drugs on intradialytic hypotension and its observational emulation in patients on hemodialysis.

Supplemental Table 2. Demographic and clinical characteristics of the whole study population and of patients divided according to antihypertensive drug classes.

Supplemental Table 3. Patients' comorbidities of the whole study population as well as of patients divided according to antihypertensive drug classes.

Supplemental Table 4. Detailed information about the names of antihypertensive drugs prescribed in coincidence of all hemodialysis sessions considered in the study ($N=623,875$).

Supplemental Table 5. Pairwise standardized mean difference (SMD) of demographic data and clinical biomarkers after inverse probability treatment weighting (IPTW) between the reference group (patients on treatment with calcium channel blockers) and the remaining treatment groups.

Supplemental Table 6. Pairwise standardized mean difference (SMD) of background comorbidities after inverse probability treatment weighting (IPTW) between the reference group (patients on treatment with calcium channel blockers) and the remaining treatment groups.

Supplemental Table 7. Pairwise standardized mean difference (SMD) of demographic data and clinical biomarkers after inverse probability treatment weighting (IPTW) among treatment groups other than calcium channel blockers.

Supplemental Table 8. Pairwise standardized mean difference (SMD) of background comorbidities after inverse probability treatment weighting (IPTW) among treatment groups other than calcium channel blockers.

Supplemental Table 9. Inverse probability treatment weighted generalized estimated equation (GEE) models of repeated episodes of intradialytic hypotension adjusting for baseline predialysis systolic BP (or predialysis diastolic BP) and follow-up time.

Supplemental information on effect modification analysis and **Supplemental Figure 1.**

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