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The Impact of Midodrine on Outcomes in Patients with Intradialytic Hypotension

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Keywords
Dialysis · Hypotension · Outcomes

Abstract
Background: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis, and is associated with significant morbidity and mortality. Off-label use of the alpha-1 andrenergic receptor agonist midodrine to reduce the frequency and severity of IDH is common. However, limited data exist to support this practice. This study sought to examine real-world efficacy of midodrine with respect to relevant clinical and hemodynamic outcomes. ***Methods:*** Here, we compared a variety of clinical and hemodynamic outcomes among adult patients who were prescribed midodrine (n = 1,046) and matched controls (n = 2,037), all of whom were receiving in-center hemodialysis treatment at dialysis facilities in the United States (July 2015 – September 2016). Mortality, all-cause hospitalization, cardiovascular hospitalization, and hemodynamic outcomes were considered from the month following the initiation of midodrine (or corresponding month for controls) until censoring for discontinuation of dialysis, transplant, loss to follow-up, or study end (September 30, 2016). Rate outcomes were compared using Poisson models and quantitative outcomes using linear mixed models; all models were adjusted for imbalanced patient characteristics. ***Results:*** Compared to nonuse, midodrine use was associated with higher rates of death (adjusted incidence rate ratio 1.37, 95% CI 1.15–1.62), all-cause hospitalization (1.31, 1.19–1.43) and cardiovascular hospitalization (1.41, 1.17–1.71). During follow-up, midodrine use tended to be associated with lower pre-dialysis systolic blood pressure (SBP), lower nadir SBP, greater fall in SBP during dialysis, and a greater proportion of treatments affected by IDH. ***Conclusion:*** Although residual confounding may have influenced the results, the associations observed here are not consistent with a potent beneficial effect of midodrine with respect to either clinical or hemodynamic outcomes.

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Introduction

Intradialytic hypotension (IDH) is a relatively common complication of hemodialysis. It can result in a wide range of symptoms, including dizziness, nausea, vomiting, cramps, chest pain, and syncope. Beyond these symptoms, IDH can lead to hypoperfusion of the brain, heart, and gut, ultimately resulting in ischemic brain damage [1–4], myocardial stunning [5–7], and gut endotoxin translocation [8–10] respectively. This end-organ damage over time likely contributes to the elevated mortality risk that is associated with frequent IDH [11].

Because IDH is associated with increased morbidity and mortality, approaches have been sought to reduce its prevalence. Clinical practices that may reduce the prevalence of IDH include the withholding of anti-hypertensive medications prior to dialysis, avoiding eating during dialysis, and cooling of the dialysate [12]. Despite application of these and other methods to reduce the frequency of IDH, it remains a fairly common complication of dialysis, affecting 10–70% of treatments, depending on the definition used and study population considered [11].

An additional strategy to limit the occurrence of IDH is the administration of vasoconstrictive medications, of which midodrine is the most commonly used. Midodrine is the prodrug of desglymidodrine, an alpha-1 andrenergic receptor agonist, whose administration causes constriction of both veins and arteries. It is currently approved by the US Food and Drug Administration for treatment of orthostatic hypotension, but its off-label use for preventing IDH is common. Midodrine is typically administered orally 15–30 min preceding dialysis; its levels in circulation peak after <1 h, and is removed by the dialysis treatment, with a half-life of 2–4 h [13].

To date, 10 single-center trials have evaluated the use of midodrine for IDH [14–22]. A meta-analysis of these trials found that administration of midodrine prior to the dialysis session was associated with 13.3 mm Hg (95% CI 8.6–18.0) higher nadir systolic blood pressure (SBP) [23]. No serious adverse events were reported in any of the 10 trials. However, these data regarding the efficacy of midodrine must be interpreted with caution given that the 10 trials represent only 117 patients in aggregate, did not examine any hard clinical outcomes such as cardiovascular events or death, and were subject to other limitations with regard to study design and duration of follow-up [23].

Thus, the use of midodrine as a means to reduce the frequency of IDH is supported by relatively weak clinical evidence. To date, no retrospective observational studies have evaluated the real-world efficacy of midodrine with respect to IDH or other outcomes among dialysis patients [24]. In order to provide a more nuanced context for the use of midodrine for the treatment of IDH, we conducted a retrospective, observational study to evaluate associations between midodrine use and a variety of hard clinical outcomes and hemodynamic outcomes in a cohort of contemporary hemodialysis patients.

Methods

Study Patients and Data Sources

The source cohort for this study consisted of patients who, during the time period July 1, 2015 – September 30, 2016, were ≥18 years of age and were receiving thrice-weekly in-center hemodialysis at dialysis facilities that were participating providers with the DaVita Institute for Patient Safety, Inc. Patients were excluded if more than 30 days had elapsed between the start of dialysis and the beginning of electronic health record (EHR) data availability (to ensure that historical data were complete or nearly complete); if they had begun midodrine in the first 90 days on dialysis (to allow for titration of therapies upon initiation of dialysis); or if they were Veterans Affairs beneficiaries (contractual stipulation).

All study data were derived from statistically de-identified EHR. Because this study was conducted using de-identified patient data, according to title 45, part 46 of the US Department of Health and Human Services' Code of Federal Regulations, it was deemed exempted from institutional review board or Ethics Committee approval (Quorum institutional review board, Seattle, WA, USA). We adhered to the Declaration of Helsinki and informed consent was not required.

Exposure Status and Matching

The exposure of interest was midodrine use, defined as an open record for midodrine visible in the patient's EHR. For each patient who initiated midodrine, an index date was assigned as the start date of the first visible midodrine record. For each such patient, eligible controls were those who, as of the start of the corresponding month, had similar values for dialysis vintage (within ±6 months), mean monthly pre-dialysis SBP (within ±5 mm Hg), mean monthly nadir SBP (within ±5 mm Hg) and percentage of treatments impacted by IDH (within ±5% treatments), defined as nadir SBP <90 mm Hg [11]. Midodrine patients were randomly matched to up to 2 eligible controls. Although midrodrine patients and controls were well-matched at the start of the index month, differences emerged by the index date due to changes in clinical status that occurred in the time between the start of the month and the index date. To minimize this effect, the analytic cohort was limited to matched groups whose index date fell within the first 10 days of the month. Within this analytic cohort, good balance existed between midrodrine patients and controls with respect to vintage, SBP, and IDH (online Suppl. Information; for all online suppl. material, see www.karger.com/doi/10.1159/000494806 for additional details).

Table 1. Patient characteristics in unmatched, matched, and analytic cohorts

	Unmatched		Analytic[c,d]	
	control[a] (*N* = 887,735)	midodrine[b] (*N* = 3,201)	control[b] (*N* = 2,037)	midodrine[b] (*N* = 1,046)
Vintage, months, mean ± SD	30.7±21.8	27.6±22.4*	27.1±21.4	27.2±21.7
Pre-dialysis SBP, mean ± SD	149±20	128±20*	128±21	127±20
Nadir SBP, mean ± SD	112±18	91±14*	91±13	90±13*
IDH, % treatments, mean ± SD	18.1±22.8	50.0±31.3*	49.8±30.6	50.8±30.6*

[a] *N* represents patient-months, not unique patients.
[b] *N* represents unique patients.
[c] Values presented are as of index date.
[d] Includes only midodrine patients (and matched controls) whose index dates were within 10 days of the start of the index months.
* Significantly different from control, $p < 0.05$.
IDH, intradialytic hypotension; SBP, systolic blood pressure.

Outcomes

Patients were followed forward in time from index until the earliest of study end (September 30, 2016) or censoring for death, transfer, withdrawal, renal recovery, modality change, or transplant. Outcomes considered were rates of death, all-cause hospitalization, cardiovascular hospitalization; and mean monthly values of the percent of treatments in the month affected by IDH (defined as nadir SBP of <90 mm Hg [11]), pre-dialysis SBP, nadir SBP, SBP difference (pre-dialysis - nadir), and ultrafiltration (UF) volume.

Statistical Analysis

Patient characteristics were summarized as means and SD, medians and interquartile ranges, or counts and proportions as appropriate. Standardized differences were calculated as described [25]. Comparisons across exposure categories were made using *t* tests or and chi-square tests, as dictated by data type.

Death, all-cause hospitalization, and cardiovascular hospitalization were expressed as rates (events per patient-year) and compared using Poisson models. Percent of treatments affected by IDH and other hemodynamic outcomes were expressed as mean values during each month of follow-up and compared using linear mixed models. All models were adjusted for baseline values of age, sex, race, etiology of end-stage renal disease, pre-dialysis SBP, nadir SBP, percent of treatments affected by IDH, UF volume, and target weight; time-updated values for dialysis vintage, vascular access type, albumin, creatinine, hemoglobin, and Kt/V; and time-updated presence of a diagnosis of coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes, and peripheral vascular disease.

All analyses were performed using Stata version 10.0 MP (College Station, TX, USA).

Results

Baseline Characteristics and Matching

A total of 3,201 patients with an open midodrine order were identified in the source population. Pre-dialysis SBP, nadir SBP, dialysis vintage, and percent of treatments affected by IDH were examined in the month prior to the first visible midodrine order among exposed patients, and during all patient-months for eligible controls (Table 1). Compared to eligible controls, patients with a midodrine order had slightly shorter dialysis vintage, markedly lower pre-dialysis SBP and nadir SBP, and a much higher percent of treatments affected by IDH (Table 1, Fig. 1a).

After matching, the analytic cohort consisted of 1,043 midodrine patients and 2,033 controls. In this cohort, all 4 of the variables considered in the matching strategy remained well balanced at index (Table 1, Fig. 1b). In particular, mean pre-dialysis SBP and nadir SBP during dialysis differed by <1 mm Hg, and the percent of treatments impacted by IDH differed by <1 percentage point. A more extensive comparison of baseline characteristics is presented in Table 2. Midodrine patients in the analytic cohort were, on average, older, more likely to be white and less likely to be black, were more likely to have congestive heart failure, and had lower serum albumin than controls. Subsequent analyses were adjusted for these (and other) patient characteristics.

Clinical Outcomes

Control and midodrine patients contributed a total of 1,755 and 811 patient-years of follow-up time respectively. Midodrine use was associated with a crude rate of 0.33 deaths/patient-year compared to a rate of 0.19 deaths/patient year for non-use (Table 3). Following adjustment for imbalanced patient characteristics, midodrine use was associated with a 37% higher rate of death (Fig. 2), corre-

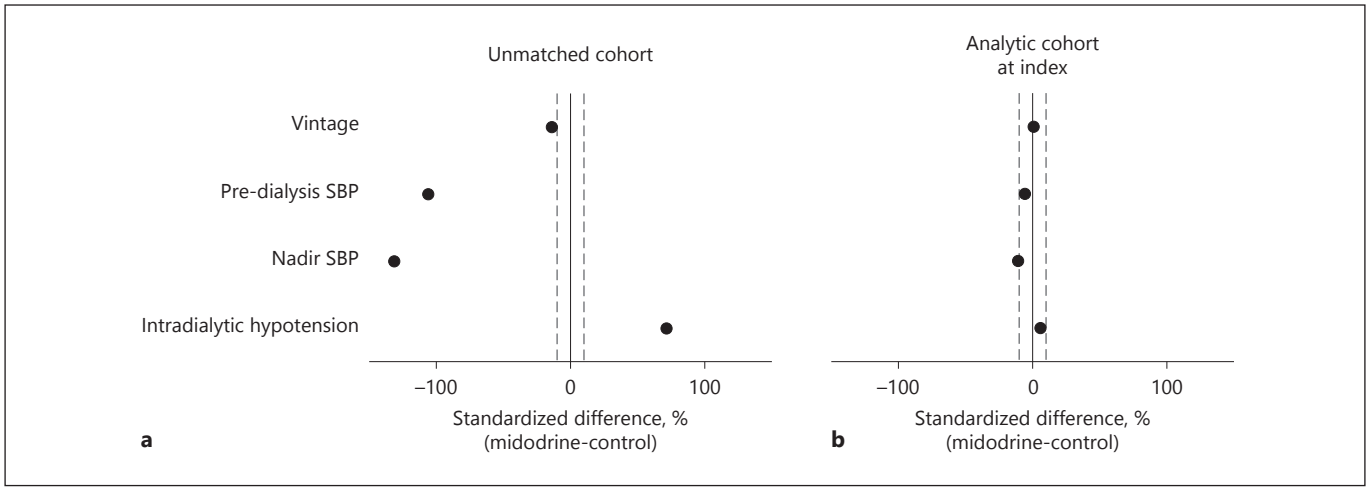

Fig. 1. Vintage and blood pressure characteristics in study cohort. **a** Values of standardized difference for dialysis vintage, pre-dialysis systolic blood pressure (SBP), nadir SBP, and percent of treatments affected by intradialytic hypotension in the unmatched cohort are presented. Dashed grey lines indicate standardized differences of + and –10%; differences of greater magnitude than these are considered indicative of a high likelihood of confounding. **b** As for (**a**), but considering the analytic cohort.

sponding to an incremental 0.04 (95% CI 0.02–0.04) events/patient year. Similarly, with respect to all-cause hospitalization, midodrine use was associated with a crude rate of 2.3 events/patient-year, compared to 1.8 events/year for non-use. After adjustment, this corresponded to a 31% higher rate of hospitalization, or an incremental 0.42 (95% CI 0.26–0.58) events per patient-year. Midodrine use was also associated with a higher rate of cardiovascular hospitalization (0.4 events/patient-year, compared to 0.3 events/patient-year for non-use). Following adjustment for differences in patient characteristics, midodrine use was associated with a 41% higher rate of cardiovascular hospitalization, corresponding to an incremental 0.08 (95% CI 0.03–0.13) events/patient-year. Similar results were obtained when patients were stratified by the use of a central venous catheter for vascular access, by the presence of a diagnosis of either congestive heart failure or diabetes, or by age (online suppl. Information).

Hemodynamic Outcomes

Within the analytic cohort, there was no statistically significant difference between midodrine and control patients with respect to pre-dialysis SBP as of index (Fig. 3a). In subsequent study months, midodrine use was associated with a trend toward lower crude mean values for pre-dialysis SBP compared to non-use, although the values across the 2 exposure categories tended to converge over time. Midodrine use was also associated with lower nadir SBP at index and throughout follow-up; these values did not tend to converge with corresponding values in the control group (Fig. 3b). The net effect of these trends is reflected in the blood pressure change during dialysis (Fig. 3c), which did not differ between the midodrine and control groups at the beginning of follow-up, but diverged over study time, with midodrine use being associated with a greater fall in SBP during dialysis. The percent of treatments affected by IDH was higher in the midodrine group than the controls at index and tended to remain higher throughout follow-up time (Fig. 3d). UF volumes were comparable across exposure groups at index and did not change meaningfully over follow-up time (Fig. 3e).

Discussion

To our knowledge, this is the first large study to evaluate the impact of midodrine on IDH and the first study of any size to examine derivative effects on hospitalization and mortality. A matching strategy was employed to identify patients who, based on their dialysis vintage, pre-dialysis SBP, nadir SBP, and proportion of treatments affected by IDH, were comparable to those who were prescribed midodrine. After adjustment for differences in patient characteristics, midodrine use was associated with substantially higher rates of mortality, hospitalization, and cardiovascular hospitalization than non-use. Mido-

Table 2. Baseline characteristics of the analytic cohort

	Control (*n* = 2,037)	Midodrine (*n* = 1,046)	Standardized difference	*p* value
Age, years, mean ± SD	66.9±14.2	69.0±12.3	15.5	<0.001
Gender, female, *n* (%)	922 (45.3)	478 (45.7)	0.9	0.81
Race, *n* (%)				<0.001
White	961 (47.2)	588 (56.2)	18.1	
Black	920 (45.2)	374 (35.8)	–19.2	
Other/unknown/missing	156 (7.7)	84 (8.0)	1.4	
Vascular access, *n* (%)				0.03
Arteriovenous fistula	1,329 (65.2)	633 (60.5)	–9.8	
Arteriovenous graft	330 (16.2)	189 (18.1)	5.0	
Central venous catheter	378 (18.6)	224 (21.4)	7.1	
Dialysis vintage, months				0.82
Mean ± SD	27.1±21.4	27.3±21.7	0.8	
Median (p25, p75)	20 (9, 41)	21 (9, 41)		
Target weight, kg, mean ± SD	82.6±24.0	83.9±23.8	5.8	
Etiology of ESRD, *n* (%)				0.02
Diabetes	881 (43.3)	505 (48.3)	10.1	
Hypertension	584 (28.7)	288 (27.5)	–2.5	
Other	572 (28.1)	253 (24.2)	–8.9	
Diabetes, *n* (%)	1,445 (70.9)	771 (73.7)	6.2	0.11
Congestive heart failure, *n* (%)	274 (13.5)	185 (17.7)	11.7	0.002
Coronary artery disease, *n* (%)	219 (10.8)	129 (12.3)	4.9	0.19
Cerebrovascular disease, *n* (%)	19 (0.9)	13 (1.2)	3.0	0.42
Peripheral vascular disease, *n* (%)	82 (4.0)	45 (4.3)	1.4	0.71
Albumin, g/dL , mean ± SD	3.7±0.4	3.6±0.5	–22.8	<0.001
Creatinine, mg/L, mean ± SD	7.8±2.9	7.5±2.8	–9.1	0.02
Kt/V, mean ± SD	1.6±0.3	1.5±0.3	–10.1	0.009
Pre-dialysis SPB, mm Hg, mean ± SD	128±21	127±20	–5.7	0.14
Nadir SPB, mm Hg, mean ± SD	91±13	90±13	–10.8	0.005
Interdialytic hypotension, % of Tx	49.8±30.6	52.8±30.5	9.7	0.01
Hemoglobin, g/dL, mean ± SD	10.8±1.2	10.8±1.3	–5.1	0.17
UF volume, L, mean ± SD	2.1±1.0	2.0±1.0	–3.0	0.42
Antihypertensive medications, mean ± SD	1.8±1.5	1.4±1.3	–28.7	<0.001

ESRD, end-stage renal disease; SPB, systolic blood pressure; Tx, treatment; UF, ultrafiltration.

drine use was also associated with a tendency toward lower pre-dialysis and nadir SBP, corresponding to a greater intra-dialysis blood pressure change. Midodrine use was associated with a higher proportion of treatments affected by IDH throughout follow-up time; no tendency toward equalization of this parameter across exposure categories was observed.

Although midodrine use was associated with a tendency toward lower pre-dialysis SBP throughout the study, pre-dialysis SBP values tended to converge between the midodrine and control groups over the course of follow-up time. This tendency may be explained in part by the fact that pre-dialysis SBP is measured immediately prior to the start of treatment (i.e., 15–30 min after midodrine is typically administered), a time window during which the biological effects of midodrine may be relatively potent. Conversely, nadir SBP typically occurs late in the dialysis treatment, up to several hours after midodrine administration. Because midodrine is removed by dialysis treatment [13], its ability to impact nadir SBP (and therefore IDH) may be limited. Midodrine use did appear to be associated with greater UF volume over study time, although differences were very modest (on the order of 0.1 L per treatment). This additional fluid removal might counteract any beneficial effects of midodrine with respect to raising nadir SBP. However, if the vasoconstrictive effects of midodrine can be counterbalanced by removal of ~0.1 L of additional fluid, this would argue against a marked effect of midodrine with respect to raising SBP in this context.

Table 3. Clinical outcomes by midodrine status

	Control (n = 2,037)	Midodrine (n = 1,046)
Time at risk, pt-years	1,755	811
Death		
Events, n	341	275
Crude rate, per pt-year	0.2	0.3
Adjusted rate difference (95% CI)[a]	0 (ref.)	0.04 (0.02–0.07)
All-Cause hospitalization		
Events, n	3,072	1,897
Crude rate, per pt-year	1.8	2.3
Adjusted rate difference (95% CI)[a]	0 (ref.)	0.42 (0.26–0.58)
Cardiovascular hospitalization		
Events, n	468	306
Crude rate, per pt-year	0.3	0.4
Adjusted rate difference (95% CI)[a]	0 (ref.)	0.08 (0.03–0.13)

[a] Adjusted for baseline values of age, sex, race, etiology, pre-dialysis SBP, nadir SBP, percent of treatments with IDH, UF volume, and target weight; and time-updated values for vintage, access, CAD, CHF, CVD, DM, PVD, albumin, creatinine, hemoglobin, and Kt/V scaled to mean value for continuous variables and most common value for categorical variables.

pt-year, patient-year; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; IDH, intradialytic hypotension; PVD, peripheral vascular disease; UF, ultrafiltration volume.

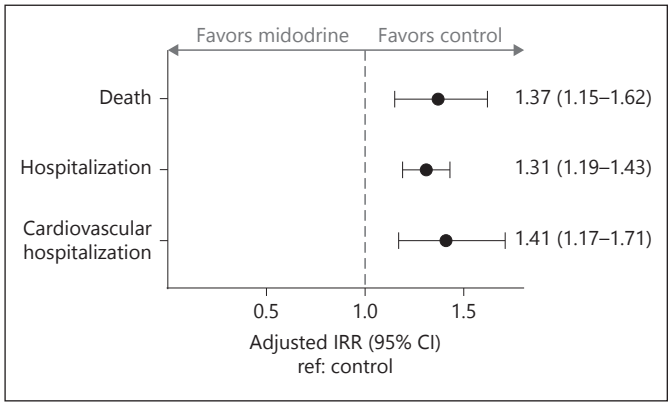

Fig. 2. Clinical outcomes by midodrine exposure status. Point estimates for the adjusted incidence rate ratio and corresponding 95% CI for the outcomes of death, all-cause hospitalization, and cardiovascular hospitalization are displayed, referent to control (i.e., no midodrine exposure). Comparisons were adjusted as described in the Methods section. IRR, incidence rate ratio.

This study applied both matching and multivariable adjustment strategies designed to limit the impact of residual confounding on the reported associations. Nonetheless, it is likely that some residual confounding remains, that is, midodrine is likely prescribed to "sicker" patients. However, given the magnitude of the associations between midodrine use and risk of mortality, all-cause hospitalization, and cardiovascular hospitalization, it is unlikely that midodrine use conveys a pronounced clinical benefit. The possibility that midodrine use is in fact associated with clinical harm cannot be excluded. At minimum, these results are inconsistent with a potent protective effect of midodrine with respect to hard clinical outcomes, various measures of SBP, or the proportion of treatments affected by IDH.

The findings of this study may inform the status of midodrine in the context of other interventions that may be used to stabilize blood pressure during dialysis, such as cool dialysate temperature, higher dialysate calcium concentration, dialysate sodium profiling, UF rate profiling, longer treatment times, and more frequent dialysis. In the context of limited resources for prospective trials to investigate the clinical and cardiac effects of these interventions, selection of interventions for more detailed study must be made judiciously. Although prior work has explored the benefits and liabilities of many of the other approaches to management of IDH, up until this point very little evidence existed with respect to midodrine. Given the essentially negative findings of the study presented here, interventions other than midodrine may be of higher priority for future prospective clinical trials in IDH management.

This study should be interpreted in the context of its limitations. This was a retrospective, observational study. Although multiple strategies were employed to limit the

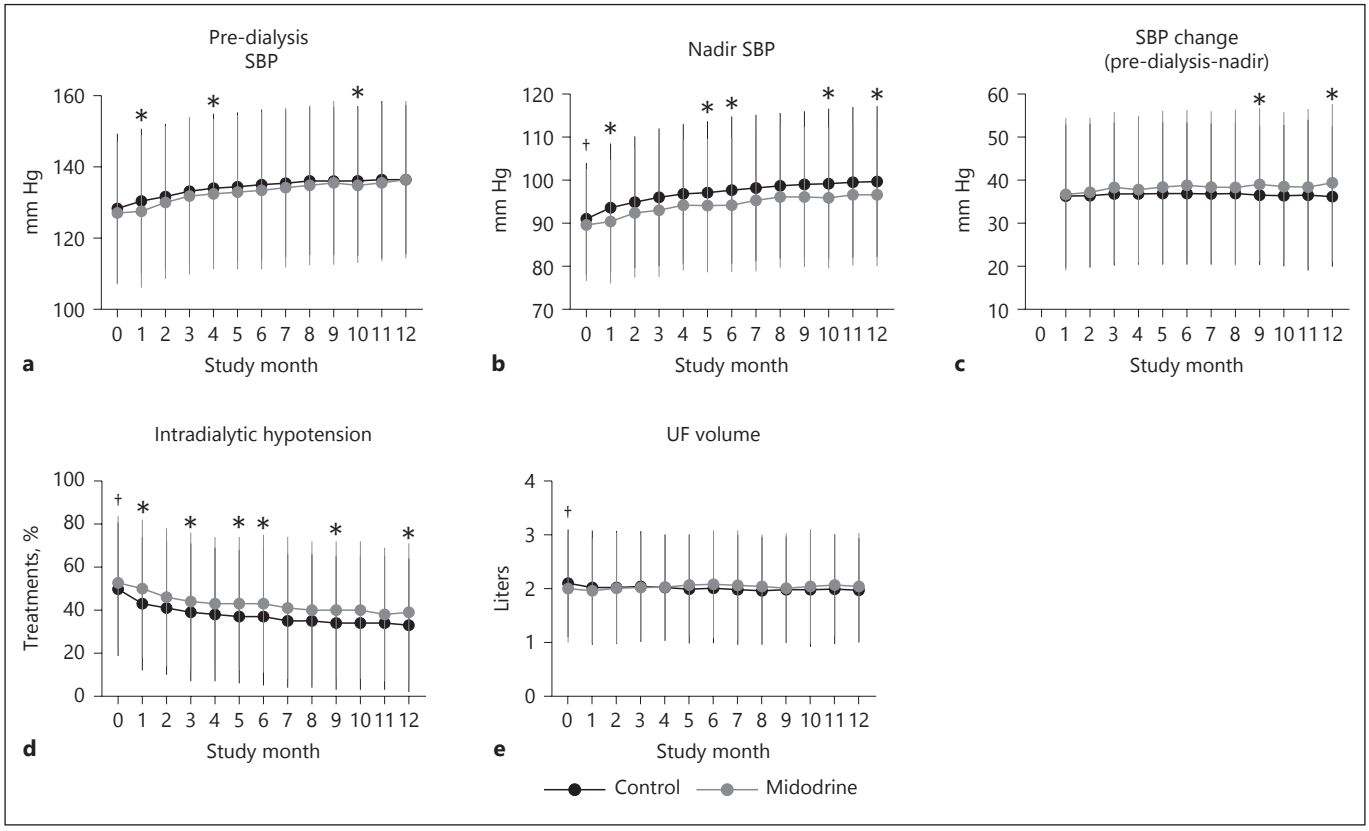

Fig. 3. Hemodynamic outcomes over follow-up time by midodrine exposure status. **a** Crude mean monthly values (± SD) for pre-dialysis systolic blood pressure (SBP) are displayed for midodrine (grey symbols and lines) and control (black symbols and lines) groups. Month 0 corresponds to the index month, months 1–12 represent follow-up time. **b** Crude mean monthly values (± SD) for nadir SBP values are presented as in (**a**). **c** Crude mean monthly values (± SD) for SBP change, corresponding to the pre-dialysis SBP value minus the nadir SBP value, are presented as for (**a**). **d** Crude mean values (± SD) of the percent of treatments affected by intradialytic hypotension (nadir SBP <90 mm Hg) in the month are presented as for (**a**). **e** Crude mean monthly values (± SD) for UF volume are presented as in (**a**). † Statistically significant difference between midodrine and control at index based on *t* test, $p < 0.05$. * Statistically significant difference between midodrine and control based on adjusted mean difference, $p < 0.05$. SBP, systolic blood pressure; UF, ultrafiltration.

impact of confounding on the reported associations, residual confounding may have influenced the results. Due to data limitations, this study could not evaluate associations between midodrine use and patient-reported occurrence of relevant symptoms during dialysis. The use of concurrent interventions to control IDH (e.g., cool dialysate, extra hemodialysis sessions, extended treatment time) was not evaluated. Because of its observational nature, the effects observed in this study are associations only; cause and effect are not determined.

In summary, this study represents the largest analysis to date of the efficacy of midodrine with respect to clinical and hemodynamic outcomes among dialysis patients. Although residual confounding may have influenced the results, the associations observed are not consistent with a pronounced clinical benefit of midodrine with respect to any outcome analyzed. Further research, including prospective clinical trials, is needed to identify more effective interventions to reduce the frequency and severity of IDH.

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Ethics Statement

The authors have no ethical conflicts to disclose.

Disclosure Statement

D.V.W. owns stock/options in DaVita Inc. SMB's spouse is an employee of AstraZeneca.

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Authors Contributions

Study design: S.M.B. Data acquisition: G.M. Data analysis/interpretation: S.M.B, D.E.C., and D.V.W. Statistical analysis: S.M.B.

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