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ORIGINAL

# Effect of midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the intensive care unit (MIDAS): an international randomised clinical trial

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## Abstract

**Purpose:** ICU discharge is often delayed by a requirement for intravenous vasopressor medications to maintain normotension. We hypothesised that the administration of midodrine, an oral $\alpha_1$-adrenergic agonist, as adjunct to standard treatment shortens the duration of intravenous vasopressor requirement.

**Methods:** In this multicentre, randomised, controlled trial including three tertiary referral hospitals in the US and Australia, we enrolled adult patients with hypotension requiring a single-agent intravenous vasopressor for ≥ 24 h. Subjects received oral midodrine (20 mg) or placebo every 8 h in addition to standard care until cessation of intravenous vasopressors, ICU discharge, or occurrence of adverse events. The primary outcome was time to vasopressor discontinuation. Secondary outcomes included time to ICU discharge readiness, ICU and hospital lengths of stay, and ICU readmission rates.

**Results:** Between October 2012 and June 2019, 136 participants were randomised, of whom 132 received the allocated intervention and were included in the analysis (modified intention-to-treat approach). Time to vasopressor discontinuation was not different between midodrine and placebo groups (median [IQR], 23.5 [10–54] vs 22.5 [10.4–40] h; difference, 1 h; 95% CI − 10.4 to 12.3 h; $p = 0.62$). No differences in secondary endpoints were observed. Bradycardia occurred more often after midodrine administration (5 [7.6%] vs 0 [0%], $p = 0.02$).

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**Conclusion:** Midodrine did not accelerate liberation from intravenous vasopressors and was not effective for the treatment of hypotension in critically ill patients.

**Keywords:** Midodrine, Oral vasopressor, Persistent hypotension, ICU discharge

## Introduction

Patients admitted to intensive care units (ICU) often require intravenous vasoactive medications to maintain normotension or other clinically indicated blood pressure goals [1]. A subset of patients with resolution of acute episodes of shock remain with persistent vasopressor-dependent hypotension without evidence of overt end-organ hypoperfusion. This continued vasoplegia, which can be pathophysiologically heterogeneous [2], presents a barrier to ICU discharge and may prolong length of stay. In hypotensive patients without impairment of tissue oxygenation, there is obvious appeal in using oral agents that could facilitate weaning from intravenous vasopressors and lead to earlier discharge.

Midodrine, an oral $\alpha_1$-adrenergic agonist, received accelerated approval by the U.S. Food and Drug Administration in 1996 for the treatment of symptomatic orthostatic hypotension. In 2010, the agency proposed withdrawing midodrine due to a lack of post-marketing studies demonstrating clinical benefits [3]. A memorandum was issued calling for further clinical studies [4], which revealed equivocal results [5, 6]. Midodrine has been increasingly used as an off-label medication to facilitate liberation from intravenous vasopressors and promote ICU discharge [7]. However, while the use of midodrine for the treatment of hypotension in the ICU has some observational support [7–9], it has not been studied in interventional clinical trials.

In this study, we prospectively examined the use of midodrine for the treatment of hypotension in ICU patients. We hypothesised that the administration of midodrine as an adjunct to standard treatment of persistent hypotension in otherwise resuscitated patients shortens the duration of intravenous vasopressor requirement and allows for earlier ICU and hospital discharge.

**Take-home message**

In critically ill patients, oral midodrine did not accelerate liberation from intravenous vasopressors, but resulted in more bradycardia. These findings do not support the use of midodrine in the ICU.

## Methods

### Study design

This multicentre, randomised, double-blind, placebo-controlled trial was conducted between October 2012 and June 2019 at three tertiary referral hospitals in the United States and Australia: Beth Israel Deaconess Medical Center (Boston, USA), Massachusetts General Hospital (Boston, USA), and Sir Charles Gairdner Hospital (Perth, Australia). The study was approved by the local institutional review boards at each study site. In the United States, this study was conducted under IND 113,330 filed with the U.S. Food and Drug Administration. For the Australian study site, a clinical trials notification was submitted to the Therapeutic Goods Administration of the Australian Department of Health (CT-2016-CTN-00226-1 v3). The study protocol has been previously published [10] and is available in the Supplementary Material (eText 1).

### Study participants

Hypotensive patients aged 18 years or older who were admitted to an ICU or high dependency unit were eligible for inclusion if they required single-agent intravenous vasopressor treatment (< 100 mcg/min phenylephrine, < 8 mcg/min norepinephrine, or < 60 mcg/min metaraminol) and were unable to be liberated from vasopressors for at least 24 h while maintaining desired blood pressure goals. Patients had to be otherwise resuscitated and reversible causes of hypotension had to be treated. Patients receiving vasopressor doses higher than the specified infusion rates or more than one vasopressor during the 24 h preceding randomisation were still eligible as long as the criterion of single-agent intravenous vasopressor requirement below the specified cut-off values was met at the time of randomisation. Patients with clinical evidence of inadequate tissue oxygenation (based on clinical judgment), hypovolaemic shock or hypotension due to adrenal insufficiency, liver failure, chronic renal failure (serum creatinine > 2 mg/dL), severe organic heart disease (left ventricular ejection fraction < 30%), acute urinary retention, pheochromocytoma, thyrotoxicosis, or bradycardia (heart rate < 50 beats/min) were excluded from this study. Patients who were pregnant, received midodrine prior to enrolment, had a known allergy to midodrine, were enrolled in another trial, or were unable to receive medications enterally were also excluded. All subjects or their legally authorised representatives provided written informed consent.

### Randomisation and masking

Participants were randomised in a 1:1 ratio to receive 20 mg of midodrine or placebo (matched in appearance) using a computer-generated randomisation list stratified by study site. The randomisation sequence was generated by an independent statistician and provided directly to the compounding pharmacy. The clinical teams, study personnel, and participants were masked to the treatment allocation.

### Interventions

Oral doses of midodrine or placebo were administered every 8 h, while intravenous vasopressor treatment was continued as needed. Both groups received other medications following standard of care guidelines. Study drugs were administered until ICU discharge or until any of the following occurred: worsening hypotension requiring high-dose vasopressors (> 100 mcg/min phenylephrine, > 8 mcg/min norepinephrine, or > 60 mcg/min metaraminol), epinephrine requirement, signs or symptoms of organ failure or hypoperfusion, adverse events related to midodrine, including serious allergic reactions, or death. If the blood pressure goal was met for at least 24 h without intravenous vasopressors, the study drug could be discontinued at the discretion of the clinical team following a standardised weaning protocol (eText 2 in Supplementary Material).

### Outcomes

The primary outcome was length of time, measured in hours, from study drug initiation until discontinuation of intravenous vasopressors. To account for brief interruptions in the use of vasopressors during the weaning phase, we defined discontinuation as a vasopressor-free period of at least 24 h. Secondary outcomes included time to ICU discharge readiness, ICU and hospital lengths of stay, and rates of ICU readmissions during the hospital stay.

In post hoc analyses, we assessed time to vasopressor discontinuation as well as length of ICU and hospital stay using time-to-event analyses. To evaluate the effect of midodrine in subgroups of participants with and without epidural analgesia as well as stratified by indication for ICU admission, we assessed the interaction between treatment group and the respective subgroup. Post hoc sensitivity analyses included time to vasopressor discontinuation stratified by centre and enrolment year. Additionally, we assessed the primary endpoint in patients receiving at least two doses of the study drug, patients receiving at least two study drug doses before intravenous vasopressor discontinuation, and patients receiving the study drug until intravenous vasopressor discontinuation or longer. With an exploratory intent, we assessed opioid administrations during the first 24 h after study drug initiation (eText 3 in Supplementary Material), since opioid analgesics are known to impair gastric emptying which subsequently may lead to delayed intestinal absorption of orally administered drugs [11–13]. Lastly, we performed a post hoc per protocol analysis including only patients without protocol violations.

### Adverse event assessment

Hypertension was predefined as systolic blood pressure > 160 mmHg or an increase by ≥ 20% from the pre-specified goal set by the primary team. Short-term spikes in blood pressure, which commonly occur during mobilisation or other ICU interventions, were not considered adverse events. Bradycardia was defined as heart rate < 40 beats/min or a decrease by ≥ 20% from the pre-specified goal. Haemodynamically significant tachyarrhythmias were characterised by a drop in systolic blood pressure > 20 mmHg. New-onset organ failure was defined by inadequate tissue oxygenation, liver or renal failure (based on clinical judgment). Adverse events were collected daily from medical records for the period of study drug administration.

### Statistical analysis

A sample size of 50 subjects per group was needed to detect a difference of 6 h in time to vasopressor discontinuation between participants receiving midodrine and those receiving placebo with a two-sided alpha of 0.05 and a power of 80%. The expected effect size was based on observational research [14]. To account for dropouts and withdrawals, a minimum sample size of 120 patients was targeted.

Data analysis was performed using a modified intention-to-treat approach, including all randomised patients who received at least one dose of study medication. Continuous data are expressed as mean (standard deviation) or median (interquartile range), as appropriate based on variable distribution; differences between groups were compared using a $t$ test or Mann–Whitney $U$ test, respectively. Categorical data are presented as frequencies (proportions); differences between groups were analysed using a $\chi^2$ or Fisher exact test, as appropriate. Differences between groups are presented with 95% confidence intervals. For subgroup analyses, we fitted negative binomial regression models for the outcome of time to vasopressor discontinuation and included an interaction term between treatment group and subgroup; results are reported as incidence rate ratios with 95% confidence intervals. No data for the analysis of the primary endpoint were missing. In post hoc time-to-event analyses, Kaplan–Meier curves and log-rank tests were used to compare time to vasopressor discontinuation and ICU/hospital lengths of stay between groups. No adjustment for multiple testing was performed; therefore, all results from secondary and

post hoc analyses should be interpreted as exploratory and hypothesis generating. A two-sided $p<0.05$ was considered as statistically significant. Statistical analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX, USA). A statistical analysis plan is provided in the Supplementary Material (eText 1).

## Results

### Study population

Between October 2012 and June 2019, 530 patients were assessed for eligibility, of whom 213 met eligibility criteria. Written informed consent was obtained for 139 patients, of whom 136 were randomised and 132 received the allocated intervention and were included in the analysis; 66 (50%) were administered midodrine and 66 (50%) received placebo (Fig. 1). Two randomised patients in each study arm discontinued vasopressor treatment after randomisation and were not administered a study drug. Patients had a mean (SD) age of 68 (14) years, were predominantly male (68/132 [51.5%]), and presented with a mean APACHE II score of 14.7 (5.5). Baseline characteristics are presented in Table 1 and, stratified by study centre, in the Supplementary Material (eTable 1). Baseline laboratory results were similar between groups (eTable 2 in Supplementary Material). Details on vasopressor use and haemodynamic parameters during the first 24 h after the first study drug administration are provided in eTable 3.

### Primary outcome

The median time to discontinuation of intravenous vasopressors was 23.5 (IQR, 10–54) h in the midodrine group and 22.5 (IQR, 10.4–40) h in the placebo group, with no significant difference between groups (difference, 1 h; 95% CI − 10.4 to 12.3 h; $p=0.62$) (Table 2). Post hoc time-to-event analyses confirmed a lack of significant differences in vasopressor duration after study drug initiation between treatment arms ($p=0.54$) (Fig. 2).

### Secondary outcomes

Times to ICU discharge readiness were similar in the midodrine and placebo grops (median, 5 [IQR, 4–7] vs 5 [IQR, 4–6.5] days, respectively; difference, 0 days; 95% CI − 1 to 1 days; $p=0.64$) (Table 2). In the midodrine group, median ICU length of stay was 6 (IQR, 5–8) days compared to 6 (IQR, 4–8) days in the placebo group (difference, 0 days; 95% CI − 0.5 to 0.5 days; $p=0.46$) (Table 2). Hospital length of stay was not different between groups (median, 11 [IQR, 9–21] vs 14 [IQR, 9–22] days, difference, − 3.0 days; 95% CI − 6.3 to 0.3 days; $p=0.45$) (Table 2). Time-to-event analyses revealed no differences in ICU and hospital length of stay between groups ($p=0.59$ and 0.52, respectively) (eFigure 1 in Supplementary Material). In the midodrine group, 1 (1.5%) participant was readmitted to the ICU during their hospital stay compared to 3 (4.5%) participants in the placebo group (difference, − 3%; 95% CI − 8.9% to 2.8%; $p=0.62$) (Table 2).

### Study drug administration

Study drugs were administered for a median duration of 42.4 (IQR, 23.5–71.3) h in the midodrine group and 47.5 (IQR, 34.1–72.4) h in the placebo group. In the midodrine group, 1 (0.8%) participant received the first dose of study medication at the same time as intravenous vasopressor treatment was initiated; 3 (2.3%) participants in the placebo arm received the study drug despite vasopressors being discontinued or paused at the time of study drug initiation. Analyses were performed using data from all randomised participants who received at least one dose of study medication (modified intention-to-treat). In a post hoc per protocol analysis, the four randomised and dosed, but ineligible, patients were excluded: no differences in time to vasopressor discontinuation were seen between midodrine and placebo (median, 23.7 [IQR, 11.5–54] h vs 23 [IQR, 11–47] h; difference, 0.7 h; 95% CI − 10.8 to 12.1 h; $p=0.79$).

### Post hoc subgroup analyses

In post hoc interaction analyses, we observed a significant modification of the effect of midodrine on time to vasopressor discontinuation by the use of epidural analgesia ($p$ for interaction = 0.03). In 31 (23.5%) participants with epidural analgesia, time to vasopressor discontinuation was significantly shorter with midodrine compared to placebo (difference, − 18.4 h; 95% CI − 33.5 to − 3.3 h; incidence rate ratio, 0.53; 95% CI 0.28 to 0.99 $p=0.045$); whereas, no difference was seen in patients without epidural analgesia (Table 3). We further examined possible effect modification by indication for ICU admission; no significant interactions between study group and reason for ICU admission were observed (Table 3).

### Post hoc sensitivity analyses

To account for the long recruitment period across multiple centres, we stratified the primary analysis by study centre and year of enrolment. No differences in time to vasopressor discontinuation were seen across different study sites or enrolment years (eTables 4 and 5 in Supplementary Material).

To assure adequate plasma concentrations of the study drug had been achieved, we re-evaluated the primary endpoint in post hoc sensitivity analyses across patients receiving at least two doses of the study drug (129/132 [97.7%]), at least two doses before intravenous vasopressor discontinuation (103/132 [78%]), and receiving the

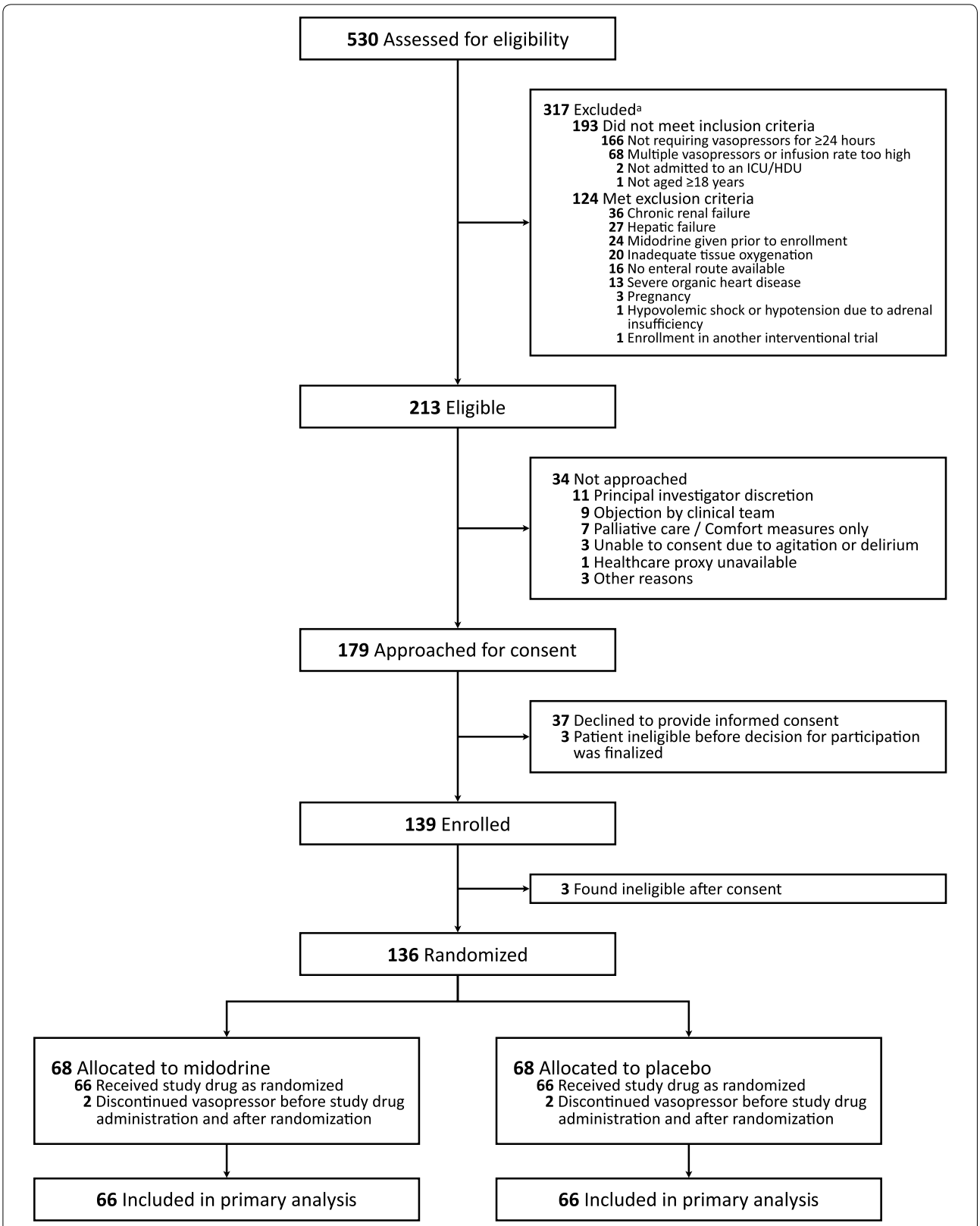


**Fig. 1** Participants flowchart. ICU indicates intensive care unit, HDU indicates high dependency unit. [a]Numbers of participants not meeting inclusion or exclusion criteria are nonexclusive

**Table 1 Characteristics of study participants by treatment group**

| Characteristics | Midodrine ($n=66$) | Placebo ($n=66$) |
|---|---|---|
| Demographics | | |
| Sex, *n* (%) | | |
| Male | 36 (54.5%) | 32 (48.5%) |
| Female | 30 (45.5%) | 34 (51.5%) |
| Age, years | 70.0 (12.6) | 66.7 (14.7) |
| Patient-reported race, *n* (%) | | |
| White/Caucasian | 64 (97%) | 62 (93.9%) |
| Other | 1 (1.5%) | 1 (1.5%) |
| Unknown/not specified | 1 (1.5%) | 3 (4.5%) |
| Weight, kg[a] | 78.6 (22.4) | 82.3 (23.5) |
| Height, cm[a] | 169 (10) | 166 (10) |
| Body mass index (BMI), kg/m$^2$[a] | 27.9 (8.8) | 29.8 (8.8) |
| APACHE II score[b] | 14.7 (5.2) | 14.8 (5.9) |
| SOFA score[c] | | |
| Day 1 | 4 (3, 5) | 5 (3, 7) |
| Day 2 | 3 (3, 5) | 4 (3, 6) |
| Day 3 | 3 (1, 5) | 3 (1, 4) |
| Day 4 | 3 (0.5, 4.5) | 3 (1, 5) |
| Day 5 | 3 (1.5, 3) | 3 (1, 8) |
| Indication for ICU admission | | |
| Postoperative/surgical | 45 (68.2%) | 42 (63.6%) |
| Sepsis | 13 (19.7%) | 13 (19.7%) |
| Medical/other reason | 8 (12.1%) | 11 (16.7%) |
| Epidural analgesia, *n* (%) | 18 (27.3%) | 13 (19.7%) |
| Duration of vasopressor administration | | |
| Total duration, h | 76.6 (50.5, 107.4) | 60.6 (44.3, 92) |
| Before study drug administration, h | 35.5 (28, 55) | 35.4 (24.7, 43.8) |
| Baseline mean arterial blood pressure, mmHg | 75.9 (9.4) | 72.8 (8.2) |
| Vasopressor dose at enrolment, mcg/kg/min[d] | | |
| Norepinephrine ($n=41$) | 0.06 (0.04, 0.08) | 0.06 (0.02, 0.09) |
| Phenylephrine ($n=28$) | 0.61 (0.37, 0.84) | 0.43 (0.2, 1.1) |
| Metaraminol ($n=60$) | 0.6 (0.38, 0.72) | 0.61 (0.46, 0.83) |

Data are expressed as mean (standard deviation), frequency (prevalence in %), or median (interquartile range (25th–75th percentile), values separated by comma)

[a] Documented in 120/132 participants (height and BMI) and 129/132 participants (weight)

[b] Data available for APACHE II calculation in 131/132 participants

[c] SOFA scores were available in 114/132 (day 1), 114/132 (day 2), 101/132 (day 3), 59/132 (day 4), and 39/132 (day 5) participants, respectively

[d] Weight-adjusted vasopressor doses were available in 129/132 participants; three participants were missing data on weight

study drug until vasopressor discontinuation or longer (116/132 [87.9%]). In none of these post hoc analyses, significant differences in time to vasopressor discontinuation between treatment arms were noted (eTable 6).

### Post hoc analyses of opioid administration

To address the possibility of delayed or impaired gastrointestinal absorption of the study drug due to opioid analgesics, we retrospectively assessed opioid doses administered during the first 24 h after study drug initiation. Total administered opioid doses were not different between the midodrine and placebo groups (median, 7.50 [IQR, 0–39] vs 3.75 [IQR, 0–45] mg; difference, 3.75 mg; 95% CI − 12.73 to 20.23 mg; $p=0.65$). Times to vasopressor discontinuation did not differ between intervention groups, both in participants receiving opioids (70/132 [53%]; median, 28.5 [IQR, 14.1–54] vs 23 [IQR, 9.8–51] h; difference, 5.5 h; 95% CI − 14.4 to 25.4 h; $p=0.55$) and those without opioid administration during the first 24 h (62/132 [47%]; median, 19

**Table 2 Primary and secondary outcomes**

| Outcomes | Midodrine ($n=66$) | Placebo ($n=66$) | Difference (95% CI) | $p$ value |
|---|---|---|---|---|
| ***Primary outcome*** | | | | |
| Time to vasopressor discontinuation, h | 23.5 (10, 54) | 22.5 (10.4, 40) | 1 (− 10.4 to 12.3) | 0.62 |
| ***Secondary outcomes*** | | | | |
| Time to ICU discharge readiness, days[a] | 5 (4, 7) | 5 (4, 6.5) | 0 (− 1 to 1) | 0.64 |
| ICU length of stay, days | 6 (5, 8) | 6 (4, 8) | 0 (− 0.5 to 0.5) | 0.46 |
| Hospital length of stay, days | 11 (9, 21) | 14 (9, 22) | − 3 (− 6.3 to 0.3) | 0.45 |
| ICU readmission rate, *n* (%) | 1 (1.5%) | 3 (4.5%) | − 3% (− 8.9 to 2.8) | 0.62 |

Data are expressed as median (interquartile range (25th–75th percentile), values separated by comma) or frequency (prevalence in %). Secondary analyses were not adjusted for multiple testing and should be interpreted as exploratory

[a] Time to ICU discharge readiness was available in 127 participants

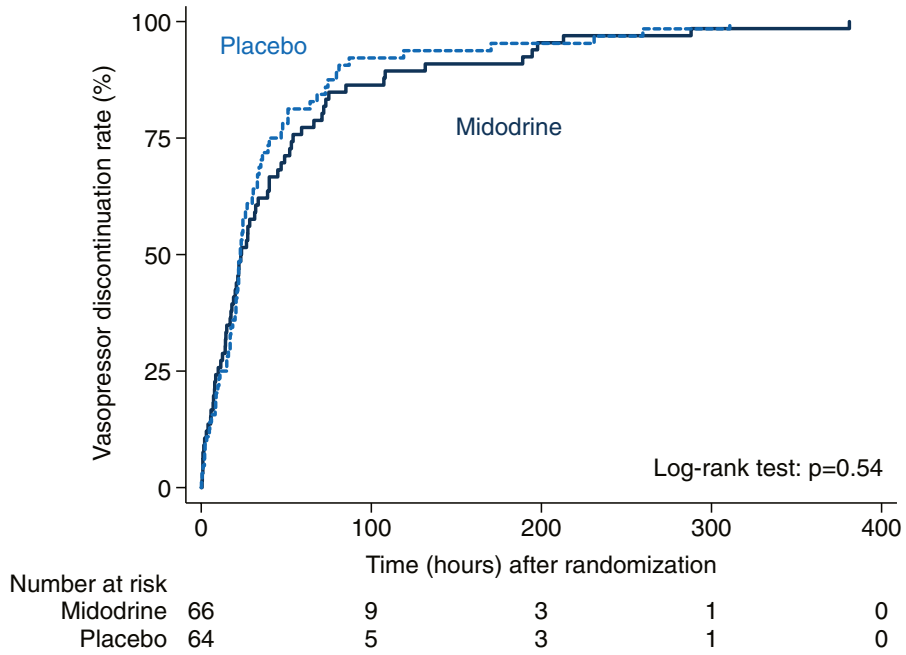


**Fig. 2** Post hoc time-to-event analysis for time to vasopressor discontinuation. Kaplan–Meier curves for time to vasopressor discontinuation showed no difference in time to vasopressor discontinuation between the midodrine (navy blue solid line) and placebo (light blue dashed line) groups

[IQR, 7–45] vs 22 [IQR, 11–33] h; difference, − 3 h; 95% CI − 17.5 to 11.5 h; $p=0.77$).

### Adverse events

Adverse event rates were similar between treatment groups (eTable 7 in Supplementary Material): 20 (30.3%) participants receiving midodrine and 17 (25.8%) receiving placebo experienced at least one adverse event ($p=0.56$). The most common adverse events were cardiovascular events: Hypertension occurred in 7 (10.6%) subjects receiving midodrine and 3 (4.6%) receiving placebo ($p=0.19$). In the midodrine group, 5 (7.6%) participants experienced bradycardia compared to no bradycardic episodes in the placebo group ($p=0.02$). Atrial fibrillation was observed in 3 (4.6%) and 1 (1.5%) participants, respectively ($p=0.31$). No differences in the occurrence of other adverse events were noted (eTable 7 in Supplementary Material).

## Discussion

In this study, midodrine did not decrease time to vasopressor discontinuation or length of stay in the ICU or hospital. The use of midodrine, however, resulted in more bradycardic events.

**Table 3 Subgroup analyses**

| Effect modifier | Time to vasopressor discontinuation, h | | | IRR (95% CI) | *p* value |
|---|---|---|---|---|---|
| | Midodrine | Placebo | Difference (95% CI) | | |
| ***Epidural analgesia (p for interaction = 0.03)*** | | | | | |
| Epidural analgesia (*n* = 31) | 14.8 (5.5, 21.5) | 33.1 (20.4, 47) | − 18.4 (− 33.5 to − 3.3) | 0.53 (0.28 to 0.99) | 0.045 |
| No epidural analgesia (*n* = 101) | 31.7 (14.2, 71.5) | 22 (9.8, 36) | 9.7 (− 6.3 to 25.7) | 1.48 (0.92 to 2.35) | 0.103 |
| ***Indication for ICU admission (p for interaction = 0.171 and 0.066)***[a] | | | | | |
| Postoperative/surgical (*n* = 87) | 22.2 (12.5, 47) | 23.8 (9.8, 51) | − 1.6 (− 13.1 to 9.9) | –[b] | –[b] |
| Sepsis (*n* = 26) | 40 (7, 108.2) | 24 (17, 39.3) | 16 (− 65.7 to 97.7) | –[b] | –[b] |
| Medical/other reason (*n* = 19) | 24.1 (10, 53.5) | 15 (1.9, 23.5) | 9.1 (− 18.1 to 36.2) | –[b] | –[b] |

Data are expressed as median (interquartile range (25th–75th percentile), values separated by comma)

*IRR* incidence rate ratio

[a] *p* values for interaction terms are reported for sepsis and medical/other reason, respectively. Postoperative/surgical indication was considered as reference group

[b] Only descriptive data are reported; no subgroup analyses were performed in the absence of significant interaction

Intravenous vasopressor requirement often poses a barrier to ICU discharge, as many hospitals mandate intensive care settings for the infusion of vasoactive agents [15]. Replacing intravenous agents with an oral vasopressor represents an intuitive approach to facilitate liberation of ICU patients from intravenous vasopressors and promote ICU discharge. Midodrine is increasingly used for this off-label indication [7, 9, 16], despite an absence of evidence from randomised clinical trials, and a paucity of supportive observational data. Supported by a case report [17], two small case series were published which indicated that oral midodrine treatment may help to avoid ICU admissions or shorten length of stay in otherwise resuscitated patients who needed ICU-level care only due to intravenous vasopressor requirements [18, 19]. In both reports, patients who conventionally would have received intravenous vasopressor treatment received oral midodrine instead, which resulted in cost savings due to shorter stays. In an observational study in surgical patients who met ICU discharge criteria except for an intravenous vasopressor requirement, midodrine treatment was associated with faster rates of decline of intravenous vasopressors [14]. Of note, there was substantial heterogeneity of effect in the latter study [14]. Two retrospective, observational trials demonstrated an association between midodrine administration and shorter duration of vasopressor use, lower rates of vasopressor reinstitution after discontinuation [15], as well as faster ICU discharge once vasopressors were discontinued [20]. This randomised controlled trial does not support the view that midodrine facilitates liberation from intravenous vasopressors.

The significant effect modification by the use of epidural analgesia observed in post hoc subgroup analyses could have two potential explanations. First, the mechanism of hypotension during epidural analgesia and orthostatic hypotension, for which midodrine's efficacy has been demonstrated in randomised trials [21, 22], is identical, namely neural vasoplegia resulting from dilation of both resistance and capacitance vessels in the anaesthetised area [23]. The pathophysiology of vasoplegia in sepsis and systemic inflammatory response is markedly different to neural vasoplegia, and is driven by multiple mechanisms, including increases in production of nitric oxide, prostanoids, endothelin-1 and reactive oxygen species [2]. Second, it is possible that epidural analgesia may improve the absorption of oral medications like midodrine. Epidural analgesia has been shown to facilitate recovery of gastrointestinal function [24–26], which is often impaired in critically ill patients and patients recovering from surgery [27, 28]. Even though the observed subgroup effect of midodrine in patients with neuraxial analgesia is interesting, it can only be considered hypothesis generating and warrants further investigation. Future prospective trials are required to address any potential effect of midodrine in patients with neurogenic hypotension.

While the total number of adverse events did not differ between groups, patients receiving midodrine had a higher incidence of bradycardia, which has been reported previously [29]. Midodrine-induced bradycardia may be explained by an activation of the baroreceptor reflex, similar to other $\alpha_1$-agonists. The higher rate of bradycardic events associated with midodrine may indicate a narrow therapeutic range. Consequently, ICU-level cardiac monitoring may be required in patients even after successful liberation from intravenous vasopressor infusion requirement.

The main advantage of the present study lies in its prospective and blinded design. Given the limited evidence regarding clinical benefits of midodrine and the lack of randomised controlled studies of its use in the ICU, our

study provides important evidence on this widespread off-label use of midodrine. The multicentric study design, including patients from three academic centres across two continents, and broad eligibility criteria, including a wide spectrum of critically ill patients, contribute to the generalisability of our findings. Several limitations apply: The broad eligibility criteria may have resulted in a heterogeneous cohort with different underlying aetiologies of vasopressor-dependent hypotension and excluding patients already receiving midodrine in the ICU prior to enrolment may have increased the possibility of selection bias. Furthermore, the sample size was low, but the absence of any trend towards effectiveness of midodrine suggests that the drug is ineffective in the broad range of patients in the studied setting. An additional limitation arises from the lack of pre-specified subgroup analyses, which prevents us from drawing any conclusions on the use of midodrine in patients receiving epidural analgesia. Finally, the study was conducted in two high-income countries and may, therefore, not be applicable to lower income settings.

In conclusion, midodrine did not reduce time to discontinuation of intravenous vasopressors in critically ill patients with persistent hypotension. The lack of effectiveness, combined with a higher rate of bradycardia, do not support the routine use of midodrine as off-label medication to accelerate liberation from intravenous vasopressors in the ICU.

**Electronic supplementary material**
The online version of this article (https://doi.org/10.1007/s00134-020-06216-x) contains supplementary material, which is available to authorized users.

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**Author contributions**
Concept and design: MHA, TTH, ME. Acquisition, analysis, or interpretation of data: PS, MHA, MDP, BW, BT, DS, SS, CSP, TTH, ME. Drafting of the manuscript: PS, MHA, BT, ME. Critical revision of the manuscript for important intellectual content: PS, MHA, MDP, BW, BT, DS, SS, CSP, TTH, ME. Statistical analysis: PS, TTH, ME. Supervision: MHA, ME. ME had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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**Data availability**
De-identified data collected during the trial will be made available upon reasonable request to researchers who provide a methodologically sound proposal, after approval by the study authors, and with a signed data access agreement. Questions about data are handled by the corresponding author.

**Compliance with ethical standards**

**Conflicts of interest**
Matthias Eikermann has received unrestricted funds from philanthropic donors Jeffrey and Judy Buzen and grants from Merck & Co. outside of the submitted work. All other authors declare no conflicts of interest.

**Ethical approval**
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local institutional review boards at Massachusetts General Hospital (Partners Human Research Committee, #2016P002045), Sir Charles Gairdner Hospital (Sir Charles Gairdner Hospital HREC, #2015-098), and Beth Israel Deaconess Medical Center (Committee on Clinical Investigations, #2018P000162).

**Informed consent**
Written informed consent was obtained from all subjects or their legally authorised representatives.

## Publisher's Note



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