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Beyond vasopressor liberation: early midodrine initiation and recurrent documented hypotension during sepsis recovery - a sequential target-trial emulation

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Abstract

Background: Midodrine studies during recovery from sepsis-associated circulatory dysfunction have largely focused on the time needed to discontinue intravenous vasopressors. This process measure does not directly describe recurrent hemodynamic instability. This study evaluated repeated, documented hypotension after clinically timed midodrine initiation decisions and examined the effect of the outcome observation-time definition.

Methods: MIMIC-IV version 3.1 data were used to construct sequential six-hour treatment-decision windows among patients receiving sustained low-dose intravenous vasopressors for sepsis-associated circulatory dysfunction. The compared strategies were midodrine initiation within six hours and deferral during ongoing index-ICU care. A hypotension episode required documented MAP recovery followed by two qualifying low readings. The originally reported outcome counted index-ICU events per alive day through 72 hours; a post hoc sensitivity aligned the denominator with observed time alive in the index ICU. Cross-fitted treatment-probability weighting and 400 patient-cluster bootstrap refits were used.

Results: The cohort comprised 4,011 patients and 33,969 eligible decision windows, of which 150 had observed midodrine initiation within six hours. The originally reported weighted rates were 0.5908 and 0.6019 episodes per alive day for early initiation and deferral, respectively (difference, -0.0111; 95% CI, -0.1244 to +0.1191). With the observation-aligned denominator, rates were 0.6740 and 0.6273 episodes per index-ICU day (difference, +0.0467; 95% CI, -0.0789 to +0.1824). The paired difference between these strategy contrasts was +0.0578 (95% CI, +0.0132 to +0.1098). Neither individual treatment contrast excluded zero.

Conclusions: Assessing recurrent documented hypotension adds a clinically distinct outcome to midodrine research focused on vasopressor liberation. No clear difference between initiation strategies was demonstrated,

while the direction of the point estimate changed when observation time was aligned with where MAP events were recorded. The findings show why event ascertainment and time-at-risk definitions matter when evaluating hemodynamic stability with routinely collected critical-care data.

Trial registration: Not applicable (retrospective observational analysis; no prospective assignment to interventions).

Keywords
midodrine; recurrent hypotension; sepsis-associated circulatory dysfunction; target trial emulation; clone-censor-weight; while-alive outcome; MIMIC-IV.

Background

Recovery from sepsis-associated circulatory dysfunction is not a single moment. Patients can approach intravenous vasopressor discontinuation while their blood pressure continues to fluctuate, raising a practical question for teams managing the transition from urgent resuscitation to ongoing critical care: is circulatory stability sustained, or does low blood pressure recur? Sepsis definitions and resuscitation guidelines recognize the importance of circulatory dysfunction and hemodynamic support [1, 2]. Observational studies relate low mean arterial pressure (MAP) exposure to organ injury and mortality [3, 4, 5], while trials of blood-pressure targets illustrate the clinical trade-offs inherent in vasopressor management [6, 7]. Yet a single MAP measurement or the time an infusion ends cannot fully describe recurrent hypotension during recovery.

Oral midodrine, an alpha-1 adrenergic agonist, has been used off-label to facilitate the reduction of intravenous vasopressors. Early reports and prescribing cohorts documented this practice, and observational comparisons subsequently examined vasopressor exposure and care transitions [8, 9, 10, 11, 12]. Randomized or feasibility trials, including MIDAS, MAVERIC and LIBERATE, mainly assessed vasopressor discontinuation or related recovery outcomes [13, 14, 15]. Sepsis-focused trials have also considered adjunctive midodrine, often through vasopressor-use or mortality outcomes [16, 17]. Reviews continue to synthesize mixed and limited evidence [18, 19], and the 2026 Surviving Sepsis Campaign guideline judged the evidence insufficient to recommend for or against oral midodrine in septic shock with ongoing vasopressor requirements [20]. This literature leaves a

separate, clinically meaningful question: what happens to the burden of recurrent, documented low-MAP episodes after the decision to initiate midodrine?

The endpoint used to answer that question matters. Midodrine may increase vascular tone, but pharmacologic activity and the timing of infusion cessation are not interchangeable with episode-free hemodynamic recovery [21, 22, 23]. A recurrent-event endpoint recognizes that one patient may experience several distinct low-pressure events; requiring recovery and repeated low MAP recordings creates an operational definition of documented recurrence rather than treating every isolated low reading as a separate episode. Because death ends the opportunity to experience further recurrent events, while-alive rate concepts offer a useful starting point for outcome construction [24, 25]. In electronic health records, however, the opportunity to observe MAP also changes when a patient leaves the monitored ICU setting. The numerator and denominator of an event rate must therefore describe a coherent observation period.

This study addresses two linked questions using MIMIC-IV [26]. First, at repeated times when a patient remains eligible for a treatment decision, how do rates of recurrent, confirmed low-MAP events compare between initiation of midodrine within six hours and deferral for at least six hours? Sequential eligibility, a common decision-time origin and strategy-compatible follow-up were used to make the initiation decision explicit [27, 28, 29, 30]. Second, how does interpretation change when the denominator of an index-ICU-documented event rate is aligned with the time during which those events can be observed? The first question addresses a clinical treatment decision; the second, examined with a post hoc denominator sensitivity analysis, addresses a measurement choice relevant to studies of circulatory recovery.

Methods

Study design, setting and eligibility

This retrospective observational analysis used the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, version 3.1, distributed through PhysioNet [26, 31]. MIMIC-IV contains deidentified electronic health records from Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. Access is restricted to credentialed researchers who complete the required training and sign a PhysioNet data use agreement. The reporting was informed by guidance for observational studies using routinely collected data [32]. Eligible

treatment decisions were emulated at six-hour intervals [27-30]. Eligibility began no earlier than 24 hours after ICU admission and no earlier than 24 hours after first positive-dose intravenous vasopressor exposure. Infection-related records and organ dysfunction estimates compatible with sepsis were required to precede T0. Historical lactate >2 mmol/L had to be temporally associated with positive-dose vasopressor treatment; current lactate elevation was not required at every subsequent decision time. Because fluid resuscitation could not be verified consistently, these criteria identified sepsis-associated circulatory dysfunction with historical shock-compatible evidence rather than confirmed Sepsis-3 septic shock in every patient [1, 33]. Derived SOFA and sepsis timestamps may reflect retrospective data processing.

At T0, the norepinephrine-equivalent intravenous vasopressor dose had to be >0 and <=0.20 micrograms/kg/min. Positive-dose coverage had to extend across >=22 of the preceding 24 hours and >=5 of the preceding six hours. Prior actual midodrine administration during the hospitalization excluded a window, as did a decision time at or after recorded hospital death. A patient could contribute more than one eligible decision window.

Treatment strategies and six-hour grace period

Each eligible decision window was assigned the common T0 and cloned into both strategies. Under the implemented dynamic early-initiation strategy, midodrine had to be administered within six hours while the patient remained alive and in the index ICU; death or index-ICU discharge before six hours ended that obligation. Under deferral, midodrine was not initiated during the same interval while index-ICU care continued; initiation after six hours was permitted. For a patient still in the ICU at six hours, an early-initiation clone without treatment was artificially censored at six hours. A deferral clone was censored at actual initiation if treatment occurred before six hours. Events confirmed before artificial censoring remained eligible for analysis. Treatment assignment was not randomized [27, 28, 29]. The ICU-conditional grace-period wording describes the implemented code and was clarified after a post hoc consistency audit, not prospectively registered.

Recurrent documented hypotension

Episodes were constructed from derived MAP values, which could incorporate invasive and noninvasive measurements. A confirmed episode required an observed recovery MAP >=70 mmHg, a first MAP <65 mmHg within 90 minutes of recovery, and a second MAP <65 mmHg within a further 90 minutes. Confirmation was assigned to the second low recording. A new episode required a new observed recovery to >=70 mmHg; a qualifying recovery within 90 minutes before T0 could anchor an episode confirmed after T0. Events were counted only after T0 and before index-ICU discharge, death, or the relevant horizon. This algorithm identified repeated-measurement-supported hypotension clusters, not continuous hypotension duration. Its 90-minute confirmation rule was finalized after internal timing audits and was not prospectively registered.

Outcome definitions and survival ascertainment

The initial 72-hour full-horizon, while-alive outcome concept was a rate formed from each eligible decision window's recurrent hypotension count divided by time alive through death or 72 hours, multiplied by 24. It was informed by recurrent-event and while-alive estimand methods [24, 25]. In the implemented analysis, the unit of aggregation was the eligible decision entry: a person contributing several windows was represented several times, so the quantity is a decision-window-weighted rate rather than a unique-patient-weighted PWWA estimand. MAP observation beyond index-ICU departure was not consistently available for the full horizon.

Following the observation-time review, the 72-hour index-ICU-documented rate per alive day was retained as the originally reported principal comparison. It equaled 24 times the number of qualifying episodes recorded during index-ICU follow-up before death or 72 hours, divided by time alive through death or 72 hours. This index-ICU event definition was a post hoc endpoint refinement. The numerator stopped at index-ICU exit; alive time could continue thereafter. The operational quantity thus reflects the frequency of episodes documented in the index ICU relative to the chosen alive-time denominator.

A separate exploratory full-horizon decision-window-rate analysis, previously labeled PWWA, used inverse-probability weights for complete MAP observation through death or the 72-hour horizon [34]. This explored an event process extending beyond the index ICU, with observation modeled from measured decision-time covariates.

In the mortality audit, hospital death timestamps agreed with the pre-existing death-time field, and patient-level death dates agreed with hospital death dates when both existed. Across the overlapping decision windows, 3,612 had an exact hospital death within 72 hours, including 189 after index-ICU departure. A further 54 date-only death records fell entirely within the horizon, and 43 overlapped its boundary. A date-only death record was not converted to an observed precise death time. The refitted principal analyses used exact hospital death timestamps; the date-only uncertainty was examined separately with the earlier untruncated estimator.

Post hoc denominator-alignment sensitivity

To quantify the impact of the observation-time definition, a post hoc sensitivity analysis replaced the 72-hour alive-time denominator of the index-ICU-documented event rate with time alive and under observation in the index ICU through the earliest of death, index-ICU exit or 72 hours. The qualifying low-MAP event count, eligible decision windows, treatment-strategy compatibility rules, weight limits and window-weighted aggregation were otherwise unchanged. The analysis used 400 paired patient-cluster bootstrap resamples with the same five-fold cross-fitted hourly initiation model refitted in each sample. The index-ICU observation model was not applied to either index-ICU-defined rate. The change between the two resulting treatment-strategy contrasts was calculated within bootstrap resamples. The aligned-denominator outcome was a post hoc change of estimand, rather than a prespecified test of treatment-effect modification.

Treatment and observation weighting

The six-hour initiation process was modeled in one-hour intervals with regularized logistic regression and five-fold cross-fitting grouped by patient. ICU observation was modeled across 12 six-hour intervals with three-fold patient-grouped cross-fitting. Predictors measured or summarized before T0 included age, sex, SOFA, recent lactate and creatinine, log ICU time, norepinephrine-equivalent dose and preceding dose change, mean MAP, MAP trend, and the preceding proportion of MAP readings below 65 mmHg. Missing covariates were median-imputed with missingness indicators. The model used decision-time baseline predictors and did not continually update MAP, vasopressor dose or other evolving clinical status within the six-hour grace period. Measured covariate balance was summarized with standardized mean differences (SMDs) [35, 36].

The reported 72-hour comparisons applied strategy-compatibility weights to the horizon-level decision-window-rate estimator. Departure from the index ICU ended documented event accrual, so ICU-observation weights were not applied to either index-ICU-defined outcome. The exploratory full-horizon calculation combined treatment and ICU-observation weights. Overlap weighting was evaluated as a separate weighting approach targeting the population with greater treatment overlap [37]. The reported horizon-level weighted rate estimator did not implement a fully time-updated, event-specific longitudinal CCW outcome estimator.

Bootstrap inference and weight sensitivity

Patient-cluster bootstrap sampling preserved each patient's repeated decision windows. In each of 400 replicates, the treatment and ICU observation logistic coefficients were refitted with bootstrap multiplicity weights. The imputation and scaling transformations, patient-grouped cross-fit fold assignments, model specifications, and penalties were fixed. Percentile confidence intervals therefore incorporated coefficient refitting but not uncertainty from every preprocessing decision.

Untruncated refitting produced isolated very large inverse-probability weights. After that audit, the fitted original-sample 99th percentile of initiation weights (418.398) was fixed as the initiation cap; the deferral cap was 10, with caps of 5 and 20 as sensitivity analyses. For exploratory full-horizon PWWA, original-sample complete-window ICU observation weights were capped at the 99th (2.123) or 99.5th (2.506) percentile. These cutoffs were chosen post hoc; truncation reduced numerical instability but can introduce bias. The analysis reports both capped inverse-probability and overlap-weighted results, with their different target populations clearly distinguished [34, 35, 37].

Computational consistency audit

An implementation audit reconstructed treatment-strategy clone endpoints, event-confirmation timestamps, the supported event-time weight contributions and index-ICU rate arithmetic. No mismatches were found between event support and clone histories, and recalculated event contributions reproduced the recorded implementation. Reporting was informed by target-trial and routinely collected data guidance [30, 32]. Technical definitions and audit details are provided in Additional file 1.

Use of generative AI for manuscript preparation

ChatGPT (OpenAI) assisted with English-language editing, editorial restructuring and manuscript formatting. This assistance did not involve access to participant-level data or computation of the reported statistical analyses. The sole author is responsible for the scientific content and final submission.

Results

Eligible treatment decisions and baseline characteristics

Sequential screening identified 51,053 candidate windows from 6,569 ICU stays (Figure 1). The historical lactate-vasopressor criterion retained 34,134 windows from 4,319 stays; exclusion of 165 windows at or after recorded death yielded 33,969 eligible decision windows from 4,268 ICU stays and 4,011 patients. Midodrine was administered within six hours in 150 windows, whereas 33,819 windows had no administration in that interval. Median time to initiation was 3.20 hours (IQR, 1.46-4.49 hours). Repeated eligibility windows represented multiple clinically plausible initiation times within the same patient trajectory.

Table 1 describes the measured clinical state at T0. Among initiation and noninitiation windows, median age was 69 (IQR, 56.25-77.00) and 67 (57.00-77.00) years; median SOFA was 8 and 9; and elapsed ICU time was 141 and 120 hours, respectively. Median norepinephrine-equivalent doses were 0.08 and 0.09 micrograms/kg/min. Recent lactate was missing in 36.7% versus 23.3% of windows. Baseline weighting reduced the maximum absolute SMD from 0.296 to 0.127. Residual SMDs of 0.127 for lactate and 0.115 for preceding MAP trend are reported to characterize measured balance.

Documented hypotension and outcome observation

The repeated-MAP definition yielded 56,350 qualifying event contributions across overlapping decision windows; 14,286 windows contained at least two supported episodes. These quantities describe trial-entry event contributions, not distinct episodes counted once per patient. MAP observation extended through death or 72 hours for 29,818 windows (87.8%). Index-ICU departure before 72 hours occurred in 4,129 windows, and 37 had no follow-up MAP readings; the categories describe overlapping observation characteristics rather than a mutually exclusive partition. Early ICU departure was observed in 25.33% of early-initiation windows and

12.10% of noninitiation windows. The difference in observation opportunity motivates the paired denominator comparison.

Main 72-hour index-ICU-documented comparison

For the original index-ICU-documented outcome, capped inverse-probability weighting yielded 0.5908 low-MAP episodes per alive day under early initiation and 0.6019 under deferral (initiation-minus-deferral difference, -0.0111; 95% CI, -0.1244 to +0.1191; Table 2 and Figure 2). Changing the deferral-weight cap from 5 to 10 to 20 produced the same rounded contrast and percentile interval. An overlap-weighted comparison yielded -0.0090 episodes per alive day (95% CI, -0.1175 to +0.1003; Table 3). The treatment-strategy intervals encompassed both lower and higher episode rates with early initiation.

Post hoc index-ICU denominator-alignment sensitivity

Of 2,318,828.47 total alive-time hours across overlapping decision windows, 112,942.17 hours (4.8707%) accrued after index-ICU departure; 4,129 windows contributed some post-ICU alive time. Restricting the denominator to 2,205,886.31 hours of observed index-ICU alive time, with the event numerator and treatment-weight implementation unchanged, yielded rates of 0.6740 and 0.6273 episodes per index-ICU day under initiation and deferral, respectively (difference, +0.0467; 95% CI, -0.0789 to +0.1824; Tables 2 and 3; Figure 2). The direction of the estimated treatment contrast therefore differed between the two defined rates.

In the paired 400-replicate patient-cluster analysis, the aligned-minus-original change in the between-strategy contrast was +0.0578 episodes per day (95% percentile CI, +0.0132 to +0.1098). Under overlap weighting, the aligned index-ICU-day contrast was +0.0501 (95% CI, -0.0710 to +0.1718), and its paired change from the original definition was +0.0591 (95% CI, +0.0153 to +0.1152). The original 400 bootstrap results were numerically reproduced before the denominator was changed. These paired quantities describe the consequences of specifying different outcome denominators.

Exploratory full-horizon PWWA and related analyses

In the exploratory full-horizon while-alive decision-window-rate calculation, the 99th-percentile ICU-observation-weight cap yielded rates of 0.6692 and 0.6325 episodes per alive day (difference, +0.0367; 95% CI, -0.1049 to +0.1817). The 99.5th-percentile cap yielded +0.0360 (95% CI, -0.1052 to +0.1790), and the

overlap-weighted analysis with the 99th-percentile cap yielded +0.0210 (95% CI, -0.1086 to +0.1505; Table 3 and Figure 2). These exploratory estimates address the modeled full-horizon event process and are shown separately from index-ICU-defined outcomes.

Internal stability and six-hour grace-period audit

Across 400 patient-cluster bootstrap refits, sensitivity analyses using deferral-weight caps of 5, 10 and 20 produced the same rounded contrasts within each index-ICU outcome definition. Overlap weighting gave similar directional results within its own target population. The explicit post hoc denominator comparison was performed as a paired within-resample analysis.

The treatment-strategy audit reconstructed 67,938 clone records from 33,969 decision windows. Artificial censoring was recorded for 33,552 early-initiation and 150 deferral clones. Of 56,350 source event contributions, 4,985 were confirmed before early-initiation clone endpoints and 56,091 before deferral clone endpoints. Event-support mismatches were zero for both strategies; computed weighted contributions matched the earlier implementation. The audit also classified all 267 noninitiating early-initiation clones that ended before the six-hour landmark: 209 ended with death and 58 with live index-ICU exit. Additional file 1 provides the event-timing and numerical influence checks.

Discussion

What this study adds

The central contribution of this study is to shift evaluation of midodrine from an infusion-discontinuation endpoint to an explicitly defined, repeatedly observed feature of circulatory recovery: recurrence of documented low MAP after a time-specific treatment decision. In 4,011 patients contributing 33,969 eligible decision windows, the early-initiation contrast for the originally reported index-ICU-documented outcome was -0.0111 episodes per alive day (95% CI, -0.1244 to +0.1191). When the same event counts were divided by time actually observed in the index ICU, the post hoc contrast was +0.0467 episodes per index-ICU day (95% CI, -0.0789 to +0.1824). The paired change was +0.0578 (95% CI, +0.0132 to +0.1098). Individual treatment comparisons did not show a clear difference, but the difference between these outcome definitions was

consequential for the direction of the point estimate. The finding links a practical clinical question to a broader principle of electronic health record research: outcome observation time is part of the outcome.

Why recurrent hypotension complements vasopressor-liberation endpoints

The end of an intravenous vasopressor infusion is a treatment-process milestone, not a direct record of subsequent hemodynamic experience. Recurrent documented hypotension addresses a different question: following a plausible initiation decision, does the monitored patient experience repeated low MAP after having previously recovered? Requiring repeated low values and a distinct recovery before another event makes the outcome responsive to multiple episodes rather than one arbitrary blood-pressure measurement. This distinction is particularly relevant during the transition from sustained low-dose support to possible ICU discharge. The alpha-1 adrenergic activity of midodrine offers a biological rationale for studying this phenomenon [21, 22], but the question of recurrent episodes cannot be answered by the mechanism alone. In this setting, the study contributes an operationally defined, clinically interpretable complementary endpoint, without redefining low-MAP clusters as organ injury or patient-reported instability.

How this evidence complements previous midodrine studies

MIDAS tested time to intravenous vasopressor discontinuation and identified a bradycardia signal, while MAVERIC and LIBERATE focused on vasopressor-weaning or feasibility outcomes [13, 14, 15]. A sepsis-specific randomized trial examined mortality and norepinephrine use [17]; observational series and pooled reviews have similarly emphasized treatment duration, discharge or major clinical outcomes [8, 9, 11, 12, 18, 19]. The MID-STEP protocol plans a different, pragmatic randomized test, with time alive and off intravenous vasopressors as its primary endpoint [38]. Against this backdrop, the present study contributes two additional design elements: repeated eligibility at actual six-hour decision times, and an endpoint based on renewed, confirmed low-MAP events. It therefore addresses a question that can sit alongside randomized effectiveness studies rather than replacing their treatment-effect evidence. The continued uncertainty reflected in the 2026 sepsis guideline [20] makes such complementary endpoint evidence relevant to the next generation of trials.

What the observation-time comparison reveals

The event numerator was limited to MAP episodes recorded before index-ICU departure. Under the original definition, however, time alive after ICU exit remained in the rate denominator. Across eligible decision windows this amounted to 112,942.17 hours, or 4.8707% of alive time. Restricting the denominator to the time for which the index-ICU event process was actually observed changed the treatment contrast from -0.0111 per alive day to +0.0467 per index-ICU day. The paired shift persisted under overlap weighting. The observation is not that one drug effect reversed, but that two operational rate estimands answered different questions. Clinically, moving out of a monitored setting changes the opportunity to document recurrent hypotension; analytically, it changes the amount of time assigned to recorded events. This finding supplies a concrete reason to state both numerator capture and denominator follow-up when designing hemodynamic endpoints.

Implications for acute and critical care research

The findings offer a practical template for future work spanning emergency resuscitation and subsequent critical-care recovery. Treatment studies can define the decision time before observing who eventually receives midodrine, distinguish recurrent low-MAP events from vasopressor-liberation milestones, and prespecify how discharge from a monitored unit changes outcome ascertainment. For clinical readers, the results separate two distinct judgments: whether oral midodrine should be initiated, and how convincingly the available blood-pressure data demonstrate sustained stability. In the present observational comparison, the estimates are not a basis for changing bedside midodrine prescribing, but the endpoint and observation-time distinctions can inform trial design and interpretation of routine-care evidence.

Study strengths

This study has several features that make the question more precise than a conventional ever-versus-never midodrine comparison. First, repeated six-hour eligibility windows bring the treatment contrast closer to the time clinicians make decisions during persistent low-dose vasopressor use. Second, a recovery-anchored, two-reading MAP rule operationalizes recurrent documented episodes instead of relying on a single hypotensive value. Third, patient-grouped cross-fitting and 400 patient-cluster bootstrap refits recognize the dependence created by multiple windows per person. Fourth, a paired analysis holds the eligible windows, event numerator and treatment-weight implementation constant while changing only the observation-time denominator, directly

quantifying the effect of that definition. Finally, clone, event-timing and arithmetic audits increase traceability of the implemented calculations. Together, these choices make the clinical question, recorded event process and sensitivity of interpretation explicit.

Limitations

The six-hour initiation strategy was observed in only 150 windows, with extreme inverse-probability weights requiring post hoc truncation. Measured covariate balance remained incomplete for lactate and preceding MAP trend; clinician treatment selection and evolving hemodynamic status after T0 were not fully represented in baseline-only weighting. The analytic estimator aggregated horizon-level weighted rates across decision entries instead of using fully time-updated event-specific longitudinal CCW estimation. These features limit identification and precision of any causal midodrine comparison. The ICU-conditional grace rule, the repeated-MAP algorithm and the index-ICU endpoint were clarified through retrospective audit rather than prospectively registered. Observation and treatment weight cutoffs were also selected post hoc, and the 400-refit bootstrap did not re-estimate all preprocessing and cross-fitting choices.

The originally reported index-ICU numerator did not observe MAP after ICU departure, even though 4.8707% of its alive-time denominator accrued after exit; the post hoc aligned outcome remains affected by informative ICU disposition. In the aligned analysis, 267 windows had less than six hours of index-ICU observation, including 27 with less than one hour, potentially producing unstable short-window rates. The exploratory full-horizon calculation additionally depended on modeled observation beyond ICU departure. Episodes derived from mixed invasive and noninvasive MAP values and retrospectively reconstructed sepsis and SOFA criteria may be misclassified; the event algorithm was not externally validated. Date-only deaths lacked exact times, dosing after initiation varied, repeated decisions overlapped within patients, and all records came from one institution. Neither endpoint provides definitive evidence of efficacy, harm or equivalence, and the paired between-estimand change must not be interpreted as a treatment-effect interaction.

Conclusions

This study evaluates early midodrine initiation through a question not captured by vasopressor-discontinuation time alone: recurrent documented low-MAP episodes during recovery from sepsis-associated circulatory

dysfunction. The observational treatment-strategy contrasts did not identify a clear difference in episode rates. More importantly for interpreting this type of outcome, the point-estimate direction changed when the denominator was aligned with the period of index-ICU event observation. Recurrent hemodynamic outcomes should therefore be reported with explicit definitions of event confirmation, observation setting and time at risk. This provides a concrete framework for interpreting routine-care data and for designing future midodrine studies around circulatory stability as well as vasopressor liberation.

List of abbreviations

CCW, clone-censor-weight; CI, confidence interval; DOD, date of death; ICU, intensive care unit; IPW, inverse-probability weighting; IQR, interquartile range;

MAP, mean arterial pressure; MIMIC-IV, Medical Information Mart for Intensive Care IV; NEE, norepinephrine equivalent; PWWA, patient-weighted while-alive; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; T0, eligible decision time.

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this study as all data were extracted from the publicly available and de-identified MIMIC-IV database, with appropriate certification (certification ID: 77742674).

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Code availability

Custom analysis scripts were used for cohort extraction and statistical analyses. Due to restrictions imposed by the PhysioNet Data Use Agreement, the raw scripts cannot be deposited in a public repository. Qualified researchers with valid PhysioNet credentials may request the analysis scripts by contacting the corresponding author. Any reuse of the shared scripts must comply with the PhysioNet Data Use Agreement and journal-specific policies.

Competing interests

The authors declare no competing interests.

Funding

Not applicable.

Authors' contributions

Zheng Yao (ZY) was responsible for conceptualisation, data curation, formal analysis, methodology, software, validation, visualisation, writing the original draft, and reviewing and editing the manuscript. The sole author read and approved the final manuscript.

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Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting or dissemination plans of this secondary analysis of an existing deidentified database.

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Tables

Table 1. Baseline characteristics by observed six-hour initiation status

Characteristic	Initiate <=6h (n=150)	No start <=6h (n=33,819)	Baseline-IPW |SMD|
Age, years	69.00 [56.25, 77.00]	67.00 [57.00, 77.00]	0.014
Male sex	84 (56.0%)	20,186 (59.7%)	0.004
SOFA score	8.00 [6.00, 11.00]	9.00 [6.00, 12.00]	0.052
Lactate, mmol/L	1.70 [1.30, 2.10]	1.70 [1.30, 2.20]	0.127
Lactate, mmol/L missing	55 (36.7%)	7867 (23.3%)	0.047
Creatinine, mg/dL	1.35 [0.90, 2.10]	1.50 [0.90, 2.40]	0.007
Creatinine, mg/dL missing	0 (0.0%)	18 (0.1%)	0.033

Characteristic	Initiate <=6h (n=150)	No start <=6h (n=33,819)	Baseline-IPW |SMD|
ICU time at T0, hours	141.00 [84.00, 262.50]	120.00 [66.00, 222.00]	0.03
NEE dose at T0, mcg/kg/min	0.08 [0.05, 0.12]	0.09 [0.05, 0.13]	0.021
NEE change over preceding 6h	0.00 [-0.02, 0.00]	-0.01 [-0.03, 0.00]	0.005
NEE change over preceding 6h missing	2 (1.3%)	678 (2.0%)	0.077
Mean MAP in preceding 6h, mmHg	71.00 [65.83, 75.79]	71.33 [66.83, 76.40]	0.008
Mean MAP in preceding 6h, mmHg missing	0 (0.0%)	7 (0.0%)	0.02
MAP change over preceding 6h, mmHg	-0.75 [-3.70, 4.30]	0.00 [-3.67, 3.71]	0.115
MAP change over preceding 6h, mmHg missing	0 (0.0%)	8 (0.0%)	0.022
Fraction of preceding MAP readings <65	0.17 [0.00, 0.38]	0.17 [0.00, 0.33]	0.011
Fraction of preceding MAP readings <65 missing	0 (0.0%)	7 (0.0%)	0.02

Values are median [IQR] or n (%). Baseline initiation-probability |SMD| is not a full longitudinal clone-censor-weight balance diagnostic. Groups reflect observed initiation, not random allocation. NEE, norepinephrine equivalents; MAP, mean arterial pressure; SMD, standardized mean difference.

Table 2. Contrasts across 72-hour observation-time definitions

Outcome	Initiate	Defer	Difference (95% CI)
Index-ICU-documented / alive day (main)	0.5908	0.6019	-0.0111 (-0.1244, 0.1191)
Index-ICU / index-ICU day (post hoc denominator alignment)	0.6740	0.6273	+0.0467 (-0.0789, +0.1824)
Full-horizon / alive day (exploratory)	0.6692	0.6325	+0.0367 (-0.1049, 0.1817)

The first and exploratory results are episodes per alive day; the aligned result is episodes per observed index-ICU alive day. Estimates average eligible decision windows, not unique patients. Intervals are percentile 95% CIs from 400 patient-cluster bootstrap refits; estimand refinement was post hoc.

Table 3. Weighting and post hoc denominator sensitivity analyses

Analysis	Initiate	Defer	Difference (95% CI)
Index ICU | IPW, B cap 5	0.5908	0.6019	-0.0111 (-0.1244, 0.1191)
Index ICU | IPW, B cap 10	0.5908	0.6019	-0.0111 (-0.1244, 0.1191)
Index ICU-aligned | IPW, B cap 10 (post hoc)	0.6740	0.6273	+0.0467 (-0.0789, +0.1824)
Paired contrast change | aligned minus original, IPW B cap 10	—	—	+0.0578 (+0.0132, +0.1098)
Index ICU | IPW, B cap 20	0.5908	0.6019	-0.0111 (-0.1244, 0.1191)
Index ICU | Overlap weighting	0.6147	0.6237	-0.0090 (-0.1175, 0.1003)
Index ICU-aligned | Overlap (post hoc)	0.7034	0.6533	+0.0501 (-0.0710, +0.1718)
Paired contrast change | aligned minus original, overlap	—	—	+0.0591 (+0.0153, +0.1152)
Full PWWA | IPW, B cap 10, exit cap 99%	0.6692	0.6325	+0.0367 (-0.1049, 0.1817)
Full PWWA | IPW, B cap 10, exit cap 99.5%	0.6685	0.6325	+0.0360 (-0.1052, 0.1790)
Full PWWA | Overlap, exit cap 99%	0.6789	0.6579	+0.0210 (-0.1086, 0.1505)

IPW, inverse-probability weighting; B cap, deferral-strategy weight cap; CI, confidence interval; PWWA, patient-weighted while-alive (historical label; estimand here weights decision windows). Index-ICU, index intensive care unit. The paired contrast change compares distinct denominators, not a treatment effect. Truncation and denominator changes were post hoc; overlap weighting targets a different population.

Figure legends

Figure 1. Sequential decision-window construction. Flow diagram showing eligibility criteria, historical shock-compatible evidence, and observed initiation categories at a six-hour landmark. Eligible decision windows were subsequently represented under both compatible strategies.

Figure 2. Initiation-minus-deferral contrasts for recurrent documented low-MAP rates under different observation-time definitions. The originally reported index-ICU-documented episodes per alive day, the post hoc index-ICU episodes per observed index-ICU alive day, and the exploratory modeled full-horizon while-alive decision-window rate are shown. Circles indicate capped inverse-probability weighting; squares show overlap weighting. Bars are 95% percentile intervals from 400 patient-cluster bootstrap refits. The paired change from the original to aligned denominator is reported in Table 3.

Additional files

Additional file 1 (DOCX): Supplementary Methods and Target Trial Specification, including eligibility, event rules, weights, and post hoc sensitivity analyses. No participant-level data or executable scripts are included.

Figures

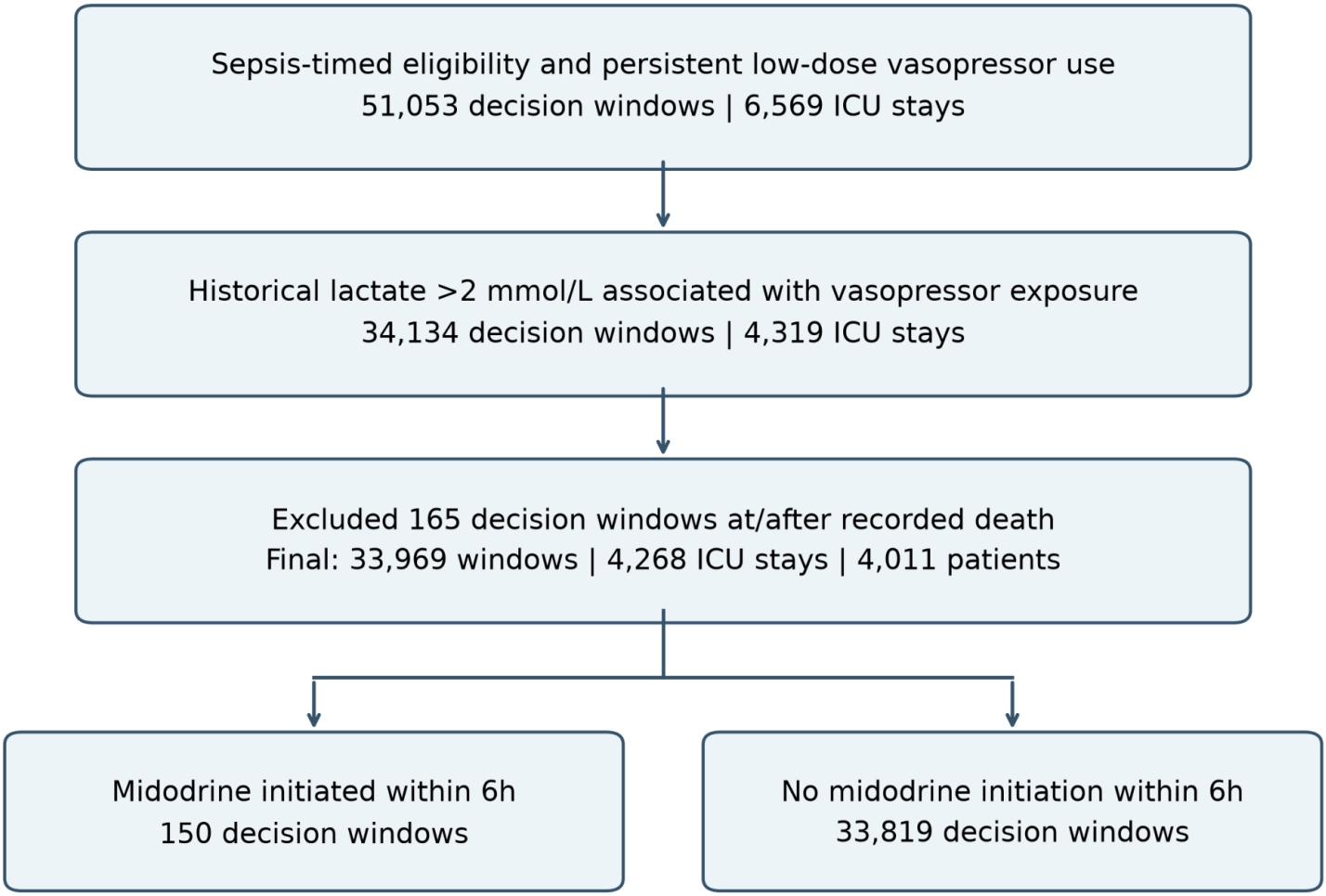

Figure 1

Sequential decision-window construction. Flow diagram showing eligibility criteria, historical shock-compatible evidence, and observed initiation categories at a six-hour landmark. Eligible decision windows were subsequently represented under both compatible strategies.

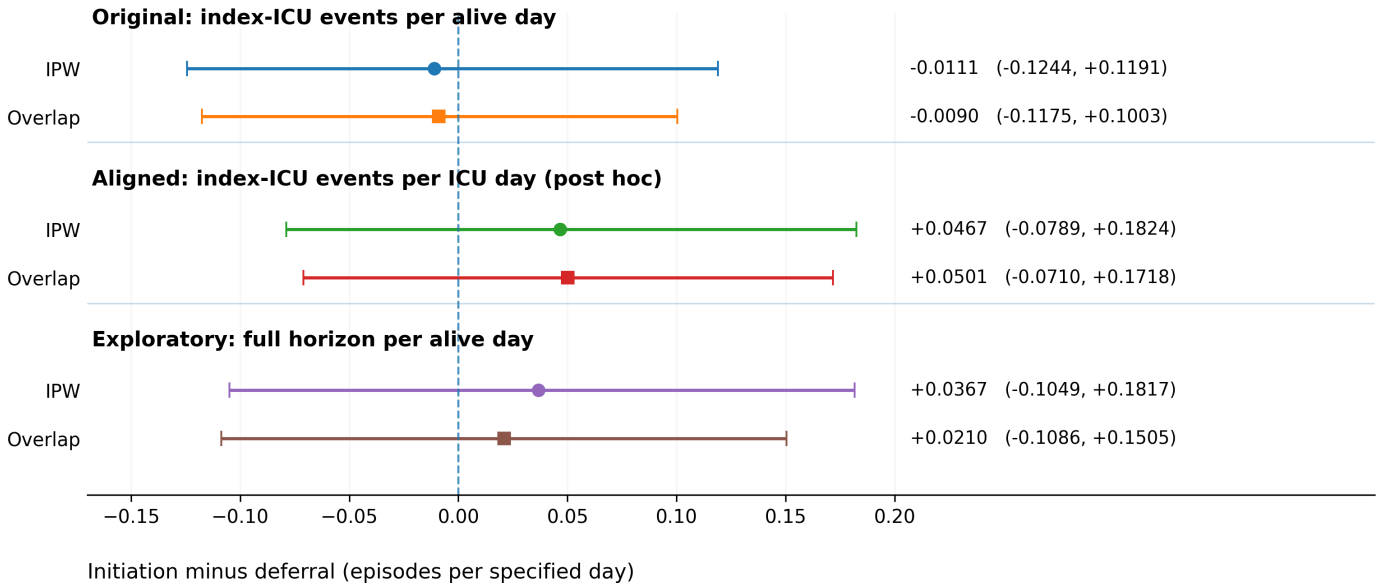

Figure 2

Initiation-minus-deferral contrasts for recurrent documented low-MAP rates under different observation-time definitions. The originally reported index-ICU-documented episodes per alive day, the post hoc index-ICU episodes per observed index-ICU alive day, and the exploratory modeled full-horizon while-alive decision-window rate are shown. Circles indicate capped inverse-probability weighting; squares show overlap weighting. Bars are 95% percentile intervals from 400 patient-cluster bootstrap refits. The paired change from the original to aligned denominator is reported in Table 3.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1SupplementaryMethods.docx