Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials

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Take home message:	Vasopressin has similar 28-day mortality to norepinephrine but a different side effect profile (more digital ischaemia, fewer arrhythmias). We found no clear evidence for differential subgroup effects.

ABSTRACT

Purpose

We performed an individual patient data meta-analysis to investigate the possible benefits and harms of vasopressin therapy in adults with septic shock both overall and in pre-defined subgroups.

Methods

Our pre-specified study protocol is published on PROSPERO, CRD42017071698. We identified randomised clinical trials up to January 2019 investigating vasopressin therapy versus any other vasoactive comparator in adults with septic shock. Individual patient data from each trial were compiled. Conventional two-stage meta-analyses were performed as well as one-stage regression models with single treatment covariate interactions for subgroup analyses.

Results

Four trials were included with a total of 1,453 patients. For the primary outcomes, there was no effect of vasopressin on 28-day mortality (relative risk (RR) 0.98, 95% CI 0.86 to 1.12) or serious adverse events (RR 1.02, 95% CI 0.82 to 1.26). Vasopressin led to more digital ischaemia (absolute risk difference (ARD) 1.7%, 95% CI 0.3% to 3.2%) but fewer arrhythmias (ARD -2.8%, 95% CI -0.2% to -5.3%). Mesenteric ischaemia and acute coronary syndrome events were similar between groups. Vasopressin reduced the requirement for renal replacement therapy (RRT) (RR 0.86, 95% CI 0.74 to 0.99) but this finding was not robust to sensitivity analyses. There were no statistically significant interactions in the pre-defined subgroups (baseline kidney injury severity, baseline lactate, baseline norepinephrine requirement and time to study inclusion).

Conclusions

Vasopressin therapy in septic shock had no effect on 28-day mortality although the confidence intervals are wide. It appears safe but with a different side effect profile to norepinephrine. The finding on

reduced RRT should be interpreted cautiously. Future trials should focus on long term outcomes in select patient groups as well as incorporating cost effectiveness analyses with regard to possible reduced RRT use.

INTRODUCTION

Vasopressor therapy is used in septic shock to increase vascular resistance, raise mean arterial pressure and maintain perfusion of critical body tissues and organ systems [1]. The traditional approach involves using catecholamines but these are associated with risks including myocardial ischaemia and tachycardia with beta-agonists [1, 2]. These adverse effects have led to interest in adjunctive therapeutic strategies.

In shock states vasopressin acts as a potent vasoconstrictor via V1a receptors on vascular smooth muscle [3]. A relative deficiency of vasopressin in septic shock has been described [4] and administration of exogenous vasopressin reduces catecholamine requirements with the hypothesis that it may therefore also diminish the likelihood of catecholamine related side effects. Furthermore vasopressin may have additional benefits in terms of organ perfusion, due to the distribution of the family of vasopressin receptors in different vascular beds, and additional immunological effects compared to norepinephrine [5].

The Vasopressin and Septic Shock Trial (VASST) was the first large randomised comparison of vasopressin with norepinephrine [6]. Although there was no significant mortality benefit to addition of low dose vasopressin in the overall population, there was a lower mortality in the subgroup of patients with less severe shock (<15 μg/min norepinephrine). Subsequent post-hoc analyses and other studies suggested a potential reduction in renal dysfunction with higher dose vasopressin, [7-9] as well as a potentially synergistic interaction with corticosteroid treatment [10, 11]. This was specifically investigated in the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial which found that early vasopressin use compared to norepinephrine did not increase the number of renal failure-free days and there was no interaction with corticosteroids [12]. However, the investigators

noted that the confidence interval for renal-failure free days included a potentially clinically relevant benefit for vasopressin, as well as a reduced use of renal replacement therapy (RRT).

Although trials have not demonstrated a clear benefit for vasopressin, it is uncertain whether particular subgroups of patients benefit from this treatment. In particular, the following subgroups: duration of shock before receiving therapy, severity of shock by lactate level or by norepinephrine requirement and severity of kidney injury. The Surviving Sepsis Campaign 2016 guidelines use the totality of evidence to date to recommend low dose vasopressin as a potential adjunctive vasopressor to norepinephrine [13].

Individual patient data (IPD) meta-analyses are considered the gold standard for synthesising information from RCTs [14]. They provide a means to explore further some of the aforementioned uncertainties around the possibility of different effects for different subgroups, and to standardise the analysis of outcomes. The provision of the IPD increases statistical power for investigating differential treatment effects [15]. Therefore, the aim of this study was to use IPD meta-analyses to quantify the efficacy and safety of vasopressin therapy within RCTs for septic shock, both overall and in *a priori* defined subgroups. We hypothesised that there might be beneficial effects of vasopressin therapy in specific sub-groups despite the overall outcomes reported thus far by large trials.

METHODS

The protocol for this study was published in the online PROSPERO database (CRD42017071698) prior to the analysis. The protocol is available at:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017071698

This manuscript has been prepared in line with the guidelines by the PRISMA-IPD group and a checklist is available with the Supplementary Appendix [16].

Trial identification, selection and acquisition of data

We performed a comprehensive search using MeSH and free-text terms for various forms of the terms 'septic shock' and 'vasopressin', including specific drug names. The exact search strategy is listed in Appendix 1 of the study protocol. The following electronic databases were searched from inception to January 2019: MEDLINE, Embase, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal. Additional articles or abstracts were retrieved by manually scrutinising the reference list of relevant publications. There were no restrictions on language. We also searched conference abstracts from major critical care conferences for the last 3 years (full details in study protocol).

Publications were selected for review if they satisfied the following inclusion criteria: non-crossover randomised controlled trial, human adults with septic shock requiring vasopressor therapy (as defined by the trial investigators or the International Consensus definitions for Sepsis (1992, 2001, 2016)), intervention (vasopressin) versus any other vasoactive comparator with minimum duration for therapy of three hours and/or until ICU discharge.

After removal of clearly irrelevant records, two authors (MN, ACG) independently screened abstracts for potentially eligible studies. Full text reports were then assessed for eligibility. Where there was not enough information to make a decision on inclusion from published information, study authors were contacted for further details. Authors of eligible studies were invited to supply anonymised individual patient datasets. The variables requested of authors are detailed in Appendix 2 of our study protocol. Risk of bias was assessed by applying the Cochrane Risk of Bias tool (performed by MN, who was not involved in the conduct of any included studies) [17].

Our primary efficacy outcome was mortality at day 28 and our primary safety outcome was total number of serious adverse events (SAEs). Secondary outcomes included rates of use of RRT (in patients without end stage renal failure), duration of RRT, duration of shock, duration of ventilation, renal failure free days to day 28, shock free days to day 28, ventilation free days to day 28, ICU free days to day 28, long term mortality (maximum follow up day 60-180), ICU length of stay and hospital length of stay. For duration of time outcomes results were also reported for survivors and non-survivors separately due to the competing risk of death.

Statistical analysis

We estimated the overall intervention effects and generated forest plots using a conventional two-stage approach (trial summary measures that are then combined by standard meta-analytical methods) [18]. For dichotomous outcomes such as proportion dead at day 28, we used the numbers of events and patients to calculate the risk ratio. For continuous outcomes such as length of stay, we used the mean and standard deviation to calculate the mean difference. These estimates were then combined in a fixed-effect model (Mantel-Haenszel method) that stratified by trial. Although some continuous data

may not be normally distributed, this was explored in a sensitivity analysis (see below) and no variables were transformed for the main analysis.

We planned to assess the following *a priori* defined subgroups: early versus late onset of shock to study inclusion (early defined as ≤12 hours, late defined as >12 hours), low versus high baseline vasopressor requirement (low defined as <15 μg of norepinephrine per minute or equivalent, high defined as ≥15 μg), low versus high baseline lactate (low defined as lactate level ≤ 2mmol/l, high defined as >2mmol/l), low versus high severity of acute kidney injury at baseline (low defined as no acute kidney injury (AKI) and stage 1 AKI [19] or Risk (RIFLE criteria) [20], high defined as stage 2 & 3 AKI [19] or Injury & Failure (RIFLE criteria) [20]) and studies considered low versus high trial risk of bias (low defined as all domains judged at low risk, high defined as any domain judged at unclear or high risk).

To explore the effect of patient characteristics on outcomes, we fitted one-stage regression models with single treatment covariate interactions. Three specifications of model were assessed as detailed in the Addendum to Tables S4-S7 in the supplementary Appendix. Model fit was compared using the Akaike information criterion (AIC) [21].

We also planned sensitivity analyses to assess the impact of not transforming skewed data to approximate normality (see Addendum to Table S8 in the supplementary Appendix for further details) and to assess for model robustness through both one- and two-stage models with either trial fixed or trial random-effects approaches. No adjustments were made for multiple comparisons and this should be kept in mind when interpreting 95% confidence intervals for secondary outcomes. All analyses were performed in Stata SE version 12.1 (College Station, TX).

RESULTS

The electronic search was performed initially in July 2017 and then updated to January 2019. It yielded 5,952 records in total for further assessment (see figure S1 in the supplementary Appendix). There were no extra records identified by conference abstract searching that were not already selected in the electronic search. After screening, 21 full text records were assessed of which 10 were excluded immediately. Reasons for exclusion of full text records are detailed in Figure S1 in the supplementary Appendix. Authors for all 11 potentially includable studies were contacted to determine full eligibility and obtain IPD. Two replies confirmed that no outcomes of interest had been collected and these studies were then excluded [22, 23]. Owing to a lack of replies from five studies, only four remained for inclusion in the analysis [6, 12, 24, 25].

The samples from four of the five unavailable studies [8, 26-28] were relatively small (median 30 patients, range 23 to 42) but the trial by Oliveira *et al.* had a sample size of 387 [29]. However, there was no public protocol, no entry in a trial registry and no peer-reviewed manuscript for this trial (only two abstracts dating from 2011 and 2014). All five non-included studies were rated overall at high risk of bias (see Table S1 in the supplementary appendix for risk of bias assessment for all nine potentially includable studies). The three trials VASST (n=779), VANISH (n=409) and VANCS II (n=250) were rated at low risk of bias in all domains. The trial by Dunser *et al*. (n=15) was rated overall at high risk of bias. Individual patient data were available for these four studies and no important issues were identified during checking of the data.

Baseline patient characteristics of the combined dataset are displayed in Table 1. There were a total of 1,453 eligible patients and norepinephrine was the control in all four trials. Median age and APACHE II score were 64 years and 26 respectively. Approximately 71% were ventilated at baseline (Table 1).

Although just under 40% of patients had a stage 2 or greater AKI at baseline, only 3% were receiving RRT (Table 1). Vasopressin dosing was lower in VASST compared to the other trials (VASST: 0.01 to 0.03 U/min, VANISH: up to 0.06 U/min, VANCS II: 0.01 to 0.06 U/min, Dunser *et al.*: up to 0.066U/min). The trial by Dunser *et al.* enrolled 48 patients in total but we only included the 15 patients with septic shock for our analysis.

Crude outcome data is displayed in Table 2. Overall 28-day mortality was 38% (49% when restricting to the 904 patients with a lactate >2mmol/l satisfying the septic shock 3.0 definition[30]) and varied between trials (VASST (37%), VANISH (29%), VANCS II (55%), Dunser *et al.* (60%)). For the primary outcomes, there was no evidence of an effect of vasopressin on 28-day mortality (relative risk (RR) 0.98, 95% CI 0.86 to 1.12) or SAEs (RR 1.02, 95% CI 0.82 to 1.26). Both analyses had no evidence of significant between-trial heterogeneity (I^2 0% and 8% respectively) and forest plots are shown in Figures 1a & 1b.

Serious adverse events, stratified by type, are displayed in Table 3. Although the overall number of events was similar, the side effect profile between vasopressin and norepinephrine was different. Vasopressin led to more digital ischaemia (absolute risk difference (ARD) 1.7%, 95% CI 0.3% to 3.2%) but fewer arrhythmias (ARD -2.8%, 95% CI -0.2% to -5.3%). Mesenteric ischaemia and acute coronary syndrome events were similar between groups.

For the secondary outcomes, vasopressin reduced the requirement for RRT (RR 0.86, 95% CI 0.74 to 0.99) with no evidence of between-trial heterogeneity (I^2 27%, see figure 1c). There was no evidence for an effect of vasopressin on any other secondary outcome (see Tables S2a in the supplementary Appendix).

There were no significant treatment covariate interactions in the *a priori* defined subgroups that we investigated (see Tables S4-7 in the supplementary Appendix). Forest plots stratified by subgroup for the two primary outcomes and for two exploratory secondary outcomes are shown in Figures 2 and 3 respectively.

In sensitivity analyses, there was no material difference in primary outcome results with a random-effects specification or one-stage analyses (full results in Tables S2b, S3a and S3b in the supplementary Appendix). There was no material difference in the relative risk of 28-day mortality when using aggregate data from the five non-included studies where mortality was reported (see Figures S2 in the supplementary appendix). For secondary outcomes, there was no material difference in results with one-stage analyses but the reduced RRT requirement with vasopressin was non-significant with a random-effects specification (RR 0.83, 95% CI 0.67 to 1.01, see table S2b in the supplementary Appendix). Where skewed continuous data were transformed to approximate normality, the only material difference in results pertained to duration of shock (defined as an ongoing requirement for vasopressors). Here, vasopressin consistently demonstrated a longer duration of shock in all patients (1.2 hours, 95% CI 1.1 to 1.4) and in only survivors (1.2 hours, 95% CI 1.0 to 1.4) that was statistically though not clinically significant (median shock duration in the total population was 50 hours (interquartile range (IQR) 28 to 91 hours)), see Table S8 and the Addendum to Table S8 in the supplementary Appendix for further details.

DISCUSSION

This is the first individual patient data meta-analysis of vasopressin in septic shock and there are four main findings. First, we found no evidence of a statistically significant reduction in 28-mortality with the use of vasopressin therapy in adults with septic shock. In our analysis, observed 95% CIs were consistent with an effect that ranges between a 14% relative reduction and a 12% relative increase in the risk of 28-day mortality with vasopressin therapy. Second, vasopressin appears safe with regard to serious adverse events overall and in all planned subgroups but with a different side effect profile to norepinephrine borne out by more digital ischaemia and fewer arrhythmias. Third, there is weak evidence for vasopressin resulting in a reduced requirement for RRT. Fourth, we had hypothesized that that there might be beneficial effects of vasopressin therapy in specific sub-groups but the subgroup interactions were not statistically significant although the 95% confidence intervals imply considerable uncertainty.

Comparing our findings to the existing literature requires caution for several reasons. Most existing non-IPD meta-analyses assess not only vasopressin but also its analogues and these are assessed in distributive shock states other than just sepsis (e.g. vasoplegia post cardiac surgery). Also, the as yet unpublished VANCS II trial has not been included in any meta-analyses to date [24]. McIntyre and colleagues found a reduced 28-day mortality in the subgroup of septic trials [31]. However, these trials also included terlipressin and limiting to only vasopressin resulted in a non-significant estimate. Vasopressin did not have a material impact on ICU or hospital length of stay and this was in line with our results. A recent non-IPD meta-analysis by Nedel *et al*. found no significantly reduced incidence of RRT in the subgroup of septic patients receiving vasopressin (OR 0.75, 95% CI 0.54 to 1.04) but the effect estimate was broadly similar to ours [32]. The variation in event rates among the four included trials is

not unexpected given the different inclusion/exclusion criteria and trial timeframes that they encompass [33].

The high number of critical care trials that have found no mortality benefit for a proposed intervention has resulted in increasing attention toward enrichment strategies and identification of specific subgroups that disproportionately benefit from a therapy. Our IPD meta-analysis did not show significant interactions in the subgroups. In a re-analysis of the VASST trial, Russell and colleagues assessed the impact of the new septic shock 3.0 definitions on the original trial results [34]. They found that vasopressin was not efficacious in the new septic shock 3.0 cohort but was beneficial in patients with a lactate level ≤2 mmol/l. Bhatraju *et al*. investigated the response to vasopressin in two distinct AKI sub-phenotypes. 328 patients from the VASST trial who had IL-8, Ang-1 and Ang-2 measured were classified into two groups with a significantly improved 90-day mortality only found in one of the groups [35]. However, Antcliffe and colleagues performed a *post-hoc* analysis of 176 VANISH trial patients with blood samples enabling categorisation into two groups according to their transcriptomic sepsis response signatures and found no significant interaction between vasopressin/norepinephrine and 28-day mortality for the two groups [36]. These studies highlight the differential responses to vasopressin for some but not all phenotypes.

The data on serious adverse events also merits attention. It may surprise clinicians that vasopressin, at these low doses, does not increase the incidence of mesenteric ischemia. Vasopressin results in a decreased incidence of arrhythmias, possibly by decreasing the use of adrenergic vasopressors. This result is consistent with the SOAP2 trial where dopamine led to more arrhythmias than norepinephrine (dopamine has far greater beta-adrenergic activity than norepinephrine) [2]. Our findings provide actionable evidence for clinicians when choosing a vasopressor for septic shock patients: greater

concern for arrhythmia will favour vasopressin while concern about digital ischaemia may favour norepinephrine.

Our findings have several implications. First, they may inform future versions of the Surviving Sepsis Campaign guidelines which currently recommend vasopressin only as an adjunct agent [13]. In practice this means that vasopressin is often used only as a rescue therapy. Additional guidance could recommend earlier use in those with dysrhythmias or a tachycardia. Second, our results agree with the finding of reduced RRT use initially identified in the VANISH trial (although the overall evidence is weak considering the sensitivity analysis that does not achieve statistical significance and the multiple secondary outcomes assessed in this analysis) [12]. Therefore, this finding should be viewed as hypothesis generating only. RRT is an expensive critical care therapy [37] and future trials should incorporate health economic assessments that investigate the cost effectiveness of vasopressin in this regard. Third, long term mortality may be a more appropriate outcome for future vasopressin trials (at least 90 days). The ubiquitous provision of RRT in modern intensive care units ensures that renal failure is rarely a direct, early cause of mortality but renal injury may contribute to downstream longer term effects such as secondary episodes of sepsis and spiralling multi-organ failure which are only apparent in mortality beyond the first month [38, 39].

The main strengths of our study are: a systematic and comprehensive search (with pre-published protocol and analysis plan), the explicit inclusion of only randomised trial data, collection of individual patient data with which to facilitate standardised subgroup analyses and the use of models for assessing treatment-covariate interactions that accounted for aggregation bias where applicable. Our findings must also be considered in light of several limitations. First, not all trials reported data on every outcome of interest. Second, there are multiple comparisons with no adjustment made. Third, there were five trials that may potentially have provided additional data but that we excluded due to lack of

further information from study authors [8, 26-29]. Our analysis included 1,453 patients from a total pool of 1,975 (74%) if these five trials had also been included. As mentioned in the results, four of the studies have very small sample sizes [8, 26-28] and the fifth remains unregistered and unpublished [29]. Only one of these five trials included data on RRT requirement [8]. It is unclear how inclusion of data from these studies may have altered our results. Fourth, the trials included span 14 years in which there have been major shifts in the management of septic shock that may have differentially affected trial populations [40, 41].

Conclusions

We found vasopressin therapy in septic shock had no effect on 28-day mortality although the confidence intervals are wide. It appears safe but with a different side effect profile to norepinephrine. . The finding of reduced RRT should be interpreted cautiously given the multiple secondary outcomes assessed and the fact that the result was not robust to sensitivity analyses. Future trials should focus on long term outcomes in select patient groups, as well as incorporating cost effectiveness analyses with regard to possible reduced RRT requirements.

Author Contributions

ACG conceived the study. MN, JAR, KRW, SJB, GDP, AJM, DA and ACG designed the protocol. JAR, KRW, LH and ACG provided individual patient data for the analysis. MN performed the analysis and wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and approved the final version. MN and ACG are the guarantors.

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Conflicts of interest

LH reports that outside of this work she has received speaker fee from Amomed Pharma.
ACG reports that outside of this work he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution.

JAR reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis and related to the use of vasopressin in septic shock. JAR is an inventor on these patents. JAR was a founder, Director and shareholder in Cyon Therapeutics Inc. JAR is a shareholder in Molecular You Corp. JAR reports receiving consulting fees in the last 3 years from:

1. Asahi Kesai Pharmaceuticals of America (AKPA)(developing recombinant thrombomodulin in sepsis).
2. SIB Therapeutics LLC (developing a sepsis drug).
3. Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin).

JAR is no longer actively consulting for the following:

1. La Jolla Pharmaceuticals (developing angiotensin II; JAR chaired the DSMB of a trial of angiotensin II from 2015 - 2017).
2. Cubist Pharmaceuticals (now owned by Merck; formerly was Trius Pharmaceuticals; developing antibiotics).
3. Grifols (sells albumin).
4. CytoVale Inc. (developing a sepsis diagnostic).
5. PAR Pharma (sells prepared bags of vasopressin).

JAR reports having received an investigator-initiated grant from Grifols (entitled “Is HBP a mechanism of albumin’s efficacy in human septic shock?”) that was provided to and administered by University of British Columbia.

Figure legends

Figure 1. Forest plot of primary outcomes (a) 28-day mortality, (b) serious adverse events and secondary outcome (c) requirement for renal replacement therapy (RRT).

Figure 2. Subgroup analysis for primary outcomes (28-day mortality and serious adverse events).

Figure 3. Subgroup analysis for exploratory secondary outcomes (90-day mortality and requirement for renal replacement therapy (RRT)).

Table 1. Patient characteristics in combined individual patient dataset.

Characteristic	**Vasopressin** (n=735)	**Norepinephrine** (n=718)	**Total** (n=1,453)
Age - yr, median (IQR)	63 (52-73)	64 (52-74)	64 (52-73)
Male - no. (%)	431 (58.6)	428 (59.6)	859 (59.1)
Caucasian ethnicity - no. (%)	617 (84.0)	613 (85.4)	1230 (84.7)
APACHE II score, median (IQR)	26 (21-31)	26 (21-31)	26 (21-31)
Physiological variables, median (IQR)			
Heart rate (bpm)	100 (85-113)	99 (85-114)	99 (85-114)
Mean arterial pressure (mmHg)	70 (63-77)	70 (63-77)	70 (63-77)
Lactate (mmol/l)	2.4 (1.5-4.1)	2.5 (1.5-4.7)	2.4 (1.5-4.6)
PaO2/FiO2 ratio (mmHg)	196 (134-296)	200 (134-286)	198 (134-290)
Creatinine (µmol/l)	138 (87-240)	140 (86-238)	140 (86-239)
Bilirubin (µmol/l)	22 (11-49)	22 (11-48)	22 (11-49)
Platelets (x1000/µl)	162 (85-270)	169 (92-259)	165 (88-263)
GCS, median (IQR)	12 (6-15)	13 (6-15)	12 (6-15)
Mechanical ventilation - no. (%)	519 (70.6)	518 (72.1)	1037 (71.4)
Renal replacement therapy - no. (%)	22 (3.0)	21 (2.9)	43 (3.0)
Time to study drug (hrs), median (IQR)	6.2 (3.2-14.1)	5.8 (3-12.9)	6 (3-13.5)
Norepinephrine equivalent dose (µg/min), median (IQR)	12 (6.9-24)	14 (7.6-25)	13.1 (7-25)
AKI severity - no. (%)			
No AKI or stage 1	425 (60.5)	426 (61.0)	851 (61.3)
Stage 2 or 3	277 (39.5)	260 (37.9)	537 (38.7)
Trial - no. (%)			
Dunser 2003	8 (1.0)	7 (1.0)	15 (1.0)
VASST 2008	397 (54.0)	382 (53.2)	779 (53.6)
VANISH 2016	205 (27.9)	204 (28.4)	409 (28.2)
VANCS II 2018	125 (17.0)	125 (17.4)	250 (17.2)

Continuous data are median (IQR), categorical variables are N (%).

Abbreviations

AKI – Acute kidney injury; APACHE – Acute Physiology and Chronic Health Evaluation; CRP – C-reactive protein; GCS – Glasgow coma scale; IQR – interquartile range.

Table 2. Primary and secondary outcomes.

OUTCOME	Vasopressin	Norepinephrine	Total	Patients	Data availability
PRIMARY					
28-day mortality, no. / total (%)	278 / 733 (37.9)	277 / 718 (38.6)	555 / 1451 (38.3)	1451	99.9%
SAEs, no. / total (%)	124 / 735 (16.9)	120 / 718 (16.7)	244 / 1453 (16.8)	1453	100.0%
SECONDARY					
90-day mortality no. / total (%)	267 / 525 (50.9)	287 / 511 (56.2)	554 / 1036 (53.5)	1036	71.3%
RRT requirement, no. / total (%)	215 / 735 (29.3)	243 / 717 (33.9)	458 / 1452 (31.5)	1452	99.9%
Duration of RRT (days), median (IQR)					
All patients	3 (2 to 7)	3 (2 to 8)	3 (2 to 7)	151	27.1%
Survivors	4 (2 to 8)	5 (2 to 9)	4 (2 to 8)	74	
Non-survivors	2 (1 to 7)	3 (2 to 7)	3 (2 to 7)	77	
Duration of shock (hrs), median (IQR)					
All patients	56 (32 to 97)	47 (25 to 87)	50 (28 to 91)	959	66.0%
Survivors	56 (36 to 97)	47 (26 to 87)	51 (30 to 91)	734	
Non-survivors	57 (27 to 102)	44 (22 to 87)	48 (23 to 91)	223	
Duration of ventilation (days), median (IQR)					
All patients	3 (2 to 9)	3 (2 to 11)	3 (2 to 10)	393	31.3%
Survivors	5 (2 to 11)	4 (2 to 13)	5 (2 to 12)	225	
Non-survivors	3 (1 to 5)	3 (2 to 6)	3 (1 to 5)	168	
Renal failure free days to day 28 (days), median (IQR)	23 (6 to 28)	23 (5 to 28)	23 (5 to 28)	1433	98.6%
Shock free days to day 28 (days), median (IQR)	19 (1 to 24)	19 (1 to 25)	19 (1 to 25)	1434	98.7%
Ventilator free days to day 28 (days), median (IQR)	13 (1 to 24)	13 (0 to 24)	13 (0 to 24)	1423	97.9%
ICU free days to day 28 (days), median (IQR)	6 (0 to 22)	7 (0 to 23)	7 (0 to 22)	672	46.2%
ICU length of stay (days), median (IQR)					
All patients	7 (4 to 12)	6 (3 to 13)	6 (3 to 12)	672	46.2%
Survivors	8 (5 to 15)	6 (3 to 13)	7 (4 to 13)	407	
Non-survivors	6 (2 to 10)	5 (2 to 11)	6 (2 to 10)	265	
Hospital length of stay (days), median (IQR)					
All patients	14 (7 to 29)	14 (7 to 27)	14 (7 to 28)	655	45.1%
Survivors	23 (12 to 42)	20 (12 to 46)	23 (12 to 42)	399	

Non-survivors	7 (2 to 12)	6 (2 to 14)	6 (2 to 13)	256	

Abbreviations

ICU – intensive care unit; RRT – renal replacement therapy; SAE – serious adverse events.

Table 3. Serious adverse events.

OUTCOME	Vasopressin	Norepinephrine	ARD† (95% CI)
Serious adverse events, no. / total (%)	124 / 735 (16.9)	120 / 718 (16.7)	0.2 (-3.7 to 4.0)
Digital ischaemia	21 / 735 (2.9)	8 / 718 (1.1)	1.7 (0.3 to 3.2)
Mesenteric ischaemia‡	14 / 727 (1.9)	18 / 711 (2.5)	-0.6 (-2.1 to 0.9)
Acute coronary syndrome	18 / 735 (2.5)	17 / 718 (2.4)	0.1 (-1.5 to 1.7)
Arrhythmia	39 / 735 (5.3)	58 / 718 (8.1)	-2.8 (-0.2 to -5.3)

† Percentage absolute risk difference

‡ The reduced denominator for mesenteric ischaemia is due to no available data on this serious adverse event in the trial by Dunser *et al*.

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