Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial

Anthony C Gordon, MD[1]; Alexina J Mason, PhD[2]; Neeraja Thirunavukkarasu, MSc[3]; Gavin D Perkins, MD[4]; Maurizio Cecconi, MD[5]; Magda Cepkova, MD[6]; David G Pogson, MB BCh[7]; Hollmann D. Aya[5], MD; Aisha Anjum[3], BSc; Gregory J Frazier, MSc[3]; Shalini Santhakumaran[3], MSc; Deborah Ashby[3], PhD; Stephen J Brett, MD[8]

[1]Section of Anaesthetics, Pain Medicine and Intensive Care Medicine,
Department of Surgery and Cancer
Imperial College London,
London, UK

[2]Faculty of Public Health and Policy,
London School of Hygiene and Tropical Medicine,
London, UK

[3]Imperial Clinical Trials Unit
School of Public Health
Imperial College London
London, UK

[4]Warwick Clinical Trials Unit
Warwick Medical School and Heart of England NHS Foundation Trust
University of Warwick
Coventry, UK

[5]Anaesthesia and Intensive Care Medicine
St George's University Hospitals NHS Foundation Trust and St George's
University of London
London, UK

[6]Intensive Care Unit
Whittington Health NHS
Magdala Avenue
London N19 5NF

[7]Academic Department of Critical Care,
University of Portsmouth & Portsmouth Hospitals NHS Trust,
Portsmouth, UK

[8]Centre for Perioperative and Critical Care Research
Imperial College Healthcare NHS Trust
London, UK

Corresponding author:
Prof Anthony C Gordon
ICU 11N, Charing Cross Hospital
Imperial College London
Fulham Palace Road
London W6 8RF, UK
Tel: +44 20 3313 0657
anthony.gordon@imperial.ac.uk

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Abstract:

Importance: Norepinephrine is currently recommended as the first line vasopressor in septic shock; however, early vasopressin use has been proposed as an alternative.

Objective: To compare the effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock.

Design, Setting and Participants: A factorial (2x2), double-blind, randomized clinical trial conducted in 18 general adult intensive care units in the United Kingdom between February 2013 and May 2015, enrolling adult patients who had septic shock requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after the onset of shock.

Interventions: Patients were randomly allocated to vasopressin (titrated up to 0.06 units/minute) and hydrocortisone (n=101), vasopressin and placebo (n=104), norepinephrine and hydrocortisone (n=101), or norepinephrine and placebo (n=103).

Main outcomes and measures: The primary outcome was kidney failure free days during the 28-day period after randomization, summarized as (1) the proportion of patients who never developed kidney failure and (2) median number of days alive and free of kidney failure for patients who did not survive, who experienced kidney failure, or both. Rates of renal replacement therapy, mortality and serious adverse events were secondary outcomes.

Results: A total of 409 patients (median age 66 years, 58.2% men) were included in the study with a median time to study drug administration of 3.5 hours after diagnosis of shock. The number of survivors who never developed kidney failure was 94/165 (57.0%) in the vasopressin group and 93/157

(59.2%) in the norepinephrine group (difference -2.3% [95%CI -13.0, 8.5]). The median number of kidney failure free days for patients who did not survive, who experienced kidney failure, or both was 9 days (interquartile range, 1–24) in the vasopressin group and 13 days (interquartile range, 1–25) in the norepinephrine group (difference -4 days [95%CI -11, 5]). There was less use of renal replacement therapy in the vasopressin group 25.4% *vs* 35.3% in the norepinephrine group (difference -9.9% [95%CI -19.3, -0.6]). There was no evidence of a difference in mortality rates between groups. In total 22/205 (10.7%) patients had a serious adverse event in the vasopressin group *vs* 17/204 (8.3%) in the norepinephrine group (difference 2.5% [95%CI -3.3, 8.2]).

Conclusions and Relevance: Among adults with septic shock, the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure free days. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

Trial registration number: ISRCTN 20769191

Introduction:

In 2015, it was estimated that there are more than 230,000 cases of septic shock with more than 40,000 deaths in the US each year.[1] In addition to treating the underlying infection, the mainstay of cardiovascular resuscitation in septic shock is intravenous fluids and vasopressor treatment. Norepinephrine is the recommended first line vasopressor[2] but since a relative vasopressin deficiency in septic shock was described there has been growing interest in the use of vasopressin as an adjunctive agent.[3] Preclinical and small clinical studies have suggested that vasopressin may be better able to maintain glomerular filtration rate and improve creatinine clearance compared with norepinephrine.[4-6]

The largest trial of vasopressin to date, the Vasopressin and Septic Shock Trial (VASST),[7] found no difference in mortality overall when vasopressin (up to 0.03 U/minute) was added to existing norepinephrine treatment compared with norepinephrine alone but there was a significantly lower mortality in the vasopressin treated patients who had less severe shock (defined as a dose of norepinephrine <15μg/min). Additional analyses from VASST and other investigations have suggested that early vasopressin might prevent deterioration in organ function,[5,8] particularly kidney function and that higher doses of vasopressin (up to 0.06 U/minute) may be more effective.[9] In addition it has been proposed that there may be an interaction between vasopressin and corticosteroids when used to treat septic shock and that the combination of vasopressin and corticosteroids may improve survival[10] and reduce the duration of shock.[11]

The Vasopressin *vs* Norepinephrine as Initial therapy in Septic Shock (VANISH) trial was designed to test whether early vasopressin use, titrated up to 0.06 U/min, would improve kidney outcomes compared with norepinephrine.

Methods:

Trial design and participants

The VANISH trial was a factorial (2x2), multi-center, double-blind, randomized clinical trial. It was conducted in 18 general adult intensive care units (ICU) in the United Kingdom between February 2013 and May 2015. The trial protocol is available in supplement 1 and the statistical analysis plan in supplement 2.

Oxford A research ethics committee approved the trial (12/SC/0014). In view of the emergency nature of the trial a waiver of initial consent was granted. Patients could be enrolled into the trial without prospective consent and then written consent was obtained from the patient, or a personal or professional legal representative as soon as practically possible. In cases where a legal representative gave consent, retrospective written consent was sought once the patient regained decision-making capacity.

Adult patients (≥16 years) who had sepsis (2/4 systemic inflammatory response criteria due to known or suspected infection[12]) and who required vasopressors despite adequate intravenous fluid resuscitation, as assessed by clinical examination, central venous pressure / oxygen saturation, or other physiological parameters using repeated fluid challenges, were eligible for the trial. Exclusion criteria were patients who had received a previous continuous

infusion of vasopressors during this ICU admission, an ongoing requirement for systemic steroid treatment (*i.e.* known adrenal insufficiency or regular systemic steroid therapy within the last three months), end-stage kidney failure, known mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis or other vasospastic disease, if the medical team were not committed to full active treatment, known pregnancy, enrollment in another interventional trial that might interact with the study drugs, or hypersensitivity to any of the study drugs.

Ethnicity was classified based on medical records, as most patients lacked capacity to provide this information at the time of their study enrollment. Documentation of ethnicity in patients' medical records is standard practice within UK National Health Service. The main categories of ethnicity were White, Black, Asian and Other. Since the vast majority of study participants were white, the descriptive statistics utilized a simplified dichotomization of White versus Other.

Randomization and masking:

Enrollment, randomization and data collection were via an online system (InForm™, Oracle Corp, California, USA). Patients were assigned to one of four treatment groups (vasopressin and hydrocortisone, vasopressin and placebo, norepinephrine and hydrocortisone, or norepinephrine and placebo) on a 1:1:1:1 basis with variable block size randomization (four and eight) using computer-generated random numbers, stratified by center. The allocation sequence was prepared by an independent statistician in the Imperial Clinical Trials Unit and concealed from all investigators and treating clinicians.

Ampoules of vasopressin (Ferring Pharmaceuticals, Canada), norepinephrine (Aguettant Ltd, UK) and hydrocortisone phosphate (Amdipharm Ltd, UK) were masked by over-labeling on the body and neck of normal drug ampoules. Matching placebo ampoules (0.9% saline) were manufactured by Sharp Clinical Services (Powys, UK) who carried out all labeling and treatment pack preparation.

Clinical Management:

Patients were allocated to receive either vasopressin (titrated up to 0.06 units / minute) or norepinephrine (titrated up to 12μg / minute) as the initial vasopressor infusion (study drug 1) via a central venous catheter, and titrated to maintain the target mean arterial pressure (MAP). The protocol recommended a MAP of 65-75mmHg but this could be altered by the treating physician if clinically indicated.

Once the maximum infusion rate of study drug 1 was reached patients received study drug 2, either 50mg hydrocortisone phosphate or placebo, administered as an intravenous bolus 6-hourly for 5 days, 12-hourly for 3 days and then once daily for 3 days, as previously reported.[13] The drug could be weaned more quickly if the shock had already resolved.

If the patient was still hypotensive after the first dose of study drug 2 then additional open-label catecholamine vasopressors could be administered. As the patient recovered, open-label catecholamine vasopressors were reduced first and only once the patient was weaned off open label vasopressors was study drug 1 then reduced. Once study drug 1 was weaned off, if there was recurrent

hypotension within 24 hours the study drug was restarted; if hypotension recurred after 24 hours open-label vasopressors were used at local physician discretion. All other treatment was at physician discretion, based on the Surviving Sepsis Campaign guidelines at that time.[14]

Patients could present and be recruited from any part of the hospital prior to ICU admission. Although the aim was to use study drug 1 as the initial vasopressor, study drugs could not be stored in multiple locations within the hospitals. Therefore, in an emergency when immediate treatment was required patients could be initially resuscitated using usual (open-label) clinically prescribed vasopressors. In this situation the patient had to be enrolled into the trial within six hours of commencing the open-label vasopressor infusion. As the study drug infusion was titrated up, as detailed above, the initial open-label vasopressor infusion was weaned off as quickly as possible in order to maximize the study drug infusion rate.

Outcome measures:

The primary outcome of the trial was kidney failure free days, *i.e.* the number of days alive and free of kidney failure, defined by the Acute Kidney Injury Network (AKIN) group stage 3 definition[15], during the 28 days after randomization, with no additional penalty for death. This outcome measure was not normally distributed and had a large spike in frequency at 28 days, the point at which the measure was truncated, representing survivors who never developed kidney failure. Therefore the prospective plan was to report the data using two summary measures 1) the proportion of survivors who never developed kidney failure (the spike at 28 days) and 2) the median number of

days alive and free of kidney failure for the other patients who did not survive, who experienced kidney failure, or both at any time.

Secondary outcomes included rates and duration of renal replacement therapy, length of kidney failure in survivors and non-survivors, 28-day, ICU and hospital mortality rates, organ failure free days in the first 28 days, assessed using the sequential organ failure assessment (SOFA) score.[16]

Statistical Analysis:

A sample size of 400 was chosen to provide 80% power to detect a 20-25% relative reduction of risk of developing kidney failure if treated with vasopressin compared to norepinephrine, assuming an overall incidence of acute kidney failure of 30% to 50%[8,11] and a significance level of 0.05. The calculations were based on simulation, assuming a Mann-Whitney U test for analysis. To allow for a 3% withdrawal of consent, in line with previous critical care studies within the UK[17], 412 patients was the recruitment target.

The primary analysis tested for a difference between the distribution of kidney failure free days for all patients randomized to vasopressin compared to those randomized to norepinephrine using a Mann-Whitney U test. The main analysis was a modified intention-to-treat basis (patients who did not receive study drug as they had died or recovered or were found to be ineligible after randomization were excluded). However, because not all patients would require study drug 2, analysis was also carried out on an "as treated" basis, with patients not requiring study drug 2 allocated to the placebo group, and re-allocation of any cross-overs. A further "per protocol" analysis was carried out in

which any patients not receiving the allocated study drugs or cross-overs were excluded. Logistic regression models and Cox regression models were used to compare renal replacement therapy and mortality between the four treatment groups and test for a potential vasopressin / hydrocortisone interaction, on an intention to treat basis, accounting for study site using a hierarchical model for the logistic regression and stratification for the Cox model. All analyses were carried out using R version 3.1.3.[18], and a p-value < 0.05 was considered statistically significant using 2-sided tests.

Results:

Figure 1 shows the patient flow in the trial. The most frequent reason for screening failure was exceeding the six-hour recruitment window. A total of 421 patients were randomized. Seven patients were found to be ineligible after randomization but before receiving any study drug and five patients or legal representatives withheld or withdrew consent after inclusion in the trial; these patients were excluded from all analyses. One patient refused ongoing participation in the trial after inclusion, including 28-day follow-up, but allowed existing data to be included in the analyses. Therefore, 409 patients were included at baseline, for safety data and some secondary outcome analyses as indicated, and 408 patients were included in the primary "intention-to-treat" analysis. In total eight patients in placebo groups were given open-label hydrocortisone as "rescue" therapy or for other clinical indications and two patients in the norepinephrine groups were given open-label vasopressin (one of whom was also one of the eight given open-label hydrocortisone), and these patients were included as cross-overs in the "as treated" analysis. The patients who did not receive study drug 2 (see figure 1) were allocated to the placebo group in the "as treated" analysis. All cross-overs and patients not receiving the second study drug were excluded from the "per protocol" analysis.

The treatment groups were well balanced at baseline (Table 1). The study drugs were started at a median of 3.5 hours after the diagnosis of shock. In 15% of patients study drug 1 was the first vasopressor administered. For the 309 (76%) of patients on norepinephrine at randomization, the median dose of open-label norepinephrine at baseline was 0.16 µg/kg/min. The mean arterial

pressure in all treatment groups was similar at baseline and over the first seven days (Figure 2a + eFigure 1a) and vasopressin spared the total dose of norepinephrine required to maintain the blood pressure (Figure 2b).

There was no significant difference in the distribution of kidney failure free days between vasopressin and norepinephrine groups, p = 0.88 (Figure 3a). The number of survivors who never developed kidney failure was 94/165 (57.0%) in the vasopressin group and 93/157 (59.2%) in the norepinephrine group (absolute difference -2.3, 95%CI -13.0, 8.5%) (Table 2). The median number of kidney failure free days in the other patients who died, experienced kidney failure, or both at any time was 9 (interquartile range 1–24) in the vasopressin group and 13 (interquartile range 1–25) in the norepinephrine group (absolute difference -4, 95%CI -11, 5 days). Similar results were obtained when using the serum creatinine values and urine output values separately to define kidney failure (eTable 2), and the "as treated" and "per protocol" analyses gave similar results (eTable 3).

Similar quantities of intravenous fluid were given to all groups, and total fluid balance, serum lactate levels and heart rate were similar in all groups (eTables , 4, 5, 6 and 7). Serum creatinine levels were lower and urine output slightly higher over the first seven days in the vasopressin group compared to the norepinephrine group (Figure 3b and 3c, and eTable 8a and 9a) and the rate of renal replacement therapy use was 25.4% in the vasopressin group and 35.3% in the norepinephrine group (Table 2), odds ratio 0.40, 95%CI 0.20-0.73. There was no significant difference in mortality rates between vasopressin and norepinephrine groups (28-day mortality, vasopressin group 30.9% versus

norepinephrine group 27.5%, absolute difference 3.4%, 95%CI -5.4, 12.3), and hydrocortisone and placebo groups (28-day mortality, hydrocortisone group 30.8% v placebo group 27.5%, absolute difference 3.3%, 95%CI -5.5, 12.1) (Table 2 and Figure e4a), and there was no significant interaction between vasopressin and hydrocortisone (p=0.98 from Cox regression model for 28 day mortality). There were no differences in rates of other new organ failures or organ failure free days between vasopressin and norepinephrine groups (eTable 10).

In the vasopressin group 22 patients had a total of 29 serious adverse events and 17 patients in the norepinephrine group had 19 events. The breakdown of all serious adverse events by treatment group is given in Table 2. In serious adverse events judged by the treating physician as at least "possibly related" to the study drugs, the mean dose of vasopressin on the day of the event or the day before was 0.06 units/minute and the mean dose of norepinephrine/epinephrine was 0.55 µg/kg/minute (0.33 µg/kg/minute in the vasopressin group and 0.79 µg/kg/minute in the norepinephrine group).

Rates of vasopressin and norepinephrine infusion are shown in eFigures 1b-d and 2. There was no difference in serum creatinine, urine output, rates of kidney failure, use of renal replacement therapy, mortality, or serious adverse events between the hydrocortisone group and the placebo group (eTables 8b, 9b, 11 and eFigures e3 and 4b).

Discussion

In this multi-center, factorial (2x2), double-blind, randomized clinical trial early use of vasopressin to treat septic shock did not increase the number of kidney failure free days compared to norepinephrine. Mortality rates were similar between all groups and there was no interaction on outcome between vasopressin and corticosteroids. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

The rationale for this trial was based on the results of the previous VASST study.[7] Although there was no significant difference in mortality rates in the overall septic shock population in that trial, there was a lower mortality rate in the a priori defined subgroup of patients who had less severe shock treated with vasopressin compared to norepinephrine (28-day mortality relative risk 0.74 95% CI, 0.55 to 1.01, p=0.05). There was no difference in mortality in those who had more severe shock (defined as norepinephrine ≥15μg/min at baseline). Possible explanations for the VASST result might be 1) that vasopressin was more effective when used earlier before patients had become too sick (the mean time to study drug initiation was approximately 12 hours after meeting eligibility), 2) that the patients with more severe shock might have required a higher dose of vasopressin as the maximum rate of vasopressin was limited to 0.03 units/minute, 3) that there was a harmful interaction between vasopressin and high dose norepinephrine, or 4) it could have been a chance finding in a subgroup analysis, although the subgroups were large, prospectively defined and

randomization was stratified by subgroup.

Further analyses from VASST suggested that vasopressin might improve kidney function in patients at risk of kidney failure and reduce rates of progression to kidney failure and loss, but that it had no effect if acute kidney failure was already established at the time of study inclusion.[8] This was supported by evidence from a study by Lauzier *et al*[5], that demonstrated an improvement in creatinine clearance when vasopressin was started in the first 12 hours of developing vasodilatory shock. Similarly in VASST patients enrolled in the first 12 hours tended to have better outcomes with vasopressin treatment compared with norepinephrine, but not if enrolled after 12 hours.[7] For this reason patients in this study were randomized as early as possible, and at a maximum of six hours after developing hypotension. Despite this early recruitment a number of patients already had developed acute kidney failure at the time of inclusion. However, there was no significant difference in the number of patients who had kidney failure at any time or progressed to kidney failure after randomization. Although there was no significant difference in rates of kidney failure, there was a lower rate of use of renal replacement therapy in the vasopressin treated patients. The use of renal replacement therapy was not controlled in this trial, and it was started based on local clinical decision. It is therefore not possible to know why renal replacement therapy was or was not started. As the trial was double-blinded it is unlikely to be due to any obvious clinician bias. It is possible the difference in rates of renal replacement therapy reflects the slightly lower creatinine values and higher urine outputs seen in the vasopressin treated patients, particularly on days 3-6. Although use of renal

replacement therapy was not the primary outcome of this trial, it is an important patient-centered outcome and therefore this result may be important when planning patient treatment strategies.

To ensure that patients with more severe shock were treated with an adequate dose of vasopressin the dose of vasopressin was titrated up to 0.06 units /minute, double the dose used in VASST. In another randomized clinical trial, a dose of 0.067 units /minute restored cardiovascular function more effectively than 0.033 units /minute, without a difference in adverse events.[9] In the previous pilot trial an infusion rate of 0.06 units /minute of vasopressin led to mean plasma levels of around 300 pmol/l, well above the physiological levels seen in other shock states.[11] Although the trial by Lauzier and colleagues[5], that had demonstrated an improved creatinine clearance, used a vasopressin dose up to 0.2 units /minute there was concern that higher doses might lead to adverse effects, such as ischemia from excessive vasoconstriction. The mean dose of vasopressin was 0.06 units /min, and the mean dose of norepinephrine/epinephrine was 0.55 μg/kg/min, when the potentially drug-related serious adverse events occurred. In view of the uncertainty about what is the ideal blood pressure to target in septic shock,[19] clinicians need to balance the potential benefits of an increased blood pressure against the risk of vasopressor related adverse events, particularly at high dose and should set blood pressure targets for individual patients.

The other potentially important finding from VASST that informed this trial was the potential interaction with corticosteroids.

There are several possible biological interactions including that vasopressin

binds to V1b receptors in the anterior pituitary that then leads to adrenocorticotropin hormone release[20] and corticosteroids have been shown to restore cytokine-mediated down-regulation of vasopressin receptors.[21] Patients in VASST who received vasopressin and corticosteroids had reduced mortality rates compared with patients who received norepinephrine and corticosteroids. In contrast to patients who did not receive corticosteroids, patients treated with norepinephrine had better outcomes.[10] Other retrospective studies also suggested that patients treated with the combination of vasopressin and corticosteroids had reduced mortality rates compared with patients receiving vasopressin alone.[22,23] In view of the Surviving Sepsis Guidelines that recommend only using hydrocortisone (200mg/day) if hypotension is not responding to fluid and vasopressor therapy[2], corticosteroids were only administered once study drug 1 was at its maximal infusion rate (vasopressin 0.06 units /minute or norepinephrine 12μg /minute). As in the pilot study[11] corticosteroids reduced vasopressin requirements but there was no difference in mortality rates and no evidence of an interaction between vasopressin and corticosteroids on outcome. Although not all patients required study drug 2 (hydrocortisone or placebo) the results were similar in the "as treated" and the "per protocol" analyses. However, since many patients did not require or receive study drug 2 the power to assess an interaction was limited and restricts the interpretation of this finding.

Limitations of this study need to be considered. The multi-center nature of the trial was designed to test the effectiveness of early vasopressin use in the treatment of septic shock in normal clinical practice. Other co-interventions,

timing of initiation of renal replacement therapy or levels of hemodynamic monitoring were not controlled, other than specifying that sites should follow the international guidelines.[14] As the trial was blinded and randomization was stratified by center we would expect these other factors to be balanced between groups and therefore unlikely to affect the overall result. Another important limitation is that only short time outcomes, 28-day and hospital mortality were collected, and therefore any long-term differences between treatment groups cannot be assessed. Similarly, no formal health economic analysis was originally planned but the lower rate of renal replacement therapy in the vasopressin treated patients mean that this could be an important future assessment. Although there was no difference in the distribution or number of kidney failure free days between vasopressin and norepinephrine groups, the 95% confidence intervals of the difference between groups has an upper limit of five days in favor of vasopressin, which would be clinically important. Therefore, these results are still consistent with a potentially clinically important benefit for vasopressin but a larger trial would be needed to confirm or refute this.

Conclusion:

Among adults with septic shock, the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure free days. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

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Authorship contributions:

VANISH investigators:

Imperial clinical trials unit: Deborah Ashby, Jane Warwick, Sandra Griffiths, Mary Cross, Neeraja Thirunavukkarasu, Aisha Anjum, Alexina Mason, Gregory Frazier, Shalinin Santhakumaran, Nayan Das.

Trial Steering committee: Geoff Bellingan (independent Chair), Anthony Gordon, Stephen Brett, Gavin Perkins, Deborah Ashby, Richard Beale (independent member), Frances Banks (independent lay-member), Terence Watts (independent lay-member).

Data Monitoring Ethics Committee: Peter Andrews (Chair), Daniel McAuley, Timothy Collier:

Charing Cross Hospital: Maie Templeton, Emily Errington, Kirsty Gladas, Anthony Gordon (Principal Investigator)

Hammersmith Hospital: Dorota Banach, David Kitson, Rosemary Matthew-Thomas, Stephen Brett (Principal Investigator)

St Mary's Hospital: Verena Hauer, Adaeze Ochelli-Okpue, Martin Stotz (Principal Investigator)

Guy's and St Thomas' NHS Foundation Trust: Marlies Ostermann, , Katie Lei, Kathryn Chan, John Smith, Manu Shankar-Hari (Principal Investigator)

Chelsea and Westminster NHS Foundation Trust: Jamie Carungcong, Jonathan Handy (Principal Investigator)

King's College Hospital NHS Foundation Trust: Phil Hopkins, Clair-Louise Harris, Fiona Wade-Smith, Sian Birch, Tom Hurst (Principal Investigator)

St George's University Hospitals NHS Foundation Trust: Johannes Mellinghoff, Nora Di Tomasso, Claudia Ebm, Fabrizio Iannucceli, Maurizio Cecconi (Principal Investigator)

The Royal London Hospital, Barts Health NHS Trust: Christopher J Kirwan, Thais Creary, Carmen Correia, John R Prowle (Principal Investigator)

The Royal Berkshire NHS Foundation Trust: Nicola Jaques, Abby Brown, Andrew Walden (Principal Investigator)

Wexham Park Hospital: Jozef Joscak, Josephine Bangalan, Tiina Tamm, Lisa Snow, Clare Stapleton (Principal Investigator)

The Whittington Hospital NHS Trust: Sheik M Y Pahary, Magda Cepkova (Principal Investigator)

Bristol Royal Infirmary: Tim Gould, Jeremy Bewley, Katie Sweet, Lisa Grimmer, Sanjoy Shah (Principal Investigator)

Dorset County Hospital NHS Foundation Trust: Sarah Williams, Mark Pulletz (Principal Investigator)

University Hospital Southampton NHS Trust: Kim Golder, Clare Bolger, Karen Salmon, Benjamin Skinner (Principal Investigator)

Royal Bournemouth and Christchurch NHS Trust: Emma Vickers, Michelle Scott (Principal Investigator)

Academic Department of Critical Care, Portsmouth Hospitals NHS Trust & University of Portsmouth: Steve Rose, Nikki Lamb, Johanna Mouland, David Pogson (Principal Investigator)

Royal Blackburn Hospital: Lynne Bullock, Martin Bland, Donna Harrison-Briggs, Kate Wilkinson, Anton Krige (Principal Investigator)

University Hospital Coventry: Geraldine Ward, Jeffrey Ting, Christopher Bassford (Principal Investigator)

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Figure legends:

Figure 1: Recruitment, randomization and patient flow in the VANISH trial

* Patients could meet more than one exclusion criteria

Figure 2: a) Mean arterial pressure over the first seven days. **b)** Maximum total (study and open-label) norepinephrine dose over the first seven days. Black squares represent the median for vasopressin patients, white circles for norepinephrine patients. The vertical lines represent the interquartile range. Note that day 1 runs from the time of randomization to the end of the "ICU calendar day" so is therefore less than 24 hours and varies in duration between patients.

Figure 3: Kidney function outcomes a) The number of kidney failure free days in each treatment group (the primary outcome) **b)** Serum creatinine over the first seven days. **c)** Urine output over the first seven days. Black squares represent the median for vasopressin group, white circles for norepinephrine group. The vertical lines represent the interquartile range. Day 0 = baseline (most recent measurement prior to randomization up to a maximum of 24 hours). Note that day 1 runs from the time of randomization to the end of the "ICU calendar day" so is therefore less than 24 hours and varies in duration between patients.

Table 1: Baseline characteristics

	Vasopressin + hydrocortisone N=101	Vasopressin + placebo N=104	Norepinephrine + hydrocortisone N=101	Norepinephrine + placebo N=103	Total trial population N=409
Age (years)	66 (57, 76)	67 (59, 77)	63 (52, 76)	66 (54, 76)	66 (54, 77)
Male sex	59 (58)	52 (50)	62 (61)	65 (63)	238 (58)
Weight (kg)	75 (63, 90)	70 (60, 85)	75 (65, 89)	73 (64, 90)	75 (62, 87)
Body Mass Index (kg/m^2)	26 (23, 32)	24 (22, 29)	26 (23, 30)	25 (23, 30)	26 (22, 30)
Caucasian ethnicity	85 (84)	89 (86)	87 (86)	88 (85)	349 (85)
Recent surgical history[a]	17 (17)	21 (20)	18 (18)	17 (17)	73 (18)
APACHE II score	24 (19, 30)	24 (19, 29)	24 (20, 30)	23 (18, 30)	24 (19, 30)
Pre-existing conditions					
Ischemic Heart Disease	20 (20)	11 (11)	12 (12)	19 (18)	62 (15)
Severe COPD	2 (2)	4 (4)	6 (6)	3 (3)	15 (4)
Chronic Kidney Failure	9 (9)	8 (8)	5 (5)	5 (5)	27 (7)
Cirrhosis	5 (5)	3 (3)	2 (2)	5 (5)	15 (4)
Cancer	14 (14)	11 (11)	8 (8)	14 (14)	47 (11)
Immunocompromised	9 (9)	4 (4)	8 (8)	7 (7)	28 (7)
Diabetes	19 (19)	20 (19)	22 (22)	29 (28)	90 (22)
Organ failure[b]					
Respiratory	32 (32)	39 (38)	40 (40)	38 (38)	149 (37)
Kidney	19 (19)	19 (18)	24 (24)	23 (22)	85 (21)
Liver	4 (4)	4 (4)	6 (6)	6 (7)	20 (5)
Haematological	6 (6)	6 (6)	6 (6)	4 (4)	22 (6)
Neurological	33 (35)	33 (33)	32 (34)	30 (31)	128 (33)
Physiological variables					
Mean Arterial Pressure (mmHg)	71 (62, 80)	69 (62, 75)	68 (61, 75)	70 (63, 78)	70 (62, 77)
Heart Rate (beats/min)	98 (85, 109)	96 (84, 108)	99 (83, 112)	96 (84, 110)	97 (84, 110)
Central venous pressure (mmHg)[c]	12 (9, 17)	13 (10, 16)	13 (9, 17)	13 (8, 17)	13 (9, 17)
Lactate (mmol/l)	2.1 (1.4, 4.3)	2.3 (1.5, 3.9)	2.6 (1.4, 4.5)	2.2 (1.4, 3.2)	2.3 (1.4, 4)
PaO$_2$/FiO$_2$ (mmHg)	190 (122,318)	189 (122,301)	171 (104,264)	195 (130,328)	188 (121,302)
Creatinine (mg/dl)	1.36 (0.89,2.69)	1.26 (0.83,2.02)	1.44 (0.83,2.26)	1.5 (0.84,2.32)	1.38 (0.84,2.32)
Bilirubin (mg/dl)	0.94 (0.47,1.62)	0.99 (0.53,1.67)	0.85 (0.51,1.42)	0.79 (0.45,1.45)	0.88 (0.47,1.58)

Platelets (x10^9/l)	194 (122, 289)	176 (116, 284)	182 (125, 293)	198 (122, 270)	188 (121, 288)
GCS	14 (6, 15)	14 (4, 15)	14 (3, 15)	14 (5, 15)	14 (4, 15)
Mechanical ventilation	55 (54)	58 (56)	62 (61)	61 (59)	236 (58)
Renal Replacement therapy	2 (2)	4 (4)	2 (2)	3 (3)	11 (3)
Volume of IV fluid in previous 4 hours (mls)	1200 (757, 2021)	1092 (725, 2010)	1168 (606, 2000)	1100 (613, 2132)	1134 (662, 2039)
Patients receiving open-label vasopressor at randomisation	91 (90)	89 (86)	86 (85)	82 (80)	348 (85)
Time from onset of shock to receiving first study drug (hrs)	3.2 (1.8, 5)	3.5 (2, 5.4)	3.7 (1.7, 5)	3.5 (1.4, 5.4)	3.5 (1.8, 5.2)
Norepinephrine dose at randomisation (μg/kg/min)	0.16 (0.1, 0.3) (n=76)	0.15 (0.1, 0.28) (n=79)	0.2 (0.12, 0.42) (n=81)	0.16 (0.1, 0.27) (n=73)	0.16 (0.1, 0.31) (n=309)
Source of infection					
Lung	43 (44)	39 (38)	44 (45)	39 (38)	165 (41)
Abdomen	20 (20)	26 (25)	25 (26)	22 (22)	93 (23)
Soft tissue or line	5 (5)	5 (5)	3 (3)	6 (6)	19 (5)
Other	30 (31)	32 (31)	26 (27)	35 (34)	123 (31)

Median (interquartile range) for continuous variables and n (%) for dichotomous and categorical variables. COPD – chronic obstructive pulmonary, APACHE – Acute Physiology and Chronic Health Evaluation (range 0-72, a higher score corresponds to more severe illness and a higher risk of death), GCS- Glasgow Coma Score (range 3-15, a lower score corresponds to a greater depression of consciousness)

[a] Recent surgery is defined as admitted to intensive care unit following surgery [b]kidney failure is defined as having Acute Kidney Injury stage 3; other organ failures defined as having a SOFA score of ≥ 3. [c] Central venous pressure was only recorded in 234 patients at baseline. See supplemental etable 1 for numbers of other missing values at baseline.

Table 2. Outcome data in the four treatment groups, and comparing the vasopressin group to norepinephrine group

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute difference[b] (95% CI)
	Hydrocortisone[a]	Placebo	Total[a]	Hydrocortisone	Placebo	Total	
28-day survivors who never developed kidney failure, N/Total (%)[c]	46/81 (56.8)	48/84 (57.1)	94/165 (57.0)	46/77 (59.7)	47/80 (58.8)	93/157 (59.2)	-2.3 (-13.0, 8.5)*
Kidney failure free days in other patients, days, median (IQR) [d]	5 (0-23)	12 (1-25)	9 (1-24)	13 (0-25)	14 (1-24)	13 (1-25)	-4 (-11, 5)*
28-day mortality, N/Total (%)	33/100 (33.0)	30/104 (28.8)	63/204 (30.9)	29/101 (28.7)	27/103 (26.2)	56/204 (27.5)	3.4 (-5.4, 12.3)
ICU mortality, N/Total (%)	32/100 (32.0)	26/104 (25.0)	58/204 (28.4)	24/101 (23.8)	27/103 (26.2)	51/204 (25.0)	3.4 (-5.2, 12.0)
Hospital mortality, N/Total (%)	35/100 (35.0)	33/104 (31.7)	68/204 (33.3)	31/101 (30.7)	29/103 (28.2)	60/204 (29.4)	3.9 (-5.1, 12.9)
Kidney Failure, N/Total (%)	41/101 (40.6)	46/104 (44.2)	87/205 (42.4)	46/101 (45.5)	51/103 (49.5)	97/204 (47.5)	-5.1 (-15.2, 5.0)
Survivors	21/67 (31.3)	26/74 (35.1)	47/141 (33.3)	26/72 (36.1)	29/76 (38.2)	55/148 (37.2)	−3.8 (-15.5,7.9)
Non-survivors	20/33 (60.6)	20/30 (66.7)	40/63 (63.5)	20/29 (69)	22/27 (81.5)	42/56 (75)	−11.5 (-29.6,6.6)
Duration of Kidney Failure, days, median (IQR)	4 (1,7)	2 (1,6)	3 (1,7)	3 (2,6)	4 (2,8)	4 (2,8)	-1 (2, 0)
Survivors	4 (2,7)	3 (2,8)	4 (2,8)	4 (2,8)	4 (3,8)	4 (2,8)	0 (-3, 2)
Non-survivors	2 (1,7)	2 (1,3)	2 (1,7)	3 (2,5)	2 (1,8)	3 (2,7)	-1 (-3, 0)
Use of renal replacement therapy, N/Total (%)	29/101 (28.7)	23/104 (22.1)	52/205 (25.4)	32/101 (31.7)	40/103 (38.8)	72/204 (35.3)	-9.9 (-19.3, -0.6)
Survivors	15/67 (22.4)	13/74 (17.6)	28/141 (19.9)	15/72 (20.8)	18/76 (23.7)	33/148 (22.3)	−2.4 (-12.5,7.7)
Non-survivors	14/33 (42.4)	10/30 (33.3)	24/63 (38.1)	17/29 (58.6)	22/27 (81.5)	39/56 (69.6)	−31.5 (-50.2,-12.9)
Duration of renal replacement therapy, days	4 (2,7)	3 (2,5)	3 (2,7)	3 (2,8)	4 (2,8)	3 (2,8)	0 (-2, 2)

median (IQR)							
Survivors	4 (2, 8)	3 (3,14)	4 (2,10)	4 (2,10)	6 (2,12)	5 (2,11)	-1 (-4, 2)
Non-survivors	4 (1,7)	2 (1,4)	2 (1,6)	3 (2,4)	3 (2,6)	3 (2,6)	-1 (-2, 2)
Numbers weaned from vasopressors for >24hrs, N/Total (%)	88/101 (87.1)	91/104 (87.5)	179/205 (87.3)	91/101 (90.1)	88/103 (85.4)	179/204 (87.7)	0.4 (-6.8, 6.0)
Time to shock reversal, hours, median (IQR)	50 (28,92)	59 (27,112)	51 (28,99)	46 (23,72)	44 (23,90)	45 (23,75)	6 (-4, 20)
Use of inotropes[e], N/Total (%)	31/101 (30.7)	24/104 (23.1)	55/205 (26.8)	24/101 (23.8)	17/103 (16.5)	41/204 (20.1)	6.7 (-1.5, 14.9)
Duration of mechanical ventilation, days median (IQR)	5 (2,10)	6 (3,12)	5 (2,10)	5 (2,16)	5 (2,12)	5 (2,13)	0 (-2, 2)
Mean total SOFA score, Mean ± SD	6.1 (3.4)	5.8 (3.1)	6.0 (3.3)	6.1 (3.1)	6.3 (3.5)	6.2 (3.3)	-0.2 (-0.9,0.4)
ICU length of stay, days median (IQR)	6 (3,10)	7 (3,14)	7 (3,11)	5 (3,15)	6 (3,11)	5 (3,13)	2 (-1, 3)
Hospital length of stay, days median (IQR)	13 (7,31)	17 (9,40)	16 (7,36)	16 (8,42)	15 (8,36)	16 (8,38)	0 (-5, 4)
Patients who had one or more serious adverse events, N/Total (%)	9/101 (8.9)	13/104 (12.5)	22/205 (10.7)	11/101 (10.9)	6/103 (5.8)	17/204 (8.3)	2.5 (-3.3, 8.2)
Subcategories of serious adverse events[f]							
Digital ischemia, N/Total (%)	4/101 (4.0)	7/104 (6.7)	11/205 (5.4)	2/101 (2.0)	1/103 (1.0)	3/204 (1.5)	3.9 (-0.1, 7.9)
Mesenteric ischemia, N/Total (%)	2/101 (2.0)	3/104 (2.9)	5/205 (2.4)	4/101 (4.0)	1/103 (1.0)	5/204 (2.5)	0.0 (-3.0, 3.0)
Life threatening arrhythmia, N/Total (%)	2/101 (2.0)	0/104 (0.0)	2/205 (0.98)	1/101 (1.0)	4/103 (3.9)	5/204 (2.5)	-1.5 (-4.5, 1.5)
Acute Coronary Syndrome, N/Total (%)	4/101 (4.0)	3/104 (2.9)	7/205 (3.4)	2/101 (2.0)	0/103 (0.0)	2/204 (1.0)	2.5 (-0.9, 5.8)
Other, N/Total (%)	2/101 (2.0)	2/104 (1.9)	4/205 (2.0)	3/101 (3.0)	1/103 (1.0)	4/204 (2.0)	0.0 (-2.7, 2.7)

Median (interquartile range) for continuous variables and n (%) for dichotomous and categorical variables. SOFA – Sequential Organ Failure Assessment (range 0-20, a higher score corresponds to more severe organ failure)

* Primary outcome [a] One patient in the vasopressin and hydrocortisone group refused ongoing participation in the trial after inclusion, including 28-day follow-up, but allowed existing data to be included in the analyses. Their data has been used where possible, therefore the denominator varies between 104/105 or 204/205. [b] Absolute difference in percentage for binary variables and difference in medians for continuous variables. 95% confidence intervals for the difference in medians calculated using bootstrapping; figures may not add due to rounding. [c] 28 day survivors as a proportion of patients with no kidney failure at baseline (one patient with no baseline kidney failure data was excluded. [d] Other patients = those who died and / or had kidney failure at any time. [e] inotropes defined as dobutamine, epinephrine, milrinone, dopamine, dopexamine. [f] The N of serious adverse events represents the number of patients who had that subcategory of event. Patients may have had more than one event.