Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

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Objectives: **There has long-been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock. The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock.**

Data Sources: **A systematic search of the MEDLINE, Embase, Scopus, and CENTRAL databases, and of Google Scholar, up to June 30, 2011.**

Study Selection and Data Extraction: **All studies providing information on the outcome of patients with septic shock treated with dopamine compared to norepinephrine were included. Observational and randomized trials were analyzed separately. Because time of outcome assessment varied among trials, we evaluated 28-day mortality or closest estimate. Heterogeneity among trials was assessed using the Cochrane Q homogeneity test. A Forest plot was constructed and the aggregate relative risk of death was computed. Potential publication bias was evaluated using funnel plots.**

Methods and Main Results: **We retrieved five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 who received norepinephrine and 1,294 who received dopamine). In observational studies, among which there was significant heterogeneity ($p < .001$), there was no difference in mortality (relative risk, 1.09; confidence interval, 0.84–1.41; $p = .72$). A sensitivity analysis identified one trial as being responsible for the heterogeneity; after exclusion of that trial, no heterogeneity was observed and dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; $p < .01$). In randomized trials, for which no heterogeneity or publication bias was detected ($p = .77$), dopamine was associated with an increased risk of death (relative risk, 1.12; confidence interval, 1.01–1.20; $p = .035$). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; $p = .001$).**

Conclusions: **In patients with septic shock, dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration. (Crit Care Med 2012; 40:725–730)**

KEY WORDS: adrenergic agents; adverse effects; mortality; outcome; vasopressor

Septic shock is a life-threatening condition associated with mortality rates close to 50% (1, 2). Despite generous fluid administration, vasopressor agents are often required to correct hypotension. Among the available vasopressors, dopamine and norepinephrine are used most frequently (3). These adrenergic agents have different pharmacologic properties. Both agents stimulate α-adrenergic receptors, resulting in vasopressor effects, but this effect is weaker for dopamine than for norepinephrine. However, dopamine stimulates β-adrenergic receptors more than norepinephrine, and this may result in a greater increase in cardiac output. However, this β-adrenergic stimulation can also promote tachycardia and arrhythmic events, increase cellular metabolism, and may be immunosuppressive (4). Finally, dopamine also stimulates dopaminergic receptors, which may result in increased splanchnic and renal perfusion, although this effect does not appear to prevent organ failure in critically ill patients (5). Dopaminergic stimulation can also alter hypothalamopituitary function, resulting in a marked decrease in prolactin and growth hormone levels (6).

Current guidelines recommend the use of either dopamine or norepinephrine as the first choice vasopressor in patients with septic shock (7–10). Several observational studies have suggested that dopamine administration may be associated with higher mortality rates than norepinephrine administration (3, 11, 12), although one study reported the reverse (13). In 2004, a meta-analysis conducted by the Cochrane group (14) identified only three randomized studies, including 62 patients in total, that compared the effects of dopamine and norepinephrine in patients with septic shock and provided information on outcome. They concluded that these trials were underpowered and that the evidence available at that time was insufficient to determine whether one agent was superior to the other. Since then, the number of trials comparing dopamine and norepinephrine has markedly increased. In particular, two randomized trials have specifically evaluated the impact of dopamine on outcome. A large-scale, multicenter, randomized trial that included 1679 patients with shock, of whom 1044 had septic shock, found no significant differences in outcome in patients treated with norepi-

***See also p. 981.**

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nephrine compared to those treated with dopamine, but arrhythmic events occurred more frequently with dopamine than with norepinephrine (15). Another single-center trial reported similar findings (16). Two recent systematic reviews by Vasu et al (17) and by Havel et al (18) have evaluated the effects of dopamine and norepinephrine on the outcome of patients with shock, but these reviews also included data from patients with other types of shock than septic shock, which may have driven the results (15). The publication of this new evidence prompted us to conduct a meta-analysis of observational and interventional trials comparing the effects of dopamine and norepinephrine on outcome from septic shock.

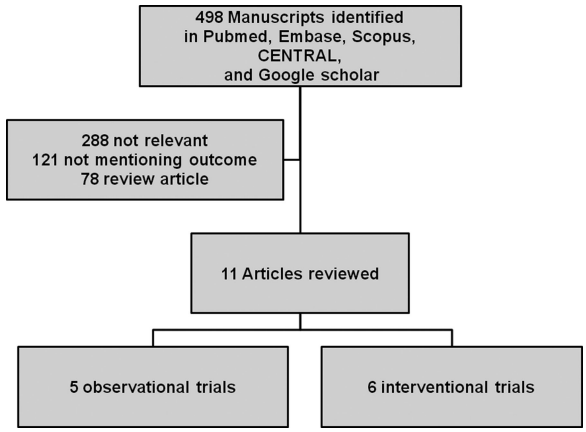

Figure 1. Flow chart of systematic search.

MATERIALS AND METHODS

Data Selection and Extraction

We conducted a systematic search of the MEDLINE, Embase, and Scopus databases and the Cochrane registry of clinical trials (last access June 30, 2011) using the terms "sepsis," "septic shock," "shock," "dopamine," "noradrenaline," "norepinephrine," "vasopressor agent," "outcome," and "mortality" (search strategy provided in supplemental data [Supplemental Digital Content 1, http://links.lww.com/CCM/A360]). We performed an additional search using Google Scholar. We also searched trial registries (clinical trials.org and controlled-trials.com) and abstracts of major congresses (Society of Critical Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, and European Society of Intensive Care Medicine) from 2005 to 2010. We included all studies that provided information on the use, in isolation or combined with other agents, of dopamine compared to norepinephrine in patients with septic shock and provided outcome data. We excluded animal trials (because these results cannot be directly translated to humans), pediatric trials (because infants may behave differently from adults), and clinical trials with a cross-over design (because the cross-over design does not allow identification of the role of each intervention on outcome). Two investigators (D.D.B. and C.A.) independently screened studies by title and abstract to evaluate whether the trial fitted the inclusion criteria. The time at which mortality was reported in the original articles was variable. We chose to use 28-day mortality as the outcome assessment criterion for the purposes of our meta-analysis because this was the primary end point in the largest randomized trials (15, 16). For trials that did not provide 28-day mortality rates, the mortality rate closest to this value was selected. We also collected information about adverse effects (as defined in the original articles), intensive care unit length of stay, and organ dysfunction (vasopressor-free, ventilator-free, and renal support-free days).

Two authors extracted data independently on a predefined data extraction form. A two-by-two summary table was completed for each outcome and for each trial, summarizing the number of patients who experienced the event or outcome for each group and the total number of patients in each group. These data were double-checked. If there was any disagreement, then the source data were evaluated jointly. Data of patients with septic shock were extracted from trials including patients with septic together patients with other types of shock (3, 15).

For randomized trials, two authors independently collected information from all studies to assess the risk of bias using the Cochrane risk of bias tool (19). We collected information on: allocation to treatment concealment; explicit inclusion and exclusion criteria; adequacy of the population description; similarity of patient care during the study period; whether the data were analyzed in an intention-to-treat fashion; adequacy of outcome description; blinding of the clinical staff to the intervention; and blinding of the outcome assessor to the intervention. We assigned "yes" or "no" to each item of the Cochrane risk of bias tool. Finally, we also collected data on exposure time to trial drug. Data are reported in accordance to the PRISMA guidelines for systematic reviews (20).

Statistical Analysis

We analyzed observational and randomized trials separately. For each type of trial, we used the risk ratio (RR) as the summary measure of association. We evaluated statistical heterogeneity among studies using Cochrane Q and I^2 statistics (21). We evaluated publication bias by means of visual inspection of the funnel plot and using Egger test (22). We estimated the aggregate effect and 95% confidence intervals using the DerSimonian and Laird random effects model (23). We *a priori* planned to perform sensitivity analyses based on exposure time and time of outcome assessment, and to evaluate whether the results could have been affected by a single study in case heterogeneity was detected, defined as $I^2 > 75\%$. Meta-regression was also performed using age, Acute Physiology and Chronic Health Evaluation II score, Simplified Acute Physiology Score II score, Sequential Organ Failure Assessment score, mean arterial pressure at baseline, mean arterial pressure during therapy, heart rate at baseline, heart rate during therapy, dopamine dose, and norepinephrine dose as covariates. Data were analyzed using IBM SPSS Statistics 19 for windows (IBM Corporation, Somers, NY) and SAS version 9.2 (SAS Institute, Cary, NC). All reported p values are two-sided and $p < .05$ was considered to be statistically significant.

RESULTS

A total of 498 studies were identified, of which 487 were excluded (irrelevant, animal, or reviews) so that 11 trials were kept for analysis. Five of these studies were observational and six studies were interventional studies (Fig. 1).

Observational Trials

We identified five observational studies (3, 11–13, 24) that evaluated the effects of dopamine or norepinephrine against other vasopressor agents in a total of 1360 septic patients (Table 1). One trial evaluated the use of norepinephrine vs. all other agents (including dopamine) (11), whereas the others compared use of

Table 1. Characteristics of observational studies

First Author (Year)	Type of Comparison	Dopa/Norepi (n = 562/798)	Exposure Time	Mortality Rates
Martin (2000) (11)	Norepi vs. others	40/57	NA[a]	28-day + hospital
Hall (2004) (24)	Dopa vs. norepi	51/49	NA[a]	28-day
Sakr (2006) (3)	Dopa vs. others (norepi mostly)	174/292	NA[a]	Intensive care unit + 30-day + hospital
Povoa (2009) (13)	Dopa or norepi vs. others	231/334[b]	NA[a]	Hospital
Boulain (2009) (12)	Dopa vs. others (norepi mostly) matched pairs	66/66	NA[a]	Intensive care unit + 28-day + hospital

NA, not available.

[a]Not available because of the retrospective nature of these studies. Use of the agent was considered as at least once during the shock episode but there was no certitude that the drug was used during the entire shock period; [b]the total number of patients is higher (565) than the total number of patients included in the trial (458) because some patients were treated both with norepinephrine and dopamine.

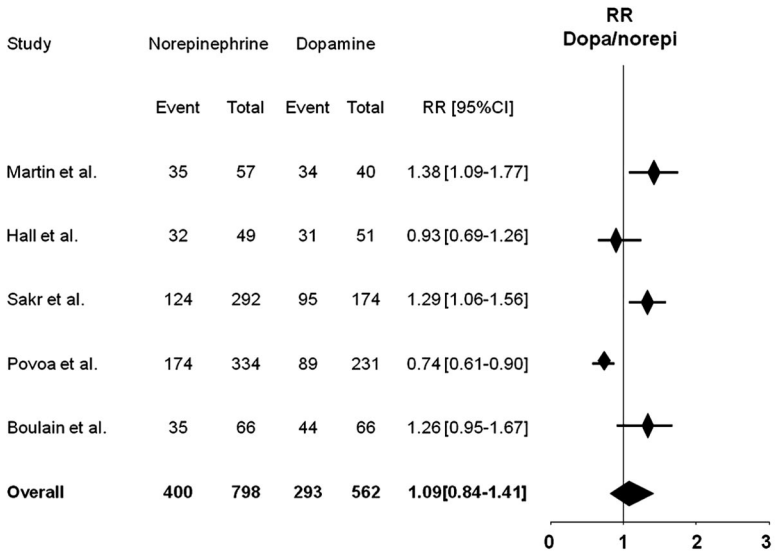

Figure 2. Forest plot of risk ratio (*RR*) of death (28 days or nearest estimate) in observational trials. The *p* value for aggregate RR of dopamine (*dopa*) compared to norepinephrine (*norepi*) in observational studies was .72. Relative weights of the different trials in the analysis: Martin et al (11) 20%; Hall et al (24) 18%; Sakr et al (3) 21%; Povoa et al (13) 21%; and Boulain et al (12) 19%. There was significant heterogeneity among the trials ($p < .001$, $I^2 = 79.3$; confidence interval, 50.9%–91.3%); the trial by Povoa et al (13) was identified to be responsible for the heterogeneity (see text for details). *CI*, confidence interval.

dopamine to nonuse of dopamine (3, 12, 13, 24). One trial matched patients who received dopamine to those who received norepinephrine (12).

There was significant heterogeneity among the trials ($p < .001$; $I^2 = 79.3$; confidence interval, 50.9%–91.3%). There was no difference in the aggregate relative risk (RR) of death for dopamine use compared to norepinephrine use (RR, 1.09; confidence interval, 0.84–1.41; $p = .72$) (Fig. 2). Publication bias was unlikely from funnel-plot analysis (Supplemental Fig. 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A360]) or using the Egger test ($p = .78$). A sensitivity analysis by Povoa et al (13) identified that one trial was responsible for the heterogeneity. After excluding this trial, no heterogeneity was observed ($p = .22$; I^2 32.3; confidence interval, 0.0%–75.9%) and dopamine use was then associated with an increased risk of death compared to norepinephrine use (RR, 1.23; confidence interval, 1.05–1.43; $p < .01$) (Supplemental Fig. 2 [Supplemental Digital Content 1, http://links.lww.com/CCM/A360]). The Egger test showed no evidence of publication bias ($p = .35$). Meta-regression could not be performed because information on the various covariates was available only in a minority of the trials.

Interventional Studies

The six interventional trials (Table 2) included a total of 1408 septic patients, of whom 732 were allocated to receive dopamine and 676 norepinephrine. The two largest trials used 28-day mortality as their primary end point. In these trials the patients had a longer exposure time to either dopamine or norepinephrine than in the other trials that used hemodynamic end points as a primary outcome variable. The latter trials were also relatively small in size. There was no significant heterogeneity among trials ($p = .77$; $I^2 = 0$; confidence interval, 0%–25%). The aggregate RR of death with dopamine use was significantly higher than with norepinephrine use (RR, 1.12; confidence interval, 1.01–1.20; $p = .035$) (Fig. 3). Neither the funnel-plot analysis (Supplemental Fig. 3 [Supplemental Digital Content 1, http://links.lww.com/CCM/A360]) nor the Egger test (RR, 0.43) revealed any publication bias. Restricting the analysis to the three trials with maximal exposure to dopamine or norepinephrine gave similar results (RR, 1.11; confidence interval, 0.99–1.23; $p = .06$). Restricting the analysis to the two trials providing 28-day mortality gave similar results (RR, 1.10; confidence interval, 0.99–1.22; $p = .09$).

Adverse Effects and Other Outcomes

Arrhythmic events were reported in two interventional trials but in none of the observational trials (15, 16). In both trials, there was a significant increase in arrhythmic events in dopamine-treated patients; as a result, the aggregated RR of development of arrhythmias was significantly higher with dopamine compared to norepinephrine (Supplemental Fig. 4 [Supplemental Digital Content 1, http://links.lww.com/CCM/A360]).

Intensive care unit and hospital length of stay were reported in two interventional trials (15, 16). There were no differences in intensive care unit (RR, −0.3; confidence interval, −1.5 to 1.0; $p = .67$) or in hospital (RR, 0.0; confidence interval, −2.8 to 2.6; $p = .95$) length of stay between patients who received dopamine and those who received norepinephrine.

Data on other adverse events and outcomes were only provided in the study by

Table 2. Characteristics of interventional studies

	Martin (1993) (27)	Marik (1994) (30)	Ruokonen (2003) (29)	Mathur (2007) (25)	De Backer (2010) (15)	Patel (2010) (16)
Dopamine, n	16	10	5	25	542	134
Norepinephrine, n	16	10	5	25	502	118
Exposure time	Weaning or dead	3 hrs	3 hrs	6 hrs	Maximum 28 days	Maximum 28 days
Type of patients	Sepsis	Sepsis	Sepsis	Sepsis	Sepsis[a]	Sepsis
Mortality rate	Hospital	Not defined	Not defined	Not defined	28 day[b]	28 day
Cochrane risk of bias in included studies						
Concealment on allocation	No	Yes	No	No	Yes	Yes (odd or even)
Inclusion/exclusion	Yes	Yes	Yes	Yes	Yes	Yes
Patient description	No	No	No	No	Yes	Yes
Similar care	Yes	Yes	No	Yes	Yes	Yes
Blinding of caregivers	No	No	No	No	Yes	No
Blinding of assessors	No	No	No	No	Yes	No
Intention to treat	Yes	Yes	Yes	Yes	Yes	Yes
Free from selective reporting	Yes				Yes	Yes
Risk of bias for secondary outcomes assessment in included studies						
Adverse events						
Defined	No	No	No	No	No	Yes
Assessed	No	No	No	No	No	Yes
Time of assessment	No	No	No	No	No	Yes
Organ function						
Defined	No	No	No	No	Yes	Yes
Assessed	No	No	No	No	Yes	Yes
Time of assessment	No	No	No	No	Yes	Yes

[a]In this trial, patients with other sources of shock were also included. The intention-to-treat analysis covers the whole population of 1679 patients included in the trial. The authors extracted data of patients with sepsis only for this analysis. Other trials only included patients with sepsis; [b]in this trial, 28-day mortality was the primary outcome, intensive care unit, hospital, and 6-month and 12-month mortality were also provided.

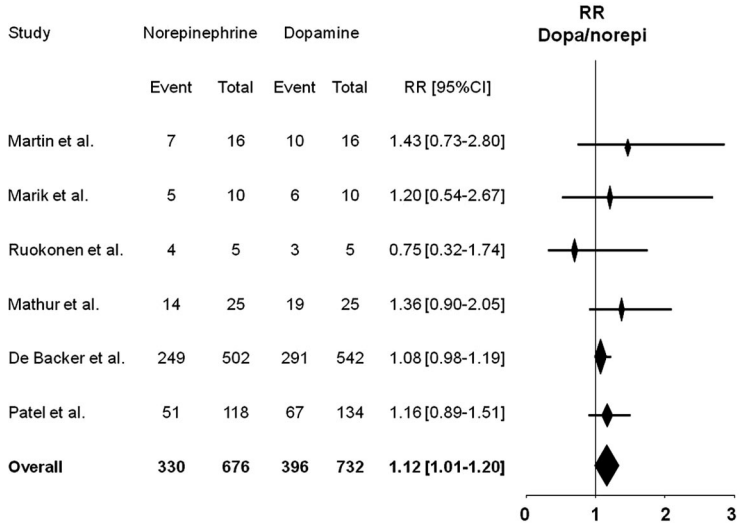

Figure 3. Forest plot of risk ratio (*RR*) of death (28 days or nearest estimate) in interventional trials. The *p* value for aggregate RR of dopamine (*dopa*) compared to norepinephrine (*norepi*) in interventional studies was .035. Relative weights of the different trials in the analysis: Martin et al (27) 2%; Marik et al (30) 1%; Ruokonen et al (29) 1%; Mathur et al (25) 4%; De Backer et al (15) 81%; and Patel et al (16) 10%. No heterogeneity was observed ($p = .77$; $I^2 = 0$; confidence interval, 0%–25%).

De Backer et al (15) and could not be analyzed.

DISCUSSION

This systematic review reveals that dopamine use in patients with septic shock is associated with an increased risk of death compared to norepinephrine use. Dopamine use was also associated with an increased risk of development of arrhythmias. Interestingly, these results are in agreement with a subgroup analysis of the trial by De Backer et al (15), which showed an increased risk of death in patients with cardiogenic shock who received dopamine compared to those who received norepinephrine.

The results of this meta-analysis are in agreement with the review by Vasu et al (17) but differ slightly from those of Havel et al (18). All trials had a similar trend in aggregate point of estimate, but this trend was significant in our trial and in that by Vasu et al (17) (RR, 1.10; confidence interval, 1.01–1.20) but failed to reach significance in the trial by Havel et al (18) (RR, 1.05; confidence interval, 0.97–1.15). Importantly, unlike our analysis, both these reviews (17, 18) included patients with types of shock other than septic shock. Inclusion of patients with cardiogenic shock, in whom dopamine is associated with a significant increase in risk of death (15), may have driven the results in the analysis by Vasu et al (17). Although the review by Havel et al (18) also included patients with cardiogenic shock, this review was limited by the fact that these authors incorporated only the 1036 patients with 12-month outcome data from the trial by De Backer et al (15).

In addition, they inverted survival and death rates from the study by Mathur et al (25), which favored the null hypothesis. Our trial, focusing on patients with septic shock and on the primary outcome assessment time of each trial, confirms this general trend and provides new and important information for this important group of patients.

The comparison of interventional studies with observational studies yielded some interesting results. The lack of a significant difference in outcomes between dopamine and norepinephrine in observational studies was mostly attributable to considerable heterogeneity in the results and design of the various observational trials. Most of these trials included different vasopressor agents as the alternative comparator, which further increased variability, making them difficult to compare. Patients treated with dopamine alone may differ from those treated with norepinephrine alone, because norepinephrine is a more potent vasopressor and the vasopressor response to norepinephrine is more consistent (26, 27) than the response to dopamine (15, 27, 28). As a result, patients treated with a single vasopressor agent may have different intrinsic disease severity compared to those treated with several vasopressors (28), which makes comparisons more difficult. Nevertheless, using multivariate analyses (3) or matching pairs (12), several observational studies have suggested an increased risk of death in patients treated with dopamine compared to those who received norepinephrine. Interestingly, the magnitude of the effect was similar in observational and in interventional trials, and also became significant in observational studies when excluding the trial that was identified as being responsible for most of the heterogeneity.

A major strength of this analysis is that the risk of having missed any trials is small because we conducted a systematic search of the main databases of medical literature, without language restriction. No other trials were identified from clinical trial registries or from abstracts of major congresses from 2005 to 2010. Although we used different search terms than those in the recent meta-analyses by Vasu et al (17) and Havel et al (18), we identified the same clinical trials. Another strength is the relatively large total number of patients included. Finally, in contrast to other reviews (17, 18), this systematic review only included data from patents with septic shock.

This study has several limitations. First, the end points of the various trials differed. Many of the interventional trials had hemodynamic end points as their primary goals (25, 27, 29, 30). Survival was reported in these trials, but these do not have the same statistical weight as the two trials in which mortality was the primary end point (15, 16). Second, the time at which outcome was evaluated also varied, although it varied less than in other reviews (18). To harmonize the mortality assessment as much as possible, we decided to align the outcome time assessment at 28 days, which was used as the primary outcome in the two largest randomized trials (15, 16). It was also the fixed end point provided in the majority of the observational trials. Hence, 28-day mortality end point was provided in 92% of patients included in interventional trials and in 65% of those included in observational trials. Admittedly, treatment effects may sometimes vary over time. Nevertheless, there was no indication that this occurred from the large randomized trial by De Backer et al (15) in which the RR of death was 1.19 (confidence interval, 0.98–1.44) at intensive care unit discharge (median time in intensive care unit, 5 days), 1.17 (confidence interval, 0.97–1.42) at 28 days, 1.06 (confidence interval, 0.86–1.31) at 6 months, and 1.15 (confidence interval, 0.91–1.46) at 1 year (with follow-up of 1036 patients up to that time point). Restricting the meta-analysis to the two trials that provided information on 28-day mortality (15, 16) provided a similar point estimate than when incorporating all interventional studies. Third, the influence of therapy on mortality beyond 28 days could not be assessed, but it is unlikely that the type of vasopressor agent had such a prolonged influence. The median time of exposure to vasopressors was only 2 days and difference in Kaplan-Meier curves was already noticed at approximately day 5, whereas the evolution was parallel thereafter (15, 16). Expanding the analysis to the longest estimate provided similar information. Fourth, we decided, *a priori*, to use the random effects method to aggregate results. We preferred to use this strategy to limit the weight of the two large trials because this model gives more weight to the results of smaller trials than the fixed-effect model (20). If anything, this favored the null hypothesis, as a fixed-effect analysis tends to give narrower confidence intervals than a random-effects analysis. Nevertheless, we observed a significant increase in risk of death with dopamine therapy in interventional trials. Fifth, the time of exposure in a randomized fashion to dopamine or norepinephrine was limited to a few hours in some of the randomized trials (25, 29, 30), and there was no mention of which vasopressor agent was used thereafter in these patients (patients may have received the alternate drug later on in their course). Any exposure to dopamine or norepinephrine may influence outcome and incorporating trials with short exposures in the analysis may limit the chance to disclose differences between the agents. Nevertheless, limiting the analysis to the three trials that ensured maximal exposure to trial drugs provided similar results. Finally, this study focused on patients with septic shock, which were a subgroup of patients in two of the trials (3, 15). It should not be considered as an intention-to-treat analysis. Expanding the analysis to the whole population of these trials gave similar results (Supplemental Digital Content 1, http://links.lww.com/CCM/A360).

We chose to include observational trials even though these may be affected by undetected confounding factors, as illustrated by the considerable variability among the studies. Admittedly, also, with the exception of the trial of Boulain et al (12), these observational studies did not purely compare dopamine to norepinephrine. One agent (most often dopamine (3, 13) but norepinephrine in one study (11)) was isolated and compared to the other agents. Nevertheless, in most trials the alternate comparator was most commonly norepinephrine or dopamine, with other agents being used in a minority of cases. Acknowledging these limitations, the incorporation of observational trials provided an important message because the aggregate effects were of similar magnitude, supporting the use of observational trials to compute sample size for interventional trials.

The trial by Povoa et al (13) had to be excluded from the analysis. This exclusion had a statistical basis because this trial was identified as driving the heterogeneity of the results. One of the potential reasons for this heterogeneity compared to other studies may have been the unique way in which the results were analyzed by the authors; patients were identified either as receiving dopamine or not (n = 231) and as receiving norepinephrine or not (n = 334), which resulted in some patients being counted

twice because the total number of patients (n = 565) identified this way exceeded the number of patients in septic shock included in this study (n = 458). Data from patients receiving dopamine vs. patients not receiving dopamine (or patients receiving norepinephrine vs. patients not receiving norepinephrine), which would have led to the only meaningful comparison, were not available. It was not possible to include patients treated exclusively with norepinephrine or dopamine from this trial, because this would have induced a major bias. It has been shown that patients who remain hypotensive and require addition of norepinephrine to dopamine have a marked increase in risk of death compared to patients who can be treated by dopamine alone (28). Restricting analysis to patients who receive dopamine in isolation would, by definition, limits this group to the less severe cases, as illustrated by a 28-day survival rate of approximately 80% in these patients compared to 59% in all patients receiving dopamine, in isolation or combined with norepinephrine, in the trial by Povoa et al (13). Furthermore, even though this study (13) was relatively large, its relative weight in analysis was only 13% (and this was even overestimated because we had to count 565 patients for this trial instead of the 458 patients included), so we did not exclude one of the most important trials.

In summary, this systematic analysis shows that dopamine, compared to norepinephrine, is associated with a higher incidence of arrhythmias and with an increased risk of death in patients with septic shock.

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