Meta-Analysis: Low-Dose Dopamine Increases Urine Output but Does Not Prevent Renal Dysfunction or Death

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Background: **Surveys have documented the continued popularity of low-dose dopamine to influence renal dysfunction even though few data support it and editorials and reviews have discouraged its use.**

Purpose: **To evaluate the effects of low-dose dopamine (≤5 μg/kg of body weight per minute) compared with placebo or no therapy in patients with or at risk for acute renal failure.**

Data Sources: **MEDLINE (1966–January 2005), EMBASE (1980–week 5, 2005), CANCERLIT (1975–2002), CINAHL (1982–January 2005), and CENTRAL (The Cochrane Library, fourth quarter, 2004); bibliographies of retrieved publications; and additional information from 50 trials.**

Study Selection: **Two reviewers independently selected parallel-group randomized and quasi-randomized controlled trials of low-dose dopamine versus control.**

Data Extraction: **Study methods, clinical and renal physiologic outcomes, and adverse events (arrhythmias and myocardial, limb, and cutaneous ischemia) were extracted.**

Data Synthesis: **61 trials that randomly assigned 3359 patients were identified. Meta-analyses using random-effects models showed no effect of low-dose dopamine on mortality (relative risk, 0.96 [95% CI, 0.78 to 1.19]), need for renal replacement therapy (relative risk, 0.93 [CI, 0.76 to 1.15]), or adverse events (relative risk, 1.13 [CI, 0.90 to 1.41]). Low-dose dopamine increased urine output by 24% (CI, 14% to 35%) on day 1. Improvements in serum creatinine level (4% relative decrease [CI, 1% to 7%]) and measured creatinine clearance (6% relative increase [CI, 1% to 11%]) on day 1 were clinically insignificant. There were no significant changes on days 2 and 3 of therapy.**

Limitations: **Statistically significant between-study heterogeneity in physiologic but not clinical outcomes was unexplained by prespecified hypotheses.**

Conclusion: **Low-dose dopamine offers transient improvements in renal physiology, but no good evidence shows that it offers important clinical benefits to patients with or at risk for acute renal failure.**

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Dopamine is a catecholamine with dose-dependent effects on the systemic and renal vasculature. In healthy participants, low-dose dopamine increases renal blood flow and promotes natriuresis through stimulation of renal D1, D2, and D4 receptors and thus may protect the kidney from acute tubular necrosis (1). The concept of low-dose or renal-dose dopamine has persisted since the first clinical description of its use in patients with congestive heart failure (2). Few controlled trials have demonstrated any benefit, and as a result, several editorials have discouraged its use (3–6). Nevertheless, recent surveys have documented dopamine's continued popularity. For example, 17 of 24 New Zealand intensive care units (7) and 18 of 19 pediatric and neonatal intensive care units in the Netherlands (8) use low-dose dopamine to treat renal dysfunction or oliguria. Moreover, this therapy continues to attract substantial research resources: Several randomized trials have been published each year, and at least 1 large trial is ongoing (9).

Two recent systematic reviews have addressed low-dose dopamine. Both reviews (10, 11) had several methodologic limitations. Neither review analyzed dopamine's effects on urine output and adverse events. Other authors (12) have discussed the limitations of 1 review (10) and have called for a rigorous, updated meta-analysis conducted by independent researchers (13).

Given the limited scope and methodologic concerns of previous systematic reviews and the ongoing widespread use and study of low-dose dopamine, we conducted a systematic review and meta-analysis by using a comprehensive search strategy to determine its effect on a broad range of clinical and renal physiologic outcomes and adverse events.

METHODS

Search Strategy

We searched the OVID versions of MEDLINE (1966–January, week 4, 2005), EMBASE (1980–week 5, 2005), CANCERLIT (1975–October 2002), CINAHL (1982–January, week 3, 2005), and CENTRAL (Cochrane Central Register of Controlled Trials, The Cochrane Library, fourth quarter, 2004). We also searched the Renal Health Library (available at www.update-software.com/publications/Renal/) on 3 February 2005. Two authors conducted independent search strategies. The first MEDLINE search strategy retrieved citations containing the subject heading *dopamine* (limited to the publication types clinical trial and meta-analysis) or the text words *low dose dopamine* or *renal dose dopamine*. The second MEDLINE

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search strategy retrieved citations containing the subject heading *dopamine* combined with exploded subject headings describing renal disease (*kidney diseases* and *kidney*) and physiology (*kidney function tests*, *urine*, and *renal circulation*) or text words describing low-dose dopamine appearing in close proximity to each other (*low*, *renal*, *kidney*, *dose*, and *dopamine*). We limited citations from the second search to randomized, controlled trials using a maximally sensitive strategy (14). We modified these searches for other databases. Full details of both search strategies are available from the authors. We screened reference lists from all retrieved articles and from recent review articles (8, 10, 11, 15–24) to identify additional studies. There were no language restrictions.

Study Selection and Characteristics

We selected parallel-group randomized, controlled trials that included any patient sample, compared low-dose dopamine ($\leq$5 μg/kg of body weight per minute) with placebo or no therapy, and recorded any of the following outcomes: all-cause mortality, requirement for renal replacement therapy, renal physiologic variables (urine output, serum creatinine level, or measured creatinine clearance on days 1, 2, or 3 after starting therapy), or adverse effects. We also included trials in which patients were allocated in alternating fashion or by hospital registry number (quasi-randomization) and trials with pharmacologic co-interventions (such as mannitol, diuretics, or diltiazem) that were equally applied to both groups. We defined a priori adverse effects of interest likely to be detected by routine patient monitoring: arrhythmias, myocardial ischemia, and limb or cutaneous ischemia.

Data Abstraction

Two reviewers independently screened studies for inclusion; retrieved all potentially relevant studies; and extracted data on study sample, intervention, prespecified outcomes, and methods from included trials. In both phases, disagreements between reviewers that remained after contacting study authors were resolved by consensus. We assessed agreement between the 2 reviewers on the selection of articles for inclusion by using Cohen's κ (25).

Validity Assessment

We extracted methodologic information important for the assessment of internal validity: method of allocation and concealment of the randomization schedule, blinding of caregivers and outcomes assessors, and the number of and reasons for postrandomization withdrawals. We determined whether fluid and diuretic therapies were standardized or equally applied in dopamine and control groups. We attempted to contact all authors of trials that met our inclusion criteria.

Quantitative Data Synthesis

For each outcome of interest, we pooled all studies reporting the outcome on the basis of the a priori expectation of similar direction and magnitude of treatment effect. For mortality and renal replacement therapy, we combined studies reporting these outcomes at any time after randomization. For studies with 2 or more dopamine groups receiving different doses, we combined data from all doses to determine an overall outcome measure for the dopamine group.

We used Review Manager 4.2 (The Cochrane Collaboration, Oxford, United Kingdom) to aggregate data for each outcome by using a random-effects model (26), and we considered a P value of 0.05 or less to be statistically significant. All pooled effect estimates are presented with 95% CIs, and all P values are 2-sided. Results for binary outcomes (mortality, need for renal replacement therapy, and adverse effects) are reported as relative risks. For studies with no events in one arm, 0.5 is added to all cells. (Studies with no events in either arm are not included in the pooled analysis.) The summary relative risk is calculated on the natural logarithm scale. The weight of each study is calculated as the inverse of the variance of the natural logarithm of its relative risk. In the presence of between-study heterogeneity, each study's weight is adjusted (26). Because clinical outcomes occurred infrequently in many trials, we also analyzed these outcomes by using other effect measures, including Peto's odds ratios and random-effects risk differences (by using Review Manager 4.2) and exact odds ratios (by using StatXact 6.1 [Cytel Software Corp., Cambridge, Massachusetts]). These alternate methods gave very similar pooled treatment effects and CIs, and we therefore present only the random-effects relative risk data.

Some papers reported 2 of the renal physiologic outcomes, urine output and creatinine clearance, in units that were adjusted for body weight or body surface area. However, trials did not consistently provide average patient weights, which are required to convert these measures into values with identical units, and they enrolled highly variable study samples that included adults, children, and neonates. Identical measurement units are necessary to statistically analyze the results by using weighted mean difference as the measure of treatment effect. One alternative approach would have pooled these measures by using the standardized mean difference (the absolute treatment effect in pooled SD units). However, we chose to summarize the treatment effect for each continuous outcome by using the relative change in the dopamine group compared with the control group. This approach provides a more clinically meaningful summary of treatment effect than the standardized mean difference. For each continuous outcome, we calculated the ratio of the mean value in the dopamine group to the mean value in the control group for each study and calculated a standard error for the natural logarithm–transformed ratio (see Appendix, available at www.annals.org). We aggregated the natural logarithm–transformed ratios across studies by using the generalized inverse variance method (27).

In studies where investigators obtained the total urine output over 24 hours by addition of urine outputs over several time periods, we calculated the variance of the total urine output by using the method of Follmann and colleagues (28). We assumed a moderate correlation (ρ) of 0.4

between urine outputs at different time periods. Sensitivity analyses using correlations of 0 and 0.8 did not change the results. We considered only first-order correlations.

We assessed between-study homogeneity for each pooled comparison by using the Cochran Q-test (29), with a P value of 0.10 or less indicating significant heterogeneity (30). We also report the I^2 statistic, which is the proportion of total variation among studies that is explained by between-study heterogeneity rather than chance (31, 32). Substantial heterogeneity exists when I^2 exceeds 50%. We developed several a priori hypotheses to explain statistically significant heterogeneity: 1) population—greater treatment effect in trials enrolling surgical patients (fewer comorbid conditions) compared with medical patients; 2) baseline risk—greater treatment effect when low-dose dopamine was given for treatment rather than prevention of acute renal failure; 3) dose–response relationship—greater treatment effect with a dopamine dose ≥ 3 μg/kg per minute vs. <3 μg/kg per minute; 4) duration of therapy—greater treatment effect in trials where dopamine was given for the entire time period before measurement of the outcome; and methods—smaller treatment effect 5) in studies with adequate allocation concealment (vs. all other studies) and 6) in studies with blinding of caregivers. For each hypothesis, we statistically tested the difference in estimates of treatment effect between the 2 subgroups using a Z test (33), and we considered a P value of 0.05 or less to be statistically significant.

Role of the Funding Source

There was no funding for this study.

DATA SYNTHESIS

Trial Flow

The 2 search strategies identified 1978 and 2977 citations, respectively, from bibliographic databases, excluding the Renal Health Register, which we searched separately. After detailed evaluation, we included 61 randomized and quasi-randomized controlled trials enrolling 3359 patients (34–94) (see Appendix Figure, available at www.annals.org). The first electronic search strategy identified 59 trials, and the second electronic search strategy identified 60 trials. We identified the 61st trial (58) from reviewing reference lists of retrieved articles.

Forty-eight authors clarified methodologic information or provided additional clinical outcome or adverse event data for 49 trials (34–51, 53–56, 58, 61–68, 70–77, 79–82, 86, 89, 91–94). Eleven of these 48 authors (37, 40, 45, 47, 49, 50, 53, 71, 72, 75, 91) and 1 other author (90) provided additional renal physiologic outcomes data. Seven authors (of 8 trials) informed us that no additional data were available (52, 57, 78, 83, 85, 87, 88). One author did not provide additional data before publication (59), and we could not contact the remaining 2 authors (60, 69).

We excluded 70 retrieved studies for the following reasons: sample size too small (3 patients) to allow statistical analysis (95), dopamine dose (8 μg/kg per minute) greater than 5 μg/kg per minute (96), not randomized or not quasi-randomized (97–127) crossover design (128–133), combined intervention compared with control (134–139), active therapy given to control group (140–155), duplicate publication (156, 157), partial duplicate publication (158–160), wrong topic (161, 162), and editorial (163, 164). We excluded 4 randomized trials without group-specific data because we could not contact the authors (165), the authors did not provide data before publication (166, 167), or no additional data were available from the authors (168).

Study Characteristics and Methodologic Quality

Table 1 describes the included studies, and **Appendix Table 1** (available at www.annals.org) provides further information. Four studies were published in abstract form only (37, 58, 66, 91). One report (78) described 2 separate trials, and data from 1 trial were distributed in 2 reports (84, 85). Three studies (48, 49, 91) randomly assigned patients to 4 groups, with each pair differing only by the presence of dopamine but with 1 pair receiving an additional co-intervention (48, 49) or diuretic protocol (91). We counted these 3 studies as 3 trials but analyzed each pair of randomized groups separately. The patient populations included patients having cardiac surgery (18 trials), patients having vascular surgery (4 trials), patients having other surgery (18 trials), patients receiving intravenous contrast dye (8 trials), patients receiving other nephrotoxic medications (3 trials), neonates (5 trials), and patients with miscellaneous indications (5 trials). The median number of patients randomly assigned per trial was 40 (range, 12 to 347). Only 5 trials included 100 or more patients (37, 41, 49, 66, 90). The largest trial enrolled 347 patients after abdominal or urologic surgery who were at risk for renal dysfunction (66). The next largest, and only multicenter, trial, organized by the Australian and New Zealand Intensive Care Society (ANZICS), enrolled 328 critically ill patients with early renal dysfunction (90). Most trials included patients with normal or near-normal renal function who were at risk for acute renal failure from a surgical or pharmacologic intervention. Only 6 trials used dopamine therapeutically for patients developing acute renal dysfunction as a result of critical illness (90, 91), intravenous contrast dye (78), malaria (92), congestive heart failure (94), or preeclampsia (93).

The median dopamine dose of 2.5 μg/kg per minute (range, 1 to 5 μg/kg per minute) was infused for a median of 31 hours (range, 0.4 to 192 hours). Only 8 trials studied doses higher than 3 μg/kg per minute, of which 3 and 4 contributed data to the analyses of clinical and renal physiologic outcomes, respectively. Nine trials included a pharmacologic co-intervention given to both dopamine and control groups: mannitol (49, 57, 71, 81), diltiazem (48), a diuretic (61, 92, 94), and both mannitol and a diuretic (59). Twenty-five trials reported protocols (explicit instructions or general guidelines) for intravenous fluid administration either immediately before or during the study pe-

Table 1. **Description of Included Studies of Low-Dose Dopamine***

Study, Year (Reference)	Patients, *n*	Dopamine Dose, *μg/kg per minute*	Duration of Dopamine Administration, *h*	Other Features†	Concealment‡	Caregiver Blinding§	Zero Withdrawals‖
Patients having cardiac surgery							
Costa et al., 1990 (34)	24	2.5	2–3		No	Yes	No
Wierda et al., 1990 (35)	12	2	24		NR	No	Yes
Myles et al., 1993 (36)	52	200 μg/min	24	Diuretic protocol	Yes	Yes	No
Lauwers et al., 1994 (37)	225	2 or 3	48	Diuretic protocol	Yes	Yes	No
Gårdebäck and Settergren, 1995 (38)	23	2.5	16		Yes	No	Yes
Chaiyaroj and Tatoulis, 1999 (39)	52	3	24		Quasi	Yes	No
McNicol et al., 1999 (40)	16	3	2		Yes	Yes	Yes/No
Schneider et al., 1999 (41)	100	2	24		Envelopes	Yes	Yes
Sharpe et al., 1999 (42)	20	4	1		Envelopes	Yes	Yes
Tang et al., 1999 (43)	40	2.5–4	48	Fluid protocol	Yes	Yes	Unclear
Dural et al., 2000 (44)	24	3	3–4	Fluid protocol; no diuretics given	Yes	No	Yes
Lassnigg et al., 2000 (45)	84	2	48		Yes	Yes	Yes/No
Sumeray et al., 2001 (46)	48	2.5	48	Diuretic protocol	Yes	Yes	Yes/No
Woo et al., 2002 (47)	50	3	48		Yes	No	Yes/No
Yavuz et al., 2002 A (48)¶	30	2	72		Quasi	Yes	Yes
Yavuz et al., 2002 B (48)¶	30	2	72	Both groups received diltiazem	Quasi	Yes	Yes
Carcoana et al., 2003 A (49)¶	50	2	~4	Intraoperative diuretic protocol	Yes	Yes	No
Carcoana et al., 2003 B (49)¶	50	2	~4	Intraoperative diuretic protocol; both groups received mannitol	Yes	Yes	No
Piper et al., 2003 (50)	40	2.5	48	Fluid and diuretic protocols	Yes	Yes	Yes/No
Gatot et al., 2004 (51)	89	3–5	48	Fluid and diuretic protocols	Yes	Yes	Yes/No
Patients having vascular surgery							
Baldwin et al., 1994 (52)	37	3	24	Fluid protocol; no diuretics given	Yes	Yes	Yes
de Lasson et al., 1995 (53)	30	3	24	Fluid protocol; no diuretics given	Yes	Yes	Yes/No
Soong et al., 1995 (54)	19	3	24		Yes	No	Yes
Sprung et al., 2000 (55)	20	2	12		Yes	Yes	Yes
Patients having other surgery**							
Grundmann et al., 1982 (56)	50	2	96		Yes	No	Yes
Swygert et al., 1991 (57)	48	3	48	Fluid and diuretic protocols; both groups received mannitol	NR	Double	No
Whelan et al., 1993 (58)	60	3	72		NR	No	Yes
Carmellini et al., 1994 (59)	60	3	Unclear	Both groups received mannitol; preoperative fixed diuretic dose	NR	NR	Yes
Ohata et al., 1994 (60)	20	3	3–4		NR	NR	Yes
Parks et al., 1994 (61)	23	3	48	Preoperative fluid protocol; fixed diuretic dose	Yes	No	Yes
Watanabe et al., 1995 (62)	16	3	~3		NR	No	Yes
Tanaka et al., 1997 (63)	21	5	0.4	Fluid protocol	Yes	No	Yes
Cregg et al., 1999 (64)	30	3	24	Fluid protocol	Quasi	Yes	Yes
Dönmez et al., 1999 (65)	40	2	48		Yes	Yes	Yes
Schulze et al., 1999 (66)	347	2	~48	Fluid and diuretic protocol	Yes	No	Yes/No
Kasaba et al., 2000 (67)	20	5	0.5	Preoperative colloid protocol	Quasi	No	Yes
Wahbah et al., 2000 (68)	20	2.5	48	No diuretics given	Yes	No	Yes
Niiya et al., 2001 (69)	14	2	24		NR	NR	Yes
Schilling et al., 2001 (70)	16	5	24	Fluid protocol	Yes	Yes	Yes

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Table 1—**Continued**

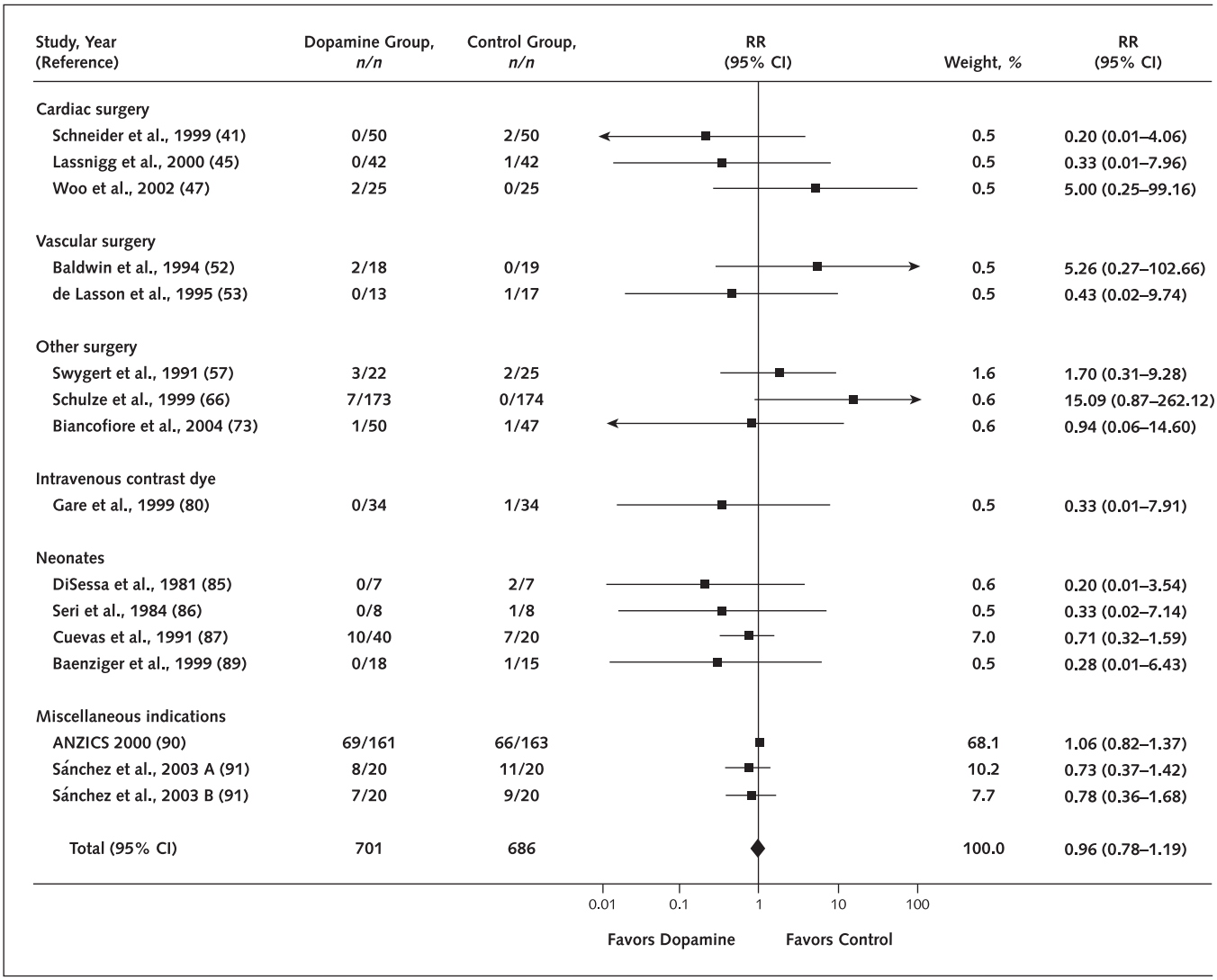
Study, Year (Reference)	Patients, *n*	Dopamine Dose, *μg/kg per minute*	Duration of Dopamine Administration, *h*	Other Features†	Concealment‡	Caregiver Blinding§	Zero Withdrawals‖
O'Hara et al., 2002 (71)	35	3	5-6	Intraoperative fluid protocol; both groups received mannitol	Yes	No	No
Pérez et al., 2002 (72)	40	2	2	Fluid protocol	Yes	Yes	Yes/No
Biancofiore et al., 2004 (73)	97	3	100	Diuretic protocol	Yes	Yes	No
Patients receiving intravenous contrast dye							
Hans et al., 1990 (74)	60	2.5	12	Fluid protocol	Quasi	No	Yes
Weisberg et al., 1994 (75)	30	2	2	Fluid protocol	Yes	Yes	Yes/No
Kapoor et al., 1996 (76)	40	5	6.5–8.5	No diuretics given	Yes	No	Yes
Hans et al., 1998 (77)	55	2.5	12		Quasi	No	Yes
Abizaid et al., 1999 A (78)††	40	2.5	14	Fluid protocol	NR	No	Yes
Abizaid et al., 1999 B (78)††	72	2.5	Unclear	Fluid protocol	NR	No	Yes
Diez et al., 1999 (79)	50	2	~1	Fluid protocol	Quasi	No	Yes
Gare et al., 1999 (80)	68	2	48	Fluid protocol	Yes	Yes	No
Patients receiving other nephrotoxic medications							
Somlo et al., 1995 (81)	42	2	48	Both groups received mannitol	Yes	Yes	Yes
Cormier et al., 1997 (82)	42	2	~84	Fluid protocol; no diuretics given	Yes	No	Yes
Camp et al., 1998 (83)	72	3	192		NR	No	No
Neonates							
DiSessa et al., 1981 (85); Leitner et al., 1980 (84)‡‡	14	2.5	65–70	Pretrial colloid or blood protocol	NR	Double	Yes/NR
Seri et al., 1984 (86)	16	2 or 4	48	Fluid protocol; no diuretics given	Yes	No	Yes/No
Cuevas et al., 1991 (87)	60	1 or 2.5	72	Fluid protocol; no diuretics given	Yes	No	No
Fajardo et al., 1992 (88)	26	2	42		NR	NR	Yes
Baenziger et al., 1999 (89)	33	4	38	Diuretic protocol	Yes	No	Yes/No
Patients with miscellaneous indications							
Lumlertgul et al., 1989 (92)	19	1	96	Fixed diuretic dose in all patients	Quasi	No	Yes
Mantel and Makin, 1997 (93)	40	1–5	6		Yes	Yes	Yes/No
Varriale and Mossavi, 1997 (94)	20	2	~107	Fixed diuretic dose in all patients	Quasi	No	Yes
ANZICS, 2000 (90)	328	2	~113		Yes	Yes	No
Sánchez et al., 2003 A (91)¶	40	2	≤168	No diuretics given	Yes	No	Yes/No
Sánchez et al., 2003 B (91)¶	40	2	≤168	Diuretic protocol	Yes	No	Yes/No

* ANZICS = Australian and New Zealand Intensive Care Society; NR = not reported.
† Other features include pharmacologic co-interventions given equally to both groups and fluid or diuretic protocols (defined as general guidelines or explicit instructions).
‡ We note whether randomization was concealed. "Envelopes" denotes trials that used envelopes to conceal randomization but did not provide further details (opacity or numbering). "Quasi" refers to quasi-randomized trials.
§ "Blinding" refers to caregiver blinding. "Double" means that the authors report double-blinding without further specification.
‖ "Zero withdrawals" refers to randomly assigned patients who were withdrawn from clinical or renal physiologic outcomes.
¶ These patients were randomly assigned into 4 groups in the same trial and were reported in the same publication.
** "Other surgery" includes 4 trials in patients undergoing renal transplantation (56, 58, 59, 65).
†† These patients were randomly assigned in 2 separate trials and were reported in the same publication.
‡‡ Data from this trial were distributed in 2 publications.

riod. Eleven other trials, in which clinicians prescribed fluids according to discretion, reported the actual volume of fluid infused. Fewer trials reported protocols or fixed-dose diuretic administration immediately before or during the study period (15 trials), reported the number of patients receiving diuretics (7 trials), or explicitly stated that diuretics were never used (8 trials).

Table 1 describes the methodologic features of included studies, and **Appendix Table 2** (available at www.annals.org) provides further details. Fifty-two trials were described as randomized. The randomization schedule was clearly concealed in 37 trials, was probably concealed in 2 trials by sealed envelopes without definite opacity or numbering, was not concealed in 1 trial, and was not reported in 12 trials. Nine other trials allocated patients in alternating fashion or by hospital registry number. In these trials, we had insufficient informa-

Figure 1. **Effect of low-dose dopamine on mortality.**



Weight refers to the contribution of each study to the overall estimate of treatment effect. The pooled estimate is calculated by using a random-effects model. The summary relative risk is calculated on the natural logarithm scale. The weight of each study is calculated as the inverse of the variance of the natural logarithm of its relative risk. The size of the symbol denoting the point estimate does not represent the weighting of the study. See the Methods section for a discussion of the weighting. ANZICS = Australian and New Zealand Intensive Care Society; *n/n* = numbers of deaths/patients randomly assigned; RR = relative risk.

tion to establish whether a random process was used to determine in which treatment group the first enrolled patient was assigned. Twenty-nine trials reported blinding of at least caregivers or outcome assessors (27 trials) or used the term "double-blind" (2 trials). All trials, including those explicitly reporting crossovers (51, 82, 83), analyzed patients according to assigned group for clinical outcomes. Most trials reported no postrandomization withdrawals (33 trials) or only withdrawals in analyses of renal physiologic outcomes (16 trials). Two trials (56, 91) reporting renal replacement therapy had standardized criteria for initiation.

Quantitative Data Synthesis

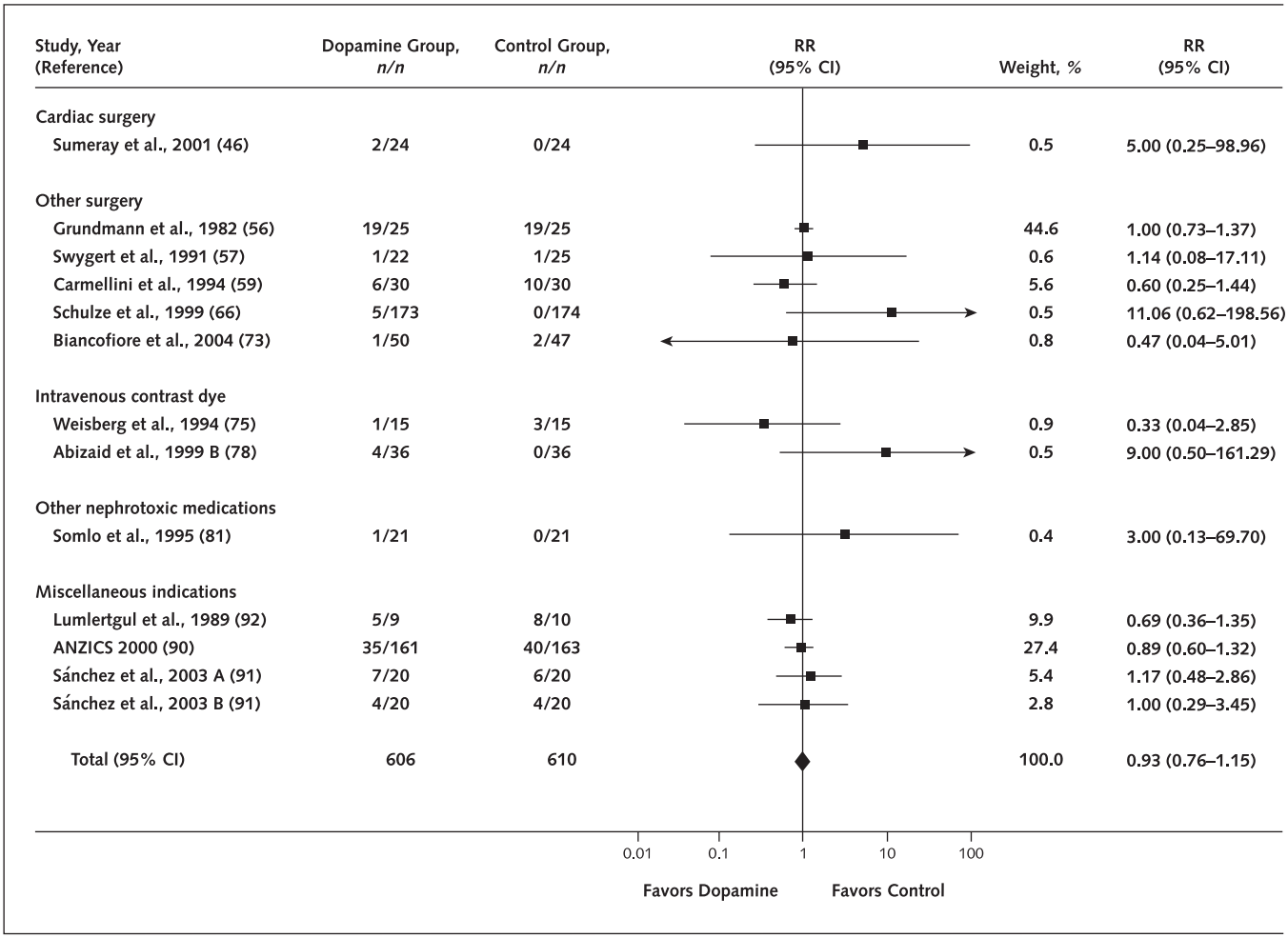
The 2 reviewers achieved excellent agreement on the selection of trials for inclusion ($\kappa = 0.98$ [95% CI, 0.96 to 1.00]).

Effect of Low-Dose Dopamine on Clinical Outcomes

Fifty-four trials reported mortality and 54 trials reported renal replacement therapy, of which 15 and 12 trials, respectively, reported at least 1 event (**Table 3** and **Figures 1** and **2**). Pooled analyses showed no effect of low-dose dopamine on mortality (relative risk, 0.96 [CI, 0.78 to 1.19]) or need for renal replacement therapy (relative risk, 0.93 [CI, 0.76 to 1.15]). There was no statistical evidence of between-study heterogeneity for these outcomes.

The ANZICS trial (90) contributed the most events to both pooled analyses and also found no effect on mortality or need for renal replacement therapy. Post hoc sensitivity analyses excluding the ANZICS trial did not substantially change the results for mortality (relative risk, 0.79 [CI, 0.54 to 1.14]) or renal replacement therapy (relative risk

Figure 2. **Effect of low-dose dopamine on need for renal replacement therapy.**



Weight refers to the contribution of each study to the overall estimate of treatment effect. The pooled estimate is calculated by using a random-effects model. The summary relative risk is calculated on the natural logarithm scale. The weight of each study is calculated as the inverse of the variance of the natural logarithm of its relative risk. The size of the symbol denoting the point estimate does not represent the weighting of the study. See the Methods section for a discussion of the weighting. ANZICS = Australian and New Zealand Intensive Care Society; *n/n* = numbers of patients requiring renal replacement therapy/patients randomly assigned; RR = relative risk.

with the ANZICS trial excluded, 0.95 [CI, 0.73 to 1.23]; relative risk with the most heavily weighted trial [56] also excluded, 0.92 [CI, 0.59 to 1.45]; each $P > 0.2$ for difference between relative risks).

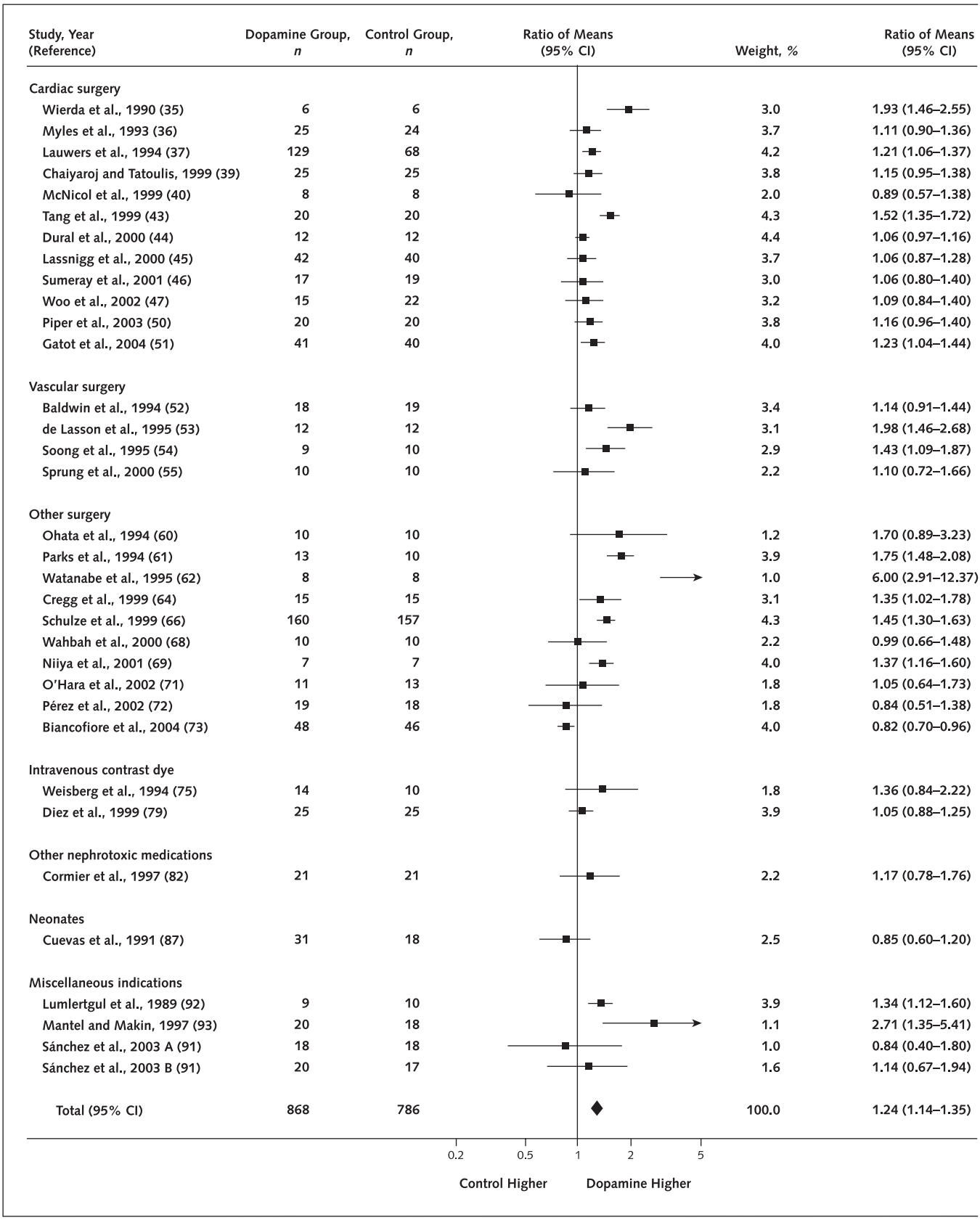
Adverse Effects

In the 50 trials reporting adverse effects, 178 patients receiving dopamine (of 1450 patients randomly assigned) and 129 control patients (of 1370 patients randomly assigned) experienced arrhythmias or myocardial, limb, or cutaneous ischemia. Patients in the ANZICS trial (90) accounted for most of these events. Adverse events included myocardial infarctions (4 patients receiving dopamine and 2 control patients), cutaneous ischemia from extravasation injury (2 patients receiving dopamine) or skin-blanching in neonates (7 patients receiving dopamine), and worsening of Raynaud disease (1 patient receiving dopamine). The remaining patients had tachyarrhythmias. The pooled analysis did not show a significant difference in adverse events (relative risk, 1.13 [CI, 0.90 to 1.41]). A post hoc sensitivity analysis showed that excluding the ANZICS trial did not significantly change this estimate (relative risk, 1.19 [CI, 0.89 to 1.60]; $P > 0.2$). Another post hoc sensitivity analysis excluding the nonblinded trials (in which outcome assessors may have differentially monitored or reported adverse events between groups) resulted in a nonsignificant reduction in the pooled estimate (relative risk, 1.05 [CI, 0.81 to 1.35] for blinded trials vs. 1.44 [CI, 0.85 to 2.46] for nonblinded trials; $P > 0.2$ for difference between relative risks).

Effect of Low-Dose Dopamine on Renal Physiologic Outcomes

The pooled analysis (**Table 3** and **Figure 3**) showed an increase in urine output (ratio of means, 1.24 [CI, 1.14 to 1.35]; $P < 0.001$) on the first day after initiation of low-dose dopamine therapy. The effect on urine output was no longer significant on day 2 (ratio of means, 1.09 [CI, 0.99 to 1.20]; $P = 0.07$) or on day 3 (ratio of means, 1.02 [CI,

Figure 3. **Effect of low-dose dopamine on day 1 urine output.**



Weight refers to the contribution of each study to the overall estimate of treatment effect. Ratio of means is mean value in dopamine group divided by the mean value in control group. The pooled estimate is calculated by using a random-effects model.

Table 2. **Effect of Low-Dose Dopamine on Clinical and Renal Outcomes**

Outcome	Trials (Patients) with Outcomes Data, *n (n)**	Treatment Effect (95% CI)†	*P* Value	Homogeneity‡	
				I^2 Statistic, %	*P* Value
Mortality	15 (1387)	Relative risk, 0.96 (0.78–1.19)	>0.2	0	>0.2
Need for renal replacement therapy	12 (1216)	Relative risk, 0.93 (0.76–1.15)	>0.2	0	>0.2
Adverse effects	18 (1660)	Relative risk, 1.13 (0.90–1.41)	>0.2	6	>0.2
Urine output (day 1)	33 (1654)	Ratio of means, 1.24 (1.14–1.35)	<0.001	77	<0.001
Urine output (day 2)	17 (723)	Ratio of means, 1.09 (0.99–1.20)	0.07	75	<0.001
Urine output (day 3)	8 (326)	Ratio of means, 1.02 (0.87–1.20)	>0.2	85	<0.001
Creatinine level (day 1)	32 (1807)	Ratio of means, 0.96 (0.93–0.99)	0.01	73	<0.001
Creatinine level (day 2)	26 (1301)	Ratio of means, 0.99 (0.92–1.08)	>0.2	92	<0.001
Creatinine level (day 3)	15 (741)	Ratio of means, 0.97 (0.88–1.07)	>0.2	94	<0.001
Creatinine clearance (day 1)	22 (1077)	Ratio of means, 1.06 (1.01–1.11)	0.02	0	>0.2
Creatinine clearance (day 2)	12 (580)	Ratio of means, 1.02 (0.90–1.15)	>0.2	54	<0.01
Creatinine clearance (day 3)	8 (339)	Ratio of means, 1.09 (0.96–1.24)	0.18	36	0.14

* For mortality, renal replacement therapy, and adverse effects, trials are counted only if they reported ≥1 event. The numbers of trials (patients) with any data, including those with 0 events, were 54 (2977) for mortality, 54 (3058) for renal replacement therapy, and 50 (2817) for adverse effects. The number of trials used to calculate treatment effects and CIs is greater than that shown for clinical outcomes and day 1 and 2 renal physiologic outcomes, where trials with 2 separately analyzed subgroups (48, 49, 91) contributed data and are counted twice.
† We used the random-effects model for all analyses. Ratio of means = mean value in dopamine group divided by mean value in control group.
‡ We assessed homogeneity by using the Cochran Q-test (29) (*P* value shown) and I^2 statistic (31).

0.87 to 1.20]; $P > 0.2$). On day 1, serum creatinine level decreased (ratio of means, 0.96 [CI, 0.93 to 0.99]; $P = 0.01$) and creatinine clearance increased (ratio of means, 1.06 [CI, 1.01 to 1.11]; $P = 0.02$). Neither effect was statistically significant after the first day.

These analyses excluded the ANZICS trial (90) because investigators did not record daily serum creatinine level values, cumulative urine output, and measured creatinine clearance (Bellomo R. Personal communication).

Substantial between-study heterogeneity was evident, with I^2 values ranging from 36% to 94%, for 8 of the 9 renal physiologic outcomes; the exception was day 1 creatinine clearance (**Table 2**). Without adjustment for several comparisons, we found only 5 statistically significant subgroup effects among 48 comparisons tested (6 hypotheses tested for each of 8 outcomes) (**Table 3**). However, 2 of the significant analyses had only 1 or 2 trials in 1 of the comparison groups. Most statistically significant subgroup effects were related to study methods (blinding in 3 analyses and allocation concealment in 1 analysis), with more conservative treatment effects in the blinded and concealed trials.

Funnel plots of standard error against treatment effect for clinical and renal physiologic outcomes and adverse effects did not suggest the presence of publication bias.

DISCUSSION

This systematic review of low-dose dopamine for preventing and treating acute renal failure identified 61 randomized and quasi-randomized controlled trials enrolling 3359 patients. Methodologic quality varied. Most trials achieved nearly complete patient follow-up, and many trials clearly concealed randomization (61%) or blinded caregivers (48%). The 95% CIs for pooled relative risks for mortality and renal replacement therapy are wide and do not exclude clinically important benefit or harm. However, both point estimates are close to unity. This means that the best estimate of low-dose dopamine's effect on these out-

Table 3. **Hypotheses Explaining Heterogeneity in Renal Physiologic Outcomes***

Outcome	Hypothesis	Ratio of Means (95% CI)†	Trials, *n*	*P* Value‡
Creatinine level (day 1)	Blinding	Blind: 0.99 (0.95–1.04)	16	0.005
		Not blind: 0.91 (0.88–0.95)	16	
Urine output (day 2)	Blinding	Blind: 0.98 (0.92–1.04)	6	0.03
		Not blind: 1.17 (1.01–1.35)	11	
Creatinine level (day 3)	Blinding	Blind: 1.08 (0.93–1.25)	7	0.01
		Not blind: 0.88 (0.84–0.93)	8	
Urine output (day 2)	Allocation concealment	Concealment: 1.07 (0.97–1.17)	15	0.045
		No concealment: 1.29 (1.11–1.52)	2	
Urine output (day 3)	Illness severity	Therapy of ARF: 1.39 (1.28–1.52)	1	<0.001
		Prevention of ARF: 0.97 (0.88–1.07)	7	

* We found statistically significant heterogeneity in pooled analyses for all renal physiologic outcomes except for day 1 creatinine clearance, and we explored subgroup effects according to 6 prespecified hypotheses for each outcome (see text). Only statistically significant results are shown. The number of trials used to calculate treatment effects and CIs is greater than that shown for day 1 and 2 renal physiologic outcomes, where trials with 2 separately analyzed subgroups (48, 49, 91) contributed data and are counted twice. ARF = acute renal failure.
† Ratio of means = mean value in dopamine group divided by mean value in control group.
‡ *P* values for differences between subgroups were calculated by using a *Z* test.

comes is nil, an interpretation that is strengthened by the lack of between-study statistical heterogeneity. The novel findings of our review are that low-dose dopamine 1) increased urine output by 24% (CI, 14% to 35%) on the first day of therapy, with the effect decreasing and not statistically significant thereafter, and 2) did not statistically significantly increase adverse events. The early diuretic effect and apparent safety of low-dose dopamine may explain its continued popularity.

The clinical data from the ANZICS trial (90), the second-largest and only multicenter trial, dominated the clinical outcomes analyses (with a weight of 68.1% for mortality and 27.4% for renal replacement) because of its large sample size (324 patients) and high proportion of patients with events. The heavy weighting of 1 trial may lead to criticism that the meta-analysis simply restates the results of the dominant trial. Our sensitivity analyses showed that the clinical outcomes results did not substantially change when the ANZICS trial (90) is excluded, suggesting that the results of the remaining trials are consistent with those of the dominant trial. This interpretation is supported by the renal physiologic outcomes analyses (excluding the ANZICS trial [90], which provides no data) in which trials had similar weights. Our finding of small and short-term improvements in these renal physiologic outcomes is congruent with and may explain the lack of improvements in the clinical outcomes.

The ANZICS trial (90) was not included in the pooled urine output analysis because it measured hourly urine output at prespecified time points rather than cumulative urine output. However, by using additional data provided by the ANZICS investigators (Bellomo R. Personal communication), we calculated that their trial also showed a trend toward increased hourly urine output at 24 hours (corrected for baseline urine output) in the dopamine group compared with the control group ($P = 0.08$). Hourly urine output did not differ at 48 hours.

The lack of effect on important clinical outcomes was consistent across trials. In contrast, analyses of 8 renal physiologic outcomes showed substantial heterogeneity. Blinding or allocation concealment was associated with 4 of the 5 statistically significant subgroup effects detected, with methodologically more rigorous trials providing more conservative estimates of treatment effect. No other prespecified subgroup hypothesis covering patient population, intervention, illness severity, and study method consistently explained heterogeneity. These analyses may suggest that trials without allocation concealment or blinding inflate treatment effects. However, we did not find this result for half of the physiologic outcomes exhibiting heterogeneity. In addition, a qualitative interaction (a statistically significant differential effect with benefit in 1 subgroup and harm in another) was not evident.

Our subgroup analyses found no dose–response effect when comparing trials using a dose of 3 μg/kg per minute or greater with those using a dose less than 3 μg/kg per minute. Some may question the inclusion of trials using doses greater than 3 μg/kg per minute in a meta-analysis of low-dose dopamine. However, several studies in healthy volunteers and critically ill patients have shown great individual variation in dopamine clearance, resulting in poor correlation between plasma levels and infusion rates (169–172). The threshold of 5 μg/kg per minute is also supported in clinical reviews (8, 10, 11, 15). Very few trials of dopamine at doses greater than 3 μg/kg per minute contributed data to the pooled analyses. Because of limited data, we cannot reliably evaluate the effect of dopamine at a dose greater than 3 μg/kg per minute on renal physiology.

Given that many subgroups have few trials, our meta-analysis may have been underpowered to detect true subgroup effects, and we could not explore subgroup interactions. Meta-regression (173) or subgroup analyses using individual-patient data (174) may overcome these limitations and identify a subgroup with greater improvements in renal physiology. However, it is unclear that low-dose dopamine would be clinically beneficial in any such subgroup, given that our meta-analyses of clinical outcomes found no between-study heterogeneity and showed no benefit.

Our pooled analysis did not demonstrate a statistically significant difference in adverse effects between low-dose dopamine and control groups. Although this result is consistent with the ANZICS trial (90), it should be interpreted with caution. The confidence limits are wide, and we cannot exclude a relative risk increase in adverse effects of as much as 41%. Because all trials were published before recent guidelines on the reporting of harm (175), they did not define, ascertain, analyze, or report adverse events similarly. We attempted to reduce detection bias and select clinically homogeneous adverse effects by choosing predefined adverse events for which patients would be routinely monitored. We requested specific information about these adverse events from every author and obtained data from all but 11 trials. However, no trial reported a blinded adverse event adjudication committee, and very few trials prespecified harm outcomes. Outcome assessors in the unblinded trials may have differentially monitored for or reported adverse events. For example, 1 trial (83) monitored only the patients receiving dopamine with telemetry and reported tachyarrhythmias in 7 patients receiving dopamine and only 1 control patient. Our post hoc sensitivity analysis showed that unblinded trials had a non–statistically significant higher relative risk for adverse events than blinded trials. Finally, other adverse events noted in a few trials (for example, gastrointestinal complications [41]) may have been related to dopamine but were not routinely reported. We did not include these events and therefore may have underestimated the risk for adverse effects.

Strengths of our systematic review include the following: 1) an exhaustive search of several databases without age or language restrictions; 2) duplicate independent searches, citation screening, and data abstraction; 3) acqui-

sition of additional unpublished data from authors of 82% of trials (and confirmation that no additional data were available from authors of 13% of trials); 4) the use of explicit criteria for methodologic assessment; 5) evaluation of a comprehensive set of clinical and renal physiologic outcomes; and 6) the use of a random-effects model for each pooled analysis. (For the renal physiologic outcomes in which heterogeneity was statistically significant, the random-effects model provides more conservative confidence limits for the point estimate of the pooled treatment effect [176].)

Our review also has limitations. We did not systematically search the "gray" literature (such as conference proceedings). Despite several attempts, we could not obtain additional information from some authors, which may have led to a systematic underestimation of trial quality and imprecision in assessing treatment effects. The meta-analysis included many trials with low event rates, decreasing the precision of the pooled estimates of clinical outcomes and adverse effects. Finally, we could not consistently explain heterogeneity of the renal physiologic outcomes despite several prespecified hypotheses.

As discussed in the introduction, 2 other systematic reviews of low-dose dopamine have recently been published. Both reviews (10, 11) used a less exhaustive search strategy and included fewer trials (17 and 15 trials, respectively). Kellum and Decker (10) found no effect on mortality and need for renal replacement therapy but did not analyze renal physiologic outcomes. They included some studies in which dopamine was compared with active therapy (such as dobutamine [137] and furosemide [177]) or was used in combination with other therapies (135), which limits the interpretability of their meta-analysis. Marik's (11) review specifically excluded neonatal trials and found no effect on the change in serum creatinine level or development of acute renal failure. In contrast to our review, Marik's meta-analysis included some trials with diuretics applied similarly between dopamine and control groups (36, 45, 57, 61, 80, 90) while excluding other trials (34, 92) and included 1 study in which the control group received active therapy (140). The method of estimating the covariance between baseline and follow-up creatinine level values, required when calculating the variance of the difference between correlated measurements, was also unclear.

In summary, we believe that our meta-analysis of controlled trials provides the most comprehensive systematic review to date of low-dose dopamine. There is no good evidence that low-dose dopamine offers important clinical benefits to patients with or at risk for acute renal failure. An alternative interpretation of our results is that low-dose dopamine causes small and short-term improvements in renal physiology without statistically significantly increasing adverse events. Both conflicting interpretations are consistent with the results of our meta-analysis and suggest that the use of low-dose dopamine for renal dysfunction will probably remain controversial. The small and temporary improvements in renal physiology, if these are surrogate markers for clinical improvement, suggest that an extremely large randomized trial would be required to demonstrate improved clinical outcomes. Given our results, a possible outcome of such a trial would be substantially more adverse effects in dopamine-treated patients, dominating any clinically important benefit.

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Appendix: Calculating the Variance of a Ratio of Continuous Variables

For a study reporting a continuous outcome, let the mean, SD, and number of patients be denoted by $\overline{D}$, s_D, and n_D, respectively, in the dopamine group and $\overline{C}$, s_C, and n_C, respectively, in the control group. We calculated the ratio $\overline{D}/\overline{C}$ and estimated the variance (*Var*) of its natural logarithm as follows (178):

$$Var\left[\ln\left(\frac{\overline{D}}{\overline{C}}\right)\right] = Var\left[\ln(\overline{D}) - \ln(\overline{C})\right]$$

$$= Var\left[\ln(\overline{D})\right] + Var\left[\ln(\overline{C})\right] \text{ [since the groups are independent]}$$

$$= \left(\frac{1}{\overline{D}}\right)^2 Var\,(\overline{D}) + \left(\frac{1}{\overline{C}}\right)^2 Var\,(\overline{C}) = \frac{1}{n_D}\left(\frac{s_D}{\overline{D}}\right)^2 + \frac{1}{n_C}\left(\frac{s_C}{\overline{C}}\right)^2$$

$$\left[\text{since for random variable } X,\ Var\,(\overline{X}) = \frac{Var\,(X)}{n_X} = \frac{s_X^2}{n_X}\right]$$

We aggregated the natural logarithm–transformed ratios across studies by using the generalized inverse variance method (27) and back-transformed to obtain a pooled ratio and 95% CI, as follows:

$$95\%CI = \exp\left\{\left[\ln\left(\frac{\overline{D}}{\overline{C}}\right)\right] \pm 1.96\sqrt{Var\left[\ln\left(\frac{\overline{D}}{\overline{C}}\right)\right]}\right\}$$

Appendix Table 1. **Description of Studies of Low-Dose Dopamine for Acute Renal Failure Included in the Meta-Analysis***

Study, Year (Reference)	Patients, *n*	Main Eligibility Criteria	Dopamine Regimen		Fluids†	Diuretics†
			Dose, *μg/kg per minute*	Start; Duration; Other Medications‡		
Patients having cardiac surgery						
Costa et al., 1990 (34)	24	All cardiac surgery; creatinine clearance ≤ 0.83 mL/s (≤50 mL/min)	2.5	Start to end of cardiopulmonary bypass	Clinician discretion; similar volume	Clinician discretion; frequent and similar
Wierda et al., 1990 (35)	12	Elective CABG; no renal disease	2	Start of cardiopulmonary bypass; 24 h	Not reported	Not reported
Myles et al., 1993 (36)	52	Elective CABG; creatinine level ≤ 300 μmol/L (≤3.4 mg/dL)	200 μg/min	Induction; 24 h	Clinician discretion; similar volume	Protocol; infrequent and similar
Lauwers et al., 1994 (37)	225	High-risk cardiac surgery (valve, redo procedure, combined valve and CABG, renal dysfunction, or diabetes mellitus)	2 or 3	After aortic cross-clamping; 48 h (or longer if ARF developed)	Clinician discretion	Protocol; frequent; more common in placebo group
Gårdebäck and Settergren, 1995 (38)	23	CABG or valve	2.5	Induction; 16 h after cardiopulmonary bypass	Not reported	Not reported
Chaiyaroj and Tatoulis, 1999 (39)	52	CABG; creatinine level > 110 μmol/L (>1.2 mg/dL)	3	Induction; 24 h	Not reported	Not reported
McNicol 1999 (40)	16	Elective CABG; creatinine level ≤ 250 μmol/L (≤2.8 mg/dL)	3	Start of cardiopulmonary bypass; 2 h	Not reported	Not reported
Schneider et al., 1999 (41)	100	First-time CABG; creatinine level ≤ 120 μmol/L (≤1.4 mg/dL)	2	Induction; 24 h	Not reported	Not reported
Sharpe et al., 1999 (42)	20	Elective CABG	4	6 h after cardiopulmonary bypass; 1 h	Not reported	Not reported
Tang et al., 1999 (43)	40	Elective CABG; creatinine level ≤ 120 μmol/L (≤1.4 mg/dL)	2.5–4.0	Induction; 48 h	Protocol	Not reported
Dural 2000 (44)	24	Elective CABG; creatinine level ≤ 115 μmol/L (≤1.3 mg/dL)	3	Induction; duration of operation	Protocol	Not used
Lassnigg et al., 2000 (45)	84	Elective CABG or valve; creatinine level < 177 μmol/L (<2.0 mg/dL)	2	Induction; 48 h or until ICU discharge	Clinician discretion; similar volume	Clinician discretion; frequent and similar
Sumeray et al., 2001 (46)	48	Elective CABG or valve; creatinine level < 160 μmol/L (<1.8 mg/dL)	2.5	Induction; 48 h	Clinician discretion	Protocol; infrequent and similar
Woo et al., 2002 (47)	50	High-risk CABG or valve (age > 70 y, creatinine level > 120 μmol/L [>1.4 mg/dL], diabetes mellitus, or left ventricular dysfunction)	3	Induction; 48 h	Clinician discretion; similar volume	Clinician discretion; similar mean dose in each group
Yavuz et al., 2002 A (48)§	30	CABG; creatinine level < 124 μmol/L (<1.4 mg/dL)	2	24 h before operation; 72 h	Not reported	Not reported
Yavuz et al., 2002 B (48)§	30	CABG; creatinine level < 124 μmol/L (<1.4 mg/dL)	2	24 h before operation; 72 h; both groups received intravenous diltiazem, 2 μg/kg per minute	Not reported	Not reported
Carcoana et al., 2003 A (49)§	50	Elective CABG; creatinine level ≤ 133 μmol/L (≤1.5 mg/dL)	2	Induction until 1 h after cardiopulmonary bypass (about 4 h)	Clinician discretion; authors state "no differences" in volume	Intraoperative protocol; infrequent and similar
Carcoana et al., 2003 B (49)§	50	Elective CABG; creatinine level ≤ 133 μmol/L (≤1.5 mg/dL)	2	Induction until 1 h after cardiopulmonary bypass (about 3 h); both groups received mannitol, 1 g/kg, in bypass circuit	Clinician discretion; authors state "no differences" in volume	Intraoperative protocol; infrequent and similar
Piper et al., 2003 (50)	40	Elective CABG or valve; creatinine level ≤ 177 μmol/L (≤2.0 mg/dL)	2.5	After operation; 48 h	Protocol	Protocol; frequent and similar
Gatot et al., 2004 (51)	89	CABG; creatinine level ≤ 220 μmol/L (≤2.5 mg/dL)	3–5	After operation; 48 h	Protocol	Protocol; mean dose higher in control group for initial 24 h
Patients having vascular surgery						
Baldwin et al., 1994 (52)	37	Elective infrarenal abdominal aortic aneurysm repair or aortobifemoral grafting	3	After operation; 24 h	Protocol	Not used
de Lasson et al., 1995 (53)	30	Elective aortobifemoral or aortobiiliac grafting; normal nuclear renography	3	Beginning of operation until 24 h after operation	Protocol	Not used
Soong et al., 1995 (54)	19	Elective abdominal aortic aneurysm repair	3	Induction; 24 h	Clinician discretion; more fluid given in dopamine group	Not reported

Appendix Table 1–**Continued**

Study, Year (Reference)	Patients, *n*	Main Eligibility Criteria	Dopamine Regimen		Fluids†	Diuretics†
			Dose, *μg/kg per minute*	Start; Duration; Other Medications‡		
Sprung et al., 2000 (55)	20	Peripheral vascular surgery; creatinine level ≤ 141 μmol/L (≤1.6mg/dL)	2	After epidural placement; 12 h (until 5 h after operation)	Clinician discretion; similar volume	Not reported
Patients having other surgery						
Grundmann et al., 1982 (56)	50	Cadaveric renal transplantation; donor creatinine level ≤ 221 μmol/L (≤2.5 mg/dL)	2	After transplantation; 96 h	Not reported	Not reported
Swygert et al., 1991 (57)	48	Liver transplantation without anuria	3	During surgery; 48 h; both groups received mannitol, 0.5 g/kg	Protocol	Protocol; frequent and similar
Whelan et al., 1993 (58)	60	Cadaveric renal transplantation	3	After transplantation; 72 h	Not reported	Not reported
Carmellini et al., 1994 (59)	60	Cadaveric renal transplantation	3	At declamping of graft; given until urine output ≥100 mL/h or hemodialysis required; both groups received 20 g of mannitol	Not reported	Both groups received furosemide, 1 g, before transplantation
Ohata et al., 1994 (60)	20	Age > 65 y undergoing surgery (not explicitly described)	3	Start until end of operation	Clinician discretion; similar volume	Not reported
Parks et al., 1994 (61)	23	Elective surgery for obstructive jaundice	3	Induction; 48 h	Preoperative protocol	Both groups received furosemide, 1 mg/kg, before surgery
Watanabe et al., 1995 (62)	16	Surgery (not explicitly described); no renal failure	3	5 min after intubation; duration of surgery (about 3 h)	Clinician discretion; similar volume	Not reported
Tanaka et al., 1997 (63)	21	Elective gynecologic surgery with epidural anesthesia	5	10 min before epidural; 25 min	Protocol	Not reported
Cregg et al., 1999 (64)	30	Age 6–18 y; elective corrective surgery for scoliosis; no renal disease	3	Induction until 24 h after operation	Protocol	Not reported
Dönmez et al., 1999 (65)	40	Renal transplantation	2	After renal artery anastomosis; 48 h	Not reported	Not reported
Schulze et al., 1999 (66)	347	Urologic or abdominal surgery with postoperative ventilation; no renal failure	2	After operation; ICU stay (median, 2 d)	Protocol	Protocol; frequent in control group and infrequent in dopamine group
Kasaba et al., 2000 (67)	20	Elective lobectomy or mastectomy with epidural analgesia	5	5 min after epidural placement; 30 min	Preoperative colloid protocol	Not reported
Wahbah et al., 2000 (68)	20	Elective surgery for obstructive jaundice; no renal disease	2.5	Before surgery; 48 h	Clinician discretion	Not used
Niiya et al., 2001 (69)	14	Age > 65 y; surgery for abdominal cancer; normal creatinine level	2	First postoperative day; 24 h	Clinician discretion; similar volume	Not reported
Schilling et al., 2001 (70)	16	Elective abdominal surgery; no renal failure	5	First postoperative day; 24 h	Protocol	Not reported
O'Hara et al., 2002 (71)	35	Solitary kidney; surgery for cancer in remaining kidney; creatinine level ≤ 194 μmol/L (≤2.2 mg/dL)	3	Induction; 5–6 h (duration of operation); both groups received 50 g of mannitol	Intraoperative protocol	Not reported
Pérez et al., 2002 (72)	40	Laparoscopic colorectal surgery; no renal disease	2	Induction; 2 h	Protocol	Not reported
Biancofiore et al., 2004 (73)	97	Liver transplantation; creatinine level ≤ 133 μmol/L (≤1.5 mg/dL)	3	Induction; 96 h after operation	Clinician discretion	Protocol; similar dose in each group
Patients receiving intravenous contrast dye						
Hans et al., 1990 (74)	60	Angiography of abdominal or leg vessels; creatinine level, 110–310 μmol/L (1.3–3.5 mg/dL)	2.5	Start of angiography; 12 h	Protocol	Not reported
Weisberg et al., 1994 (75)	30	Elective cardiac catheterization with creatinine level ≥ 159 μmol/L (≥1.8 mg/dL)	2	Start of catheterization; 2 hours	Protocol	Not reported
Kapoor et al., 1996 (76)	40	Cardiac catheterization in diabetic patients	5	30 min before catheterization until 6–8 h after procedure	Not reported	Not used
Hans et al., 1998 (77)	55	Angiography of abdominal or leg vessels; creatinine level, 124–309 μmol/L (1.4–3.5 mg/dL)	2.5	1 h before angiography; 12 h	Clinician discretion; authors state "similar" volume	Not reported
Abizaid et al., 1999 A (78)‖	40	Cardiac catheterization with creatinine level ≥ 133 μmol/L (≥1.5 mg/dL) but no renal failure	2.5	2 h before catheterization; 14 h	Protocol	Not reported
Abizaid et al., 1999 B (78)‖	72	ARF (creatinine level ≥ 25% more than baseline level) after cardiac catheterization	2.5	From enrollment until normalization of creatinine level	Protocol	Not reported

Appendix Table 1—**Continued**

Study, Year (Reference)	Patients, *n*	Main Eligibility Criteria	Dopamine Regimen		Fluids†	Diuretics†
			Dose, *μg/kg per minute*	Start; Duration; Other Medications‡		
Diez et al., 1999 (79)	50	Cardiac catheterization or peripheral angiogram; creatinine level < 133 μmol/L (<1.5 mg/dL)	2	30 min before catheterization; duration of catheterization	Protocol	Not reported
Gare et al., 1999 (80)	68	Cardiac catheterization with creatinine level of 131–200 μmol/L (1.5–2.3 mg/dL) or diabetes mellitus	2	Start of catheterization; 48 h	Protocol	Clinician discretion; rare and similar
Patients receiving other nephrotoxic medications						
Somlo et al., 1995 (81)	42	Chemotherapy and peripheral stem-cell transplantation	2	12 h before chemotherapy; 48 h; both groups received 25 g of mannitol	Not reported	Not reported
Cormier et al., 1997 (82)	42	Interleukin-2 given for metastatic renal-cell carcinoma or melanoma	2	12 h before interleukin-2; mean duration, 84 h	Protocol	Not used
Camp et al., 1998 (83)	72	Patients with leukemia or undergoing autologous bone marrow transplantation and receiving amphotericin B	3	Before test dose; 192 h	Clinician discretion; similar volume	Not reported
Neonates						
DiSessa et al., 1981 (85); Leitner et al., 1980 (84)¶	14	Asphyxiated full-term neonates weighing > 2 kg	2.5	After stabilization; 65–70 h	Pretrial protocol for colloid or blood	Not reported
Seri et al., 1984 (86)	16	Neonates with patent ductus arteriosus requiring indomethacin	2 or 4	At first indomethacin dose; 48 h	Protocol	Not used
Cuevas et al., 1991 (87)	60	Premature neonates with respiratory distress syndrome being mechanically ventilated	1 or 2.5	At enrollment; 72 h	Protocol	Not used
Fajardo et al., 1992 (88)	26	Neonates (gestational age < 36 wk) with patent ductus arteriosus requiring indomethacin	2	6 h before first dose of indomethacin; 42 h	Clinician discretion; authors state "similar" volume	Clinician discretion; rare and similar
Baenziger et al., 1999 (89)	33	Neonates with patent ductus arteriosus requiring indomethacin	4	2 h before first dose of indomethacin; 38 h	Clinician discretion; similar volume	Protocol; frequent and similar
Patients with miscellaneous indications						
Lumlertgul et al., 1989 (92)	19	ARF secondary to malaria	1	At enrollment; 96 h	Clinician discretion	Both groups received 200 mg of furosemide every 6 h for 96 h
Mantel and Makin, 1997 (93)	40	Postpartum women with preeclampsia and oliguria unresponsive to fluid challenge; no recent diuretic use	1–5 (titrated to urine output)	At enrollment; 6 h	Clinician discretion; similar volume	Clinician discretion; rare and similar
Varriale and Mossavi, 1997 (94)	20	Chronic congestive heart failure with pulmonary or peripheral edema and creatinine level of 133–256 μmol/L (1.5–2.9 mg/dL)	2	At enrollment; up to 120 h	Not reported	Both groups received 1 mg of bumetanide twice daily for up to 120 h
ANZICS, 2000 (90)	328 (23 centers)	≥2 systemic inflammatory response criteria within 24 h and early renal dysfunction (oliguria or creatinine level >150 μmol/L [>1.7 mg/dL] or increase > 80 μmol/L [>0.9 mg/dL] in <24 h); baseline creatinine level ≤ 300 μmol/L (≤3.4 mg/dL); no recent ARF or renal transplantation	2	At enrollment; until prespecified end point reached (mean, 113 h)	Not reported	Clinician discretion; frequent and similar
Sánchez et al., 2003 A (91)§	40	≥2 sepsis criteria; oliguria; creatinine clearance < 1.0 mL/s (<60 mL/min); recent normal creatinine level	2	At enrollment; 7 d, discharge from ICU, or until adverse event	Clinician discretion	Not used
Sánchez et al., 2003 B (91)§	40	≥2 sepsis criteria, oliguria; creatinine clearance < 1.0 mL/s (<60 mL/min); recent normal creatinine level	2	At enrollment; 7 d, discharge from ICU, or until adverse event	Clinician discretion	Protocol

* ANZICS = Australian and New Zealand Intensive Care Society; ARF = acute renal failure; CABG = coronary artery bypass grafting; ICU = intensive care unit.
† We assessed whether fluids and diuretics were administered by protocol (defined as general guidelines or explicit instructions) or clinician discretion. We recorded whether groups received similar fluid volumes if administration was discretionary and whether diuretics were given rarely (<10% of patients), infrequently (10%–25%) or frequently (>25%).
‡ We have noted whether pharmacologic co-interventions (excluding diuretics) were administered.
§ These patients were randomly assigned into 4 groups in the same trial and were reported in the same publication.
‖ These patients were randomly assigned in 2 separate trials and were reported in the same publication.
¶ Data from this trial were distributed in 2 publications.

Appendix Table 2. **Methodologic Quality of Included Studies***

Study, Year (Reference)	Allocation Concealment†	Participants Blinded‡	Postrandomization Withdrawals§
Patients having cardiac surgery			
Costa et al., 1990 (34)	No (table of random numbers with all numbers visible)	Caregivers (except anesthetists)	3 of 12 dopamine-treated patients (may have received diuretics)
Wierda et al., 1990 (35)	Not reported	None	None
Myles et al., 1993 (36)	Yes (coded syringes)	Caregivers, outcomes assessors	Both groups: 3 of 52 patients (operative complications in 2 patients)
Lauwers et al., 1994 (37)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical and renal outcomes: 20 of 149 dopamine-treated patients; 8 of 76 control patients (arrhythmias and other complications)
Gårdebäck and Settergren, 1995 (38)	Yes (central randomization)	None	None
Chaiyaroj and Tatoulis, 1999 (39)	Quasi-randomized (registry numbers)	Caregivers, outcomes assessors	1 of 26 dopamine-treated patients; 1 of 26 control patients (unstable hemodynamics)
McNicol et al., 1999 (40)	Yes (central randomization)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 1 of 8 dopamine-treated patients; 2 of 8 control patients
Schneider et al., 1999 (41)	Probably (sealed envelopes)	Caregivers, outcomes assessors	None
Sharpe et al., 1999 (42)	Probably (sealed envelopes)	Caregivers, outcomes assessors	None
Tang et al., 1999 (43)	Yes (central randomization)	Caregivers, outcomes assessors	Number unclear (patients developing cardiac dysfunction excluded)
Dural et al., 2000 (44)	Yes (sealed opaque envelopes)	Data collectors	None
Lassnigg et al., 2000 (45)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 2 of 42 control patients (reoperation)
Sumeray et al., 2001 (46)	Yes (coded syringes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 3 of 48 dopamine-treated patients (oliguria in 2 patients); 9 of 48 control patients
Woo et al., 2002 (47)	Yes (sequentially numbered sealed opaque envelopes)	None	Clinical outcomes: none Renal measures: 10 of 25 dopamine-treated patients; 3 of 25 control patients (operative complications in 5 dopamine-treated patients and all control patients)
Yavuz et al., 2002 A and B (48)	Quasi-randomized (registry numbers)	Caregivers, outcomes assessors	None
Carcoana et al., 2003 A and B (49)	Yes (local independent randomization)	Caregivers, outcomes assessors, data analysts	Mortality and need for renal replacement therapy: none Adverse effects and renal measures: 2 control groups: 17 of 67 patients; 2 dopamine groups: 18 of 68 patients (changed or prolonged operative procedure or antifibrinolytic therapy administered)
Piper et al., 2003 (50)	Yes (sealed opaque envelopes)	Caregivers	Clinical outcomes: none Renal measures: 1 of 21 dopamine-treated patients; 1 of 21 control patients (operative complications)
Gatot et al., 2004 (51)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, investigators	Clinical outcomes: none Renal measures: 3 of 44 dopamine-treated patients; 5 of 45 control patients (operative complications and 4 crossovers to dopamine group)
Patients having vascular surgery			
Baldwin et al., 1994 (52)	Yes (sealed sequentially numbered drug packs)	Caregivers	None
de Lasson et al., 1995 (53)	Yes (sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 1 of 13 dopamine-treated patients; 5 of 17 control patients (complications in 4 patients)
Soong et al., 1995 (54)	Yes (sealed opaque envelopes)	Study personnel	None
Sprung et al., 2000 (55)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers	None
Patients having other surgery			
Grundmann et al., 1982 (56)	Yes (central randomization)	None	None
Swygert et al., 1991 (57)	Not reported	Double	Both groups: 1 of 48 patients (nephrectomy)
Whelan et al., 1993 (58)	Not reported	None	None
Carmellini et al., 1994 (59)	Not reported	Not reported (placebo)	None
Ohata et al., 1994 (60)	Not reported	Not reported	None
Parks et al., 1994 (61)	Yes (sequentially numbered sealed opaque envelopes)	None	None
Watanabe et al., 1995 (62)	Not reported	None	None
Tanaka et al., 1997 (63)	Yes (sealed opaque envelopes)	None	None
Cregg et al., 1999 (64)	Quasi-randomized (hospital number)	Caregivers	None
Dönmez et al., 1999 (65)	Yes (one coin flip per patient)	Caregivers (except anesthetists), outcomes assessors	None

Appendix Table 2—**Continued**

Study, Year (Reference)	Allocation Concealment†	Participants Blinded‡	Postrandomization Withdrawals§
Schulze et al., 1999 (66)	Yes (sequentially numbered sealed opaque envelopes)	None	Clinical outcomes: none Renal measures: up to 13 of 173 dopamine-treated patients; up to 17 of 174 control patients (early discharge from ICU)
Kasaba et al., 2000 (67)	Quasi-randomized (alternate allocation)	None	None
Wahbah et al., 2000 (68)	Yes (sequentially numbered sealed opaque envelopes)	None	None
Niiya et al., 2001 (69)	Not reported	Not reported	None
Schilling et al., 2001 (70)	Yes (central randomization)	Caregivers, outcomes assessors	None
O'Hara et al., 2002 (71)	Yes (sequentially numbered sealed opaque envelopes)	None	Both groups: 11 of 35 patients (operative complications)
Pérez et al., 2002 (72)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: both groups, 3 of 40 patients (operative complications in 2 patients and hemodynamic instability in 1 patient)
Biancofiore et al., 2004 (73)	Yes (sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 2 of 50 dopamine-treated patients; 1 of 47 control patients ("incomplete sample collections")
Patients receiving intravenous contrast dye			
Hans et al., 1990 (74)	Quasi-randomized (alternate allocation)	None	None
Weisberg et al., 1994 (75)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, outcomes assessors	Urine output: 5 of 15 dopamine-treated patients; 1 of 15 control patients Other outcomes: none
Kapoor et al., 1996 (76)	Yes (sequentially numbered sealed opaque envelopes)	None	None
Hans et al., 1998 (77)	Quasi-randomized (alternate allocation)	None	None
Abizaid et al., 1999 A (78)	Not reported	None	None
Abizaid et al., 1999 B (78)	Not reported	None	None
Diez et al., 1999 (79)	Quasi-randomized (alternate allocation)	None	None
Gare et al., 1999 (80)	Yes (coded medication vials)	Caregivers, outcomes assessors	1 of 34 dopamine-treated patients; 1 of 34 control patients (cardiac complications)
Patients receiving other nephrotoxic medications			
Somlo et al., 1995 (81)	Yes (central randomization)	Caregivers, outcomes assessors	None
Cormier et al., 1997 (82)	Yes (central randomization)	None	None
Camp et al., 1998 (83)	Not reported	None	Both groups: 1 of 72 patients
Neonates			
DiSessa et al., 1981 (85); Leitner et al., 1980 (84)	Not reported	Double	Clinical outcomes: none Renal measures: not reported
Seri et al., 1984 (86)	Yes (sequentially numbered sealed opaque envelopes)	None	Clinical outcomes: none Renal measures: 1 of 8 control patients (death)
Cuevas et al., 1991 (87)	Yes (sealed opaque envelopes)	None	7 of 40 dopamine-treated patients (adverse effects)
Fajardo et al., 1992 (88)	Not reported	Not reported (placebo)	None
Baenziger et al., 1999 (89)	Yes (central randomization)	None	Clinical outcomes: none Renal measures: 1 of 15 dopamine-treated patients (death); 4 of 18 control patients (diuretic use)
Patients with miscellaneous indications			
Lumlertgul et al., 1989 (92)	Quasi-randomized (alternate allocation)	None	None
Mantel and Makin, 1997 (93)	Yes (sequentially numbered sealed opaque envelopes)	Caregivers, outcomes assessors	Clinical outcomes: none Renal measures: 2 of 20 control patients (pulmonary edema)
Varriale and Mossavi, 1997 (94)	Quasi-randomized (alternate allocation)	None	None
ANZICS, 2000 (90)	Yes (coded medication packs)	Caregivers, outcomes assessors, data analysts	2 of 165 dopamine-treated patients; 2 of 163 control patients
Sánchez et al., 2003 A and B (91)	Yes (sequentially numbered sealed opaque envelopes)	None	Clinical outcomes: none Renal measures: up to 5 of 20 dopamine-treated patients; up to 6 of 20 control patients

* ANZICS = Australian and New Zealand Intensive Care Society; ICU = intensive care unit.
† We note the method of allocation concealment for randomized trials or whether the trial was quasi-randomized. We characterized allocation by envelopes as concealed only if the envelopes were described as opaque.
‡ We assessed whether caregivers and outcomes assessors were blind to treatment assignment. "Not reported" indicates that the trial did not report blinding; we note whether it used a placebo control. "Double" means that the authors report double-blinding without further specification.
§ We note the number of randomly assigned patients without outcomes data and the reasons for exclusion where they may have been related to therapy received or influenced the outcome.

Appendix Figure. **Trials evaluated at each stage of the systematic review.**