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SYSTEMATIC REVIEW

Catherine L. Tacon
John McCaffrey
Anthony Delaney

Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials

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C. L. Tacon (✉) · A. Delaney
Intensive Care Unit, Royal North Shore Hospital, St Leonards, Sydney, NSW, Australia
e-mail: ctacon@live.com.au
Tel.: +61-2-99267111
Fax: +61-2-94398418

J. McCaffrey
Department of Anaesthesia and Critical Care, Belfast City Hospital, Belfast, Northern Ireland

A. Delaney
Northern Clinical School, University of Sydney, St Leonards, Sydney, NSW, Australia

Abstract *Purpose:* Dobutamine is recommended for patients with severe heart failure; however uncertainty exists as to its effect on mortality. This study aims to critically review the literature to evaluate whether dobutamine, compared with placebo or standard care, is associated with lower mortality and a range of secondary outcomes, in patients with severe heart failure. *Methods:* A systematic review and meta-analysis of randomised controlled trials was performed. PubMed, EMBASE, the Cochrane Central Trials Registry, the metaRegister of Controlled Trials and bibliographies of retrieved articles were searched. Randomised trials comparing dobutamine with placebo or standard care, in human, adult patients with severe heart failure, were included if they reported at least one outcome of interest. Data regarding trial validity, methodological processes and clinical outcomes were extracted, and a meta-analysis was performed. *Results:* Fourteen studies, with 673 participants, met the inclusion criteria and were included; 13 studies reported mortality. There was minimal heterogeneity ($I^2 = 4.5\%$). The estimate of the odds ratio for mortality for patients with severe heart failure treated with dobutamine compared with standard care or placebo was 1.47 (95% confidence interval 0.98–2.21, $p = 0.06$). *Conclusions:* This meta-analysis showed that dobutamine is not associated with improved mortality in patients with heart failure, and there is a suggestion of increased mortality associated with its use, although this did not reach the conventional level of statistical significance. Further research to define the role of dobutamine in treatment of severe heart failure should be a priority.

Keywords Heart failure · Drugs · Dobutamine · Meta-analysis · Inotropic agents

Introduction

Heart failure is a significant cause of morbidity and mortality in developed countries, and its prevalence is increasing [1]. In 2009, the prevalence of heart failure was estimated to be more than 15,000,000 throughout the European continent [1] and 5,800,000 in the USA [2]. With hospital mortality of approximately 12% [3], heart failure is clearly a significant issue. For patients with moderate heart failure, good evidence exists to guide therapy with angiotensin-converting enzyme inhibitors [4, 5], aldosterone antagonists [6, 7] and cardiac resynchronisation therapy [8], all of which result in significant reductions in mortality. Furthermore, of particular note is the reduction in mortality that is associated with use of beta blockers [9–13] in the management of heart failure.

When patients with more severe cardiac failure decompensate, they generally require escalated supportive

therapy. Use of non-invasive ventilation to support patients with acute pulmonary oedema due to decompensated heart failure is supported by high-level evidence [14]. However, for patients with acute heart failure who develop symptoms related to low cardiac output and poor tissue perfusion, there is little strong evidence to guide clinicians. Current clinical guidelines recommend use of inotropic agents [1] in such patients. Dobutamine remains a recommended inotrope in international guidelines [1] and is commonly used in patients admitted with severe heart failure [3]. Dobutamine is a synthetic sympathomimetic amine which stimulates $\beta 1$ and to a lesser extent $\beta 2$ receptors to produce a dose-dependent inotropic and chronotropic response [15]. While this leads to an increase in cardiac output, myocardial oxygen demand is also increased, increasing the risk of myocardial ischaemia, tachyarrhythmias and ventricular dysfunction [15]. While dobutamine remains recommended for use, there remains concern and uncertainty regarding the balance of benefit and harm associated with its use in this population [16].

The principal aim of this study is therefore to critically review the literature to evaluate whether dobutamine, compared with placebo or standard care, is associated with lower mortality, as well as a range of secondary outcomes, in patients with severe heart failure.

Methods

We sought prospective randomised clinical trials that compared dobutamine with either placebo or standard care for inclusion in this review. Only studies that included adult participants were considered for inclusion. There were no language restrictions placed on the search. Studies needed to report mortality, for any length of follow-up, or one of the secondary outcomes of the study to be considered eligible for inclusion.

The electronic search for randomised control trials (RCTs) was conducted using PubMed, EMBASE and the Cochrane Central Trials Registry. The PubMed inquiry used search terms "dobutamine" [MESH] and "heart failure" [MESH], with a sensitivity filter for RCTs [17]. EMBASE was searched using terms "dobutamine" combined with "severe heart failure" and a sensitivity filter for RCTs [18]. The Cochrane Central Trials Registry was searched using "dobutamine" combined with "heart failure". No language restrictions were used. The search was performed independently by three investigators (C.L.T., A.D. and J.M.) and was completed on 11 February 2011. The metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct) including the medical editors trials amnesty was also searched using the term "dobutamine". Finally, bibliographies of retrieved articles, previous review articles and meta-analyses were reviewed to identify any additional unpublished or unrecognised trials.

Two authors (C.L.T. and A.D.) reviewed all abstracts to determine if they could potentially meet the inclusion criteria. Full-text reports or abstracts were retrieved for full review by two authors (C.L.T. and A.D.) to determine if they met the eligibility criteria. Disputes were resolved by discussion, with resort to a third investigator (J.M.) if needed. Studies considered eligible for inclusion were RCTs of dobutamine compared with placebo or no specific additional treatment other than standard care, in human, adult patients with severe heart failure [as defined by New York Heart Association (NYHA) classification III or IV]. For inclusion the study must have reported at least one outcome of interest. These outcomes were: mortality, length of stay in intensive care, coronary care unit or hospital, arrhythmias, acute myocardial infarction and change in symptoms. Studies that failed to meet more than one inclusion criteria were classified as not relevant.

All included studies were assessed independently by two authors (C.L.T. and A.D.) for validity. Any disagreements were resolved by discussion. A component approach to the assessment of the validity of the included studies was utilised [19]. The validity criteria assessed were use of a randomisation method that maintained allocation concealment, use of blinding for outcome assessment, presentation of an intention-to-treat analysis [20] and presentation of predefined outcomes. We also assessed the degree of loss to follow-up and baseline differences between the control and treatment groups. When the report did not contain sufficient information to assess the validity criteria, attempts were made to contact the authors by email. If it remained unclear if a criterion was present, it was assessed as being absent [20].

Data were extracted independently by the two authors onto specific data collection forms. Data collected included the baseline characteristics of the study and control groups (including inpatient or outpatient population defined as where the patients were recruited into the study), demographics of the study groups, heart failure definition used in the study, dose and duration of dobutamine therapy, duration of follow-up, haemodynamic and clinical outcomes. Again if outcome data were not clearly presented, attempts were made to contact the authors by email.

The potential for small study bias was assessed by use of a funnel plot and the statistical test described by Egger [21]. Heterogeneity among studies was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating at least moderate heterogeneity [22], and a χ^2 test. We planned to pool the mortality results for the primary analysis using a fixed effect model [23] to produce a pooled odds ratio (OR) [24]. Sensitivity analysis was performed by combining the results with a random effects model. We assessed the effect of validity parameters (blinding, allocation concealment and intention-to-treat analysis), population included in the RCT (inpatient versus outpatient) and comparison group (placebo or standard care) on the estimate of treatment effect, by assessing the interaction term in a single covariate meta-regression analysis. An influence analysis was undertaken to assess the

estimate of treatment effect with each study that reported at least one event omitted from the analysis. Other outcomes were reported too infrequently and inconsistently to allow reasonable synthesis, apart from symptomatic improvements which were simply tabulated. All analyses were performed using STATA 11.1 (College Station, TX).

Results

The search returned a total of 654 reports. After application of the inclusion criteria, 14 studies [25–38] including a total of 673 participants were included in the systematic review, and 13 [25, 27–38] studies reported mortality data and were included in the meta-analysis. One study reported a change in symptoms and was included in the qualitative synthesis only [26]. The flow of studies and reasons for exclusion are shown in Fig. 1.

The characteristics of the included studies are presented in Table 1. The results of the validity assessments of the included studies are presented in Table 2. It is noteworthy that only three studies described an adequate method of allocation concealment and only two studies met all of the validity criteria.

Mortality data were available in 13 studies. There was no asymmetry of the funnel plot (shown as Electronic Appendix 1), nor was there evidence of bias as assessed by Egger's test (bias = −0.45, $p = 0.35$). There was minimal heterogeneity ($I^2 = 4.5\%$). The pooled result of the 13 studies reporting mortality is shown in Fig. 2. The estimate of the OR for mortality for patients with severe heart failure treated with dobutamine compared with standard care or placebo was 1.47 (95% confidence interval 0.98–2.21, $p = 0.06$).

The result of the pooled analysis was similar when a random effects model was used to pool the results, with an estimate of the OR for mortality associated with the use of dobutamine compared with placebo for patients with severe heart failure of 1.44 (95% confidence limits 0.92–2.27, $p = 0.11$). The results of the pre-specified subgroup analysis based upon the validity assessments, patient populations and control group are presented in Table 3. There was no evidence that the effect of dobutamine was different in patients who were recruited in an inpatient setting (OR 1.48, 95% confidence limits 0.9–2.46, $p = 0.13$) compared with those who were recruited in an outpatient setting (OR 1.47, 95% confidence limits 0.98–2.21, $p = 0.29$), with the test for the interaction non-significant ($p = 0.84$), as shown in Appendix 2. There was no evidence that any aspect of study validity was associated with a differential estimate of treatment effect. There was no evidence that any of the studies exerted undue influence over the pooled results, as shown in Electronic Appendix 3.

Symptomatic improvements following administration of dobutamine or placebo were not reported in a sufficiently comparable fashion to allow pooled analysis. Table 4 presents a summary of the reports of the effect of dobutamine compared with placebo on symptoms in patients with severe heart failure. Table 4 also presents a summary of the adverse events reported in each trial.

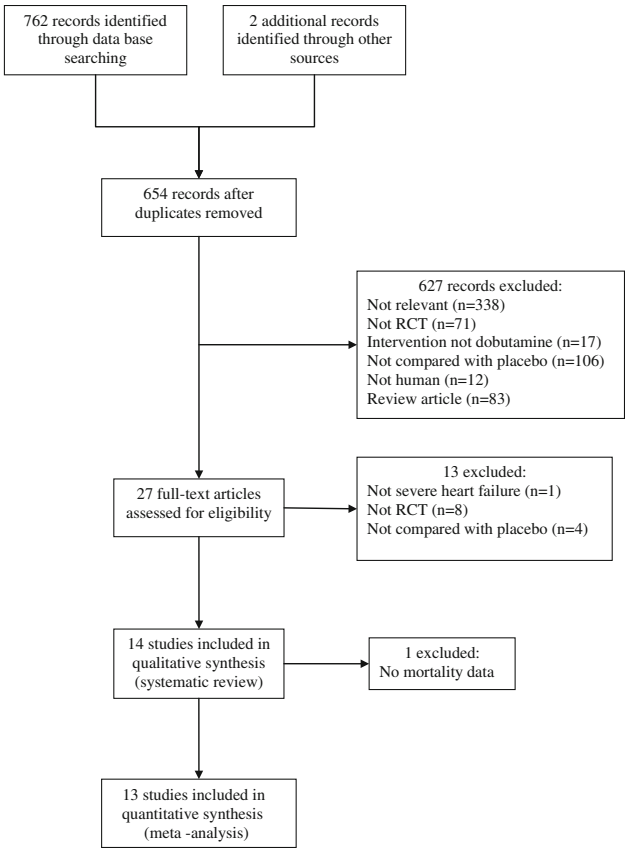

Fig. 1 Flow diagram showing the results of the search and reasons for exclusion of studies

Discussion

We performed a systematic review and meta-analysis to assess the effect of dobutamine compared with control for patients with severe heart failure. While there are a significant number of trials that have assessed this relationship, all are relatively small and the methodological quality of the reports is poor. Dobutamine is not associated with improved mortality in patients with heart failure, and there is some suggestion of increased mortality associated with use of dobutamine in patients with severe heart failure, although this did not reach the conventional level of statistical significance. The reporting of symptomatic improvements or adverse events was not sufficiently standardised to allow general conclusions to be drawn, although there was no clear evidence that dobutamine was associated with improvements in

Table 1 Characteristics of randomised trials of dobutamine compared to control for patients with severe heart failure

Author	Year	Population	NYHA Class	Heart function (mean)	Mean age	Male %	Dobutamine dose	Dobutamine duration	Comparison group	Duration of follow-up
Leier [32]	1982	Outpatients	III/IV	CI 2.1 L/min/m^2	51.7	65.4	2.5–10 μg/kg/min	4 h/week for 24 weeks	Standard care	24 weeks
Liang [33]	1984	Outpatients	III/IV	CI 1.7 L/min/m^2	54.3	86.7	15–35 μg/kg/min	72 h	Placebo	4 weeks
Dies [29]	1986	Outpatients	III/IV	LVEF 20%	NR	NR	8.1 μg/kg/min[a]	48 h/week for 24 weeks	Placebo	8 weeks
Erlemeier [31]	1992	Inpatients	IV	CI 2.0 L/min/m^2	57.1	90	2.5–10 μg/kg/min	24 h every 3 days for 4 weeks	Placebo	4 weeks
Adamopolous [26]	1995	Outpatients	II/III/IV	LVEF 21%	63.5	95	10–25 μg/kg/min	30 min/day, 4 days/week for 3 weeks	Placebo	6 weeks
Elis [30]	1998	Outpatients	III/IV	LVEF 24.5%	67.7	78.9	1–7.5 μg/kg/min	24 h every 2 weeks for 6 weeks then every 3 weeks for 6 months	Placebo	32 months
Sindone [37]	1998	Inpatients	IV	CI 1.9 L/min/m^2	49	89.6	5 μg/kg/min	6 days	Standard care	12 months
Oliva [36]	1999	Outpatients	III/IV	LVEF 22.5% CI 1.9 L/min/m^2	66.5	81.6	2.5–5 μg/kg/min	72 h per week	Standard care	6 months
Wimmer [38]	1999	Outpatients	III/IV	CI < 2.5 L/min/m^2	52.5	95	2.5–5 μg/kg/min	7 days	Placebo	7 days
Nieminen [35]	2000	Outpatients	III/IV	LVEF 25.5%	63.4	89.3	6 μg/kg/min	24 h	Placebo	9 days
CASINO [28]	2004	Inpatients	III/IV	LVEF < 35%	71	71	NR	24 h	Placebo	6 months
Nanas [34]	2004	Outpatients	IV	LVEF 23.3%	62.6	86.7	10 μg/kg/min	8 h/day twice weekly	Placebo	2 years
Adamopolous [25]	2006	Inpatients	III/IV	LVEF 26%	69	82.6	5–10 μg/kg/min	24 h	Standard care	4 months
Bader [27]	2010	Inpatients	III/IV	LVEF 21%	62.4	82.2	2.5–15 μg/kg/min	48 h	Placebo	3 days

NYHA New York Heart Association, *CI* cardiac index, *LVEF* left ventricular ejection fraction, *NR* not reported

[a] Mean dose of dobutamine delivered

symptoms in patients with severe heart failure. These data would suggest that clinicians should be cautious about use of dobutamine in patients with severe heart failure.

Conventional medical treatment for patients with severe cardiac failure would include use of agents to improve cardiac output [1]. It is clear that dobutamine, acting via B adrenergic receptors, will increase heart rate and contractility and lead to improved cardiac output [39, 40]; it will also increase myocardial oxygen consumption [39]. However, just as use of anti-arrhythmic drugs reduced ventricular ectopy while increasing mortality [41], improvements in surrogate outcomes, such as cardiac output, are not always associated with improved patient-oriented outcomes, such as mortality. As approximately 70% of patients in Western societies who develop heart failure do so as a consequence of underlying ischaemic heart disease [42], it is possible that induction of myocardial ischaemia and subsequent myocardial infarction and dysrhythmias would act as a mechanism by which dobutamine could lead to an increase in mortality [43].

It must be noted that the estimate of the OR for mortality, while favouring use of placebo or standard care over dobutamine, did not reach the conventional threshold for statistical significance and that the observed increase in mortality associated with use of dobutamine may be a chance finding. There are also limitations to this study that warrant consideration when interpreting the results. The quality of the reports of the RCTs included in this systematic review was suboptimal. In particular, only three RCTs reported a method of randomisation that maintained allocation concealment. As lack of allocation concealment is associated with bias of up to 40% [20], the fact that this aspect of the RCTs was so poorly reported leaves some doubt as to the results. The standard care delivered to the participants in these was often poorly specified, varied between the studies and likely changed over time. This could affect the external validity of the results of this review. The duration of follow-up in the included studies varied greatly. It was notable that the studies with longer follow-up tended to favour dobutamine. Further research in this field should have a standardised duration of follow-up that takes into account the mortality associated with the underlying pathology. There were three studies included in this meta-analysis that were published only as abstracts, and these studies accounted for more than 50% of the weighted results in the pooled analysis. It is notable that the CASINO [28] study, including almost 600 patients, has never passed through the scrutiny of peer review. Serious questions have been raised at the non-publication of the results of studies such as this [44, 45]. The conclusions that can be drawn from the results of this meta-analysis are also hampered by the lack of reporting of other outcomes of interest such as intensive care unit (ICU) and hospital length of stay, and in particular adverse events that might be attributable to dobutamine such as episodes of myocardial ischaemia, as well as the inconsistent reporting of

Table 2 Summary of the validity assessments of randomised clinical trials of dobutamine compared to control in patients with severe heart failure

Author	Allocation concealment	Intention to treat analysis	Blinding	Prospectively defined outcomes	Loss to follow-up >5%	Baseline differences
Leier [32]	No	No	No	Yes	Yes	No
Liang [33]	Yes	Yes	Yes	Yes	No	No
Dies [29]	No	Yes	Yes	Yes	No	No
Erlemeier [31]	No	Yes	Yes	No	No	No
Adamopolous [26]	Yes	Yes	Yes	Yes	No	No
Elis [30]	No	Yes	Yes	No	No	No
Sindone [37]	No	Yes	No	No	No	Yes
Oliva [36]	Yes	Yes	No	Yes	No	No
Wimmer [38]	No	Yes	No	Yes	No	No
Nieminen [35]	No	Yes	No	Yes	No	No
CASINO [28]	No	No	Yes	No	No	No
Nanas [34]	No	Yes	Yes	Yes	No	No
Adamopolous [25]	No	Yes	No	Yes	No	No
Bader [27]	No	Yes	No	Yes	No	No

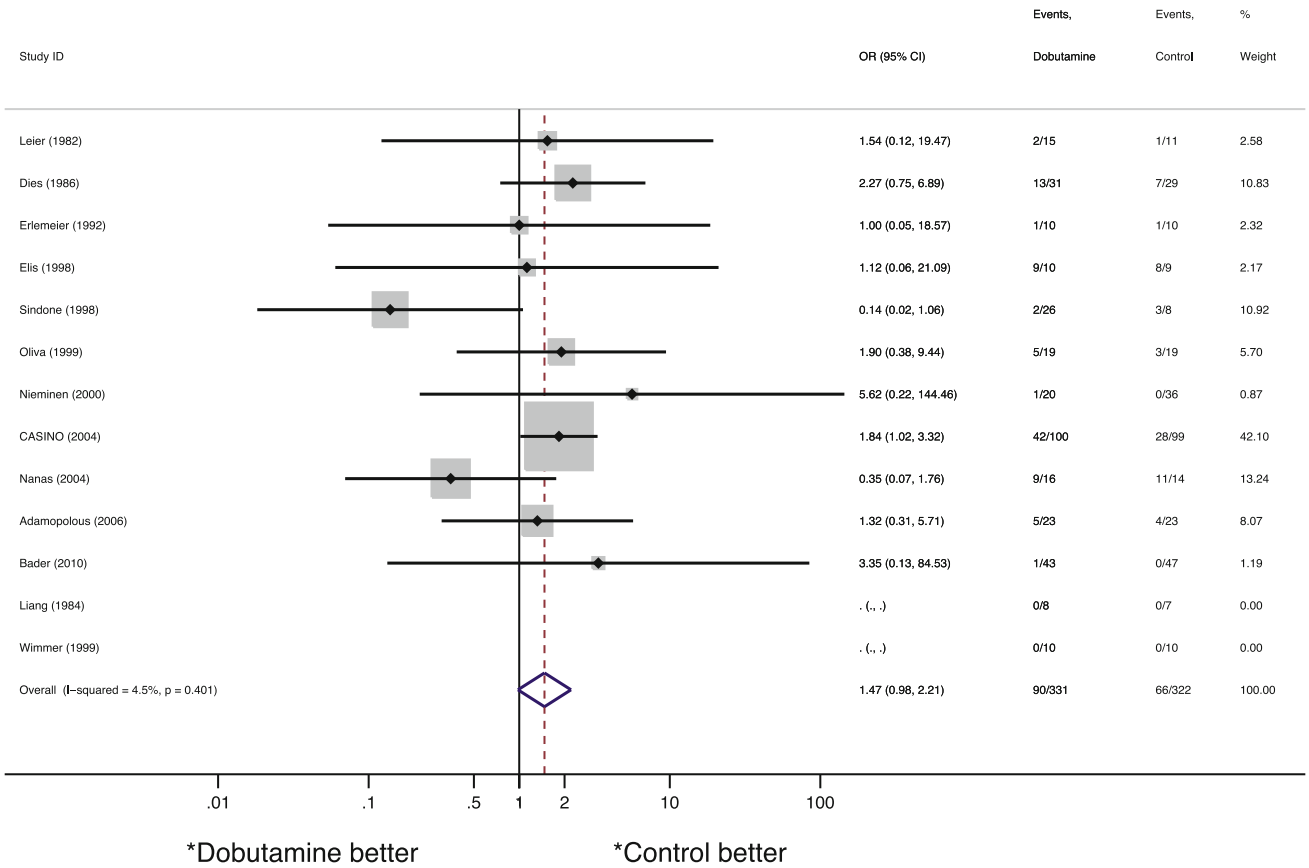

Fig. 2 Forrest plot showing the pooled estimate of the odds ratio for mortality for dobutamine compared with placebo or standard care in patients with severe heart failure

other patient-focussed outcomes such as improvements in symptoms. Finally, while it is noted that there was little statistical heterogeneity apparent in this study, there was considerable clinical heterogeneity. The dosing regimens and duration of administration were quite variable. It is also possible that the effect of dobutamine may be different in differing sub-populations, such as those with and without ischaemic heart disease. It is not possible to unravel these effects in a meta-analysis without individual patient data, data not available in this study. Further studies should consider choosing more homogeneous populations and a common dosing regimen.

Table 3 Results of subgroup analysis

Subgroup	Number of studies	Estimate of OR	95% CI	*P* value for interaction
Allocation concealment				
Yes	2	1.91	0.38–9.44	0.69
No	11	1.45	0.95–2.2	
Blinding				
Yes	6	1.22	0.56–2.68	0.64
No	7	1.58	0.98–2.53	
Intention to treat				
Yes	11	1.19	0.67–2.12	0.41
No	2	1.82	1.02–3.23	
Population				
Inpatient	5	1.45	0.73–2.88	0.84
Outpatient	8	1.48	0.98–2.21	
Control group				
Standard care	4	0.99	0.42–2.33	0.33
Placebo	9	1.65	1.04–2.62	

OR odds ratio, *CI* confidence interval

Table 4 Summary of reports of symptomatic changes and adverse events in trials comparing dobutamine and control

Study	Symptomatic change	Adverse events
Leier [32]	2/11 (control) vs. 12/15 (dobutamine) improved at least one NYHA class	NR
Liang [33]	2/7 (control) vs. 6/8 (dobutamine) improved at least one NYHA class	NR
Adamopolous [26]	Mean breathlessness score; 3.0/7 (control) vs. 1.8/7 (dobutamine), $p < 0.05$ Mean tiredness score; 3.4/7 (control) vs. 2.6/7 dobutamine), $p < 0.05$	NR
Elis [30]	Mean admissions to hospital for heart failure 2.1 (control) vs. 2.2 (dobutamine), $p = 0.11$	NR
Sindone [37]	Spielberger anxiety questionnaire; 24% reduction (control) vs. 24% reduction (dobutamine) General health questionnaire; 43% reduction (control) vs. 40% reduction (dobutamine)	NR
Oliva [36]	5 (control) vs. 7 (dobutamine) required hospitalisation for heart failure Median NYHA class at 6 months; 3 (control) and 2.5 (dobutamine)	1 (dobutamine) showed increased rate of non-sustained VT on Holter
Wimmer [38]	NR	2 (dobutamine) complained of repeated palpitations
Nieminen [35]	NR	20% (placebo) vs. 35% (dobutamine) reported adverse events including hypertension, tachycardia and arrhythmias 1 (control) vs. 5 (dobutamine) experienced tachycardia
Nanas [34]	Mean NYHA at 6 months fell from 4 to 2.2 (control) and from 4 to 2.3 (dobutamine)	NR
Bader [27]	NR	2 (control) vs. 0 (dobutamine) experienced sustained VT 6 (control) vs. 11 (dobutamine) experienced new-onset SVT 3 (control) vs. 9 (dobutamine) experienced dysrhythmia 6 (control) vs. 18 (dobutamine) met Morganroth criteria for pro-arrhythmia

NYHA New York heart association, *VT* ventricular tachycardia, *SVT* Supraventricular tachycardia, *NR* Not reported

There were a number of strengths of this review. The methods of the study closely paralleled current guidelines for the reporting of systematic reviews [46]. We were able to locate a number of unpublished studies, and there was no evidence of small study or publication bias. The pooled estimate of treatment was robust to the method used to combine the results, and there was little heterogeneity amongst the included studies.

Given the strengths and limitations of this study, what are the implications for clinicians? The results of this study alone, given the lack of a strong statistically significant result, and the poor methodological quality of the included studies, may not be sufficient to drive a change in clinical practice. It should be noted that the results of this study are in accord with large observational studies that have also suggested harm associated with use of dobutamine in patients with severe heart failure [47, 48]. Taken together, this evidence should cause clinicians to reconsider their use of dobutamine in patients with heart failure, particularly those most at risk of the adverse effects, those with underlying ischaemic heart disease. There is already significant doubt regarding the efficacy of alternative agents such as milrinone, particularly in patients with cardiac failure due to underlying ischaemic heart disease [49]. Other inotropic agents such as calcium sensitisers have been suggested to be of use for patients who present with severe heart failure who are deemed to require inotropic support, although the efficacy of such agents is yet to be proven in large-scale clinical trials [50, 51].

Use of inotropic agents is still recommended in the guidelines for treatment of severe acute heart failure [1, 52]. There are certainly some patients with low cardiac output who appear to benefit in the short term from administration of positive inotropic agents such as dobutamine, yet there is little apparent longer-term mortality benefit from administration of these medications. Further research to define a population of patients most likely to benefit, or conversely to define a population most likely to experience harm, from the administration of dobutamine appears to be a priority. While the reference standard for the determination of efficacy of an agent such as dobutamine would be a placebo-controlled RCT, the feasibility and logistics of conducting such a trial would be challenging.

Conclusions

This systematic review of the effect of dobutamine on mortality in severe heart failure found a total of 14 studies, of which 13 reported mortality data that were included in the meta-analysis. Dobutamine was not found to be associated with improved mortality in patients with heart failure, and a trend towards an increase in mortality with use of dobutamine compared with placebo or standard care was evident, although this did not reach statistical significance. Overall, the included studies had a poor level of methodological reporting, with several only being published in abstract form, limiting the conclusions that can be made from this meta-analysis. However, given the widespread use of dobutamine in management of severe heart failure, further methodologically sound studies would be beneficial to identify which patient populations are most likely to receive benefit, or indeed harm, from this agent.

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Conflict of interest The authors have no conflicts of interest.

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