Journal of Cardiothoracic and Vascular Anesthesia 32 (2018) 2225–2232

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Vasopressin in Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

Martin W. Dünser, MD[*,1], Olivier Bouvet[†], Hans Knotzer, MD[‡], Nish Arulkumaran, MD[§], Ludhmila Abrahao Hajjar, MD[‖], Hanno Ulmer, PhD[¶], Walter R. Hasibeder, MD[**]

[*]*Department of Anesthesiology and Intensive Care Medicine, Kepler University Hospital and Johannes Kepler University Linz, Linz, Austria*
[†]*Amomed Pharma GmbH, Vienna, Austria*
[‡]*Department of Anesthesiology and Critical Care Medicine II, Klinikum Wels, Wels, Austria*
[§]*Department of Critical Care, University College of London Hospital, London, UK*
[‖]*Department of Cardiopneumology, InCor, University of Sao Paulo, Sao Paulo, Brazil*
[¶]*Institute of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria*
[**]*Department of Anesthesiology and Critical Care Medicine, Krankenhaus St. Vinzenz in Zams, Zams, Austria*

Objective: To summarize the results of randomized controlled trials on the use of vasopressin as a vasopressor agent in cardiac surgery.
Design: Meta-analysis.
Participants: Six-hundred-twenty-five adult patients undergoing elective or emergency cardiac surgery.
Interventions: Arginine vasopressin infusion (n = 313) or control/standard therapy (n = 312).
Measurements and Main Results: The rates of perioperative complications and postoperative mortality were used as primary and secondary endpoints, respectively. Fixed and/or random effects models were used to compare pooled odds ratios. Arginine vasopressin reduced the pooled odds ratio (OR) of perioperative complications (OR, 0.33; 95% confidence interval [CI], 0.2-0.54; $p < 0.0001$). A sensitivity analysis excluding the largest trial showed an unchanged reduction in perioperative complications (OR, 0.35; 95% CI, 0.18-0.69; $p = 0.002$). When analyzing each perioperative complication separately, vasopressin reduced the pooled OR of vasodilatory shock (OR, 0.4; 95% CI, 0.16-0.97; $p = 0.04$) and new-onset atrial fibrillation (OR, 0.42; 95% CI, 0.21-0.82; $p = 0.01$). The pooled OR of postoperative death was not different between patients treated with arginine vasopressin and those receiving standard therapy or placebo (OR, 0.83; 95% CI, 0.45-1.53; $p = 0.55$). The funnel plot for the primary endpoint suggested a relevant publication bias. All included trials suffered from a high risk of bias.
Conclusion: Our meta-analysis suggests that arginine vasopressin may reduce the rate of perioperative complications in patients undergoing elective or emergency cardiac surgery. No difference in postoperative mortality was observed. An adequately powered multicenter trial is required for reliable estimation of the effects of arginine vasopressin on perioperative complication rates and mortality in cardiac surgical patients.

Key Words: Arginine vasopressin; cardiac surgery; mortality; perioperative complications; acute kidney injury; atrial fibrillation; vasodilatory shock

PERIOPERATIVE HYPOTENSION due to low systemic vascular resistance is common in patients undergoing cardiac surgery with the use of cardiopulmonary bypass (CPB).[1] With increasing severity of peripheral vasodilation, perfusion of

Olivier Bouvet works for a company that sells arginine vasopressin.

[1]Address reprint requests to PD Dr. Martin Dünser, DESA, EDIC, Department of Anesthesiology and Intensive Care Medicine, Kepler University Hospital and Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria.
E-mail address: martin.duenser@i-med.ac.at (M.W. Dünser).

https://doi.org/10.1053/j.jvca.2018.04.006
1053-0770/

vital and visceral organs is impaired and vasodilatory or distributive shock occurs. Patients who develop vasodilatory shock after cardiac surgery are at a high risk for organ failure and death.[2] Adrenergic agents such as norepinephrine or epinephrine are the most frequently used vasopressor drugs in cardiac surgery. However, catecholamines have a narrow therapeutic range and have been associated with adverse cardiac events, particularly at higher doses and with prolonged applications.[3] Beta-receptor mediated tachycardia and tachyarrhythmia especially predispose cardiac surgical patients for perioperative myocardial ischemia.[4]

Arginine vasopressin is a physiologic vasopressor hormone that, in 1998, was first reported to reverse the loss of vascular tone in cardiac surgical patients with postcardiotomy shock.[5] Subsequent observational studies described beneficial hemodynamic effects of a low-dose vasopressin infusion in patients undergoing cardiac surgery with the use of CPB.[6–8] Several randomized controlled trials (RCTs) have evaluated the effects of vasopressin as a vasopressor agent on outcome after cardiac surgery. All of these trials were, however, performed at single institutions, and multicenter trials or meta-analyses are lacking.

The purpose of the present study was to conduct a meta-analysis integrating and summarizing the results of RCTs on the use of vasopressin as a vasopressor agent in adult patients undergoing cardiac surgery. The endpoints of the analysis were the rate of perioperative complications (primary) and mortality (secondary).

Materials and Methods

This meta-analysis was designed according to the recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group.[9] The methods and analysis plan were prepublished in the international Prospective Register of Systematic Reviews (PROSPERO) database (CRD42017067344).

Eligibility Criteria

RCTs evaluating the use of a vasopressin derivative as a vasopressor agent in adult patients undergoing cardiac surgery were considered eligible. Observational and experimental studies, trials without an intervention group, and trials including patients aged < 18 years were excluded.

Information Sources and Search Strategy

Published trials were identified by searching electronic databases, reference lists of screened trial reports, and review articles. Date restrictions were not applied. The last search update was in August 2017. In addition to searching electronic databases, previous review articles on the subject were handsearched for further references. A Boolean search strategy was designed and applied to the National Library of Medicine's MEDLINE database (PubMed) as well as Google Scholar.

The search strategy included (but was not limited to) variations in the terms "vasopressin," "cardiac surgery," and "complications following cardiac surgery." Where possible, the authors used controlled vocabulary (Medical Subject Headings) and key words. The following search terms were entered into PubMed: *"(vasopressin OR terlipressin OR ornipressin) AND (heart surgery OR cardiac surgery OR cardiopulmonary bypass) AND (postcardiotomy OR vasodilatory OR shock)."* The search was limited to original published manuscripts. After retrieving initial results, results were amalgamated and duplicates removed using EndNote reference manager.

Study Selection and Data Extraction

Two authors (M.W.D., O.B.) performed the literature search. In a first step, publications were screened by title and abstract review. Articles that obviously did not meet the eligibility criteria were excluded. Disagreement was solved by consensus and the decision reviewed by 2 further authors (H.K., W.R.H.). Full texts of the remaining studies were evaluated in detail. One author (M.W.D.) designed a data extraction sheet and pilot-tested it on 3 randomly selected publications, which were included in this analysis. Two authors (M.W.D., O.B.) then independently extracted the following data from all selected trials: name of first author, publication year, study design, inclusion criteria, trial arms, number of patients included, type and timing of study intervention, use of concomitant vasopressor/inotrope therapy, primary outcome parameter, type and incidence of perioperative complications, and postoperative mortality.

Primary and Secondary Endpoints

The primary endpoint of the quantitative meta-analysis was the composite rate of perioperative complications. To determine the composite rate of perioperative complications, the authors extracted and summarized the rates of single complications reported in each trial. The authors used postoperative morality (reported closest to postoperative day 30) as the secondary endpoint, since both the overall number of patients to be included in this meta-analysis and the postoperative mortality rates were considered to be too low to allow for adequate statistical power.

Risk of Bias Assessment

The risk of publication or small trial bias was assessed by visual and statistical analysis of contoured funnel plots generated for both the primary and secondary endpoint. To identify unpublished trials, meeting abstracts (wherever available and accessible) and the following registries were scanned: the clinical trials register of the U.S. National Institutes of Health, the European clinical trials register, the Clinical Trials Registry-India, the current controlled trials register (ISRCTN registry), the Global Trial Bank, and the World Health Organization International Clinical Trials Registry Platform.

The risk of bias of included trials was evaluated using the 2016 revised Cochrane risk of bias tool. The following domains were assessed for each trial: random sequence

generation, allocation concealment, blinding of sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias in each domain was judged as either low, high, or unclear. To assess the risk of bias, the authors only relied on the information presented in the publications. The overall risk of each trial was classified as high if 1 or more domains indicated a high or unclear risk of bias.

Statistical Analysis

The Review Manager for Mac (version 5.1, Cochrane Collaboration, Oxford, UK) program was used for statistical analysis. Extracted data of individual trials were combined and analyzed using DerSimonian and Laird models. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated for primary and secondary endpoints. The authors calculated the inconsistency factor (I^2) to determine heterogeneity among trials. Fixed and/or random effects models were used as indicated by the results of the I^2 statistics. Two-tailed tests were performed and the probability of a type I error set at 5%. The authors separately assessed the pooled OR for single perioperative complications, which informed the primary study endpoint. Since 1 trial contributed almost half of the patients to this meta-analysis, the authors performed a sensitivity analysis that excluded this trial. Further sensitivity analyses were conducted for the following patient populations: cardiac surgical patients with vasodilatory shock, patients undergoing emergency/elective cardiac surgery, and cardiac surgical patients receiving arginine vasopression (AVP) because of chronic angiotensin-converting enzyme (ACE) inhibitor intake.

Results

Of 160 publications identified in the primary search process, 8 RCTs involving a total of 625 patients (vasopressin, n = 313; control/standard therapy, n = 312) were included in the qualitative and quantitative analysis (Fig 1).[10–17] Characteristics of each trial are summarized in Table 1. The vast majority of study patients underwent cardiac surgery on CPB (594/625, 95%). Cardiac surgical procedures involved coronary, valvular, and/or aortic surgery. In all trials, AVP was the vasopressin derivative used and infused continuously at 0.01-0.067 IU/min. AVP was initiated before CPB in 3 trials[11,13,15] and during weaning or after CPB in 5.[10,12,14,16,17] One trial included 3 study arms,[12] of which the authors included the vasopressin (ramipril continued until morning of surgery) and its respective control arm (ramipril continued until morning of surgery). Seven trials enrolled only patients undergoing cardiac surgery,[11–17] whereas 1 trial enrolled patients with

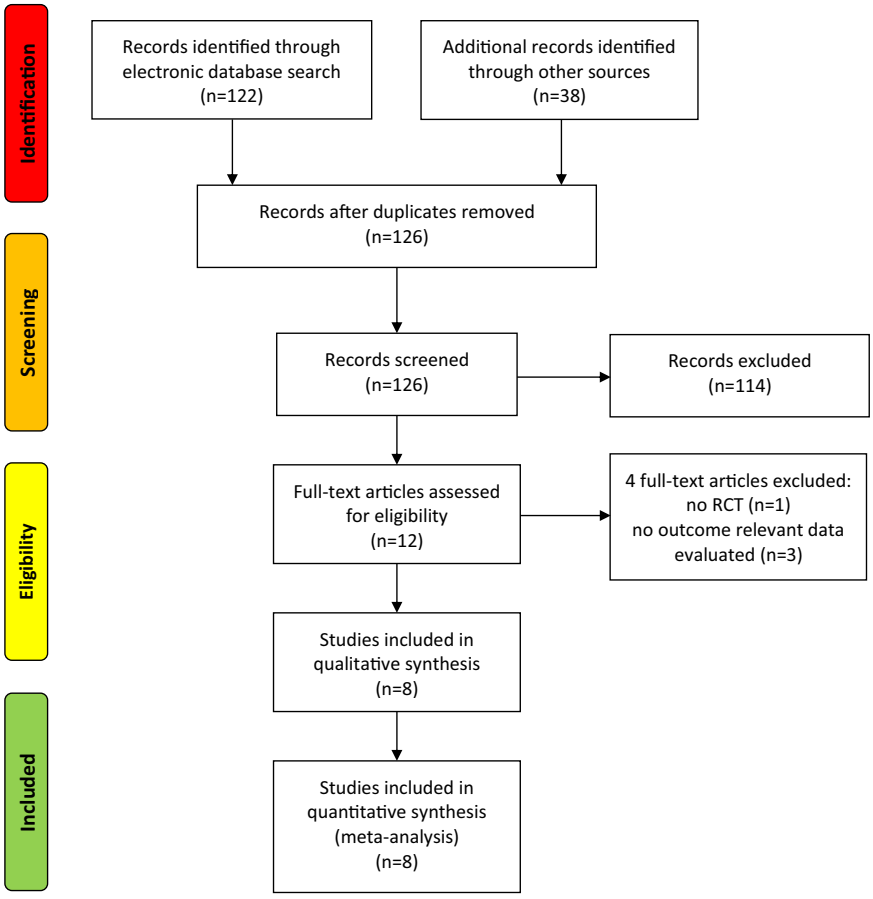

Fig 1. PRISMA flow chart. Adjusted from the PRISMA 2009 flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1
Characteristics of Included Trials

First Author, Year	Design	Inclusion Criteria	Groups	n	Intervention	Start of Intervention	Concomitant Vasopressor/ Inotrope Therapy	Primary Outcome Parameter	Comment
Dünser MW, 2003[10]	RCT	Advanced vasodilatory shock after cardiac surgery	A: AVP plus norepinephrine B: standard treatment	A: n = 10 B: n = 9	A: AVP at 0.067 IU/min B: norepinephrine	Onset of advanced vasodilatory shock (norepinephrine dose > 0.5 μg/kg/min)	Nor-epinephrine, milrinone	Differences in cardiovascular function	The study included patients with advanced vasodilatory shock of various origin; only data from patients with vasodilatory shock after cardiac surgery extracted for this meta-analysis
Morales DLS, 2003[11]	RCT	Cardiac surgery using CPB and previous ACEI treatment	A: AVP B: normal saline	A: n = 17 B: n = 16	A: AVP at 0.03 IU/min B: normal saline	20 min before CPB	Nor-epinephrine	Incidence of hypotensive episodes	AVP prematurely discontinued in 4 patients in AVP group; 2 patients in control group received open label AVP
Hasija S, 2010[12]	RCT	Elective CABG using CPB and previous ACEI treatment	A: ACEI continued + AVP B: ACEI continued	A: n = 15 B: n = 16	A: AVP at 0.03 IU/min B: normal saline	Onset of rewarming on CPB	Dopamine, epinephrine, and/or nor-epinephrine	Differences in cardiovascular function and pressor requirements	The study included 3 groups; patients from 1 group (ACEI stopped 24 hours before surgery) were not included in this meta-analysis
Papadopoulos G, 2010[13]	RCT	Elective CABG, previous ACEI treatment, and LVEF 30%-40%	A: AVP B: normal saline	A: n = 25 B: n = 25	A: AVP at 0.03 IU/min B: normal saline	20 min before CPB	Nor-epinephrine and/or epinephrine	Incidence of postoperative vasodilatory shock	The study drug was stopped 4 hours after termination of CPB
Elgebaly AS, 2012[14]	RCT	Elective CABG and mild to moderate LV dysfunction	A: AVP B: normal saline	A: n = 10 B: n = 10	A: AVP at 0.03 IU/min B: normal saline	10 min before separation of CPB	Phenylephrine and/or epinephrine	Differences in cardiovascular function	The study drug was stopped 1 hour after termination of CPB
Okamoto Y, 2014[15]	RCT	Elective and emergency cardiac surgery in patients > 20 years	A: AVP B: normal saline	A: n = 47 B: n = 45	A: AVP at 0.03 IU/min B: normal saline	After anesthesia induction	Nor-epinephrine, epinephrine, phenyl-ephrine, dopamine, dobutamine, and/or a PDEI	Myocardial enzyme levels at 0, 6, and 12 hours postoperatively	16 patients in AVP group underwent cardiac surgery without CPB, 15 patients in control group underwent cardiac surgery without CPB
Hajjar LA, 2017[16]	RCT	Vasodilatory shock after cardiac surgery	A: AVP B: normal saline	A: n = 149 B: n = 151	A: AVP at 0.01-0.06 IU/min B: normal saline	Onset of advanced vasodilatory shock (MAP < 65 mmHg resistant to fluid challenge and CI > 2.2 L/min/m^2)	Nor-epinephrine, dobutamine	Differences in 30-day mortality or severe postoperative complications	Primary study endpoint changed during study (initial endpoint: days alive and free of organ dysfunction at 28 days)
Jahangirifard A, 2017[17]	RCT	Elective CABG surgery and LVEF 35%-50%	A: AVP B: normal saline	A: n = 40 B: n = 40	A: AVP at 0.03 IU/min B: normal saline	30 min before separation of CPB	Dopamine	Differences in cardiovascular function	The study drug was stopped 1 hour after termination of CPB

Abbreviations: ACEI, angiotensin converting enzyme-inhibitor; AVP, arginine vasopressin; CABG, coronary artery bypass graft; CI, cardiac index; CPB, cardiopulmonary bypass; IU, international units; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial blood pressure; PDEI, phosphodiesterase inhibitor; RCT, randomized controlled trial.

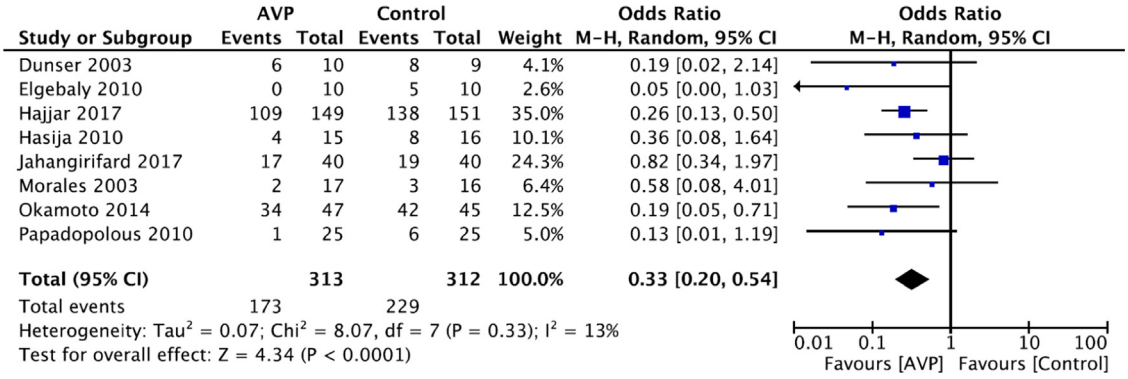

Fig 2. Forest plot indicating the effects (pooled odds ratio) of AVP on the perioperative complication rate (primary study endpoint). AVP, arginine vasopressin; CI, confidence interval.

vasodilatory shock of different origin.[10] From the latter trial, the authors extracted all patients (AVP, n = 10; standard therapy, n = 9) who experienced vasodilatory shock following cardiac surgery.

Primary Endpoint

The following perioperative complications were reported in the trials: acute kidney injury, vasodilatory shock (only extracted from the 6 trials in which vasodilatory shock was not used as an inclusion criterion), new-onset tachyarrhythmia, acute mesenteric ischemia, digital ischemia, myocardial infarction, stroke, hyponatremia/water intoxication, hepatic insufficiency, and right heart failure. AVP reduced the pooled OR of perioperative complications (Fig 2). When analyzing each perioperative complication separately, AVP reduced the OR of vasodilatory shock and new-onset atrial fibrillation (Table 2).

A sensitivity analysis excluding the largest trial[16] showed an unchanged reduction in the overall rate of perioperative complications (OR, 0.35; 95% CI, 0.18-0.69; p = 0.002), but not a reduction in the rate of new-onset atrial fibrillation alone (OR, 0.43; 95% CI, 0.13-1.43; p = 0.17). When analyzing the 3 different indications for AVP infusion used in the included trials, AVP significantly reduced the pooled OR of perioperative complications for cardiac surgical patients with vasodilatory shock (OR 0.25; 95% CI, 0.13-0.48; p < 0.0001) and patients undergoing emergency/elective cardiac surgery (OR 0.33; 95% CI, 0.12-0.94; p = 0.04), but not cardiac surgical patients receiving AVP because of chronic ACE inhibitor intake (OR 0.3; 95% CI, 0.07-1.27; p = 0.1) (Fig S1).

Secondary Endpoint

The pooled OR of postoperative death was not different between patients treated with AVP and those receiving standard therapy or placebo (Fig 3).

Risk of Bias Assessment

Funnel plots for the primary and secondary study endpoint are presented in Figure 4. The search of trial registries and meeting abstracts revealed 3 further registered trials, of which 1 was ongoing and 1 was published as a meeting abstract. The latter trial was terminated early after inclusion of 25 cardiac surgical patients with preoperative ACE inhibitors or angiotensin receptor blockers and did not report differences in postoperative complications or vasopressor/inotrope requirements

Table 2
Pooled Effects of Arginine Vasopressin on Specific Perioperative Complications

Nonsurgical Perioperative Complications	Trials Reporting	Events		Heterogeneity		Fixed or Random Effects Model		
		Vasopressin	Control	I^2 (%)	p value	Pooled OR	95% CI	p value
Vasodilatory shock	6	17/154	34/152	29	0.23	0.40	0.16-0.97	0.04
Acute kidney injury	5	34/233	70/231	72	0.01	0.58	0.17-1.98	0.38
New-onset atrial fibrillation	5	120/249	162/246	39	0.16	0.42	0.21-0.82	0.01
Myocardial infarction	4	11/191	18/182	0	0.20	0.60	0.28-1.30	0.20
Acute mesenteric ischemia	4	3/191	2/192	N/A	N/A	1.53	0.25-9.30	0.64
Digital ischemia	4	5/191	3/192	0	0.87	1.67	0.38-7.34	0.50
Stroke	3	4/174	4/176	N/A	N/A	1.01	0.25-4.13	0.98
Hyponatremia/water intoxication	3	10/174	12/176	N/A	N/A	0.83	0.35-1.99	0.68
New-onset tachyarrhythmia (non-AF)	2	30/164	40/167	47	0.17	0.58	0.20-1.68	0.31

NOTE: No pooled effects could be calculated for hepatic insufficiency and acute right heart failure as only 2 and 1 trial reported these complications, respectively.
Abbreviations: CI, confidence interval; N/A, not applicable; OR, odds ratio.

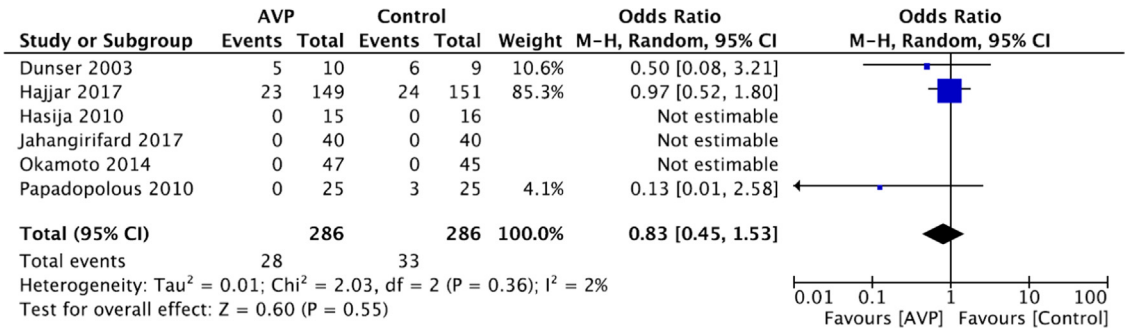

Fig 3. Forest plot indicating the effects (pooled odds ratio) of AVP on postoperative mortality (secondary study endpoint). AVP, arginine vasopressin; CI, confidence interval.

between patients receiving a vasopressin infusion (0.04 IU/min) or placebo (alpha-level, 0.01). Although the authors contacted the principal investigator of the third registered trial, they could not determine whether this trial had been competed or published.

All included trials suffered from a high risk of overall bias (Fig 5). Only 1 trial did not show a high risk of bias in a single domain. Three trials had 1 domain, 2 trials had 2 domains, and 2 trials had 3 domains in which they showed a high risk of bias.

Discussion

The results of the meta-analysis suggest that the use of AVP reduces the rate of perioperative complications in patients undergoing elective or emergency cardiac surgical procedures. Although the specific indication for the use of AVP differed between the studies included (vasodilatory shock *v* elective/emergency cardiac surgery with or without previous ACE inhibitor intake), the underlying cardiovascular pathology of reduced vascular tone was uniform throughout all trials of this meta-analysis. The overall reduction in complications mainly was due to a decrease in the rate of vasodilatory shock and new-onset atrial fibrillation. AVP is a potent non-adrenergic vasopressor agent that exerts its vasoconstrictive effects via stimulation of V1a receptors on the vascular smooth muscle cells of middle to large resistance arterioles.[18] These effects likely explain the finding that vasodilatory shock was observed less frequently in cardiac surgical patients who received AVP compared to placebo. Because angiotensin II is a physiologic secretagogue of AVP,[19] 3 trials specifically included cardiac surgical patients on chronic ACE inhibitor or angiotensin II receptor antagonist therapy.[11–13] A lower rate of new-onset atrial fibrillation in cardiac surgical patients receiving AVP likely is due to absent beta-adrenergic and relevant catecholamine-sparing effects.[7] In view of the fact that the incidence of new-onset atrial fibrillation in this meta-analysis was relatively high (48.2% in vasopressin-treated patients *v* 65.9% in control patients) and the pooled effect failed to reach the significance level after exclusion of the largest trial, the results may have overestimated the effects of AVP on this specific perioperative complication.

Given the comparatively low incidence of other perioperative complications, this meta-analysis was underpowered to determine the effects of AVP on their specific frequency. Although the trials' definitions of "vasodilatory shock," "acute kidney injury," and "new-onset atrial fibrillation" were similar, large variations were observed in the definition of other conditions, such as perioperative myocardial infarction. This may have been the reason why only 3 of 8 trials reported its incidence. One trial specifically aimed to elucidate the effects of the use of AVP on the postoperative course of cardiac

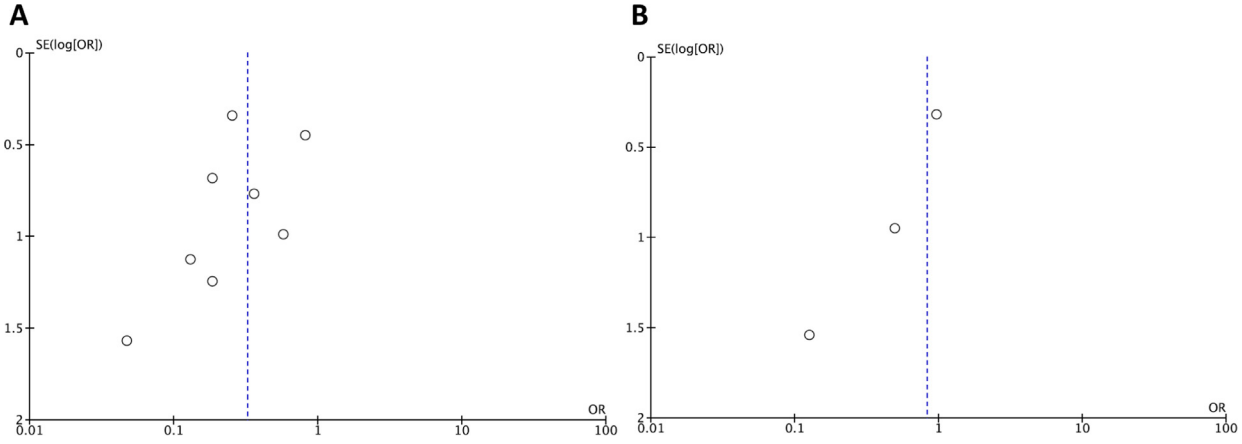

Fig 4. Funnel plots indicating the publication and small trial bias of this meta-analysis. Figure 4, *A* presents funnel plots for the primary study endpoint (perioperative complication rate) and Figure 4, *B* presents funnel plots for the secondary study endpoint (perioperative mortality).

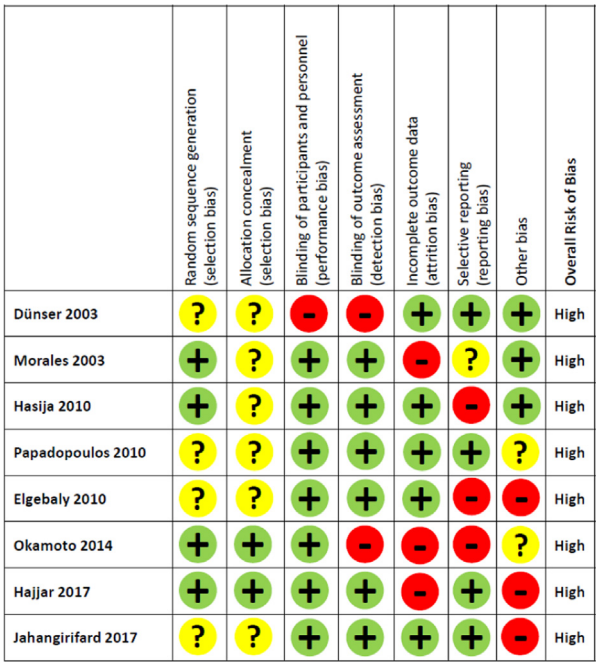

Fig 5. Summary of the risk of bias of included trials according to the 2016 revised Cochrane risk of bias tool. Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias.

enzymes and did not report any difference between AVP and placebo.[15] The lacking differences in the rate of potentially vasopressin-related side effects (ie, acute mesenteric or digital ischemia, hepatic insufficiency, hyponatremia) between study groups suggest that AVP is relatively safe in cardiac surgical patients.

Despite of a reduction in the overall rate of perioperative complications, the authors did not observe a lower postoperative mortality rate in subjects treated with AVP. An absolute difference in mortality between groups of 1.7% was observed. The number of patients included in this analysis, however, rendered it a statistical power of about 10% to detect a significant mortality difference. Larger studies, therefore, are required to determine the effects of AVP as a vasopressor on postoperative mortality in cardiac surgery.

Three meta-analyses on the use of vasopressin derivatives in vasodilatory shock so far have been published. The report by Serpa Neto et al. summarized 9 trials and a total of 998 adult patients with vasodilatory shock. Only 29 of these patients suffered from vasodilatory shock following cardiac surgery. The authors found no difference in the rate of adverse events but a decreased mortality in septic shock patients treated with vasopressin compared to placebo.[20] The second meta-analysis included 10 RCTs and 1,134 adult and pediatric patients, of whom only 19 underwent cardiac surgery. The authors neither detected a difference in the rate of serious adverse events nor crude short-term mortality.[21] The largest meta-analysis evaluating the effects of non-adrenergic vasopressor drugs on survival separately analyzed 4 trials, which included 226 cardiac surgical patients. No mortality difference between cardiac surgical patients receiving vasopressin or placebo/standard therapy was observed. When the results of 3 trials evaluating the use of methylene blue were added, the authors found that the use of non-adrenergic vasopressors reduced mortality after cardiac surgery.[22] None of the 3 meta-analyses specifically evaluated the rate of perioperative complications as done in the analysis.

Important limitations need to be considered when interpreting the results of this meta-analysis. Asymmetry of the funnel plot generated for the analysis of the primary endpoint indicates the presence of a publication bias and/or small study effect. Indeed, a systematic search of clinical trial registries and meeting abstracts revealed unpublished studies as well as a prematurely stopped trial that could not identify a decrease in the rate of vasodilatory shock in cardiac surgical patients treated with AVP. Since no dedicated database to search for meeting abstracts exists, the authors cannot exclude that they may have missed other unpublished trials. Overall, the presence of a publication bias and/or small study effect implies that the beneficial effects of vasopressin on the rate of perioperative complications likely are overestimated by this meta-analysis. In addition, none of the included studies passed rigorous testing for a risk of bias using the 2016 Cochrane tool. The fact that 1 trial contributed almost half of the patients of this meta-analysis is unlikely to have influenced relevantly the study results (primary endpoint), as a sensitivity analysis excluding this trial confirmed the results of the main analysis.

In conclusion, this meta-analysis, which included 8 trials with a high risk of bias, suggests that AVP may reduce the rate of perioperative complications in patients undergoing elective or emergency cardiac surgery. No difference in postoperative mortality was observed. An adequately powered multicenter trial is required to reliably estimate the effects of AVP on perioperative complication rates and mortality in cardiac surgical patients.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jvca.2018.04.006.

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