

# Alpha-2 Adrenergic Agonists to Prevent Perioperative Cardiovascular Complications: A Meta-analysis

Duminda N. Wijesundera, MD, Jennifer S. Naik, MD, W. Scott Beattie, MD, PhD

**PURPOSE:** To investigate the effects of  $\alpha_2$ -adrenergic agonists on perioperative mortality and cardiovascular complications in adults undergoing surgery.

**METHODS:** MEDLINE (1966 to May 2002), EMBASE (1980 to May 2002), the Cochrane Clinical Trials Register, the Science Citation Index, and bibliographies of included articles were searched without language restriction. Randomized trials comparing preoperative, intraoperative, or postoperative (first 48 hours) administration of clonidine, dexmedetomidine, or mivazerol with controls were included. Studies had to report any of the following outcomes: mortality, myocardial infarction, ischemia, or supraventricular tachyarrhythmia. Treatment effects were calculated using the fixed-effects model. Heterogeneity was assessed using the Q test.

**RESULTS:** Twenty-three trials comprising 3395 patients were included. Overall,  $\alpha_2$ -adrenergic agonists reduced mortality (relative risk [RR] = 0.64; 95% confidence interval [CI]: 0.42 to

0.99;  $P = 0.05$ ) and ischemia (RR = 0.76; 95% CI: 0.63 to 0.91;  $P = 0.003$ ) significantly. They also reduced mortality (RR = 0.47; 95% CI: 0.25 to 0.90;  $P = 0.02$ ) and myocardial infarction (RR = 0.66; 95% CI: 0.46 to 0.94;  $P = 0.02$ ) during vascular surgery. During cardiac surgery,  $\alpha_2$ -adrenergic agonists reduced ischemia (RR = 0.71; 95% CI: 0.54 to 0.92;  $P = 0.01$ ) and were associated with trends toward lower mortality (RR = 0.49; 95% CI: 0.12 to 1.98;  $P = 0.3$ ) and a reduced risk of myocardial infarction (RR = 0.83; 95% CI: 0.35 to 1.96;  $P = 0.7$ ).

**CONCLUSION:** Alpha-2 adrenergic agonists reduce mortality and myocardial infarction following vascular surgery. During cardiac surgery, they reduce ischemia and may also have effects on mortality and myocardial infarction. Large randomized trials are needed to evaluate these agents during cardiac and vascular surgery. *Am J Med.* 2003;114:742-752. ©2003 by Excerpta Medica Inc.

Cardiovascular complications following cardiac and noncardiac surgery increase mortality, morbidity, and health care costs (1-4). Approximately 4.5% of patients undergoing cardiac surgery will have a perioperative myocardial infarction (1), whereas about 30% of patients undergoing noncardiac surgery have, or are at risk of, coronary artery disease (3). The direct health care costs of these complications have been estimated at U.S. \$20 billion (3).

The surgical stress response is important in the pathogenesis of cardiovascular complications (5,6). The  $\alpha_2$ -adrenergic agonists currently used in clinical practice—clonidine, dexmedetomidine, and mivazerol—attenuate the stress response and therefore potentially reduce car-

diovascular complications. Unlike  $\alpha_1$ -antagonists (e.g., prazosin), which act on peripheral adrenergic receptors to inhibit vasoconstriction directly,  $\alpha_2$ -agonists act on central and presynaptic receptors to inhibit central sympathetic outflow (7) and reduce peripheral norepinephrine release (8). Alpha-2 agonists dilate poststenotic coronary vessels (9) and attenuate the severity of perioperative hemodynamic abnormalities (10,11), and consequently were conferred a grade IIb recommendation in the 2002 American College of Cardiology/American Heart Association Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery (12). This recommendation, however, was based on one study (13).

A prior meta-analysis concluded that clonidine reduced perioperative ischemia significantly (14). However, the review was underpowered (664 patients in seven studies), searched only English-language literature, and reported effects only on ischemia, a surrogate outcome. It did not include trials of mivazerol or dexmedetomidine, which have enrolled up to 1900 patients (13). A systematic review of perioperative  $\alpha_2$ -agonists is therefore justified.

From the Department of Anesthesia (DNW, JSN, WSB), University of Toronto, and Toronto General Hospital (WSB), University Health Network, Toronto, Ontario, Canada.

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Requests for reprints should be addressed to W. Scott Beattie, MD, PhD, Department of Anesthesia, University of Toronto, EN 3-453, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4, Canada, or scott.beattie@uhn.on.ca.

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**Table 1.** Characteristics of Included Studies

First Author (Reference)	Number of Patients	Coronary Artery Disease	Procedure	Alpha-2 Agonist	Control	Blinding	Concealed Allocation	Jadad Score*
Cardiac surgery								
Abi-Jaoude (21)	24	+	Coronary bypass grafting	Oral clonidine 5 $\mu\text{g}/\text{kg}$ 120 minutes before surgery	Placebo	+	Unclear	3
Boldt (22)	44	+	Coronary bypass grafting	Intravenous clonidine 0.05 $\mu\text{g}/\text{kg}/\text{min}$ from induction to cardiopulmonary bypass	Placebo	+	Unclear	3
Dorman (23)	43	+	Coronary bypass grafting	Oral clonidine 5 $\mu\text{g}/\text{kg}$ 90 minutes before surgery, and 5 $\mu\text{g}/\text{kg}$ before cardiopulmonary bypass	Placebo	+	Unclear	3
Ghignone (24)	24	+	Coronary bypass grafting	Oral clonidine 5 $\mu\text{g}/\text{kg}$ 90 minutes before surgery	Control	–	Unclear	1
Helbo-Hansen (26)	40	+	Coronary bypass grafting	Intravenous clonidine 7 $\mu\text{g}/\text{kg}$ in three divided intraoperative bolus doses	Placebo	–	Unclear	1
Jalonen (27)	80	+	Coronary bypass grafting	Intravenous dexmedetomidine 50 $\text{ng}/\text{kg}/\text{min}$ before surgery for 30 minutes, 7 $\text{ng}/\text{kg}/\text{min}$ intraoperatively	Placebo	+	Unclear	3
Loick (29)	45	+	Coronary bypass grafting	Intravenous clonidine 4 $\mu\text{g}/\text{kg}$ before surgery, 1 $\mu\text{g}/\text{kg}/\text{min}$ intraoperatively, and 0.2–0.5 $\mu\text{g}/\text{kg}/\text{min}$ for 48 hours postoperatively	Control	–	Unclear	2
Myles (31)	150	+	Coronary bypass grafting	Oral clonidine 5 $\mu\text{g}/\text{kg}$ 90 minutes before surgery, and 5 $\mu\text{g}/\text{kg}$ before coronary bypass grafting	Placebo	+	Unclear	4
Quintin (33)	26	+	Coronary bypass grafting	Oral clonidine 2.5 $\mu\text{g}/\text{kg}$ 90 minutes before surgery	Placebo	+	Unclear	3
Venn (38)	105	+	Mixed (83% cardiac)	Intravenous dexmedetomidine 1 $\mu\text{g}/\text{kg}$ within 1 hour after surgery, and 0.2–0.7 $\mu\text{g}/\text{kg}/\text{h}$ for 6–24 hours	Placebo	+	Unclear	4
Noncardiac surgery								
Ellis (8)	61	+	Noncardiac surgery (82% vascular)	Transdermal clonidine (0.2 $\text{mg}/\text{d}$ ) for 72 hours from night before surgery, and 0.3 $\text{mg}$ orally 60–90 minutes before surgery	Placebo	+	+	4
Ghignone (25)	30	+	Nonvascular surgery	Oral clonidine 5 $\mu\text{g}/\text{kg}$ 90 minutes before surgery	Control	–	Unclear	2
Lipszyc (28)	40	+	Carotid artery surgery	Oral clonidine 4 $\mu\text{g}/\text{kg}$ 90 minutes before surgery	Placebo	+	Unclear	2
Mangano (10)	317	+	Vascular surgery	Two intravenous mivazerol regimens: low (2 $\mu\text{g}/\text{kg}$ bolus and 0.75 $\mu\text{g}/\text{kg}/\text{h}$ ), high (4 $\mu\text{g}/\text{kg}$ bolus and 1.5 $\mu\text{g}/\text{kg}/\text{h}$ ). Bolus given 20 minutes before surgery; infusion until 72 hours after surgery	Placebo	+	Unclear	4
Matot (30)	36	Unclear	Airway surgery	Oral clonidine 300 $\mu\text{g}$ 90 minutes before surgery	Placebo	+	Unclear	3
Oliver (13)	1897 <sup>†</sup>	+	Noncardiac surgery	Intravenous mivazerol 4 $\mu\text{g}/\text{kg}$ 20 minutes before surgery, and 1.5 $\mu\text{g}/\text{kg}/\text{h}$ for 72 hours	Placebo	+	+	4
Pluskwa (32)	30	+	Carotid artery surgery	Oral clonidine 300 $\mu\text{g}$ 90 minutes before surgery	Placebo	+	+	5
Quintin (34)	24	+	Aortic surgery	Oral clonidine 6 $\mu\text{g}/\text{kg}$ 120 minutes before surgery, and 3 $\mu\text{g}/\text{kg}$ intravenously after surgery	Placebo	+	Unclear	4
Stuhmeier (35)	297	+	Vascular surgery	Oral clonidine 2 $\mu\text{g}/\text{kg}$ 90 minutes before surgery	Placebo	+	Unclear	5

Table 1. Continued

First Author (Reference)	Number of Patients	Coronary Artery Disease	Procedure	Alpha-2 Agonist	Control	Blinding	Concealed Allocation	Jadad Score*
Talke (11)	25	+	Vascular surgery	Intravenous dexmedetomidine given in three doses [low (2.64 µg/kg), medium (5.31 µg/kg), high (8.03 µg/kg)] as 48-hour infusion from start of surgery	Placebo	+	Unclear	4
Talke (36)	41	+	Vascular surgery	Intravenous dexmedetomidine: 140 µg intraoperative infusion, and 0.15 µg/min until 48 hours after surgery	Placebo	+	Unclear	4
Venn (39)	20	Unclear	Nonvascular surgery	Intravenous dexmedetomidine 2.5 µg/kg within 1 hour after surgery, and 0.2–0.5 µg/kg/h for 6–24 hours	Intravenous propofol 1 mg/kg and 1–3 mg/kg/h infusion	–	Unclear	2
Mixed surgery types Triltsch (37)	30	Unclear	Mixed (53% cardiac)	Intravenous dexmedetomidine 6 µg/kg within 6 hours after surgery, and 0.4 µg/kg/h for 72 hours	Placebo	+	Unclear	4

\* On a scale of 0 to 5.

† Results for additional 957 patients at risk for coronary artery disease were not presented.

+ = present; – = absent.

## METHODS

This review adhered to the recommendations of the Quality of Reporting of Meta-analyses (QUOROM) group (15).

### Inclusion and Exclusion Criteria

Eligible studies were published, randomized controlled trials that enrolled adults (age >18 years) who were undergoing surgery under general or neuroaxial (spinal or epidural) anesthesia. Trials that recruited patients undergoing local anesthesia or peripheral nerve blockade alone were excluded. We also excluded trials that recruited patients who were pregnant, organ transplant recipients, or suffering from substance withdrawal.

The interventions assessed were preoperative (within 24 hours), intraoperative, or postoperative (within 48 hours) administration of clonidine, dexmedetomidine, or mivazerol via intravenous, intramuscular, oral, or transdermal routes. Trials had to report any of the following outcomes: death, myocardial infarction, myocardial ischemia, or supraventricular tachyarrhythmia. We did not employ a uniform definition of myocardial infarction given the lack of a standardized criterion in the literature. Ischemia was defined as ST-segment deviation on an electrocardiogram or new wall motion abnormalities on a transthoracic echocardiogram. Supraventricular tachyarrhythmias included atrial fibrillation, atrial flutter, and supraventricular tachycardia.

### Search Strategy

We identified eligible trials using MEDLINE (1966 to May 2002), EMBASE (1980 to May 2002), and the Cochrane Clinical Trials Register (The Cochrane Library, Issue 2, 2002) (16). The search included the following medical subject headings: *clonidine* or *dexmedetomidine* or *mivazerol* and *postoperative*, *perioperative*, *intraoperative*, *complications*, *period*, *preoperative*, or *care*. Included trials were entered into the Science Citation Index to identify other articles. We also searched the bibliographies of included articles and published reviews. No language restrictions were applied. Unpublished trials were not sought, but authors of included studies were contacted for additional data.

### Methods of Review

Two reviewers independently performed the literature searches and assessed all identified full papers or abstracts for inclusion. The reasons for exclusion were documented for all excluded studies. Three reviewers independently abstracted the following onto data abstraction forms: number of patients, prior medications, type of surgery, and type of treatments, as well as the incidence of several outcomes, including deaths (all-cause), myocardial infarction, ischemia, supraventricular tachyarrhythmia, heart failure, hypotension (requiring pharmacologic

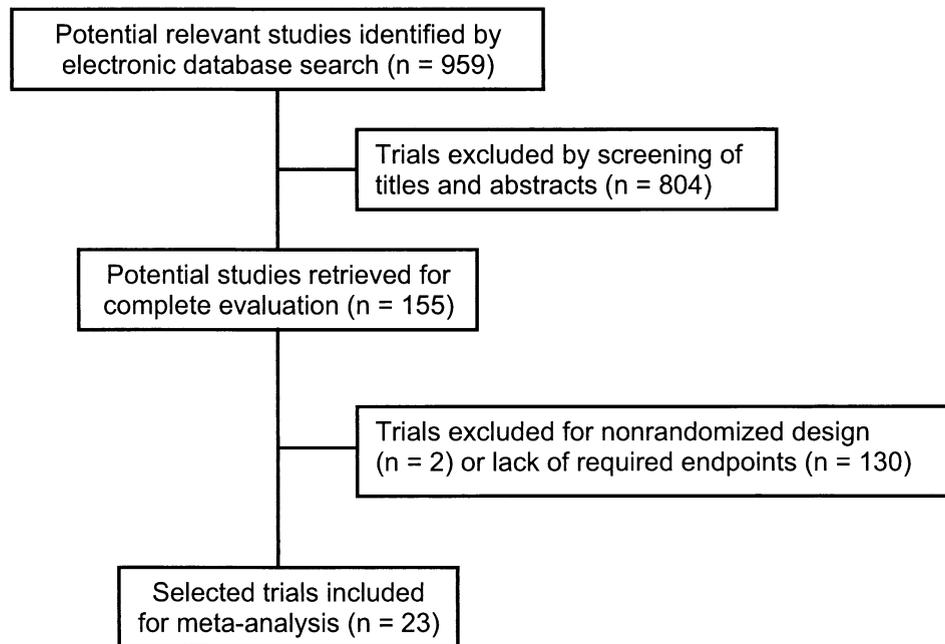


Figure 1. Flow diagram of meta-analysis.

or intra-aortic balloon pump treatment), and bradycardia (requiring pharmacologic or pacemaker treatment). Three reviewers rated study quality independently using the scale of Jadad et al (17). The minimum score required was 1. Reviewers were not blinded to the names of authors, institutions, or journals when performing data abstraction or quality assessment. Where possible, data were abstracted only for comparisons of  $\alpha_2$ -agonists with placebo. All disagreements were resolved by consensus.

### Statistical Analysis

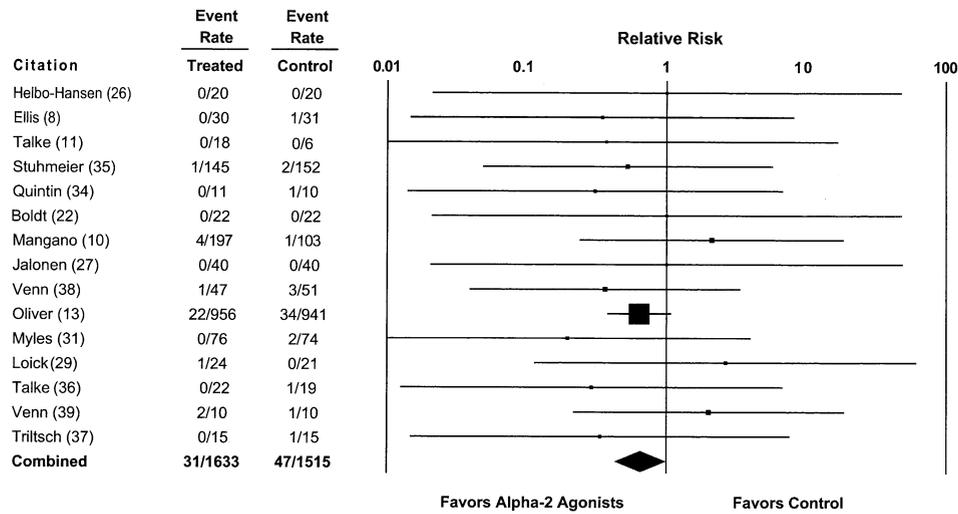
Analyses were performed using Review Manager 4.1.1 (Cochrane Collaboration, Oxford, United Kingdom). We calculated the effects of  $\alpha_2$ -agonists on the primary outcome (mortality) and several secondary outcomes (myocardial infarction, ischemia, heart failure, hypotension, and bradycardia). Treatment effects were expressed as pooled relative risks, with 95% confidence intervals. Initially, heterogeneity was assessed using the Q statistic, with statistically significant heterogeneity defined by  $P$  values  $<0.1$ . In the absence of significant heterogeneity, relative risks were calculated using the fixed-effects model (18). If there was significant heterogeneity, the random-effects model (19) was used; in addition, we carried out post hoc analyses to explain the heterogeneity. Statistical significance for treatment effects was defined by  $P$  values  $<0.05$ .

Given that differences in preoperative medication use may confound the results, we compared the use of beta-blockers and calcium antagonists using meta-analytic

methods. Differences in medication use were expressed as relative risks calculated with the fixed-effects model.

**Subgroup analyses.** Two subgroup analyses were performed to compare the treatment effects for each  $\alpha_2$ -agonist (clonidine, dexmedetomidine, and mivazerol) on mortality, myocardial infarction, and ischemia, as well as to study the effects of procedure type (cardiac, vascular, and nonvascular surgery) on these three outcomes. If several surgical procedures were included in a study, we attempted to obtain subgroup-specific results from the authors. If such data were not available, and more than 75% of patients underwent the same class of surgery, the study was allocated to that specific subgroup. Failing that, the study was excluded from the subgroup analysis involving procedure type.

**Sensitivity analyses.** Several sensitivity analyses were conducted to determine whether the choice of included studies or statistical model influenced treatment effects. The first analysis was restricted to analyses that had identified statistically significant treatment effects. We removed trials in increasing order of relative risks (i.e., trials favoring  $\alpha_2$ -agonists the most were removed first). We measured the proportion of studies and patients that were removed to make the treatment effect statistically nonsignificant. The second analysis assessed the relation between study quality and treatment effects. The meta-analyses were repeated in subgroups of high-quality studies (Jadad score  $\geq 3$ ) (17). The third analysis examined the effect of the statistical model on treatment effects.



**Figure 2.** Effect of  $\alpha_2$ -agonists on mortality during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.64 (95% CI: 0.42 to 0.99;  $P$  for heterogeneity = 0.92).

Analyses that employed the fixed-effects model were repeated using the random-effects model. The fourth analysis used funnel plots (20) to assess publication bias.

**RESULTS**

Twenty-three studies comprising 3395 patients were included (Table 1; Figure 1). A list of excluded studies is available from the authors.

Ten studies involved cardiac surgery, eight involved vascular noncardiac surgery, and three involved nonvascular noncardiac surgery (Table 1). One noncardiac surgery study (13) presented subgroup-specific results for both vascular and nonvascular procedures. Fifteen studies assessed clonidine, six assessed dexmedetomidine, and two assessed mivazerol. Treatment duration ranged from a single preoperative dose to a 72-hour course of treatment. All studies allowed for comparison of  $\alpha_2$ -agonists with placebo, with the exception of a nonvascular surgery trial (39) that compared intravenous dexmedetomidine with intravenous propofol. There were no direct comparisons of  $\alpha_2$ -agonists with beta-blockers.

The mean age of participants ranged from 48 to 69 years. Men comprised 47% to 100% of participants. Approximately 74% of the studies were high quality (Jadad score  $\geq 3$ ). The median Jadad score was 3 (range, 1 to 5).

*Mortality and Cardiovascular Complications*

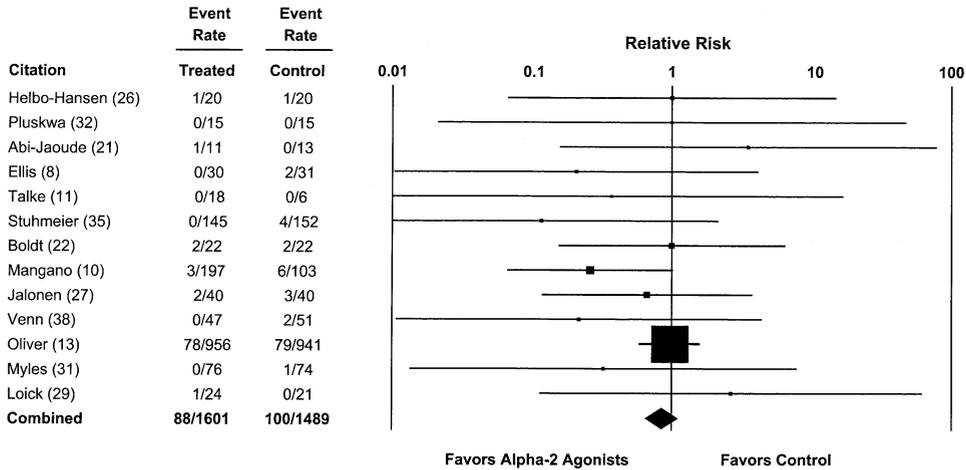
Fifteen studies reported deaths, with an incidence of 2.5% ( $n = 78$ ) among 3128 patients (Figure 2). Alpha-2 agonists reduced mortality (relative risk [RR] = 0.64; 95% confidence interval [CI]: 0.42 to 0.99;  $P = 0.05$ ), without

statistically significant heterogeneity ( $P = 0.92$ ). Clonidine (RR = 0.48; 95% CI: 0.15 to 1.60;  $P = 0.2$ ), dexmedetomidine (RR = 0.57; 95% CI: 0.17 to 1.88;  $P = 0.4$ ), and mivazerol (RR = 0.69; 95% CI: 0.42 to 1.15;  $P = 0.15$ ) had similar effects on mortality.

Thirteen studies reported myocardial infarctions, with an incidence of 6% ( $n = 188$ ) among 3090 patients (Figure 3). Alpha-2 agonists were associated with a nonsignificant reduction in myocardial infarction (RR = 0.85; 95% CI: 0.65 to 1.11;  $P = 0.2$ ). There was no statistically significant heterogeneity for this analysis ( $P = 0.55$ ), although clonidine (RR = 0.61; 95% CI: 0.25 to 1.48;  $P = 0.3$ ) and dexmedetomidine (RR = 0.47; 95% CI: 0.11 to 2.03;  $P = 0.3$ ) appeared to reduce infarction to a greater degree than did mivazerol (RR = 0.91; 95% CI: 0.68 to 1.21;  $P = 0.5$ ).

Sixteen studies reported ischemia, with an incidence of 25.5% ( $n = 336$ ) among 1320 patients (Figure 4). Alpha-2 agonists reduced ischemia (RR = 0.76; 95% CI: 0.63 to 0.91;  $P = 0.003$ ), without statistically significant heterogeneity ( $P = 0.59$ ). Clonidine appeared to reduce ischemia (RR = 0.67; 95% CI: 0.54 to 0.84;  $P = 0.0005$ ) to a greater degree than did dexmedetomidine (RR = 0.85; 95% CI: 0.57 to 1.27;  $P = 0.4$ ) or mivazerol (RR = 1.14; 95% CI: 0.67 to 1.97;  $P = 0.6$ ).

Four studies reported supraventricular tachyarrhythmias (11,27,38,39), with an incidence of 12% ( $n = 33$ ) among 243 patients. Alpha-2 agonists had little effect on supraventricular tachyarrhythmia (RR = 1.04; 95% CI: 0.56 to 1.93;  $P = 0.9$ ), without statistically significant heterogeneity ( $P = 0.87$ ).



**Figure 3.** Effect of  $\alpha_2$ -agonists on myocardial infarction during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.85 (95% CI: 0.65 to 1.11;  $P$  for heterogeneity = 0.55).

There were no obvious trends in treatment efficacy by dosage, duration of treatment, or event rate.

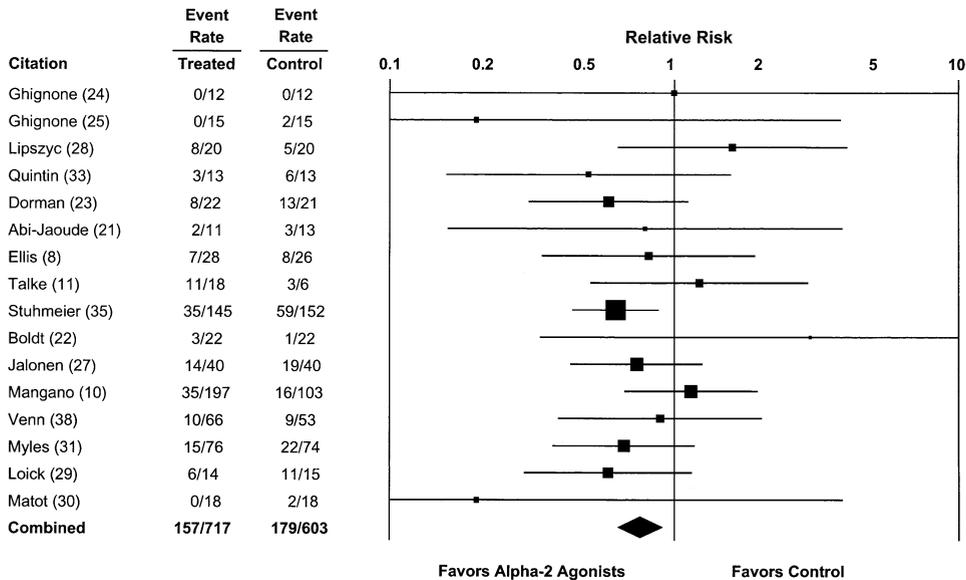
**Cardiac Surgery**

Alpha-2 agonists reduced myocardial ischemia significantly (RR = 0.71; 95% CI: 0.54 to 0.92;  $P$  = 0.01). They also reduced mortality (RR = 0.49; 95% CI: 0.12 to 1.98;  $P$  = 0.3) and myocardial infarction (RR = 0.83; 95% CI: 0.35 to 1.96;  $P$  = 0.7), although these estimates did not

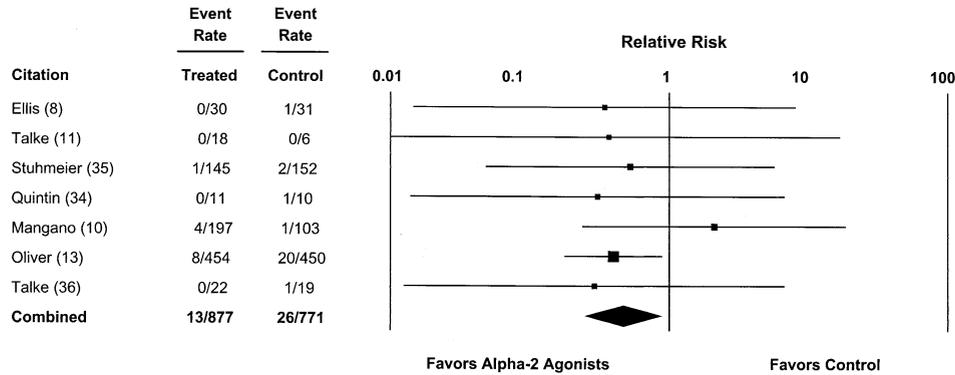
achieve statistical significance. There was no statistically significant heterogeneity for effects on death ( $P$  = 0.47), infarction ( $P$  = 0.86), and ischemia ( $P$  = 0.88).

**Vascular Surgery**

Among patients undergoing vascular surgery,  $\alpha_2$ -agonists reduced mortality (RR = 0.47; 95% CI: 0.25 to 0.90;  $P$  = 0.02; Figure 5) and myocardial infarction (RR = 0.66; 95% CI: 0.46 to 0.94;  $P$  = 0.02; Figure 6). Alpha-2



**Figure 4.** Effect of  $\alpha_2$ -agonists on myocardial ischemia during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.76 (95% CI: 0.63 to 0.91;  $P$  for heterogeneity = 0.59).



**Figure 5.** Effect of  $\alpha_2$ -agonists on mortality during vascular surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.47 (95% CI: 0.25 to 0.90;  $P$  for heterogeneity = 0.82).

agonists were associated with trends toward reduced ischemia (RR = 0.83; 95% CI: 0.64 to 1.07;  $P$  = 0.15). There was no statistically significant heterogeneity for effects on death ( $P$  = 0.82), infarction ( $P$  = 0.21), and ischemia ( $P$  = 0.16).

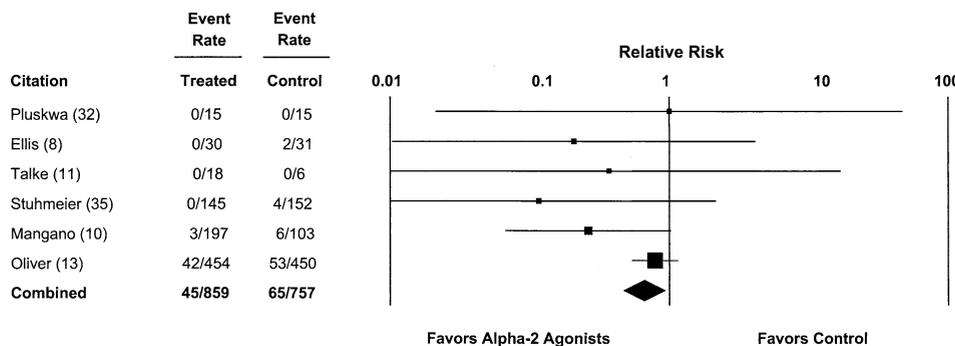
**Nonvascular Surgery**

The studies that reported deaths following nonvascular surgery (13,39) found that  $\alpha_2$ -agonists had little effect on mortality (RR = 1.05; 95% CI: 0.52 to 2.09;  $P$  = 0.9), without statistically significant heterogeneity ( $P$  = 0.55). The one study that reported infarction (13) within this subgroup found that  $\alpha_2$ -agonists increased the incidence of infarction (RR = 1.35; 95% CI: 0.83 to 2.21;  $P$  = 0.2), although this estimate was not statistically significant. Alpha-2 agonists were, however, associated with a nonsignificant reduction in ischemia (RR = 0.20; 95% CI: 0.02 to 1.62;  $P$  = 0.13).

**Prior Medication Use**

Fourteen studies reported calcium antagonist use (8,10,11,13,21–23,26,27,30,31,33–35), with an overall prevalence of 45% (n = 1373) among 3043 patients. There was no difference in calcium antagonist use between  $\alpha_2$ -agonist and control arms (RR = 0.95; 95% CI: 0.88 to 1.03;  $P$  = 0.2;  $P$  for heterogeneity = 0.94).

Fifteen studies reported beta-blocker use (8,10,11,13, 21–23,26,27,29,30,31,33–35). The overall prevalence was 34% (n = 1037) among 3088 patients, with patients in  $\alpha_2$ -agonist arms more likely to receive beta-blockers (RR = 1.11; 95% CI: 1.01 to 1.22;  $P$  = 0.04;  $P$  for heterogeneity = 0.82). In a post hoc analysis, patients in cardiac surgery trials who were assigned to  $\alpha_2$ -agonist arms were as likely to receive beta-blockers as were those assigned to control arms (RR = 1.05; 95% CI: 0.91 to 1.21;  $P$  = 0.5). In noncardiac surgery trials, however, patients assigned to  $\alpha_2$ -agonist arms were significantly more likely to receive



**Figure 6.** Effect of  $\alpha_2$ -agonists on myocardial infarction during vascular surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.66 (95% CI: 0.46 to 0.94;  $P$  for heterogeneity = 0.21).

**Table 2.** Effect of Removing Favorable Studies on Estimated Treatment Effects

Type of Surgery	Outcome	Initial Analysis		Favorable Trials Removed to Eliminate Statistical Significance	
		Trials	Patients	Trials Remaining	No. of Patients (% Initial Sample)
All	Death	15	3128	14	2978 (95.2)
All	Ischemia	16	1320	10	860 (65.2)
Cardiac	Ischemia	9	539	6	442 (82.0)
Vascular	Death	7	1648	4	1525 (92.5)
Vascular	Infarction	6	1616	5	1258 (77.8)

beta-blockers (RR = 1.13; 95% CI: 1.00 to 1.27;  $P = 0.05$ ).

Given that beta-blockers decrease perioperative mortality following noncardiac surgery (40,41), we carried out post hoc analyses to estimate the change in mortality attributable to differential beta-blocker use. During noncardiac surgery, the prevalence of beta-blocker use was 31% in  $\alpha_2$ -agonist arms and 27% in control arms. Assuming that beta-blockers are associated with an 80% reduction in the risk of cardiac death and myocardial infarction (41), differential beta-blocker use accounted for a 4% relative risk reduction in mortality.

### Adverse Events

Nine studies reported heart failure (8,10,11,21,27,30,31,37,39). Alpha-2 agonists were associated with a reduction in heart failure that was not significant (RR = 0.82; 95% CI: 0.49 to 1.36;  $P = 0.4$ ). There was no statistically significant heterogeneity for this analysis ( $P = 0.91$ ).

Twelve studies reported hypotension (10,11,13,21,22,25,30–32,34,37,39). The incidence of hypotension, although increased, was not significant (RR = 1.09; 95% CI: 0.94 to 1.27;  $P = 0.20$ ;  $P$  for heterogeneity = 0.15). Hypotension was significantly increased among patients who received  $\alpha_2$ -agonists during cardiac surgery (RR = 1.76; 95% CI: 1.04 to 2.96;  $P = 0.03$ ;  $P$  for heterogeneity =

0.52), but not during noncardiac surgery (RR = 1.03; 95% CI: 0.89 to 1.21;  $P = 0.7$ ;  $P$  for heterogeneity = 0.22).

Thirteen studies reported bradycardia (10,11,13,22,23,29–32,34,35,37,39). The increase in bradycardia associated with  $\alpha_2$ -agonist use was not significant (RR = 1.36; 95% CI: 0.91 to 2.04;  $P = 0.13$ ); however, there was significant heterogeneity ( $P = 0.009$ ). Post hoc subgroup analyses did not explain this heterogeneity.

### Sensitivity Analyses

Sequential exclusion of the most favorable studies (i.e., studies with low relative risks) had variable effects on statistically significant treatment effects (Table 2). Treatment effects were generally unaffected by study quality and choice of statistical model (Table 3). Funnel plots revealed no obvious publication bias with regard to reporting of death, infarction, or ischemia.

Because results may have been highly influenced by a single large study (13), we estimated treatment effects when this study was excluded. Effects on mortality during all surgical procedures (RR = 0.65; 95% CI: 0.30 to 1.40;  $P = 0.3$ ) and vascular surgery (RR = 0.66; 95% CI: 0.22 to 2.00;  $P = 0.5$ ) were qualitatively unchanged, but effects on myocardial infarction during all surgical procedures (RR = 0.47; 95% CI: 0.25 to 0.91;  $P = 0.02$ ) and vascular

**Table 3.** Effect of Study Quality and Statistical Model on Estimated Treatment Effects

Type of Surgery	Outcome	All Trials		High-Quality Trials*		Random-Effects Model	
		Relative Risk (95% Confidence Interval)	$P$ Value	Relative Risk (95% Confidence Interval)	$P$ Value	Relative Risk (95% Confidence Interval)	$P$ Value
All	Mortality	0.64 (0.42–0.99)	0.05	0.59 (0.38–0.93)	0.02	0.64 (0.41–1.01)	0.05
All	Infarction	0.85 (0.65–1.11)	0.2	0.84 (0.64–1.10)	0.2	0.88 (0.67–1.16)	0.4
All	Ischemia	0.76 (0.63–0.91)	0.003	0.75 (0.62–0.91)	0.004	0.75 (0.62–0.90)	0.002
Cardiac	Mortality	0.49 (0.12–1.98)	0.3	0.28 (0.05–1.68)	0.16	0.50 (0.11–2.37)	0.4
Cardiac	Infarction	0.83 (0.35–1.96)	0.7	0.71 (0.27–1.86)	0.5	0.85 (0.34–2.15)	0.7
Cardiac	Ischemia	0.71 (0.54–0.92)	0.01	0.72 (0.54–0.97)	0.03	0.68 (0.52–0.89)	0.005
Vascular	Mortality	0.47 (0.25–0.90)	0.02	0.47 (0.25–0.90)	0.02	0.46 (0.23–0.90)	0.02
Vascular	Infarction	0.66 (0.46–0.94)	0.02	0.66 (0.46–0.94)	0.02	0.47 (0.20–1.10)	0.08
Vascular	Ischemia	0.83 (0.64–1.07)	0.15	0.79 (0.61–1.03)	0.08	0.92 (0.64–1.34)	0.7

\* Jadad score  $\geq 3$ .

surgery (RR = 0.21; 95% CI: 0.07 to 0.66;  $P = 0.008$ ) were improved.

## DISCUSSION

Our results show that  $\alpha_2$ -agonists reduce perioperative mortality and myocardial ischemia following cardiac and noncardiac surgery. No single treatment regimen was clearly superior. These perioperative benefits may depend largely on the surgical procedure involved, with the largest benefits observed in patients undergoing vascular and cardiac surgery. Compared with a prior systematic review of perioperative clonidine (14), our meta-analysis included all commonly used  $\alpha_2$ -agonists, used a more extensive literature search, utilized a larger data set, and calculated treatment effects on important clinical outcomes, namely mortality and myocardial infarction.

Among noncardiac surgical procedures, vascular surgery is associated with the highest risk of cardiovascular complications (42). Alpha-2 agonists reduced mortality and myocardial infarction significantly following vascular surgery. Treatment effects on mortality were unaffected by study quality and choice of statistical model, and remained statistically significant even when 35% to 45% of the most favorable studies were removed. Alpha-2 agonists were not associated with significant increases in bradycardia or hypotension during vascular surgery.

During cardiac surgery,  $\alpha_2$ -agonists reduced myocardial ischemia significantly, but not mortality and myocardial infarction, which is likely due to the inadequate power of the subgroup analysis. Nonetheless,  $\alpha_2$ -agonists were associated with significant increases in hypotension during cardiac surgery.

There are limited data to support the use of  $\alpha_2$ -agonists during nonvascular surgery. Only two trials reported effects on death or myocardial infarction within this subgroup (13,39). Furthermore, the estimates of treatment effect were uncertain, with wide 95% confidence intervals.

The dose and duration of  $\alpha_2$ -agonist regimens were similar and did not appear to affect treatment efficacy. The effective dose of clonidine appears to be a single oral or intravenous dose of 2 to 6  $\mu\text{g}/\text{kg}$  before surgery. There is no evidence of added benefit from additional intraoperative or postoperative doses of clonidine, which has a half-life of 12 hours (43). Dexmedetomidine should be administered as a 1- to 6- $\mu\text{g}/\text{kg}$  intravenous bolus during or immediately after surgery, followed by a 0.2- to 0.7- $\mu\text{g}/\text{kg}/\text{h}$  infusion for 48 hours. The effective mivazerol treatment regimen appears to be a 4- $\mu\text{g}/\text{kg}$  intravenous bolus before surgery, followed by a 1.5- $\mu\text{g}/\text{kg}/\text{h}$  infusion for 72 hours. Nonetheless, further study is needed to determine the optimal timing for initiating and terminating perioperative therapy.

Alpha-2 agonists are generally safe. Aside from hypotension during cardiac surgery, this analysis did not find statistically significant increases in hypotension, bradycardia, or heart failure. The effect on bradycardia, although statistically nonsignificant, should be viewed cautiously in light of its heterogeneity and wide 95% confidence intervals. Although discontinuation of long-term  $\alpha_2$ -agonist therapy has been associated with rebound hypertension (44) and mortality (45), these adverse effects did not appear to be clinically important during perioperative therapy.

This study has several limitations. The overall results were dominated by a single large study (13). Exclusion of this study did not qualitatively change the results. The meta-analysis also lacked sufficient power to examine the effects of  $\alpha_2$ -agonists on specific subgroups (e.g., cardiac surgery, nonvascular surgery) and outcomes (e.g., supraventricular tachyarrhythmia, heart failure, bradycardia). Our results may have been biased by the different use of beta-blockers among studies, which decrease mortality after cardiac (46) and noncardiac (40,41) surgery. In noncardiac surgery trials, patients assigned to  $\alpha_2$ -agonist arms were more likely to have received beta-blockers preoperatively. Nonetheless, differential beta-blocker use accounted for only a 4% relative risk reduction in mortality, and does not explain the 53% relative risk reduction in mortality during vascular surgery.

We did not include any direct comparisons of  $\alpha_2$ -agonists and beta-blockers. Prior meta-analyses (47,48) have shown that beta-blockers reduce supraventricular tachyarrhythmias during cardiac surgery; however, these analyses did not report effects on death or infarction. A systematic review (49) of beta-blocker use during noncardiac surgery identified five randomized controlled trials (40,41,50–52) comprising 586 patients. The numbers needed to treat for beta-blockers to prevent a perioperative cardiovascular complication ranged from 2.5 (ischemia) (51), to 3.2 (cardiac death or myocardial infarction, 18% event rate) (41), to 3.8 (myocardial infarction, 10% event rate) (50). In contrast, the numbers needed to treat for  $\alpha_2$ -agonists to prevent a postoperative death following vascular surgery ranged from 19 (10% event rate) to 38 (5% event rate). We were also unable to determine if  $\alpha_2$ -agonists have synergistic or additive effects when used with beta-blockers. The combination of the medications is unlikely to have adverse effects, given that  $\alpha_2$ -agonists continue to have beneficial effects among patients concurrently receiving beta-blockers.

The quality of included trials may have biased treatment effects (53). The majority of studies were double-blind, placebo-controlled trials with Jadad scores of 3 or greater. However, we found that allocation concealment was generally poorly described, which may have increased estimates of treatment benefit (53).

Our results support the use of  $\alpha_2$ -agonists for preventing perioperative cardiovascular complications following vascular or cardiac surgery. The most compelling evidence shows that  $\alpha_2$ -agonists decrease perioperative mortality and myocardial infarction during vascular surgery. Their potential in improving perioperative outcomes should be clarified in large randomized controlled trials.

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