CLINICAL PRACTICE GUIDELINE: SYSTEMATIC REVIEW

Perioperative Beta Blockade in Noncardiac Surgery: A Systematic Review for the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

A Report of the American College of Cardiology/American Heart Association
Task Force on Practice Guidelines

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OBJECTIVE To review the literature systematically to determine whether initiation of beta blockade within 45 days prior to noncardiac surgery reduces 30-day cardiovascular morbidity and mortality rates.

METHODS PubMed (up to April 2013), Embase (up to April 2013), Cochrane Central Register of Controlled Trials (up to March 2013), and conference abstracts (January 2011 to April 2013) were searched for randomized controlled trials (RCTs) and cohort studies comparing perioperative beta blockade with inactive control during noncardiac surgery. Pooled relative risks (RRs) were calculated under the random-effects model. We conducted subgroup analyses to assess how the DECREASE-I (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography), DECREASE-IV, and POISE-1 (Perioperative Ischemic Evaluation) trials influenced our conclusions.

RESULTS We identified 17 studies, of which 16 were RCTs (12,043 participants) and 1 was a cohort study (348 participants). Aside from the DECREASE trials, all other RCTs initiated beta blockade within 1 day or less prior to surgery. Among RCTs, beta blockade decreased nonfatal myocardial infarction (MI) (RR: 0.69; 95% confidence interval [CI]: 0.58 to 0.82) but increased nonfatal stroke (RR: 1.76; 95% CI:1.07 to 2.91), hypotension (RR: 1.47; 95% CI: 1.34 to 1.60), and bradycardia (RR: 2.61; 95% CI: 2.18 to 3.12). These findings were qualitatively unchanged after the DECREASE and POISE-1 trials were excluded. Effects on mortality rate differed significantly between the DECREASE trials and other trials. Beta blockers were associated with a trend toward reduced all-cause mortality rate in the DECREASE trials (RR: 0.42; 95% CI: 0.15 to 1.22) but with increased all-cause mortality rate in other trials (RR: 1.30; 95% CI: 1.03 to 1.64). Beta blockers reduced cardiovascular mortality rate in the DECREASE trials (RR:0.17; 95% CI: 0.05 to 0.64) but were associated with trends toward increased cardiovascular mortality rate in other trials (RR: 1.25; 95% CI: 0.92 to 1.71). These differences were qualitatively unchanged after the POISE-1 trial was excluded.

CONCLUSIONS Perioperative beta blockade started within 1 day or less before noncardiac surgery prevents nonfatal MI but increases risks of stroke, death, hypotension, and bradycardia. Without the controversial DECREASE studies, there are insufficient data on beta blockade started 2 or more days prior to surgery. Multicenter RCTs are needed to address this knowledge gap.

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INTRODUCTION

Perioperative cardiac complications are an important concern for the 230 million individuals who undergo surgery worldwide every year (1). After surgery, 2% of these patients suffer major cardiac complications (2), and 8% show evidence of significant myocardial injury (3). Perioperative beta blockade showed early promise as a means of preventing these complications, with enthusiasm driven by promising results in 2 RCTs (4,5).

Consequently, perioperative beta blockade was recommended for a fairly broad spectrum of surgical patients in initial versions of the American College of Cardiology (ACC)/American Heart Association (AHA) clinical practice guidelines (CPGs). For example, among patients with untreated hypertension, known coronary artery disease, or cardiac risk factors, perioperative beta blockade received a Class II recommendation in 1996 (6) and a Class IIa recommendation in 2002 (7). Nonetheless, for several reasons, the strength and scope of these recommendations diminished over successive iterations of these CPGs (8-10). First, subsequent moderate-sized RCTs failed to demonstrate significant benefits from beta blockade (11,12). Second, in the POISE-1 trial of almost 9000 participants, it was found that although perioperative beta blockade prevented perioperative MI, this benefit was accompanied by increased rates of death, stroke, hypotension, and bradycardia (13). Although the POISE-1 trial has been criticized for starting long-acting beta blockers at high doses shortly prior to surgery (14), its results highlighted

the potential for important risks from perioperative beta blockade. Third, the validity of work led by Poldermans, including 2 influential perioperative beta-blockade RCTs (5,15), has been scrutinized because of concerns about scientific misconduct (16,17). Consequently, it has been suggested that CPGs re-evaluate and potentially exclude these data from the evidence base used to inform recommendations about perioperative beta blockade (18).

On the basis of the "American College of Cardiology Foundation/AHA clinical practice guideline methodology summit report" (19), the ACC/AHA Task Force on Practice Guidelines (Task Force) recognized the need for an objective review of available RCTs and observational studies by an independent Evidence Review Committee (ERC) to inform any recommendations about perioperative beta blockade in the 2014 ACC/AHA perioperative CPG (20). The ERC undertook this review to address a specific clinical question framed by the writing committee for this CPG (with input from the ERC): *What is the evidence that initiating beta blockade within 45 days prior to noncardiac surgery reduces perioperative cardiovascular morbidity and mortality within 30 days after surgery?* Our objectives were to summarize evidence relevant to this question and assess the degree to which studies led by Poldermans influenced our overall conclusions.

METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (21) and to recommendations of the "American College of Cardiology Foundation/AHA clinical practice guideline methodology summit report" (19).

Eligibility Criteria

We included RCTs or cohort studies comparing perioperative beta blockade against inactive control, including placebo, in adults (≥18 years of age) undergoing noncardiac surgery. Otherwise eligible cohort studies were included only if the sample size exceeded 100 participants. Perioperative beta blockade was defined as beta-blocker therapy (except sotalol) started at any point between 45 days prior to surgery and 24 hours after surgery. Treatment also had to be continued until at least hospital discharge or the second day after surgery (whichever occurred first). This minimum duration of postoperative therapy was specified because perioperative MI generally occurs during the first 3 days after surgery (22). Otherwise eligible studies also had to report any of 4 prespecified outcomes: MI, all-cause death, cardiovascular death, or stroke.

Search Strategy

Eligible studies were identified using PubMed (up to April 2013), Embase (up to April 2013), and the Cochrane

Central Register of Controlled Trials (up to March 2013). The search strategies used within these databases are presented in the Online Data Supplement 1 to 3. The ERC also hand-searched abstracts from conferences of specific scientific societies (ACC, AHA, American Society of Anesthesiologists, European Society of Anesthesiology, European Society of Cardiology, International Anesthesia Research Society, and Society of Cardiovascular Anesthesiologists) occurring between January 2011 and April 2013 and searched bibliographies of previous relevant systematic reviews (18,23–26). No language restrictions were applied. Unpublished trials were not sought, but when necessary, we contacted authors of included studies for additional data.

Methods of Review

Teams of paired reviewers (i.e., D. Duncan and C. Nkonde-Price, S. S. Virani and J. B. Washam) independently performed study eligibility screening, study quality evaluation, and data abstraction. Abstracted data were entered on previously pilot-tested forms developed within the DistillerSR (Evidence Partners Inc., Ottawa, Ontario, Canada) and Indico Clinical Guideline Platform (Indico Solutions Pty. Ltd., Melbourne, Victoria, Australia) web-based software platforms. Disagreements were resolved through consensus and, where necessary, involvement of a third reviewer (D. N. Wijeysundera). For each included study, the ERC abstracted details on participant eligibility criteria, participant number, surgery types, beta-blocker treatment regimen, participant characteristics (i.e., age, sex, coronary artery disease, prior MI, current angina), duration of follow-up, and surveillance protocols for postoperative MI. In addition, the proportion of participants receiving long-term beta-blocker treatment before recruitment was reported for any included RCT. We documented the definition and event rates for the following outcomes occurring during or within 30 days after surgery: nonfatal MI, all-cause death, cardiovascular death, acute stroke, heart failure, significant hypotension, and significant bradycardia. Overall study quality was assessed on the basis of risk of bias, relevance to the study question, and fidelity of implementation (19). With regard to evaluation of risk of bias, we used the Cochrane Collaboration Risk of Bias Tool for RCTs (27) and the Newcastle-Ottawa Scale for cohort studies (28). A RCT was assigned an *overall* rating of low-to-intermediate risk of bias if the trial was not deemed to be at high risk of bias for any assessed domain of study quality.

Statistical Analysis

Analyses were performed in STATA Version 13 statistical software (StataCorp LP, College Station, Texas). Statistical significance was defined by a 2-tailed p value <0.05, and no adjustment was made for multiple comparisons. Given the major methodological differences between RCTs and cohort studies, the 2 study types were analyzed separately. Initially, we assessed both clinical and statistical heterogeneity across the included studies. Statistical heterogeneity was characterized with the I^2 statistic (29), which describes the proportion of total variation explained by between-study variation instead of chance. Higher I^2 statistic values imply more heterogeneity between studies than would be expected by chance alone. The random-effects model of DerSimonian and Laird was used to calculate pooled RRs with 95% CIs (30).

We conducted several prespecified subgroup analyses to examine the influence of the DECREASE and POISE-1 trials on the overall results (5,13,15). First, treatment effects within the DECREASE trials were compared against pooled effects in the remaining RCTs. Second, after excluding the DECREASE trials (i.e., DECREASE-I and DECREASE-IV) from the analysis, we compared treatment effects in the POISE-1 trial against pooled effects in the remaining trials. The rationale for this second subgroup analysis was to determine whether there was any signal of a treatment effect independent of the single large RCT (i.e., the POISE-1 trial) in the meta-analysis. Random-effects meta-regression was used to test for statistical significance of any subgroup effects. The ERC visually inspected funnel plots to assess for possible publication bias (31) and also used Egger's, Harbord's, and Peters' tests to formally test for any funnel plot asymmetry (31-33).

RESULTS

Please see the Online Data Supplement for more information.

We identified 17 eligible studies: 16 RCTs and 1 cohort study (Online Data Supplement 7). The 16 RCTs contributed data from 12,043 participants (4,5,11-13,15,34-42), and the cohort study contributed relevant data from 348 participants (43). The characteristics of participants, surgical procedures, and perioperative beta-blockade protocols in the included studies are presented in Tables 1 and 2. Except for the DECREASE-I and DECREASE-IV trials (5,15), all RCTs began beta-blocker therapy within 1 day or less prior to surgery.

Of the 16 included RCTs, 8 trials had a low-to-intermediate overall risk of bias (Online Data Supplement 4) (4,11-13,38,40,42,44). Fourteen trials showed intermediate-to-high relevance with regard to their study populations, interventions, and outcomes measures (4,5,11-13,15,35-42), and 10 trials assessed interventions that were implemented with intermediate-to-high fidelity (Online Data Supplement 4) (4,5,11-13,37,38,40-42). When assessed with the Newcastle-Ottawa Scale, the included cohort study did not rate consistently well across all study quality domains (Online Data Supplement 5).

Nonfatal MI

Sixteen RCTs reported effects on nonfatal MI among 11963 participants (Figure 1). Perioperative beta blockade caused an overall moderate reduction in nonfatal MI, based on a RR of 0.68 (95% CI: 0.57 to 0.81; p<0.001) with no measurable statistical heterogeneity (I²=0%). Nonetheless, differences in treatment effects between the DECREASE trials and the remaining RCTs bordered on statistical significance (p=0.08). When the DECREASE trials were excluded (Figure 2), the pooled RR remained essentially unchanged at 0.72 (95% CI: 0.59 to 0.86), with no qualitative differences in effects observed between the POISE-1 trial and the remaining RCTs.

Nonfatal Stroke

Nonfatal strokes were reported by 10 trials that included 11 611 participants (Figure 3). Beta blockade caused a significant overall increase in the risk of nonfatal stroke (RR: 1.79; 95% CI: 1.09 to 2.95; p=0.02), with no measurable statistical heterogeneity (I²=0%). When DECREASE trials were excluded (Figure 4), the effects in the POISE-1 trial (RR: 1.93; 95% CI: 1.01 to 3.68) were qualitatively similar to those in the remaining trials (RR: 1.72; 95% CI: 0.67 to 4.40).

All-Cause Death

Sixteen trials reported effects on rates of all-cause death among 11,963 participants (Figure 5). There was a statistically significant subgroup difference (p=0.02) between the DECREASE trials and the remaining RCTs. Among the DECREASE trials, beta blockade was associated with a trend toward a reduced risk of all-cause death (RR: 0.42; 95% CI: 0.15 to 1.22; p=0.11), whereas in the remaining trials, beta blockers significantly increased the risk of all-cause death (RR: 1.30; 95% CI: 1.03 to 1.63; p=0.03), with no measurable statistical heterogeneity (I²=0%). When the DECREASE trials were excluded (Figure 6), effects in the POISE-1 trial (RR: 1.33; 95% CI: 1.03 to 1.73) were qualitatively similar to effects in the remaining trials (RR: 1.17; 95% CI: 0.70 to 1.94).

Cardiovascular Death

Cardiovascular deaths were reported by 13 trials encompassing 11,607 participants. There was statistically significant evidence of a subgroup difference (p=0.004) between the DECREASE trials and the remaining RCTs (Online Data Supplement 8). Beta blockers significantly reduced the risk of cardiovascular death in the DECREASE trials (RR: 0.17; 95% CI: 0.05 to 0.64; p=0.008), whereas they showed a trend toward an increased risk of cardiovascular death (RR: 1.25; 95% CI: 0.92 to 1.71; p=0.16) in the remaining trials.

Perioperative Adverse Effects

Eight trials reported effects on heart failure among 11,378 participants (Online Data Supplement 9). Overall, beta blockade had no statistically significant effect on perioperative heart failure (RR: 1.15; 95% CI: 0.91 to 1.45; p=0.23), without measurable statistical heterogeneity (I²=0%). Ten trials reported effects on perioperative hypotension or bradycardia, albeit with highly variable definitions across studies (Online Data Supplement 6) (4,11-13,35-38,41,44). Notably, the DECREASE-I and DECREASE-IV trials did not separately report rates of hypotension or bradycardia (5,15). Nine trials reported effects on hypotension among 10,448 participants (Online Data Supplement 10). Overall, beta blockers significantly increased the risk of perioperative hypotension, with no qualitative differences in effects seen between the POISE-1 trial (RR: 1.55; 95% CI: 1.38 to 1.74) and other studies (pooled RR: 1.37; 95% CI: 1.20 to 1.56). Significant bradycardia was reported by 9 trials encompassing 10,458 participants (Online Data Supplement 11). Risks of bradycardia were significantly increased among patients receiving beta blockers, with no qualitative differences in effects seen between the POISE-1 trial (RR: 2.74; 95% CI: 2.19 to 3.43) and other studies (pooled RR: 2.41; 95% CI: 1.75 to 3.32).

Post Hoc Analysis

In a post hoc analysis, the ERC excluded the DECREASE trials and used pooled RRs from the remaining trials to calculate numbers of avoided or excess nonfatal MIs, all-cause deaths, and nonfatal strokes per 1,000 population. Within a hypothetical population with a baseline 6% risk of nonfatal MI, 2% baseline risk of 30-day all-cause death, and 0.5% baseline risk of nonfatal stroke, perioperative beta blockade leads to 17 fewer nonfatal MIs, 6 excess all-cause deaths, and 4 excess nonfatal strokes in every 1000 treated patients.

Publication Bias

Visual inspection of funnel plots showed no clear evidence of publication bias with regard to effects on nonfatal MI, nonfatal stroke, heart failure, hypotension, and bradycardia. These plots did suggest some publication bias with regard to all-cause and cardiovascular death. Specifically, some trials showing an increased mortality rate with beta blockade may not have been published. Nonetheless, formal testing did not reveal any statistically significant evidence of publication bias for any assessed outcomes.

DISCUSSION

This systematic review found the literature to be consistent with regard to effects of perioperative beta blockade

on MI, stroke, hypotension, and bradycardia after noncardiac surgery. Previous trials consistently demonstrated that rates of nonfatal MI were reduced with beta blockade. Although there may be some differences between the DECREASE trials and other trials, these differences relate only to the *magnitude* of benefit. Whereas the DECREASE trials found larger and, arguably, somewhat implausible effect sizes, with RR reductions ranging from 60% to 95% (5,15), other trials had a more realistic, moderate pooled effect size. Available data also consistently show increased risks of stroke, hypotension, and bradycardia with perioperative beta blockade. These findings are noteworthy because the increased risk of these complications in the POISE-1 trial has often been attributed to the trial's use of high-dose, long-acting metoprolol (45). The ERC instead found that preceding trials, despite using different dosing regimens, demonstrated a consistent signal of increased stroke (albeit statistically nonsignificant), as well as significant increases in risks for hypotension and bradycardia. Thus, the increased risks of these complications appear to be a more general concern with perioperative beta blockade, as opposed to one associated only with a specific drug-dosing regimen. Notably, there are very few data on stroke, hypotension, and bradycardia from the DECREASE trials, with the only reported events being 7 strokes in the DECREASE-IV trial (15).

The major discrepancy between the DECREASE trials and the other RCTs relates to effects on all-cause and cardiovascular death. The DECREASE trials demonstrated very large reductions in mortality rate, with RR reductions ranging from 58% to 91%. Again, such large benefits attributable to a single intervention are, arguably, somewhat implausible. Conversely, the remaining RCTs found a significant overall increase in mortality rate. Although this pooled estimate was dominated by the POISE-1 trial, which accounted for 80% of the relevant underlying data, it is noteworthy that even when data from the POISE-1 trial were excluded, the pooled effect in the remaining studies was qualitatively similar. Thus, data at the time of publication suggest that the increased mortality rate observed in the POISE-1 trial may not be unique to that specific dosing protocol.

Influence of the DECREASE Trials

The DECREASE trials do influence the overall conclusions of our review, but largely with regard to effects on mortality rates. Specifically, in the absence of the DECREASE trials, other RCTs indicate that beta blockade significantly reduces the risk of postoperative MI but at the cost of increased rates of stroke, hypotension, bradycardia, and death. The major change induced by inclusion of the DECREASE trials in the meta-analysis is

a shift of the pooled effect on death to a null effect. Nonetheless, exclusion of these trials has major implications for the *generalizability* of current RCTs to clinical practice. Aside from the DECREASE trials, all RCTs initiated beta blockade no more than 1 day prior to surgery. Notably, several cohort studies have shown that shorter durations ($\leq$7 days) of preoperative beta-blocker therapy are associated with worse outcomes than are longer durations of preoperative therapy (46-48). Although some authors have emphasized the importance of both longer durations of therapy prior to surgery and preoperative dose-titration to an optimal heart rate, the evidence for substantial preoperative modification of beta-blocker dosing in the DECREASE trials is not compelling. Stated otherwise, the vast majority of patients in these studies presented to surgery receiving the same dose of bisoprolol on which they were started. In addition, once the DECREASE trials were excluded, only 4 included RCTs evaluated oral beta blockers aside from metoprolol (4,40,41,44). Importantly, several cohort studies have found metoprolol to be associated with worse outcomes than those seen with more beta-1 selective agents, such as atenolol or bisoprolol (49-53).

Thus, the strength of evidence that a longer duration of preoperative therapy with selective oral beta blockers safely reduces the risk of perioperative MI is entirely dependent on the DECREASE trials. Such reliance on controversial studies points to the need for new, adequately powered RCTs of clinically sensible, perioperative beta-blockade regimens. The ERC proposes that such trials evaluate beta-blockade regimens started at least several days prior to surgery, preferably with more beta-1 selective agents. In light of the consistent signals of increased harm associated with beta blockade initiated very close to surgery, the onus lies with the perioperative medical community to demonstrate that such alternative dosing regimens are safe and efficacious with regard to prevention of perioperative MI.

Limitations

The present systematic review also has several important limitations. First, exclusion of the DECREASE-I, DECREASE-IV, and POISE-1 trials leaves few data from which to make firm conclusions about the efficacy and safety of perioperative beta blockade. For example, none of the pooled effects on MI, death, and stroke were statistically significant within this smaller subgroup of studies. Consequently, comparison of this subgroup with the POISE-1 trial focused simply on qualitative comparisons of pooled effects. Second, as with most systematic reviews, our review is limited by the possibility of

unpublished data and heterogeneity of outcome definitions used in the original studies. Third, the included trials did not systematically report treatment effects in clinically sensible subgroups, such as strata defined by Revised Cardiac Risk Index scores (54). Several prior observational studies have suggested that the treatment effects of perioperative beta blockade vary across these strata, with benefits confined to high-risk individuals who have at least 2 to 3 clinical risk factors (50,55). Further exploration of such subgroup differences within the context of RCTs will entail an individual patient data meta-analysis. Fourth, we did not adjust for multiple comparisons when conducting subgroup analyses. The results of these subgroup analyses should therefore be viewed as hypothesis generating as opposed to definitive.

Fifth, in spite of an extensive literature search for observational studies, only 1 cohort study was included in this systematic review (43). Despite still informing an overall understanding of the risks and benefits of beta blockade in noncardiac surgery, several potentially relevant observational studies did not meet our inclusion criteria (50,55,56). For example, a 2005 multicenter cohort study did not capture preadmission beta-blocker use (55). Thus, the investigators could not differentiate between ongoing, long-term beta-blocker use and new perioperative beta-blocker use for cardiac risk reduction. Similarly, a 2010 single-center study also included patients undergoing cardiac surgery and grouped all individuals receiving beta blockers prior to surgery into a single category, regardless of the duration of preoperative therapy (56). Most recently, a 2013 multicenter cohort study defined perioperative beta blockade on the basis of on any relevant prescription on either the day of surgery or the subsequent day (50). Nonetheless, the study did not analyze the dose or duration of inpatient beta-blocker prescriptions; hence, it did not meet our criterion for minimum duration of postoperative beta-blocker therapy. Additionally, the data sources in all 3 studies could not differentiate between beta blockade for *preventing* cardiac events and beta blockade for *treating* postoperative complications (e.g., myocardial ischemia). The importance of distinguishing between prophylactic and therapeutic interventions is underscored by the observation that, in some RCTs of perioperative beta blockade, 7% to 10% of participants in the control arm still received open-label beta blockers, possibly to treat new postoperative complications (4,12).

Conclusions

In summary, this systematic review found that perioperative beta blockade started within 1 day or less before noncardiac surgery helps prevent nonfatal MI but at the cost of increased risks of stroke, death, hypotension, and bradycardia. The DECREASE-I and DECREASE-IV trials differed from other trials with regard to design in that they are the only RCTs that assessed beta blockade started 2 or more days before surgery. Their results differed significantly from other RCTs in that perioperative mortality rate was decreased, as opposed to increased, with beta-blocker therapy. In the absence of these controversial studies, there are insufficient robust data on the efficacy and safety of perioperative beta-blocker regimens that use agents aside from metoprolol or initiate treatment 2 to 45 days prior to surgery.

PRESIDENTS AND STAFF

| TABLE 1 | Summary of Included Studies |

Study (Year)	N	Inclusion Criteria	Exclusion Criteria	Types of Surgery	Long-Term Preoperative Beta-Blocker Therapy	Participant Characteristics
Randomized Controlled Trials						
Mangano et al. (1996) (4) 8929262	200	Known CAD or ≥2 risk factors (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	Pacemaker dependency, resting ECG abnormalities (left bundle-branch block, marked ST-T abnormalities)	Elective vascular (41%), intra-abdominal (21%), orthopedic (14%), neurosurgical (9%), or other (16%) procedures	13%	Mean age 67.5 y, 39% with known CAD
Jakobsen et al. (1997) (34) 9327317	100	Pts undergoing thoracotomy for lung resection with no known current or previous cardiovascular disease	NR	Intrathoracic (100%) procedures	NR	66% males, mean age 60.4 y
Bayliff et al. (1999) (35) 10086546	99	Pts >18 y of age undergoing major thoracic operation	Prior beta-blocker use, asthma, HF, heart block, supraventricular tachyarrhythmias, prior specific drug use (digoxin, quinidine, procainamide, amiodarone, diltiazem, verapamil)	Intrathoracic (100%) procedures	0%	62% males, mean age 62.5 y, 6% with prior MI, 5% with current angina
DECREASE-I (1999) (5) 10588963	112	Pts with ≥1 cardiac risk factor (>70 y of age, angina; prior MI, HF, diabetes mellitus, limited exercise capacity, ventricular arrhythmias) and positive result on dobutamine stress echocardiography.	Prior beta-blocker use, asthma, very high-risk dobutamine stress echocardiography result (extensive wall-motion abnormalities, strong evidence of left main or severe 3-vessel CAD)	Major vascular (100%) procedures	0%	87% males, mean age 67.5 y, 100% with known CAD, 52% with prior MI, 32% with current angina
Raby et al. (1999) (36) 10071990	26	Pts with preoperative myocardial ischemia detected by 24-h ECG monitoring performed within 1–12 d before surgery	Baseline ST-T abnormalities on ECG that preclude accurate interpretation of ECG monitoring for ischemia	Major vascular (100%) procedures	35%	46% males, mean age 68.1 y, 38% with prior MI or current angina
Zaugg et al. (1999)* (44) 10598610	43	Pts ≥65 y of age	Prior beta-blocker use, other prior drugs (beta-adrenergic agonists, glucocorticoids, anticonvulsants), heart block, rhythm other than sinus on ECG, HF, bronchospasm, systemic infection, neurological disorders	Intra-abdominal (81%), orthopedic (7%), and other (12%) procedures	0%	40% males, mean age 74.6 y, 37% with known CAD
Urban et al. (2000) (37) 10825304	107	Pts 50–80 y of age undergoing elective total knee arthroplasty with known CAD or ≥1 risk factor (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	Specific ECG abnormalities (heart block, bundle-branch block, atrial arrhythmias, LV hypertrophy with repolarization abnormalities), LVEF <30%, symptomatic mitral or aortic valvular disease, bronchospasm	Orthopedic (100%) procedures	28%	Mean age 69.5 y, 17% with prior MI, 31% with current angina
POBBLE (2005) (38) 15874923	103	Pts undergoing major elective infrarenal vascular surgery under general anesthesia	Prior MI in past 2 y, unstable angina, positive dobutamine stress test, prior beta-blocker use, asthma, aortic stenosis, heart rate ≤45 beats/min, systolic BP <100 mm Hg	Major vascular procedures (100%)	0%	78% males, median age 73 y

TABLE 1   Continued

Study (Year)	N	Inclusion Criteria	Exclusion Criteria	Types of Surgery	Long-Term Preoperative Beta-Blocker Therapy	Participant Characteristics
DIPOM (2006) (11) 16793810	921	Pts with diabetes mellitus >39 y of age undergoing noncardiac surgery with expected duration >1 h	Long-term beta-blocker use, conditions indicating beta blocker treatment, severe HF, heart block	Orthopedic (33%), intra-abdominal (28%), neurosurgical (8%), vascular (7%), gynecological (5%), and other (19%) procedures	0%	59% males, mean age 64.9 y, 8% with prior MI, 11% with current angina
Lai et al. (2006) (39) 16687084	60	Pts ≥65 y of age undergoing esophagectomy for esophageal cancer with no known prior CAD	Prior beta-blocker use, heart rate ≤55 beats/min, systolic BP ≤100 mm Hg, heart block	Intrathoracic (100%) procedures	0%	82% males, median ages 66 y (beta blocker arm) and 67 y (control arm),
MaVS (2006) (12) 17070177	496	Pts (ASA-PS Class ≤3) undergoing major vascular (abdominal aortic repair, infra-inguinal, or axillo-femoral bypass) surgery	Long-term beta-blocker use, current amiodarone use, reactive airways disease, HF, heart block	Major vascular (100%) procedures	0%	76% males, mean age 66.1 y, 14% with prior MI, 9% with current angina
Neary et al. (2006) (40) 16764198	38	Pts undergoing emergency surgery with ≥1 of the following criteria: CAD, cerebrovascular disease (prior stroke or TIA), ≥2 minor risk criteria (≥65 y of age, hypertension, smoker, diabetes mellitus, hypercholesterolemia)	Prior beta-blocker use, heart rate <55 beats/min, heart block, chronic obstructive airway disease, asthma, cardiovascular collapse, uncorrected hypovolemia	Intra-abdominal (29%), amputation (24%), major vascular (21%), orthopedic (16%), and other (10%) procedures	0%	NR
BBSA (2007) (41) 17585213	219	Pts undergoing surgery with spinal anesthesia with known CAD or ≥2 risk factors (≥65 y of age, hypertension, current smoker, elevated cholesterol level, diabetes mellitus)	Prior beta-blocker use, significant HF, heart block, severe asthma, left bundle-branch block	Orthopedic (67%), urologic (25%), and other (8%) procedures	0%	55% males, mean age 70.0 y, 8% with prior MI, 6% with current angina
POISE-1 (2008) (13) 18479744	8,351	Pts ≥45 y of age and ≥1 of the following criteria: CAD, PAD, stroke, hospitalization for HF within past 3 y, major vascular surgery, or ≥3 minor risk factors (HF, TIA, diabetes mellitus, renal insufficiency, age >70 y, nonelective surgery, intrathoracic surgery, or intraperitoneal surgery)	Prior beta-blocker use, verapamil use, heart rate <50 beats/min, heart block, asthma, CABG surgery in previous 5 y with no subsequent ischemia, low-risk surgery	Vascular (41%), intraperitoneal (22%), orthopedic (21%), and other (16%) procedures	0%	63% males, mean age 69.0 y, 43% with known CAD
Yang et al. (2008) (42) 18953854	102	Pts ≥45 y of age with ≥1 of the following criteria: CAD, PAD, stroke, hospitalization for HF in prior 3 y, or ≥3 minor risk factors (HF, diabetes mellitus, ≥65 y of age, hypertension, hypercholesterolemia, smoker, intrathoracic surgery, or intraperitoneal surgery)	Prior beta-blocker use, heart rate <50 beats/min, cardiac pacemaker, heart block, asthma, chronic obstructive pulmonary disease	Intra-abdominal and intrathoracic procedures	0%	59% males, mean age 71.0 y
DECREASE-IV (2009) (15) 19474688	1,066	Pts ≥40 y of age undergoing elective noncardiovascular surgery with an estimated 1%–6% perioperative cardiovascular risk	Current use, or contraindication to use, of beta blockers or statins	General surgical (39%), urologic (19%), orthopedic (16%), ear-nose-throat (12%), and other surgical (14%) procedures	0%	60% males, mean age 65.4 y, 6% with current angina, 5% with previous MI

TABLE 1	Continued

Study (Year)	N	Inclusion Criteria	Exclusion Criteria	Types of Surgery	Long-Term Preoperative Beta-Blocker Therapy	Participant Characteristics
Cohort Studies						
Matyal et al. (2008)†(43) 18503921	348	Pts undergoing supra- and infrainguinal vascular surgery	NR	Major vascular (100%) procedures	0%†	60% males

*Information on 2 of the study arms (preoperative/postoperative atenolol *versus* no beta-blocker therapy). The third study arm (intraoperative atenolol) did not meet the review definition for eligible perioperative beta-blockade.
†Only data on the subgroup of 348 pts who were not previously receiving preoperative long-term beta-blocker therapy.

 ASA-PS indicates American Society of Anesthesiologists Physical Status; BBSA, Beta Blocker in Spinal Anesthesia; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; ECG, electrocardiogram; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; pts, patients; and TIA, transient ischemic attack.

TABLE 2	Perioperative Beta-Blocker Regimens, Duration of Follow-Up, and Comparison Arms in Included Studies

| Study (Year)	Beta-Blocker Type	Perioperative Beta-Blocker Regimen	Preoperative Beta-Blocker Dose-Titration	Duration of Postoperative Treatment	Control Arm	Routine Surveillance for Postoperative MI	Duration of Postoperative Follow-Up
Randomized Controlled Trials							
Mangano et al. (1996) (4) 8929262	Atenolol	IV atenolol 5-10 mg immediately prior to surgery, and oral atenolol 50-100 mg once daily for up to 7 d after surgery	None	7 d or hospital discharge	Placebo	Yes	2 y
Jakobsen et al. (1997) (34) 9327317	Metoprolol tartrate	Oral metoprolol 100 mg 90 min prior to surgery, and continued once daily for 4–10 d after surgery	None	4–10 d	Placebo	No	4–10 d
Bayliff et al. (1999) (35) 10086546	Propranolol	Oral propranolol 10 mg started prior to surgery (timing not defined) and continued every 6 h for 5 d after surgery	None	5 d	Placebo	No	Hospital discharge
DECREASE-I (1999) (5) 10588963	Bisoprolol	Oral bisoprolol 5-10 mg once daily starting at least 7 d prior to surgery, and continued for 30 d after surgery	Yes-titration occurred over ≥7 (average 37) d prior to surgery. In 75% of pts, the starting dose was *not* changed.	30 d	No beta-blocker therapy	Yes	30 d
Raby et al. (1999) (36) 10071990	Esmolol	IV esmolol 100-300 mcg/kg/min starting after surgery and continued for 48 h	None	2 d	Placebo	No	2 d
Zaugg et al. (1999)* (44) 10598610	Atenolol	IV atenolol 5-10 mg 30 min prior to surgery, and continued twice daily for 3 d after surgery	None	3 d	No beta-blocker therapy	Yes	3 d
Urban et al. (2000) (37) 10825304	Esmolol (intraoperative), metoprolol tartrate (postoperative)	IV esmolol 250 mg/h started 1 h after surgery, which was then substituted by oral metoprolol 25-50 mg on the first morning after surgery. Beta-blocker therapy was continued for 2 d after surgery.	None	2 d	No beta-blocker therapy	No	2 d
POBBLE (2005) (38) 15874923	Metoprolol tartrate	Oral metoprolol 25-50 mg twice daily starting 1 d prior to surgery (minimum of 2 preoperative doses) and continued for 7 d after surgery. In addition, IV metoprolol (2-4 mg) was given during surgery.	None	7 d	Placebo	Yes	30 d

TABLE 2	**Continued**						
Study (Year)	Beta-Blocker Type	Perioperative Beta-Blocker Regimen	Preoperative Beta-Blocker Dose-Titration	Duration of Postoperative Treatment	Control Arm	Routine Surveillance for Postoperative MI	Duration of Postoperative Follow-Up
DIPOM (2006) (11) 16793810	Metoprolol succinate	Oral metoprolol 50-100 mg 1 d prior to surgery, and continued once daily for up to 8 d after surgery	None	Hospital discharge	Placebo	Yes	Median 18 mo follow-up (range 6-30 mo)
Lai et al. (2006) (39) 16687084	Metoprolol tartrate	IV metoprolol 0.06-mg/kg boluses started immediately prior to surgery and repeated as needed to achieve target heart rates during surgery. After surgery, this IV regimen was substituted by oral metoprolol 25 mg 3 times daily and continued for 3 d after surgery.	None	3 d	No beta blocker therapy	Yes	3 d
MaVS (2006) (12) 17070177	Metoprolol tartrate	Oral metoprolol 25-100 mg 2 h prior to surgery, and continued twice daily for up to 5 d after surgery	None	5 d or hospital discharge	Placebo	Yes	6 mo
Neary et al. (2006) (40) 16764198	Atenolol	IV atenolol 1.25 mg starting with surgery, and repeated every 30 min up to a maximum of 5 mg. After surgery, oral atenolol 50 mg once daily was continued for 7 d after surgery.	None	7 d	Placebo	Yes	1 y
BBSA (2007) (41) 17585213	Bisoprolol	Oral bisoprolol 5-10 mg 3 h prior to surgery, and continued once daily for up to 10 d after surgery	None	10 d or hospital discharge	Placebo	Yes	1 y
POISE-1 (2008) (13) 18479744	Metoprolol succinate	Oral metoprolol 100 mg within 2-4 h prior to surgery, and oral metoprolol 100-200 mg once daily for 30 d after surgery	None	30 d	Placebo	Yes	30 d
Yang et al. (2008) (42) 18953854	Metoprolol tartrate	Oral metoprolol 25 mg within 2 h prior to surgery, followed by titrated IV (immediately after surgery) and oral (remaining postoperative period) metoprolol for 30 d after surgery	None	30 d	Placebo	Yes	30 d
DECREASE-IV (2009) (15) 19474688	Bisoprolol	Oral bisoprolol 2.5-10 mg once daily started at least 21 d prior to surgery, and continued for 30 d after surgery	Yes-titration occurred over ≥21 (median 34) d prior to surgery. In 99% of pts, the starting dose was *not* changed.	30 d	No beta-blocker therapy	Yes	30 d
Cohort Studies							
Matyal et al. (2008) (43) 18503921	Not defined	Beta-blocker therapy started immediately prior to or after surgery, and continued for up to 3 d after surgery	Not described (observational study)	3 d or hospital discharge	No beta-blocker therapy	No routine surveillance	Hospital discharge

*Information on 2 of the study arms (preoperative/postoperative atenolol *versus* no beta-blocker therapy). The third study arm (intraoperative atenolol) did not meet the review definition for eligible perioperative beta blockade.

BBSA indicates Beta Blocker in Spinal Anesthesia; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; IV, intravenous; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; and pts, patients.
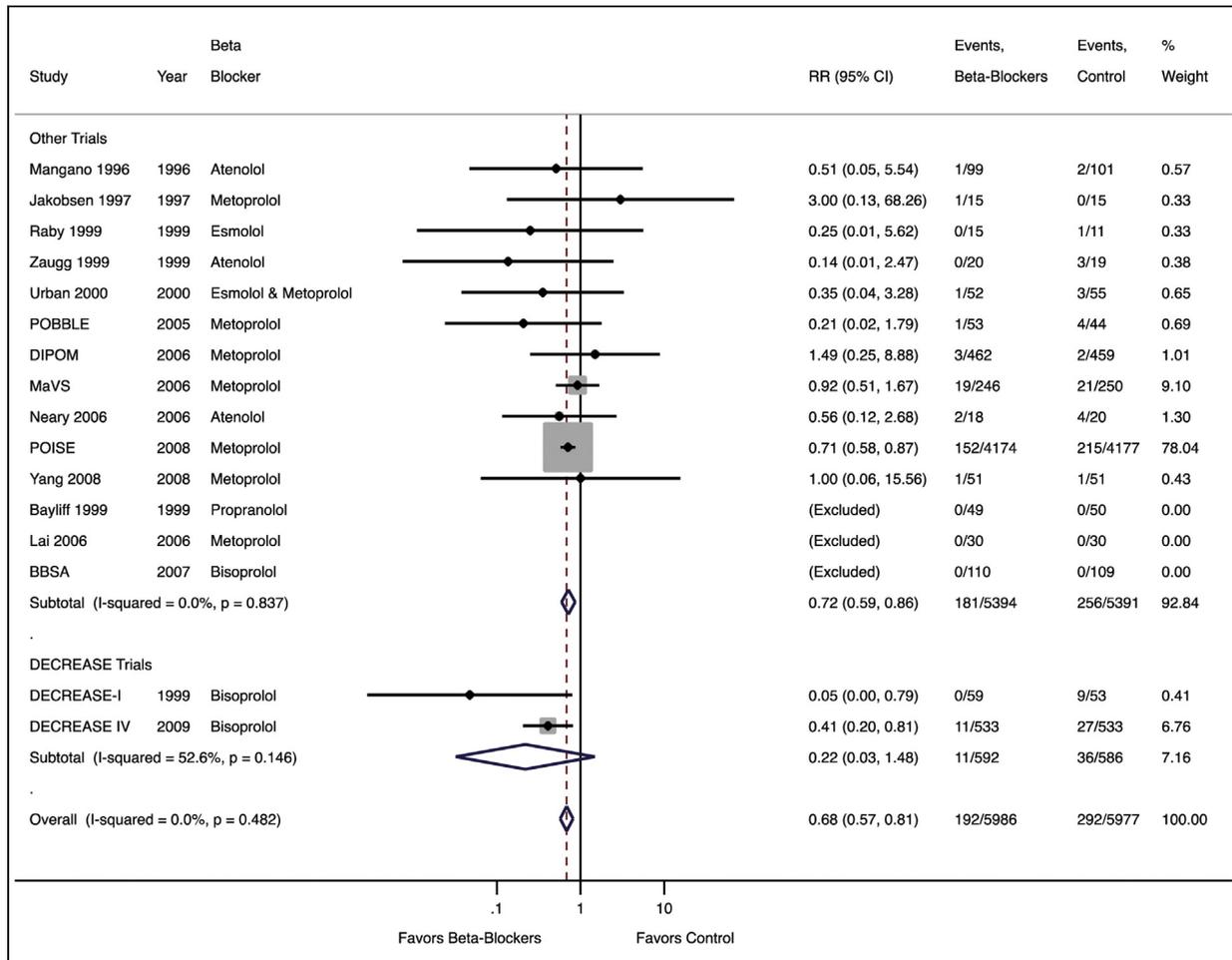
FIGURE 1 Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal MI in RCTs Within Subgroups Defined by DECREASE Trials Versus Other Trials

The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal MIs) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 0.68; 95% CI: 0.57–0.81; p<0.001), as well as the DECREASE subgroup (RR: 0.22; 95% CI: 0.03–1.48; p=0.12) and the subgroup of other trials (RR: 0.72; 95% CI: 0.59–0.86; p<0.001). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis, 52.6% for DECREASE subgroup, and 0% for the subgroup of other trials. Differences between pooled estimates from the 2 subgroups bordered on statistical significance (p=0.08).

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.
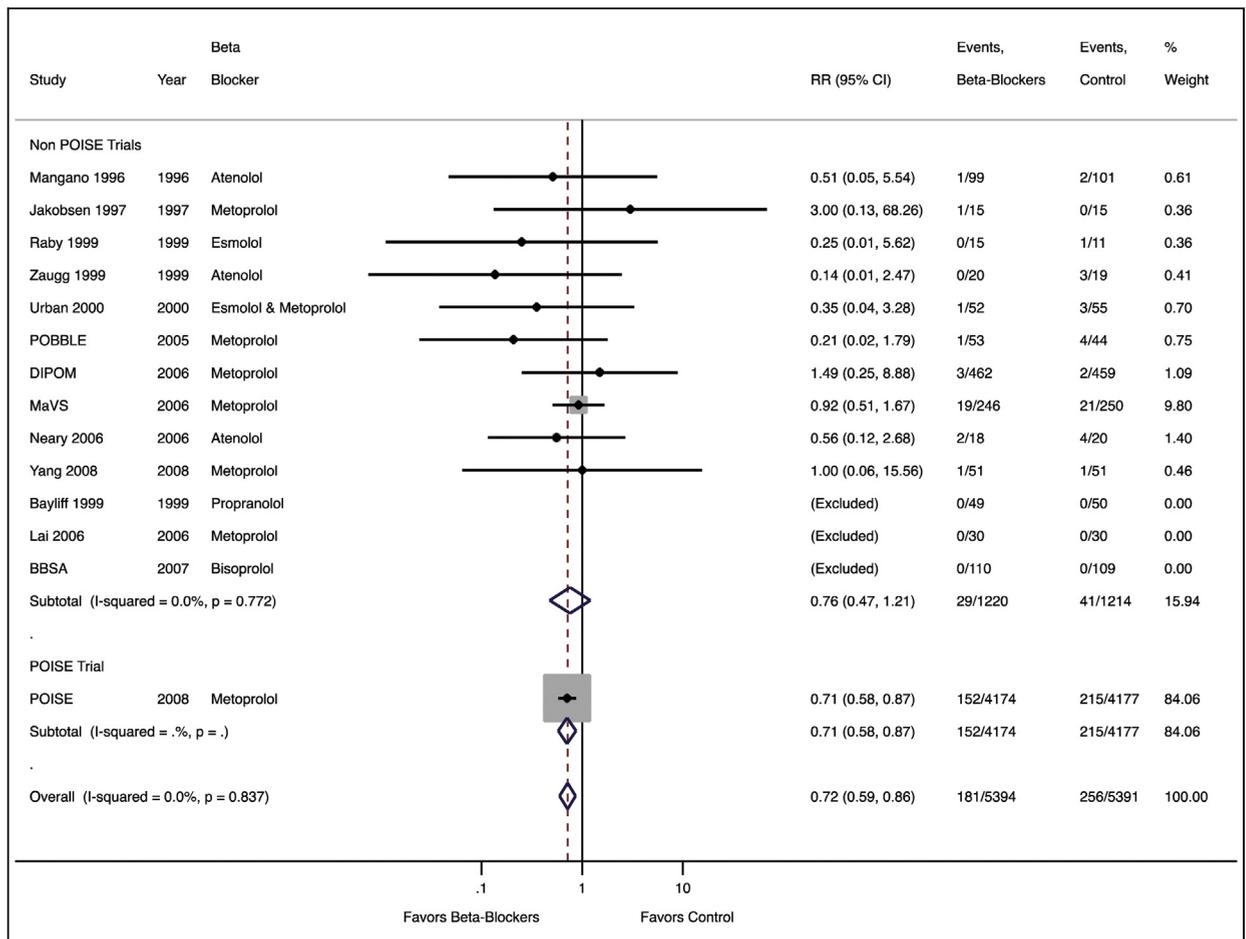
FIGURE 2 **Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal MI in RCTs After Exclusion of the DECREASE Family of Trials, Within Subgroups Defined by the POISE-1 Trial Versus Other Trials**

The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal MIs) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 0.72; 95% CI: 0.59-0.86), as well as the POISE-1 trial (RR: 0.70; 95% CI: 0.57-0.86) and the subgroup of other trials (RR: 0.76; 95% CI: 0.47-1.21). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; MI, myocardial infarction; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.

Study	Year	Beta Blocker	RR (95% CI)	RR (95% CI)	Events, Beta-Blockers	Events, Control	% Weight
Other Trials							
Mangano 1996	1996	Atenolol		4.08 (0.46, 35.87)	4/99	1/101	5.31
DIPOM	2006	Metoprolol		4.97 (0.24, 103.19)	2/462	0/459	2.72
MaVS	2006	Metoprolol		1.27 (0.35, 4.67)	5/246	4/250	14.77
BBSA	2007	Bisoprolol		4.95 (0.24, 102.03)	2/110	0/109	2.74
POISE	2008	Metoprolol		1.93 (1.01, 3.68)	27/4174	14/4177	60.44
Yang 2008	2008	Metoprolol		0.20 (0.01, 4.07)	0/51	2/51	2.76
Bayliff 1999	1999	Propranolol		(Excluded)	0/49	0/50	0.00
POBBLE	2005	Metoprolol		(Excluded)	0/53	0/44	0.00
Lai 2006	2006	Metoprolol		(Excluded)	0/30	0/30	0.00
Subtotal				1.86 (1.09, 3.16)	40/5274	21/5271	88.74
DECREASE Trials							
DECREASE IV	2009	Bisoprolol		1.33 (0.30, 5.93)	4/533	3/533	11.26
Subtotal				1.33 (0.30, 5.93)	4/533	3/533	11.26
Overall				1.79 (1.09, 2.95)	44/5807	24/5804	100.00

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Favors Beta-Blockers   Favors Control

FIGURE 3 **Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal Stroke in RCTs Within Subgroups Defined by DECREASE Trials Versus Other Trials**

The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal strokes) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 1.79; 95% CI: 1.09–2.95; p=0.02), as well as the DECREASE subgroup (RR: 1.33; 95% CI: 0.30–5.93; p=0.71) and the subgroup of other trials (RR: 1.86; 95% CI: 1.09–3.16; p=0.02). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.
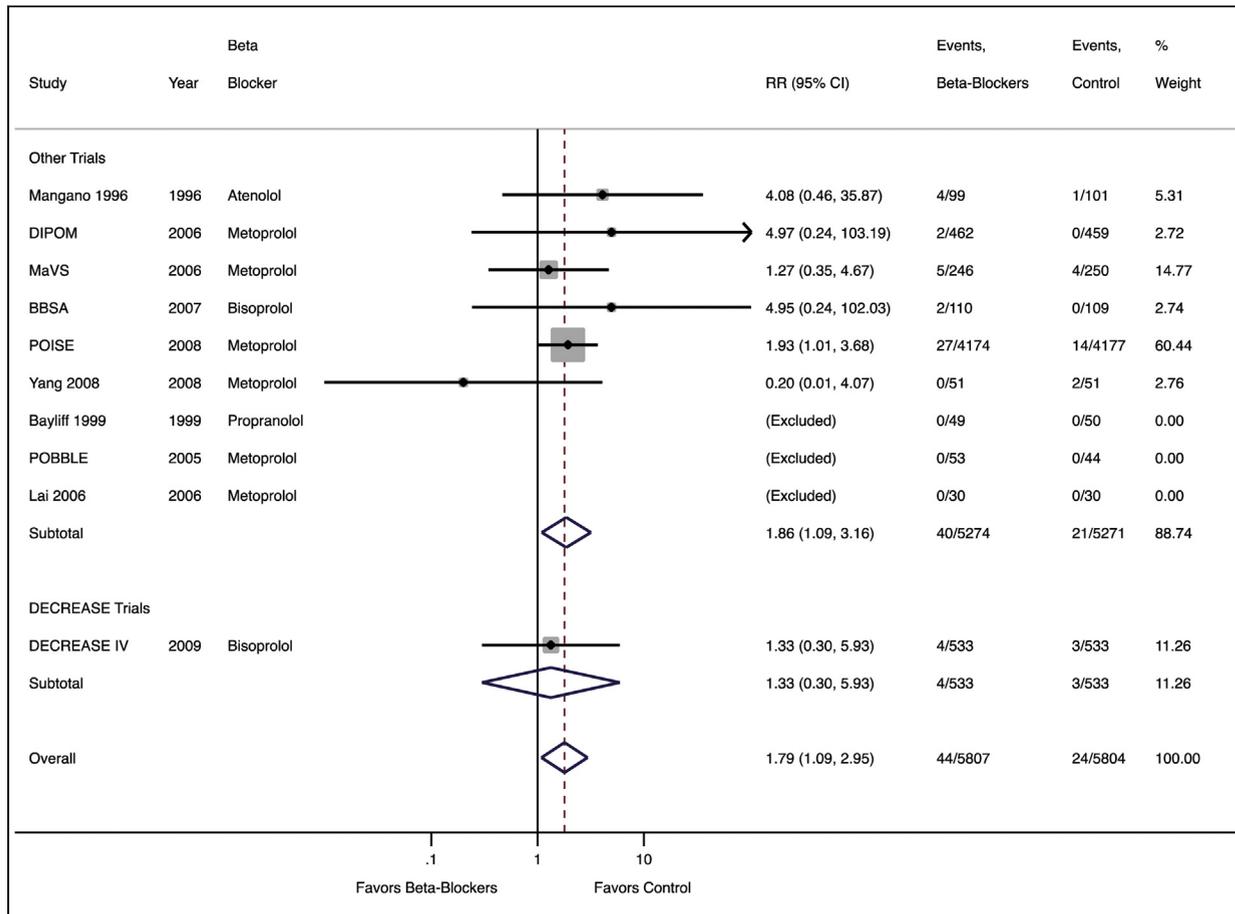
BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.
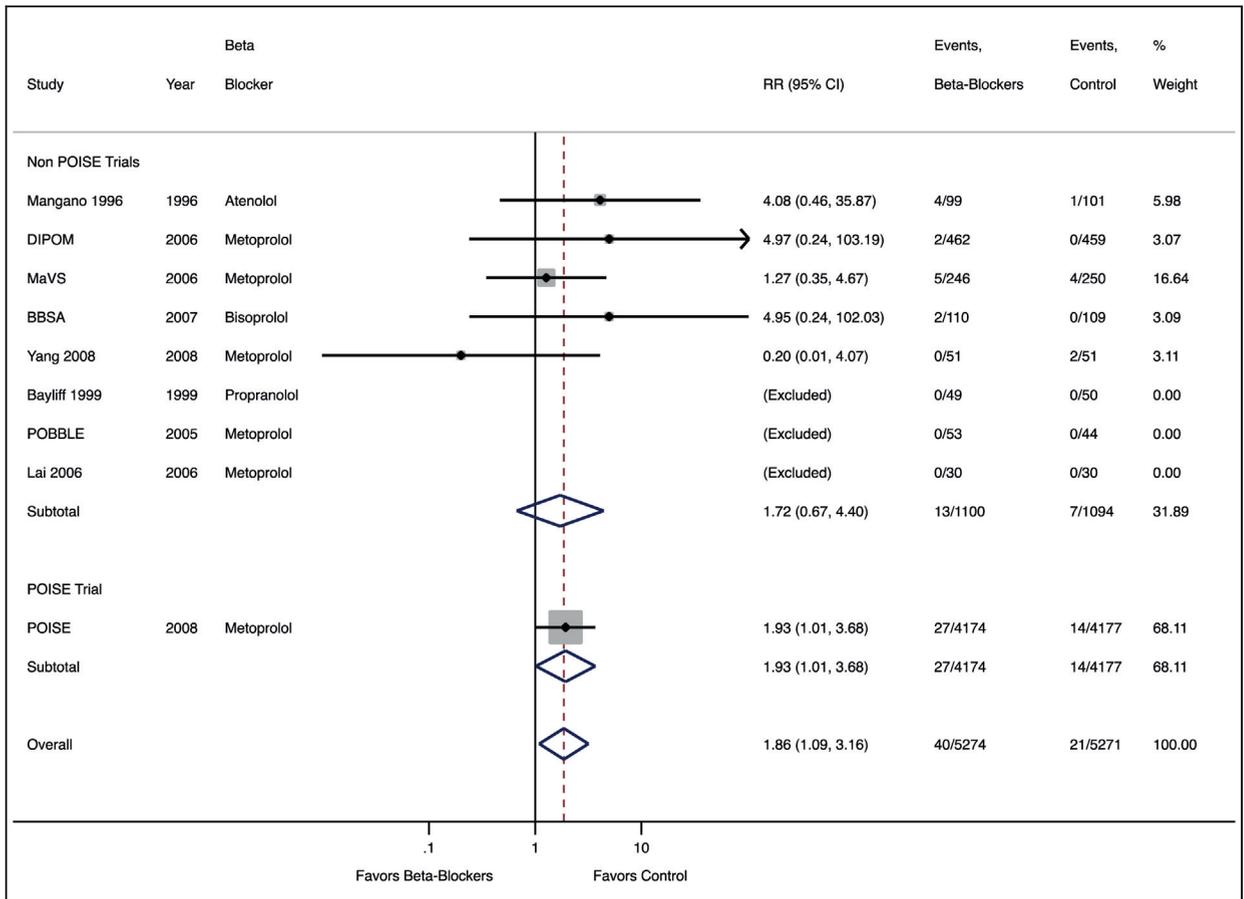
FIGURE 4   Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Nonfatal Stroke in RCTs After Exclusion of the DECREASE Family of Trials, Within Subgroups Defined by the POISE-1 Trial Versus Other Trials

The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer nonfatal strokes) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 1.86; 95% CI: 1.09–3.16), as well as the POISE-1 trial (RR: 1.93; 95% CI: 1.01–3.68) and the subgroup of other trials (RR: 1.72; 95% CI: 0.67–4.40). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

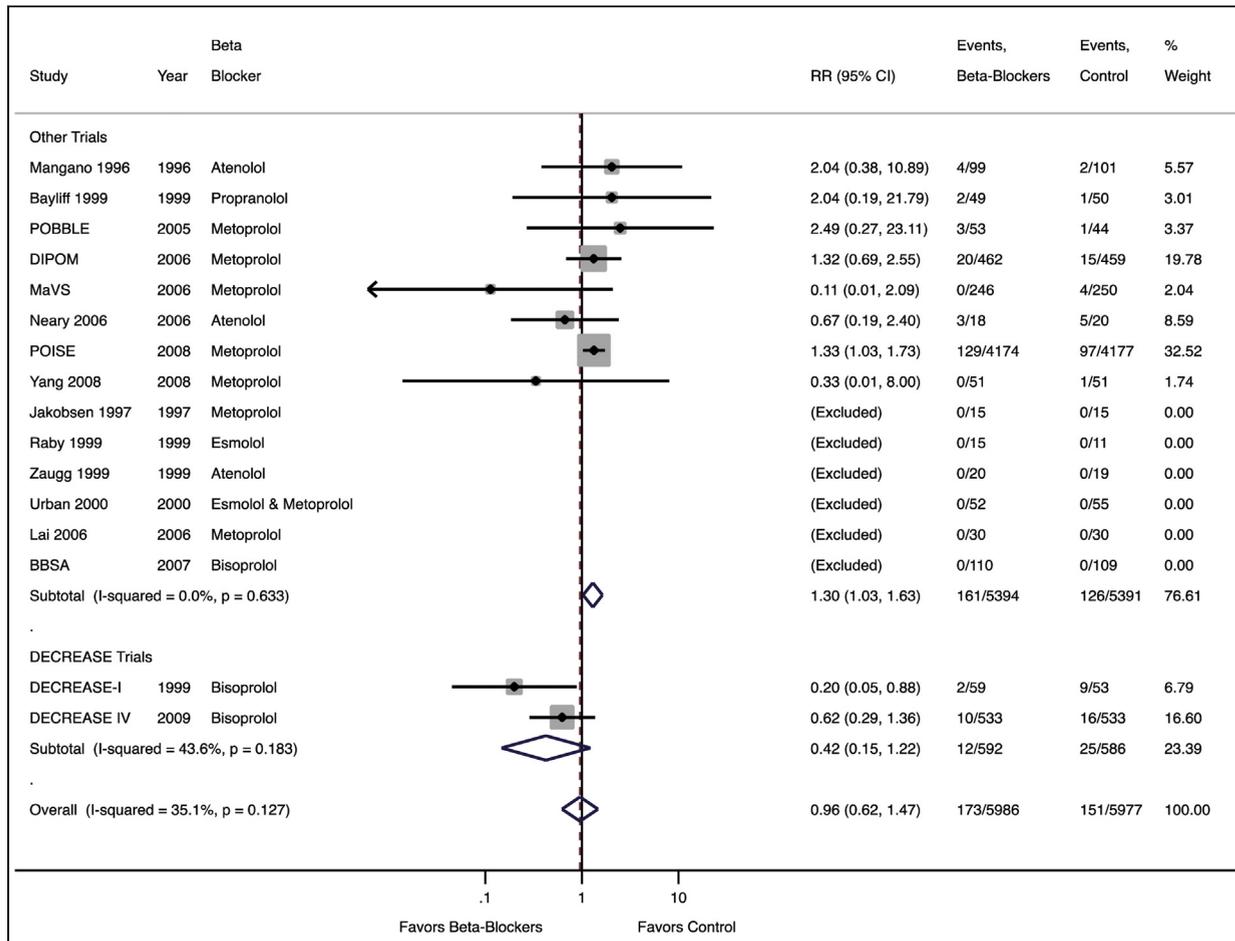BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.

Study	Year	Beta Blocker		RR (95% CI)	Events, Beta-Blockers	Events, Control	% Weight
Other Trials							
Mangano 1996	1996	Atenolol		2.04 (0.38, 10.89)	4/99	2/101	5.57
Bayliff 1999	1999	Propranolol		2.04 (0.19, 21.79)	2/49	1/50	3.01
POBBLE	2005	Metoprolol		2.49 (0.27, 23.11)	3/53	1/44	3.37
DIPOM	2006	Metoprolol		1.32 (0.69, 2.55)	20/462	15/459	19.78
MaVS	2006	Metoprolol		0.11 (0.01, 2.09)	0/246	4/250	2.04
Neary 2006	2006	Atenolol		0.67 (0.19, 2.40)	3/18	5/20	8.59
POISE	2008	Metoprolol		1.33 (1.03, 1.73)	129/4174	97/4177	32.52
Yang 2008	2008	Metoprolol		0.33 (0.01, 8.00)	0/51	1/51	1.74
Jakobsen 1997	1997	Metoprolol		(Excluded)	0/15	0/15	0.00
Raby 1999	1999	Esmolol		(Excluded)	0/15	0/11	0.00
Zaugg 1999	1999	Atenolol		(Excluded)	0/20	0/19	0.00
Urban 2000	2000	Esmolol & Metoprolol		(Excluded)	0/52	0/55	0.00
Lai 2006	2006	Metoprolol		(Excluded)	0/30	0/30	0.00
BBSA	2007	Bisoprolol		(Excluded)	0/110	0/109	0.00
Subtotal (I-squared = 0.0%, p = 0.633)				1.30 (1.03, 1.63)	161/5394	126/5391	76.61
.							
DECREASE Trials							
DECREASE-I	1999	Bisoprolol		0.20 (0.05, 0.88)	2/59	9/53	6.79
DECREASE IV	2009	Bisoprolol		0.62 (0.29, 1.36)	10/533	16/533	16.60
Subtotal (I-squared = 43.6%, p = 0.183)				0.42 (0.15, 1.22)	12/592	25/586	23.39
.							
Overall (I-squared = 35.1%, p = 0.127)				0.96 (0.62, 1.47)	173/5986	151/5977	100.00

.1   1   10

Favors Beta-Blockers   Favors Control

FIGURE 5   Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Mortality Rate in RCTs Within Subgroups Defined by DECREASE Trials Versus Other Trials
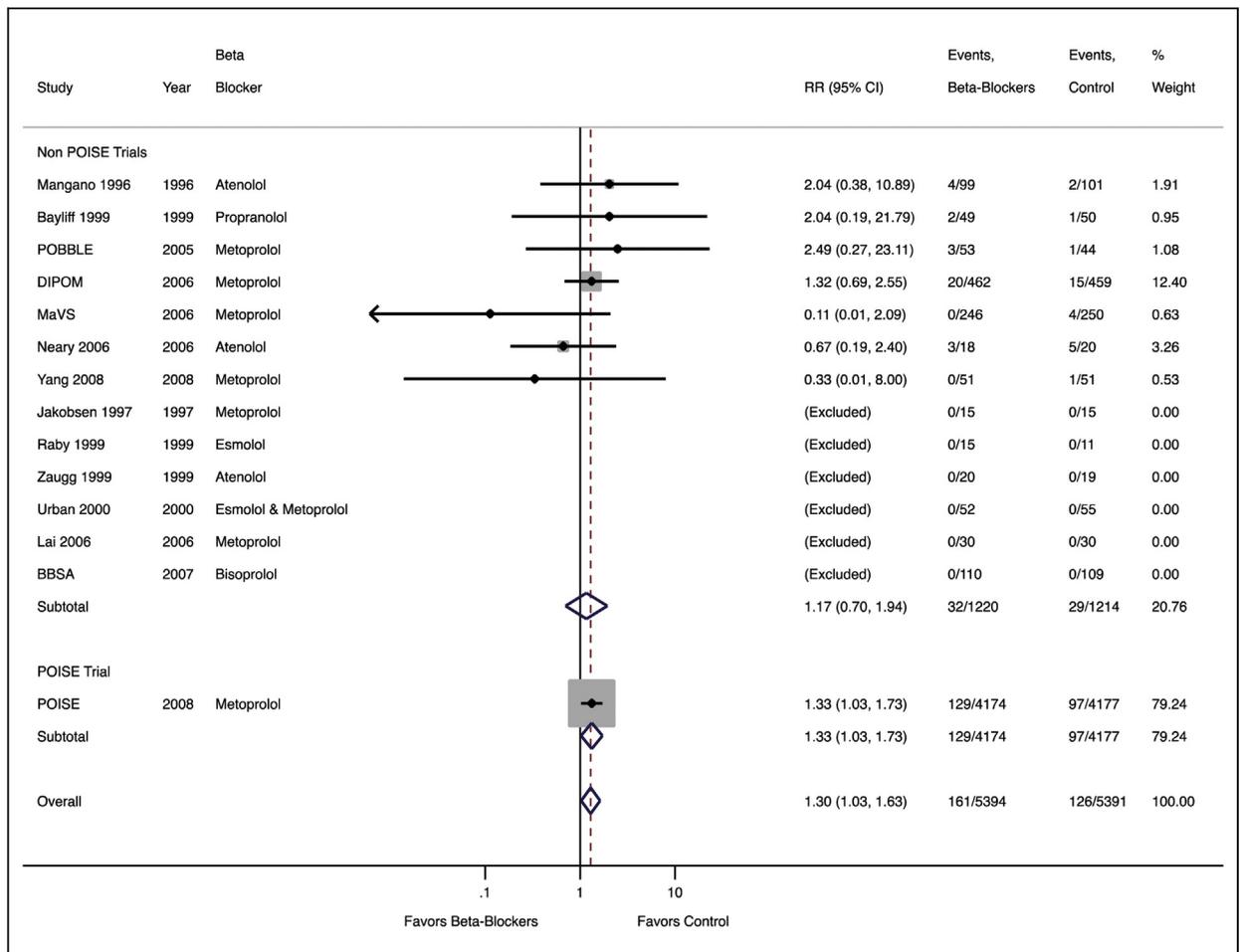
The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer deaths) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 0.96; 95% CI: 0.62–1.47; p=0.84), as well as the DECREASE subgroup (RR: 0.42; 95% CI: 0.15–1.22; p=0.11) and the subgroup of other trials (RR: 1.30; 95% CI: 1.03–1.63; p=0.03). Statistical heterogeneity, as measured by the I^2 statistic, was 35.1% for the overall analysis, 43.6% for DECREASE subgroup, and 0% for the subgroup of other trials. There was statistically significant evidence (p=0.02) of a difference between the pooled estimates in the 2 subgroups. BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.

FIGURE 6   **Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Mortality Rate in RCTs After Exclusion of the DECREASE Family of Trials, Within Subgroups Defined by POISE-1 Trial Versus Other Trials**

The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each gray square correlates with its contribution toward the pooled summary estimates. Horizontal lines denote 95% CIs. Estimates to the left of the line of unity (i.e., RR: 1) indicate superior clinical outcomes (i.e., fewer deaths) with beta blockade ("*Favors Beta-Blockers*"), whereas estimates to the right of the line of unity indicate superior clinical outcomes with control ("*Favors Control*"). The blue diamonds represent the pooled estimates for all studies (RR: 1.30; 95% CI: 1.03–1.63), as well as the POISE-1 trial (RR: 1.33; 95% CI: 1.03–1.73) and the subgroup of other trials (RR: 1.17; 95% CI: 0.70–1.94). Statistical heterogeneity, as measured by the I^2 statistic, was 0% for the overall analysis.

BBSA indicates Beta Blocker in Spinal Anesthesia; CI, confidence interval; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POBBLE, Perioperative Beta Blockade; POISE, Perioperative Ischemic Evaluation; RCT, randomized controlled trial; and RR, relative risk.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)*— PERIOPERATIVE BETA BLOCKADE IN NONCARDIAC SURGERY: A SYSTEMATIC REVIEW FOR THE 2014 ACC/AHA GUIDELINE ON PERIOPERATIVE CARDIOVASCULAR EVALUATION AND MANAGEMENT OF PATIENTS UNDERGOING NONCARDIAC SURGERY (JULY 2014)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Duminda N. Wijeysundera (ERC Chair)	Li Ka Shing Knowledge Institute of St. Michael's Hospital—Scientist; Toronto General Hospital—Staff, Department of Anesthesia and Pain Management; University of Toronto—Assistant Professor, Department of Anesthesia and Institute of Health Policy Management and Evaluation; Institute for Clinical Evaluative Sciences—Adjunct Scientist	None	None	None	None	None	None
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This table represents the relationships of ERC members with industry and other entities that were determined to be relevant to this initiative. These relationships were reviewed and updated in conjunction with all conference calls of the ERC during the evidence review process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*For transparency, the ERC members' comprehensive disclosure information is available as an Online Supplement.

ACC indicates American College of Cardiology; AHA, American Heart Association; ERC, Evidence Review Committee; UCSF, University of California, San Francisco; and VA, Veterans Affairs.