

# 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

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### Data Supplement 1. Electronic Search Terms Within PubMed Database

Search set	Search Terms
1	beta-block* OR b-block* OR acebutolol OR atenolol OR bendroflumethiazide OR betaxolol OR bisoprolol OR bupranolol OR carteolol OR celiprolol OR labetalol OR levobunolol OR metipranolol OR metoprolol OR nadolol OR oxprenolol OR penbutolol OR propranolol OR timolol OR sectral OR tenormin OR zebeta OR esmolol OR landiolol OR corgard OR bystolic OR inderal LA[Title/Abstract] OR "Adrenergic beta-Antagonists"[Mesh] OR "Propanolamines"[Mesh]
2	peri-operativ*[tiab] OR pre-operativ*[tiab] OR intra-operativ*[tiab] OR post-operativ*[tiab] OR perioperative*[tiab] OR post-surgery[tiab] OR "Perioperative Period"[Mesh] OR "Perioperative Care"[Mesh] OR "Intraoperative Period"[Mesh] OR "Postoperative Period"[Mesh] OR "Preoperative Period"[Mesh] OR "Intraoperative Complications"[Mesh] OR "Postoperative Complications"[Mesh] OR "Monitoring, Intraoperative"[Mesh]
3	"Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Young Adult"[Mesh]
4	"Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Comparative Study"[Publication Type] OR "Cohort Studies"[Mesh] OR "Random Allocation"[Mesh] OR "Epidemiologic Methods"[Mesh] OR "Multicenter Study"[Publication Type] OR quasi-randomiz*[Title/Abstract] OR multi-institution*[Title/Abstract] OR randomized [Title/Abstract] OR randomly[Title/Abstract] OR placebo OR groups[Title/Abstract] OR RCT [Title/Abstract] OR trial[Title/Abstract] OR cohort*[Title]
5	"Humans"[Mesh]
6	#1 AND #2 AND #3 AND #4 AND #5

## Data Supplement 2. Electronic Search Terms Within Embase Database

Search Set	Search Terms
1	'beta adrenergic receptor blocking agent'/exp OR 'beta blockade.tw.' OR 'b blocker.tw.' OR 'acebutolol'/exp OR 'atenolol'/exp OR 'betaxolol'/exp OR 'bisoprolol'/exp OR 'bupranolol'/exp OR 'carteolol'/exp OR 'celiprolol'/exp OR 'labetalol'/exp OR 'levobunolol'/exp OR 'metipranolol'/exp OR 'metoprolol'/exp OR 'nadolol'/exp OR 'oxprenolol'/exp OR 'penbutolol'/exp OR 'propranolol'/exp OR 'timolol'/exp OR 'tenormin'/exp OR 'esmolol'/exp OR 'landiolol'/exp OR neivolol OR 'propranolamine derivative'/exp AND [embase]/lim
2	perioperative.tw. OR preoperative.tw. OR intraoperative.tw. OR postoperative.tw. OR peri\$operative.tw. OR pre\$operative.tw. OR post\$operative.tw. OR intra\$operative.tw. OR 'peroperative complication'/exp OR 'peroperative period'/exp OR 'intraoperative period'/exp OR 'postoperative period'/exp OR 'preoperative period'/exp OR 'intraoperative complications'/exp AND [embase]/lim
3	'adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR 'young adult'/exp AND [embase]/lim
4	'comparative study'/exp OR 'controlled study'/exp OR 'controlled clinical trial'/exp OR 'randomized controlled trial'/exp OR 'quasi randomized.ab.' OR 'multicenter study'/exp OR 'cohort analysis'/exp OR 'multi institution.twab.' OR randomiz*.ab. OR randomly.ab. OR placebo.ab. OR groups.ab. OR rct.twab. OR trial.twab. OR cohort.tw.
5	'human'/exp NOT 'animal experiment'/exp
6	'mortality'/exp OR 'death'/exp OR 'heart death'/exp OR 'heart arrest'/exp OR 'heart infarction'/exp OR 'heart muscle ischemia'/exp OR 'sudden death'/exp OR mace.tw. AND

	[embase]/lim
7	#1 AND #2 AND #3 AND #4 AND #5
8	#1 AND #2 AND #3 AND #4 AND #5 AND #6
9	'heart surgery'/exp
10	#7 NOT #9
11	#8 OR #10

### Data Supplement 3. Electronic Search Terms Within Cochrane Central Register of Controlled Trials

Search Set	Search Terms
1	mw adrenergic beta-antagonists OR ti beta-block* OR "beta adrenergic receptor block*" OR ab acebutolol OR ab atenolol OR ab bendroflumethiazide OR ab betaxolol OR ab bisoprolol OR ab bupranolol OR ab carteolol OR ab celiprolol OR ab labetolol OR ab levobunolol OR ab metipranolol OR ab metoprolol OR ab nadolol OR ab oxprenolol OR ab penbutolol OR ab propanolamines OR mw propanolamines
2	ti peri\$operative OR mw perioperative OR mw preoperative OR mw postoperative OR mw intraoperative* OR preoperative* OR mw preoperative care OR mw surgery OR mw surgical procedure* OR ti noncardiac surgery OR ti perioperative OR ti intraoperative OR ti postoperative OR ti preoperative
3	mw adult OR mw aged OR mw "middle aged" OR mw "young adult"
4	mw humans
5	#1 AND #2 AND #3 AND #4

#### Data Supplement 4. Relevance, Fidelity, and Risk of Bias\* of Included RCTs

Study (Year)	Cochrane Collaboration Risk of Bias Tool							Relevance of Study Sample, Interventions, Outcome, Follow-Up Period, and Setting	Fidelity–Assessment of Monitoring, Protocol Adherence, and Data Validity
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias		
Mangano et al. (1996) (1)	Green	Green	Green	Green	Green	Yellow	Yellow	High	Intermediate
Jakobsen et al. (1997) (2)	Yellow	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Low	Low
Bayliff et al. (1999) (3)	Yellow	Yellow	Yellow	Green	Red	Yellow	Green	Intermediate	Low
DECREASE-I (1999) (4)	Green	Yellow	Red	Green	Green	Green	Yellow	High	Intermediate
Raby et al. (1999) (5)	Green	Yellow	Red	Green	Yellow	Green	Green	Intermediate	Low
Zaugg et al. (1999) (6)	Yellow	Yellow	Red	Green	Yellow	Green	Yellow	Low	Low
Urban et al. (2000) (7)	Yellow	Yellow	Red	Green	Yellow	Green	Green	Intermediate	Intermediate
POBBLE (2005) (8)	Green	Green	Yellow	Yellow	Yellow	Green	Yellow	High	Intermediate
DIPOM (2006) (9)	Green	Green	Green	Green	Yellow	Green	Green	High	High
Lai et al. (2006) (10)	Green	Yellow	Red	Red	Green	Green	Yellow	Intermediate	Low
MaVS (2006) (11)	Yellow	Yellow	Yellow	Green	Yellow	Green	Green	High	Intermediate
Neary (2006) (12)	Yellow	Yellow	Yellow	Green	Yellow	Green	Yellow	High	Intermediate
BBSA (2007) (13)	Yellow	Yellow	Yellow	Green	Yellow	Green	Yellow	High	Intermediate
POISE-1 (2008) (14)	Green	Green	Green	Green	Yellow	Green	Green	High	High
Yang et al. (2008) (15)	Green	Yellow	Yellow	Yellow	Yellow	Green	Yellow	High	Intermediate
DECREASE-IV (2009) (16)	Green	Yellow	Red	Yellow	Yellow	Green	Yellow	High	Critically flawed

\*Risk of bias is denoted as low risk of bias (green box), high risk of bias (red box), or unclear risk of bias (yellow box).

BBSA indicates Beta Blocker in Spinal Anesthesia; 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 Study Evaluation; and RCT, randomized controlled trial.

### Data Supplement 5. Quality and Results of Included Observational Studies

Study (Year)	Quality Assessed by Newcastle-Ottawa Scale†			Relevance of Study Sample, Interventions, Outcome, Follow-Up Period, and Setting	Study Findings
	Selection	Comparability	Outcome		
Matyal et al. (2008) (17)	***	Zero stars	***	High	These results apply to the subgroup of 348 pts previously not receiving long-term preoperative beta-blocker therapy. Perioperative MI occurred in 3.3% of individuals receiving perioperative beta blockade, and 6.3% of individuals in the control arm; this corresponds to a relative risk of 0.54 (95% CI: 0.20–1.46; p=0.23). Perioperative mortality occurred in 0% of individuals receiving perioperative beta blockade, and 1.8% of individuals in the control arm (Fisher exact test p=0.10).

†Observational studies can receive up to a maximum of 9 stars across all 3 domains of the Newcastle-Ottawa scale.

CI indicates confidence interval; MI, myocardial infarction and pts, patients.

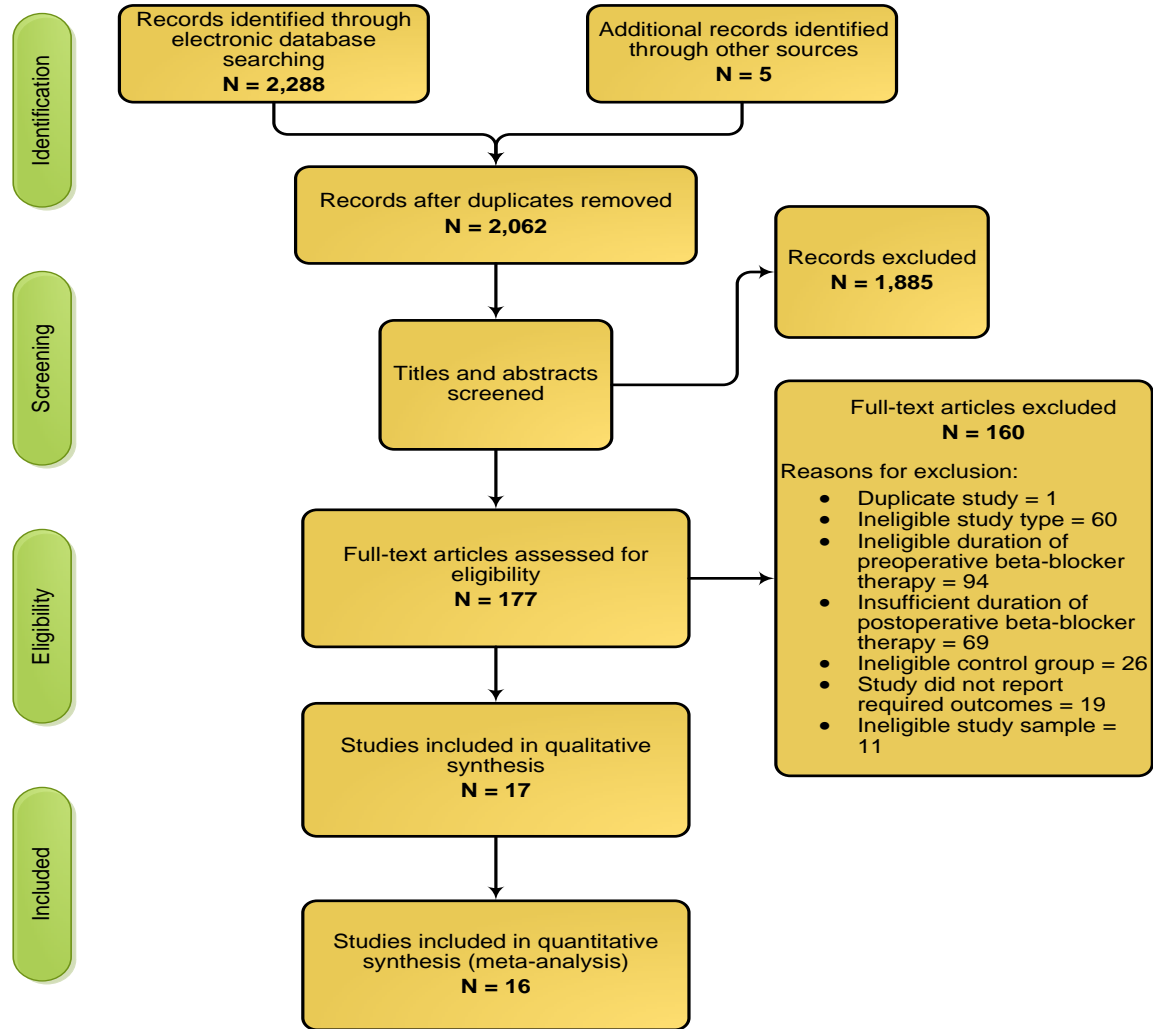
### Data Supplement 6. Definitions of Significant Perioperative Hypotension and Bradycardia in Included RCTs

Study (Year)	Definition of Perioperative Hypotension	Definition of Perioperative Bradycardia
Mangano et al. (1996) (1)	Systolic BP <90 mm Hg on d 1 to 7 after surgery	Heart rate <40 beats/min on d 1 to 7 after surgery
Bayliff et al. (1999) (3)	Systolic BP <100 mm Hg requiring administration of IV fluids	Heart rate <60 beats/min
Raby et al. (1999) (5)	Hypotension requiring discontinuation of study drug	Bradycardia requiring discontinuation of study drug
Zaugg et al. (1999) (6)	Systolic BP <90 mm Hg on first or second d after surgery	Heart rate <40 beats/min on first or second d after surgery
Urban et al. (2000) (7)	Not reported	Not defined in report
POBBLE (2005) (8)	Requirement for inotropes to maintain cardiovascular stability	Not reported

DIPOM (2006) (9)	Systolic BP <90 mm Hg that was deemed a serious adverse event	Heart rate <45 beats/min that was deemed a serious adverse event
MaVS (2006) (11)	Intraoperative systolic BP <90 mm Hg requiring treatment by attending anesthesiologist	Intraoperative heart rate <50 beats/min requiring treatment by attending anesthesiologist
BBSA (2007) (13)	Systolic BP <100 mm Hg	Heart rate <50 beats/min
POISE-1 (2008) (14)	Systolic BP <90 mm Hg that necessitates fluid resuscitation, intra-aortic balloon pump, an inotropic agent, or study drug discontinuation	Bradycardia that necessitates requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation

BBSA indicates Beta Blocker in Spinal Anesthesia; BP, blood pressure; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; IV, intravenous; POBBLE, Perioperative Beta Blockage; POISE, Perioperative Ischemic Study Evaluation; and RCTs, randomized controlled trials.

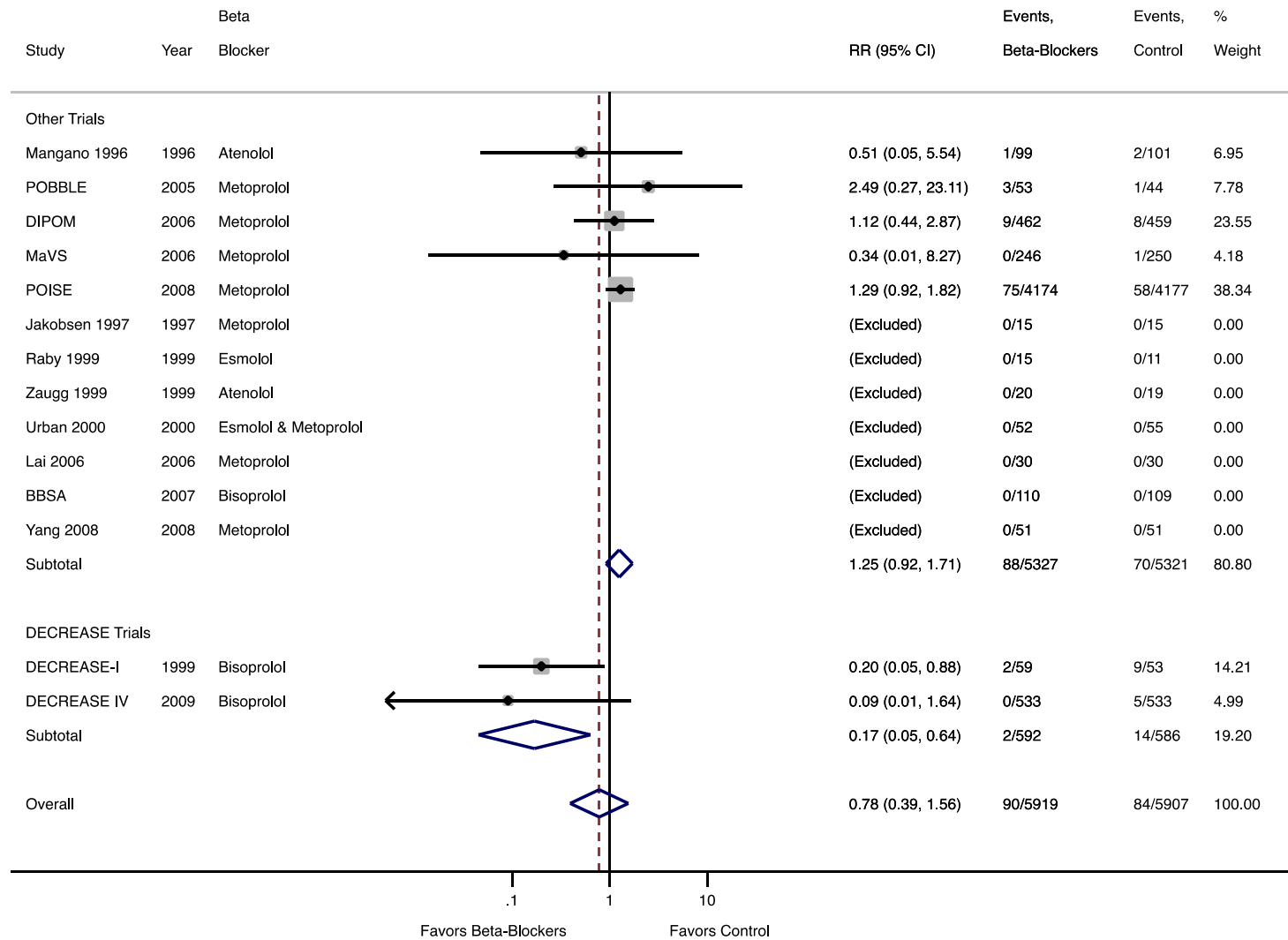
## Data Supplement 7. Flow Diagram Describing Literature Search Results for the Systematic Review



Note that the total number of reasons for exclusion exceeds the total number of excluded articles because some individual papers had multiple reasons for exclusion from the review.



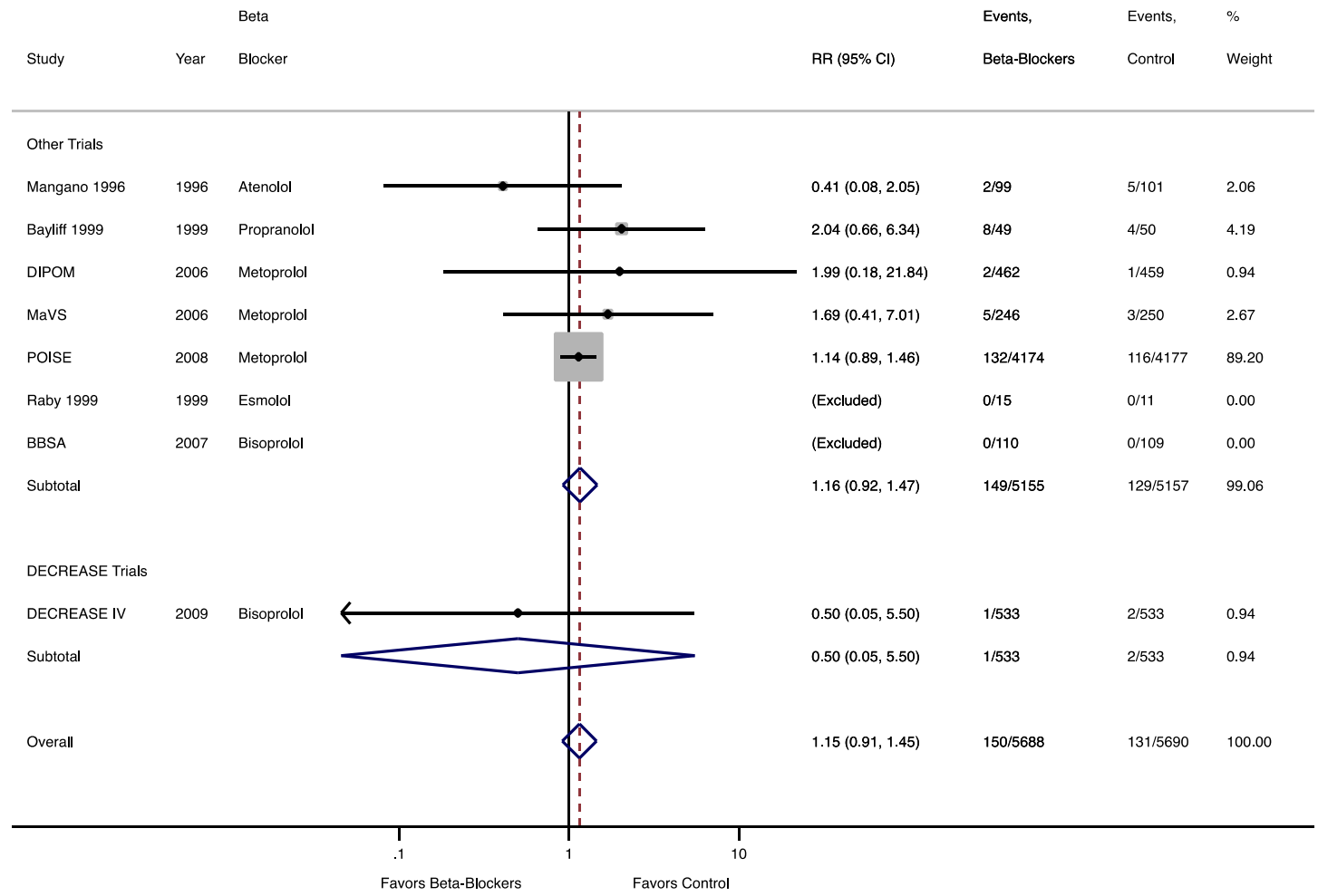
## Data Supplement 8. Effect of Perioperative Beta Blockade on In-Hospital or 30-Day Cardiovascular Death in RCTs



Effect of perioperative beta blockade on in-hospital or 30-day cardiovascular death, 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 grey square correlates with its contribution towards 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 cardiovascular deaths) with beta blockade (*Favors Beta-Blockers*), while 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: 0.78; 95% CI: 0.39–1.56;  $p=0.49$ ), as well as the DECREASE subgroup (RR: 0.17; 95% CI: 0.05–0.64;  $p=0.008$ ) and other trials (RR: 1.25; 95% CI: 0.92–1.71;  $p=0.16$ ) subgroups. Statistical heterogeneity, as measured by the  $I^2$  statistic, was 41.2% for the overall analysis. There was statistically significant evidence ( $p=0.01$ ) of a difference between the DECREASE trials versus pooled estimates from the other trials.

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 Study Evaluation; RCT, randomized controlled trial; and RR, relative risk.

### Data Supplement 9. Effect of Perioperative Beta Blockade on In-Hospital or 30-Day HF in RCTs

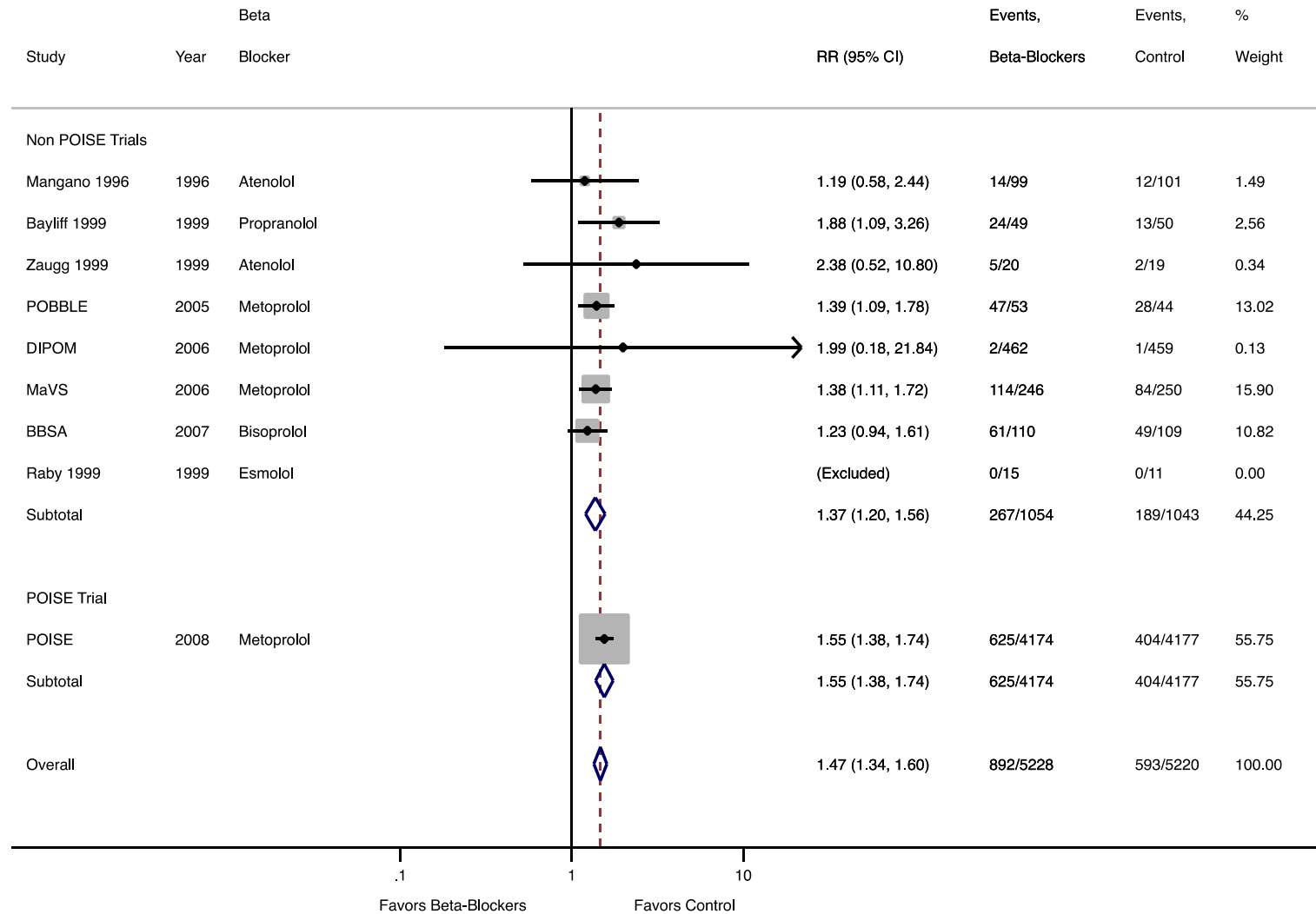


Effect of perioperative beta blockade on in-hospital or 30-day HF, within subgroups defined by DECREASE trials versus other trials. The pooled effect is expressed as a pooled RR with associated 95% CI. The solid black diamonds represent point estimates in individual RCTs. The area of each grey square correlates with its contribution towards 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

episodes of HF) with beta blockade (“*Favors Beta-Blockers*”), while 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: 1.15; 95% CI: 0.91–1.45; p=0.23), as well as the DECREASE IV trial (RR: 0.50; 95% CI: 0.05–5.50; p=0.57) and subgroup of other trials (RR: 1.16; 95% CI: 0.92–1.47; p=0.21). Statistical heterogeneity, as measured by the I<sup>2</sup> 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; HF, heart failure; MaVS, Metoprolol After Vascular Surgery; POISE, Perioperative Ischemic Study Evaluation; RCT, randomized controlled trial; and RR, relative risk.

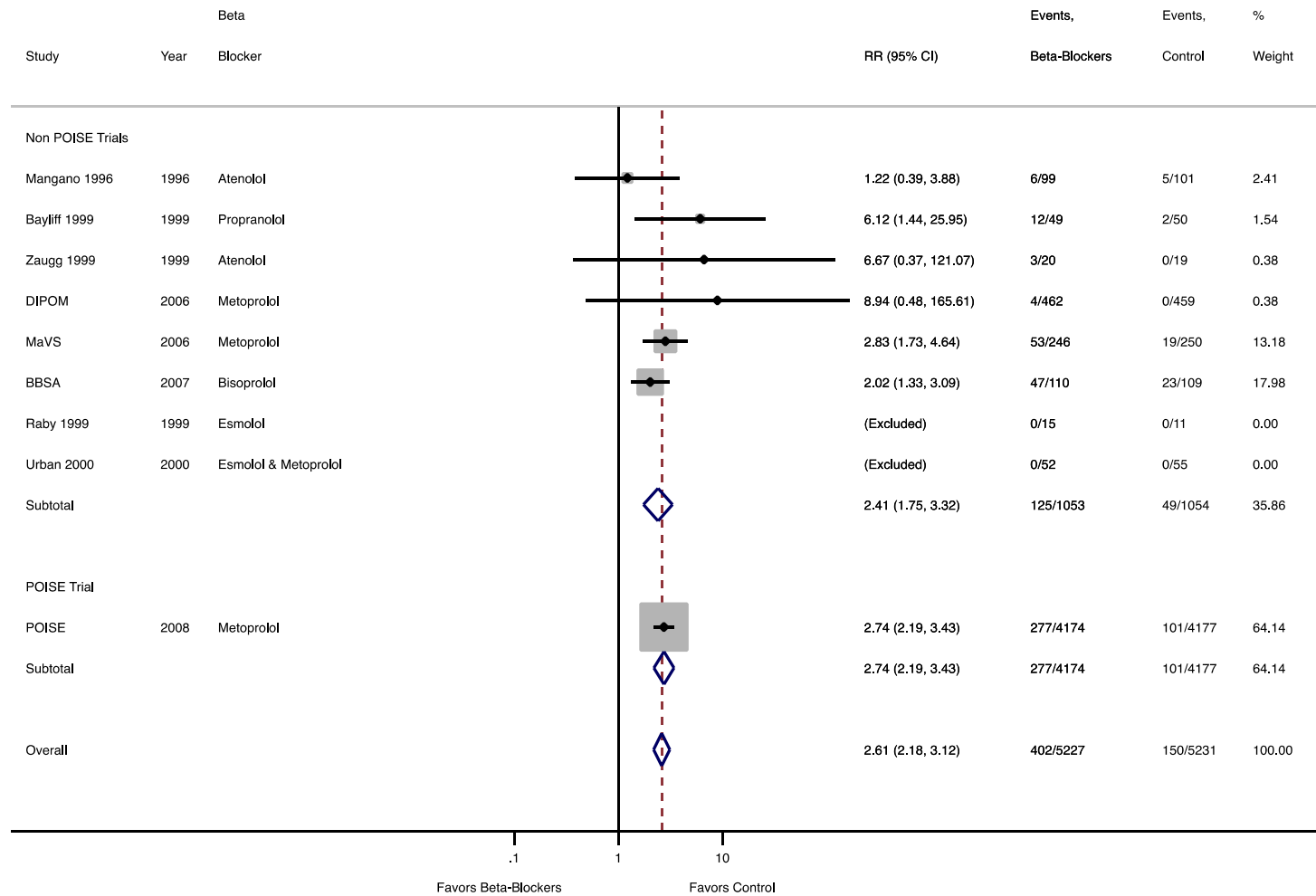
### Data Supplement 10. Effect of Perioperative Beta Blockade on Perioperative Hypotension in RCTs



Effect of perioperative beta blockade on perioperative bradycardia, 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 grey square correlates with its contribution towards 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 episodes of hypotension) with beta blockade (“Favors Beta-Blocker”), while 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: 1.47; 95% CI: 1.34–1.60; p<0.001), as well as the POISE-1 trial (RR: 1.55; 95% CI: 1.38–1.74; p<0.001) and subgroup of other trials (RR: 1.37; 95% CI: 1.20–1.56; p<0.001) subgroups. Statistical heterogeneity, as measured by the I<sup>2</sup> statistic, was 0% for the overall analysis.

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

### Data Supplement 11. Effect of Perioperative Beta Blockade on Perioperative Bradycardia in RCTs



Effect of perioperative beta blockade on perioperative bradycardia, 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 grey square correlates with its contribution towards 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 episodes of bradycardia) with beta blockade (“*Favors Beta-Blockers*”), while 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: 2.61; 95% CI: 2.18–3.12;  $p < 0.001$ ), as well as the POISE-1 trial (RR: 2.74; 95% CI: 2.19–3.43;  $p < 0.001$ ) and subgroup of other trials (RR: 2.41; 95% CI: 1.75–3.32;  $p < 0.001$ ) subgroups. 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; DIPOM, Diabetic Postoperative Mortality and Morbidity; MaVS, Metoprolol After Vascular Surgery; POISE, Perioperative Ischemic Study Evaluation; RCT, randomized controlled trial; and RR, relative risk.

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