Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery

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ABSTRACT

Background Current European and American guidelines recommend the perioperative initiation of a course of β-blockers in those at risk of cardiac events undergoing high- or intermediate-risk surgery or vascular surgery. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) family of trials, the bedrock of evidence for this, are no longer secure. We therefore conducted a meta-analysis of randomised controlled trials of β-blockade on perioperative mortality, non-fatal myocardial infarction, stroke and hypotension in non-cardiac surgery using the secure data.

Methods The randomised controlled trials of initiation of β-blockers before non-cardiac surgery were examined. Primary outcome was all-cause mortality at 30 days or at discharge. The DECREASE trials were separately analysed.

Results Nine secure trials totalling 10 529 patients, 291 of whom died, met the criteria. Initiation of a course of β-blockers before surgery caused a 27% risk increase in 30-day all-cause mortality (p=0.04). The DECREASE family of studies substantially contradict the meta-analysis of the secure trials on the effect of mortality (p=0.05 for divergence). In the secure trials, β-blockade reduced non-fatal myocardial infarction (RR 0.73, p=0.001) but increased stroke (RR 1.73, p=0.05) and hypotension (RR 1.51, p<0.00001). These results were dominated by one large trial.

Conclusions Guideline bodies should retract their recommendations based on fictitious data without further delay. This should not be blocked by dispute over allocation of blame. The well-conducted trials indicate a statistically significant 27% increase in mortality from the initiation of perioperative β-blockade that guidelines currently recommend. Any remaining enthusiasts might best channel their energy into a further randomised trial which should be designed carefully and conducted honestly.

INTRODUCTION

Physicians across Europe are still advocated by guidelines to initiate a course of perioperative β-blockade in three classes of patients:

'… [those] who have known IHD or myocardial ischaemia according to pre-operative stress testing',

'… [those] scheduled for high-risk surgery' and

'… [those] scheduled for intermediate-risk surgery'. The joint guidelines produced by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) also endorse perioperative β-blockade in patients undergoing vascular or intermediate-risk surgery with coronary artery disease (CAD), or with more than one risk factor for CAD, or with pre-existing β-blockade (table 1).

The principal evidence for mortality benefit has been the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)[2] family of studies which were discredited almost 2 years ago[3] and subsequently underwent lengthy internal investigation, the results of which have been public for some time.[4] Nevertheless, neither the European Society of Cardiology (ESC) nor the AHA guidelines have been retracted.

All studies investigated in the DECREASE family for which data had not been lost were found to be insecure because of serious flaws (table 2). In one case it was clear that the entire study dataset had been fabricated. DECREASE I,[5] published in 1999, escaped investigation as the terms of the investigation only reached back 10 years.

Individual clinicians may feel powerless to act independently in contravention of guidelines. The ESC has recently reiterated that its guideline was 'based on the contributions of many European experts and on available evidence-based medicine including many studies from different nations. They are, therefore, the result of a group discussion and not of an individual position'.[6]

We therefore conducted a meta-analysis of the remaining secure intention-to-treat randomised controlled trial (RCT) data on the initiation of a course of β-blockade for the prevention of all-cause mortality and other secondary endpoints in the perioperative period for patients undergoing non-cardiac surgery.

METHODS

We included published RCTs that compared the initiation of a course of β-blocker therapy in the pre-operative period with placebo in adults undergoing non-cardiac surgery. There were no language restrictions. We searched Medline (1966 to 1 April 2013), the Cochrane Central Register of Randomised Controlled Trials, the WHO International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/), Excerpta Medica Database (EMBASE) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) using the search terms available in the online supplement on 23 March 2013 (see online supplementary appendix 1). We also hand-searched previous reviews and meta-analyses for other studies. We excluded non-

Table 1 Guideline recommendations for initiation of perioperative β-blockade

Patient group	2007	2009
ACCF/AHA guidelines		
Vascular surgery and ischaemia on preoperative testing	Class I	Class IIa with dose titration
Vascular surgery and established coronary artery disease	Class IIa	Class IIa with dose titration
Vascular surgery and more than one risk factor	Class IIa	Class IIa with dose titration
Intermediate-risk surgery and coronary artery disease or more than one risk factor	Class IIa	Class IIa with dose titration
ESC guidelines		
Established coronary artery disease or ischaemia on preoperative stress testing		Class I, with dose titration
High-risk surgery		Class I, with dose titration
Intermediate-risk surgery		Class IIa, with dose titration

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology.

randomised studies, studies comparing β-blockers with another treatment, studies using a one-off dose preoperatively rather than a course of β-blockers extending into the postoperative period and studies which did not report intention-to-treat data.

All-cause mortality on intention-to-treat-basis

The primary endpoint was all-cause mortality from the date of randomisation without excluding the in-hospital postoperative window. The time point was 30 days or, if this was not available, until hospital discharge. The secondary endpoints were non-fatal myocardial infarction (MI), stroke and hypotension.

Data extraction was performed in duplicate by MJS and SB with any disagreements resolved by DPF.

We performed the meta-analysis excluding studies from the DECREASE family because every study in it that had enough documentation to be investigated was found to be insecure (table 2).

We used the I^2 statistic to measure the level of heterogeneity.[7] A random effects model was used to synthesise the data with Mantel–Haenszel risk ratios calculated. Review Manager V.5.2.1 was used to perform the meta-analysis.[8]

Assessment of quality of trials

All studies were assessed for quality using the Cochrane 'risk of bias' tool[9] which considers the risk of selection, performance, detection, attrition and reporting bias. Publication bias was assessed using a funnel plot.

RESULTS

Identification of trials

We identified 300 publications; 265 were initially found on PubMed (see online supplementary appendix 2), 3 from the Cochrane Central Register of Randomised Controlled Trials, 19 from the CINAHL, 1 from EMBASE and 12 via hand searching of references. A total of 282 were excluded after reading the abstract (of which 39 received premedication only) and a further seven were excluded after reading the full text for the following reasons: two were duplicates of other studies,[10 11] one could not be included because 10 patients were excluded after randomisation including one who had pulmonary oedema in the metoprolol arm,[12] three did not meet the time point criteria of 30 days or until discharge,[13–15] and one initiated the β-blockade postoperatively[16] (see online supplementary appendix 2). A total of 11 RCTs met the eligibility criteria (figure 1), of which two were from the DECREASE family (DECREASE I and DECREASE IV[5 17]).

Included studies

The β-blocker administered varied between studies. Three trials used bisoprolol,[5 14 17] five metoprolol,[18–22] two atenolol[23 24] and one propranolol.[25] β-Blockers were initiated between 37 days[5] and 30 min[23] before surgery and continued between 5[25] and 30 days[21] after surgery (table 3). Nine studies had 30-day all-cause mortality available. One of these studies[23] separated post-discharge from in-hospital mortality and therefore it was

Table 2 Grounds on which the DECREASE family of trials are considered discredited

DECREASE VI	Fictitious methods. 97% of the patients did not undergo a stress echo and the surgery as specified. No consent forms. Falsified description of method of outcome adjudication Fictitious database.
DECREASE V	Falsified methods of patient assessment (myocardial infarction and renal failure) Fictitious adjudication committee No record of the stress echo images or of the '5-member panel' said to have evaluated them No research patient records No evidence of written informed consent
DECREASE IV	Fictitious 'adjudication committee' of cardiologist, anaesthiologist and surgeon (in reality adjudications made by surgeon alone). Fictitious events that did not match hospital records or clinical discharge reports
DECREASE III	Not investigated in detail because: No source data could be found to investigate No written consent forms. No contemporaneous documentation, only current verbal assurances
DECREASE II	Fictitious method of establishing outcome
(DECREASE I	Not investigated as it was more than 10 years old)

Figure 1 Source of studies considered for inclusion.
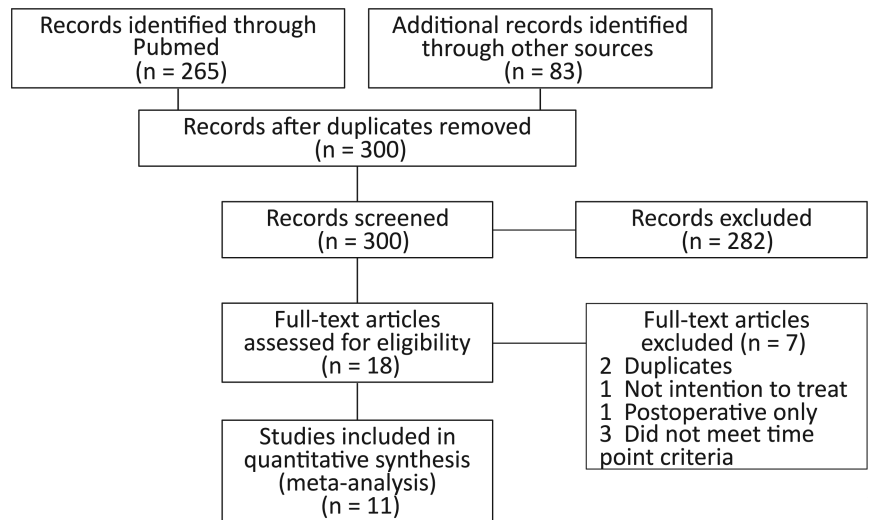
necessary to sum the two time windows to obtain events from the time of randomisation (see online supplementary appendix 3). In two studies all-cause mortality data were only available to discharge.[24 25]

Assessment of quality of trials

The risk of bias is shown in table 4. Publication bias was assessed using a funnel plot (see online supplementary appendix 4) which did not show significant asymmetry, but this cannot definitively exclude publication bias.

All-cause mortality

In total there were 10 529 patients in nine secure trials, with 162 deaths in 5264 patients randomised to β-blockers and 129 deaths in 5265 patients randomised to placebo. In the nine secure studies, β-blockers caused a statistically and clinically significant increase in mortality of 27% (RR 1.27, 95% CI 1.01% to 1.60%, $p=0.04$). There was little heterogeneity between studies ($I^2=0\%$, $p=0.68$; figure 2).

We conducted a separate meta-analysis of the two insecure studies (figure 3). These show a consensus effect of a non-statistically significant decrease in mortality by more than half (RR 0.42, 95% CI 0.15 to 1.23, $p=0.11$). There was moderate heterogeneity between the two studies ($I^2=44\%$, $p=0.18$).

The contrast between the secure and the DECREASE studies was statistically significant ($p=0.05$, figure 4).

Secondary endpoints

Six secure trials provided data for MI; β-blockade was reported to reduce non-fatal MI (RR 0.73, 95% CI 0.61 to 0.88, $p=0.001$). The DECREASE studies also reported a reduction (RR 0.21, 95% CI 0.03 to 1.61, $p=0.13$), with no significant contrast between the secure and the DECREASE studies ($p=0.23$, figure 5).

Six secure studies provided data for stroke; β-blockers significantly increased stroke (RR 1.73, 95% CI 1.00 to 2.99, $p=0.05$). DECREASE I reported stroke (RR 1.33, 95% CI 0.30 to 5.93, $p=0.71$), which was not significantly different from the secure studies ($p=0.75$, figure 6).

Six secure studies reported hypotension, which occurred more frequently in the β-blocker group than in the control group (15.2% vs 10.0%, RR 1.51, 95% CI 1.37 to 1.67, $p<0.00001$, figure 7).

DISCUSSION

The initiation of a course of β-blockers preoperatively in patients undergoing non-cardiac surgery increases mortality by 27%, which is both statistically and clinically significant. DECREASE trials I and IV report findings inconsistent with the intention-to-treat results of secure RCTs on the initiation of β-blockers on perioperative all-cause mortality.

Although β-blockers reduce non-fatal MI, they also increase hypotension and stroke. It is conceivable that an increase in death due to hypotension or stroke was overcoming a reduction in death from MI, leaving a net increase in deaths. However, there are insufficient quantitative data on the subclasses of death to be certain: deaths are relatively few and difficult to classify reliably by cause.

Residual uncertainty

Cardiologists might be tempted to hope that careful uptitration of β blockade (rather than initiation directly to a standard maintenance dose as in the POISE trial) might give benefits without inducing harm. However, the principal grounds for this hope are the DECREASE trials. The investigation committee established that there was no evidence that the published β-blocker uptitration was really done.[3 4]

Cardiologists might also hope that the 100 mg dose that increased mortality in the POISE trial might have been excessive and that commoner dosages such as metoprolol 25 mg three times a day instead might be beneficial rather than harmful. However, the higher headline value of 100 mg in the POISE trial is of metoprolol CR/XL which is a slow-release once-daily preparation with a bioavailability 25–30% lower than that of standard metoprolol.[26 27] Thus, the dosage of 100 mg CR/XL in the POISE trial is equivalent to the 75 mg/day that accrues with 25 mg three times a day of immediate-release metoprolol, whose initiation cardiologists might consider conventional. The POISE trial was therefore not high-dose.

Clinical implications

Within the ESC guidelines and associated meta-analysis, the inclusion of non-secure data caused them to reach a conclusion that β-blockers had a neutral effect on mortality and allowed them to focus on the reduction of non-fatal MI as a surrogate endpoint. This resulted in β-blockers receiving a class I/IIa

Table 3 Characteristics of the 11 included randomised controlled trials

Study (intervention/control)	Date	Methods	Participants	Type of surgeries	Interventions	Follow-up
Mangano (99/101)	1996	Randomised double-blind placebo-controlled trial	Inclusion: previous myocardial infarction (MI), typical angina or atypical angina with a positive stress test, or at risk of coronary artery disease (CAD) as indicated by two of: age >65, hypertension, current smoking, cholesterol concentration >6.2 mmol/L and diabetes	Major vascular, intra-abdominal, orthopaedic, neurosurgical or other surgery	5–10 mg intravenous (IV) or 50–100 mg oral atenolol 30 min pre surgery and continued until discharge, or a maximum of 7 days post surgery	6-month, 1-year and 2-year outcomes
Bayliff (49/50)	1999	Randomised double-blind placebo-controlled trial	Inclusion: age >18. Exclusion: asthma, congestive heart failure (CHF), second or third degree heart block, history of supraventricular tacchyarrythmias, on a β-blocker, diltiazem, digoxin, quinidine, procainamide, amiodarone, verapamil, or sensitivity to β-blockers	Lobectomies, pneumonectomies, oesophagectomies.	Propanolol 10 mg four times 1 day pre surgery, and continued for 5 days post surgery	Outcomes at hospital discharge
DECREASE I (59/53)	1999	Randomised controlled study	Inclusion: at least one cardiac risk factor (age >70 years, prior MI, CHF, ventricular arrhythmia, diabetes, limited exercise capacity), who had a positive dobutamine echocardiogram (DSE). Exclusion: already on β-blockers, extensive wall motion abnormalities, asthma	Elective vascular surgery	5–10 mg oral bisoprolol from an average of 37 (at least 7) days pre surgery and continued for 30 days post surgery	30-day outcomes
POBBLE (55/48)	2005	Randomised double-blind placebo-controlled trial	Inclusion: all patients not excluded. Exclusion: already taking or intolerant to β-blockers, asthma, aortic stenosis, bradycardia, hypotension, previous MI in the past 2 years, unstable angina or angina with a positive DSE	Vascular surgery	Oral or intravenous metoprolol day before surgery, then 25–50 mg oral metoprolol twice a day until 7 days after surgery	30-day outcomes
DIPOM (462/459)	2006	Randomised double-blind placebo-controlled trial	Inclusion: age >39 years, with diabetes. Exclusion: on or allergic to β-blockers, NYHA class IV, third degree atrioventricular block, pregnant, breast feeding or in previous DIPOM trial	Orthopedic, intra-abdominal, neurological, vascular, gynaecological or other surgery	50–100 mg oral metoprolol 1 day before surgery and continued until hospital discharge, or a maximum of 8 days post surgery	Median follow-up of 18 months (range 6–30 months)
MaVS (246/250)	2006	Randomised double-blind placebo-controlled trial	Inclusion: ASA class ≤3. Exclusion: current or recent β-blocker use, amiodarone, airflow obstruction requiring treatment, history of CHF or atrioventricular (AV) block, previous adverse reaction, previous participation in MaVS study	Vascular surgery	25–100 mg oral metoprolol within 2 h pre surgery, then oral or IV metoprolol until hospital discharge or 5 days post surgery	30-day and 6-month outcomes
Neary (18/20)	2006	Randomised placebo-controlled trial	Inclusion: one of previous MI or ischaemia on ECG, history of angina, history of stroke or transient ischaemic attack; or two of age >65 years, hypertension, current smoking, cholesterol > 6.2 mmol/L, diabetes. Exclusion: already on or intolerant to β-blockers, bradycardia, COPD or asthma, second or third degree heart block, cardiovascular collapse or hypovolaemia, anaesthetist feels patient not fit for β-blockers	Emergency general or orthopaedic surgery	1.25 mg IV atenolol in the anaesthetic room, then every 30 min during surgery, then oral or IV atenolol daily for 7 days post surgery	Mortality to hospital discharge and at 1 year
BBSA (110/109)	2007	Randomised double-blind placebo-controlled trial	Inclusion: CAD indicated by previous MI, angina, atypical angina with a positive stress test or previous coronary procedure or the presence of at least two of: hypertension, diabetes, hypercholesterolaemia, age >65 years and active smoking, Exclusion: chronic β-blockade, CHF, high degree AV block active asthma, left bundle branch block	Orthopaedic, urological, abdominal, gynaecological, plastic or vascular surgery	5–10 mg oral bisoprolol 3 h before surgery and continued until hospital discharge or a maximum of 10 days post surgery	30-day and 1-year outcomes
POISE (4174/4177)	2008	Randomised double-blind placebo-controlled trial	Inclusion: age >45 years, with a history of CAD, peripheral vascular disease, stroke, hospitalisation for CHF within the last 3 years, or with 3 of the following: intrathoracic or intraperitoneal surgery, CHF, transient ischaemic attack, creatinine >175 μmol/L, >70 years old, diabetes or undergoing emergent or urgent surgery	Vascular, intraperitoneal, orthopaedic surgery	100 mg oral extended-release metoprolol 2–4 h pre surgery and then 200 mg once a day for 30 days post surgery	30-day outcomes
Yang (51/51)	2008	Randomised double-blind placebo-controlled trial	Inclusion: age >45 years and a history of CAD or peripheral vascular disease, stroke or hospitalisation for CHF in the last 3 years or any three of the following: high-risk surgery, CHF, diabetes, age >65 years, hypertensive, smoker or high cholesterol. Exclusion: heart rate <50, pacemaker, high degree AV block, active recent asthma, bronchospasm,	Intrathoracic or intra-abdominal surgery	Oral or IV metoprolol from 2 h before surgery to 30 days after surgery	30-day outcomes

Continued

Table 3 Continued

Study (intervention/control)	Date	Methods	Participants	Type of surgeries	Interventions	Follow-up
DECREASE IV (533/533)	2009	Randomised open-label placebo-controlled trial	COPD, adverse reaction to β-blockers, low-risk surgery, taking verapamil, liver or kidney dysfunction, emergency surgery Inclusion: age >40 years with an estimated risk of perioperative cardiovascular event of 1–6% Exclusion: already on or contraindication to a β-blocker or statin, previous participation in the trial, inability to consent, emergency surgery	General, urological, orthopaedic, ear nose and throat, gynaecological, plastic or other surgery	2.5–10 mg oral bisoprolol started a median of 34 days pre surgery and continued for 30 days post surgery	30-day outcomes

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

recommendation, despite secure trials indicating that they increase mortality.

The β-blocker section of the 2009 ESC Guidelines for Perioperative Cardiac Risk Assessment and Management[1] requires reconsideration; without the DECREASE studies the profound adverse findings of the large POISE trial are the dominant contributor.

The POISE trial had a protocol of initiating a dose considered by some to be high (100 mg extended-release metoprolol) shortly (2–4 h) before surgery. This has been argued to be unrepresentative of clinical practice, but not been borne out by surveys of practice[28] and is similar to the total daily metoprolol dose from other regimens such as 25 mg three times a day which might not be considered dramatic. Nevertheless, POISE-like regimes now have no reason for continuance.

If the appropriateness of the POISE protocol is doubted, then the remaining secure data are not sufficient to guide physicians either way.

Although there is a retrospective study reporting that β-blockade is associated with lower mortality in high-risk but not in low-risk patients,[29] the lead author of the most reliable prospective RCT stated that 'the groups at highest risk looked like they benefited the least, not the most. The notion of targeting high-risk people is not supported by POISE'.[30]

Opportunity to prevent perioperative deaths
In the present analysis the RR of mortality from randomisation to β-blockade for non-cardiac surgery is 1.27 (95% CI 1.01 to 1.60) or, conversely, randomisation to not having β-blockade has a RR of 0.79 (95% CI 0.63 to 0.99), indicating a 21% reduction. In the UK,[31] for example, almost 2.5 million high- or intermediate-risk procedures are performed per year, with deaths at 30 days totalling 47 286.

Refraining from this ESC guideline[1] would therefore be expected[32] to prevent up to 10 000 iatrogenic deaths each year in the UK.

Could we have found this earlier?
Any one of three considerations might have opened this opportunity earlier. First, with a strong pointer in 2008 that the introduction of β-blockers before surgery increases mortality, we could have avoided the siren call of reduction in non-fatal MI. If a patient succumbs after intervention, knowing that he or she was prevented from having a MI is no consolation.

Second, we could have realised that not all trial data are of equal reliability. The POISE[21] investigators prominently carried out anti-bias steps including record-keeping and scrutiny for anomalies which were acted on. For example, they flew to Colombia and Iran to investigate suspicious returns, resulting in invalidation of data from one centre in Colombia and the entire dataset for Iran.

Third, we could have acted on a 2008 meta-analysis[33] flagging DECREASE I to be at high risk of bias 4 years before the DECREASE family was formally declared insecure.

Could DECREASE I have been valid?
There is no proof that the DECREASE I[5] study was unreliable.[34 35] No investigation has been conducted, nor is one on the horizon.

Data storage appeared to be haphazard for the DECREASE family of studies.[4] Of the five investigated DECREASE studies, the only one for which raw data existed was DECREASE VI, but the investigation concluded that this was 'fictitious data'.
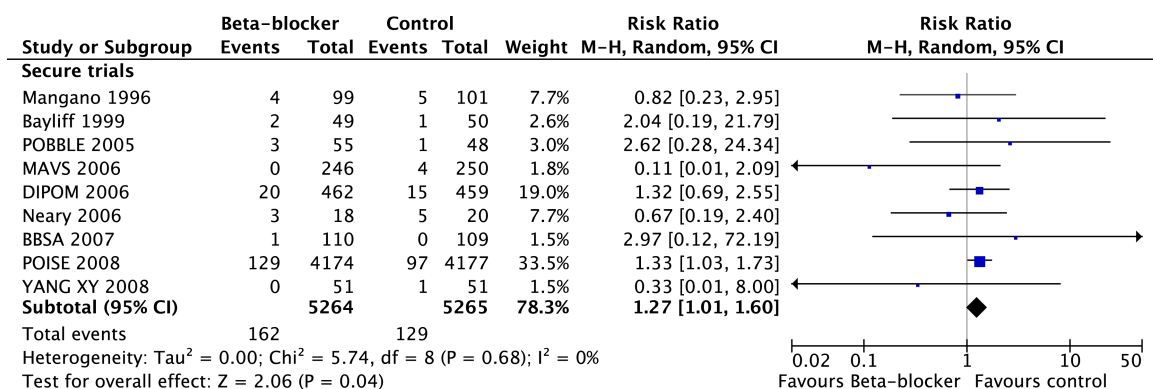
Table 4 Risk of bias of the 11 included randomised controlled trials

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other biases
Mangano (1996)	Computer generated randomised list	Only pharmacy held the list	All blinded, list held by pharmacy	2 patients did not complete the study protocol but were analysed as ITT	Only post discharge deaths are mentioned in the primary endpoint.	No
Bayliff (1999)	Blocks of 4	Only one investigator knew the code kept on the patient's health record in a sealed envelope.	Blinded	1 patient did not undergo major resection and was not continued. 8 patients were withdrawn but were analysed as ITT	No	No
POBBLE (2005)	Centrally at Sealedenvelope.com. Blocks of size 2, 4 and 6 within 4 stratification factors (centre, age, sex and planned use of aortic cross clamping)	4 digit trial number assigned	Anaesthetists were unblinded. All other clinicians and trial coordinators were blinded	1 death occurred after randomisation in a patient who was too ill to tolerate surgery which is not included	No	No
DIPOM (2006)	Computer generated. Blocks of 8 stratified for sex, age, perioperative stress, history of coronary artery disease and malignant disease	Telephone voice response	Blinded	188 patients did not receive the allocated intervention but were analysed as ITT	No	No
MaVS (2006)	Blocks of 4	Not specified	Blinded	117 did not complete the study protocol but were analysed as ITT	No	No
Neary (2006)	Packs containing medication or placebo were selected at random by the study investigator	Sealed envelope	Allocation was available to the anaesthetic team in an emergency	19 patients withdrew their consent and were excluded	No	No
BBSA (2007)	Block randomisation in a 1:1 ratio	Not specified	Blinded design but β-blocker was titrated to heart rate, so likely effective unblinding	5 patients who could not undergo spinal anaesthesia were excluded	No	No
POISE (2008)	Computerised randomisation using block randomisation stratified by centre. Randomisation in a 1:1 ratio.	Central phone randomisation	Participants, healthcare providers, data collectors and outcome adjudicators were blinded but analysts were not	20 patients were lost to follow-up but were analysed as ITT	No	No
Yang (2008)	Computer generated random table	Not specified	Yes	No	No	No
DECREASE IV (2009)	Non-secure					
DECREASE I (1999)	Non-secure					

ITT, intention to treat.

Even for recent studies such as DECREASE V, not a single case record form (CRF) could be found in any location for the 101 patients. In DECREASE IV the key data required to judge outcomes were missing and the adjudication committee was fabricated. A review of the hospital computer information system found that 'in a large number of cases a myocardial infarct which the researchers had recorded could not be confirmed' in the hospital records. DECREASE III could not be

Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
Secure trials							
Mangano 1996	4	99	5	101	7.7%	0.82 [0.23, 2.95]	
Bayliff 1999	2	49	1	50	2.6%	2.04 [0.19, 21.79]	
POBBLE 2005	3	55	1	48	3.0%	2.62 [0.28, 24.34]	
MAVS 2006	0	246	4	250	1.8%	0.11 [0.01, 2.09]	
DIPOM 2006	20	462	15	459	19.0%	1.32 [0.69, 2.55]	
Neary 2006	3	18	5	20	7.7%	0.67 [0.19, 2.40]	
BBSA 2007	1	110	0	109	1.5%	2.97 [0.12, 72.19]	
POISE 2008	129	4174	97	4177	33.5%	1.33 [1.03, 1.73]	
YANG XY 2008	0	51	1	51	1.5%	0.33 [0.01, 8.00]	
Subtotal (95% CI)		**5264**		**5265**	**78.3%**	**1.27 [1.01, 1.60]**	
Total events	162		129				

Heterogeneity: Tau² = 0.00; Chi² = 5.74, df = 8 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

Favours Beta–blocker Favours control

Figure 2 Meta-analysis of nine secure randomised controlled trials showing a significant increase in mortality with perioperative β-blockade.
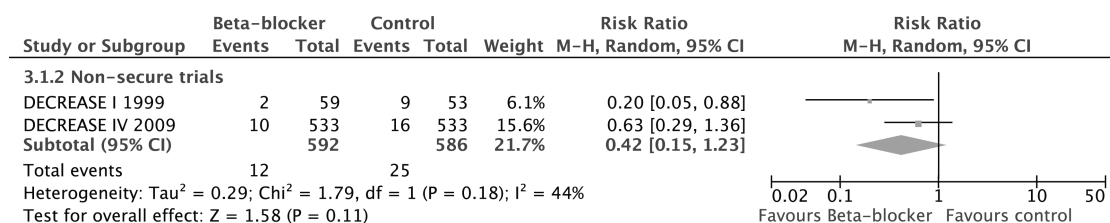
Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
3.1.2 Non-secure trials							
DECREASE I 1999	2	59	9	53	6.1%	0.20 [0.05, 0.88]	
DECREASE IV 2009	10	533	16	533	15.6%	0.63 [0.29, 1.36]	
Subtotal (95% CI)		592		586	21.7%	0.42 [0.15, 1.23]	
Total events	12		25				

Heterogeneity: Tau^2 = 0.29; Chi^2 = 1.79, df = 1 (P = 0.18); I^2 = 44%
Test for overall effect: Z = 1.58 (P = 0.11)

Figure 3 Studies in the DECREASE family have been shown to have been composed of fictitious data, have fabricated endpoints, missing data and patient records and are now discredited.

investigated as all the source documentation was lacking. For DECREASE II only half the CRFs were found and study outcomes were again realised not to have been assessed as described in the publication. The investigation did not attempt to evaluate the distant DECREASE I.

All we know is that the later DECREASE family of studies fell far short of the standards assumed by clinical readers. There are two hypotheses. The first is that standards started high in the uninvestigated DECREASE I and then declined subsequently as more experience was gained as an international perioperative clinical research centre, ultimately reaching the depths of the entirely fictitious DECREASE VI. The alternative hypothesis is that that honesty was low throughout.

Study limitations

This meta-analysis can only include data of which we are aware. There may be further unreported trials. Our group has no direct knowledge of the process that went on in the DECREASE family other than what has been reported by the two investigations conducted by the Board of the Erasmus Medical Centre.[3] [4]

While there was minimal evidence that heterogeneity was assessed by Cochrane's I^2 among the secure trials, this measure may be low powered to detect such a difference. In addition to vascular surgery, the studies included a wide range of surgeries including abdominal, orthopaedic, urological, gynaecological and plastic surgery, among others. It may therefore be difficult
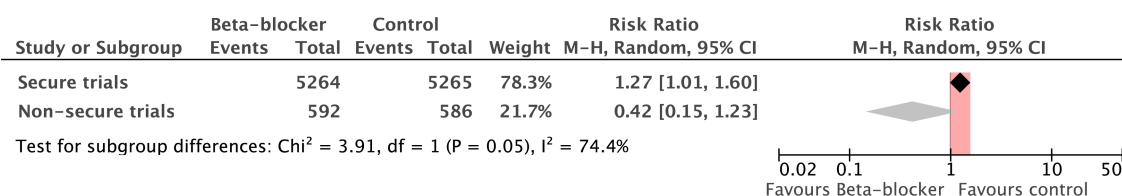
Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
Secure trials		5264		5265	78.3%	1.27 [1.01, 1.60]	
Non-secure trials		592		586	21.7%	0.42 [0.15, 1.23]	

Test for subgroup differences: Chi^2 = 3.91, df = 1 (P = 0.05), I^2 = 74.4%

Figure 4 Difference in the estimate of effect size between secure and non-secure studies.

Study or Subgroup	Beta-blocker Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
Secure trials							
Bayliff 1999	0	49	0	50		Not estimable	
POBBLE 2005	3	55	5	48	6.0%	0.52 [0.13, 2.08]	
MAVS 2006	19	246	21	250	22.0%	0.92 [0.51, 1.67]	
DIPOM 2006	3	462	2	459	3.8%	1.49 [0.25, 8.88]	
BBSA 2007	1	110	0	109	1.2%	2.97 [0.12, 72.19]	
POISE 2008	152	4174	215	4177	47.2%	0.71 [0.58, 0.87]	
Subtotal (95% CI)		5096		5093	80.2%	0.73 [0.61, 0.88]	
Total events	178		243				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.25, df = 4 (P = 0.69); I^2 = 0%
Test for overall effect: Z = 3.23 (P = 0.001)

Non-secure trials							
DECREASE I 1999	0	59	9	53	1.6%	0.05 [0.00, 0.79]	
DECREASE IV 2009	11	533	27	533	18.2%	0.41 [0.20, 0.81]	
Subtotal (95% CI)		592		586	19.8%	0.21 [0.03, 1.61]	
Total events	11		36				

Heterogeneity: Tau^2 = 1.43; Chi^2 = 2.31, df = 1 (P = 0.13); I^2 = 57%
Test for overall effect: Z = 1.50 (P = 0.13)

Total (95% CI)		5688		5679	100.0%	0.67 [0.47, 0.96]	
Total events	189		279				

Heterogeneity: Tau^2 = 0.06; Chi^2 = 8.40, df = 6 (P = 0.21); I^2 = 29%
Test for overall effect: Z = 2.20 (P = 0.03)
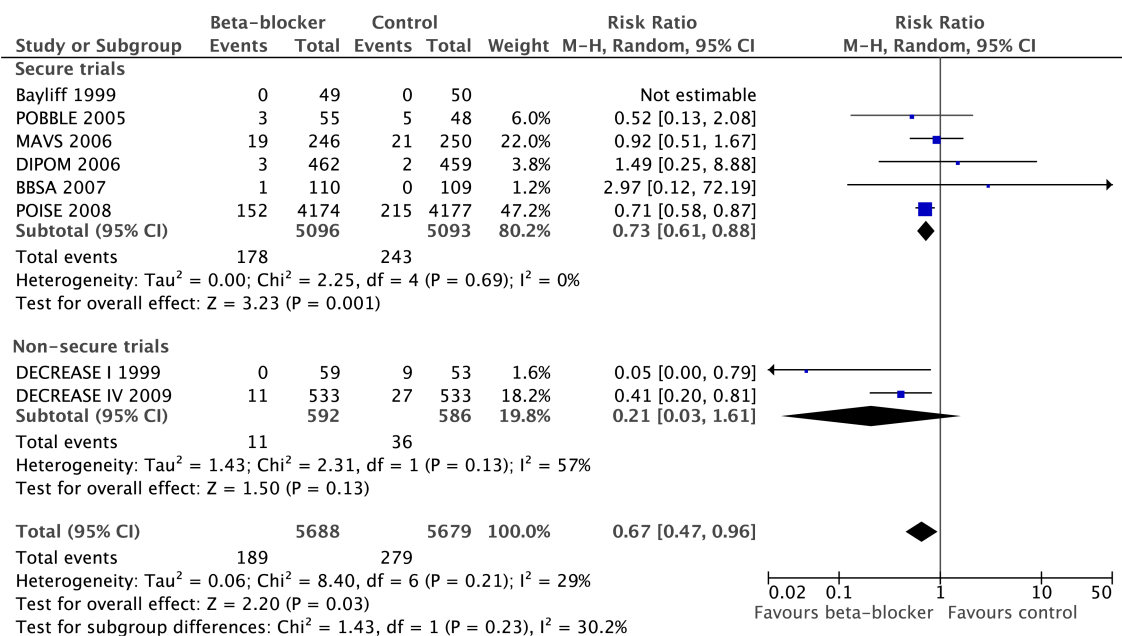Test for subgroup differences: Chi^2 = 1.43, df = 1 (P = 0.23), I^2 = 30.2%

Figure 5 Comparison of effect of perioperative β-blockade on non-fatal myocardial infarction in secure and non-secure trials.
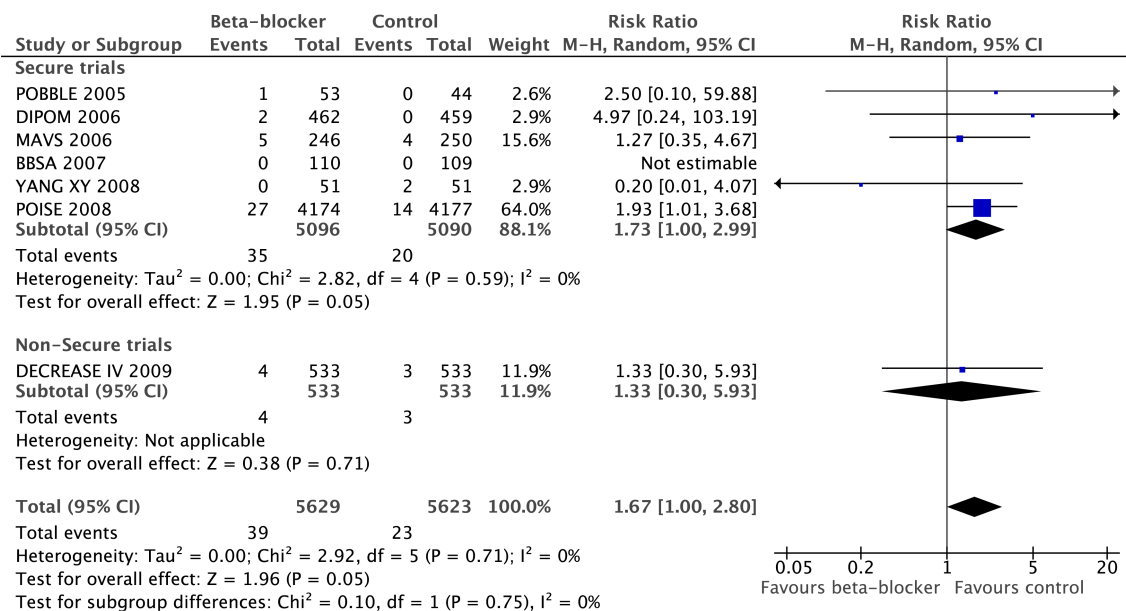
Figure 6 Comparison of effect of perioperative β-blockade on non-fatal strokes in secure and non-secure trials.
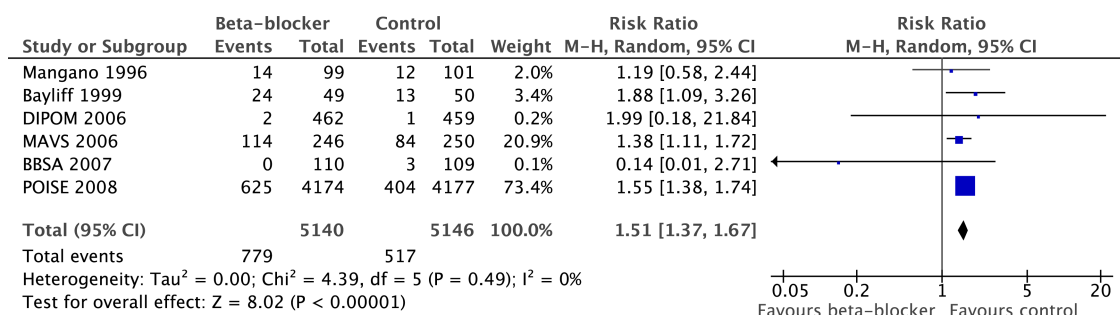

Figure 7 Prevalence of hypotension in β-blocker and control groups. Note: In the MaVS trial the intraoperative hypotension rate is reported.

to see if the initiation of a course of β-blockers before surgery in certain patient groups is beneficial.

The meta-analysis is heavily influenced by the POISE trial.[21] However, this is appropriate because the POISE trial is by far the largest study and it was well conducted. Without it there is little remaining evidence base.

A statistically significant increase in all-cause mortality has overwhelming clinical significance which cannot be compensated for by a simultaneous reduction in non-fatal events. The use non-fatal MI as a surrogate for death therefore may not be valid for perioperative β-blockade.

CONCLUSION

Perioperative initiation of a course of β-blockers appears to increase postoperative mortality by 27%. This has emerged because the DECREASE family of studies has been discredited.[3][4]

Patient safety being paramount, guidelines for perioperative β-blocker initiation should be retracted without further delay. Future guidelines should be accompanied by a commitment from named individuals to retract them immediately if the advice given is later revealed to be harmful.

Routine initiation of β-blockers for this indication should not be recommended, except in the context of RCTs which should be designed carefully, conducted honestly and reported truthfully.

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