



EVIDENCE CENTRE CRITICAL APPRAISAL

Prophylactic β -adrenergic blocking agents given
perioperatively for preventing post-operative cardiac
adverse events

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Southern Health Care Network



<h2 style="text-align: center;">Evidence Summary Therapy</h2> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> Prophylactic β-adrenergic blocking agents given in the perioperatively for preventing post-operative cardiac adverse events. </div>	Boylan, J.F., O'Leary, G., Weisel, R.D., Ivanov, J., Mickle, D.A. & Teasdale, S.J. (1990). A comparison of diltiazem, esmolol, nifedipine and nitroprusside therapy of post-CABG hypertension. <i>Canadian Journal of Anaesthesia</i> , 37, S156.	Daudon, P., Corcos, T., Gandjbakhch, I., Levasseur, J.P., Cabrol, A. & Cabrol, C. (1986). Prevention of atrial fibrillation or flutter by acebutolol after coronary bypass grafting. <i>American Journal of Cardiology</i> , 58, 933-6.
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Randomised controlled trial II	Randomised controlled trial II
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: 77 patients with post-coronary artery bypass grafting hypertension.</p> <p>Intervention: Intravenous esmolol titrated to maintain a mean arterial pressure of 85 mm Hg.</p> <p>Comparison: Intravenous sodium nitroprusside, diltiazem, or nifedipine.</p> <p>Outcome: Haemodynamic data including left ventricular pressures and volumes, end-systolic pressure-volume relationship, left ventricular stroke work index, myocardial lactate production and oxygen extraction.</p> <p>Entry Criteria: Not stated.</p>	<p>Patients: 100 patients undergoing elective coronary artery bypass grafting without additional cardiac surgical procedures.</p> <p>Intervention: Acebutolol administered orally twice a day from the 36th hour post-surgery until discharge. Dose was 200 mg initially and then modified to maintain a heart rate at rest between 60 and 90 beats per minute.</p> <p>Comparison: No β blockers after surgery.</p> <p>Outcome: Occurrence of supraventricular tachyarrhythmias as diagnosed by 24 hour electrocardiographic monitoring.</p> <p>Entry Criteria: Exclusions due to contraindication to β blockers, left ventricular aneurysm, major renal failure, history of cardiac arrhythmias or arrhythmias arising during the immediate postoperative period, low cardiac output requiring catecholamine support at 36 hours after surgery.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Yes, unspecified.</p> <p>All patients accounted for: Unstated.</p> <p>Patients treated equally: Unstated.</p> <p>Similar groups: Yes.</p>	<p>Randomisation: Yes, unspecified</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Unstated.</p> <p>Similar groups: Intervention group had younger patients.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	All agents effectively reduced mean arterial pressure. Heart rate was decreased with esmolol and diltiazem. The cardiac index decreased with esmolol. sodium nitroprusside enhanced, while esmolol depressed, systolic function and myocardial performance.	One patient in each group experienced a myocardial infarction. Twenty patients in the control group had supraventricular tachyarrhythmias. 17 had atrial fibrillation and 3 had atrial flutter. No patient in the acebutolol group had a supraventricular tachyarrhythmia.
AUTHORS COMMENTS: Risk/benefit, limitations	"Pharmacologic reduction of postoperative hypertension-induced anaerobic metabolism is optimally achieved with agents which depress systolic function."	"Oral acebutolol is recommended as a standard therapeutic regimen in prevention of supraventricular tachyarrhythmias after coronary artery bypass grafting."

<h2 style="text-align: center;">Evidence Summary Therapy</h2> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> Prophylactic β-adrenergic blocking agents given in the perioperatively for preventing post-operative cardiac adverse events. </div>	<p>Reves, J.G., Croughwell, N.D., Hawkins, E., Smith, L.R., Jacobs, J.R., Rankin, S., Lowe, J. & VanTrigt, P. (1990). Esmolol for treatment of intraoperative tachycardia and/or hypertension in patients having cardiac operations. Bolus loading technique. <i>Journal of Thoracic and Cardiovascular Surgery</i>, 100, 221-7.</p>	<p>Mangano, D.T., Layug, E.L., Wallace, A. & Tateo, I. (1996). Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. <i>New England Journal of Medicine</i>, 335, 1713-20.</p>
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Randomised controlled trial II	Randomised controlled trial II
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: 30 patients scheduled for myocardial revascularisation surgery. Intervention: Administration of 80 mg bolus of esmolol followed by an infusion of 12 mg per minute, intravenously post-surgery and when systolic blood pressure was greater than 140 mm Hg and a heart rate of more than 70 beats per minute or an isolated heart rate of more than 80 beats per minute. Comparison: Placebo. Outcome: Cardiac output, and central venous and pulmonary pressures taken at the start of bolus (0 minutes) and at 1, 3, 5, and 10 minutes after initiation of therapy. Entry Criteria: Inclusions – males and non-pregnant females with systolic blood pressures between 140 and 180 mm Hg and heart rates between 70 and 105 beats per minute or with systolic blood pressures below 180 mm Hg and heart rates between 80 and 150 beats per minute, and who were maintained on β blockers until the night before the operation. Exclusions – patients younger than 21 years; American Surgical Association class V; presence of atrioventricular fibrillation, flutter, atrioventricular conduction block greater than first degree; history of myocardial infarction or asthma; evidence of severe renal or hepatic failure; intake of monoamine oxidase inhibitors less than a month prior to study; or those on cocaine, heroin, LSD, or mood-altering drugs.</p>	<p>Patients: 200 patients at risk for coronary artery disease who were scheduled for elective non-cardiac surgery requiring general anaesthesia. Intervention: Administration of atenolol before induction of anaesthesia, immediately after surgery, and daily until discharge. Comparison: Placebo. Outcome: Two year follow-up for mortality, mortality from cardiac causes, and incidence of myocardial infarction, unstable angina, or congestive heart failure. Entry Criteria: Presence of coronary artery disease as defined by clinical history and ancillary laboratory values.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Yes, unspecified. All patients accounted for: Yes. Patients treated equally: Unstated. Similar groups: Intervention group had lower baseline heart rate.</p>	<p>Randomisation: Yes, unspecified All patients accounted for: Yes. Patients treated equally: Yes. Similar groups: Intervention group had higher proportion receiving treatment for hypertension.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>Esmolol caused a significant reduction in heart rate but did not affect blood pressure, pulmonary artery diastolic pressure, right atrial pressure, cardiac output, or systemic vascular resistance. No differences in rates of hypotension, hypertension, bradycardia, or tachycardia. Two patients in esmolol group and three in placebo group had ST segment changes consistent with ischaemia.</p>	<p>194 patients were discharged alive, and follow-up data was available for 192 patients. 30 died in the two years of follow-up (intervention group: 9 deaths, 4 due to cardiac causes; control group: 21 deaths, 12 due to cardiac causes). No substantial difference between the groups at eight months of follow-up. Differences were apparent at one year.</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>"Bolus loading with esmolol to treat tachycardia is a safe, simple, and rapid alternative to continuous infusion loading."</p>	<p>"In patients who have or at risk for coronary heart disease and who must undergo major non-cardiac surgery, mortality and the incidence of cardiovascular events after hospital discharge can be reduced by the use of beta-adrenergic blockade throughout the hospital stay."</p>

<h2 style="text-align: center;">Evidence Summary Therapy</h2> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> Prophylactic β-adrenergic blocking agents given in the perioperatively for preventing post-operative cardiac adverse events. </div>	<p>Poldermans, D., Boersma, E., Bax, J.J., Thomson, I.R., van de Ven, L.L., Blankensteijn, J.D., Baars, H.F., Yo, T.I., Trocino, G., Vigna, C., Roelandt, J.R. & van Urk, H. (1999). The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. <i>New England Journal of Medicine</i>, 341, 1789-94.</p>	<p>Stone, J.G., Foex, P., Sear, J.W., Johnson, L.L., Khambatta, H.J. & Triner, L. (1988). Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. <i>Anesthesiology</i>, 68, 495-500.</p>
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Randomised controlled trial II	Randomised controlled trial II
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: 112 patients with clinical predictors of cardiac risk and positive results on dobutamine echocardiography who were undergoing elective abdominal aortic or infrainguinal arterial reconstruction.</p> <p>Intervention: Oral bisoprolol at 5 mg once a day for one week, initially. After reassessment, dose was increased to a maximum of 10 mg per day if heart rate remained above 60 beats per minute. The dose was maintained until 30 days postoperatively.</p> <p>Comparison: Standard perioperative care.</p> <p>Outcome: Death from cardiac causes or nonfatal myocardial infarction thirty days after surgery.</p> <p>Entry Criteria: Clinical risk factors examined were age over 70 years; angina; prior myocardial infarction; compensated (or a history of) congestive heart failure; current treatment for ventricular arrhythmias, diabetes mellitus; or limited exercise capacity. Exclusions – extensive wall-motion abnormalities, asthma, strong evidence of left main or severe three-vessel coronary artery disease during stress testing.</p>	<p>Patients: 128 patients who underwent major operations necessitating general endotracheal anaesthesia.</p> <p>Intervention: Single oral tablet of labetalol (100 mg), atenolol (50 mg) or exprenolol (20 mg) prior to induction of anaesthesia.</p> <p>Comparison: No pre-treatment medication.</p> <p>Outcome: Presence of myocardial ischaemia based on electrocardiographic assessment.</p> <p>Entry Criteria: Three blood pressure measurements between 160/90 and 200/100 mm Hg taken at least 1 hour apart on the day before surgery, and not to have received any antihypertensive medication for at least a year. Exclusions – patients with angina pectoris, active coronary artery disease, left bundle branch block, or left ventricular hypertrophy and strain.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Yes, unspecified.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Similar groups: Intervention group had lower baseline and perioperative heart rates.</p>	<p>Randomisation: Yes, unspecified.</p> <p>All patients accounted for: Yes.</p> <p>Patients treated equally: Yes.</p> <p>Similar groups: Yes.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>Nine patients in the standard-care group dies of cardiac causes during the perioperative period versus two in the intervention group. Nine patients in the standard care group had a nonfatal myocardial infarction compared with none in the intervention group.</p>	<p>Myocardial ischaemia occurred in 11 of 39 untreated patients and in two of 89 patients pretreated with a β blocker.</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>"Bisoprolol reduces the perioperative incidence of death from cardiac causes and of nonfatal myocardial infarction in high-risk patients undergoing abdominal aortic or infrainguinal arterial reconstructive surgery."</p>	<p>"The risk of myocardial ischaemia can be diminished 12-fold by the preoperative administration of a single small oral dose of a beta-adrenergic blocking agent."</p>

<h2 style="text-align: center;">Evidence Summary Therapy</h2> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> Prophylactic β-adrenergic blocking agents given in the perioperatively for preventing post-operative cardiac adverse events. </div>	<p>Wallace, A., Layug, B., Tateo, I., Li, J., Hollenberg, M., Browner, W., Miller, D. & Mangano, D.T. (1998). Prophylactic atenolol reduces postoperative myocardial ischemia. <i>Anesthesiology</i>, 88, 7-17.</p>	<p>Balser, J.R., Martinez, E.A., Winters, B.D., Perdue, P.W., Clarke, A.W., Huang, W., Tomaselli, G.F., Dorman, T., Campbell, K., Lipsett, P., Breslow, M.J. & Rosenfeld, B.A. (1998). Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. <i>Anesthesiology</i>, 89, 1052-9.</p>
STUDY DESIGN & NHMRC LEVELS OF EVIDENCE	Randomised controlled trial II	Randomised controlled trial II
DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Patients: 200 patients at high risk for coronary artery disease who were scheduled to undergo noncardiac surgery. Intervention: Two intravenous infusions of 5 mg atenolol 30 minutes prior to surgery, and every 12 hours for seven days after surgery. 50 or 100 mg tablets of atenolol were given in place of intravenous administration if patients were capable of receiving them. Comparison: Placebo. Outcome: Incidence and severity of myocardial ischaemia. Entry Criteria: Inclusions – patients scheduled for elective noncardiac surgery with definite coronary artery disease. Exclusions – presence of left bundle branch block, cardiac pacemaker dependency, or marked resting ST-T wave abnormalities.</p>	<p>Patients: 63 noncardiac surgical patients with recent-onset supraventricular tachyarrhythmia. Intervention: 12.5 mg intravenous bolus of esmolol followed by 25 to 50 mg boluses every 3 to 5 minutes until heart rate decreased to less than 110 beats per minute. Dose was increased incrementally according to set criteria. Comparison: 20 mg loading infusion of diltiazem over 2 minutes followed by a 10 mg per hour maintenance infusion. Dose was increased incrementally according to set criteria. Outcome: Supraventricular tachyarrhythmias, morbidity, mortality. Entry Criteria: Exclusions – haemodynamic instability requiring cardioversion, contraindications to β blockade, dependence on cardiac inotropes, documented bronchospastic disease.</p>
VALIDITY: Methodology, rigour, selection, opportunity for bias	<p>Randomisation: Yes. All patients accounted for: Yes. Patients treated equally: Yes. Similar groups: Intervention group had higher incidence of chronic preoperative β blocker and antihypertensive therapy on admission.</p>	<p>Randomisation: Yes, unspecified. All patients accounted for: Yes. Patients treated equally: Yes. Similar groups: Yes.</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>17 patients in the intervention group had myocardial ischaemia compared to 34 patients in the placebo group. After two years of follow-up, 31 patients in the intervention group and 47 in the placebo group had myocardial ischaemia. Of these patients, 6 in the intervention group and 14 in the placebo died.</p>	<p>20 of 34 patients receiving esmolol converted to sinus rhythm after two hours of therapy compared to 10 of 33 given diltiazem. No effect on conversion in the subpopulation with atrial fibrillation. No substantial differences in mortality, length of ICU stay, or blood pressure support.</p>
AUTHORS COMMENTS: Risk/benefit, limitations	<p>"Perioperative administration of atenolol for 1 week to noncardiac surgical patients at high risk for cardiac morbidity is safe and reduces the incidence of in-hospital postoperative myocardial ischaemia."</p>	<p>"β blockade and calcium channel blockade are equally effective for controlling ventricular rate during postsurgical supraventricular tachyarrhythmias."</p>

SUMMARY STATEMENT

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Publication of materials – please use the following format when citing this article:

Centre for Clinical Effectiveness. Prophylactic β -adrenergic blocking agents given perioperatively for preventing post-operative cardiac adverse events. Southern Health Care Network / Monash Institute of Public Health & Health Services Research, Clayton, 2000.

<http://www.med.monash.edu.au/publichealth/cce>

REQUEST

Do peri-operative beta-blockers reduce myocardial ischaemia, myocardial infarction, and death?

REQUESTED BY

Dr Mark Hurley, Staff Anaesthetist, Department of Anaesthesia, Monash Medical Centre, Clayton

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to predefined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomized controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Search terms:

The following search terms were used to scour electronic databases and websites:

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient-related	Patients undergoing surgery
Intervention-related	Beta-blockers, beta adrenergic antagonists, pre-operative, intraoperative
Comparison-related	
Outcome-related	All

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library (Issue 2, 2000)
- Best Evidence
- Medline (OVID, July Week 4, 2000)
- Agency for Healthcare Research and Quality (AHRQ)
- NHS Centre for Reviews and Dissemination (NHS CRD)
- Aggressive Research Intelligence Facility (ARIF)

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on June 12, 2000. We placed no limitations on dates and applied the following inclusion and exclusion criteria:

Inclusion Criteria

- Randomised or pseudo-randomised controlled trials of perioperative administration of β adrenergic antagonists versus placebo or active control in humans.

Exclusion Criteria

- Study was a crossover trial
- Study examined less than 20 patients
- Study was published in a language other than English
- Study presented data included in a previously published report

RESULTS

The search strategy yielded a total of 90 pertinent articles, the abstracts of which were retrieved and reviewed. Application of the inclusion and exclusion criteria trimmed the total to 32 studies of which only 8 (25%) met the inclusion and exclusion criteria.

EVIDENCE SUMMARIES

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design with level of evidence available according to NHMRC guidelines (1998), patient description, scientific validity of the article, results, and pertinent remarks from the authors.

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

1. Balser, J.R., Martinez, E.A., Winters, B.D., Perdue, P.W., Clarke, A.W., Huang, W., Tomaselli, G.F., Dorman, T., Campbell, K., Lipsett, P., Breslow, M.J. & Rosenfeld, B.A. (1998). Beta-adrenergic blockade accelerates conversion of postoperative supraventricular tachyarrhythmias. *Anesthesiology*, 89, 1052-9.
2. Boylan, J.F., O'Leary, G., Weisel, R.D., Ivanov, J., Mickle, D.A. & Teasdale, S.J. (1990). A comparison of diltiazem, esmolol, nifedipine and nitroprusside therapy of post-CABG hypertension. *Canadian Journal of Anaesthesia*, 37, S156.
3. Daudon, P., Corcos, T., Gandjbakhch, I., Levasseur, J.P., Cabrol, A. & Cabrol, C. (1986). Prevention of atrial fibrillation or flutter by acebutolol after coronary bypass grafting. *American Journal of Cardiology*, 58, 933-6.
4. Mangano, D.T., Layug, E.L., Wallace, A. & Tateo, I. (1996). Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *New England Journal of Medicine*, 335, 1713-20.
5. Poldermans, D., Boersma, E., Bax, J.J., Thomson, I.R., van de Ven, L.L., Blankensteijn, J.D., Baars, H.F., Yo, T.I., Trocino, G., Vigna, C., Roelandt, J.R. & van Urk, H. (1999). The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *New England Journal of Medicine*, 341, 1789-94.
6. Reves, J.G., Croughwell, N.D., Hawkins, E., Smith, L.R., Jacobs, J.R., Rankin, S., Lowe, J. & VanTrigt, P. (1990). Esmolol for treatment of intraoperative tachycardia and/or hypertension in patients having cardiac operations. Bolus loading technique. *Journal of Thoracic and Cardiovascular Surgery*, 100, 221-7.
7. Stone, J.G., Foex, P., Sear, J.W., Johnson, L.L., Khambatta, H.J. & Triner, L. (1988). Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. *Anesthesiology*, 68, 495-500.
8. Wallace, A., Layug, B., Tateo, I., Li, J., Hollenberg, M., Browner, W., Miller, D. & Mangano, D.T. (1998). Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology*, 88, 7-17.

OTHER REFERENCES

1. National Health and Medical Research Council. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: Commonwealth of Australia, 1999.

APPENDIX

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Levels of Evidence

As defined by "A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 1998):

Level I	Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II	Evidence obtained from at least one properly designed randomised controlled trials.
Level III	
-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV	Evidence obtained from case series (either post-test or pre-test and post-test), opinions of respected authorities, descriptive studies, reports of expert (i.e. consensus) committees, case studies.