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Reducing cardiac risk in non-cardiac surgery: evidence from the DECREASE studies

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Ischaemic cardiac events are a major cause of perioperative morbidity and mortality in non-cardiac surgery; 10–40% of the perioperative deaths are due to myocardial infarction (MI). Drugs that influence myocardial oxygen balance (e.g. beta-blockers) or improve plaque stability (e.g. statins) would be expected to reduce perioperative MI. Evidence for the benefit of beta-blockers in high-risk patients undergoing non-cardiac surgery comes from various studies including the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study, in which perioperative bisoprolol significantly reduced short- and long-term cardiac death and MI. DECREASE IV found that bisoprolol also significantly reduced 30-day cardiac death and MI in intermediate-risk patients, with a non-significant trend towards a beneficial effect of fluvastatin XL. DECREASE III showed that in high-risk patients undergoing major vascular surgery, fluvastatin XL reduced myocardial ischaemia and the combined endpoint of cardiovascular death and MI. DECREASE II showed that patients identified as intermediate risk on the basis of clinical assessment did not need pre-operative echocardiographic cardiac stress testing, provided that they received bisoprolol to maintain tight heart rate control. DECREASE V found that in high-risk patients with extensive stress-induced ischaemia, coronary revascularization (added to tight heart rate control with bisoprolol) did not produce any additional reduction in death and MI.

Keywords Non-cardiac surgery • Beta-blockers • Perioperative management • Post-operative complications

Introduction

Ischaemic heart disease (IHD) leading to angina pectoris, myocardial infarction (MI), and chronic heart failure is one of the most important health issues confronting western societies. For example, angina pectoris affects up to 20% of men older than 74 years.[1] Overall, the prognosis of patients with IHD is poor; 5.5% of men with angina pectoris will die due to cardiovascular causes within 2 years of diagnosis.[1] However, prognosis also varies greatly and is related to the presence and treatment of underlying co-morbidities such as diabetes, hypertension, smoking, and hyperlipidaemia.

Treatment of patients with known coronary artery disease (CAD) and IHD is focused not only on symptomatic management, but also on improving prognosis, i.e. preventing acute cardiovascular events and the development of left ventricular (LV) dysfunction. Lifestyle changes (smoking cessation, diet, and exercise) are required, along with pharmacological management.

For example, in stable angina pectoris, management may include anti-platelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors for patients with coincident ACE inhibitor indications, and beta-blockers. Beta-blockers reduce oxygen demand by reducing heart rate, contractility, and blood pressure. ESC guidelines recommend them as first-line anti-anginal agents for their effects on ischaemic symptoms.[1] They also state that they should be used for their long-term preventative benefits in all post-MI patients (discussed subsequently) and in those with LV dysfunction. The guidelines state that, for tolerability, $beta_1$-selective agents such as bisoprolol, metoprolol, and atenolol should be preferred. To achieve 24 h efficacy with once-daily dosing, they suggest using a $beta_1$-selective agent with a long half-life (e.g. bisoprolol) or a formulation providing an extended plasma concentration profile (e.g. metoprolol succinate).

Beta-blockers also play a pivotal part in the management of post-MI patients, in whom long-term beta-blockade reduces the risk of death by about 23%.[2] Current ESC guidelines therefore recommend that beta-blockers should be used long-term in all patients who have recovered from an acute MI (in the absence of contraindications).[3] Normally, treatment will start before the patient leaves hospital and continue indefinitely.

With the benefits of beta-blockers in IHD well-established, attention has turned in the last decade to another situation in which they can prevent ischaemia and save lives: non-cardiac surgery. Cardiac complications are the commonest cause of

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death following major surgery, with MI accounting for 10–40% of post-operative fatalities.[4] Exact data on post-operative outcomes in Europe are scarce. Given that some 40 million surgical procedures are performed annually in Europe and in a large survey from the Netherlands, the incidence of perioperative MI and death is 1 and 0.3%, respectively; it is estimated that about 400 000 of non-cardiac surgical patients suffer an MI each year and about 133 000 die from cardiovascular causes.[5]

The high prevalence of cardiac events associated with non-cardiac surgery reflects the high prevalence of underlying CAD in the general population, upon which the additional stresses of surgery are overlaid. The pathophysiology of perioperative MI is complex, but may include myocardial oxygen demand/supply mismatch associated with tachycardia, hypertension, and pain. Coronary plaque instability and subsequent rupture may also be involved. Thus, drugs that influence plaque stability and myocardial oxygen balance would be expected to reduce the incidence and severity of perioperative MI.

The guidelines of the American Heart Association/American College of Cardiology (AHA/ACC)[6] focus largely on beta-blockers as the most extensively researched pharmacological approach to reducing perioperative cardiac risk in non-cardiac surgery. Beta-blockers improve myocardial oxygenation by decreasing heart rate and myocardial contractility,[6] and this may explain their beneficial effects on cardiac events in high-risk patients undergoing non-cardiac surgery. A recent meta-analysis of 15 studies in 1077 high-risk patients indicated that beta-blockade could reduce the risk of perioperative cardiac death or non-fatal MI by 67%.[7] There is also evidence (albeit less extensive) for a beneficial role of statins. Non-pharmacological measures include surgical and anaesthetic techniques and pre-operative revascularization.

This review briefly summarizes the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) series of studies (*Table 1*).[8–13] These randomized controlled trials have made a significant contribution to our understanding of how to prevent ischaemic events in patients undergoing non-cardiac surgery, using evidence-based evaluation and management strategies.

DECREASE: evidence for beta-blockade in high-risk patients

The first major study establishing a benefit of beta-blockers in reducing cardiac mortality in non-cardiac surgery was DECREASE.[8,9] This study selected a high-risk group of patients with proven CAD undergoing vascular surgery (a high-risk procedure). A total of 1351 patients were screened, 846 of whom had one or more cardiac risk factors. Of these, 173 had stress-induced ischaemia during dobutamine echocardiography and 112 of these were randomized to bisoprolol ($n = 59$) or standard care alone ($n = 53$). Bisoprolol was dosed at 5–10 mg once daily, starting at least 1 week before surgery (average 37 days) and continuing for 30 days post-operatively.

In the bisoprolol group, 2 patients (3.4%) died of cardiac causes within 30 days, compared with 9 patients (17%) who received standard care ($P = 0.02$) (*Figure 1*). Nine patients (17%) in the standard care group had a non-fatal MI, compared with none in the bisoprolol group ($P < 0.001$). The primary endpoint, the combined incidence of cardiac deaths and non-fatal MI, occurred in 3.4% in the bisoprolol group and in 34% in the standard care group ($P < 0.001$). During a 2-year follow-up, long-term administration of bisoprolol produced a significant three-fold reduction in cardiac death and MI (12% for bisoprolol vs. 32% in the standard care group).[8]

As noted in the AHA/ACC guidelines, not all studies show a benefit of perioperative beta-blockade in non-cardiac surgery. Negative results have been reported from some studies with metoprolol.[14,15] However, the AHA guidelines state that 'the weight of evidence—especially in aggregate—suggests a benefit to perioperative beta-blockade during non-cardiac surgery in high-risk patients.[6] Issues raised by the very recent Perioperative Ischemic Evaluation (POISE) with extended-release metoprolol succinate[16] are discussed below.

Table 1 Summary of key findings of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) series of studies

Trial	Risk category	Conclusion
DECREASE I	High	In high-risk patients undergoing non-cardiac surgery, perioperative beta-blockade with bisoprolol significantly reduces cardiac death and MI in the short- and long-term
DECREASE II	Low, intermediate, high	Patients identified as intermediate risk on the basis of a simple clinical assessment do not need pre-operative echocardiographic cardiac stress testing, provided that they receive bisoprolol to maintain resting heart rate at 60–65 b.p.m.
DECREASE III	High	In high-risk patients undergoing major vascular surgery, fluvastatin XL significantly reduces myocardial ischaemia and the combined endpoint of cardiovascular death and MI
DECREASE IV	Intermediate	In intermediate-risk patients, bisoprolol significantly reduces cardiac death and MI, with a non-significant trend towards a beneficial effect of fluvastatin XL
DECREASE V	High	In high-risk patients with extensive stress-induced ischaemia, coronary revascularization (added to tight heart rate control with bisoprolol) does not produce any additional reduction in death and MI and delays surgery

Reference numbers to be added when references are finalized.

DECREASE IV: evidence for beta-blockade in intermediate-risk patients

The AHA/ACC guidelines divide patients undergoing non-cardiac surgery into various risk categories, based on clinical predictors established in observational studies.[17,18] With regard to intermediate-risk patients, the 2007 AHA/ACC recommendations (*Table 2*) state only that beta-blockade 'might be reasonable'. A firm recommendation could not be made on the basis of the available evidence, despite the fact that intermediate-risk patients represent the vast majority of surgical patients evaluated for cardiac risk in everyday practice. However, the issue of whether beta-blockade is beneficial in intermediate-risk patients has recently been addressed by the DECREASE IV study.[12,19]

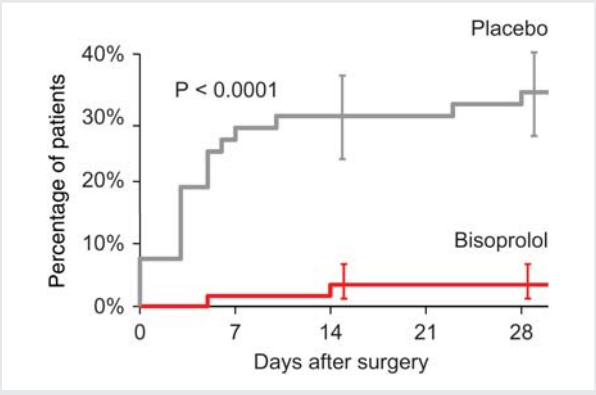

Figure 1 DECREASE showed that in high-risk patients undergoing non-cardiac surgery, perioperative beta-blockade with bisoprolol significantly reduced the combined primary endpoint of cardiac death and myocardial infarction. Reproduced with permission from Poldermans *et al.*[9]

Table 2 Summary of ACC/AHA recommendations on patient selection for perioperative beta-blockade

Potential candidates for perioperative beta-blockade	Strength of recommendation
Patients already receiving beta-blockers	Recommended
Vascular surgery in patients with ischaemia on pre-operative testing	Recommended
Vascular surgery in patients with coronary disease	Reasonable
Vascular surgery in patients with multiple clinical risk factors	Reasonable
Intermediate- or high-risk surgery in patients with coronary disease or multiple clinical risk factors	Reasonable
Intermediate- or high-risk surgery in patients with a single clinical risk factor	Might be reasonable
Vascular surgery in low-risk patients	Might be reasonable

Based on Fleisher *et al.*[6]

DECREASE IV evaluated the effect of bisoprolol and fluvastatin on 30-day cardiac outcome in intermediate-risk patients after elective non-cardiac surgery. Patients were assessed as intermediate risk if they had one or two risk factors on the Revised Cardiac Risk Index Score (one point for each of high-risk surgery, CAD, heart failure, stroke, diabetes mellitus, renal failure). Patients had to be both beta-blocker- and statin-naive, which meant that 45 000 patients had to be screened in order to randomize the final cohort of 1066 patients. The mean age of the patients was 64 years, and 60% were male. About 5% had a history of angina or MI, and 11% had diabetes. This meant that they were at much lower risks than those included in previous studies.

Prior to surgery, patients were randomized to bisoprolol, fluvastatin, the combination or control therapy. Medication was started at a median 34 days before surgery. The starting dose of bisoprolol was 2.5 mg daily, titrated to a perioperative heart rate of 50–70 b.p.m. Fluvastatin was prescribed at a fixed daily dose of 80 mg. The primary endpoint was the composite of cardiac death and MI at 30 days after surgery.

This endpoint occurred in 43 (4.0%) patients: 5 (1.9%) on bisoprolol, 11 (4.1%) on fluvastatin, 6 (2.2%) on the combination, and 21 (7.8%) on double control. The beneficial effect of bisoprolol on the primary endpoint was statistically significant [hazard ratio (HR) 0.34; 95% confidence interval (CI): 0.17–0.67; $P = 0.002$]. Patients receiving fluvastatin had a lower incidence of the primary endpoint than fluvastatin controls (HR 0.65; 95% CI 0.35–1.20), but statistical significance was not reached ($P = 0.17$) (*Figure 2*). The beneficial effects of bisoprolol were not modified by fluvastatin (*P*-value for heterogeneity 0.26).

DECREASE III: evidence for statins in high-risk patients

Statins may act to prevent perioperative cardiac events in non-cardiac surgery by stabilizing coronary plaques, due to their pleiotropic anti-inflammatory effects. The 2007 AHA/ACC guidelines state that 'the evidence accumulated thus far suggests a protective effect of perioperative statin use on cardiac complications during non-cardiac surgery', but note that most of the evidence is observational. A meta-analysis of 12 retrospective and three prospective trials found a 44% reduction in mortality with statins, when both cardiac and non-cardiac surgeries were included.[20]

Recently, the evidence for a beneficial effect of statins has been augmented by DECREASE III, a large randomized controlled trial. This shows that extended-release fluvastatin significantly reduces myocardial ischaemia and the combined endpoint of cardiovascular death and MI in high-risk patients undergoing major vascular surgery.[11]

DECREASE III included 500 statin-naive patients randomized to receive either placebo ($n = 247$) or fluvastatin ($n = 253$)-extended release at a dose of 80 mg once daily—on top of beta-blocker therapy (73% on bisoprolol). The primary endpoint was myocardial ischaemia, as assessed by a combination of continuous ECG monitoring in the first 72 h and then intermittent troponin-T measurements and further ECGs until the end of follow-up (30 days).

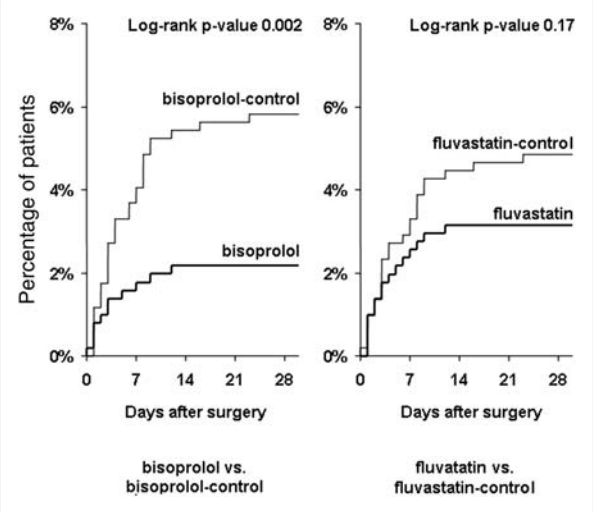

Figure 2 DECREASE IV showed that in intermediate-risk patients undergoing non-cardiac surgery, bisoprolol or bisoprolol plus fluvastatin significantly reduced 30-day cardiac death and myocardial infarction. Fluvastatin alone showed a non-significant trend towards an improved outcome. Reproduced with permission from Dunkelgrun *et al.*[19]

There was a clear reduction in the primary endpoint in the fluvastatin group. One month after surgery, 27 patients in the fluvastatin group (10.9%) had experienced myocardial ischaemia, compared with 47 (18.9%) in the placebo group (OR 0.55; 95% CI 0.34–0.88, $P = 0.013$). The number needed to treat to prevent one patient experiencing myocardial ischaemia was 12.5. Similarly, the combined secondary endpoint of cardiac death or non-fatal MI occurred in 12 (4.8%) patients of those taking fluvastatin, compared with 25 (10.0%) of those on placebo (OR 0.47; CI 0.24–0.94).

DECREASE II: evidence that, with tight heart rate control, non-invasive cardiac testing is unnecessary in intermediate-risk patients

Current guidelines of the ACC/AHA recommend non-invasive cardiac testing to detect CAD in all patients about to undergo major vascular surgery.[6] However, non-invasive testing often delays surgery and carries its own risks. The success of bisoprolol in DECREASE therefore raises an important clinical question: given the protection offered by beta-blockade, is pre-operative echocardiographic stress testing necessary in all patients? DECREASE II was conducted to answer this question in intermediate-risk patients scheduled for major vascular surgery.[10]

DECREASE II included 1476 patients assessed according to a standard set of clinical criteria. Those assessed as low risk (0 risk factors; 24%) were given beta-blocker therapy if they were not already receiving it and proceeded to surgery without further testing. High-risk patients (three or more risk factors; 23%) were referred for further cardiac testing. The remaining 770 patients were categorized as intermediate risk (one to two risk factors) and were randomly assigned to cardiac testing or no cardiac testing.

All patients were prescribed perioperative beta-blockers. Those already receiving beta-blockers continued their medication and those without beta-blockers started on bisoprolol 2.5 mg once daily at the screening visit. Beta-blocker dose was adjusted at admission and on the day before surgery to achieve a resting HR of 60–65 b.p.m. After discharge, patients continued on beta-blockade to maintain resting HR at the same level.

Intermediate-risk patients randomized to no testing had an incidence of cardiac death or MI similar to those who had undergone testing (1.8 vs. 2.3%, $P = 0.62$). The upper limit of the 95% CI of the absolute risk difference in favour of cardiac testing was 1.2%, which indicates that the no-testing strategy was non-inferior to the testing strategy. Patients assigned to pre-operative testing waited an average of 3 weeks longer for their surgery (53 days between screening and surgery vs. 34 days in the no-testing group; $P < 0.001$). This implies that pre-operative echocardiography can be safely omitted among intermediate-risk patients reducing the delay to surgery and beta-blockers should be prescribed aiming at tight heart rate control. Tight heart rate control is important, as poor heart rate control predicted a worse outcome at 30 days.

DECREASE V: evidence that, with tight heart rate control, pre-operative revascularization is not necessary in high-risk patients

The DECREASE V pilot study[13] was designed to determine whether prophylactic coronary revascularization improves post-operative outcomes in high-risk patients with multiple risk factors and extensive stress-induced ischaemia. It screened 1880 patients scheduled for major vascular surgery. Of these, 343 were identified as high risk (three or more risk factors), all of whom received stress testing. Mild or no ischaemia was found in 242 of the high-risk patients. The remaining 101 patients, who had extensive stress-induced ischaemia, were randomized to revascularization ($n = 49$) or no revascularization ($n = 52$). All patients received bisoprolol to maintain tight heart rate control.

Among these high-risk patients with extensive stress-induced ischaemia, those assigned to revascularization had a 30-day outcome similar to those without. The composite endpoint of death or MI occurred in 33% of the revascularization group and in 27% of the no-revascularization group ($P = 0.48$). Two-year follow-up also showed no difference between the groups (*Figure 3*). Moreover, pre-operative cardiac workup delayed surgery, and two patients died between revascularization and operation. The findings of DECREASE V are consistent with those of the Coronary Artery Revascularization Prophylaxis (CARP) study.[21]

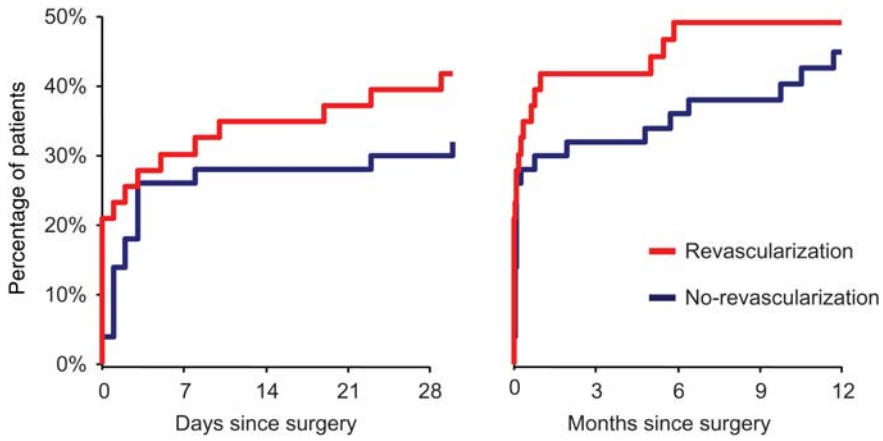

Figure 3 DECREASE V showed that pre-operative revascularization did not improve the outcome (composite endpoint: incidence of all-cause death or MI) for high-risk patients undergoing vascular surgery. Reproduced with permission from Poldermans *et al.*[13]

On the basis of these findings, the 2007 AHA/ACC guidelines[6] note that 'the usefulness of pre-operative coronary revascularization is not well-established in high-risk ischaemic patients'. They therefore restrict their recommendations for pre-operative revascularization to patients with a range of additional specific indications.

Stroke and perioperative beta-blockade: evidence from combined analysis of the DECREASE studies

Concerns have been raised recently by POISE with extended-release metoprolol succinate in patients undergoing non-cardiac surgery.[16] This showed that although metoprolol reduced the risk of cardiac events (cardiac death and non-fatal MI), it increased the risk of severe stroke and overall death.

In contrast, in an analysis of all 3889 patients in the DECREASE trials, there was no evidence of any increase in perioperative stroke.[22] The overall incidence of perioperative stroke was significantly lower in the DECREASE trials compared with POISE: 0.46 vs. 0.98%, $P = 0.006$. Among beta-blocker users, the incidence was 0.5% in the DECREASE trials and 1.0% in the POISE study. In the DECREASE trials, all strokes were of ischaemic origin. Patients were more likely to have a perioperative stroke if they already had a history of stroke, but there was no association with either bisoprolol therapy.

The reasons for the different findings regarding stroke in the DECREASE series of studies and POISE remain the subject of debate.[23] However, it should be noted that the doses of metoprolol succinate used in POISE were high. A 100 mg dose was given 2–4 h before surgery, 100 mg during 6 h after surgery, and 200 mg daily starting 12 h after surgery for 30 days thereafter. Thus, at the day of surgery, the patients received up to 400 mg, which is the maximum recommended therapeutic dose for metoprolol succinate. Moreover, the 100 mg starting dose in POISE was two to eight times the recommended starting dose in other indications. In contrast, in the DECREASE trials, the average dose of bisoprolol was 2.5 mg once daily, only 12.5% of the maximum recommended therapeutic dose.

When beta-blockers are started could also be important. In the DECREASE trials, the low-dose bisoprolol regimen started at least 30 days prior to surgery, whereas in POISE, metoprolol was started 2–4 h before surgery. It is therefore reasonable to recommend that doses of beta-blockers used in non-cardiac surgery should be low (2.5 mg daily for bisoprolol as in the DECREASE trials and 25–50 mg daily for metoprolol succinate). Additionally, the drug should be started 30 days prior to surgery.

Conclusions

DECREASE and other randomized controlled trials provide a firm foundation for the use of beta-blockers to prevent perioperative ischaemic events in high-risk patients (and probably also intermediate-risk patients). Evidence for a beneficial effect of statins is also accumulating. Moreover, tight heart rate control with beta-blockade appears to enable us to dispense with routine non-invasive pre-operative testing in intermediate-risk patients and prophylactic coronary revascularization in high-risk patients. Thus, many patients could proceed to surgery earlier, which has important clinical and economic implications. Although many questions still remain to be answered, it is clear that, in future, new strategies in pharmacological therapy should markedly reduce the heavy burden of cardiac events associated with non-cardiac surgery today.

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