

CORRESPONDENCE



Fluvastatin in Patients Undergoing Vascular Surgery

TO THE EDITOR: The results of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III (DECREASE III) study (Current Controlled Trials number, ISRCTN83738615) reported on by Schouten et al. (Sept. 3 issue)¹ should be interpreted carefully. The reduction of cardiac complications observed in the fluvastatin group cannot be generalized to all patients undergoing vascular surgery. Indeed, inclusion criteria required at least 51 points on a prespecified risk index. This requirement excluded 356 patients from the study. In addition, 798 patients who were already receiving statins were excluded; this was probably an initial response to the guidelines on perioperative evaluation from the American College of Cardiology and the American Heart Association which recommended the use of these drugs.² These guidelines were published after the results of our randomized, controlled trial on this subject.³ In that trial, we found that the use of 20 mg of atorvastatin reduced cardiac events in all patients referred for vascular surgery. De-

spite the fact that we did not have prespecified risk index as an exclusion criterion, we conclude that the available evidence does not provide support for the use of statins to reduce the risk of cardiac events among all patients.

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TO THE EDITOR: Schouten et al. report that fluvastatin reduced postoperative cardiac complications in the DECREASE III trial. However, ischemia was monitored by means of continuous 12-lead electrocardiographic (ECG) recording for only 48 hours after surgery and followed later by three samples of 12-lead ECG recordings and troponin T measurements only on postoperative days 3, 7, and 30. The widely separated timing of the subsequent ECG and troponin T data cannot account for the daily changes in the rates of ischemia, myocardial infarction, and death from cardiovascular causes shown in Figure 1 of the article.

Moreover, since the rates of death and myocardial infarction did not diverge until postoperative day 3, the initial 48 hours of continuous monitoring for ischemia contributed minimally to the reported differences.

Myocardial infarction was diagnosed if two of three criteria (chest pain, ECG changes, or an elevation in troponin T level) were present. This definition is inconsistent with the referenced universal definition of myocardial infarction published in 2007.¹

Multiple studies have shown that typical ischemic chest pain is rare postoperatively, ST-segment elevation ischemia occurs in only 0 to 2% of events, and short-duration ST-segment deviation has minimal, if any, effect on postoperative cardiac complications and survival.²⁻⁴

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THE AUTHORS REPLY: Statins are recommended for patients with peripheral arterial disease. The focus of the DECREASE III trial was whether these drugs should be initiated before surgery in patients who have not received statins, since safety concerns had been raised in previous guidelines.¹ The study by Durazzo et al. evaluated the effect of atorvastatin in patients who had undergone vascular surgery. Though the trial was not powered to assess 30-day postoperative outcomes, there was a trend suggesting a beneficial effect of atorvastatin (odds ratio, 0.23; 95% confidence interval, 0.09 to 1.30).² The present study was sufficiently powered and confirmed these initial results. We disagree with Gualandro et al. that

the population in the current study did not reflect daily clinical practice. In fact, the study population was comparable to that in the study by Durazzo et al., since 91% of the patients in that trial had a risk index of more than 51 points (Durazzo AE: personal communication) and 20% of the patients in the current study were at low risk for postoperative cardiac events.³ The recent guidelines on perioperative care from the European Society of Cardiology also recommend perioperative statins for all patients who undergo vascular surgery.⁴

With regard to the comments by Landesberg et al.: symptoms of perioperative cardiac complications are difficult to recognize in the early postoperative phase. Therefore, objective tests such as ECG monitoring and troponin T measurements are of critical importance. These tests were repeated with a low threshold for suspecting complications, adding information beyond the prespecified times of monitoring. However, approximately 75% of episodes of myocardial ischemia occurred within the first 3 days after surgery. Continuous ECG monitoring improved the understanding of the pathophysiology of perioperative cardiac events. Indeed, the vast majority of patients had ST-segment depression, but fatal cardiac events were preceded by ST-segment elevations in nearly all patients. Since the study protocol was designed in 2003, the definitions of myocardial infarction from 2000 were used and should have been referenced.⁵ However, all patients who were classified as having a myocardial infarction had troponin T levels above the 99th percentile in addition to either symptoms of ischemia or ECG changes that were indicative of new ischemia, or the development of pathologic Q waves in the ECG; this definition of myocardial infarction was recommended in the universal definition proposed in 2007.

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Denosumab, Osteoporosis, and Prevention of Fractures

TO THE EDITOR: In the August 20 issue, Smith et al.¹ and Cummings et al.² report on findings that may herald a new era in therapy for osteoporosis. In spite of an adequate safety profile, concerns remain about adverse effects of denosumab in the long term. Do the authors have data on how effectively denosumab administered twice yearly

blocks the receptor activator of nuclear factor- κ B (RANK) signaling in cells other than osteoclasts (such as immune cells, activated endothelial cells, or hepatocytes)? Are there any metabolic effects that may translate into clinical harm (or benefit) over decades?

No excess risk of acute infections was reported

Table 1. Association of Serum Levels of Soluble RANKL and Osteoprotegerin with the Risk of New-Onset Cancer and Deaths from Cancer among 894 Subjects.*

Risk and Model	Soluble RANKL		Osteoprotegerin	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Incidence of cancer in 146 subjects				
Cox model adjusted for age and sex	0.92 (0.79–1.07)	0.28	1.17 (0.99–1.39)	0.07
Multivariate Cox model†	0.94 (0.81–1.09)	0.40	1.15 (0.95–1.40)	0.15
With follow-up restricted to 1995–2005‡	0.93 (0.77–1.13)	0.39	1.19 (0.95–1.50)	0.12
With time-dependent covariates†§	1.00 (0.87–1.14)	0.94	1.13 (0.96–1.29)	0.16
Men	0.89 (0.75–1.07)	0.22	1.16 (0.91–1.48)	0.24
Women	1.03 (0.79–1.35)	0.81	1.13 (0.83–1.55)	0.44
Deaths from cancer in 81 subjects				
Cox model adjusted for age and sex	0.88 (0.73–1.07)	0.20	1.13 (0.90–1.42)	0.30
Multivariate Cox model†	0.91 (0.75–1.11)	0.34	1.10 (0.85–1.43)	0.46
With follow-up restricted to 1995–2005‡	0.88 (0.71–1.10)	0.25	1.04 (0.77–1.40)	0.81
With time-dependent covariates§	0.88 (0.74–1.04)	0.13	1.06 (0.90–1.25)	0.49
Men	0.85 (0.68–1.06)	0.15	1.08 (0.79–1.48)	0.63
Women	1.10 (0.73–1.65)	0.65	1.13 (0.70–1.84)	0.62

* Hazard ratios and 95% confidence intervals were derived from Cox regression models and calculated for an increase of 1 SD in soluble receptor activator of nuclear factor- κ B ligand (RANKL) and osteoprotegerin. The analysis included 894 subjects who were free of cancer in 1990 (age at baseline, 40 to 79 years); this number included 11 subjects who had recovered from a previous cancer. Cancer status was determined by self-report and a careful review of all medical records of the study subjects and confirmed by histologic findings. Cancer subsumes all malignant conditions except for squamous-cell skin cancer. Follow-up (1990–2005) for cancer was 100% complete.

† Multivariate models are adjusted for age (years), sex, smoking status, C-reactive protein level (milligrams per liter), body-mass index, social status, and the use or nonuse of hormone-replacement therapy.

‡ In this model, baseline (1990) variables were analyzed in relation to the incidence of cancer and cancer deaths occurring between 1995 and 2005.

§ In this model, all variable levels were entered as time-dependent variables, with an update of variable levels every 5 years.