

## PREVENTING CARDIAC COMPLICATIONS AFTER NON-CARDIAC NON-VASCULAR SURGERY BY USING PERIOPERATIVE STATIN THERAPY – A PROSPECTIVE STUDY IN CONSTANTA COUNTY, ROMANIA

IRINEL-RALUCA PAREPA<sup>1#\*</sup>, ANDRA-IULIA SUCEVEANU<sup>1#</sup>, LAURA MAZILU<sup>1#</sup>, AQEL MOHAMED<sup>2#</sup>, DANIEL NIȚĂ<sup>2#</sup>, LILIANA-ANA TUȚĂ<sup>1#</sup>

<sup>1</sup>"Ovidius" University, Faculty of Medicine, Constanța, Romania

<sup>2</sup>"Vasile Cârdeza" Army Centre for Cardiovascular Diseases, Bucharest, Romania

\*corresponding author: irinel\_parepa@yahoo.com

#All authors had equal scientific contribution.

Manuscript received: January 2016

### Abstract

The aim of the study was to evaluate if statins reduce the risk of cardiac events when given during perioperative period in patients who undergo non-cardiac, non-vascular surgery. 1,380 "statin-naive" patients with no evidence of cardiac disease were randomised for: rosuvastatin 10 mg/day (n = 691), and placebo (n = 689), given 10 days before and 20 days after surgery and were followed-up 3 months after surgery. Endpoint was defined as new-onset angina, silent cardiac ischemia, non-fatal acute coronary syndrome or fatal coronary heart disease. 82 patients (5.95%) suffered cardiac events during follow-up: 31 from statin arm and 51 from placebo arm (p = 0.0029). After adjusting for variables, the statin arm had a relative-risk reduction of 39% (p = 0.0189) for cardiac events. No significant decrease in LDL-cholesterol was found in statin patients (p = 0.5664). Perioperative statin therapy was protective against cardiac complications of non-cardiac non-vascular surgery, irrespective of its lipid-lowering effect.

### Rezumat

Scopul studiului a fost evaluarea efectului statinelor administrate perioperator la pacienți cu intervenții chirurgicale electiv noncardiace, nonvasculare asupra riscului complicațiilor cardiace. 1380 pacienți fără antecedente cardiace și "naivi" la statine au fost randomizați pentru: rosuvastatină 10 mg/zi (n = 691), respectiv placebo (n = 689), administrată 10 zile înainte și 20 zile după intervenție; pacienții au fost urmăriți 3 luni după operație pentru angină pectorală *de novo*, ischemie cardiacă silențioasă și sindroame coronariene acute nefatale/fatale. 82 pacienți (5,95%) au avut evenimente cardiace: 31 din brațul cu statină, 51 din brațul placebo (p = 0,0029). După ajustare statistică pentru variabile, riscul relativ de evenimente cardiace a fost cu 39% (p = 0,0189) mai mic în brațul cu statină, fără a exista o reducere semnificativă a LDL-colesterol față de brațul placebo. Administrarea perioperatorie a statinei a protejat față de complicații cardiace la pacienți cu chirurgie electivă noncardiacă nonvasculară.

**Keywords:** statins, cardiac complications, non-cardiac non-vascular surgery

### Introduction

Immediate and late morbidity and mortality after general surgery are particularly related to cardiac complications [1]. Despite the advances of anaesthesia techniques and patient's perioperative monitoring, the mortality from myocardial infarction after non-cardiac non-vascular surgery is reported to be more than 10% [2]. This is a challenging issue for the pre-operative patient's evaluation, because the ischemic heart disease is often asymptomatic and increasingly prevalent world-wide.

The perioperative cardiac events are precipitated by the surgical and the anaesthesia stress. These factors trigger myocardial overload, due to blood loss during surgery, impaired secretion of catecholamines and glucocorticoids, tachycardia, blood pressure instability,

pain and other local and systemic conditions [1, 3, 4]. Patients with heart disease - overt or silent - have a higher risk, because the pathophysiology of acute ischemic cardiac events implies the rupture of an unstable coronary atheromatous plaque [5].

Some studies showed that the risk of perioperative myocardial infarction is correlated with the stability of the coronary atheromatous plaque rather than with the degree of coronary obstruction [6, 7]. These data suggest that cardiac complications after non-cardiac non-vascular surgery may be reduced with drugs that stabilize blood pressure, heart rhythm and/or coronary atherosclerotic plaques.

Beta blockers already demonstrate significant effects in reducing the adverse outcomes during and after surgery, due to their antiadrenergic, metabolic and

antiarrhythmic actions [8]. Statins are promising for the same perioperative setting, due to their effects against endothelial dysfunction - which finally stabilize the atherosclerotic plaques and decrease vascular inflammation [9 - 13].

There are overwhelming evidences implying statins for the outcome improvement after vascular surgery [14 - 18]. Some studies reported that statins could also be beneficial when given during perioperative period in non-cardiac non-vascular surgery [19 - 21], but other studies showed controversial results [22], so there is still a great need for large clinical trials regarding this issue.

Given these preliminary background data, the aim of our study was to evaluate if statins reduce the risk of cardiac events when given during perioperative period in non-cardiac, non-vascular surgery, even in patients with no previous evidence of cardiac disease (so having a lower risk for surgically-related cardiac complications).

### Materials and Methods

1,380 patients undergoing elective non-cardiac, non-vascular surgery were randomised for perioperative statin therapy during 1 year (1<sup>st</sup> of February 2011 - 31<sup>st</sup> of January 2012), in the General Surgery Department of Constanța County Hospital, Romania. Patients were initially evaluated by a cardiologist and had no previous evidence of cardiac disease: they had normal resting ECG, normal blood pressure and no history of exertional dyspnoea, effort angina or acute

coronary syndromes. All patients were included in our study regardless their baseline serum cholesterol levels and all patients were "naive" for treatment (no previous statin therapy). The study was approved by the Ethics Committee of the Hospital and patients signed the informed consent before enrolling.

Patients were randomised in two arms: one arm received rosuvastatin 10 mg/day (n = 691), and the second arm received placebo (n = 689), for 10 days before and 20 days after surgery. Both arms received a low-dose selective beta-1 blocker (bisoprolol 1.25 mg) for 3 days before and 5 days after surgery. Patients were followed-up 3 months after surgery: after 30 days (clinical history, clinical exam, ECG and LDL-cholesterol sampling) and after 3 months (clinical history, clinical exam, ECG).

The primary endpoint was defined as a composite cardiovascular event – new-onset angina, silent cardiac ischemia, non-fatal acute coronary syndrome or fatal coronary heart disease.

### Results and Discussion

The demographic statistical analysis of the 1,380 patients enrolled in our study showed the following results: the majority of patients (59.4%) were males (820 males vs. 560 females); mean age of the studied patients was 64.2 years, but among male patients mean age was slightly lower, comparing with females (60.8 years vs. 67.6 years); most patients (62.7%) came from urban environment (Table I).

**Table I**  
Demographic data of the studied patients

Age/environment	Patients enrolled	Male	Female
	1,380	820 (59.4%)	560 (40.6%)
Mean age (years)	64.2	60.8	67.6
Urban environment	866 (62.7%)	620 (75.6%)	246 (43.9%)
Rural environment	514 (37.3%)	200 (24.4%)	314 (56.1%)

The majority of the studied patients (94.3%) underwent general anaesthesia; the rest underwent neuroaxial (spinal) anaesthesia, therefore so in our study the choice of anaesthesia did not statistically influence the cardiac morbidity (Table II).

Both arms of our study had nearly identical biochemical characteristics, as it can be seen in Table III.

**Table II**  
Type of anaesthesia among patients enrolled in the study

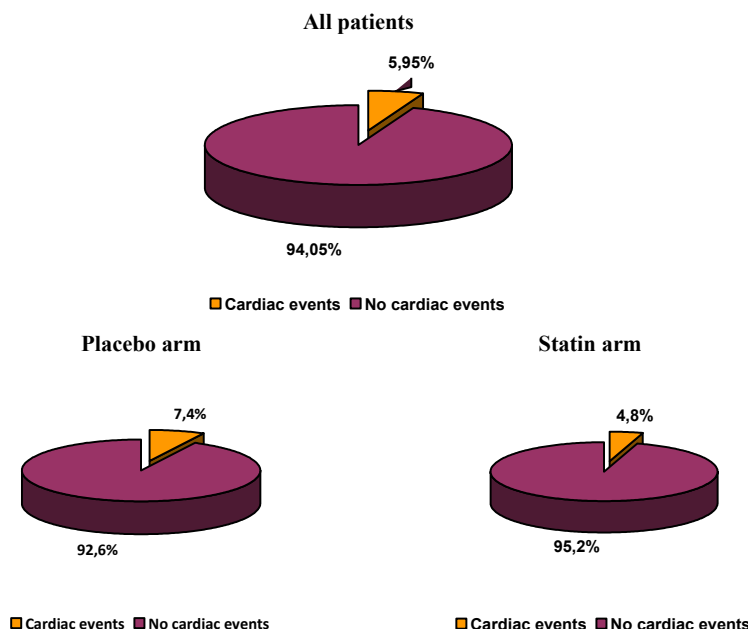
Type of anaesthesia	Patients
General	1,302 (94.3%)
Neuroaxial	78 (5.7%)

**Table III**  
General characteristics of enrolled patients

Characteristic	Statin arm	Placebo arm
Mean age (years)	63.8	64.7
Male (%)	59.1	59.8
Female (%)	40.7	39.9
Mean LDL-cholesterol level (mg/dL)	113 ± 3.8	111 ± 4.2
Mean blood pressure (systolic/diastolic) (mmHg)	135 ± 3.6/82 ± 2.2	134 ± 3.9/82 ± 2.6
Diabetes mellitus or altered glucose tolerance subjects (%)	1.30	1.01
Smokers (> 10 cigarettes/day) (%)	6.9	7.2

At baseline, the average LDL-cholesterol level of the subjects in both study arms was  $112 \pm 3.4$  mg/dL. After 30 days mean LDL-cholesterol was  $108 \pm 4.7$  mg/L, showing a slight but not statistically significant decrease (OR = 1.075; 95% CI 0.7400 - 1.563; p = 0.7749).

In both of the study arms, 82 patients (5.95%) underwent a cardiac complication during follow-up period: 31 patients from statin arm and 51 patients from placebo arm, with a significantly lower incidence among statin patients (4.8% vs 7.4%; OR = 0.3695; 95% CI 0.1965 - 0.6947; p = 0.0029) (Figure 1).



**Figure 1.**

Composite cardiac events in all patients, statin arm and placebo arm

After adjusting for age, sex, LDL-cholesterol and other risk factors (smoking, diabetes mellitus, blood pressure), the statin arm had a relative risk reduction of 39% (OR = 0.4536; 95% CI 0.2429 - 0.8468; p = 0.0189) for composite cardiac events during follow-up period.

The severity of coronary events was lower in the statin arm, the number of patients experiencing

acute fatal/non-fatal coronary syndromes being significantly lower in the active study arm than in the placebo arm (7 vs 19; OR = 0.1357; 95% CI 0.03984 - 0.4624; p = 0.0020); new-onset angina and silent ischemia were also lower in the statin arm, but with no statistical significance (24 vs 32; OR = 0.5625; 95% CI 0.2661 - 1.189; p = 0.1857) (Table IV).

**Table IV**

Distinct coronary events in statin arm and placebo arm

Coronary event	Statin arm	Placebo arm
	No. of patients/%	No. of patients/%
New-onset angina	12 (38.7%)	15 (29.4%)
Silent ischemia	12 (38.7%)	17 (33.3%)
Non-fatal acute coronary syndromes	5 (16.1%)	12 (23.5%)
Fatal coronary heart disease	2 (6.4%)	7 (13.7%)
<b>Total</b>	<b>31</b>	<b>51</b>

In order to reduce the burden of cardiac complication after non-cardiac non-vascular surgery, clinical guidelines already established an accurate presurgical evaluation of selected patients [23]. However, many clinical trials emphasize that cardiac risk may still be substantially reduced by active prophylactic measures in larger categories of patients. Our study pointed out a significant cardiac protective role of statins in the perioperative period, showing a 39% relative risk reduction for global cardiac events. This result

superposed on other observational studies and one small randomized study results [24], which have shown that perioperative statin therapy in non-cardiac non-vascular surgery lowers the risk of cardiac major events, with relative risk reductions ranging between 80% and 30% compared with patients not receiving statins.

In our study this protection proved not to be given by the lipid lowering effect of statins: the average LDL-cholesterol level of the patients enrolled in

our study was  $112 \pm 3.4$  mg/dL, a value close to normal range for patients with mild-to-moderate cardiovascular risk [25, 26], and after completing the 30-days treatment with a moderate dose of a potent statin (10 mg rosuvastatin) the average LDL-cholesterol level showed only a slight, non-significant decrease to  $108 \pm 4.7$  mg/dL ( $p = 0.7749$ ). Thus, in our study the cardioprotection of perioperative-given statins seems to be much more related to a possible stabilization of silent unstable coronary atherosclerotic lesions, due to the "pleiotropic" effects of statins: increasing endothelial NO synthetase, decreasing endothelin-1 production, decreasing inflammation, decreasing oxidative stress, decreasing C-reactive protein levels, inhibiting metalloproteinase synthesis and inhibiting the thrombogenic response [27]. This process may start shortly after the beginning of statin treatment, as the improving of endothelial function starts immediately after first pill administration [28, 29].

### Conclusions

In our study perioperative statin therapy had a protective role against cardiovascular complications of non-cardiac, non-vascular surgery, with a relative risk reduction of major cardiac events of 39%, in patients with no previous evidence of cardiac disease and independent of LDL-cholesterol levels. This effect seemed to be related to the improvement of endothelial function enhanced by statins. Larger randomized studies are still needed to prove this effect and to establish the optimal dosage as well as timing and length of perioperative statin therapy.

### Conflicts of interest

The authors declare no conflict of interest.

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