

# Effects of high-dose statin administered prior to coronary angioplasty on the incidence of cardiac events in patients with acute coronary syndrome

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## Abstract

**Introduction:** Statins given after acute coronary syndrome without ST elevation (NSTEMI-ACS) reduce the incidence of major adverse cardiac events (MACE) in long-term follow-up.

**Aim:** To evaluate the effects of high-dose statin administered in patients with NSTEMI ACS and increased CRP level prior to percutaneous coronary intervention (PCI) on the incidence of MACE in long-term follow-up.

**Methods:** The study involved 140 consecutive patients with NSTEMI ACS and increased CRP level at baseline. Patients from group A (n=54) did not receive statin before PCI, whereas subjects in group B (n=86) were given 80 mg of atorvastatin. Patients in both groups received typical cardiological therapy including aspirin, thienopyridine and low molecular weight heparin. After PCI all patients received 40 mg of atorvastatin. Incidence of MACE (death, myocardial infarction (MI), re-PCI) during long-term follow-up was evaluated in both groups.

**Results:** Study groups did not differ with respect to demographic parameters and rate of ischaemic heart disease risk factors. Also, no differences occurred regarding CRP level (group A vs. B: hsCRP 10.8±1.8 mg/l vs. 8.2±2.8 mg/l; p=NS) and TIMI Risk Score (group A vs. B: 4.3±0.71 vs. 4.37±0.79; p=NS). During long-term follow-up the incidence of MI (9.25% vs. 1.2%, p=0.03), composite endpoint: death + MI (14.8% vs. 2.32%, p=0.013) and death + MI + re PCI (25.9% vs. 8.1%, p=0.006) was significantly higher in group A than group B.

**Conclusions:** Administration of high-dose statin in NSTEMI ACS patients before PCI was associated with significant reduction of MACE in long-term follow-up. This effect was observed despite the same therapy given after PCI.

**Key words:** acute coronary syndrome, statin, inflammation, coronary angioplasty

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## Introduction

Results of randomised clinical trials confirmed the effectiveness of statins in primary and secondary prevention of ischaemic heart disease. Long-term use of statins was associated with reduction of frequency of major adverse cardiac events (MACE) such as death, myocardial infarction (MI) and repeat revascularisation [1-3]. However, this effect was frequently reached after several months, even years, of statin use in patients with stable coronary artery

disease. Over time studies on the effectiveness of statins in the therapy of acute coronary syndromes (ACS) have been undertaken. Percutaneous coronary intervention (PCI), which is a recommended approach to the treatment of ACS, is often limited to the single culprit lesion and does not affect all pathophysiological changes underlying ACS. Therefore, the need for optimisation of medical therapy of ACS patients was emphasised. Due to the primary role of inflammation in ACS pathogenesis and the strong

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**Table I.** Characteristics of the studied groups

	Group A (n=54)	Group B (n=86)
Age (years)	59.9±10.5	58.1±10
Men (%)	83	77
Diabetes (%)	16.7	18.6
Arterial hypertension (%)	66.7	73.2
Myocardial infarction (%)	42.6	53.5
Cholesterol (mmol/l)	5.5±1.1	5.0±1.3
LDL-cholesterol (mmol/l)	3.43±0.94	3.3±0.82
HDL-cholesterol (mmol/l)	1.07±0.24	1.12±0.21
Triglyceride (mmol/l)	1.92±0.82	1.81±0.75
Positive troponin test (%)	57.4	59.3
Ejection fraction (%)	53.2±9.5	55.8±8.8
hs CRP mg/l	10.8±1.8	8.2±2.8
TIMI Risk Score	4.3±0.71	4.37±0.79

*Differences between groups A and B – NS*

anti-inflammatory potential of statins these agents were attempted to be used in subsequent studies as early as possible after confirming the diagnosis [4, 5].

Immediate effects of statins are essential in therapy of patients with ACS. In animal model studies the effects of this group of drugs such as inhibition of adhesion and migration of activated leukocytes and increase of nitric oxide synthesis were observed as soon as after 18 hours [6]. One of our previous studies concluded that short-term therapy with high-dose statin in patients with unstable coronary artery disease prior to PCI significantly reduced CRP level, which is a sensitive marker of inflammation [7]. The aim of this study was to assess whether short-term therapy with high-dose statin before PCI also produces long-term clinical benefits.

## Methods

The register involved 140 consecutive patients with non-ST-segment elevation acute coronary syndrome (NSTEMI ACS) hospitalised at our Department between Dec. 2002 and May 2003 and referred for invasive treatment. The inclusion criteria were as follows: age 18-75 years, diagnosis of NSTEMI ACS, referral for PCI, activation of inflammatory reaction confirmed with increased level of hsCRP >3 mg/l, and patient's consent to participate in the study. Exclusion criteria were as follows: contraindications to invasive treatment, presence of active inflammation (e.g. rheumatoid arthritis), contraindications to statin therapy, and indications for urgent PCI. Patients were divided into two groups: group A (n=54) comprised patients who received no statin before angioplasty,

whereas subjects in group B (n=86) were given 80 mg of atorvastatin for 3 days prior to the intervention. Patients in both groups received typical medical therapy: 75 mg of aspirin, 75 mg of clopidogrel with initial loading dose of 300 mg, enoxaparin 1 mg/kg per body weight b.i.d.,  $\beta$ -blocker, ACE inhibitor, and nitrates. After PCI all patients received 40 mg of atorvastatin. In both groups the incidence of MACE during hospitalisation and long-term follow-up was analysed (death, MI, and need for repeat revascularisation (re-PCI)) as well as incidence of composite endpoints: death + MI and death + MI + re-PCI. Mean follow-up was 641±373 days in group A and 592±360 days in group B (NS).

## Statistical analysis

Results are shown as means  $\pm$  standard deviation or percentage of patients. Continuous and dichotomous variables were analysed with Wilcoxon pair test, U Mann-Whitney's test and Fisher's exact test, respectively. The results were found statistically significant if p value was <0.05. The cumulative survival free from MACE was estimated with Kaplan-Meier method and the differences between treated groups were evaluated with the log rank test.

## Results

At baseline, the study groups did not differ with respect to demographic parameters and frequency of ischaemic heart disease risk factors (Table I). Also, no significant differences were found regarding baseline CRP levels and TIMI Risk Score. In group A coronary angioplasty of the left anterior descending coronary artery (LAD) accounted for 46.8%, the left circumflex coronary artery (CX) – 30.6% and the right coronary artery (RCA) – 22.6% of all procedures. Multi-vessel interventions comprised 14.8% of all procedures in group A. In group B, LAD was treated with PCI in 44.9%, CX in 31.6% and RCA in 23.5% of cases. Multi-vessel angioplasties comprised 13.9% of all procedures performed in group B. No significant differences were found between groups with respect to the distribution of vessels treated with PCI and the number of multi-vessel procedures.

In group A stent was inserted in 66.7% of procedures, in group B – in 67.4% of interventions (NS). In both groups only bare metal stents were inserted. In group A platelet IIb/IIIa receptor inhibitor (abciximab – ReoPro) was used in 11.1% of patients, in group B – in 11.6% of cases (NS). Mean duration of hospitalisation was 5.4±0.5 days in group A and 5.8±0.4 days in group B (NS). During hospitalisation

neither deaths, infarctions nor urgent re-PCI were observed in the study groups.

During the long-term follow-up the incidence of MI as well as the occurrence of both composite endpoints, death + MI and death + MI + re-PCI, was significantly higher in group A than in group B (Table II). Mortality also tended to be higher in group A as well as the need for re-PCI.

The Kaplan-Meier curves of freedom from fatal events and MI in the studied groups are shown in Figure 1.

## Discussion

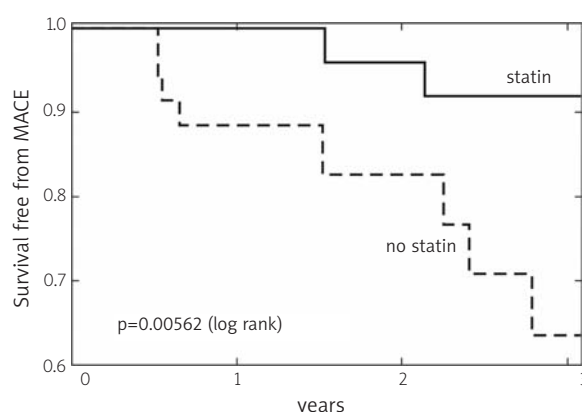
This study compared the long-term clinical outcomes of patients in whom 80 mg of atorvastatin was given prior to PCI with a group of subjects who at the same time received no statin. Analysis of MACE rate during follow-up revealed that short-term therapy with high-dose statin before PCI in patients with NSTEMI/ACS was associated with a significant reduction of incidence of MACE in nearly two-year follow-up.

Recent studies compared the effectiveness of so-called standard with aggressive statin therapy and 80 mg of atorvastatin was the most often used dose. The PROVE-IT or TNT trials, in which significant decrease of primary endpoint was reached, confirmed the concept of aggressive treatment with high dose of statin [5, 8]. However, in the IDEAL study a similar significance level failed to be met with respect to primary endpoints with benefits present only with respect to secondary endpoints [9].

Lately, the approach to statins as a group of drugs which if used for a prolonged period only decrease cholesterol level thus reducing the risk of recurrent cardiovascular events, has changed. Currently, the expectations for statins are related to their fast action and rapid effects in patients with ischaemic heart disease exacerbated to ACS. Potential benefits associated with statin use in ACS are mainly due to their non-lipid action [10, 11]. Statins have antiinflammatory, antithrombotic, and fibrinolytic properties; they modify platelet function and influence endothelium [12]. Due to the essential role of inflammation in the pathogenesis of atherosclerosis, the most promising hopes for the improvement of outcomes of ACS treatment are placed on the antiinflammatory activity of statins [13-15]. Activation of inflammatory reaction within the entire coronary bed associated with ACS is not only limited to the culprit lesion targeted on coronary angiography [16]. At the turn of 2002 and 2003, when the study started, the dose of 80 mg of atorvastatin

**Table II.** Incidence of MACE in long-term follow-up

	Group A (n=54)	Group B (n=86)	p
Mean follow-up (days)	641±373	592±373	NS
Mortality (%)	5.5	1.2	NS
MI (%)	9.25	1.2	0.03
rePCI (%)	11.1	5.8	NS
Death + MI (%)	14.8	2.32	0.013
Death + MI + rePCI (%)	25.9	8.1	0.006



**Figure 1.** Kaplan-Meier survival curves

was rarely used, even at clinical units. Meanwhile, recent metaanalyses confirmed that administration of highdose (80 mg) atorvastatin is safe and does not increase the risk of adverse reactions [17].

One potential explanation of the presented results may be that statin treatment limits ASC-related inflammatory reactions and attenuates PCI-induced inflammation associated with instrument insertion into the coronary artery [18]. One of the available reports showed that 40 mg of atorvastatin significantly reduced CRP levels in ACS patients after a mean of 4 days of therapy [19]. We obtained similar results in one of our previous studies, in which 80 mg of atorvastatin was found to significantly decrease CRP levels as soon as after 3 days of therapy. Additionally, administration of atorvastatin was associated with a significant decrease in postprocedural CRP elevation, which is commonly observed after invasive procedures [7]. CRP was initially found to be a marker of only inflammatory reaction. Recently, more and more data confirm the direct involvement of CRP in formation and progression of atherosclerotic lesions; hence rapid reduction of its concentration after administration of atorvastatin in ACS patients may considerably influence further clinical course.

In a majority of ACS patients noticeable endothelial dysfunction is observed, which itself is an unfavourable predictor of increased risk of recurrent coronary events [20]. Statins increase the activity of nitric oxide directly and indirectly by degradation of nitric oxide synthase, which improves endothelial function. One report demonstrated improvement of endothelial function at 24 hours of administration of the first dose of statin [12]. Also, in one of our recent studies rapid improvement of endothelial function was shown as a result of aggressive short-term atorvastatin at a dose of 80 mg in NSTEMI ACS patients [21]. Rapid improvement of endothelial function in ACS patients is associated with better prognosis [20].

Another concept related to the effects of statins on clinical outcome of ACS patients is their direct effect on morphology and volume of atherosclerotic plaque. As was presented in the REVERSAL trial, statin impact on plaque volume may be detectable no sooner than after 2 years of atorvastatin 80 mg treatment. It should be emphasised that in the referenced report in the group of patients aggressively treated with atorvastatin reduction of plaque volume was not achieved but only inhibition of its progression was documented [22]. On the other hand, the ASTEROID trial confirmed high effectiveness of rosuvastatin, resulting in considerable reduction of atherosclerotic plaque volume after 24 months of treatment [23]. In the light of these results it seems almost certain that our short-term therapy with high-dose statin given prior to PCI could not influence plaque volume and effect further clinical course in this way.

One possible mechanism of the action of statins that may impact further clinical outcome could be inhibition of the ACS-related thrombotic process. Aggressive statin therapy is effective in rapid reduction of CRP levels, which through release of tissue factor directly participates in activation of the thrombotic process [24]. Additionally, statins inhibit the reaction between soluble CD40L and its receptor CD40 located also on platelets. The blockage of the CD40L/CD40 complex restrains thrombus formation [25].

Due to a range of non-lipid actions of statins including anti-inflammatory potential, their administration as soon as possible after diagnosis of ACS is a valuable additional treatment to PCI in ACS patients. On the other hand, therapy with high-dose statin started even very soon will not prevent all recurrent coronary events. It seems to be essential to search for new therapeutic approaches involving drugs with a direct anti-inflammatory effect.

## Conclusions

Short-term aggressive medical therapy started immediately after diagnosis of ACS may significantly influence further clinical course. Administration of high-dose statin, e.g. 80 mg of atorvastatin, in NSTEMI ACS patients before PCI is associated with reduction of MACE rate in long-term follow-up compared with patients who did not receive statin before invasive treatment.

This effect was observed despite the same statin dosage in both groups after PCI.

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## Wpływ wysokiej dawki statyny stosowanej przed zabiegiem angioplastyki wieńcowej na częstość ponownych zdarzeń kardiologicznych u pacjentów z ostrym zespołem wieńcowym

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### Streszczenie

**Wstęp:** Statyna zastosowana po ostrym zespole wieńcowym bez uniesienia odcinka ST (NSTEMI ACS) redukuje częstość poważnych zdarzeń kardiologicznych (MACE) w obserwacji odległej.

**Cel:** Ocena wpływu wysokiej dawki statyny zastosowanej u pacjentów z NSTEMI ACS i podwyższonym poziomem CRP przed angioplastyką wieńcową (PCI) na częstość MACE w obserwacji odległej.

**Metodyka:** Do badania zakwalifikowano 140 kolejnych pacjentów z NSTEMI ACS i wyjściowo podniesionym poziomem białka CRP. W grupie A (n=54) pacjenci przed PCI nie otrzymywali statyn, natomiast w grupie B (n=86) w analogicznym okresie otrzymywali 80 mg atorwastatyny. Pacjenci w obu grupach otrzymywali typowe leczenie kardiologiczne obejmujące aspirynę, tienopirydynę oraz heparynę drobnocząsteczkową. Po zabiegu wszyscy pacjenci otrzymywali atorwastatynę w dawce 40 mg. W obu grupach analizowano częstość poważnych zdarzeń kardiologicznych w obserwacji odległej (zgon, zawał serca, ponowne PCI – rePCI).

**Wyniki:** Badane grupy nie różniły się w zakresie parametrów demograficznych oraz częstości występowania czynników ryzyka choroby niedokrwiennej serca. Nie było także różnic w zakresie poziomu CRP (Grupa A vs B: hs CRP  $10,8 \pm 1,8$  vs  $8,2 \pm 2,8$ ; p=NS) oraz punktacji TIMI Risk Score (Grupa A vs B:  $4,3 \pm 0,71$  vs  $4,37 \pm 0,79$ ; p=NS). W obserwacji odległej w grupie A w porównaniu z grupą B znacząco częściej obserwowano: zawały serca (9,25% vs 1,2%, p=0,03), złożony punkt końcowy: zgon + zawał serca (14,8% vs 2,32%, p=0,013) oraz zgon + zawał + rePCI (25,9% vs 8,1%, p=0,006).

**Wnioski:** Zastosowanie wysokiej dawki statyny u pacjentów z NSTEMI ACS przed PCI wiąże się ze znaczącą redukcją częstości MACE w obserwacji odległej. Efekt ten obserwowano pomimo tej samej terapii po zabiegu PCI.

**Słowa kluczowe:** ostry zespół wieńcowy, statyna, zapalenie, angioplastyka wieńcowa

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