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Adress: Univerzitetski trg 2, 18000 Niš, YU, Tel: +381 18 547-095 Fax: +381 18 547-950
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LONG-TERM EFFECT OF CAPTOPRIL ON PLASMA LIPIDS IN ACUTE MYOCARDIAL INFARCTION: POSSIBLE MECHANISM OF ANTIATHEROSCLEROTICAL EFFECT OF ACE INHIBITION

Zorana Vasiljević[1], *Aneta Bošković*[1], *Miodrag Ostojić*[1], *Milica Prostran*[2], *Nikola Kocev*[3]

[1]*Institute for Cardiovascular Diseases, Belgrade, Yugoslavia*
[2]*Department of Clinical Pharmacology, Pharmacology and Toxicology, School of Medicine, Belgrade, Yugoslavia*
[3]*Institute for Medical Statistics, Belgrade, Yugoslavia*

Summary. *It is known that ACE inhibitors have beneficial effects on the left ventricular function and cardiovascular events after myocardial infarction. Also, it is important that ACE inhibitors are lipid neutral, with no deleterious effects on the lipid status. The lipid status could influence progression of atherosclerosis and coronary artery related events. There is no reported long-term clinical study of ACE inhibitor treatment in and after acute myocardial infarction on a lipid status.*
In the placebo-controlled open label randomized study, 104 patients with acute myocardial infarction were observed for a period of seven years: 52 patients with standard therapy (con group) and 52 patients with captopril therapy (cap group), 6.25 mg the first 12 h after the onset of AMI, followed by 6.25 mg to 25 mg two times daily. No differences were observed between the groups at baseline. The seven years period was reached by 80 patients; in the captopril group, there were less patients with cardiovascular events ($p<0.05$), less patients with clinical signs of heart failure, less mortality, and higher levels ($p<0.02$) of HDL cholesterol.
Despite the small group of patients (n=52), statistically significant increase in HDL cholesterol values and less pronounced mortality and morbidity during the entire period of seven years were observed in the cap group.

Key words: *Captopril, lipids, myocardial infarction*

Introduction

It is well known that angiotensin-converting enzyme inhibitors can ameliorate the deleterious effects of elevated renin and angiotensin II levels in patients with acute myocardial infarction. The results of several important clinical trials (e.g. SAVE, AIRE, ISIS IV, GISSI III) have shown that ACE inhibitors significantly reduce cardiovascular morbidity and mortality by attenuation of the left ventricular enlargement and heart failure, and also by reductions in the occurrence of acute coronary artery disease-related events. The mechanism by which inhibition of the renin-angiotensin-aldosterone system leads to these beneficial results have not been ascertained, but may be related to the effect of angiotensin II and aldosterone on the development of atherosclerosis, endothelial dysfunction, plaque rupture, or thrombosis after plaque rupture.

There were many experimental, but no clinical studies about antiatherogenic ACE inhibitor effects: the drug decreased plaque cholesterol content and cellularity. Observations in a primate paradigm have demonstrated similar effects. There are only a few reports about long-term changes in lipid blood levels (e.g. total cholesterol, HDL and LDL cholesterol, triglycerides) during therapy with ACE inhibitors in hypertension, but not one report of the long-term effect of ACE inhibitors on the lipid status in acute myocardial infarction. In the TOMHS study, decreases in HDL cholesterol were observed during long-term enalapril therapy of hypertension (1). In another study with captopril therapy of hypertension, Pollare et al. reported that captopril had beneficial effects on lipid metabolism (2).

The aim of this study was to investigate the effects of captopril in acute myocardial infarction and during seven years of treatment, on plasma lipids and on cardiovascular mortality and morbidity.

Materials and Methods

This study was an open label randomized controlled clinical study of captopril treatment in the first acute myocardial infarction. The captopril (cap) group of 52 patients was on standard therapy plus captopril 6.25 mg

within the first 12 h of admission and subsequently up to 25 mg two times daily. The control (con) group of 52 patients was on standard therapy. Standard therapy consisted of acetylsalicylic acid l00 mg/day, isosorbid dinitrate 30 mg/day, streptokinase 1.5 mil unit/30 min when indicated and concomitant therapy (i.e. digitalis, heparin, diuretics, beta-blockers, antiarrhythmics) when required. The captopril therapy was continued throughout seven years of follow-up. There were 9 visits during seven years: on admission, after 6 months and after every year, and blood pressure, heart rate, data about clinical signs of heart failure, symptoms of angina pectoris, reinfarctus, PTCA, by pass operation and laboratory tests were performed. The groups were matched for all baseline parameters: age, sex, localization of the infarction, risk factors, body mass index, clinical findings: arterial pressure, heart rate, frequency of heart failure, and laboratory analysis results: total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

Results

There were 77 males and 27 females, with a male/female ratio of 38/15 in the con and 39/12 in the cap group. Patients were 32-70 years of age, the mean value in the con group being 56.22 (10.85) and 56.35 (10.54) in the cap group (Table 1). There were no dropouts because of hypotension. Three patients in the cap group had to abandon therapy because of a persistent dry cough. The seven years evaluation refers to 80 patients: 21 deaths occurred during this time.

Table 1. Clinical characteristics of the patients with captopril in acute myocardial infarction-seven years follow-up study

	Captopril group	Control group
Age (yr)	56.35 ±10.54	56.22 ± 10.85
Sex (m/f)	37/14	39/11
Body mass index	27.22 ± 3.41	27.36 ± 3.33
Localization of AMI		
anterior/inferior/nonQ	25/26/4	23/27/2
Risk factors		
hypertension	31	22
smokers	26	31
hyperlipidemia	11	10
diabetes mellitus	11	10
family history of CAD	28	18

Clinical data

There were no differences between groups concerning heart rate and arterial pressure during the study (Table 2). The values of body mass index at the beginning of the study and during seven years between groups, and between the first and the last visit in the same group demonstrated no significant differences (Table 1).

Clinical signs of heart failure were present in 29 patients at the beginning of the study: 14/52 patients in the con (13.9%) and 15/52 patients in the cap group (14.9 %). There was no difference in the heart failure rate between groups. At the end of the study, there were more patients with clinical signs of heart failure in the con than in the cap group, but this difference did not reach statistical significance. After seven years, there were 12/37 patients (32.4 %) with heart failure in the con group (11 patients in Killip II group and one in Killip III group) and 5/43 patients (11.5%) in the cap group (all patients in Killip II group) (Table 2).

Table 2. Clinical data during study in treatment groups

	Captopril group	Control group
Heart rate		
on admission	81.69 ± 15.43	82.74 ± 24.56
after seven years	76.44 ± 9.77	73.89 ± 11.13
Systolic pressure		
on admission	142.08 ± 27.06	137.52 ± 21.98
after seven years	137.09 ± 14.07	137.03 ± 18.91
Diastolic pressure		
on admission	94.14 ± 12.76	86.34 ± 10.99
after seven years	87.67 ± 8.82	87.77 ± 10.65
Clinical signs of heart failure		
on admission	15/52	14/52
after seven years	5/43	12/37

Recurrent myocardial infarction was observed in 6 patients with captopril and in 10 patients without captopril treatment. The incidence of coronary revascularisation procedures was similar in both groups, 3 patients in captopril and 4 in control group. Only one patient needed PTCA in control group and none in the captopril group. All clinical events (e.g. reinfarction, revascularisation and PTCA) were observed in 9 in the captopril and 15 in the control group. There were less clinical events in the captopril group, but the difference was not statistically significant.

The number of patients requiring hospitalization during seven years because of heart failure or unstable angina was smaller in the captopril (7 patients) than in the control group (17). The difference between groups was statistically significant ($p=0.03$).

There was a difference in mortality between groups in favor of captopril treatment: after seven years, the mortality was 15.5% (8/52) in the cap and 26% (13/52) in the con group. Cardiovascular mortality was 7/52 in the cap and 11/52 in the con group. The difference did not reach statistical significance. Sudden death was registered in 5/52 patients in the cap and 8/52 patients in the con group. The difference between the groups was not significant. No difference in mortality between groups concerning sex, age and infarct localization was observed.

Laboratory analysis

At the beginning, there were no differences in blood values of total cholesterol (con group 6.3±1.3 mmol/l; cap group 6.6±1.5 mmol/l), LDL cholesterol (con group 4.2±1.1 mmol/l; cap group 4.5±1.2 mmol/l), HDL cho-

lesterol (con group 1.07±0.29 mmol/l; cap group 1.05±0.25 mmol/l) and triglycerides (con group 2.32±1.2 mmol/l; cap group 2.33±1.1 mmol/l) between groups. In all subsequent visits, there were no observed differences between groups in values of total cholesterol, LDL cholesterol and triglycerides, but there were differences in HDL cholesterol values between groups. After seven years, total cholesterol was 6.46± 1.23 mmol/l in the con group and 6.54±1.26 mmol/l in the cap group; LDL cholesterol 4.47±1.14 mmol/l in the con and 4.36±1.14 mmol/l in the cap group, and triglycerides 2.15±1.11 mmol/l in the con and 2.1±0.93 mmol/l in the cap group. There were no significant differences between groups in blood values of total cholesterol, LDL cholesterol and triglycerides. However, there was a statistically significant difference between the con group (1.05±0.20 mmol/l) and the cap group (1.17± 0.26 mmol/l) in blood values of HDL cholesterol ($p<0.02$) (Fig 1).

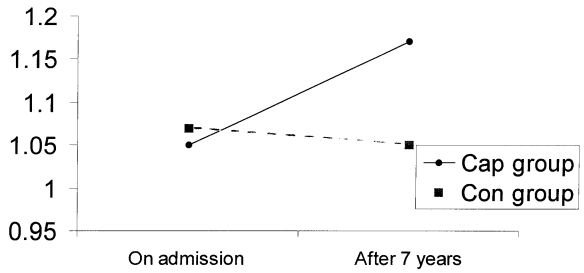

Fig. 1. HDL cholesterol on admission and after 7 years follow-up of AMI.

Discussion

Effects of ACE inhibitors on the lipid status which could influence the progression of endothelial dysfunction, consecutive atherosclerosis and coronary artery events have been reported in many experimental investigations.

Chobanian et al. show that animals fed on an atherosclerotic diet develop pathologic evidence of atherosclerosis, whereas animals fed on an identical diet plus ACE inhibitor produced significantly less evidence of vascular atherosclerosis (3). Recently, it was suggested that angiotensin II has an oxidant effect and increases the oxidation of LDL cholesterol, and lipid uptake into the endothelium (4). Aldosteron has also been implicated in the development of atherosclerosis. There appears to be an inverse correlation between aldosteron levels and serum high-density lipoprotein (HDL) cholesterol levels (5). It has also been suggested that aldosterone is of importance in the development of endothelial dysfunction and progression of atherosclerosis (6). Animals fed on an atherosclerotic diet develop endothelial dysfunction, whereas animals fed on an identical diet plus an ACE inhibitor maintained normal endothelial function, with preserved vasodilatation response (7) Patients with multiple risk factors have also been demonstrated to have endothelial dysfunction (8).

There are fewer clinical studies which have showed that ACE inhibitors could improve endothelial dysfunction (9).

ACE inhibitors might be effective in prevention of endothelial dysfunction, progression of atherosclerosis and coronary artery events by blocking the production of aldosteron and the conversion of angiotensin I to angiotensin II, and by influence upon the lipid status.

In our study, captopril treatment in acute myocardial infarction and during seven years of follow-up improved survival and reduced the number of adverse cardiovascular events. Also, captopril improved blood values of HDL cholesterol, which protect the artery from excessive accumulation of cholesterol. It is possible that one of the positive effects of captopril on progression of coronary artery events is by positive changes in lipids metabolism. This study could demonstrate the connection between improved clinical outcome and increased values of HDL cholesterol in patients with acute myocardial infarction, and this finding could increase indication for ACE inhibition treatment in patients with coronary artery disease.

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DUGOTRAJNO DEJSTVO KAPTOPRILA NA LIPIDE PLAZME U AKUTNOM INFARKTU MIOKARDA: MOGUĆI MEHANIZAM DEJSTVA ACE INHIBITORA U PREVENCIJI ATEROSKLEROZE

Zorana Vasiljević[1], *Aneta Bošković*[1], *Miodrag Ostojić*[1], *Milica Prostran*[2], *Nikola Kocev*[3]

[1]*Institut za kardiovaskularne bolesti,*
[2]*Institut za klinicku farmakologiju, farmakologiju i toksikologiju,*
[3]*Institut za medicinsku statistiku, Beograd*

Kratak sadržaj: *Poznato je da ACE inhibitori imaju povoljno dejstvo na funkciju leve komore i kardiovaskularne dogadjaje posle infarkta miokarda. Prema kliničkim iskustvima inhibitori ne ispoljavaju negativno dejstvo na lipidni status ("neutralni"), koji utiče na progresiju ateroskleroze i koronarnu bolest. Za sada, nema rezultata dugotrajnih kliničkih studija o uticaju ACE inhibitora na lipidni status bolesnika posle akutnog infarkta miokarda.*
U ovoj otvorenoj randomiziranoj kontrolisanoj kliničkoj studiji uz primenu placeba, učestvovalo je 104 bolesnika sa akutnim infarktom miokarda, koji su praćeni 7 godina. U kontrolnoj grupi (n=52) primenjivana je standardna farmakoterapija, dok je druga grupa (n=52) primala i kaptopril 6,25 mg 12 sati posle akutnog infarkta miokarda, a zatim od 6,25 mg do 25 mg, dva puta na dan, sve do kraja studije.
Sedmogodišnji period je preživelo 80 bolesnika. U grupi lečenih kaptoprilom bilo je manje bolesnika sa kardiovaskularnim neželjenim ishodom ($p<0,05$), kao i manje bolesnika sa kliničkim znacima srčane insuficijencije. Osim toga, u grupi lečenoj kaptoprilom, zapažen je povisen nivo HDL holesterola i manji mortalitet nego u kontrolnoj grupi.

Ključne reči: Kaptopril, lipidi, infarkt miokarda

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