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Long Term Angiotensin Converting Enzyme-inhibition in Patients after Coronary Artery Bypass Grafting Reduces Levels of Soluble Intercellular Cell Adhesion Molecule-1

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Objective: *to examine the effect of angiotensin converting enzyme inhibition (ACEI) on soluble intercellular adhesion molecule 1 (sICAM-1) and C-reactive protein (CRP) in patients requiring coronary artery bypass grafting (CABG).*
Method: *subgroup analysis of 42 patients randomised to Quinapril (40 mg daily determined) and 45 to placebo. sICAM-1 and CRP were ≥4 weeks before and 1 year after surgery.*
Results: *there was no difference in sICAM-1 at baseline (142.2 μg/L vs 136.6 μg/L). There was significant reduction in s-ICAM-1 in patients receiving quinapril (142.2 ± 10.8 μg/L vs 125.6 ± 9.4 μg/L, p < 0.05) but not placebo (136.6 ± 10.2 μg/L vs 131.2 ± 11.7 μg/L, p = NS). Levels of C-reactive protein remained unchanged in both groups (3.70 ± 0.85 vs 2.73 ± 0.32 mg/L, 2.85 ± 0.48 vs 3.16 ± 0.50 mg/L).*
Conclusions: *ACEI reduces sICAM-1 in patients undergoing CABG. The benefits of ACEI may partly be due to a reduction of the vascular inflammatory response.*

Key Words: Angiotensin-converting-enzyme-inhibitor; Inflammation; Atherosclerosis; Coronary heart disease; Cell adhesion molecules; C-reactive protein.

Introduction

Angiotensin-converting-enzyme (ACE)-inhibitors reduce morbidity and mortality in patients atherosclerotic vascular disease[1] through their haemodynamic effects and, possibly, though beneficial effects on the endothelium. *In vitro* studies suggest these might include a reduction in cellular adhesion molecule (CAM) expression[2–7] and leucocyte adhesion.[8,9] Soluble CAM levels are elevated in patients with atherosclerosis[10–12] but, to date, the effects of ACE-inhibitors on these levels is unknown. The aim of this study was to determine the effect of ACE-inhibition on levels of soluble intercellular adhesion molecule 1 (sICAM-1) and C-reactive protein (CRP) in patients undergoing coronary artery bypass grafting (CABG).

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Materials and Methods

The current study was performed in a subgroup of 87 patients from the randomised, double-blind, placebo-controlled QUO VADIS trial that was designed to evaluate the effect of ACE-inhibition (Quinapril 40 mg once daily) on ischaemic events up to 1 year post-CABG.[13,14] This subgroup was solely defined by the availability of a stored (at −80 °C) blood sample taken ≥4 weeks before and 1 year after surgery. Institutional Review Board approval and written informed consent were obtained. sICAM were determined using in-house ELISA.[15] CRP was measured using an ELISA assay with a sensitivity of 20 ng/L.[16] Both samples were analyzed at the same time in duplicate. No other measurements were performed. A p-value <0.05 was considered statistically significant. The baseline descriptive statistics for the continuous variables are mean and standard error of the mean. For normally distributed continuous variables, differences between quinapril and placebo were evaluated by a two-sided Student's T-test. For skewed distributed continuous endpoints (p-value Shapiro–Wilk test for normality

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<0.05), a Wilcoxon 2-sample test was used. Qualitative parameters (categorical or ordered), frequency counts and percentages of each category were calculated by treatment group. Differences between quinapril and placebo were then evaluated using a Chi-square test. To evaluate the effect of quinapril versus placebo on the change of levels of s-ICAM from baseline to 1 year, a repeated measurement analysis of variance was used. Clinically relevant co-variates with a p-value <0.20 in univariate analysis were considered as potential confounders and included in a multivariable model. To evaluate the change of s-ICAM within the treatment subgroups, two additional repeated measurement analyses of variance were performed in the quinapril treated patients and placebo treated patients separately. For additional computations of correlations between s-ICAM and C-reactive protein, the Spearman correlation coefficients, with accompanying p-values were calculated (Prob $>$ R under Ho: Rho $= 0$). For all analyses, commercially available computer software (Statistical Analysis System version 6.12, SAS Institute, Cary, NC, U.S.A.) was used.

Results

Of the 87/149 randomised patients studied (Table 1), 45 received placebo and 42 quinapril. Despite the small sample size the two groups were well matched (Tables 2–4). sICAM did not differ significantly between groups at baseline (136.6 ± 10.2 μg/L vs 142.2 ± 10.8 μg/L, $p =$ NS). However, in quinapril group, levels significantly decreased from

Table 1. Baseline characteristics of included versus excluded patients.

	Included ($n = 87$)	Excluded ($n = 62$)	p-value
Age (y)	63 (±0.9)	61 (±1.2)	0.52
Male (n(%))	75 (86)	51 (82)	0.65
Medical history (n(%))			
Myocardial infarction	36 (41)	27 (44)	0.87
Cardiovascular intervention	11 (13)	9 (15)	0.81
Hypertension (n(%))			
None	69 (79)	46 (74)	0.49
Past	3 (3)	1 (1)	
Current	15 (17)	15 (24)	
Diabetes mellitus (n(%))	9 (10)	0 (0)	0.01
Smoking (n(%))			
None	15 (17)	11 (18)	0.1
Past	56 (64)	42 (76)	
Current	16 (18)	4 (6)	
Family history of cardiovascular disease (n(%))	38 (44)	26 (42)	0.87
Co-medication (n(%))			
ASA	70 (80)	43 (69)	0.13
Coumarines	13 (15)	20 (32)	0.02
Beta-blockers	78 (90)	51 (83)	0.23
Calcium antagonists	66 (76)	42 (68)	0.35
Nitrates	66 (76)	54 (87)	0.1
Lipid lowering	36 (41)	20 (32)	0.3
Blood pressure (mmHg)			
Systolic	143 (±1.9)	145 (±2.6)	0.66
Diastolic	84 (±1.0)	85 (±1.1)	0.94
Body mass index (kg/m^2)	26 (±0.3)	27.5 (±0.4)	0.02
NYHA (n(%))			
Class I	4 (5)	1 (1)	0.46
Class II	36 (42)	25 (40)	
Class III	44 (51)	32 (52)	
Class IV	1 (2)	4 (7)	
Total cholesterol (mmol/L)	6.23 (±0.14)	6.25 (±0.15)	0.72
HDL-cholesterol (mmol/L)	1.02 (±0.03)	1.16 (±0.05)	0.01
LDL-cholesterol (mmol/L)	4.21 (±0.12)	4.30 (±0.13)	0.58
Triglycerides (mmol/L)	2.09 (±0.15)	1.88 (±0.15)	0.34

Data are expressed as means ± standard error of the mean. n(%) equals the number of patients (percentage). A p-value less than 0.05 is considered as clinically significant.

Table 2. Patient characteristics of the analyzed patients per treatment group at baseline.

	Placebo ($n = 45$)	Quinapril ($n = 42$)	p-value
Age (y)	63 (± 1.4)	62 (± 1.2)	0.41
Male (n(%))	38 (84)	37 (88)	0.76
Medical history (n(%))			
Myocardial infarction	16 (36)	20 (48)	0.28
Cardiovascular intervention	7 (16)	4 (10)	0.52
Hypertension (n(%))			
None	35 (78)	34 (90)	0.86
Past	2 (4)	1 (2)	
Current	8 (18)	7 (17)	
Diabetes mellitus (n(%))	2 (4)	7 (17)	0.08*
Smoking (n(%))			
None	9 (20)	6 (14)	0.66
Past	29 (64)	27 (64)	
Current	7 (16)	9 (21)	
Family history of cardiovascular disease (n(%))	14 (31)	24 (57)	0.02*
Co-medication (n(%))			
ASA	34 (76)	36 (86)	0.29
Coumarines	7 (16)	6 (14)	1.00
Beta-blockers	45 (90)	38 (91)	1.00
Calcium antagonists	34 (76)	32 (76)	1.00
Nitrates	36 (80)	30 (71)	0.45
Lipid lowering	18 (40)	18 (43)	0.83
Blood pressure (mmHg)			
Systolic	142 (± 2.4)	145 (± 3.0)	0.44
Diastolic	82 (± 1.4)	85 (± 1.3)	0.53
Body mass index (kg/m^2)	26 (± 0.5)	26 (± 0.4)	0.86
NYHA (n(%))			
Class I	2 (4)	2 (5)	0.38
Class II	15 (33)	21 (51)	
Class III	27 (60)	17 (42)	
Class IV	1 (2)	1 (2)	
Total cholesterol (mmol/L)	6.01 (± 0.16)	6.46 (± 0.23)	0.19*
HDL-cholesterol (mmol/L)	1.04 (± 0.04)	1.00 (± 0.04)	0.83
LDL-cholesterol (mmol/L)	4.14 (± 0.15)	4.28 (± 0.19)	0.56
Triglycerides (mmol/L)	1.78 (± 0.16)	2.42 (± 0.26)	0.04*

Data are expressed as means ± standard error of the mean. n equals the number of patients. A p-value less than 0.05 is considered as clinically significant.
*Indicates variables that were tested in a multivariate model.

142.2 ± 10.8 to 125.6 ± 9.4 μg/L ($p < 0.05$). There was no such change in the placebo group (136.6 ± 10.6 μg/L vs 131.2 ± 1.7 μg/L) (Fig. 1). To exclude a possible confounding effect of obscure concomitant disease such as infection or malignancy, the analysis was repeated after excluding three patients with extremely elevated (>3 SD above the mean) CRP. It did not alter the outcome and all three patients were assigned to placebo. Without these patients mean levels of s-ICAM were 134.5 ± 10.9 μg/L at baseline and 132.5 ± 11.2 μg/L after one year ($n = 42$, p = NS).

CRP was similar in both groups at baseline and did

Table 3. Blood pressure and lipid levels at baseline and at the end of the study per treatment group.

	Quinapril ($n = 42$)		Placebo ($n = 45$)	
	Baseline	End of study	Baseline	End of study
Blood pressure				
Systolic (mmHg)	145 (± 3.0)	151 (± 2.9)	142 (± 2.4)	150 (± 3.3)
Diastolic (mmHg)	82 (± 1.4)	84 (± 1.6)	85 (± 1.3)	85 (± 1.4)
Total cholesterol (mmol/L)	6.5 (± 1.5)	6.0 (± 1.1)	6.0 (± 1.1)	5.7 (± 1.1)
Triglycerides (mmol/L)	2.4 (± 1.7)	1.8 (± 1.1)	1.78 (± 1.1)	1.7 (± 0.9)

Blood pressure and lipid levels are expressed as mean ± standard error of the mean. n equals the number of patients.

Table 4. Use of statins and salicylates (ASA) during the study per treatment group.

Treatment status	Statins (*n*(%))		ASA (*n*(%))	
	Quinapril $n = 42$	Placebo $n = 45$	Quinapril $n = 42$	Placebo $n = 45$
Never	17 (41)	21 (47)	2 (5)	4 (9)
Discontinued	1 (2)	1 (2)	8 (19)	4 (9)
Started during study	17 (41)	16 (36)	28 (66)	30 (67)
Already	7 (17)	7 (16)	4 (10)	7 (16)

Drug use is expressed as number of patients (percentage of the group); ASA means salicylates. *n* equals the number of patients.

not change during the study period. In the quinapril group levels were 3.70 ± 0.85 mg/L at baseline vs 2.73 ± 0.32 mg/L after 1 year (Fig. 2). In the placebo group levels were 2.85 ± 0.48 mg/L at baseline vs 3.16 ± 0.50 mg/L after 1 year.

There was a weak correlation between CRP and s-ICAM at baseline ($r = 0.30$, $p < 0.01$) and after one year ($r = 0.29$, $p < 0.01$).

Discussion

The beneficial effects of ACE-inhibitors in left ventricular hypertrophy and chronic heart failure[17,18] were attributed mainly to the reduction of myocardial remodelling. The benefits in atherosclerosis are equally clear but harder to explain.[1,8] The anti-inflammatory effects of ACE-inhibition have been previously demonstrated in patients with heart failure, other mechanisms than modification of the atherosclerotic process may have accounted for the results in these studies.[19,20] The present study has shown that 12 months of ACE-inhibition leads to a significant reduction in sICAM-1 but not CRP in patients who have undergone CABG. sICAM is a powerful independent predictor of the risk of developing coronary heart disease.[21] It is reasonable assume, therefore, that a decrease in levels of s-ICAM reflects a diminution of cardiovascular risk. This assumption is currently investigated in the BIological Markers of Endothelial Dysfunction (BIMED) study is capable of inducing pro-inflammatory cellular activity.[22–25] It is present and active in the most vulnerable parts of the atherosclerotic plaque[26] and it elevates s-ICAM in humans.[27] The reduction in s-ICAM observed here can be explained by the fact that quinapril reduces angiotensin II formation in human vasculature.[14] On the other hand, ACE-inhibition improves endothelial function by increasing the bioavailability of nitric oxide.[28] Perhaps surprisingly, treatment did not lead to a significant reduction in CRP.[21,29–33] This study does have limitations. The patients were part of a larger cohort, selection bias cannot be ruled out, the original study was not primarily designed to study the effects of quinapril on levels of s-ICAM and CRP, and the small sample size did not permit the analysis of the link between s-ICAM and the occurrence of clinical endpoints.

In conclusion, this study demonstrated for the first time that a treatment with quinapril (40 mg once daily) significantly reduces the s-ICAM levels in patients with atherosclerosis requiring CABG. This supports the contention that the beneficial effects of ACE-inhibition are partly the result of a reduced vascular inflammatory response. The larger BIMED trial is currently underway and will hopefully verify this hypothesis.

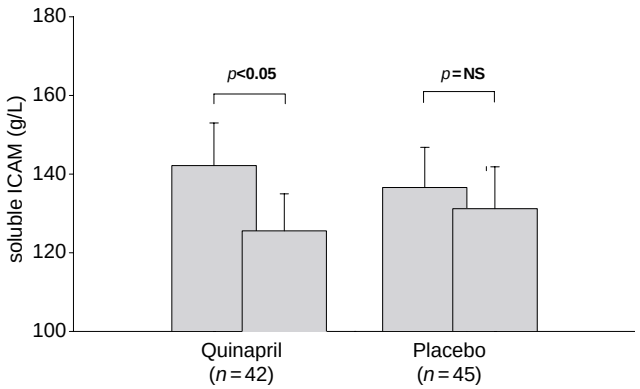

Fig. 1. Levels of s-ICAM at baseline and after treatment.

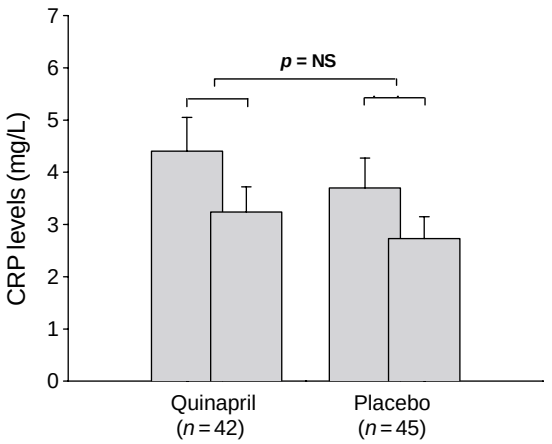

Fig. 2. Levels of CRP at baseline and after treatment.

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