Comparative Effect of ACE Inhibition and Angiotensin II Type 1 Receptor Antagonism on Bioavailability of Nitric Oxide in Patients With Coronary Artery Disease
Role of Superoxide Dismutase

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Background—Flow-dependent, endothelium-mediated vasodilation (FDD) and activity of extracellular superoxide dismutase (EC-SOD), the major antioxidative enzyme of the arterial wall, are severely impaired in patients with coronary artery disease (CAD). We hypothesized that both ACE inhibitor (ACEI) and angiotensin II type 1 receptor antagonist (AT₁-A) increase bioavailability of nitric oxide (NO) by reducing oxidative stress in the vessel wall, possibly by increasing EC-SOD activity.

Methods and Results—Thirty-five patients with CAD were randomized to 4 weeks of ACEI (ramipril 10 mg/d) or AT₁-A (losartan 100 mg/d). FDD of the radial artery was determined by high-resolution ultrasound before and after intra-arterial N-nitro-L-arginine (L-NMMA) to inhibit NO synthase and before and after intra-arterial vitamin C to determine the portion of FDD inhibited by oxygen free radicals. EC-SOD activity was determined after release from endothelium by heparin bolus injection. FDD was improved after ramipril and losartan (each group P<0.01), and in particular, the portion of FDD mediated by NO, ie, inhibited by L-NMMA, was increased by >75% (each group P<0.01). Vitamin C improved FDD initially, an effect that was lost after ramipril or losartan. After therapy, EC-SOD activity was increased by >200% in both groups (ACEI, 14.4±1.1 versus 3.8±0.9 and AT₁-A, 13.5±1.0 versus 3.9±0.9 U·mL⁻¹·min⁻¹; each P<0.01).

Conclusions—Four weeks of therapy with ramipril or losartan improves endothelial function to similar extents in patients with CAD by increasing the bioavailability of NO. Our results suggest that beneficial long-term effects of interference with the renin-angiotensin system may be related to reduction of oxidative stress within the arterial wall, mediated in part by increased EC-SOD activity. (Circulation. 2001;103:799-805.)

Key Words: inhibitors ■ angiotensin ■ endothelium ■ coronary disease ■ superoxide dismutase

In patients with coronary artery disease (CAD), endothelial dysfunction contributes to the abnormal vasomotor response to exercise, exposure to cold, or mental stress and may trigger myocardial ischemia. In addition, the long-term follow-up of patients with endothelial dysfunction suggests that reduced bioavailability of nitric oxide (NO) may even have prognostic implications and contribute to progression of coronary atherosclerosis, because impaired endothelium-mediated vasomotion is associated with future cardiovascular events. Therefore, restoring endothelial function represents an attractive novel therapeutic target in patients with CAD. The Trial on Reversing Endothelial Dysfunction (TREND) has shown that ACE inhibitor (ACEIs) improve coronary endothelium-dependent vasomotor function in patients with CAD, a mechanism that may well contribute to the beneficial effects of ACE inhibition on cardiovascular mortality. Angiotensin II type 1 (AT₁)–receptor antagonists are popular drugs frequently prescribed for treatment of hypertension or heart failure, and experimental data suggest that AT₁-receptor antagonists have the potential to improve endothelium-mediated vasomotion. The comparative effects of ACEI and AT₁-receptor antagonists on endothelial function in patients with CAD, however, are controversial.

There is evidence that increased inactivation of NO by superoxide anions contributes to impaired endothelial function in patients with CAD. Experimental data suggest that AT₁-receptor antagonists improve endothelial function by reducing NADH oxidase–mediated superoxide anion formation. So far, however, it is unclear whether AT₁-receptor antagonists affect the activity of vascular antioxidative enzyme systems, such as extracellular superoxide dismutase (EC-SOD). We recently showed that activity of vascular...
EC-SOD, the major antioxidative enzyme system of the human arterial wall, is severely reduced in patients with CAD and is closely related to NO-mediated vasodilatation, supporting the concept that reduced activity of EC-SOD contributes to increased oxidative stress in patients with CAD, leading to reduced bioavailability of NO. Fukai and colleagues demonstrated that the bioavailability of NO modulates the activity of vascular EC-SOD, raising the question of whether therapeutic interventions that increase the bioavailability of NO increase EC-SOD activity. Short-term intra-arterial infusion of an ACEI has the potential to increase the bioavailability of NO during flow-dependent, endothelium-mediated vasodilatation (FDD). In the present study, we tested the hypothesis that 4 weeks of oral therapy with the ACEI ramipril or the AT₁-receptor antagonist losartan increases the bioavailability of NO and the activity of EC-SOD and improves endothelium-mediated vasodilatation in patients with CAD.

### Methods

Thirty-five patients with angiographically documented CAD (≥1 diameter stenosis ≥60%) were studied. All patients were clinically stable whites without present indications for interventional or surgical revascularization. All patients were on long-term therapy with aspirin, and with the exception of 1 patient in each group, all were on long-term therapy with β-blockers. Aspirin and β-blockers were used on the day of measurement as they were every day. Calcium antagonists, diuretics, and sustained-release or long-acting preparations of nitrates were not used by the patients. Short-acting nitrates were withheld and alcohol and caffeine were prohibited for ≥12 hours before the study. Because we were interested in evaluating the long-term effect of ramipril and losartan rather than the short-term effect of an oral dose after long-term therapy, we elected to study our patients >12 hours after the last dose in the morning of the following day, beginning between 9 and 10 AM. A breakfast including clear liquids (no juice) and cereals was allowed before the measurements. Characteristics of the patients are shown in Table 1. Patients with uncontrolled hypertension (Riva-Rocci sphygmomanometer >140/90 mm Hg at rest despite therapy), diabetes mellitus, current tobacco use, congestive heart failure, significant valvular heart disease, or severe renal or hepatic disease were excluded from the study by careful history, physical examination, ECG, and laboratory analysis. Patients who had previously received ACEIs, AT₁-receptor antagonists, or antioxidant vitamin supplements were not included in the protocol. Written informed consent was obtained for all subjects, and the protocol was approved by the local ethics committee.

### Protocol

Patients were randomized to 4 weeks of treatment with the maximally approved dose of ramipril (5 mg BID) or losartan (50 mg BID). At baseline and after 4 weeks of therapy, FDD of the radial artery was determined. FDD was measured before and after intra-arterial infusion of the NO synthase inhibitor N-nomethyl-L-arginine (L-NMMA) to determine the NO-mediated portion of FDD, ie, the bioavailability of NO. In addition, FDD was determined before and after intra-arterial infusion of the antioxidant vitamin C to determine the portion of FDD inhibited by oxygen free radicals. Furthermore, endothelium-bound EC-SOD (eEC-SOD) activity was measured before and after 4 weeks of treatment.

### Measurement of FDD

Radial artery diameter was measured by high-resolution ultrasound (Axulab). This method is well established in our laboratory, has an excellent reproducibility and variability, and was used as described recently. Blood flow velocity was recorded continuously, and radial artery diameter was determined every 30 seconds until stable baseline conditions were obtained (∼30 minutes). Then a wrist arterial occlusion (8 minutes) was performed, and FDD in response to reactive hyperemic blood flow was assessed at baseline and after intra-arterial infusion of L-NMMA (Clinalfa; 7 μmol/min; 5 minutes). When radial artery diameter and blood flow had returned to baseline values, FDD was determined again after intra-arterial infusion of vitamin C (25 mg/min; 10 minutes), followed by determination of FDD after coinfusion of vitamin C and L-NMMA. Finally, all subjects received an intra-arterial infusion of sodium nitroprusside (SNP; 10 μg/min; 5 minutes) to assess endothelium-independent vasodilatory capacity. Six patients with CAD were randomized to receive intra-arterial infusion of placebo before vitamin C. Blood flow and diameter data reported for L-NMMA, vitamin C, and SNP represent measurements during the last minute of each infusion. All measurements were recorded, and subsequently, vessel diameter and blood flow velocity were analyzed by 2 investigators unaware of the sequence of interventions and treatment assignment.

### Determination of eEC-SOD Activity In Vivo

EC-SOD is specifically released from endothelium into plasma by heparin bolus injection, allowing determination of eEC-SOD activity in humans in vivo. In brief, to measure plasma activity at baseline, 2 arterial (brachial artery) and 2 venous (antecubital vein) blood samples were drawn. Then 5000 U of heparin was injected into the brachial artery, and blood samples were drawn from the antecubital vein of the same arm (1, 3, 5, 7, and 10 minutes after heparin injection). eEC-SOD activity (U/mL·min⁻¹) was calculated as area under the curve of the increase of plasma SOD activity within 10 minutes after heparin injection. The time interval of 10 minutes was used because maximum increase of plasma SOD activity was approached within this time. The coefficient of variation for determination of eEC-SOD activity was 7.6%. For blood sampling, EDTA-containing vacuum tubes were used to avoid the cellular leakage of Cu,Zn-SOD from vascular and skeletal muscle cells observed after use of a tourniquet. Tubes were immediately centrifuged (2000g, 15 minutes, 4°C), and plasma was stored at −80°C. Activity of SOD was measured at pH 8.2 by a modified nitrite method. Superoxide generated by hypoxanthine and xanthine oxidase was changed to nitrite ion by hydroxylamine. Nitrite ion was measured by color densitometry at 550 nm using a coloring reagent. The amount of SOD necessary to inhibit the rate of nitrite ion generation by 50% was defined as 1 U of SOD activity, according to McCord and Fridovich. Calibrations were performed with known amounts of purified bovine SOD. To distinguish between cytidine-sensitive isoenzymes (Cu,Zn-SOD and EC-SOD) and the resistant one (Mn-SOD), 2 mmol/L cyanide was used. For specific analysis of EC-SOD activity in plasma, chromatography on Con A-Sepharose (Pharmacia Biotech) was performed as described previously. Unlike Cu,Zn-SOD and Mn-SOD, the glycoprotein EC-SOD binds to the lectin concanavalin A. Cu,Zn-SOD activity was calculated as cytidine-sensitive SOD activity minus EC-SOD activity. Reagents were from Sigma-Aldrich.
Statistical Analysis
All data are expressed as mean±SEM. Comparisons of >2 measurements were done by 1-way ANOVA for repeated measures followed by Student-Newman-Keuls test (comparisons within 1 group of patients and between the different groups of patients). A value of \( P<0.05 \) was considered to be statistically significant.

Results
Flow-Dependent, Endothelium-Mediated Vasodilation
After release of wrist occlusion, a significant increase in radial artery diameter was noted (Table 2), representing FDD, defined as percent increase in vessel diameter. Before therapy, FDD during control conditions was similar in patients randomized to receive ramipril or losartan (Table 2, Figure 1). The effects of 4 weeks of treatment with ramipril or losartan on radial artery diameter at baseline and during FDD are given in Table 2. FDD was significantly increased after 4 weeks of treatment with ramipril or losartan (Figure 1, Table 2). There was no significant difference between the effects of ramipril and losartan on FDD. The portion of FDD mediated by NO (represented by the portion of FDD inhibited by L-NMMA) was significantly increased after 4 weeks of treatment with ramipril (6.3±0.6% versus 2.6±0.6%; \( P<0.01 \)) or losartan (5.5±0.6% versus 1.8±0.6%; \( P<0.01 \)), with no significant difference between the 2 drugs. Intra-arterial infusion of vitamin C improved FDD at baseline, but not after 4 weeks of treatment with ramipril and losartan (Figure 2; Table 2). Intra-arterial SNP increased radial artery diameter to a similar extent before and after treatment with losartan or ramipril (before/after ramipril, 3.02±0.1 to 3.50±0.1/3.04±0.1 to 3.53±0.1 mm; before/after losartan, 3.04±0.1 to 3.57±0.1/3.00±0.1 to 3.59±0.1 mm; each \( P<0.01 \) versus before SNP).

The effects of L-NMMA and vitamin C on radial artery blood flow before and after treatment with losartan or ramipril are shown in Table 3.

Table 2. Effect of 4 Weeks of ACE Inhibition or AT1-Receptor Blockade on Radial Artery Diameter at Baseline and During FDD

<table>
<thead>
<tr>
<th>Diameter, mm</th>
<th>Control</th>
<th>L-NMMA</th>
<th>Vitamin C</th>
<th>Vitamin C+ L-NMMA</th>
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<tbody>
<tr>
<td>Group 1 (4 weeks ramipril; n=18)</td>
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<tr>
<td>Before treatment</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>3.01±0.1</td>
<td>3.02±0.1</td>
<td>3.01±0.1</td>
<td>3.01±0.1</td>
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<tr>
<td>FDD</td>
<td>3.19±0.1</td>
<td>3.12±0.1*</td>
<td>3.34±0.1*</td>
<td>3.13±0.1*</td>
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<tr>
<td>After treatment</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.00±0.1</td>
<td>3.01±0.1</td>
<td>3.02±0.1</td>
<td>3.00±0.1</td>
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<tr>
<td>FDD</td>
<td>3.31±0.1</td>
<td>3.13±0.1*</td>
<td>3.32±0.1</td>
<td>3.15±0.1*</td>
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<tr>
<td>Group 2 (4 weeks losartan; n=17)</td>
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<tr>
<td>Before treatment</td>
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<tr>
<td>Baseline</td>
<td>3.00±0.1</td>
<td>3.00±0.1</td>
<td>3.02±0.1</td>
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<tr>
<td>FDD</td>
<td>3.18±0.1</td>
<td>3.13±0.1*</td>
<td>3.30±0.1*</td>
<td>3.15±0.1*</td>
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<tr>
<td>After treatment</td>
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<tr>
<td>Baseline</td>
<td>3.02±0.1</td>
<td>3.02±0.1</td>
<td>3.01±0.1</td>
<td>3.02±0.1</td>
</tr>
<tr>
<td>FDD</td>
<td>3.30±0.1</td>
<td>3.13±0.1*</td>
<td>3.31±0.1</td>
<td>3.14±0.1*</td>
</tr>
</tbody>
</table>

*\( P<0.01 \) vs control.

Figure 1. Flow-dependent dilation in patients with CAD before (open bars) and after (solid bars) L-NMMA; effect of 4 weeks of treatment with ramipril (n=18) or losartan (n=17). *\( P<0.01 \) vs before L-NMMA.

Figure 2. Effect of intra-arterial infusion of vitamin C on flow-dependent dilation (%) in patients with CAD before and after 4 weeks of treatment with ramipril (n=18) or losartan (n=17).
Systemic blood pressure and heart rate did not change during the experimental protocol. There was no significant difference of systemic blood pressure after 4 weeks of treatment with losartan or ramipril (data not shown).

**eEC-SOD Activity**

eEC-SOD activity was increased by >200% after treatment with losartan and ramipril (before/after losartan, $3.9\pm0.9$ versus $13.5\pm1.0$; before/after ramipril, $3.8\pm0.9$ versus $14.4\pm1.1\ \text{U}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$; $P<0.01$ versus before treatment; Figure 3). There was no significant difference between the effects of losartan and ramipril on eEC-SOD activity. There was a positive relationship between increase of NO bioavailability during FDD and increase of EC-SOD activity after 4 weeks of treatment (ramipril, $r=0.82$; losartan, $r=0.78$; each $P<0.01$; Figure 4, top). In addition, there was a positive relationship between increase of EC-SOD activity after 4 weeks and reduction of the short-term effect of intra-arterial vitamin C on FDD ($\equiv$ effect of vitamin C on FDD before therapy minus effect of vitamin C on FDD after 4 weeks of therapy; ramipril, $r=0.82$; losartan, $r=0.78$; each $P<0.01$; Figure 4, bottom). Thus, there was a marked reduction of the effect of vitamin C on FDD in patients with a large increase

![Figure 3](image-url). eEC-SOD activity in patients with CAD before and after 4 weeks of treatment with ramipril (n=18) or losartan (n=17).

![Figure 4](image-url). Top, Relationship between increase of NO bioavailability and increase of EC-SOD activity after 4 weeks of therapy with ramipril (1 A; n=18) or losartan (1 B; n=17) in patients with CAD. Bottom, Relationship between reduction of vitamin C effect on FDD and increase of EC-SOD activity after 4 weeks of therapy with ramipril (2 A; n=18) or losartan (2 B; n=17) in patients with CAD.
of EC-SOD activity after 4 weeks of therapy with ramipril or losartan.

**Discussion**

The major findings of the present study are as follows. (1) Four weeks of therapy with the ACEI ramipril or with the AT₁-receptor antagonist losartan improves endothelium-dependent vasodilation to a similar extent in patients with CAD. (2) The beneficial effect of ramipril and losartan on endothelium-dependent vasodilation is mediated by an increased bioavailability of NO, because the portion of FDD mediated by NO was increased after treatment with ramipril and losartan. (3) The antioxidant vitamin C improved FDD at baseline but not after treatment with ramipril and losartan, suggesting that reduction of oxidative stress in the vessel wall contributes to the beneficial effect of ramipril and losartan on endothelial function. (4) The activity of eEC-SOD, the major antioxidative enzyme system of the human arterial wall, was increased by >200% after treatment with ramipril and losartan. This effect of ramipril and losartan on eEC-SOD activity may represent one of the underlying mechanisms responsible for the observed antioxidative effect of losartan and ramipril.

The HOPE study, which involved more than 9000 patients with preserved left ventricular function, showed that ACE inhibition results in a marked reduction of cardiovascular events largely independent of the effect on systemic blood pressure.⁵ The beneficial effect of ACE inhibition emerged after 6 months of therapy, raising the possibility that functional aspects of the vascular wall, including endothelial function, may be involved. Because it is unclear whether AT₁-receptor antagonists have vascular effects similar to those of ACEIs, the present study compared the effect of the target dose of ramipril in the HOPE study with the maximal recommended doses of the AT₁-receptor antagonist losartan on endothelium-dependent vasodilation in patients with CAD. We found that ACE inhibition and AT₁ antagonism improved endothelium-dependent vasodilation to a similar extent in patients with CAD by increasing the bioavailability of NO. The results cannot be explained by an antihypertensive effect of ramipril or losartan, because blood pressure was unchanged after treatment. Therefore, a specific effect of ramipril and losartan on the function of the arterial wall must account for the increased bioavailability of NO during FDD after 4 weeks of therapy. There is increasing evidence that inactivation of NO by superoxide anions contributes to impaired endothelium-dependent vasodilation in patients with CAD.¹⁰,²⁴,²⁵ raising the question of whether the beneficial long-term effect of ACEIs on endothelial function¹ and cardiovascular mortality and morbidity³ is mediated in part by antioxidative properties of the drug. Angiotensin II stimulates superoxide anion generation in vascular smooth muscle cells.²⁶ We therefore hypothesized that both ACEIs and AT₁-receptor antagonists, by preventing the vascular actions of angiotensin II, increase the bioavailability of NO by reducing superoxide anion generation within the vessel wall. To estimate the contribution of superoxide anion–mediated inactivation of NO in vivo, we determined the effect of the antioxidant vitamin C on endothelium-dependent vasodilation before and after treatment with ramipril and losartan.¹⁰,¹⁷ Before treatment with ramipril or losartan, vitamin C improved NO-mediated vasodilation in all patients, an effect that was lost after 4 weeks of both therapy regimens. This suggests that both drugs have antioxidative properties during long-term therapy.

EC-SOD has recently been reported to be a major antioxidative enzyme system of the human arterial vessel wall²⁷,²⁸ located strategically between endothelium and vascular smooth muscle cells in the compartment of the vessel wall in which NO is expected to be inactivated by superoxide anions. Inhibition of vascular SOD activity resulted in impaired endothelium-dependent vasodilation in bovine coronary arteries, suggesting that SOD levels are critical for the ability of NO to modulate vascular tone.²⁹ We recently showed that vascular EC-SOD activity is substantially reduced in patients with CAD and positively related to endothelium-dependent vasodilation.¹¹ Furthermore, vascular EC-SOD activity was inversely related to the effect of the antioxidant vitamin C on FDD, consistent with the notion that reduced vascular EC-SOD activity contributes to impairment of endothelium-mediated vasodilation in patients with CAD. In the present study, we observed a marked increase of eEC-SOD activity after 4 weeks of therapy with ramipril and losartan. In addition, we found a positive correlation between the increase of EC-SOD activity and the increase of NO bioavailability after 4 weeks of therapy in both therapy groups. This suggests that restoration of EC-SOD activity is associated with improvement of endothelial function in patients with CAD; it does not, however, establish a cause-and-effect relationship. Furthermore, we found a positive correlation between increase of EC-SOD activity and reduction of therapeutic effect of vitamin C on FDD, suggesting that increased EC-SOD activity is associated with reduced oxidative stress in vivo. Our results are therefore consistent with the notion that improved activity of EC-SOD contributes to the antioxidative effects of ramipril and losartan in addition to the reduction of angiotensin II–induced radical formation, as suggested by recent experimental work.⁷ An alternative explanation for the improved EC-SOD activity after therapy with ramipril and losartan is that both drugs increase the bioavailability of NO, possibly by activation of the bradykinin-NO cascade,¹₆,₃₀ which in turn may enhance the expression and activity of EC-SOD. This concept would be consistent with data of Fukai et al¹² demonstrating that EC-SOD activity is severely reduced in eNOS-deficient mice but increased in response to enhanced bioavailability of NO.

It may be surprising that we did not observe a significant difference between the effect of ACE inhibition and AT₁-receptor blockade on endothelium-mediated vasodilation in patients with CAD, as was observed recently.⁸ This may be explained by the lower dose of losartan used in the Brachial Artery Normalization of Forearm Function (BANFF) study (50 mg/d) than in our study (100 mg/d).
Furthermore, in the BANFF study, endothelium-mediated vasodilation of the brachial artery was determined, whereas the radial artery was used in our protocol. Because it is known that flow-mediated vasodilation is inversely related to the vessel size, it may be easier to detect changes of endothelium-mediated vasodilation after therapy by use of our method. Because measurements after therapy were performed only at 1 point in time (4 weeks), it cannot be concluded from the present study that both agents have similar effects during longer therapy, because the 2 drugs may have different time courses in terms of their vascular effects.

We have previously shown that bradykinin is involved in the vascular effects of ACE inhibition in healthy subjects, which may be secondary to reduced bradykinin breakdown or interference with sequestration of the B2-bradykinin receptor. These results raised the possibility that ACE inhibition might have a superior effect on endothelium-dependent vasodilation compared with AT1-receptor antagonists. There is now increasing experimental evidence, however, that AT1-receptor blockade may lead to bradykinin-dependent release of NO from the endothelium, effects mediated by increased AT1-receptor stimulation.

Study Limitations

The study was not blinded, which represents a possible limitation. To deal with this potential bias, measurements were performed by investigators unaware of randomization status (B.H., U.L., C.K.). In addition, all measurements were recorded, and subsequently, vessel diameter and blood flow velocity were analyzed by 2 investigators unaware of the sequence of interventions or treatment assignment (B.H., U.L.).

There is evidence that losartan increases uric acid excretion in normal control subjects and patients with hypertension. Because uric acid may exert oxidative stress, this effect of losartan might contribute to the antioxidative effects observed in our study. Losartan does not lower uric acid plasma concentrations, however, which may be more relevant for oxidative stress within the vascular wall. Thus, although we cannot exclude the possibility that increased uric acid excretion was a contributing factor, it is very unlikely that the uricosuric effect of losartan can explain the effects of losartan on the endothelium-mediated vasodilation and activity of EC-SOD observed in the present study.

In conclusion, our present work suggests that the ACEI ramipril and the AT1-receptor antagonist losartan have comparable effects on endothelial function after 4 weeks of therapy, ie, both drugs increase bioavailability of NO, improve NO-mediated vasodilation, and increase EC-SOD activity to a similar extent in patients with CAD. These effects are mediated at least in part by a reduction of oxidative stress within the vessel wall, because the antioxidant vitamin C improves endothelium-mediated vasodilation before but not after therapy with ramipril and losartan. Increased EC-SOD activity may well represent 1 mechanism contributing to the antioxidative properties of ACEIs and AT1-receptor antagonists in patients with CAD.

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