Can ACE Inhibitors Promote Detrimental Vascular Effects After Percutaneous Injury?

To the Editor:

Zhuo et al reported interesting observations in vivo about the effects of angiotensin-converting enzyme (ACE) inhibition with perindopril on plasma ACE levels and cellular expression of ACE, AT1 receptors, and nitric oxide synthase (NOS) isoforms in human blood vessels.

Oral ACE inhibition at conventional doses (perindopril 4 mg/d) decreased plasma ACE activity by 70% and vascular ACE immunoactivity to 65% of control subjects detected by immunocytochemistry, and increased endothelial NOS (eNOS) and inducible NOS (iNOS) expression in the vascular wall. However, the authors also observed a dramatic 80% increment of the AT1 receptor binding in vascular smooth muscle cells, which might increase the potential of these receptors to counterbalance the beneficial effects of suppressed angiotensin II formation if AT1 receptors were activated by alternative sources of angiotensin II.

Whether the overexpression of AT1 receptors may somehow limit, or even reverse, the beneficial effects of ACE inhibitors in specific clinical situations of vascular disease has stimulated the following comments.

So far, mostly beneficial vascular effects have been reported in patients treated with ACE inhibitors. However, 2 recent publications have shown that oral administration of ACE inhibitors following stented angioplasty actually augmented the incidence of restenosis instead of reducing it. Conversely, the administration of AT1 antagonist valsartan in the VAL-PREST Trial reduced the occurrence of stent restenosis in a small but placebo-controlled randomized trial. Although these studies were not aimed at evaluating the clinical outcome, the angiographic findings are consistent with an opposite-to-the-expected effect of ACE inhibitors and a possible favorable outcome with AT1 antagonists.

In-stent restenosis is a proliferative response of the vessel wall to the injury caused by coronary stenting, and this phenomenon correlates in humans with plasma ACE concentration. Furthermore, tissue ACE is upregulated locally during the vascular healing process. ACE-inhibition was thought to potentially contribute to the prevention of its occurrence, but emerging evidence does not support this hypothesis.

A large angiographic analysis addressing this issue is being performed by our group. Although retrospective in nature, the preliminary analysis of nearly 1000 consecutive patients yielded a much higher restenosis rate in 282 ACE-inhibited patients (36.6%) compared with 615 nontreated patients (22.9%) (OR=1.94, 95% CI: 1.45–2.59). Such a difference persisted after normalization for covariates. By multivariate analysis, ACE inhibition emerged as an independent predictor of stent restenosis (OR=1.84, 95% CI: 1.35–2.52, P=0.001). Zhuo et al provide a valuable piece of information that supports these observations and allows us to speculate that the interactions between plasma and tissue ACE levels and the intracellular signaling of angiotensin II in patients treated with ACE inhibitors may be involved in the mechanisms that lead to exuberant neointimal growth through the over-expression of AT1 membrane receptors. This might happen as a consequence of the chronic enzyme depletion that induces AT1-receptor over-expression and/or enhanced intracellular signaling of angiotensin II formed by the noninhibited fraction of plasma ACE, or by alternative metabolic pathways such as ACE-independent, chymase-mediated angiotensin II.

The integration of the evidence briefly summarized in this letter supports the hypothesis formulated to explain the augmented incidence of in-stent restenosis in ACE-inhibited patients.

Flavio Ribichini
Valeria Ferrero
Division of Cardiology
University of Piemonte Orientale
Novara, Italy
E-mail flavio_ribichini@hotmail.com

William Wijns
Cardiovascular Center OLVZ
Aalst, Belgium

Giuseppe Matullo
Alberto Piazza
Institute of Human Genetics
University of Turin
Turin, Italy

Eugenio Uslenghi
Department of Cardiology
Ospedale Santa Croce
Cuneo, Italy

Response

We appreciate the great interest of Ribichini et al in our article on the effects of chronic ACE inhibition with perindopril on ACE, AT₁ receptor, and nitric oxide synthase expression in human blood vessels. In their letter, Ribichini et al speculated that increased vascular AT₁ receptor expression during chronic ACE inhibition, as we observed, may limit or reverse the beneficial effects of ACE inhibitors and promote restenosis after percutaneous injury or coronary stenting. Because our study was not designed to assess clinical outcomes of chronic ACE inhibition with perindopril, we cannot speculate whether increased vascular AT₁-receptor expression during chronic ACE inhibition has detrimental effects on coronary artery restenosis as proposed by Ribichini et al.

In theory, it is possible that ACE inhibition–induced upregulation of vascular AT₁ receptors may have some unwanted effects, because Ang II generated by ACE-independent chymase in humans may act on AT₁ receptors to induce vasoconstriction, cell proliferation, or hypertrophy. However, the beneficial effects of ACE inhibitors are well supported by both animal and human studies. Indeed, ACE inhibitors have been shown to be effective in preventing and treating hypertension and chronic heart failure in large randomized, double-blinded, and placebo-controlled, multiple-center clinical trials. Moreover, the recently published HOPE studies further extend the benefits of chronic ACE inhibition to possible prevention or treatment of human coronary atherosclerotic disease. ACE inhibitors exert multiple beneficial cardiovascular effects by inhibiting plasma and tissue Ang II formation, augmenting tissue kinins levels, and increasing bioavailability of NO. All of these effects of chronic ACE inhibition oppose the Ang II–induced vasoconstrictor and proliferation- or growth-promoting effects.

Currently, there is no conclusive evidence to support the hypothesis that ACE inhibitors can promote, whereas AT₁ receptor antagonists (ARBs) reduce, coronary restenosis after percutaneous coronary injury or stenting. Apart from the studies on the patients with the DD genotype as cited by Ribichini et al, ACE inhibitors have been shown to be effective in significantly reducing the risk of cardiovascular events, inhibiting neointima formation in porcine coronary artery balloon-injury model, preventing accelerated atherosclerosis in diabetic apolipoprotein E–deficient mice, and reducing the incidence of restenosis after percutaneous transluminal coronary angioplasty or stenting. Likewise, ARBs have been shown to be either effective or inconclusive in preventing coronary restenosis in pigs or humans. We should wait for the outcomes of several large ongoing randomized, double-blinded, placebo-controlled, and multiple-center clinical trials before drawing a conclusion about whether ACE inhibitors can promote restenosis after percutaneous coronary injury or stenting.

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Flavio Ribichini, Valeria Ferrero, William Wijns, Giuseppe Matullo, Alberto Piazza and Eugenio Uslenghi

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