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Importance of local renin-angiotensin systems and anti-ischemic effects of ACE-inhibitors in patients with coronary artery disease.

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Part I of this thesis discusses the importance of the circulating and tissue localized renin-angiotensin system. Although tissue or local ACE seems quantitatively and qualitatively far more important than circulating or plasma ACE, elevated plasma ACE activity is shown to be a significant and independent predictor of the development of left ventricular dilation after myocardial infarction *(Chapter 1)*. The effects of manipulation of the renin-angiotensin system through ACE inhibitors, drugs reducing the conversion of angiotensin I to angiotensin II, was evaluated in the first part of the QUO VADIS study. The effects of long-term *oral* treatment of ACE inhibitors on local ACE concentration, i.e. local angiotensin II formation, are described. Treatment with quinapril not only results in a statistically significant reduction of plasma ACE, but also in a statistically significant reduction of local angiotensin II formation *(Chapter 2)*.

Treatment with ACE inhibitors reduce the risk of mortality and myocardial infarction in patients with coronary artery disease. This risk reduction may be due to anti-ischemic effects of ACE inhibitors. In part II, a review article describes various mechanisms for the anti-ischemic effects of ACE inhibitors *(Chapter 3)*. In the second part of the QUO VADIS study, the efficacy of ACE inhibitor treatment on ischemia in patients, who underwent coronary artery bypass grafting was evaluated. Chronic treatment with quinapril significantly reduces clinical ischemic events over the first year after coronary artery bypass surgery, providing evidence for the anti-ischemic properties of ACE inhibitors *(Chapter 4)*.

In part III, the importance of alternative pathways are described. The formation of angiotensin II does not seem to depend only on ACE, but also on other angiotensin II forming enzymes, such as chymase. Angiotensin II receptor blockers provide the opportunity to study alternative pathways. The effects of ACE inhibition and angiotensin II receptor blockade on angiotensin-mediated responses in the human vasculature were compared. In an *in vitro* study, the ACE inhibitor captopril incompletely and the angiotensin II-AT1 receptor antagonist irbesartan completely blocks angiotensin II formation. Indeed, these differences might be explained by non-ACE (chymase) angiotensin II formation and seem especially important during an activated renin-angiotensin system *(Chapter 5)*.

The importance of interactions is also described in part III. ACE inhibitors and aspirin are widely and concomitantly used in patients with coronary artery disease. Both drugs exert their protective effect through a related-prostaglandin mediated pathway. Aspirin does not attenuate the beneficial effects of ACE inhibition after acute myocardial infarction, but independently reduces left ventricular dilation in patients after myocardial infarction. Since relatively low doses of aspirin effectively block the formation of thromboxane A_2, without significantly affecting prostaglandin formation, the negative interaction seems negligible *(Chapter 6)*.

Conclusions and future prospectives

In patients with coronary artery disease, elevated plasma and tissue ACE, as a result of activation of the renin-angiotensin system, was proven to be harmful. Therefore, manipulation of the renin angiotensin system by reducing plasma and tissue ACE and angiotensin II may be beneficial. ACE inhibitors, by reducing angiotensin II activity, seem the drug of first choice. In the QUO VADIS trial, quinapril significantly reduced plasma ACE and local angiotensin II. However, the ACE inhibitor captopril did not reduce local angiotensin II formation, indicating a difference in tissue specificity between various ACE inhibitors. Eventually, the reduction in local angiotensin II formation, by quinapril, resulted in the reduction in clinical ischemic events. The results of the HOPE study support our findings of anti-ischemic effects of ACE inhibitors. However, the patients in QUO VADIS were comprised of a very special post-CABG population of low risk patients, which was excluded from the HOPE study. Recently, the IMAGINE trial has been initiated, evaluating the effects of ACE inhibitors when started within 7 days of coronary artery bypass surgery. During one year, a total of 2200 patients will receive either quinapril or placebo. Since various ACE inhibitors do not uniformly reduce local angiotensin II, and may therefore have various anti-ischemic properties, there is a need for a comparing clinical trial between different ACE inhibitors.

Recent reports indicate that angiotensin II receptor blockers are more specific in reducing angiotensin II. In contrast to ACE inhibitors, the angiotensin II receptor blockers lack their effect on bradykinin breakdown, and consequently nitric oxide production. Therefore, *anti-ischemic properties* may be a specific feature of ACE inhibitors. There is a strong need for a long-term study to evaluate possible benefits on morbidity and mortality of adding an angiotensin receptor blocker to ACE inhibitor therapy, *in patients with coronary artery disease*. Recently, the results of RESOLVD indicated that in patients with *symptomatic heart failure*, the combination of an angiotensin II receptor blocker and an ACE inhibitor was more beneficial for preventing left ventricular remodeling than either drug alone. We are expecting the results of the long-term studies in patients with symptomatic heart failure, the VaL-HeFT and the CHARM, in the next years.

The safety of the coadministration of ACE inhibitors and aspirin still remains questioned due to their divergent effects on the vascular synthesis of vasodilating prostaglandins. In the HOPE trial, a negative interaction between aspirin and ramipril was found, the effects of ramipril being significantly less marked in patients receiving aspirin. However, a post-hoc analysis of the CATS study revealed that aspirin did not attenuate the beneficial effects of ACE inhibition after acute myocardial infarction. Of course, the patient populations and analyses were not comparable, but concomitant use

of ACE inhibitors and aspirin seemed safe. However, theoretically one could expect there would be no interaction between angiotensin receptor blockers and aspirin and therefore their concomitant use would be safer.