For an approximate screening of atherosclerosis, non-invasive methods may have limited value: the relationship between ultrasonographically detected carotid atherosclerosis and the presence of coronary atherosclerosis is an example. The weak correlation between the extent of coronary atherosclerosis and clinical symptoms of coronary artery disease remains another logistic problem. There is little consensus on the practical question: should an entirely asymptomatic patient with proven significant coronary atherosclerosis be treated by all available means including revascularization? Clearly, improving the possibility of establishing a diagnosis of coronary atherosclerosis in asymptomatic humans presents a new dilemma: full treatment or watchful waiting?

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Blockade of the renin angiotensin system in heart failure: the potential place of angiotensin II receptor blockers

See page 53 for the article to which this Editorial refers

Neurohormonal activation is one of the hallmarks of chronic heart failure and inhibition of the neurohormonal systems, in particular the sympathetic nervous system and the renin angiotensin system, have become important targets in chronic heart failure. Indeed, the favourable effect of angiotensin converting enzyme (ACE) inhibitors in chronic heart failure has largely been attributed to blockade of angiotensin II production, the target hormone of the renin angiotensin system. For several years, however, it has been known that production or formation of angiotensin II may also occur via other, non-ACE pathways, such as the enzyme chymase. This so-called escape from suppression of the renin angiotensin system during ACE inhibition is often encountered in circumstances of increased activity, such as chronic heart failure, but the clinical relevance of this escape is largely unknown.

In the present issue Roig et al. report on 70 patients treated with full-dose ACE inhibitors, in whom plasma angiotensin II levels were examined. They found that 50% of patients had increased angiotensin II levels, despite high-dose enalapril or captopril. More importantly, they showed that these patients not only had higher plasma neurohormones, but that their prognosis was also significantly worse compared to those in whom angiotensin II remained suppressed.

Activation of the renin angiotensin system, and increased angiotensin II levels, are known to correlate
with mortality in patients with chronic heart failure\[3\], but the present study now shows that if suppression of the renin angiotensin system by ACE inhibition is incomplete or inadequate, this also bears prognostic value. It therefore appears tempting to speculate that add-on suppression by an angiotensin II receptor blocker could be clinically effective, especially in patients with increased plasma angiotensin II levels despite ACE inhibition. Another argument in favour of add-on therapy is the difference in mode of action between ACE inhibitors and angiotensin II receptor blockers. ACE inhibitors not only decrease angiotensin II formation, but additionally inhibit the breakdown of bradykinin, which might partially account for their effect in chronic heart failure. Interestingly, it has recently been suggested that angiotensin II receptor blockers, in addition to blockade of the angiotensin II-AT\(_1\) receptor, might stimulate bradykinin through the unprotected AT\(_2\) receptor\[4\]. Although these findings will need further confirmation, ACE inhibitors decrease stimulation of the AT\(_2\) receptor, while angiotensin II receptor blockers increase stimulation of the AT\(_2\) receptor. Therefore, while the clinical significance of these differences remain to be established, the difference in mode of action theoretically favours add-on therapy. This hypothesis was confirmed in a recent double-blind study in a relatively small group of patients, in which exercise capacity increased and symptoms decreased when losartan was added to maximal ACE inhibition in patients with chronic heart failure\[5\]. From the study by Roig et al.\[2\], the clinical relevance of measurement of angiotensin II plasma levels becomes clear. It should be noted, however, that this measurement in plasma is technically difficult, which can only be done in experienced laboratories.

Two years ago, the publication of the ELITE (Evaluation of Losartan In The Elderly) Study\[6\] stirred a lot of commotion, since it somewhat unexpectedly showed that the angiotensin II receptor blocker losartan, when added to digoxin and diuretics in elderly patients with chronic heart failure, had a more favourable effect on mortality than captopril. While that study was not intended to be a mortality trial, and only 722 patients were studied, the results were intriguing, since for the first time it was shown that direct (angiotensin II) receptor blockade could be as beneficial as ACE inhibition, which up until then had been the cornerstone in the treatment of chronic heart failure. The results of the ELITE study subsequently generated a considerable amount of speculation concerning the potential place of angiotensin II receptor blockers in chronic heart failure. The first (defensive) approach would be that angiotensin II receptor blockers might be a good alternative in chronic heart failure patients who do not tolerate ACE inhibitors because of side-effects, such as cough. Second, angiotensin II receptor blockers might also be used as add-on therapy in patients already treated with ACE inhibitors, which might be particularly effective in those in whom escape from suppression is found. The third, and most provocative approach could be that in future angiotensin II receptor blockers might even replace ACE inhibitors as the cornerstone in the treatment of chronic heart failure.

To examine these questions, three trials with different angiotensin II receptor blockers (losartan, valsartan and candesartan) are currently underway, which will together study >13 000 patients with chronic heart failure. The ELITE-II study, which compares the effect of losartan vs captopril on mortality in 3149 patients (>60 years) with chronic heart failure, is the first of these three trials, and the results should have been available at the end of 1999. The Val-HeFT (Valsartan Heart Failure Trial) has already recruited more than 4500 patients, and will evaluate the effect of valsartan in patients with chronic heart failure, regardless of whether ACE inhibitors are used (expected to be around 90%); its results will probably be available in the middle of 2000. The third and largest trial is CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) which will investigate the effect of this angiotensin II receptor blocker on all-cause mortality in 6000 patients with chronic heart failure. This study has three arms: in the first, the effects of candesartan will be studied in patients who are ACE inhibitor intolerant, and who have an impaired left ventricular ejection fraction <0.40; in the second, the effects of this angiotensin II receptor blocker will be examined when added to ACE inhibitors in patients with left ventricular ejection fraction <0.40, and in the third, the effects of candesartan in chronic heart failure patients with left ventricular ejection fraction >0.40 (presumably those with diastolic dysfunction) will be studied.

These three large trials will provide important information about the potential place of angiotensin II receptor blockers in patients with chronic heart failure, and obviously their results are eagerly awaited, since the prognosis of patient with chronic heart failure is still poor. Until this time, however, ACE inhibitors remain the cornerstone of the treatment in chronic heart failure, despite their limitations, since their value in these patients is beyond doubt.

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