ACE inhibitors and proteinuria

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Introduction

The history of the use of angiotension converting enzyme (ACE) inhibitors shows a number of remarkable paradoxes. Their mechanism of action is to block the formation of angiotensin II, the effector hormone of the renin-angiotensin system. It was therefore initially expected that ACE inhibitors would be particularly effective in renovascular hypertension since this disease state is characterized by a hyperactive renin-angiotensin system. Nowadays the use of ACE inhibitors in renovascular hypertension turns out to be a relative contraindication due to the potential deterioration of renal function. A similar, but less frequently noted paradox involves their effect on proteinuria. In 1979, Prins et al. and Hoorn et al. described in a number of case reports that the ACE inhibitor captopril caused proteinuria and could thus be potentially nephrotoxic [1-3]. This unanticipated side effect was subsequently also reported by others [4-6]. In retrospect, this may have been a chance finding. Biopsy studies showed that untreated hypertensives sometimes have preexistent subclinical renal disease [7]. These renal diseases are generally progressive, which may result in urinary protein loss, independent of treatment. The nephrotoxicity of ACE inhibitors was further questioned by the finding that proteinuria disappeared spontaneously in some of these patients, although ACE inhibitor therapy was continued. Moreover, if proteinuria actually is a side effect, it appears to be related to the high captopril dosages that were initially used. Most patients that developed proteinuria received 400 to 600 mg of captopril, which was not an uncommon daily dosage at the end of the 1970s. With the current lower dosages of captopril, proteinuria is only very rare [8].

Shortly after these case reports, articles were published stating that ACE inhibitors would effectively reduce proteinuria [9-13]. This has since been confirmed in dozens of well-documented, prospective studies in several patient categories. It appears that proteinuria is reduced by 40 to 50%. Thus, ACE inhibitors may incidentally cause proteinuria, but in general they have an antiproteinuric effect.

Proteinuria as a risk factor

What is the clinical importance of proteinuria? If the kidney has sustained damage, regardless of the cause, a progressive deterioration of renal function generally follows. The measure of progression of renal function loss varies among patients, but seems to be of a remarkably constant nature in each individual. This phenomenon occurs independently of the original renal disorder. There is controversy over the causes of this deterioration. Currently, the most widely accepted concept takes the hemodynamic overload of nephrons as a starting point. After renal damage, regardless of the cause, a portion of nephrons is destroyed. As a result, the remaining nephrons are exposed to an increased blood flow. This results in an elevated intraglomerular pressure, and therefore in an
also in the case of proteinuria due to primary renal disease (that is, 7.3 gram/24 hours), it is known that the measure of urinary protein loss is correlated with the rate of renal function deterioration [17].

Several studies show that the antiproteinuric effect of ACE inhibition is superior [30]. ACE inhibitors reduced urinary protein loss by a mean 43% vs. a 17% reduction with other antihypertensives, while blood pressure responses were similar (12% vs. 11% reduction, respectively) (Figure 2). Because of this superior antiproteinuric efficacy, ACE inhibitors are used in nephrology practice for the symptomatic treatment of patients with nephrotic syndrome.

Calcium channel antagonists may be an exception to the rule that other antihypertensives have less antiproteinuric efficacy than ACE inhibitors. Our meta-analysis indicates that there is a great variability in antiproteinuric efficacy among the different drugs within this class. Nifedipine, for example, reduces proteinuria to a significantly smaller extent than other calcium antagonists: 8 vs. 21% [30]. The suggestion that some calcium antagonists are more effective in reducing protein loss than others is supported by the findings in studies which directly compare effects of different calcium channel antagonists. In these studies it appeared that nifedipine reduces proteinuria significantly less than diltiazem, nitrendipine and verapamil [31-33].

The antiproteinuric effect of ACE inhibition

Not only ACE inhibitors but also other antihypertensives are reported to reduce proteinuria. This could give the impression that each antihypertensive agent reduces urinary protein loss. However, this impression is distorted by the so-called publication bias. In the placebo-controlled studies investigating the effect of antihypertensives, blood pressure will naturally be the primary study parameter. Results with respect to other parameters, such as proteinuria, will only be reported in case of a marked favorable change. In general therefore, the literature will tend to make a positive selection of results with respect to secondary study parameters. In order to avoid such bias, studies are required in which the antiproteinuric effect of an antihypertensive is compared with that of another blood pressure lowering agent. In such a comparative study design, negative results with one of either drugs with respect to proteinuria are more likely to be reported. In a meta-analysis of such studies, we demonstrated that the antiproteinuric effect of ACE inhibitors is superior [30]. ACE inhibitors reduced urinary protein loss by a mean 43% vs. a 17% reduction with other antihypertensives, while blood pressure responses were similar (12% vs. 11% reduction, respectively) (Figure 2). Because of this superior antiproteinuric efficacy, ACE inhibitors are used in nephrology practice for the symptomatic treatment of patients with nephrotic syndrome.

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