Letters to the editor

Do angiotensin converting enzyme inhibitors represent a progress in hypertension care in diabetes mellitus?

“Bona meliora tuluntur”

Dear Sir,

In the article by Sawicki et al. [1], the authors make an attempt to challenge the present view that angiotensin converting enzyme (ACE) inhibitors offer a series of advantages in the treatment of hypertensive diabetic patients. We feel, however, that the authors ask the wrong question and give a number of wrong answers.

First of all, Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes should be kept apart as strictly as possible when talking about hypertension, since both *metabolic disturbance* and *pathogenesis of hypertension* differ largely between both types of diabetes.

Approximately 40% of Type 1 diabetic patients are known to develop *secondary hypertension* as a consequence of nephropathy [2] after years of being diabetic. The basis of the metabolic disturbance is *insulin deficiency*.

In striking contrast, more than 50% of Type 2 diabetic patients already have *essential hypertension* and more than 30% suffer from coronary artery disease at the onset of their diabetes [3, 4]. They have been insulin resistant and *hyperinsulinaemic* before.

The therapeutic aim of antihypertensive treatment is long-term *prevention of renal failure* in Type 1 diabetes and *reduction of the dramatically elevated cardiovascular risk* in Type 2 diabetes.

Two parameters which are currently regarded as being of central importance in nephropathy and the syndrome of metabolic cardiovascular risk factors [5] have been shown to be positively influenced by angiotensin converting enzyme inhibitors, namely glomerular hypertension [6] and insulin resistance [7, 8].

Insulin resistance not only occurs in manifest Type 2 diabetes, but also in impaired glucose tolerance, obesity, essential hypertension and even in 25% of subjects with normal glucose tolerance [9], i.e. in a variety of “pre-diabetic states”. The question therefore, is not how to reduce blood pressure, but how to slow down renal function loss in Type 1 and to reduce coronary risk in Type 2 diabetes and all other insulin resistant states.

Thus, angiotensin converting enzyme inhibitors offer the progress of an intervention that may correct an underlying defect (i.e. glomerular hypertension and insulin resistance, respectively) instead of treating one symptom (hypertension) at the cost of aggravating the apparently causal disturbance (hyperinsulinaemia). This applies not only for hypertension care in diabetes, but in general.

Finally, we would like to adress a number of wrong statements given by the authors: (1) There is no doubt, that beta-blocking agents are effective drugs in the secondary prevention of coronary heart disease. However, due to serious methodological shortcomings of the studies quoting it, this is still fiction rather than fact in primary prevention [10]. (2) The argument, that Type 2 diabetic patients are in “geriatric age range” and have already developed atherosclerotic disease is not an argument against, but rather for early intervention with ACE inhibitors, since the underlying insulin resistance as well as structural changes of the arterial wall are obviously being positively influenced [8, 11]. (3) We do not understand, why special caution should be warranted concerning ACE inhibitor

treatment in severe chronic heart failure, since its beneficial effect is well established already in moderate and even milder forms of heart failure [12]. (4) It may be true, that Type 2 diabetic patients frequently show renal arterial stenoses on autopsy [1]. However, the haemodynamic and thus the clinical relevance of such post mortem data remain obscure.

Yours sincerely,

K. Rett, M. Wicklmayr, G. Dietze and H. Mehnert

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Response from the Authors

Dear Sir,

We feel that Rett et al. are asking the *right* question: "... Not how to reduce blood pressure, but how to slow down renal function loss ... and reduce coronary risk ...?", or more precisely: How to prolong life in hypertensive Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic patients? In our article, we intended to provide answers exactly to these questions based on controlled studies rather than on pathophysiological speculation.

Beta-blocking agents have been shown to reduce mortality in Type 1 [1, 2] and Type 2 [3] diabetes and in patients with essential hypertension [4]. We agree with Rett et al. that some methodological aspects of these prospective controlled long-term trials may be questionable. However, such trials still represent the best and only available rationale for any therapeutic intervention since *mortality* rather than risk factors/indicators have been defined as end-points of these studies. No such trials have ever been performed for angiotensin converting enzyme (ACE) inhibitors.

Rett et al. propose a specific advantage of ACE inhibitors over conventional treatment regarding diabetic nephropathy and insulin resistance. Such a hypothetical advantage can only be documented by studies comparing ACE inhibitors with other antihypertensive treatments. There is only one prospective study comparing ACE inhibitors with beta-blockers in overt diabetic nephropathy [5]. This short-term study showed a significant rise in serum creatinine and a drop in proteinuria only in the enalapril group while no change occurred in the metoprolol group. These results could actually be interpreted as a specific *adverse* effect of ACE inhibitors in diabetic nephropathy [6]. A meta-analysis of different antihypertensive treatments in diabetic nephropathy demonstrated a significantly lower decrease in blood pressure and proteinuria with ACE inhibitors while no differences in the decrease of glomerular filtration rate were noticed when compared to conventional antihypertensive treatment [7]. Preliminary results of antihypertensive treatment in incipient diabetic nephropathy showed no difference in reduction of albuminuria between perindopril and nifedipine [8]. Hence, specific nephroprotection by ACE inhibitors still remains wishful thinking than proven fact.

Improvement of insulin sensitivity has been suggested not only for ACE inhibitors but also for prazosin [9], metoprolol [10] and atenolol [10]. However, these were placebo controlled trials and a non-specific effect of blood pressure reduction independent of the antihypertensive drug used has not been excluded. In studies comparing several antihypertensive drugs the adverse potentially confounding side-effects of potassium loss and weight gain on glucose sensitivity need be taken into account. Studies not including such data [11] or demonstrating a significant drop in serum potassium after thiazide administration [12] or weight gain after beta-blockade [13] must be interpreted with caution: Under such circumstances any *specific* effect of a drug is impossible to demonstrate. In any case, the clinical relevance of such experimental investigations remains uncertain. Recent preliminary results of a double-blind, placebo controlled, prospective study in Type 2 diabetes showed no change in HbA_{1c} and other parameters of insulin sensitivity and metabolic control after ACE inhibitors vs beta-blocker treatment [14].

We still do not accept that the evidence as available in present literature provides any justification for replacing an antihypertensive therapy (i.e. conventional antihypertensive treatment with diuretics, cardioselective beta-blockers and vasodilators) which has been proven to reduce morbidity and mortality in hypertensive diabetic patients by a newer, as yet incompletely evaluated therapeutic principle (i.e. ACE inhibitors). This cautious attitude based upon considerations of efficacy, safety and cost-effectiveness has most recent-

ly been confirmed by an official statement issued jointly by the German Hypertension League and the German Diabetes Association [15].

Yours sincerely,

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