Cardiovascular Diabetology

Commentary

Losartan and diabetic nephropathy: commentaries on the RENAAL study

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Abstract

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study is a multinational, double-blind, randomized, placebo controlled trial which was recently published. It was aimed to evaluate the effect of the angiotensin receptor blocker losartan in patients with diabetic nephropathy. The primary efficacy measure was the time to the first event of the composite end point of a doubling of serum creatinine, end-stage renal disease, or death. The conclusion was that losartan led to significant improvement in renal outcomes, that was beyond that attributable to blood pressure control in patients with type 2 diabetes and nephropathy.

The perusal of the report raises concern, regarding to both the patient population as well as the outcome measures. At randomization, the placebo group included more patients with angina, myocardial infarction and lipid disorders than the losartan group. Information on glucose metabolism was disregarded, and data on antihyperglycemic therapy – which may have undesirable influences on cardiac performance – were not included in a multivariate analysis. In addition, only data on first hospitalization were reported, whilst information on total specific-cause hospitalizations was disregarded, thus potentially masking further unfavorable events. Furthermore, creatinine seems not to be a reliable surrogate end point. Based on its mechanism of action, losartan may possess favorable renoprotective properties. However, due to the methodological flaws and the incomplete data in the RENAAL study, the question of the effectiveness and safety of this drug in diabetic nephropathy remains yet unanswered.

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study is a multinational, double-blind, randomized, placebo controlled trial which was recently published [1]. The study aimed to evaluate the effect of the angiotensin receptor blocker losartan – alone or in combination with other antihypertensive drugs (excluding angiotensin-converting enzyme inhibitors) – in patients with diabetic nephropathy. The primary efficacy measure was the time to the first event of

the composite end point of a doubling of serum creatinine, end-stage renal disease, or death. The conclusion of the study was that losartan led to significant improvement in renal outcomes, that was beyond that attributable to blood pressure control in patients with type 2 diabetes and nephropathy.

Three main factors can be identified in the framework of a clinical trial: the therapeutic intervention, the patient population and the outcome measures by which the different therapy groups will be compared [2]. In the present case, the results of the trial depend on the interplay between the therapeutic intervention in the RENAAL study, i.e. losartan 50 or 100 mg daily, a large patient population presenting with diabetic nephropathy, and the a priori defined outcome measures over the mean follow-up period. Are the design of the RENAAL study and the analysis of data in compliance with the requirements of evidence-based medicine? The perusal of the report [1] raises concern, regarding to both the patient population as well as the outcome measures.

Patient population

Randomization

The losartan group and the placebo group were not completely equal, and this might influence the results: in the placebo group there were 10 more patients with angina than in the losartan group, 19 more with myocardial infarction, and 37 more with lipid disorders. Triglyceride level was also higher in the placebo group. Albeit the differences were not significant when separately considered, the cumulative influence of these clinical features on patients' outcome cannot be excluded. For instance, it can be presumed that a history of myocardial infarction is of overwhelming importance for the rate of hospitalization due to heart failure. This point is of special relevance in view of the higher rate of first hospitalization due to heart failure in the placebo group as compared with losartan group. Thus, a conceivable explanation for this outcome is that patients in the placebo group were more prone to suffer from heart failure than their counterparts on losartan treatment.

Glucose metabolism

It is disappointing that glycosylated hemoglobin values are reported only at baseline. Moreover, data on plasma glucose levels are not reported at all. Such information should not be disregarded in a study dealing with diabetic patients. The relationship between hyperglycemia and mortality is roughly linear, including asymptomatic patients with impaired fasting glucose [3], and tight glucose control reduces the risk of micro vascular complications such as renal disease [4]. Thus, information on glucose metabolism characteristics is crucial, since glycosylated hemoglobin or glucose levels *per se* could be a factor of strong repercussion on patients' outcome.

Antihyperglycemic drugs

The significance of hypertension in diabetic patients controlled on diet only versus those pharmacologically treated is different [5]. In this context, data on antihyperglycemic medication is essential. Moreover, sulfonylureas – which constitute a mainstay therapy in the diabetic patient – may have undesirable influences on cardiac performance, especially in the presence of a previously damaged myocardium [6]. Moreover, the widely used combined treatment of glyburide (a sulfonylurea known also as glibenclamide in European countries) and metformin is associated with increased mortality, in both patients with ischemic heart disease [7] and in the general population [8]. It would be advisable to collect data on antihyperglycemic therapy for both the losartan and placebo groups and to include these data in a multivariate analysis, since it seems almost obvious that these therapeutic agents could affect primary and secondary end points. Such data are missing in the final report of the RENAAL study [1].

Outcome measures

Composite endpoint

The RENAAL study employed a composite end point consisting of a doubling of serum creatinine, end-stage renal disease, or death in order to assess the efficacy of losartan. The employment of combined end points that use a combination of nonfatal events with death has been criticized [2,9], since they may lead to the camouflage of a negative outcome or result in a dilution of the effects of the therapeutic agent on mortality [10]. The methodological drawbacks of employing a composite end point are clearly perceived in the study: while substantial risk reductions were reported for the losartan group with regard to doubling of serum creatinine and end-stage renal disease, the death rate was relatively higher. It is possible that this could reflect a somewhat longer follow-up period in this group, as the authors state. In any case, the results evidently show no benefit in mortality rates in the losartan group.

Serum creatinine

The doubling of serum creatinine in the RENAAL study represents a surrogate end point. This is defined as a 'marker' or laboratory measurement that is used in therapeutic trials as a substitute for a meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy [11]. Surrogates are thought to reflect the activity of the underlying process that leads to an adverse outcome, since both surrogate and real end points are expected to move in the same direction [12]. In the RENAAL study the doubling of creatinine was defined as the first serum creati-

nine value that was twice the baseline value, confirmed by a similar second value at least four weeks after the initial doubling. Does creatinine represent a reliable surrogate? The response seems to be negative, since creatinine can increase acutely from dietary ingestion of cooked meat and can be blocked by some commonly used medications like cimetidine and trimethoprim [13].

Hospitalizations

Hospitalization is a commonly used outcome reflecting morbidity. Regarding secondary outcomes, no significant differences were documented between the losartan group and the placebo group in the rates of most cardiovascular end points, excepting first hospitalization due to heart failure. In this aspect, the risk was reduced by 32% in favor of the losartan group. The problem with this outcome is that its meaningfulness is limited when only data on first hospitalization are reported whilst information on total specific-cause hospitalizations is disregarded, thus potentially masking further unfavorable events [9].

Final comment

Recent reports have suggested that angiotensin receptor blockers [14] similarly to angiotensin-converting enzyme inhibitors [15], provide renoprotective effects in diabetic patients. In this context, based on its mechanism of action, losartan may share these favorable properties. Recent data from the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial [16] indicate that losartan was significantly more effective than the beta blocker atenolol in reducing cardiovascular morbidity and death in hypertensive patients with left ventricular hypertrophy . Indeed, patients taking losartan were less likely to develop type 2 diabetes during the study, and a separate analysis of diabetic patients showed a reduced risk of cardiovascular mortality. However, due to the methodological flaws and the incomplete data in the RENAAL study [1], the question of the effectiveness and safety of this drug in the specific setting of patients with diabetic nephropathy remains yet unanswered. Further elucidation of the issues that we discuss may contribute to clarify the uncertainties.

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