

Randomized Clinical Trials on Surrogate End Points: Are They Useful for Evaluating Cardiovascular and Renal Disease Protection in Hypertension? The Case for Yes

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Hard end point studies represent the best available evidence for demonstrating the cardiovascular and renal protection that is achievable with a given treatment in hypertensive patients, yet properly designed end point studies require large cohorts of patients and long follow-up, are expensive, and do not provide any insight on the mechanisms that lead to the clinical manifestations. Studies that are based on the incidence of preclinical alterations, *i.e.*, the surrogate end points, may circumvent these limitations provided that their relationship with the major cardiovascular events is scientifically proved. In this respect, among the many surrogate end points that are under investigation, left ventricular hypertrophy, microalbuminuria, and treatment-induced diabetes seem most promising for replacing the hard end points in view of their undisputed mechanistic relationship with the clinical events and of the mounting evidence indicating that from their changes it is possible to predict the clinical outcome of patients. In addition, the limited resources that are required to carry out this kind of investigations make them preferable to hard end point studies for anticipating the cardiovascular and renal benefit associated with the use of antihypertensive agents.

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Hard end point studies, *i.e.*, those that are based on the incidence of major cardiovascular (CV) events such as myocardial infarction, stroke, and heart failure or renal events such as the development of ESRD, are considered the gold standard for comparing the cardiac and renal protection that is achievable with two different treatments. However, this kind of study has a number of logistic, mechanistic, and economic limitations (Table 1), and this led to the idea of replacing them with the surrogate, or intermediate, end point studies, *i.e.*, those that are based on the incidence of subclinical alterations, some of which are listed in Table 2. The use of these alternative end points is rationally conceivable because many of them represent the logic transition phase between the exposure to CV risk factors and the manifestation of the clinical events. However, before whichever surrogate end point is accepted as a valid alternative of the hard end point, two prerequisites need to be satisfied: (1) Proof of its biologic relevance for causing the event and (2) a convincing demonstration of the relationship between the progression/regression of the surrogate end point and the increase/decrease of the relevant clinical events.

Herein I address these issues taking advantage of the results of some recent intervention trials and of some observational studies to demonstrate that at least some of these surrogate end points, namely left ventricular hypertrophy (LVH), microalbuminuria (MA), and new-onset diabetes, do indeed fulfil these requirements and, therefore, can and should be used as an

alternative to the major clinical events for predicting CV and renal protection.

LVH

There is plenty of evidence that LVH is the initial step toward the development of major CV events such as congestive heart failure, cardiac ischemia and arrhythmias, and stroke. Such evidence goes back to more than 30 yr, when the Framingham Study clearly demonstrated that LVH, recognized by electrocardiogram, is a strong predictor of CV events (1). Subsequent echocardiographic studies confirmed these early observations (2). In agreement with these findings, Verdecchia *et al.* (3) showed that in hypertensive patients with a left ventricular mass (LVM) >125 g/m², the rate of CV events is almost three times higher than in patients with LVM <125 g/m². Similar results supporting the value of electrocardiographic LVH in predicting CV morbidity were obtained by Levy *et al.* (4). More recent studies have shown also that differences in the geometry of the left ventricle can affect the CV prognosis in hypertensive patients, in that for similar values of LVM, patients with concentric LVH have a significantly greater incidence of CV events than those with the eccentric geometry (5,6). The combination for LVH with electrocardiographic ST depression also is relevant for patient's prognosis; indeed, the Strong Heart Study that was conducted with American Indians has shown that the concomitant presence of both of these cardiac alterations is associated with a four-fold increase in CV mortality with respect to patients who harbor just one of them (7). Moreover, echocardiographic studies have shown that the antihypertensive treatment can induce the reversal of LVH and that the

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Table 1. Limitations of hard end point studies

Low incidence of events
Big numbers and long follow-up
Lack of information of preclinical lesions
Uncertainty on the protection mechanism of treatment
Difficulties in establishing the correct cost-benefit ratio of treatment
High cost (mostly affordable by possibly biased sponsors)

Table 2. Potentially useful surrogate end points^a

LVH and LV geometry
ECG alterations (ST depression)
Atherosclerotic vascular lesions
Microalbuminuria
C-reactive protein
New-onset diabetes
Reduction in renal function
Arterial stiffness
Endothelial dysfunction

^aLV, left ventricular; LVH, LV hypertrophy; ECG, electrocardiographic.

reduction of LVM is associated with a reduction of the risk for subsequent CV disease (8,9). In this respect, the study of Verdecchia *et al.* (3) has shown that during a follow-up of several years, the event rate in patients with the regression of LVH was four-fold lower than that observed in patients who had no regression with treatment.

MA

MA has been recognized as an independent risk factor in the recent European Society of Hypertension/European Society of Cardiology guidelines on hypertension (10); this occurred as a result of the increasing evidence indicating that an excess of urinary albumin excretion (UAE) rather than being a simple marker of renal damage is associated with an increased rate of CV events not only in hypertensive patients and patients with diabetes but also in the general population. In a cohort of almost 10,000 individuals who were 55 yr or older and had a history of previous CV disease or diabetes, Gerstein *et al.* (11) found that MA significantly increased the adjusted relative risk for major CV events, all-cause deaths, and hospitalization for congestive heart failure to 1.8, 2.1, and 3.2, respectively, these increments being similar for patients with and without diabetes. Moreover, these authors observed that compared with patients of the lowest quartile of the urinary albumin/creatinine ratio (UACR), those in the highest quartile had a two-fold increase in the relative risk for the primary aggregate end point; they also noticed that there is not a clear-cut threshold value of MA for indicating an increased CV risk, because for every 0.4 mg/mmol increase in UACR, the adjusted hazard of major CV events increased by 5.9%.

Along this line of research, in the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study that was conducted in the Netherlands in a cohort of 85,421 patients who were aged 28 to 75 yr, Hillege *et al.* (12) found a positive dose-response relationship between increasing UAE and CV and non-CV mortality even after adjustment for conventional CV risk factors; moreover, a two-fold increase in UAE was associated with a 29% increase in the relative risk for CV mortality. Results of these studies led several authorities in the field to recommend a redefinition of the normal threshold for MA, suggesting that the levels of MA that are associated with an increased CV risk may be much lower than was previously appreciated (13). MA also increases the mortality risk associated with electrocardiographic ST changes; in fact, it has been shown that in patients with the combination of these two surrogate end points, the hazard ratio for CV deaths is four times higher than in those with ST segment changes alone (14). Further evidence in favor of MA as an independent risk factor comes from studies in hypertensive patients. Agrawal *et al.* (15) reported that in a large cohort of hypertensive patients with and without diabetes, those with MA at baseline had a significantly greater prevalence of coronary artery disease, LVH, stroke, and peripheral vascular disease. These findings were reinforced by a subanalysis of the recent Losartan Intervention for End Point Reduction (LIFE) Study (16) in which among the 8206 hypertensive patients with LVH, those in the lowest decile of UACR (<0.26) had a rate of primary composite end points four times lower than those in the highest decile (>12) irrespective of whether they were treated with losartan or atenolol. In the same study, when patients were stratified by time-varying UACR, the rate of CV end points was significantly related to the degree of albumin excretion throughout the 5 yr of follow-up. In addition, it has been calculated that 17% of the benefit of losartan relative to atenolol in preventing CV events was explained by its effect on albuminuria.

A retrospective analysis of the Reduction in End-Point in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study (17) that was conducted in hypertensive patients who had type 2 diabetes and mild to severe renal insufficiency and were treated with losartan-based *versus* conventional drug-based therapy has shown that the rate of the renal end points was related directly to the levels of proteinuria at entry and inversely to its changes from baseline to 6 mo of treatment; moreover, after adjustment for other risk factors, the same stratification of baseline and in treatment UAE was significantly related to the incidence of CV end points, providing evidence, for the first time, that the reduction of protein excretion can predict both the renal and the CV outcomes.

New-Onset Diabetes

There is mounting evidence from recent clinical trials that some antihypertensive agents, namely β blockers and diuretics, may augment the propensity of hypertensive patients to develop type 2 diabetes (18). This is relevant because it is widely known that hypertensive patients are already exposed to a higher risk for developing type 2 diabetes with the attendant burden of CV disease; in addition, the prevalence of diabetes

Table 3. Advantages of surrogate end point studies

Sound and rational relationships with cardiovascular and renal hard end points
Require smaller number of patients and shorter duration
Provide insight into the mechanisms of disease
Provide scientific evidence for concentrating the therapeutic efforts on specific patients
Reduce the cost-benefit ratio of treatment

and hypertension increases in parallel with the increases in obesity and aging of the populations throughout the world (19). Therefore, the treatment-induced onset of diabetes can be considered as a plausible surrogate end point of subsequent CV events. This concept has been challenged by the result of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Study in which the greater incidence of new diabetes in patients of the chlorthalidone group compared with the amlodipine and lisinopril groups was not accompanied by a greater incidence of CV mortality and morbidity (20).

However, several previous studies have shown that the treatment-induced diabetes is far from being a benign condition. Indeed, Alderman *et al.* (21) showed that after adjustment for age and gender, the rate of CV diseases in hypertensive patients who developed diabetes while on antihypertensive treatment was similar to that of patients who already had diabetes at the time of entry in the study. Along this line of observation, Dunder *et al.* (22) reported that in middle-aged treated hypertensive patients, the increase in fasting blood glucose levels was the most powerful predictive index of subsequent myocardial infarction. Moreover, Verdecchia *et al.* (23) in a long-term follow-up study confirmed that the rate of CV events in treated hypertensive patients was similar in those with new or previously known diabetes and significantly higher than in those without diabetes despite similar levels of BP; in addition, in that study, the relative risk for CV events was roughly doubled for all three groups of patients with diabetes when LVH also was present.

Conclusion

It seems that at least some surrogate end points do fulfill the criteria for reliably replacing the major events as primary end point in clinical trials that aim to establish the cardio/renal protection of treatments. The surrogate end points have the additional advantages listed in Table 3; among these, the reduction in duration and cost is particularly attractive in view of the increasing limitation in financial resources facing even the most affluent societies.

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