Fewer Mega-Trials and More Clinically Oriented Studies in Hypertension Research? The Case of Blocking the Renin-Angiotensin-Aldosterone System

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In recent years, medical practice has been influenced substantially by several factors, including the overwhelming development of evidence-based medicine, which is a consequence of the impressive, growing number of large clinical trials, the so-called “mega-trials.” These clinical studies are designed mostly to investigate the effects of drugs or treatments on hard end points that cannot be tested by individual physicians in their daily clinical practice. The growing role of this epidemiologic approach to medicine, which is based mostly on the assessment of the average response or behavior of large populations rather than of individuals, is systematically replacing the former knowledge and reference points of the physician, as a substitute rather than as an aid. Taking into account the case of hypertension and particularly the renin-angiotensin system–blocking agents, this article reviews the issues and limitations of transferring evidence from mega-trials to clinical practice and suggests new strategies to make trials more effective and transferable to the case of individual patients.


In the past two decades, medical practice has been influenced and modified substantially by several factors, including the overwhelming development of evidence-based medicine (EBM), which is a consequence of the impressive, growing number of large clinical trials, the so-called “mega-trials.” These clinical studies are designed mostly to investigate the effects of drugs or treatments on hard end points, such as overall cardiovascular mortality, myocardial infarction, ischemic stroke, heart failure, ESRD, and, more in general, major prognostic outcomes, all items that cannot be tested by individual physicians in their daily clinical practice. The growing role of this epidemiologic approach to medicine, which is based mostly on the assessment of the average response or behavior of large population samples rather than of individuals, is systematically replacing the former knowledge and reference points of the physician, as a substitute rather than as an aid. Besides and beyond the personal clinical experience and professional skills and a sufficient knowledge of pathophysiologic mechanisms and pharmacologic drug properties, today each individual physician is required to be aware of the results of many trials and to transfer them to her or his clinical activity. Any significant deviation from the strict application of EBM to therapeutic management of the clinical cases may seem not to be justified.

In fact, the results of large international trials are more and more perceived not as a valid basis for therapeutic decisions but rather as the only evidence that can validate a treatment or an intervention. As a consequence, doctors are becoming more prone to accept acritically the conclusions of a mega-trial (and sometimes also the results of a small, “well-published” trial) and to choose a specific and often life-long treatment, as the results suggest. This phenomenon often happens because practicing physicians may feel intimidated by their own lack of statistical training or limited skills in data analysis and interpretation. Therefore, this process, which is dictated by a relatively restricted number of individuals or key opinion leaders and in most is cases financed by industries, has a heavy influence on individual physician behavior and on health care systems. However, the mechanistic application of EBM to clinical practice presents several misleading aspects. As an example, for reasons that are intrinsic to the scientific basis of the mega-trials, group-averaged data are transferred to individual care often with weak demographic, ethnic, and clinical associations. In fact, a key feature that makes a trial influential is the size of the study population. Important trials need to be large, but the size is not a “liberal” choice, because it is dictated by the need of a large sample to demonstrate an effect or a difference that is expected to be small. In fact, the largest is the sample size, the smallest difference expected. In addition, the price to pay to achieve a large population sample often is represented by heterogeneity of clinical characteristics, presence of comorbidities, and associated therapies in the study population, as well as by limited and less rigorous control of hard end points.

In this view, in designing a trial that will have enough power to detect statistically significant differences between two or more antihypertensive treatments in terms of cardiovascular mortality and morbidity, thousands of hypertensive individuals with different pathophysiologic, demographic, and clinical profiles will be put together, randomly assigned, and analyzed...
with the assumption (or, in the best case, the missed interpretation) that any eventual difference then could be applied to any of them. However, the promise of such a conclusion would be that all hypertensive individuals are alike or share the same pathophysiologic mechanism, thereby allowing trialists to assign the patients randomly and indiscriminately to any experimental drug. Such an assumption definitely would be wrong. In fact, within the population of the trial, the risk for cardiovascular or renal events is distributed unevenly among individuals, even if they fall within the same category of BP or cholesterol or creatinine levels. The reason that we accept EBM as a scientific discipline to be integrated with pathophysiology is that despite these and other limitations, it may provide helpful information with a rigorous approach based on a properly dimensioned and randomly assigned population sample, which is analyzed prospectively and blindly.

In other words, there is no question that the systematic use of EBM in the scientific process has brought significant progress in common clinical conditions, such as cardiovascular disease, renal disease, or neoplastic disease, often generating severe events or death. Physicians would not be able to predict effects of treatments on hard end points on the basis of their clinical practice or anecdotal experience. Therefore, they need to rely on large, controlled studies to define whether a treatment is effective not only in preventing death, myocardial infarction, stroke, or ESRD (hard endpoints) but also in reducing left ventricular hypertrophy, peripheral atherosclerosis, and microalbuminuria (intermediate or surrogate end points).

However, scientific and medical communities need to attribute the real value to the “mega-trials” approach. This area of clinical science should add to rather than substitute for the accumulated biochemical, physiologic, or pharmacologic knowledge. Indeed, it becomes a valuable tool with the potential to improve care and patient outcomes, when applied rationally to all of those clinical conditions for which science is incomplete and multiple therapies are available with uncertainty existing. Much caution, however, must be used in the correct reading of a mega-trial, taking into consideration results rather than conclusions, primary end points rather than the secondary or the tertiary ones. Finally, effort should be put in the process of education of physicians in learning how to read and to interpret a mega-trial, besides the suggestions of the authors.

Changing View of Clinical Trials across Centuries

The beginning of the history of clinical trials dates back to more than 2 centuries ago, when a small group of sailors were randomly assigned to receive limes to prevent scurvy on Captain Cook’s ship while traveling the oceans (1). In the past 40 yr, the clinical trial has become the leading method to guide objectively medical practice. In fact, this scientific method surpasses and implements individual clinical experience or uncontrolled observations. This approach, mostly based on the prospective study of subjects who are randomly assigned to either placebo or active therapy and the blinding of both participants and investigators, provides a reliable and helpful tool for testing therapeutic efficacy and, to a lesser extent, safety. Development of clinical trials for specific categories of drugs or treatments often has required very small samples of a population to test the efficacy of treatment with clear-cut, unequivocal effects, as in the case of penicillin or other antibacterial compounds (1).

Much more complex is the case of conditions, such as hypertension, diabetes, and associated cardiovascular diseases, for which multiple factors play a pathophysiologic role and the cause is unclear. In fact, when testing antihypertensive or lipid-lowering agents, we do not expect full prevention of cardiovascular events but rather small changes in the probabilities of developing these events. Therefore, large sample size, rigorous methods, and strict analytic criteria are needed to get scientific and significant answers. A sort of “think big” rule indeed has become the scientific manner to answer every question.

The initial trials on antihypertensive therapy were designed to assess whether BP reduction in patients with hypertension would be effective in reducing cardiovascular outcomes and be safe at the same time (2–11). The availability of tolerable and effective oral antihypertensive agents, such as β blockers and angiotensin-converting enzyme inhibitors (ACE-I), had transformed malignant hypertension from a rapid and often fatal multisystem disease into a chronic, although still harmful, condition (2–11). After these first experiences, in the past 2 decades, especially during the past 10 yr, an impressive number of clinical trials have been designed and undertaken to investigate whether different antihypertensive agents provide different cardiovascular protection benefits independent of substantially comparable BP-lowering properties (2–31). To achieve significant information on hard end points, these studies involved and observed for several years large cohorts of hypertensive patients ranging from a few hundred to several thousand individuals. The most common population profile was represented by individuals with mild to moderate hypertension with the purpose to define whether the benefit of BP could be extrapolated to the general population of individuals whose BP was elevated.

A further, consistent development of the scientific discipline based on large, controlled studies coincided with the experiences of antihypertensive treatment and, mostly, with the development of ACE-I in the early 1980s. These compounds were made available for the clinical use at a time in which multicenter studies were planned to be multinational for a number of reasons, including patients’ recruitment to achieve the needed numbers, regulatory and ethical issues, and marketing strategies (2–15). In fact, this was a lucky coincidence because ACE-I were found to be effective compared with placebo in heart failure (2–5,9,10,19,26), ischemic heart disease (6–8,22,23,25,29,30), diabetic nephropathies (14–18,25,29,30), and other clinical settings, as shown in Table 1. A positive study meant that the net effect of the intervention was favorable in comparison with placebo in terms of outcomes. This approach was used widely also to test the superiority of an active treatment versus another active treatment in the same condition and was extended throughout the spectrum of medicines, and more than 1 million patients with hypertension have been enrolled in this type of
study (32). These studies obviously showed that strokes and heart attacks were not eliminated but rather that there was a change in the probability of their occurrence (33).

### Head-to-Head Mega-Trials in Hypertension: Are They Useful or Useless?

In hypertension, major head-to-head studies, which had the hypothesis to test the superiority of one antihypertensive drug over another, mostly failed to match the primary end point and actually tended to corroborate the ancestral and debated concept that all that matters in the treatment of hypertension is to lower BP, because comparisons of end points mostly showed no difference. Certainly, some of the most important recent mega-trials suggested that the failure to achieve the postulated end points could be attributed largely to the experimental design or to unfortunate choices in the dosage of the drugs or in the study population. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (20), despite the generous effort of the agency that supported the study and of the investigators to demonstrate differences

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### Table 1. Most recent clinical trials performed with ACE-I and ARB

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug Class</th>
<th>Clinical Condition</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS I (1987)</td>
<td>ACE-I versus placebo</td>
<td>Congestive heart failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>CONSENSUS II (1992)</td>
<td>ACE-I versus placebo</td>
<td>Post-myocardial infarction</td>
<td>Neutral</td>
</tr>
<tr>
<td>REIN (1991)</td>
<td>ACE-I versus placebo</td>
<td>Renal failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>SOLVD I (1991)</td>
<td>ACE-I versus placebo</td>
<td>Ventricular dysfunction</td>
<td>Favorable</td>
</tr>
<tr>
<td>SOLVD II (1992)</td>
<td>ACE-I versus placebo</td>
<td>Post-myocardial infarction</td>
<td>Favorable</td>
</tr>
<tr>
<td>SAVE (1992)</td>
<td>ACE-I versus placebo</td>
<td>Post-myocardial infarction + myocardial infarction</td>
<td>Favorable</td>
</tr>
<tr>
<td>AIRE (1993)</td>
<td>ACE-I versus placebo</td>
<td>Post-myocardial infarction + myocardial infarction</td>
<td>Favorable</td>
</tr>
<tr>
<td>TRACE (1995)</td>
<td>ACE-I versus placebo</td>
<td>Post-myocardial infarction + myocardial infarction</td>
<td>Favorable</td>
</tr>
<tr>
<td>ELITE (1997)</td>
<td>ARB versus ACE-I</td>
<td>Congestive heart failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>ATLAS (2000)</td>
<td>ACE-I versus placebo</td>
<td>Congestive heart failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>ELITE II (2000)</td>
<td>ARB versus ACE-I</td>
<td>Congestive heart failure</td>
<td>Neutral versus ACE-I</td>
</tr>
<tr>
<td>HOPE (2000)</td>
<td>ACE-I versus placebo</td>
<td>High-risk profile</td>
<td>Favorable</td>
</tr>
<tr>
<td>PROGRESS (2001)</td>
<td>ACE-I versus placebo</td>
<td>Stroke</td>
<td>Favorable</td>
</tr>
<tr>
<td>IDNT (2001)</td>
<td>ARB versus placebo/amlodipine</td>
<td>Diabetes, renal failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>IRMA 2 (2001)</td>
<td>ARB versus placebo</td>
<td>Hypertension, diabetes microalbuminuria</td>
<td>Favorable</td>
</tr>
<tr>
<td>RENAAL (2001)</td>
<td>ARB versus placebo</td>
<td>Diabetes, renal failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>Val-HeFT (2001)</td>
<td>ARB versus placebo</td>
<td>Congestive heart failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>ALLHAT (2002)</td>
<td>ACE-I/chlorthalidone/amlodipine</td>
<td>Hypertension, high-risk profile</td>
<td>Neutral</td>
</tr>
<tr>
<td>LIFE (2002)</td>
<td>ARB vs atenolol</td>
<td>Hypertension with left ventricular hypertrophy</td>
<td>Favorable</td>
</tr>
<tr>
<td>OPTIMAAL (2002)</td>
<td>ARB versus ACE-I</td>
<td>Post-myocardial infarction + myocardial infarction</td>
<td>Neutral versus ACE-I</td>
</tr>
<tr>
<td>EUROPA (2003)</td>
<td>ACE-I versus placebo</td>
<td>Chronic stable coronary artery disease</td>
<td>Favorable</td>
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<tr>
<td>ANBP2 (2003)</td>
<td>ACE-I versus diuretics</td>
<td>Hypertension, elderly</td>
<td>Favorable</td>
</tr>
<tr>
<td>VALIANT (2003)</td>
<td>ARB versus ACE-I</td>
<td>Post-myocardial infarction + myocardial infarction</td>
<td>Neutral versus ACE-I</td>
</tr>
<tr>
<td>CHARM (2003)</td>
<td>ARB versus placebo</td>
<td>Congestive heart failure</td>
<td>Favorable</td>
</tr>
<tr>
<td>VALUE (2004)</td>
<td>ARB versus amlodipine</td>
<td>Hypertension</td>
<td>Neutral</td>
</tr>
<tr>
<td>BENEDICT (2004)</td>
<td>ACE-I</td>
<td>Diabetes</td>
<td>Favorable</td>
</tr>
<tr>
<td>DETAIL (2004)</td>
<td>ARB versus ACE-I</td>
<td>Diabetes, microalbuminuria</td>
<td>Neutral versus ACE-I</td>
</tr>
<tr>
<td>PEACE (2004)</td>
<td>ACE-I</td>
<td>Post-myocardial infarction</td>
<td>Neutral</td>
</tr>
<tr>
<td>ASCOT (2005)</td>
<td>ACE-I + CCB/β blockers + diuretics</td>
<td>Hypertension, high-risk profile</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

*ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium-channel blockers.
among treatment groups (receiving therapies based on chlorthalidone, amlopidine, or lisinopril; the doxazosin arm was interrupted prematurely), no statistical difference in the composite primary cardiovascular end point was found, and differences in specific components of the primary end points could be explained with the ethnic influence; for example, only in the black subgroup was the chlorthalidone arm superior to the lisinopril arm. Overall, the results of the study, which was performed with approximately 40,000 patients and cost $160 million, were negative. The conclusions of the authors, however, sounded very positive, heralding a victory of one treatment (diuretics) over the others. Even though the conclusion that the comparable effectiveness of a cheaper drug to a modern and more expensive therapy may seem to be sufficiently rewarding for doing the study, this would be attractive only in the hypothesis that all or most hypertensive patients could be treated effectively with a diuretic monotherapy for a long time.

This hypothesis obviously is denied by reality, because (1) only a small percentage of hypertensive patients can achieve the target BP levels with a diuretic monotherapy; (2) a certain amount of hypertensive patients could be treated effectively with a renin-angiotensin system (RAS)-inhibiting drug or a calcium antagonist in monotherapy; (3) most hypertensive patients will need a combination therapy; (4) global risk profile, comorbidities, side effects, and mostly pathophysiologic mechanisms underlying hypertension will differ in various patients; and (5) in the ALLHAT (20), the vast percentage of black individuals (approximately one third) precluded largely the effectiveness of ACE-I. Nonetheless, the ALLHAT mega-trial (20) has heavily affected North American Joint National Committee VII recommendations (34) for treating hypertension, several national health care systems, media reports, and physicians’ behavior. Physicians, in fact, often have perceived the ALLHAT results (20) as a superiority of the cheapest diuretic treatment that could be extended to all hypertensive individuals.

In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) mega-trial (27), performed with more than 15,000 hypertensive patients with a very heterogeneous high-risk profile, the postulated superiority of the valsartan-based treatment over the amlopidine-based therapy in the cardiovascular end point could not be demonstrated. However, because the patients were simply and directly “rolled over” from their pre-study treatment as in the ALLHAT mega-trial (20) and because of the relatively low initial dosage of valsartan, which was up-titrated slowly for at least 6 mo, the two arms of the study largely and consistently were unbalanced in terms of BP reductions across the study but especially in the first 6 mo. The larger BP reduction that was observed in the amlopidine group heavily affected the outcome, as discussed and demonstrated extensively by the authors in a vast post hoc analysis (35). In conclusion, he hypothesis of the study could not be tested because of the pitfalls in the design, and to acknowledge that a better control of BP may generate better outcomes probably did not need such a study.

Some aspects of these two mega-trials also clarify why it sometimes is difficult to translate EBM to clinicians. For instance, the “intention-to-treat” analysis, which is more than acceptable from the scientific standpoint and represents an essential requirement of objectivity in a trial, is unacceptable and impossible to understand from a clinical standpoint. For instance, in the ALLHAT (20) and VALUE (27) mega-trials, almost 25% of the patients cross-switched to other drugs, often including the comparator, but they still were considered as belonging to the original treatment group. Another example is that in ALLHAT (20), because of the experimental design and protocol, the rational combinations were denied to the patients, and the combinations that were used to achieve BP targets were not rational and often were obsolete. This is hardly transferable to the clinical practice, and, in the end, the results achieved represent almost a theoretical exercise.

In addition, the results of a trial should be applied only for the time frame of the observations (usually approximately 5 yr). In contrast, they often are extrapolated to a life-long treatment. In this regard, the case of new-onset diabetes clearly shows that this extrapolation is unwarranted. In fact, both the ALLHAT (20) and VALUE (27) trials clearly showed a higher new onset of diabetes (e.g., chlorthalidone in the ALLHAT [20]) versus the drug blocking the RAS. This may suggest an expected, projected risk of a specific treatment beyond the time borders of the study. With regard to the issue of combination therapy, the most frequent approach to hypertension, it also is evident that all of the head-to-head studies mostly were designed to show superiority of one drug to the other in a combination model and contributed very little to learning about which is the best approach to combination.

It is of interest that other studies that included hypertensive patients but used more homogeneous populations, from the point of view of the natural history of the disease, as reflected by the presence of a certain target organ disease (e.g., left ventricular hypertrophy, microalbuminuria) (14–18,28,29,36,37) or risk profile (12,21,27), originated more positive and meaningful results on primary end points (Figure 1). As a consequence, the focus of interventional trials probably should change and shift toward more clinically oriented targets. In this regard, the use of intermediate informative end points, such as left ventricular structure or (systolic/diastolic) function, atrial fibrillation, microalbuminuria and renal function, vascular structural and functional abnormalities, metabolic disorders, or new-onset diabetes, may prove to be more fruitful and more economic at the same time (36,38–43) (Figure 1).

There is little question that this approach may yield results that are closer to clinical reality and be more easily verifiable. In fact, the results of a single trial can be applied to a specific patient profile. In addition, the prevention or the regression of a certain clinical marker (e.g., left ventricular hypertrophy, peripheral vascular atherosclerosis, microalbuminuria) (14–18,28,29,36,37) can be checked by the physician in her or his clinical practice, something that could not be done with hard end points. In this regard, some recent trials that were performed with drugs that act on the RAS (ACE-I and angiotensin II receptor blockers [ARB]) demonstrated a better efficacy and tolerability in hypertensive patients in different settings among the cardiovascular continuum, as reported in Table 1.
The Case of RAS in Clinical Trials: Benefits beyond BP Control?

In interpreting the results of a mega-trial in hypertension and transferring the conclusions to daily practice, it must be considered that the potential benefit on outcomes depends largely on individual absolute cardiovascular risk. In addition, unrecognized pathophysiologic features of the patients may affect the response to various drugs, especially when comparing mechanistically different compounds that may exert different effects on BP and outcomes. In this view, despite comparable effects on BP, different antihypertensive agents may have different effects on target organ damage or outcomes. For instance, the individual renin profile (high or low) may affect the response to the antihypertensive agents (larger benefit for a drug’s counteracting the RAS in a high-renin patient). The case of RAS-blocking agents (ACE-I and ARB) indeed is very intriguing and debated, and it probably is for this reason that it is investigated extensively also in mega-trials. After the “ACE-I age,” now it is the time for ARB to be the most investigated class of drugs in cardiovascular and renal disorders.

In this regard, a large body of evidence has been provided in support of a role for drugs that interact with the RAS in the treatment of hypertensive patients with different comorbidities. Blocking the RAS with an ACE-I or an ARB has been shown to reduce cardiovascular end points in a variety of conditions, including isolated systolic hypertension (40), left ventricular hypertrophy (36), atrial fibrillation (41,42), ischemic stroke (43), acute myocardial infarction and coronary artery disease (23,25,30), heart failure with left ventricular dysfunction (10,11,19,26), microalbuminuria, and type 2 diabetes (14–18,28,29,37).

Figure 1. Central role of intermediate end points in the cardiovascular and renal continuum and new targets of therapy. LVH, left ventricular hypertrophy; LVD, left ventricular dysfunction; CHF, congestive heart failure; AMI, acute myocardial infarction; IGT, impaired glucose tolerance.

In this view, the most selective way of blocking the RAS is to use an ARB, because of the specific action, e.g., blockade of the interaction between angiotensin II and the AT1 receptor (44). This selectivity also may be important because the interaction between residual, unbound angiotensin II and the AT2 subtype receptors may result in an amplification of the beneficial effects of AT1 blockade and may favor vasorelaxation and reduce development of hypertrophy and cardiovascular remodeling (44). This complex pathophysiologic structure of the RAS can hardly be faced when interpreting a mega-trial, although this attempt has been made frequently (9,45). Recently, a growing number of mega-trials have supported a role for ARB in primary and secondary prevention of cardiovascular and renal disease.

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study (21) has strongly suggested benefits that go beyond BP reduction in hypertensive patients with left ventricular hypertrophy. In the presence of comparable BP reductions with a treatment regimen that is based on the ARB losartan versus a treatment regimen that is based on the β blocker atenolol, the losartan-based treatment significantly reduced the risk for the primary combined endpoint of cardiovascular death, stroke, and acute myocardial infarction by 13% and the incidence of fatal and nonfatal stroke by 25% compared with atenolol in >9000 patients who were selected on the basis of the presence of essential hypertension and left ventricular hypertrophy. Further substudies on the population of the LIFE Study have demonstrated beneficial effects of losartan on intermediate end points that could not be ascribed to simple BP reductions, in particular in patients with isolated systolic hy-
mental metabolic effects of the comparators (diuretics and 
blockade (50) and cannot be accounted for only by the detri-
able to specific mechanisms (49) associated with angiotensin II 
ward ESRD. This favorable impact of the drugs’ inhibiting the 
dition, it is widely known that development of diabetes in 
pertensive treatment is associated with poor prognosis. In ad-
don, recent studies (47,48) show that new-onset diabetes during long-term antihy-
ertensive treatment is associated with poor prognosis. In ad-
ition, it is widely known that development of diabetes in 
hypertension accelerates renal impairment and evolution to-
toward ESRD. This favorable impact of the drugs’ inhibiting the 
RAS, particularly ARB, on development of diabetes is attribut-
able to specific mechanisms (49) associated with angiotensin II 
blockade (50) and cannot be accounted for only by the detri-
mental metabolic effects of the comparators (diuretics and β 
blockers). Renal protection is another important goal of therapy in 
diabetes, hypertension, and atherosclerotic diseases and has a 
significant influence on the overall prognosis of patients. 
Blocking the RAS represents a successful strategy to slow the 
progression of renal impairment in these diseases, and this has 
been confirmed in three large clinical trials with ARB in dia-
betic nephropathy (16–18,29). In fact, ARB have been demon-
strated to delay the progression from microalbuminuria to 
macroalbuminuria in the Irbesartan Microalbuminuria type 2 
Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial (17) and 
even to delay the further progression from macroalbumin-
uria to ESRD in the Irbesartan Diabetic Nephropathy Trial 
(IDNT) (16) and in the Reduction of Endpoints in Non-Insulin-
Dependent Diabetes Mellitus with the Angiotensin II Antago-
nist Losartan (RENAAL) study (18). In addition, the 
MicroAlbuminuria Reduction with VALsartan (MARVAL) 
study (15) showed that in presence of strictly similar BP reduc-
tion, a treatment that is based on the ARB valsartan signifi-
cantly reduces microalbuminuria excretion more than a regi-
men that is based on calcium-channel blocker amlodipine. 
Recently, in the Diabetics Exposed to TelmisArtan and Enala-
prIL (DETAIL) Study (29), the ARB telmisartan was shown not to 
be inferior to the ACE-I enalapril in providing renoprotection 
in patients with type 2 diabetes and early nephropathy. On 
the basis of this clinical evidence, the most recent management 
guidelines (34,51) recommend the early inhibition of RAS, par-
ticularly in patients with nephropathy, and the use of a thera-
petic regimen that is based on ARB as the first choice in 
patients with type 2 diabetes.

Conclusion
The epidemiologic “trialist” community needs to alter its 
approach, namely by seeking to add to rather than to substitute 
for the accumulated biochemical, physiologic, and pharma-
ologic knowledge about hypertension and cardiovascular dis-
ease. The powerful tools that are offered by an epidemiologic 
approach to hypertension need to be integrated more properly 
into the overall network of pathophysiology and clinical sci-
ence to create the best medical practice and should not be used to 
dismantle it.

Reasonable changes and alternative strategies in designing 
clinical trials will be required to address the large and growing 
number of key epidemiologic and clinical issues that still need 
answers. After the impressive and, sometimes, unreasonable 
rush to challenge drugs by comparisons on major hard end 
points, which often has been generated for marketing reasons, 
rather than from genuine scientific needs, it is time now to 
move toward more pragmatic models. The new studies in 
hypertension should be of smaller size, be less expensive, be 
more independent, involve more homogeneous populations 
(from this point of view, the more selected population sample, 
used in recent studies, provides an excellent example), and 
address end points that are relevant to practice and verifiable 
by physicians.

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