Role of Outcome Trials in Providing Information on Antihypertensive Treatment: Importance and Limitations

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“Trials tell the truth, nothing but the truth, but not the whole truth.”

There is no question that current knowledge on antihypertensive treatment owes a great deal to morbidity and mortality trials. Their merits in shaping present concepts on why and how to treat hypertensive patients stand on three pillars. First, morbidity and mortality trials have shown that compared to the untreated condition treated hypertensives have fewer cardiovascular morbid and fatal events, which means that treatment meets the ultimate goal of managing patients with a blood pressure (BP) elevation—namely, to prevent increased cardiovascular risk. Second, morbidity and mortality trials have made use of study sizes that have allowed their conclusions to be based on adequate statistical power, ie, to be reasonably free from the risk of “chance” results. Third, morbidity and mortality trials have in most instances adopted procedures such as randomization of patients to different treatments or placebo, double-blind follow-up of treated individuals, and objective independent validation of the event nature, which guarantee against bias or differences in cardiovascular event rates caused by differences in the original clinical characteristics of the patients rather than treatment.

Yet, in the last few years morbidity and mortality trials have been the target of growing dissatisfaction and criticism, which have emphasized that this type of research has technical limitations, that its results cannot easily be applied to clinical practice, and that its nature does not allow to address a number of questions which are crucial for hypertension.

Patient Drop-Out and Unplanned Cross-Over

Morbidity and mortality trials on antihypertensive treatment are usually characterized by a large (up to 30% to 40%) drop-out from initial treatment, ie, by many patients who for a variety of reasons (side effects, withdrawal of consensus, decision of the investigator, etc) stop taking the treatment regimen to which they have been randomized and move to “free” treatment or no treatment at all. They are rather frequently also characterized by what can be called an “unplanned” cross-over, which means that rather than taking the drug or placebo to which they were originally assigned, they take also or only the comparison treatment. However data have to be analyzed on an intention-to-treat basis, that is, as if the original treatments were continued to preserve the clinical similarity of the treatment groups at the trial beginning. Nonetheless having a large number of patients in whom treatment is not different between comparison groups represents a powerful dilution factor that can 1) underestimate the protection offered by antihypertensive treatment when compared with placebo; 2) mask possible differences in event rate between different treatments; and 3) minimize side effects or other inconveniences a treatment type may have in comparison to another. This is illustrated by two examples.

In the Medical Research Council Trial, which investigated in mild-to-moderate hypertensives the benefit of lowering BP by a diuretic or a β-blocker, about 40% of patients randomized to placebo were actually given antihypertensive drugs. Obviously this led to a considerable underestimation of the ability of treatment to reduce cardiovascular disease, questioning the authors’ conclusion that a large number of patients with a mild-to-moderate elevation in BP have to be treated to prevent just one event. In the ALLHAT trial between 20% and 25% of the patients randomized to chlorthalidone were given, either in addition or along, drugs in the two classes to which chlorthalidone was compared. Conversely between 20% and 25% of the patients randomized to amlodipine or lisinopril were given diuretics in addition or alone. This may have favored the finding that the primary end-point...
(coronary disease) was not different in the three treatment groups. It may also have minimized the differences that were found on some secondary endpoints as well as the inconveniences that emerged in the diuretic-treated group such as new-onset diabetes and hypokalemia. For example the more common occurrence of new-onset diabetes in the diuretic-treated versus other groups (15% to 40%) could have been one third to one half greater, this being the case also for the four- to eightfold greater incidence of hypokalemia.

Thus morbidity and mortality trials of antihypertensive treatment have most likely produced results that minimize the protective effect of lowering elevated BP. They have also most likely favoured “pseudoequivalence” of both benefits and inconveniences between different treatments. One may wonder whether this played a role in the fact that of the 15 morbidity and mortality trials comparing different antihypertensive drug treatments, 13 have shown the incidence of cardiovascular events to be similar between groups, the difference being only marginally significant in one of the remaining two trials4–16 (Fig. 1).

### Applicability of Trial Results to Clinical Practice

Much has been said on the difficulty of applying results of morbidity and mortality trials on antihypertensive treatment to clinical practice.17,18 The argument is that these trials involve patients who are poorly representative of those seen routinely. For example, trials select their patients from a much larger number of screenees to come up with a population that fits entrance criteria and guarantees a reasonable long-term compliance with treatment and permanence in the study. An example is the Systolic Hypertension in the Elderly Program (SHEP) trial, which screened >350,000 individuals to randomize to treatment only about 5000.19 Furthermore trials are performed by physicians who combine greater than average expertise than average, without greater than average desire to motivate patients. This may explain why, for similar clinical characteristics, patients recruited for and followed in trials not infrequently have better outcomes than those coming from clinical practice, sometimes with a more optimistic perception also of treatment-related inconveniences and side effects. The latter has in some instance been favored also by the legitimate desire to limit the number of subjects dropping, thus preserving as much as possible the trial ability to show between-treatment differences. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial on the effect of angiotensin-converting enzyme inhibitors (with or without a diuretic) on stroke recurrence, patients were recruited only if in the run-in period a short-term administration of the study drug did not cause problems.20 This has been also the approach adopted in trials on cardiovascular protection by treatments other than the antihypertensive ones. As one observer noted in the Heart Protection Study (HPS), the very small number of side effects in the group treated with statin may have been favored by selection of patients without statin-related problems in the pre-randomization phase.21

Applicability of results of morbidity and mortality trials to routine management of hypertension meets, however, with additional and more significant difficulties. Morbidity and mortality trials provide evidence on the net benefit of a given treatment and cannot exclude the possibility that in, subgroups, results differ from the average or aggregate ones reported in trials. This is customarily taken care of by subanalyses of patients with specific demographic and clinical characteristics, which, however, often lack statistical power and at any rate cannot exclude effects at odd with the main effect in some individuals. Information provided by morbidity and mortality trials should thus be considered more as a scenario for decisions to be taken based on clinical and pathophysiologic criteria than as an obligation to treat indiscriminately all patients according to average findings, as is unfortunately often recommended.

This is reinforced by two major additional differences between the setting of morbidity and mortality trials on antihypertensive treatment and clinical practice. First, in trials patients have to move from progressively greater doses of a single drug to the addition of a predetermined second and more rarely a third drug, even when the initial treatment is associated with side effects (except the serious ones) or with no substantial BP lowering. This compulsory strategy is far away from the much more flexible attitude typical of most practicing physicians who hardly keep on board drugs that are ineffective or that cause problems to the patient. It can be argued that the latter is an unsuccesful strategy because moving from one drug to another in the attempt to find a simple drug that is both effective an well tolerated is time-consuming and not rarely inane against a multiregulated variable such as BP. There are

### FIG. 1. Trials comparing the effect on primary endpoint of treatments based on different antihypertensive drugs. Primary endpoint was either cardiovascular (*) or cardiac (°) morbidity and mortality. Data are shown as differences in hazard ratio (HR) and 95% confidence intervals (CI). αB = α blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II antagonist; BB = β-blocker; CCB = calcium antagonist; Conv = conventional treatment (based on diuretic or β-blocker or both); D = diuretic. Data from Refs.4–16

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment (“Control” vs “ Study”</th>
<th>HR (95% CI)</th>
<th>“ A” better “ B” better</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAPPY*</td>
<td>BB vs D</td>
<td>0.98 (0.80-1.20)</td>
<td>a = 0.6569</td>
</tr>
<tr>
<td>IPPHY*</td>
<td>BB vs D</td>
<td>0.99 (0.79-1.24)</td>
<td>a = 0.6357</td>
</tr>
<tr>
<td>CAPP*</td>
<td>ACEI vs Conv.</td>
<td>1.05 (0.90-1.22)</td>
<td>a = 10985</td>
</tr>
<tr>
<td>STOP*</td>
<td>ACEI vs Conv.</td>
<td>1.01 (0.84-1.22)</td>
<td>a = 4418</td>
</tr>
<tr>
<td>ANP2*</td>
<td>ACEI vs D</td>
<td>0.89 (0.75-1.00)</td>
<td>a = 6083</td>
</tr>
<tr>
<td>ALLATT*</td>
<td>ACEI vs D</td>
<td>0.99 (0.91-1.08)</td>
<td>a = 9554</td>
</tr>
<tr>
<td>STOP2*</td>
<td>CCB vs Conv.</td>
<td>0.97 (0.80-1.17)</td>
<td>a = 4209</td>
</tr>
<tr>
<td>NORDIL*</td>
<td>CCB vs Conv.</td>
<td>1.00 (0.87-1.16)</td>
<td>a = 10881</td>
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<tr>
<td>INSIGHT*</td>
<td>CCB vs D</td>
<td>1.01 (0.91-1.14)</td>
<td>a = 6321</td>
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<tr>
<td>ALLATT*</td>
<td>CCB vs D</td>
<td>0.98 (0.90-1.07)</td>
<td>a = 9048</td>
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<tr>
<td>INVEST*</td>
<td>CCB vs BB</td>
<td>0.98 (0.90-1.06)</td>
<td>a = 22599</td>
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<tr>
<td>ALLATT*</td>
<td>oB vs D</td>
<td>1.83 (9.00-1.71)</td>
<td>a = 24335</td>
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<tr>
<td>SCOPE*</td>
<td>ARB vs Others</td>
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<td>a = 4506</td>
</tr>
<tr>
<td>LIFE*</td>
<td>ARB vs BB</td>
<td>0.87 (0.77-0.98)</td>
<td>a = 9593</td>
</tr>
<tr>
<td>VALUE*</td>
<td>ARB vs CCB</td>
<td>1.03 (0.94-1.14)</td>
<td>a = 15245</td>
</tr>
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</table>
serious problems, however, also in the strategy based on the compulsory combination of several drugs used in clinical trials, which may have a higher rate of inconveniences (patients dropping out, metabolic alterations, etc) and may not be necessary in a number of patients. A trial comparing these two treatment approaches for their effects on BP, cardiovascular outcome, and patients’ persistency with treatment would be highly desirable. Second, in trials, forced uptitration of treatment leads to BP control (ie, to values <140/90 mm Hg) in many more patients (Fig. 2) than in clinical practice, in which control is rare and persisting on-treatment hypertensive values are the rule rather than the exception (Fig. 3), the number of high-risk patients reaching the lower target BP values advised under this circumstance being a truly minimal one. This means that the results pertain to a clinical situation that is not the real-life one, with potentially serious errors as far as which treatment type is appropriate to which patient. It may be, for example, that trial data that different antihypertensive drugs classes have a similar ability to protect the cardiovascular system only holds when the protective effect of the BP lowering per se is maximized by optimal or nearly optimal BP control. That is, aggressive BP reductions may mask the specific protective effect of drugs, which may be more evident when the BP-related protection is more limited, keeping in mind that (as mentioned above) this is unfortunately what most often happens in the medical practice.

**Short-Term and Selective Nature of Trial Evidence**

Another limitation of morbidity and mortality trials on antihypertensive treatment has a paramount importance. That is because of their high cost, complex worldwide organization, and difficulty of keeping patients on predetermined treatment regimens, these trials can only last few years, usually 3 to 5. This means that information on the protective effect of treatment is relatively short-term, and in middle-age patients it only accounts for a small fraction of life expectancy. It also means that, because of the need of having a sufficiently high number of events within a short time, only patients at an overall high cardiovascular risk can be involved, with the exclusion of those with a mild BP elevation unless accompanied by an advanced age, several additional cardiovascular risk factors, a history of cardiovascular disease or prognostically adverse organ damage. The consequence is that information provided by morbidity and mortality trials is limited to elderly or high-risk hypertensive patients with an obvious difference from the very large range of total cardiovascular risk (ie, the risk of an event in 10 years) presented by the general hypertensive population. More specifically the information provided by trials tells little about individuals in the young to the middle-age range with a less than severe BP increase and a low to moderate risk who, however, represent the larger fraction of the individuals with a BP.

**FIG. 2.** Average systolic blood pressure (SBP) and diastolic blood pressure (DBP) values before (B) and during treatment (T) in Trials on antihypertensive drugs performed from 1990.
These individuals are treated because of extrapolation from data obtained in elderly or high-risk groups, whose results are used also to make treatment lifelong, thus extrapolating evidence of short-term to long-term protection.

I am not against extrapolation of scientific data, which is necessary to integrate patchy research evidence in a harmonic context that makes the practice of medicine possible. It would be unwise, however, not to wonder whether and to what extent the above extrapolations are correct. Trial evidence, for example, indicates that in hypertension cardiovascular protection is primarily caused by BP lowering per se, regardless of how it is obtained. However it is by no means unreasonable to consider the possibility that this is the case mainly in elderly or high-risk patients with clinical or subclinical disease in whom the immediate protection offered by BP reduction may represent the only chance of protection left, and that in younger patients at lower risk the specific tissue protective properties of different drugs documented in pathophysiologic studies may also play an important role. This role may be more apparent in the long-term, ie, over a temporal dimension unexplored by morbidity and mortality trials. It may be also more apparent when protection against subclinical organ damage is taken into account. This is not considered by guidelines on antihypertensive treatment and cardiovascular prevention efforts that are excessively driven by morbidity and mortality data. These guidelines, however, overlook the fact that in young or middle-age patients who are not at high risk, treatment does not aim to prevent the remote chance of an event in the next few years but rather aims at stopping or delaying the progression of silent organ damage that could emerge as an event many more years later. In other words it aims to prevent the occurrence and progression of cardiovascular disease the mechanisms of which may not invariably be identical to those triggering a cardiovascular event. The mechanisms involved in the formation of a thrombus occluding a coronary or a cerebral artery and causing necrosis of the dependant anatomical area, for example, may not be the same as those causing progression in the same vessels of an atherosclerotic plaque or that, by favoring left ventricular hypertrophy, make the consequences of coronary occlusion more severe. It cannot at all be excluded that drugs differ for their effect on mechanisms of disease more than they do for their effects on mechanisms of events.

**Future Options**

Attempts have been made, and continue to be made, to modify the design of morbidity and mortality trials on antihypertensive treatment and thus cope with their limitations. For example, in some recent trials, recruitment criteria have allowed patients with a greater clinical heterogeneity to enter randomization to reflect more appropriately clinical practice. Furthermore treatment strategies have been made less rigid. Finally, efforts have increased to keep as many patients as possible under treatment, to follow drop-outs in addition to

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**FIG. 3.** Summary of hypertension treatment response in populations in different countries. Gray portion of circles indicates the percentage of hypertensive patients in whom treatment reduced systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg, ie, with blood pressure controlled. Data from studies performed in different countries (Ref. 23–31).
patients carefully, and to analyze and rely not only on intention-to-treat but also on on-treatment data.

However, this does not remove a major limitation of this approach, ie, short-term results largely limited to high-risk patients. Addressing the question of the long-term effect of antihypertensive treatment on cardiovascular morbidity and fatal events will probably require data to be collected in the context of suitably performed observational studies. Long-term cardiovascular protection in young or middle-aged hypertensive patients at low to moderate risk will also require a much greater emphasis on studies of prevention of subclinical organ damage. This is opposed by those who consider measures of organ damage as well as any endpoint other than morbid or fatal events as unreliable based on studies in which “surrogate” measures of the benefit obtained by antiarrhythmic, lipid-lowering, or inotropic agents (antiarrhythmic effect, improvement in lipid profile, or increase in exercise tolerance) were associated with an increased event rate. This overlooks, however, the fact that events do not occur on a healthy cardiovascular system but are preceded by organ damage that is the necessary intermediate step. It also makes a general rule out of a few unfortunate attempts that tell us only that the choice of the “surrogates” was inappropriate and that their use should be preceded by a thorough prognostic validation in untreated and treated individuals. This has been done for hypertension, which can count on a variety of measures of subclinical organ damage for which there is evidence that their occurrence is accompanied by a greater incidence of cardiovascular morbidity and mortality. (Table 1). Some of these measures cannot be proposed for large prospective trials because of their dependence on expensive technology or on the skill of a restricted number of investigators around the world. On the other hand, measures such as left ventricular thickness or mass, urinary protein excretion, and large-artery wall thickness, although making a trial more complex than that based on clinical events, are of large use and thus offer a more realistic possibility. This is even more the case because in some instances (eg, left ventricular hypertrophy and proteinuria), the changes in these measures induced by treatment have been shown to reflect,

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Intermediate (surrogate) end points with prognostic relevance</th>
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<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>Silent myocardial ischemia</td>
</tr>
<tr>
<td>Silent cerebral ischemia</td>
<td>Microalbuminuria/proteinuria</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>Large arteries intima/media thickness</td>
</tr>
<tr>
<td>Small arteries media-to-lumen ratio</td>
<td>Arterial stiffness</td>
</tr>
<tr>
<td>Large arteries intima/media thickness</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Insulin resistance</td>
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</tbody>
</table>

in the absence of BP differences, changes in patients’ cardiovascular outcomes. It seems to me that resorting to studies on long-term modification of subclinical organ damage (as well as on long-term modification of total cardiovascular risk by treatment) should not be regarded as an option but rather as a necessary complement to morbidity and mortality trials if we want to do the following: 1) expand our knowledge of how to protect hypertensive patients outside the niche of elderly or high-risk individuals to which these trials have restricted us; 2) focus on the fact that cardiovascular prevention also means protecting patients with low to moderate cardiovascular risk from reaching high-risk conditions; and 3) overcome that paradox that in hypertension we know much about cardiovascular preventive strategies—mainly in patients in whom there is not much left to prevent.

References


