Knowledge on the benefit of antihypertensive treatment owes a great deal to antihypertensive drug trials based on incidence of morbidity and mortality [1]. These trials have demonstrated that antihypertensive drugs reduce cardiovascular morbid and fatal events of hypertensive individuals, counteracting their increased cardiovascular risk. They also demonstrated that this reduction occurs in males and females of different ages, ethnicities and clinical conditions and that thus the protection is virtually universal across the demographic and pathophysiological spectrum that characterizes an elevated blood pressure. They have finally demonstrated that drugs capable of lowering blood pressure protect hypertensive patients via sizes and designs that exclude even the remote possibility of ‘chance’ results as well as of errors due to selection bias, investigators’ and patients’ expectations, and inappropriate or unbalanced identification of events.

The above has generated the widespread opinion that information provided by morbidity/mortality trials is the most important one in a hypothetical scale of scientific soundness [2], and the only one on which Guidelines on antihypertensive treatment should be based on. This, however, overlooks the fact that morbidity/mortality trials on antihypertensive treatment are not devoid of limitations and that failure to appreciate them can endanger proper interpretation of available data and make it more difficult to devise studies that allow further progress to be made [3].

First limitation of clinical trials — selection bias

One of the limitations of morbidity/mortality trials derives from the need to ensure, through a stringent selection process, that the population under study is relatively homogeneous and compliant to treatment, in order to minimize confounders that can make interpretation of the data more difficult. This, however, makes the study population different from that seen...
in clinical practice in which the disease addressed by the trial much more frequently coexists with demographic conditions and morbidities that make the population much more heterogeneous. Furthermore, in trials, physicians’ expertise and patients’ motivation and compliance are in general better than those encountered in clinical practice, in which therapeutic mistakes and inadequacies are more common, with an overall outcome that can be worse than that of patients followed in trials even when no active treatment is given [4].

Morbidity/mortality trials, however, have three additional limitations, which may be even more important than the previous one. One limitation is that the trial results show the prevailing effect of the treatment under study without guaranteeing the evidence that it does, on average, more good than harm throughout the recruited population. This is customarily addressed by subgroup analysis of the data (for which the statistical power is often insufficient), but no analysis can exclude the fact that those interventions shown to be beneficial in the overall study population, be they a specific antihypertensive treatment regimen or a target blood pressure value, are harmful to some individuals. Advocates of an indiscriminate and mandatory application of trial results to clinical practice should give this limitation greater consideration.

Second limitation of clinical trials — ‘intention to treat’ analysis

A second limitation is that trials include patients who (1) drop out from prescribed treatment because of side effects, withdrawal of the initial consensus and/or decision of the investigator, (2) take the comparison drug(s) in addition to or instead of the prescribed one(s) and (3) are lost, for a variety of reasons, to follow-up information. In well-performed hypertension trials, this last phenomenon can be kept at a minimum, whereas the former two may involve up to 30–40% and 20–25% of the recruited population, respectively [5,6]. This means a large reduction in the number of patients under truly different treatment regimens with a substantial loss of statistical power and a serious bias (given that the analysis has to be done on an ‘intention to treat’ basis to ensure full similarity of the comparison groups at start of treatment) in favour of ‘pseudo-equivalence’, i.e. of lack of differences between treatment regimens. It is not unrealistic to speculate that this might have played a role in the almost invariable absence of differences in morbidity and mortality between different antihypertensive treatments reported in trials. Indeed, in 15 trials comparing different antihypertensive drugs, a between-group difference in cardiovascular morbidity and mortality was seen in only two trials [2].

Third limitation of clinical trials — time and age scale

A third and important limitation concerns the trial time scale. Because of their cost and organizational complexity, trials can only last a few years (usually 3 to 5 years), during which time the number of events has to be high enough to give them the required statistical power. This means that only individuals at high cardiovascular risk are suitable candidates for recruitment, information being thus largely limited to those in whom severe hypertension, multiple cardiovascular risk factors, diabetes, a history of cardiovascular or renal diseases or an advanced age are present. It also means that the benefit of antihypertensive treatment in lower risk young or middle age individuals is only inferential. It finally means that evidence is limited to only a small fraction of the life expectancy (20–30 years) of many patients. This poses several questions to which morbidity/mortality trials have not provided an answer. First question: is the benefit of antihypertensive treatment seen in elderly/high-risk individuals shared by young/low-risk patients to an extent that makes the cost/benefit ratio worthwhile? Second question: is the benefit seen over the few years of trial duration maintained over the following years? Third question: the conclusion has been reached by trials that the cardiovascular protection provided by antihypertensive treatment depends substantially on blood pressure reduction ‘per se’ (regardless of how it is obtained). Does this conclusion hold true only for elderly and/or high-risk individuals in whom the cardiovascular system is already damaged and the blood pressure reduction possibly the only defence left, but not in young patients with incipient damage? And finally, does trial evidence on reduction of cardiovascular morbidity and mortality in high-risk/elderly patients miss a fundamental aspect of prevention, i.e. to prevent in young or middle-age subjects at lower risk the progression towards a high-risk condition? This last question is of crucial importance because once the cumulative effect of risk factors favours the progression to a high-risk state, no treatment can obtain full reversal, the cardiovascular risk remaining relatively high even when all interventions of proven benefit are implemented [7].

Design of future clinical trials

The problem of how to effectively obtain evidence addressing the above issue is of crucial relevance to plan future research and achieve progress in the cardiovascular prevention area. Obviously, morbidity/mortality trials are not suited for this purpose, because this would require an excessive number of young/middle-aged or otherwise low-risk subjects and a study duration which no one can afford. A further consideration is that the mechanisms responsible for the
progression of subclinical disease are not identical to or superimposable upon those triggering clinical events. What is the best option? In our opinion, trials should focus on the question whether a given treatment improves total cardiovascular risk and prevents delays or regresses subclinical organ damage. Clinical events ultimately depend on the presence of such subclinical target organ damage, because no event occurs unless it is preceded by subclinical structural and/or functional target organ alterations. This is the goal of treatment in young and middle-aged hypertensive individuals at lower risk. The rationale to reduce blood pressure is not to prevent an unlikely event in the subsequent 3 or 4 years, but to prevent the progression of organ damage which will present as an event many years later.

If one presents evidence of protection based on effects of treatment of risk factors and/or organ damage alone, this is persistently countered by the argument that these endpoints are ‘soft’ or ‘surrogate’, as compared to the ‘hard’ ones provided by morbidity/mortality trials. The opposition also makes use of previous studies in which improvement of the ‘surrogate’ goal was not paralleled by a significant effect on clinical morbid or fatal events which may have even gone in an opposite direction. Past negative experience, however, does not detract from the soundness of the concept that these intermediate endpoints are clinically valid and can provide evidence on a fundamental aspect of prevention which morbidity/mortality trials cannot address. The above-mentioned discrepancies between soft and hard endpoints only underline the fact that the choice of ‘surrogates’ must be a careful one. Only surrogates fitting a number of criteria should be selected and used.

The requirements should be that they are non-invasive and quantifiable in a reproducible fashion without an excessive degree of expertise and time required, so that the results can eventually be transferred to clinical practice. Furthermore, the measures employed should have been clinically validated — which means that the organ dysfunction they show should be associated with and be responsible for a worse outcome — and the outcome should have been shown to improve when the dysfunction is corrected by treatment. Several measures of organ damage have been shown to be of prognostic significance (Table 1), although in a number of instances lack of a standardized approach as well as the sophisticated nature of the technologies and cost involved makes it difficult to adopt them on a large scale, and renders the planning of such trials problematic. Nevertheless, evidence has recently been obtained of an independent association between the improvement of organ damage by treatment and concomitant reduction in the incidence of cardiovascular events. This has been the case for treatment-induced reduction of urinary protein excretion [8,9] and of left ventricular hypertrophy [10–12]. Thus use of these well-validated measures is today acceptable as a marker of cardiovascular protection.

**Conflict of interest statement.** None declared.

**References**


7. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 1979; 242: 2562–2571


**Table 1. Measures of end organ damage with impact on cardiovascular prognosis**

- Concentric/eccentric left ventricular hypertrophy
- Systolic left ventricular dysfunction
- Mild renal damage
- Microalbuminuria/Proteinuria
- Carotid (and femoral) artery wall thickening
- Arterial stiffening
- Coronary calcium content
- Endothelial dysfunction (coronary/peripheral)
- Arteriolar remodelling

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**References**


7. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the hypertension detection and follow-up program I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 1979; 242: 2562–2571


