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How can the benefits of antihypertensive treatment be evaluated?

A. Zanchetti

The article by Prof. Wink [1] is one with which I both disagree and agree.

Disagreement: inconsistencies of the trial results

In his article Prof. Wink insists that randomized trials of antihypertensive therapy have given inconsistent results as far as outcome reduction is concerned. This is a rather unfair interpretation of the results. Although there are reasonable differences from trial to trial, mostly because of the low power of several of them (as correctly remarked by Prof. Wink), it appears ungenerous to neglect the fact that in all trials of active treatment versus placebo or less active treatment there was a regular trend toward less events in the active treatment group, and that practically all trials are consistent in showing a significant reduction in strokes. It is not understood why strokes (prevention of which has always been considered the most important goal of antihypertensive therapy) are never mentioned in Prof. Wink's article. Insisting on prevention of mortality ignores an important point raised by Collins and Peto [2], namely, that because of the relatively short duration of trials of antihypertensive therapy, analyses of mortality are potentially unreliable and "less informative than indirect assessment of that effect, based on analyses of the proportional effects of treatment on total stroke and on total coronary events". This argument should appeal to Prof. Wink, who makes a good point of the short duration of trials (see below).

In his analysis of trials, Prof. Wink never mentions the meta-analysis approach, that has repeatedly been used in evaluating the overall outcomes of antihypertensive treatment trials [2, 3], with impressive results showing highly significant reduction in stroke (38 %) and in coronary events (16 %), and significant reductions in cardiovascular and all-cause mortalities as well. Admittedly, meta-analyses have limitations and I have underlined these limitations myself [4], but placebo-controlled randomized trials of antihypertensive therapy have more similarities than dissimilarities and make meta-analyses safe. Nonetheless, future meta-analyses should be prospectively planned rather than retrospectively performed, and a project of prospective overview is ongoing [5, 6].

In conclusion, there is no doubt, in my opinion, that randomized trials of antihypertensive treatment have been an invaluable instrument of establishing, as they have indeed established, that antihypertensive therapy is indeed beneficial, particularly in reducing strokes and congestive heart failure and, to a lesser but significant extent, coronary events.

Agreement: limitations of trials in assessing treatment benefits

Prof. Wink [1] is perfectly right when he points out that randomized trials of antihypertensive therapy provide an un-

derestimation of treatment benefits, although he may have recognized that this concept had already been formulated and stressed several times in the past [7–9] and is embedded in both international [10, 11] and American [12] guidelines for the management of hypertension.

I have previously commented [9] that the average treatment benefit calculated from meta-analyses of available trials [2, 3] is that produced by a modest blood pressure decrease (5–6 mmHg in diastolic blood pressure), and it is arbitrary and incorrect to take it as the benefit of antihypertensive treatment "tout court". It is, on the contrary, quite likely that this is an underestimation of the possible benefit achievable if the treatment goal is that indicated by the World Health Organization/International Society of Hypertension guidelines, namely the maximum tolerated blood pressure reduction [10, 11]. The results of the HOT study have recently been published [13], and have shown diastolic blood pressure can be reduced by 20–25 mmHg, with a maximum benefit at an achieved diastolic blood pressure of 80–85 mmHg.

Prof. Wink is also right in underlining the low level of risk of many hypertensive patients included in many randomized treatment trials, the underestimation of benefit caused by placebo patients switched to active treatment and by patients lost to follow-up, problems also considered in guidelines [10–12] and extensively discussed by Linjer and Hansson [14].

Finally, it is from 1992 that I am stressing the concept that trials, being by necessity of a relatively short duration (3–5 years), can only assess short-term benefits, and therefore are an excellent measure of benefit of antihypertensive treatment in the elderly, such as in subjects older than 70 years whose life expectancy is not much longer than the average duration of an intervention trial. In younger patients with mild to moderate hypertension, the goals of treatment are long-term ones and benefits cannot correctly be assessed by relatively short-term studies [7–9]. Assessing the long-term benefits of antihypertensive treatment is a difficult endeavor, and we have previously suggested different solutions [8, 15]. One is using observational data of secular trends in hypertension control, such as those reported by the Framingham Heart Study for the period 1950–1990 [16], also mentioned by Prof. Wink; the other is using actuarial data, such as those provided by the Statistical Bureau of the Metropolitan Life Insurance Company, based on experience accumulated during the period 1935–1954 when no antihypertensive therapy was available [17]. Both approaches suggest a long-term treatment benefit at least twice as large as the one indicated by short-term randomized trials.

Conclusions

Readers may be interested in knowing how values and limitations of randomized trials of antihypertensive therapy are presented in the recently prepared 1999 World Health Organiza-

tion/International Society of Hypertension guidelines on hypertension management [11].

1. Effects of blood pressure lowering treatments on mortality and morbidity from cardiovascular disease

Previous randomized controlled trials involving a total of about 47,000 patients with hypertension have collectively demonstrated that, over an average of about 5 years, such treatment produced much of the epidemiologically expected benefit of the achieved blood pressure reductions. A net reduction of 5–6 mmHg in usual diastolic blood pressure was associated with a 38 % (SD 4) reduction in stroke risk and a 16 % (SD 4) reduction in coronary heart disease risk, with similar effects on fatal and non-fatal events. The proportional reductions in the risks of stroke and coronary heart disease in these trials appeared to be broadly similar in patients with mild, moderate or more severe hypertension, in older or younger patients, and in patients with or without a history of cerebrovascular disease.

2. Underestimation of the effects of blood pressure lowering treatment in randomized controlled trials

- Estimates of treatment effects in the trials of blood pressure lowering regimens generally provide conservative estimates of the full potential effects of treatment
- In the trials, there was considerable “cross-over” between treatment groups:
 - a proportion of patients assigned to active therapy groups stopped treatment; and
 - a proportion of those assigned to control groups began active treatment.
- Such cross-over is likely to have reduced the average difference in diastolic blood pressure between groups by 1–2 mmHg, in which case, the full relative effects of treatment on stroke and coronary heart disease would be somewhat greater than the effects observed.
- The average duration of treatment in the trials was only about 5 years, and it is possible that longer-term treatment over many years, as is usual for hypertensive patients, might have led to larger relative risk reductions.
- Low-risk patients were recruited to many trials, and the absolute effects of treatment among higher risk patients seen in broader clinical practice are, therefore, likely to be greater than those typically observed.

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