New developments in the treatment of hypertension: are some antihypertensives more equal than others?

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ABSTRACT

In 2002, a major topic of discussion in the field of clinical hypertension was the efficacy of the various types of antihypertensive agents. The results of three large endpoint studies have recently been published and it was hoped that these would provide some answers. What could be concluded from their findings is that angiotensin II receptor (A II) antagonists can now also be allowed as initial treatment for uncomplicated essential hypertension. Thiazide diuretics remain the treatment of choice in patients with uncomplicated essential hypertension because of low costs. Recent trials suggest however, that agents that interfere in the renin-angiotensin system, such as ACE inhibitors and A II antagonists, may be superior in preventing end-organ damage. We therefore propose that subgroups of patients should be defined, in which specific agents should be preferentially used because of proven efficacy.

INTRODUCTION

In 2002, the main development in the field of clinical hypertension was the issue whether some blood pressure lowering agents are superior to others in the initial treatment of hypertension for the prevention of end-organ damage. The history underlying this question started with the well-known meta-analyses by Collins and MacMahon. These authors showed that there is a log-linear association between untreated blood pressure and the incidence of end-organ damage.[1] That this association implies a cause-effect relationship was suggested by their subsequent finding that when blood pressure is reduced with antihypertensive treatment, the incidence of cerebrovascular disease is diminished in comparison with placebo, with exactly the same proportion as might be expected from the induced change in blood pressure.[2] In remarkable contrast to the evidence for stroke, the reduction in coronary heart disease seen with active treatment versus placebo fell significantly short of the difference expected from the observational epidemiological evidence (14 instead of 24% risk reduction). Many hypotheses have been put forward to explain this discrepancy. One of the most cited has been that these early placebo-controlled trials were performed with diuretics and β-blockers. These drug classes are known to induce adverse metabolic effects, such as a rise in serum glucose and blood lipids. These negative metabolic events were supposed to offset the beneficial effects of blood pressure lowering on the incidence of especially cardiovascular events.

A number of trials have since been published that compared the effects on cardiovascular morbidity and mortality of conventional (i.e. diuretics and β-blockers) versus newer antihypertensives (i.e. calcium channel antagonists and ACE inhibitors). The latter groups of agents are known to have a more favourable metabolic profile. In general, these trials found no relevant differences in prevention of hypertension-related endpoints. Because of these findings national and international guidelines state that agents from all four drug classes may be chosen as initial treatment of uncomplicated essential hypertension. On the basis of costs, however, the preference is given to diuretics and β-blockers.[3]

STAESSEN'S META-REGRESSION ANALYSIS

Since the publication of these guidelines at least two studies have been published that question whether all antihypertensives are equally efficacious.[4,5] This led Staessen *et al.* to perform a meta-analysis in 2001, in which they systematically analysed all available randomised controlled hypertension trials.[6] Compared with conventional drugs, calcium channel antagonists and ACE inhibitors offered similar overall cardiovascular protection, but calcium channel blockers provided more reduction in the risk of stroke (13.5%, p=0.03), whereas the risk of myocardial infarction was increased (19.2%, p=0.01). Significant heterogeneity was observed among the included studies, especially with regard to differences in achieved blood pressure. This may have influenced the results obtained. Therefore, the authors decided to investigate further the relation between odds ratios expressing benefit and achieved blood pressure difference. This meta-regression analysis across 27 trials (136,124 patients) showed that odds ratios could be fully explained by achieved differences in systolic pressure (*figure 1*). The authors, therefore, emphasise the importance of adequate blood pressure control, and they conclude that, on average, all antihypertensive drugs have similar long-term efficacy.

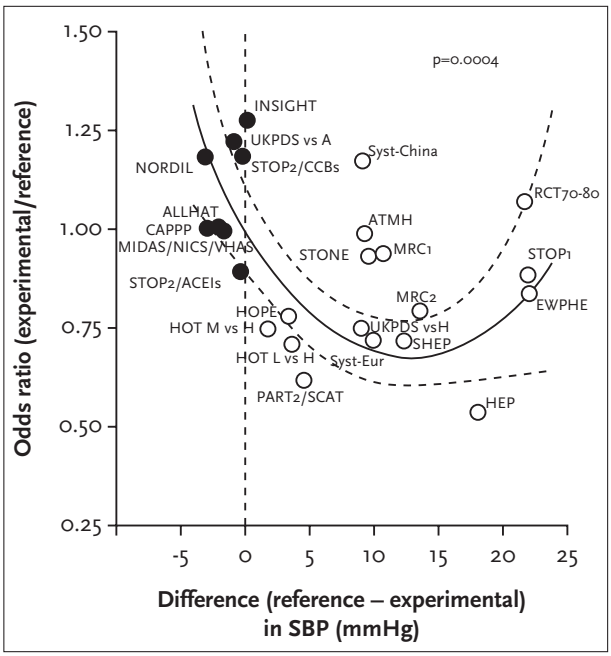

Figure 1

Relation between odds ratios for fatal and nonfatal stroke and corresponding differences in systolic blood pressure[6]

Regression lines were plotted with 95% CI and were weighted for the inverse of the variance of individual odds ratios. SBP = systolic blood pressure.

Interpretation

This meta-analysis pools data from trials that included rather different populations (e.g. diabetics versus non-diabetics, isolated systolic hypertensives versus diastolic hypertensives) and different interventions (e.g. primary versus secondary prevention, placebo versus active control treatment). It is questionable whether such heterogeneous studies can be pooled into one meta-analysis. Schunkert *et al.* point out that, by using the same dataset but plotting it in a different way, results diametrical to the conclusion of Staessen *et al.* can be reached.[7] These authors therefore argue that meta-regression analysis, although tempting, is not justifiable according to the principles of biomedical statistics. It is furthermore remarkable that the obtained 95% confidence interval (CI) of the aggregate dataset is wider than that of many of the individual trials whereas by increasing power by pooling a great number of datasets, a narrower 95% CI was to be expected. Even so, a large proportion of the included trials lie outside the 95% CI, thus questioning the statistical methods used (*figure 1*). We conclude therefore that, although a valuable effort, this meta-regression analysis cannot provide the definite answer to the question whether some antihypertensives may be superior to others in preventing end-organ damage. This answer can perhaps be obtained from three large endpoint studies that were recently published, the ALLHAT, LIFE and ANBP-2 studies.

THE ALLHAT STUDY

The trial that was supposed to end all discussion on the aforementioned question is the Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack (ALLHAT) study.[8] This study was designed to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowers the incidence of coronary heart disease events versus treatment with a diuretic. It is the largest prospective randomised controlled trial thus far in medicine. A total number of 33,357 subjects, aged 55 years or older with essential hypertension and at least one other coronary heart disease risk factor, were randomly assigned to receive chlorthalidone, amlodipine or lisinopril. Mean follow-up was 4.9 years. Systolic blood pressures were significantly higher in the amlodipine and lisinopril groups compared with the chlorthalidone-treated group (*figure 2*). As expected the thiazide diuretic induced unfavourable metabolic effects, such as an increase in serum glucose and cholesterol, and a decrease in serum potassium. No difference, however, was observed between the three treatments in the incidence of the primary outcome parameter of fatal or nonfatal myocardial infarction (*figure 3*). For amlodipine versus chlorthalidone, all four secondary outcomes were similar (all-cause mortality, combined coronary heart disease,

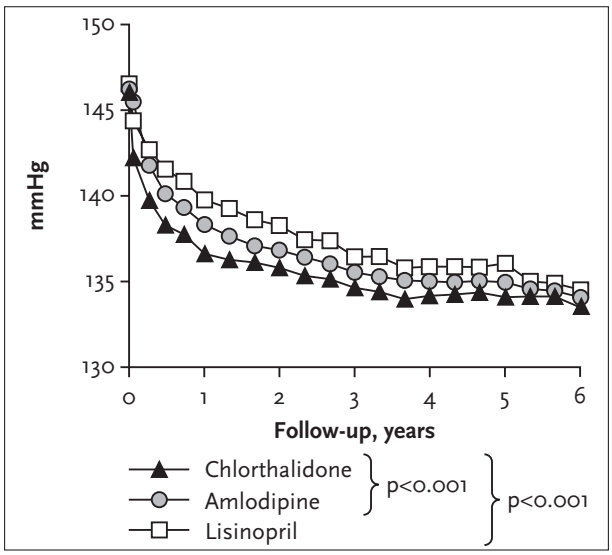

Figure 2
Mean systolic blood pressure during follow-up in ALLHAT in chlortalidone (n=15,255), amlodipine (n=9048) and lisinopril (n=9054) treated patients[8]

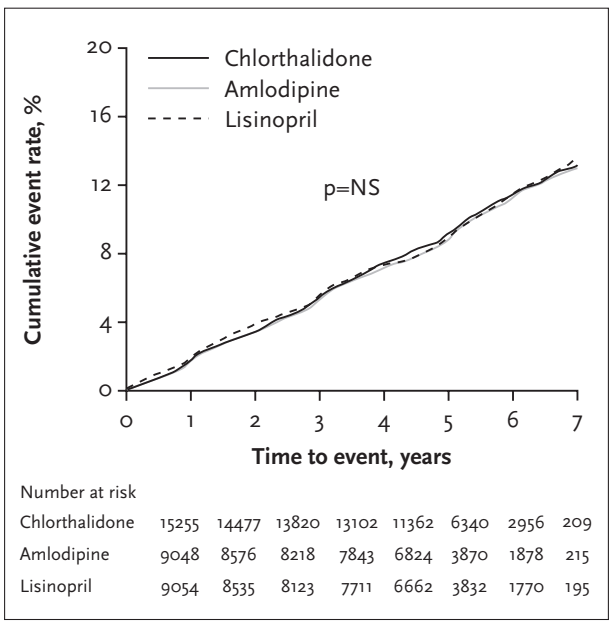

Figure 3
Cumulative event rates in ALLHAT for the primary composite outcome (fatal coronary heart disease or nonfatal myocardial infarction)[8]

stroke and combined cardiovascular disease). Only one out of a number of tertiary outcome parameters was observed more frequently with amlodipine, namely heart failure (*figure 4*). For lisinopril versus chlorthalidone, from the four secondary outcome parameters both stroke and cardiovascular disease (especially the component heart failure) occurred more often with lisinopril (*figure 4*).

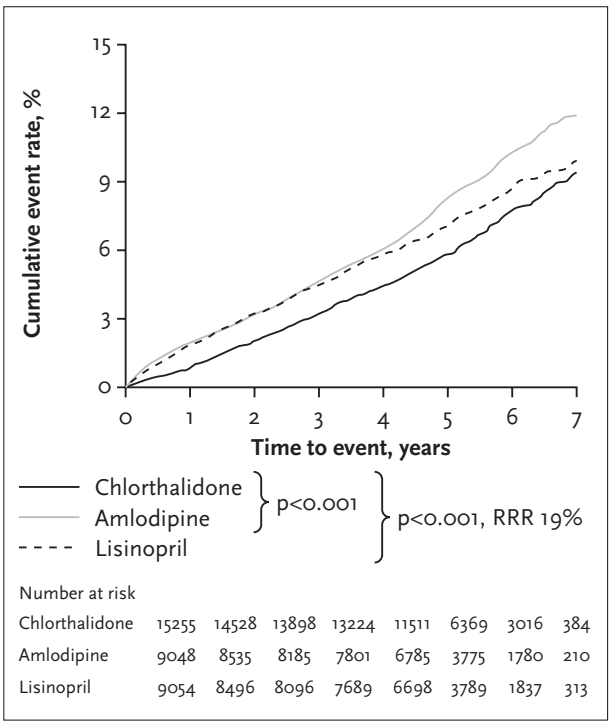

Figure 4
Cumulative event rates in ALLHAT for heart failure in patients treated with chlorthalidone (n=15,255), amlodipine (n=9,048) and lisinopril (n=9,054)[8]

Interpretation

The ALLHAT study is unique in that it is the largest prospective randomised controlled trial ever performed, and that it has been government coordinated and not industry driven. Its design was rather ambitious; a so-called 2 by 4 factorial design. Participants were randomised either to receive placebo or an HMG-CoA reductase inhibitor, and to one of four different antihypertensive treatment groups. The results with regard to lipid control are discussed elsewhere in this supplement. With regard to the present publication on the effects of blood pressure control it appears that the internal validity of the hypertension arm of the ALLHAT study is limited by the fact that blood pressure control was not similar in the three treatment groups (*figure 2*). It is now difficult, if not impossible, to decide whether one or more of the investigated drugs has a blood pressure independent effect, which after all was the primary objective of the ALLHAT study. The difference in incidence of stroke for instance between the chlorthalidone- and lisinopril-treated patients can at least partly be explained by the difference in blood pressure control. The external validity of this trial is limited for several reasons. First, unlike the West-European situation, less then half of the patients were of Caucasian descent. It is generally agreed that in Afro-Americans ACE inhibitors are of limited value, especially in cases when a diuretic is not used concomitantly.[9] In the ALLHAT study prescription

of a diuretic in the ACE inhibitor group was precluded per protocol. This flaw in study design is expected to influence the results that will be obtained if many blacks are included. Subgroup analysis of the ALLHAT confirms this assumption. The beneficial effects of chlorthalidone were purely limited to black patients, whereas in non-blacks no differences were found. Second, mean baseline blood pressure in the population under study was 146/84 mmHg. This is lower than in any of the previously published antihypertensive treatment trials. According to present guidelines many of these patients should not have been treated with blood pressure lowering agents. Furthermore, during the study blood pressure was far lower than in any other hypertension trial, even significantly lower than in the intensive treatment arm of the HOT (Hypertension Optimal Treatment) study. Third, chlorthalidone was chosen as the representative of thiazide diuretics. This agent, however, is not commonly used. Whether results obtained with chlorthalidone can be extrapolated to hydrochlorothiazide, the thiazide diuretic that is used by most clinicians, is questionable. Hydrochlorothiazide has a markedly shorter half-life. Fourth, in case of insufficient blood pressure control open-label agents could be added. By protocol the choice was restricted to clonidine, reserpine, atenolol or hydralazine. Three of these agents are now obsolete. In clinical practice physicians tend to co-prescribe hydrochlorothiazide if an ACE inhibitor provides insufficient blood pressure control. These two drug classes are known to potentiate each other's antihypertensive efficacy. The fact that the combination of an ACE inhibitor and a diuretic was excluded by protocol flaws the results obtained, especially in blacks, as discussed above. Fifth, surprisingly heart failure was more common with the ACE inhibitor than the diuretic. The explanation probably lies in the fact that during the prerandomisation phase many of the patients were on diuretics. When patients were randomised to the ACE inhibitor or the calcium channel antagonist group, their diuretics were withdrawn. Heart failure, already present in some patients before start of the study but compensated for by the use of diuretics, becomes clinically apparent at the moment the diuretic is withdrawn. *Figure 4* shows that the difference between the diuretic and the two other antihypertensives was already near maximal in the first months of the study. This observation clearly pleads for the aforementioned explanation. Of note, at the end of follow-up the line of the ACE inhibitor tends to cross the line of the diuretic (*figure 4*). This probably indicates the specific cardioprotective effect of the ACE inhibitor.

THE LIFE STUDY

In ALLHAT two drug classes were not investigated, β-blockers and angiotensin II receptor (A II) antagonists. This limitation was overcome in the 'Losartan Intervention For Endpoint reduction in hypertension' (LIFE) study.[10] In this study 9193 patients aged 55 to 80 years with essential hypertension and left ventricular hypertrophy (LVH) ascertained by ECG were randomly assigned to the A II antagonist losartan or the β-blocker atenolol. If blood pressure control was inadequate, first hydrochlorothiazide and then other antihypertensives could be added (the choice for which specific agent being left to the discretion of the treating physician). Mean follow-up was 4.7 years. Of the participants, 92% were of Caucasian descent. Mean baseline blood pressure was 174/98 mmHg and similar in the losartan versus atenolol group. Blood pressure control during follow-up was also similar in the two treatment groups. The relative risk for the incidence of the primary composite endpoint, namely death or nonfatal stroke or myocardial infarction, was with 0.87 statistically significant in favour of the A II antagonist. This difference in the incidence of the primary composite endpoint could be fully explained by the lower incidence of stroke with the A II antagonist, since the incidence of myocardial infarction was similar to slightly higher. In this trial 57 patients had to be treated to prevent one event. Patients on losartan had fewer adverse effects and discontinued study medication significantly less. Diabetes mellitus developed in statistically significantly fewer patients on the A II antagonist than on the β-blocker. The results in the subgroup of patients with diabetes mellitus at baseline were shown in a separate publication.[11]
In these high-risk patients the results obtained were more outspoken, both with regard to relative as well as to absolute risk reduction. Only 17 patients had to be treated to prevent one death or nonfatal stroke or myocardial infarction.

Interpretation

The LIFE study is the first hypertension trial to show that one antihypertensive is superior to another with regard to the prevention of the combined primary outcome parameter of cardiovascular mortality, stroke and myocardial infarction. In this respect it can be called a landmark study. The internal validity of this study appears quite solid. No differences, for instance, were observed between the two treatment groups in baseline characteristics or in blood pressure control. External validity is limited by the fact that only subjects with LVH were included. In only a quarter of patients with hypertension is LVH present. Furthermore, in daily practice it is quite uncommon to assess whether a patient has LVH before antihypertensive treatment is started. Interestingly, subgroup analysis suggests that the beneficial effect of the A II antagonist is not dependent on left ventricular mass. Such subgroup analyses should, however, be interpreted with caution.

THE ANBP-2 STUDY

In the second 'Australian National Blood Pressure' (ANBP-2) study 6083 elderly subjects with essential hypertension, who were 65 to 84 years of age, were randomised to receive either an ACE inhibitor (predominantly enalapril) or a diuretic (predominantly hydrochorothiazide).[12] Subjects were followed for 4.1 years in this prospective, randomised, open-label study with blinded endpoints. At baseline, the treatment groups were well matched in terms of age, sex and blood pressure (167/91 versus 168/91 mmHg, respectively). By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mmHg). The hazard ratio for the primary composite endpoint (death or cardiovascular event) was significantly in favour of the ACE inhibitor (0.89 with 95% CI 0.71 to 0.97; p=0.02). Among male subjects the hazard ratio was 0.83, whereas among female subjects the hazard ratio was 1.00. The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE inhibitor treatment, albeit not statistically significantly. A similar number of strokes occurred in each group, although there were more fatal strokes in the ACE inhibitor group.

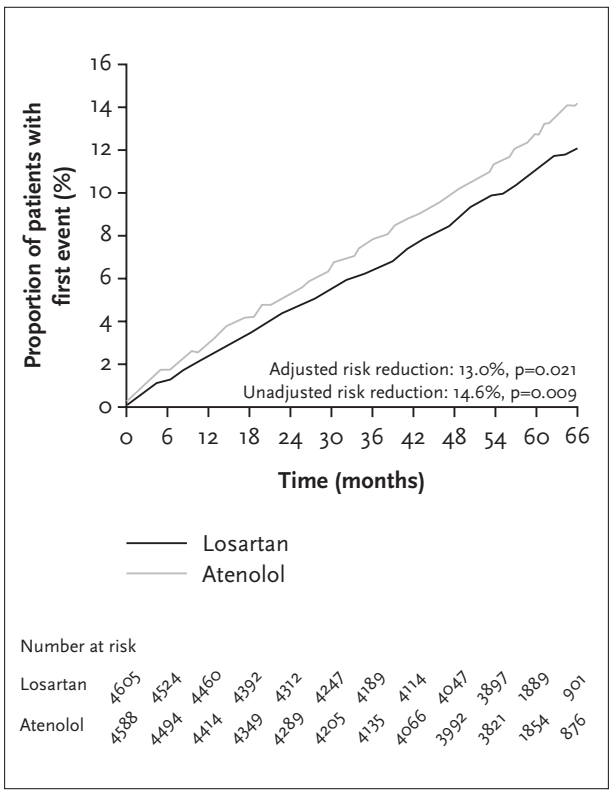

Figure 5
Cumulative event rates in LIFE for the primary outcome (cardiovascular mortality, stroke and myocardial infarction) in patients treated with atenolol (n=4,588) and lisinopril (n=4,605)[10]

Interpretation

The ANBP-2 study is, after the LIFE study, the second outcome trial that shows that one antihypertensive is superior to another, with regard to the prevention of the combined primary outcome parameter. Interestingly, in both studies agents interfere with the renin-angiotensin system, which proves to be advantageous. Concerning the internal validity of this study there are no major problems. External validity is limited by the fact that only elderly subjects aged 65 to 84 years were included. In daily practice, however, the vast majority of the patients with essential hypertension belong to this age category. Although the primary and most of the composite endpoints were in favour of the ACE inhibitor, fatal stroke occurred significantly more often in patients using this drug. This finding was also observed with ACE inhibitors in the CAPPP (Captopril Prevention Project)[5] and the ALLHAT[8] study. In these two trials this may have been caused by the blood pressure difference between the two treatment groups, in both to the detriment of the ACE inhibitor. No such difference in blood pressure control was, however, present in the ANBP-2 study. This brings forward the question whether ACE inhibitors may be disadvantageous with respect to cerebroprotection. This is in contrast to the findings with the other class of agents that interfere with the renin-angiotensin system. With A II antagonists it has been found that there is a significant reduction in cerebrovascular endpoints.[11,13] A possible difference between ACE inhibitors and A II antagonists in cerebropotection is an interesting issue that needs further study. We want to emphasise that the main message of the ANBP-2 study is that use of ACE inhibitors in older subjects leads to better overall outcome than treatment with diuretic agents, despite similar reductions in blood pressure.

DO ALLHAT, LIFE AND ANBP-2 CONTRADICT EACH OTHER?

The above-mentioned limitations of the ALLHAT study seriously hamper the relevance of the results obtained. Its over-ambitious design and lack of surveillance with regard to the blood pressure control during the trial resulted in findings that are difficult to interpret and extrapolate. In our opinion the results obtained do not support the conclusion of the authors that 'thiazide diuretics are superior in preventing cardiovascular disease'. What can be concluded from this study in our view is that calcium channel blockers (dihydropyridine) appear safe, despite the recent turmoil on this point. Furthermore, thiazide diuretics are efficacious in lowering blood pressure and preventing cerebrovascular and cardiovascular endpoints. The statistically significant and clinically relevant difference in blood pressure control to the disadvantage

of the ACE inhibitor, together with the large percentage of Afro-Americans, preclude firm conclusions with regard to this latter class of drugs for the Dutch situation.
The LIFE study suggests that in hypertensive patients with LVH, an A II antagonist is superior to a β-blocker in preventing hypertension-related end-organ damage. One could reason that since the findings of the LIFE study are so surprising, one should await a second study. During the meeting of the International Society of Hypertension in 2002 the results of the 'Study on Cognition and Prognosis in the Elderly' (SCOPE) were presented.[12] In this study the A II antagonist candesartan was compared with open treatment in elderly patients with predominantly isolated systolic hypertension. Although the results obtained were not statistically significant because of lack of power, the relative risk reduction in the incidence of the primary composite endpoint, stroke and new-onset diabetes was remarkably similar to the figures obtained in the LIFE study. These studies, different in patient selection (essential hypertension and LVH versus elderly patients with predominantly isolated systolic hypertension) and design (A II antagonist compared with β-blocker versus A II antagonist compared with open treatment), thus show similar results. The ANBP-2 study emphasises once again the role that angiotensin II may have in the pathophysiology of cardiovascular disease.

CONCLUSIONS

With the above data in mind, we conclude that after the recent publications the present guidelines for the initial treatment of hypertension do not have to be changed drastically. The differences that we propose are that after the publication of the LIFE study, A II antagonists can now also be allowed as initial treatment for uncomplicated essential hypertension. Thiazide diuretics were and will remain the treatment of choice in patients with uncomplicated essential hypertension because of low costs. The recent LIFE, ANBP-2 and SCOPE studies suggest, however, that agents that interfere in the renin-angiotensin system, such as ACE inhibitors and A II antagonists, may be superior in preventing end-organ damage. However, as long as these agents are under patent, and thus more expensive, their initial use instead of diuretics in the population at large does not seem cost-effective. The crux of the story lies in our opinion in the definition of subgroups in which specific agents should be preferentially used because of proven efficacy. For instance, in diabetic nephropathy ACE inhibitors or A II antagonists are the treatment of choice, whereas in angina β-blockers should be preferred. We should consider adding left ventricular hypertrophy to this list. In such patients A II antagonists can be started as primary treatment, especially in patients with diabetes where cost-effectiveness seems adequate. Needless to say that the discussion as to who decides what is cost-effective in saving lives, and on which grounds, resembles a Gordian knot and is beyond the scope of this commentary.

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