Invited review

Morbidity and mortality trials: black and white or shades of grey?

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Abstract

The evidence base for the drug treatment of hypertension is robust (black and white). The importance of rigorous blood pressure control is reasonably well established. The advantages or disadvantages of particular drug classes or regimens is much less clear (shades of grey). Even carefully conducted meta-analyses have failed to identify important differences in morbidity and mortality. Some drugs may have advantages for some end points (including intermediate or surrogate outcomes) but the overall influence on the individual is likely to be neutral. The future focus should be on strategies to control blood pressure rather than a futile search for benefit beyond blood pressure reduction.

Key words: morbidity, mortality.

Introduction

It has long been recognised that blood pressure is a critical determinant of cardiovascular morbidity and mortality [1]. A meta-analysis of data from over one million adults has reinforced the importance of the relationship between blood pressure, both systolic and diastolic, and cardiovascular risk [2]. Blood pressure is strongly and continuously related to all forms of vascular mortality and all cause death, without evidence of a lower threshold down to 115/75 mm Hg, at all ages up to 89 years. Absolute risk is graded and is greater in older age groups. Since the relationship between blood pressure and cardiovascular mortality is log-linear, each increase of 20 mm Hg in systolic blood pressure (10 mm Hg diastolic blood pressure) is associated with a doubling of the risk of stroke and lesser but significant increases in coronary heart disease and other vascular deaths. Thus, any change in blood pressure would be predicted to have the same proportional impact on outcome regardless of starting blood pressure.

These epidemiological findings strongly suggest that lowering of blood pressure should reduce cardiovascular morbidity and mortality. Furthermore, rigorous control of blood pressure should provide additional benefits. Numerous antihypertensive agents are available and there is speculation that some drugs or regimens might provide benefits beyond blood pressure reduction. Over the last 40 years, many large outcome trials have explored these issues. The resultant evidence varies in quality. Some is robust (black and white) while often the conclusions can best be described as uncertain (shades of grey).

Black and white

The evidence base for blood pressure reduction by antihypertensive therapy is among the strongest in any area of medicine. Seventeen unconfounded, prospective, randomised clinical trials in 50,000 hypertensive individuals demonstrated reduction in the risk of stroke, coronary heart disease, vascular mortality and all cause mortality [3]. Up to the early 1990s, trials were in predominantly middle-aged subjects with diastolic hypertension. Most studies used thiazide or thiazide-like diuretics as the basis of treatment, at dose (e.g. hydrochlorothiazide 50 mg daily) which might be considered industrial by current standards, with little attention to metabolic complications. Therapy based on β-blockers appeared to be similar but no better than diuretics in preventing stroke or coronary heart disease [4]. The benefits were clear cut despite only modest reduction in blood pressure (10–12/5–6 mm Hg) compared with control therapy. The average duration of these trials was five years. Since events were evenly spaced across the trials, mean time to an event was only 2.5 years. Thus, small reductions in blood pressure for short periods corrected all (or most) of the long-term cardiovascular morbidity and mortality predicted from epidemiological studies [1, 2].

Since then, the evidence for blood pressure lowering has been extended to older individuals with isolated systolic hypertension [5] and it has become clear that blood pressure lowering regimens provide broadly similar protection in men and women [6]. Until recently, however, there was uncertainty whether benefit extended to individuals aged 80 years or older. This was an important caveat since this age group is the fastest growing segment of the population and is almost invariably associated with systolic hypertension [7]. The few data available were not encouraging [8].

This important unsettled issue was addressed by the Treatment of Hypertension in Patients 80 years of Age or Older [9]. The findings were so convincing that the trial was stopped prematurely after an average of 1.8 years of treatment because of strong evidence of benefit with an average blood pressure difference of 15/6 mm Hg between active treatment and placebo. Death from cardiovascular disease was reduced by 23%, death from all causes by 21%, stroke by 30% and heart failure by 64%. Thus, it appears that antihypertensive drug treatment has clear benefits in ambulant individuals of any age.

Clinical trials [10, 11] have demonstrated clearly the critical importance of rigorous blood pressure control in reducing the risk of cardiovascular disease. Compared with less intensive control, tight blood pressure control reduces stroke and major cardiovascular events significantly, while there are trends for reduced coronary heart disease events, heart failure, cardiovascular death and all cause mortality [12]. Under-reporting of events in the largest individual trial may have led to an underestimate of benefit [11].

The benefits of tight blood pressure control is most apparent in individuals at particularly high risk e.g. those with type 2 diabetes mellitus. In the Hypertension Optimal Treatment (HOT) study [11], a difference in achieved diastolic blood pressure of only 4 mm Hg (81 mm Hg vs. 85 mm Hg) was associated with a 51% reduction in major cardiovascular events in patients with type 2 diabetes at randomisation. Likewise, a blood pressure reduction of 12/5 mm Hg reduced stroke risk by 28% in patients with prior cerebrovascular events [13]. Reductions of similar magnitude were observed for cardiovascular events. The benefits were proportionally similar in those with hypertension and in those with normal blood pressure i.e. independent of baseline blood pressure as predicted from epidemiology [2].

A meta-analysis [12] of trials comparing more intensive vs. less intensive therapy, active therapy vs. placebo, and different antihypertensive regimens has demonstrated that the benefits of antihypertensive treatment is proportional to reduction in blood pressure. For both stroke and coronary heart disease events, relative risks cluster closely to the regression line for differences in systolic blood pressure. Deviations for differences between antihypertensive drugs are modest (<10%) suggesting that blood pressure changes dominate any drug-related influences.

Shades of grey

In early trials with thiazide and thiazide-like diuretics as first-line therapy, the magnitude of reduction in stroke events was exactly that predicted from long-term epidemiological studies for the differences in systolic and diastolic blood pressure achieved [3]. The reduction in the predominant complication of hypertension in Western populations (coronary heart disease), while significant, was rather less than expected. Deleterious metabolic effects of diuretics might explain this shortfall [14-18].

The suggestion that thiazide or thiazide-like diuretics, at the low doses used currently, have a detrimental influence on coronary heart disease outcomes does not withstand careful scrutiny [19]. Because diuretics have no known beneficial effect on cardiovascular events independent of blood pressure reduction, these agents are the appropriate standard against which newer agents should be tested. The question of interest is whether newer drugs are superior to diuretics in preventing coronary heart disease for the same reduction in

blood pressure; that is, having benefits beyond blood pressure control.

The first challengers were the β-blockers. There were great expectations in the 1980s that these drugs would be superior to diuretics, particularly because β-blockers reduce the risk of reinfarction or death in patients with coronary heart disease [20]. The hypothesis was tested in a series of large-scale controlled trials [21-25]. The results were inconclusive and, in some cases, divisive [24, 25]. Thus, diuretics and β-blockers have been bracketed as "conventional therapy".

Newer agents have potential advantages over diuretics and β-blockers based on influences on surrogate end points. Results of large outcome trials did not appear until 20 years after the introduction of the newer drugs [26-29]. The wait was hardly worthwhile. No single trial detected a significant difference in coronary heart disease events between therapy based on newer drugs and that based on conventional agents, and the precision of the comparisons was weak with wide 95% confidence intervals for differences. Since clinically useful differences between therapies could not be excluded in any of the trials, these were not informative.

Individual trials had shortcomings which cloud interpretation. In the Captopril Antihypertensive Prevention Project (CAPPP) [29], it is almost certain that failure in the randomisation procedure rendered the results unreliable [30]. The Swedish Trial of Old Patients with Hypertension – 2 (STOP-2) [28] and the International Nifedipine GITS Study Intervention as a Goal in Hypertension (INSIGHT) [26] had withdrawal rates from randomised therapy that were unacceptably high. This leads to an underestimation of differences between treatments that would have been seen if there had been full adherence with randomised regimens. The apparent advantage of ACE inhibitor over calcium channel blocker in STOP-2 [28] must be treated with caution since it arose from a subset analysis.

The only information on the relative value of α-blockers in coronary heart disease prevention comes from the prematurely discontinued arm of the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) [31]. The primary reason for the early closure of this arm was an apparent excess risk of heart failure in doxazosin-treated patients compared with those randomised to chlorthalidone. However, several factors make interpretation difficult. The diagnostic criteria for heart failure were unconvincing, on-treatment blood pressure was higher in doxazosin-treated subjects, and the discontinuation rate was about twice as high in patients randomised to the α-blocker. The other reason for the early discontinuation was futility: even if continued, the chance of detecting an advantage of doxazosin over chlorthalidone for coronary heart disease was less than 1%. Although ALLHAT was the only study with sufficient power to assess the impact on coronary heart disease separately, we are left, probably for ever, with the conclusion that α-blocker therapy may be 10% better or 17% worse than diuretic therapy for this outcome.

In the face of uncertainty from individual trial, it is fashionable to resort to meta-analyses. To date, this approach has not taken the matter of differential protection much further forward [10, 12]. Differences in cause-specific outcomes were of borderline significance. Compared with conventional therapy or ACE inhibitors, calcium channel blocker-based therapy was associated with a modest reduction in stroke and an increased risk of coronary heart disease of similar magnitude. For both outcomes, 95% confidence intervals for differences were wide and the sizes of the true differences could not be determined reliably. The quality of a meta-analysis depends on the quality of the studies included; some (e.g. CAPPP and STOP-2) had major shortcomings.

In the first decade of the 21st century, several influential studies have been published. These are reviewed critically in the following section.

HOPE

In the Heart Outcomes Prevention Evaluation (HOPE) study [32], participants had to have evidence of cardiovascular disease but no heart failure; about 50% had treated hypertension and 40% type 2 diabetes. Although not a pure comparison a new drug against conventional therapy in hypertension, the results have been widely interpreted as showing an advantage of ACE inhibition beyond blood pressure control. That active treatment (ramipril) was better than placebo in reducing heart attack and other cardiovascular events is hardly surprising, but the magnitude of the reduction was greater than that predicted from epidemiological data for the small observed difference in blood pressure. However, the reduction in cardiovascular events per mm Hg difference in blood pressure was no greater than that seen in other similarly high risk populations treated with other forms of anti-hypertensive therapy [11, 33] (Table I). Also shown in Table I are findings from the similar EUROPA Study [34] of patients with coronary heart disease in which perindopril has been suggested to have benefits not explained by blood pressure reduction. Although baseline blood pressure was relatively low in HOPE and EUROPA, the log-linear relationship with events [2] predicts that any change in blood pressure should have the same proportional influences risk regardless of the starting level. In the absence of a positive control group in HOPE,

treated with another agent providing equivalent blood pressure control, no definitive conclusion can be reached. In fact, a small ambulatory blood pressure substudy of HOPE [35] suggests that the influence of ramipril on blood pressure in HOPE may have been underestimated (Figure 1).

ALLHAT

The largest randomised trial of antihypertensives ever conducted was designed specifically to have sufficient power to examine coronary heart disease as the primary outcome [36]. The trial randomised 42,418 individuals with hypertension and at least one additional cardiovascular risk factor to double blind therapy based on chlorthalidone or one of three other antihypertensive treatments: amlodipine, lisinopril or doxazosin. The α-blocker arm was stopped prematurely [31], leaving 33,357 participants who were followed for around five years.

There was no difference between the treatments for coronary heart disease or all cause mortality. However, lisinopril was associated with statistically higher rates for combined cardiovascular disease and for stroke. Heart failure was reported significantly more often in subjects randomised to amlodipine and lisinopril.

The authors concluded that thiazide-like diuretics are superior to newer drugs in preventing cardiovascular disease and are less expensive, making these drugs the preferred first-line antihypertensive therapy. However, concerns have been raised about the study conduct with high rates of discontinuation from randomised therapy, the precision of the comparison (wide 95% confidence intervals for differences) particularly in pre-specified subgroups, the veracity of the diagnosis of cause-specific events notably heart failure, and the use of obsolescent drugs as add-on therapy [37]. The major shortcoming was the non-equivalence of blood pressure control in the treatment arms.

A fundamental requirement of comparisons of outcomes with antihypertensive agents is that blood pressure in each group should be the same or similar. This was not the case in ALLHAT. Five year systolic blood pressure was significantly higher in the amlodipine and lisinopril groups compared with chlorthalidone. Differences in systolic blood pressure early in the trial were even greater. Although the authors are dismissive of the influence of these blood pressure differences, meta-regression analysis of data from outcome trials suggests that minor differences can have major influences on outcome [38]. This may be particularly important in high risk populations [11, 33] such as that studied in ALLHAT. The differences in systolic blood pressure control between the lisinopril and chlorthalidone groups could readily explain the observed excess risk of stroke in patients randomised to the ACE inhibitor.

Table I. Cardiovascular risk reduction for blood pressure differences in selected trials in high risk patients HOPE [32], EUROPA [34], SYST-EUR (DM) [33], HOT (DM) [11]

	HOPE	EUROPA	SYST-EUR (DM)	HOT (DM)
Treatment	ACEI	ACEI	CCB	CCB
DBP [mm Hg]	79	82	85	85
CV risk reduction [%]	22	20	68	51
△ DBP [mm Hg]	2	2	3.3	4.1
CV risk reduction per mm Hg [%]	11	10	20.6	12.4

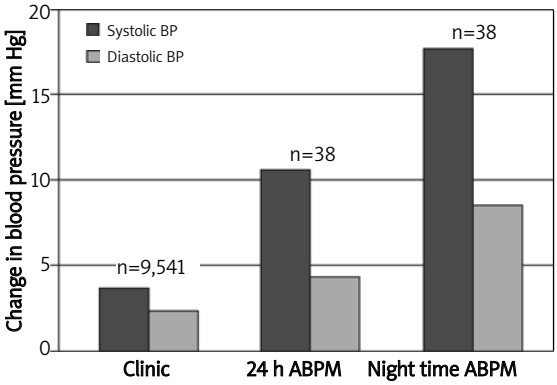

Figure 1. Changes in blood pressure in HOPE (n=9541) and the HOPE ambulatory blood pressure substudy (n=38). Derived from ref. [32] and [38]

Early blood pressure differences may be crucially important in determining outcomes and the findings of ALLHAT should be adjusted to take account of such discrepancies.

ALLHAT was a prodigious undertaking not only in size but also in the clinically relevant questions addressed. Was the effort worthwhile? Clinical trials should be informative and, sadly, ALLHAT joins the ranks of uninformative trials. There are too many imponderables to allow reliable conclusions. It is easy to be seduced by findings from very large trials and to overlook any shortcomings – never mind the quality, feel the width! A really decisive trial needs quality as well as width. Size is not everything.

Soon after publication, the conclusion that ACE inhibitors offer no advantage over diuretics was challenged by the findings of the Second Australian National Blood Pressure Study [39]. In that trial, initiation of antihypertensive therapy including ACE inhibitors in older people was associated with better outcomes than treatment based on diuretic agents, despite similar blood pressure control. However, the advantage of ACE inhibitors was significant only in men. Thus, the issue of whether blockade of the renin-angiotensin system has added benefit remained unresolved.

VALUE

The Valsartan Antihypertensive Long-term Use Evaluation addressed directly the issue of whether antihypertensive therapy based on blockade of the renin-angiotensin system had advantages in cardioprotection [40]. In VALUE, 15,245 hypertensive individual aged 50 years or over, characterised as being at high risk of cardiovascular events were randomised to therapy based on either the angiotensin receptor blocker, valsartan, or the calcium channel blocker, amlodipine with other antihypertensive drugs added as necessary to achieve rigorous blood pressure control. Follow up was around five years.

As in ALLHAT, there were major differences in blood pressure control between the treatment arms. Throughout the trial, blood pressure was lower in the amlodipine arm. At 2 months after randomisation, systolic blood pressure difference was over 4 mm Hg and, even at the final visit, a difference of 2 mm Hg persisted, despite the addition of other agents. Nevertheless, the primary composite end point (rate of cardiac events) did not differ between valsartan and amlodipine-based treatment.

There is strong suspicion that inequalities in blood pressure control influenced the results. In the first three months, when systolic blood pressure difference averaged 3.8 mm Hg, the findings for the primary end point significantly favoured amlodipine but as the study progressed and blood pressure control in the two arms approached equivalence, no such difference was apparent. To evaluate the influence of blood pressure differences, the technique of serial median matching was applied to the VALUE results [41]. This exploratory analysis confirmed the critical importance of blood pressure dependent effect of antihypertensive therapy (valsartan and amlodipine-based) for the primary outcome and also stroke, all cause mortality, myocardial infarction and heart failure hospitalisation. Serial median matching identified 5,006 pairs (n=10,012) of participants who had equivalent systolic blood pressure at 6 months (in the valsartan and amlodipine arms). In these subjects, there were trends in favour of angiotensin receptor blocker-based therapy for most outcomes, and the trend was significant for heart failure hospitalisation. These findings further emphasise the need to allow for blood pressure control when assessing the relative impact of antihypertensive agents. Although serial median matching has been criticised [42], such an approach is probably the only way to allow for time-dependent differences in blood pressure between randomised treatments.

ASCOT

The Anglo Scandinavian Cardiac Outcomes Trial [43] compared treatment strategies rather than first-line antihypertensive agents. Contemporary therapy (amlodipine ± perindopril) was set against conventional therapy (atenolol ± bendroflumethiazide) with the same protocol for additional antihypertensive agents to achieve rigorous blood pressure control in both arms. Again, relatively elderly hypertensive individuals with other cardiovascular risk factors were recruited.

Compared with conventional therapy, contemporary therapy was associated with improved outcomes including total coronary endpoints, total cardiovascular events and procedures, cardiovascular mortality, fatal and non-fatal stroke, and all-cause mortality. However, contemporary therapy was not significantly better for the primary outcome, non-fatal myocardial infarction (including silent events) and fatal coronary heart disease.

At first sight, the results are impressive, but as in ALLHAT [36] and VALUE [40], blood pressure control was significantly better in one arm (amlodipine ± perindopril). The mean difference over the five years of follow up was 2.7/1.9 mm Hg, very similar to that in VALUE [40]. Once again, attempts were made to allow for this difference, here using serial mean matching [44]. The conclusion of this post hoc analysis was that blood pressure differences might explain all the benefits in stroke but only partially explained the coronary benefits. Others have argued that all the reduction in risk for coronary heart disease, cardiovascular events and stroke can be predicted from the observed differences in systolic blood pressure [45]. Further controversy arose with the identification of potential synergy between lipid lowering and blood pressure lowering in ASCOT [46]. Thus, amlodipine-based therapy was superior to atenolol-based therapy in preventing non-fatal plus fatal coronary heart disease and cardiovascular events and precuedures only in subjects randomised to concomitant atorvastatin (Table II). The benefit for stroke prevention appears independent of lipid lowering therapy but may be attributed to blood pressure differences [44]. Thus, ASCOT fails to provide robust evidence that one antihypertensive therapy is superior to another in reducing cardiovascular risk independent of blood pressure.

Some support for the combination of a calcium channel blocker and renin-angiotensin system blocker is suggested in the, as yet unpublished Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study [47]. Excellent blood pressure control was achieved both in those treated with combined amlodipine plus benazepril and combined hydrochlorothiazide plus benazepril but

the former combination provided significantly greater protection for all pre-specified outcomes. Although rigorous blood pressure control was achieved in both arms, levels were significantly lower in the calcium channel blocker/ACE inhibitor group. Therefore, as advocated by some of the ACCOMPLISH authors [41], techniques, such as serial median matching, to allow for differences in blood pressure control between the treatment arms should be applied to the data. Until then, it may be that ACCOMPLISH has merely demonstrated that calcium channel blockers are more effective than low-dose thiazides as blood pressure lowering agents in elderly people with systolic hypertension.

LIFE

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study is unusual among outcome trials of antihypertensive therapies in that blood pressure in both arms of the trial were very similar, eliminating the confounding influence of differential control [48]. Throughout follow-up of 4.8 years, losartan-based therapy reduced blood pressure by only about 1 mm Hg relative to that after atenolol-based therapy in hypertensive individuals with ECG evidence of left ventricular hypertrophy. About 80% of participants in each arm received study drug in combination with hydrochlorothiazide. Losartan-based therapy was associated with a significant reduction in the primary composite endpoint (fatal and non-fatal coronary heart disease, fatal and non-fatal stroke and fatal cardiovascular events), driven by a 25% reduction in stroke events. Benefits were particularly marked in individuals with type 2 diabetes at randomisation [49].

A meta-analysis by one of the principal authors of LIFE [50] has cast doubt on the significance of the LIFE findings. This meta-analysis questioned whether β-blockers, such as atenolol used in LIFE, should remain first choice in the treatment of primary hypertension. Although heavily influenced by the results of ASCOT [43] and LIFE [48], β-blockers appear inferior in protection against cardiovascular outcomes, particularly stroke, in comparison with other antihypertensive drug classes. Thus, it may be that atenolol was a weak comparator and that any advantage of losartan was exaggerated in the LIFE study.

JIKEI Heart Study

This study [51] was not strictly a trial of antihypertensive therapies but an evaluation of an angiotensin receptor blocker in patients with established cardiovascular disease. In many ways, the design was similar to that of HOPE [32]. The JIKEI Heart Study had two unusual features: one of the first randomised trials conducted in Japan and achievement of blood pressure equivalence in the treatment arms.

Table II. Potential synergy between lipid-lowering and blood pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. Derived from ref. [46]

Event rates per 1000 patients years			
	Amlodipine	Atenolol	HR
Atorvastatin			
Non-fatal MI + fatal CHD	4.6	7.5	0.61
CV events and procedures	21.3	27.0	0.79
Stroke	4.2	6.5	0.65
Placebo			
Non-fatal MI + fatal CHD	9.8	9.0	1.09
CV events and procedures	29.4	31.7	0.93
Stroke	6.1	8.6	0.71

HR – hazard ratio

The JIKEI Heart Study randomised 3,081 patients to add-on therapy with valsartan or non-angiotensin receptor blocker with the aim to achieve rigorous blood pressure control. Blood pressure control at randomisation was good and achieved blood pressure was even better (mean 131/77 mm Hg); reduction from baseline was 8.2/4.7 mm Hg on valsartan and 7.7/3.7 mm Hg in the non-angiotensin receptor blocker arm. Additional valsartan was associated with a highly significant reduction in the primary end point, a composite of cardiovascular mortality and morbidity (stroke or transient ischaemic attacks, myocardial infarction, hospitalisation for congestive heart failure or angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction), doubling of serum creatinine or transition to dialysis. Significant benefits were also observed for most individual cause- specific outcomes.

Although the findings suggest a benefit of angiotensin receptor blocker independent of blood pressure, doubts remain. The study was small raising the question of type 1 statistical error (i.e. chance). More importantly, the PROBE (Prospective Randomised Open Blinded Endpoint) design may have led to bias in the ascertainment of some of the endpoints such as angina or transient ischaemic attacks. Therefore, the results of the JIKEI Heart Study cannot be considered to be conclusive. Furthermore, another Japanese study in high risk hypertension showed no particular advantage of angiotensin receptor blockade [52].

Cause-specific outcomes

Early comparisons of antihypertensive drugs compared with placebo or control suggested that

protection against stroke was closely dependent on blood pressure reduction [3] and little gain could be expected from particular antihypertensive drugs. However, comparative studies have suggested differential effects on stroke prevention [36, 40, 43, 48]. In primary prevention of stroke, meta-analysis suggests that compared with conventional therapy (diuretics and β-blockers), calcium channel blockers and angiotensin receptor blockers offer a modest advantage while ACE inhibitors may be less effective in preventing stroke [53]. *Post-hoc* subset analysis of data from PROGRESS [13] underpins the hypothesis that ACE inhibitor therapy alone underperform while the benefit predicted from blood pressure reduction was seen only in subjects treated with perindopril in combination with indapamide [54]. A meta-analysis supports the benefit of diuretic-based therapy in the secondary prevention of stroke while ACE-inhibitor therapy had no significant effect [53].

These disparate observations have fuelled the hypothesis that drugs which increase circulating levels of angiotensin II (diuretics, calcium channel blockers and angiotensin receptor blockers) may be more effective in stroke prevention than drugs which reduce angiotensin II (β-blockers and ACE inhibitors). Although not tested directly, there is further supporting circumstantial evidence. Two relatively small and unusually designed and analysed trials, ACCESS [55] and MOSES [56], suggest a benefit of angiotensin receptor blockers beyond blood pressure reduction. Furthermore, a meta-analysis suggests that calcium channel blockers have significant advantages in stroke prevention compared with ACE inhibitors [57].

In contrast, the same meta-analysis [57] suggested that ACE inhibitors were superior to calcium channel blockers in protection against coronary heart disease. A recent comprehensive meta-analysis of trials has suggested that ACE inhibitors have a cardioprotective effect beyond that expected from blood pressure reduction while angiotensin receptor blockers had no such advantage [58]. Indeed, it has been proposed that angiotensin receptor blockers do not protect against myocardial infarction and may even increase the risk of cardiac events [59].

Thus, there is speculation that the way blood pressure is reduced might influence cause-specific outcomes. Even the way the renin-angiotensin system is blocked might be important. These issues have been addressed in three recent trials.

ONTARGET

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial compared an ACE inhibitor with an angiotensin receptor blocker and with a combination of the two [60]. The trial design and population was based on those in HOPE [32]. The sample size was large with 25,620 patients randomised to double-blind therapy. The main objective was satisfied: telmisartan was not inferior to ramipril for the primary composite outcome and the same outcome as used in HOPE. The monotherapies were also not different for cause-specific outcomes (cardiovascular death, myocardial infarction, stroke, heart failure hospitalisation and all-cause mortality). However, the combination of ACE inhibitor and angiotensin receptor blockers was not superior to ramipril alone. Telmisartan was better tolerated than ramipril but the combination was poorly tolerated.

One message from ONTARGET is "black and white" but others represent "shades of grey". The equal cardioprotection of the two monotherapies contradicts the claim that angiotensin receptor blockers are less effective than ACE inhibitor in protection against myocardial infarction [59]. Only two trials provide evidence from direct comparisons of evidence-based doses of ACE inhibitors and adequate doses of angiotensin receptor blockers, ONTARGET [60] and VALIANT [61]. Neither showed a difference for myocardial outcomes. Surely, this issue is now settled.

In other respects, the results may be biased against telmisartan. At the end of the dosage interval, blood pressure in the monotherapy arms was similar but, since telmisartan has a smoother 24 h blood pressure profile [62], ramipril is likely to have induced lower blood pressure for much of the period between doses. Furthermore, cough was an infrequent cause of discontinuation from ramipril therapy since 60% of participants were on ACE inhibitors prior to randomisation, intolerance to an ACE inhibitor was an exclusion criterion for ONTARGET and ramipril was given for three to four weeks in a single blind run in period so that those who were intolerant of the ACE inhibitor did not proceed to randomisation. Thus, the major adverse effect of ACE inhibitors was minimised by design, negating the well known lesser adverse effect profile of angiotensin receptor blockers. Telmisartan was boxing with one arm tied behind its back.

Adding telmisartan to ramipril conferred no added benefit but more side effects, notably more progressive renal dysfunction. This is likely to be attributable to excessive lowering of blood pressure in vulnerable patients since the design of ONTARGET did not allow individualised dose titration. Overall, mean blood pressure reduction on the combination was 2.4/1.4 mm Hg relative to ramipril alone. Again, the difference in blood pressure profile between telmisartan and ramipril [62] may have resulted in an overestimate of the blood pressure difference over 24 h. The failure of the combination to provide added benefit was a surprise to expert nephrologists who have

incorporated this approach into clinical management of patients with proteinuric chronic kidney disease [63, 64]. However, the population studied in ONTARGET was at high cardiovascular risk but at low risk of chronic kidney disease. ONTARGET provides no evidence relevant to proteinuric/microalbuminuric renal disease. Indeed, the best "evidence" in favour of the combination of ACE inhibitor and angiotensin receptor blocker in such patients [65] has recently come under major criticism [66, 67]. Nor did ONTARGET provide evidence for the benefit of the combination in patients with congestive heart failure where benefit has previously been reported [68, 69]. The findings from ONTARGET are much more in keeping with the results from VALIANT [61] where the combination had no added benefit but more side effects in patients with prior myocardial infarction.

TRANSCEND

Patients with known intolerance to ACE inhibitors or who had ACE inhibitor induced side effects in the single-blind phase of ONTARGET were eligible for randomisation in the companion study, the Telmisartan Randomised Assessment Study in ACE intolerant Subjects with Cardiovascular Disease [70]. This trial was similar to HOPE [32] with telmisartan substituted for ramipril. Despite a mean blood pressure reduction of 4.0/2.2 mm Hg, no significant reduction in the primary outcome was observed although risk reduction for the outcome used in HOPE was of borderline statistical significance.

The likely explanation for these findings was that TRANSCEND was hopelessly underpowered. Less than 6,000 patients were included compared with over 9,000 in HOPE. Also, the use of cardioprotective agents (statins, β-blockers and antiplatelet agents) was much higher in TRANSCEND than in HOPE. This is reflected in much lower rates for myocardial infraction and heart failure in the placebo arm of TRANSCENT compared with HOPE.

PROFESS

The Prevention Regimen for Effectively Avoiding Second Strokes Study [71] investigated whether early blood pressure reduction after stroke would be beneficial. PROFESS evaluated the effects of therapy with the angiotensin receptor blocker, telmisartan, compared with placebo in 20,392 patients with prior ischaemic stroke. Blockade of the renin-angiotensin system is said to reduce the risk of stroke independent of blood pressure [32, 56]. Indeed, a small study of unusual design [55] suggested that an angiotensin receptor blocker started soon after stroke reduced rates of death and cardiovascular events despite no blood pressure reduction.

Since PROFESS employed a factorial design allowing comparison of two antiplatelet regimens, patients with haemorrhagic stroke were excluded. All patients received treatment for blood pressure control at the discretion of the investigators. The primary outcome was recurrent stroke. Secondary outcomes included major cardiovascular events.

The median interval to randomisation was 15 days post stroke and median follow up was 2.5 years. During follow up, blood pressure fell in both groups, but more so in the telmisartan arm (mean blood pressure difference 3.8/2.0 mm Hg).

The results strongly support the null hypothesis. Hazard ratios were close to unity for recurrent stroke and for major cardiovascular events. There were no interactions with the anti-platelet regimens.

The landmark PROGRESS trial [13] demonstrated reduced risk of recurrent stroke and cardiovascular events with blood pressure lowering commenced at least two weeks after stroke although the median time to randomisation was eight months. In contrast, PROFESS failed to provide evidence of benefit when treatment was started after a median period of 15 days. Time to randomisation was 10 days or less in 40% of participants and this subgroup showed results similar to those in the entire group. However, about 50% of the PROFESS population was randomised beyond two weeks, as in PROGRESS [13], but experienced no benefit from blood pressure reduction.

The PROFESS authors suggest that lesser blood pressure lowering may explain the findings. They note that most of the benefit in PROGRESS [13] was seen in the group receiving perindopril plus indapamide where blood pressure reduction was 12.3/5.0 mm Hg while those receiving perindopril alone experienced a blood pressure reduction of only 4.9/2.8 mm Hg and no significant benefit. This explanation is unconvincing if there is indeed a blood pressure independent beneficial effect of blocking the renin-angiotensin system as speculated by the PROFESS authors. In fact, the study design was not optimal for teasing out the potentially competing influences of blood pressure reduction and mode of action.

There is concern that PROFESS was underpowered. The protocol specified a sample size of 15,500 patients which would yield 2,170 with recurrent stroke during four years' follow up. Despite an increase in sample size to over 20,000, only 1,814 participants had recurrent strokes in 2.5 years of follow up. Perhaps, the PROFESS investigators now regret the decision to modify the power calculation during the study. Furthermore, the mean duration of therapy may have been too short at 2.5 years; assuming constant hazard, average time to event was only 1.25 years.

In trials of new interventions to prevent further cardiovascular events when added to existing therapies, only moderate (10-15%) benefits can be realistically expected. To ensure that full benefit is apparent, treatment periods have to be prolonged. This is perhaps the most important message from PROFESS. The pressure to design and conduct major trials in order to generate results as quickly as possible must be resisted. Otherwise, the huge investment both financial and in patients may be wasted. After more than 50,000 patient-years devoted to PROFESS, we simply cannot declare whether or not early reduction of blood pressure following stroke has long-term benefits and we certainly can make no reliable claim to support any advantage or disadvantage of renin-angiotensin system blockade. Expediency may have resulted in the baby being thrown out with the bathwater.

What can be salvaged from the wreckage of TRANSCEND and PROFESS?

Post hoc explanatory analyses of these trials [70, 71] suggest the possibility of time-dependent benefit with telmisartan. No significant benefit was seen up to six months after randomisation although a small but significant advantage for stroke and cardiovascular events was seen thereafter. The differences between the two periods was significant and adjustment for post-randomisation blood pressure did not markedly affect the estimates. Although these analyses must be seen as hypothesis generating, there is some support from other trials. In PROGRESS [13], HOPE [32] and LIFE [48], little benefit was apparent in the first 6 months with graded and continuing lessening of rates of stroke and major cardiovascular events thereafter. These findings are consistent with other trials of antihypertensive agents [12] and lipid lowering therapy [72, 73].

Intermediate endpoints

Perhaps driven by the failure to demonstrate clear differences between antihypertensive therapies for hard outcomes, attention has reverted to surrogate end points. Thus, it has been observed that conventional drugs, β-blockers and diuretics, particularly in combination, tend to accelerate the development of diabetes, while drugs which block the renin-angiotensin system appear to protect against diabetes [74]. Individuals who develop diabetes during antihypertensive therapy are at high risk of diabetes and high cardiovascular risk prior to initiation of treatment [75, 76]. To what extent the arbitrary diagnosis of diabetes influences prognosis in these people is unknown. Therefore any benefits of blockers of the renin-angiotensin system may be illusory rather than real. Recent evidence suggests that the antidiabetic potential of ACE inhibitors [77] and angiotensin receptor blockers [71] may have been exaggerated.

ACE inhibitors and angiotensin receptor blockers are also claimed to reduce the incidence of new-onset atrial fibrillation in treated hypertension [78].

THE UNKNOWN

As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

– Feb. 12, 2002,
Department of Defense news briefing

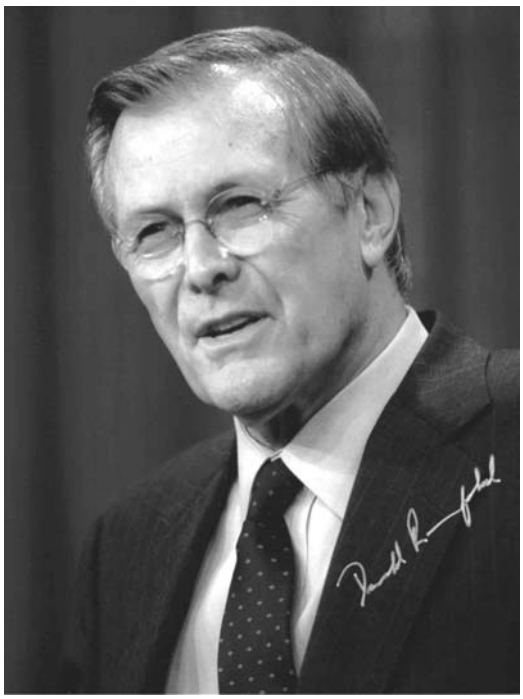

Figure 2. The poetry of Donald Rumsfeld

Again findings are inconsistent. In PROFESS [71], for instance, atrial fibrillation was significantly more common in patients randomised to telmisartan.

Conclusions

The recent morbidity and mortality trials of antihypertensive therapy have provided few practical lessons (black and white conclusions) while many leave questions unanswered (shades of grey). It appears that for equivalent changes in blood pressure, all drugs are equivalent in preventing overall cardiovascular complications.

The short duration of trials may have contributed to the failure to detect differential efforts. Clinical trials provide short-term answers to long-term problems and are, in effect, surrogates for real life where treatment is usually given for many years.

The critical importance of rigorous control of blood pressure is established. It is notable that no treatment with inferior blood pressure control has been associated with better outcomes. In the majority of hypertensive individuals, tight blood pressure control necessitates the use of two or more antihypertensive agents. The benefits of additional blood pressure lowering far outweighs any possible differential effect between drugs. The time has come to stop worrying about which drug to prescribe and to instead devote our attention to lowering blood pressure using all available therapies.

The voyage across the sea of mortality and morbidity trials brings to mind the poetry of Donald Rumsfeld (Figure 2). The known knowns were that blood pressure is a critical determinant of cardiovascular risk, and that reducing blood pressure reduces strokes, heart attacks and other cardiovascular events. The known unknowns were whether rigorous blood pressure control resulted in greater benefits and whether contemporary agents are superior to conventional drugs. The latter is still a known unknown. The unknown unknowns of course remain unknown but a decade ago we had no idea of the potential importance of short-term small differences in blood pressure or the possible relevance of surrogate endpoints such as new onset diabetes or new atrial fibrillation. These have been promoted to known unknows but future unknown unknowns are certain to lie in wait.

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