Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial

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Lancet 2011; 377: 312–320

Published Online January 13, 2010 DOI:10.1016/S0140-6736(10)62003-X

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Summary

Background **Short-term studies have suggested that the use of initial combination therapy for the control of blood pressure improves early effectiveness. We tested whether a combination of aliskiren and amlodipine is superior to each monotherapy in early control of blood pressure without excess of adverse events, and if initial control by monotherapy impairs subsequent control by combination therapy.**

Methods: **We did a double-blind, randomised, parallel-group, superiority trial at 146 primary and secondary care sites in ten countries, with enrolment from Nov 28, 2008, to July 15, 2009. Patients eligible for enrolment had essential hypertension, were aged 18 years or older, and had systolic blood pressure between 150 and 180 mm Hg. Patients were randomly assigned (1:1:2) to treatment with 150 mg aliskiren plus placebo, 5 mg amlodipine plus placebo, or 150 mg aliskiren plus 5 mg amlodipine. Random assignment was through a central interactive voice response system and treatment allocation was masked from the patients. From 16–32 weeks, all patients received combination therapy with 300 mg aliskiren plus 10 mg amlodipine. Our primary endpoints, assessed on an intention-to-treat basis (ie, in patients who received the allocated treatment), were the adjusted mean reduction in systolic blood pressure from baseline over 8 to 24 weeks, and then the final reduction at 24 weeks. This trial is registered with ClinicalTrials.gov, number NCT00797862.**

Findings **318 patients were randomly assigned to aliskiren, 316 to amlodipine, and 620 to aliskiren plus amlodipine. 315 patients initially allocated to aliskiren, 315 allocated to amlodipine, and 617 allocated to aliskiren plus amlodipine were available for analysis. Patients given initial combination therapy had a 6·5 mm Hg (95% CI 5·3 to 7·7) greater reduction in mean systolic blood pressure than the monotherapy groups (p<0·0001). At 24 weeks, when all patients were on combination treatment, the difference was 1·4 mm Hg (95% CI –0·05 to 2·9; p=0·059). Adverse events caused withdrawal of 85 patients (14%) from the initial aliskiren plus amlodipine group, 45 (14%) from the aliskiren group, and 58 (18%) from the amlodipine group. Adverse events were peripheral oedema, hypotension, or orthostatic hypotension.**

Interpretation **We believe that routine initial reduction in blood pressure (>150 mm Hg) with a combination such as aliskiren plus amlodipine can be recommended.**

Funding **Novartis Pharma AG.**

Introduction

Hypertension is a complex disorder, and target blood pressure in most patients cannot be achieved with monotherapy.[1] Yet guidelines give muted advice on starting treatment with a combination of drug classes, and only the β blocker–diuretic combinations are licensed for this use in the UK.[2,3] There are two reasons why initial treatment with combination regimens might be advantageous for patients. First is the short-term gain from the rapid reduction of the patient's risk from raised pressure. Second is the gain from improved long-term blood pressure control. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, in which there was a 3·8/2·2 mm Hg difference in blood pressure between the valsartan and amlodipine groups after treatment for 3 months, provides circumstantial evidence for both gains.[4] There was a 75% early excess of cardiovascular morbidity and an almost three-times increase in all-cause mortality in the valsartan group, and 5 years later blood pressure was still 1·8/1·5 mm Hg higher in this group despite greater use of diuretic add-on treatment. Put simply, blood pressure control never caught up. Similar early and later differences in blood pressure have been recorded in other trials, such as the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT).[5,6]

Previous comparisons of combination treatment with monotherapy have been short-term (average 6 weeks) and included too few patients at high doses to exclude symptomatic hypotension as a complication.[7] In most of the trials, patients were transferred from previous treatment rather than receiving the combination de novo.

To test whether long-term blood pressure might be determined by initial treatment we designed a trial in which all patients at the time of the trial's primary endpoint were in receipt of the same treatment—a

combination of amlodipine and aliskiren—but half the patients would start the combination 6 months earlier and half would start monotherapy with either amlodipine or aliskiren. Our hypothesis was that initial treatment with two drugs of complementary mechanisms would achieve earlier, larger, and more sustained reductions in blood pressure than a sequential add-on regimen. The mechanistic rationale for this hypothesis was that compensatory haemodynamic or neuroendocrine responses to individual drugs might attenuate their effectiveness, prevent catch up when a second drug is added, and contribute to adverse events that lead to the discontinuation of treatment.

Methods

Participants

We did a double-blind, randomised, parallel-group, superiority trial in 146 primary and secondary care sites in ten countries (Canada, Costa Rica, France, Germany, Greece, Guatemala, South Africa, Switzerland, the UK, and Venezuela), with enrolment from Nov 28, 2008, to July 15, 2009. Patients of both sexes aged 18 years or older were eligible if seated systolic blood pressure at the time of random assignment was between 150 mm Hg and 180 mm Hg, and diastolic blood pressure was less than 110 mm Hg.

Procedure

After a screening visit, patients completed a single-blind placebo run-in, during which any existing treatment with antihypertensive drugs was stopped. The run-in lasted a minimum of 2 weeks, with a further 2 weeks if the previously treated patients' systolic blood pressure did not rise to meet the inclusion criteria, or differed by more than 20 mm Hg from the measurement at screening. After the single-blind placebo run-in there were three sequential phases of double-blind active treatment. In the first phase, weeks 0–16, half the patients started monotherapy with either aliskiren or amlodipine, and half started a combination of aliskiren plus amlodipine. In the second phase (weeks 16–24), all patients received the same combination of aliskiren plus amlodipine. In the third phase, all patients, dependent on their blood pressure, received a third tablet—hydrochlorothiazide or placebo. The primary endpoints were measured at the end of the second phase; the third phase allowed an extended assessment of the sustained effect of the difference in randomly assigned drug in the first phase, without withholding clinically desirable treatment escalation.

Eligible patients were randomly assigned at a ratio of 1:1:2 to treatment with 150 mg aliskiren plus placebo, 5 mg amlodipine plus placebo, or 150 mg aliskiren plus 5 mg amlodipine. At 8 weeks, the dose was doubled. After 16 weeks, all patients received the combination of 300 mg aliskiren plus 10 mg amlodipine. At week 24, patients received 12·5 mg hydrochlorothiazide or placebo if systolic blood pressure was greater than 140 mm Hg or diastolic blood pressure was greater than 90 mm Hg. The study ended at 32 weeks.

At the first visit to a care site, patients were registered by a central interactive voice response system (IVRS; Almac Clinical Technologies, Yardley, PA, USA), and a unique medication number was obtained for the placebo run-in. At the second visit, patients who met the inclusion criteria were randomly assigned via IVRS to one of the three treatment regimens. Random assignment was

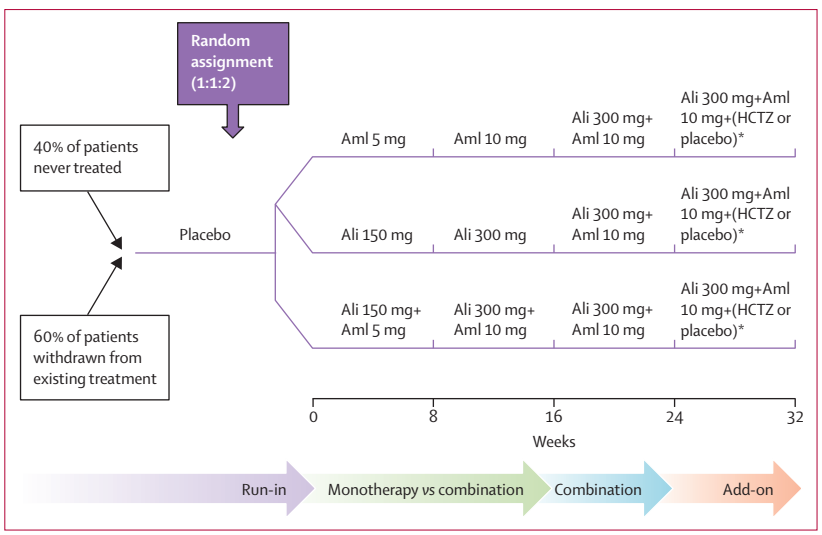

Figure 1: **Planned drug and dose allocation**
Aml=amlodipine. Ali=aliskiren. HCTZ=hydrochlorothiazide. *HCTZ 12·5 mg for patients with systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, otherwise placebo.

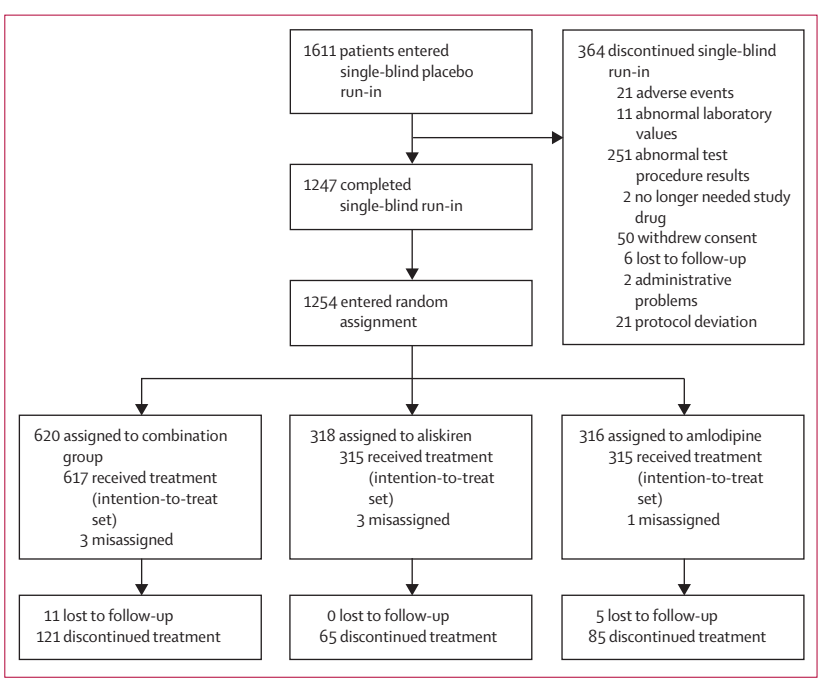

Figure 2: **Trial profile**

	Aliskiren plus amlodipine group (N=620)*	Aliskiren group (N=318)*	Amlodipine group (N=316)*
Age (years)	58·1 (10·8)	58·4 (10·8)	58·1 (10·9)
Number of women	305 (49%)	154 (48%)	160 (50%)
Ethnic origin			
White	477 (77%)	251 (79%)	245 (78%)
Black	32 (5%)	17 (5%)	16 (5%)
Asian	13 (2%)	4 (1%)	6 (2%)
Native American	19 (3%)	9 (3%)	8 (3%)
Other	79 (13%)	37 (12%)	41 (13%)
Body-mass index (kg/m^2)	29·8 (5·6)	29·5 (5·2)	29·8 (5·7)
Number of smokers	89 (14%)	48 (15%)	37 (12%)
Number of treatment-naive patients	270 (44%)	133 (42%)	118 (37%)
Number with diabetes	77 (12%)	42 (13%)	37 (12%)
Systolic blood pressure (mm Hg)	161·8 (8·4)	161·2 (8·5)	161·1 (8·2)
Diastolic blood pressure (mm Hg)	92·5 (9·0)	92·0 (10·6)	93·0 (9·1)

Data are mean (SD) or n (%). *The number of patients attending the baseline visit before random assignment.

Table 1: **Demographic and baseline characteristics**

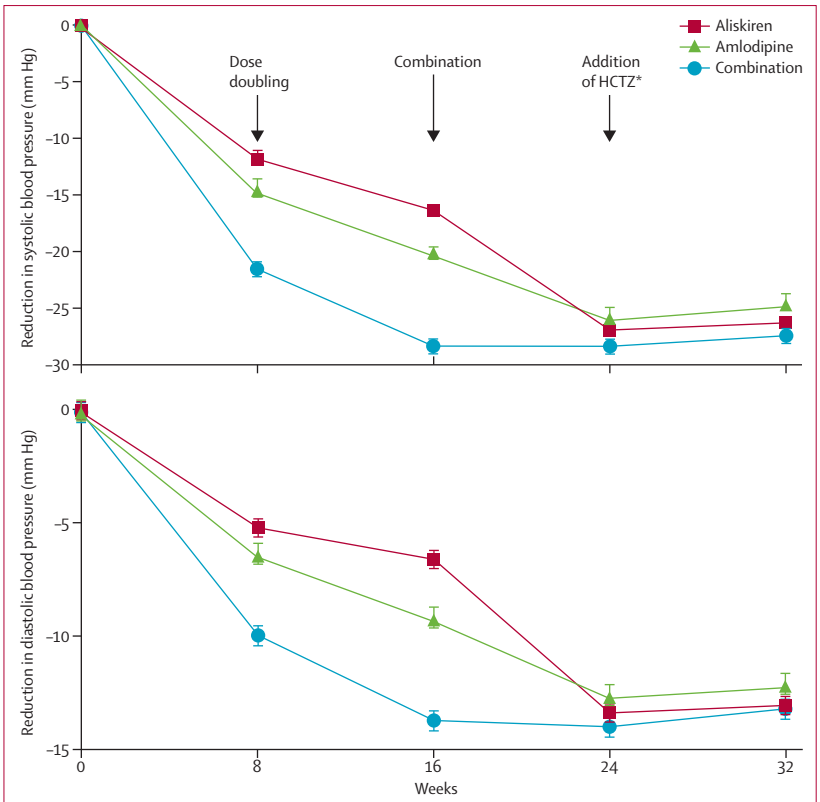

Figure 3: **Reductions in blood pressure**

Data are unadjusted means (95% CI). All patients had a doubling of their doses at 8 weeks. At 16 weeks, patients on monotherapy advanced to combination treatment. HCTZ=hydrochlorothiazide *At 24 weeks, HCTZ was added if systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

stratified by study centre. Aliskiren film-coated tablets and matching placebo and amlodipine hard gelatine capsules and matching placebo were given in a double-dummy fashion to maintain masking in the combination and monotherapy groups. Emergency code breaks via the central IVRS were available if deemed absolutely necessary, otherwise masking was maintained until database lock.

Trough blood pressure, recorded by an approved automated monitor (Omron, Kyoto, Japan), was measured at each visit as the mean of three readings after at least 5 minutes in the sitting position. Blood was drawn for plasma electrolytes. Plasma renin activity (PRA) and concentration (mass) were measured in a subset of patients.

Our study had two sequential primary endpoints and hypotheses. The first, was the mean reduction from baseline of systolic blood pressure over weeks 8, 16, and 24, testing for superiority between the aliskiren plus amlodipine (initial combination) group and mean of each of the monotherapies. The second, tested only if the first hypothesis was positive, was the reduction from baseline in systolic blood pressure at week 24, a point in the study when all patients were in receipt of the same treatment, with the test of superiority favouring patients initially treated with the combination. Secondary endpoints included the reduction in diastolic blood pressure from baseline at 16 and 24 weeks, the reductions in systolic and diastolic blood pressure at 32 weeks, the effect of baseline variables on response at each timepoint, and an analysis of the reduction in systolic and diastolic blood pressure that compared initial combination therapy with each of the monotherapies. We also established the proportion of randomly assigned patients who achieved target blood pressure (<140/<90 mm Hg), and the response rates defined as the proportion of patients with systolic blood pressure lower than 140 mm Hg or reduction greater than 20 mm Hg. The proportion of patients with adverse events, and withdrawals, were also summarised by treatment group.

Statistical analysis

We needed a sample size of 988 patients to provide 80% power to detect a 2·5 mm Hg difference in change in systolic blood pressure from baseline at week 24 between the initial combination and combined monotherapy treatment groups. For this calculation we assumed an SD of 14 mm Hg. To allow for a 20% drop-out rate, we aimed to randomly assign 1236 patients. We aimed for 40% of our patients to be naive (ie, never treated). This proportion was deemed sufficiently high to reach conclusions relevant to initial treatment, while being achievable at a level of blood pressure where most patients have previously been started on treatment. Primary outcome was assessed with a repeated measures ANCOVA model. Treatment, visit, treatment by visit interaction, and geographical region were factors in the model and baseline systolic blood pressure was a covariate. Since it was anticipated that the change in blood pressure from baseline would vary from visit to visit across treatment regimens, treatment by visit

	Aliskiren plus amlodipine (N=617)		Aliskiren (N=315)				Amlodipine (N=315)			
	SBP	DBP	SBP	Difference* (95% CI)	DBP	Difference* (95% CI)	SBP	Difference* (95% CI)	DBP	Difference* (95% CI)
Week 0	161·8 (8·4)	92·4 (9·0)	161·2 (8·2)	..	92·1 (10·5)	..	161·0 (8·0)	..	93·0 (9·1)	..
Week 8	140·3 (13·6)	82·4 (9·1)	149·6 (15·0)	−9·6 (−11·3 to −7·8)	86·9 (11·5)	−4·7 (−5·6 to −3·7)	146·7 (13·1)	−6·7 (−8·5 to −5·0)	86·6 (10·0)	−3·8 (−4·8 to −2·8)
Week 16	133·4 (13·8)	78·8 (9·1)	144·7 (15·1)	−11·6 (−13·5 to −9·8)	85·6 (10·1)	−7·0 (−8·1 to −5·9)	140·6 (12·0)	−8·0 (−9·9 to −6·1)	83·9 (8·9)	−4·9 (−6·0 to −3·9)
Week 24	133·5 (12·8)	78·8 (8·7)	134·4 (13·1)	−1·0 (−2·8 to 0·8)	78·8 (9·5)	−0·4 (−1·5 to 0·6)	134·9 (13·3)	−1·9 (−3·7 to 0·0)	80·6 (9·2)	−1·4 (−2·5 to −0·3)
Week 32	134·6 (12·7)	79·6 (8·8)	135 (13·5)	−0·7 (−2·6 to 1·2)	79·3 (8·9)	0·0 (−1·1 to 1·1)	136·2 (13·8)	−2·1 (−4·0 to −0·2)	81·4 (9·0)	−1·3 (−2·5 to −0·2)

Data are mean (SD) or difference (95% CI). N=the number of patients randomly assigned to each initial treatment. SBP=systolic blood pressure. DBP=diastolic blood pressure. *Difference in least squares mean change from baseline between initial combination and each monotherapy.

Table 2: **Absolute blood pressure at each visit and adjusted differences between the reductions on each initial treatment regimen**

	Aliskiren plus amlodipine (N=604)	Aliskiren (N=312)		Amlodipine (N=313)	
Week 8	379 (62·7%)	103 (33·0%)	3·5 (2·61 to 4·68); <0·0001	128 (40·9%)	2·49 (1·87 to 3·31); <0·0001
Week 16	478 (79·1%)	149 (47·8%)	4·19 (3·11 to 5·66); <0·0001	186 (59·4%)	2·63 (1·94 to 3·56); <0·0001
Week 24	465 (77·0%)	232 (74·4%)	1·13 (0·82 to 1·55); 0·47	222 (70·9%)	1·36 (1·00 to 1·87); 0·05
Week 32	465 (77·0%)	230 (73·7%)	1·17 (0·85 to 1·61); 0·35	206 (65·8%)	1·75 (1·28 to 2·38); 0·0004

Data are n (%) or odds ratio (95% CI); p value. Responders achieved a systolic blood pressure less than 140 mm Hg or at least 20 mm Hg reduction in systolic blood pressure from baseline. N=number of patients attending at least one visit after random assignment.

Table 3: **Number of responders in each treatment regimen and their comparison with combination therapy**

	Aliskiren plus amlodipine (N=617)	Aliskiren (N=315)	p value for aliskiren plus amlodipine *vs* aliskiren	Amlodipine (N=315)	p value for aliskiren plus amlodipine *vs* amlodipine
Deaths	0	0	..	0	..
Serious adverse events	14 (2·3)	9 (2·9)	0·66	9 (2·9)	0·66
Any adverse events	410 (66·5)	215 (68·3)	0·61	207 (65·7)	0·83
Peripheral oedema	132 (21·4)	53 (16·8)	0·10	76 (24·1)	0·36
Dizziness	30 (4·9)	11 (3·5)	0·40	12 (3·8)	0·51
Discontinuations due to any adverse event	85 (13·8)	45 (14·3)	0·84	58 (18·4)	0·07
Discontinuations due to peripheral oedema	44 (7·1)	20 (6·3)	0·78	36 (11·4)	0·04*
Potassium					
<3·5 mmol/L	8 (1·4)	4 (1·3)	1·00	6 (2·0)	0·57
>5·5 mmol/L	4 (0·7)	6 (2·0)	0·10	3 (1·0)	0·69
≥6·0 mmol/L	1 (0·2)	1 (0·3)	1·00	0	1·00
Blood urea nitrogen					
>14·28 mmol/L	0	0	..	0	..
Creatinine					
>176·8 umol/L	1 (0·2)	0	1·00	1 (0·3)	1·00

Data are n (rate per 100) or p value. The denominator for adverse events is the number of patients who were randomly assigned and took initial treatment. For laboratory assessments, the denominator is the number of patients with non-missing post-baseline data (583 for aliskiren plus amlodipine, 307 for aliskiren, and 297 for amlodipine). p values were calculated with a two-sided Fisher exact test. *Statistical significance at 0·05 level.

Table 4: **Adverse events and laboratory abnormalities**

interaction was included in the model to best extract the primary result of reduction in blood pressure over weeks 8, 16, and 24. The calculated reductions in blood pressure from baseline and differences between treatment arms are presented as least square means (LSM). The intention-to-treat primary analysis was done for all patients assigned to the initial treatment regimens. Secondary analyses were done on both the intention-to-treat and a prespecified per-protocol set of patients.

All patients gave written informed consent. The protocol was approved by the UK multicentre research ethics committee and research ethical review boards in other countries. A data monitoring committee was deemed unnecessary, since both drugs are licensed for use alone or in combination and no excess adverse events for the combination have been reported in several previous trials.[8,9] This trial is registered with ClinicalTrials.gov, number NCT00797862.

Role of the funding source

The sponsor converted the study and analysis plans, written by the British Hypertension Society (BHS) research working party, into the detailed protocol. Provision of drugs, recruitment of sites, and data collection were done by the sponsor. Data tables completed by the sponsor, and each participant's raw data, were released to all authors. The analysis plan in the protocol was done by the sponsor, and interpretation was by the BHS authors (MJB, GTM, TMM). Two authors (CCP, JZ) are employed by the sponsor. These authors commented on drafts after the first version prepared by the BHS authors, and shared, without modification, all authors' approval of the final version written by the corresponding author. The sponsor had no other input to the paper. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the allocated drugs and doses used in our study and figure 2 shows the trial profile. Table 1 shows the demographic and baseline characteristics of the patients. 812 patients assigned to a treatment group were recruited in Europe (France, Germany, Greece, Switzerland, UK); 247 in Latin America (Costa Rica, Guatemala, Venezuela), 148 in South Africa, and 47 in Canada.

The primary endpoint of mean adjusted reduction in systolic blood pressure from baseline over weeks 8 to 24, was 25·3 mm Hg (SE 0·44) in the initial combination group, and 18·9 mm Hg (0·43) across the monotherapy groups. The LSM difference between groups was –6·5 mm Hg (95% CI –7·7 to –5·3; p<0·0001). At 24 weeks, the reduction in systolic blood pressure was 27·4 (0·55) mm Hg in the initial combination group and 25·9 mm Hg (0·54) across the monotherapy groups. The LSM difference was –1·4 mm Hg (–2·9 to 0·05; p=0·059).

The secondary endpoint of mean adjusted reduction in diastolic blood pressure from baseline over weeks 8 to 24, was 12·4 mm Hg (0·25) in the initial combination group, and 8·7 mm Hg (0·24) in the monotherapy groups. The LSM difference between groups was –3·7 mm Hg (95% CI –4·4 to –3·0; p<0·0001). Initial combination was superior to each individual monotherapy, with LSM differences of –7·4 (–8·9 to –6·0)/–4·0 (–4·8 to –3·2) mm Hg versus aliskiren (p<0·0001), and –5·5 (–7·0 to –4·1)/–3·4 (–4·2 to –2·5) mm Hg versus amlodipine (p<0·0001). For diastolic blood pressure, initial combination was also superior to initial monotherapy at week 24 when all patients were in receipt of the combination. The LSM difference was –0·90 mm Hg (–1·8 to –0·02; p=0·044). Figure 3 shows the unadjusted reductions in blood pressure at each timepoint.

Table 2 shows the absolute systolic and diastolic blood pressures for each regimen at each visit, together with

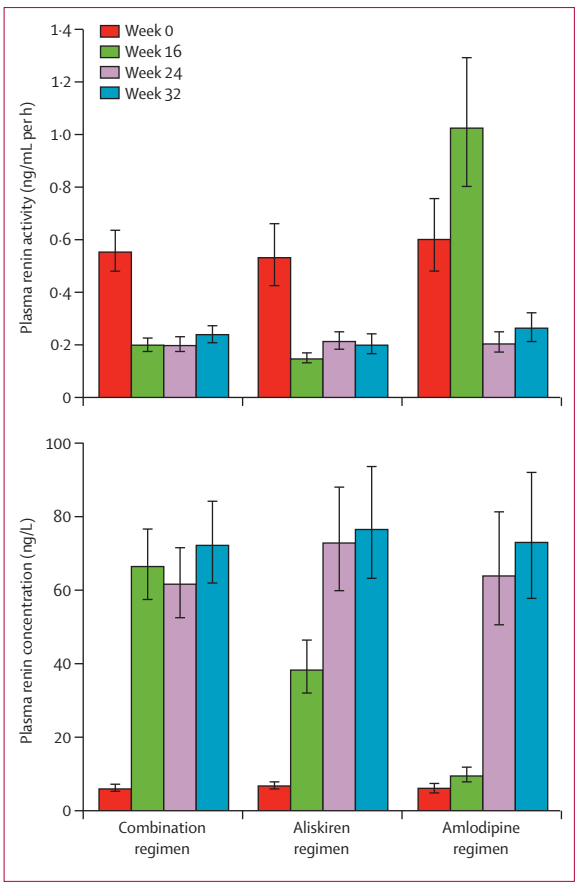

Figure 4: **Plasma renin activity and concentration**
Data are geometric mean (95% CI).

the LSM differences (in reductions from baseline) between initial combination and each of the monotherapy regimens. The efficacy of initial combination in the second half of the study—adjusted reductions of 27·4 (0·55)/13·6 (0·32) mm Hg at 24 weeks and 26·4 (0·57)/13·0 (0·32) mm Hg at 32 weeks—was no greater than sequential aliskiren and then amlodipine, but was numerically superior to sequential amlodipine and then aliskiren, whose reductions were 25·5 (0·78)/12·3 (0·46) mm Hg at 24 weeks and 24·3 (0·82)/11·6 (0·47) mm Hg at 32 weeks.

A similar proportion of patients in each group received hydrochlorothiazide as add-on treatment at 24 weeks: 164 (27%) of 617 on initial combination therapy versus 162 (26%) of 630 on initial monotherapy. Despite the addition of hydrochlorothiazide, a difference in control rates in patients who responded to treatment between initial combination treatment (372 [62%] of 604) and amlodipine (167 [53%] of 313) was recorded at week 32 (p=0·019). This difference was magnified in the planned comparison of responder rates (table 3).

Summary statistics showed a similar reduction in blood pressure by initial combination treatment at 24 weeks in

previously treated patients (28·2/13·4 mm Hg from a baseline of 162·4/92·1 mm Hg) as in naive patients (28·6/14·6 mm Hg from 161·2/93·6 mm Hg). Differential drop out could not be the only explanation for the superiority of initial combination since the same difference was in the per-protocol analysis as in the intention-to-treat dataset: the LSM differences in reduction in blood pressure between the initial combination and amlodipine groups were –1·2 (–3·2 to 0·9; p=0·26)/–1·2 (–2·4 to 0·01; p=0.052) mm Hg at 24 weeks, and –2·1 (–4·2 to 0·00; p=0·050)/–1·3 (–2·5 to –0·1; p=0·037) mm Hg at 32 weeks.

Table 4 lists the adverse events and serious adverse events. Only six serious events were deemed by the investigator as being potentially related to the masked treatment: angio-oedema, cardiac failure, hypertensive crisis, peripheral oedema (in two patients), and sigmoiditis. Peripheral oedema was also the most common adverse event overall (261 patients). It was the commonest reason for withdrawal from therapy, with the 11·4% discontinuation rate from initial amlodipine approaching a two-times excess over the other groups. Hypotension or orthostatic hypotension was reported as an adverse event for five (0·8%) of 583 patients in the combination group, one (0·3%) of 307 in the aliskiren group, and two (0·6%) of 297 in the amlodipine group. Only these last two patients withdrew because of hypotension. Table 4 also summarises the numbers of patients with elevated potassium or renal function indices—there were no withdrawals due to biochemical abnormalities.

Figure 4 shows analyses of plasma renin activity and plasma renin concentration. As expected, the combination therapy and aliskiren reduced initial activity of plasma renin, but increased the concentration. Amlodipine caused a small initial increase in both activity and concentration, but there was no difference in the final values for either measure between the three regimens.

Discussion

Our findings show that patients randomly assigned to initial combination treatment with both aliskiren and amlodipine had substantially better mean blood pressure reduction over the first 24 weeks than did patients starting on either drug as monotherapy, with no cost in adverse events or withdrawals. Once the monotherapy patients progressed to combination therapy, their blood pressure fell towards, but never numerically caught up with, that of the initial combination group. Although the difference in systolic blood pressure between groups after 8 weeks on the combination regimen was less than the pre-trial hypothesis of 2·5 mm Hg, 95% CIs suggest that a sustained difference of this order cannot be excluded. Indeed, for all eight of the point estimates of blood pressure after week 16 (figure 3), and many of the planned secondary endpoints (tables 2 and 3), there was a consistent numerical benefit of starting on the combination regimen. This benefit was substantial by comparison with initial amlodipine, which achieved similar early efficacy as in other studies of monotherapy in patients older than 55 years,[4,6,10] but finished with the highest withdrawal and lowest responder rates. The unadjusted reductions in systolic blood pressure at both weeks 24 and 32 in patients on amlodipine were 2·5 mm Hg less than that in the patients the initial combination regimen (figure 3).

Several previous studies have compared initial combination with monotherapy, but have been short-term, aimed mainly at achieving registration of a fixed-dose combination (panel). In a meta-analysis of 11 000 patients from all trials that compared combination regimens with monotherapy,[7] the average size was 270 patients, followed up for only 6 weeks. Initial combination regimen was five-times more effective in reducing blood pressure than an increase in the dose of single treatment. The meta-analysis did not report on adverse events, and its conclusion that combination therapy should become first-line therapy was unlikely to be realised without reassurance from larger individual studies about the low risk of symptomatic hypotension. Some individual trials within the meta-analysis have shown that the incidence of adverse events from single drugs is not additive.[11,12] The meta-analysis omitted recent trials that compared a combination of calcium channel and angiotensin blockers with the individual drugs; some of these trials were larger than previous comparisons,

***Panel:* Research in context**

Systematic review

Previous randomised controlled trials have compared combination therapy with monotherapy in hypertension. These were reviewed in Wald and colleagues' meta-analysis of 11 000 patients in 42 trials,[7] which shows that the combination treatment is five-times more effective than doubling the dose of a single drug. The trials in the meta-analysis were short-term, average duration 6 weeks, and randomly assigned an average of 270 patients. Few of these patients were previously untreated, and trial treatment was either substituted or added to existing treatment. The meta-analysis did not report adverse events, and the individual trials were too small to assess symptomatic hypotension.

A-priori evidence that initial differences in blood pressure response between randomised treatment regimens might have a long-term influence on control of blood pressure was derived from the review of morbidity and mortality studies in the Blood Pressure Treatment Triallists Collaboration.[5] Two trials, VALUE and ASCOT, were selected because they reported differences in systolic blood pressure greater than 3 mm Hg between groups during the 3 months after random assignment; in these trials, there remained greater than 1 mm Hg difference 4 years later, despite greater eventual use of add-on treatment in the group with poorer initial control.

Interpretation

ACCELERATE is the first trial to test the medium-term efficacy and safety of full doses of two antihypertensive drugs as first-line treatment for patients with a systolic blood pressure greater than 150 mm Hg, by comparison with sequential add-on treatment with the same drugs. Over 6 months, initial combination achieved superior reduction of blood pressure and tolerability, and can be advocated as the preferable treatment strategy to the convention of starting with one drug before the other.

with about 2000 patients studied over 8 weeks.[13,14] But the many permutations of dose left only 150–160 patients in receipt of doses equivalent to those in ACCELERATE. In general, none of the previous trials were designed to detect the longer-term effect of initial treatment, and in particular to detect the outcome of starting with the UK's most widely prescribed first-line antihypertensive drug, amlodipine.

Some guidelines have already recommended the consideration of initial combination treatment: in patients more than 20/10 mm Hg above target blood pressure in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[2] and the use of low-dose combinations in European guidelines.[3] So far, even these muted recommendations have neither been widely practised, nor influenced the licensing of such combinations—because of concern by regulators about the benefit-to-risk ratio of early hypotension. Excluding the double-diuretic combinations, the only combinations licensed in the UK for the initial treatment of hypertension contain β blockers and diuretics. Yet such combinations were inferior to alternatives in the Losartan Intervention For Endpoint reduction (LIFE) study and ASCOT, and are discouraged in UK guidance.[6,15,16] Newer combinations were compared in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[17] which reported serious dizziness in fewer than 1% of 11 500 patients; however, 97% of patients in ACCOMPLISH were previously treated.We believe that ACCELERATE, with more than 500 newly diagnosed patients, will reassure physicians and guideline committees of the safety of even full-dose initial combination, and lead to the preference of this option in view of early and sustained superiority. We randomly assigned patients with a systolic blood pressure of 150 mm Hg or greater (median 160 mm Hg) so that half the patients recruited had blood pressure of less than 20 mm Hg above target—the threshold value for consideration of initial combination therapy in JNC 7. Despite our use of usual starting doses of each drug, doubled after 8 weeks, hypotension was rare, and led to withdrawal of only two patients from the amlodipine monotherapy group. With enough patients to compare withdrawal rates, not only does the combination of these drugs not combine the incidence of adverse events, but also the pattern is in the opposite direction. The cumulative withdrawal rate, due to adverse events, was 13·8% in the initial combination treated group, compared with 16·3% in the monotherapy groups.

Previous studies have suggested that blockers of the renin-angiotensin system reduce peripheral oedema, an adverse effect of dihydropyridine calcium channel blockers, maybe because postcapillary venular dilatation reduces the effect of precapillary sphincter dilatation upon intracapillary hydrostatic pressure.[18–20] The new finding in ACCELERATE is that serious ankle oedema (that led to withdrawal) was almost twice as common in the patients that received amlodipine before aliskiren, than in those that received aliskiren before or with amlodipine.

Although reassurance about tolerability and safety is a necessary precondition for starting combination treatment, the principal motivation derives from the improved effectiveness. The large mean difference in blood pressure (6·5/3·7 mm Hg during the first 6 months) between maximum doses of combination treatment compared with monotherapy was even greater than the 3·8/2·2 mm Hg difference between groups over the first 3 months in the VALUE study.[4] This difference was associated with almost two-times excess risk of stroke, 75% excess of all primary endpoints, and an almost three-times increase in mortality.[4] Our population was not selected for risk of cardiovascular endpoints, and ACCELERATE was not powered for these endpoints. But hypertension behaves as a quantitative trait, and we would be surprised if the rate of blood pressure reduction were not a substantial quantitative influence on outcome.[5,21,22] So, with absence of evidence of adverse symptoms developing into evidence of absence, the issue now becomes the lowering of blood pressure as quickly as possible once the diagnosis of hypertension is secure.

Our study was designed to detect both early and late superiority of combination therapy—ie, before and after all patients received combination treatment. The unusual trial design, and use of sequential co-primary endpoints, allowed us to explore the interesting and previously untested biological hypothesis, of compensatory response to treatment, without splitting the α value between the two primary hypotheses. Essential to our design, by contrast with previous studies, was that the co-primary endpoint was measured at a time when all patients in the trial had been force-titrated to maximum doses of the same two drugs to detect the effect of initial not current treatmtent;[23] and to confirm this effect by showing a continuation of any difference until the study end after a further 8 weeks. During this extension, add-on treatment was allowed in patients whose blood pressure remained above target despite use of two drugs. Although the late superiority of initial combination treatment was just less than postulated, it is enough—especially the 2/1 mm Hg compared with initial amlodipine—to imply that choice of initial treatment does have a lasting effect. In prospective studies a 2/1 mm Hg difference substantially increases risk, and blood pressure reductions from any starting level proportionally reverse this risk.[21,24] Both the large-early and smaller-sustained superiority of combination will probably influence guidelines. Meanwhile, physicians will note that their current first-choice drug, amlodipine, achieves lower blood pressures, and almost half the risk of severe ankle oedema, if started in combination rather than alone.

The idea that we might find a sustained difference between initial and sequential combination strategies arose from long-term trials in which later add-on treatment was unable to fully eliminate a substantial early deficit in blood pressure control.[4,6] The expectation of compensatory responses to single drugs is in part a theoretical one that stems from the physical equation of pressure with force over area, and consequent requirement for increased pressure to entail either an increase in volume of blood in the circulation, or reduction in the diameter of resistant arteries.[25,26] Most antihypertensive drugs are directed selectively at vasoconstriction or volume, and some compensatory responses are not controversial, such as the rise in plasma renin on diuretics.[10,25,27,28] Calcium channel blockers stimulate both renin-angiotensin system and sympathetic activity, and these might contribute to the lower efficacy and tolerability of amlodipine when started before aliskiren in ACCELERATE.[29]

The co-primary hypotheses addressed the general principle that starting treatment with two complementary drugs would achieve superior control of blood pressure compared with the conventional strategy of monotherapy before dual therapy treatment. However, ACCELERATE studied two specific drugs, and the degree of renin-angiotensin system activation by calcium channel blockers (figure 4) is generally less than with diuretics. A replication study is therefore in progress—a British Heart Foundation funded comparison of initial losartan plus hydrochlorothiazide versus initial monotherapy in 600 patients that will report in 2013. Another weakness is that, as with all new treatments, very rare side-effects of initial combination therapy might emerge only after entering common use. A further limitation is that ACCELERATE was done in a defined, predominantly white population who remained eligible after placebo run-in. Finally, the outcomes of ACCELERATE were blood-pressure changes, which are generally accepted surrogates for cardiovascular outcome. An adequately-powered outcome study is unlikely to be either practical or affordable. In our replication study, cardiac MRI is being used to compare reduction of left-ventricular mass after 1 year in the two groups.

A move towards routine initial reduction of blood pressure with combination therapy can now be advocated.

Contributors

MJB, GM, and TM represented the British Hypertension Society (BHS) Research Working Party, chaired by MJB. The trial concept and design originated with the BHS authors, who also reviewed and agreed the full protocol and analysis plan, wrote the draft report, and did subsequent revisions after discussion with coauthors. MJB wrote the final draft of the report. CC wrote the statistical plan, in discussion with MJB, GM, and TM, and did the planned analyses. JZ participated in the study planning meetings, oversaw conversion of the study plan into the full protocol, and was responsible for recruitment of sites and implementation of the protocol. All authors participated in discussion of the results, and contributed to the writing of the report.

Conflicts of interest

MJB has served on an advisory board for and received an honorarium, travel expenses, and lecture fees from Novartis. GTM has received consultancy fees, lecture fees, and travel expenses from Novartis. TMM has received an honorarium, consultancy fees, and travel expenses from Novartis. JZ and CCP are employees of Novartis.

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