Side-effects and tolerability of combination blood pressure lowering according to blood pressure levels – an analysis of the PROGRESS and ADVANCE trials

Short title: Tolerability of combination BP lowering

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Abstract

Objective

To measure the placebo-controlled effects of combination therapy on hypotension, treatment discontinuation and major renal outcomes, according to baseline blood pressure.

Methods

We conducted an analysis of the ADVANCE and PROGRESS trials, including 14,684 participants allocated combination therapy or placebo. The mean age was 65 years, 61% were male and 64% were receiving background blood pressure lowering therapy. Participants were stratified into five subgroups by baseline systolic blood pressure (SBP) <120mmHg, 120-129mmHg, 130-139mmHg, 140-159mmHg, and ≥160mmHg. Discontinuation of study treatment during the active run-in phase and post-randomization follow-up was assessed for hypotension/dizziness and other causes. Major renal outcomes (sustained doubling in creatinine or renal death) were also assessed.

Results

Discontinuation during the 4-6-week active run-in phase due to hypotension/dizziness ranged from 3.6% in those with SBP<120mmHg to 1.3% in those with SBP≥160mmHg. Median follow-up in the randomized phase was 5.6 years, and discontinuation for hypotension was higher with combination therapy compared to placebo in the <120mmHg group (4.7% vs. 1.2%). However, for each subgroup with baseline SBP 120-129, 130-139 and 140-159mmHg the absolute excess of discontinuation due to hypotension with combination therapy was 0.7%. Total discontinuations were only increased in the <120mmHg group (18.4% vs. 12.5%) and the 120-129mmHg subgroup

(17.6% vs. 14.2%). There were no clear differences across the SBP subgroups for the combined renal outcome (overall, 0.8% vs. 0.6%).

Conclusion

Compared to those with baseline SBP140-159mmHg, side-effects of dual combination blood-pressure lowering are essentially the same for people with SBP130-139mmHg and only modestly increased among patients with SBP120-129mmHg. During long-term therapy, side-effects sufficient to stop treatment that are treatment related (i.e. occur in excess of rates seen with placebo) occur at <0.5%/year in patients with baseline SBP120-139mmHg. These results have important implications in assessing the likely balance of benefits and side-effects of blood-pressure lowering with combination therapy among those with SBP120-139mmHg.

Key words:

Blood pressure, combination therapy, tolerability, hypotension, cough, discontinuation

Introduction

Combination blood-pressure lowering therapy provides greater blood pressure reduction than monotherapy and therefore greater reductions in major cardiovascular events.[1,2] Combination therapy has been a central component of trials that successfully achieved blood pressure targets for most patients.[3,4] One concern however is that combination therapy produces higher rates of adverse effects, particularly among those with baseline systolic blood pressure below 140mmHg. For example, an increase in hypotension and some renal outcomes were reported in the SPRINT[4] and ACCORD[5] trials, which both compared 120 mmHg vs. 140mmHg systolic blood pressure goals. However, these trials were unblinded and involved more titration visits in the intensive care group, leading to the possibility of differential rates of detection and reporting of side-effects. Placebo control is ideal to obtain unbiased estimates of side-effects. The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE)[6] and the perindopril protection against recurrent stroke study (PROGRESS)[7] are two long-term placebo controlled trials of fixed dose combination therapy that recruited participants with a wide range of blood pressure levels and therefore provide a unique opportunity to investigate side-effects of combination therapy according to baseline blood pressure levels.

Methods

We conducted an analysis of two large, long-term randomized double-blind placebo-controlled multi-center trials, ADVANCE and PROGRESS.

ADVANCE and PROGRESS trial methods

The design and main results of the ADVANCE trial have been published elsewhere.[8] Briefly, the ADVANCE trial was a multinational, randomized, double-blind controlled trial

of perindopril plus indapamide versus placebo in people with type 2 diabetes mellitus aged over 55 years with at least one other cardiovascular risk factor. Existing treatments were continued, with the exception of ACE-inhibition which was withdrawn with optional open-label perindopril offered in its place. There was a 6-week active run-in on perindopril 2mg plus indapamide 0.625mg. After randomization, participants received a fixed dose combination of perindopril 2mg plus indapamide 0.625mg for the first three months, then 4mg/1.25mg thereafter. Follow-up visits were at 3, 4, and 6 months, then every 6 months up to five years, with additional information collected during 2 and 4 years' follow-up visits.[6] Those receiving active treatment had reductions in macro- and microvascular events, cardiovascular death and all-cause death.[6]

The PROGRESS study design and main results have been published previously.[7,9] PROGRESS was also a randomized, double-blind, controlled trial of perindopril 4mg, with the option of adding indapamide 2.5mg (2mg in Japan), versus placebo in people with a history of stroke or transient ischemic attack, with no definite indication for or against treatment with angiotensin converting enzyme inhibitors. Those with uncontrolled hypertension were recommended non-ACE-inhibitor antihypertensive therapy before entry in the trial. There was a 4-week active run-in, with two weeks on 2mg perindopril followed by another 2 weeks of 4mg perindopril. The study clinician allocated patients to the combination therapy or monotherapy arms before patients were randomized to active therapy or placebo. Only the former group are included in the primary analyses here. There were five study visits in the first year, with follow-up visits every six months after that up to four-and-a-half years' follow-up. Those receiving active treatment had reductions in stroke and major vascular events.[7]

Outcomes

The discontinuation outcomes are cessation of study treatment due to hypotension/dizziness, cough, or other reasons during pre-randomization active run-in phase and during post-randomization long-term follow-up. Major renal outcomes were defined as participants experiencing sustained (i.e. still present at end-of-study or on final recorded measure) doubling in creatinine or death due to renal cause.

Statistical Analysis

Individual patient data were analyzed. The sample for this analysis included participants receiving combination therapy or placebo: all participants in ADVANCE and the participants allocated combination therapy or double placebo in PROGRESS. Participants were stratified into five groups by baseline SBP <120mmHg, 120-129mmHg, 130-139mmHg, 140-159mmHg, and ≥160mmHg, with baseline defined as the registration visit.

Mean difference in BP between active and placebo during the randomized trial period was estimated using three linear mixed models. Models were fitted for ADVANCE and PROGRESS separately in which treatment effect, SBP categories, and their interactions were included. The overall model included treatment, SBP category, their interactions, and study as covariates. The BP measurements used were at randomization, at 3, 6, 12 months after randomization and every 6 months thereafter to the end of the study, where both ADVANCE and PROGRESS had measurements.

The discontinuation of treatment was evaluated according to baseline SBP categories during the run-in period as well as during the following randomized period using the logistic regression model. Discontinuation during run-in for hypotension/dizziness,

cough, and other reasons were compared across the five BP categories in the models adjusted for study, with p-value for trend per one SBP category increase. The effect of randomised treatment on discontinuation was compared across SBP category and in the group with baseline SBP<120mmHg and SBP 120-129mmHg individually, wherein the adjustment was made for study, SBP category, treatment, and interaction of SBP category and for study, respectively. The trend in stopping study treatment to initiate open label therapy by SBP category was investigated in the study adjusted model. Subgroup analysis was performed for the treatment effects on BP reduction and the proportion of discontinuation by age groups (<60, 60 to <75, and ≥75 years), by sex (men/women), by diabetic status (diabetic/non-diabetic), by prior experience of coronary heart disease (CHD) and stroke (presence/absence), by baseline use of antihypertensive agents other than study medication (presence/absence), and by study (ADVANCE/PROGRESS).

Pooled hazard ratios were calculated by combining ADVANCE and PROGRESS data for all major cardiovascular events and all-cause mortality. The subgroup-specific effects of blood pressure lowering on major cardiovascular events and all-cause mortality were also estimated using Cox proportional hazards model stratified by study where treatment effect, index subgroup and their interaction were included. Relative risk of sustained doubling of creatinine was calculated using log-binomial model for all participants. Two-tailed tests were used.

All statistical analyses conducted using SAS version 9.3 and SAS Enterprise Guide 5.1 software (SAS Institute, Cary, New Carolina, USA). Statistical significance was set at the 5% level.

Results

Study population

Combining the ADVANCE and PROGRESS trial participants receiving combination therapy provided a sample size of 14,684 participants (11,140 from ADVANCE and 3,544 from PROGRESS). Mean blood pressure at baseline for the combined sample was 146/82mmHg, mean age was 65 years, and 61% were male (Table 1). Approximately 79% of the study sample had diabetes, 22% had Stage 3 or greater chronic kidney disease (estimated glomerular filtration rate [eGFR] <60), 27% had cerebrovascular disease and 17% had CHD. The mean difference in blood pressure between the active and placebo groups was -5.5/-2.4mmHg (<120mmHg -5.5/-2.9, 120-129mmHg -5.0/-2.7, 130-139mmHg -5.6/-2.1, 140-159mmHg -5.2/-2.1, ≥160mmHg -6.1/-2.3). The blood pressure reduction achieved in PROGRESS was greater than that in ADVANCE (-10.0/-4.7 vs. -5.3/-2.1mmHg).

Discontinuation

Figure 1 shows the proportion of participants in each category who entered the active run-in phase of the study. This includes all ADVANCE and all PROGRESS participants, including those later randomized to monotherapy. Six participants (0.2%) were not randomized due to serious adverse events (SAEs; PROGRESS: 1 hypotension, 2 dizziness; ADVANCE: 1 hypotension, 2 dizziness; all baseline BP>130mmHg). Discontinuation due to hypotension/dizziness ranged from 3.6% in those with SBP<120 mmHg to 1.3% in those with SBP≥160mHg ($p<0.01$ for heterogeneity). Overall 2.6% discontinued due to cough, with rates not varying by BP level ($p=0.36$ for trend). Other reasons for discontinuation were higher in those with SBP<130mmHg than in those with SBP>130mmHg ($p<0.01$ for trend).

Discontinuation in the randomized follow-up phase is shown in Figure 2, overall and by study in Web Figure 1. Discontinuation due to hypotension was almost four-fold higher in active compared to placebo in the <120mmHg group (4.7% active vs. 1.2% placebo, p=0.039), this translates to an excess of 0.9% per year in the combination group. There was no clear difference in the rates of discontinuation due to hypotension in the combination versus placebo groups across the blood pressure 120-129, 130-139 and 140-159mmHg categories (p=0.07 for interaction trend); each with an absolute increase of 0.7% over all follow-up, i.e. <0.2% per year. There was no difference between active and placebo in discontinuation due to hypotension in the ≥160mmHg group.

An alternative way of reporting these data is to consider the likelihood that hypotension occurring while on treatment is due to that treatment. For the <120mmHg group, 80% of all discontinuations due to hypotension occurred in the active group i.e. if someone develops hypotension while on treatment, there is a 4:1 chance that it is due to active treatment. However, for the 120-159 groups, 67-73% of all discontinuations due to hypotension were in the active group i.e. if someone develops hypotension while on treatment there is a 2:1 or 3:1 chance it is due to active treatment.

There was a positive association between baseline blood pressure and stopping for reasons other than cough or hypotension – this appeared to be at least in part to stopping of study medication and initiation of open label blood pressure lowering therapy, as the proportion of patients who stopped study treatment and were on open-label BP lowering at the end of follow-up were 8.8%, 10.4%, 11.1%, 13.1% and 15.1% in the <120, 120-129, 130-139, 140-159 and ≥160mmHg groups respectively (p<0.01 for trend). Overall, there was an excess of discontinuation for any reason in the active group only in those with SBP <130mmHg. In absolute terms, this amounted to an excess discontinuation

rate of active over placebo of 1.3% per year in those <120 mmHg (p<0.01) and 0.8% per year in the 120-129 mmHg group (p=0.045).

Subgroup analyses for discontinuation are shown in Table 2. There were similar blood pressure changes between patients aged <60 years, 60 to <75 years, and those aged ≥75 years (-6.0/-2.4 vs. -6.0/-2.2 vs. -6.8/-2.3mmHg) but greater variation between other subgroups. The absolute excess of discontinuation for any reason in the active versus placebo groups was greatest in the previously untreated and prior CHD groups, among whom the excess was over 2% over the course of the trial. Among patients aged under 60 years, there were fewer patients discontinued from active treatment than from placebo (11.6% vs. 15.2%, p=0.03).

Renal outcomes

There were few renal events, with less than 1% of the sample experiencing doubling of creatinine >200µmol/L or renal death. The incidence of major renal events in combination versus placebo groups were 0.8% vs. 0.6% (RR 1.33, 0.89-1.97, p=0.16). Overall, 44 patients receiving active combination therapy and 27 receiving placebo experienced a sustained doubling in creatinine to >200 µmol/l (0.6% vs. 0.4%, RR 1.64, 1.02-2.64, p=0.043). There were 32 renal deaths in total, 16 in the active group and 16 in placebo (Web Table 1). Most events occurred in those with baseline SBP ≥160mmHg: active, 1.1% (n=19) active: placebo, 0.9% (n=16).

Cardiovascular outcomes

Combination therapy reduced major cardiovascular events (9.7% vs. 12.1%; HR 0.79, 0.71-0.87) and total mortality (7.7% vs. 9.0%; HR 0.85, 0.76-0.95), with no clear difference in effects by baseline BP, age, and sex. While there was no heterogeneity by baseline BP level, there was a borderline significant reduction in major cardiovascular

events for patients with baseline SBP 120-139mmHg, 191 (8.6%) vs. 232 (10.3%) (HR 0.81, 0.67-0.99, p=0.036), whereas for those with baseline SBP <120mmHg major CV events were 50 (7.4%) vs. 38 (5.9%) (HR1.28, 0.84-1.35, p=0.25).

Discussion

This is the first analysis, to our knowledge, to assess discontinuation rates with combination therapy compared to placebo, according to baseline blood pressure levels. The results show little or no difference in the discontinuation rates due to hypotension or other reasons among patients with SBP 120-139mmHg as compared to those with 140-159mmHg. Among patients with baseline SBP <120mmHg, combination therapy led to a fourfold increase in discontinuation due to hypotension (4.7% vs. 1.2% over 5.6 years), while among patients with SBP over 160mmHg there was no clear difference (0.6% vs. 0.6%). Major renal outcomes were rare in both treated and control groups.

Several strengths and weaknesses of this analysis should be considered. A strength is the use of placebo-control, which is particularly important for reliable attribution of symptomatic outcomes, such as hypotension. Furthermore, follow-up visits occurred at the same frequency in active and placebo groups, minimizing the chance of detection bias. There was a large sample size with over 14,500 participants in total. Finally, individual-level data were available, allowing detailed subgroup analyses. In terms of limitations, these analyses were post-hoc and, due to the trial entry criteria, the participants have a higher prevalence of diabetes, stroke, and coronary heart disease than a typical clinical hypertension population. Many were already receiving blood-pressure lowering treatment, and therefore the baseline blood pressure is not an untreated baseline. There was some heterogeneity between the two studies, in terms of the doses of agents used and the blood pressure reductions achieved. Furthermore, the

long-term results only apply to the 80-85% of people who completed an active run-in – while for most patients the reasons for not continuing to randomization related to non-adherence to trial procedures or patient reconsideration of participation, for a minority of patients it was due to early side-effects and lack of tolerability. Finally, classification of main reason for stopping treatment may not be accurate in all cases, and in a blinded clinical trial sometimes study treatment is stopped in order to initiate open-label therapy.

Consideration should be given to these results in the light of previous randomized evidence on tolerability and adverse effects of blood pressure lowering. The recently reported HOPE3 trial is the only other trial to report data on the long-term tolerability of combination BP lowering compared to placebo.[10] In HOPE3, as with ADVANCE and PROGRESS, there were no BP entry criteria and mean baseline BP was 138/82mmHg.[10] The tolerability findings in HOPE3 were very similar to those reported here. Overall in HOPE3 13.5% were excluded after an active run-in of candesartan16mg, hydrochlorthiazide12.5mg and rosuvastatin 10mg, with 1.9% excluded for hypotension. Over a median follow-up of 5.6 years, there was a 6/3mmHg average BP difference and an increase in discontinuation due to dizziness/lightheadedness/hypotension of 217 (3.4%; active) vs. 130 (2.0%; placebo) – this equates to an annual excess discontinuation rate for hypotension of around 0.3% per year which is similar to the 0.12% per year observed overall for this analysis. Renal outcomes were reported as renal dysfunction or abnormalities in the serum potassium level (32 [0.5%] vs.20 [0.3%], P= 0.13) and renal dialysis or transplantation (2 vs. 4 patients).

Of the three long-term placebo-controlled trials of combination therapy the two reviewed here (ADVANCE and PROGRESS) evaluated angiotensin-converting-enzyme inhibitor (ACE-I) and thiazide-like diuretic, and HOPE3 evaluated an angiotensin receptor blocker (ARB) and a thiazide diuretic. It is uncertain if other combinations would be more or less

tolerable than these regimens given the lack of long-term randomized comparisons. The only long-term randomized trial comparing two different combinations in which all participants received combination therapy reported no difference in side effects for ACE-I and CCB compared to ACE-I and thiazide.[11] Another large trial reported that a strategy of ACE-I plus as-needed CCB had fewer side effects than a strategy of beta-blocker plus as-needed thiazide.[12]

More broadly, the main potential adverse outcomes from intensive blood pressure lowering that have been discussed in the literature are cardiovascular events, falls and fractures, symptomatic hypotension, and acute kidney injury. A paradoxical increase in cardiovascular events with blood pressure lowering in those with average or below average blood pressure has been termed the "J-curve" phenomenon. The current results were underpowered at lower SBP levels and unable to differentiate between a moderate increase or decrease in cardiovascular events. A 6mmHg SBP difference would be expected to confer a 15% reduction in major cardiovascular events, which in turn requires around 1,000 events to assess reliably. However, a systematic review of all randomized trials indicates benefits for trials with mean baseline SBP 130-139mmHg[13] (major cardiovascular events 11.4% vs. 12.4%, $p<0.001$ with over 10,000 events in these trials) and in those with mean baseline SBP <130mmHg (major cardiovascular events 11.9% vs. 13.7%, $p<0.001$ with over 1,000 events in these trials); and two large recent trials with much larger BP reductions at lower BP levels ruled out any major increase in cardiovascular events, indeed tended to show the opposite.[3,4,13] The present analysis could not assess fractures or falls, but recent randomized trials have shown no increase in fractures or falls with active blood pressure lowering.[4,14] Although there are few data in the frail elderly, the largest trial in the very elderly did not identify frailty as a major effect modifier.[15]

While blood pressure lowering and in particular ACE-I and ARBs have an established role in preventing kidney failure in patients with proteinuric chronic renal failure,[16,17] the effects of blood pressure lowering on incidence of chronic renal failure among patients with preserved renal function remains uncertain. There is an established short-term, reversible increase in creatinine levels with BP lowering, particularly with ACEI and ARBs. This effect is due to reduced glomerular perfusion pressure, which is thought to mediate the reduction in renal failure among people with increased intraglomerular pressure (manifested clinically as proteinuria) with intensive BP lowering.[17] Among patients with preserved renal function increases in creatinine, including increased rates of acute kidney injury, are seen with intensive BP lowering[4,5,18] and in this analysis there was a small excess (0.5% vs 0.3%, p=0.04) in sustained doubling in serum creatinine overall. However, BP lowering also reduced proteinuria in ADVANCE,[19] a benefit also seen in ACCORD and SPRINT.[4,5] Very few incident renal failure events were observed in this analysis or in other trials of patients without renal failure at baseline and it remains uncertain whether long-term blood pressure lowering increases or decreases incidence of chronic renal failure.[10,20]

Finally, in terms of symptomatic hypotension, which is the most common side-effect of blood pressure lowering, it is informative to compare these results with previous trials that achieved larger blood pressure reductions. In SPRINT and ACCORD[4,5], a more intensive blood pressure reduction regimen was implemented with mandatory additional visits and up-titration until blood pressure targets were met, or no further up-titration was planned. This approach led to a blood pressure separation that was about double that seen in PROGRESS and ADVANCE overall and in HOPE3. There was therefore a higher incidence of hypotensive side-effects in SPRINT and ACCORD (e.g. in SPRINT,[4] hypotension SAEs were 3.3% vs. 2.0% and syncope SAEs were 3.4% vs. 2.3%). However, there was also evidence of a greater cardiovascular event reduction with

greater blood pressure reduction, at least in terms of stroke and heart failure,[4,5,21] which is consistent with previous trials.[20,22]

Conclusion

Rational therapy involves balancing benefits and adverse effects. Such decisions must be guided by clinical trial data for preventive measures such as blood pressure lowering, since it is impossible at a clinical level to identify prevented events and there is a tendency to over-ascribe adverse outcomes to study treatment, when sometimes they would have occurred anyway.[23,24] While the benefits of blood pressure lowering in high risk patients have been well established,[13] and the increased risks associated with discontinuation are clear,[25] there have been comparatively much fewer data on side-effects, particularly placebo-controlled data. The present results suggest that combination blood pressure lowering among people with SBP 120-139mmHg has a similar side-effect profile compared to those with SBP 140-159mmHg, with symptomatic hypotension sufficient to warrant treatment withdrawal occurring in up to 5% in the first month and then at <0.5% per year thereafter. The clinical challenge therefore is to identify patients at sufficiently high risk for whom the benefits of blood pressure lowering outweigh these small but significant excesses of side-effects.

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