Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial

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Objective **To explore the likely optimum blood pressure (BP) level for patients with a history of cerebrovascular disease.**

Methods **The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in 6105 patients with cerebrovascular disease. The present study comprises two series of post hoc analyses. The first was designed to investigate the effects of randomized treatment on recurrent stroke by baseline BP levels, and the second was a corresponding observational analysis investigating the association between achieved follow-up BP levels and recurrent stroke risk.**

Results **Analyses of the randomized treatment comparisons showed that BP lowering with combination therapy produced similar risk reductions in each of four subgroups defined by baseline BP of less than 120, 120–139, 140–159, and 160 mmHg or greater (*P* homogeneity = 0.5). The effects of single-drug therapy were also comparable across these subgroups (*P* homogeneity = 0.2), but consistently greater benefits were observed with combination compared to single-drug therapy. The analyses of achieved follow-up BP showed that the lowest risk of recurrence was among the one-quarter of participants with the lowest follow-up BP levels (median 112/72 mmHg), and that risks rose progressively with higher follow-up BP levels. Minor side-effects were progressively more common at lower BP levels (*P* homogeneity = 0.04), but there was no excess of serious complications (all *P* homogeneity > 0.2).**

Conclusion **These analyses provide no evidence of a J-curve relationship between BP level and stroke risk among patients with cerebrovascular disease, and identify no patient group among whom more intensive BP lowering would not be expected to produce greater risk reductions. *J Hypertens* 24:1201–1208 © 2006 Lippincott Williams & Wilkins.**

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Conflict of interest: J.C. and S.M. have received research grants from Servier, as chief investigators for PROGRESS and ADVANCE administered by the University of Sydney. J.C., M.W., C.A., A.R., S.M., and B.N. have received honoraria from Servier for presentations regarding the study at scientific meetings.

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Introduction

Despite clear evidence that blood pressure (BP) lowering is effective for secondary prevention in patients with cerebrovascular disease [1–3] there is significant uncertainty about the optimal target BP in this population. This is a consequence of apparently conflicting epidemiological data suggesting either benefit [4–6] or harm [7] from low BP levels after stroke, together with an absence of randomized data addressing the question of the optimal level to which BP should be reduced. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed the benefits of BP lowering for the prevention of stroke in patients with cerebrovascular disease and a wide range of entry BP levels [1,3]. Subsidiary analyses of this study have already demonstrated that both hypertensive and non-hypertensive patients achieved comparable benefits [1,8]. We provide here more detailed information about the effects of randomized treatment at lower baseline BP levels, and report the findings of new observational analyses designed to identify what might be the optimum BP target for maximum risk reduction in this high-risk group.

Methods

Study design and participants

The design of PROGRESS has been described in detail elsewhere [1]. Briefly, 6105 participants were recruited between May 1995 and November 1997. Participants were

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eligible if they had a history of a cerebrovascular event (stroke or transient ischaemic attack but not subarachnoid haemorrhage) within the previous 5 years. In addition, participants were required to have no clear indication for, or contraindication to, treatment with an angiotensin-converting enzyme inhibitor. Given previous epidemiological data showing a linear reduction in stroke rates with lower BP values among both 'hypertensive' and 'normotensive' individuals [4], there were no BP criteria for entry into PROGRESS. The institutional ethics committee of each collaborating centre approved the trial and all participants provided written, informed consent.

Randomized treatment

In the PROGRESS trial, participants who tolerated at least 4 weeks of run-in therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or placebo. Active treatment comprised a flexible regimen based on perindopril (4 mg a day), with the addition of indapamide (2.5 mg a day, or 2 mg a day in Japan) in those participants for whom the responsible study physician felt that there was no specific indication for, nor contraindication to, the use of a diuretic. Those participants assigned placebo received tablets identical in appearance to the active agent(s).

Follow-up

In the year of randomization, participants were seen on seven occasions (entry, randomization, and at 1, 3, 6, 9, and 12 months after randomization). In the second and subsequent years, follow-up was 6-monthly. Mean participant follow-up was 3.9 years.

Blood pressure measurements

Blood pressure was measured in duplicate, with an interval of at least 2 min, to the nearest 2 mmHg after 5 min of quiet rest in the seated position using a standard mercury sphygmomanometer. BP recordings were made at every visit and the mean of the two measurements was used. Groups of participants defined by the same four systolic blood pressure (SBP) ranges (< 120, 120–139, 140–159, and ≥ 160 mmHg) were used for both the analyses by baseline BP levels and the analyses by achieved follow-up BP levels.

Outcomes

The primary outcome of the present investigation was total stroke. Stroke was defined according to standard criteria [9] (codes 431, 433, 434, 436, and 437 in the 9th revision of the International Classification of Diseases). Strokes were subclassified into ischaemic and haemorrhagic stroke according to the International Classification of Diseases 9th revision codes, following review and validation by an endpoint adjudication committee [1]. Secondary outcomes for the present analyses included major vascular events (non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause), deaths, hospital admissions, and discontinuation of study treatment (premature discontinuation of all study tablets before the end of scheduled follow-up or death). Only the first event of the relevant outcome type was included in each analysis.

Statistical analysis

Effects of randomized treatment in participant subgroups defined by baseline blood pressure levels

The effects of randomized treatment on stroke, major vascular events, death, and hospitalization were calculated using univariate Cox's proportional hazards models according to the principle of intention-to-treat. The effects of randomized treatment on premature discontinuation of study treatment were analysed using logistic regression models, because no specific date of onset was available for this outcome. The mean reductions in BP achieved with randomized treatment were estimated using linear mixed models. Comparisons of treatment effects across the four participant groups, defined on the basis of baseline BP, were performed by adding an interaction term to identify any trend of treatment effect across the groups. Percentage risk reductions were calculated as $[(1 - \text{hazard ratio}) \times 100]$.

Associations of achieved follow-up blood pressure levels with stroke risk

A pooling of repeated observations method was used [10,11]. In brief, each participant's follow-up was divided into a series of intervals defined by the follow-up visits. For each interval the BP level recorded at the visit performed at the commencement of the interval was assigned and the presence or absence of the relevant outcome event during the interval was documented. Missing follow-up BP values were imputed by using the BP level recorded in the previous interval. The 6105 participants generated 63 395 intervals with follow-up SBP levels for the intervals ranging from 74 to 242 mmHg. The intervals were divided into the four achieved follow-up BP groups specified and the annualized rate of each type of outcome event in each achieved follow-up BP group was estimated using a Poisson linear regression model including age, sex, current smoking, diabetes, randomized study treatment, and planned use of combination therapy as covariates [12]. Comparisons of event rates across the four achieved follow-up BP groups were made by fitting a model with a linear term for achieved follow-up BP [12]. The constancy of the relationship of achieved follow-up BP level with events in different subgroups of participants (for example active compared with placebo-treated individuals) was evaluated by adding an interaction term to the model.

Results

Baseline characteristics

The characteristics of the four participant subgroups defined by baseline SBP levels of less than 120, 120–139,

Table 1 Baseline characteristics according to baseline systolic blood pressure levels

	SBP (mmHg)			
	< 120 ($n = 350$)	120–139 ($n = 1787$)	140–159 ($n = 2396$)	≥ 160 ($n = 1572$)
Demographic				
Mean age (years) (SD)	60 (10)	62 (10)	65 (9)	66 (9)
Women (%)	29	27	30	35
Asian[a] (%)	46	44	36	34
Cerebrovascular disease history				
Ischaemic stroke (%)	66	70	71	72
Haemorrhagic stroke (%)	13	11	11	9
Stroke of unknown type (%)	5	4	5	5
TIA (%)	25	23	22	22
Median time since qualifying event, months (interquartile interval)	11 (4–24)	10 (4–23)	9 (4–23)	8 (4–19)
Other medical history (%)				
Current smoker	25	21	19	19
Diabetes	9	11	13	15
CHD[b]	18	16	15	17
Carotid disease[c]	2	4	5	5
Blood pressure				
Median SBP (mmHg) (interquartile interval)	114 (110–118)	130 (126–135)	149 (143–153)	169 (162–178)
Median DBP (mmHg) (interquartile interval)	73 (69–79)	80 (75–87)	88 (80–92)	92 (85–100)
Medication (%)				
Antihypertensive therapy[d]	31	42	52	61
Antiplatelet therapy	67	72	72	74
Oral anticoagulants	13	9	10	8
Lipid-lowering therapy	16	16	14	12
Study treatment regimen (%)				
Active treatment	50	50	50	50
Combination therapy or double placebos	42	53	58	68

CHD, Coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack. [a]Participants recruited from People's Republic of China or Japan. [b]History of myocardial infarction or coronary revascularization, or angina (supported by documented electrocardiographic or angiographic evidence). [c]Previous carotid endarterectomy, previous carotid angioplasty or carotid stenosis greater than 50% (confirmed by angiogram or Doppler). [d]Currently treated hypertension.

140–159, and 160 mmHg or greater are summarized in Table 1. The participant subgroups with higher baseline SBP levels were older and more likely to be using antihypertensive therapy at baseline. There was also a clear trend towards less use of combination therapy in the subgroups with lower baseline BP levels. Within each subgroup there were no significant differences in any baseline characteristics between those assigned active and control.

Effects of randomized treatment on stroke among patient subgroups defined by baseline blood pressure levels

Median values of baseline SBP were 114, 130, 149, and 169 mmHg for the four participant subgroups defined by baseline SBP levels of less than 120, 120–139, 140–159, and 160 mmHg or greater, respectively. In these four subgroups, the reductions in SBP produced by randomized treatment ranged between 9.3 and 14.2 mmHg for combination therapy and between 4.4 and 5.7 mmHg for single-drug therapy (Fig. 1). There was no evidence of differences in the magnitude of the effects of treatment on stroke risk across the four subgroups defined by baseline SBP for either combination therapy or single-drug therapy, although BP reductions and risk reductions were consistently greater with combination therapy than single-drug therapy (Fig. 1).

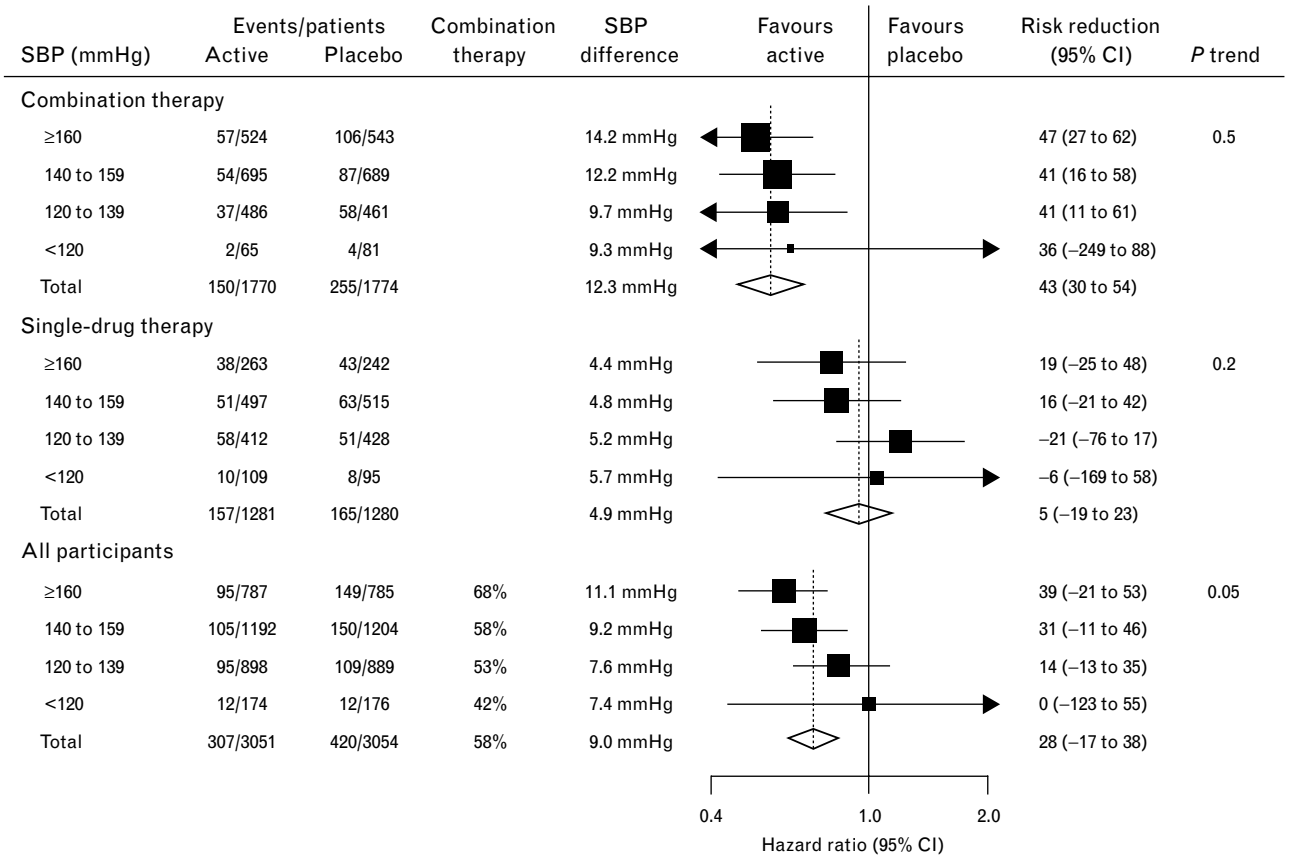
When the results for combination therapy and single-drug therapy were combined in one analysis, there was a clear pattern of smaller BP differences between randomized groups (P trend < 0.0001) and corresponding lesser risk reductions (P trend $= 0.05$) with lower baseline BPs (Fig. 1). This was clearly a consequence of progressively less use of combination therapy in the participant subgroups with lower entry BP levels.

There was no substantive difference in the patterns observed for ischaemic and haemorrhagic stroke, with consistent treatment effects observed for combination therapy across baseline BP groups for both subtypes and large reductions for haemorrhagic stroke at all baseline BP levels (Fig. 2). Analyses based on diastolic blood pressure (DBP) are not shown here but provided similar results across a range of baseline DBP levels extending from 73 to 103 mmHg. Likewise, the same patterns were observed for the outcome 'major vascular events'.

Associations of achieved follow-up blood pressure levels with stroke risk

For the four groupings of participant follow-up intervals defined by achieved SBP levels of less than 120, 120–139, 140–159, and 160 mmHg or greater, the median values of achieved follow-up SBP were 112, 130, 148, and

Fig. 1



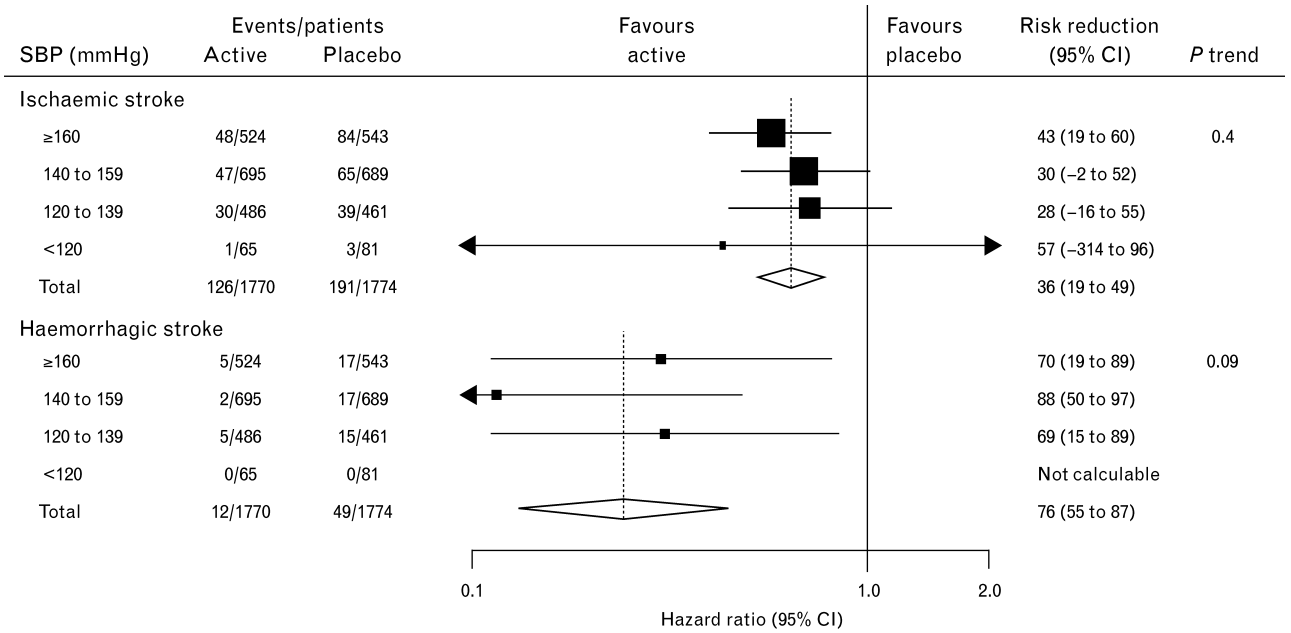
Effects of randomized treatment on the risk of stroke according to baseline systolic blood pressure levels among participants treated with combination and single-drug therapy and all participants. SBP difference indicates the mean reduction in systolic blood pressure (SBP) produced by randomized treatment. Solid boxes represent estimates of subgroups, and diamonds represent estimates and 95% confidence intervals (CI) for overall effects. Centres of the boxes are placed at the estimates of effect; areas of the boxes are proportional to the number of events. Horizontal lines represent 95% CI; vertical broken lines represent point estimates for overall effects. The '*P* trend' tested the consistency of the treatment effect in subgroups.

168 mmHg, respectively. Achieved follow-up BP groupings were not necessarily identical to but were strongly associated with baseline BP groupings. In these four groupings, the number of stroke events/person-years were 73/3264, 253/9004, 247/7354, and 154/2779, respectively. The association of stroke incidence with achieved follow-up SBP level was strong and continuous with no evidence of a J-curve in the range of achieved follow-up SBP from 112 to 168 mmHg (P trend < 0.0001; Fig. 3). This association remained strong even after controlling for the effects of other cardiovascular risk factors and of randomized treatment, and was not altered after adjustment for baseline BP (P trend < 0.0001). Similar associations were observed for both ischaemic and haemorrhagic stroke (Fig. 4) although the relationship of haemorrhagic stroke with achieved follow-up SBP level was stronger than that of ischaemic stroke (P homogeneity $= 0.003$). The patterns were similar when the analyses were repeated separately for the active and control treated groups (all P homogeneity > 0.2). Results of analyses based on achieved follow-up DBP are not shown here but showed similar patterns for a range of achieved follow-up DBP levels from 72 to 102 mmHg. There was also a strong and continuous relationship of achieved follow-up BP levels with the outcome 'major vascular events'.

Safety of blood pressure lowering at different baseline blood pressure levels

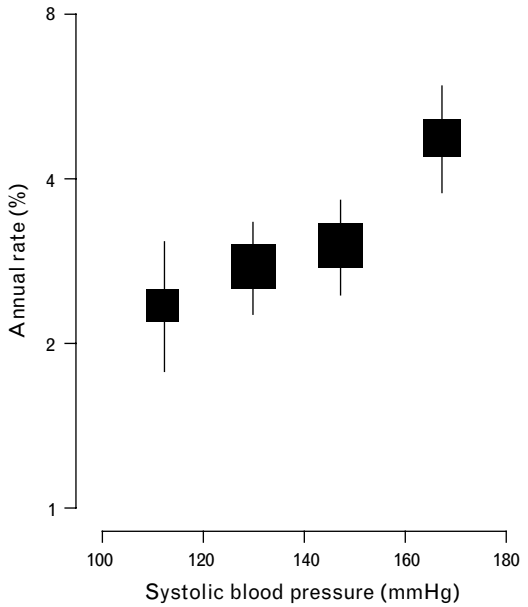
The effects of randomized treatment on total deaths, hospital admissions, and premature discontinuation of study treatment among the four participant subgroups defined by baseline SBP levels of less than 120, 120–139, 140–159, and 160 mmHg or greater are shown (Fig. 5). The relative risk of study treatment on the discontinuation of randomized treatment increased progressively across the subgroups with lower baseline SBP levels at entry (P trend $= 0.04$; Fig. 5), but there was no

Fig. 2



Effects of combination therapy on the risks of ischaemic and haemorrhagic stroke according to baseline systolic blood pressure levels. Conventions as for Fig. 1.

Fig. 3



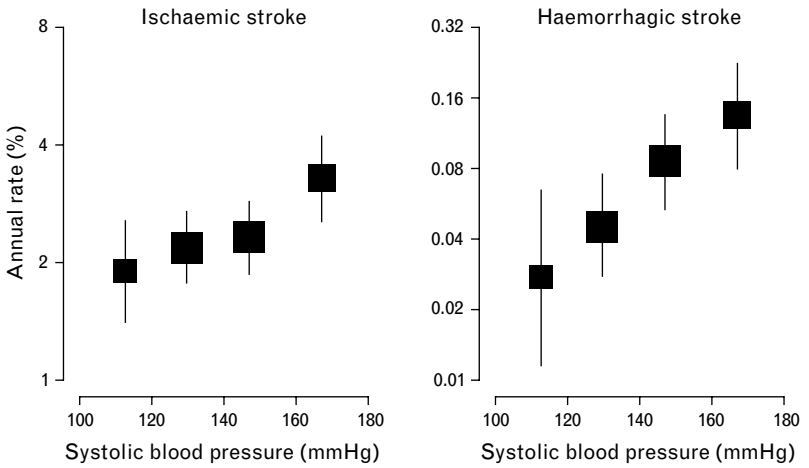
Annual rates of stroke according to achieved follow-up systolic blood pressure levels. Annual incidence rates and *P* values were controlled for age, sex, smoking, diabetes, study treatment, and combination therapy. Solid boxes represent estimates of annual incidence rates of stroke. Centres of the boxes are placed at the estimates of annual incidence rates and at median values of systolic blood pressure; areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence intervals. *P* trend < 0.0001.

corresponding detectable difference in the effects of randomized treatment on the risks of death or hospital admission (both *P* trend > 0.2; Fig. 5). Likewise, randomized treatment produced no differences in the relative risks of hypotension, renal dysfunction, electrolyte disturbance, hip fracture, or depression between patients with different levels of baseline BP at baseline (all *P* trend > 0.1), and there was no evidence that any side-effects occurred more or less frequently at different baseline BP levels in participants with ischaemic stroke compared with haemorrhagic stroke at entry (all *P* homogeneity > 0.05).

Discussion

The main results from the PROGRESS trial showed that a heterogeneous group of patients with established cerebrovascular disease had much to gain from routine BP lowering with a regimen based on an angiotensin-converting enzyme inhibitor and a diuretic [1]. In addition, earlier subsidiary analyses have indicated that the benefits of treatment were comparable for patients who were and were not hypertensive at baseline [1,8]. The analyses reported here now expand on these earlier reports and suggest net beneficial effects of treatment for baseline BP levels extending down to approximately 115/75 mmHg. Furthermore, for every patient subgroup, including that with the lowest baseline BP level, there appeared to be greater reductions in stroke risk with combination compared with single-drug therapy, strongly

Fig. 4



Annual rates of ischaemic and haemorrhagic stroke according to achieved follow-up systolic blood pressure levels. Conventions as for Fig. 3. *P* trend for ischaemic stroke = 0.0005, for haemorrhagic stroke < 0.0001. *P* homogeneity = 0.003.

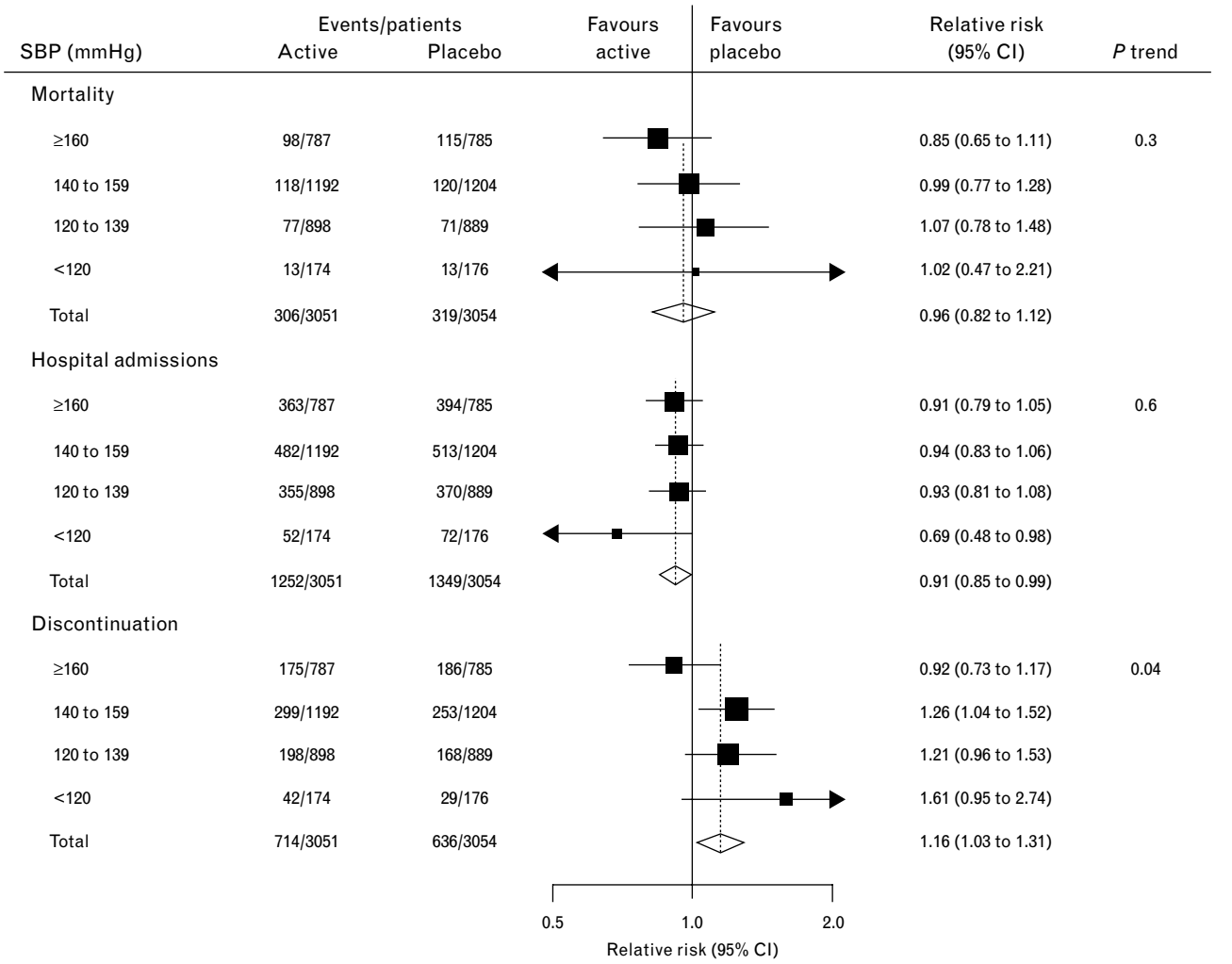
suggesting that previously observed increased risks of recurrent stroke at low BP levels (the J-curve phenomenon) were a consequence of confounding. The likely veracity of the findings reported here is supported by the separate observational analyses of the association of achieved follow-up BP levels with stroke risk, which also clearly showed that the lower achieved follow-up BP levels down to approximately 115/75 mmHg were associated with the lower incidence of stroke. Although side-effects leading to the discontinuation of treatment were progressively more common at lower baseline BP levels there was no excess of serious complications. On balance, these results suggest that among patients with cerebrovascular disease, BP lowering to 'low normal' levels is likely to be safe and maximally protective for the majority.

The findings of this study are consistent with the hypothesis generated by previous observational studies concerning the likely optimal BP for stroke avoidance. Large-scale cohort studies have clearly demonstrated that lower BP levels are continuously associated with lower risks of initial ischaemic and haemorrhagic stroke, down to very low BP levels [13,14]. More limited evidence from studies in patients with a history of cerebrovascular disease have also suggested that lower BP levels are associated with lower risks of stroke recurrence [4–6]. Although one study among patients with cerebrovascular disease did suggest a J-shaped association, where both the highest and the lowest BP levels were associated with increased risks of recurrence [7], its interpretation and clinical significance have been uncertain. Whereas that non-linear association might reflect adverse effects of low BP on disease risks in that particular patient group, 'reverse causality' (whereby the most severe cerebrovascular disease lowers BP and independently worsens prognosis) has been identified as a plausible alternative explanation [15]. On the basis of the new data provided here, reverse causation as a result of the confounding effects of disease on BP would appear to be the most likely explanation. The present findings suggest that in the long term, patients with cerebrovascular disease would have the lowest risk of recurrence if their BP could be lowered to approximately 115/75 mmHg.

In PROGRESS, it is quite clear that combination therapy produced consistently larger reductions in the risk of stroke compared with single-drug therapy, irrespective of the BP level at baseline. Differences in characteristics between those who received combination and single-drug therapy were slight [1], and it is almost certain that the large differences in treatment effect represent the benefits of greater BP reduction with combination compared with single-drug therapy, rather than some interaction of treatment with unidentified characteristics of the patients [1,16]. This assumption is supported by direct evidence from other randomized trials in different patients groups, which have shown that more intensive BP lowering confers greater reductions in stroke risk [17].

PROGRESS is the largest trial to have investigated the effects of BP lowering on recurrent cerebrovascular disease, but subgroup analyses of the trial still had only limited power to define the efficacy and safety of treatment at low-normal baseline BP levels. By conducting concurrent non-randomized analyses of achieved follow-up BP levels, it was possible to increase greatly the volume of data and the consequent reliability of conclusions about the likely safety of BP lowering among individuals with lower baseline BP levels. Although the

Fig. 5



Effects of randomized treatment on the risks of total deaths, hospital admissions, and premature discontinuation of study treatment according to baseline systolic blood pressure levels. Conventions as for Fig. 1.

analyses of achieved follow-up BP levels are non-randomized, the comparability of the findings with those obtained with the intention-to-treat subgroup analyses provides considerable reassurance that they were not substantially biased. Although the participants in PROGRESS were limited to patients who had survived an initial stroke or transient ischaemic attack and those with no clear indication for, or contraindication to, an angiotensin-converting enzyme inhibitor, it seems likely that the findings reported here are more broadly applicable to patients with cerebrovascular disease, because previous trials have found the benefits of BP lowering to be similar across a wide range of patient populations [18–21].

Despite clear evidence that BP lowering is effective for secondary prevention in patients with cerebrovascular disease [1–3], BP control in clinical practice in this high-risk group remains poor [22]. One likely reason is that clinicians remain concerned about the possible risks of cerebral hypotension and iatrogenic ischaemic stroke after BP-lowering treatment, particularly among patients with atherosclerotic cerebrovascular disease. The data presented here should allay that concern. Although the optimum targets for BP lowering are unlikely to be established without additional data from randomized controlled trials evaluating the effects of treating patients with cerebrovascular disease to lower BP targets, clinicians should feel confident in using multiple therapies to achieve the current goals of less than 130–140/80–90 mmHg recommended in existing guidelines [23–27]. We also believe that for patients with cerebrovascular disease the progressive reduction of BP levels towards targets of approximately 115/75 mmHg over a period of time should be both safe and maximally protective, provided it is well tolerated.

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