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Prior Events Predict Cerebrovascular and Coronary Outcomes in the PROGRESS Trial

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Background and Purpose—The relationship between baseline and recurrent vascular events may be important in the targeting of secondary prevention strategies. We examined the relationship between initial event and various types of further vascular outcomes and associated effects of blood pressure (BP)–lowering.

Methods—Subsidiary analyses of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, a randomized, placebo-controlled trial that established the benefits of BP–lowering in 6105 patients (mean age 64 years, 30% female) with cerebrovascular disease, randomly assigned to either active treatment (perindopril for all, plus indapamide in those with neither an indication for, nor a contraindication to, a diuretic) or placebo(s).

Results—Stroke subtypes and coronary events were associated with 1.5- to 6.6-fold greater risk of recurrence of the same event (hazard ratios, 1.51 to 6.64; $P=0.1$ for large artery infarction, $P<0.0001$ for other events). However, 46% to 92% of further vascular outcomes were not of the same type. Active treatment produced comparable reductions in the risk of vascular outcomes among patients with a broad range of vascular events at entry (relative risk reduction, 25%; $P<0.0001$ for ischemic stroke; 42%, $P=0.0006$ for hemorrhagic stroke; 17%, $P=0.3$ for coronary events; P homogeneity$=0.4$).

Conclusions—Patients with previous vascular events are at high risk of recurrences of the same event. However, because they are also at risk of other vascular outcomes, a broad range of secondary prevention strategies is necessary for their treatment. BP–lowering is likely to be one of the most effective and generalizable strategies across a variety of major vascular events including stroke and myocardial infarction. **(*Stroke*. 2006;37:1497-1502.)**

Key Words: antihypertensive agents ■ myocardial infarction ■ randomized controlled trials ■ recurrence ■ stroke

Despite many effective strategies for the secondary prevention of major vascular events,[1] patients remain at high risk of both recurrence of the baseline event[2–4] and of other manifestations of vascular disease.[2,3,5–8] These findings are consistent with progression of a common underlying mechanism, such as atherosclerosis, affecting a number of target organs including the heart, the brain, and the kidneys. They could also reflect the multifactorial effects of a heterogeneous group of risk factors such as suboptimal control of blood pressure (BP), cholesterol, or diabetes. A better understanding of the pattern of recurrence of further vascular events may be helpful for better targeting of existing treatments and in devising effective new strategies for secondary prevention in these high-risk patients.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial was a randomized, placebo-controlled trial that established the effects of BP–lowering in patients with cerebrovascular disease.[9] Previous reports of the association between the types of index cerebrovascular event and recurrent strokes in the PROGRESS trial were limited to the 2 broad categories of ischemic and hemorrhagic stroke.[10] In this article, we provide additional information about the relationship between ischemic stroke subtypes and coronary heart disease (CHD) occurring before randomization and during follow-up in the PROGRESS trial. We also studied the effects of BP–lowering treatment on the association between particular prior events and various types of vascular events during follow-up.

Materials and Methods

Study Design and Participants

The design of PROGRESS has been described in detail elsewhere.[9] Briefly, 6105 participants were recruited between May 1995 and November 1997. Participants were eligible if they had a history of a

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cerebrovascular event (stroke or transient ischemic attack [TIA], but not subarachnoid hemorrhage) 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. There were no formal BP thresholds for entry. The institutional ethics committee of each collaborating center approved the trial, all participants provided written informed consent, and procedures followed were in accordance with institutional guidelines.

Randomized Treatment

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 daily), with the addition of indapamide (2.5 mg daily; or 2 mg daily 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).

Definition of Baseline Vascular Events

Baseline cerebrovascular events were defined as the most recent stroke or TIA by local study investigators using evidence from the medical history and physical examination supplemented by clinical records or radiological findings if available. The nature of the index cerebrovascular event was confirmed with neuroimaging in 90% of total participants and in 94% of participants with ischemic stroke.[9,10] Diagnoses of stroke and TIA were defined according to standard criteria[11] (codes 431, 433, 434, 436, and 437 in the 9th revision of the International Classification of Diseases [ICD9]). Baseline strokes were subclassified as ischemic (ICD9 codes 433 to 434), hemorrhagic (431) or unknown type (436–437). According to definitions provided in the study protocol, baseline ischemic strokes were further subclassified into the following: (i) lacunar infarction (symptoms of a lacunar syndrome, normal consciousness and cortical functions, and normal computerized tomographic findings or a small, relevant subcortical/brain stem infarct), (ii) cardioembolic infarction (no lacunar characteristics, no definite evidence of large artery disease, and a cardioembolic source [nonvalvular atrial fibrillation 64%, valvular heart disease 17%, and other cardioembolic sources 19%]), (iii) large artery infarction (no lacunar characteristics, no cardioembolic source, and evidence of large artery disease), or (iv) unknown ischemic stroke. For subjects experiencing >1 cerebrovascular event, only the most recent event was used in the analysis.

The presence of major CHD at baseline was defined by local study investigators using evidence from the medical history and physical examination supplemented by clinical records, electrocardiographic, echocardiographic, and angiographic findings if available. Major CHD was defined as prior myocardial infarction diagnosed with the combination of an appropriate clinical history supported by electrocardiographic changes and an elevation of cardiac enzymes.[9]

Outcomes

The outcomes of the present investigation were total major vascular events (nonfatal stroke, nonfatal myocardial infarction, or death attributable to any vascular cause), stroke, and major CHD. Classification of outcome stroke subtypes during follow-up was based on radiographic evidence or autopsy reports in 89% of patients.[9,10] Strokes were subclassified into ischemic and hemorrhagic type according to the ICD9 codes in the same way as baseline strokes. However, whereas the further classification for baseline ischemic stroke was according to definitions provided in the protocol, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[12] were used to further subclassify ischemic stroke recorded during follow-up as one of lacunar infarction, cardioembolic infarction, large artery infarction, or ischemic stroke of unknown type. Major CHD during follow-up was defined as nonfatal myocardial infarction or death attributable to CHD. All these events were reviewed and validated by an end point adjudication committee that was blinded to study treatment.[9] It should be noted that although the end point adjudication committee had no information regarding initial events, it is possible that imaging reports of outcome events might have provided some information regarding initial events. Only the first event relevant to each outcome was included in each analysis.

Statistical Analysis

The associations between the vascular event before randomization and major vascular outcomes during follow-up were investigated using Cox proportional hazards models including the covariates age, gender, current smoking, diabetes, systolic BP, randomized study treatment, and planned use of combination therapy. The relative effects of randomized treatment on major vascular events were calculated using univariate Cox proportional hazards models, and the absolute effects were calculated as percentage difference in the rates of events over 5 years according to the principle of intention-to-treat. BP differences between randomized groups were estimated from linear mixed models. Because the overall effects of treatment on BP and events were greater among participants treated with combination therapy than among those treated with single-drug therapy,[9] treatment effects on BP and events in subgroups were standardized for the proportions of the study population for whom combination (58%) or single-drug therapy (42%) was prescribed, by taking weighted averages of the estimates obtained for the 2 therapies.[9] Percentage risk reductions were calculated as (1−hazard ratio)×100 and reported with 95% CI.

Results

Baseline Characteristics

The characteristics of randomized participants have been reported previously[9,10] and are summarized in Table 1. Mean age was 64 years (men 64 years, women 65 years). Mean age varied in the different cerebrovascular and CHD subgroups, but similar patterns were observed for both men and women (Table 1). There were no significant differences in these baseline characteristics between randomized groups for any of the patient groups with different cerebrovascular and CHD histories.

Association Between Initial and Outcome Vascular Events

During a mean follow-up of 3.9 years, a total of 1062 major vascular events occurred (4.8% per annum). The risk of major vascular outcomes was 41% (95% CI, 18% to 70%; $P=0.0002$) greater among patients with an index event of stroke than among those with TIA, after adjusting for other cardiovascular risk factors and randomized treatment. In patients with prior stroke, recurrent strokes accounted for 637 of 934 recurrent vascular events (68%; 95% CI, 63% to 73%). Recurrence of the same stroke subtype as the original index stroke varied between 13% (large artery infarction) and 81% (all ischemic stroke), as shown in Table 2 and Figure 1. A history of ischemic stroke was associated with a 59% (95% CI, 30% to 94%; $P<0.0001$) greater relative risk of further ischemic stroke compared with patients without previous ischemic stroke, after adjusting for other cardiovascular risk factors and randomized treatment (Figure 2). Similarly, significant associations between index stroke and recurrence of the same subtype were observed for lacunar, cardioembolic, and hemorrhagic subtypes, an effect known as "tracking" (Figure 2).[10]

The risk of major vascular events was 69% (95% CI, 40% to 104%; $P<0.0001$) greater among patients with cerebrovascular disease and comorbid CHD at baseline than among those with cerebrovascular disease alone. Among patients

TABLE 1. Baseline Characteristics Among Patients With Different Cerebrovascular and CHD Histories

	Cerebrovascular Disease History*				CHD History	
	Ischemic (n=4262)	Hemorrhagic (n=611)	Unknown (n=251)	TIA (n=981)	Major CHD (n=427)	No Major CHD (n=5678)
Demographic						
Mean age, y (SD)	64 (9)	61 (10)	68 (10)	64 (10)	68 (8)	64 (10)
Women, %	29	29	36	34	16	31
Asian,† %	42	58	10	19	17	40
Body mass index (kg/m^2)	25.6 (3.8)	25.1 (3.7)	26.1 (4.2)	26.0 (3.8)	26.4 (3.8)	25.6 (3.8)
Major vascular event history, %						
Qualifying event						
Ischemic stroke	100	5	6	0	71	71
Hemorrhagic stroke	1	100	1	0	4	11
Unknown stroke	1	0	100	0	7	4
TIA	8	4	16	100	30	22
Median time since qualifying event, months (interquartile interval)	9 (4–23)	12 (5–25)	9 (4–23)	7 (4–17)	9 (4–22)	9 (4–22)
Major CHD	7	2	12	9	100	0
Other medical history, %						
Current smoker	21	16	19	19	17	20
Current alcohol use‡	39	29	51	50	49	40
Diabetes						
Non–insulin-dependent diabetes	12	9	8	8	12	11
Insulin-dependent diabetes	2	1	2	1	3	1
Carotid disease‡	7	1	10	11	13	6
Atrial fibrillation	8	4	9	8	11	8
BP						
Mean SBP, mm Hg (SD)	147 (19)	145 (18)	150 (22)	147 (20)	147 (20)	147 (19)
Mean DBP, mm Hg (SD)	86 (11)	87 (11)	84 (11)	85 (11)	84 (11)	86 (11)
Hypertension,§ %	48	50	44	46	43	48
Medication, %						
Antihypertensive therapy¶	50	68	45	43	51	50
Antiplatelet therapy	77	18	85	82	81	72
Oral anticoagulants	10	1	9	10	16	9
Lipid-lowering therapy	15	8	9	16	25	13
Study treatment, %						
Active treatment	50	50	47	50	50	50
Combination therapy	59	59	50	57	60	58

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*The most recent stroke or TIA; †participants recruited from People's Republic of China or Japan; ‡consumers at least 1 alcoholic drink per week, §previous carotid endarterectomy, previous carotid angioplasty or carotid stenosis >50% (confirmed by angiogram or Doppler); ¶SBP≥160 mm Hg or DBP≥90 mm Hg; ‖currently treated hypertension.

with cerebrovascular disease and comorbid CHD, recurrent CHD accounted for 63 of 127 recurrent vascular events (50%; Table 2 and Figure 1), and a history of major CHD was associated with a 3.4-fold greater relative risk of further coronary outcomes compared with patients without previous heart disease after adjusting for other cardiovascular risk factors and randomized treatment (hazard ratio, 3.44; 95% CI, 2.58 to 4.59; $P<0.0001$; Figure 2). Further adjustment for body mass index, alcohol intake and concomitant therapies (antiplatelet therapy, oral anticoagulants, and lipid-lowering therapy) did not alter the findings for stroke and major CHD. Sensitivity analyses indicated that there were no important differences in the strength of associations between subgroups of age, sex, geographic region, and history of hypertension.

Treatment Effects on BP and the Risk of Recurrent Vascular Events

During follow-up, the mean difference in BP between participants assigned active treatment and those assigned placebo was 9.1/4.0 mm Hg in patients with a prior ischemic stroke, 10.8/4.4 mm Hg in those with prior hemorrhagic stroke, and 9.1/3.4 mm Hg in those with major CHD at entry (*P* homo-

TABLE 2. Risks of Cause-Specific Major Vascular Events Among Patients With Different Cerebrovascular and CHD Histories

	Cerebrovascular Disease History*								CHD History	
Outcome Event	All IS (n=4262)	LI (n=2031)	CEI (n=236)	LAI (n=950)	UI (n=1045)	HS (n=611)	US (n=251)	TIA (n=981)	Major CHD (n=427)	No Major CHD (n=5678)
Major vascular event	764 (4.9%)	354 (4.8%)	45 (5.3%)	177 (5.1%)	188 (5.0%)	110 (4.9%)	60 (7.0%)	128 (3.6%)	127 (9.0%)	935 (4.5%)
All stroke	518 (3.3%)	243 (3.3%)	31 (3.6%)	124 (3.5%)	120 (3.2%)	86 (3.8%)	33 (3.8%)	71 (2.0%)	59 (4.1%)	649 (3.1%)
All IS	422 (2.7%)	195 (2.6%)	27 (3.1%)	98 (2.8%)	102 (2.7%)	30 (1.3%)	23 (2.6%)	57 (1.6%)	52 (3.6%)	480 (2.3%)
LI	112 (0.7%)	72 (0.9%)	5 (0.6%)	20 (0.5%)	15 (0.4%)	10 (0.4%)	2 (0.2%)	12 (0.3%)	10 (0.6%)	126 (0.6%)
CEI	29 (0.2%)	9 (0.1%)	10 (1.1%)	2 (0.1%)	8 (0.2%)	0 (0.0%)	1 (0.1%)	3 (0.1%)	4 (0.3%)	29 (0.1%)
LAI	50 (0.3%)	17 (0.2%)	3 (0.3%)	16 (0.4%)	14 (0.4%)	2 (0.1%)	8 (0.9%)	10 (0.3%)	9 (0.6%)	61 (0.3%)
UI	231 (1.4%)	97 (1.3%)	9 (1.0%)	60 (1.7%)	65 (1.7%)	18 (0.8%)	12 (1.3%)	32 (0.9%)	29 (1.9%)	264 (1.2%)
HS	46 (0.3%)	28 (0.4%)	2 (0.2%)	9 (0.2%)	7 (0.2%)	45 (1.9%)	2 (0.2%)	6 (0.2%)	3 (0.2%)	96 (0.4%)
US	61 (0.4%)	27 (0.4%)	2 (0.2%)	19 (0.5%)	13 (0.3%)	14 (0.6%)	10 (1.1%)	8 (0.2%)	7 (0.4%)	86 (0.4%)
Major CHD	188 (1.2%)	81 (1.1%)	8 (0.9%)	45 (1.3%)	54 (1.4%)	17 (0.8%)	22 (2.6%)	42 (1.2%)	63 (4.5%)	206 (1.0%)

Values are No. of events (annual rates).

IS indicates ischemic stroke; LI, lacunar infarction; CEI, cardioembolic infarction; LAI, large artery infarction; UI, unknown ischemic stroke; HS, hemorrhagic stroke; US, unknown stroke.

*Cerebrovascular disease history indicates the most recent stroke or TIA.

geneity=0.1 for systolic BP difference, 0.4 for diastolic BP difference).

Active treatment significantly reduced the relative risk of major vascular events during follow-up in subgroups with prior ischemic (relative risk reduction 25%; 95% CI, 13% to 35%; $P<0.0001$) and hemorrhagic stroke (42%; 95% CI, 14% to 60%; $P=0.0006$; Figure 3). However, in participants with major CHD at entry numbering only 427, there was a 17% (95% CI, −18% to 42%; $P=0.3$) nonsignificant trend toward a reduction, possibly reflecting the small number of subjects (Figure 3). There were no differences in the size of the relative treatment effect in patients with prior ischemic stoke, hemorrhagic stroke, or major CHD (P homogeneity=0.4). There were also comparable benefits obtained from active treatment on relative risks of both recurrence of the initial vascular event and the incidence of other vascular outcomes in the subgroups with prior ischemic stroke, hemorrhagic stroke, or major CHD (P homogeneity >0.1). These results were similar for men and women in each subgroup. Adjustment for various baseline characteristics (age, gender, body mass index, current smoking, diabetes, alcohol intake, systolic BP), study treatment, and concomitant therapy (antiplatelet therapy, oral anticoagulants, and lipid-lowering therapy) did not alter the findings.

The absolute treatment effects on major vascular events amounted to 4.7% (95% CI, 2.2% to 7.2%; $P=0.0003$), 7.9% (95% CI, 1.1% to 14.6%; $P=0.02$), and 5.3% (95% CI, −5.0% to 15.6%; $P=0.3$) over 5 years among patients with prior ischemic stroke, hemorrhagic stroke, and major CHD, respectively (P homogeneity=0.7; Figure 3). A significant

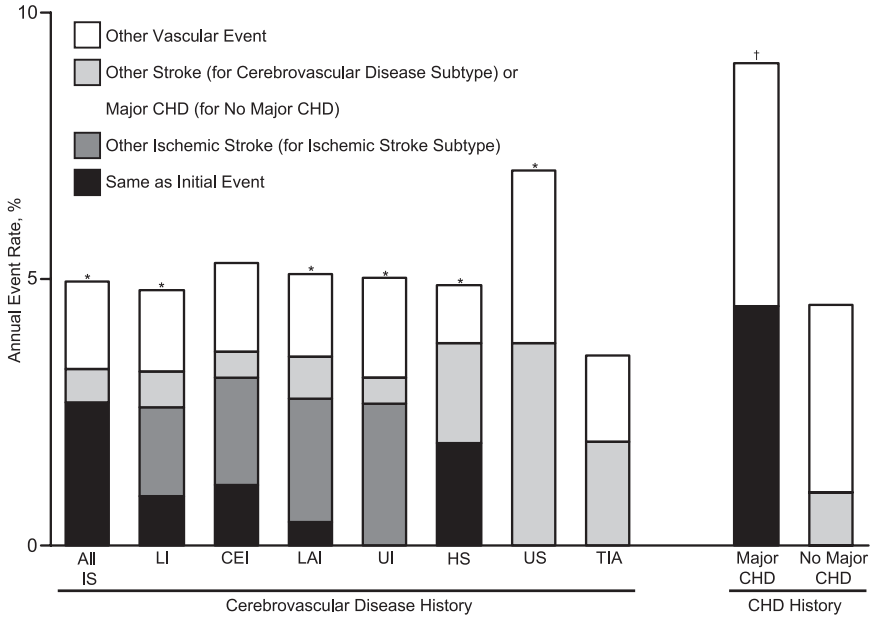

Figure 1. Incidence of cause-specific major vascular events among patients with different cerebrovascular and CHD histories. IS indicates ischemic stroke; LI, lacunar infarction; CEI, cardioembolic infarction; LAI, large artery infarction; UI, unknown ischemic stroke; HS, hemorrhagic stroke; US, unknown stroke; *$P<0.05$ versus TIA; †$P<0.05$ versus no major CHD.

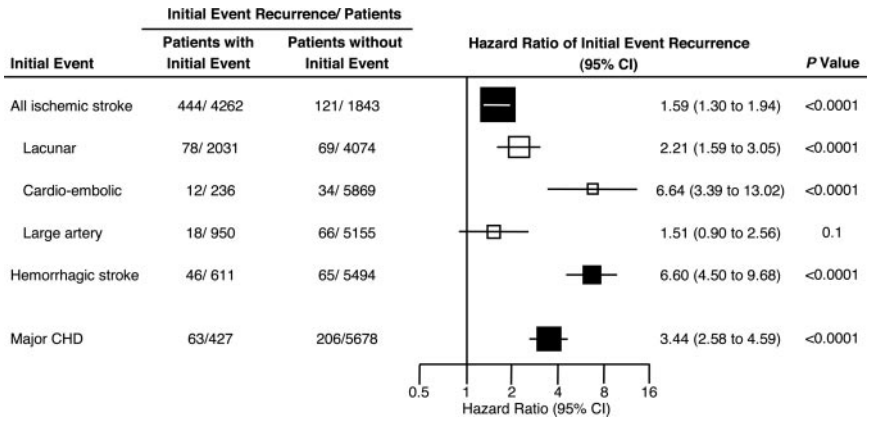

Figure 2. Hazard ratio of initial event recurrence among patients with different cerebrovascular and CHD histories. Solid boxes represent estimates of hazard ratio on ischemic stroke, hemorrhagic stroke, and major CHD; unfilled boxes, estimates of hazard ratio on ischemic stroke subtypes. Centers of the boxes are placed at the estimates of hazard ratio; areas of the boxes are proportional to the number of events. Horizontal lines represent 95% CI.

portion of the absolute benefits of therapy was attributable to reduction in the risks of recurrence of the initial event. In patients with a baseline ischemic stroke, hemorrhagic stroke, and major CHD, this amounted to 48%, 70%, and 78%, respectively, of the total absolute risk reduction in vascular events (Figure 3).

Discussion

The present analysis from the PROGRESS trial demonstrated that the most common type of recurrent vascular event was one that was identical to the patient's initial manifestation of vascular disease, an effect known as "tracking".[10] This finding supports earlier reports suggesting tracking effects[2,3] of vascular events. Previous observational studies have also demonstrated that recurrent strokes are often of the same type as the initial event in many patients.[13–17] Similarly, patients with a history of CHD are at higher risk of recurrence of cardiac events than of other vascular outcomes.[2] These results provide strong evidence for the tracking of stroke subtypes and of associated CHD.

The present analysis from the PROGRESS trial also demonstrated that patients with a history of vascular disease were at high risk of other vascular events, though somewhat less than for the same event. These findings are consistent with previous reports[2,3,5–8,13–17] that while patients with a history of cerebrovascular disease experience stroke risks of 4% to 6% annually, they experience other vascular events, at a lower level of 1% to 3% per year.[2,3] This may reflect progression of a common underlying pathophysiological mechanism, such as atherosclerosis affecting a number of target organs. In order to provide the maximum benefits of vascular prevention, it is, therefore, important to concentrate not only on treatment of the cause of the original event but also on the management of a heterogeneous group of vascular risk factors.

This large-scale randomized trial also demonstrated that perindopril-based BP–lowering treatment produced comparable reductions in the risk of major vascular outcomes among a heterogeneous group of patients with different vascular events at entry. A large part of absolute risk reduction was obtained from reductions of the same subtype as prior episode, but this reflects the higher absolute risks of the tracked events. Benefits obtained from active treatment were comparable for both recurrence of the initial event and the incidence of other vascular outcomes. This suggests that the beneficial effects of BP–lowering treatment are generalizable across a variety of major vascular events with different underlying etiologies.

This study has a number of strengths and limitations. Although this is the largest patient sample used to address the

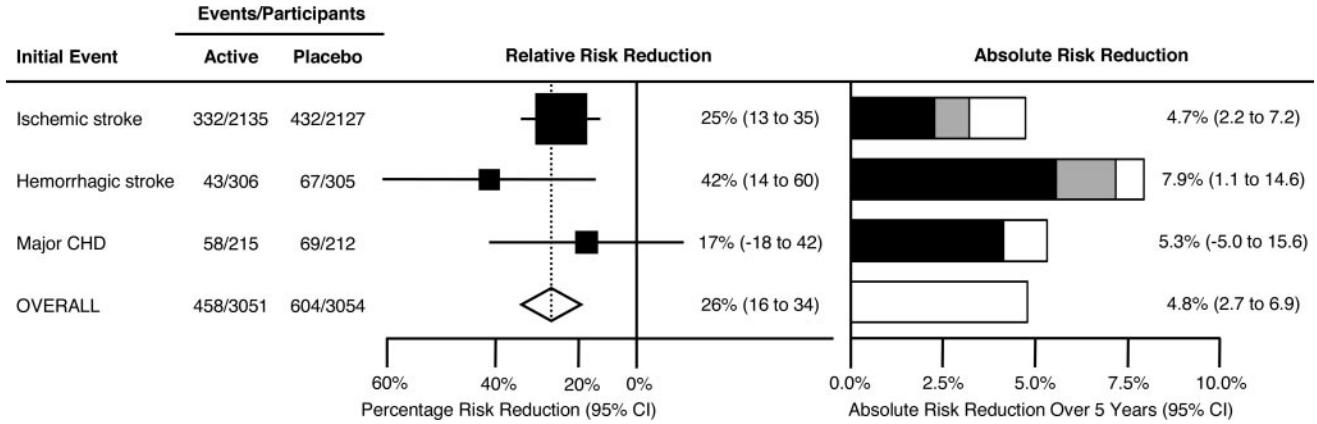

Figure 3. Relative and absolute effects of randomized treatment on the risk of major vascular events among patients with prior ischemic stroke, hemorrhagic stroke, and major CHD. Left panel: Solid boxes represent estimates of effect in subgroups; diamonds, estimate and 95% CI for overall effect. The vertical broken line represents point estimate for overall effect. Other conventions as for Figure 2. Right panel: Solid, slashed, and blank columns represent the absolute risk reductions for tracked event, other stroke (for ischemic stroke and hemorrhagic stroke), and other major vascular event, respectively.

question of tracking to date, the strength of the evidence about the tracking of event types and about the effects of BP–lowering on cause-specific vascular outcomes is limited by the small number of certain events. Another limitation is that the participants in PROGRESS were limited to patients who survived an initial stroke or TIA, and the present findings may not be generalizable to early recurrence or to severe stroke leading to early death. Several factors may have potentially reduced the statistical power to detect the influence of initial stroke subtype on recurrent events. The first is that the definition used for subclassification of baseline ischemic stroke, as described in the Materials and Methods section, was similar but not identical to that of follow-up stroke (TOAST criteria[12]); the second is that the control group used for estimation of the effects of vascular events before randomization was a cerebrovascular disease population which is at higher risk of vascular outcomes than a general population; and the third is that a relatively large number of follow-up ischemic strokes was adjudicated to constitute an "unknown" ischemic stroke, attributable to overlapping mechanisms or insufficient supporting investigations.

Summary

Patients with a history of major vascular events are at high risk both of recurrences of the same type and of other vascular outcomes. A broad range of secondary prevention strategies will be necessary for these high-risk patients. BP–lowering therapy is likely to be the most effective and generalizable of such strategies that can be applied to patients with a history of various vascular events such as stroke and myocardial infarction. Routine BP–lowering should be considered for all patients presenting with a history of any major vascular event.

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