Effects of a perindopril-based blood pressure lowering regimen on cardiac outcomes among patients with cerebrovascular disease

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Aim To determine the effects of a perindopril-based blood pressure lowering regimen on major cardiac events among hypertensive and non-hypertensive patients with a history of cerebrovascular disease.

Methods and results A total of 6105 individuals with a history of stroke or transient ischaemic attack were randomly assigned active treatment (n=3051) or placebo (n=3054). Active treatment comprised the angiotensin-converting-enzyme inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. Over a mean of 3.9 years of follow-up, active treatment reduced blood pressure by 9/4 mmHg compared with placebo and reduced the primary outcome, stroke, by 28%. Major coronary events occurred in 269 participants (active 3.8%, placebo 5.0%) and heart failure was diagnosed in 264 participants (active 3.7%, placebo 4.9%). Active treatment reduced the risk of major coronary events by 26% (95% CI: 6–42%; p=0.02) and the risk of congestive heart failure by 26% (5–42%; p=0.02). For each of these outcomes, there was no clear evidence of differences between the treatment effects in participants classified as hypertensive or non-hypertensive, and those with or without a history of coronary heart disease.

Conclusions Among individuals with cerebrovascular disease, blood pressure lowering with a regimen involving perindopril and indapamide not only reduced the risk of stroke, but also substantially reduced the risks of cardiac outcomes.

Introduction

By the early 1990s, randomised trials of various blood pressure lowering regimens among patients with hypertension had demonstrated beneficial effects of treatment on the risks of stroke, coronary heart disease, and heart failure.[1–3] Other trials, conducted among both hypertensive and non-hypertensive individuals, demonstrated that treatment with certain blood pressure lowering agents also produced important benefits in patients with heart failure[4,5] and in patients with acute myocardial infarction.[6,7] Over the last few years, the findings of new trials have further extended evidence of the benefits of blood pressure lowering treatments to include high-risk patient groups defined on the basis of established vascular disease or diabetes.[8] Such benefits appear to have been achieved irrespective of baseline levels of blood pressure.

Until recently, few individuals with cerebrovascular disease had been included in such studies

and the effects of blood pressure lowering regimens on the risks of recurrent vascular events among this large patient population remained uncertain.[9] Patients with cerebrovascular disease are not only at very high risk of stroke, but also have substantially elevated risks of cardiac events and left ventricular dysfunction.[10–12] Since both cerebrovascular and cardiac events are strongly related to blood pressure among individuals with or without established vascular disease,[13–16] there is a strong rationale for expecting that blood pressure lowering may reduce the risk of both types of vascular events. In addition, there is some evidence that agents that inhibit the renin angiotensin system may produce beneficial effects on both stroke and cardiac outcomes that are, at least in part, independent of their blood pressure lowering effects.[8,17,18]

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was designed to determine the effects of an angiotensin-converting-enzyme (ACE) inhibitor-based blood pressure lowering regimen on the risks of stroke and major vascular events among individuals with a history of stroke or transient ischaemic attack.[9] There were substantial benefits of this regimen for the risk of stroke,[19] and we report here the effects of study treatment on the risks of coronary heart disease events and congestive heart failure.

Methods

Study design

The design of the PROGRESS study has been described in detail elsewhere.[9,19] Briefly, 6105 participants were recruited from 172 collaborating centres in 10 countries from Australasia, Europe, and Asia between 1995 and 1997. The institutional ethics committee of each collaborating centre approved the trial, and all participants provided written, informed, consent. Individuals were potentially eligible if they had a history of cerebrovascular disease (ischaemic stroke, haemorrhagic stroke, or transient ischaemic attack, but not subarachnoid haemorrhage) within the previous 5 years, and no clear indication for, or contraindication to, treatment with an ACE inhibitor. There were no blood pressure criteria for entry.

Potential participants who tolerated, and adhered to, at least 4 weeks of run-in therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or matching placebo(s). Active treatment comprised a flexible treatment regimen based on perindopril

(4 mg daily) in all participants, with the addition of indapamide (2.5 mg daily; or 2 mg daily in Japan) in those 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 one or two tablets identical in appearance to the active agent(s). 'Combination therapy' (perindopril and indapamide or double placebo), rather than 'single drug therapy' (perindopril or single placebo), was used wherever possible, with the intent being to maximise the reduction in blood pressure. However, as many investigators had concerns about the safety of blood pressure lowering in patients with stroke (particularly in those with average or below average levels of blood pressure), it was necessary to provide some flexibility with respect to the intensity of treatment. All other aspects of medical care of the patients were left to the discretion of the responsible physician.

Data collection and follow-up

Prior to randomisation, information was collected about history of vascular disease, other vascular risk factors, and current medications. The presence of coronary heart disease at baseline was based on a history of myocardial infarction or coronary revascularisation, or a history of angina supported by documented electrocardiographic or angiographic evidence of coronary disease. Following randomisation, participants were scheduled to be seen on five occasions in the first year, and every 6 months thereafter until the end of the scheduled follow-up period or prior death. At each visit, seated blood pressure was measured in duplicate by trained observers, to the nearest 2 mmHg, using a standard mercury sphygmomanometer. Information concerning adherence to study treatment, including reasons for withdrawal of randomised therapy, was routinely recorded, as were details of all serious adverse events including those resulting from coronary heart disease or heart failure.

Outcomes

The main outcomes for these analyses were: (1) major coronary events, defined as non-fatal myocardial infarction or death ascribed to coronary heart disease; (2) total coronary events, defined as non-fatal myocardial infarction, death ascribed to coronary heart disease, coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), or hospitalisation due to unstable angina; and (3) congestive heart failure

resulting in death, hospitalisation, or requiring withdrawal of randomised therapy.

All outcomes were coded according to the ninth revision of the International Classification of Diseases (ICD9). The diagnosis of myocardial infarction was based on the combination of an appropriate clinical history supported by electrocardiographic changes and/or an elevation of cardiac enzymes or other biochemical markers of myocardial injury. A myocardial infarction was classified as non-fatal if the patient was alive 28 days after the event occurred. Death from coronary heart disease included death due to myocardial infarction and other acute, subacute, or chronic forms of ischaemic heart disease (ICD9 codes 410–414.9). Sudden deaths were excluded from this outcome due to uncertainty about the cause of death in this population with pre-existing cerebrovascular disease. Congestive heart failure, due to any underlying cause, was defined as above (ICD9 codes 428.0, 428.1, 428.9, 402.01, 402.11, 402.91, and 398.91).

An endpoint adjudication committee, blind to study treatment allocation, reviewed source documentation for every potential myocardial infarction, stroke, and for all deaths recorded during the study follow-up period. All other endpoints were determined by local study investigators on the basis of clinical findings and investigations, and were not subject to central adjudication.

Statistical analysis

All analyses were conducted according to the principle of intention-to-treat. Average differences in blood pressure between the randomised groups throughout the follow-up period were estimated using linear mixed models. Cumulative event curves were estimated using the Kaplan–Meier procedure and the effects of treatment on outcomes were estimated from unadjusted Cox's proportional hazards models. Among participants who experienced more than one outcome event during follow-up, survival time to the first relevant event was used in each analysis. If a participant had more than one type of event (e.g. a non-fatal myocardial infarction followed by death due to coronary heart disease), each event would contribute to the relevant cause-specific analysis, but only one event from any individual contributed to any composite outcome (e.g. major coronary events). Relative risk reductions are described in the text and figures as percentage reductions ([1−hazards ratio]×100). All p-values were calculated from two-sided tests of statistical significance.

Separate analyses were conducted for patient subgroups defined by the planned study drug regimen (combination drug therapy or single drug therapy), the presence or absence of hypertension at baseline (SBP≥160 mmHg or DBP≥90 mmHg), and the presence or absence of coronary heart disease at baseline. Standardised estimates of treatment effects in subgroups were calculated by combining subgroup-specific estimates of the effects of combination therapy and of single drug therapy,[20] with each component weighted by the study-wide proportion for which combination therapy (58%) or single drug therapy (42%) was planned at entry. Tests of homogeneity of the effects in subgroups were performed by adding an interaction term to the appropriate statistical model.

Results

Study population and baseline characteristics

Of 7121 individuals registered for the study, 1016 were ineligible for randomisation or withdrew for reasons described elsewhere.[19] A total of 6105 were randomised: 3051 were assigned active treatment and 3054 were assigned placebo (Fig. 1). Fifty-eight percent of participants received combination therapy or double placebo and the remainder received single drug therapy or single placebo. Baseline characteristics of study participants have been described in detail elsewhere[19,21] and are summarised in Table 1. Sixteen percent of the study population had a history of coronary heart disease. The active treatment and placebo groups were well balanced for mean blood pressure, prevalence of major risk factors for coronary heart disease or congestive heart failure, and the use of concomitant medications.

Effects of treatment on blood pressure

During a mean follow-up period of 3.9 years, the mean reduction in blood pressure among participants assigned active treatment was 9/4 mmHg (SE 0.3/0.2) greater than among those assigned placebo. Among the 58% of participants treated with combination therapy, the mean difference in blood pressure reduction achieved in active compared to placebo treated participants was 12/5 mmHg (SE 0.5/0.3), whereas among those treated with single drug therapy it was 5/3 mmHg (SE 0.5/0.3) (p for homogeneity <0.0001 for both systolic and diastolic blood pressure).
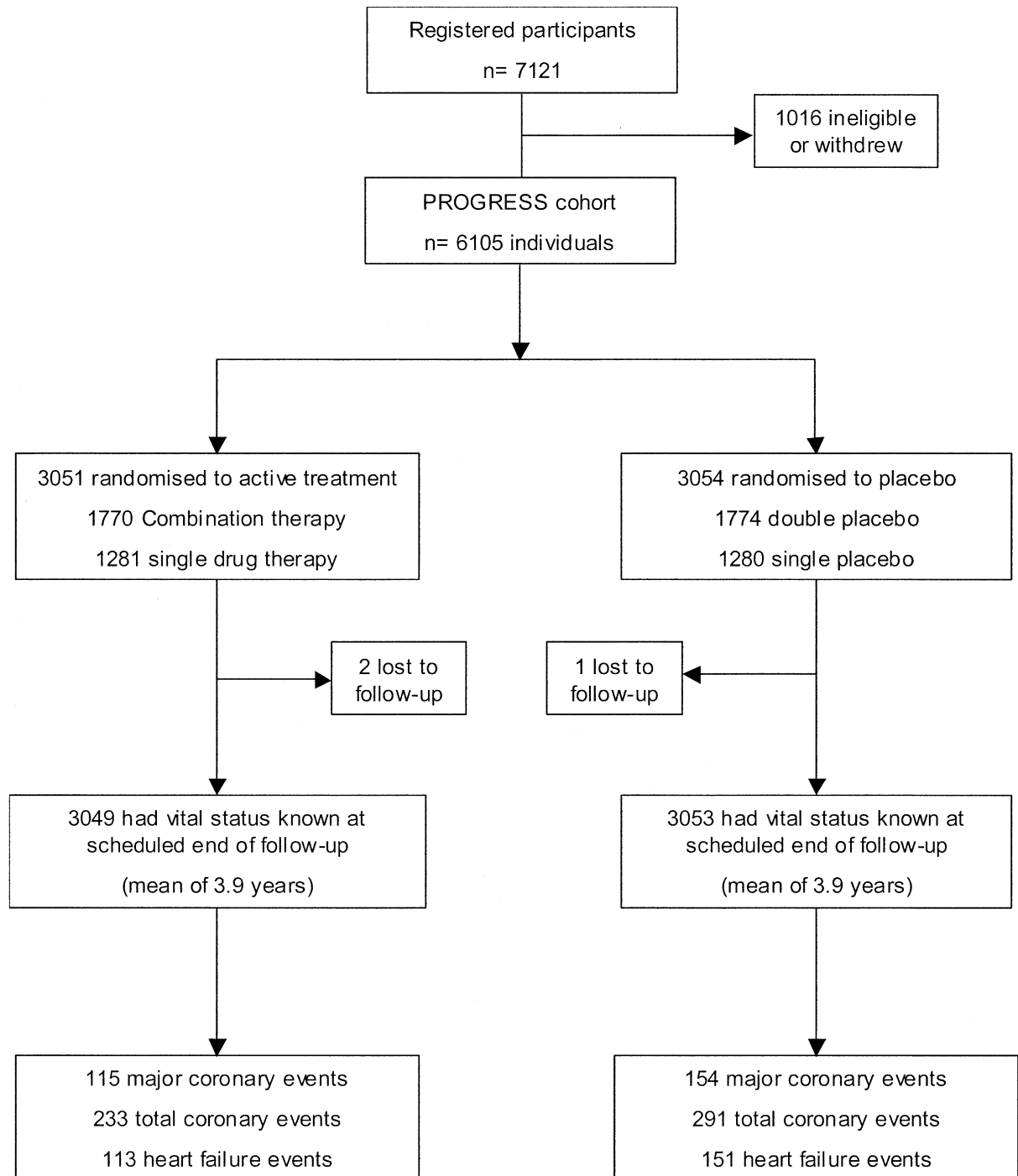
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                    ┌─────────────────────────┐
                    │  Registered participants │
                    │        n= 7121           │
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                              │                         │  1016 ineligible │
                              │                         │   or withdrew    │
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                    ┌─────────────────────────┐
                    │    PROGRESS cohort       │
                    │    n= 6105 individuals   │
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┌───────────────────────────────────┐   ┌───────────────────────────────────┐
│ 3051 randomised to active treatment│   │   3054 randomised to placebo   │
│ 1770 Combination therapy   │   │   1774 double placebo   │
│ 1281 single drug therapy   │   │   1280 single placebo   │
└───────────────────────────────────┘   └───────────────────────────────────┘

┌──────────────┐   ┌──────────────┐
│ 2 lost to   │   │ 1 lost to   │
│ follow-up   │   │ follow-up   │
└──────────────┘   └──────────────┘

┌───────────────────────────────────┐   ┌───────────────────────────────────┐
│ 3049 had vital status known at   │   │ 3053 had vital status known at   │
│ scheduled end of follow-up   │   │ scheduled end of follow-up   │
│ (mean of 3.9 years)   │   │ (mean of 3.9 years)   │
└───────────────────────────────────┘   └───────────────────────────────────┘

┌───────────────────────────────────┐   ┌───────────────────────────────────┐
│ 115 major coronary events   │   │ 154 major coronary events   │
│ 233 total coronary events   │   │ 291 total coronary events   │
│ 113 heart failure events   │   │ 151 heart failure events   │
└───────────────────────────────────┘   └───────────────────────────────────┘

Fig. 1   Trial profile.

Effects of treatment on risk of major coronary events

During follow-up, a total of 269 participants experienced at least one major coronary event (non-fatal myocardial infarction or death from coronary heart disease): 115 (3.8%) of those assigned active treatment and 154 (5.0%) of those assigned placebo. The cumulative event curves diverged early and continued to separate throughout follow-up (Fig. 2). Active treatment reduced the risk of a major coronary event by 26% (95% CI: 6–42%, p=0.02) (Fig. 3). There was a trend towards a greater effect of active treatment among participants treated with combination therapy (risk reduction 35% [95% CI: 12–52%]) than in those

Table 1 Baseline characteristics of randomised participants

	Active (*n*=3051)	Placebo (*n*=3054)
Mean age (SD)	64 (10)	64 (10)
Female (%)	30	30
Asian[a] (%)	39	39
Vascular disease history		
Mean (SD) systolic blood pressure (mmHg)	147 (19)	147 (19)
Mean (SD) diastolic blood pressure (mmHg)	86 (11)	86 (11)
History of hypertension[b] (%)	48	48
History of coronary heart disease[c] (%)	16	16
History of atrial fibrillation (%)	8	8
Left ventricular hypertrophy (on ECG) (%)	7	7
Peripheral arterial disease (%)	4	4
Other medical history		
Current smoker (%)	20	20
History of diabetes (%)	13	12
Current medications		
Beta-blockers (%)	17	18
Calcium channel blockers (%)	40	40
Diuretics (%)	11	12
Other antihypertensives (%)	11	12
Antiplatelet agents (%)	73	72
Statins (%)	8	8
Oral anticoagulants (%)	9	10

[a] Participants recruited from People's Republic of China or Japan.
[b] Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg.
[c] History of myocardial infarction or coronary revascularisation, or angina (supported by documented electrocardiographic or angiographic evidence of coronary disease).
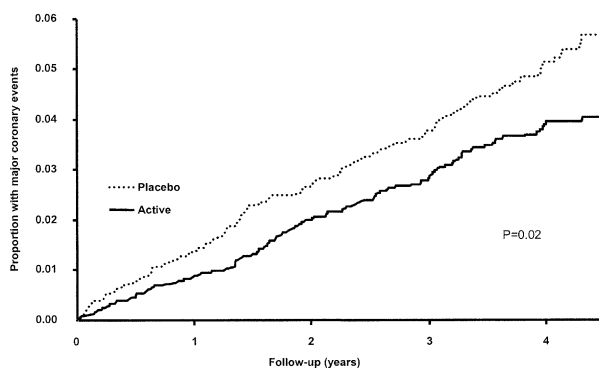

Fig. 2 Cumulative incidence of major coronary events among participants assigned treatment and those assigned placebo.

treated with single drug therapy (risk reduction 7% [95% CI: −37−38%]). However, there was no statistically significant difference between these results (*p* for homogeneity=0.2). Likewise, there was no clear evidence of any differences between the effects of treatment on major coronary events in the other subgroups studied (*p* for homogeneity both >0.7) (Fig. 3).

Effects of treatment on risk of total coronary events

In addition to the 269 patients who experienced a major coronary event, a further 255 underwent coronary revascularisation or were hospitalised for unstable angina. Therefore, a total of 524 (8.5%) participants experienced a coronary event: 233 (7.6%) among those assigned active treatment and 291 (9.5%) among those assigned placebo. Active treatment reduced the risk of total coronary events by 21% (6−33%, *p*=0.008) (Fig. 4). There was no clear evidence of any differences between patient subgroups in the effects of treatment on total coronary events (*p* for homogeneity all >0.2)

Effects of treatment on risk of congestive heart failure

A total of 264 participants were diagnosed with congestive heart failure during follow-up, among whom 331 events were recorded (51 deaths, 134 hospitalisations, and 146 withdrawals from randomised treatment). Heart failure was diagnosed in 113 (3.7%) of those assigned active treatment and
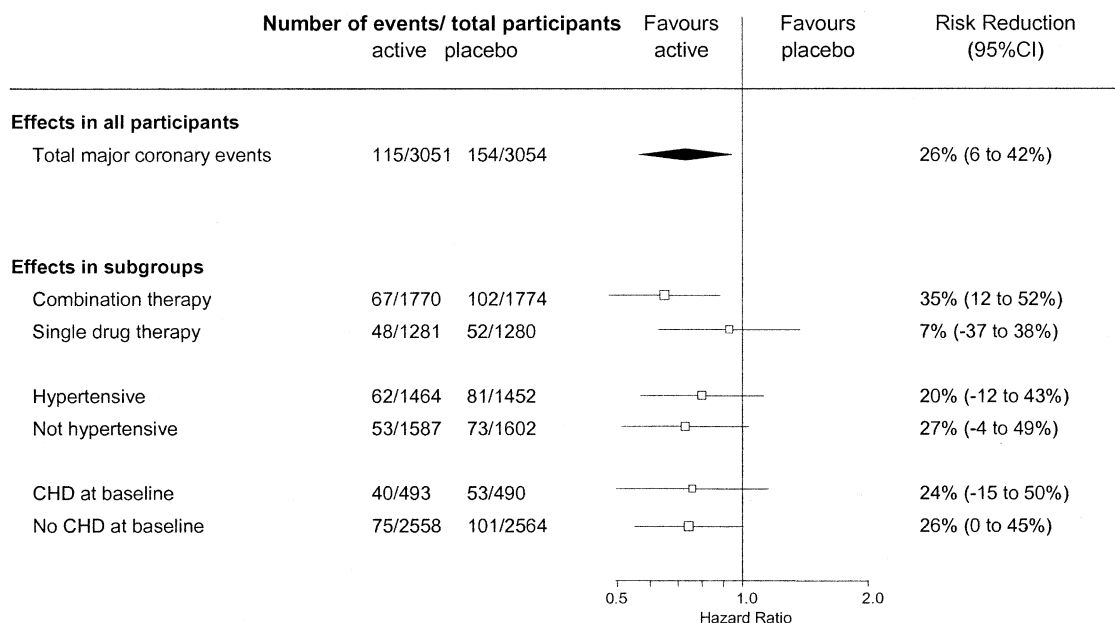
	Number of events/ total participants		Favours active	Favours placebo	Risk Reduction (95%CI)
	active	placebo			
Effects in all participants					
Total major coronary events	115/3051	154/3054			26% (6 to 42%)
Effects in subgroups					
Combination therapy	67/1770	102/1774			35% (12 to 52%)
Single drug therapy	48/1281	52/1280			7% (-37 to 38%)
Hypertensive	62/1464	81/1452			20% (-12 to 43%)
Not hypertensive	53/1587	73/1602			27% (-4 to 49%)
CHD at baseline	40/493	53/490			24% (-15 to 50%)
No CHD at baseline	75/2558	101/2564			26% (0 to 45%)

0.5   1.0   2.0
Hazard Ratio

Fig. 3 Effects of treatment on risks of major coronary events. Hazard ratios (and 95% CIs) for risk of major coronary events for all participants and subgroups of participants standardised to study-wide proportions of participants for whom combination or single drug therapy was planned. p Values for homogeneity for all subgroups >0.1. The centre of each box is placed at the point estimate of effect and the area of the box is proportional to the number of events. The horizontal lines represent 95% CIs. The diamond represents the overall effect with the centre at the point estimate of effect and the tips at the 95% CI.
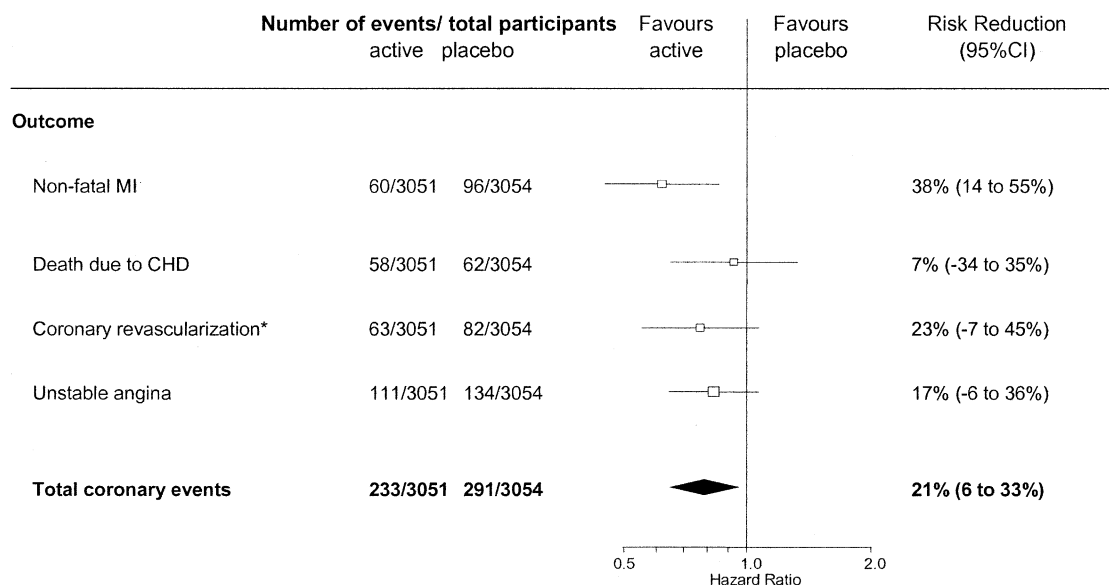
	Number of events/ total participants		Favours active	Favours placebo	Risk Reduction (95%CI)
	active	placebo			
Outcome					
Non-fatal MI	60/3051	96/3054			38% (14 to 55%)
Death due to CHD	58/3051	62/3054			7% (-34 to 35%)
Coronary revascularization*	63/3051	82/3054			23% (-7 to 45%)
Unstable angina	111/3051	134/3054			17% (-6 to 36%)
Total coronary events	**233/3051**	**291/3054**			**21% (6 to 33%)**

0.5   1.0   2.0
Hazard Ratio

Fig. 4 Effects of treatment on risk of coronary outcomes and total coronary events. Hazard ratios (and 95% CIs) for individual coronary outcomes and total coronary events for all participants. Conventions as for Fig. 3. *One hundred and forty-five participants underwent a total of 152 coronary revascularisation procedures: 76 percutaneous coronary interventions (36 active, 40 placebo), and 76 coronary artery bypass operations (29 active, 47 placebo).

151 (4.9%) of those assigned placebo. The cumulative event curves diverged early and remained separated throughout the study (Fig. 5). Active treatment reduced the risk of congestive heart failure by 26% (95% CI: 5–42%, p=0.02) (Fig. 6). As

for major coronary events, there was a trend towards a greater effect of active treatment among participants treated with combination therapy (risk reduction 34% [95% CI: 7–53%]) than in those treated with single drug therapy (risk reduction 16%
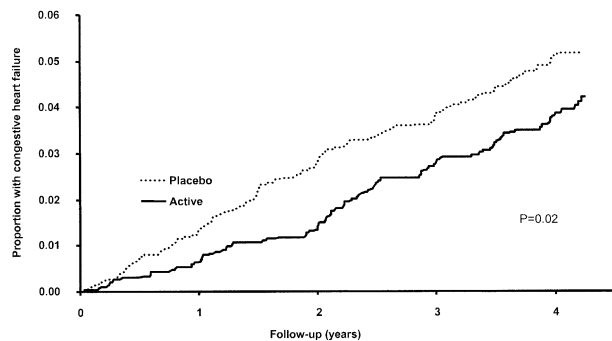
Fig. 5 Cumulative incidence of congestive heart failure among participants assigned treatment and those assigned placebo.

[95% CI: −19 to 41%]). However, once again these results did not differ significantly (*p* for homogeneity=0.3). Likewise, there was no clear evidence of any differences between the effects of treatment on congestive heart failure in either of the other subgroups studied (*p* for homogeneity both >0.2) (Fig. 6).

Discussion

This large-scale randomised trial among individuals with previous stroke or TIA showed that a perindopril-based blood pressure lowering regimen not only reduced the risk of stroke,[19] but also reduced the risks of coronary heart disease events and congestive heart failure. Active treatment reduced the risks of major coronary events and congestive heart failure each by about one-quarter and the risk of total coronary events, including coronary revascularisation and hospitalisation for unstable angina, by about one-fifth. These benefits were observed against a background of standard care that included antiplatelet agents and non-study blood pressure lowering drugs for the majority of participants. Furthermore, the effects appeared to be similar in both hypertensive and non-hypertensive individuals, and in those with, and those without, coronary heart disease at baseline.

Prior to the initiation of this study, the beneficial effects of ACE inhibitors on a broad range of major cardiac outcomes among patients selected on the basis of impaired left ventricular function[22–24] or acute myocardial infarction[4,6,25] were well established. Since then, several newly completed trials, and overviews of these trials, have confirmed beneficial effects of ACE inhibitor-based regimens on major vascular outcomes for a range of other high-risk patient groups, including both hypertensive and non-hypertensive individuals.[8] In the largest of these studies, the Heart Outcomes

Prevention Evaluation (HOPE) study, conducted primarily among patients with coronary heart disease or diabetes,[17] ACE inhibitor therapy produced proportional reductions in the risks of myocardial infarction and heart failure that were comparable in magnitude to those now observed in PROGRESS among patients with cerebrovascular disease. Since patients with cerebrovascular disease are at high risk of both coronary disease events and left ventricular dysfunction,[10–12] the finding of markedly reduced risks of major cardiac events in PROGRESS is of considerable clinical significance.

While there is no doubt that various blood pressure lowering regimens reduce the risks of major cardiac events in a variety of patient populations, there remains considerable uncertainty about the mechanism of action by which the benefits are achieved—in part because of possible disparities between the size of the benefits provided by different drug classes.[8] In particular, there is uncertainty about the proportion of the observed benefit that is the consequence of blood pressure lowering and the proportion that is due to other independent drug effects. In PROGRESS, the 26% (95% CI: 6–42%) reduction in the risk of major coronary events achieved with a 9/4 mmHg reduction of blood pressure is proportionally about twice as great as that which would have been predicted from trials of mainly diuretic- and beta-blocker-based regimens among patients with hypertension, in which a blood pressure reduction of 10–12/5–6 mmHg was associated with a 16% (8–23%) reduction in major coronary events.[1,2] Similarly, in the HOPE study, ACE inhibitor therapy produced a modest fall in blood pressure and a 20% (10–30%) reduction in the risk of myocardial infarction. Previous trials of ACE inhibitors have reported similar reductions in the risk of major coronary events.[4] While these findings raise the possibility that ACE inhibitors may have greater effects on cardiac outcomes than diuretics or beta-blockers, the randomised trials that have directly compared regimens based on ACE inhibitors with those based on diuretics or beta-blockers have identified no clear differences for any major vascular outcome, including major coronary events.[8] While there is some evidence of a reduced risk of coronary heart disease events among patients taking ACE inhibitors compared to those taking calcium antagonists, the limited data currently available are too unreliable to draw definitive conclusions.[8] In the recently completed Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study,[26] a blood pressure lowering regimen based on an angiotensin receptor blocker provided greater protection against stroke than a regimen based on a
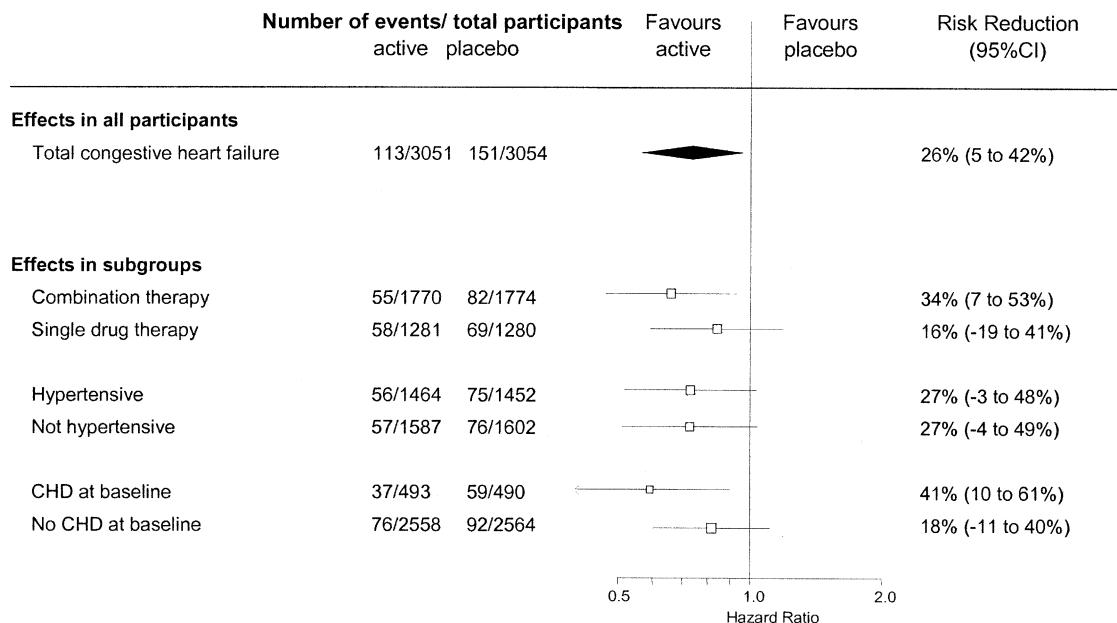
	Number of events/ total participants		Favours active	Favours placebo	Risk Reduction (95%CI)
	active	placebo			
Effects in all participants					
Total congestive heart failure	113/3051	151/3054			26% (5 to 42%)
Effects in subgroups					
Combination therapy	55/1770	82/1774			34% (7 to 53%)
Single drug therapy	58/1281	69/1280			16% (-19 to 41%)
Hypertensive	56/1464	75/1452			27% (-3 to 48%)
Not hypertensive	57/1587	76/1602			27% (-4 to 49%)
CHD at baseline	37/493	59/490			41% (10 to 61%)
No CHD at baseline	76/2558	92/2564			18% (-11 to 40%)

0.5 1.0 2.0
Hazard Ratio

Fig. 6 Effects of treatment on risk of congestive heart failure. Hazard ratios (and 95% CIs) for risk of congestive heart failure for all participants and subgroups of participants standardised to study-wide proportions of participants for whom combination or single drug therapy was planned. *p* Values for homogeneity for all subgroups >0.2. Conventions as for Fig. 3.

beta-blocker but there was no evidence of any difference in the effects on myocardial infarction. To date, however, these trials provide only limited statistical power to detect plausibly modest differences between the effects, on cardiac outcomes, of active blood pressure lowering regimens based on different drug classes.

Exploration of the effects of single drug therapy and combination therapy on cardiac events and stroke in PROGRESS provides an opportunity to indirectly assess the likely contribution of blood pressure-specific effects of the study treatment regimen to the prevention of vascular events. Among participants who received combination therapy with both perindopril and indapamide, there was a large reduction in both blood pressure (12/5 mmHg) and the risk of stroke (risk reduction 43%, [95% CI: 30–54%]). Among those who received single drug therapy with perindopril alone, at a relatively modest dose of 4 mg, the effect on blood pressure was much smaller (5/3 mmHg) and there was a correspondingly smaller effect on the risk of stroke (risk reduction 5% [95% CI: –19 to 23%]).[19] For both major coronary events and congestive heart failure, there were similar trends toward greater benefits for combination therapy than single drug therapy, suggesting that the extent of blood pressure lowering is also likely to be an important determinant of the size of the benefits achieved for these outcomes. However, the confidence limits for these estimates of treatment effects on cardiac

outcomes were wide and, unlike the results for stroke, there was no significant heterogeneity of treatment effect between those who received combination therapy and those who received single drug therapy. Nevertheless, the results are broadly compatible with those of an overview of earlier trials comparing blood pressure lowering regimens of differing intensity, which showed that regimens producing larger blood pressure reductions also produced greater reductions in major coronary events.[8] Further evidence will be provided by planned overviews of recent and ongoing randomised trials that directly compare the effects of regimens of differing intensity.[8,27] Other relevant evidence will be provided by ongoing trials of ACE inhibitors, including ALLHAT[28] and a European trial investigating the effects of a higher dose of perindopril (8 mg daily) on the risk of cardiac events in patients with stable coronary artery disease (EUROPA).[29]

In summary, PROGRESS has demonstrated that blood pressure lowering with a regimen involving perindopril for all patients, and indapamide for just over half, reduced the risks of coronary events and heart failure, as well as the risk of stroke. This regimen resulted in the avoidance of one stroke, coronary event or case of heart failure among every 17 (95% CI: 12–27) patients treated for 5 years.[19] Treatment with both agents simultaneously over the same period resulted in the avoidance of one such event in every 10 (95% CI: 8–15) patients.

PROGRESS therefore provides a strong rationale to consider implementing such a combination blood pressure lowering regimen routinely among all individuals with a history of stroke or transient ischaemic attack, irrespective of their level of blood pressure.

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