PROGRESS (Perindopril Protection Against Recurrent Stroke Study): regional characteristics of the study population at baseline

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Objective: To determine the effects of an angiotensin-converting enzyme (ACE) inhibitor-based blood pressure lowering regimen on the risk of stroke among patients with a history of cerebrovascular disease. Secondary aims include investigation of the effects of treatment on other cardiovascular events, dementia, and disability.

Design and Methods: PROGRESS (Perindopril Protection Against Recurrent Stroke Study) is a double-blind, placebo-controlled, randomized trial being conducted in 172 centres in 10 countries (Australia, Belgium, China, France, Italy, Ireland, Japan, New Zealand, Sweden, and the United Kingdom). Patients were randomly assigned to treatment with the ACE inhibitor perindopril (and the diuretic indapamide for those with no definite indication for or contraindication to treatment with a diuretic) or matching placebo(s). Both hypertensive and normotensive patients were eligible for inclusion. Follow-up is scheduled for completion in 2001.

Results: Of 6105 patients randomly allocated to study groups on completion of recruitment in November 1997, 1110 were recruited from Australia and New Zealand, 1520 from China, 713 from France and Belgium, 557 from Italy, 815 from Japan, 675 from Sweden, and 715 from the UK and Ireland. Regional differences in the baseline characteristics included a greater rate of diabetes, lacunar infarction, and cerebral haemorrhage in patients from China and Japan, and a more frequent history of myocardial infarction in Australia and New Zealand. Previous treatment with calcium antagonists was very frequent in Japan and China, whereas diuretic treatment was most often documented in the UK and Ireland.

Conclusions: Analysis of baseline characteristics of patients recruited from seven distinct geographic regions revealed some interesting differences, but more striking was the consistency of characteristics of patients recruited from many different countries across the world. *J Hypertens* 18 (suppl 1):S13–S19 © 2000 Lippincott Williams & Wilkins.

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Note: The study is an investigator-initiated and -conducted randomized trial endorsed by the Joint Liaison Committee of the World Health Organization and the International Society of Hypertension, and co-ordinated by the Clinical Trials Research Unit of the University of Auckland and the Institute for International Health Research and Development of the University of Sydney.

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Introduction

The primary aim of PROGRESS (Perindopril Protection Against Recurrent Stroke Study) is to determine the effects that lowering blood pressure by means of a regimen based on an angiotensin-converting enzyme (ACE) inhibitor would have on the risk of stroke in patients with a history of cerebrovascular disease [1]. The rationale for the study has been described previously, and is based on evidence of the association between blood pressure values and risk of stroke derived both from observational studies and from randomized controlled trials of blood pressure lowering [1,2]. The observational data have established that, for both primary and secondary stroke and in both eastern and western populations, the association of blood pressure with stroke risk is steep and continuous, with no lower value identified below which the risk of stroke does not continue to decline [3–7]. As this suggests that benefits could extend to blood pressures in the normotensive range, PROGRESS is being conducted in both normotensive and hypertensive patients with a history of transient ischaemic attack or stroke. In addition to providing data on the effects of treatment on stroke risk, PROGRESS will also provide evidence about the effects of blood pressure lowering on cognitive function and the development of dementia.

Recruitment into the study was completed with the allocation of 6105 patients to study groups by November 1997. The characteristics of this study population as a whole at

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Table 1 Number of study centres and patients randomized by region

Region	Centres registered	Patients randomized	Combination treatment† (%)
Australia and New Zealand	25	1110	65
People's Republic of China	26	1520	85
France and Belgium	25	713	48
Italy	17	557	43
Japan	33	815	7
Sweden	23	675	74
United Kingdom and Ireland	23	715	55
All regions	172	6105	58

†Perindopril and indapamide or matching placebos.

baseline is described in a separate publication [2]. In this paper, we report the separate characteristics of the study populations recruited in each of the seven distinct geographic regions in which the study was conducted – Australia and New Zealand, China, France and Belgium, Italy, Japan, Sweden, and the United Kingdom (UK) and Republic of Ireland.

Methods

The design and methods of PROGRESS have been previously described in full [1]. The pilot study, completed in November 1995, confirmed that treatment with perindopril was well tolerated by both hypertensive and normotensive patients with cerebrovascular disease [8]. The recruitment strategy proved effective, as reported in July 1996 [9].

Study organization

PROGRESS is being conducted in 172 collaborating centres in seven regions worldwide (Table 1). Regional coordinating centres were established in each of these regions, with international coordination provided by centres in Australia and New Zealand.

Inclusion criteria

Patients with ischaemic stroke, haemorrhagic stroke, or a stroke of unknown pathological type were all eligible for inclusion in the study, but those with subarachnoid haemorrhage were not. Both normotensive and hypertensive patients were eligible for inclusion. It was a condition of the study that those included did not have either a clear indication for, nor a definite contraindication to, treatment with an ACE inhibitor.

Run-in phase and randomization

Potentially eligible patients entered a 4-week run-in period during which they received open-label oral perindopril (2 mg daily for 2 weeks, followed by 4 mg daily for another 2 weeks). Eligible patients who adhered to the treatment and tolerated it were randomly assigned, on a double-blind basis, to receive the combination of perindopril (4 mg) daily and indapamide (2.5 mg daily, or 2 mg daily in Japan) or matching placebo(s), unless the investigators considered that indapamide was contraindicated, in which case patients received perindopril alone or matching placebo. The randomization was performed by fax or telephone between the collaborating clinical centres and the study randomization centre in Auckland, as described previously [1,2].

Assessment and follow-up

Following the first year after their random allocation to study groups, patients are seen at 6-monthly intervals. Follow-up is scheduled to end early in 2001, with an average duration of follow-up of about 4.25 years. Blood pressure is measured with a standard mercury sphygmomanometer at all visits, and assessment of cognitive function and dependency is made at annual visits [1,2].

Study outcomes

The primary study outcome is stroke, either ischaemic or haemorrhagic, defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 h. Secondary outcomes include fatal or disabling stroke, with disability assessed 6–12 months after the stroke, using the Lindley Classification System [10]. Other secondary outcomes include total serious cardiovascular events (stroke, myocardial infarction, or cardiovascular death), death from cardiovascular disease, cognitive function assessed at annual visits using the Mini-Mental State Examination (MMSE), dementia according to the criteria of the American Psychiatric Association [11], and disability and dependency assessed at annual visits using the Barthel [12] and Lindley [10] Classification Systems.

Study power, sample size calculations, and substudies are described elsewhere [1,2].

Results

Recruitment

Recruitment began with the pilot phase conducted in Adelaide and Auckland between May and November 1995 [8]. Recruitment at other centres began early in 1996 and was completed in November 1997. A total of 7098 potentially eligible patients entered the open-label run-in phase between May 1995 and November 1997. During this phase, 993 patients (14%) were withdrawn; their distribution among the regions and the main reasons cited for withdrawal are shown in Table 2. The rate of withdrawal during the run-in phase ranged from 9% in Italy to 18% in the UK and Australasia.

Table 2 Principal reasons for withdrawal from run-in phase

Region	Dizziness (%)†	Cough (%)	Other intolerance (%)	Patient decision (%)	Deterioration in biochemistry (%)	Poor adherence (%)	Proportion withdrawn overall‡ (%)
Australia and New Zealand	5	4	5	9	1	1	17
China	2	3	2	5	1	3	10
France and Belgium	3	2	4	6	1	2	14
Italy	3	1	1	6	0	2	8
Japan	4	2	4	6	1	2	13
Sweden	4	7	3	6	1	2	17
UK and Ireland	4	3	5	11	1	3	18
All regions	4	3	3	7	1	2	14

†Percentages represent proportion of all patients registered. ‡More than one reason for withdrawal may be cited, so that the sum of percentages in the six left-hand columns may exceed the total proportion withdrawn overall (right-hand column).

Table 3 Baseline characteristics among all patients randomized

Characteristic	Australia and New Zealand ($n=1110$)	China ($n=1520$)	France and Belgium ($n=713$)	Italy ($n=557$)	Japan ($n=815$)	Sweden ($n=675$)	UK and Ireland ($n=715$)	All regions ($n=6105$)
Mean age (years)	67	59	63	64	64	67	66	64
Females (%)	30	29	27	33	25	35	36	30
Mean SBP (mmHg)	144	146	146	148	144	153	152	147
Mean DBP (mmHg)	82	87	87	88	83	87	85	86
Current treatment for hypertension (%)	39	64	46	54	50	43	45	50
Current treatment for hypertension or DBP>95 mmHg or SBP>160 mmHg (%)	51	71	59	64	62	63	62	62
Smoker (%)	13	21	19	20	24	19	23	20
Drinker (%)	57	14	51	49	39	38	55	40
Mean weight (kg)	76	69	74	72	60	78	74	72
History of acute myocardial infarction (%)	15	3	4	6	3	9	9	7
History of diabetes mellitus								
Insulin-dependent (%)	1	0	2	3	1	4	1	2
Non-insulin-dependent (%)	9	10	12	13	17	9	7	11

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

After the run-in phase, a total of 6105 patients were allocated randomly to groups to receive active treatment or placebo (Table 1). Of these, 1110 were recruited from Australia and New Zealand, 1520 patients were from China, and 815 from Japan. The remainder were recruited from the other four regions (Table 1). Fifty-nine percent of patients were white and 38% were Asian (Chinese or Japanese).

Baseline characteristics by region

The average blood pressure for the recruited patients as a whole was 147/86 mmHg (Table 3). The average blood pressure was very similar in all seven regions, but the systolic blood pressure was slightly greater in Sweden, and in the UK and Ireland, whereas the diastolic pressure was marginally greater in Italy. The lowest blood pressures were recorded in Australasia and Japan. There were only minor differences in the age and sex distributions among the regions, the only notable difference being the younger average age of the patients in China (59 years compared with 64 years for the study cohort as a whole).

A history of myocardial infarction was most frequently reported in Australia and New Zealand and least often in China and Japan. The greatest incidence of diabetes was recorded in participants recruited in Japan, 17% of whom had non-insulin-dependent diabetes (Table 3).

Baseline drug treatments by region

The pattern of previous antihypertensive drug treatment differed considerably amongst the patients recruited from the seven regions (Table 4). More than 50% of the patients from China and Japan were taking calcium antagonists, whereas only 25% or fewer were taking these drugs in Australasia, Sweden, and the UK and Ireland. Only 2% of patients in Japan were receiving diuretics, whereas 30% of patients in the UK were taking these drugs.

History of cerebrovascular disease at entry to the study, by region

Eighty-four percent of recruited patients had a documented history of stroke, and 20% had a history of transient ischae-

Table 4 Baseline drug treatments among all patients randomized

Treatment	Australia and New Zealand (%)	China (%)	France and Belgium (%)	Italy (%)	Japan (%)	Sweden (%)	All regions UK and Ireland (%)	($n=6105$) (%)
β-Blocker	22	11	18	10	8	34	19	17
Calcium channel blocker	25	59	34	41	54	25	24	40
Diuretic	13	7	9	12	2	13	30	11
Other antihypertensive agent	5	25	6	21	7	3	5	11
Any blood pressure decreasing agent	50	72	52	60	58	53	55	59
Aspirin	76	54	59	52	25	69	81	60
Other antiplatelet agent	5	11	19	31	47	13	5	17
HMG-CoA reductase inhibitor	11	2	9	5	12	10	7	8
Other cholesterol decreasing agent	5	14	13	2	5	1	2	7
Nitrates	6	9	4	8	4	3	5	6
Oral anticoagulants	14	3	13	5	7	18	10	9
Hormone replacement therapy	4	<1	2	1	<1	7	3	2

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Table 5 Cerebrovascular diagnoses among all patients randomized

Cerebrovascular disease history†	Australia and New Zealand (%)	China %)	France and Belgium (%)	Italy (%)	Japan (%)	Sweden (%)	UK and Ireland (%)	All regions ($n=6105$) (%)
Ischaemic stroke								
Lacunar	23	43	29	41	53	25	23	35
Cardioembolic	5	1	6	3	5	7	4	4
Large artery	18	20	16	9	16	13	14	16
Unclassified	18	13	29	10	8	32	18	18
Cerebral haemorrhage	6	18	9	7	14	8	7	11
Stroke of any kind	77	92	87	70	93	82	77	84
Transient cerebral ischaemic attack	30	10	17	34	11	24	27	20
Amaurosis fugax	4	3	3	1	1	3	4	3
Dependent	16	9	16	11	7	9	22	13
Not fully recovered from previous stroke	64	66	55	51	67	53	60	61

†Some patients had more that one type of cerebrovascular event.

mic attack (Table 5). There were quite marked differences in the stroke subtypes in the various regions. For example, more than 50% of the patients in Japan had a history of lacunar stroke, whereas only 23% of patients in Australia and New Zealand or in the UK and Ireland had suffered this type of stroke. Haemorrhagic stroke was more than twice as common in Japan and China than in the other five regions (Table 5).

Assignment to combination treatment or to monotherapy with perindopril alone

There were marked regional variations in the percentage of patients assigned to combination treatment with perindopril and indapamide (or matching placebos) compared with those assigned to receive monotherapy with perindopril alone (or matching placebo) (Table 1). The biggest difference was between China, where 85% of patients were assigned to combination treatment, and Japan, where 93% received monotherapy.

Discussion

The first major hurdle for a major randomized clinical trial is timely recruitment of the desired number of patients. The target of 6000 patients for PROGRESS was achieved and, indeed, surpassed with the recruitment of 6105 patients by November 1997. With planned follow-up of about 4.25 years, the study should be completed early in 2001.

This paper has reported the differences observed between participants recruited from seven geographic regions spanning 10 countries, but the more striking feature was the consistency of characteristics of the patients recruited from very different countries at opposite ends of the world. Some of the differences noted include the greater frequency of diabetes in Asian patients, of myocardial infarction in Australasian patients, and of lacunar and haemorrhagic stroke among the Asian patients. There were also some differences in the frequency of treatment with a calcium antagonist – favoured in China and Japan – and diuretics, which were more popular in the UK, Australia, and Sweden.

The patients recruited into the study are remarkably similar in many respects. However, they do differ in some ways that provide the opportunity for interesting comparisons of the effects of blood pressure lowering interventions on the risk of secondary stroke and of the other study outcomes. These include the opportunity to compare the effects in an Asian subgroup making up 38% of all patients and a white subgroup of 59%. Another possible comparison will be between patients with a history of hypertension or with

hypertension on admission to the study (over 64%) and normotensive patients with no history of increased blood pressure. A third comparison planned will be between individuals older than 65 years and those younger than 65 years. Finally, the effects of treatment with the combination of ACE inhibitor and diuretics or matching placebos in patients assigned to dual treatment will be compared with the effects of treatment with ACE inhibitor alone or placebo in patients assigned to monotherapy. These a-priori subgroup analyses will add substantial additional information when the final results of PROGRESS are published.

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Appendix

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