

Evidence Based Medicine – what’s new?

PROGRESS study – Reducing recurrences after strokes (study summary)

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Objective

Randomised placebo controlled trial designed to determine the effects of a blood pressure-lowering regimen on the risks of stroke and other major vascular events in hypertensive and non hypertensive patients with a history of stroke or TIA.

Rationale

- 50 million people suffer a stroke¹
- Strokes kill about 5 million people each year¹
- Cerebrovascular disease is the 2nd leading cause of death worldwide
- One in 5 survivors suffer another stroke within 5 years³
- Need to identify safe and effective treatments for the prevention of recurrent stroke
- Existing treatment for patients with ischaemic stroke or TIA
 - Antiplatelet therapy
 - Carotid endarterectomy for patients with symptomatic stenosis^{6,7}
 - Anticoagulant – therapy for patients with arterial fibrillations
- Existing treatment for patients with hemorrhagic stroke
 - No proven treatment

Aim

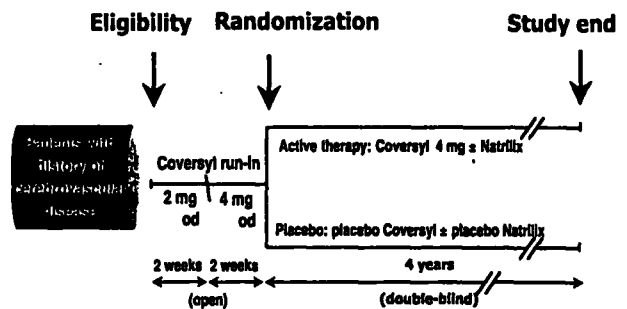
- To determine the balance of benefits and risks conferred by an ACE inhibitor (Perindopril) based blood pressure lowering regimen among patients with a history of cerebrovascular disease and a wide range of blood pressure at entry.

Design

- Investigator-initiated and conducted (WHO/ISH Proposed)
- randomised, placebo controlled
- Four week open run – in. phase on active Perindopril before randomisation

- Central, computer based randomisation
- 10 countries, 172 centres
- Four years double-blind treatment
 - * Recruitment began in 1996
 - * Follow up ended in 2001

Design



Reference: Neal B, MacMahon S. *J Hypertens*. 1995;13:1869-1873

Study end points

- **Primary outcome**
 - stroke (fatal or non fatal)
- **Secondary outcomes**
 - fatal or disabling stroke
 - total major vascular events (composite of non fatal stroke, non fatal myocardial infarction, or death due to any vascular cause)
 - total and cause specific deaths
 - hospital admissions
 - dementia and cognitive decline

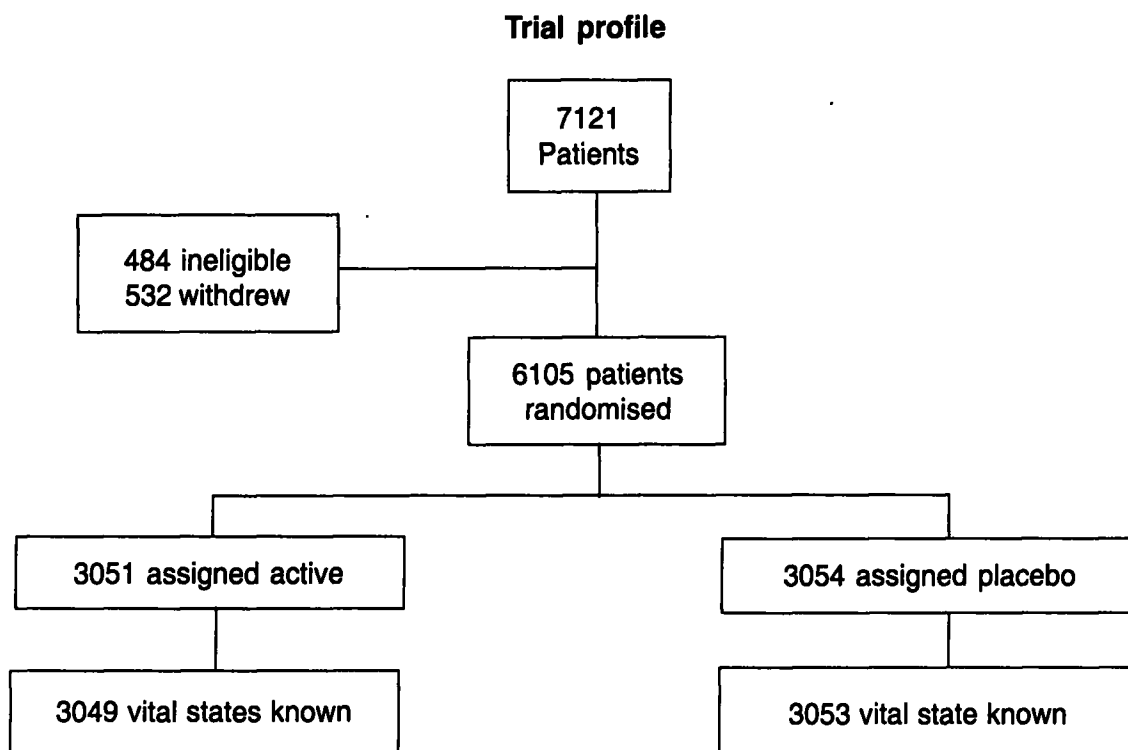
Eligibility

- History of cerebrovascular disease within the previous 5 years
- No definite indication for treatment with an ACE inhibitor (e.g. heart failure)
- No definite contraindication to such treatment
- No blood pressure entry criteria
- Recommended that hypertensive individuals should be stabilized
- No restriction on time of enrolment following a stroke

* Professor of Medicine, University of Colombo.

Randomization to study treatments

- Patients randomised to active therapy received Perindopril (Coversyl) 4 mg oncedaily
- Addition of Indepamide (Natrlix) 2.5mg where there was no specific indication for or contraindication to a diuretic
- The decision to use both active treatments was made by the treating physician



Withdrawal from treatment

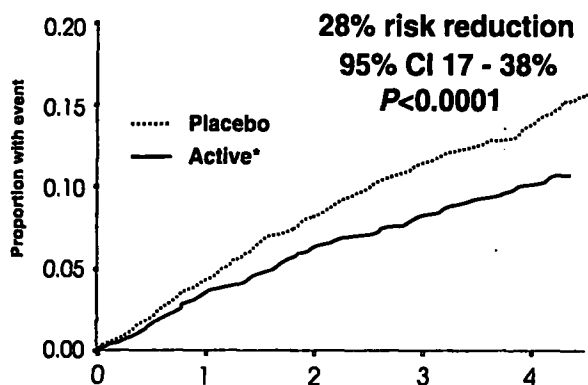
Main reasons for withdrawal,

Reason	Active*	placebo
Participant decision	7.6%	8.2%
Cough	2.2%	0.4%
Hypotension	2.1%	0.9%
Heart failure	2.2%	2-3%

Results

- 28% Reduction for total stroke
- 50% Reduction for hemorrhagic stroke
- 26% Reduction in major vascular events
- 36% Reduction in myocardial infarction
- 34% Reduction in dementia
- 45% Reduction in cognitive decline
- 38% Reduction in fatal & disabling stroke
- 48% Reduction of all stroke in Asian Population

Stroke risk reduction



*Active: Coversyl 4 mg ± Natrilix
Reference: Lancet 2001; 358: 1033-41

Absolute Benefits

Overall

- 1/ prevented among every 23 patients treated for 05 years (about 1% per year)
- 1 major vascular event prevented among every 18 patients treated for 05 years
- Similar benefits in all age groups
- Greater benefits in Asia
- Greater benefits after hemorrhagic stroke
- Greater benefits with combination therapy

"These are some of the largest benefits ever seen in the prevention of chronic disease"

Prof. Stephan MacMahon

Quotable quotes

On stroke

• Stroke is a huge global health problem. It is the second leading cause of disability – **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

• Options are very limited for the care of stroke patients. Aspirin provides moderate benefits for some patients, but can't be given to all. Other treatment are available only to a very small minority of patients.

– **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

On PROGRESS Results

• Overall one in ten PROGRESS patients given both study treatments avoided a stroke, heart attack or death from cardiovascular disease. – **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

• The PROGRESS results provide clear evidence of major health gains for these high risk patients. If the findings are applied widely many millions of stroke sufferers world-wide would be spared unnecessary suffering.

– **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

• We have shown that Perindopril and Indapamide have beneficial effects, not only for those with high blood pressure, but also for the much longer number of stroke patients with normal blood pressure.

– **Prof. John Chalmers, University of Sydney and PROGRESS Principal Investigator**

• PROGRESS benefits are too large to be kept in the bottom drawer but to bring it to clinical practice.

– **Prof. John Chalmers, University of Sydney and PROGRESS Principal Investigator**

On the future of stroke treatment

• PROGRESS has major implications for the management of patients with stroke. Each year there are about 15 million people worldwide who survive a stroke and the PROGRESS results are of direct relevance to their care.

– **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

• There is a strong case for making PROGRESS drugs available to most stroke patients, irrespective of their age and blood pressure and irrespective of the other treatment they may be receiving.

– **Prof. Stephen MacMahon, University of Sydney and PROGRESS Principal Investigator**

• The PROGRESS results will change the way we view stroke treatment. We are looking at a breakthrough that is the statin equivalent for the brain.

– **Prof. John Chalmers, University of Sydney and PROGRESS Principal Investigator**

References

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5. Barnett H, Taylor D, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998; **339**:1415-1425.
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