INVESTIGATOR'S BROCHURE

Prevention Of Decline in Cognition After Stroke Trial (PODCAST): A factorial randomised controlled trial of intensive versus guideline lowering of blood pressure and lipids

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Short title:	Prevention Of Decline in Cognition After Stroke Trial
Acronym:	PODCAST
Trial Registration:	ISRCTN85562386
EUDRACT:	None – No Clinical Trials Authorisation required †
Ethics Reference:	09/H0403/71
Sponsor Reference:	09012
Trial Sponsor:	University of Nottingham
Funding Source:	The Stroke Association UK, Alzheimer's Society UK
Website:	www.podcast-trial.org/

† MHRA has confirmed that the trial is not within the scope of the Clinical Trials Directive.

BACKGROUND INFORMATION AND RATIONALE

1.1 INTRODUCTION

Stroke and dementia are common, economically costly to society, and devastating to patients and their family. Hence, their combined effect is catastrophic. 30% of people develop dementia after stroke (post stroke dementia, PSD) and 50% of people with dementia have significant cerebrovascular disease, with UK annual care costs close to £30 billion. Despite this, the evidence base for the prevention of cognition decline and dementia post-stroke is negligible, perhaps because:

- People with stroke and dementia are a disadvantaged group who attract little medical interest
- Cognitive and physical disability reduces medication compliance

Elevated BP and cholesterol are common after stroke. There is good trial evidence and guideline support for blood pressure(1) and cholesterol(2) lowering treatment to prevent recurrent vascular events. As a result, most patients with a previous stroke need to receive life-style advice and have their BP lowered, and those with ischaemic stroke usually need a statin. Although BP-lowering post-stroke may reduce cognitive decline and dementia (PROGRESS, secondary outcomes(3, 4)) there is little evidence, so far, that lipid lowering is effective in preventing cognitive decline after stroke. Critically, it is unknown whether BP and cholesterol should be lowered intensively rather than more modestly as per guidelines.(5)

The PODCAST study will counter this negativity by:

- Actively seeking out people with stroke who are at risk of cognitive decline
- Aiming to reduce post stroke cognitive decline by ~20%
- Concentrating on ensuring compliance with management regimes
- Empirically testing the feasibility and applicability of therapeutic strategies for optimising BP and lipid control

The trial may offer the last opportunity to test these questions. Conclusive evidence that intensive BP/lipid lowering prevents cognitive decline would benefit patients, carers and society, and influence clinical management.

1.2 CURRENT MEDICAL LITERATURE

1.2.1 *Blood pressure lowering*

There are no definitive strategies for preventing post-stroke cognitive decline or dementia. High BP is a risk factor for stroke recurrence, and lowering BP, not just treating hypertension, reduces recurrence and other vascular events after ischaemic stroke and PICH.(1, 3) Midlife high BP is associated with dementia in later life.(6)
The results of those BP trials that studied cognition are confounded as:

- Cognition was only ever a secondary outcome
- Various cognitive outcome measures were used
- Most studies included patients at relatively low risk of developing cognitive decline
- Trials had relatively short follow-up (0.5-4.5 years) although observational studies suggest that treatment may be needed for >5 years

Figure 1: Effect of antihypertensive agents on cognitive decline; data from 3 randomised controlled trials: Syst-Eur, SCOPE and PROGRESS (MRC Older and SHEP did not provide appropriate data for inclusion).

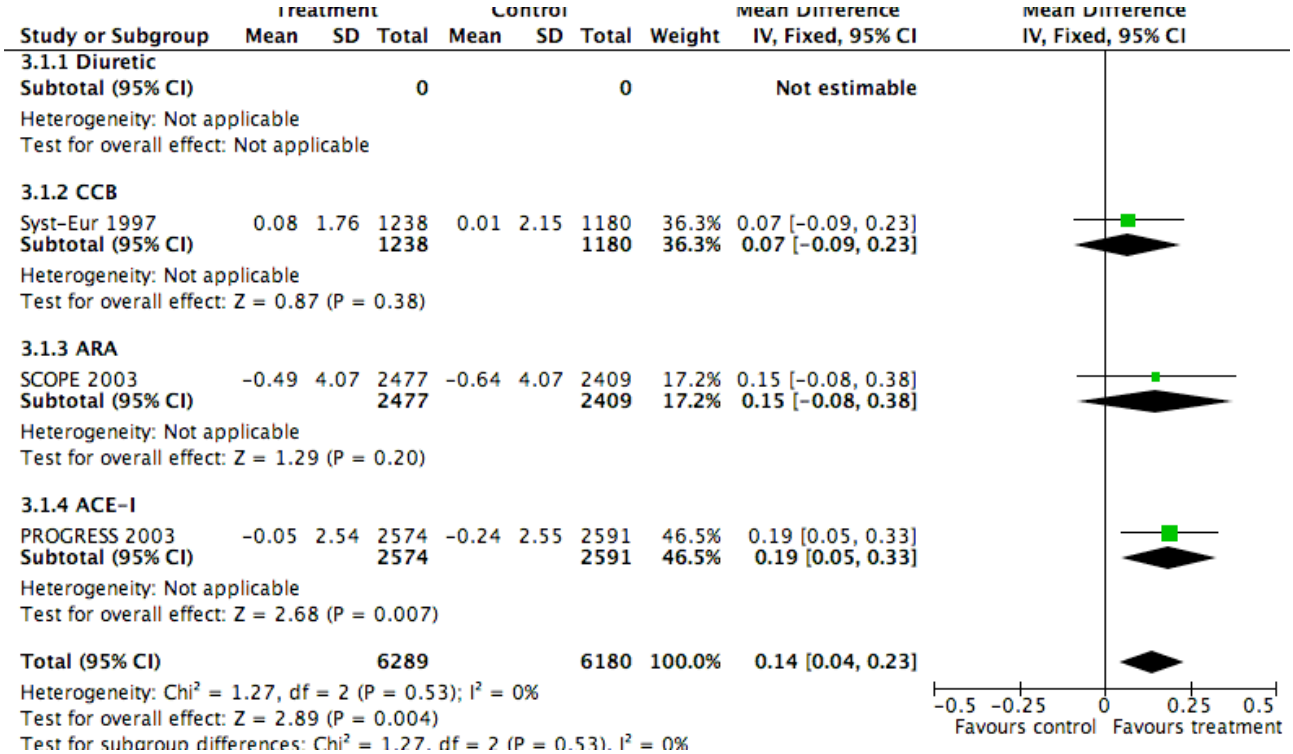
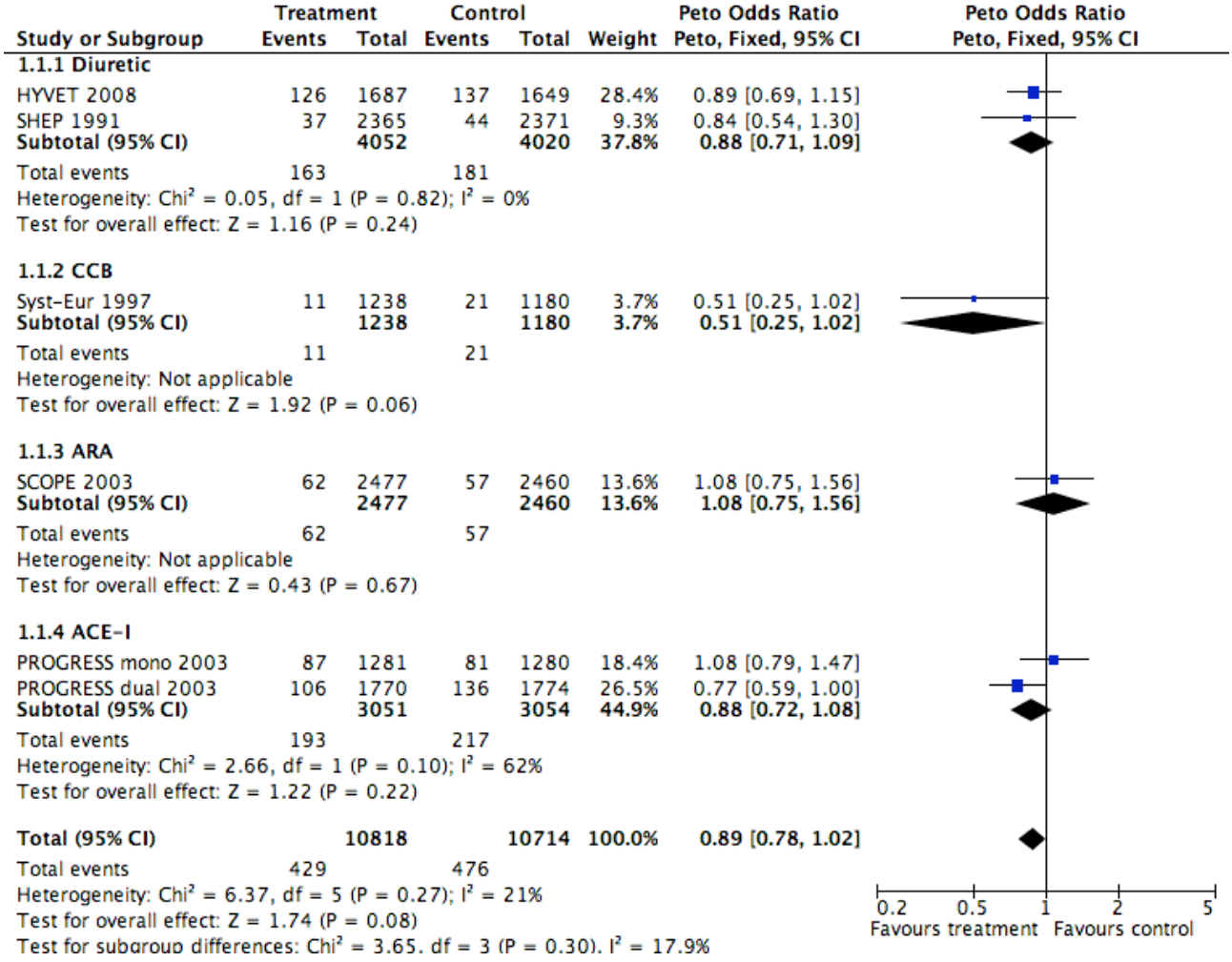


Figure 2: Effect of antihypertensive agents on all dementia; data from 5 randomised controlled trials: SHEP, Syst-Eur, SCOPE, HYVET and PROGRESS (MRC Older did not report dementia); the PROGRESS data are shown separately for dual and mono therapy.



Older trials (SHEP, MRC Older(7, 8)) were neutral and newer ones (Syst-Eur, SCOPE, PROGRESS (4, 9, 10)) positive for cognitive outcomes.(11). Overall, lowering BP was associated with reduced cognitive decline (weighted mean difference 0.14, 95% CI 0.04-0.23, p=0.004, 3 trials; Bath, unpublished, **figure 1**) and a trend to reduced dementia (RR 0.89%, 95% CI 0.77-1.04, p=0.13, **figure 2**).

The likely driver for reductions in cognitive impairment is the magnitude of fall in BP as the relative risk reduction (RRR) for dementia was associated with the difference in diastolic BP between active and control treatment groups (rs=0.95, p=0.014; Bath, unpublished); a similar relationship exists for reductions in systolic BP and secondary stroke.(1)

In the 2008 PRoFESS trial (n=20,332), final cognition (MMSE 27.3 vs. 27.4) and post stroke dementia (PSD, 4.7% vs. 4.7%), as well as stroke and vascular events, did not differ between telmisartan and placebo; however, BP difference was small (3/2 mmHg) and follow-up short (2.5 years). BP lowering (indapamide with/without perindopril) was associated with trends to reduced cognitive decline (MMSE, HR 0.93, 95% CI 0.82-1.05) and dementia (HR 0.86, 95% CI 0.67-1.09) in the 2008 HYVET

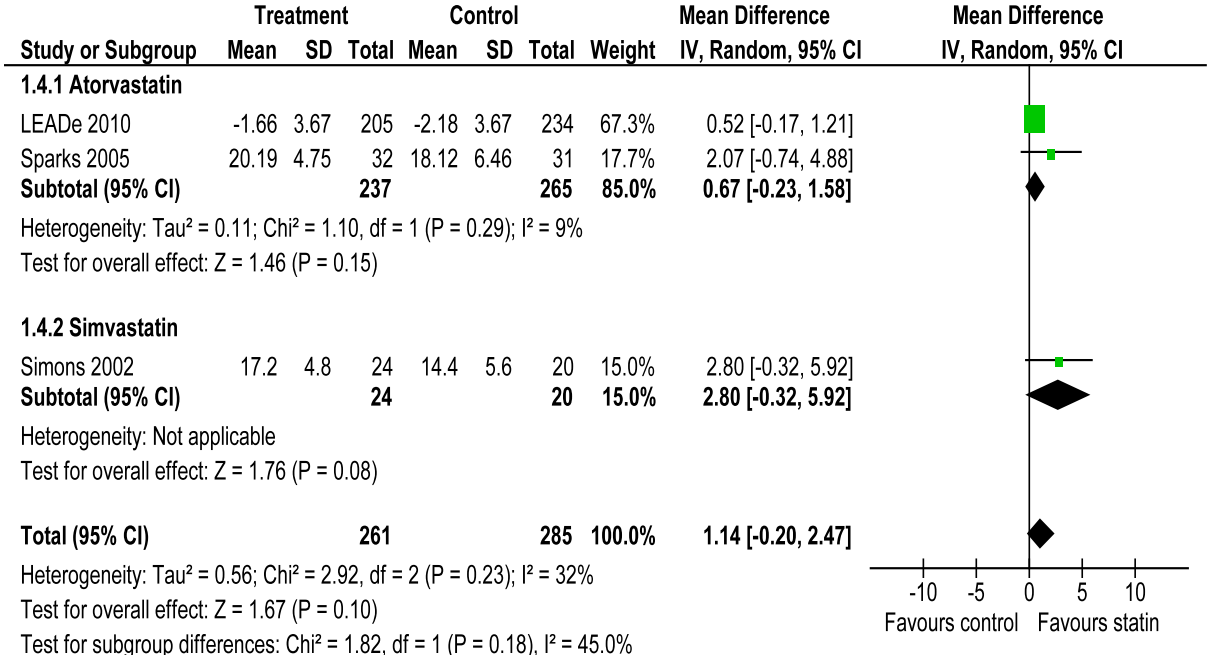
trial in the very elderly (n=3,845).(12) Although BP difference was large (15/6 mmHg); follow-up was, again, short at 2 years so that effects on cognition were probably under-estimated.

However, the intensity of lowering BP on cognition has not been studied. HOT (n=18,790) did not achieve its 5 mmHg differences in target diastolic BP (3 treatment groups).(13) In the PROGRESS trial, patients with previous stroke who took 2 BP agents (perindopril, indapamide) rather than 1 (perindopril) had larger reductions in BP (-12/-5 vs. -5/-3 mmHg), stroke risk (primary outcome, RRR 43% vs. 5 %) and 'all dementia' (secondary outcome, RRR 23% vs. RRR -8%), as compared with control.(3, 4) However, patients were not assigned randomly to dual/mono therapy so treatment intensity was not compared directly. Critically, no large antihypertensive trial has set out to assess the effect of BP lowering on cognition as the primary outcome. Intensive BP lowering may have additional benefits, e.g. improved well-being,(14) and appears to be safe and effective in preventing recurrence.(15)

1.2.2 *Lipid lowering*

High cholesterol is a risk factor for ischaemic stroke. Lowering cholesterol with a statin prevents stroke in patients with vascular disease (pravastatin, simvastatin)(16) or an elevated C-reactive protein (rosuvastatin), vascular events in patients with prior stroke (simvastatin),(17, 18)and stroke recurrence (atorvastatin).(2) Lowering cholesterol could reduce cognitive decline and dementia, in part by preventing stroke, but the evidence to date is limited; cross-sectional, prospective and case control studies are conflicting.(19) Of 3 small trials of statins in patients with Alzheimer's Disease (AD), 2 suggested efficacy (20, 21)(**figure 3)** and one found no effect (LEADe, n=600)(22). The results of large randomised control trials have not found significant effects of statins on cognition (HPS, PROSPER); (17, 23, 24)however, these studies involved individuals with modest high cholesterol and low risk of developing cognitive decline. ALLHAT-LLA, ASCOT-LLA & SPARCL did not assess lipids and cognition.(2, 25)

Figure 3:Effect of statins on cognition (MMSE) in 3 randomised controlled trials. The varied reporting of cognition/dementia (absolute score, change scores, z-scores, differing scales, qualitative results) mean that it is not possible to assess all the trials together.



1.3 ONGOING TRIALS

Few ongoing trials are addressing blood pressure and lipid management on cognition. A PRoFESS (26) sub study with detailed cognitive assessment in 600 patients will be published in 2009 (Chief Investigator=Ford). SPS3 is assessing anti-platelet and BP-lowering strategies (SBP<130 vs. <150 mmHg) on stroke recurrence in patients with sub-cortical infarcts (n=2,500); cognition over 3 years is a secondary outcome and patients with cortical infarcts or haemorrhage are excluded (http://clinicaltrials.gov/ct/show/NCT00059306).(27) A small statin (simvastatin) trial has recently been completed in Alzheimer's disease (CLASP, n=400) (http://clinicaltrials.gov/ct2/show/NCT00053599). We are not aware of ongoing BP/lipid trials aiming to prevent cognitive decline as the primary outcome.

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