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Clinical trials for preventing post stroke cognitive impairment

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ABSTRACT

Post stroke dementia (PSD) develops in up to 40% of patients and often co-exists with Alzheimer's disease in the elderly. Unsurprisingly, the combination of stroke and dementia is associated with considerable morbidity and mortality, and is devastating to patients and carers. Limited trial evidence suggests that lowering high blood pressure reduces the development of cognitive decline, vascular dementia and PSD, although whether this relates to the magnitude of BP reduction or specific drug classes remains unclear. Biological plausibility and/or existing studies suggest that other types of drug treatments might also be effective, including choline esterase inhibitors, lipid lowering agents, antiplatelet agents, and selective serotonin reuptake inhibitors. Preventing cognitive decline and dementia post stroke is critical and large definitive trials are now needed.

1. Introduction

Stroke and dementia are each common, and are devastating to patients, their families and to society through lost work and long-term care costs. Unsurprisingly, the combination of stroke and dementia is catastrophic. Post stroke dementia (PSD) refers to dementia following a diagnosis of symptomatic stroke and has a prevalence at one year of between 7% and 41%, depending on the type of study; dementia increases at an average rate of 3% per year [1]. PSD overlaps the criteria for vascular dementia, which is dementia in patients who have evidence of cerebrovascular disease, but not necessarily following a symptomatic stroke [2]. Alzheimer's pathology often coexists with cerebrovascular disease in post stroke patients and they agonise each other to increase cognitive impairment [3–6]. Post stroke cognitive impairment (PSCI) is a broader term than PSD and includes all cognitive consequences following stroke, including those that do not meet the criteria for dementia, i.e. cognitive impairment/no dementia (CIND) [7].

Several mechanisms play a role in the development of PSCI and PSD. Both large and small vessel cerebrovascular disease can cause strategic infarcts, micro and macro cerebral infarction and micro and macro haemorrhage. These lead to disruption of cortical–subcortical circuits and cortical deactivation as well as direct neuronal damage. However, silent small vessel white matter disease is also an important contributor [8]; and follows the damaging effects of aging, hypertension and beta amyloid (the peptide involved in Alzheimer's pathology), leading to cerebral hypoperfusion, blood brain barrier breakdown, oxidative stress and eventually neuronal death [9]. In addition, impaired vascular autoregulatory mechanisms may occur as a consequence of vascular risk factors and trigger Alzheimer's pathology although the evidence for this is conflicting [10–13].

While PSCI and PSD are directly associated with considerable morbidity and mortality, they are also associated independently with poor functional outcome after stroke, this being independent of age and other comorbidities [14,15].

The strong relationship between vascular risk factors and development of stroke means that modification of blood pressure, blood cholesterol levels, thrombosis [16], and blood viscosity could also reduce PSCI and PSD. This review focuses on clinical trials involving blood pressure, lipid lowering and choline esterase inhibitors in preventing post stroke cognitive impairment and dementia. In the absence of prevention trials, we have drawn inference from data in the treatment of cognitive impairment and dementia.

2. Lowering blood pressure

2.1. Prevention

Several large randomised trials have assessed the effect of lowering BP (or treating hypertension) on cognitive function as a secondary outcome (Table 1); [17–24] these studied most of the major antihypertensive drug classes: angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor antagonists (ARA), β-

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Table 1
Characteristics of completed randomised controlled trials of blood pressure lowering, lipid lowering and choline esterase inhibitors in preventing/slowing cognitive decline and dementia.

Trial	Year	Intervention	Size (with stroke)	Age (years)	Follow-up (years)	Target risk factor, at baseline[a]	Placebo-treatment target risk factor difference on follow up	Cognition baseline	Cognition outcome measure	Cognition control	Cognition treatment	Dementia control (%)	Dementia active (%)
BP lowering													
HYVET[b] [58]	2008	Indapamide (diuretic, ± perindopril, ACE-I)	3336 (216)	83.5	2.2	SBP-173.0	SBP-15.0 DBP-5.9	Median MMSE 26	MMSE <24 or decline > 3 in 1 year	29.5%	28.7%	8.3	7.5
MRC[b] [17]	1996	Hydrochlorthiazide with amiloride (diuretic) or atenolol (β-RA)	2584	70.3	4.5	SBP-184.7 DBP-90.7	SBP-15.8	Mean PALT 17.0 Mean TMT 59.9	Mean PALT coeff Mean TMT coeff	−0.30–3.01	−0.33 Aten −0.31 Diur −2.08 Aten −2.73 Diur	–	–
PRoFESS[b] [22,23]	2008	Telmisartan (ARA)	20,332 (20,332)	66.1	2.4	SBP-144.1 DBP-83.8	SBP-3.8 DBP-2.0	Median MMSE 28	MMSE decline ≥3 MMSE ≤24	11.0% 15.0%	11.0% 15.2%	4.7	4.7
PROGRESS[b] [19,58]	2003	Perindopril (ACE-I, ± indapamide, diuretic)	6105 (6105)	64	3.9	SBP-147.0 DBP-86.0	SBP-9.0 DBP-4.0	Median MMSE 29	MMSE decline ≥3	**11.0%**	**9.1%**	7.1	6.3
SHEP[b] [24,58]	1994	Chlorthalidone (diuretic) ± atenolol or reserpine	4736 (66)	71.6	4.5	SBP-170.3 DBP-76.5	SBP-11.1 DBP-3.4	Mean short-CARE score 0.37	Mean short-CARE; change from baseline	−0.06	−0.11	1.9	1.6
SCOPE[b] [20,59]	2003	Candesartan (ARA)	4937 (193)	76.4	3.7	SBP-166.2 DBP-90.3	SBP-3.2 DBP-1.6	Mean MMSE 28.5	MMSE decline >3	5.2%	4.7%	2.3	2.5
Syst-Eur[b] [18]	1998	Nitrendipine (CCB)	2418 (58)	69.9	2.0	SBP-173.5 DBP-86.1	SBP-8.3 DBP-3.8	Median MMSE 29	MMSE change from baseline	0.01	0.08	**1.7**	**0.8**
Lipid lowering													
HPS[b] [29,30]	2002	Simvastatin	20,536 (3280)	–	5.0	LDL-C 3.4 TC 5.9	LDL-C-1.0 TC-1.2	–	TICS-M <22 (stroke)	24.2% (33.3%)	23.7% (31.9%)	0.3	0.3
PROSPER[b] [31]	2002	Pravastatin	5804 (649 stroke or TIA)	75.4	3.2	LDL-C 3.8 TC 5.7	LDL-C-1.0	Mean MMSE 28	MMSE change from baseline bw groups	NS	NS	–	–
Simons[c] [36]	2002	Simvastatin	44	68.2	0.5	LDL-C 3.51	LDL-C-1.59	Mean ADAS-cog 31.1 Mean MMSE 17.5	Change from baseline between groups	**MMSE p value <0.02** ADAS-cog NS		–	–
Sparks[c] [37]	2005	Atorvastatin	63	78.5	1	TC 5.38 LDL-C 3.18	TC-1.94	Mean ADAS-cog 20.2	Difference between groups	Mean MMSE 20.8 ADAS-cog (p value=0.055) MMSE p value 0.25		–	–
LEADe[c]	2010	Atorvastatin	640	73.6	1.4	LDL-C 3.69 TC 5.79	LDL-C-1.6	Mean ADAS-cog 22.4	ADAS-cog[d]	5.98	6.82		
Choline esterase inhibitors													
Study 307/309 [e] [60]	2003	Donepezil	603 (435 stroke or TIA)	73.9	0.5	–	–	LSM ADAS-cog Placebo: 20.1 Donepezil: 21.0	ADAS-cog[f]	**0.72**	**−0.96: 5 mg −1.52: 10 mg**	–	–
Study 308/309 [e] [61]	2003	Donepezil	616 (410)	75.0	0.5	–	–	LSM ADAS-cog Placebo: 18.8 Donepezil: 20.7	ADAS-cog[f]	**−0.10**	**−1.75: 5 mg −2.19: 10 mg**	–	–
GAL-INT-6[e] [44,62]	2004	Galantamine	188 (VaD)	–	0.5	–	–	–	ADAS-cog[g]	−0.4	−2.4	–	–
GAL-INT-26[e] [44,63]	2007	Galantamine	788	–	0.5	–	–	–	ADAS-cog[g]	**−0.3**	**−1.8**	–	–

Some of the data has been estimated from the published paper.
ACE-I: angiotensin converting enzyme inhibitors; ADAS-Cog LSM: Alzheimer's disease assessment scale-cognitive subscale, least squares mean; ARA: angiotensin receptor antagonists; Aten: Atenolol; Diur: Diuretics; β-RA: β-receptor antagonists; CCB: calcium channel blockers; LSM: least squares mean; MMSE: Mini-Mental State Examination; NS: not significant; PALT coeff: Paired Associate Learning Test Coefficient (measuring rate of change in score over time, more negative the coefficient, the greater the cognitive deterioration over time); SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; TICS-M: Telephone Interview of Cognitive Status-Modified; TMT coeff: Trail Making Test Coefficient (measuring rate of change in score over time - less negative the coefficient, lesser the improvement in performance over time); VaD: vascular dementia.
Bold: Statistically significant results.
[a] Blood pressure in mm Hg and cholesterol levels in mmol/l.
[b] Dementia prevention studies.
[c] Studies in patients with Alzheimer's disease.
[d] Least squares means change from baseline at 18 months.
[e] Studies in patients with vascular dementia.
[f] Least squares mean change from baseline score difference between groups at endpoint.
[g] Mean change from baseline score between groups.

receptor antagonists (β-RA), calcium channel blockers (CCB) and diuretics. Two of these studies, PROGRESS and PRoFESS [19,23], only included patients with a previous stroke. Although only two of the trials were positive individually on cognitive outcomes (PROGRESS, Syst-Eur) [18,19], meta-analysis of the combined studies is positive (Fig. 1). Specifically, lowering BP was associated with reduced cognitive decline (reduction in Mini-Mental Stroke Examination [MMSE] by 3 to 4 or more points), odds ratio (OR) 0.92 (95% confidence intervals [CI] 0.85–1.00, p = 0.04, Fig. 1). Similarly, dementia was reduced non-significantly, OR 0.93 (95% CI 0.82–1.05, p = 0.22, Fig. 2).

The likely driver for these reductions appears to be the magnitude of fall in BP rather than the type of drug. First, there was little evidence of heterogeneity between drug classes in the meta-analyses (Figs. 1, 2). Second, trials with small reductions in BP were uniformly neutral for cognitive outcomes (Table 1). Third, analysis by meta-regression suggests the odds ratio for dementia was associated with the difference in BP between active and control treatment groups (Fig. 3); a similar relationship exists for reductions in systolic BP and secondary stroke [25]. Last, the PROGRESS trial compared indirectly the effect of lowering BP by a small or large amount; patients with previous stroke who took two BP agents (perindopril and indapamide) rather than one (perindopril) had larger reductions in BP (−12/−5 mm Hg vs. −5/−3 mm Hg), stroke recurrence (primary outcome, RRR 43% vs. 5%) and 'all dementia' (secondary outcome, RRR 23% vs. RRR −8%), as compared with control [19].

A number of confounding factors can modulate the results of BP lowering trials. First, achieving adequate differences in BP between active and control treatment groups is challenging since many patients, whether or not they have overt hypertension after stroke, will need antihypertensive therapy for vascular prophylaxis [25]; as a result, control patients will usually need active therapy. Second, the length of follow-up is critical and studies with a short follow-up were mostly neutral (Table 1). By example, the HYVET trial observed a large difference in BP (15/6 mm Hg) but only found trends to reduced cognitive decline (Hazard Ratio [HR] 0.93, 95% CI 0.82–1.05) and dementia (HR 0.86, 95% CI 0.67–1.09) after just two years of follow-up [21] Last, the age of participants at baseline is important since younger individuals have a very low absolute rate of developing cognitive decline and dementia. A further problem unfortunately, is that some large trials of BP lowering did not assess cognition at all, e.g. ASCOT-BP, ALLHAT-BP and PATS [26–29].

3. Lowering blood cholesterol

3.1. Prevention

Two large randomised controlled trials have assessed the effect of lipid lowering with statins on cognition in patients with vascular disease but no dementia. (HPS, PROSPER, Table 1) [29–31]; neither found any effect of lipid lowering on cognition and their results have not been combined as different cognitive measures were assessed. Importantly, both trials included individuals with only modest elevations in cholesterol, had a low risk of developing cognitive decline with low age and good cognition at baseline, and had a relatively short follow-up.

An interesting observation in the cholesterol lowering trials was that intracerebral haemorrhage (ICH) was increased in statin-treated patients with prior cerebrovascular disease [32]; this finding suggests that patients with ICH should not receive stains, and will influence the design of future trials of the effect of statins on cognition after stroke. As for studies of BP lowering, many large trials of lipid lowering have

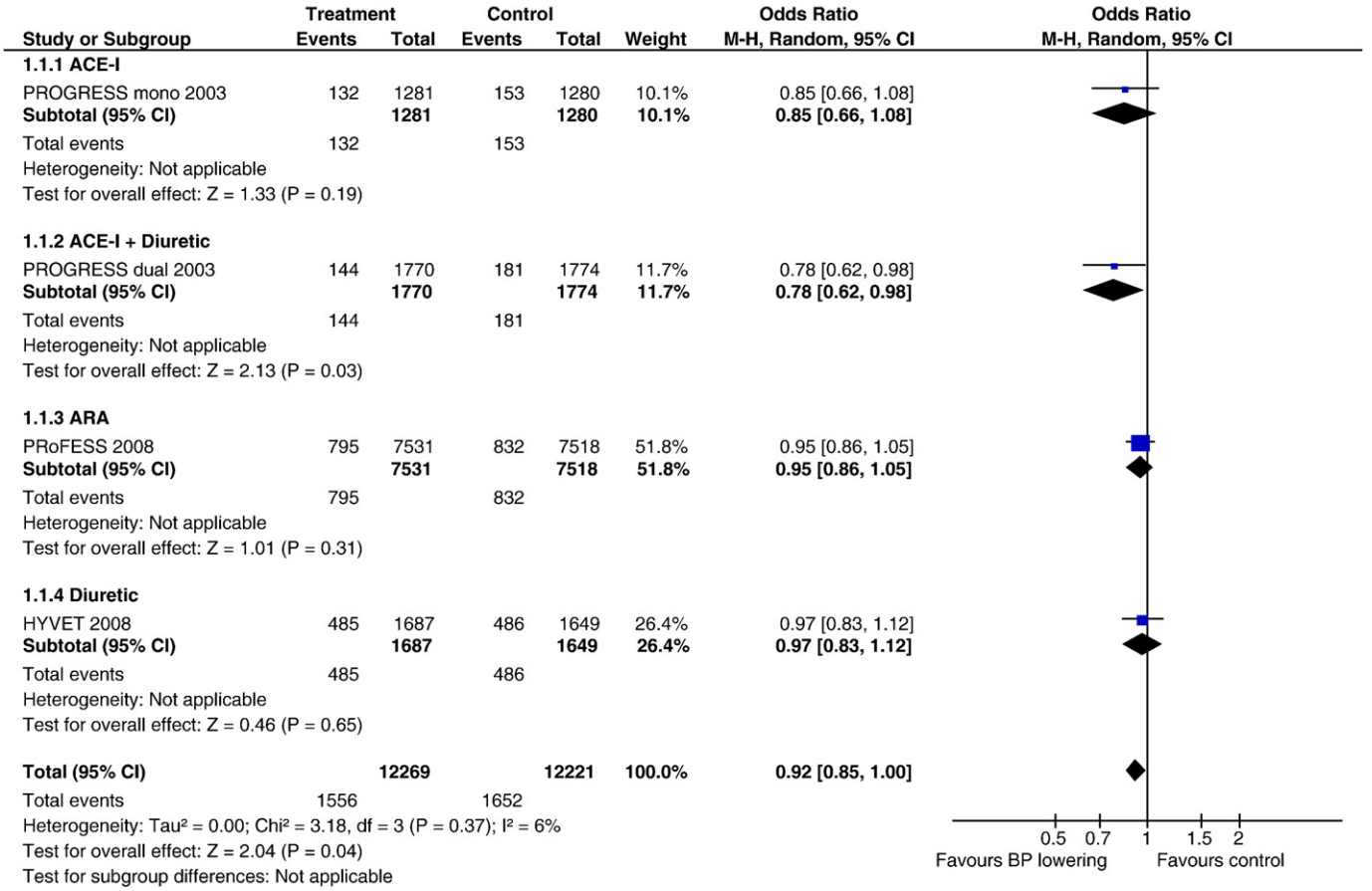

Fig. 1. Effect of blood pressure lowering on cognitive decline, as assessed by Mini-Mental State examination, in three randomised clinical trials reporting cognitive decline. PROGRESS data are shown separately for dual and monotherapy.

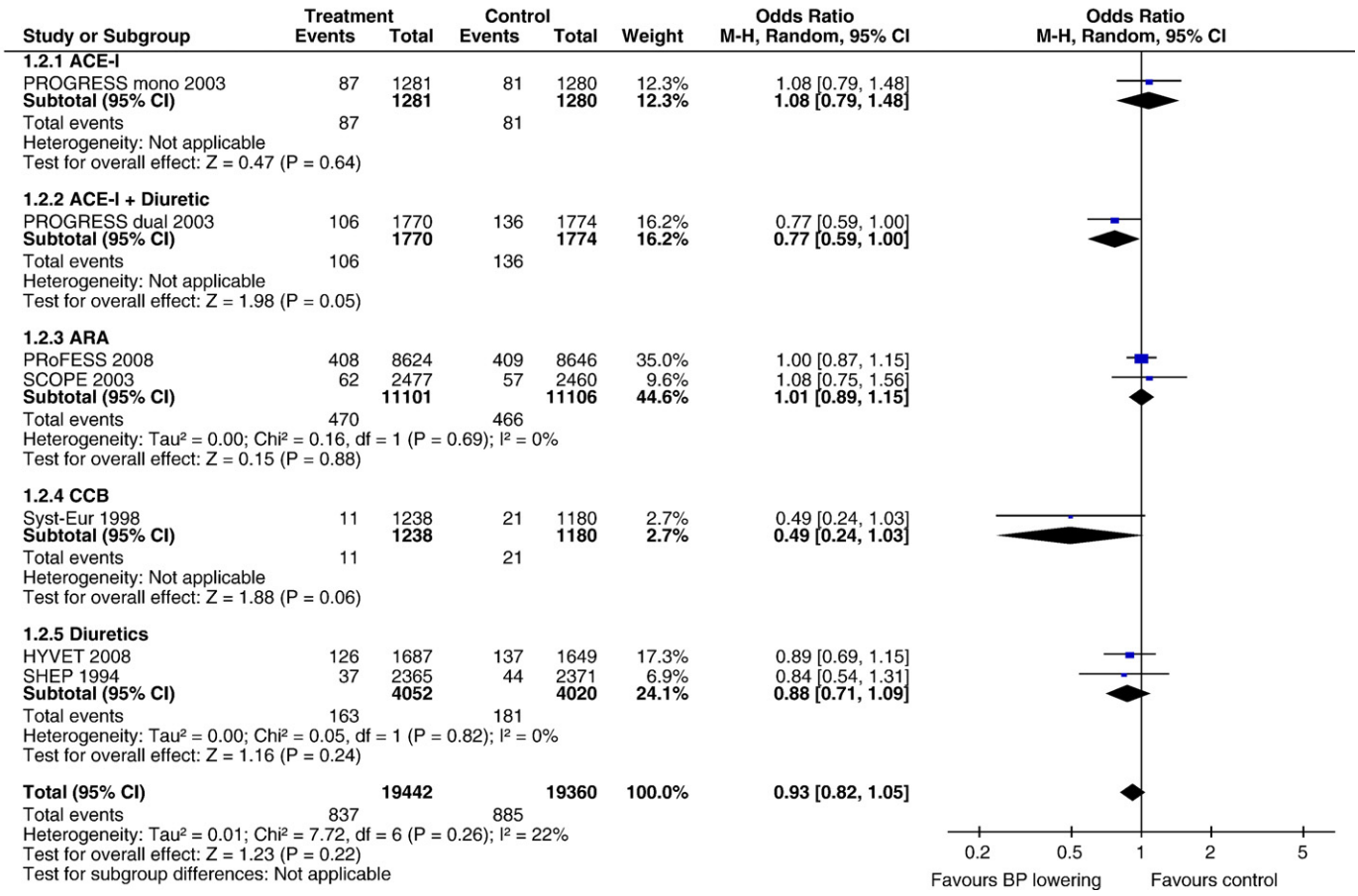

Fig. 2. Effect of blood pressure lowering on dementia in six randomised controlled trials reporting dementia: HYVET, PRoFESS, PROGRESS, SCOPE, SHEP and Syst-Eur (MRC older did not report dementia). PROGRESS data are shown separately for dual and monotherapy.

not included measures of cognition, including ALLHAT-LLA, ASCOT-LLA, and SPARCL [33–35].

3.2. Treatment

Although there are no randomised trials of treating established PSD with lipid lowering agents, three short-term studies have assessed the effect of statins on cognition in patients with mild to moderate Alzheimer's disease [36–38]. A meta-analysis of all the three trials is neutral for MMSE, mean difference 1.14 (95% CI −0.20 to 2.47, p = 0.10) (Fig. 4) and for ADAS-Cog (data not shown); no significant difference was noted between simvastatin and atorvastatin. A similar finding was seen in a very recent Cochrane systematic review [39]. A further statin trial (simvastatin) has recently been completed in mild to moderate Alzheimer's disease (CLASP, n = 400, see http://www.clinicaltrials.gov/ct2/show/NCT00053599 downloaded 25 August 2010); although unpublished, the results are reported as being neutral [40].

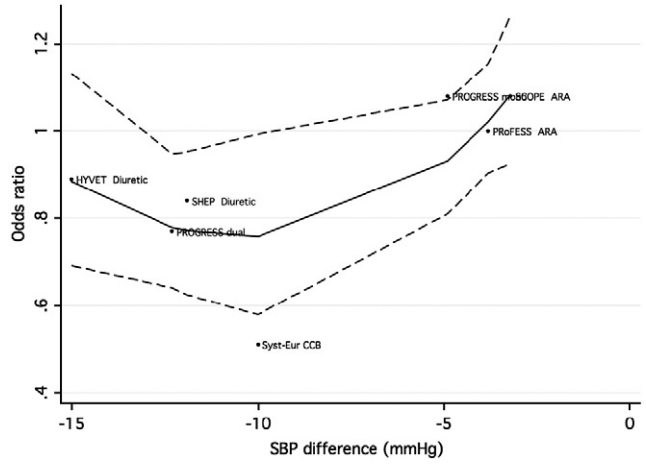

Fig. 3. Relationship by meta-regression between blood pressure difference and dementia. Trials with small SBP difference between treatment and control groups (SCOPE, PRoFESS and PROGRESS monotherapy) were uniformly neutral.

4. Choline esterase inhibitors

4.1. Prevention

There are no randomised trials of choline esterase inhibitors for the prevention of PSD or PSCI.

4.2. Treatment

Ascending cholinergic pathways in the cerebral white matter may be affected in the cerebrovascular ischaemic process [41], and it is biologically plausible that cholinesterase inhibitors may have a beneficial role in preventing or delaying VaD in addition to their small but useful benefit in Alzheimer's disease [42].

A meta-analysis of two trials with similar design (total n = 1219) which studied the effects of donepezil on established, i.e. treatment of mild to moderate vascular cognitive impairment, was positive showing improved cognitive function as assessed using the MMSE and ADAS-Cog [43]. In contrast, a meta-analysis of two trials (total

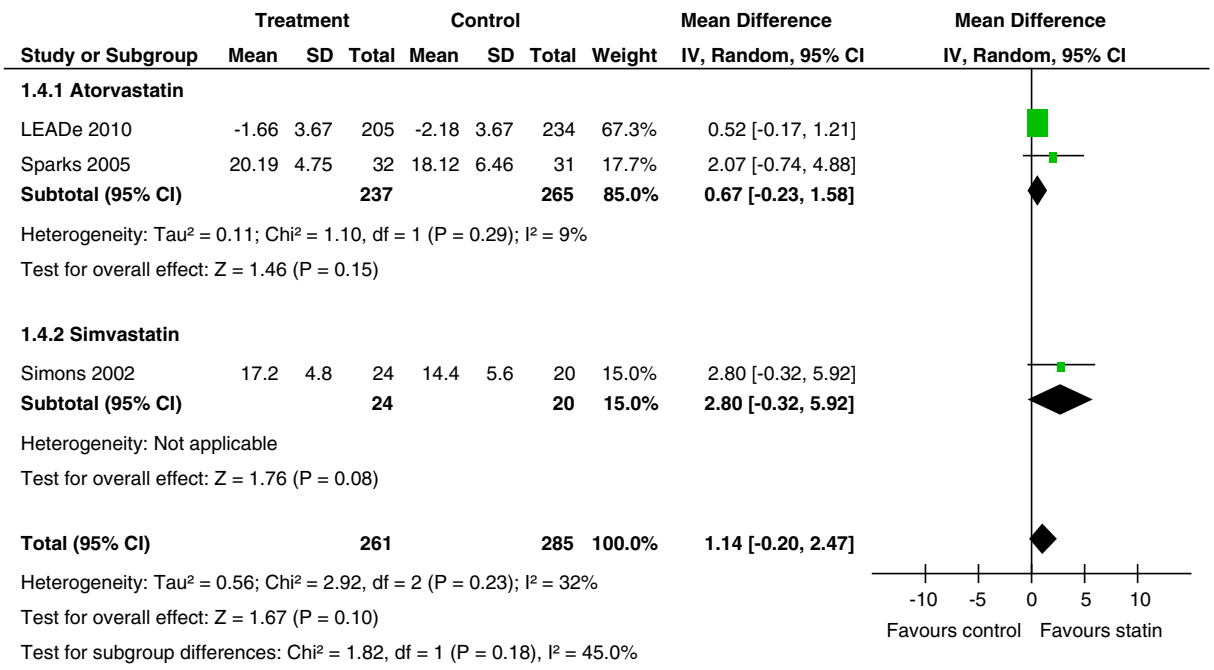

Fig. 4. Effect of lipid lowering on cognition, as assessed by Mini-Mental State Examination, in three randomised controlled trials in Alzheimer's disease. LEADe 2010: Difference in the least squares means change from baseline at 18 months. Sparks 2005: Mean MMSE scores at 1 year estimated from the published graph. Simons 2002: MMSE scores at the end of treatment period.

n = 928) of galantamine was inconclusive [44]. No randomised trials of rivastigmine have been reported [45].

5. Other interventions

Trials have been completed with a variety of other interventions. Although the role of antiplatelets, especially aspirin [46], remains unclear, antiplatelet regimes do not appear to differ from each other in their effect on cognition and dementia, e.g. combined aspirin and dipyridamole vs. clopidogrel [23]. While observational studies suggest that non-steroidal anti-inflammatory drugs (NSAIDS) may be beneficial in preventing Alzheimer's disease (rather than VaD) [47,48], a large randomised treatment trial (ADAPT) found no effect in established Alzheimer's pathology [49]. Trials of selective serotonin reuptake inhibitors have shown some benefit in cognitive enhancement after stroke, both as a consequence of their antidepressant effects and through other independent routes [50,51]. However, none of these studies was definitive.

6. Lessons learnt from completed trials

The failure of these various interventions to convincingly demonstrate efficacy in preventing and reducing VaD and PSD, reflects a variety of reasons.

1. Some interventions may, simply, not alter cognitive function.
2. Cognition was not assessed, as seen in some BP and lipid lowering studies.
3. Most trials were not large enough.
4. Participants were at low risk of developing cognitive impairment, e.g. they were too young or had good cognition to start with; age and baseline cognitive function are key prognostic factors.
5. Treatment intensity was insufficient, as seen in some BP lowering trials.
6. Treatment was not given for long enough, typically for only 0.5 to 4.5 years (Table 1). Observational studies suggest that it may take five years or more for cognitive impairment to develop. Further, the effect of interventions may take time to develop as seen with antihypertensives in preventing stroke, and with NSAIDS and dementia [52].
7. Suboptimal measures of cognition were used which are insensitive to change and/or suffer from ceiling or floor effects. Although the memory-biased MMSE is widely used and trends or statistical differences were present in some of the quoted trials and meta-analyses, it may not be ideal for vascular trials where executive dysfunction may be more important, at least initially, in detecting the development of dementia.
8. The diagnosis of dementia varied. DSM III, DSM IV, clinical interview, and informant interviews have each been used. Use of informant interview, e.g. IQCODE [53], may be useful in long-term studies.
9. Cognition/dementia was not the primary outcome in any of the BP and lipid lowering trials.
10. Suboptimal statistical analysis; although cognitive measures are continuous or ordinal in nature, they are often collapsed into a binary outcome which is inefficient statistically and may mean that trials fail to detect real treatment effects.
11. As a result of the above, the existing trials were not optimised for assessing or analysing the effect of interventions on cognition and dementia. Future trials need to take account of these issues if they are to successfully show that CIND and VaD, including PSD, can be prevented.
12. The distinction between preventing and treating dementia is not always clear in studies. This is important since the population of participants, study design, sample size and outcome measures differ between the two.

7. Ongoing randomised controlled trials or other studies

Several studies are ongoing or planned and these address some of the above issues.

7.1. Secondary prevention of small subcortical stroke (SPS3) trial

SPS3 is ongoing with an aim of recruiting 2500 patients, aged 40 or more, with MRI positive lacunar stroke or TIA within the preceding six

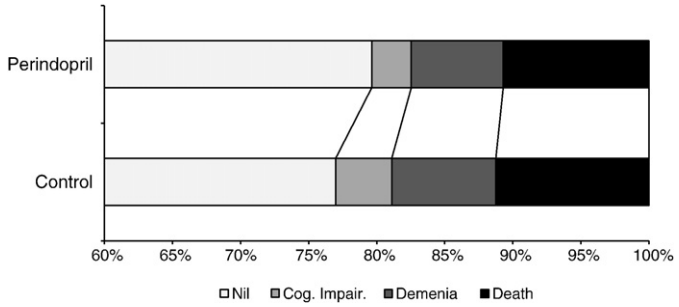

Fig. 5. Ordinalised cognition data from the PROGRESS trial (approximately 3000 patients in each arm). 2000 patients without cognitive impairment (of the total ~3300 patients) have been removed from each treatment group to make the illustration of cognition more clear. Perindopril-based BP lowering improved patients outcome when assessed as an ordinal outcome (dead, dementia, cognitive impairment, nil, Mann—Whitney U, $p = 0.021$) as opposed to assessment as a binary outcome ($p = 0.22$).

months. The study is recruiting patients from the US, Canada, Mexico, Latin America and Spain. It has a factorial design with the antiplatelet arm comparing combined aspirin and clopidogrel with aspirin and placebo; the BP arm is testing intensity of lowering, i.e. systolic BP <130 mm Hg vs. <150 mm Hg. The primary outcomes are ischaemic stroke recurrence and haemorrhagic stroke. Cognitive outcome is a secondary outcome in the antiplatelet comparison. (See: http://www.clinicaltrials.gov/ct2/show/NCT00059306 downloaded 25 August 2010).

7.2. Prevention of decline in cognition after stroke trial (PODCAST)

PODCAST will study patients with ischaemic stroke or primary intracerebral haemorrhage within 3–7 months post stroke. The study has a partial factorial design; all patients will be randomised to intensive (systolic BP <125 mm Hg) vs. guideline BP lowering (systolic BP <140 mm Hg). Additionally, patients with a prior ischaemic stroke (but not primary haemorrhage) will also be randomised to intensive vs. guideline lipid lowering (LDL-cholesterol <2 mmol/l vs. <3 mmol/l). The primary outcome measure is the Addenbrooke's Cognitive Examination; secondary outcomes include dementia, other cognitive scales (Stroop, Trail making A/B, IQCODE, MMSE, MoCA, TICS-M), functional outcomes and vascular events. (See: http://www.podcast-trial.org/, ISRCTN85562386— downloaded 25 August 2010).

7.3. Optimising analysis of cognition (OA-Cog) collaboration

The OA-Cog collaboration aims to optimise the analysis of cognition measures in trials by comparing different statistical methods on existing trial datasets. This approach will mirror a similar collaboration, which set out to optimise the analysis of stroke trials [54–56]. One approach will be to ordinalise cognition and dementia, as shown for the PROGRESS trial (Fig. 5) [19,57]. In this example, perindopril-based BP lowering shifted patients from dementia/dead to no or some cognitive dysfunction (Mann–Whitney U, $p = 0.021$) as opposed to assessment of dementia as a binary outcome ($p = 0.22$). Potential benefits of using ordinal data include more powerful analyses [54] and/or smaller sample sizes [55].

8. Conclusion

While several trials have assessed the effects of antihypertensives, statins, antiplatelets, and choline esterase inhibitors, there is no convincing evidence as yet that such interventions prevent PSCI and PSD. Ongoing and planned trials may define whether such interventions reduce cognitive decline and dementia.

Declarations and conflict of interest

PB was a member of the PRoFESS Trial Steering Committee and is Chief Investigator of the PODCAST and OA-Cog studies. SA and CH are working on PODCAST and OA-Cog and are funded, in part, by the Medical Research Council and British Heart Foundation. PB is Stroke Association Professor of Stroke Medicine. The funding sources had no involvement in the presented analyses or their interpretation.

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