Web Material

Closing the Gap Between Observational Research and Randomized Controlled Trials for Prevention of Alzheimer Disease and Dementia

Melinda C. Power, Brittany Engelman, Jingkai Wei, M. Maria Glymour

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Web Table 1. Overview of Randomized Controlled Trials Testing the Impact of Blood Pressure Lowering Through Antihypertensive Medication Use on Cognition

Trial	Target Population	Intervention and Control Conditions	Primary Trial Outcome	Primary Cognitive Outcome	Primary Cognitive Finding
ACCORD-MIND (1, 2)	People with type 2 diabetes mellitus on diabetes therapy for at least 3 months, age 55-79 or age 40-54 with a history of clinical CVD, at high risk for CVD events, SBP 130-180 mmHg[a], no cognitive impairment or dementia	2 x2 factorial design to (1) active treatment to achieve HBa1C <6.0% or 7.0–7.9%, (2) active treatment to achieve SBP <120 mmHg or <140 mmHg)[a]	Composite outcome (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death)	Change in cognitive function (40-month DSST scores)	Difference in adjusted 40-month DSST mean scores -0.26 (95%CI -0.11, 0.59), p=0.55
ADVANCE (3)	People aged 55 and older with type 2 diabetes and a history of major macrovascular or microvascular disease, or at least one other cardiovascular risk factor	2 x 2 factorial design to (1) perindopril-indapamide vs placebo, (2) intensive glucose control strategy (HbA1C target of 6.5% or less) vs standard glucose control strategy (A1C target defined by local guidelines)	Composite of macrovascular (cardiovascular death, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events	Dementia, cognitive decline (decrease in MMSE score ≥3 points from baseline)	-27% (95%CI -88%, 13%) relative risk reduction for dementia, 2% (95% CI -7%, 11%, p=0.01) relative risk reduction for cognitive decline
HOPE-3 (4, 5)	People aged 70 or older[b] with at least one cardiovascular risk factor (elevated waist-to-hip ratio, low HDLc, tobacco use, dysglycemia, family history of premature coronary disease, mild renal function) but without cardiovascular disease	2 x 2 factorial design to (1) combination of candesartan and hydrochlorothiazide vs placebo and (2) rosuvastatin vs placebo	Composite 1: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, Composite 2: Composite 1 or resuscitated cardiac	Change in cognitive function (DSST score)	Mean difference in DSST score change -0.92 (95% CI -2.55, 0.42)

	or an indication or contraindication for statins		arrest, heart failure, or revascularization		
HYVET-COG (6, 7)	People ages 80 and older with SBP 160–199 mmHg and DBP <110 mmHg, without diagnosed dementia	Active treatment (indapamide with or without perindopril) to a target 150 mmHg SBP and 80 mmHg DBP vs placebo	Fatal or nonfatal stroke	Dementia	HR: 0.86 (95%CI 0.67, 1.09)
MRC (8, 9)	People ages 65–74 with SBP 160–209 mmHg and DBP <115 mmHg who do not take antihypertensive medication, and do not have heart failure or diabetes.	Diuretic vs beta blocker vs placebo, allowing for modifications of active treatment if SBP did not reach target (150 or 160 mm Hg depending on baseline) and initiation of outside-protocol treatment from a GP for those on placebo if SBP<210 mmHg or DBP >115 mmHg	Stroke, coronary events, all-cause mortality	Change in cognitive function (based on PALT and TMT -A scores)	No difference in cognitive change across diuretic, beta blocker, or placebo groups (p=0.33 for TMT-A, p=0.86 for PALT)
ONTARGET (10, 11)	People aged 55 and older with evidence of coronary artery, peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, without heart failure	Telmisartan, ramipiril, or combination of telmisartan and ramipiril	Composite outcome (cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure)	Cognitive impairment (confirmed diagnosis of dementia, or MMSE $\leq$ 23 in those without reported dementia or impairment at baseline), cognitive decline (drop of $\geq$3 MMSE points from baseline)	Telmisartan vs ramipril: cognitive impairment OR: 0.90 (95%CI 0.80, 1.01), cognitive decline OR: 0.97 (95%CI 0.98, 1.06) Combination vs ramipril: cognitive impairment – OR: 0.95 (95%CI 0.85, 1.07); cognitive

					decline – OR: 0.95 (95%CI 0.88, 1.04)
PRoFESS (12, 13)	People aged 55 or older with ischemic stroke in past 90 days or people aged 50–54 or those with stroke 90-120 days with 2 additional risk factors (diabetes mellitus, hypertension, smoker at time of smoke, obesity, previous vascular disease, end organ damage, or hyperlipidemia)	2 x 2 factorial design to (1) low-dose aspirin and extended-release dipyridamole vs clopidogrel (2) telmisartan vs placebo on top of existing antihypertensive medication use	Recurrent stroke	Significant cognitive decline (decrease in MMSE score ≥3 points from baseline), cognitive impairment (MMSE ≤24)	For telmisartan vs placebo, MMSE decrease, RR: 1.01 (95%CI 0.94, 1.09), MMSE ≤24, RR: 0.95 (95%CI 0.87, 1.05)
PROGRESS (14, 15)	People with history of stroke or transient ischemic attack within past 5 years	Active treatment (perindopril with or without indapamide) vs placebo	Fatal and nonfatal stroke	Dementia, substantial cognitive decline (decline of ≥3 points between baseline and last recorded MMSE score)	12% (95%CI -8%, 28%, p=0.20) reduction in risk of dementia, 19% (95% CI 4%, 32%, p=0.01) reduction in risk of cognitive decline
SCOPE (16)	People between the ages of 70–89 with treated or untreated SBP of 160–179 mmHg and/or DBP of 90–99 mmHg and MMSE score of 24 or greater	Candesartan, allowing for addition of treatment with hydrochlorothiazide in either group if SBP >160 mmHg, DBP >90 or SBP did not drop by at least 10 mmHg from baseline, vs usual treatment plus placebo	Major cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, non-fatal stroke)	Dementia, significant cognitive decline (reduction of MMSE of 4 points or more at 2 consecutive visits in comparison with baseline)	MMSE score mean difference of 0.15 (95% CI, -0.08 to 0.38), RR for dementia: 1.08 (calculated from reporting of incidence rates), p>0.20 (reported)
SHEP (17, 18)	People ages 60 and older with SBP 160–219 mmHg and DBP	Drug treatment (step 1 chlorthalidone, step 2	Fatal and nonfatal stroke	Cognitive impairment	No difference in cognitive

	<90 mmHg if not using or after withdrawal of antihypertensive mediation (i.e., isolated systolic hypertension), and absence of other cardiovascular disease or dementia	atenolol or reserpine) with a goal in both arms of a 20 mmHg decrease in SBP in those with baseline SBP 160-179 mmHg and to below 160 mmHg in those with baseline SBP >179 mmHg vs placebo			impairment across groups
SPRINT-MIND (19, 20)	People aged 50 or older with SPB between 130–180 mmHg with increased cardiovascular risk who do not have dementia, history of stroke, or diabetes	Active pharmacologic treatment to achieve SBP of <120 mmHg or <140 mmHg	Composite outcome (MI, other acute coronary syndromes, stroke, heart failure, cardiovascular death)	Dementia	HR 0.93 (95% CI 0.73–1.18), excluding extended follow-up
SPS3 (21, 22)	People aged ≥30 with lacunar stroke confirmed by MRI within previous 6 months, with modified Rankin score >3 and MMSE score ≥24	2 x 2 factorial design to (1) aspirin plus placebo vs aspirin plus clopidogrel, (2) active treatment to SBP <130 mmHg vs 130–149 mmHg	Time to recurrent stroke	Cognitive function (as measured by CASI), incident MCI (based on cognitive test battery performance)	No difference in change in CASI (p=0.52), or incident MCI (p=0.55)
SYST-EUR (23, 24)	People 60 years and older with SBP 160–219 mmHg and DBP <95 mmHg who do not have dementia or congestive heart failure	Active treatment (nitrendipine, with/replaced by or without enalapril and/or hydrochlorothiazide) to reduce SBP by at least 20 mmHg to below 150 mmHg vs placebo	Fatal and nonfatal stroke	Dementia	Reduced incidence of dementia from 7.7 to 3.8 cases per 1000 person years, p=0.05
TRANSCEND (10, 25)	People aged 55 and older with evidence of coronary artery,	Telmisartan vs placebo	Composite outcome (cardiovascular	Cognitive impairment	Cognitive impairment OR:

	peripheral vascular, or cerebrovascular disease or diabetes with end-organ damage, without heart failure, with history of intolerance to ACE inhibitors	death, myocardial infarction, stroke, hospitalization for heart failure)	(confirmed diagnosis of dementia, or MMSE $\leq$ 23 in those without reported dementia or impairment at baseline), cognitive decline (drop of $\geq$3 MMSE points from baseline)	0.97 (95%CI 0.81, 1.17); cognitive decline OR: 1.10 (95%CI 0.95, 1.27)

Abbreviations: ACCORD-MIND, Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CASI, Cognitive Assessment Screening Instrument; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSST, digit-symbol substitution test; GP, general practitioners; HDLc, high density lipoprotein cholesterol; HbA1C, glycated hemoglobin; HOPE-3, Heart Outcomes Prevention Evaluation - 3; HR, hazard ratio; HYVET-COG, Hypertension in the Very Elderly Trial – Cognitive Function Assessment; MMSE, Mini-Mental State Examination; MI, myocardial infarction; MRC, Medical Research Council; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; OR, odds ratio; PALT, paired associate learning test; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes Trial; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RR, relative risk; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SPRINT-MIND, Systolic Blood Pressure Intervention Trial – MIND; SPS-3, Secondary Prevention of Small Subcortical Strokes; SYST-EUR, Systolic Hypertension in Europe; TMT-A, Trail Making Test, Part A; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease

[a]ACCORD-MIND used a double 2x2 factorial design to HbA1c targets and either SBP targets or fenofibrate vs placebo. We report here only on those who could have been randomized to SBP targets.

[b]Age criterion for the HOPE-3 cognitive sub-study only; HOPE-3 included men ages 55 and older and women ages 65 and older

References for Web Materials

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