Question 9 evidence tables

Question 9: What is the optimal management for secondary stroke prevention in CADASIL?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

CADASIL = Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I^2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
303	Y. Li et al. (2015). Cholinesterase inhibitors for rarer dementias associated with neurological conditions. *Cochrane Database of Systematic Reviews,* 2015:3 CD009444	Cochrane SR, 8 studies, diverse neurological conditions with cognitive impairment. Only 1 RCT/study of CADASIL (Dichgans et al, summarised below)	Donepezil 10mg daily vs placebo	Cognitive change only. change from baseline in the score on the vascular AD assessment scale cognitive subscale (V-ADAS-cog) at 18 weeks.	Primary endpoint: least-squares mean change from baseline score was –0·81 (SE 0·59) in the placebo group and –0·85 (SE 0·57) in the donepezil group (p=0·956)	++
306	A. Watanabe-Hosomi et al. (2020). Effect of lomerizine hydrochloride on preventing strokes in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Clinical Neuropharmacology,* 43:5 146-150	Before and after study, non randomised, 30 patients, 17 male	Lomerizine 10mg daily (in divided doses). No control – patients served as own controls	No primary or secondary outcomes prespecified. Analysis 1: Stroke recurrence post treatment vs pre treatment in all patients n=30 Analysis 2: Stroke recurrence post treatment vs pre treatment in those with any stroke pre Tx n=15 Analysis 3: Stroke recurrence post treatment vs pre treatment in those with stroke pre Tx within 2 years n=10	Analysis 1: IR 0.46; 95% confidence interval [CI], 0.19–1.12 Analysis 2: IR 0.33 (95% CI, 0.12–0.94) analysis 3: IR 0.17 (95% CI, 0.04–0.67)	-

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
				Incidence rate ratios compared		
306	A. Watanabe-Hosomi et al. (2020). Effect of lomerizine hydrochloride on preventing strokes in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Clinical Neuropharmacology,* 43:5 146-150	Pilot study, open-label trial in 30 patients with confirmed CADASIL	Lomerizine 10mg/d added to participants previous therapy	Number of symptomatic stroke episodes 2 years before and after starting Lomerizine	In patients with previous stroke episodes Lomerizine reduced stroke recurrence IR (95% CI 0.12-0.94)	**0** Unacceptable Small sample size with risk of bias
304	F. C. Moreton et al. (2021). Brain imaging factors associated with progression of subcortical hyperintensities in CADASIL over 2-year follow-up. *European Journal of Neurology,* 28:1 220-228	Setting: Hospital-based Design: Cohort study Patients: CADASIL. N=22	Intervention: None Comparator: None	Outcome: MRI biomarkers of SVD Timepoint: 2 years	Over 2 years, new stroke or transient ischaemic attack (TIA) occurred in five (23%) subjects and new significant disability in one (5%). There were significant increases in number of lacunes, subcortical hyperintensity volume and microbleeds, and a decrease in brain volume. CBF declined by 3.2 (4.5) ml/100 g/min over 2 years.	**+** Comment: Small sample size. No intervention/comparator.
305	L. Puy et al. (2017). Cerebral microbleeds and the risk of incident ischemic stroke in	Setting: Two-centre Design: cohort study Patients: 369 patients with CADASIL.	Intervention: Microbleeds Comparator: No microbleeds	Outcome: Ischaemic stroke Timepoint: Mean 39 months (up to 54 months)	The risk of incident ischemic stroke was higher in patients with microbleeds than in patients without (35.8%	**+** Comment: Non-randomised. Prognostic information only.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). *Stroke,* 48:10 2699-2703				versus 19.6%, hazard ratio, 1.87; 95% confidence interval, 1.16–3.01; P=0.009). These results persisted after adjustment for history of ischemic stroke, age, sex, vascular risk factors, and antiplatelet agents use (hazard ratio, 1.89; 95% confidence interval, 1.10–3.26; P=0.02).	
302	E. Jouvent et al. (2016). Prediction of 3-year clinical course in CADASIL. *Neurology,* 87:17 1787-1795	Hospital-based cohort study (Munich-Paris), n=369 patients with CADASIL followed for 39 months.	Observational only. The exposure of interest was cerebral microbleeds at baseline.	Ischaemic stroke.	The risk of incident ischemic stroke was higher in patients with microbleeds than in patients without (35.8% versus 19.6%, hazard ratio, 1.87; 95% confidence interval, 1.16–3.01; P=0.009). These results persisted after adjustment for history of ischemic stroke, age, sex, vascular risk factors, and antiplatelet agents use (hazard ratio, 1.89; 95% confidence interval, 1.10–3.26; P=0.02). There were no ICH recorded. 326 patients were taking antiplatelet drugs.	+
307	M. Dichgans et al. (2008). Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol,* 7:4 310-8	RCT 168 patients with CAA 161 analysed	Donepezil 10mg daily vs placebo	Cognitive change only. change from baseline in the score on the vascular AD assessment scale cognitive subscale (V-ADAS-cog) at 18 weeks. Secondary endpoints - scores on the ADAS-cog, MMSE, TMT A time and B	Primary endpoint: least-squares mean change from baseline score was –0·81 (SE 0·59) in the placebo group and –0·85 (SE 0·57) in the donepezil group (p=0·956)	++

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
				time, Stroop, executive interview-25 (EXIT25), CLOX, disability assessment for dementia, and sum of boxes of the clinical dementia rating scale		
309	M. Mancuso et al. (2020). Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. *Eur J Neurol,* 27:6 909-927	EAN Guideline	None. 'few data on management of CADASIL and a paucity of RCTs'	None	Opinion based recommendations only	**N/A**