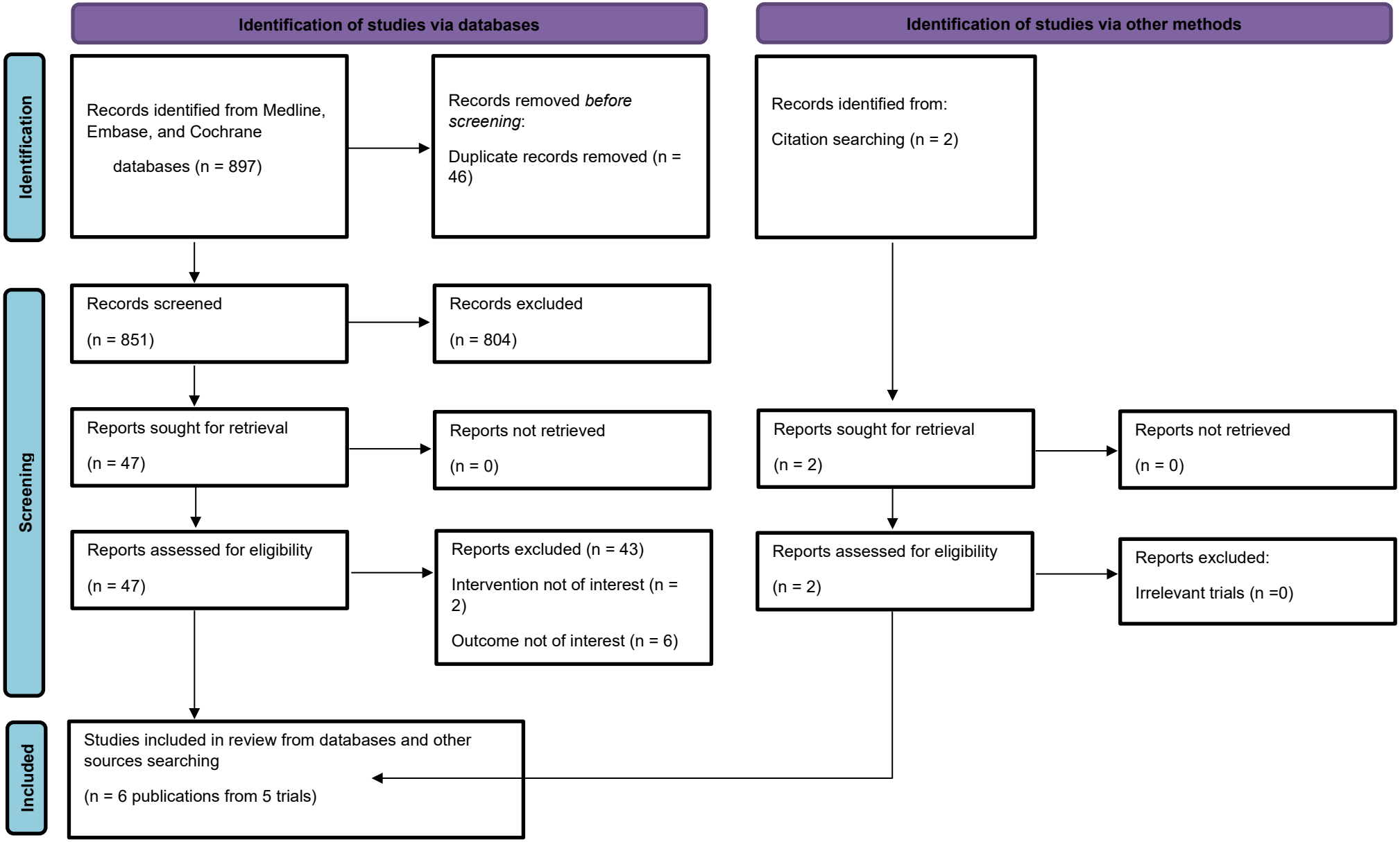
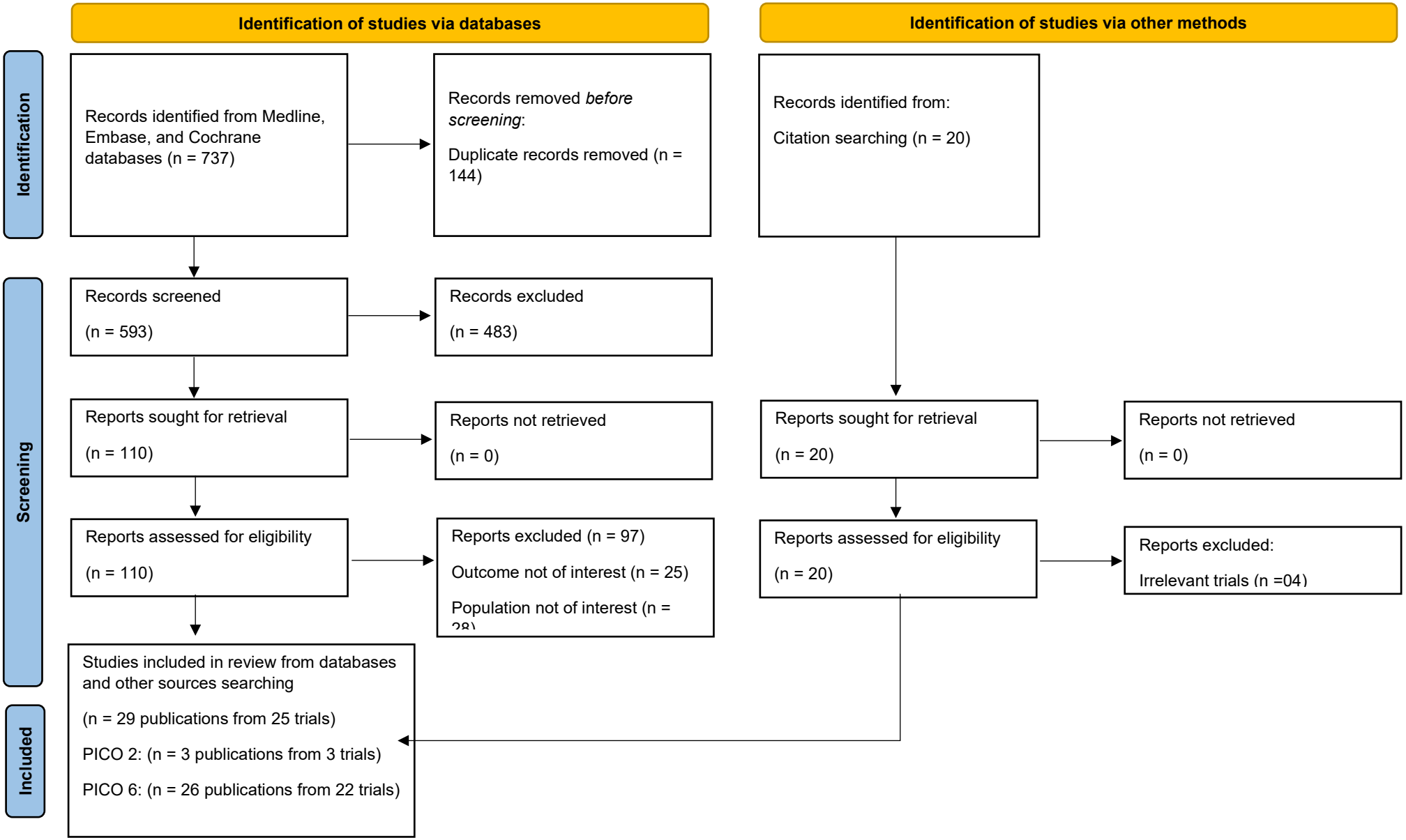
Supplementary Figures PRISMA Flow Diagrams

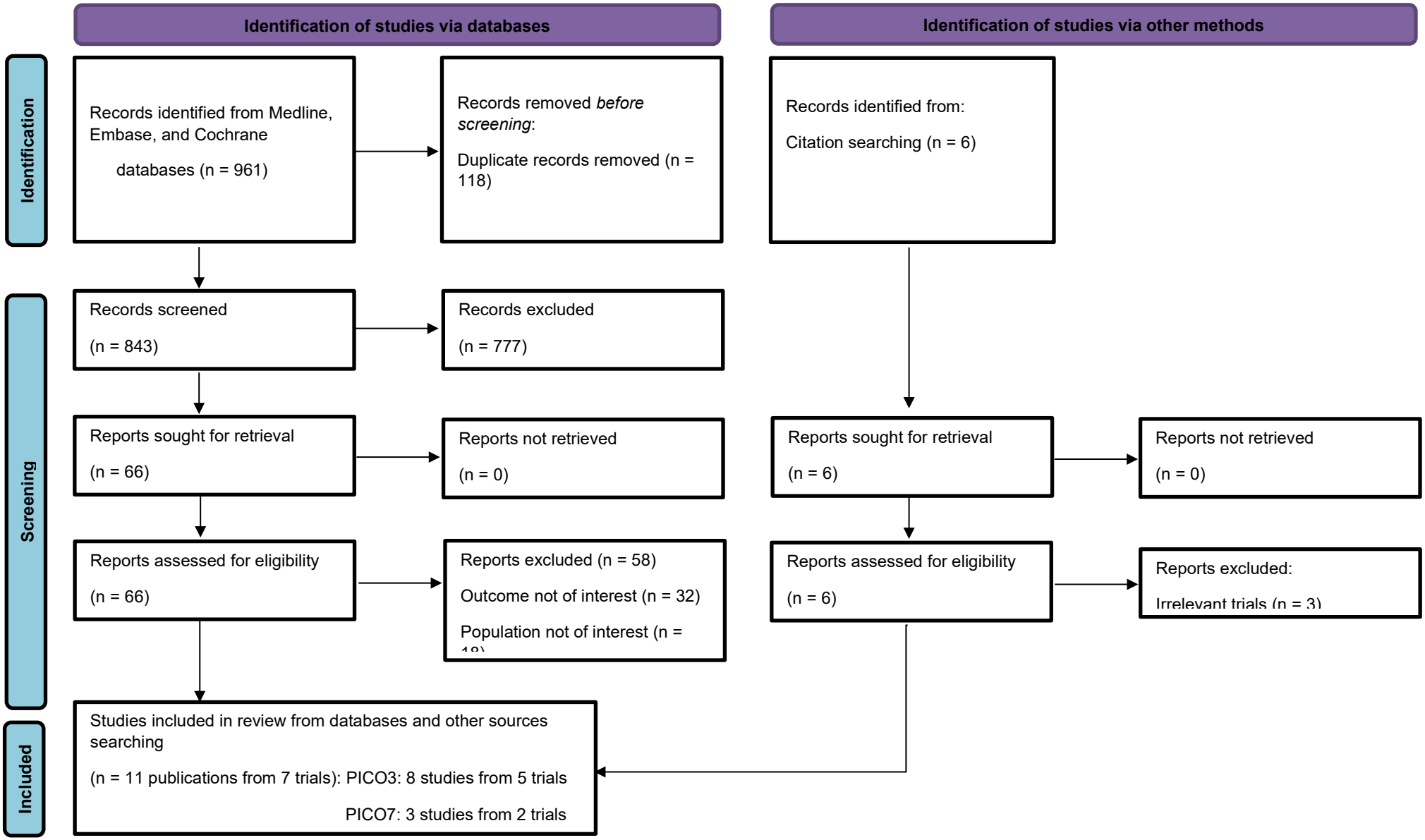
Supplementary Figure 1 Results of search for PICO 1



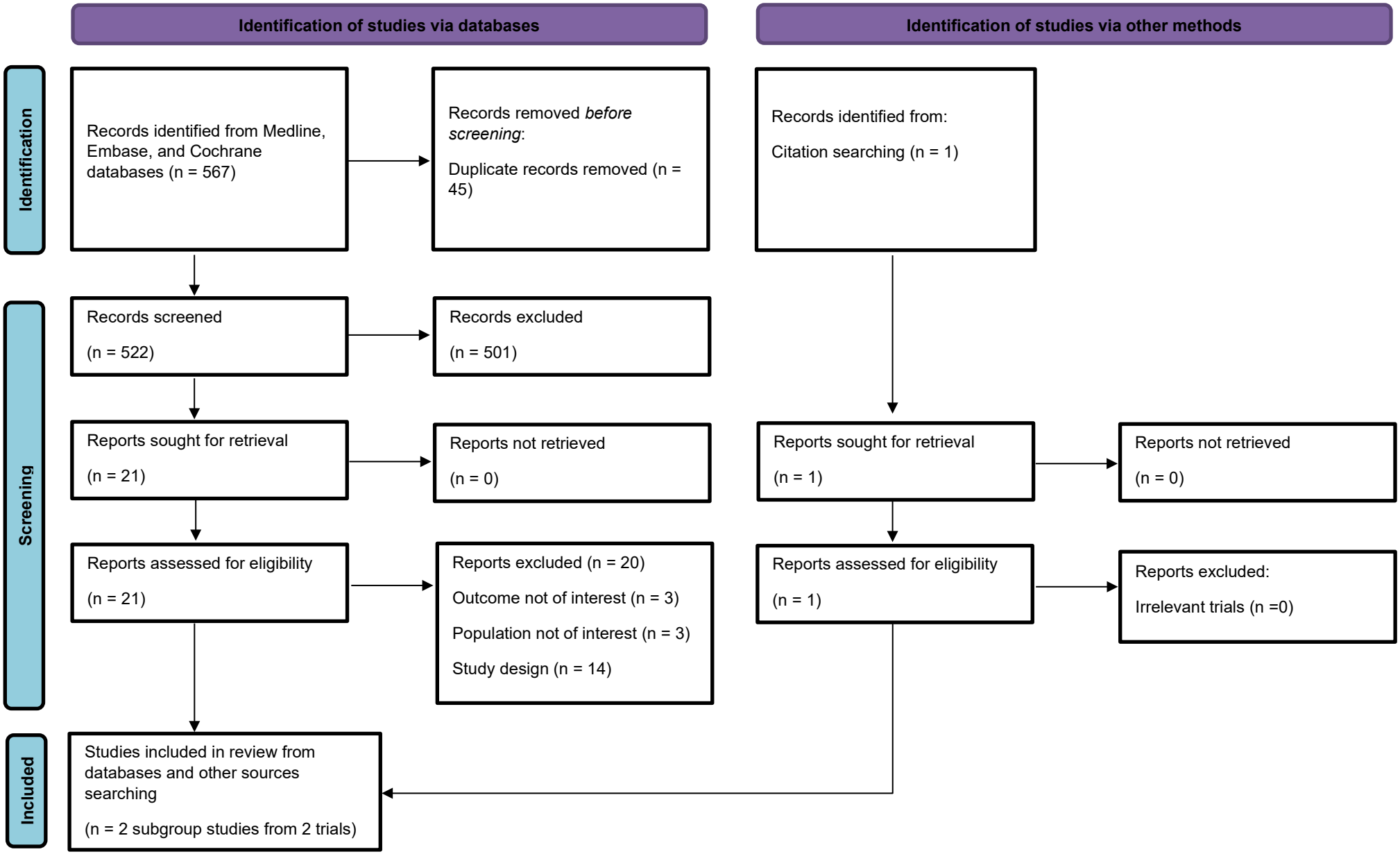
Supplementary Figure 2 Results of search for PICO 2 and 6



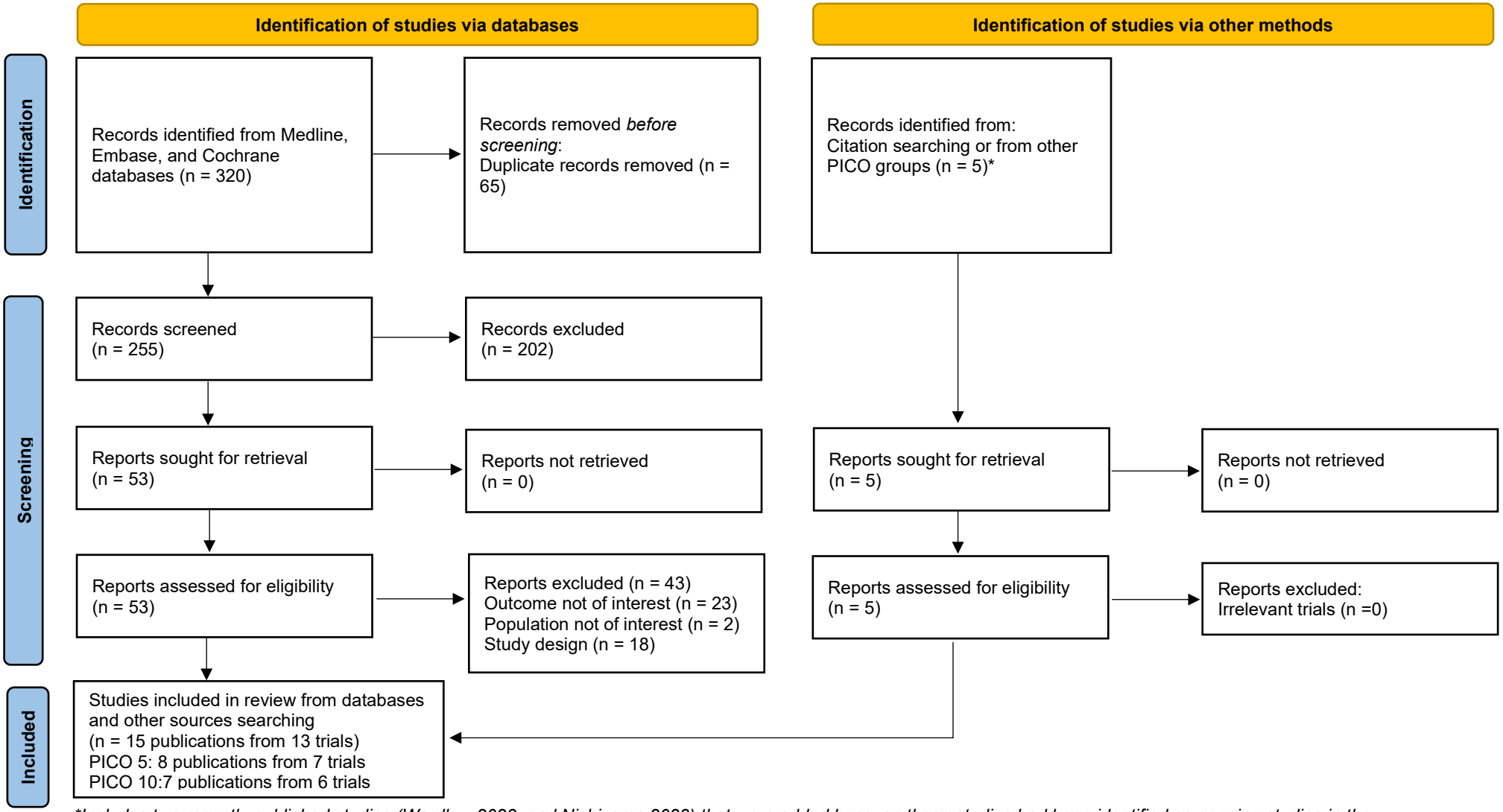
Supplementary Figure 3 Results of search for evidence for PICO 3 and 7



Supplementary Figure 4 Results of search for PICO 4

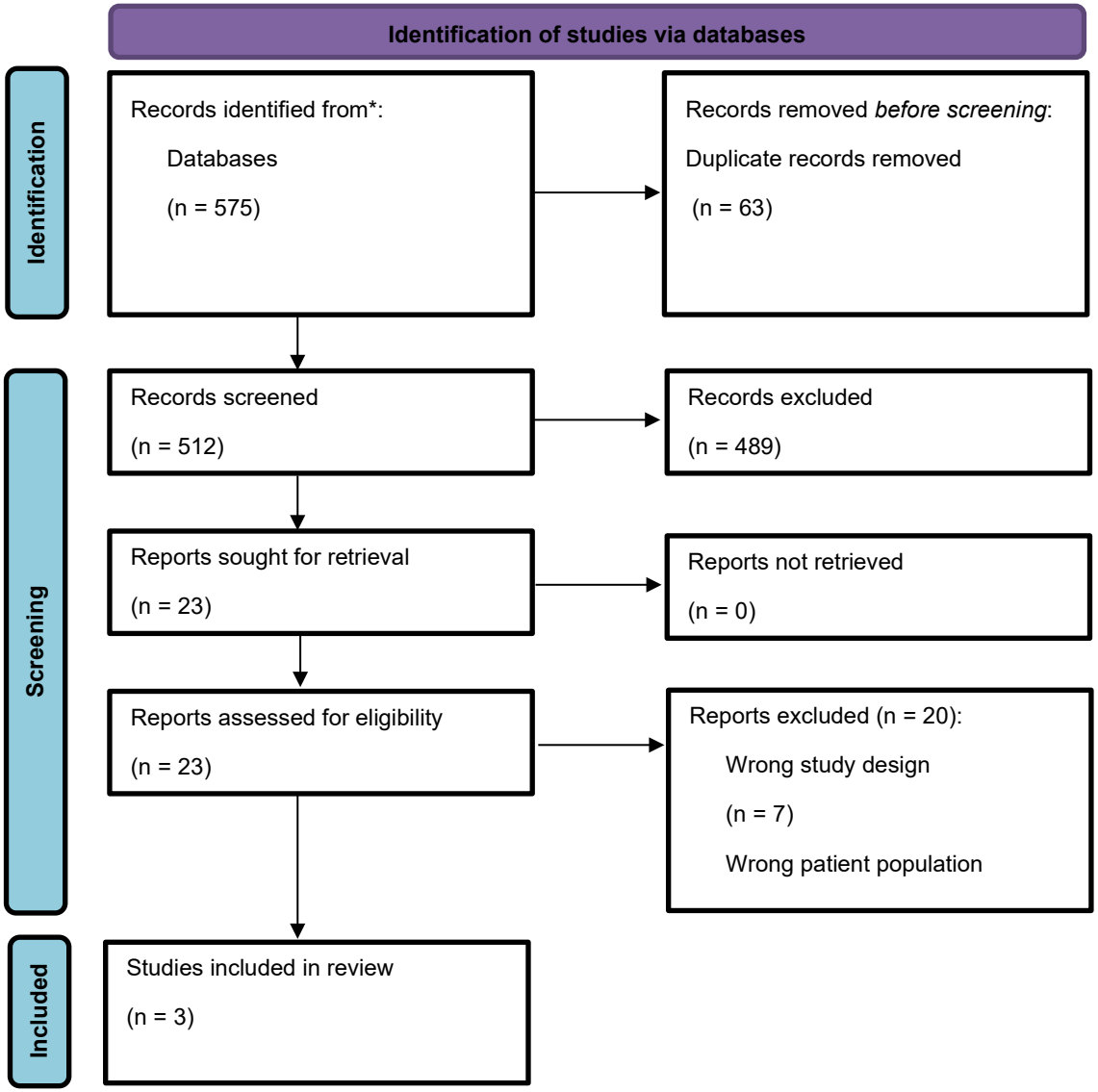


Supplementary Figure 5 Results of search for PICO 5 and 10

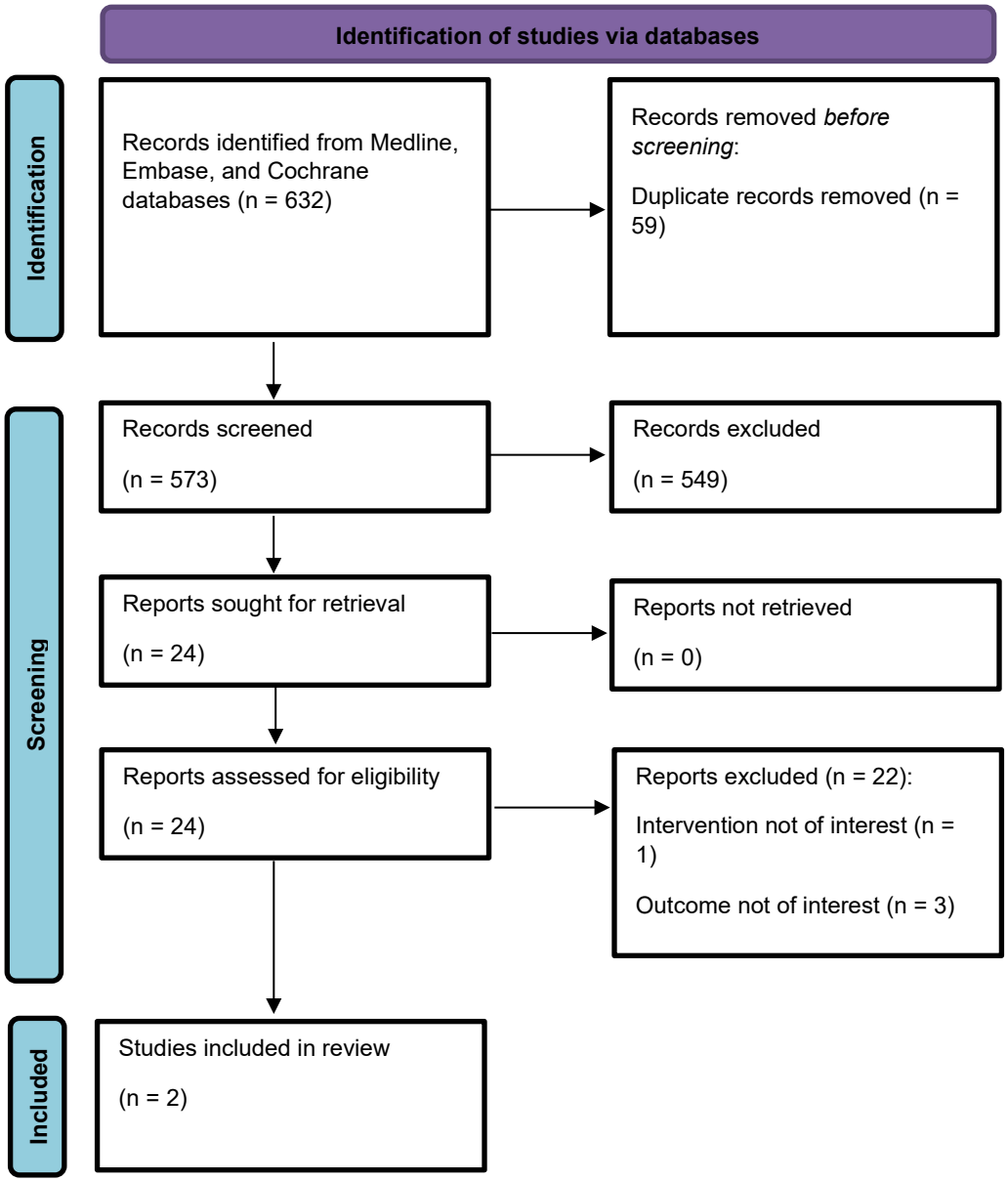


**Includes two recently published studies (Wardlaw 2023, and Nishiyama 2023) that were added because these studies had been identified as ongoing studies in the literature search*

Supplemental Figure 6 Results of search for PICO 8



Supplemental Figure 7 Results of search for PICO 9



Supplementary Tables

Contents

Supplementary Table 1. Conflicts of interest of module working group members

Module working group member	Discipline and affiliation	Intellectual and financial disclosures
Joanna M Wardlaw	Prof JM Wardlaw CBE, MB ChB(Hons), MD, FRCR, FRCP, FMedSci, FRSE Professor of Applied Neuroimaging, Honorary Consultant Neuroradiologist Head of Division, Neuroimaging Sciences, Director, Edinburgh Imaging, Foundation Chair, UK Dementia Research Institute University of Edinburgh and NHS Lothian Chancellor's Building 49 Little France Crescent, Edinburgh, EH16 4SB	Intellectual disclosures: Grants from EU H2020, UK Dementia Research Institute (funded by UK MRC, Alzheimer's Society and Alzheimer's Research UK), UK MRC, BBSRC, Age UK, Fondation Leducq, Wellcome Trust, UK Stroke Association, British Heart Foundation, Alzheimer's Society, Alzheimer's Research UK, The Hilary and Galen Weston Foundation, The Row Fogo Charitable Trust, for research into epidemiology, clinical and cognitive impacts and mechanisms of vascular dysfunction in small vessel disease. Chief Investigator of the Lacunar Intervention trial 2, LACI-2 testing two repurposed drugs to prevent adverse outcomes after lacunar stroke. Financial disclosures: None
Hugues Chabriat	Professor of Neurology, University Paris Cité and APHP, France	Steering Committees of clinical trials HOVID and BIOGEN
Frank-Erik de Leeuw	Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands.	Intellectual disclosures: grants from Dutch Heart Foundation, ZonWM, Dutch Brain Foundation, Abbott. Financial: none Ass Editor International Journal of Stroke
Stéphanie Debette	Epidemiologist, Neurologist (University of Bordeaux, Bordeaux University Hospital, Inserm)	Intellectual: Grants from EU H2020, JPND, ANR, Claude Pompidou foundation, for research on environmental and genetic determinants of stroke, cerebral small vessel disease, MRI-markers of brain aging, cognitive decline and dementia; PI on national investment for the future / France 2023 programs on vascular brain disease (RHU SHIVA; IHU VBHI) Financial: none
Martin Dichgans	Clinical neuroscience, neurogenetics	European Union - Horizon 2020 - Stroke and Dementia Foundation Leducq - Small vessel disease

	Institute for Stroke and Dementia Research (ISD) **Ludwig-Maximilians-University Munich, Medical Center**	**Bayer Vital** **Pfizer Pharma GmbH** **Bristol MYERS SQUIBB**
Fergus Doubal	**Honorary Reader of Stroke Medicine, Stroke Physician Centre for Clinical Brain Sciences, University of Edinburgh**	**Co-applicant and investigator LACI2 BHF grant, research grants from Stroke Association, Alzheimers's Society, BHF Salary funding from NHS Research Scotland**
Hanna Jokinen	**Division of Neuropsychology, HUS Neurocenter, Helsinki University Hospital and University of Helsinki** **Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland**	**Research funding from Academy of Finland, and Helsinki and Uusimaa Hospital District**
Aristeidis Katsanos	**Neurology, McMaster University & Population Health Research Institute, Hamilton, ON, Canada**	**None**
Raffaele Ornello	**Neurology / Department of Biotechnological ad Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy**	**Personal fees from Eli Lilly, Novartis, Teva** **Non-financial support from Allergan/Abbvie, Novartis, Teva** **Associate Editor for Frontiers in Neurology, section Headache and Neurogenic Pain** **Junior Editorial Board member for The Journal of Headache and Pain**
Leonardo Pantoni	**Neurology, Department of Biomedical and Clinical Sciences, University of Milan, Italy**	**Editorial board member of Neurology, Stroke, European Stroke Journal, Cerebrovascular Diseases, Cerebral Circulation Cognition and Behavior. Associate Editor Neurological Sciences.**
Marco Pasi	**Department of Neurology, University of Tours, France**	**None**
Aleksandra M. Pavlovic	**Neurologist** **University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia**	**None**
Salvatore Rudilosso	**Neurology.**	**NA**

	Functional Unit of Cerebrovascular Diseases. Hospital Clínic of Barcelona, and August Pi i Sunyer Biomedical Research Institute (IDIBAPS). Barcelona, Spain	
Reinhold Schmidt	**Neurology, Department of Neurology, Medical University Graz, Austria**	**None**
Julie Staals	**Department of Neurology, Maastricht UMC+, the Netherlands** **School for cardiovascular diseases (CARIM), Maastricht University, the Netherlands**	**Intellectual disclosures: None** **Financial disclosures:** **Funded research: EU H2020 SVDs@target project; grant agreement No 666881; EU H2020 CRUCIAL project; grant agreement No 848109**
Martin Taylor-Rowan	**School of Health and Wellbeing; General Practice and Primary Care**	**None**
Arne G Lindgren	**M.D., PhD, Professor of Neurology; Senior Consultant Neurology.** **Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden; Department of Neurology, Skåne University Hospital, Lund, Sweden**	**Grants from: The Swedish Heart and Lung Foundation (nr. 20210672); The Swedish Government (under the "Avtal om Läkarutbildning och Medicinsk Forskning, ALF") (2022-Projekt0279); Lund University; Region Skåne; NIH (1R01-NS114045); The Fremasons Lodge of Instruction Eos in Lund; The Swedish Stroke Association.** **Dr Lindgren has served as national leader for Sweden and Denmark for the NAVIGATE study. He is national leader for Sweden for 2 ongoing stroke trials. He is local PI for the StrokeCLOSE study.** **Personal fees from Bayer, Astra Zeneca, BMS Pfizer, Novo Nordisk, and Portola.**

Supplementary Table 2. List and rating of the selected outcomes for each PICO question.

PICO	Outcome	Average score
PICO 1 In patients with suspected lacunar ischaemic stroke, does thrombolytic treatment (including at extended time window and wake-up stroke, alteplase/tenecteplase/other), compared to avoiding this intervention/other thrombolytic/dose/etc, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	dependency death cognitive impairment or dementia haemorrhagic stroke	3.6 1.7 1 1.5
PICO 2 In patients with suspected acute lacunar ischaemic stroke, does acute treatment with antiplatelets (considering single/dual, duration, and whether any particular antiplatelet or combination of antiplatelets is better), compared to avoiding/less of/alternative antiplatelet intervention, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke dependency haemorrhagic stroke MACE	3 2 1.3 1.7
PICO 3 In patients with suspected acute lacunar ischaemic stroke, does immediate antihypertensive treatment (considering agent and BP target), compared to avoiding this intervention, reduce recurrent ischaemic stroke, dependency,	recurrent ischaemic stroke dependency death MACE	2 2.3 1.4 1.7

death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?		
PICO 4 In patients with suspected acute lacunar ischaemic stroke and progressing symptoms, does acute treatment with antiplatelets/anticoagulants/thrombolysis/other agent, compared to less intense or avoiding this intervention, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke dependency death haemorrhagic stroke MACE	1.7 3.6 1.3 1 1
PICO 5 In patients with suspected acute lacunar ischaemic stroke, does acute treatment with other agents such as Phosphodiesterase inhibitors-3 inhibitors [e.g. cilostazol, pentoxifylline], anti-inflammatory agents [e.g. minocycline], anticoagulants, Nitric Oxide donors [e.g. transdermal glyceryl trinitrate], Phosphodiesterase inhibitors-5 [sildenafil, tadalafil, dipyridamole], or other relevant agents not addressed in the other PICOs, compared to less intense or avoiding this intervention, reduce any recurrent stroke, recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia (5.4), haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke dependency cognitive impairment or dementia MACE	1.7 3.2 1.3 1.2
PICO 6 In patients with lacunar ischaemic stroke, does long term treatment with antiplatelets (single or dual, duration, and whether any particular	recurrent ischaemic stroke dependency haemorrhagic stroke	3.2 1.4 1

antiplatelet or combination of antiplatelets is better), compared to avoiding/less of/alternative antiplatelet intervention, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	MACE	2
PICO 7 In patients with lacunar ischaemic stroke, does antihypertensive treatment considering a particular agent or target, compared to less intense or avoiding this intervention given long term, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke cognitive impairment or dementia haemorrhagic stroke MACE	3 1.3 1.3 1.9
PICO 8 In patients with lacunar ischaemic stroke, does treatment with lipid lowering agents (considering a particular agent, dose, target), compared to less intense or avoiding this intervention, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke death cognitive impairment or dementia MACE	3.05 1.1 1.25 2.05
PICO 9 In patients with lacunar ischaemic stroke, does treatment with lifestyle interventions [e.g. smoking cessation, dietary interventions, weight reduction, physical exercise, cognitive/behavioural or social interventions, sleep/CPAP, or a mixture of these], compared to less intense or avoiding	recurrent ischaemic stroke dependency cognitive impairment or dementia MACE	2.8 1.3 1.8 2.3

this intervention, reduce recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?		
PICO 10 In patients with lacunar ischaemic stroke, do other treatments as secondary prevention, such as phosphodiesterase inhibitors [e.g. cilostazol, pentoxifylline, sildenafil, tadalafil], anticoagulants, anti-inflammatory agents (e.g. minocycline), nitric oxide donors [e.g. transdermal glyceryl trinitrate], or other relevant agents, compared to less intense or avoiding this intervention, reduce any recurrent stroke, recurrent ischaemic stroke, dependency, death, cognitive impairment or dementia, haemorrhagic stroke, MACE, mobility or gait disorder, and mood disorders?	recurrent ischaemic stroke dependency cognitive impairment or dementia MACE	2.5 1.4 2 1.6

Supplementary Table 3: Results of the votes for the Expert Consensus Statements

PICO 1 Expert Consensus Statement 1. Twelve of 12 MWG members agreed that in patients with suspected acute lacunar ischaemic stroke, with no contraindication to thrombolytic treatment according to current clinical guidelines for thrombolytic treatment (including wake up stroke), there is no evidence for withholding thrombolytic treatment. Therefore these patients should receive intravenous alteplase at standard dose (0.9mg/kg) as quickly as possible according to current clinical guidelines. 2. Twelve of 12 MWG members agreed that in patients with suspected acute lacunar ischaemic stroke there are insufficient data to support use of thrombolytic drugs other than alteplase, or a lower dose of alteplase, at the present time.	12/12 writing group members agree. 12/12 writing group members agree.
PICO 2 Expert Consensus Statement Twelve of 12 MWG members agree to the statement that in patients with suspected lacunar ischaemic stroke, initiation of antiplatelet therapy should be started as soon as possible after stroke onset.	11/12 writing group members agree.
PICO 3 Expert Consensus Statement 1. Twelve of 12 MWG members agreed that there is insufficient evidence at present to provide a precise timeframe during which BP lowering agents should be avoided in patients with suspected acute lacunar ischaemic stroke. Based on current limited evidence, blood pressure lowering therapy should be avoided for at least 24 hours after symptom onset. 2. When antihypertensive drugs need to be used in patients with suspected acute lacunar ischaemic stroke undergoing intravenous thrombolysis and with BP > 180/105mmHg, twelve of 12 MWG members agreed that there is no	12/12 writing group members agree. 12/12 writing group members agree.

advantage/disadvantage of one antihypertensive medication over another, hence any antihypertensive drug may be used, as long as blood pressure is closely monitored. 3. Eleven of 12 MWG members agreed that in patients with suspected acute lacunar ischaemic stroke not treated with intravenous thrombolysis and blood pressure >220/120 mmHg, careful blood pressure reduction (<15% systolic blood reduction in 24 hours) is reasonable. No specific blood pressure lowering agent can be recommended.	11/12 writing group members agree.
PICO 4 Expert Consensus Statement 1. Twelve of 12 MWG members agreed that in patients with suspected lacunar ischaemic stroke and progressing symptoms there is no evidence to recommend any particular antiplatelet regimen (intensive or single), BP management regimen (raising or lowering), rt-PA, anticoagulation, statin, or other treatment. 2. Twelve of 12 MWG members agreed that in patients with suspected lacunar ischaemic stroke and progressing symptoms they should be included in all trials in acute lacunar ischaemic stroke but identified as a specific subgroup with prespecified planned analysis of the treatment effect in this subgroup. 3. Twelve of 12 MWG members agreed that in patients with suspected lacunar ischaemic stroke and progressing symptoms there is an urgent need to agree a consensus definition for progressing symptoms.	12/12 writing group members agree. 12/12 writing group members agree. 12/12 writing group members agree.
PICO 6 Expert Consensus Statement 1. In patients with suspected lacunar ischaemic stroke twelve of 12 MWG members recommend against the use of long-term* dual or triple antiplatelet therapy. Instead, single antiplatelet therapy should be used as per the Evidence	12/12 writing group members agree.

Based Recommendation, unless other conditions warrant a combination of these medications. *) Defined as more than 2-4 weeks 2. In patients with suspected lacunar ischaemic stroke, eleven of 12 MWG members agreed that the current evidence was inadequate to recommend routine use of cilostazol to prevent adverse long term outcomes.	11/12 writing group members agree.
PICO 7 Expert Consensus Statement 1. Twelve of 12 MWG members suggest that: BP should be appropriately monitored and well controlled, when possible through use of out of office blood pressure measurements. We cannot advise any specific antihypertensive treatment. 2. Eleven of 12 MWG members agree that aiming for BP <130/80 mmHg as generally recommended for patients with previous ischaemic stroke or TIA may be reasonable, but that drastic BP reductions and important BP variability should be avoided, probably targeting SBP between 125 and 130 mmHg and DBP between 70 and 80 mmHg.	12/12 writing group members agree. 11/12 writing group members agree.
PICO 8 Expert Consensus Statement Twelve of 12 MWG members agreed that patients with lacunar ischaemic stroke should receive lipid lowering therapy given there is some evidence of benefit and no clear evidence of harm.	12/12 writing group members agree.
PICO 9 Expert Consensus Statement Despite lack of direct evidence, twelve of 12 MWG members suggest that it is advisable to promote healthy lifestyle modifications in patients with lacunar stroke as recommended in secondary prevention for stroke and VCI. These include regular	12/12 writing group members agree.

physical exercise, maintaining healthy body weight, avoiding smoking and excess alcohol, and eating a healthy balanced diet with low sodium intake.	
PICO 10 Expert Consensus Statement 1. In patients with lacunar ischaemic stroke without AF, twelve of 12 MWG members recommend against the use of anticoagulation for secondary prevention, if there is no other indication. 2. In patients with lacunar ischaemic stroke and AF, twelve of 12 MWG members recommend for the use of anticoagulation for secondary prevention. The evidence for efficacy of anticoagulants over antiplatelet is strong in patients with AF, overruling stroke subtype. However, since the risk of ICH is increased in patients with lacunar stroke and severe SVD, we recommend strict risk factors control.	12/12 writing group members agree. 12/12 writing group members agree.

Supplementary Table 4 – Summary of clinical trial findings relevant to PICO 1: thrombolysis for suspected acute lacunar ischaemic stroke.

Study author; year	Trial name/ NCTID	Population	Inter-vention	Compar-ator	Mean age (Years)	Trial duration/ Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/ HR	Comments/ Notes
								N event	N total	N event	N total		
Recurrent Ischaemic Stroke													
Haemorrhagic stroke													
Barow et al, 2019	WAKE-UP	Lacunar stroke - MRI (subgroup) in patients with wake up stroke or unknown symptoms onset	alteplase 0.9mg/kg	Placebo	63	90 days	Symp-tomatic ICH post thromb-olysis	1	55	0	53	Not estimable	per NINDS, SITS-MOST, ECASS II & ECASS III definitions
Barow et al, 2019	WAKE-UP	Lacunar stroke - MRI (subgroup) in patients with wake up stroke or unknown symptoms onset	alteplase 0.9mg/kg	Placebo	63	90 days	Paren-chymal haemorrhage post thromb-olysis	1	55	0	53	Not estimable	type II parenchymal haemorrhage in follow-up CT
Zhou et al; 2021	ENCHANTED	Lacunar stroke within 4.5 hrs from symptoms onset (subgroup)	alteplase 0.6mg/kg	alteplase 0.9mg/kg	64	90 days	Sympto-matic ICH post thrombo-lysis	1	241	0	249	Not estimable	per SITS-MOST criteria

Zhou et al; 2021	ENCHANTED	Lacunar stroke within 4.5 hrs from symptoms onset (subgroup)	alteplase 0.6mg/kg	alteplase 0.9mg/kg	64	90 days	Any ICH	11	241	7	249	adjusted OR=1.50 (0.56, 3.99)	per SITS-MOST criteria. Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [modified Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group)
Cognitive impairment or dementia													

Mobility or Gait disorder													
Mood disorders													
MACE													
Dependency													
Barow et al, 2019	WAKE-UP	Lacunar stroke - MRI (subgroup) in patients with wake up stroke or unknown symptoms onset	alteplase 0.9mg/kg	Placebo	63	90 days	mRS 4 & 5	3	55	4	53	Not provided	Estimated by subtracting deaths from the death & dependency outcome
Zhou et al; 2021	ENCHANTED	Lacunar stroke within 4.5 hrs from symptoms onset (subgroup)	alteplase 0.6mg/kg	alteplase 0.9mg/kg	64	90 days	mRS 3-5	43	238	29	243	Not provided	Estimated after subtracting death cases from mRS 3-6. Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [modified

													Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group)
Death													
Barow et al, 2019	WAKE-UP	Lacunar stroke - MRI (subgroup) in patients with wake up stroke or unknown symptoms onset	alteplase 0.9mg/kg	Placebo	63	90 days	all-cause death at 90 days	1	55	0	53	Not estim-able	
Zhou et al; 2021	ENCHANTED	Lacunar stroke within 4.5 hrs from symptoms onset (subgroup)	alteplase 0.6mg/kg	alteplase 0.9mg/kg	64	90 days	all-cause death at 90 days	1	241	2	249	adjusted OR=0.44 (0.03, 5.71)	Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale

													[NIHSS] score, time from stroke onset to randomization, premorbid function [modified Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group)
Favorable functional outcome/ excellent functional outcome													
NINDS collaborators; 1995	NINDS	Small vessel occlusion within 3 hrs from symptoms onset (subgroup)	alteplase 0.9mg/kg	Placebo	N/A	90 days	mRS 0-1	32	51	12	30	Not provided	Calculated based on the percentages provided in Table

Barow et al, 2019	WAKE-UP	Lacunar stroke - MRI (subgroup) in patients with wake up stroke or unknown symptoms onset	alteplase 0.9mg/kg	Placebo	63	90 days	mRS 0-1	31	55	24	53	adjusted OR=1.67 (0.77, 3.64)	adjusted for age and symptom severity
IST-3 collaborators; 2012	IST-3	Lacunar stroke within 6 hrs from symptoms onset (subgroup)	alteplase 0.9mg/kg	Placebo	N/A	90 days	Oxford Handicap Score 0-2	100	168	103	164	adjusted OR=0.91 (0.48, 1.72)	adjusted for age, NIHSS, and delay in tretment
Zhou et al; 2021	ENCHANTED	Lacunar stroke within 4.5 hrs from symptoms onset (subgroup)	alteplase 0.6mg/kg	alteplase 0.9mg/kg	64	90 days	mRS 0-1	162	238	172	243	adjusted OR=0.85 (0.56, 1.28)	Calculated after inverting values for mRS 2-6 provided in the Figure. Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [modified Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other

													antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group)

Supplementary Table 5: Summary of clinical trial findings relevant for PICO 2: antiplatelet treatment in suspected acute lacunar ischaemic stroke

Study author; year	Trial name/NCTID	Population	Intervention	Comparator	Mean age (Years)	Trial duration/Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/HR	Comments/Notes
								N event	N total	N event	N total		
Recurrent Ischaemic Stroke													
Bath, 2018	TARDIS	lacunar stroke (subgroup) within 48hrs	(combined aspirin, clopidogrel, and dipyridamole)	combined aspirin and dipyridamole, or clopidogrel alone	N/A	90 days	Recurrent ischaemic stroke or TIA	N/A	646	N/A	642	OR=1.0 (0.6-1.5)	N of events not provided
Haemorrhagic stroke													
Cognitive impairment or dementia													
Mobility or Gait disorder													
Mood disorders													

MACE													
CAST collaborative group; 1997	CAST	Lacunar infarct	Aspirin	Placebo	NA	4 weeks	Any stroke, MI (?), death	78	3117	88	3146	RR: 0.89 (0.66-1.21)	data extracted direct from Kwok 2015 meta-analysis.
Dependency													
IST collaborators, 1997	IST	lacunar stroke (subgroup) within 48hrs	Aspirin	no aspirin	N/A	6 months	Death or dependency	1112	2308	1116	2308	OR 0.99 (95%CI:0.88-1.11)	
Death													

Supplementary Table 6 – Summary of clinical trial findings relevant to PICO 3: blood pressure lowering in suspected acute lacunar ischaemic stroke.

Study	Trial name	Population	Intervention	Comparator	Timing of intervention	Timing from onset to randomisation	Mean age ± SD (yrs)	Follow-up	Out-comes	Inter-vention		Compar-ator		OR/HR (95%CI), ± P or P interaction*	Favors BP lowering
										N event	N total	N event	N total		
Haemorrhagic stroke															
Zhou, 2020	ENCHANTED	Lacunar ischaemic stroke (subgroup) treated with intravenous alteplase	SBP 130-140 mmHg	SBP < 180 mmHg	≤ 6 hrs of stroke	3 hrs	64±12	90 days	Adjudicated ICH	10	238	7	216	OR: 1.57 (0.57-4.32)	N (NS)
									Intracranial haemorrhage	13	238	9	216	OR: 1.59 (0.65-3.89)	N (NS)
									Symptomatic ICH	1	238	0	216	NR	
Major adverse cardiovascular events (MACE)															
Sandset 2015	SCAST	Lacunar ischaemic stroke (subgroup) with SBP ≥140 mmHg (8% thombolysis) †	Cande-sartan	Placebo	≤ 30 hrs of stroke	18 hrs	70±11	6 months	Vascular death, stroke, or myocardial infarction	23	244	20	266	HR: 1.28 (0.71-2.34)	N (NS)
Oh, 2015	VENTURE	Lacunar ischaemic stroke (subgroup) with SBP 150-185 mm Hg, non thrombolyzed	Valsartan	Placebo	≤ 48 hrs of stroke	12 hrs	64.1±11.5 (valsartan) 65.6±11.7 (control)	90 days	Nonfatal stroke, nonfatal myocardial infarction, and vascular death	2	77	1	93	OR: 2.45 (0.22-27.58) P interaction 0.90	N (NS)
Dependency															

He 2014	CATIS	Lacunar ischaemic stroke (subgroup) with SBP 140-220 mmHg, non thrombolysed	Antihyper-tensive treatment aimed at BP < 140/90mmHg within 7 days	Discontinue all antihypertensives	≤ 48 hrs of stroke	15 hrs	62±11	14 days or discharge	mRS 3-6	66	366	78	338	OR: 0.73 (0.51-1.06)	Y (NS)
Sandset[$] 2015	SCAST	Lacunar ischaemic stroke (subgroup) with SBP ≥140 mmHg (8% thombolysis) †	Cande-sartan	Placebo	≤ 30 hrs of stroke	18 hrs	70±11	6 months	mRS 3-6	64 NR	242 264	57 NR	265 291	OR: 1.31 (0.87 - 1.97) [$] HR: 1.34 (0.88 – 2.05)	N (NS) N (NS)
Hornslien 2015	SCAST	Lacunar ischaemic stroke (subgroup) with SBP ≥140 mmHg (8% thombolysis) †	Cande-sartan	Placebo	≤ 30 hrs of stroke	18 hrs	70±11	6 months	Barthel index (ordinal logistic regression)	NR	264	NR	291	OR: 1.75 (1.24-2.47), P interaction 0.02	N
ENOS trial invest-igators, 2015	ENOS	Lacunar ischaemic stroke (subgroup) with SBP 140-220 mmHg (10-12% thrombolysis) ‡	Continuing anti-hyper-tensives	Stopping	≤ 48 hrs of stroke	26 hrs	73±11	90 days	Shift in mRS score distribution mRS 3-6	NR	301 301	NR	323 323	OR: 1.15 (0.87, 1.52), P interaction 0.63 OR: 0.97 (0.67, 1.41)	N (NS) Y (NS)
			Trans-dermal GTN (for 7 d)	No GTN	≤ 48 hrs of stroke		70±12	90 days	Shift in mRS score distri-bution	NR	695	NR	702	OR: 0.99 (0.82–1.19), P interaction 0.077	Y (NS)

									mRS 3-6	NR	695	NR	702	OR: 1.02 (0.80, 1.29)	N (NS)
Oh, 2015	VENTURE	Lacunar ischaemic stroke (sub-group) with SBP 150-185 mm Hg, non throm-bolysed	Valsartan	Placebo	≤ 48 hrs of stroke	12 hrs	64.1±11.5 (valsartan) 65.6±11.7 (control)	90 days	mRS 3-6	13	77	14	93	0R: 1.15 (0.50-2.61), P interaction 0.62	N (NS)
Anderson 2019	ENCHANTED	Lacunar ischaemic stroke (sub-group) with i.v. alteplase	SBP 130-140 mmHg	SBP < 180 mmHg	≤ 6 hrs of stroke	3 hrs	64±12	90 days	Shift in mRS score distribution	NR	333	NR	290	OR: 0.84 (0.63-1.12), P interaction 0.90	N (NS)
Zhou, 2020	ENCHANTED	Lacunar ischaemic stroke (sub-group) with i.v. alteplase	SBP 130-140 mmHg	SBP < 180 mmHg	≤ 6 hrs of stroke	3 hrs	64±12	90 days	mRS 2-6	61	238	55	216	OR: 0.98 (0.63-1.53), P interaction 0.67	Y (NS)
									mRS 3-6	29	238	26	216	OR: 1.00 (0.55-1.81), P interaction 0.97	-
Death															
Zhou, 2020	ENCHANTED	Lacunar ischaemic stroke (sub-group) with i.v. alteplase	SBP 130-140 mmHg	SBP < 180 mmHg	≤ 6 hrs of stroke	3 hrs	64±12	90 days	END^ or death within 24 hrs	14	238	10	216	OR: 1.40 (0.60-3.25)	N (NS)
									END^ or death within 72 hrs	15	238	14	216	OR: 1.06 (0.49-2.27)	N (NS)

									Death overall	1	238	1	216	OR: 0.91 (0.06-14.59)	Y (NS)
Post stroke depression															
Zhu 2022	CATIS	Lacunar ischaemic stroke (subgroup) with SBP 140-220 mmHg, non thrombolyzed	Antihyper-tensive treatment aimed at BP < 140/90m mHg within 7 days	Discontinue all antihyper-tensives	≤ 48 hrs of stroke	15 hrs	62±11	14 days or discharge	Hamilton depres-sion scale > 7 at 3 months	56	102	48	104	OR: 1.42 (0.82-2.46)	N (NS)

$ top row OR is calculated from the raw numbers provided in the paper by the Guideline Methodologist, lower row HR was provided by the SCAST principal author Sandset. * P interaction: P-value for interaction across ischaemic stroke subtypes; ^END: early neurological deterioration; GTN = glyceryl trinitrate; ICH: intracerebral haemorrhage; i.v. = intravenous; † before randomisation; ‡ in the overall group, no specific information on the % of patients with lacunar ischaemic stroke undergoing thrombolysis

Supplementary Table 7 Summary of clinical trial findings relevant for PICO 4. RCTs in progressive stroke

Author, year	Design	Population	Clinical progression / fluctuation definition	Intervention	Outcomes	Total sample	No. patients per intervention	Results	Comments / limitations
Shimizu H, 2013(90)	RCT.	patients with non-cardioembolic stroke	progressive stroke: NIHSS ≥4 points on day 3 and/or 5	cilostazol 200mg/d + standard care treatment vs. no cilostazol + standard care treatment	Primary endpoints: rate of progressive stroke, and a mRS score of 0 to 1 at 3 months (but mRS not reported in the lacunar subgroup)	507 (343 lacunar type)	Cilostazol group: 251 (64% lacunar type). Control group: 256 (71% lacunar type)	Progressive stroke lacunar only : cilostazol group 7/154 (4.5%) vs. control group 9/173 (5.2%) OR 0.87 (0.32-2.39) [mRS 0-2 all patients: 221/251 (88.1%) vs 217/256 (84.8%). OR 1.32 (0.79 - 2.21)	Open label; unclear if outcomes blinded; heterogeneity of basal treatment; subgroup of non-lacunar stroke seems to benefit in terms of mRS at 3 months (results for lacunar group not provided).
Nishi R, 2016(93)	RCT	Patients with acute lacunar stroke or BAD within 48h after onset confirmed on MRI within 48 hrs of admission.	Stroke progression: ≥2 points in NIHSS on the seventh day of admission	Argatroban + aspirin + clopidogrel (AAC) vs. argatroban + aspirin (AA)	Stroke progression mRS at 3 months	54 (29 lacunar stroke 23 BAD)	AAC: 28 AA: 26	The incidence of progressive stroke (AAC vs AA): 0 (0%) vs. 4 (16%), p=0.04; mRS 0-2 at 3m (AAC vs AA): 22/28 (78%) vs 17/25 (68%), OR 1.73 (0.50 to 5.92)	Randomization by sealed enveloppe; Open label; Follow was by the recruiting site (unclear if blinded). Recruitment from Nov and Dec 2013, follow up until Sept 2014.

Supplementary Table 8 PICO 4: observational studies relevant to progressive lacunar stroke

Author, year	Design	Population	Clinical progression / fluctuation definition	Intervention	Outcomes	Total sample	No. patients per intervention	Results	Comments / limitations
Patients with lacunar stroke and fluctuating/progressing symptoms. **Antiplatelets** (vs. others) as intervention; **mRS, NIHSS, ICH, recurrent stroke, stopping progression** as outcome									
Berberich A 2019(97)	Retrospective Observational	Patients with lacunar stroke. Subgroup of patients with progressing lacunar stroke (END)	END: worsening of existing clinical symptoms (≥3 total NIHSS, or ≥2 NIHSS for limb paresis, or fluctuating clinical symptoms).	DAPT vs. no DAPT after END	Primary: NIHSS at discharge ≤ admission. Secondary: mRS at discharge, further clinical fluctuations, symptomatic bleeding complications	Lacunar stroke: 458 Progressing lacunar stroke: 130	Progressing lacunar stroke treated with: DAPT 97/130 (75%), no DAPT 33/130 (25%).	DAPT vs. no DAPT. 1° outcome (NIHSS): 68%/35%, p=0.002. Further fluctuation absent in 79% vs. 33%, p<0.001. mRS, 80% vs 73%, p=0.76). No symptomatic bleedings	High risk of selection bias. Baseline clinical differences between patients receiving or not DAPT are not available.
Hawkes M, 2019(93)	Retrospective Observational	Patients with stuttering lacunar syndrome and confirmed lacunar infarct on imaging	Stuttering lacunar syndrome: neurologic deficit with periods of improvement and worsening (with or without full resolution)	DAPT, single antiplatelet. Heparin, IV rt-PA	Improvement: (1) fluctuations stopped and severity of residual deficits was milder than the deficits on worst fluctuation. 2) chronologically related to the intervention 3) documented by the treating physician	40	DAPT 11, single APT 11, aspirin + heparin 3, IV rt-PA 6	Outcome achieved: aspirin-clopidogrel in 11/17 cases; IV rt-PA in 4/6 cases; BP augmentation in 1/3 cases; aspirin in 1/7 cases.	High risk of selection bias. Small cohort. Basal clinical between different interventions not reported,

Foschi M, 2022(88)	Retrospective Observational	Patients with CWS	CWS: ≥3 stereotyped episodes of lacunar symptoms within 72 hours, with complete neurological resolution between episodes	DAPT IV rt-PA	3-month cumulative stroke incidence.	33	DAPT: 16 Single AP: 14	Stroke incidence (DAPT vs single AP): 2 (12.5%) vs. 8 (57.1%); p= 0.010	Descriptive work focused on difference between CWS, and TIA. Unblinded. No baseline comparison between. treatment groups
Liu Y, 2022(98)	Prospective, open-label, cohort study (historical controls).	Patients with CWS all of whom received IV rt-PA.	CWS: physician judgment	IV rt-PA +Tirofiban vs. IV rt-PA alone	mRS at 3 months	20	IV rt-PA + Tirofiban group (October 2019 - June 2021): 12 IV rt-PA alone group (January 2018 – March 2019): 8	Median (IQR) mRS at 3 months (intervention vs. control): 0.00 (0.00–0.00) vs. 1.00 (0.25–1.75), p=0.003. No hemorrhagic complications.	Very small cohort. Clinical protocol and assessment may change in historical cohorts.
Li W, 2019(90)	Retrospective observational	Patients with CWS	CWS: ≥3 stereotyped episodes in 24 hours	iv. tirofiban bolus (0.4 μg/kg /min) over 30 min followed by a continuous iv. infusion (0.1 μg/ kg/min) for 24 hours, plus DAPT +/- rt-PA	mRS at 3 months (0-2 good outcome), ICH	23	Tirofiban group: 15. Other treatments (including aspirin, clopidogrel LMWH, IV rt-PA): 8	Good outcome: 15 (100%) Tirofiban group vs 7 (88%). No ICH in both groups.	Small cohort. High heterogeneity in treatments used. Combination of several treatments seem to be safe.
Nair D, 2012 (abstract only)(99)	Retrospective observational	Patients with fluctuating lacunar syndrome	NA	IV abciximab within 24 hours of IV rt-PA thrombolysis. No comparator	NIHSS at discharge	12	-	Overall mean NIHSS improvement of 6 points. No hemorrhagic complications	Abstract, few data available
Parker S, 2014 (abstract only)(100)	Retrospective observational	Patients with fluctuating lacunar syndrome	NA	IV abciximab within 24 hours of IV rt-PA	NIHSS at discharge	51	-	Overall mean NIHSS improvement of 1.9 points. No	Full article in Japanese

				thrombolysis. No comparator				hemorrhagic complications	
Patients with lacunar stroke and fluctuating/progressing symptoms. **IV thrombolysis** (vs. others) as intervention; **mRS, NIHSS, ICH, recurrent stroke** as outcome									
Vivanco-Hidalgo R. 2008(101)	Case series assessing patients receiving IVT.	Patients with CWS	Episodes of pure motor or sensorimotor fluctuations within 24h	IV rt-PA. No comparator	NIHSS and mRS at discharge	4	4	3/4 patients experienced full recovery and NIHSS 0 at discharge. One patient had NIHSS 12 and mRS 4 at discharge.	No comparator, case series.
Tassi R, 2013(92)	Retrospective observational,	Stroke warning syndrome	≥2 stereotyped episodes occurring within 48 h of pure motor hemiparesis, sensory hemiparesis, sensory motor hemiparesis, or ataxic hemiparesis	IV rt-PA vs. no IV rt-PA	mRS 0-2 at 90 days	18	IVT: 9 No IVT: 9	mRS 0-2: IVT 3 (33%) vs. no IVT 5 (55%), p=0.34. No bleeding complications	Small cohort
Camps-Renom P, 2015(89)	Retrospective observational	Patients with CWS	CWS: ≥3 episodes of motor or sensory-motor lacunar syndrome within 72 h, with a complete resolution of symptoms between them.	IV rt-PA	Functional recovery at 3-month follow-up: mRS 0-2	42	IV rt-PA: 12 No IV rt-PA: 30	mRS 0-2: IV rt-PA: 9 (75%) vs. no IV rt-PA: 30 (100%), p=0.004	Limited sample size. Baseline difference according between groups not available

He L 2019(91)	Retrospective observational	Patients with CWS	CWS: ≥3 stereotyped episodes within a period 48 h, with a complete resolution between episodes.	IV rt-PA vs. no IVT (only antiplatelets)	mRS 0-2 at 3 months. ICH	72	IV rt-PA: 27 No IV rt-PA: 45	mRS 0-2: IV rt-PA: 23 (85%) vs. no IV rt-PA: 38 (84%), p=0.993. No ICH reported.	Unblinded. IV-rtPA seems to be safe.
Patients with lacunar stroke and fluctuating/progressing symptoms. **Other** interventions: **mRS, NIHSS, ICH, recurrent stroke** as outcome									
Dobkin BH 1983(102)	Case series	Progressive lacunar stroke	Progression of the pure motor deficit	IV heparin. No comparator	NIHSS at discharge. Functional recovery at end-follow-up (4-7 weeks)	4	4	All patients progressed to hemiplegia despite heparin during admission. At end follow-up all patient slightly recovered and could walk with device assistance	No comparator, case series.
Lim TS, 2011(85)	Retrospective. Observational,	Patients with lacunar motor progression	NIHSS ≥ 1	phenylephrine-induced hypertension (target BP increase 20%) vs. conventional.	Good outcome: mRS 0-2 at discharge. Mean NIHSS at discharge:	82	Phenylephrine group: 52. Conventional group: 30	Intervention vs control. mRS 0-2: 62% vs. 50%, p=0.044. Mean NIHSS at discharge: 1.1 (SD 1.47) vs. 1.86 (SD 1.92), p=0.042. Target 20% BP increase in phenylephrine group 42%.	Less than half the patients receiving phenylephrine achieved target BP increase. Patients who did not receive phenylephrine had already mean higher BP compared to intervention group.
Kang MJ, 2017(86)	Retrospective observational	Patients with lacunar stroke confirmed on	NIHSS ≥ 1 in motor score	Phenylephrine vs. no Phenylephrine	NIHSS and mRS (0-2) at discharge. mRS	66	Phenylephrine: 41 Control: 25	Int vs. control. NIHSS at discharge: 4.4	Patients who did not received

		MRI and motor progression			(0-2) at 3 months			± 2.5 vs. 6.0 ± 3.7, p=0.036 mRS (0-2) at discharge: 21 (84%) vs. 20 (49%), p= 0.004. mRS (0-2) at 3m: 18 (72%) vs. 15 (36.6%), p= 0.011	phenylephrine had higher systolic blood pressure. Results are crude.
Neurological progression as outcome in patients with lacunar stroke;									
Yamamoto Y, 2011(83)	Prospective observational, historical cohorts	Patients with large lacunar infarcts (10-20 mm on DWI)	Progressive motor deficit (≥1 NIHSS) within 5 days from onset	cilostazol 100 mg/12h and edaravone 30 mg iv /12h. vs other drugs (argatroban, ozagrel sodium, urokinase)	Motor progression	218	Combined treatment: 100 Conventional treatment group: 118	Motor progression: (int. vs. control): 49 (49%) vs. 55 (47%), p=0.83	Historical cohorts. Unblinded. Heterogeneity in conventional treatment.
Yamamoto Y, 2013(84)	Prospective observational, historical control cohort	Patients with lacunar stroke confirmed on MRI (<20mm in DWI) and SBP ≥160 mmHg	Progressive motor deficit (≥1 NIHSS) within 5 days from onset	Valsartan 80-160mg +/- indapamide according to SBP goal (<180 mmHg during the first 7 days after admission; <160 mmHg days 7-14,<140 mm Hg after day 14)	Motor progression	119	Intensive BP lowering cohort: 59. Controls (historical cohort): 60	Motor progression (int vs control): 14 (24%) vs. 16 (27%), p= 0.87	Historical cohorts. BP was similar between groups in the first 1-14 days. Data on antithrombotic treatment are not available.
Nakase T, 2014(82)	Retrospective Observational historical cohort study according to local clinical practice protocol	Patients with small vessel occlusion (classified as lacunar stroke or branch atheromatous disease)	END: increase in NIHSS >2 points within 48h	Aspirin vs cilostazol	END, length of hospital stay, mRS at 1 month	453	Aspirin cohort (April 2007 - March 2009): 220 Cilostazol cohort (April 2010 - March 2012): 233	Cilostazol vs. aspirin. - END: 18.5% vs 31.4%, p=0.002). Length of hospital (18.6 (SD 11.5) vs. 21.2 (SD 21.2) days, p=0.032.	Retrospective study based on clinical records. Possible bias due to changes in clinical protocols and clinical evaluations between the 2

								Mean mRS at one month: (1.9 (SD 1.5) vs. 2.3 (SD 1.5), p=0.011)	temporal cohorts.
Fukuma K, 2015 (abstract only)(81)	Retrospective observational	Patients with lacunar stroke	END: increase of ≥4 in NIHSS or recurrence of symptomatic ischaemic stroke within 30 days after the onset.	DAPT, anticoagulation, statins	END	277 (24 had END)	NA	statin intervention [OR: 0.22; 95% CI: 0.06-0.68, p<0.01]	Abstract, few data available
Chausson, 2014(87)	Retrospective observational	Patients with anterior choroidal ischaemic stroke	any persistent neurologic worsening	IV rt-PA	Clinical progression	100; 46 had progression	IV rt-PA: 21 No IV rt-PA: 79	12/46 (26.1%) who progressed vs. 9/54 (16.7) who did not progress, received rt-PA, p=0.3	65% infarct size >15mm, including cortical strokes (3%). Patients who progressed had more severe strokes at admission.

Supplementary Table 9. Summary of clinical trial findings relevant for PICO 5: other treatments for suspected acute lacunar ischaemic stroke.

Study author; year	Trial name/ NCTID	Population	Inter-vention	Comp-arator	Mean age (Years)	Trial duration/ Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/HR	Comments/ Notes
								N event	N total	N event	N total		
Any recurrent stroke													
Recurrent Ischaemic Stroke													
Cilostazol													
Han; 2013	ECLIPse	Lacunar stroke in the previous 7 days . N=203	Cilostazol 100mg twice daily + aspirin	Placebo + aspirin	65	90 days	Recurrent ischaemic stroke	1	100	1	103	UNK (HR around 1)	
Haemorrhagic stroke													
Cognitive impairment or dementia													
Xueshuantong													
Gui; 2013		MRI confirmed lacunar infarction; onset <24h; N=64	Xueshuantong 450mg iv once daily 4 weeks	-	79.9	4 weeks	MMSE admission to discharge	NA	31	NA	33	intervention group 24.2 ±3.7 to 24.5 ±3.6; control group 24.3 ±3.4 to 24.2 ±3.7; NS	
Mobility or Gait disorder													
Mood disorders													
MACE													

Dependency													
Magnesium													
Muir; 2004	IMAGES	Acute ischaemic stroke; stroke onset <12h. N=2386; 765 with lacunar syndrome	MgSO4 intravenously, 16 mmol bolus in 15 min and then 65 mmol over 24 h	Placebo	70 (total group)	90 days	joint binary outcome of death and disability at 90 days (Barthel score and mRS score)		382		383	OR 0.70 (0.53–0.92)	(common odds ratio for death or disability, therefore only denominator populations (N) can be quoted)
Afshari; 2013		Acute ischaemic stroke; stroke onset <12h. N=107; 41 with lacunar syndrome	MgSO4 intravenously, 4g in 15 min and then 16g over 24 h	Placebo	67.4 (total group)	90 days	NIHSS at 90 days	NA	21	NA	20	1.61 ±1.43 (intervention) vs 3.30 ±1.92 (control); p = 0.003	
Glyceryltrinitrate (GTN)													
Bath; 2015 / Appleton; 2020	ENOS	Acute ischaemic or hemorrhagic stroke; stroke onset <48h. N=4011; 623 with lacunar stroke and compatible scan	GTN dermal patch 5mg 7 days	Placebo	68.7	90 days	mRS at 90 days	NA	308	NA	315	OR 1.09 (0.82-1.45)	
Anticoagulation													

TOAST investigators; 1998	TOAST	Acute ischaemic stroke; stroke onset <24h. N=1275; 306 with small artery occlusion	Danaparoid iv adjusted to anti-factor Xa activity, 7 days	Placebo	65.5 (total group)	90 days	Favorable outcome at 90 days (combination of GOS and Barthel index)	144	158	134	149	OR 1.07 (0.49-2.34)	
Bath; 2001	TAIST	Acute ischaemic stroke; stroke onset <48h. N=1484; 534 with lacunar stroke	Tinzaparin 1:1 high-dose (175 anti-Xa IU/kg daily), medium-dose (100 anti-Xa IU/kg daily) sc., 10 days	Aspirin 300mg	74 (total group)	180 days	mRS 0-2 at 180 days		190 (high dose) : 166 (medium dose)		178	In total group, tinzaparin at high or medium dose did not improve functional outcome compared with aspirin. No dfference in effect in prespecified lacunar subgroup (numbers not shown).	
Xueshuantong													
Gui; 2013		MRI confirmed lacunar infarction; onset <24h; N=64	Xueshuantong 450mg iv once daily 4 weeks	-	79.9	4 weeks	admission to discharge NIHSS reduction	NA	31	NA	33	st. beta 0.327. (p=0.008)	
Death													

Supplementary Table 10. Summary of clinical trial findings relevant for PICO 6: antiplatelet therapy long term in patients with lacunar ischaemic stroke

* indicates: not included in NMA

Study author; year	Trial name/ NCTID	Population	Intervention	Comparator	Mean age (Years)	Trial duration / Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/HR	Comments/ Notes
								N event	N total	N event	N total		
Recurrent Ischaemic Stroke													
Nishiyama; 2023	CSPS.com	Lacunar stroke-TOAST & MRI (subgroup)	Aspirin	Clopidogrel	69.6 (SD 9.2)	1.4 years	Recurrent ischaemic stroke	9	195	22	265	RR 0.56 (0.26-1.18)	
Bousser; 1983	AICLA	Probable lacune (subgroup)	Aspirin + Dipyridamole	Aspirin alone or Placebo alone	About 63 in the whole AICLA cohort	3 years	Ischaemic stroke	2	34	Aspirin: 3 Placebo: 9	Aspirin: 30 Placebo:34	Aspirin vs placebo RR: 0.38 (0.11, 1.27) Aspirin + dipyridamole vs aspirin alone RR: 0.59 (0.11,3.29) Aspirin + dipyridamole vs placebo RR: 0.22 (0.05-0.95)	extracted from table 9. Events worked out based on reported % in Table 9
Benavente; 2012	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	3.4 years	Ischaemic stroke	100	1517	124	1503	HR=0.82 (0.63, 1.09)	
Diener; 2004	MATCH	Lacunary stroke-TOAST (subgroup)	Clopidogrel + Aspirin	Clopidogrel	66 for whole smaple (not given for subgroup)	18 months	Ischaemic stroke	160	1590	161	1558	RR: 0.97 (0.79-1.20)	Data on events extracted by the meta-analysis of Kwok et al
Kitazono; 2021	PRASTRO-I	Lacunar stroke-TOAST (subgroup)	Prasugrel	Clopidogrel	62	96 weeks	Ischaemic stroke	18	583	22	593	HR=0.81 (0.43, 1.51)	calculated N from %

Shinohara; 2008	S-ACCESS	Lacunar stroke (CT or MRI)	Sarpogrelate	Aspirin	65 (SD 10) (whole stroke population, unknown in lacunar subgroup)	mean 1.59 y	Ischaemic stroke	46 (5.95%/y)	484	35 (4.53%/y)	479	HR=1.31 (0.84 - 2.04)	number of events calculated from annual rate
Gotoh; 2000, Matsumoto; 2006	CSPS	Lacunar infarction--confirmed by CT or MRI (subgroup)	Cilostazol	Placebo	65 (total group)	2 years	Recurrent ischaemic stroke	20	400	39	394	RRR: 43.4% (3.0-67.0) , p=0.0373	REPEATED (MATSUMOTO 2006)
Han; 2013	ECLIPSE	Lacunar stroke (TOAST)	Cilostazol + Aspirin	Aspirin	65	90 days	Ischaemic stroke	1	100	1	103	RR: 1.03 (0.07-16.24)	
Blair; 2019	LACI-1	lacunar stroke-MRI or CT	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	66.1 (SD 11.1)	Follow-up at 11 weeks (meds taken for 9 weeks)	Ischaemic stroke	1	41	0	15	not provided	Events taken from text description in section 4.4 and supp materials. Note, zero events in one arm may cause issues in meta-analysis…Both, delayed start=15 (of which 1 was not followed up); ISMN alone=15; Cilostazol=13; Both, start immediately=14
Toyoda; 2019, Nishiyama; 2023	CSPS.com	Lacunar stroke-TOAST & MRI (subgroup)	Cilostazol + Aspirin or Clopidogrel	Aspirin or Clopidogrel	69	1.4 years	Ischaemic stroke	12	464	31	461	HR unadjusted=0.41 (0.21–0.81) HRadjusted=0.43 (0.22–0.85)	

Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	Recurrent stroke	11	178	8	180	aOR 1.35, (0.51, 3.57), p=0.55	
Haemorrhagic stroke													
Benavente; 2012	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	3.4 years	Intracranial haemorrhage	21	1517	13	1503	HR=1.65 (0.83, 3.31)	
Kitazono; 2021	PRASTRO-I	Lacunar stroke-TOAST (subgroup)	Prasugrel	Clopidogrel	62	96 weeks	Hemorrhagic stroke	2	583	1	593	HR=1.92 (0.17, 21.23)	calculated N from %
Nishiyama; 2023	CSPS.com	Lacunar stroke-TOAST & MRI (subgroup)	Cilostazol + Aspirin or Clopidogrel	Aspirin or Clopidogrel	69	1.4 years	Hemorrhagic stroke	2	464	4	461	HR=0.53 (0.10–2.88)	
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	Intracranial haemorrhage	0	182	0	181	NA	
Any stroke													
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Aspirin	Placebo	66	2 years	Any stroke	70	609	93	681	HR=0.82 (0.60–1.11)	IS & hemorrghagic stroke not provided seperately
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Dipyridamole	Placebo	66	2 years	Any stroke	73	651	93	681	HR=0.80 (0.59–1.08)	IS & hemorrghagic stroke not provided seperately
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Aspirin + dipyridamole	Placebo	66	2 years	Any stroke	52	659	93	681	HR=0.56 (0.40–0.78)	IS & hemorrghagic stroke not provided seperately
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Aspirin + dipyridamole	Aspirin	66	2 years	Any stroke	52	659	70	609	HR=0.68 (0.48–0.97)	IS & hemorrghagic stroke not provided seperately

Benavente; 2012	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	3.4 years	Any stroke (incl. unknown)	125	1517	138	1503	HR=0.92 (0.72–1.16)	
Sacco; 2008	PRoFESS	Lacunar stroke-TOAST (subgroup)	Aspirin + Dipyridamole	Clopidogrel	66	2.5 years	Any stroke	418	5292	437	5286	HR=0.96 (0.84-1.09)	
Gent; 1989, Kwok; 2015	CATS	lacunar stroke subgroup (compatible CT)	Ticlopidine	Placebo	65	2 years	Any stroke (recurrent stroke)	14	137	27	137	HR=0.52 (0.28-0.95)	Data from Kwok et al 2015
Gorelick; 2003	AAASPS	Lacunar stroke-TOAST (subgroup)	Ticlopidine	Aspirin	N/A	2 years	Any stroke (recurrent stroke)	38	600	40	621	RR=0.98 (0.64.1.51)	
Han; 2017	MAESTRO	Lacunar stroke (TOAST - poor clopidogrel metabolisers	Triflusal	Clopidogrel	N/A	2.7 years	Any stroke	4	124	7	140	0.68 (0.20–2.32)	Only poor metabolisers by genotyping included
Kitazono; 2021	PRASTRO-I	Lacunar stroke-TOAST (subgroup)	Prasugrel	Clopidogrel	62	96 weeks	Any stroke	20	583	23	593	HR=0.86 (0.47, 1.56)	calculated N from %
Han; 2013	ECLIPSE	Lacunar stroke (TOAST)	Cilostazol + Aspirin	Aspirin	65	90 days	Ischaemic stroke	1	100	1	103	RR: 1.03 (0.07-16.24)	
Nishiyama; 2023	CSPS.com	Lacunar stroke-TOAST & MRI (subgroup)	Cilostazol + Aspirin or Clopidogrel	Aspirin or Clopidogrel	69	1.4 years	Any stroke	14	464	35	461	HRunadjusted=0.43 (0.23–0.79) HRadjusted=0.45 (0.24–0.84)	
Shinohara; 2010	CSPS 2	Lacunar stroke-TOAST (subgroup)	Cilostazol	Aspirin	N/A	29 months	Any stroke	59	869	85	874	HR=0.75 (0.54–1.04)	
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	Recurrent stroke	11	178	8	180	aOR 1.35, (0.51, 3.57), p=0.55	
Cognitive impairment or dementia													
Pearce; 2014	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	2.7 years	Incident mild cognitive impairment (per study definition)	189	721	187	692	9.7%/y versus 9.9%/y	

							during follow-up						
Blair; 2019	LACI-1	Lacunar stroke- MRI or CT	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	66.1 (SD 11.1)	8 weeks	Cognitive Trail Making Tests (TMT) A and B	NA	41	NA	15	**<u>Cilostazol vs no cilostazol:</u>** ***TMT A points***=MD −1.1 (95%CI −3.6, 1.5) ***TMT B points***=MD -2.2 (95%CI -5.1-0.7) ***TMT A (time)***=MD −4.0 (95%CI −12.7, 4.7) TMT (time)***=MD −3.***4 (95%CI −22.7, 16.0)	Both, delayed start=15(of which 1 was not followed up); ISMN alone=15; Cilostazol=13; Both, start immediately= 14
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	7 level cognitive score based on DSM-5	85	153	99	155	aOR 0.88, (0.57, 1.37), p=0.58	
Wardlaw; 2923	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	MOCA	18,6		18,1		adjusted mean difference 0.37, (-0.37, 1.11), p=0.33	
Mobility or Gait disorder													
Mood disorders													
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	Zung depression scale (/102.5)	48,4		51,4		adusted mean difference -3.34, (-6.81, 0.14), p=0.06	
MACE													

Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Aspirin	Placebo	66	2 years	Nonfatal stroke, nonfatal myocardial infarction, a nonfatal other vascular event (deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion, or venous retinal vascular events), or vascular death.	101	609	128	681	HR=0.86 (0.66-1.11)	IS & hemorrghagic stroke not provided seperately
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Dipyridamole	Placebo	66	2 years	ditto	108	651	128	681	HR=0.86 (0.67-1.12)	IS & hemorrghagic stroke not provided seperately
Ariesen; 2006	ESPS-2	Lacunar stroke-study definition	Aspirin + dipyridamole	Placebo	66	2 years	ditto	82	659	128	681	HR=0.64 (0.48, 0.84)	IS & hemorrghagic stroke not provided seperately
Ariesen 2006	ESPS-2	Lacunar stroke-study definition	Aspirin + Dipyridamole	Aspirin	66	2 years	ditto	82	659	101	609	HR=0.74 (0.55, 0.99)	IS & hemorrghagic stroke not provided seperately
Kwok; 2015 *	ESPS-2	Lacunar stroke-study definition	Aspirin or dipyridamole	Placebo	66	2 years	Any stroke, MI, death	209	1260	128	681	RR: 0.88 (0.72-1.08)	

Kwok; 2015 *?	ESPS-2	Lacunar stroke-study definition	Dipyridamole	Aspirin	66	2 years	Any stroke, MI, death	108	651	101	609	RR: 1.00 (0.78-1.28)	
Benavente; 2012	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	3.4 years	Stroke, MI, CV death	153	1517	174	1503	HR=0.89 (0.72, 1.11))	
ESPRIT; 2006	ESPRIT	Lacunar stroke	Aspirin + Dipyridamole	Aspirin	not given for subgroup but approx 63	3.5 years	Any stroke, MI, death	96	687	106	690	RR:0.91 (0.70-1.17)	data extracted direct from Kwok meta-analysis.
Uchiyama; 2009	N/A	Lacunar stroke-MRI (subgroup)	Ticlodipine	Clopidogrel	Not available for subgroup but prob around 64	52 weeks	Ischaemic stroke, MI, death	19	677	22	664	RR: 0.85 (0.46-1.55)	
Kitazono; 2021	PRASTRO-I	Lacunar stroke-TOAST (subgroup)	Prasugrel	Clopidogrel	N/A	96 weeks	IS, MI, CV death	19	583	23	593	HR=0.82 (0.45, 1.50)	calculated N from %
Amarenco; 2017	SOCRATES	Lacunar stroke-ASCOD (subgroup)	Ticagrelor	Aspirin	N/A	90 days	Stroke, MI, death	143	1946	152	1893	HR=0.91 (0.72, 1.14)	there are also two additional definitions
Bousser; 2011	PERFORM	lacunar stroke subtype (compatible brain imaging)	Terutroban	Aspirin	67 (whole cohort)	28.3 months (whole cohort)	composite of fatal or nonfatal ischaemic stroke, fatal or non-fatal myocardial infarction, or other vascular death (excluding haemorrhagic death)	54	856	61	877	HR 0.90 (0.62–1.31)	

Morrow; 2013	TRA 2°P-TIMI 50	Prior atherothrombosis or stroke (2 week to 12 months before enrolment). N=26449; 2262 lacunar stroke subgroup	Vorapaxar 2.5 mg daily + standard antiplatelet therapy (2% none)	standard antiplatelet therapy (2% none)	64	24 months	Composite of cardiovascular death, myocardial infarction, or any stroke.	11.4%	Information not available	11.3%	Information not available	HR: 0.99 (0.75-1.31)	
Nishiyama; 2023	CSPS.com	lacunar stroke-TOAST & MRI (subgroup)	Cilostazol + Aspirin or Clopidogrel	Aspirin or Clopidogrel	69	1.4 years	Stroke, MI, *vascular* death	15	464	39	461	unadjusted HR: 0.41 (0.23–0.74); adjusted HR: 0.42 (0.23–0.77)	
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	Recurrent stroke, MI, death,	15	178	11	180	not calculated seperately	
Dependency													
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	mRS >2	18	156	29	166	aOR 0.46 (0.22, 0.95), p=0.037	
Death													
Benavente; 2012	SPS3	Lacunar stroke-MRI	Clopidogrel + Aspirin	Aspirin	63	3.4 years	All deaths	113	1517	77	1503	HR=1.52 (1.14, 2.04)	
Nishiyama; 2023	CSPS.com	Lacunar stroke-TOAST & MRI (subgroup)	Cilostazol + Aspirin or Clopidogrel	Aspirin or Clopidogrel	69	1.4 years	Death from any cause	3	464	1	461	HR: 3.20 (0.33-30.8)	
Wardlaw; 2023	LACI-2	Lacunar stroke (clinical, CT or MRI)	Cilostazol + Clopidogrel or Aspirin	Clopidogrel or Aspirin	64	1 year	All deaths	2	178	2	180	aOR 0.90, (0.08, 10.26), p=0.93	

Supplementary Table 11, PICO 6: Network meta-analysis results comparing the effects of different interventions for any stroke outcome (N = 9 RCTs) including risk ratios (RR) and 95% CIs. RR < 1 means the bottom-right intervention is protective [RR > 1 favors the intervention in the column].

Aspirin + Dipyridamole										
0.71 (0.51,1.00)	**Aspirin**									
0.79 (0.53,1.19)	1.11 (0.88,1.40)	**Clopidogrel + Aspirin**								
0.70 (0.04,11.23)	0.98 (0.06,15.46)	0.88 (0.06,14.01)	**Cilostazol + Aspirin**							
1.02 (0.64,1.62)	1.43 (1.04,1.97)	1.29 (0.87,1.91)	1.46 (0.09,23.46)	**Cilostazol**						
0.96 (0.84,1.09)	1.34 (0.94,1.92)	1.20 (0.79,1.85)	1.37 (0.08,22.10)	0.94 (0.58,1.52)	**Clopidogrel**					
0.70 (0.50,0.99)	0.99 (0.73,1.34)	0.89 (0.61,1.30)	1.01 (0.06,16.17)	0.69 (0.44,1.07)	0.74 (0.51,1.06)	**Dipyridamole**				
1.08 (0.59,1.97)	1.52 (0.76,3.02)	1.36 (0.66,2.82)	1.55 (0.09,26.57)	1.06 (0.50,2.26)	1.13 (0.63,2.04)	1.54 (0.77,3.06)	**Prasugrel**			
0.83 (0.52,1.32)	1.17 (0.81,1.67)	1.05 (0.68,1.61)	1.19 (0.07,19.21)	0.81 (0.50,1.32)	0.87 (0.54,1.41)	1.18 (0.76,1.83)	0.77 (0.36,1.64)	**Ticlopidine**		
1.48 (0.44,4.97)	2.08 (0.59,7.31)	1.87 (0.52,6.70)	2.12 (0.10,43.97)	1.45 (0.40,5.31)	1.55 (0.46,5.17)	2.10 (0.60,7.40)	1.37 (0.36,5.24)	1.78 (0.49,6.53)	**Triflusal**	
0.56 (0.41,0.77)	0.79 (0.60,1.04)	0.71 (0.50,1.01)	0.81 (0.05,12.88)	0.55 (0.36,0.84)	0.59 (0.42,0.83)	0.80 (0.60,1.06)	0.52 (0.26,1.03)	0.68 (0.46,1.00)	0.38 (0.11,1.33)	**Placebo**

Supplementary Table 12, PICO 6: Network meta-analysis results comparing the effects of different interventions for ischaemic stroke outcome (N = 8 RCTs) including risk ratios (RR) and 95% CIs. RR < 1 means the bottom-right intervention is protective [RR > 1 favours the intervention in the column].

Aspirin + Dipyridamole								
0.59 (0.11,3.29)	**Aspirin**							
0.68 (0.12,3.88)	1.16 (0.91,1.48)	**Clopidogrel + Aspirin**						
0.57 (0.02,14.74)	0.97 (0.06,15.31)	0.84 (0.05,13.32)	**Cilostazol + Aspirin**					
0.44 (0.09,2.07)	0.75 (0.20,2.79)	0.64 (0.17,2.46)	0.77 (0.04,16.38)	**Cilostazol**				
0.63 (0.11,3.63)	1.08 (0.80,1.45)	0.93 (0.76,1.13)	1.11 (0.07,17.76)	1.44 (0.37,5.56)	**Clopidogrel**			
0.76 (0.12,4.84)	1.29 (0.65,2.56)	1.11 (0.58,2.12)	1.33 (0.08,22.81)	1.73 (0.39,7.62)	1.20 (0.65,2.22)	**Prasugrel**		
0.45 (0.08,2.66)	0.77 (0.50,1.17)	0.66 (0.41,1.08)	0.79 (0.05,12.89)	1.03 (0.26,4.10)	0.71 (0.43,1.20)	0.59 (0.27,1.33)	**Sarpogrelate**	
0.22 (0.05,0.95)	0.38 (0.11,1.27)	0.33 (0.09,1.12)	0.39 (0.02,7.91)	0.51 (0.30,0.85)	0.35 (0.10,1.22)	0.29 (0.07,1.17)	0.49 (0.14,1.77)	**Placebo**

Supplementary Table 13, PICO 6: Network meta-analysis results comparing the effects of different interventions for Major Adverse Cardiovascular Event (MACE) (N = 5 RCTs) including risk ratios (RR) and 95% CIs. RR < 1 means the bottom-right intervention is protective [RR > 1 favours the intervention in the column].

Aspirin + Dipyridamole						
0.83 (0.69,1.00)	**Aspirin**					
0.95 (0.72,1.26)	1.15 (0.93,1.41)	**Clopidogrel + Aspirin**				
0.79 (0.62,1.01)	0.96 (0.76,1.21)	0.83 (0.61,1.14)	**Dipyridamole**			
0.91 (0.68,1.21)	1.09 (0.88,1.36)	0.95 (0.70,1.29)	1.14 (0.83,1.57)	**Ticagrelor**		
0.92 (0.61,1.37)	1.10 (0.77,1.57)	0.96 (0.64,1.45)	1.15 (0.75,1.76)	1.01 (0.67,1.53)	**Terutroban**	
0.70 (0.56,0.88)	0.84 (0.68,1.05)	0.74 (0.54,0.99)	0.88 (0.70,1.11)	0.77 (0.57,1.05)	0.77 (0.50,1.16)	**Placebo**

Supplementary Table 14 Summary of clinical trial findings for PICO 7: blood pressure lowering in long-term secondary prevention after lacunar ischaemic stroke.

Author; year	Trial name	Population	Intervention	Comparator	Timing of intervention	Mean age ± SD (Years)	Follow-up	Outcomes	Intervention		Comparator		OR/RR/HR
									N event	N total	N event	N total	
Recurrent Stroke													
SPS3, 2013	SPS3	MRI confirmed lacunar stroke	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	63± 11	3.7 years	Recurrent stroke	112	1501	131	1519	HR: 0.84 (0-66-1.09), p=0.19
Markus, 2021	PRESERVE	MRI confirmed lacunar stroke and confluent WMH	<125 mmHg	130–140 mmHg	> 3 months after stroke	68	24 months	Recurrent stroke	3	56	3	55	NR
Blum, 2020	SPS3 secondary	MRI confirmed lacunar stroke | aged > 65 yrs	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	74± 6	3.9 years	Recurrent stroke	57	618	67	645	HR: 0.91 (0.64-1.29)
		MRI confirmed lacunar stroke | aged > 65 yrs & severe WMH							18	169	34	206	HR: 0.61 (0.34-1.09)
		MRI confirmed lacunar stroke | aged > 65 yrs & moderate WMH							15	196	23	208	HR: 0.71 (0.37-1.37)
		MRI confirmed lacunar stroke | aged > 65 yrs & mild WMH							23	244	9	213	HR: 2.45 (1.13-5.33)
Ikeme, 2019		MRI confirmed lacunar stroke | top WMH tertile				63± 11	3.7 years	Recurrent stroke	40	381	61	439	HR: 0.73 (0.49–1.09)
		MRI confirmed lacunar stroke | middle WMH tertile							32	471	45	466	HR: 0.67 (0.43–1.06)
		MRI confirmed lacunar stroke | top WMH tertile							44	626	37	584	HR: 1.13 (0.73–1.75)
Shoamanesh, 2017		MRI confirmed lacunar stroke | with CMB				63± 11	3.3 years	Recurrent stroke	NR	NR	NR	NR	HR 0.49 (0.27-0.92)
		MRI confirmed lacunar stroke | no CMB							NR	NR	NR	NR	HR 0.74 (0.43-1.30)

Haemorrhagic stroke													
SPS3, 2013	SPS3	MRI-confirmed lacunar stroke	<130mm Hg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	63± 11	3.7 years	All intracranial haemorrhage ||	13	1501	21	1519	HR 0.61 (0.31-1.22); p=0.16
								Intracerebral haemorrhage	6	1501	16	1519	HR 0.37 (0.15-0.95); p=0.03
Cognitive impairment or dementia													
Pearce, 2014	SPS3	MRI confirmed lacunar stroke & MMSE ≥ 24	<130 mmHg	130 - 149 mmHg	> 2 wks post-stroke (median 62 days)	63± 11	2.7 years	Incident MCI	192	713	184	700	10% vs 9.5% incident MCI; P interaction 0.84
Markus, 2021	PRESERVE	MRI confirmed lacunar stroke and confluent WMH	<125 mmHg	130–140 mmHg	> 3 months after stroke	68	24 months	Cognitive decline (baseline, 1, 2 years)	NA	56	NA	55	No association of treatmentwith change in Global Cognition (p=0.66), Executive Function (p=0.37), processing speed (p= 0.58) or verbal memory (p=0.33).
Blum, 2020	SPS3 secondary	MRI confirmed lacunar stroke | aged > 65 yrs	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	74± 6	3.9 years	Incident MCI (CASI score)	91	288	99	293	HR 0.94 (95% CI: 0.70 - 1.25)
		MRI confirmed lacunar stroke | aged > 65 yrs & severe WMH							26	72	21	69	HR 1.07 (95% CI: 0.59 - 1.94)
		MRI confirmed lacunar stroke | aged > 65 yrs & moderate WMH							28	87	32	92	HR 1.01 (95% CI: 0.60 - 1.70)
		MRI confirmed lacunar stroke | aged > 65 yrs & mild WMH							35	124	41	118	HR 0.85 (95% CI: 0.54 - 1.35)
MACE													
SPS3, 2013	SPS3	MRI confirmed lacunar stroke	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	63± 11	3.7 years	MACE	160	1501	188	1519	HR 0.84 (0.68-1.04) p=0.10
Blum, 2020	SPS3 secondary	MRI confirmed lacunar stroke | aged > 65 yrs	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	74± 6	3.9 years	MACE	77	618	85	645	HR 0.97 (95% CI: 0.71 - 1.32)
		MRI confirmed lacunar stroke | aged > 65 yrs & severe WMH							25	169	40	206	HR 0.70 (95% CI: 0.42 - 1.17)

		MRI confirmed lacunar stroke | aged > 65 yrs & moderate WMH							23	196	30	208	HR 0.84 (95% CI: 0.49 - 1.46)
		MRI confirmed lacunar stroke | aged > 65 yrs & mild WMH							28	244	13	213	HR 2.08 (95% CI: 1.07 - 4.03)
Death													
SPS3, 2013	SPS3	MRI confirmed lacunar stroke	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	63± 11	3.7 years	All-cause death	106	1501	101	1519	1.03 (0.79-1.35) p=0.82
Markus, 2021	PRESERVE	MRI confirmed lacunar stroke	<125 mmHg	130–140 mmHg	> 3 months after stroke	68	24 months	All-cause death	1	39	2	42	NR
Blum, 2020	SPS3 secondary	MRI confirmed lacunar stroke | aged > 65 yrs	<130 mmHg	130 - 149 mmHg	≥ 2 wks post-stroke (median 62 days)	74± 6	3.9 years	All-cause death	64	618	67	645	HR 0.97 (95% CI: 0.69 - 1.37)
		MRI confirmed lacunar stroke | aged > 65 yrs & severe WMH							26	169	31	206	HR 0.98 (95% CI: 0.58 - 1.66)
		MRI confirmed lacunar stroke | aged > 65 yrs & moderate WMH							21	196	23	208	HR 0.96 (95% CI: 0.52 - 1.74)
		MRI confirmed lacunar stroke | aged > 65 yrs & mild WMH							16	244	10	213	HR 1.33 (95% CI: 0.60 - 2.95)
Shoamanesh, 2017		MRI confirmed lacunar stroke | with CMB				63± 11	3.3 years	All-cause death	NR	NR	NR	NR	HR 0.85 (0.4-1.8)
		MRI confirmed lacunar stroke | no CMB							NR	NR	NR	NR	HR 0.84 (0.48-1.5)

*Abstract; ** Perindopril (4 mg daily) ± indapamide (2 mg daily); § MACE: major adverse cardiovascular event, defined in SPS3 by need for acute admission to hospital for a major vascular event; || All intracranial haemorrhage: intracerebral, subdural, epidural, other

Supplementary Table 15 – Summary of clinical trial findings relevant to PICO 8: lipid lowering in lacunar ischaemic stroke

Study author; year	Trial name/NCTID	Population	Intervention	Comparator	Mean age (Years)	Trial duration/Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/HR	Comments/Notes
								N event	N total	N event	N total		
Recurrent Ischaemic Stroke													
Amarenco et al., Stroke 2008	SPARCL	Subgroup analysis of the SPARCL trial, SVD stroke subtype according to TOAST	Atorvastatin 80 mg	Placebo	Intervention:63.8 (0.4) comparator: 63.7 (0.4)	median : 4.9 years	Stroke: ischaemic and haemorr-hagic	93	708	109	701	HR 0.85 (0.64-1.12); p=0.249	Subgroup analyses; stroke outcome combined haemorrhagic + ischaemic
Amarenco et al., Stroke 2008	SPARCL	Subgroup analysis of the SPARCL trial, SVD stroke subtype according to TOAST	Atorvastatin 80 mg	Placebo	Intervention:63.8 (0.4) comparator: 63.7 (0.4)	median : 4.9 years	Stroke or TIA: ischaemic and haemorr-hagic	124	708	138	701	HR 0.89 (0.70-1.13); p=0.346	Subgroup analyses; stroke outcome combined haemorrhagic + ischaemic + TIA
Hosomi et al 2015	J STARS	Subgroup analysis of patients in trial with SVD stroke as qualifying event NB results in supple-mentary table	Pravstatin 10mg	Placebo	66.2 yrs	4.9 yrs +/- 1.4	Ischaemic stroke only	38	502	40	504		only IS

Hosomi et al 2015	J STARS	Subgroup analysis of patients in trial with SVD stroke as qualifying event NB results in supplementary table	Pravastatin 10mg	Placebo	66.2 yrs	4.9 yrs +/- 1.4	Stroke/TIA	49	502	47	504		combined ICH and IS in outcome
Haemorrhagic stroke													
Hosomi et al 2015	J STARS	Subgroup analysis of patients in trial with SVD stroke as qualifying event NB results in supplementary table	Pravstatin 10mg od	placebo	66.2 yrs	4.9 yrs +/- 1.4	ICH	11	502	7	504		Only ICH as outcome
Cognitive impairment or dementia													
Mobility or Gait disorder													
Mood disorders													
MACE													

Amarenco et al., Stroke 2008	SPARCL	Subgroup analysis of the SPARCL trial, SVD stroke subtype according to TOAST	Atorvastatin 80 mg	Placebo	Intervention:63.8 (0.4) comparator: 63.7 (0.4)	median : 4.9 years	stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest	120	708	141	701	HR 0.84 (0.66-1.08); p=0.170	Subgroup analyses
Dependency													
Shinichi Yoshimura et al. 2017	ASSORT Trial (Administration of Statin on Acute Ischaemic Stroke Patient)	Subgroup analysis for lacunar stroke (TOAST definition)	Early statin use: within 24 hours form symptom onset and continues for 12 weeks	Delayed statin users: started on the 7th day from stroke onset and then for 11 weeks	Not available for the subgroup with lacunar stroke			NA	56/131	NA	56/126		
Death													
Amarenco et al., Stroke 2008	SPARCL	Subgroup analysis of the SPARCL trial, SVD stroke subtype according to TOAST	Atorvastatin 80 mg	Placebo	Intervention:63.8 (0.4) comparator: 63.7 (0.4)	median : 4.9 years	death	77	708	64	701	HR 1.20 (0.86-1.67); p=0.280	Subgroup analyses

Supplementary Table 16. Summary of clinical trial findings relevant for PICO 9: lifestyle interventions

Study author, year	Trial	Population	Intervention	Comparator	Mean age	Trial duration	Outcomes	N (intervention)	N (comparator)	Main results
Steen Krawczyk et al. 2019; Krawczyk et al. 2023	HITPALS	Patients with lacunar stroke (TOAST definition)	High-intensity interval training (15 min a day, 5 days a week) with weekly telephone calls to ensure compliance	Advice on self-managed lifestyle changes	63.7	Intervention 12 weeks, follow-up 6 and 12 months	Primary: cardiorespiratory fitness, Secondary: physical activity, fatigue, depression, mental well-being, stress, cognition, cardiovascular function, and recurrent stroke	31	32	High-intensity interval training was feasible and safe; however, no effect of physical activity was proven on any of the primary or secondary outcomes
Ting et al. 2017	VITATOPS	Patients with recent lacunar stroke and cognitive impairment no dementia	2 mg folic acid, 25 mg vitamin B6, and 0.5 mg vitamin B12	Placebo	67	5 years	Primary: cognitive tests	118	112	No effect of dietary intervention on cognitive function

Supplementary Table 17 Summary of clinical trial findings relevant for PICO 10: other treatments for lacunar ischaemic stroke

Study author; year	Trial name/NCTID	Population	Intervention	Comparator	Mean age Years	Trial duration/Duration of follow-up	Outcomes	Intervention		Comparator		OR/RR/HR	Comments / Notes
								N event	N total	N event	N total		
Any stroke													
Cilostazol													
Shinohara; 2010 / Uchiyama 2014	CSPS-2	Non-cardioembolic cerebral infarction in the previous 26 weeks. N=2672; 1743 lacunar subgroup	Cilostazol 100mg twice daily	Aspirin 81 mg once daily	63.4 (total group)	29 months	Stroke (ischaemic and hemorrhagic)	59	869	85	874	HR: 0.752 (0.542–1.042), p=0.0867	
Toyoda; 2019 (Nishiyama; 2023)	CSPS.com	Non-cardioembolic ischaemic stroke 1-25 weeks before enrolment, with intra- or extracranial stenosis or ≥2 risk factors. N=1879; 925 lacunar subgroup	Cilostazol 100mg twice daily plus aspirin or clopidogrel	Monotherapy aspirin or clopidogrel	69.5	1.4 years	Any stroke	14	464	35	461	HR 0.43 (0.23-0.79), p=0.005	
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	Cilostazol 100mg twice daily during 1 year	No cilostazol	64.0	1 year	Stroke or TIA	11	178	8	180	Adjusted OR: 1.35 (0.51- 3.57), p=0.55	
ISMN													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	ISMN 25mg twice daily during 1 year	no ISMN	64.0	1 year	Stroke or TIA	4	178	15	180	Adjusted OR: 0.23 (0.07-0.74), p=0.01	

Recurrent Ischaemic Stroke													
Cilostazol													
Gotoh; 2000	CSPS	Non-cardioembolic cerebral infarction (1-6 months before enrolment). N=1052; 794 lacunar subgroup	Cilostazol 100mg twice daily	Placebo	65 (total group)	2 years	Recurrent ischaemic stroke	20	400 (673 patient-years)	39	394 (743 patient-years)	RRR: 43.4% (3.0-67.0) , p=0.0373	
Toyoda; 2019 (Nishiyama; 2023)	CSPS.com	Non-cardioembolic ischaemic stroke 1-25 weeks before enrolment, with intra- or extracranial stenosis or ≥2 risk factors. N=1879; 925 lacunar subgroup	Cilostazol 100mg twice daily plus aspirin or clopidogrel	Monotherapy aspirin or clopidogrel	69.5	1.4 years	Recurrent ischaemic stroke	12	464	31	461	HR: 0.41 (0.21-0.81)	
Blair; 2019	LACI-1	Lacunar stroke in the past 4 years. N=57	Cilostazol 100mg twice daily during 8 weeks	no cilostazol	66.1	followup 11 weeks	Recurrent ischaemic stroke	1	42	0	15	ns	
ISMN													
Blair; 2019	LACI-1	Lacunar stroke in the past 4 years. N=57	ISMN 25mg twice daily during 8 weeks	no ISMN	66.1	followup 11 weeks	Recurrent ischaemic stroke	1	44	0	13	ns	
Haemorrhagic stroke													
Cilostazol													

Toyoda; 2019 (Nishiyama; 2023)	CSPS.com	Non-cardioembolic ischaemic stroke 1-25 weeks before enrolment, with intra- or extracranial stenosis or ≥2 risk factors. N=1879; 925 lacunar subgroup	Cilostazol 100mg twice daily plus aspirin or clopidogrel	Monotherapy aspirin or clopidogrel	69.5	1.4 years	Haemorrhagic stroke	2	464	4	461	HR 0.53 (0.10-2.88), p=0.46	
Cognitive impairment or dementia													
Cilostazol													
Blair; 2019	LACI-1	Lacunar stroke in the past 4 years. N=57	Cilostazol 100mg twice daily during 8 weeks	no cilostazol	66.1	followup 11 weeks	TMT A and B— time		27		29	A: MD −4.0 (−12.7, 4.7), p=0.37; B: MD −3.4 (−22.7, 16.0), p=0.73	
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	Cilostazol 100mg twice daily during 1 year	No cilostazol	64.0	1 year	Cognitive impairment (t-MoCA<20 or TICS-m<25)	81	178	94	180	Adjusted OR: 0.71 (0.41-1.21), p=0.21	
ISMN													
Blair; 2019	LACI-1	Lacunar stroke in the past 4 years. N=57	ISMN 25mg twice daily	no ISMN	66.1	followup 11 weeks	TMT A and B— time		29		27	A: MD −4.2 (−12.8, 4.4), p=0.34; B: MD −3.1 (−22.4, 16.3), p=0.76	
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	ISMN 25mg twice daily during 1 year	no ISMN	64.0	1 year	Cognitive impairment (t-MoCA<20	78	178	97	180	Adjusted OR: 0.66 (0.39-	

							or TICS-m<25)					1.14), p=0.13	
Mobility or Gait disorder													
Mood disorders													
Cilostazol													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	Cilostazol 100mg twice daily during 1 year	No cilostazol	64.0	1 year	Zung depression scale	Mean 48.4 SD (16.8)		Mean 51.4 (SD 17.7)		Adjusted MD −3.34 (−6.81-0.14), p=0.06	
ISMN													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	ISMN 25mg twice daily during 1 year	no ISMN	64.0	1 year	Zung depression scale	Mean 48.5 (SD 16.3)		Mean 51.3 (SD 18.1)		Adjusted MD −2.23 (−5.70-1.24), p=0.21	
MACE													
Cilostazol													
Toyoda; 2019 (Nishiyama; 2023)	CSPS.com	Non-cardioembolic ischaemic stroke 1-25 weeks before enrolment, with intra- or extracranial stenosis or ≥2 risk factors. N=1879; 925 lacunar subgroup	Cilostazol 100mg twice daily plus aspirin or clopidogrel	Monotherapy aspirin or clopidogrel	69.5	1.4 years	Composite of stroke, myocardial infarction and vascular death.	15	464	39	461	HR 0.41 (0.23-0.74); p=0.003	
Vorapaxar													

Morrow; 2013	TRA 2°P-TIMI 50	Prior atherothrombosis or stroke (2 week to 12 months before enrolment). N=26449; 2262 lacunar stroke subgroup	Vorapaxar 2.5mg daily + standard TAR	Placebo + standard TAR	64	24 months	Composite of cardiovascular death, myocardial infarction, or any stroke.	11.4%		11.3%		HR: 0.99 (0.75-1.31)	
Dependency													
Cilostazol													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	Cilostazol 100mg twice daily during 1 year	No cilostazol	64.0	1 year	mRS>2	18	178	29	180	Adjusted OR: 0.46 (0.22-0.95), p=0.04	
ISMN													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	ISMN 25mg twice daily during 1 year	no ISMN	64.0	1 year	mRS>23	19	178	28	180	Adjusted OR: 0.65 (0.32-1.33), p=0.24	
Death													
Cilostazol													
Toyoda; 2019 (Nishiyama; 2023)	CSPS.com	Non-cardioembolic ischaemic stroke 1-25 weeks before enrolment, with intra- or extracranial stenosis or ≥2 risk factors. N=1879; 925 lacunar subgroup	Cilostazol 100mg twice daily plus aspirin or clopidogrel	Monotherapy aspirin or clopidogrel	69.5	1.4 years	Death from any cause	3	464	1	461	HR 3.20 (0.33-30.8); p=0.31	

Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	Cilostazol 100mg twice daily during 1 year	No cilostazol	64.0	1 year	Death from any cause	2	178	2	180	Adjusted OR: 0.90 (0.08-10.26), p=0.93	
ISMN													
Wardlaw; 2023	LACI-2	Lacunar stroke. N=363	ISMN 25mg twice daily during 1 year	no ISMN	64.0	1 year	Death from any cause	1	178	3	180	Adjusted OR: 0.32 (0.02-5.61), p=0.44	