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European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack

Jesse Dawson[1], Yannick Béjot[2,3], Louisa M Christensen[4], Gian Marco De Marchis[5], Martin Dichgans[6,7], Guri Hagberg[8,9], Mirjam R Heldner[10], Haralampos Milionis[11], Linxin Li[12], Francesca Romana Pezzella[13], Martin Taylor Rowan[1], Cristina Tiu[14,15] and Alastair Webb[12]

Abstract

Recurrent stroke affects 9% to 15% of people within 1 year. This European Stroke Organisation (ESO) guideline provides evidence-based recommendations on pharmacological management of blood pressure (BP), diabetes mellitus, lipid levels and antiplatelet therapy for the prevention of recurrent stroke and other important outcomes in people with ischaemic stroke or transient ischaemic attack (TIA). It does not cover interventions for specific causes of stroke, including anticoagulation for cardioembolic stroke, which are addressed in other guidelines. This guideline was developed through ESO standard operating procedures and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. The working group identified clinical questions, selected outcomes, performed systematic reviews, with meta-analyses where appropriate, and made evidence-based recommendations, with expert consensus statements where evidence was insufficient to support a recommendation. To reduce the long-term risk of recurrent stroke or other important outcomes after ischaemic stroke or TIA, we recommend: BP lowering treatment to a target of <130/80 mmHg, except in subgroups at increased risk of harm; HMGCoA-reductase inhibitors (statins) and targeting a low density lipoprotein level of <1.8 mmol/l (70 mg/dl); avoidance of dual antiplatelet therapy with aspirin and clopidogrel after the first 90 days; to not give direct oral anticoagulant drugs (DOACs) for embolic stroke of undetermined source and to consider pioglitazone in people with diabetes or insulin resistance, after careful consideration of potential risks. In addition to the evidence-based recommendations, all or the majority of working group members supported: out-of-office BP monitoring;

[1]Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
[2]Dijon Stroke Registry, Department of Neurology, University Hospital of Dijon, Dijon, France
[3]Pathophysiology and Epidemiology of Cardio-Cerebrovascular disease (PEC2), University of Burgundy, Dijon, France
[4]Dept of Neurology, Copenhagen University Hospital Bispebjerg, Kobenhavn, Denmark
[5]Department of Neurology and Stroke Center, University Hospital Basel and University of Basel, Basel, Switzerland
[6]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany
[7]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[8]Oslo Stroke Unit, Department of Neurology, Oslo University Hospital, Ullevål, Norway
[9]Department of medical research, Bærum Hospital Vestre Viken Hospital Trust, Drammen, Norway
[10]Stroke Research Center Bern, Department of Neurology, University and University Hospital Bern, Bern, Switzerland
[11]Department of Internal Medicine, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina, Greece
[12]Wolfson Centre for Prevention of Stroke and Dementia, Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[13]Stroke Unit, Department of Neuroscience, San Camillo Forlanini Hospital, Rome, Italy
[14]Department of Clinical Neurosciences, University of Medicine and Pharmacy 'Carol Davila', Bucuresti, Romania
[15]Department of Neurology, University Hospital Bucharest, Bucharest, Romania

Corresponding author:
Jesse Dawson, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Queen Elizabeth University Hospital, Glasgow G12 9QQ, UK.
Email: jesse.dawson@glasgow.ac.uk

use of combination treatment for BP control; consideration of ezetimibe or PCSK9 inhibitors when lipid targets are not achieved; consideration of use of low-dose DOACs in addition to an antiplatelet in selected groups of people with coronary or peripheral artery disease and aiming for an HbA1c level of <53 mmol/mol (7%) in people with diabetes mellitus. These guidelines aim to standardise long-term pharmacological treatment to reduce the burden of recurrent stroke in Europe.

Keywords
Guideline, systematic review, stroke, hypertension, dyslipidaemia, diabetes, antiplatelet

The full version of this guideline appears online.

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Introduction

Approximately 1.1 million people in Europe suffer a stroke each year.[1] The majority of these are ischaemic, with approximately half as many people again experiencing a transient ischaemic attack (TIA).[2] People with a history of ischaemic stroke or TIA are at an increased risk of recurrent stroke and cardiovascular events, including myocardial infarction. Following ischaemic stroke, the rate of any recurrent stroke has been reported to range between 9% and 15% after 1 year, dependent on stroke aetiology.[3] The rate of recurrent stroke at 10 years is reported as being between 27% and 40%. People with large artery disease have a reported rate of acute coronary syndrome of 22% over 10 years. In a recently reported international cohort study, 6% of people with TIA suffered a stroke within 1-year and 12% suffered a stroke or TIA.[4]

Several advances have recently been made in pharmacological preventative strategies for first and recurrent stroke. These include new drug classes for antithrombotic and lipid lowering therapy and for treatment of diabetes mellitus. In addition, several studies have assessed treatment targets for cholesterol and blood pressure (BP) level and compared investigative strategies to detect modifiable causes such as atrial fibrillation. Most cases of stroke can be explained by known cerebrovascular risk factors, with over 80% of the population attributable risk being explained by hypertension, smoking, diet, diabetes, alcohol use, psychological factors, activity levels and cardiac causes.[5] There is therefore extensive opportunity to prevent recurrent stroke in people with stroke and TIA through readily available treatments. However, this can be hard to achieve in practice with several studies reporting sub-optimal risk factor control.[6]

The European Stroke Organisation (ESO) prepared a European Stroke Action Plan in 2018 which set targets to reduce the number of strokes in Europe by 10%.[7] Effective secondary prevention measures, that are implementable on a wide scale, are key to this aim. The aim of this guideline is to provide recommendations to physicians treating people with ischaemic stroke or TIA to help them reach decisions regarding antithrombotic, BP lowering and lipid lowering treatment and regarding blood glucose control for prevention of recurrent stroke. The use of short term dual antiplatelet therapy early after minor stroke and high-risk TIA,[8] secondary prevention in people with atrial fibrillation[9] or haemorrhagic stroke[10] and acute management after stroke or TIA[11] are covered in other guidelines. The use of lifestyle measures to prevent stroke will be discussed in future guidelines.

Methods

Composition and approval of the Module Working Group

These guidelines were initiated by the ESO. Two chairpersons (JD and AW) were selected to assemble and coordinate the Guideline Module Working Group (MWG). The final group contained 13 experts. The ESO Guideline Board and Executive Committee reviewed the intellectual and financial disclosures of all MWG members and approved the composition of the group. The full details of all MWG members and their disclosures is included in Supplemental Materials.

Development and approval of clinical questions

The guidelines were developed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology[12] and the ESO Standard Operating Procedure (SOP),[13] as described previously. In brief, the MWG developed a list of topics, and corresponding outcomes of clinical interest, within four key topic areas: (1) BP management; (2) lipid-lowering therapy; (3) antithrombotic therapy and (4) management of diabetes mellitus. The topics and outcomes were independently rated by each group member as critical, important or of limited importance according to GRADE criteria. The list of outcomes and results of voting are given in Table 1. Critical outcomes were defined as having either a mean or median score of 7 or more. Once critical outcomes had been identified, we established whether they were critical for all four key topic areas. Any stroke, ischaemic stroke and major cardiovascular events were viewed as critical for all four topic areas. Bleeding outcomes were agreed as critical for lipid lowering and antithrombotic population, intervention, comprator, outcome (PICO) questions. To avoid duplication, we included haemorrhagic stroke as a critical outcome but not intracranial bleeding. Functional outcome was initially rated as critical, but it was agreed that this would be downgraded to important and not be used to influence summary GRADE certainty assessment as there would be little data on this outcome in secondary prevention trials. Dementia was rated as important and was included as an outcome for the PICO questions as we agreed readers would be interested in this outcome if data were available. However, it was not used to influence summary of GRADE certainty. In addition, we defined in advance that the outcome for PICO question 2 was blood pressure level. For our overall assessment of quality of evidence for each PICO question we used the lowest level of evidence for a critical outcome unless otherwise stated.

A series of PICO questions were then developed and approved by the ESO Guideline Board and the ESO Executive Committee.

Literature search

Search terms were developed by the MWG and guideline methodologist. Where a validated search strategy was available, this was used or adapted. A single broad search was performed for each topic area. Identified titles were then reviewed separately for each PICO question. Where there was a recent relevant systematic review on the question of interest, the corresponding search strategy and results were used and updated as necessary. Search strategies are described in the Supplemental Materials. MTR, JD and AW agreed on the search terms for each PICO question.

The search was performed by the ESO Guideline methodologist (MTR). The following databases were searched: the Cochrane Library, Embase and Medline from inception to 9th April 2021. Search results were run through the Cochrane machine learning randomised controlled trial classifier, to restrict results to randomised controlled trials only.[14] Reference lists of review articles, the authors' personal reference libraries, and previous guidelines were also searched for additional relevant records.

Search results were loaded into the web-based Covidence platform (Health Innovation, Melbourne, Australia) for assessment by the MWG. Two or more MWG members were assigned to independently screen the titles and abstracts of publications registered in Covidence and then assess the full text of studies determined to be potentially relevant. All disagreements were resolved by discussion between the two reviewers or by a third MWG member.

We excluded publications with only conference abstracts available. For a study to be considered eligible, all of the following criteria needed to be met: report of data from a randomised controlled trial; performed only in adults ($\geqslant$18 years) with ischaemic stroke or TIA (or reported outcomes separately for this group); inclusion of at least 50 participants per treatment group; at least 3 months follow up; and assessment of an intervention specified by one of the included PICO questions. As PICO 2 assessed the efficacy of outpatient blood pressure monitoring, it included studies with a primary outcome of blood pressure control at 3 months or more.

Data analysis

Data extraction and analysis was performed by the ESO methodologist. In the case that relevant data were not reported in an eligible study, the corresponding author was contacted. In the case of no response, the co-authors of the study were also contacted. If no answer was received, data were considered as missing.

Where appropriate, fixed or random-effects meta-analyses were conducted using Review Manager (RevMan) software (Cochrane). Results were presented as estimates of effect with associated 95% confidence interval (95% CIs). Statistical heterogeneity across studies was assessed using the I^2 statistic, and classified as moderate ($\geqslant$30%), substantial ($\geqslant$50%) and considerable ($\geqslant$75%).[15]

Evaluation of the quality of evidence and formulation of recommendations

The risk of bias of each included randomised trial was assessed with the Cochrane Rob2 tool.[16] As recommended, the evidence synthesis did not use a quality 'score' threshold but classified overall risk of bias at study level and then in aggregate.[17]

The results of data analysis were imported into the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.) For each PICO question, and each outcome, the following were considered: risk of bias based on the type of available evidence (randomised or observational studies); inconsistency of results; indirectness of evidence, imprecision of results and other possible bias. GRADE evidence profiles/summary of findings tables were generated and used to prepare recommendations. 'Evidence-based Recommendations' were based on the GRADE methodology. The direction, strength and formulation of the recommendations were determined according to the GRADE evidence profiles and the ESO-SOP.[12,13,18]

Finally, Expert Consensus Statements were added whenever the MWG considered that there was insufficient evidence available to provide Evidence-based Recommendations and where practical guidance is needed for routine clinical practice. The Expert Consensus Statements were based on voting by all expert MWG members. Importantly, these Expert Consensus Statements should not be regarded as Evidence-based Recommendations, since they only reflect the opinion of the writing group.

Drafting of the document, revision and approval

Each PICO question was addressed in distinct sections, in line with the updated ESO SOP.[13] First, 'Analysis of current evidence' summarised current pathophysiological considerations followed by a summary and discussion of the results of the identified RCTs and other studies. Second, 'Additional information' was added when more details on the studies referred to in the first section were needed to provide information on

Table 1. List of outcomes included and results of voting.

Outcome	MWG 1	MWG 2	MWG 3	MWG 4	MWG 5	MWG 6	MWG 7	MWG 8	MWG 9	Mean score	Median score
Ischaemic stroke	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**8**	**9**	**8.89**	**9**
Any stroke	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9.00**	**9**
Functional outcome	**6**	**9**	**6**	**9**	**8**	**9**	**9**	**8**	**9**	**8.11**	**9**
Haemorrhagic stroke	**9**	**9**	**9**	**9**	**7**	**9**	**9**	**8**	**9**	**8.67**	**9**
Myocardial infarction	**6**	**9**	**9**	**9**	**4**	**8**	**9**	**7**	**9**	**7.78**	**9**
Major cardiovascular events	**7**	**9**	**9**	**9**	**6**	**8**	**9**	**7**	**9**	**8.11**	**9**
Death	**8**	**9**	**9**	**9**	**8**	**8**	**8**	**9**	**9**	**8.56**	**9**
Cardiovascular death	**8**	**9**	**9**	**9**	**9**	**9**	**9**	**8**	**9**	**8.78**	**9**
Intracranial bleeding	**7**	**9**	**9**	**6**	**7**	**9**	**9**	**8**	**9**	**8.11**	**9**
Any major bleeding episode	**7**	**7**	**8**	**4**	**7**	**6**	**6**	**9**	**7**	**6.78**	**7**
Quality of life	6	5	6	6	6	6	7	6	5	5.89	6
Mild cognitive impairment	5	4	6	5	4	7	6	6	4	5.22	5
Dementia	6	6	6	5	6	8	7	6	6	6.22	6
White matter hyperintensity	3	4	4	5	3	5	5	3	3	3.89	4
Microbleeds	3	4	4	5	3	6	6	4	3	4.22	4
Brain atrophy	3	3	4	5	3	5	5	4	3	3.89	4
Extra-cranial bleeding	7	6	7	4	6	6	6	8	6	6.22	6
Renal failure	5	4	6	4	4	4	4	7	4	4.67	4
Fracture	5	2	3	3	5	2	2	5	2	3.22	3
Falls	5	2	4	3	4	2	3	5	2	3.33	3
Hypoglycaemia	5	3	5	3	5	2	3	5	4	3.89	4

Outcomes shown in bold were rated as critical on round 1 of voting.

key subgroup analyses of the included studies, on ongoing or future RCTs and on other studies which can provide important clinical guidance on the topic.

Third, an 'Expert Consensus Statement' paragraph was added whenever the MWG considered that insufficient evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for everyday clinical practice.

The Guideline document was reviewed several times by all MWG members and modified using a Delphi approach until consensus was reached. The final submitted document was peer-reviewed by two external reviewers, two members of the ESO Guideline Board and one member of the Executive Committee.

Results

Blood pressure lowering

> **PICO question 1:** In people with a history of ischaemic stroke or TIA, does blood pressure lowering treatment compared to no blood pressure lowering treatment reduce the risk of any recurrent stroke?

Analysis of current evidence

Hypertension is a key risk factor for stroke. BP level has a log-linear relationship with risk of stroke. A 20 mmHg systolic or 10 mmHg diastolic increase in BP is associated with an approximate doubling of the risk of stroke.[19] Elevated BP after ischaemic stroke or TIA is also a risk factor for recurrence.[19,20]

Our systematic review and search of associated reference lists identified 5482 titles, of which 281 were reviewed in full. Ten trials of antihypertensive drugs versus placebo after TIA or stroke were eligible,[21–30] including reports of secondary prevention subgroups in larger trials of mixed populations. The shortest reported period from stroke to randomisation was a median of 15 days[23] with most trials enrolling people months after stroke.

Results for all considered outcomes and GRADE scoring are available in Table 2. On meta-analysis of data from nine trials,[21–29] with a median duration of follow-up ranging from 2 to 4.5 years, there was a significant reduction in the odds of recurrent stroke by almost 20% (OR 0.81, 95% CI 0.71–0.92, $p=0.002$) with BP lowering treatment (Figure 1; Table 2). The use of BP lowering treatment would be expected to lead to 17 fewer strokes per 1000 people treated. There was substantial heterogeneity ($I^2=53$, $p=0.03$), giving only moderate certainty, largely due to the largest trial with one of the smallest achieved BP differences between groups (the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS)). An exploratory analysis removing PROFESS[23] resulted in a 25% reduction in stroke risk (OR 0.75, 95% CI 0.68–0.83) with no residual heterogeneity ($I^2=0$).

Table 2. GRADE evidence profile for PICO question 1: In people with a history of ischaemic stroke or TIA, does blood pressure lowering treatment compared to no blood pressure lowering treatment reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Does blood pressure lowering treatment	No blood pressure lowering treatment	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
9	Randomised trials	Not serious	Serious[a]	Not serious	Not serious	None	1631/19,107 (8.5%)	1905/19,215 (9.9%)	OR 0.81 (0.71–0.92)	17 fewer per 1000 (from 27 fewer to 7 fewer)	⊕⊕⊕◯ Moderate	Critical
Ischaemic stroke												
3	Randomised trials	Not serious	Serious[a]	Not serious	Very serious[b]	None	1028/13,367 (7.7%)	1137/13,334 (8.5%)	OR 0.85 (0.68–1.05)	12 fewer per 1000 (from 25 fewer to 4 more)	⊕⊕⊕◯ Moderate	Critical
Haemorrhagic stroke												
2	Randomised trials	Not serious	Serious[a]	Not serious	Very serious[b]	None	96/13,197 (0.7%)	143/13,240 (1.1%)	OR 0.66 (0.38–1.13)	4 fewer per 1000 (from 7 fewer to 1 more)	⊕◯◯◯ Very low	Critical
Major cardiovascular events												
7	Randomised trials	Not serious	Serious[a]	Not serious	Not serious	None	2309/17,471 (13.2%)	2637/17,470 (15.1%)	OR 0.80 (0.69–0.94)	26 fewer per 1000 (from 42 fewer to 8 fewer)	⊕⊕⊕◯ Moderate	Critical
Myocardial infarction												
6	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	299/17,374 (1.7%)	343/17,373 (2.0%)	OR 0.85 (0.69–1.04)	3 fewer per 1000 (from 6 fewer to 1 more)	⊕⊕◯◯ Low	Critical
Death												
7	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	1350/17,543 (7.7%)	1364/17,467 (7.8%)	OR 0.97 (0.90–1.05)	2 fewer per 1000 (from 7 fewer to 4 more)	⊕⊕◯◯ Low	Critical
Cardiovascular death												
6	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	589/17,374 (3.4%)	663/17,373 (3.8%)	OR 0.88 (0.78–0.99)	4 fewer per 1000 (from 8 fewer to 1 fewer)	⊕⊕⊕⊕ High	Critical
Dementia												
2	Randomised trials	Not serious	Not serious	Serious[c]	Very serious[b]	None	601/11,675 (5.1%)	626/11,700 (5.4%)	NA	NA	⊕◯◯◯ Very low	Important
Functional outcome												
1	Randomised trials	Not serious	Not serious	Serious[c]	Very serious[b]	None	400/795 (50.3%)	405/838 (48.3%)	OR 1.08 (0.89–1.32)	20 more per 1000 (from 28 fewer to 68 more)	⊕◯◯◯ Very low	Important

CI: confidence interval; OR: odds ratio; NA: not analysed (data for this outcome were not pooled).
[a]Significant heterogeneity according to I^2 statistic. However, heterogeneity significantly reduced following removal of one trial (PROFESS), justifying a 'Moderate Grading' for ischaemic stroke.
[b]Fails to rule out harm (confidence intervals cross 1).
[c]Restricted population sample.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
PROGRESS	0.702	0.600	0.821	-4.435	0.000
HOPE	0.852	0.557	1.305	-0.735	0.462
PROFESS	0.941	0.854	1.036	-1.241	0.215
PATS	0.706	0.571	0.872	-3.234	0.001
HSCS	0.796	0.489	1.294	-0.922	0.357
SCOPE	0.360	0.134	0.973	-2.015	0.044
DUTCH TIA	0.837	0.571	1.229	-0.906	0.365
TEST	1.013	0.711	1.445	0.072	0.942
FEVER	0.812	0.583	1.130	-1.236	0.216
	0.808	0.709	0.922	-3.173	0.002

Odds ratio and 95% CI

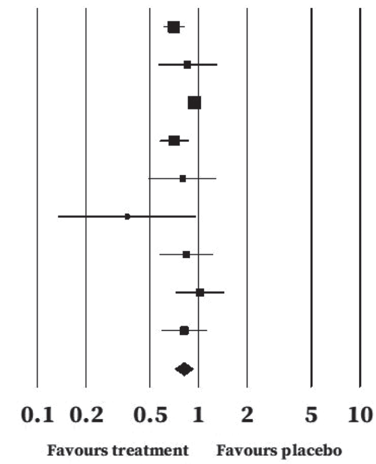


Figure 1. Forest plot for the risk of any stroke in randomised trials of antihypertensive medication versus placebo after stroke or TIA. Heterogeneity; $I^2 = 53$, $p = 0.03$.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
PROGRESS	0.716	0.627	0.819	-4.899	0.000
PROFESS	0.928	0.858	1.005	-1.832	0.067
PATS	0.750	0.618	0.909	-2.930	0.003
HSCS	0.690	0.448	1.062	-1.685	0.092
SCOPE	0.315	0.147	0.678	-2.954	0.003
DUTCH TIA	1.039	0.767	1.407	0.246	0.806
TEST	0.902	0.664	1.224	-0.665	0.506
	0.802	0.686	0.938	-2.771	0.006

Odds ratio and 95% CI

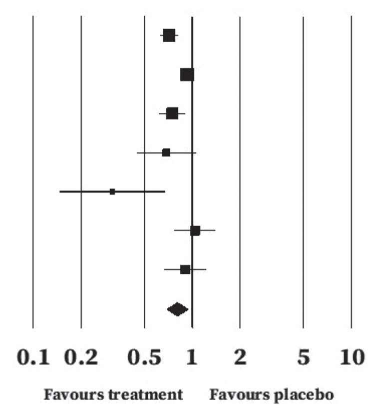


Figure 2. Forest plot for the risk of recurrent major adverse cardiovascular events in randomised trials of antihypertensive medication versus placebo after stroke or TIA. Heterogeneity: $I^2 = 72.506$; $Q = 21.823$; $p = 0.001$.

On meta-analysis of data from three trials[22,23,30] there was a non-significant reduction in ischaemic stroke (OR 0.85, 95% CI 0.68–1.050, p=0.13). On meta-analysis of data from two trials[22,23] there was a non-significant reduction in haemorrhagic stroke (OR 0.66, 0.38–1.13, p=0.13) but certainty was rated as very low due to a small number of events. There was a significant reduction in major cardiovascular events (seven trials,[22–28] OR 0.80, 95% CI 0.69–0.94, p=0.006, I^2=72.5, Figure 2, Table 2) and cardiovascular death (six trials,[21,23–25,27,28] OR 0.88, 95% CI 0.78–0.99, p=0.026, I^2=0) with antihypertensive therapy (Table 2). There was no significant reduction in myocardial infarction (six trials,[21,23–25,27,28] OR 0.85, 95% CI 0.69–1.04, p=0.11) and all cause death (seven trials,[21,23–25,27,28] OR 0.97, 95% CI

0.90–1.05, $p=0.51$, $I^2=0$). There were insufficient data to allow analysis of the effect of antihypertensive medication on dementia and functional outcome and there were no significant differences seen for these outcomes in any individual trial we reviewed (Table 2).

There was no important concern of significant bias in the results, but there was substantial heterogeneity between studies for the outcomes of any stroke and major cardiovascular events. This led to a rating of only moderate certainty for these outcomes. However, as described above, this heterogeneity predominantly resulted from inclusion of PROFESS[23] which produced a more conservative estimate of the effect size. Exclusion of the PROFESS trial data from the analyses resulted in a greater difference between the intervention and control groups and removed our concerns regarding inconsistency. Therefore, taking this into account and because the level of certainty was high for cardiovascular death, we rated the overall quality of evidence as high for this PICO question. Achieved BP differences were variable between studies, ranging from 3.2/2.0 mmHg in PROFESS to 25.0/12.0 mmHg in HSCS.

Additional information

The conclusions of our meta-analyses are consistent with those of recent meta-analyses performed in 2018[31] and 2017,[32] based upon a very similar groups of trials. The latter of these analyses also supported a linear relationship between degree of BP reduction in these studies and achieved differences in outcomes. Furthermore, the effect of BP lowering in our meta-analysis is highly consistent with the benefits of BP lowering in primary prevention of stroke and other secondary prevention populations. In the largest available individual participant-level meta-analysis, there was an approximate 10% reduction in the risk of major adverse cardiovascular events for each 5 mmHg reduction in systolic BP in both primary and secondary prevention populations. In people with prior cardiovascular disease, there was a reduction in all major cardiovascular events by 11% (OR 0.89, 95% CI 0.86–0.92) and stroke by 11% (OR 0.89, 95% CI 0.85–0.94), but no effect for all cause death.[33]

Benefits of BP reduction in individual participant-level meta-analyses in primary prevention were consistent regardless of baseline BP level, even down to normotensive levels (120/70 mmHg). However, confidence in benefits at these lower BP levels is limited due to heterogeneity between populations and smaller numbers.[33] The benefit of antihypertensive treatment in secondary prevention of stroke at mildly hypertensive levels is supported by the PROGRESS trial, in which the risk of recurrent stroke was reduced by treatment in both hypertensive and non-hypertensive populations, with hypertension defined as BP greater than 140/90 mmHg.

The timing of intervention in the studies included in our meta-analysis varied significantly, but treatment was not initiated in the acute phase in any of these trials, and the risk of recurrent events was consistently reduced during follow-up. As such, our recommendations apply for all people after an ischaemic stroke or TIA, but do not provide a specific recommendation regarding the timing of initiation of therapy.

Evidence-based recommendation
In people with previous ischaemic stroke or TIA, we recommend blood pressure lowering treatment to reduce the risk of recurrent stroke.

Quality of evidence: **High** ⊕⊕⊕⊕
Strength of recommendation: **Strong for intervention** ↑↑

PICO question 2: In people with a history of ischaemic stroke or TIA starting antihypertensive therapy, does use of out-of-office blood pressure measurements compared to clinic measurements provide better long-term control of blood pressure?

Analysis of current evidence

Our systematic review and search of associated reference lists identified 5482 titles, of which 281 were reviewed in full. For this question we identified three trials comparing out-of-office BP measurements versus in office BP measurements in people after stroke or TIA.[34–36]

The Trial of the Effectiveness of Self-monitoring/Treatment of BP after Stroke (TEST-BP) trial[36] randomised 171 participants with a recent stroke or TIA to self-BP monitoring with or without guided self-management of BP treatment versus treatment as usual. The primary outcome was difference in daytime ambulatory systolic BP (SBP) at 6 months. There were no significant mean between-group differences at 6 months (difference treatment as usual minus self monitoring and management, 2.69 mmHg (95% CI −2.59 to 7.97; $p=0.31$); treatment as usual minus self monitoring only, 3.00 mmHg (95% CI −2.53 to 8.54; $p=0.28$). Self-BP monitoring did not result in more participants achieving target BP, defined as daytime blood pressure on ambulatory monitoring of ⩽120/75 mmHg (treatment as usual 12/52 (23%), treatment as usual 8/51 (16%), self monitoring and management 13/51 (26%), $p>0.05$).

In the study by Kerry et al.[35] 381 participants with hypertension and a history of stroke or TIA were randomised to home BP monitoring or usual care. The primary outcome was a fall in systolic BP after 12 months. There was no significant mean between-group difference (0.3 mmHg, 95% CI −1.36 to 4.2). Subgroup analysis showed significant interaction with disability due to stroke ($p=0.03$ at 6 months) and baseline BP ($p=0.03$ at 12 months).

The Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups (TASMIN-SR) Trial[34] randomised 552 participants with a history of stroke or TIA, coronary heart disease, diabetes chronic kidney disease and

Table 3. GRADE evidence profile for PICO question 2: in people with a history of ischaemic stroke or TIA starting antihypertensive therapy, does use of out of office blood pressure measurements compared to outpatient clinic measurements provide better long-term control of blood pressure?.

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-monitoring	Treatment as usual	Relative (95% CI)	Absolute (95% CI)		
Systolic blood pressure												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	276	285	–	MD 2.34 mmHg greater decline (1.45 fewer to 6.13 more)	⊕⊕◯◯ Low	Critical

CI: confidence interval; MD: mean difference.
[a]Fails to rule out harm.

baseline BP of at least 130/80 mmHg to a self-monitoring of BP combined with an individualised self-titration algorithm versus usual care. The primary outcome was the difference in systolic BP between intervention and control groups at the 12-month office visit. After 12 months, there was a mean systolic BP difference of 9.2 mmHg (95% CI 5.7–12.7) between the groups without increasing adverse events. In a prespecified subgroup analysis including 77 participants with a history of stroke, there was no significant mean between-group difference (8.9 mmHg, 95% CI −1.1 to −19.1) at 12 months.

On meta-analysis of data from these three trials, there was no significant mean between-group difference (−2.34 mmHg, 95% CI −1.45 to 6.13, $p=0.227$) in BP (Figure 3; Table 3). There was no substantial heterogeneity ($I^2=26$, $p=0.26$) between the trials, and an exploratory analysis removing TASMIN-SR[34] resulted in a smaller mean difference (MD 1.15, 95% CI −1.96 to 4.27) with no residual heterogeneity ($I^2=0$). The level of certainty was rated as low due to imprecision.

Supporting information to the expert consensus statement

Our meta-analysis did not find significantly better BP control by home monitoring, but confidence intervals were wide and heterogeneous groups of participants were in included in the trials. We conclude that in people with previous ischaemic stroke or TIA, there are insufficient data to provide a recommendation for the PICO question. As there was no reported harm in the secondary prevention population, a consensus decision was reached based partly on previous evidence and guidance for primary prevention. In the TASMIN-SR trial,[34] self-monitoring of BP combined with an individualised self-titration algorithm resulted in a significant reduction in BP at 12 months. As shown in the study from Kerry et al.[35] a subgroup analysis revealed significant interaction with disability due to stroke, where 30% required the help of a care provider to take their BP, and age ranged from 30 to 94 years. Out-of-office monitoring is currently recommended in the 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice with self-monitoring of BP when feasible,[37] as it may have a beneficial effect on medication adherence and BP control,[38] especially in treated higher-risk people. However, patient

Evidence-based recommendation
–
Quality of evidence: –
Strength of recommendation: –

Expert consensus statement
In people with previous ischaemic stroke or TIA, we support the use of out of office blood pressure measurements wherever feasible, to achieve better long-term control of blood pressure.

Study name	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
TASMIN-SR	8.900	5.070	25.705	-1.037	18.837	1.755	0.079
TEST-BP (S-MAN)	3.000	2.790	7.785	-2.469	8.469	1.075	0.282
Kerry 2013	0.300	1.983	3.934	-3.588	4.188	0.151	0.880
	2.340	1.935	3.745	-1.453	6.133	1.209	0.227

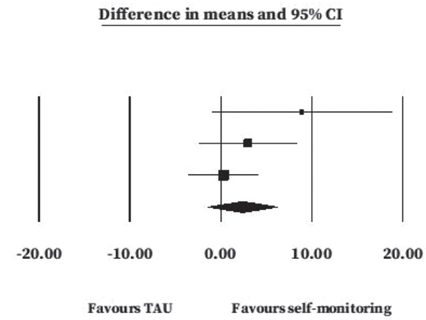


Figure 3. Forest plot for the difference in achieved mean blood pressure between 'treatment as usual' and introduction of home or remote blood pressure monitoring after stroke or TIA. Heterogeneity: $I^2 = 0.000$; $Q = 1.509$; $p = 0.470$.

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPS3	0.817	0.637	1.047	-1.596	0.110
PAST-BP	0.140	0.007	2.717	-1.300	0.194
RESPECT	0.730	0.474	1.123	-1.433	0.152
	0.787	0.635	0.975	-2.187	0.029

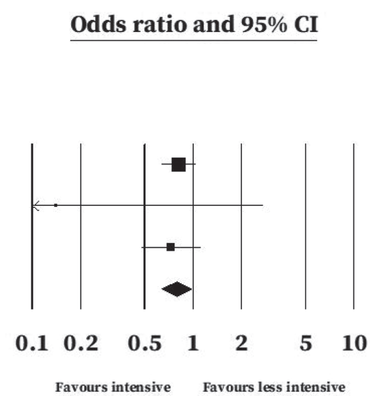


Figure 4. Forest plot for the reduction in the risk of recurrent stroke after TIA or minor stroke in participants randomised to an intensive blood pressure lowering strategy (<130/80) versus a less intensive strategy (<140/90). Heterogeneity: $I^2 = 0.000$; $Q = 1.509$; $p = 0.470$.

> In adult people with ischaemic stroke or TIA there is continued uncertainty over the use of out-of-office blood pressure measurements.

selection seems essential to ensure the effectiveness of home monitoring. The panel voted by 12/12 members for the following consensus statement (Supplemental Table 2).

> **PICO question 3:** In people with a history of ischaemic stroke or TIA starting or increasing antihypertensive therapy, does treating to a more intensive (i.e. blood pressure <130/80) versus less intensive (<140/90 mmHg) target reduce the risk of recurrent stroke?

Analysis of current evidence

Our systematic review and search of associated reference lists identified 5482 titles, of which 281 were reviewed in full. For this question we identified three trials in which an intensive BP reduction strategy was compared with a standard BP target and reported risk of recurrent stroke in people with a history of stroke or TIA.[39–41] The Secondary Prevention of Small Subcortical Strokes (SPS3)[39] trial included 3020 participants with MRI-confirmed symptomatic lacunar ischaemic stroke within 180 days to compare a SBP target of 130 to 149 mmHg versus a SBP < 130 mmHg. After a mean follow-up of 44 months, the primary endpoint (all strokes) was observed in 125 (2.25%) participants in the intensive SBP target group versus 152 (2.77%) participants in the standard SBP target group (HR 0.81, 95% CI 0.64–1.03, p=0.08). The intensive SBP reduction strategy was associated with a reduction in haemorrhagic stroke (HR 0.37, 95% CI 0.15–0.85, p=0.03). No statistically significant difference was observed between groups for other secondary outcomes including ischaemic stroke (HR 0.84, 95% CI 0.66–1.09, p=0.19), myocardial infarction (HR 0.88, 95% CI 0.56–1.39, p=0.59), major vascular events (HR 0.84, 95% CI 0.68–1.04, p=0.1), all-cause death (HR 1.03, 95% CI 0.79–1.35, $p=0.82$) and vascular death (HR 0.86, 95% CI 0.55–1.35, $p=0.52$). There was no significant difference in terms of serious adverse events. The Prevention After Stroke-Blood Pressure (PAST-BP) trial[40] enrolled 529 participants from 99 General Practices in England identified from the practice's TIA/stroke register. A total of 52% had suffered TIA and the remainder stroke. The type of stroke was not defined. Participants were randomised to intensive SBP reduction defined as SBP target <130 or a 10 mmHg reduction if baseline SBP was <140 mmHg versus standard SBP target (<140 mmHg). The primary outcome was change in SBP between baseline and 12 months. A recurrent stroke was observed in no participant in the intensive SBP target group versus 3 participants in the standard SBP target (RR 0.14, 95% CI 0.01–2.72). There was no difference between groups regarding major vascular events, myocardial infarction, total death vascular death, as well as adverse symptoms.

In the Recurrent Stroke Prevention Clinical Outcome Study (RESPECTS),[41] 1280 participants with a history of stroke <3 years (of whom 85% had a history of ischaemic stroke and 15% had intracerebral haemorrhage) were randomised to intensive BP reduction (BP target <120/80 mmHg) versus standard BP reduction (<140/90or <130/80 mmHg for people with diabetes, chronic kidney disease a history of myocardial infarction). The primary endpoint (any recurrent stroke) was observed in 39 (1.65%) participants in the intensive treatment group versus 52 (2.26%) in the standard treatment group after a mean follow-up of 3.9 years (HR 0.73, 95% CI 0.49–1.11). Intracerebral haemorrhage was less frequent in the intensive BP reduction group (HR 0.09, 95% CI 0.01–0.70), whereas no difference was observed for major vascular events, myocardial infarction all-cause death. Serious adverse events were similar between the two groups.

Additionally, our literature search found a single-blinded trial conducted in South Korea by Park et al.[42] A total of 132 participants with a recent (7–42 days) ischaemic stroke related to intracranial atherosclerotic stenosis were randomly allocated to intensive (SBP 110–120 mmHg) or standard (SBP 130–140 mmHg) BP control groups. The primary endpoint was the white matter lesion volume change on MRI between baseline and 24 weeks. This did not differ between groups. At 24 weeks, a new ischaemic stroke event was reported in one participant in both the intensive and the standard BP reduction groups. There were no vascular deaths in the study and the frequency of adverse events did not differ between the two groups.

Results for all considered outcomes and GRADE scoring, is available in Table 4. On meta-analysis of data from three trials[39–41] there was a significant reduction in recurrent stroke with intensive BP treatment compared with a standard BP reduction strategy (OR 0.79, 95% CI 0.64–0.98, $p=0.029$) (Figure 4). There was no evidence of heterogeneity and the level of certainty was rated as high. Use of an intensive blood pressure target would be expected to lead to 17 fewer cases of stroke per 1000 treated. There was a non-significant reduction in ischaemic stroke with intensive BP treatment on meta-analysis of data from three trials[39,41,42] (OR 0.87, 95% CI 0.69–1.09, $p=0.228$).

On meta-analysis of data from two trials,[39,41] there was a significant reduction in haemorrhagic stroke with intensive BP reduction (OR 0.25, 95% CI 0.07–0.90, $p=0.033$, Table 4, Figure 5). There was no significant difference between groups for the outcomes of major vascular events, myocardial infarction, all-cause death vascular death on meta-analysis (Table 4). Finally, functional outcome was only assessed in the SPS3 trial.[39] There was no significant difference between intensive and standard BP reduction groups for poor outcome defined as a mRS score ⩾3 (OR 0.82, 95% CI 0.54–1.25).

Additional information

There was some heterogeneity between trials in terms of participants enrolled; SPS3[39] only included people with lacunar stroke, PAST-BP[40] included people with TIA and stroke, RESPECTS[41] included people with haemorrhagic stroke, and Park's trial focussed on people with ischaemic stroke related to intracranial atherosclerotic stenosis. Outcomes were not reported according to baseline characteristics meaning it is difficult to generalise recommendations for specific subgroups. Other studies suggest caution regarding intensive BP reduction for some groups of people. For instance, pooled data from the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed that there was a relationship between higher stroke risk and lower blood pressure in people with bilateral severe (⩾70%) internal carotid artery stenosis.[43] In addition, the mean age of participants from the trials identified in our meta-analysis ranged between 63 and 72 years old, which is lower than that observed in population-based registries and in clinical practice.[44] This reflects the fact that elderly people were under-represented in randomised clinical trials, particularly those with frailty.[45] Indeed, in one study these participants had a greater risk of stroke with intensive treatment (adjusted HR 1.93; 95% CI 1.04–3.60, $p=0.038$), without a difference in wider cardiovascular outcomes or all-cause mortality, and an increased risk of hypotension and syncope.[45] Considering that pre-existing mild cognitive impairment is common in people with stroke,[46,47] additional research is needed to clarify the best BP target in people with stroke and cognitive impairment. In general, BP reduction in older people (aged >80 years) can be expected to reduce risk of stroke as shown in a large study of indapamide with or without an ACE inhibitor.[48] Another issue is the impact of intensive versus usual BP control on kidney function. A sub-analysis of SPS3 demonstrated a greater likelihood of rapid kidney function decline with intensive BP reduction, although this was not associated with an increased risk of clinically important events.[49] This was also seen in the Systolic Blood Pressure Intervention Trial (SPRINT), where intensive BP reduction was associated with a reduction in estimated glomerular filtration rate, although this effect was outweighed by

Table 4. GRADE evidence profile for PICO question 3: In people with a history of ischaemic stroke or TIA starting or increasing antihypertensive therapy, does treating to a more intensive (i.e. BP<130/80) versus less intensive (<140/90 mmHg) target reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A more intensive (i.e. BP<130/80) target	A less intensive (<140/90 mmHg) target	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	164/2400 (6.8%)	207/2412 (8.6%)	OR 0.79 (0.64–0.98)	17 fewer per 1000 (from 30 fewer to 2 fewer)	⊕⊕⊕⊕ High	Critical
Ischaemic stroke												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	151/2193 (6.9%)	173/2201 (7.9%)	OR 0.87 (0.69–1.09)	10 fewer per 1000 (from 23 fewer to 7 more)	⊕⊕◯◯ Low	Critical
Haemorrhagic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	None	7/2134 (0.3%)	27/2149 (1.3%)	OR 0.25 (0.07–0.90)	9 fewer per 1000 (from 12 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	Critical
Major cardiovascular events												
4	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	221/2466 (9.0%)	264/2475 (10.7%)	OR 0.83 (0.68–1.00)	17 fewer per 1000 (from 31 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	Critical
Myocardial infarction												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	42/2400 (1.8%)	45/2412 (1.9%)	OR 0.94 (0.62–1.44)	1 fewer per 1000 (from 7 fewer to 8 more)	⊕⊕◯◯ Low	Critical
Death												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious[c]	None	138/2400 (5.8%)	139/2412 (5.8%)	OR 1.00 (0.78–1.28)	0 fewer per 1000 (from 12 fewer to 15 more)	⊕⊕◯◯ Low	Critical
Cardiovascular death												
3	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	44/2400 (1.8%)	52/2412 (2.2%)	RR 0.86 (0.58–1.27)	3 fewer per 1000 (from 9 fewer to 6 more)	⊕⊕◯◯ Low	Critical
Functional outcome												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	49/1501 (3.3%)	49/1519 (3.2%)	OR 0.82 (0.54–1.26)	6 fewer per 1000 (from 15 fewer to 8 more)	⊕⊕◯◯ Low	Important

CI: confidence interval; RR: risk ratio; OR: odds ratio.
[a]Fails to rule-out harm (confidence intervals cross over 1).
[b]Few events and moderate sample size (optimal information size (OIS) not met).
[c]Fails to rule out benefit or harm (confidence intervals cross over 1). There were no data for dementia and major bleeding outcomes.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPS3	0.377	0.147	0.966	-2.032	0.042
RESPECT	0.089	0.011	0.692	-2.312	0.021
	0.247	0.068	0.895	-2.129	0.033

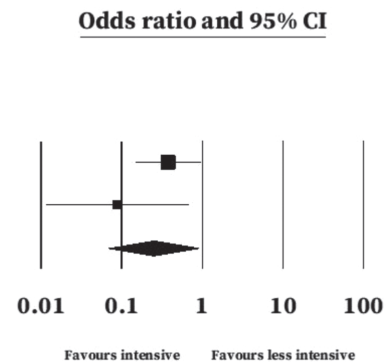


Figure 5. Forest plot for the reduction in the risk of recurrent haemorrhagic stroke after TIA or stroke in participants randomised to an intensive blood pressure lowering strategy (<130/80) versus a less intensive strategy (<140/90). Heterogeneity: $I^2 = 36.402$; $Q = 1.572$; $p = 0.210$.

cardiovascular and all-cause mortality benefits,[50] and the impact on longer-term kidney outcomes remains to be determined. As such, a more cautious approach to intensive blood pressure lowering may be warranted in people with bilateral, severe carotid stenosis, older age, cognitive impairment or pre-existing renal disease. Overall, we rated the quality of evidence as moderate, although it was high for the outcome of any stroke.

> **PICO question 4:** In people with a history of ischaemic stroke or TIA starting antihypertensive therapy, does initiation of two blood pressure lowering medications compared to monotherapy reduce the risk of recurrent stroke?

Analysis of current evidence

The systematic review identified no trials in which initiation of a combination of antihypertensive medications was directly compared to initiation of a single agent in the secondary prevention of stroke or TIA, and no trial in which a specific combination of blood pressure lowering medications was compared to another combination of blood pressure lowering medications.

The perindopril protection against recurrent stroke (PROGRESS) trial was the only trial identified that randomised participants to a defined combination treatment, but the treating physician had discretion to choose whether monotherapy or combination treatment was used.[21] As such, the perindopril and indapamide versus perindopril alone comparison is not a randomised comparison. In addition, the combination treatment arm was slightly more hypertensive at baseline. Nonetheless, combination treatment was associated with a greater reduction in blood pressure compared to placebo (12.5/5.0 mmHg) than monotherapy treatment versus placebo (4.9/2.8 mmHg), as well as a proportionately greater relative reduction in the risk of recurrent stroke (43% vs 5%).

Supporting information to the expert consensus statement

We conclude that in people with previous ischaemic stroke or TIA, there are insufficient data to provide a recommendation for the PICO question. Given that blood pressure lowering appears to have consistent effects in the setting of primary and secondary prevention with regard to stroke, we used data from primary prevention studies to help us reach a consensus. Trials have explored the use of combined therapy versus monotherapy in people with essential hypertension and show that this leads to better control of BP.[51,52] A large systematic review and meta-analysis shows that the extra blood pressure reduction from combining two drug classes is approximately five times greater than doubling the dose of one drug.[53] Large observational cohort studies have demonstrated that initiation of combination therapy is associated with improved blood pressure control[53,54] and improved adherence[55,56] compared with monotherapy and with minimal additional side-effects, associated with significant reductions in clinical events compared to placebo.[53] This evidence underpins the current European Society of Hypertension and European Society of Cardiology guidelines[57] which recommend initiation of antihypertensive treatment with combination treatment, except in people at increased risk of hypotension and those with mild hypertension and low cardiovascular risk (not applicable to our stroke population). In the absence of alternative specific evidence for secondary prevention in stroke, and supportive evidence for the potential benefit of combination treatment in PROGRESS,[21] this European guidance is therefore applicable for most people with prior stroke. Where possible, combination treatment should be provided as a single tablet where possible, to improve adherence.[58]

There is limited direct evidence to guide the choice of medications to use in a combination regimen. In primary prevention trials, calcium channel blockers (CCBs) appear to be slightly more efficacious than other classes in prevention of stroke, at the cost of an increased risk of symptomatic heart failure.[59,60] This effect may be due to a greater consistency of blood pressure control with CCBs and thiazide-like diuretics. In contrast, inhibitors of the renin angiotensin system (RAS) are particularly effective in prevention of coronary artery disease and renal dysfunction, and angiotensin receptor blockers (ARB) have an excellent side effect profile.[61] RAS inhibition plus a CCB was superior to RAS inhibition plus a diuretic in the The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[62] but this was not confirmed in further less well powered trials.[63,64] Therefore, based on primary prevention guidelines, plus supportive evidence from drug classes used in trials such as PROGRESS, initiation of treatment with a combination of antihypertensive medication, usually containing either a thiazide-like diuretic (such as indapamide) or a CCB (such as amlodipine or felodipine), combined with a RAS inhibitor (ACE inhibitor or angiotensin 2 receptor blocker) is reasonable. If a third agent is needed, a CCB or thiazide can then be added if not already in use. Further studies are required to determine optimal combinations, especially in secondary prevention of stroke the potential benefit of three drug combinations, as is currently being tested after intracerebral haemorrhage in the Triple Therapy Prevention of Recurrent Intracerebral Disease EveNts (TRIDENT) trial (NCT02699645). The panel voted by 10/12 members for the following consensus statement (Supplemental Table 2).

Evidence-based recommendation

–

Quality of evidence: –
Strength of recommendation: –

Expert consensus statement

In people with ischaemic stroke or TIA, we support initiation of a combination of two blood pressure lowering drugs to reduce the risk of recurrent stroke, with consideration of monotherapy where there are potential risks of hypotension, such as in frail, elderly people and people with borderline hypertension

In adult people with ischaemic stroke or TIA there is continued uncertainty over the initiation of two blood pressure lowering medications compared to monotherapy.

Lipid lowering therapy

PICO question 5: In people with ischaemic stroke or TIA does use of an HMGCoA reductase inhibitor compared to no lipid-lowering therapy reduce the risk of recurrent stroke?

Evidence-based recommendation

In people with previous ischaemic stroke or TIA, we suggest aiming for a blood pressure target of <130/80 mmHg to reduce the risk of recurrent stroke.

Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Weak for intervention** ↑?

Analysis of current evidence

Our systematic review and search of associated reference lists identified 1986 titles, of which 301 were reviewed in full. We found five trials[65–69] which directly addressed this PICO question. These trials included a total of 10,169 participants.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial,[66] which was published in 2006, included 4731 participants who had had an ischaemic stroke or TIA within 1 to 6 months before study entry. Participants were randomised to receive either 80 mg atorvastatin daily or placebo. The primary outcome was any nonfatal or fatal stroke. The mean age of participants was 63 years and the mean duration of follow up was 4.9 years. There was a significant reduction in the primary outcome with atorvastatin 80 mg daily (adjusted HR 0.84, 95% CI 0.71–0.99).

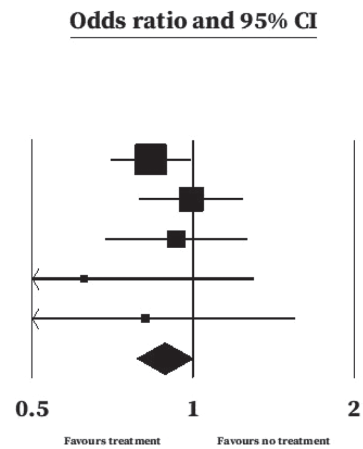
The Heart Protection Study Collaborative (HPSC),[65] included 20,536 people aged between 40 and 80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/l (135 mg/dl). Of these, 3280 had a history of prior cerebrovascular disease and these outcomes were reported separately; 63% of these had a history of non-disabling non-haemorrhagic stroke, 46% a history of TIA, 10% had undergone carotid endarterectomy and 2% carotid angioplasty. People with a stroke within the previous 6 months were excluded. In the main trial, participants were randomised to 40 mg simvastatin daily or placebo. The primary outcome was occurrence of any stroke. The mean age of participants was 65 years, the mean duration of follow up was 4.8 years and the mean interval since the most recent stroke or TIA was 4.3 years. There was a significant reduction in the primary outcome with simvastatin 40 daily (HR 0.75, 95% CI 0.66–0.85).

The Japan Statin Treatment Against Recurrent Stroke (J-STARS) trial, which was published in 2015,[67] included 1578 participants (although a sample size of 3000 was initially planned) aged 45 to 80 years with a history of non-cardioembolic ischaemic stroke within the preceding 1 month to 3 years. Participants were randomised to remgceive pravastatin 10 mg daily or no HMGCoA reductase inhibitor therapy. The primary outcome was stroke (expressed as rate (%) per year). The mean age of participants was 66 years and the mean duration of follow up was 4.9 years. Stroke rate was similar between the two arms with an annual rate of 2.4% with pravastatin versus 2.5% in the comparison group (adjusted HR 0.95, 95% CI 0.71–1.28).

The Cholesterol and Recurrent Events (CARE) trial was a secondary prevention trial comparing pravastatin 40 mg/day after myocardial infarction.[68] A total of 4159 participants

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPARCL	0.834	0.700	0.993	-2.038	0.042
HPSC	0.992	0.792	1.242	-0.069	0.945
J-STARS	0.930	0.686	1.263	-0.463	0.643
CARE	0.625	0.301	1.300	-1.258	0.208
LIPID	0.814	0.428	1.550	-0.626	0.531
	0.885	0.784	0.999	-1.969	0.049

(Statistics for each study)



Meta Analysis

Figure 6. Forest plot for the risk of any stroke in trials comparing treatment with HMGCoA reductase inhibitors versus placebo after TIA or stroke. Heterogeneity: $I^2 = 0.000$; Q-value = 2.473.

aged between 21 and 75 years were enrolled after a mean of 10 months from the index event. The median follow-up period was 5 years. A total of 100 participants in the placebo group and 111 participants in the pravastatin group had a history of prior stroke/TIA. HMGCoA reductase inhibitor treatment in this subgroup of participants led to a 37% relative risk reduction in stroke or TIA (95% CI 23–68).[68]

The LIPID (the Long-Term Intervention with Pravastatin in ischaemic Disease) trial randomised 9014 participants with a median age of 62 years and a history of myocardial infarction or unstable angina during the previous 3 to 36 months to receive pravastatin 40 mg/day or placebo.[69] Prespecified secondary end points included stroke from any cause. The mean duration of follow-up was 6.1 years. A total of 610 participants ($n = 325$ in the intervention group) had a history of cerebrovascular disease. Pravastatin treatment in these participants was associated with a relative risk of stroke of 0.72 (95% CI 0.46–1.12).[70]

Results for all considered outcomes and GRADE scoring is available in Table 5. On meta-analysis of data from five trials[65–69] there was a significant reduction in the rate of any stroke in people treated with a HMGCoA reductase inhibitor compared to no lipid-lowering therapy (OR 0.89, 95% CI 0.78–0.99, $p = 0.049$) with little heterogeneity among the trials ($I^2 = 0$, p for heterogeneity = 0.65, Figure 6). The level of certainty was rated as high. Data suggest that use of a HMGCoA reductase inhibitor would be expected to lead to 13 fewer cases of stroke per 1000 treated.

Results were also consistent when the analysis was confined to the two trials that recruited participants early after their index ischaemic stroke (Supplemental Figure 1).

On meta-analysis of data from two trials,[65,71] there was a significant reduction in the rate of ischaemic stroke in people treated with a HMGCoA reductase inhibitor compared to no lipid-lowering therapy (OR 0.79, 95% CI 0.67–0.92; equivalent to 20 fewer events per 1000, 95% CI from 30 fewer to 7 fewer) (Table 5). The level of certainty was rated as high.

On meta-analysis of data from three trials[65–67] there was a significant increase in the rate of haemorrhagic stroke in people treated with HMGCoA reductase inhibitors compared to no lipid-lowering therapy (OR 1.55, 95% CI 1.09–2.21); equivalent to six more events per 1000 (from 1 more to 14 more) (Figure 7; Table 5). The level of certainty was rated as high.

On meta-analysis of data from two trials[65,71] there was a significant reduction in the rate of any major cardiovascular event in people treated with a HMGCoA reductase inhibitor compared to no lipid-lowering therapy (OR 0.78, 95% CI 0.70–0.87); equivalent to 40 fewer per 1000 (from 55 fewer to 22 fewer) (Table 5). The level of certainty was rated as high.

Only one trial reported data on the rate of myocardial infarction.[67] This showed that that there was no significant reduction in the rate of myocardial infarction in people treated with a HMGCoA reductase inhibitor compared to no lipid-lowering therapy (HR 0.55, 95% CI 0.16–1.89); four fewer per 1000 (from seven fewer to eight more). The level of certainty was rated as very low due to imprecision.

On meta-analysis of data from two trials[67,71] there was no reduction in the rate of death in people treated with a HMGCoA reductase inhibitor compared to no lipid-lowering therapy (OR 1.03, 95% CI 0.87–1.24) (Table 5). There was also no significant reduction in cardiovascular death (OR 0.78, 95% CI 0.58–1.06). The level of certainty was rated as low. Only one trial reported data on the rate of dementia.[67] This showed that that there was no significant

Table 5. GRADE evidence profile for PICO question 5: In people with ischaemic stroke or TIA does use of an HMGCoA reductase inhibitor compared to no lipid-lowering therapy reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HMGCoA reductase inhibitors	No lipid-lowering therapy	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	558/5081 (11.0%)	622/5088 (12.2%)	HR 0.89 (0.78–0.99)	13 fewer per 1000 (from 25 fewer to 0 fewer)	⊕⊕⊕⊕ High	Critical
Ischaemic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	318/4006 (7.9%)	396/4005 (9.9%)	OR 0.79 (0.67–0.92)	20 fewer per 1000 (from 30 fewer to 7 fewer)	⊕⊕⊕⊕ High	Critical
Haemorrhagic stroke												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	87/4799 (1.8%)	56/4790 (1.2%)	OR 1.55 (1.09–2.21)	6 more per 1000 (from 1 more to 14 more)	⊕⊕⊕⊕ High	Critical
Major cardiovascular events												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	740/4006 (18.5%)	895/4005 (22.3%)	OR 0.78 (0.70–0.87)	40 fewer per 1000 (from 55 fewer to 22 fewer)	⊕⊕⊕⊕ High	Critical
Myocardial infarction												
1	Randomised trials	Very serious[b]	Not serious	Not serious	Very serious[a]	None	4/793 (0.5%)	7/785 (0.9%)	HR 0.55 (0.16–1.89)	4 fewer per 1000 (from 7 fewer to 8 more)	⊕◯◯◯ Very low	Critical
Death												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[c]	None	259/3158 (8.2%)	246/3151 (7.8%)	HR 1.03 (0.87–1.24)	3 more per 1000 (from 10 fewer to 17 more)	⊕⊕◯◯ Low	Critical
Cardiovascular death												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	78/2365 (3.3%)	98/2366 (4.1%)	HR 0.78 (0.58–1.06)	9 fewer per 1000 (from 17 fewer to 2 more)	⊕⊕◯◯ Low	Critical
Dementia												
1	Randomised trials	Very serious[b]	Not serious	Not serious	Very serious[a]	None	33/793 (4.2%)	33/785 (4.2%)	OR 0.90 (0.79–1.03)	4 fewer per 1000 (from 9 fewer to 1 more)	⊕◯◯◯ Very low	Important
Functional outcome												
1	Randomised trials	Very serious[b]	Not serious	Not serious	Not serious	None	–/793	–/785	Not estimable		⊕⊕◯◯ Low	Important

CI: confidence interval; HR: hazard ratio; OR: odds ratio.
There were no data for major bleeding and intracranial bleeding outcomes.
[a]Small effect size and fails to rule out harm (confidence intervals cross over 1).
[b]Study is at high risk of bias.
[c]Small effect size and fails to rule out benefit (confidence intervals cross over 1).

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPARCL	1.683	1.089	2.602	2.344	0.019
HPSC	1.919	0.922	3.992	1.743	0.081
J-STARS	0.906	0.397	2.066	-0.234	0.815
	1.552	1.090	2.210	2.437	0.015

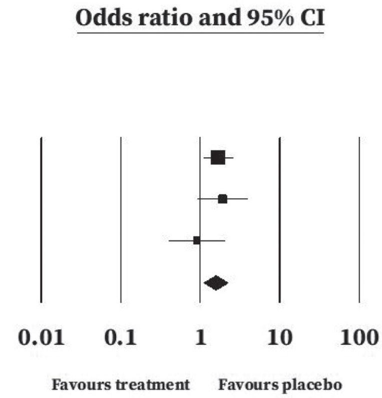


Figure 7. Forest plot for the risk of haemorrhagic stroke in trials comparing treatment with HMGCoA reductase inhibitors versus placebo after TIA or stroke. $I^2=4.423$; $q=2.093$, $p=0.351$.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
ODYSSEY OUTCOMES	0.900	0.520	1.559	-0.376	0.707
IMPROVE-IT	0.600	0.379	0.949	-2.185	0.029
FOURIER	0.900	0.680	1.191	-0.738	0.461
	0.812	0.636	1.038	-1.661	0.097

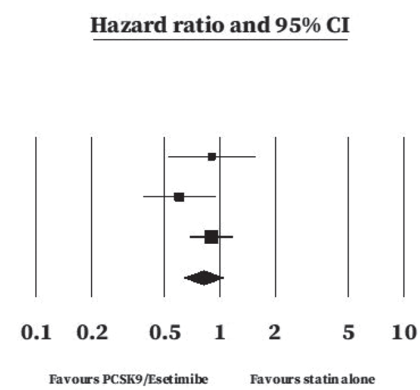


Figure 8. Forest plot for the risk of recurrent stroke in trials comparing treatment with PCSK9 inhibitors or ezetimibe versus placebo after TIA or stroke. Heterogeneity: $I^2=13.843$; Q-value $=2.321$, $p=0.313$.

reduction in the rate of dementia (OR 0.89, 95% CI 0.79–1.03). The level of certainty was rated as very low.

Additional information

Overall, we rated the quality of evidence as high. High quality evidence suggests that use of a HMGCoA reductase inhibitor reduces risk of ischaemic stroke and major cardiovascular events in people with previous ischaemic stroke or TIA. The effect on myocardial infarction in this population is less clear, although HMGCoA reductase inhibitors significantly reduce the risk of myocardial infarction in other groups. Our analysis showed that the risk of haemorrhagic stroke is increased with use of an HMGCoA reductase inhibitor. However, analysis showed a trend towards a reduction in total stroke, and in cardiovascular death, suggesting a net beneficial effect in people with previous ischaemic stroke and TIA. It is important to note that the SPARCL trial included a small number of people with haemorrhagic stroke, but the increase in haemorrhagic stroke during follow-up was still seen when these participants were excluded from analyses. Therefore, even if this increase is real, our data show that use of an HMGCoA reductase inhibitor may cause six haemorrhagic strokes per 1000 people treated but prevent 40 major cardiovascular events. Participants in the SPARCL trial received atorvastatin 80 mg daily and when this is considered alongside the data for PICO question 6 below, we believe this is an appropriate dose for most people with ischaemic stroke or TIA.

PICO question 6: In people with ischaemic stroke or TIA does working to an intensive cholesterol treatment target, compared to a less intensive target, reduce the risk of recurrent stroke?

Analysis of current evidence

Our systematic review and search of associated reference lists identified 1986 titles, of which 301 were reviewed in full. We found one randomised trial which directly addressed this PICO question. The Treat Stroke to Target trial included 2860 people with a stroke in the previous 3 months or a TIA within the previous 15 days.[72] It was a parallel-group trial conducted in France and South Korea. Participants were randomised to an LDL target of <1.8 mmol/l (<70 mg/dl) or to a target LDL of 2.3 to 2.8 mmol/l (90–110 mg/dl). Investigators were allowed to use any type or dose of HMGCoA reductase inhibitor or other lipid lowering therapy to reach these targets. The primary outcome was occurrence of a major cardiovascular event. The median duration of follow up was 3.5 years. There was a higher rate of HMGCoA reductase inhibitor use (94% vs 66%) and a higher rate of combined HMGCoA reductase inhibitor and ezetimibe use (35% vs 6%) in the low target group. The study showed a significant reduction in the risk of major cardiovascular events (HR 0.78, 95% CI 0.61–0.98; p = 0.04) in the intensive treatment group. There was a non-significant reduction in risk of cerebral infarction or intracranial haemorrhage (HR 0.82, 95% CI 0.63–1.07). There were also non-significant reductions in MI, (HR 0.64, 95% CI 0.37–1.13), cerebral infarction or TIA (HR 0.97, 95% CI 0.73–1.30), total mortality and cardiovascular mortality (HR 0.69, 95% CI 0.40–1.18). There was a non-significant increase in intracranial haemorrhage (HR 1.38, 95% CI 0.68–2.82).

Additional information

Post hoc analyses give further information concerning the benefits of intensive control of LDL cholesterol levels. Analysis from the Treat Stroke to Target trial showed that participants achieving LDL cholesterol <1.8 mmol/l (<70 mg/dl) had a lower risk of ischaemic stroke (OR 0.74, 95% CI 0.55–0.99).[72] In a post-hoc analysis of the SPARCL trial,[71] participants with a LDL cholesterol reduction of ⩾50% from baseline had a 35% reduction in the risk of all stroke (HR 0.65, 95% CI 0.52–0.81). In a post hoc analysis of the J-STARS study,[73] participants were divided into groups according to post-randomised LDL cholesterol levels (i.e. <2.1 mmol/l (80 mg/dl) (n = 89), 2.1–2.6 mmol/l (80–100 mg/dl) (n = 319), 2.6–3.1 mmol/l (100–120 mg/dl) (n = 478), 3.1–3.6 mmol/l (120–140 mg/dl) (n = 419), ⩾3.6 mmol/l (140 mg/dl) (n = 212)). The HR for stroke and TIA was lower with a post randomised LDL cholesterol level of 2.1 to 2.6 mmol/l (80–100 mg/dl) (p = 0.23, for the trend) after adjustment for baseline LDL cholesterol, body mass index, hypertension, diabetes mellitus and HMGCoA reductase inhibitor usage. Overall, we rated the level of certainty as moderate for this PICO question.

> **Evidence-based recommendation**
> In people with ischaemic stroke or TIA, we recommend aiming for an LDL cholesterol level of <1.8 mmol/l (70 mg/dl) to reduce the risk of major cardiovascular events.
>
> Quality of evidence: **Moderate** ⊕⊕⊕
> Strength of recommendation: **Strong for intervention** ↑↑

PICO question 7: In people with a previous ischaemic stroke or TIA who do not achieve recommended LDL-C targets despite taking a maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks, is the addition of ezetimibe and/or a PCSK9-inhibitor superior to an HMGCoA reductase inhibitor alone to reduce the risk of recurrent stroke?

> **Evidence-based recommendation**
> In people with previous ischaemic stroke or TIA we recommend use of a HMGCoA reductase inhibitor to reduce the risk of recurrent ischaemic stroke.
>
> Quality of evidence: **High** ⊕⊕⊕⊕
> Strength of recommendation: **Strong for intervention** ↑↑

Analysis of current evidence

Our systematic review and search of associated reference lists identified 1986 titles, of which 301 were reviewed in full. We did not identify any randomised controlled trial that directly compared the add-on therapy with ezetimibe and/or PCSK-9 inhibitor versus HMGCoA reductase inhibitor alone in people with a history of ischaemic stroke or TIA. However, subgroup analyses of three randomised clinical trials, mostly in people with coronary heart disease[74–76] have indirectly addressed the PICO question, albeit with limited precision due a small number of outcomes.

The Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial[75] was a double-blinded, randomised trial involving 18,144 participants who were hospitalised for a recent acute coronary syndrome who had a LDL cholesterol level between 1.3 and 3.2 mmol/l (50 and 125 mg/dl) if not taking lipid lowering therapy or a LDL level between 1.3 and 2.6 mmol/l (50 and 100 mg/dl) if they were. Participants were randomised to ezetimibe plus simvastatin versus placebo plus simvastatin. Ezetimibe led to a significant relative reduction of major cardiovascular events (7-year risk 32.7% vs 34.7%; HR 0.94, 95% CI 0.89–0.99, p = 0.016). The effect appeared to be consistent for any stroke (HR 0.86, 95% CI 0.73–1.00, p = 0.05) and for ischaemic stroke (HR 0.79, 95% CI 0.67–0.94, p = 0.008), without a significant increase in haemorrhagic stroke (HR 1.38, 95% CI 0.93–2.04, p = 0.11). A small number of participants (n=682, 3.8% of trial population) had a history of stroke at baseline.[77] The mean age was 68 years, with 29% being female. The baseline mean LDL was 87 mg/dl (2.2 mmol/l). In the subgroup of people with previous stroke, the results were consistent with the main analysis. There was a non-significant reduction of major cardiovascular disease with ezetimibe compared to placebo (HR 0.78, 95% CI 0.59–1.02). There was a significant reduction in risk of any stroke (HR 0.60, 95% CI 0.38–0.95), and ischaemic stroke (HR 0.52, 95% CI 0.31–0.86) but there were only 77 outcomes. There was no reduction in myocardial infarction (HR 0.85, 0.59–1.24), all-cause mortality (HR 0.96, 95% CI 0.71–1.30) or cardiovascular death (HR 1.11, 95% CI 0.70–1.76). There was no significant increase in haemorrhagic stroke (HR 1.69, 95% CI 0.40–7.06).

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY outcomes) trial was a multicentre, randomised, double-blind, placebo-controlled trial[74] comparing alirocumab, which is a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9), versus placebo in 18,924 participants aged 40 years or older, who had been hospitalised with an acute coronary syndrome 1 to 12 months before randomisation. Baseline lipid levels were measured after a minimum of 2 weeks of treatment with moderate or high intensity HMGCoA reductase inhibitors or the maximum tolerated dose of these HMGCoA reductase inhibitors. Participants all had an LDL cholesterol level of at least 1.9 mmol/l (70 mg/dl), a non-HDL cholesterol level of at least 2.6 mmol/l (100 mg/dl) or an apolipoprotein B level of at least 80 mg/dl. The trial found that alirocumab reduced the risk of recurrent ischaemic cardiovascular events (4-year risk=12.5% vs 14.5%; hazard ratio HR 0.85, 95% CI 0.73–0.98) compared to placebo. Moreover, alirocumab also reduced the risk of fatal or nonfatal ischaemic stroke by 27% (HR 0.73, 95% CI 0.57–0.93) without increasing the risk of haemorrhagic stroke (HR 0.83, 95% CI 0.42–1.65).[78] In ODYSSEY outcomes, there were 944 patients (5.0%) who also had a history of cerebrovascular disease at baseline.[71] In this subgroup, the mean age was 63 years and approximately a third were women (31.9%). Baseline mean LDL was 91 mg/dl (2.4 mmol/l) and 84.7% were on a high-intensity HMGCoA reductase inhibitor. Although the trend was consistent with the overall study result, based on 51 outcomes, there was no significant reduction in stroke with alirocumab (HR 0.90, 95% CI 0.52–1.56).

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial[76] was a multinational, randomised, double-blind, placebo-controlled trial comparing evolocumab, another monoclonal antibody that inhibits PCSK9, to placebo in 27,564 high-risk people aged 40 to 85 years with a history of myocardial infarction, non-haemorrhagic stroke or symptomatic peripheral artery disease. All participants had a baseline LDL of 70 mg/dl (1.8 mmol/l) or more, or a non-HDL cholesterol level of at least 100 mg/dl (2.6 mmol/l) whilst on optimised lipid lowering therapy. In the whole intention-to-treat population, evolocumab reduced risks of major cardiovascular events by 15% (9.8% vs 11.3%; HR 0.85, 95% CI 0.79–0.92) compared to placebo. Of note, evolocumab was also associated with a 25% reduction in risks of ischaemic stroke (HR 0.75, 95% CI 0.62–0.92) without a significant increase in haemorrhagic stroke (HR 1.16, 95% CI 0.68–1.98). In line with the main results, among the subgroup of 5337 (19%) participants who had a history of ischaemic stroke at baseline (mean age 65 years, 22.2% female, mean LDL=2.4 mmol/l), evolocumab was associated with a 15% reduction of major cardiovascular events (HR 0.85, 95% CI 0.72–1.00) compared to placebo, driven by a reduction in myocardial infarction (HR 0.74, 95% CI 0.55–1.00).[72] However, based on 200 outcomes in total, there was no significant reduction in risk of recurrent stroke (HR 0.90, 95% CI 0.68–1.19), recurrent ischaemic stroke (HR 0.92, 95% CI 0.68–1.25), haemorrhagic stroke (HR 0.99, 95% CI 0.47–2.07) and cardiovascular death (HR 1.11, 95% CI 0.80–1.56).[72,79]

Results for all considered outcomes and GRADE scoring, is available in Table 6.

On meta-analysis of data from the subgroup of participants with history of cerebrovascular disease from the above three trials,[74–76] there was no significant reduction in any stroke with add-on therapy with ezetimibe and/or PCSK9-inhibitor (HR 0.81, 95% CI 0.64–1.04). The level of certainty was rated as low (Figure 8).

On meta-analysis of data from two trials,[77,79] there was no significant reduction in ischaemic stroke (HR 0.72, 95% CI 0.41–1.25, Table 6) with add on therapy and there was no difference in rate of haemorrhagic stroke (HR 1.11, 95% CI 0.57–2.14; Table 6). The level of certainty for these outcomes was rated as low.

On meta-analysis of data from two trials,[77,79] there was a significant reduction in major cardiovascular events (HR 0.83, 95% CI 0.72–0.96; Table 6, Figure 9) and myocardial infarction (HR 0.78, 95% CI 0.62–0.99); Table 6) with add on therapy. There was little evidence of heterogeneity, and the level of certainty was rated as high.

Additional information

As mentioned in PICO question 6, the recent Treat Stroke to Target trial showed that a lower target LDL cholesterol <70 mg/dl (1.8 mmol/l) was superior to a target of 90 to 110 mg/dl (2.3–2.8 mmol/l) for preventing major cardiovascular events in participants with ischaemic stroke or TIA with evidence of atherosclerosis.[72] There is also evidence that each 1.0 mmol/l reduction in LDL (39 mg/dl) reduces the risks of major vascular events by about one-fifth.[80] This effect is also seen for the prevention of any stroke in wider populations of people at risk of cardiovascular disease.[81] However, there is a lack of direct evidence in the stroke population. Overall, we rated the level of certainty as low.

Table 6. GRADE evidence profile for PICO question 7: In people with ischaemic stroke or TIA who do not achieve the recommended LDL-C targets despite taking maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks, is the addition of ezetimibe and/or PCSK9-inhibitor superior to HMGCoA reductase inhibitor alone to reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Addition of ezetimibe and/or PCSK9-inhibitor	To HMGCoA reductase inhibitor alone	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
3	Randomised trials	Serious	Not serious	Not serious	Very serious[a]	None	149/3509 (4.2%)	179/3464 (5.2%)	HR 0.81 (0.64–1.04)	10 fewer per 1000 (from 18 fewer to 2 more)	⊕⊕◯◯ Low	Critical
Ischaemic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	103/3022 (3.4%)	130/2997 (4.3%)	HR 0.72 (0.41–1.25)	12 fewer per 1000 (from 25 fewer to 11 more)	⊕⊕◯◯ Low	Critical
Haemorrhagic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	19/3022 (0.6%)	17/2977 (0.6%)	HR 1.11 (0.57–2.14)	1 more per 1000 (from 2 fewer to 6 more)	⊕⊕◯◯ Low	Critical
Major adverse cardiovascular events												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	352/3022 (11.6%)	417/2977 (14.0%)	HR 0.83 (0.72–0.96)	22 fewer per 1000 (from 37 fewer to 6 fewer)	⊕⊕⊕⊕ High	Critical
Myocardial infarction												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	126/3022 (4.2%)	160/2977 (5.4%)	HR 0.78 (0.62–0.99)	12 fewer per 1000 (from 20 fewer to 1 fewer)	⊕⊕⊕⊕ High	Critical
Death												
1	Randomised trials	Serious[c]	Not serious	Not serious	Very serious[a]	None	83/336 (24.7%)	85/346 (24.6%)	HR 0.96 (0.71–1.30)	9 fewer per 1000 (from 64 fewer to 61 more)	⊕◯◯◯ Very low	Critical
Cardiovascular death												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	111/3022 (3.7%)	99/2977 (3.3%)	HR 1.11 (0.85–1.46)	4 more per 1000 (from 5 fewer to 15 more)	⊕⊕◯◯ Low	Critical

CI: confidence interval; HR: hazard ratio.
There were no data for major bleeding, dementia, functional outcome and intracranial bleeding outcomes.
[a]Effect size is small and fails to exclude appreciable harm (confidence intervals cross over 1).
[b]Effect size is small and fails to exclude benefit (confidence intervals cross over 1).
[c]Uncertain risk of bias in study.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
IMPROVE-IT	0.780	0.593	1.026	-1.779	0.075
FOURIER	0.850	0.721	1.002	-1.939	0.052
	0.831	0.722	0.957	-2.578	0.010

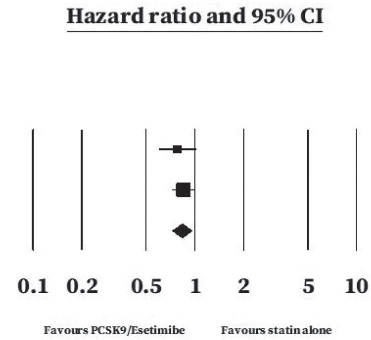


Figure 9. Forest plot for the risk of any major cardiovascular event in trials comparing treatment with PCSK9 inhibitors versus placebo after TIA or stroke. Heterogeneity: $I^2 = 0.000$; $Q = 0.278$; $p = 0.598$.

Supporting information to the expert consensus statement

There is insufficient evidence to support a recommendation concerning add-on therapy with ezetimibe and/or PCSK9-inhibitor to reduce risk of recurrent stroke in people with ischaemic stroke or TIA who do not achieve the recommended LDL-C targets despite taking maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks. This was due to imprecision and potential selection bias as all data are derived from subgroup analyses of trials. However, there is some evidence, albeit indirect for the TIA and ischaemic stroke population, that the addition of ezetimibe and/or PCSK-9 inhibitor is superior to HMGCoA reductase inhibitor alone to reduce the overall risk of recurrent major cardiovascular events in this population. Moreover, there is evidence that a more intensive cholesterol treatment target compared to a less intensive target, which includes use of ezetimibe in some people, reduces the risk of recurrent ischaemic stroke and major cardiovascular events. The use of a PCSK9 inhibitor could be considered in people who have ischaemic heart disease, or who have ischaemic stroke and would have met the criteria for the FOURIER trial, where LDL targets cannot be obtained using a HMGCoA reductase inhibitor and ezetimibe. The panel voted by 12/12 members for the following consensus statement (Supplemental Table 2).

Evidence-based recommendation
–
Quality of evidence: –
Strength of recommendation: –

Expert consensus statement
In people with ischaemic stroke or TIA who do not achieve the recommended LDL-C targets despite taking maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks, we support the addition of ezetimibe as an option to reduce the risk of recurrent major cardiovascular events.

In adult people with ischaemic stroke or TIA there is continued uncertainty over the use of ezetimibe and/or PCSK9-inhibitors to reduce risk of recurent stroke.

Anti-thrombotic therapy

PICO question 8: In people with ischaemic stroke or TIA, does long-term antiplatelet therapy compared to no antiplatelet therapy reduce the risk of recurrent stroke?

Analysis of current evidence

The literature search identified 6332 titles and 645 full texts were identified for review. For this PICO question, 11 studies and a total of 13,369 participants were included.[82–92] Eight trials compared aspirin to placebo,[82–89] one trial compared cilostazol with placebo[92] and one compared ticlopidine versus placebo.[91] One trial compared aspirin and dipyridamole to placebo[87] and one trial included an aspirin and dipyryidamole arm as well as an aspirin monotherapy arm.[90] For our quantitative synthesis we only included data on antiplatelet monotherapy in our primary analysis as the use of dual antiplatelet therapy was addressed in PICO question 9. We explored whether inclusion of data from the European Stroke Prevention Study (ESPS) trial would materially alter the conclusions in an additional analysis because this compared aspirin and dipyridamole with placebo. Time from index event to inclusion in the study ranged from 1 week to 1 year, with the majority being within 3 months. Follow-up ranged between 2 and 7 years (mean 2 years). The dose of aspirin used ranged from 50 to 1300 mg daily.

The Trial of Aspirin in Transient Ischaemia (AITIA) Trial[82] was a double-blind RCT including 178 participants with a TIA or retinal occlusion who were randomised to either aspirin 1300 mg or placebo. The primary outcome was mortality, cerebral or retinal infarction and follow-up was for 2 years. There was no difference between groups in the rate of the primary outcome.

The Canadian cooperative study[83,84] was a double-blind RCT including 585 participants with 'threatened stroke' who were randomised to either aspirin 1300 mg, sulfinpyrazone 800 mg, both these drugs or placebo. The mean follow-up was 26 months and the primary outcome was TIA, stroke or death. There was a significant reduction in the primary outcome in the aspirin group.

The Accidents Ischimiques Cerebraux Lies a L'Atherosclerose (AICLA) trial[84] was a three arm double blind study in people with a recent TIA or cerebral infarction. Participants were randomised to receive either aspirin (1000 mg), aspirin and dipyridamole (1000 mg + 225 mg) or placebo. Follow-up was for 3-year and the primary outcome was cerebral infarction. Treatment with aspirin and treatment with aspirin plus dipyridamole reduced the risk of stroke compared to placebo.

The Danish cooperative study[85] was a randomised double-blinded study of 203 participants comparing aspirin (1000 mg) with placebo. Mean follow-up was 25-month and the primary outcome was stroke or death. The study did not find any statistical difference between groups.

The Swedish cooperative study[86] was a double-blind placebo controlled trial of 1500 mg aspirin daily versus placebo in 505 participants within 3-week of cerebral infarction. Participants were followed for up to 2 years and the primary outcome were stroke or death. The study showed no difference between groups.

The UK-TIA trial[88] randomised 2435 participants with TIA or minor stroke to either aspirin 300 or 1200 mg or placebo in a double-blinded study with a mean follow-up of 4 years. The primary outcome was major stroke, myocardial infarction and vascular death. There was a significant reduction in the primary endpoint with aspirin treatment.

The Swedish Aspirin Low-Dose Trial (SALT) collaboration[89] was a double-blinded study which randomised participants to aspirin (75 mg) versus placebo. The mean duration of follow up was 32 months. The primary outcome was occurrence of stroke or death and there was a significant reduction with aspirin treatment.

ESPS 2[90] was a four-arm double-blinded randomised trial of aspirin 50 mg, dipyridamole 400 mg, aspirin plus dipyridamole (50 + 400 mg) or placebo. Follow up was for 2 years and the primary endpoint was stroke or death. The study found a significant benefit of all the antiplatelet strategies.

The Canadian American ticlopidine study (CATS) randomised 1072 people between 1 week and 4 months after an ischaemic stroke to ticlopidine (250 mg bd) or placebo, for up to 3 years.[91] The primary outcome was a composite of stroke, myocardial infarction or vascular death. There was a significant reduction in the primary outcome from 15.3% in the placebo group to 10.8% in the ticlopidine group (RRR 30.2%, 95% CI 7.5–48.3, $p = 0.006$).

The ESPS study[87] randomised 2500 participants to either aspirin 990 mg plus diyridamole 225 mg or placebo in a double blinded study. Participants were followed for 2-year, and the primary outcome was stroke or death. There was a significant reduction in the primary outcome with aspirin and dipyridamole.

The cilostazol stroke prevention study (CSPS) was a double-blind randomised trial testing cilostazol versus placebo[92] on 1095 participants. The primary outcome was recurrence of cerebral infarction. There was a 41.7% relative risk reduction with cilostazol (95% CI 9.2–62.5, $p = 0.015$).

Results from meta-analysis for all outcomes and GRADE scoring, is available in Table 7. On meta-analysis of data from nine trials[82,84–86,88–92] antiplatelet therapy reduced the risk of any stroke (OR 0.82, 95% CI 0.73–0.92, $I^2 = 0\%$, Figure 10, Table 7). The level of certainty was rated as high. Use of an antiplatelet would be expected to lead to 24 fewer cases of stroke per 1000 treated.

On meta-analysis of data from five trials,[82,84–86,89] antiplatelet therapy reduced the risk of ischaemic stroke (OR 0.67, 95% CI 0.54–0.85, $I^2 = 11.4\%$, $p = 0.001$, Table 7).

On meta-analysis of data from seven trials,[84,86,88–92] antiplatelet therapy reduced the risk of major cardiovascular events (OR 0.78, 95% CI 0.67–0.90, $I^2 = 44\%$, Figure 11, Table 7).

On meta-analysis of data from four trials[82,84,86,89] including 2718 participants, antiplatelet therapy did not significantly increase the risk of haemorrhagic stroke (OR 1.93, 95% CI 0.78–4.76, $I^2 = 0\%$, Table 7) but the level of certainty was rated as low. On meta-analysis of data from three trials,[89–91] antiplatelet therapy increased the risk of a major bleeding episode (OR 2.51, 95% CI 1.42–4.42, $I^2 = 0\%$, $p = 0.002$, Table 7). Use of an antiplatelet would be expected to lead to nine more cases of major bleeding per 1000 treated.

On meta-analysis of data from nine trials,[82,84–86,88–92] antiplatelet therapy reduced the risk of myocardial infarction (OR 0.77, 95% CI 0.61–0.98, $I^2 = 0\%$, $p = 0.56$ Table 7). On meta-analysis of data from 10 trials[82–85,87–92] including 10,869 participants, antiplatelet therapy did not significantly reduce the risk of death (OR 0.90, 95% CI 0.80–1.02, $I^2 = 0\%$, $p = 0.107$, Table 7). On meta-analysis of data from nine trials[82–86,88,89,91,92] including 7471 participants, antiplatelet therapy did not significantly reduce the risk of cardiovascular death (OR 0.94, 95% CI 0.79–1.13, $I^2 = 0\%$, Table 7) or improve functional outcome (OR 1.01, 95% CI 0.72–1.42). There were no data concerning the effect on risk of dementia.

Additional information

Most of the included studies tested aspirin antiplatelet therapy. Previous other meta-analyses have found results consistent with our findings. In 1994, the Antiplatelet Trialists Collaboration published a collaborative and comprehensive overview of antiplatelet therapy trials up to March 1990.[93] They concluded there was a significant benefit from antiplatelet use in people with stroke and found the optimal

Table 7. GRADE evidence profile for PICO question 8: In people with ischaemic stroke or TIA, does long-term antiplatelet therapy compared to no antiplatelet treatment reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-term antiplatelet therapy	No antiplatelet treatment	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
9	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	681/5255 (13.0%)	689/4462 (15.4%)	OR 0.82 (0.73–0.92)	24 fewer per 1000 (from 37 fewer to 10 fewer)	⊕⊕⊕⊕ High	Critical
Ischaemic stroke												
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	167/1714 (9.7%)	237/1756 (13.5%)	OR 0.67 (0.54–0.85)	39 fewer per 1000 (from 58 fewer to 17 fewer)	⊕⊕⊕⊕ High	Critical
Haemorrhagic stroke												
4	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	14/1215 (1.2%)	7/1230 (0.6%)	OR 1.93 (0.78–4.76)	5 more per 1000 (from 1 fewer to 21 more)	⊕⊕◯◯ Low	Critical
Major cardiovascular events												
7	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	993/5458 (18.2%)	997/4657 (21.4%)	OR 0.78 (0.67–0.90)	39 fewer per 1000 (from 59 fewer to 17 fewer)	⊕⊕⊕⊕ High	Critical
Myocardial infarction												
6	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	127/3403 (3.7%)	164/3427 (4.8%)	OR 0.77 (0.61–0.98)	11 fewer per 1000 (from 18 fewer to 1 fewer)	⊕⊕⊕⊕ High	Critical
Death												
10	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	600/5881 (10.2%)	538/4988 (10.8%)	OR 0.90 (0.80–1.02)	10 fewer per 1000 (from 20 fewer to 2 more)	⊕⊕◯◯ Low	Critical
Cardiovascular death												
9	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	305/4132 (7.4%)	232/3339 (6.9%)	OR 0.94 (0.79–1.13)	4 fewer per 1000 (from 14 fewer to 9 more)	⊕⊕◯◯ Low	Critical
Any major bleeding episode												
3	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	42/2850 (1.5%)	17/2861 (0.6%)	OR 2.51 (1.42–4.43)	9 more per 1000 (from 2 more to 20 more)	⊕⊕⊕◯ Moderate	Critical
Functional outcome												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[a]	None	100/1722 (5.8%)	54/916 (5.9%)	OR 1.01 (0.72–1.42)	1 more per 1000 (from 16 fewer to 23 more)	⊕⊕◯◯ Low	Important

CI: confidence interval; OR: odds ratio.
[a]Fails to rule out benefit. Confidence intervals cross 1.0.
[b]Fails to rule out harm. Confidence intervals cross 1.0.
[c]Limited sample size/number of events. There were no data for the outcome dementia.

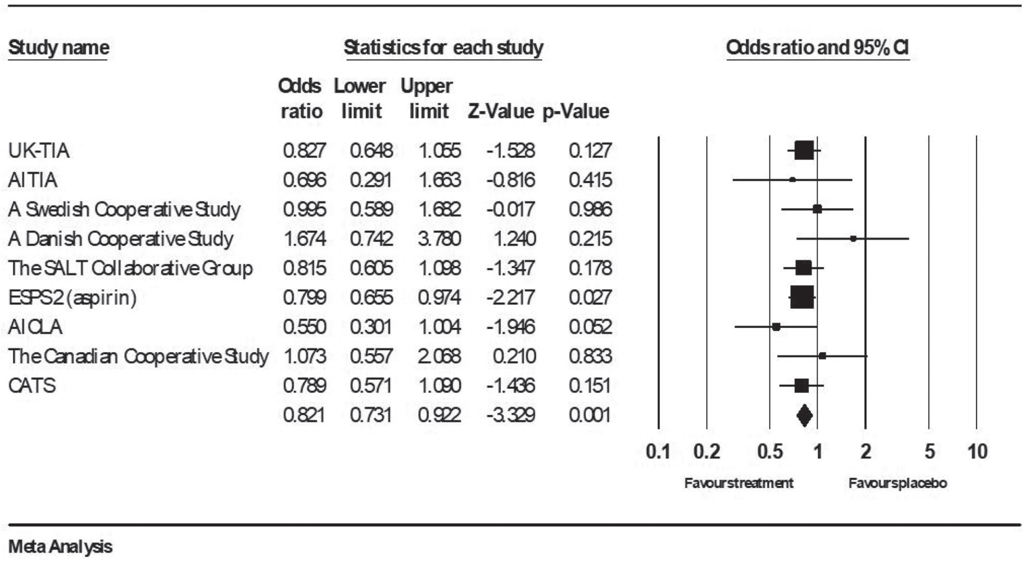


Figure 10. Forest plot for the risk of any stroke in trials comparing treatment with an antiplatelet versus placebo after TIA or stroke. $I^2 = 0.000$; $q = 6.075$, $p = 0.639$. With ESPS1 included, OR = 0.78 (0.68–0.89).

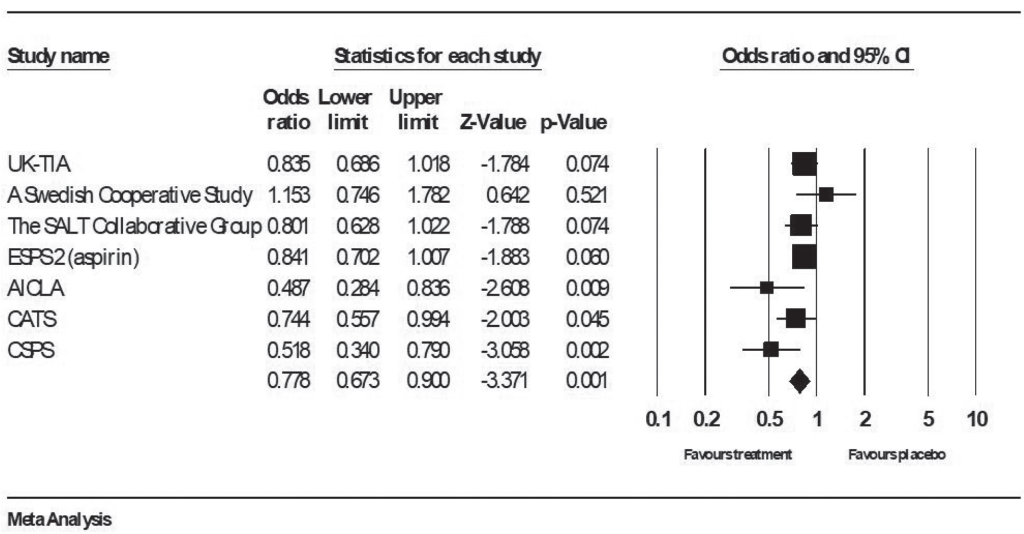


Figure 11. Forest plot for the risk of major cardiovascular events in trials comparing treatment with an antiplatelet versus placebo after TIA or stroke. $I^2 = 44.134$; $q = 10.740$; $p = 0.097$.

dose of aspirin was 75 to 325 mg/day based on limited additional benefit of higher doses but increased bleeding risk. Our results were similar with and without inclusion of data from the ESPS trial.

Since these studies were conducted, a number of new antiplatelets have been developed and studied in people with stroke. Broadly, these studies suggest that they are of at least similar benefit to aspirin. For example, in the PRoFESS trial, there was a similar rate of recurrent stroke with aspirin and dipyridamole (9%) than with clopidogrel (8.8%) (HR 1.01, 95% CI 0.92–1.11). Our recommendations cover use of antiplatelet therapy generally and choice of drug regimen may differ in some regions. Overall, we rated the quality of evidence as being moderate as, while it was high for any stroke, ischaemic stroke and major cardiovascular events, it was low for haemorrhagic stroke due to imprecision and moderate for major bleeding.

Evidence-based recommendation
In people with previous ischaemic stroke or TIA, we recommend long-term use of antiplatelet therapy to reduce the risk of recurrent stroke.

Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Strong for intervention** ↑↑

PICO question 9: In people with TIA and ischaemic stroke, does treatment with dual antiplatelet therapy for longer than 90 days with aspirin plus clopidogrel or aspirin plus dipyridamole, compared to a single antiplatelet, reduce the risk of recurrent stroke?

Analysis of current evidence

The literature search identified 6332 titles and 645 full texts were identified. For this specific PICO question, six studies[90,94–98] and a total of 41,309 participants were included in the qualitative and quantitative synthesis. This PICO question does not address use of dual antiplatelets early after minor ischaemic stroke and TIA.

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial[94] enrolled 7599 people with ischaemic stroke or TIA in the previous 3 months, with one or more of five risk factors (history of ischaemic stroke, history of myocardial infarction, angina pectoris, diabetes mellitus symptomatic peripheral arterial disease). Participants were randomised to clopidogrel 75 mg daily and aspirin 75 mg daily or clopidogrel 75 mg daily and placebo. The duration of follow-up was 18 months. In the dual antiplatelet (DAPT) arm, the RRR for any stroke was 2.0% (95% CI −13.8 to 15.6), for ischaemic stroke was 7.1% (95% CI −8.5 to 20.4) and for major cardiovascular events was 5.9% (95% CI −7.1 to 17.3). The absolute risk increase in major bleeding was 1.36% (95% CI 0.86–1.86).

Two trials[95,96] compared aspirin and clopidogrel with aspirin and placebo. The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation Management and Avoidance (CHARISMA) trial[95] enrolled 15,603 people with multiple atherothrombotic risk factors, coronary disease, cerebrovascular disease symptomatic peripheral arterial disease. Participants were randomised to aspirin in a daily dose ranging from 75 to 162 mg and clopidogrel 75 mg daily or aspirin and placebo. In participants with cerebrovascular disease, median follow-up was 2.1 years. In the DAPT arm, the HR for any stroke was 0.80 (95% CI 0.62–1.03), for ischaemic stroke it was 0.80 (95% CI 0.60–1.05), for haemorrhagic stroke it was 1.11 (95% CI 0.45–2.74) and for major cardiovascular events it was 0.84 (95% CI 0.69–1.03). The SPS3 trial[96] enrolled people with a recent lacunar infarct. Participants were randomised to aspirin 325 mg daily and clopidogrel 75 mg daily or aspirin 325 mg daily and placebo. The mean duration of follow-up was 3.4 years. In the DAPT arm, HR for any stroke was 0.92 (95% CI 0.72–1.16), for ischaemic stroke it was 0.82 (95% CI 0.63–1.09), for haemorrhagic stroke it was 1.65 (95% CI 0.83–3.31) and for major cardiovascular events it was 0.89 (95% CI 0.72–1.11).

Three trials[90,97,98] compared aspirin and extended-release (ER) dipyridamole versus single antiplatelet therapy. The PRoFESS trial[98] enrolled 20,322 people with an ischaemic stroke within the prior 3 months. Participants were randomised to aspirin 25 mg daily and dipyridamole 200 mg twice daily or clopidogrel 75 mg daily. The median duration of follow-up was 25 months for participants with cerebrovascular disease. In the DAPT arm, the HR for any stroke was 1.01 (95% CI 0.92–1.11), for ischaemic stroke it was 0.80 (95% CI 0.60–1.05), for intracranial haemorrhage it was 1.42 (95% CI 1.11–1.83) and for major cardiovascular events it was 0.99 (95% CI 0.92–1.07).

The ESPS-2 trial[90] enrolled 6602 people with ischaemic stroke or TIA within the preceding 3 months. Participants were randomised to aspirin 50 mg daily, or modified-release dipyridamole 400 mg daily, both these drugs combined, or placebo. In the original publication, stroke was not divided into haemorrhagic and ischaemic subtypes. Here, we consider the comparison of aspirin combined with dipyridamole versus aspirin alone. We computed the ORs based on the crude rates published. In the DAPT arm, compared to aspirin alone, the OR for any stroke was 0.74 (95% CI 0.59–0.92) and for major cardiovascular events it was 0.74 (95% CI 0.61–0.90).[90]

The European/Australasian Stroke Prevention in Reversible Ischaemia (ESPRIT) trial[97] enrolled 2739 people within 6 months of a non-disabling ischaemic stroke and TIA. Participants were randomised to aspirin (30–325 mg daily) and dipyridamole 400 mg daily or aspirin alone. The mean duration of follow up was 3.5 years. In the DAPT arm, the OR for ischaemic stroke was 0.82 (95% CI 0.62–1.09), the OR for major adverse cardiovascular events was 0.76 (95% CI 0.60–0.95) and the OR for death was 0.87 (95% CI 0.65–1.16).

Results for meta-analysis of all outcomes and GRADE scoring are shown in Table 8. In the meta-analysis including five randomised controlled trials,[90,94–96,98] use of dual antiplatelets did not significantly reduce the risk of recurrent stroke (Figure 12, Table 8), but there was a significant reduction in the risk of ischaemic stroke (OR = 0.92, 95% CI 0.85–0.99, Table 8). The level of certainty was rated as very low due to imprecision and inconsistency.

However, in three randomised controlled trials,[95,96,98] use of dual antiplatelets was associated with a significantly increased risk of haemorrhagic stroke (Figure 13; Table 8). The level of certainty was rated as high. The use of DAPT would be expected to lead to four more cases of haemorrhagic stroke per 1000 treated.

Additional information

Overall, we rated the quality of evidence as being very low. Three trials assessed clopidogrel and aspirin dual anti-platelet therapy and three assessed aspirin and dipyridamole dual anti-platelet therapy. There was no evidence of net benefit of dual anti-platelet therapy in the trials of clopidogrel and aspirin therapy. There was no benefit of aspirin and dipyridamole therapy compared to clopidogrel in the PRoFESS trial but risk of intracerebral haemorrhage was increased. Adverse events and discontinuation of treatment were also more common with aspirin and

Table 8. GRADE evidence profile for PICO question 9: In people with TIA and ischaemic stroke, does treatment with dual antiplatelet therapy for longer than 90 days with aspirin plus clopidogrel or aspirin plus dipyridamole, compared to a single antiplatelet, reduce the risk of recurrent stroke?.

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dual antiplatelet therapy for longer than 90 days with aspirin plus clopidogrel or aspirin plus ticagrelor	Single antiplatelet	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
5	Randomised trials	Not serious	Serious[a]	Not serious	Very serious[b]	None	1642/19,302 (8.5%)	1720/19,268 (8.9%)	OR 0.90 (0.80–1.02)	8 fewer per 1000 (from 17 fewer to 2 more)	⊕◯◯◯ Very low	Critical
Ischaemic stroke												
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	1385/19,015 (7.3%)	1494/18,995 (7.9%)	OR 0.92 (0.85–0.99)	6 fewer per 1000 (from 11 fewer to 1 fewer)	⊕⊕⊕⊕ High	Critical
Haemorrhagic stroke												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	178/13,855 (1.3%)	125/13,817 (0.9%)	OR 1.42 (1.13–1.78)	4 more per 1000 (from 1 more to 7 more)	⊕⊕⊕⊕ High	Critical
Major adverse cardiovascular events												
6	Randomised trials	Not serious	Serious[a]	Not serious	Not serious	None	2460/20,665 (11.9%)	2645/20,644 (12.8%)	OR 0.87 (0.78–0.97)	15 fewer per 1000 (from 25 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	Critical
Myocardial infarction												
5	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	360/19,302 (1.9%)	374/19,268 (1.9%)	OR 0.96 (0.83–1.11)	1 fewer per 1000 (from 3 fewer to 2 more)	⊕⊕◯◯ Low	Critical
Death												
5	Randomised trials	Not serious	Serious[a]	Not serious	Very serious[c]	None	1331/18,508 (7.2%)	1323/18,481 (7.2%)	OR 1.03 (0.90–1.17)	2 more per 1000 (from 7 fewer to 11 more)	⊕◯◯◯ Very low	Critical
Cardiovascular death												
4	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	659/17,498 (3.8%)	712/17,492 (4.1%)	OR 0.92 (0.83–1.03)	3 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕◯◯ Low	Critical
Intracranial bleeding												
4	Randomised trials	Not serious	Not serious	Not serious	Very serious[c]	None	98/16,820 (0.6%)	87/16,811 (0.5%)	OR 1.22 (0.81–1.83)	1 more per 1000 (from 1 fewer to 4 more)	⊕⊕◯◯ Low	Critical
Any major bleeding episode												
6	Randomised trials	Not serious	Very serious[a]	Not serious	Very serious[c]	None	700/20,627 (3.4%)	553/20,623 (2.7%)	OR 1.39 (0.95–2.02)	10 more per 1000 (from 1 fewer to 26 more)	⊕◯◯◯ Very low	Critical
Functional outcome												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[c]	None	42/1517 (2.8%)	40/1503 (2.7%)	HR 1.06 (0.69–1.64)	2 more per 1000 (from 8 fewer to 17 more)	⊕⊕◯◯ Low	Important

CI: confidence interval; HR: hazard ratio; OR: odds ratio.
[a]Significant degree of heterogeneity according to I^2.
[b]Fails to rule out harm. Confidence intervals cross 1.0.
[c]Fails to rule out benefit. Confidence intervals cross 1.0. There were no data for the outcome dementia.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPS3	0.888	0.689	1.144	-0.917	0.359
CHARISMA	0.794	0.610	1.033	-1.715	0.086
MATCH	0.976	0.834	1.142	-0.302	0.763
ESPS2 (aspirin)	0.737	0.591	0.918	-2.725	0.006
PROFESS	1.019	0.925	1.122	0.377	0.706
	0.903	0.797	1.022	-1.612	0.107

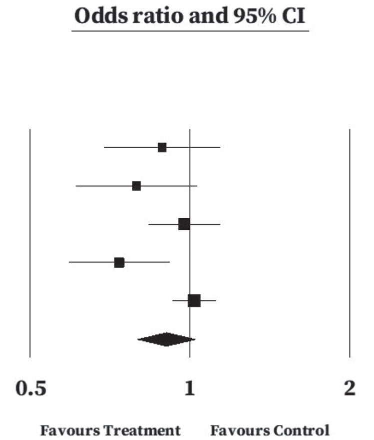
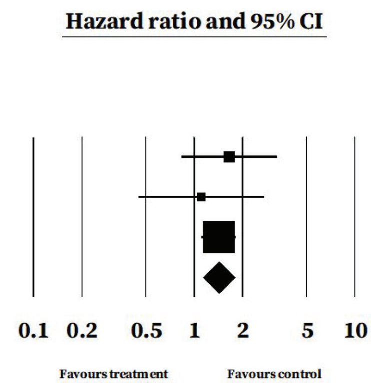


Figure 12. Forest plot for the risk of recurrent stroke in trials comparing treatment with dual versus single antiplatelets for more than 90 days after TIA or stroke. Heterogeneity $I^2 = 57.089$; $q = 9.322$, $p = 0.054$.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
SPS3	1.650	0.826	3.295	1.419	0.156
CHARISMA	1.110	0.450	2.739	0.226	0.821
PRoFESS	1.420	1.106	1.823	2.749	0.006
	1.421	1.132	1.784	3.026	0.002



Meta Analysis

Figure 13. Forest plot for the risk of haemorrhagic stroke in trials comparing treatment with dual versus single antiplatelets for more than 90 days after TIA or stroke.

dipyridamole. The ESPRIT and ESPS-2 trials showed benefit from aspirin and dipyridamole compared to aspirin for some outcomes. Network meta-analyses have attempted to establish the best long-term anti-platelet therapy and suggest that clopidogrel or aspirin and dipyridamole in combination are the best strategies.[99] We performed additional analyses to assess whether the effect of dual antiplatelet therapy with aspirin and clopidogrel appears similar to that of aspirin and dipyridamole. Note there are no head-to-head comparisons of these strategies. Results were broadly consistent for the outcomes of any stroke and haemorrhagic stroke but rates of any major bleeding episode with aspirin and clopidogrel were higher than with monotherapy (Supplemental Figures 2 and 3). However, these analyses were limited by heterogeneity. Overall, we conclude that the evidence favours use of antiplatelet monotherapy and indirect data suggest that clopidogrel is preferable to aspirin. Local practice regarding the choice of agent differs across Europe.

Evidence-based recommendation
In people with previous ischaemic stroke or TIA, we recommend against use of dual antiplatelet therapy with aspirin and clopidogrel in the long-term and recommend use of single antiplatelet to reduce the risk of recurrent stroke.

Quality of evidence: **Very low ⊕**
Strength of recommendation: **Weak against intervention ↓?**

PICO Question 10: In people with ischaemic stroke or TIA and atherosclerosis, with no other indication for anticoagulation, does antiplatelet therapy combined with a low-dose direct oral anticoagulant compared to antiplatelet therapy alone reduce the risk of recurrent stroke?

Analysis of current evidence

The literature search identified 6332 titles and 645 full texts were identified. No randomised trials were found which directly addressed this PICO question in this population.

One trial addressed this treatment in people with other types of cardiovascular disease. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) included 27,395 people with stable atherosclerotic disease.[100] Participants had either a history of coronary artery disease or peripheral vascular disease. Participants with coronary artery disease who were <65 years of age were required to have arterial disease in two vascular beds or have two additional risk factors, one of which could be non lacunar ischaemic stroke >1 month ago. The definition of peripheral arterial disease included history of previous carotid revascularisation or an asymptomatic carotid artery stenosis of >50%.

People with a history of stroke within 1 month or any history of haemorrhagic or lacunar stroke were excluded. In total, 3.8% of trial participants had a history of previous stroke. A total of 7470 people were enrolled with a history of peripheral vascular disease and 26% of these had a history of previous carotid artery disease or asymptomatic carotid artery stenosis >50%.

The trial compared three treatment strategies. These were rivaroxaban 2.5 mg twice daily plus aspirin 100 mg, rivaroxaban 5 mg twice daily and aspirin 100 mg daily. The combination of rivaroxaban plus aspirin reduced the risk of the primary outcome of cardiovascular death, stroke myocardial infarction compared to aspirin alone (HR 0.76, 95% CI 0.66–0.86, $p < 0.001$). Rivaroxaban was not superior to aspirin alone. The risk of stroke was reduced by the combination of rivaroxaban plus aspirin compared to aspirin alone (HR 0.58, 95% CI 0.44–0.76) with an absolute risk reduction of 0.7%. The risk of ischaemic stroke was also reduced (HR 0.51, 95% CI 0.38–0.68). There was no significant increase in the risk of haemorrhagic stroke (HR 1.49, 95% CI 0.67–3.31) but there were few events and a potentially important increase cannot be excluded. An exploratory analysis showed that the combination of rivaroxaban plus aspirin reduced the risk of cardioembolic stroke and embolic stroke of undetermined source.[101] In subgroup analyses of participants with a history of peripheral artery disease, and in those with carotid artery disease, the results were consistent with those from the whole study population.[102] In a subgroup analysis of people with previous stroke results were also similar but this was based on a small number of events (n=29).[103]

A recent systematic review and meta-analysis on low dose direct oral anticoagulation therapy combined with antiplatelet therapy in people with cardiovascular disease included seven randomised trials.[104] In addition to the COMPASS trial, three of these trials included people with acute coronary syndrome[105–107,] one included people with heart failure,[108] one included people with peripheral arterial disease[109] and one included people with atrial fibrillation[110] (although in this trial antiplatelet use was not protocol defined). There was a trend towards a reduction in risk of stroke on meta-analysis (IRR 0.73, 95% CI 0.53–1.01, random effects model) with combination therapy. There was no increased risk of intracranial haemorrhage. None of these trials has reported results for the subgroup of people with history of stroke and people with stroke or recent stroke were excluded.

Supporting information for consensus statement

Overall, we rated the quality of evidence as low due to indirectness; there is no direct evidence to support a recommendation for use of antiplatelet therapy combined with a low-dose direct oral anticoagulant in people with a history of ischaemic stroke or TIA. In particular, it is important to note that people with ischaemic stroke within the past month were excluded from the COMPASS trial. However, many people with stroke have a history of coronary artery disease or peripheral arterial disease. The effect in people with carotid artery disease was also consistent with the main trial results. The use of antiplatelet therapy combined with a low-dose direct oral anticoagulant may be an appropriate option for some people with a history of ischaemic stroke or TIA, more than 1 month previously, if they have co-existing coronary or peripheral arterial disease and this is being used to optimise treatment of these conditions. Note that only rivaroxaban has been studied in this context so other DOACs should not be used for this purpose. The panel voted by 12/12 members for the following consensus statement (Supplemental Table 2).

Evidence-based recommendation
–
Quality of evidence: –
Strength of recommendation: –

Expert consensus statement
The use of antiplatelet therapy combined with a low-dose direct oral anticoagulant (rivaroxaban) can be considered to optimise treatment of coronary artery disease or peripheral arterial disease in people with a history of ischaemic stroke or TIA more than 1 month previously. It should not be considered in people with ischaemic stroke or TIA who do not have coronary artery disease or peripheral arterial disease.

In adult people with ischaemic stroke or TIA there is continued uncertainty over the use of use of antiplatelet therapy combined with a low-dose direct oral anticoagulant.

PICO Question 11: In people with an embolic stroke of undetermined source (ESUS) does treatment with a direct oral anticoagulant drug compared to an antiplatelet reduce the risk of recurrent stroke?

Analysis of current evidence

The literature search identified 6332 titles and 645 full texts were identified. For this specific PICO question, two studies and a total of 12,603 participants were included in the qualitative and quantitative synthesis. These two studies were randomised clinical trials comparing a DOAC to an antiplatelet to reduce the risk of stroke in people with ESUS.

The New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial is a multicenter, double-blinded, randomised trial which compared rivaroxaban 15 mg once daily with aspirin 100 mg once daily in 7213 people with recent (between 7 days and 6 months) ESUS.[111] The mean follow-up duration was 2 years. In this trial, ESUS was defined as non-lacunar ischaemic stroke, not associated with extracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of ischaemia, or with identified risk factors for a cardiac source of embolism. The use of rivaroxaban did not reduce the risk of recurrent stroke compared to aspirin (HR 1.08, 95% CI 0.87–1.34, $p=0.47$). Major bleeding was increased with rivaroxaban (HR 2.72, 95% CI 1.68–4.39, $p<0.001$). The trial was stopped prematurely was because of a lack of benefit on stroke risk and bleeding associated with rivaroxaban.

The Randomised, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RESPECT ESUS) trial is a multicenter, randomised, double-blind trial which compared dabigatran 150 or 110 mg (for participants aged ⩾75 years and/or with creatinine clearance 30 to <50 ml/minute) twice daily with aspirin 100 mg once daily in 5390 people who had experienced an ESUS within the prior 3 months (or within the prior 6 months if they had at least one additional vascular risk factor, or if they were aged 18–59 years (20–59 in Japan) and had at least one additional vascular risk factor).[112] The median follow-up duration was 19 months. The definition of ESUS was similar to that used in NAVIGATE. In this trial, dabigatran was not superior to aspirin in preventing stroke (HR 0.85, 95% CI 0.69–1.03, $p=0.10$) or ischaemic stroke. Major bleeding was not increased with dabigatran (HR 1.19, 95% CI 0.85–1.66).

Results for meta-analysis of all outcomes and GRADE scoring is available in Table 9. On meta-analyses of data from these two trials, there was no difference in the rate of any stroke (OR 0.96, 95% CI 0.75–1.22, Table 9). The level of certainty was rated as low. There was also no difference in the rate of ischaemic stroke (OR 0.92, 95% CI 0.76–1.10, Table 9). The rate of haemorrhagic stroke was increased in one trial but on meta-analysis of data from the two trials, the rate of intracranial bleeding (OR 1.87, 95% CI 0.48–7.26, Table 8) and major bleeding episodes (OR 1.78, 95% CI 0.80–3.94, Table 8) were not significantly increased (Table 9).

Additional information

There is no evidence to suggest DOAC in preference to antiplatelets in people with ESUS as defined in the RESPECT and NAVIGATE trials. Although a DOAC was equally effective with regard to rate of stroke, bleeding risk was increased in one trial and point estimates for any stroke were inconsistent in the two trials. Overall, we rated the quality of evidence as low. Ongoing trials are investigating whether use of serum, ECG or echocardiographic biomarkers can identify people with ischaemic stroke who do benefit from a DOAC.[113] However, one trial which adopted this approach, the Apixaban for treatment of embolic stroke of undetermined source (ATTICUS) trial, was stopped early due to futility.

Evidence-based recommendation
In people with an embolic stroke of undetermined source, we suggest use of antiplatelet therapy and not a DOAC to reduce the risk of recurrent stroke.

Quality of evidence: **Low** ⊕⊕
Strength of recommendation: **Weak against intervention ↓?**

Diabetes mellitus

PICO Question 12: In people with diabetes mellitus and ischaemic stroke or TIA, does intensive control of glycated haemoglobin level (HbA1c) compared to less intensive HbA1c control reduce the risk of recurrent stroke?

Analysis of current evidence

People with diabetes mellitus are at a two-folds increased risk of stroke and the relative risk of stroke is reported to increase by approximately 15% with each 1% increase in glycated haemoglobin (HbA1c) level.[114,115] Intensive control of blood glucose levels in people with diabetes reduces the risk of microvascular complications such as retinopathy, nephropathy and neuropathy. However, it is less certain whether intensive control lowers risk of major cardiovascular events, including stroke.

Our systematic review literature search identified 1286 titles and 138 full texts were screened. For this specific PICO question, we were unable to identify any randomised

Table 9. GRADE evidence profile for PICO question 11: In people with an embolic stroke of undetermined source does treatment with a DOAC compared to an antiplatelet reduce the risk of recurrent stroke?

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment with a DOAC	An antiplatelet	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
2	Randomised trials	Not serious	Serious[a]	Not serious	Serious[b]	None	348/6304 (5.5%)	365/6299 (5.8%)	OR 0.96 (0.75–1.22)	2 fewer per 1000 (from 14 fewer to 12 more)	⊕⊕◯◯ Low	Critical
Ischaemic stroke												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	330/6304 (5.2%)	359/6229 (5.8%)	OR 0.92 (0.76–1.10)	5 fewer per 1000 (from 13 fewer to 6 more)	⊕⊕◯◯ Low	Critical
Haemorrhagic stroke												
1	Randomised trials	Not serious	Not serious	Not serious	Serious[c]	None	13/3609 (0.4%)	2/3604 (0.1%)	HR 6.50 (1.47–28.80)	3 more per 1000 (from 0 fewer to 15 more)	⊕⊕⊕◯ Moderate	Critical
Major adverse cardiovascular events												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	414/6304 (6.6%)	427/6229 (6.9%)	OR 0.97 (0.84–1.11)	2 fewer per 1000 (from 10 fewer to 7 more)	⊕⊕◯◯ Low	Critical
Myocardial infarction												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious[b]	None	17/3609 (0.5%)	23/3604 (0.6%)	HR 0.74 (0.39–1.38)	2 fewer per 1000 (from 4 fewer to 2 more)	⊕⊕◯◯ Low	Critical
Death												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[d]	None	121/6304 (1.9%)	110/6229 (1.8%)	OR 1.10 (0.85–1.43)	2 more per 1000 (from 3 fewer to 7 more)	⊕⊕◯◯ Low	Critical
Cardiovascular death												
2	Randomised trials	Not serious	Not serious	Not serious	Very serious[d]	None	37/3903 (0.9%)	24/3904 (0.6%)	OR 1.54 (0.92–2.58)	3 more per 1000 (from 1 fewer to 10 more)	⊕⊕◯◯ Low	Critical
Intracranial bleeding												
2	Randomised trials	Not serious	Very serious[a]	Not serious	Very serious[d]	None	52/6303 (0.8%)	37/6229 (0.6%)	OR 1.87 (0.48–7.26)	5 more per 1000 (from 3 fewer to 36 more)	⊕◯◯◯ Very low	Critical
Any major bleeding episode												
2	Randomised trials	Not serious	Very serious[a]	Not serious	Very serious[d]	None	139/6303 (2.2%)	87/6229 (1.4%)	OR 1.78 (0.80–3.94)	11 more per 1000 (from 3 fewer to 39 more)	⊕◯◯◯ Very low	Critical
Functional outcome												
2	Randomised trials	Not serious	Very serious[a]	Not serious	Very serious[b]	None	66/6303 (1.0%)	73/6229 (1.2%)	OR 0.90 (0.36–2.21)	1 fewer per 1000 (from 7 fewer to 14 more)	⊕◯◯◯ Very low	Important

CI: confidence interval; HR: hazard ratio; OR: odds ratio.
[a]Considerable heterogeneity according to I^2.
[b]Fails to rule out harm. Confidence intervals cross 1.0.
[c]Small sample/event size.
[d]Fails to rule out benefit. Confidence intervals cross 1. There were no data for the outcome dementia.

controlled trials specifically designed to test the effect of the intensive control of glycaemia on risk of recurrent stroke in people with ischaemic stroke or TIA and diabetes mellitus.

Several trials have reported the effect of intensive glycaemic control on cardiovascular events in other populations of people with diabetes mellitus. The UK Prospective Diabetes Study (UKPDS) included 4209 people with newly diagnosed type 2 diabetes, with a median age of 53 years.[116] Only 2% of participants had a history of myocardial infarction and 1% had a history of stroke or TIA on enrolment. Participants were randomly assigned to either a diet policy, with the aim of maintaining a fasting plasma glucose level of <15 mmol/l, or to an active policy, with the aim of maintaining fasting plasma glucose <6 mmol/l. Intensive treatment reduced the risk of microvascular complications but not macrovascular disease. Of the 4209 participants, 1704 were overweight; 411 were randomised to conventional treatment, 342 were randomised to intensive treatment with metformin and 951 to intensive control.[117] Participants treated with metformin had significant reductions in risk of any diabetes-related endpoint (32%, 95% CI 13–47, $p=0.002$) compared to conventional therapy and lower all cause mortality ($p=0.021$) and risk of stroke ($p=0.032$) compared to those treated with other glucose lowering drugs.

More recently, three randomised trials[118–120] compared intensive glucose control (target HbA1c of <6% (42 mmol/mol) or 6.5% (48 mmol/mol)) with less intensive control and included a greater number of people with a history of cardiovascular disease. Approximately 40% of participants in the Veterans Affairs Diabetes Trial (VADT)[120] and 35% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial had pre-existing cardiovascular disease, but the number of people with stroke was not reported. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, 9% of participants had a history of stroke. None of the trials demonstrated a reduction in the rate of major cardiovascular events with intensive treatment. A prespecified subgroup analysis of data from the ACCORD study suggested that people with no history of cardiovascular disease, or with baseline HbA1C ⩽ 8% had fewer fatal or non-fatal cardiovascular events with intensive therapy. An increase in mortality in the intensive control arm led to the premature cessation of the ACCORD study.

A meta-analysis of seven trials of intensive glucose control versus conventional glucose control found that intensive glucose control led to a reduction in major cardiovascular events of 10% (RR 0.90, 95% CI 0.85–0.96, $p<0.001$).[121] There was no effect on risk of stroke and hypoglycaemia was increased. Subgroup analysis demonstrated that people with shorter duration of diabetes, a longer duration of follow up and lower baseline HbA1c level had a greater benefit from intensive treatment. A further meta-analysis showed a 'U' shaped association between HbA1c level and mortality, with a HbA1c of 7.5% being associated with the lowest HR for all-cause mortality.[122]

Supporting information to the expert consensus statement

There is insufficient evidence to support a recommendation concerning intensive glucose control to prevent recurrent stroke in people with previous history of ischaemic stroke or TIA. However, many people with stroke will have a new or recent diagnosis of diabetes mellitus and all people with diabetes mellitus are at increased risk of microvascular and macrovascular complications. People with ischaemic stroke or TIA and diabetes mellitus should, like all people with diabetes mellitus, have their glucose control assessed and their treatment reviewed in accordance with relevant guidelines for the treatment of diabetes. The panel voted by 12/12 members for the following consensus statement (Supplemental Table 2).

Evidence-based recommendation
–
Quality of evidence: –
Strength of recommendation: –

Expert consensus statement
In people with ischaemic stroke or TIA and diabetes mellitus, we support aiming for an HbA1c level of <53 mmol/mol (7%, 154 mg/dl) to reduce risk of microvascular and macrovascular complications. However, this target may need to be individualised based on duration of diabetes, age and comorbidities.

In adult people with ischaemic stroke or TIA there is continued uncertainty over the role of intensive control of glycated haemoglobin level (HbA1c) compared to less intensive HbA1c control.

PICO Question 13: In people with ischaemic stroke or TIA, does use of pioglitazone compared to no pioglitazone reduce the risk of recurrent stroke?

Analysis of current evidence

Pioglitazone is an oral drug from the thiazolidinedione class of peroxisome proliferator-activated receptor γ (PPAR-γ) agonists. It is an insulin sensitising drug and has been shown to reduce the risk of cardiovascular events in people with type 2 diabetes mellitus.[123] Clinical trials of the effect of pioglitazone on cardiovascular events in people with stroke and insulin resistance have also been performed.

Our systematic literature search identified 1286 titles and 138 full texts were screened. For this specific PICO question, we identified three randomised controlled trials[124–126] including 2488 people with ischaemic stroke or TIA treated with pioglitazone and 2492 people with ischaemic stroke or TIA treated with control. One study included people with ischaemic stroke or high-risk TIA and insulin resistance,[125] one study included people with ischaemic stroke or TIA and insulin resistance or newly diagnosed type 2 diabetes mellitus,[126] and one study included people with type 2 diabetes mellitus and macrovascular disease[123] with specific reporting of outcomes for people with previous stroke.[124] One additional study included people with hypertension or dyslipidaemia who had either silent cerebral infarcts or carotid arterial disease (the effects of pioglitazone on macrovascular events in patients with type 2 diabetes mellitus at high risk of stroke, PROFIT-J trial).[127] This was not included in our analysis due to the lack of a symptomatic event, but findings were broadly in keeping with those of the included studies.

Three studies reported the outcome of any stroke and death[124–126,] two reported the outcome of ischaemic stroke,[125,126] haemorrhagic stroke,[125,126] major cardiac events,[124,125] one trial reported myocardial infarction.[125] No trials reported data for the outcomes of cardiovascular death, dementia, intracranial bleeding, major bleeding or functional outcome.

Results for all considered outcomes and GRADE scoring, are available in Table 10. The meta-analysis of three included studies[124–126] showed a significant reduction in risk of any stroke with pioglitazone (HR 0.70, 95% CI 0.52–0.95, p=0.021, Figure 14, Table 10). This finding is similar to that of a previous meta-analysis[128] and the effect was consistent across all included studies. The level of certainty was rated as moderate. Use of pioglitazone would be expected to lead to 25 fewer cases of stroke per 1000 treated. The meta-analysis of two included studies[125,126] showed a significant reduction in risk of ischaemic stroke with pioglitazone (HR 0.72, 95% CI 0.57–0.90, p=0.005, Table 10). The meta-analysis of two included studies[125,126] showed no reduction in risk of haemorrhagic stroke with pioglitazone (HR 0.99, 95% CI 0.51–1.95, p=0.984, Table 10). The meta-analysis of two included studies[125,127] showed no significant reduction in rate of myocardial infarction (OR 0.75, 95% CI 0.53–1.06, p=0.104. The meta-analysis of three included studies[124–126] showed no significant reduction in risk of death with pioglitazone (HR 0.93, 95% CI 0.75–1.15, p=0.486). The level of certainty was rated as low.

Additional information

Pioglitazone is not widely used for secondary prevention of stroke, despite the result of the Insulin Resistance Intervention After Stroke Trial (IRIS) and other trials. This is largely because of reported side effects. Pioglitazone increases risk of weight gain, bone fracture and heart failure. There are also reports of increased risk of bladder cancer. Fracture is a particular concern in people with stroke.[129] In the IRIS trial the risk of fracture was increased with pioglitazone (13.6% vs 8.8%, HR 1.53, 95% CI 1.24–1.89).[130] The majority of these fractures were low energy, such as following fall, and just under 50% were serious requiring surgery or hospitalisation. The risk of serious fractures was increased by 1.6% (4.7% vs 3.1%, HR 1.47, 95% CI 1.03–2.09). For comparison, the absolute risk reduction for MI and stroke in the IRIS trial was 2.8% giving a number needed to treat of 36 to prevent one stroke or MI. The corresponding number to harm for serious fracture is 62. An increase in fracture was also reported in the PROactive trial.[131] Risk of heart failure was not increased in the IRIS trial[132] but there was a trend towards an increase in the The prospective pioglitazone clinical trial in macrovascular events (PROactive) trial.[124] It is therefore possible that risk of heart failure will not be increased in people who have insulin resistance and no diabetes mellitus, provided there are attempts to identify heart failure and oedema, with dose reduction if this is found. The risk of bladder cancer may be increased with long-term cumulative exposure and has been demonstrated in meta-analyses of both clinical trials (n=9114 participants, OR 1.84, 95% CI 0.99–3.42) and observational studies (n=4,846,088, OR 1.13, 95% CI 1.03–1.25).[133] The dose of pioglitazone used in trials was typically 45 mg daily, but trial protocols allowed lower doses to be used in the event of side effects. It is unclear whether use of lower doses will be effective and cause fewer side effects. Due to the concerns regarding side effects, pioglitazone should only be used after careful consideration of risk of fracture, bladder cancer and heart failure and counselling of the person. It is also important to note that in the IRIS trial, people with TIA were only included if they had motor weakness and aphasia and this should be considered when using pioglitazone in people with insulin resistance and no diabetes mellitus who have has a TIA. Overall, we rated the quality of evidence as moderate.

Evidence-based recommendation
In people with ischaemic stroke or TIA, who have insulin resistance or type 2 diabetes mellitus, we suggest pioglitazone be used to reduce risk of recurrent stroke.

Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Weak for intervention** ↑?

Discussion

This guideline document was developed following the GRADE methodology and aims to assist physicians in decision-making regarding pharmacological interventions for the secondary prevention of recurrent stroke after ischaemic stroke or TIA. All recommendations and Expert consensus statements are summarised in Table 11.

Wherever possible, recommendations are provided on the basis of a meta-analysis of randomised controlled trials in defined populations with ischaemic stroke or TIA or from subgroups of these participants. However, such evidence was not always available but there were often studies in primary prevention or in people with other cardiovascular indications. In this context, expert consensus statements were formulated and agreed by the MWG. The principal outcome for each PICO question was the occurrence of recurrent stroke rather than all cardiovascular events. However, other outcomes were rated as critical so were also considered when formulating our recommendations.

Table 10. GRADE evidence profile for PICO question 13: In people with ischaemic stroke or TIA, does use of pioglitazone compared to no pioglitazone reduce the risk of any recurrent stroke?.

Certainty assessment							No. of participants		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pioglitazone	Placebo	Relative (95% CI)	Absolute (95% CI)		
Any stroke												
3	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	None	158/2488 (6.4%)	212/2492 (8.5%)	HR 0.70 (0.52–0.95)	25 fewer per 1000 (from 40 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	Critical
Ischaemic stroke												
2	Randomised trials	Very serious[b]	Not serious	Not serious	Not serious	None	126/2002 (6.3%)	175/1994 (8.8%)	HR 0.72 (0.57–0.96)	24 fewer per 1000 (from 37 fewer to 8 fewer)	⊕⊕◯◯ Low	Critical
Haemorrhagic stroke												
2	Randomised trials	Very serious[b]	Not serious	Not serious	Very serious[c]	None	17/2002 (0.8%)	17/1994 (0.9%)	OR 0.99 (0.51–1.95)	0 fewer per 1000 (from 4 fewer to 8 more)	⊕◯◯◯ Very low	Critical
Major adverse cardiovascular events												
2	Randomised trials	Serious[d]	Not serious	Not serious	Not serious	None	269/2425 (11.1%)	337/2435 (13.8%)	HR 0.78 (0.65–0.95)	28 fewer per 1000 (from 47 fewer to 7 fewer)	⊕⊕⊕◯ Moderate	Critical
Myocardial infarction												
2	Randomised trials	Serious[b]	Not serious	Serious[e]	Serious[f]	None	5/234 (2.1%)	4/247 (1.6%)	OR 0.75 (0.53–1.06)	4 fewer per 1000 (from 7 fewer to 1 more)	⊕◯◯◯ Very low	Critical
Death												
3	Randomised trials	Serious[a]	Not serious[f]	Not serious	Serious[f]	None	183/2488 (7.4%)	197/2492 (7.9%)	OR 0.93 (0.75–1.15)	5 fewer per 1000 (from 18 fewer to 10 more)	⊕⊕◯◯ Low	Critical

CI: confidence interval; HR: hazard ratio; OR: odds ratio.
[a]Two out of three studies at risk of bias but largest study at low risk of bias.
[b]One study at high risk of bias.
[c]Very small sample size.
[d]One study at uncertain risk of bias.
[e]One of two studies not exclusively a stroke population.
[f]Confidence intervals crossover 1.00. There were no data for the outcomes cardiovascular death, major bleeding, intracranial bleeding, dementia and functional outcome.

Table 11. Synoptic table of all recommendations and expert consensus statements.

Recommendation	Expert consensus statement
PICO question 1 In people with a history of ischaemic stroke or TIA, does blood pressure lowering treatment compared to no blood pressure lowering treatment reduce the risk of any recurrent stroke?	
In people with previous ischaemic stroke or TIA, we recommend blood pressure lowering treatment to reduce the risk of recurrent stroke. Quality of evidence: **High** ⊕⊕⊕⊕ Strength of recommendation: **Strong for intervention** ↑↑	
PICO question 2 In people with a history of ischaemic stroke or TIA starting antihypertensive therapy, does use of out of office blood pressure measurements compared to outpatient clinic measurements provide better long-term control of blood pressure?	
	In people with previous ischaemic stroke or TIA, we support the use of out of office blood pressure measurements wherever feasible, to achieve better long-term control of blood pressure
PICO question 3: In people with a history of ischaemic stroke or TIA starting or increasing antihypertensive therapy, does treating to a more intensive (i.e. BP $<$ 130/80) versus less intensive ($<$140/90 mmHg) target reduce the risk of recurrent stroke?	
In people with previous ischaemic stroke or TIA, we suggest aiming for a blood pressure target of $<$130/80 mmHg to reduce the risk of recurrent stroke. Quality of evidence: **Moderate** ⊕⊕⊕ Strength of recommendation: **Weak for intervention** ↑?	
PICO question 4: In people with a history of ischaemic stroke or TIA starting antihypertensive therapy, does initiation of two blood pressure lowering medications compared to monotherapy reduce the risk of recurrent stroke?	
	In people with ischaemic stroke or TIA, we support initiation of a combination of two blood pressure lowering drugs to reduce the risk of recurrent stroke, with consideration of monotherapy where there are potential risks of hypotension, such as in frail, elderly people and people with borderline hypertension
PICO question 5: In people with ischaemic stroke or TIA does use of an HMGCoA reductase inhibitor compared to no lipid-lowering therapy reduce the risk of recurrent stroke?	
In people with previous ischaemic stroke or TIA we recommend use of a HMGCoA reductase inhibitor to reduce the risk of recurrent ischaemic stroke. Quality of evidence: **High** ⊕⊕⊕⊕ Strength of recommendation: **Strong for intervention** ↑↑	
PICO question 6: In people with ischaemic stroke or TIA does working to an intensive cholesterol treatment target, compared to a less intensive target, reduce the risk of any stroke?	
In people with ischaemic stroke or TIA, we recommend aiming for an LDL cholesterol level of $<$1.8 mmol/l (70 mg/dl) to reduce the risk of major cardiovascular events Quality of evidence: **Moderate** ⊕⊕⊕ Strength of recommendation: **Strong for intervention** ↑↑	
PICO question 7: In people with a previous ischaemic stroke or TIA who do not achieve recommended LDL-C targets despite taking a maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks, is the addition of ezetimibe and/or a PCSK9-inhibitor superior to an HMGCoA reductase inhibitor alone to reduce the risk of recurrent stroke?	

(Continued)

Table 11. (Continued)

Recommendation	Expert consensus statement
	In people with ischaemic stroke or TIA who do not achieve the recommended LDL-C targets despite taking maximally tolerated dose of a HMGCoA reductase inhibitor for at least 6 weeks, we support the addition of ezetimibe as an option to reduce the risk of recurrent major cardiovascular events
PICO question 8: In people with ischaemic stroke or TIA, does long-term antiplatelet therapy compared to no antiplatelet treatment reduce the risk of recurrent stroke?	
In people with previous ischaemic stroke or TIA, we recommend long-term use of antiplatelet therapy to reduce the risk of recurrent stroke. Quality of evidence: **Moderate** ⊕⊕⊕ Strength of recommendation: **Strong for intervention** ↑↑	
PICO question 9: In people with TIA and ischaemic stroke, does treatment with dual antiplatelet therapy for longer than 90 days with aspirin plus clopidogrel or aspirin plus dipyridamole, compared to a single antiplatelet, reduce the risk of recurrent stroke?	
In people with previous ischaemic stroke or TIA, we recommend against use of dual antiplatelet therapy with aspirin and clopidogrel in the long-term and recommend use of single antiplatelet to reduce the risk of recurrent stroke. Quality of evidence: **Very Low** ⊕ Strength of recommendation: **Weak against intervention ↓?**	
PICO question 10: In people with ischaemic stroke or TIA and atherosclerosis, with no other indication for anticoagulation, does antiplatelet therapy combined with a low-dose direct oral anticoagulant compared to antiplatelet therapy alone reduce the risk of recurrent stroke?	
	The use of antiplatelet therapy combined with a low-dose direct oral anticoagulant (rivaroxaban) can be considered to optimise treatment of coronary artery disease or peripheral arterial disease in people with a history of ischaemic stroke or TIA more than 1 month previously. It should not be considered in people with ischaemic stroke or TIA who do not have coronary artery disease or peripheral arterial disease
PICO question 11: In people with an embolic stroke of undetermined source (ESUS) does treatment with a direct oral anticoagulant drug compared to an antiplatelet reduce the risk of recurrent stroke?	
In people with an embolic stroke of undetermined source, we suggest use of antiplatelet therapy and not a DOAC to reduce the risk of recurrent stroke. Quality of evidence: **Low** ⊕⊕ Strength of recommendation: **Weak against intervention** ↓?	
PICO question 12: In people with diabetes mellitus and ischaemic stroke or TIA, does intensive control of glycated haemoglobin level (HbA1c) compared to less intensive HbA1c control reduce the risk of recurrent stroke?	
	In people with ischaemic stroke or TIA and diabetes mellitus, we support aiming for an HbA1c level of <53 mmol/mol (7%, 154 mg/dl) to reduce risk of microvascular and macrovascular complications. However, this target may need to be individualised based on duration of diabetes, age and comorbidities.
PICO question 13: In people with ischaemic stroke or TIA, does use of pioglitazone compared to no pioglitazone reduce the risk of recurrent stroke?	
In people with ischaemic stroke or TIA, who have insulin resistance or type 2 diabetes mellitus, we suggest pioglitazone be used to reduce risk of recurrent stroke. Quality of evidence: **Moderate** ⊕⊕⊕ Strength of recommendation: **Weak for intervention** ↑?	

Study name	Statistics for each study				
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
IRIS trial	0.820	0.611	1.101	-1.319	0.187
PROactive	0.530	0.335	0.838	-2.716	0.007
J-Spirit	0.660	0.184	2.363	-0.638	0.523
	0.700	0.517	0.947	-2.310	0.021

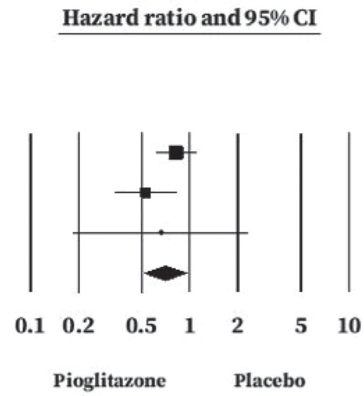


Figure 14. Forest plot for the risk of any stroke in trials comparing treatment with pioglitazone versus placebo in people with TIA or stroke and diabetes or impaired glucose tolerance. Heterogeneity: $I^2 = 19.462$; $Q = 2.483$.

Broadly, the recommendations for interventions for blood pressure lowering or lipid lowering supported a principle of intensive treatment to rigorous targets. In the case of blood pressure reduction, this was applicable for all people except in specific groups who may be at an increased risk of hypotension. Our guideline also covered use of combination antihypertensive treatment, out of office monitoring of blood pressure and addition of novel lipid lowering therapies (ezetimibe or PCSK9 inhibitors). However, while these approaches may be beneficial in many people after stroke, specific evidence in the setting of secondary prevention was often lacking and differences in specific subgroups of stroke remain unknown. Developing this evidence should be a key area of future research. This guideline has not specifically considered use of fibrate, niacin or bempedoic acid therapy either as an add on or in addition to statin therapy. With regard to treatment targets in diabetes mellitus, there was very limited evidence for optimal HbA1c targets after stroke, and limited evidence for the use of specific drugs. Indeed, although we support current primary prevention guidance to optimise control of HbA1c to prevent microvascular targets, the evidence for prevention of macrovascular outcomes remains particularly uncertain and should become a key focus of future research. It would also be important to clarify whether the reduction in stroke seen with GLP1 receptor antagonists in people with diabetes are seen in the secondary prevention setting.

There have been a large number of recent studies exploring antithrombotic strategies. Although antiplatelet therapy has long been established for the secondary prevention of ischaemic stroke, evidence for antiplatelet monotherapy compared to placebo is heavily based upon older trials which used aspirin. We did not specifically address the choice of antiplatelet but given the limited differences in direct comparisons between aspirin and other antiplatelets,[22] we believe that there is likely equivalent benefit from other antiplatelets such as clopidogrel. Although recent studies have suggested much of the benefit occurs early after initiation of treatment,[134] in the absence of trials excluding potential harms of stopping antiplatelets, long-term antiplatelet monotherapy is indicated. Long-term dual antiplatelet treatment with aspirin and clopidogrel carries an increased risk of harm so we do no recommend this regimen. There are numerous ongoing trials in this area so it is likely that recommendations will be required to be updated in time.

The validity of the recommendations and consensus statements in this guidance results from the systematic approach, GRADE methodology and for many interventions, the availability of high quality randomised controlled trials. However, there are limitations. Firstly, this guideline was specifically restricted to the long-term prevention of recurrent stroke, and therefore does not apply to decisions in the acute phase of stroke. Secondly, it only applies to pharmacological risk factor management after ischaemic events as aetiology-specific interventions are covered in separate guidelines, whilst lifestyle factors will be a focus of future guidance. We recognise that in the coming years treatment is likely to become more specific for the underlying aetiology and that these guidelines may need to be refined. Thirdly, for many of our PICO questions, there remains limited data in specific populations with previous ischaemic stroke or TIA in whom further research is strongly advocated – particularly to better define the role of novel antithrombotic strategies, choice of blood pressure lowering drugs, add on therapy to achieve lipid targets and the role of new treatments for type 2 diabetes mellitus. Finally, we recognise that female participants are often under-represented in clinical trials. We did not specifically address this in our evidence appraisal as this has been covered in a recent ESO guideline.

Plain language summary

This guideline is provided for doctors and other clinicians to help them to decide which medications should be given to most people after an ischaemic stroke or mini-stroke to reduce the risk of future strokes or related problems, such as heart attacks.

Having searched extensively for research published on each of the key questions identified, the most important recommendations we have made, based on available evidence, are:

1. People who have had an ischaemic stroke or transient ischaemic attack should be prescribed medication to lower their blood pressure, if this is raised.
2. Treatment should aim to achieve a blood pressure level below 130/80 mmHg except in some people at an increased risk of problems, such as the very elderly, people with kidney problems and those with severe narrowing of the large blood vessels to the brain.
3. People who have had an ischaemic stroke or transient ischaemic attack should be prescribed HMGCoA reductase inhibitors (statins) to lower their cholesterol.
4. Lipid lowering treatments should aim to keep the low-density cholesterol (bad cholesterol) level below 1.8 mmol/l (70 mg/dl)
5. In the longer term, people who have had an ischaemic stroke or transient ischaemic attack, who do not have a specific reason to have a stronger anticoagulant blood thinner, should be prescribed antiplatelet, but only one such medication at a time.
6. In people with diabetes, or early evidence of it, the anti-diabetic medicine pioglitazone reduces the risk of recurrent stroke, but this should be balanced against an increased risk of broken bones, heart failure and bladder cancer.

Also, where there was insufficient published research to specifically address the question posed, the majority of the working group agreed that:

1. Monitoring blood pressure at home is likely to improve blood pressure control.
2. When treating blood pressure starting treatment with more than one drug is likely to be beneficial for most people.
3. In people whose cholesterol level is not controlled with HMGCoA reductase inhibitors (statins), addition of further drugs should be considered.
4. In some people with narrowing of blood vessels in the heart or the peripheral arteries, the addition of a low-dose anticoagulant blood thinner (a 'DOAC') to an antiplatelet may be considered but this should not be done to treat their stroke.
5. Control of blood sugar to an HbA1c level of <53 mmol/mol (7%, 154 mg/dl) in people with diabetes mellitus and ischaemic stroke or transient ischaemic attack is likely to be beneficial in reducing the risk of cardiovascular events and other complications of diabetes.

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Ethical approval

Ethical approval was not necessary for the work described in this paper.

Informed consent

Not applicable.

Guarantor

The guarantors of the content of this guideline are Prof Jesse Dawson and Prof Alastair Webb, co-chairs of the Module Working Group.

Contributorship

All members of the MWG were responsible for drafting individual PICO questions. JD and AW wrote the first draft of the manuscript. MTR conducted the statistical analyses. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iDs

Jesse Dawson https://orcid.org/0000-0001-7532-2475
Louisa M Christensen https://orcid.org/0000-0003-1448-5646
Gian Marco De Marchis https://orcid.org/0000-0002-0342-9780
Linxin Li https://orcid.org/0000-0002-3636-8355
Cristina Tiu https://orcid.org/0000-0001-8532-6218
Alastair Webb https://orcid.org/0000-0002-0630-8204

Supplemental material

Supplemental material for this article is available online.

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