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Guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack

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Disclosures

Intellectual Disclosures:

(Associate) editors for Frontiers in Neurology (YB, LL, AW, MH), Stroke (GM, YB), J of Atherosclerosis Prevention (HM), BMC Neurology (MH)

Co-chair SAP-E implementation committee (FP), Chair ESO Education Committee (AW), ESO Board of Directors (LC), President of ESO (MD).

Research funding from BMS , Pfizer (JD)

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Lecture fees from BMS, Pfizer, Medtronic, Amgen, Boehringer-Ingelheim, Daicchi Sanyko, Astra-Zeneca, Bayer, Merck, Biogen, Novartis, Roche, Viatris/

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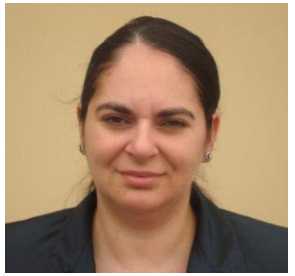

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Secondary Prevention : Topic Areas

- Blood Pressure
- Dyslipidaemia
- Antithrombotics
- Diabetes
- (AF, carotid stenosis not included)

Evidence-based Recommendation: Blood Pressure

PICO 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?

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** ↑↑

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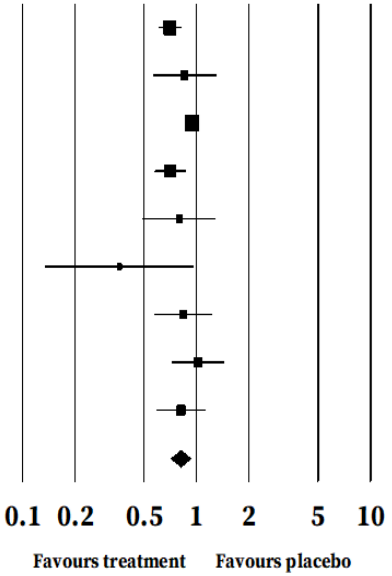
Supporting Information

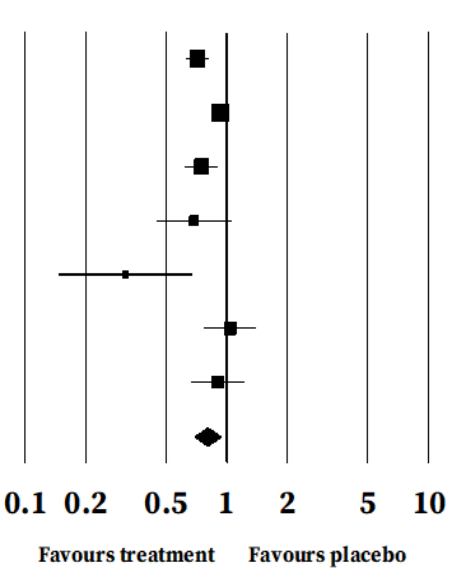
Recurrent Stroke

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



MACE

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



- Significant benefits for CV death (0.88, 0.78 – 0.99); NS for Death, MI, functional outcome. No data for dementia
- Heterogeneity goes with removal of PROFESS, with small achieved BP difference

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Evidence-based Recommendation: Blood Pressure

PICO 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?

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** ↑?

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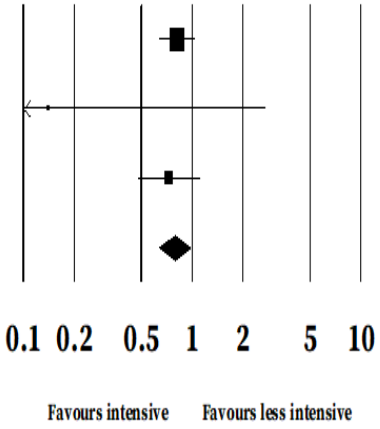
Supporting Information

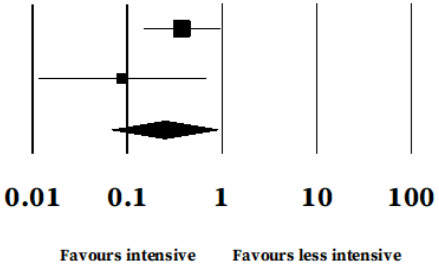
Any Stroke

Study name	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



ICH

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



- NS for ischaemic stroke, MACE, death, CV death, MI, functional outcome.
- Limited, heterogeneous trials, in specific populations (ie SPS3).

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Expert Consensus Statements: Achieving BP control

PICO 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?

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 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

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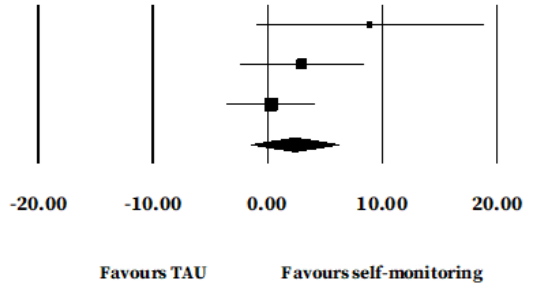
Supporting Information: Achieving BP Control

Out-of-office monitoring:

Study name	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



Combination Treatment:

- No direct comparisons
- Greater benefit with combination in PROGRESS (perindopril + indapamide)
- Suggest use of CCB or thiazide-like diuretic plus RASi first.

Recommendations based on stronger evidence / guidance in primary prevention

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Evidence-based Recommendation: Lipid lowering

PICO 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 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** ↑↑

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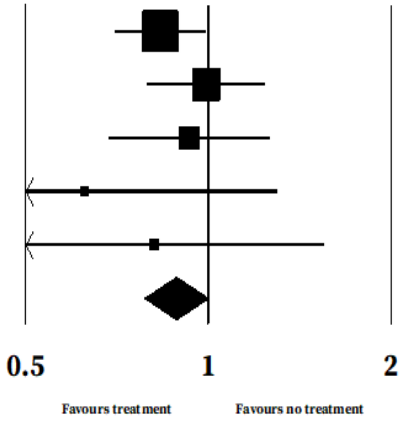
Supporting Information

Recurrent Stroke

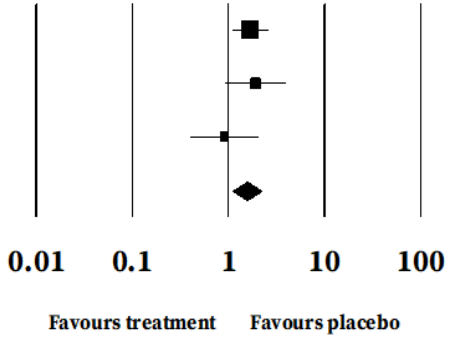
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
SPARCL	0.834	0.700	0.993	-2.038	0.042
HPSC	0.992	0.792	1.242	-0.069	0.945
J-STARS	0.930	0.686	1.263	-0.463	0.643
CARE	0.625	0.301	1.300	-1.258	0.208
LIPID	0.814	0.428	1.550	-0.626	0.531
	0.885	0.784	0.999	-1.969	0.049



Meta Analysis

ICH

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



- Significant benefits for ischaemic stroke (0.79, 0.67-0.92), MACE (0.78, 0.70-0.87); NS for Death, MI, functional outcome, dementia
- Treatment reduces 13 fewer strokes per 1000 cases, with 6 per 1000 more ICH

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Evidence-based Recommendation: Lipid lowering

PICO 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?

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** ↑↑

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Supporting Information

- Only 1 trial: Treating Stroke to Target (TST):
  - Significant reduction in MACE (HR 0.78, 95% CI 0.61 to 0.98; P=0.04).
  - Non-significant reductions in risk of cerebral infarction or intracranial haemorrhage (HR 0.82, 95% CI 0.63 to 1.07), death, CV death etc.

- Supported by post-hoc analyses of achieved control in other studies (SPARCL, JSTARS)

- Strongly supported by primary prevention data.

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Expert Consensus Statements: Achieving Lipid Control

PICO 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?

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.

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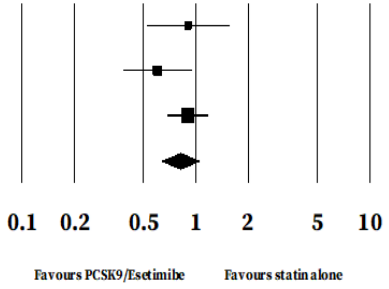
Supporting Information: Achieving Lipid Control

- No Dedicated secondary prevention trials
- Post-hoc analyses of primary prevention trials in small cerebrovascular subgroups

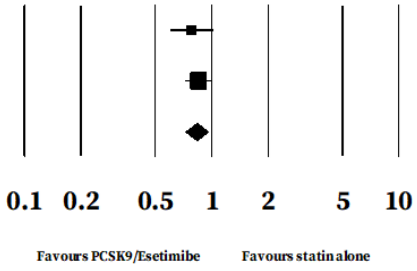
Recurrent Stroke

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



MACE

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



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Evidence-based Recommendation: Antithrombotics

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

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** ↑↑

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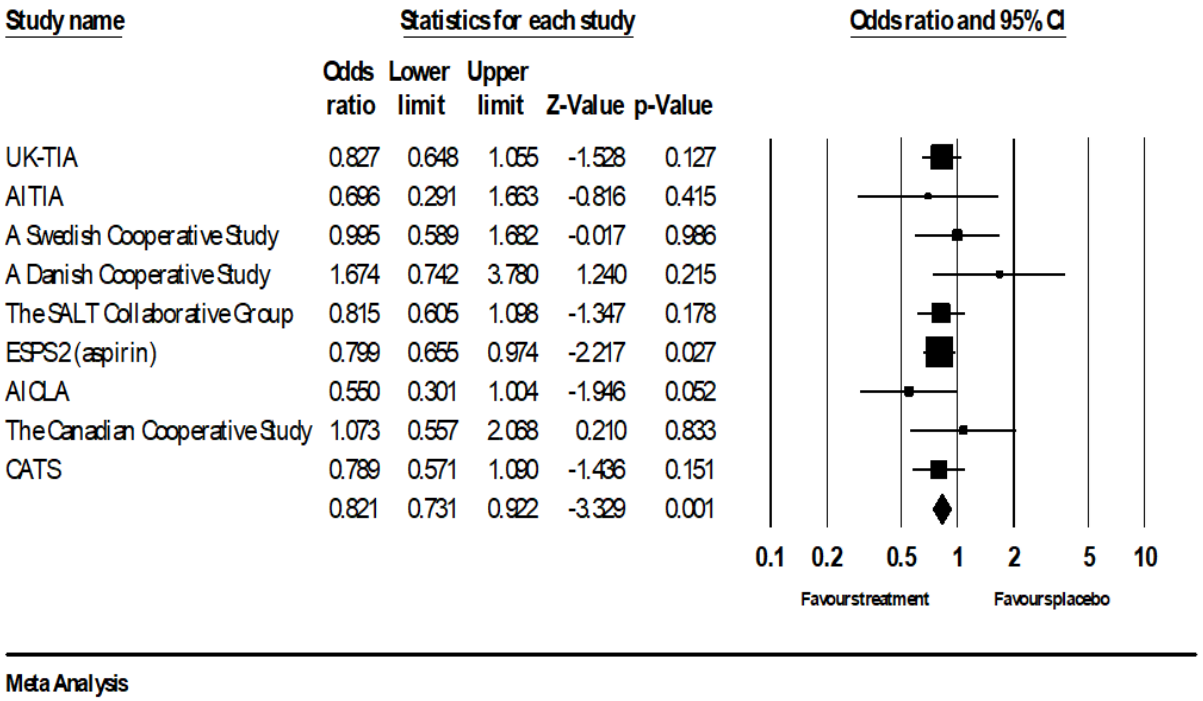
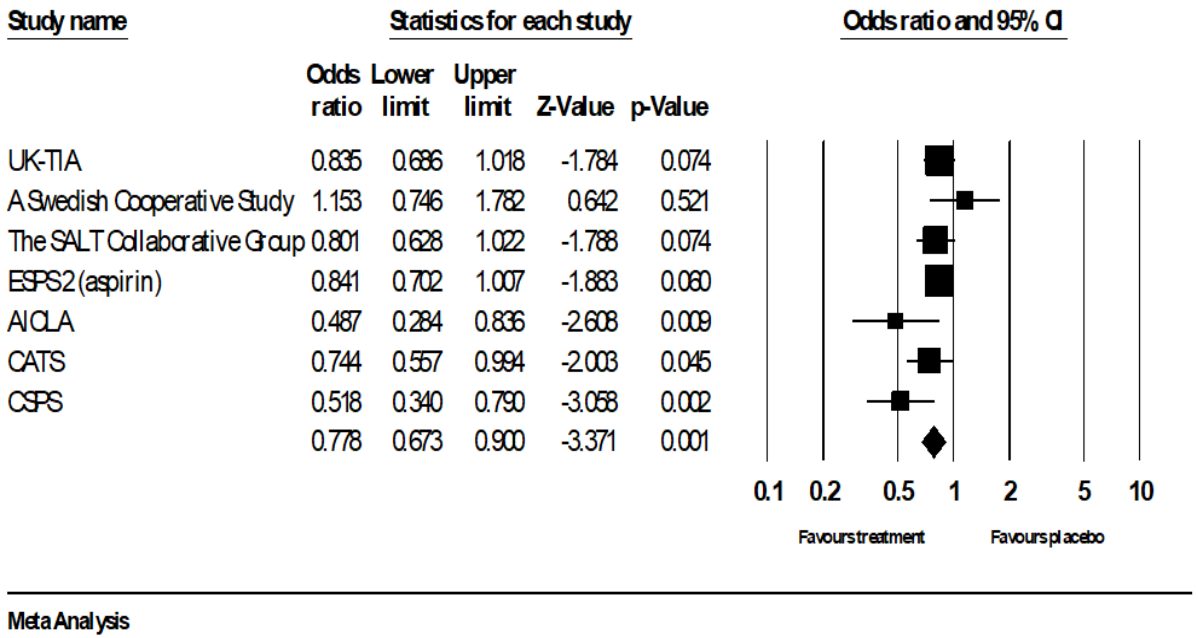
Supporting Information

Recurrent Stroke



MACE



- Significant benefits for ischaemic stroke (0.67, 0.54-0.85), MACE (0.78, 0.67-0.90), MI (0.77, 0.61-0.98); NS for death, CV death, functional outcome
- Significant harms from any major bleeding (2.51, 1.42 – 4.43); NS increase for ICH.
- Mostly studies with aspirin. Later studies suggest at least equivalent efficacy with other single antiplatelets

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Evidence-based Recommendation: Antithrombotics

PICO 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?

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 ↓?**

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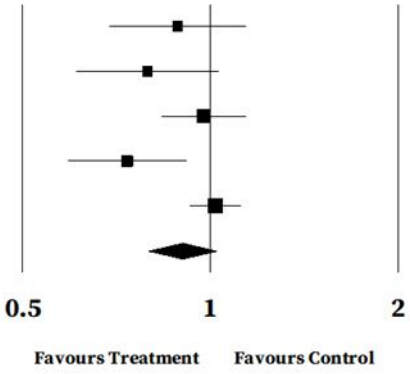
Supporting Information

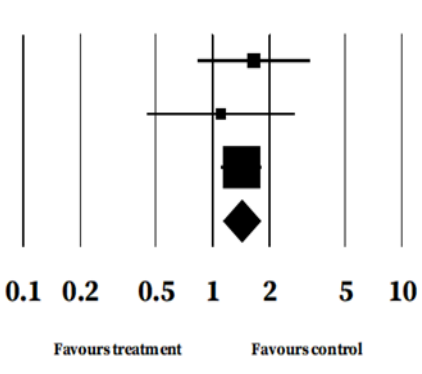
Recurrent Stroke

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



ICH

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

- Non-significant reduction in recurrent stroke → NNT 8 per 1000
- Significant increase in intracerebral haemorrhage → NNH 4 per 1000

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Alternative Strategies: NOACs

PICO 10 Expert Consensus Statement: Low dose NOAC + Antiplatelet

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 one 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 11 Evidence-based Recommendation: NOAC vs Antiplatelet in ESUS

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** ↓?

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Supporting Information

- **PICO 10: Low dose NOAC + antiplatelet:**
  - Only trial is COMPASS in primary prevention, limited stroke patients, but more with carotid stenosis
  - Where stroke patients fulfil inclusion criteria for COMPASS, this approach is reasonable.

- **PICO 11: NOAC versus antiplatelet in ESUS:**

  - NAVIGATE and RESPECT (Atticus presented at ESOC 2022)
  - No significant benefit of treatment:
    - Any Stroke: OR 0.96, 95% CI 0.75 to 1.22,

Expert Consensus Statements: Diabetes

PICO 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?

Expert Consensus Statement

In people with ischaemic stroke or TIA and diabetes mellitus, we support aiming for an HbA1c level of <53mmol/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.

- No Secondary Prevention Evidence
- Based upon primary prevention guidance

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Evidence-based Recommendation: Diabetes

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

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** ↑?

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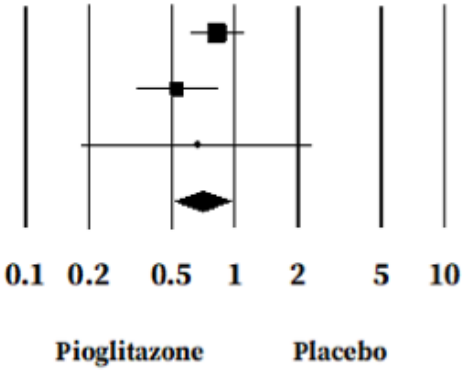
Supporting Information

Recurrent Stroke

Study name	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



Caution in at risk groups:

- IRIS trial fracture risk, tx vs control: 13.6% vs. 8.8%, HR 1.53, 95% CI 1.24 to 1.89
- **NNT for stroke and MI 36, NNH for serious fracture 62**
- Possible caution for heart failure and bladder cancer

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Areas of future research

Blood Pressure

- Optimal drug class / combination is unclear
- Benefits of home BP monitoring
- Benefits in specific subgroups, particularly for intensive treatment, is unknown

Lipid lowering

- Are PCSK9 inhibitors beneficial after stroke?
- Fibrates, niacin, bempedoic acid etc…

Anthrombotic strategies

- Benefit of low-dose NOAC in stroke specific populations
- Personalised medicine (pharmacogenomic approaches)
- New antithrombotics (Factor XIa / XII)

Diabetes

- Is there benefit from targeting a low HbA1C in diabetes after stroke to prevent macrovascular complications?
- Is there benefit from GLP1 receptor antagonists?

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Conclusions

- Secondary prevention strategies work, but there is large residual burden
- Secondary prevention specific evidence is often lacking, so treatment choices depend on primary prevention guidance.
- Active control of blood pressure and LDL-C, to intensive targets, is beneficial, and strategies to achieve lower targets are likely to bring added benefits
- A long-term single antiplatelet strategy is the best supported antithrombotic strategy, but this is likely change
- Long-term glucose control after stroke, both in terms of target and preferred agent, remains very unclear.

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