Antithrombotic treatment after stroke due to intracerebral haemorrhage

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Antithrombotic treatment after stroke due to intracerebral haemorrhage

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Abstract

Background

This is an update of the Cochrane Review last published in 2017. Survivors of stroke due to intracerebral haemorrhage (ICH) are at risk of major adverse cardiovascular events (MACE). Antithrombotic (antiplatelet or anticoagulant) treatments may lower the risk of ischaemic MACE after ICH, but they may increase the risk of bleeding.

Objectives

To determine the overall effectiveness and safety of antithrombotic drugs on MACE and its components for people with ICH.

Search methods

We searched the Cochrane Stroke Group Trials Register (5 October 2021). We also searched the Cochrane Central Register of Controlled Trials (CENTRAL: the Cochrane Library 2021, Issue 10), MEDLINE Ovid (from 1948 to October 2021) and Embase Ovid (from 1980 to October 2021). The online registries of clinical trials searched were the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (5 October 2021). We screened the reference lists of included randomised controlled trials (RCTs) for additional, potentially relevant randomised controlled trials (RCTs).

Selection criteria

We selected RCTs in which participants with ICH of any age were allocated to a class of antithrombotic treatment as intervention or comparator.

Data collection and analysis

In accordance with standard methodological procedures recommended by Cochrane, two review authors assessed each selected RCT for its risk of bias and extracted data independently. The primary outcome was a composite of MACE, and secondary outcomes included death, individual components of the MACE composite, ICH growth, functional status and cognitive status. We estimated effects using the frequency of outcomes that occurred during the entire duration of follow-up and calculated a risk ratio (RR) for each RCT. We grouped RCTs separately for analysis according to 1) the class(es) of antithrombotic treatment used for the intervention and comparator, and 2) the duration of antithrombotic treatment use (short-term versus long-term). We pooled the intention-to-treat populations of RCTs using a fixed-effect model for meta-analysis, but used a random-effects model if RCTs differed substantially in their design or there was considerable heterogeneity ($I^2 \geq 75\%$) in their results. We applied GRADE to assess the certainty of the evidence.

Main results

We identified seven new completed RCTs for this update, resulting in the inclusion of a total of nine RCTs based in secondary care, comprising 1491 participants (average age ranged from 61 to 79 years and the proportion of men ranged from 44 to 67%). The proportion of included RCTs at low risk of bias, by category was: random sequence generation (67%), allocation concealment (67%), performance (22%), detection (78%), attrition (89%), and reporting (78%).

For starting versus avoiding short-term prophylactic dose anticoagulation after ICH, no RCT reported MACE. The evidence is very uncertain about the effect of starting short-term prophylactic dose anticoagulation on death (RR 1.00, 95% CI 0.59 to 1.70, P = 1.00; 3 RCTs; very low-certainty evidence), venous thromboembolism (RR 0.84, 95% CI 0.51 to 1.37, P = 0.49; 4 RCTs; very low-certainty evidence), ICH (RR 0.24, 95% CI 0.04 to 1.38, P = 0.11; 2 RCTs; very low-certainty evidence), and independent functional status (RR 2.03, 95% CI 0.78 to 5.25, P = 0.15; 1 RCT; very low-certainty evidence) over 90 days.

For starting versus avoiding long-term therapeutic dose oral anticoagulation for atrial fibrillation after ICH, starting long-term therapeutic dose oral anticoagulation probably reduces MACE (RR 0.61, 95% CI 0.40 to 0.94, P = 0.02; 3 RCTs; moderate-certainty evidence) and probably reduces all major occlusive vascular events (RR 0.27, 95% CI 0.14 to 0.53, P = 0.0002; 3 RCTs; moderate-certainty evidence), but probably results in little to no difference in death (RR 1.05, 95% CI 0.62 to 1.78, P = 0.86; 3 RCTs; moderate-certainty evidence), probably increases intracranial haemorrhage (RR 2.43, 95% CI 0.88 to 6.73, P = 0.09; 3 RCTs; moderate-certainty evidence), and may result in little to no difference in independent functional status (RR 0.98, 95% CI 0.78 to 1.24, P = 0.87; 2 RCTs; low-certainty evidence) over 1-3 years.

For starting versus avoiding long-term antiplatelet therapy after ICH, the evidence is uncertain about the effects of starting long-term antiplatelet therapy on MACE (RR 0.89, 95% CI 0.64 to 1.22, P = 0.46; 1 RCT; moderate-certainty evidence), death (RR 1.08, 95% CI 0.76 to 1.53, P = 0.66; 1 RCT; moderate-certainty evidence), all major occlusive vascular events (RR 1.03, 95% CI 0.68 to 1.55, P = 0.90; 1 RCT; moderate-certainty evidence), ICH (RR 0.52, 95% CI 0.27 to 1.03, P = 0.06; 1 RCT; moderate-certainty evidence) and independent functional status (RR 0.95, 95% CI 0.77 to 1.18, P = 0.67; 1 RCT; moderate-certainty evidence) over a median follow-up of 2 years.

For adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a clinical history of prior ICH, there was no evidence of an effect of long-term cilostazol compared to aspirin on MACE (RR 1.33, 95% CI 0.74 to 2.40, P = 0.34; subgroup of 1 RCT; low-certainty evidence), death (RR 1.65, 95% CI 0.55 to 4.91, P = 0.37; subgroup of 1 RCT; low-certainty evidence), or ICH (RR 1.29, 95% CI 0.35 to 4.69, P = 0.70; subgroup of 1 RCT; low-certainty evidence) over a median follow-up of 1.8 years; all major occlusive vascular events and functional status were not reported.

Authors' conclusions

We did not identify beneficial or hazardous effects of short-term prophylactic dose parenteral anticoagulation and long-term oral antiplatelet therapy after ICH on important outcomes. Although there was a significant reduction in MACE and all major occlusive vascular events after long-term treatment with therapeutic dose oral anticoagulation for atrial fibrillation after ICH, the pooled estimates were imprecise, the certainty of evidence was only moderate, and effects on other important outcomes were uncertain. Large RCTs with a low risk of bias are required to resolve the ongoing dilemmas about antithrombotic treatment after ICH.

Plain language summary

Drugs to prevent clots after bleeding in the brain

Review question

What are the benefits and risks of drugs used to prevent clots (known as 'antithrombotic drugs') in the short-term and long-term after a stroke due to bleeding in the brain (known as 'brain haemorrhage')?

Background

People with stroke due to brain haemorrhage are more likely to develop clots in their blood vessels than people without brain haemorrhage. Immobility early after the stroke can cause clots in the veins of the legs and pelvis. Patients' underlying medical conditions in both the short- and long-term after the stroke can also cause clots in the arteries of the lungs, brain, heart, legs or other organs. These clots can cause serious illness or death. Antithrombotic drugs can prevent clots. However, these drugs can also lead to bleeding problems, which can cause serious illness or death. Whether antithrombotic drugs benefit or harm patients after brain haemorrhage is unknown. This is an update of a Cochrane review, which was last published in 2017.

Study characteristics

We updated our extensive searches for randomised controlled trials, which are the fairest tests of treatment, in October 2021. We found nine trials, which included 1491 people with a brain haemorrhage in the past. Four trials studied short-term use of injected blood thinning drugs (known as 'anticoagulants') in immobile brain haemorrhage survivors. Three trials studied long-term use of oral anticoagulants in brain haemorrhage survivors with an irregular heart beat (known as 'atrial fibrillation'). One trial studied long-term use of oral blood thinning drugs (known as 'antiplatelet drugs') after brain haemorrhage, and another trial compared two different types of antiplatelet drug.

Key results

We did not identify significant benefits or risks of short-term injected anticoagulants or long-term oral antiplatelet drugs. Although long-term oral anticoagulants reduced the risk of any major bleeding or clotting event in brain haemorrhage survivors with atrial fibrillation, the findings were not precise, and we were only moderately certain about the evidence. We did not identify significant differences in benefits or risks when comparing two long-term antiplatelet drugs (cilostazol versus aspirin) for people who had both a stroke or mini-stroke due to clotting and a brain haemorrhage in the past.

Conclusion

Although antithrombotic drugs appear to be promising after brain haemorrhage, we cannot be certain on the basis of the trials that have been done so far. Larger trials are needed to be sure about the effects of these drugs after brain haemorrhage. Eight ongoing trials will help resolve these uncertainties if they recruit large numbers of participants.

Summary of findings

Summary of findings 1

Summary of findings table - Starting short-term prophylactic dose anticoagulation compared to avoiding anticoagulation for survivors of stroke due to intracerebral haemorrhage

Starting short-term prophylactic dose anticoagulation compared to avoiding anticoagulation for survivors of stroke due to intracerebral haemorrhage

Patient or population: survivors of stroke due to intracerebral haemorrhage
Setting: Secondary care
Intervention: starting short-term prophylactic dose anticoagulation
Comparison: avoiding anticoagulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with avoiding anticoagulation	Risk with starting short-term prophylactic dose anticoagulation				
Major adverse cardiovascular events - not reported	-	-	-	-	-	
Death assessed with: clinical assessment follow-up: 90 days	175 per 1000	**175 per 1000** (103 to 297)	**RR 1.00** (0.59 to 1.70)	258 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	
Venous thromboembolism assessed with: clinical assessment follow-up: 90 days	142 per 1000	**119 per 1000** (72 to 195)	**RR 0.84** (0.51 to 1.37)	333 (4 RCTs)	⊕⊖⊖⊖ Very low[a,b,d]	
Intracerebral haemorrhage (ICH) assessed with: brain imaging and clinical assessment follow-up: 90 days	103 per 1000	**25 per 1000** (4 to 143)	**RR 0.24** (0.04 to 1.38)	119 (2 RCTs)	⊕⊖⊖⊖ Very low[a,e]	
Functional status: mRS 0-2 assessed with: clinical assessment follow-up: 90 days	143 per 1000	**290 per 1000** (111 to 750)	**RR 2.03** (0.78 to 5.25)	73 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_424458755853554175.

[a] The included RCTs have serious risk of bias due to lack of blinding to treatment, and random sequence generation and allocation concealment not being adequately described.
[b] The optimal information size (OIS) criterion is not met. The sample size of this study is probably lower than the minimum number of participants required for a trial adequately powered to identify a statistically significant difference for this outcome.
[c] Very small pooled sample size
[d] Low pooled sample size and event rate
[e] Extremely small pooled sample size

Summary of findings 2

Summary of findings table - Starting long-term therapeutic dose oral anticoagulation compared to avoiding anticoagulation for survivors of stroke due to intracerebral haemorrhage with atrial fibrillation

Starting long-term therapeutic dose oral anticoagulation compared to avoiding anticoagulation for survivors of stroke due to intracerebral haemorrhage with atrial fibrillation

Patient or population: survivors of stroke due to intracerebral haemorrhage with atrial fibrillation
Setting: Secondary care
Intervention: starting long-term therapeutic dose oral anticoagulation
Comparison: avoiding anticoagulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with avoiding anticoagulation	Risk with starting long-term therapeutic dose oral anticoagulation				
Major adverse cardiovascular events (MACE) assessed with: clinical assessment follow-up: range 1 years to 3 years	259 per 1000	**158 per 1000** (104 to 244)	**RR 0.61** (0.40 to 0.94)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	
Death assessed with: clinical assessment follow-up: range 1 years to 3 years	136 per 1000	**143 per 1000** (84 to 242)	**RR 1.05** (0.62 to 1.78)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	
All major occlusive vascular events assessed with: clinical assessment follow-up: range 1 years to 3 years	210 per 1000	**57 per 1000** (29 to 111)	**RR 0.27** (0.14 to 0.53)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	
Intracranial haemorrhage assessed with: clinical assessment follow-up: range 1 years to 3 years	31 per 1000	**75 per 1000** (27 to 208)	**RR 2.43** (0.88 to 6.73)	334 (3 RCTs)	⊕⊕⊕⊖ Moderate[a,c]	
Functional status (mRS 0-2) assessed with: clinical assessment follow-up: 1 years	490 per 1000	**480 per 1000** (382 to 607)	**RR 0.98** (0.78 to 1.24)	288 (2 RCTs)	⊕⊕⊖⊖ Low[b,d]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431448658702855854.

[a] All included randomised trials were open label, but these outcomes were objective.
[b] These are the results of a small number of events being observed in three RCTs with relatively small sample sizes.
[c] The pooled estimate was imprecise due to the small number of outcome events
[d] All included randomised trials were open label, and this outcome was subjective

Summary of findings 3

Summary of findings table - Starting long-term oral antiplatelet therapy compared to avoiding antithrombotic therapy for survivors of stroke due to intracerebral haemorrhage

Starting long-term oral antiplatelet therapy compared to avoiding antithrombotic therapy for survivors of stroke due to intracerebral haemorrhage

Patient or population: survivors of stroke due to intracerebral haemorrhage
Setting: Secondary care
Intervention: starting long-term oral antiplatelet therapy
Comparison: avoiding antithrombotic therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with avoiding antithrombotic therapy	Risk with starting long-term oral antiplatelet therapy				
Major adverse cardiovascular events (MACE) assessed with: clinical assessment follow-up: median 2 years	228 per 1000	**203 per 1000** (146 to 278)	**RR 0.89** (0.64 to 1.22)	536 (1 RCT)	⊕⊕⊕⊖ Moderate[a,b]	
Death assessed with: clinical assessment follow-up: median 2 years	187 per 1000	**201 per 1000** (142 to 285)	**RR 1.08** (0.76 to 1.53)	536 (1 RCT)	⊕⊕⊕⊖ Moderate[a,b]	
All major occlusive vascular events assessed with: clinical assessment follow-up: median 2 years	142 per 1000	**146 per 1000** (96 to 220)	**RR 1.03** (0.68 to 1.55)	536 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	
Intracerebral haemorrhage (ICH) assessed with: clinical assessment follow-up: median 2 years	86 per 1000	**45 per 1000** (23 to 88)	**RR 0.52** (0.27 to 1.03)	536 (1 RCT)	⊕⊕⊕⊖ Moderate[a,b]	
Fnctional status (mRS 0-2) assessed with: clinical assessment follow-up: 1 years	433 per 1000	**411 per 1000** (333 to 511)	**RR 0.95** (0.77 to 1.18)	461 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431448890153987933.

[a] The included randomised trial was open label but outcomes were objective.
[b] Only one randomised trial with 537 participants.

Summary of findings 4

Summary of findings table - Cilostazol compared to aspirin for adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a clinical history of prior intracerebral haemorrhage

Cilostazol compared to aspirin for adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a clinical history of prior intracerebral haemorrhage

Patient or population: adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a clinical history of prior intracerebral haemorrhage
Setting: Secondary care
Intervention: cilostazol
Comparison: aspirin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with aspirin	Risk with cilostazol				
Major adverse cardiovascular events (MACE) assessed with: clinical assessment follow-up: median 1.8 years	116 per 1000	**155 per 1000** (86 to 279)	**RR 1.33** (0.74 to 2.40)	288 (1 RCT)	⨁⨁⊖⊖ Low[a,b]	
Death assessed with: clinical assessment follow-up: median 1.8 years	34 per 1000	**57 per 1000** (19 to 168)	**RR 1.65** (0.55 to 4.91)	288 (1 RCT)	⨁⨁⊖⊖ Low[b]	
All major occlusive vascular events - not reported	-	-	-	-	-	
Intracerebral haemorrhage (ICH) assessed with: clinical assessment follow-up: median 1.8 years	27 per 1000	**35 per 1000** (10 to 128)	**RR 1.29** (0.35 to 4.69)	288 (1 RCT)	⨁⨁⊖⊖ Low[b]	
Functional status - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431449016706363235.

[a] The report of the sub-group of the PICASSO trial did not report major extracerebral haemorrhage, DVT or functional status.
[b] Small sample size from a sub-group of the PICASSO trial

Background

Stroke was the second-leading cause of death worldwide in 2019, when stroke due to spontaneous (non-traumatic) intracerebral haemorrhage (ICH) constituted 28% of all incident strokes and 48% of disability-adjusted life years due to stroke (GBD 2019 Stroke Collaborators 2021). Half of those with ICH die within one year (mostly due to the ICH), leaving 20.7 million prevalent ICH survivors worldwide (GBD 2019 Stroke Collaborators 2021). ICH survivors are at high risk of major adverse cardiovascular events (MACE), such as stroke, myocardial infarction, and death due to a vascular cause. Antithrombotic drugs (Table 1) reduce the risk of

MACE overall for many patients, by reducing the risk of ischaemic events despite an increase in the risk of haemorrhagic events. However, the effects of antithrombotic drugs on ICH survivors are uncertain, which makes this a common therapeutic dilemma in everyday clinical practice.

Description of the condition

Survivors of ICH are at high risk of ischaemic and haemorrhagic MACE. Cerebral small vessel diseases, which underlie more than 85% of ICH (Samarasekera 2015), may also cause ischaemic stroke and vascular dementia. Adults with ICH are approximately 75 years old and usually have high blood pressure (BP), multiple co-morbidities, and other risk factors for ischaemic or haemorrhagic MACE, which have already affected one third of adults before their ICH (GBD 2019 Stroke Collaborators 2021; Li 2021). Survivors of ICH are at higher future risk of ischaemic MACE than population controls (Gaist 2022; Murthy 2021). Overall, the rate of ischaemic MACE appears to exceed the rate of recurrent ICH, and these rates appear higher early after ICH (Banerjee 2020; Li 2021; Poon 2014). If ICH is in a lobar location recurrent ICH is more likely, whereas atrial fibrillation (AF) is the main risk factor for ischaemic stroke after ICH (Banerjee 2020; Casolla 2019; Li 2021; Nielsen 2022). In population-based cohort studies of incident ICH in the UK, the annual rate of MACE ranged from 7% to 19%, dependent on survivors' medical history (Li 2021). These rates are even higher in low-middle income countries (Chen 2020). Most people with MACE after ICH die or are left disabled, so they cause a huge burden on health and care services worldwide (GBD 2019 Stroke Collaborators 2021; Li 2021).

Description of the intervention

The only intervention proven to reduce stroke after ICH is BP lowering (Chapman 2004), and most guidelines focus on prevention of recurrent ICH (AHA ICH guideline 2015; Canadian ICH best practice recommendation 2020; Chinese Stroke Association guidelines 2019; ESO guideline on antithrombotic treatment 2019; ESO ICH Guideline 2014; National Clinical Guideline for Stroke 2016). However, despite widespread implementation of BP lowering after ICH, which has been associated with better BP control and outcome, the annual rate of all MACE for ICH survivors has remained between 7% and 19% in the last two decades (Banerjee 2020; Casolla 2019; Chen 2020; Li 2021; Poon 2014). Therefore, better secondary prevention of all MACE after ICH is needed in standard clinical practice.

Antithrombotic drugs, which have various mechanisms of action (Table 1), are usually dichotomised into antiplatelet and anticoagulant drugs according to their use in clinical practice. These drugs reduce the risk of thrombosis and thromboembolism, but consequently increase the risk of bleeding. Anticoagulation may be prescribed in lower 'prophylactic' doses for prevention of venous thromboembolism for immobile patients, or higher 'therapeutic doses' for prevention of systemic embolism for patients in AF. The anticoagulant drugs used subcutaneously at a lower dose for prophylaxis are the heparin group, whereas the anticoagulants used orally at a therapeutic dose for AF are the vitamin K antagonists, direct thrombin inhibitors, and direct factor Xa inhibitors (Table 1). The antiplatelet drugs used orally for prevention of occlusive vascular events are the platelet aggregation inhibitors (Table 1).

How the intervention might work

Antiplatelet drugs disrupt the formation of platelet plugs. They are used for preventing arterial thromboembolism, such as myocardial infarction or ischaemic stroke. Aspirin achieves this by inhibiting platelet activation, while clopidogrel, cilostazol and tirofiban impede aggregation.

Anticoagulant drugs disrupt the coagulation cascade to stop a fibrin mesh forming around the platelet plug and are generally used to prevent venous thromboembolism. Heparin and enoxaparin bind to a naturally occurring anticoagulant (antithrombin) to amplify its effect, while direct (non-vitamin K) oral anticoagulants (DOACs) and warfarin directly inhibit the coagulation cascade.

Antithrombotic drugs also increase the risk of bleeding as a result of their effect on clotting and platelet aggregation.

Although antithrombotic drugs are known to be of net benefit (i.e. when considering their effects on both clotting and bleeding) in people without a history of bleeding (Antithrombotic Trialists' Collaboration 2009; Benz 2021; Hart 2007), the balance of benefit and harm is uncertain after ICH.

Why it is important to do this review

People with ICH were excluded from randomised controlled trials (RCTs) of prophylactic dose anticoagulation after acute stroke (Wang 2021), and secondary prevention of MACE with antiplatelet therapy (Antithrombotic Trialists' Collaboration 2009; Benz 2021), or therapeutic dose anticoagulation for AF (Hart 2007).

A network meta-analysis of RCTs of pharmacological thromboprophylaxis versus intermittent pneumatic compression to prevent venous thromboembolism after ICH was unable to make meaningful comparisons between prophylactic dose anticoagulation and the current clinical standard of care with intermittent pneumatic compression (Yogendrakumar 2020).

A systematic review and meta-analysis of cohort studies of patients with any type of intracranial haemorrhage (i.e. intracerebral, subarachnoid, or subdural haemorrhage) found lower risks of ischaemic MACE (RR 0.61, 95% CI 0.48 to 0.79) and no evidence of a difference in haemorrhagic MACE risk (RR 0.84, 95 %CI 0.47 to 1.51) associated with resumption compared with avoidance of antiplatelet therapy (Ding 2018).

A systematic review and meta-analysis of cohort studies of patients with spontaneous intracranial haemorrhage and AF comparing oral anticoagulation with either antiplatelet agents or no antithrombotic therapy mostly found associations between oral anticoagulation and lower risks of ischaemic MACE, but no significant change in the risk of haemorrhagic MACE, although these studies are susceptible to selection bias (Korompoki 2017).

The evidence available has left guidelines unable to recommend antithrombotic drugs after ICH (AHA ICH guideline 2015; Canadian ICH best practice recommendation 2020; Chinese Stroke Association guidelines 2019; ESO ICH Guideline 2014; ESO guideline on antithrombotic treatment 2019; National Clinical Guideline for Stroke 2016). Consequently, there has been variation in clinical practice, evident from the proportion of patients starting antithrombotic drugs after ICH varying between 11% to 45% in different countries (Pasquini 2014).

In the most recent version of this Cochrane review, we analysed two RCTs including 121 participants, and concluded that there was insufficient evidence from RCTs to support or discourage the use of antithrombotic treatment after ICH (Perry 2017). However, several RCTs have been published since the first version of this review, so we performed this update.

Objectives

To determine the overall effectiveness and safety of antithrombotic drugs on major adverse cardiovascular events (MACE) and its components for people with ICH.

Methods

Criteria for considering studies for this review

Types of studies

We sought all RCTs that made comparisons of starting versus avoiding antithrombotic drugs, or direct comparisons of different antithrombotic classes or agents after stroke due to ICH. We included RCTs published in any language and planned to arrange translation where the language of publication was not English.

Types of participants

Eligible patients survived spontaneous ICH in the brain parenchyma diagnosed by CT or MRI scan. We included patients regardless of whether they were on antithrombotic therapy at the time of ICH.

Types of interventions

We sought RCTs that compared starting any antithrombotic drug with avoiding antithrombotic treatment, as well as RCTs that compared different antithrombotic classes or agents (Table 1). We placed no constraints on dosage, route of administration, or duration of administration. We separated RCTs investigating short-term treatment (e.g. with low-molecular-weight heparin or unfractionated heparin to prevent venous thromboembolism early after ICH onset) from those RCTs investigating long-term secondary prevention (e.g. with oral anticoagulant or antiplatelet drugs).

If the effects of antithrombotic drugs might have been confounded by the administration of another active drug to participants (e.g. if allocation to this additional treatment was not evenly distributed between groups in an RCT, or was not randomly allocated) we planned to explore this in our risk of bias assessment and in sensitivity analyses.

Types of outcome measures

We restricted inclusion to RCTs reporting our clinical primary or secondary outcomes (after seeking information about these outcomes if they were not included in the report of the RCT).

Primary outcomes

Composite outcome of all serious vascular events, commonly known as MACE (which we defined as ischaemic stroke, myocardial infarction, other major ischaemic event, ICH, major extracerebral haemorrhage, or vascular death) during the scheduled follow-up period.

Secondary outcomes

- Death during the scheduled follow-up period.
- The individual components of the composite MACE primary outcome: ischaemic stroke, myocardial infarction, other major ischaemic event (deep vein thrombosis, pulmonary embolism or venous thromboembolism), ICH, major extracerebral haemorrhage, and vascular death.

- Growth of ICH (as classified/reported by each RCT).
- Functional status (where measured using validated scales, such as the modified Rankin Scale) at the end of the scheduled follow-up period.
- Cognitive status (where measured using validated scales, such as the Montreal Cognitive Assessment or the Mini-mental State Examination) at the end of the scheduled follow-up period.

Search methods for identification of studies

We searched for RCTs in any language and planned to arrange for the translation of relevant articles where necessary.

Electronic searches

We designed a search strategy with the help of the Cochrane Stroke Group's Information Specialist, who ran the searches on the 5 October 2021.

We searched the following electronic databases:

- Cochrane Stroke Group Trials Register
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 10) in the Cochrane Library
- MEDLINE Ovid, 1946 to October 2021
- Embase Ovid, 1946 to October 2021

We searched the following online registries of clinical trials:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 5 October 2021)
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch; searched 5 October 2021)
- In the previous version of this review, we searched the Stroke Trials Registry of the Internet Stroke Center (www.strokecenter.org/trials/) on 2 March 2017.

Searching other resources

We screened the reference lists of relevant studies to identify RCTs for potential inclusion in the review. In the event that we could not locate the full text of a RCT, or required a specific data extract, we contacted the researchers or the relevant data sharing platform.

Data collection and analysis

We imported the results of the searches into Covidence, removed duplicates, and applied the following methods to select, extract and analyse data. RASS was not involved in decisions about included studies for which he was the Chief Investigator (RESTART 2019 and SoSTART 2021); decisions about these studies were made by AC, CC, and co-authors without a competing interest.

Selection of studies

Two review authors (AC and CC) independently screened titles and abstracts and full texts for eligibility, resolving conflicts by discussion with a third review author to reach consensus.

We retrieved full-text articles for potentially eligible references, and the same three review authors independently screened these full-text articles to identify RCTs for inclusion, and identified and recorded reasons for the exclusion of ineligible studies. We resolved any disagreements through discussion. We collated multiple reports of the same RCT, and chose the report at lowest risk of bias, so that each RCT was the unit of interest.

We recorded the cumulative results of the searches and the selection process (i.e. including the prior version of this review Perry 2017) and completed a flow diagram (Figure 1).

Data extraction and management

We created and independently completed an electronic data collection form in Microsoft Word (that had been piloted and used for the prior version of this review) for each included RCT. Two review authors (CC and AC) extracted data from included studies independently on methods, risk of bias, participant characteristics, intervention, comparator, and outcomes. We extracted outcome event frequencies without the need for transformation. Another review author checked all data extraction, queried errors, and agreed the final results in discussion with CC and AC.

We sought and obtained unpublished data from one RCT (NASPAF-ICH 2020). We sought the data on a subgroup of participants with prior ICH from another RCT (ELDERCARE-AF 2020), but data sufficient for analysis were not provided by the study Sponsor via the Vivli data sharing platform in time for inclusion in this review.

Assessment of risk of bias in included studies

Two review authors (AC and CC) assessed risks of bias for each study independently using the RoB 1 tool and the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Another review author reviewed all classifications, and achieved consensus via discussion. We assessed the risks of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other potential bias

We graded the risk of bias for each domain as high, low or unclear and provide information from the study report, together with a justification for our judgement, in the risk of bias tables.

Measures of treatment effect

We converted categorical data using numeric frequencies of outcomes and group sizes to estimates of effect using the risk ratio (RR), without adjustment.

Unit of analysis issues

Repeated observations on participants

We planned to analyse functional and cognitive status at end of follow-up or a period of follow-up available for all RCTs being pooled, and not to use repeat observations during follow-up. If one RCT (or only a few RCTs) had a much longer period of follow-up than the majority of RCTs

(e.g. two years compared with six months in the majority of trials) we intended to perform a sensitivity analysis using the six-month observations from all RCTs.

Events that may recur

We analysed the first event in all participants, and not later events.

Multiple intervention groups

Where a RCT contained multiple treatment groups that were all compared with just one control group, we intended to ensure that the control group was shared between the multiple treatment groups by dividing it into the appropriate number of subgroups and conducting separate, independent comparisons.

Dealing with missing data

We intended to contact RCT authors for unpublished data if relevant data were missing. If only a minority (less than half) of data were missing, we planned to ignore the missing data and perform a 'complete set analysis'. If more substantial amounts of data were missing, and there was a chance that data were not missing at random, we planned to perform sensitivity analyses assuming both a best-case and a worst-case scenario, or apply statistical imputation or models, or both, to account for the missing data. A best-case scenario meant that we assumed that all missing data in the intervention group represent good outcomes and all missing data in the control group represent poor outcomes. A worst-case scenario meant that we assumed that all missing data in the intervention group represent poor outcomes and all missing data in the control group represent good outcomes.

Assessment of heterogeneity

We investigated heterogeneity between included RCTs using the I^2 statistic. We interpreted this value using the guide provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022):

- 0% to 74%: inconsiderable heterogeneity
- 75% to 100%: considerable heterogeneity

If we observed considerable heterogeneity in our data, we intended to use sensitivity analysis to elucidate which factors might explain the heterogeneity.

Assessment of reporting biases

We included all published and unpublished data and secondary publications from RCTs. If we had included a sufficient number of RCTs (more than 10), we planned to assess the likelihood of reporting biases through the use of a funnel plot.

Data synthesis

We included RCTs regardless of their risk of bias. If RCTs were sufficiently similar, we planned to conduct a meta-analysis by pooling the appropriate data using RevMan Web (RevMan Web 2022). We calculated the RR for each outcome from data extracted from included RCTs using a fixed-effect model, or a random-effects model if there was considerable qualitative or quantitative heterogeneity ($I^2 \geq 75\%$).

Subgroup analysis and investigation of heterogeneity

We pre-specified the following subgroup analyses, which could modify the effects of antithrombotic drugs on ischaemic or haemorrhagic clinical outcome events.

- Participants
    - age
    - sex
    - stroke severity
- Different classes of antithrombotic drugs (antiplatelet versus anticoagulant)
- Different intensities of antithrombotic treatment (low dose versus high dose)
- Different times of starting treatment (e.g. within one month of ICH versus later, or within 10 to 30 weeks or later)
- Participants who were on antithrombotic treatment before ICH (restarters) versus participants who were not receiving these treatments before ICH (starters)
- Different levels of risk for future ischaemic events (e.g. because of differences in age, sex, history of hypertension, history of AF (with further stratification by the CHA_2DS_2-VASc score))
- Different levels of risk for future ICH (lobar versus non-lobar ICH location)
- Biomarkers of bleeding or clotting risk on brain computed tomography (CT) or magnetic resonance imaging (MRI) (e.g. brain microbleeds on MRI)

Sensitivity analysis

If there was considerable qualitative or quantitative evidence of heterogeneity, we planned to use sensitivity analysis to investigate how the results differed when we excluded RCTs (e.g. those with a high risk of bias). We planned to perform other sensitivity analyses to explore reasons for heterogeneity, for example, where there is an active co-intervention other than an antithrombotic drug that is not balanced by the randomisation process.

Summary of findings and assessment of the certainty of the evidence

Outcome importance: Given the number of pre-specified outcomes and comparisons in this review, we prioritised the five following clinically important outcomes for reporting in the Summary of findings tables and abstract: (1) MACE, (2) death, (3) major occlusive vascular events, (4) ICH, and (5) functional outcome.

Summary of findings: We created summary of findings tables using the GRADEpro Guideline Development Tool (GRADEpro GDT).

Certainty of the evidence: We classified the certainty of the evidence as being 'high', 'moderate', 'low', or 'very low', based on the presence and extent of the following five criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022):

- limitations in the design and implementation of the contributing trials;
- indirectness of evidence;
- unexplained heterogeneity of results;

- imprecision of results;
- high probability of publication bias.

We provided justification in the footnotes when we downgraded the certainty from 'high'.

Results

Description of studies

After screening 10,635 records (Figure 1), we excluded 10,586, assessed 49 full text articles (20 of which were duplicate records), excluded 12 RCTs (Excluded studies), identified eight ongoing RCTs (Ongoing studies), and included nine RCTs in qualitative and quantitative syntheses (Included studies).

Results of the search

We included nine parallel-group RCTs in our review (APACHE-AF 2021; Dickmann 1988; NASPAF-ICH 2020; Orken 2009; PICASSO sub-group 2020; PREVENTIHS 2020; Qian 2021; RESTART 2019; SoSTART 2021).

We grouped these RCTs for description and analysis into four groups:

- short-term prophylactic dose anticoagulation (start versus avoid);
- long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid);
- long-term antiplatelet therapy (start versus avoid);
- long-term antiplatelet therapy (cilostazol versus aspirin).

Short-term prophylactic dose anticoagulation (start versus avoid)

Dickmann 1988 took place in inpatient units in Germany. All 46 participants were administered 5000 units of heparin every eight hours, with the intervention group starting at day four after ICH and the control group at day 10. Re-bleeding, thrombosis, pulmonary embolism and death were recorded until day 10.

Orken 2009 took place in Turkey and randomised 75 participants 48 hours after admission to 48 mg enoxaparin per day or compression stockings. Outcomes were measured on day seven and 21.

PREVENTIHS 2020 was conducted in Italian hospitals. The trial was discontinued because of low recruitment rates, but randomised 73 patients to 4000 units of enoxaparin or no treatment. Outcomes were measured up to day 90.

Qian 2021 took place in Helsinki and randomised 139 patients to the intervention of 2000 units of enoxaparin 12 or 24 hours after ICH, or to the placebo group who received saline injections. After the initial 72 hours, both groups received treatment with the same does of enoxaparin. Outcomes were measured up to day 90 after ICH.

Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid)

NASPAF-ICH 2020 took place in Canada. It compared the effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) to aspirin in 30 participants with prior ICH and AF randomised in a 2:1 ratio. Outcomes were measured between 10.5 months and 2.8 years after ICH.

SoSTART 2021 took place in the UK, included 203 participants who had AF and recent ICH, randomly assigned them to either start or avoid an oral anticoagulant (34 (33%) of the participants in the avoid oral anticoagulation group took antiplatelet monotherapy), and identified outcomes for up to three years after randomisation.

APACHE-AF 2021 took place in the Netherlands, recruited 101 participants who had recent ICH and were already taking anticoagulation for AF, randomly assigned them to apixaban 5 mg twice daily or to avoid oral anticoagulation (26 (51%) of the participants in the avoid oral anticoagulation group took antiplatelet therapy), and identified outcomes for up to three years after randomisation.

Long-term antiplatelet therapy (start versus avoid)

RESTART 2019 took place in the UK and included 537 participants who had been taking an antithrombotic drug until the time of ICH, and randomised them to starting or avoiding antiplatelet therapy. Participants were followed up for a minimum of six months.

Long-term antiplatelet therapy (cilostazol versus aspirin)

PICASSO sub-group 2020 was a separate report of a subgroup of a factorial trial which took place in 67 centres in Asian countries. The subgroup included 268 patients with history of ICH, randomised to cilostazol or aspirin either with or without probucol.

Excluded studies

Excluded studies

We excluded 10 RCTs.

Boeer 1991 was an extension phase of Dickmann 1988, but randomisation was not described.

CAST 1997 and IST 1997 were two RCTs investigating the use of antiplatelet treatment after acute ischaemic stroke, and inadvertently included several hundred participants with ICH who were randomised before CT had been performed to establish the pathological subtype of stroke. Data on the ICH subpopulation of these studies were reported in a systematic review (Keir 2002) and the individual patient data from IST 1997 (Sandercock 2011). These sources reported that this population included spontaneous ICH (52%) and haemorrhagic transformation of ischaemic stroke (48%), but unfortunately the chief investigator informed us that it would be impossible to isolate the participants with spontaneous ICH (IST 1997).

Frontera 2014 and Kuramatsu 2018 were not randomised.

Li 2013 assessed transfusion of frozen apheresis platelets in patients with ICH and on aspirin.

Venturelli 2014 was a post-hoc analysis of a RCT in which antithrombotic treatment was not randomly assigned, making this analysis observational in nature.

Yan 2014 included a population of patients with and without cerebral microbleeds after acute ischaemic stroke, but not ICH.

RESTART extended follow-up was a two-year extension of RESTART 2019, but participants and their primary care practitioners had been told the results of RESTART 2019, which put the extended follow-up at higher risk of bias than the main report, so we included RESTART

2019 and excluded RESTART extended follow-up.

ChiCTR2000040166 used two traditional Chinese medicines which are not proven to have antithrombotic effects and therefore did not meet the criteria for the review.

Studies awaiting classification

ELDERCARE-AF 2020 and PRAGUE-17 2020 were suitable for inclusion in our review, but ELDERCARE-AF 2020 did not provide data that were sufficient for accurate analysis and the corresponding author of PRAGUE-17 2020 was unable to provide the data for the subgroup of patients with prior ICH in time for inclusion in this review, so these studies are categorised as Studies awaiting classification.

Risk of bias in included studies

We assessed all included RCTs for their risk of bias (Figure 2).

Allocation

Sixty-seven per cent of included RCTs were at low risk of bias in random sequence generation.

Sixty-seven per cent of included RCTs were at low risk of bias in allocation concealment.

Blinding

Twenty-two per cent of included RCTs were at low risk of performance bias due to blinding of participants and personnel.

Seventy-eight per cent of included RCTs were at low risk of detection bias in blinding of outcome assessment.

Incomplete outcome data

Eighty-nine per cent of included RCTs were at low risk of attrition bias.

Selective reporting

Seventy-eight per cent of included RCTs were at low risk of reporting bias.

Other potential sources of bias

We did not identify any other major sources of bias.

Effects of interventions

Short-term prophylactic dose anticoagulation (start versus avoid)

We included four RCTs, all of which compared a parenteral anticoagulant to no treatment, although there was considerable qualitative heterogeneity between the RCTs' interventions, comparators, and timing of assessment, so we used random-effects models to pool their effect estimates (Dickmann 1988; Orken 2009; PREVENTIHS 2020; Qian 2021). We present our summary of findings in Summary of findings table 1. We did not need to make post-hoc decisions that could have led to selective outcome reporting.

Primary outcome

We were unable to extract data on our primary outcome and some secondary outcomes (ischaemic stroke, myocardial infarction, vascular death, and cognitive status) from any of the RCTs, and we did not succeed in obtaining these outcomes from the corresponding authors.

Secondary outcomes

We did not find significant differences with starting versus avoiding short-term prophylactic dose anticoagulation in the secondary outcomes that were reported.

- Death of any cause (23/132 versus 22/126; RR 1.00, 95% CI 0.59 to 1.70, P = 1.00; 3 published RCTs; 258 participants; very low-certainty evidence; Analysis 1.1).
- We considered the relevant clinically important composite of major occlusive events for this treatment comparison to be venous thromboembolism (21/171 versus 23/162; RR 0.84, 95% CI 0.51 to 1.37, P = 0.49; 4 published RCTs; 333 participants; very low-certainty evidence; Analysis 1.4).
- ICH (1/61 versus 6/58; RR 0.24, 95% CI 0.04 to 1.38, P = 0.11; 2 published RCTs; 119 participants; very low-certainty evidence; Analysis 1.5).
- Functional independence, graded 0-2 on the modified Rankin Scale (mRS) score (11/38 versus 5/35; RR 2.03, 95% CI 0.78 to 5.25, P = 0.15; 1 published RCT; 73 participants; very low-certainty evidence; Analysis 1.8).
- ICH growth (8/110 versus 8/104; RR 0.96, 95% CI 0.38 to 2.41, P = 0.93; 2 published RCTs; 214 participants; Analysis 1.7).
- Major extracerebral haemorrhage (1/148 versus 0/139; RR 2.77, 95% CI 0.12 to 65.82, P = 0.53; 3 published RCTs; 287 participants; Analysis 1.6).
- Deep vein thrombosis (13/133 versus 12/127; RR 0.96, 95% CI 0.49 to 1.86, P = 0.9; 3 published RCTs; 260 participants; Analysis 1.2).
- Pulmonary embolism (6/171 versus 13/162; RR 0.50, 95% CI 0.22 to 1.14, P = 0.1; 4 published RCTs; 333 participants; Analysis 1.3).

Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid)

We included three RCTs, all of which compared long-term therapeutic dose of an oral anticoagulant (almost exclusively DOACs) to avoidance of anticoagulation (in which some patients took long-term antiplatelet therapy and others avoided all antithrombotic drugs) (APACHE-AF 2021; NASPAF-ICH 2020; SoSTART 2021). We present our summary of findings in Summary of findings table 2. We did not need to make post-hoc decisions that could have led to selective outcome reporting.

Primary outcome

We found a significant reduction in the composite primary outcome of MACE with starting versus avoiding long-term oral anticoagulation (26/172 versus 42/162; RR 0.61, 95% CI 0.40 to 0.94, P = 0.02; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.1).

Secondary outcomes

The effects of starting versus avoiding long-term oral anticoagulation for atrial fibrillation on secondary outcomes were:

- Death (24/172 versus 22/162; RR 1.05, 95% CI 0.62 to 1.78, P = 0.86; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.2).
- Major occlusive vascular events (9/172 versus 34/162; RR 0.27, 95% CI 0.14 to 0.53, P = 0.0002; 3 RCTs; moderate-certainty evidence; Analysis 2.5)
- Intracranial haemorrhage (12/172 versus 5/162; RR 2.43, 95% CI 0.88 to 6.73, P = 0.09; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.6).
- Functional independence, graded 0-2 on the modified Rankin Scale (mRS) score (11/38 versus 5/35; RR 0.98, 95% CI 0.78 to 1.24, P = 0.87; 2 published RCTs; 288 participants; very low-certainty evidence; Analysis 2.9).
- Myocardial infarction (0/172 versus 4/162; RR 0.20, 95% CI 0.02 to 1.71, P =0.14; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.4).
- Major extracerebral haemorrhage (2/172 versus 3/162; RR 0.58, 95 %CI 0.13 to 2.57, P = 0.47; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.7).
- Ischaemic stroke (9/172 versus 26/162; RR 0.35, 95% CI 0.17 to 0.71; P = 0.004; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.3).
- Vascular death (13/172 versus 9/162; RR 1.47, 95% CI 0.65 to 3.32, P = 0.36; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.8).
- Modified Rankin Scale score 0 to 2 at one year (69/143 versus 71/145; RR 0.98, 95% CI 0.78 to 1.24, P = 0.87; 2 published RCTs; 288 participants; moderate-certainty evidence; Analysis 2.9).
- Any stroke (21/172 versus 30/162; RR 0.70, 95% CI 0.42 to 1.15, P = 0.16; 2 published and 1 unpublished RCTs; 334 participants; moderate-certainty evidence; Analysis 2.10).
- Any stroke or vascular death (25/151 versus 35/153; RR 0.72, 95% CI 0.46 to 1.15, P = 0.17; 2 published RCTs; 304 participants; moderate-certainty evidence; Analysis 2.11).

Long-term antiplatelet therapy (start versus avoid)

We included one RCT which compared long-term antiplatelet therapy (with aspirin ± dipyridamole ± clopidogrel) to avoidance of antithrombotic therapy in 537 participants, one of whom withdrew from follow-up (RESTART 2019). We present our summary of findings in Summary of findings table 3. We did not need to make post-hoc decisions that could have led to selective outcome reporting.

Primary outcome

We did not find a significant difference in the composite primary outcome of MACE with starting versus avoiding long-term oral antiplatelet therapy (54/268 versus 61/268; RR 0.89, 95% CI 0.64 to 1.22, P = 0.46; 1 published RCT; 536 participants; moderate-certainty evidence; Analysis 3.1).

Secondary outcomes

The effects of starting versus avoiding long-term oral antiplatelet therapy on secondary outcomes were:

- Death (54/268 versus 50/268; RR 1.08, 95% CI 0.76 to 1.53, P = 0.66; 1 published RCT; 536 participants; moderate-certainty evidence; Analysis 3.2).
- All major occlusive vascular events (39/268 versus 38/268; RR 1.03, 95% CI 0.68 to 1.55, P = 0.90; 1 published RCT; moderate-certainty evidence; Analysis 3.5).
- ICH (12/268 versus 23/268; RR 0.52, 95% CI 0.27 to 1.03, P = 0.06; 1 published RCT; 536 participants; moderate-certainty evidence; Analysis 3.6).
- Functional independence, graded 0-2 on the modified Rankin Scale (mRS) score (95/230 versus 100/231; RR 0.95, 95% CI 0.77 to 1.18, P = 0.67; 1 RCT; moderate-certainty evidence; Analysis 3.9).
- Major vascular events as defined by the Antithrombotic Trialists' Collaboration (45/268 versus 65/268; RR 0.69, 95% CI 0.49 to 0.97; P = 0.03; 1 published RCT; 536 participants; moderate-certainty evidence; Analysis 3.12).
- Major extracerebral haemorrhage (8/268 versus 3/268; RR 2.67, 95% CI 0.72 to 9.94, P = 0.14; 1 published RCT; moderate-certainty evidence; Analysis 3.7).
- Ischaemic stroke (19/268 versus 27/268; RR 0.70, 95% CI 0.40 to 1.23, P = 0.22; 1 published RCT; moderate-certainty evidence; Analysis 3.3).
- Myocardial infarction (5/268 versus 8/268; RR 0.63, 95% CI 0.21 to 1.89, P = 0.40; 1 published RCT; moderate-certainty evidence; Analysis 3.4).
- Deep vein thrombosis (6/268 versus 2/268; RR 3.00 (95% CI 0.61 to 14.73, P = 0.18; 1 published RCT; moderate-certainty evidence; Analysis 3.10).
- Vascular death (18/268 versus 27/268; RR 0.67 (95% CI 0.38 to 1.18, P = 0.16; 1 published RCT; moderate-certainty evidence; Analysis 3.8).
- All major haemorrhagic events (18/268 versus 25/268; RR 0.72 (95% CI 0.40 to 1.29, P = 0.27; 1 published RCT; moderate-certainty evidence; Analysis 3.11).

Long-term antiplatelet therapy (cilostazol versus aspirin)

We included a subgroup of one RCT including adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a high risk of bleeding (PICASSO 2018), in which the reporting of outcomes for 288 participants with prior ICH was separate from the other participants (PICASSO sub-group 2020). We present our summary of findings for this sub-group in Summary of findings table 4. We did not need to make post-hoc decisions that could have led to selective outcome reporting.

Primary outcome

We did not find a significant difference in the composite primary outcome of MACE with long-term cilostazol versus aspirin (22/142 versus 17/146; RR 1.33, 95% CI 0.74 to 2.40), P = 0.34; 1 published RCT; 288 participants; low-certainty evidence; Analysis 4.1).

Secondary outcomes

The effects of long-term cilostazol versus aspirin on secondary outcomes were:

- Death (8/142 versus 5/146; RR 1.65, 95% CI 0.55 to 4.91, P = 0.37; 1 published RCT; 288 participants; low-certainty evidence; Analysis 4.2).

- ICH (5/142 versus 4/146; RR 1.29, 95% CI 0.35 to 4.69, P = 0.70; 1 published RCT; 288 participants; low-certainty evidence; Analysis 4.5).
- All major occlusive vascular events were not reported.
- Functional status was not reported.
- Ischaemic stroke (12/142 versus 13/146; RR 0.95, 95% CI 0.45 to 2.01, P = 0.89; 1 published RCT; 288 participants; moderate-certainty evidence; Analysis 4.3).
- Myocardial infarction (5/142 versus 0/146; RR 11.31, 95% CI 0.63 to 202.63, P = 0.10; 1 published RCT; 288 participants; moderate-certainty evidence; Analysis 4.4).
- Vascular death (3/142 versus 0/146; RR 7.35, 95% CI 0.38 to 143.61, P = 0.19; 1 published RCT; 288 participants; moderate-certainty evidence; Analysis 4.6).
- Any stroke (16/142 versus 17/146; RR 0.97, 95% CI 0.51 to 1.84, P = 0.92; 1 published RCT; 288 participants; moderate-certainty evidence; Analysis 4.7).

Subgroup analyses

We did not extract subgroup data from comparisons addressed by only one RCT, each of which was under-powered to estimate overall effects. Subgroups of interest were not reported for RCTs of short-term prophylactic dose anticoagulation. Two RCTs of long-term therapeutic dose anticoagulation for AF reported data in subgroups (APACHE-AF 2021; SoSTART 2021); however, the classifications of the subgroups and outcomes reported did not permit pooling of data for subgroup analysis.

Discussion

In this updated review, we found seven new completed RCTs for a total of nine completed RCTs including 1491 participants, addressing four distinct questions about antithrombotic treatment after ICH:

- short-term prophylactic dose anticoagulation (start versus avoid);
- long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid);
- long-term antiplatelet therapy (start versus avoid);
- long-term antiplatelet therapy (cilostazol versus aspirin).

Summary of main results

Short-term prophylactic dose anticoagulation (start versus avoid)

No RCT reported this review's primary outcome of MACE. The evidence is very uncertain about the effect of starting short-term prophylactic dose anticoagulation on death, venous thromboembolism, ICH and independent functional status over 90 days.

Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid)

Starting long-term therapeutic dose oral anticoagulation for AF after ICH probably reduces MACE (RR 0.61, 95% CI 0.40 to 0.94, P = 0.02; 3 RCTs; moderate-certainty evidence) and probably reduces all major occlusive events (RR 0.27, 95% CI 0.14 to 0.53, P = 0.0002; 3

RCTs; moderate-certainty evidence), but probably results in little or no difference in death, probably increases intracranial haemorrhage, and may result in little to no difference in independent functional status.

Long-term antiplatelet therapy (start versus avoid)

The evidence is uncertain about the effects of starting long-term antiplatelet therapy after ICH on MACE, death, all major occlusive events, ICH, and independent functional status.

Long-term antiplatelet therapy (cilostazol versus aspirin)

For adults within 180 days of non-cardioembolic ischaemic stroke or transient ischaemic attack and a clinical history of prior ICH, there was no evidence of an effect of long-term cilostazol compared to aspirin on MACE, death, or ICH. All major occlusive vascular events and functional status were not reported.

Overall completeness and applicability of evidence

All data were available for RCTs of short-term prophylactic dose anticoagulation. The included RCTs were representative of clinical practice in Italy, Germany, Turkey and Finland.

Data sufficient for analysis were not provided by the authors of ELDERCARE-AF 2020 and PRAGUE-17 2020. ELDERCARE-AF 2020 shared the entire trial dataset, but we were unable to extract data on the subgroup of 80 participants with ICH, which would have increased the data in our pooled analyses of the effects of long-term therapeutic dose oral anticoagulation for AF by 80/334 (24%). The RCTs that were included reflected standard clinical practice in the UK, the Netherlands and Canada.

The number of patients with prior ICH in PRAGUE-17 2020 was not reported and was not quantified by the corresponding author in communication with us; this RCT would have been the only RCT contributing data to a new comparison of DOAC versus left atrial appendage closure for AF after ICH.

Only one RCT addressed long-term antiplatelet therapy after ICH, and this was based in the UK (RESTART 2019).

Only one RCT compared different types of antiplatelet therapy after ICH, and this was based in South Korea, Hong Kong, and the Philippines (PICASSO sub-group 2020).

Quality of the evidence

The methodological quality of the included RCTs varied, and tended to be best for the RCTs comparing starting versus avoiding long-term therapeutic dose oral anticoagulation for AF after ICH and the RCT comparing starting versus avoiding long-term antiplatelet therapy after ICH.

Most RCTs did not blind patients and professionals to treatment allocation, so the body of evidence was most vulnerable to performance bias, although all of our outcomes were objective with the exception of functional status. The proportion of included RCTs at low risk of bias, by category was: random sequence generation (67%), allocation concealment (67%), performance (22%), detection (78%), attrition (89%), and reporting (78%).

Heterogeneity between the RCTs' results varied according to the comparisons and outcomes being analysed, but I^2 was less than 75% for all 15 analyses that pooled at least two RCTs.

The risk of bias of the included RCTs and the imprecision of individual or pooled RCTs meant that the GRADE certainty of evidence was very low for RCTs of short-term prophylactic dose anticoagulation, low-moderate for RCTs of long-term therapeutic dose oral anticoagulation for AF, moderate for long-term antiplatelet therapy and low for long-term cilostazol versus aspirin.

Potential biases in the review process

We minimised the effects of publication bias by conducting extensive searches for published and unpublished RCTs, reviewing bibliographies for additional RCTs, and by seeking missing data directly from authors.

We minimised selection bias by involving two review authors in study selection and data extraction, with arbitration and independent checking by a third review author.

We collected data for all outcomes that were reported (and added pulmonary embolism, venous thromboembolism, and various variants of the MACE composite outcome relevant to the assessment of efficacy and net benefit).

Agreements and disagreements with other studies or reviews

We identified two systematic reviews of short-term antithrombotic treatment after ICH in RCTs (Keir 2002; Paciaroni 2011), and a third systematic review of long-term antiplatelet therapy after ICH (Cheng 2021).

Keir 2002 included individual participant data from IST 1997 and CAST 1997 on participants with not only ICH (52%), but also haemorrhagic transformation of cerebral infarction (48%), although it did not describe results for patients with ICH alone, who are the focus of this systematic review. This review's conclusions did not differ from ours.

Paciaroni 2011 and Cheng 2021 pooled non-randomised studies as well as RCTs, which is a less methodologically rigorous approach than pooling RCTs alone. These reviews' conclusions did not differ from ours.

Authors' conclusions

Implications for practice

On the basis of the available evidence, we could not be certain about benefit or harm from antithrombotic treatment after intracerebral haemorrhage (ICH).

We did not identify beneficial or hazardous effects of short-term prophylactic dose parenteral anticoagulation on our primary or secondary outcomes, so there are no implications for clinical practice.

The reduction of MACE overall and ischaemic stroke by long-term treatment with therapeutic dose oral anticoagulation for atrial fibrillation after ICH provides some reassurance for the use of this treatment (Analysis 2.1). However, the pooled estimate was imprecise, none of the individual RCTs was conclusive, there was some heterogeneity between the RCTs, we were only moderately certain about the evidence, and the possibility of an increase in recurrent ICH remains, so we cannot identify specific implications for clinical practice.

Clinical guidelines that are being updated following the publication of these RCTs are yet to publish their recommendations for clinical practice (AHA ICH guideline 2015; ESO ICH Guideline 2014; National Clinical Guideline for Stroke 2016).

We did not identify beneficial or hazardous effects of starting versus avoiding long-term oral antiplatelet therapy, or particular antiplatelet agents, after ICH on the primary outcome of MACE. However, the results of RESTART 2019 provide some reassurance about the hazards of antiplatelet therapy after ICH (Analysis 3.6) as well as the potential for a reduction in stroke, myocardial infarction or vascular death (Analysis 3.12; Antithrombotic Trialists' Collaboration 2009). Consequently, guidelines that followed the publication of RESTART 2019 have concluded that antiplatelet therapy may be considered for survivors of antithrombotic drug-associated ICH (Canadian ICH best practice recommendation 2020; Chinese Stroke Association guidelines 2019).

Implications for research

More RCTs are required to resolve the ongoing uncertainties about antithrombotic treatment after ICH. These RCTs should be at low risk of bias and sufficiently large to reliably exclude or confirm the direction and magnitude of the effects suggested by our pooled analyses of pilot phase RCTs. Even if some of these RCTs recruit an insufficient sample size to be conclusive in their own right, their data will contribute substantially to a further update of this Cochrane review, which will increase the precision and certainty of the pooled estimates of effects.

We are not aware of any ongoing RCTs investigating the effects of starting versus avoiding short-term prophylactic dose anticoagulation after ICH. Further RCTs seem justified if there is uncertainty in clinical practice about using prophylactic dose anticoagulation in addition to intermittent pneumatic compression in clinical practice.

Several ongoing RCTs are investigating the effects of starting versus avoiding long-term therapeutic dose oral anticoagulation for atrial fibrillation after ICH (NCT03186729; NCT03243175; NCT03907046; NCT03950076; PRESTIGE-AF). Some of these RCTs may be conclusive in their own right when completed, but together they should certainly provide sufficient data for an update of this Cochrane review to be conclusive about our primary and secondary outcomes. Further RCTs do not appear to be required to investigate effects overall, but large numbers of participants will be required to investigate heterogeneity of effects in subgroups. The emphasis should be on completing recruitment to the ongoing RCTs as soon as possible.

Some ongoing RCTs are investigating the effects of starting versus avoiding long-term antiplatelet therapy after ICH (NCT02966119; NCT03186729; NCT04522102; NCT04820972). However, the sample sizes of these RCTs make each of them very unlikely to be definitive about effects on our primary and secondary outcomes, and they are unlikely to be definitive when pooled, since NCT04522102 estimates that more than 4,000 participants are required to generate definitive evidence about starting versus avoiding long-term antiplatelet therapy after ICH. Therefore, a further, large, definitive RCT seems justified to investigate effects both overall and in subgroups. If starting antiplatelet therapy proves to be beneficial, then further RCTs comparing different antiplatelet agents would be justified.

Only one ongoing RCT is comparing the effects of long-term therapeutic dose oral anticoagulation for AF after ICH to the left atrial appendage closure device (NCT03243175), although another RCT is comparing the left atrial appendage closure device to any antithrombotic prescribing strategy for the same indication (STROKECLOSE,

NCT02830152). If long-term therapeutic dose oral anticoagulation for AF after ICH is beneficial as suggested by this review (Analysis 2.1), the non-inferiority or superiority of this device to long-term therapeutic dose oral anticoagulation will need to be investigated.

Further updates of this Cochrane review and the individual participant data meta-analysis planned by the Collaboration Of Controlled Randomised trials of Oral Antithrombotic agents after intraCranial Haemorrhage (COCROACH, CRD42021246133) will be required to provide the most precise estimates of the effects of antithrombotic treatments after stroke due to ICH.

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Luke A Perry, Eivind Berge (now deceased), Joshua Bowditch, Elisabeth Forfang, Ole Morten Rønning, Graeme J Hankey, Elmer Villanueva, and Rustam Al-Shahi Salman developed, designed, and delivered the protocol for this review on 8 April 2016, and published the first version of this review on 25 May 2017.

We acknowledge and thank the Cochrane Stroke Group's Information Specialists Joshua Cheyne and his predecessor Brenda Thomas for their assistance in developing the search strategies for this review.

Special thanks to our two consumer reviewers, Odie Geiger and U Hla Htay, for generously providing their feedback on the first version of this review.

Data and analyses

Comparison 1

Short-term prophylactic dose anticoagulation (start versus avoid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	3	258	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.59, 1.70]
1.2 Deep vein thrombosis	3	260	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.49, 1.86]
1.3 Pulmonary embolism	4	333	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.14]
1.4 Venous thromboembolism	4	333	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.37]
1.5 Intracerebral haemorrhage	2	119	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.04, 1.38]
1.6 Major extracerebral haemorrhage	3	287	Risk Ratio (M-H, Random, 95% CI)	2.77 [0.12, 65.82]
1.7 Growth of qualifying intracerebral haemorrhage	2	214	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.38, 2.41]
1.8 Functional status (modified Rankin Scale 0-2)	1	73	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.78, 5.25]

Comparison 2

Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All major adverse cardiovascular events (MACE)	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.94]
2.2 Death	3	334	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.78]
2.3 Ischaemic stroke	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.71]
2.4 Myocardial infarction	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.71]
2.5 All major occlusive vascular events	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.14, 0.53]
2.6 Intracranial haemorrhage	3	334	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.88, 6.73]
2.7 Major extracerebral haemorrhage	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.13, 2.57]
2.8 Vascular death	3	334	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.65, 3.32]
2.9 Functional status (modified Rankin Scale score 0-2) at 1 year	2	288	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.24]
2.10 Any stroke (ischaemic or haemorrhagic)	3	334	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.42, 1.15]
2.11 Any stroke (ischaemic or haemorrhagic) or vascular death	2	304	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.46, 1.15]

Comparison 3

Long-term antiplatelet therapy (start versus avoid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All major adverse cardiovascular events (MACE)	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.22]
3.2 Death	1	536	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.76, 1.53]
3.3 Ischaemic stroke	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.40, 1.23]
3.4 Myocardial infarction	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.21, 1.89]
3.5 All major occlusive vascular events	1	536	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.68, 1.55]
3.6 Intracerebral haemorrhage	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.27, 1.03]
3.7 Major extracerebral haemorrhage	1	536	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.72, 9.94]
3.8 Vascular death	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.38, 1.18]
3.9 Functional status (modified Rankin Scale score 0-2) at 1 year	1	461	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.18]
3.10 Deep vein thrombosis	1	536	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.61, 14.73]
3.11 All major haemorrhagic events	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.40, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.12 Major vascular events as defined by the Antithrombotic Trialists' Collaboration	1	536	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.97]

Comparison 4

Long-term antiplatelet therapy (cilostazol versus aspirin)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All major adverse cardiovascular events (MACE)	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.74, 2.40]
4.2 Death	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.55, 4.91]
4.3 Ischaemic stroke	1	288	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.45, 2.01]
4.4 Myocardial infarction	1	288	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [0.63, 202.63]
4.5 Intracerebral haemorrhage	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.35, 4.69]
4.6 Vascular death	1	288	Odds Ratio (M-H, Fixed, 95% CI)	7.35 [0.38, 143.61]
4.7 Any stroke (ischaemic or haemorrhagic)	1	288	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.51, 1.84]

What's new

Date	Event	Description
5 October 2021	Amended	Literature search updated

History

Protocol first published: Issue 4, 2016
Review first published: Issue 5, 2017

Date	Event	Description
5 January 2021	Amended	Date of search

Contributions of authors

RASS, GJH, OMR and other co-authors of the protocol conceived the review; RASS, OMR, and GJH designed the review; RASS co-ordinated the review; AC and CC reviewed the results of the search and selected studies for inclusion in the review; AC and CC collected data for the review; AC and CC assessed the risk of bias in the included studies; AC and CC assessed the certainty in the body of evidence; AC and CC interpreted data; RASS, AC and CC wrote the review, which all authors reviewed and approved.

Declarations of interest

Alexia Cochrane: none

Chen Chen: none

Jacqueline Stephen: none

Ole Morten Rønning: Trial Steering committee member for NCT03186729.

Craig S Anderson: Trial steering committee member for NCT04522102.

Graeme J Hankey: in the past three years, GJH has received honoraria from AC Immune for chairing the data safety monitoring committee of two clinical trials of vaccines for Alzheimer's disease, from Bayer for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, and from Medscape, Web MD for participating in a discussion about stroke prevention in atrial fibrillation for theheart.org. NCT04522102 Trial Steering Committee member.

Rustam Al-Shahi Salman: UK chief investigator of RESTART 2019, SoSTART 2021, and NCT03950076. Trial Steering Committee member for NCT03186729, NCT04522102, and NCT02966119.

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Differences between protocol and review

Pooling of included RCTs: We grouped RCTs investigating short-term and long-term treatment separately, instead of performing subgroup analyses.

Types of intracranial haemorrhage: Most of the RCTs were restricted to participants with intracerebral haemorrhage (ICH), but some included a small number of participants with other forms of intracranial haemorrhage; similarly, some of the RCTs reported an outcome of intracranial haemorrhage, not just ICH.

Outcome nomenclature: We retained the primary outcome pre-specified in the protocol, but renamed it major adverse cardiovascular events (MACE), to reflect the commonest terminology for this composite outcome.

Outcome inclusion: We retained the secondary outcomes, including individual components of the MACE composite primary outcome, and added outcomes that had not been mentioned specifically in the protocol, but which are most appropriate for the comparison of start versus avoid short-term prophylactic dose anticoagulation: deep vein thrombosis, pulmonary embolism, venous thromboembolism and ICH growth. We added three composite outcomes reported by the included RCTs that had not been pre-specified in our protocol, because there is no standardised definition of MACE and these variations on the MACE composite provide

clinically informative assessments of safety, efficacy, and effectiveness: (1) any stroke (ischaemic or haemorrhagic); (2) any stroke (ischaemic or haemorrhagic) or vascular death; and (3) major vascular events as defined by the Antithrombotic Trialists' Collaboration.

Outcome importance: Given the number of pre-specified outcomes and comparisons in this review, we prioritised the five following clinically important outcomes for reporting in the Summary of Findings tables, Abstract, and Plain Language Summary (according to the MECIR R12 standard): (1) MACE, (2) Death, (3) Major occlusive vascular events, (4) ICH, and (5) Functional outcome.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

APACHE-AF 2021

Study characteristics	
Methods	**Design:** randomised controlled PROBE parallel group phase 2 trial **Setting:** multicentre (16 hospitals) in the Netherlands **Dates:** 15 January 2015 to 6 July 2020
Participants	**Sample size:** 101 participants **Diagnosis:** ICH **Inclusion criteria** • Age ≥ 18 years • ICH (including isolated spontaneous intraventricular haemorrhage), documented with CT or MRI, during treatment with anticoagulation (VKA, any direct thrombin inhibitor, any factor Xa inhibitor, or heparin or low- molecular-weight heparin at a therapeutic dose) • ICH occurred between 7 and 90 days before randomisation • Diagnosis of paroxysmal or persistent/permanent non-valvular AF, documented on electrocardiography • CHA_2DS_2-VASc score ≥ 2 • Score on the mRS ≤ 4 **Exclusion criteria** • Conditions other than AF for which the participant requires long-term anticoagulation • A different clinical indication for the use of an antiplatelet drug even if treated with apixaban, such as clopidogrel for recent coronary stenting • Mechanical prosthetic heart valve (biological prosthetic heart valves are allowed) or rheumatic mitral valve disease • Serious bleeding event in the previous 6 months, except for ICH • High risk of bleeding (e.g. active peptic ulcer disease, a platelet count of < 100,000/mL or haemoglobin level of < 6.2 mmol/L) • Ischaemic stroke in the previous 7 days • Current alcohol or drug misuse • Life expectancy of < 1 year • Severe renal insufficiency (a serum creatinine level of > 221 µmol per litre or a calculated creatinine clearance of < 15 ml per minute) • Alanine aminotransferase or aspartate aminotransferase level > 2 times the upper limit of the normal range or a total bilirubin > 1.5 times the upper limit of the normal range, unless a benign causative factor (e.g. Gilbert's syndrome) is known or identified • Allergy to apixaban • Use of strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors (e.g. systemic azole-antimycotics as ketoconazole or HIV protease inhibitors such as ritonavir) • Women of childbearing potential or who were pregnant or breastfeeding **Age:** median age was 78 years (IQR 73–83) overall; 77 years (74–83) in the intervention group and 79 years (72–83) in the comparator group **Sex:** 55 (54%) were men overall; 27 (54%) in the intervention group and 28 (55%) in the comparator group
Interventions	**Intervention:** apixaban oral dose of 5 mg twice daily, or a reduced dose of 2.5 mg twice daily if their creatine clearance was 30 mL/min or less, or if two of three of the following criteria were present: age 80 years or older, bodyweight 60 kg or lower, or serum creatinine 133 µmol/L or greater (50 participants) **Comparator:** no antithrombotic treatment or oral antiplatelet treatment (acetylsalicylic acid 80 mg once daily; carbasalate calcium 100 mg once daily; clopidogrel 75 mg once daily; or a combination of dipyridamole 200 mg twice daily with either acetylsalicylic acid 80 mg once daily or carbasalate calcium 100 mg once daily) at the discretion of the treating physician. (51 participants; 26 of these received antiplatelet therapy)

Outcomes	**Primary outcome** • Non-fatal stroke (ischaemic stroke, ICH, or SAH) or vascular death, whichever came first, during follow-up **Secondary outcomes** • ICH • SAH • Traumatic intracranial haemorrhage • Major extracranial haemorrhage • Clinically relevant non-major bleeding • Ischaemic stroke • Unclassified stroke • Any stroke • Myocardial infarction • Pulmonary embolism • Systemic embolism • Vascular death • All-cause death **Duration of follow-up:** median 1·9 years (IQR 1·0–3·1), with a total of 222 person-years
Notes	**Declarations of interest:** FHBMS reports two grants from the Dutch Heart Foundation (grant 2012T077 for this study; and grant 2019T060 outside the submitted work). DWD reports funding from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences & Health, and unrestricted grants from Penumbra, Stryker, Medtronic, Thrombolytic Science, and Cerenovus for research outside the current work, all paid to their institution. JS reports grants to their institution outside the submitted work (H2020 programme). JMC reports research funding from Portola, Boehringer, and Bayer, outside the submitted work. HBvdW reports fees for consultancy from Bayer and LivaNova, all paid to their institution; and grants outside the submitted work (EU Horizon 2020 programme; Dutch Heart foundation; and Stryker, of which the last two are through the CONTRAST consortium). CJMK reports grants from the Dutch Heart Foundation (grant 2012T077; this study), and grants outside the submitted work: The Netherlands Organization for Health Research and Development, ZonMw (grant 015008048); support of the Netherlands Cardiovascular Research Initiative, which is supported by the Dutch Heart Foundation, CVON2015-01: CONTRAST; and the support of the Brain Foundation Netherlands (HA2015.01.06). All other authors declare no competing interests. **Sources of funding:** Dutch Heart Foundation (grant 2012T077)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computerised randomisat ion system. Treatment allocation was stratified by intention to start an antiplatelet agent or not in the avoid group, and subsequently based on proportional minimisation, according to age (≤75 years vs > 75 years) and location of the ICH (lobar vs non-lobar)
Allocation concealment (selection bias)	Low risk	Prof Bart van der Worp confirmed that allocation was concealed by the randomisation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, their treating physicians, and local investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome event adjudication was done by LJK and GJER masked to the patient's identity, treatment allocation, and antithrombotic drug use
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported

Dickmann 1988

Study characteristics	
Methods	**Design:** parallel group RCT **Setting:** inpatient admissions to the neurology unit of one hospital in Göttingen, Germany **Dates:** not described
Participants	**Sample size:** 46 participants **Diagnosis:** ICH **Inclusion criteria:** diagnosis of ICH by CT with onset 24 hours before admission **Exclusion criteria:** bleeding diathesis, diastolic blood pressure higher than 120 mmHg, and deep coma with clinical signs of brain herniation **Age (years, mean (SD)):** 62 (SD not described) (intervention group), 60 (SD not described) (comparator group) **Sex:** 52% female (intervention group), 48% female (comparator group)
Interventions	**Intervention:** 5000 units of heparin administered subcutaneously 8-hourly starting at day 4 (23 participants) **Comparator:** 5000 units of heparin subcutaneously 8-hourly starting at day 10 (23 participants) Both groups had the same treatment otherwise, with compression stockings and physical treatment
Outcomes	**Primary outcome:** not specified **Secondary outcomes**: not specified **Outcomes:** rebleeding occurring during the trial period; thrombosis of abdomen or legs at day 2 and day 10; pulmonary embolism at day 10; death **Duration:** the duration of follow-up is not specified, but is assumed to be 10 days
Notes	**Declations of interest:** not described **Sources of funding:** not described Rebleeding was not defined by the authors of this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open trial, comparing two timings of heparin
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All scintigrams were read by the same blinded investigators"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	Low risk	All outcomes planned in the Methods section were reported in full in the Results section. Additionally, most expected outcomes of interest were reported in this study

NASPAF-ICH 2020

Study characteristics	
Methods	**Design:** randomised controlled PROBE parallel group (2:1) phase 2 trial **Setting:** multicentre at 8 hospitals in Canada **Dates:** April 2017 to May 2019

Participants	**Sample size:** 30 participants **Diagnosis:** ICH **Inclusion criteria** • Prior ICH • AF • $CHADS_2 \geq 2$ **Exclusion criteria** • Non-stroke absolute indication for antiplatelet or anticoagulant therapy • Recent ICH within 14 days • Platelet count less than 100,000/mm^3 at enrollment or other bleeding diathesis • Prior symptomatic lobar ICH other than the qualifying event • Uncontrollable hypertension consistently above SBP/DBP of 160/100 mmHg • Known hypersensitivity to either aspirin or NOACs • Inability to adhere to study procedures • Pregnant or breastfeeding • Unexpected to survive 6 months **Age(years, mean (SD))**: 77.7 (SD 9.2) intervention versus 75.8 (SD 5.5) comparator **Sex (male):** 12/21 (57%) intervention versus 5/9 (56%) comparator
Interventions	**Intervention:** NOAC (apixaban or dabigatran or edoxaban or rivaroxaban) and BP control to target < 130/80mmHg (21 participants) **Comparator:** acetylsalicylic acid 81 mg/day and BP control to target < 130/80mmHg (9 participants)
Outcomes	**Primary outcomes** • The mean number of patients randomised per site per year • Composite of ischaemic stroke and recurrent ICH **Secondary outcomes** • Refusal (average number of eligible patients per site who refuse consent) • Retention (randomised patients who completed 6 months of follow-up on drug or died during trial participation) • Ischaemic stroke (acute neurologic deficit in conjunction with brain imaging consistent with acute/subacute ischaemic stroke) • ICH (a neurologic deficit associated with an ICH or IVH on CT or MRI scan, or as demonstrated by surgery or autopsy) • Fatal stroke (due to ischaemic stroke or ICH) • Myocardial infarction • All-casue mortality • Systemic thromboembolism (emboli to the arterial circulation excluding myocardial infarction, ischaemic stroke or ICH) • Major haemorrhage (bleeding accompanied by one or more of the following - a decrease in the haemoglobin level of ≥ 20 g per liter over a 24-hour period, transfusion of ≥ 2 units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding) • Intracranial haemorrhage (signs or symptoms associated with an epidural, subdural, subarachnoid, ICH or IVH on CT or MRI scan, or as demonstrated by surgery or autopsy) • Composite of all stroke, myocardial infarct, systemic thromboembolism or death • mRS • MOCA • Weighted net clinical benefit (weighted net clinical benefit factoring the impact of ischaemic stroke, ICH, non-intracerebral intracranial haemorrhage, major extracranial haemorrhage and myocardial infarction on death and disability) **Duration of follow-up:** mean 1.53 years (SD 0.54)
Notes	**Declarations of interest:** Daiichi Sankyo Ltd, Bayer AG, Octapharma Canada, Portola pharmaceuticals, BMS/Pfizer, Servier Canada Inc **Sources of funding:** not specified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal correspondence with the chief investigator confirmed that central, web-based randomisation was used, with allocation concealment
Allocation concealment (selection bias)	Low risk	Personal correspondence with the chief investigator confirmed that central, web-based randomisation was used, with allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% complete follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported

Orken 2009

Study characteristics	
Methods	**Design:** parallel group RCT **Setting:** inpatient admissions to Sisli Etfal Education and Research Hospital, Department of Neurology in Turkey **Dates:** January 2006 - March 2008
Participants	**Sample size:** 75 participants **Diagnosis:** ICH **Inclusion criteria** • Primary ICH > 48 hours after admission **Exclusion criteria** • Early death before heparin treatment • death before 7th day investigations (see below) • secondary ICH due to aneurysm, arteriovenous malformations, trauma and tumours • excessive anticoagulation (INR > 2.0) • contraindication to contrast agents **Age (years, mean (SD))**: 68 ± 11 (intervention) 66 ± 10 (comparator) **Sex:** 56% female (intervention), 22% female (comparator)
Interventions	**Intervention:** subcutaneous LMWH (enoxaparin sodium 40mg/d) (39 participants) **Comparator:** long compression stockings (36 participants)
Outcomes	**Primary outcome:** not described **Secondary outcomes:** not described **Outcomes** • Haematoma enlargement (increase in ICH volume of > 33% or 12.5 mL) at 72 hours, 7 days and 21 days • Systemic bleeding complications • DVT or PE based on CTPA and bilateral venous Doppler at 7 days **Duration of follow-up:** 21 days
Notes	**Declarations of interest:** not described **Sources of funding:** not described **Other:** it is not clear whether 4 patients who were excluded because of "death before 7th day investigations" were excluded before or after randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation was said to be done, "after the first 48 hours according to the order of hospital admission dates" which seems to be predictable and at high risk of bias
Allocation concealment (selection bias)	High risk	Randomisation was said to be done, "after the first 48 hours according to the order of hospital admission dates" which seems to be predictable and at high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	The intervention and comparator could not be blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "All radiologic material was prospectively evaluated by 2 radiologists ... who were blinded to the clinical findings and cranial CTs of the patients" The methods did not explicitly state that the radiologists were also blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete

Selective reporting (reporting bias)	Low risk	All outcomes planned in the Methods section were reported in full in the Results section. Additionally, most expected outcomes of interest were reported in this study

PICASSO sub-group 2020

Study characteristics	
Methods	**Design:** randomised controlled, 2 × 2 factorial parallel group trial **Setting:** multicentre, 67 hospitals in three Asian countries **Dates:** 1 August 2009 to 31 August 2015
Participants	**Sample size:** 1534 participants overall (288 with prior ICH in the subgroup analysis included in this meta-analysis) **Diagnosis:** non-cardioembolic ischaemic stroke or transient ischaemic attack within 180 days and clinical history of prior ICH **Inclusion criteria** • Age > 20 years • Non-cardioembolic ischaemic stroke or transient ischaemic attack within 180 days before study entry • History of ICH defined as clinical or radiological findings or the presence of multiple (two or more) cerebral microbleeds, or asymptomatic ICH found incidentally as a slit-like curvilinear lesion on MRI, without an overt history of ICH **Exclusion criteria** • ICH within 6 months before study entry • Presence of contraindications for long-term use of an antiplatelet drug • Presence of severe cardiomyopathy or congestive heart failure • Occurrence of myocardial infarction or a coronary artery procedure within 4 weeks before screening **Age** (years, mean (SD)): unknown for this subgroup with prior ICH **Sex:** unknown for this subgroup with prior ICH
Interventions	**Intervention:** cilostazol 100 mg orally twice daily (matching the comparator) **Comparator:** aspirin 100 mg orally once daily (matching the intervention)
Outcomes	**Primary outcomes** • The efficacy outcome was defined as time to first occurrence of a composite of major vascular events, including stroke, myocardial infarction, and vascular death • The safety outcome was defined as time to first occurrence of ICH, which included spontaneous ICH and SAH, confirmed with CT or MRI **Secondary outcomes** • Stroke • Ischaemic stroke • Myocardial infarction • Other predefined vascular events • Cardiovascular death and all-cause mortality were also assessed during follow-up as predefined tertiary outcomes **Duration of follow-up:** at least 12 months.
Notes	**Declarations of interest:** SUK declares grants from Korea Otsuka Pharmaceutical Company. All other authors declare no competing interests **Sources of funding:** Korea Otsuka Pharmaceutical Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive web-based system. each participant received a subject number generated by the computer of the central randomisation service and was randomly assigned (1:1:1:1) to receive cilostazol (with aspirin placebo), aspirin (with cilostazol placebo), cilostazol plus probucol (with aspirin placebo), or aspirin plus probucol (with cilostazol placebo) using centralised blocks (block size 4) stratified by centre
Allocation concealment (selection bias)	Low risk	The analysis of cilostazol versus aspirin (antiplatelet arm) was double-blinded, and the interactive web response system was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Cilostazol, aspirin, and placebos—used as a double dummy—were provided every 3 months in boxes within sealed opaque envelopes, with instructions to be taken twice a day
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	High risk	Not all were reported

PREVENTIHS 2020

Study characteristics	
Methods	**Design:** parallel group RCT **Setting:** multicentre at hospitals in Italy **Dates:** 1 May 2016 to 30 March 2020
Participants	**Sample size:** 73 participants **Diagnosis:** ICH **Inclusion criteria** • Bedridden (score of 3 or 4 on item 6 of the NIHSS or the impossibility to maintain an upright position such as in the case of ataxia in patients with haemorrhagic cerebellar stroke) • 18 years of age or older • Spontaneous ICH on CT scan or intracranial haemorrhage during treatment with oral anticoagulants (after reversal) • > 72 hours after symptom onset **Exclusion criteria** • 10% increase in ICH volume between diagnostic CT and CT performed before randomisation at 72 hours after symptom onset. • ICH due to vascular malformation • SAH • Subdural haematoma • Bleeding disorders (defined by a prothrombin time > 30% longer than the control value or a platelet count of < 100,000 per mm^3) • Renal failure defined as a creatinine clearance of < 30 • Severe hepatic failure • Known neoplastic disease • Pregnancy • Need for therapeutic anticoagulant or antiplatelet agents for concomitant disease • Participation in other ongoing clinical trials • Patient refusal to consent **Age (years, mean (SD)):** 70 +/-14 (intervention) versus 72 +/- 12 (comparator) **Sex:** 22/38 (intervention) versus 18/35 (comparator) were male
Interventions	**Intervention:** enoxaparin 0.4mL (4000 units) once daily for 10 days ± 1 day plus standard therapy (38 participants) **Comparator:** standard therapy alone (35 participants)
Outcomes	**Primary outcome** • Symptomatic VTE objectively documented as proximal/distal DVT or PE, or asymptomatic proximal/distal DVT documented by ultrasound at 10 days **Secondary outcomes** • Any VTE at 90 days • Any increase of 10% or more in the baseline ICH volume • Major extracranial haemorrhage (the presence in critical organ sites including the retroperitoneal and intraocular spaces, a reduction of 2 or more g/dL of haemoglobin, the need to carry out a transfusion of 2 or more units of concentrate red blood cells, or fatal bleeding) • Death or disability (mRS ≥ 3) at 90 days • Death at 90 days **Duration:** CT brain and venous eco-color-Doppler examination with a compression test performed bilaterally on the lower limbs 10 +/- 1 day following the start of treatment. Clinical follow-up was done 90 days after randomisation
Notes	**Declarations of interest:** Maurizio Paciaroni - member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer, Bristol Meyer Squibb, Daiichi Sankyo, and Pfizer. Giancarlo Agnelli - member of the speaker bureau of Boehringer Ingelheim and Bayer. Cecilia Becattini - member of the speaker bureau of Bristol Meyer Squibb and Bayer. Valeria Caso - received honoraria as a member of the speaker bureau and as consultant or advisory board of Boehringer Ingelheim. Walter Ageno - received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and has received research support from Bayer and Boehringer Ingelheim **Sources of funding:** Ministero della Salute (Health Minister) of the Italian Government (n. FARM12L9JE) **Other:** this trial was stopped prematurely because of slow recruitment
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were centrally randomised over the phone using a random list of numbers (even numbers – treatment A; odd numbers – treatment B) closed in an envelope."
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were centrally randomised over the phone using a random list of numbers (even numbers – treatment A; odd numbers – treatment B) closed in an envelope." It is not clear if the envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label (participants and personnel were aware of allocated treatment)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome assessment was described as being blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data for randomised participants were reported
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported
Other bias	Unclear risk	Premature termination due to slow recruitment

Qian 2021

Study characteristics	
Methods	**Design:** randomised placebo-controlled parallel group trial **Setting:** multicentre at 4 hospitals in Finland. **Dates:** 2008 to 2015

Participants	**Sample size:** 149 participants **Diagnosis:** ICH **Inclusion criteria** • Age >17 years • Unable to walk unassisted due to motor impairment, with a score of > 2 on the paretic lower extremity on the NIHSS • Admitted to the emergency room within 12 hours of the onset of ICH **Exclusion criteria** • Other type of ICH than acute primary ICH • Patients who need neurosurgery • Previous VTE • Glasgow Coma Scale score < 8 • Pre-ICH mRS > 2 • Thrombolytic treatment within the preceding week • Major surgery or major trauma within the preceding 3 months • Life expectancy less than 3 months due to comorbid disorders • Confirmed malignant disease (cancer) • Hepatitis and/or liver cirrhosis • Renal failure • Infectious disease (HIV, endocarditis etc.) • Current or previous haematologic disease • Recent active and untreated gastric/duodenal ulcer • Allergy or known hypersensitivity to enoxaparin or heparins • Known hypersensitivity to benzyl alcohol • Women of childbearing age if pregnant • Participation in another study within the preceding 30 days **Age (years, mean (SD))**: 66 ± 19 in the intervention group and 68 ± 6 in the comparator group **Sex** (male): 36/71 (51%) in the intervention group and 36/68 (53%) in the comparator group
Interventions	**Intervention:** subcutaneous injections of enoxaparin were started 24 hours after the onset of ICH and repeated twice daily at 12-hour intervals. Each injection contained 20 mg (2000 IU) of enoxaparin, implying a daily dose of 40 mg. Treatment was stopped once the patient was able to walk independently, or if a severe recurrence of bleeding was observed. Intermittent pneumatic compression devices were used until discharge to home or to another institute (68 participants) **Comparator:** subcutaneous injections of the placebo were started 24 hours after the onset of ICH and repeated twice daily at 12-hour intervals. Each injection contained saline injections according to the same regime as the intervention, and this was replaced with enoxaparin 72 hours after the onset of the stroke. Enoxaparin treatment was stopped once the patient was able to walk independently, or if a severe recurrence of bleeding was observed. Intermittent pneumatic compression devices were used until discharge to home or to another institute (71 participants)
Outcomes	**Primary outcome** • Confirmed VTE, defined as the composite of symptomatic or asymptomatic DVT, or symptomatic or fatal PE (death related to VTE) occurring during the treatment period (up to 90 days after the onset of the ICH related symptoms) **Secondary outcomes** • Significantly increased ICH volume (> 33%) observed in a head CT or autopsy, including recurrent ICH • Other severe bleeding complications • Cardiovascular death • Death due to any cause occurring within the treatment period **Duration of follow-up:** 3 months
Notes	**Declarations of interest:** none **Sources of funding:** TT received academic grants for ICH research from Helsinki University Central Hospital, University of Gothenburg, Sahlgrenska University Hospital, and Sigrid Juselius Foundation. ST received academic grants from Finnish Medical Foundations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Subcutaneous injections were obtained from the hospital pharmacy. There were always 2–3 sets of injections ready for all eligible study patients i.e. enoxaparin or placebo. All the injection sets looked the same whether they included enoxaparin or saline. The investigator randomly chose one of the injection sets and the code for the injection set was placed in the sealed envelope together with the patient study number The same information was sealed for the emergency envelope. One emergency envelope was opened during the study due to severe rebleeding 36 hours after the onset, and in that case, the patient had received the placebo. The patient study code and ID were sealed in another envelope, which was opened only after the study
Allocation concealment (selection bias)	Low risk	Enoxaparin and saline placebo looked identical

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The envelopes containing patient study code and the injection set code were opened during a witnessed meeting only after the end of the study. It is not clear whether outcomes were identified and adjudicated before the end of the study, or afterwards
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up data existed for all 139 patients
Selective reporting (reporting bias)	High risk	Cardiovascular death was pre-specified in the trial register, but was not reported

RESTART 2019

Study characteristics	
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre at 122 hospitals in the UK **Dates:** 22 May 2013 to 31 May 2018
Participants	**Sample size:** 537 participants **Diagnosis:** ICH **Inclusion criteria** • Patient age ≥ 18 years • Spontaneous primary or secondary ICH • Patient had taken antithrombotic drug(s) for the prevention of vaso-occlusive disease before ICH onset • Randomisation > 24 hours after ICH onset • Patient and their doctor are uncertain about whether to start or avoid antiplatelet drugs • Patient is registered with a general practitioner • Brain imaging that first diagnosed the ICH is available • Participant or representative consent • Brain MRI substudy: MRI done after ICH but before randomisation **Exclusion criteria** • ICH due to preceding trauma or haemorrhagic transformation of ischaemic stroke • Patient is taking an anticoagulant drug following ICH • Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception • Patient is being treated or followed up in another CTIMP • Patient and carer unable to understand spoken or written English • Brain MRI substudy: no claustrophobia. MRI not contraindicated **Age(years, median (IQR)):** 77 (69–82) in the intervention group versus 76 (69–82) in the comparator group **Sex** (male): 173 (65%) in the intervention group versus 187 (70%) in the comparator group
Interventions	**Intervention:** one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 hours of randomisation with doses determined at the discretion of the consultant responsible for the participant **Comparator:** policy of avoiding antiplatelet medication

Outcomes	**Primary outcome** • Fatal or non-fatal radiographically or pathologically proven recurrent symptomatic ICH **Secondary outcome measures** • Composite of all major haemorrhagic events (recurrent symptomatic ICH, other forms of symptomatic spontaneous or traumatic intracranial haemorrhage, and symptomatic major extracranial haemorrhage at any site (requiring transfusion or endoscopic treatment or surgery, or resulting in death within 30 days)) • Composite of all major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; DVT; PE; and carotid, coronary, or peripheral arterial revascularisation procedures) • Composite of all major haemorrhagic or occlusive vascular events (as defined above) • Protocol-defined composite secondary outcome of all major vascular events defined by the Antithrombotic Trialists' Collaboration (non-fatal myocardial infarction, non-fatal stroke (ischaemic, haemorrhagic, or uncertain cause), or death from a vascular cause) **Duration of follow-up:** at least 6 months (1064 person-years)
Notes	**Declarations of interest:** RA-SS and GDM report a grant from the British Heart Foundation (SP/12/2/29422) paid to the University of Edinburgh for the conduct of RESTART. RA-SS reports grants from The Stroke Association, Chest Heart and Stroke Scotland, and GE Healthcare Limited, outside the submitted work. DEN reports grants and personal fees from AstraZeneca, Eli Lilly, Bristol Myers Squibb, and Jansen, during the conduct of the study. PAGS reports funding from Bayer outside the submitted work. NS reports a grant from National Institute for Health Research (NIHR) Health Technology Assessment for the TICH-2 trial, outside the submitted work. JMW reports grants from EU Framework 7, Medical Research Council, and the British Heart Foundation, outside the submitted work. DJW reports personal fees from Bayer and JFB consulting, outside the submitted work. PMW reports personal fees from Stryker Global Advisory Board on Haemorrhagic Stroke and MicroVention-Terumo, and a grant from MicroVention-Terumo outside the submitted work. WNW reports a Chief Scientist Office of the Scottish Government Health Department Senior Fellowship (SCAF_17_01) and a grant from the European Stroke Organisation, outside the submitted work. MSD, JS, and CLMS declare no competing interests. **Sources of funding:** British Heart Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation system with minimisation algorithm
Allocation concealment (selection bias)	Low risk	The web interface displayed each participant's unique study identification number and their allocation to either starting or avoiding antiplatelet therapy, which was also sent in an email to all investigators at the hospital site, having been concealed until that point
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment allocation was open to the clinicians caring for patients in primary and secondary care, and local investigators and to participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome adjudication was blinded to treatment allocation and receipt of antiplatelet therapy during follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 (0.2%) participant withdrew from follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported

SoSTART 2021

Study characteristics

Methods	**Design:** randomised, open-label, assessor-masked, parallel group, pilot-phase, non-inferiority trial **Setting:** multicentre at 67 hospitals in the UK **Dates:** 29 March 2018 to 27 February 2020

Participants	**Sample size:** 203 participants **Diagnosis:** spontaneous intracranial haemorrhage **Inclusioncriteria** • Adults (≥ 18 years) • Symptomatic spontaneous intracranial haemorrhage (i.e. ICH, non-aneurysmal SAH, IVH, or SDH) that was not known to be due to an underlying macrovascular cause (e.g. intracranial aneurysm, arteriovenous malformation, cerebral cavernous malformation, dural arteriovenous fistula, or intracranial venous thrombosis), head injury, or haemorrhagic transformation of cerebral infarction • Survived for at least 24 hours after intracranial haemorrhage • AF (persistent or paroxysmal) or atrial flutter • CHA_2DS_2-VASc score ≥ 2 **Exclusion criteria** • Prosthetic mechanical heart valve or severe (haemodynamically significant) native valve disease • LAAO performed or planned • Oral or parenteral anticoagulation was going to be prescribed • Allocated treatment strategy would be implemented for less than 1 year • Antiplatelet therapy would also be prescribed if allocated to start oral anticoagulation • Patient or their doctor was certain about whether or not to start oral anticoagulation • Brain imaging that first diagnosed the intracranial haemorrhage was not available • Patient not registered with a primary care practitioner • Patient pregnant, breastfeeding, or of childbearing age and not taking contraception • Patient and their carer were unable to understand spoken or written English • Intolerant of lactose • Contraindication to any of the permitted oral anticoagulants other than recent intracranial haemorrhage • Life expectancy less than 1 year • Patient already randomly assigned in SoSTART **Age (years), median (IQR):** 79 (74–85) intervention versus 79 (74–84) comparator **Sex (male):** 62/101 (61%) intervention versus 65/102 (64%) comparator
Interventions	**Intervention:** start oral anticoagulation, restricted to the use of either a DOAC (factor Xa inhibitor (apixaban, rivaroxaban, or edoxaban) or direct thrombin inhibitor (dabigatran etexilate)) or vitamin K antagonist (warfarin sodium, acenocoumarol, or phenindione) at full treatment dose (with adjustment if required by renal function, age, bodyweight, or concomitant medications), initiated within 24 hours of randomisation (101 participants) **Comparator:** standard clinical practice without oral anticoagulation (either an antiplatelet agent or no antithrombotic agents). Participants were permitted to start or discontinue anticoagulant or antiplatelet agents if clinically indicated by outcome events during follow-up, regardless of treatment allocation (102 participants) **Duration of follow-up:** median 1.2 years, 251 person-years
Outcomes	**Primary outcome** • Recurrent symptomatic spontaneous intracranial haemorrhage **Secondary outcomes** • Symptomatic major vascular events (recurrent symptomatic spontaneous intracranial haemorrhage, ischaemic stroke, myocardial infarction, sudden cardiac death, death from another vascular cause, or death of an unknown cause) • Individual symptomatic vascular events (major haemorrhagic events, symptomatic ischaemic events, revascularisation procedures, or stroke of uncertain subtype) • Individual types of fatal events (vascular deaths (within 30 days of outcome events or from another vascular cause), sudden cardiac deaths, deaths of an unknown cause, or deaths from a non-vascular cause) • Annual ratings of participant dependence and quality of life
Notes	**Declarations of interest:** JMW reports grants from EU Horizon 2020, Medical Research Council, Fondation Leducq, The Stroke Association, Alzheimer's Society, and the British Heart Foundation, outside the submitted work. PMW reports personal fees from Stryker Global Advisory Board on Haemorrhagic Stroke and MicroVention-Terumo, and institutional grants from MicroVention-Terumo, Penumbra, Stryker, and Medtronic, outside the submitted work. GYHL reports consultancy and speaker fees (not received personally) from Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo, outside the submitted work. A-PJ declares personal fees from Alexion Pharmaceuticals, outside the submitted work. **Sources of funding:** British Heart Foundation, Medical Research Council, Chest Heart & Stroke Scotland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central, web-based, computerised randomisation system incorporating a minimisation algorithm randomly assigned participants
Allocation concealment (selection bias)	Low risk	Concealed allocation on the web application until all baseline data were entered

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome event adjudicator was masked to participant identity, treatment allocation, and drug use by redaction of this information from source documents
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrew. All others were followed-up for at least 1 year or until death
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported

AF: atrial fibrillation
BP: blood pressure
CHA_2DS_2-VASc: a score for predicting the risk of stroke or thromboembolism in AF, based on congestive heart failure [1 point]; hypertension [1 point]; age ≥75 years [2 points]; diabetes [1 point]; previous stroke, transient ischaemic attack, or thromboembolism [2 points]; vascular disease [1 point]; age 65–74 years [1 point]; and sex category [1 point for female]).
CT: computed tomography
CTPA: CT pulmonary angiography
DOAC: direct oral anticoagulant
DVT: deep vein thrombosis
ICH: intracerebral haemorrhage
INR: international normalised ratio
IQR: interquartile range
IVH: intraventricular haemorrhage
LAAO: left atrial appendage occlusion
LMWH: low-molecular-weight heparin
MOCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
mRS: modfield Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
NOAC: novel oral anticoagulants
PE: pulmonary embolism
RCT: randomised controlled trial
SAH: subarachnoid haemorrhage
SD: standard deviation
SDH: subdural haemorrhage
VKA: vitamin K antagonist
VTE: venous thromboembolism

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Boeer 1991	This is an extension phase of Dickmann 1988 that introduces non-randomised data to the previously published data
CAST 1997	This trial included some people with ICH who were randomised prior to CT. These data were not available in the original manuscript. We had hoped that there would be useable data published in the Keir 2002 systematic review, but this did not separate spontaneous ICH from haemorrhagic transformations of acute ischaemic stroke and we were therefore unable to include data from CAST 1997 in this review

Study	Reason for exclusion
ChiCTR2000040166	This is an ongoing randomised controlled study included patients with cerebral haemorrhage. The two intervention groups are traditional Chinese medicines, Musk huayu Xingnao and Vermiculus huoxue Tong yu granules, which are not proven to have an antithrombotic effect. We excluded the trial because the intervention was not an antithrombotic drug
Frontera 2014	This is a controlled clinical trial that was not randomised
IST 1997	This trial included several hundred participants with ICH who were randomised prior to CT. These data were not available in the original manuscript. We had hoped that data from the Keir 2002 systematic review or the published individual data forms (Sandercock 2011) would yield useable data for this review, but Keir 2002 did not report spontaneous ICH separately from haemorrhagic expansion of an acute ischaemic stroke, and after contacting the chief investigator of IST 1997 we discovered that it was not possible to extract data on spontaneous ICH separately
Kuramatsu 2018	This study used data from an observational study, German-wide multicenter analysis of oral anticoagulation associated intracerebral haemorrhage (RETRACE). The study was excluded because it was not randomised
Li 2013	The intervention randomised in this study is transfusion of frozen apheresis platelets in participants on aspirin and with ICH, not an antithrombotic drug
RESTART extended follow-up	This study reported extended follow-up of the RESTART trial cohort, first reported in 2019. Patients were aware of their treatment allocation throughout, and were aware of the results of the main report of the trial when undergoing extended follow-up. Therefore, there was more opportunity for bias in this open trial, arising from awareness of the main results during extended follow-up, so we included RESTART 2019 in preference to this
Venturelli 2014	This is a post-hoc analysis of the INTERACT2 trial. The intervention that is the subject of this analysis, prophylactic subcutaneous heparin after ICH, was not randomly assigned in INTERACT2. Therefore, this analysis is observational in nature
Yan 2014	The participant group did not have spontaneous ICH; it was a cohort of people with and without cerebral microbleeds and haemorrhagic transformation, with acute ischaemic stroke following rtPA treatment

CT: computed tomography
ICH: intracerebral haemorrhage
rtPA: Recombinant tissue plasminogen activator

Characteristics of studies awaiting classification [ordered by study ID]

ELDERCARE-AF 2020

Methods	Phase 3, multicentre, randomised, double-blind, placebo-controlled, event-driven trial
Participants	Eligible patients were 80 years of age or older, had a history of nonvalvular atrial fibrillation documented on an electrocardiogram or on a monitor recording obtained within 1 year before consent was given, and had a $CHADS_2$ score of 2 or higher. Eligible patients were also considered to be inappropriate candidates for oral anticoagulants (i.e., warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the recommended therapeutic strength (in the case of warfarin) or at approved doses for one or more of the following reasons: a low creatinine clearance (15 to 30 ml per minute), a history of bleeding from a critical area or organ or gastrointestinal bleeding, low body weight (≤45 kg), continuous use of nonsteroidal antiinflammatory drugs (NSAIDs), or current use of an antiplatelet drug.
Interventions	15 mg of edoxaban once daily versus placebo.
Outcomes	The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis. Secondary efficacy end points included the composite of stroke, systemic embolism, or death from cardiovascular causes; major adverse cardiovascular events (the composite of nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, or death from cardiovascular causes or bleeding); the composite of stroke, systemic embolism, or death from any cause; net clinical benefit (the composite of stroke, systemic embolism, major bleeding, or death from any cause); and death from any cause. Secondary safety end points included the composite of major bleeding or clinically relevant nonmajor bleeding; clinically relevant nonmajor bleeding; minor bleeding; and all bleeding.
Notes	

PRAGUE-17 2020

Methods	Investigator-initiated, multicentre, prospective, open-label, randomised, noninferiority trial conducted at 10 cardiac centres in the Czech Republic.
Participants	Moderate- or high-risk patients with nonvalvular AF were eligible if indicated for anticoagulation and had: 1) history of bleeding requiring intervention or hospitalization; 2) history of a cardioembolic event while taking anticoagulation agents; or 3) a moderate to high risk profile, defined as CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category [female]) of ≥3 plus HAS-BLED (uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) of ≥2. Key exclusion criteria included mechanical valve prosthesis, mitral stenosis, comorbidities other than AF mandating anticoagulation, patent foramen ovale with large atrial septal aneurysm, mobile aortic plaque, symptomatic carotid arterial atherosclerosis, clinically significant bleeding within 30 days, cardioembolic event within 30 days, and creatinine clearance of <30 ml/min.
Interventions	Left atrial appendage closure versus non-vitamin K direct oral anticoagulant (DOAC). Patients randomised to the DOAC group could receive either rivaroxaban, apixaban, or dabigatran at the manufacturer-recommended dose.

Outcomes	The primary outcome was a composite of safety and efficacy characteristics of both strategies: 1) stroke (ischaemic or haemorrhagic) or TIA; 2) systemic embolism; 3) clinically significant bleeding; 4) cardiovascular death; or 5) significant peri-procedural or device-related complications. Clinically significant bleeding was a composite of major and nonmajor clinically relevant bleeding (NMCRB), according to the International Society on Thrombosis and Hemostasis (ISTH) criteria. Major bleeding includes either a decrease in haemoglobin of ≥2.0 g/dl during a 24-h period, transfusion of ≥2 units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. NMCRB is defined as bleeding requiring hospitalization or an invasive procedure but not meeting ISTH major criteria. Complications included pericardial effusion requiring drainage/pericardiocentesis or surgery, cardioembolism, peri-procedural bleeding requiring surgical revision or transfusion, device embolisation, device-related thrombus with cardioembolism, or others as assessed by the operator and clinical endpoint committee (CEC). Secondary endpoints included the individual components of the primary endpoint.
Notes	

a Patients such as those not eligible for continued administration at the approved dosage for the drug due to concerns about bleeding risk, or those who have not been administered available oral anticoagulants at the approved dosage but are expected to have a high bleeding risk from available oral anticoagulants at the approved dosage.

b For warfarin, INR controlled between 1.6 and 2.6.

c Subcutaneous bleeding will be included if there is at least 1 hematoma with a maximal diameter of at least 5 cm, and urinary findings will be included if frank hematuria is observed.

d History of mitral valve repair is allowed in the trial. CHADS2, Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or transient ischemic attack; INR, international normalized ratio.

Characteristics of ongoing studies [ordered by study ID]

NCT02966119

Study name	REstart or STop Antithrombotic Randomised Trial in France (RESTART-Fr)
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre in the North of France **Dates:** December 2016 to December 2022
Participants	**Sample size:** 292 **Diagnosis:** ICH **Inclusion criteria** • Patient age ≥ 18 years • Spontaneous ICH confirmed by imaging • Patient had been taking antithrombotic drug(s) for the prevention of vaso-occlusive disease for at least 1 week before ICH onset • Randomisation more than 24 hours after ICH onset • Patient and their doctor are uncertain about whether to start or avoid antiplatelet drugs • Brain imaging that first diagnosed the ICH is available • Participant or representative consent **Exclusion criteria** • ICH associated with: a vascular malformation (AVM, arterial aneurysm, cavernoma); a secondary haemorrhagic infarction; a cerebral venous thrombosis; a tumour • Patients with a formal indication for restarting OAC despite the ICH (e.g. mechanical heart valves or pulmonary embolism under 6 months)
Interventions	**Intervention:** antiplatelet agent (aspirin or clopidogrel or dypyridamole), chosen by the patient's physician before the randomisation **Comparator:** avoid antiplatelet drugs
Outcomes	**Primary outcome:** symptomatic ICH (fatal or non fatal) proven radiologically **Secondary outcomes** • Serious vascular events fatal (symptomatic haemorrhagic events, symptomatic ischaemic events, stroke of undetermined nature) • Other fatal events (death without pre-defined vascular cause) • Functional outcome (mRS 0-1-2 versus 3 or more) **Duration of follow-up:** 2 years
Starting date	7 December 2016

Contact information	Contact information: Professor Charlotte Cordonnier charlotte.cordonnier@chru-lille.fr
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT03186729

Study name	STudy of Antithrombotic Treatment after IntraCerebral Haemorrhage (STATICH)
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre in Nordic countries **Dates:** July 2018 to June 2023

Participants	**Sample size:** 500 participants
	Diagnosis: ICH
	Inclusion criteria
	• Patient age ≥ 18 years
	• Spontaneous ICH, of ≥ 1 day, but not more than 180 days after onset of qualifying ICH, i.e.:
	  ○ no preceding traumatic brain injury, based on history from the patient/witness of spontaneous symptom onset, and brain imaging appearances consistent of spontaneous ICH (i.e. any brain/bone/soft tissue appearances of trauma must have occurred secondary to a spontaneous ICH)
	  ○ no 'secondary' or underlying structural cause (e.g. haemorrhagic transformation of an ischaemic stroke, aneurysm, tumour, AVM, or intracerebral venous thrombosis)
	• Patient has indication for antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of ischaemic events, either antiplatelet drugs (for patients with vascular disease), or anticoagulant drug for patients with AF
	• Consent to randomisation from the patient (or personal/legal/professional representative if the patient does not have mental capacity)
	• MRI (or CT) is performed before randomisation
	Exclusion criteria
	• Clear indication for antiplatelet or anticoagulant treatment (e.g. prosthetic heart valves)
	• Contraindications to the antithrombotic drug that will be administered
	• Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception
	• Malignancy with life expectancy less than 2 years
	For MRI substudy: contraindication for MRI

Interventions	**Intervention:** antithrombotic treatment (for patients with vascular disease and indication for antiplatelet drugs: antiplatelet drugs; for patients with AF and indication for anticoagulant drugs: anticoagulant drugs) **Comparator:** no antithrombotic treatment
Outcomes	**Primary outcome:** • Fatal or non-fatal symptomatic ICH (neurological deterioration or death associated with ICH found on CT scan, MRI, or autopsy) **Secondary outcomes** • mRS score • Death of any cause • Death of vascular cause • Symptomatic epidural, SDH, or SAH (neurological deterioration or death associated with epidural, subdural, or SAH found on CT scan, MRI, or autopsy) • Symptomatic major extracranial haemorrhage (clinically overt bleeding associated with one or more of: transfusion of > 2 red cell units of blood; a fall in haemoglobin of 2 g/dL (1.24 mmol/L); bleeding into retroperitoneum, intraocular space or major joint; bleeding leading to permanent treatment cessation) • Ischaemic events • Cognitive outcome (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)) **Duration of follow-up:** 2 years
Starting date	1 July 2018
Contact information	Torgeir Bruun Wyller t.b.wyller@medisin.uio.no
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT03243175

Study name	Avoiding Anticoagulation After IntraCerebral Haemorrhage (A3ICH)
Methods	**Design:** randomised controlled PROBE 3-arm trial (1:1:1) **Setting:** multicentre, France **Dates:** January 2019 to December 2023
Participants	**Sample size:** 300 participants **Diagnosis**: ICH **Inclusion criteria** • Adult (older than 18 years old, no upper age limit); • with a history of paroxysmal, persistent or long-standing non-valvular AF (documented on an electrocardiogram); • and a CHA_2DS_2VASc score of 2 or more who have an indication for long-term anticoagulation; • who suffered from a spontaneous ICH (while being treated with oral anticoagulants or not) documented with brain CT or MRI; • more than 14 days before randomisation (no upper delay limit); • for whom there is a clinical equipoise regarding the choice of the best preventive strategy to avoid future vascular events **Exclusion criteria for all treatment groups** • Pre-randomisation mRS of 4 or 5 • Conditions other than AF for which the patient requires long term anticoagulation (fe.g. prosthetic mechanical heart valve) • Serious bleeding events within the 6 months before randomisation (except for ICH) • Life expectancy of less than 1 year • Pregnancy or breastfeeding **Exclusion criteria related to LAAO only** • Contraindications due to local, anatomical reasons (such as thrombus in the left atrial appendage, infection with a risk of endocarditis) • Patients older than 85 years • Patient or attending physician are unwilling to undergo/perform LAAO **Exclusion criteria related to DOAC only** • Chronic renal insufficiency (clearance of creatinine by Cockcroft method < 30ml/min) • Body weight lower than 50 kg • Allergy to apixaban • Coexisting conditions predisposing to head trauma (e.g. gait disturbance, uncontrolled seizures disorder) • Patient or attending physician are unwilling to use DOAC
Interventions	**Intervention:** apixaban 5mg twice daily **Intervention:** LAAO **Comparator:** no OAC or LAAO. May include antiplatelet agents (in the setting of co-morbidities) or no antithrombotic drugs at all
Outcomes	**Primary outcome** • Composite of all fatal or non-fatal major cardiovascular/cerebrovascular ischaemic or haemorrhagic intracranial/extracranial events **Secondary outcomes** • Each individual component of the composite outcome (fatal or non-fatal major cardiovascular/cerebrovascular ischaemic or haemorrhagic intracranial/extracranial events) • Death of any cause • mRS • EQ-5D (EuroQoL) Score • Complications of LAAO up to 30 days including device related complications **Duration of follow-up:** 2 years
Starting date	24 January 2019
Contact information	Prof Charlotte Cordonnier, MD, PhD e-mail: charlotte.coprdonnier@chru-lille.fr
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT03907046

Study name	Anticoagulation in ICH Survivors for Stroke Prevention and Recovery (ASPIRE)

Methods	**Design:** randomised controlled parallel group quadruple blind trial **Setting:** multicentre at NIH/NINDS StrokeNet sites in the USA **Dates:** January 2020-April 2024
Participants	**Inclusion criteria** • Age at least 18 years • ICH (including spontaneous intraventricular haemorrhage) confirmed by brain CT or MRI • Can be randomised within 14-120 days after ICH onset • Non-valvular AF (defined as atrial fibrillation or atrial flutter), documented by electrocardiography or a physician-confirmed history of prior AF • CHA_2DS_2-VASc score ≥ 2 • Provision of signed and dated informed consent form by patient or legally authorised representative • Able to comply with all study procedures and available for duration of the study • For females of reproductive potential: use of highly effective contraception **Exclusion criteria** • History of ICH before index event • Active infective endocarditis • Lobar ICH with cerebral amyloid angiopathy • Clear indication for anticoagulant drugs (e.g. requires anticoagulation for deep vein thrombosis or pulmonary embolism) or antiplatelet drugs (e.g. requires aspirin or clopidogrel for recent myocardial infarction) • Previous or planned LAAO • Clinically significant bleeding diathesis • Serum creatinine ≥ 2.5 mg/dL • Active hepatitis or hepatic insufficiency with Child-Pugh score B or C • Anaemia (haemoglobin < 8 g/dL) or thrombocytopaenia (< 100 x 109/L) that is chronic in the judgment of the investigator • Life expectancy < 1 year • Pregnant or breastfeeding • Known allergy to aspirin or apixaban • Concomitant participation in a competing therapeutic trial • Considered by the investigator to have a condition that precludes safe participation in the trial • Unwilling to discontinue prohibited medications
Interventions	**Intervention:** apixaban 5mg twice daily, or 2.5mg twice daily in the setting of ≥ 2 of the following: age ≥ 80 years, body weight ≤6 0 kg, or serum creatinine 1.5-2.4 mg/dL, or patient is taking a strong CYP3A4/pGP inhibitor (e.g. ketoconazole, itraconazole, ritonavir, or clarithromycin) **Comparator:** aspirin 81mg once daily
Outcomes	**Primary outcome** • Stroke of any type (ischaemic or haemorrhagic) or death from any cause **Secondary outcome** • mRS score at 12 months **Duration:** 12-36 months.
Starting date	28 January 2020
Contact information	Kevin N Sheth (kevin.sheth@yale.edu), Hooman Kamel (hok9010@med.cornell.edu)
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT03950076

Study name	EdoxabaN foR IntraCranial Hemorrhage survivors with Atrial Fibrillation (ENRICH-AF)
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre, international **Dates:** September 2019 to July 2023

Participants	**Sample size:** 1200 participants **Diagnosis:** symptomatic, spontaneous and non-traumatic ICH, IVH, and/or convexity SAH, and symptomatic spontaneous or non-penetrating traumatic SDH **Inclusion criteria** • Written informed consent provided • Age ≥ 45 years, at the time of signing the informed consent • Previous intracranial haemorrhage (symptomatic, spontaneous and non-traumatic ICH, IVH, and/or cSAH, and symptomatic spontaneous or non-penetrating traumatic SDH) on or off antithrombotic therapy, and confirmed to have stabilised on neuroimaging • Documented AF (paroxysmal, persistent, permanent) • CHA_2DS_2-VASc score ≥ 2 **Exclusion criteria** • Recent intracranial haemorrhage (within 14 days) • Secondary macrovascular, neoplastic or infectious causes of intracranial haemorrhage (except for antithrombotic treatment or non-penetrating traumatic SDH) • Traumatic or aneurysmal cSAH • Need for ongoing oral anticoagulant therapy for indication other than AF (e.g. mechanical heart valve, venous thromboembolic disease) • Need for ongoing antiplatelet therapy for indication where edoxaban would not be a suitable substitute • Plans for LAAO • Estimated creatinine clearance (CrCl) < 15 mL/min or other creatinine clearance following local product monograph (Canada < 30mL/min) • Platelet count less than 100,000mm^3 at enrollment or other bleeding diathesis • Persistent, uncontrolled hypertension (systolic BP averaging > 150 mmHg) • Chronic use of NSAID • Clinically significant active bleeding, including gastrointestinal bleeding • Lesions or conditions at increased risk of clinically significant bleeding, e.g. active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of haemostasis • Antiphospholipid antibody syndrome • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk • Known hypersensitivity to edoxaban • Estimated inability to adhere to study procedures • Pregnancy or breastfeeding • Estimated life expectancy < 6 months at the time of enrollment • Close affiliation with the investigational site; e.g. a close relative for the investigator, dependent person (e.g. employee or student of the investigational site) • Post menopausal female participants must be amenorrhoeic for ≥ 12 months prior to screening or ≥ 6 weeks post-surgical bilateral oophorectomy (with or without hysterectomy) prior to screening. Women of childbearing potential must have negative serum pregnancy test within 7 days prior to randomisation or urine pregnancy testing within 24 hours of randomisation. Heterosexually active women of childbearing potential must use highly effective methods of contraception for 32 days after discontinuation (duration of study drug plus 30 days duration of one ovulatory cycle)
Interventions	**Intervention:** edoxaban 60 mg (or 30 mg as determined by clinical criteria) **Comparator:** non-anticoagulant medical therapy as determined by the local investigator includes 1) no antithrombotic therapy, 2) antiplatelet monotherapy, including de novo indication for antiplatelet monotherapy during course of the study

Outcomes	**Primary outcomes** • Stroke (composite of ischaemic, haemorrhagic and unspecified) • Major haemorrhage as defined byt the International Society on Thrombosis and Haemostasis (ISTH) criteria **Secondary outcomes** • Ischaemic stroke (development of an acute neurologic deficit in conjunction with brain imaging consistent with acute/subacute ischaemic stroke) • Cardiovascular death • Haemorrhagic stroke (development of an acute neurologic deficit in conjunction with brain imaging consistent with acute/subacute ICH, IVH or SAH) • Disabling/fatal stroke (disabling stroke is defined as stroke resulting in a clinical outcome that is associated with a mRS of 4 or 5. Fatal stroke is defined as death occurring within 30 days of stroke) • Composite of all stroke, myocardial infarction, systemic thromboembolism, or all-cause death (components of composite outcome (adjudicated) includes stroke (ischaemic, haemorrhagic, and undefined stroke, TIA with positive neuroimaging), myocardial infarction, systemic thromboembolism or all-cause death) • Net clinical benefit (composite of stroke, myocardial infarction, cardiovascular death, fatal bleeding, and symptomatic bleeding into a critical organ or area) • mRS at 12 month visit • All intracranial haemorrhage (ICH, IVH, SDH, SAH). Intracranial haemorrhage as defined by signs or symptoms associated with an epidural, SDH, SAH, ICH or IVH on CT or MRI scan, or as demonstrated by surgery or autopsy • Fatal intracranial haemorrhage (defined as signs or symptoms associated with an epidural, SDH, SAH, ICH or IVH on CT or MRI scan, or as demonstrated by surgery or autopsy with death occurring within 30 days of stroke) • SDH (defined as signs or symptoms associated with a SDH on CT or MRI scan, or as demonstrated by surgery or autopsy) • Hospitalisation for any cause **Duration of follow-up:** median 2 years
Starting date	20 September 2019
Contact information	Kevin Reeh ENRICH-AF@phri.ca
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT04522102

Study name	Antiplatelet Secondary Prevention International Randomised trial after INtracerebral haemorrhaGe (ASPIRING) - pilot phase
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre hospital sites in China and Australia **Dates:** September 2021 to June 2023
Participants	**Sample size:** 120 participants **Diagnosis:** ICH **Inclusion criteria** • Patient age ≥ 18 years • Symptomatic stroke due to spontaneous (non-traumatic) ICH • Patient is at least 24 hours after ICH symptom onset • Patient and their doctor are both uncertain about whether to start or avoid antiplatelet monotherapy • Consent to randomisation from the patient (or personal/legal/professional representative if the patient does not have mental capacity) **Exclusion criteria** • ICH due to head injury, in the opinion of the investigator • ICH due to haemorrhagic transformation of an ischaemic stroke, in the opinion of the investigator • Patient is already taking antiplatelet therapy, or full dose anticoagulant therapy, after ICH • Patient is pregnant, breastfeeding, or of childbearing age and not taking contraception • Patient and carer unable to understand spoken or written local language
Interventions	**Intervention:** start antiplatelet monotherapy (one antiplatelet drug available in local standard clinical practice, chosen by patient's physician pre-randomisation) **Comparator:** avoid antiplatelet therapy

Outcomes	**Primary outcome** • Receipt of regulatory approvals in China, Australia and New Zealand separately, including Ethics, Human Genetics Resources Administration of China (HGRAC) **Secondary outcomes** • Trial database structure and data flows that comply with data privacy and information governance regulations in China, Australia and New Zealand • Participation of 20 sites in China and 10 sites in Australia and New Zealand • Frequency of ICH survivors who are screened, eligible, approached, consented, and randomised by month and site from activation • Barriers to randomisation of eligible patients • Frequency of protocol deviations and violations • Adherence to the allocated intervention by investigators and participants • Frequency of withdrawal and loss to follow-up • Completeness of follow-up assessments • Characteristics of randomised participants compared with eligible patients who were not recruited • Composite of all serious vascular events (non-fatal stroke, non-fatal myocardial infarction or death from a vascular cause) • Any serious adverse event • Any serious adverse reaction • Suspected unexpected serious adverse reactions **Duration of follow-up:** up to 3 years
Starting date	3 September 2021
Contact information	Rustam Al-Shahi Salman, +44 131 242 7014, Rustam.Al-Shahi@ed.ac.uk Lily Song, +86 13916466400, lsong@georgeinstitute.org.cn
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

NCT04820972

Study name	Early-start antiplatelet treatment after neurosurgery in patients with spontaneous intracerebral haemorrhage
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre in China **Dates:** 1 May 2021 to May 2023

Participants	**Sample size:** 250 participants
	Diagnosis: post-operative ICH
	Inclusion criteria
	• 18-70 years old
	• Nontraumatic spontaneous ICH
	• Postoperative patients with high risk of major adverse cardiac/cerebrovascular and peripheral vessel events (MACCPE):
	  ○ previous history of cerebral infarction or TIA
	  ○ previous history of coronary heart disease or myocardial infarction
	  ○ use ASCVD Risk Estimator Plus (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/) to assess the risk of ischaemic events for patients with no previous history of cerebral infarction, TIA, or coronary heart diseases or myocardial infarction, 10 years risk > 10% is defined as a high risk of cardiovascular ischaemic events
	  ○ The Caprini Risk Scale is used to assess the risk of venous thrombosis in the lower extremities. Score > 2 is defined as a high risk of venous thrombosis
	• Patients who received neurosurgical procedures to remove the haematoma, including craniotomy, endoscopic haematoma removal and haematoma aspiration
	• Patients who signed informed consent
	• No history of allergy to salicylic acid preparation
	• Patients who complete the preintervention assessment and meet these criteria:
	  ○ postoperative head CT showed no new infarction or haemorrhage
	  ○ postoperative venous ultrasound of the lower extremity did not reveal deep vein thrombosis
	  ○ postoperative electrocardiogram and myocardial enzyme examination did not show acute myocardial ischaemia or myocardial infarction
	Exclusion criteria
	• There are structural cerebrovascular lesions (such as intracranial aneurysms, cerebrovascular malformations, etc) or tumours in the area of bleeding or the bleeding is suspected to be related to these lesions
	• Ischaemic stroke with haemorrhagic conversion
	• Secondary bleeding due to venous embolism
	• A malignant tumour and expected to have a survival of no more than 3 months
	• Taking antithrombotic agents (vitamin K antagonists (warfarin,) new anticoagulants (dabigatran or rivaroxaban)) in addition to antiplatelet agents
	• Previous history of thrombocytopaenia or coagulation disorders
	• Previous history of AF

Interventions	**Intervention:** aspirin 100 mg once daily antiplatelet therapy starting from the third day after surgery **Comparator:** 'traditional'
Outcomes	**Primary outcomes** • Intracranial haemorrhage • Major adverse cardiac/cerebrovascular and peripheral vessel events **Secondary outcomes:** none specified **Duration of follow-up:** 90 days
Starting date	1 May 2021
Contact information	JUN WU, MD wujunslf@126.com Shuo Wang, MD captain9858@126.com
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** not specified in trials register

PRESTIGE-AF

Study name	PREvention of STroke in Intracerebral haemorrhaGE survivors with Atrial Fibrillation (PRESTIGE-AF)
Methods	**Design:** randomised controlled PROBE parallel group trial **Setting:** multicentre international in Europe **Dates:** 3 June 2019 to 30 November 2022
Participants	**Sample size:** 654 participants **Diagnosis:** ICH **Inclusion criteria:** not reported **Exclusion criteria:** not reported

Interventions	**Intervention:** DOAC (dabigatran, apixaban, rivaroxaban, or edoxaban) **Comparator:** no OAC. If the patient is randomized in this arm investigators will use their best judgment to decide upon the prescription of an antiplatelet drug of their choice or no such therapy
Outcomes	**Primary outcomes** • Ischaemic stroke • Recurrent ICH **Secondary outcomes** • All stroke • Systemic embolism • Major adverse cardiac events • All-cause mortality • Rate of cardiovascular mortality • Major haemorrhage • Intracranial haemorrhage • All strokes, systemic embolic event, myocardial infarction, cardiovascular mortality and major bleeding • Myocardial infarction • Major bleeding • Quality of life (EQ-5D-3L) • Cognitive function: the Montreal Cognitive Assessment (MoCA) • Psychological morbidity: the Hospital Anxiety and Depression Scale (HADS) **Duration of follow-up:** 3 years
Starting date	3 June 2019
Contact information	Kirsten H Harvey hello@prestige-af.org; kirsten.harvey@imperial.ac.uk
Notes	**Declarations of interest:** not specified in trials register **Sources of funding:** EU Horizon 2020

AF: atrial fibrillation
AVM: arteriovenous malformation
CCA: common carotid artery
cSAH: convexity subarachnoid hemorrhage
CT: computed tomography
DBP: diastolic blood pressure
DOAC: direct oral anticoagulant
ICH: intracerebral haemorrhage
IVH: intraventricular haemorrhage
LAAO: left atrial appendage occlusion
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NOAC: novel oral anticoagulant
NSAID: non-steroidal anti-inflammatory drug
OAC: oral anticoagulation
SAH: subarachnoid haemorrhage
SBP: systolic blood pressure
SDH: subdural haemorrhage
TIA: transient ischaemic stroke
VKA: vitamin K antagonist

Appendices

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Basal Ganglia Hemorrhage] explode all trees

#2 MeSH descriptor: [Intracranial Hemorrhages] this term only

#3 MeSH descriptor: [Intracranial Hemorrhage, Hypertensive] this term only

#4 MeSH descriptor: [Cerebral Hemorrhage] this term only

#5 MeSH descriptor: [Hemorrhagic Stroke] this term only

#6 (((brain* or cerebr* or cerebell* or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher*) NEAR/5 (h?emorrhag* or h?ematoma* or bleed*))):ti,ab,kw

#7 (ICH or ICHs):ti,ab,kw

#8 {or #1-#7}

#9 MeSH descriptor: [Anticoagulants] explode all trees

#10 MeSH descriptor: [Vitamin K] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]

#11 MeSH descriptor: [Thrombin] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]

#12 MeSH descriptor: [Factor Xa] this term only

#13 MeSH descriptor: [Blood Coagulation Factors] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]

#14 MeSH descriptor: [Antithrombins] explode all trees

#15 MeSH descriptor: [Hirudin Therapy] this term only

#16 (anticoagul* or antithromb*):ti,ab,kw

#17 (Vitamin K antagonist* or VKA or VKAs):ti,ab,kw

#18 (direct* NEAR/3 thrombin NEAR/3 inhib*):ti,ab,kw

#19 (DTI*):ti,ab,kw

#20 ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) NEAR/3 inhib*):ti,ab,kw

#21 (activated NEAR/3 (factor X or factor 10) NEAR/3 inhib*):ti,ab,kw

#22 (acenocoumarol* or dicoumarol* or ethyl biscoumacetate* or phenprocoumon* or warfarin* or ancrod* or citric acid* or coumarin* or chromonar* or coumestro* or esculi* or ochratoxin* or umbelliferone* or dermatan sulfate* or dextran* or edetic acid* or enoxaparin* or gabexate* or heparin* or lmwh* or nadroparin* or pentosan sulfuric polyester* or phenindione* or protein c or protein s or tedelparin*):ti,ab,kw

#23 (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate* or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216):ti,ab,kw

#24 (Marevan or Fragmin* or Fraxiparin* or Klexane):ti,ab,kw

#25 (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin* or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil):ti,ab,kw

#26 (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717):ti,ab,kw

#27 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees

#28 MeSH descriptor: [Platelet Glycoprotein GPIIb-IIIa Complex] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]

#29 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg* or (platelet* NEAR3 inhibit*) or (thrombocyt* NEAR3 inhibit*)):ti,ab,kw

#30 (alprostadil* or aspirin* or acetylsalicylic acid or acetyl salicylic acid* or acetyl?salicylic acid or epoprostenol* or ketanserin* or ketorolac tromethamine* or milrinone* or mopidamol* or procainamide* or thiophen* or trapidil* or picotamide* or ligustrazine* or levamisol* or suloctidil* or ozagrel* or oky046 or oky-046 or defibrotide* or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib* or gp iib*) NEAR/5 (antagonist* or inhibitor*)) or GR144053 or GR-144053 or triflusal):ti,ab,kw

#31 (Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel):ti,ab,kw

#32 (Dispril or Albyl* or Ticlid* or Persantin* or Plavix or ReoPro or Integrilin* or Aggrastat):ti,ab,kw

#33 {or #8-#32}

#34 #8 AND #33

Appendix 2. MEDLINE (Ovid) search strategy

The search consists of antithrombotics and stroke subject searches (lines 1-5 and 6-25) which have been linked to the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format (lines 15-25), as referenced in the Box 3.c in the Technical Supplement to Chapter 4: Searching for and selecting studies in the Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022) (Lefebvre 2022). Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from: www.training.cochrane.org/handbook.

1. exp basal ganglia hemorrhage/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/ or hemorrhagic stroke/

2. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

3. ((h?emorrhag$ or bleed$) adj5 (stroke or apoplex$)).tw.

4. (ICH or ICHs).tw.

5. or/1-4

6. exp anticoagulants/

7. exp Vitamin K/ai or thrombin/ai or factor Xa/ai or exp Blood coagulation factors/ai

8. exp antithrombins/ or hirudin therapy/

9. (anticoagul$ or antithromb$).tw.

10. (Vitamin K antagonist$ or VKA or VKAs).tw.

11. (direct$ adj3 thrombin adj3 inhib$).tw.

12. DTI$1.tw.

13. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj3 inhib$).tw.

14. (activated adj3 (factor X or factor 10) adj3 inhib$).tw.

15. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw,nm.

16. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw,nm.

17. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw,nm.

18. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.

19. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw,nm. 20. exp platelet aggregation inhibitors/ or exp platelet glycoprotein gpiib-iiia complex/ai

21. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj3 inhibit$) or (thrombocyt$ adj3 inhibit$)).tw.

22. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw,nm.

23. (Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw,nm.

24. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw,nm.

25. or/6-24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. randomized.ab.

29. placebo.ab.

30. drug therapy.fs.

31. randomly.ab.

32. trial.ti.

33. groups.ab.

34. or/26-33

35. exp animals/ not humans.sh.

36. 34 not 35

37. 5 and 25 and 36

Appendix 3. Embase (Ovid) search strategy

1. basal ganglion hemorrhage/ or brain hemorrhage/ or brain ventricle hemorrhage/ or cerebellum hemorrhage/

2. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

3. ((h?emorrhag$ or bleed$) adj5 (stroke or apoplex$)).tw.

4. (ICH or ICHs).tw.

5. 1 or 2 or 3 or 4

6. anticoagulant agent/ or antivitamin k/ or exp blood clotting inhibitor/ or exp coumarin anticoagulant/ or defibrotide/ or dextran sulfate/ or fluindione/ or glycosaminoglycan polysulfate/ or exp heparin derivative/ or lupus anticoagulant/ or phenindione/

7. (anticoagul$ or antithromb$).tw.

8. (Vitamin K antagonist$ or VKA or VKAs).tw.

9. (direct$ adj3 thrombin adj3 inhib$).tw.

10. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj3 inhib$).tw.

11. (activated adj3 (factor X or factor 10) adj3 inhib$).tw.

12. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw.

13. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw.

14. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw.

15. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw.

16. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw.

17. or/6-16

18. exp antithrombocytic agent/

19. fibrinogen receptor/dt [Drug Therapy]

20. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw.

21. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw.

22. (Argatroban or Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw.

23. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw.

24. or/18-23

25. 17 or 24

26. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/ 27. Randomization/ 28. Controlled clinical trial/ or "controlled clinical trial (topic)"/ 29. control group/ or controlled study/ 30. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/

31. Crossover Procedure/

32. Double Blind Procedure/

33. Single Blind Procedure/ or triple blind procedure/

34. placebo/ or placebo effect/

35. (random$ or RCT or RCTs).tw.

36. (controlled adj5 (trial$ or stud$)).tw.

37. (clinical$ adj5 trial$).tw.

38. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

39. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

40. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

42. (cross-over or cross over or crossover).tw.

43. (placebo$ or sham).tw.

44. trial.ti.

45. (assign$ or allocat$).tw.

46. controls.tw.

47. or/26-46

48. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)

49. 5 and 25 and 47

50. 49 not 48

Appendix 4. Trials register search strategies

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) AREA[StudyType] EXPAND[Term] COVER[FullMatch] "Interventional" AND AREA[ConditionSearch] Intracerebral Haemorrhage AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[01/14/2020, 01/05/2021]

World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/) Basic search: intracerebral haemorrhage OR intracerebral hemorrhage OR ICH Phases are: ALL

In the previous version of this review, we searched the Stroke Trials Registry of the Internet Stroke Center (www.strokecenter.org/trials/) on 2 March 2017.

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Figures and tables

Additional tables

Table 1

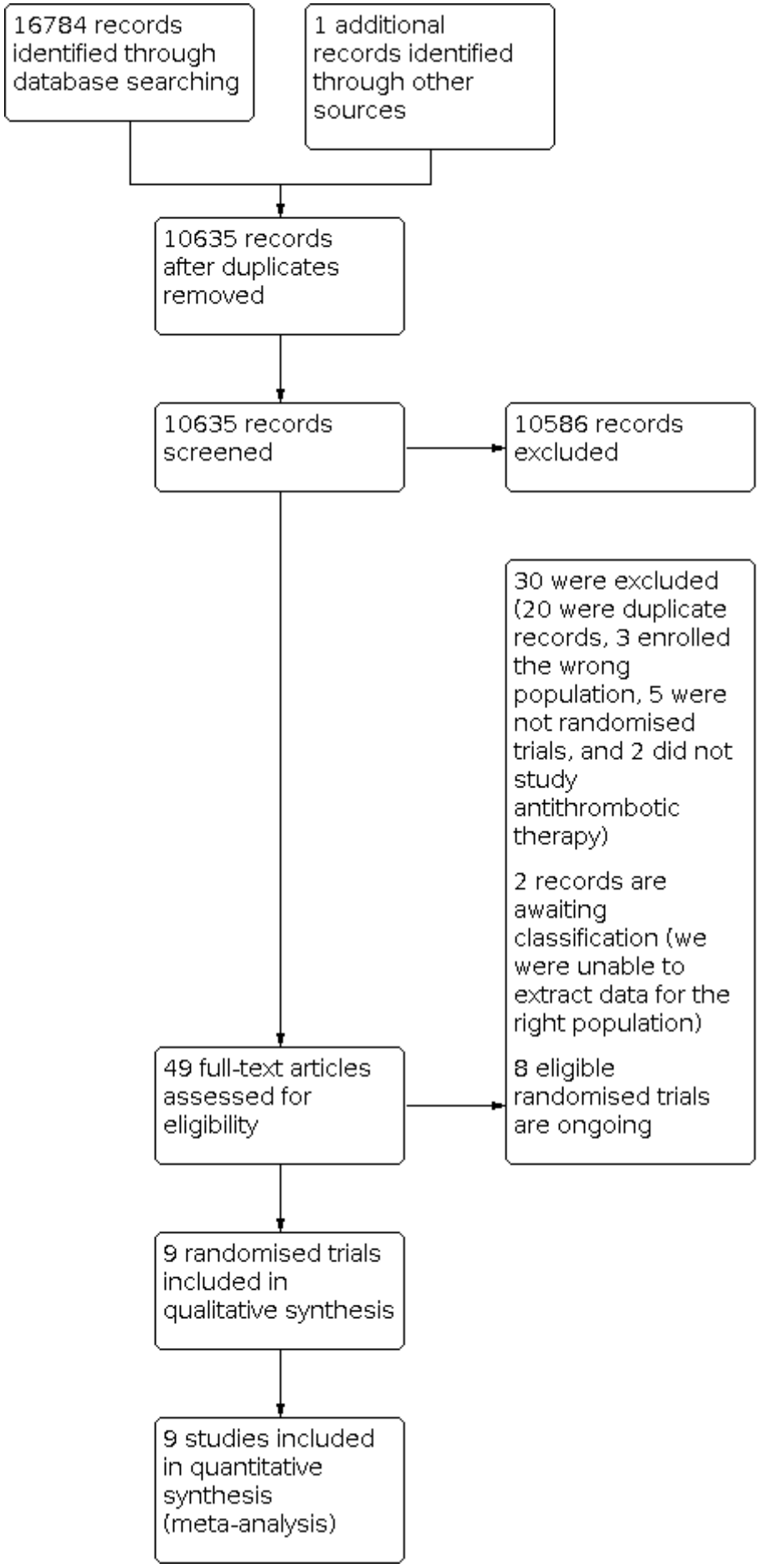
Non-enzymatic antithrombotic agents with defined daily doses within group B01A of the World Health Organization Anatomical Therapeutic Chemical Classification System

Antithrombotic class	Antithrombotic agents
Vitamin K antagonists	Dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate
Heparin group	Heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, sulodexide, bemiparin
Platelet aggregation inhibitors excluding heparin	Clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, carbasalate calcium, epoprostenol, indobufen, iloprost, abciximab, aloxiprin, eptifibatide, tirofiban, triflusal, beraprost, treprostinil, prasugrel, cilostazol, ticagrelor, cangrelor, vorapaxar, selexipag
Direct thrombin inhibitors	Desirudin, lepirudin, argatroban, melagatran, ximelagatran, bivalirudin, dabigatran etexilate*
Direct factor Xa inhibitors	Rivaroxaban*, apixaban*, edoxaban*
Other antithrombotic agents	Defibrotide, fondaparinux

www.whocc.no/atc_ddd_index/?code=B01A

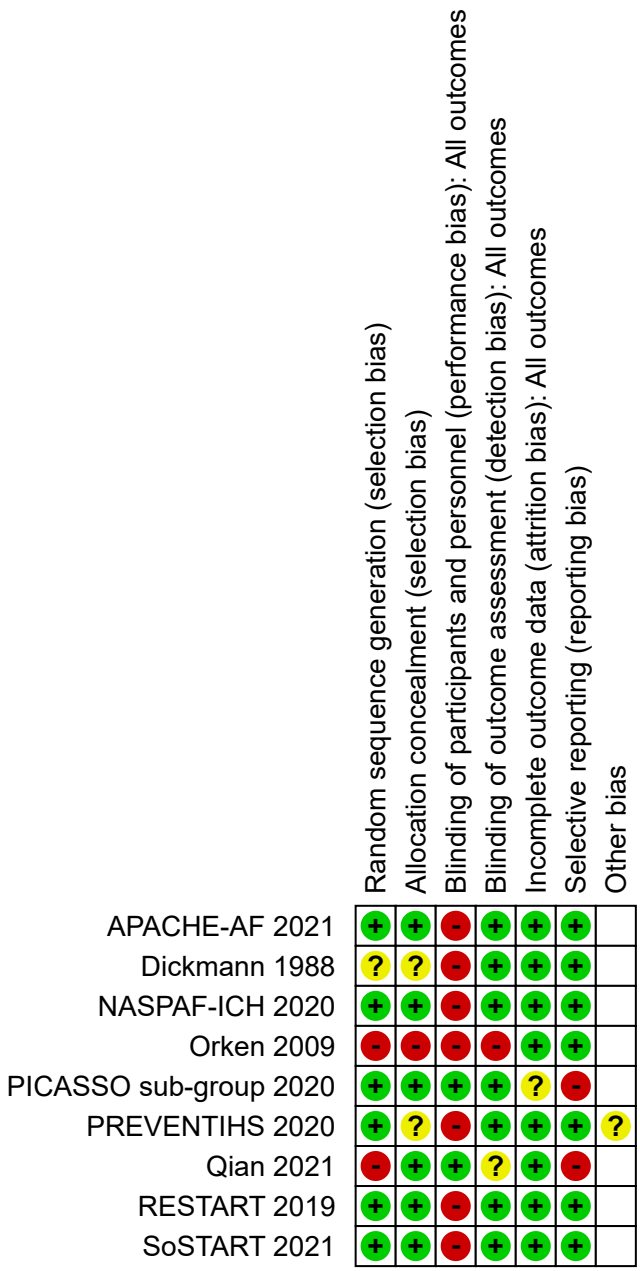
* Non-vitamin K (direct) oral anticoagulants

Figure 1



Flow diagram of study screening, eligibility assessment and inclusion

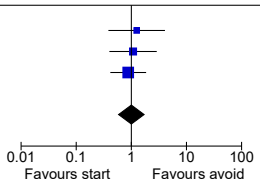
Figure 2

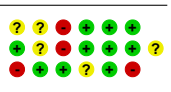

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias): All outcomes
Blinding of outcome assessment (detection bias): All outcomes
Incomplete outcome data (attrition bias): All outcomes
Selective reporting (reporting bias)
Other bias
APACHE-AF 2021
Dickmann 1988
NASPAF-ICH 2020
Orken 2009
PICASSO sub-group 2020
PREVENTIHS 2020
Qian 2021
RESTART 2019
SoSTART 2021

Analysis 1.1

Study or Subgroup	Start anticoagulation Events	Total	Avoid anticoagulation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dickmann 1988	5	23	4	23	20.3%	1.25 [0.38 , 4.07]
PREVENTIHS 2020	7	38	6	35	29.0%	1.07 [0.40 , 2.89]
Qian 2021	11	71	12	68	50.7%	0.88 [0.42 , 1.85]
Total (95% CI)		**132**		**126**	**100.0%**	**1.00 [0.59 , 1.70]**
Total events:	23		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable





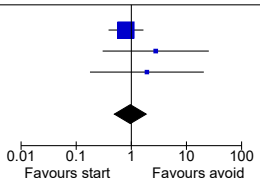
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

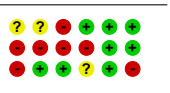
Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 1: Death

Analysis 1.2

Study or Subgroup	Start anticoagulation Events	Total	Avoid anticoagulation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dickmann 1988	8	23	10	23	83.2%	0.80 [0.39 , 1.66]
Orken 2009	3	39	1	36	9.0%	2.77 [0.30 , 25.43]
Qian 2021	2	71	1	68	7.8%	1.92 [0.18 , 20.64]
Total (95% CI)		**133**		**127**	**100.0%**	**0.96 [0.49 , 1.86]**
Total events:	13		12			

Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable





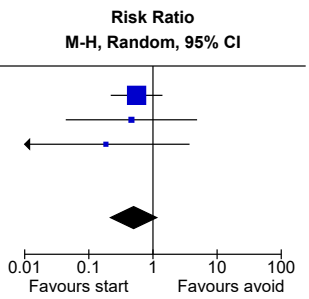
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 2: Deep vein thrombosis

Analysis 1.3

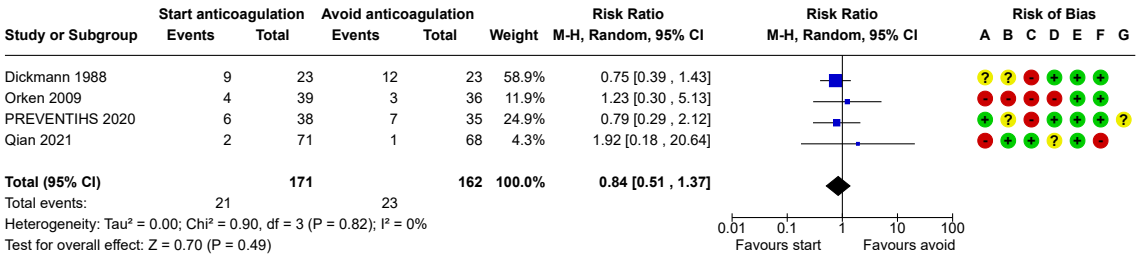
Study or Subgroup	Start anticoagulation Events	Total	Avoid anticoagulation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dickmann 1988	5	23	9	23	80.0%	0.56 [0.22 , 1.41]
Orken 2009	1	39	2	36	12.4%	0.46 [0.04 , 4.88]
PREVENTIHS 2020	0	38	2	35	7.6%	0.18 [0.01 , 3.72]
Qian 2021	0	71	0	68		Not estimable
Total (95% CI)		**171**		**162**	**100.0%**	**0.50 [0.22 , 1.14]**
Total events:	6		13			

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 3: Pulmonary embolism

Analysis 1.4

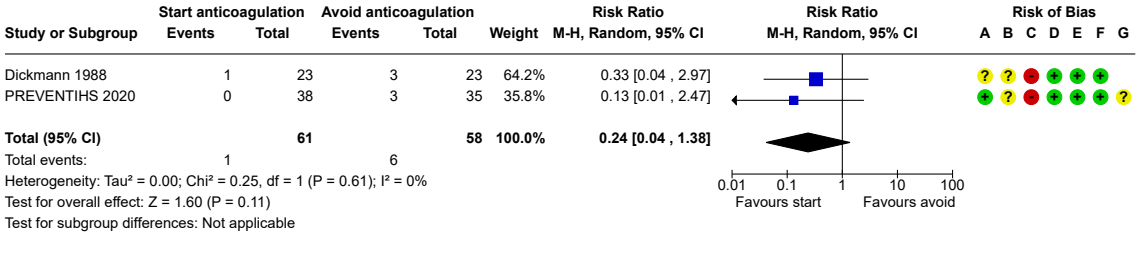


Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 4: Venous thromboembolism

Analysis 1.5

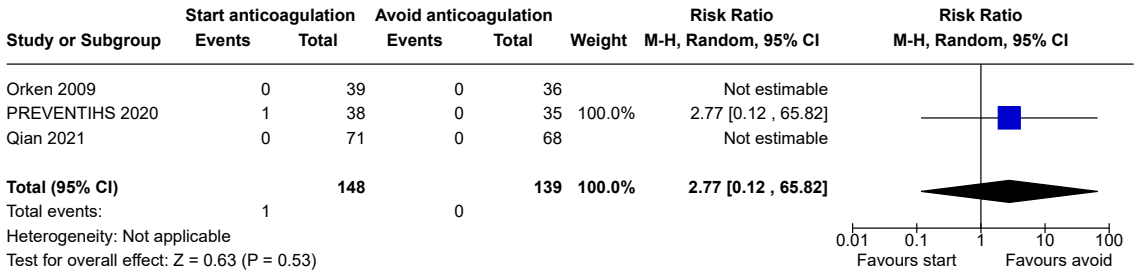


Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 5: Intracerebral haemorrhage

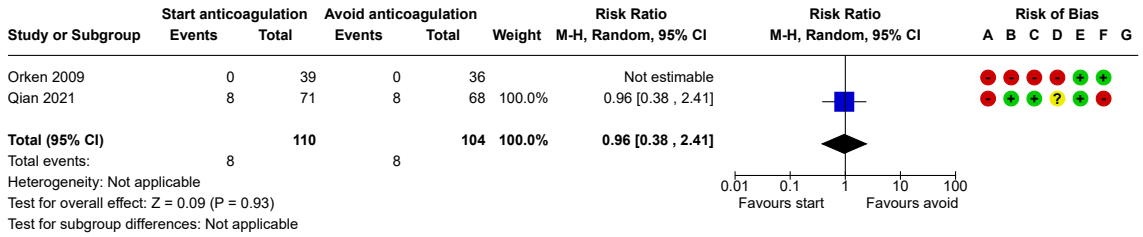
Analysis 1.6



Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 6: Major extracerebral haemorrhage

Analysis 1.7

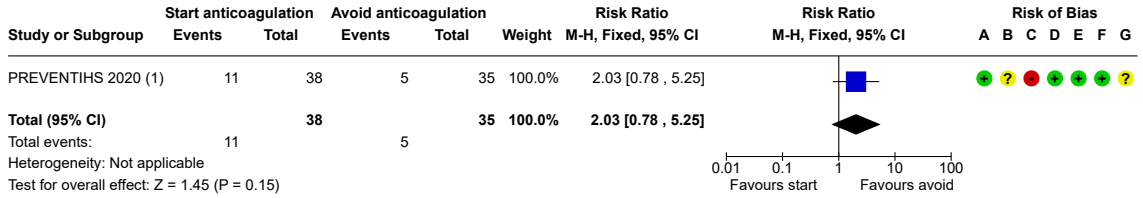


Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 7: Growth of qualifying intracerebral haemorrhage

Analysis 1.8



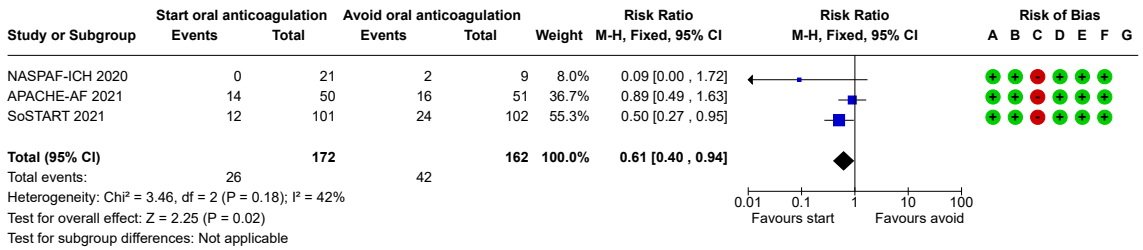
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable

Footnotes
(1) The functional status outcome was Modified Rankin Scale score 0-2

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Short-term prophylactic dose anticoagulation (start versus avoid), Outcome 8: Functional status (modified Rankin Scale 0-2)

Analysis 2.1



Heterogeneity: Chi² = 3.46, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable

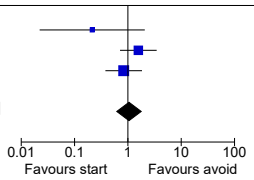
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

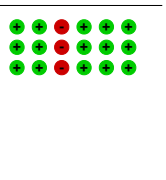
Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 1: All major adverse cardiovascular events (MACE)

Analysis 2.2

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	1	21	2	9	12.4%	0.21 [0.02 , 2.07]
SoSTART 2021	14	101	9	102	39.5%	1.57 [0.71 , 3.46]
APACHE-AF 2021	9	50	11	51	48.1%	0.83 [0.38 , 1.84]
Total (95% CI)		**172**		**162**	**100.0%**	**1.05 [0.62 , 1.78]**
Total events:	24		22			

Heterogeneity: Chi² = 3.20, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable





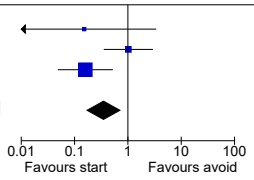
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

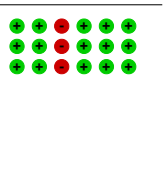
Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 2: Death

Analysis 2.3

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	1	9	7.7%	0.15 [0.01 , 3.40]
APACHE-AF 2021	6	50	6	51	22.1%	1.02 [0.35 , 2.95]
SoSTART 2021	3	101	19	102	70.3%	0.16 [0.05 , 0.52]
Total (95% CI)		**172**		**162**	**100.0%**	**0.35 [0.17 , 0.71]**
Total events:	9		26			

Heterogeneity: Chi² = 5.87, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 2.91 (P = 0.004)
Test for subgroup differences: Not applicable





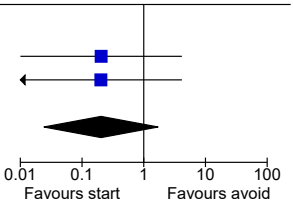
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 3: Ischaemic stroke

Analysis 2.4

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	0	9		Not estimable
APACHE-AF 2021	0	50	2	51	49.9%	0.20 [0.01 , 4.14]
SoSTART 2021	0	101	2	102	50.1%	0.20 [0.01 , 4.16]
Total (95% CI)		**172**		**162**	**100.0%**	**0.20 [0.02 , 1.71]**
Total events:	0		4			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

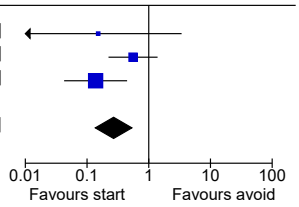


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 4: Myocardial infarction

Analysis 2.5

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	1	9	5.9%	0.15 [0.01 , 3.40]
APACHE-AF 2021	6	50	11	51	31.3%	0.56 [0.22 , 1.39]
SoSTART 2021	3	101	22	102	62.8%	0.14 [0.04 , 0.45]
Total (95% CI)		**172**		**162**	**100.0%**	**0.27 [0.14 , 0.53]**
Total events:	9		34			

Heterogeneity: Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 3.76 (P = 0.0002)
Test for subgroup differences: Not applicable

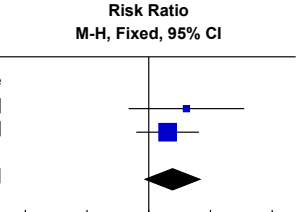


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 5: All major occlusive vascular events

Analysis 2.6

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	0	9		Not estimable
APACHE-AF 2021	4	50	1	51	19.9%	4.08 [0.47 , 35.25]
SoSTART 2021	8	101	4	102	80.1%	2.02 [0.63 , 6.50]
Total (95% CI)		**172**		**162**	**100.0%**	**2.43 [0.88 , 6.73]**
Total events:	12		5			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable

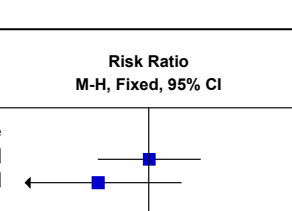


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 6: Intracranial haemorrhage

Analysis 2.7

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SoSTART 2021	0	101	0	102		Not estimable
APACHE-AF 2021	2	50	2	51	49.0%	1.02 [0.15 , 6.96]
NASPAF-ICH 2020	0	21	1	9	51.0%	0.15 [0.01 , 3.40]
Total (95% CI)		**172**		**162**	**100.0%**	**0.58 [0.13 , 2.57]**
Total events:	2		3			

Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable

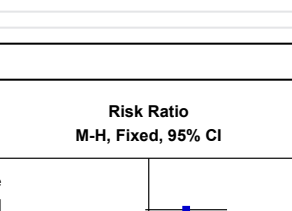


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 7: Major extracerebral haemorrhage

Analysis 2.8

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	0	9		Not estimable
SoSTART 2021	8	101	2	102	22.3%	4.04 [0.88 , 18.56]
APACHE-AF 2021	5	50	7	51	77.7%	0.73 [0.25 , 2.14]
Total (95% CI)		**172**		**162**	**100.0%**	**1.47 [0.65 , 3.32]**
Total events:	13		9			

Heterogeneity: Chi² = 3.31, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable

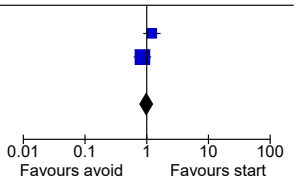


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 8: Vascular death

Analysis 2.9

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
APACHE-AF 2021	31	45	25	44	35.8%	1.21 [0.88 , 1.68]
SoSTART 2021	38	98	46	101	64.2%	0.85 [0.61 , 1.18]
Total (95% CI)		**143**		**145**	**100.0%**	**0.98 [0.78 , 1.24]**
Total events:	69		71			

Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable

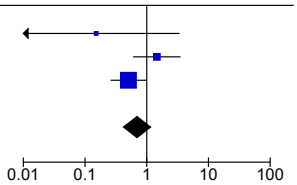


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 9: Functional status (modified Rankin Scale score 0-2) at 1 year

Analysis 2.10

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NASPAF-ICH 2020	0	21	1	9	6.7%	0.15 [0.01 , 3.40]
APACHE-AF 2021	10	50	7	51	22.4%	1.46 [0.60 , 3.53]
SoSTART 2021	11	101	22	102	70.9%	0.50 [0.26 , 0.99]
Total (95% CI)		**172**		**162**	**100.0%**	**0.70 [0.42 , 1.15]**
Total events:	21		30			

Heterogeneity: Chi² = 4.49, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

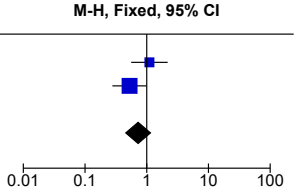


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 10: Any stroke (ischaemic or haemorrhagic)

Analysis 2.11

Study or Subgroup	Start oral anticoagulation Events	Total	Avoid oral anticoagulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
APACHE-AF 2021	13	50	12	51	34.2%	1.10 [0.56 , 2.18]
SoSTART 2021	12	101	23	102	65.8%	0.53 [0.28 , 1.00]
Total (95% CI)		**151**		**153**	**100.0%**	**0.72 [0.46 , 1.15]**
Total events:	25		35			

Heterogeneity: Chi² = 2.42, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

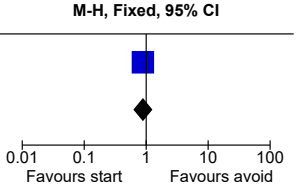


Comparison 2: Long-term therapeutic dose oral anticoagulation for atrial fibrillation (start versus avoid), Outcome 11: Any stroke (ischaemic or haemorrhagic) or vascular death

Analysis 3.1

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	54	268	61	268	100.0%	0.89 [0.64 , 1.22]
Total (95% CI)		**268**		**268**	**100.0%**	**0.89 [0.64 , 1.22]**
Total events:	54		61			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

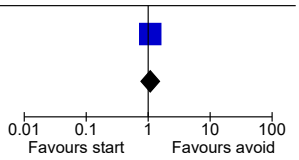


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 1: All major adverse cardiovascular events (MACE)

Analysis 3.2

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	54	268	50	268	100.0%	1.08 [0.76 , 1.53]
Total (95% CI)		**268**		**268**	**100.0%**	**1.08 [0.76 , 1.53]**
Total events:	54		50			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable

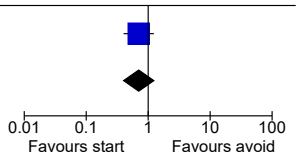


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 2: Death

Analysis 3.3

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	19	268	27	268	100.0%	0.70 [0.40 , 1.23]
Total (95% CI)		**268**		**268**	**100.0%**	**0.70 [0.40 , 1.23]**
Total events:	19		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable

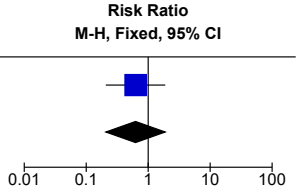


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 3: Ischaemic stroke

Analysis 3.4

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	5	268	8	268	100.0%	0.63 [0.21 , 1.89]
Total (95% CI)		**268**		**268**	**100.0%**	**0.63 [0.21 , 1.89]**
Total events:	5		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable

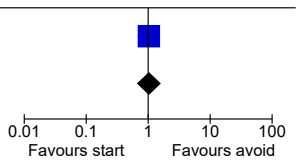


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 4: Myocardial infarction

Analysis 3.5

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	39	268	38	268	100.0%	1.03 [0.68 , 1.55]
Total (95% CI)		**268**		**268**	**100.0%**	**1.03 [0.68 , 1.55]**
Total events:	39		38			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable

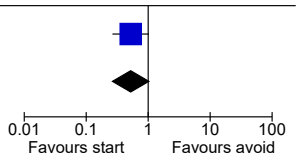


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 5: All major occlusive vascular events

Analysis 3.6

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	12	268	23	268	100.0%	0.52 [0.27 , 1.03]
Total (95% CI)		**268**		**268**	**100.0%**	**0.52 [0.27 , 1.03]**
Total events:	12		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Not applicable

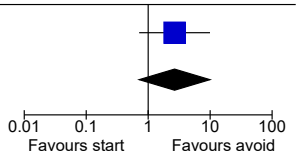


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 6: Intracerebral haemorrhage

Analysis 3.7

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	8	268	3	268	100.0%	2.67 [0.72 , 9.94]
Total (95% CI)		**268**		**268**	**100.0%**	**2.67 [0.72 , 9.94]**
Total events:	8		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

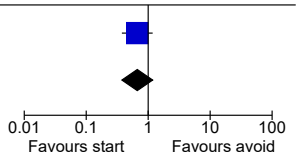


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 7: Major extracerebral haemorrhage

Analysis 3.8

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	18	268	27	268	100.0%	0.67 [0.38 , 1.18]
Total (95% CI)		**268**		**268**	**100.0%**	**0.67 [0.38 , 1.18]**
Total events:	18		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)
Test for subgroup differences: Not applicable

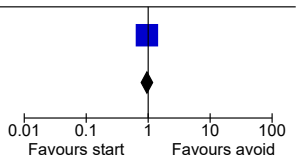


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 8: Vascular death

Analysis 3.9

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	95	230	100	231	100.0%	0.95 [0.77 , 1.18]
Total (95% CI)		**230**		**231**	**100.0%**	**0.95 [0.77 , 1.18]**
Total events:	95		100			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

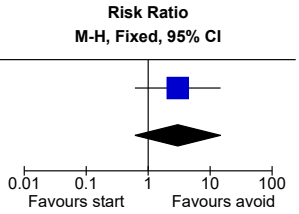


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 9: Functional status (modified Rankin Scale score 0-2) at 1 year

Analysis 3.10

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	6	268	2	268	100.0%	3.00 [0.61 , 14.73]
Total (95% CI)		**268**		**268**	**100.0%**	**3.00 [0.61 , 14.73]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

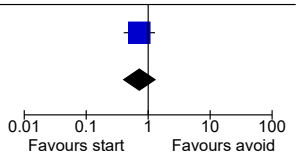


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 10: Deep vein thrombosis

Analysis 3.11

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	18	268	25	268	100.0%	0.72 [0.40 , 1.29]
Total (95% CI)		**268**		**268**	**100.0%**	**0.72 [0.40 , 1.29]**
Total events:	18		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

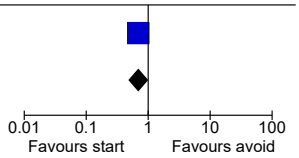


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 11: All major haemorrhagic events

Analysis 3.12

Study or Subgroup	Start antiplatelet therapy Events	Total	Avoid antiplatelet therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTART 2019	45	268	65	268	100.0%	0.69 [0.49 , 0.97]
Total (95% CI)		**268**		**268**	**100.0%**	**0.69 [0.49 , 0.97]**
Total events:	45		65			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable

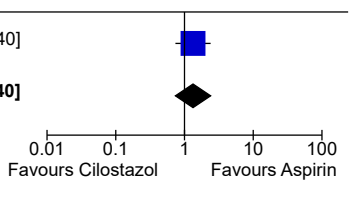


Comparison 3: Long-term antiplatelet therapy (start versus avoid), Outcome 12: Major vascular events as defined by the Antithrombotic Trialists' Collaboration

Analysis 4.1

Study or Subgroup	Cilostazol Events	Total	Aspirin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	22	142	17	146	100.0%	1.33 [0.74 , 2.40]
Total (95% CI)		**142**		**146**	**100.0%**	**1.33 [0.74 , 2.40]**
Total events:	22		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

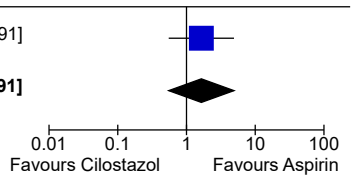


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 1: All major adverse cardiovascular events (MACE)

Analysis 4.2

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	8	142	5	146	100.0%	1.65 [0.55 , 4.91]
Total (95% CI)		**142**		**146**	**100.0%**	**1.65 [0.55 , 4.91]**
Total events:	8		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

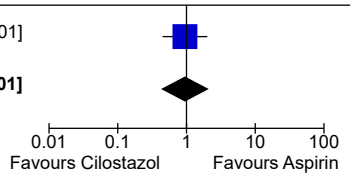


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 2: Death

Analysis 4.3

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	12	142	13	146	100.0%	0.95 [0.45 , 2.01]
Total (95% CI)		**142**		**146**	**100.0%**	**0.95 [0.45 , 2.01]**
Total events:	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

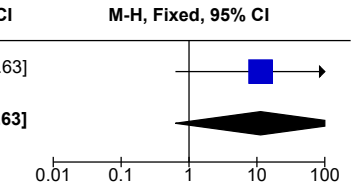


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 3: Ischaemic stroke

Analysis 4.4

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	5	142	0	146	100.0%	11.31 [0.63 , 202.63]
Total (95% CI)		**142**		**146**	**100.0%**	**11.31 [0.63 , 202.63]**
Total events:	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable

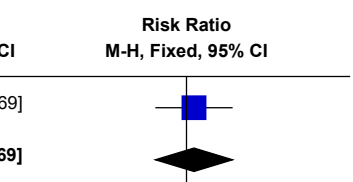


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 4: Myocardial infarction

Analysis 4.5

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	5	142	4	146	100.0%	1.29 [0.35 , 4.69]
Total (95% CI)		**142**		**146**	**100.0%**	**1.29 [0.35 , 4.69]**
Total events:	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

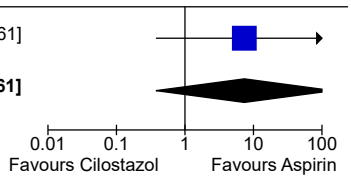


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 5: Intracerebral haemorrhage

Analysis 4.6

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	3	142	0	146	100.0%	7.35 [0.38 , 143.61]
Total (95% CI)		**142**		**146**	**100.0%**	**7.35 [0.38 , 143.61]**
Total events:	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

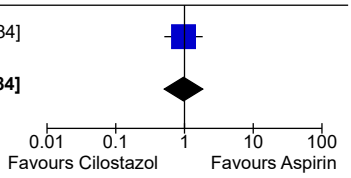


Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 6: Vascular death

Analysis 4.7

Study or Subgroup	Cilostazol Events	Cilostazol Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PICASSO sub-group 2020	16	142	17	146	100.0%	0.97 [0.51 , 1.84]
Total (95% CI)		**142**		**146**	**100.0%**	**0.97 [0.51 , 1.84]**
Total events:	16		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Comparison 4: Long-term antiplatelet therapy (cilostazol versus aspirin), Outcome 7: Any stroke (ischaemic or haemorrhagic)


Antithrombotic treatment after stro…


Antithrombotic treatment after stro…