Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate

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CRD summary

The review used indirect evidence to conclude that in patients with atrial fibrillation, dabigatran etexilate significantly reduced the risk of stroke, systemic embolism and mortality compared to placebo, reduced stroke compared to aspirin and reduced stroke and systemic embolism compared to aspirin plus clopidogrel. Study heterogeneity and sensitivity analyses implied that the authors' conclusions should be treated with caution.

Authors' objectives

To compare the safety and efficacy of dabigatran etexilate to other treatments for stroke prevention in patients with atrial fibrillation.

Searching

MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS and The Cochrane Library were searched to August 2009 for publications in any language; search terms were not reported. Reference lists from relevant systematic reviews and meta-analyses were handsearched. Letters and comment articles were excluded.

Study selection

Randomised controlled trials (RCTs) of patients with atrial fibrillation who were treated for prevention of stroke were eligible for inclusion. Eligible trials had to include at least one of the active interventions: adjusted dose vitamin K antagonists; fixed low-dose warfarin with or without aspirin; aspirin monotherapy; aspirin plus clopidogrel; indobufen; idraparinux; triflusal; ximelagatran; and dabigatran etexilate. Phase 1 studies, short-term phase 2 studies, studies with subgroup or pooled analyses, secondary prevention studies and studies with no outcome data were excluded. Eligible outcomes were (all) stroke, ischaemic stroke, systemic embolism, all-cause mortality, intracranial haemorrhage (haemorrhagic stroke excluded), extracranial haemorrhage (major bleeds) and acute myocardial infarction. Haemorrhagic stroke, fatal or disabling strokes and pulmonary embolism were eligible outcomes but, due to lack of data and/or low event counts and/or inconsistent reporting, relevant data were presented in an online appendix for haemorrhagic stroke and the other two outcomes were not included in the meta-analysis. Excluded outcomes were transient ischaemic attack, minor bleeds, "any bleeds" and adverse events including dyspepsia.

Dabigatran etexilate was given at the two recommended dose levels in the studies (110mg twice a day and 150mg twice a day). Twelve out of 20 trials used the recommended target international normalised ratio (INR) of 2.0 to 3.0 in the adjusted dose vitamin K antagonists arm. Mean age of patients ranged from 65.0 to 83.5 years. The percentage of males ranged from 39% to 100%.

Two independent reviewers performed the selection. Disagreements resolved by discussion with a third reviewer.

Assessment of study quality

Methodological quality was assessed using the Jadad scale of randomisation, blinding, withdrawals and drop-outs (maximum score 5). Studies that scored 2 or less were excluded from the meta-analysis.

The authors did not report how many reviewers performed the quality assessment.

Data extraction

Numbers of events for each outcome were extracted to enable calculation of the relative risk (RR) and 95% confidence intervals (CI).

The authors did not report how many reviewers performed data extraction.

Methods of synthesis

Meta-analyses were only performed for trials with a Jadad score of at least 3. Relative risks with 95% CIs were determined using mixed log-binomial models with a separate fit for each outcome. The model included a fixed treatment effect, a random study effect and fixed effect for the mean length of follow-up centred on the mean. Separate analyses were performed for the two dabigatran etexilate doses (110mg twice a day and 150mg twice a day). Dabigatran etexilate was compared to placebo, aspirin monotherapy, aspirin plus clopidogrel and adjusted dose vitamin K antagonists (any dose).

Three sensitivity analyses were performed. One compared dabigatran etexilate with adjusted dose vitamin K antagonists using only trials with the recommended target INR of 2.0 to 3.0 in the adjusted dose vitamin K antagonists arm. Another analysis excluded trials that used medications not approved or infrequently used for stroke prevention (relevant treatment options analysis, non-relevant treatment options were considered to be fixed low dose warfarin with or without aspirin, indobufen, idraparinux, triflusal and ximelagatran). The third analysis included the ACTIVE A trial that was excluded from the primary analysis as it included data only from patients ineligible for anticoagulation. Numbers needed to treat (NNT) were calculated.

Results of the review

Twenty-four RCTs were identified, but data were reported only for the 21 RCTs with a Jadad score of at least 3 (n=52,748 participants, range 75 to 18,113). Mean follow-up ranged from 10 to 42 months.

Compared to placebo, 150mg dabigatran etexilate significantly reduced the risk of all stroke by 75% (RR 0.25, 95% CI 0.12 to 0.51), ischaemic stroke by 77% (RR 0.23, 95% CI 0.14 to 0.38), systemic embolism by 83% (RR 0.17, 95% CI 0.05 to 0.50) and mortality by 36% (RR 0.64, 95% CI 0.45 to 0.91). There were no significant differences for extracranial haemorrhage or acute myocardial infarction.

Compared to aspirin monotherapy, 150mg dabigatran etexilate significantly reduced the risk of all stroke by 63% (RR 0.37, 95% CI 0.20 to 0.69) and ischaemic stroke by 52% (RR 0.48, 95% CI 0.27 to 0.84). There were no significant differences for the other outcomes.

Compared to aspirin plus clopidogrel, 150mg dabigatran etexilate significantly reduced the risk of all stroke by 61% (RR 0.39, 95% CI 0.21 to 0.72), ischaemic stroke by 63% (RR 0.37, 95% CI 0.23 to 0.61) and systemic embolism by 79% (RR 0.21, 95% CI 0.07 to 0.61). There were no significant differences for the other outcomes.

Compared to adjusted dose vitamin K antagonists, 150mg dabigatran etexilate significantly reduced the risk of any stroke by 35% (RR 0.65, 95% CI 0.45 to 0.94). There were no significant differences for the other outcomes.

Compared to placebo, 110mg dabigatran etexilate significantly reduced the risk of all stroke by 65% (RR 0.35, 95% CI 0.17 to 0.71), ischaemic stroke by 67% (RR 0.33, 95% CI 0.21 to 0.54), systemic embolism by 81% (RR 0.19, 95% CI 0.06 to 0.57) and mortality by 34% (RR 0.66, 95% CI 0.47 to 0.93).

Compared to aspirin monotherapy, 110mg dabigatran etexilate significantly reduced the risk of all stroke by 48% (RR 0.52, 95% CI 0.28 to 0.96).

Compared to aspirin plus clopidogrel, 110mg dabigatran etexilate significantly reduced the risk of ischaemic stroke by 46% (RR 0.54, 95% CI 0.33 to 0.87), systemic embolism by 76% (RR 0.24, 95% CI 0.08 to 0.70) and all stroke by 45% (RR 0.55, 95% CI 0.30 to 1.00; borderline significance).

Compared to adjusted dose vitamin K antagonists, 110mg dabigatran etexilate significantly reduced the risk of intracranial haemorrhage by 67% (RR 0.33, 95% CI 0.15 to 0.72). There were no significant differences for other outcomes.

Numbers needed to treat and data for the numbers of trial arms for each treatment by outcome were reported. Results for the sensitivity analyses were reported in an online appendix, which changed the significance of some results, especially for 110 mg dabigatran etexilate and particularly when the ACTIVE trial was included in analyses.

Authors' conclusions

Indirect evidence suggested that treatment with dabigatran etexilate offered benefits for the prevention of stroke, systemic embolism and mortality over antiplatelets and placebo in patients with atrial fibrillation. There was no indication of increased intracranial or extracranial haemorrhage with dabigatran etexilate compared to antiplatelet agents.

CRD commentary

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language. It appeared that unpublished studies were not specifically searched for and so some relevant studies may have been missed. Publication bias was not assessed. Study quality was assessed using suitable criteria and low quality studies were excluded from the meta-analysis; no details of the quality of individual studies were reported. Study selection was carried out in duplicate to reduce error and bias; the authors did not report whether this process was applied to other aspects of the review process. Relevant study details were reported. Drug dosage details were reported only for dabigatran etexilate.

The statistical method used for the meta-analysis was unusual, but the authors found that the results were similar to those when conventional analyses was used. The authors expected there to be statistical heterogeneity, but limited relevant study design data were reported. Relevant sensitivity analyses were performed. The authors commented that the older studies appeared to be of lower quality.

Heterogeneity between the studies and the changes in results when sensitivity analyses were performed implied that the authors' conclusions should be treated with caution.

Implications of the review for practice and research

Practice: The authors stated that dabigatran etexilate represented a treatment alternative to warfarin for patients deemed to be unsuitable for warfarin.

Research: The authors did not state any implications for research.

Funding

Boehringer Ingelheim.

Bibliographic details

Roskell NS, Lip GY, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. Thrombosis and Haemostasis 2010; 104(6): 1106-1115

PubMedID

20967400

DOI

10.1160/TH10-10-0642

Original Paper URL

http://www.schattauer.de/en/magazine/subject-areas/journals-a-z/thrombosis-and-haemostasis/contents/archive/issue/1290/manuscript/13878.html

Additional Data URL

http://www.schattauer.de/fileadmin/assets/zeitschriften/thrombosis_ and_ haemostasis/supplemetary_ material/105_ 2/TH105.2_ Roskell_ Suppl_ Material.pdf

Indexing Status

Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Anticoagulants /adverse effects /therapeutic use; Atrial Fibrillation /blood /complications /drug therapy; Benzimidazoles /adverse effects /therapeutic use; Clinical Trials as Topic; Dabigatran; Evidence-Based Medicine; Female; Hemorrhage /chemically induced; Humans; Male; Platelet Aggregation Inhibitors /adverse effects /therapeutic use; Pyridines /adverse effects /therapeutic use; Risk Assessment; Risk Factors; Stroke /blood /etiology /prevention & control; Treatment Outcome

AccessionNumber
12011000181

Date bibliographic record published
13/04/2011

Date abstract record published
02/11/2011

Record Status
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