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ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Hart RG rivaroxaban versus Aspirina	RCT	172	+	+	+	+

Characteristics of studies

Hart RG, [unknown year]

Population

1. Additional exclusion criteria were a history of atrial fibrillation , severely disabling stroke (modified Rankin score of ,â•4 at screening; scores range from 0 to 6, with higher scores representing worse functional deficits), a specific indication for anticoagulation or for antiplatelet therapy, ongoing regular use of conventional nonsteroidal antiinflammatory drugs, major bleeding within the previous 6 months, and previous nontraumatic intracranial hemorrhage.

	2. Trial Population Patients who had ischemic stroke, as identified on cerebral imaging, that had occurred between 7 days and 6 months before screening were eligible if the stroke was not lacunar and was not associated with extracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of ischemia or with identified risk factors for a cardiac source of embolism (atrial fibrillation, left ventricular thrombus, mechanical prosthetic cardiac valve, or severe mitral stenosis) and if no other cause of stroke could be found. 3. METHODS We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source.
Intervention	1. 6,7 Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to country and age of the patient (<60 years vs. ,â•60 years), with the use of an interactive Webresponse system, to receive either rivaroxaban at a dose of 15 mg (immediate-release, film-coated tablets) plus placebo or aspirin at a dose of 100 mg (enteric coated tablets) plus placebo; in each group, the two tablets (active drug and placebo) were taken orally once daily. 2. METHODS We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source. 3. A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin.
Outcomes	1. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding. 2. Secondary efficacy outcomes were a composite of death from cardiovascular causes, recurrent stroke, systemic embolism, and myocardial infarction; death from any cause; disabling stroke (modified Rankin scale score of 4 or 5 at hospital discharge) or fatal stroke (modified Rankin scale score of 6); and individual components of the primary and secondary efficacy outcomes. 3. Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; P<0.001).

Bias	Judgement	Support for judgement
Random sequence generation	low	1. 6,7 Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to country and age of the patient (<60 years vs. ,â•60 years), with the use of an interactive Webresponse system, to receive either rivaroxaban at a dose of 15 mg (immediate-release, film-coated tablets) plus placebo or aspirin at a dose of 100 mg (enteric coated tablets) plus placebo; in each group, the two tablets (active drug and placebo) were taken orally once daily. 2. A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. 3. Investigators and patients were unaware of the treatment assignments during the trial.
Allocation concealment	low	1. Investigators and patients were unaware of the treatment assignments during the trial. 2. The median time from the qualifying stroke to randomization was 37 days (interquartile range, 14 to 88); 25% of the patients were entered within 2 weeks. 3. The mean age of the patients was 67 years, and 62% of the patients

		were men.
Blinding of participants and personnel	low	1. Investigators and patients were unaware of the treatment assignments during the trial. 2. Potential outcome events that did not meet all the trial protocol criteria were adjudicated by stroke experts who were fluent in the language of the participating clinical site and who reviewed untranslated source documents and, if there was disagreement with the local investigator, by the secondary review of translated source documents by the chairs of the central adjudication committee, all of whom were unaware of the treatment assignments. 3. Active medication and identical placebos were taken with food; adherence to assigned therapy was assessed by means of interview and pill counts at each clinic visit.
Blinding of outcome assessment	low	1. 6,7 Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to country and age of the patient (<60 years vs. ,â•60 years), with the use of an interactive Webresponse system, to receive either rivaroxaban at a dose of 15 mg (immediate-release, film-coated tablets) plus placebo or aspirin at a dose of 100 mg (enteric coated tablets) plus placebo; in each group, the two tablets (active drug and placebo) were taken orally once daily. 2. Potential outcome events that did not meet all the trial protocol criteria were adjudicated by stroke experts who were fluent in the language of the participating clinical site and who reviewed untranslated source documents and, if there was disagreement with the local investigator, by the secondary review of translated source documents by the chairs of the central adjudication committee, all of whom were unaware of the treatment assignments. 3. Exploratory analyses of prespecified subgroups were undertaken with the variables of age, sex, geographic region, time from the index stroke to randomization, and renal function, but the trial was not powered for subgroup comparisons .