Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Warfarin was not more effective than aspirin and increased adverse events in symptomatic intracranial arterial stenosis

Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. **Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis.** N Engl J Med. 2005;352:1305-16.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hematol/Thrombo ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with symptomatic intracranial arterial stenosis, how does aspirin compare with warfarin?

METHODS

Design: Randomized controlled trial (Warfarin-Aspirin Symptomatic Intracranial Disease [WASID] Trial).
Allocation: Concealed.*
Blinding: Blinded (patients and outcome assessors).*
Follow-up period: Mean 1.8 years.
Setting: 59 sites in North America.
Patients: 569 patients ≥ 40 years of age (mean age 64 y, 61.5% men) with transient ischemic attack or nondisabling stroke in the previous 90 days caused by angiographically verified 50% to 99% stenosis of a major intracranial artery and a modified Rankin score ≤ 3. Exclusion criteria included tandem 50% to 99% stenosis of the extracranial carotid artery, nonatherosclerotic stenosis of an intracranial artery, and a cardiac source of embolism.
Intervention: Aspirin, 1300 mg/d (n = 280), or warfarin, 5 mg/d initial dose, which was adjusted to achieve an international normalized ratio (INR) target range of 2.0 to 3.0 (n = 289).
Outcomes: Primary composite endpoint of ischemic stroke, brain hemorrhage, and death from vascular causes other than stroke; and adverse events.
Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

Aspirin and warfarin did not differ for the primary composite endpoint or for death from vascular or nonvascular causes (Table). Warfarin was associated with higher rates of all-cause death, major hemorrhage, and myocardial infarction or sudden death than aspirin (Table).

CONCLUSION

In patients with symptomatic intracranial arterial stenosis, warfarin was not more effective than aspirin and increased the rates of all-cause death, major hemorrhage, and myocardial infarction or sudden death.

Sources of funding: National Institutes of Health; Bristol-Myers Squibb; Bayer.

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*See Glossary.

Aspirin vs warfarin for symptomatic intracranial arterial stenosis at mean 1.8 years†

Outcomes	Aspirin	Warfarin	HR (95% CI)	RRI (CI)	NNH
Primary composite endpoint‡	22.1%	21.8%	1.04 (0.73 to 1.48)	4% (–25 to 40)	Not significant
				RRR (CI)	NNT (CI)
All-cause death	4.3%	9.7%	0.46 (0.23 to 0.90)	53% (10 to 76)	20 (14 to 108)
Death from vascular causes	3.2%	5.9%	0.56 (0.25 to 1.26)	43% (–25 to 74)	Not significant
Death from nonvascular causes	1.1%	3.8%	0.30 (0.08 to 1.07)	70% (–7 to 92)	Not significant
Major hemorrhage	3.2%	8.3%	0.39 (0.18 to 0.84)	60% (15 to 81)	18 (13 to 67)
Myocardial infarction or sudden death	2.9%	7.3%	0.40 (0.18 to 0.91)	59% (9 to 81)	24 (17 to 158)

†HR = hazard ratio. Other abbreviations defined in Glossary; NNT and CI calculated from data in article.
‡Primary composite endpoint = ischemic stroke, brain hemorrhage, and death from vascular causes other than stroke.

COMMENTARY

Uncertainty has existed on whether aspirin or warfarin should be the preferred antithrombotic in selected patients at high risk for noncardioembolic stroke, and whether aspirin is effective and safe for primary prevention of cardiovascular disease in women.

The WASID trial did not show any difference in efficacy between warfarin (target INR 2.0 to 3.0) and aspirin for preventing stroke or nonstroke vascular death in patients with symptomatic major intracranial artery stenosis. However, the study had to be stopped early because of evidence of harm with warfarin.

The high incidence of bleeding in patients treated with warfarin (5/100 patient-y) is surprising. This may be due to the broad definition of major bleeding. The high dose of aspirin used in this study (1300 mg/d) may have selectively increased bleeding in patients treated with aspirin (1), reducing the difference between the 2 treatments. Nevertheless, a clear excess of bleeding with warfarin remained evident. The increased all-cause mortality with warfarin compared with aspirin is unexplained. Previous randomized trials suggest that moderate-intensity warfarin (INR 2.0 to 3.0) is at least as effective as aspirin for preventing major vascular events (2). Yet, warfarin in the WASID trial was associated with a consistent pattern of excess deaths from both vascular and nonvascular causes, including myocardial infarction, sudden death, and cancer. This is unlikely to be explained by the efficacy of high-dose aspirin because, unlike safety, no convincing evidence exists to suggest that the efficacy of aspirin is dose-related (1, 3). The optimal dose of aspirin is less clear from these data but, when considered in the context of what we already know, a strong argument can be made to use the lowest proven effective dose (75 to 150 mg/d), thereby minimizing the risk for bleeding complications.

In 2002, the U.S. Preventive Services Task Force concluded that good evidence existed to suggest that aspirin lowers the incidence of coronary artery disease in adults without previous symptomatic cardiovascular disease (4). This conclusion was based on a review of 5 randomized trials involving > 50 000 persons. However, aspirin did not reduce stroke and the evidence was less clear for women because only 20% of trial participants were women.

The Women's Health Study randomized almost 40 000 initially healthy women. In contrast to previous trials, aspirin did not reduce myocardial infarction or death but lowered the incidence for ischemic

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Low-dose aspirin lowered stroke risk but not risk for MI or cardiovascular death in women

Ridker PM, Cook NR, Lee IM, et al. **A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women.** N Engl J Med. 2005;352:1293-304.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Neurology ★★★★★★★

QUESTION

Is low-dose aspirin effective for the primary prevention of cardiovascular disease in women?

METHODS

Design: Randomized placebo-controlled trial (Women's Health Study).
Allocation: {Concealed}†.*
Blinding: Blinded {health care providers, participants, data collectors, and outcome assessors}†.*
Follow-up period: Mean 10 years.
Setting: United States and Puerto Rico.
Participants: 39 876 women ≥ 45 years of age (mean age 55 y) who had no history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness or contraindication to the study medications; were not taking aspirin, nonsteroidal anti-inflammatory drugs, anticoagulants, or corticosteroids; and were not taking vitamin A or E, or β-carotene supplements more than once per week.
Intervention: Aspirin, 100 mg every other day (n = 19 934), or placebo (n = 19 942).
Outcomes: First major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes; individual cardiovascular endpoints; and adverse events.
Patient follow-up: 97% (intention-to-treat analysis).

MAIN RESULTS

Women receiving aspirin and those receiving placebo did not differ for rates of a first major cardiovascular event, death from cardiovascular causes, or fatal or nonfatal myocardial infarction (Table). Women receiving aspirin had lower rates of stroke and transient ischemic attack but a higher rate of gastrointestinal bleeding requiring transfusion than did those receiving placebo (Table).

CONCLUSION

Low-dose aspirin lowered risk for stroke but not risk for myocardial infarction or death from cardiovascular causes.

Sources of funding: National Heart, Lung, and Blood Institute and National Cancer Institute.

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*See Glossary.
†Information provided by author.

Aspirin vs placebo for primary prevention of cardiovascular disease in women at mean 10 years‡

Outcomes	Aspirin	Placebo	RRR (95% CI)	NNT (CI)
Major cardiovascular event§	2.4%	2.6%	9% (–3 to 20)	Not significant
Stroke	1.1%	1.3%	17% (1 to 31)	445 (227 to 10377)
Death from cardiovascular causes	0.60%	0.63%	5% (–22 to 26)	Not significant
Transient ischemic attack	0.93%	1.2%	22% (6 to 36)	385 (216 to 1687)
			RRI (CI)	**NNH (CI)**
Fatal or nonfatal myocardial infarction	0.99%	0.97%	2% (–16 to 25)	Not significant
Gastrointestinal bleeding requiring transfusion	0.6%	0.5%	40% (7 to 83)	554 (305 to 2751)

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
§Major cardiovascular event = nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

COMMENTARY

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stroke and transient ischemic attack. These benefits were partly counterbalanced by an increase in gastrointestinal ulcers and bleeding, highlighting the potential for toxicity even if low doses of aspirin are taken every other day, and the importance of balancing risks and benefits when making decisions about the use of aspirin for primary prevention of cardiovascular disease.

Controversy concerning apparent sex differences in the antiplatelet effects of aspirin is not new. Subgroup analyses from early randomized aspirin trials suggested that men, but not women, benefited from aspirin (5, 6); later, large trials and systematic reviews (3) confirmed a benefit for both. In the Women's Health Study, the low event rates and use of a potentially suboptimal aspirin dose may have contributed to the apparent lack of benefit of aspirin for preventing myocardial infarction. However, lack of evidence of benefit is not the same as evidence of lack of benefit; the 95% CI of the risk estimates do not exclude a 16% reduction in myocardial infarction or a 20% reduction in major cardiovascular events with aspirin treatment. Nevertheless, if a benefit exists, it is small in absolute terms.

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