

Warfarin alone or with aspirin was superior to aspirin alone after acute myocardial infarction but increased bleeding

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med.* 2002;347:969-74.

QUESTION

In patients who had an acute myocardial infarction (MI), what is the efficacy and safety of long-term treatment with warfarin plus aspirin, warfarin alone, or aspirin alone?

DESIGN

Randomized (allocation concealed*), blinded {data collectors, outcome assessors, monitoring committee, and data analysts}†,* controlled trial with mean follow-up of 1445 days (about 4 y) (Warfarin, Aspirin, Reinfarction Study [WARIS II]).

SETTING

20 hospitals in Norway.

PATIENTS

3630 patients < 75 years of age who were hospitalized for, and had survived, an acute MI. Exclusion criteria included malignant disease. Follow-up was 99.6%.

INTERVENTION

Patients were allocated to warfarin, with the goal of achieving an international normalized ratio (INR) of 2.0 to 2.5, plus aspirin, 75 mg daily ($n = 1208$); warfarin with the goal of achieving an INR of 2.8 to 4.2 ($n = 1216$); or aspirin, 160 mg daily ($n = 1206$).

MAIN OUTCOME MEASURES

The main outcome was the composite measure of death, nonfatal reinfarction, or thromboembolic stroke, whichever occurred first. These outcomes were also separately reported.

MAIN RESULTS

Analysis was by intention to treat. Both warfarin groups had lower rates for the main composite measure, nonfatal reinfarction, and thromboembolic stroke than the aspirin-alone group (Table); the 2 warfarin groups did not differ for these outcomes. The 3 groups did not differ for overall mortality. Both warfarin groups had higher rates for nonfatal major bleeding episodes than the aspirin-alone group (Table); the 2 warfarin groups did not differ for this outcome.

CONCLUSION

In patients who had an acute myocardial infarction, long-term treatment with war-

farin in combination with aspirin or warfarin alone led to a lower risk for the composite outcome of death, nonfatal reinfarction, or thromboembolic stroke than aspirin alone, but increased the risk for nonfatal major bleeding.

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*See Glossary.

†Information provided by author.

Warfarin or warfarin plus aspirin (Asp) vs Asp after acute myocardial infarction at mean follow-up of 1445 days‡

Outcomes	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Composite outcome [§]	Warfarin + Asp vs Asp	15% vs 20%	25% (11 to 37)	20 (12 to 51)
	Warfarin vs Asp	17% vs 20%	16% (1 to 29)	30 (16 to 483)
Nonfatal reinfarction	Warfarin + Asp vs Asp	6% vs 10%	41% (22 to 56)	25 (16 to 53)
	Warfarin vs Asp	7% vs 10%	24% (1 to 41)	43 (22 to 1364)
Thromboembolic stroke	Warfarin + Asp vs Asp	1% vs 3%	47% (6 to 70)	80 (41 to 797)
	Warfarin vs Asp	1% vs 3%	47% (6 to 70)	80 (41 to 721)
			RRI (CI)	NNH (CI)
Nonfatal major bleeding	Warfarin + Asp vs Asp	2% vs 0.7%	249% (63 to 650)	60 (37 to 137)
	Warfarin vs Asp	3% vs 0.7%	309% (93 to 767)	49 (31 to 93)

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

§Composite outcome = death, nonfatal reinfarction, or thromboembolic stroke, whichever occurred first.

COMMENTARY

The trial by Hurlen and colleagues will have a limited effect on clinical practice because the liabilities of an aspirin and warfarin combination are well-known. In this trial, the marked increase in bleeding counterbalances the benefit of efficacy in the composite endpoint. The problems about the need for INR surveillance and the open-trial design are also notable. The most important contribution of the trial is to show that aspirin alone is not adequate, and future trials of more attractive combinations, such as aspirin plus clopidogrel, or aspirin and an oral direct thrombin inhibitor, are in progress. Ultimately, improved efficacy without significant incremental bleeding is the goal for a patient-friendly, post-MI thromboprophylaxis strategy. Accordingly, although the current trial was well-done, its main contribution is a proof of concept that aspirin monotherapy is insufficient. In select patients with left ventricu-

lar dysfunction or atrial fibrillation after MI, the aspirin and warfarin combination may be useful but it is hoped that better strategies will be validated in the future.

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AUTHOR RESPONSE

The incidence of major nonfatal bleeding associated with warfarin did not counterbalance the benefit in terms of the composite endpoint (neither by number nor severity of disease). We believe that analysis by the intention-to-treat principle compensated for the open-trial design. This trial stresses the importance of anticoagulation in addition to platelet inhibition.