

# Review: Oral anticoagulants plus antiplatelet agents reduce thromboembolism and all-cause mortality for heart valve prostheses

Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol*. Feb 2001;37:569-78.

## QUESTION

In patients with mechanical prosthetic heart valves, are combined oral anticoagulants and antiplatelet therapy more efficacious than anticoagulants alone?

## DATA SOURCES

Studies were identified by searching MEDLINE (1966 to November 1999) with the terms heart-valve prosthesis, mechanical heart-valve, thromboembolism, anticoagulant, antiplatelet, and hemorrhage. Bibliographies of studies, reviews, meta-analyses, and consensus statements were also checked.

## STUDY SELECTION

Full text and abstracts of randomized controlled trials were selected if patients with prosthetic heart valves were studied, oral anticoagulation plus antiplatelet agents were compared with oral anticoagulation alone, and objective methods were used to assess outcomes and adverse effects.

## DATA EXTRACTION

Data were extracted on study characteristics and quality; interventions, including type and duration of anticoagulation and antiplatelet agents; target international normalized ratio (INR) or prothrombin time ratio; and outcomes (all-cause mortality,

thromboembolism [VTE], and major hemorrhagic events).

## MAIN RESULTS

10 RCTs (2199 patients) met the inclusion criteria. 6 studies evaluated dipyridamole, and 4 evaluated aspirin. All trials reported VTE events and all-cause mortality; 2 trials did not report hemorrhagic events. The combination of antiplatelet agents and oral anticoagulants reduced the incidence of VTE events ( $P < 0.001$ ) and all-cause mortality ( $P < 0.001$ ), while increasing the rate of major hemorrhagic events ( $P = 0.03$ ) (Table). Both aspirin and dipyridamole showed similar reductions in all-cause mortality and VTE events. Because the recommended dose of aspirin has decreased over time, subgroup analyses were done for trials before and after

1990. Early trials showed that major bleeding events were increased (odds ratio [OR] 2.23, 95% CI 1.28 to 3.87); later trials showed no difference (OR 0.88, CI 0.37 to 2.16).

## CONCLUSIONS

Adding antiplatelet agents to oral anticoagulants decreases thromboembolic events and all-cause mortality in patients with mechanical prosthetic heart valves. The increased incidence of major bleeding events with combined therapy has diminished in the current, lower-dose era.

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For correspondence: Dr. D. Massel, London Health Sciences Center, Room 205, Colborne Building, Victoria Campus, 375 South Street, London, Ontario N6A 4G5, Canada. FAX 519-667-6687/6648. ■

### Antiplatelet therapy added to oral anticoagulants (combined therapy) vs anticoagulants alone (single therapy) for patients with mechanical prosthetic heart valves (follow-up 1 to 2.5 y)\*

Outcomes	Weighted event rates		RRR (95% CI)	NNT (CI)
	Combined therapy	Single therapy		
Thromboembolic events	5.5%	8.9%	57% (38 to 70)	30 (19 to 62)
All-cause mortality	5.8%	9.5%	49% (35 to 67)	27 (18 to 35)
			RRI (CI)	NNH (CI)
Hemorrhagic events	6.4%	5.0%	45% (3 to 106)	72 (31 to 222)

\*Abbreviations defined in Glossary; weighted event rates, RRI, and NNH and related CIs calculated from data in article.

## COMMENTARY

A commonly followed scheme for prophylaxis of VTE events from prosthetic valves on the basis of task force recommendations (1) and consideration of the evidence for valve type and location as they affect the incidence of VTE events is included in a review by Fuster and Verstraete (2).

Before the addition of platelet inhibitors, VTE rates for mechanical valves remained substantial despite meticulous anticoagulant treatment. Several studies adding aspirin, 500 to 1000 mg/d, or dipyridamole showed reductions in VTE events with increases in serious hemorrhages. Turpie and colleagues (3) showed that low-dose aspirin (50 to 100 mg/d) reduced VTE events without an increase in major hemorrhage. This finding was verified by Meschengieser and colleagues (4), who found that VTE events could be controlled by warfarin with lower target INR plus low-dose aspirin.

By using extensive meta-analysis techniques, Massel and Little showed that addition of a platelet inhibitor to warfarin reduced the risk for both VTE events and all-cause mortality, although the risk for bleeding was increased. They found further that dipyridamole and high-dose aspirin used in the older studies probably increased bleeding more than did low-dose aspirin (3, 4). The results of these studies combined with the different propensities of mechanical and

tissue valves in mitral or aortic positions to embolize led to the current practice of combining anticoagulation therapy with warfarin and low-dose aspirin (1, 2).

Jay S. Meisner, MD, PhD  
Aung Hla, MD  
Albert Einstein College of Medicine  
Bronx, New York, USA

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