Warfarin, acetylsalicylic acid or both?

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347(13): 969-74.

Background: Acetylsalicylic acid's (ASA, or aspirin) effect as a platelet-inhibiting agent has made it the mainstay of secondary prevention after myocardial infarction. Yet, it is known that coagulation proteases are directly involved not only in thrombosis but also in the inflammatory and cellular processes that are involved in promoting atherosclerosis and coronary thrombosis. Thus several studies have examined the usefulness of using warfarin, alone or in combination with ASA for the secondary prevention of myocardial infarction and death. Earlier trials may have used too low a dose of warfarin.

Question: Which of the following drug therapies results in fewer combined adverse outcomes defined as death, nonfatal reinfarction or thromboembolic stroke: warfarin at a dose targeted to achieve an international normalized ratio (INR) of 2.8–4.2, 160 mg of ASA daily, or 75 mg of ASA daily combined with warfarin (to achieve an INR of 2.0–2.5)?

Design: This was a multicentre, open-label, randomized controlled trial conducted in Norway by investigators with no declared conflicts of interest and funded by the Norwegian Council on Cardiovascular Disease. After myocardial infarction, patients were allocated randomly to one of the 3 groups before they left hospital and followed for up to 5 years. The randomization was centrally administered, and the data were stratified by site.

Results: The 3630 patients (about 75% of whom were men) entered in the study were all less than 75 years of age. Average follow-up after randomization was 4 years, and only 14 patients were lost to follow-up. The distribution of risk factors for subsequent reinfarction was similar in the 3 treatment groups. A primary outcome event occurred in 241 (20%) of patients treated with ASA alone, 203 (16.7%) treated with warfarin alone and 181 (15.0%) with the combination of warfarin and ASA. The rate ratios were as follows: ASA plus warfarin compared with ASA alone (0.71, 95% confidence interval [CI] 0.60–0.83); warfarin compared with ASA (0.81, 95% CI 0.69–0.95). Major bleeding episodes occurred in 8 patients taking ASA, 33 taking warfarin alone, and 28 receiving the combination of ASA and warfarin. Of patients taking ASA, 191 were withdrawn from the study, compared to 387 on warfarin, and 480 for ASA and warfarin. The most common reason for withdrawal in the latter 2 groups was coronary artery bypass grafting and percutaneous coronary intervention.

Commentary: This is a carefully done study with almost complete follow-up. The fact that it was multicentred makes it more likely that the results can be anticipated in the usual hospital and office settings where patients with myocardial infarction are treated and followed. The doses of both warfarin and ASA are typical of those commonly employed. The main benefit of warfarin, alone or in combination with ASA, was the prevention of nonfatal reinfarction and nonfatal thromboembolic stroke. The mortality across all 3 groups, however, was almost identical.

Implications for practice: This study creates another dilemma for clinicians. The nontrivial gains resulting from combining warfarin with ASA to achieve an INR of 2.0–2.5 compared to usual therapy with ASA in a dose of 75 mg daily must be balanced against the increased risks of a serious bleeding episode and the fact that life does not appear to be prolonged, at least over the 4-year follow-up of this study. In an accompanying editorial in the same issue of the Journal, Richard Becker, who is supported in his work in part by pharmaceutical companies and who has received speaking fees from Aventis, says that adding oral anticoagulation should be "strongly considered," particularly in patients at risk for thromboembolic events.

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BOOKS RECEIVED

Ashley BM, O'Rourke KD. **Ethics of health care: an introductory textbook**. 3rd ed. Washington: Georgetown University Press; 2002. pp. 272 $27.50 ISBN: 0-87840-375-2

Bonnicksen AL. **Crafting a cloning policy: from Dolly to stem cells**. Washington: Georgetown University Press; 2002. pp. 232 $21.95 (paper) ISBN: 0-87840-371-X $39.95 (cloth) ISBN: 0-87840-370-1

Faiz O, Moffat D. **Anatomy at a glance**. Oxford: Blackwell Publishing; 2002. pp. 176 US$24.95 ISBN 0-632-05934-6

Henderson DA, Inglesby TV, O'Toole T, editors. **Bioterrorism: guidelines for medical and public health management**. Chicago: AMA Press; 2002. pp. 256 US$29.95 ISBN 1-57947-280-X

Herring MA, Roberts MM. **Complementary and alternative medicine: fast facts for medical practice**. Malden (MA): Blackwell; 2002. pp. 142 US$22.95 ISBN 0-632-04583-3

Jackson G, editor. **Cardiology: current perspectives**. London: Martin Dunitz; 2002. pp. 404 $75 ISBN 1-85317-629-X

McDonald Lynn, editor. **Florence Nightingale: an introduction to her life and family**. Waterloo (ON): Wilfrid Laurier University Press; 2002. pp. 920 $95 ISBN 0-88920-387-3