Sibrafiban was more toxic than aspirin for prevention of cardiovascular events after acute coronary syndromes

The SYMPHONY Investigators. **Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial.** Lancet. 2000 Jan 29; 355:337-45.

QUESTION

Is high-dose or low-dose sibrafiban as efficacious and safe as aspirin for prevention of cardiovascular events after acute coronary syndromes (ACSs)?

DESIGN

90-day randomized (allocation concealed*), blinded {patients, clinicians, and outcome assessors}*†, controlled trial (Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes [SYMPHONY]).

SETTING

670 sites in 33 countries.

PATIENTS

9233 patients (median age 60 y, 72% men, 86% white) who had chest pain or angina-equivalent symptoms for ≥ 20 minutes and elevated cardiac enzyme levels (creatine kinase or troponin) or ischemic electrocardiographic changes. Patients also had to have been clinically stable for 12 hours, to be in Killip class II or lower, and to have no continuing ischemia. Exclusion criteria were serious illness, predisposition to bleeding, previous stroke, serum creatinine level > 133 μmol/L, treatment with other oral antiplatelet agents or warfarin, or need for long-term nonsteroidal anti-inflammatory drugs or steroids. 78% of patients completed the specified course of therapy (median duration 91 d).

INTERVENTION

3105 patients were allocated to low-dose sibrafiban (dosage to achieve ≥ 25% steady-state inhibition of platelet aggregation); 3039 were allocated to high-dose sibrafiban (dosage to achieve ≥ 50% inhibition); and 3089 were allocated to aspirin, 80 mg twice daily.

MAIN OUTCOME MEASURES

Combined end point of death, nonfatal infarction or reinfarction, or severe recurrent ischemia at 90 days and combined major and minor bleeding.

MAIN RESULTS

99% of patients received ≥ 1 dose of the study drug and had ≥ 13 days of follow-up or an efficacy event within 13 days of beginning the drug; these patients were included in the intention-to-treat analysis of the primary end point. The high- and low-dose sibrafiban groups did not differ from the aspirin group for the frequency of the combined end point (10.1% for both high- and low-dose sibrafiban vs 9.8% for aspirin) but had higher rates of combined major and minor bleeding (Table).

CONCLUSION

Sibrafiban in high or low doses was not better than aspirin for prevention of cardiovascular events after acute coronary syndromes but was associated with a greater frequency of combined major and minor bleeding.

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*See Glossary.

†Information provided by author.

Combined major and minor bleeding in high- and low-dose sibrafiban (HDS and LDS) vs aspirin after an acute coronary syndrome at 90 days‡

Comparison	Event rates	RRI (95% CI)	NNH (CI)
HDS vs aspirin	25% vs 13%	94% (74 to 117)	9 (7 to 10)
LDS vs aspirin	19% vs 13%	44% (28 to 61)	18 (14 to 26)

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

COMMENTARY

Antiplatelet therapy with aspirin is currently the mainstay of therapy for secondary prevention of recurrent cardiovascular events after ACSs, such as myocardial infarction and unstable angina. Because aspirin is a relatively weak platelet inhibitor, such agents as glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists, which exert a more powerful inhibitory effect on platelet function, may improve treatment of atherothrombotic disorders. Several large clinical trials have shown the effectiveness of short-term intravenous GPIIb/IIIa antagonists in reducing 30-day recurrent fatal and nonfatal events in patients with ACS, particularly those having percutaneous coronary revascularization (1).

Researchers hoped that extended platelet inhibition with oral GPIIb/IIIa antagonists would provide longer-term benefits in patients with ACS. However, the results from the SYMPHONY trial showed no difference in 90-day cardiovascular events among patients who received either low- or high-dose sibrafiban and those who received aspirin; bleeding associated with either dose of sibrafiban increased slightly. The disappointing results of this and 2 other recent clinical trials (2) suggest that existing oral GPIIb/IIIa antagonists provide no additional benefit over aspirin for secondary prevention of atherothrombotic events. As discussed in an accompanying commentary (3), one possible explanation for the relative lack of efficacy of these agents is the importance of the additional anti-inflammatory effect of aspirin. Furthermore, a beneficial effect of GPIIb/IIIa antagonists may only be shown in clinically unstable or "high-risk" patients, who were excluded from the SYMPHONY trial. Further analysis of other clinical trial data is needed.

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References

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