News and Views from the Literature

Antithrombotic Agents

Fondaparinux in Acute Coronary Syndromes: Improved Efficacy and Safety

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Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes

Yusuf S, Mehta SR, Chrolavicius S, et al, the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators

N Engl J Med. 2006;354(14):1464-1476

Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: the OASIS-6 Randomized Trial

Yusuf S, Mehta SR, Chrolavicius S, et al, the OASIS-6 Trial Group

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The optimal antithrombotic agent to use in patients with acute coronary syndromes (ACS) has been under considerable evolution since it was first appreciated that antithrombotic therapy reduced the adverse outcomes associated with these conditions. Antiplatelet and antithrombotic therapies are now accepted as critical, and early therapy is essential. Although unfractionated heparin has been the principal antithrombotic agent used, a number of studies have shown the superiority of low-molecular-weight heparin (LMWH) in ACS. Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor 10a. Like heparin and LMWH, it requires binding with antithrombin 3 to become active. But unlike these agents, fondaparinux has no further activity on platelets or other coagulation pathway factors. It has a long half-life, and in clinical trials it has been more effective than enoxaparin in preventing deep vein thrombophlebitis in orthopedic patients; it has similar effectiveness in patients with deep vein thrombosis. Early pilot studies in ACS patients suggested at least equal efficacy to LMWH. The fifth and sixth studies by the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) investigators were 2 large, parallel trials conducted to evaluate the safety and efficacy of fondaparinux in patients with high-risk unstable angina/non-ST elevation myocardial infarction (STEMI) (OASIS-5) and with acute STEMI (OASIS-6).

OASIS-5

The OASIS-5 trial was a multicenter, multinational, randomized, double-blind, double-dummy trial in high-risk ACS patients.[1] The study randomized 20,078 patients with ACS to receive either fondaparinux (2.5 mg/d) or

enoxaparin (1 mg/kg twice daily) for up to 7 days. It was sized as a non-inferiority trial. The combined primary endpoint was death, myocardial infarction, or refractory ischemia at 9 days. The secondary endpoints included the outcomes at 30 and 180 days. Safety was also assessed at each time point, and the net clinical benefit was the combination of the primary efficacy and primary safety endpoints.

Results

The primary endpoint showed no difference between the groups at 9 days, but the rate of bleeding was markedly lower with fondaparinux (2.2% versus 4.1%). At both 30 days and 180 days, the composite efficacy endpoint was significantly lower with fondaparinux due to a significant reduction in mortality. Bleeding continued to be lower, leading to a significantly better net benefit in the fondaparinux group. Almost 40% of the patients underwent percutaneous coronary intervention (PCI) during the initial hospitalization. In this group, there was no difference in the primary efficacy endpoint, but there was a significant reduction in bleeding at the 9-, 30-, and 180-day time points. The only concern raised in the study was a small but significantly higher rate of catheter thrombus in the fondaparinux group. This increase was partially resolved with the use of heparin flushes during the PCI procedure, but the groups were not completely equalized.

The findings of this study are startling in a number of regards. It is not surprising that these 2 drugs have equal efficacy at 9 days, since both are effective antithrombotic drugs. However, the very significant differences in outcome at 30 and 180 days are unexpected, particularly since they were largely a result of lower mortality in the fondaparinux patients. The lower bleeding rates were also dramatic and consistent throughout the study time points. The majority of bleeding was within the first week, and the benefit was seen in both minor and major bleeds. The reason for the reduction in mortality is unexplained, but it may have been due to the lower bleeding rates. Other studies have shown an adverse relationship between bleeding, anemia, or transfusion and outcome. Of those subjects who died, the majority had a serious bleeding episode that suggested a possible relationship. The study would support the use of fondaparinux in patients with ACS, particularly those who are not undergoing PCI. In patients undergoing PCI, the net balance of fondaparinux may be neutral given the higher risk of catheter thrombosis but lower risk of bleeding.

OASIS-6

The OASIS-6 trial was a parallel trial that evaluated fondaparinux versus usual care in 12,092 patients with STEMI.[2] The protocol was complex since it tried to evaluate all the current management strategies in STEMI. Patients were randomized into 2 strata: those who did not need heparin and those who did. Patients in the first group received streptokinase, and patients in the second group received a fibrin-specific agent or PCI. The dose of fondaparinux was lower for patients who were also receiving a glycoprotein IIb/IIIa agent. The treatment was continued for 8 days or until hospital discharge.

Results

At 30 days, the combined primary endpoint of death or reinfarction occurred significantly less in the fondaparinux group than in the usual care group (9.7% versus 11.2%; hazard ratio, 0.86; $P = .008$). These benefits persisted for 180 days. The individual components, namely death and reinfarction, were also significantly different between the groups. As in OASIS-5, the bleeding rates were significantly lower in the fondaparinux group. In patients undergoing primary PCI, the primary endpoint was not different between the 2 groups, and neither were the bleeding rates. When unfractionated heparin was not used in those randomized to fondaparinux and undergoing primary PCI, complications were higher in the fondaparinux group. Thus, when heparin was used, the outcomes were similar between the 2 agents.

These 2 studies will undoubtedly change the use of antithrombotic therapy in acute coronary syndromes.

The results of this study are in concert with those of the OASIS-5 trial and support the use of fondaparinux in patients with STEMI, whether they receive heparin or not. There does not appear to be any advantage of using fondaparinux in patients undergoing PCI, but conversely, if heparin is given during the procedure there is no adverse outcome as well. These 2 studies will undoubtedly change the use of antithrombotic therapy in ACS. PCI is frequently used in the United States in ACS and STEMI, but it is much less commonly used in other parts of the world. The prolonged duration of action, lower cost, and reduced bleeding and mortality of fondaparinux over enoxaparin will make it the preferred drug in those patients who are not likely to need or receive an early PCI. ■

Dr. Faxon is a consultant for Sanofi-Aventis and Bristol-Myers Squibb.

References

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2. Yusuf S, Mehta SR, Chrolavicius S, et al, the OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295:1519-1530.