THERAPEUTICS

Fondaparinux reduced death or reinfarction in acute ST-segment elevation myocardial infarction

Yusuf S, Mehta SR, Chrolavicius S, et al. **Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial.** JAMA. 2006;295:1519-30.

Clinical impact ratings: Emergency Med ★★★★★☆ Hospitalists ★★★★★☆ Cardiology ★★★★★☆ Hematol/Thrombo ★★☆☆☆☆

QUESTION

In patients with acute ST-segment elevation myocardial infarction (STEMI), is fondaparinux better than usual care for reducing death or reinfarction?

METHODS

Design: Randomized placebo-controlled trial (Organization for the Assessment of Strategies for Ischemic Syndromes [OASIS-6]).
Allocation: Unclear allocation concealment.*
Blinding: Blinded (clinicians and patients).*
Follow-up period: 3 to 6 months.
Setting: 447 centers in 41 countries.
Patients: 12 092 patients (mean age 62 y, 72% men) who presented with STEMI within 24 hours of pain onset (shortened to < 12 h after about 4300 patients had been enrolled). Exclusion criteria were contraindication to anticoagulants, receipt of oral anticoagulants, or creatinine levels > 265.2 mg/dL (3.0 mmol/L).
Intervention: Patients were stratified by no indication for use of unfractionated heparin (UFH) or indication for UFH. Patients with no indication for UFH received fondaparinux, 2.5 mg subcutaneously (n = 2823), or placebo (n = 2835) for up to 8 days or hospital discharge. Patients for whom UFH was indicated received fondaparinux, 2.5 mg subcutaneously, plus UFH placebo (n = 3213) or fondaparinux placebo plus a bolus injection of UFH, 60 IU/kg, followed by an infusion of 12 IU/kg per hour for 24 to 48 hours (n = 3221).
Outcomes: A composite endpoint of death or reinfarction at 30 days. Secondary outcomes were the composite endpoint assessed at 9 days and at study end (3 to 6 mo) and bleeding.
Patient follow-up: 99.7% (intention-to-treat analysis).

MAIN RESULTS

Patients who received fondaparinux had a lower incidence of the composite endpoint at 30 days than did patients who received placebo or UFH (Table). The reduction was also seen at 9 days and persisted to study end (Table). Groups did not differ for major bleeding using TIMI and OASIS-5 definitions (Table). The effect of fondaparinux was not heterogenous between the 2 strata at 9 or 30 days, and effect sizes were almost identical by study end. In stratum 2 patients, no benefit of fondaparinux over UFH was seen in those having percutaneous coronary intervention (PCI).

CONCLUSION

In patients with acute ST-segment elevation myocardial infarction, fondaparinux reduced death or reinfarction better than usual care without increasing bleeding.

Sources of funding: Sanofi-Aventis; Organon; GlaxoSmithKline.

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*See Glossary.

Fondaparinux vs placebo or unfractionated heparin (UFH) for ST-segment elevation myocardial infarction†

Outcomes	Follow-up	Fondaparinux	Placebo or UFH	RRR (95% CI)	NNT (CI)
Composite endpoint‡	30 d	9.7%	11.2%	13% (3.8 to 22)	68 (41 to 237)
	9 d	7.4%	8.9%	16% (5.7 to 26)	69 (44 to 196)
	Study end	13.4%	14.8%	11% (2.8 to 20)	61 (35 to 244)
Severe hemorrhage (TIMI)	9 d	1.0%	1.3%	23% (–7.9 to 45)	Not significant
Major bleeding (OASIS-5)	9 d	1.8%	2.1%	17% (–5.9 to 36)	Not significant

†TIMI = Thrombolysis in Myocardial Infarction; OASIS = Organization for the Assessment of Strategies for Ischemic Syndromes. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from hazard ratios and control event rates in article.
‡Death or reinfarction.

COMMENTARY

The OASIS-5 (1) and OASIS-6 studies legitimize fondaparinux, a synthetic factor Xa inhibitor, as a treatment option to UFH or low-molecular-weight heparin (LMWH) in acute coronary syndromes. In OASIS-6, fondaparinux was superior to placebo in reducing death or MI in STEMI, and inexplicably did so with lower bleeding rates. These results support the use of anticoagulant therapy in patients with STEMI not receiving reperfusion therapy, as recently shown with LMWH in the CREATE trial (2).

Compared with UFH, fondaparinux also reduced the primary endpoint, with lower bleeding rates. However, the primary angioplasty group did worse with fondaparinux than with UFH, and there was a disturbing excess of guiding catheter thrombosis in the fondaparinux group. Thus, fondaparinux use in primary angioplasty is unlikely. Whereas fondaparinux seemed superior to UFH in patients not treated with primary PCI, streptokinase was the predominant lytic agent–a factor limiting applicability in North America, where second- and third-generation fibrinolytics are the norm. Moreover, patients not receiving lytic therapy were analyzed with patients who were, so the results cannot be compared with enoxaparin therapy in the ExTRACT-TIMI 25 study (3), where all patients received lytic therapy. Furthermore, the 8-day duration of fondaparinux therapy, instead of 2 days of heparin therapy, may explain its superiority. Both OASIS-6 and ExTRACT-TIMI-25 (3) suggest that anticoagulant therapy in STEMI should be continued for longer than the currently recommended 48 hours of UFH.

One might think that a less expensive, safer, and more effective drug would simplify management of patients with STEMI and become dominant or universal. But concerns about the use of fondaparinux in the cardiac catheterization laboratory may limit its use in North America.

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References

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3. **Antman EM, Morrow DA, McCabe CH, et al.** N Engl J Med. 2006; 354:1477-88.