

Dalteparin reduced death and MI at 1 but not 3 months in unstable coronary artery disease managed noninvasively

FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet*. 1999 Aug 28;354:701-7.

QUESTION

In patients receiving noninvasive treatment for unstable coronary artery disease (CAD), does dalteparin reduce myocardial infarction (MI) and death?

DESIGN

Randomized (allocation concealed*), blinded {patients, clinicians, and outcome assessors},*† placebo-controlled trial with 6-month follow-up.

SETTING

58 Scandinavian centers.

PATIENTS

Patients were eligible if they had symptoms of ischemia with the last episode occurring \leq 48 hours before enrollment. Myocardial ischemia was confirmed by ST depression or T-wave inversion on electrocardiography or by elevated biochemical markers (creatinine kinase-MB or troponin-T). Only patients who had a contraindication to early revascularization or had been randomized to the noninvasive strategy in the FRISC II study were included in this analysis. 2267 patients were randomized, and 2105 entered the double-blind treatment period (median age 67 y, 68% men). Follow-up was 93% for the primary outcome and 99% for secondary outcomes.

INTERVENTION

Randomization was stratified by center, and all patients initially received open-label treatment with subcutaneous dalteparin, 120 IU/kg of body weight every 12 h for \geq 5 days. Patients were allocated to dalteparin ($n = 1140$) or placebo ($n = 1127$) in twice-daily subcutaneous injections for 3 months. Dalteparin was given in doses of 5000 IU for men who weighed < 70 kg and women who weighed < 80 kg and 7500 IU for all others.

MAIN OUTCOME MEASURES

The primary outcome was a composite of death and MI at 3 months. The secondary outcome was a composite of death, MI, and need for revascularization at other time points.

MAIN RESULTS

Dalteparin did not reduce the primary composite outcome at 3 months ($P = 0.17$)

or 6 months ($P > 0.2$) more than did placebo. Dalteparin led to a greater decrease in the primary composite outcome at 1 month ($P = 0.002$) and in the secondary composite outcome at 3 months ($P = 0.03$) than did placebo (Table).

CONCLUSION

In patients who received noninvasive management for unstable coronary disease, dalteparin reduced death and myocardial infarction at 1 month but not at 3 months.

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*See Glossary.

†Information provided by author.

Dalteparin vs placebo in patients receiving noninvasive treatment for unstable coronary artery disease†

Outcomes	Dalteparin	Placebo	RRR (95% CI)	NNT (CI)
Death, MI, or both at 1 mo	3.1%	5.8%	47% (20 to 65)	37 (23 to 102)
Death, MI, or need for revascularization at 3 mo	29%	33%	13% (2 to 23)	24 (13 to 208)

‡MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Clear evidence supports the use of heparin and antiplatelet therapy in patients who have unstable CAD with no ST elevation (1). Low-molecular-weight heparin (LMWH) has attracted recent interest because it may be more efficacious, cost-effective, and easier to give than intravenous unfractionated heparin; LMWH does not require regular monitoring of anticoagulation intensity and infusion-dose adjustment.

The FRISC-II study shows a substantial benefit of dalteparin in reducing the composite outcome of death, MI, and revascularization procedures at 3 months in patients with unstable CAD, but the primary study outcome (a composite of death and MI) was only significantly decreased at 1 month. The dose of dalteparin chosen for this trial seemed to suppress markers of ongoing thrombogenesis (2). It is not clear, however, whether an increased incidence of major bleeding in patients receiving dalteparin contributed to the decreasing treatment effect between 6 weeks and 3 months.

In the FRIC study (3), dalteparin and unfractionated heparin led to a similar combined rate of death, MI, and recurrent ischemia. However, another LMWH, enoxaparin, showed substantial benefits over unfractionated heparin in the ESSENCE study (4). Although some differences may result from the trial design, subtle differences may also be present among the LMWHs. It is not clear whether LMWH is more effective than standard unfractionated heparin in all groups of patients. More work is needed to compare the different types of heparins available.

Although previous studies comparing invasive and noninvasive strategies have been equivocal, the FRISC-II study suggests that an early invasive strategy is preferable to a noninvasive one in patients with unstable CAD and leads to a substantial reduction in death and MI (4). Nevertheless, the positive results of FRISC-II could be related to improvements in the management of unstable CAD and to the better outcomes of more recent invasive and revascularization

(continued on page 83)

An invasive strategy reduced the combined rate of death and myocardial infarction in unstable coronary artery disease

FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet*. 1999 Aug 28;354:708-15.

QUESTION

In patients with unstable coronary artery disease (CAD), does an early invasive strategy in addition to optimal background medication reduce death and myocardial infarction (MI)?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessors)*, controlled trial with 6-month follow-up.

SETTING

58 hospitals in Scandinavia.

PATIENTS

2457 patients (median age 66 y, 70% men) with symptoms of ischemia at rest and of myocardial ischemia confirmed by ST depression or T-wave inversion on electrocardiography or by elevated biochemical markers. Exclusion criteria included increased risk for bleeding episodes, anemia, thrombolysis in the previous 24 hours, angioplasty in the previous 6 months, coronary revascularization, being on a waiting list for revascularization, severe illness, or previous open-heart surgery. Follow-up was 99%.

INTERVENTION

Randomization was stratified by center, and all randomized patients initially received

dalteparin, 120 IU/kg of body weight, for ≥ 5 days. Patients were allocated to 1 of 4 groups: invasive treatment and dalteparin ($n = 611$), invasive treatment and placebo ($n = 611$), noninvasive treatment and dalteparin ($n = 621$), and noninvasive treatment and placebo ($n = 614$). Invasive treatment consisted of coronary angiography within a few days of enrollment with the aim of revascularization within 7 days for patients with substantial coronary obstruction ($\geq 70\%$) in ≥ 1 coronary artery. Noninvasive treatment included coronary angiography in patients with refractory or recurrent symptoms after maximum medical treatment. Dalteparin was given in subcutaneous injections twice daily, with doses of 5000 IU for women who weighed < 80 kg and men who weighed < 70 kg and 7500 IU for the rest.

MAIN OUTCOME MEASURE

Composite outcome of death and MI at 6 months.

MAIN RESULTS

Analysis was by intention to treat. The invasive strategy led to fewer occurrences of the composite outcome than did the noninvasive strategy ($P = 0.031$) (Table). Dalteparin and placebo did not differ at 6 months in any group.

CONCLUSIONS

In patients with unstable coronary artery disease, an invasive strategy was more effective in reducing the composite outcome of death and MI than a noninvasive strategy. At 6 months, dalteparin did not reduce death and MI more than did placebo.

Sources of funding: Pharmacia and Upjohn; Swedish Heart-Lung Foundation; local health authorities and county councils.

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*See Glossary.

Invasive vs noninvasive strategy for unstable coronary artery disease†

Outcome at 6 mo	Invasive strategy	Noninvasive strategy	RRR (95% CI)	NNT (CI)
Death, MI, or both	9%	12%	22% (2 to 38)	37 (20 to 398)

†MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY (continued from page 82)

procedures. Further, this study does not take into account the possible difference in outcomes between patients treated with dalteparin and those treated with unfractionated heparin during the initial period of open-label antithrombotic treatment before randomization. It is also unclear whether the serious adverse event rates were significantly different between invasive and noninvasive groups and between dalteparin and placebo groups.

An early invasive strategy should be used, especially in such high-risk patients as older persons; men; and persons with longer duration of angina, rest pain, ST depression on electrocardiography, and elevated levels of troponin T. In FRISC-II, more patients had revascularization after the initial hospital stay in the noninvasive strategy group, which suggests that a noninvasive strategy may simply be delaying the invasive procedure and subsequent revascularization while subjecting these patients to an increased risk for MI or death in the interim.

Long-term LMWH has a substantial role in high-risk patients with unstable CAD who have contraindications for or who are awaiting revascularization. Nevertheless, patients with unstable CAD should be considered for early invasive treatment in addition to standard antithrombotic and anti-ischemic therapy, especially if high-risk factors are present.

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