Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study

*FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators**

Summary

Background In unstable coronary-artery disease early invasive procedures are common, despite lack of evidence for the superiority of this approach. We compared an early invasive with a non-invasive treatment strategy in unstable coronary-artery disease .

Methods In a prospective randomised multicentre study, we randomly assigned 2457 patients in 58 Scandinavian hospitals (median age 66 years, 70% men) an early invasive or non-invasive treatment strategy with placebo-controlled long-term low-molecular-mass heparin (dalteparin) for 3 months. Coronary angiography was done within the first 7 days in 96% and 10%, and revascularisation within the first 10 days in 71% and 9% of patients in the invasive and non-invasive groups, respectively. We followed up patients for 6 months. Analysis was by intention to treat.

Findings After 6 months there was a decrease in the composite endpoint of death or myocardial infarction of 9·4% in the invasive group, compared with 12·1% in the non-invasive group (risk ratio 0·78 [95% CI 0·62–0·98], p=0·031). There was a significant decrease in myocardial infarction alone (7·8 *vs* 10·1%, 0·77 [0·60–0·99]; p=0·045) and non-significantly lower mortality (1·9 *vs* 2·9%, 0·65 [0·39–1·09]; p=0·10). Symptoms of angina and re-admission were halved by the invasive strategy. Results were independent of the randomised dalteparin treatment. The greatest advantages were seen in high-risk patients.

Interpretation The early invasive approach should be the preferred strategy in most patients with unstable coronary-artery disease who have signs of ischaemia on electrocardiography or raised biochemical markers of myocardial damage.

Lancet 1999; **354:** 708–15
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Introduction

In unstable coronary-artery disease, early invasive procedures are common, despite lack of evidence for the superiority of this approach in randomised trials. No previous randomised trial[1–4] has shown any significant decrease in death and myocardial infarction in the invasively treated cohort. The VANQWISH trial[3] showed raised mortality with an invasive approach early after non-Q-wave myocardial infarction. However, many observational studies and the randomised TIMI IIIb trial[2,4,5] have shown shorter hospital stays, fewer readmissions, less ischaemia, and fewer symptoms with an early invasive approach. Because of this controversial information, the use and timing of revascularisation in unstable coronary-artery disease is variable, which might have important consequences for patients and costs of treatment.

The treatment of patients with unstable coronary-artery disease has developed substantially since the first randomised trials were published. Anti-ischaemic treatment with β-blockade and nitrates and antithrombotic treatment with aspirin and heparin, preferably low-molecular-mass heparin, is currently recommended for all patients in the acute phase.[6–10] The results of invasive procedures have been improved by the use of stenting and glycoprotein IIb/IIIa blockade during percutaneous coronary interventions[11–14] and by technical improvements in surgical procedures, anaesthesia, and postoperative care.[15]

We designed the Fast Revascularisation during InStability in Coronary artery disease (FRISC II) invasive trial to compare an early invasive with a non-invasive strategy in patients with unstable coronary-artery disease in addition to optimum background antithrombotic medication. Since the optimum duration of low-molecular-mass heparin treatment in unstable coronary-artery disease has yet to be determined, we used a factorial design.

Patients and methods

Patients

We recruited patients between June 17, 1996, and May 7, 1998, in 58 Scandinavian hospitals, 16 of which were interventional centres. Patients were eligible for inclusion if they had symptoms of ischaemia that were increasing or occurring at rest, or that warranted the suspicion of acute myocardial infarction, with the last episode within 48 h before the start of dalteparin or standard heparin treatment. Myocardial ischaemia had to be verified by electrocardiography (ST depression ⩾0·1 mV or T-wave inversion ⩾0·1 mV) or by raised biochemical markers (creatine kinase [CK]-MB >6 ug/L, troponin-T >0·10 ug/L, qualitative troponin-T test positive, or catalytic activity of CK, CK-B, or CK-MB higher than the local diagnostic limit for myocardial infarction). Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 months, being on a

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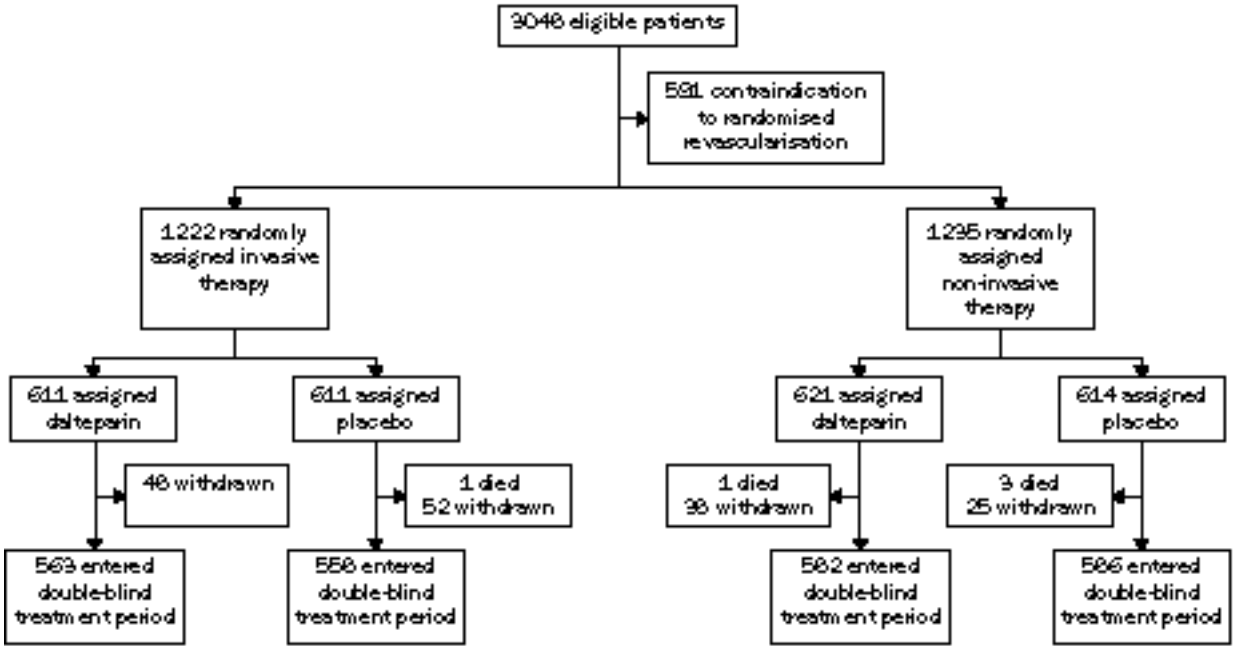

Figure 1: **Trial profile**

waiting list for coronary revascularisation, other acute or severe cardiac disease, renal or hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomised drugs, anticipated difficulties with cooperation or participation in this or another clinical trial. Patients with previous open-heart surgery, advanced age (eg, >75 years), or other disorders that made randomisation to early revascularisation inappropriate.

Study design

The FRISC II, study was a prospective, randomised, multicentre trial with parallel groups. We compared invasive and non-invasive treatments by factorial design. Randomisation was done by telefax through an independent organisation (Clinical Data Care, Lund, Sweden). Half of the patients in each group were randomly assigned long-term treatment with subcutaneous dalteparin or placebo for 3 months. The comparison of the invasive and non-invasive strategies was open and the comparison of long-term dalteparin treatment with placebo was double-blind. Eligible patients who met the entry criteria were started on routine acute-phase treatment with open-label subcutaneous dalteparin twice daily (or an infusion of standard heparin). As soon as possible after admission, up to 72 h after the start of open-label dalteparin (or standard heparin), we randomly allocated patients, stratified by centre, to one of four treatment groups: invasive treatment and dalteparin; invasive treatment and placebo; non-invasive treatment and dalteparin; non-invasive treatment and placebo (figure 1). In the invasive groups, the target was to perform all invasive procedures within 7 days of starting open-label dalteparin. We followed up patients in hospital, by telephone after 2 weeks, by outpatient visits at 6 weeks, 3 months, and 6 months, and by telephone contact at 12 months and 24 months.

The direct invasive treatments were coronary angiography within a few days of enrolment, aiming for revascularisation within 7 days of the start of open-label treatment. Revascularisation was recommended in all patients with an obstruction of at least 70% of the diameter of any artery supplying a substantial proportion of the myocardium. Percutaneous coronary intervention was recommended if there were one or two target lesions, and coronary-artery bypass surgery was preferred in patients with three-vessel or left main-artery disease.

Non-invasive treatment included coronary angiography in patients with refractory or recurrent symptoms, despite maximum medical treatment, or severe ischaemia on a symptom-limited exercise test before discharge.[16] The exercise-test criteria

Variable	Invasive (n=1222)	Non-invasive (n=1235)
Age and sex		
Median (range) age (years)	66 (40–84)	65 (37–83)
Men	874 (71%)	834 (68%)
Coronary risk factors		
Hypertension	366 (30%)	377 (31%)
Cholesterol >5·5 mmol/L*	701 (58%)	696 (57%)
Current smoker	362 (30%)	383 (31%)
Diabetes mellitus	155 (13%)	144 (12%)
Previous and current cardiac disease		
Previous myocardial infarction	278 (23%)	268 (22%)
Angina history >48 h	841 (69%)	832 (67%)
CCSA 3–4†	384 (41%)	348 (37%)
Chest pain at rest	987 (81%)	994 (81%)
ST-depression at entry	542(45%)	572 (46%)
Troponin-T ⩾0·1 ug/L‡	666 (57%)	682 (58%)
Left-ventricular ejection fraction <45%§	129 (14%)	120 (12%)
Medication at admission		
Aspirin	444 (36%)	423 (34%)
β-blockade	391 (32%)	394 (32%)
Angiotensin-converting-enzyme inhibitor	168 (14%)	135 (11%)
Calcium antagonist	225 (18%)	213 (17%)
Long-acting nitrate	241 (20%)	233 (19%)
Diuretic	181 (15%)	186 (15%)
Statin	131 (10%)	118 (10%)

CCSA=Canadian Cardiovascular Society score for angina. *Measured at entry in 1209/1220 patients. †Assessed in 939/945 patients. ‡Measured at randomisation in 1163/1168 patients. §Measured in 941/1003 patients.

Table 1: **Baseline characteristics**

Variable	Invasive (n=1222)	Non-invasive (n=1235)
Coronary angiography	1201 (98%)	585 (47%)
Days to angiography*	4 (2–6)	17 (6–132)
Coronary angiography ⩽7 days†	96%	10%
Coronary vessels with ⩾50% stenosis†		
0	14%	9%
1	30%	26%
2	26%	28%
3	23%	30%
Left main-artery disease	8%	8%

*Median (10th to 90th percentile). †Percentages of patients with coronary angiograms.

Table 2: **Results of coronary angiography in invasive and non-invasive groups**

Variable	Invasive (n=1222)	Non-invasive (n=1235)
Percutaneous coronary intervention		
Total	522	220
Proportion with stent*	61%	70%
Proportion received abciximab*	10%	10%
Mean (SD) treated segments*	1·35 (0·67)	1·34 (0·72)
Successfully treated segment*	95%	91%
Days to percutaneous coronary intervention†	4 (2–7)	16·5 (5–132)
⩾7 days*	94%	20%
Coronary-artery bypass surgery		
Total	430	233
Left internal mammary artery‡	95%	96%
⩾3 distal anastomoses‡	85%	86%
Mortality in hospital‡	1·2%	0·4%
Mortality within 30 days‡	2·1%	1·7%
Days to coronary-artery bypass surgery‡	7 (5–13)	28 (10–139)
Surgery ⩽10 days‡	82%	13%

*Percentages of patients with percutaneous coronary intervention. †Median (10th to 90th percentile) in patients with respective procedure. ‡Percentages of patients with coronary-artery bypass surgery.

Table 3: **Coronary procedures in invasive and non-invasive groups**

for performing angiography and revascularisation were: ST depression ⩾0·3 mV; limiting chest pain associated with a low maximum work load (<90 W in men or <70 W in women) or a decrease in blood pressure; or ST elevation without preceding concomitant Q waves, or T-wave inversion on exercise testing. During long-term follow-up, invasive procedures were considered, irrespective of randomised strategy, for all patients with incapacitating symptoms, recurrence of instability, or myocardial infarction.

On admission, patients were initially treated with open-label subcutaneous dalteparin or standard heparin infusion adjusted for activated partial thromboplastin time. From randomisation, all patients received dalteparin, 120 IU/kg every 12 h subcutaneously (maximum dose 10 000 IU), for at least 5 days in the non-invasive group and until procedures were done in the invasive group. Thereafter, patients received twice-daily subcutaneous injections of dalteparin or placebo. Women who weighed less than 80 kg and men who weighed less than 70 kg received 5000 IU dalteparin or placebo, and those who weighed more than these values received 7500 IU. This regimen was continued for 3 months, with patients self-injecting from prefilled single-dose syringes after discharge from hospital. The last injection of open-label or double-blind dalteparin treatment was given no later than 12 h before coronary procedures. After angioplasty, dalteparin or placebo were restarted 2–6 h after sheath removal. After administration of an infusion of the glycoprotein IIb/IIIa inhibitor abciximab, dalteparin or placebo were not restarted until 24 h after infusion. After coronary-artery bypass surgery, all patients received open-label dalteparin 5000 IU twice daily until mobilisation, and double-blind treatment was started a few days before discharge. We

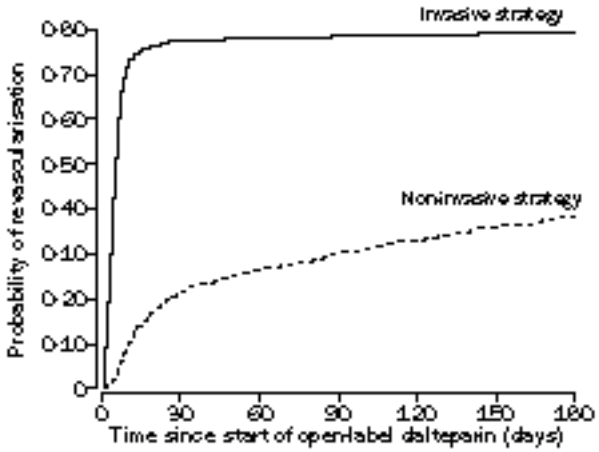

Figure 2: **Timing of first revascularisation in invasive and non-invasive groups**

	Invasive (n=1207)	Non-invasive (n=1226)	Risk ratio (95% CI)	p
Death, MI, or both*	113 (9·4%)	148 (12·1%)	0·78 (0·62–0·98)	0·031
MI	94 (7·8%)	124 (10·1%)	0·77 (0·60–0·99)	0·045
Death	23 (1·9%)	36 (2·9%)	0·65 (0·39–1·09)	0·10

MI=myocardial infarction.
*In invasive group, six (0·5%) of events occurred before randomised revascularisation procedure.

Table 4: **Death, myocardial infarction, or both after 6 months**

monitored compliance by asking patients to record all injections in diaries and by counting returned or unused syringes at outpatient visits.

We gave aspirin to all patients on admission at an initial dose of 300–600 mg, followed by a maintenance dose of 75–320 mg once daily. β-blockade was given unless contraindicated. Organic nitrates and calcium antagonists could be added as required. Lowering of cholesterol with statins, angiotensin-converting-enzyme inhibitors for left-ventricular dysfunction, and aggressive antidiabetic treatment were recommended according to modern treatment guidelines. We encouraged use of abciximab during percutaneous coronary interventions. We recommended ticlopidine for 3–4 weeks after stent placement.

On admission, or at the latest at randomisation, blood samples were locally analysed for haemoglobin concentrations, white-cell count, platelet count, prothrombin time, creatinine, glucose, haemoglobin A_{1c} if necessary, triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol. Biochemical markers of myocardial damage were analysed at entry, after new episodes of severe chest pain, and before and 4–24 h after revascularisation. The most frequently used marker of myocardial damage was CK-MB mass, but some centres used catalytic activity of total-CK, CK-B, or both. Quantitative determination of troponin-T was available in most hospitals. For screening purposes we provided all centres with a qualitative test for troponin-T, the second-generation Cardiac-T (Roche-Boehringer Mannheim, Mannheim, Germany). At randomisation, we took blood samples from all patients, which we stored frozen at –70°C for central analysis of troponin-T and other markers.

Conventional 12-lead electrocardiography was done on admission, at randomisation, within 24 h before invasive procedures, at hospital discharge, at 3-month and 6-month outpatient visits, and on any suspicion of recurrent unstable angina or myocardial infarction. Patients in the non-invasive group who had no contraindications did a symptom-limited bicycle exercise test[16] before discharge. Echocardiography with a standard assessment of left-ventricular function was done in 1951 patients before discharge and always before invasive procedures. All exercise-test results and echocardiograms were sent to a central laboratory for assessment.

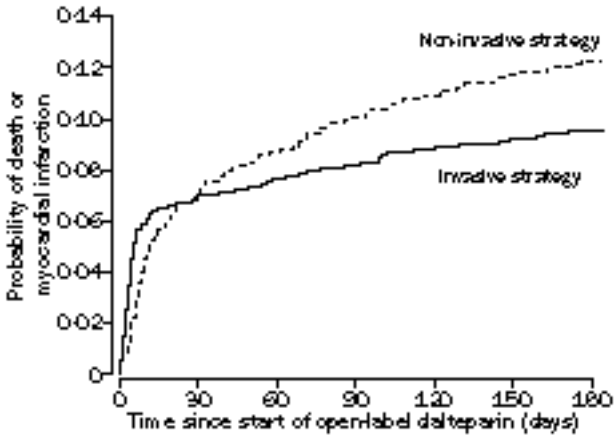

Figure 3: **Probability of death or myocardial infarction in invasive and non-invasive groups**

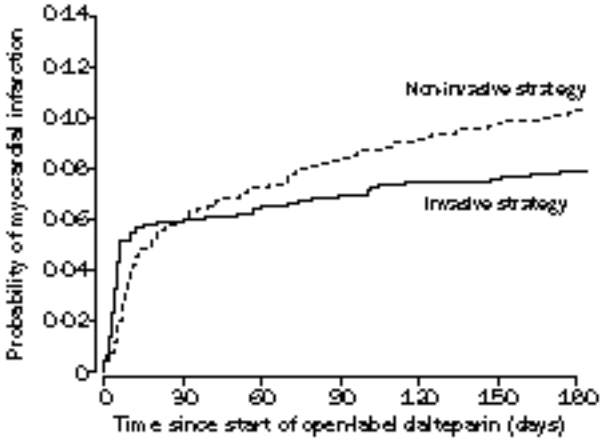

Figure 4: **Probability of death in invasive and non-invasive groups**

Endpoints

Our primary objective was to compare the effects of invasive and non-invasive strategy on the composite endpoint of death and myocardial infarction after 6 months. Other predefined endpoints were total death, myocardial infarction, symptoms of angina, need for late coronary angiography and revascularisation, bleeding episodes, and stroke. The trial should also report effects of the two treatment strategies in predefined subgroups based on age, sex, hypertension, smoking, diabetes, previous myocardial infarction, history of angina, chest pain at rest, ST-depression on electrocardiography at entry, raised troponin-T (⩾0·1 ug/L) at entry, and randomised long-term dalteparin treatment. The influences on quality of life and health costs will be reported separately.

Myocardial infarction was defined by the occurrence of two of the three conventional criteria—typical chest pain, diagnostic electrocardiography recording (mainly new Q-wave), or a raised biochemical marker of myocardial damage according to the following definitions. For non-procedure-related myocardial infarction: concentration of CK-MB mass higher than the local hospital's diagnostic limit for myocardial infarction at one measurement; catalytic activity of CK, CK-B, or CK-MB higher than the local limit at two subsequent measurements; catalytic activity of CK, CK-B, or CK-MB higher than the double local limit at one measurement. For myocardial infarction in relation to percutaneous coronary interventions: CK-MB mass 1·5 times the local hospital's diagnostic limit for myocardial infarction at one measurement; catalytic activity of CK, CK-B, or CK-MB at one measurement three times higher than the limit; or at two measurements 1·5 times the local limit. We used only new Q waves for the diagnosis of myocardial infarction in association with coronary-artery bypass surgery. We recommended that causes of death be established by necropsy. All reported deaths, myocardial infarctions, raised biochemical markers in relation to percutaneous coronary interventions, and new Q waves on electrocardiography reported by the core laboratory were adjudicated by an independent clinical-event committee.

We defined serious adverse events as those that were life threatening or those resulting in death or new or long-term hospital stay, disability, or requiring intervention to prevent permanent damage. The main safety variables were bleeding episodes, thrombocytopenia, and allergic reactions. A major bleeding episode was defined as at least one of: leading to death; intracranial bleed; need for blood transfusion; decrease in haemoglobin of 40 g/L or more, irrespective of symptoms; and decrease in haemoglobin of more than 20 g/L associated with symptoms of bleeding. Other bleeding episodes were classified as minor. Major safety endpoints were continuously monitored by an independent data and safety monitoring board.

We ensured quality of data by continuous source-data verification of all case-record forms by external monitors employed by the sponsoring pharmaceutical company. All cardiac events (efficacy endpoints) and adverse-event data were continuously sent directly from the centres to the data and safety monitoring board. The study complied with the Declaration of Helsinki, and all local ethics committees approved the protocol.

Statistical analysis

Our hypothesis was that there would be a 32% decrease from 11·0% to 7·5% in the primary composite endpoint of death or myocardial infarction at 6 months with the early invasive strategy compared with the non-invasive strategy. To show such a decrease, a sample size of 2400 was required to obtain 80% power to show a significant difference at $2\alpha=0{\cdot}05$.

We did statistical analyses according to intention to treat. The primary efficacy analysis was based on events occurring from start of open-label dalteparin treatment to 6-month follow-up. We also did analyses in predefined subgroups. Our primary reason for using a factorial design was not to estimate interaction but to make efficient use of the patients' data. The efficacy analyses were point estimates that included only patients with an adjudicated event or with recorded absence of the assessed event until at least 150 days of follow-up. We used the Mantel-Haenszel χ^2 analysis to test the significance of the overall degree of association. The results are presented as risk ratios and 95% CI. Graphs of the Kaplan-Meier estimate of the survival function were used without statistical tests. Data processing and statistical analyses were done independently at Department of Biostatistics and Data management, Pharmacia and Upjohn, Sweden, and by the coordinating investigators on SAS version 6.12 and SPSS version 9.0, respectively.

Results

2457 of 3048 eligible patients were randomly assigned treatment (figure 1). The reasons for exclusion of 591 patients were: previous open heart surgery (256), old age (282), and other reasons (53). Of those excluded for old age, the median age was 80·4 years.

The two groups did not differ significantly for baseline characteristics (table 1).

Details of coronary angiography are shown in table 2. Revascularisation procedures (table 3, figure 2) were done within the first 10 days in 71% and 9% and within 6 months in 77% and 37%, respectively, in invasive and non-invasive groups. Percutaneous coronary interventions were used in 84% of single, 62% of double, and 12% of triple and left main-artery disease. One patient who had a percutaneous coronary intervention died in hospital. The proportion of patients who had coronary-artery bypass surgery in single, double, and triple and left main-artery disease were, respectively, 5%, 31%, and 83%.

The median duration of open-label dalteparin treatment was 6 days in the invasive (range 1–38) and non-invasive (1–33) groups. Among the 2289 patients

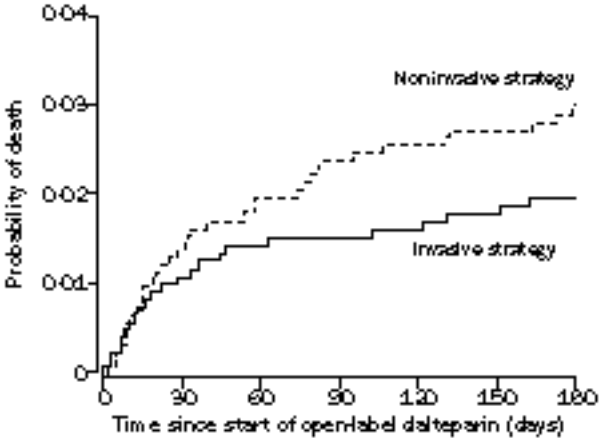

Figure 5: **Probability of myocardial infarction in invasive and non-invasive groups**

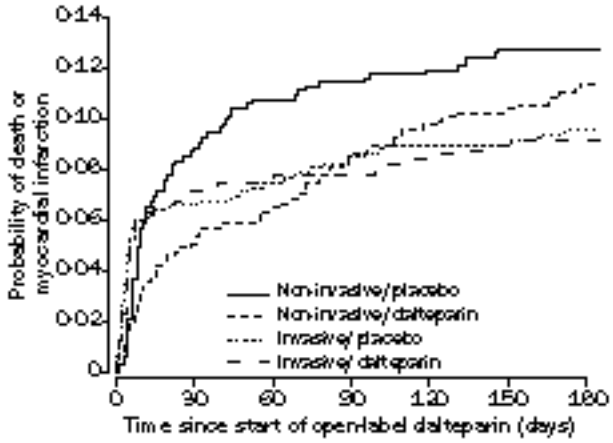

Figure 6: **Probability of death or myocardial infarction in all treatment groups**

who started double-blind treatment, the median duration of treatment was 85 days (2–115) in the invasive dalteparin group, 87 days (1–111) in the invasive placebo group, 87 days (2–102) in the non-invasive dalteparin group, and 88 days (2–110) in the non-invasive placebo group.

There was a significant 22·0% relative and 2·7% absolute decrease in death and myocardial infarction in the invasive compared with the non-invasive group after 6 months (table 4, figures 3–5). During the first 2 weeks, there was a higher event rate associated with the procedures in the invasive than in the non-invasive groups. After the first 2 weeks, however, the event rate was lower in the invasive than in the non-invasive groups, and the hazard curves crossed after about 4 weeks. Thereafter, the event rate was consistently lower for both parts of the composite primary endpoint in the invasive group. After 6 months, myocardial infarction was significantly decreased and total mortality was lower, although not significantly so.

	n*	Invasive	Non-invasive	Risk ratio (95% CI)
Dalteparin	(606/617)	55 (9·1%)	70 (11·3%)	0·80 (0·57–1·12)
Placebo	(601/609)	58 (9·7%)	78 (12·8%)	0·75 (0·55–1·04)
Men	(863/828)	77 (8·9%)	115 (13·9%)	0·64 (0·49–0·84)
Women	(344/398)	36 (10·5%)	33 (8·3%)	1·26 (0·80–1·97)
Age ⩾65 years	(648/633)	68 (10·5%)	100 (15·8%)	0·66 (0·50–0·89)
Age <65 years	(559/593)	45 (8·1%)	48 (8·1%)	1·00 (0·67–1·47)
Diabetes mellitus	(153/143)	28 (18·3%)	35 (24·5%)	0·75 (0·48–1·16)
No diabetes	(1054/1083)	85 (8·1%)	113 (10·4%)	0·77 (0·59–1·01)
Angina history >3 months	(437/424)	43 (9·8%)	71 (16·7%)	0·59 (0·41–0·84)
Angina history ⩽3 months	(769/802)	70 (9·1%)	77 (9·6%)	0·95 (0·70–1·29)
Not smoking	(853/848)	83 (9·7%)	124 (14·6%)	0·66 (0·51–0·86)
Current smoker	(354/378)	30 (8·5%)	24 (6·3%)	1·34 (0·80–2·24)
Previous MI	(274/266)	39 (14·2%)	53 (19·9%)	0·71 (0·49–1·04)
No previous MI	(933/960)	74 (7·9%)	95 (9·9%)	0·80 (0·60–1·07)
Hypertension	(363/376)	45 (12·4%)	59 (15·7%)	0·79 (0·55–1·13)
No hypertension	(844/850)	68 (8·1%)	89 (10·5%)	0·77 (0·57–1·04)
Chest pain at rest	(975/986)	88 (9·0%)	122 (12·4%)	0·73 (0·56–0·95)
No chest pain at rest	(231/239)	24 (10·4%)	25 (10·5%)	0·99 (0·58–1·69)
TnT ⩾0·1 ug/L†	(659/677)	67 (10·2%)	91 (13·4%)	0·73 (0·56–1·02)
TnT <0·1 ug/L	(490/485)	41 (8·4%)	50 (10·3%)	0·80 (0·55–1·20)
ST depression at inclusion	(535/567)	55 (10·3%)	88 (15·5%)	0·66 (0·48–0·91)
No ST depression at inclusion	(645/639)	54 (8·4%)	57 (8·9%)	0·94 (0·66–1·34)

MI=myocardial infarction; TnT=troponin-T.
*Figures in parentheses show assessed patients in invasive/non-invasive groups.
†Analysed in plasma samples obtained at randomisation.

Table 5: **Effect of invasive and non-invasive treatment strategies on death, myocardial infarction, or both at 6 months in predefined strata and subgroups**

	Invasive	Non-invasive	Risk ratio (95% CI)	p
Angina				
6-week visit (1153/1184)	234 (20%)	617 (52%)	0·39 (0·34–0·44)	<0·001
3-month visit (1175?1188)	243 (21%)	517 (44%)	0·48 (0·42 –0·54)	<0·001
6-month visit (1174/1177)	256 (22%)	455 (39%)	0·56 (0·50–0·64)	<0·001
Canadian Cardiovascular Society angina class III–IV				
6-week visit (1157/1184)	24 (2%)	144 (12%)	0·17 (0·11–0·26)	<0·001
3-month visit (1173/1186)	29 (2%)	104 (9%)	0·28 (0·19–0·42)	<0·001
6-month visit (1170/1170)	32 (3%)	81 (7%)	0·38 (0·25–0·56)	<0·001
Re-admission since last visit				
6-week visit (1157/1195)	172 (15%)	286 (24%)	0·62 (0·34–0·44)	<0·001
3-month visit (1177/1197)	115 (10%)	228 (19%)	0·51 (0·42–0·63)	<0·001
6-month visit (1190/1186)	168 (14%)	281 (24%)	0·60 (0·50–0·72)	<0·001
Re-admission during 6 months (1167/1204)	357 (31%)	594 (49%)	0·62 (0·60–0·69)	<0·001

Numbers in parentheses show assessed patients in invasive/non-invasive groups.

Table 6: **Symptoms, re-admission, and medication during 6 months' follow-up in invasive versus non-invasive groups**

During the first months of treatment, the event rate was lower in the non-invasive dalteparin group than in any other group (figure 6). After 6 months, the event rate was still lower in the non-invasive dalteparin group than in the placebo group (risk ratio 0·89 [95% CI 0·65–1·20]). In the invasive group, there was no significant effect of dalteparin treatment compared with placebo (0·94 [0·66–1·34]). In multiple logistic-regression analysis there was no significant interaction between dalteparin and placebo or the invasive and non-invasive strategies for effects of the invasive strategy after 6 months. There was a heterogeneous effect of the invasive strategies in some subgroups (table 5). Invasive treatment provided the greatest advantages at older age, in men, and with longer duration of angina, chest pain at rest, and ST-segment depression.

There was around a 50% relative decrease in symptoms in the invasive compared with the non-invasive group and a corresponding difference in Canadian Cardiovascular Society score for angina (table 6). The need for nitrates was halved in the invasive group (table 7). The decreases in symptoms and medication were similar and without heterogeneity between any of the subgroups (table 8). During the trial, the prophylactic use of aspirin in 93% of patients, statins in 55%, and angtiotensin-converting-enzyme inhibitors in 18% were similar in the invasive and non-invasive groups (table 7).

The need for re-admission was about halved during the 6 months of follow-up in the invasive group compared with the non-invasive group (table 6). This difference was explained partly by the continuously increasing need for invasive procedures in the non-invasive group, because of incapacitating symptoms or recurrences of unstable angina or myocardial infarction. In the non-invasive group 23% of patients had a revascularisation procedure after the initial hospital stay compared with 5·6% in the invasive group during the 6-month follow-up (p<0·001).

	Invasive (n=1170)	Non-invasive (n=1182)	Risk ratio (95% CI)	p
Aspirin	1083 (93%)	1107 (94%)	0·99 (0·97–1·01)	0·34
β-blocker	865 (74%)	989 ()84%)	0·88 (0·85–0·92)	<0·001
Long-acting nitrates	201 (17%)	447 (38%)	0·45 (0·39–0·53)	<0·001
Calcium antagonist	206 (18%)	266 (23%)	0·78 (0·67–0·92)	0·003
Angiotensin-converting-enzyme-inhibitor	196 (17%)	218 (18%)	0·91 (0·76–1·08)	0·31
Statin	650 (56%)	652 (55%)	1·00 (0·94–1·08)	0·88

Table 7: **Medication in invasive and non-invasive groups after 3 months' follow-up**

	n*	Invasive	Non-invasive	Risk ratio (95% CI)
Dalteparin	(591/598)	129 (22%)	242 (40%)	0·54 (0·45–0·65)
Placebo	(583/579)	127 (22%)	213 (37%)	0·59 (0·49–0·71)
Men	(841/791)	163 (19%)	287 (36%)	0·53 (0·45–0·65)
Women	(333/386)	93 (28%)	168 (44%)	0·64 (0·52–0·79)
Age ⩾65 years	(624/600)	131 (21%)	234 (40%)	0·53 (0·44–0·64)
Age <65 years	(550/577)	125 (23%)	217 (38%)	0·60 (0·50–0·73)
Diabetes mellitus	(140/128)	34 (24%)	53 (41%)	0·59 (0·41–0·84)
No diabetes	(1034/1049)	222 (22%)	402 (38%)	0·56 (0·49–0·64)
Angina history >3 months	(421/401)	150 (25%)	274 (45%)	0·55 (0·45–0·67)
Angina history ⩽3 months	(752/776)	105 (20%)	181 (35%)	0·56 (0·48–0·67)
Smoking	(347/366)	82 (24%)	139 (38%)	0·62 (0·49–0·78)
Not smoking	(827/811)	174 (21%)	316 (39%)	0·54 (0·46–0·63)
Previous MI	(261/250)	66 (25%)	95 (38%)	0·66 (0·51–0·86)
No previous MI	(913/927)	190 (21%)	360 (39%)	0·54 (0·46–0·62)
Hypertension	(352/354)	89 (25%)	141 (40%)	0·64 (0·51–0·79)
No hypertension	(822/823)	167 (20%)	314 (38%)	0·53 (0·45–0·62)
Chest pain at rest	(947/947)	220 (23%)	369 (39%)	0·60 (0·52–0·69)
No chest pain at rest	(226/230)	35 (16%)	86 (37%)	0·41 (0·29–0·59)
TnT ⩾0·1 ug/L†	(639/647)	134 (21%)	228 (35%)	0·60 (0·50–0·72)
TnT <0·1 ug/L	(480/471)	113 (24%)	202 (43%)	0·55 (0·45–0·66)
ST depression at inclusion	(517/533)	112 (22%)	195 (37%)	0·59 (0·49–0·72)
No ST depression at inclusion	(631/626)	138 (22%)	249 (40%)	0·55 (0·46–0·66)

MI=myocardial infarction; TnT=Troponin-T.
*Numbers in parentheses show assessed patients in invasive/non-invasive groups.
†Analysed in plasma samples obtained at randomisation.

Table 8: **Effect of invasive and non-invasive treatment strategies on symptoms of angina pectoris in different predefined strata and subgroups at 6 months**

There were slightly more major bleeding episodes in the invasive than in the non-invasive groups (table 9). There were, however, no differences in stroke, intracranial bleeding, or thrombocytopenia. During the double-blind treatment period, after the randomised procedures, patients receiving dalteparin had a raised risk of bleeding episodes (table 10). There were no adverse interactions between dalteparin and the invasive regimen for side-effects. Of the strokes in 24 patients, seven were caused by intracranial bleeds, all of which occurred in the dalteparin groups—five in the non-invasive and two in the invasive strategies during double-blind treatment.

Discussion

We showed a significant decrease in death and myocardial infarction with an early invasive treatment strategy in unstable coronary-artery disease. The population investigated was recruited in three countries and included primary, secondary, and tertiary hospitals, with and without invasive facilities. We succeeded in recruiting patients at intermediate to high risk, a substantial proportion of whom were elderly men with chest pain at rest and signs of continuing ischaemia, myocardial damage, or both.[9,10] Therefore, the coronary angiograms in the invasive group showed substantial coronary lesions in 85% of patients, which in 77% led to revascularisation. The effects seen were obtained in addition to background treatment of unstable coronary-artery disease with acute-phase low-molecular-mass heparin and long-term aspirin, β-blockade in almost all, and statins in half of patients. No previous trial of invasive compared with non-invasive treatment in coronary-artery disease has used such aggressive medication[17] at baseline.

The magnitude of the difference in the event rate depends on the interpretation of signs of myocardial damage associated with the procedures. For the primary endpoint, we used the most liberal definition of myocardial infarction related to percutaneous coronary intervention, which equalised a transient slight rise in CK-MB mass without any other signs with a non-procedure-related myocardial infarction. Although a difference in long-term outcome between patients with and without procedure-related rises in biochemical markers has been reported,[18] the consequences of procedure-related myocardial damage might not be comparable to those of non-procedural events. The increasing use of abciximab in association with percutaneous coronary interventions and stenting[11,12,14] will lower the rate of events related to percutaneous coronary interventions by around 50%. Thus, the observed 2·7% absolute and a 22·0% relative decrease in the composite endpoint of death and myocardial infarction is probably the minimum benefit obtained by an invasive strategy. Furthermore, the decrease in mortality strongly supports the importance of the observed difference in the composite endpoint between groups.

Dalteparin treatment provided no benefit when continued after revascularisation. However, as shown in the accompanying report (see page 701),[19] long-term dalteparin decreased the rate of cardiac events in the non-invasive group during the first month of treatment. The event rate in the non-invasive dalteparin group did not rise to higher than that in the invasive groups for the first 90 days. However, even when the early beneficial effects of the dalteparin treatment are taken into account, there was, after 6 months, a significant advantage of the early invasive compared with the non-invasive approach, with no significant heterogeneity between the dalteparin and the placebo groups. Despite dalteparin treatment, the risk of bleeding associated with revascularisation procedures was low. Therefore, dalteparin treatment can safely be used in patients who are candidates for percutaneous coronary intervention or coronary-artery bypass surgery. The early effects of long-term dalteparin treatment are therefore useful for protection against further events while patients are waiting for invasive procedures.

Open-label treatment period	Invasive (n=1222)	Non-invasive (n=1235)
Any serious adverse event	47 (3·8%)	20 (1·6%)
Major bleeding episodes	19 (1·6%)	9 (0·7%)
Minor bleeding episodes	93 (7·6%)	72 (5·8%)
Thrombocytopenia*	1 (0·1%)	1 (0·1%)
Allergic reaction	12 (1·0%)	3 (0·2%)
Total stroke	2 (0·2%)	3 (0·2%)

*Defined as platelet count $<100\times10^9$/L.

Table 9: **Adverse events in invasive and non-invasive treatment strategies for open-label treatment with dalteparin**

Double-blind treatment period*	Invasive		Non-invasive	
	Dalteparin	Placebo	Dalteparin	Placebo
Any serious adverse event	83 (14·8%)	62 (11·1%)	69 (11·9%)	62 (10·6%)
Major bleeding episodes	13 (2·3%)	7 (1·3%)	21 (3·6%)	11 (1·9%)
Minor bleeding episodes	126 (22·5%)	38 (6·8%)	133 (23·1%)	47 (8·1%)
Thrombocytopenia†	2 (0·4%)	0	0	2 (0·3%)
Allergic reaction	15 (2·7%)	18 (3·2%)	13 (2·3%)	8 (1·4%)
Total stroke	6 (1·1%)	5 (0·9%)	6 (1·0%)	5 (0·9%)

*Including only patients who entered the double-blind treatment period.
†Defined as platelet count $<100\times10^9$/L.

Table 10: **Adverse events in invasive and non-invasive treatment strategies for double-blind treatment with dalteparin**

We found a rapid decrease in symptoms and severity of angina in the invasive group. The corresponding decreases in the use of antianginal drugs and re-admissions make the potential bias by the open-label treatment design unlikely. The credibility of the symptomatic effect is further supported by the low need for new interventions in the invasive group and the continuous increase in symptom-driven or ischaemia-driven coronary angiography and revascularisation in the non-invasive group. The decrease in symptoms and ischaemia in the invasive group were in accordance with previous comparisons of invasive and non-invasive regimens in unstable[2,4] and stable angina pectoris.[20–22]

In earlier trials[1–4] of invasive compared with non-invasive strategies, the results have been equivocal for death or myocardial infarction in the unstable coronary syndrome. The differences between previous studies and the FRISC II trial might be explained by the differences in antianginal and antithrombotic medication, the timing of procedures, the proportion of procedures in each strategy, the improved technology used in procedures, and the low mortality associated with bypass surgery in our trial. Our favourable invasive results were based on an initial period of stabilisation with a combination of antianginal and intense antithrombotic medication before invasive procedures. The large difference in intervention rates between the invasive and non-invasive groups (71 *vs* 9% at 10 days and 77 *vs* 37% at 6 months) contrasts with the TIMI IIIb trial[2] (61 *vs* 49% at 42 days) and the VANQWISH trial.[3] (44 *vs* 33% after about 1 year). Our results are in accordance with the DANAMI trial,[23] which showed a 47% relative decrease in myocardial infarction during 2·4 years of follow-up for an invasive compared with a non-invasive strategy, with 82% compared with 2% procedures done within the first 2 months in 503 randomised patients after myocardial infarction with exercise-induced ischaemia.

We did not assess the effects of immediate coronary angiography and the urgent use of percutaneous coronary interventions of the "culprit lesion" as the preferable strategy in patients with unstable coronary-artery disease. As with previous trials,[2–5,11,12] the mortality associated with percutaneous coronary intervention was almost negligible. In our trial, 30-day mortality after coronary-artery bypass surgery was very low at about 2% in each group. This surgical result compares well with Scandinavian experiences in the past few years.[24] Coronary-artery bypass surgery is known to lengthen life in three-vessel or left main-coronary-artery disease, and, therefore, the early surgery in these 38% of patients might be a major reason for the superior outcome in the invasive groups.[15,20,21]

Our subgroup analyses show that the benefit of an early invasive regimen on the risk of death or subsequent myocardial infarction was greatest in patients with any indicator of higher risk at entry. There were also some subgroups of patients at low risk of non-procedural events, such as women and current smokers, who had a higher rate of cardiac events because of the risk of early events at procedures. However, the analyses of low-risk subgroups with few events should be taken with caution and need further exploration after longer-term follow-up. Furthermore, the symptom relief seen with the early invasive strategy was similar in all subgroups.

Our results suggest the need for a change in the treatment of unstable coronary-artery disease. Early invasive procedures will decrease event rates and change the natural course of the disease. Invasive procedures, although associated with a periprocedural risk, seem to transform unstable coronary-artery disease into a stable disorder with a low event rate. Thus, to further improve outcome, focus should be placed on lowering the risks associated with coronary procedures.

An early invasive treatment strategy, with procedures within 7 days, lowers the risk of death and myocardial infarction in moderate-risk and high-risk patients with unstable coronary-artery disease. This regimen also leads to a substantially better and more rapid symptom relief, and fewer re-admissions than a non-invasive approach. With a non-invasive strategy, around half of patients will still need invasive assessment and, most commonly, revascularisation within 6 months. Therefore, an early invasive approach should be the preferred strategy for most patients with unstable coronary-artery disease who have signs of ischaemia in electrocardiography or raised biochemical markers of myocardial damage. An early invasive strategy might, however, be preferable only if the quality of the invasive procedures and the medical pretreatment are similar to those in this trial.

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Acknowledgments

This study was supported by and organised in collaboration with Pharmacia and Upjohn, Sweden. The project organisation within the research group was supported by the Swedish Heart-Lung Foundation. The randomised invasive procedures were possible because of support from the local health authorities and county councils in charge of funding in the participating hospitals. We thank the patients and the research nurses, monitors, investigators, coordinators, core laboratories, endpoint committee, and data safety monitoring board.

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