Acute Management — How Should We Intervene?

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Summary: A crucial question in the acute management of the patient with unstable coronary artery disease (UCAD) is whether to carry out early intervention, performing angiography soon after presentation and following this with revascularization where appropriate, or whether to follow a noninvasive medical strategy as far as possible unless symptoms necessitate intervention. The body of literature addressing this question is sparse, but the recent Fast Revascularization during InStability in Coronary artery disease (FRISC II) study has provided new insights into the problem.

Using a factorial design to randomize patients to invasive or noninvasive management strategies, and to short- or long-term treatment with the low-molecular-weight heparin (LMWH) dalteparin sodium (Fragmin®), it was shown in FRISC II that early invasive treatment (within 7 days), when combined with optimal medical pretreatment with dalteparin sodium, aspirin, and appropriate antianginal medication, is associated with improved clinical outcomes, relative to a “watchful waiting” approach based on noninvasive therapy. Thus, an early invasive approach following aggressive medical pretreatment should be the preferred strategy for patients with UCAD who present with signs of ischemia on the electrocardiogram or raised biochemical markers of myocardial damage at admission.

Key words: unstable coronary artery disease, invasive intervention, myocardial infarction, low-molecular-weight heparin, dalteparin sodium, noninvasive management

Introduction

There is a continuing debate over whether early intervention or a more conservative strategy is most appropriate for

the acute management of patients with unstable coronary artery disease (UCAD); that is, should angiography be performed early after presentation, followed by revascularization where indicated, or should intervention be reserved for those patients in whom medical therapy has failed? A recent study¹ has provided important data concerning this issue by demonstrating that, when combined with optimal medical treatment with the low-molecular-weight heparin (LMWH) dalteparin sodium (Fragmin®), aspirin, and appropriate antianginal medications, an early invasive approach is preferable for patients with UCAD, in whom signs of ischemia are visible on the electrocardiogram (ECG) or biochemical markers of myocardial damage are raised.

Background

During the past 10 years, there have been only two randomized trials comparing invasive versus noninvasive strategies in the management of patients with UCAD: the Thrombolysis In Myocardial Infarction (TIMI IIIB)² and Veterans' Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH)³ studies. The TIMI IIIB study randomized patients to either angiography within 48 h of admission, followed by revascularization as appropriate (740 patients); or to a more conservative medical strategy, with revascularization being undertaken only when indicated for the treatment of recurrent ischemia (733 patients). Numbers reaching the primary composite endpoint of death, nonfatal myocardial infarction (MI), or signs of ischemia on exercise testing at 6 weeks did not differ significantly between the two groups (18.1% in the conservative group, 16.2% in the early intervention group, $p=0.33$).² Furthermore, similar incidence rates were recorded for the double endpoint of death or MI in the two groups on follow-up at 1 year (12.2% among conservatively managed patients vs. 10.8% in the early intervention group, $p=0.42$).⁴ However, the early invasive strategy was associated with significant reductions in the length of hospitalization, the number of rehospitalizations, and the use of antianginal medication, indicating some advantages for routine early revascularization.

The VANQWISH study³ included only men with non-Q-wave myocardial infarction (NQMI) and randomized patients to similar invasive or conservative strategies within 72 h of the onset of NQMI. Treatment efficacy was assessed

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by means of a primary double endpoint of death or nonfatal MI. This study found a significant increase in the rate of unfavorable — and in particular fatal — outcomes among patients assigned to early intervention, relative to those managed conservatively. Incidence rates of the primary double endpoint were significantly higher among patients managed invasively than among the conservatively managed group at hospital discharge (7.8 vs. 3.3%, $p=0.004$), at 30 days (10.4 vs. 5.7%, $p=0.012$) and at 12 months (24.0 vs. 18.6%, $p=0.05$). Rates of death alone among the invasive versus conservative management groups were 4.5 versus 1.3% ($p=0.007$) at hospital discharge, 5.0 versus 2.0% ($p=0.21$) at 30 days, and 12.6 versus 7.9% ($p=0.025$) at 1 year. Rates of nonfatal MI did not differ significantly between the two treatment groups either at hospital discharge or during follow-up.

In view of the lack of a sizeable evidence base or one that allowed any definitive conclusions to be drawn, the Fast Revascularization during InStability in Coronary artery disease (FRISC II) study was designed to compare a routine early invasive with a conservative, noninvasive management strategy against a background of optimal antithrombotic medication in patients with UCAD.¹

The FRISC II Study

The FRISC II study was a prospective, randomized, multicenter trial with parallel groups. A factorial design was applied to compare invasive versus noninvasive management and prolonged versus acute-phase dalteparin sodium. The primary objective of the invasive versus noninvasive arm of FRISC II was to compare clinical outcomes obtained with an early invasive strategy versus those associated with a noninvasive, medical therapy-based approach in patients with UCAD. The primary endpoint for this open comparison was a composite of death or MI at 6 months; secondary endpoints assessed effects on symptoms of angina, readmission rates, the need for late revascularization procedures, and incidences of stroke and hemorrhage.

The FRISC II study population comprised 3,489 patients in total: men of at least 40 years of age and postmenopausal women who, within the previous 48 h, had experienced an episode of chest pain associated with ECG changes or elevated biochemical marker levels. Patients were considered eligible for study admission if they exhibited symptoms of ischemia that were either increasing, occurring at rest, or that warranted the suspicion of acute MI. Important exclusion criteria for the FRISC II trial included an increased risk of bleeding, indication for or treatment with thrombolysis during the last 24 h, percutaneous transluminal coronary angioplasty (PTCA) within the last 6 months, and a contraindication to randomized early revascularization (i.e., previous open-heart surgery, advanced age, or other concomitant illnesses).

Patients awaiting coronary revascularization, or with any other acute or severe cardiac disease, were also excluded.

On admission, all eligible patients received aspirin, beta blockers, calcium antagonists, and nitrates according to current clinical guidelines. As soon as possible after admission (within 72 h), patients were randomly allocated to one of four treatment strategies: long-term dalteparin sodium and a noninvasive strategy; long-term placebo and a noninvasive strategy; long-term dalteparin sodium and an invasive strategy; long-term placebo and an invasive strategy (Fig. 1). Patients with a contraindication to early revascularization ($n=666$) and late inclusions ($n=366$) were assigned to a noninvasive strategy and randomized to receive long-term dalteparin sodium or placebo. Prior to randomization (within 72 h of study admission), patients also received open-label dalteparin sodium 120 IU/kg/12 h or standard unfractionated heparin (UFH). Following randomization, all patients received subcutaneous dalteparin sodium 120 IU/kg twice daily for at least 5 days or until early revascularization procedure. (In the invasive management group this was carried out within 7 days of the start of open-label treatment). Revascularization procedures were carried out in patients assigned to noninvasive management only in the event of refractory angina, signs of severe ischemia on exercise testing, or reinfarction.

Randomized patients ($n=2,457$) in the invasive and noninvasive management groups were well matched for baseline demography. Some selected patient characteristics are shown in Table I. On the basis of the patient characteristics at study admission, the population of the invasive versus noninvasive management arm of FRISC II could be classified as a medium- to high-risk group.

Results

Overall, percutaneous coronary intervention (PCI) procedures were performed in 42.7% of the invasive group and 17.8% of the noninvasive group. Median times to PCI in the two groups were 4.0 and 16.5 days, respectively. Coronary artery bypass graft (CABG) was performed in 35.2% of patients randomized to invasive management and 18.9% of the noninvasive group, with median times to procedure of 7.0 and 28.0 days, respectively. Surgical mortality rates were low: 2.1% in the invasive group and 1.7% in the noninvasive group. Adverse events related to treatment are summarized in Table II. There was an increase in bleeding in the invasive group, but all other adverse events were rare.

During the initial 6 months of the FRISC II study, the double endpoint of death or MI was reached by 12.1% of the noninvasive group, compared with 9.4% of the invasive group — a significant relative risk reduction of 22% ($p=0.031$) (Fig. 2). A higher event rate was noted among patients randomized to invasive treatment than among the noninvasively managed group during the first 2 weeks of the trial, reflecting the risk

FIG. 1 FRISC II study design. ST-depress. = ST depression, T-inv.=T-wave inversion, CKMB = creatine-kinase MB, TNT = troponin T, PTCA = percutaneous transluminal angioplasty, CABG = coronary artery bypass graft, AMI = acute myocardial infarction, d = days, m = months, CCS = Canadian Society class, Cor. ai = coronary angiography.

TABLE I Selected baseline characteristics of patient groups

	Invasive management group (n=1,222)	Noninvasive management group (n=1,235)
Median age (years)	66	65
Proportion of males in group (%)	71	68
Hypertension (%)	30	31
Diabetes mellitus (%)	13	12
Previous MI (%)	23	22
ST-segment depression at entry (%)	45	46
Troponin-T level $\geq 0.1 \mu\text{g/l}$ (%)	57	58
LVEF $<45\%$ (%)	14	12
Current smokers (%)	30	31

Abbreviations: MI = myocardial infarction, LVEF = left ventricular ejection fraction.

associated with invasive procedures. However, after 2 weeks a lower event rate was seen in the invasive than in the noninvasive group. The hazard curves crossed at around 4 weeks and, from this point onward, the separation of the two curves showed an increasing benefit for invasive compared with noninvasive patient management.

Routine early invasive treatment significantly reduced incidences of MI alone: 6-month rates were 10.1% for the noninvasive group and 7.8% for the invasive group ($p=0.045$). A non-significant reduction in mortality rates was observed, from 2.9% in the noninvasive group to 1.9% in the invasive group ($p=0.10$). Incidences of the secondary endpoints were also reduced by early invasive management, as summarized in Table III.

Thus, the results of the FRISC II study clearly demonstrate that, in most patients with UCAD, an early invasive strategy following medical pretreatment with dalteparin

TABLE II Adverse events with invasive and noninvasive treatment strategies during treatment with dalteparin sodium

Treatment phase	Open-label		Double-blind	
Management strategy group	Invasive (n=1,222)	Noninvasive (n=1,235)	Invasive (n=563)*	Noninvasive (n=582)*
Any serious AE (%)	3.8	1.6	14.8	11.9
Major bleeding (%)	1.6	0.7	2.3	3.6
Minor bleeding (%)	7.6	5.8	22.5	23.1
Stroke (%)	0.2	0.2	1.1	1.0
Allergic reaction (%)	1.0	0.2	2.7	2.3
Thrombocytopenia (%)	0.1	0.1	0.4	0.0

Abbreviation: AE = adverse events.

*Patients randomized to long-term-treatment with dalteparin sodium.

sodium, aspirin, and indicated antianginal medication reduces rates of mortality and nonfatal MI. In this trial, the advantages of early invasive treatment, which were still apparent at the end of the 6-month observation period, were most marked in patients of higher age, in men, and in those with angina of longer duration, chest pain at rest, or ST-segment depression on the ECG.

The findings of FRISC II differ quite profoundly from those of previous trials comparing invasive with noninvasive management strategies in patients with UCAD, which had indicated either no significant difference in patient outcomes with these two strategies² or pointed to an excess of adverse outcomes with an approach of routine early intervention.³ The discrepancies between the findings of these studies and those of FRISC II may be explained by differences in antianginal and antithrombotic medications, timings of procedures, proportions of procedures carried out in each of the patient groups, improvements in technology and equipment during the intervening period, and the low risk of mortality associated with CABG in FRISC II. This low mortality is typical of the rates generally found in Scandinavian institutions.

The FRISC II study further differs from other similar trials in that a comparatively long time period — up to 7 days — elapsed before the early intervention procedures were carried out. While there is no universally accepted definition of “early”, the term is often taken to imply that coronary angiography is performed after just 24 to 48 h of medical pretreatment.⁵ In the TIMI IIIB study, patients were recruited within 24 h of an episode of chest pain at rest and were randomized to either a conservative strategy or to coronary angiography at 18 to 48 h followed by revascularization as soon as possible, where appropriate. Under the VANQWISH study protocol, patients were randomized within 24 to 72 h, and coronary an-

giography was performed soon afterward (a median of 2 days from randomization to intervention). It may be that an optimal period exists for stabilization with antithrombotic therapy, and that carrying out the intervention procedure before this period has lapsed results in an increased risk of negative clinical outcomes.

Also worthy of consideration is the fact that no other study comparing invasive versus noninvasive management strategies in UCAD has used such aggressive medication at baseline. In the FRISC II study, the background medical treatment consisted of acute-phase LMWH (dalteparin sodium), long-term aspirin, and beta blockade unless contraindicated, and patients in the early intervention group received open-label dalteparin sodium for a median of 6 days (120 IU/kg subcutaneous twice daily until the procedure, followed by 5,000 or 7,500 IU twice daily or placebo). In addition, nitrates, calcium antagonists and statins were included as required, and angiotensin-converting enzyme (ACE) inhibitors and antidiabetic treatments were administered in line with current guidelines. The placement of stents and administration of abciximab during PCI were also encouraged. This optimization of medical pretreatment and intervention technologies may have contributed significantly to the relatively favorable patient outcomes, as reflected by the low rate of interventions in the noninvasive group (9% at 10 days and 37% at 6 months), compared with other studies (49% at 42 days in the TIMI IIIB trial and 33% after 12 months in the VANQWISH trial).

FIG. 2 FRISC II invasive arm — death or myocardial infarction (MI) during 6 months. RR = relative risk, CI = confidence interval. Reproduced from Ref. 1 with permission from Fragmin and Fast Revascularization during InStability in Coronary artery disease Investigators: Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999 Aug 28;354(9180):708–715. ©The Lancet Ltd. 1999

TABLE III Symptoms and readmissions during 6 months' follow-up

	Invasive management group	Noninvasive management group	Risk ratio (95% confidence interval)	p-value
Angina (%)				
6 Weeks	20	52	0.39 (0.34–0.44)	<0.001
3 Months	21	44	0.48 (0.42–0.54)	<0.001
6 Months	22	39	0.56 (0.50–0.64)	<0.001
Canadian Cardiovascular Society angina class III–IV (%)				
6 Weeks	2	12	0.17 (0.11–0.26)	<0.001
3 Months	2	9	0.28 (0.19–0.42)	<0.001
6 Months	3	7	0.38 (0.25–0.56)	<0.001
Readmissions since last visit (%)				
6 Weeks	15	24	0.62 (0.34–0.44)	<0.001
3 Months	10	19	0.51 (0.42–0.63)	<0.001
6 Months	14	24	0.60 (0.50–0.72)	<0.001
Total readmissions during 6 months (%)	31	49	0.62 (0.60–0.69)	<0.001

Conclusions

The main conclusion to be drawn from the FRISC II study is that an early invasive approach (intervention within 7 days), following optimal medical treatment with dalteparin sodium, aspirin, and antianginal medications, should be the preferred strategy for the majority of patients with UCAD who have signs of ischemia on ECG, or raised levels of biochemical markers indicating myocardial damage at admission. This regimen not only reduces the risk of death and MI, but also results in improved symptom control, fewer hospital readmissions, and decreased use of beta blockers, long-acting nitrates, and calcium antagonists.

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