

Acute Coronary Syndromes: Extending Medical Intervention for Five Days Before Proceeding to Revascularization

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Intensive medical therapy before percutaneous coronary intervention appears to improve results in patients with unstable angina and non-ST-segment elevation myocardial infarction (MI). In this review of treatment strategies for patients with acute coronary syndromes, an "aggressive conservative" approach based on that used in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial is recommended. In FRISC II, an early (but not emergent) invasive therapeutic procedure undertaken within 7 days of starting open-label dalteparin lowered the risk of death and MI in moderate- and high-risk patients and resulted in better and more rapid symptom relief and fewer hospital readmissions than the noninvasive approach. The early

treatment period represents a critical juncture in the spectrum of care for patients with unstable angina and affords physicians the best opportunity to educate them about the importance of risk factor modification. Informed consent is also an important issue, particularly in the event of ad hoc coronary intervention. The optimal treatment plan must include considerations of length of hospitalization, medication requirements, and the potential for symptom recurrence or need for hospital readmission. Finally, tailoring therapy for individual patients and establishing appropriate timing of procedures will help ensure the best possible outcome. ©2000 by Excerpta Medica, Inc.

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During the past several decades, percutaneous transluminal coronary angioplasty (PTCA) has been established as an effective treatment option for patients with acute coronary syndromes.¹ In recent years, however, a controversy has emerged surrounding the question of whether PTCA should be used routinely in patients with unstable angina and non-ST-segment elevation myocardial infarction (MI). Those who opt for an aggressive, invasive approach believe that all patients with acute coronary syndromes should undergo early cardiac catheterization for risk stratification, with revascularization (PTCA or coronary artery bypass grafting [CABG]) if appropriate. Others prefer a more conservative, noninvasive approach that involves stabilizing the vessel, alleviating symptoms, and opting for invasive methods later in the treatment course, only if clinically required.

In evaluating the treatment strategies for patients with unstable angina, several critical issues must be addressed: length of hospitalization, medication requirements, recurrence of symptoms, need for hospital readmission, and economic factors. Informed consent is another important consideration, particularly in the event of ad hoc coronary intervention (percutaneous revascularization performed at the same sitting as diagnostic cardiac catheterization). Although the latter strategy appears to be very efficient, it would not be

appropriate if informed consent has not been obtained from the patient before the procedure. This is difficult because before angiography, there is no exact knowledge of the specific anatomy, and it is therefore difficult to discuss risk/benefit ratios.²

An aggressive approach to treatment may be selected on the basis of restrictions on length of hospitalization and other issues related to cost-effectiveness. A conservative approach may be chosen with the idea of tailoring therapy for individual patients and waiting until patients develop recurrent symptoms. Passivating the plaque or decreasing the volume of thrombus until percutaneous coronary intervention can be undertaken is another potential advantage of a delayed approach and may decrease complications.

The early period in which a patient is treated for an acute coronary syndrome represents a critical juncture in the spectrum of care. In addition to ensuring appropriate risk stratification and recommendations for treatment, this is optimal time for the clinician to educate patients about coronary artery disease and to advise them about modification of their coronary risk factors. It is the time at which patients are most concerned and, thus, may be most receptive to information on secondary prevention.³⁻⁷

Most patients with non-ST-segment elevation MI and unstable angina will eventually require angiography and possible revascularization. Whether patients are treated conservatively or aggressively, they are at increased risk for coronary events. Intensive medical treatment before intervention appears to improve results.

In this review, an "aggressive conservative" approach to treatment will be explored, one which involves stabilizing the patient for at least 5 days before invasive procedures are undertaken. This approach is

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The treatment approach presented herein was developed in an educational debate format designed to explore possible strategies for management of acute coronary syndromes. The text represents a defense of 1 of 5 propositions, but not necessarily the author's personal recommendation or endorsement of this particular treatment strategy.

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based on that used in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial,⁸ which was the first randomized study to show benefit from the invasive approach. Other trials comparing invasive versus conservative treatment approaches in patients with unstable coronary artery disease will also be discussed.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

Combined, intense antianginal and antithrombotic medication administered before invasive procedures is a thoughtful approach, which takes into consideration the underlying pathophysiology of acute coronary syndromes. Early changes that precede the formation of lesions of atherosclerosis take place in the endothelium, with each atherosclerotic lesion representing a different stage in a chronic inflammatory process.⁹ The prevalent view that atherosclerosis is an inflammatory, or healing, response of the intima to injury has been advanced by Ross and other investigators.^{10–15} Endothelial injury is assigned a primary role in the response to injury hypothesis. Early injury is generally characterized by modulation of endothelial cell function without loss of cells, a concept replacing that of earlier models of traumatic denudation.¹⁶ Beginning lesions are associated with an increased adherence of circulating monocytes to the endothelium, representing an early response to hypercholesterolemia. The entry of adherent monocytes into the subendothelial space leads to foam cell formation which, in turn, leads to the first ubiquitous lesion of atherosclerosis—the fatty streak.¹⁷ Lesion initiation or progression may be influenced by such factors as cigarette smoking, hypertension, increased serum lipid concentrations, immunologic mechanisms, and viral injury.¹⁶ Continuance of risk factors such as hypercholesterolemia creates a climate for the inflammatory response to also continue. Although it may begin as a protective response, the chronic inflammatory condition may become deleterious and eventually be converted to an acute clinical event by plaque rupture that leads to thrombosis.^{15,17}

Most clinical symptoms of coronary heart disease, including angina, MI, and death, occur as a result of development of a thrombus large enough to protrude into the vessel lumen and acutely decrease blood flow. Davies has described the major cause of unstable angina as “a culprit plaque over which thrombus is arrested at an intermediate stage in which it is neither occlusive nor resolved sufficiently to allow the plaque to reseal and heal.”¹⁴ Fuster et al¹⁵ characterize the responsible lesion of non-Q-wave MI as being similar in morphology to that seen in unstable angina but speculate that in non-Q-wave infarction, the plaque damage or thrombogenic risk factors are worse than in unstable angina, resulting in more persistent thrombotic occlusion. In Q-wave infarction, plaque disruption may be associated with deep arterial damage and ulceration leading to occlusive thrombi.¹⁵ In other acute coronary syndromes, the culprit lesion may be only mildly or moderately stenotic, which implicates

plaque disruption with superimposed nonobstructive thrombus.¹⁵

CLINICAL TRIALS FOR TREATMENT OF ACUTE ISCHEMIC SYNDROMES

The primary goals of treatment for patients with unstable angina and non-Q-wave MI are to relieve symptoms, stabilize the plaque, and reduce mortality and morbidity. No randomized clinical trials or observational studies have shown a clear advantage for routine catheterization in these patients. Proponents of both the aggressive and conservative treatment approaches have used data from the Thrombolysis in Myocardial Ischemia (TIMI) IIIB trial¹⁸ and the Organisation to Assess Strategies for Ischemic Syndromes (OASIS) Registry^{19,20} to support their arguments. Results were less equivocal in the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,²¹ which favored a conservative approach, and FRISC II⁸ which, as mentioned above, was the first randomized trial to favor an early invasive strategy.

TIMI IIIB: The TIMI IIIB trial was designed to investigate the role of a thrombolytic agent added to conventional medical therapies and to compare an early invasive (early coronary arteriography followed by revascularization when the anatomy was suitable) versus an early conservative strategy (coronary arteriography followed by revascularization if initial medical therapy failed) in 1,473 patients diagnosed with unstable angina or non-Q-wave MI.¹⁸ All patients received conventional anti-ischemic medical therapies. Patients assigned to the invasive group underwent coronary angiography within 48 hours of randomization; then revascularization procedures were undertaken, if necessary. The conservative group of patients who did not respond to initial therapy designed to prevent recurrent ischemia underwent catheterization. The composite primary endpoint was death, nonfatal MI, and a failed exercise tolerance test at 6-week follow-up. For patients in the invasive group, the endpoint was reached in 16.2% of cases; for those in the conservative group, it was 18.1%, a statistically insignificant difference. Delayed revascularization did not have a negative impact on outcomes in conservatively managed patients. There was a significant reduction in the average length of initial hospital stay, incidence of rehospitalization within the 6-week period, and days of rehospitalization in the group treated according to an early invasive strategy.

OASIS Registry: The OASIS Registry was a prospective registry of approximately 8,000 patients with non-ST-segment elevation acute coronary syndrome from 95 hospitals in 6 countries.¹⁹ The registry examined regional differences in the clinical management, frequency and timing of invasive procedures (angiography, percutaneous transluminal coronary angioplasty [PTCA], and coronary artery bypass grafting [CABG]). In the initial findings of the OASIS Registry, there was a wide variation in rates of angiography among countries during the first 7 days. The catheterization rates ranged from 60% in Brazil and 58% in

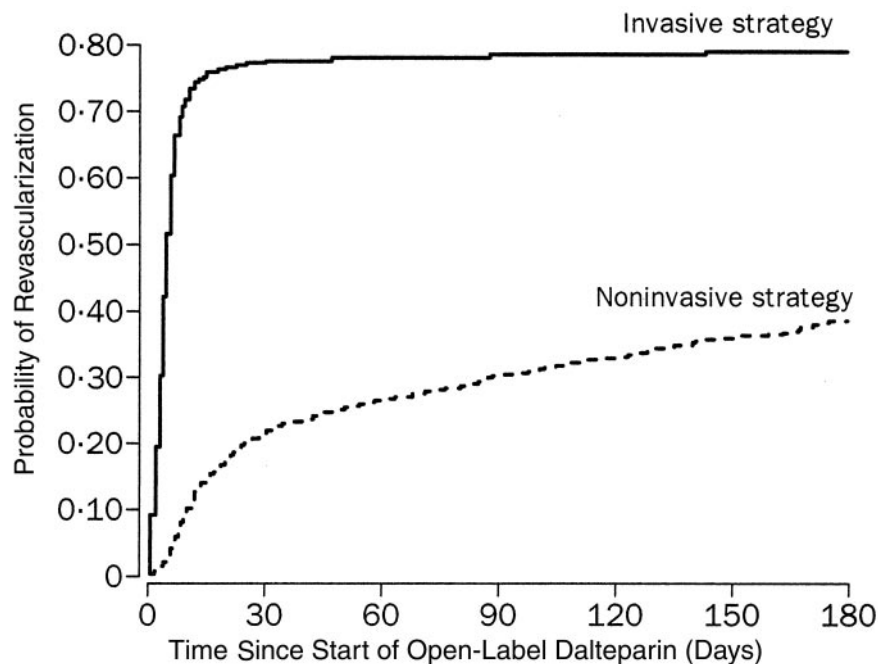


FIGURE 1. Timing of first revascularization in the invasive and noninvasive groups in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial. (Reprinted with permission from *Lancet*.⁸) Copyright© by The Lancet Ltd, 1999.

the United States to 15% in Hungary and 2% in Poland.²⁰ Even with this wide disparity in catheterization rates, the frequency of major cardiac events between countries was very similar. The composite endpoint of death and MI after 7 days was 4.7% in all nations (range, 3.8–5.6%). After 6 months, the rates were similar, with an average of 10.7%. No significant advantage was found with routine catheterization; aggressive procedures were associated with increased bleeding complications.

VANQWISH: A significant advantage was shown toward conservative management across all patient groups in the VANQWISH trial, another large-scale study directly comparing outcomes in patients with non-Q-wave MI assigned to a conservative or invasive treatment strategy.²¹ In this trial, 920 patients were randomly assigned to an invasive (462 patients) or conservative (458 patients) management; the latter involved medical therapy and noninvasive testing, with subsequent invasive procedures if indicated by the development of spontaneous or inducible ischemia within 72 hours of onset of a non-Q-wave infarction. The combined primary endpoint included death or nonfatal infarction. During a follow-up of 23 months, no differences were seen in endpoints between groups—30.0% in the invasive group and 26.9% in the conservatively managed group. However, there were significant differences shown in endpoints reached at 1 year—111 patients (24%) in the invasive-strategy group versus 85 (19%) in the conservative group; $p = 0.05$. The investigators concluded that a conservative, ischemia-guided initial approach was more beneficial than routine, early invasive management in patients with non-Q-wave MI.

THE AGGRESSIVE CONSERVATIVE STRATEGY: FRISC II

The FRISC II trial was an important study in which patients were randomly assigned to an early invasive or noninvasive strategy with placebo-controlled long-term low-molecular-weight heparin (dalteparin) for 3 months.⁸ In this trial, an early, but not emergent, invasive therapeutic procedure within 7 days of administering open-label dalteparin was found to decrease the risk of death and MI in moderate- and high-risk patients and to result in better and more rapid symptom relief and fewer hospital readmissions than the noninvasive approach.

TABLE 1 Results of Coronary Angiography in Invasive and Noninvasive Groups: FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) Trial

Variable	Invasive (n = 1,222)	Noninvasive (n = 1,235)
Coronary angiography	1,201 (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–90th percentile).

[†]Percentages of patients with coronary angiograms.

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TABLE 2 Revascularization Procedures in Invasive and Noninvasive Groups: FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II)

Variable	Invasive (n = 1,222)	Noninvasive (n = 1,235) intervention
Percutaneous coronary intervention		
Total	522	220
Proportion with stent*	61%	70%
Proportion receiving abciximab*	10%	10%
Mean (SD) treated segments*	1.35 (0–67)	1.34 (0–72)
Successfully treated segments*	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 CABG	7 (5–13)	28 (10–139)
Surgery ≤10 days	82%	13%

*Percentages of patients with percutaneous coronary intervention.
[†]Median (10th–90th percentile) in patients with respective procedure.
[‡]Percentages of patients with coronary artery bypass surgery.
CABG = coronary artery bypass grafting.
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TABLE 3 30-Day Mortality in Patients Undergoing Revascularization Procedures: FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) and Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH)

	CABG		PTCA	
	Invasive	Noninvasive	Invasive	Noninvasive
FRISC II				
N	430	233	522	220
30-day death (%)	2.1	1.7	1.3	1.4
VANQWISH				
N	95	87	98	55
30-day death (%)	11.6	3.4	0	3.6

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.
Data are adapted from *Lancet*⁸ and *N Engl J Med*.²¹

The trial enrolled 2,457 patients in 58 Scandinavian hospitals (median age, 66 years; 70% men). Eligible patients who met the study criteria were given dalteparin twice daily (or an intravenous infusion of standard heparin). As soon as possible after admission up to 72 hours after the start of open-label dalteparin (or heparin), patients were randomly assigned to 1 of 4 treatment groups: invasive treatment and dalteparin, invasive treatment and placebo, noninvasive treatment and dalteparin, noninvasive treatment and placebo. From the time of randomization, all patients received dalteparin (120 IU/kg every 12 hours) subcutaneously to a maximum dose of 10,000 IU, for at least 5 days in the noninvasive group and until procedures were done in the invasive group. The goal was to perform all invasive procedures within 7 days of administering open-label dalteparin.

Factors related to coronary angiography for the invasive and noninvasive groups are shown in Table 1.⁸ Within the first 10 days, 71% of patients underwent coronary revascularization in the invasive group,

and 9% underwent revascularization in the conservative group. By 6-month follow-up, 77% of patients in the invasive group and 37% in the noninvasive group had undergone revascularization procedures (Figure 1). The dilatation performance data from FRISC II show that approximately 60–70% of the patients underwent stent implantation, and 10% received abciximab (Table 2).⁸ In contrast to the high mortality rates associated with CABG in the VANQWISH trial, mortality rates in the FRISC II trial were very low (Table 3).^{8,21} That may be a major factor accounting for the differences in the conclusions between these 2 trials regarding patient populations and treatment strategies.

A comparison of event rates for the invasive and noninvasive groups revealed a significant 22.0% relative and 2.7% absolute decrease in death and MI in the invasive compared with the noninvasive group at 6-month follow-up (Figure 2). During the early period, however, as shown in Figure 3, there was an increased incidence of MI in the invasive group. After the first 2 weeks, the event rate was lower in the

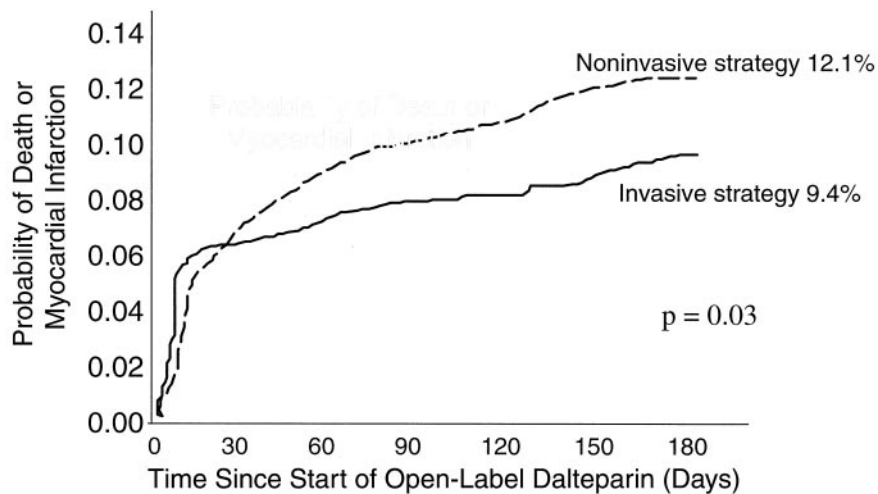


FIGURE 2. Probability of death or myocardial infarction in invasive and noninvasive groups in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial. (Reprinted with permission from *Lancet*.⁸) Copyright© by The Lancet Ltd, 1999.

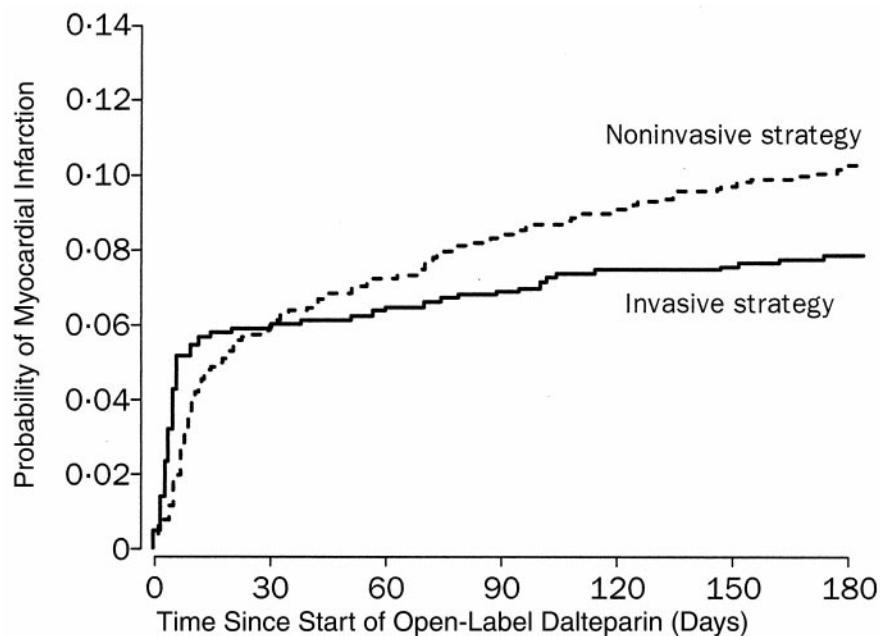


FIGURE 3. Probability of myocardial infarction in the invasive and noninvasive groups in the FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) trial. (Reprinted with permission from *Lancet*.⁸) Copyright© by The Lancet Ltd, 1999.

invasive than in the noninvasive group. As mentioned above, only 10% of these patients received abciximab, which may have contributed to this outcome. Even after early intervention and the use of dalteparin, however, there was an early hazard with the development of acute MI—at least, as measured by enzymatic markers alone.

A heterogeneous effect of invasive strategies was found in some subgroups in the trial. The investigators found the greatest advantages with invasive treatment among men, patients of older age, and those with a

longer duration of angina, chest pain at rest, and ST-segment depression.

In FRISC II, measurement of the serum troponin T level, a surrogate marker for thrombus formation, helped identify a high-risk subset of patients with refractory unstable angina who would benefit from antiplatelet therapy. In the C7E3 fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) trial, the use of abciximab was associated with dramatic improvement in the outcome of patients with elevated troponin T levels.²² Abciximab may not be

necessary in patients with acute ischemic syndromes who do not have elevated troponin T or I; stent placement alone may be adequate for a good outcome.

CONCLUSION

How does the FRISC II trial differ from the other trials? The primary difference is related to the initial period of stabilization, with the use of combined anti-anginal and intensive antithrombotic medications before the invasive procedures. An important advantage of this approach is that it will help risk-stratify patients with acute coronary syndromes. The appropriate timing of intervention will allow the physician to tailor therapy and will ensure that the patient is prepared. The informed consent and accompanying patient education will have been accomplished in an appropriate format. Within the right context, it is the optimal time to intervene and educate the patient about modification of risk factors. Physicians should have an understanding of the pathophysiologic roles of risk factors, as well as the evidence from epidemiologic studies and clinical trials for their association with coronary heart disease. Watchful waiting is not enough. Intensive medical therapy before intervention appears to improve the results.

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