CLINICAL STUDIES   **Acute Coronary Syndromes**

A Long-Term Perspective on the Protective Effects of an Early Invasive Strategy in Unstable Coronary Artery Disease
Two-Year Follow-Up of the FRISC-II Invasive Study

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OBJECTIVES   We sought to report the first and repeat events and to separate spontaneous and procedure-related events over two years in the Fast Revascularization during InStability in Coronary artery disease (FRISC-II) invasive trial.

BACKGROUND   The FRISC-II invasive trial compared the long-term effects of an early invasive versus noninvasive strategy, in terms of death and myocardial infarction (MI) and the need for repeat hospital admissions and late revascularization procedures in patients with coronary artery disease (UCAD).

METHODS   In the FRISC-II trial, 2,457 patients with UCAD were randomized to an early invasive or noninvasive strategy.

RESULTS   At 24 month follow-up, there were reductions in mortality (n = 45 [3.7%] vs. 67 [5.4%]; risk ratio 0.68 [95% confidence interval (CI) 0.47 to 0.98]; p = 0.038), MI (n = 111 [9.2%] vs. 156 [12.7%]; risk ratio 0.72 [95% CI 0.57 to 0.91]; p = 0.005), and the composite end point of death or MI (n = 146 [12.1%] vs. 200 [16.3%]; risk ratio 0.74 [95% CI 0.61 to 0.90]; p = 0.003) in the invasive compared with the noninvasive group. Procedure-related MIs were two to three times more common, but spontaneous ones were three times less common in the invasive than in the noninvasive group. After the first year, there was no difference in mortality (n = 20 [1.7%]) between the two groups and fewer MIs in the invasive group (p = 0.031).

CONCLUSIONS   In UCAD, the early invasive approach leads to a sustained reduction in mortality, cardiac morbidity, and the need for repeat hospital admissions and late revascularization procedures. Although the benefits are greatest during the first months, during the second year, cardiac morbidity is lower and the need for hospital care is less in the invasive group.   (J Am Coll Cardiol 2002;40:1902–14) © 2002 by the American College of Cardiology Foundation

An early invasive strategy using coronary angiography and, if appropriate, revascularization has recently become the recommended treatment for the majority of patients with unstable coronary artery disease (UCAD) in the Western countries (1). Evidence for the superiority, with respect to

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event-free survival, of an invasive treatment over a more conservative approach has been lacking for a long time. In the early Veterans Affairs study of unstable angina, comparing coronary artery bypass graft surgery (CABG) with

medical treatment, there was no survival benefit, except in patients with poor left ventricular function (2,3). In the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial including men with non–Q-wave myocardial infarction (MI), the early invasive strategy was associated with higher early mortality, which was sustained for more than a year (4). The Thrombolysis In Myocardial Infarction (TIMI-IIIB) trial of non–ST-segment elevation acute coronary syndrome reported shorter hospital stays and less need for anti-anginal medication, but no difference in cardiac events by using an early invasive approach (5).

The Fast Revascularization during InStability in Coronary artery disease (FRISC-II) trial was the first randomized study to convincingly demonstrate a better outcome in patients treated with an early invasive strategy, with a reduction in the primary composite end point of death/MI after six months (6). At 12-month follow-up, there were significant reductions in both mortality and MI alone (7). These results were supported by the recently reported

Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CI	= confidence interval
FRISC-II	= Fast Revascularization during InStability in Coronary artery disease trial
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
UCAD	= unstable coronary artery disease

TACTICS–TIMI-18 trial, which showed a lower rate of MI and composite events in the early invasive cohort after six months (8).

This report presents a two-year perspective on the effects of an invasive strategy on mortality, MI, early and late revascularization, and repeat hospital admission in the FRISC-II trial. The analysis also includes data on procedure-related and spontaneous MIs and repeat events in the same patients.

METHODS

Study design. The objective of the invasive part of the FRISC-II trial was to compare an early invasive with an early noninvasive strategy in patients with UCAD with a primary composite end point of death or MI at six months. Other predefined end points were death, MI, late revascularizations, and repeat admissions to the hospital, as well as cardiac symptoms at 6, 12, and 24 months. The results at 6 and 12 months have already been published (6,7). The FRISC-II study was a prospective, randomized, multicenter trial with parallel groups. The invasive versus noninvasive comparison was carried out in a factorial design. Half of the patients within each group were also randomized to continued treatment with subcutaneous dalteparin or placebo for three months.

Patients, medications, and procedures. Between June 17, 1996 and August 28, 1998, 2,457 patients were included and randomized to the invasive or noninvasive arm of FRISC-II in 58 Scandinavian hospitals. The detailed inclusion criteria, exclusion criteria, study design, and results up to 12 months have previously been published (6,7). In short, patients were eligible if they were admitted with symptoms of UCAD with the last episode of chest pain within 48 h

before the start of treatment with low-molecular-weight heparin (dalteparin) or regular heparin and if they had demonstrated signs of myocardial ischemia (i.e., ST-segment depression, T-wave inversion, raised biochemical myocardial markers). Excluded were patients with an indication for thrombolysis or those treated with thrombolysis within the past 24 hours, angioplasty within the last six months, previous open-heart surgery, advanced age (e.g., >75 years), or other conditions that made randomization to early revascularization inappropriate. All patients received aspirin and open-label dalteparin for at least five days; in the invasive group, they always received it until the evening before revascularization. Beta-blockers were given unless contraindicated. Statins and angiotensin-converting enzyme inhibitors were recommended according to modern treatment guidelines.

In the invasive strategy, the aim was to perform coronary angiography and, if appropriate, revascularization within seven days of hospital admission. Revascularization was recommended in all patients with ≥70% diameter stenosis in any artery supplying a significant proportion of the myocardium. Percutaneous coronary intervention (PCI) was recommended in one or two significant lesions, whereas CABG was the preferred treatment in patients with three-vessel or left main coronary artery disease. The noninvasive strategy recommended coronary angiography in patients with refractory or recurrent symptoms, despite maximal medical treatment or severe ischemia on a predischarge symptom-limited exercise test. During long-term follow-up, invasive procedures should be considered, regardless of the randomized strategy, for all patients with incapacitating symptoms, recurrence of instability, or MI.

Events. The patients' outcome events while in the hospital were evaluated by telephone contact after two weeks, by outpatient visits after six weeks, three months, and 6 months, and by telephone contact after 12 and 24 months. The vital status of patients lost to follow-up was collected in hospital records and national population registries. During the first six months, all reported deaths, MIs, elevation of biochemical markers in relation to PCI procedures, and new Q waves reported by the electrocardiography core laboratory were adjudicated by an independent Clinical Events Committee. After the first six months, information on further

Table 1. Mortality During Two Years in Six-Month Periods in the Invasive and Noninvasive Groups

	n*	Invasive Group	Noninvasive Group	Risk Ratio	95% CI	p Value
First week†	1,222/1,235	5 (0.4%)	4 (0.3%)	1.26	0.34–4.69	
Second week to 6 months	1,217/1,231	18 (1.5%)	32 (2.6%)	0.57	0.32–1.01	
7 to 12 months	1,199/1,199	4 (0.3%)	12 (1.0%)	0.33	0.11–1.03	
13 to 18 months	1,195/1,187	11 (0.9%)	9 (0.8%)	1.21	0.50–2.92	
19 to 24 months	1,184/1,178	7 (0.6%)	10 (0.8%)	0.70	0.27–1.82	
Total 0 to 24 months	1,222/1,235	45 (3.7%)	67 (5.4%)	0.68	0.47–0.98	0.038

*Figures show evaluated patients in the invasive/noninvasive groups. †The first six-month period is subdivided into the first week and second week to six months.
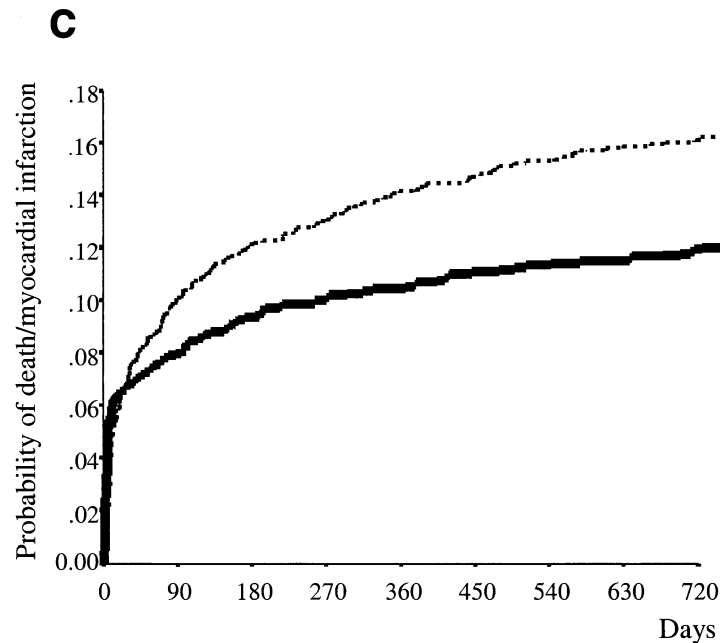
CI = confidence interval.

A

Numbers at risk

Invasive	1222	1199	1195	1185	1157
Non-invasive	1235	1200	1187	1179	1159

B
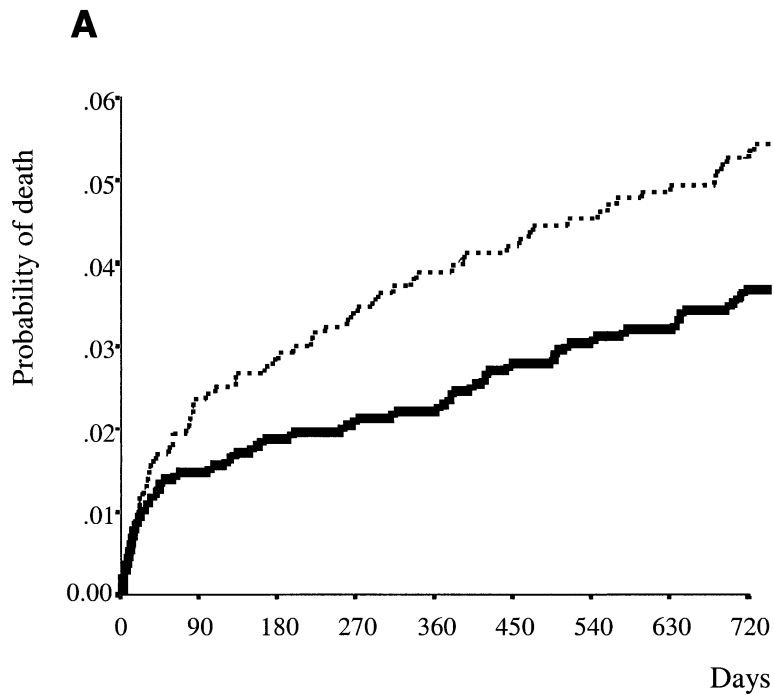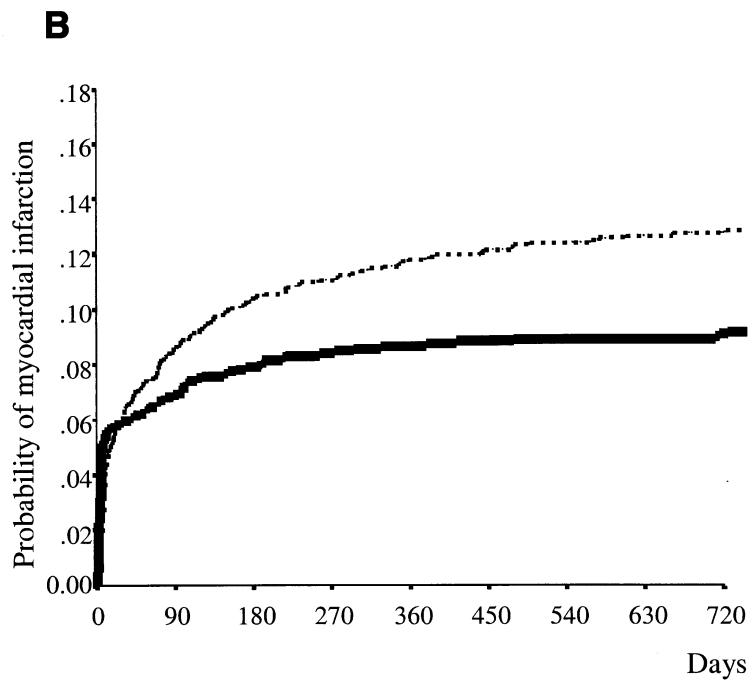
Numbers at risk

Invasive	1222	1103	1088	1073	1046
Non-invasive	1235	1082	1055	1039	1018

Figure 1. Probability of death **(A)**, myocardial infarction **(B)**, and death or myocardial infarction **(C)** in the invasive (n = 1,222, **continuous broad line**) and noninvasive (n = 1,235, **dotted narrow line**) groups, illustrated by Kaplan-Meier (1 − survival) curves. *Continued on next page.*

C

Numbers at risk

Invasive	1222	1103	1088	1073	1046
Non-invasive	1235	1082	1055	1039	1018

Figure 1 Continued.

events was based on investigator report forms, outpatient visits, or telephone contact with all surviving patients. In case of repeat admission to the hospital, the diagnosis was obtained from the hospital records. The reasons for death after six months were either based on hospital records or death certificates. During the first six months, the Clinical Events Committee classified the MIs as "spontaneous" or "procedure-related." Thereafter, all MIs occurring on the day of or the day after a coronary procedure were considered "procedure-related", and the others, accordingly, as "spontaneous."

Statistics and data management. All statistical analyses were performed on an intention-to-treat basis. The efficacy analyses were based on events occurring from the start of open-label dalteparin treatment until 24 months. The efficacy analyses were point estimates including only patients with an adjudicated event or with a recorded absence of the evaluated event until at least 670 days of follow-up. The differences between the groups were evaluated for the whole period of follow-up and for shorter intervals (i.e., initial 7 days, 2nd week to 6 months, 7 to 12 months, 13 to 18 months, and 19 to 24 months). The chi-squared test was used to test the significance of the degree of association between dichotomous variables, if not otherwise stated. The results are presented as the risk ratio with 95% confidence interval (CI). The Kaplan-Meier estimate of survival function was used, and differences between survival curves were estimated by the log-rank test. Data processing and statis-

Table 2. Patients With Myocardial Infarctions During Two Years in Six-Month Periods in the Invasive and Noninvasive Groups

	n*	Invasive Group	Noninvasive Group	Risk Ratio	95% CI	p Value
First week†	1,222/1,235	63 (5.2%)	32 (2.6%)	1.99	1.31–3.02	
Second week to 6 months	1,213/1,223	32 (2.6%)	93 (7.6%)	0.35	0.23–0.51	
7 to 12 months	1,192/1,193	13 (1.1%)	18 (1.5%)	0.72	0.36–1.47	
13 to 18 months	1,185/1,180	7 (0.6%)	11 (0.9%)	0.63	0.25–1.62	
19 to 24 months	1,171/1,169	5 (0.4%)	9 (0.8%)	0.56	0.19–1.65	
Total 0 to 24 months	1,210/1,227	111 (9.2%)	156 (12.7%)	0.72	0.57–0.91	0.005

*Figures show evaluated patients in the invasive/noninvasive groups. †The first six-month period is subdivided into the first week and second week to six months.
CI = confidence interval.
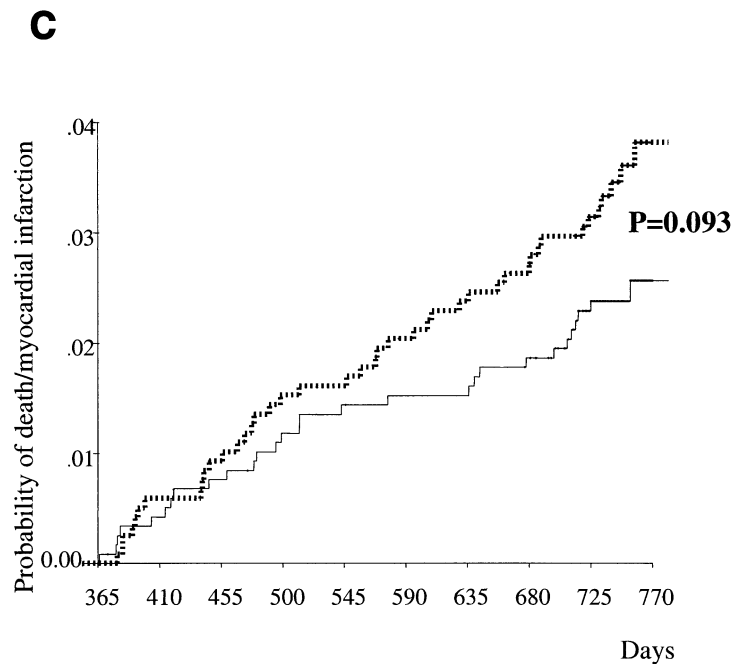
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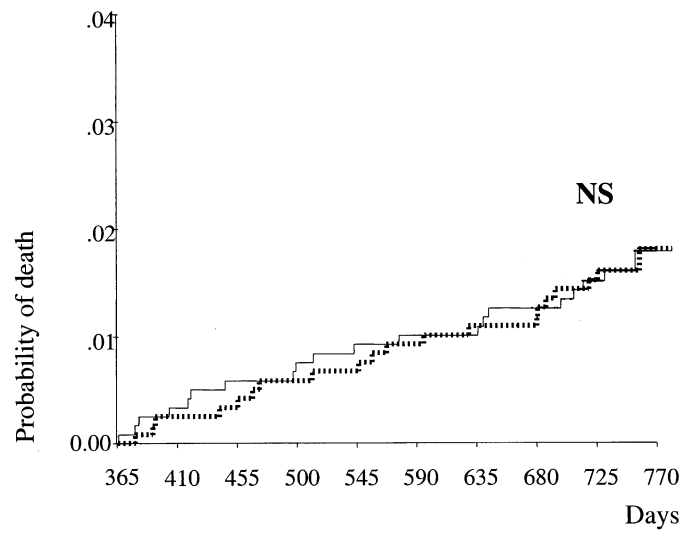
Numbers at risk

Invasive	1185	1171	1167	323
Non-invasive	1179	1162	1154	331

B
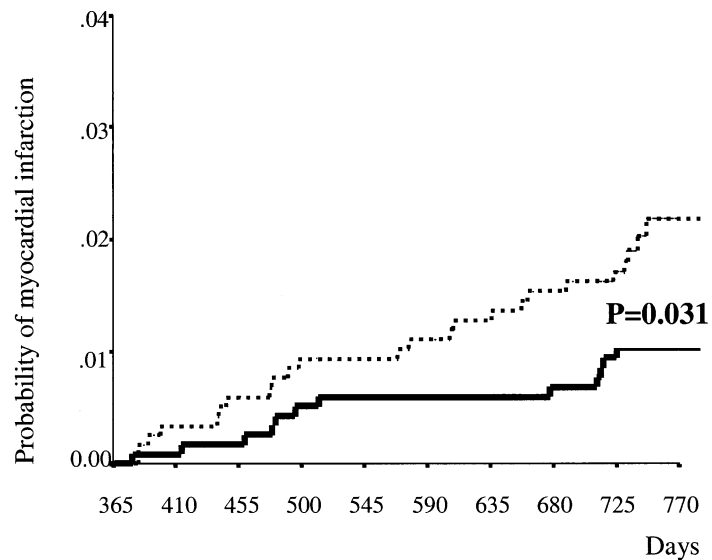
Numbers at risk

Invasive	1185	1171	1167	323
Non-invasive	1179	1162	1154	331

Figure 2. Probability of death **(A)**, myocardial infarction **(B)**, and death or myocardial infarction **(C)** in the invasive **(continuous broad line)** and noninvasive **(dotted narrow line)** groups in the period from 12 months until the last follow-up contact, illustrated by Kaplan-Meier (1 − survival) curves. The p value was derived by the log-rank test between the two groups. *Continued on next page.*

C

Numbers at risk

Invasive	1185	1171	1167	323
Non-invasive	1179	1162	1154	331

Figure 2 Continued.

tical analyses were performed by the coordinating center, using the SPSS version 10.0 statistical program on a personal computer. The study complied with the Declaration of Helsinki, and all local Ethics Committees approved the protocol.

RESULTS

In May 2001, the vital status was known for all 2,457 patients up to 670 days after randomization. Complete information on other events was lacking in 22 patients (0.9%)—13 in the invasive and 9 in the noninvasive group—mainly because of requests from or the inability to track these patients.

Table 3. Number of Spontaneous and Procedure-Related MIs* During the First Six Months in the Invasive and Noninvasive Groups

	Invasive Group (n)	Noninvasive Group (n)
Procedure-related MIs	66	26
CABG-related	13	8
PCI-related	51	13
Angiography-related	2	5
Spontaneous MIs	36	113

*Classified as procedure-related or spontaneous by the independent Clinical End Point Committee.
CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

The 24-month follow-up contact usually occurred later than planned; the median time was 749 days (735 to 773 days for 25th to 75th percentile). As previously reported (6), there were no significant differences in the baseline characteristics between the randomized groups. In short, the median age was 65 years; 70% were men; 30% were treated for hypertension; 12% had diabetes; and 23% had experienced a previous MI.

Mortality. In the first week, there were few deaths in either group (Table 1). During the remainder of the first six months, there were 18 deaths in the invasive group and 32 deaths in the noninvasive group. Also, from 6 to 12 months, there were fewer deaths in the invasive group, with a 12-month mortality rate of 2.2% in the invasive group compared with 3.9% in the noninvasive group. This absolute difference of 1.7% was maintained throughout the second year (Fig. 1A). During the second year, 18 patients died in the invasive group and 19 in the noninvasive group. Therefore, at 24 months, there were still less deaths in the invasive group (n = 45 [3.7%]) than in the noninvasive group (n = 67 [5.4%], p = 0.038) (Table 2 and Fig. 1A). Of the 75 patients who died during the first 12 months, 56 (75%) died suddenly or from known cardiac reasons or stroke: 19 in the invasive group and 37 in the noninvasive group. During the second year, the cause of death was sudden death, known cardiac reasons,
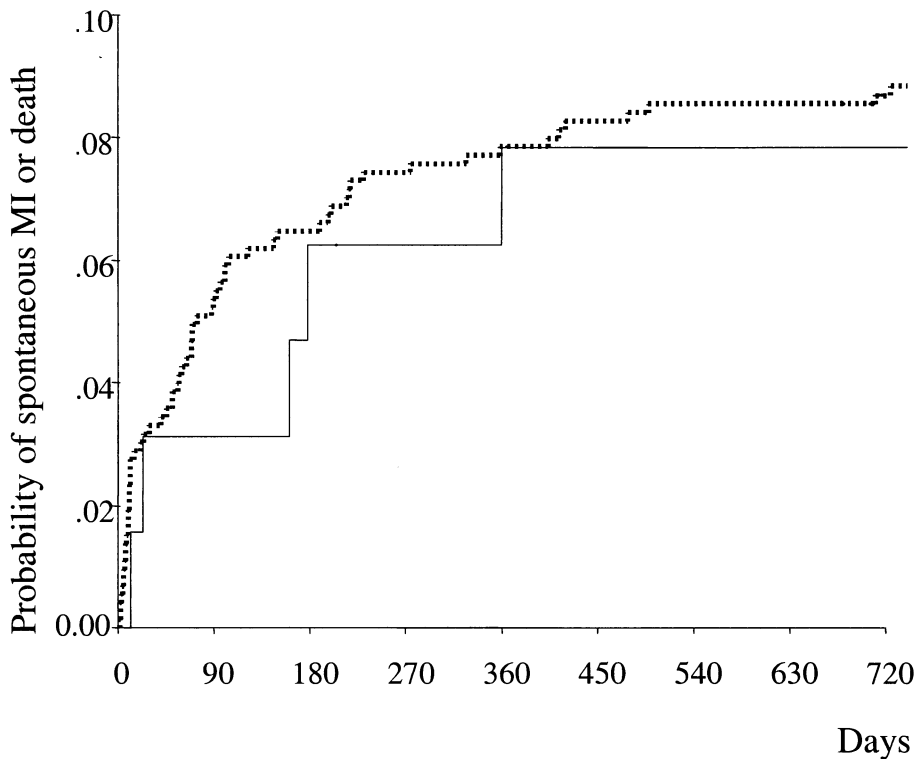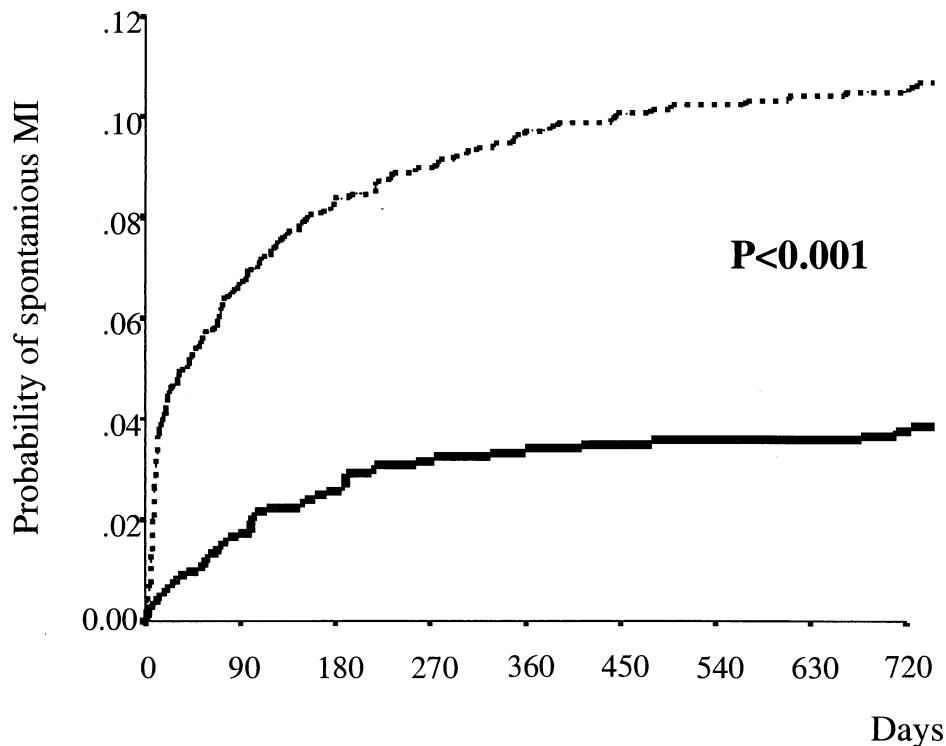
Figure 3. Timing of spontaneous myocardial infarctions (MIs) or death in percutaneous coronary intervention (PCI)-treated patients with (n = 64, **continuous line**) or without (n = 726, **broken line**) PCI-related MIs.

or stroke in 21 patients, noncardiac-related in 6, and unknown in 10.

Myocardial infarctions. Most MIs in both groups occurred in the first six months. During the first week, there were more patients with MI in the invasive group than in the noninvasive group. In contrast, after the first week, there were more MIs in the noninvasive group than in the invasive group (Table 2, Fig. 1B). Although the risk was lower during the second half of the year, the relative benefit of the invasive strategy also remained during this period. Also during the second year, the event curves for MI continued to diverge for the two treatment strategies. Therefore, the absolute reduction in MIs at 12 months (3.0%) had increased to 3.5% at 24-month follow-up. The timing of MIs after the first year of follow-up is illustrated in Figure 2.

Spontaneous and procedure-related MIs. During the first six months, 241 events were classified as MIs by the End Point Committee. In this period, two-thirds of the MIs in the invasive group were considered "procedure-related" (Table 3), most of them occurring after coronary angioplasty. In contrast, four of five MIs in the noninvasive

group were considered as "spontaneous." Thus, during the first six months, procedure-related MIs were 2.5 times more common in the invasive than in the noninvasive group (n = 66 [5.4%] vs. 26 [2.1%]; risk ratio 2.57 [95% CI 1.64 to 4.01]; p < 0.001). In contrast, spontaneous MIs occurred only in one-third as many patients in the invasive group (n = 33 [2.7%]) as in the noninvasive group (n = 103 [8.5%]; risk ratio 0.32 [95% CI 0.22 to 0.48]; p < 0.001). Most of the procedure-related MIs occurred within the first months. In the invasive group, 63 of the 68 MIs during the first hospital period were procedure-related. When the procedure-related MIs were related to PCI, the prognosis was not different from that of PCI-treated patients without procedure-related MIs. None of the patients with a PCI procedure-related MI died during the whole follow-up period, compared with 13 (1.8%) of 726 PCI-treated patients without PCI-related MIs (p = NS). Five of the patients (7.8%) with a PCI-related MI had a nonprocedure-related MI during follow-up, compared with 55 (7.6%) of PCI-treated patients without PCI-related MIs (p = NS). The timing of the events is illustrated in Figure 3. In the noninvasive group, 10 patients had procedure-related and

Figure 4. Probability of "spontaneous" myocardial infarction (MI) in the invasive **(continuous broad line)** and noninvasive **(dotted narrow line)** groups, illustrated by Kaplan-Meier (1 − survival) curves. See text for explanation. The p value was derived by the log-rank test between the two groups.

21 had spontaneous MIs during the first hospital period. During the first six months after discharge, most MIs occurred in the noninvasive cohort, and most of these were spontaneous. Of the 95 patients in the noninvasive group with MI after discharge but within six months, 14 had only procedure-related MIs, 3 had both spontaneous and procedure-related MIs, and 78 had only spontaneous MIs. Only three patients in the invasive group had procedure-related MI during this period.

Also in the period after six months, spontaneous MIs occurred less often in the invasive group (n = 18 [1.5%]) than in the noninvasive group (n = 34 [2.8%]; risk ratio 0.53 [95% CI 0.30 to 0.93]; p = 0.025). The event curves of all spontaneous MIs are shown in Figure 4.

Death or MI. Most combined events (death/MI) occurred during the first six months, with a concentration of procedure-related events in the first week in the invasive group and spontaneous events during the first six months in the noninvasive group (Table 4). The difference in event rates between the two strategies continued to increase during the

two years of follow-up. At 12 months, the absolute reduction of death/MI was 3.7%, which increased to 4.2% at 24 months. These event curves continued to diverge during the second year, although this further separation was not statistically significant (Fig. 2C). In the noninvasive group, more patients without revascularizations during the first year tended to have an event during the second year of follow-up (n = 26 [3.9%]), as compared with patients revascularized during the first year (n = 11 [2.1%]; p = 0.087).

Revascularizations. In the invasive group, 60.6% of the patients were revascularized within the first week, 75.9% during the first hospital period, and 78% at one year. Between 12 and 24 months, no additional patients were revascularized in this group, although a few patients needed a repeat intervention during the second year (Table 5). In the noninvasive group, most revascularizations were performed after the first week but within the first six months. In this group, the revascularization rates were 43% and 45% at 12 and 24 months, respectively. Thus, in patients ran-

Table 4. Death or Myocardial Infarction in Six-Month Periods in the Invasive and Noninvasive Groups

	n*	Invasive Group	Noninvasive Group	Risk Ratio	95% CI	p Value
First week†	1,222/1,235	67 (5.5%)	36 (2.9%)	1.88	1.26–2.80	
Second week to 6 months	1,214/1,230	48 (4.0%)	118 (9.6%)	0.41	0.30–0.57	
7 to 12 months	1,193/1,194	17 (1.4%)	28 (2.3%)	0.61	0.33–1.10	
13 to 18 months	1,190/1,182	17 (1.4%)	20 (1.7%)	0.84	0.44–1.60	
19 to 24 months	1,179/1,174	11 (0.9%)	18 (1.5%)	0.61	0.29–1.28	
Total 0 to 24 months	1,210/1,227	146 (12.1%)	200 (16.3%)	0.74	0.61–0.90	0.003

*Figures show evaluated patients in the invasive/noninvasive groups. †The first six-month period is subdivided into the first week and second week to six months.

CI = confidence interval.

domized to an early invasive strategy, 44% underwent PCI and 38% had CABG during the 24 months, as compared with 23% and 25%, respectively, in the noninvasive group.

After the first week, most revascularizations were performed in the noninvasive strategy group (Table 5). These unplanned and late revascularizations were the primary intervention in most patients in this group. In the invasive group, nearly all of these were repeat interventions. However, repeat interventions still were proportionally less common among the revascularized patients in the invasive than in the noninvasive group. In the invasive group, a second intervention was performed in 76 (14.3%) of the 530 patients primarily treated with angioplasty, as compared with 56 (21.5%) of 260 patients in the noninvasive group (risk ratio 0.67, 95% CI 0.49 to 0.91; p = 0.011). In the 690 patients who had CABG as the first procedure, only 23 had another revascularization during the follow-up period: 7 (1.6%) in the invasive group and 16 (6.0%) in the noninvasive group (risk ratio 0.27, 95% CI 0.11 to 0.65; p = 0.002). The mean time between the first and second intervention did not differ between the two groups: 157 ± 173) days and 136 ± 172) days in the invasive group and noninvasive group, respectively.

The timing of the events are illustrated in Figure 5, where the patients are classified into groups according to the type of their first revascularization. In the invasive group, there was a significant difference in MIs between the different revascularization types, with the highest rate in PCI-treated patients. This difference could not be seen in spontaneous MIs (Fig. 5C). The mortality was also low in the PCI-treated patients in the invasive group (Fig. 5A).

Repeat hospital admissions. Repeat admissions to hospitals were more common among patients randomized to a noninvasive strategy (Table 6), both early after discharge and later on during follow-up. Less than half of the repeat admissions were registered as caused by angina pectoris. Repeat admissions due to angina pectoris were less frequent in the invasive group (n = 209 [17.1%]) than in the noninvasive group (n = 348 [28.2%]; p < 0.001; risk ratio 0.61, 95% CI 0.52 to 0.71) during the first 24 months. During the second year, repeat admissions due to angina pectoris were less frequent in the invasive group (n = 54 [4.6%]) than in the noninvasive group (n = 84 [7.1%]; risk ratio 0.64, 95% CI 0.46 to 0.89).
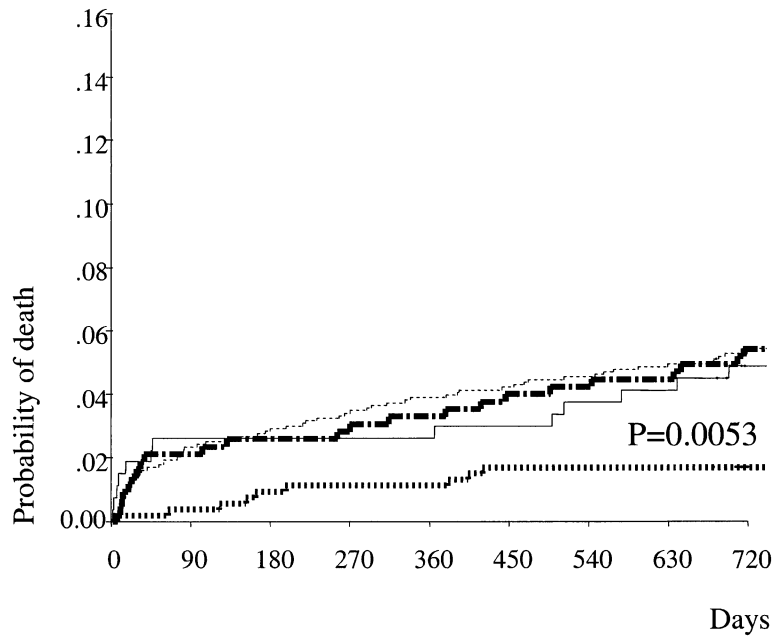
DISCUSSION

The 24-month follow-up of the FRISC-II trial showed a comforting sustained reduction and continuous divergence in the event rates by use of an early invasive strategy in patients with UCAD. Thus, the absolute difference in events was larger at two years than at one-year follow-up. There was a further increase in MIs in the invasive group, with a continuous separation of the event curves of the two strategies after the first year. The difference in mortality observed at 12 months was sustained during the second year. The total event rate was low after the first year, as only ~2% of patients had MI in the noninvasive group and half in the invasive group. However, during follow-up, almost half of the patients in the noninvasive group had "crossed over" and become revascularized, most of them during the first year. In the noninvasive group, most of the events

Table 5. Revascularized Patients During Two Years in Six-Month Periods in the Invasive and Noninvasive Groups

	n*	Invasive Group	Noninvasive Group	Risk Ratio	95% CI	p Value
First week†	1,222/1,235	741 (60.6%)	58 (4.7%)	12.91	10.00–16.67	
Second week to 6 months	1,213/1,223	261 (21.5%)	408 (33.4%)	0.65	0.56–0.74	
7 to 12 months	1,192/1,193	21 (1.8%)	85 (7.1%)	0.25	0.15–0.40	
13 to 18 months	1,185/1,180	8 (0.7%)	32 (2.7%)	0.25	0.12–0.54	
19 to 24 months	1,171/1,169	5 (0.4%)	14 (1.2%)	0.36	0.13–0.99	
Total 0 to 24 months	1,222/1,235	955 (78.2%)	561 (45.4%)	1.72	1.61–1.84	< 0.001

*Figures show evaluated patients in the invasive/noninvasive groups. †The first six-month period is subdivided into the first week and second week to six months.

CI = confidence interval.

A

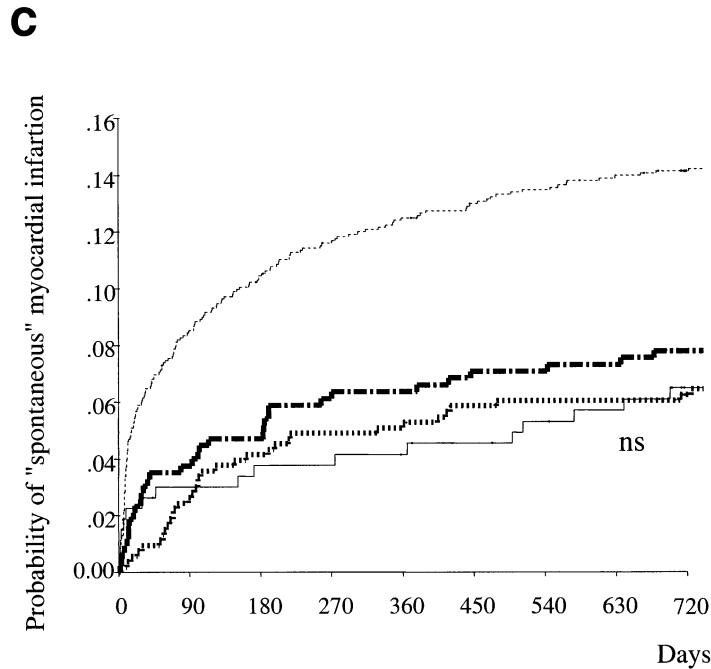Probability of death (y-axis: 0.00, .02, .04, .06, .08, .10, .12, .14, .16)

Days (x-axis: 0, 90, 180, 270, 360, 450, 540, 630, 720)

P=0.0053

Numbers at risk

Invasive	1222	1199	1195	1185	1157
Non-invasive	1235	1200	1187	1179	1159

B

Probability of myocardial infarction (y-axis: 0.00, .02, .04, .06, .08, .10, .12, .14, .16)

Days (x-axis: 0, 90, 180, 270, 360, 450, 540, 630, 720)

P<0.001
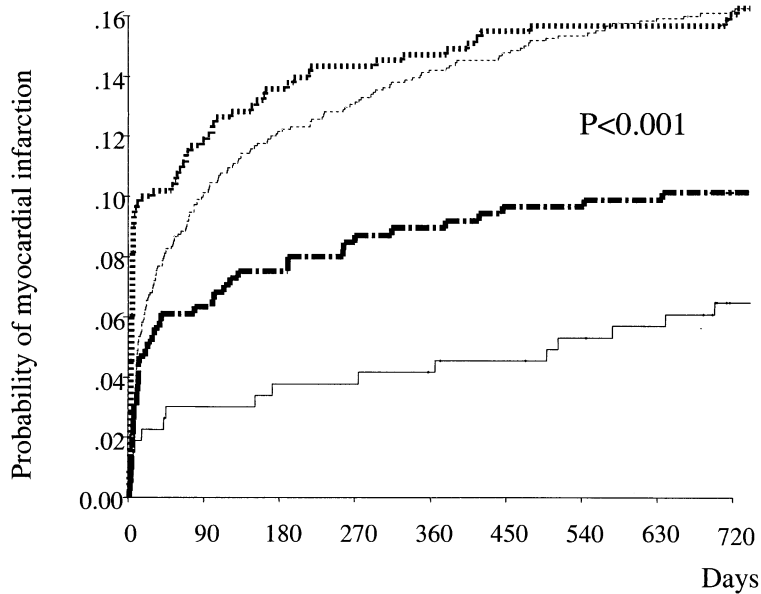
Numbers at risk

Invasive	1222	1103	1088	1073	1046
Non-invasive	1235	1082	1055	1039	1018

Figure 5. Probability of death **(A)**, myocardial infarction **(B)**, and "spontaneous" myocardial infarction **(C)** in the invasive cohort with percutaneous coronary intervention as the first invasive procedure (n = 530, **small dotted line at bottom**), with coronary artery bypass graft surgery as the first invasive procedure (n = 425, **thick short and long dotted line**), and without any revascularization (n = 267, **continuous narrow line**), and the noninvasive cohort (n = 1,235, **broken narrow line**), illustrated by Kaplan-Meier (1 − survival) curves. The p value was derived by the log-rank test between the three different treatments in the invasive cohort. *Continued on next page.*

C

Figure showing Probability of "spontaneous" myocardial infarction (y-axis, 0.00 to .16) versus Days (x-axis, 0 to 720), with "ns" labeled on the curves.

Numbers at risk

Invasive	1222	1103	1088	1073	1046
Non-invasive	1235	1082	1055	1039	1018

Figure 5 Continued.

during the second year occurred in patients who were not revascularized during the first year. This "under-revascularization" could probably explain the continuing difference in the event rate during the second year.

The long-term results of this study demonstrate that an early invasive strategy in combination with appropriate preventive medical treatment rapidly transforms UCAD into a stable condition, with a yearly rate of death or MI of ~1% to 3%. In addition, other reports on angioplasty in patients with UCAD have reported long-term outcomes similar to those of patients with stable coronary disease, even after 10 years of follow-up (9,10). This low event rate is also in accordance with the low event rates in populations

with stable coronary heart disease (11). There was a proportionally lower rate of repeat interventions after early interventions, compared with when the procedures were done later, as in the noninvasive group. The invasively treated patients in the two randomized groups did not differ with respect to the completeness of revascularization or stent use (6). However, the revascularized patients in the noninvasive group contained a higher proportion patients with multivessel disease, which may, at least partly, explain the higher "re-do" rate.

The present FRISC-II trial is still the only study that has documented a decrease in mortality with an early invasive strategy in patients with UCAD. In the TACTICS–

Table 6. Patients Re-Admitted to the Hospital During Two Years in Six-Month Periods in the Invasive and Noninvasive Groups

	n*	Invasive Group	Noninvasive Group	Risk Ratio	95% CI	p Value
First week†	1,222/1,235	12 (1.0%)	32 (2.6%)	0.38	0.20–0.73	
Second week to 6 months	1,213/1,223	346 (28.5%)	574 (46.9%)	0.61	0.55–0.68	
7 to 12 months	1,192/1,193	190 (15.9%)	256 (21.4%)	0.74	0.63–0.88	
13 to 18 months	1,185/1,180	107 (9.0%)	160 (13.6%)	0.66	0.53–0.84	
19 to 24 months	1,171/1,169	127 (10.8%)	159 (13.6%)	0.80	0.64–0.99	
Total 0 to 24 months	1,222/1,235	547 (44.8%)	796 (64.5%)	0.69	0.64–0.75	< 0.001

*Figures show evaluated patients in the invasive/noninvasive groups. †The first six-month period is subdivided into the first week and second week to six months.
  CI = confidence interval.

TIMI-18 trial, the early invasive strategy was associated with a reduction in the combined end point of death/MI/repeat hospital admission. There was, however, no difference in death alone (8): 3.3% and 3.5%, respectively, in the invasive and conservative groups at six months. The gain in events in the TACTICS–TIMI-18 trial was mainly seen in the first weeks, whereas in the FRISC-II trial there was, after the first weeks, a continuous increase in benefit during the two-year follow-up period. In the FRISC-II trial, there appeared to be an early hazard, with a higher rate of MI in the invasive group. The present analysis demonstrates that this was entirely caused by procedure-related MIs, mainly elevations of cardiac markers after angioplasty without any other symptoms or signs of MI or any immediate clinical consequences. This analysis also showed that this early hazard after one month, and even more so after longer follow-up, was compensated by a pronounced reduction in spontaneous MIs. Furthermore, there were no indications that the increased rate of procedure-related MIs was related to any increased rate of late deaths or repeat MIs. Thus, the negative impact on survival and repeat MI by small procedure-related MIs is probably less than that by spontaneous MIs. The lower rate of early procedure-related MI in the TACTICS–TIMI-18 trial might be mainly explained by the fact that all patients were treated with a glycoprotein IIb/IIIa inhibitor, which is known to halve the risk of procedure-related MIs (12–14). In contrast, in the FRISC-II trial, only 9% of angioplasty-treated patients in the invasive group were treated with a glycoprotein IIb/IIIa inhibitor. Therefore, it is likely that more frequent use of glycoprotein IIb/IIIa inhibitors in the FRISC-II study should had resulted in an even lower event rate in invasively treated patients.

There are few other randomized studies of an invasive versus noninvasive strategy in patients with UCAD. Studies with longer follow-up periods are even rarer. The Veterans Affairs study of unstable angina that started >25 years ago (2) compared CABG with medical treatment. There was a weak trend toward lower mortality in the surgical group in the beginning, but this trend disappeared during the 10-year follow-up period. In a subset of patients with poor left ventricular function, there was initially lower mortality, but this difference was not significant after 10 years (3). In the VANQWISH trial, the patients were followed for an average of 23 months (4). The initial advantage of the conservative strategy disappeared during long-term follow-up. After CABG, the 30-day mortality rate was very high in the invasive group (11.6%) and in the conservative group (3.4%); the corresponding mortality rates in FRISC-II were 2.1% and 1.7%, respectively. Furthermore, in the VANQWISH trial at one year, the revascularization rate in the invasive arm was only 44%, fairly similar to that in the noninvasive arm (33%), in contrast to 78% and 43%, respectively, at the same time in the invasive and noninvasive groups of the FRISC-II trial. Thus, provided that the early procedure-related hazards at CABG can be kept at a

low rate, an early invasive strategy will lead to improved survival and a reduced risk of MI, as shown in the long-term follow-up of the FRISC-II trial. Furthermore, the early invasive strategy will also be associated with lower cardiac morbidity and less consumption of health-care resources later, as shown by the reductions in repeat admissions and late revascularization procedures in this two-year follow-up in the FRISC-II trial.

Study limitations. The independent End Point Committee only adjudicated events up to six months. Thereafter, the presence of an event was collected by telephone contact with the patients and evaluation of the medical records by the local investigator. During the first six months, minor elevations in myocardial markers were routinely recorded in connection with angioplasty and used as the basis for the diagnosis of MI, even without any other symptoms or signs. Thereafter, the diagnosis of MI, with or without angioplasty, was established by local clinical routine. Therefore, the number of procedure-related MIs in the noninvasive group might have been underestimated.

Conclusions. In patients with UCAD, the early invasive approach leads to a sustained reduction in mortality, cardiac morbidity, and the need for repeat hospital admissions and late revascularization procedures. The early increased risk of procedure-related MIs is compensated for by a later reduction in spontaneous MIs. Although the benefits in the invasive group are greatest during the first months, there is still lower cardiac morbidity and less need for hospital care during the second year.

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