

Equivocal EGG

1. An abnormal Q wave or ST-T segment elevation plus T-wave inversion on just one lead.
2. A recent and lasting T-wave inversion
3. A recent bundle branch block.

A Q-wave

- > 0,04 s wide and >1 mm deep or
- > 0,03 s wide and Q/R >1/3 and > 1 mm deep

ST-T segment elevation

- > 1 mm in leads I, II, III, aVL, aVF, V5, V6
- > 2 mm in leads V1, V2, V3, V4

R-wave disappearance

A complete disappearance of the R-wave and a reduction by the R-amplitude by > 3 mm in, at least, 2 leads at two registrations during a 24 h period.

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Enzymatic criterias

1. Abnormal enzymes:

Max CK and CK-B (alt. ASAT, LD) > twice the upper limits of normal or CK-B (alt. ASAT, LD) > the upper limit of normal on two occasions.

2. Equivocal enzymes:

One isolated enzyme above the upper limit of normal.

Abnormal enzymes of a non-ischaemic cause (defibrillation, surgery injections, etc).

Definitions of myocardial ischemia at exercise tests

Based on results in previous studies one or several of the following criteria will be tested as definitions of myocardial ischemia as they are known to have different sensitivity and specificity regarding both the extent of coronary artery disease and risk for future complications

1. Occurrence of ST-depression ≥ 0.1 mV (1 mm) in relation to ECG at rest
2. Occurrence of ST-depression or maximal load < 100 W in men and < 80 W in women
3. Occurrence of ST-depression or chest pain
4. Occurrence of ST depression with respectively without concomitant chest pain
5. Occurrence of ST-depression or maximal load < 100 W in men and < 80 W in women or limiting chest pain
6. Occurrence of any of the following three findings
 - a/ ST-depression in ≥ 3 leads
 - b/ ST-depression in 1 - 2 leads with load < 130 W in men, < 100 W in women
 - c/ $W_{max} < 100$ W in men, < 80 W in women

Based on results in previous studies the following parameters will be used as quantitative estimations of myocardial ischemia in comparisons between treatment groups

1. Number of leads with ST-depression ≥ 0.1 mV (1 mm) in relation to ECG at rest
2. Maximal depth of ST-depression in relation to ECG at rest
3. Maximal load in watts
4. Load in watts at ST-depression ≥ 0.1 mV (1 mm) in relation to ECG at rest
5. Maximal elevation of systolic blood pressure compared to determination at rest
6. Maximal elevation of heart rate compared to determination at rest
7. Product of maximal heart rate and maximal systolic blood pressure
8. Product of maximal rise of heart rate and maximal rise of blood pressure compared to corresponding determinations at rest

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10.3 Indications for coronary artery angiography (FRISC)

Contraindications to and timing for coronary angiography and revascularization was judged by the physician's responsible for each patient. The following guidelines were to be followed as indicated for coronary angiography and revascularization:

For coronary angiography, the patient had to fulfill both A and B as follows:

- A. Suitable candidate for early revascularisation.
- B. Fulfill at least one of the following five criteria:
 - Disabling angina despite medication.
 - ST-depression in at least three adjacent leads during exercise test.
 - ST-elevation during exercise test occurring in at least 2 leads without Q-waves and with normal ST-segment and normal T-waves in ECG at rest.
 - ST-depression associated with either low Wmax (males <100 W, females <80 W) or fall in blood pressure (≥ 15 mm Hg at one or ≥ 10 mm Hg at two consecutive determinations during exercise test).
 - Limiting chest pain associated with either low Wmax (males <100 W, females <80 W) or fall in blood pressure (≥ 15 mm Hg at one or ≥ 10 mm Hg at two consecutive determinations during exercise test).

During and after the coronary angiography was performed, the patient was instructed to continue taking study drug, to continue with the study program (ECG, exercise tests and laboratory tests), and to complete the 6 months follow-up procedures if the patient's condition permitted.

ST-depression was defined as ST-segment level below baseline, that is the level of the PQ-segment, and ST-depression of ≥ 0.1 mV, measured 0.06 seconds after the J-point. If resting ECG showed ST-depression, a further depression of ≥ 0.1 mV was required.

10.4 Indications for coronary artery angiography (FRIC)

Indications for coronary angiography

The following guidelines were to be followed as an indication for coronary angiography.

The patient had to fulfill both A and B as follows:

A. Suitable candidate for early revascularization.

B. Fulfill at least one of the following criteria:

- Disabling angina despite medication.
- ST-elevation during exercise test occurring in at least 2 leads without Q-waves and with normal ST-segment and normal T-waves in ECG at rest.
- ST-depression associated with either low W_{max} (treadmill, less than 5 METS and cycle ergometer, men <100 W, women <80 W) or a fall in blood pressure (≥ 15 mmHg at one or ≥ 10 mmHg at two consecutive determinations during the exercise test).
- Limiting chest pain associated with either low W_{max} (treadmill, less than 5 METS and cycle ergometer, men <100 W, women <80 W) or a fall in blood pressure (≥ 15 mmHg at one or ≥ 10 mmHg at two consecutive determinations during the exercise test).
- ST-depression ≥ 5 minutes during recovery phase.

ST-depression was defined as an ST-segment level below baseline (defined as the level of the PQ-segment) and ST-depression of ≥ 0.1 mV, measured 0.06 sec after the J-point. If a resting ECG showed ST-depression, a further depression of ≥ 0.1 mV was required.

Sponsor's Material, FRIC, Page 8/10/38

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10.5 Exercise test protocol (FRISC 8/3/50-52)

Translation

EXERCISE TEST.

Appendix 5.

- Time:** At the earliest 5 days after myocardial infarction and when the patient has been free from rest pain (anginal) and pain at mobilization for at least 2 days with medication.
 Not myocardial infarction:
 At the earliest 2 days without rest pain and without daily pain attacks at mobilization with medication.
- Exercise test should be performed day 6(5-8) and day 45 (40-50)
- Referral:** Write always the FRISC-trial on the referral. To the exercise test day 6 (5-8), shall the whole journal with actual day-notes, temperature-list, laboratory-list and ECG-serie be submitted with the patient.
- Safety:**
- Physician present
 - Defibrillator, emergency-bag and emergency-tray in the room
 - Nitroglycerine sublingual if pain that has not disappeared 4 minutes after discontinuation of the exercise test
- Contraindications for starting the exercise test:**
- Myocardial infarction <5 days
 - Newly developed (<48 hours) changes in rest-ECG
 - Ongoing chestpain or daily pain attacks at rest or during light exercise
 - Manifest heart failure, on the day of exercise test
 - Circumstances which make it impossible to performe the exercise test e.g physical handicap.
- Discontinuation of the exercise test:**
- Chestpain, grade 5 (Borg 10-grade scale)
 - Effort, grade 17 (Borgs 20-grade scale)
 - Deteriorating general condition
 - Fall in blood pressure ≥ 15 mmHg at one determination or ≥ 10 mmHg at two consecutive determinations
 - Serious arrhythmia: ventricular tachycardia ≥ 3 consecutive VES or couplets, >5 VES in bigeminy, AV-block II-III or appearance of atrial fibrillation
 - Ischemic ST-depression ≥ 3 mm
- ECG:** Extremity leads and Wilson chestleads (V1-V6), both during rest and exercise test (50 mm/s)

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EXERCISE TEST.

Performance:

- Meanvalue-ECG if possible.
- If Case 12 (Marquette) is available there will be special "FRISC-procedure" distributed on discett
- Minute step cycling with start at 30 W and increase with 10 W/minute by steps or continuous. Start at 10 W if the patient can be expected to have limited exercise capacity or easily started angina.
- Measure systolic blood pressure during exercise with Doppler*
- Give careful instruction about the Borgs-scales before the exercise test
- Note effort according to Borgs 20-grade scale (whole number) and chest pain and breathlessness according to Borgs 10-grade scale (whole number)

Note: Ongoing medication, length, weight, subjective inconvenience and cause of stopping the should be noted in the patient protocol.

Measurements:

	ECG	Heart rate	Blood pr. S/D	Breath rate	Borg 10 (chestp)	Borg 20 (effort)
Rest	yes	yes	S/D	yes	yes	-
Rest at cycle	yes	yes	S	-	-	-
During cycle ergo.	every 3 min	every min	every 3 min	every 3 min	every 3 min	every 3 min
Before discontin.	yes	yes	yes	-	yes	yes
After exercise	after 2,4,10 min	after 10 min	S/D after 10 min	-	10 min	-

S=systolic D=diastolic

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Borg-scale:

Chest pain, Borgs 10-grade scale.

- 0 Nothing
- 0,5 Very, very weak (just noticeable)
- 1 Very weak
- 2 Weak (light)
- 3 Moderate
- 4 Somewhat strong
- 5 Strong (heavy)
- 6
- 7 Very strong
- 8
- 9
- 10 Very, very strong (almost maximum)
- o Maximum

Effort grade, Borgs 20-grade scale.

- 6
- 7 Very, very light
- 8
- 9 Very light
- 10
- 11 Fairly light
- 12
- 13 Somewhat hard
- 14
- 15 Hard
- 16
- 17 Very hard
- 18
- 19 Very, very hard
- 20

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10.6 Indications for revascularization (FRISC)

For revascularisation, the patient had to fulfill at least one of the following criteria:

- Left main disease.
- 3-vessel disease.
- Proximal LAD stenosis.
- Proximal stenosis in coronary artery supplying a large part of viable myocardium.
- In the presence of disabling angina, a significant stenosis in any major coronary artery suitable for revascularisation.

In case of indication for revascularization, study drug was continued until the day before intervention. After revascularisation the patient was instructed to continue the study program (ECG, exercise tests and laboratory tests) and 6-months follow-up procedures were to be performed if the patient's condition permitted.

Sponsor's Material, Page 8/1/71

10.7 Dosing ranges

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Table 7. Dosing, volume (mL) per weight class

	Body Weight (kg)					
	<50	50-59	60-69	70-79	80-89	≥90
Fragmin 150 IU/kg/12 hrs or matching Placebo	0.70	0.85	1.00	1.15	1.30	1.45
Fragmin 120 IU/kg/12 hrs or matching Placebo	0.55	0.65	0.75	0.90	1.00	1.00

The time between the first and second injections could vary from 8 to 16 hrs depending on the time of admission to the trial. The table used for adjusting the injection time is found in Appendix 3 of the protocol (see Appendix A.1). The following injections were given preferably at 8:00 pm (± 1 hour) and 8:00 am (± 1 hour).

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10.8 Death and/or MI by center

		No		Yes		TOTAL
		N	Percent	N	Percent	
Linköping	Fragmin	80	98.8	1	1.2	81
	Placebo	80	96.4	3	3.6	83
Norrköping	Fragmin	42	97.7	1	2.3	43
	Placebo	40	97.6	1	2.4	41
Västervik	Fragmin	40	97.6	1	2.4	41
	Placebo	40	97.6	1	2.4	41
Oskarshamn	Fragmin	25	100.0	0	0	25
	Placebo	24	92.3	2	7.7	26
Kalmar	Fragmin	42	97.7	1	2.3	43
	Placebo	43	95.6	2	4.4	45
Värnamo	Fragmin	28	96.6	1	3.4	29
	Placebo	29	96.7	1	3.3	30
Jönköping	Fragmin	56	100.0	0	0	56
	Placebo	52	94.5	3	5.5	55
Eksjö	Fragmin	44	97.8	1	2.2	45
	Placebo	42	97.7	1	2.3	43
Motala	Fragmin	16	88.9	2	11.1	18
	Placebo	15	93.8	1	6.3	16
Uppsala	Fragmin	66	98.5	1	1.5	67
	Placebo	61	96.8	2	3.2	63
Västerås	Fragmin	28	100.0	0	0	28
	Placebo	28	96.6	1	3.4	29
Köping	Fragmin	14	100.0	0	0	14
	Placebo	13	86.7	2	13.3	15
Ludvika	Fragmin	14	100.0	0	0	14
	Placebo	18	94.7	1	5.3	19

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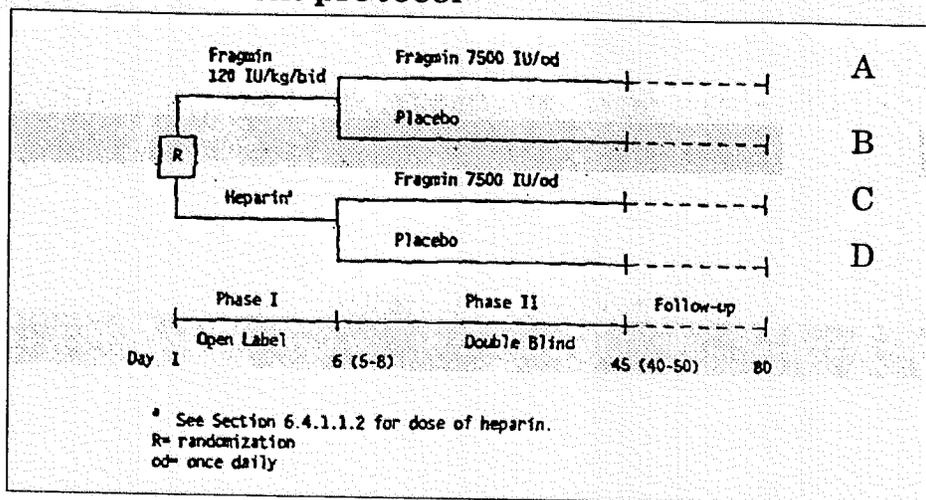
		No		Yes		TOTAL
		N	Percent	N	Percent	N
Mora	Fragmin	6	85.7	1	14.3	7
	Placebo	9	90.0	1	10.0	10
Falun	Fragmin	58	98.3	1	1.7	59
	Placebo	55	91.7	5	8.3	60
Sandviken	Fragmin	16	94.1	1	5.9	17
	Placebo	16	88.9	2	11.1	18
Gävle	Fragmin	15	100.0	0	0	15
	Placebo	14	100.0	0	0	14
Hudiksvall	Fragmin	2	100.0	0	0	2
	Placebo	3	100.0	0	0	3
Bollnäs	Fragmin	15	100.0	0	0	15
	Placebo	16	100.0	0	0	16
Avesta	Fragmin	9	100.0	0	0	9
	Placebo	8	80.0	2	20.0	10
Karlstad	Fragmin	18	100.0	0	0	18
	Placebo	18	94.7	1	5.3	19
Danderyd	Fragmin	46	100.0	0	0	46
	Placebo	47	95.9	2	4.1	49
SöS, Sthlm	Fragmin	48	98.0	1	2.0	49
	Placebo	50	96.2	2	3.8	52
TOTAL	Fragmin	728	98.2	13	1.8	741
	Placebo	721	95.2	36	4.8	757

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10.9 FRIC treatment protocol



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10.10 Definitions of death, MI, recurrent angina, revascularization, and ischemia during the exercise test in FRIC.

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- **Death:** The cause of death was established if possible by post-mortem examination. All deaths, irrespective of cause, were recorded throughout the trial period.
- **MI:** MI was confirmed with at least one of the following three criteria:
 1. CK-MB greater than the normal upper limit
 2. Total CK greater than twice the normal upper limit (if CK-MB not available).
 3. Major (≥ 0.03 msec) new Q-waves in two or more leads.

Central evaluation was performed blinded by the Steering Committee (Amendment 4).

- **Recurrence of Angina:** During Phase I, recurrence of angina was defined as restart of nitroglycerine infusion due to anginal chest pain. The event should not have been related to the inclusion event (Amendment 2).

During Phase II, recurrence of angina was defined as hospitalization and start of nitroglycerine or heparin infusion due to chest pain.

Complete definitions are provided in the protocol (Appendix A.1).

2. Secondary variables

Revascularization and ischaemia during the exercise test were defined as follows:

- **Revascularization:** PTCA or CABG surgery was to be performed according to the indication for revascularization in the protocol.
- **Ischaemia during the exercise test:** Two exercise tests were to be performed in all patients, if not contraindicated, the first Day 5-8 and the second Day 40-50. The tests were evaluated in terms of presence of ischaemia, based on ST-depression ≥ 1 mV and/or typical chest pain.

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10.11 FRIC patients enrolled but not in ITT group

PHARMOCIA - TSM 91-128 FRIC. Low Molecular Weight Heparin (Fragmin)
in the Treatment of Unstable Coronary Artery Disease. A Multicenter Study
Investigator: Professor W Klein, University Hospital, Graz, Austria

Item 14 Table 9.1.1.a
Randomized patients who received no study drug

Patient Number	Randomized treatment	INTENTION TO TREAT, PERIOD 1	Date of Inclusion	Fragmin inj No 1 given	Saline injection of Heparin 2400 IU	Heparin injection No 1 given	Patient withdrawn	Date of withdrawal
1417	Fragmin-Fragmin	No	30/06/94	No	.	.	No	.
1507	Fragmin-Fragmin	No	27/10/93	No	.	.	Yes	27/10/93
1608	Fragmin-Fragmin	No	13/02/94	No	.	.	Yes	11/03/94
1813	Heparin-Placebo	No	08/03/94	No	No	No	Yes	08/03/94
3043	Fragmin-Fragmin	No	09/03/95	No	.	.	Yes	09/03/95
10433	Heparin-Placebo	No	26/08/94	No	.	.	Yes	26/08/94
10403	Fragmin-Fragmin	No	12/08/94	No	.	.	Yes	16/08/94
11325	Fragmin-Placebo	No	22/07/94	No	.	.	Yes	22/07/94
11416	Fragmin-Fragmin	No	30/11/93	.	.	.	Yes	22/07/94
11710	Heparin-Placebo	No	29/04/94	.	No	No	Yes	29/04/94
12122	Fragmin-Placebo	No	30/03/95
12211	Heparin-Placebo	No	24/10/94	.	.	.	Yes	30/03/95
12663	Heparin-Placebo	No	14/08/94
12706	Heparin-Placebo	No	30/05/94
14201	Heparin-Placebo	No	23/06/94	.	No	.	.	.
14287	Heparin-Fragmin	No	

N = 16

Sponsor's Material, FRIC, Page 8/

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11. REFERENCES

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 - ¹⁰ Selwyn, AP, Braunwald E, Chap 244, Ischemic heart disease, *Harrison's Principles of Internal Medicine*, 14 th edition on CD.