

For the endpoint of death alone, Fragmin was numerically worse than placebo in both the ITT group (Fragmin 1.5%/ heparin 0.4%, and in the per-protocol group (Fragmin 1.2%/heparin 0.7%).

#### **3.2.2.10.4 Phase II**

None of the endpoints was achieved in the ITT or per-protocol groups.

For the endpoint of death and/or MI, Fragmin had a numerical advantage over placebo, in the per-protocol group (Fragmin 3.0%/placebo 5.9%,  $p=0.073$ ) and in the ITT group (Fragmin 4.3%/ placebo 4.7%,  $p=0.766$ ).

Furthermore, the per-protocol group contains only 365 of 753 originally randomized to Fragmin, and only 392 of 746 originally randomized to placebo.

#### **3.2.2.10.5 Variability among centers**

No center appeared to contribute to the results disproportionately

#### **3.2.2.11 FRIC safety summary**

##### **3.2.2.11.1 Sponsor-defined endpoints**

The sponsor-defined safety endpoints are summarized in Table 31.

The incidence of major bleeding was similar in the Fragmin and heparin groups in Phase I and in the Fragmin and placebo groups in Phase II.

The incidence of minor bleeding during Phase II was almost twice as great in the Fragmin group as in the placebo group.

There was a higher mortality in the Fragmin group in Phase I, while in Phase II the mortality was higher in the placebo group.

Allergic reactions occurred more frequently in the heparin or placebo groups than in the Fragmin groups.

Thrombocytopenia occurred more often in the heparin group than in the Fragmin group.

Table 31: Safety results: Phase I and II

Safety variable	Phase I						Phase II					
	Fragmin			Heparin			Fragmin			Placebo		
	N	n	%	N	n	%	N	n	%	N	n	%
Major bleeding	744	9	1.2	729	7	1.0	552	3	0.5	544	1	0.2
Minor bleeding	744	23	3.1	729	24	3.3	552	26	4.7	544	13	2.4
Death	749	9	1.2	729	4	0.5	567	4	0.7	566	9	1.6
Thrombocytopenia	738	2	0.3	727	5	0.7	562	0	0.0	560	0	0.0
Allergic reactions	747	3	0.4	730	6	0.8	563	4	0.7	562	7	1.2

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3.2.2.11.2 Deaths

Deaths by reason are summarized in Table 32. There were more deaths in the phase I Fragmin group, as noted above. There were also more deaths in the Fragmin groups during follow-up.

Table 32: Death reason assessed by investigator by study phase

Reason for death	Phase 1		Phase 2		Follow-up after phase 1		Follow-up after phase 2	
	HEPARIN	FRAGMIN	FRAGMIN	PLACEBO	HEPARIN	FRAGMIN	FRAGMIN	PLACEBO
	N	N	N	N	N	N	N	N
Myocardial infarction	2	4	2	6	3	3	5	2
Sudden death	0	1	2	2	2	1	1	0
Other heart death	2	2	0	1	1	0	3	1
Bleeding (not cerebral)	0	0	0	0	0	0	1	0
Cerebral bleeding	0	1	0	0	0	0	1	0
Cerebral emboli - infarction	0	0	0	0	0	1	0	0
Unspecified stroke	0	0	0	0	1	1	0	0
Other cause	0	1	0	0	1	4	3	0
TOTAL	4	9	4	9	8	10	16	3

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**3.2.2.11.3 Serious adverse events during treatment phase**

Serious adverse events occurring during the treatment phases are summarized in Table 33.

The serious adverse event that occurred the most in both phases was cardiac failure. It was reported in five patients in Phase I (Fragmin 3, heparin 2) and 2 patients in Phase II (Fragmin 0, placebo 2).

Seriousness was not available for 6 events.

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**Table 33: Incidence of serious adverse events during Phase I and Phase II by preferred term**

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Preferred term	Phase I		Phase II	
	Fragmin (N=751) n	Heparin (N=731) n	Fragmin (N=567) n	Placebo (N=566) n
Anaemia	1	0	0	0
Asthma	0	0	1	0
Cardiac arrest	2	1	0	0
Cardiac failure	3	2	0	2
Cardiac tamponade	0	1	0	0
Cerebrovascular disorder	0	1	1	0
Circulatory failure	0	1	0	0
Claudication intermittent	0	1	0	0
Convulsions	0	0	1	0
Depression	0	1	0	1
Embolism pulmonary	0	0	0	1
Fibrillation ventricular	0	2	1	1
Hepatic enzymes increased	1	0	0	0
Hypotension	0	0	0	1
Injection site inflammation	0	1	0	0
Nausea	0	0	1	0
Nonprotein nitrogen increased	1	0	0	0
Pleural effusion	0	1	0	0

Preferred term	Phase I		Phase II	
	Fragmin (N=751) n	Heparin (N=731) n	Fragmin (N=567) n	Placebo (N=566) n
Pneumonia	0	1	2	1
Pulmonary oedema	0	1	1	2
Retinal detachment	0	0	1	0
Skin disorder	0	0	0	1
Testis neoplasm malignant	1	0	0	0
Thrombocombolism	0	0	1	0
Thrombophlebitis leg	0	1	0	0
Vertigo	0	0	1	0
Vomiting	0	0	1	0

**3.2.2.11.4 Adverse events, serious and non serious combined during treatment period**

The incidence of adverse events that occurred during treatment is summarized in Table 34

Three adverse event were reported in more than 1% of the patients in a treatment group in Phase I. Headache was reported in 4.7% of the patients who received Fragmin and 4.1% of the patients who received heparin.

Bradycardia was reported in 1.3% of the patients who received Fragmin and 1.4% of the patients who received heparin.

Dyspepsia was reported in 0.5% of the patients who received Fragmin and 1.1% of the patients who received heparin.

During Phase II, headache and dizziness were the only adverse events reported in more than 1% of a treatment group.

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Table 34: Incidence of adverse events, by preferred term and study phase

**Table 34. Incidence of systemic adverse events that occurred during Phase I and II in two or more patients in a treatment group by preferred term**

Preferred term	Phase I		Phase II	
	Fragmin (N=751) n	Heparin (N=731) n	Fragmin (N=567) n	Placebo (N=566) n
Abdomen enlarged	0	0	2	1
Abdominal pain	3	4	3	3
Anxiety	0	4	1	0
Arrhythmia	2	2	1	0
Back pain	1	2	2	3
Bradycardia	10	10	0	2
Cardiac arrest	2	2	0	0
Cardiac failure	7	5	3	3
Confusion	2	2	0	0
Constipation	3	5	4	0
Coughing	3	0	0	0
Depression	0	2	0	1
Diarrhoea	2	2	2	0
Dizziness	5	3	7	6

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Preferred term	Phase I		Phase II	
	Fragmin (N=751) n	Heparin (N=731) n	Fragmin (N=567) n	Placebo (N=566) n
Dyspepsia	4	8	1	1
Dyspnoea	2	1	1	2
Fatigue	1	2	1	5
Fever	5	5	3	1
Fibrillation atrial	4	3	1	2
Fibrillation ventricular	0	2	1	1
Gout	0	2	0	0
Headache	35	30	7	10
Hepatic function abnormal	2	0	0	0
Hypertension	2	2	1	0
Hypaesthesia	1	2	0	0
Hypokalemia	0	3	1	0
Hypotension	5	1	0	1
Influenza-like symptoms	1	3	4	3
Insomnia	2	4	1	2
Leg pain	4	4	1	1
Malaise	1	2	1	1
Nausea	5	6	4	3
Oedema legs	1	0	3	4
Pain	3	3	3	1
Palpitation	0	0	2	1
Pharyngitis	0	0	2	1
Pneumonia	1	2	2	1
Pulmonary oedema	2	1	1	3
Rigors	0	0	2	1

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Preferred term	Phase I		Phase II	
	Fragmin (N=751) n	Heparin (N=731) n	Fragmin (N=567) n	Placebo (N=566) n
Skeletal pain	0	3	0	0
Skin ulceration	2	1	0	0
Upper respiratory tract infection	0	0	0	3
Vomiting	3	4	4	2

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### 3.2.2.11.5 Adverse events, serious and non serious, during follow-up phase

Adverse events, serious and non-serious combined, that occurred during follow-up are summarized in Table 35.

Atrial fibrillation was reported most frequently. It was reported most often in patients who only received treatment in Phase I (Follow-up I) (Fragmin 3, Heparin 7).

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Table 35: Adverse events, serous and non serious, during follow-up (reported in 2 or more patients)

Preferred term	Follow-up I		Follow-up II	
	Fragmin n	Heparin n	Fragmin n	Placebo n
Abdominal pain	0	0	2	2
Anaemia	1	1	0	2
Atrial fibrillation	3	7	1	1
Back pain	1	0	3	0
Bradycardia	0	2	0	1
Cardiac failure	3	0	2	0
Cerebrovascular disorder	1	1	3	0
Dyspnoea	0	2	2	1
Fatigue	0	0	2	0
Fever	2	1	1	0
Headache	1	2	2	1
Leg pain	0	2	0	1
Nausea	1	3	0	2
Pain	2	1	1	0
Pharyngitis	0	2	0	0
Pulmonary oedema	1	2	0	0
Renal failure acute	1	2	1	0

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### 3.2.2.12 Conclusion

The sponsor did not show that Fragmin reduced the primary endpoint (death, myocardial infarction and/or recurrence of angina between day 6-45) either numerically or statistically.

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#### 4. REVIEW OF SAFETY (FRISC and FRIC combined)

##### 4.1 Overall exposure

A total of 2461 patients were included in the safety analysis for the FRISC and FRIC trials. Of them, 1235 were exposed to Fragmin. The following summaries include data on all of the FRIC patients and those FRISC patients exposed to 120 IU/kg Fragmin or its placebo control (Table 36).

**Table 36: Overall exposure to Fragmin in FRISC and FRIC studies**

Treatment	Acute Treatment Phase			Chronic Treatment Phase		
	FRISC	FRIC	Total	FRISC	FRIC	Total
Placebo for 120 IU/kg	760	NA	760	614	566	1180
Placebo for 150 IU/kg	53	NA	53	46	NA	46
Fragmin 120 IU/kg	746	751	1497	618*	567	1185
Fragmin 150 IU/kg	63	NA	63	50	NA	50
Heparin	NA	731	731	NA	NA	NA
<b>Grand total</b>	<b>1622</b>	<b>1482</b>	<b>3104</b>	<b>1328</b>	<b>1133</b>	<b>2461</b>

Source: FRISC [1], FRIC [2]

\* Patient 21101 died the day after the start of the chronic treatment phase. By study definition, this patient is included in the safety analysis for the acute treatment phase and therefore is not included here.

Abbreviation: NA = not applicable

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#### 4.2 Deaths

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##### 4.2.1 Overall Number of deaths

The number of patients who died during the treatment or follow-up period (6 months in FRISC, 90 days in FRIC) was similar in the Fragmin and placebo arms of FRISC, and among the four treatment arms in FRIC (Table 37).

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**Table 37: Overall Number of deaths in FRISC and FRIC**

	FRISC Treatment		FRIC Treatment Sequence			
	Placebo	Fragmin	H-F	F-F	H-P	F-P
Patients treated	760	746	368	378	363	373
Patients who died	43	44	14	15	15	17

Source: FRISC [1], FRIC [2]  
 Abbreviations: H-F = heparin in acute phase and Fragmin in chronic phase; F-F = Fragmin in acute and chronic phases; H-P = heparin in acute phase and placebo in chronic phase; F-P = Fragmin in acute phase and placebo in chronic phase

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**4.2.2 Incidence and cause of death during or after acute treatment**

The incidence of death during the acute phase was 1.0% in patients treated with Fragmin (14/1497), 0.5% in patients treated with heparin (4/730), and 0.5% in patients treated with placebo (4/760)(Table 38). Most of the deaths were associated with myocardial infarction of other heart disease.

**Table 38: Incidence and cause of death during or after acute treatment in FRISC and FRIC trials**

Cause of Death	Acute Treatment Phase						Follow-Up After Acute Treatment §							
	FRISC and FRIC						FRISC				FRIC			
	Placebo N = 760		Fragmin N = 1497		Heparin N = 730		Placebo N = 138		Fragmin N = 118		Fragmin N = 112		Heparin N = 118	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Overall Incidence	4*	0.5	15†	1.0	4‡	0.5	17	12.3	8	6.8	10	8.9	8	6.8
Cerebral bleeding	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cerebral embol/infarction	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0
Myocardial infarction	4	0.5	8	0.5	2	0.3	11	8.0	2	1.7	3	2.7	3	2.5
Other cause	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2¶	1.8	0	0.0
Other heart death	0	0.0	5	0.3	2	0.3	2	1.4	3	2.5	2	1.8	3	2.5
Post-operative	0	0.0	0	0.0	0	0.0	2	1.4	0	0.0	0	0.0	0	0.0
Sudden death	0	0.0	1	0.1	0	0.0	2	1.4	3	2.5	1	0.9	1	0.8
Unspecified stroke	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.9	1	0.8

Source: FRISC [1], FRIC [2], Safety Lists VIII A b, VIII B

\* This total does not include patients 13035, 17043, 27018, or 31009 (all from the FRISC study) who died on or before study day 6 but had been discontinued from treatment prior to death. In this table, these deaths are counted in the follow-up period.

† This total does not include patients 19018 (FRISC), 14002 (FRIC), or 1508 (FRIC) who died on or before study day 6 but had been discontinued from treatment prior to death. In this table, these deaths are counted in the follow-up period.

‡ This total includes patient 1406 (FRIC) who is not counted in the ISE with the deaths during the acute treatment phase. The death occurred after study day 6 although the patient was still receiving heparin according to the acute treatment regimen.

§ See pages 11 and 42 for definitions of follow-up periods.

¶ Corporate Pharmacovigilance narratives (appended to this Integrated Summary of Safety) indicate cause of death as multiple organ failure for patient 1310 and unknown for patient 3049.

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## 4.2.3 Incidence and cause of death during or after chronic treatment

The incidence of death during the chronic treatment phase was 0.6% in patients treated with Fragmin (7/1185) and 1.1% in patients treated with placebo (13/1180). The incidence of death during or after the chronic treatment phase is shown in Table 39.

Table 39: Incidence and cause of death during or after chronic treatment in FRISC and FRIC trials

Cause of Death	Chronic Treatment				Follow-Up After Chronic Treatment *							
	FRISC and FRIC				FRISC				FRIC			
	Placebo N = 1180		Fragmin N = 1185		Placebo N = 609		Fragmin N = 609		Placebo N = 454		Fragmin N = 450	
	n	%	n	%	n	%	n	%	n	%	n	%
Overall Incidence	13	1.1	7	0.6	18	3.0	27	4.4	3	0.7	14	3.1
Accident	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0
Bleeding (not cerebral)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Cerebral bleeding	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2
Cerebral emboli/infarction	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0
Myocardial infarction	8	0.7	4	0.3	4	0.7	13	2.1	2	0.4	5	1.1
Other cause	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2†	0.4
Other heart death	1	0.1	1	0.1	1	0.2	2	0.3	1	0.2	5	1.1
Post-operative	0	0.0	0	0.0	7	1.1	5	0.8	0	0.0	0	0.0
Pulmonary emboli	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0
Sudden death	4	0.3	2	0.2	3	0.5	6	1.0	0	0.0	0	0.0

Source: FRISC [1], FRIC study report [2], Safety Lists VIII A b, VIII B  
 \* See pages 11 and 42 for definitions of follow-up periods.  
 † Patient 11017 had a disseminated malignancy with metastasis in the liver; patient 12102 had seizures and dyspnea leading to acute pulmonary insufficiency and death.

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## 4.3 Serious adverse events

## 4.3.1 Sponsor-defined safety endpoints

## 4.3.1.1 Sponsor-defined safety endpoints during acute phase

The incidence of the sponsor-defined safety endpoints during the acute phase are summarized in Table 40. Serious bleeding events during the acute treatment phase were more common in Fragmin (0.8%) and heparin (1.4%) as compared to placebo (0.3%).

Table 40: Summary of serious events during the acute phase of FRISC and FRIC trials

Type of Event	Placebo N = 760*		Fragmin 120 IU/kg N = 1497†		Heparin N = 731‡	
	n	%	n	%	n	%
Bleeding (major or minor)	2	0.3	12	0.8	10	1.4
Thrombocytopenia	1	0.1	2	0.1	1	0.1
Allergic reaction	0	0.0	0	0.0	0	0.0
Laboratory changes§	0	0.0	0	0.0	NA	NA
Other complications	5	0.7	17	1.1	15	2.1

Source: Safety Table 14a. Supplemental Information for Safety Table 14

- \* No information available: thrombocytopenia = 5 patients
- † No information available: bleeding events = 7 patients; thrombocytopenia = 16 patients; allergic reaction = 4 patients
- ‡ No information available: bleeding events = 2 patients; thrombocytopenia = 4 patients; allergic reaction = 1 patient
- § Changes without other concomitant adverse events. This category applies to the FRISC trial only. For the FRIC trial, withdrawals due to changes in laboratory values are included with other complications.

Abbreviation: NA = not applicable

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4.3.1.2 Sponsor-defined safety endpoints during the chronic phase

Sponsor-defined safety endpoints are summarized in Table 41. 5 Fragmin and 2 placebo patients had bleeding.

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**Table 41: Summary of sponsor-defined safety endpoints during the chronic phase of FRISC and FRIC trials**

Type of Event	Placebo N = 1180*		Fragmin N = 1185†	
	n	%	n	%
Bleeding (major or minor)	2	0.2	5	0.4
Thrombocytopenia	0	0.0	0	0.0
Allergic reaction	1	0.1	0	0.0
Laboratory changes‡	1	0.1	0	0.0
Other complications	19	1.6	30	2.5

Source: Safety Table 14c, Supplemental Information for Safety Table 14

- \* No information available: bleeding events = 23 patients; thrombocytopenia = 10 patients; allergic reaction = 4 patients
- † No information available: bleeding events = 17 patients; thrombocytopenia = 10 patients; allergic reaction = 5 patients
- ‡ Changes without other concomitant adverse events. This category applies to the FRISC trial only. For the FRIC trial, withdrawals due to changes in laboratory values are included with other complications. (Patient 1803: increased serum creatinine.)

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#### 4.3.1.3 Incidence of serious complications

Complications, other than the sponsor-defined safety endpoints are described in this section.

##### 4.3.1.3.1 Incidence of serious complications during the acute phases

The incidence of other serious complications during the acute phase is summarized in Table 42.

The only serious events that occurred in more than one patient were pneumonia, cerebrovascular disorder, and cardiac events. 2 patients had cardiac arrest and 5 patients had cardiac failure in the Fragmin group. Rates were proportional with the heparin group.

Table 42: Incidence of serious complications during acute phase of FRISC and FRIC trials by treatment

Type of Disorder	Preferred Term	Placebo N = 760		Fragmin 120 IU/kg N = 1497		Heparin N = 731	
		n	%	n	%	n	%
Application site	Injection site inflammation	0	0.0	0	0.0	1	0.1
Body as a whole - general	Syncope	1	0.1	0	0.0	0	0.0
Cardiovascular system	Cardiac failure	0	0.0	5	0.3	2	0.3
	Circulatory failure	0	0.0	0	0.0	1	0.1
Gastrointestinal system	Diverticulitis	0	0.0	1	0.1	0	0.0
Heart rate and rhythm	Cardiac arrest	0	0.0	2	0.1	1	0.1
	Fibrillation ventricular	0	0.0	0	0.0	2	0.3
Liver and biliary system	Cholangitis	1	0.1	0	0.0	0	0.0
	Hepatic enzymes increased	0	0.0	1	0.1	0	0.0
Metabolic and nutritional	Hyperglycemia	0	0.0	1	0.1	0	0.0
	NPN increased	0	0.0	1	0.1	0	0.0
	Uremia	1	0.1	0	0.0	0	0.0
Myo- endo- pericardial and valve	Cardiac tamponade	0	0.0	0	0.0	1	0.1
Neoplasm	Neoplasm NOS	0	0.0	1	0.1	0	0.0
	Testis neoplasm malignant	0	0.0	1	0.1	0	0.0
Psychiatric	Depression	0	0.0	0	0.0	1	0.1
Red blood cell	Anemia	0	0.0	1	0.1	0	0.0
Respiratory system	Asthma	0	0.0	1	0.1	0	0.0
	Pleural effusion	0	0.0	0	0.0	1	0.1
	Pneumonia	1	0.1	1	0.1	1	0.1
	Pulmonary edema	0	0.0	0	0.0	1	0.1
Vascular (extracardiac)	Cerebrovascular disorder	1	0.1	1	0.1	1	0.1
	Claudication intermittent	0	0.0	0	0.0	1	0.1
	Thrombophlebitis leg	0	0.0	0	0.0	1	0.1

Source: Safety Table 15b  
 \* Serious adverse events other than major bleeding, minor bleeding, thrombocytopenia, and allergic reaction  
 Abbreviations: NOS = not otherwise specified; NPN = non-protein nitrogen

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4.3.1.4 Incidence of serious complications during the chronic phases

The incidence of serious complications during the chronic phase of FRISC and FRIC is summarized in Table 43. Although there were 32/1185 events in the Fragmin group and 20/1180 in the placebo group, there is no adverse event that predominates.

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