4. THE EFFICACY OF LEPIRUDIN COMPARED TO UNFRACTIONATED HEPARIN

This section summarizes the efficacy findings for lepirudin in comparison to unfractionated heparin in ACS.

The efficacy assessment is based primarily on the OASIS-2 study with supportive evidence coming from OASIS-1. Further evidence in support of the claim of efficacy is provided by analyses of the combined results of OASIS-1 and OASIS-2 and comparisons of the combined OASIS results with those for GUSTO-2b [49]. In addition, the OASIS findings are reviewed in the light of findings for other drugs recently approved for this indication.

The OASIS studies were performed as active control comparisons with heparin because the use of unfractionated heparin in conjunction with aspirin is routine practice in patients with ACS. A placebo-controlled trial would have been unethical in this setting. As a substitute, the efficacy of lepirudin plus aspirin has been compared to that of a "putative placebo" control (aspirin alone). The results of this analysis are provided in *Section 5*, page 45.

4.1 OASIS-1 results

The key findings are summarized in the following table. Since all patients completed their 7-day assessment, the MITT population presented here included <u>all</u> patients randomized, i.e. the MITT population is the same as the ITT population.

OASIS-1: Key efficacy findings (MITT population)

Comp. endpoint / Time period	N (%) patients with events: Heparin N=371	Low-dose lepirudin N=271	Medium-dose lepirudin N=267	Relative risk (95% CI)	p-value
				Low vs. heparin / Med. vs. heparin	Low vs. H / Med. vs. H
CV death, new MI, refractory or severe angina					
72 hours	44 (11.9%)	21 (7.7%)	19 (7.1%)	Low: 0.62 (0.36–1.08)	0.0764
				Med: 0.57 (0.32–1.00)	0.0418
7 days	58 (15.6%)	34 (12.5%)	25 (9.4%)	Low: 0.77 (0.49–1.22)	0.2791
				Med: 0.56 (0.34–0.92)	0.0176
35 days	73 (19.7%)	45 (16.6%)	40 (15.0%)	Low: 0.81 (0.54–1.22)	0.3525
				Med: 0.72 (0.47–1.10)	0.0640
End of study [a]	86 (23.2%)	50 (18.5%)	46 (17.2%)	Low: 0.75 (0.51–1.11)	0.1676
				Med: 0.69 (0.46–1.03)	0.0331
CV death, new MI or refractory angina					
72 hours	15 (4.0%)	7 (2.6%)	5 (1.9%)	Low: 0.63 (0.25–1.57)	0.3019
				Med: 0.45 (0.16–1.26)	0.1069
7 days	24 (6.5%)	12 (4.4%)	8 (3.0%)	Low: 0.67 (0.33–1.36)	0.3106
				Med: 0.45 (0.20–1.01)	0.0436
35 days	39 (10.5%)	20 (7.4%)	19 (7.1%)	Low: 0.68 (0.39–1.19)	0.2364
				Med: 0.65 (0.37–1.16)	0.1266
End of study [a]	50 (13.5%)	25 (9.2%)	25 (9.4%)	Low: 0.65 (0.39–1.08)	0.1291
				Med: 0.66 (0.40–1.10)	0.1040

[a] 180 days in OASIS-1a and 120 days in OASIS-1b

OASIS-1: Key efficacy findings (MITT population), *continued*

Comp. endpoint / Time period	N (%) patients with events: Heparin N=371	Low-dose lepirudin N=271	Medium-dose lepirudin N=267	Relative risk (95% CI): Low vs. heparin / Med. vs. heparin	p-value: Low vs. H / Med. vs. H
CV death or new MI					
72 hours	10 (2.7%)	4 (1.5%)	5 (1.9%)	Low: 0.54 (0.17–1.74)	0.2979
				Med: 0.69 (0.23–2.04)	0.4803
7 days	18 (4.9%)	7 (2.6%)	7 (2.6%)	Low: 0.52 (0.21–1.26)	0.1787
				Med: 0.53 (0.22–1.28)	0.1493
35 days	31 (8.4%)	15 (5.5%)	17 (6.4%)	Low: 0.64 (0.34–1.22)	0.2373
				Med: 0.75 (0.40–1.38)	0.3083
End of study [a]	41 (11.1%)	20 (7.4%)	23 (8.6%)	Low: 0.64 (0.37–1.12)	0.1561
				Med: 0.76 (0.44–1.30)	0.2862

[a] 180 days in OASIS-1a and 120 days in OASIS-1b

The composite endpoint of CV death, new MI, or refractory or severe angina at 7 days, which was considered the most important composite endpoint in the primary analysis of efficacy, occurred in 25 (9.4%) medium-dose lepirudin patients, compared with 58 (15.6%) heparin patients (relative risk 0.56 [95% CI: 0.34–0.92]; p=0.0176). Qualitatively, the results of OASIS-1 revealed great consistency with those of OASIS-2 (see *Section 4.2*, page 21). The magnitude of the effect across endpoints tended to be larger in OASIS-1.

The beneficial effects of lepirudin were obtained predominantly during the treatment period and the immediate post-treatment period up to 7 days. The early absolute benefit achieved with lepirudin was well preserved over time. The strongest relative contribution of the individual endpoint components came from new MI at all times, both in terms of incidence and treatment effect.

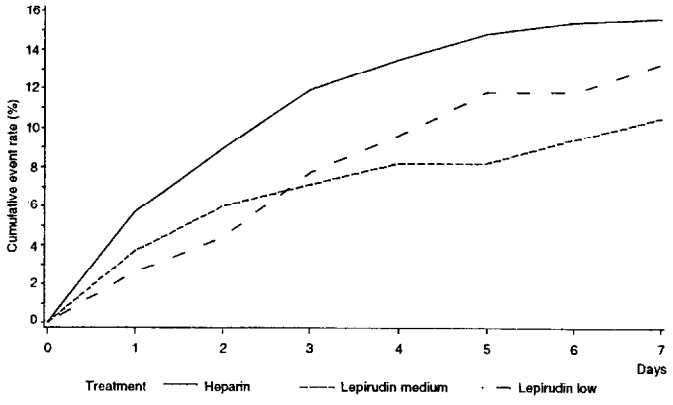
The following table shows the absolute and relative benefits of lepirudin treatment in this study as determined for the quadruple endpoint of CV death, new MI, or refractory or severe angina:

OASIS-1: Absolute and relative benefit of lepirudin in comparison with heparin (CV death, new MI, refractory or severe angina; MITT population)

Time period	Medium-dose vs. heparin: Absolute benefit (%)	Medium-dose vs. heparin: Rel. risk reduction (%)	Low-dose vs. heparin: Absolute benefit (%)	Low-dose vs. heparin: Rel. risk reduction (%)
72 hours	–4.74	43	–4.11	38
7 days	–6.27	44	–3.09	23
35 days	–4.70	28	–3.07	19
End of study [a]	–5.95	31	–4.73	25

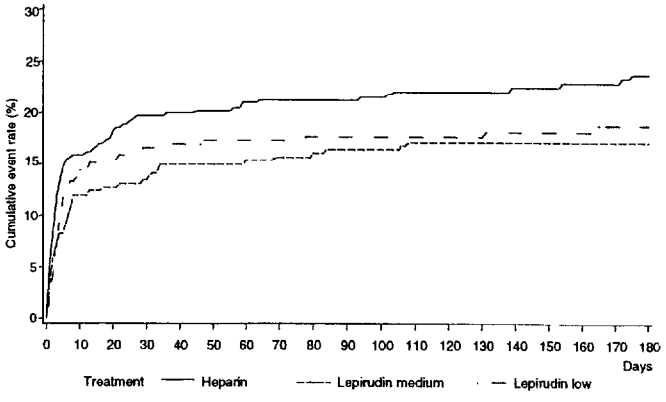
[a] 180 days in OASIS-1a and 120 days in OASIS-1b

The Kaplan-Meier curves for the quadruple endpoint were as follows:



CV death, new MI, refractory or severe angina:

Up to 7 days



CV death, new MI, refractory or severe angina:

Up to end of study

As shown in the following table, there were only very few non-CV deaths in the study.

OASIS-1: Non-CV deaths (MITT population)

Time period	Heparin N=371	Low-dose lepirudin N=271	Medium-dose lepirudin N=267
72 hours	0	0	0
7 days	1	0	0
35 days	1	1	0
End of study [a]	4	1	1

[a] 180 days in OASIS-1a and 120 days in OASIS-1b

Inclusion of all-cause mortality rather than CV death in the composite endpoints would thus slightly improve the treatment benefit of lepirudin beyond 72 hours.

4.2 OASIS-2

The **efficacy results** of the OASIS-2 study comprise both cross-sectional analyses of various endpoints at specific timepoints and longitudinal analyses of specific endpoints over time. In order to give a clear and stringent overview of the totality of data, we have separated "key" efficacy analyses from "supportive" efficacy analyses in this document. This distinction was made after the study was unblinded at the sponsor, but the analyses were prespecified in the SAP, unless otherwise specified below.

- The **key analyses of efficacy** were the analyses of the double composite endpoint of CV death or new MI, the triple composite endpoint of CV death, new MI or refractory angina, and the individual components of the composite endpoints at 72 hours, 7 days, 35 days and 180 days. The primary analysis of efficacy was the analysis of the double composite endpoint at 7 days, the key secondary analysis was the analysis of the triple composite endpoint at 7 days.
- **Supportive analyses of efficacy** comprised the analyses of the double and triple composite endpoints using all-cause death rather than CV death as the mortality component, as well as additional endpoints and analyses.

Unless otherwise specified, all efficacy analyses presented in this briefing document are based on the **MITT population**. This population was prespecified by the sponsor as the primary efficacy analysis population in the statistical analysis plan. The use of the MITT rather than the ITT population was considered to be justified and appropriate because the central call-in randomization process and the double-blind, double-dummy study design did not allow bias to be introduced. Therefore, it could be assumed that any events occurring prior to start of lepirudin or heparin would be randomly distributed between the groups and dilute the study results by adding noise. The requirement of a completed 7-day efficacy assessment in the MITT population minimized the need for assumptions and imputations. As reviewed in *Section 4.2.1.4* (page 23), the results were very similar and consistent between the MITT and ITT study populations.

For reference purposes, the key OASIS-2 efficacy results are displayed for the pure ITT population (all patients randomized) in Appendix A of this briefing document.

4.2.1 Key analyses of efficacy

The findings for the double composite endpoint of CV death or new MI and the triple composite endpoint of CV death, new MI or refractory angina were as follows:

OASIS-2: Key efficacy findings from randomization to 180 days (MITT population) [a]

Composite endpoint Time period	N (%) patients with events Heparin N=5,033	Lepirudin N=5,045	Relative risk [b] (95% CI)	p-value [c]
CV death or new MI				
72 hours	132 (2.6%)	99 (2.0%)	0.74 (0.57–0.97)	0.0229
7 days [d]	**211 (4.2%)**	**178 (3.5%)**	**0.83 (0.68–1.02)**	**0.0714**
35 days	377 (7.5%)	337 (6.7%)	0.88 (0.76–1.03)	0.0896
180 days	541 (10.7%)	517 (10.2%)	0.95 (0.83–1.08)	0.3377
CV death, new MI or refractory angina				
72 hours	199 (4.0%)	154 (3.1%)	0.76 (0.62–0.95)	0.0108
7 days [e]	**336 (6.7%)**	**279 (5.5%)**	**0.82 (0.69–0.96)**	**0.0138**
35 days	675 (13.4%)	633 (12.5%)	0.92 (0.82–1.04)	0.1600
180 days	1,055 (21.0%)	1,026 (20.3%)	0.96 (0.87–1.06)	0.3559

[a] For comparison of MITT with ITT see *Section 4.2.1.4*, page 23. For ITT results see Table 1 of Appendix A
[b] Stratified by pooled center and treatment
[c] Corrected for center
[d] The primary analysis of efficacy
[e] The key secondary analysis of efficacy

The event rates for the composite endpoints CV death or new MI and CV death, new MI or refractory angina were consistently lower in lepirudin patients than in heparin patients at all time points.

4.2.1.1 Primary analysis of efficacy

From randomization to day 7, the double composite endpoint of CV death or new MI occurred in fewer lepirudin than heparin patients, resulting in a 17% relative risk reduction in lepirudin patients compared with heparin patients. The difference between treatment groups approached statistical significance (p=0.0714).

4.2.1.2 Key secondary analysis of efficacy

From randomization to day 7, the triple composite endpoint of CV death, new MI or refractory angina occurred in fewer lepirudin than heparin patients up to day 7, resulting in an 18% relative risk reduction in lepirudin patients compared with heparin patients. The difference between treatment groups was statistically significant (p=0.0138).

4.2.1.3 Benefit of lepirudin in the first 72 hours

The beneficial effects of lepirudin in comparison to heparin were predominantly achieved during the treatment period and, thus, were already apparent at 72 hours. At this timepoint, statistically significant relative risk reductions in favor of lepirudin were found for both composite endpoints (double: 26%, p=0.0229; triple: 24%, p=0.0108). In the light of the pharmacology of lepirudin, these findings are biologically plausible.

4.2.1.4 Comparability across study populations

The results of the analyses for the double and triple composite endpoints at 7 days and throughout the study were consistent across the MITT and ITT populations.

OASIS-2: Comparison of key efficacy findings in the MITT and ITT populations

Composite endpoint Time period	MITT population			ITT population		
	Event rate (%)		RR; p-value	Event rate (%)		RR; p-value
	Heparin N=5,033	Lepirudin N=5,045		Heparin N=5,058	Lepirudin N=5,083	
CV death or new MI						
72 hours	2.6%	2.0%	0.74; 0.0229	2.6%	2.0%	0.76; 0.0342
7 days [a]	**4.2%**	**3.5%**	**0.83; 0.0714**	**4.2%**	**3.6%**	**0.84; 0.0863**
35 days	7.5%	6.7%	0.88; 0.0896	7.5%	6.7%	0.89; 0.1093
180 days	10.7%	10.2%	0.95; 0.3377	10.8%	10.2%	0.95; 0.3219
CV death, new MI or refractory angina						
72 hours	4.0%	3.1%	0.76; 0.0108	4.0%	3.1%	0.78; 0.0157
7 days [b]	**6.7%**	**5.5%**	**0.82; 0.0138**	**6.7%**	**5.6%**	**0.82; 0.0163**
35 days	13.4%	12.5%	0.92; 0.1600	13.4%	12.6%	0.93; 0.1705
180 days	21.0%	20.3%	0.96; 0.3559	21.0%	20.3%	0.96; 0.3189

[a] The primary analysis of efficacy [b] The key secondary analysis of efficacy

The relative risk reductions and p-values obtained in the per-protocol population were similar to those for the MITT and ITT populations. Analysis of the MITT population using efficacy events as assessed by investigators also strongly supported the findings in the MITT population using adjudicated data.

4.2.1.5 Incidence of individual endpoint components

The incidence of the individual components (CV death, new MI and refractory angina) of the composite endpoints was lower in the lepirudin group than in the heparin group at all time points.

OASIS-2: Incidence of individual endpoint components (MITT population) [a]

Time period Component [b]	N (%) patients with events	
	Heparin N=5,033	Lepirudin N=5,045
72 hours		
CV death	45 (0.9%)	39 (0.8%)
New MI	87 (1.7%)	60 (1.2%)
Refractory angina	67 (1.3%)	55 (1.1%)
7 days		
CV death	77 (1.5%)	69 (1.4%)
New MI	134 (2.7%)	109 (2.2%)
Refractory angina	125 (2.5%)	101 (2.0%)

[a] For ITT results see Table 2 of Appendix A [b] Most serious outcome

In the double composite endpoint, the relative contribution of new MI to the overall beneficial effect of lepirudin up to 7 days was stronger than that of CV death (absolute difference between treatment

groups: 25 patients with MI and 8 CV deaths). In the triple composite endpoint, the third component, refractory angina, contributed to the beneficial effect of lepirudin up to 7 days to the same extent as new MI (absolute difference between treatment groups: 24 episodes of refractory angina in patients without CV death or new MI).

4.2.1.6 Preservation of benefit of lepirudin over time

The absolute and relative benefits of lepirudin treatment observed over time were as follows:

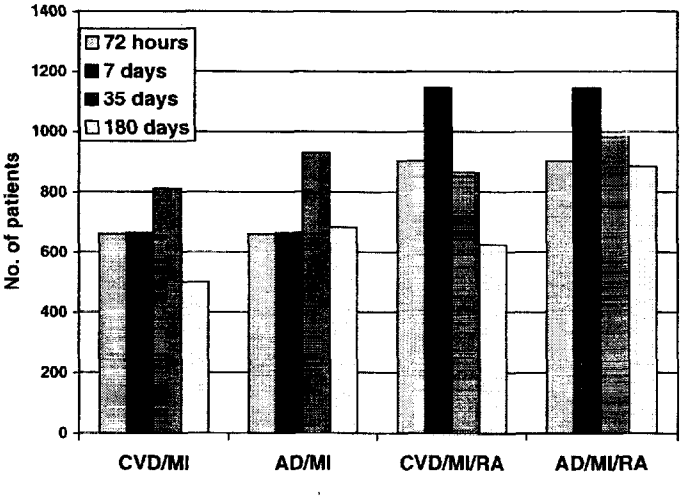
OASIS-2: Absolute and relative benefit of lepirudin in comparison with heparin (MITT population) [a]

Composite endpoint Time period	N (%) of patients with events Heparin N=5,033		Lepirudin N=5,045		Absolute benefit (%)	Rel. risk reduction (%) [b]
CV death or new MI						
72 hours	132	(2.6%)	99	(2.0%)	-0.66	26
7 days	211	(4.2%)	178	(3.5%)	-0.66	17
35 days	377	(7.5%)	337	(6.7%)	-0.81	12
180 days	541	(10.7%)	517	(10.2%)	-0.50	5
CV death, new MI or refractory angina						
72 hours	199	(4.0%)	154	(3.1%)	-0.90	24
7 days	336	(6.7%)	279	(5.5%)	-1.15	18
35 days	675	(13.4%)	633	(12.5%)	-0.86	8
180 days	1,055	(21.0%)	1,026	(20.3%)	-0.62	4

[a] For ITT results see Table 3 of Appendix A [b] Stratifed by pooled center and treatment

The absolute benefit of lepirudin over heparin at the four timepoints is shown as follows:

OASIS-2: Number of patients without endpoints per 100,000 patients treated with lepirudin instead of heparin (MITT, N=10,078)



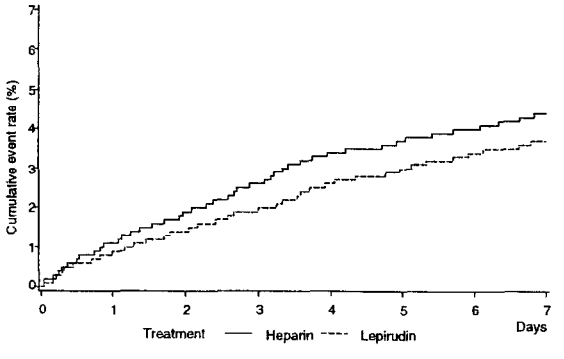
CVD: cardiovascular death; AD: all-cause death; MI: myocardial infarction; RA refractory angina

NOTE: Also included in this figure are the composite endpoints of all-cause death or new MI and all-cause death, new MI or refractory angina. The data for these endpoints are presented in *Section 4.2.2.1*, page 26

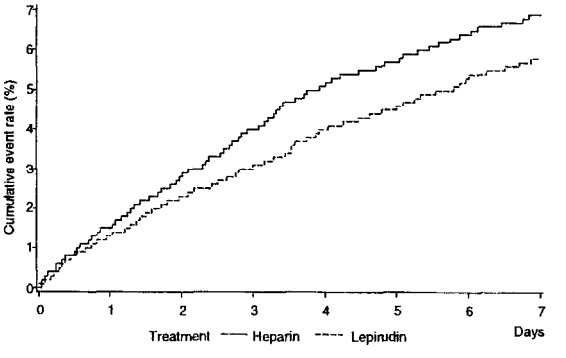
For both composite endpoints, the absolute benefit of lepirudin treatment over heparin observed after 72 hours was maintained up to 35 days and, to a large extent, up to the 180-day follow-up assessment. In particular, there was no loss in the benefit after treatment was discontinued. As might be expected, the absolute treatment benefit of lepirudin over heparin was higher at all timepoints for the triple composite endpoint than for the double composite endpoint.

These findings are corroborated by the time-to-event analyses for the double and triple composite endpoints. These analyses provide further strong support that the early absolute beneficial effect of lepirudin over heparin was largely maintained during the 6-month follow-up. The Kaplan-Meier curves for the periods from randomization to day 7 and day 180 in the MITT population were as follows (for 7-day curves based on ITT population see Figures 1 and 2 of Appendix A):

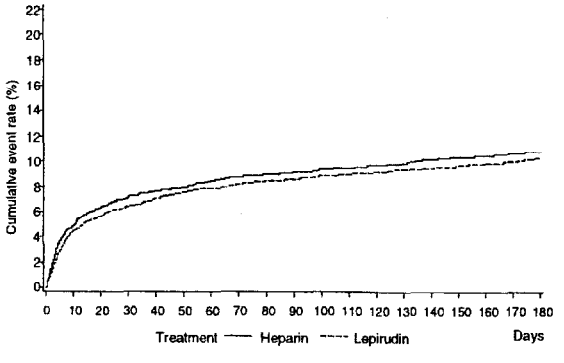
CV death or new MI to 7 days (MITT population)



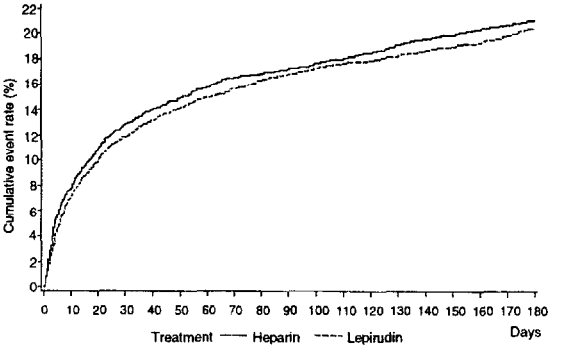
CV death, new MI or refract. angina to 7 days (MITT population)



CV death or new MI to 180 days (MITT population)



CV death, new MI or refract. angina to 180 days (MITT population)



The Kaplan-Meier curves clearly diverged up to 3 days for both composite endpoints. Thereafter, the curves remained essentially parallel throughout the study to the end of follow-up at 6 months. Importantly, at no point did the curves cross. The findings confirm that the absolute treatment benefit was well preserved up to 6 months. The time-to-event analyses for the ITT population followed the same pattern as those for the MITT population.

4.2.1.7 Confirmation rates in the adjudication process

A total of only 25 MIs (lepirudin: 8; heparin: 17) were not confirmed in the adjudication process, translating into a confirmation rate for new MI of 98% in the lepirudin group and 95% in the heparin group. For refractory angina, the confirmation rates were 91% in the lepirudin group and 98% in the heparin group.

4.2.1.8 Patients lost to follow-up

There were 4 patients who had no 7-day efficacy assessment and a further 7 patients who had their 7-day efficacy assessments completed early. Imputation methods were defined prior to unblinding the study database to investigate the effect of these no/early assessment patients via further analyses. These involved using (i) the observed treatment-specific event rates and (ii) twice the lepirudin observed event rate with no event for heparin, in a modified Mantel-Haenszel analysis. Not surprisingly the effect of even the extreme 'worst case' imputation technique was minimal, with the p-value from the ITT analysis being slightly increased from 0.0863 to 0.0910.

4.2.2 Supportive analyses of efficacy

4.2.2.1 All-cause mortality

When all-cause death rather than CV death was considered as the mortality component, the findings for the double and triple composite endpoints were as follows:

OASIS-2: Efficacy findings, with all-cause death instead of CV death (MITT population) [a]

Composite endpoint Time period	N (%) of patients with events Heparin N=5,033		Lepirudin N=5,045		Absolute benefit (%)	Rel. risk reduction (%) [b]	p-value [c]
All-cause death or new MI							
72 hours	132	(2.6%)	99	(2.0%)	-0.66	26	0.0229
7 days	211	(4.2%)	178	(3.5%)	-0.66	17	0.0714
35 days	385	(7.6%)	339	(6.7%)	-0.93	13	0.0553
180 days	568	(11.3%)	535	(10.6%)	-0.68	7	0.2136
All-cause death, new MI or refractory angina							
72 hours	199	(4.0%)	154	(3.1%)	-0.90	24	0.0108
7 days	336	(6.7%)	279	(5.5%)	-1.15	18	0.0138
35 days	683	(13.6%)	635	(12.6%)	-0.98	8	0.1147
180 days	1,082	(21.5%)	1,040	(20.6%)	-0.88	5	0.2120

[a] For ITT results see Table 4 of Appendix A
[b] Stratified by pooled center and treatment [c] Corrected for center

With all-cause rather than CV death, both composite endpoints showed slightly more favorable findings for lepirudin at 35 days and 180 days, while the results at 72 hours and 7 days were unaffected since no non-CV deaths occurred in this early period. The improved outcome of lepirudin patients in the longer-term follow-up was supported by time-to-event analyses based on all-cause mortality.

4.2.2.2 Non-parametric analyses of covariance

Non-parametric analyses of covariance using three sets of covariates were conducted for the double composite endpoint of CV death or new MI to adjust for imbalances in these factors between treatments. One set of covariates was defined in the SAP and comprised: age (≤65 years, >65 years), baseline ECG (ST depression vs. other), previous MI, current smoker (vs. never or former), and history of heart failure. A second set was identified prior to unblinding as independently predictive of outcome: ECG abnormal/normal, baseline ECG (ST depression vs. other), history of diabetes, entry diagnosis (suspected unstable angina or non-Q-wave MI), age (≤65 years, >65 years), and sex. Centers were accounted for in the model. A third analysis was conducted on the combined set of covariates (9 in total, since two covariates were common to both of the first two analyses).

All three models led to lower p-values than the primary analysis. The reduction was modest at 7 days (p=0.0636, 0.0699, and 0.0665) and more pronounced at 35 days (p=0.0628, 0.0738, and 0.0656), indicating that the covariates examined had a greater influence on the efficacy outcome at 35 days than at 7 days.

4.2.2.3 Subgroup analyses of efficacy

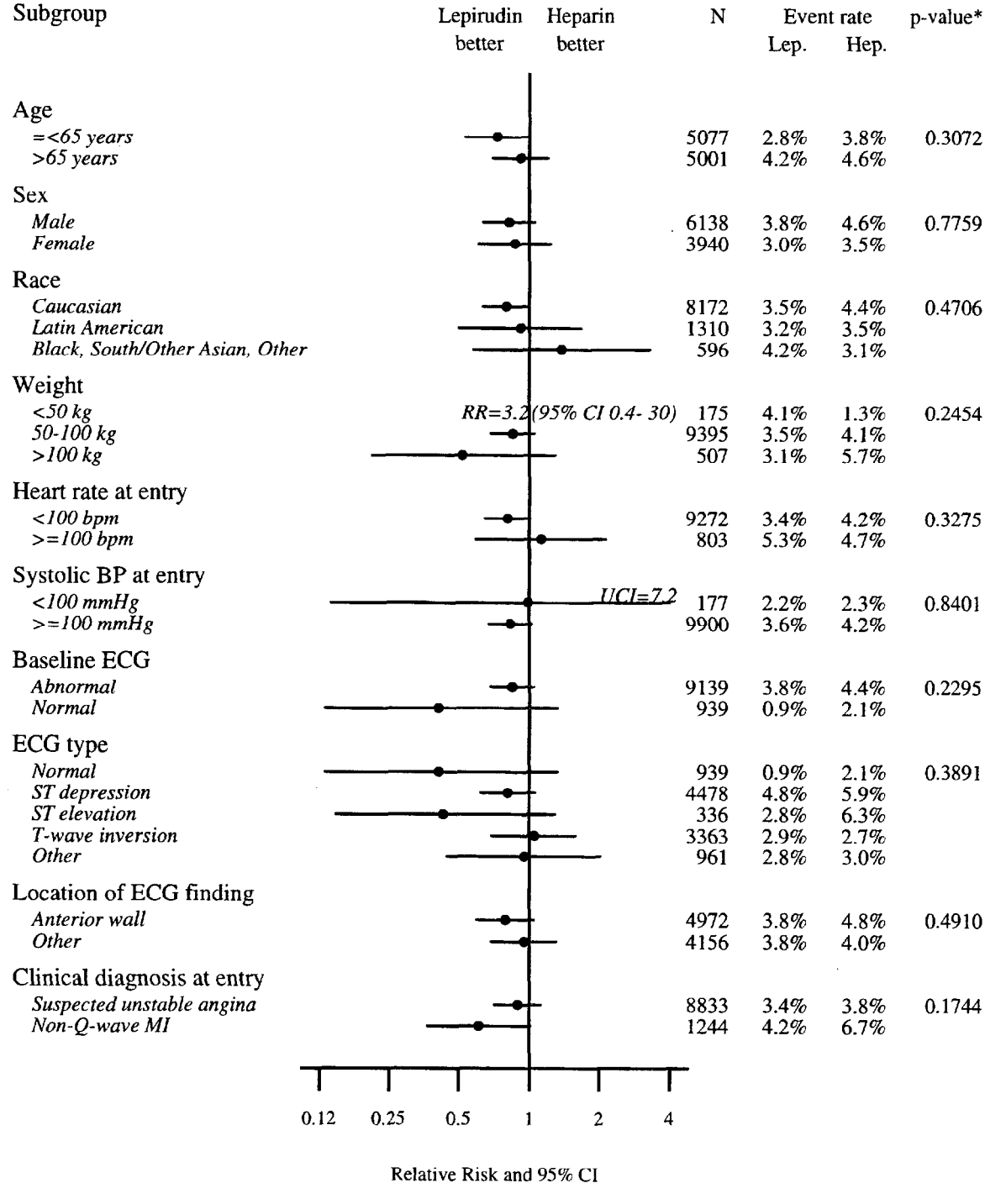
The graphs on the following pages show the results of the prespecified individual subgroup analyses of the double composite endpoint of CV death or new MI at 7 days.

Overall, the subgroup analyses revealed consistency of the treatment effect for CV death or new MI at 7 days across the subgroups of 26 factors investigated. At the screening level of p≤0.10, there was statistical evidence for inconsistency in treatment effect for only 3 factors (12%). This is compatible with the rate expected by chance (10%). The three subgroups were "other evidence of CAD" (p=0.0443), "history of diabetes" (p=0.0516) and "center size" (p=0.0885). At the conventional significance level of p≤0.05, only 1 of the 26 factors (4%), "other evidence of CAD", showed statistical evidence of treatment inconsistency, again compatible with chance (5%).

"Other evidence of CAD" denoted CAD history other than previous MI, PTCA or CABG. The observed treatment effect of lepirudin over heparin was notably better in patients without this history (relative risk 0.67) than in those with the history (1.01). Further investigation indicated that the difference was attributable to a lack of treatment benefit in patients subcategorized with history of chronic stable angina (relative risk 1.15). It is likely that these patients were included in the study on the basis of fluctuations in their underlying condition rather than due to an acute thrombotic event. They would therefore be expected to have lower event rates and a smaller benefit from treatment with antithrombotic agents than patients with an acute thrombotic event.

Diabetic patients appeared to respond less well to lepirudin (relative risk vs. heparin 1.16) than those without diabetes (0.74). However, there was no evidence of inconsistencies in the treatment effect for the double composite endpoint at 72 hours and the triple composite endpoint at 72 hours and 7 days. Furthermore, in contrast to OASIS-2, lepirudin was found to be consistently superior to heparin in diabetic patients in OASIS-1. In fact, due to excessively high event rates in diabetic heparin patients in OASIS-1, the beneficial effect of lepirudin appeared to be even more pronounced in diabetic patients than in non-diabetic patients. It seems likely therefore that the initial subgroup finding in OASIS-2 was a chance observation.

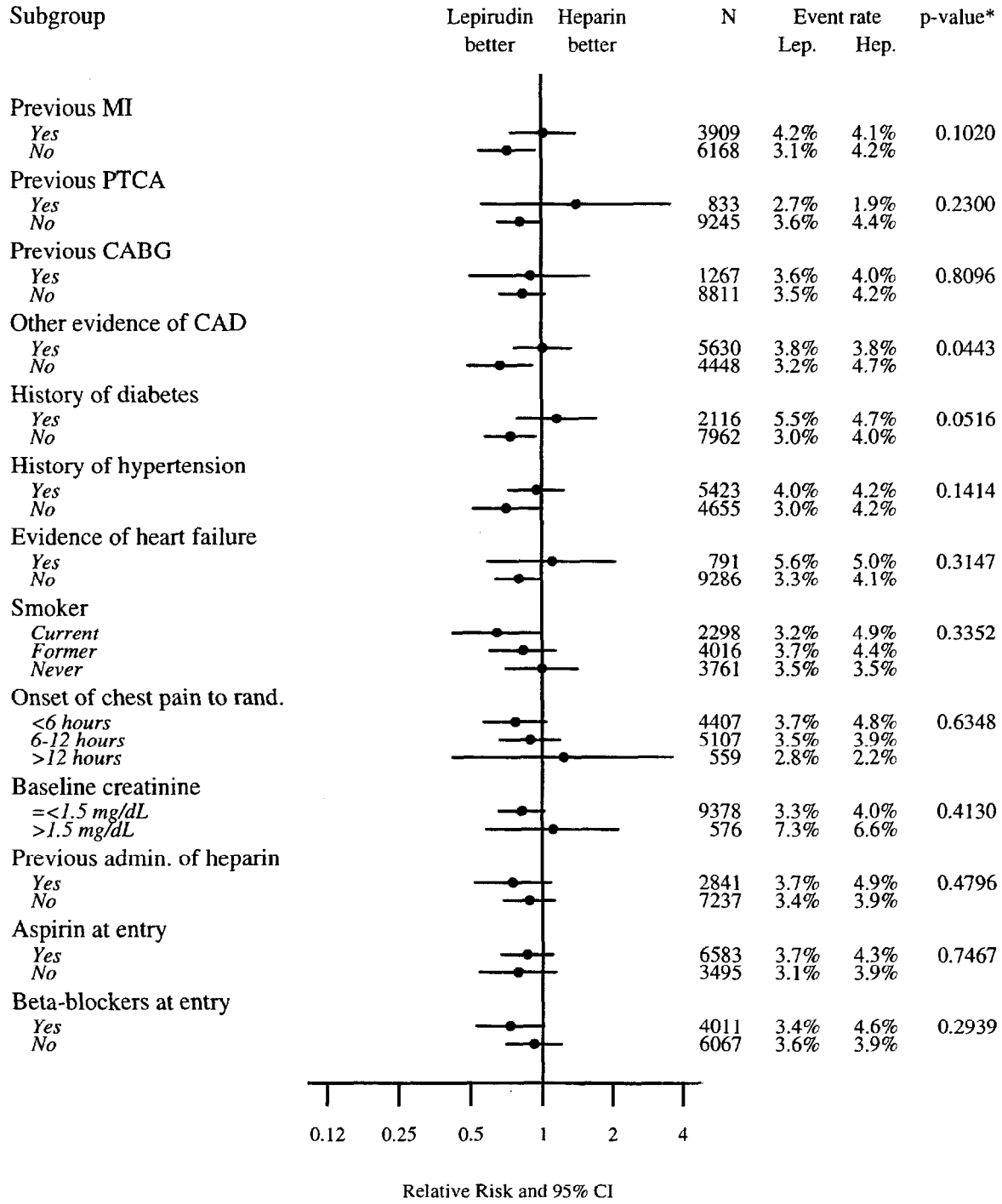
Subgroup analyses of influence of prespecified factors on incidence of CV death or new MI at 7 days (MITT population)



Subgroup	N	Event rate Lep.	Event rate Hep.	p-value*
Age				
=<65 years	5077	2.8%	3.8%	0.3072
>65 years	5001	4.2%	4.6%	
Sex				
Male	6138	3.8%	4.6%	0.7759
Female	3940	3.0%	3.5%	
Race				
Caucasian	8172	3.5%	4.4%	0.4706
Latin American	1310	3.2%	3.5%	
Black, South/Other Asian, Other	596	4.2%	3.1%	
Weight				
<50 kg	175	4.1%	1.3%	0.2454
50-100 kg	9395	3.5%	4.1%	
>100 kg	507	3.1%	5.7%	
Heart rate at entry				
<100 bpm	9272	3.4%	4.2%	0.3275
>=100 bpm	803	5.3%	4.7%	
Systolic BP at entry				
<100 mmHg	177	2.2%	2.3%	0.8401
>=100 mmHg	9900	3.6%	4.2%	
Baseline ECG				
Abnormal	9139	3.8%	4.4%	0.2295
Normal	939	0.9%	2.1%	
ECG type				
Normal	939	0.9%	2.1%	0.3891
ST depression	4478	4.8%	5.9%	
ST elevation	336	2.8%	6.3%	
T-wave inversion	3363	2.9%	2.7%	
Other	961	2.8%	3.0%	
Location of ECG finding				
Anterior wall	4972	3.8%	4.8%	0.4910
Other	4156	3.8%	4.0%	
Clinical diagnosis at entry				
Suspected unstable angina	8833	3.4%	3.8%	0.1744
Non-Q-wave MI	1244	4.2%	6.7%	

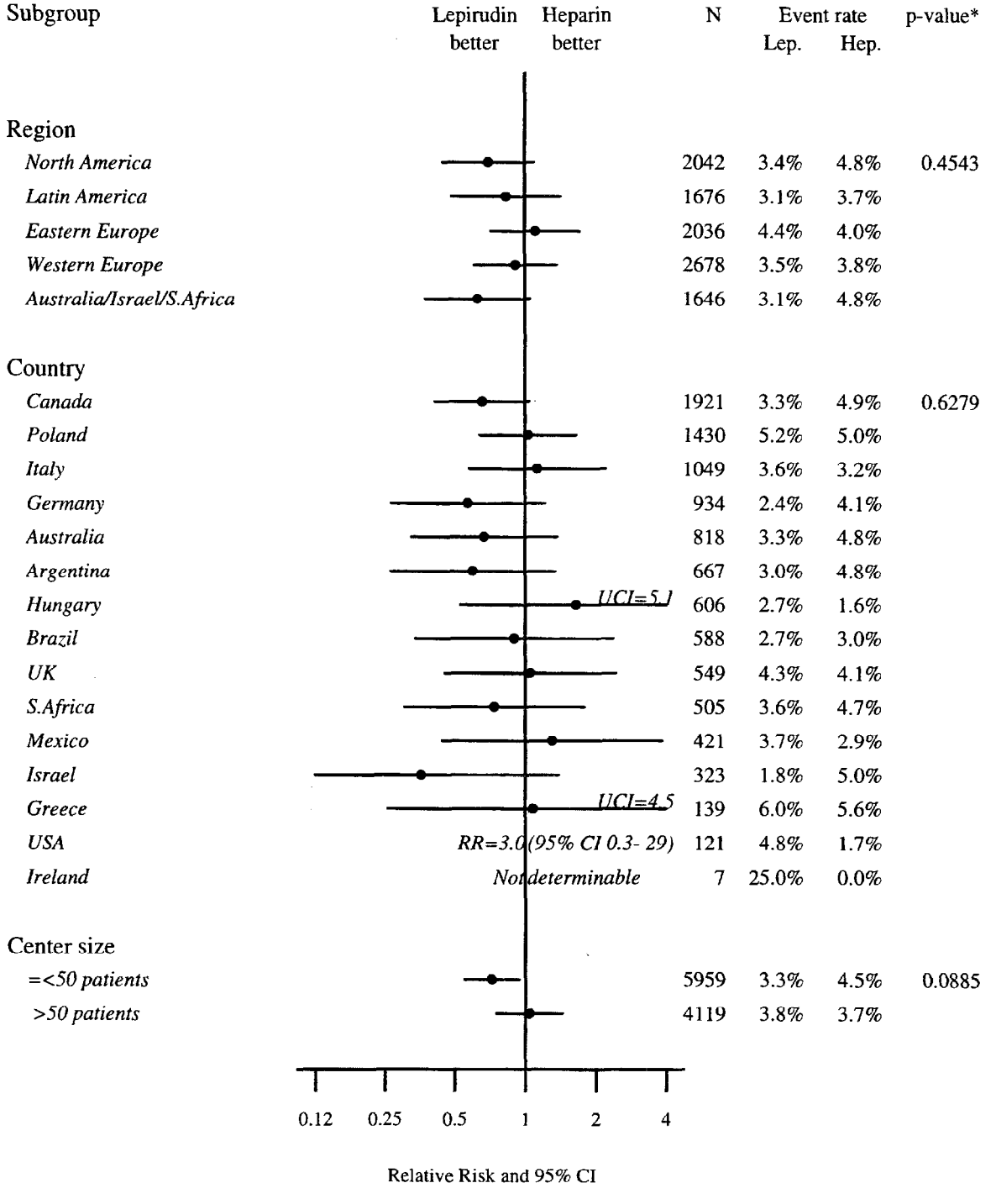
* Test for consistency of treatment effect across subgroup levels.

Subgroup analyses of influence of prespecified factors on incidence of CV death or new MI at 7 days (MITT population)



* Test for consistency of treatment effect across subgroup levels.

Subgroup analyses of influence of prespecified factors on incidence of CV death or new MI at 7 days (MITT population)



* Test for consistency of treatment effect across subgroup levels.

4.2.2.4 CV death, new MI, or refractory or severe angina

From randomization to day 7, the quadruple composite endpoint of CV death, new MI, or refractory or severe angina occurred in fewer lepirudin patients than heparin patients (9.6% vs. 10.5%, relative risk 0.90 [95% CI: 0.79-1.03]; p=0.1091).

4.2.2.5 Associated MI

19.0% of patients had an associated MI (MI associated with the presenting symptoms at entry to the study; lepirudin 18.8%, heparin 19.2%). Slightly more lepirudin than heparin patients reported the associated MI before or at randomization (11.4% vs. 10.9%). In contrast, slightly fewer lepirudin than heparin patients reported the associated MI after randomization (7.3% vs. 8.2%). Although no major impact of lepirudin on associated MIs was anticipated prior to the study, the lower incidence of such MIs in the lepirudin group raises the possibility of a beneficial effect of lepirudin on evolving MIs.

4.2.2.6 Periprocedural MI

In OASIS-2, periprocedural MIs were defined using the same criteria as MIs independent of cardiac procedures. This is because it was anticipated that the proportion of patients undergoing early revascularization would be low, and the use of further specifications for periprocedural MIs could even introduce bias if the rates of revascularization procedures were different between the treatment groups. Furthermore, it was the intention of the protocol to provide guidance rather than over-regulation and to make use of the investigators' judgement of the patients' clinical presentation rather than to disrupt clinical practice. This approach was deemed to be acceptable because only investigator-reported events were used for the efficacy analyses and all MIs were to undergo central blinded adjudication.

After submission of the supplemental NDA, a separate, *post hoc* analysis of periprocedural MIs was performed to evaluate any potential impact on the results of such MIs. For this purpose, "periprocedural MI" was defined as any MI occurring within 24 hours of an invasive therapeutic procedure (PCI or CABG). A total of 13 periprocedural MIs were reported up to 7 days. All of these were confirmed by the adjudication process (7 lepirudin patients, 6 heparin patients). Twelve of the 13 cases met the protocol criteria for new MI. In the remaining case, the patient had no symptoms and no ECG evidence but did have highly positive peak cardiac enzymes (CK 2,105 U/L, CK-MB 83 U/L).

In addition, to test the validity of the diagnosis of the periprocedural MIs, more stringent laboratory criteria (CK or CK-MB) were applied:

- after CABG surgery, an increase to at least 5 times the upper limit of normal was required;
- after PCI, an increase to at least 3 times the upper limit of normal was required.

The requirements were considered to be met if either CK or CK-MB was increased to the defined level.

Three of the 13 periprocedural MIs did not meet these more stringent CK or CK-MB criteria: 2 lepirudin patients and 1 heparin patient. In all 3 cases, both the additional MI criteria (characteristic symptoms, ECG evidence) were met.

Thus, there is strong evidence that all 13 periprocedural MIs were "real" MIs. Applying more stringent laboratory criteria would, if anything, only slightly modify the overall results of the study in favor of lepirudin.

4.2.2.7 Cardiac interventions

From randomization to day 7, significantly fewer lepirudin patients (6.7%) than heparin patients (8.1%) required cardiac interventions other than cardiac catheterization, i.e. early therapeutic interventions, including PCI (PTCA or atherectomy with or without stent), CABG, thrombolytic therapy and/or intra-aortic balloon pump (p=0.0109).

OASIS-2: Therapeutic cardiac interventions up to 7 days (MITT population) [a]

Intervention	N (%) patients		p-value
	Heparin N=5,033	Lepirudin N=5,045	
Any intervention, excluding cardiac cath.	**406 (8.1%)**	**340 (6.7%)**	**0.0109**
PCI	259 (5.1%)	212 (4.2%)	0.0248
CABG	96 (1.9%)	95 (1.9%)	0.9286
Thrombolysis	53 (1.1%)	36 (0.7%)	0.0686
Intra-aortic balloon pump	33 (0.7%)	33 (0.7%)	0.9923

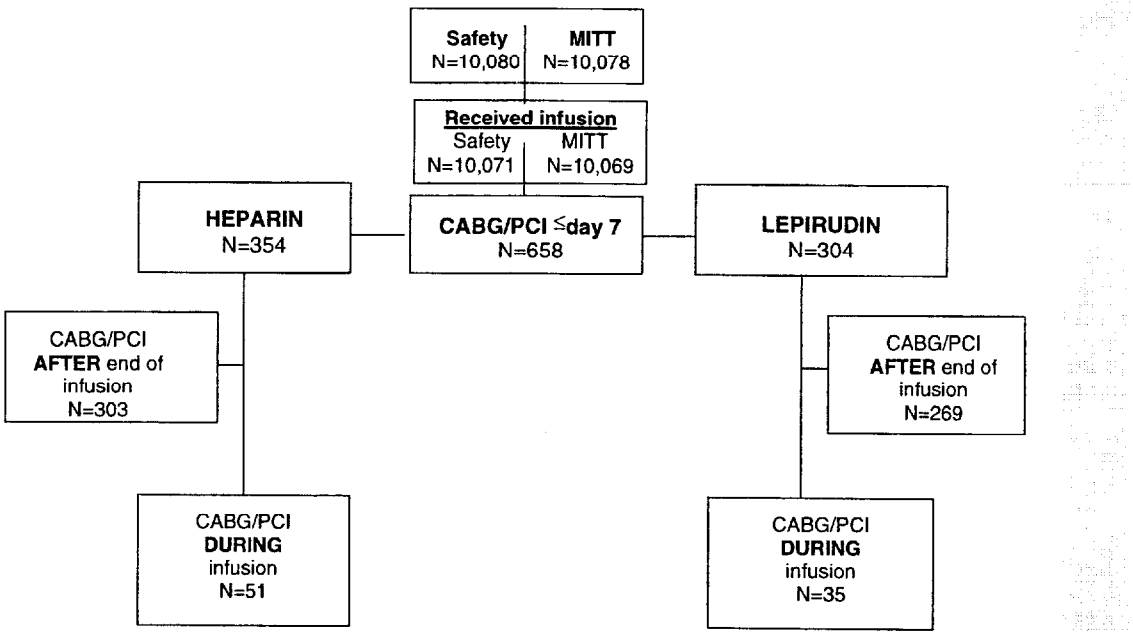
[a] For ITT results see Table 5 of Appendix A

It can be assumed that the majority of the early therapeutic interventions were probably symptom-driven and following thrombotic coronary events, while the majority of delayed/elective interventions were more likely to be anatomy-driven, i.e. due to the nature of the underlying disease.

After submission of the supplemental NDA, a *post hoc* analysis of the OASIS-2 data was performed to assess the clinical outcome in the patients undergoing PCI or CABG between the start and end of lepirudin infusion.

The following flowchart shows the numbers of patients undergoing PCI or CABG up to day 7, together with information on how many occurred during study infusion or after the end of study infusion (the numbers were the same for both the MITT population and the safety population; the corresponding flowchart for the ITT population is given in Figure 3 of Appendix A.).

OASIS-2: Numbers of patients undergoing PCI or CABG during or after end of study infusion



Fewer lepirudin than heparin patients underwent PCI or CABG up to day 7 (304 vs. 354 patients; p=0.0403), indicating a protective effect of lepirudin. Differences in favor of lepirudin were observed for interventions both before and after the end of study infusion. Only in 35 lepirudin and 51 heparin patients was the intervention performed during study infusion.

The **clinical outcome** in the patients with PCI or CABG during study infusion was as follows:

OASIS-2: Efficacy and safety up to 7 days in patients undergoing PCI or CABG during study infusion [a]

Endpoint	Heparin (N=51)			Lepirudin (N=35)		
	Total	Patients with event BEFORE intervention	AFTER intervention	Total	Patients with event BEFORE intervention	AFTER intervention
	N (%) [b]	N (%) [b]	N (%) [c]	N (%) [b]	N (%) [b]	N (%) [c]
Efficacy						
CV death/new MI	9 (17.6%)	5 (9.8%)	4 (8.7%)	2 (5.7%)	0	2 (5.7%)
CV death/new MI / ref. angina	16 (31.4%)	11 (21.6%)	5 (12.5%)	8 (22.9%)	6 (17.1%)	2 (6.9%)
Safety						
Minor bleed	14 (27.5%)	2 (3.9%)	12 (24.5%)	7 (20.0%)	1 (2.9%)	6 (17.6%)
Major bleed	0	0	0	0	0	0
Stroke	0	0	0	0	0	0

[a] For ITT results see Table 6 of Appendix A

[b] Denominator for percents includes all patients undergoing PCI or CABG.

[c] Denominator for percents excludes patients who had an event of the respective type prior to intervention.

Although the number of post-procedural events was small, it appears that lepirudin patients had lower 7-day event rates (double and triple composite endpoints) than heparin patients. The rate of minor

bleeds was also lower in the lepirudin group than in the heparin group. No major bleeds or strokes were observed. Thus, the results do not suggest an increased post-procedural safety risk for lepirudin patients.

4.2.2.8 Radiological evidence of heart failure

In the first 24 hours after randomization, slightly more lepirudin than heparin patients had radiological evidence of heart failure (2.9% vs. 2.5%; relative risk 1.18 [95% CI: 0.92–1.50], p=0.1987). However, the occurrence of heart failure within the first 24 hours is probably associated with the index episode of chest pain and is generally diagnosed based upon the first chest X-ray (which is usually prior to randomization). The underlying event in such cases could not have been prevented by the use of lepirudin or heparin.

In the prespecified period from day 2 to day 7, the incidence of radiological evidence of heart failure was significantly lower in lepirudin patients than in heparin patients (1.8% vs. 2.7%, relative risk 0.69 [95% CI: 0.52–0.90], p=0.0064). This may be reflective of the reduced rate of severe ischemic damage in lepirudin patients.

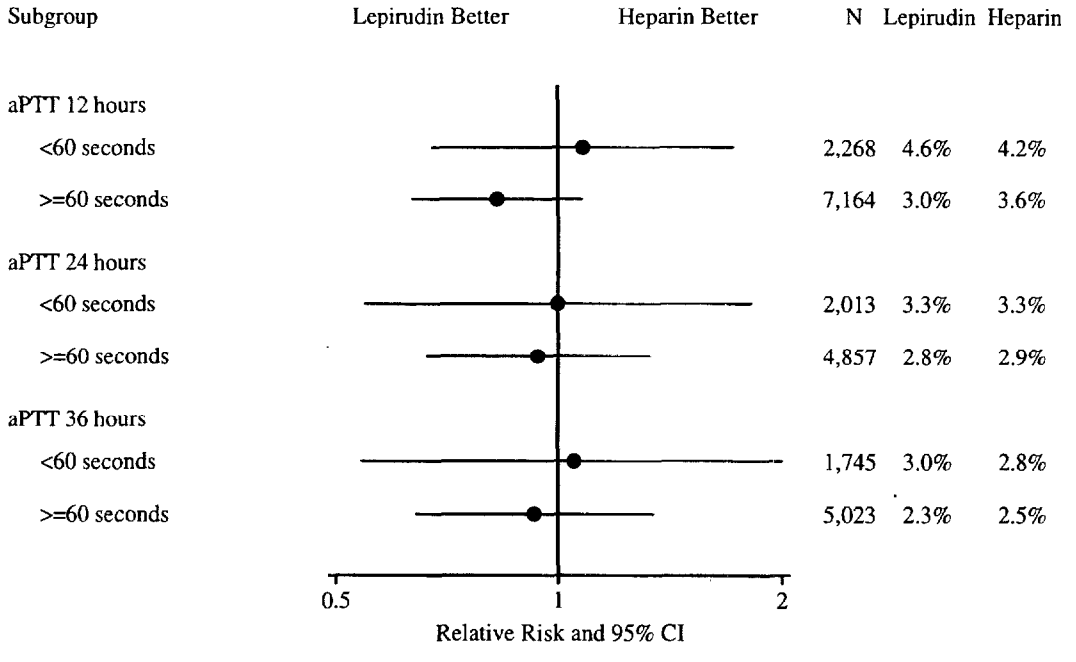
4.2.2.9 aPTT

Regardless of pre-study heparin status, mean baseline aPTT values were the same in both treatment groups (41 seconds). During the infusion period (from >3 to ≤72 hours), mean aPTT was maintained between 78 and 81 seconds in the lepirudin group. During the same period, aPTT fluctuated more in the heparin group, with mean aPTT values ranging from 71 to 92 seconds. Mean aPTT for heparin patients peaked at 92 seconds (between >3 and ≤6 hours after start of infusion) and gradually decreased to around 71 seconds between 12 and 24 hours after the start of the infusion.

The extent of coagulation in terms of aPTT values was much more stable and predictable in lepirudin patients. Fewer lepirudin patients required bi-directional dose adjustments, and the number of patients without any dose adjustments was much higher in the lepirudin group. On the other hand, premature termination of study medication due to aPTT out of range occurred in more lepirudin patients than heparin patients (for data see table in *Section 2.4*, page 13).

Subgroup analysis of the effect of aPTT on the primary efficacy outcome produced the following results:

OASIS-2: Influence of aPTT on CV death or new MI at 7 days (MITT population)



Treatment effect and aPTT were found to be correlated, with the strongest effects on CV death or new MI at 7 days seen in lepirudin patients with aPTT values of 60 seconds or more at 12 h, 24 h and 36 h after randomization.

4.2.2.10 Warfarin substudy analyses

A total of 3,793 (37%) patients were randomized in the warfarin substudy. 949 of 1,899 lepirudin patients and 963 of 1,894 heparin patients received warfarin. The remaining patients in each group received standard therapy.

The substudy recruitment rate was at least 30% lower than planned, and warfarin therapy was discontinued early in 39% of warfarin patients (irrespective of lepirudin/heparin randomization).

Coupled to the problem of low recruitment, there was some evidence of bias in the selection of patients for the warfarin randomization. The decision to include patients in the warfarin randomization was largely based on the physician's assessment of a patient's suitability for inclusion. Patients who had died could not, of course, be included in the randomization, and patients with an efficacy endpoint or those in a poor physical condition were more likely to be scheduled for surgery or to be considered unsuitable for randomization. Consequently, it was possible that the patients included in the warfarin randomization would comprise a subset of patients with a better prognosis than those excluded from the randomization.

This was found to have occurred. Generally, patients in the warfarin substudy had lower event rates for the double and triple composite endpoints than those who were not randomized into the substudy (e.g. double endpoint at 7 days: 2.5% and 2.7% for the warfarin and standard therapy groups respectively compared with 4.8% for patients excluded from randomization). These differences were much more pronounced than any differences between warfarin and standard therapy or among the four strata in the warfarin substudy.

Subgroup analyses revealed no indication of treatment effect inconsistency across the warfarin subgroups.

OASIS-2: Influence of warfarin on CVD/MI at 7 days (MITT population)

Subgroup	N (%) patients with events				Relative risk	p-value [a]
	Heparin		Lepirudin			
Warfarin	27/963	(2.8%)	20/949	(2.1%)	0.75	0.9617
Standard therapy	27/931	(2.9%)	24/950	(2.5%)	0.87	
No warfarin available	38/843	(4.5%)	36/876	(4.1%)	0.91	
Not randomized	119/2296	(5.2%)	98/2270	(4.3%)	0.83	

[a] Test for consistency of treatment effect across subgroup levels

The treatment benefit of lepirudin over heparin was apparent in all warfarin subgroups, with no indication of any inconsistency of the effect across the subgroups. Also, the numbers randomized to the warfarin substudy were exactly balanced between the treatment groups (37.6% in both groups). Had there been an early lepirudin-heparin treatment effect that led to patient differences between treatments in those randomized to the warfarin substudy, one would have expected some imbalance in the numbers randomized to the warfarin substudy between the two groups.

Based on these analyses, it seems highly unlikely that the selection process for the warfarin randomization or warfarin as a medication had an impact on the rate of the primary outcome up to 7 days.

4.3 OASIS-1&2 combined results

Analyses of the double and triple composite endpoints were also performed on the combined data from the OASIS studies in order to investigate the treatment effects of lepirudin in a population even larger than that offered by OASIS-2 alone.

Although pooling of the OASIS-1 and OASIS-2 data was **not** prespecified in the OASIS-2 SAP, the following arguments are considered to justify the combined analyses of the results:

- similarity of the principal design elements, such as inclusion and exclusion criteria, treatment and monitoring regimens, endpoint definitions, timing of endpoint assessments,
- direct access to the individual patient data from both studies, and
- the combined analysis was not performed as primary, but as a supportive analysis in order to make full use of all available data.

The possibility of performing these supportive analyses was discussed with the FDA at pre-NDA meetings on February 26, 1998 and February 24, 1999. The FDA considered it acceptable to perform the analyses and to include them in the *Integrated Summary of Effectiveness*.

For the purpose of the combined efficacy analyses, the results of the two lepirudin dose regimens tested in OASIS-1 were pooled. This approach was taken to provide a conservative estimate of the medium-dose lepirudin efficacy, while using the maximum information available. The estimate is conservative since the efficacy of low-dose lepirudin can be assumed to be the same or less than medium-dose lepirudin, and thus the efficacy of the combined lepirudin OASIS-1 arms is a lower-bound OASIS-1 estimate for the medium-dose lepirudin efficacy.

The results of the combined analysis were as follows:

OASIS-1&2 combined results (MITT populations) [a]

Composite endpoint Time period	N (%) patients with events Heparin N=5,404	 Lepirudin N=5,583	Absolute benefit (%)	Rel. risk reduction (%)	p-value
CV death or new MI [b]					
72 hours	142 (2.6%)	108 (1.9%)	-0.69	27	0.0132
7 days	229 (4.2%)	192 (3.4%)	-0.80	20	0.0268
35 days	408 (7.5%)	369 (6.6%)	-0.94	14	0.0434
End of study [b]	582 (10.8%)	560 (10.0%)	-0.74	8	0.1813
CV death, new MI or refractory angina [c]					
72 hours	214 (4.0%)	166 (3.0%)	-0.99	26	0.0039
7 days	360 (6.7%)	299 (5.4%)	-1.31	21	0.0043
35 days	714 (13.2%)	672 (12.0%)	-1.18	10	0.0769
End of study [b]	1,105 (20.4%)	1,076 (19.3%)	-1.18	6	0.1827

[a] For ITT results see Table 7 of Appendix A

[b] Corrected for study and center within study

[c] 120 days in OASIS-1b and 180 days in OASIS-1a and OASIS-2

In the combined analyses, lepirudin was clearly more effective than heparin in the treatment of ACS.

Like in the individual studies, the differences in favor of lepirudin were predominantly obtained during the treatment period and were well preserved over time up to the end of study. For the double composite endpoint of CV death or new MI, the effect of lepirudin remained significantly superior to that of heparin at all timepoints up to 35 days. For the triple composite endpoint of CV death, new MI, or refractory angina, the effect of lepirudin over heparin remained highly significant up to 7 days and was borderline significant up to 35 days. For both composite endpoints, the absolute benefit of lepirudin was clearly maintained up to the end of the study, indicating durability of the results over time.

An alternate approach is to combine the two studies but excluding the OASIS-1 low-dose lepirudin arm. As seen in the following table, the results are highly similar:

OASIS-1&2 combined results, excluding low-dose lepirudin group from OASIS-1 (MITT populations) [a]

Composite endpoint Time period	N (%) patients with events Heparin N=5,404	Lepirudin N=5,312	Absolute benefit (%)	Rel. risk reduction (%)	p-value
CV death or new MI [a]					
72 hours	142 (2.6%)	104 (2.0%)	-0.67	27	0.0174
7 days	229 (4.2%)	185 (3.5%)	-0.75	19	0.0355
35 days	408 (7.5%)	354 (6.7%)	-0.89	13	0.0577
End of study [b]	582 (10.8%)	540 (10.2%)	-0.60	7	0.2358
CV death, new MI or refractory angina [a]					
72 hours	214 (4.0%)	159 (3.0%)	-0.97	26	0.0043
7 days	360 (6.7%)	287 (5.4%)	-1.26	21	0.0044
35 days	714 (13.2%)	652 (12.3%)	-0.94	9	0.0906
End of study [b]	1,105 (20.4%)	1,051 (19.8%)	-0.66	6	0.2213

[a] Corrected for study and center within study

[b] 120 days in OASIS-1b and 180 days in OASIS-1a and OASIS-2

4.4 OASIS-1&2 in the perspective of other hirudin trials

4.4.1 Characteristics of hirudins

Apart from lepirudin, the most widely studied recombinant hirudin is desirudin. The two compounds have very similar characteristics (lepirudin: original NDA; desirudin: [18, 50]):

Characteristics of lepirudin and desirudin

Characteristic	Lepirudin	Desirudin
Active substance	[Leu^1,Thr^2]-63-desulfohirudin	[Val^1,Val^2]-63-desulfohirudin
Source	*Saccharomyces cerevisiae*	*Saccharomyces cerevisiae*
No. of disulfide bridges	3	3
Molecular weight	6,979.5 Dalton	6,963 Dalton
Isoelectric point (pI)	3.7	3.8-4.3
Inhibition constant (K_i)	118 fM	237 fM
Specific activity	16,000 ATU[a]/mg	18,000 ATU[a]/mg
Systemic clearance	160-254 mL/min	146-189 mL/min
Distribution volume V_{ss} [b]	13.3-22.4 liters	14.7-17.5 liters
Terminal half-life $t_{1/2\beta}$ [b]	0.8-1.6 h	2.1 h

[a] Antithrombin units [b] After single dose IV application

The slight differences in specific activity and terminal half-life may be of potential clinical relevance. However, a study performed in 1993 using a standardized assay procedure showed that the specific activities of natural hirudin and four recombinant hirudins (including lepirudin and desirudin) from four different manufacturers were similar [51]. Thus, the differences in the specific activities of lepirudin and desirudin may be assay-related rather than compound-specific. In contrast, the longer terminal half-life of desirudin may be associated with higher steady-state plasma concentrations at the same infusion dose of desirudin as compared with lepirudin.

4.4.2 Data from other hirudin trials

In order to identify any additional pertinent information on the use of hirudins in ACS, a systematic literature survey was performed using the search terms "hirudin, lepirudin, HBW 023, desirudin, and CGP 39393" and "unstable angina/acute coronary syndromes". A total of 82 publications were found for the period from January 1990 to May 1999. Among these, there were only four original reports from clinical studies of hirudins other than lepirudin; all these studies investigated desirudin:

- the GUSTO-2a study [48]
- a study by Topol *et al.* [52]
- the HELVETICA study [53]
- the GUSTO-2b study [49]

Only GUSTO-2b was considered to be suitable for comparison with the OASIS studies. The reasons for not considering the other 3 studies were early termination due to increased risk of intracerebral bleeding (GUSTO-2a), small size (N=166, Topol et al.), and PTCA study (HELVETICA).

4.4.3 Comparison of combined OASIS studies with GUSTO-2b non-ST

The study most comparable to the OASIS studies is GUSTO-2b, and in particular, its pre-specified stratum of 8,011 patients without ST elevation (hereafter referred to as GUSTO-2b non-ST).

The desirudin dosage tested in GUSTO-2b (bolus 0.1 mg/kg, infusion 0.1 mg/kg/hour) was similar to the low dose of lepirudin investigated in OASIS-1. However, there are three factors to consider in comparing the initial doses of desirudin and lepirudin: (1) due to the slight differences in the half-lives of the two compounds (see above), the differences in the resulting hirudin plasma concentrations were probably smaller than one would expect from only considering the doses; (2) both programs used similar aPTT-based monitoring and dosage adjustment guidelines; and (3) the treatment duration was 3 – 5 days in GUSTO-2b non-ST, as compared with 72 hours in OASIS-1 and OASIS-2. Therefore, the 0.1 mg/kg/hour infusion dose regimen of desirudin may have been roughly equivalent to the 0.15 mg/kg/hour rather than the 0.1 mg/kg/hour infusion dose regimen of lepirudin. Other pivotal elements of the studies were very similar, except that no information on refractory angina was collected in GUSTO-2b non-ST.

Analyses have been performed to compare the main efficacy data from the three studies. The possibility of supplying such *post hoc* supportive analyses was discussed and agreed upon with the FDA at pre-NDA meetings on February 26, 1998 and February 24, 1999.

As for the combined OASIS-1&2 analyses described in *Section 4.3* (page 37), the data for the two lepirudin dose regimens from OASIS-1 were pooled in these analyses. Furthermore, to match the GUSTO-2b non-ST analyses as closely as possible, the ITT populations of the OASIS studies and the composite endpoint of all-cause death or new MI were used in the comparisons. The results are shown in the following table:

OASIS-1&2 and GUSTO-2b non-ST: All-cause death or new MI (ITT populations)

Time period Study/Analysis	N (%) patients with events Heparin	Hirudin	Absolute benefit (%)	Rel. risk reduction (%)	p-value
72 hours					
OASIS-1&2 (N=11,050) [a]	144 (2.7%)	112 (2.0%)	-0.66	25	0.0224
GUSTO-2b non-ST (N=8,011)	169 (4.2%)	126 (3.2%)	-1.05	26	0.0124
Combined (N=19,061) [a]	313 (3.3%)	238 (2.5%)	-0.84	26	0.0007
7 days					
OASIS-1&2 [a]	232 (4.3%)	196 (3.5%)	-0.79	19	0.0336
GUSTO-2b non-ST	262 (6.5%)	216 (5.4%)	-1.11	18	0.0353
Combined [a]	494 (5.2%)	412 (4.3%)	-0.94	18	0.0028
30/35 days					
OASIS-1&2 [a]	419 (7.7%)	377 (6.7%)	-1.01	14	0.0400
GUSTO-2b non-ST	366 (9.1%)	332 (8.3%)	-0.80	10	0.2050
Combined [a]	785 (8.3%)	709 (7.4%)	-0.94	12	0.0179

[a] Corrected for study (OASIS-1, OASIS-2 and GUSTO-2b non-ST)

As indicated in the table, the results of GUSTO-2b non-ST were highly consistent with those of the OASIS-1&2 analysis, confirming the benefit of hirudin vs. heparin. The relative risk reductions for the composite endpoint of all-cause death or new MI in OASIS-1&2 and in GUSTO-2b non-ST were 25% and 26% up to 72 hours, and 19% and 18% up to 7 days, respectively.

In a combined analysis of OASIS-1&2 and GUSTO-2b non-ST, there was a highly significant benefit of hirudin over heparin for the composite endpoint of all-cause death or new MI up to 72 hours (relative risk reduction 26%; p=0.0007), 7 days (relative risk reduction 18%; p=0.0028), and 30/35 days (relative risk reduction 12%; p=0.0179). The absolute treatment benefit that was observed at 72 hours (–0.84%) was fully preserved up to 30/35 days (–0.94%).

4.5 Comparison of hirudin with alternative products

The field of ACS has been studied extensively over the last few years. Apart from hirudin and other direct thrombin inhibitors, there has been special interest in the classes of low-molecular-weight (LMW) heparins and glycoprotein (GP) IIb/IIIa inhibitors. The LMW heparins enoxaparin [43, 44], dalteparin [42] and nadroparin [47], and the GP IIb/IIIa inhibitors eptifibatide [54], tirofiban [45, 46] and lamifiban [55] have been investigated in large cohorts of conservatively managed patients. Enoxaparin, dalteparin, eptifibatide and tirofiban have recently been approved for the treatment of ACS in the United States and/or Europe.

The supplemental NDA for lepirudin presented limited comparisons to put the hirudin results into perspective with recent drug approvals and results in other drug developments. This section of the briefing document presents more extensive information on this topic and presents the findings graphically to facilitate interpretation.

The presentations focus on comparisons of hirudin with data from the main trials of alternative products for medical management of ACS. Abciximab (ReoPro®) is not included in the comparisons because the trials with that drug have been performed primarily in an interventional setting.

4.5.1 Comparison of primary endpoints across ACS studies

The following table summarizes information regarding the types of primary efficacy endpoints used in the OASIS studies in comparison with those of the large published studies testing desirudin, LMW heparins and GP IIb/IIIa inhibitors versus unfractionated heparin in conservatively managed patients with ACS.

Comparison of primary efficacy endpoints across ACS studies

Study	Lit Ref.	No. of pats.	Primary endpoint	
			Type[a]	Time
Lepirudin				
OASIS-1		909	Quadruple	7 days
OASIS-2		10,141	Double	7 days
Desirudin				
GUSTO-2b non-ST	[49]	8,011	Double	30 days
Enoxaparin				
ESSENCE	[43]	3,171	Triple	14 days
TIMI-11B	[44]	3,910	Triple	43 days
Dalteparin				
FRIC	[42]	1,482	Triple	6 days
Nadroparin				
FRAX.I.S	[47]	3,468	Quadruple	14 days
Eptifibatide				
PURSUIT	[54]	10,948	Double	30 days
Tirofiban				
PRISM	[45]	3,232	Triple	48 hours
PRISM-PLUS	[46]	1,915	Triple	7 days
Lamifiban				
PARAGON A	[55]	2,282	Double	30 days

[a] "Double" = (CV) death/MI, "Triple" = (CV) death/MI + one angina component, "Quadruple" = (CV) death/MI + two angina components.

[b] At least one statistically significant finding in favor of the investigational drug at a published timepoint ≤35 days. "+" denotes significant finding.

Only 4 out of the 11 studies reviewed (OASIS-2, GUSTO-2b non-ST, PURSUIT, PARAGON A) used the double composite of (CV) death and MI as the primary endpoint. All other studies except OASIS-1 and FRAX.I.S used a triple composite as the primary endpoint. The definition of the quadruple composite endpoint used in OASIS-1 is comparable to that of most of the triple composite endpoints used in the LMW heparin and GP IIb/IIIa inhibitor studies. The definition of the triple

composite endpoint used as the key secondary outcome at 7 days in OASIS-2 was more stringent than that used in most of the other trials.

The timing of the primary endpoint assessment varied between 48 hours (PRISM) and 43 days (TIMI-11B). Seven studies assessed the primary endpoint prior to 30 days.

4.5.2 Comparison of relative risks across ACS studies

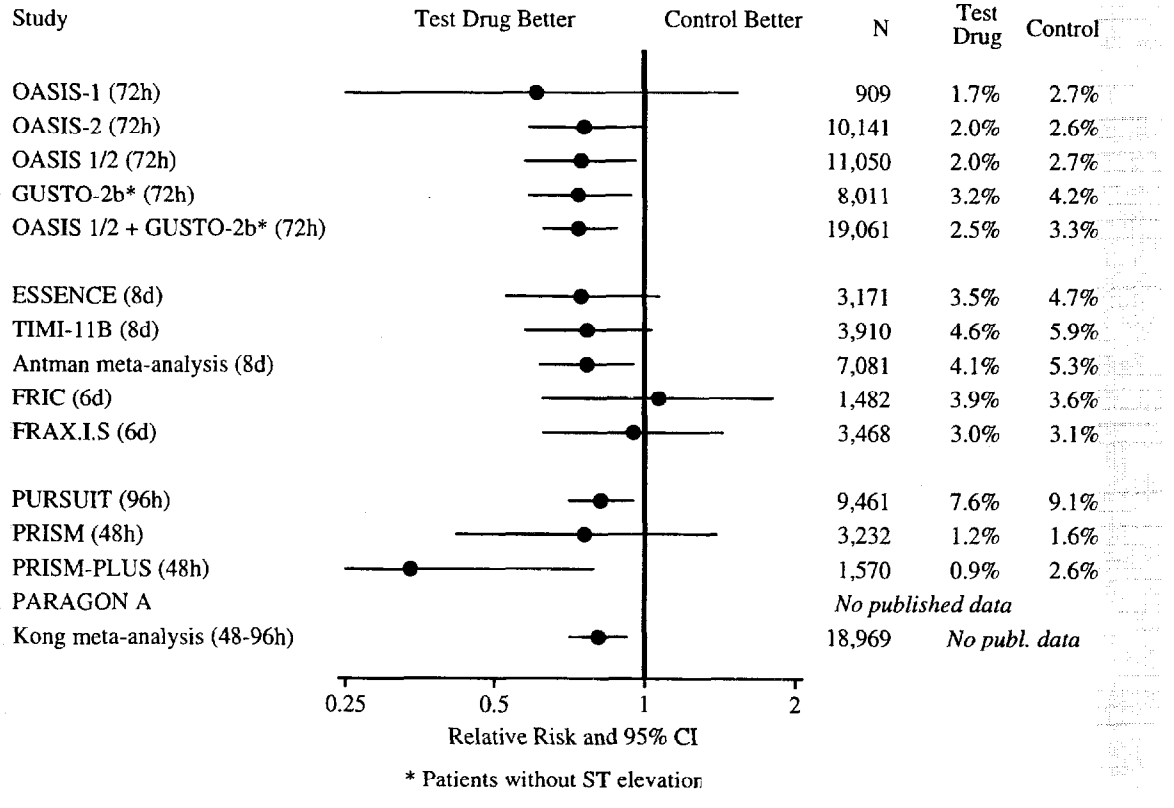
In order to overcome the limitations due to different endpoints (double, triple, quadruple) and timepoints across ACS studies, we have attempted to put the OASIS data into perspective with the other trials by comparing the incidence of all-cause death or MI at two given timepoints: at or around the end of treatment and at about 35 days.

In addition to comparing the individual hirudin, LMWH and GP IIb/IIIa inhibitor studies, our investigations included the findings of the meta-analyses performed on the OASIS and GUSTO-2b non-ST data, the findings of the meta-analysis of ESSENCE and TIMI-11B by Antman [56] and the findings of the meta-analysis of GP IIb/IIIa trials by Kong [57].

The findings were as shown in the following graphs.

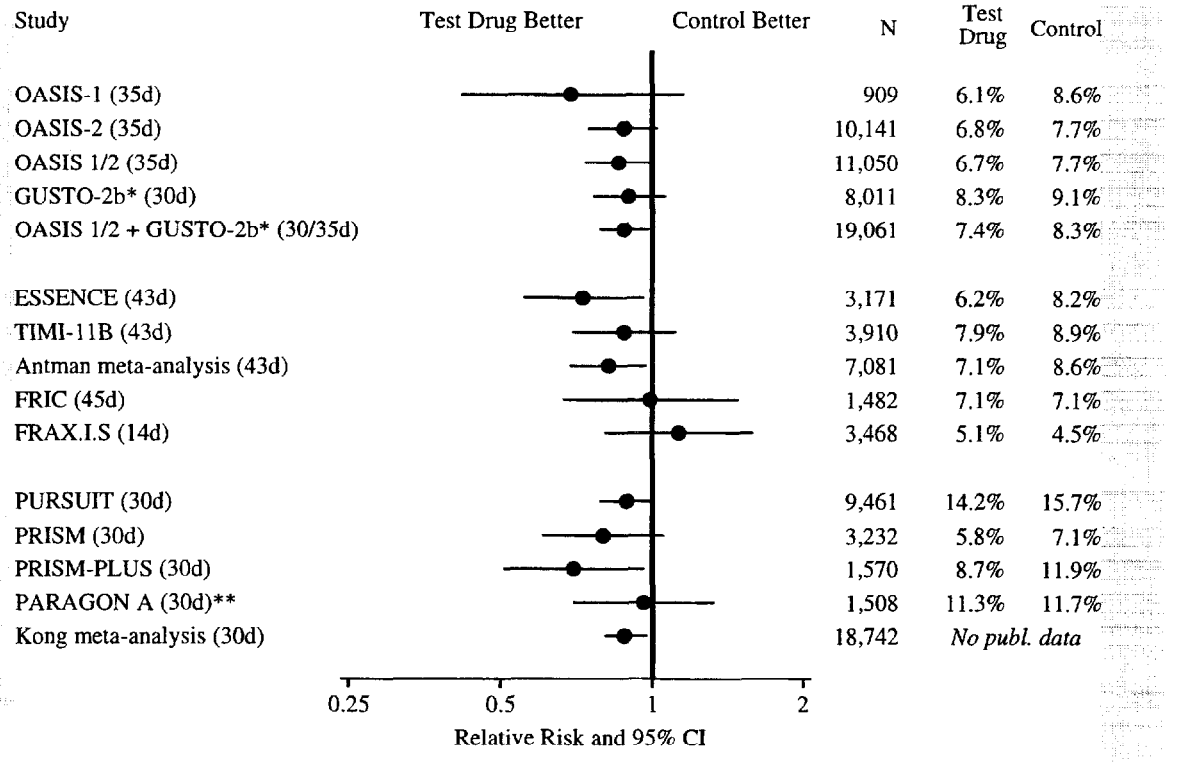
The rates of all-cause death or MI in the OASIS studies at or close to the end of treatment were at the lower end of the range observed across the trials at this timepoint. Overall, it appears that the treatment effects of lepirudin were comparable to those of LMW heparins and GP IIb/IIIa inhibitors.

All-cause death or MI at or close to the end of treatment in ACS studies



* Patients without ST elevation

All-cause death or MI at around 35 days in ACS studies



* Patients without ST elevation. ** Excluding patients that received lamifiban alone