6. THE SAFETY OF LEPIRUDIN

As patients treated with thrombin inhibitors are at an increased risk of hemorrhagic adverse events (AEs), the main area of possible safety concern with lepirudin is the occurrence of minor and major bleeds, especially intracranial or other life-threatening bleeds. In ACS, the initial 7-day period can be considered the most important for the safety of lepirudin because patients are treated with the drug for 72 hours, and the half-life of the drug is only about 1 hour.

6.1 Design aspects

Both OASIS studies placed particular emphasis on the collection of information on major and minor bleeds and stroke. Information on bleeds and stroke was collected throughout the trials. The following specific definitions were used:

- A **major bleed** was defined in the study protocols as any bleed that was fatal, life-threatening (in the opinion of the investigator), permanently or significantly disabling, required transfusion of 2 or more units of packed red blood cells or equivalent, or required surgical intervention. In addition, all intracranial bleeds (including all strokes of uncertain type) were classified as major bleeds in the analyses.
  Before CCC unblinded the OASIS-2 database, they recognized, however, that the investigators had sometimes specified "life-threatening" as the only criterion for major bleed, although the bleeding event itself was not intracranial, did not require surgical intervention or transfusion, nor did it lead to a drop in hemoglobin.
  Therefore, for the analyses, CCC introduced a new, objective definition of life-threatening bleed, which included all fatal bleeds, intracranial bleeds, and bleeds requiring surgical intervention or transfusion of ≥4 units of blood or blood products. The cut-off for transfusion (≥4 units) in this definition corresponds well with the cut-off for hemoglobin (drop by ≥5 g/dL) in the widely used TIMI definition of major bleed [64]. CCC informed the sponsor of this new definition only when they supplied the summary preliminary OASIS-2 results on June 27, 1998 (i.e. after finalization of the OASIS-2 SAP). The new, objective definition of "life-threatening bleed" is applied in the presentation of bleeding events in the OASIS-1 and OASIS-2 study reports, in the summary documents accompanying the efficacy supplement, and in this briefing document.
- A **minor bleed** was any bleed that did not meet the criteria for major bleed.
- **Stroke** was defined in the protocols as the presence of a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting >24 hours. All strokes were classified as hemorrhagic, ischemic or type uncertain. For the analyses, strokes of uncertain type were further considered to be intracranial bleeds, in order to avoid any potential under-estimation of the rate of intracranial bleeds.

All major bleeds and strokes were to be adjudicated by the blinded Adjudication Committee of each study. The adjudication results were binding for the final analyses.

Comprehensive information on AEs was collected over the entire study period in OASIS-1. OASIS-2 focused on the initial 7-day period for the collection of AEs: from randomization up to 7 days, all serious AEs and all unexpected non-serious AEs were to be documented; beyond day 7, information was to be recorded only for fatal AEs and unexpected serious AEs possibly related to study medication.

Consistent with the approach to the collection of safety data, the analyses of the safety of lepirudin focus primarily on the findings for major and minor bleeds and stroke. In addition, the overall profile of serious AEs and other events of interest is addressed. In general, the acute on-treatment and immediate post-treatment period from randomization to day 7 is considered separately from the later time periods as this is the most important period for the safety of lepirudin. The data is presented separately for each study, since the OASIS-2 data dominates the safety presentations. The small number of major bleeds in OASIS-1 (a total of only 9 events and no difference between the treatment groups) could not outweigh the difference between the treatments in OASIS-2. This approach to the safety presentations is in agreement with a request by the FDA.

6.2 Major and minor bleeds

6.2.1 OASIS-1

The incidence of bleeding episodes over time in OASIS-1 was as follows:

OASIS-1: Major and minor bleeds (Safety population)

Time period / Bleeding type	N (%) patients with events		
	Heparin N=369	Low-dose lepirudin N=270	Medium-dose lepirudin N=265
Any bleed	**72 (19.5%)**	**67 (24.8%)**	**84 (31.7%)**
Randomization to 7 days	**41 (11.1%)**	**46 (17.0%)**	**59 (22.3%)**
Minor bleed	39 (10.6%)	44 (16.3%)	57 (21.5%)
Major bleed	4 (1.1%)	2 (0.7%)	3 (1.1%)
Fatal	0	0	1 (0.4%)
Life-threatening [a]	3 (0.8%)	2 (0.7%)	2 (0.8%)
8 days to 35 days	**21 (5.7%)**	**21 (7.8%)**	**20 (7.5%)**
Minor bleed	19 (5.1%)	20 (7.4%)	19 (7.2%)
Major bleed	3 (0.8%)	1 (0.4%)	2 (0.8%)
36 days to end of study	**20 (5.4%)**	**10 (3.7%)**	**16 (6.0%)**
Minor bleed	16 (4.3%)	9 (3.3%)	15 (5.7%)
Major bleed	5 (1.4%)	1 (0.4%)	2 (0.8%)

[a] Includes all fatal bleeds, intracranial bleeds, and bleeds requiring surgical intervention or transfusion of ≥4 units of blood or blood products

During the course of the study, more lepirudin patients than heparin patients experienced bleeding episodes (24.8% low-dose vs. 31.7% medium-dose vs. 19.5% heparin).

The majority of the bleeds and the largest differences between the treatment groups were observed in the period from randomization to 7 days. In this period, nearly all the bleeds were minor, with higher incidences of minor bleeds in both lepirudin groups than in the heparin group. The highest incidence of minor bleeds was in the medium-dose lepirudin group. The major bleeding rate, including fatal and life-threatening bleeds, was low and similar across the three treatment groups.

Between 8 days and 35 days and between 36 days and the end of the study, the extent of bleeding was considerably lower than in the period up to 7 days and was similar in all three treatment groups.

6.2.2 OASIS-2

The incidence of bleeding episodes over time in OASIS-2 was as follows:

OASIS-2: Major and minor bleeds (Safety population)

Time period Bleeding type	N (%) patients with events Heparin N=5,033	 Lepirudin N=5,047	Relative risk (95% CI)	p-value
Any bleed	**549 (10.9%)**	**721 (14.3%)**	**1.36 (1.21–1.53)**	**0.0001**
Randomization to 7 days	**260 (5.2%)**	**441 (8.7%)**	**1.76 (1.50–2.06)**	**0.0001**
Minor bleed	226 (4.5%)	389 (7.7%)	1.78 (1.50–2.10)	0.0001
Major bleed	37 (0.7%)	60 (1.2%)	1.62 (1.08–2.44)	0.0243
Fatal	4 (0.1%)	3 (0.1%)	—	0.7261
Life-threatening (objective)[a]	22 (0.4%)	21 (0.4%)	—	0.8800
Life-threatening (subjective)	12 (0.2%)	23 (0.5%)	—	0.0890
Non-life-threatening	15 (0.3%)	40 (0.8%)	—	0.0010
Intracranial	3 (0.1%)	2 (0.0%)	—	0.6870
Surgery required	7 (0.1%)	8 (0.2%)	—	1.0000
Transfusion ≥2 units	25 (0.5%)	45 (0.9%)	—	0.0220
Disabling	6 (0.1%)	16 (0.3%)	—	0.0522
8 days to 35 days	**204 (4.1%)**	**206 (4.1%)**	**1.01 (0.83–1.23)**	**0.9598**
Minor bleed[b]	160 (3.2%)	164 (3.2%)	1.02 (0.82–1.28)	0.8655
Major bleed	52 (1.0%)	50 (1.0%)	0.96 (0.65–1.42)	0.8429
36 days to 180 days	**153 (3.0%)**	**161 (3.2%)**	**1.05 (0.84–1.32)**	**0.6883**
Minor bleed[b]	121 (2.4%)	118 (2.3%)	0.97 (0.75–1.26)	0.8445
Major bleed	35 (0.7%)	45 (0.9%)	1.28 (0.83–2.00)	0.3124

[a] Includes all fatal bleeds, intracranial bleeds, and bleeds requiring surgical intervention or transfusion of ≥4 units of blood or blood products

[b] Includes only spontaneously reported minor bleeds. Investigators were not required to report minor bleeds after day 7.

During the course of the study, more lepirudin patients than heparin patients experienced bleeding episodes (14.3% vs. 10.9%; p=0.0001). The period from randomization to 7 days accounted for the majority of bleeds and most of the difference between the treatment groups (8.7% vs. 5.2%). A time-to-event analysis for major bleeds indicated that most of the difference up to 7 days emerged from the treatment period up to 72 hours. Between 8 days and the end of the study, the extent of bleeding was considerably lower than in the period up to 7 days and was similar in both treatment groups.

In both groups, most bleeds up to 7 days were minor, but there were more such bleeds on lepirudin (relative risk 1.78 [95% CI: 1.50-2.10]; p=0.0001). Although there were also significantly more major bleeds on lepirudin (relative risk 1.62 [95% CI: 1.08-2.44]; p=0.0243), the absolute incidence of major bleeds was low. The numbers of bleeds that were fatal, life-threatening, intracranial or required surgical intervention were very low and almost identical in both groups. Among the intracranial bleeds, there were 2 strokes of uncertain type in each group and one hemorrhagic stroke

in the heparin group (see *Section 6.3.2,* page 57). The majority of major bleeds were managed with transfusions.

Thus, the higher incidence of bleeds in the lepirudin group in the period up to 7 days can be attributed almost entirely to higher rates of minor bleeds and non-life-threatening, clinically manageable major bleeds. It is possible that discontinuation of the lepirudin infusion in case of bleeding may be an effective measure to prevent progression to life-threatening bleeding. This was recommended by the OASIS study protocols and was reflected in the higher proportion of patients with premature termination of study medication due to hemorrhagic adverse events in the lepirudin group (2.6% for lepirudin vs. 1.1% for heparin; see *Section 6.4.2,* page 59).

Source of bleeding. In all three study time periods, the most common sources of major bleeding were gastrointestinal, surgical or other, not classified. The following table summarizes the data for the period up to 7 days in more detail:

OASIS-2: Most common sources of major bleeding at 7 days (Safety population)

Bleed source	Heparin N=5,033		Lepirudin N=5,047	
Any major bleed	37	(0.7%)	60	(1.2%)
Gastrointestinal	11	(0.2%)	27	(0.5%)
Hematuria	3	(0.1%)	8	(0.2%)
Other	10	(0.2%)	8	(0.2%)
Hemoptysis	0		3	(0.1%)
Puncture site	3	(0.1%)	3	(0.1%)
Retroperitoneal	2	(0.0%)	4	(0.1%)
Surgical	8	(0.2%)	7	(0.1%)

The small contribution of puncture site bleeds to the overall number of major bleeds up to 7 days is likely to be due to the relatively low rates of cardiac intervention in that period.

The most common sources of minor bleeding on lepirudin in the period up to 7 days were puncture sites (1.9% vs. 1.7% on heparin), hematuria (1.9% of patients vs. 0.6% on heparin), and epistaxis (1.3% vs. 0.6% on heparin).

Correlation between aPTT and the risk of bleeding. More lepirudin than heparin patients discontinued the study infusion due to out-of-range aPTT levels (6% vs. 3%). In an exploratory analysis, the potential correlation between aPTT and the risk of bleeding was investigated.

When the median of aPTT values prior to any bleed (75 seconds) was compared with the median of all aPTT values during study treatment of patients without bleed (74 seconds), no difference was found. However, when aPTT categories (<60 sec, 60-100 sec, and >100 sec) were compared, it was found that the proportion of patients with aPTT values >100 sec was higher among patients with major bleeds (heparin: 9.5%, lepirudin: 20.5%) than among patients without major bleed (heparin: 3.1%, lepirudin: 5.9%). The finding was more pronounced in the lepirudin than in the heparin group. Since the number of major bleeds was relatively low, the conclusions that can be drawn from this observation are rather limited. However, this finding seems to indicate that an upper limit of the therapeutic aPTT range of 100 seconds may be clinically useful.

6.2.3 Comparison with alternative products

The supplemental NDA for lepirudin presented limited comparisons to put the hirudin bleeding 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.

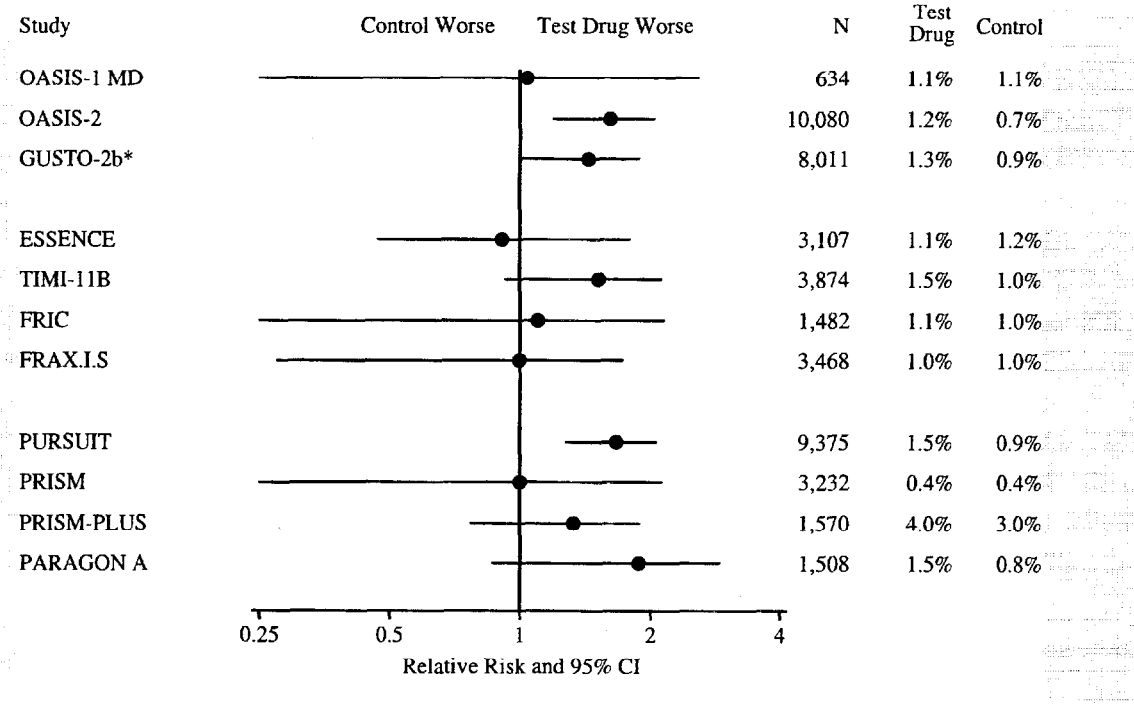
In order to assess the relevance of the bleeding findings with lepirudin, we compared the OASIS data with published bleeding data from large-scale studies investigating LMW heparins and GP IIb/IIIa inhibitors for conservative management of ACS. As the studies differ substantially with respect to bleeding definitions and other crucial characteristics (e.g. treatment duration, route of administration, observation period for safety events, baseline characteristics of the patients, rates of invasive procedures), the comparisons focus on the relative risks for bleeding (test drug vs. control) at or a few days after the end of treatment.

The bleeding risk at or a few days after the end of treatment can be considered to most reliably and closely reflect potential treatment effects. For drugs with a short half-life, bleeding events that occur at a later time most probably constitute noise and tend to dilute the relative bleeding risk.

For the published studies, the data shown are the data corresponding most closely to the definitions of "major bleeding" as used in the OASIS program.

The following figure indicates that the low absolute incidences of major bleeding in the OASIS studies were consistent with the respective rates reported from other ACS studies. Similarly, there was an increase in the relative risk of major bleeding across most of the studies and compounds tested.

Relative risk of major bleeding in ACS studies



* Patients without ST elevation

6.2.4 Conclusions

Treatment with lepirudin in the OASIS studies was associated with a significant excess of bleeding events up to 7 days that was almost exclusively accounted for by an excess of minor bleeding events and non-life-threatening, clinically manageable major bleeding events. The overall incidence of major bleeding was low. Importantly, there was no difference in the rate of life-threatening bleed between treatments, and no hemorrhagic strokes occurred in the lepirudin groups of the OASIS studies during the critical first 7 days.

The bleeding risk associated with the use of lepirudin was found to be comparable with that of other highly active antithrombotic compounds already approved for the treatment of ACS.

6.3 Stroke

6.3.1 OASIS-1

The incidence of stroke was low and similar across treatment groups in all periods in OASIS-1:

OASIS-1: Stroke (Safety population)

Time period	N (%) of patients with events		
	Heparin	Low-dose lepirudin	Medium-dose lepirudin
	N=369	N=270	N=265
Any stroke	**5 (1.4%)**	**4 (1.5%)**	**5 (1.9%)**
Randomization to 7 days	1 (0.3%)	1 (0.4%)	1 (0.4%)
8 days to 35 days	2 (0.5%)	2 (0.7%)	1 (0.4%)
36 days to end of study	2 (0.5%)	1 (0.4%)	3 (1.1%)

None of the strokes were hemorrhagic. The majority of the strokes reported were classified as ischemic (9 cases), the remainder as "type uncertain" (5 cases). Three patients died as a result of ischemic stroke (2 heparin patients between 8 days and 35 days; 1 low-dose lepirudin patient after day 35).

6.3.2 OASIS-2

The incidence of stroke over time in OASIS-2 was as follows:

OASIS-2: Stroke (Safety population)

Time period Stroke type	N (%) patients with events Heparin N=5,033	 Lepirudin N=5,047	Relative risk (95% CI)	p-value
Cumulative occurrence				
7 days	14 (0.3%)	14 (0.3%)	1.00 (0.47–2.09)	1.0000
35 days	30 (0.6%)	41 (0.8%)	1.37 (0.85–2.19)	0.2335
180 days	58 (1.2%)	72 (1.4%)	1.24 (0.88–1.76)	0.2511
Occurrence by time period				
Randomization to 7 days	**14 (0.3%)**	**14 (0.3%)**	**1.00 (0.47–2.09)**	**1.0000**
Hemorrhagic stroke	1 (0.0%)	0	—	0.4993
Ischemic stroke	11 (0.2%)	12 (0.2%)	1.09 (0.48–2.47)	1.0000
Stroke of uncertain type	2 (0.0%)	2 (0.0%)	1.00 (0.14–7.08)	1.0000
8 days to 35 days	**16 (0.3%)**	**27 (0.5%)**	**1.69 (0.91–3.11)**	**0.1255**
Hemorrhagic stroke	7 (0.1%)	1 (0.0%)	0.14 (0.02–0.86)	0.0387
Ischemic stroke	4 (0.1%)	23 (0.5%)	5.76 (2.25–14.72)	0.0003
Stroke of uncertain type	5 (0.1%)	4 (0.1%)	0.80 (0.21–2.96)	0.7535
36 days to 180 days	**28 (0.6%)**	**31 (0.6%)**	**1.10 (0.66-1.84)**	**0.7943**
Hemorrhagic stroke	2 (0.0%)	7 (0.1%)	3.49 (0.80–15.26)	0.1795
Ischemic stroke	23 (0.5%)	17 (0.3%)	0.74 (0.39–1.38)	0.3473
Stroke of uncertain type	3 (0.1%)	7 (0.1%)	2.33 (0.63–8.66)	0.3435

Overall, there was no statistically significant difference between the treatment groups in the cumulative incidence of strokes from randomization to 7 days, 35 days and 180 days.

From **randomization to 7 days**, the overall incidence of stroke and the incidences of the individual types of stroke were almost identical in both treatment groups. The majority of strokes were ischemic. There was only one hemorrhagic stroke, which occurred in the heparin group, and 2 strokes in each group could not be classified (type uncertain).

From **8 days to 35 days**, the overall incidence of stroke was slightly higher in the lepirudin group than in the heparin group (p=0.1225). While there was no difference in the incidence of stroke of uncertain type, there were unexpected imbalances in the incidences of ischemic and hemorrhagic stroke. Ischemic strokes occurred significantly more often in the lepirudin group than in the heparin group (p=0.0003). In contrast, there were significantly more hemorrhagic strokes in the heparin group than in the lepirudin group (p=0.0387).

From **36 days to 180 days**, the overall incidence of stroke was very similar in both treatment groups (p=0.7943). In both treatment groups, the majority of strokes were ischemic. No significant imbalances were observed in the types of stroke reported.

6.3.3 Comparison with published literature data

The frequency of ischemic stroke in the OASIS-2 study was compared with available literature data from the 8,000-patient OASIS registry [16] and the two other largest clinical trials in ACS, GUSTO-2b non-ST and PURSUIT [49, 65]. Altogether, 19,000 patients were enrolled in GUSTO-2b non-ST and PURSUIT.

The following table summarizes the stroke rates from OASIS-2, the OASIS registry, GUSTO-2b non-ST and PURSUIT:

Comparison of ischemic stroke rates from major clinical trials in ACS

Study		Timepoint	Rate of stroke	
			Test drug	Control
OASIS-2	(N=10,080)	35 days	0.7%	**0.3%**
GUSTO-2b non-ST	(N=8,011)	30 days	0.7%	0.7%
PURSUIT	(N=10,948) [a]	30 days	0.6%	0.7%
OASIS registry [b]	(N=7,987)	7 days	0.3%	
		6 months	1.3%	

[a] 90% of patients in PURSUIT received heparin as concomitant medication.
[b] Stroke of any cause in OASIS registry

The 35-day stroke results for lepirudin in OASIS-2 are fully consistent with the published data from the OASIS registry, GUSTO-2b non-ST and PURSUIT. In contrast, the 0.3% rate of ischemic stroke at 35 days in the heparin group of OASIS-2 was unexpectedly low, as compared to the literature-reported incidences.

6.3.4 Conclusions

No hemorrhagic strokes occurred in the lepirudin groups of the OASIS studies during the critical first 7 days. There were no differences between treatments in the cumulative incidence of stroke up to 7 days, 35 days and 180 days. In the period from 8 days to 35 days in OASIS-2, the overall incidence of stroke was slightly higher in the lepirudin group than in the heparin group, with significantly more ischemic strokes on lepirudin and significantly more hemorrhagic strokes on heparin. There is no plausible biological explanation for these imbalances. Also, the 35-day rate of ischemic stroke in the lepirudin group is fully consistent with published literature data, while that in the heparin group was unexpectedly low as compared to the literature-reported incidences.

Given the overall similarity between treatments in the incidences of stroke from randomization to 7 days and during the follow-up period in OASIS-2, the absence of a similar finding in OASIS-1, and the consistency of the ischemic stroke rate in the lepirudin group with published literature data, it seems likely that the observed imbalance in the subgroup analyses of ischemic stroke between 8 days and 35 days in OASIS-2 was a chance observation.

6.4 Overview of all adverse events

In addition to the special analyses of bleeds and strokes, all AEs reported were analyzed, subdivided into "hemorrhagic" and "non-hemorrhagic" AEs (some AEs were classed as hemorrhagic but did not qualify as bleeds, e.g. vascular aneurysms). Non-fatal MI and non-fatal angina were not considered to be drug-related AEs in this patient population, but rather to be sequelae of the underlying disease and were therefore excluded from the analyses of AEs.

6.4.1 OASIS-1

Randomization to 7 days. The overall incidence of AEs in this period was similar in all treatment groups. Hemorrhagic AEs were more frequent in the lepirudin groups than in the heparin group, with more such AEs in the medium-dose lepirudin group than the low-dose lepirudin group. The most frequently reported individual AEs were skin hemorrhage, epistaxis and hematuria. The leading source of imbalance between the lepirudin treatment groups and the heparin group was epistaxis. This reflects the higher rate of minor bleeding on lepirudin. No notable differences can be discerned between treatment groups in the numbers of patients with serious or fatal hemorrhagic AEs nor in the pattern and frequency of non-hemorrhagic AEs. The incidence of allergic reactions was low in all treatment groups.

The rates of hemorrhagic AEs did not increase from OASIS-1a to OASIS-1b as a consequence of the changes in the warfarin regimen (delayed fixed-dose regimen of low-intensity warfarin in OASIS-1a as compared to early INR-adjusted regimen of moderate-intensity warfarin in OASIS-1b). This finding formed the basis for the use of moderate-intensity warfarin in OASIS-2.

From 8 days to 180 days. After day 7, no clinically relevant major differences were detectable between the treatments with respect to AE reporting rates, in particular serious AEs and fatal AEs. Fluctuations in the rates of AEs can probably be attributed primarily to the influence of the outpatient clinical setting and to differences in reporting procedures between OASIS-1a and OASIS-1b. In addition, the relatively small sample sizes involved make it difficult to draw definite conclusions from the data.

6.4.2 OASIS-2

Randomization to 7 days. In the initial study period, the overall incidence of AEs was significantly higher in the lepirudin group than in the heparin group (14.1% vs. 10.9%; p=0.0001), essentially due to a significantly higher incidence of hemorrhagic AEs in the lepirudin treatment group (8.8% vs. 5.2%; p=0.0001).

- **Hemorrhagic AEs.** The higher incidence of hemorrhagic AEs for lepirudin was also reflected in a significantly higher incidence of serious hemorrhagic AEs (1.2% vs. 0.8%; p=0.0450) and a significantly greater number of patients discontinuing the study infusion due to hemorrhagic AEs (2.6% vs. 1.1%; p=0.0001). The findings are consistent with the pattern of bleeding episodes reported during this period. Despite the higher total numbers of hemorrhagic AEs for lepirudin, there was no difference between the treatment groups with respect to fatal hemorrhagic AEs (0.1% vs. 0.1%; p=0.5481).

  The most frequently reported serious hemorrhagic AEs, fatal hemorrhagic AEs and hemorrhagic AEs leading to discontinuation of study infusion were:

OASIS-2: Most frequent serious hemorrhagic AEs, fatal hemorrhagic AEs, and hemorrhagic AEs leading to discontinuation of study infusion - up to 7 days (Safety population)

	Heparin N=5,033		Lepirudin N=5,047	
Serious hemorrhagic AEs [a]	**40**	**(0.8%)**	**61**	**(1.2%)**
Gastrointestinal hemorrhage	11	(0.2%)	27	(0.5%)
Hematuria	3	(0.1%)	8	(0.2%)
Surgical bleed	8	(0.2%)	7	(0.1%)
Fatal hemorrhagic AEs [b]	**6**	**(0.1%)**	**4**	**(0.1%)**
Vascular aneurysm	2	(0.0%)	1	(0.0%)
Hemorrhagic AEs leading to discontinuation of infusion [a]	**53**	**(1.1%)**	**130**	**(2.6%)**
Gastrointestinal hemorrhage	17	(0.3%)	38	(0.8%)
Hematuria	9	(0.2%)	35	(0.7%)
Epistaxis	3	(0.1%)	15	(0.3%)
Injection site hemorrhage	8	(0.2%)	13	(0.3%)
Hemoptysis	4	(0.1%)	12	(0.2%)

[a] Only AEs with a frequency of >0.1% in one treatment group are listed.
[b] All other fatal hemorrhagic adverse events were reported for only 1 patient each in either treatment group or in total.

- **Non-hemorrhagic AEs.** There was essentially no difference between the treatments in the frequency and pattern of non-hemorrhagic AEs.

The most frequently reported serious non-hemorrhagic AEs, fatal non-hemorrhagic AEs and non-hemorrhagic AEs leading to discontinuation of study infusion were:

OASIS-2: Most frequent serious non-hemorrhagic AEs, fatal non-hemorrhagic AEs, and non-hemorrhagic AEs leading to discontinuation of study infusion - up to 7 days (Safety population)

	Heparin N=5,033		Lepirudin N=5,047	
Serious non-hemorrhagic AEs [a]	**174**	**(3.5%)**	**151**	**(3.0%)**
Heart arrest	20	(0.4%)	26	(0.5%)
Shock	26	(0.5%)	20	(0.4%)
MI	20	(0.4%)	18	(0.4%)
Ischemic stroke	11	(0.2%)	12	(0.2%)
Lung edema	13	(0.3%)	9	(0.2%)
Ventricular fibrillation	8	(0.2%)	9	(0.2%)
Hypotension	9	(0.2%)	5	(0.1%)
Fatal non-hemorrhagic AEs [a]	**82**	**(1.6%)**	**72**	**(1.4%)**
Heart arrest	16	(0.3%)	19	(0.4%)
MI	20	(0.4%)	18	(0.4%)
Shock	24	(0.5%)	17	(0.3%)
Non-hemorrhagic AEs leading to discontinuation of infusion [a]	**69**	**(1.4%)**	**62**	**(1.2%)**
Heart arrest	7	(0.1%)	9	(0.2%)
Shock	12	(0.2%)	6	(0.1%)

[a] Only AEs with a frequency of >0.1% in one treatment group are listed.

The frequency of allergic reactions was low in both treatment groups (0.1% serious and 0.4–0.5% non-serious). The only allergic reaction reported by >0.1% of patients was rash (0.3% in each treatment group).

From 8 days to 180 days. Generally, differences between the treatment groups in the AE pattern during the follow-up periods were small, although the overall rates of AEs tended to be lower in the lepirudin group, mainly due to a smaller number of non-hemorrhagic AEs. The only relevant imbalance was related to the incidences of the individual types of stroke between 8 days and 35 days. Differences in the pattern of individual fatal non-hemorrhagic AEs may be attributable to inconsistencies between investigators in ascertaining the underlying cause of CV death in out-patients. Overall, the incidence of fatal non-hemorrhagic AEs was lower on lepirudin (5.9% vs. 6.6% on heparin).

Subgroup analyses. Subgroup analyses were performed to investigate the influence of various factors on the rate of hemorrhagic and non-hemorrhagic AEs up to 7 days, from 8 days to 35 days, and from 36 days to 180 days.

The pattern of hemorrhagic AEs up to 7 days in the subgroups was reflective of the safety population as a whole. The results for selected subgroup analyses of hemorrhagic AEs up to 7 days are summarized in the table on the following page.

There were 2 subgroups that deviated substantially from the general trend: (1) lepirudin patients with a body weight <50 kg had a markedly higher rate of hemorrhagic adverse events, suggesting that the dose of lepirudin, in contrast to what was done in OASIS-2, should be weight-adjusted in such patients as well; (2) lepirudin patients with creatinine values >1.5 mg/dL also had a markedly higher rate of hemorrhagic adverse events, indicating that lepirudin dose adjustments according to creatinine values should start at a 1.5 mg/dL threshold (in OASIS-2, a 2.0 mg/dL threshold was used).

The overall incidence of hemorrhagic adverse events was slightly increased for patients receiving certain prespecified concomitant medications (aspirin; other antiplatelet agents; non-study heparin; thrombolytic therapy; non-study oral anticoagulants) prior to randomization and, with the exception of aspirin, between randomization and the end of study infusion. Since nearly all patients received aspirin, the hemorrhagic adverse event rate for patients receiving aspirin was essentially unchanged from the population as a whole. There was no disproportionate increase in the risk of bleeding with lepirudin as compared to heparin for any of the medications investigated.

There were no relevant differences between subgroups for hemorrhagic AEs beyond 7 days or for non-hemorrhagic AEs at any time.

Warfarin substudy. Patients who were randomized to warfarin or standard therapy in the warfarin substudy generally experienced fewer hemorrhagic and non-hemorrhagic AEs up to 7 days than patients who were not randomized. Within the warfarin substudy, there were only minor differences in the frequencies of AEs between the treatment groups, regardless of whether lepirudin or heparin had been given previously. Beyond 7 days, warfarin patients, independent of prior treatment with lepirudin or heparin, had higher rates of hemorrhagic AEs than all other patients.

OASIS-2: Subgroup analyses of influence of factors on incidence of hemorrhagic AEs up to 7 days (Safety population)

Factor / Subgroup	N (%) patients with AEs			
	Heparin		Lepirudin	
Age				
≤65 years	99/2,554	(3.9%)	168/2,525	(6.7%)
>65 years	164/2,479	(6.6%)	278/2,522	(11.0%)
Sex				
Male	160/3,098	(5.2%)	262/3,041	(8.6%)
Female	103/1,935	(5.3%)	184/2,006	(9.2%)
Diabetes				
Yes	61/1,056	(5.8%)	110/1,060	(10.4%)
No	202/3,977	(5.1%)	336/3,987	(8.4%)
History of hypertension				
Yes	166/2,724	(6.1%)	238/2,700	(8.8%)
No	97/2,309	(4.2%)	208/2,347	(8.9%)
Weight				
<50 kg	4/77	(5.2%)	16/98	(16.3%)
50 - 100 kg	244/4,677	(5.2%)	408/4,720	(8.6%)
>100 kg	15/279	(5.4%)	22/228	(9.6%)
Renal function (creatinine)				
≤1.5 mg/dL	244/4,681	(5.2%)	386/4,699	(8.2%)
>1.5 mg/dL	16/288	(5.6%)	54/288	(18.8%)
Co-med. within 2 days before randomization				
Aspirin	188/3,246	(5.8%)	320/3,338	(9.6%)
Any non-study heparin	89/1,062	(8.4%)	129/1,121	(11.5%)
Non-study oral anticoagulants	0/28		3/24	(12.5%)
Other anti-platelets	16/197	(8.1%)	21/137	(15.3%)
Thrombolytic therapy	0/8		0/7	
Co-med. between randomization and end of infusion.				
Aspirin	236/4,729	(5.0%)	416/4,769	(8.7%)
Any non-study heparin	21/118	(17.8%)	25/130	(19.2%)
Non-study oral anticoagulants	4/49	(8.2%)	3/41	(7.3%)
Other anti-platelets	24/238	(10.1%)	23/199	(11.6%)
Thrombolytic therapy	5/20	(25.0%)	1/13	(7.7%)

6.5 Laboratory variables

Laboratory findings (hemoglobin, creatinine and platelets) in the OASIS studies did not reveal any additional safety concerns beyond the observed increase in the risk of bleeding.

In OASIS-1a, the rates of antibody conversion (low-dose group: 9%; medium-dose group: 18%) were higher than in other non-HIT populations (5–10%), but were clearly lower than in HIT patients (45%). Since no correlation between antibodies and adverse clinical outcome has been established in any lepirudin study, and the rate of allergic reactions was very low in OASIS-1a, no antibody analyses were performed in OASIS-1b or OASIS-2.