5. THE EFFICACY OF LEPIRUDIN COMPARED TO A "PUTATIVE PLACEBO"

5.1 Introduction and purpose

The OASIS studies provide evidence that lepirudin is superior to an active control (unfractionated heparin), when administered with standard care including aspirin in the treatment of unstable angina or acute MI without ST elevation. Because heparin is well established and routinely used for this indication, it serves as an active or "positive" control. The superiority of lepirudin + aspirin over heparin + aspirin implies that the efficacy of lepirudin + aspirin would likely have exceeded that of aspirin alone.

This section will examine the possible statistical significance and risk reduction attributable to lepirudin if it had been compared to placebo instead of heparin. This "putative placebo" analysis was suggested by the FDA at the pre-NDA meeting on February 26, 1998, and the methodology proposed by the sponsor was discussed with the FDA during the pre-NDA meeting on February 24, 1999.

It should be noted that one needs to use historical heparin + aspirin versus aspirin data because it was considered unethical to do a direct lepirudin + aspirin versus placebo + aspirin study. Comparisons using historical data have less scientific rigor than direct randomized comparisons. However, given the ethical difficulties involved, such comparisons provide useful information not otherwise available.

To estimate the risk reduction and p-value associated with lepirudin versus the "putative placebo" (lepirudin + aspirin vs. aspirin alone), the lepirudin data were integrated with results from published studies comparing heparin + aspirin to aspirin alone in similar populations of patients with unstable angina. A focused literature review was conducted of all relevant controlled clinical trials of heparin + aspirin versus aspirin alone in the treatment of unstable angina in order to develop a realistic range of expected event rates and risk reductions for the same clinical endpoints (death and MI). Articles found from a valid existing meta-analysis were one main source of material.

5.2 Selection of heparin + aspirin vs. placebo + aspirin studies

Randomized, controlled clinical studies evaluating intravenous heparin and/or oral aspirin in patients with unstable angina were identified by a literature search using the MEDLINE database and the search terms "aspirin," "heparin," and "unstable angina". To be included, studies had to meet the same criteria identified by Oler *et al.* in their meta-analysis report: 1) were randomized, 2) enrolled patients admitted with diagnosis of unstable angina or non-Q-wave MI, 3) included intravenous heparin + aspirin and aspirin alone treatment groups, and 4) reported the incidence of MI and death while on randomized treatment [14].

None of the clinical trials identified by the MEDLINE search (except the ones already considered by Oler *et al.*) included heparin + aspirin and aspirin alone treatment groups within the same study. However, two dalteparin studies, FRISC [15] and FRIC [42], of similar design offered the opportunity to derive data on heparin + aspirin versus aspirin alone in patients with unstable angina. In FRISC, dalteparin + aspirin was compared to aspirin alone; in FRIC, dalteparin + aspirin was compared to heparin + aspirin. By combining the studies and factoring out the dalteparin-treatment

groups, a comparison between the aspirin alone and heparin + aspirin groups could be made. None of the other clinical trials offered this opportunity because: 1) the same drug was not common to multiple studies; 2) all treatment groups received heparin and aspirin; 3) heparin and/or aspirin was used variably across the treatment groups; 4) there was no aspirin alone group; or 5) the entry criteria, study drug administration or endpoint assessments were incompatible with Oler/OASIS.

Therefore, only the dalteparin studies offered the potential to update the estimate of the "true effect" of heparin + aspirin vs. aspirin alone. These studies were included in the pooled estimate of relative risk for heparin versus placebo by using an appropriately weighted average of component relative risks. The incidences of clinical endpoints (death or MI) in heparin and control groups of each study were tabulated, along with relative risks and 95% confidence intervals [58]. Standard methods for combining results from 2x2 tables were used to obtain an overall estimate of risk reduction associated with heparin [59]. Approximate 95% confidence intervals were obtained for the pooled estimate of relative risk.

5.3 Statistical approaches for deriving lepirudin vs. putative placebo effect

Statistical methods for the putative placebo comparison were applied to the double composite endpoint of death or new MI over both the 72-hour and 7-day post-randomization periods. Two basic approaches were used:

Direct estimation. This combination of odds ratios approach is a natural extension of methodology used for meta-analyses. Data from lepirudin and historical heparin studies are used to derive the relative risk for lepirudin vs. putative placebo (lepirudin + aspirin vs. aspirin alone). The relative risk of an outcome event was calculated directly as the product of two terms: (1) the relative risk for lepirudin versus heparin and (2) the relative risk for heparin versus placebo. The product of relative risks is additive on a logarithmic scale and, because the two sets of studies are statistically independent, the variance of the sum of the natural logs is equal to the sum of their variances. Assuming that log-transformed relative risks are normally distributed, a putative relative risk and corresponding confidence interval were then constructed for lepirudin versus placebo. Note that a similar analysis was undertaken to support the efficacy of enoxaparin in the ESSENCE trial [60] as well as for the approval of clopidogrel using CAPRIE data by the Cardio-Renal Advisory Committee [61]. The approach satisfies criteria set forth by Fleming for interpreting the efficacy of a drug from a positive control trial [62]. Likewise, the direct method of combining relative risks is similar to an approach developed by Bucher *et al.* [63] using odds ratios to integrate results of a positive control trial with historical placebo data.

Sensitivity analysis. This alternate approach estimates the outcome of the OASIS-2 study had placebo (aspirin alone) been used as the comparator, calculated over a range of assumptions for the "true" heparin vs. placebo relative risk. This analysis assumes that OASIS-2 patients with events on heparin + aspirin would have had the events on aspirin alone, but that additional patients (than on heparin + aspirin) would have had events if on aspirin alone. The number of additional events is computed using the conditional probability distribution obtained using different assumptions for the heparin-placebo relative risk. For each heparin vs. placebo relative risk, there is then a probability distribution for events in the putative placebo + aspirin arm. Using the exact binomial, this conditional distribution allows computation of the distribution of the Mantel-Haenszel p-values for the lepirudin + aspirin vs. aspirin alone comparison. Over a wide range of heparin to placebo relative

risks, the distribution of p-values (Mantel-Haenszel tests comparing lepirudin to putative placebo) are summarized according to median, 90th, and 95th percentiles.

5.4 Results: historical estimate of heparin + aspirin vs. aspirin alone effect

A comprehensive overview of studies comparing heparin + aspirin to aspirin alone in unstable angina was performed in 1996 by Oler *et al.* [14]. Based on pooled data from 6 trials, the summary relative risk (RR) of death or MI during randomized treatment was 0.67 (95% CI: 0.44 – 1.02, p=0.06).

Updating the Oler data from two recent dalteparin studies (FRISC/FRIC) yields a pooled relative risk for heparin + aspirin versus aspirin alone of 0.58 (95% CI: 0.40 to 0.85, p=0.005) [15, 42].

This evidence suggests that heparin + aspirin reduces the risk over aspirin alone by 30-40%. Lepirudin reduces the risk over heparin by a further 26% based on the 72-hour data in OASIS-2. In the following section, the relative risk and associated p-value for the lepirudin versus putative placebo comparison will be calculated, based on heparin vs. placebo relative risks obtained from the Oler meta-analysis updated with the data from the FRISC and FRIC studies.

5.5 Results: direct estimation - lepirudin vs. "putative placebo" comparison (lepirudin + aspirin versus aspirin alone)

The following table displays the relative risk of death or MI for lepirudin versus the putative placebo (lepirudin + aspirin vs. aspirin alone) at 72 hours and 7 days, as computed by direct estimation. The relative risks are derived on the basis of the pooled OASIS-1&2 studies, using the relative risk for heparin + aspirin versus aspirin alone obtained from published literature.

Lepirudin (OASIS-1&2) versus putative placebo control
All-cause death or new MI – relative risk (95% confidence interval)
(MITT populations for observed RRs from OASIS data) [a]

Time period	Observed RR Lepirudin : Heparin	Historical RR Heparin : Placebo	Derived RR Lepirudin : Placebo	p-value
Up to 72 hours	0.73 (0.56 – 0.94)	0.58 (0.40 – 0.85) [b]	0.42 (0.27 – 0.67)	0.00023
	0.73 (0.56 – 0.94)	0.35 (0.16 – 0.78) [c]	0.26 (0.11 – 0.59)	0.00133
	0.73 (0.56 – 0.94)	0.67 (0.44 – 1.02) [d]	0.49 (0.30 – 0.80)	0.00451
Up to 7 days	0.80 (0.66 – 0.98)	0.58 (0.40 – 0.85) [b]	0.46 (0.30 – 0.71)	0.00040
	0.80 (0.66 – 0.98)	0.35 (0.16 – 0.78) [c]	0.28 (0.12 – 0.63)	0.00224
	0.80 (0.66 – 0.98)	0.67 (0.44 – 1.02) [d]	0.54 (0.34 – 0.85)	0.00854

[a] For ITT results see Table 8 of Appendix A
[b] Published meta-analysis (Oler) plus the FRISC and FRIC studies
[c] FRISC and FRIC studies alone
[d] Published meta-analysis (Oler) alone

Integrating all available data for lepirudin (OASIS-1&2) with the historical heparin vs. placebo published data, the relative risk for lepirudin versus placebo is 0.42 (95% CI: 0.27 - 0.67) at 72 hours. This risk reduction of 58% is highly statistically significant (p=0.0002). At 7 days, the relative risk for lepirudin versus placebo is 0.46 (95% CI: 0.30 - 0.71). Again, the risk reduction (54%) is highly statistically significant (p=0.0004).

It may be argued that the FRISC and FRIC are most recent, and the most methodologically similar to the OASIS trials. Therefore, the results using the heparin-to-placebo relative risks based on FRISC and FRIC are also presented. In this analysis, at 72 hours, lepirudin was associated with a risk reduction of 74% compared to placebo alone (p=0.0013). At 7 days, the risk reduction estimate is 72% (p=0.0022).

Finally, as the Oler data have been used previously for putative placebo comparisons, the analyses using the Oler data alone are presented. At 72 hours, lepirudin was associated with a risk reduction of 51% compared to placebo (p=0.0045). At 7 days, the risk reduction estimate is 46% (p=0.0085).

Likewise, highly significant relative risks were derived for lepirudin compared to putative placebo based on OASIS-2 data alone. The following table displays the relative risk of death or MI for lepirudin versus the putative placebo control group at 72 hours and 7 days, as computed by direct estimation.

Lepirudin (OASIS-2) versus putative placebo control
All-cause death or new MI - relative risk (95% confidence interval)
(MITT populations for observed RRs from OASIS data) [a]

Time period	Observed RR Lepirudin : Heparin	Historical RR Heparin : Placebo	Derived RR Lepirudin : Placebo	p-value
Up to 72 hours	0.74 (0.57 – 0.97)	0.58 (0.40 – 0.85) [a]	0.43 (0.27 – 0.68)	0.00033
	0.74 (0.57 – 0.97)	0.35 (0.16 – 0.78) [b]	0.26 (0.11 – 0.60)	0.00153
	0.74 (0.57 – 0.97)	0.67 (0.44 – 1.02) [c]	0.50 (0.30 – 0.82)	0.00570
Up to 7 days	0.83 (0.68 – 1.02)	0.58 (0.40 – 0.85) [a]	0.48 (0.31 – 0.74)	0.00081
	0.83 (0.68 – 1.02)	0.35 (0.16 – 0.78) [b]	0.29 (0.13 – 0.66)	0.00304
	0.83 (0.68 – 1.02)	0.67 (0.44 – 1.02) [c]	0.56 (0.35 – 0.89)	0.01370

[a] For ITT results see Table 9 of Appendix A
[b] Published meta-analysis (Oler) plus the FRISC and FRIC studies
[c] FRISC and FRIC studies alone
[d] Published meta-analysis (Oler) alone

In general, the relative risks derived for lepirudin versus putative placebo were highly significant in each instance (relative risk ranged from 0.43 to 0.50 for the 72-hour endpoint and from 0.48 to 0.56 for the 7-day endpoint), using the best available historical estimates of the heparin-to-placebo relative risks.

This direct estimation approach to relative risk calculation consistently demonstrates that lepirudin + aspirin would have performed significantly better than aspirin alone in preventing death and MI among patients with unstable angina.

5.6 Results: Sensitivity analysis estimating outcome if there had been a placebo control group in the OASIS-2

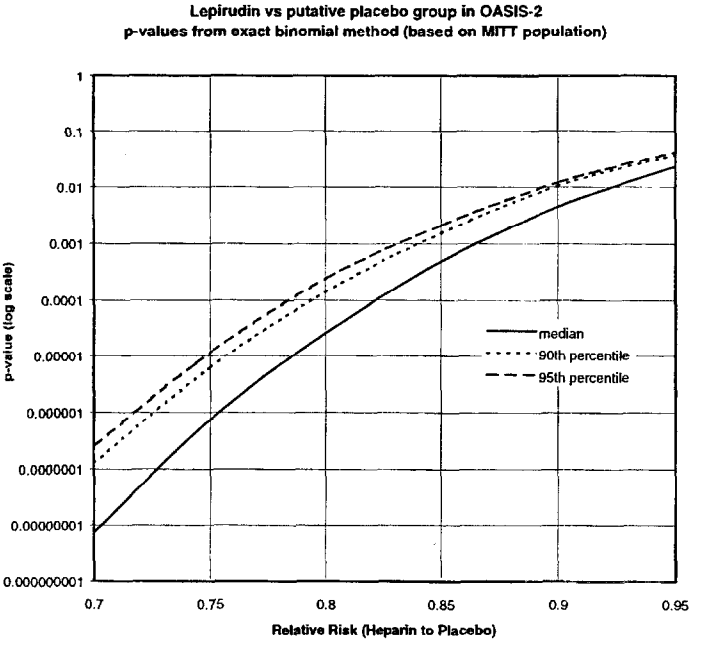
Estimates of the outcome of the OASIS-2 study had placebo (aspirin alone) been used as the comparator are given below. The following table presents the 95th percentile of the p-value distribution obtained by the exact binomial probability method for the statistical comparison of lepirudin with placebo, each generated for a given heparin-to-placebo relative risk.

Sensitivity analysis estimation of p-values for lepirudin versus a putative placebo control group in OASIS-2: All-cause death or new MI up to 7 days (based on MITT population)

Assumed RR Heparin : Placebo	95th percentile of p-value distribution [a]
0.60	0.0000000000016
0.65	0.0000000012706
0.70	0.0000002478136
0.75	0.0000116156607
0.80	0.0002403679764
0.85	0.0021004152024
0.90	0.0120862718259
0.95	0.0427677699717

[a] Exact binomial probability method.

The figure below depicts the p-value distribution generated on the basis of heparin-to-placebo relative risks ranging from 0.70 to 0.95, in increments of 0.05. The top plotted line is the value for which 95% of p-values would be smaller and 5% larger. Thus for example, if the true relative risk was 0.7, then 95% of the time the p-value for the comparison would be less than about 0.000005. Thus, if one assumes a particular relative risk the plot allows one to be assured that with 95% certainty the p-value would be less than the plotted value.



Assuming heparin-to-placebo relative risks in the most likely range (0.60-0.70), the comparison of event rates in the lepirudin and putative placebo control group in OASIS-2 would, with 95%

certainty, yield a p-value of less than 0.0000003. Even if heparin reduced the risk of death or MI over placebo by only 20% (corresponding to a relative risk of 0.80), the OASIS-2 p-value using aspirin alone as the comparator would still be extremely small (p=0.00024 with 95% certainty). Only under the most conservative assumptions about the efficacy of heparin (relative risks in excess of 0.80) would the p-value comparing lepirudin + aspirin to aspirin alone be expected to be higher than 0.00125. P-values in this low range satisfy the significance level criterion ($p = 2 * [0.025]^2$) to which a single pivotal trial may be held to constitute "statistically persuasive evidence" of efficacy.

5.7 Conclusions

In the OASIS-2 trial, the effects of lepirudin were superior to a well-established active comparator (heparin) for the majority of mortality and morbidity endpoints, including the 72-hour incidence of CV death and new MI. These beneficial effects confirmed trends in OASIS-1 and were internally consistent across study endpoints, timepoints, and subgroups.

To aid in the interpretation of these trials, two statistical approaches were applied to estimate the efficacy of lepirudin in comparison to a putative placebo control group:

- The **direct estimation** method, which integrates lepirudin data with published heparin studies, indicates that lepirudin + aspirin would reduce the risk of death or MI during treatment by over 50% compared to aspirin alone, with p-values in the range of 0.0002 to 0.0045.
- The **sensitivity analysis** method, which estimates the outcome of the OASIS-2 trial had aspirin alone been the control, indicates that the p-value comparing lepirudin + aspirin to aspirin alone in this trial would have been extremely small (p<0.0000003 with 95% certainty) for heparin-to-placebo relative risks in the most realistic range of 0.60–0.70.

There is no single established procedure for inferring efficacy vs. placebo from studies with only active controls. Thus, two approaches were taken. Results of both approaches are consistent in demonstrating that the effect of lepirudin +aspirin would have exceeded the effect of aspirin alone, even under conservative assumptions about the efficacy of the active control (heparin).