

2.0 RISK ASSESSMENT IN THE EPILOG TRIAL

This supplementary review discusses the sponsor's response to the Agency Information Request submitted July 21, 1997.

I. Background

A. Issue: The sponsor _____ w - - - - u - - -
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At randomization, only 35% of patients appeared to be classed as low risk. Further, the as randomized assessment of patient risk status differs from the assessment made on the **CRFs**; over half the patients originally classified as low risk at randomization were reclassified to high **risk** based on the CRF, leaving only 19% of patients in the **trial** classified as low risk by CRF. By the CRF classification, efficacy on the primary endpoint is not demonstrated in the **patients** in the low risk group (the number of patients and number of events becomes very small). This calls into question the reliability of the randomization risk assessment in defining patients' risk status with accuracy. Further, the CRF classification appears to identify a small subset of patients for whom the risk of cardiac ischemic complications is not high, and who derive no benefit from treatment with **Abciximab**.

The randomization assessment was based on a review of the patients clinical history and a relatively cursory review of the screening angiogram to determine if the patient had any Type B or C characteristics which would render them high risk. The **CRFs** were completed based on more detailed criteria regarding lesion morphology after completion of the index procedure, and in some cases **after** the patient's hospital discharge. Thus the **CRF** assessment was **not** made in the same way as the randomization assessment.

B. Steps Taken To Resolve this Issue: Telecons were held with the sponsor and two Information Request letters were sent by the Agency. The Agency has requested that the sponsor perform a reanalysis of a random sample of the screening angiograms in order to establish that the randomization risk status assessment was made in an unbiased manner, and that a similar assignment of risk status would be made by an independent **observer**. The sponsor has agreed to perform such a study and is preparing a protocol. This submission is provided to fulfill the Agency request for safety data by the risk subgroups, and as **part** of the continuing dialogue regarding these issues.

II. Review of This Submission

A. Contents The sponsor has included in this submission:

1. An explanation that the randomization risk assessment involved assessment of patients risk status as to whether or not they met the criteria used in the EPIC trial.

2. Bleeding data categorized by as randomized and CRF Risk status

3. A risk / benefit analysis **demonstrating** no significant additional risk of administration of Abcixirab to the very low risk patients.

4. Data **from** the **Angiographic** Substudy, comparing the Core lab reviewers' risk status assessment with the assessment made by the investigators on the **CRFs**. They show that the subset of angiograms reviewed (286) is representative of the entire study population. They contend that this satisfies the need for an independent blinded **review** of pre-procedure angioagrams.

5. References on interobserver variability, to support their position that **interobserver** agreement is unlikely in any rereview of angiograms.

B. Sponsor's Discussion of the Issues

1. Comparison to EPIC risk assessment -- the sponsor explains that patients were screened at randomization as to whether or not they fit the criteria used in the EPIC trial to **define** patients at high risk patients. This screening was conducted in the same manner as that in the EPIC trial. **The AHA/ACC** guidelines for lesion morphology **were** used as the basis for risk status assessments, as they were in the EPIC trial. The determination was made prospectively, in advance of treatment or procedure outcome.

The sponsor has invoked a number of factors which could be responsible for the different readings:

1. Interobserver and **intraobserver** variability: in many cases the **interventionalist** who performed the procedure and completed the CRF was a different individual from the referring cardiologist who read the initial screening **angiogram**. They contend that it is to be expected that rereview would lead to uncovering new findings (more complex lesion characteristics) than to "take away" previous findings.

2. A structured approach to collection of lesion morphology data-was not provided at the time of randomization. A less detailed categorization system was used.

3. Bias in the risk assessment made on the **CRFs** due to knowledge of the procedural outcome and , in some cases, the patient's hospital course.

4. Better visibility of lesions on the post procedural angiograms. Screening angiograms were most often viewed on a video system, which blurred and obscured some of the detail of the lesions. During and after the procedure, a digital system was used which permitted better visibility of the individual characteristics of the lesions.

5. An imperfect classification system.

The sponsor explains that the randomization risk assessment was planned by the investigators to simulate the assessment that is made in actual clinical practice. It was planned so that it could be done expeditiously and would not impact on patient care. They contend that the randomization risk assessment is the clinically 'relevant of the two assessments made, and that **the** data should be viewed based on the categorization made at this time. Additionally, they contend that the very low risk subgroup of patients can only be identified retrospectively in an analysis 'similar to that made on the **CRFs**; those with a very low risk of complications cannot easily be identified in advance of treatment with the agent or performance of the procedure. They explained further that the **CRF** review of lesion characteristics was performed for research purposes only, and that a detailed **pre** procedure review would have been inconsistent with clinical practice. This allowed the grouping of patients into a category that would have been eligible for treatment under the EPIC criteria (high risk) and those who would not (low risk).

C. Data on Efficacy by Risk Status

Data **are** presented showing that by the randomized risk classification, efficacy was demonstrated on the primary endpoint for both low and high risk patients when the Abciximab Low Dose arm is compared to placebo. The same is not **true** of the lower risk patients as classified by CRF data. **They** state, however, that the percent reductions for the Low Dose arm are consistent with overall trial results (see tables 1 and 2).

D. Data on Bleeding by Risk Subgroups

Tables 3 and 4 show bleeding events classified by risk subgroup at randomization and by CRF, respectively. The following can be seen **from** the data:

1. By either classification system, there appear to be higher rates of bleeding complications among high **risk** than among low **risk** patients, particularly major bleeding and RBC transfusion. (Note that minor bleeds appear increased in **low** risk patients compared to high risk by randomized category, but not by CRF category, and that the numbers are small).

2. Among the low risk patients based on **CRF** data, there were no patients with major bleeding in the Abciximab plus low dose **heparin** arm, whereas 3 placebo patients experienced this complication. **The** sponsor provides data to **show** there was more spontaneous bleeding in the placebo treated patients also (5 vs none).

3. Thrombocytopenia appears sporadic and not significantly increased among the arms. There is a slightly higher percentage of cases in the **Abciximab** arms compared to placebo by both analyses. The sponsor provides case summaries, and notes that in none of these cases did platelets drop below 50,000, and that all cases resolved spontaneously without platelet transfusion

E. Risk Benefit Analysis

The sponsor has ranked safety and efficacy events in decreasing order of severity of clinical consequences to the patient:

- Death
- Stroke or other ICH
- Urgent CABG or Q wave MI
- Other urgent intervention or **MI** with peak enzymes \geq 5x normal
- Severe thrombocytopenia ($<$ 50,000) or transfusion of platelets
- PRBC transfusion or major bleeding with a spontaneous (non-instrumented) bleeding site
- Other **MI** (peak enzymes $<$ 5x normal or **nonQ waveMI** post index hospitalization)
- Other** major bleeding
- Other revascularization**
- Other** thrombocytopenia (\geq 50,000)
- Minor bleeding

Table 5 presents the number and percentage of patients in each treatment arm (placebo and Abciximab Low Dose Heparin) **for** the patients classified as low risk by CRF only. The column at the right extrapolates **from** the data and indicates the predicted cumulative benefit of patients treated with the Abciximab arm per 1000 patients treated (i.e. the number of patients who would have had these events if they had not been treated **with** Abciximab). No deaths or strokes occurred in either arm in this group. Through the first six items on the list, from urgent **CABG/Q** wave MI through spontaneous major bleeding, there is an advantage to treatment that translates **into 23 per 1000** patients treated. Through other **revascularization** (the ninth item on the list), there appears to be an

advantage of 20 per 1000 patients treated. When the last two items are added (non-severe thrombocytopenia and minor bleeding), the balance begins to shift. The sponsor notes that the non-severe thrombocytopenia and minor bleeding events in the low dose heparin arm did not have any important adverse clinical consequences, thus the benefits of treatment appear to have outweighed the risks of treatment with **Abciximab**.

F. Angiographic Substudy Data

An **Angiographic Substudy** was conducted of 286 patients in the **EPILOG** trial. Patients at **certain** sites were randomized to the substudy, the purpose of which was to evaluate **angiographic** outcomes in these patients at 6 months, to assess the degree of **restenosis** following the index procedure. No study report has yet been submitted. Portions of the data from this **substudy** are cited in this submission by the sponsor as a means of evaluating **interobserver** variability in assessment of lesion morphology.

A **blinded** set of independent observers reread the **intraprocedural** angiograms for patients in the **substudy**. The criteria used to rate lesion morphology were those applied at the time of the CRF **reading**. Some items were not possible to assess blinded (age of a **lesion** or if a vein graft was present); in these cases, **CRF** data were used in order to keep the reviewers blinded. This allowed a comparison of the investigators' readings and of the core lab reviewers' readings on the lesion morphology criteria. These criteria were used as the basis for assessment of risk status, and overall assignments of risk category made.

The sponsor notes a high degree of variability and that mismatch occur in both directions (for example, **31** patients were classed as low risk by the **core** lab and high **risk by the investigators, and 36** patients were classed as high risk by the **core lab and low risk** by the investigators), as shown in Figures 1 and 2. Note, however, that while there is considerable disagreement on the individual characteristics, and indeed on specific patients' lesions, there is a rather consistent overall assessment by both **the** investigators and the core lab on the percentages of patients **whose overall risk status was** high or low and the proportion of patients with **A, B1, B2, or C** as the most severe characteristics present in the lesions assessed.

Length, eccentricity, and presence of **thrombus** were the attributes on which the largest differences were observed (see Figures **3, 4, and 5**).

G. References

Literature references are provided which point up the likelihood of great **interobserver** variability when angiograms are assessed by repeated observers.

1. Assessment of gross parameters such as presence or absence of lesions and **percent** stenosis showed relatively strong degrees of correlation between independent **observers**¹ (87 and 76%) in one study of coronary angiogram data in which panels were used to assess 1,830 pairs of angiograms with lesions for the Cholesterol Lowering Atherosclerosis Study. However, there was perfect agreement in only 54 percent of cases. More detailed **aspects of lesion morphology** were not assessed in this study. **The** authors state that the degree of agreement in their study was somewhat higher **than** that reported in the previous literature.

2. A study at the VA from 1975 is cited, in which 22 physicians read 13 angiograms on two different occasions. There was relatively good agreement about lesions in the right coronary artery and presence of ventricular aneurysm, but striking disagreement on assessment of LAD and **LCx**

lesions. Disagreement correlated inversely with experience in reading the angiograms².

3. An article by Stephen Ellis³ is enclosed which discusses the data on which the ACC/AHA classification of risk status for abrupt arterial closure after mechanical intervention is based. Multivariate analysis was used to identify these factors based on data from 441 procedures, sampling from a total of 4,772. The six factors found to be the most powerful predictors of abrupt closure included a) post PTCA percent stenosis, b) dissection during the procedure, c) prolonged post PTCA use of heparin, d) branch point location, e) fixed bend point location, and f) other stenoses in the vessel dilated. These factors are not possible to assess prior to the procedure, and can only be properly assessed during or after the procedure itself

4. Repeated readings of angiograms were done by different, and by the same observers in the Bypass Angioplasty Revascularization Investigation trial (manuscript in press). Of 391 readings of 72 angiograms, there was total agreement between all readers only 28% of the time. Of 181 repeat readings by the same observer, there was disagreement in 27% of the reads. The parameters assessed include the number of lesions for which angioplasty should be attempted and the location of the lesions⁴.

5. A small study of four coronary angiographers who independently assessed 20 angiograms for the presence and degree of coronary stenosis is presented. This study showed a striking degree of variability in quantifying percent stenosis (ranges of 0 to 50, 10 to 90, 40 to 100 for specific lesions) and assessing the significance of lesions, particularly in the left main artery⁵. The investigators agreed on only 9 of the 20 angiograms (45 %).

The sponsor concludes that inter-observer variability in the assessment of lesions will be great, and the ability of a reread of angiograms to validate a previous assessment may be limited by this.

III. REVIEWER COMMENTS:

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3.0 THE INDEPENDENT ANGIOGRAM RE-REVIEW STUDY

A. Overview

This review concerns a n-review-of baseline angiograms from patients in the EPILOG study submitted in response to the Agency's Information Request letter dated June 16, 1997. The Agency requested an independent review of a sample of baseline angiograms to establish confidence in the investigators' risk status assessment of patients based on the **pre-procedure** (baseline) angiogram (see the EPILOG Medical Officer's review, by this reviewer, and the Supplementary Review for the details of what led to this concern).

B. Objectives of the Angiogram Re-Review

The objectives of the study, as stated by the sponsor, were:

- a) to assess the reproducibility of angiographic **risk** classification among independent reviewers,
- b) to assess the reproducibility of the angiographic risk **classification** reported in the **EPILOG** CRF by independent reviewers, and
- c) to assess the reproducibility of the angiographic risk classification performed at the time of randomization in the EPILOG trial by independent reviewers.

C. Study Methods

Angiographic films from a randomly selected subset of EPILOG patients were sent from the individual study sites to the Cleveland Clinic Angiographic Core Lab, where they were prepared for reading. Eighteen independent cardiologists **were** identified **from** a nationwide survey. These reviewers convened for simultaneous but independent reading of the angiograms at the Cleveland Clinic over a 2 day period. Readings were **recorded** on data collection forms and sent **to** Centocor for entry into a database and data analysis.

1. Selection of Reviewers

Reviewers were identified by a market research organization, _____ Interventional cardiologists were recruited through a nationwide survey. **They** were told they would be participating in a study at the Cleveland Clinic to evaluate the utility of the **ACC/AHA** lesion classification system for patients undergoing coronary intervention. Physicians who had participated in the EPILOG trial were excluded from participation. Centocor was not involved in the selection process and was blinded to the identity of the participants until after the review was completed and the database was locked.

2. Reviewer Demographics

Eighteen interventional cardiologists were involved in the n-review. Only one of those 18 indicated that he did not use the **ACC/AHA** guidelines in clinical practice. They **came from a variety** of practice locations around the country; both academic and nonacademic institutions were represented. None were from the same practice. There were 17 **fellowship** training programs represented (2 had trained **at** Massachusetts General Hospital, in different years). Their average number of years in practice was 10; the range was 3.5 to 20. See Table 1 (next page) for a listing of re-reviewers.