CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 01/27-28/98

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AGENDA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Drug Products
83rd Meeting
January 27-28 1998

Cardiovascular and Renal Drugs Advisory Committee

National Institutes of Health
Natcher Auditorium
45 Center Drive

TUESDAY, JANUARY 27, 1998

8:30 a.m. OPEN PUBLIC HEARING
Meeting open for public comment. In the absence of such comment the committee will consider the following agenda items:

NDA 20-736, Verdia (tasosartan capsules), Wyeth-Ayerst, to be indicated for hypertension.

SPONSOR'S PRESENTATION

10:45 a.m. BREAK

11:00 a.m. COMMITTEE DISCUSSION AND RECOMMENDATIONS

FDA Medical Reviewer: Juan Carlos Pelayo, M.D.
FDA Biostatistical Reviewer: James Hung, Ph.D.
FDA Temporary Voting Member: Barry Massie, M.D.
FDA Invited Expert: Lionel Rabin, M.D., Armed Forces Institute of Pathology (WRAMC)
Committee Reviewer: Udho Thadani, M.D.

1:00 p.m. LUNCH

2:00 p.m. Discussions of intravenous inotropic therapy for congestive heart failure.

SPONSOR'S PRESENTATION: Sanofi Pharmaceuticals
NDA 19-436, Primacor (milrinone lactate), injection.
NDA 20-343, Primacor (milrinone lactate) in 5% dextrose injection.

FDA Invited Experts: Lynne Stevenson, M.D., Brigham and Women's Hospital
Christopher O'Connor, M.D., Duke University Medical Center

FDA Temporary Voting Member: Barry Massie, M.D.
Committee Reviewer: Marvin Konstam, M.D.

5:30 p.m. ADJOURN

WEDNESDAY, JANUARY 28, 1998

9:00 a.m. NDA 20-718, Integrilin (eptifibatide) injection, Cor Therapeutics, for use in the settings of percutaneous transluminal angioplasty and acute coronary syndrome.

SPONSOR'S PRESENTATION

11:00 a.m. BREAK

11:15 a.m. COMMITTEE DISCUSSION AND RECOMMENDATIONS

FDA Medical Reviewers: Isaac Hammond, M.D.
FDA Biostatistical Reviewer: Walid Nuri, Ph.D.
Committee Reviewer: John DiMarco, M.D.

3:00 p.m. ADJOURN

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January 27, 1998 - Cardiovascular and Renal Drugs Advisory Committee Meeting

Agenda for NDA No. 20-736 - Tasosartan Capsules (Wyeth-Ayerst)

Sponsor's Presentation:

Clinical Efficacy and Safety Overview - Dr. Betty Riggs, Wyeth-Ayerst

Interpretation of Liver Function Test Abnormalities in a Clinical Data Base
- Dr. Willis Maddrey, Consultant

Clinical Data on Liver Function Test Changes with Tasosartan -
- Dr. Betty Riggs, Wyeth-Ayerst

Indicators of Clinical Significance of Liver Function Test Abnormalities -
- Dr. Joel Morganroth, Consultant

Concluding Remarks - Dr. Betty Riggs, Wyeth-Ayerst

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

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QUESTIONS

Questions

eptifibatide

28 January 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

Eptifibatide is an inhibitor of platelet GP IIb/IIIa and, consequently, an inhibitor of platelet aggregation. Eptifibatide has been previously considered by the Cardiac and Renal Drugs Advisory Committee, so some of the original data regarding platelet inhibition, kinetics, etc. need not be discussed. The results of the two major clinical trials, IMPACT II and PURSUIT, will be addressed in the following questions.

The Advisory Committee is being asked to consider each trial separately and then to consider to what extent they support one another. In a draft proposal on the evidence needed to support marketing, the Agency specifically suggested that the regulatory requirement for 'independent substantiation', for an anti-platelet agent, could be met by 2 studies, one in a post-angioplasty setting and the other in acute coronary syndrome, because these settings share some pathophysiological basis. Furthermore, the draft proposal says that 2 such studies would support use in *both* clinical settings.

IMPACT II

This was a double-blind, parallel-group trial that randomized 4010 subjects undergoing coronary angioplasty (of a variety of forms) at 82 medical centers to placebo or one of 2 regimens of eptifibatide: 135 µg/kg bolus plus a 24-hour infusion at 0.5 µg/kg/min or the same bolus plus 0.75 µg/kg/min. All patients received aspirin within 24 hours of angioplasty and intravenous heparin, targeting ACT between 300 and 350 seconds and aPTT of 2 to 3 times baseline. Other therapies were at the discretion of the investigator. Within the study was another study that evaluated a "stent kit".

At the February 28, 1997 meeting, the Cardiac and Renal Drugs Advisory Committee concluded that the lower dose of eptifibatide was distinguishable from placebo and that there was a favorable trend with the higher dose, but the Committee unanimously recommended that eptifibatide not be approved on the basis of IMPACT II alone. The Agency agreed with the Advisory Committee and issued the non-approvable letter included in the Committee's background package. COR Therapeutics, in their briefing package offers some responses to the FDA reviews of IMPACT II.

1. Are there other aspects of the February 28, 1997 Advisory Committee meeting's discussion of eptifibatide that require further clarification?

2. Are there any issues relating to the facts of IMPACT II requiring further clarification?

3. Upon reconsideration, do the results of IMPACT II *alone* demonstrate a beneficial treatment effect of eptifibatide when used as adjunctive therapy in patients undergoing PTCA? If so, ...

3.1. ...what is the effect of dose?

3.2. ...are the demonstrated incidence and severity of bleeding acceptable in this patient population?

3.3. ...are these results a sufficient basis for approval of eptifibatide in this setting?

PURSUIT

This was a double-blind, parallel-group trial that randomized 10,948 subjects from 726 centers and 27 countries to placebo or one of two regimens of eptifibatide: 180 μg/kg bolus plus a 72-hour infusion at 1.3 μg/kg/min or the same bolus plus 2.0 μg/kg/min. Subjects were 75 years of age or younger and had "unstable angina" characterized by symptoms of cardiac ischemia at rest lasting at least 10 minutes within 24 hours of enrollment, any of a variety of ST-T wave abnormalities, or CK-MB elevation. All subjects received concomitant aspirin (38 to 1500 mg) and could receive intravenous heparin with a target aPTT of 50 to 70 seconds. The lower-dose arm was discontinued, resulting in randomization of 4739 subjects to placebo, 1487 subjects to the lower dose, and 4722 subjects to the higher dose.

4. The PURSUIT results were geographically heterogeneous with respect to both magnitude and direction of treatment effect. Does this fact...

- ...strengthen one's confidence in inferences drawn from the study?
- ...undermine from one's confidence in inferences drawn from the study?
- ...play no role in drawing inferences from the study?

5. These questions pertain to interim analyses in PURSUIT.

5.1. What prospective rules were established for conducting such analyses and controlling overall type I error as a result of them?

5.2. What data were available to parties performing the interim analyses?

5.3. How many interim analyses were performed?

5.4. Given the interim analyses actually performed, did the final analysis appropriately control for type I error?

5.5. There was a prospective plan to consider discontinuation of one of the active treatment arms. The implementation of this plan resulted in the discontinuation of the low-dose arm.

5.5.1. Does this trial design preserve the type I error rate?

5.5.2. With respect to preservation of the interpretability of the trial, was an appropriate decision made to discontinue an arm?

5.5.3. Is it appropriate for the final analysis to be a comparison of only the placebo and high-dose arms?

6. These questions pertain to the primary end point, an unadjusted χ^2-analysis of the proportion of subjects in each group having death or myocardial infarction in the first 30 days.

6.1. Is this a reasonable end point for such a population? If not, what is?

6.2. There were more myocardial infarctions found by the blinded Clinical Events Committee than were identified by investigators.

6.2.1. What is the explanation for this discrepancy?

6.2.2. Does this discrepancy...

- ...strengthen one's confidence in inferences drawn from the study?
- ...undermine from one's confidence in inferences drawn from the study?
- ...play no role in drawing inferences from the study?

6.3. Would a time-to-first-event method of evaluation been more appropriate?

6.4. Was there a statistically significant treatment effect favoring eptifibatide for...

6.4.1. ...the pre-specified, intent-to-treat analysis of death or myocardial infarction?

6.4.2. ...all cause mortality?

6.4.3. ...myocardial infarction?

6.5. Was there a statistically significant treatment effect favoring eptifibatide in the sub-population that had...

6.5.1. ...PTCA?

6.5.2. ...CABG?

6.5.3. ...stent placement?

7. How important are the 6-month follow-up data, which have not been submitted to the Division for review, in interpreting the trial results?

8. Are the demonstrated incidence and severity of bleeding acceptable in this patient population?

9. What was the effect of *aspirin* on...

9.1. ...efficacy?

9.2. ...risk of bleeding?

10. What was the effect of *heparin* on...

10.1. ...efficacy?

10.2. ...risk of bleeding?

11. Do the results of PURSUIT *alone* demonstrate a beneficial treatment effect of eptifibatide when used as adjunctive therapy in patients with acute coronary syndrome? If so, ...

11.1. ...what is the effect of dose?

11.2. ...are the demonstrated incidence and severity of bleeding acceptable in this patient population?

11.3. ...are these results a sufficient basis for approval of eptifibatide in this setting?

IMPACT II and PURSUIT together

12. As outlined in the following table, there have been 4 dosing regimens of eptifibatide studied in the two major trials.

Trial	Bolus µg/kg	Infusion µg/kg/min	Duration of infusion hours
IMPACT II	135	0.5	20 to 24
	135	0.75	20 to 24
PURSUIT	180	1.3	72
	180	2.0	72

12.1. What is the best estimate of the in-vitro platelet aggregation that was achieved with each of these dosing regimens?

12.2. What verification was there for this platelet effect?

13. Generally and specifically in the PTCA group, compare the severity and incidence of bleeding events between IMPACT II and PURSUIT. Are such comparisons meaningful?

14. Generally and specifically in the PTCA group, compare the magnitude of treatment effect between IMPACT II and PURSUIT. Are such comparisons meaningful?

15. Should eptifibatide be approved? If so, ...

15.1. ...for what patient population?

15.2. ...how should the treatment effect be described?

15.3. ...what should the dosing recommendation be?

15.4. ...what should the label say about concomitant use of aspirin and heparin?

Questions

IV therapy for CHF

27 January 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiorenal Advisory Committee

The Division wishes to draw the Committee's attention to issues that arise during the development and evaluation of intravenous medications for the treatment of congestive heart failure. Such a medication will sometimes also exist in an oral formulation (like amrinone* or milrinone†), but sometimes the intravenous formulation will stand alone, as is the case with dobutamine,‡ sodium nitroprusside, and others. Development of the oral formulation (if there is one) may be concurrent with that of the intravenous formulation, or the oral formulation may have been developed earlier or later. In either case, the oral formulation may or may not turn out to be useful: That is, the oral formulation may eventually be demonstrated to carry a survival benefit, a symptomatic benefit, both, or neither.

Whether or not an oral formulation is also available and useful, the intravenous preparation will presumably have been developed for use in one or more of the following settings:

- When a patient is temporarily unable to take medication by mouth, the intravenous formulation will make continued therapy possible by bridging the gap of a small number of missed oral doses, possibly doses of medication different from this one.
- When a patient sustains acute decompensation of heart failure, the intravenous formulation will be used for a day or two of intensive care.
- When myocardial dysfunction (in a patient with or without established congestive heart failure) develops during cardiopulmonary bypass, the intravenous formulation will facilitate weaning the patient from the bypass pump.
- While patients are more or less stable, the intravenous formulation will be used intermittently or continuously for maintenance, or for prophylaxis against deterioration.

Intravenous drugs for the treatment of heart failure have historically been approved after adequate demonstration of dose-dependent and "appropriate" hemodynamic effects (decrease in filling pressures, increase in cardiac output, and so on) in patients with acute or chronic heart failure. In making these decisions, the Division has assumed

- that the drug would be used only occasionally in any given patient, and then for no more than a day or two, always when the patient was hospitalized for the treatment of severe acute heart failure;

* INOCOR®, Sanofi Winthrop.

† PRIMACOR®, Sanofi Winthrop.

‡ DOBUTREX®, Lilly.

- that although standard hemodynamic changes cannot be defined (that is, one cannot specify what drop in left atrial filling pressure is always desirable), a clinician may be able to titrate a drug through its effect on hemodynamics by monitoring some other physiologic variables (urine output, height of râles), so long as there is a predictable relationship between dose and hemodynamic effect (not that the same dose will have the same effect in every patient, but at least that the useful dosing range is defined, and the dose-response relationships for the various hemodynamic responses are at least qualitatively predictable over that range);

- that when a safe and effective chronic oral regimen has been defined, the concomitant target hemodynamic changes have been adequately described, because the same changes are "appropriate" in chronic and acute heart failure; and

- that when no oral regimen exists, the short-term hemodynamic effects are suitable surrogates for short-term symptom benefit, and that no formal estimate of the mortality effect needs to be obtained, beyond whatever point estimate is incidentally obtained (probably with wide confidence limits) from the hemodynamic trials.

1. Should we reconsider current guidelines for development of an intravenous drug for the treatment of heart failure? In particular, are you satisfied with the assumptions

1(A). that the drug will be used only occasionally in any given patient, and then for no more than a day or two, always when the patient is hospitalized for the treatment of severe acute heart failure;

1(B). that a clinician who has somehow decided on target hemodynamics in a given patient can approach those target levels by dose titration, so long as there is an orderly relationship between dose and hemodynamic effect;

1(C). that when a safe and effective chronic oral regimen has been defined, the concomitant target hemodynamic changes have been adequately described;

1(D). that the target hemodynamic values are the same in short-term and long-term use;

1(E). that when no oral regimen exists, the short-term hemodynamic effects are suitable surrogates for short-term symptom benefit, and that no formal estimate of the mortality effect of short-term uses needs to be obtained, beyond whatever point estimate is incidentally obtained

(probably with wide confidence limits) from the hemodynamic trials.

2. In the setting of acute decompensation (*e.g.*, acute pulmonary edema) of chronic congestive heart failure, which of the following assessments can be made?

2(A). hemodynamics (pulmonary-artery measurements, cardiac output, and so on)?

2(B). symptoms (dyspnea, orthopnea, and so on)?

2(C). morbidity (hospitalizations)?

2(D). survival?

3. In the setting of assisting discontinuation of cardiopulmonary bypass, which of the following assessments can be made?

3(A). hemodynamics?

3(B). symptoms?

3(C). morbidity?

3(D). survival?

4. In patients with chronic congestive heart failure, which of the following assessments can be made?

4(A). hemodynamics?

4(B). symptoms?

4(C). morbidity?

4(D). survival?

5. What might be the primary endpoints (hemodynamics? symptoms? morbidity? mortality?) of trials designed to support approval of an intravenous medication to be used when a patient sustains **acute decompensation** of heart failure, and the intravenous formulation will be used for a day or two of intensive care? What could the control treatment be? Don't spend time with combinations and permutations of possible combined endpoints, but do consider the cases

5(A). when an oral formulation of the same medication exists and is of known efficacy in congestive heart failure,

5(B). when an oral formulation of the same medication exists but is known to be *ineffective* in the treatment of heart failure, and

5(C). when no such oral formulation exists.

6. What might be the primary endpoints of trials designed to support approval of an intravenous medication to be used when myocardial dysfunction (in a patient with or without established congestive heart failure) develops during **cardiopulmonary bypass**, and the intravenous formulation will facilitate weaning the patient from the bypass pump? What could the control treatment be? Again, consider the cases

6(A). when an oral formulation of the same medication exists and is of known efficacy in congestive heart failure,

6(B). when an oral formulation of the same medication exists but is known to be *ineffective* in the treatment of heart failure, and

6(C). when no such oral formulation exists.

7. What might be the primary endpoints of trials designed to support approval of an intravenous medication to be used intermittently or continuously for **maintenance**, or for prophylaxis against deterioration, in patients whose congestive heart failure is more or less stable? What could the control treatment be? Again, consider the cases

7(A). when an oral formulation of the same medication exists and is of known efficacy in congestive heart failure,

7(B). when an oral formulation of the same medication exists but is known to be *ineffective* in the treatment of heart failure, and

7(C). when no such oral formulation exists.

8. What might be the primary endpoints of trials designed to support approval of an intravenous medication to be used as **bridging therapy** for a patient temporarily unable to take medication by mouth? What could the control treatment be? Again, consider the cases

8(A). when an oral formulation of the same medication exists and is of known efficacy in congestive heart failure,

8(B). when an oral formulation of the same medication exists but is known to be *ineffective* in the treatment of heart failure, and

8(C). when no such oral formulation exists.

9. In the circulated "Evaluation of Long-Term Treatment with Cyclic-AMP-Dependent Positive Inotropic Agents," Dr. Packer concludes that "Positive inotropic agents have not been shown to be effective or safe in the treatment of heart failure during long-term use, whether given continuously or intermittently or whether given orally or intravenously. Instead, long-term treatment has been associated with a consistent increase in the risk of hospitalization and death." Do you agree? Going beyond the drugs and studies there cited, is there evidence that the same conclusion applies more broadly, either to shorter regimens or to such other drugs used intravenously in congestive heart failure as

9(A). Digoxin?

9(B). Nitroglycerin?

9(C). Sodium nitroprusside?

10. Should some of the conclusions of today's discussion be retrofitted into the labeling of intravenous medications now approved for the treatment of congestive heart failure? The facts are of course different in each case, and detailed wordsmithing is not appropriate, but (for example) should each of these drugs' labels be changed to include applicable portions of language like

> <drug name> is indicated for the intravenous treatment of patients who are hospitalized with acutely decompensated heart failure. In general, <drug name> should be added to treatment with other drugs for heart failure, including digitalis, diuretics, and ACE inhibitors (and carvedilol?).
>
> Experience with intravenous <drug name> in controlled trials does not extend beyond 48 hours of repeated boluses and/or continuous infusions. In a multicenter trial of oral <drug name>, long-term use was associated with an increased risk of hospitalization and death, and patients with NYHA class IV symptoms appeared to be at particular risk. Similar trials of other drugs with similar mechanisms of action have given similar results. There is no evidence that long-term intravenous regimens of <drug name> do not carry a similar risk.

Questions

tasosartan

27 January 1998

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiorenal Advisory Committee

Tasosartan is an angiotensin-II receptor antagonist (a "sartan"). It has an unusually long-lived active metabolite, but in other ways it is quite similar to irbesartan (AVAPRO®, Bristol-Meyers and Sanofi), losartan (COZAAR®, Merck), valsartan (DIOVAN®, Novartis), and several others in the pipeline. Wyeth-Ayerst proposes that tasosartan be approved for the treatment of hypertension.

The antihypertensive efficacy of tasosartan is well demonstrated. The Division is uncertain, however, as to the correct interpretation of some elements of the safety database. In particular, some of the data can be interpreted to suggest that tasosartan is more hepatotoxic than other sartans. Other data support the view that tasosartan is, in this respect, no different from other sartans.

Hepatotoxicity is a recognized occasional adverse effect of some approved antihypertensive agents, including methyldopa, all of the ACE inhibitors, and many others. In at least one case (labetalol (NORMODYNE®, Schering; TRANDATE®, Glaxo Wellcome)), physicians prescribing the drug are encouraged to perform periodic hepatic laboratory tests. On the other hand, hepatotoxicity has also been grounds for non-approval or withdrawal, memorably in the case of dilevalol, considered by this Committee in 1990.

1. What do the animal data suggest regarding the hepatotoxicity of tasosartan and the other sartans?

2. There were no cases of clinically apparent liver disease in the clinical trials of tasosartan, and only one case in the trials of the other sartans. How much reassurance does this provide?

3. There have been scattered post-marketing reports of clinically significant liver disease convincingly attributable to some of the sartans. Should these reports be treated as drug-specific, or do they suggest a class phenomenon?

4. In the absence of reported cases of clinically apparent liver disease, what is your interpretation of the data related to observed elevations of hepatocellular enzymes in patients enrolled in clinical trials of tasosartan and the other sartans?

5. Patients who withdrew from clinical trials of tasosartan were much more likely to have been receiving tasosartan than placebo or any of the active controls. This sartan/control difference in withdrawal rates was larger than that seen with any of the other sartans. Was the unusually large difference probably the result of chance? Was it instead more likely to have been a consequence of the tasosartan investigators' unusually frequent assays of hepatic enzymes? Does it instead suggest that tasosartan is more hepatotoxic than the other sartans?

6. Assuming that tasosartan's antihypertensive efficacy (scarcely discussed today) is beyond challenge, should tasosartan be approved for the treatment of hypertension? If not, what sort of new study result would provide sufficient reassurance to permit approval?

7. If tasosartan is approved, what should its labeling say about the effect of tasosartan on the liver? Should the labeling recommend a program of monitoring hepatic enzymes during therapy (how often?) and then taking some action (discontinuing therapy? reducing the dose?) when the enzymes are abnormal (how abnormal?)? Should any post-marketing studies be performed?

8. What should the labeling of the older sartans say about hepatotoxicity?

9. Hepatic enzymes during the tasosartan clinical trials were assayed much more frequently than in any of the other sartan programs that the Division is aware of, and tasosartan might have sailed through approval if the sponsor had been less diligent. This might lead an observer to recommend that hepatic enzymes (and other monitoring) be done no more frequently than necessary. How frequently is that?

COR COR Therapeutics, Inc.

Cardio-Renal Advisory Committee Meeting

Eptifibatide (INTEGRILIN™)

January 28, 1998

AGENDA

Michael M. Kitt, M.D.	Vice President of Clinical Research COR Therapeutics, Inc.	Overview
Daniel Gretler, M.D.	Director of Clinical Research COR Therapeutics, Inc.	IMPACT II, Clinical Pharmacology
Robert Harrington, M.D.	Assistant Professor of Medicine Duke University Medical Center	PURSUIT
Michael Lincoff, M.D.	Assistant Professor of Medicine Cleveland Clinic Foundation	Coronary Angioplasty
Michael M. Kitt, M.D.	Vice President of Clinical Research COR Therapeutics, Inc.	Conclusion

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 01/27-28/98

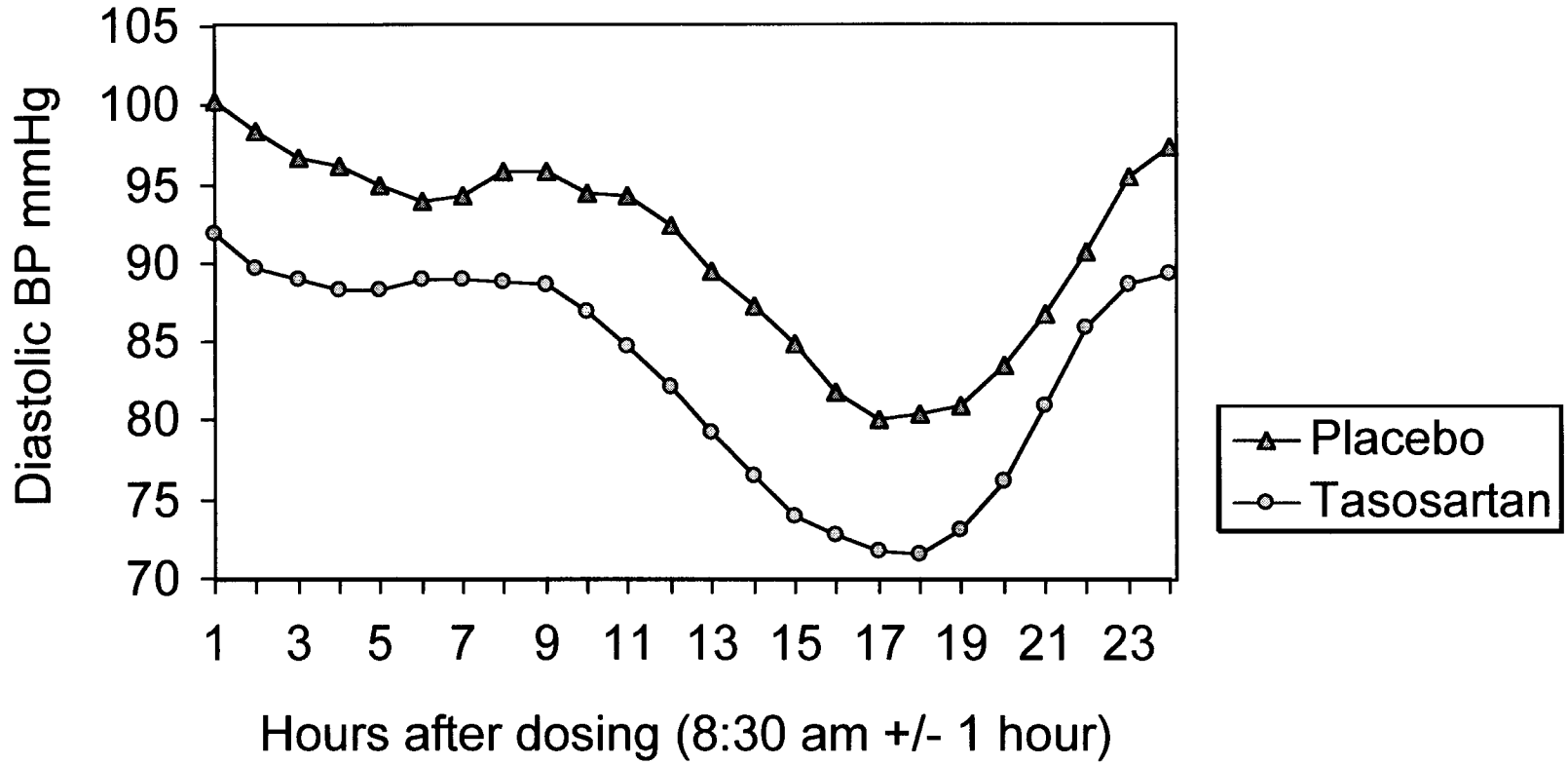
SLIDES

VERDIA (TASOSARTAN)

Betty S. Riggs, M.D.

Assistant Vice President
Clinical Research & Development
Wyeth-Ayerst Research

PROTOCOL 820A-322-US



AGENDA AND CONSULTANTS

- Agenda
  - Clinical efficacy and safety data – Betty Riggs, M.D.
  - Interpretation of liver function tests from the liver expert's perspective – Willis Maddrey, M.D.
  - Tasosartan LFT data – Betty Riggs, M.D.
  - Interpretation of LFT data from the cardiologist's perspective – Joel Morganroth, M.D.
- W-AR Consultants
  - Willis Maddrey, M.D.
  - Hyman Zimmerman, M.D.
  - Joel Morganroth, M.D.

DROPOUTS BECAUSE OF ELEVATED LFTs IN BLINDED, RANDOMIZED ANTIHYPERTENSIVE TRIALS

	Usual LFT Interval (Weeks)	Test Rx			Control Rx			Chi-Square Test with Yates' Correction
		n	Drop	%	n	Drop	%	
Irbesartan	4	1965	0	0.00	641	0	0.00	(Undefined)
Losartan	6-8	2552	4	0.16	1117	2	0.18	0.700< p<0.800
Valsartan	8-12	3719	6	0.16	1745	2	0.11	0.950< p<0.975
Xsartan	2	1778	0	0.00	874	0	0.00	(Undefined)
Ysartan##	4	2831	5	0.18	769	0	0.00	0.500< p<0.600
Tasosartan**	1	2982	13	0.44	1448	0	0.00	0.025< p<0.050
Tasosartan	1	2982	10	0.34	1448	0	0.00	0.050< p<0.100
Tasosartan*	1	2982	5	0.17	1448	0	0.00	p = 0.18
Troglitazone	NA	2510	21	0.84	NA	NA	NA	NA
Tacrine	1	663	NA	~26	NA	NA	<1	0.000< p<0.001
Labetalol	NA	940	0	0.0	NA	NA	NA	NA
Dilevilol	NA	1026	8	0.78	254	1	0.39	0.800≤ p<0.900

* Excludes dropouts after the first 12 weeks of the trials
** 3/13 dropouts may have had other reason
Events shown are from all trials, not just controlled trials

INTRODUCTION

- Tasosartan is a new, long-acting, angiotensin II receptor blocker
  - AT_1 receptor specific
  - Competitive antagonist
- Proposed indication for the treatment of hypertension, alone or in combination with other antihypertensive agents

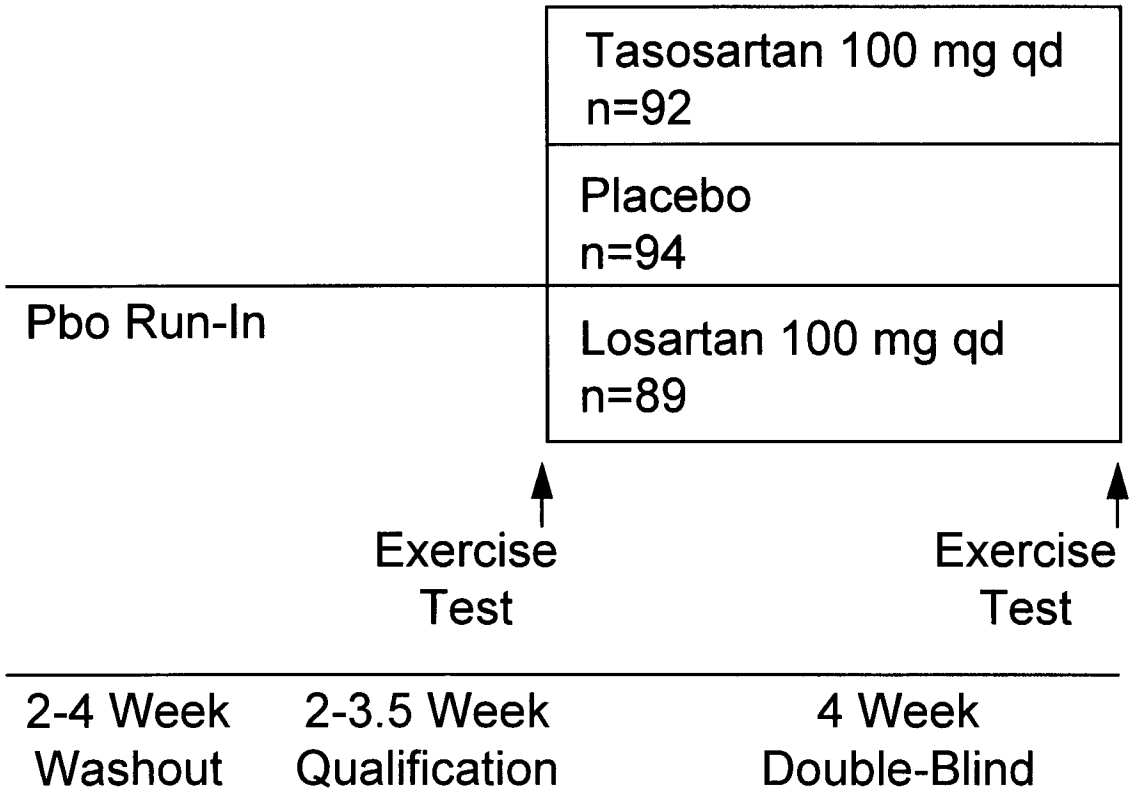
PHARMACOKINETIC PROFILE

- Absolute bioavailability = 60%
- No food effect
- Peak tasosartan plasma concentrations
  - 1-2 hours post-dose
- Dose proportional
  - between 10 and 300 mg
- Long duration of action

POST-NDA STUDIES

- Protocols 328 and 330
- Comparisons of tasosartan and losartan
- Designed to determine if tasosartan confers a benefit over an approved agent
- Important to the definition of risk to benefit ratio
- Discussed with FDA prior to initiation
  - Losartan dose = 100 mg per day
  - Maximum allowed in labeling
  - Gives comparator a fair chance to win

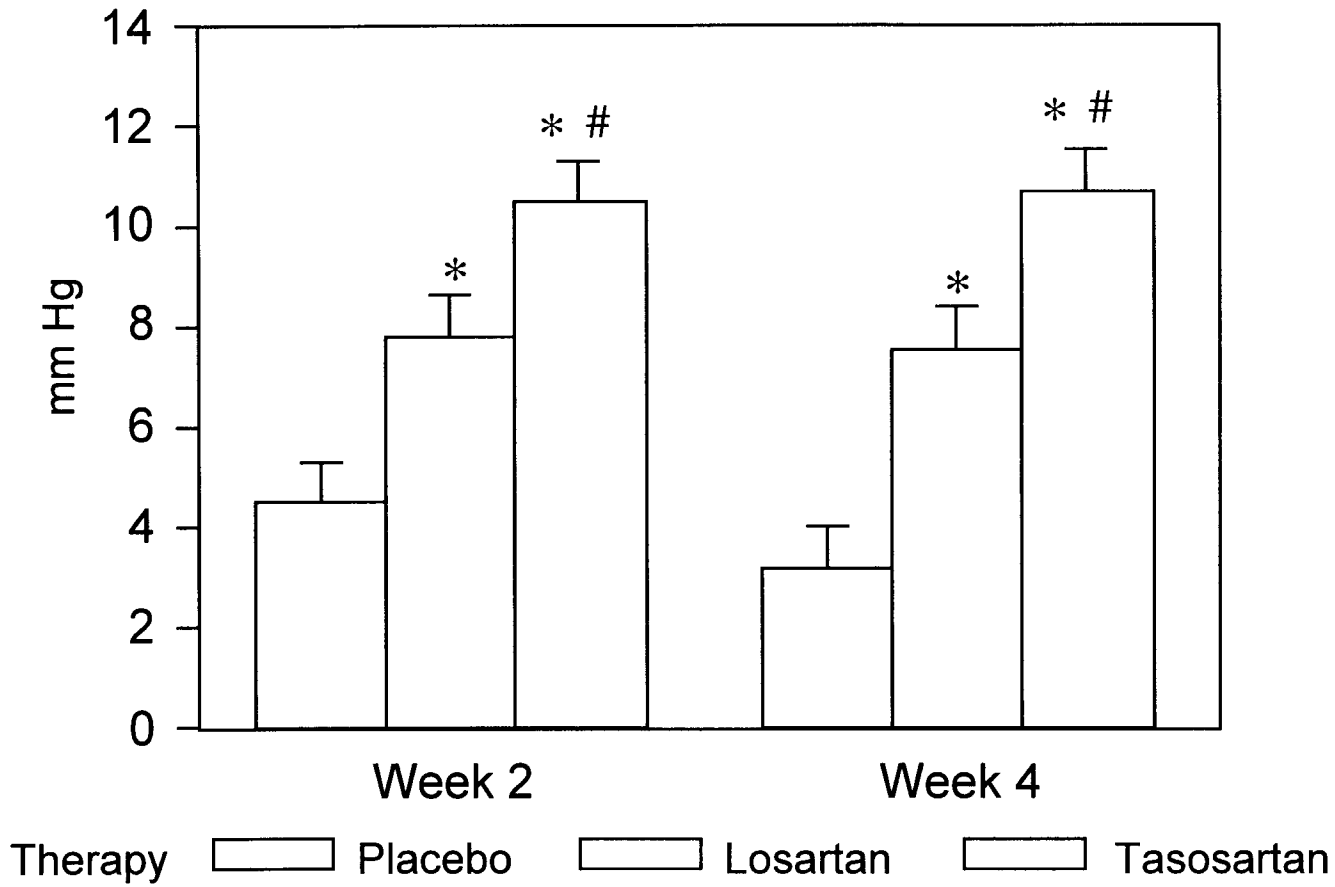
PROTOCOL 328



328-US

PROTOCOL 328

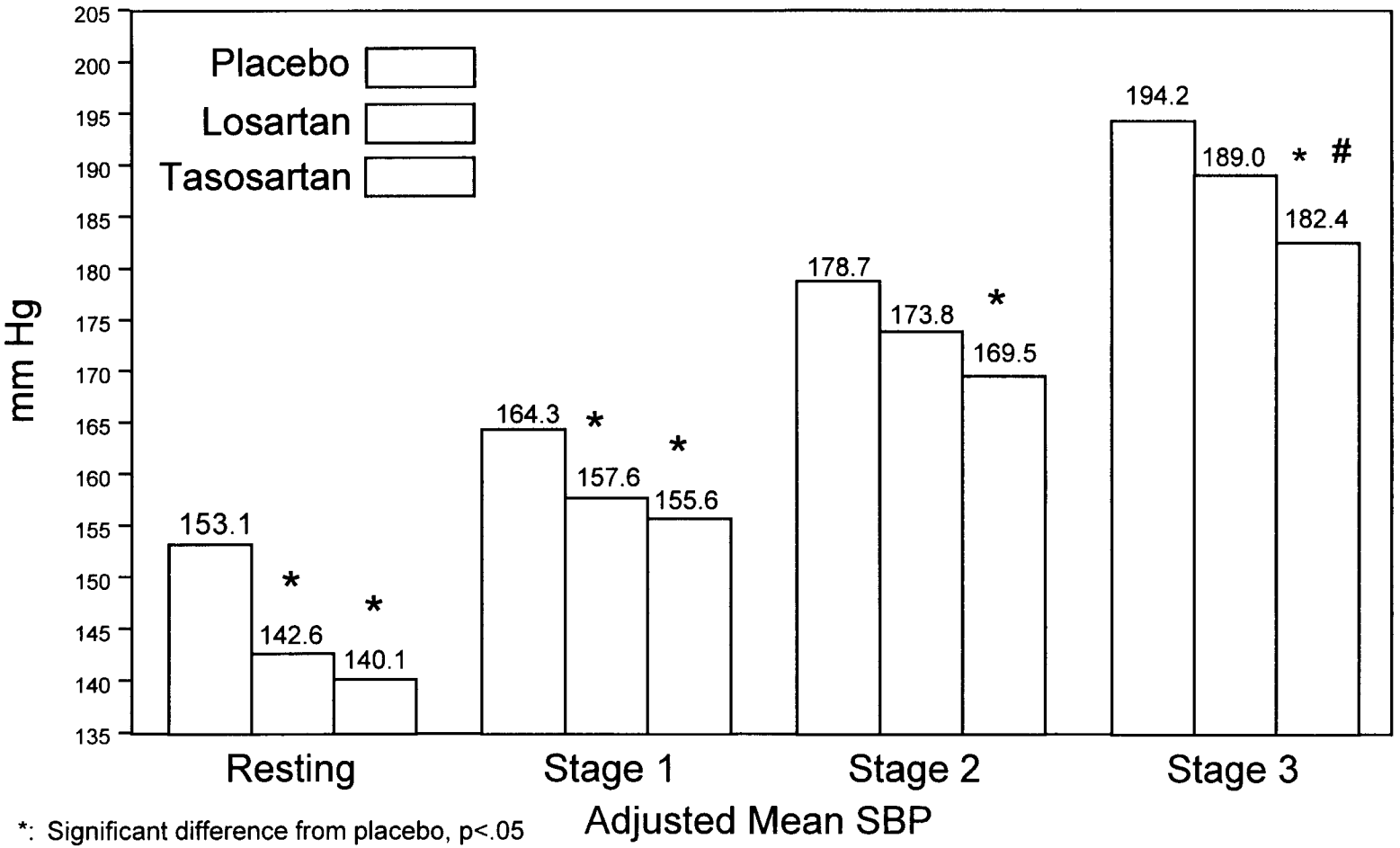
Reduction from Baseline Mean SiDBP (± SE)



*: Significant difference from placebo, p<.05
#: Significant difference from losartan, p<.05

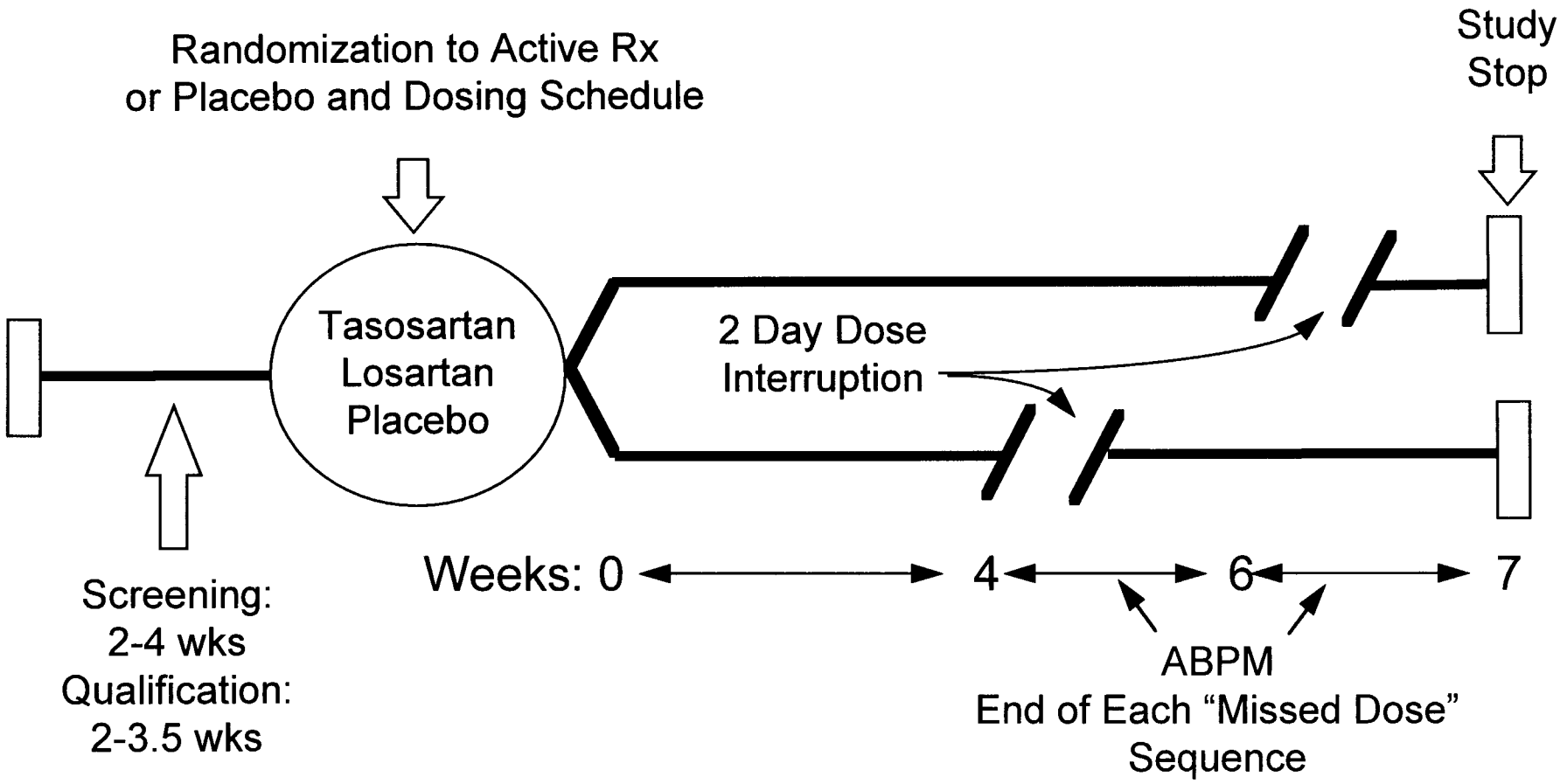
328-US

PROTOCOL 328
Systolic Blood Pressure
During the On-Therapy Exercise Stress Test

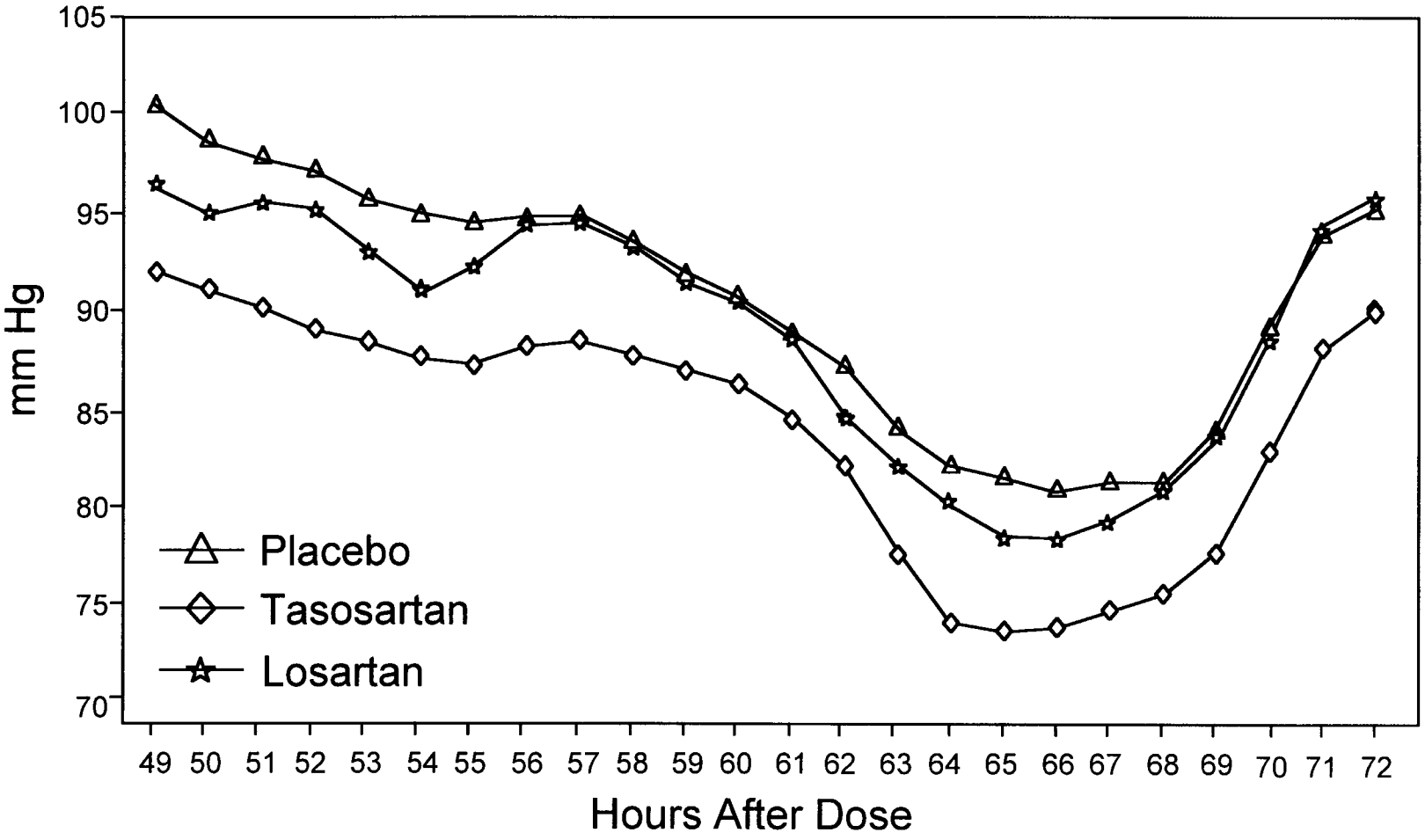


*: Significant difference from placebo, p<.05
#: Significant difference from losartan, p<.05

PROTOCOL 330: "MISSED DOSE" TRIAL



PROTOCOL 330
FINAL ABPM: 49 TO 72 HOURS POST DOSE
Diastolic BP



CORE PRESENTATION (MM#22397 WYE00195)

TASOSARTAN CONCLUSIONS

- Favorable PK Profile
- Dosage Recommendations
  - PK profile supports once daily dosing
  - Initial dose = 50 mg q day
  - Dose reduction for volume depleted, renal or hepatic impaired patients

TASOSARTAN CONCLUSIONS

- Clinical Efficacy Profile
  - Tasosartan has demonstrated efficacy compared to Pbo
  - Dose response was noted up to 100 mg daily
  - Additive effects are seen with diuretics
  - Efficacy superior to losartan was demonstrated for control of
    - Trough sitting diastolic blood pressure
    - 24 hour ambulatory pressure
    - Systolic blood pressure response during exercise
    - Blood pressure during 2 days of missed doses

SAFETY DATABASE
Exposure

- Clinical pharmacology studies - 709 patients or subjects enrolled
  - 639 received tasosartan
- Phase II - III studies - 5440 patients enrolled
  - 4132 patients treated with tasosartan
    - Doses ranged from 10 to 600 mg daily
  - Long-term exposure
    - 858 for ≥12 months
    - 122 for ≥18 months

SAFETY DATABASE

Demographic Attributes - Phases I Through III

	< 65 Years Old n=4697	≥ 65 Years Old n=1452
Mean Age (yrs)	49.6 (18 - 64)	70.7 (65 - 96)
Female	32 %	51%
Black	10 %	4%

DRUG-RELATED TREATMENT EMERGENT STUDY EVENTS IN ≥1% PATIENTS - CONTROLLED STUDIES

	Tasosartan (n=2574)		Pbo (n=516)	
Headache	241	(9)	82	(16)*
Dizziness	120	(5)	15	(3)
Asthenia	102	(4)	25	(5)
Nausea	39	(2)	10	(2)
Dyspepsia	42	(2)	6	(1)
Peripheral Edema	29	(1)	8	(2)
Diarrhea	31	(1)	7	(1)
Abdominal Pain	32	(1)	3	(<1)
Somnolence	28	(1)	3	(<1)
Any AE	771	(30)	177	(34)

*p<0.0001

PREMATURE DISCONTINUATIONS
Number (%)

Reason	Tasosartan n=2574	Pbo n=516	Atenolol n=142	Enalapril n=272	Losartan n=231
Any	316 (12.3)	67 (12.9)	29 (20.4)	67 (24.6)	19 (8.2)
AE	74 (2.9)	15 (2.9)	10 (7.0)	14 (5.1)	5 (2.1)
OME	43 (1.7)	19 (3.6)	5 (3.5)	2 (0.7)	2 (0.9)

DEATHS

- 13 deaths reported during the development program
- 4 deaths occurred ≥ 2 weeks after study completion
- None considered drug-related by the investigators
  - Cause of death was generally secondary to chronic diseases

ECG AND LABORATORY

- ECG parameters
  - No difference between treatment groups
- Laboratory parameters (except LFT's)
  - No difference between treatment groups
  - Creatine kinase (CK)
    - Analysis in some protocols performed at FDA's request
    - No differences between treatment groups

TASOSARTAN CONCLUSIONS

- Clinical Safety Profile
  - Incidence of TESE similar to placebo
  - No rebound
  - No apparent dose-related increases in study events with doses up to 600 mg daily
  - In controlled trials discontinuation rate due to clinical AEs was the same as placebo (2.9%)

INTERPRETATION OF LIVER FUNCTION TEST ABNORMALITIES

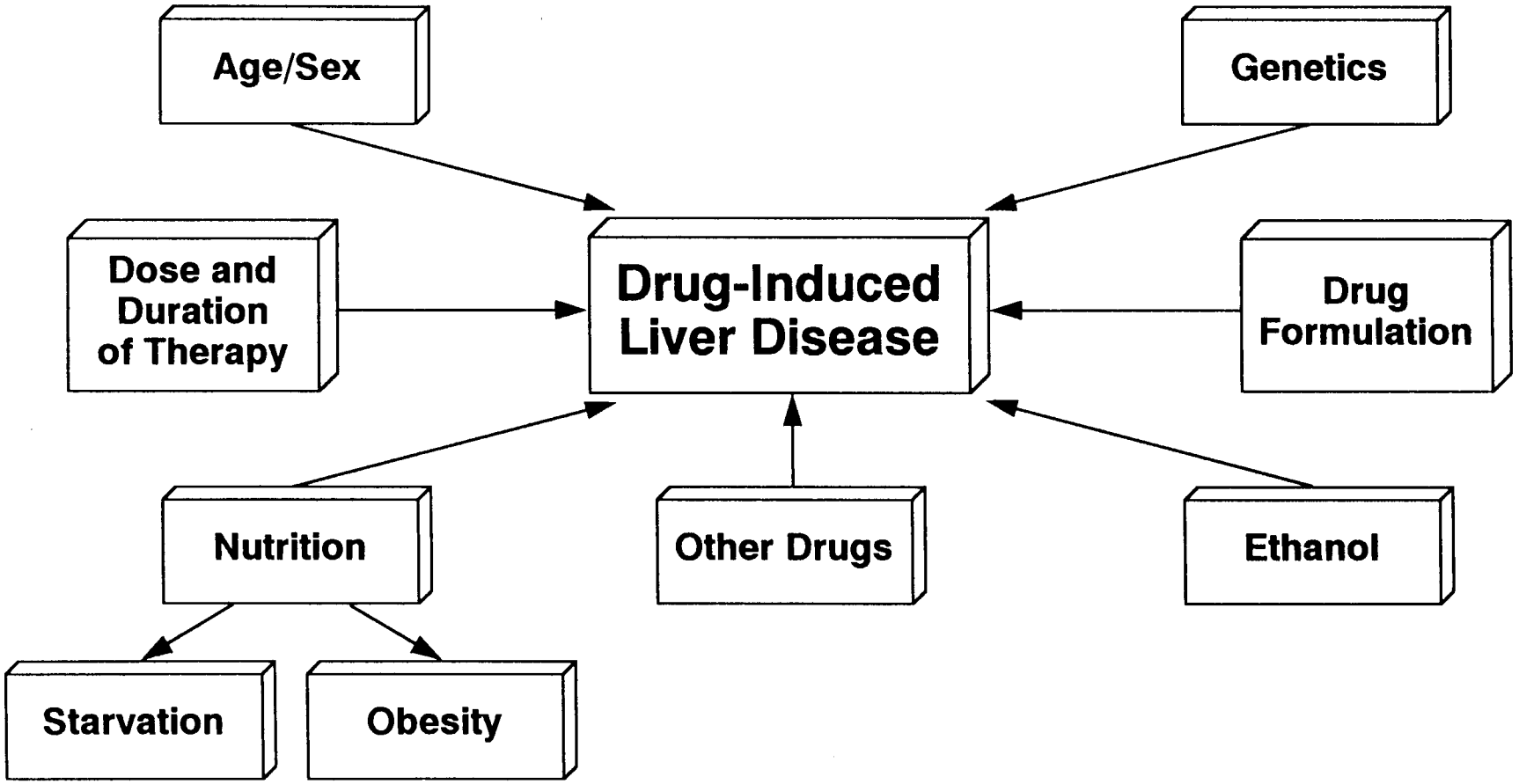
Willis C. Maddrey, MD, MACP

Executive Vice President for Clinical Affairs
The University of Texas
Southwestern Medical Center

Analysis of Liver Abnormalities in Drugs Under Evaluation

- Establish likelihood of causing liver injury
- Establish time of onset
- Establish pattern of injury (cholestatic vs hepatocellular injury)
- Establish course following withdrawal

Risk Factors for Drug-Induced Liver Disease



Limited Value From Preclinical Animal Studies

Importance of Events Observed in Clinical Trials

Factors to Consider in Analyzing a Drug Data Base

- Frequency and pattern of biochemical abnormalities
- Number/sex/age of patients
- Maximum height of abnormalities
- Association with ANY clinical manifestations
- Course of resolution following withdrawal

Isoniazid (INH)-Induced Liver Injury

- Minor elevations in ALT:
  - Observed in 10% to 20% of patients
  - Within 2 months of starting treatment
  - Most resolve without stopping INH
- Severe liver injury with jaundice:
  - 1% of treated persons
  - 2% in persons >50 years of age
  - Women at increased risk
- Fulminant hepatic failure:
  - 10% of persons who develop jaundice
  - Continued treatment during prodrome increases hepatocyte necrosis
  - Resolution in nonfatal cases

Signals Regarding Hepatotoxicity

Major:	**Development of acute liver failure**
	Development of symptoms
	Onset of clinically apparent jaundice
	Appearance of ascites, encephalopathy, coagulopathy
Intermediate:	**ALT >8x ULN**
	ALT >5x ULN
	ALT >3x ULN
Minor:	**Any elevation ALT (<3x ULN) in asymptomatic patient**

Relevance of Elevated ALT Levels

- Inexact
- Important role of associated symptoms
- >3x equals to finding inflammation on liver biopsy
- >5x considerably heightened awareness and followup
- >8x time for concern -- withdrawal

Importance of Determining What Happened to Patients Found to Have Elevated ALT Levels Who Continued to Take Drug

- % Who Resolved
- % Who Progressed
- % Who Stayed the Same

Adverse Drug Reactions in Patients with Preexisting Liver Disease

- **Risk of drug-induced liver injury generally the same in patients with or without preexisting liver disease**

Value of Planned Monitoring

- When definite risk established
- Time course of onset known
- Likelihood that stopping based on preset criteria will minimize chance of progressive injury

Limited Value of Monitoring

- Not often followed
- Not very predictive
- Timing must be based on observed abnormalities

TASOSARTAN LFT ANALYSIS

- Preclinical data
  - 17 studies
  - **No significant laboratory or histopathology findings**
- Clinical data
  - Final safety update database
- Comparison with losartan
  - Publications from the medical literature
  - FDA medical officer's reviews

DEFINITIONS

- Potential Clinical Significance
  - Based on the Fogarty Conference published in 1979
  - Defined as ALT/AST $\geq$ 3 x UNL for patients with normal baseline or $\geq$ 3 x baseline for patients with abnormal baseline
- Resolution
  - Defined as a decrease to $\leq$ 2 x UNL or baseline
- Discontinuation due to LFT's
  - Based on the primary reason as specified by the investigators

NUMBER (%) OF TASOSARTAN-TREATED PATIENTS WITH ALT/AST ELEVATIONS OF POTENTIAL CLINICAL SIGNIFICANCE

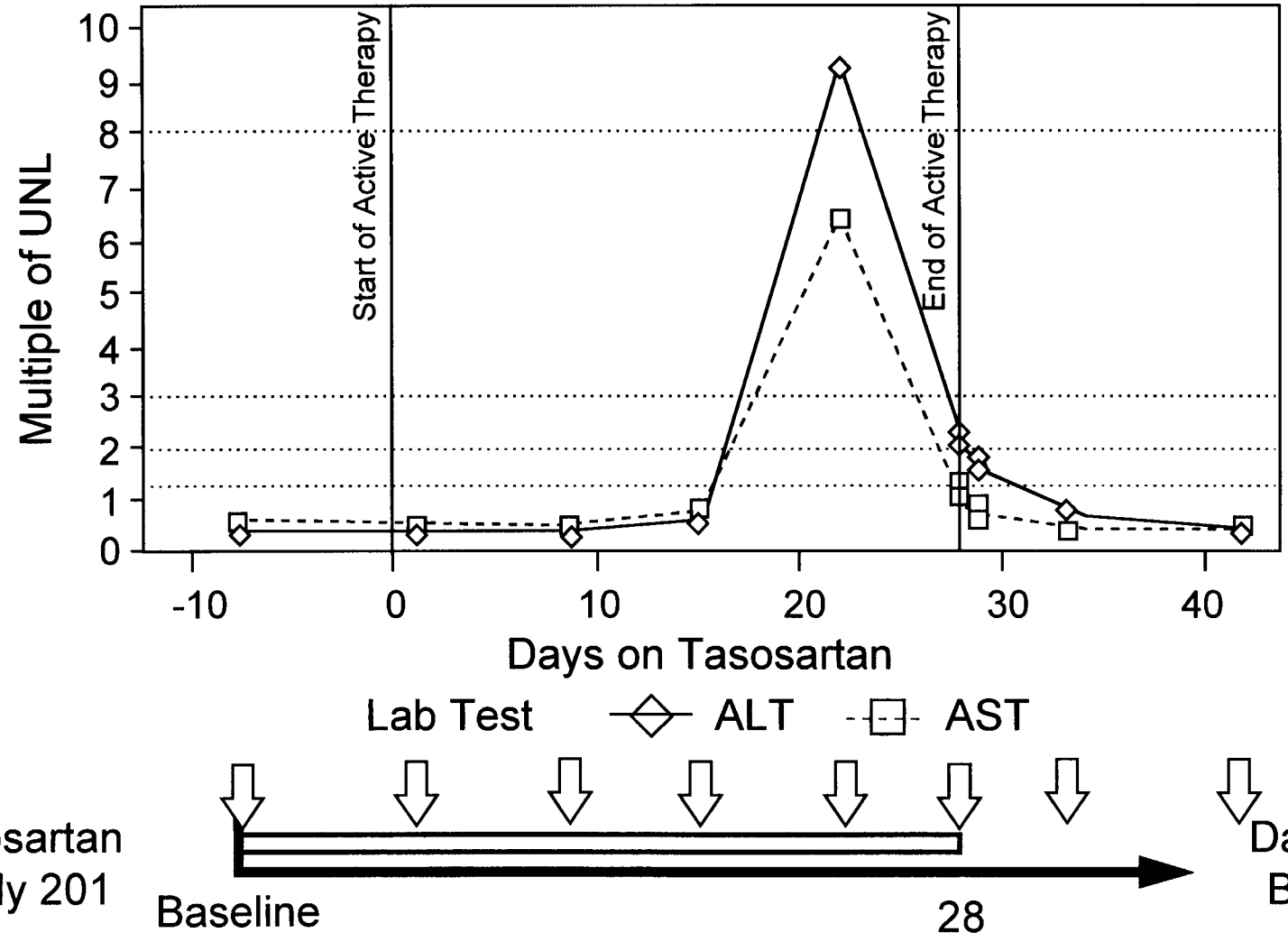
- Patients in phase II and III studies - controlled and open label
  - 4409 had at least one on-therapy laboratory evaluation
  - 83 (1.8%) of these had a potentially clinically significant ALT/AST
- Patients with normal LFT's at baseline
  - 3776 had at least one on-therapy laboratory evaluation
  - 73 (1.9%) of these had a potentially clinically significant ALT/AST

RESOLUTION OF ALT/AST ABNORMALITIES

- For patients with potentially clinically significant transaminase elevations, laboratory values resolved
  - While patients were still on tasosartan, even with maximum elevations as high as 9.5 x UNL
  - Total in both controlled and open trials, 33/49 patients (67%) resolved on-therapy

SPONTANEOUS RESOLUTION ON-THERAPY

Patient 20124-0014



CLINICAL SEQUELAE

- No patient had clinical sequelae associated with transaminase elevations
  - No cases of drug-related jaundice
  - No hospitalization for elevated liver enzymes
  - No drug-related death due to liver failure
- This was true for patients who remained on therapy despite elevations and for those who discontinued due to laboratory abnormalities

DISCONTINUATIONS DUE TO ALT/AST

- Controlled studies
  - Total n=10 of 2550 (0.39%)
    - 4 cases from the NDA
    - 6 cases from the controlled trials in the EU dossier
  - All have F/U and **all** LFT's have returned to normal
- Open-label studies
  - Total n=45 of 1859 (2.4%)
    - 43 resolved
    - 2 with final values < 3x UNL
      - 1 patient on Lopressor, Norvasc, Dyazide
      - 1 patient on Maxzide

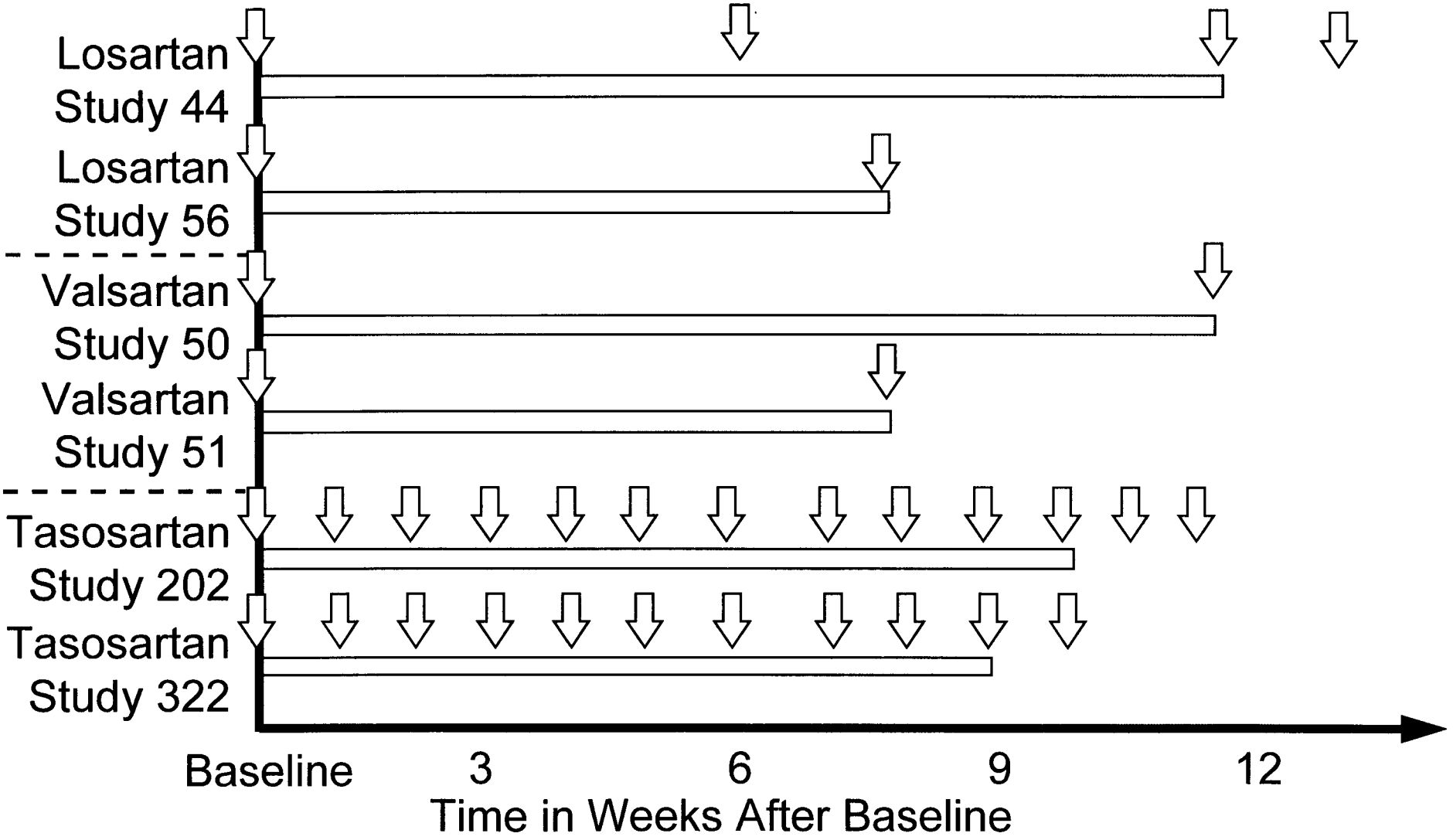
COMPARISONS WITH OTHER PROGRAMS

- Probably not valid
- Confounding factors include
  - Variability of rules regarding discontinuations
  - Different laboratory sampling regimens
  - Different duration of studies

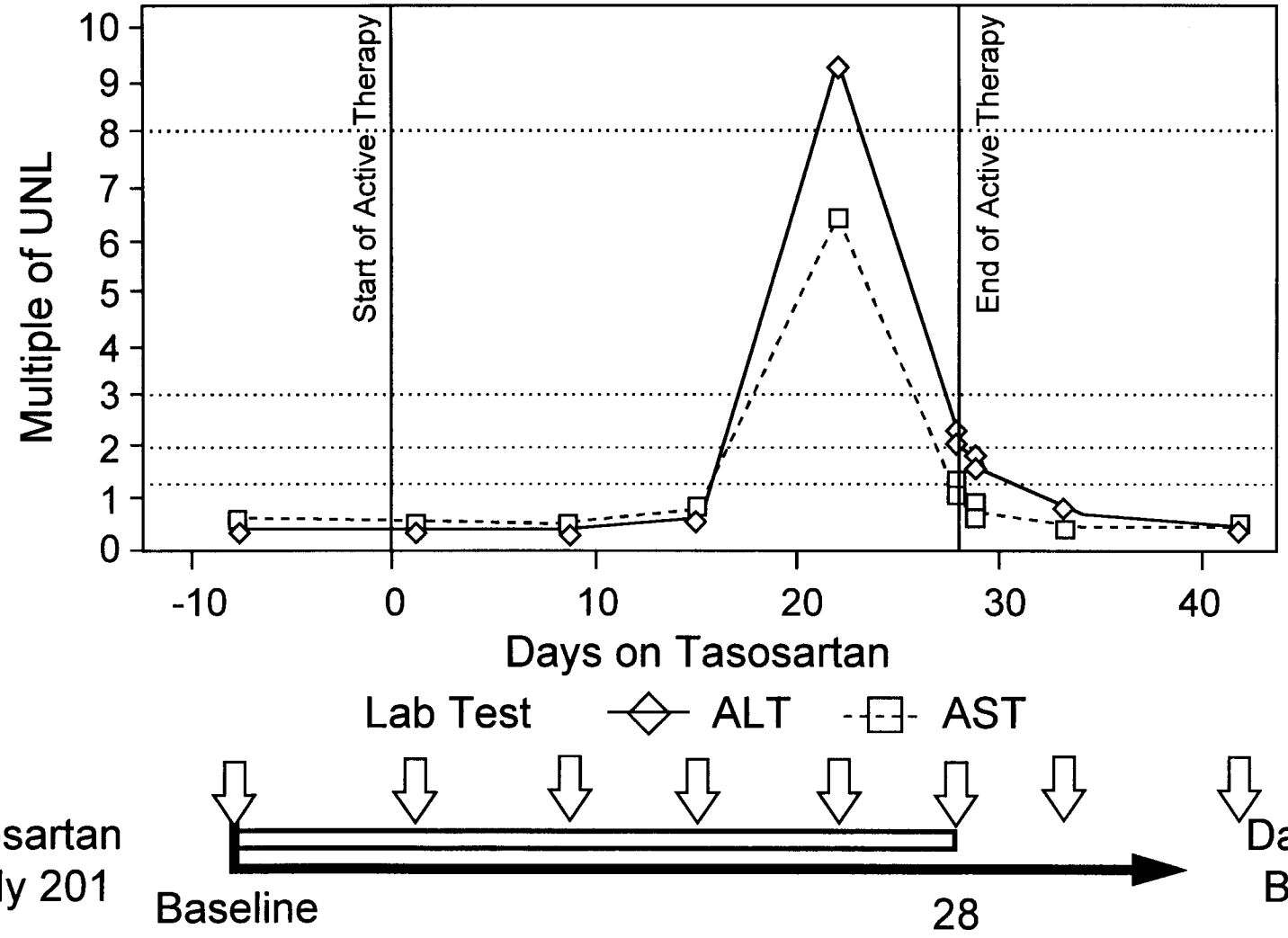
DISCONTINUATIONS

- Protocols contained no prespecified discontinuation rules for laboratory abnormalities observed in our studies
- Discontinuations reflect investigators' judgment
  - 1 site was responsible for 3 of 10 D/C's in controlled studies
    - 1 patient at this site was D/C'd for ALT/AST 2.0 x UNL

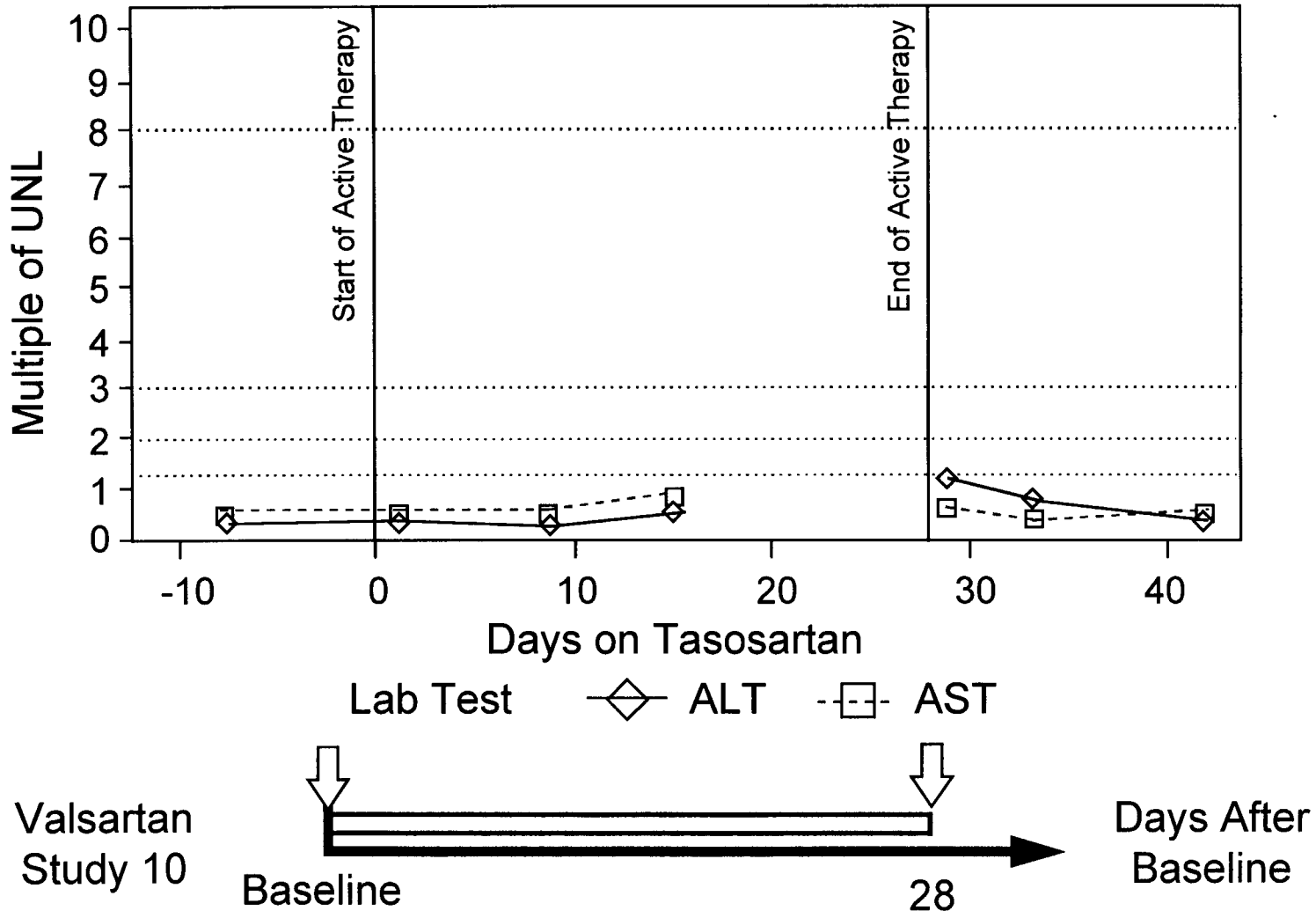
COMPARISON OF LABORATORY SAMPLING FREQUENCIES



COMPARISON OF LABORATORY SAMPLING FREQUENCIES
Patient 20124-0014



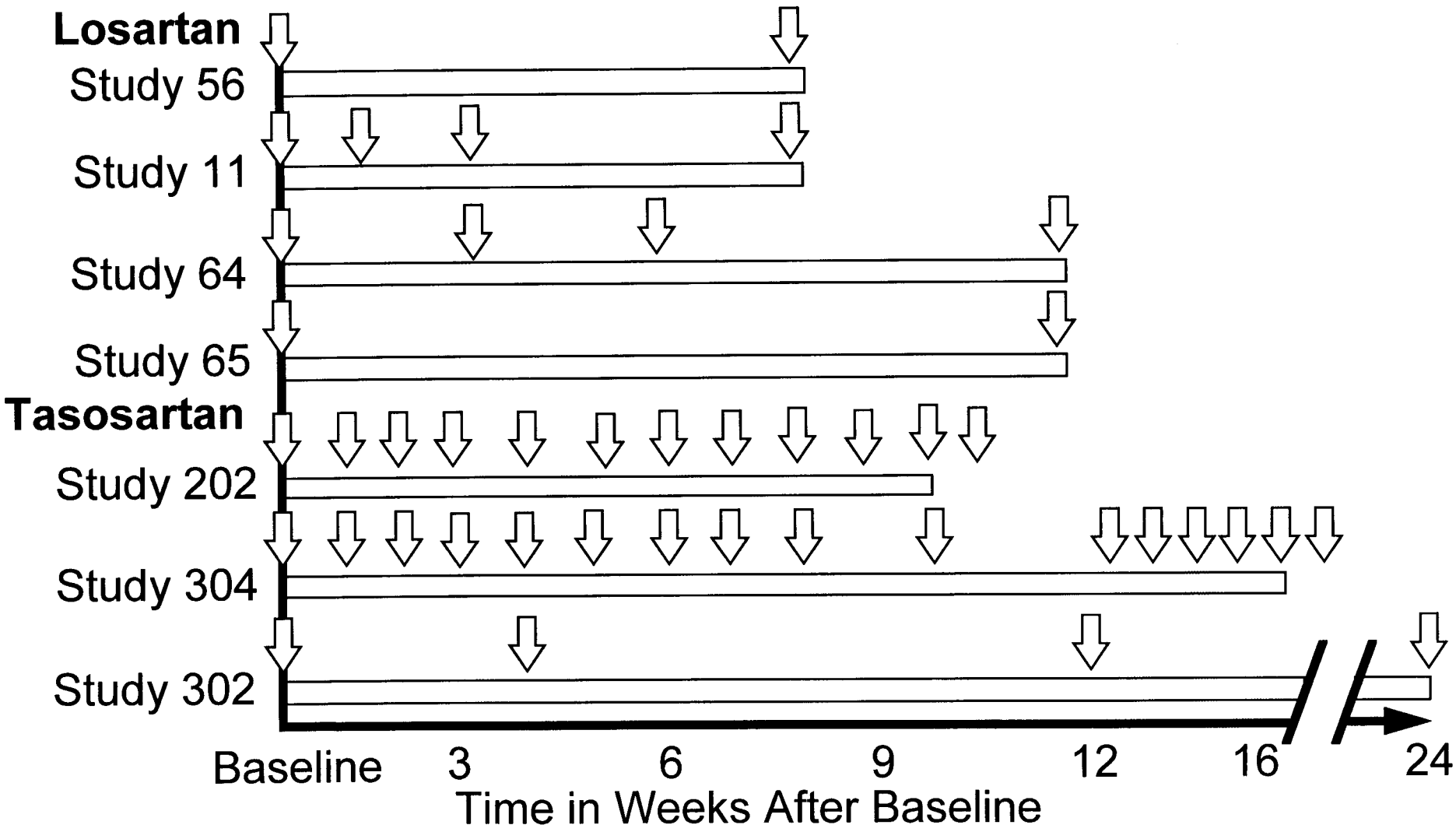
SIMULATION
Patient 20124-0014



EFFECT OF SAMPLING FREQUENCY ON INCIDENCE OF ALT/AST

- Tasosartan controlled trials using weekly sampling
  - 32 patients had ≥ 3x elevations during double-blind therapy
  - 12 of these had normal values at the last on-therapy visit
  - Incidence of elevations = 1.3%
- Simulation of controlled trials with baseline and end of double-blind sampling
  - 12/32 (38%) elevations would have been missed
  - Incidence of ALT/AST elevations in tasosartan controlled trials would have been = 0.8%

COMPARISON OF SAMPLING FREQUENCIES AND STUDY DURATION



IMPACT OF STUDY DURATION ON DISCONTINUATIONS

- 5 of 10 discontinuations occurred after 12 weeks of therapy in the controlled trials
- These would have been missed if our program had been comparable in study duration to the losartan and valsartan programs

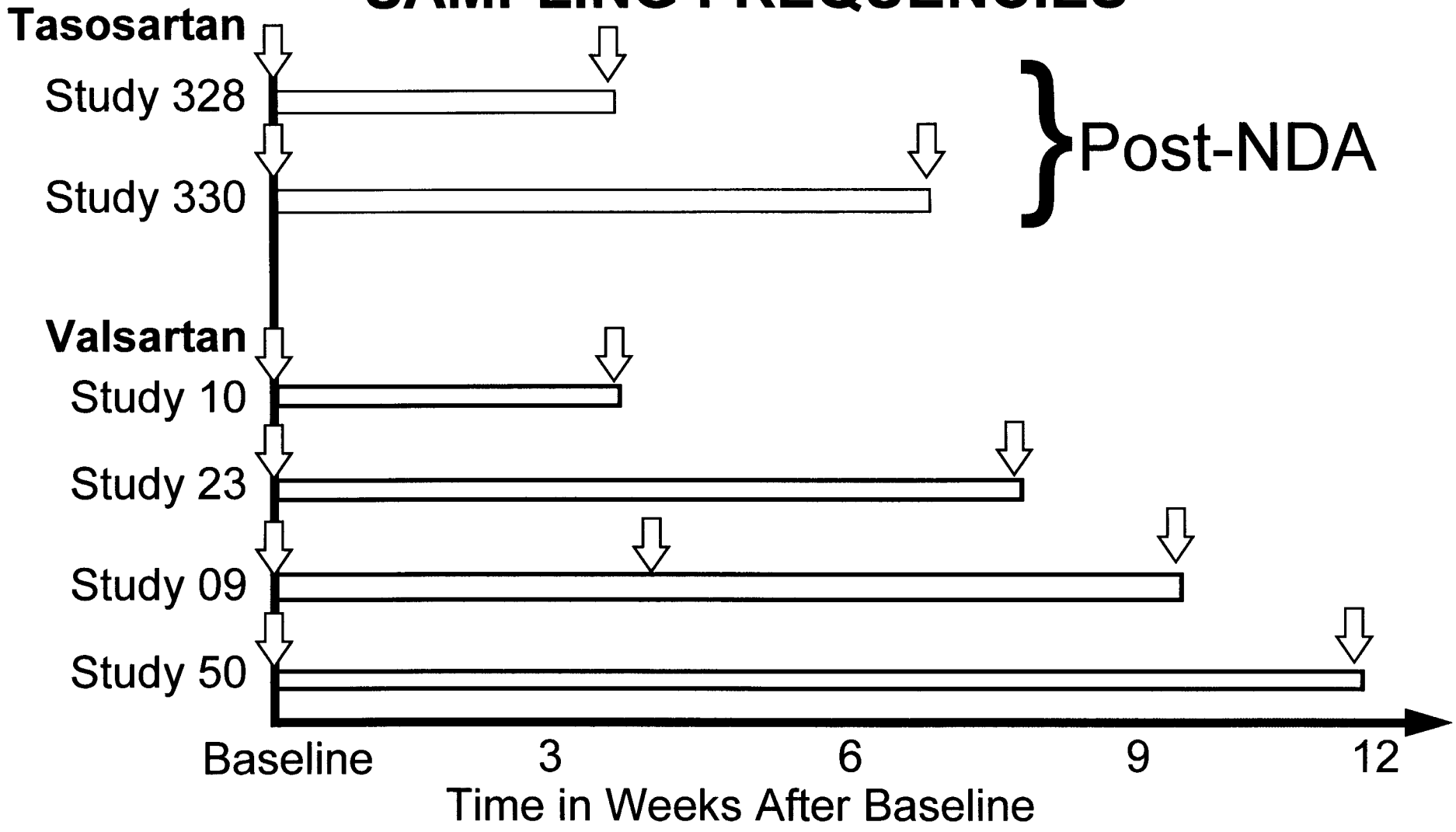
IMPACT OF STUDY DURATION ON DISCONTINUATIONS

- Tasosartan discontinuation rate if all controlled studies were ≤12 weeks
  - 0. 20%
- Valsartan discontinuation rate per FDA
  - 0.16%

IMPACT OF STUDY DURATION ON INCIDENCE RATES

- 11 of 20 elevations in the normal at baseline tasosartan monotherapy group of the controlled trials occurred after 12 weeks of therapy
  - In shorter term studies, these would not have contributed to the reported incidence of ALT/ AST abnormalities

COMPARISON OF LABORATORY SAMPLING FREQUENCIES



POST- NDA STUDIES

- Combined Protocols 328 and 330
  - Losartan n=198
  - Tasosartan n=194
  - Placebo n=203
- Potentially Clinically Significant Abnormalities
  - 1 losartan-treated pt had ALT= 3.7 x UNL
  - No tasosartan pts had ALT >3 x UNL
  - No pts discontinued due to LFT's

CLINICAL SAFETY AND TOLERABILITY OF LOSARTAN

- Safety database
- 16 double-blind and 4 open label studies
- 3800 hypertensive patients
  - 2900 treated with losartan
  - Most common laboratory adverse event was
    - Elevated ALT (1.9%)
    - Laboratory AE's were similar in placebo and losartan groups
  - Therapy was discontinued due to laboratory AE's in 7 patients

Weber M. Clinical Therapeutics. 1997;19:604-616.

LOSARTAN POST-MARKETING EXPERIENCE

- Approximately 3 years of marketing experience
- Estimated 2 million patients have received losartan
- 80 reports of liver function abnormalities

JAMA 1997; 278: 1572

TASOSARTAN CONCLUSIONS

- Tasosartan is safe and manifests no greater hepatotoxicity than other marketed antihypertensives
  - Preclinical studies demonstrated no evidence of hepatotoxicity
  - In clinical studies, 59% of patients with ALT/AST elevations did not discontinue; 67% of patients with elevations had on-therapy resolution
  - No clinical sequelae were associated with these laboratory abnormalities
  - The incidence of ALT/AST abnormalities is similar to losartan when these drugs are studied under the same conditions

INTERPRETATION OF LFT DATA FROM DRUG DEVELOPMENT DATABASES

Joel Morganroth, MD, FACC

HOW TO PREDICT LIVER TOXICITY SARTANS AND OTHER DRUG CLASSES FROM FDA AND SBAs

	Pre-Clinical	% ≥3 x	% D/C	NDA: Liver Failure Deaths	Post Market Results
Voltaren	+	2.8	0-3.4	4/2290	Deaths
Selacryn	?	23 (> UNL)	?	? 7/675	Deaths
Dilevilol	-	1.7	0.46	1/3200	Deaths
Rezulin	+	1.5	0.8	0/2510**	Deaths
Tacrine	-	25	10	0/7000*	OK
Mevacor	+	1-2	1-2.6	0/814	OK
Sartan	-	0-0.5	0-0.2	0/12,836*	OK (No Deaths)
Taso	-	0.8***	0.4	0/4132	-
Adjusted Taso	-	0.4***	0.2	0/4132	-

* = 1 Serious case
** = 2 serious cases
*** = Data from FDA "backgrounder"

APPLICATION OF TASOSARTAN NDA DATABASE

Type of Data	Results		Predictability of Having Liver Failure Deaths After Market
Preclinical data	Negative		Low
Clinical			
	Observed Taso	**Adjusted Taso**	
Liver failure deaths	0	0	High
D/C rate and % LFT elevation	Higher than other sartans	Same as other sartans	Low

1) Taso = other sartans
2) Low chance of Liver Deaths Post Market
3) Only way to tell is to measure after marketing

Eptifibatide (INTEGRILIN™)

Cardiovascular and Renal Drugs
Advisory Committee
January 28, 1998

Michael M. Kitt, M.D.

Vice President, Clinical Research

COR Therapeutics, Inc.

MK1 title

Overview

- Integrilin/Eptifibatide a GP IIb/IIIa antagonist for Unstable Angina/Non Q-wave MI and coronary angioplasty
- IMPACT II Study demonstrated efficacy and safety in coronary angioplasty
- PURSUIT Study demonstrated efficacy and safety in Unstable Angina/Non Q-wave MI

IMPACT II and PURSUIT

- Two studies in similar pathophysiological conditions
- Similar endpoint: death and myocardial Infarction
- Over one quarter of patients in PURSUIT underwent coronary angioplasty
- Over one third of patients in IMPACT II had Unstable Angina/Non Q-Wave Myocardial Infarction
- Acceptable safety profile in both studies

MK3

Indication Statement

Prevention of Death/Myocardial Infarction in patients with Unstable Angina/Non Q-Wave Myocardial Infarction

and

Prevention of ischemic complications of Coronary Angioplasty

MK4

Agenda

Michael M. Kitt, M.D.	Vice President of Clinical Research COR Therapeutics, Inc.	Overview and Conclusion
Daniel Gretler, M.D.	Director of Clinical Research COR Therapeutics, Inc.	IMPACT II, Clinical Pharmacology
Robert Harrington, M.D.	Assistant Professor of Medicine Duke University Medical Center	PURSUIT
Michael Lincoff, M.D.	Assistant Professor of Medicine Cleveland Clinic Foundation	Coronary Angioplasty

Consultants

Eric Topol, M.D.	Professor and Chairman, Dept. of Cardiology Cleveland Clinic Foundation
Judith Hochman, M.D.	Associate Professor of Medicine Columbia University
Kerry Lee, Ph.D.	Associate Professor of Biostatistics Duke University Medical Center
James Tcheng, M.D.	Associate Professor of Medicine Duke University Medical Center

MK6

Eptifibatide (INTEGRILIN™)

Cardiovascular and Renal Drugs
Advisory Committee
January 28, 1998

Daniel D. Gretler, M.D.
Director, Clinical Research

COR Therapeutics, Inc.

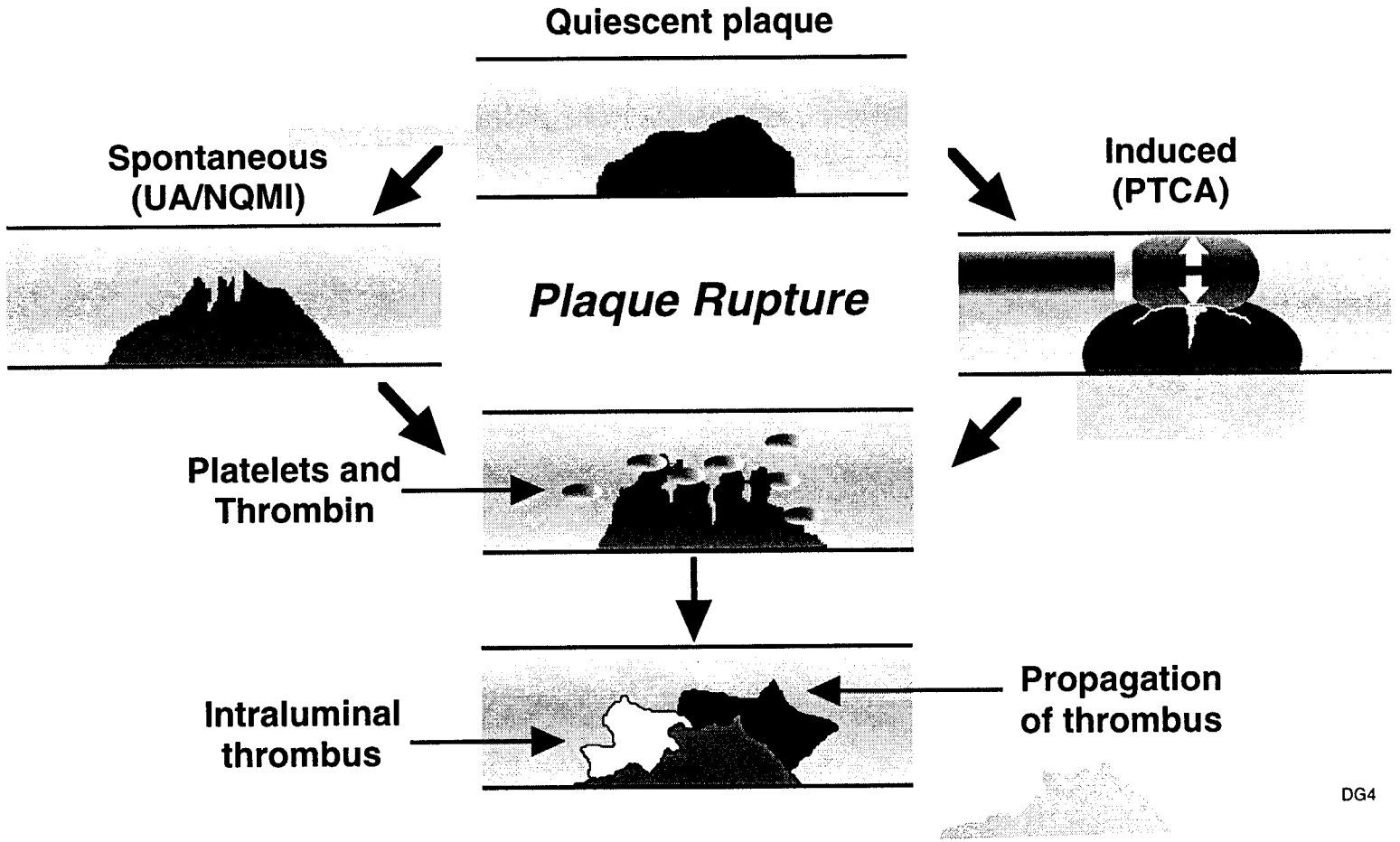
Background

- Pathophysiology and Pharmacology
- IMPACT II
- Dose Selection

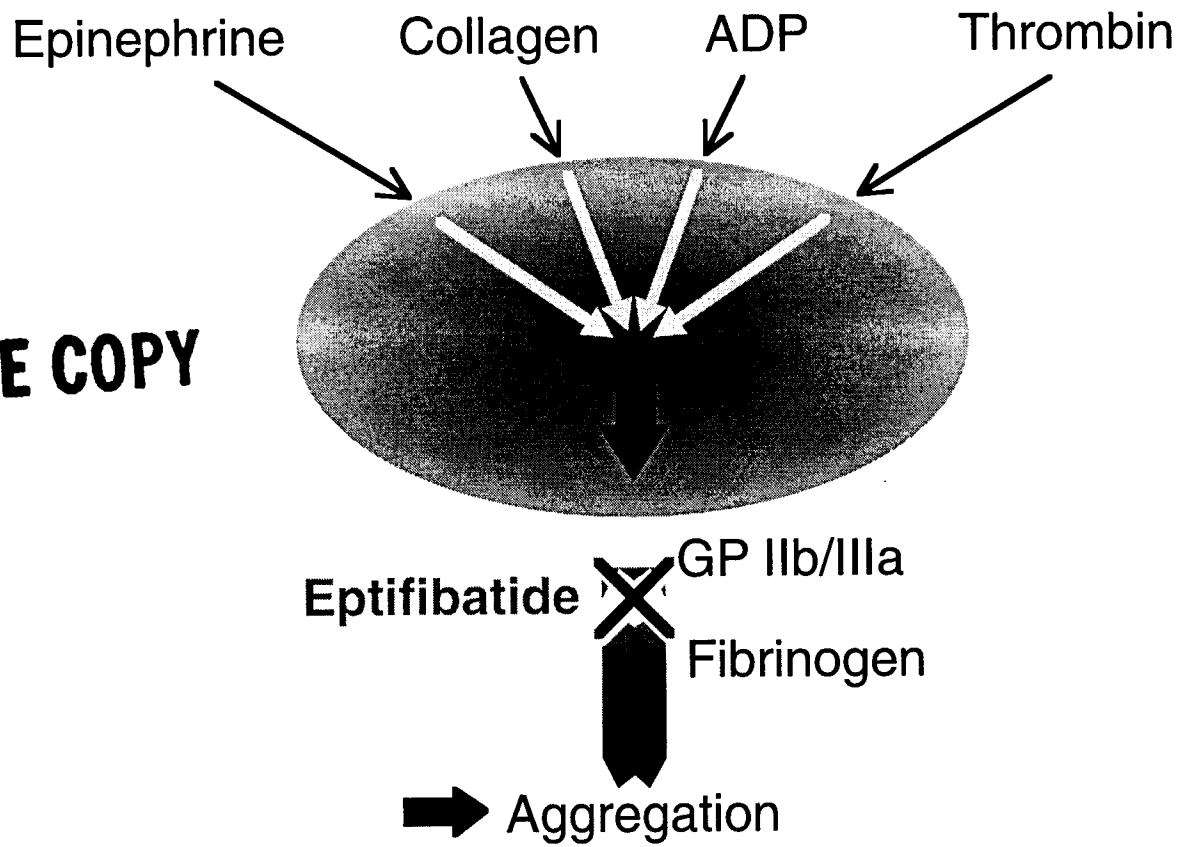
Background

- Pathophysiology and Pharmacology
  - Common pathophysiology UA/NQMI and PTCA
  - GP IIb/IIIa as pharmacologic target
  - Clinical pharmacology of eptifibatide
- IMPACT II
- Dose Selection

Common Pathophysiology



Final Common Pathway



Favorable Clinical Pharmacology Profile

- High affinity
- High selectivity
- Rapid onset of action
- Rapid reversibility
- Not immunogenic

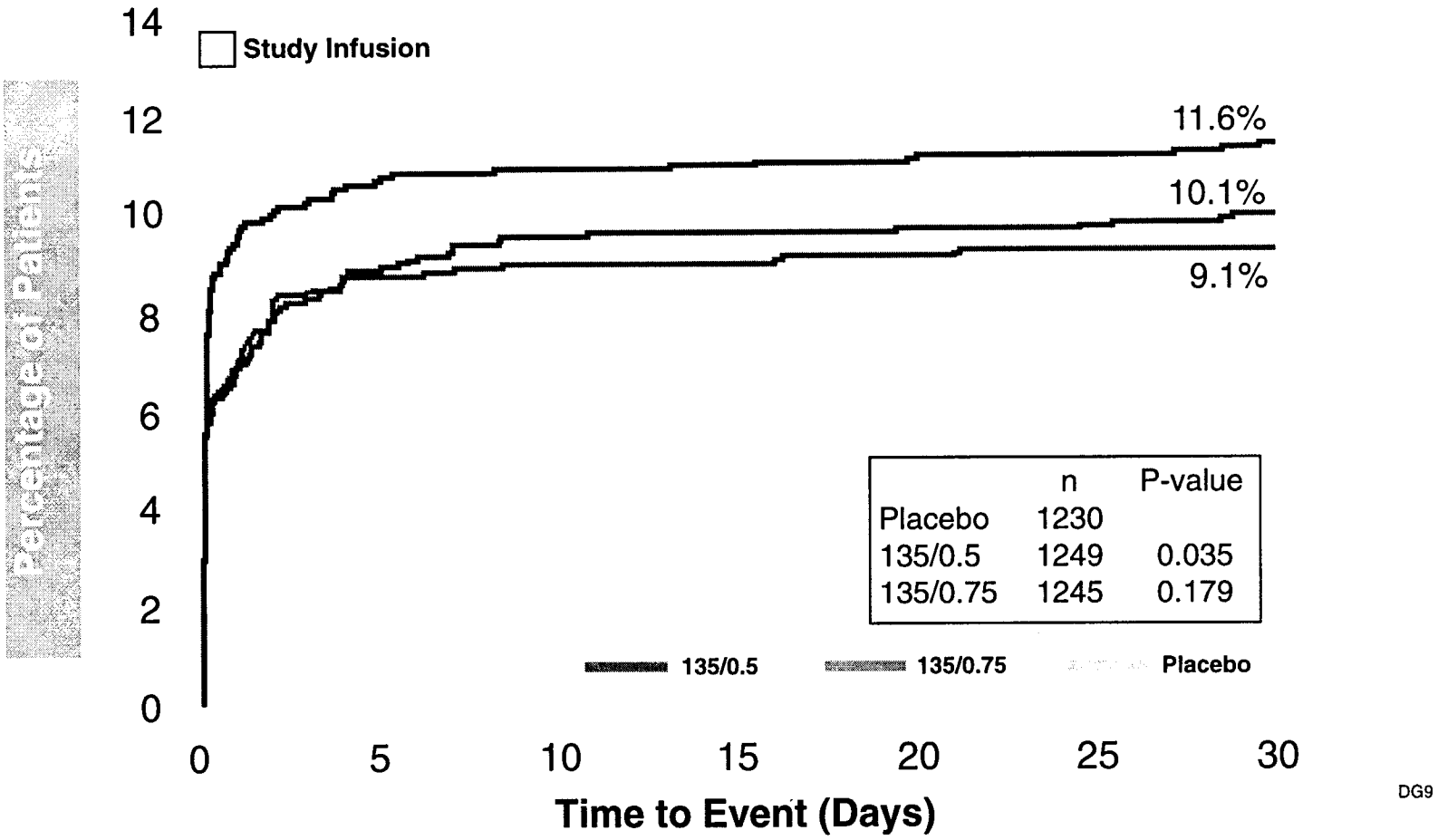
Background

- Pathophysiology and Pharmacology
- IMPACT II
  - Reviewed February 1997
  - Positive efficacy results
    - Statistical significance (primary endpoint)
  - Good safety profile
- Dose Selection

Study Design

- 4010 patients
- Elective or urgent PTCA
- Standard therapy (ASA, heparin)
- Randomization:
  - *Placebo*
  - *Eptifibatide 135/0.5*
  - *Eptifibatide 135/0.75*
- Primary endpoint: Death, MI, urgent intervention at 30 days

Primary Endpoint (Death/MI/Intervention) at 30 Days

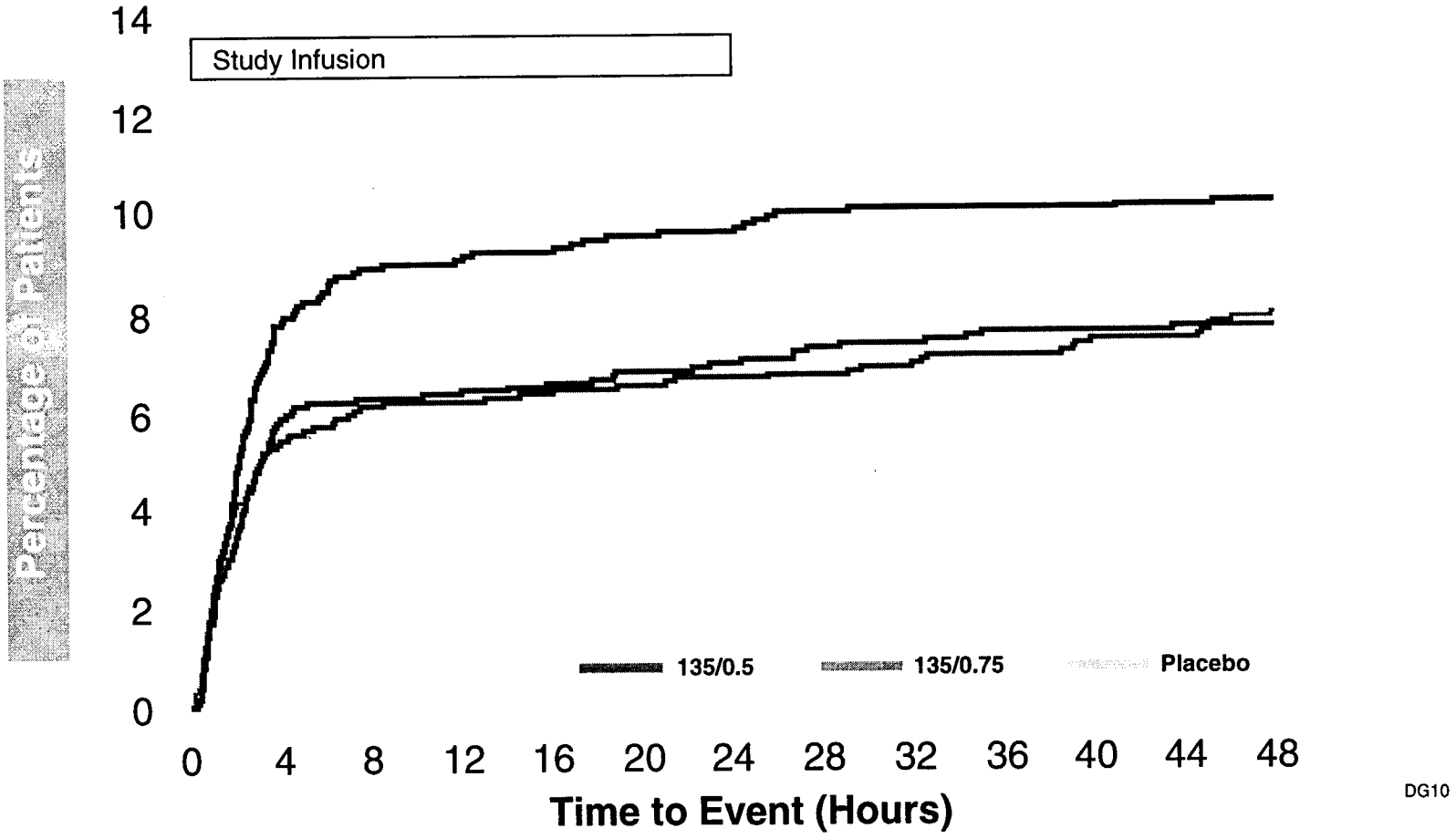


DG9

IMPACT II

Eptifibatide

Death/MI/Intervention Over 48 Hours

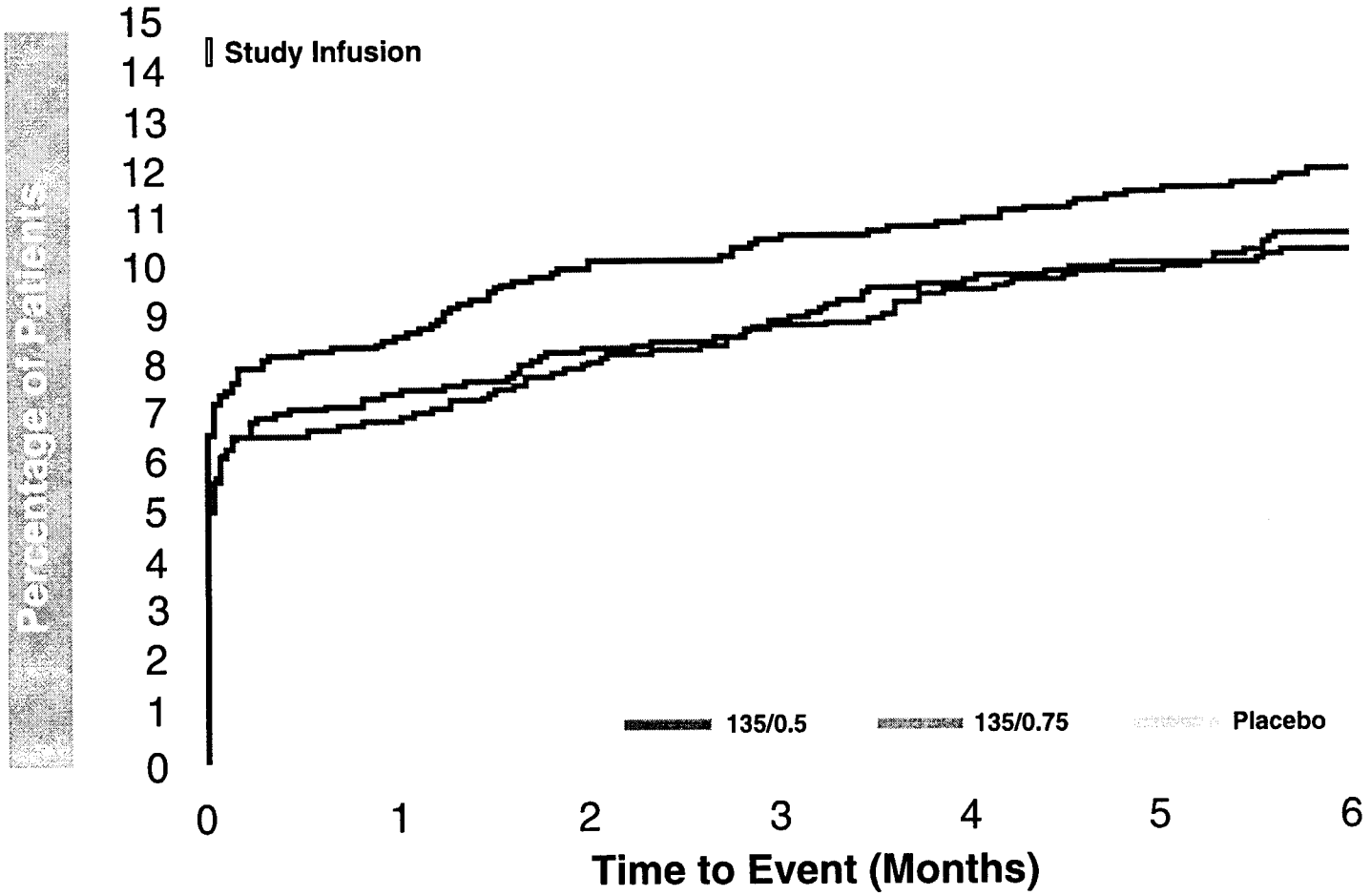


DG10

IMPACT II

Eptifibatide

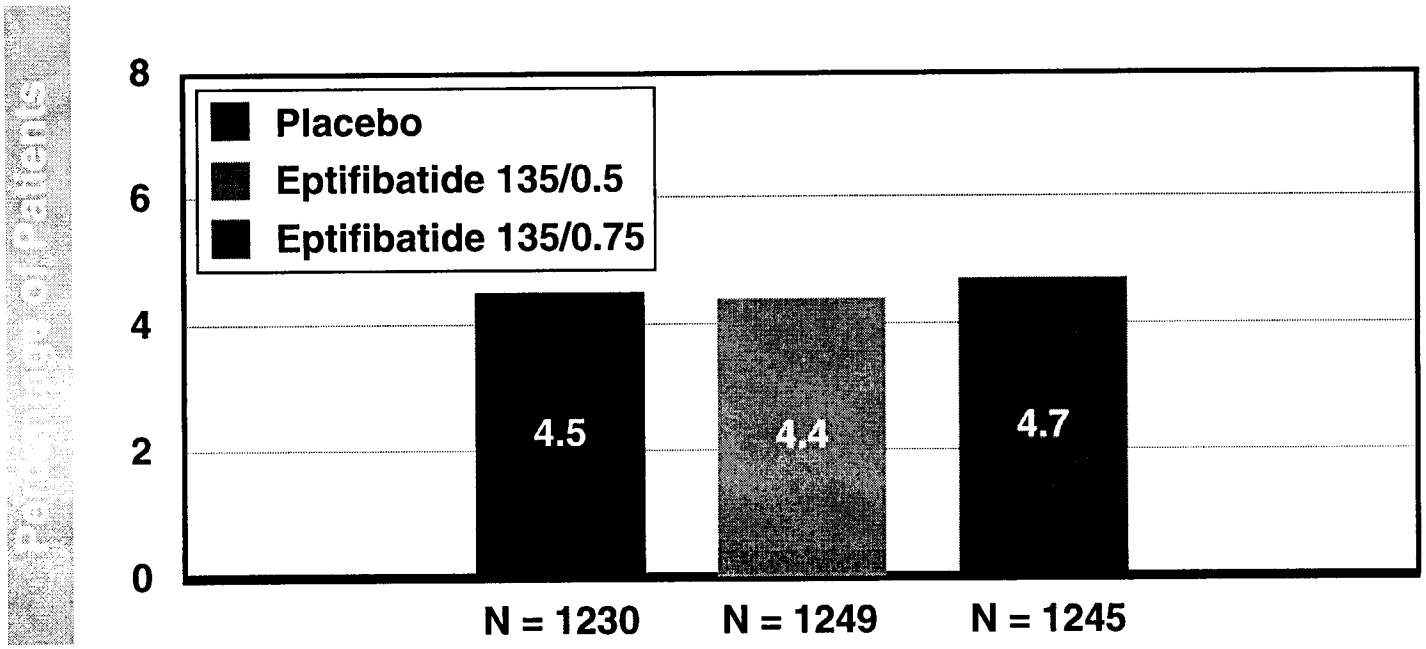
Irreversible Endpoints (Death/MI) Over 6 Months



DG11

Safety Profile

TIMI Major Bleeding

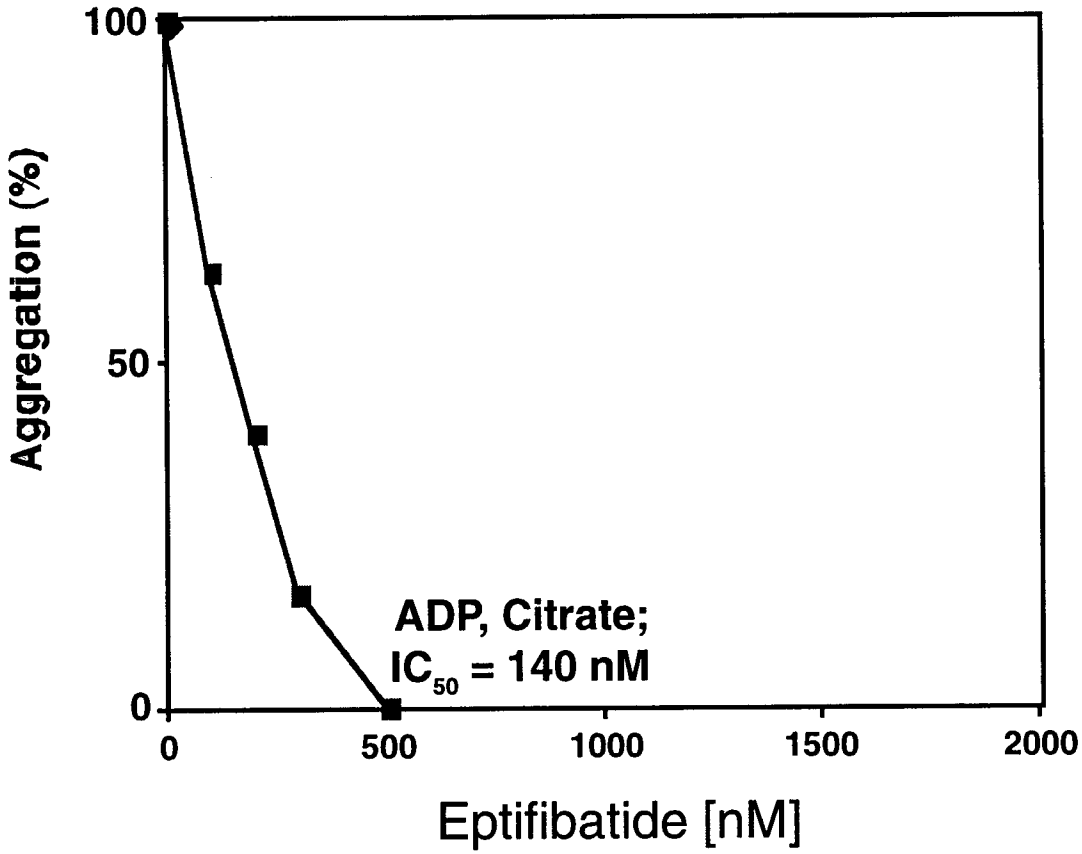


DG12

Background

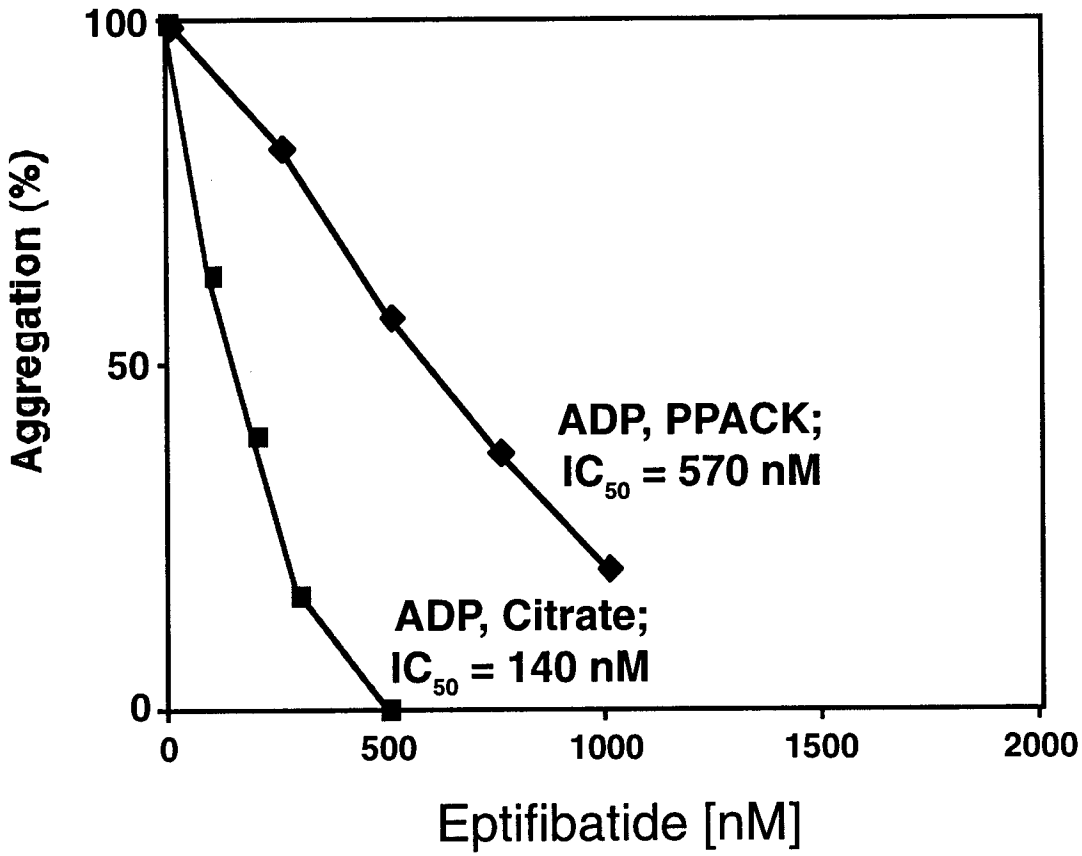
- Pathophysiology and Pharmacology
- IMPACT II
- Dose Selection
  - Dose selection for IMPACT II
  - Dose adjustment for PURSUIT

Inhibition of Platelet Aggregation by Eptifibatide



DG14

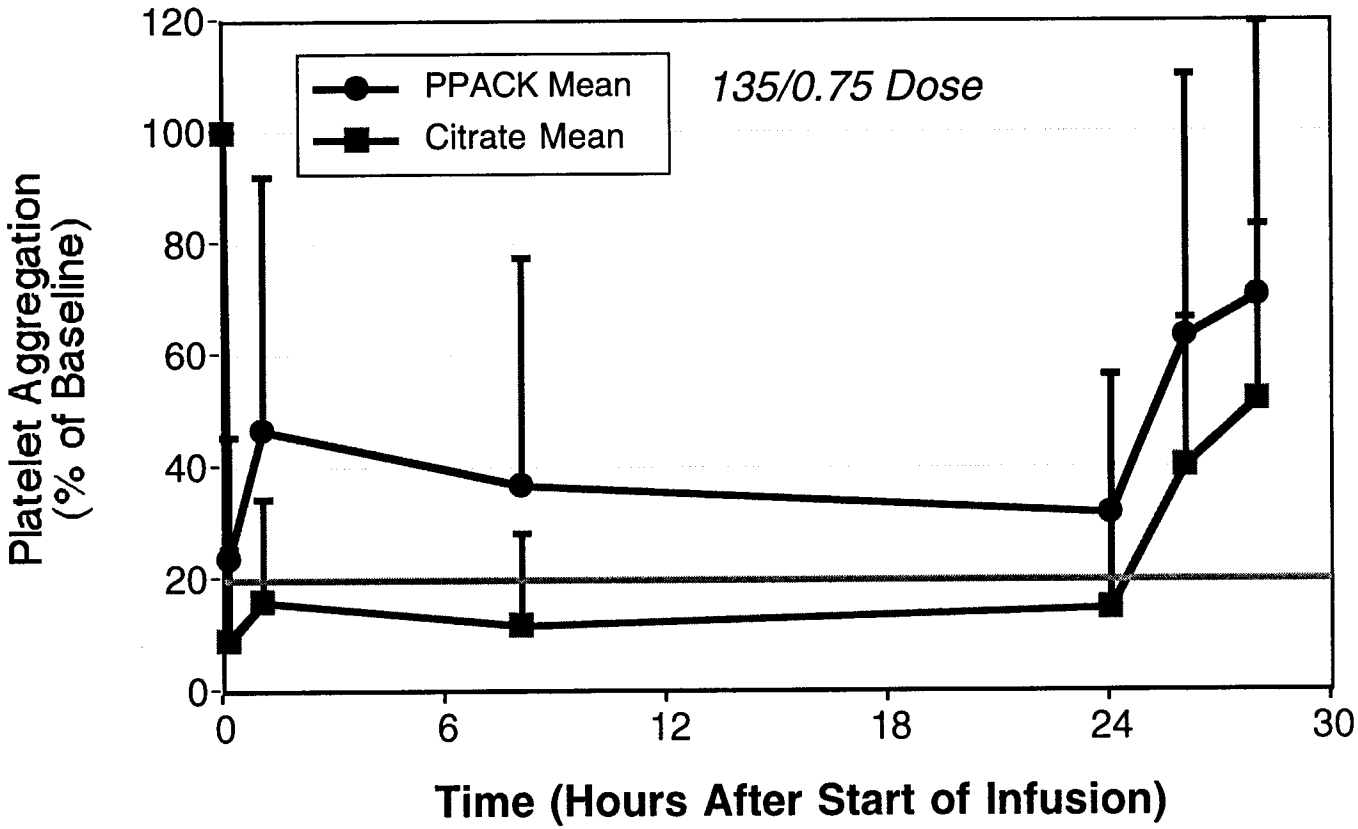
Inhibition of Platelet Aggregation by Eptifibatide



DG15

Platelet Aggregation (Citrate vs. PPACK)

"PRIDE" Study



DG16

Rationale for PURSUIT Dose Selection

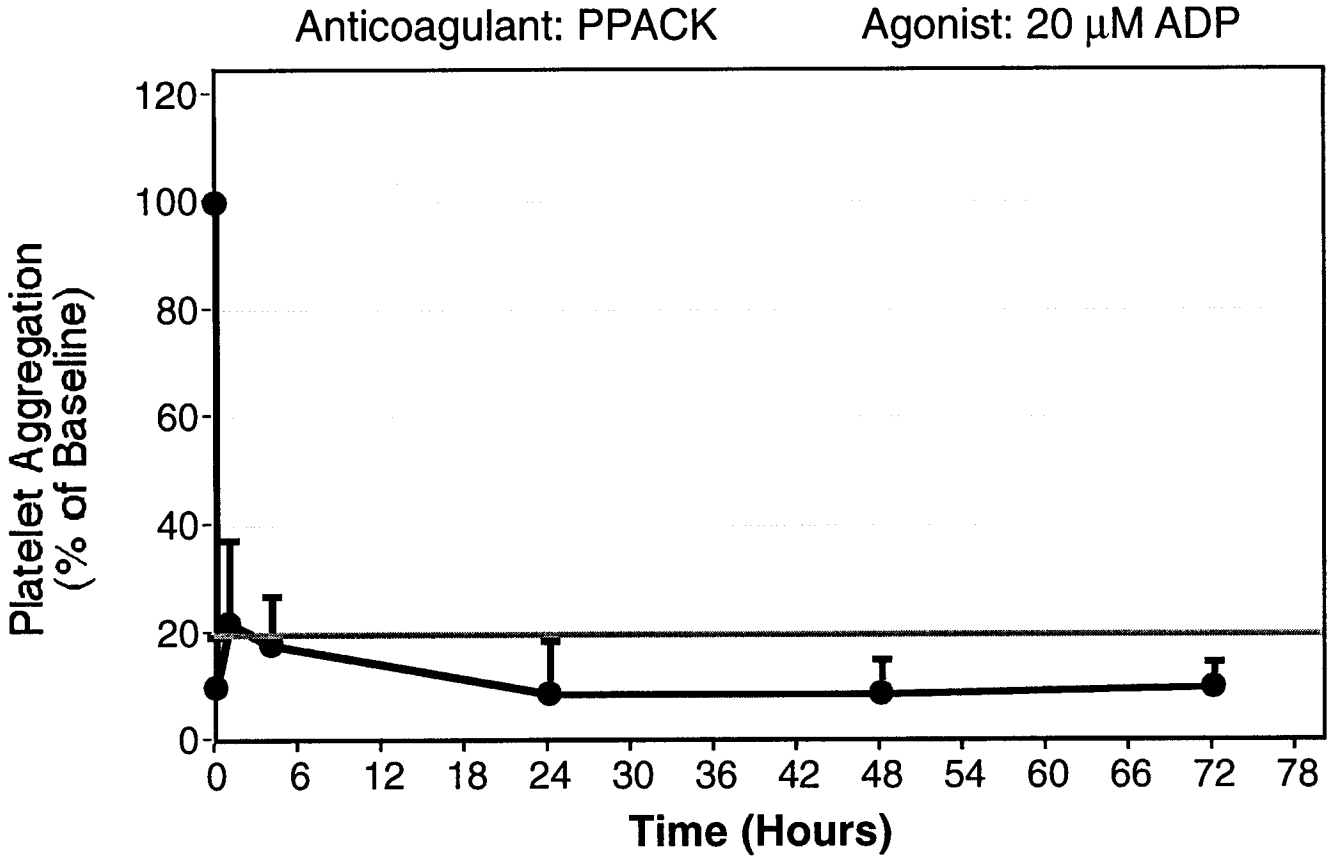
- Safety profile similar to placebo (IMPACT II)
- IC_{50} higher than previously thought
- Pharmacologic target not achieved during infusion (IMPACT II)

Goal: 80% inhibition

	IMPACT II	PURSUIT
Bolus	135 (μg/kg)	180 (μg/kg)
Infusion	0.5 (0.75) (μg/kg-min)	2.0 (μg/kg-min)

DG17

Target Aggregation Achieved in PURSUIT



DG18

Summary

- Pathophysiology and Pharmacology
  - Pathophysiology common to UA/NQMI and post PTCA
  - Pharmacology: Good match with pathophysiology
- IMPACT II
  - Efficacy and safety in patients undergoing PTCA
- Dose Selection
  - Dosing regimen increased for PURSUIT
  - Pharmacological target achieved

PURSUIT Presentation: Outline

- Background/Rationale
- PURSUIT Study Design
- Efficacy Results
- Safety Results
- Conclusion

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Unstable Angina: Background

- **Global problem**
  - > 1 million patients annually in US and Europe
- **Heterogeneous population**
  - ST↑ → Acute MI
  - ST↓ → Acute MI
    Unstable angina
    Non cardiac
- **Heterogeneous treatment**
  - Medical management
  - Invasive management

Unstable Angina Clinical Trials: Limitations/Problems

- **Narrow populations**
  - testing pathophysiologic "proof of concept"
- **Mandate management strategy**
  - cath vs. no cath
- **Forces extrapolation of results to broader, clinical practice**

PURSUIT Background

- **Broad, global population (all comers)**
- **Noninvasive / invasive treatment at MD discretion**
- **Findings applicable to clinical practice**
  - insights into heterogeneity of patients, practice, outcome

Study Design

Ischemic Pain within 24 hours
AND
ECG changes (within 12 hrs of ischemia) OR Positive CK:MB

ASA, Heparin
(MD discretion)

Randomize

Eptifibatide	Eptifibatide	Placebo
180 μg/kg bolus	180 μg/kg bolus	
2.0 μg/kg/min infusion	1.3 μg/kg/min infusion	

* Infusion up to 72 hours, up to 96 hours if post PTCA

9801BH11, 5

Trial Design—DSMC

- **Prespecified review at 3218 patients**
  - DSMC reviewed safety data only
  - DSMC selected Eptifibatide 180/1.3 arm to drop
- **Enrollment continued throughout DSMC review**
- **Seamless transition to 2 arms**

APPEARS THIS WAY
ON ORIGINAL

Exclusion Criteria

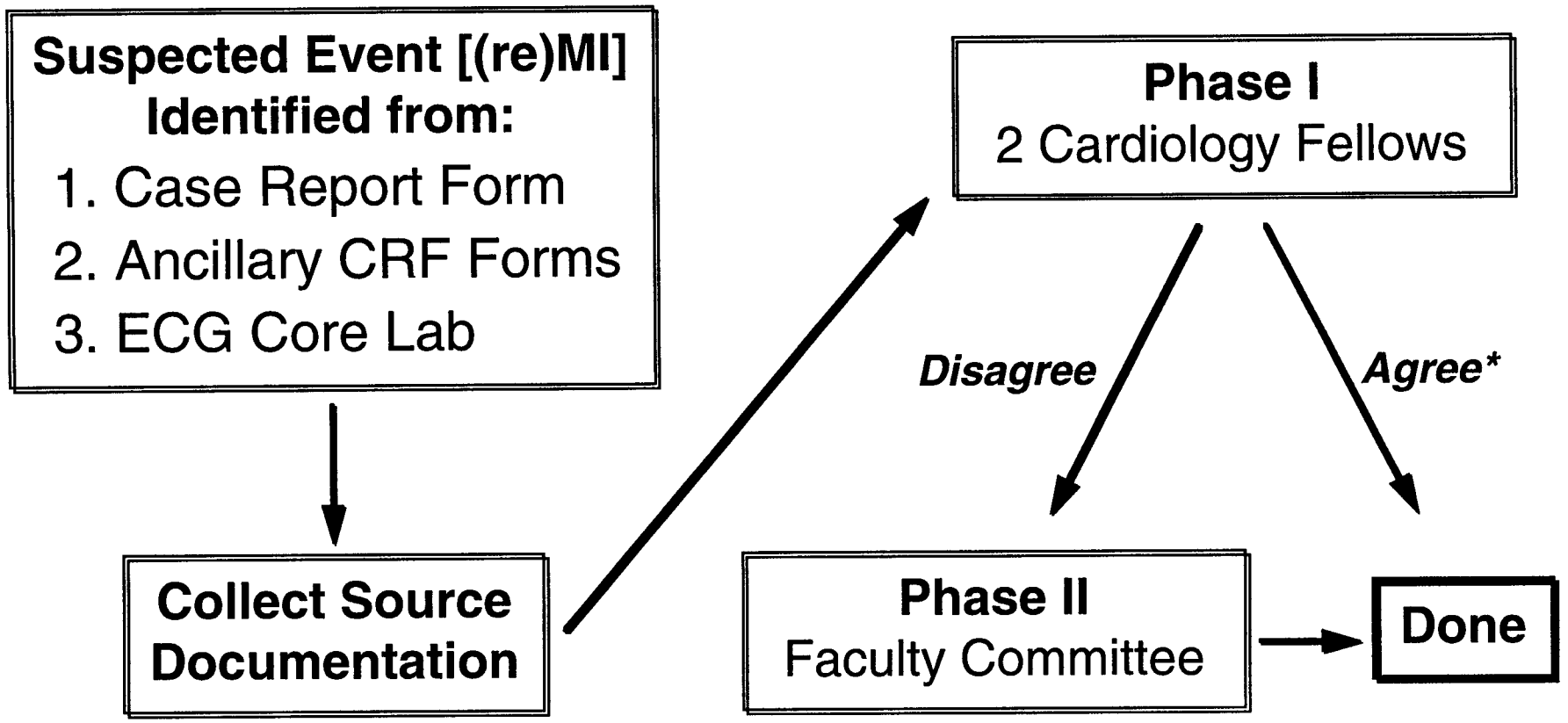
- Major bleeding $\leq$ 30 days, history of bleeding diathesis
- Major surgery $\leq$ 6 weeks
- History of known hemorrhagic stroke or any stroke $\leq$ 30 days
- INR $\geq$ 2.0, platelets < 100,000/mm^3, Hct < 30%, creatinine $\geq$ 2.0 mg/dl
- Planned use of thrombolytic agent or another GP IIb/IIIa inhibitor. Use of thrombolytic therapy within 24 hrs.
- Pregnancy
- Uncontrolled hypertension (200/110mm)

Efficacy and Safety Endpoints

- **Primary:**
  - Death or (re)MI* at 30 days
- **Secondary:**
  - Death, (re)MI at 96 hours and 7 days
  - Death, (re)MI in PTCA-treated patients
  - Death, MI, PTCA, Rehosp at 6 months
- **Bleeding**
  - GUSTO/TIMI Scales
- **Strokes***

**** Adjudicated by CEC***

Clinical Events Review Process



*10% of Phase I Agreements are reviewed at Phase II for QA

Statistical Assumptions

- Estimated placebo event rate (death, (re)MI) at 30 days: 8.5%
- Approximately 9382 patients in two treatment groups
- 80% power to detect 20% reduction (absolute reduction 1.7%)
- $\alpha = 0.05$

Enrollment by Country

U.S.	4035	Canada	323	Finland	76
Netherlands	1032	France	259	Portugal	72
Germany	724	Spain	219	Colombia	61
Poland	712	Mexico	200	Norway	60
Czech Rep	640	Austria	191	Switzerland	48
U.K.	496	Argentina	151	Chile	46
Greece	480	Italy	139	Guatemala	20
Hungary	410	Venezuela	93	Uruguay	9
Belgium	366	Sweden	81	El Salvador	5

Total Enrollment 10,948 Nov 1995 - Jan 1997

Baseline Characteristics

n	Placebo 4739	Eptifibatide 4722
Age (y)	64.0 (55.0, 71.0)	64.0 (55.0, 71.0)
Female	36.1%	34.9%
DM	23.5%	22.2%
Prior MI	32.9%	32.0%
Hx CHF	11.0%	11.1%
Prior CABG	12.0%	12.0%

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Qualifying Characteristics

n	Placebo 4739	Eptifibatide 4722
Qualifying ECG Δ		
ST↓	50.2%	49.8%
ST↑	13.8%	13.7%
T↓	50.0%	51.6%
None or Other	8.1%	7.6%
MI at enrollment	46.2%	45.1%

In-hospital Cardiac Procedures

	Placebo	Eptifibatide
n	4739	4722
Cardiac Cath	59.9	59.0
Percutaneous Intervention*	24.8	23.3
Balloon	21.8	20.5
Atherectomy	0.8	0.7
IC Stent	12.3	11.6
CABG	14.3	13.9

** Not mutually exclusive*

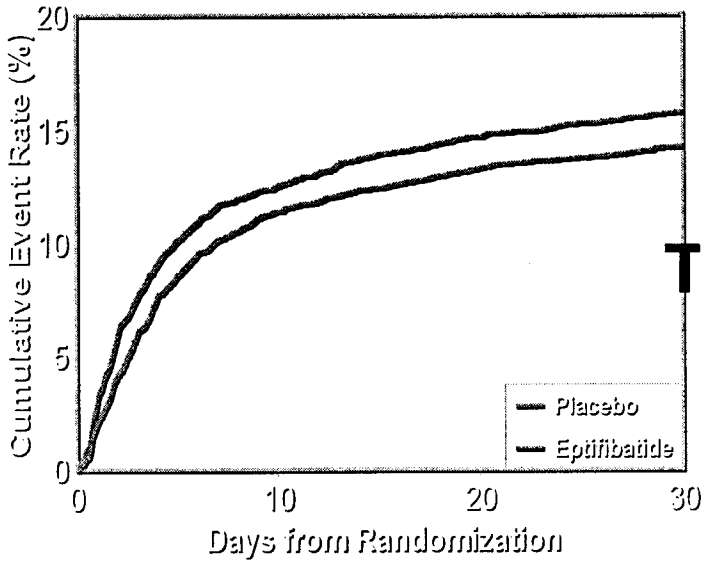
9801BH11, 14

Primary Efficacy Endpoint (30 Days)

n	Placebo 4739	Eptifibatide 4722	p-value
Death or (Re)MI*	15.7%	14.2%	0.042
Death	3.7%	3.5%	0.531
(Re)MI*	13.6%	12.6%	0.137

**Adjudicated by CEC*

9801BH11, 15



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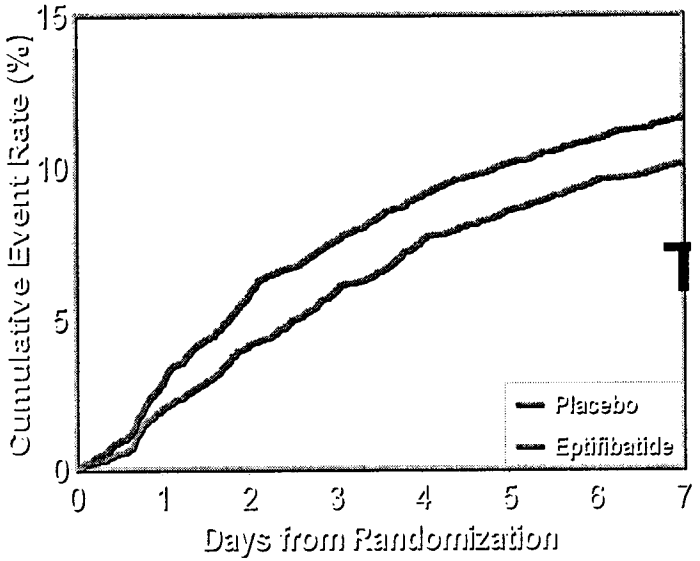

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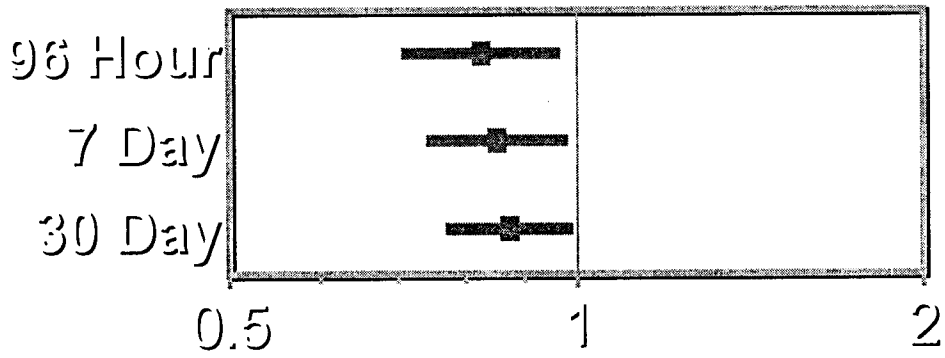
Composite Efficacy Endpoint



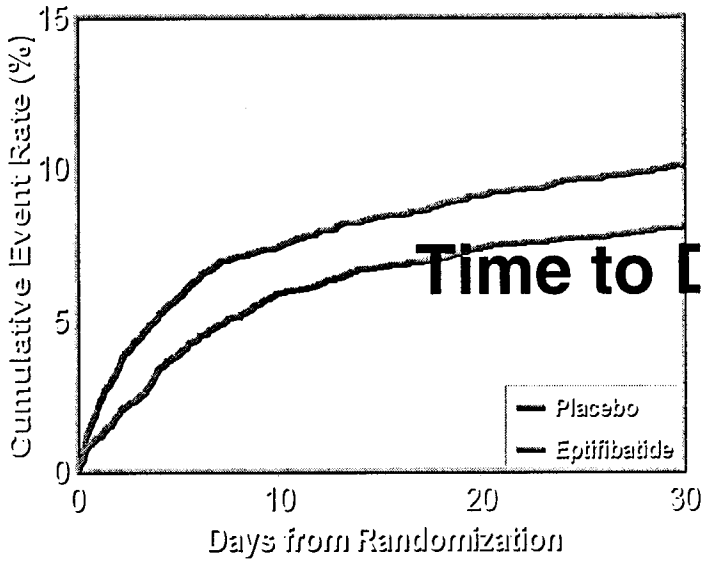
		Placebo	Eptifibatide
96 Hour	0.83 (0.71, 0.96)	9.1%	7.6%
7 Day	0.85 (0.75, 0.97)	11.7%	10.1%
30 Day	0.89 (0.79, 0.99)	15.7%	14.2%

APPEARS THIS WAY
ON ORIGINAL

Efficacy Endpoint at 30 Days

n	Placebo 4739	Eptifibatide 4722	p-value
Death or (Re)MI	10.0%	8.1%	0.001
Death	3.7%	3.5%	0.531
(Re)MI	7.8%	6.2%	0.002

Investigator's Assessment



Time to D

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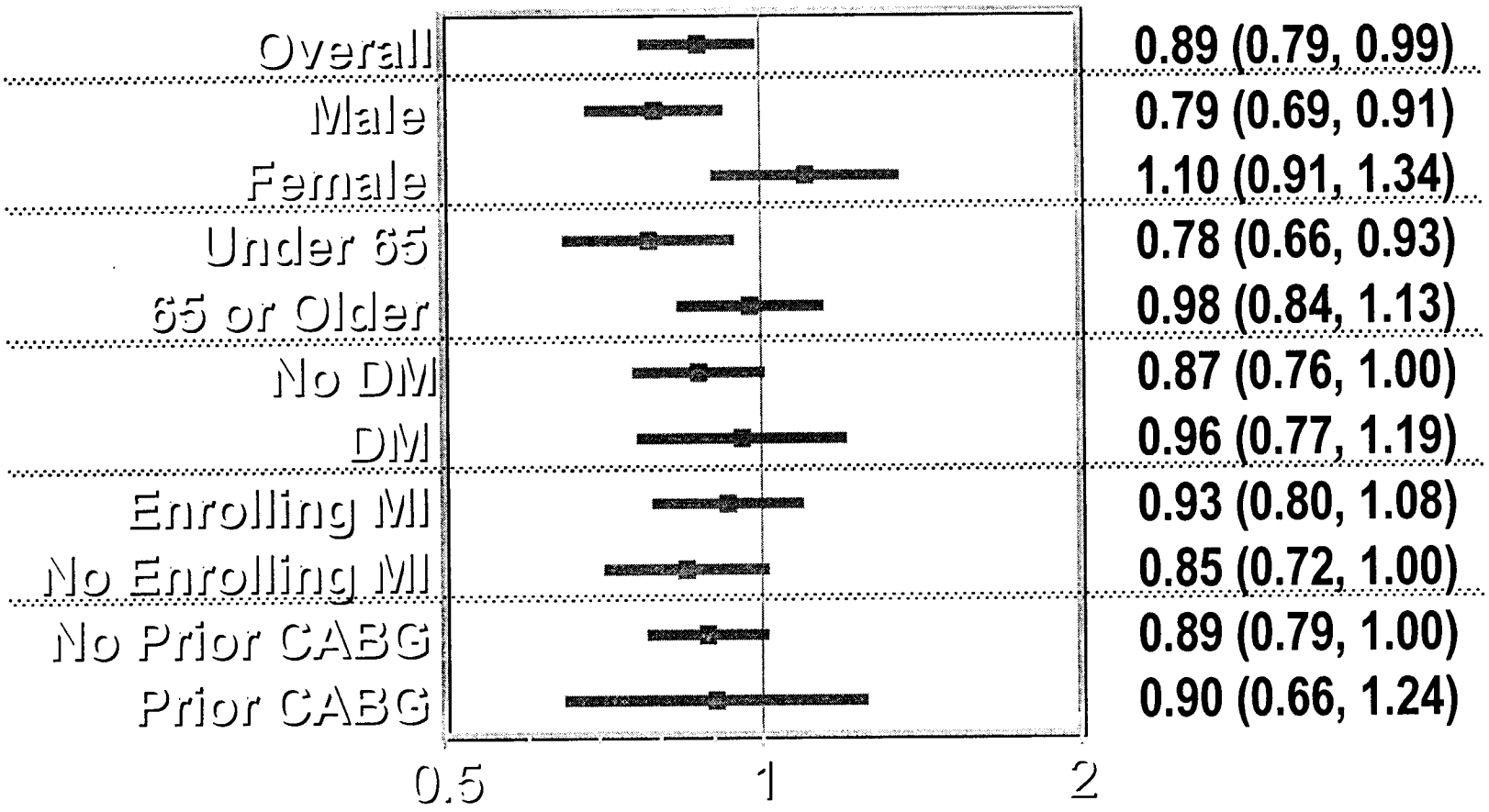
CRI

Death or MI at 30 Days



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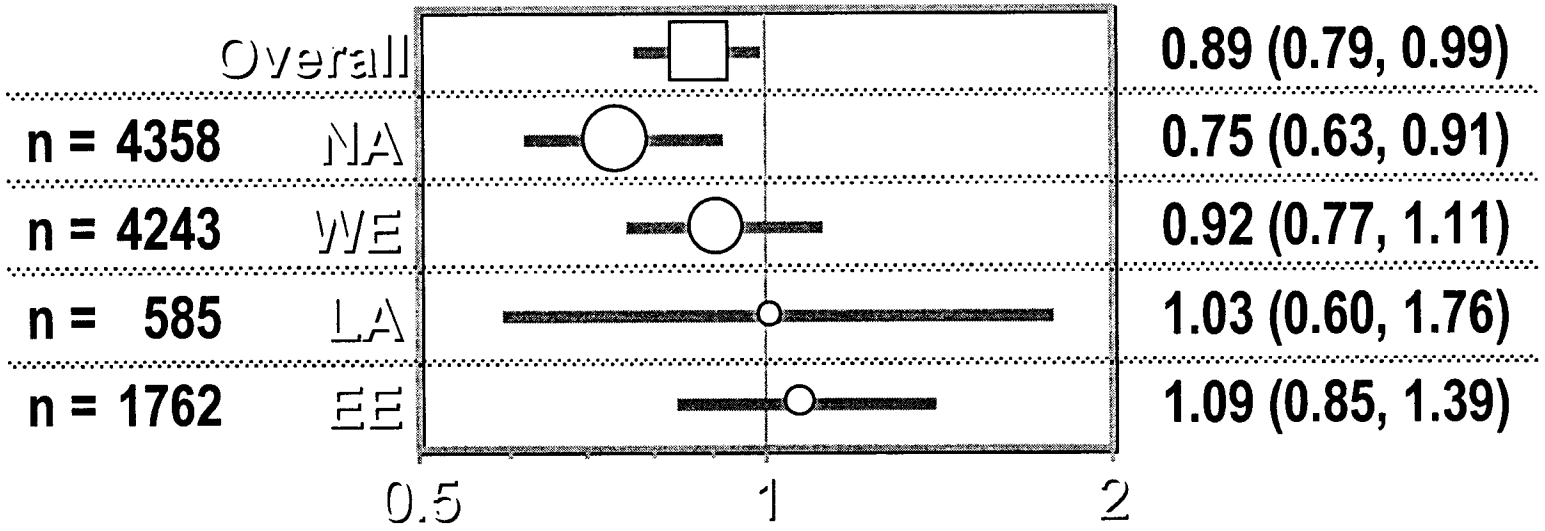
Death or MI at 30 Days



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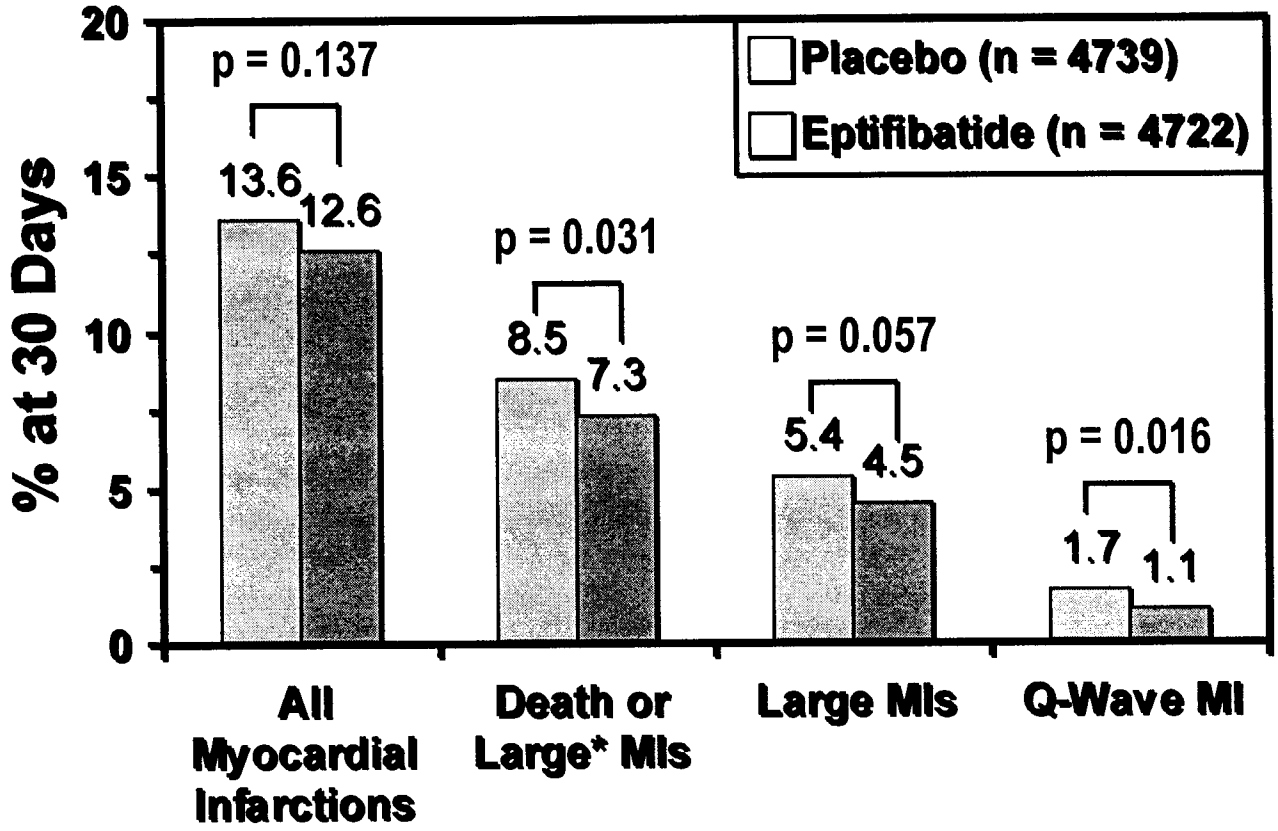
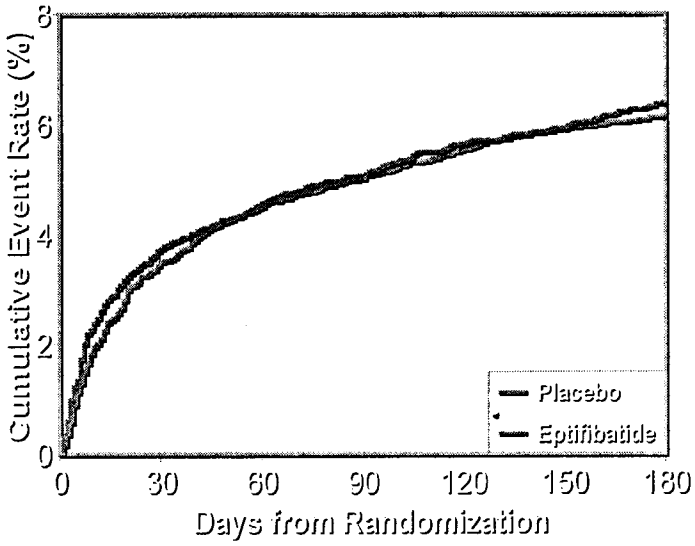
Myocardial Infarction



** Large MI: CKMB > 5x ULN*

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



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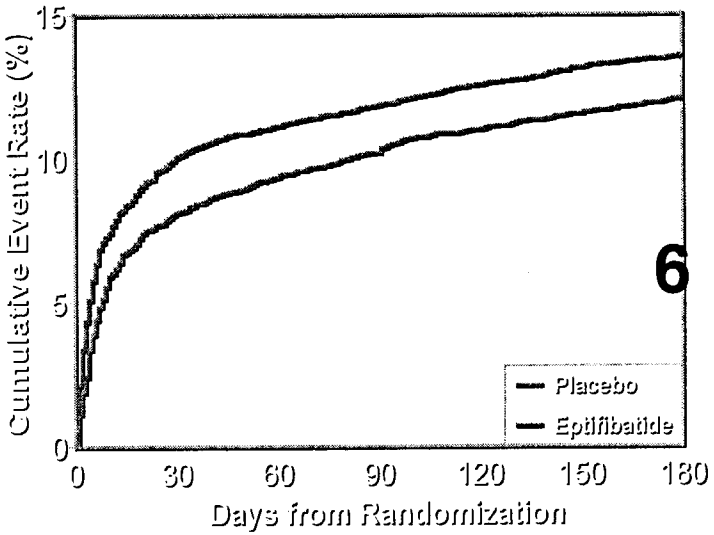


Strokes at 30 Days

n	Placebo 4696	Eptifibatide 4679
Total strokes (CEC)	39 (0.8%)	32 (0.7%)
Stroke type (CEC)		
1° Hemorrhagic	2 (< 0.1%)	3 (0.1%)
Cerebral infarct	33 (0.7%)	27 (0.6%)
Infarct w/ conversion	1 (<0.1%)	2 (< 0.1%)
Uncertain	3 (0.1%)	0 (0.0%)

Patients As Treated

Bleeding

n	Placebo 4696	Eptifibatide 4679
TIMI Scale		
Major	9.3%	10.8%
Minor	7.6%	13.1%
GUSTO Scale		
Severe	1.1%	1.8%
Moderate	8.9%	11.1%
Mild	12.7%	25.7%

Patients As Treated

Major Bleeding

n	Placebo 4577	Eptifibatide 4604
Overall	9.3%	10.8%
CABG	8.2%	8.2%
PTCA	0.6%	1.4%
Cath only	0.2%	0.6%
No procedures	0.3%	0.6%

Patients As Treated

Transfusions During Hospitalization

n	Placebo 4696	Eptifibatide 4679
Transfusions	10.4%	12.8%
PRBCs/Whole blood	9.3%	11.8%
1–2	4.4%	6.1%
3–5	3.2%	3.4%
6–10	1.3%	1.7%
Platelets	2.2%	2.6%

Patients As Treated

Transfusions

n	Placebo 4696	Eptifibatide 4679
Overall	10.4%	12.8%
CABG	8.9%	9.0%
PTCA	0.7%	1.6%
Cath only	0.3%	0.9%
No procedures	0.5%	1.3%

Patients As Treated

Thrombocytopenia (During Hospitalization)

n	Placebo 4696	Eptifibatide 4679
< 100,000/μL[a]	225 (5%)	226 (5%)
≥ 50% ↓ from baseline[b]	250 (5%)	231 (5%)
< 50,000/μL nadir[a]	19 (< 1%)	26 (1%)
< 20,000/μL nadir[a]	2 (< 1%)	9 (< 1%)

[a] Includes patients with a post-baseline value

[b] Includes patients with both a baseline and post-baseline value

Patients As Treated

Events Prevented/1000 Pts Treated

Time	Absolute Reduction	Events Prevented/ 1000 Pts Treated
96 hours	1.45% (0.34, 2.56)	14.5 (3.37, 25.6)
7 days	1.55% (0.29, 2.80)	15.5 (2.92, 28.0)
30 days (CEC)	1.49% (0.05, 2.92)	14.9 (0.5, 29.2)
30 days (Invest)	2.00% (0.88, 3.20)	20.0 (8.82, 32.0)

PURSUIT Summary

- Largest trial of ACS without persistent ST ↑
- Global distribution of patients and management strategies
- Clinically relevant and statistically significant reduction in death/MI composite observed at all time points

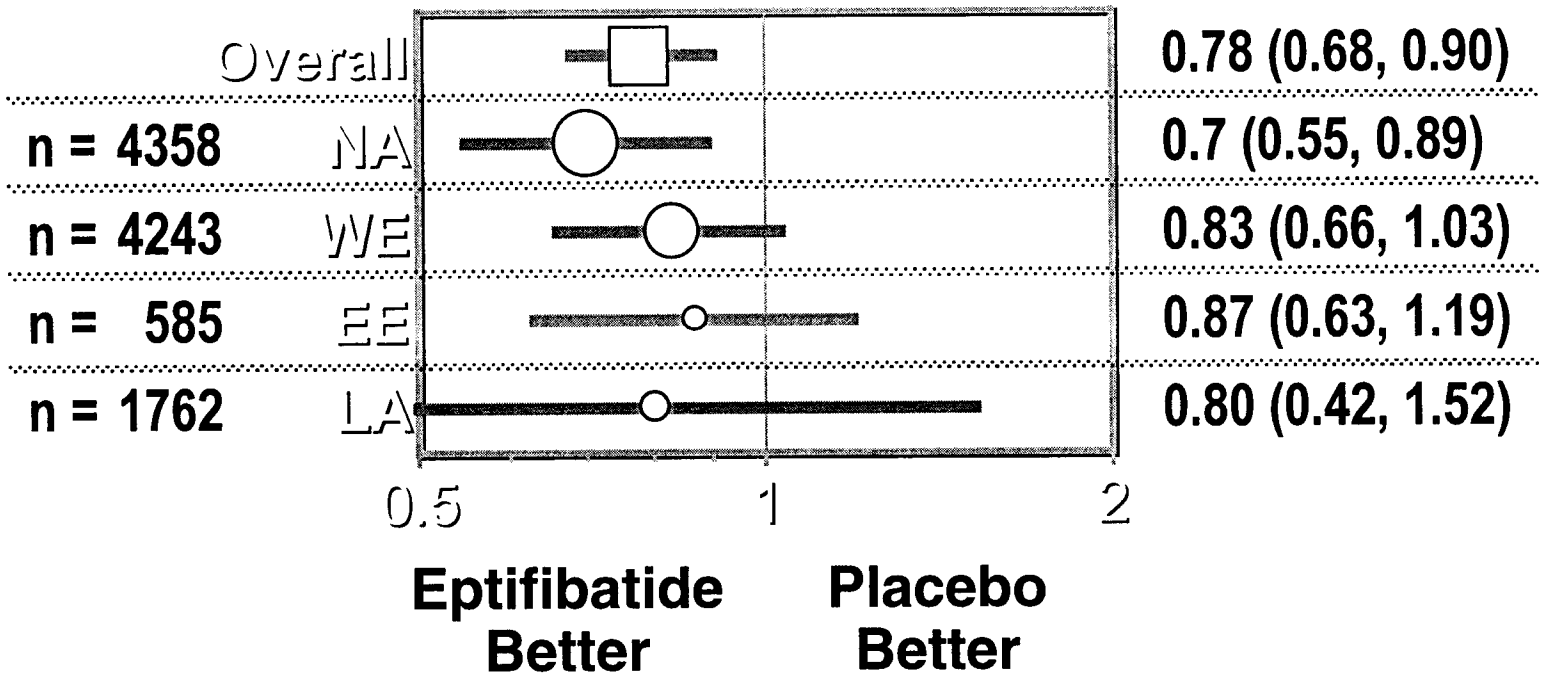
PURSUIT Summary

- **Greatest benefit of treatment with eptifibatide was observed in North America**
- **No increased risk of hemorrhagic stroke**
- **Increased bleeding with eptifibatide**
  - mostly access-related and manageable

PURSUIT Conclusions

- PURSUIT confirms the importance of platelet dependent thrombosis in the adverse complications of acute coronary syndromes.
- Eptifibatide reduced the irreversible clinical events of death and myocardial infarction with an acceptable safety profile.

Death or MI at 30 Days



Investigator's Assessment

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Angiographic Interventions

Interventions

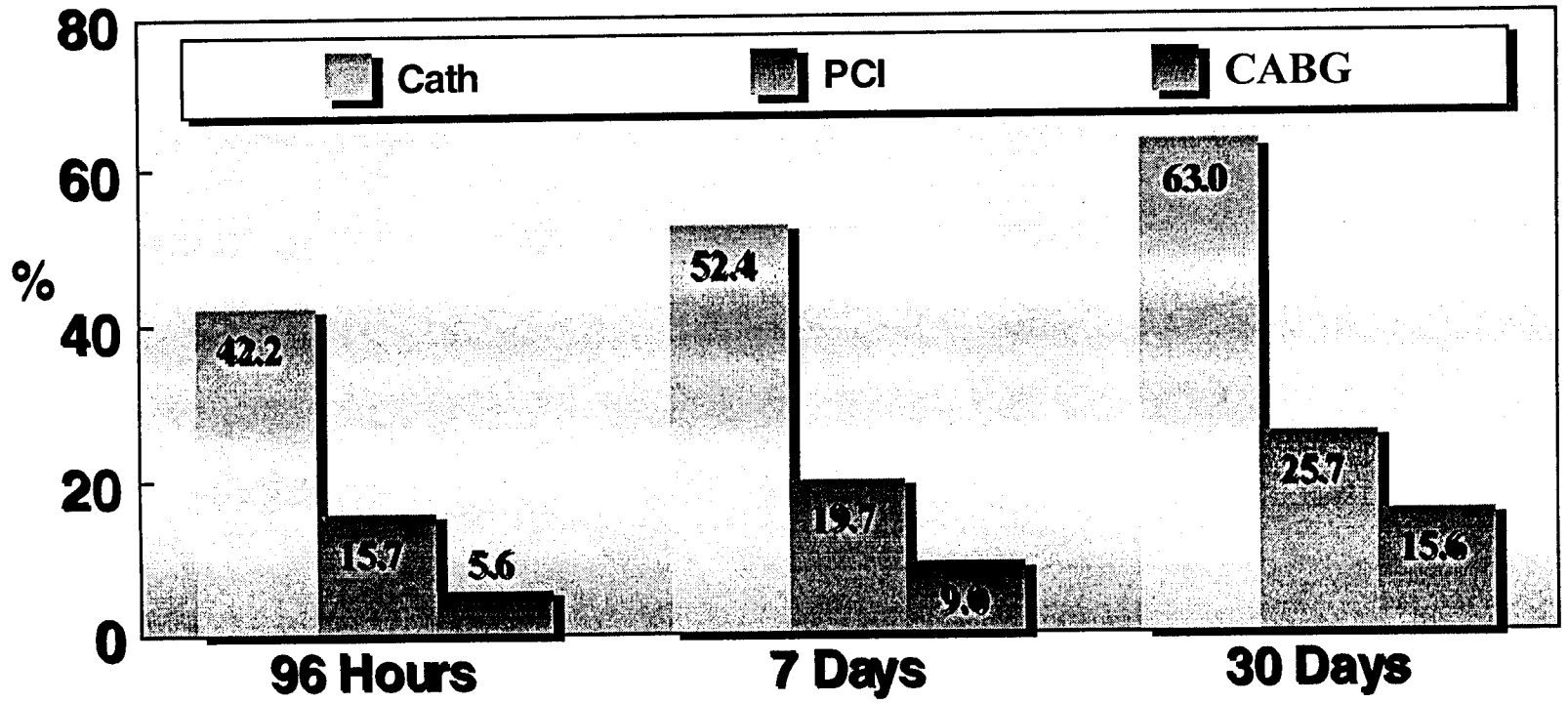
pursuit

Percutaneous Coronary Intervention

- Efficacy of eptifibatide as adjunct to different management strategies for revascularization in PURSUIT
- Provide complementary evidence to IMPACT II supportive of the indication for PCI

Interventions

Cardiac Procedures



ML-102

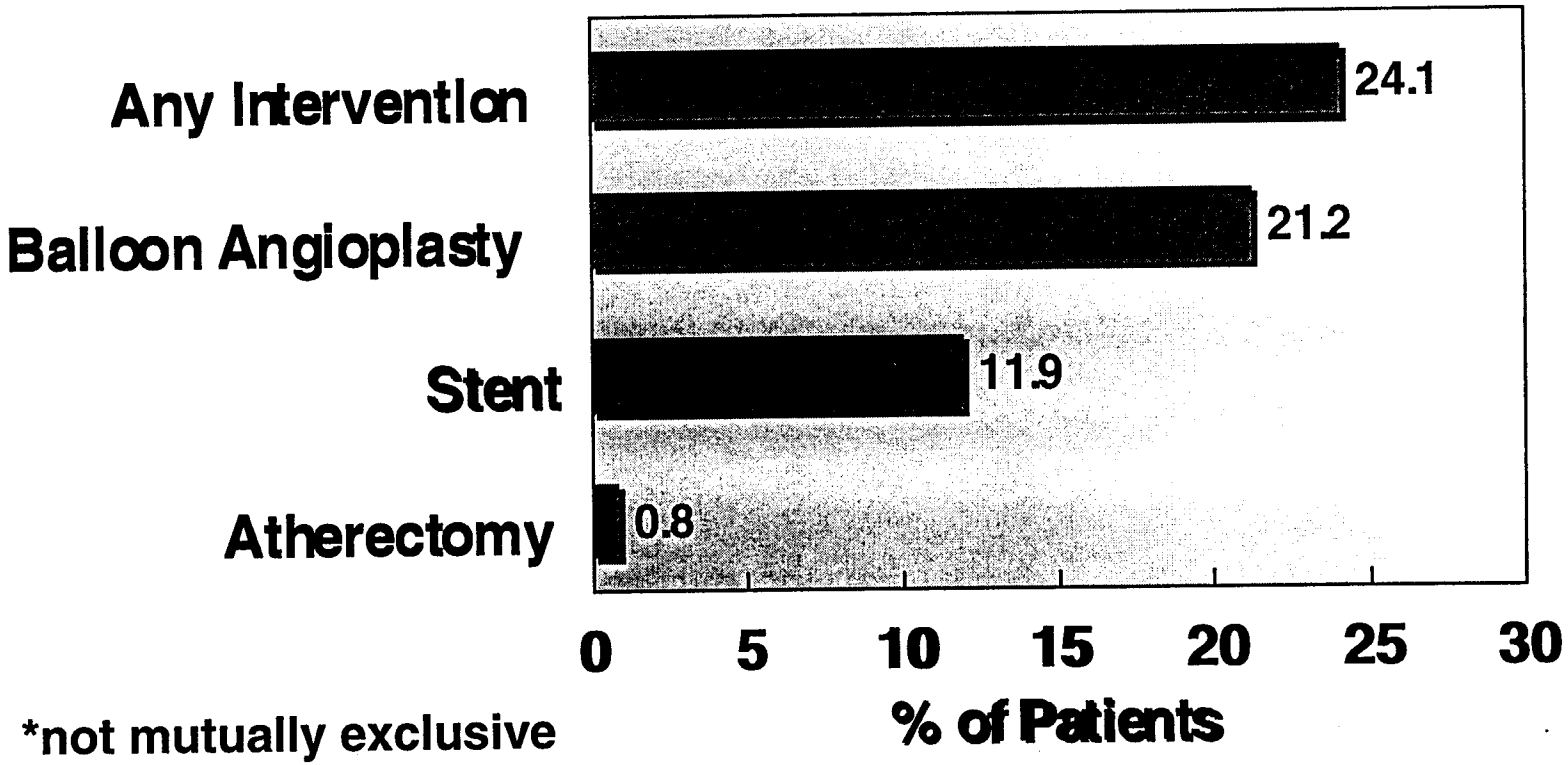
Interventions

Percutaneous Coronary Intervention

- 1228 patients in PURSUIT Rx'd with PCI during study drug infusion
  - → operator discretion, not protocol-driven
- Commonality with IMPACT II trial - revascularization procedures during study drug therapy
- Complementary data - confirm efficacy of eptifibatide during PCI in multiple clinical settings

Interventions

Percutaneous Interventions*
Initial Hospitalization



*not mutually exclusive

ML-104

Limitations of Analysis

- Catheterization and revascularization procedures NOT randomized ? multiple confounding factors
- Selection for procedure influenced by post-randomization events
- Timing of PCI:
  - on or off study drug
  - before or after endpoint events

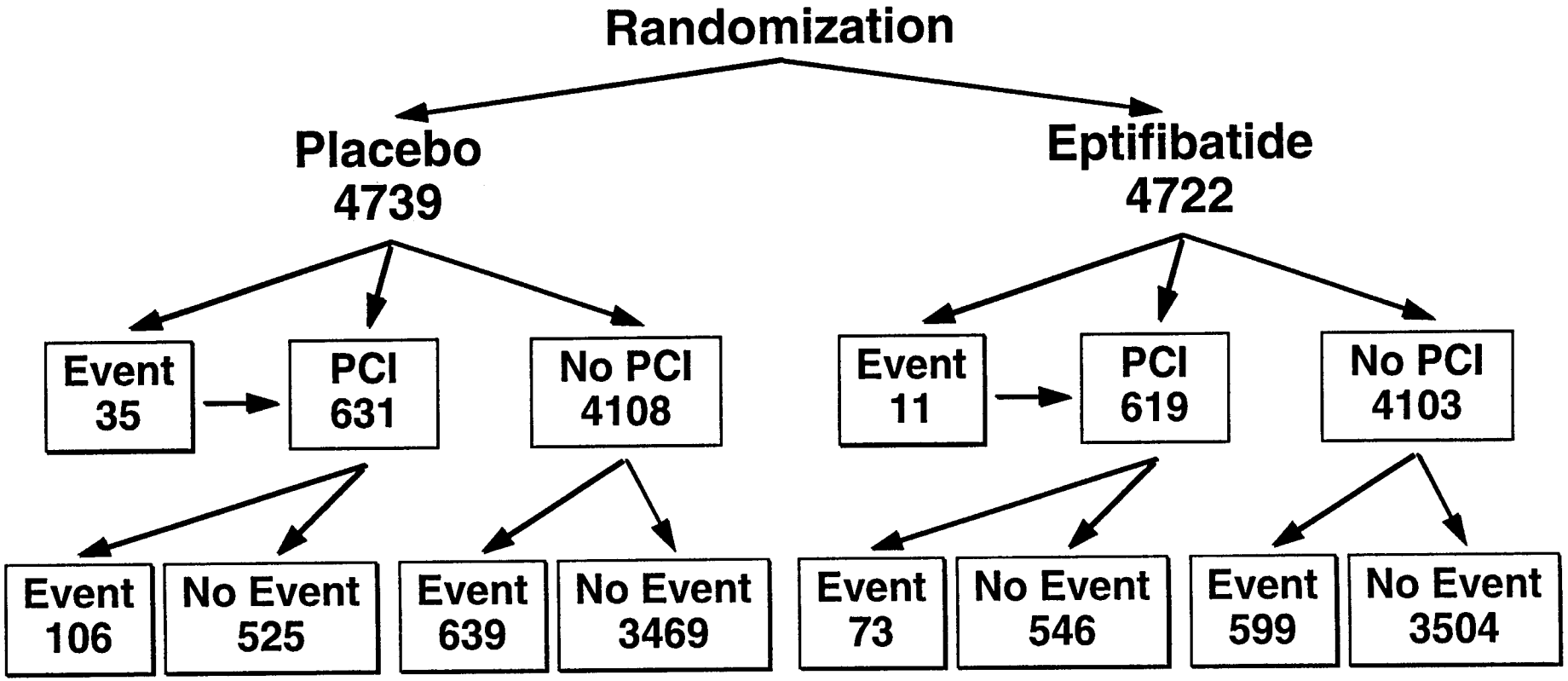
pursuit

Limitations of Analysis

- Endpoint events may:
  - occur before PCI
  - lead to PCI
  - preclude PCI
  - be due to PCI
  - occur despite PCI

Interventions

Timing of Ischemic Events and PCI*

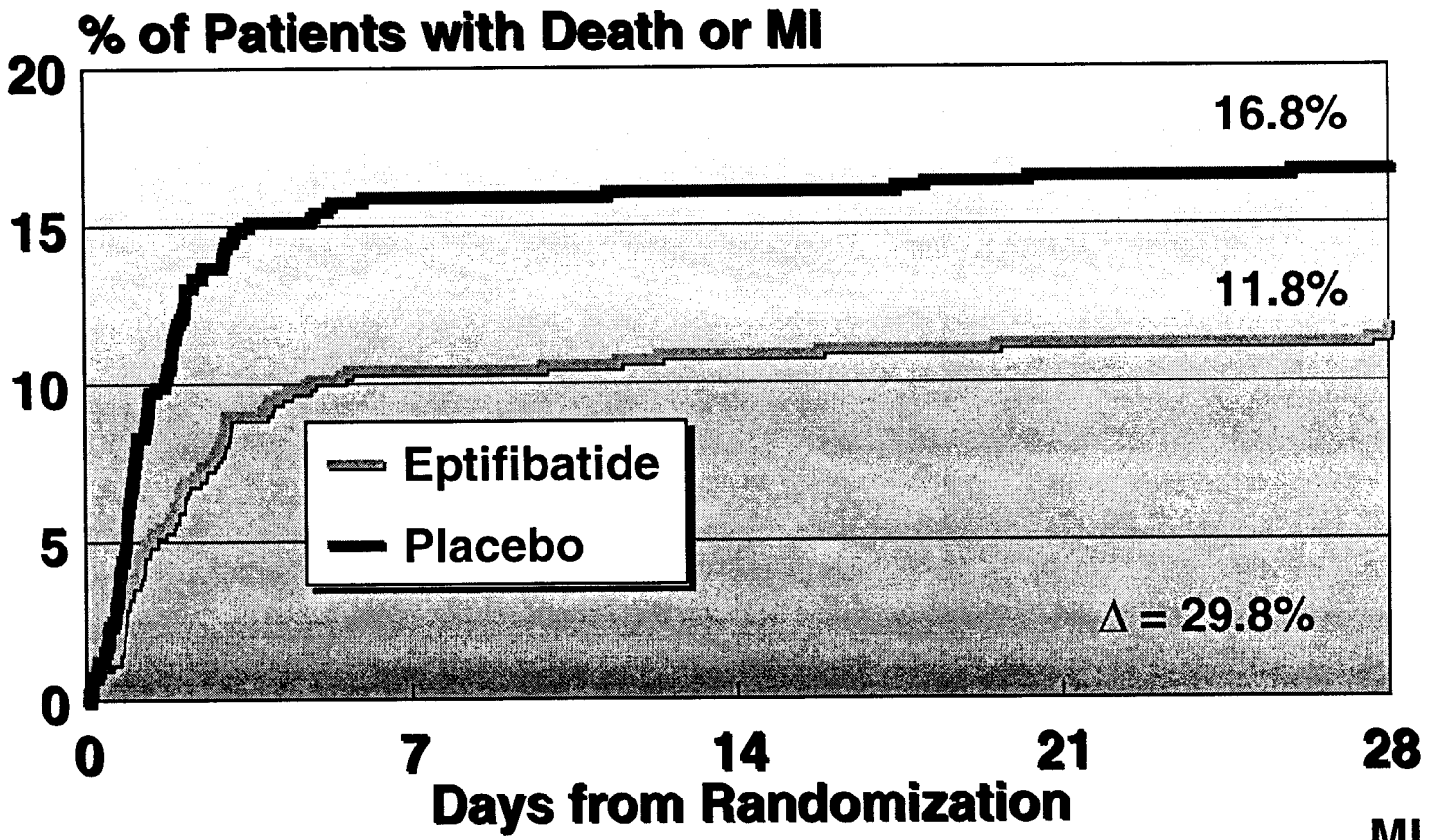


*PCI during first 72 hrs

ML-107

Interventions

Outcome in Patients Rx'd with PCI Within 72 Hrs

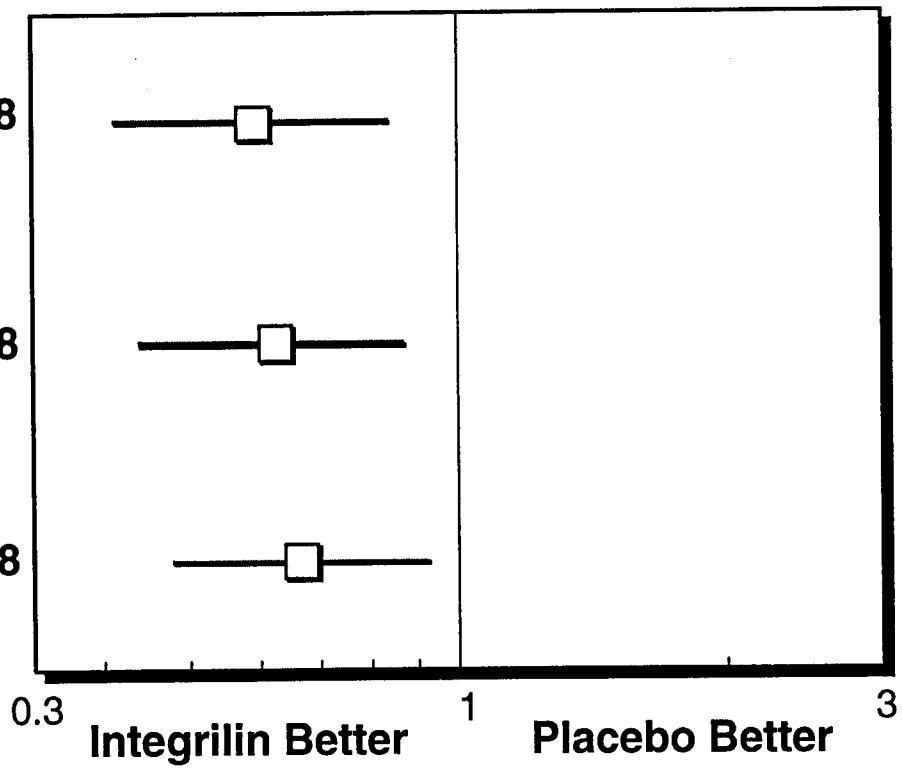


ML-108

Interventions

Death or MI
Including All Endpoint MIs

Group	N	Odds Ratio & 95% CI	Placebo	Integrilin
96 Hrs	1228		15.2%	9.5%
7 Days	1228		16.0%	10.5%
30 Days	1228		16.8%	11.8%

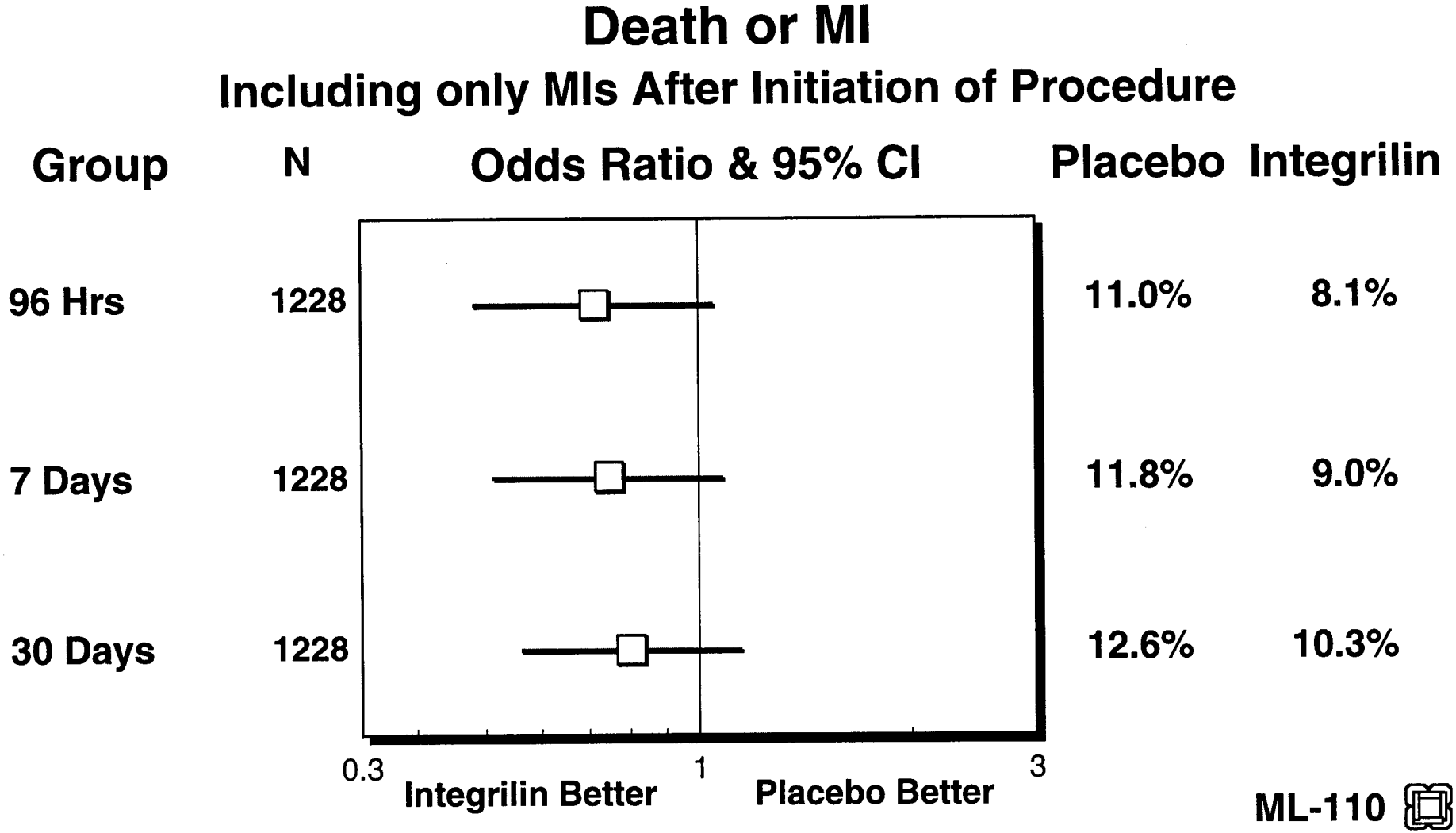


ML-109

Interventions

Death or MI

Including only MIs After Initiation of Procedure

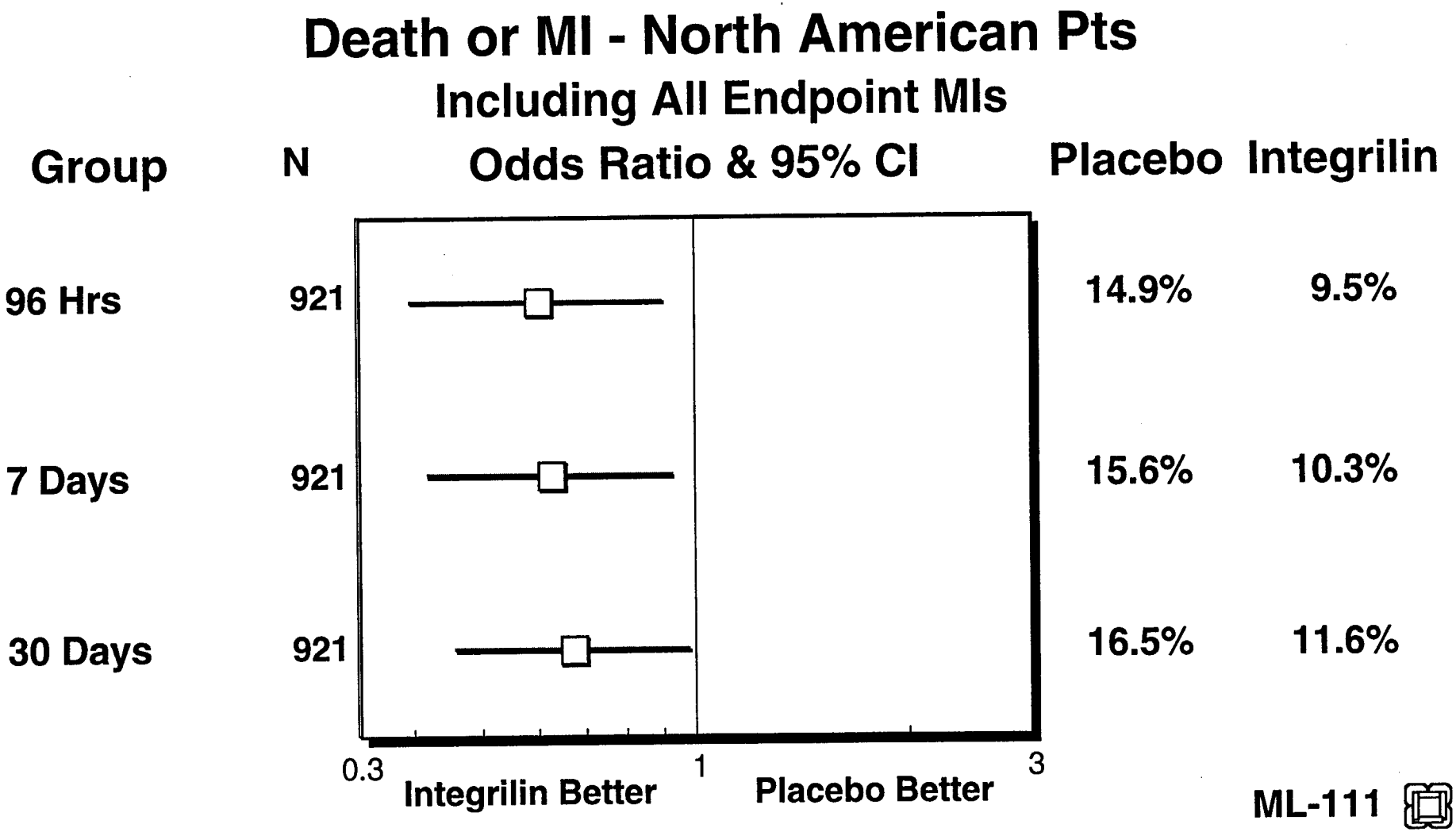


ML-110

Interventions

Death or MI - North American Pts

Including All Endpoint MIs

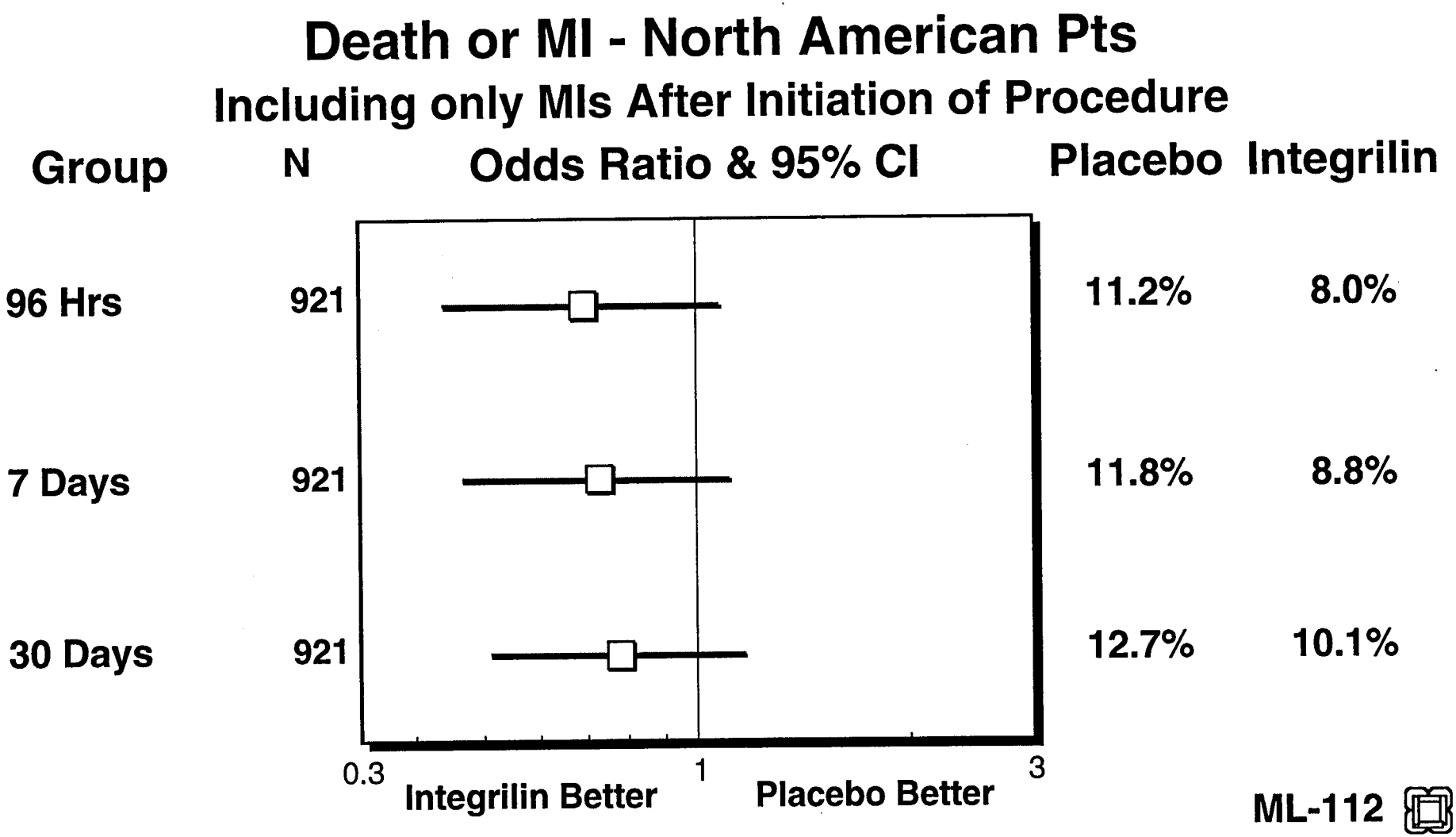


ML-111

Interventions

Death or MI - North American Pts

Including only MIs After Initiation of Procedure



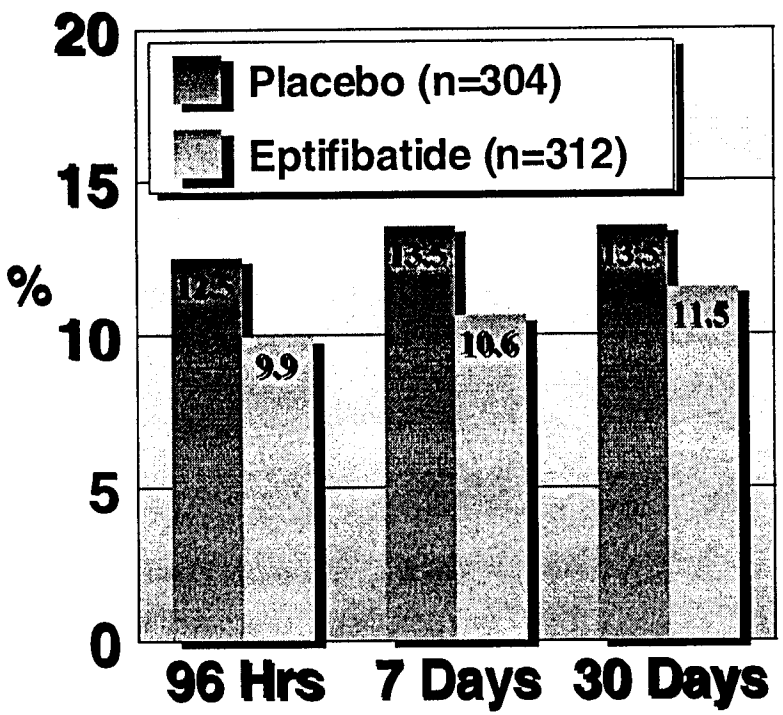
ML-112

Interventions

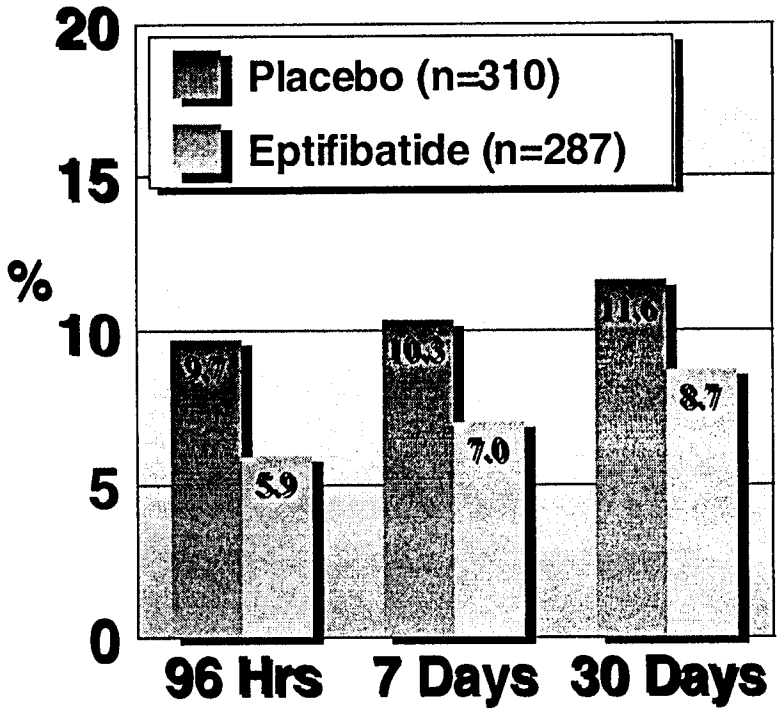
Death or MI

Including only MIs After Initiation of Procedure

Stents



No Stents

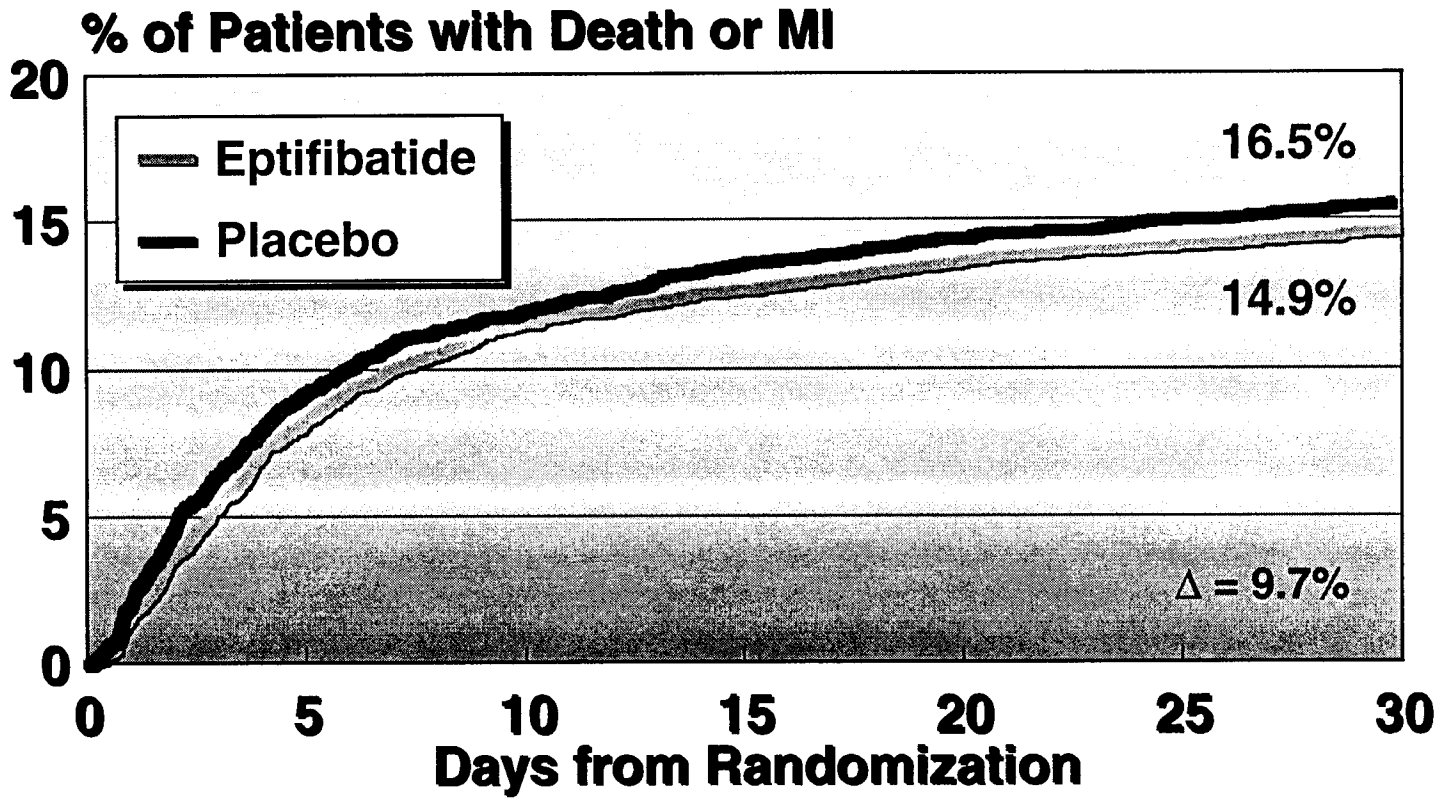


ML-113

Intervention

Outcome Without Revascularization*

Patients with Revascularization Censored at Time of Intervention

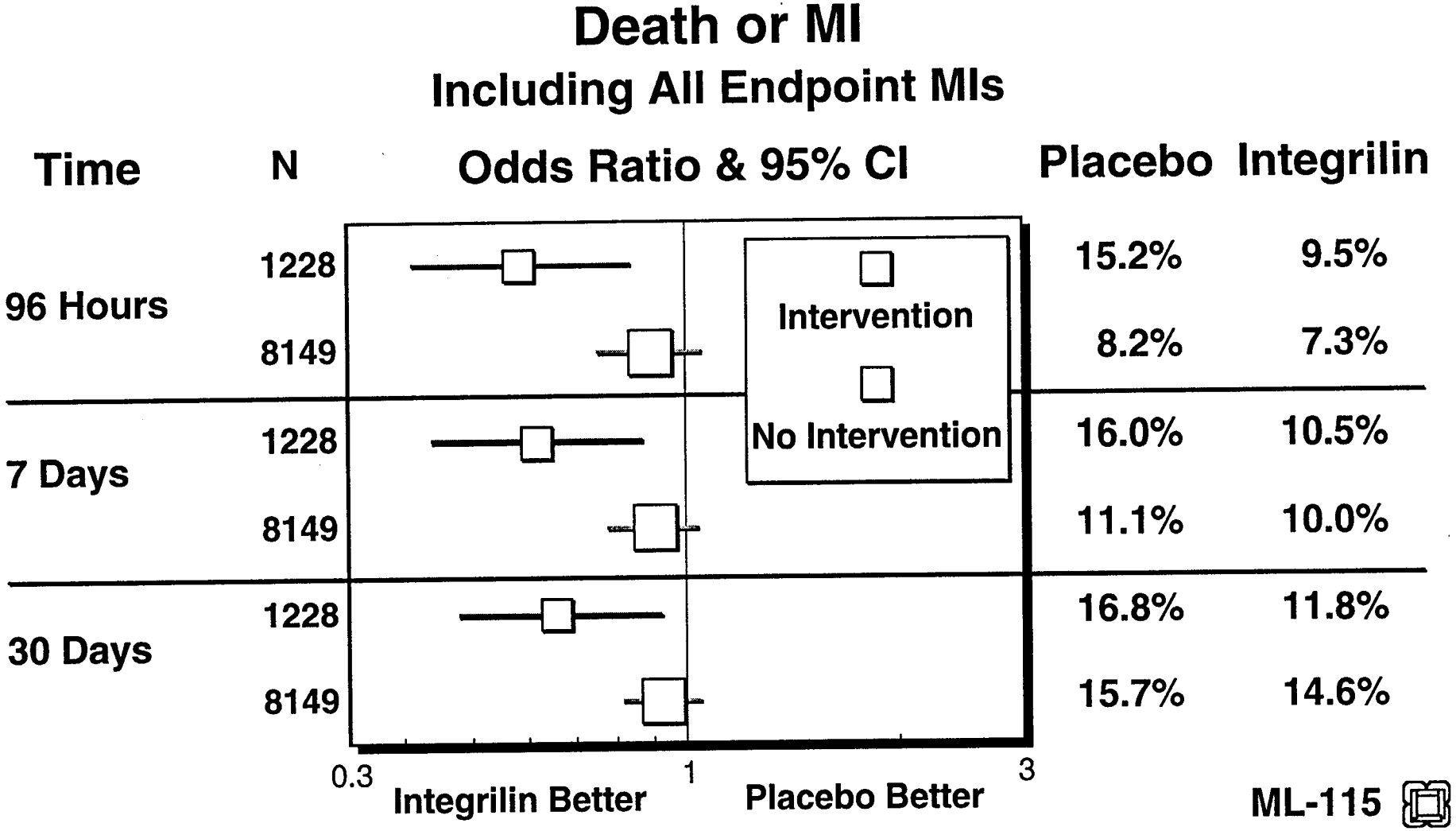


ML-114

*includes PTCA, stent, atherectomy, laser, IC lytics, CABG

Interventions

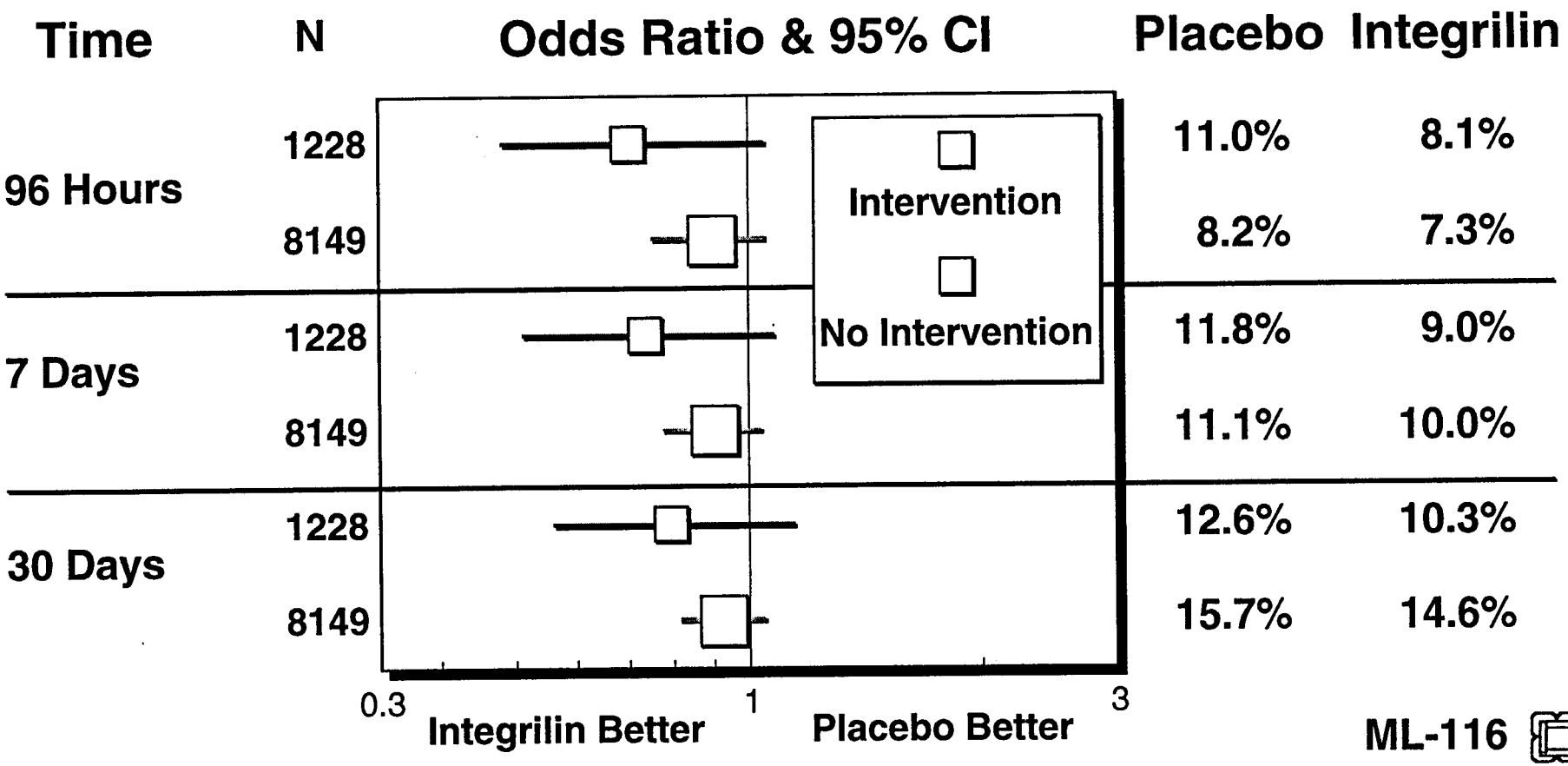
Death or MI
Including All Endpoint MIs



Interventions

Death or MI

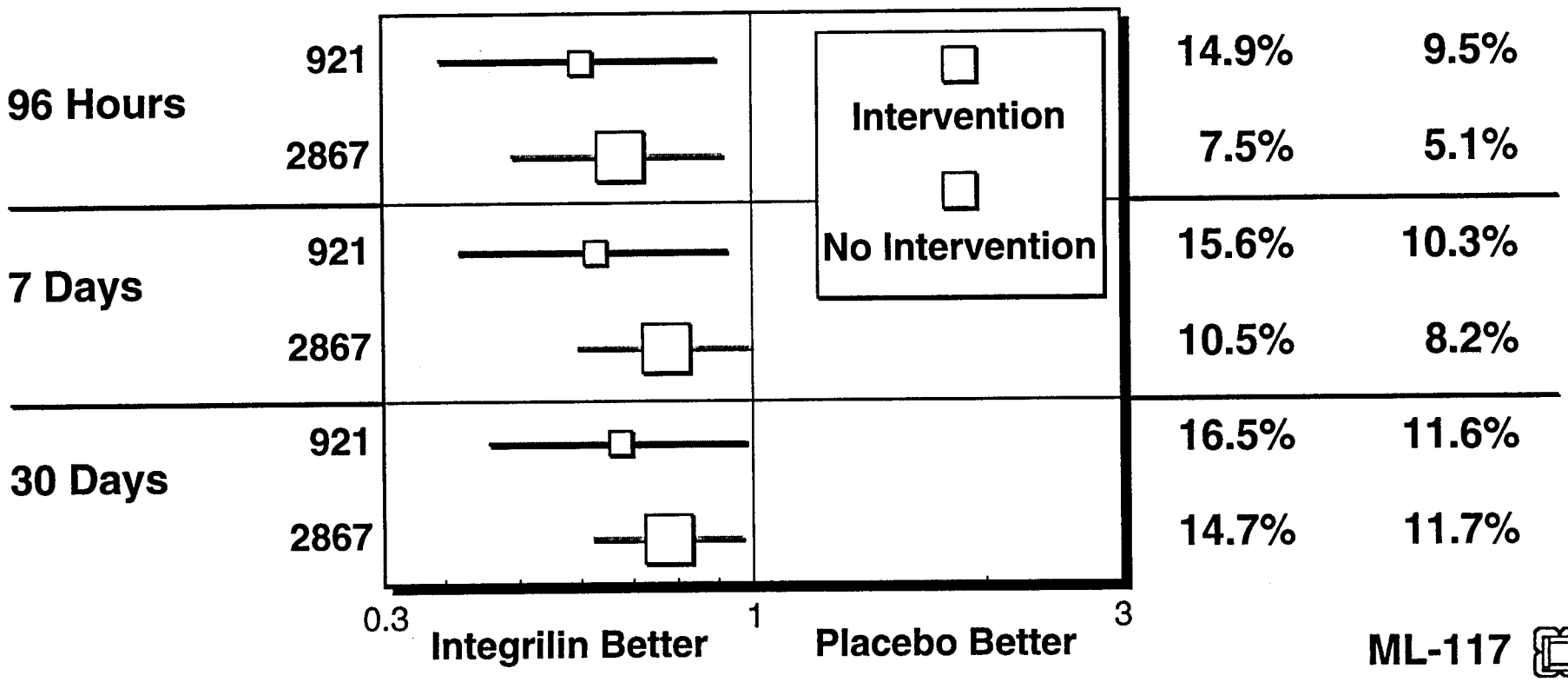
Including only MIs After Initiation of Procedure



ML-116

Interventions

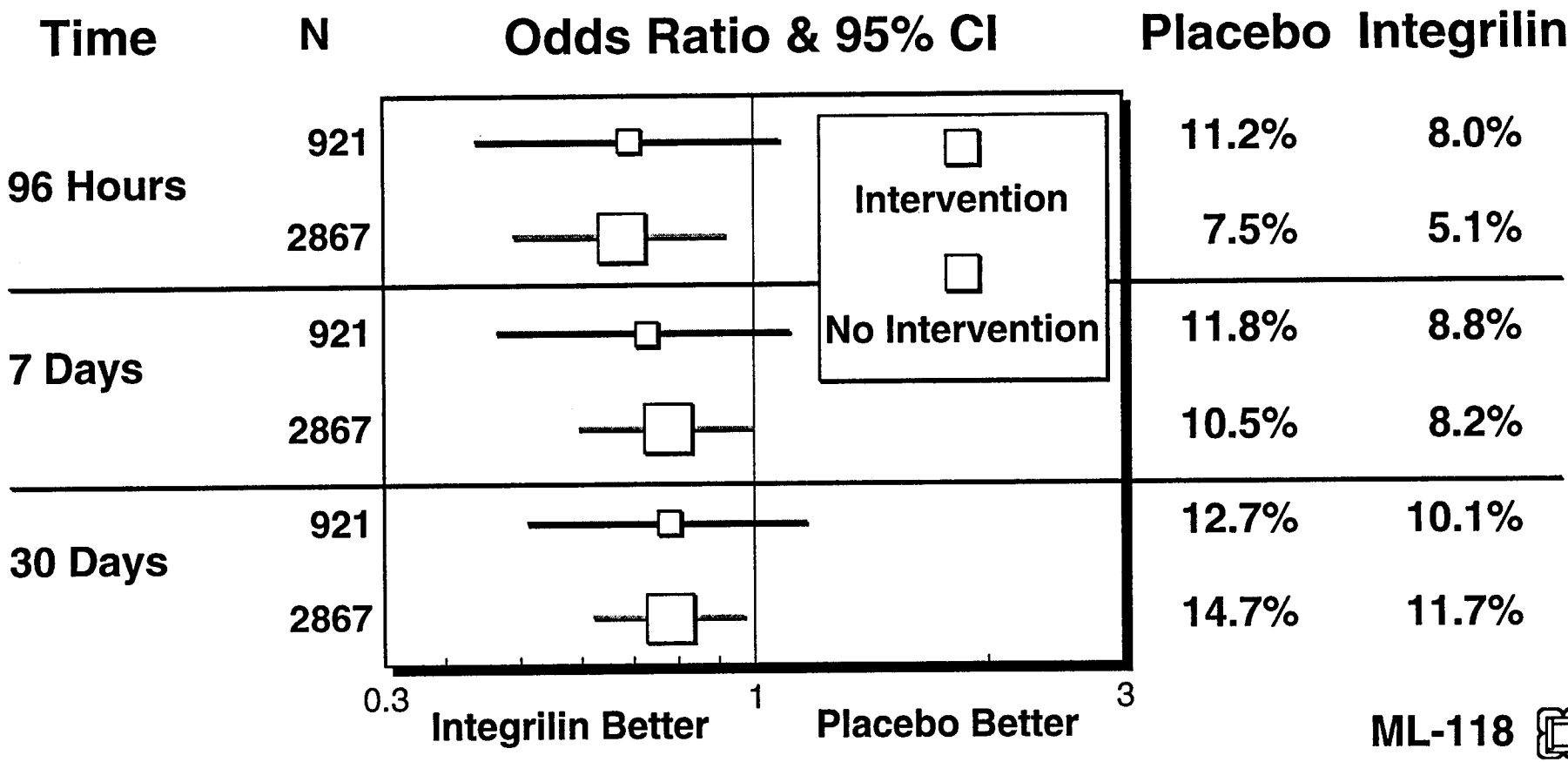
Death or MI - North American Pts
Including All Endpoint MIs



ML-117

Interventions

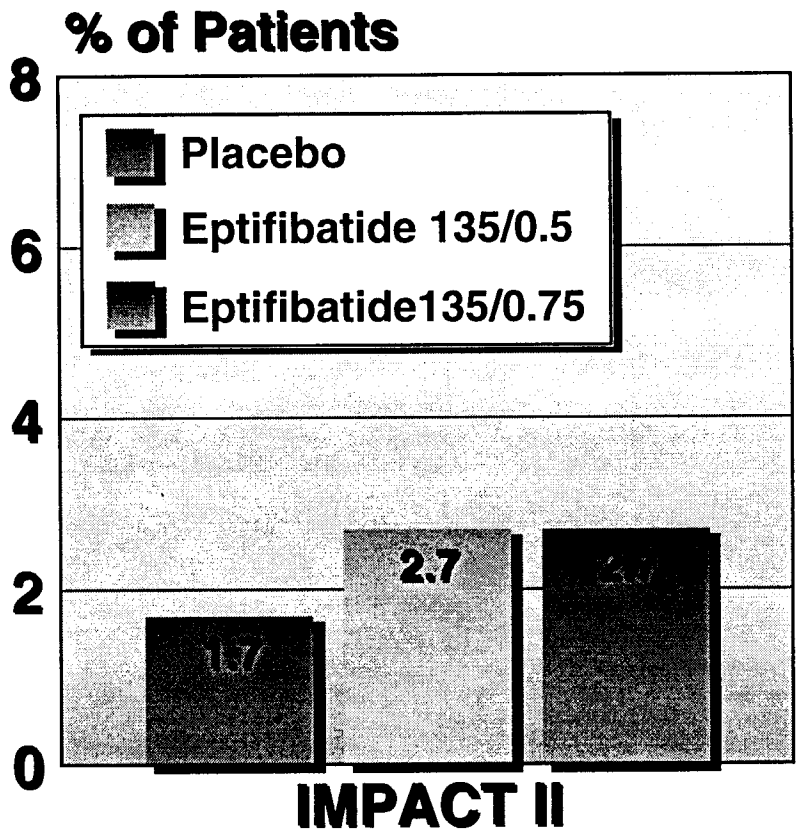
Death or MI - North American Pts
Including only MIs After Initiation of Procedure

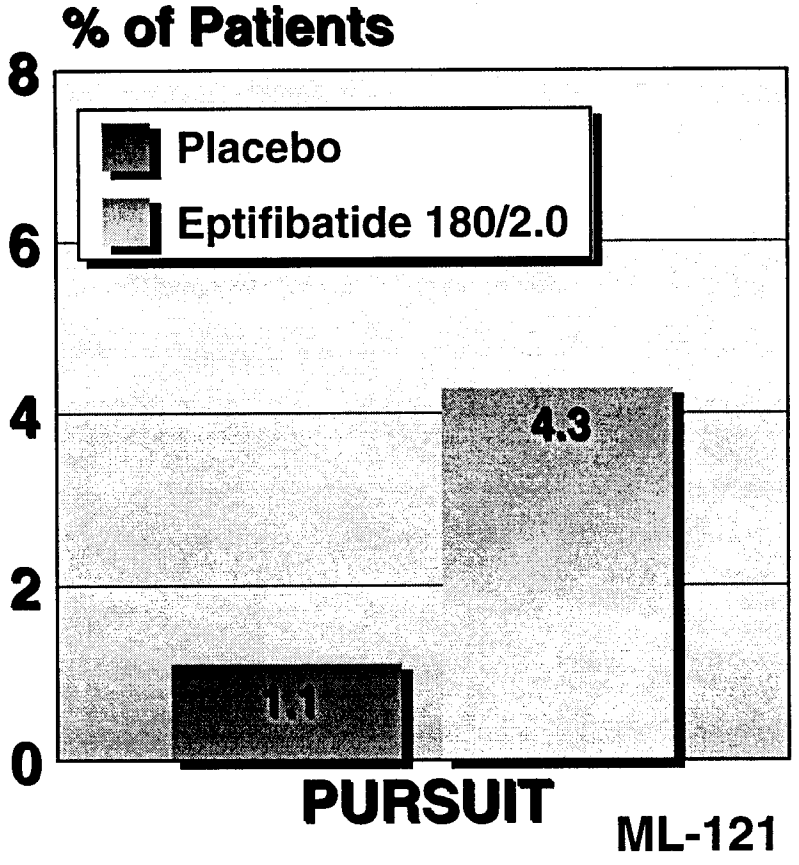


ML-118

Major Bleeding - IMPACT II vs PURSUIT

PCI Patients, Excluding CABG-Related Bleeding





ML-121

pursuit

Summary

- Subgroup analysis of a post-randomization event
- No statistical inferences drawn
- Findings observational, rather than product of a randomized analysis

Conclusions

- Treatment effect of eptifibatide observed in patients who did or did not undergo PCI during first 72 hours (on study drug)
- Trend toward greater treatment effect of eptifibatide among PCI patients
- Findings supportive of biological mechanism of action of eptifibatide - consistent with IMPACT II

Overall Conclusions

- Common pathophysiology
- Two positive studies
- Common endpoints
- Overlapping patient populations
- Data supports the use of the 180/2.0 dose