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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SLIDES (VERIDIA)

VERDIA (TASOSARTAN)

Betty S. Riggs, M.D.

Assistant Vice President
Clinical Research & Development
Wyeth-Ayerst Research

file

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

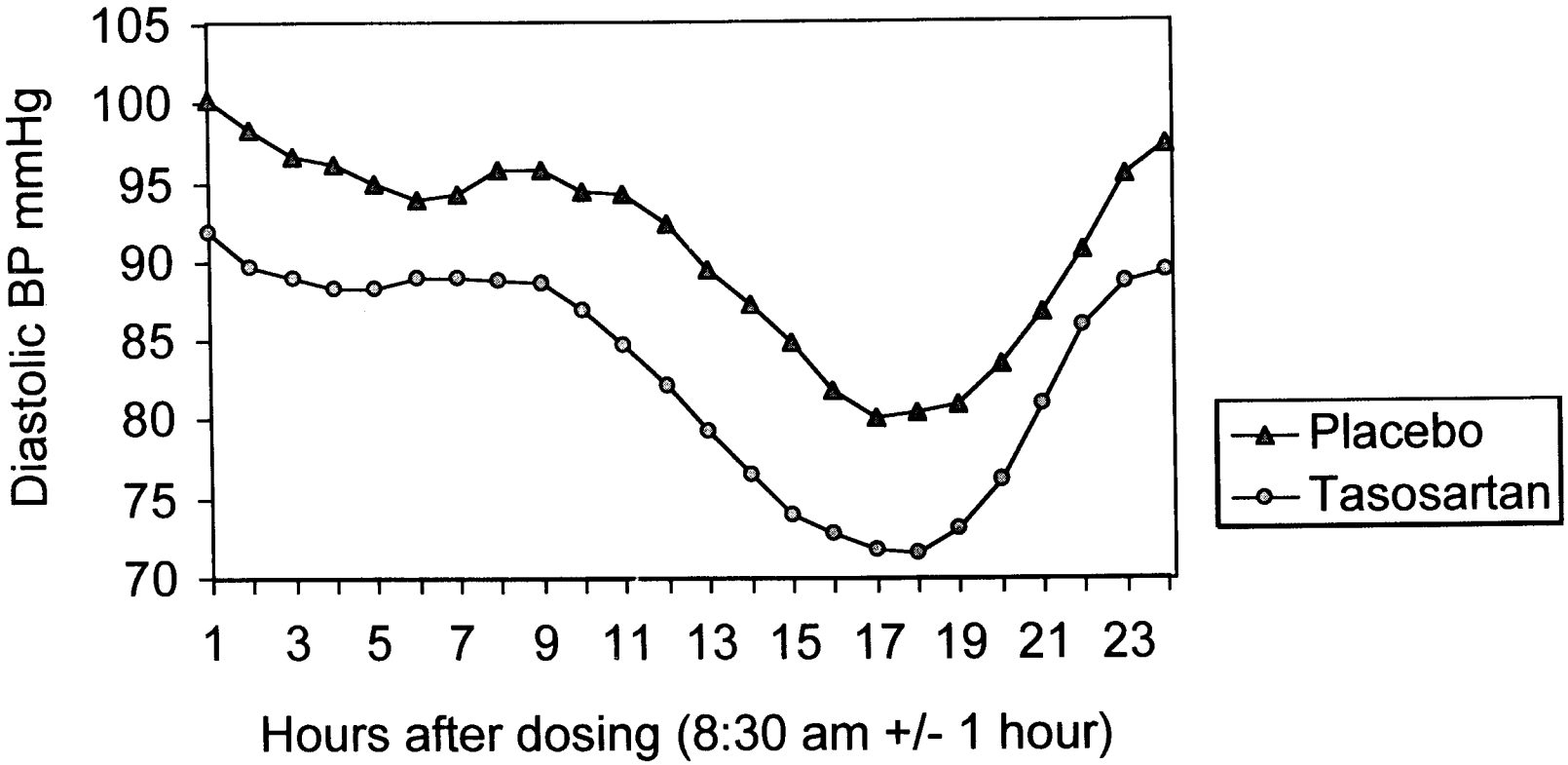
AGENDA AND CONSULTANTS

- 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.

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

PROTOCOL 820A-322-US

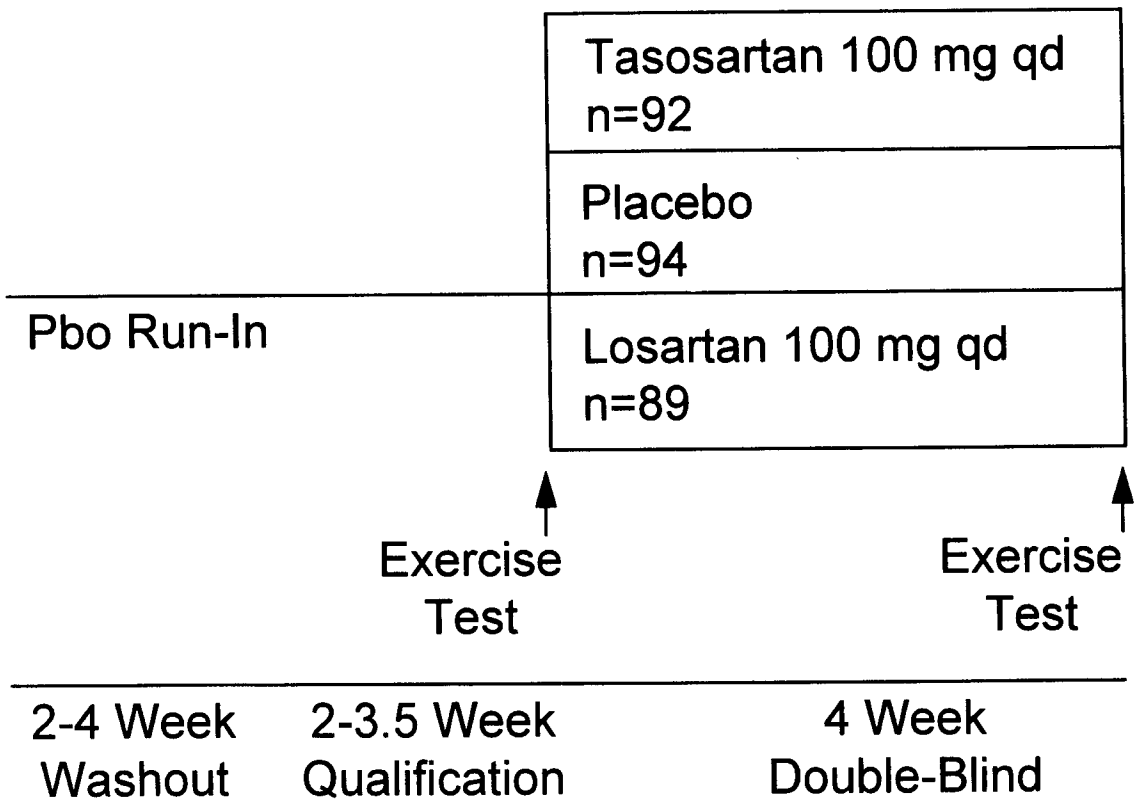


(b)(4) PRESENTATION (MM#22397 WYE00195) part 3

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

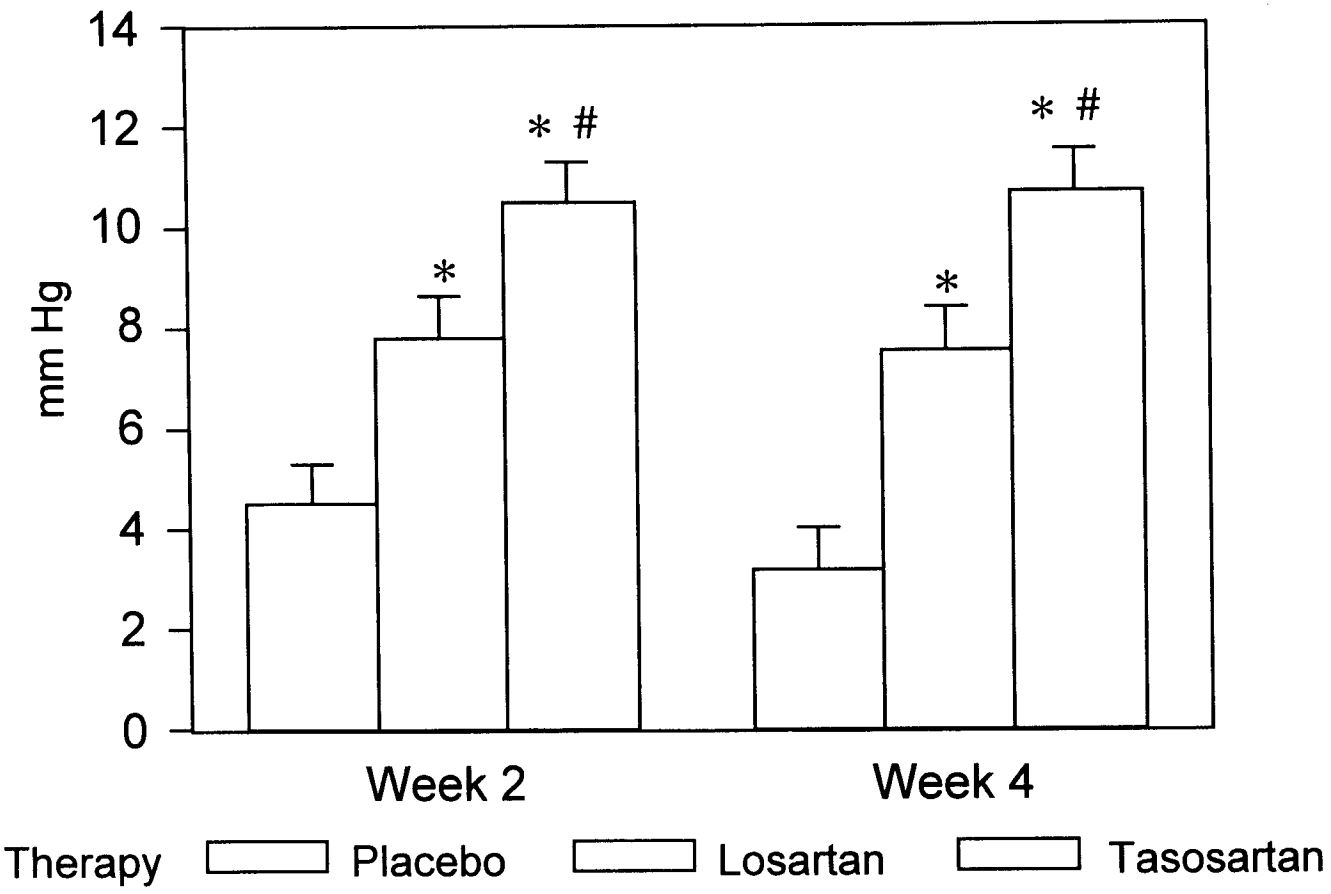
PROTOCOL 328



328-US

PROTOCOL 328

Reduction from Baseline Mean SiDBP (± SE)

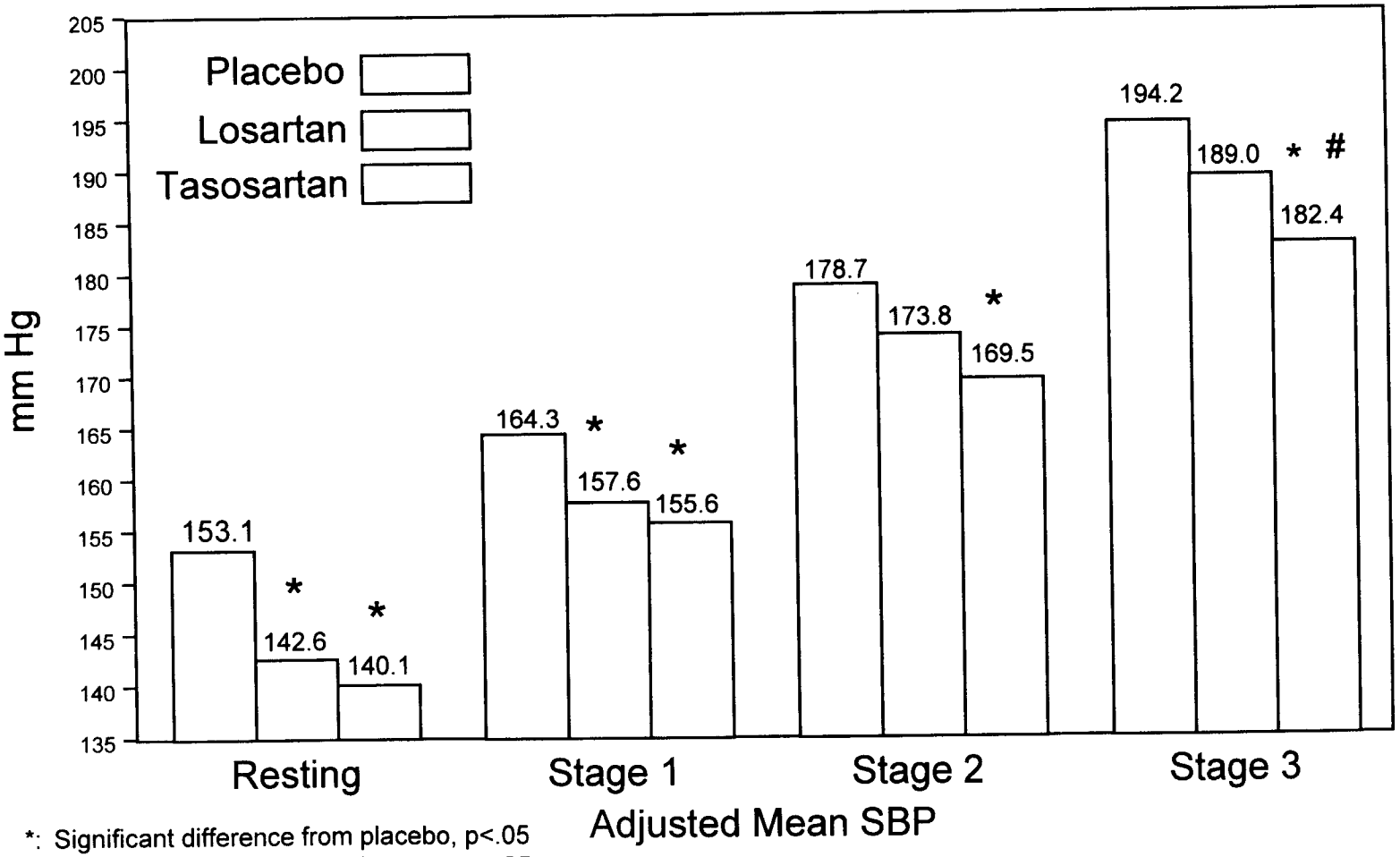


*: Significant difference from placebo, p<.05
#: Significant difference from losartan, p<.05

328-US

(b)(4) PRESENTATION (MM#22397 WYE00195)

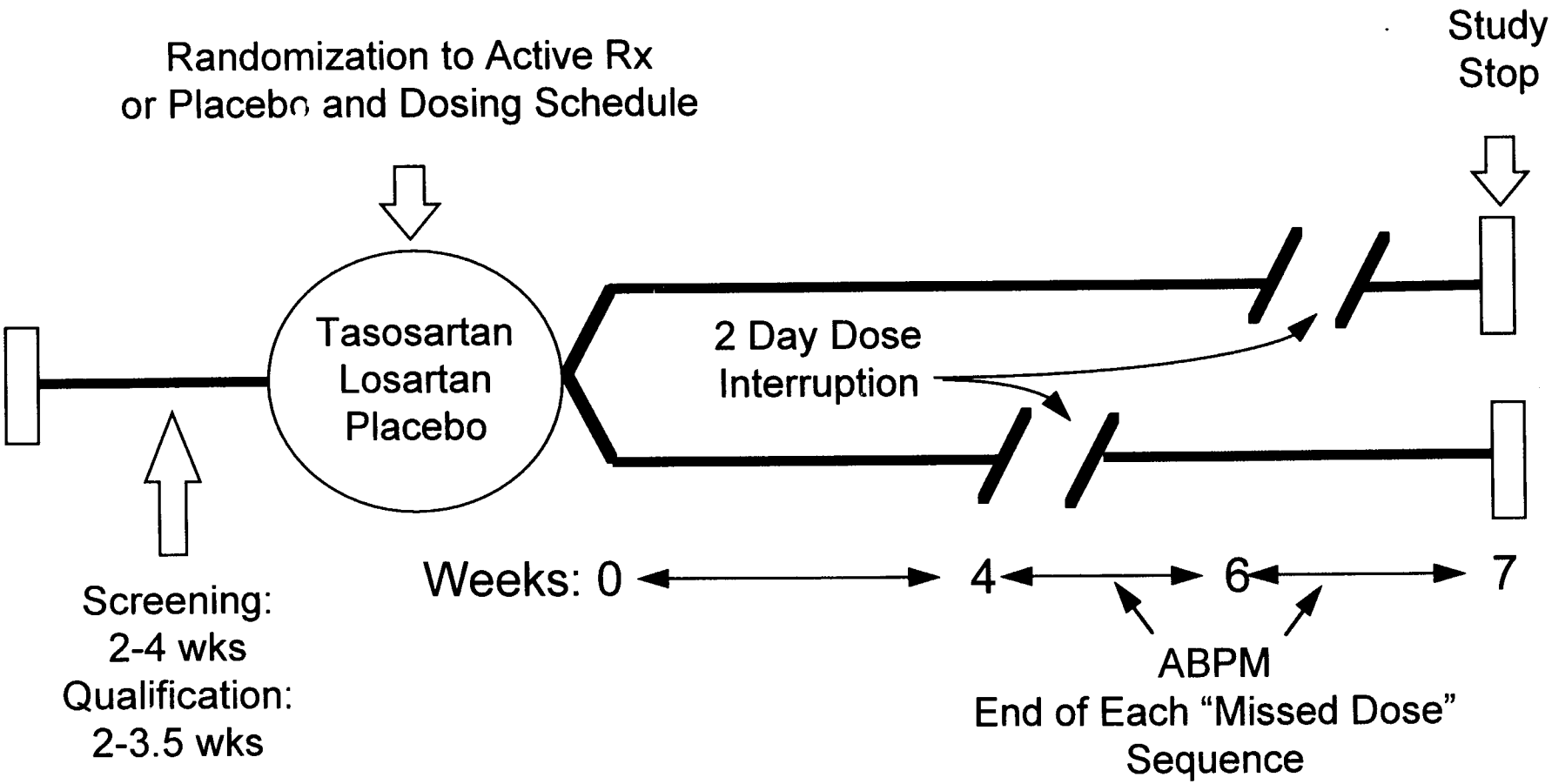
PROTOCOL 328
Systolic Blood Pressure
During the On-Therapy Exercise Stress Test



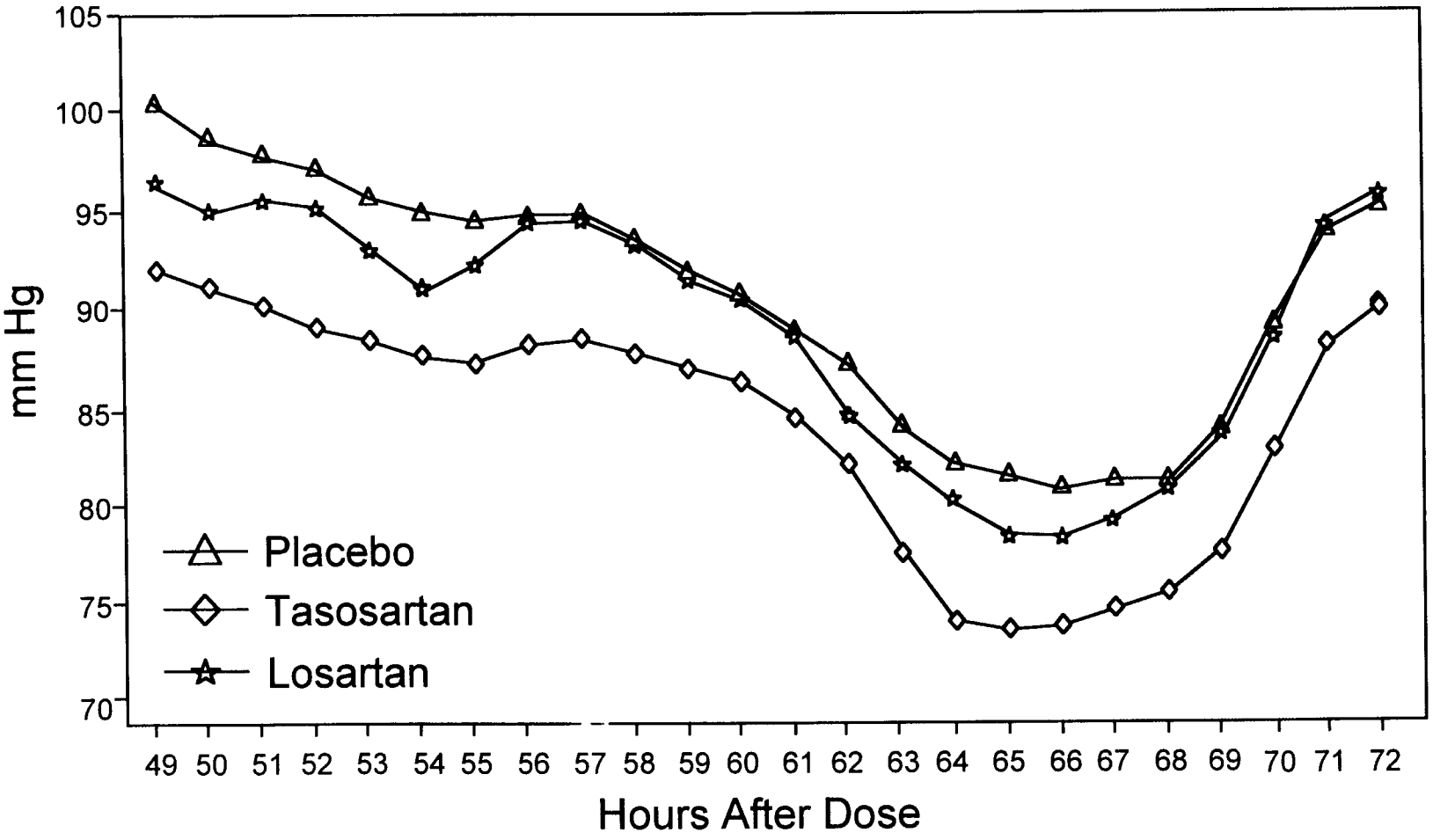
*: Significant difference from placebo, p<.05
#: Significant difference from losartan, p<.05

[redacted] PRESENTATION (MM#22397 WYE00195)

PROTOCOL 330: "MISSED DOSE" TRIAL



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



(b)(4) 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

(b)(4) PRESENTATION (MM#22397 WYE00195)

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

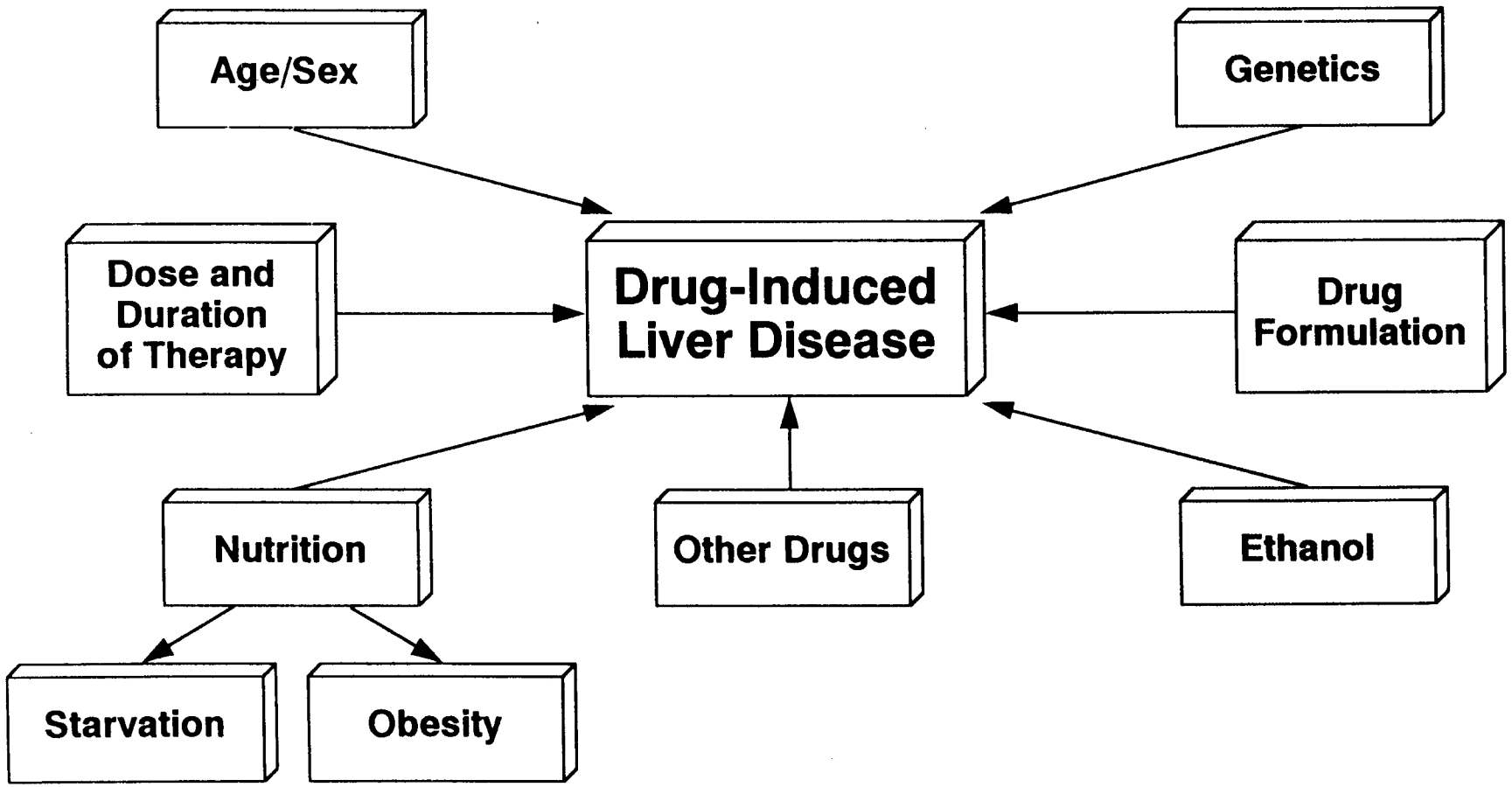
Willis C. Maddrey, MD, MACP

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

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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**

(b)(4)

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

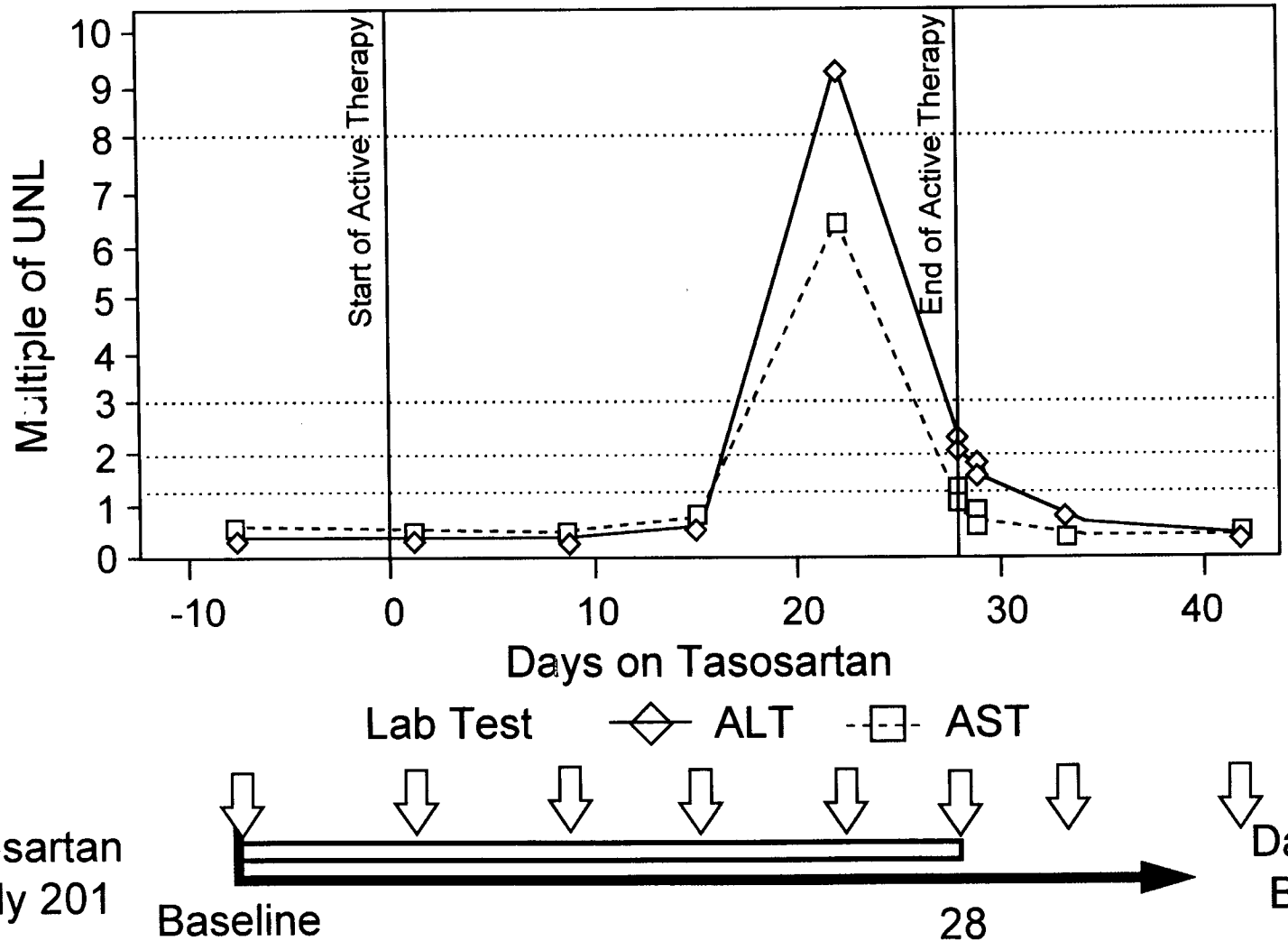
- Patients in phase II and III studies - controlled and open label
  - 4409 had at least one on-therapy laboratory evaluation
  - 83 (1.8%) of these had a potentially clinically significant ALT/AST
- Patients with normal LFT's at baseline
  - 3776 had at least one on-therapy laboratory evaluation
  -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

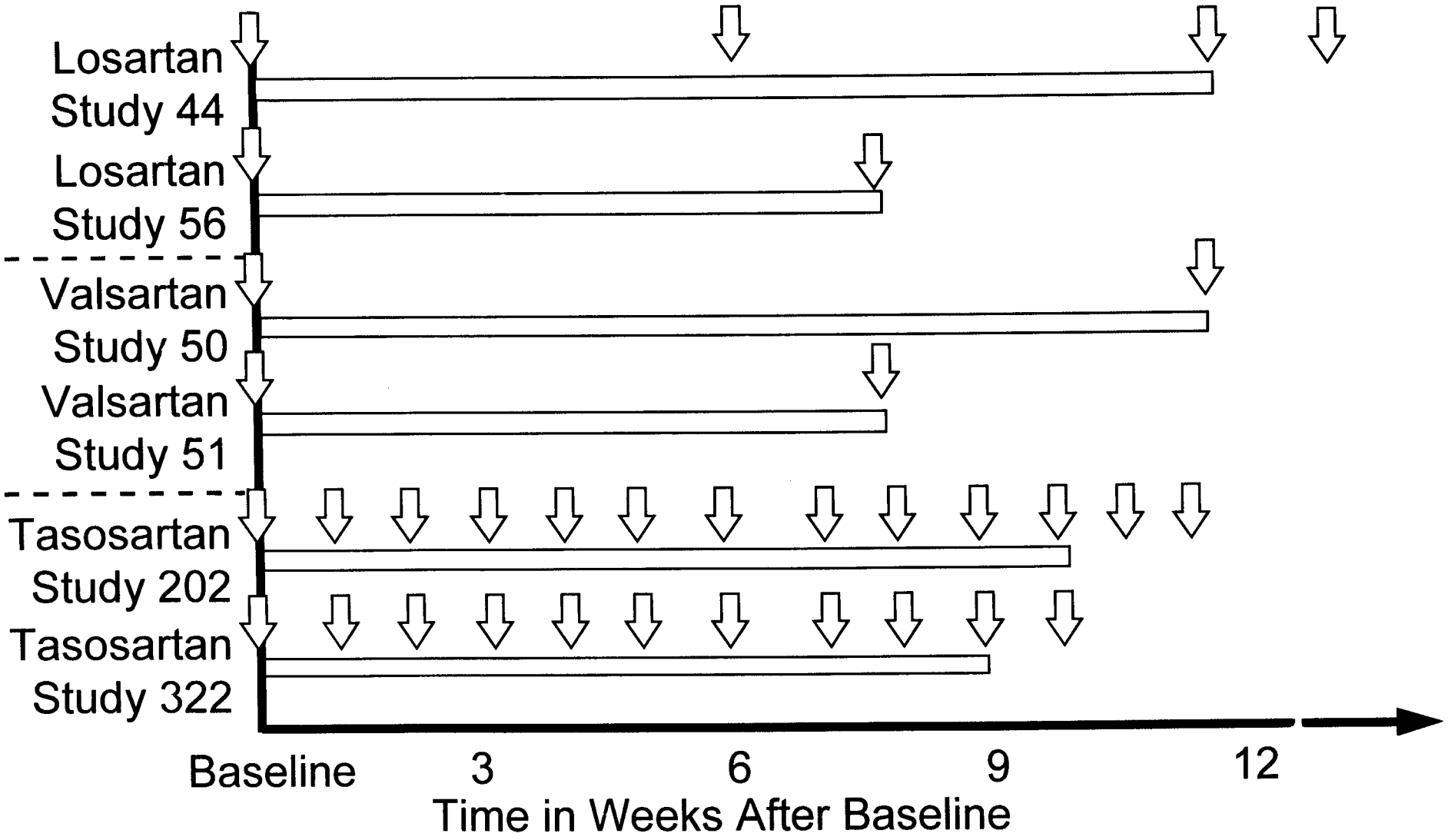
COMPARISONS WITH OTHER PROGRAMS

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

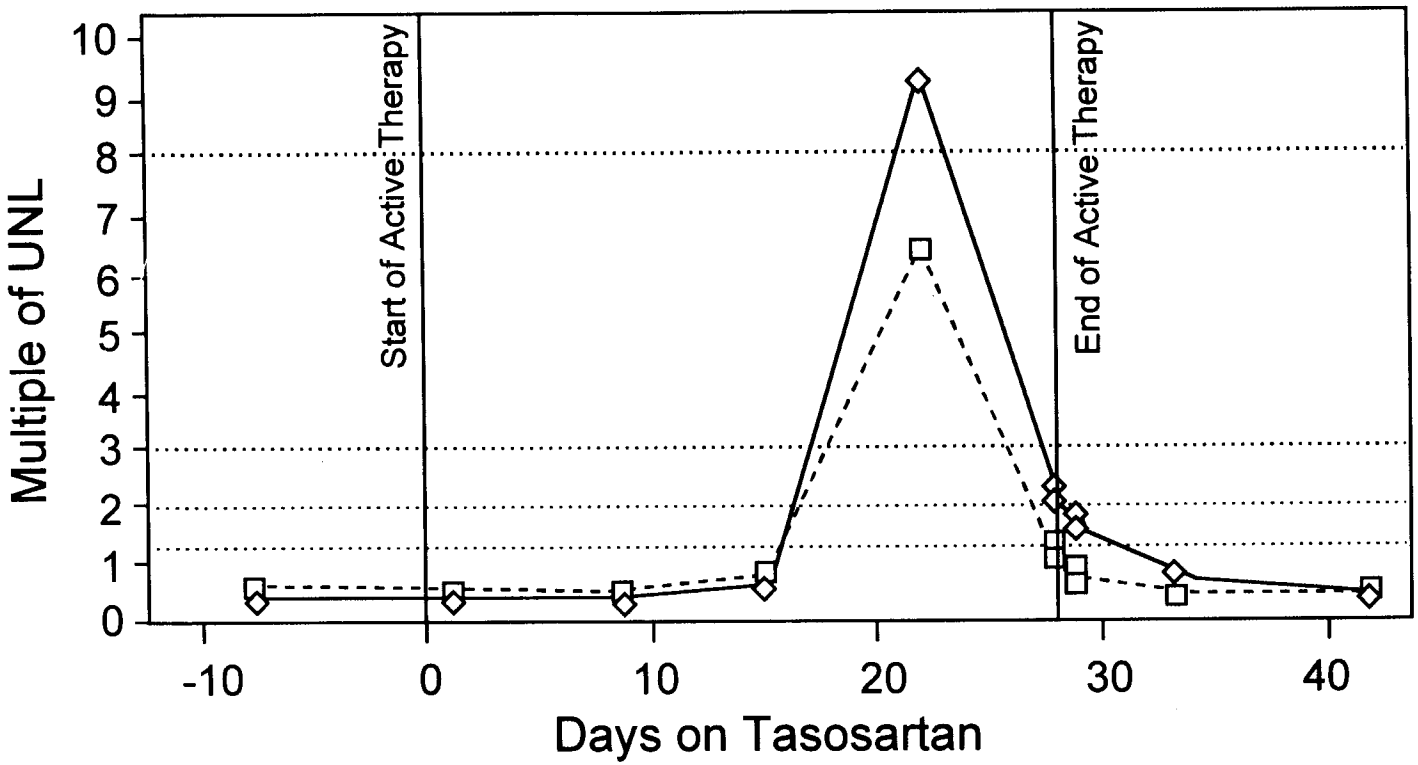
DISCONTINUATIONS

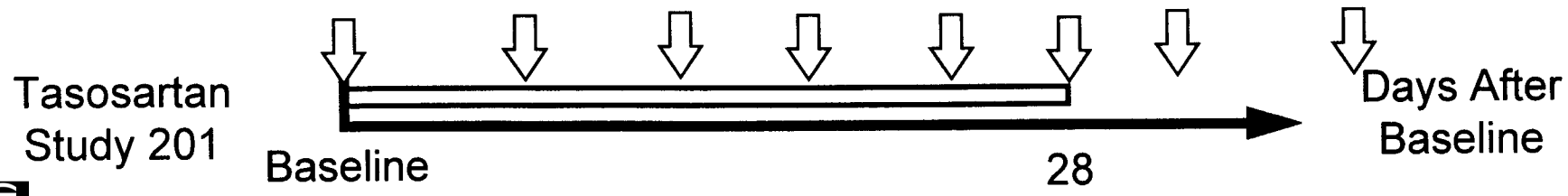
- Protocols contained no prespecified discontinuation rules for laboratory abnormalities observed in our studies
- Discontinuations reflect investigators' judgment
  - 1 site was responsible for 3 of 10 D/C's in controlled studies
    - 1 patient at this site was D/C'd for ALT/AST 2.0 x UNL

COMPARISON OF LABORATORY SAMPLING FREQUENCIES



COMPARISON OF LABORATORY SAMPLING FREQUENCIES
Patient 20124-0014





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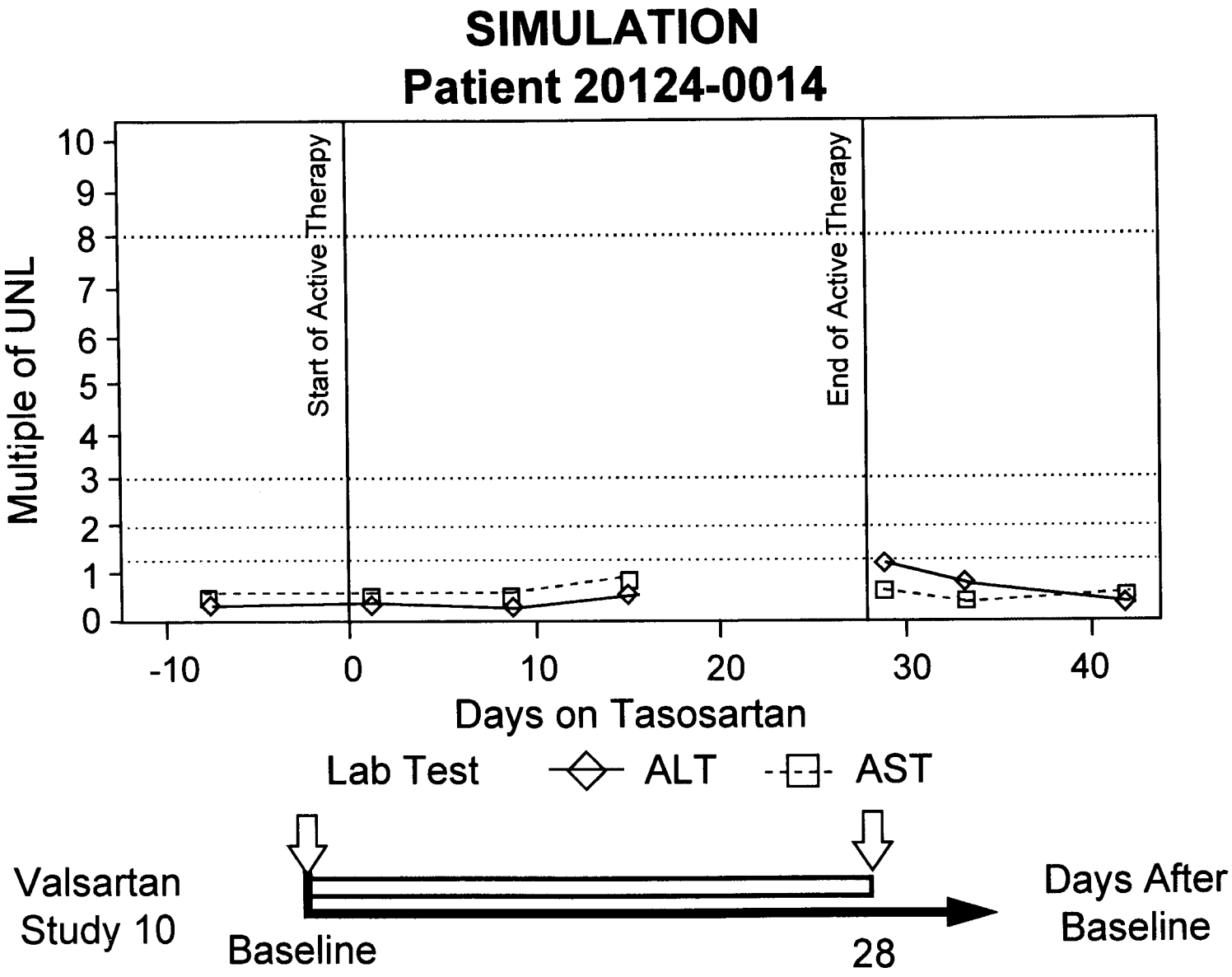
PRESENTATION (MM#22397 WYE00195)

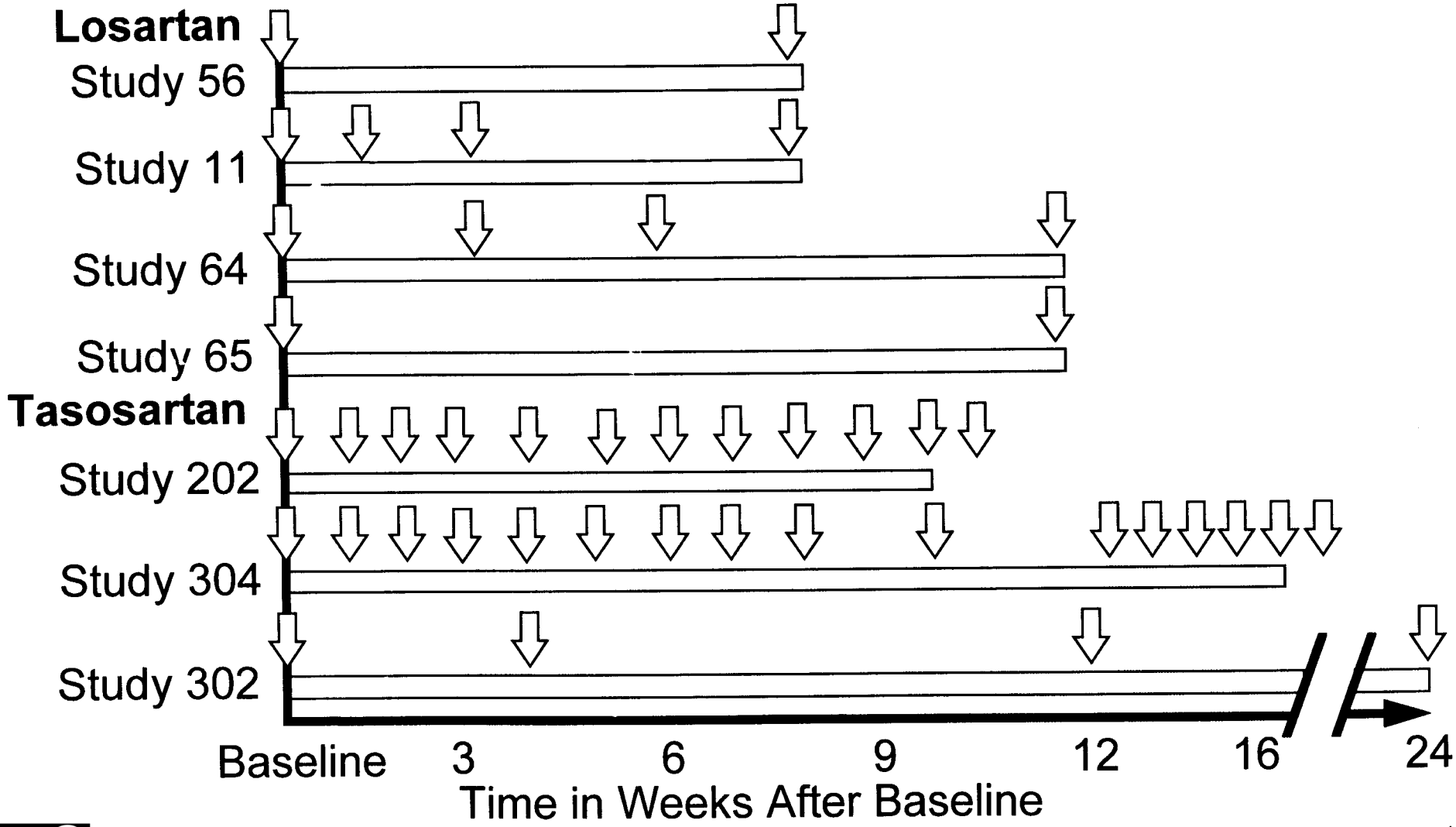


(b)(4) PRESENTATION (MM#22397 WYE00195)

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%

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

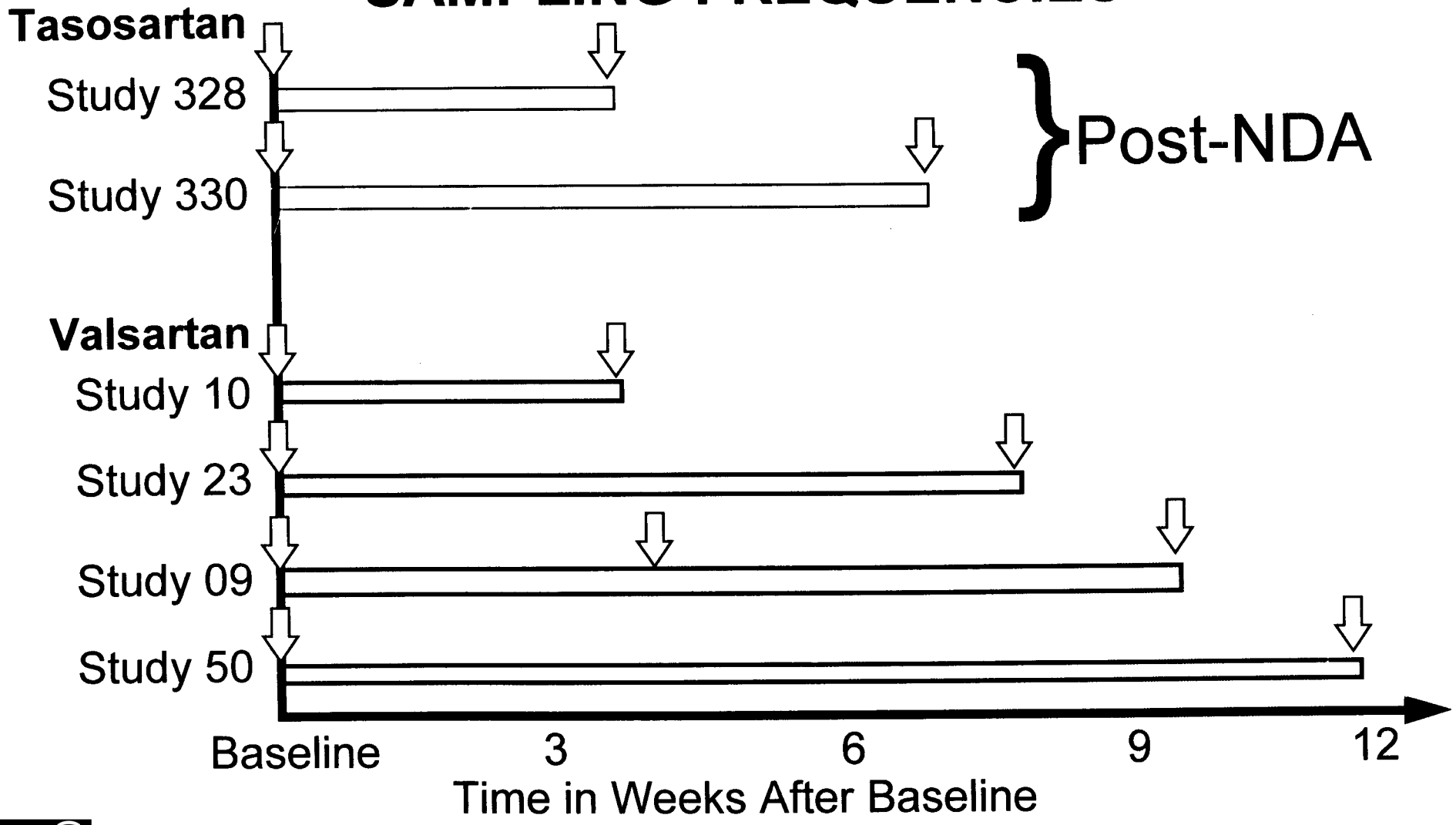
** 3/13 dropouts may have had other reason

Events shown are from all trials, not just controlled trials

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"

Morganroth-Self (WYE 00203)

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

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ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 01/27-28/98

SLIDES (INTEGRILIN)

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

MK2

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

MK5

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.

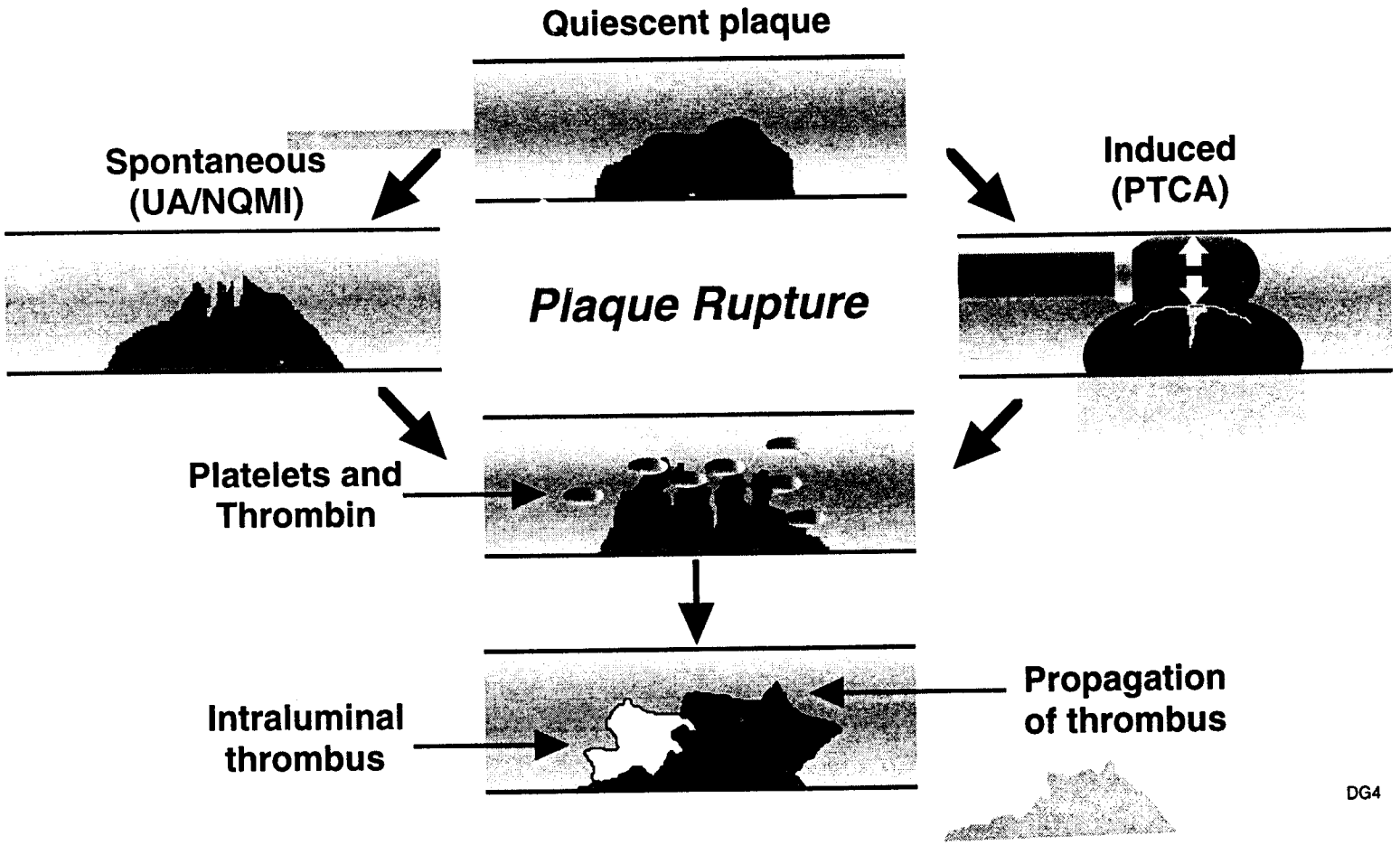
Background

- Pathophysiology and Pharmacology
- IMPACT II
- Dose Selection

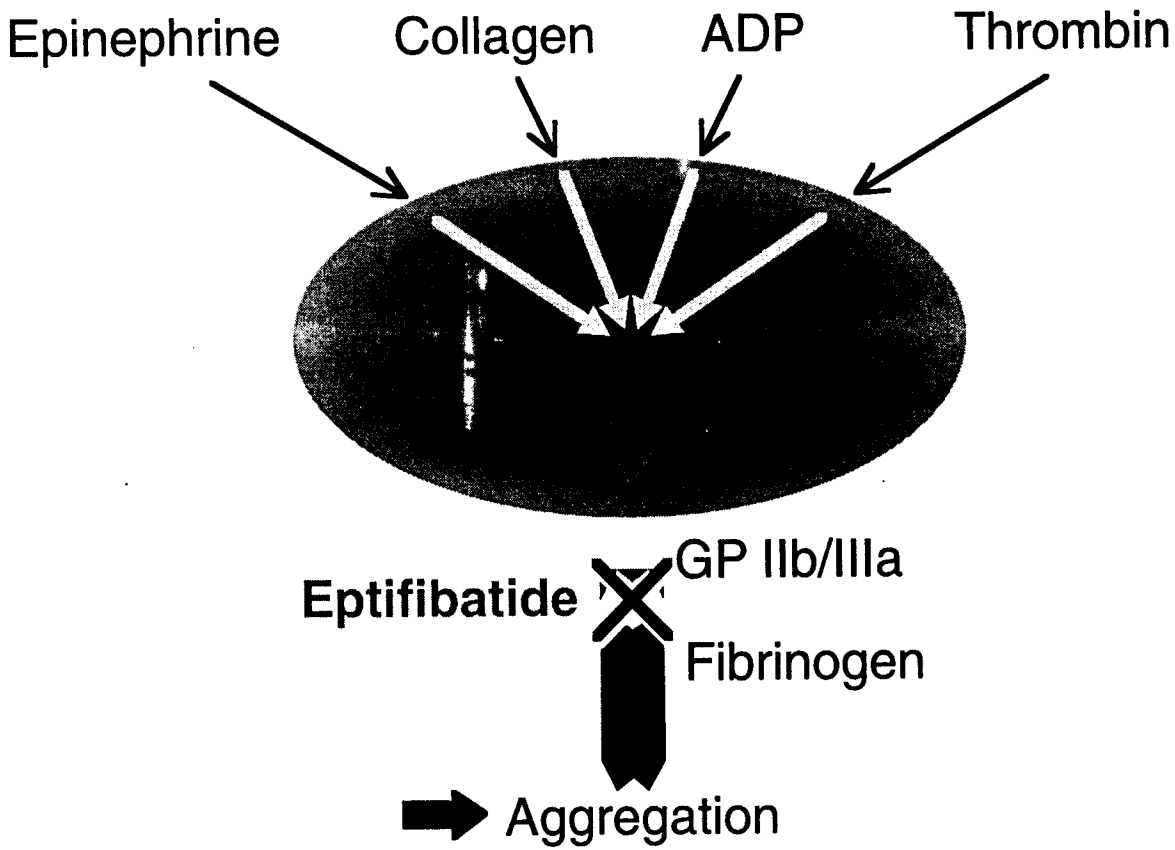
Background

- 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



DG5

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

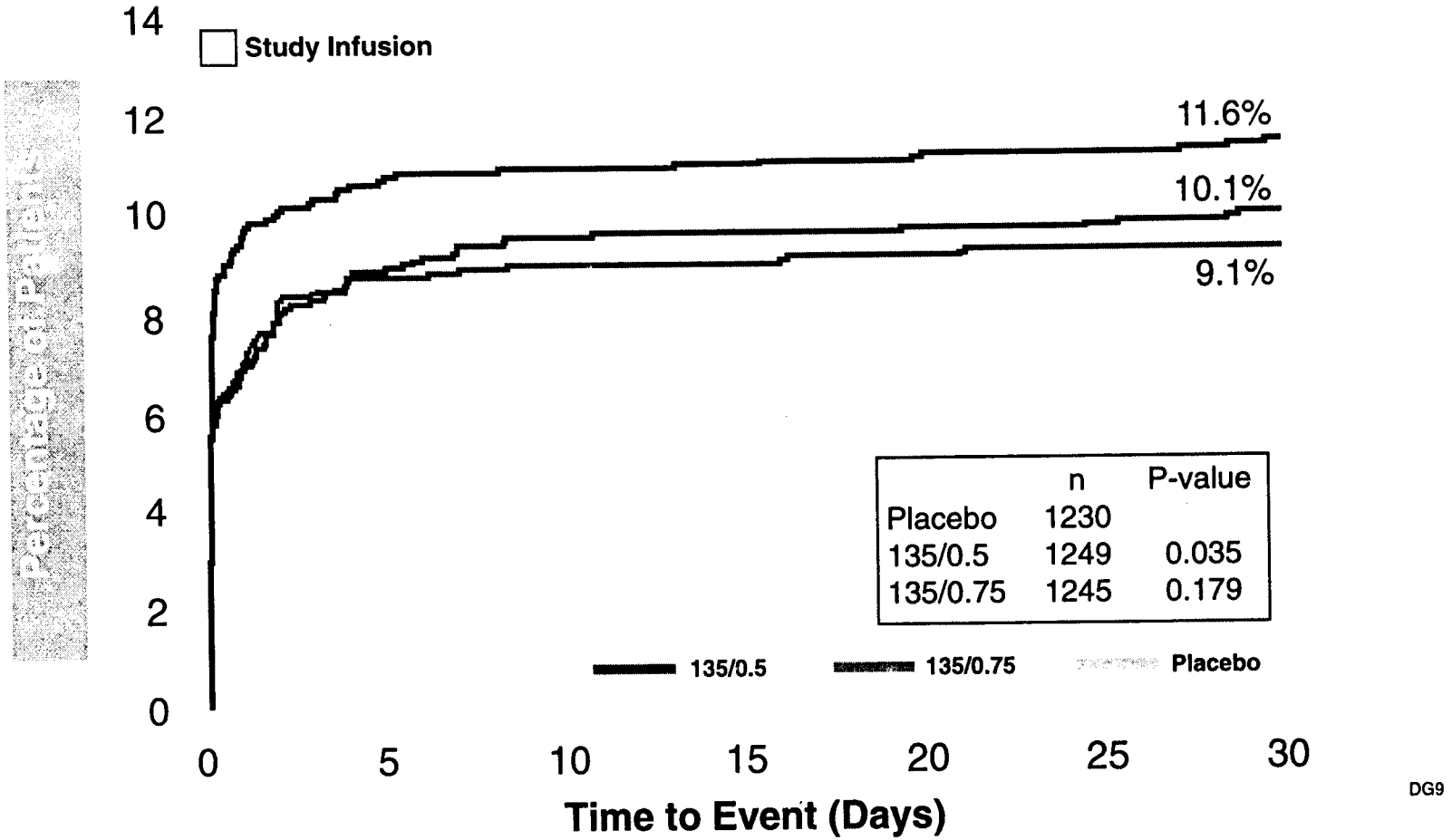
Study Design

- 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

IMPACT II

Eptifibatide

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

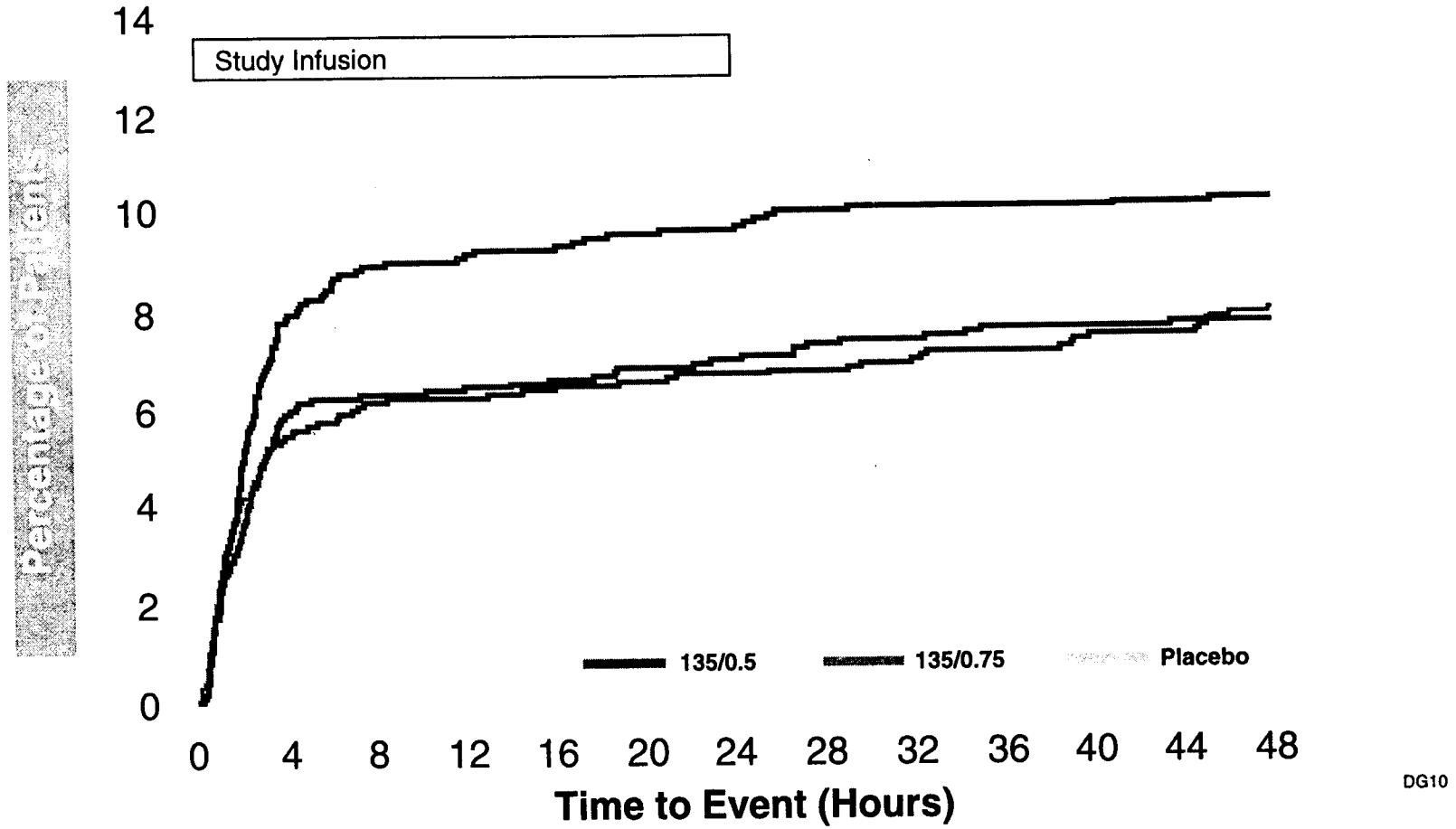


DG9

IMPACT II

Eptifibatide

Death/MI/Intervention Over 48 Hours

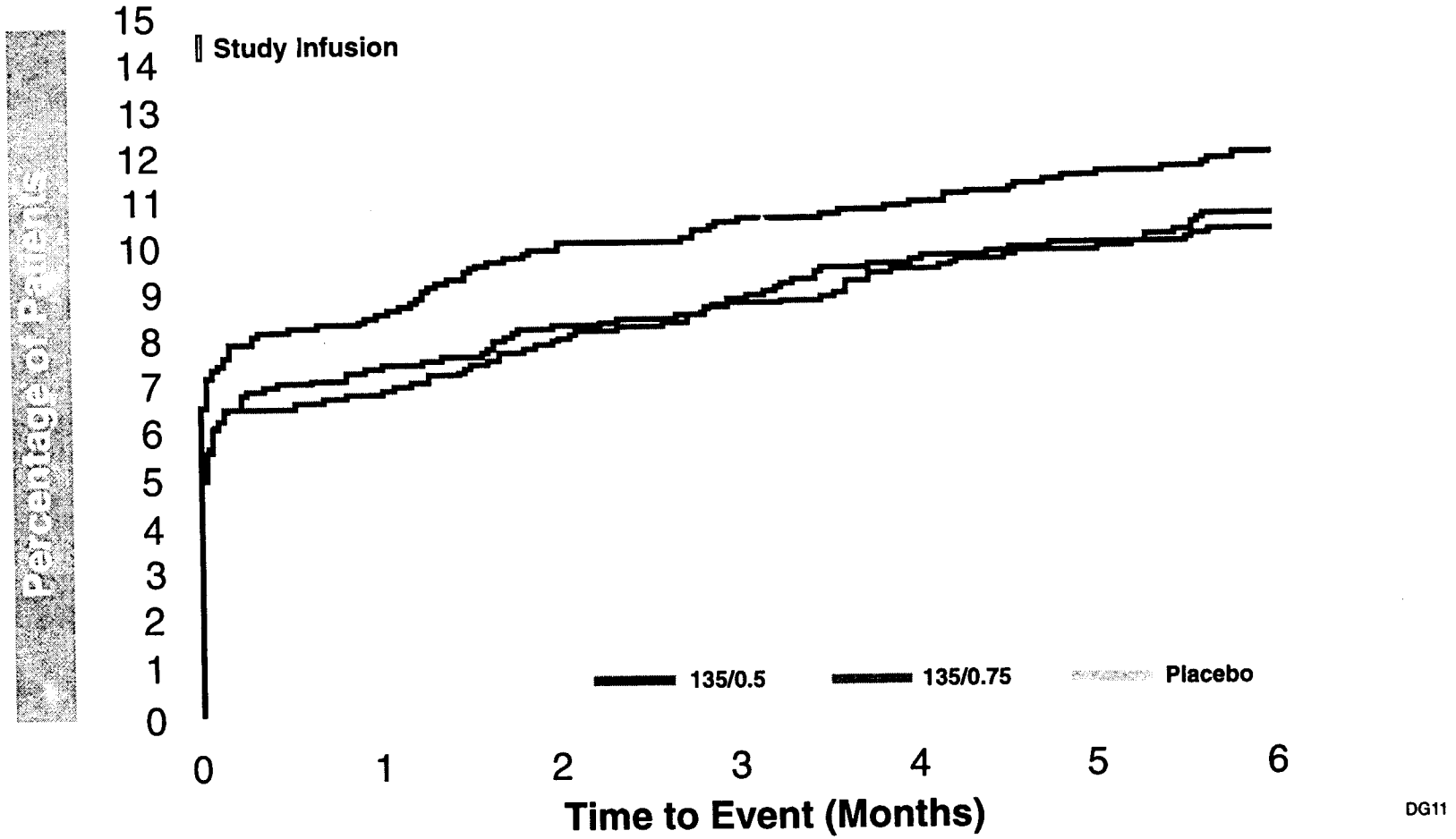


DG10

IMPACT II

Eptifibatide

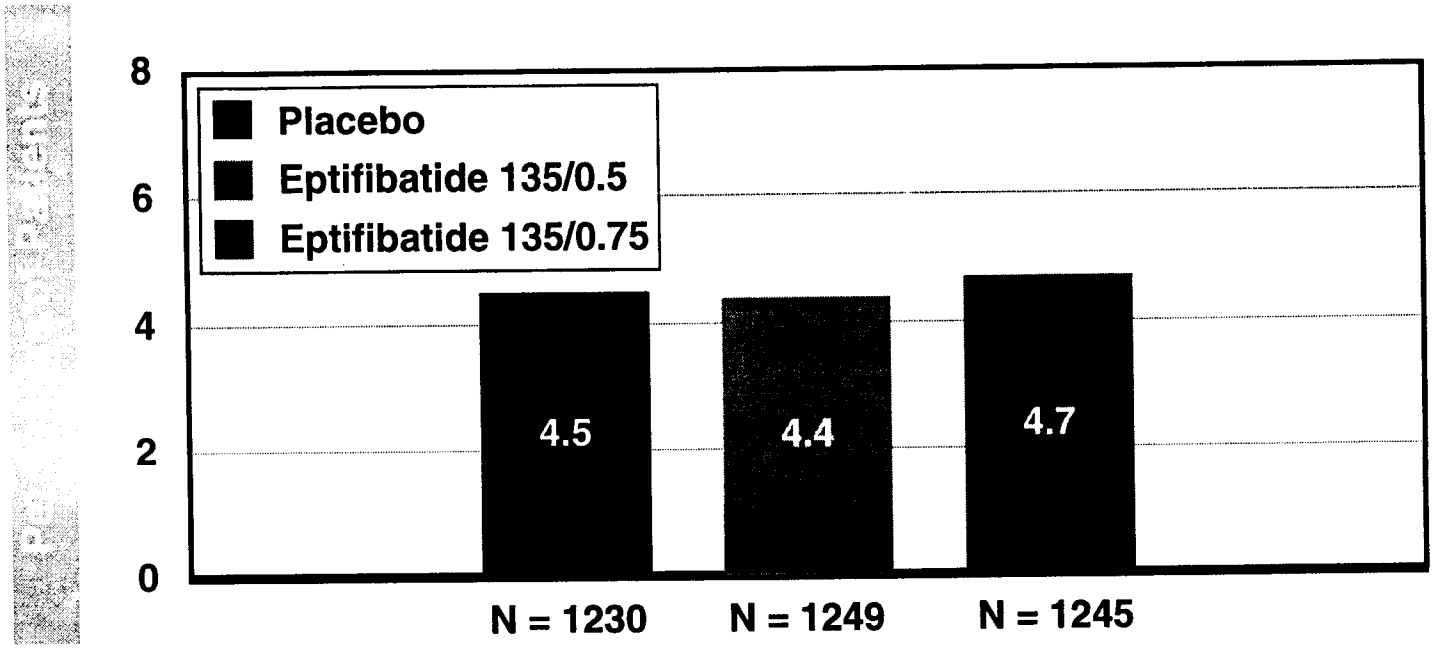
Irreversible Endpoints (Death/MI) Over 6 Months



DG11

Safety Profile

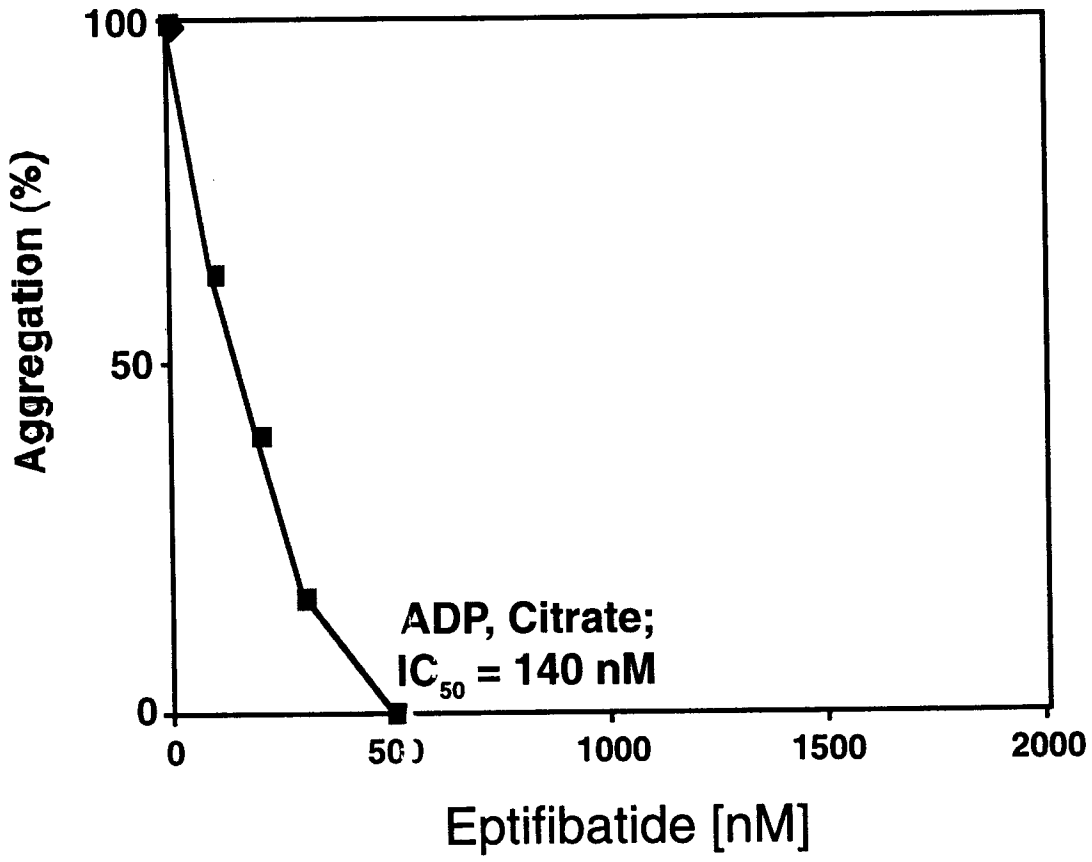
TIMI Major Bleeding



Background

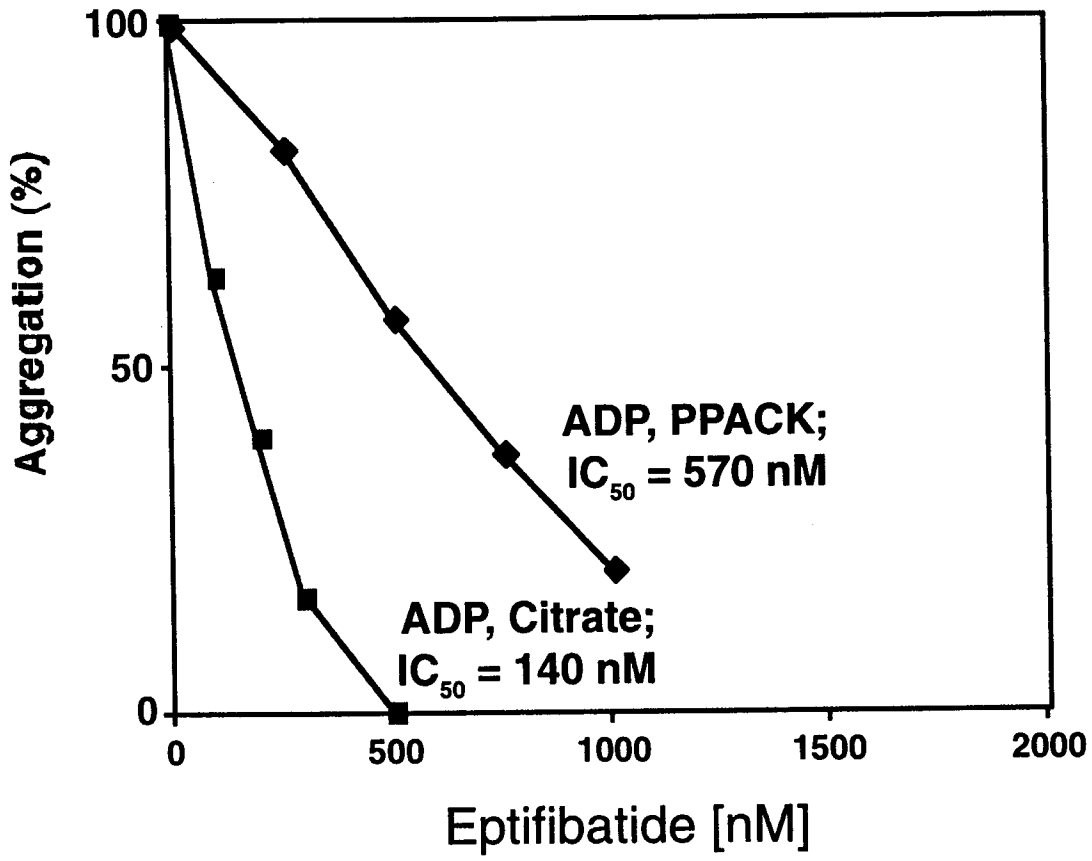
- Pathophysiology and Pharmacology
- IMPACT II
- Dose Selection
  - Dose selection for IMPACT II
  - Dose adjustment for PURSUIT

Inhibition of Platelet Aggregation by Eptifibatide



DG14

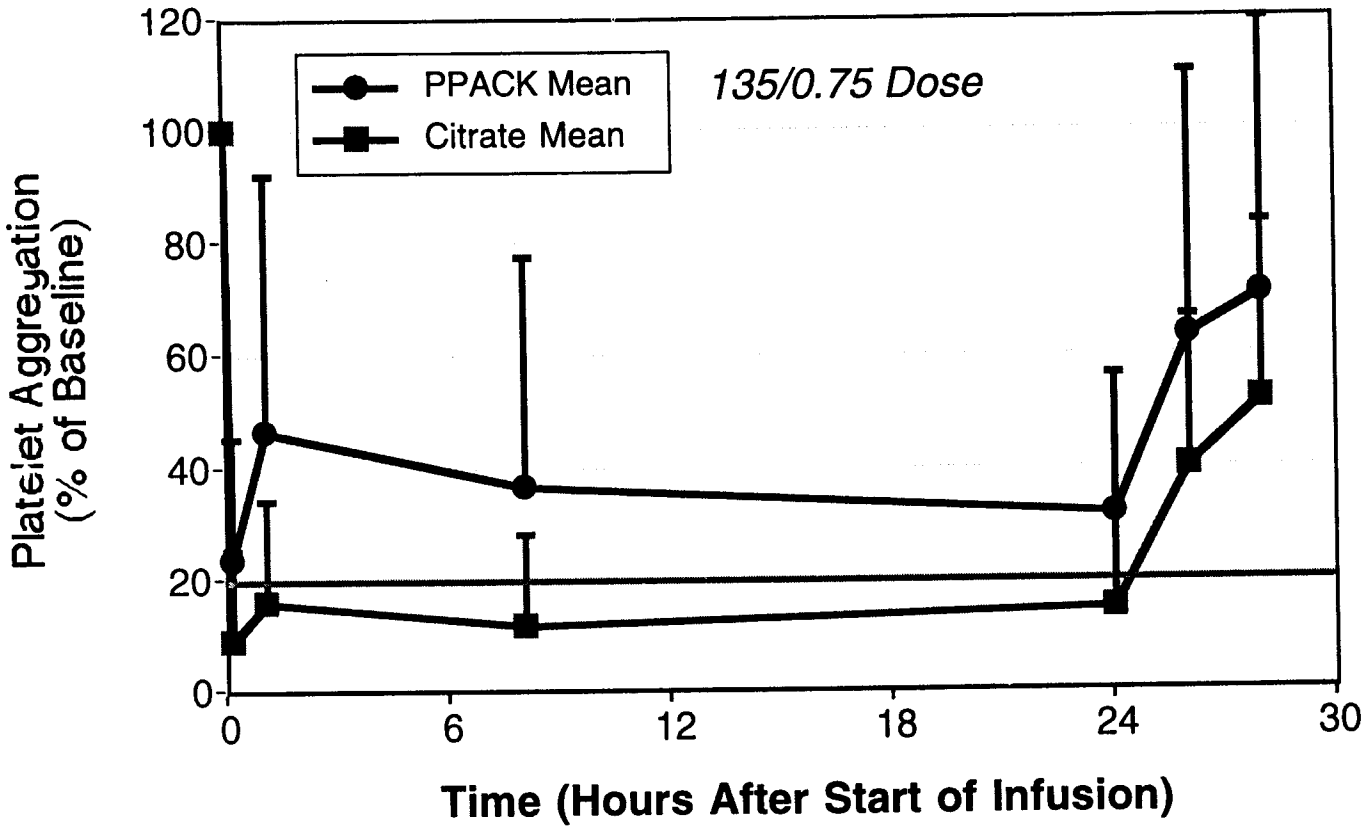
Inhibition of Platelet Aggregation by Eptifibatide



DG15

Platelet Aggregation (Citrate vs. PPACK)

"PRIDE" Study



DG16

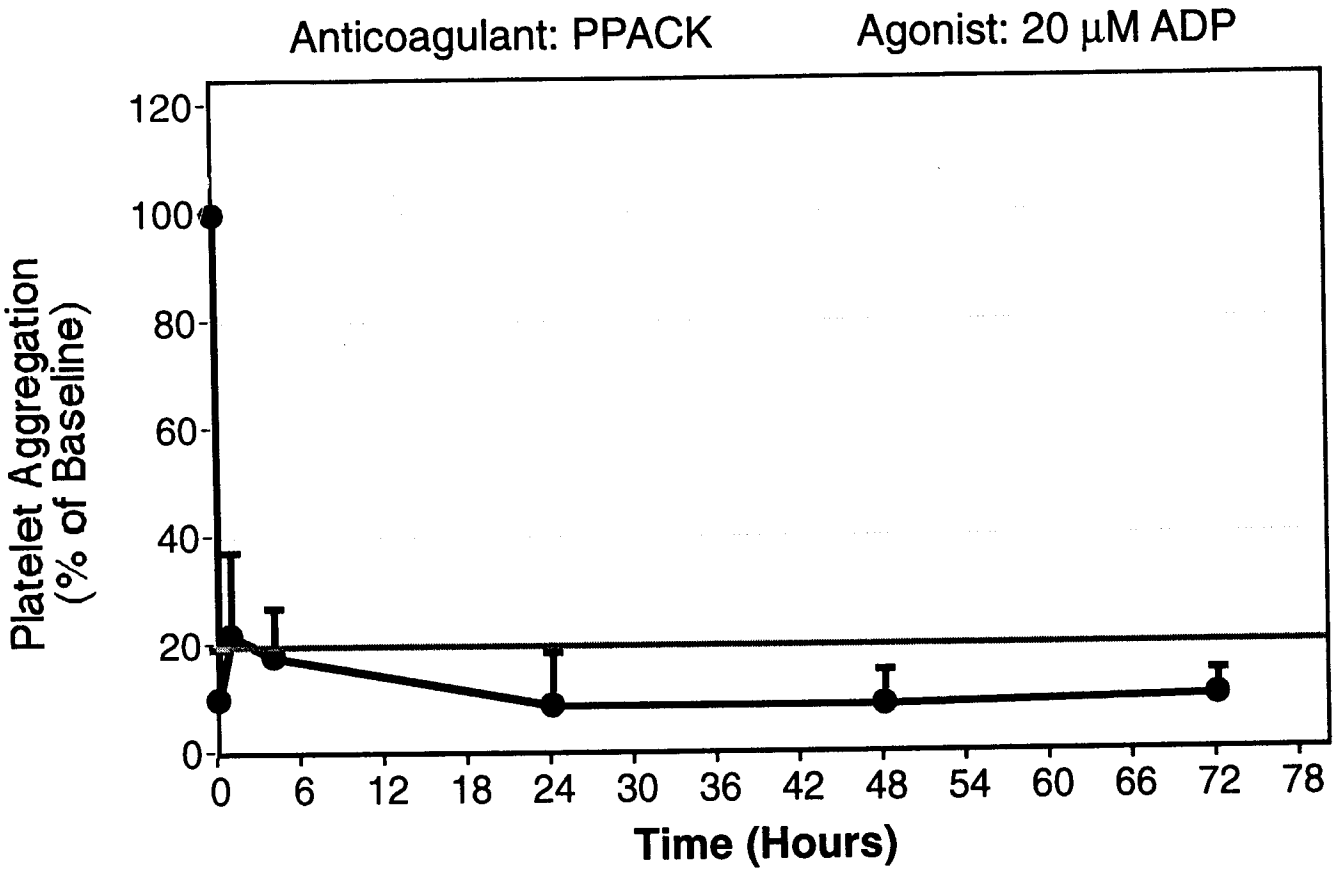
Rationale for PURSUIT Dose Selection

- 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)

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

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**

Exclusion Criteria

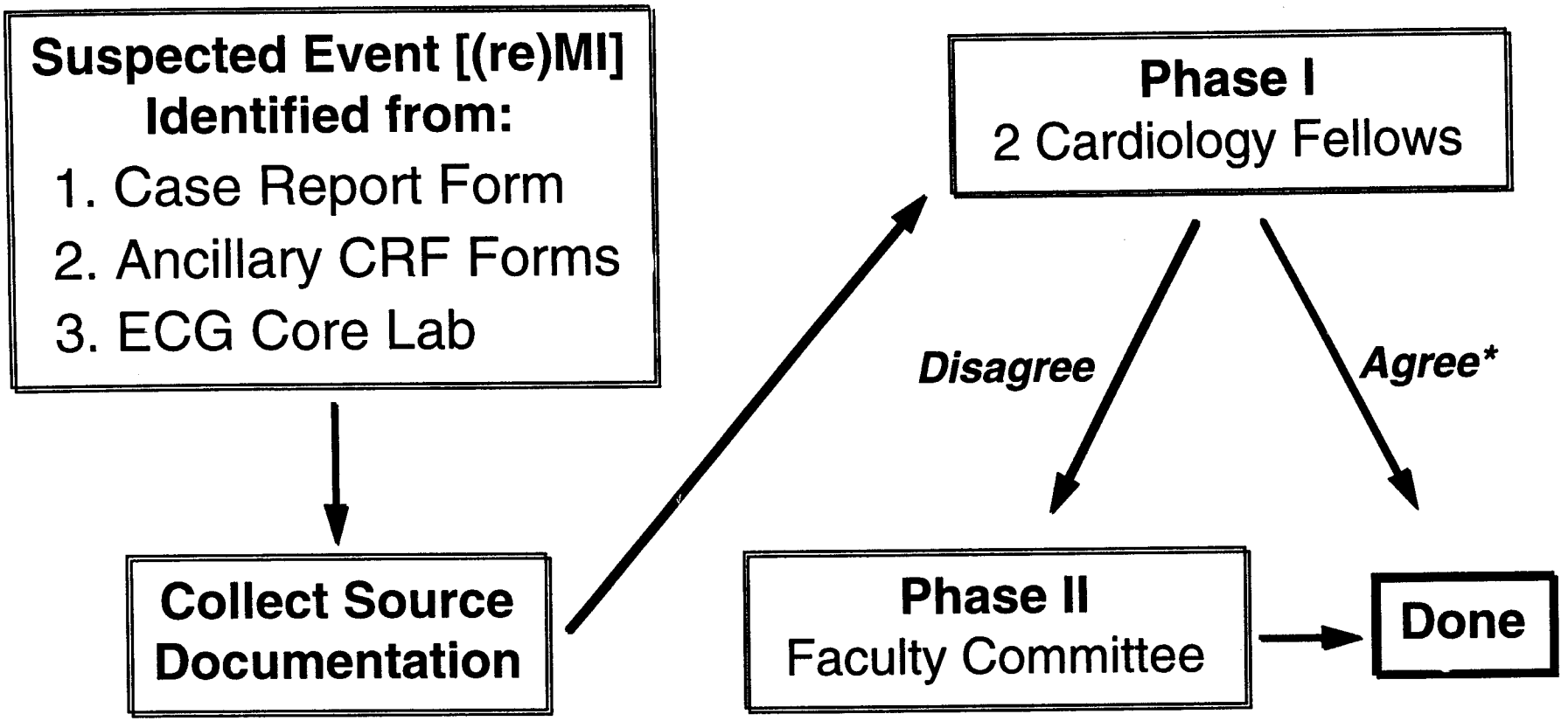
- Major bleeding ≤ 30 days, history of bleeding diathesis
- Major surgery ≤ 6 weeks
- History of known hemorrhagic stroke or any stroke ≤ 30 days
- INR ≥ 2.0, platelets < 100,000/mm^3, Hct < 30%, creatinine ≥ 2.0 mg/dl
- Planned use of thrombolytic agent or another GP IIb/IIIa inhibitor. Use of thrombolytic 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

9801BH11, 9

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*

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*

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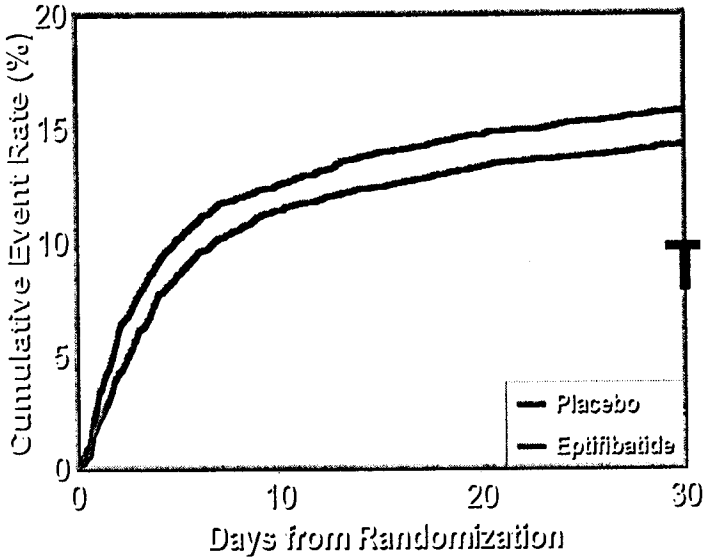

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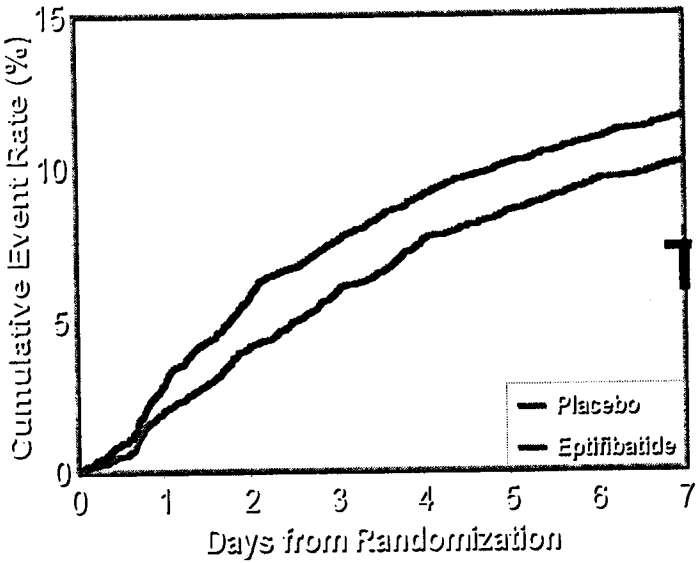

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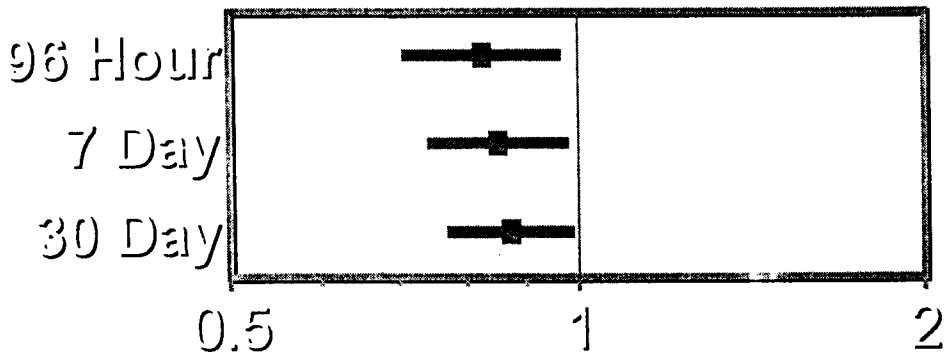
Composite Efficacy Endpoint



		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%

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

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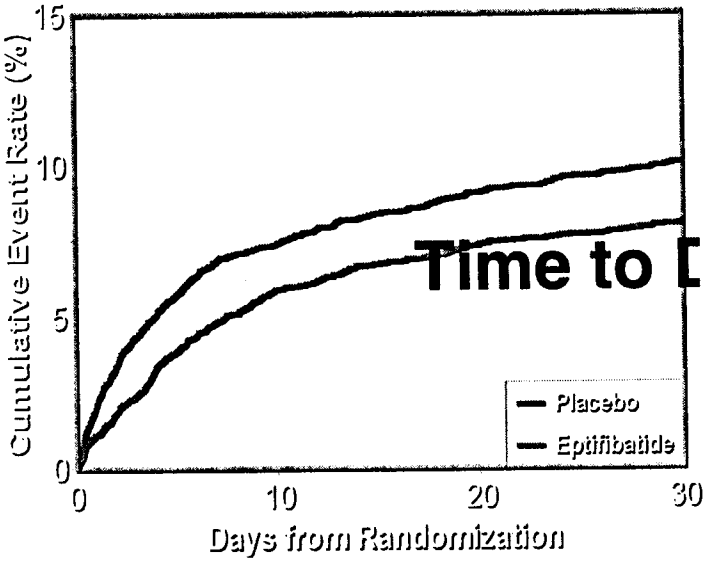

Time to D

9801BH11, 20

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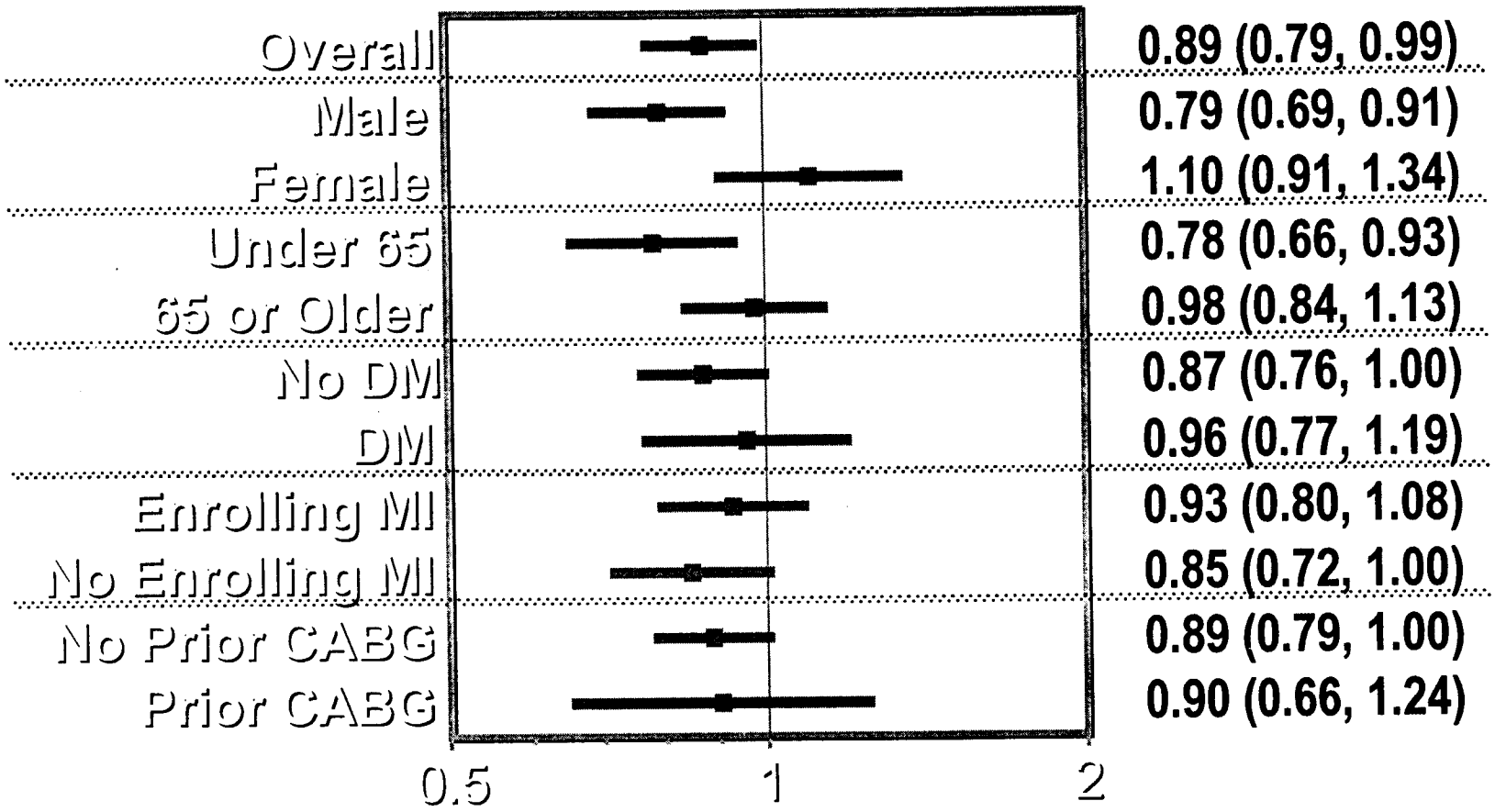
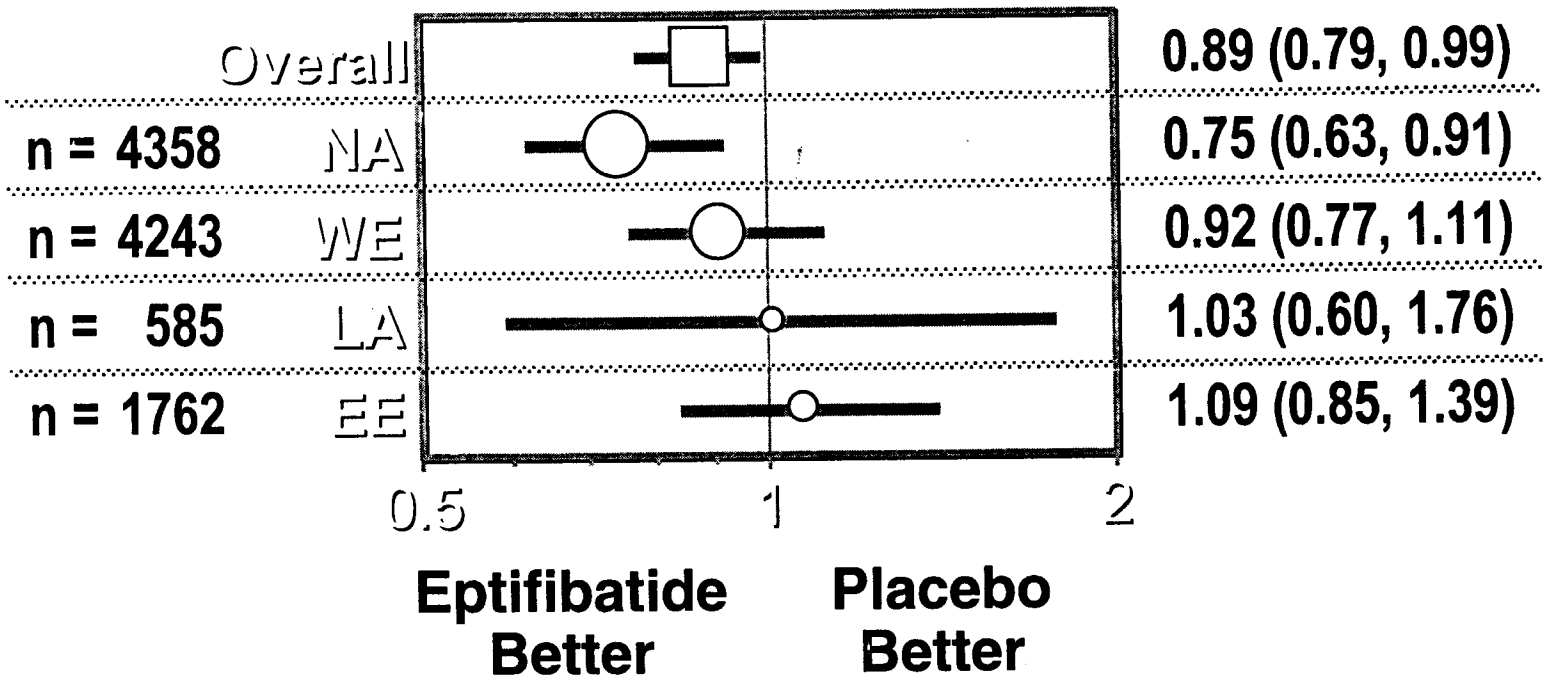
Death or MI at 30 Days

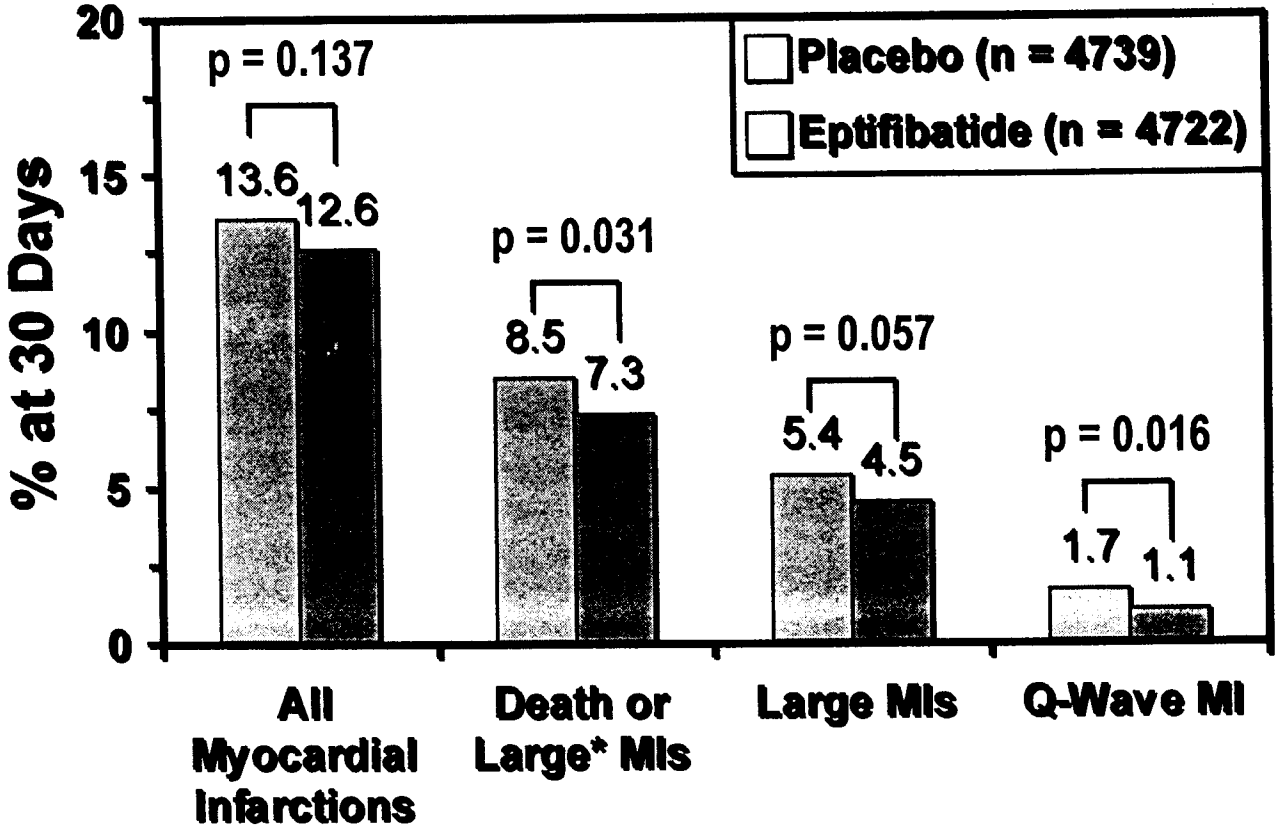


9801BH11, 21

Death or MI at 30 Days

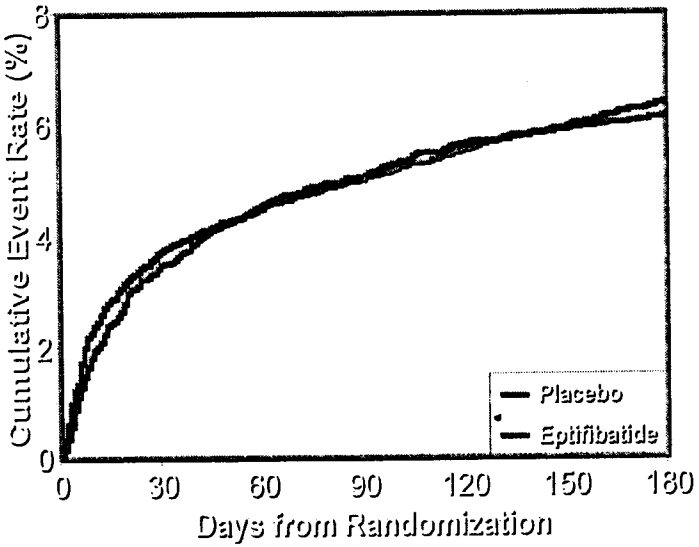


Myocardial Infarction

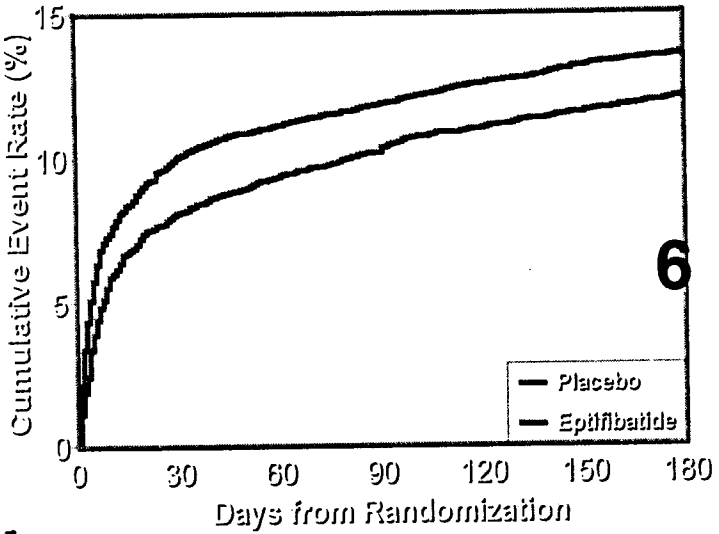


** Large MI: CKMB > 5x ULN*

9801BH11, 23



9801BH11, 24



6

9801BH11, 25

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

9801BH11, 31

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

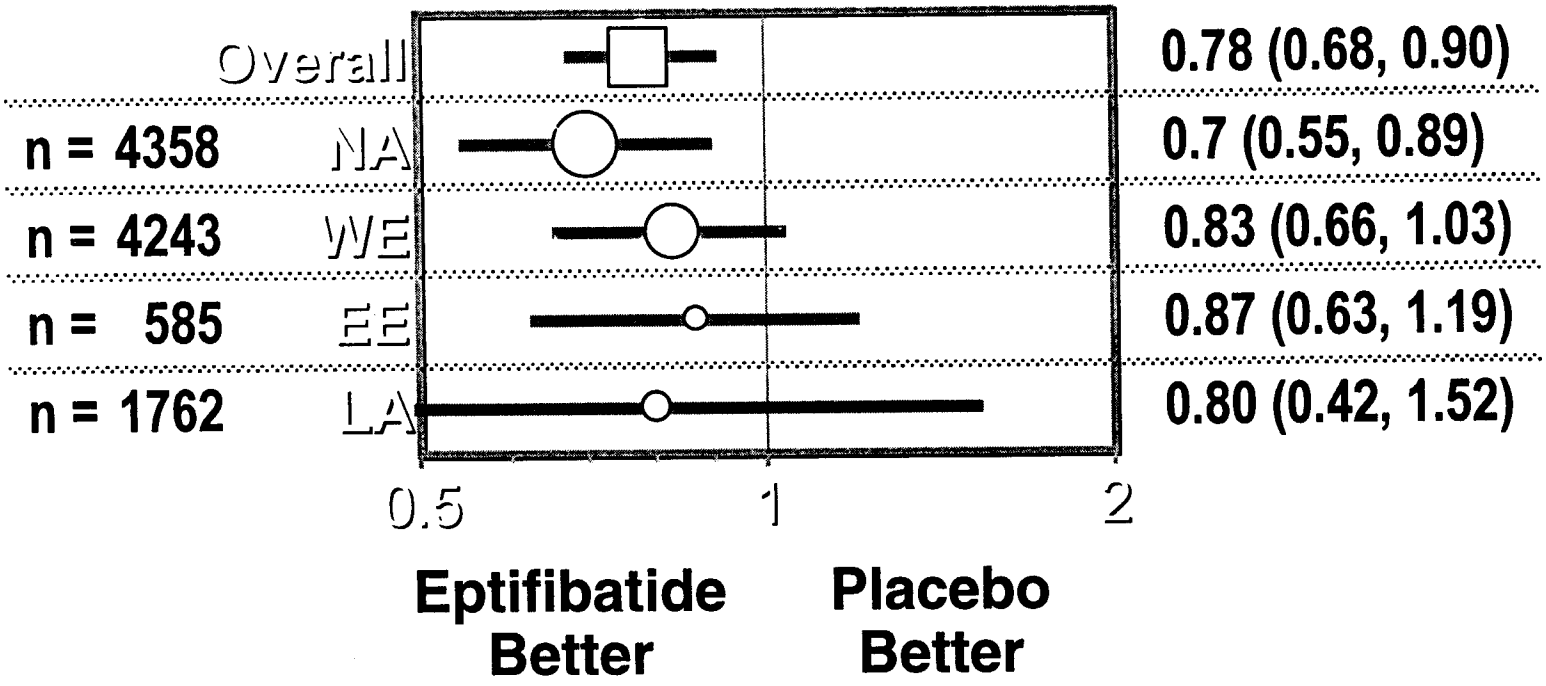
PURSUIT Summary

- **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

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Interventions

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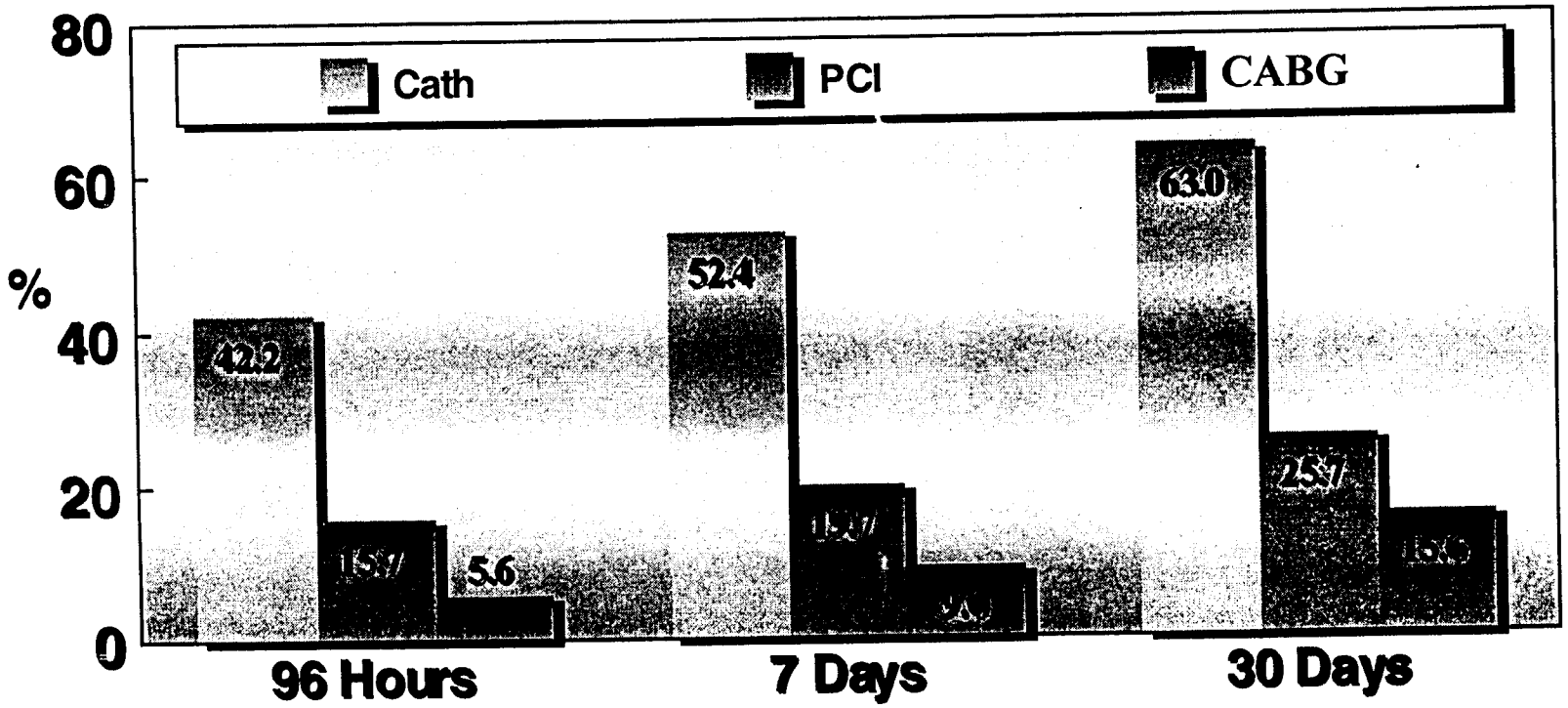
Percutaneous Coronary Intervention

- 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

(b)(4)

Cardiac Procedures



Interventions

(b)(4)

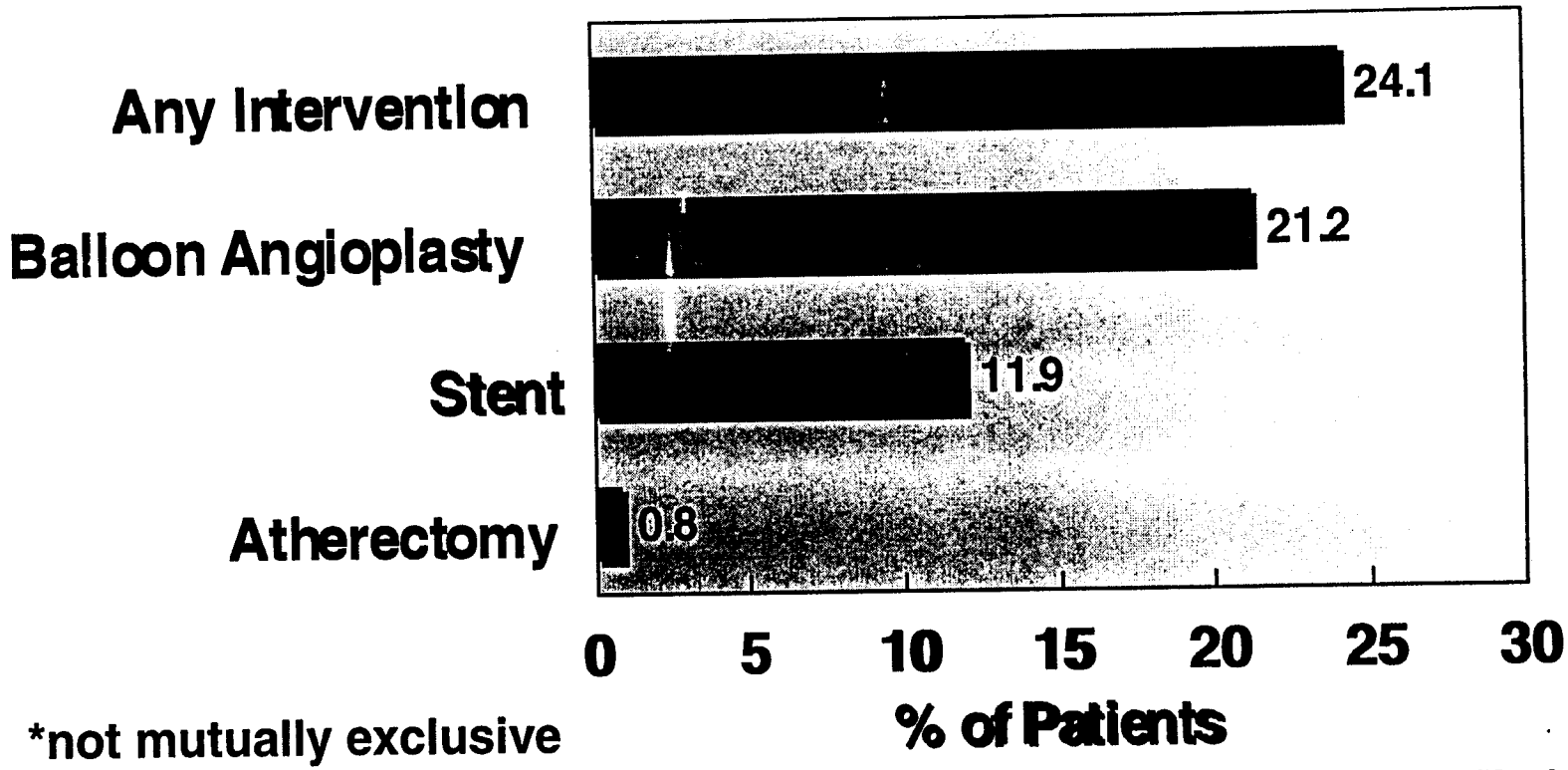
Percutaneous Coronary Intervention

- 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

(b)(4)

Percutaneous Interventions*
Initial Hospitalization



*not mutually exclusive

ML-104

Interventions

[redacted] (b)(4)

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

[redacted] (b)(4)

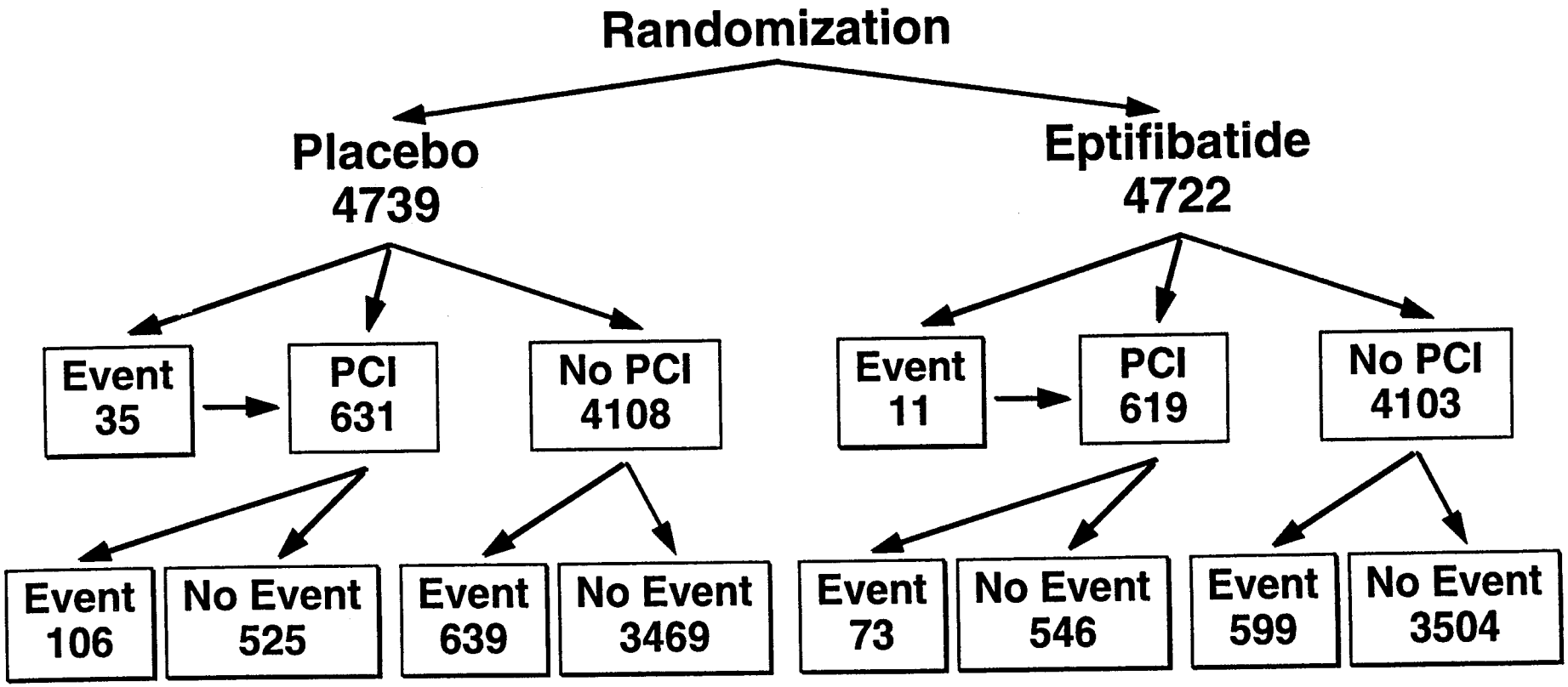
Limitations of Analysis

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

Interventions

[redacted] (b)(4)

Timing of Ischemic Events and PCI*



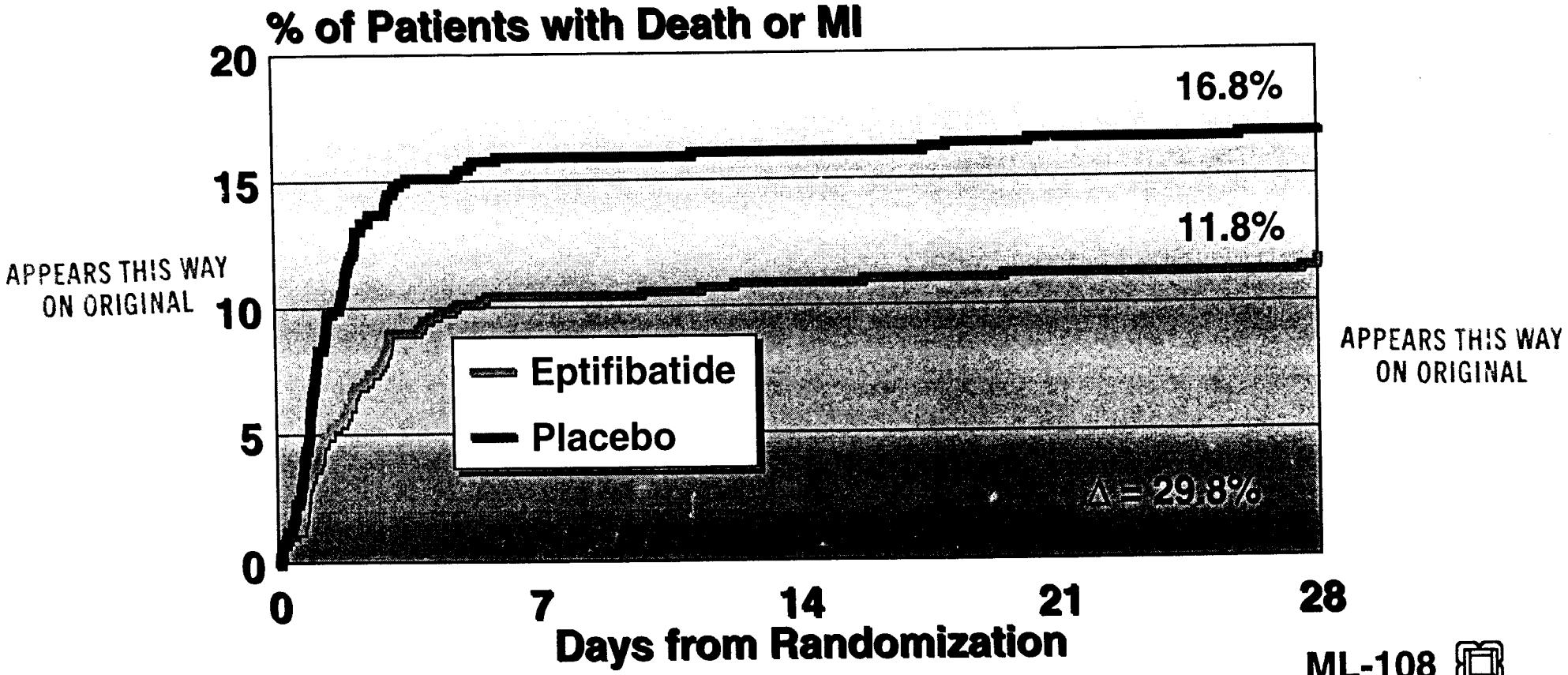
*PCI during first 72 hrs

ML-107

Interventions

[redacted] (b)(4)

Outcome in Patients Rx'd with PCI Within 72 Hrs



ML-108

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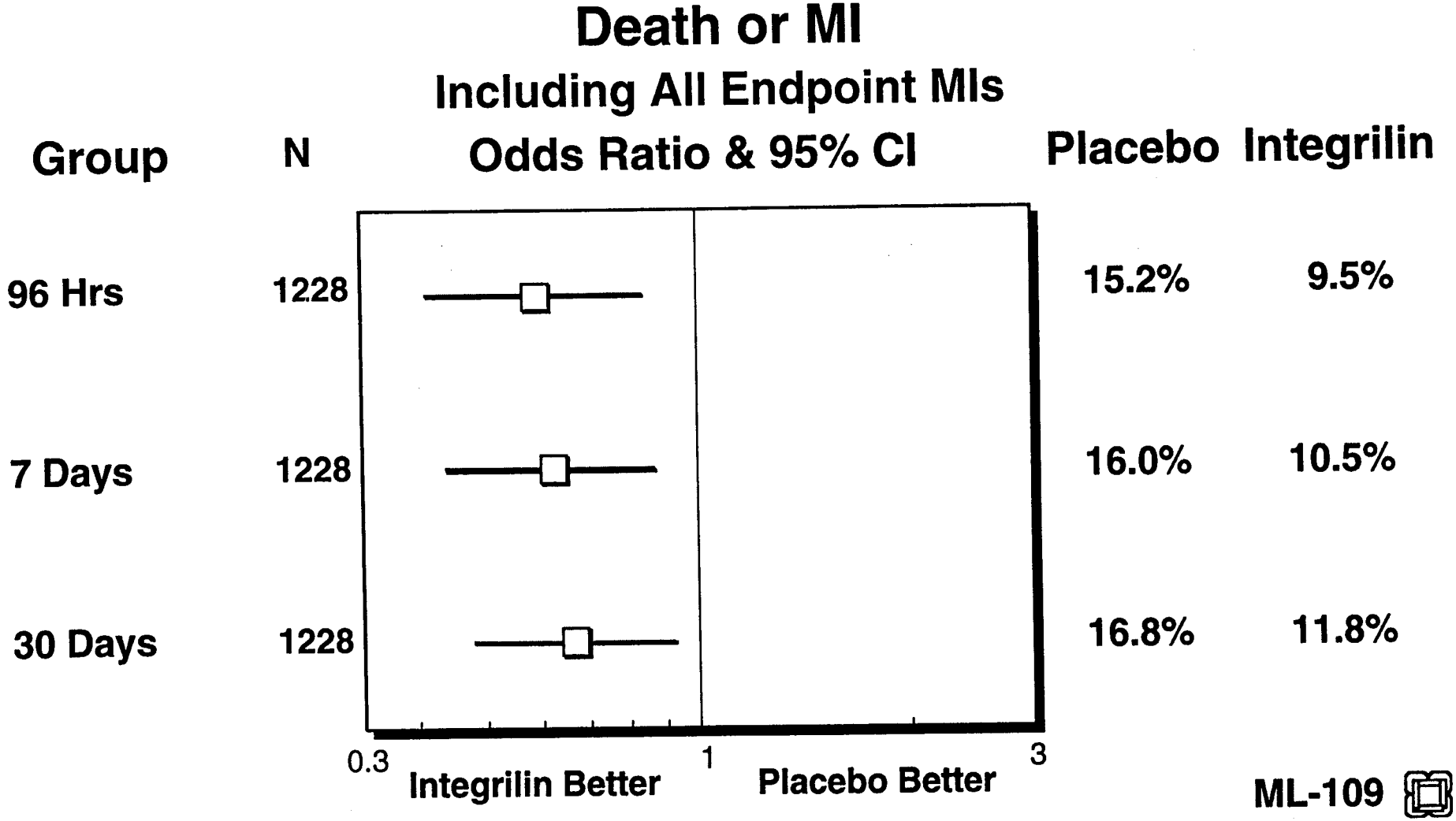
Interventions

[redacted] (b)(4)

Death or MI

Including All Endpoint MIs



ML-109

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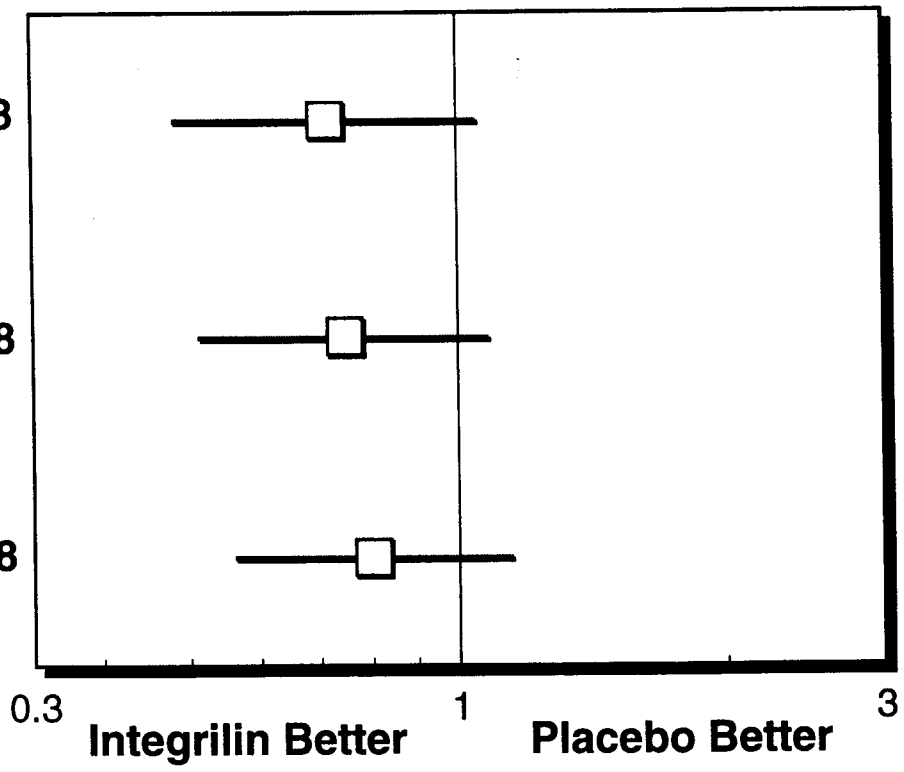
Interventions

(b)(4)

Death or MI

Including only MIs After Initiation of Procedure

Group	N	Odds Ratio & 95% CI	Placebo	Integrilin
96 Hrs	1228		11.0%	8.1%
7 Days	1228		11.8%	9.0%
30 Days	1228		12.6%	10.3%



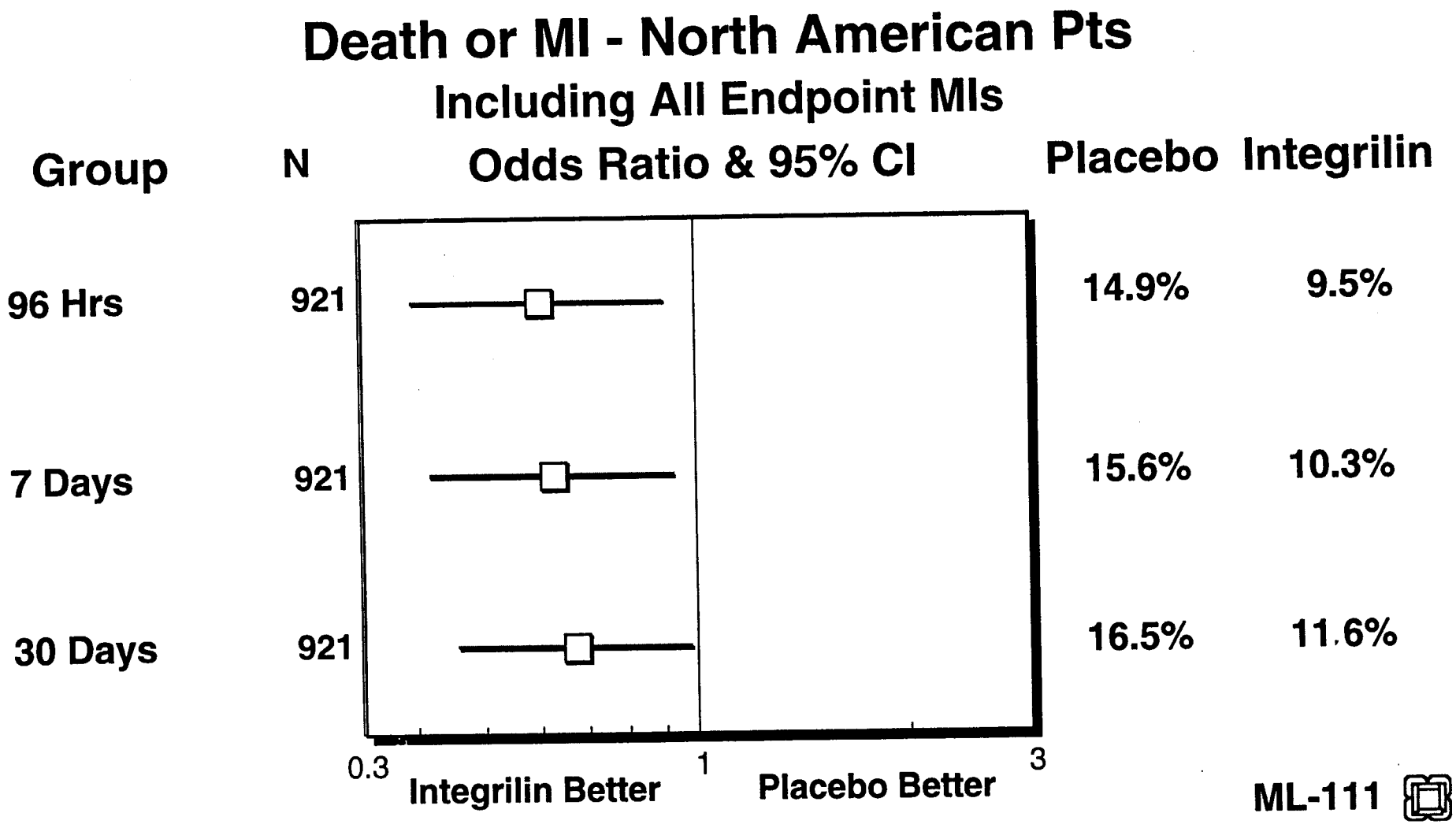
ML-110

Interventions

[redacted] (b)(4)

Death or MI - North American Pts

Including All Endpoint MIs



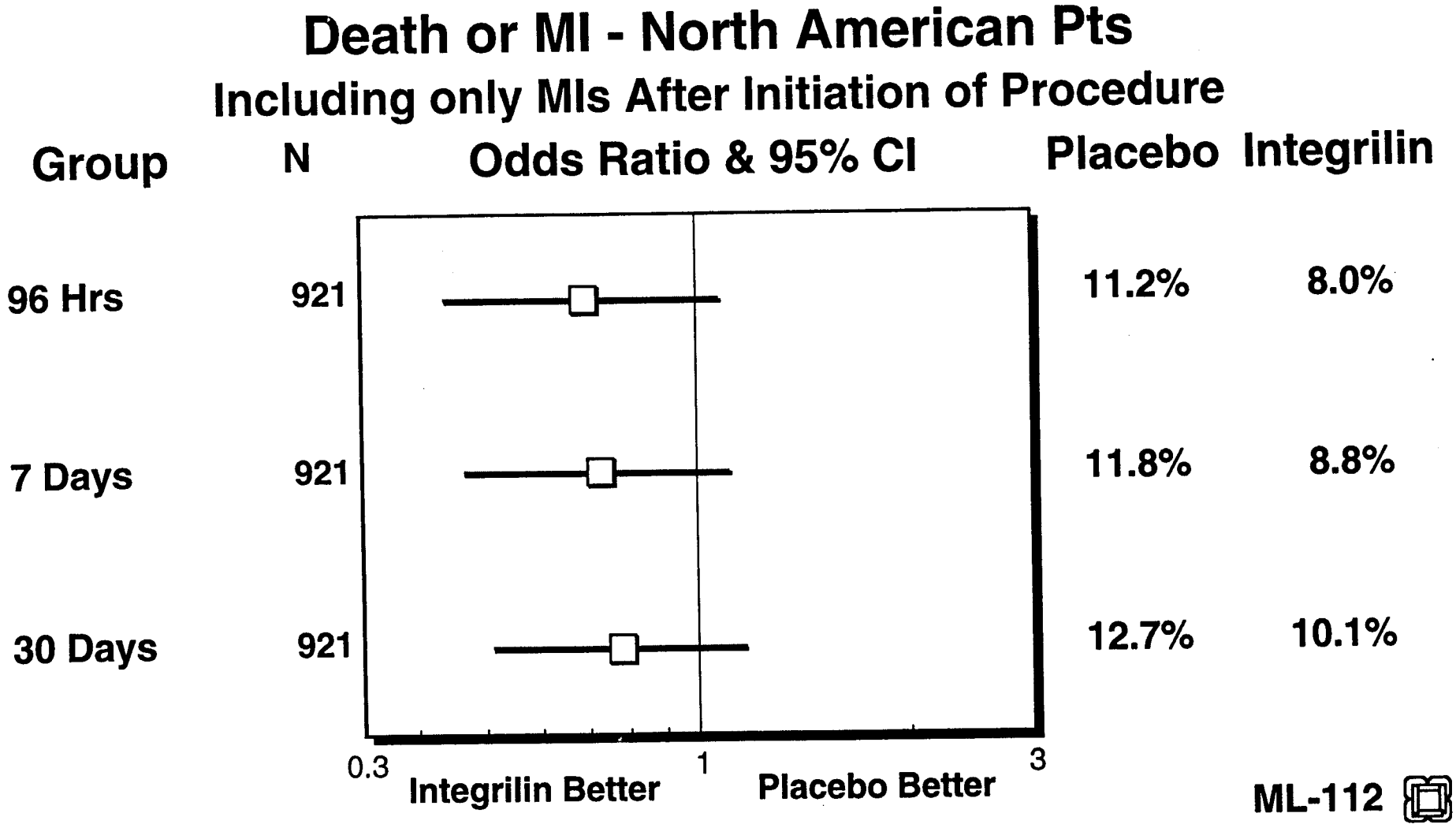
ML-111

Interventions

(b)(4)

Death or MI - North American Pts

Including only MIs After Initiation of Procedure



ML-112

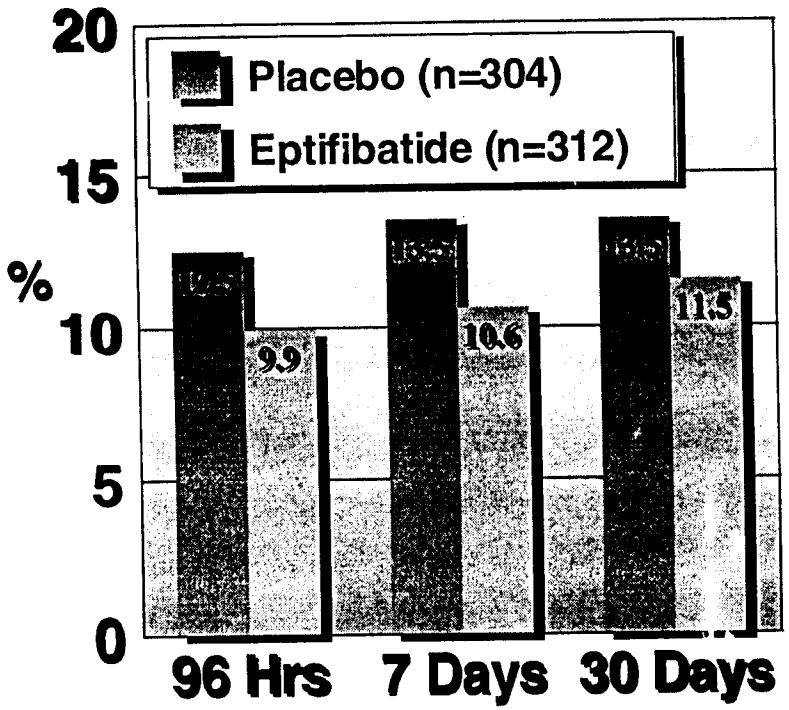
Interventions

(b)(4)

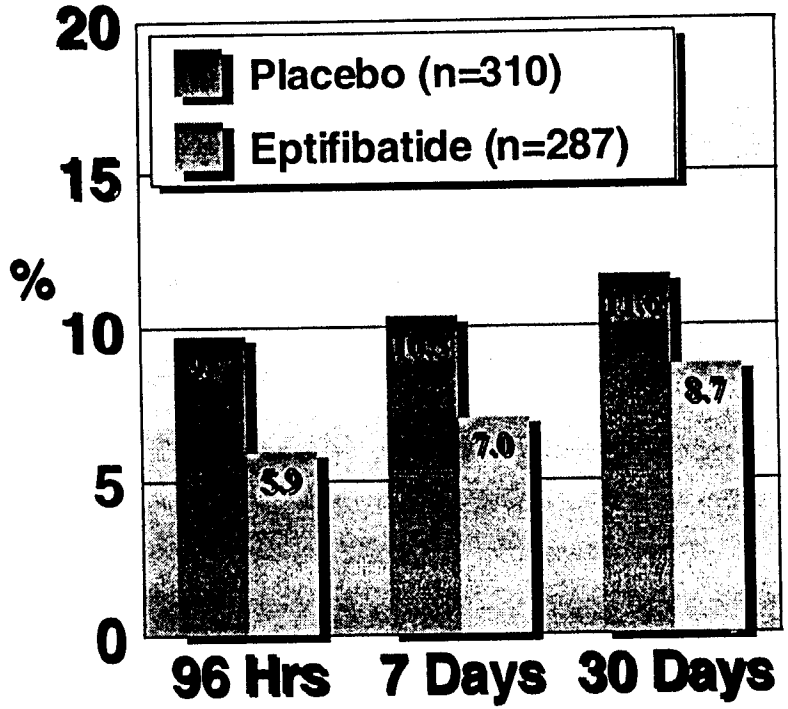
Death or MI

Including only MIs After Initiation of Procedure

Stents



No Stents



ML-113

Intervention

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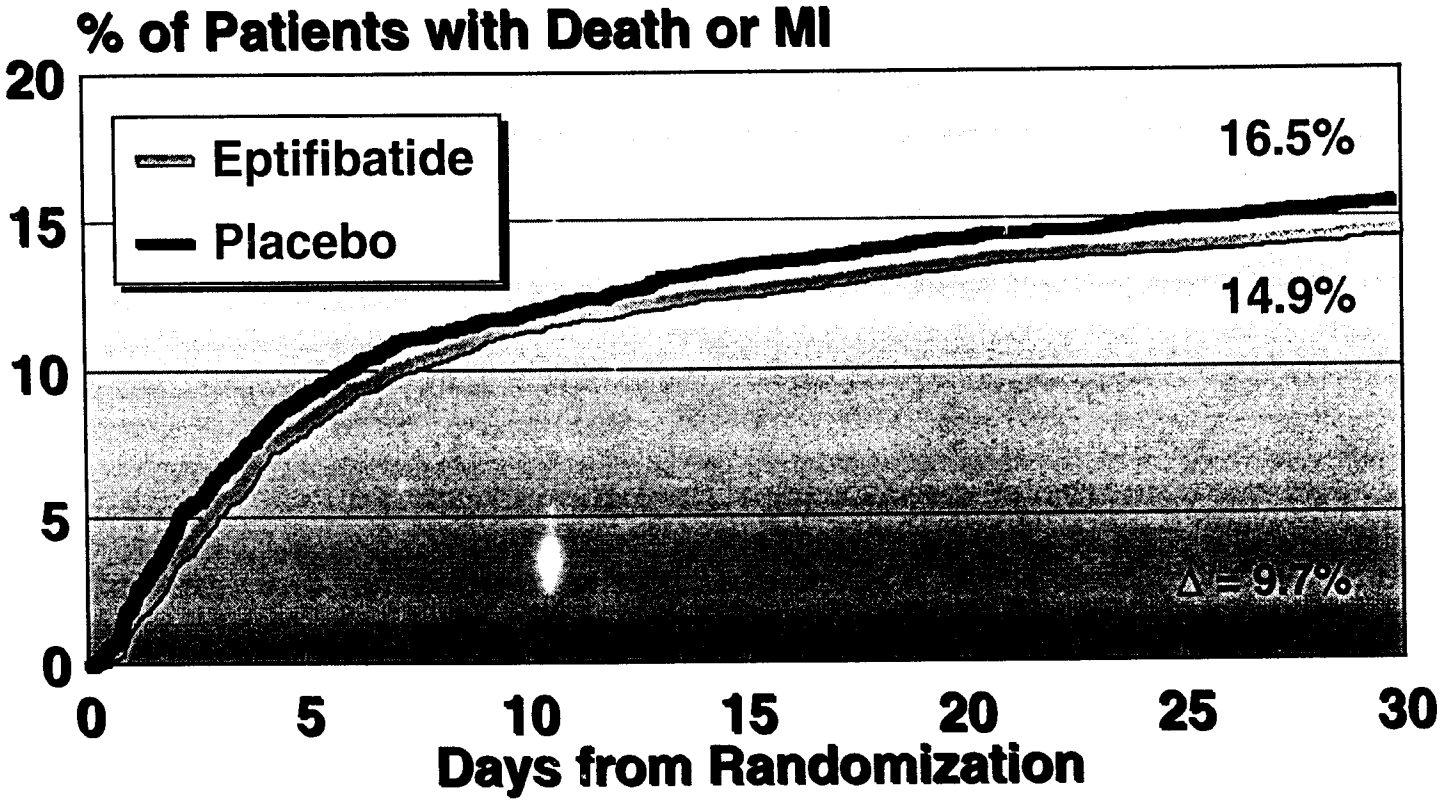
Outcome Without Revascularization*

Patients with Revascularization Censored at Time of Intervention



ML-114

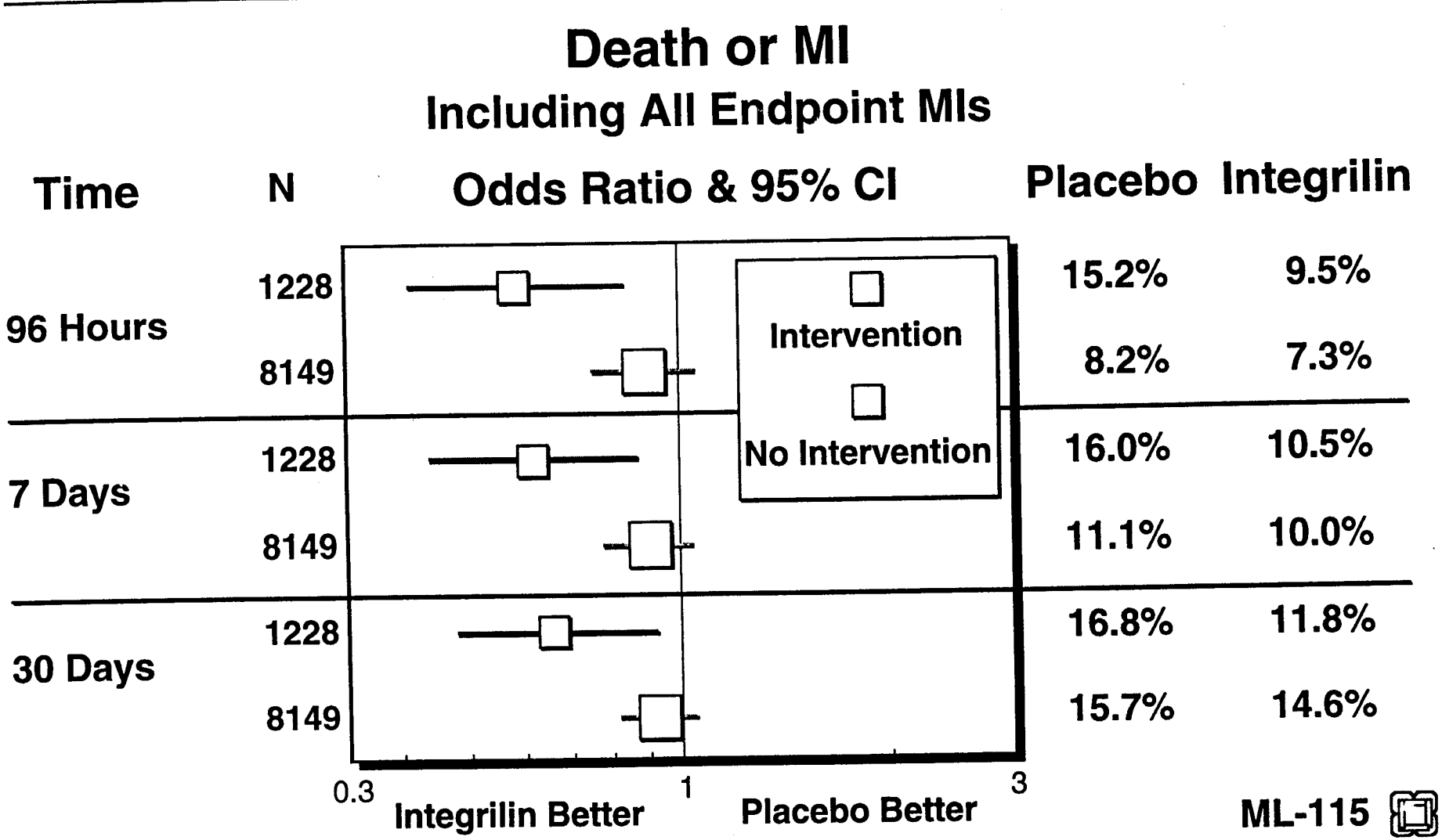
*includes PTCA, stent, atherectomy, laser, IC lytics, CABG

Interventions

[redacted] (b)(4)

Death or MI

Including All Endpoint MIs



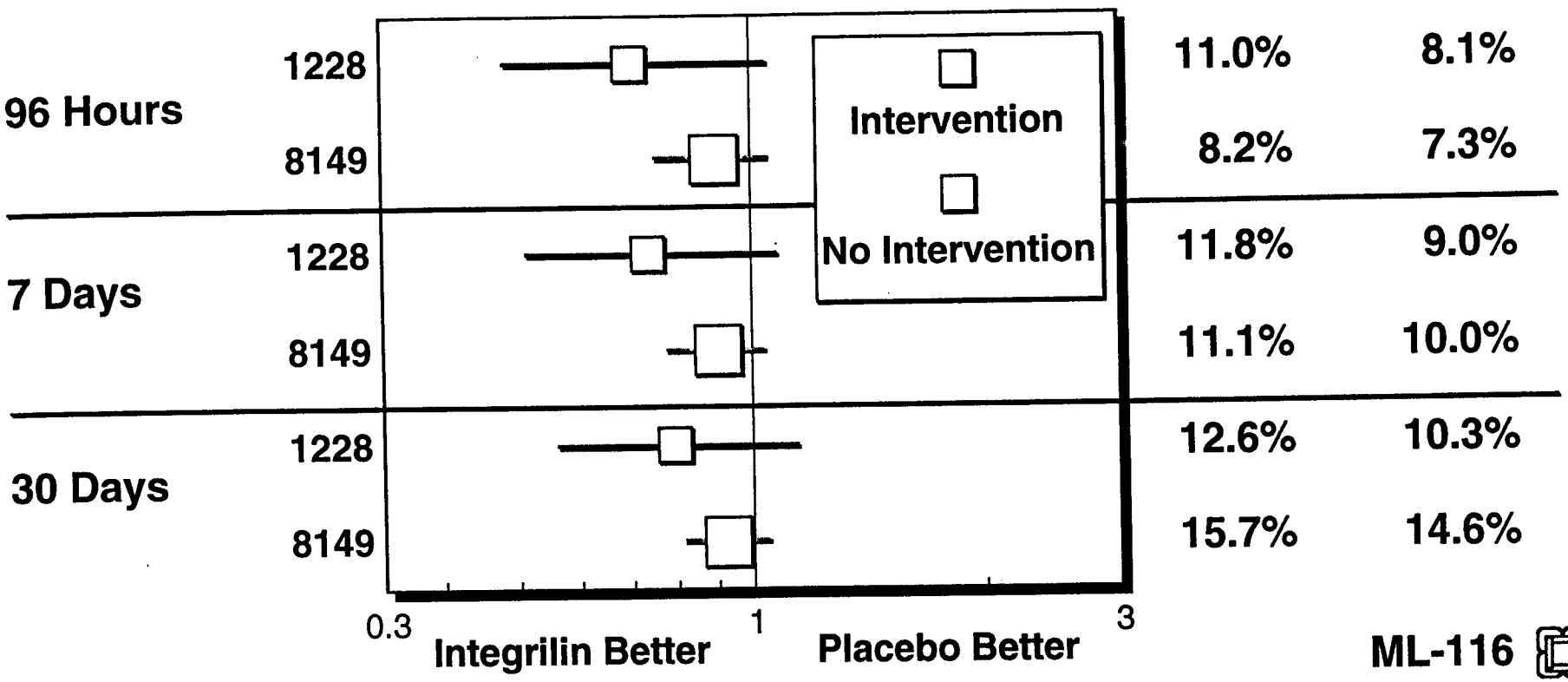
ML-115

Interventions

[redacted] (b)(4)

Death or MI

Including only MIs After Initiation of Procedure

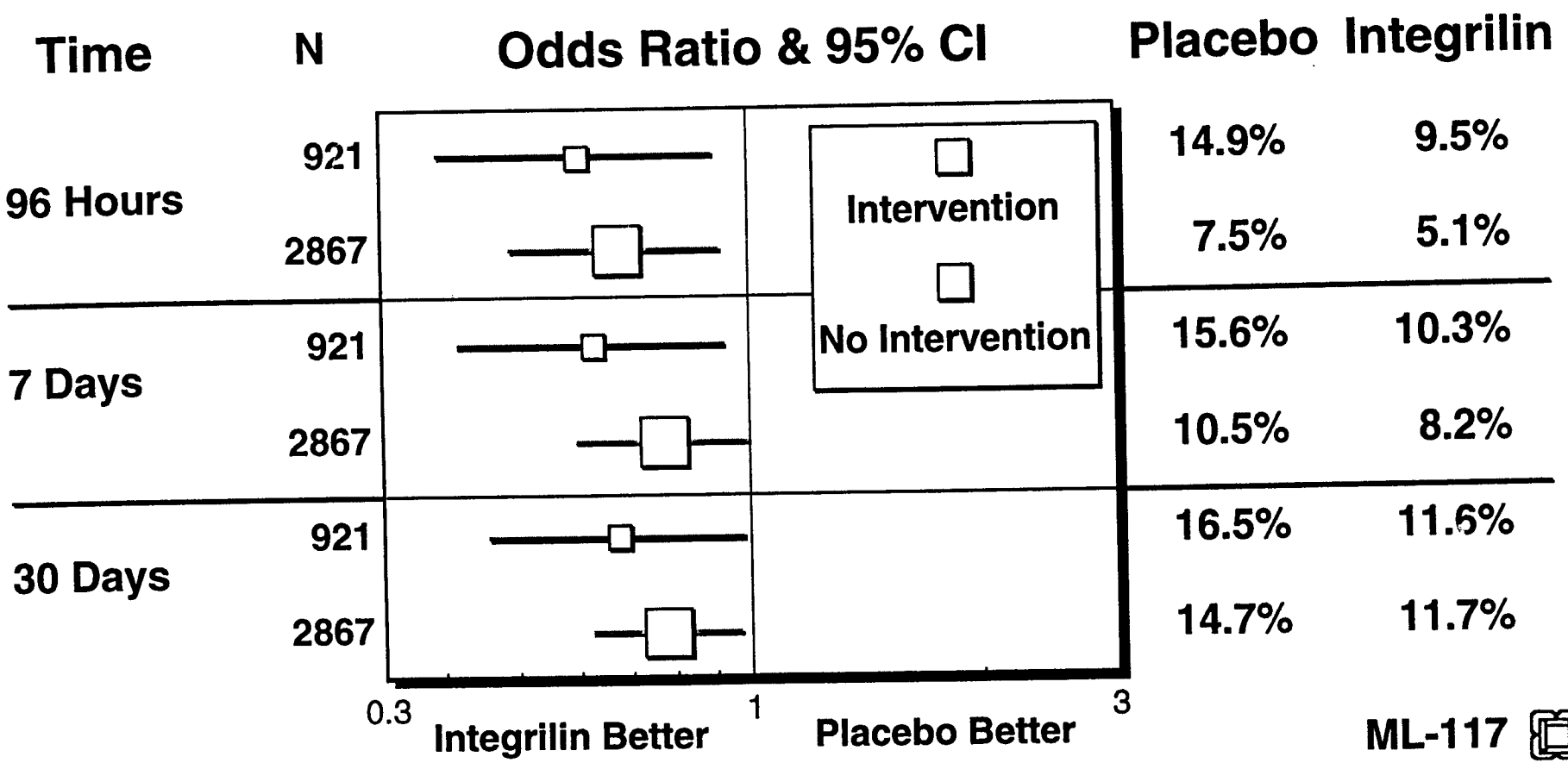


ML-116

Interventions

[redacted](b)(4)

Death or MI - North American Pts
Including All Endpoint MIs

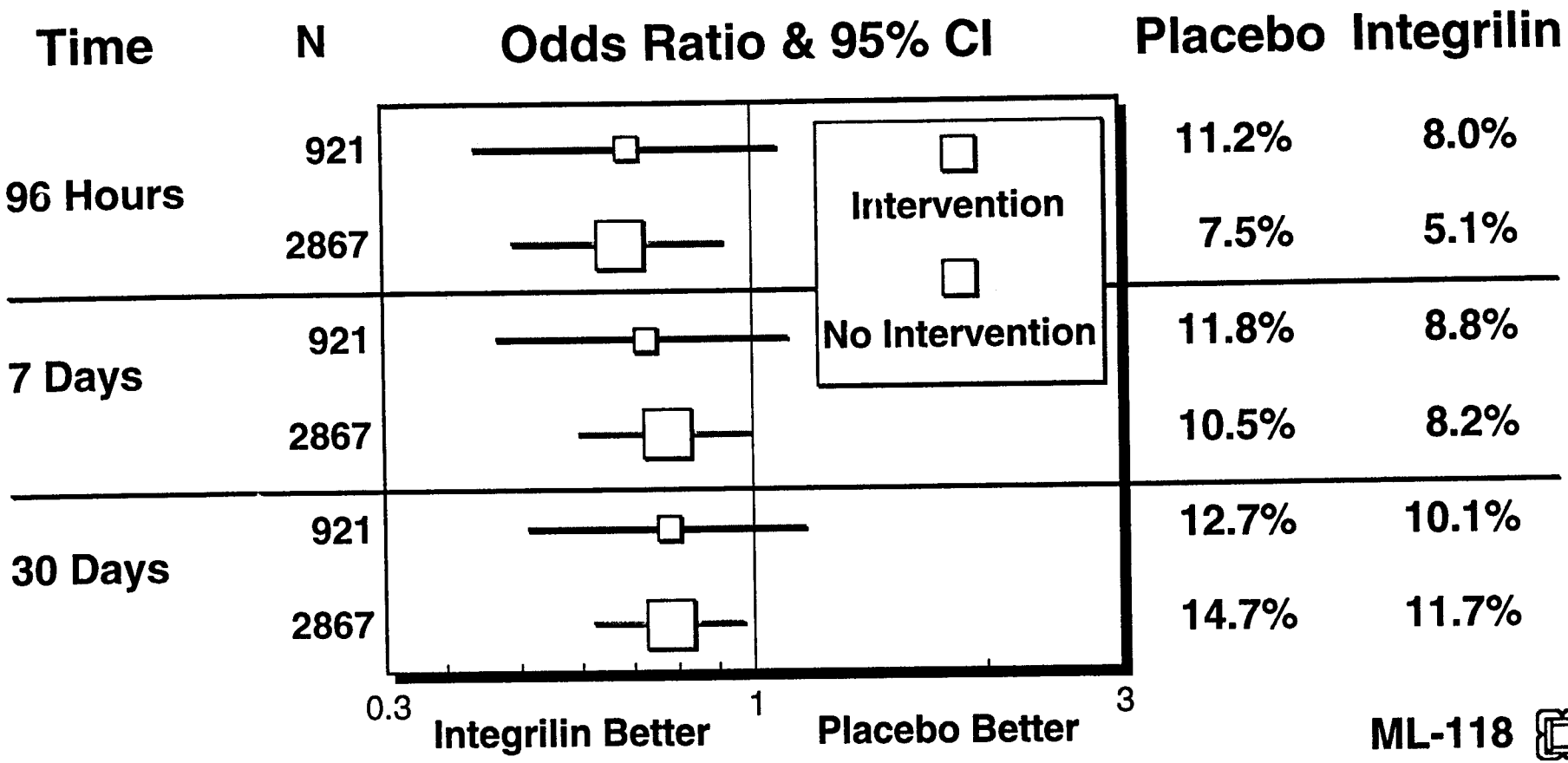


ML-117

Interventions

[redacted](b)(4)

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



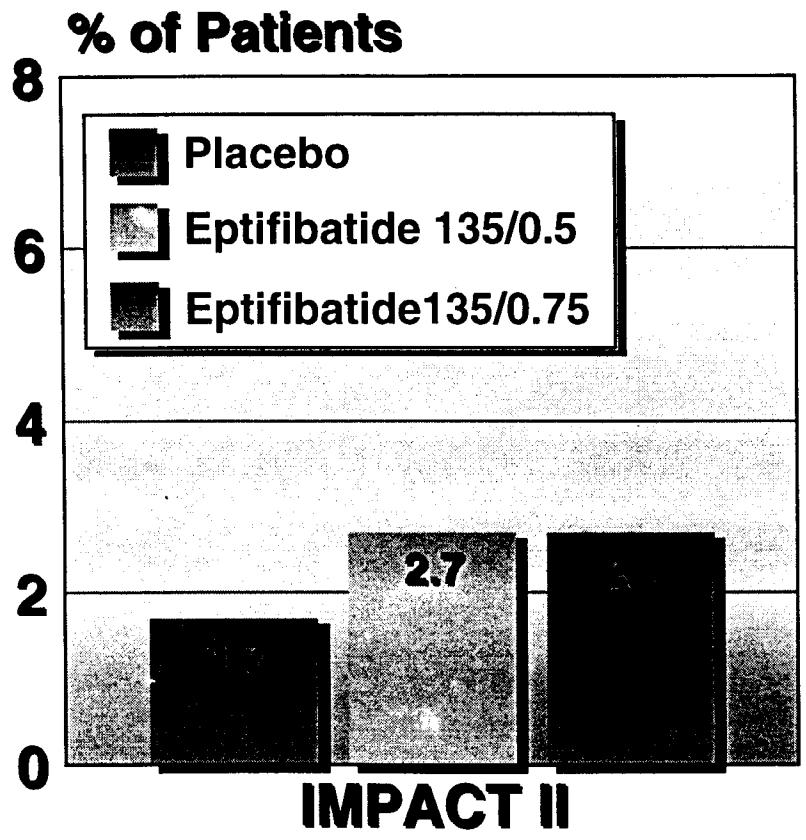
ML-118

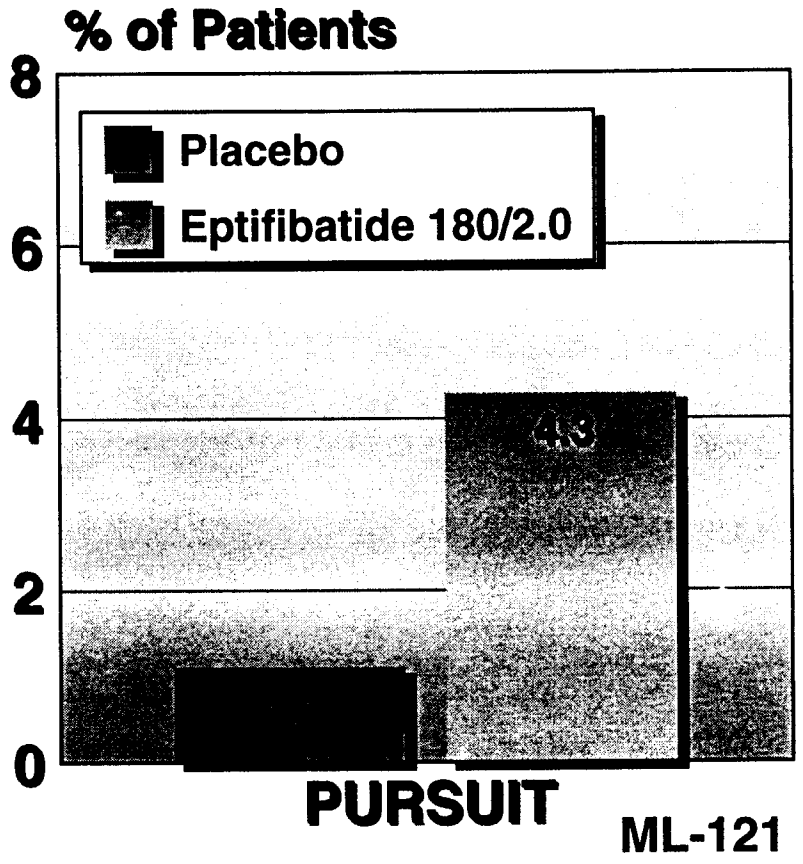
Interventions

[redacted] (b)(4)

Major Bleeding - IMPACT II vs PURSUIT

PCI Patients, Excluding CABG-Related Bleeding





ML-121

Interventions

[redacted] (b)(4)

Summary

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

Interventions

[redacted](b)(4)

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

MK7