CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 04/10/98

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SLIDES

AGGRASTAT (Tirofiban Hydrochloride)

Treatment of Patients with Unstable Angina or Non-Q-Wave Myocardial Infarction

Cardio-Renal Drug Products Advisory Committee

April 10, 1998

Merck Research Laboratories

Introduction

AGGRASTAT (Tirofiban Hydrochloride)

- Potent Non-Peptide Inhibitor of GP IIb/IIIa Receptor
- High Specificity for Receptor
- Short-Acting, Intravenous Agent
- Blocks Fibrinogen Binding
- Developed for Rapid Inhibition of Platelet Aggregation

Tirofiban Hydrochloride
Overview of the Clinical Program

- Phase II Dose-Finding Studies

- Phase III Clinical Trials

  - Three Large Endpoint Trials
  - 7,288 Patients Studied
  - Focused on UAP / NQWMI

Tirofiban Hydrochloride
Proposed Indication

"Tirofiban, in combination with heparin, is indicated to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated."

Tirofiban Hydrochloride

Merck Presentation

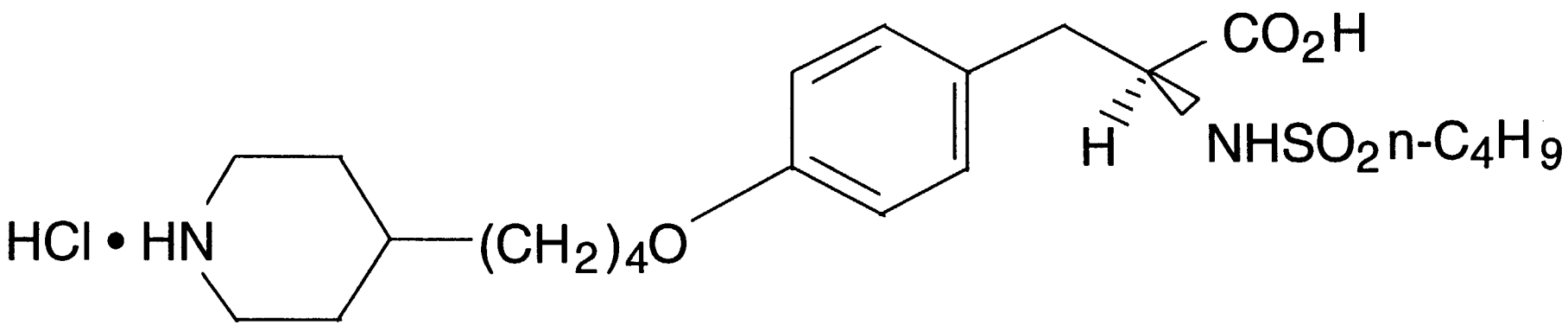
Introduction	Larry Bell, M.D.
Clinical Efficacy and Safety	Rick Sax, M.D.
Concluding Remarks	Rick Sax, M.D.

Tirofiban Hydrochloride
Consultants

Spencer B. King, III, M.D.	Professor of Medicine Emory University School of Medicine Atlanta
Neal S. Kleiman, M.D.	Associate Professor of Medicine Baylor College of Medicine Houston
Pierre Théroux, M.D.	Professor of Medicine Montreal Heart Institute
Professor Harvey D. White DSc FRACP FACC FESC	Director of Coronary Care and Cardiovascular Research Green Lane Hospital Auckland, New Zealand
Gary Koch, Ph.D.	Professor of Biostatistics University of North Carolina

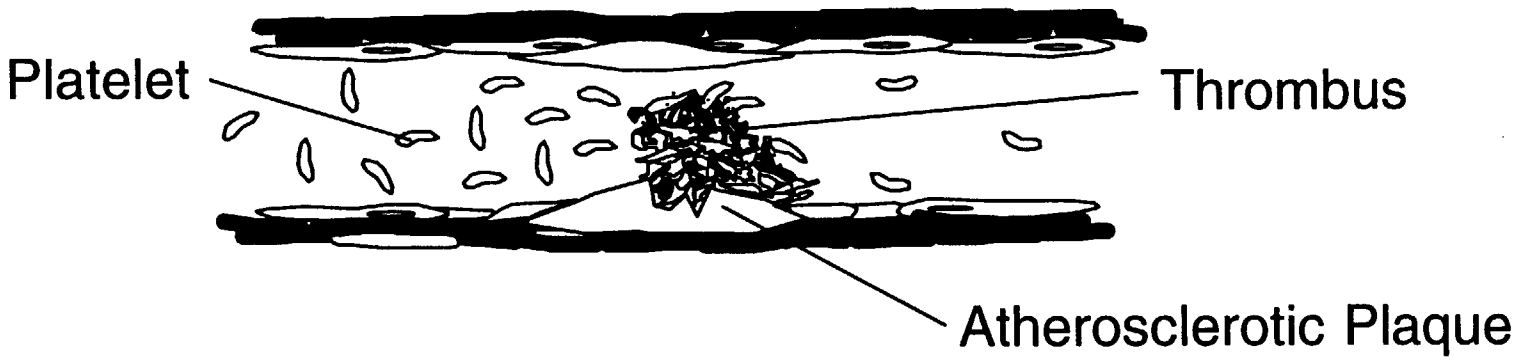
Main Presentation

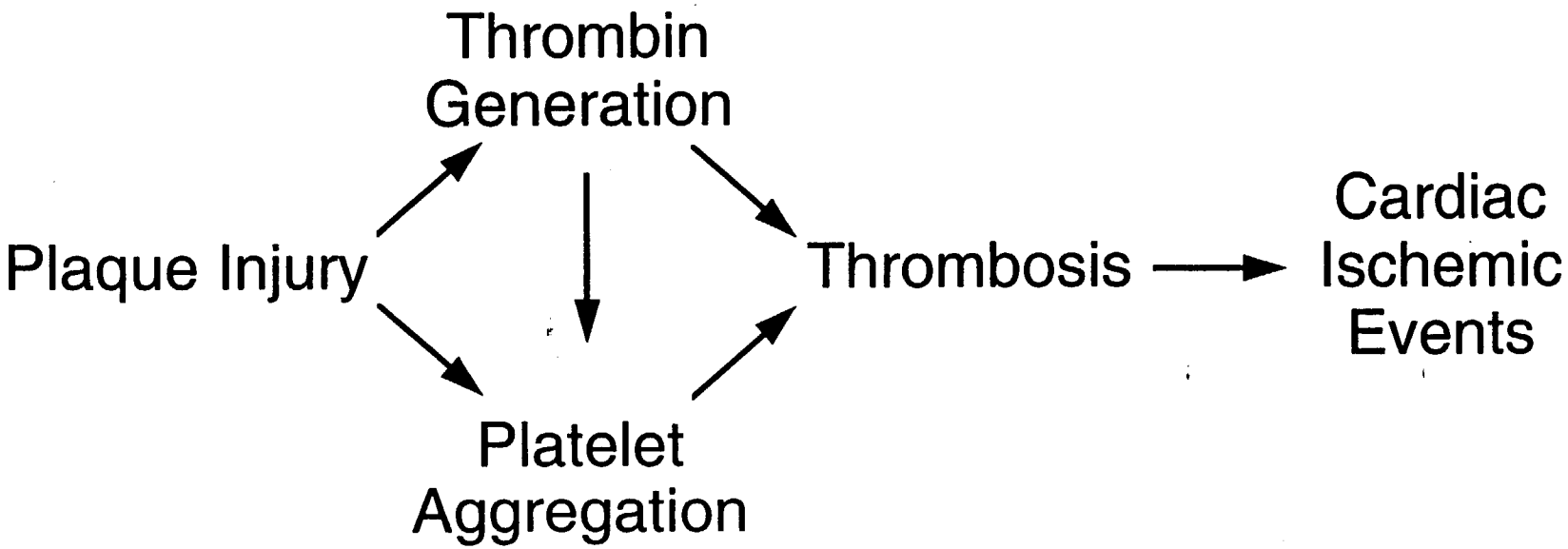
Tirofiban Hydrochloride



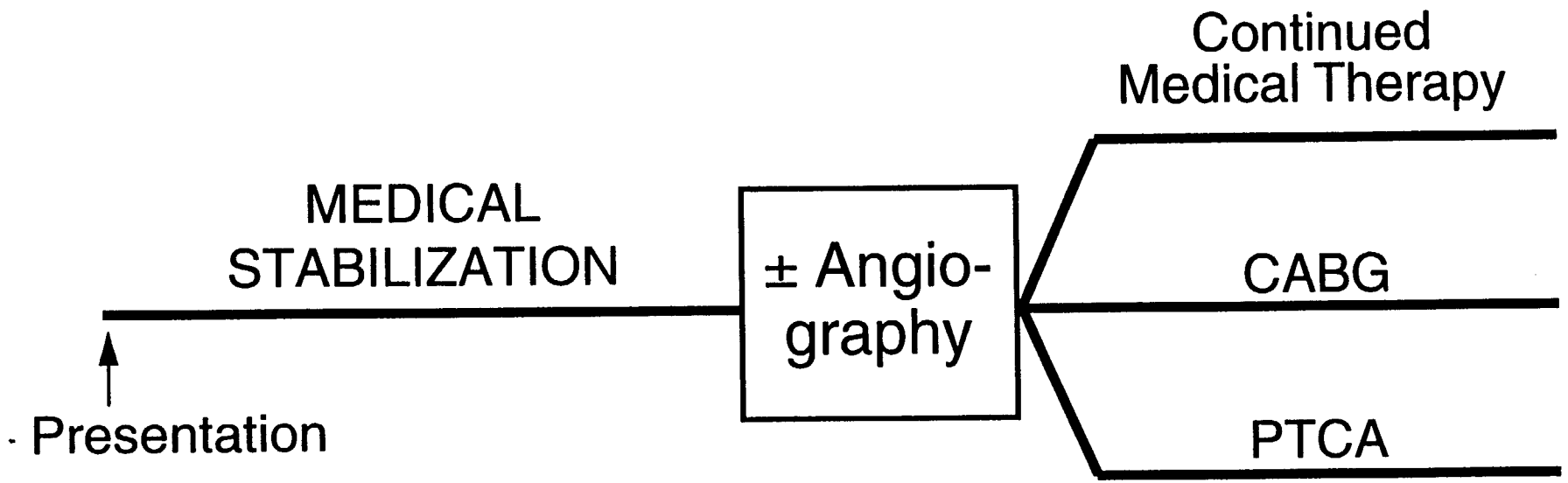
- Short-acting, intravenous agent
- Potent non-peptide inhibitor of GP IIb/IIIa
- Blocks fibrinogen binding - inhibits aggregation
- High specificity for receptor

Consequences of Coronary Plaque Injury

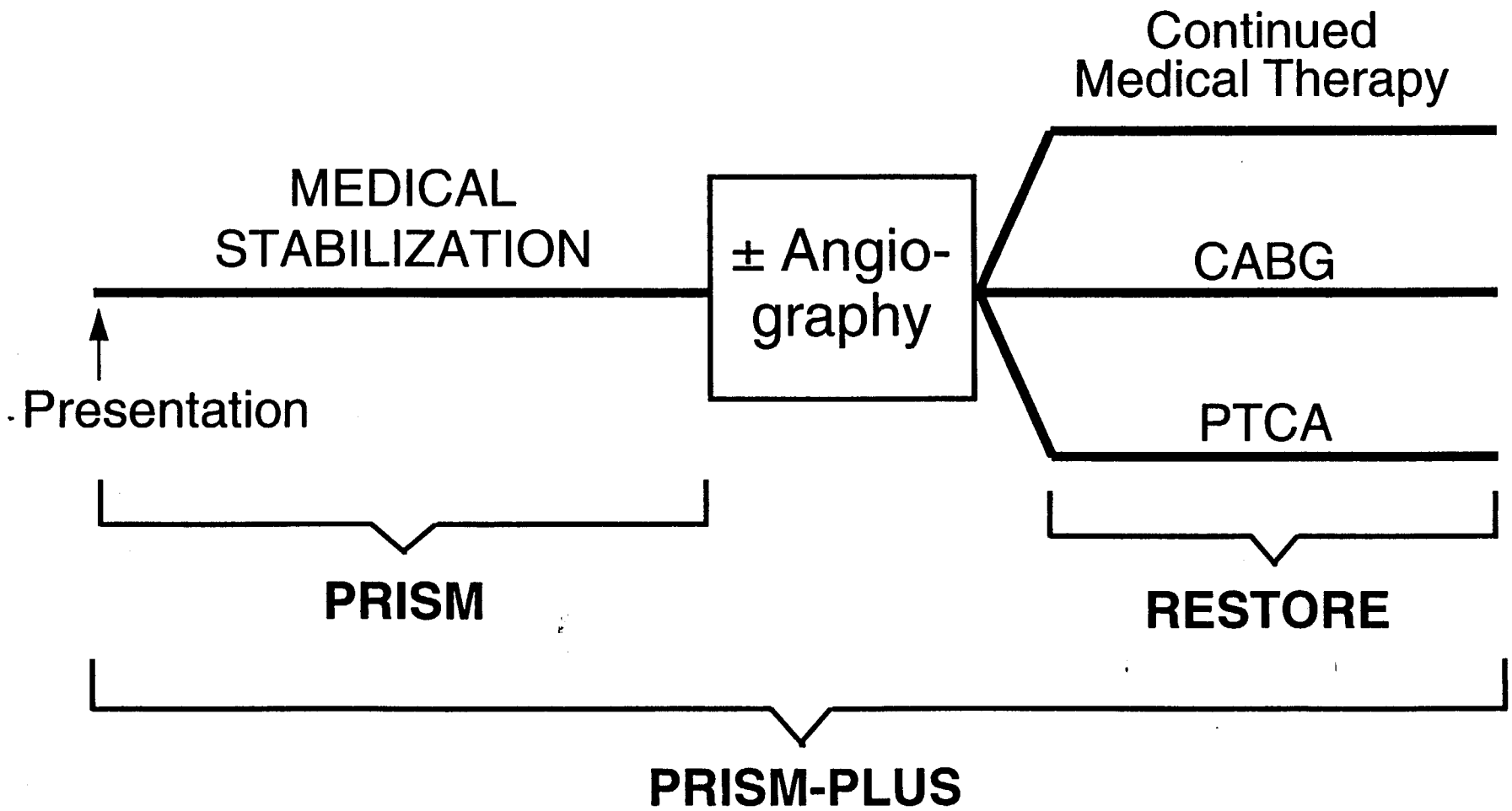




Management of UAP / NQWMI



Clinical Program for Tirofiban in UAP / NQWMI



Dose Selection

- Inhibition of platelet aggregation (IPA) > 70%, consistent across population of UAP / NQWMI
- Highest dose with acceptable bleeding profile (bleeding times; discontinuations for bleeding)
- Dosing without and with heparin

Dose-Finding with Tirofiban in UAP/NQWMI

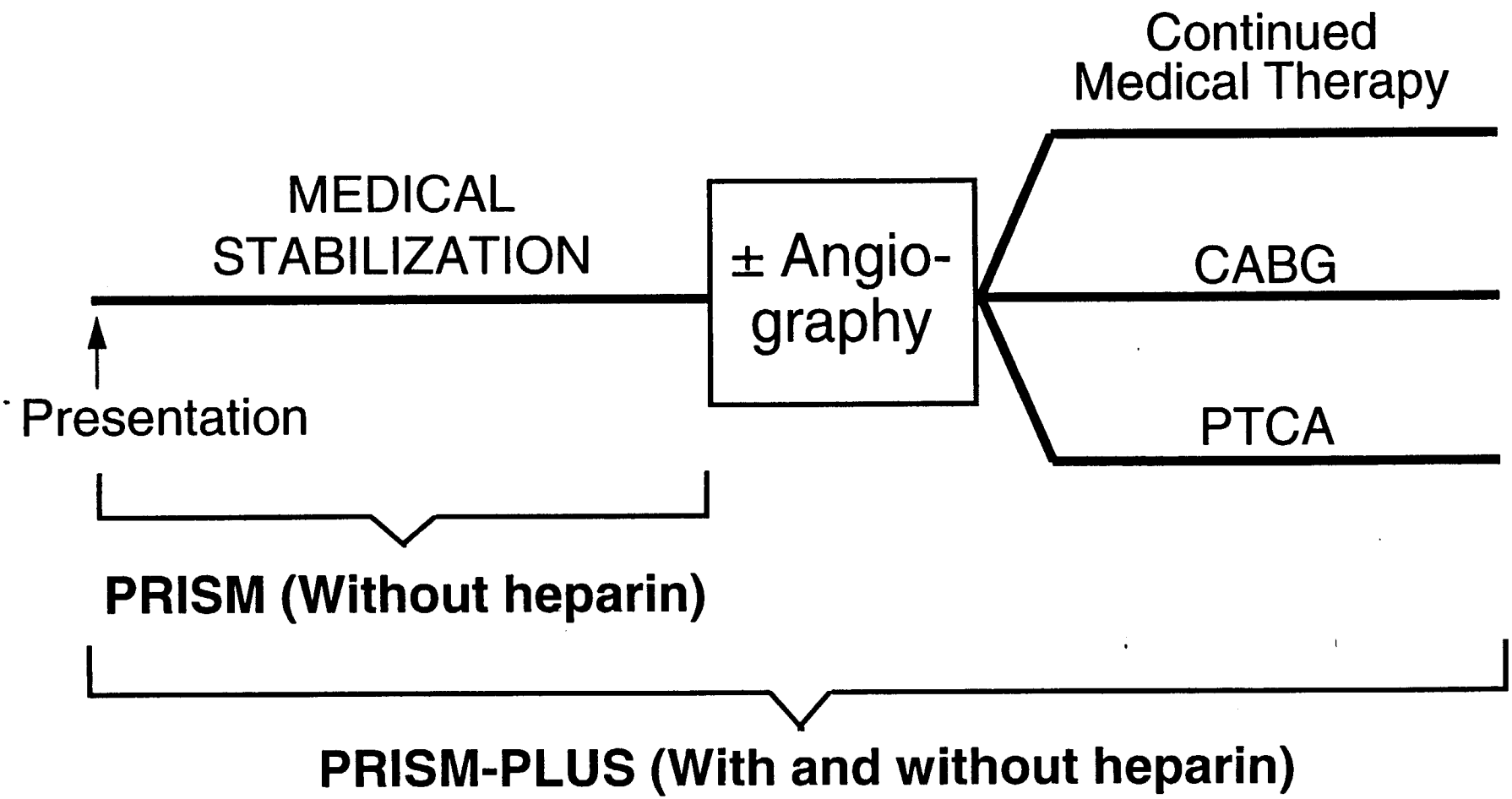
Without Heparin

Regimen (μg/kg/min) Loading/Maintenance	n	Median IPA	% Patients >70% IPA	Median Bleeding Times (min) 24hr	48hr
0.3 / 0.075	28	78%	68%	12	14
0.4 / 0.10	23	86%	74%	10	13
0.6 / 0.15	20	92%	95%	20	14

Dose-Finding with Tirofiban in UAP/NQWMI

Regimen (μg/kg/min) Loading/Maintenance	n	Median IPA	% Patients >70% IPA	Median Bleeding Times (min) 24hr	48hr
Without heparin					
0.6 / 0.15	20	92%	95%	20	14
With heparin					
0.4 / 0.10	14	89%	93%	14	20
0.6 / 0.15	13	95%	100%	26	30

Clinical Program for Tirofiban in UAP / NQWMI



UAP / NQWMI Trials Inclusion Criteria

	PRISM	PRISM-PLUS
Clinical Presentation		
UAP / NQWMI	✓	✓
Anginal Pain within:	24 hrs	12 hrs
Documentation		
ECG ischemia *or*	✓	✓
CK elevation *or*	✓	✓
History of CAD	✓	--

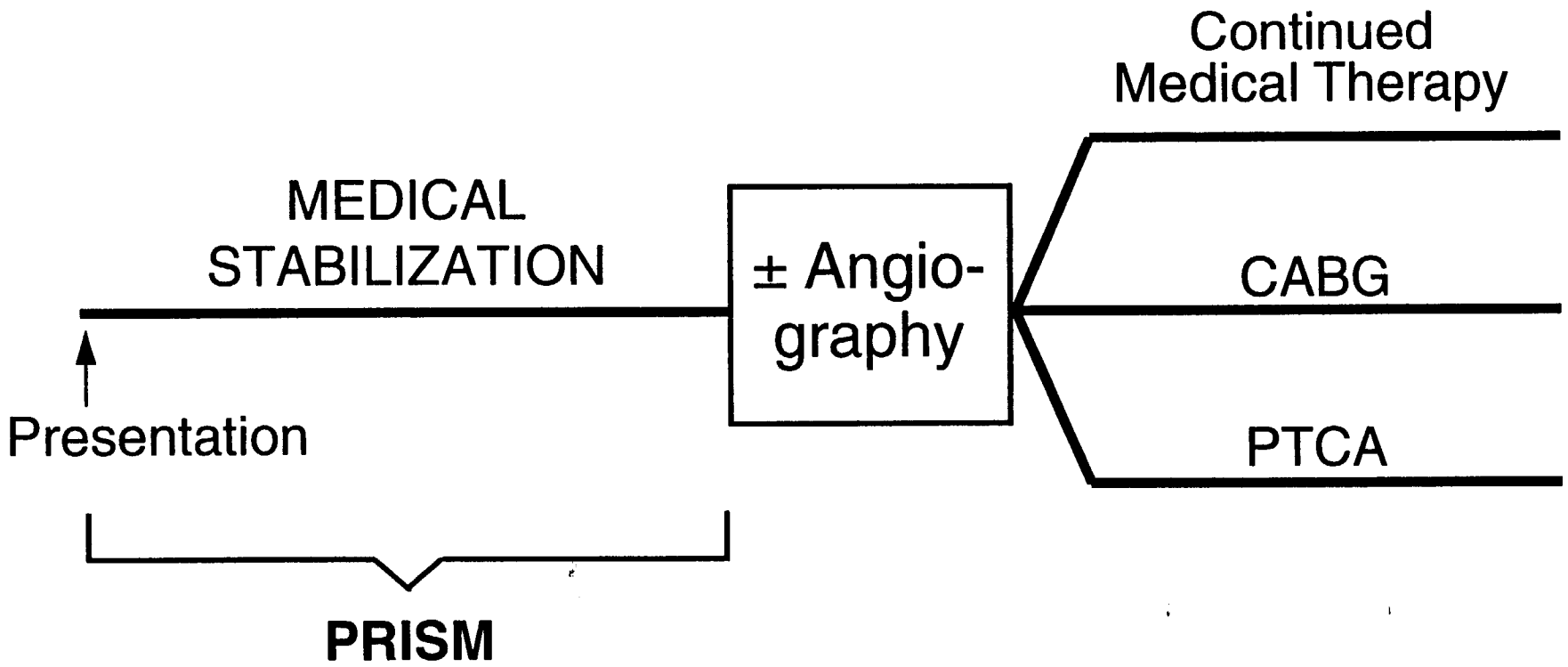
UAP / NQWMI Trials
Clinical Presentation

	PRISM (N=3232)	PRISM-PLUS (N=1915)
Entry Findings:		
ECG evidence of ischemia or elevated enzymes	74%	98%
Diagnostic Classification:		
NQWMI	25%	45%
Unstable angina pectoris	75%	55%

Clinical Program for UAP / NQWMI Baseline Demographics

	PRISM (N=3232)	PRISM-PLUS (N=1915)
• Mean Age (yrs ± SD)	62 ±11	63 ±12
• Female	32%	32%
• Race		
- Caucasian	84%	86%
- Black	5%	4%
- Other	11%	10%
• Secondary Diagnoses		
- Previous MI	47%	42%
- Hypertension	54%	55%
- Hypercholesterolemia	47%	49%
- Diabetes	21%	23%

PRISM: Medical Stabilization of UAP / NQWMI



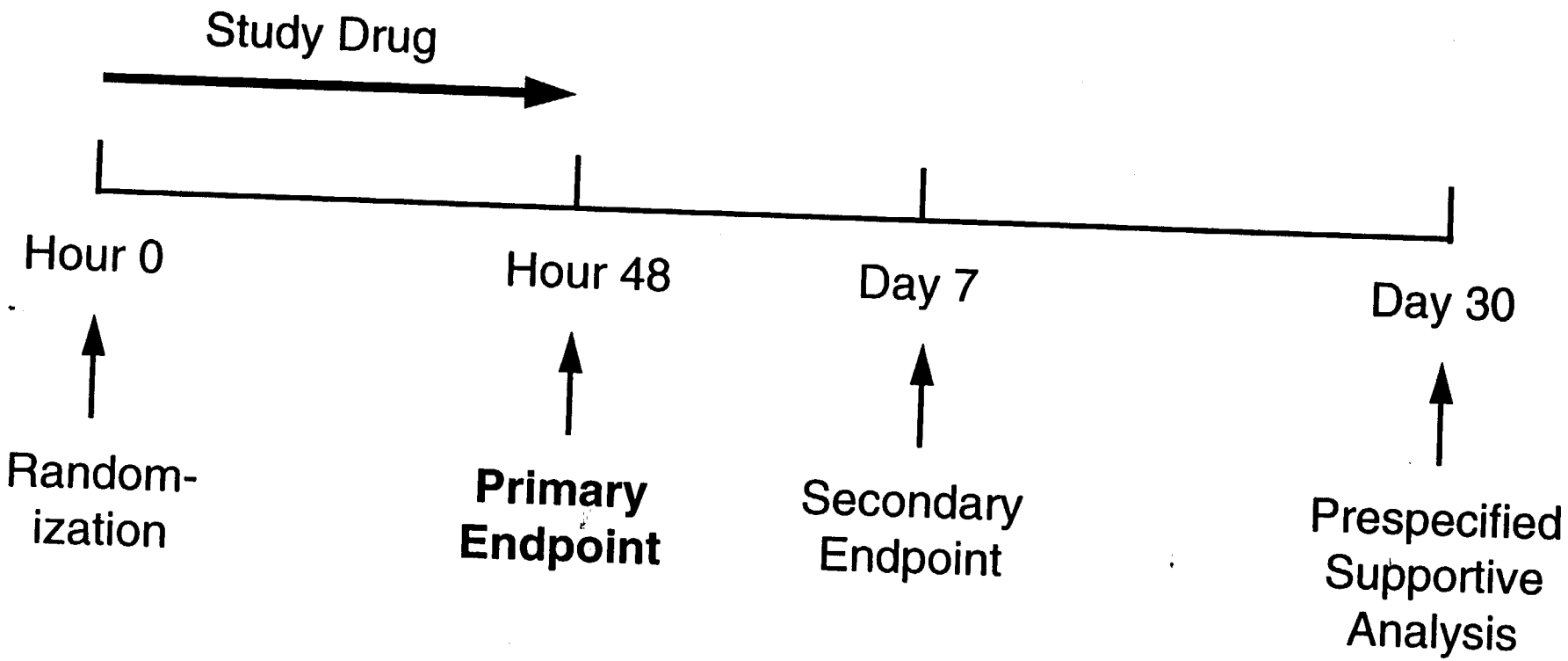
PRISM Primary Hypothesis

In patients with UAP / NQWMI, tirofiban will reduce the composite endpoint of:

- refractory ischemia,
- new myocardial infarction, and
- death (any cause)

compared with heparin, at 48 hours

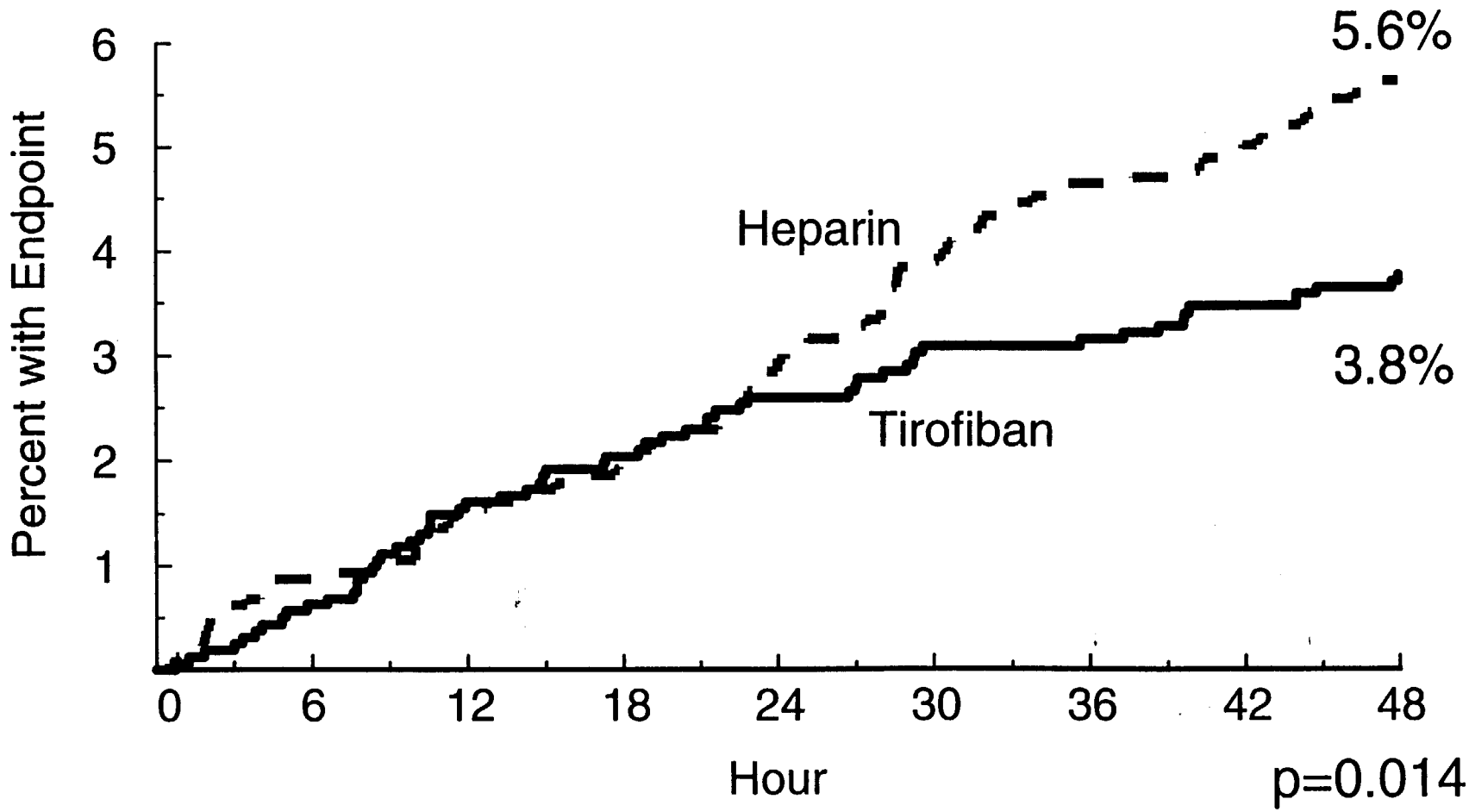
PRISM Study Design



PRISM Study Conduct

- Independent Data Safety Monitoring Board
- Two planned interim efficacy analyses:
  critical p-value set at 0.047
- Planned sample size 1000 patients / group; increased to 1550 patients / group due to low blinded pooled-group event rate
- Intention-to-treat analysis

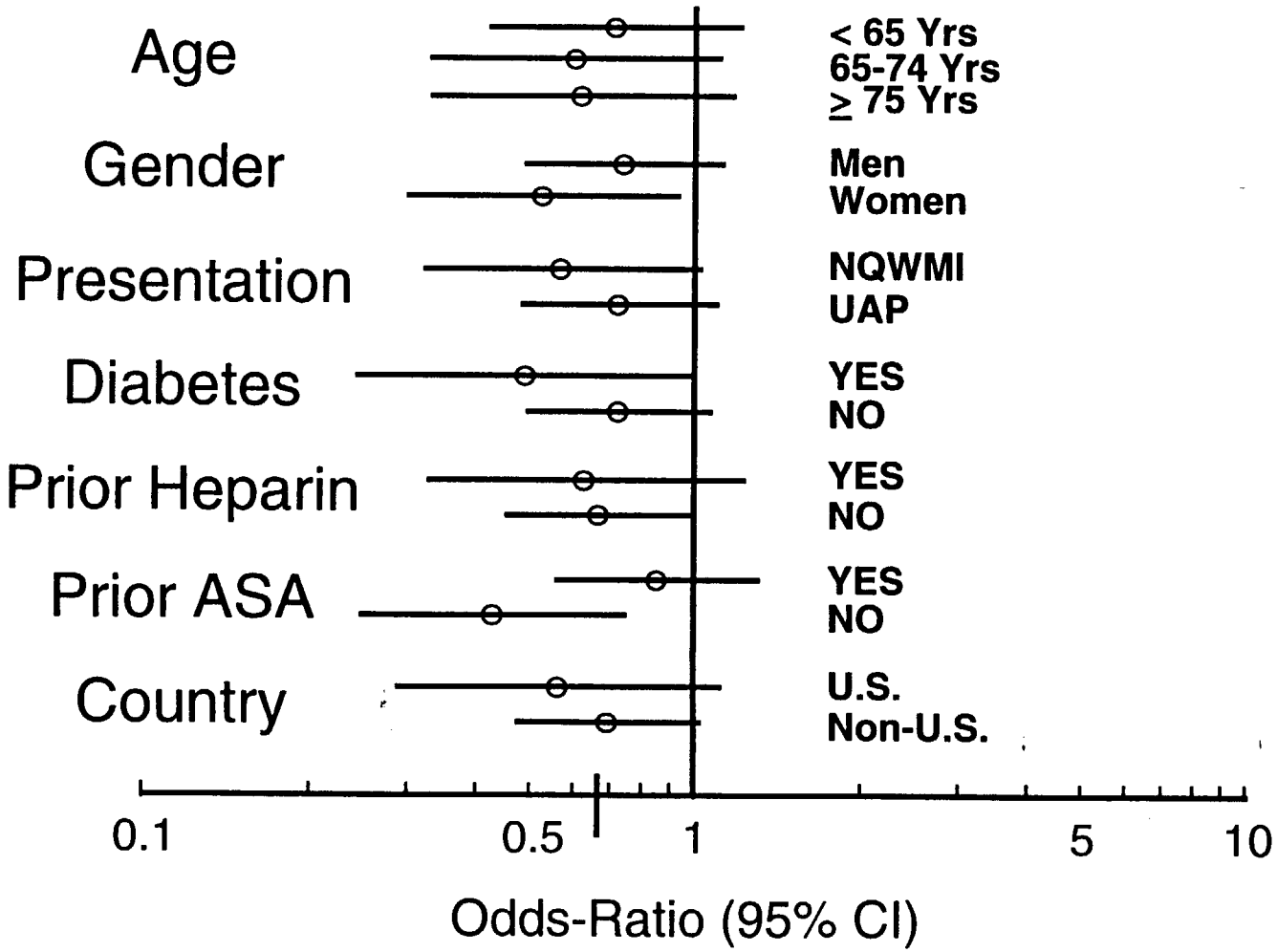
PRISM Primary Endpoint (48 Hours)



PRISM Primary Endpoint (48 Hours)

	Tirofiban N=1616	Heparin N=1616	Odds Ratio	p-value
Composite Endpoint	**3.8%**	**5.6%**	**0.66**	**0.014**
- Refractory Ischemia	3.5%	5.3%	0.64	0.011
- Myocardial Infarction	0.9%	1.4%	0.64	0.19
- Death	0.4%	0.2%	1.49	0.54

PRISM Subgroup Outcomes (48 hours)



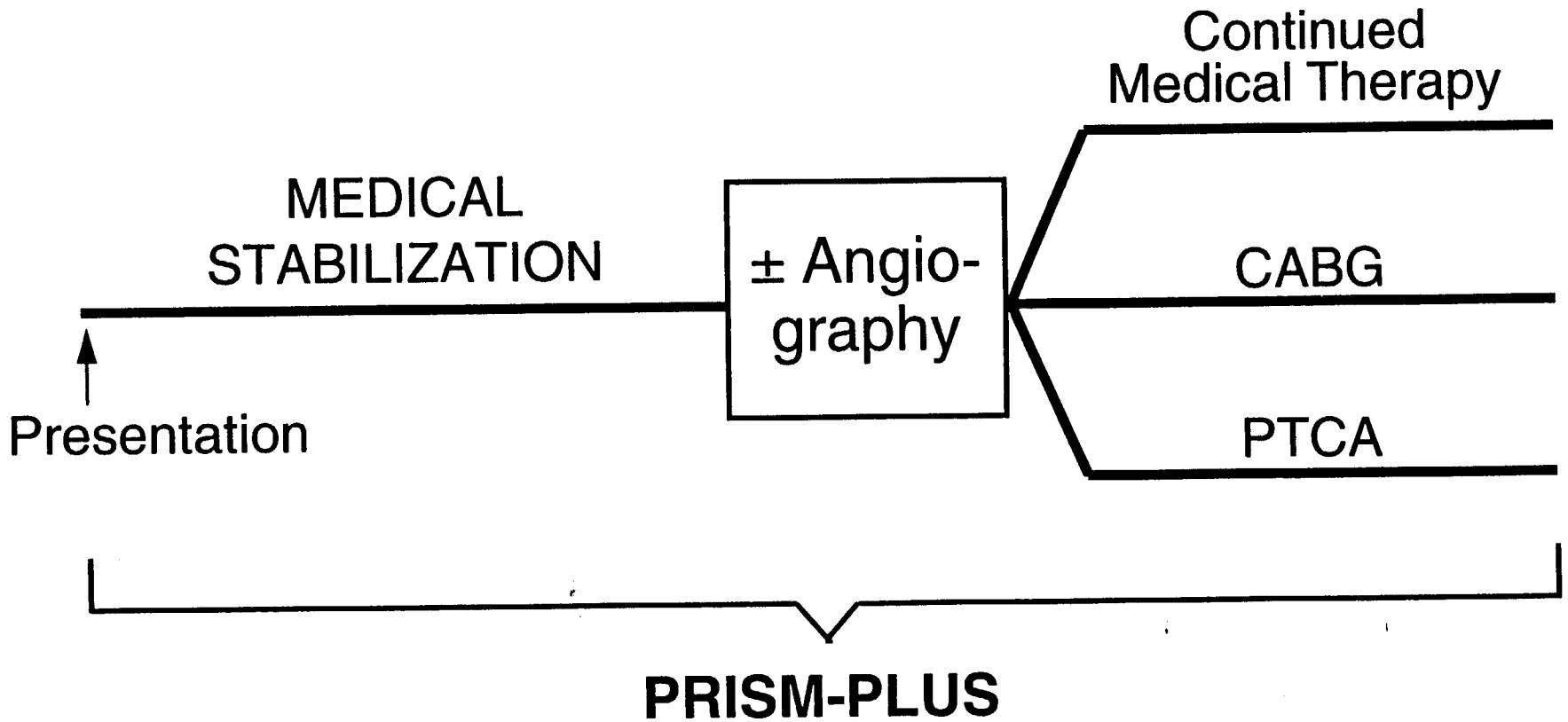
PRISM Secondary and Supportive Endpoints

	Tirofiban N=1616	Heparin N=1616	Odds Ratio	p-value
At 7 Days				
Composite Endpoint	10.3%	11.3%	0.90	0.37
At 30 Days				
Composite Endpoint	15.9%	17.1%	0.92	0.38

PRISM Summary

- In patients with UAP / NQWMI, tirofiban alone further reduces early cardiac ischemic events compared to an active control (heparin)

PRISM-PLUS: Comprehensive Treatment of UAP/NQWMI



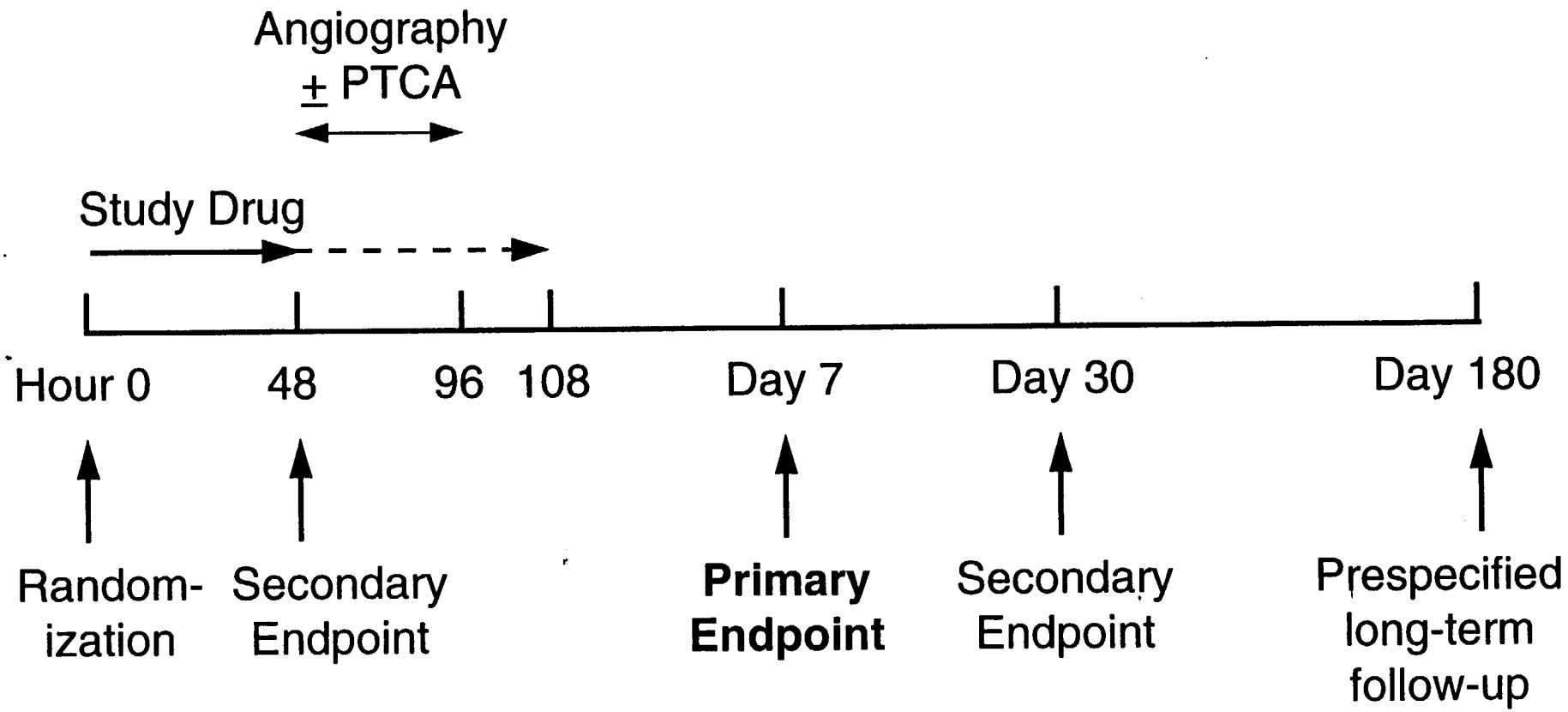
PRISM-PLUS Primary Hypothesis

Compared with heparin, either tirofiban alone or tirofiban with heparin will reduce the composite endpoint of:

- refractory ischemic conditions,
- new myocardial infarction, and
- death (any cause)

at 7 days in patients with UAP / NQWMI

PRISM-PLUS Study Design



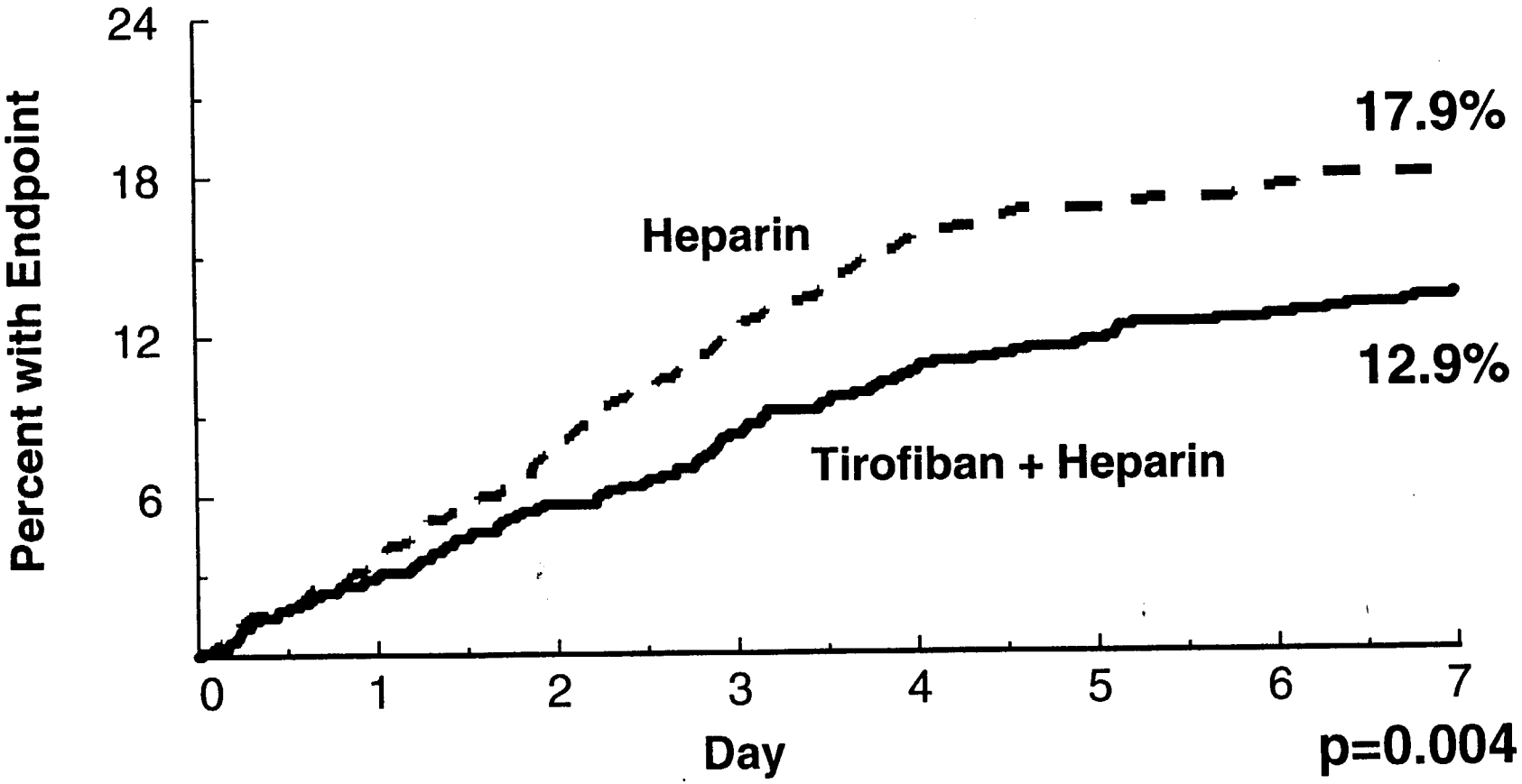
PRISM-PLUS Study Conduct

- Independent Data Safety Monitoring Board
- Adjustment for two treatment comparisons: critical p-value set at 0.025
- Planned sample size of 420 pts/group increased to 735 pts/group according to a protocol-specified rule
- Tirofiban-alone arm dropped

PRISM-PLUS Dropped Arm

- Tirofiban alone arm dropped by DSMB due to apparent excess in deaths (14 vs. 4) at 7 days
- Differences in mortality not significant at 30 days and 6 months follow-up
- Inconsistent with PRISM
- Study continued with tirofiban + heparin vs. heparin comparison; no impact on statistical analysis

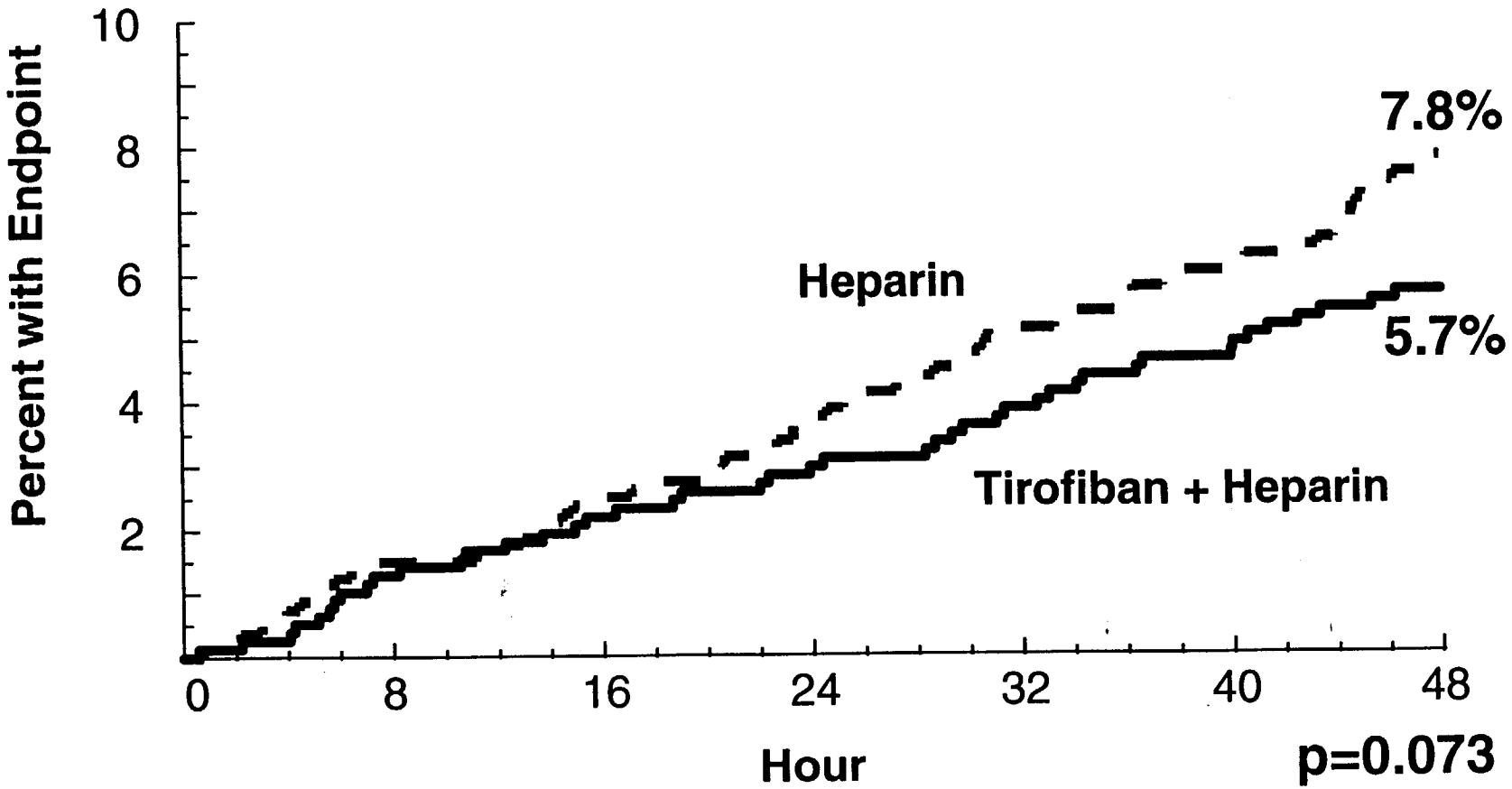
PRISM-PLUS Primary Composite Endpoint (7 Days)



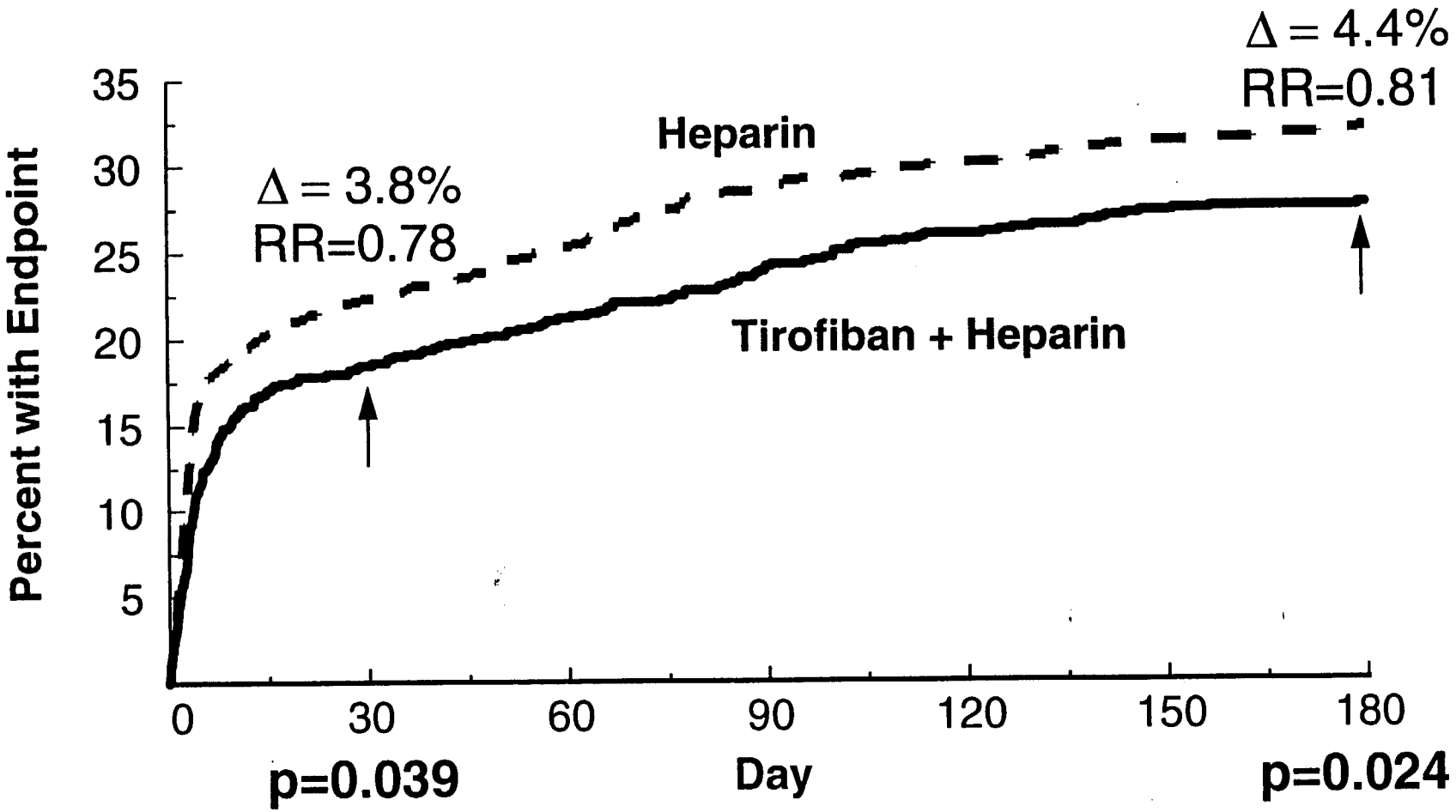
PRISM-PLUS Primary Endpoint (7 Days)

	Tirofiban + Heparin N=773	Heparin N=797	Odds Ratio	p-value
Composite Endpoint	**12.9%**	**17.9%**	**0.66**	**0.004**
- Refractory Ischemia	9.3%	12.7%	0.68	0.022
- Myocardial Infarction	3.9%	7.0%	0.53	0.006
- Death	1.9%	1.9%	1.01	0.98

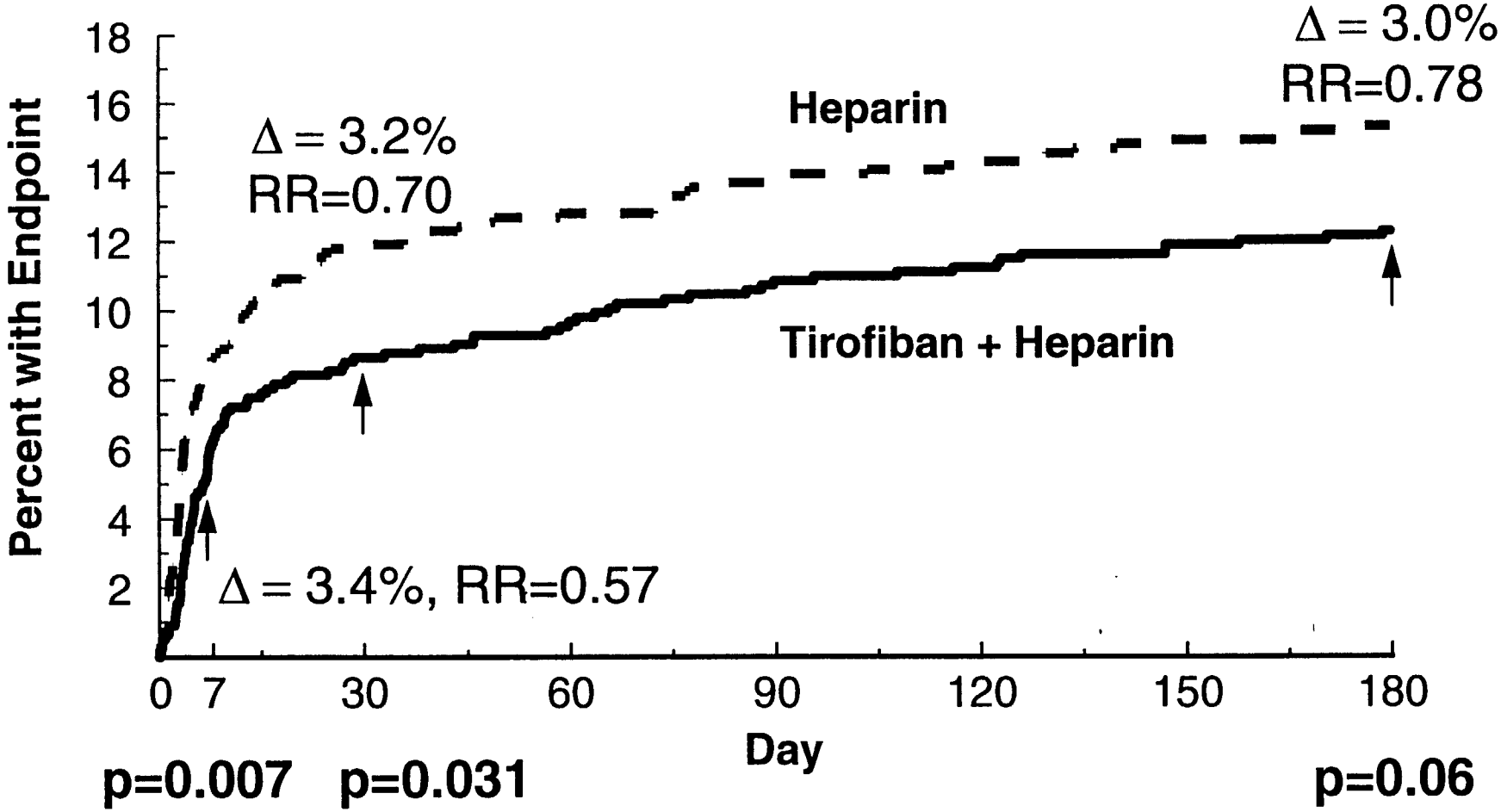
PRISM-PLUS Composite Endpoint (48 Hours)



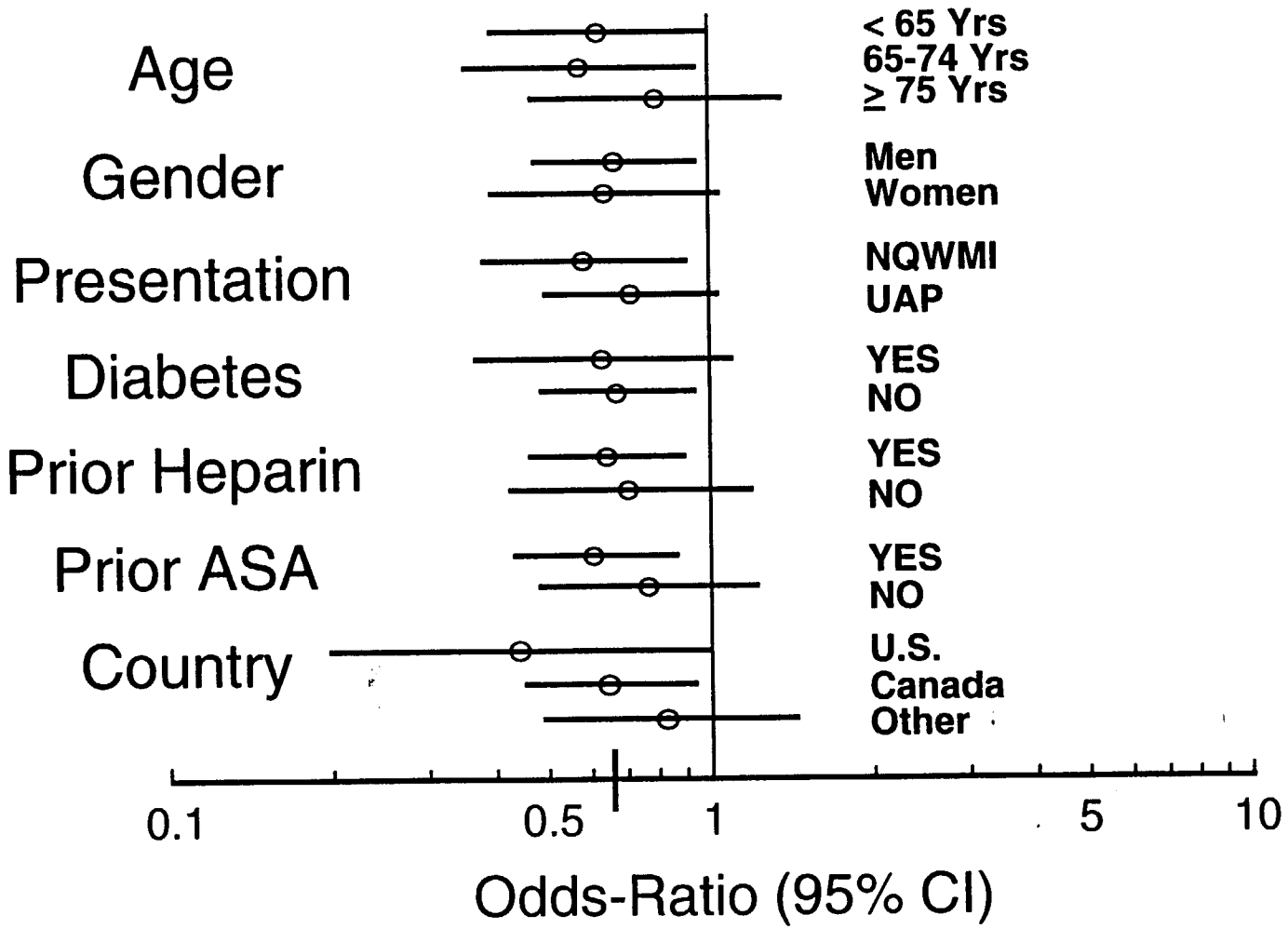
PRISM-PLUS Composite Endpoint (180 Days)



PRISM-PLUS Myocardial Infarction/Death (180 Days)



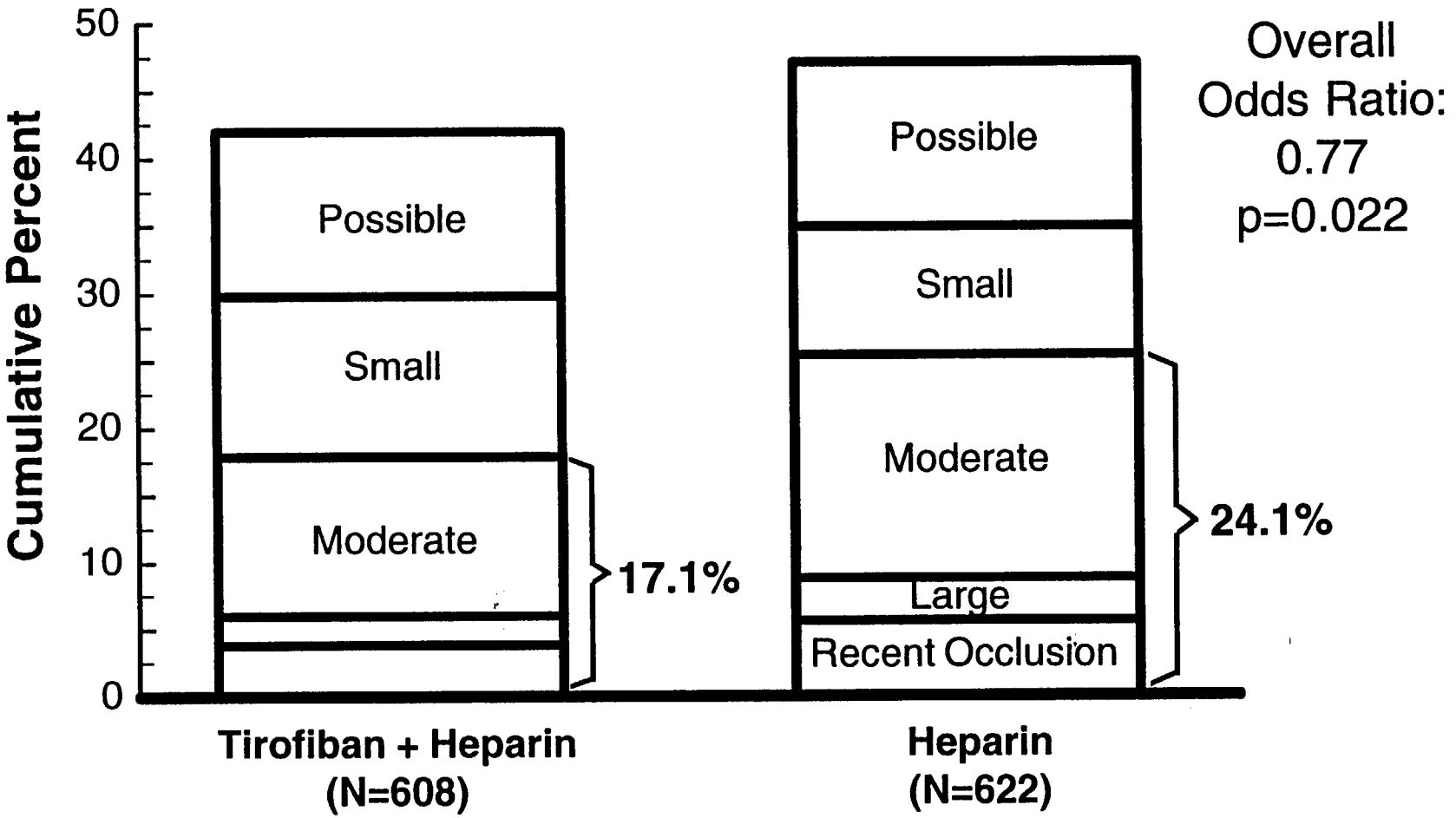
PRISM-PLUS Subgroup Outcomes (7 days)



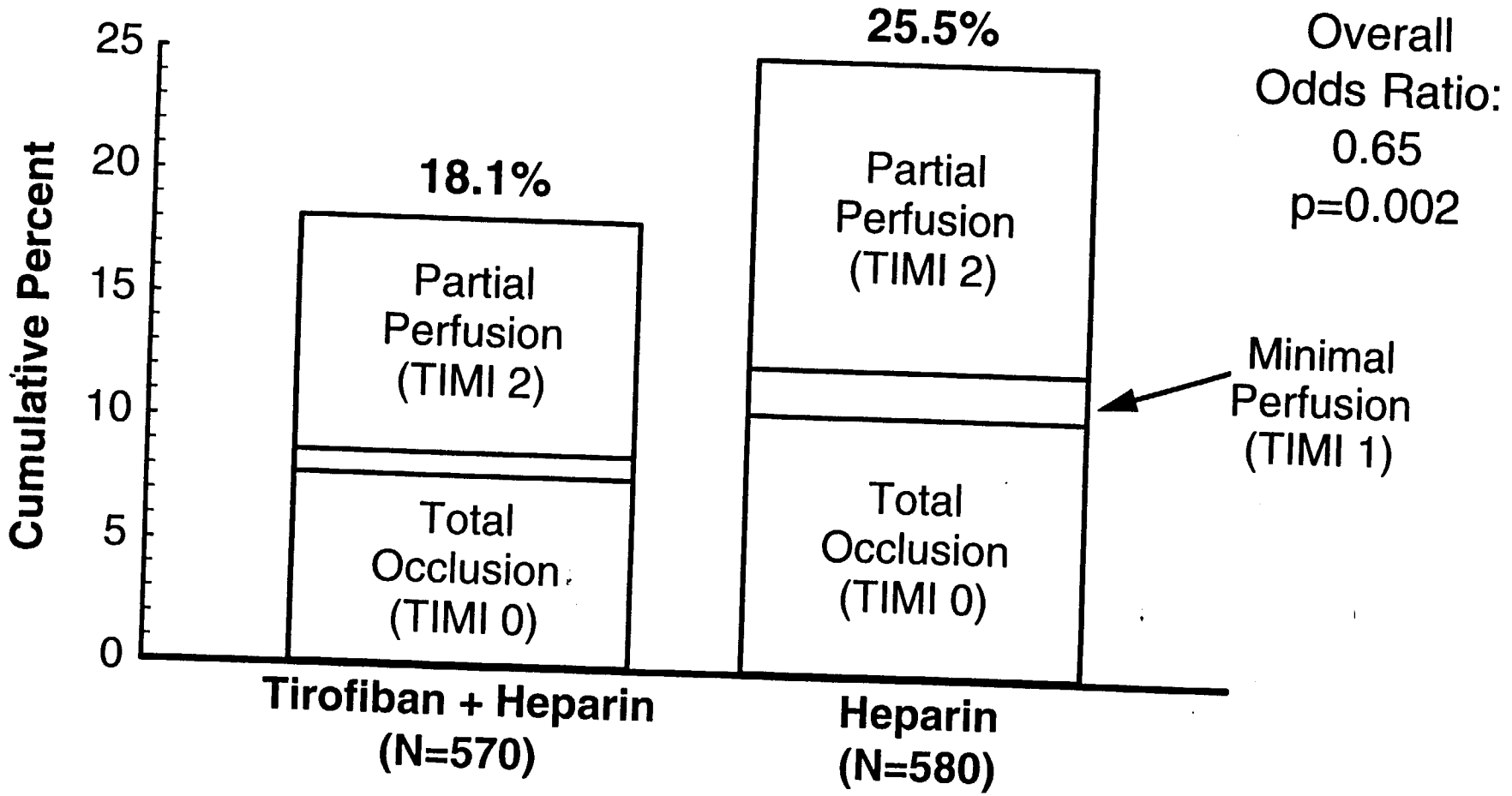
PRISM-PLUS Angiographic Substudy

- Objective: effect of tirofiban on angiographically-apparent thrombus
- Films prior to Hour 97 analyzed by blinded Core Laboratory
- 1230 films readable and analyzed (608 in tirofiban + heparin group; 622 in heparin group)

PRISM-PLUS Thrombus Grade



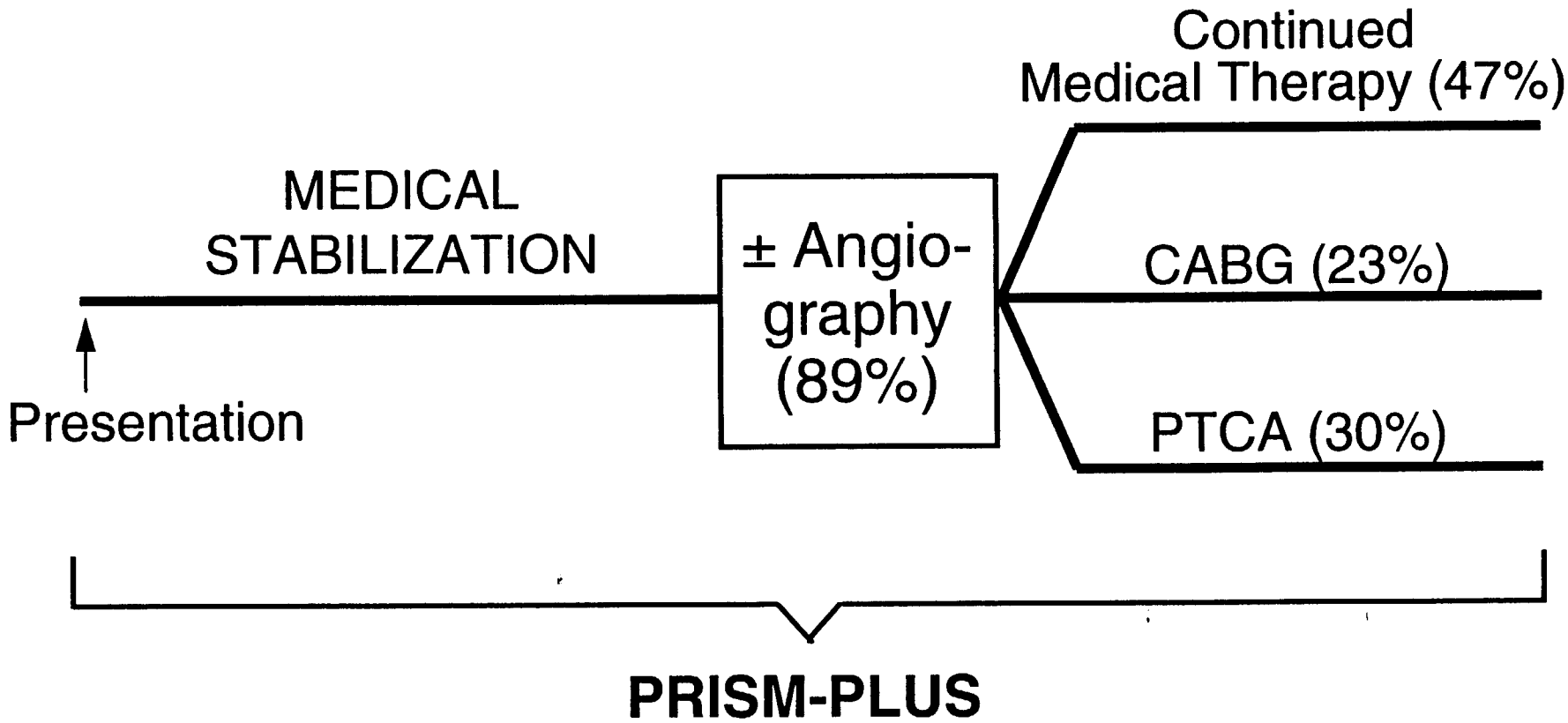
PRISM-PLUS TIMI Flow



PRISM-PLUS Summary

- Tirofiban in combination with heparin reduces cardiac ischemic events including MI / Death:
  - Before procedures
  - Through procedures
  - Sustained benefit
- Reduction of thrombus burden links pathophysiology with clinical benefit

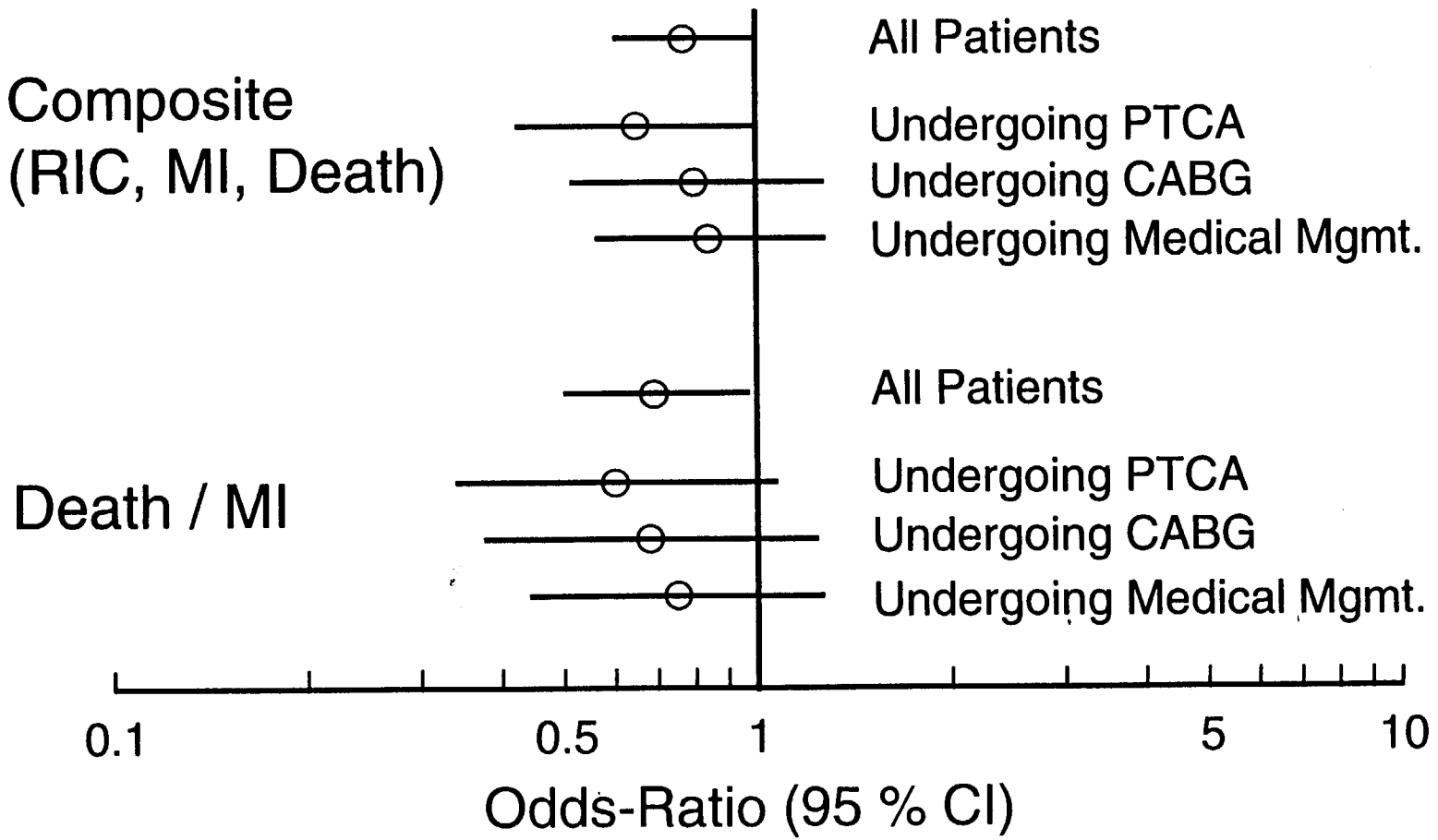
PRISM-PLUS Treatment Selections



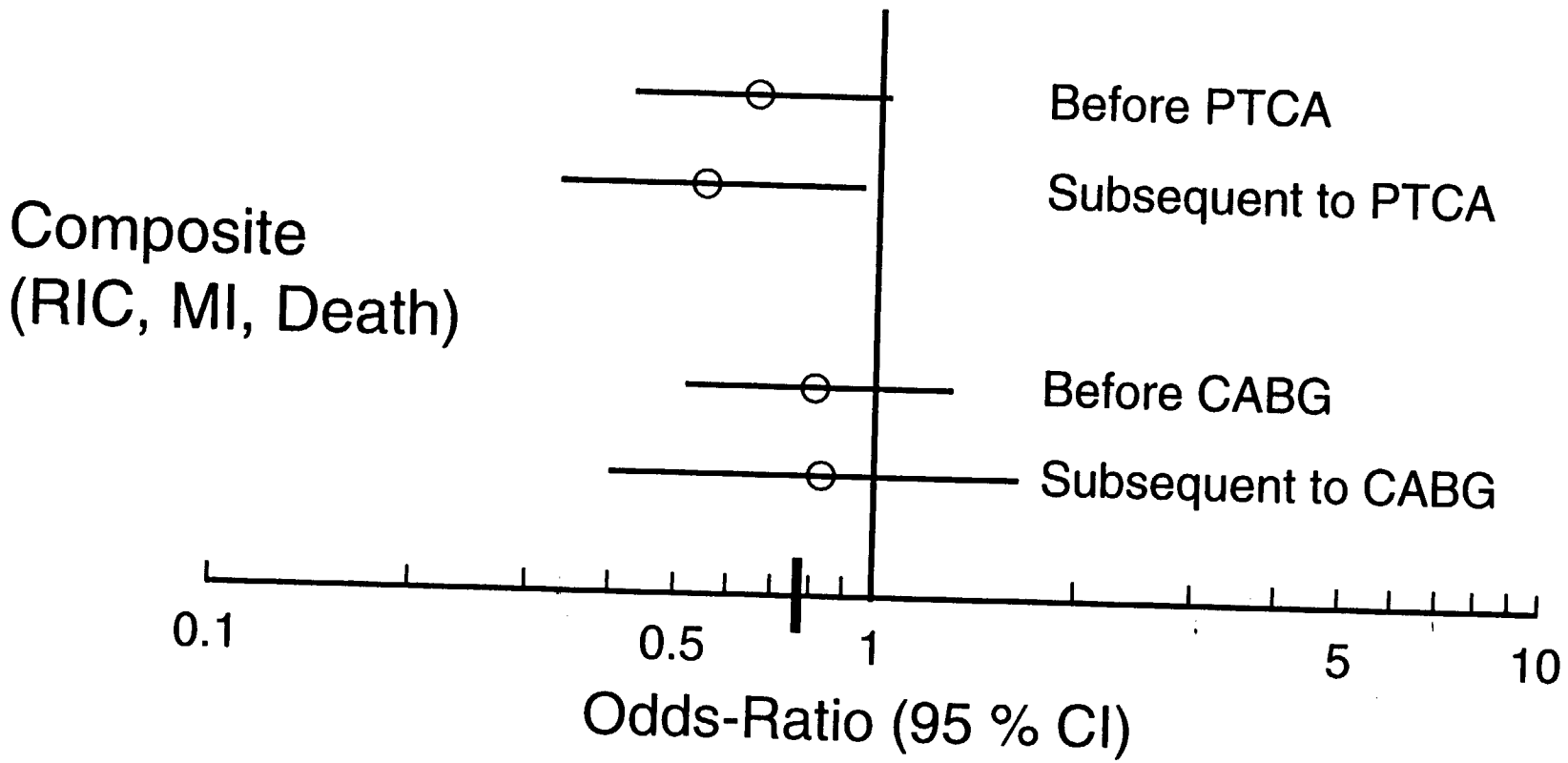
PRISM-PLUS Outcomes by Treatment Decision

- Cohorts:
  - PTCA
  - CABG
  - Medical Management
- Limitations:
  - Post randomization
  - Potentially confounded

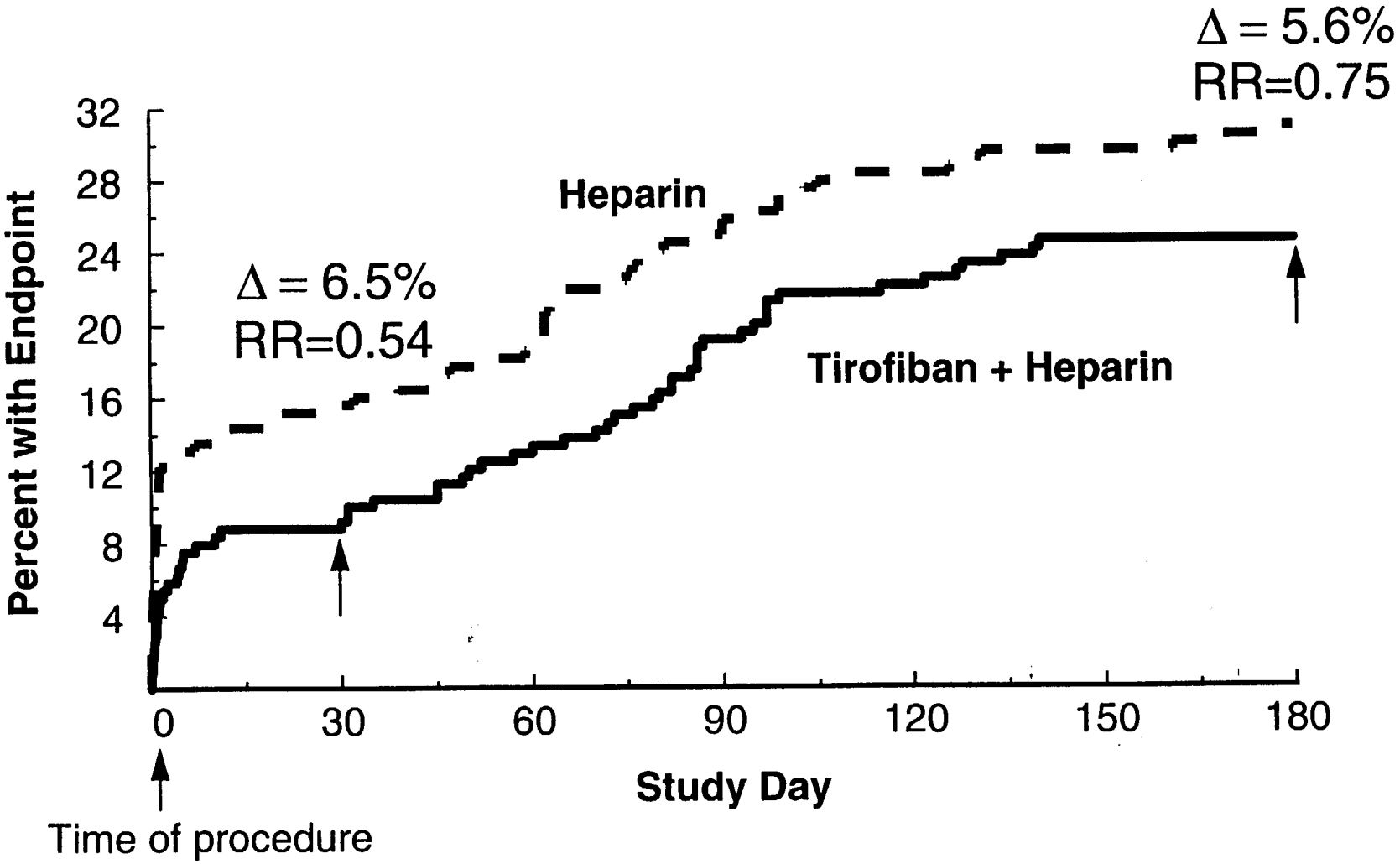
PRISM-PLUS 30-Day Endpoints in PTCA, CABG, and Medical Management Cohorts



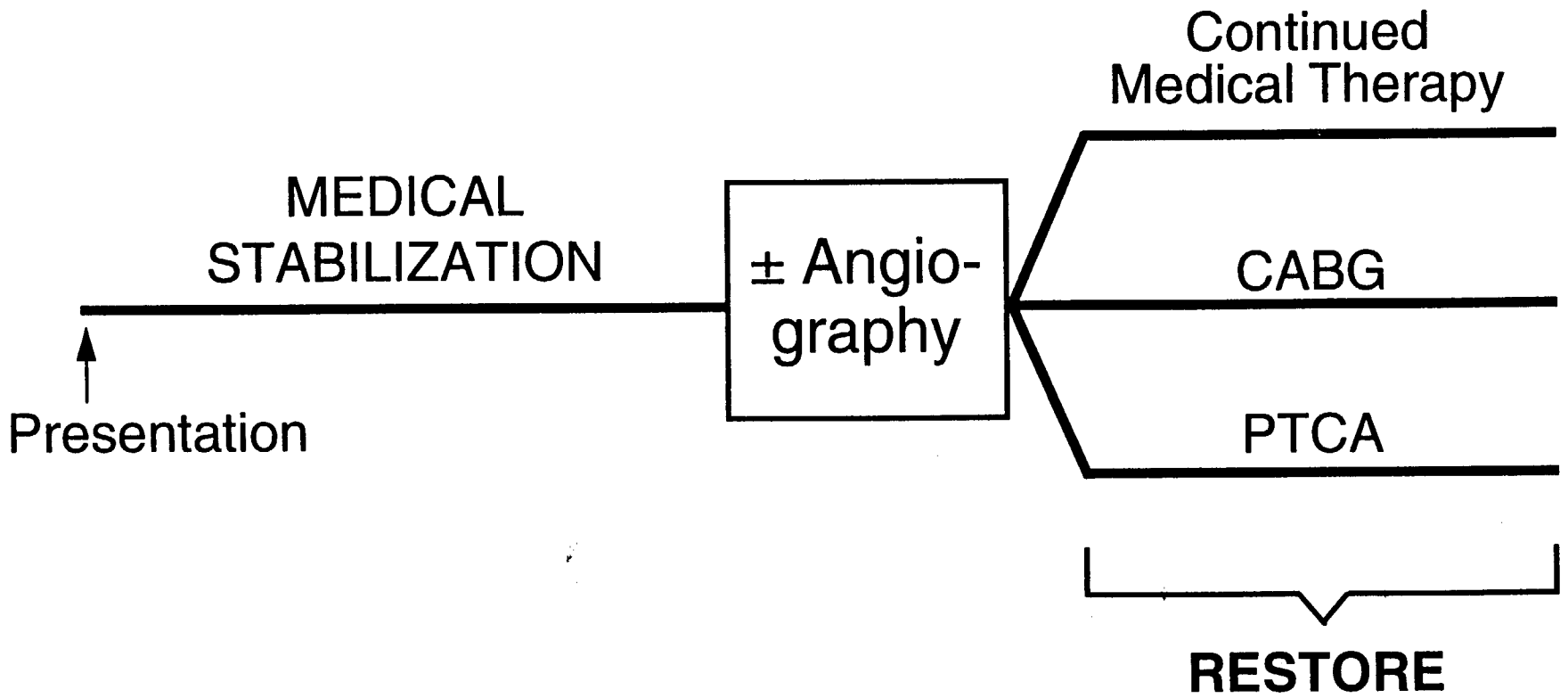
PRISM-PLUS 30-Day Endpoints in PTCA and CABG Cohorts



PRISM-PLUS Composite Endpoint in PTCA



RESTORE - Coronary Angioplasty for Acute Coronary Syndromes



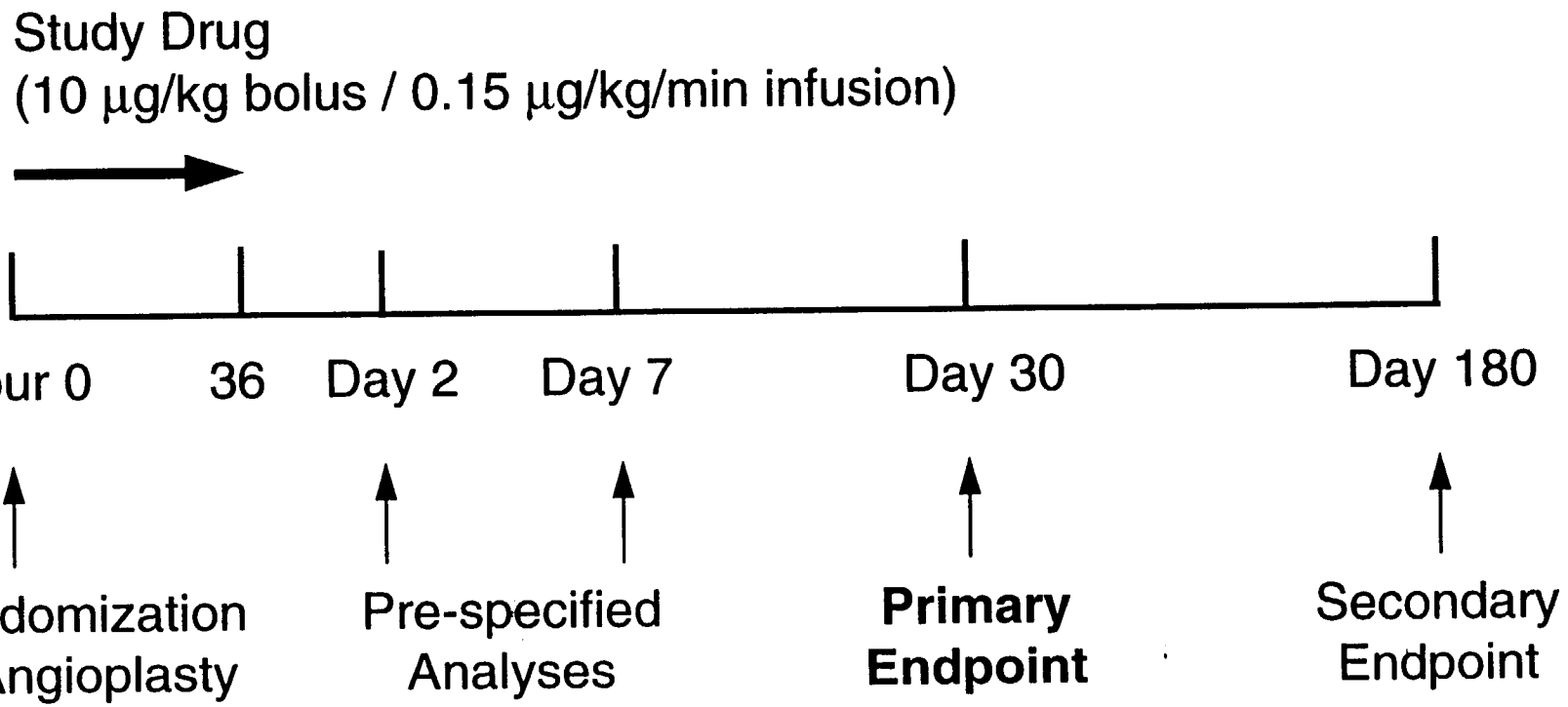
RESTORE Primary Hypothesis

Tirofiban, initiated at the time of PTCA/ atherectomy, will reduce the composite endpoint of:

- repeat revascularization due to ischemia,
- stent placement (used for abrupt closure),
- new myocardial infarction, and
- death (any cause)

compared with placebo (on a background of heparin) within 30 days

RESTORE Study Diagram



RESTORE Study Conduct

- Independent Data Safety Monitoring Board
- Two planned interim analyses:
  critical p-value set at 0.047
- Primary efficacy analysis:
  all-patients-treated analysis

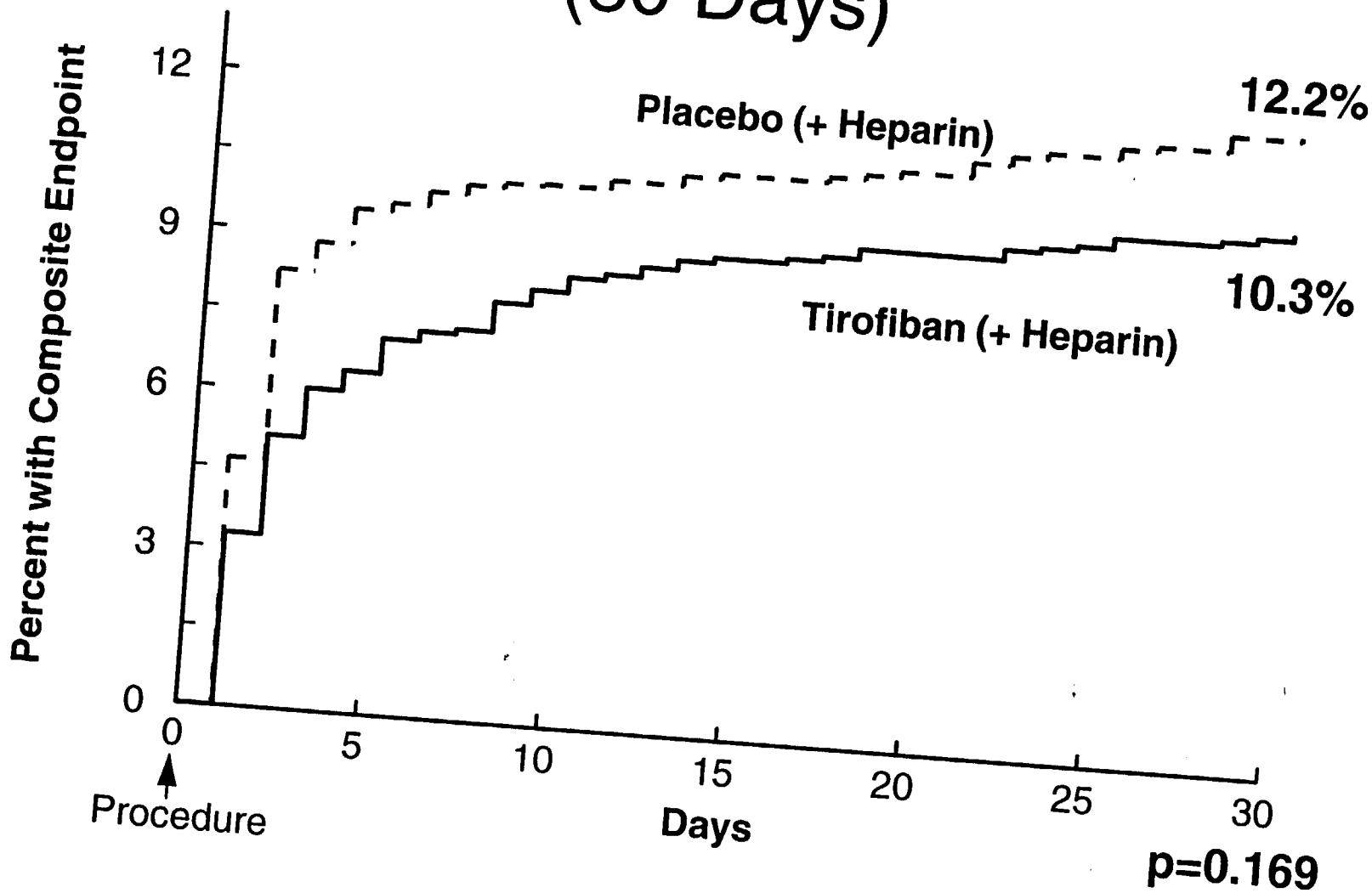
RESTORE Inclusion Criteria

	RESTORE
Clinical Presentation	
MI (Q-wave and NQWMI)	✓
UAP	✓
Anginal Pain within:	72 hrs
Documentation	
ECG ischemia *or*	✓
CK elevation *or*	✓
Angiographic thrombus	✓

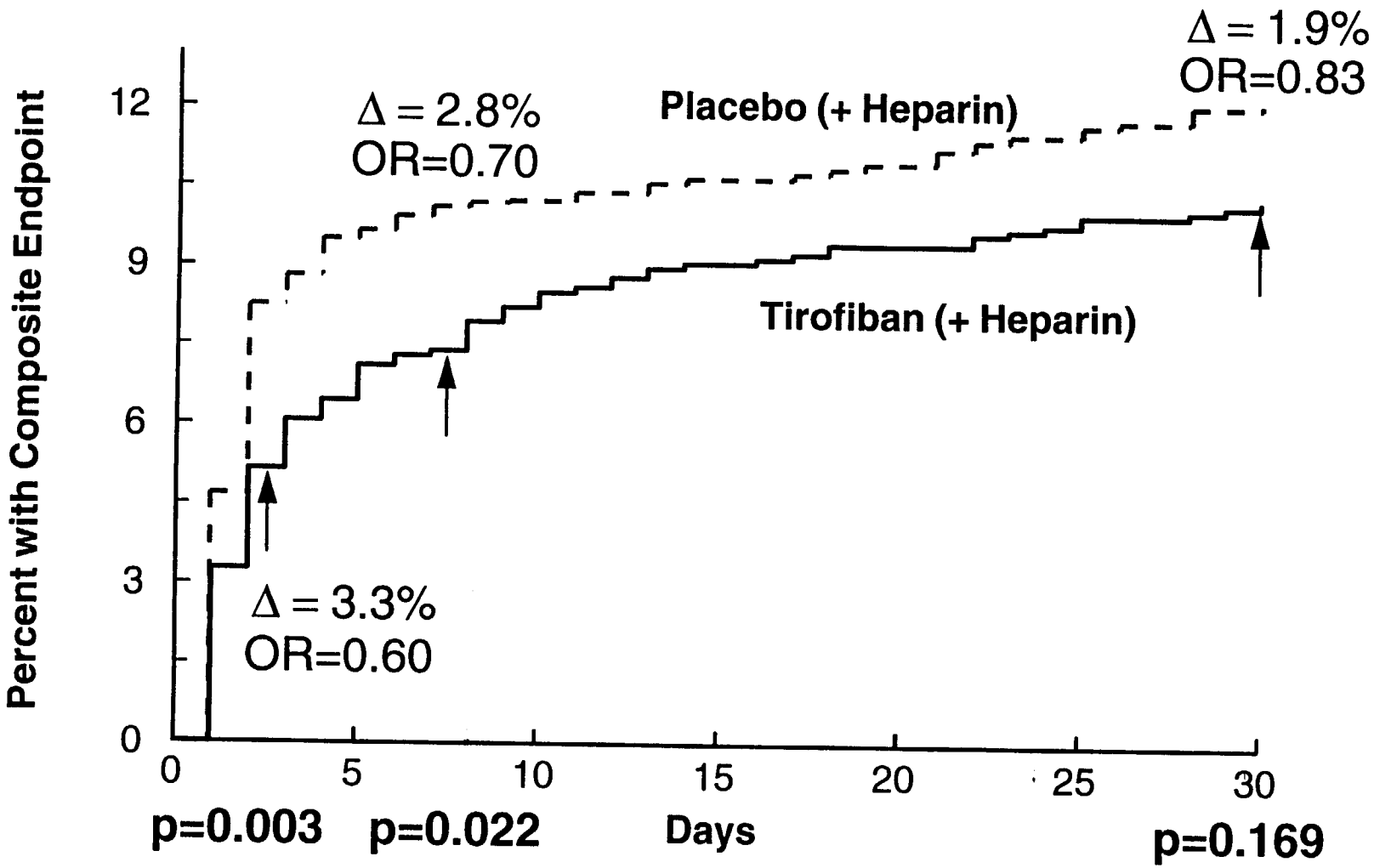
RESTORE Baseline Demographics

	RESTORE (N=2141)
• Mean Age (yrs ± SD)	59 ± 11
• Female	27%
• Race	
- Caucasian	89%
- Black	6%
• Secondary Diagnosis	
- Hypertension	55%
- Hypercholesterolemia	50%
- Diabetes	20%
• Clinical Presentation	
- UAP	68%
- Acute MI	32%

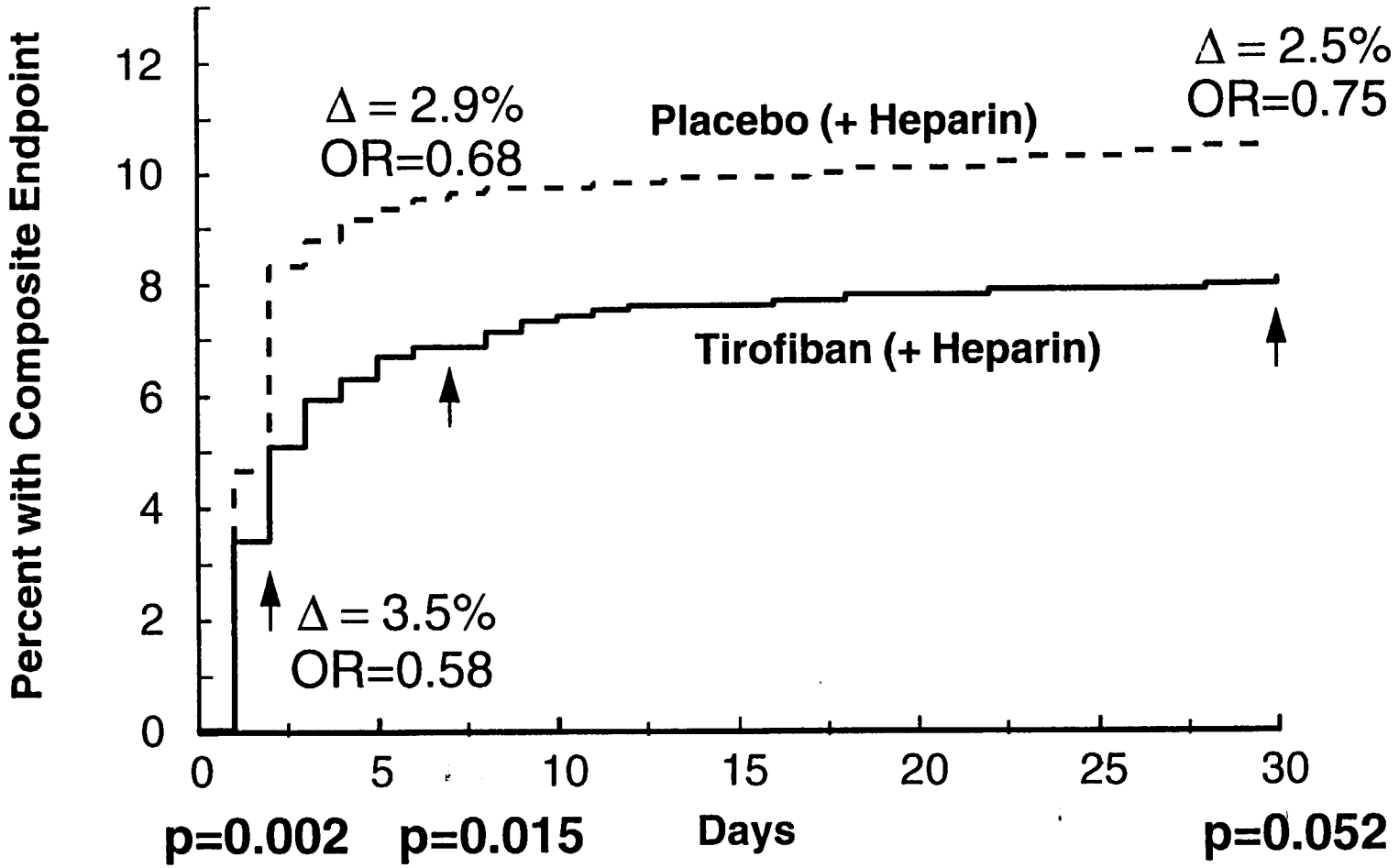
RESTORE Time to Composite Endpoint (30 Days)



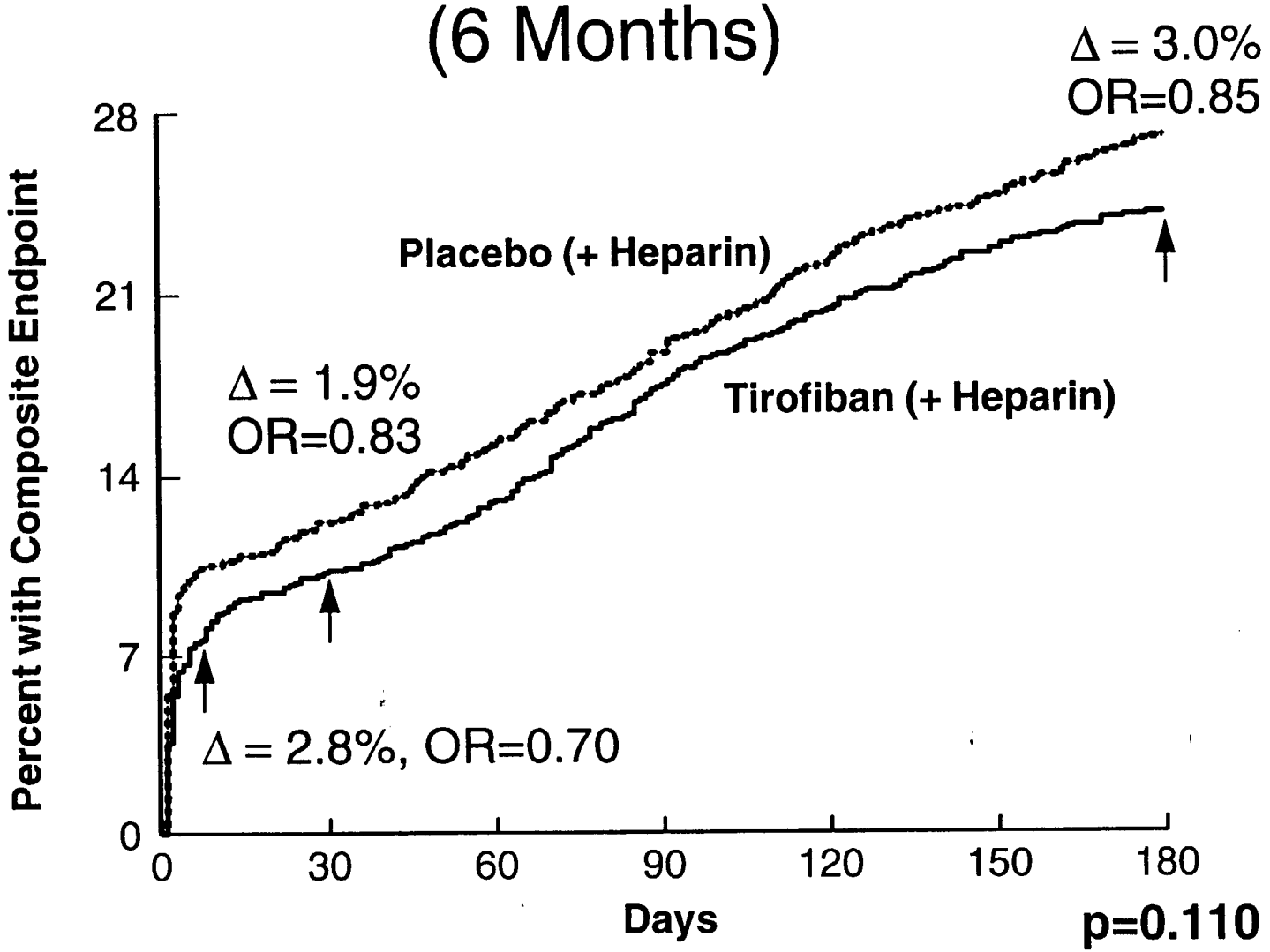
RESTORE Time to Composite Endpoint



RESTORE - Time to Composite Endpoint Reanalysis (Urgent Revascularization)



RESTORE Time to Composite Endpoint (6 Months)



RESTORE Summary

- Primary endpoint (30 days) did not achieve statistical significance
- Tirofiban (with heparin) reduced the incidence of adverse outcomes at 2 and 7 days after the procedure
- Supports use of tirofiban for patients undergoing angioplasty

Safety of Tirofiban

- Bleeding Complications
- Thrombocytopenia
- Non-bleeding Adverse Events

Bleeding Complications in UAP/NQWMI Trials

	PRISM (No Procedures)		PRISM-PLUS	
	T N=1616	H N=1616	T+H N=773	H N=797
Major Bleeding (TIMI)	0.4%	0.4%	1.4%	0.8%
- Intracranial bleeding	0.1%	0.1%	0.0%	0.0%
Minor Bleeding (TIMI)	2.0%	1.9%	10.5%	8.0%
Transfusions (PRBCs)	1.9%	1.2%	3.5%	2.3%

T=Tirofiban H=Heparin

RESTORE - Safety

	Tirofiban + Heparin (N=1071)	Placebo + Heparin (N=1070)
Major Bleeding (TIMI)	2.2%	1.6%
- Intracranial hemorrhage	0.1%	0.3%
Minor Bleeding (TIMI)	12.0%	6.3%
Transfusions (PRBCs)	4.0%	2.4%

Platelet Counts

	PRISM		PRISM-PLUS		RESTORE	
	T (N=1616)	H (N=1616)	T+H (N=773)	H (N=797)	T+H (N=1071)	P+H (N=1070)
< 90,000/mm^3	1.1%	0.4%	1.8%	0.8%	1.1%	0.8%
< 50,000/mm^3	0.4%	0.1%	0.5%	0.3%	0.2%	0.1%
< 20,000/mm^3	0.2%	0.1%	0.1%	0.0%	0.0%	0.1%

T=Tirofiban H=Heparin P=Placebo

Non-Bleeding Clinical Adverse Events

No clinically important difference between tirofiban groups and heparin control groups in:

- Overall incidence of non-bleeding adverse events
- Drug-related non-bleeding adverse events
- Discontinuations due to non-bleeding adverse events
- Serious non-bleeding adverse events

Program Conclusions

Program Conclusions

- Tirofiban in combination with heparin (PRISM-PLUS) reduces cardiac ischemic events including MI / Death in patients with UAP / NQWMI:
  - Before procedures
  - Through procedures
  - Sustained benefit
- Tirofiban alone (PRISM) further reduces early cardiac ischemic events compared to an active control (heparin)

Program Conclusions (Cont.)

- Prospective angioplasty trial (RESTORE) supports safety and clinical efficacy of tirofiban in patients undergoing PTCA
- Low incidence of major bleeding, low excess of transfusions
- Tirofiban with heparin provides short and long term benefit in patients with UAP / NQWMI

Program Summary

These data support the following Indication:

"Tirofiban, in combination with heparin, is indicated to prevent cardiac ischemic events in patients with UAP / NQWMI, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated."