CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 4/9-10/98

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AGENDA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Drug Products
84th Meeting
April 9-10, 1998

Cardiovascular and Renal Drugs Advisory Committee

National Institutes of Health
Clinical Center - Building 10
Jack Masur Auditorium
9000 Rockville Pike
Bethesda, Maryland

Parking in the Clinical Center visitor area is reserved for Clinical Center patients and their visitors. If you must drive, please use an outlying lot such as Lot 41B. Free shuttle bus service is provided from Lot 41B to the Clinical Center every eight minutes. Free shuttle bus service from the subway is also available.

THURSDAY, APRIL 9, 1998

8:30 a.m. OPEN PUBLIC HEARING
One hour allocated unless public participation does not last that long.

Discussion: Inhaled Nitric Oxide (see attached agenda).

In addition to the Cardiovascular and Renal Drugs Advisory Committee, FDA has appointed the following temporary voting members for this meeting:

Carroll E. Cross, M.D., University of California, Davis, member of the Pulmonary-Allergy Drugs Advisory Committee.

Curtis Sessler, M.D., Medical College of Virginia, Member of the Pulmonary-Allergy Drugs Advisory Committee.

Jay P. Goldsmith, M.D., Ochsner Clinic.

Peter Rothstein, M.D., Columbia/Presbyterian Medical Center.

TEMPORARY VOTING MEMBERS
APRIL 9, 1998
NITRIC OXIDE

Carroll E. Cross, M.D.
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University of California, Davis
Division of Pulmonary Critical Care Medicine
Department of Internal Medicine
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Richmond, Virginia 23219

[redacted] APPEARS THIS WAY ON ORIG

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Ochsner Clinic
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New Orleans, Louisiana 70121

Peter Rothstein, M.D.
Columbia/Presbyterian Medical Center
Babies and Childrens Hospital
622 West 168th Street, BN 440
New York, New York 10032

TEMPORARY VOTING MEMBER
APRIL 10, 1998
AGGRASTAT

Jeffrey Borer, M.D.
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CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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QUESTIONS

Questions

nitric oxide II

9 April 1998

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

This is the second time the Cardiac and Renal Drugs Advisory Committee has discussed Inhaled Nitric Oxide (INO) in a public forum. In August 1995, the Committee endorsed the idea that clinical outcome, rather than systemic oxygenation, should be used to evaluate the effectiveness of INO in neonates with hypoxic respiratory failure; appropriate endpoints were said to include some combination of death, initiation of extracorporeal membrane oxygenation (ECMO), bronchopulmonary dysplasia, and abnormal long-term neurological status.

Since 1993, the FDA has seen a proliferation of individual-investigator INDs for the use of INO in newborns to adults. Inquiries concerning new INDs often reflect the requesting physician's strong bias that INO "works" and frustration that there is no FDA-approved product. The plan today is to review the systematic studies that have been conducted, some of which are unpublished, and to allow the public and the Committee to consider:

- what is known about the safety and effectiveness of INO,
- the need for more clinical trials, and
- the goals and design of what further trials may be needed.

Ohmeda, NICHD, and a number of individual investigators have agreed to share their data in public forum to facilitate this venture. The Division has shared with the Advisory Committee medical reviews of 3 trials that were conducted in near-term infants with hypoxic respiratory failure, as well as pharmacology/toxicology reviews that supported those trials. Ohmeda and individual investigators have distributed to the Advisory Committee selected publications that contribute more information, in particular with respect to adult respiratory distress syndrome (ARDS). Invited experts are on hand to discuss issues relating to disease processes and the action of nitric oxide.

1. In what patient populations does INO unequivocally decrease pulmonary vascular resistance? What do the time course and dose-response relationships look like?

2. In neonates with hypoxic respiratory failure, does INO unequivocally improve systemic oxygenation? If so, what do the time course and dose-response relationships look like?

3. In adults with respiratory failure, does INO unequivocally improve systemic oxygenation? If so, what do the time course and dose-response relationships look like?

4. Is an effect on pulmonary vascular resistance or systemic oxygenation predictive of clinical outcome...

   4.1. ...in neonates with hypoxic respiratory failure?

   4.2. ...in ARDS?

5. Do the data presented today support the use of extracorporeal membrane oxygenation (ECMO) as a treatment for neonates with hypoxic respiratory failure? If so, ...

   5.1. ...what is the demonstrated effect on clinical outcome?

   5.2. ...what are the characteristics of candidates for ECMO?

6. Characterize the effect of INO on mortality...

   6.1. ...in neonates with hypoxic respiratory failure. Do the mortality data make it unethical to perform further studies?

   6.2. ...in ARDS. Do the mortality data make it unethical to perform further studies?

7. In each of the three randomized trials of neonates with hypoxic respiratory failure, what evidence was there in favor of a benefit of treatment?

   7.1. Did these trials find evidence for the same benefit or were these trials otherwise supportive of one another?

   7.2. Is the evidence of benefit so poor as to discourage further study of INO in neonates or so strong that a regulatory decision regarding INO might now be possible?

8. If further study of INO is indicated in neonates with hypoxic respiratory failure...

   8.1. NINOS utilized a combined endpoint of death or initiation of ECMO within 120 days. Studies INO-01 and INO-02 utilized a combined endpoint of death, initiation of ECMO, abnormal neurological sequelae, or bronchopulmonary dysplasia within 28 days.

      8.1.1. Are these the most appropriate endpoints for further study?

      8.1.2. Is mortality alone an appropriate endpoint?

   8.2. Should other aspects of ventilatory support (e.g., use of surfactant and high-frequency oscillatory ventilation) be controlled in subsequent studies? If so, should these factors be controlled...

      - ...by stratification?
      - ...by exclusion?
      - ...by factorial design?

9. Based on the brief description of results of studies of INO in adult respiratory distress (ARDS), what evidence was there in favor of a benefit of treatment?

   9.1. Did these trials find evidence for the same benefit or were these trials otherwise supportive of one another?

   9.2. Is the evidence of benefit so poor as to discourage further study of INO in ARDS or so strong that a regulatory decision regarding INO might now be possible?

10. For ARDS, the Division has supported a principal endpoint of "time alive and off respiratory support up to 120 days". If further study of INO is indicated in ARDS, is this the most appropriate endpoint?

11. Most current INDs for INO are for single-center, baseline-controlled, descriptive studies in adults, children, and neonates. Should the Division be more restrictive? Why?

Questions

tirofiban

10 April 1998

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

Tirofiban (AGGRASTAT®, Merck) inhibits binding of fibrinogen to the platelet GP IIb/IIIa receptor, thereby inhibiting platelet aggregation and clotting. In this respect, it is similar to eptifibatide (INTEGRILIN®, COR Therapeutics), which you discussed at the meeting of 28 January. Merck proposes that tirofiban be approved for use, in combination with heparin, to prevent cardiac ischemic events in patients with acute coronary syndrome and non-Q-wave myocardial infarction.

The three major clinical trials were called RESTORE, PRISM, and PRISM-PLUS.

The studied tirofiban regimens were

Regimens Used in the Tirofiban Trials

	loading dose		maintenance infusion	
trial	µg/kg	given over	µg/kg/min	duration
PRISM	18	30 min	0.15	48 h
PRISM-PLUS				
T and placebo	18	30 min	0.15	48–108 h
T and heparin	12	30 min	0.10	48–108 h
RESTORE	10	3 min	0.15	36 h

1. Do these regimens have the same effects on platelet aggregation?

2. Can you describe the time course of platelet-aggregation inhibition when tirofiban is administered according to any of these regimens?

The **PRISM** trial was a 3232-patient, randomized, double-blind, heparin-controlled trial of tirofiban in patients with acute coronary syndrome. All patients received aspirin (300–325 mg, 24 hours before start of the study drug infusion and again 24 and 48 hours later; and thereafter at daily doses of 80–325 mg). For the 48 hours starting with the start of infusion of study drug, patients were to undergo catheterization only if they had new infarctions or refractory ischemia.

The endpoint events of PRISM were deaths, nonfatal myocardial infarctions, and refractory ischemia within 48 hours of the start of the study infusion. The protocol-specified primary analysis was performed at 48 hours, but later analyses were also performed, with the results shown on the next page.

3. Did all three components of PRISM's endpoint contribute to these results?

Results of PRISM

	placebo tirofiban	heparin placebo	P
patients	1616	1616	
events **at 2 days**	**61**	**91**	**0.014**
at 7 days	166	182	0.370
at 30 days	257	276	0.380

4. Viewed in isolation, how persuasive is PRISM as to the utility of tirofiban in patients with acute coronary syndrome? For example, you might believe that the results of PRISM are

4(A). probably attributable to the play of chance.

4(B). plausible, but weaker than those of the typical successful trial.

4(C). as persuasive as the findings of a typical successful trial.

4(D). more persuasive than the findings of a typical successful trial, but less persuasive than those replicated in two or more typical successful trials.

4(E). as persuasive as a package of two or more typical successful trials.

The **PRISM-PLUS** trial was a 1915-patient, randomized, double-blind trial comparing tirofiban, heparin, and their combination in patients with acute coronary syndrome. All patients received aspirin (300–325 mg, 30 minutes before start of the study drug infusion and again 24 and 48 hours later; and thereafter at daily doses of 80–325 mg). The tirofiban-alone arm was aborted when an interim analysis suggested to the Data Safety Monitoring Board that this arm was associated with excess mortality.

The endpoint events of PRISM-PLUS were deaths, nonfatal myocardial infarctions, and refractory ischemia within 7 days of the start of the study infusion. The protocol-specified primary analysis was performed at 7 days, but other analyses were also performed, with the results shown on the next page.

5. Did all three components of PRISM-PLUS' endpoint contribute to these results?

Results of PRISM-PLUS

		placebo tirofiban	heparin placebo	heparin tirofiban	P
patients		345	797	773	
events at	2 days	26 (8%)	62 (8%)	44 (6%)	0.073
at	**7 days**	**59 (17%)**	**143 (18%)**	**100 (13%)**	**0.004**
at	30 days	81 (23%)	178 (22%)	143 (18%)	0.039
at	180 days	105 (30%)	256 (32%)	214 (28%)	0.024

6. Viewed in isolation, how persuasive is PRISM-PLUS as to the utility of tirofiban in patients with acute coronary syndrome? For example, you might believe that the results of PRISM-PLUS are

6(A). probably attributable to the play of chance.

6(B). plausible, but weaker than those of the typical successful trial.

6(C). as persuasive as the findings of a typical successful trial.

6(D). more persuasive than the findings of a typical successful trial, but less persuasive than those replicated in two or more typical successful trials.

6(E). as persuasive as a package of two or more typical successful trials.

The **RESTORE** trial was a 2141-patient, randomized, double-blind, placebo-controlled trial of tirofiban in patients who had been hospitalized because of coronary ischemia (unstable angina or acute infarction) and who had then been scheduled (for any reason) to undergo PTCA±atherectomy within 72 hours of the onset of symptoms. The loading dose of study drug was started when the guide wire was over the (first) lesion and the operator was ready to inflate the balloon. After the loading dose had been administered, the procedure was completed and a maintenance infusion was continued for 36 hours. All patients received heparin (titrated to an activated clotting time of 300–400 seconds) before the procedure and aspirin (325 mg within 24 hours before the procedure and again 24 hours later).

The endpoint events of RESTORE were deaths, nonfatal myocardial infarctions, and repeat interventions (bypass grafts, repeat percutaneous interventions, and stents) for recurrent ischemia. The protocol-specified primary

analysis was performed at 30 days, but other analyses were also performed, with the following results:

Results of RESTORE

		heparin tirofiban	heparin placebo	P
patients		1071	1070	
events at	2 days	58	93	0.003
at	7 days	81	111	0.022
at	**30 days**	**110**	**130**	**0.169**
at	180 days	258	290	0.110

In addition, the sponsor has presented a non-protocol analysis showing that tirofiban was associated with a significant reduction in the 30-day count of *urgent* revascularization procedures.

7. Did all three components of RESTORE's endpoint contribute to these results?

8. Viewed in isolation, how persuasive is RESTORE as to the utility of tirofiban in patients undergoing angioplasty/atherectomy in the setting of acute coronary syndrome? For example, you might believe that the results of RESTORE are

8(A). probably attributable to the play of chance.

8(B). plausible, but weaker than those of the typical successful trial.

8(C). as persuasive as the findings of a typical successful trial.

8(D). more persuasive than the findings of a typical successful trial, but less persuasive than those replicated in two or more typical successful trials.

8(E). as persuasive as a package of two or more typical successful trials.

9. RESTORE was similar to the IMPACT II trial that you discussed in January. As you will recall, the 30-day event counts in IMPACT II were 151 in the placebo group and 124 in the low-dose eptifibatide group. Although the IMPACT II results were nominally significant ($P=0.041$), they are not statistically distinguishable ($\chi^2 \approx 0.03$, $P>0.8$) from the 30-day results of RESTORE. Did RESTORE and IMPACT II find the same phenomenon? If not, what was different?

10. How would you characterize the incidence and severity of bleeding in the tirofiban trials? To what extent was the bleeding attributable to the concomitant use of aspirin ± heparin?

11. The Division has routinely advised sponsors that "refractory ischemia" is so subjective that it is not the appropriate endpoint, or an appropriate driving component of a combined endpoint, for a trial meant to stand on its own. Should the Division continue to give this advice?

12. Should tirofiban be approved for treatment of patients with acute coronary syndrome? If so, what regimen should be recommended? Should tirofiban be recommended for use as an adjunct to heparin, as an indifferent alternative to heparin, or as preferable to heparin?

13. Should tirofiban be approved for treatment of patients with acute coronary syndrome who are about to undergo PTCA? If so, what regimen should be recommended? Should tirofiban be recommended for use as an adjunct to heparin, as an indifferent alternative to heparin, or as preferable to heparin?

14. Should tirofiban be approved for treatment of all patients who are about to undergo PTCA? If so, what regimen should be recommended? Should tirofiban be recommended for use as an adjunct to heparin, as an indifferent alternative to heparin, or as preferable to heparin?

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 4/9-10/98

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

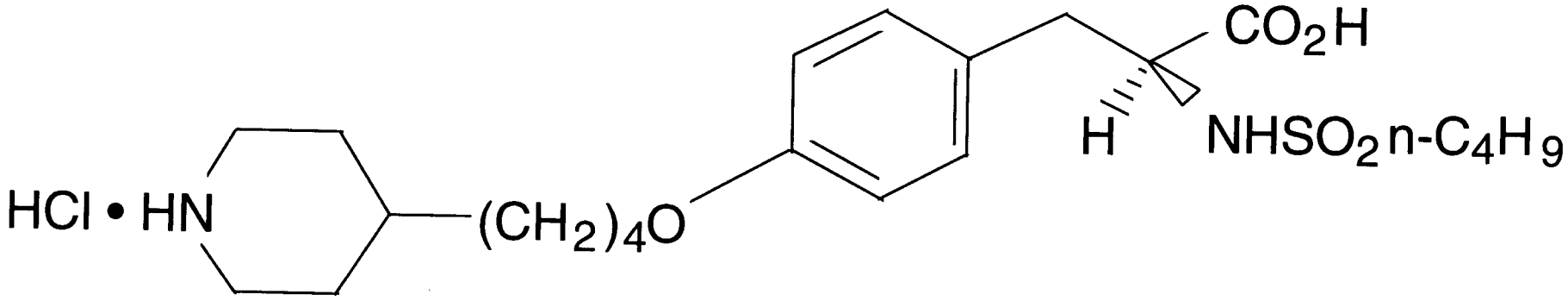
"Tirofiban, in combination with heparin, is indicated to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated."

Tirofiban Hydrochloride
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

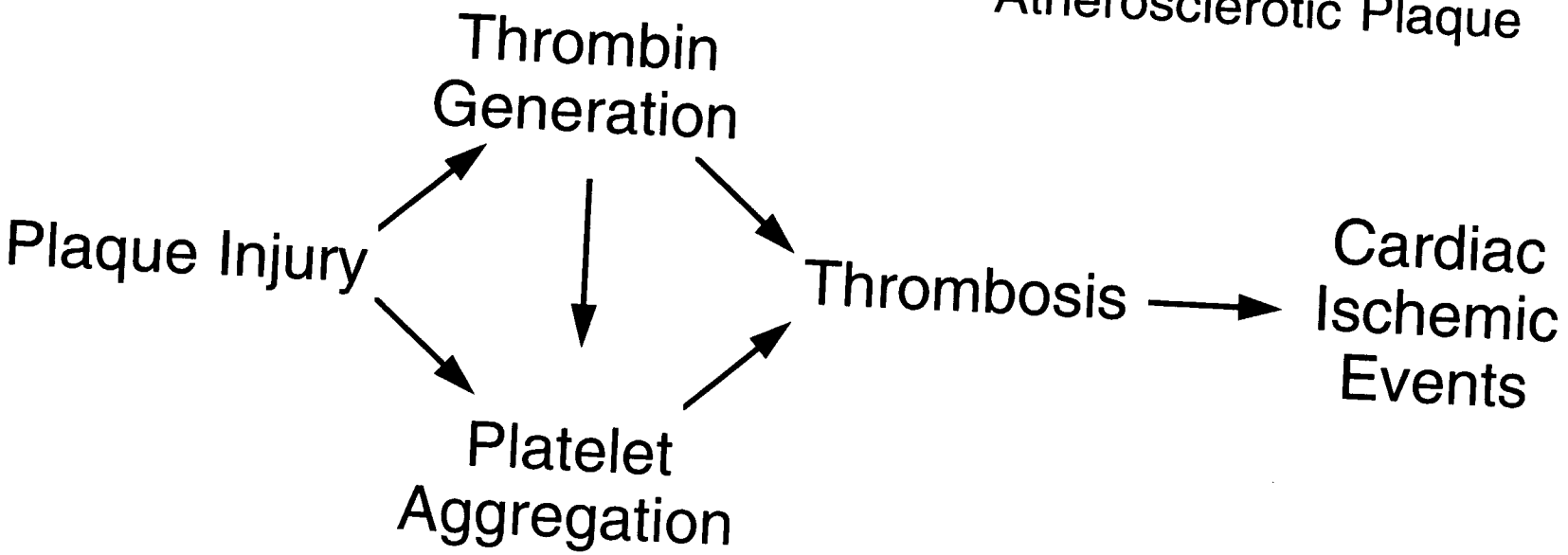
Main Presentation

Tirofiban Hydrochloride

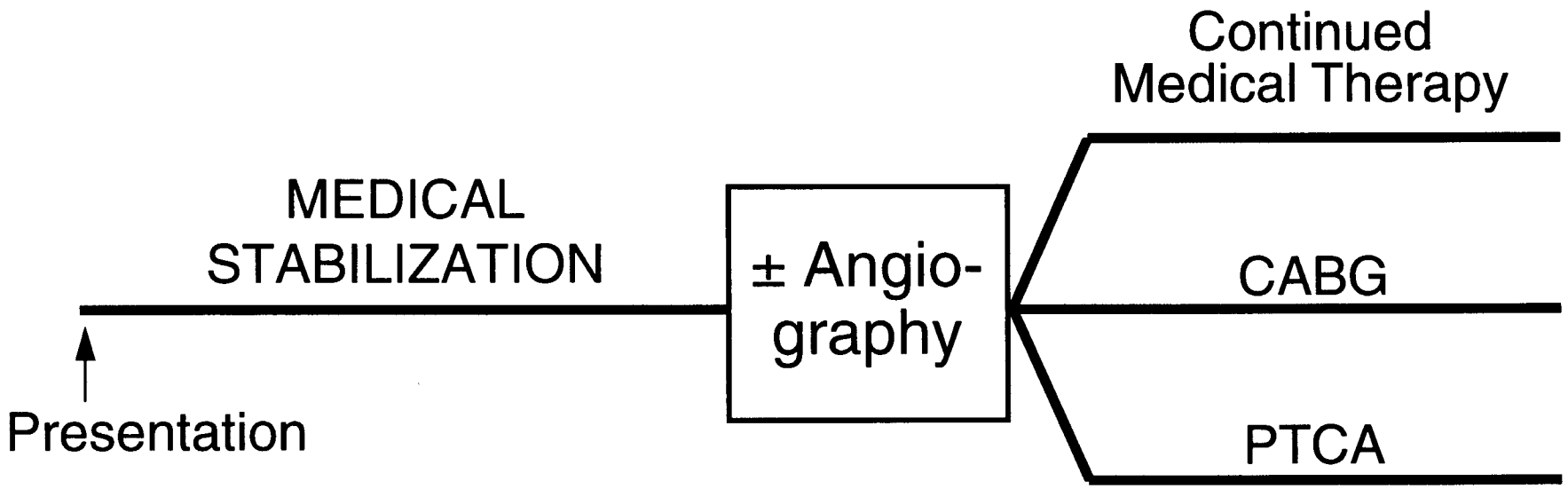


- Short-acting, intravenous agent
- Potent non-peptide inhibitor of GP IIb/IIIa
- Blocks fibrinogen binding - inhibits aggregation
- High specificity for receptor

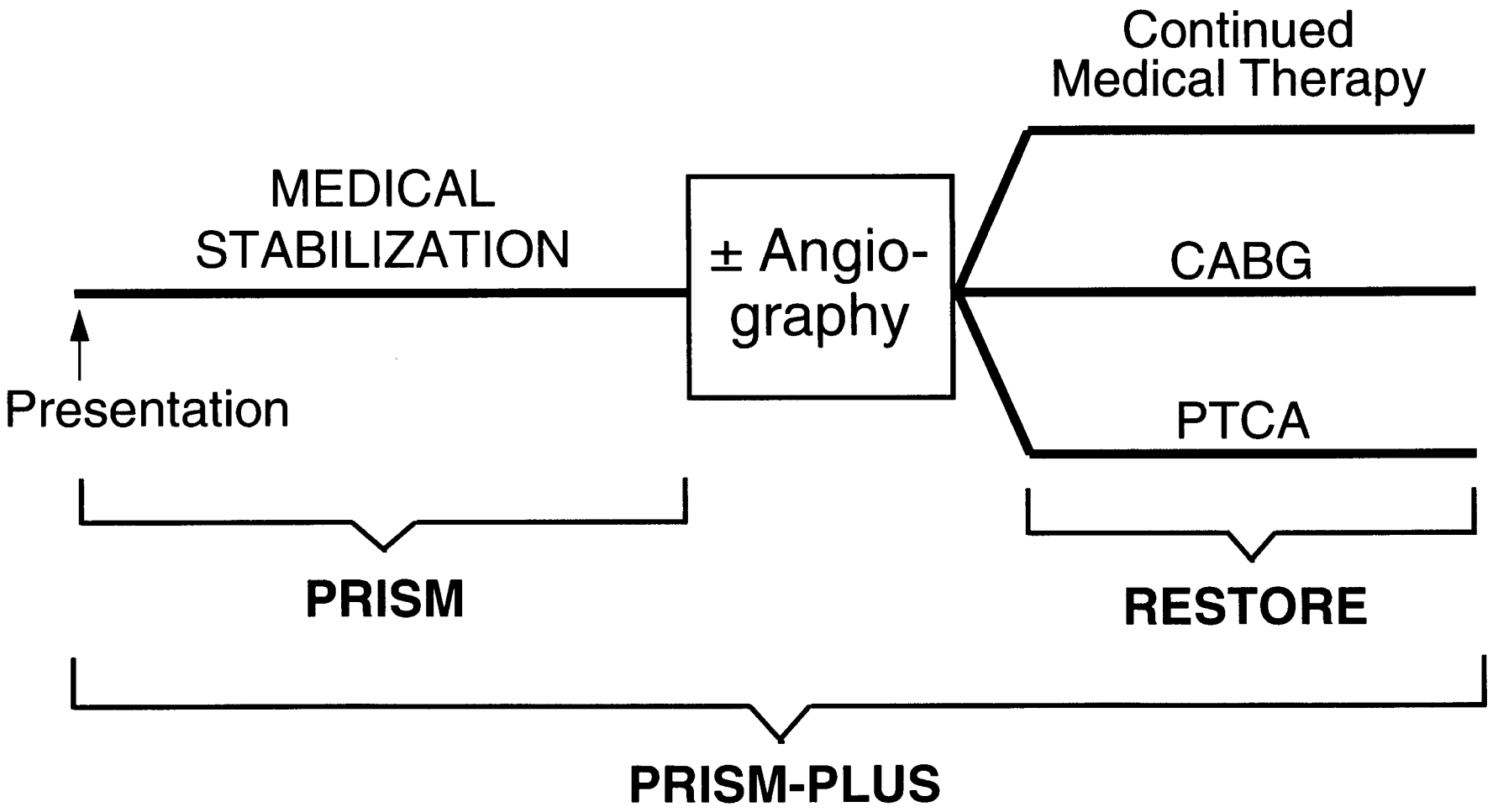
Consequences of Coronary Plaque Injury



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

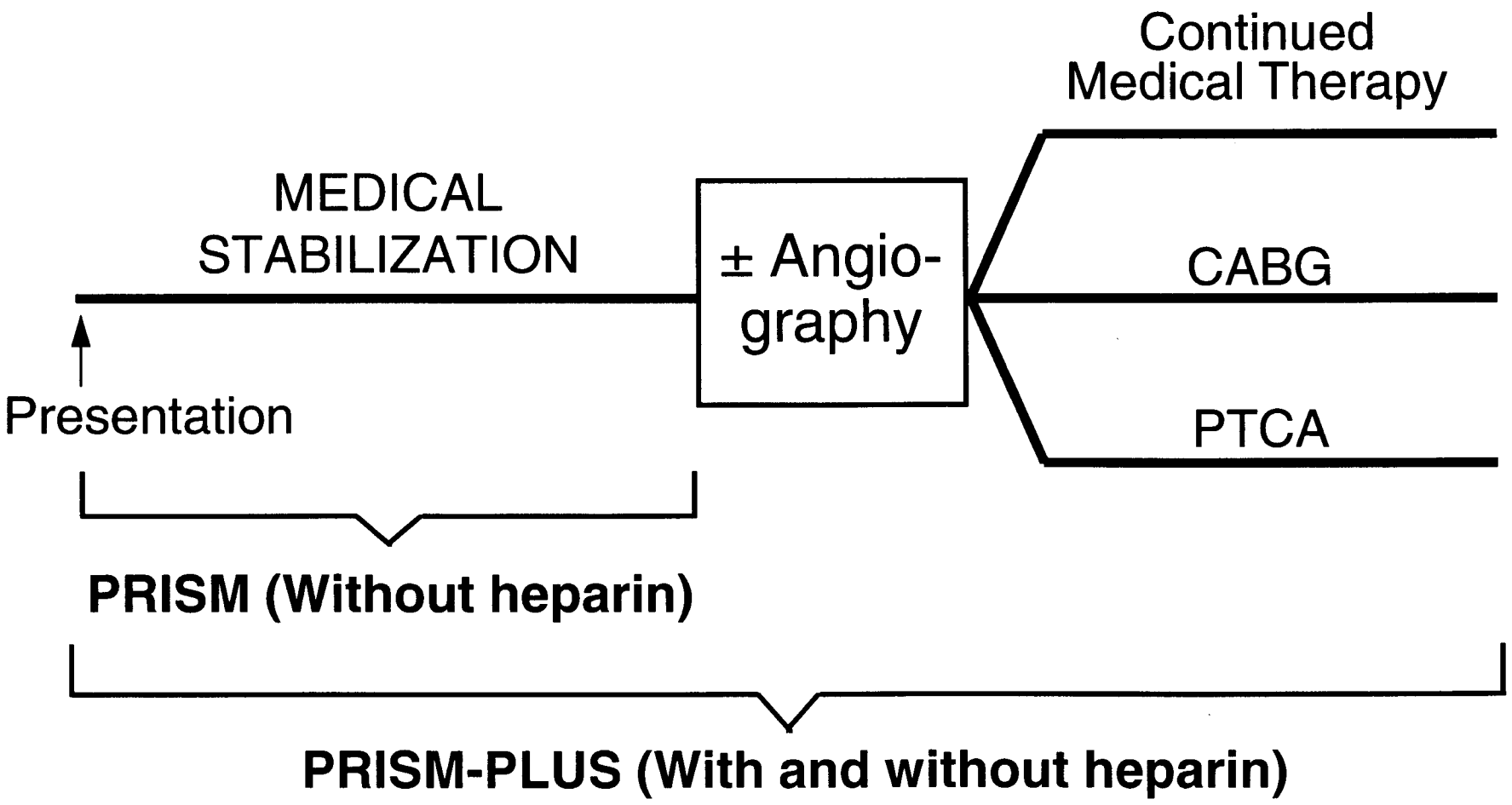
Without Heparin

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



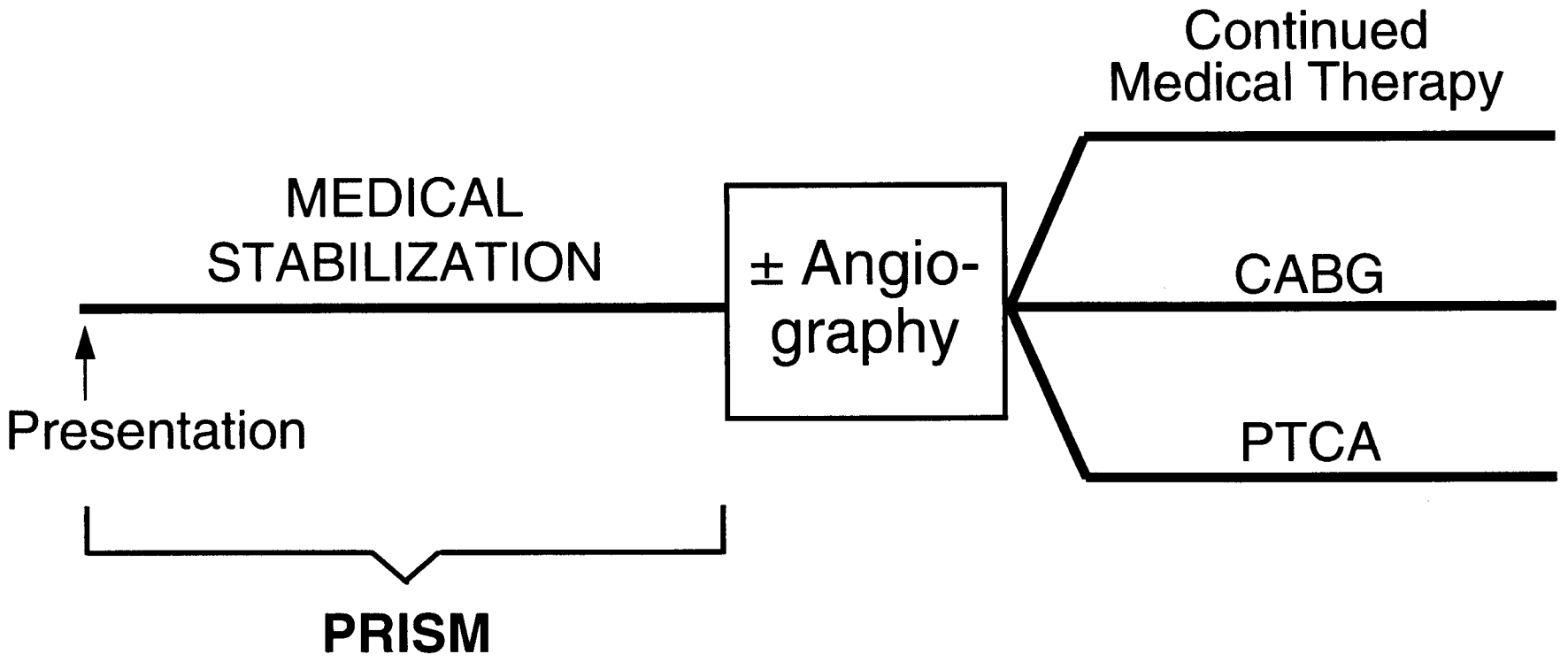
UAP / NQWMI Trials
Clinical Presentation

	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



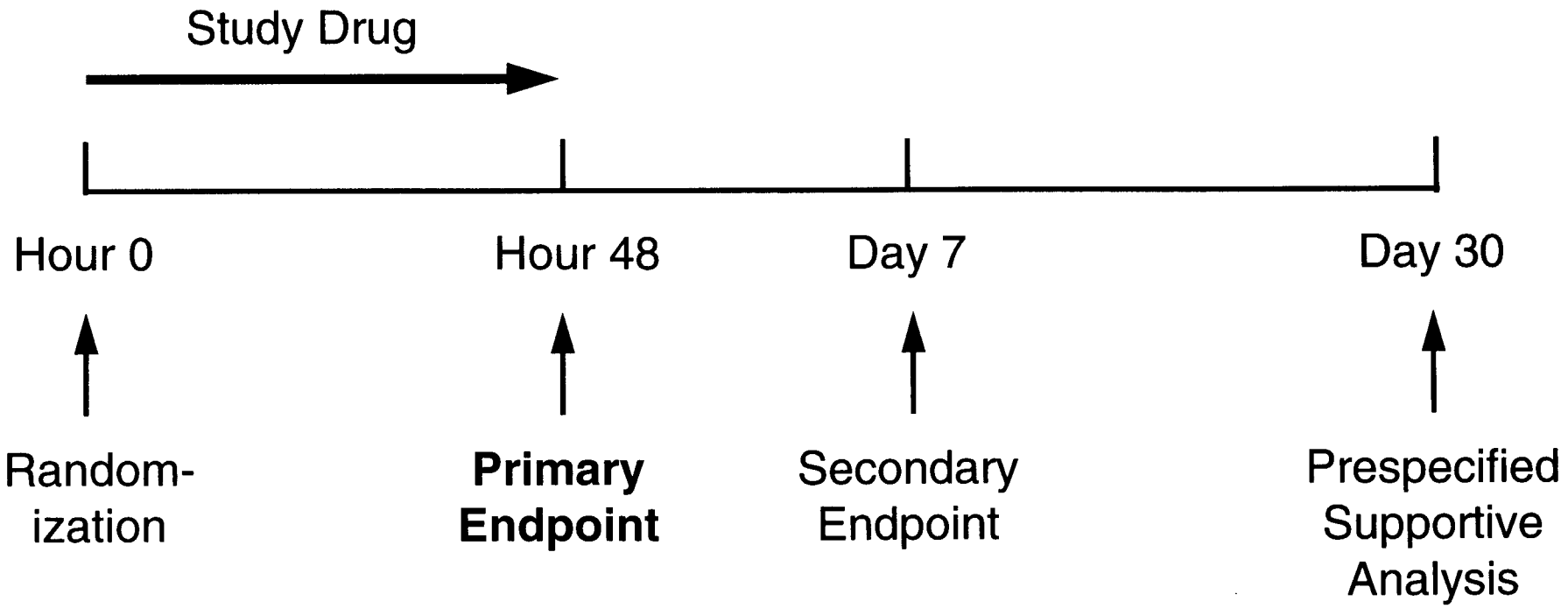
PRISM Primary Hypothesis

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

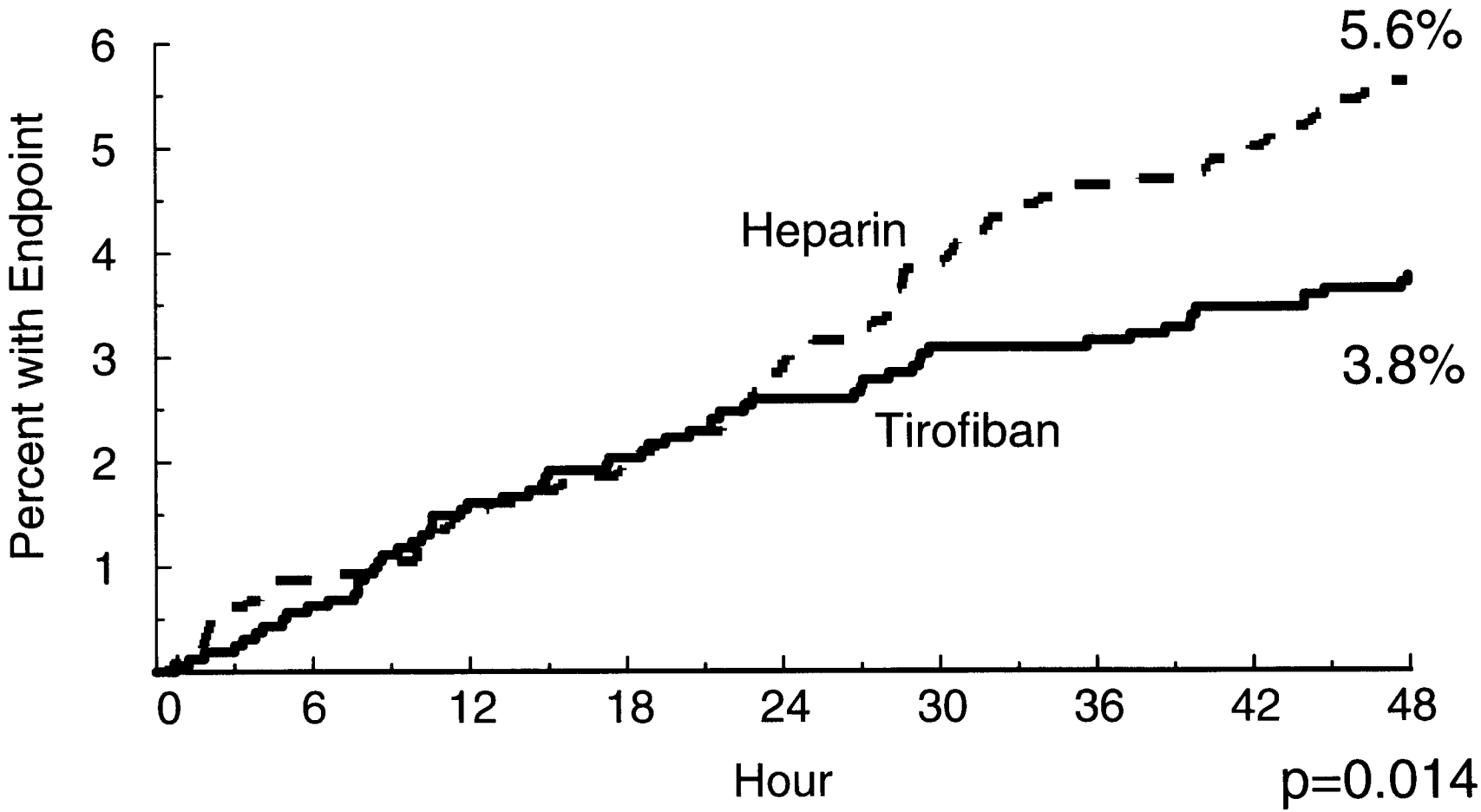
PRISM Study Design



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

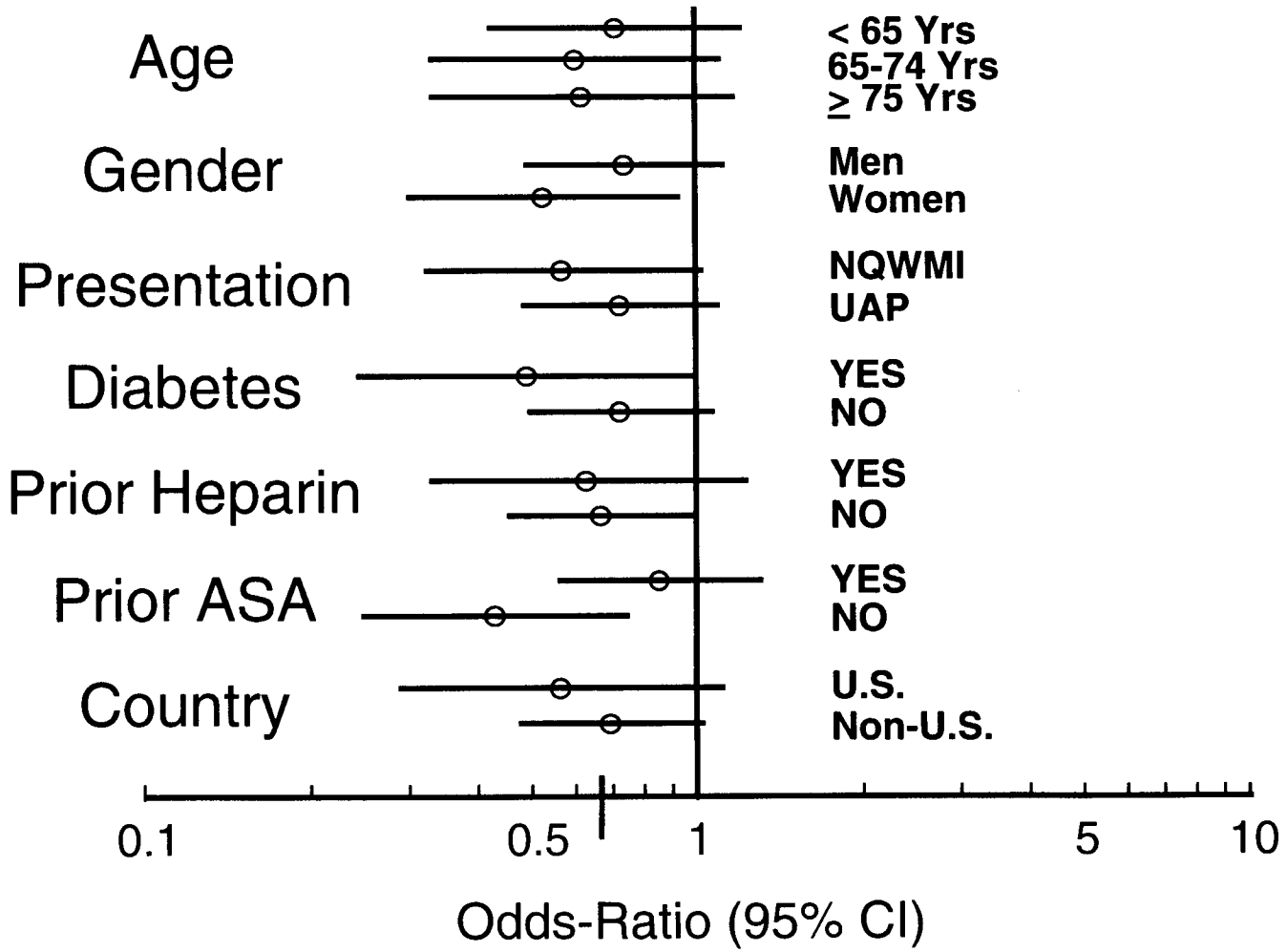
PRISM Primary Endpoint (48 Hours)



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)



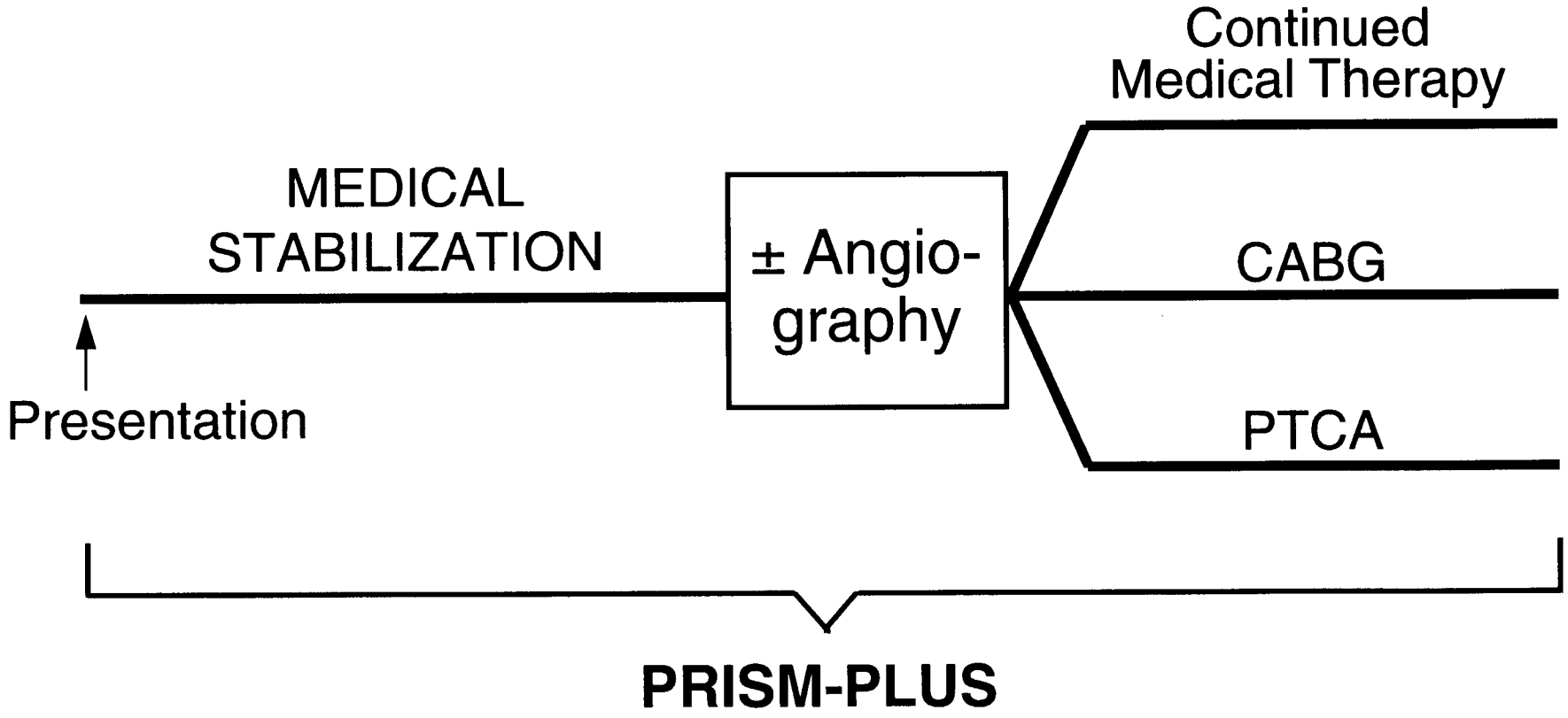
PRISM Secondary and Supportive Endpoints

	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



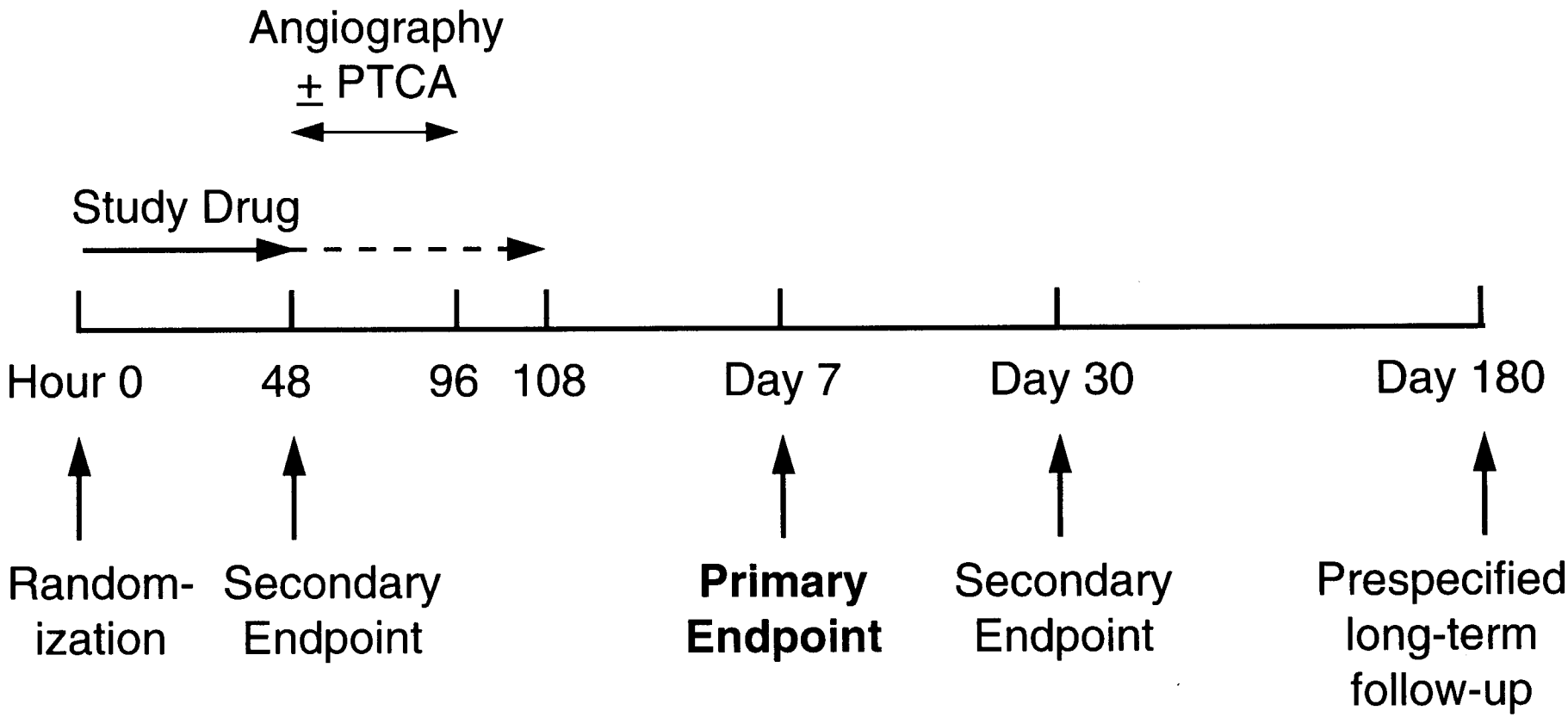
PRISM-PLUS Primary Hypothesis

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



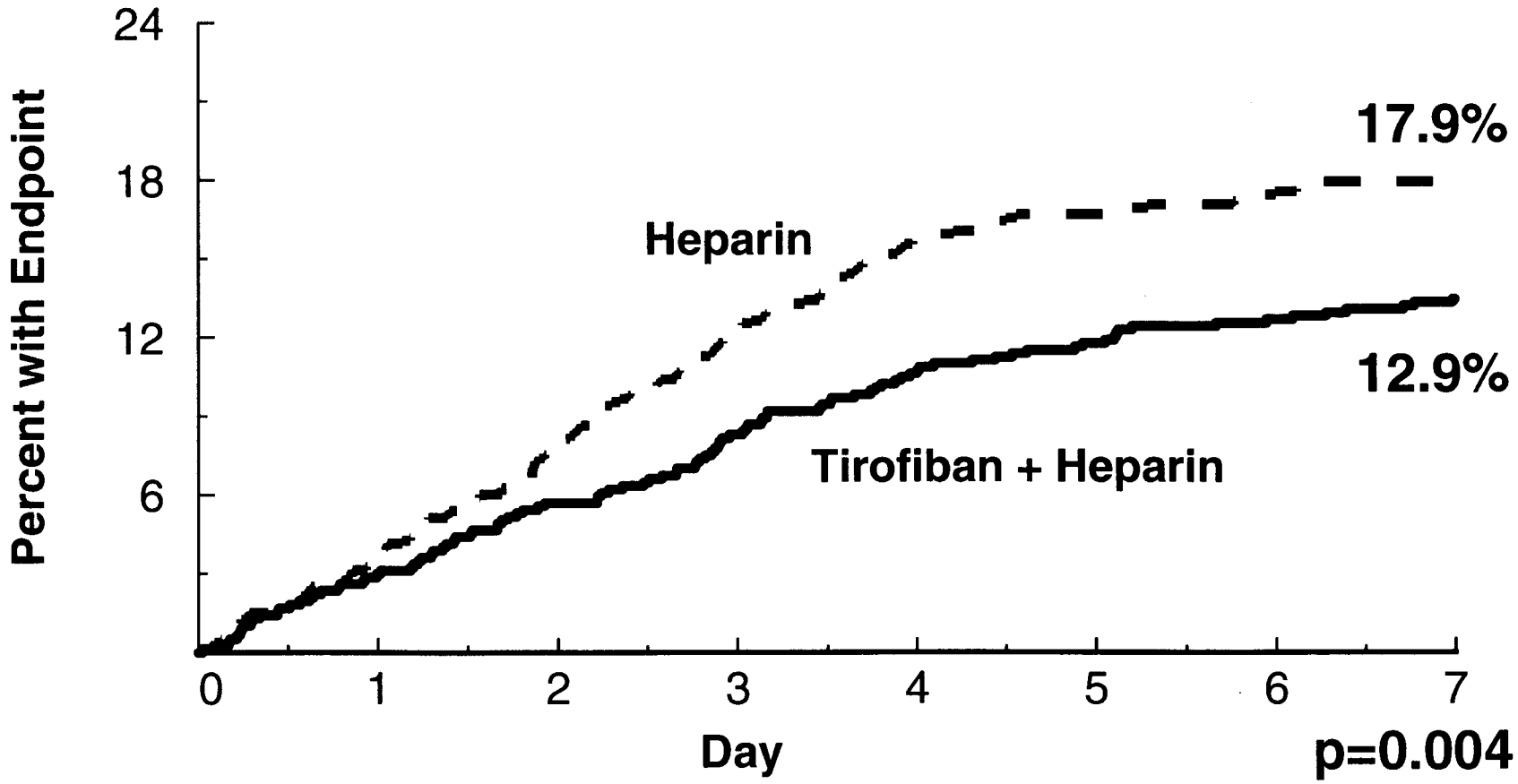
PRISM-PLUS Study Conduct

- 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

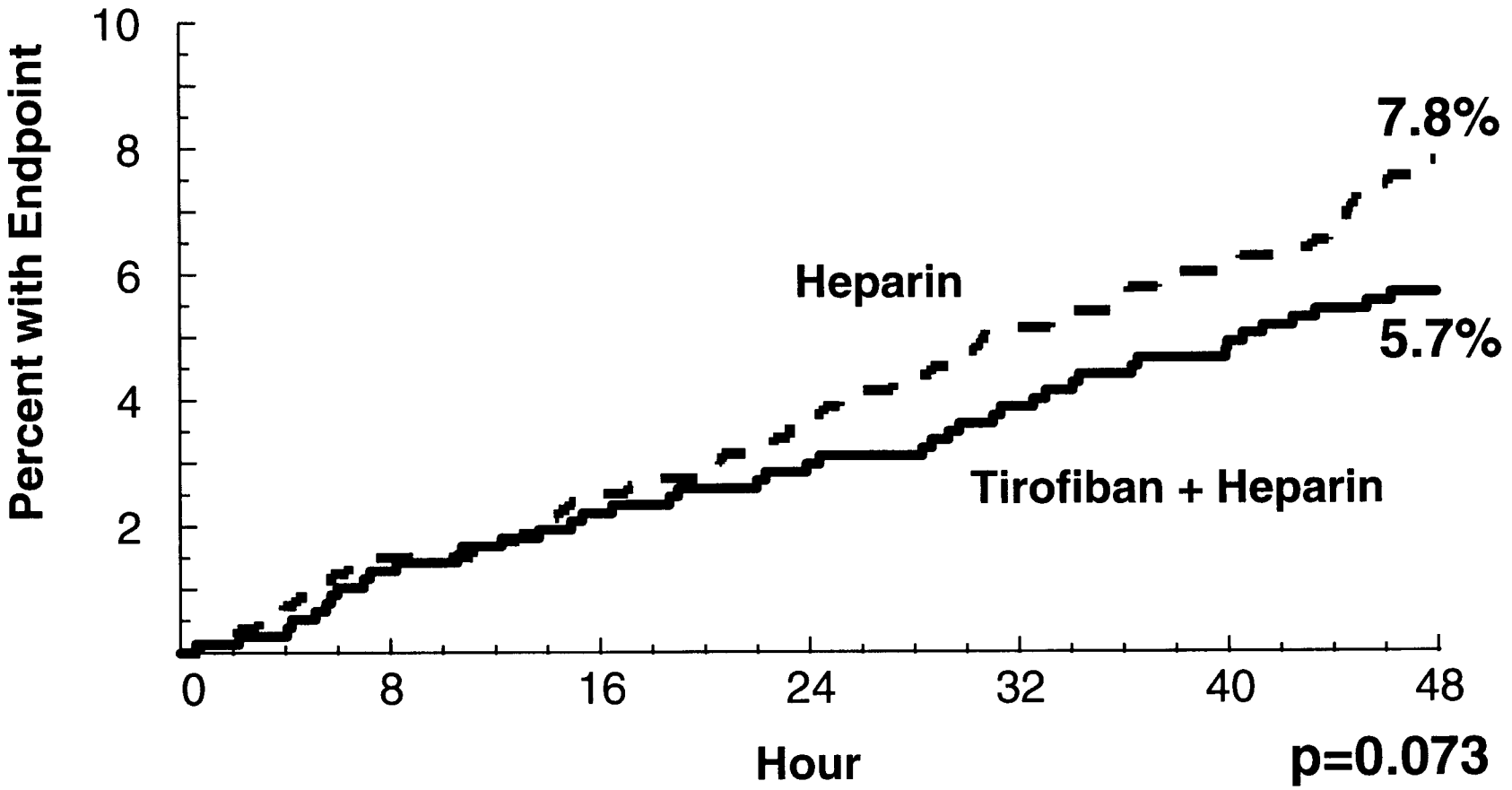
PRISM-PLUS Primary Composite Endpoint (7 Days)



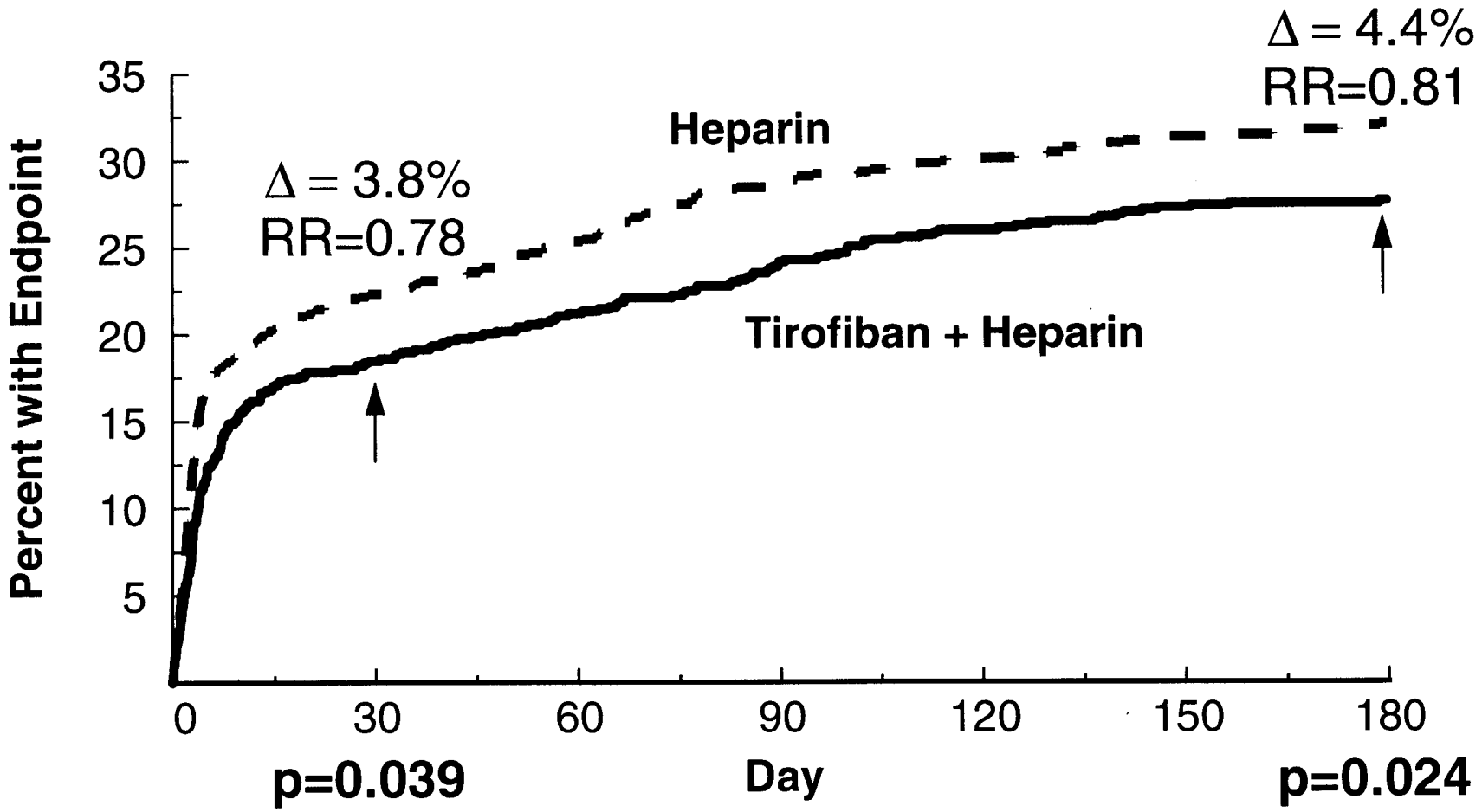
PRISM-PLUS Primary Endpoint (7 Days)

	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

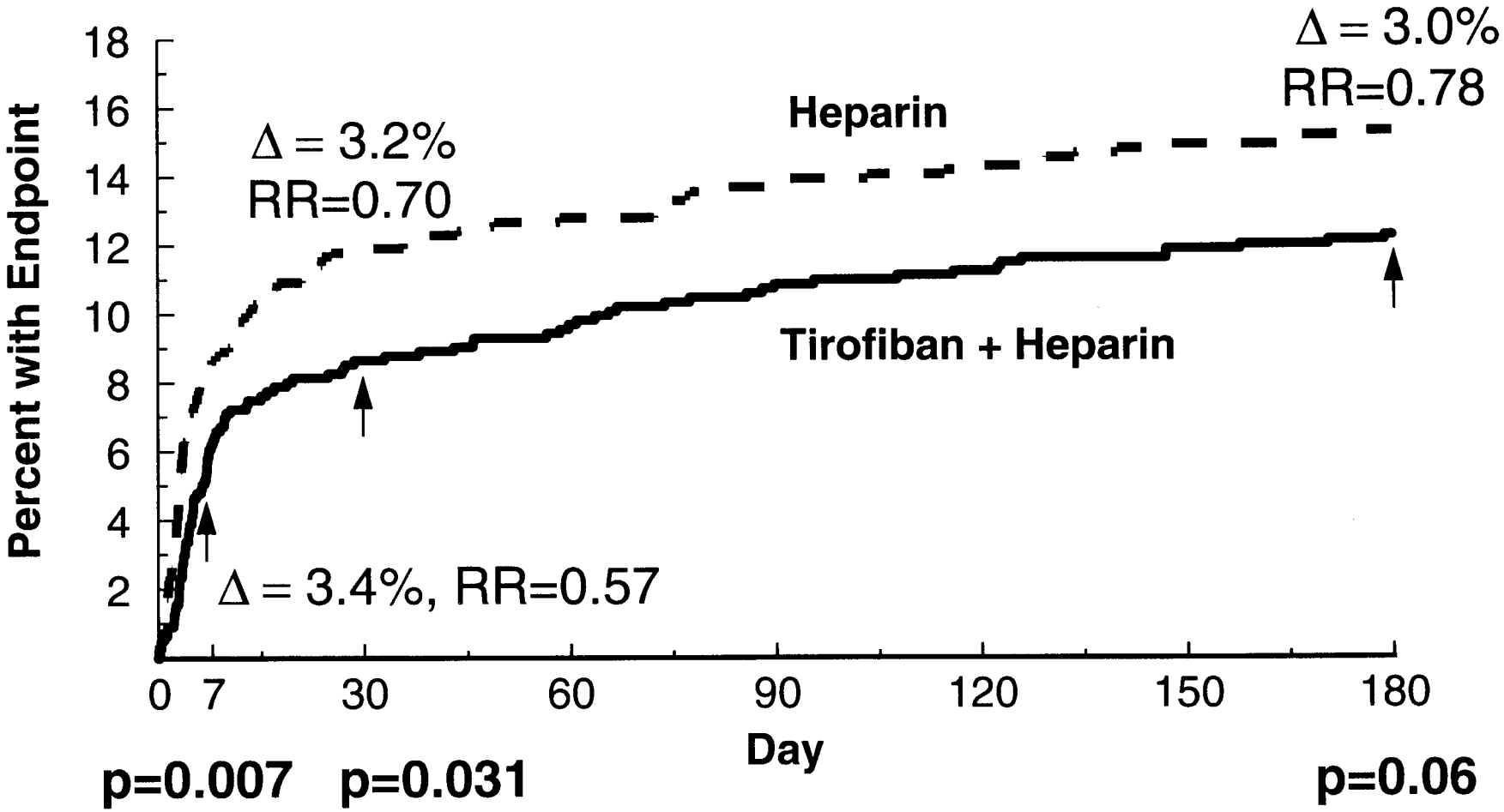
PRISM-PLUS Composite Endpoint (48 Hours)



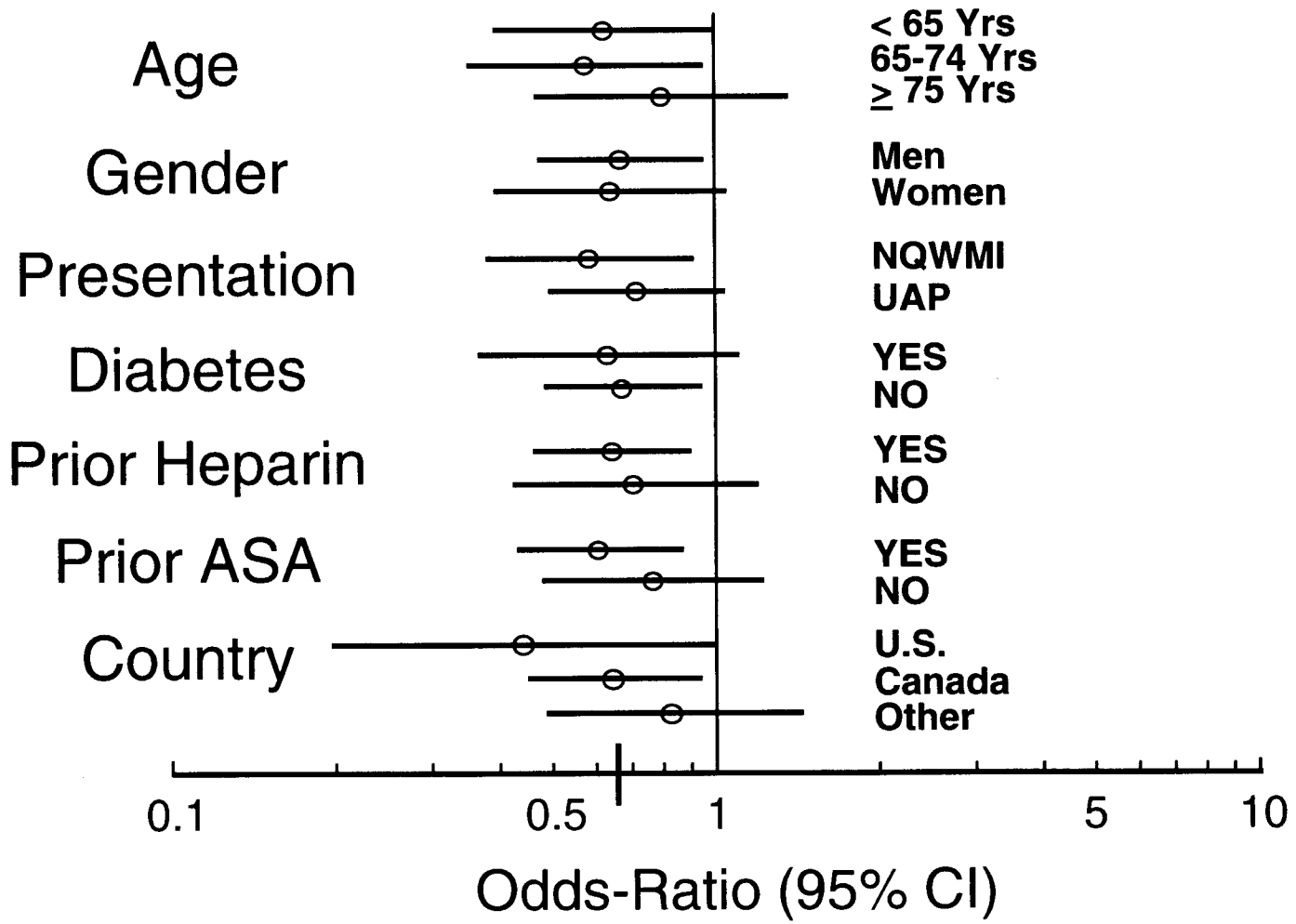
PRISM-PLUS Composite Endpoint (180 Days)



PRISM-PLUS Myocardial Infarction/Death (180 Days)



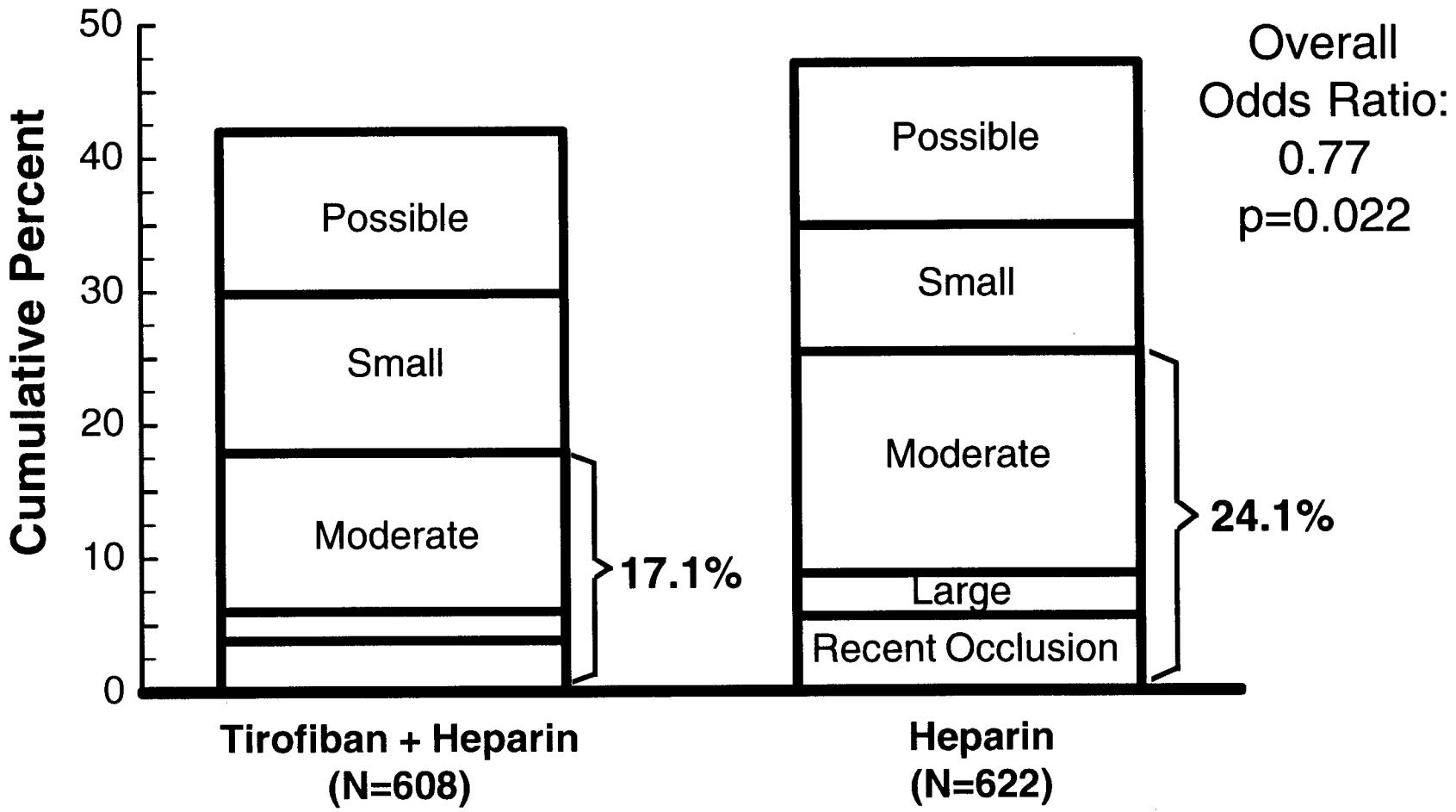
PRISM-PLUS Subgroup Outcomes (7 days)



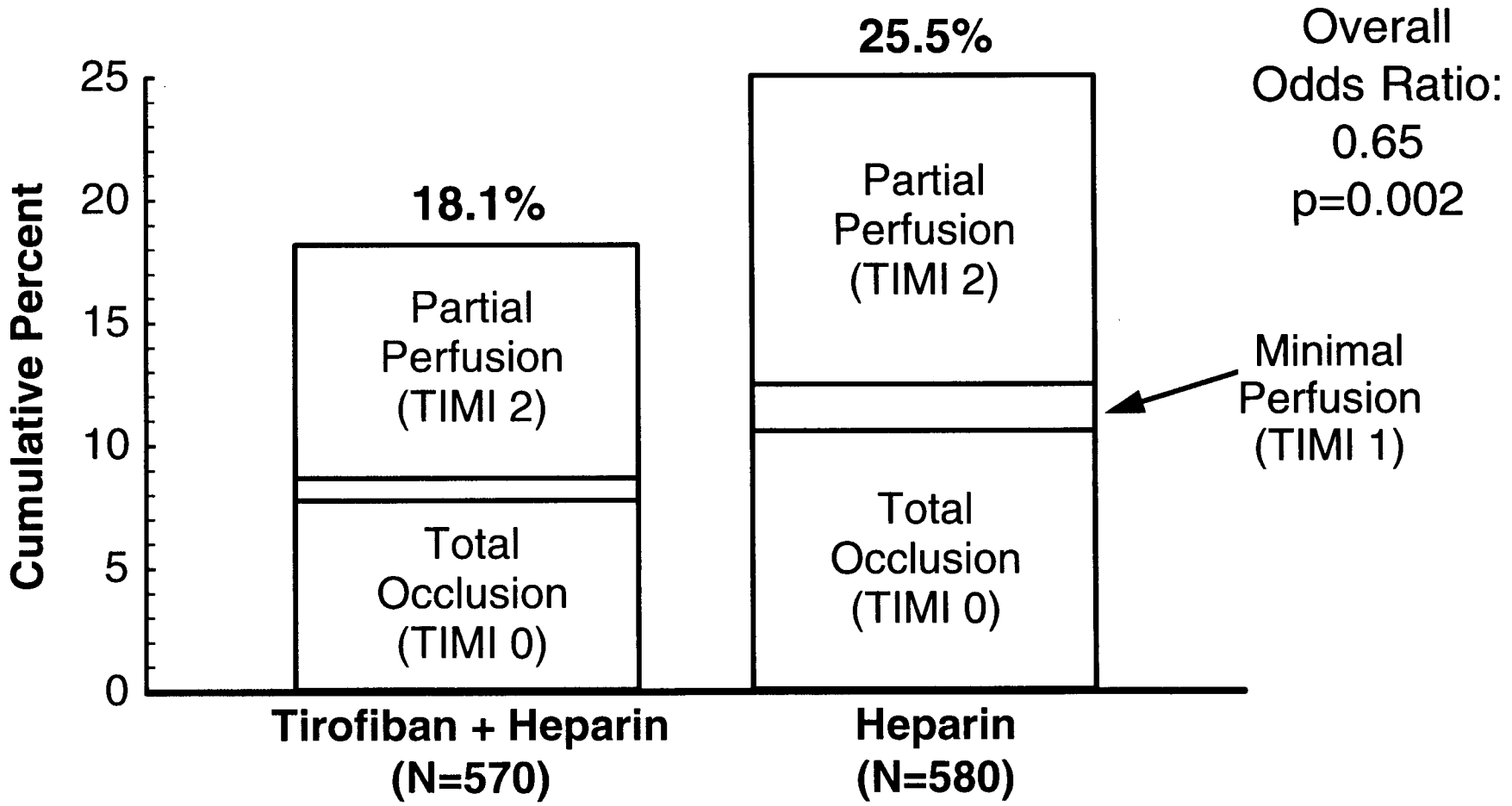
PRISM-PLUS Angiographic Substudy

- 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



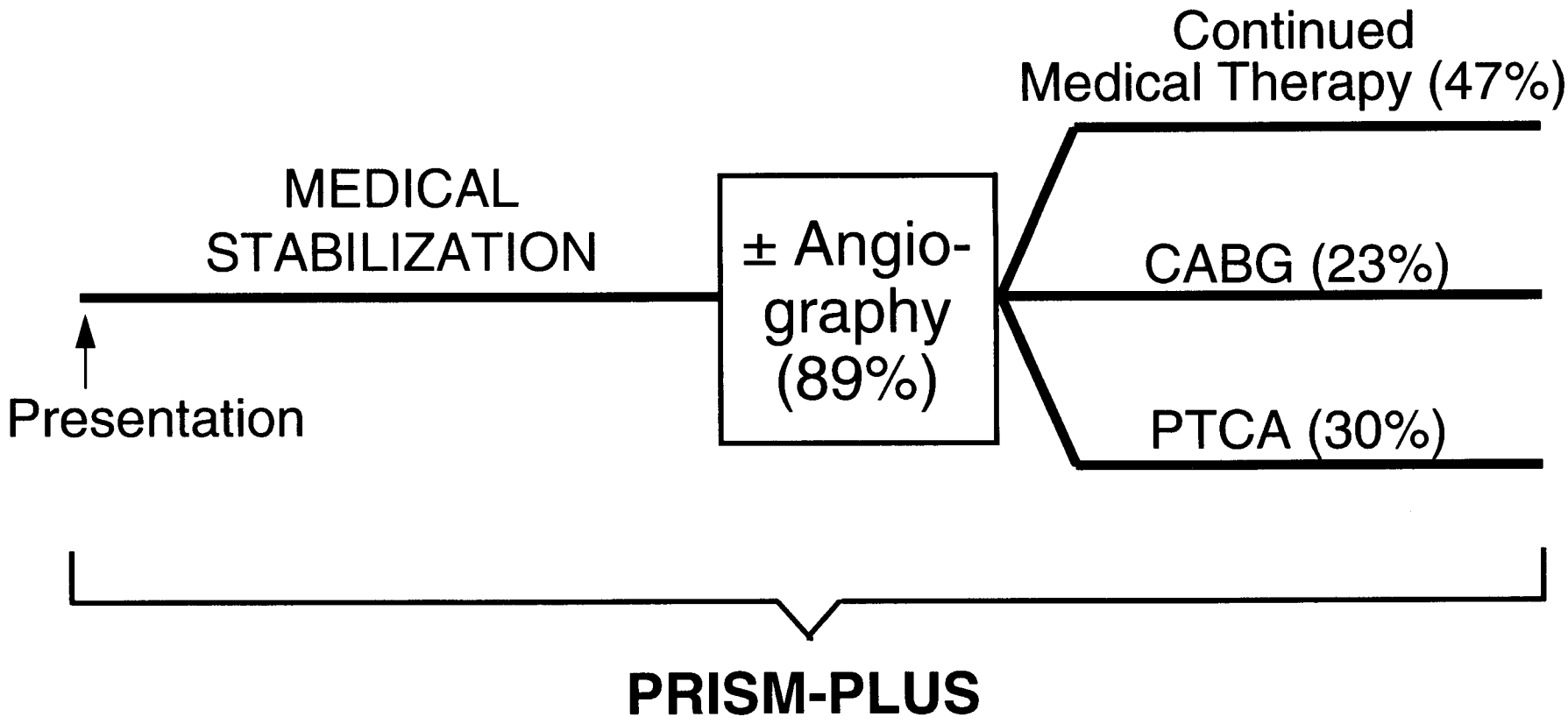
PRISM-PLUS TIMI Flow



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

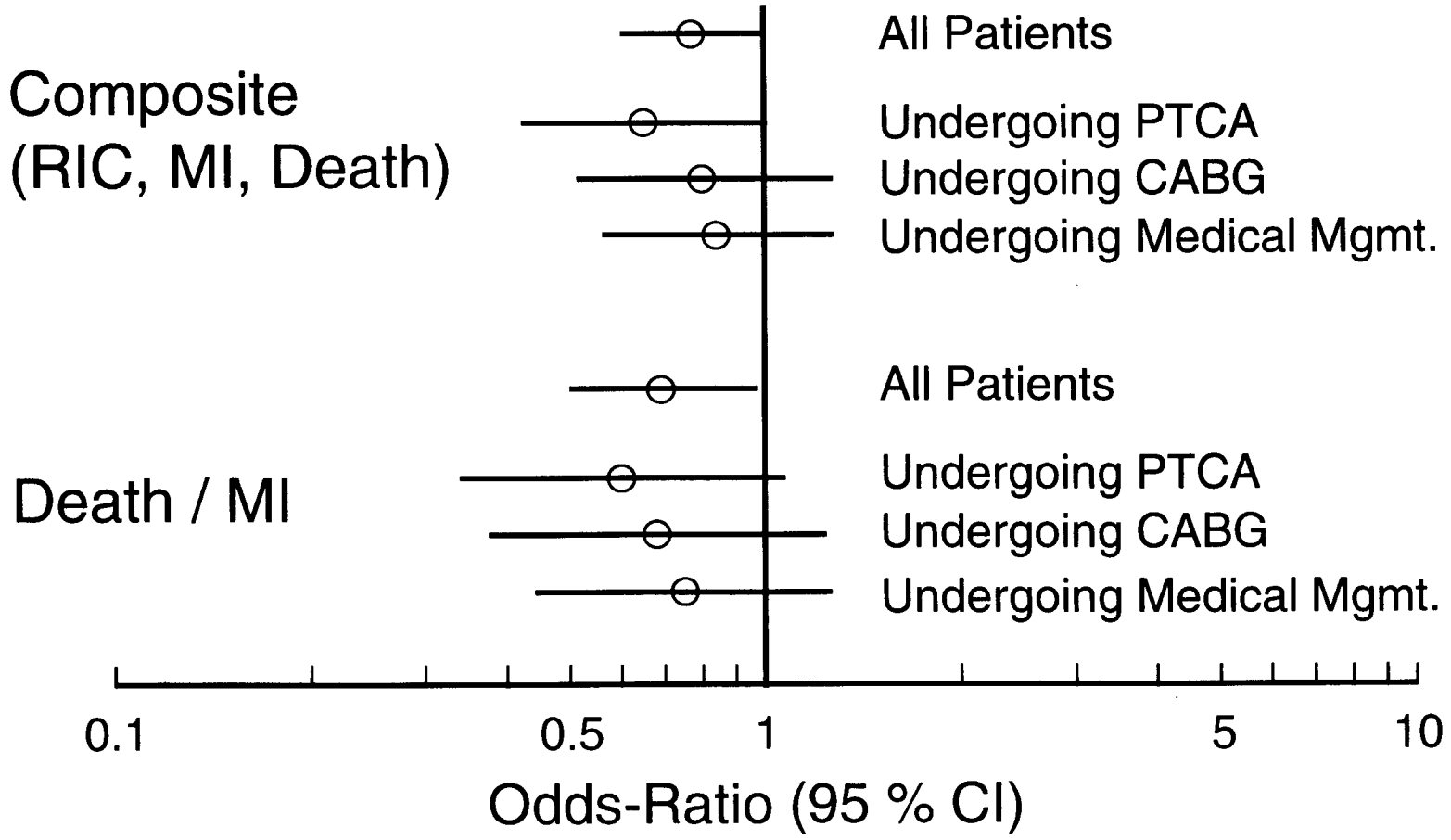
PRISM-PLUS Treatment Selections



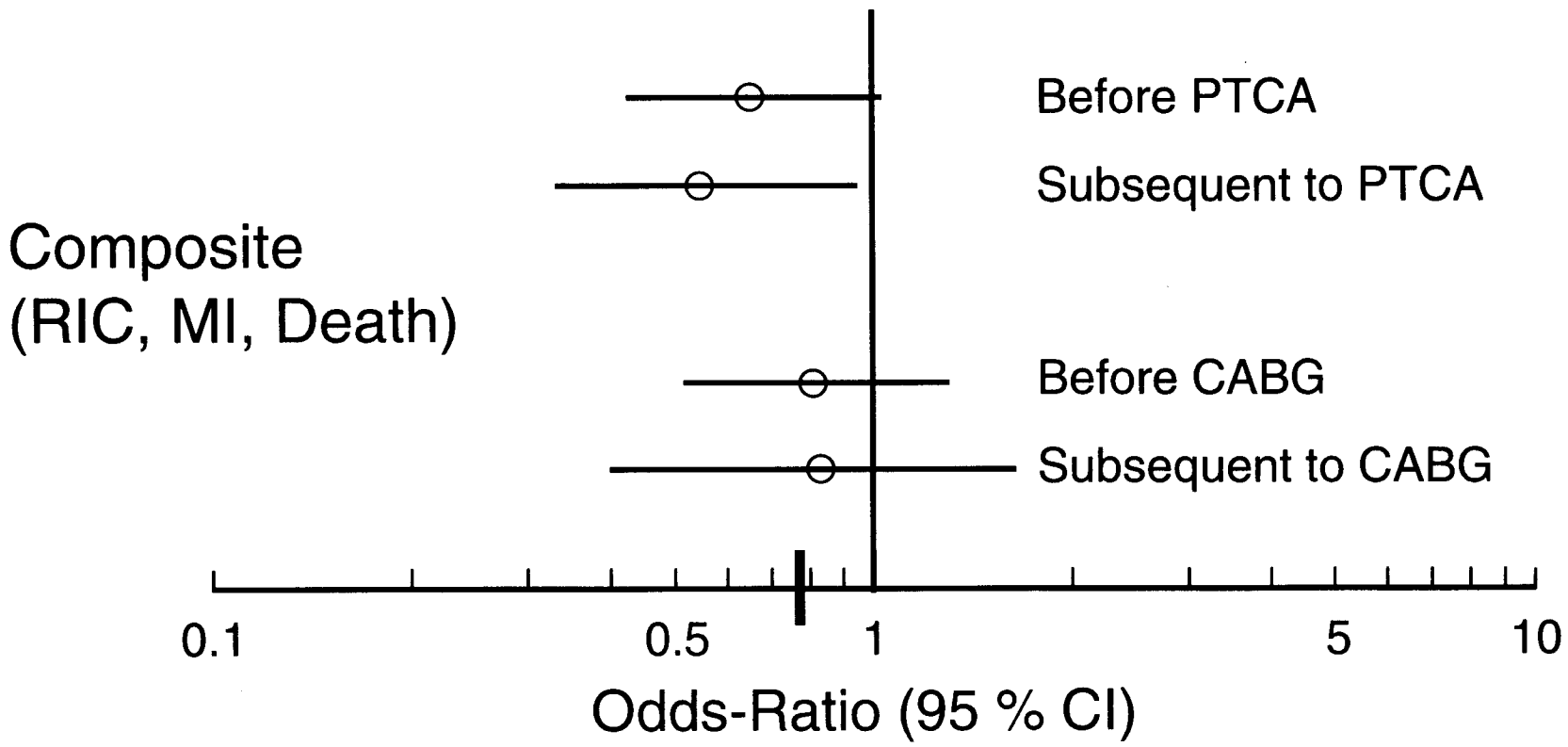
PRISM-PLUS Outcomes by Treatment Decision

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

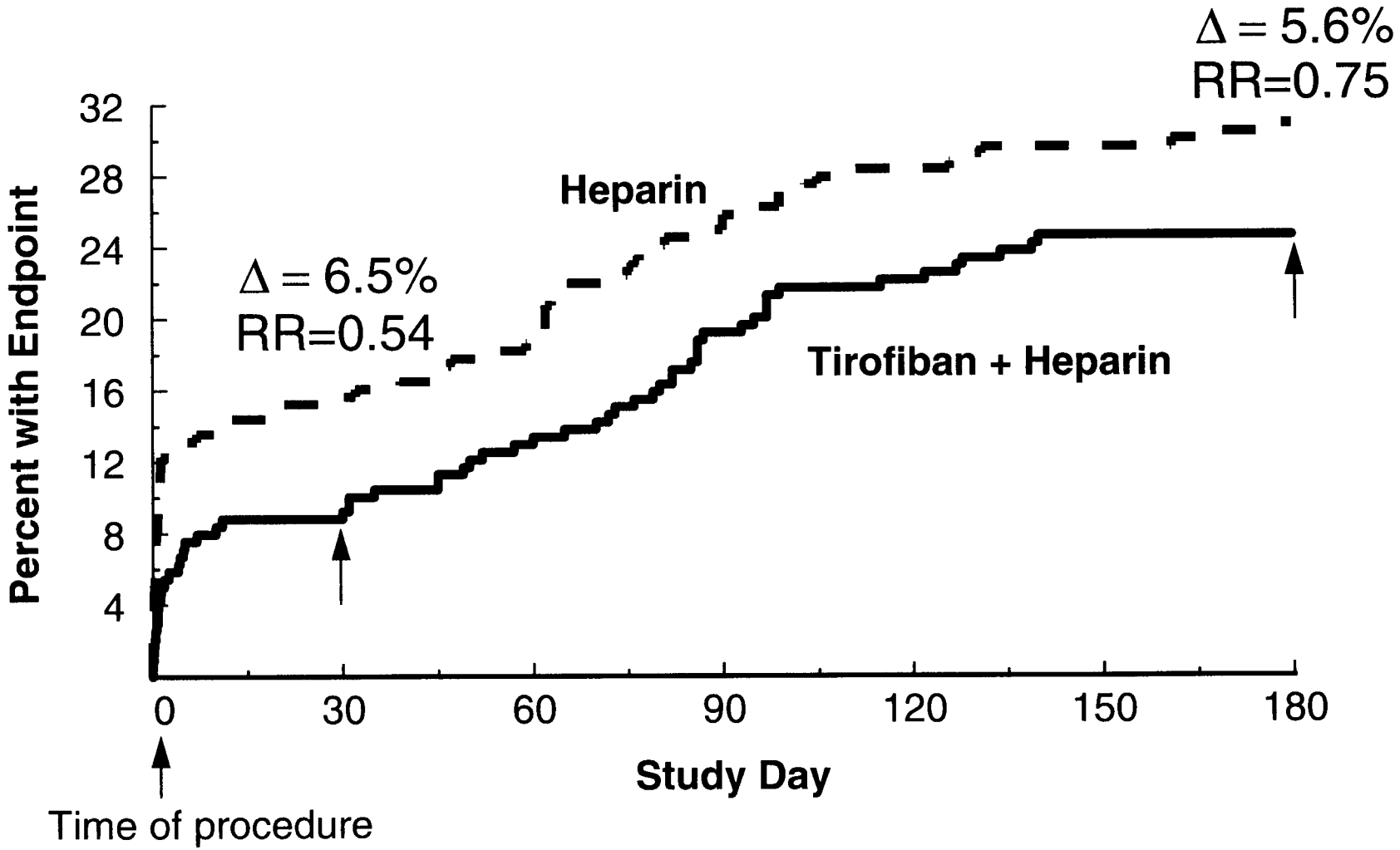
PRISM-PLUS 30-Day Endpoints in PTCA, CABG, and Medical Management Cohorts



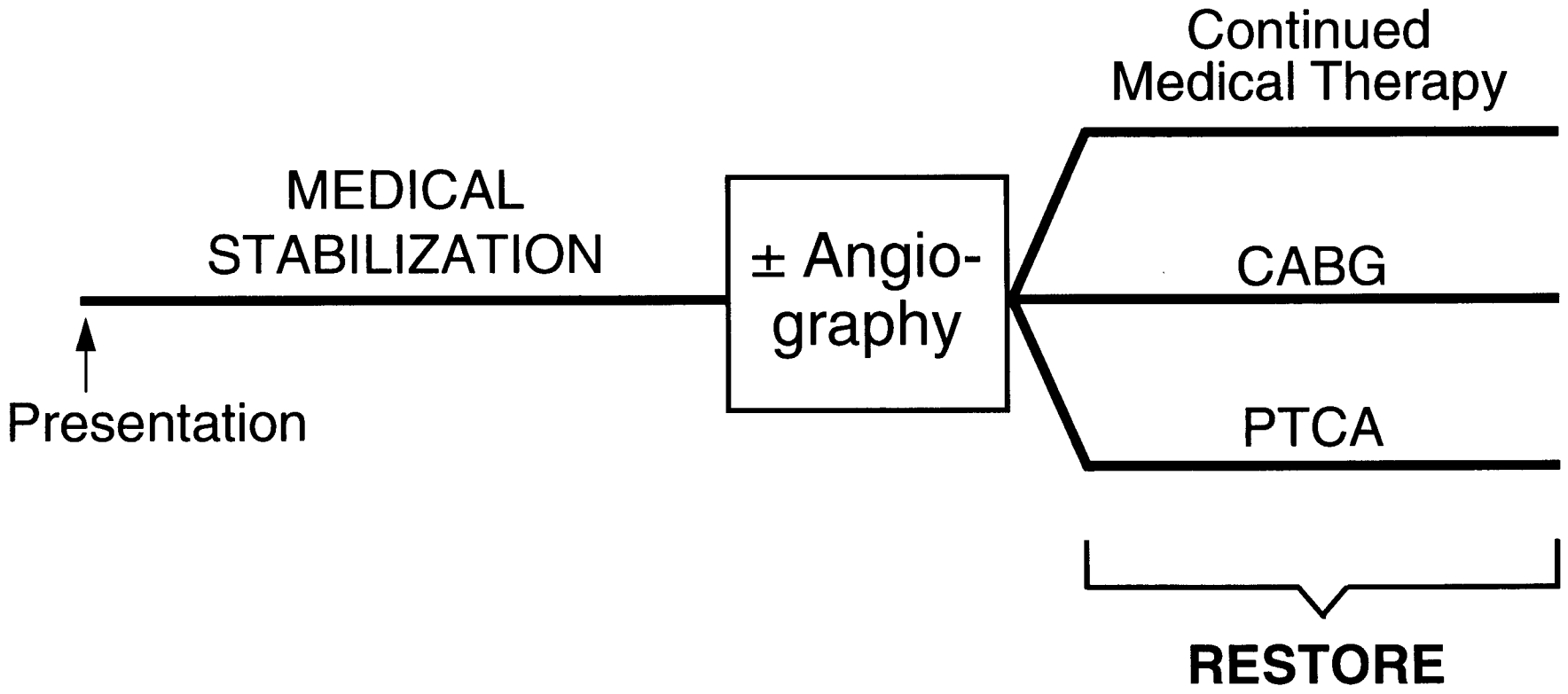
PRISM-PLUS 30-Day Endpoints in PTCA and CABG Cohorts



PRISM-PLUS Composite Endpoint in PTCA



RESTORE - Coronary Angioplasty for Acute Coronary Syndromes



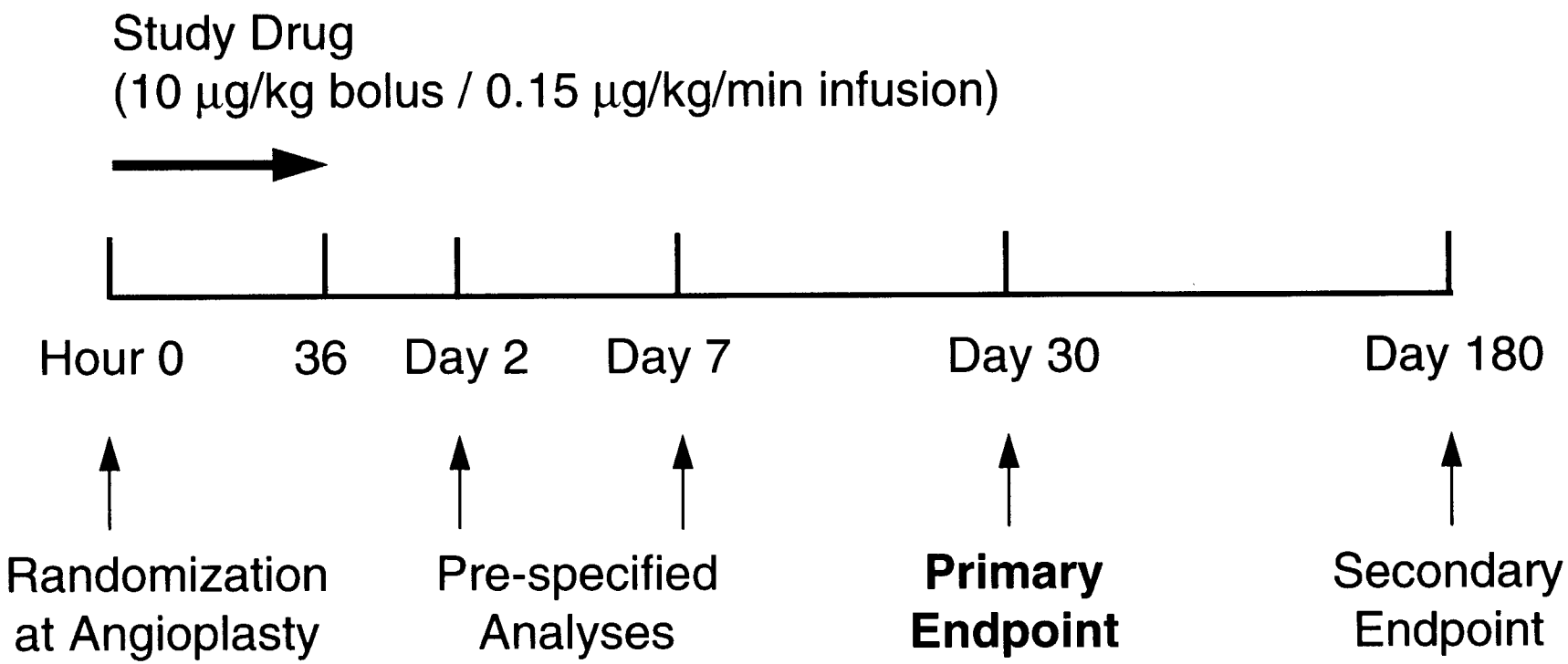
RESTORE Primary Hypothesis

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

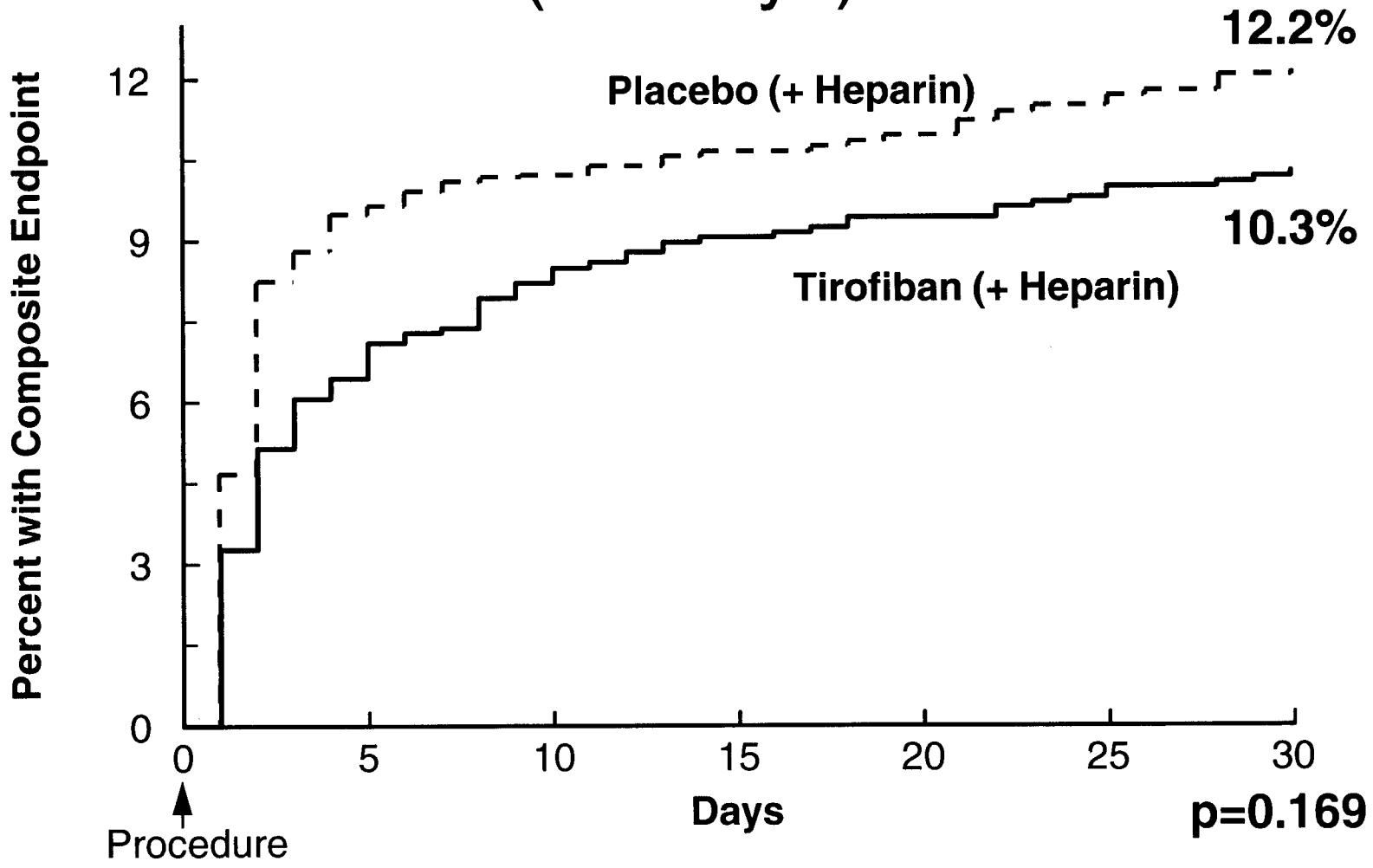
RESTORE Inclusion Criteria

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

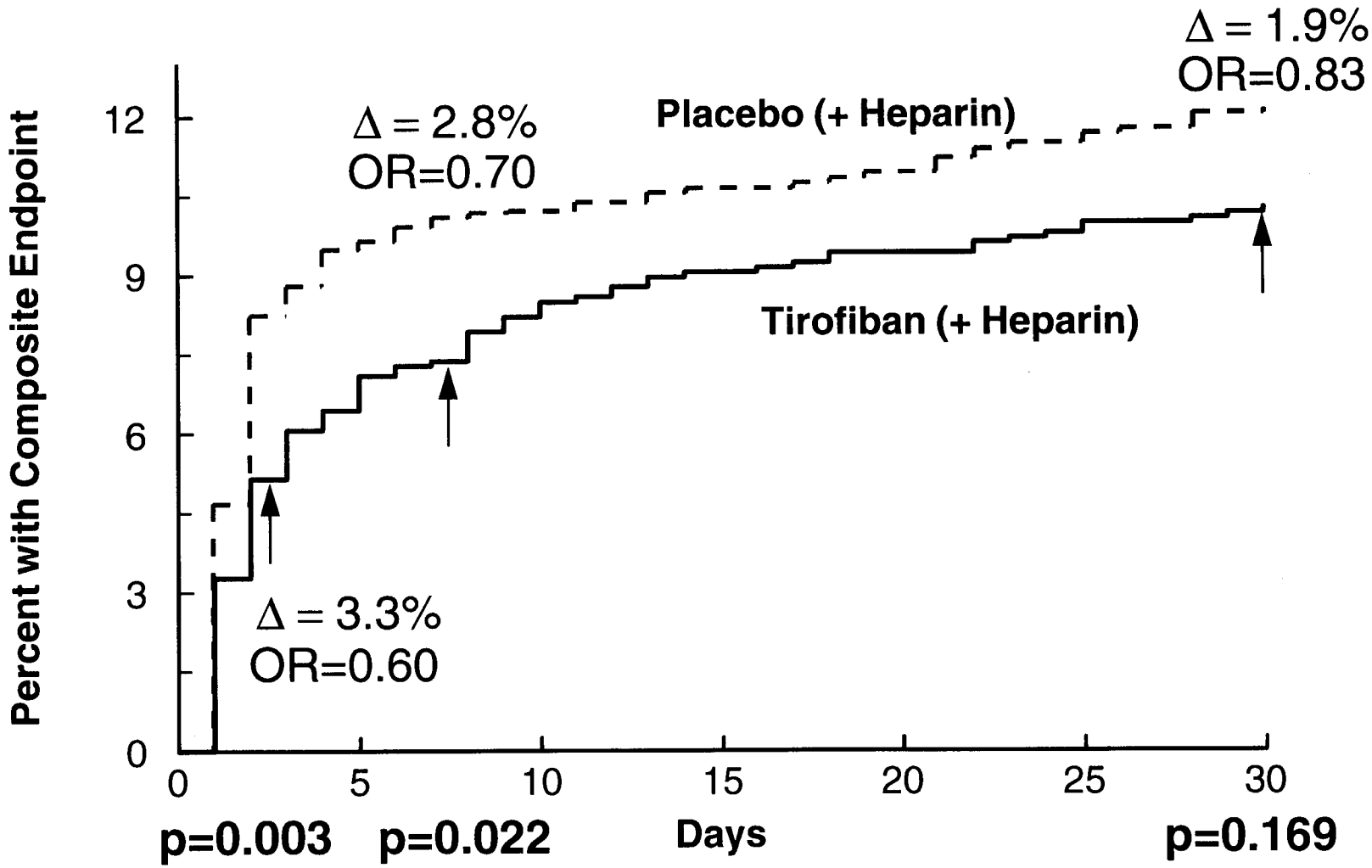
RESTORE Baseline Demographics

	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%

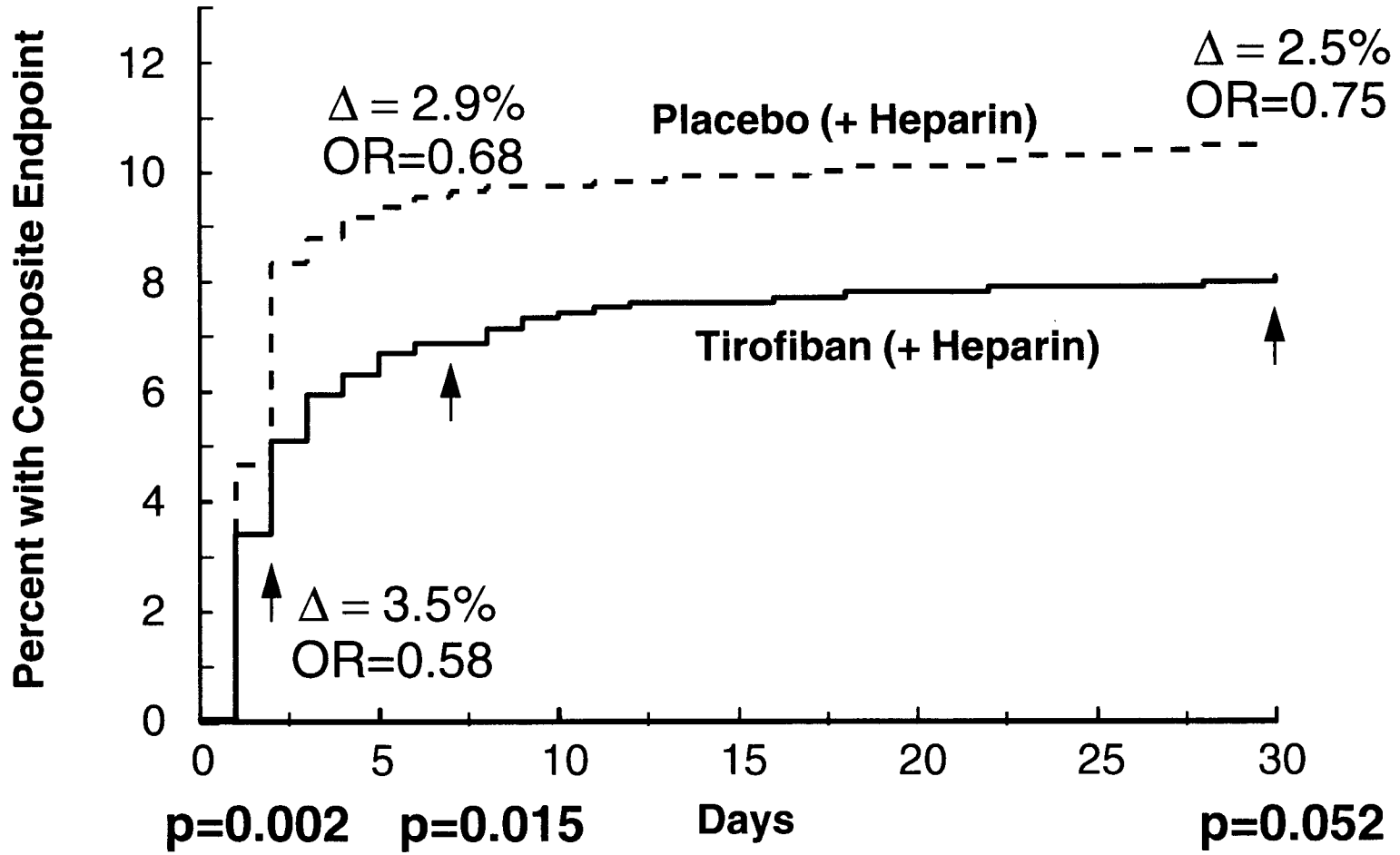
RESTORE Time to Composite Endpoint (30 Days)



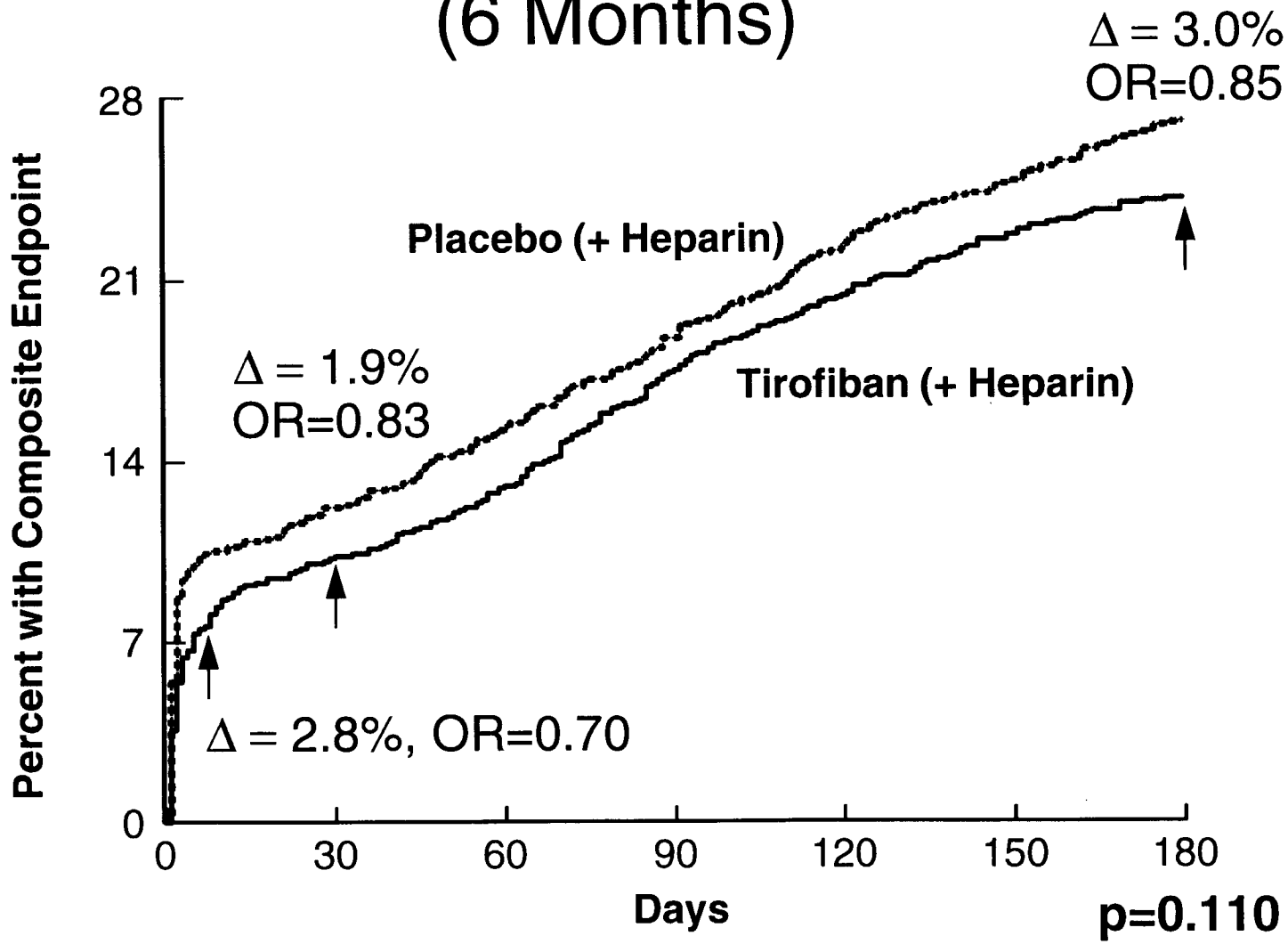
RESTORE Time to Composite Endpoint



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 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."