

Vorapaxar in Secondary Prevention of Atherothrombosis

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Agenda

Introduction

Dr. Chitkala Kalidas
Merck Regulatory Affairs

Clinical Program Overview

Dr. John Strony
Merck Clinical Research

TRA 2°P – TIMI 50
Overall Population

Dr. David Morrow
TIMI Study Group

TRA 2°P – TIMI 50
Proposed Label Population

Dr. Daniel Bloomfield
Merck Clinical Research

Vorapaxar Benefit-Risk

Dr. Eugene Braunwald
TIMI Study Group

Vorapaxar: A New Therapy for Secondary Prevention of Atherothrombosis

- Patients with a history of atherothrombotic disease are at particular risk of cardiac or cerebral events and vascular death
- Aspirin has proven benefits in secondary prevention of atherothrombosis but residual risk remains
 - Combination of aspirin and P2Y₁₂ inhibitors have demonstrated benefit only in ACS patients and is limited to 12 months following PCI
- Vorapaxar is a first-in-class PAR-1 antagonist whose mechanism of action is distinct from aspirin and P2Y₁₂ inhibitors
- Vorapaxar is the first and only antiplatelet agent added to standard of care to demonstrate long-term benefit in secondary prevention of atherothrombosis

Vorapaxar Phase 3 Program

Two Outcomes Studies for Two Separate Indications



**Non ST Elevation Acute
Coronary Syndrome
N=12,944**

Tricoci, et al. N Engl J Med.
2012;366:20-33.



**Secondary Prevention
N=26,449**

Morrow, et al. N Engl J Med.
2012;366:1404-1413.

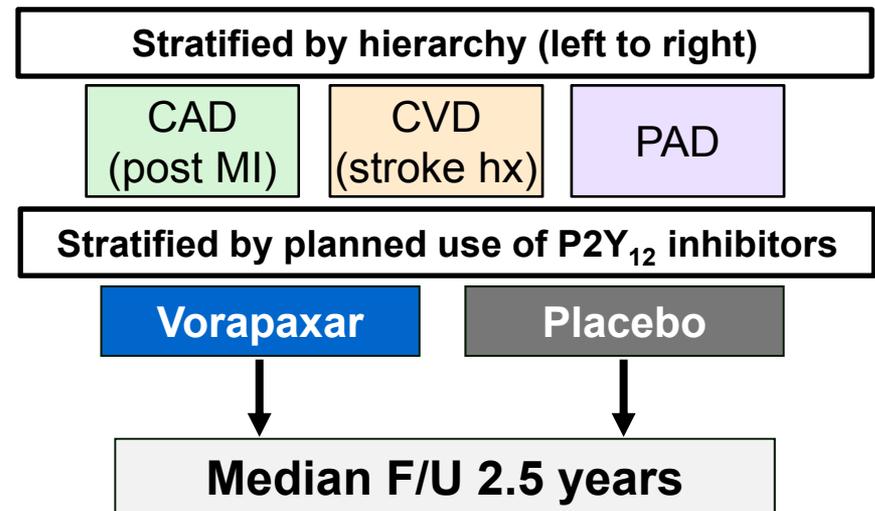
TRA 2°P – TIMI 50 Pivotal Phase 3 Study for Secondary Prevention Indication

Double-blind, placebo-controlled, global trial

- N=26,449
- Outpatient subjects with coronary arterial disease (CAD) (post MI), cerebrovascular disease (CVD), or peripheral arterial disease (PAD)
- 2.5 mg vorapaxar vs. placebo
- Standard-of-care therapy – antiplatelet agents (e.g., aspirin (ASA), P2Y₁₂ inhibitors)



Secondary Prevention



Benefit-Risk Assessment of TRA 2°P – TIMI 50 Results Led to Proposed Label Population

Vorapaxar demonstrated robust efficacy ($p=0.001$) in the Overall Population for the primary endpoint

Benefit-risk profile was then examined in sub-populations:

- Subjects with a history of stroke were at increased risk of bleeding and intracranial hemorrhage (ICH)
- In the resulting No Stroke History Population, subjects in the CAD stratum with no history of stroke had the most favorable benefit-risk profile
- In some clinical situations it can be difficult to distinguish stroke from transient ischemic attack (TIA)

**Therefore, the Proposed Label Population is defined as:
CAD (Post MI) patients with no history of stroke or TIA**

Proposed Labeling

Indications and clinical use:

- TRADEMARK (vorapaxar sulfate), an antagonist of the protease-activated receptor-1, is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). TRADEMARK has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization
- Vorapaxar use to be contraindicated in patients with:
 - History of stroke or TIA
 - History of intracranial hemorrhage

Consultant Introductions

Eugene Braunwald, MD

Distinguished Hersey Professor of Medicine,
Harvard Medical School

Founding Chairman, TIMI Study Group
Brigham and Women's Hospital

*Chairman, Executive Committee for
TRA 2°P – TIMI 50 Study*

David A. Morrow, MD, MPH

Director, Samuel A. Levine Cardiac Intensive
Care Unit

Associate Professor of Medicine,
Harvard Medical School

Senior Investigator, TIMI Study Group
Brigham and Women's Hospital

*Principal Investigator,
TRA 2°P – TIMI 50 Study*

Consultant Introductions

Robert A. Harrington, MD

Arthur L. Bloomfield Professor
Chairman, Department of Medicine
Stanford University

Study Chair, TRACER Study

Kenneth Mahaffey, MD

Professor, Stanford University School of Medicine
Vice-Chair of Clinical Research, Department of
Medicine

Principal Investigator, TRACER Study

Gary Koch, PhD

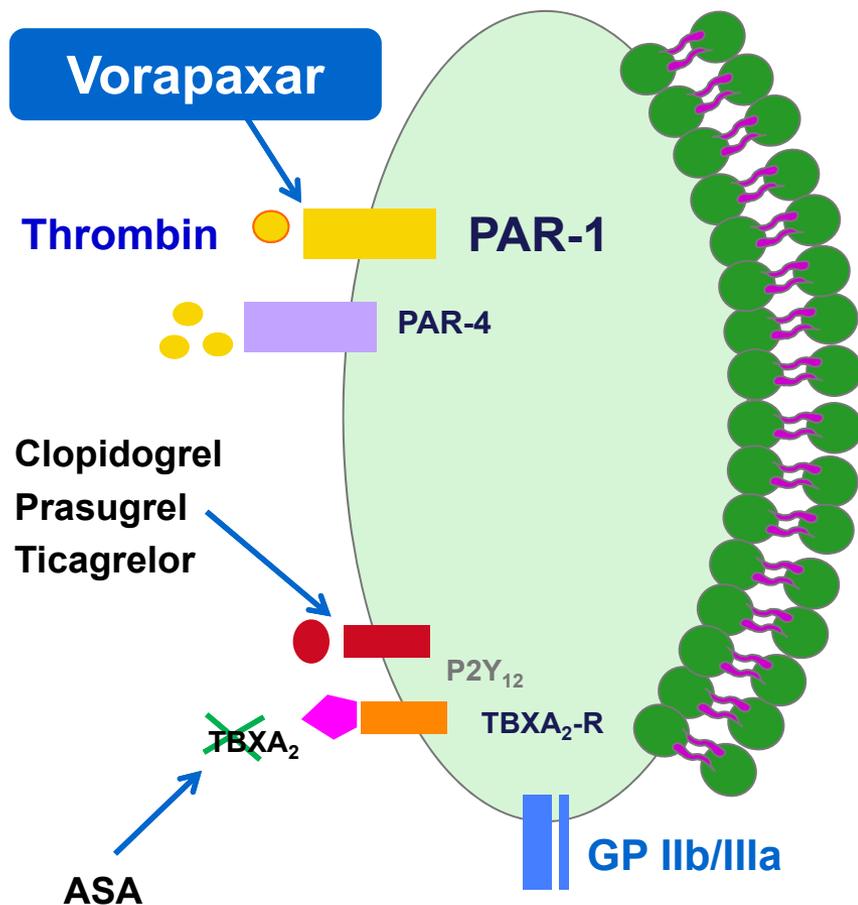
Professor, Biostatistics,
University of North Carolina School of
Public Health at Chapel Hill

Clinical Program Overview

John Strony, MD

*Executive Director, Clinical Research
Merck Research Laboratories*

Vorapaxar Was Designed to Inhibit Thrombin's Action on the Platelet



- Vorapaxar:
 - First-in-class oral PAR-1 antagonist
 - Specific to PAR-1 receptor
- Vorapaxar does not impact:
 - Platelet aggregation mediated by ADP, collagen or a thromboxane mimetic
 - Coagulation parameters
 - Bleeding time

Comprehensive Clinical Development Program in >41,000 Subjects

Program	Population	Subjects
Phase 1	21 studies: safety, tolerability, PK/PD	1060 healthy subjects exposed
Phase 2		
TRA-PCI (P03573)	Subjects undergoing non-emergent percutaneous coronary intervention (PCI)	1030
ACS (P04772)	Acute treatment in NSTEMACS population undergoing PCI	117
Stroke (P05005)	Secondary prevention in stable subjects with history of ischemic stroke	90
Phase 3		
TRACER	Acute treatment in NSTEMACS population	12,944
TRA 2°P – TIMI 50	Secondary prevention in stable subjects with established CAD, CVD, or PAD	26,449

Vorapaxar Clinical Pharmacology

- Single doses up to 120 mg and multiple doses up to 5 mg were well tolerated
- Vorapaxar's apparent plasma terminal $t_{1/2}$ is 187 hrs
- CYP3A4 plays an important role in the metabolism of vorapaxar; strong CYP3A inhibitors and inducers will affect vorapaxar PK
- Vorapaxar has low potential to affect the PK of co-administered drugs
- Several vorapaxar metabolites have been detected including a circulating active metabolite (~20% of parent)
- No need for dose adjustment based on PK across major intrinsic factors (e.g., gender, age, race, weight, and renal insufficiency)

Vorapaxar Safety in Phase 2

- In three Phase 2 studies of 60 days duration, 1237 subjects with evidence of arterial atherosclerosis received placebo or vorapaxar at doses of 0.5 mg, 1 mg, or 2.5 mg
- In these studies, TIMI major, minor, and non-TIMI bleeding were not meaningfully different between any of the vorapaxar dose levels and placebo
- Occurrences of SAEs and discontinuations due to AEs were not different between vorapaxar and placebo in these studies

Dose Justification for Phase 3

- Target engagement was assessed by TRAP-induced platelet aggregation assay, with at least 80% inhibition reflective of clinically meaningful PAR-1 inhibition
- 2.5 mg was selected for Phase 3 investigation
 - The lowest dose that consistently achieved target engagement in Phase 1 studies
 - There was no evidence of an increase in risk for TIMI major/minor bleeding with the 2.5 mg dose in Phase 2

Vorapaxar Phase 3 Program



NSTEACS 12,944 subjects



Subjects randomized in hospital
Within ~24 hours of presentation with ACS
Concomitant parenteral anticoagulants and antiplatelet agents
40 mg loading dose/ 2.5 mg daily maintenance dose

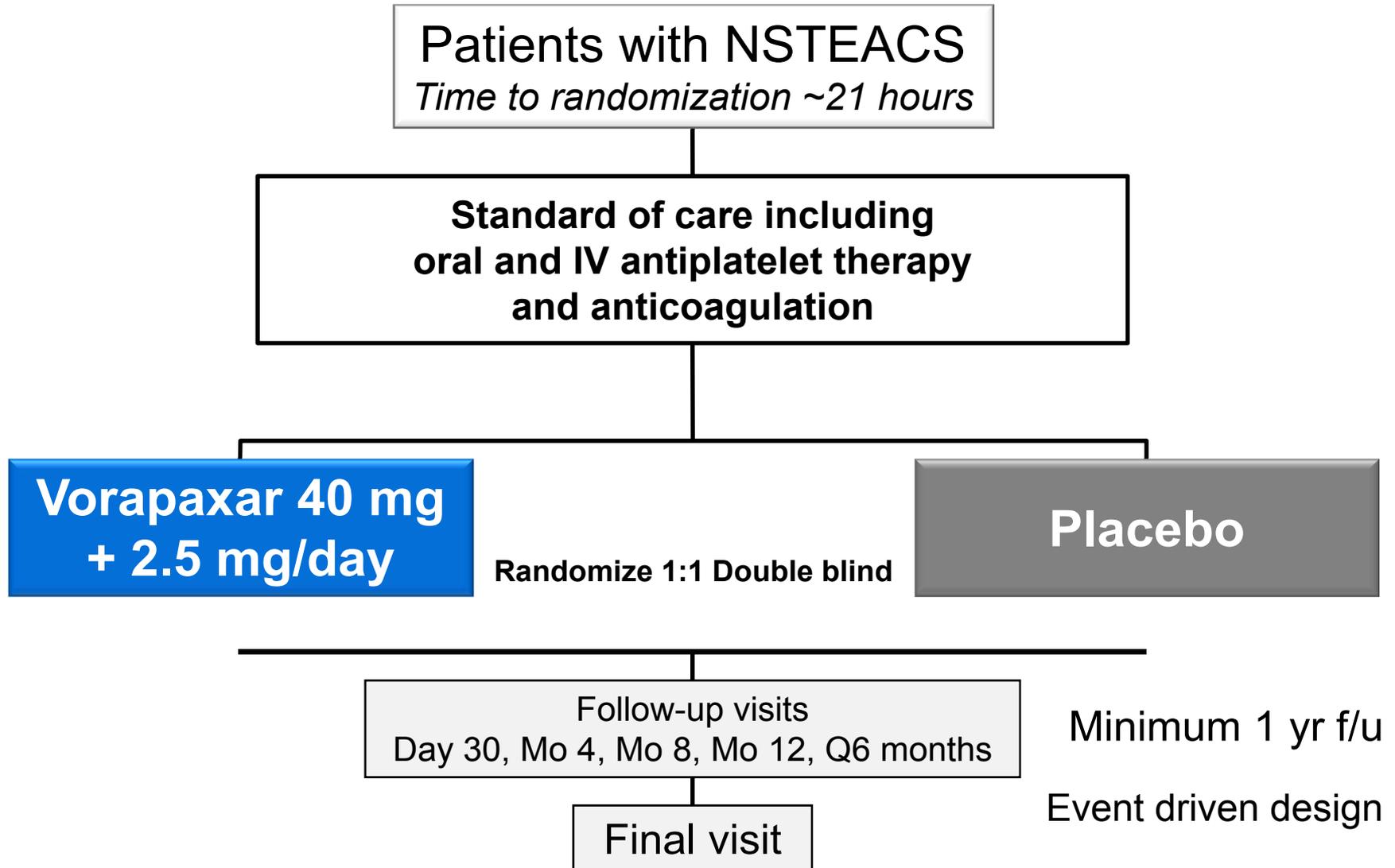


Secondary Prevention 26,449 subjects



Subjects randomized as outpatients
>2 weeks after MI
Background medications consistent with accepted secondary prevention guidance
2.5 mg daily maintenance dose

TRACER Trial Design



Data Safety Monitoring Board (DSMB) Recommendation

- January 2011, the joint TRACER and TRA 2°P – TIMI 50 DSMB announced that based on ongoing reviews of safety
 - Subjects with a history of stroke have an increased risk of ICH
- TRA 2°P – TIMI 50
 - Subjects with history of stroke in the TRA 2°P – TIMI 50 trial should have study drug discontinued
- TRACER
 - The requisite number of endpoint events had been achieved to make a determination of efficacy
 - Recommend close out of the TRACER trial in a timely and orderly fashion

TRACER

Key Baseline Demographic Characteristics

All Randomized Subjects

	Placebo (N=6471)	Vorapaxar (N=6473)
Age (yrs, median, Q1, Q3)	64 (58, 72)	64 (58, 71)
≥75 yrs (%)	17	17
Female (%)	28	28
Weight (kg, median, Q1, Q3)	80 (70, 92)	80 (70, 93)
History of MI (%)	29	29
Diabetes (%)	31	32
Heart failure (%)	10	9
CrCl <60 mL/min/1.73 m ² (%)	13	13

Comparison of TRACER and TRA 2°P – TIMI 50



NSTEACS

12,944 subjects

Vorapaxar

Placebo

Median F/U 1.4 years

29% with history of MI

6% PCI within 1 year

60% of patients completely naïve to antiplatelet therapy

10% of patients on dual antiplatelet therapy with aspirin and a thienopyridine

Comparison of TRACER and TRA 2°P – TIMI 50



NSTEACS

12,944 subjects

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29% with history of MI

6% PCI within 1 year

60% of patients completely naïve to antiplatelet therapy

10% of patients on dual antiplatelet therapy with aspirin and a thienopyridine

Proposed Label Population

16,897 subjects

Vorapaxar

Placebo

Median F/U 2.5 years

99.8% with history of MI

79% PCI within 1 year

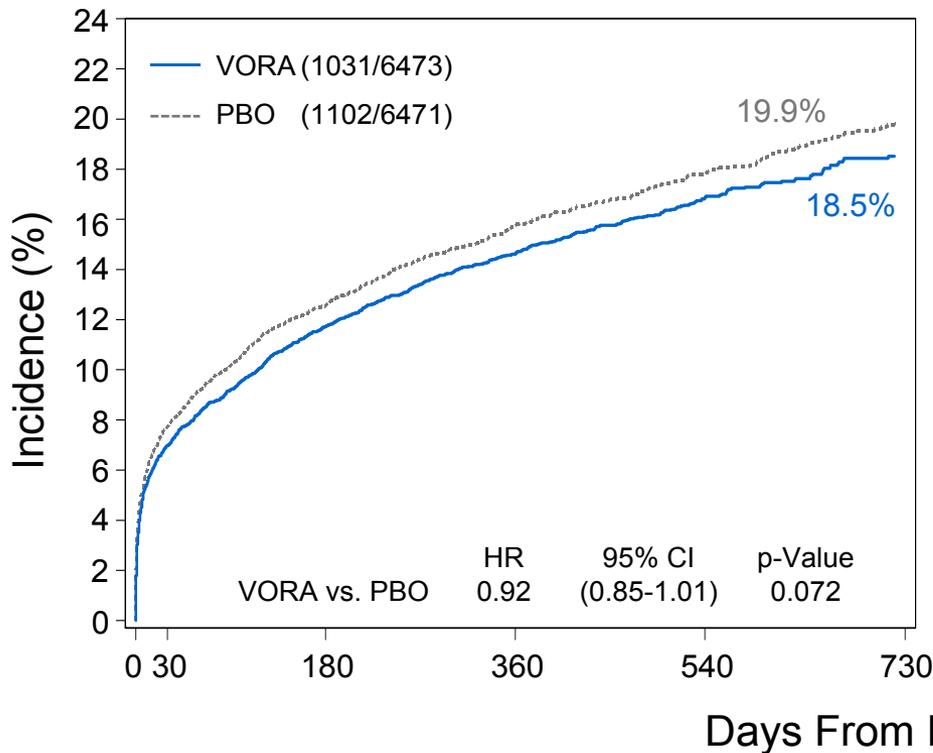
1% of patients completely naïve to antiplatelet therapy

77% of patients on dual antiplatelet therapy with aspirin and a thienopyridine

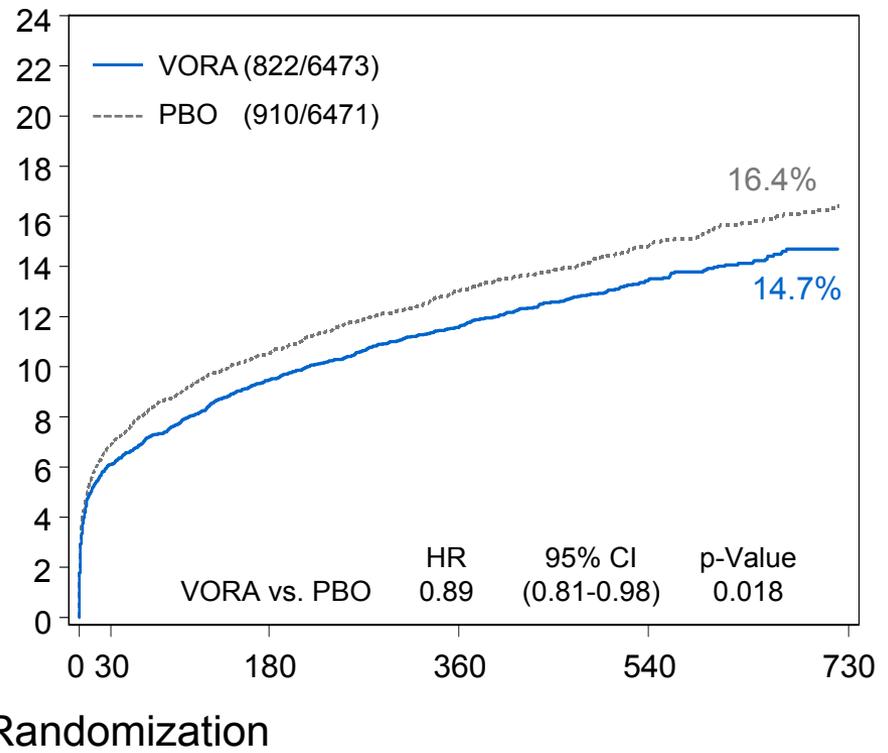
TRACER Efficacy

ITT (Randomization to Last Visit) 2-Year KM Rate

Primary Efficacy Endpoint
(CV Death, MI, Stroke, RIR[†], UCR[‡])



Key Secondary Efficacy Endpoint
(CV Death, MI, Stroke)



[†] Recurrent ischemia with rehospitalization.

[‡] Urgent coronary revascularization.

TRACER Bleeding Endpoints

As-Treated (Randomization to Last Visit) 2-Year KM Rate

	Placebo (N=6441)		Vorapaxar (N=6446)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
GUSTO bleeding categories					
Severe or moderate	332	5.8	449	7.6	1.36 (1.18-1.57)
Severe	106	1.9	172	3.0	1.62 (1.27-2.06)
Moderate	236	4.1	296	5.0	1.26 (1.06-1.49)
TIMI bleeding categories					
Clinically significant	813	14.6	1128	19.5	1.41 (1.29-1.54)
CABG-related major	68	1.2	89	1.4	1.31 (0.95-1.79)

TRACER Bleeding Endpoints (Cont.)

As-Treated (Randomization to Last Visit) 2-Year KM Rate

	Placebo (N=6441)		Vorapaxar (N=6446)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
Other categories					
Intracranial hemorrhage	19	0.4	48	1.0	2.52 (1.48-4.29)
Fatal ICH	6	0.2	13	0.3	2.15 (0.82-5.66)
Fatal bleeding	16	0.3	29	0.5	1.81 (0.98-3.34)

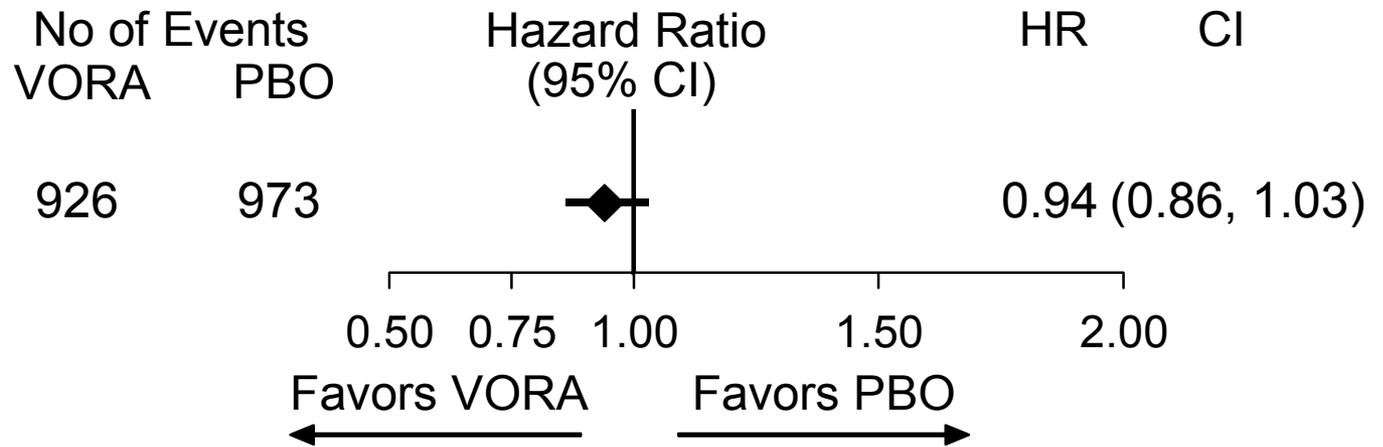
TRACER

Net Clinical Outcome

CV Death/MI/Stroke/GUSTO Severe

As-Treated (Randomization to Last Visit)

TRACER
N=12,887



Summary of TRACER

- In subjects selected in the early phase of their ACS, TRACER demonstrated that vorapaxar
 - Reduced atherothrombotic events
 - Increased risk of bleeding including GUSTO severe and ICH
- The increased risk of bleeding outweighed the potential reduction of atherothrombotic events over ~2 years of follow-up
- Merck is not pursuing an indication to ***initiate*** vorapaxar therapy in the setting of an ACS

Vorapaxar Pivotal TRA 2°P – TIMI 50 Results in the Overall Population

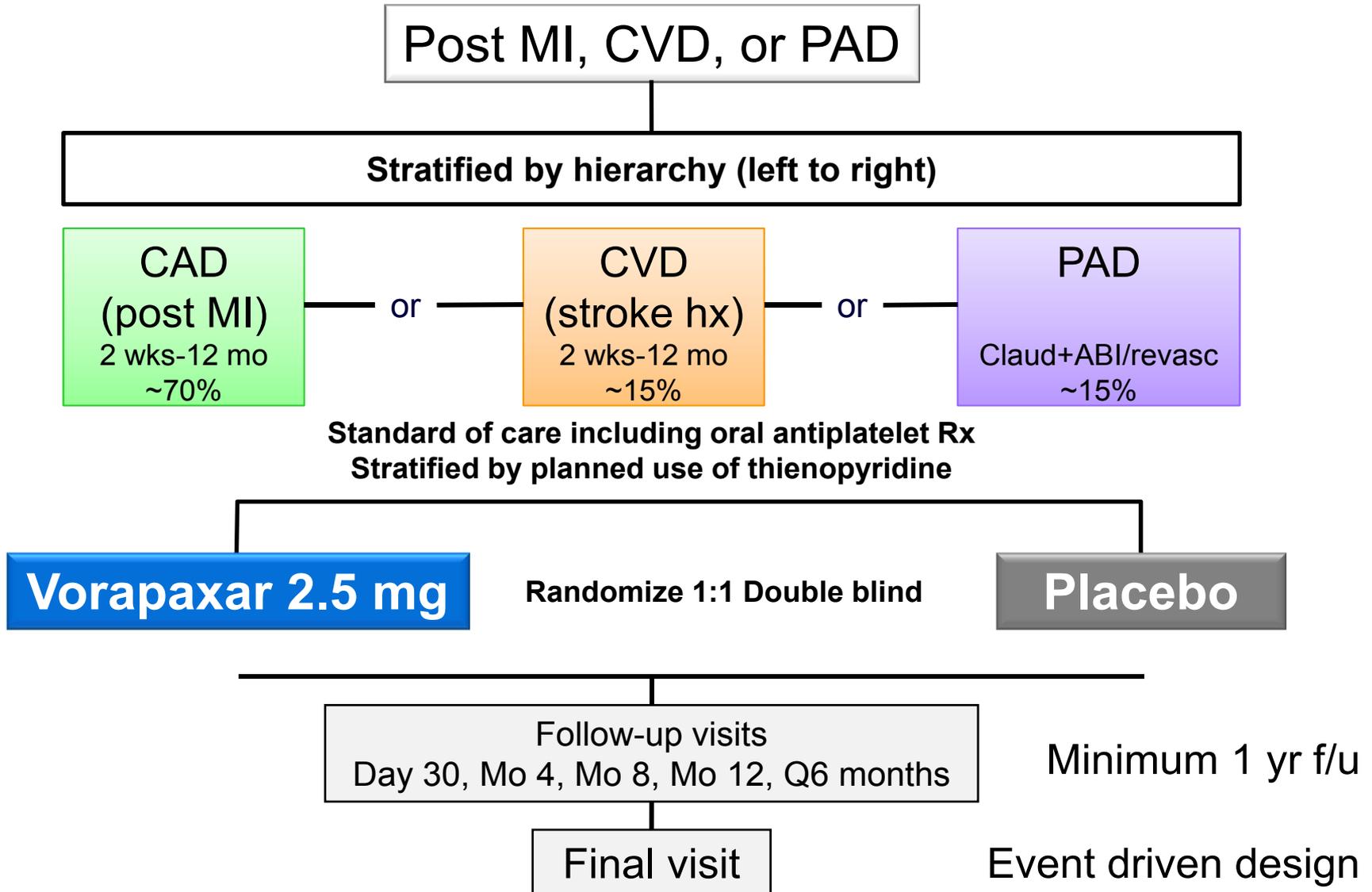
David A. Morrow, MD, MPH

*TIMI Study Group, Cardiovascular Division,
Brigham and Women's Hospital*

TRA 2°P – TIMI 50 Key Study Features

- Robustly sized, multinational, double-blind, placebo-controlled trial
- Academic leadership in collaboration with Sponsor and other trial partners
- Rigorously conducted with oversight by Thrombolysis in Myocardial Infarction (TIMI) Study Group and Sponsor
- All endpoints for efficacy and safety adjudicated by an experienced Clinical Events Committee (CEC) managed by TIMI Study Group
- Vorapaxar tested in context of current standard of care

TRA 2°P – TIMI 50 Trial Design



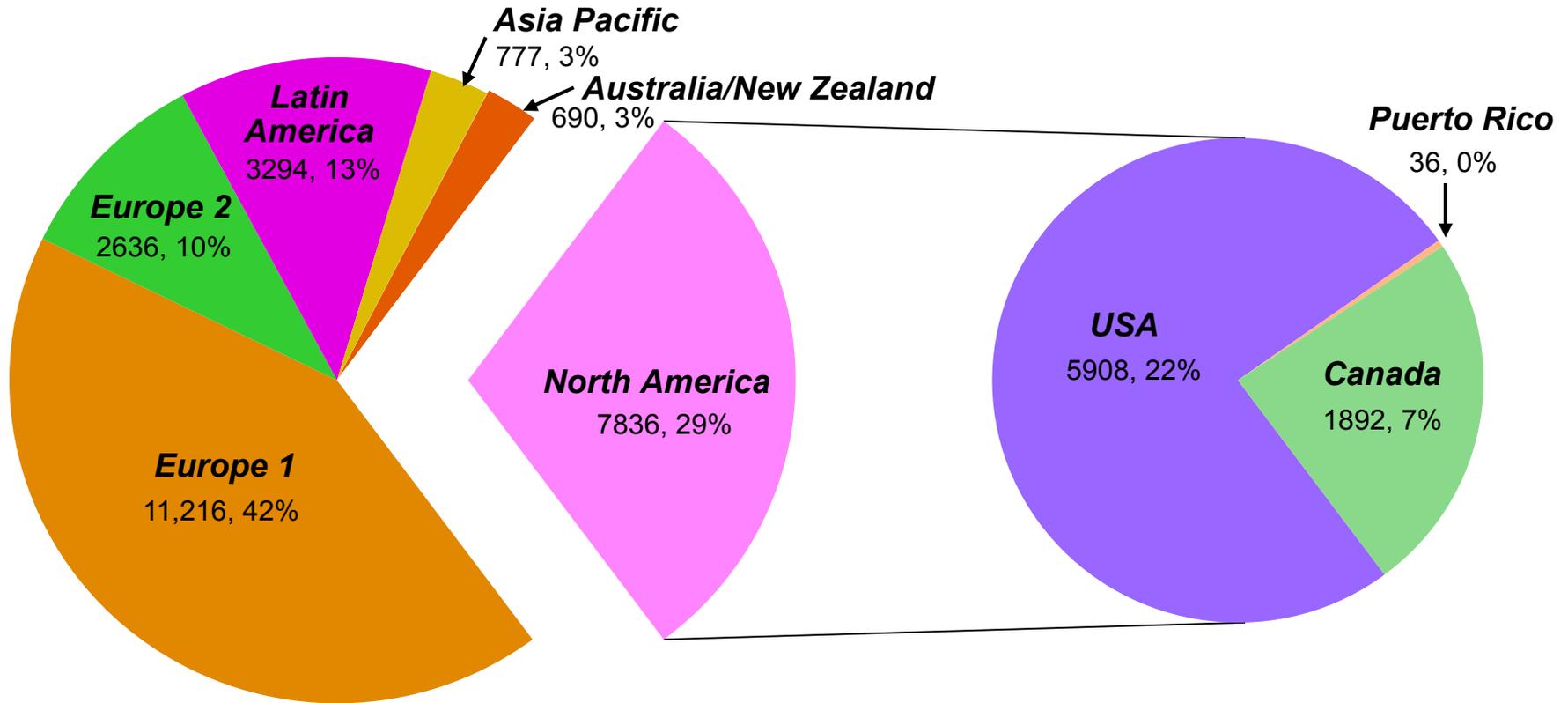
TRA 2°P – TIMI 50 Statistical Methodology

Endpoints and Analysis

- **Primary efficacy endpoint**
 - Time to first occurrence of CV death, MI, stroke, or UCR
- **Key secondary efficacy endpoint**
 - Time to first occurrence of CV death, MI, or stroke
- **Analytical method**
 - Cox proportional hazard (PH) model with covariates for treatment and two stratification factors (qualifying condition of CAD, stroke, or PAD, and planned thienopyridine use at the time of enrollment)
 - All efficacy analyses on intention-to-treat (ITT) basis
 - Hazard ratios (HR) and 95% confidence intervals (CI)
 - Kaplan-Meier (KM) estimates to 3 years were plotted

TRA 2°P – TIMI 50 Enrollment 9/07 –11/09

32 countries, 1032 sites: 26,449 subjects randomized



■ Europe 1 ■ Europe 2 ■ Latin America ■ Asia/Pacific ■ Australia/New Zealand ■ USA ■ Puerto Rico ■ Canada

■ Europe 1 includes Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom

■ Europe 2 includes Czech Republic, Hungary, Poland

TRA 2°P – TIMI 50 Operational Landmarks

Study start Sept, 2007

2009

- Jan: Amendment #1
 - Reassessment of sample size using aggregated blinded endpoint accumulation before end enrollment
 - Specify enrollment goals MI/Stroke/PAD (70%:15%:15%)
- Mar: Amendment #2
 - ↑ Sample size and ↑ target number of key secondary endpoint events to maintain power and timelines
- Nov: Enrollment completed

2010

- Feb: 50% planned interim analysis
- Oct: DSMB planned safety review
- Dec/Jan: unplanned DSMB safety review

2011

- Jan: DSMB notification - excess risk of ICH in subjects with prior stroke
- Mar: Amendment #3 as a result of DSMB notification
- Aug: Study closeout begins
- Dec: Last patient last visit

Database lock Jan, 2012

Data Safety Monitoring Board (DSMB) Recommendation

- January, 2011, DSMB announced that based on ongoing reviews of safety
 - TRA 2°P – TIMI 50: ↑ ICH with vorapaxar in subjects with prior stroke → discontinue study drug in all subjects with a stroke history or new stroke in trial
 - TRA 2°P – TIMI 50 trial should continue in subjects without a history of stroke

TRA 2°P – TIMI 50

Implementation of DSMB Recommendation

- The Executive Committee (TIMI and Sponsor) accepted the recommendation of the DSMB and implemented the following actions:
 - Study drug was discontinued in all subjects with a history of stroke prior to randomization or during the trial
 - Follow-up was completed in the CVD stratum per protocol Amendment #3
 - Exception: Subjects with a new stroke during the trial were followed for purpose of collecting complete information on subjects with a new stroke while receiving vorapaxar
 - All subjects in the CAD and PAD strata continued follow-up regardless of stroke history

TRA 2°P – TIMI 50 Subject Disposition

	Placebo (N=13,224) n (%)	Vorapaxar (N=13,225) n (%)
Received allocated intervention	13,166 (99.6)	13,186 (99.7)
Never received study drug	58 (0.4)	39 (0.3)
Completed treatment	7970 (60.3)	7779 (58.8)
Subjects with history of stroke or new stroke Discontinued study drug at recommendation of DSMB in January 2011	2248 (17.0)	2262 (17.1)
Discontinued study drug prematurely for other reasons	2948 (22.3)	3145 (23.8)
Completed the study [†]	12,932 (97.8)	12,953 (97.9)
Completed final study visit [†]	12,696 (96.0)	12,728 (96.2)
Only vital status assessed	236 (1.8)	225 (1.7)
Died	25 (0.2)	22 (0.2)
Alive	211 (1.6)	203 (1.5)
Prematurely discontinued follow-up	292 (2.2)	272 (2.1)
Lost to follow-up	15 (0.1)	17 (0.1)
Withdrew consent for follow-up	277 (2.1)	255 (1.9)
Died [‡]	589 (4.5)	556 (4.2)

[†] Includes subjects that completed per Protocol Amendment 3; and subjects who died on or before last contact date.

[‡] Died on or before last contact date.

TRA 2°P – TIMI 50 Baseline Characteristics

Overall Population

All Randomized Subjects

	Placebo (N=13,224)	Vorapaxar (N=13,225)
Age (yrs, median, Q1, Q3)	61 (53, 69)	61 (53, 69)
≥75 yrs (%)	11	11
Female (%)	24	24
Weight (kg, median, Q1, Q3)	81 (71, 93)	81 (71, 92)
<i>Qualifying stratum</i>		
CAD n=17,779 (%)	67	67
CVD n=4883 (%)	19	18
PAD n=3787 (%)	14	14
Any CAD (%)	78	78
Any prior stroke (%)	22	22
Hx of PAD (%)	19	19
Diabetes (%)	25	25
Heart failure (%)	8	8
CrCl <60 ml/min/1.73 m ² (%)	13	14

TRA 2°P – TIMI 50 Background Therapy

Overall Population

All Randomized Subjects

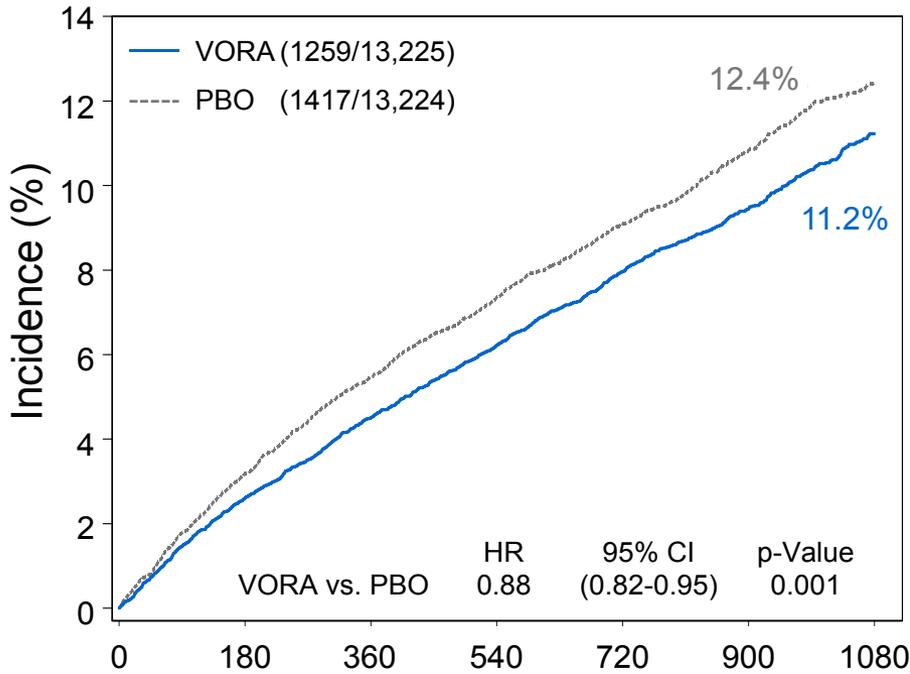
	Placebo (N=13,224)	Vorapaxar (N=13,225)
Antiplatelet Therapy (%)		
CAD		
ASA	98	98
Thienopyridine	78	78
CVD		
ASA	81	81
Thienopyridine	24	24
Dipyridamole	19	20
PAD		
ASA	88	88
Thienopyridine	37	37
Other medications at enrollment		
Lipid-lowering agent (%)	92	92
ACEI (%)	60	59
ARB (%)	16	16
Beta-blocker (qualifying MI; %)	84	84

TRA 2°P – TIMI 50
Efficacy Results in the
Overall Population

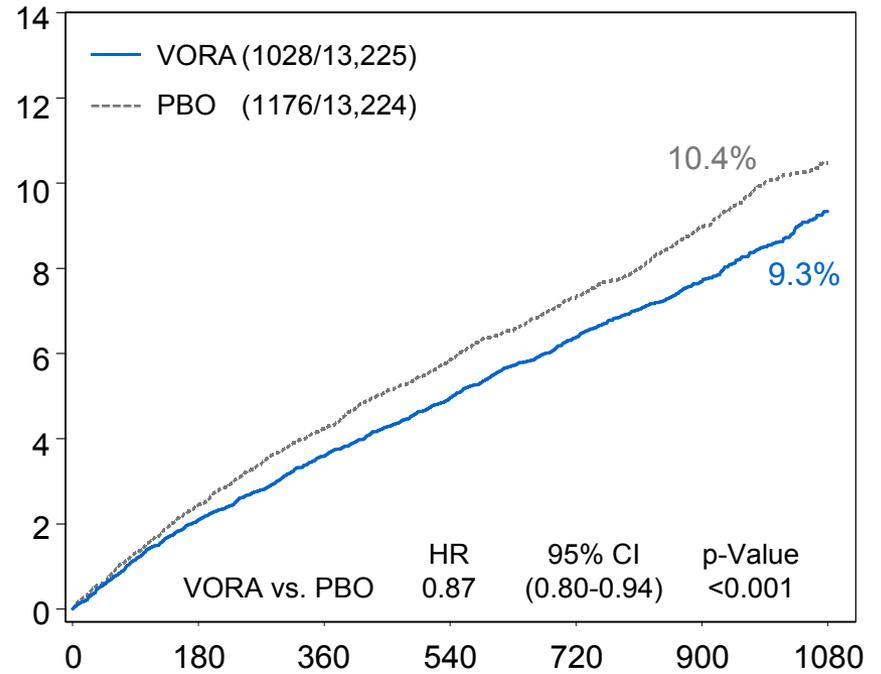
TRA 2°P – TIMI 50 Vorapaxar Demonstrated Robust Outcomes Benefit in the Overall Population

ITT (Randomization to Last Visit) 3-Year KM Rate

Primary Efficacy Endpoint
(CV Death, MI, Stroke, UCR)



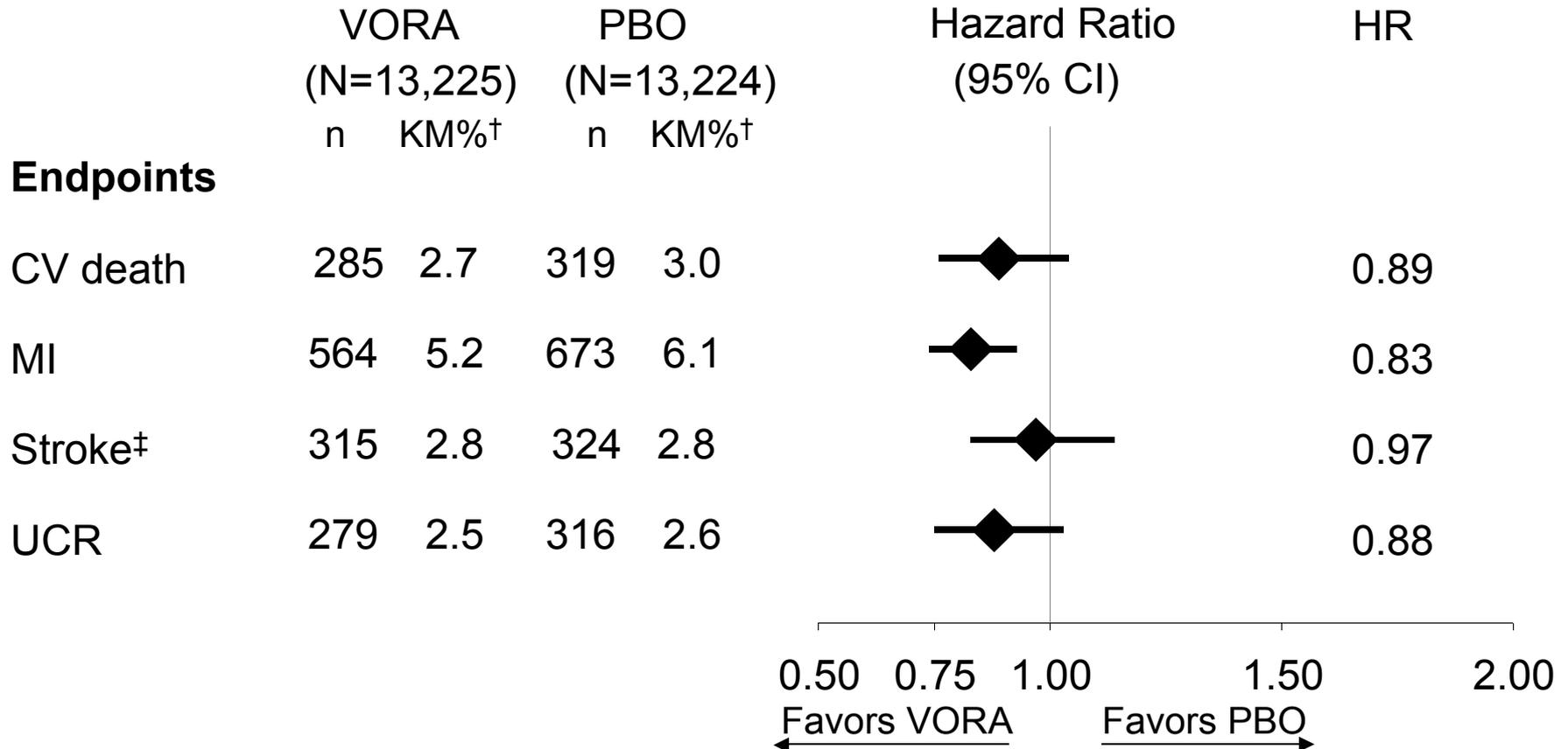
Key Secondary Efficacy Endpoint
(CV Death, MI, Stroke)



Days From Randomization

TRA 2°P – TIMI 50 Time to First Event Other Secondary Efficacy Endpoints Overall Population

ITT (Randomization to Last Visit)

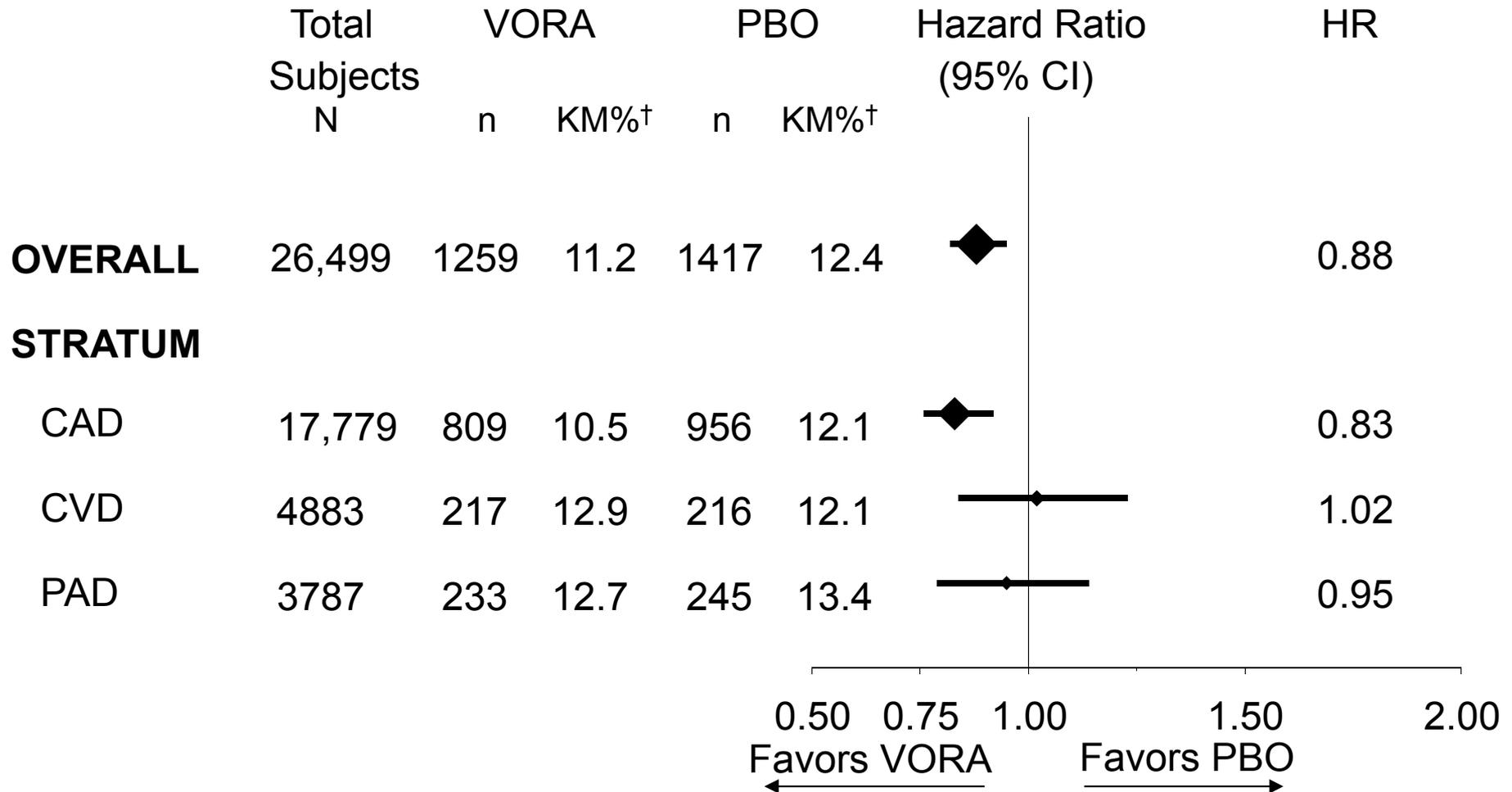


[†] KM rate at 1080 days.

[‡] Includes ischemic and hemorrhagic.

TRA 2°P – TIMI 50 Primary Efficacy Endpoint Qualifying Disease Strata

ITT (Randomization to Last Visit)



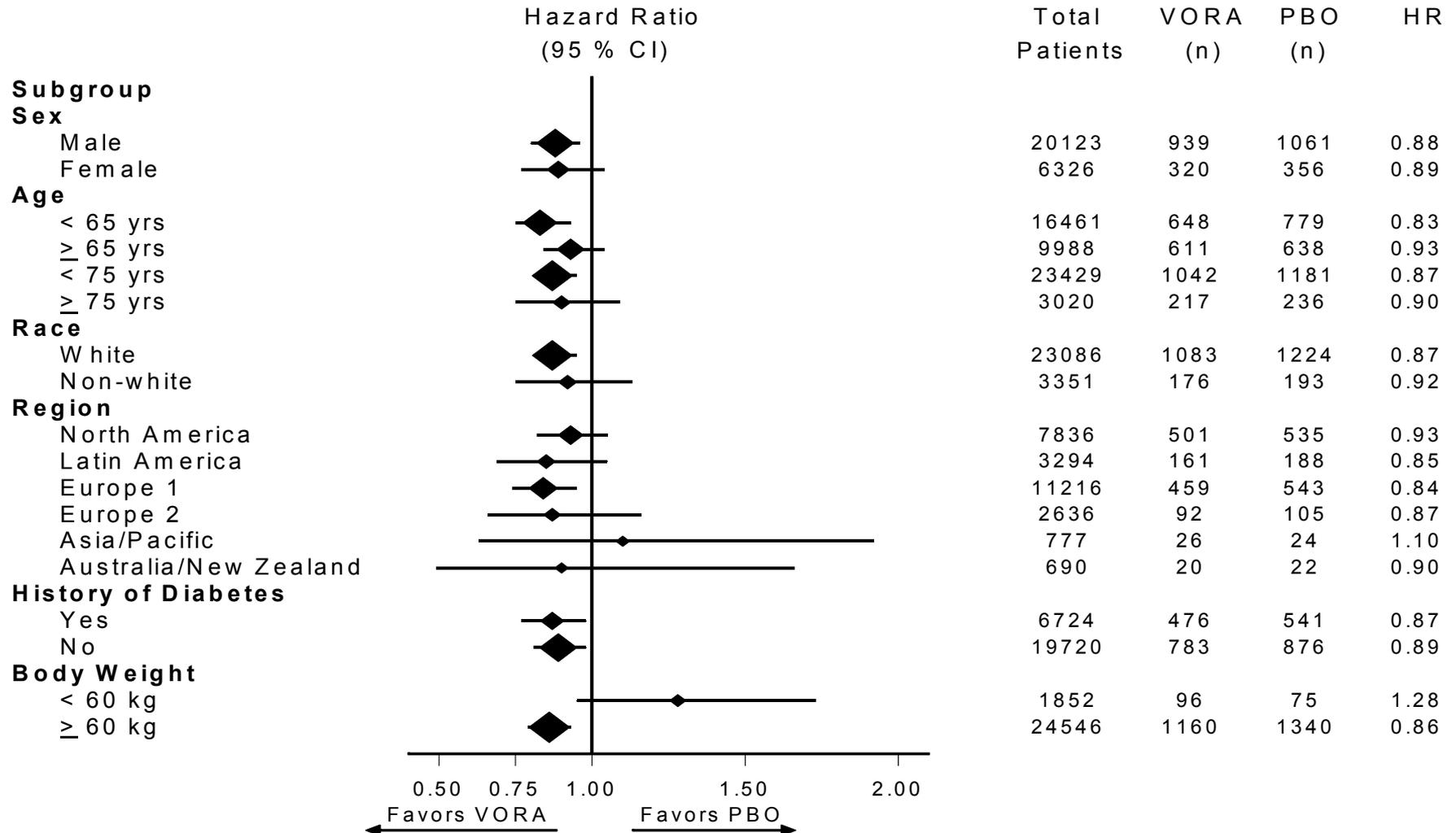
[†] KM rate at 1080 days.

TRA 2°P – TIMI 50

Primary Efficacy Endpoint by Subgroups

Overall Population

ITT (Randomization to Last Visit)



TRA 2°P – TIMI 50 Efficacy Summary Overall Population

- TRA 2°P – TIMI 50 met its primary efficacy hypothesis
- Vorapaxar significantly reduced the primary and key secondary endpoints in the Overall Population
 - 12% (p=0.001) treatment effect for the primary endpoint (CV death, MI, stroke, UCR)
 - 13% (p<0.001) treatment effect for the key secondary endpoint (CV death, MI, stroke)
- Result was statistically robust and consistent across
 - Pre-specified secondary atherothrombotic endpoints
 - Individual elements of the primary endpoint with exception of stroke
 - Major subgroups of clinical interest

TRA 2°P – TIMI 50
Safety Results in the
Overall Population

TRA 2°P – TIMI 50 Key Bleeding Endpoints and Definitions

- Bleeding was the safety endpoint of primary interest
- Bleeding endpoints in relative order of importance defined as the first occurrence of any component of the following two composites:
 - Composite of GUSTO moderate or severe bleeding
 - Moderate: requiring transfusion of whole blood or PBRCs without hemodynamic compromise
 - Severe: fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention
 - “Clinically significant bleeding”
 - TIMI major or minor, or required treatment or laboratory evaluation

TRA 2°P – TIMI 50 Bleeding Endpoints Overall Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

	Placebo (N=13,166)		Vorapaxar (N=13,186)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
GUSTO bleeding categories					
Severe or moderate	313	2.9	471	4.2	1.51 (1.31-1.74)
Severe	146	1.4	192	1.7	1.31 (1.06-1.63)
Moderate	179	1.6	290	2.6	1.62 (1.35-1.96)
TIMI bleeding categories					
Clinically significant	1324	11.3	1816	15.4	1.41 (1.31-1.51)
CABG-related major	14	0.1	13	0.1	0.92 (0.43-1.97)

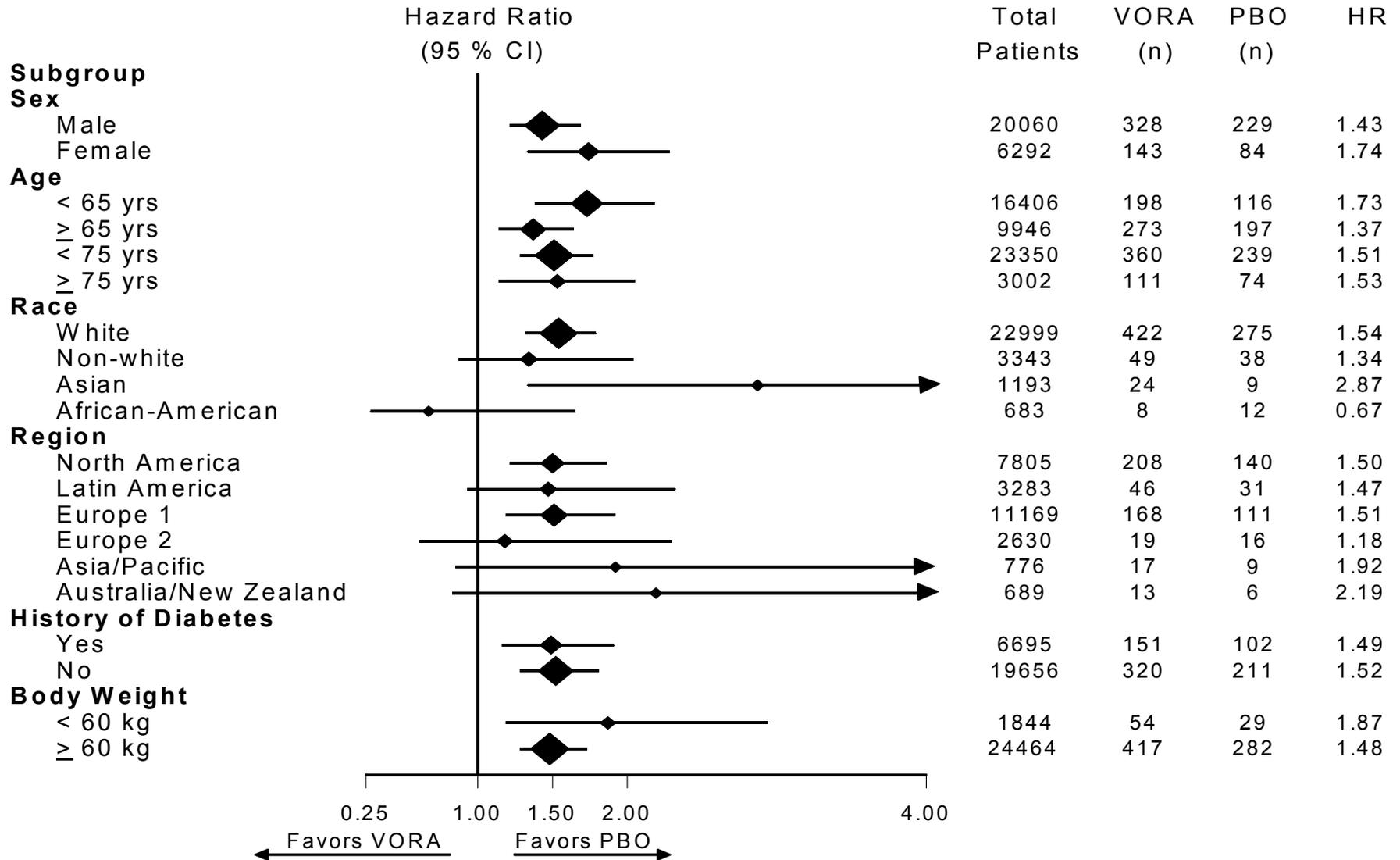
TRA 2°P – TIMI 50 Bleeding Endpoints Overall Population (Cont.)

As-Treated (Randomization to Last Visit) 3-Year KM Rate

	Placebo (N=13,166)		Vorapaxar (N=13,186)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
Other categories					
Intracranial hemorrhage	64	0.6	109	1.0	1.70 (1.25-2.32)
Fatal ICH	11	0.1	26	0.2	2.36 (1.16-4.77)
Fatal bleeding	27	0.3	38	0.4	1.40 (0.86-2.30)

TRA 2°P – TIMI 50 GUSTO Severe or Moderate Bleeding Overall Population

As-Treated (Randomization to Last Visit)



TRA 2°P – TIMI 50 Bleeding Endpoints History of Stroke/No History of Stroke

As-Treated (Randomization to Last Visit) 3-Year KM Rate

Endpoints	Placebo		Vorapaxar		Hazard Ratio (95%CI)
	n	KM%	n	KM%	
History of stroke	(N=2864)		(N=2855)		
Intracranial hemorrhage	22	0.9	56	2.7	2.55 (1.56-4.18)
Fatal ICH	1	0	11	0.8	10.90 (1.41-84.45)
Fatal bleeding	7	0.4	16	1.3	2.28 (0.94-5.54)
No history of stroke	(N=10,302)		(N=10,331)		
Intracranial hemorrhage	42	0.5	53	0.6	1.25 (0.84-1.88)
Fatal ICH	10	0.1	15	0.2	1.49 (0.67-3.32)
Fatal bleeding	20	0.3	22	0.3	1.10 (0.60-2.01)

TRA 2°P – TIMI 50

Non-bleeding Adverse Events

Overall Population

As-Treated (During Study)

	Placebo (N=13,166)	Vorapaxar (N=13,186)
	n (%)	n (%)
Any treatment-emergent (TE) other AE	10,227 (77.7)	10,208 (77.4)
Any treatment-related TE other AE	2070 (15.7)	2124 (16.1)
Any serious other AE	3255 (24.7)	3250 (24.6)
Any treatment-related serious other AE	93 (0.7)	83 (0.6)
Any discontinuation due to other AE	960 (7.3)	926 (7.0)
Any treatment-related other AE resulting in treatment discontinuation	314 (2.4)	327 (2.5)
Any other AE resulting in death	319 (2.4)	306 (2.3)

TRA 2°P – TIMI 50 All-Cause Death Overall Population

All Randomized Subjects

	Placebo (N=13,224)	Vorapaxar (N=13,225)
	n (%)	n (%)
Total deaths [†]	610 (4.6)	580 (4.4)
CV death	329 (2.5)	298 (2.3)
Non-CV death	250 (1.9)	240 (1.8)
Unknown	31 (0.2)	42 (0.3)

[†] CEC adjudicated.

TRA 2°P – TIMI 50 No Rebound Observed Overall Population

Primary Endpoints 30 Days After Off Treatment in Subjects Who Discontinued Treatment Prematurely

	Placebo (N=4920)	Vorapaxar (N=5090)
	n (%)	n (%)
Primary efficacy endpoint (CV death/MI/stroke/UCR)	85 (1.7)	74 (1.5)
CV death	39 (0.8)	40 (0.8)
MI	23 (0.5)	15 (0.3)
Stroke	20 (0.4)	16 (0.3)
Ischemic	18 (0.4)	13 (0.3)
Hemorrhagic	2 (0.0)	3 (0.1)
Uncertain	0	0
UCR	3 (0.1)	3 (0.1)

TRA 2°P – TIMI 50 Safety Summary

Overall Population

- Bleeding risk is greater in vorapaxar group vs. placebo group for all pre-specified bleeding endpoints
 - Between-group differences significant for GUSTO moderate and severe, clinically significant bleeding, and ICH
 - Fatal bleeding rates were comparable
- Overall ICH events were increased among subjects taking vorapaxar in addition to standard of care (1.0% vorapaxar vs. 0.6% placebo over a three year period)
 - Subjects with a history of stroke had very high absolute rates of ICH (2.7% with vorapaxar vs. 0.9% with placebo over 3 yrs)
 - Subjects with no stroke history had a lower overall incidence of ICH (0.6% with vorapaxar vs. 0.5% with placebo over 3 yrs)

TRA 2°P – TIMI 50 Summary of Results Overall Population

- When added to standard of care, vorapaxar was effective in reducing recurrent atherothrombotic events
 - CV death, MI, stroke, UCR
 - CV death, MI, stroke
- This improvement in thrombotic outcomes with vorapaxar was offset by an increase in GUSTO moderate or severe bleeding, including a risk of ICH that was highest in subjects with a history of stroke
- Any clinical use of vorapaxar would be guided by an assessment of the potential antithrombotic benefits vs. risk of bleeding for the individual patient

TRA 2°P – TIMI 50 Net Clinical Outcome by Strata

CV Death/MI/Stroke/GUSTO Severe

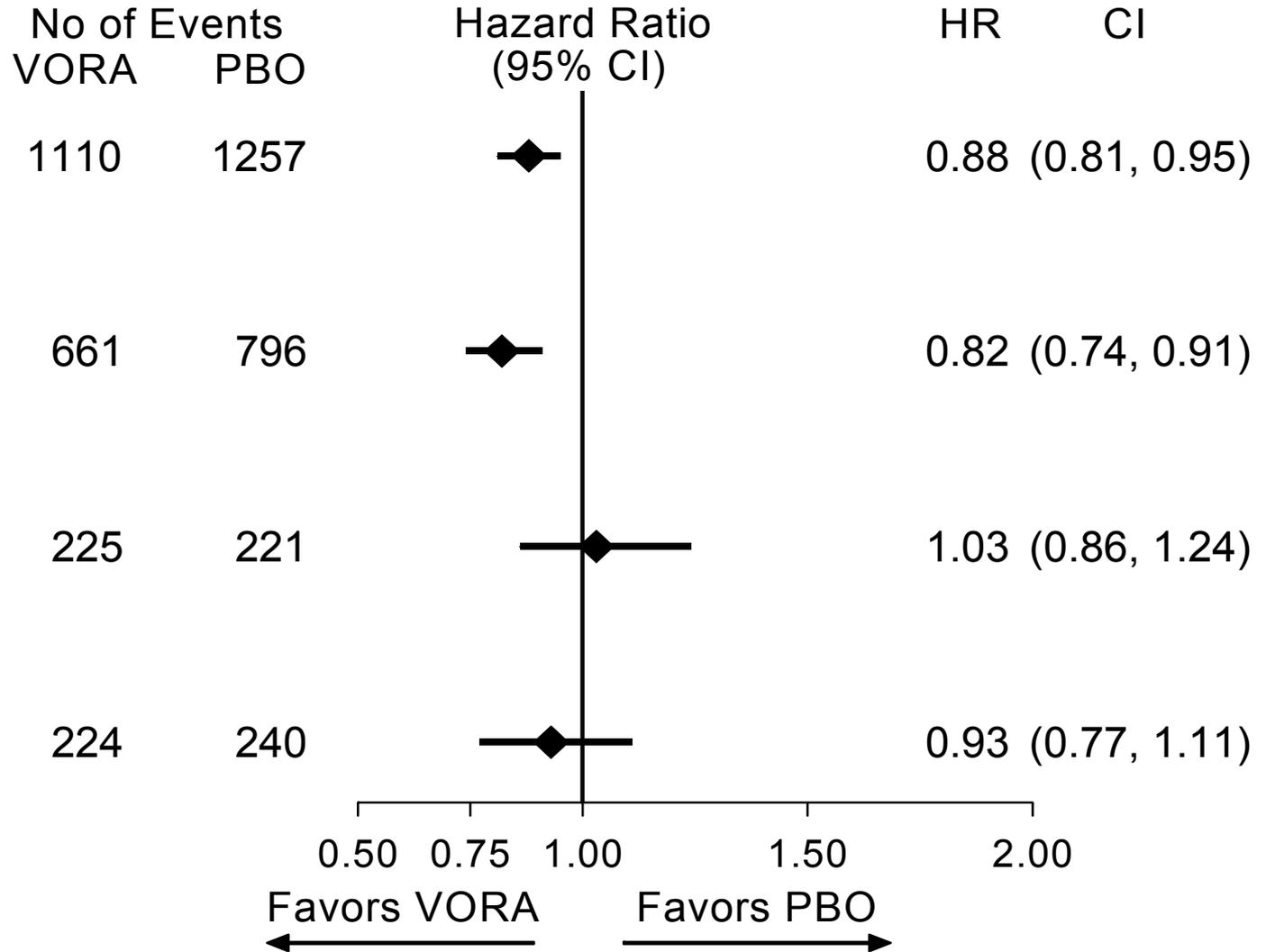
As-Treated (Randomization to Last Visit)

**Overall
Population
N=26,352**

**CAD
N=17,729**

**CVD
N=4860**

**PAD
N=3763**



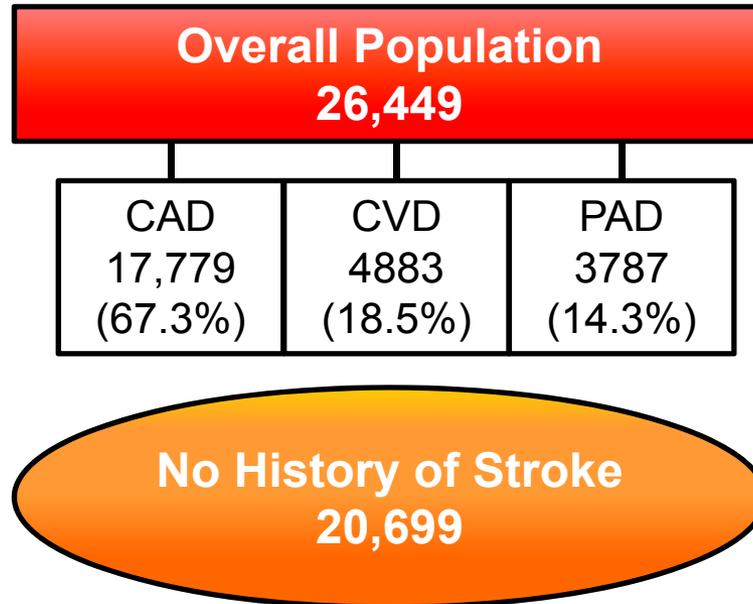
TRA 2°P – TIMI 50 Results in Proposed Label Population

Daniel Bloomfield, MD

*Vice President, Clinical Research
Therapeutic Area Head, Cardiovascular Disease
Merck Research Laboratories*

TRA 2°P – TIMI 50

Rationale for the Proposed Label Population



TRA 2°P – TIMI 50

Rationale for the Proposed Label Population Primary Efficacy Endpoint No History of Stroke

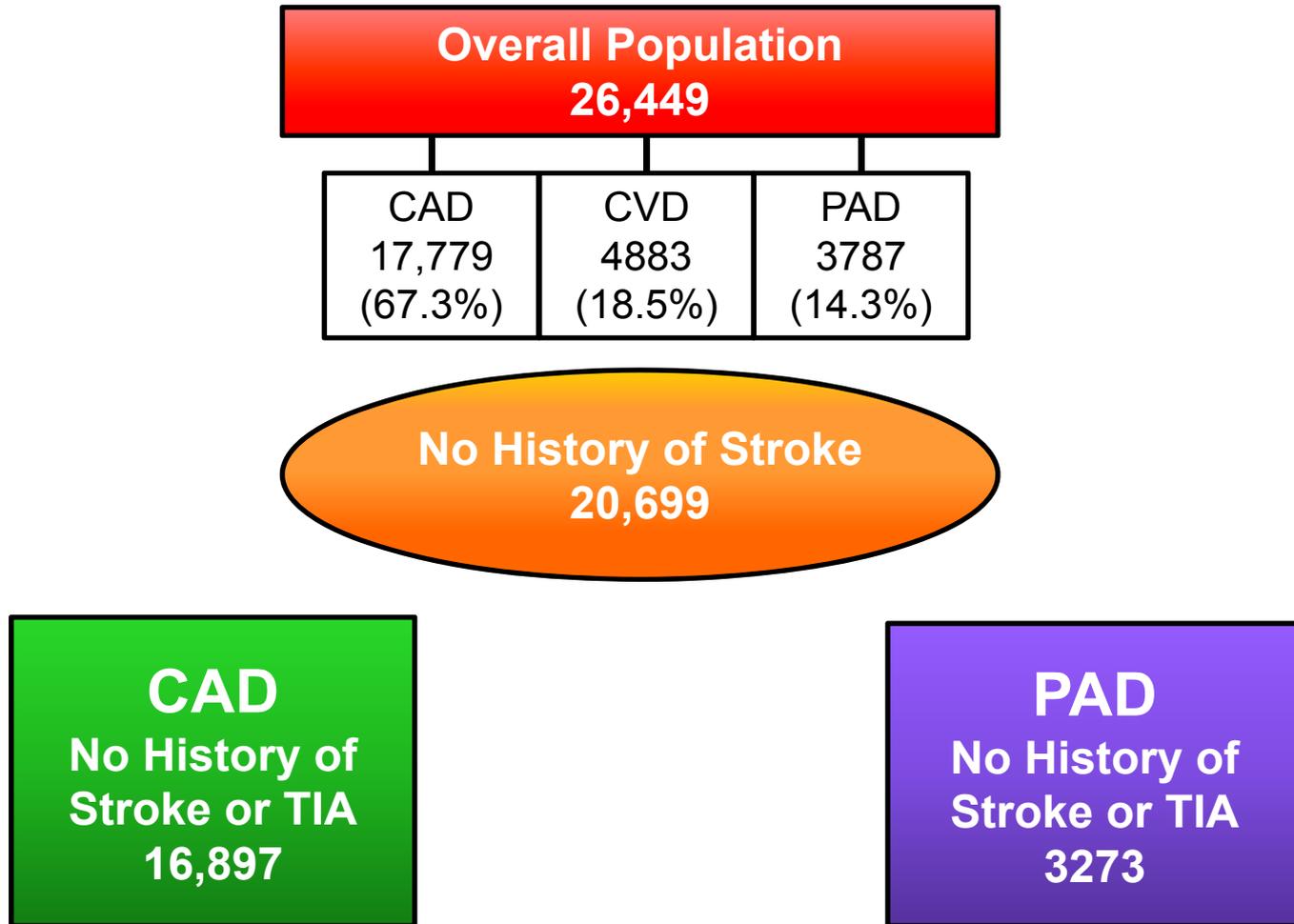
ITT (Randomization to Last Visit) 3-Year KM Rate

**No History of Stroke
20,699**

Population	Placebo		Vorapaxar		HR (95% CI)	p-Value
	n	KM%	n	KM%		
Overall	(N=13,224)		(N=13,225)			
	1417	12.4	1259	11.2	0.88 (0.82-0.95)	0.001
No history of stroke	(N=10,344)		(N=10,355)			
	1104	11.8	959	10.6	0.86 (0.79-0.94)	<0.001

TRA 2°P – TIMI 50

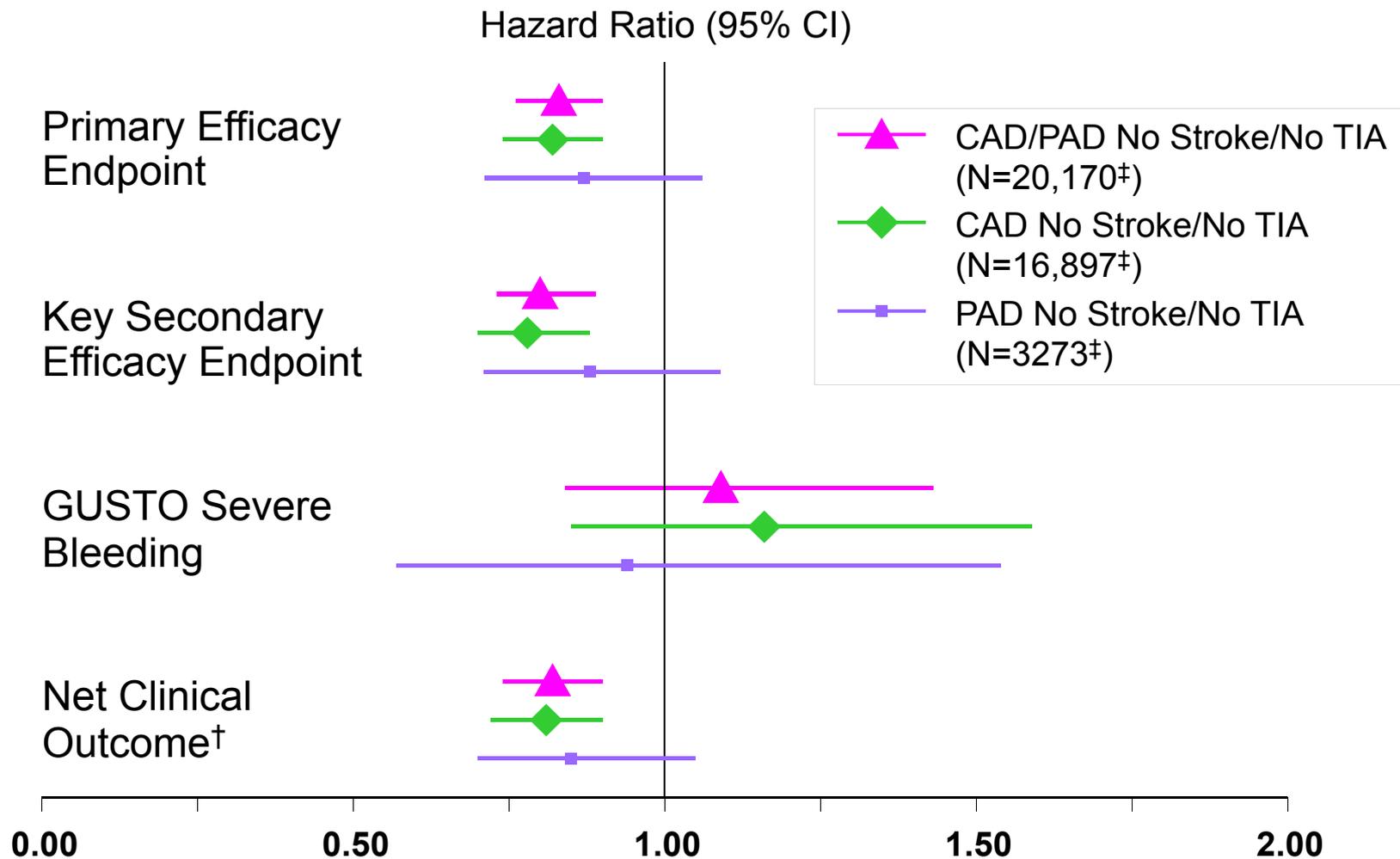
Rationale for the Proposed Label Population



Proposed Label Population

TRA 2°P – TIMI 50

CAD and PAD No History of Stroke or TIA



[†] CV death/MI/Stroke/GUSTO severe bleeding.

[‡] N corresponds to sample size associated with efficacy analysis population.

TRA 2°P – TIMI 50

Baseline Characteristics in the Proposed Label Population

**Proposed Label Population is defined as:
CAD (Post MI) patients with no history of stroke or TIA**

TRA 2°P – TIMI 50 Baseline Characteristics Proposed Label Population

All Randomized Subjects

	Placebo (N=8439)	Vorapaxar (N=8458)
Age (yrs, median Q1, Q3)	58 (51, 66)	59 (51, 66)
≥75 yrs (%)	7	7
Female (%)	20	20
Weight (kg, median Q1, Q3)	83 (73, 95)	83 (73, 93)
History of MI (%)	99.8	99.8
Any prior stroke (%)	0	0
History of PAD (%)	5	5
Diabetes (%)	21	21
Heart failure (%)	8	8
CrCl <60 mL/min/1.73 m ² (%)	8	9

TRA 2°P – TIMI 50 Background Therapy Proposed Label Population

All Randomized Subjects

	Placebo (N=8439)	Vorapaxar (N=8458)
Antiplatelet therapy (%)		
Naïve to antiplatelet therapy	1	1
ASA alone	21	21
Thienopyridine alone	1	1
ASA and Thienopyridine (DAPT)	77	77
Other medications at enrollment		
Lipid-lowering agent (%)	96	95
ACEI (%)	66	66
ARB (%)	13	12
Beta-blocker (%)	85	85

DAPT=dual antiplatelet therapy.

TRA 2°P – TIMI 50
Safety Results in the
Proposed Label Population

TRA 2°P – TIMI 50 Bleeding Endpoints Proposed Label Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

	Placebo (N=8412)		Vorapaxar (N=8444)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
GUSTO bleeding categories					
Severe or moderate	156	2.2	231	3.1	1.48 (1.21-1.82)
Severe	73	1.0	85	1.2	1.16 (0.85-1.59)
Moderate	88	1.2	152	2.1	1.73 (1.33-2.25)
TIMI bleeding categories					
Clinically significant	785	10.2	1120	14.6	1.46 (1.34-1.60)
CABG-related major	8	0.1	8	0.1	1.00 (0.37-2.66)

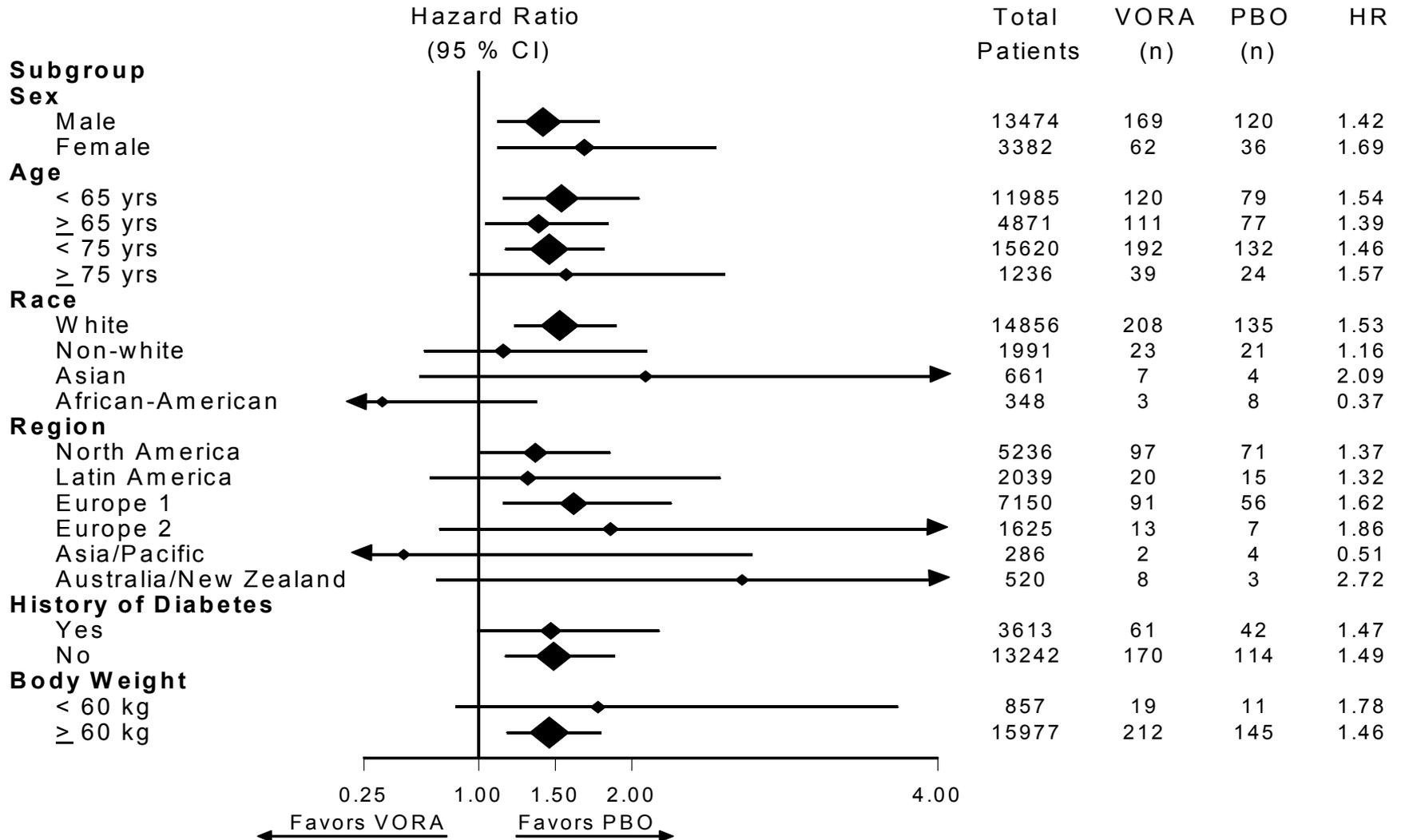
TRA 2°P – TIMI 50 Bleeding Endpoints Proposed Label Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

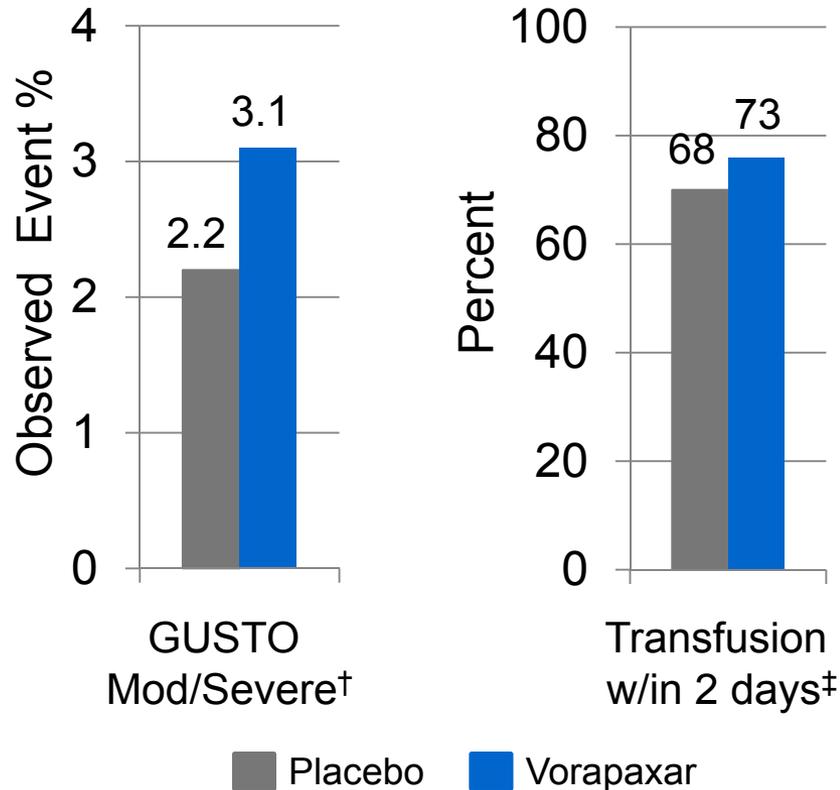
	Placebo (N=8412)		Vorapaxar (N=8444)		Hazard Ratio (95% CI)
	n	KM%	n	KM%	
Other categories					
Intracranial hemorrhage	30	0.5	38	0.5	1.26 (0.78-2.03)
Fatal ICH	8	0.1	10	0.2	1.24 (0.49-3.14)
Fatal bleeding	14	0.2	14	0.2	0.99 (0.47-2.09)

TRA 2°P – TIMI 50 GUSTO Severe or Moderate Bleeding Proposed Label Population

As-Treated (Randomization to Last Visit)



TRA 2°P – TIMI 50 Management of Bleeding Was Similar Between Vorapaxar and Placebo Proposed Label Population



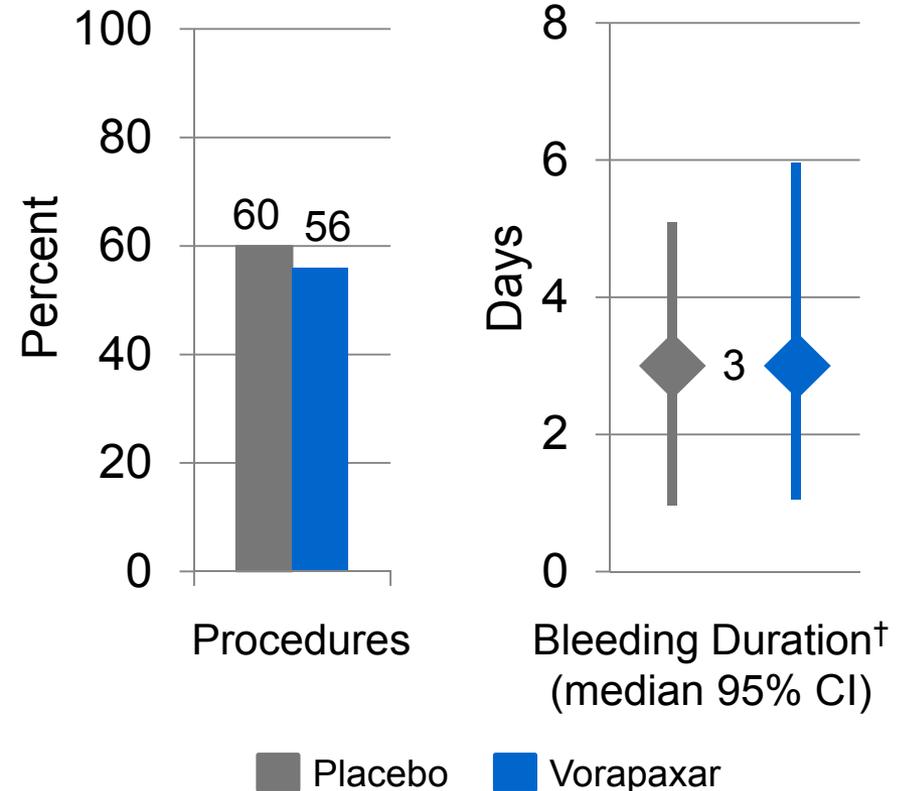
- Vorapaxar was associated with an increase in GUSTO moderate/severe bleeding
- Need for transfusions was similar with vorapaxar and placebo

† Event accrual period: from randomization to last visit.

‡ Packed red blood cells or whole blood.

TRA 2°P – TIMI 50 Management of GI Bleeding Was Similar Between Vorapaxar and Placebo Proposed Label Population

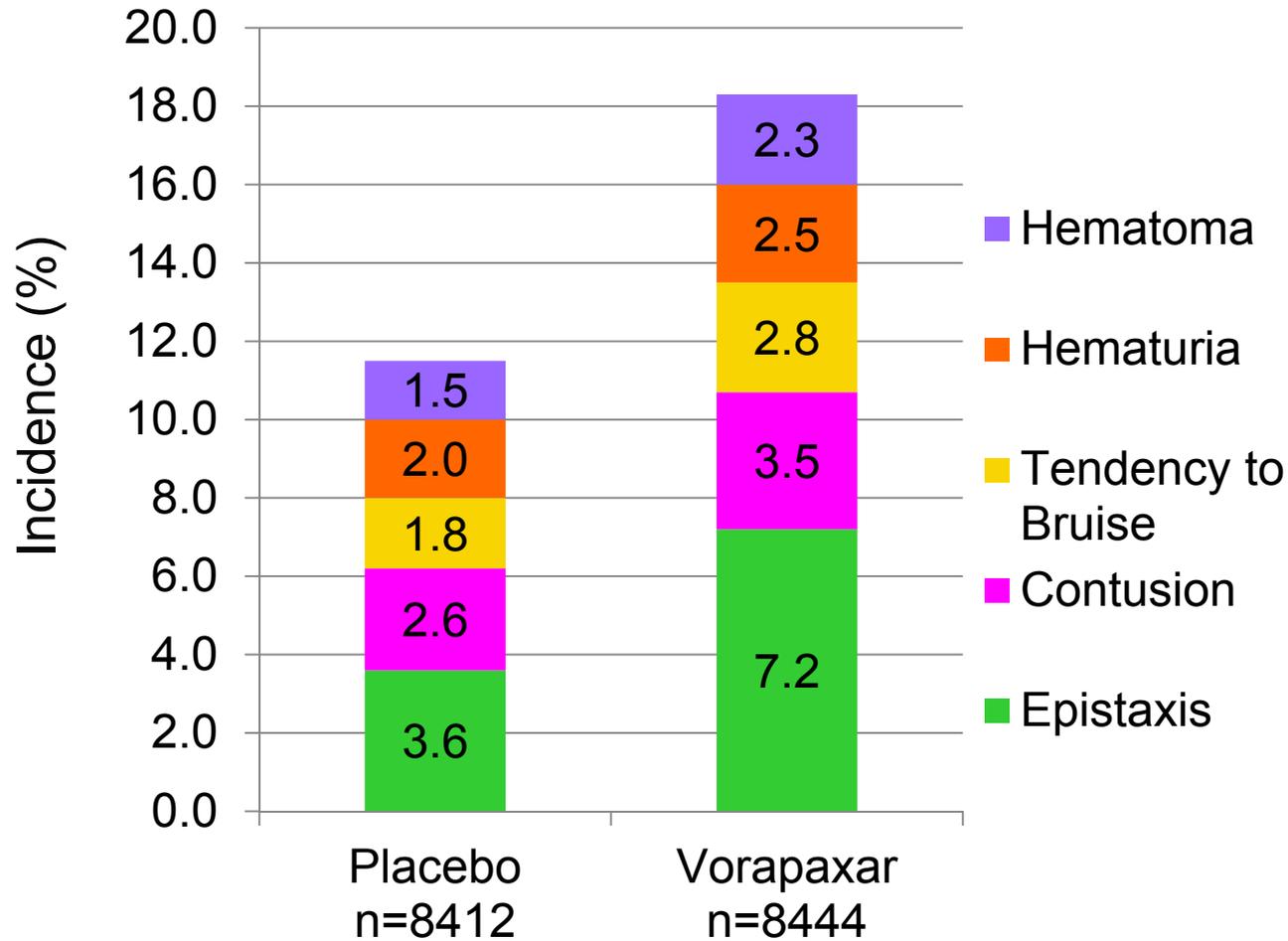
- Most common source of GUSTO moderate/severe bleeding was GI
- Vorapaxar and placebo had similar
 - Need for endoscopic procedures
 - Median bleeding duration following endoscopic procedure



† Duration from first procedure.

TRA 2°P – TIMI 50 Individual Bleeding Events Proposed Label Population

As-Treated, >2% Subjects (During Treatment)
Investigator Reported Bleeding Location



TRA 2°P – TIMI 50 Treatment Discontinuation Due to Bleeding Events Proposed Label Population

As-Treated (≥10 Subjects in Either Group)

	Placebo (N=8412)	Vorapaxar (N=8444)
	n (%)	n (%)
Subjects with any AE [†]	146 (1.7)	246 (2.9)
Epistaxis	16 (0.2)	40 (0.5)
Melena	9 (0.1)	23 (0.3)
Rectal hemorrhage	12 (0.1)	16 (0.2)
Gastrointestinal hemorrhage	6 (0.1)	10 (0.1)
Hematuria	16 (0.2)	16 (0.2)
Intracranial hemorrhage	9 (0.1)	14 (0.2)
Increased tendency to bruise	3 (<0.1)	14 (0.2)
Contusion	6 (0.1)	10 (0.1)

[†] Subjects who died during treatment were considered to have completed, and are excluded.

TRA 2°P – TIMI 50 Safety Summary

Proposed Label Population

- In the Proposed Label Population, over the 3-year duration of the study
 - The risks of GUSTO moderate or severe bleeding was greater in the vorapaxar group compared to placebo (3.1% vs. 2.2%)
 - The risks of ICH (0.5% vs. 0.5%) and fatal bleeding (0.2% vs. 0.2%) were similar with vorapaxar compared to placebo
- The risk of GUSTO severe bleeding was reduced in the Proposed Label Population compared to the Overall Population
- Most frequent site of GUSTO moderate bleeding was GI
- Management of bleeding was similar whether the bleed occurred on vorapaxar or placebo

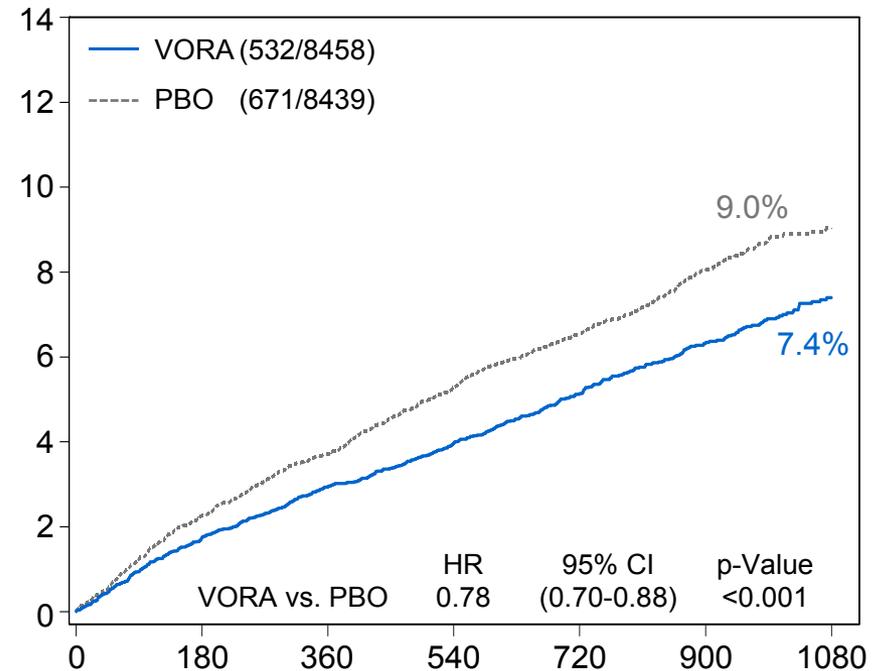
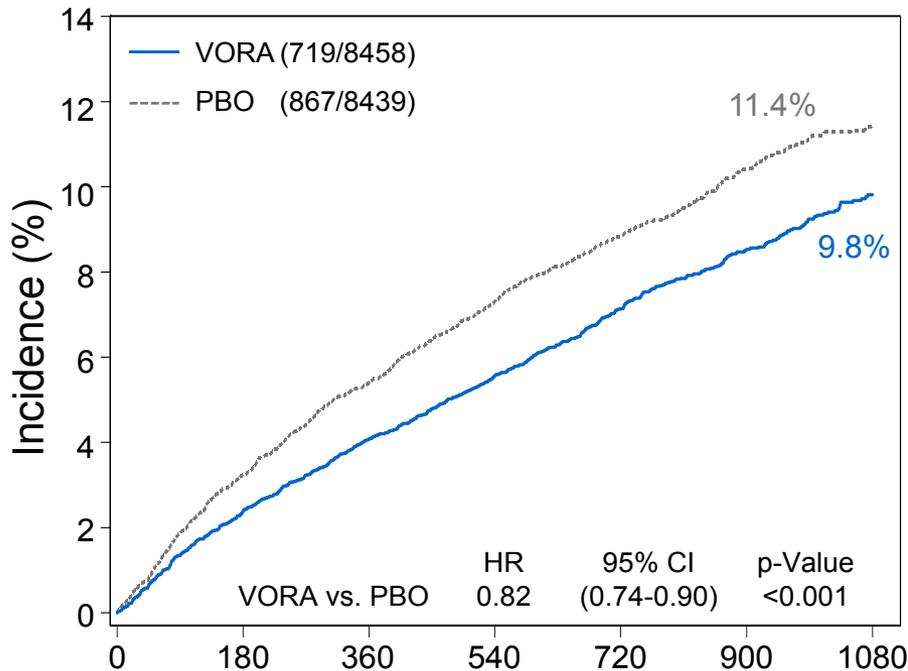
TRA 2°P – TIMI 50
Efficacy Results in the
Proposed Label Population

TRA 2°P – TIMI 50 Vorapaxar Demonstrated Robust Outcomes Benefit in the Proposed Label Population

ITT (Randomization to Last Visit) 3-Year KM Rate

Primary Efficacy Endpoint
(CV Death, MI, Stroke, UCR)

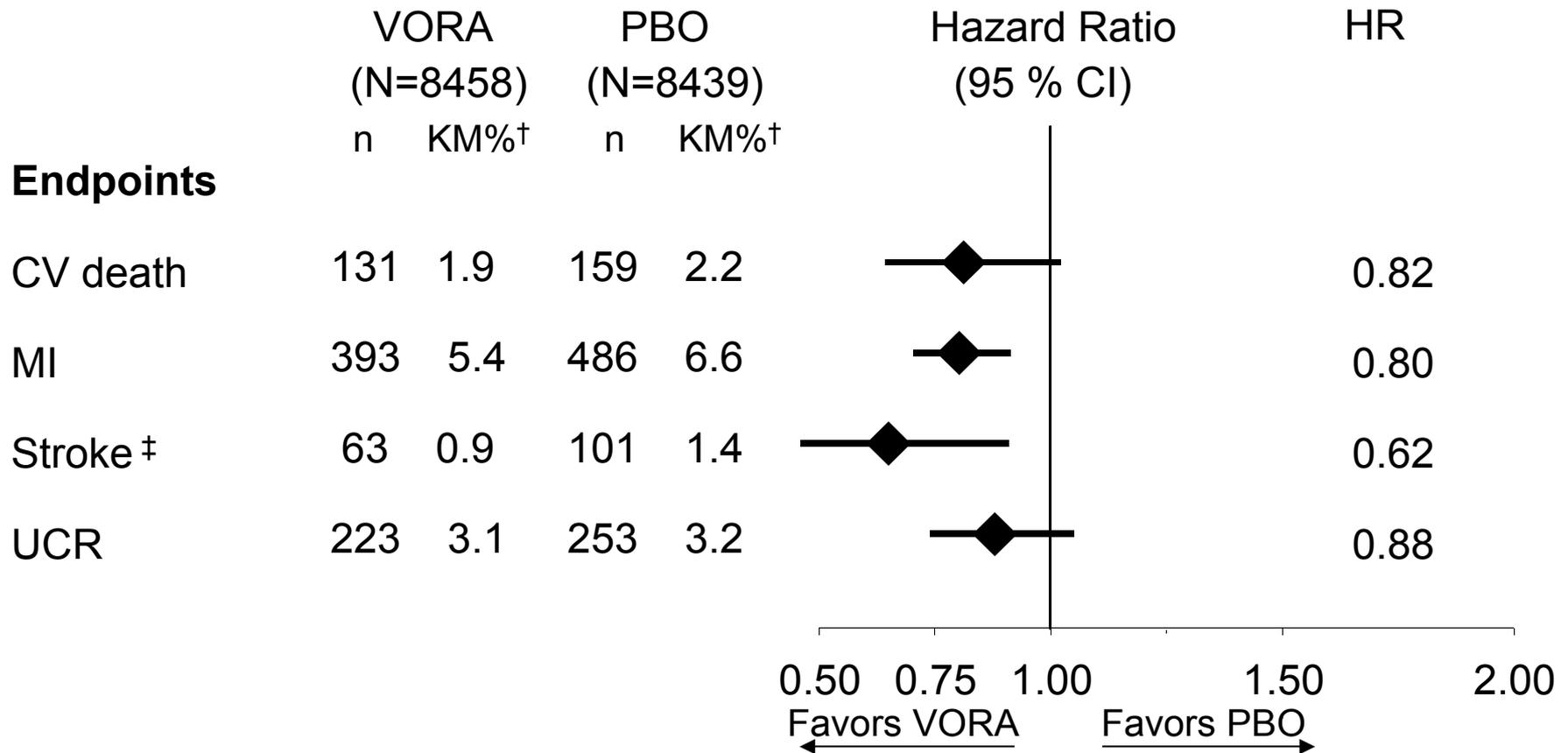
Key Secondary Efficacy Endpoint
(CV Death, MI, Stroke)



Days from Randomization

TRA 2°P – TIMI 50 Time to First Event Other Secondary Efficacy Endpoints Proposed Label Population

ITT (Randomization to Last Visit)



[†] KM rate at 1080 days.

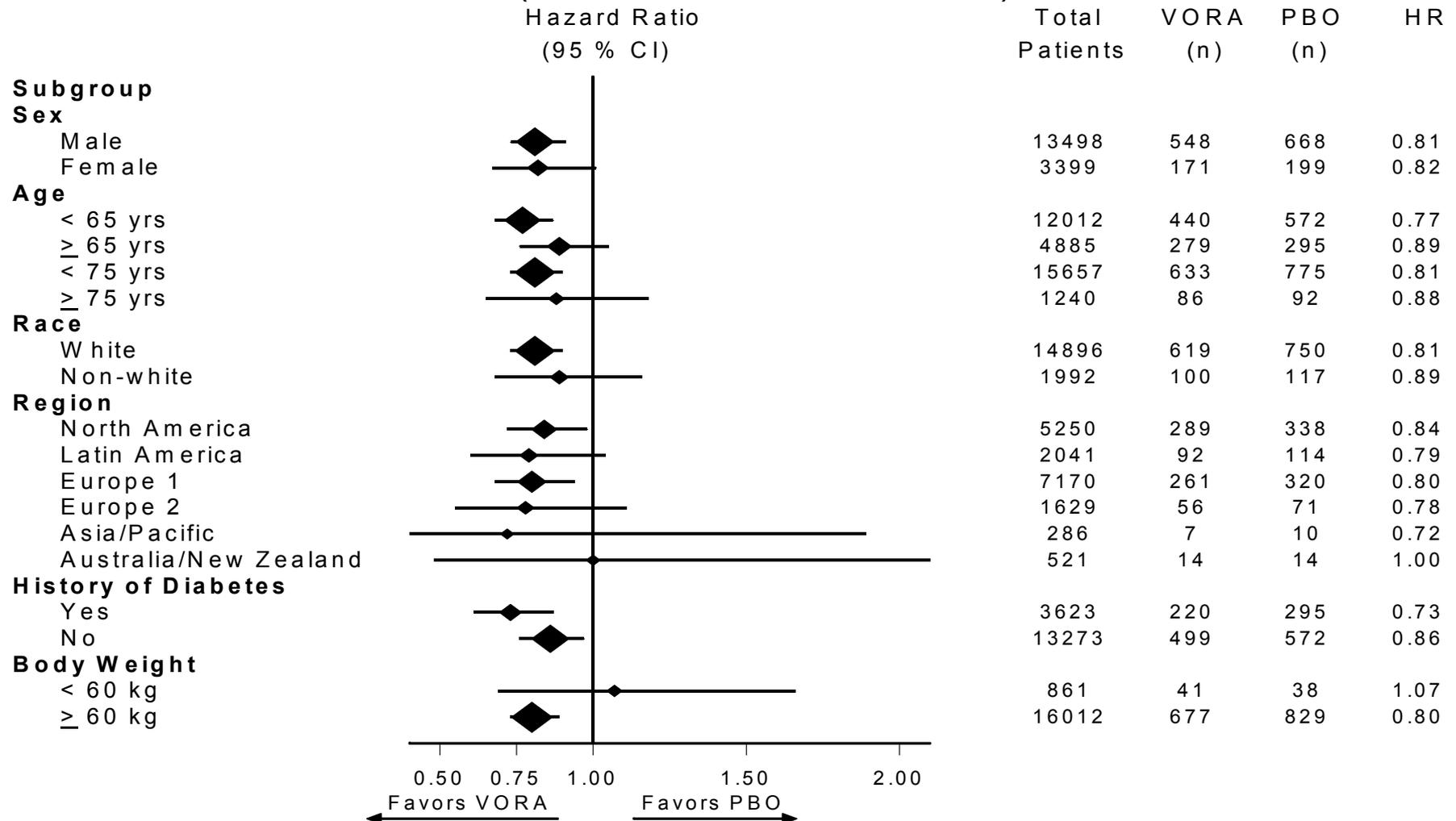
[‡] Includes ischemic and hemorrhagic.

TRA 2°P – TIMI 50

Primary Efficacy Endpoint by Subgroups

Proposed Label Population

ITT (Randomization to Last Visit)



TRA 2°P – TIMI 50 Role of Baseline Therapy

Primary Efficacy Endpoint

Proposed Label Population

ITT (Randomization to Last Visit) 3-Year KM Rate

	Placebo (N=8439)		Vorapaxar (N=8458)		Hazard Ratio (95% CI)
	n/N	KM%	n/N	KM%	
Thienopyridine use at baseline					
Yes	700/6631	11.8	576/6604	10.0	0.82 (0.73-0.91)
No	167/1808	10.2	143/1854	9.1	0.82 (0.65-1.02)
Aspirin use at baseline					
Yes	848/8298	11.4	707/8315	9.8	0.82 (0.74-0.91)
No	19/141	14.1	12/143	10.4	0.56 (0.27-1.16)

TRA 2°P – TIMI 50

Multiple Occurrences Component Events

Proposed Label Population

ITT (Randomization to Last Visit)

	Placebo (N=8439)	Vorapaxar (N=8458)	Hazard Ratio (95% CI)	p-Value
Primary efficacy endpoint (CV death/MI/stroke/UCR)	1160	936	0.80 (0.74-0.88)	<0.001
Key secondary endpoint (CV death/MI/stroke)	862	689	0.80 (0.72-0.88)	<0.001
MI	598	491	0.82 (0.72-0.92)	<0.001

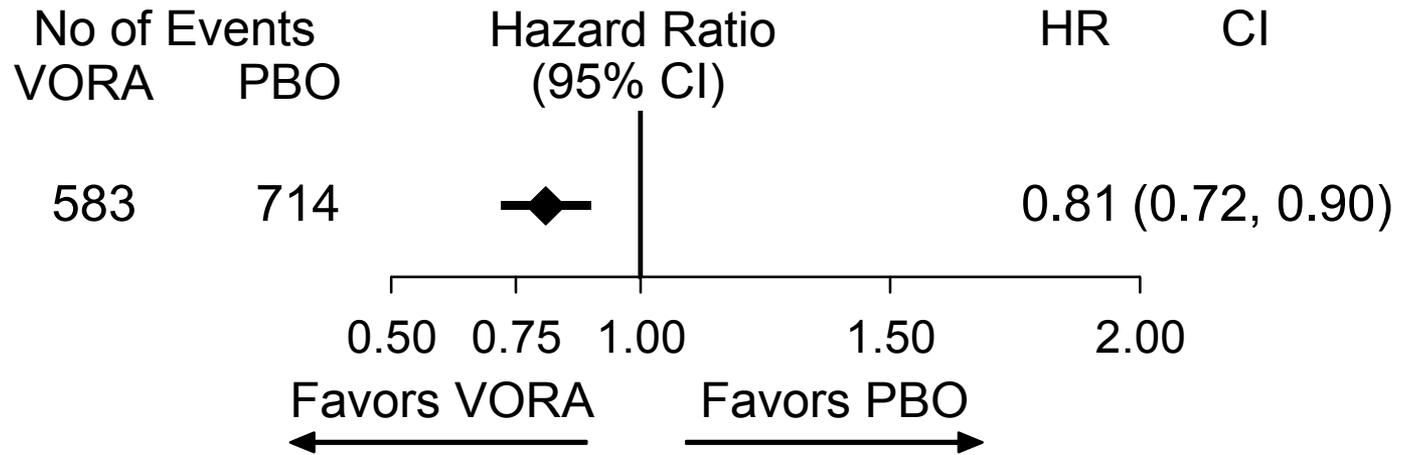
TRA 2°P – TIMI 50 Efficacy Summary

Proposed Label Population

- Vorapaxar reduced the primary and key secondary efficacy endpoint compared to placebo
 - 18% treatment effect for the primary endpoint
 - 22% treatment effect for the key secondary endpoint
- Result was robust and consistent across pre-specified secondary atherothrombotic endpoints
 - 20% reduction in MI
 - 38% reduction in first stroke
- Treatment effect was durable and persisted over the length of the study
- There was a consistency of effect among the subgroups examined with the exception of body weight <60 kg

TRA 2°P – TIMI 50 Proposed Label Population Optimizes the Benefit-Risk Net Clinical Outcome (CV Death/MI/Stroke/GUSTO Severe)

As-Treated (Randomization to Last Visit)



**Proposed
Label
N=16,856**

Vorapaxar Patient Selection

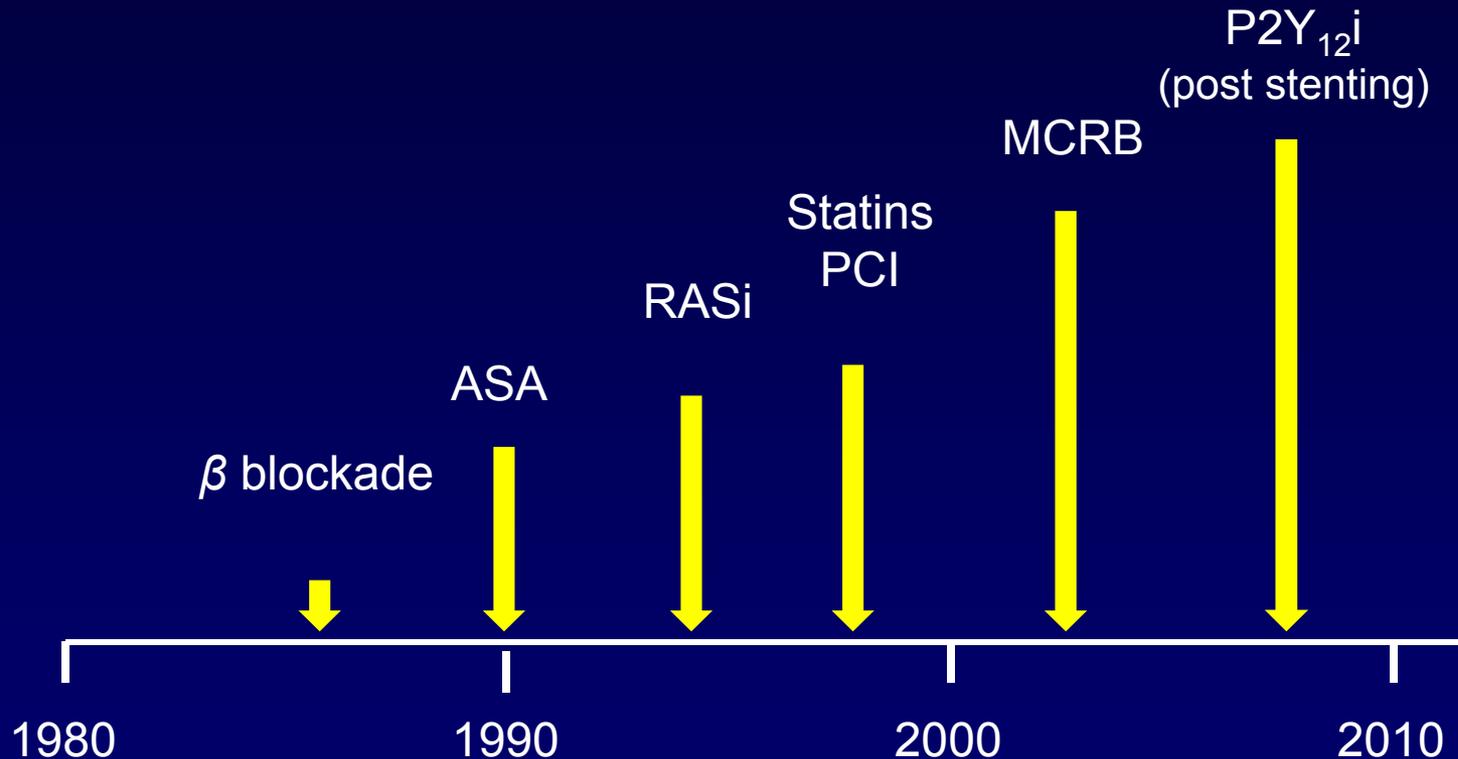
- Vorapaxar should be prescribed to appropriate post MI patients at risk for secondary atherothrombotic events
 - Initiated in stable patients >2 weeks after an MI on antiplatelet therapy
 - Not to be initiated for the first time in patients presenting with an ACS
- Vorapaxar should be contraindicated in patients with a history of stroke, TIA, ICH, or active pathological bleeding
- Vorapaxar should be used with caution in patients with the following risk factors
 - Low body weight (<60 kg)
 - Older age
 - History of bleeding diathesis

Benefit-Risk

Eugene Braunwald, MD

*Founding Chairman, TIMI Study Group
Brigham and Women's Hospital*

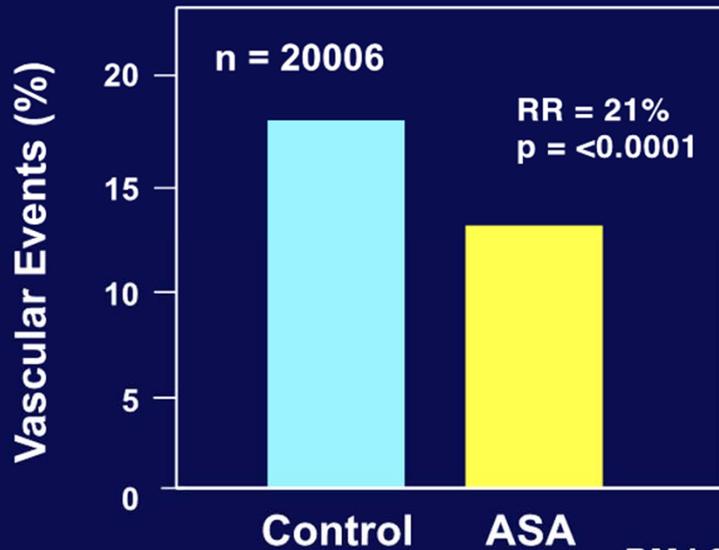
Evolution of Post AMI Therapy



ASA=aspirin; RASi=renin-angiotensin system inhibitor;
PCI=percutaneous coronary intervention; MCRB=mineralocorticoid receptor blocker.

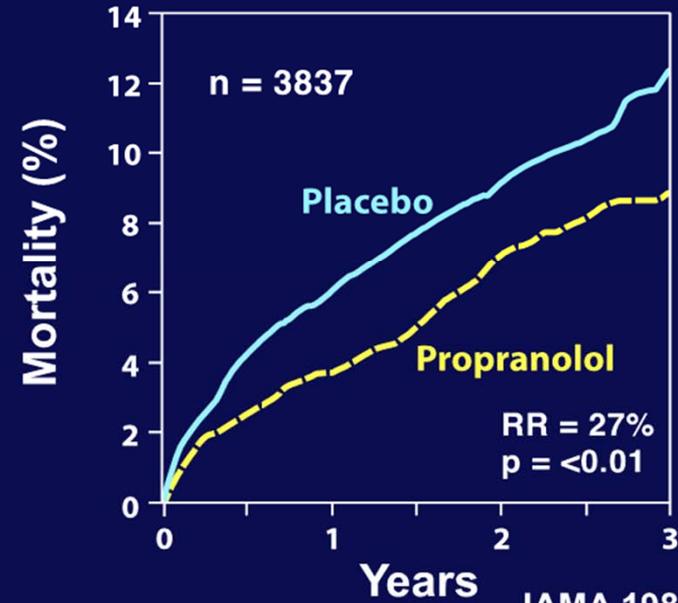
RESIDUAL RISK POST AMI – a Continuing Problem

ASA Rx Post MI



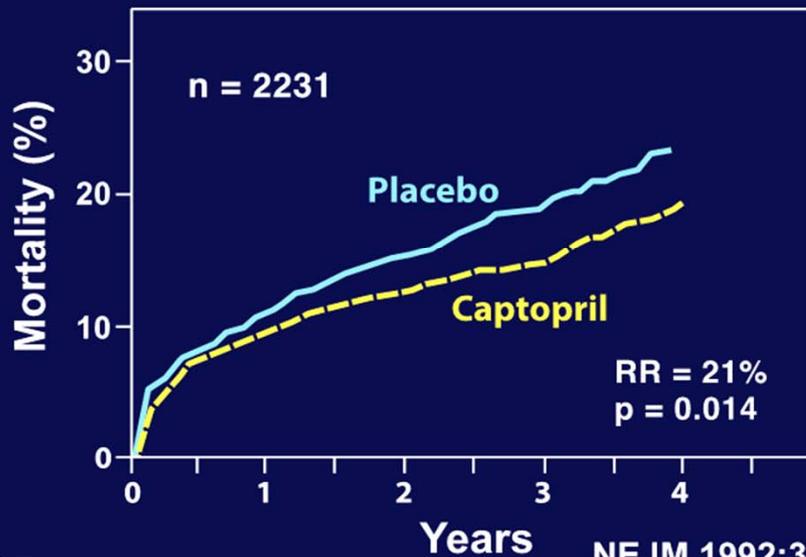
BMJ 2002;324:71

BHAT



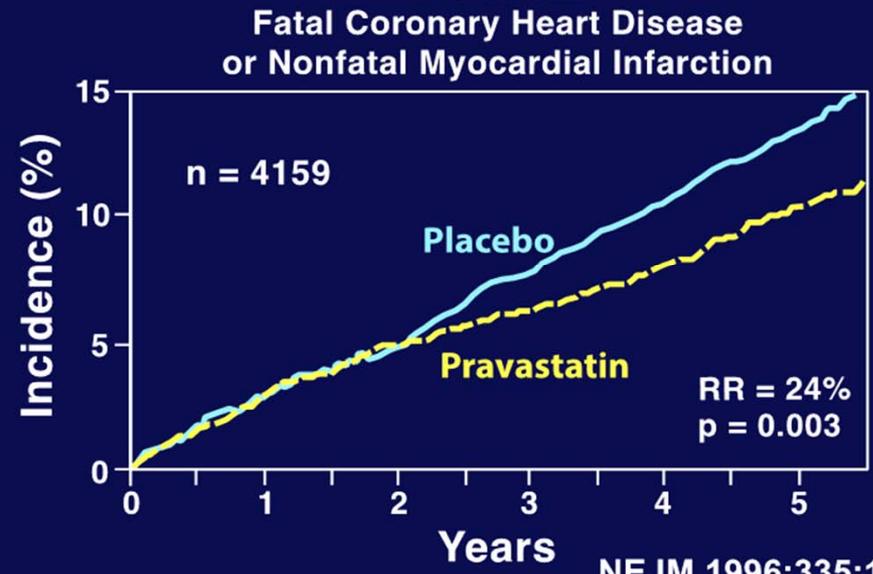
JAMA 1982;247:1707

SAVE



NEJM 1992;327:669

CARE



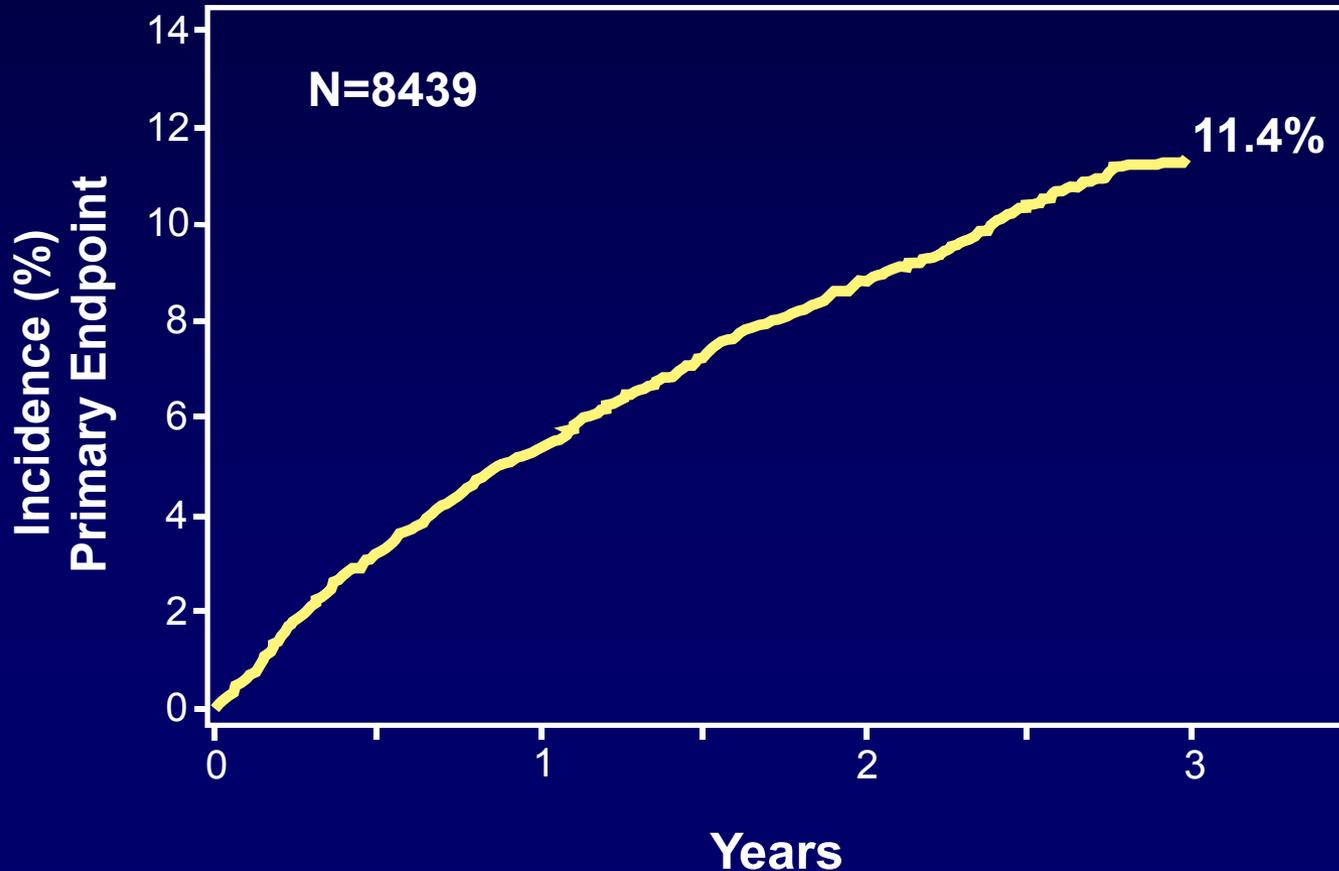
NEJM 1996;335:1001

N=16,897 pts

Baseline Treatment Percentage

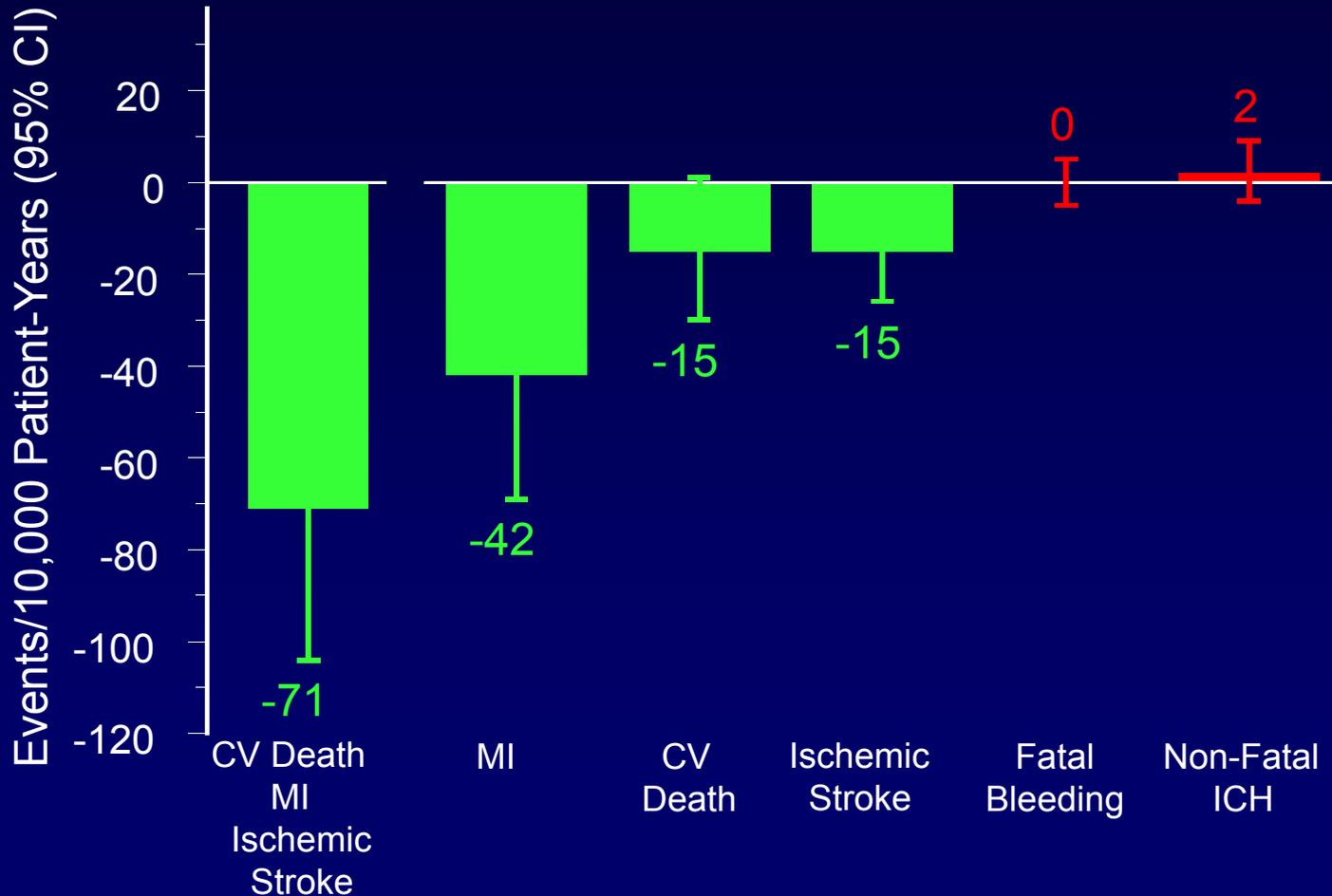
Aspirin	98.3
Statin	95.4
HO PCI	86.0
Beta-blocker	85.2
ACEi/ARB	78.6
Thienopyridine	78.3
<hr/>	
BP systolic	129 mmHg
diastolic	78 mmHg

Proposed Label Population Placebo



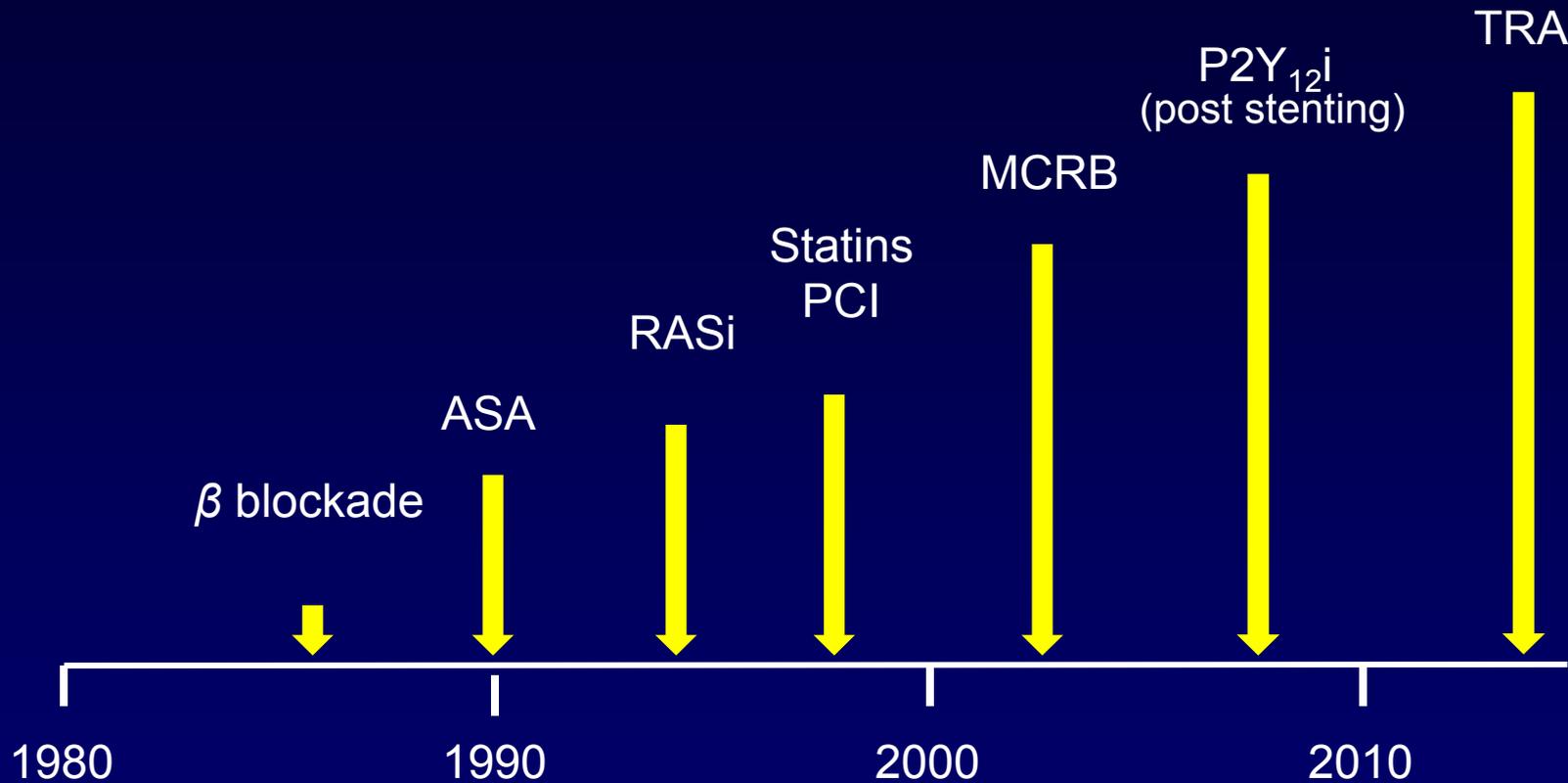
Proposed Label Population

Risk Differences – Vorapaxar vs. Placebo *First Serious (Irreversible) Events*



- Patients with an established history of MI are at risk of future cardiac (MI) or cerebral (ischemic stroke) events and vascular death
- Each year, approximately 525,000 Americans have a new MI, and approximately 190,000 have a recurrent event despite advances in therapy
- Vorapaxar provides substantial net clinical benefit to patients post MI without a history of stroke or TIA

Evolution of Post AMI Therapy



ASA=aspirin; RASi=renin-angiotensin system inhibitor;
PCI=percutaneous coronary intervention; MCRB=mineralocorticoid receptor blocker;
TRA=thrombin receptor antagonist.

TRA 2°P – TIMI 50

Efficacy Endpoints Overrun

- Sensitivity analyses to assess the effect of vorapaxar were conducted at various time points so that the numbers of pre-specified primary efficacy events (2279) or key secondary efficacy events (1400) were reached, respectively
- In addition, an additional analysis at the time point when all subjects would have been followed for at least one year was also conducted
- The 3 sensitivity analyses yielded results consistent among themselves and with the overall primary and key secondary efficacy results

TRA 2°P – TIMI 50 Sensitivity Analysis

Primary and key secondary efficacy endpoints: ITT Population
 event accrual period: Randomization to the time point when **approximately 1400**
 (reached 24JUN2010) key secondary endpoint events had occurred

	Placebo (N=13,224)	Vorapaxar (N=13,225)	Hazard Ratio (95% CI)	p-Value
	Subjects With Events (%)	Subjects With Events (%)		
Primary efficacy endpoint (CV death/MI/stroke/UCR)	945 (7.1)	808 (6.1)	0.85 (0.77-0.93)	<.001
CV death	122 (0.9)	95 (0.7)		
MI	400 (3.0)	342 (2.6)		
Stroke	207 (1.6)	200 (1.5)		
UCR	216 (1.6)	171 (1.3)		
Key secondary efficacy endpoint (CV death/MI/stroke)	757 (5.7)	646 (4.9)	0.85 (0.76-0.94)	0.002
CV death	125 (0.9)	97 (0.7)		
MI	423 (3.2)	349 (2.6)		
Stroke	209 (1.6)	200 (1.5)		

TRA 2°P – TIMI 50 Sensitivity Analysis

Primary and key secondary efficacy endpoints: ITT Population
 event accrual period: Randomization to the time point when **approximately 1322**
 (reached 12MAY2010) key secondary endpoint events had occurred

	Placebo (N=13,224)	Vorapaxar (N=13,225)	Hazard Ratio (95% CI)	p-Value
	Subjects With Events (%)			
Primary efficacy endpoint (CV death/MI/stroke/UCR)	895 (6.8)	757 (5.7)	0.84 (0.76-0.92)	<.001
CV death	114 (0.9)	91 (0.7)		
MI	376 (2.8)	318 (2.4)		
Stroke	199 (1.5)	190 (1.4)		
UCR	206 (1.6)	158 (1.2)		
Key secondary efficacy endpoint (CV death/MI/stroke)	717 (5.4)	607 (4.6)	0.84 (0.75-0.94)	0.002
CV death	117 (0.9)	93 (0.7)		
MI	399 (3.0)	324 (2.4)		
Stroke	201 (1.5)	190 (1.4)		

TRA 2°P – TIMI 50

Time to First GUSTO Severe Bleeding Event by Time of Qualifying MI

Proposed Label Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

Post MI Time	Placebo (n/N)	KM%	Vorapaxar (n/N)	KM%	Hazard Ratio (95% CI)
<3 months	33/3756	1.0	39/3681	1.2	1.20 (0.76-1.91)
3-6 months	19/2455	1.1	27/2443	1.4	1.43 (0.80-2.58)
>6 months	21/2163	1.0	19/2289	0.9	0.85 (0.46-1.58)

TRA 2°P – TIMI 50 Principal Reduction Seen in Spontaneous MI Overall Population

ITT (Randomization to Last Visit)

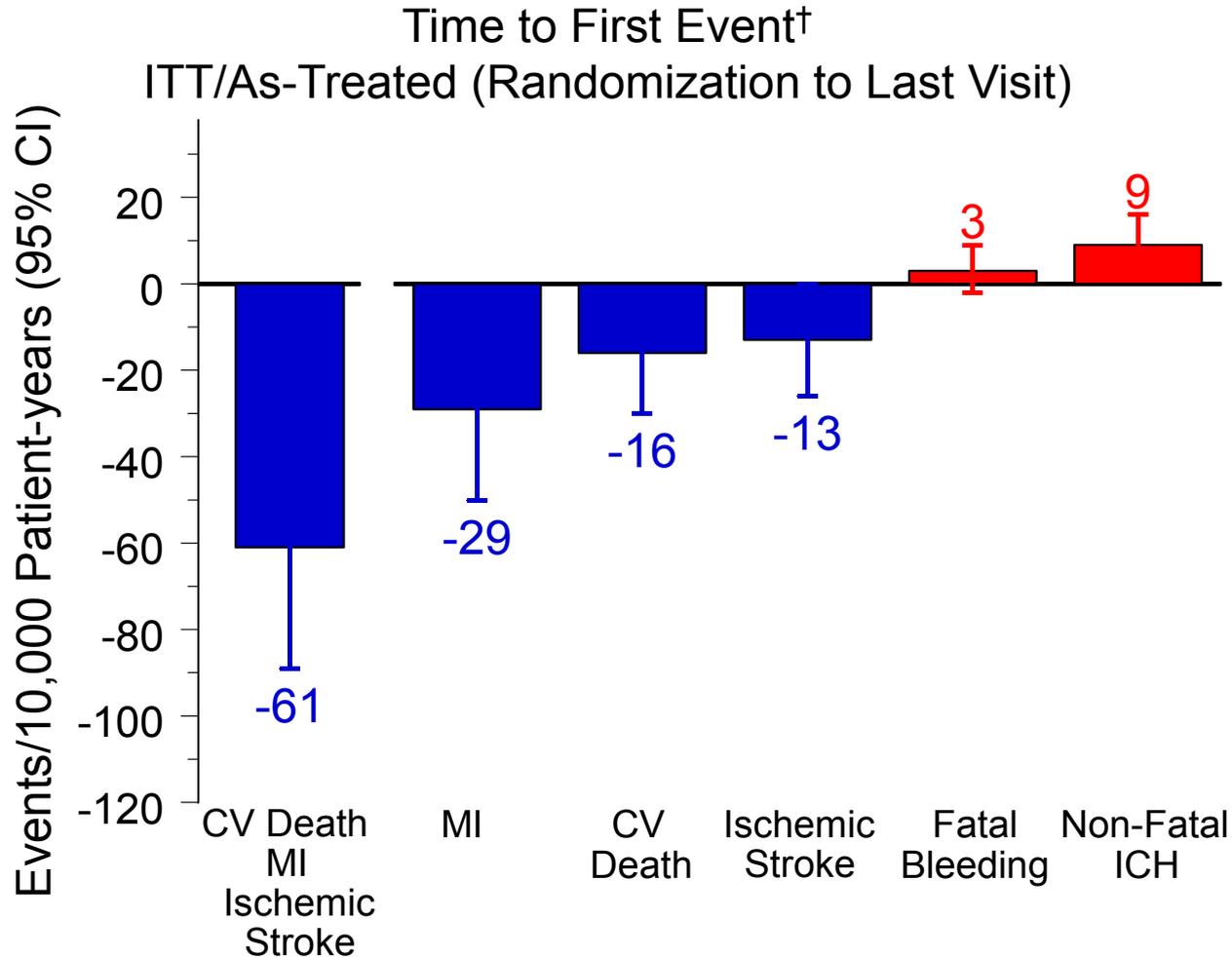
Endpoints	Placebo (N=13,224) n (%)	Vorapaxar (N=13,225) n (%)	p-Value [†]
Myocardial infarction	673	564	0.001
Type 1, spontaneous	523 (4.0)	436 (3.3)	
Type 2, secondary	69 (0.5)	55 (0.4)	
Type 3, with sudden death	2 (<0.1)	2 (<0.1)	
Type 4a, associated with PCI	7 (0.1)	13 (0.1)	
Type 4b, associated with stent thrombosis	69 (0.5)	58 (0.4)	
Type 5, associated with CABG	3 (<0.1)	0	

[†] p-Value reflects significant level from time to first occurrence.

TRA 2°P – TIMI 50

Risk Differences (Vorapaxar vs. Placebo)

Overall Population



† CV death excluding fatal bleeding, MI excluding CV death, or ischemic stroke excluding CV death.

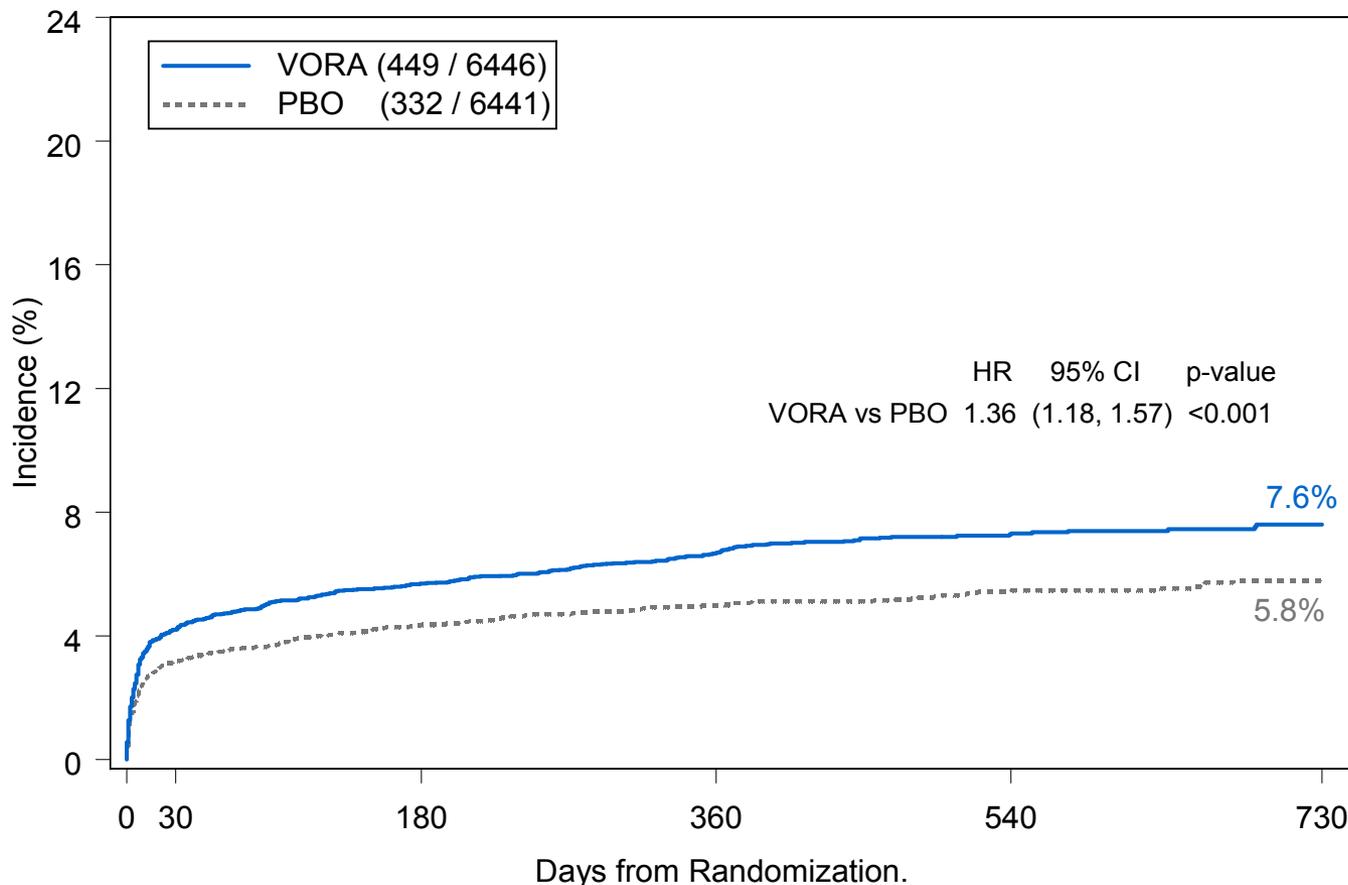
TRA 2°P – TIMI 50 GUSTO Severe or Moderate Bleeding Overall Population

Receiving Transfusion Within 2 Days of Any Bleeding Event

	Placebo n (%)	Vorapaxar n (%)
Number of subjects with a bleeding event	316	473
Any transfusion	221 (69.9)	332 (70.2)
Whole blood transfusion	46 (14.6)	71 (15.0)
Packed red blood cell transfusion	170 (53.8)	254 (53.7)
Whole blood and/or PRBC transfusion	213 (67.4)	316 (66.8)
<3 units	113 (35.8)	175 (37.0)
3-5 units	67 (21.2)	108 (22.8)
>5 units	25 (7.9)	26 (5.5)
Missing	8 (2.5)	7 (1.5)
Platelet transfusion	30 (9.5)	44 (9.3)
Fresh-frozen plasma transfusion	35 (11.1)	44 (9.3)
Cryoprecipitate transfusion	1 (0.3)	7 (1.5)
Missing	0	3 (0.6)

TRACER Time to First Occurrence of GUSTO Severe or Moderate Bleeding

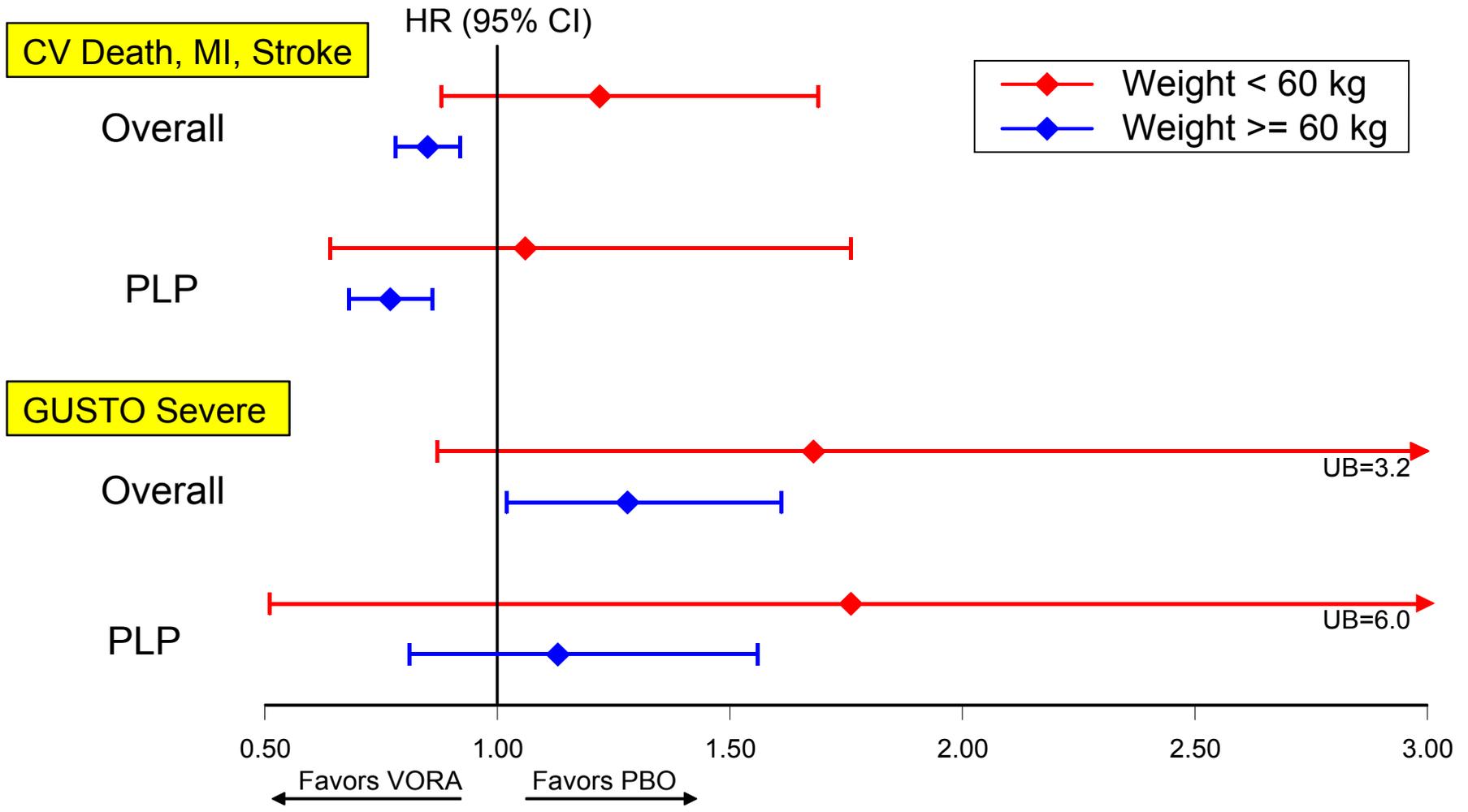
As Treated (Randomization to Last Visit) 2-Year KM Rate



No. at Risk:

	0	30	180	360	540	730
— VORA	6010	5653	4252	2520	896	
..... PBO	6048	5691	4293	2578	913	

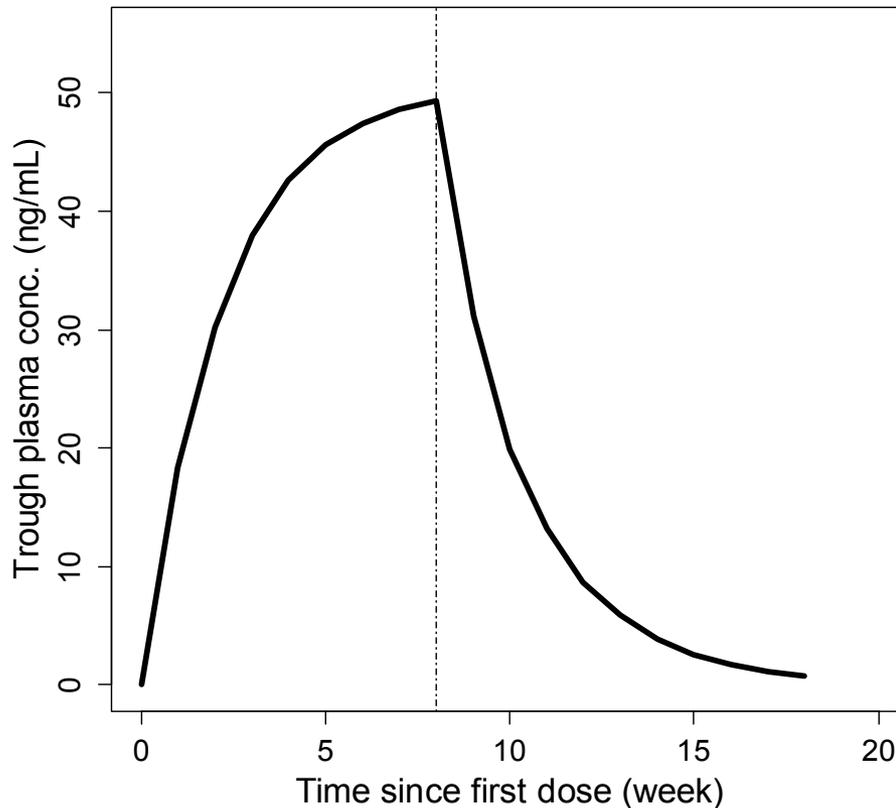
TRA 2°P – TIMI 50 Effect of Weight (<60 kg) on Safety and Efficacy of Vorapaxar



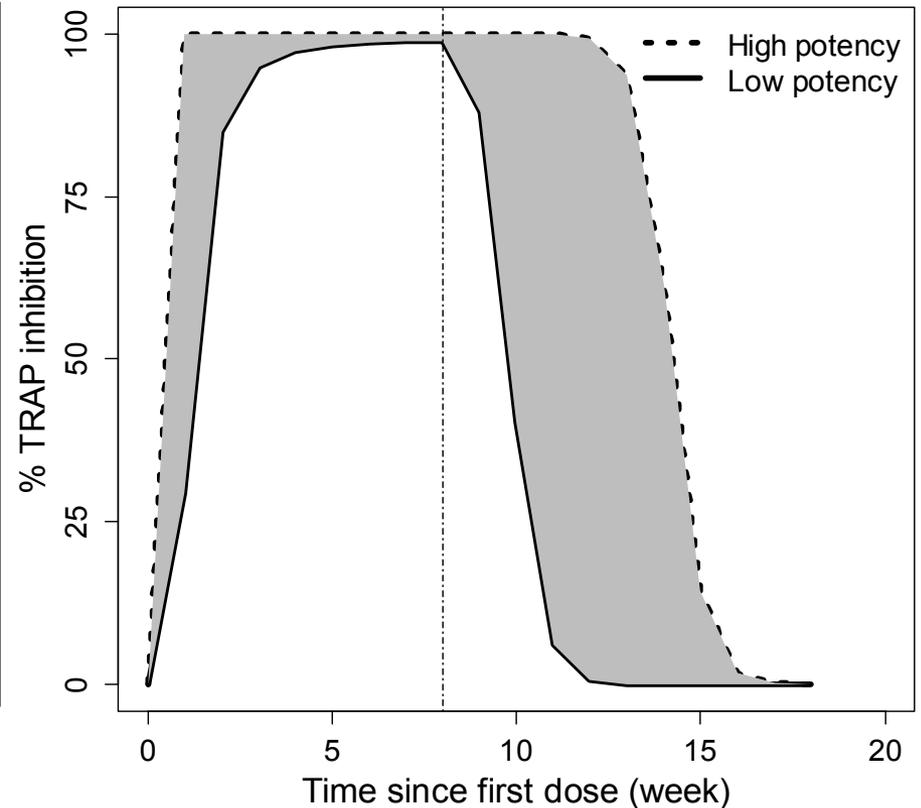
UB=upper bound of the 95% CI.

Vorapaxar PK and TRAP: On- and Off-Treatment

8 weeks of dosing and 10 weeks of washout



8 weeks of dosing and 10 weeks of washout



Vorapaxar pharmacokinetics (left panel, C_{trough}) and TRAP-induced platelet aggregation inhibition over time (right panel, TIPA) dosing 2.5 mg to steady state and subsequent cessation (vertical line). Upper and lower lines represent median TRAP response based on simulations using low EC_{50} (high potency) and high EC_{50} (low potency) estimates, respectively. Area between the two lines is shaded.

TRA 2°P – TIMI 50 Subject Disposition

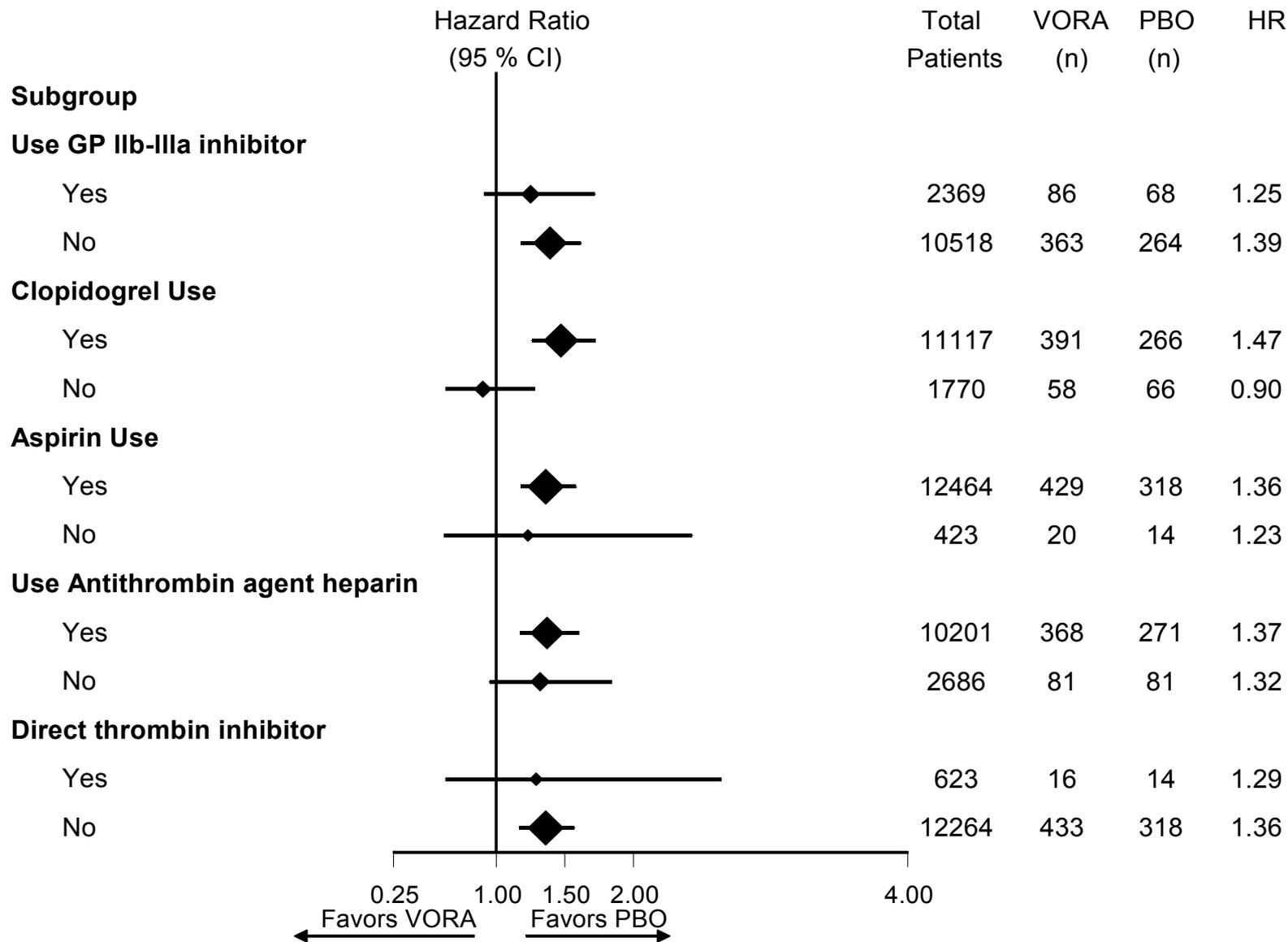
	Placebo (N=13,224) n (%)	Vorapaxar (N=13,225) n (%)
Received allocated intervention	13,166 (99.6)	13,186 (99.7)
Never received study drug	58 (0.4)	39 (0.3)
Completed treatment	7970 (60.3)	7779 (58.8)
Subjects with history of stroke or new stroke discontinued study drug at recommendation of DSMB in January 2011	2248 (17.0)	2262 (17.1)
Treatment status		
Discontinued study drug prematurely	2948 (22.3)	3145 (23.8)
Had adverse/bleeding/clinical experience	1299 (9.8)	1381 (10.4)
Withdrew consent to study treatment	1211 (9.2)	1257 (9.5)
Did not meet protocol eligibility	48 (0.4)	42 (0.3)
Non-compliance with protocol	297 (2.2)	355 (2.7)
Required prohibited medication	57 (0.4)	67 (0.5)
Other/missing	36 (0.3)	43 (0.3)
Completed the study†	12,932 (97.8)	12,953 (97.9)
Completed final study visit†	12,696 (96.0)	12,728 (96.2)
Only vital status assessed	236 (1.8)	225 (1.7)
Died	25 (0.2)	22 (0.2)
Alive	211 (1.6)	203 (1.5)
Lost to follow-up	15 (0.1)	17 (0.1)
Withdrew consent for follow-up	277 (2.1)	255 (1.9)
Prematurely discontinued follow-up	292 (2.2)	272 (2.1)
Died‡	589 (4.5)	556 (4.2)

† Includes subjects that completed per Protocol Amendment 3; and subjects who died on or before last contact date.

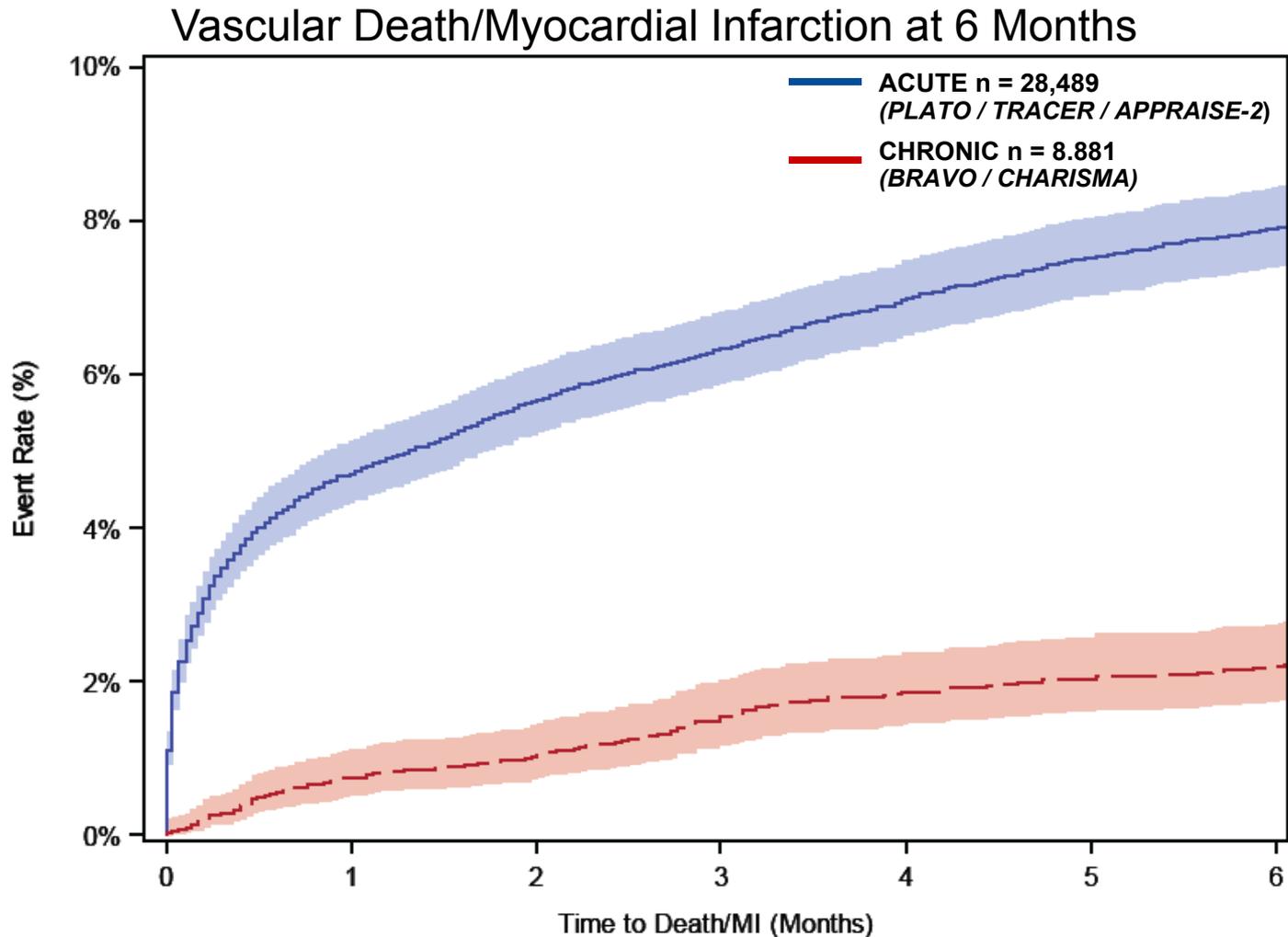
‡ Died on or before last contact date.

TRACER GUSTO Severe or Moderate Endpoints by Subgroups

As-Treated (Randomization to Last Visit)

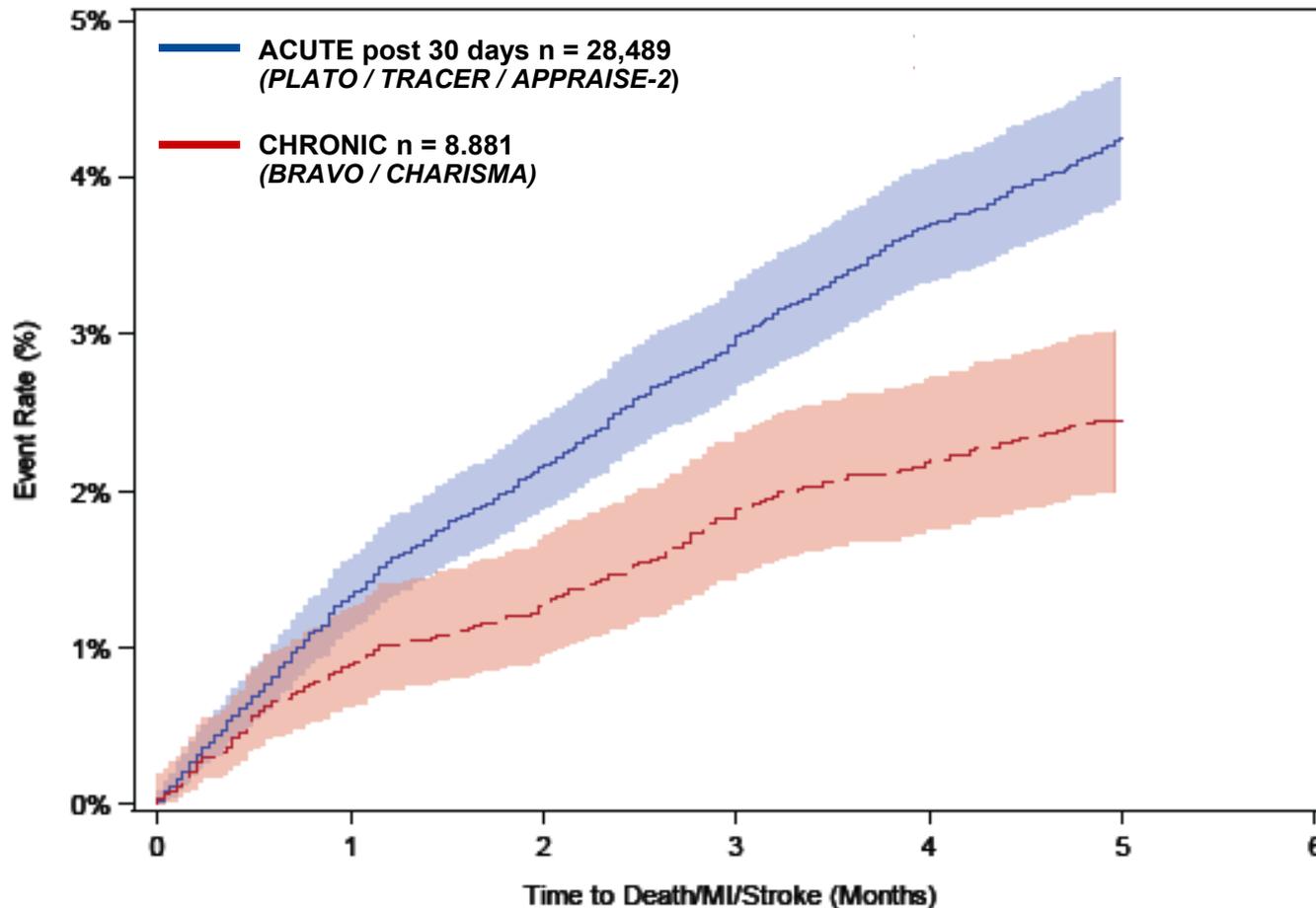


Comparison of Clinical Trial Outcome Patterns in Patients Following ACS and with Chronic Stable Atherosclerosis



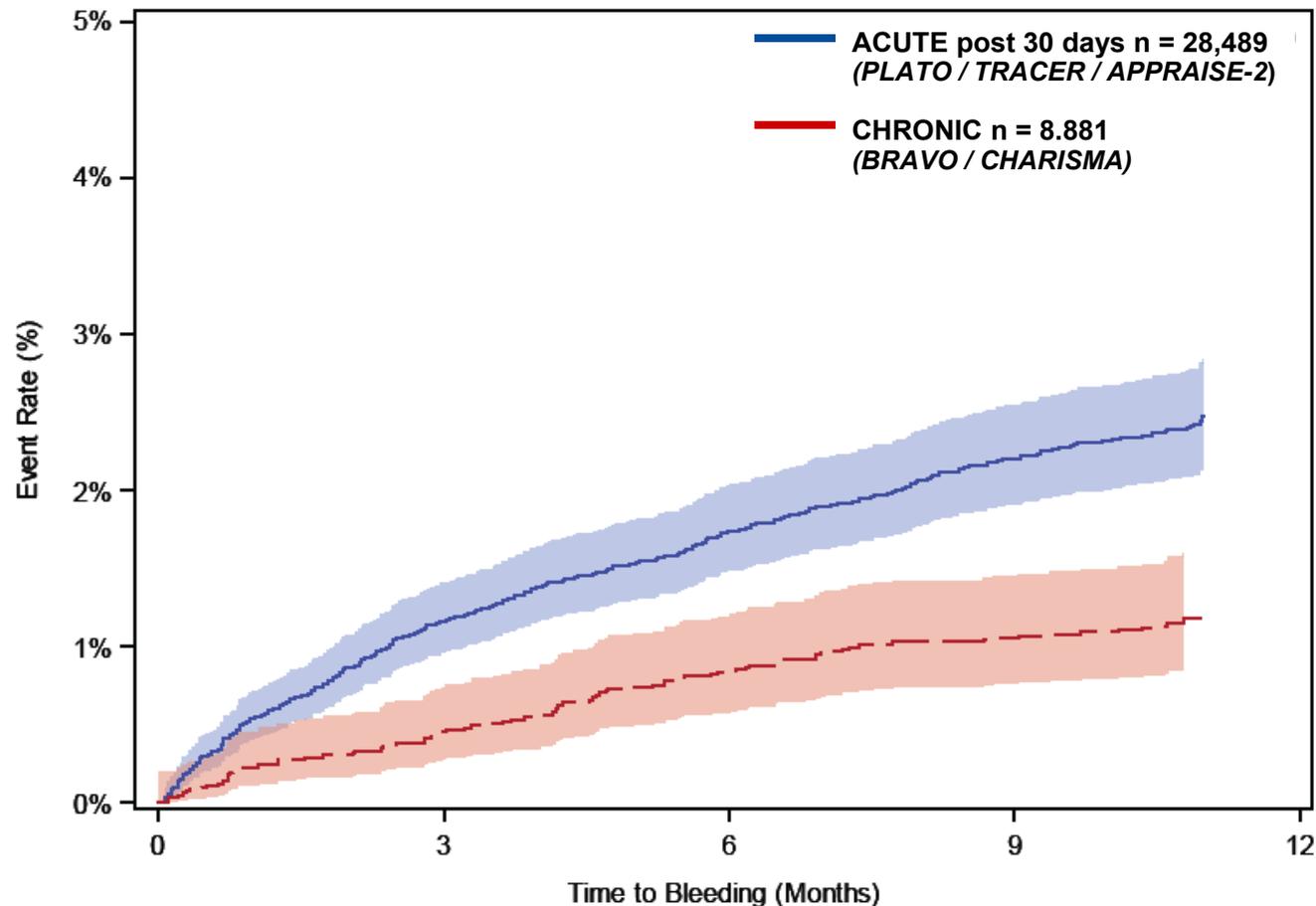
Comparison of Clinical Trial Outcome Patterns in Patients Following ACS and with Chronic Stable Atherosclerosis

CV Death/MI/Stroke at 6 Months



Comparison of Clinical Trial Outcome Patterns in Patients Following ACS and With Chronic Stable Atherosclerosis

Kaplan-Meier of GUSTO Mod/Severe Bleeding
(ACUTE post 30 days)



TRA 2°P – TIMI 50 Key Secondary Efficacy Endpoint by Time from Qualifying MI Proposed Label Population

ITT 3-Year KM Rate

Post MI Time	Placebo (n/N)	KM%	Vorapaxar (n/N)	KM%	Hazard Ratio (95% CI)
<3 Mos	320/3769	9.7	259/3687	8.4	0.82 (0.69-0.96)
3-6 Mos	193/2461	8.7	144/2446	6.7	0.74 (0.60-0.92)
6-12 Mos	156/2169	8.3	125/2293	6.4	0.75 (0.60-0.95)

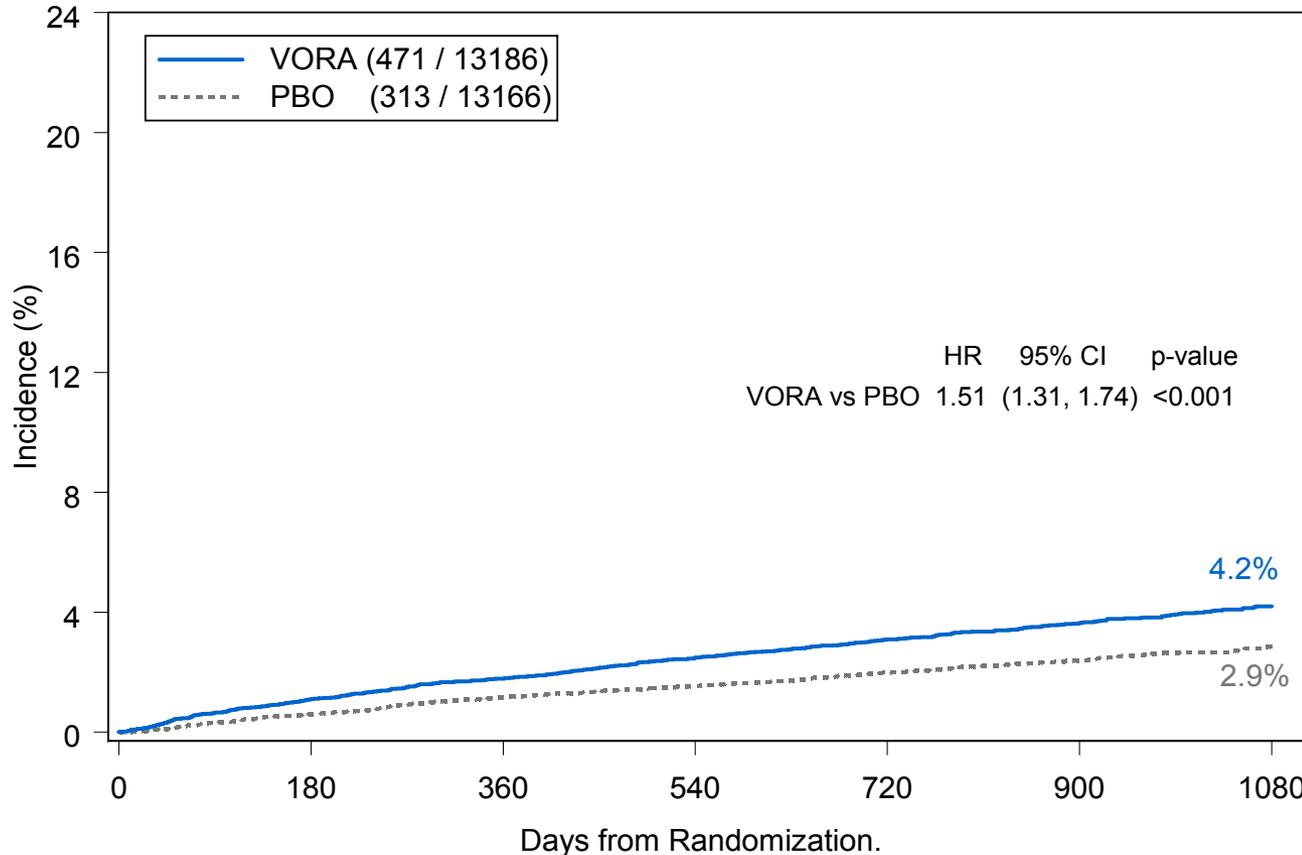
TRA 2°P – TIMI 50 GUSTO Bleeding by Time From Qualifying MI Proposed Label Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

Post MI Time	Placebo (N=8412)		Vorapaxar (N=8444)		Hazard Ratio (95%CI)
	n/N	KM%	n/N	KM%	
GUSTO moderate/severe					
<3 months	69/3756	2.3	105/3681	3.2	1.56 (1.15-2.11)
3-6 months	50/2455	2.4	71/2443	3.4	1.43 (1.00-2.05)
>6 months	36/2163	1.8	55/2289	2.8	1.45 (0.95-2.21)
GUSTO severe					
<3 months	33/3756	1.0	39/3681	1.2	1.20 (0.76-1.91)
3-6 months	19/2455	1.1	27/2443	1.4	1.43 (0.80-2.58)
>6 months	21/2163	1.0	19/2289	0.9	0.85 (0.46-1.58)
GUSTO moderate					
<3 months	37/3756	1.3	70/3681	2.1	1.94 (1.30-2.88)
3-6 months	34/2455	1.5	44/2443	2.1	1.30 (0.83-2.03)
>6 months	16/2163	0.9	38/2289	2.0	2.26 (1.26-4.05)

TRA 2°P – TIMI 50 Time to the First Occurrence of GUSTO Severe or Moderate Bleeding Overall Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

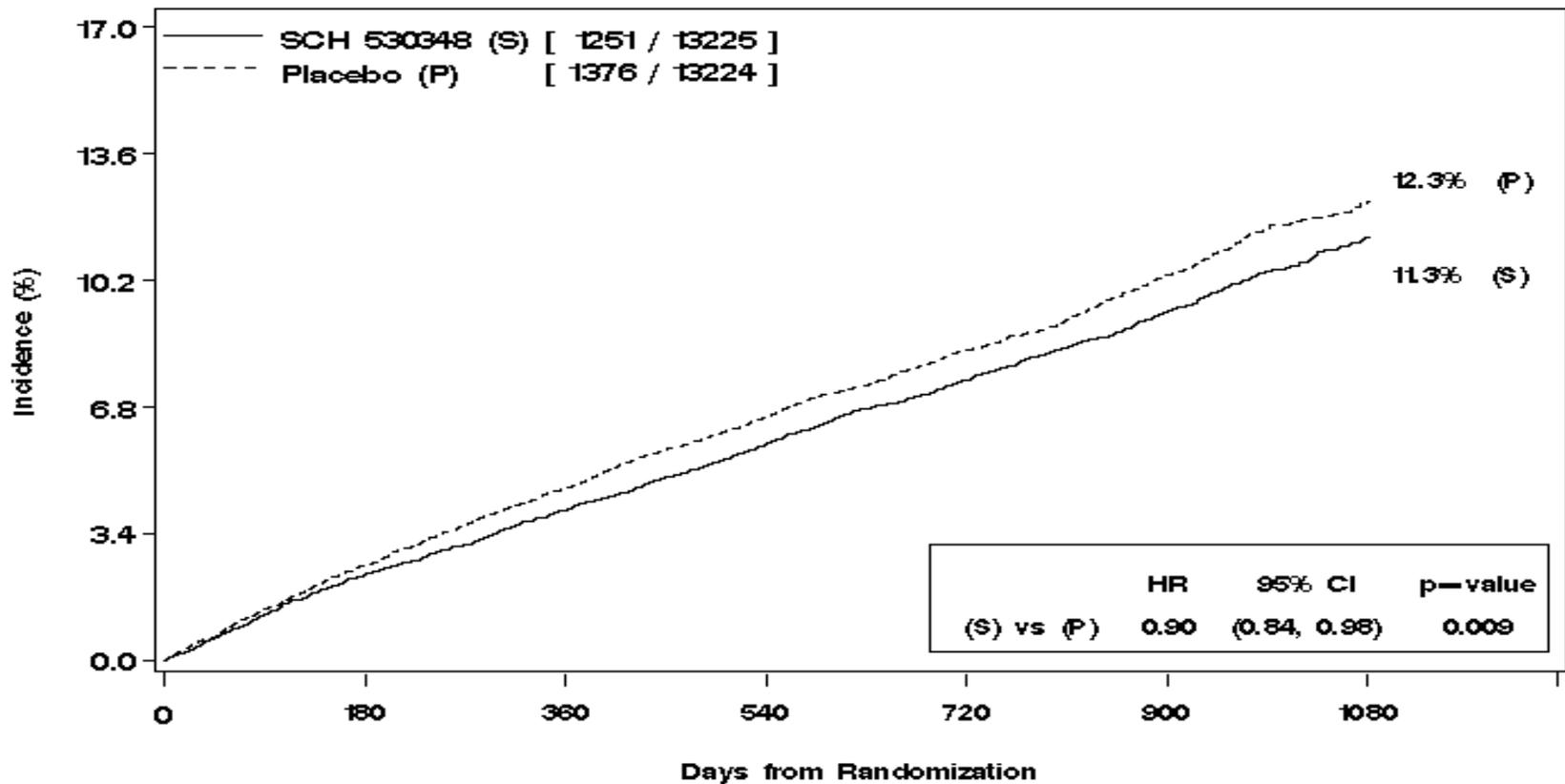


No. at Risk:

— VORA	12839	12601	12345	9694	6485	2895
- - - PBO	12882	12616	12365	9738	6553	2899

TRA 2°P – TIMI 50 Time to First Event All-Cause Death/MI/Stroke Overall Population

ITT (Randomization to Last Visit)



No. at Risk:						
SCH 530348 (S)	12784	12479	12162	9463	6287	2788
Placebo (P)	12727	12364	12013	9366	6239	2751

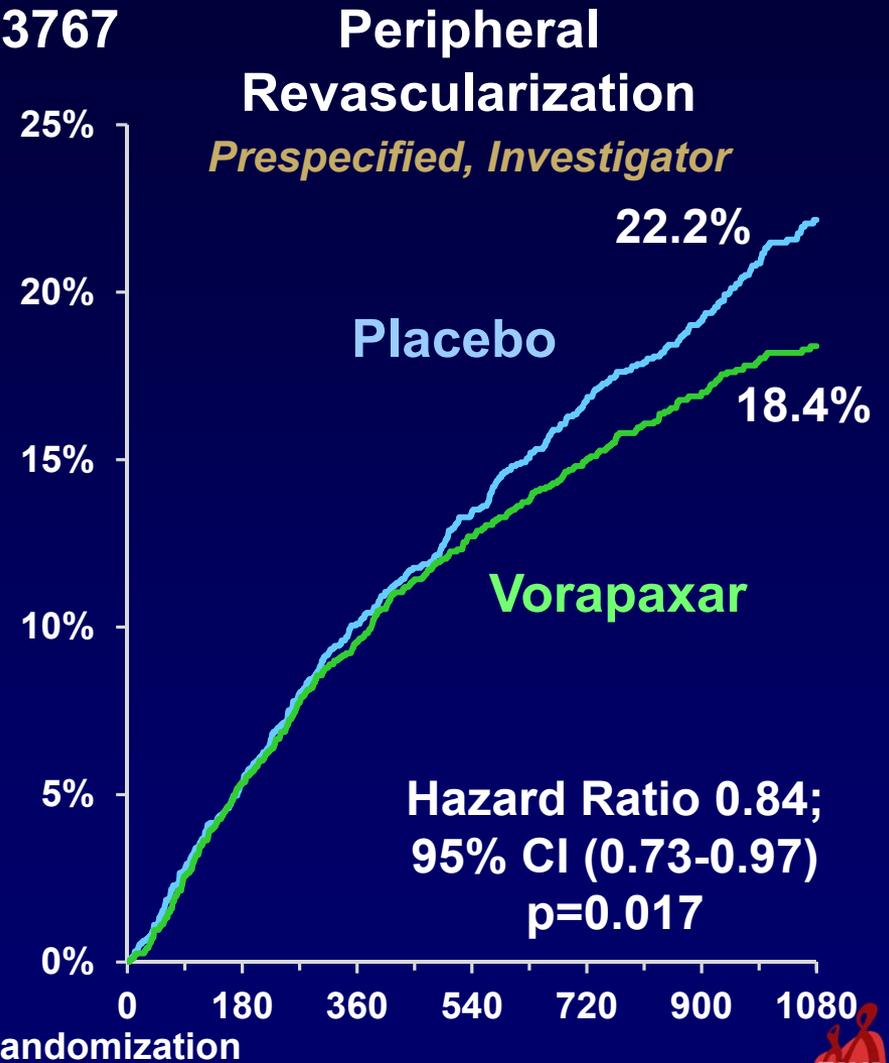
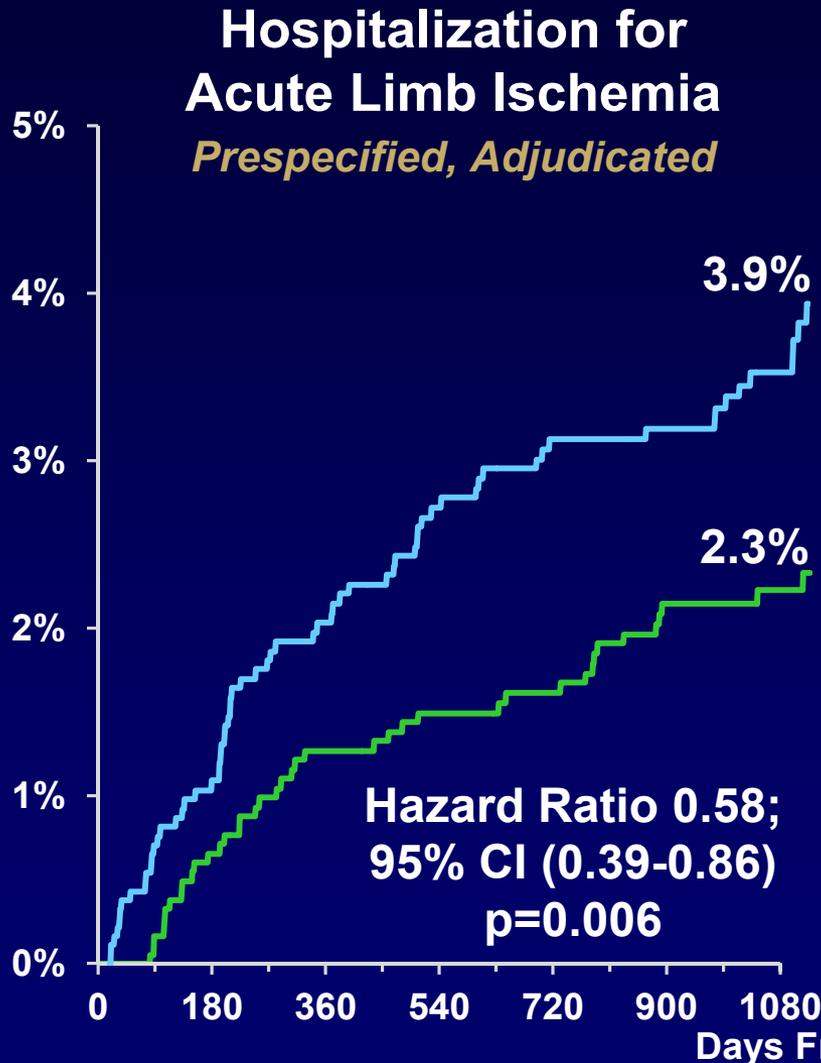
TRA 2°P – TIMI 50

Baseline Factors by Weight by Treatment Group

Primary Endpoint, Randomization to Last Visit, ITT Population

Baseline Factors & Weight Group	Placebo			Vorapaxar			Vorapaxar vs. Placebo	
	Subjects With Event (n)	Sample Size (N)	n/N x 100%	Subjects With Event (n)	Sample Size (N)	n/N x 100%	HR (95% CI)	p-Value
Gender = F								
<60 kg	54	630	8.6	63	632	10.0	1.17 (0.81, 1.69)	0.392
≥60 kg	302	2536	11.9	255	2517	10.1	0.84 (0.71, 0.99)	0.038
Gender = M								
<60 kg	21	291	7.2	33	299	11.0	1.55 (0.90, 2.68)	0.116
≥60 kg	1038	9735	10.7	905	9758	9.3	0.86 (0.79, 0.94)	0.001

Limb Vascular Efficacy



Bonaca MP et al. Circulation 2013; 127: 1522-1529.



TRA 2°P – TIMI 50

Atherothrombosis History

PAD Stratum

Regardless of Stroke History – All Randomized Subjects

	Placebo (N=1895) n (%)	Vorapaxar (N=1892) n (%)
MI		
At any time	551 (29)	524 (27.7)
>12 months	506 (26.7)	480 (25.4)
Stroke, TIA		
At any time	167 (8.8)	177 (9.3)
>12 months	122 (6.4)	301 (15.9)
TIA only, no history of stroke	97 (5.1)	112 (5.9)
Vascular ‘beds’ involved†		
Cerebrovascular bed	443 (23.4)	569 (30.1)
Peripheral arterial bed	1892 (99.8)	1890 (99.9)

† Based on cardiovascular history.

TRA 2°P – TIMI 50 Efficacy Endpoints PAD No History of Stroke or TIA (With/Without Prior MI)

ITT (Randomization to Last Visit) 3-Year KM Rate

	Without Prior MI					With Prior MI				
	Placebo (N=1183)		Vorapaxar (N=1191)		Hazard Ratio (95% CI)	Placebo (N=467)		Vorapaxar (N=431)		Hazard Ratio (95% CI)
	n	KM%	n	KM%		n	KM%	n	KM%	
CV death/MI/stroke/UCR	133	11.8	116	10.0	0.86 (0.67-1.11)	73	15.4	61	14.0	0.89 (0.64-1.25)
CV death/MI/stroke	115	10.2	105	9.1	0.90 (0.69-1.18)	65	13.7	51	11.5	0.84 (0.58-1.21)

TRA 2°P – TIMI 50 Bleeding Endpoints in Subjects Who Underwent CABG Overall Population

As-Treated (Randomization to Last Visit)
Bleeding Endpoints Within 7 Days of the Procedure

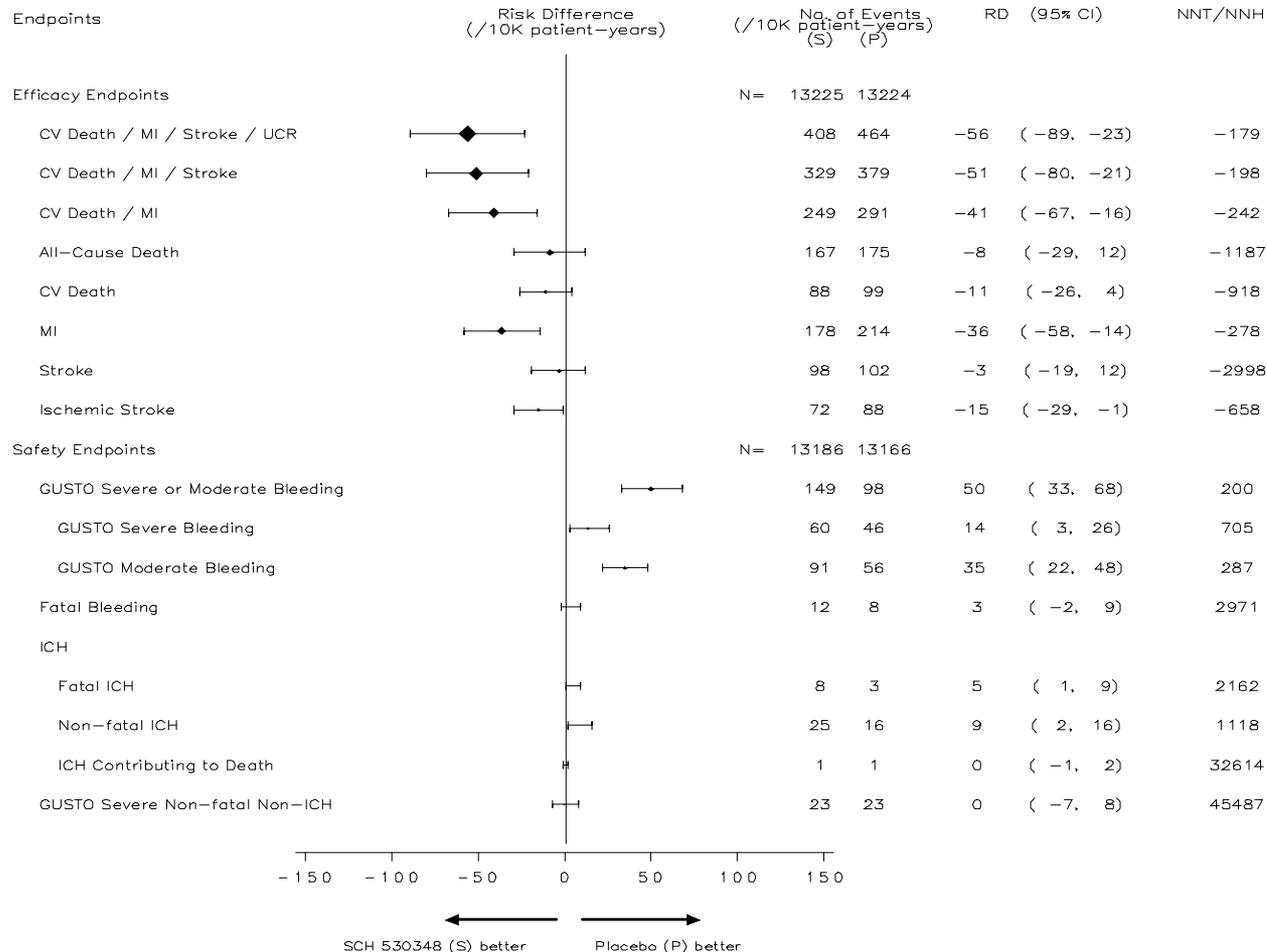
Endpoint	Placebo (N=230)	Vorapaxar (N=189)	Hazard Ratio (95% CI)
	Subjects With Events (%)		
	n (%)	n (%)	
CABG-related TIMI major	13 (5.7)	12 (6.3)	1.06 (0.48-2.33)
CABG-related fatal bleeding	1 (0.4)	0	

TRA 2°P – TIMI 50

All Endpoint Risk Differences and NNT/NNH

Overall Population

Time to First Event – ITT/As-Treated Population (Randomization to Last Visit)



SCH 530348=vorapaxar; NNT=number needed to treat; NNH=number needed to harm..

TRA 2°P – TIMI 50 Time to First GUSTO Moderate or Severe Bleeding Overall Population

As-Treated (Randomization to Last Visit) 3-Year KM Rate

	Placebo		Vorapaxar		Hazard Ratio (95% CI)
	Subjects With Events n/N	KM%	Subjects With Events n/N	KM%	
CYP2c19 extensive responders (*1/*1)	56/2011	3.4	94/2016	5.8	1.68 (1.21-2.35)
CYP2c19 ultra responders (*1/*17, *17/*17)	35/1563	2.6	52/1432	4.0	1.71 (1.11-2.62)
CYP2c19 poor and any-loss-of function (*2-*8, at least one copy of *1)	37/1095	3.7	50/1118	5.1	1.33 (0.87-2.03)