Prasugrel vs. Clopidogrel for Acute Coronary Syndromes Patients Managed without Revascularization — the TRILOGY ACS trial

On behalf of the TRILOGY ACS Investigators

Duke Clinical Research Institute

www.clinicaltrials.gov Identifier: NCT00699998

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- Michael Wilson, MS

Conflict of Interest Disclosures

- Disclosures for Drs. Roe and Ohman listed on www.dcri.org
- Disclosures for all authors listed within the manuscript

Trial Conduct

- Academic Coordinating Center: DCRI
  - Independently performed statistical analyses
  - Global project management
  - Event adjudication activities
- Global Trial Operations: Quintiles
  - Site management
  - Data management
- Sponsors: Eli Lilly and Daiichi Sankyo
- Protocol Adherence
  - Total of 18 patients lost to follow-up (0.2% of overall)
  - Median study follow-up: 17.1 months (10.4, 24.4)

TRILOGY ACS Background

- The proportion of ACS (UA/NSTEMI) patients world-wide who are managed medically without revascularization (PCI or CABG) is 40-60%
- Medically managed ACS patients have a two-fold increase in ischemic events, but have been under-represented in contemporary ACS trials
- Prasugrel, a thienopyridine $P2Y_{12}$ inhibitor, was shown to improve outcomes compared with clopidogrel in ACS patients undergoing PCI in the TRITON trial, with an increase in major bleeding

TRILOGY ACS — Inclusion Criteria

- Randomization within 10 days of a UA/NSTEMI event
  - NSTEMI: CK-MB or Troponin > ULN
  - UA: ST depression > 1 mm in 2 or more leads
- "Reasonable certainty" for a medical management strategy decision determined
  - Angiography not required, but if performed, had to be done before randomization, and evidence of coronary disease had to be seen (1 lesion > 30% or prior PCI/CABG)
- At least 1 of 4 enrichment criteria:
  - Age > 60 years
  - Diabetes Mellitus
  - Prior MI
  - Prior Revascularization (PCI or CABG)

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel**[1]: 300 mg LD + 75 mg MD
- **Prasugrel**[1]: 30 mg LD + 5 or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Clopidogrel**[1]: 75 mg MD
- **Prasugrel**[1]: 5 or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

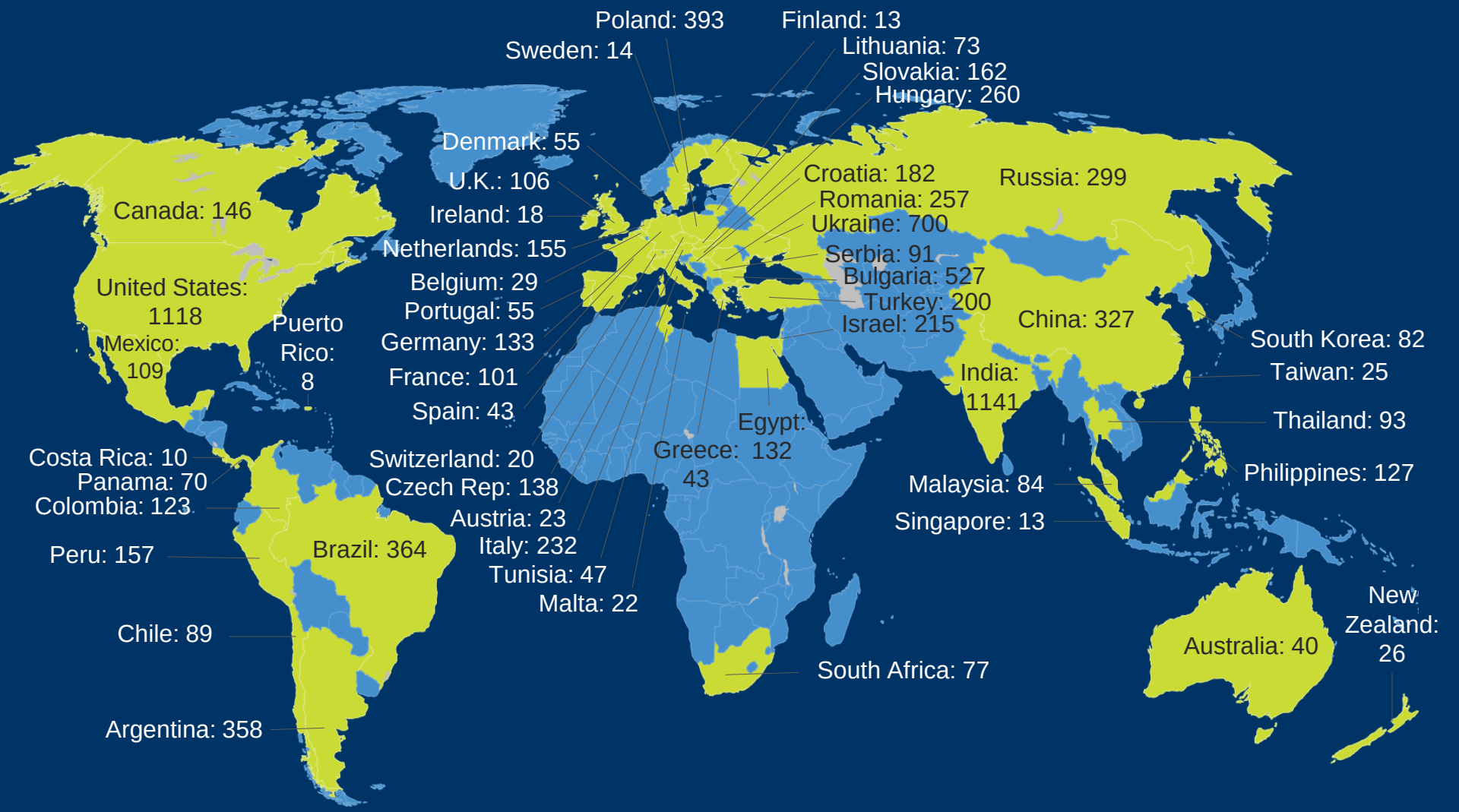
Statistical Considerations

- Event-driven trial, powered for efficacy in the primary cohort of patients < 75 yrs of age (688 events planned for 90% power for 22% RRR, 761 events accrued)
  - Exploratory analysis in the elderly (age ≥ 75 yrs) with a minimum of 2,000 patients
- Testing strategy specified first testing the primary endpoint (CV death, MI, or stroke) in patients < 75 yrs
- Conditional on successfully establishing superiority of prasugrel over clopidogrel in this group, treatment groups would be compared in the overall population (including the elderly patients)

TRILOGY ACS Enrollment:

9,326 patients in 8 regions, 52 Countries

(7,243 patients < 75 years old; 2,083 patients ≥ 75 years old)



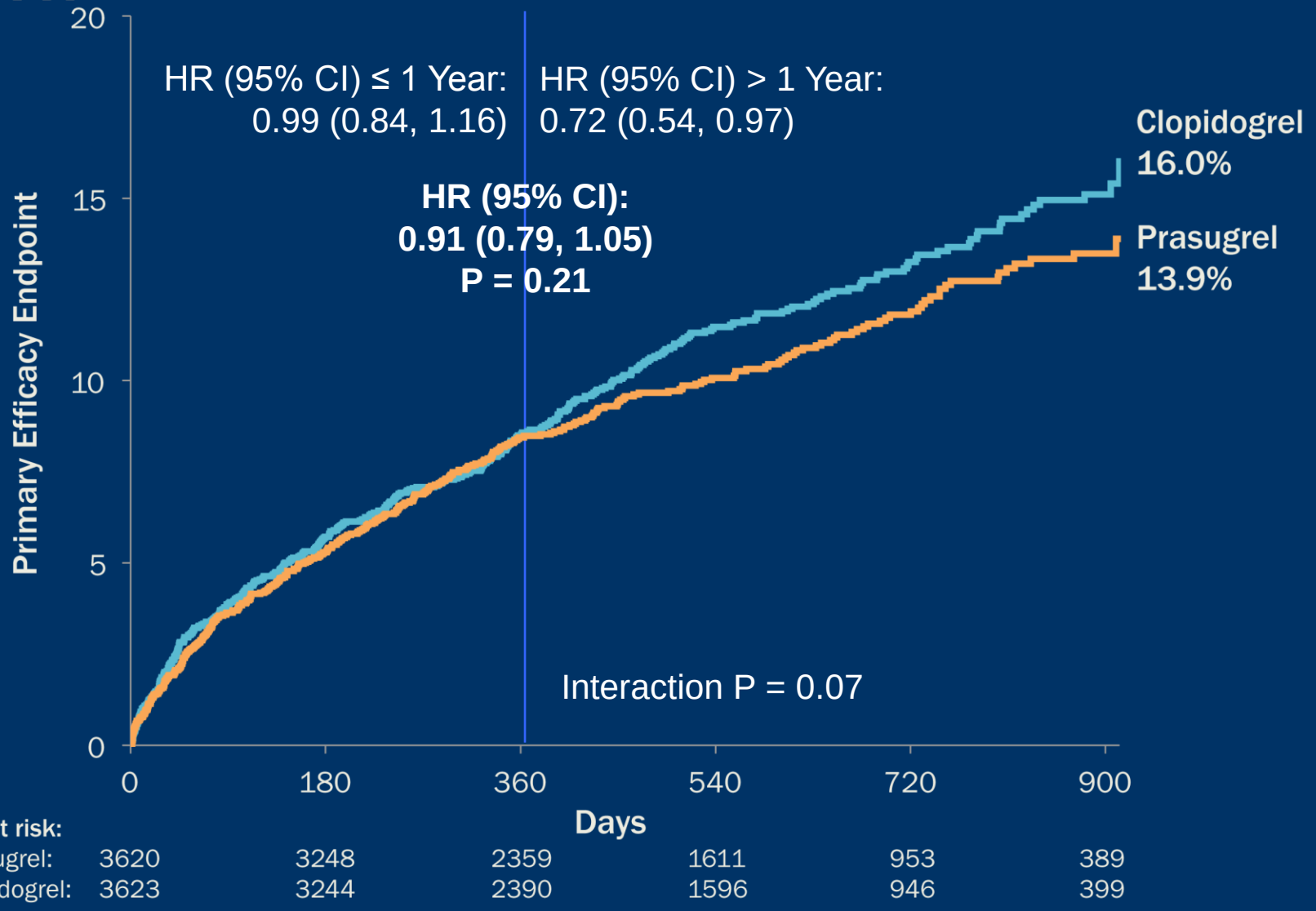
Baseline Characteristics

	Age < 75 Years (N = 7243)		**Overall Population** (N = 9326)	
	Prasugrel (N = 3620)	**Clopidogrel** (N = 3623)	**Prasugrel** (N = 4663)	**Clopidogrel** (N = 4663)
Age—yr	62 (56–68)	62 (56–68)	66 (58–74)	66 (59–73)
Female sex—%	36.2	35.6	39.2	39.1
Body weight < 60 kg—%	13.1	12.8	15.2	14.9
Disease classification—%				
NSTEMI	67.8	67.2	70.4	69.4
Unstable angina	32.2	32.8	29.6	30.6
Medical History—%				
Diabetes mellitus	38.5	39.3	37.7	38.3
Current/recent smoking	23.3	23.6	19.7	20.2
Prior myocardial infarction	43.3	44.8	42.9	43.3
Prior PCI	27.0	29.1	25.6	26.7
Prior CABG	14.6	16.3	15.2	16.1
Baseline risk assessment				
GRACE risk score	114 (101–128)	115 (102–128)	122 (105–140)	121 (106–138)
Creatinine clearance—mL/min	81 (63–104)	81 (63–102)	73 (54–97)	73 (54–96)
Angiography performed pre-randomization—%	42.1	43.1	41.2	41.4

Post-randomization revascularization performed in 7.5% of patients

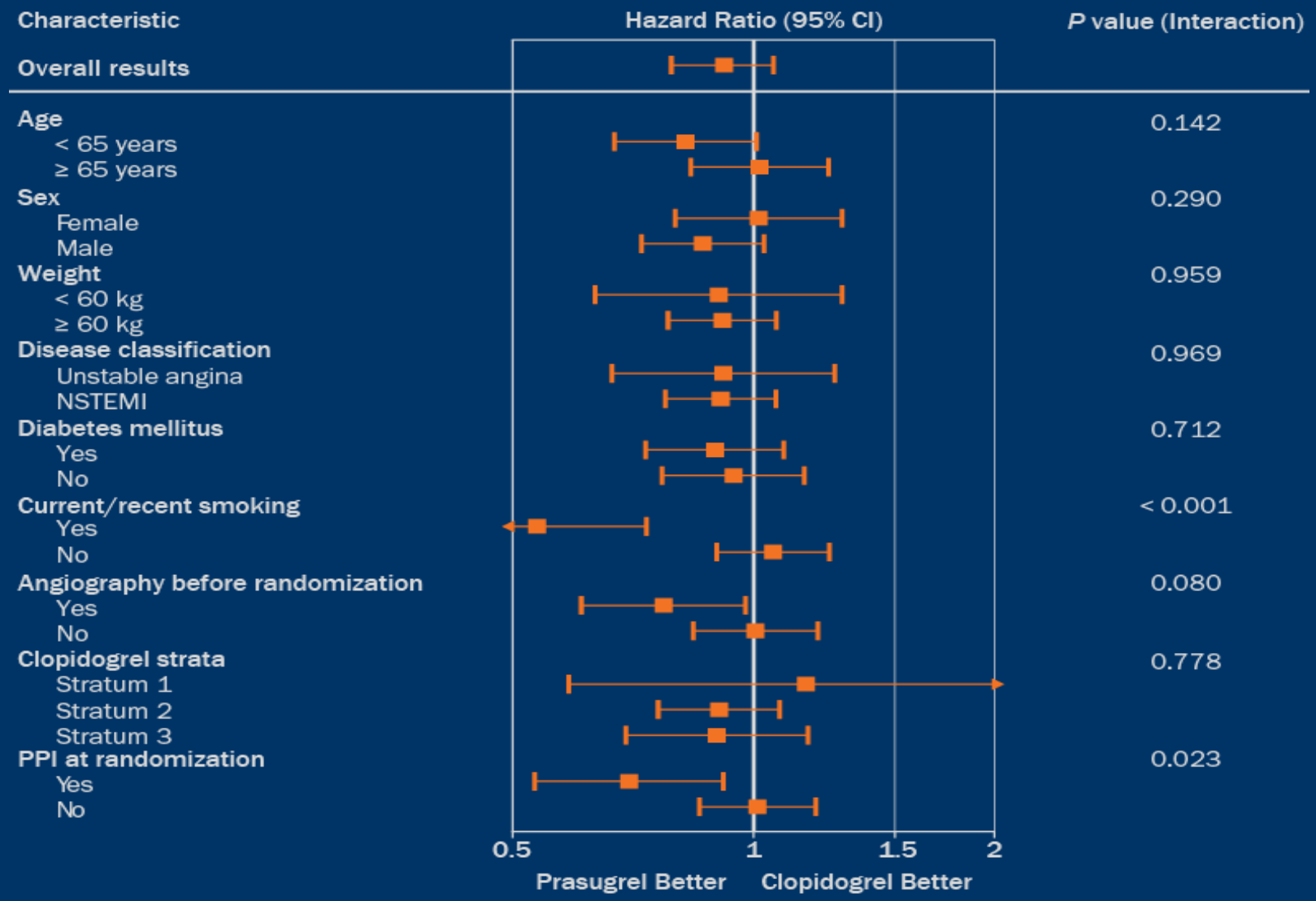
Primary Efficacy Endpoint to 30 Months

(Age < 75 years)



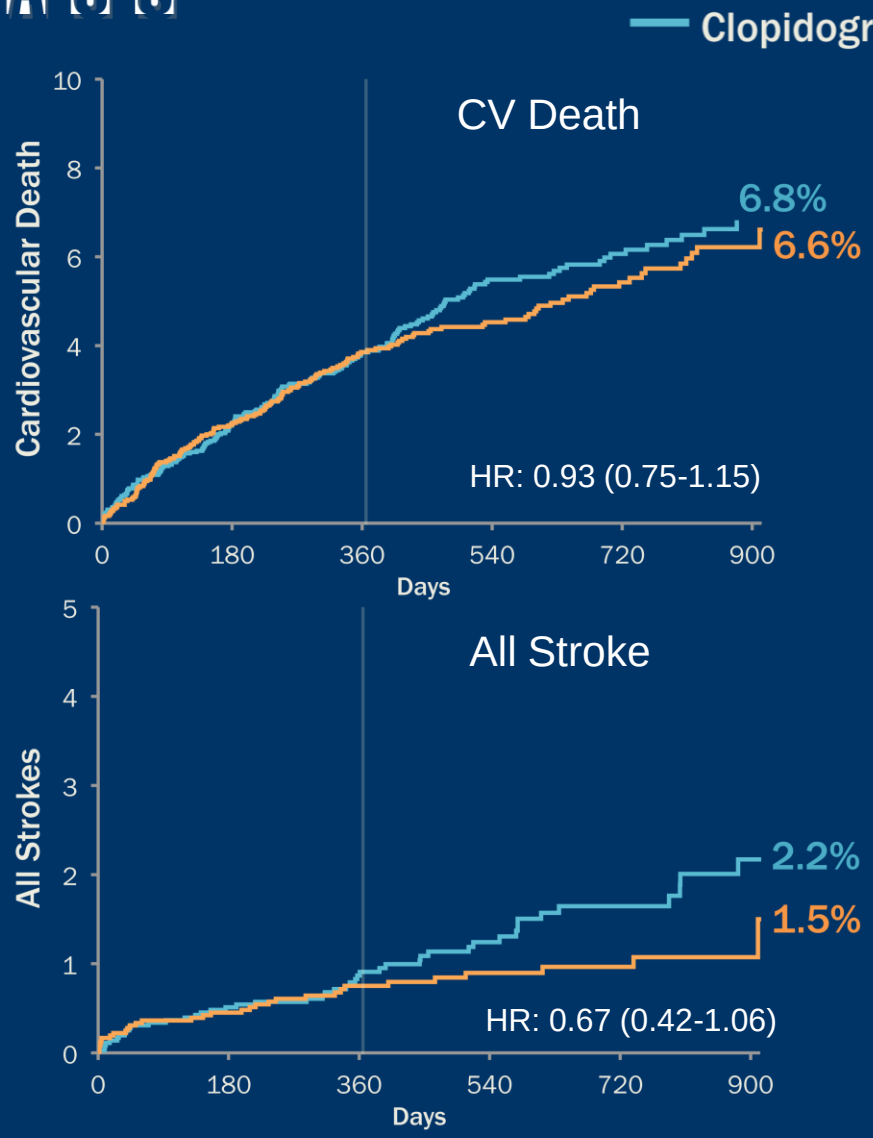
Primary Endpoint - Pre-Specified Sub-Groups

(Age < 75 years)



Efficacy Component Endpoints to 30 Months

(Age < 75 years)



	HR (95% CI) ≤ 1 Year	HR (95% CI) > 1 Year
CV Death	1.00 (0.78, 1.28)	0.75 (0.49, 1.14)
All MI	0.97 (0.78, 1.19)	0.68 (0.46, 0.99)
All Stroke	0.86 (0.50, 1.47)	0.35 (0.14, 0.88)

Evaluation of All Ischemic Events Over Time*
(Age < 75 years)

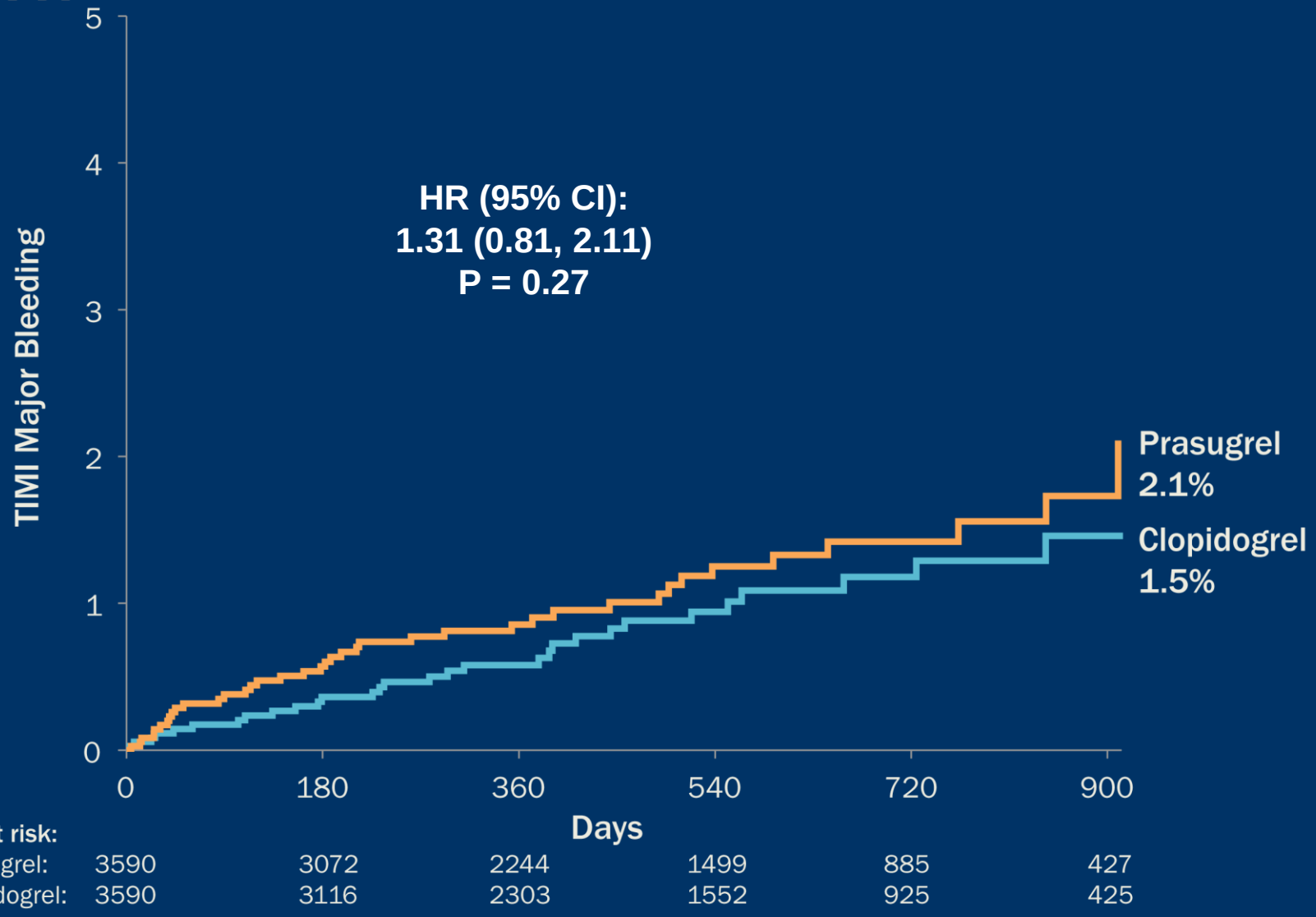
- Lower risk multiple recurrent ischemic events suggested with prasugrel using the pre-specified Andersen-Gill model (HR = 0.85, 95% CI: 0.72–1.00, P=0.04)
- Significant interaction with treatment and time (HR for > 12 mos = 0.64, 95% CI: 0.48–0.86, Interaction P=0.02)

	Prasugrel	Clopidogrel
≥ 1 event	364	397
≥ 2 events	77	109
3–7 events	18	24

* Pre-specified evaluation of all CV death, MI, or stroke events by treatment

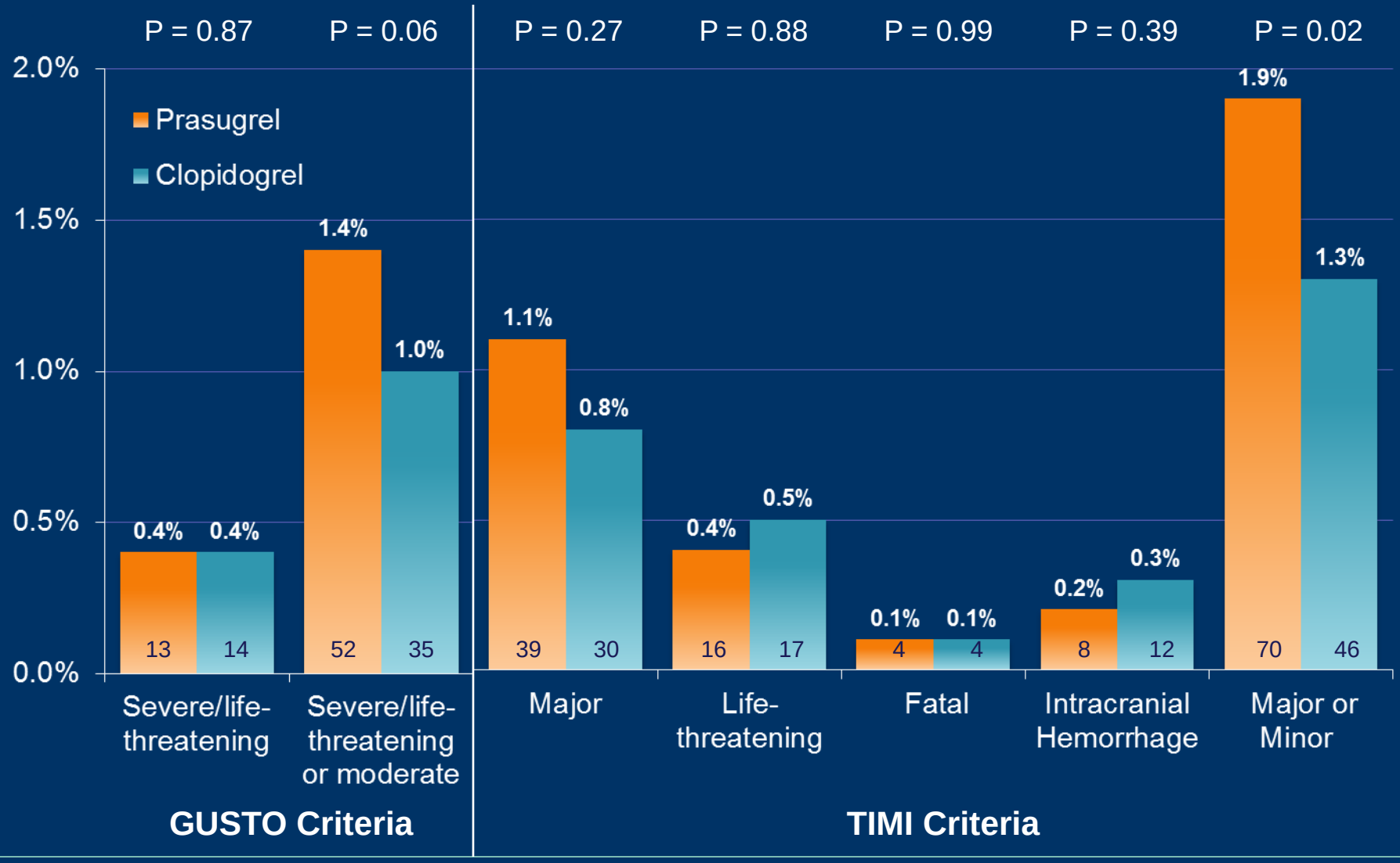
TIMI Major Bleeding to 30 Months

(Age < 75 years)



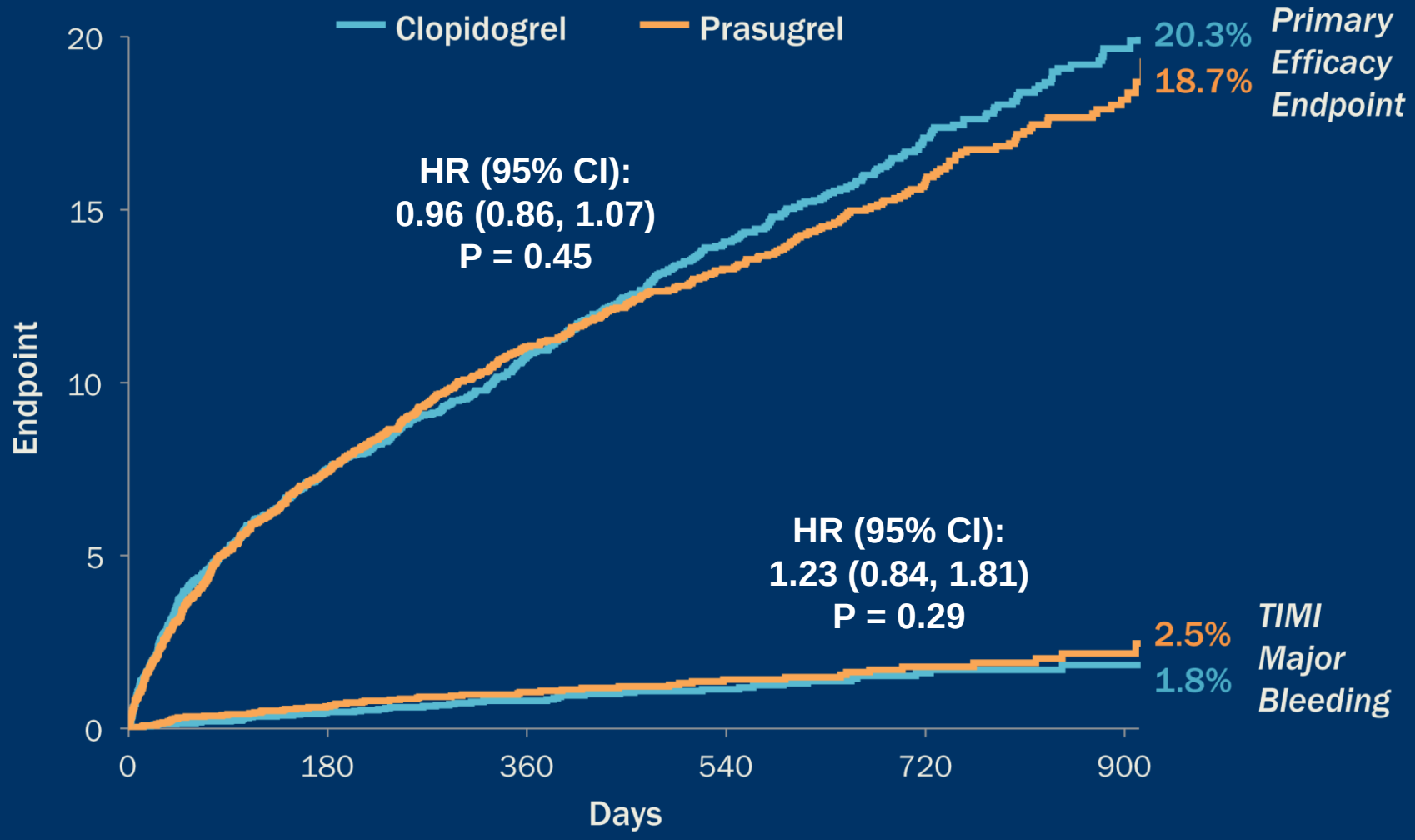
Incidence of Bleeding Outcomes

(Age < 75 years)



Primary Efficacy Endpoint and TIMI Major Bleeding Through 30 Months

(Overall population)



Incidence of Key Safety Outcomes
(Overall Population)

	Prasugrel	Clopidogrel	Hazard Ratio (95% CI)	P Value
Bleeding	(N = 4623)	(N = 4617)		
GUSTO Severe/life-threatening bleeding	22 (0.5%)	27 (0.6%)	0.83 (0.48–1.46)	0.53
TIMI Fatal Bleeding	7 (0.2%)	9 (0.2%)	0.80 (0.30–2.14)	0.68
Intracranial Hemorrhage	14 (0.3%)	19 (0.4%)	0.76 (0.38–1.51)	0.42
Neoplasm				
New, non-benign neoplasms*	82 (1.8%)	78 (1.7%)	1.05 (0.77-1.43)	0.79
Mortality	(N = 4663)	(N = 4663)		
All-cause death	385 (8.3%)	409 (8.8%)	0.94 (0.82–1.08)	0.40

*Among patients with no prior history of malignancy or prior malignancy treated with curative therapy

Conclusions

- In the largest trial to date of ACS patients managed medically without revascularization, prasugrel was not statistically different from clopidogrel during 2.5 years of follow-up among patients < 75 years of age
- Further analyses of the primary endpoint yielded several important findings favoring prasugrel treatment
  - Trend for a time-dependent benefit after 1 year
  - Fewer total recurrent ischemic events, particularly after 1 year
- No statistical differences in major, life-threatening, or fatal bleeding with prasugrel vs. clopidogrel

ORIGINAL ARTICLE

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

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