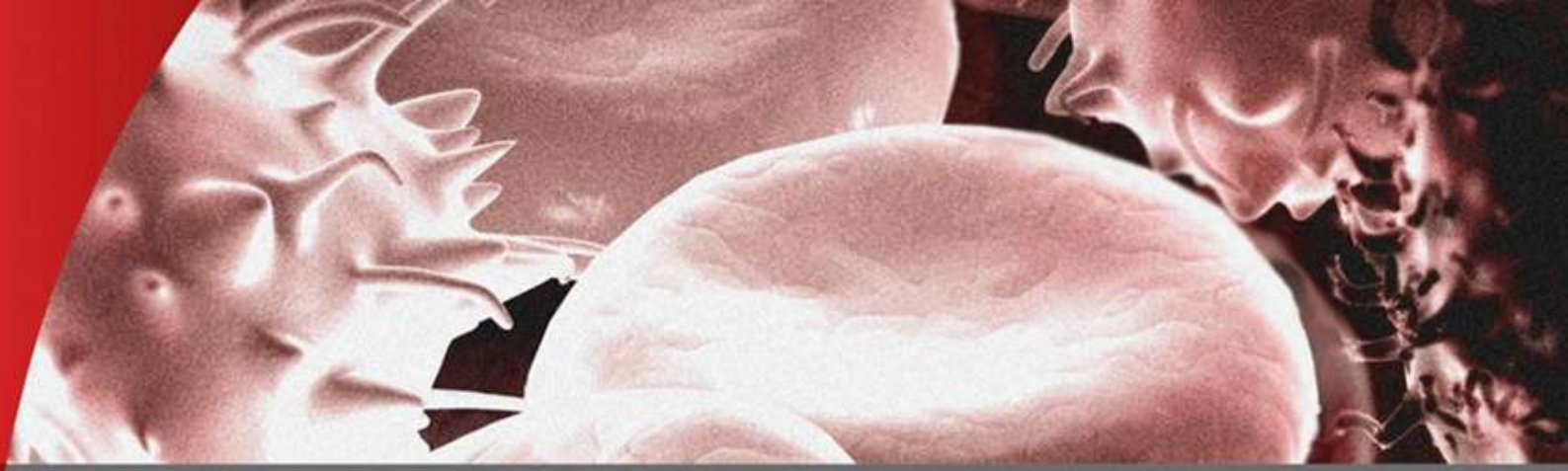


A Randomized, Double-Blind, Active Controlled Trial to Evaluate Intravenous and Oral PRT060128 (elinogrel), a Selective and Reversible $P2Y_{12}$ Receptor Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions (INNOVATE-PCI)

INNOVATE PCI

August 30, 2010

Background

- Antiplatelet therapy is essential to reduce adverse events in patients with ischemic heart disease
- Recent clinical trials demonstrate that greater platelet inhibition is associated with improved ischemic outcomes, but increased major bleeding
- Reversible platelet inhibition may mitigate these risks and further improve outcomes
- Elinogrel is a novel potent platelet inhibitor that competitively and reversibly binds to the $P2Y_{12}$ receptor and can be administered both intravenously and orally

Properties of Elinogrel

- The only reversible and competitive $P2Y_{12}$ receptor antagonist
- Direct-acting: no metabolic activation required
- Available for intravenous and oral administration, enabling acute and chronic use
- Immediate and near maximal platelet inhibition achieved with IV
- Duration of action
  - Half-life: 12 hours
- No major CYP metabolism – low potential for drug-drug interactions (including PPIs)
- Balanced clearance: 50% renal; 50% hepatic (10% metabolized to pharmacologically inactive metabolite)

INNOVATE-PCI Objectives

- Phase II study to evaluate the safety, clinical efficacy, and tolerability of IV and oral elinogrel in patients undergoing nonurgent PCI
- Examine a number of clinical and biological endpoints to understand how elinogrel dose relates to safety, clinical and biological efficacy, and tolerability
  - Not statistically powered for any specific endpoint
- Obtain pharmacodynamic (PD) data for the IV and oral elinogrel doses in a subset of trial participants

Inclusion & Exclusion Criteria

INCLUSION

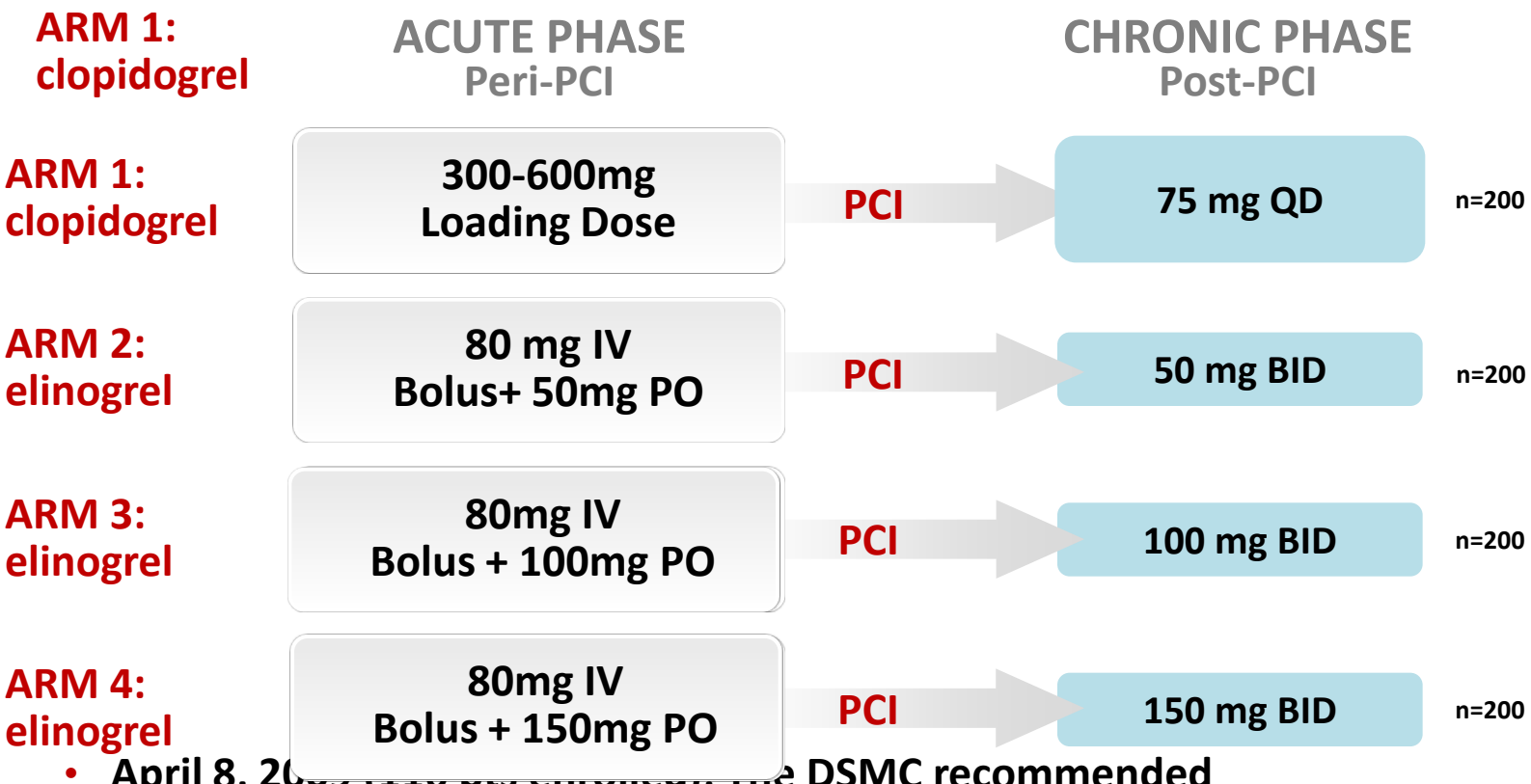
- Nonurgent PCI with ≥ 1 coronary lesion amenable to PCI

EXCLUSION

- Bleeding risk
  - Anemia/thrombocytopenia, recent trauma or bleeding, CVA or TIA within prior 5 years
- Concomitant therapies
  - Clopidogrel loading dose within 7 days prior to PCI, thrombolytics, oral anticoagulants, fondaparinux
- General
  - Age > 75 yrs, weight < 55 kg, CrCL < 45 cc/min, allergy to study drugs

Leonardi S, Rao SV, Harrington RA, et. al. *AHJ* 2010

Treatment Schema



- April 8, 2009 ([illegible] pts enrolled): The DSMC recommended discontinuation of the 50 mg BID dose and increasing IV bolus dose to 120 mg as per protocol
- April 16, 2009: Chronic phase extended from 60 days to 120 days of treatment

Endpoints

Safety – 24-hr or d/c & 120-day

- TIMI bleeding: major, minor, bleeding requiring medical attention
- Clinically relevant bleeding: major, minor, nuisance

Biological efficacy - periprocedural

- Any Troponin* elevation at 24 hrs or d/c
- Troponin* elevation > 2 X ULN at 24 hrs or d/c

Clinical efficacy

- 24-hr or d/c death, MI, stroke, uTVR, GP IIb/IIIa bailout, stent thrombosis
- 120-day death, MI, stroke, uTVR
- 120-day death, MI, stroke, uTVR, stent thrombosis

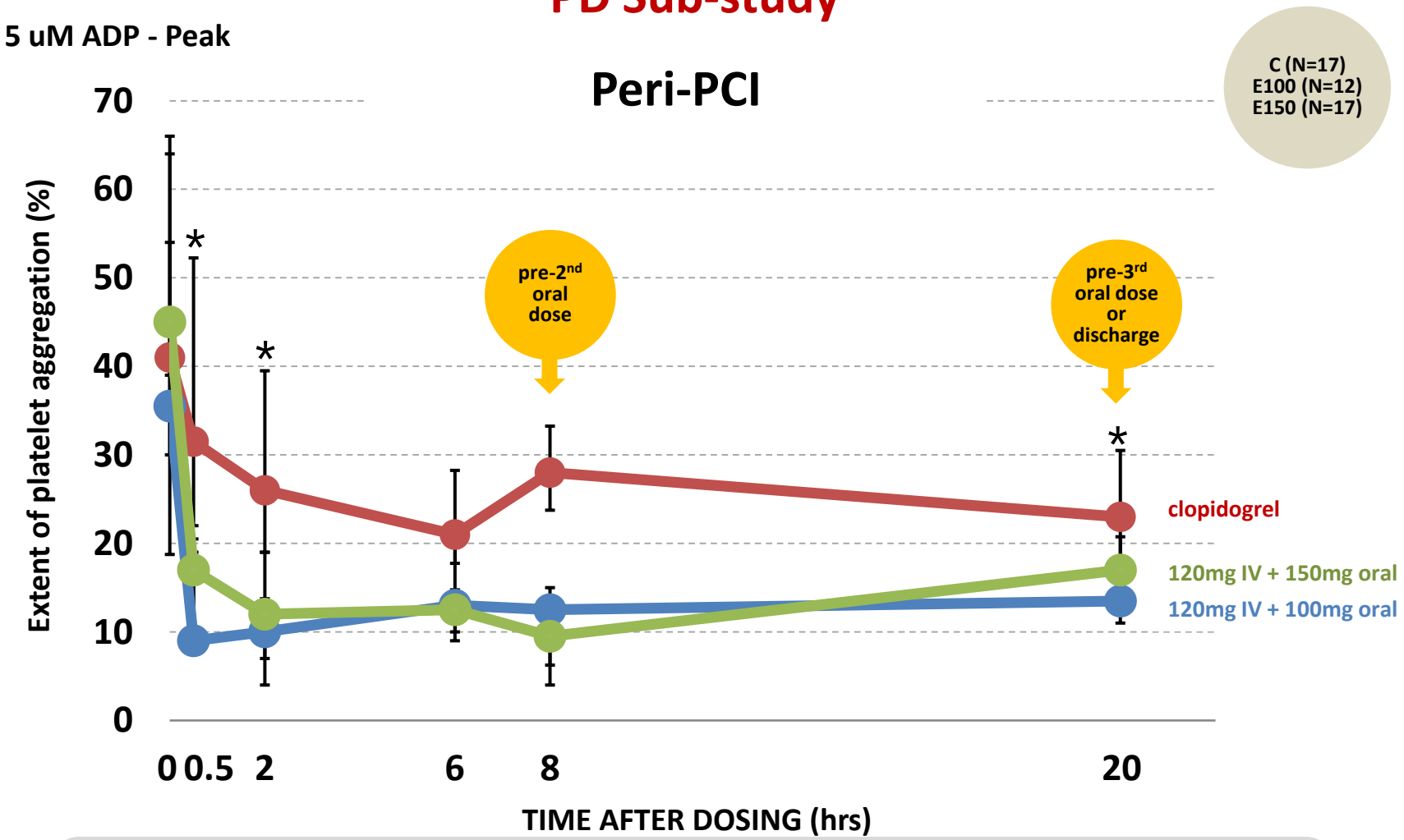
*Core lab troponin I

Baseline Characteristics

	Clopidogrel (N=208)	Pooled elinogrel 100 mg (N=201)	Pooled elinogrel 150 mg (N=207)
Median age (yrs)	61	61	61
Male (%)	77%	77%	78%
BMI (kg/m2)	29.0	28.6	29.4
Diabetes mellitus	36%	30%	40%
Prior MI	37%	36%	33%
ASA	96%	95%	93%
On maintenance clopidogrel	46%	46%	45%
Femoral access	70.7%	74.0%	75.0%
Vascular closure device	33.2%	29.5%	28.9%

Pharmacodynamic Effect of Elinogrel vs. Clopidogrel

PD Sub-study



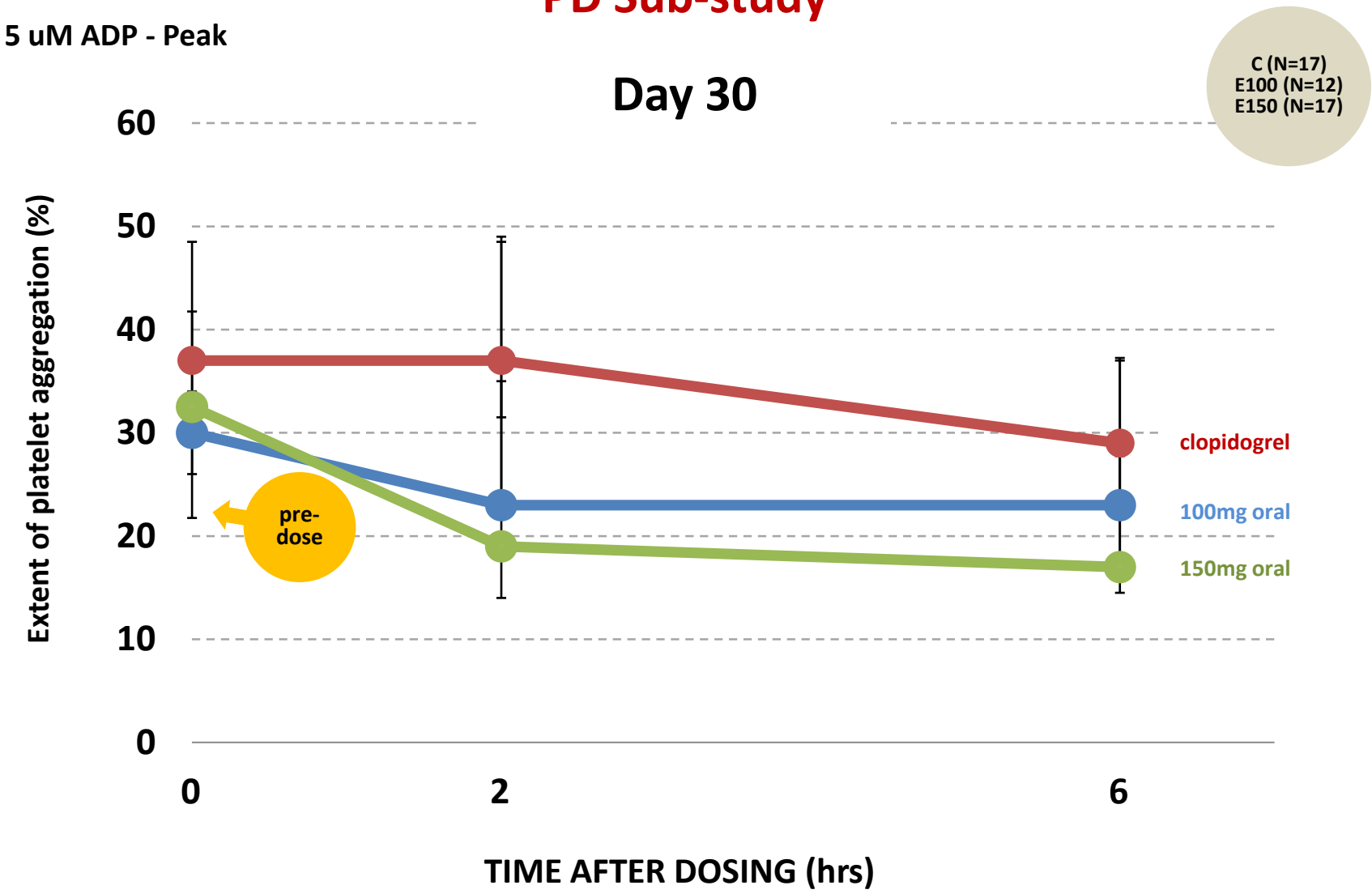
74% of pts represented above were on maintenance clopidogrel

* p<0.025 for both elinogrel vs. clopidogrel comparisons

Median, quartiles

Pharmacodynamic Effect of Elinogrel vs. Clopidogrel

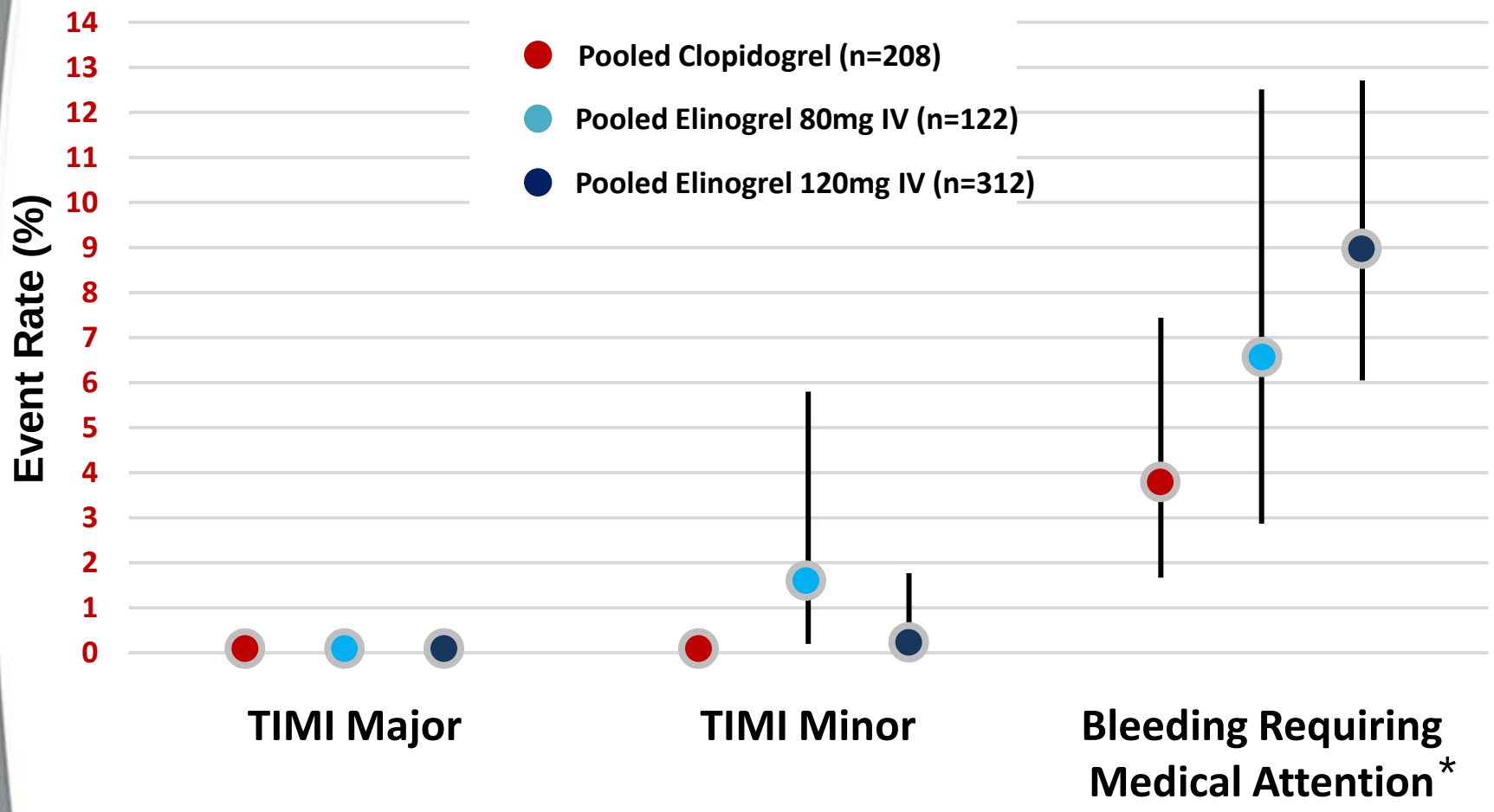
PD Sub-study



Median, quartiles

Bleeding at 24 hrs or d/c – TIMI Scale

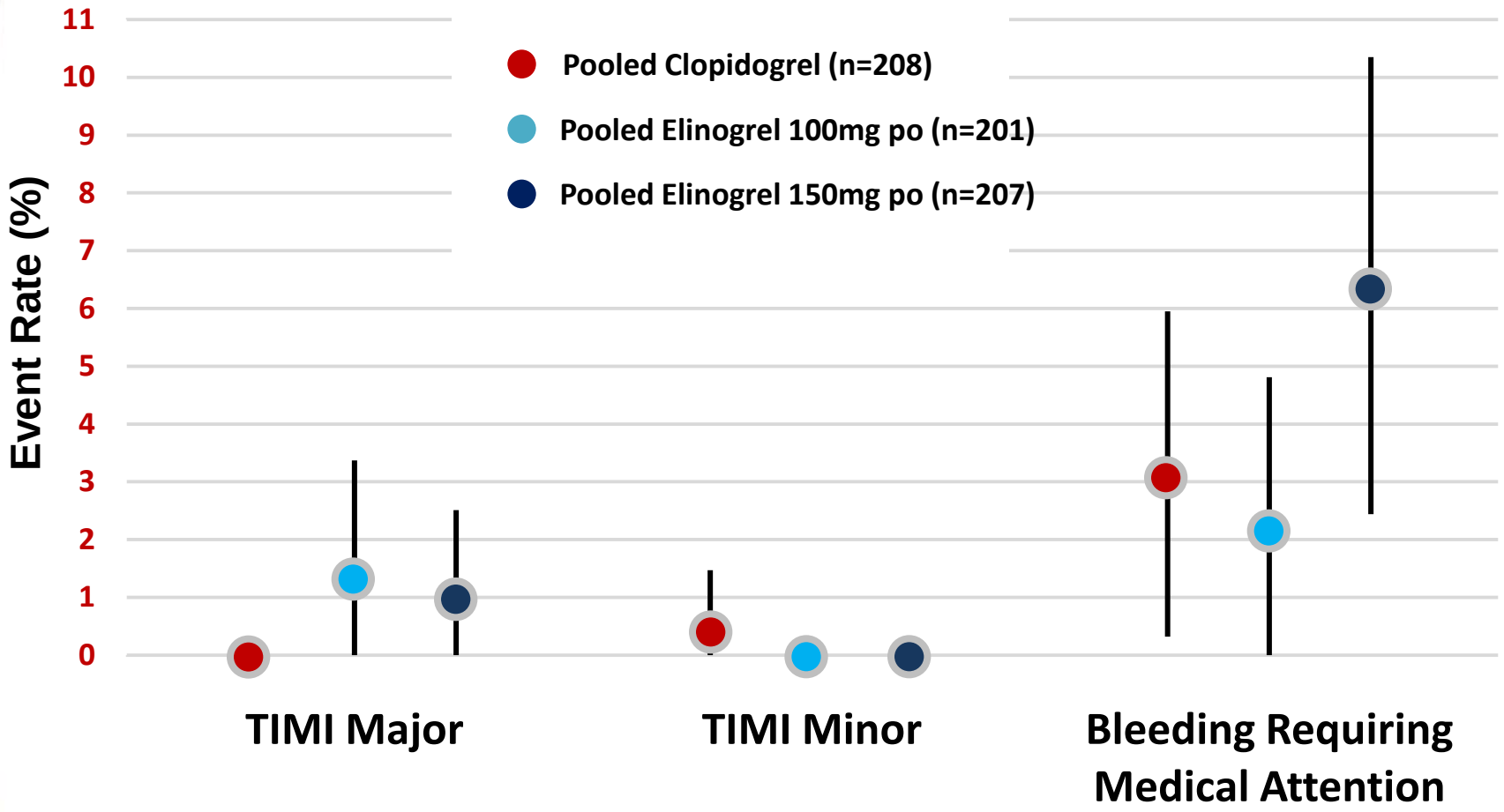
Rates and 95% confidence intervals



* Mainly at access site

Bleeding at 24h-120d – TIMI Scale

Rates and 95% confidence intervals

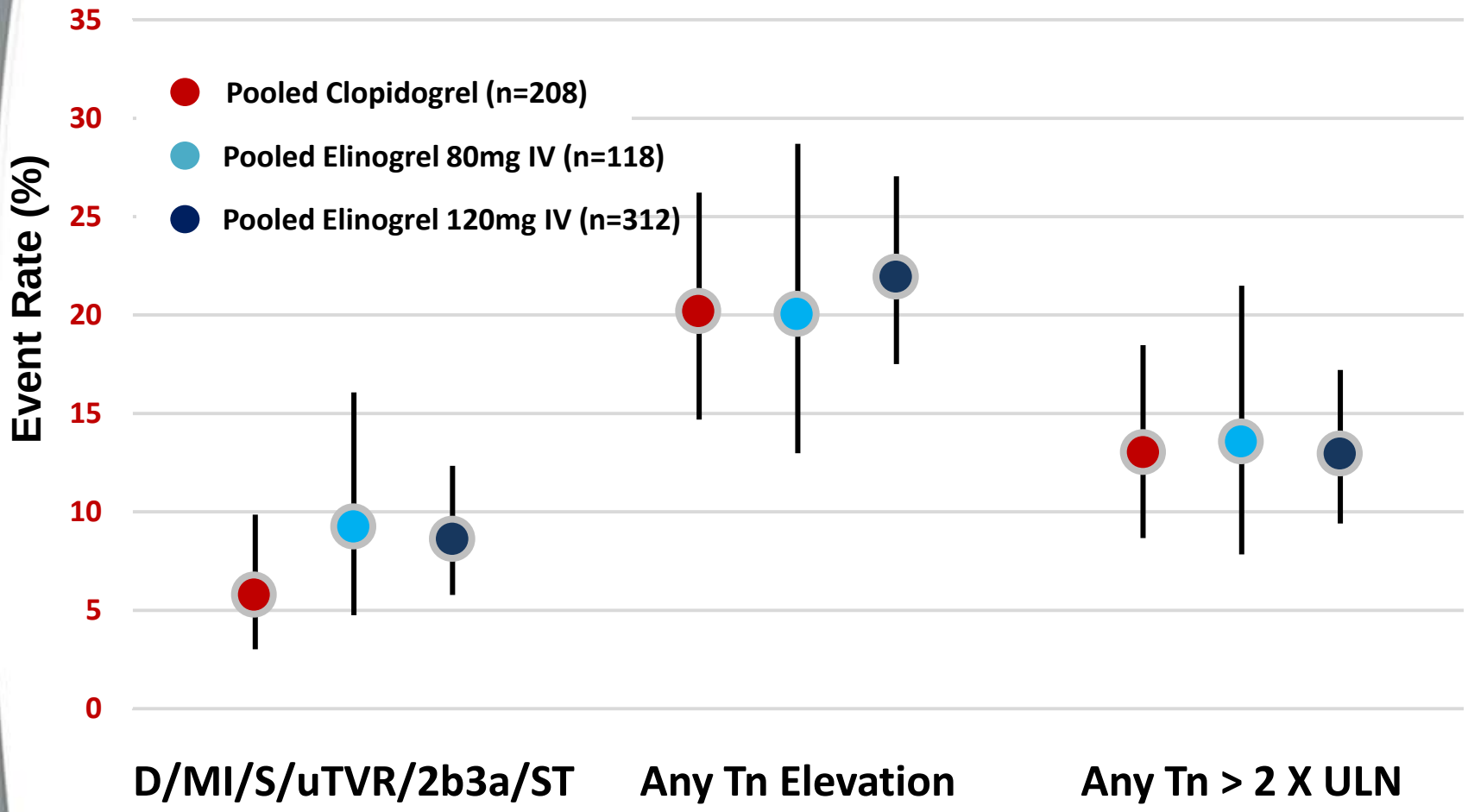


INNOVATE PCI

Efficacy at 24 hrs or Discharge

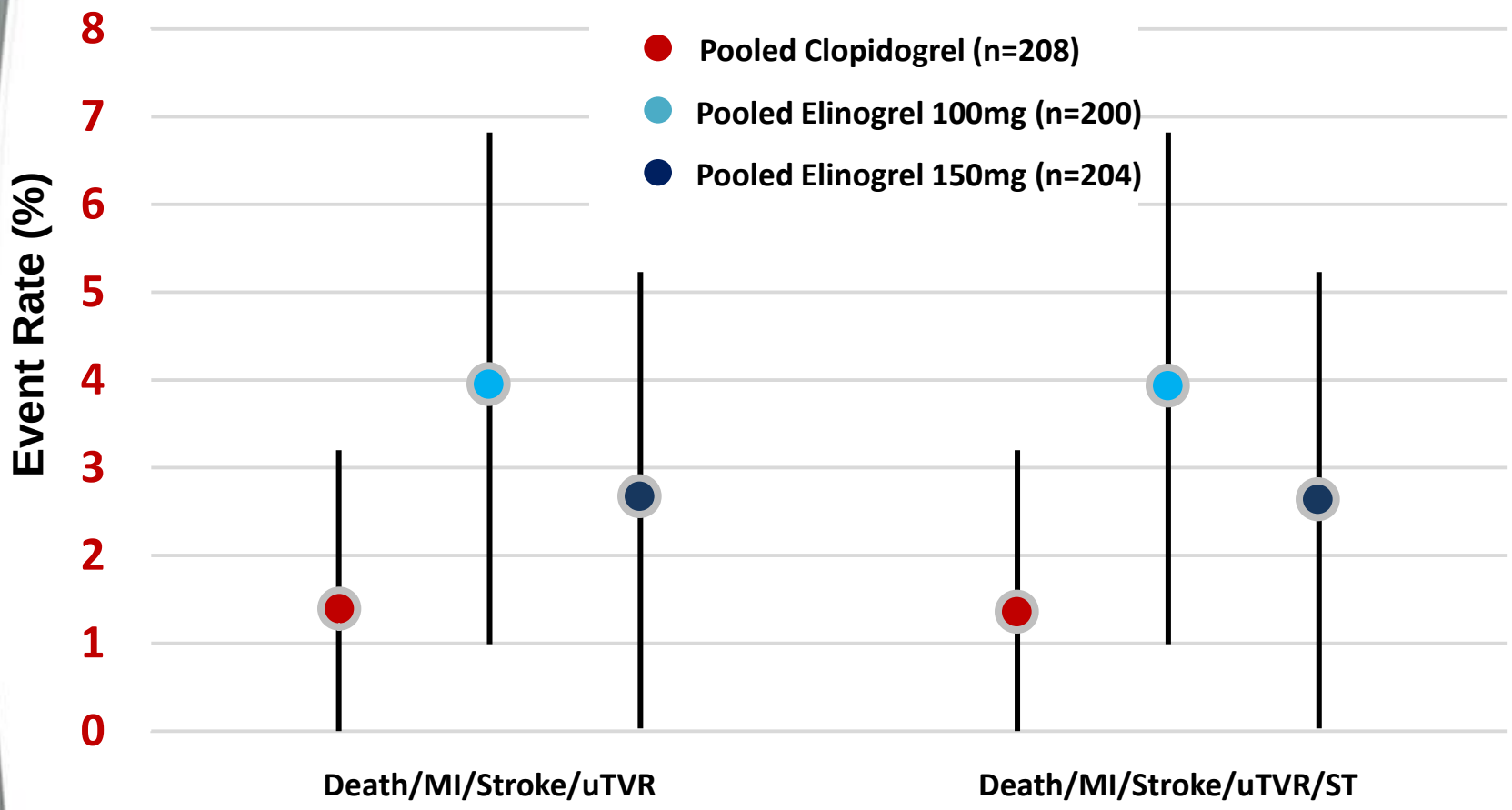
Clinical and Biological Endpoints

Rates and 95% confidence intervals



Efficacy at 24h-120 Days

Rates and 95% confidence intervals



INNOVATE PCI

Adverse Events

	Clopidogrel N=208	Pooled elinogrel 100 mg N=201	Pooled elinogrel 150 mg N=207
Any SAE	11.1%	14.9%	12.6%
Drug d/c due to AE or SAE	7.2%	7.5%	10.1%
Dyspnea*	4.3%	15.4%	12.1%
Bradycardia	0.5%	1.0%	0.5%
Syncope	0.5%	1.5%	0.5%
ALT/AST > 3x^	1.0%	4.0%	4.8%
ALT/AST > 5x	0.5%	2.0%	3.4%

*** Dyspnea was generally mild, transient, and infrequently led to discontinuation**

^ Most cases occurred within first 60 days and were asymptomatic; All cases resolved, even when treatment was continued; No Hy's Law cases.

Conclusions

- IV and oral elinogrel result in greater and more rapid antiplatelet effect than clopidogrel during both the acute and chronic phase of therapy
- No excess TIMI major or minor bleeding at both the 24-hr and 120-day timepoints
- Dose-dependent trend of increase in less severe bleeds (Bleeding Requiring Medical Attention), mostly occurring at the vascular access site in the peri-procedural period
- No significant differences in efficacy at 24 hrs or 120 days (trial not powered for efficacy)

Conclusions (2)

- Adverse events similar between elinogrel and clopidogrel
  - Dyspnea more frequent in the elinogrel arms
    - Mild, transient, infrequently led to discontinuation
  - Excess in transaminase elevation cases in the elinogrel arms
    - Occurred early and were generally asymptomatic
    - All resolved even when treatment was continued
    - No Hy's Law cases
- INNOVATE PCI data support moving forward into Phase 3