

**Treatment with ADP receptor inhibitorS:  
Longitudinal Assessment of Treatment patterns  
and Events after Acute Coronary Syndrome**

TCT 2014 First Report Investigation  
presented on behalf of the TRANSLATE-ACS Investigators

# Disclosures

Presenting Author has the following disclosures:

- Research grants to the Duke Clinical Research Institute:
  - Daiichi Sankyo
  - Eli Lilly
  - Gilead Sciences
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  - Astra Zeneca
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  - American College of Cardiology Foundation

# Study Organization

## Study Leadership

Duke Clinical Research Institute

Eric D. Peterson (PI)

Tracy Y. Wang (Co-PI)

Kevin J. Anstrom

Lisa A. McCoy

Linda Davidson-Ray

## Study Sponsor

Daiichi Sankyo and Eli Lilly

Mark B. Effron

Marjorie E. Zettler

Brian A. Baker

Douglas E. Faries

## Steering Committee

David J. Cohen

St Luke's Mid America Heart Institute

Gregg C. Fonarow

Ahmanson-UCLA

Timothy D. Henry

Cedars Sinai Medical Center

John C. Messenger

University of Colorado

Gregg W. Stone

Columbia University Medical Center

# Background

- In TRITON-TIMI 38, prasugrel reduced the risk of adverse CV events compared with clopidogrel among ACS patients treated with PCI, however a higher risk of major bleeding was also observed.
- Limited data are available on the comparative effectiveness and safety of prasugrel vs. clopidogrel therapy in routine clinical practice in the United States.

# Objectives

Compare prasugrel vs. clopidogrel among MI patients undergoing PCI:

- ***Effectiveness at 12 months***
  - **MACE** = composite of all-cause death, MI, stroke, or unplanned coronary revascularization
  - **Stent Thrombosis** = Academic Research Consortium (ARC) definite stent thrombosis
- ***Safety at 12 months***
  - **Bleeding** = GUSTO moderate or severe bleeding



# Study Design

- Multicenter, prospective, observational study
- Enrollment between April 2010 and October 2012
- **Inclusion Criteria**
  - STEMI and NSTEMI patients treated with PCI and an ADP receptor inhibitor during the index hospitalization
- **Exclusion Criteria**
  - unable to provide written consent for follow-up
  - participating in another trial that specified ADP receptor inhibitor use in the first year post-MI

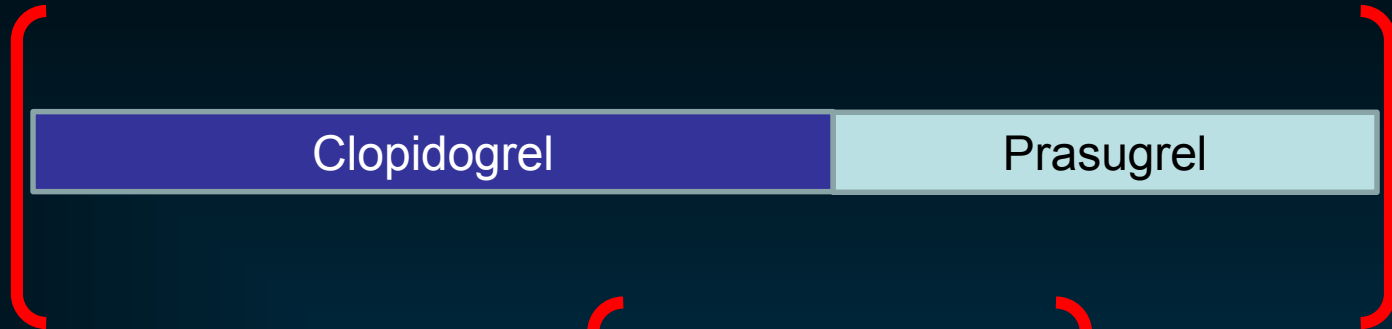
# Methods

- Events independently validated
- Cumulative incidence of events by 12 months
  - Primary approach: “as treated” – events censored >1 week after discontinuation or switch
  - Secondary approach: “intention to treat”
- Pre-specified primary multivariable analysis
  - Cox proportional hazards model using inverse probability weighting (IPW) based on propensity score – likelihood of prasugrel vs. clopidogrel

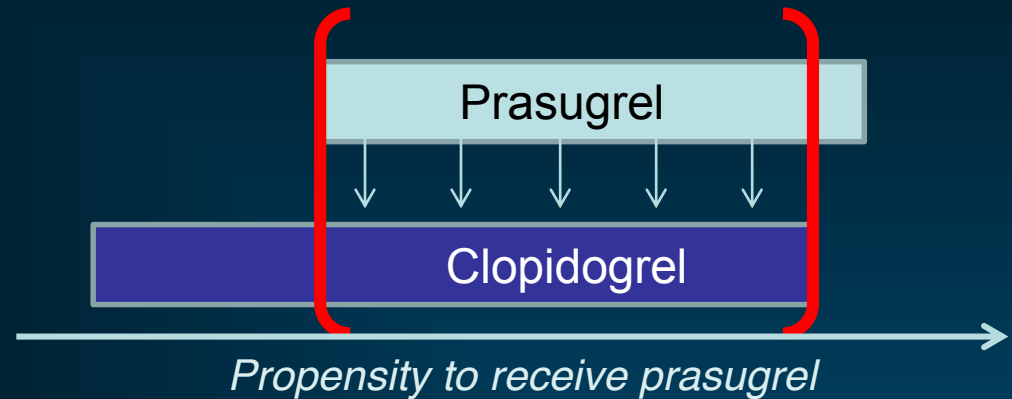
# Primary & Secondary Models

56 demographic, clinical, and procedural covariates

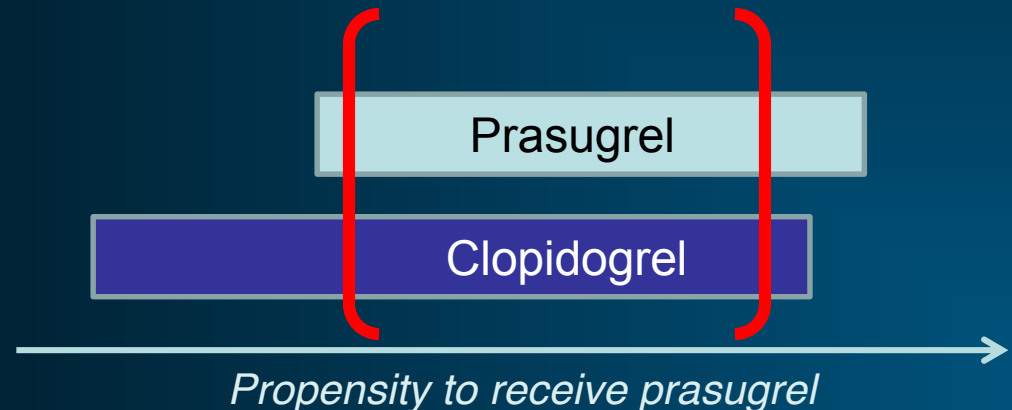
Primary Analysis  
IPW



Secondary Analyses  
Propensity Match  
1:1 match



Trimmed Population  
>90% of covariates well-balanced with  $|SD| < 0.10$



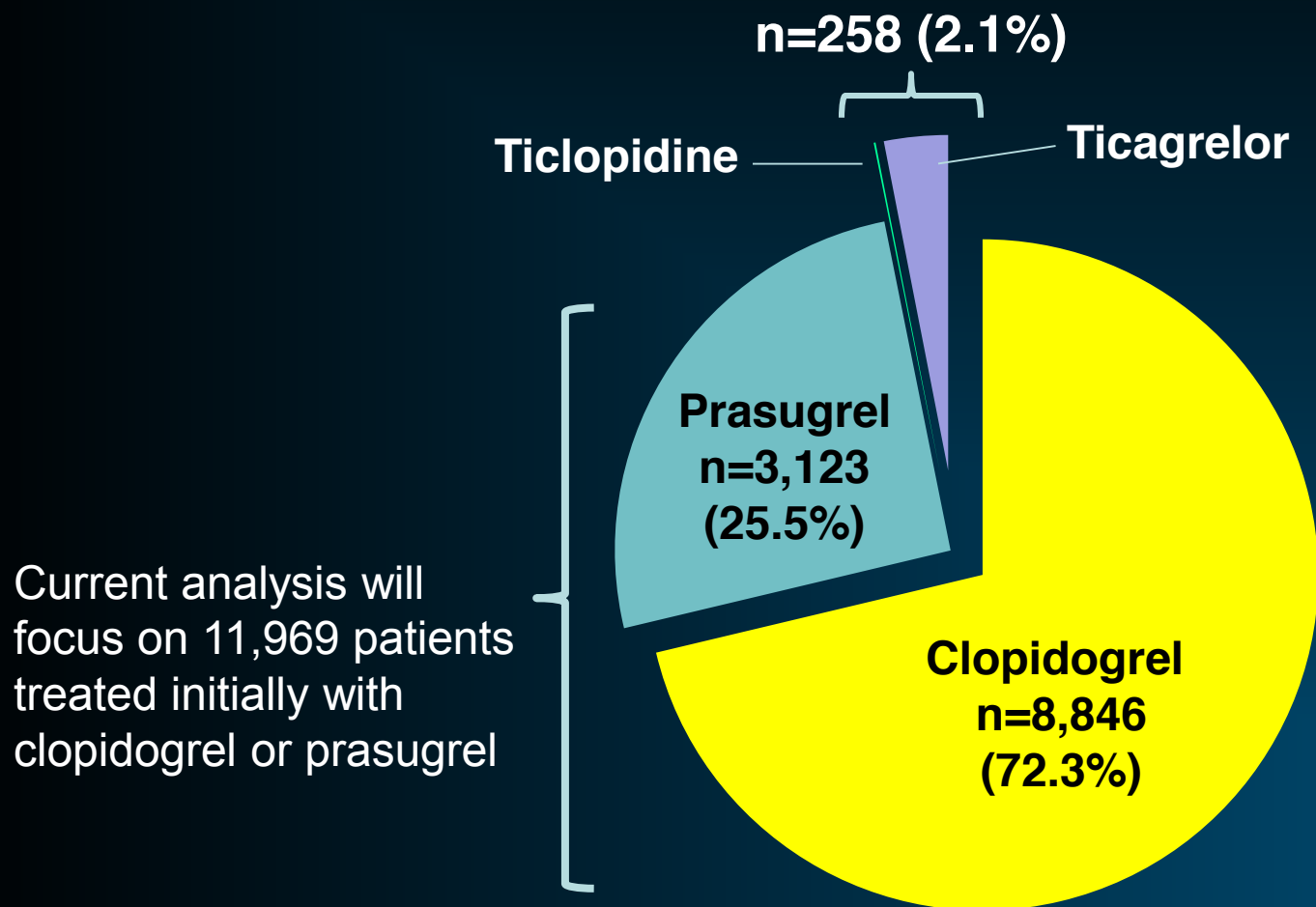


# Study Centers

12,227 MI patients treated with PCI at 233 U.S. hospitals



# ADP Receptor Inhibitor Selection



# Baseline Characteristics

|                                   | Prasugrel<br>N=3,123    | Clopidogrel<br>N=8,846  | P                 |
|-----------------------------------|-------------------------|-------------------------|-------------------|
| <b>Age*, years</b>                | <b>57 (50-63)</b>       | <b>61 (53-70)</b>       | <b>&lt;0.0001</b> |
| <b>Female</b>                     | <b>21.5%</b>            | <b>30.2%</b>            | <b>&lt;0.0001</b> |
| <b>White race</b>                 | <b>88.1%</b>            | <b>87.9%</b>            | <b>0.82</b>       |
| <b>Uninsured</b>                  | <b>16.9%</b>            | <b>14.1%</b>            | <b>0.0002</b>     |
| <b>STEMI (vs. NSTEMI)</b>         | <b>58.6%</b>            | <b>49.3%</b>            | <b>&lt;0.0001</b> |
| <b>Prior MI</b>                   | <b>14.6%</b>            | <b>21.3%</b>            | <b>&lt;0.0001</b> |
| <b>Prior PCI</b>                  | <b>17.8%</b>            | <b>23.0%</b>            | <b>&lt;0.0001</b> |
| <b>Prior CABG</b>                 | <b>5.5%</b>             | <b>10.6%</b>            | <b>&lt;0.0001</b> |
| <b>Prior stroke/TIA</b>           | <b>1.9%</b>             | <b>6.6%</b>             | <b>&lt;0.0001</b> |
| <b>Diabetes</b>                   | <b>24.6%</b>            | <b>27.2%</b>            | <b>0.003</b>      |
| <b>Baseline hemoglobin*, g/dL</b> | <b>14.7 (13.6-15.7)</b> | <b>14.1 (12.9-15.3)</b> | <b>&lt;0.0001</b> |

# Procedural Characteristics

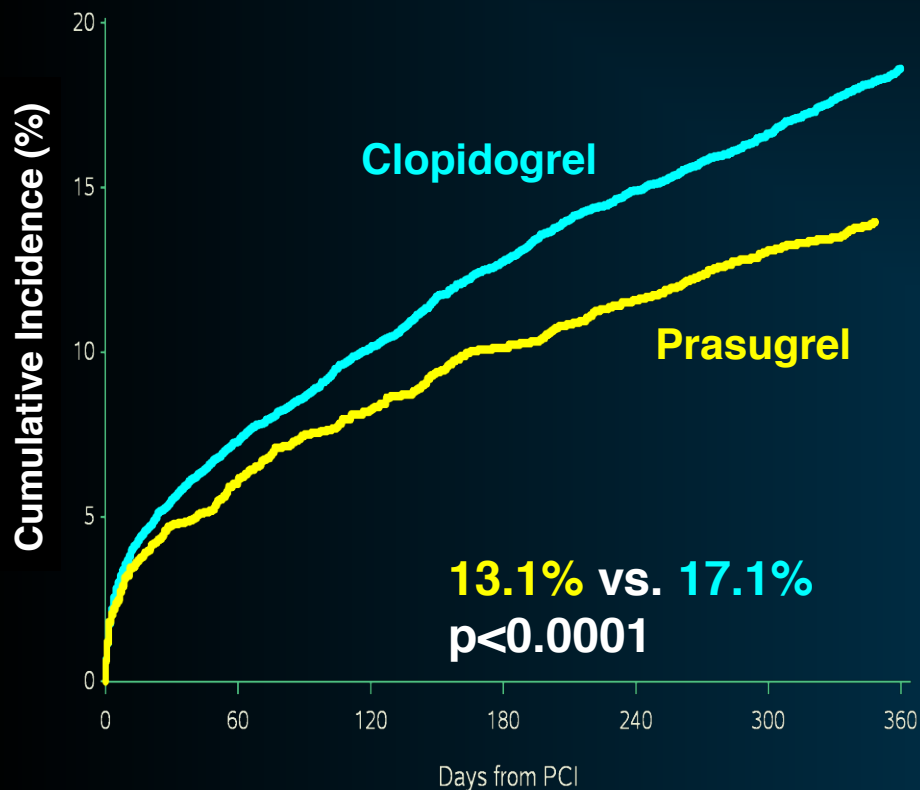
|                                  | Prasugrel<br>N=3,123 | Clopidogrel<br>N=8,846 | P       |
|----------------------------------|----------------------|------------------------|---------|
| <b>Culprit lesion location</b>   |                      |                        | <0.0001 |
| Left main                        | 0.4%                 | 1.0%                   |         |
| LAD                              | 39.9%                | 36.2%                  |         |
| Circumflex                       | 21.1%                | 23.1%                  |         |
| RCA                              | 38.1%                | 39.2%                  |         |
| <b>Lesion in graft</b>           | 2.9%                 | 5.4%                   | <0.0001 |
| <b>Previously stented lesion</b> | 6.7%                 | 7.4%                   | 0.99    |
| <b>Bifurcation lesion</b>        | 12.3%                | 10.9%                  | 0.03    |
| <b>Multivessel PCI</b>           | 24.2%                | 26.3%                  | <0.0001 |
| <b>DES used</b>                  | 75.9%                | 69.1%                  | <0.0001 |

# In-Hospital Therapies

|  | Prasugrel<br>N=3,123 | Clopidogrel<br>N=8,846 | P       |
|--|----------------------|------------------------|---------|
| <b>Aspirin</b>                         | 98.1%                | 98.4%                  | 0.35    |
| <b>Unfractionated heparin</b>          | 69.4%                | 76.6%                  | <0.0001 |
| <b>LMW heparin</b>                     | 16.4%                | 20.3%                  | <0.0001 |
| <b>Bivalirudin</b>                     | 50.5%                | 47.7%                  | 0.007   |
| <b>Fibrinolytic</b>                    | 3.0%                 | 4.3%                   | <0.0001 |
| <b>Glycoprotein IIb/IIIa inhibitor</b> | 48.4%                | 42.2%                  | <0.0001 |

# Unadjusted MACE

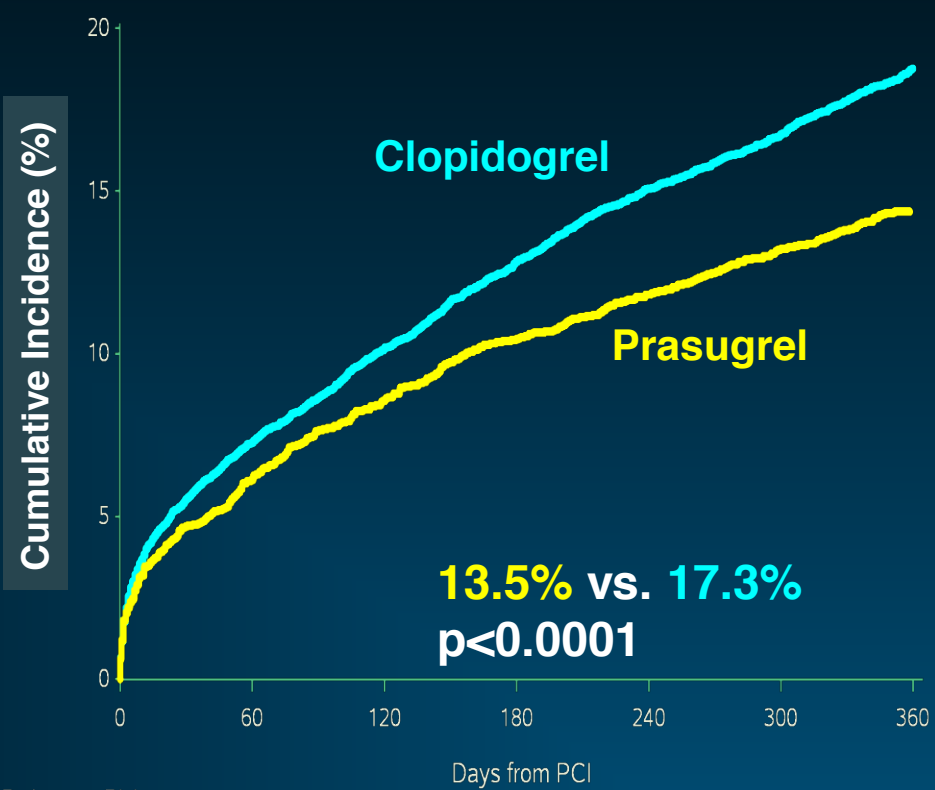
## As Treated



Patient at Risk:

|             |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|
| Clopidogrel | 8838 | 6848 | 6446 | 6070 | 5801 | 5563 |
| Prasugrel   | 3123 | 2312 | 2130 | 1994 | 1886 | 1794 |

## Intention to Treat



Patient at Risk:

|             |      |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|------|
| Clopidogrel | 8838 | 8123 | 7877 | 7624 | 7429 | 7291 | 7107 |
| Prasugrel   | 3123 | 2905 | 2819 | 2757 | 2708 | 2665 | 2620 |

# Adjusted MACE

|                                  | Adj. HR     | 95% CI             | P           |
|----------------------------------|-------------|--------------------|-------------|
| <b><u>Primary Analysis</u></b>   |             |                    |             |
| <b>IPW (as treated)</b>          | <b>1.03</b> | <b>0.92 – 1.16</b> | <b>0.59</b> |
| <b><u>Secondary Analyses</u></b> |             |                    |             |
| IPW (ITT)                        | 1.00        | 0.91 – 1.11        | 0.95        |
| Propensity-matched (as treated)  | 1.02        | 0.90 – 1.14        | 0.81        |
| Propensity-matched (ITT)         | 1.03        | 0.93 – 1.14        | 0.57        |
| Trimmed population (as treated)  | 0.89        | 0.76 – 1.05        | 0.18        |
| Trimmed population (ITT)         | 0.91        | 0.79 – 1.06        | 0.23        |

# Individual MACE Endpoints

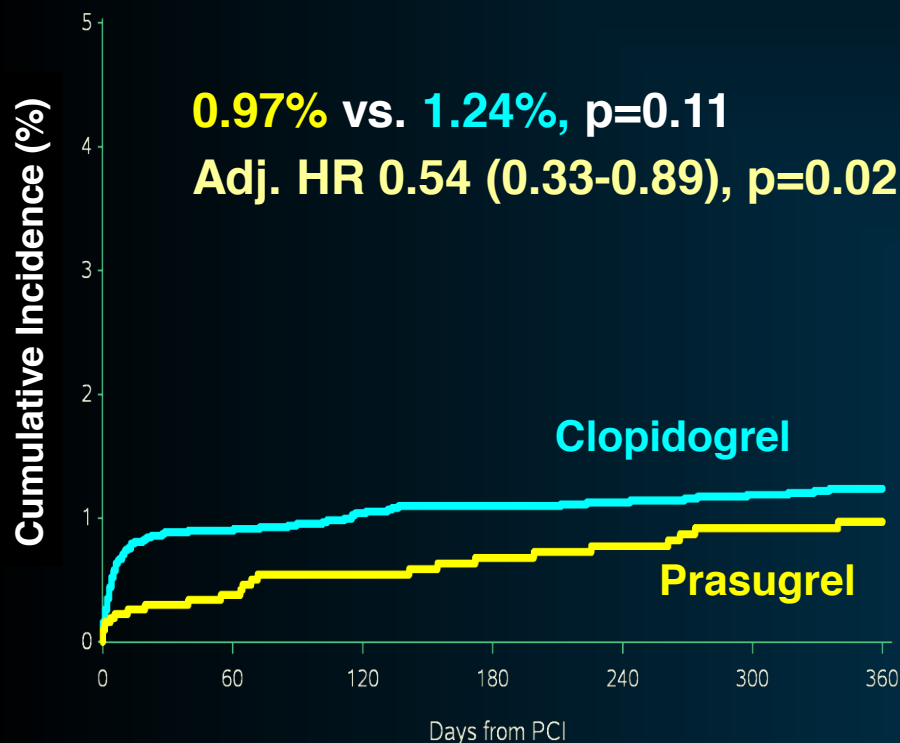
| Unadjusted event rates             | Adj. HR | 95% CI      | P    |
|------------------------------------|---------|-------------|------|
| <b>All-cause mortality</b>         |         |             |      |
| 1.3% vs. 3.4%, $p < 0.0001$        | 0.80    | 0.59 – 1.08 | 0.15 |
| <b>MI</b>                          |         |             |      |
| 3.7% vs. 5.5%, $p = 0.0001$        | 0.98    | 0.80 – 1.21 | 0.84 |
| <b>Stroke</b>                      |         |             |      |
| 0.6% vs. 1.1%, $p = 0.009$         | 0.90    | 0.55 – 1.48 | 0.69 |
| <b>Unplanned revascularization</b> |         |             |      |
| 10.7% vs. 12.0%, $p = 0.05$        | 1.12    | 0.99 – 1.28 | 0.08 |



# Stent Thrombosis

## As Treated

**0.97% vs. 1.24%, p=0.11**  
**Adj. HR 0.54 (0.33-0.89), p=0.02**

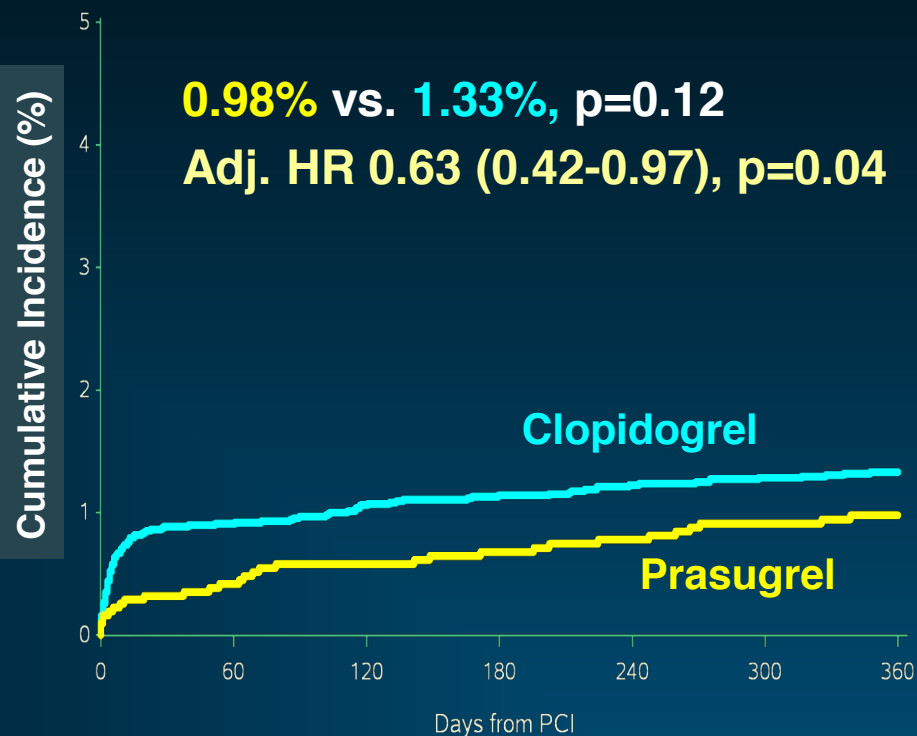


Patient at Risk:

|             | 0    | 60   | 120  | 180  | 240  | 300  | 360  |
|-------------|------|------|------|------|------|------|------|
| Clopidogrel | 8846 | 7229 | 6929 | 6639 | 6438 | 6256 | 5911 |
| Prasugrel   | 3123 | 2438 | 2279 | 2163 | 2074 | 1997 | 1854 |

## Intention to Treat

**0.98% vs. 1.33%, p=0.12**  
**Adj. HR 0.63 (0.42-0.97), p=0.04**

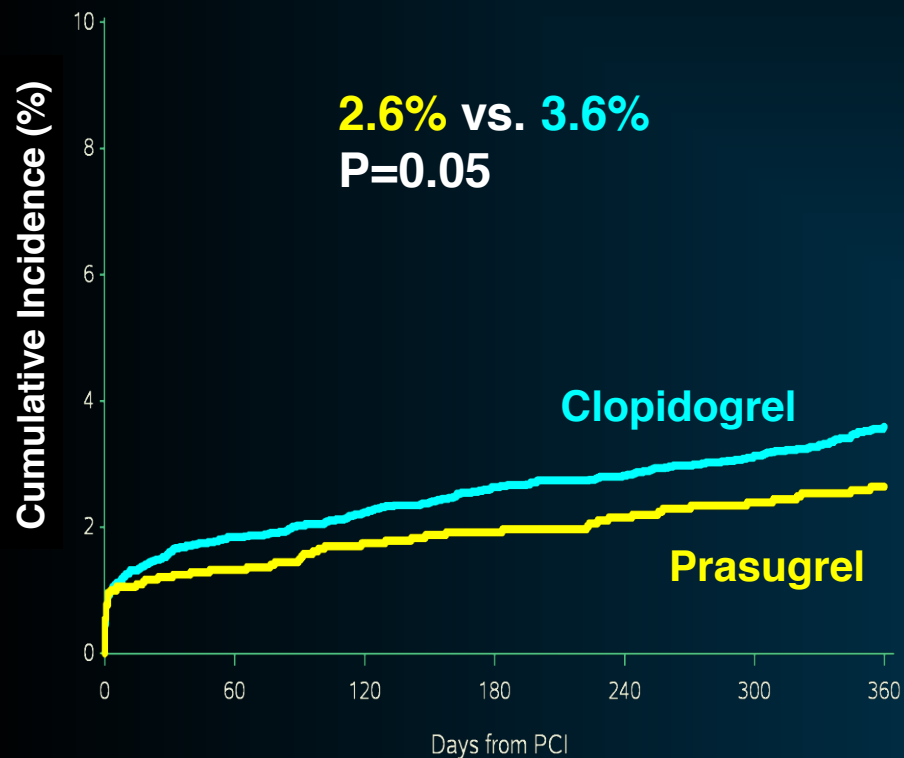


Patient at Risk:

|             | 0    | 60   | 120  | 180  | 240  | 300  | 360  |
|-------------|------|------|------|------|------|------|------|
| Clopidogrel | 8846 | 8587 | 8510 | 8414 | 8329 | 8267 | 8173 |
| Prasugrel   | 3123 | 3068 | 3036 | 3017 | 2995 | 2978 | 2946 |

# Unadjusted Bleeding

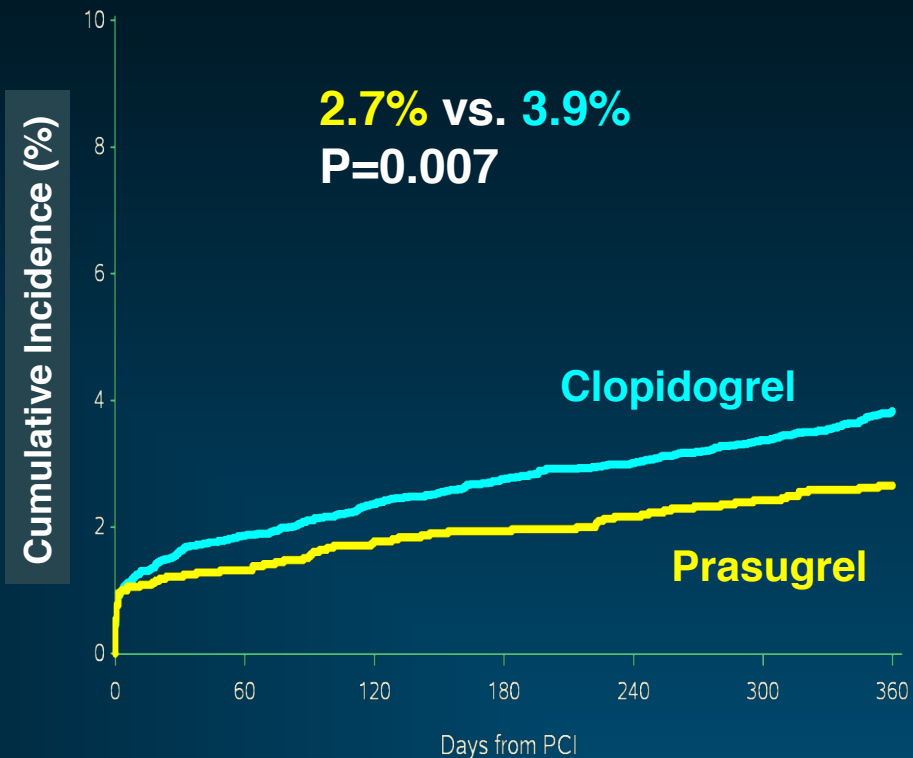
## As Treated



Patient at Risk:

|             |      |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|------|
| Clopidogrel | 8833 | 7141 | 6841 | 6540 | 6333 | 6147 | 5794 |
| Prasugrel   | 3123 | 2426 | 2267 | 2155 | 2062 | 1983 | 1843 |

## Intention to Treat



Patient at Risk:

|             |      |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|------|
| Clopidogrel | 8833 | 8499 | 8401 | 8287 | 8189 | 8111 | 7988 |
| Prasugrel   | 3123 | 3041 | 3003 | 2982 | 2956 | 2936 | 2902 |

# Adjusted Bleeding

|                                  | Adj. HR     | 95% CI             | P           |
|----------------------------------|-------------|--------------------|-------------|
| <b><u>Primary Analysis</u></b>   |             |                    |             |
| <b>IPW (as treated)</b>          | <b>1.30</b> | <b>1.04 – 1.63</b> | <b>0.02</b> |
| <b><u>Secondary Analyses</u></b> |             |                    |             |
| IPW (ITT)                        | 1.30        | 1.07 – 1.59        | 0.01        |
| Propensity-matched (as treated)  | 1.12        | 0.86 – 1.47        | 0.41        |
| Propensity-matched (ITT)         | 1.10        | 0.88 – 1.37        | 0.43        |
| Trimmed population (as treated)  | 0.94        | 0.64 – 1.36        | 0.73        |
| Trimmed population (ITT)         | 0.83        | 0.58 – 1.18        | 0.29        |

# Limitations

- Potential for residual confounding in non-randomized, observational comparison of outcomes despite multivariable adjustment
- Peri-procedural MIs may be under-reported as biomarkers are not routinely measured post-PCI in clinical practice
- Site participation was voluntary and longitudinal follow-up required informed consent. Results may not be generalized to a broader U.S. population

# Conclusions

- In U.S. community practice, patients treated with prasugrel vs. clopidogrel differ significantly.
- While unadjusted comparisons demonstrated lower MACE in patients receiving prasugrel vs. clopidogrel, these differences were not significant after risk adjustment.
  - However, prasugrel was associated with significantly lower adjusted risk of stent thrombosis.
- Prasugrel was associated with significantly higher adjusted bleeding risk relative to clopidogrel.
  - These differences were not significant among patients more likely to be treated with prasugrel in community practice.



# Thank you to all TRANSLATE-ACS Investigators Top 20 Enrollers

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Minneapolis Heart Institute  
Minneapolis, MN

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Sacramento, CA

**Anjan Gupta, MD**  
Aurora St. Luke's MC  
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**William Smith, MD**  
New Hanover Regional  
Medical Center  
Wilmington, NC

**Tracy Wang, MD**  
Duke University  
Durham, NC

**Rolf Kreutz, MD**  
Indiana University Health-  
Methodist Hospital  
Indianapolis, IN

**Richard Bach, MD**  
Washington University School  
of Medicine, St. Louis, MI

**Ron Waksman, MD**  
Washington Hospital Center  
Washington, DC

**Robert Stenberg, MD**  
Conemaugh Valley  
Memorial Hospital  
Johnstown, PA

**Mark Koenig, MD**  
Saint Thomas Hospital  
Nashville, TN

**Neal Gaither, MD**  
Winchester Medical Center  
Winchester, VA

**Peter Berger, MD**  
Geisinger Medical Center  
Danville, PA

**Harry Wallner, MD**  
Trinity Medical Center  
Rock Island, IL

**Chanwit Roongsritong, MD**  
Renown Regional Medical  
Center  
Reno, NV

**George Kramer, MD**  
Wellstar Kennestone  
Hospital  
Marietta, GA

**Luis Gruberg, MD**  
Stony Brook University  
Medical Center  
Stony Brook, NY

**Stephen Lewis, MD**  
Bethesda North Hospital  
Cincinnati, OH

**Chowdhury Ahsan, MD**  
University Medical Center  
of Southern Nevada  
Las Vegas, NV

**David Brill, MD**  
Washington Adventist  
Hospital  
Takoma Park, MD

**Thomas LeGalley, MD**  
Marquette General  
Hospital  
Marquette, MI