# Genotype-guided oral P2Y12 inhibition in patients with ST-segment elevation myocardial infarction undergoing primary PCI: a randomized, open-label, multicentre trial

## POPular Genetics

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# Declaration of interest

- I have nothing to declare

# Background

ESC European Society of Cardiology
European Heart Journal (2018) 39, 119–177
doi:10.1093/eurheartj/ehx393
ESC GUIDELINES

## 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

| Recommendations | Class[b] | Level[c] |
|---|---|---|
| **Antiplatelet therapy** | | |
| A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[186,187] | I | A |

*1: Ibanez et al. ESC STEMI guidelines, EHJ2018,*

# Background

- 30% of Caucasians show an inadequate response to clopidogrel resulting in more stent thrombosis

- CYP2C19 Wild type (*1/*1) = normal response
- *2 and *3 loss-of-function alleles = inadequate response

- In wild type patients, clopidogrel demonstrated similar efficacy compared to potent P2Y12 inhibitors[2,3]

*2: Mega et al. Lancet 2010, 3: Wallentin et al. Lancet 2010*

# Background

- Reduction in thrombotic events such as stent thrombosis in past decade[4-6]

- Bleeding is very common and strongly associated with mortality[7]

*4: Wallentin et al. PLATO, NEJM 2009, 5: Wiviott et al. TRITON-TIMI 38, NEJM 2007, 6: Sibbing et al. TROPICAL ACS, Lancet 2017*,
7: Généreux et al. *ADAPT DES JACC 2015*

# Hypothesis

- In primary PCI patients genotype-guided oral P2Y12 inhibition is as effective in preventing thrombotic events as the stronger ticagrelor and prasugrel but leads to less bleeding

# Trial organisation

- **Trial design**
  - Investigator initiated, randomised, open-label, blinded CEC
- **Sponsor & coordinating centre**
  - St. Antonius Hospital, Nieuwegein, The Netherlands
- **Funding & study support**
  - ZonMw (Efficiency research project no. 171102022)
  - Spartan Bioscience Inc.


**Participating sites**

- St. Antonius Hospital Nieuwegein – J.M. ten Berg
- Isala Hospital Zwolle – A.W.J. van't Hof
- University Medical Centre Groningen – P. van der Harst
- University Federico II Hospital, Naples – E. Barbato
- Onze Lieve Vrouw Hospital, Aalst – J. Bartun
- Rijnstate Hospital Arnhem – R.M. Tjor
  Joe Gin
- University Medical Centre Utrecht – F.W.
  Asselbergs
- Meander Medical Centre Amersfoort – A. Mosterd
- OLVG Amsterdam – J.P.R.
  Herrman

# Protocol change 2012

- **Original protocol:**
  - Standard treatment arm received clopidogrel
- **Protocol May 2012:**
  - Standard treatment arm received ticagrelor or prasugrel
  - The POPular Genetics only evaluates the patients included from May 2012

European Heart Journal (2008) **29**, 2909–2945
doi:10.1093/eurheartj/ehn416

ESC GUIDELINES

**Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation**

**The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology:**

European Heart Journal (2012) **33**, 2569–2619
doi:10.1093/eurheartj/ehs215

ESC GUIDELINES

**ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation**

**The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)**

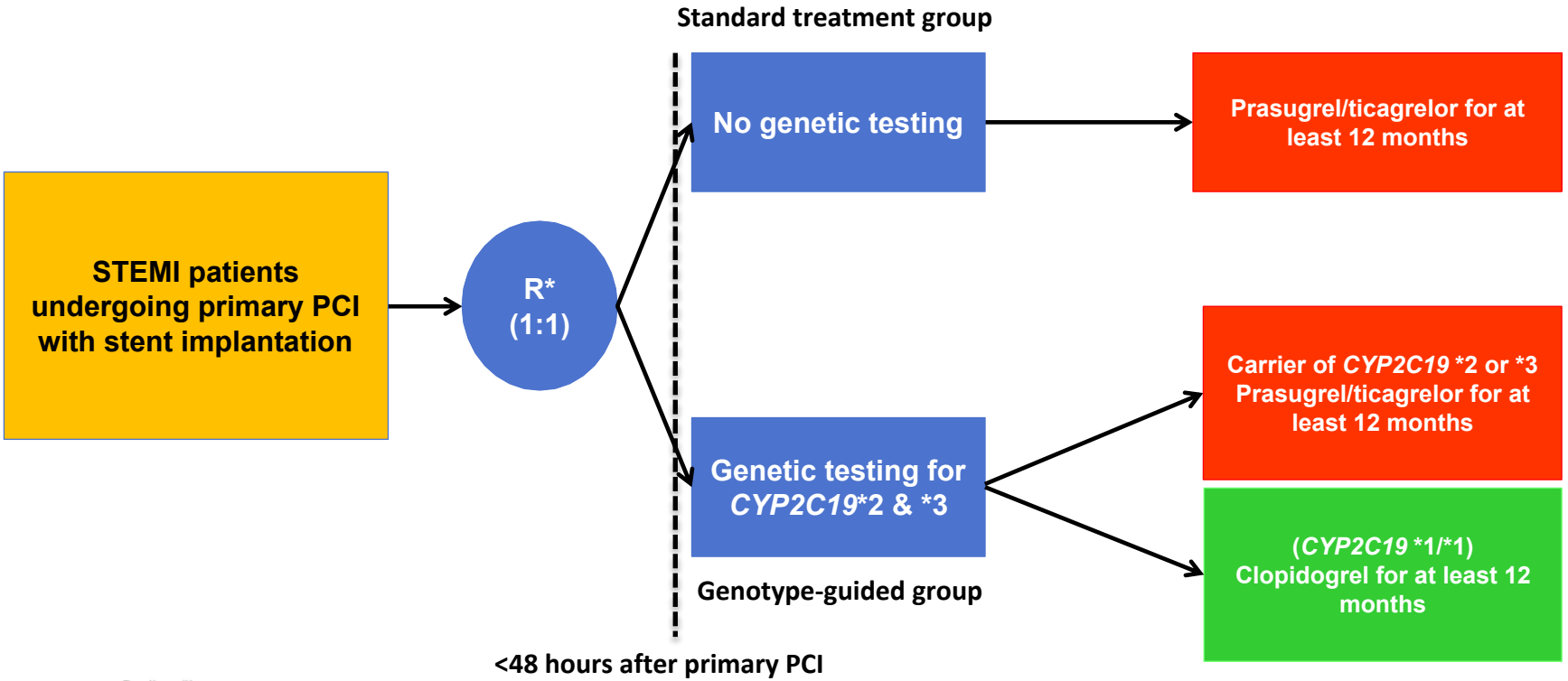
## Inclusion criteria

- Age ≥21 years old
- Signs & symptoms of STEMI >30 minutes, < 12 hours
- Primary PCI + stent implantation

## Key exclusion criteria

- Unable to obtain IC <48 hours after primary PCI
- Treatment with oral anticoagulants
- Contraindication to study drugs
- Cardiogenic shock or severe hypertension

# Trial design



# Genetic testing


Spartan RX point-of-care system in the cath lab

TaqMan StepOnePlus system

# Primary outcomes

- **Primary thrombotic & bleeding outcome:**
  - All-cause death, recurrent MI, definite stent thrombosis, stroke & PLATO major bleeding at 12 months

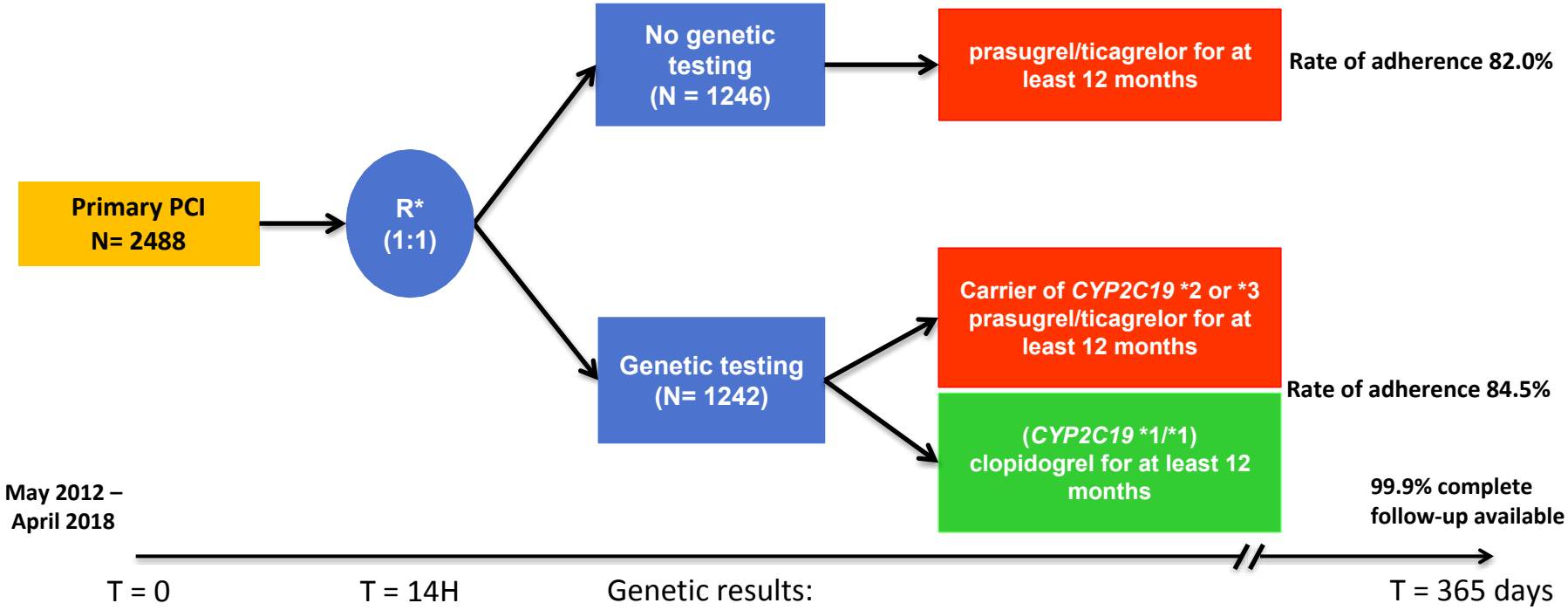
- **Co-primary bleeding outcome:**
  - PLATO major & minor bleeding at 12 months

# Sample size calculation

- **Expected event rate primary outcome:**
  - 16.9% in genotype-guided arm[1] vs. 18.8% in standard treatment arm[2]
- **Expected event rate co-primary bleeding outcome:**
  - 14.5% in genotype-guided arm[1] vs. 18.9% in standard treatment arm[2]
- Power 80%, alpha 0.05
- Absolute non-inferiority margin 2%
- 2 x 1250 patients for non-inferiority primary outcome
- Less patients for superiority co-primary bleeding outcome

1: Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: reltationship to pharmacokinteic, pharmacodynamic, and clinical outcomes. Ciculation 2009a;119:2553-60
1: Wallentin L, James S, Storey rf, ET AL. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320-8
2: Van't Hof AW, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (ON-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-46

# Trial patients and follow-up data



# Baseline characteristics

| | Genotype-guided | Standard treatment |
|---|---|---|
| **Mean Age - years** | 61.9 | 61.4 |
| **Age ≥75 years - %** | 15 | 14 |
| **Female - %** | 26 | 25 |
| **Mean Body-Mass Index** | 27.5 | 27.0 |
| **Cardiovascular risk factors - %** | | |
| **Current smoker** | 46 | 46 |
| **Diabetes Mellitus** | 12 | 11 |
| **Hypertension** | 42 | 41 |
| **Hyperlipidemia** | 21 | 21 |
| **History of CAD** | 11 | 10 |

# Procedural characteristics

| | Genotype-guided | Standard treatment |
|---|---|---|
| **Aspirin before PCI - %** | 99 | 99 |
| **$P2Y_{12}$ inhibitor before PCI - %** | 97 | 96 |
| **Radial artery access - %** | 69 | 70 |
| **Drug Eluting Stent - %** | 94 | 94 |
| **Diseased coronary vessels ≥50% - %** | | |
| **1** | 51 | 54 |
| **2** | 34 | 30 |
| **3** | 15 | 16 |
| **Vessels treated during index PCI - %** | | |
| **Left main** | 0.3 | 0.7 |
| **Left anterior descending** | 42 | 41 |
| **Ramus circumflex** | 17 | 19 |
| **Right coronary artery** | 42 | 41 |
| **Bypass graft** | 0.4 | 0.5 |

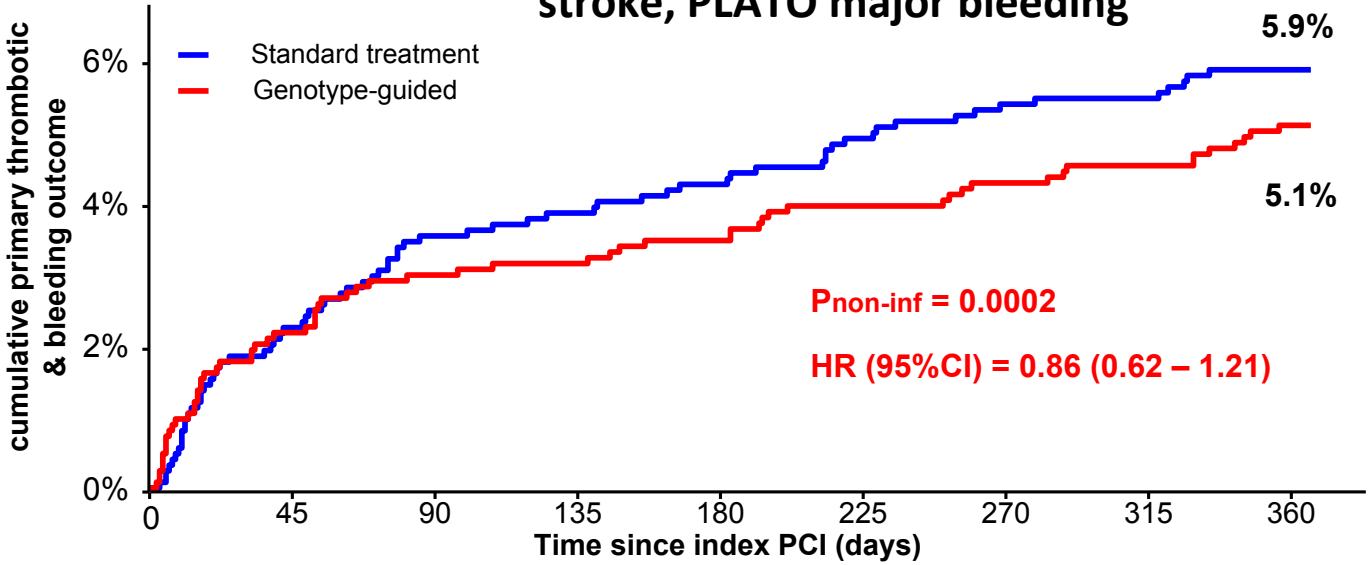
# Genetic results & discharge medication

| Genotype | % of patients |
|---|---|
| *1/*1 | 67.2 |
| Carriers of *2 or *3 LoF | 31.4 |
| Not available | 1.4 |

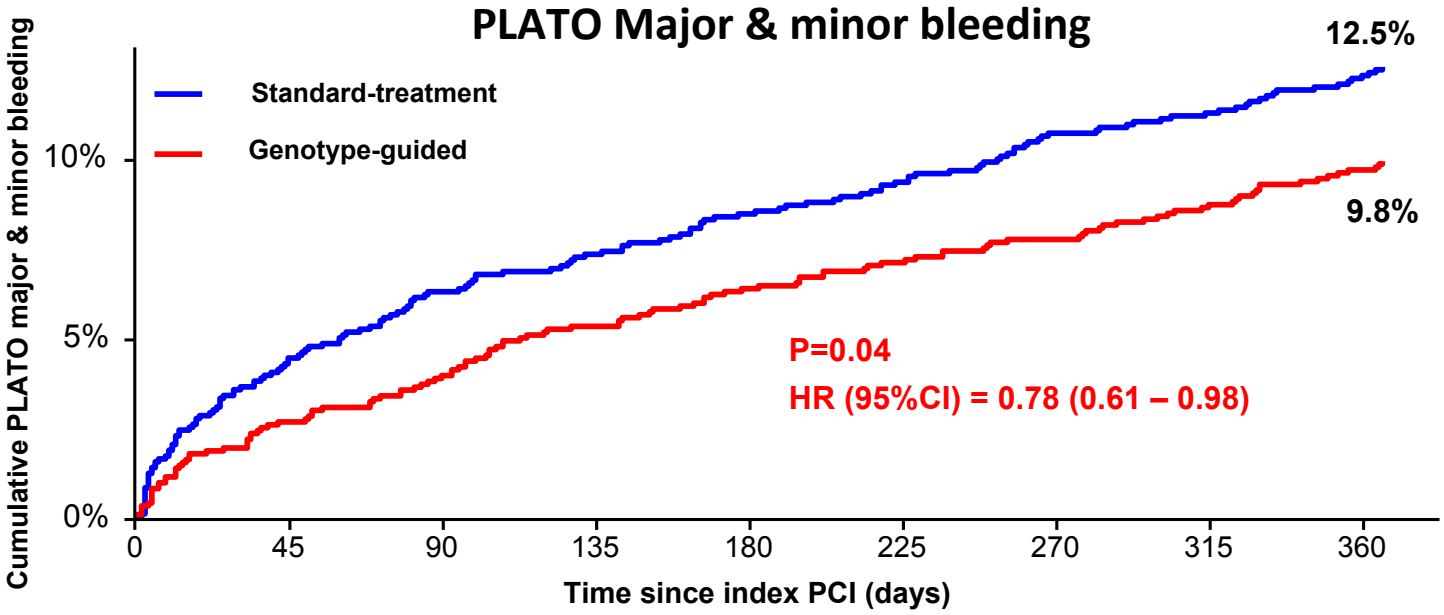
| Therapy after randomization & genotyping | | |
|---|---|---|
| | Genotype-guided | Standard treatment |
| $P2Y_{12}$ inhibitor - % | | |
| Clopidogrel | 61 | 7 |
| Prasugrel | 1 | 2 |
| Ticagrelor | 38 | 91 |

# Primary outcome

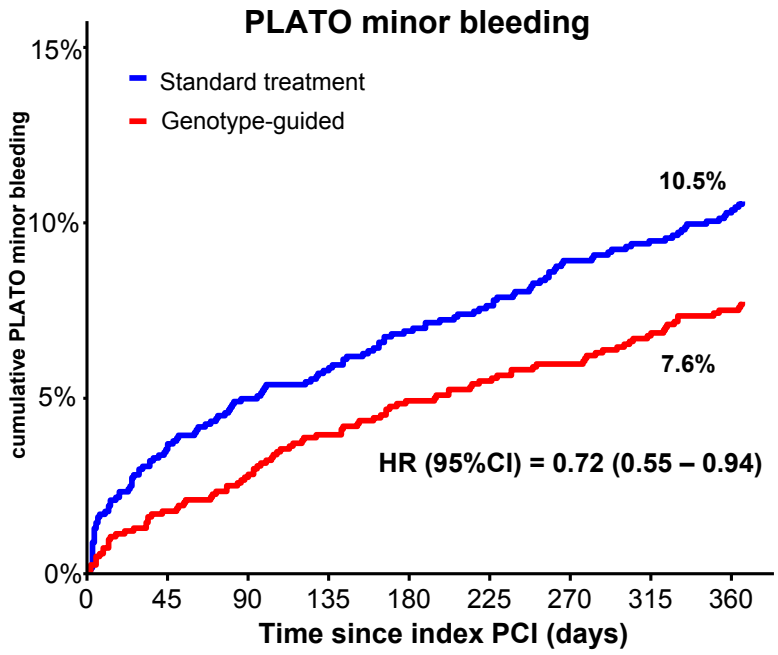
## All-cause death, MI, definite stent thrombosis, stroke, PLATO major bleeding

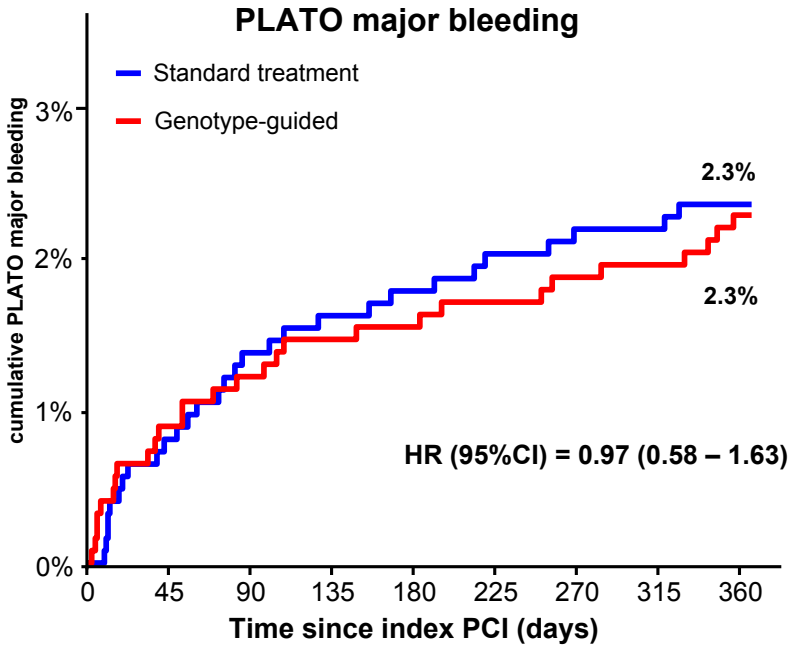


# Co-primary outcome



# Secondary bleeding outcomes



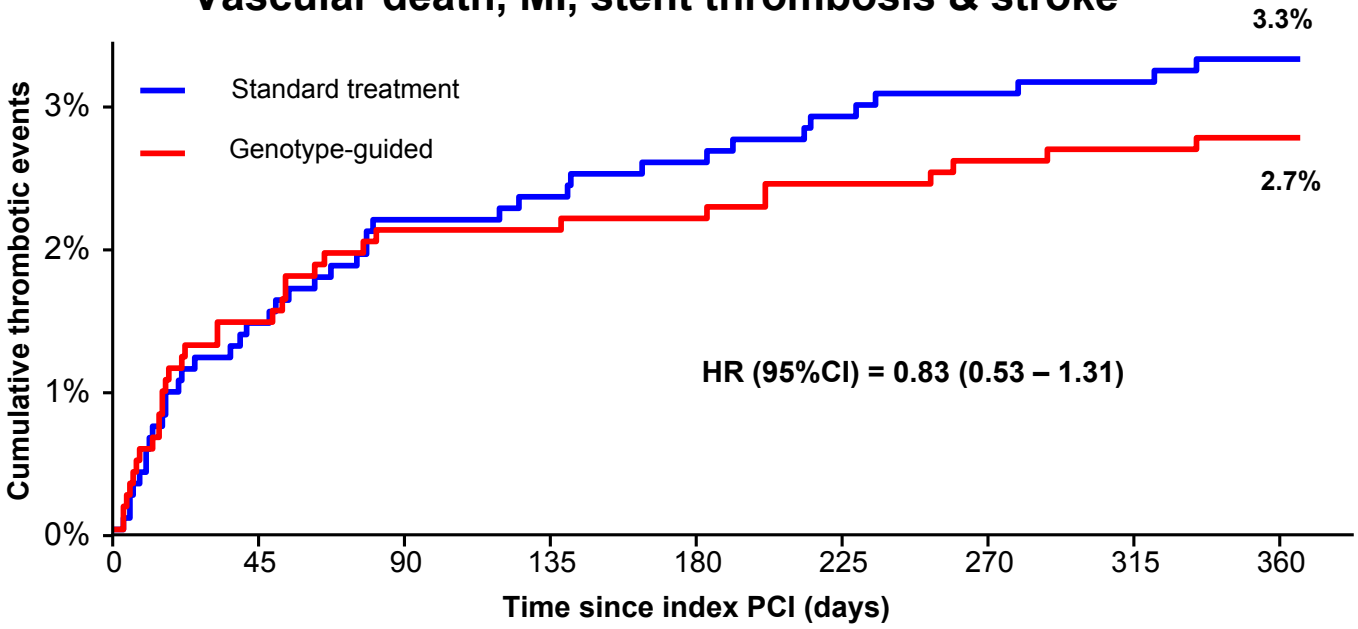




PLATO minor: Requiring medical intervention

PLATO major: Requiring ≥2U RBC transfusion, intrapericardial Hb drop >3g/dl, significantly disabling, intracranial, fatal

# Thrombotic outcome

## Vascular death, MI, stent thrombosis & stroke



# Conclusion

- POPular Genetics trial demonstrates:
  - **Genotyping is easy to use, fast results**
  - **Almost 2/3 of the patients treated with clopidogrel**
  - **No difference in thrombotic event rates**
  - **Reduction in bleeding event rates**

# Conclusion

- A simple-to-use CYP2C19 genotype-guided strategy to guide treatment early after primary PCI, resulted in less bleeding without increasing the thrombotic risk compared to standard treatment with ticagrelor or prasugrel

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ORIGINAL ARTICLE

# A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

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