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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Background

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,

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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
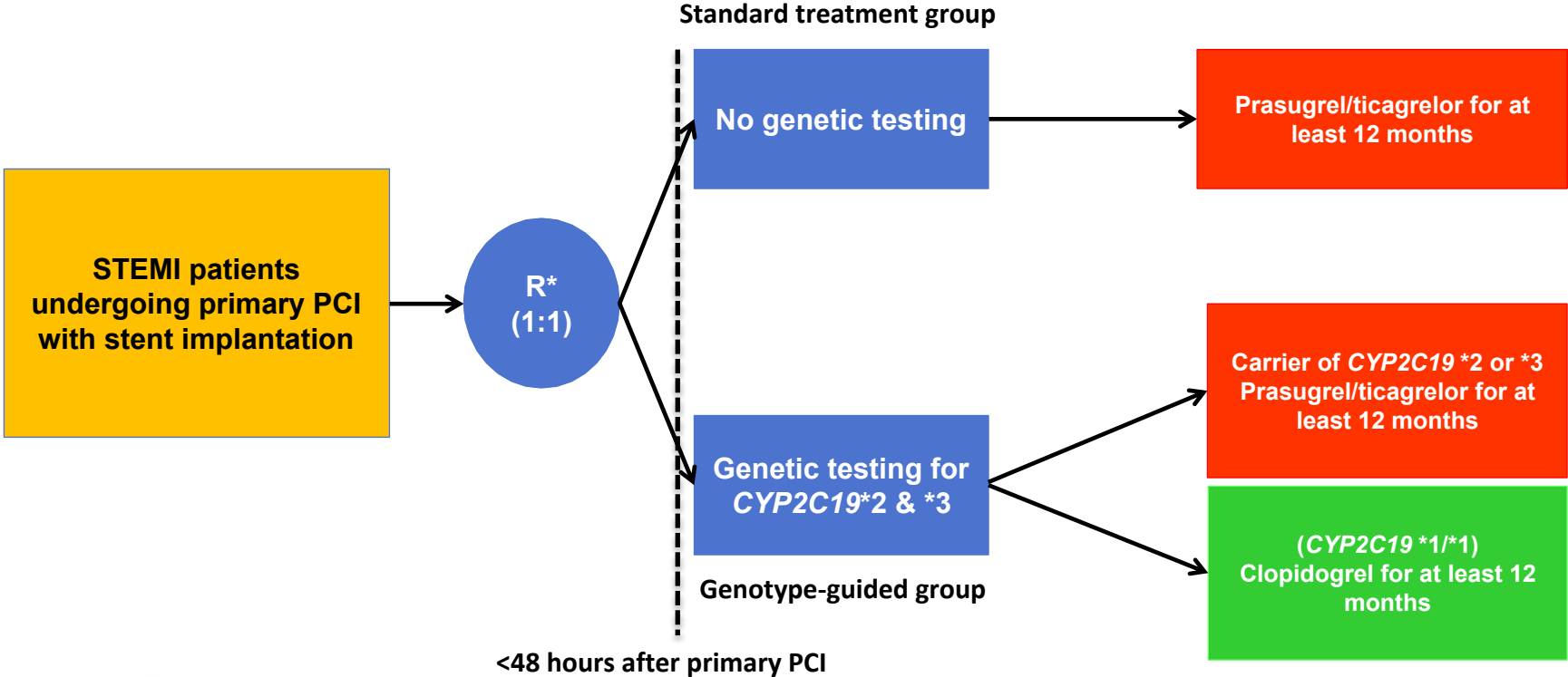
Inclusion criteria

- 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

Standard treatment group

STEMI patients undergoing primary PCI with stent implantation → R* (1:1)

No genetic testing → Prasugrel/ticagrelor for at least 12 months

Genetic testing for *CYP2C19*2 & *3*

Genotype-guided group

Carrier of *CYP2C19* *2 or *3 Prasugrel/ticagrelor for at least 12 months

(*CYP2C19* *1/*1) Clopidogrel for at least 12 months

<48 hours after primary PCI

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
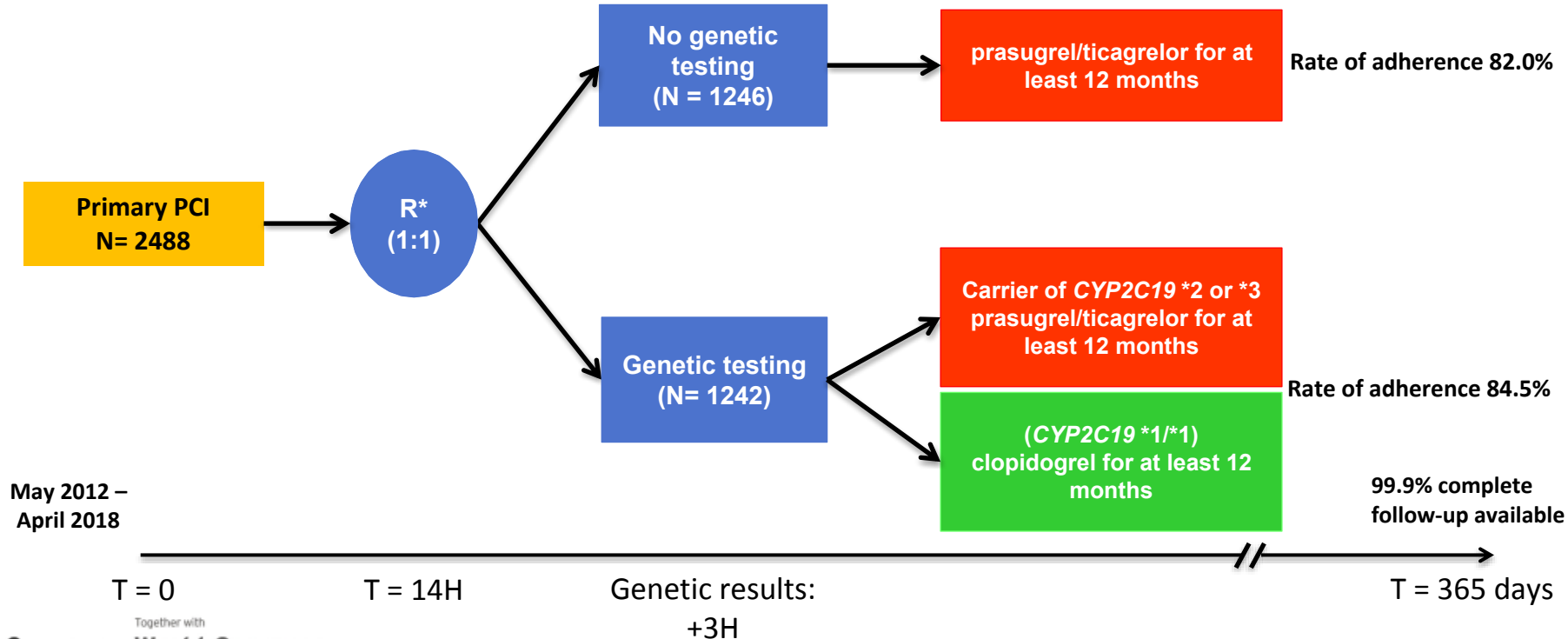
Baseline characteristics

	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

Legend:
- Standard treatment
- Genotype-guided

5.9%
5.1%

Pnon-inf = 0.0002

HR (95%CI) = 0.86 (0.62 – 1.21)

Y-axis: cumulative primary thrombotic & bleeding outcome (0%, 2%, 4%, 6%)

X-axis: Time since index PCI (days) (0, 45, 90, 135, 180, 225, 270, 315, 360)

Co-primary outcome
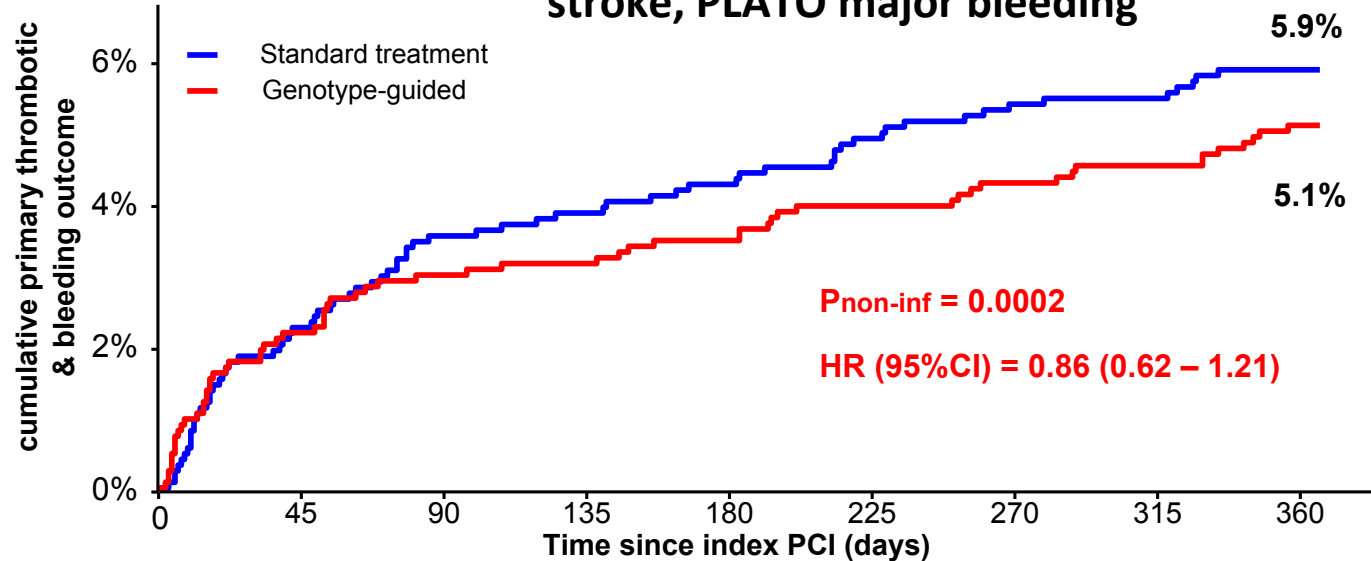
PLATO Major & minor bleeding
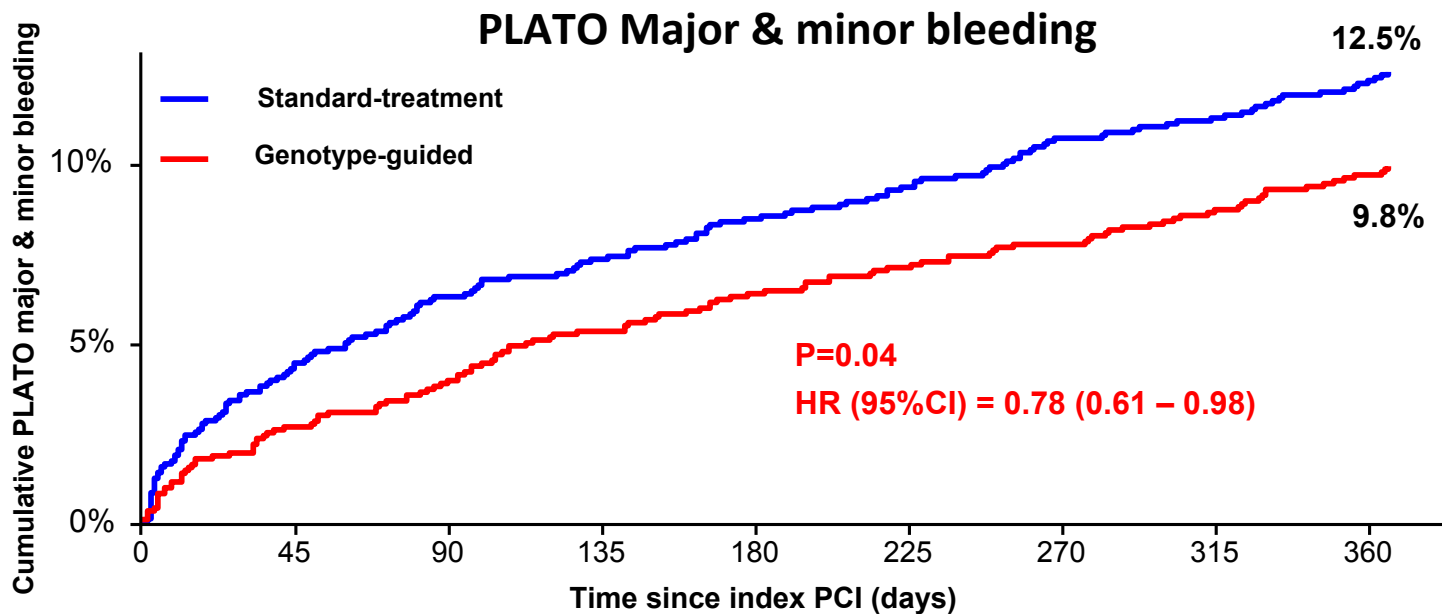
Secondary bleeding outcomes

PLATO minor bleeding

- Standard treatment
- Genotype-guided

cumulative PLATO minor bleeding

15%

10% — 10.5%

5%

7.6%

0%

HR (95%CI) = 0.72 (0.55 – 0.94)

0   45   90   135   180   225   270   315   360

Time since index PCI (days)

PLATO major bleeding

- Standard treatment
- Genotype-guided

cumulative PLATO major bleeding

3%

2% — 2.3%

2.3%

1%

0%

HR (95%CI) = 0.97 (0.58 – 1.63)

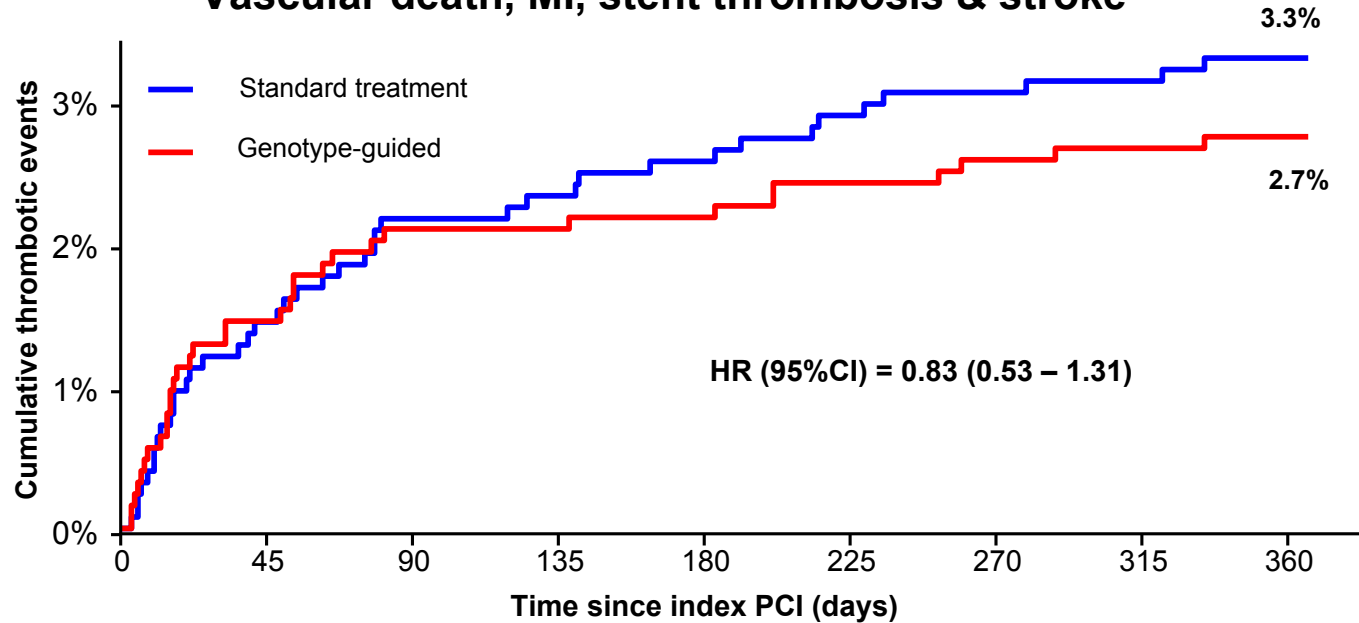0   45   90   135   180   225   270   315   360

Time since index PCI (days)
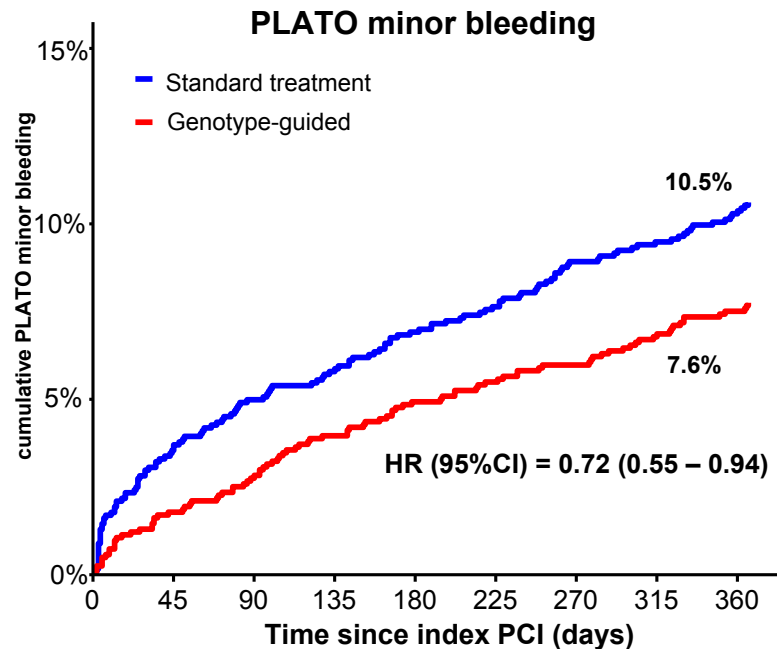
PLATO minor: Requiring medical intervention
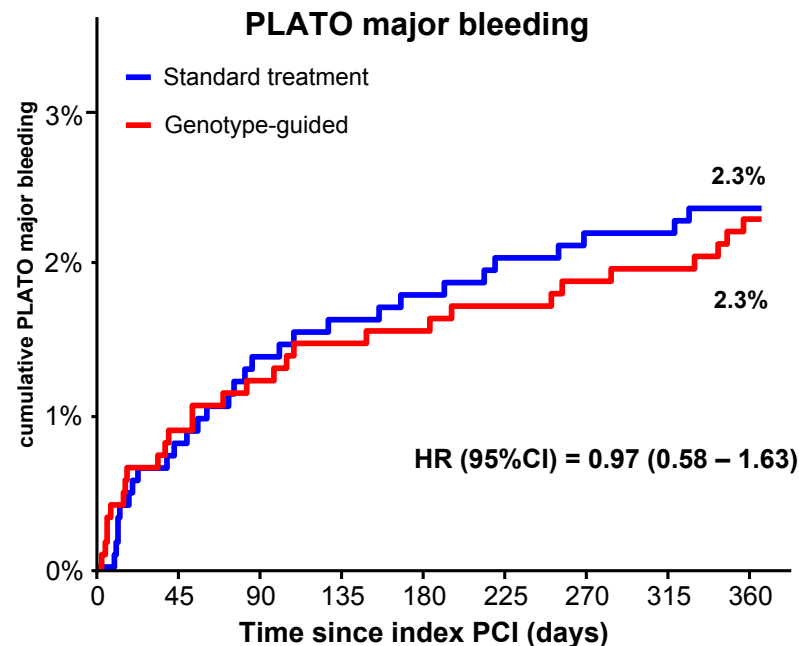
PLATO major: Requiring ≥2U RBC transfusion, intrapericardial Hb drop >3g/dl, significantly disabling, intracranial, fatal

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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