Conoscere e Curare il Cuore 2015

LA GENETICA NELLA SCELTA DELL'INIBITORE P2Y12 PIÙ ADATTO

Diego Ardissino

Unità Operativa di Cardiologia
Azienda Ospedaliero-Universitaria di Parma

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION 2012

DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI

CLASS I

EVIDENCE A

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Management of coronary intervention 2014

Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel

CLASS I

EVIDENCE A

EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

Non ST Segment Elevation ACS

ANTITHROMBOTIC THERAPY

Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated

CLASS I

EVIDENCE B

Exclusion Criteria
TRITON TIMI 38 trial

1. Cardiogenic shock at the time of randomization
2. Refractory ventricular arrhythmias
3. New York Heart Association class IV congestive heart failure
4. Fibrin-specific fibrinolytic therapy less than 24 h before randomization
5. Non–fibrin-specific fibrinolytic therapy less than 48 h before randomization
6. Active internal bleeding or history of bleeding diathesis
7. Clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding
8. Any of the following:

   (a) History of hemorrhagic stroke

   (b) Intracranial neoplasm, arteriovenous malformation, or aneurysm

   (c) Ischemic stroke within 3 months prior to screening

Exclusion Criteria
TRITON TIMI 38 trial

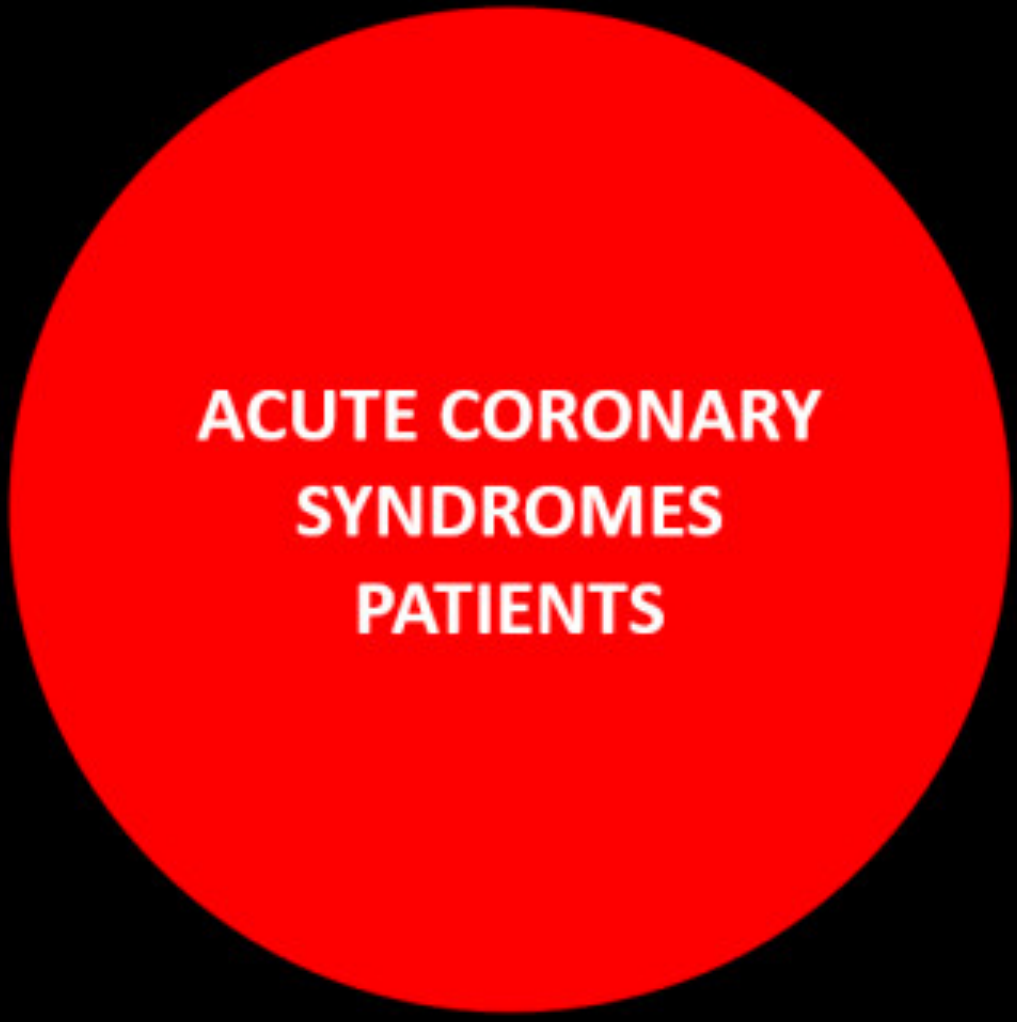
9. International normalized ratio known to be greater than 1.5 at the time of screening
10. Platelet count of less than 100 000/mm^3 at the time of screening
11. Anemia (hemoglobin <10 g/dL) at the time of screening
12. One or more doses of a thienopyridine 5 d or less before PCI
13. Oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
14. Daily treatment with nonsteroidal antiinflammatory drugs or cyclooxygenase-2 inhibitors
15. Investigative site personnel directly affiliated with the study or immediate family
16. Treatment within the last 30 d with an investigational drug or are presently enrolled in another drug or device study

Exclusion Criteria
TRITON TIMI 38 trial

17. Previously completed or withdrawn from this study or any other study investigating prasugrel
18. Women who are known to be pregnant, have given birth within the past 90 d, or are breast-feeding
19. Concomitant medical illness that in the opinion of the investigator is associated with reduced survival over the expected treatment period
20. Known severe hepatic dysfunction
21. Any condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
22. Intolerance of or allergy to aspirin, ticlopidine, or clopidogrel
23. May be unable to cooperate with protocol requirements and follow-up procedures

Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world



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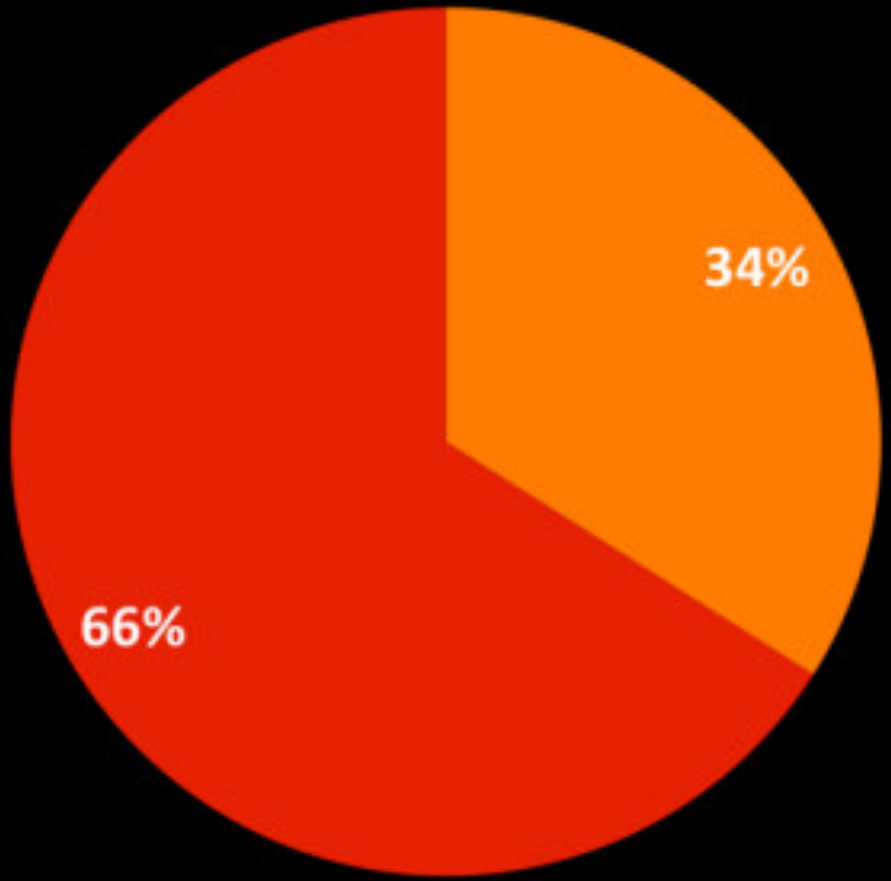
Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world



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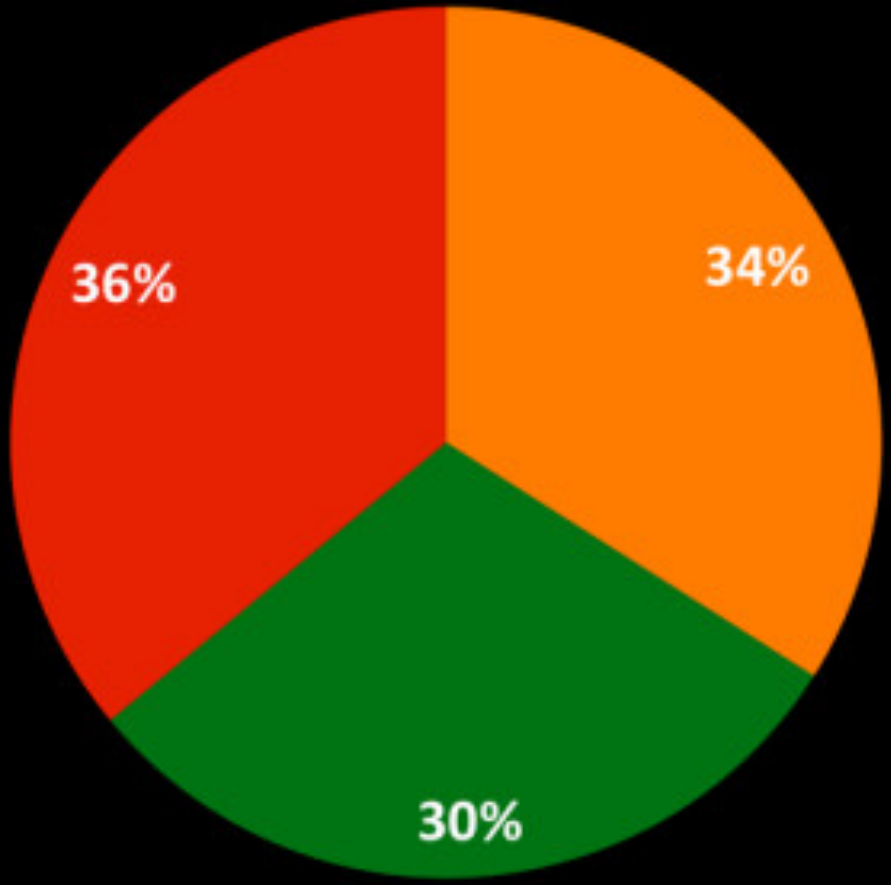
Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world

Age > 75 years



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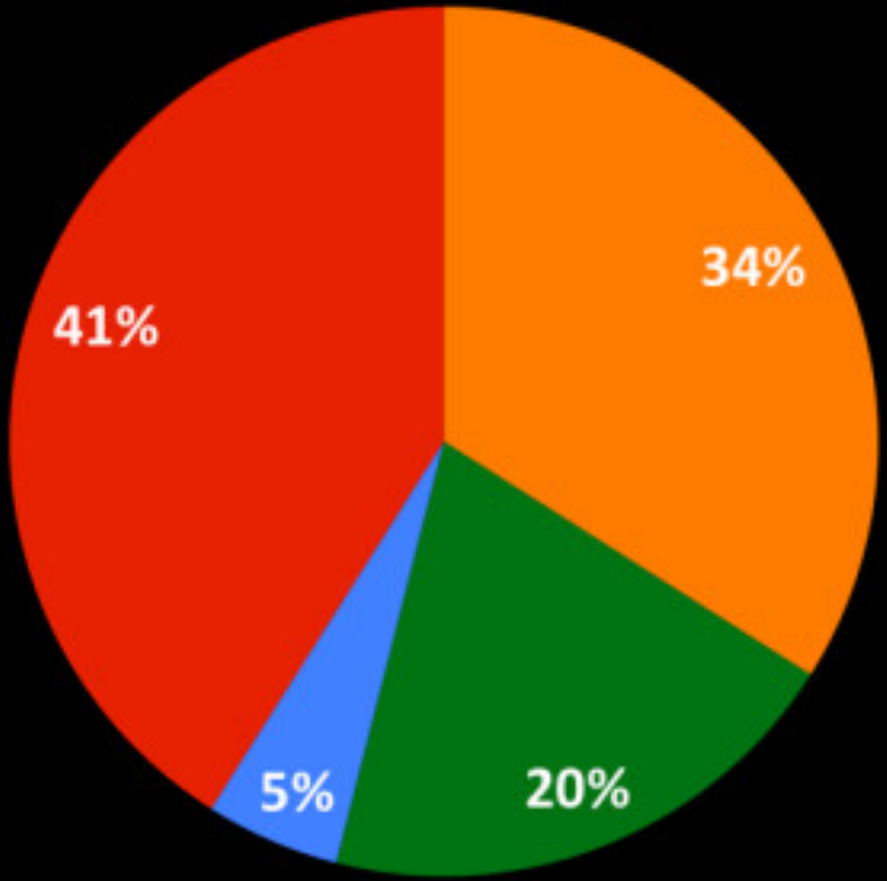
Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world

Body weight less than 60 kg



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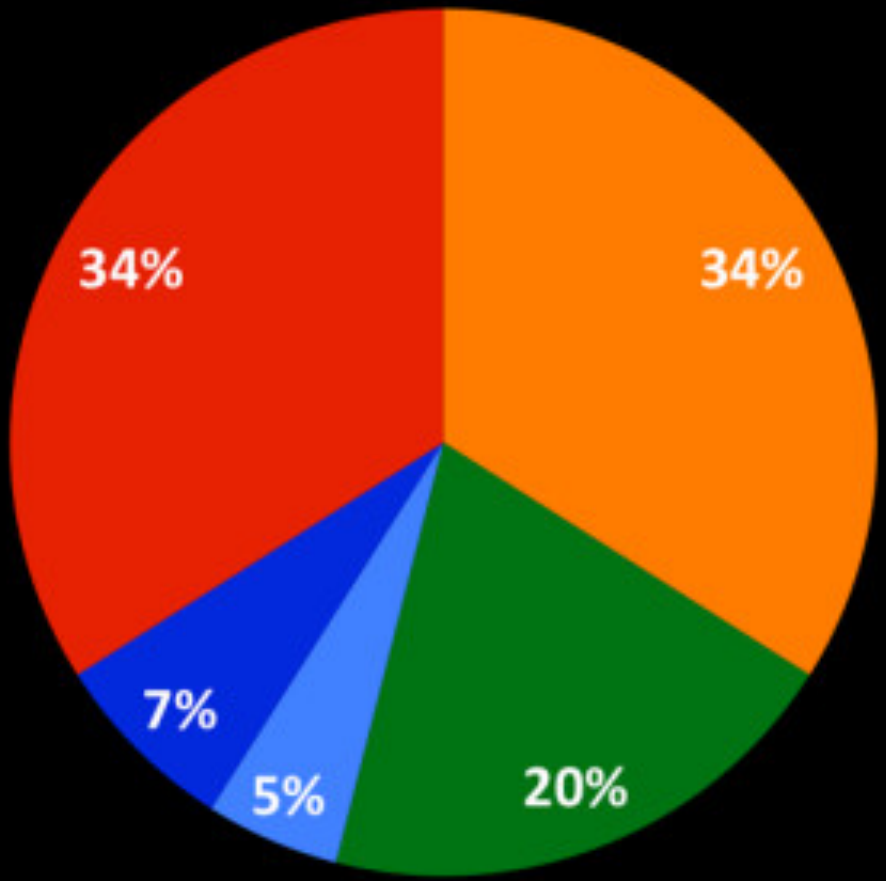
Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world

History of stroke or transient ischemic attack



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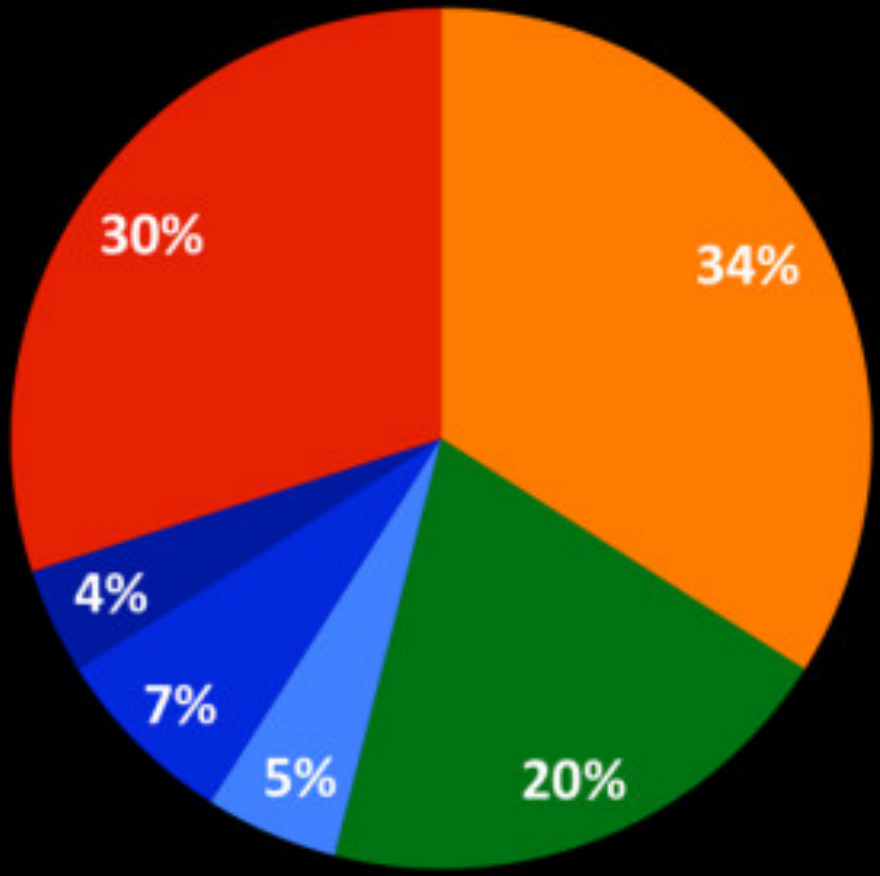
Prasugrel eligible patients in clinical practice

From TRITON TIMI-38 to the real world

Other TIMI 38 exclusion criteria



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Exclusion Criteria
PLATO trial

1. Contraindication or other reason that clopidogrel or AZD6140 should not be administered (eg, hypersensitivity, active bleeding, moderate or severe liver disease, history of previous intracranial bleed, GI bleed within the past 6 months, major surgery within 30 days)
2. Index event is an acute complication of PCI
3. Patient has undergone PCI after the index event and before the first dose of study treatment
4. Oral anticoagulation therapy that cannot be stopped (ie, patient requires chronic therapy)
5. Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation (eg, for STEMI or PE)

Exclusion Criteria
PLATO trial

12. Concomitant oral or intravenous therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers which cannot be stopped for the course of the study

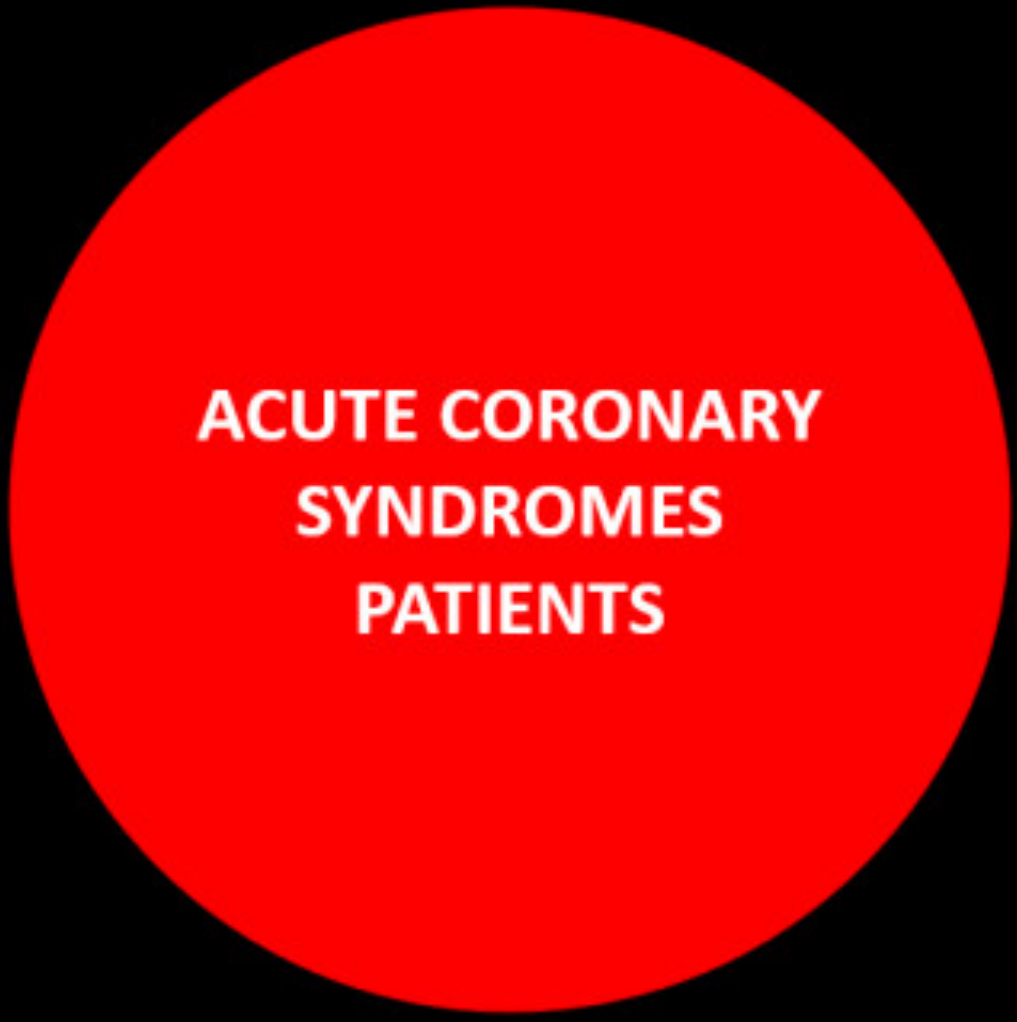
13. Any other condition which in the opinion of the investigator, may either put the patient at risk or influence the result of the study (eg, cardiogenic shock or severe haemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

14. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

15. Previous enrolment or randomisation of treatment in the present study

Ticagrelor eligible patients in clinical practice

From PLATO to the real world



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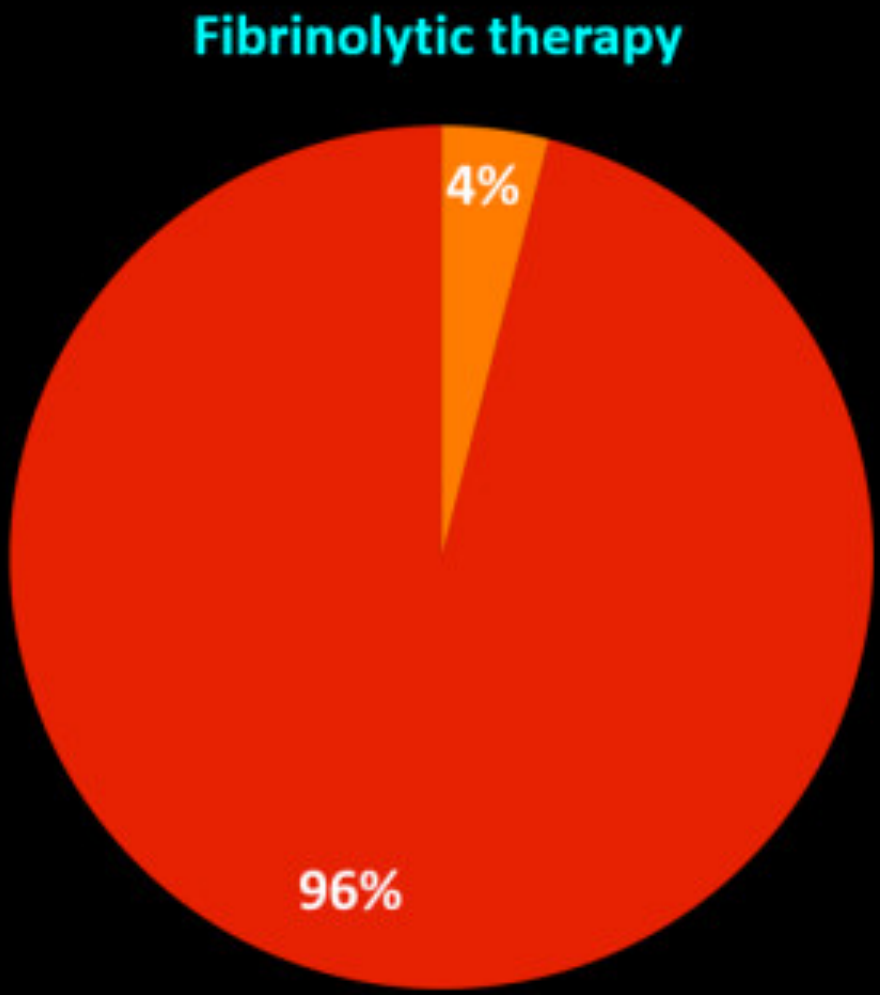
Ticagrelor eligible patients in clinical practice

From PLATO to the real world



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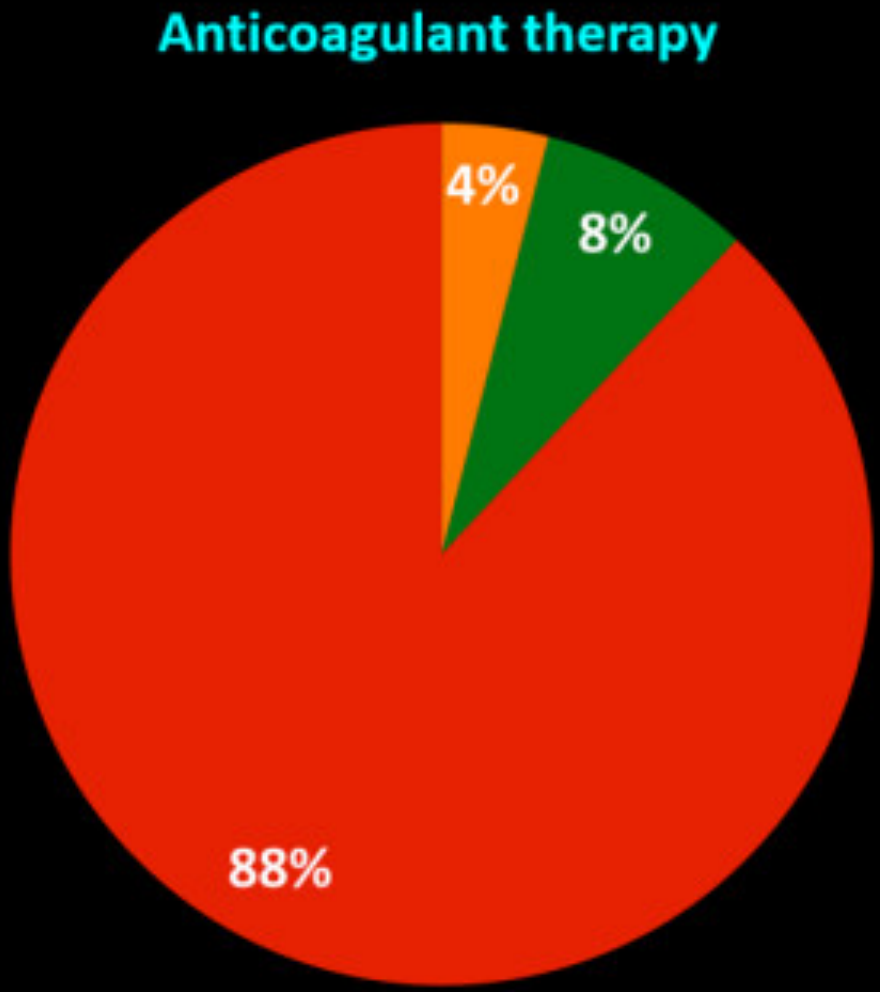
Ticagrelor eligible patients in clinical practice

From PLATO to the real world



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Ticagrelor eligible patients in clinical practice

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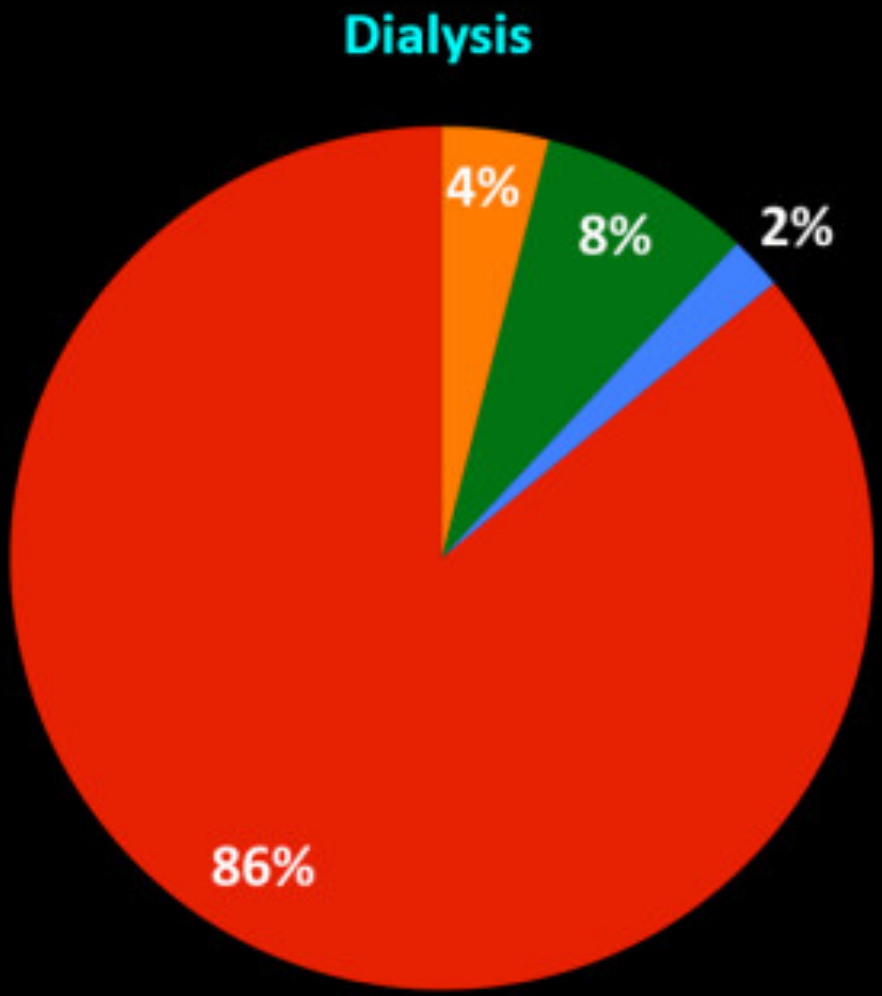

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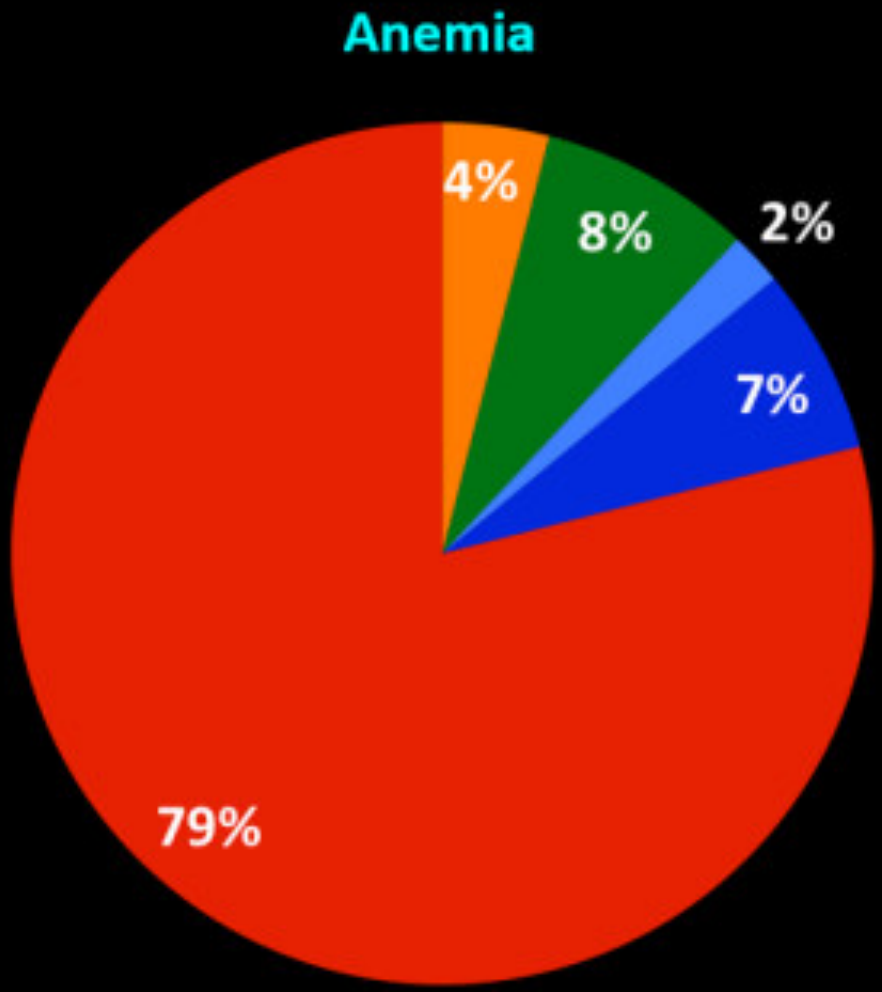
Ticagrelor eligible patients in clinical practice

From PLATO to the real world



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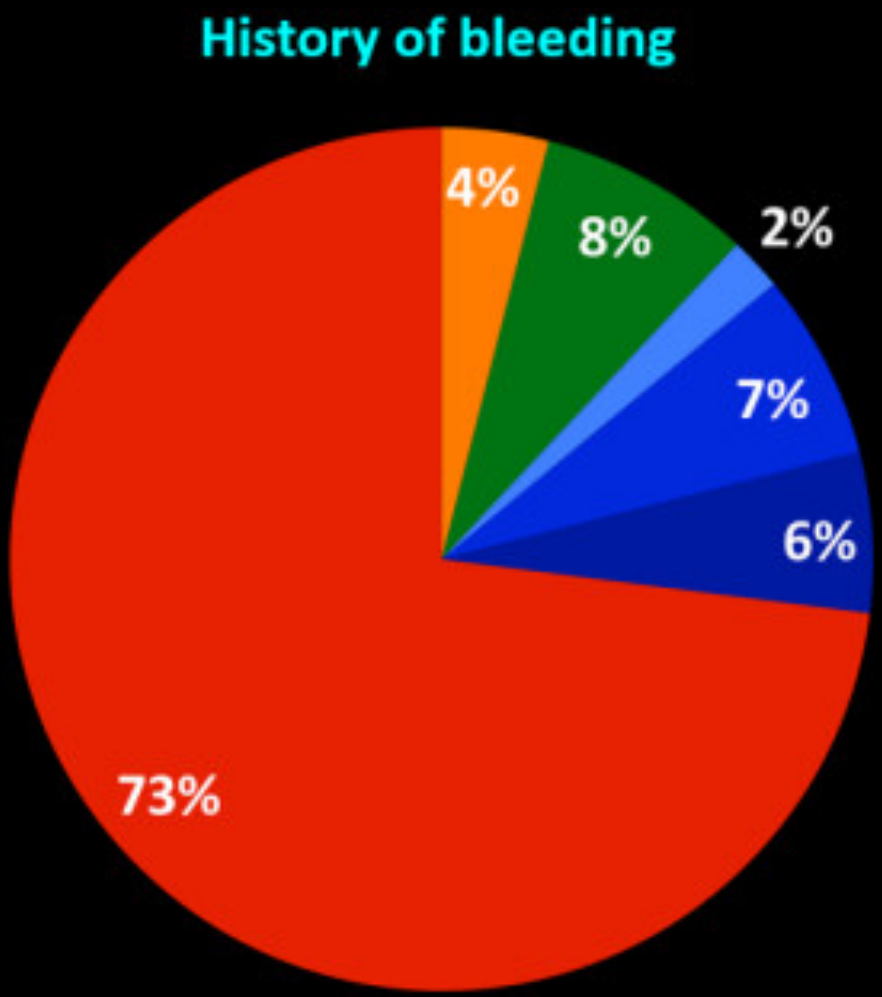
Ticagrelor eligible patients in clinical practice

From PLATO to the real world



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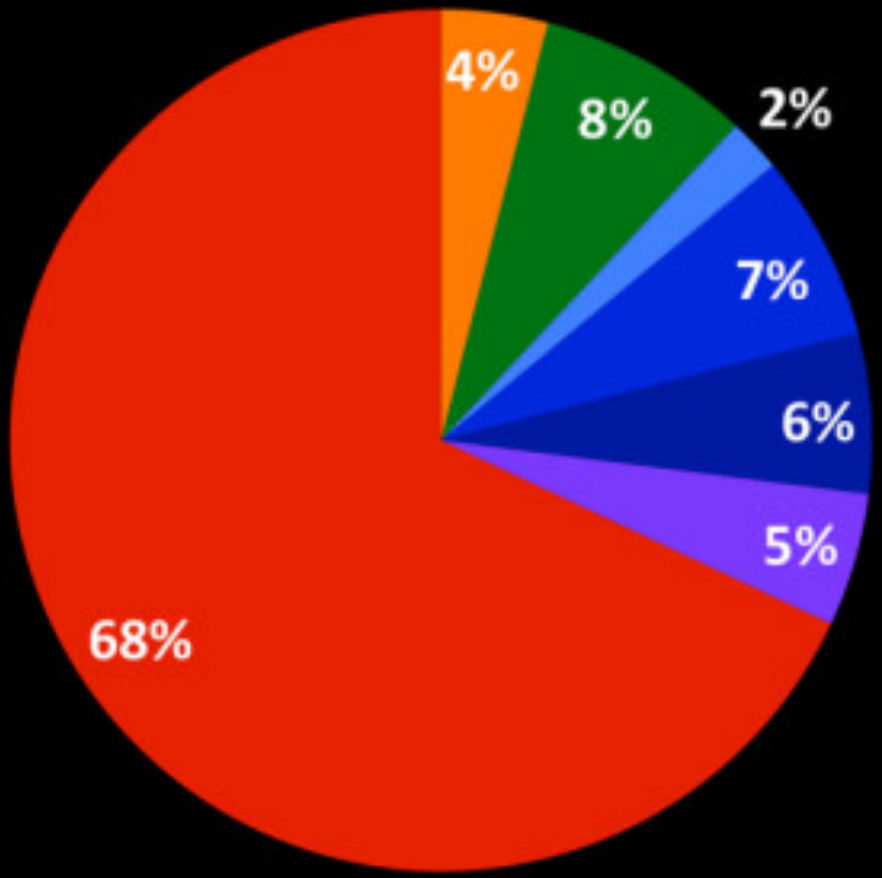
Ticagrelor eligible patients in clinical practice

From PLATO to the real world

Increased risk of bradycardic events



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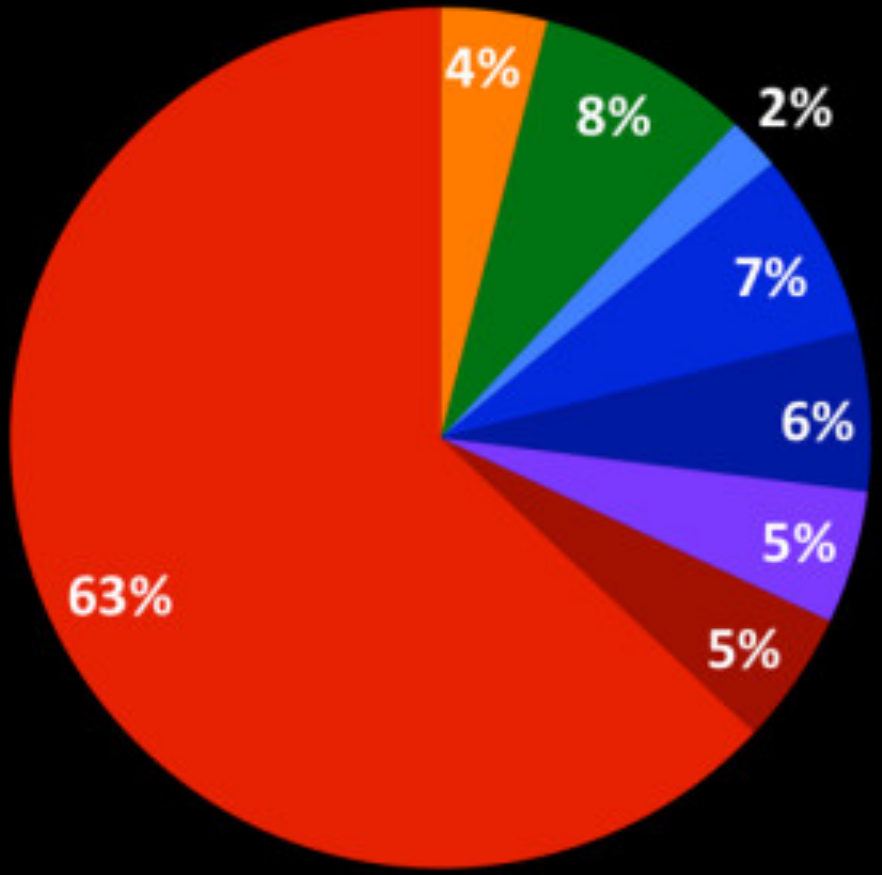
Ticagrelor eligible patients in clinical practice

From PLATO to the real world

Other PLATO exclusion criteria



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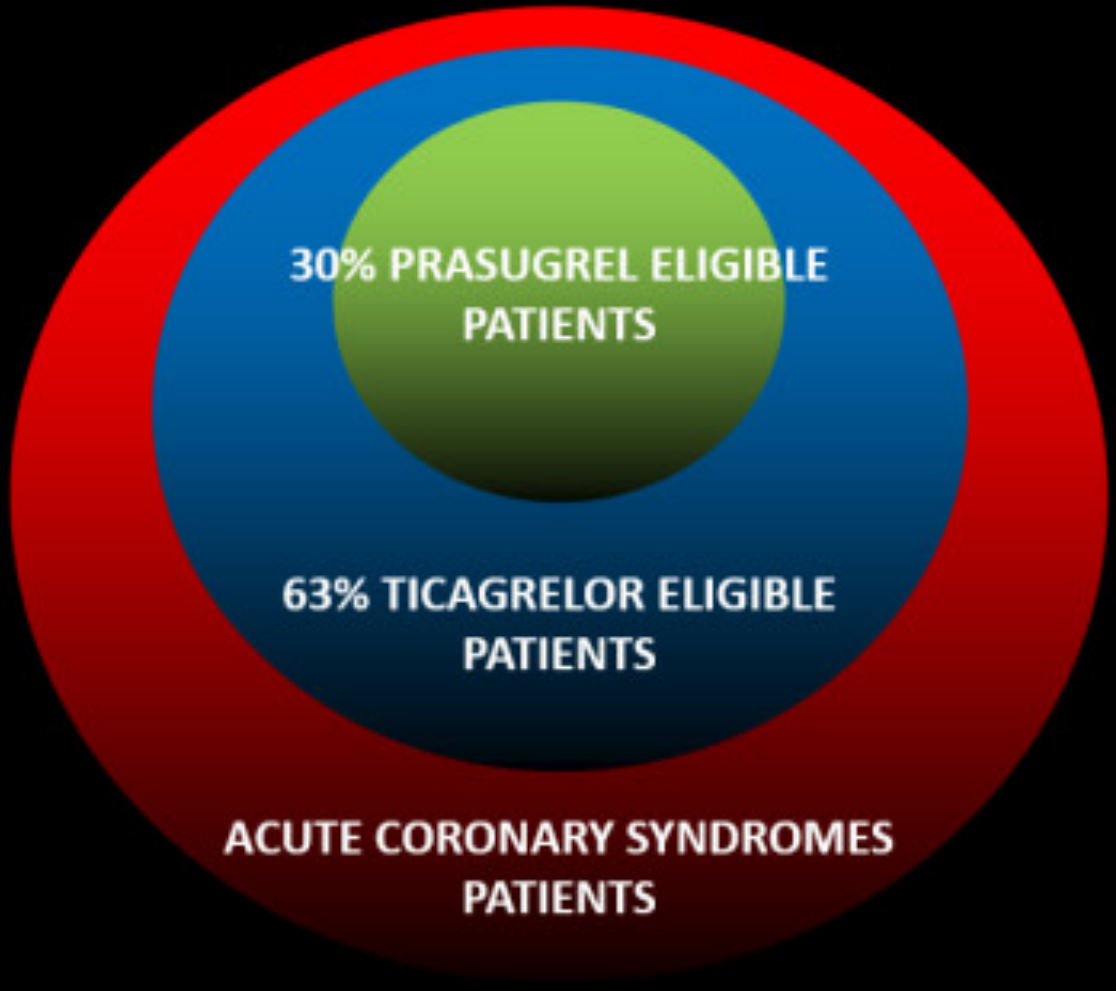
New P2Y12 ADP receptor antagonists in clinical practice



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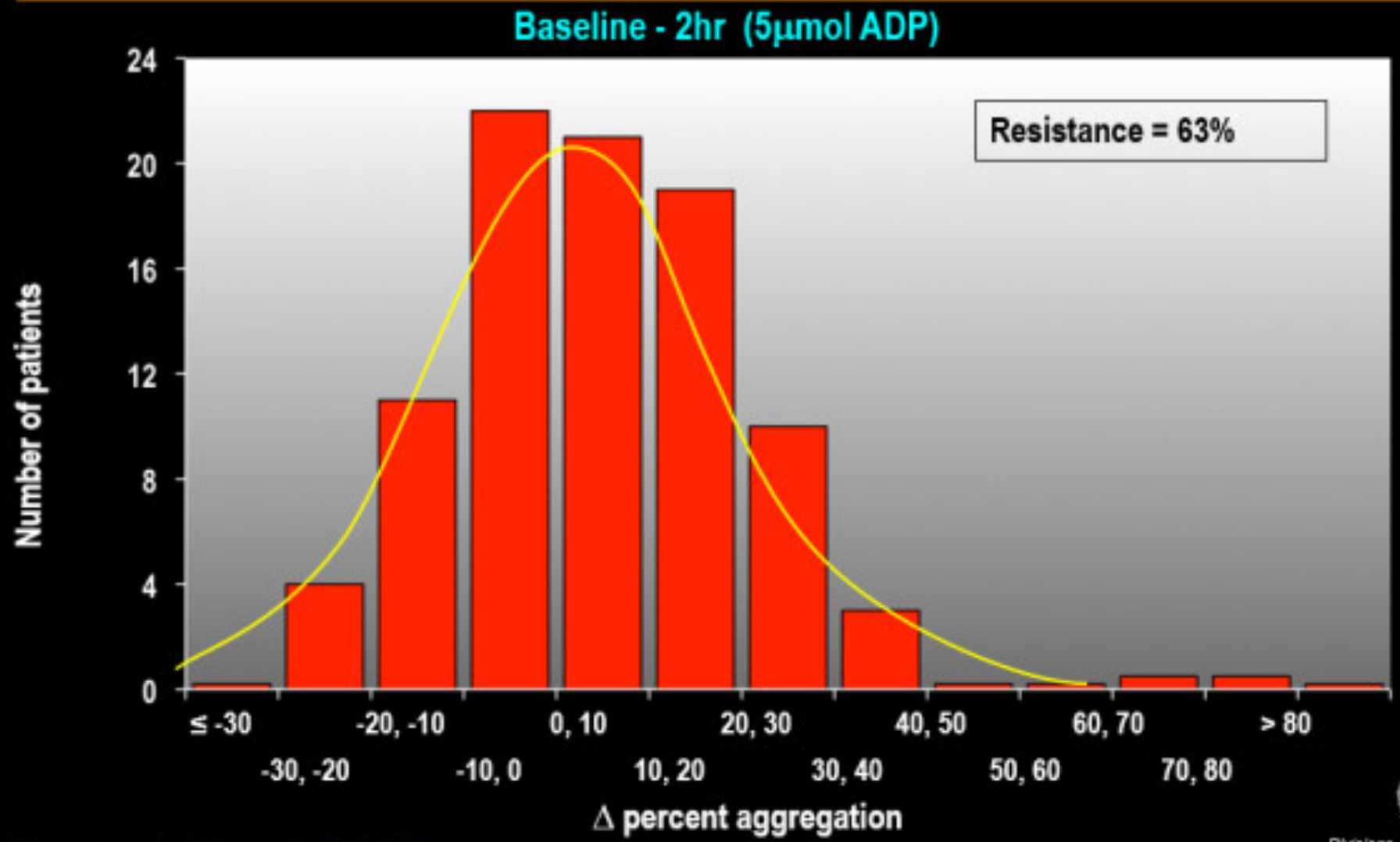
Clopidogrel Response Variability



Gurbel PA et al. Circulation 2003; 107:2908

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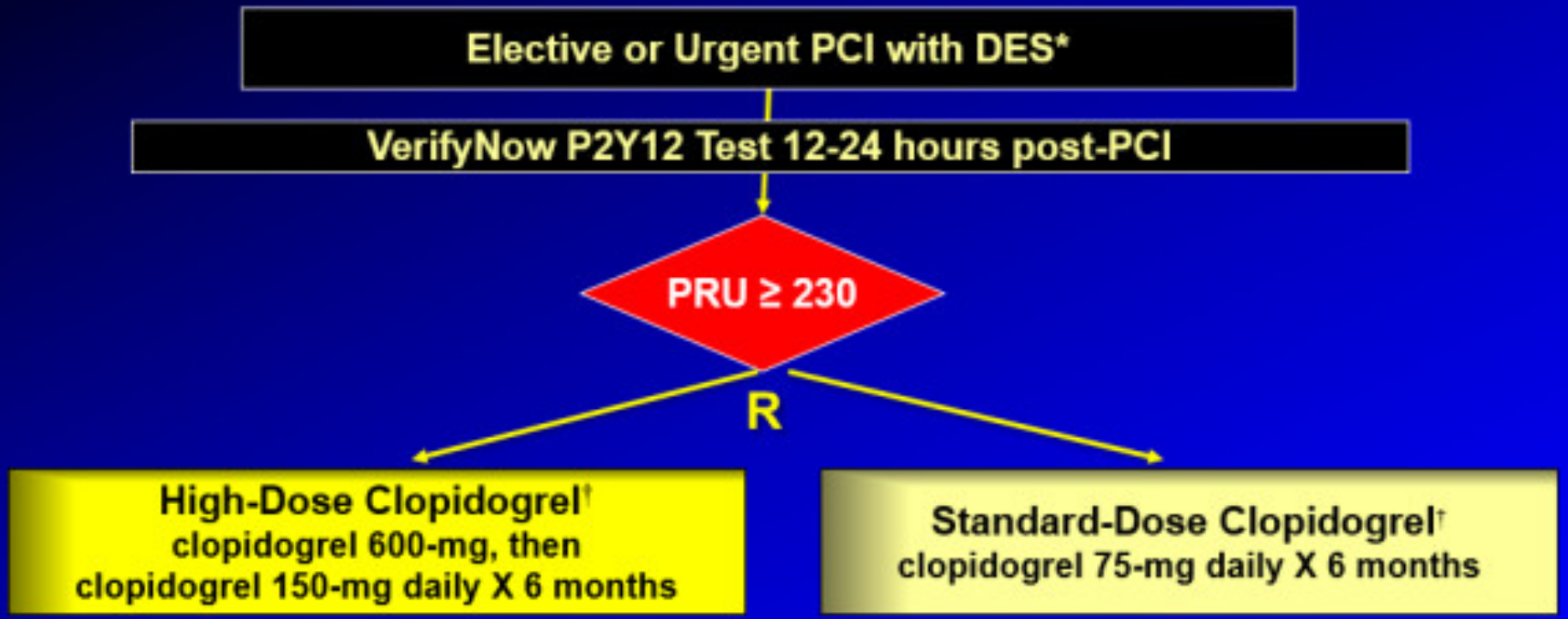
GRAVITAS Study Design



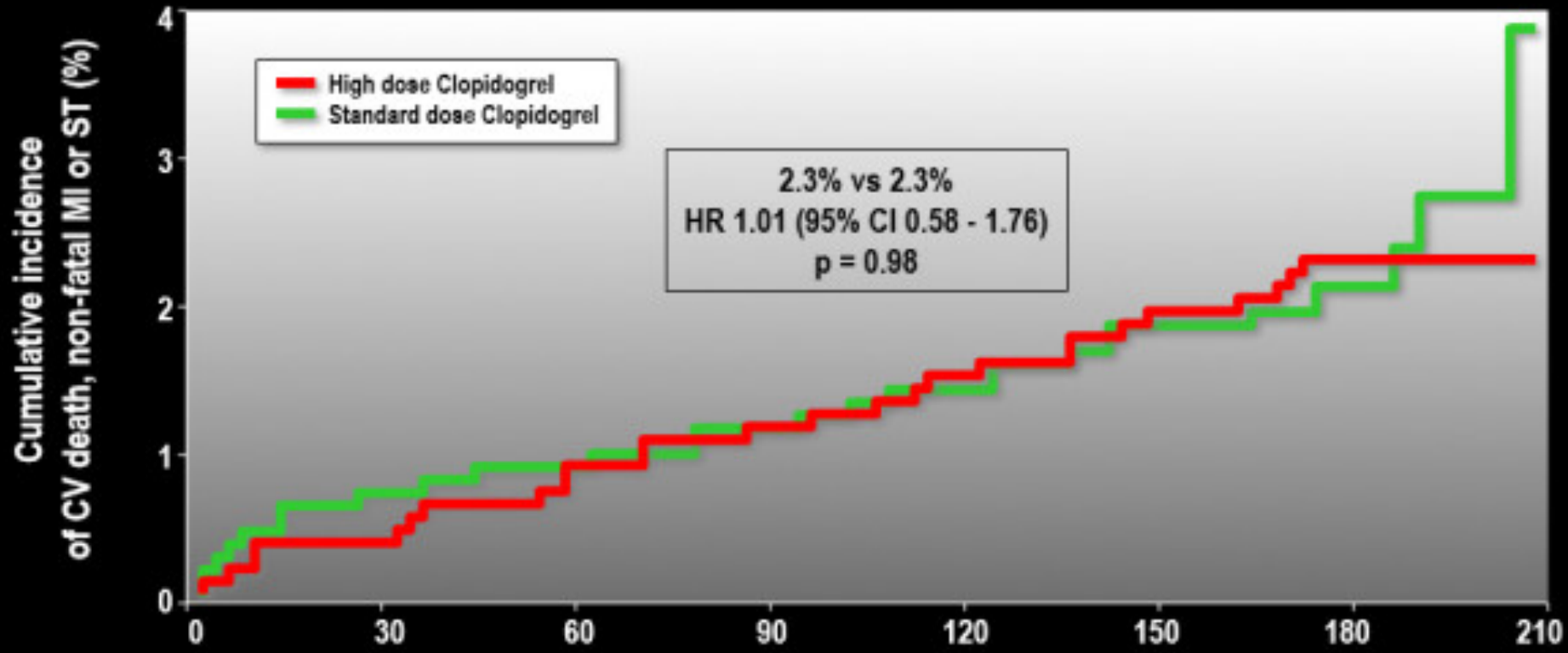
Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo
Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs

†placebo-controlled All patients received aspirin (81-162mg daily)

The GRAVITAS Trial

Primary Endpoint: CV Death, MI, Stent Thrombosis



Number at risk								
High dose	1109	1056	1029	1017	1007	998	747	54
Standard dose	1105	1057	1028	1020	1015	1005	773	53

Prince MJ et al, JAMA 2011; 305: 1097-1105

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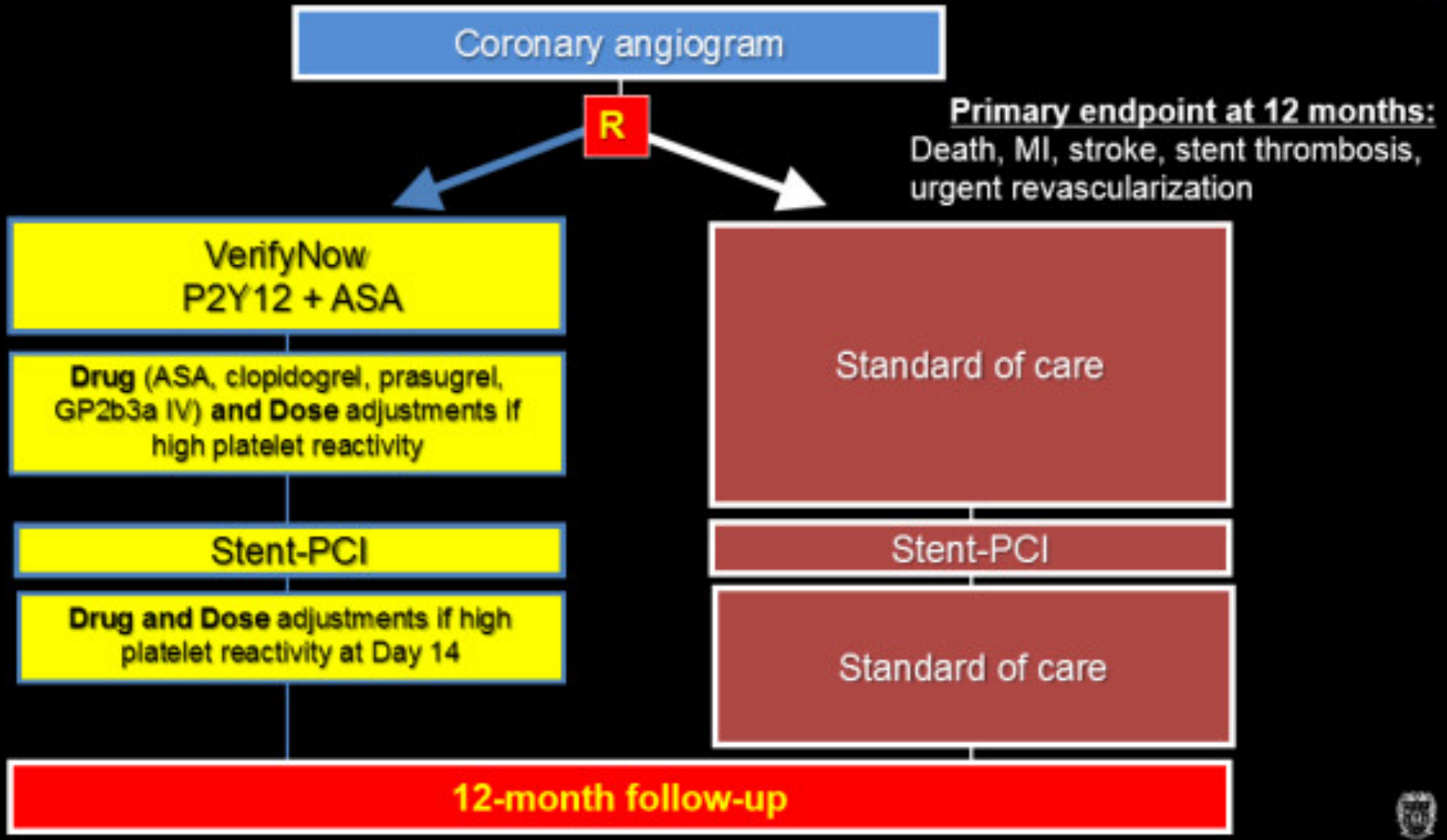
ARCTIC trial
Study design



ARCTIC study protocol - Collet JP, et al. Am Heart J 2011;161:5-12

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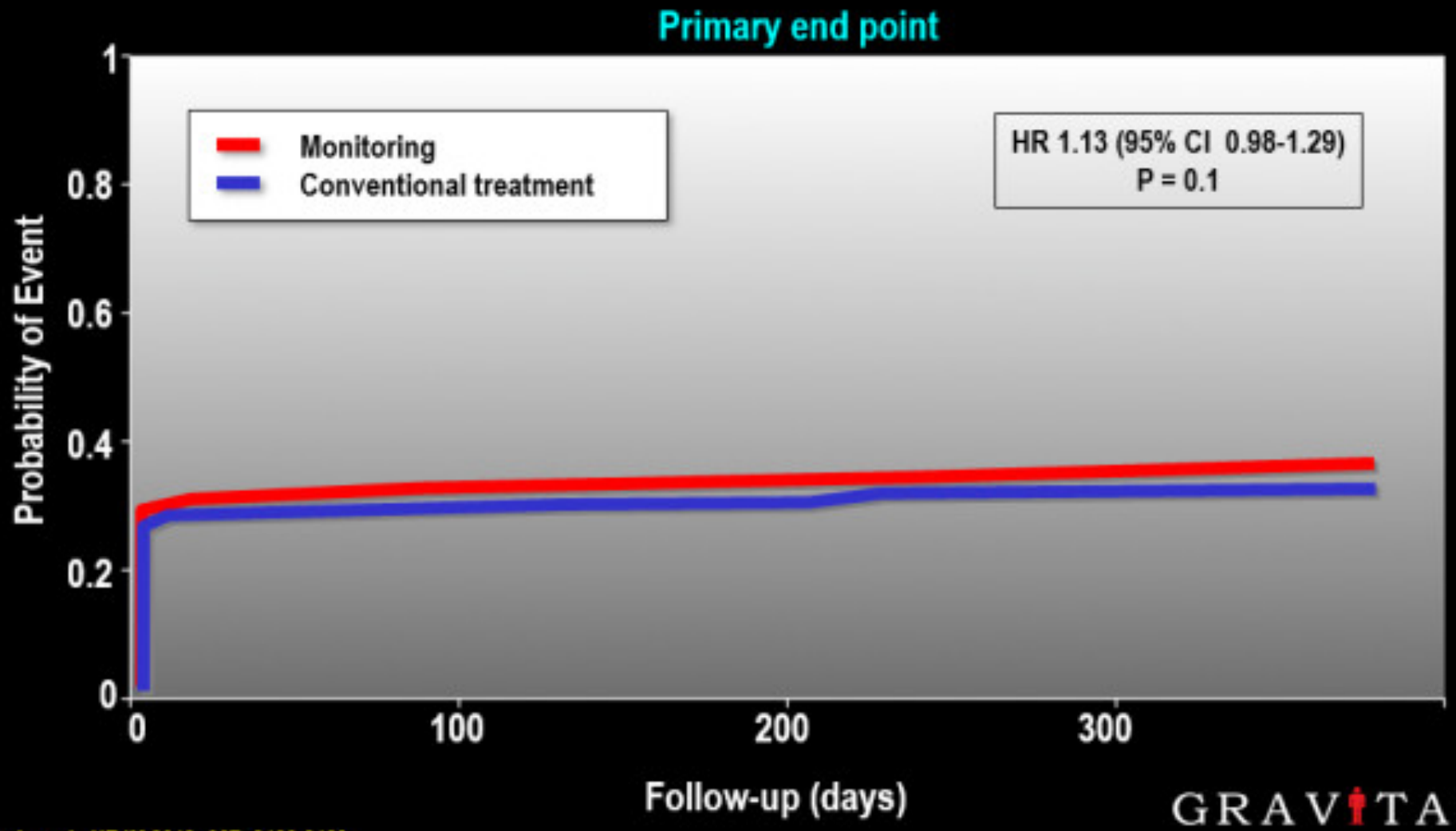
ARCTIC trial

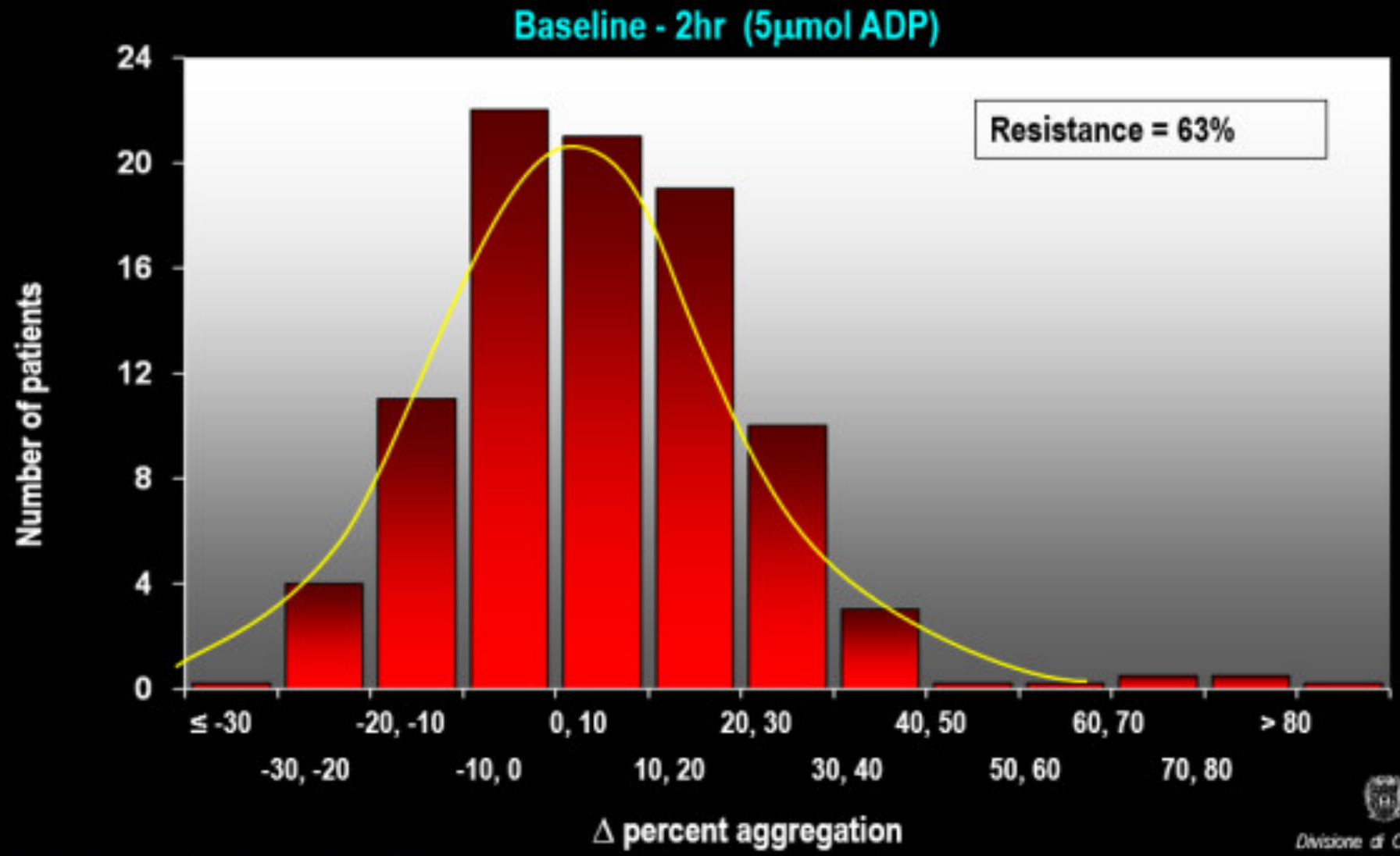
Bedside monitoring to adjust antiplatelet therapy for coronary stenting



GRAVITAS

Collet J. et al, NEJM 2012; 367: 2100-2109

Clopidogrel Response Variability



Gurbel PA et al. Circulation 2003; 107:2908

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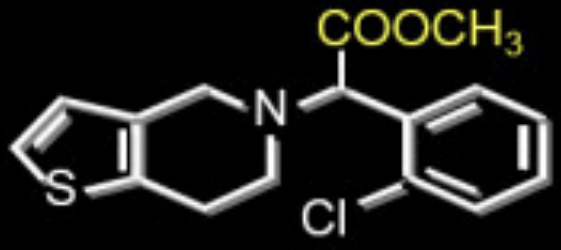
Genetic targets potentially modulating Clopidogrel induced antiplatelet effects

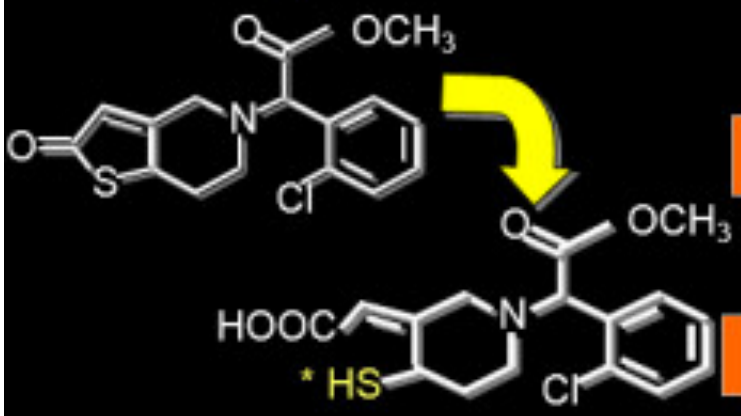


Clopidogrel

Pro-drug

Pre-hepatic metabolism
Esterases in blood (Small Intestine)

ABCB1



PON 1

1 step:
CYP1A2
CYP2C19
CYP2B6

2 step:
CYP3A
CYP2C9
CYP2C19
CYP2B6

Hepatic Metabolism

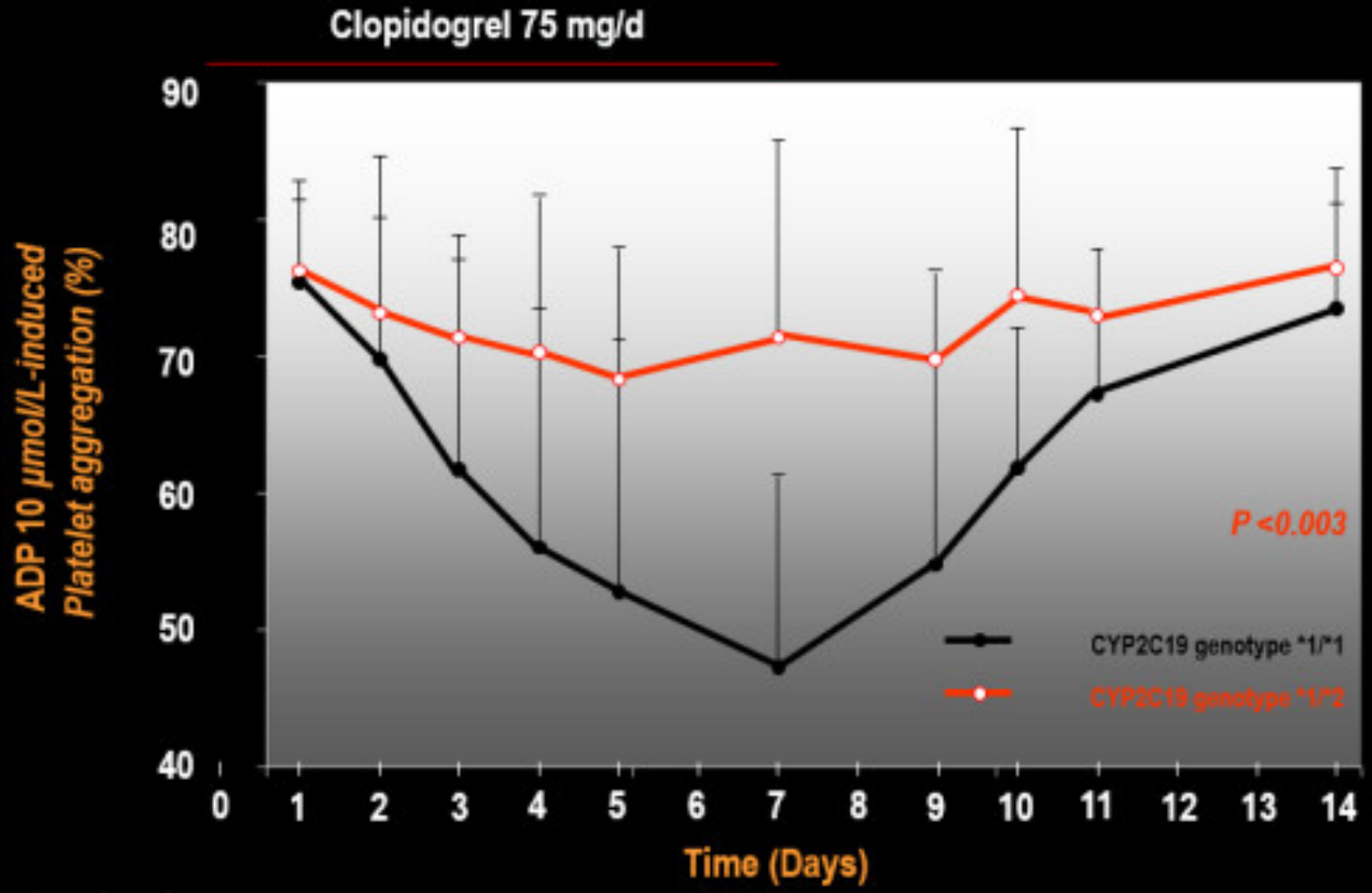
Platelet inhibitions

Platelet membrane receptors
P2Y12, GP IIb/IIIa, GPIa

Marin et al, JACC 2009, 54: 1041-1057

Cytochrome P450 2C19 polymorphism

Time course of ex-vivo platelet aggregation in response to 10 µM ADP



Hulot et al. Blood 2006; 106:2244-47

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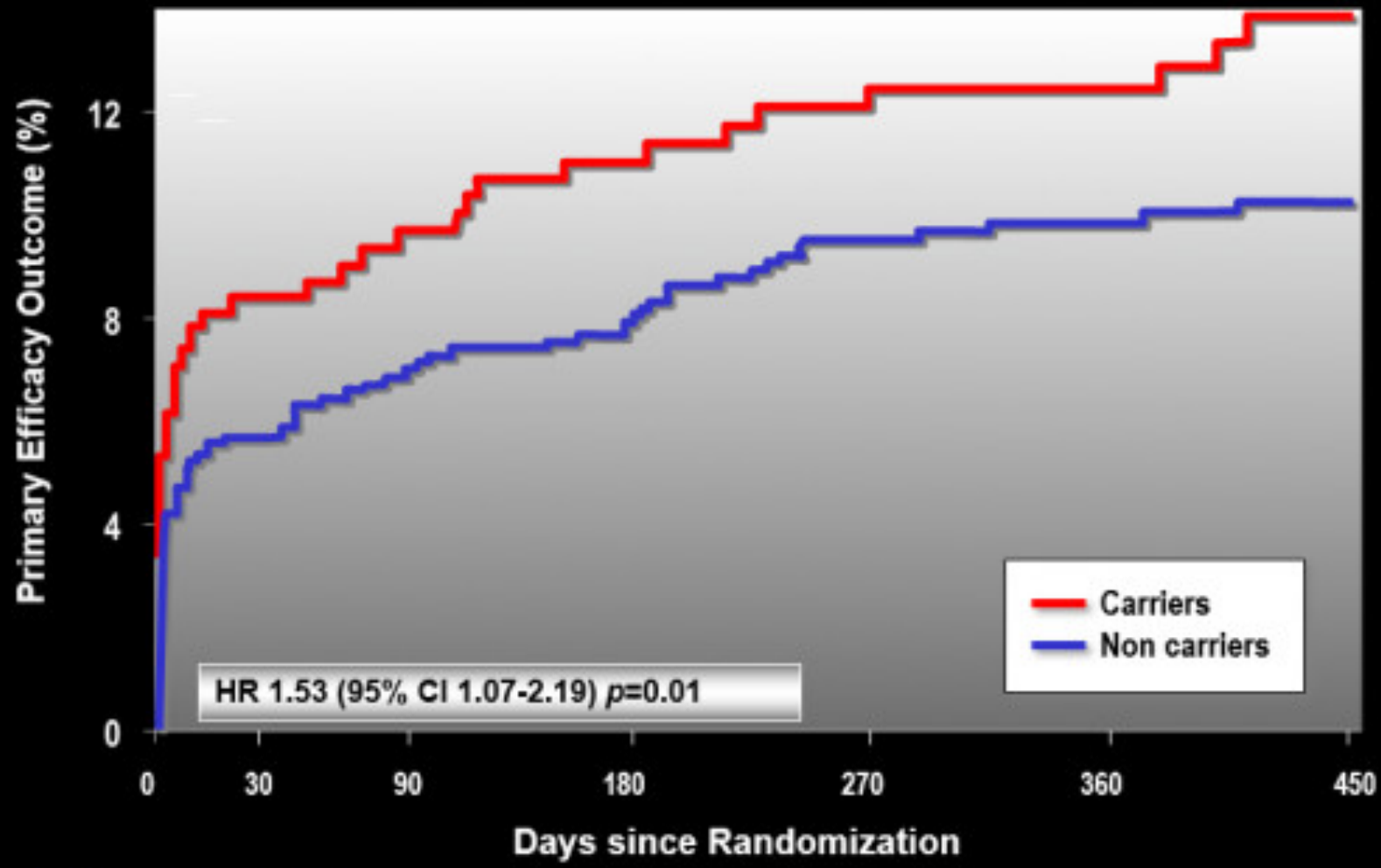
Outcome after MI according to CYP2C19 genotype

TRITON TIMI-38 clopidogrel arm (n=1477)



Mega J L et al, N Engl J Med 2009; 360: 354-62

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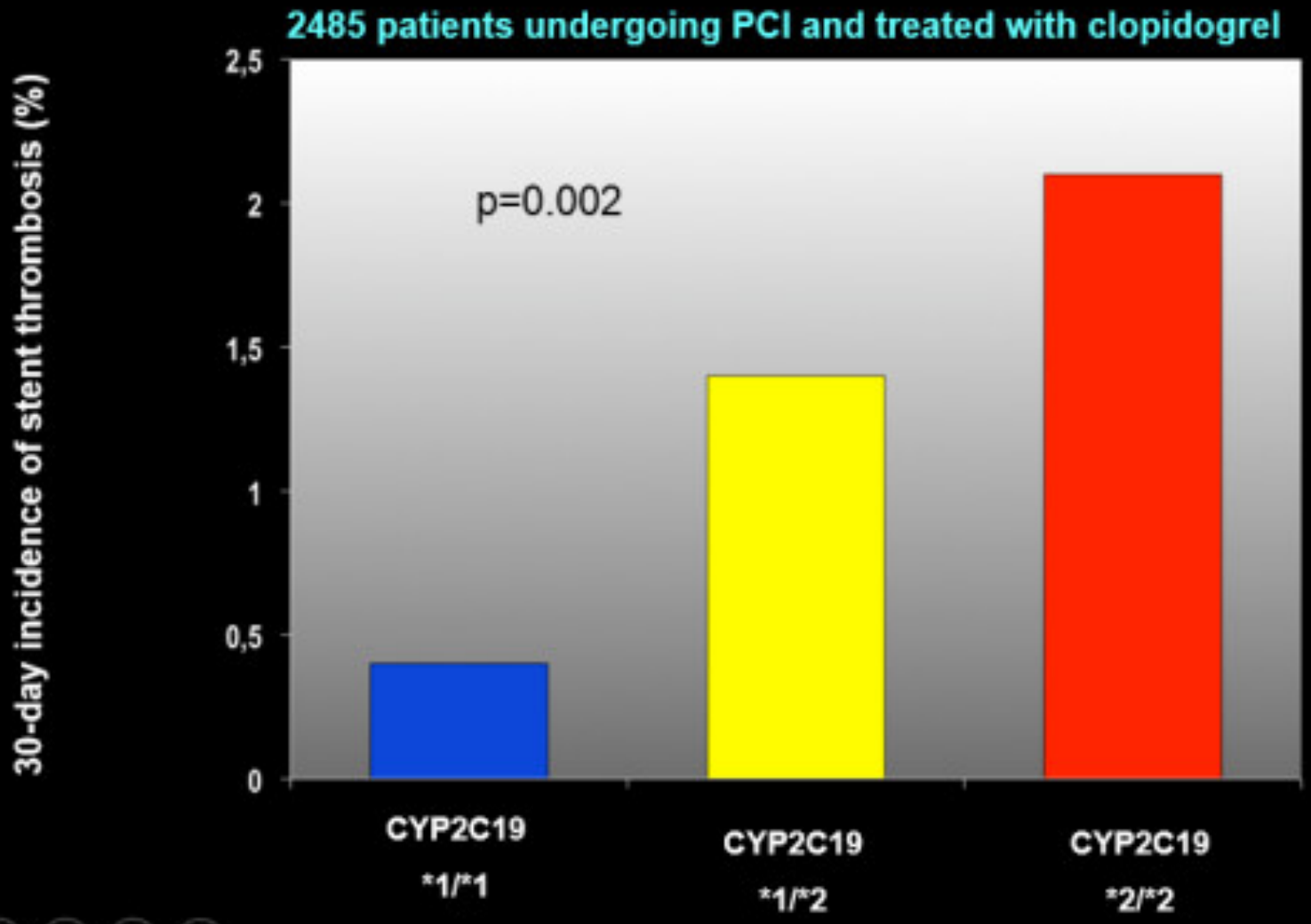
Cytochrome P450 2C19 polymorphism and stent thrombosis



Sibbing et al. Eur Heart Journal 2009; 30: 916-922

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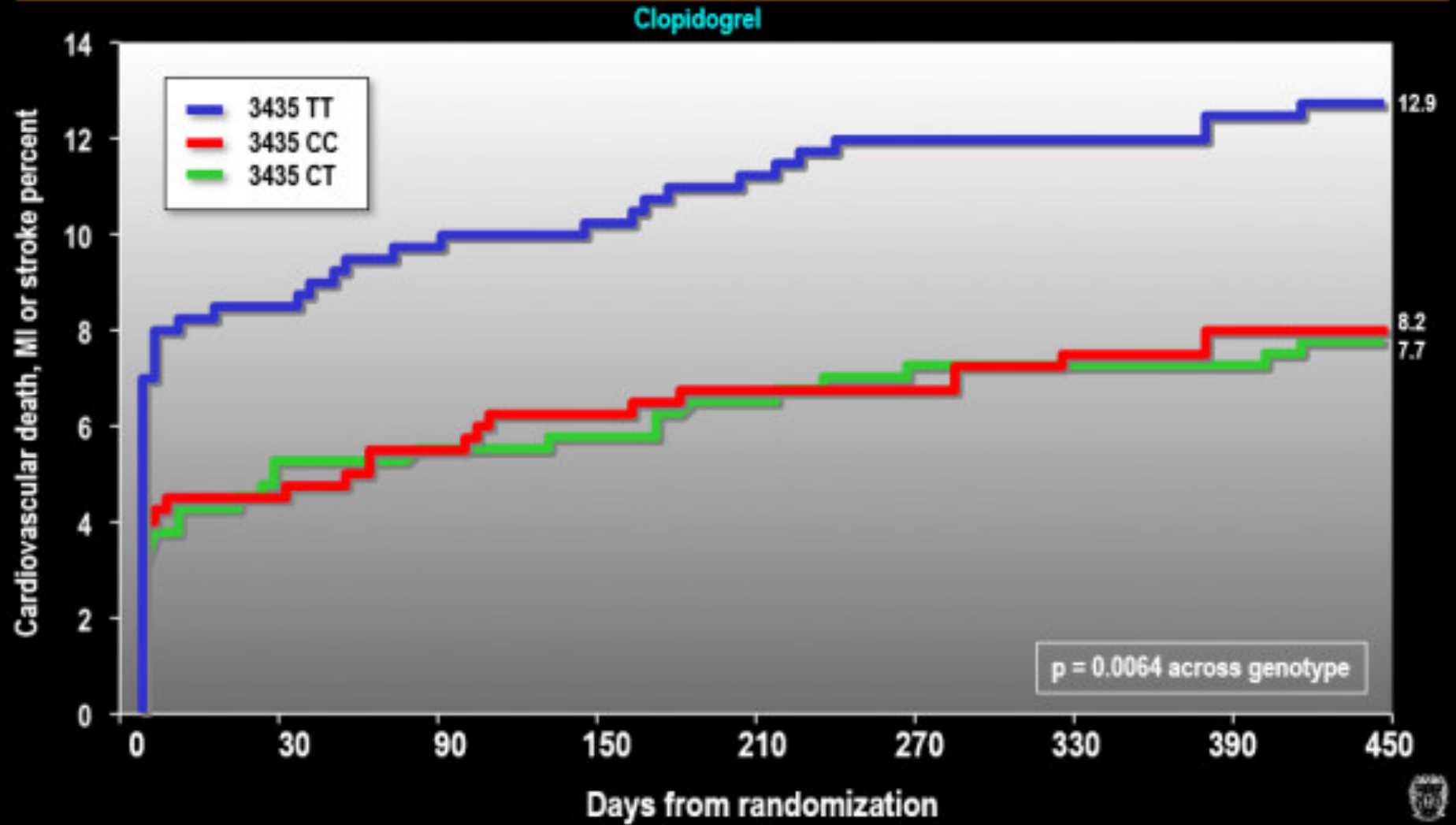
Cardiovascular outcomes by ABCB1 genotype

TRITON-TIMI 38 pharmacogenetic analysis



Mega J et al. Lancet 2010; published on line 29 August

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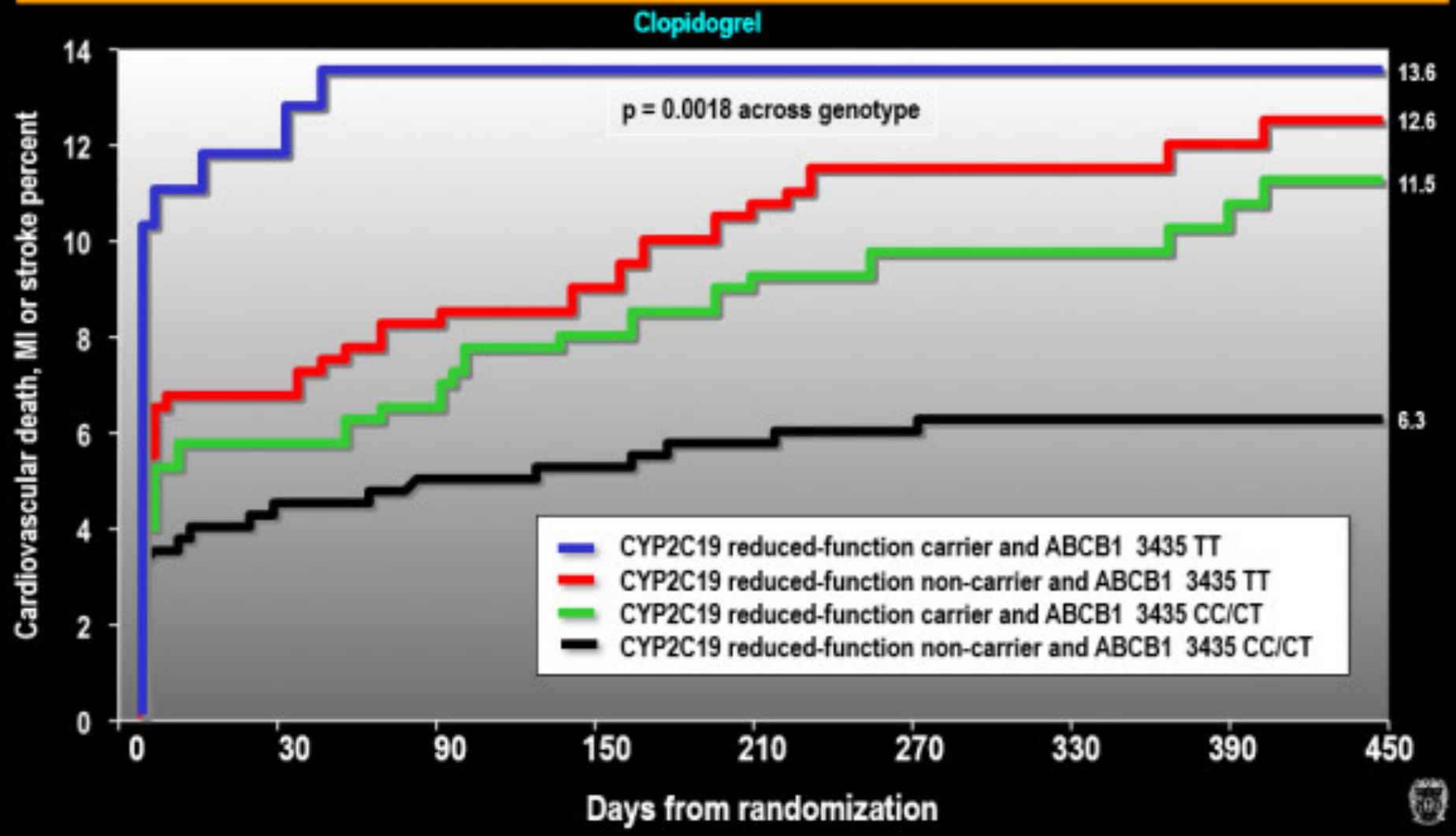
Cardiovascular outcomes by ABCB1 and CYP2C19 genotype
TRITON-TIMI 38 pharmacogenetic analysis



Mega J et al. Lancet 2010; published on line 29 August

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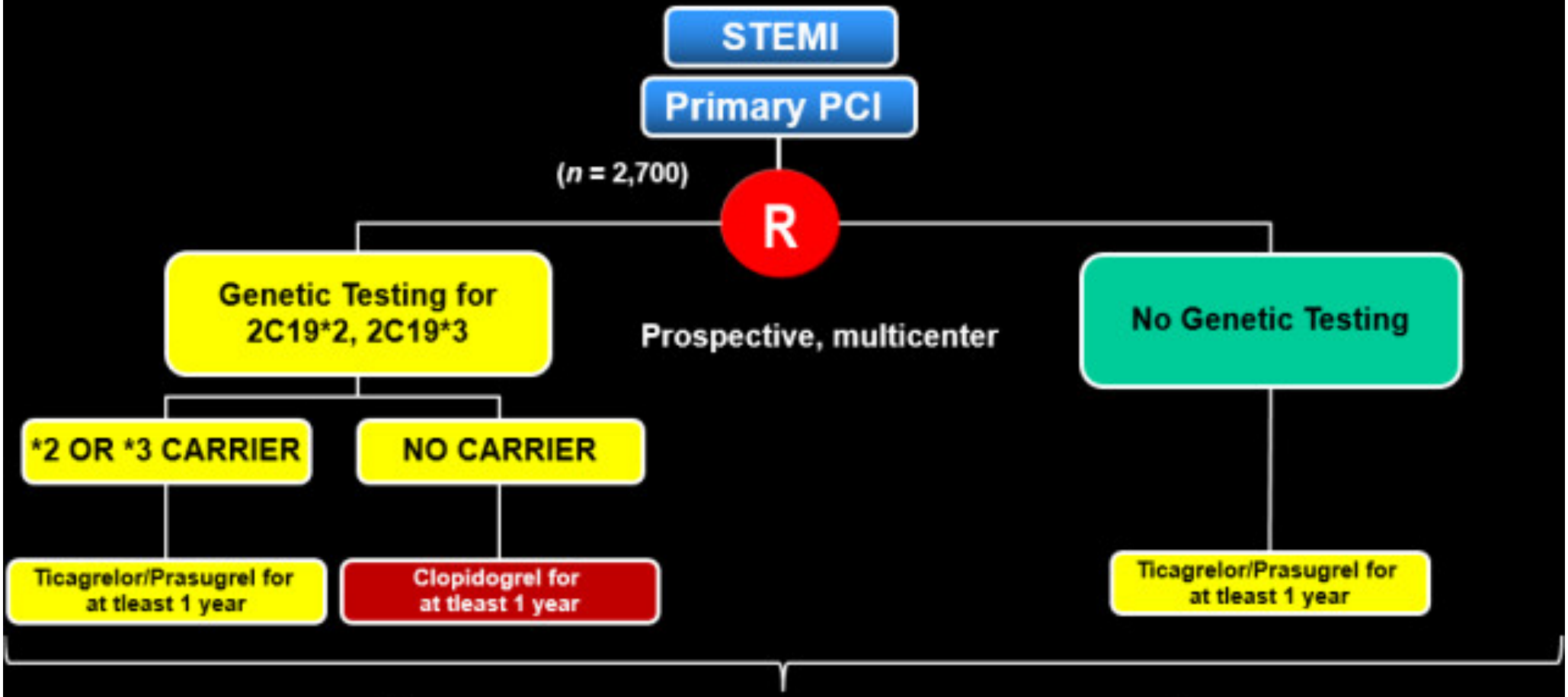
POPular Genetics

Patient Outcome after primary PCI Genetics study



Combines endpoint of death, MI, stent thrombosis, stroke and PLATO major bleeding at 1 year

Berrmeijer et al. 2014 Am Heart J

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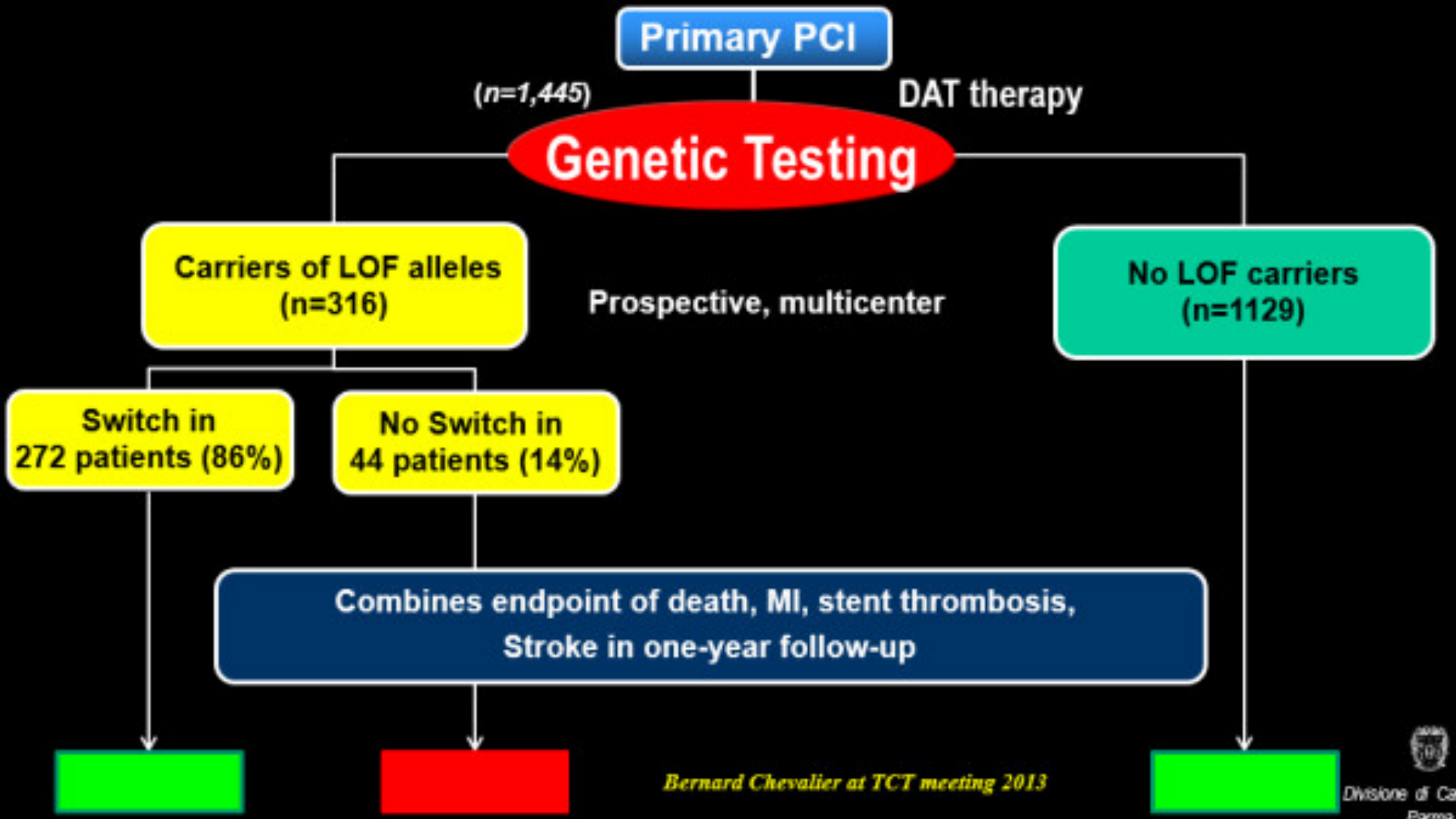
The GIANT trial

Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment



Bernard Chevalier at TCT meeting 2013

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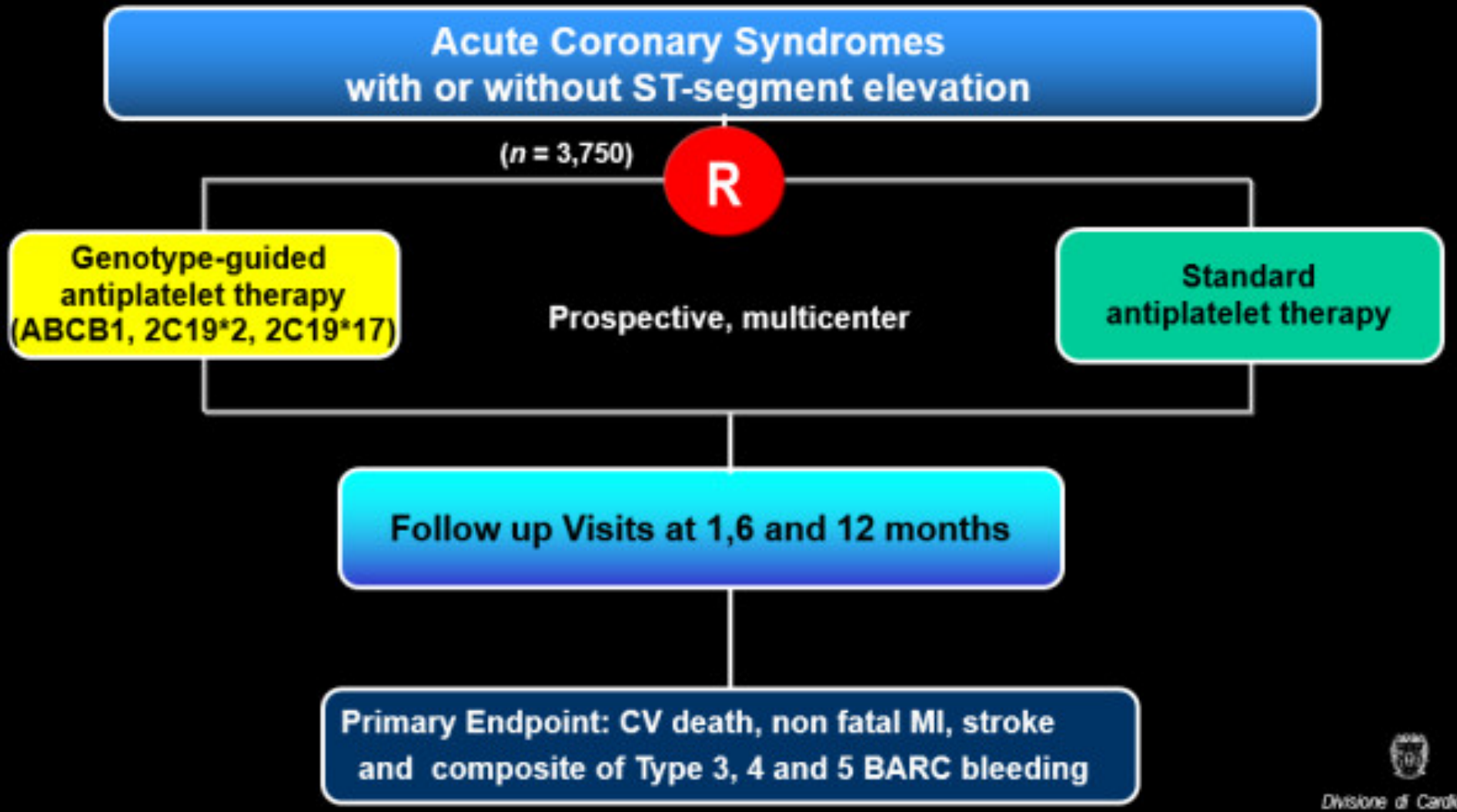
Genotyping into clinical practice

Impact of clopidogrel pharmacogenetics on outcomes in ACS



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TAKE HOME MESSAGES

- La scelta della DAPT è un problema clinico rilevante. Prasugrel e ticangrelor aiutano molto ma non sono la soluzione per tutti i pazienti. Clopidogrel resta un farmaco indispensabile per una larga proporzione di pazienti con ACS.
- Il monitoraggio piastrinico allo stato attuale delle conoscenze non è utile nello scegliere la DAPT
- La genomica del clopidogrel, se confermata da più studi prospettici, potrebbe aiutare a scegliere la DAPT più appropriata su base individuale
- Questo utilizzo sarebbe il primo timido tentativo di portare la farmacogenomica nell'arena clinica della Cardiologia

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