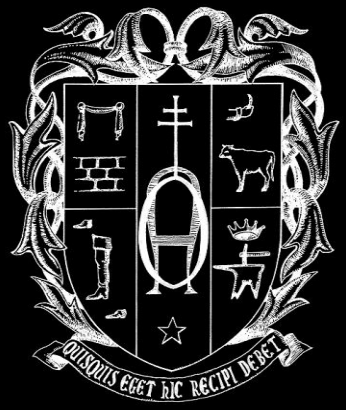
Orlando, March 10-12 2018,
American College of Cardiology
67° Annual Scientific Session & Expo

The PHARMCLO study

A prospective, randomised, multicentre study of a pharmacogenomic approach to the selection of antiplatelet therapy in acute coronary syndromes



Diego Ardissino, MD

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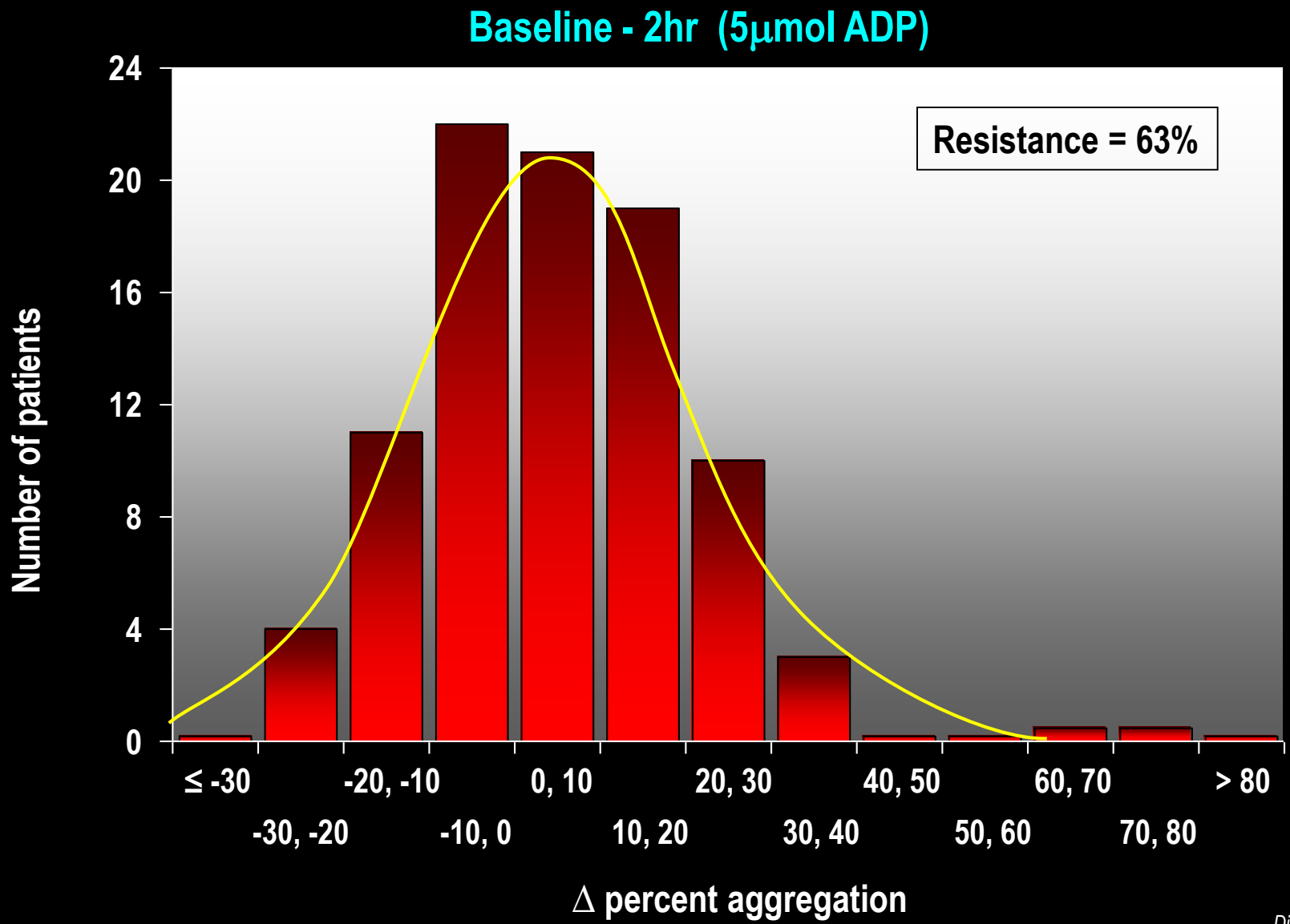
Disclosures

All authors have no relationships relevant to this presentation to disclose.

The PHARMCLO study - Background

Clopidogrel Response Variability



Gurbel PA et al. Circulation 2003; 107:2908-13

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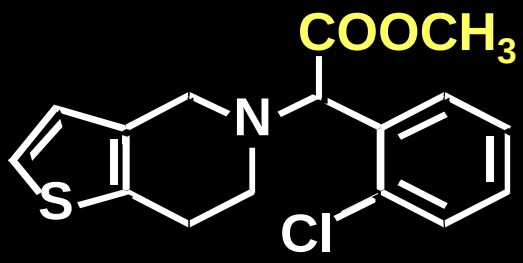
Genetic targets modulating Clopidogrel antiplatelet effects

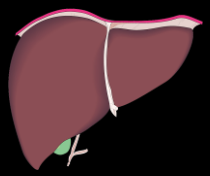


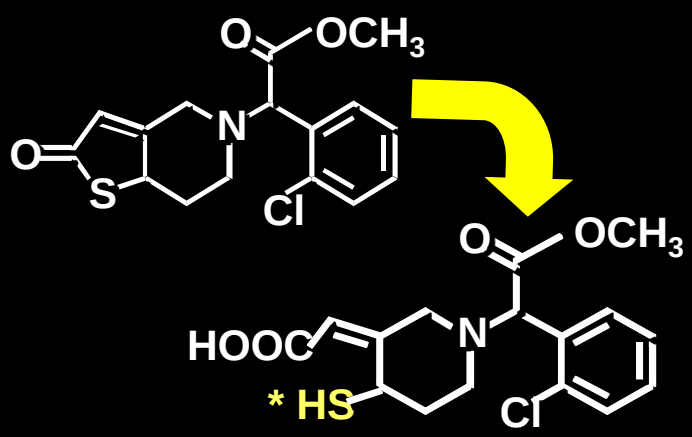
Clopidogrel

Pro-drug

Pre-hepatic metabolism
Esterases in blood (Small Intestine)

ABCB1





Hepatic Metabolism

1 step:
CYP1A2
CYP2C19
CYP2B6

2 step:
CYP3A
CYP2C9
CYP2C19
CYP2B6

Platelet inhibition

Platelet membrane receptors
P2Y12, GP IIb/IIIa, GPIa

Marín F et al. J Am Coll Cardiol. 2009;54:1041-57

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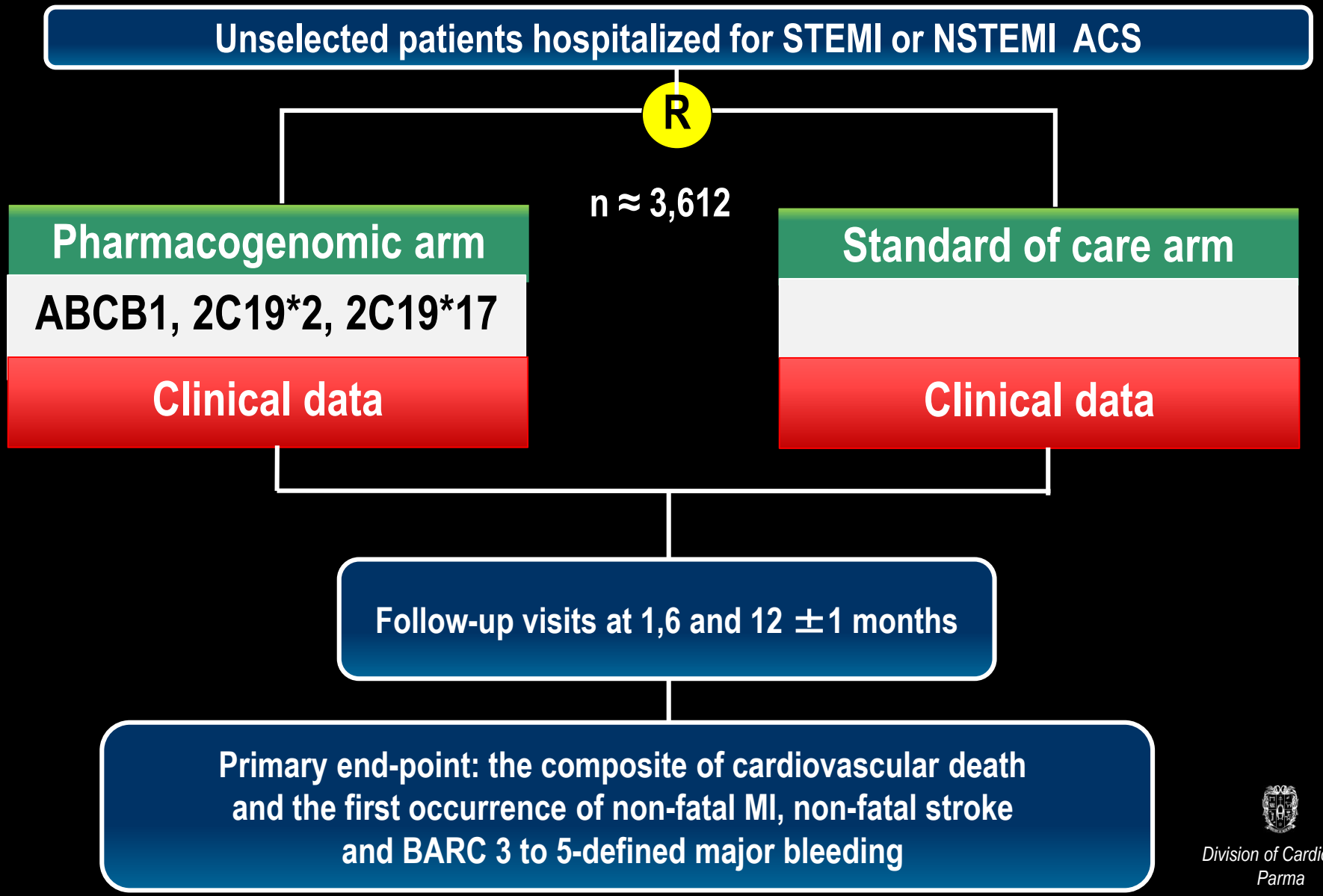
Study design



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Patient population

Inclusion Criteria:

The diagnosis of acute coronary syndromes was based on the presence of at least two of the following criteria:

- **ischemic symptoms at rest lasting >20 minutes**
- **electrocardiographic changes**
  - **ST-segment elevation**
  - **ST-segment depression**
- **the typical rise and fall of cardiac biomarker troponin I or T levels**

Exclusion criteria:

- **an inability to provide informed consent or follow study procedures**
- **any contraindication to the use of P2Y12 receptor antagonists**
- **a life expectancy of <1 year**
- **thrombolytic therapy within the previous 24 hours**
- **enrolment in another randomised trial or observational registry**
- **prior knowledge of the patients' ABCB1, CYP2C19*2 or CYP2C19*17 genotype**

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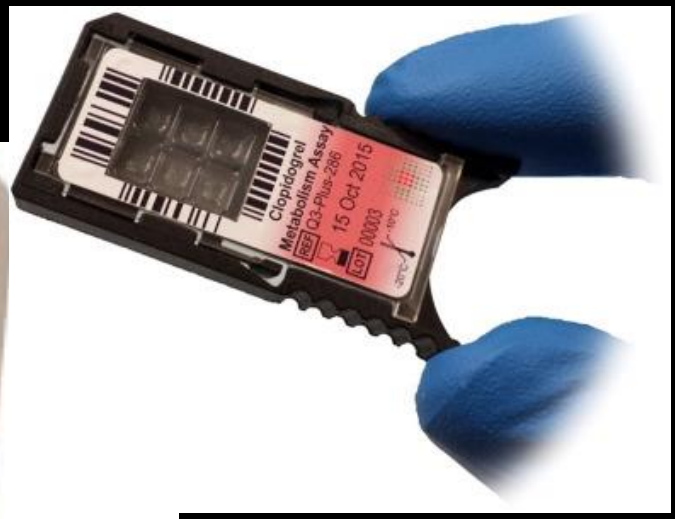
ST Q3 system



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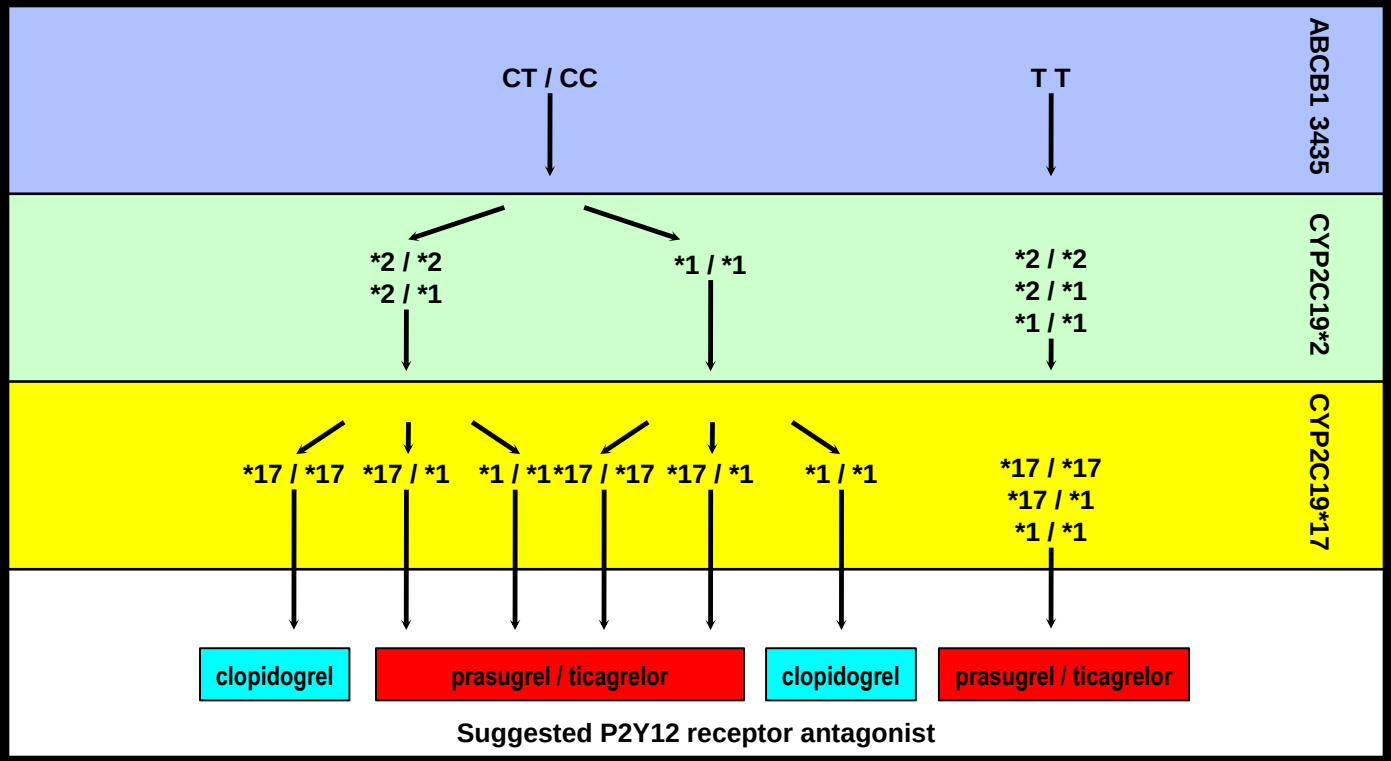
Algorithm for the selection of P2Y12 receptor antagonist

Clinical data

- age
- weight
- Grace score
- Crusade score
- diabetes
- prior history of stroke/TIA
- intracranial bleeding
- history of bleeding
- active bleeding
- anemia
- chronic kidney disease
- warfarin treatment

ABCB1, 2C19*2, 2C19*17



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Participating Centres

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Premature discontinuation

A total of 888 patients were recruited between 12 June 2013 and 18 February 2015; 448 patients were randomised to the pharmacogenomic arm and 440 to the standard of care arm. This represents 24.6% of the pre-specified sample size because, on 18 February 2015, the Ethics Committee of Modena (Italy) required that the trial should be prematurely stopped and all of the patients followed up as planned because of the lack of in vitro diagnosis (IVD) certification for the ST Q3 instrument.

Notice: Q3-Evo Reader is for use in research and for all other fields except the field of in vitro diagnostics. Therefore, while waiting for more information, the Ethics Committee orders the immediate stopping of enrolment and asks the PI for an urgent update on study progress, including the number of patients enrolled and their clinical condition during follow-up.

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Demographic and clinical characteristics

Characteristics	All patients (n=888)	Pharmacogenomic arm (n=448)	Standard of care arm (n=440)
Mean age ± SD, years	70.9 (± 12.2)	71.1 (± 12.3)	70.7 (± 12.1)
<70 years	361/888 (40.6)	186/448 (41.5)	175/440 (39.8)
70-80 years	275/888 (31.0)	130/448 (29.0)	145/440 (33.0)
>80 years	252/888 (28.4)	132/448 (29.5)	120/440 (27.2)
Female sex - No.(%)	283/888 (32.0)	153/448 (34.2)	130/440 (29.6)
Previous MI	191/888 (21.5)	96/448 (21.4)	95/440 (21.6)
Previous PCI	169/888 (19.0)	81/448 (18.1)	88/440 (20.0)
Chronic kidney disease	76/888 (8.6)	35/448 (7.8)	41/440 (9.3)

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Clinical and revascularization characteristics

Characteristics	All patients (n=888)	Pharmacogenomic arm (n=448)	Standard of care arm (n=440)
STEMI	244/888 (27.5)	114/448 (25.5)	130/440 (29.5)
NSTEMI	602/888 (67.8)	316/448 (70.5)	286/440 (65)
Unstable angina	17/888 (1.9)	7/448 (1.6)	10/440 (2.3)
Angiography	855/888 (96.3)	433/448 (96.6)	422/440 (95.9)
PCI	532/855 (62.2)	268/433 (61.8)	264/422 (62.6)
CABG	92/855 (10.7)	49/433 (11.3)	43/422 (10.1)
Aspirin	860/888 (97.0)	437/448 (97.6)	423/440 (96.1)
Lipid-lowering drug	761/888 (85.6)	386/448 (86.2)	375/440 (85.2)

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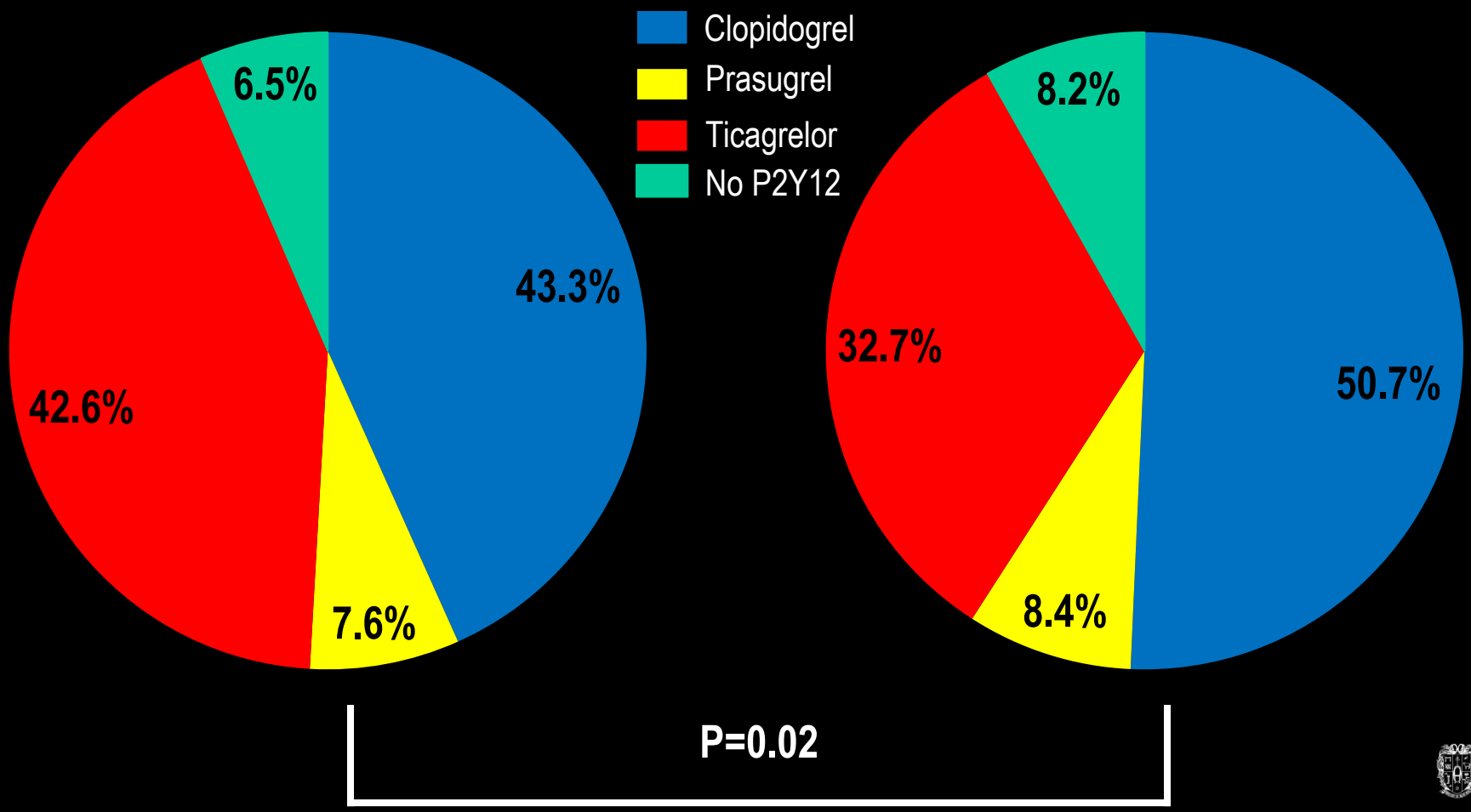
Frequency distribution of selected P2Y12 receptor antagonist



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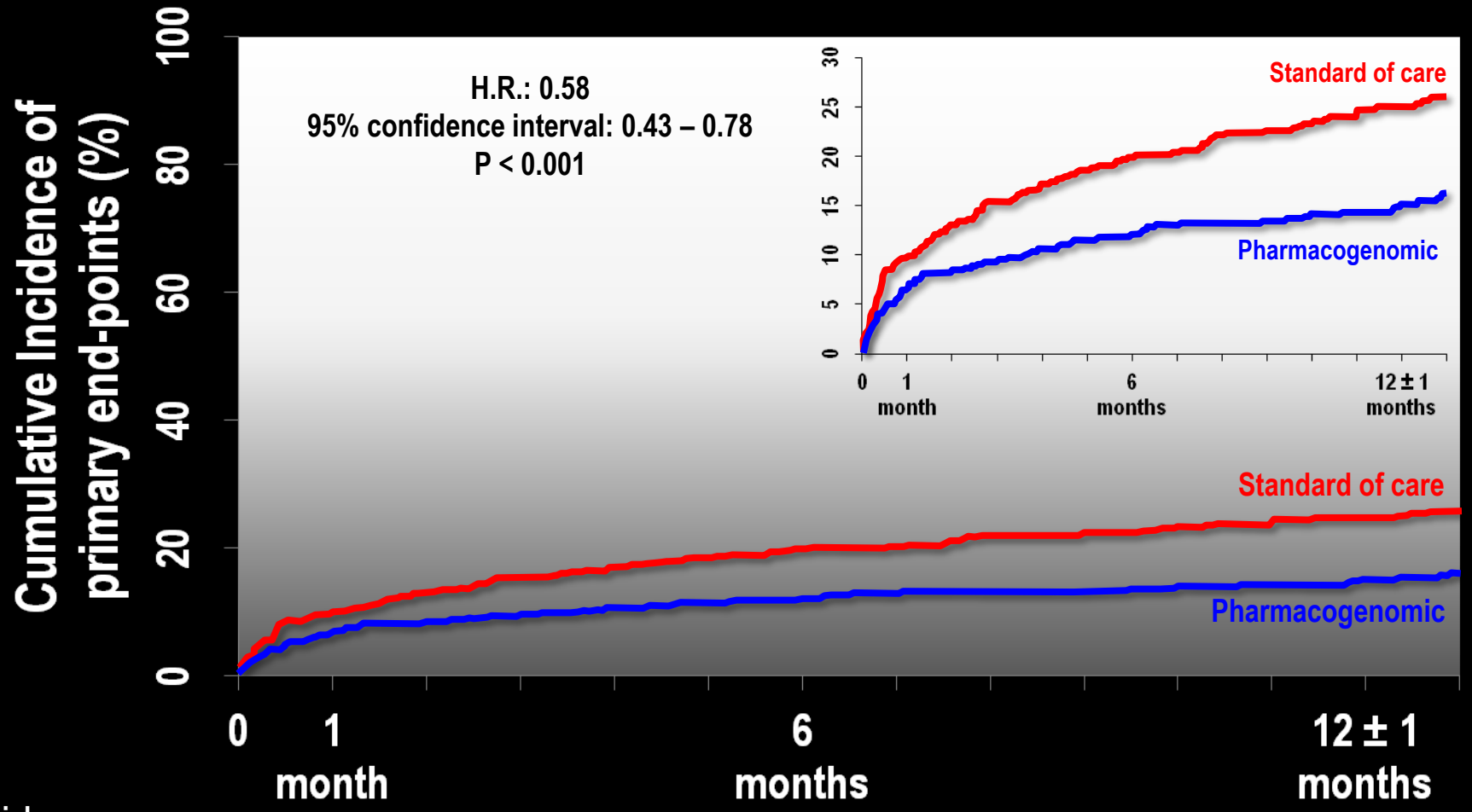
Primary composite end-point



No. at risk				
Pharmacogenomic arm	448	516	390	295
Standard of care arm	440	397	349	280

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Individual components of the primary composite end-point

Primary end-point	Pharmacogenomic arm (n=448)	Standard of care arm (n=440)	HR [95% CI]
Cardiovascular death	28	34	0.80 [0.49-1.33]
Non-fatal myocardial infarction	21	47	0.42 [0.25-0.70]
- Post-PCI MI	1	7	
- Post-CABG MI	1	9	
Non-fatal stroke	5	7	0.70 [0.22-2.18]
Combined major bleeding (BARC*3+4+5)	17	26	0.64 [0.35-1.18]
Primary composite end-point	71	114	0.58 [0.43-0.78]

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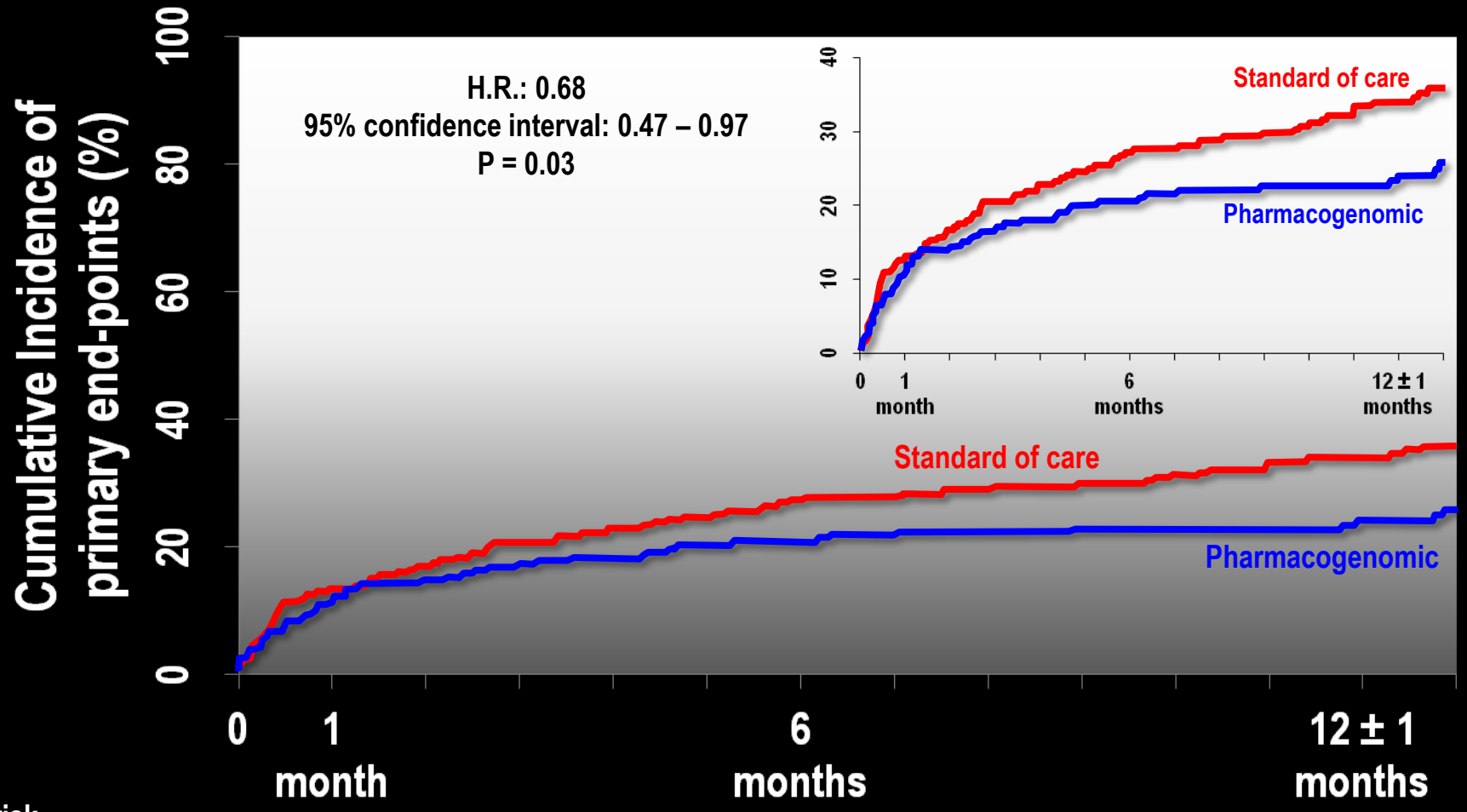
Primary composite end-point in clopidogrel-treated patients



No. at risk				
Pharmacogenomic arm	194	173	152	102
Standard of care arm	223	195	161	127

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Conclusions

- The implementation of multiple genotyping to guide the antiplatelet therapy in acute coronary syndromes is feasible across different institutions

- A more personalised approach to the selection of antiplatelet therapy may lead to a clinically meaningful reduction in ischemic and bleeding complications

- Future studies of genotype-guided antiplatelet therapy are required to confirm these data and clarify the cost-efficacy of genotyping in the challenging setting of acute coronary syndromes before implementing it in everyday clinical practice

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JACC cover page

Accepted Manuscript

Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Acute Coronary Syndromes: PHARMCLO trial

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