Double Antiplatelet Therapy and Coronary Artery Disease

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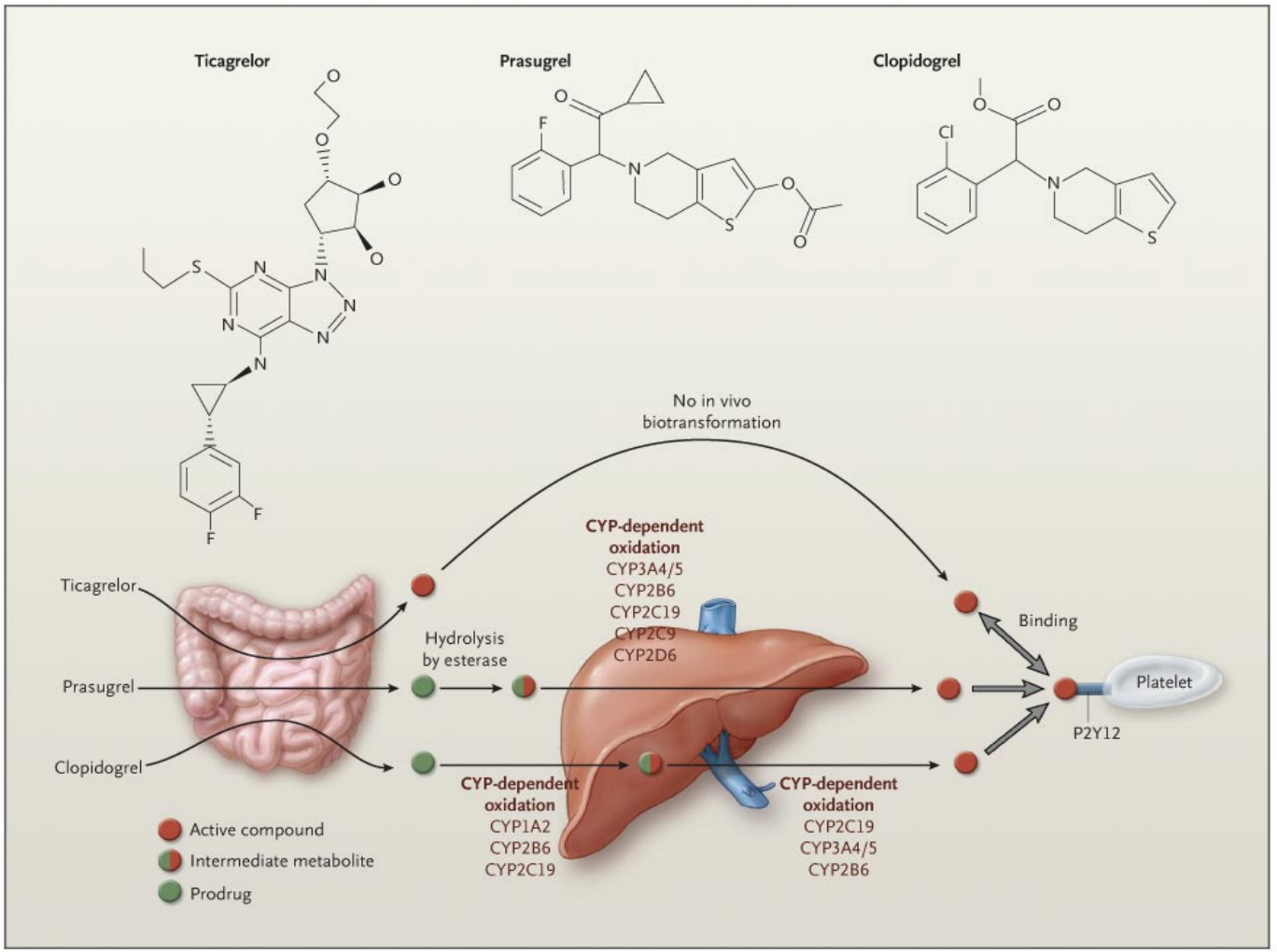
Objectives

- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor: P2Y12 Receptor

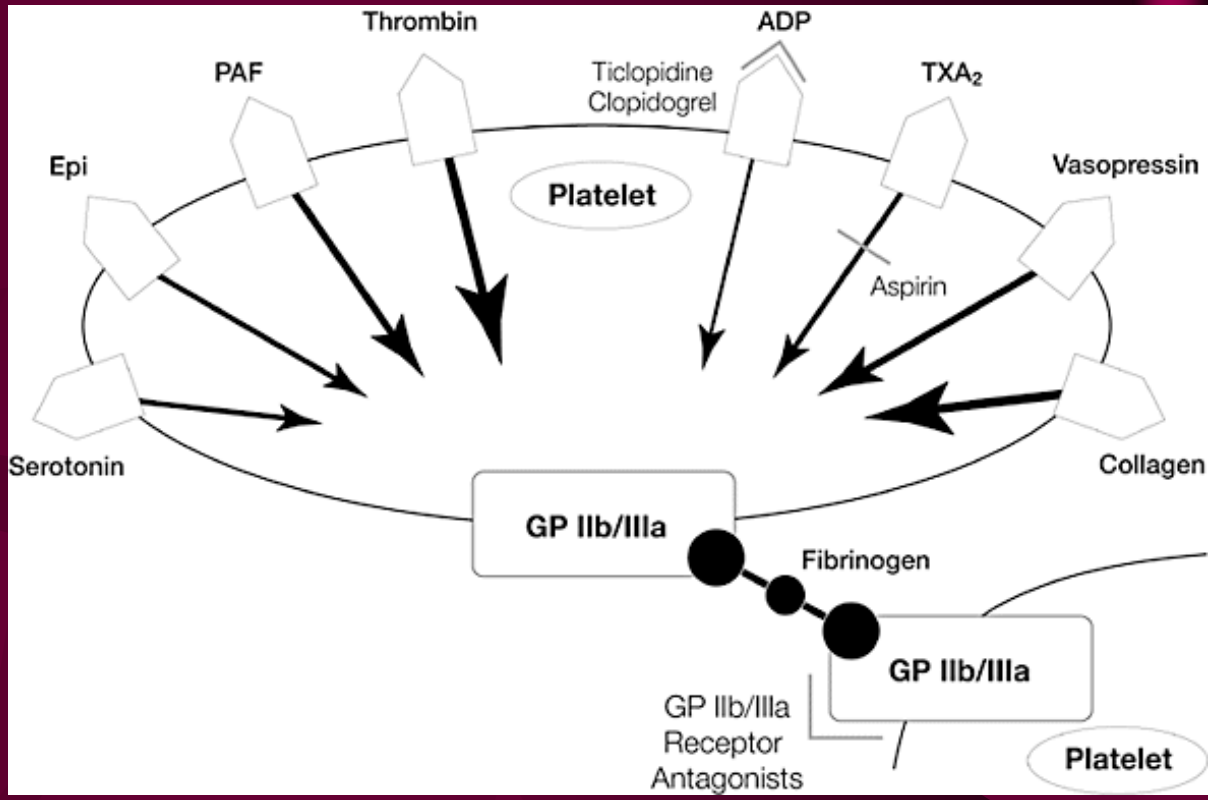


Schömig A. N Engl J Med 2009;361:1108-1111.

The NEW ENGLAND JOURNAL of MEDICINE

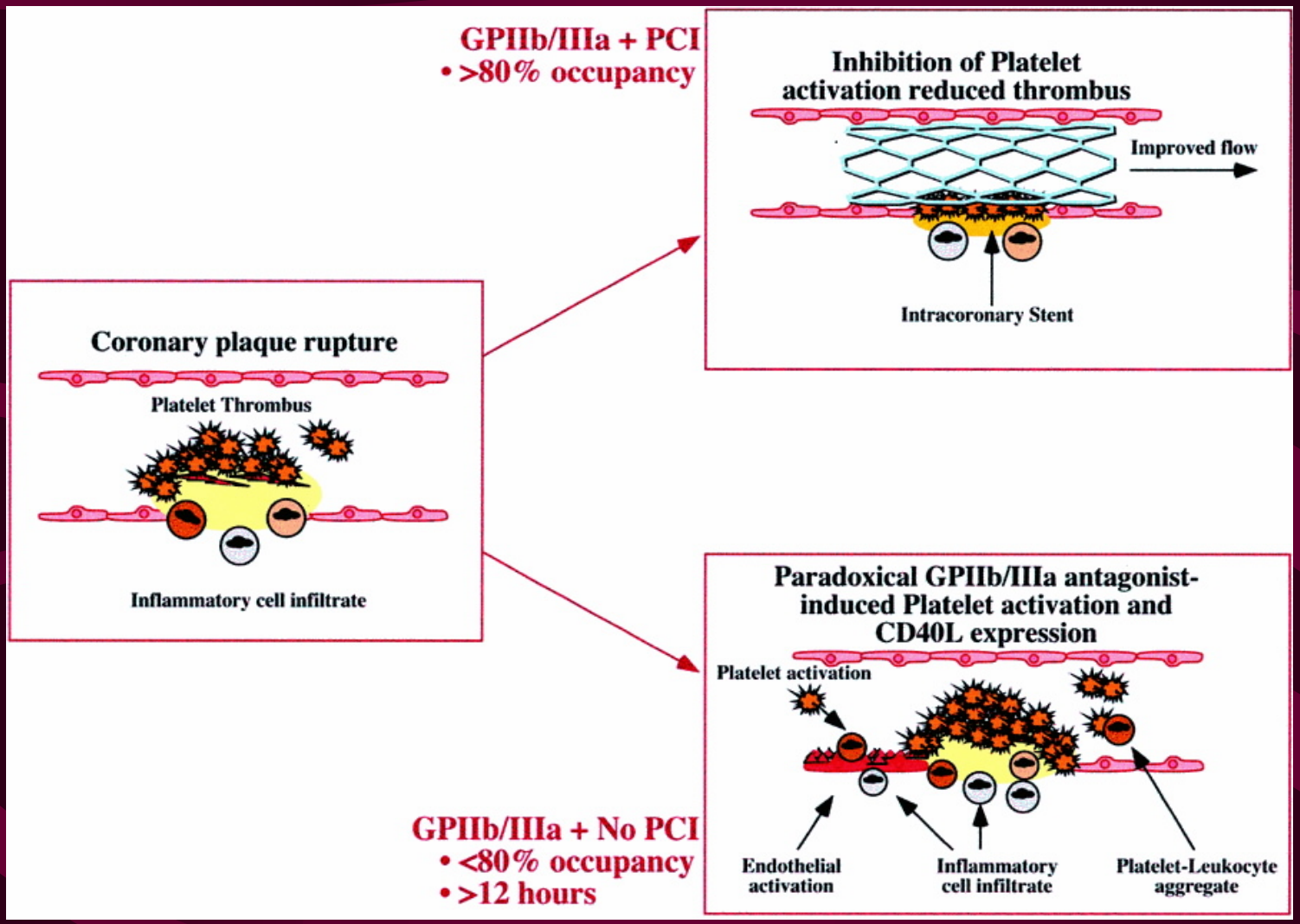
Platelet activation and aggregation

- Hemostasis and Thrombosis
- (GP) Ib – vWF interaction
- Activation of GP IIb/IIIa receptors
- Ligand binding* and platelet aggregation



*** Fibinogen, vWF, fibronectin, vitronectin**

Prolonged exposure to low levels of platelet inhibition (<80%), enables paradoxical expression of GP IIb/IIIa pro-thrombotic effect



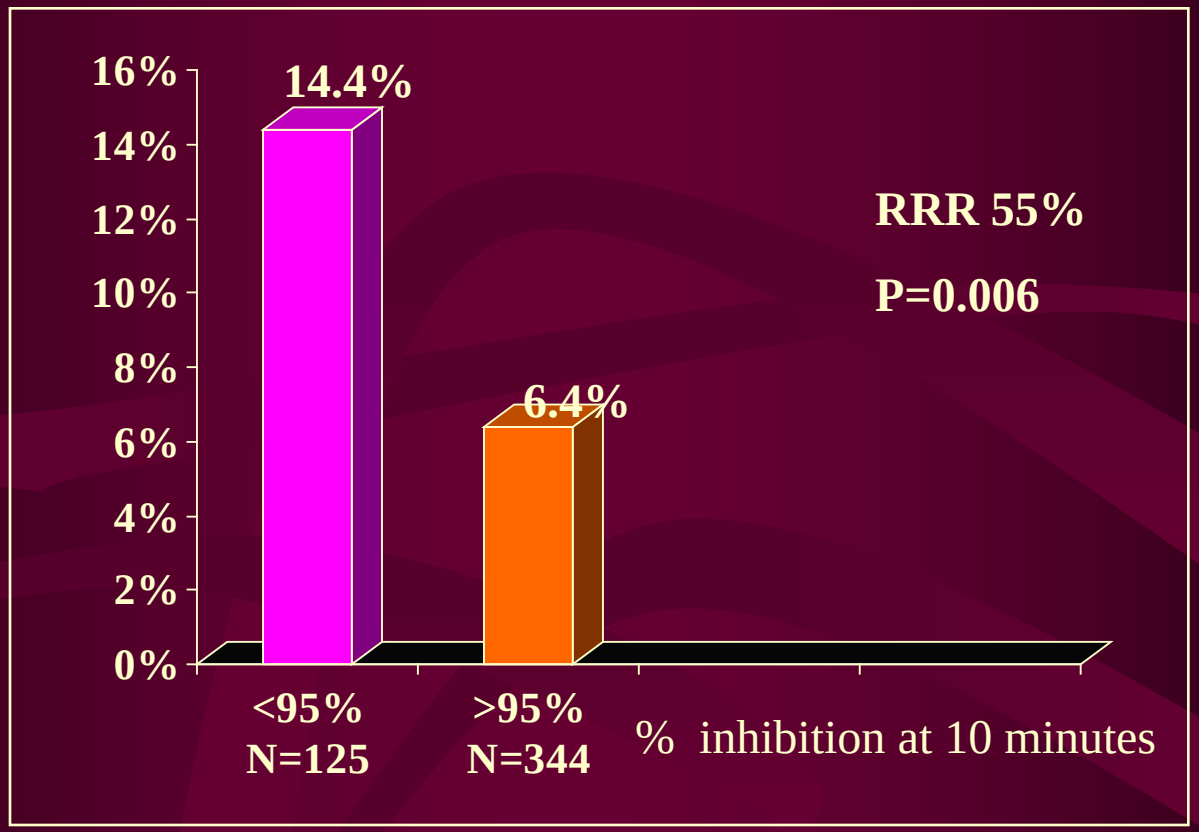
Quinn et al. *Circulation 2002;106:379-85.*

GP IIb/IIIa Antagonists

- Abciximab
  - Murine Monoclonal Antibody
  - Binds rapidly – dissociates slowly
  - Not IIb/IIIa integrin-specific (Mac-1, Vitronectin)
  - Inhibits Thrombin generation
  - 6% anti-abciximab antibodies

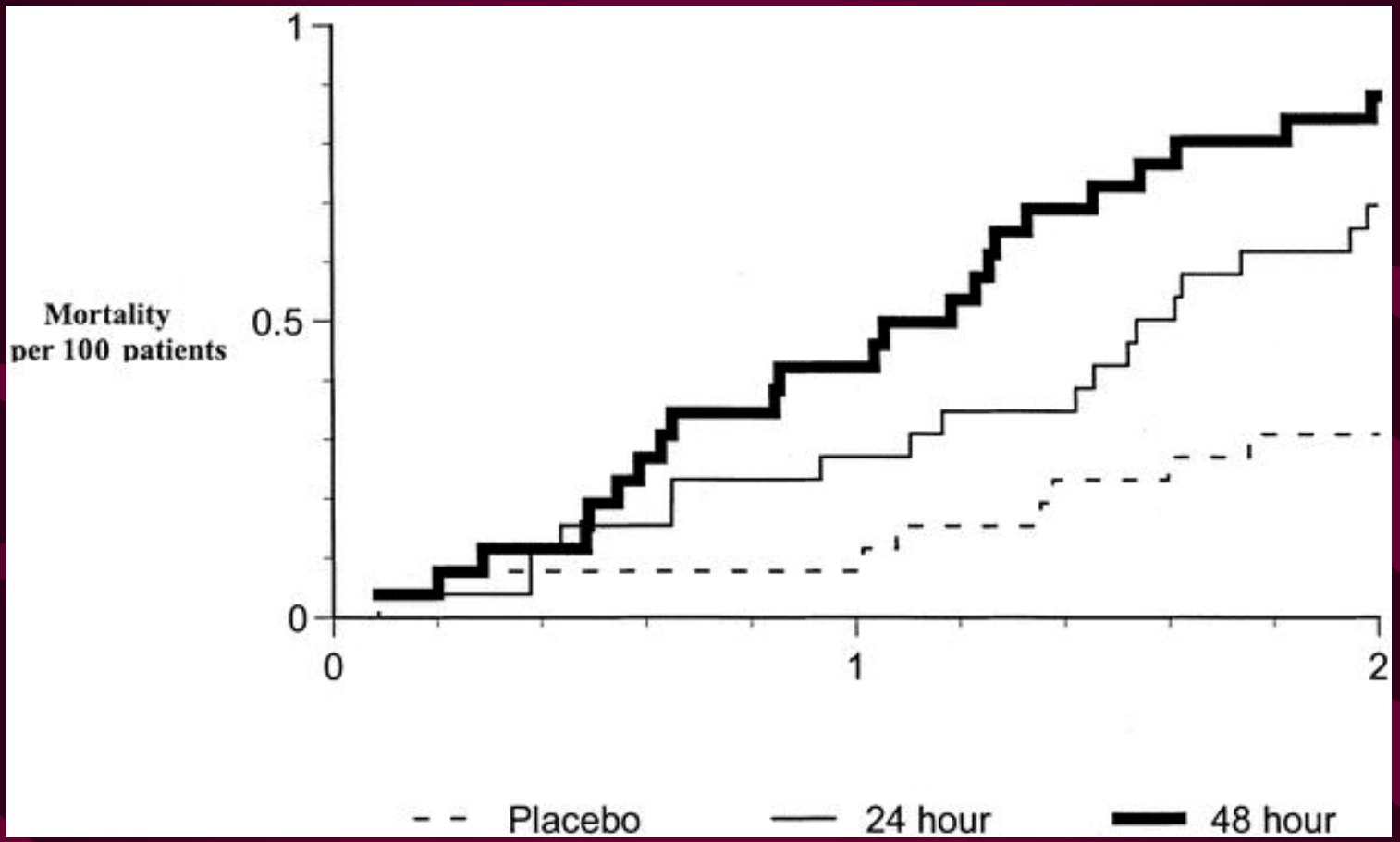
- Eptifibatide - Tirofiban
  - Synthetic peptide (Sistrurus M. Barbouri - Echistatin)
  - Binds and dissociates rapidly
  - GP IIb/IIIa Integrin specific
  - Not immunogenic

MACE Versus Platelet Inhibition by RPFA



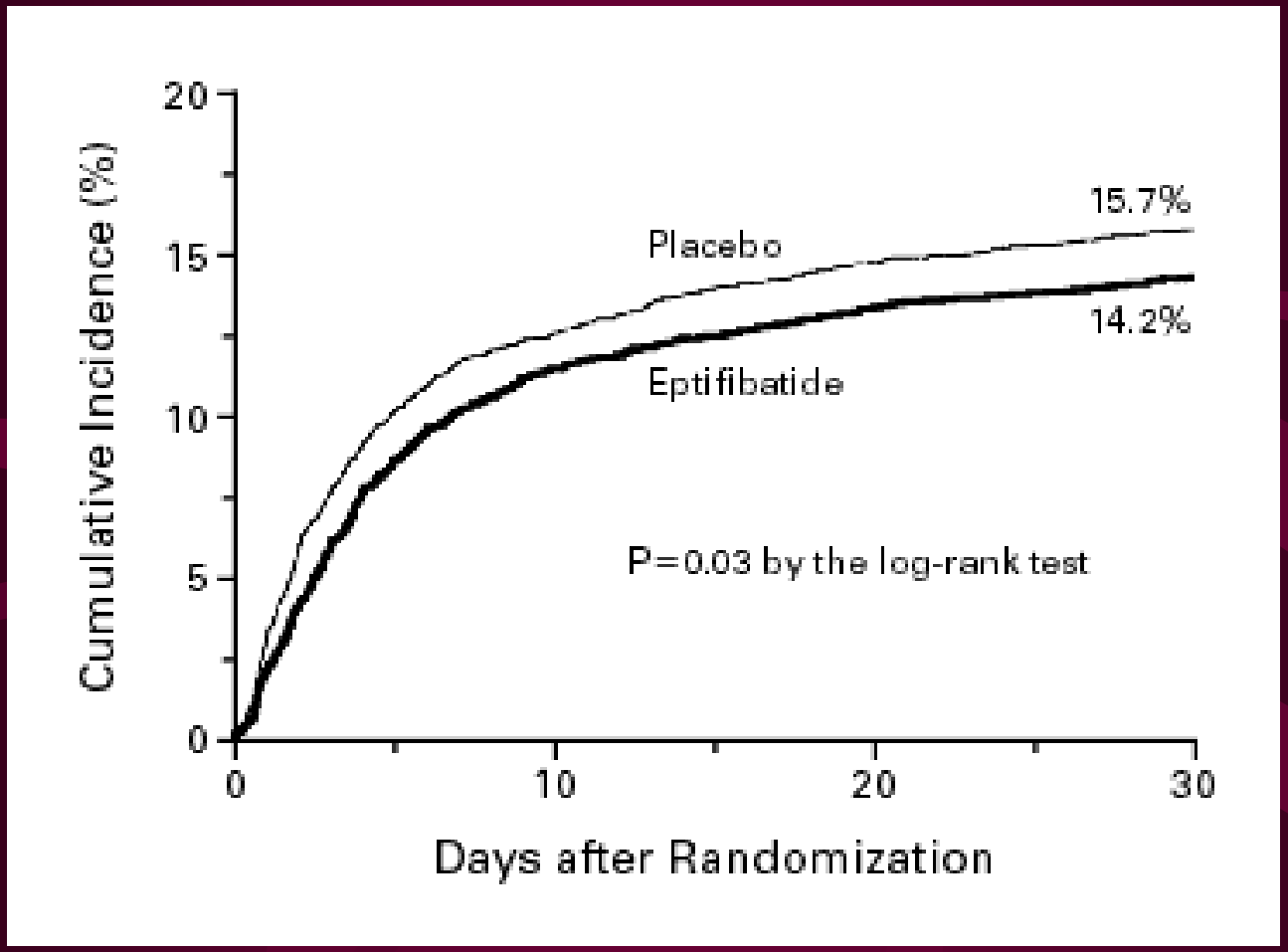
The GOLD Trial. ***Circulation 2001;103:2572-78.***

Clinical Implications: GUSTO IV-ACS



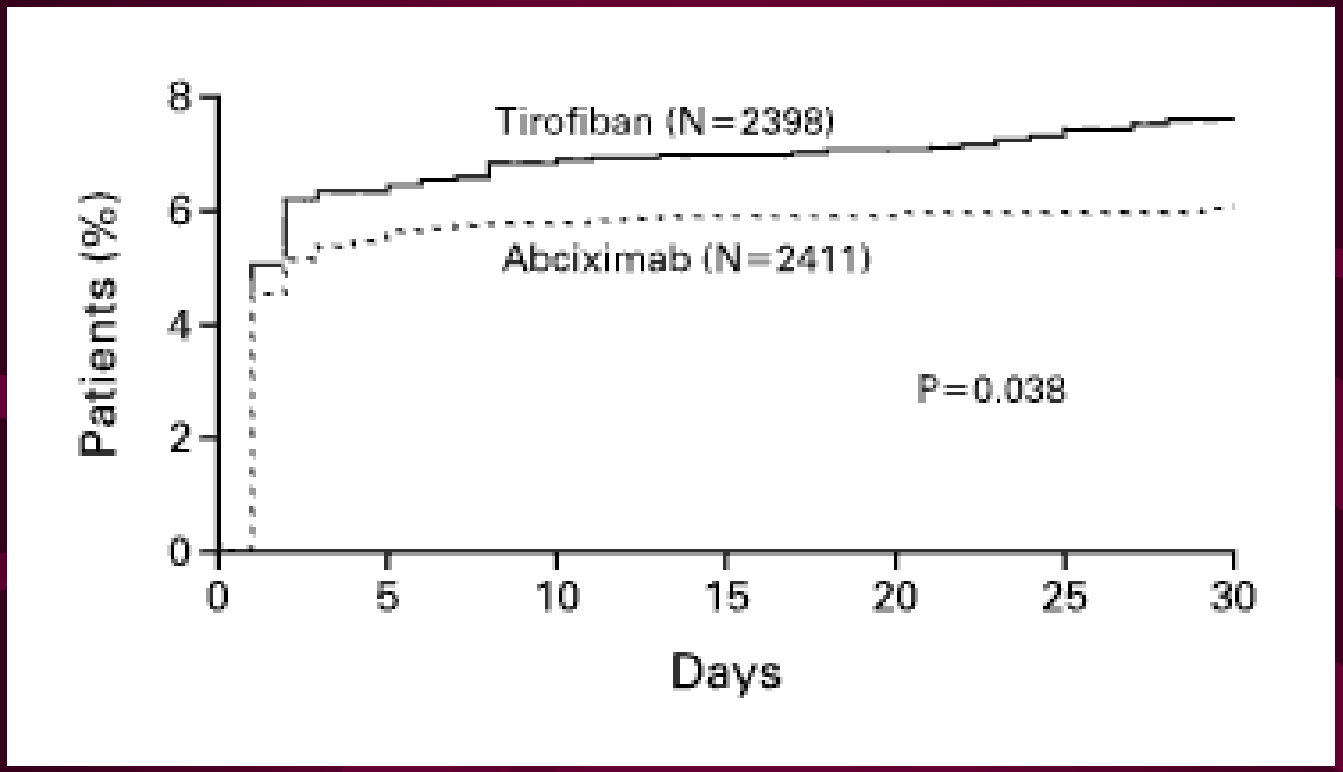
Increased mortality in the 24-hr (p=0.048) and 48-hr (p=0.007) abciximab groups. The curves separate early an continue to separate after 24 hrs. **Circulation 2002;106:379**

Clinical Implications: PURSUIT (ACS)



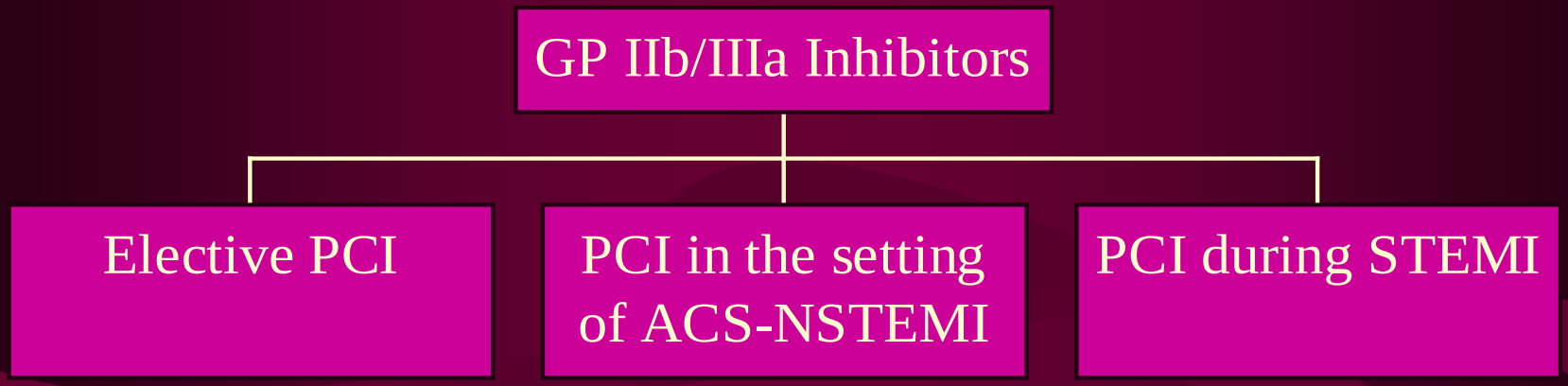
Kaplan–Meier Curves Showing the Incidence of Death or Nonfatal Myocardial Infarction at 30 Days. **N Engl J Med 1998;339:436-443.**

Clinical Implications: TARGET



TARGET: Incidence of the Primary End Point, a Composite of Death, Nonfatal Myocardial Infarction, or Urgent Target-Vessel Revisualization, in the First 30 Days after Enrollment. **N Engl J Med 2001;344:1888-1942.**

Trials with GP IIb/IIIa Inhibitors during PCI



EPILOG* (Low Risk UA)
EPISTENT (40% SA)
ERASER
Kini et al (HSRA)
Tamburino et al
IMPACT
IMPACT-II* (42% ACS)
ESPRIT (12% ACS)
Harrington et al
Kereiakis et al

EPIC* (high-risk PCI)
EPISTENT (37% UA)
CAPTURE
Simoons et al
ISAR-2
IMPACT-II* (42% ACS)
RESTORE

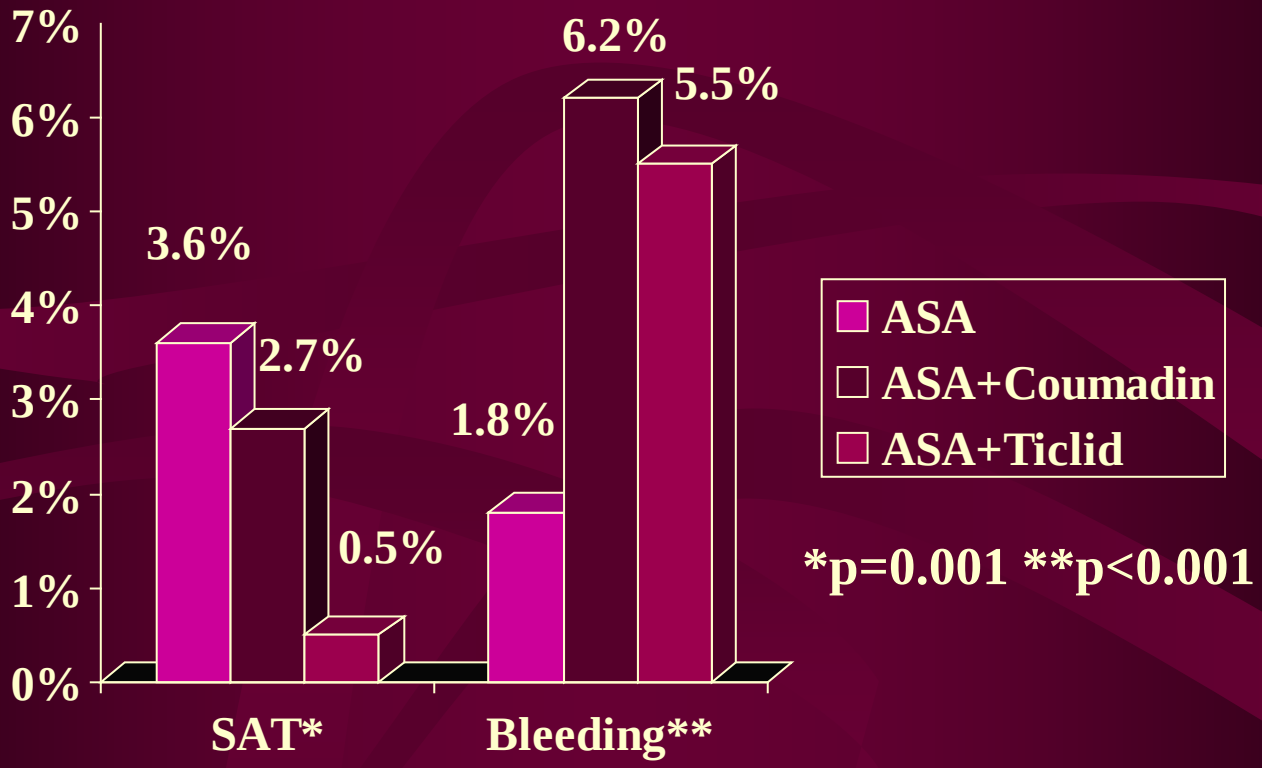
RAPPORT
ADMIRAL
CADILLAC
Petronio et al (Rescue PTCA)

Modified from Karvouni et al. *J Am Coll Cardiol 2003;41:26-32.*

Objectives

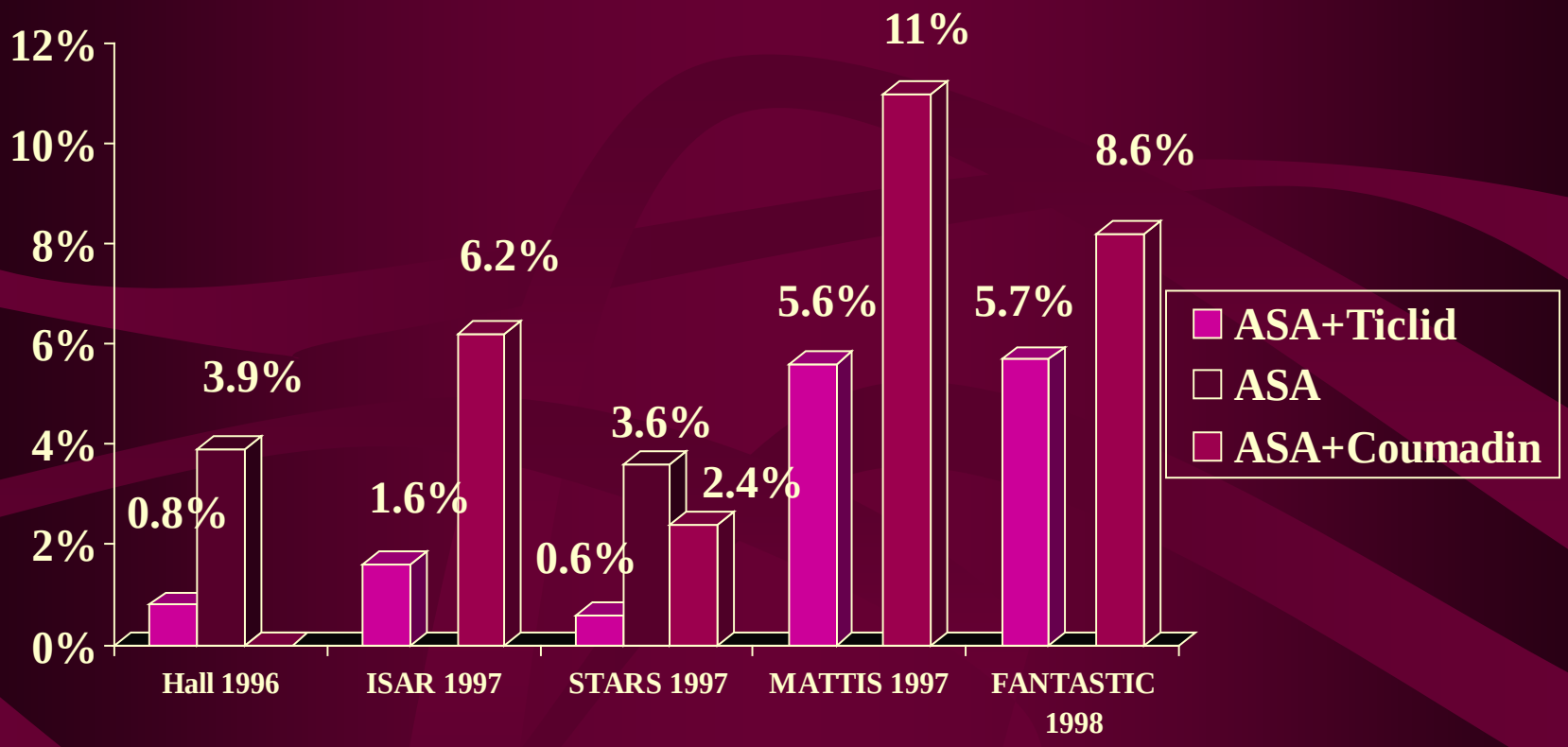
- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

ASA+Ticlopidine (No loading) in the setting of elective PCI with high-pressure inflation (n=1965)



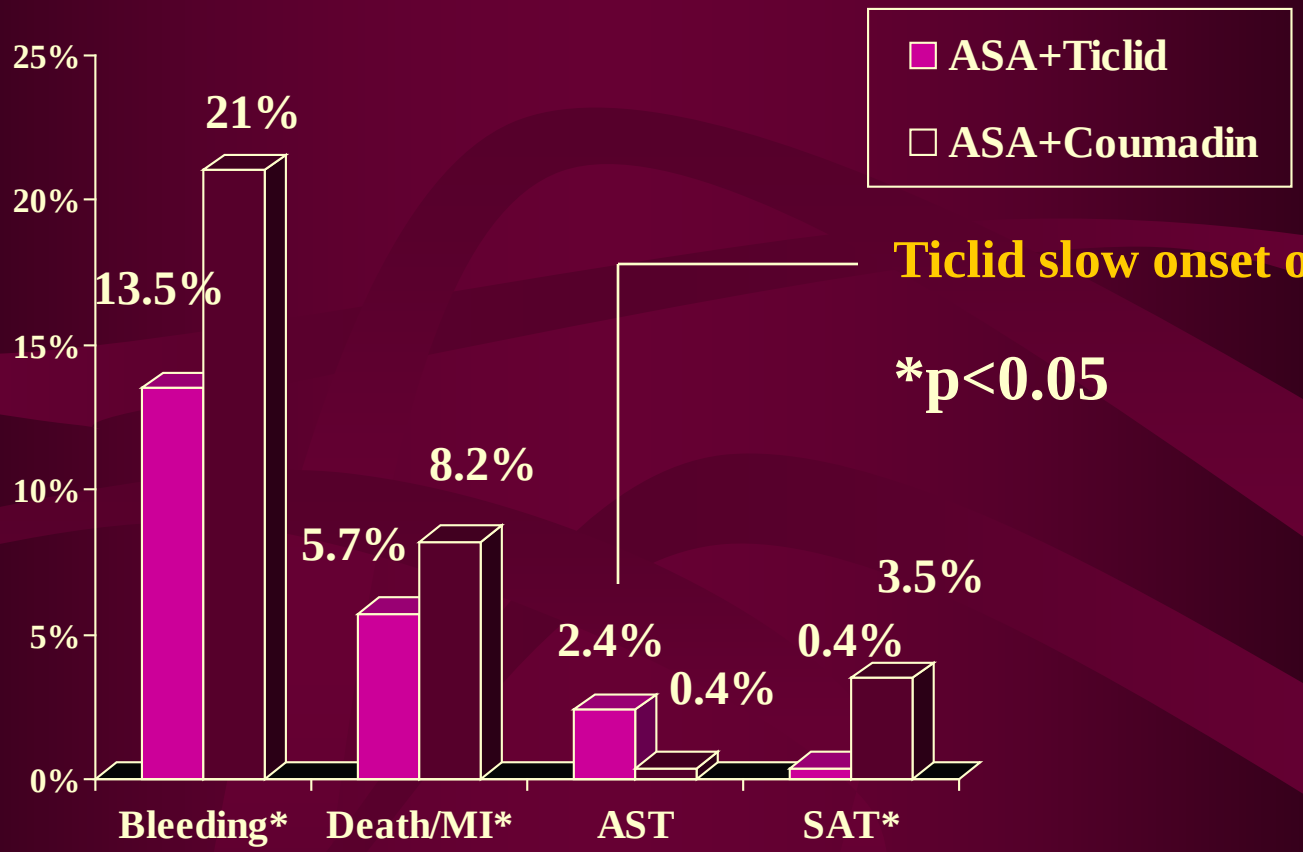
N Engl J Med 1998;339:1665-71.

Randomized Trials comparing ASA+Ticlopidine versus ASA+Coumadin or Coumadin alone



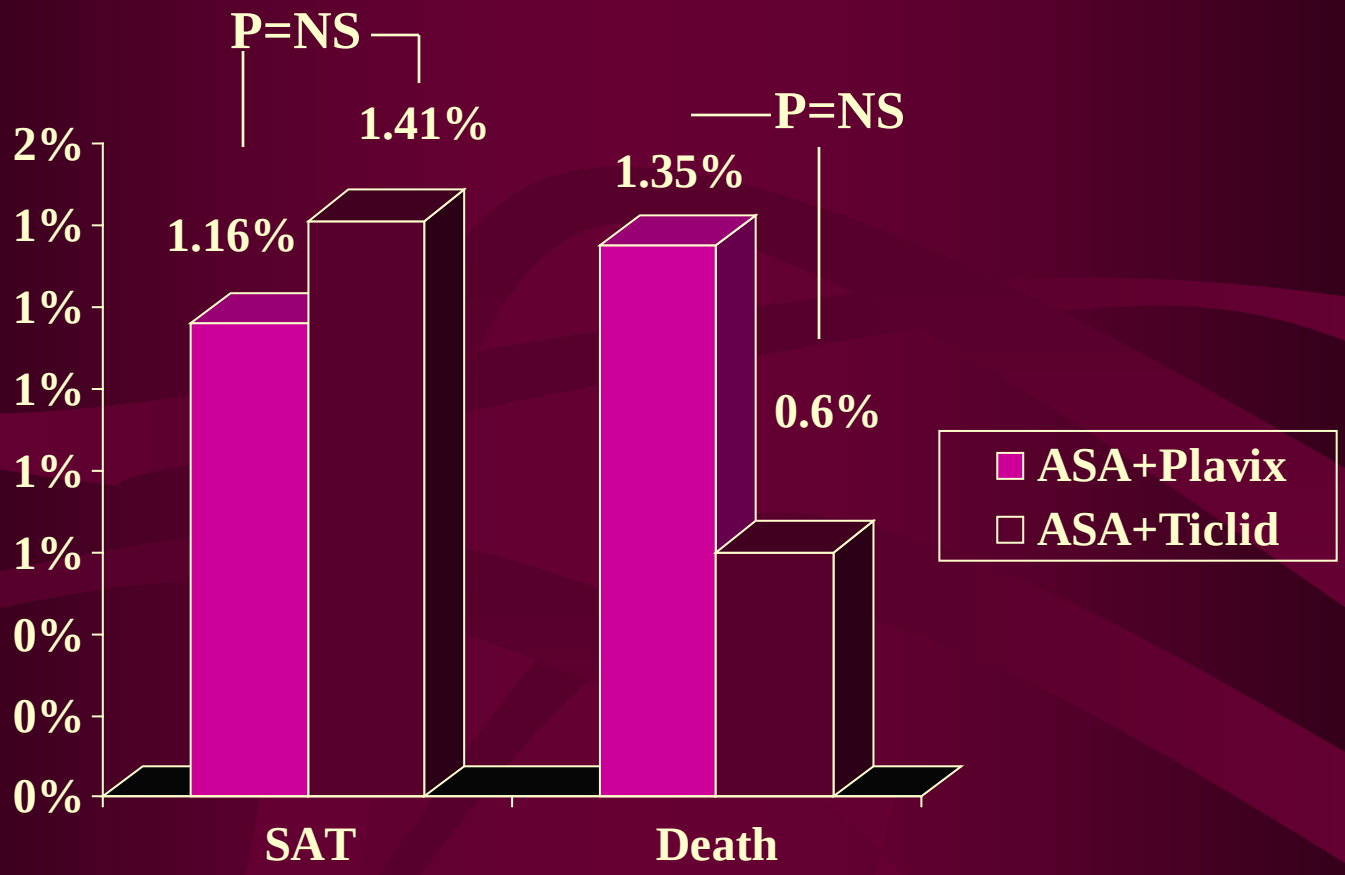
Cumulative Event Rates in 5 randomized Trials comparing three regimens post PCI. ***J Interven Cardiol 2002;15:85-93.***

ASA+Ticlopidine in Unplanned and Elective PCI (n=482): The FANTASTIC Trial: 6 weeks results



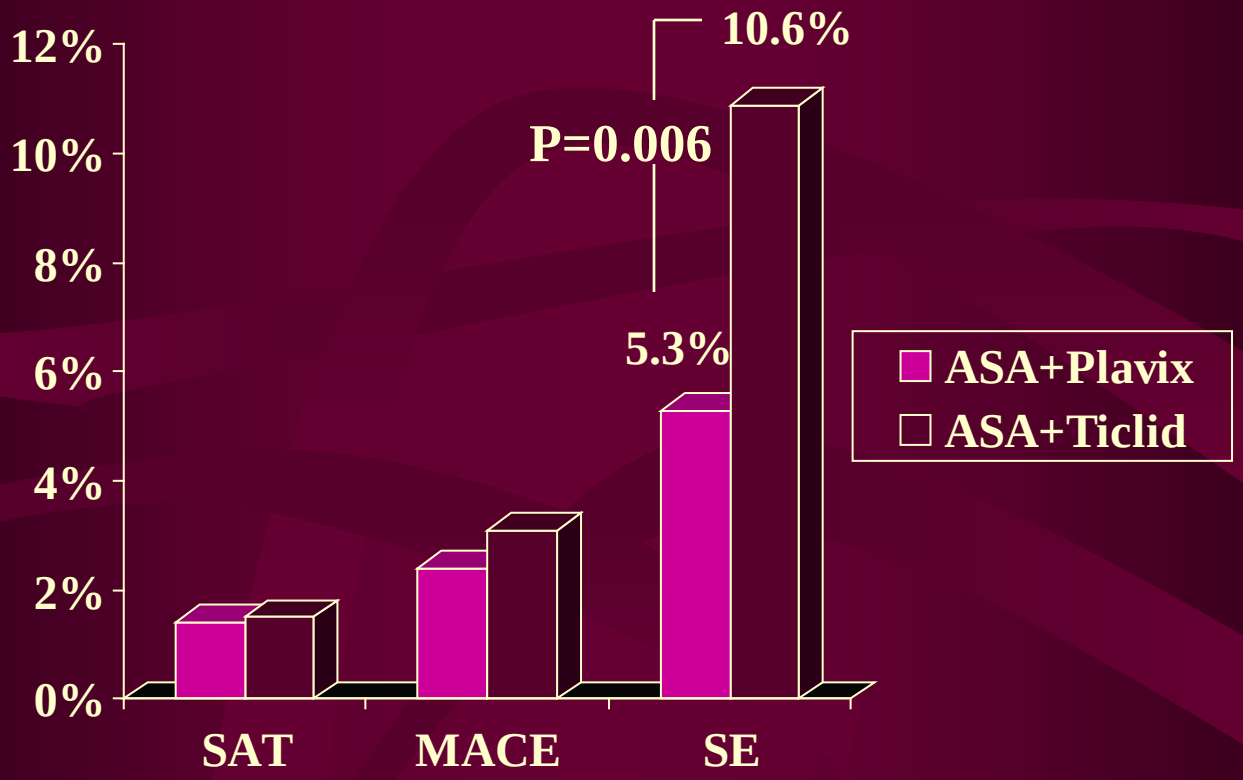
Circulation 1998;98:1597-1603.

Clopidogrel versus Ticlopidine in the setting of PCI



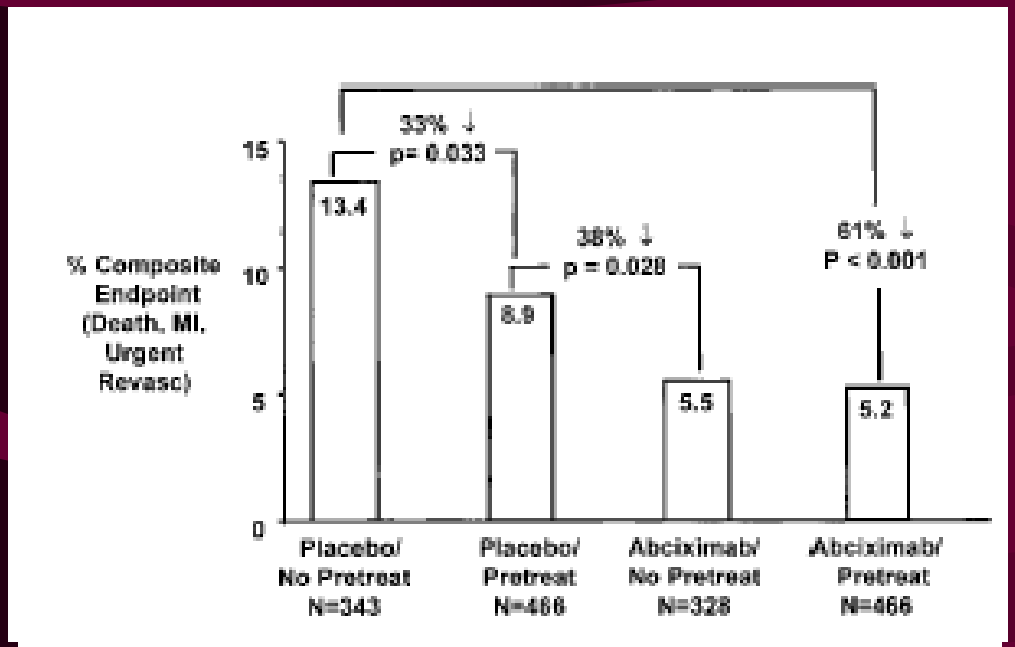
The TOPPS Study. Circulation 1999;100(Suppl. I):I:-379.

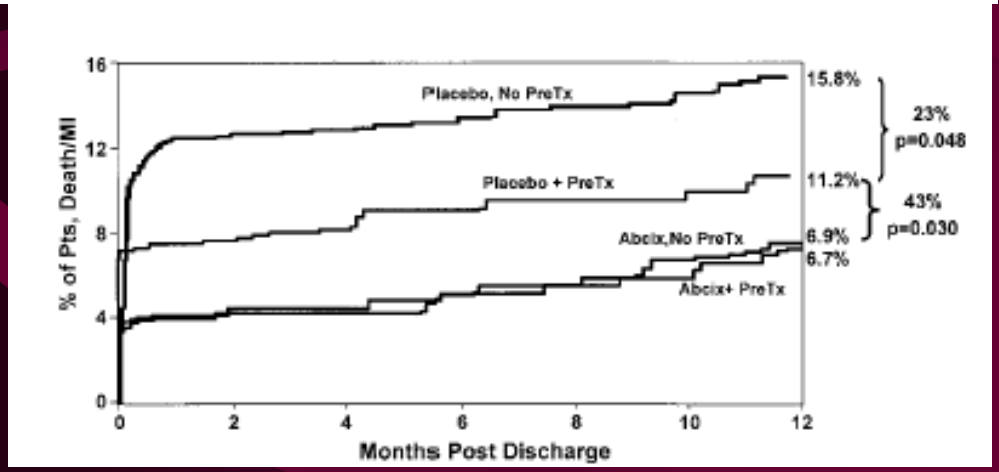
Clopidogrel versus Ticlopidine for the prevention of SAT and safety profile



Circulation 1999;99:2364-66.

Ticlopidine Pretreatment in the EPISTENT Trial

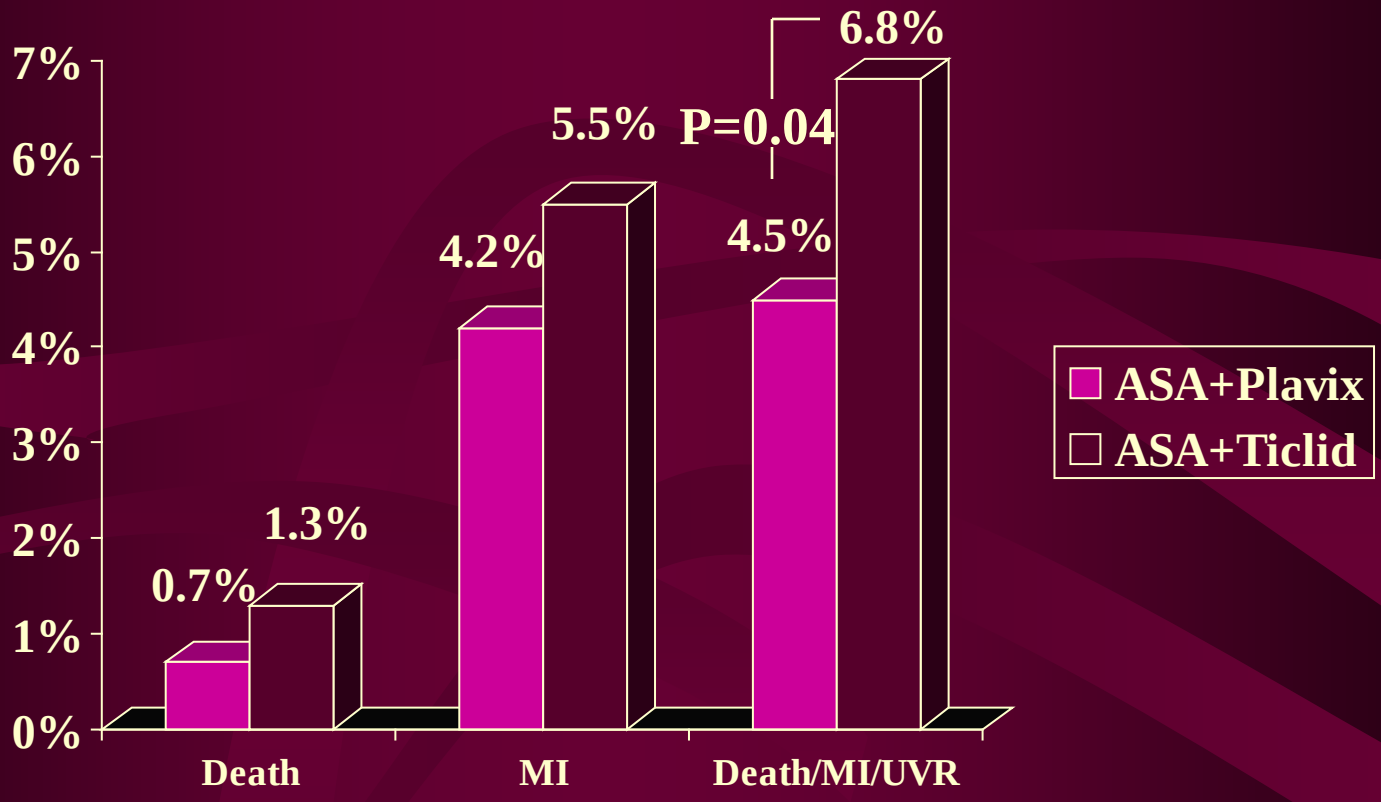




30-days and 1-year composite end point based on Ticlopidine pretreatment status.

Circulation 2001;103:1403-9.

High-Loading Dose of Clopidogrel during PCI with or without abciximab (60%)



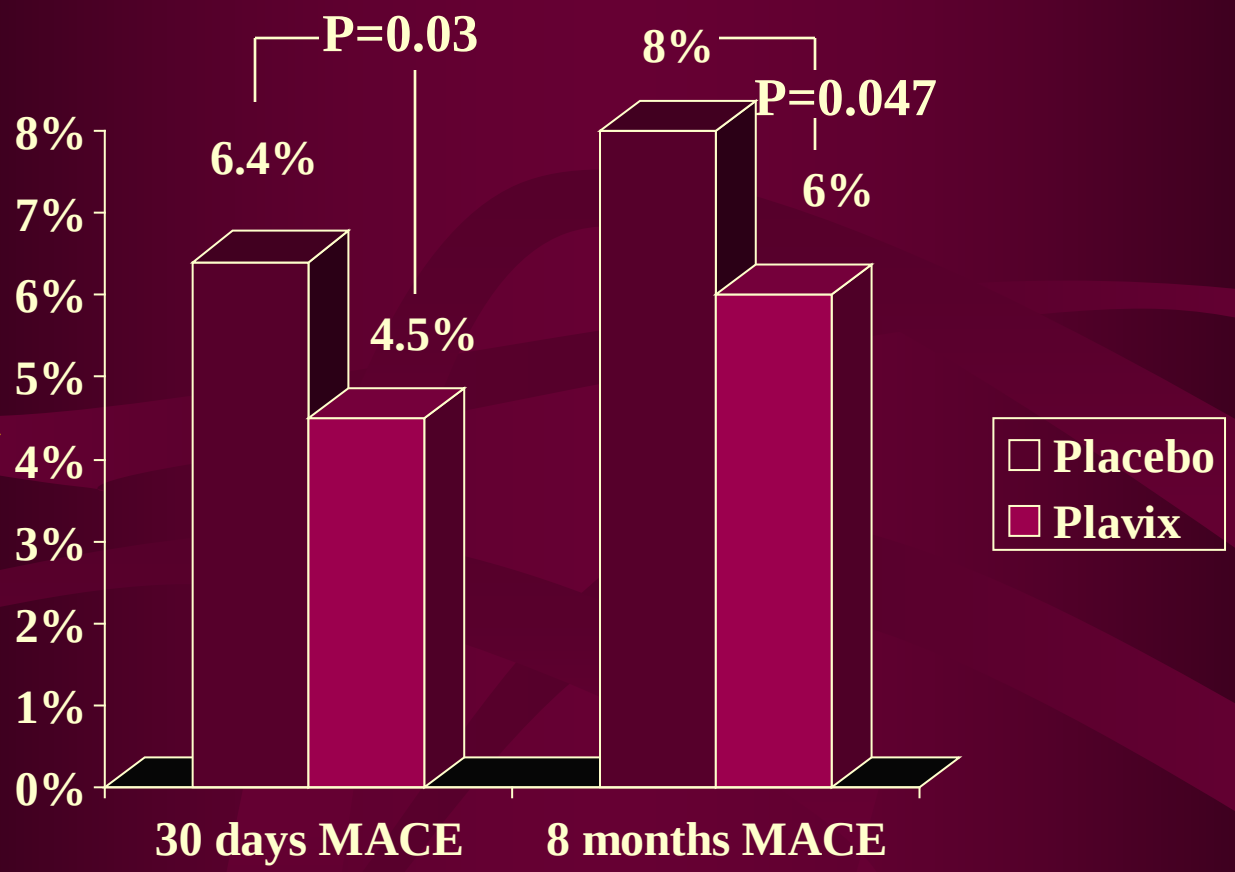
Clopidogrel: 600 mg load + 150 mg/d x 4 days + 75 mg/d x 4 weeks.
Ticlopidine: 500 mg load + 500 mg/d x 4 weeks.

Cathet Cardiovasc Intervent 2002;55:436-41.

The PCI-CURE Study

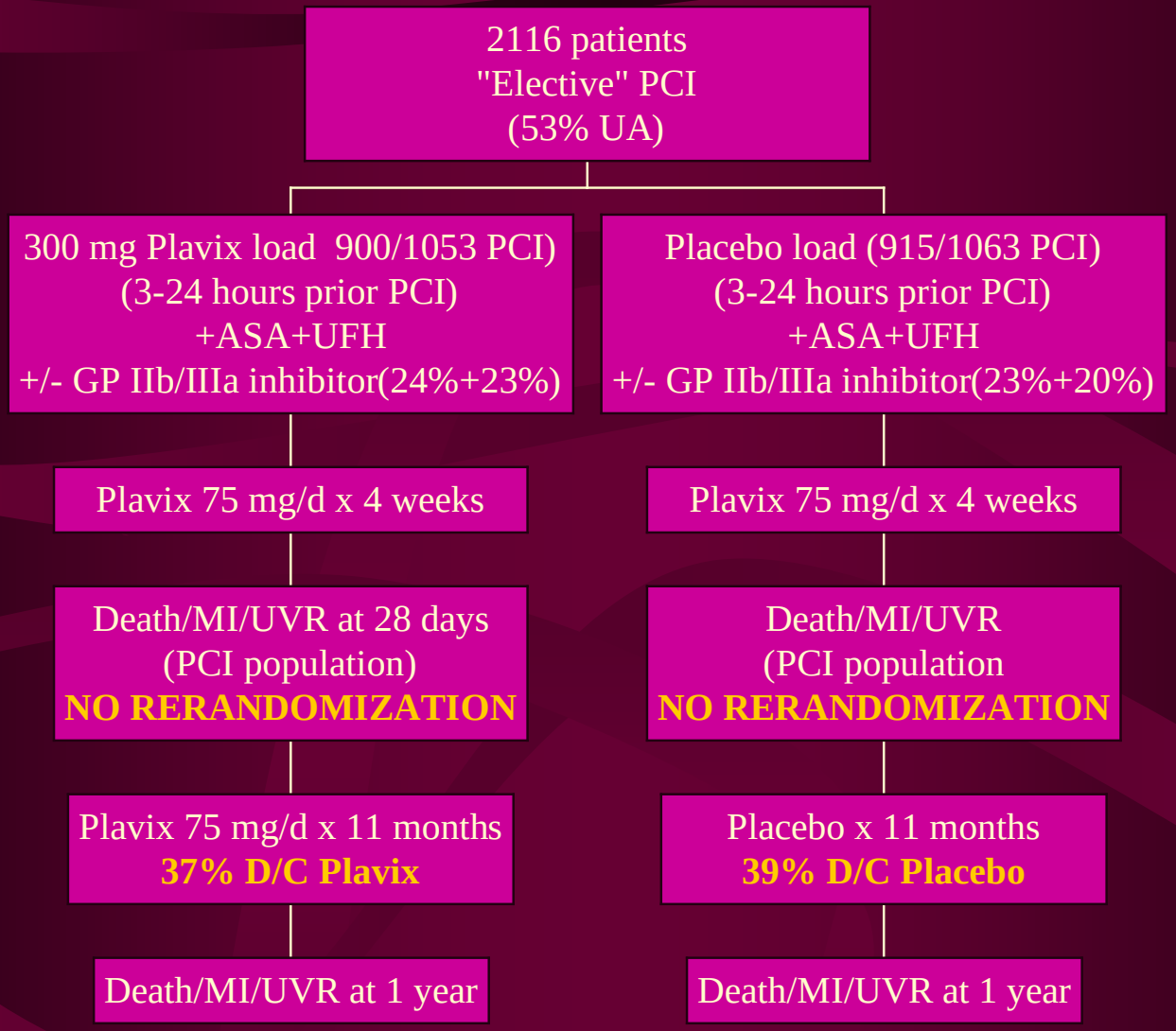
MACE:

Death/MI/UVR



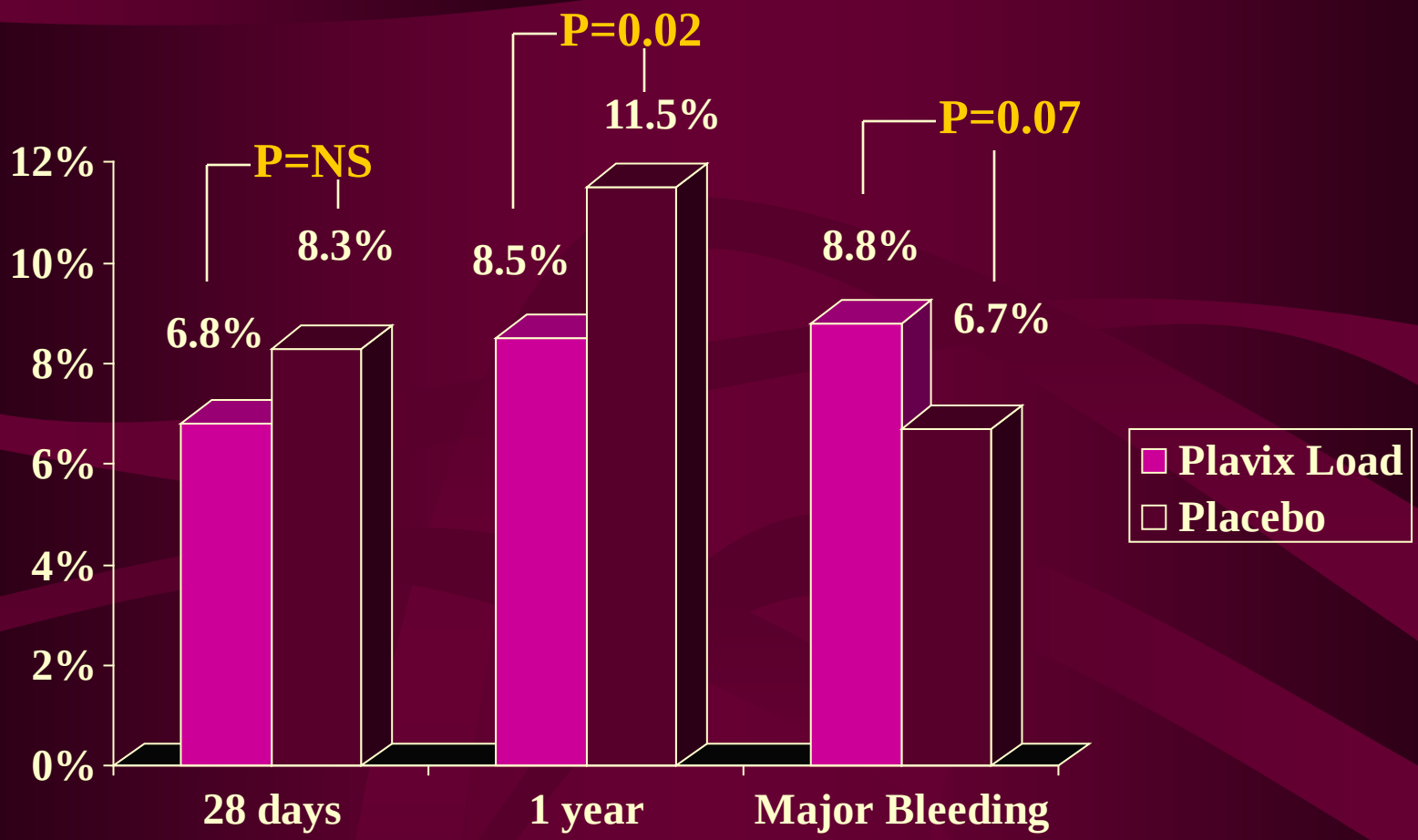
Lancet 2001;358:527-33.

The CREDO Trial: How much and for how long?



JAMA 2002;288:2411-2420.

CREDO Results



JAMA 2002;288:2411-2420.

Prasugrel-TRITON-TIMI 38

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6813)	Clopidogrel (N=6795)	Hazard Ratio for Prasugrel (95% CI)	P Value†
	no. of patients (%)			
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

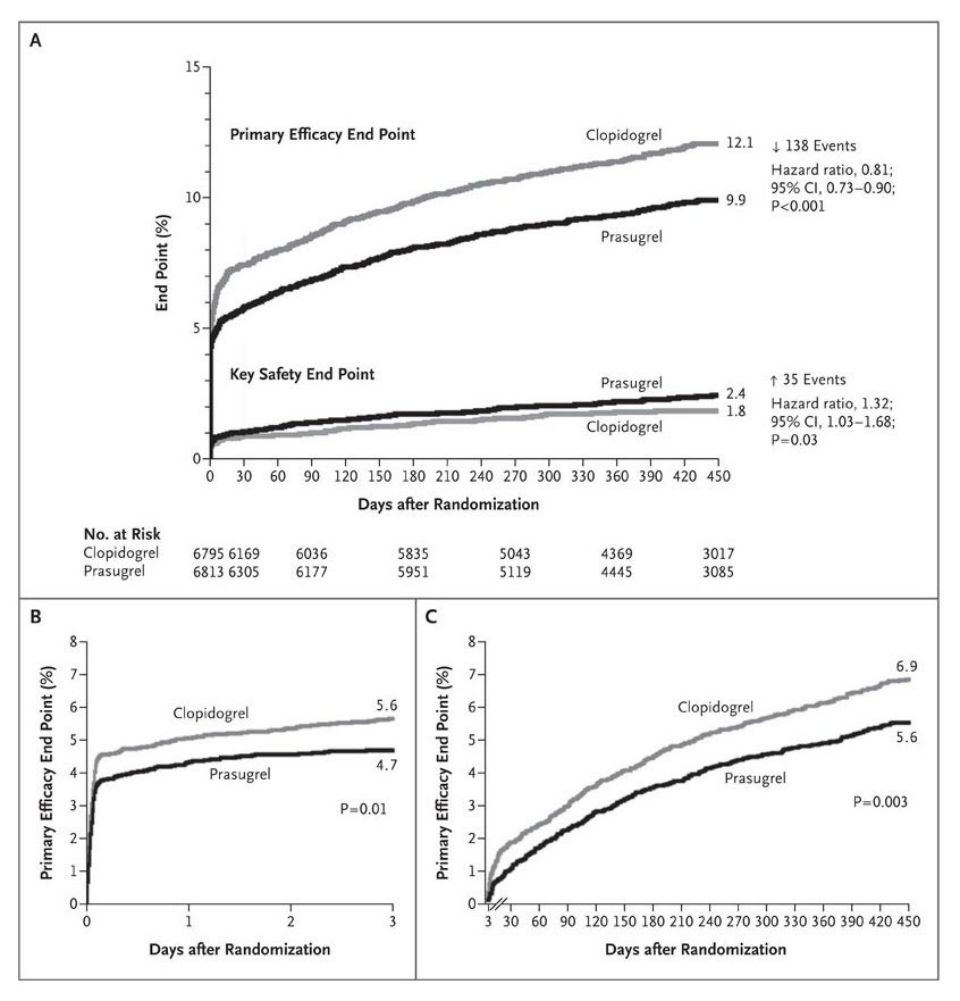
* The percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. Death from cardiovascular causes and fatal bleeding (Table 3) are not mutually exclusive, since intracranial hemorrhage and death after cardiovascular procedures that were complicated by fatal bleeding were included in both end points. MI denotes myocardial infarction.

† P values were calculated with the use of the log-rank test. The prespecified analysis for the primary end point used the Gehan–Wilcoxon test, for which the P value was less than 0.001.

‡ Stent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium; the numbers of patients at risk were all patients whose index procedure included at least one intracoronary stent: 6422 patients in each of the two treatment groups.

Major Efficacy End Points in the Overall Cohort at 15 Months – NEJM 2007;357:2001

Prasugrel-TRITON-TIMI 38



Cumulative Kaplan-Meier Estimates of the Rates of Key Study End Points during the Follow-up Period

Prasugrel-TRITON-TIMI 38

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

* The data shown are for patients who received at least one dose of the study drug and for end points occurring within 7 days after the study drug was discontinued or occurring within a longer period if the end point was believed by the local investigator to be related to the use of the study drug. Percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. CABG denotes coronary-artery bypass grafting.

† The most frequent sites of life-threatening bleeding were gastrointestinal sites, intracranial sites, the puncture site, and retroperitoneal sites.

‡ One patient in the clopidogrel group had a fatal gastrointestinal hemorrhage while receiving the study medication, but hemoglobin testing was not performed and, therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied and the data do not appear in this table.

§ Transfusion was defined as any transfusion of whole blood or packed red cells.

¶ For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel or clopidogrel before undergoing CABG: 179 and 189, respectively. The ratio is the odds ratio, rather than the hazard ratio, and was evaluated with the use of the Cochran–Mantel–Haenszel test.

TIMI Bleeding End Points in the Overall Cohort at 15 Months

Ticagrelor-PLATO Trial

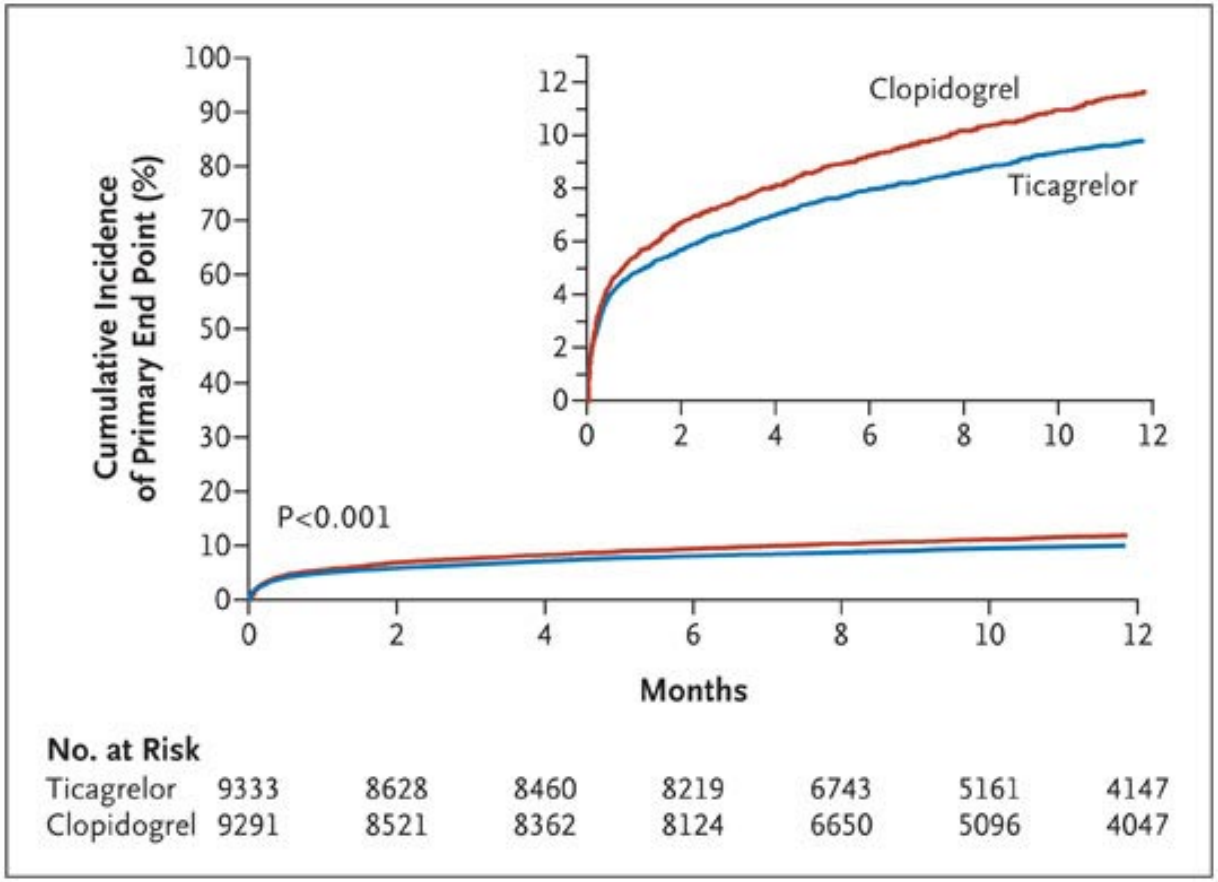
Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

* The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes. MI denotes myocardial infarction, and TIA transient ischemic attack.
† P values were calculated by means of Cox regression analysis.
‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.
§ A plan for invasive or noninvasive (medical) management was declared before randomization.
¶ Patients with any primary event during the first 30 days were excluded.

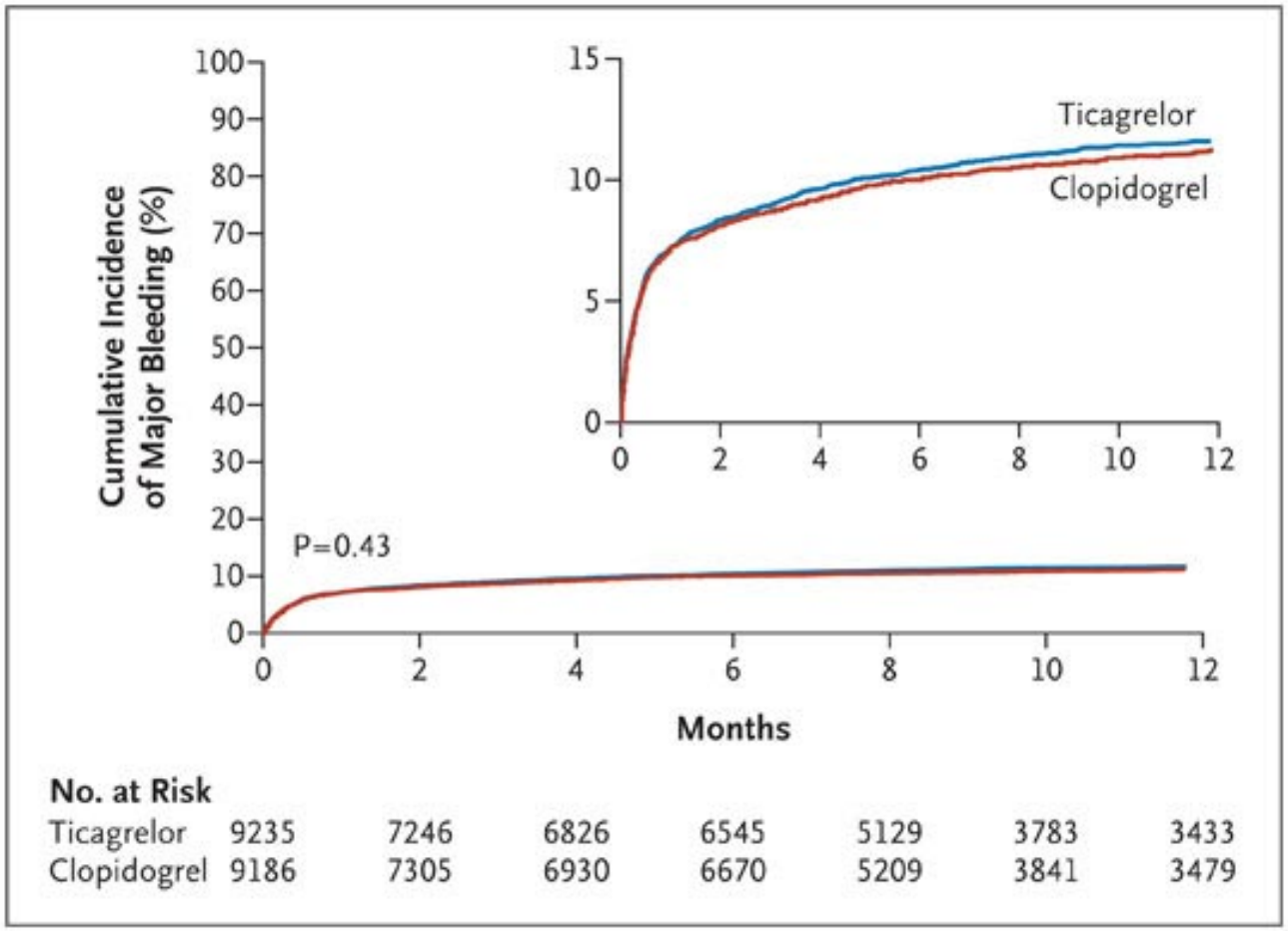
Major Efficacy End Points at 12 Months – NEJM 2009;361:1045

Ticagrelor-PLATO Trial



Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point

Ticagrelor-PLATO Trial



Cumulative Kaplan-Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria

Long time before professional life!

Objectives

- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

CHARISMA Study Overview

- The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial compared clopidogrel plus aspirin with aspirin alone for reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes in patients with stable cardiovascular disease or multiple cardiovascular risk factors
- There was no difference between the treatment groups in this outcome

Bhatt, D. et al. N Engl J Med 2006;354:1706-1717

Composite and Individual Primary and Secondary End Points

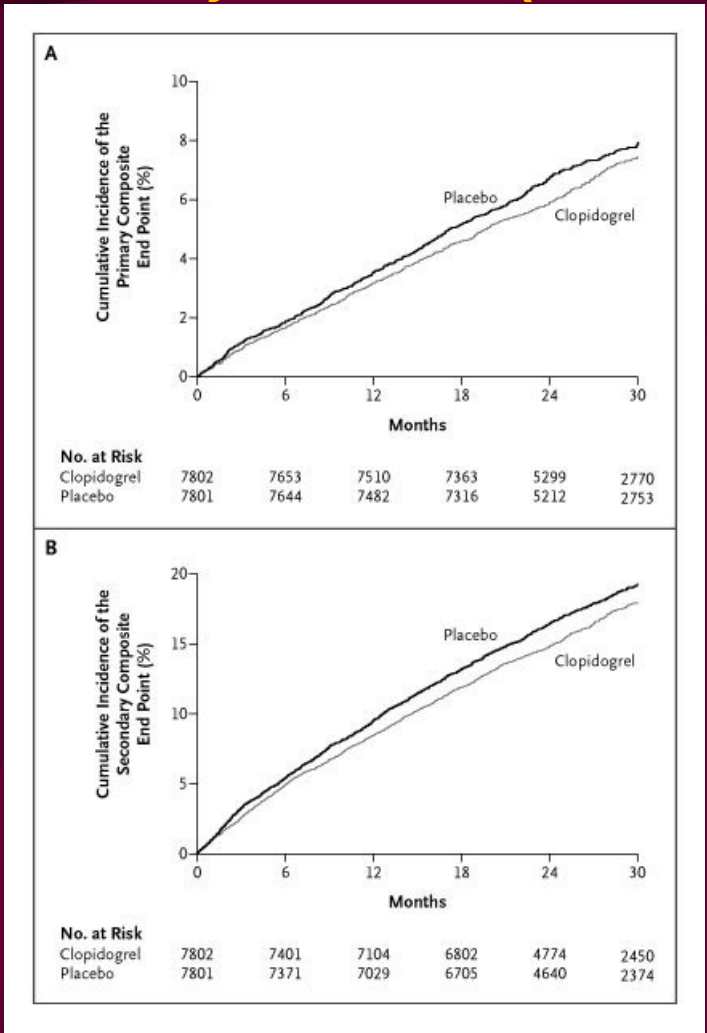
Table 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Efficacy end points				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

* CI denotes confidence interval.
† The secondary efficacy end point was the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral).

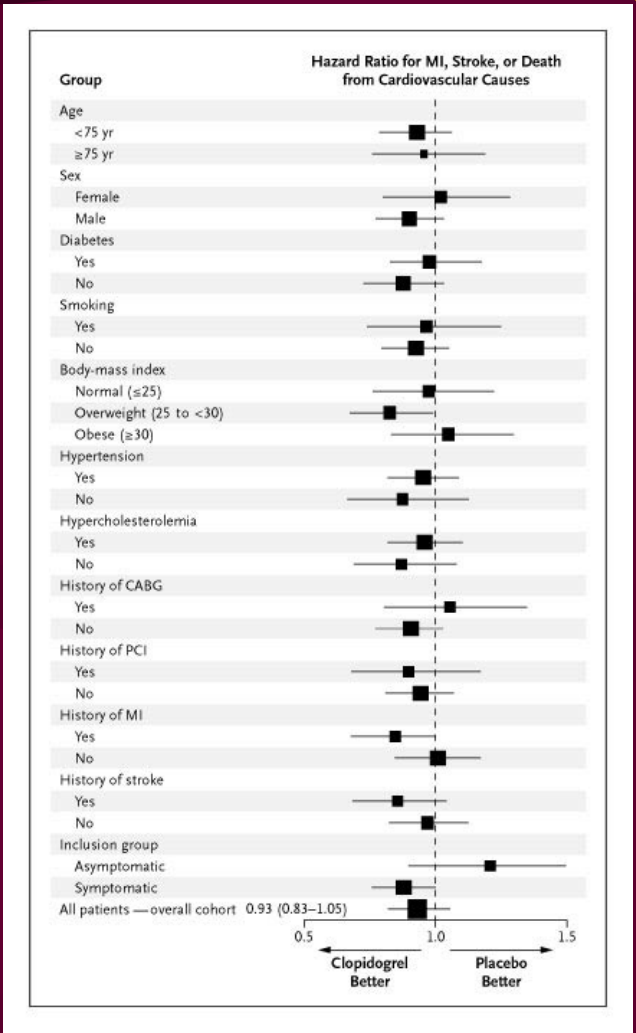
Bhatt, D. et al. N Engl J Med 2006;354:1706-1717

Cumulative Incidence of the Primary End Point (Panel A) and of the Secondary End Point (Panel B)



Bhatt, D. et al. N Engl J Med 2006;354:1706-1717

Hazard Ratios for Myocardial Infarction (MI), Stroke, or Death from Cardiovascular Causes in Each of the Subgroups Examined



Bhatt, D. et al. N Engl J Med 2006;354:1706-1717

The NEW ENGLAND JOURNAL of MEDICINE

CHARISMA Conclusion

- In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors
- Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes

DAPT and stable CAD (NORd-Pas-de-Calais)

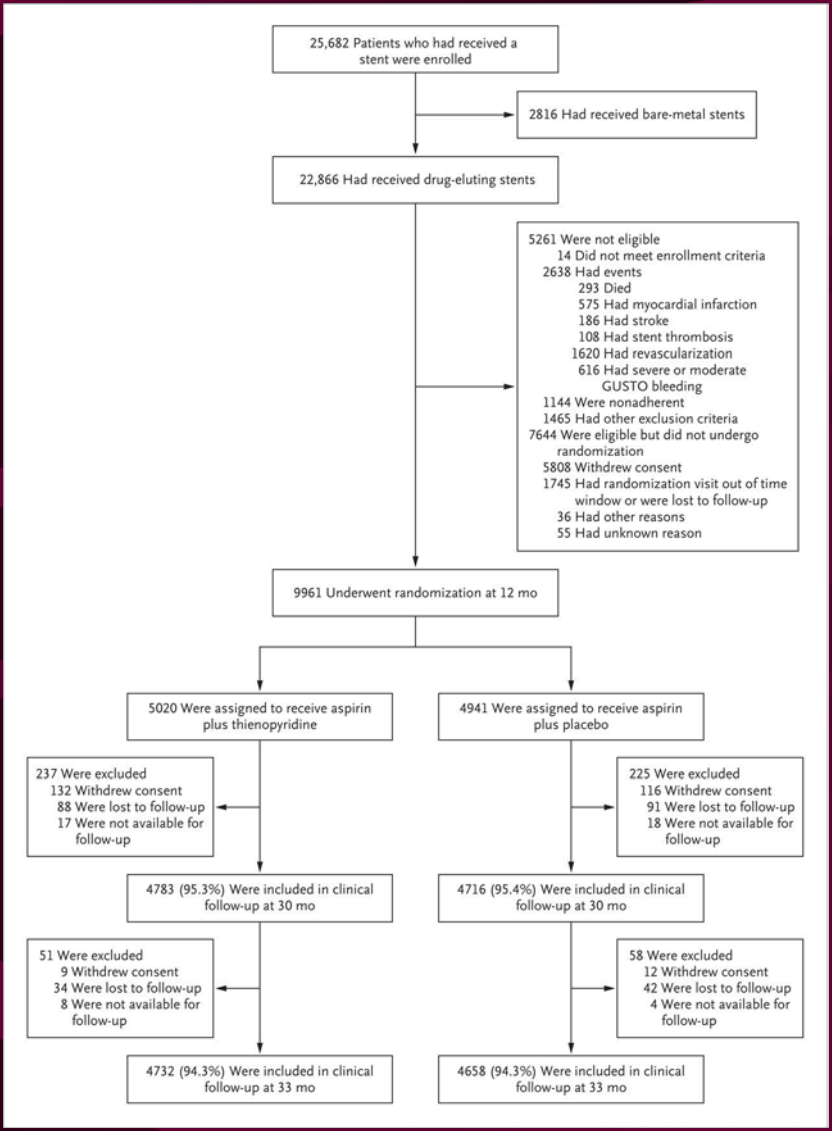
- 24% CAD patients receive DAPT
- Positive Factors
  - Angina, increased BMI, MI 1-3 years, Revasularization in the last 3 years, multivessel CAD, DES implantation, PVD
- Negative Factors
  - Increased age, prior CABG, LVEF
- Primary outcome at 2 years same including outcomes after propensity score matching (5,7% with SAPT vs 5,5% with DAPT)

Mauri L et al. N Engl J Med 2014;371:2155-2166

Objectives

- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

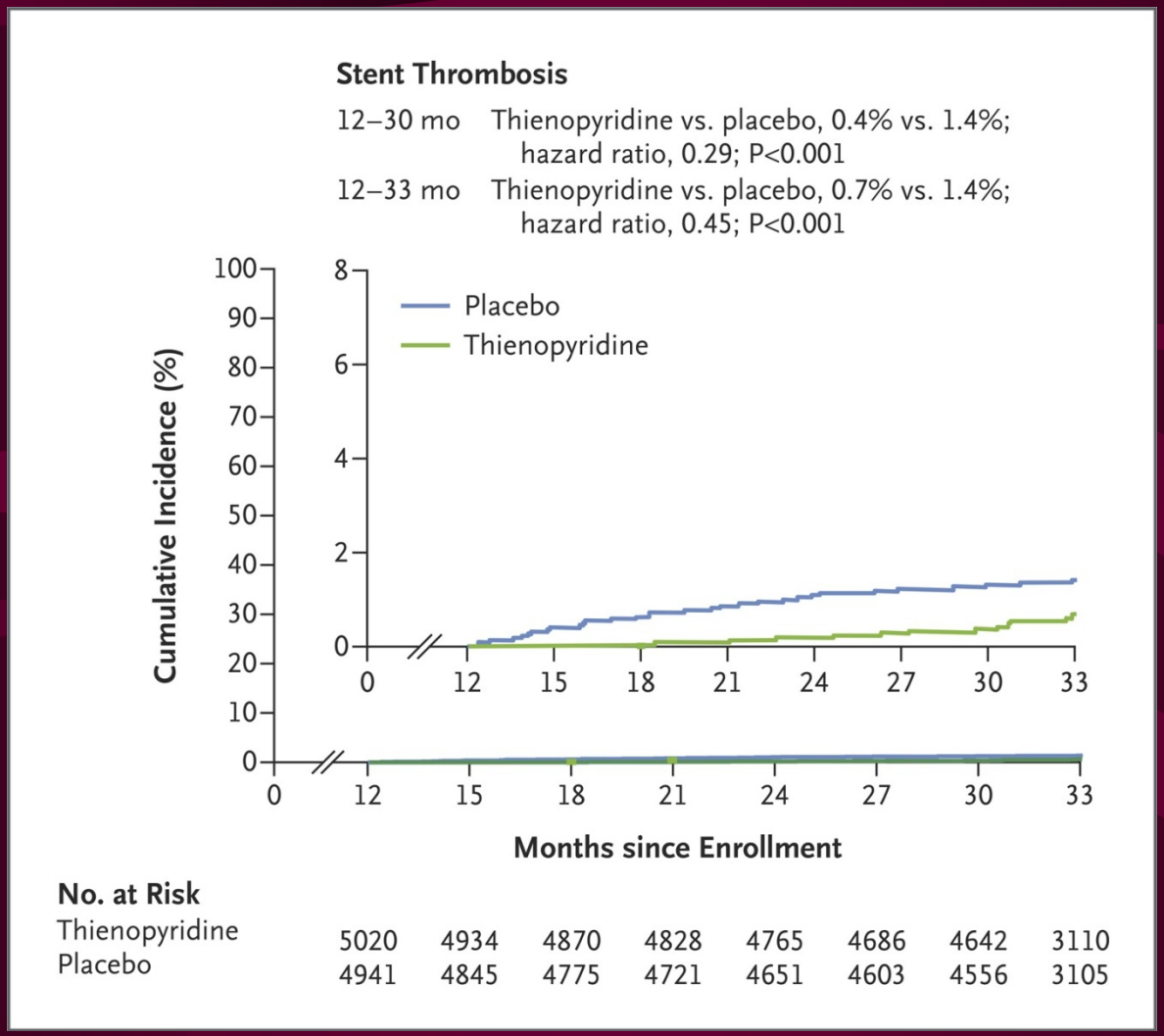
DAPT Trial: Enrollment, Randomization, and Follow-up.



- Patients who had received a drug-eluting stent and then dual antiplatelet therapy for 12 months were randomly assigned to 18 more months of therapy or aspirin alone.
- Continued therapy resulted in lower rates of stent thrombosis and major adverse cardiovascular events but more bleeding.

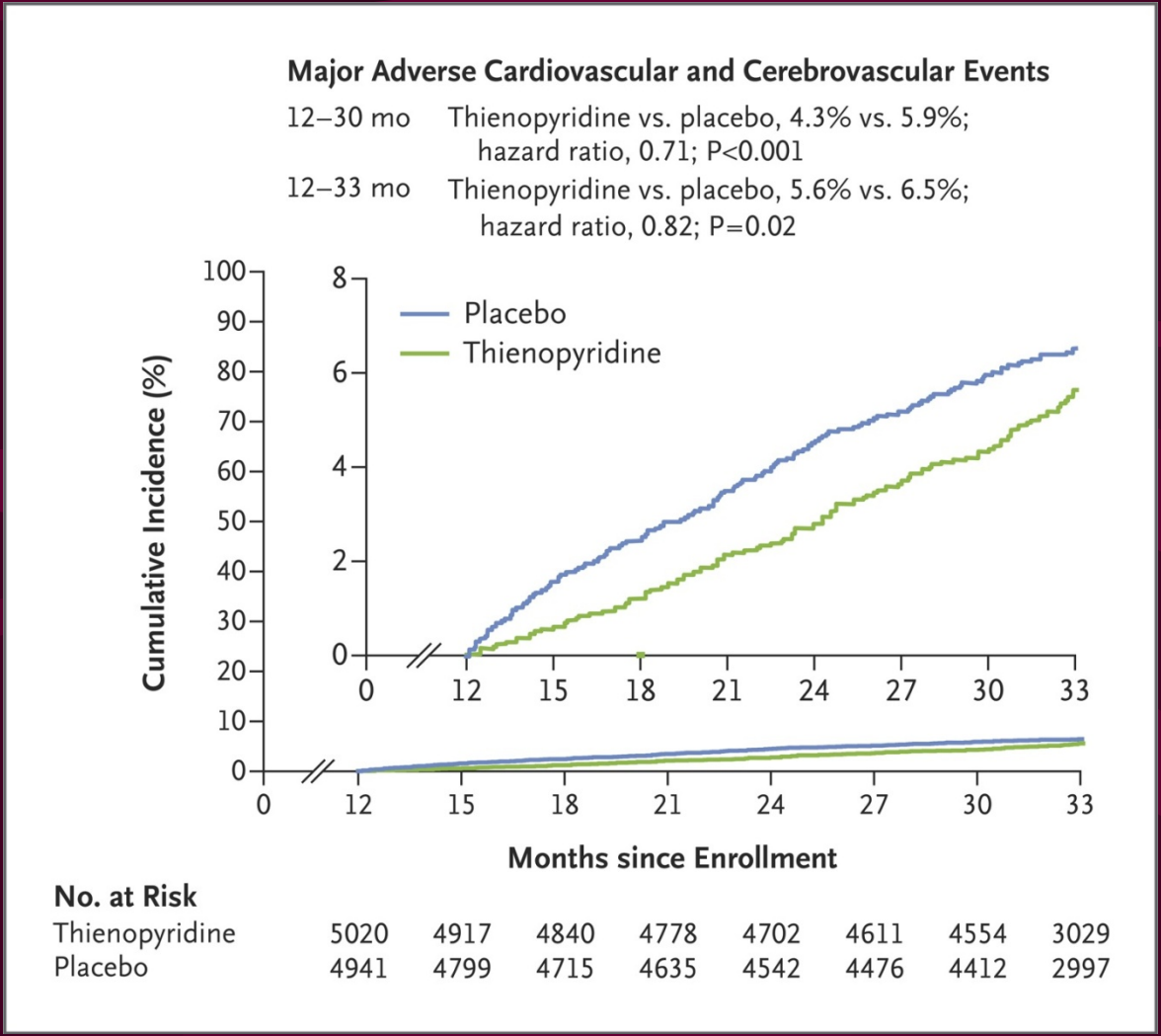
Mauri L et al. N Engl J Med 2014;371:2155-2166

Cumulative Incidence of Stent Thrombosis, According to Study Group - DAPT Trial



Mauri L et al. N Engl J Med 2014;371:2155-2166

Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events - DAPT Trial



Mauri L et al. N Engl J Med 2014;371:2155-2166

Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events - DAPT Trial

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N = 5020)	Placebo (N = 4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

* At 12 months after placement of a drug-eluting stent, patients were randomly assigned to receive either continued thienopyridine therapy plus aspirin or placebo plus aspirin for 18 months. Data are presented for the intention-to-treat population. The primary analysis was performed on data from the period of 12 to 30 months after enrollment, and the study coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events. Percentages are Kaplan–Meier estimates.

† The hazard ratios and P values were stratified according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. P values were calculated with the use of a log-rank test.

‡ Definite and probable stent thrombosis were determined according to the criteria of the Academic Research Consortium.

§ The end point of major adverse cardiovascular and cerebrovascular events was a composite of death, myocardial infarction, or stroke.

Mauri L et al. N Engl J Med 2014;371:2155-2166

Bleeding End Point during Month 12 to Month 30 - DAPT Trial

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

* The primary safety end point was moderate or severe bleeding as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria. The one-sided test of noninferiority (based on a noninferiority margin of 0.8%) was calculated according to the Farrington–Manning approach. Only patients who could be evaluated were included in this analysis (i.e., patients whose last contact date was ≥510 days after randomization or who had any adjudicated bleeding event at or before 540 days). Patients could have had more than one bleeding episode. The secondary analysis of bleeding, as assessed according to the criteria of the Bleeding Academic Research Consortium (BARC), is shown according to subtype in Table S5 in the Supplementary Appendix.

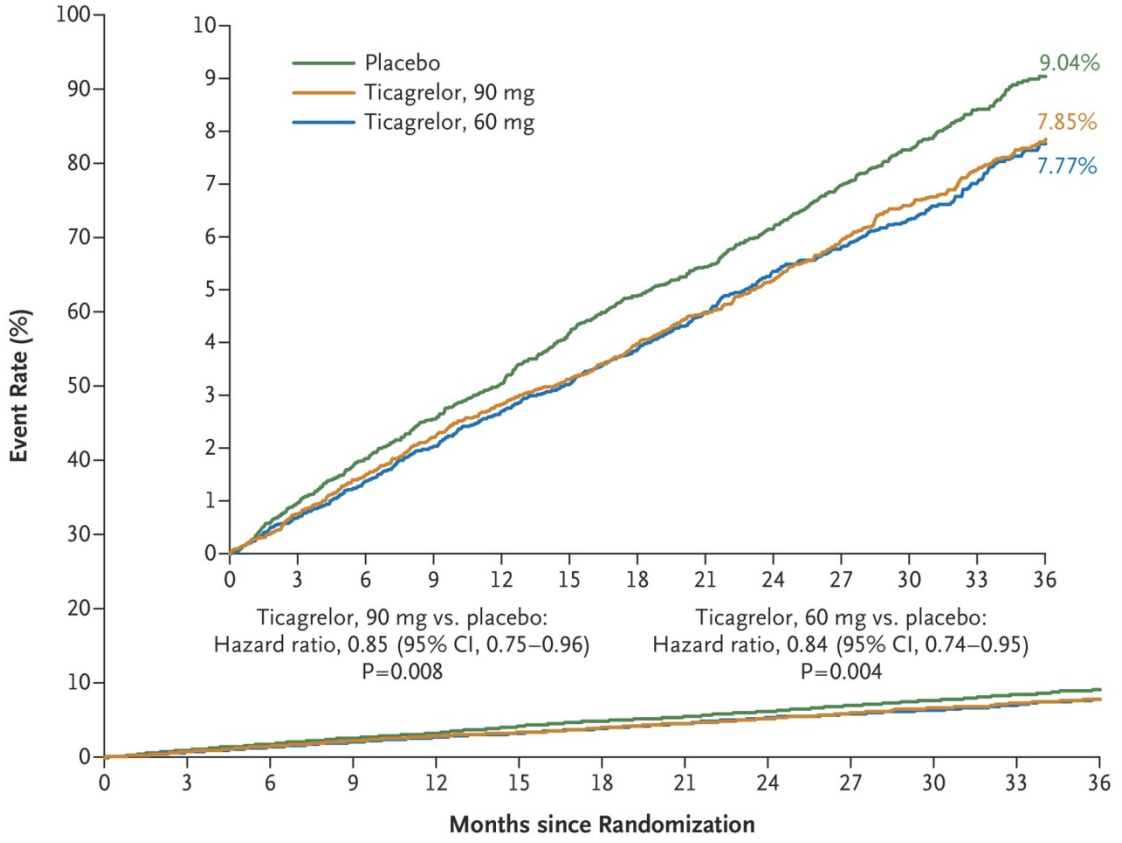
† One-sided P=0.70 for noninferiority.

Mauri L et al. N Engl J Med 2014;371:2155-2166

Conclusions – DAPT Trial

- Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

Kaplan–Meier Rates of Cardiovascular Death, Myocardial Infarction, and Stroke through 3 Years, According to Study Group PEGASUS-TIMI 54



No. at Risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Bonaca MP et al. N Engl J Med 2015;372:1791-1800

Efficacy End Points as 3-Year Kaplan–Meier Estimates-PEGASUS TIMI 54

Table 2. Efficacy End Points as 3-Year Kaplan–Meier Estimates.

End Point	Ticagrelor, 90 mg (N = 7050)	Ticagrelor, 60 mg (N = 7045)	Placebo (N = 7067)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Cardiovascular death, myocardial infarction, or stroke	493 (7.85)	487 (7.77)	578 (9.04)	0.85 (0.75–0.96)	0.008	0.84 (0.74–0.95)	0.004
Death from coronary heart disease, myocardial infarction, or stroke	438 (6.99)	445 (7.09)	535 (8.33)	0.82 (0.72–0.93)	0.002	0.83 (0.73–0.94)	0.003
Cardiovascular death or myocardial infarction	424 (6.79)	422 (6.77)	497 (7.81)	0.85 (0.75–0.97)	0.01	0.85 (0.74–0.96)	0.01
Death from coronary heart disease or myocardial infarction	350 (5.59)	360 (5.75)	429 (6.68)	0.81 (0.71–0.94)	0.004	0.84 (0.73–0.96)	0.01
Cardiovascular death	182 (2.94)	174 (2.86)	210 (3.39)	0.87 (0.71–1.06)	0.15	0.83 (0.68–1.01)	0.07
Death from coronary heart disease	97 (1.53)	106 (1.72)	132 (2.08)	0.73 (0.56–0.95)	0.02	0.80 (0.62–1.04)	0.09
Myocardial infarction	275 (4.40)	285 (4.53)	338 (5.25)	0.81 (0.69–0.95)	0.01	0.84 (0.72–0.98)	0.03
Stroke							
Any	100 (1.61)	91 (1.47)	122 (1.94)	0.82 (0.63–1.07)	0.14	0.75 (0.57–0.98)	0.03
Ischemic	88 (1.41)	78 (1.28)	103 (1.65)	0.85 (0.64–1.14)	0.28	0.76 (0.56–1.02)	0.06
Death from any cause	326 (5.15)	289 (4.69)	326 (5.16)	1.00 (0.86–1.16)	0.99	0.89 (0.76–1.04)	0.14

Bonaca MP et al. N Engl J Med 2015;372:1791-1800

Safety End Points as 3-Year Kaplan–Meier Estimates-PEGASUS TIMI 54

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

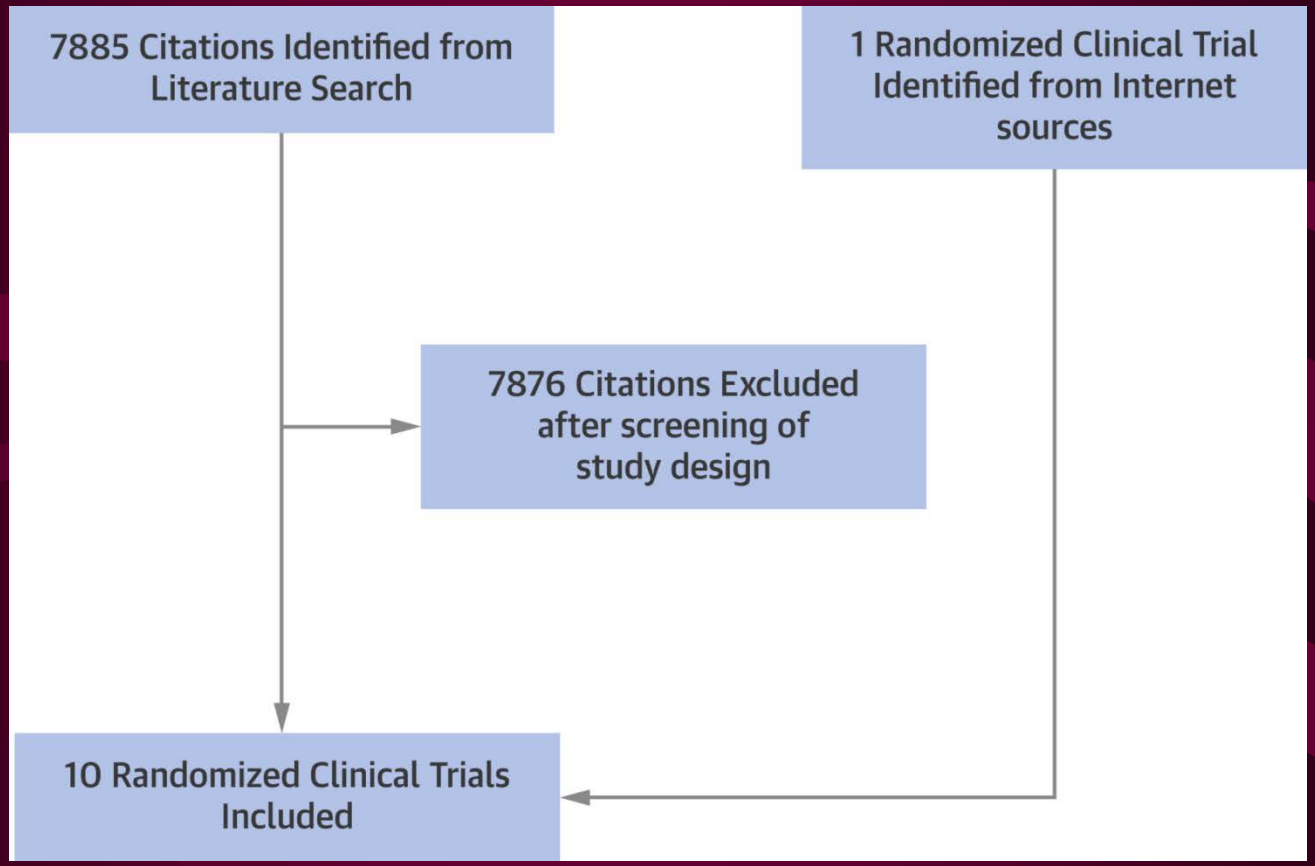
End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
Renal event	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

* TIMI denotes Thrombolysis in Myocardial Infarction.

Bonaca MP et al. N Engl J Med 2015;372:1791-1800

Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J Am Coll Cardiol. 2015;65(13):1298-1310. doi:10.1016/j.jacc.2015.01.039



Meta-Analysis Flow Diagram

After exclusion, 10 randomized controlled (n = 32,135) were included in the meta-analysis.

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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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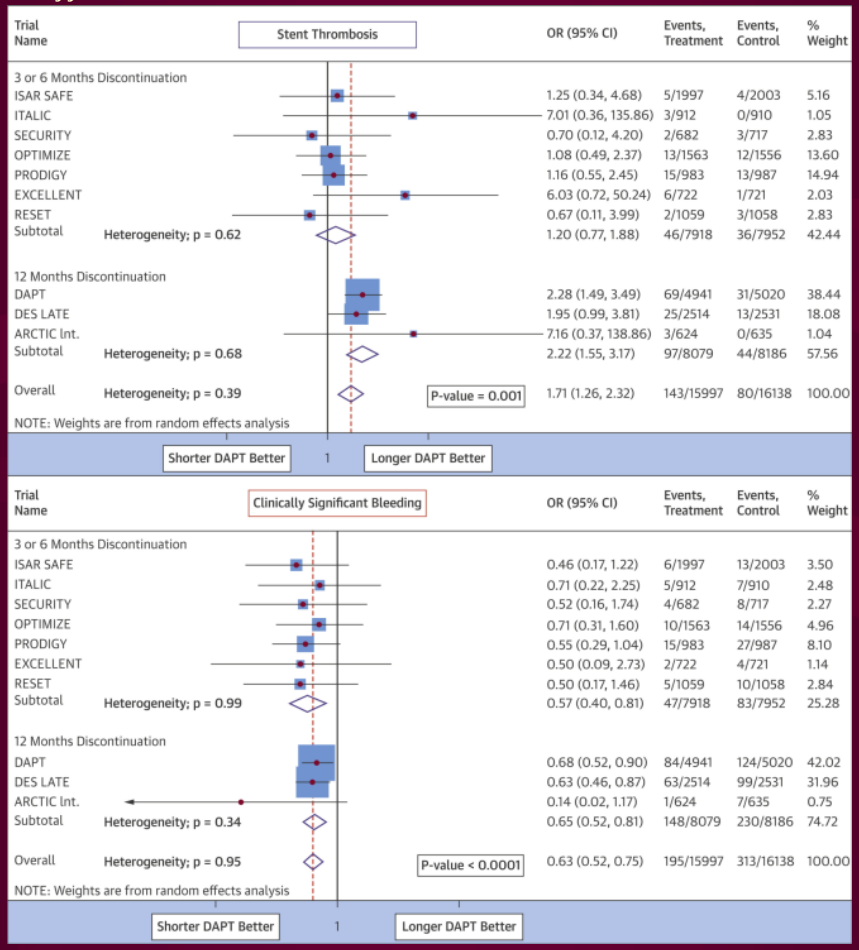

Stent Thrombosis and Clinically Significant Bleeding in Randomized Clinical Trials

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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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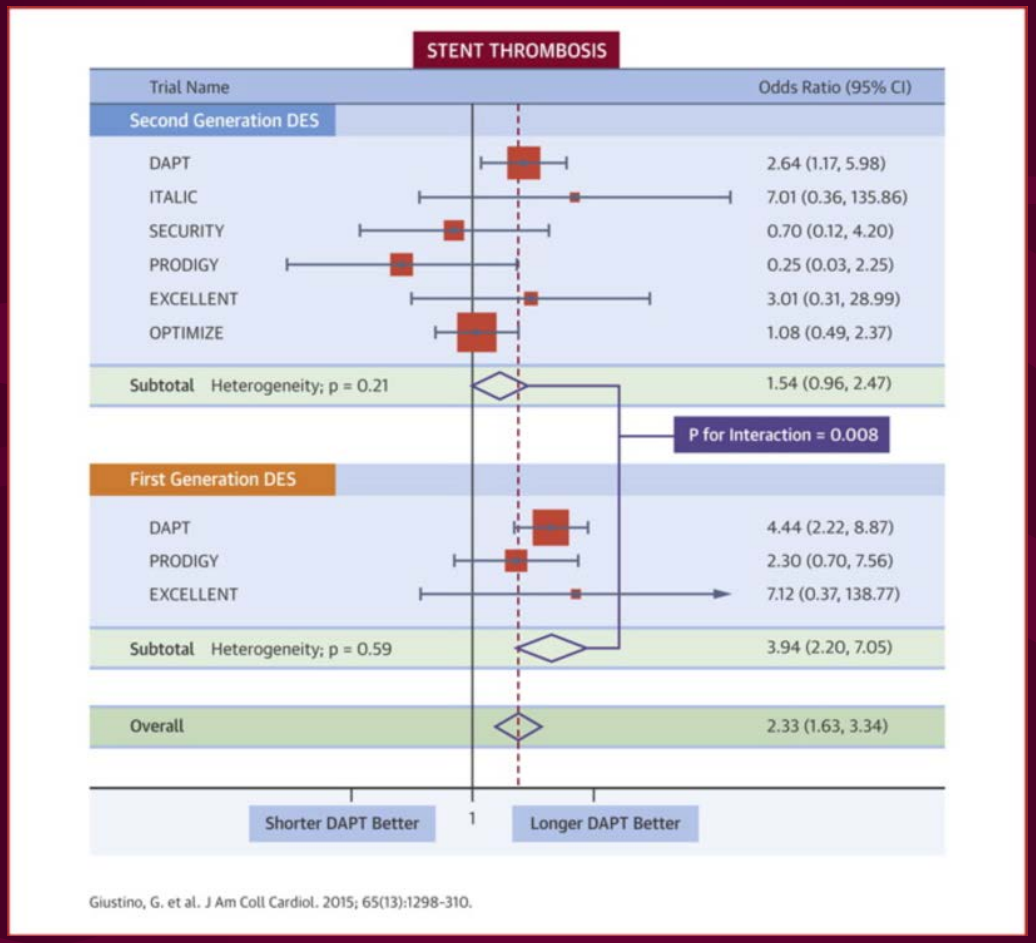

Stent Thrombosis With First- and Second-Generation Drug-Eluting Stents

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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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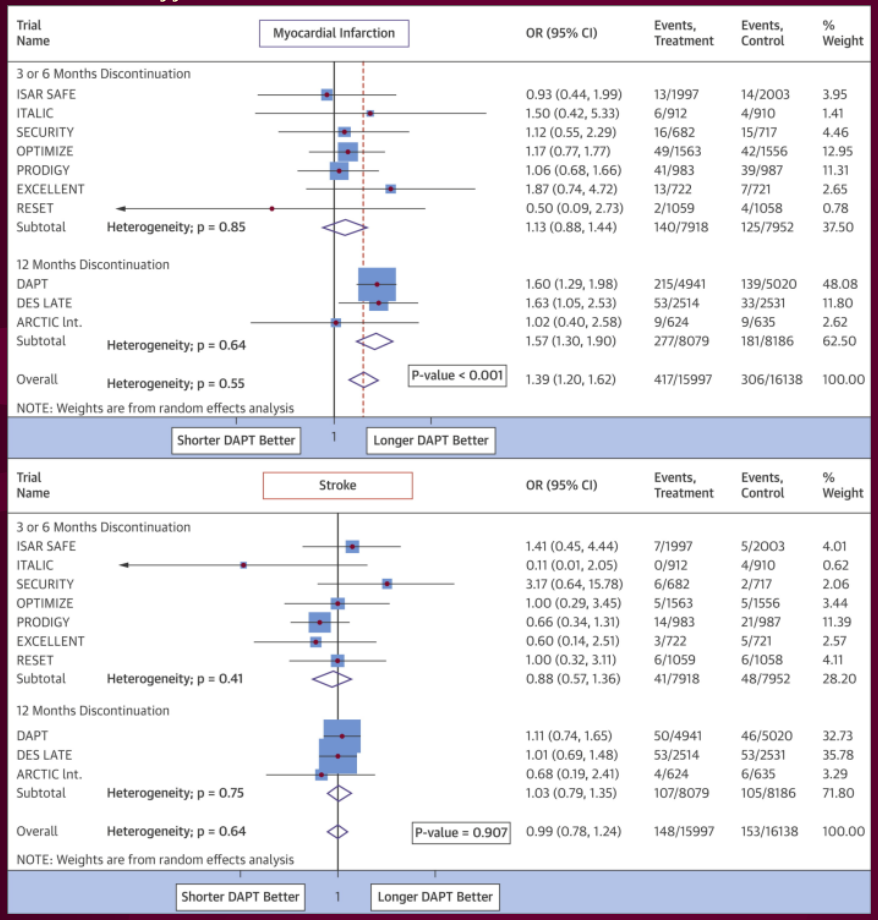

Myocardial Infarction and Stroke in Randomized Clinical Trials

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Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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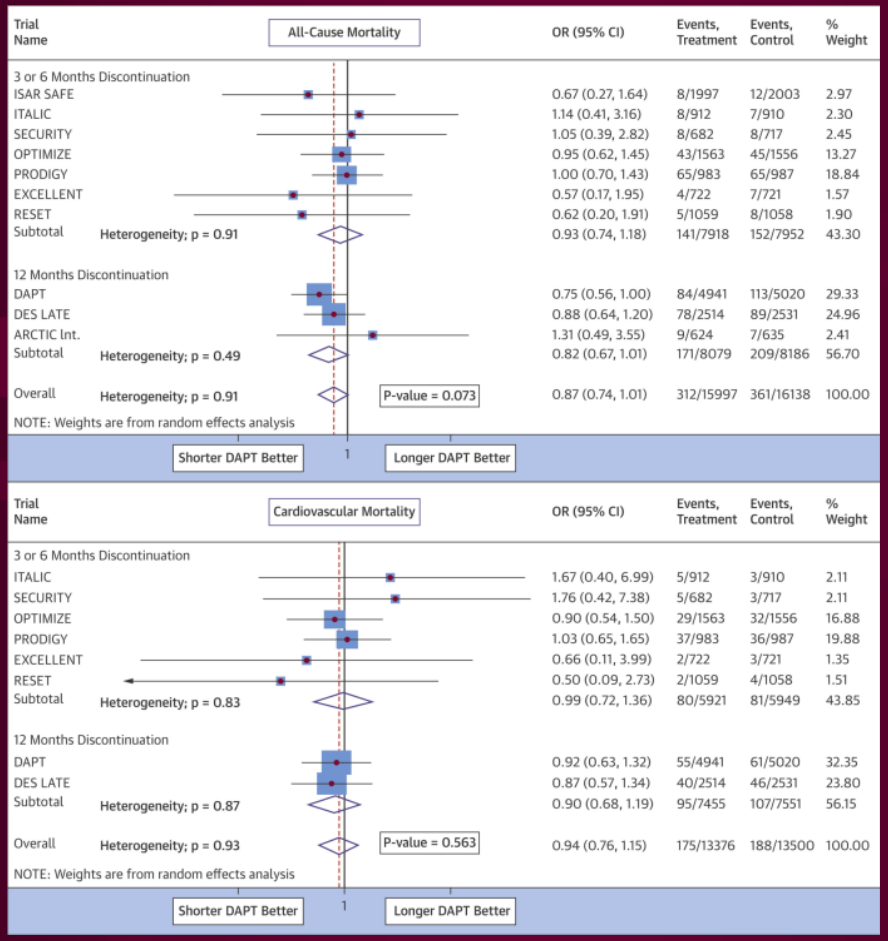

All-Cause and Cardiovascular Mortality in Randomized Clinical Trials

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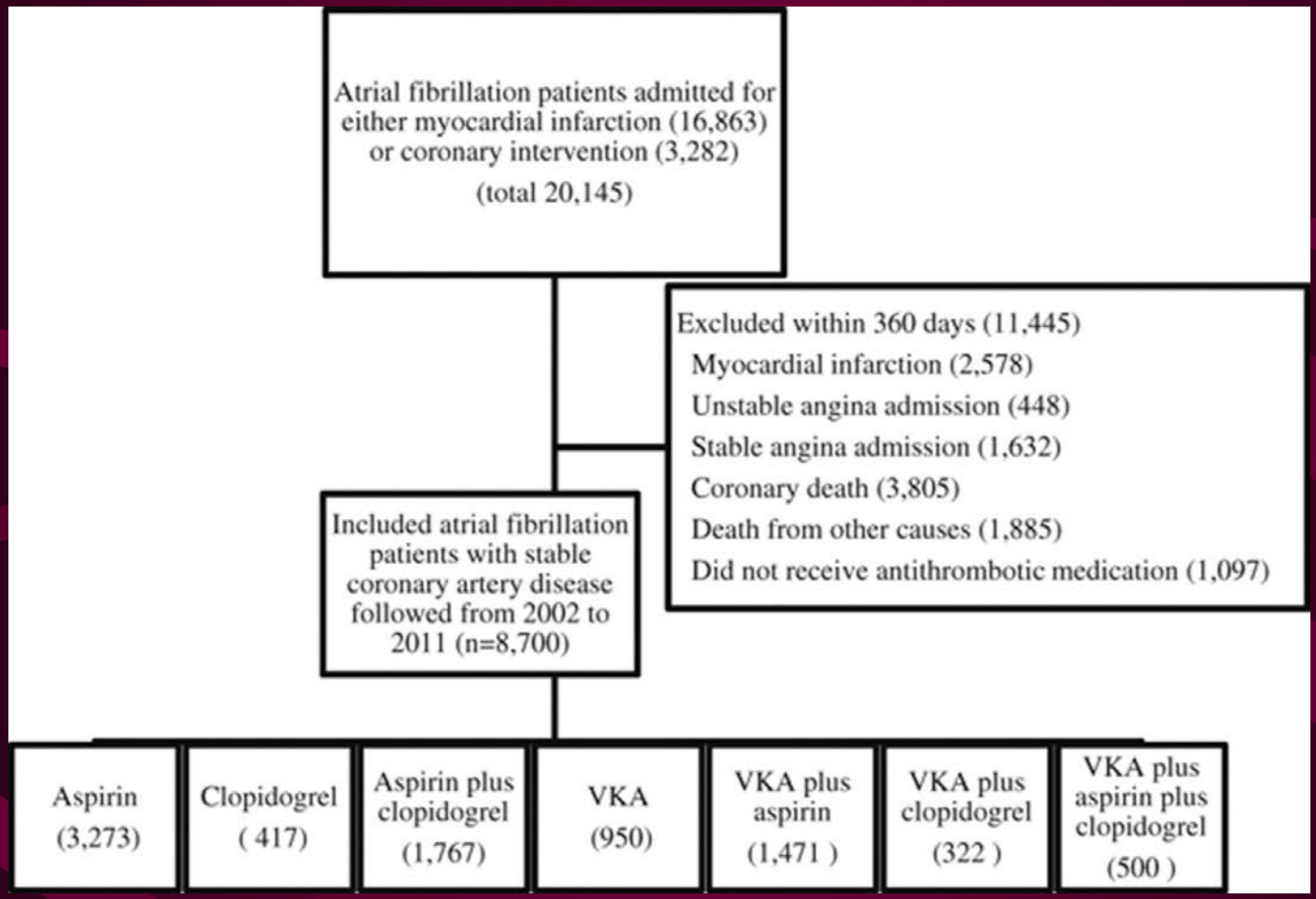
Objectives

- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

DAPT and PVD

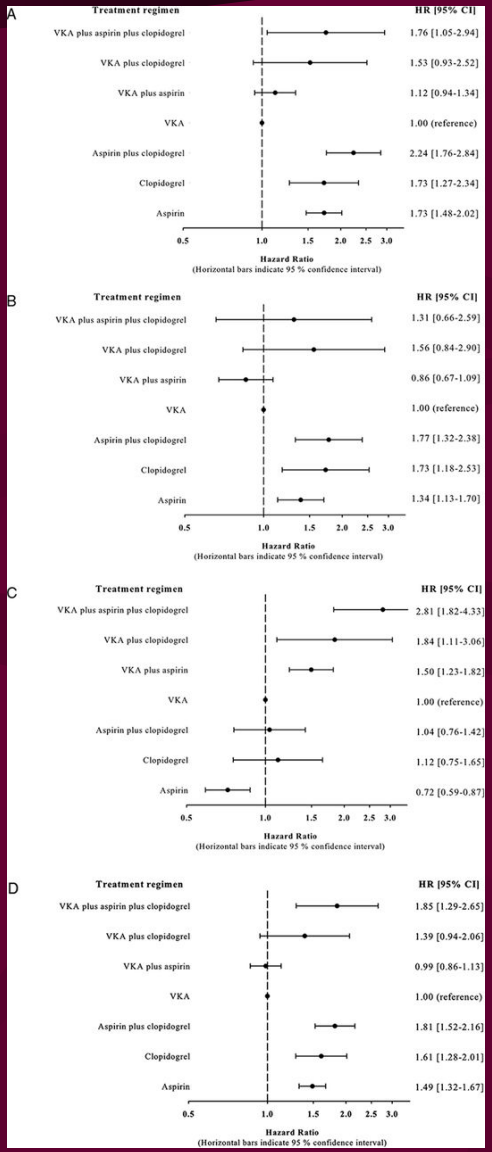
The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovasular riks (CHARISMA substudy) – Level of Evidence B / 2011

DAPT and Chronic Anticoagulation (Danish Nationwide Study)



Circulation 2014;129:1577

Risk of myocardial infarction/coronary death (A), thromboembolism (B), bleeding (C), and all-cause death (D)



DAPT and TAVI

	PARTNER	ACC/STS	CCS
Pre-procedural ASA 80 mg	y	-	-
Pre-procedural Clopidogrel 300 mg	y	-	
Procedural			
- Heparin	y	y	y
Post procedural			
- ASA 80 mg	y	y	
- Clopidogrel 75 mg	y (3 mos)	y (3-6 mos)	y (1-3 mos)
		Warfarin alone	

I indeed was in the marines!

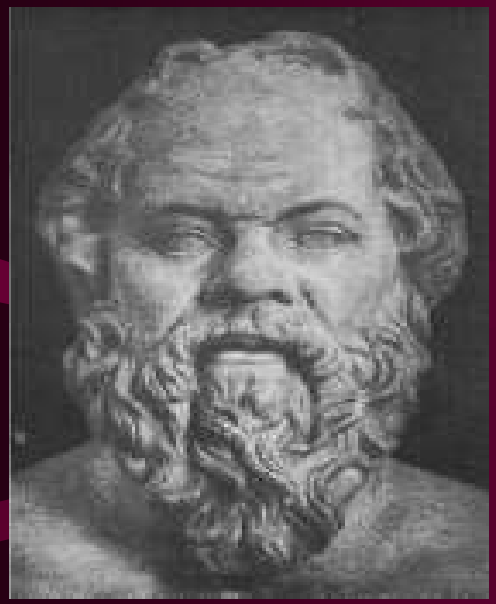
Objectives

- Platelet function and inhibition
- Current antiplatelet agents
- Double antiplatelet therapy
  - Stable CAD
  - Percutaneous coronary interventions
  - Peripheral vascular disease
  - Other subsets
- Key Notes

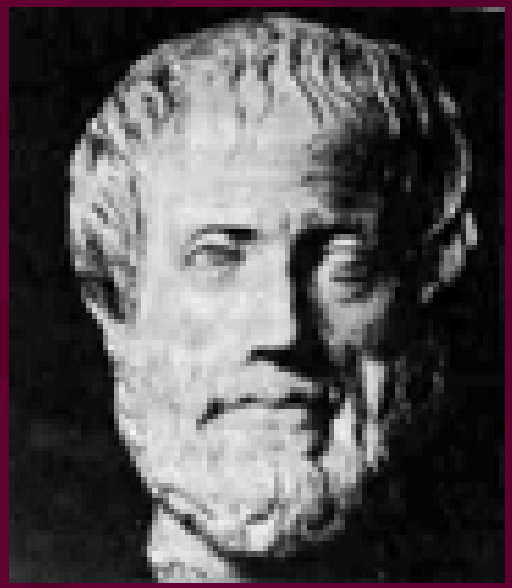
Conclusions

- Platelet inhibition is important in reducing cardiovascular risk
- All patients who undergo PCI with DES, should receive double antiplatelet therapy (DAPT - combination of Aspirin and P2Y12 receptor blocker) for 12 months (6 months ESC guidelines)
- Acute coronary syndrome, complex PCI, prior stent thrombosis, DM patients should probably receive DAPT for at least 12 months
- For patients who have tolerated therapy there are data to support treatment for additional 18 months
- Patient ischemic-bleeding to be encountered when consider DAPT in other subsets

The struggle for evidence...



Socrates (469-399 BC)

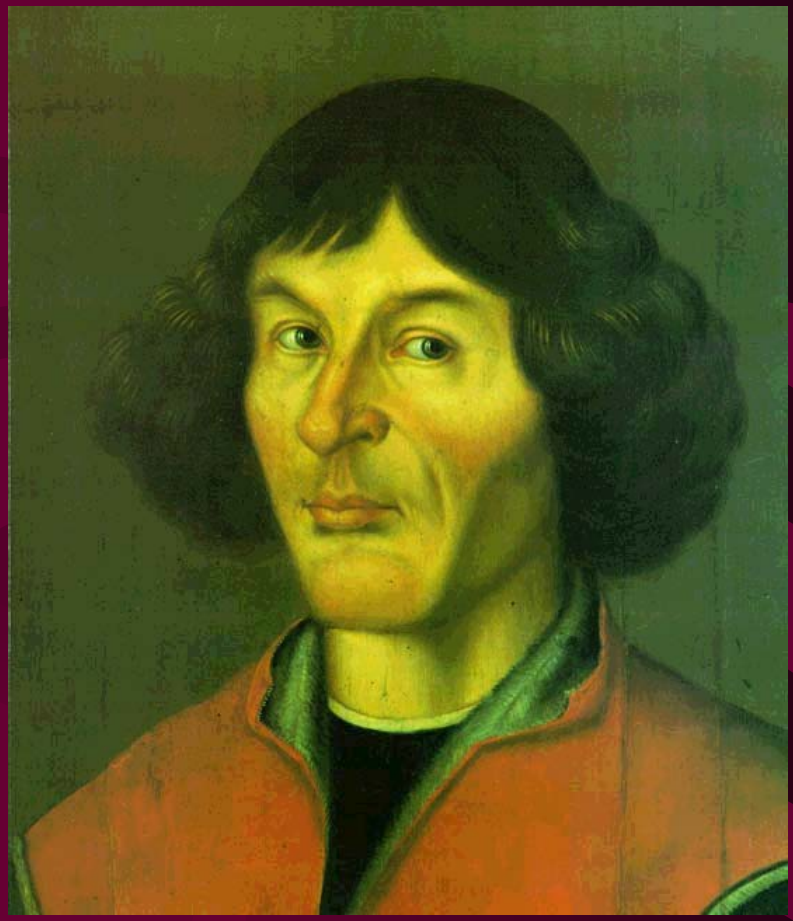


Aristotle (384-322 BC)

Plato (428-347 BC)

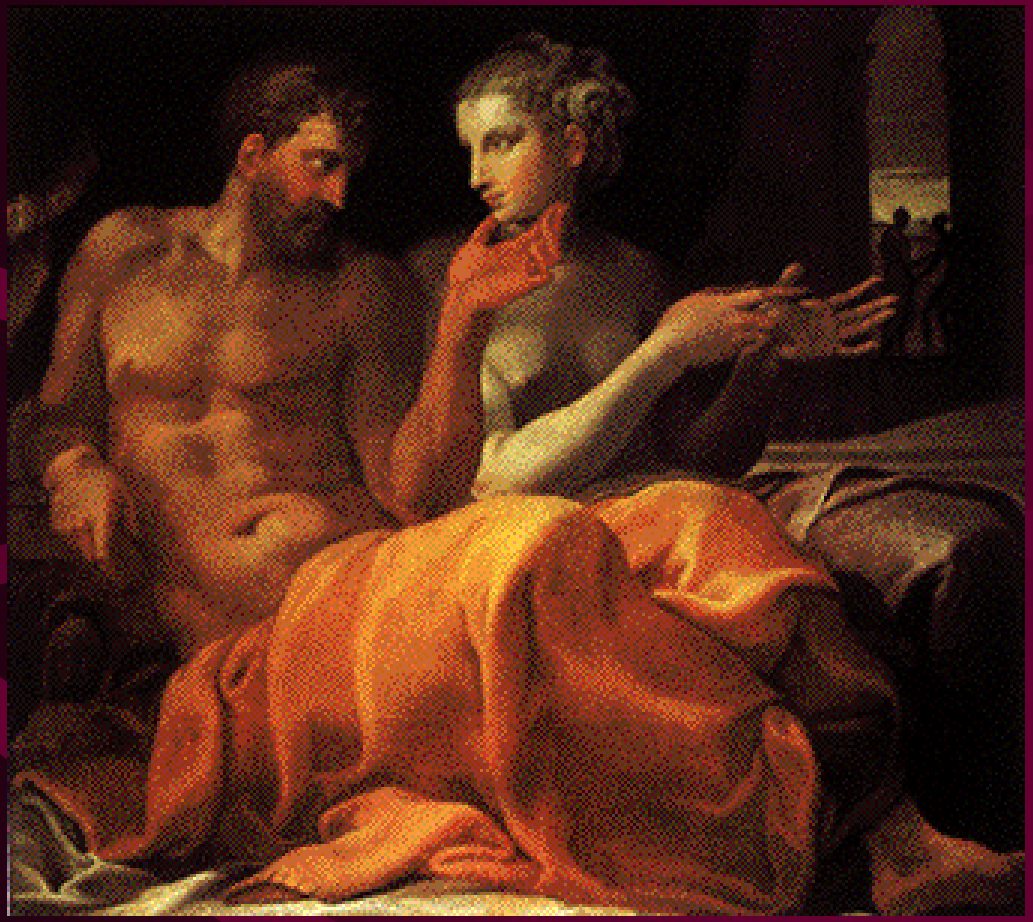
The persistence in evidence...

G. Galilei (1564-1642 AC)



N. Copernicus (1473-1543 AC)

The journey to evidence...



Odysseus and Penelope.

"When you sail for Ithaca

wish that your trip be long,

full of adventures,

full of knowledge..."

K. P. Kavafis (1863-1933)

Acknowledgements

Thank you so much…