

Faut-il bloquer les récepteurs plaquettaires à l' ADP avant
une angioplastie primaire en phase aiguë d' infarctus ?

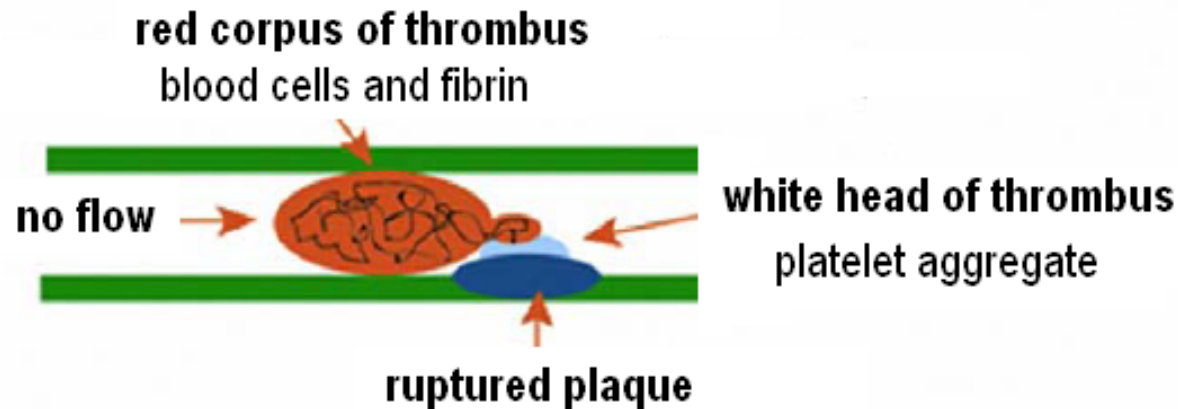


Docteur Pierre Meyer
Institut Arnault Tzanck
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France

APPAC 2012

Results from clinical trials on ST-elevation myocardial infarction in a historic perspective with some pathophysiological aspects.

Otterstad JE, Brosstad F. Scand Cardiovasc J 2003;37:316-23.

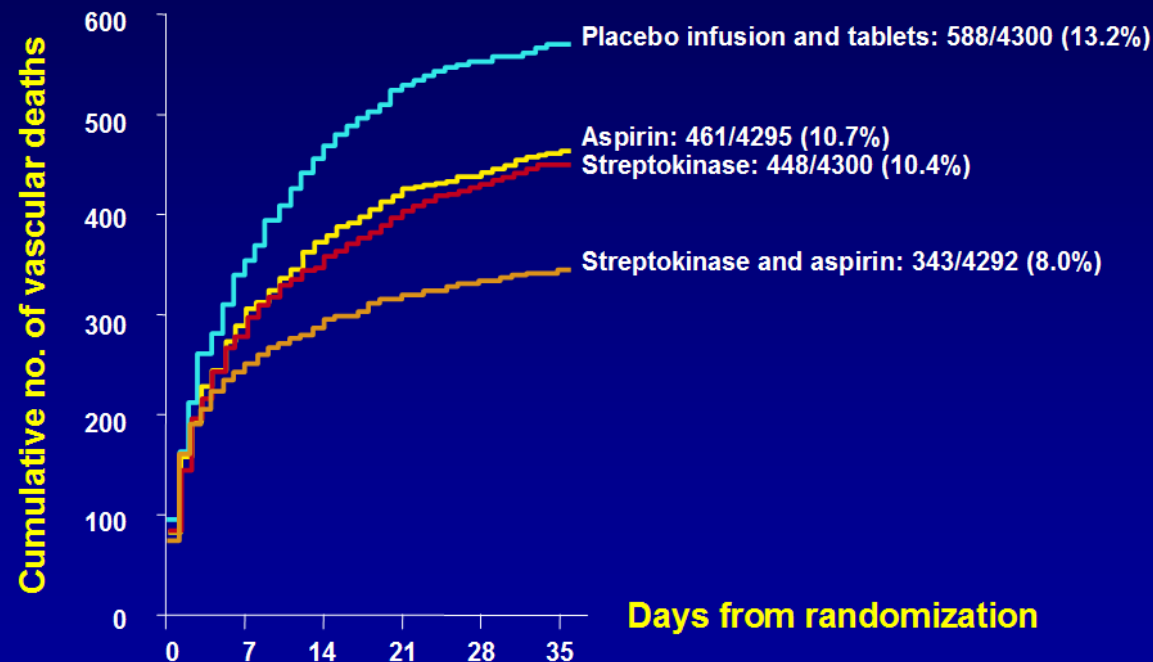


The most common underlying cause of Acute Coronary Syndrome is atherothrombosis, the unhealthy coupling of atherosclerosis with superimposed acute thrombosis.

Platelet activation plays a critical role both in spontaneous coronary artery thrombosis due to atherosclerotic plaque rupture and in thrombotic complications following percutaneous coronary intervention.

L'étude ISIS II a définitivement démontré le bénéfice vital de l'aspirine administrée en phase aiguë d'infarctus, aussi intense que celui de la recanalisation par streptokinase et synergique lorsque les deux thérapeutiques sont couplées

Randomized, placebo-controlled trial in 17,187 STEMI patients comparing streptokinase vs. 1-month aspirin vs. both active treatments vs. neither

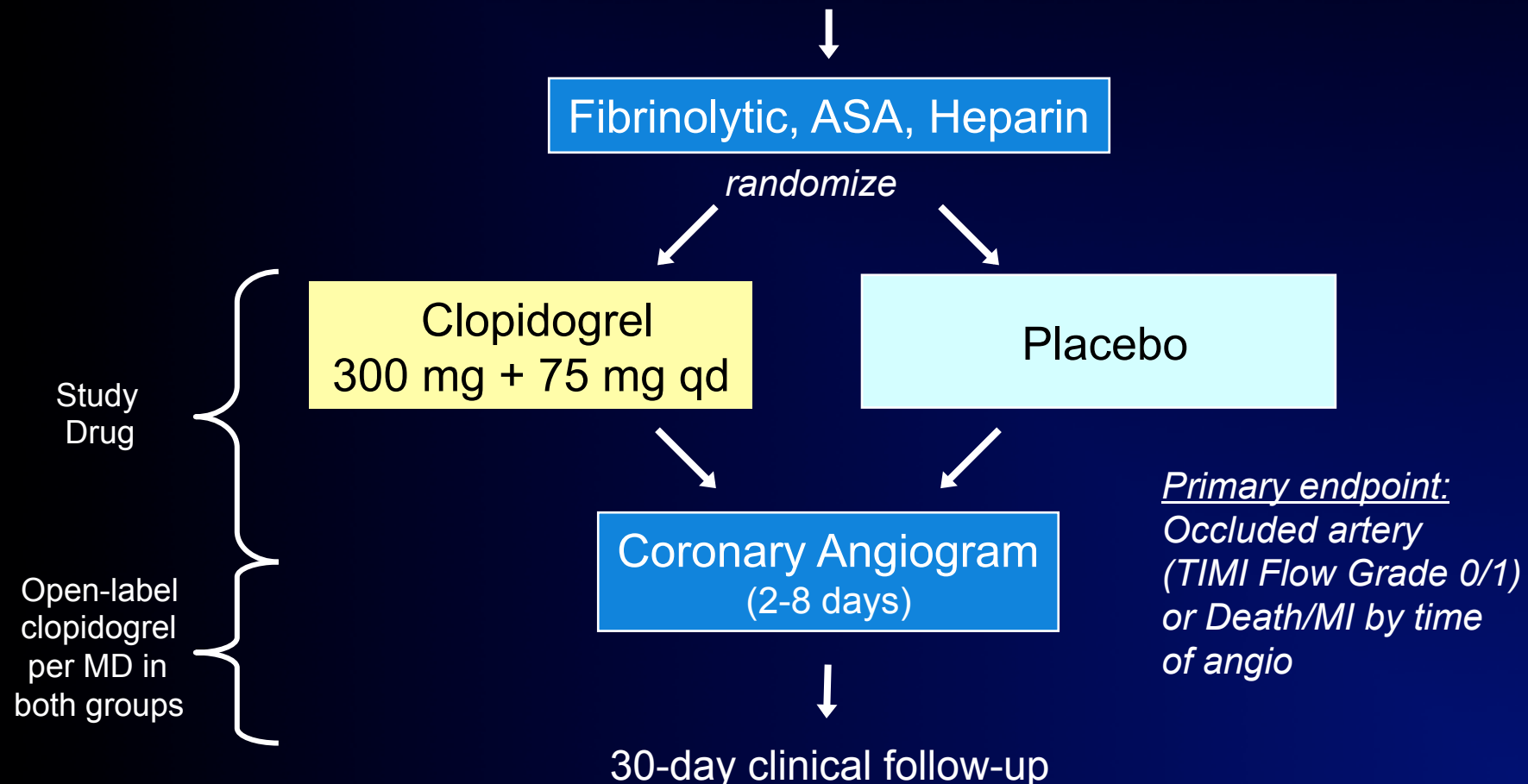


ISIS-2 Collaborative Group. Lancet 1988;2:349-60



Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation.
Sabatine MS et al. *N Engl J Med.* 2005;352:1179-1189.

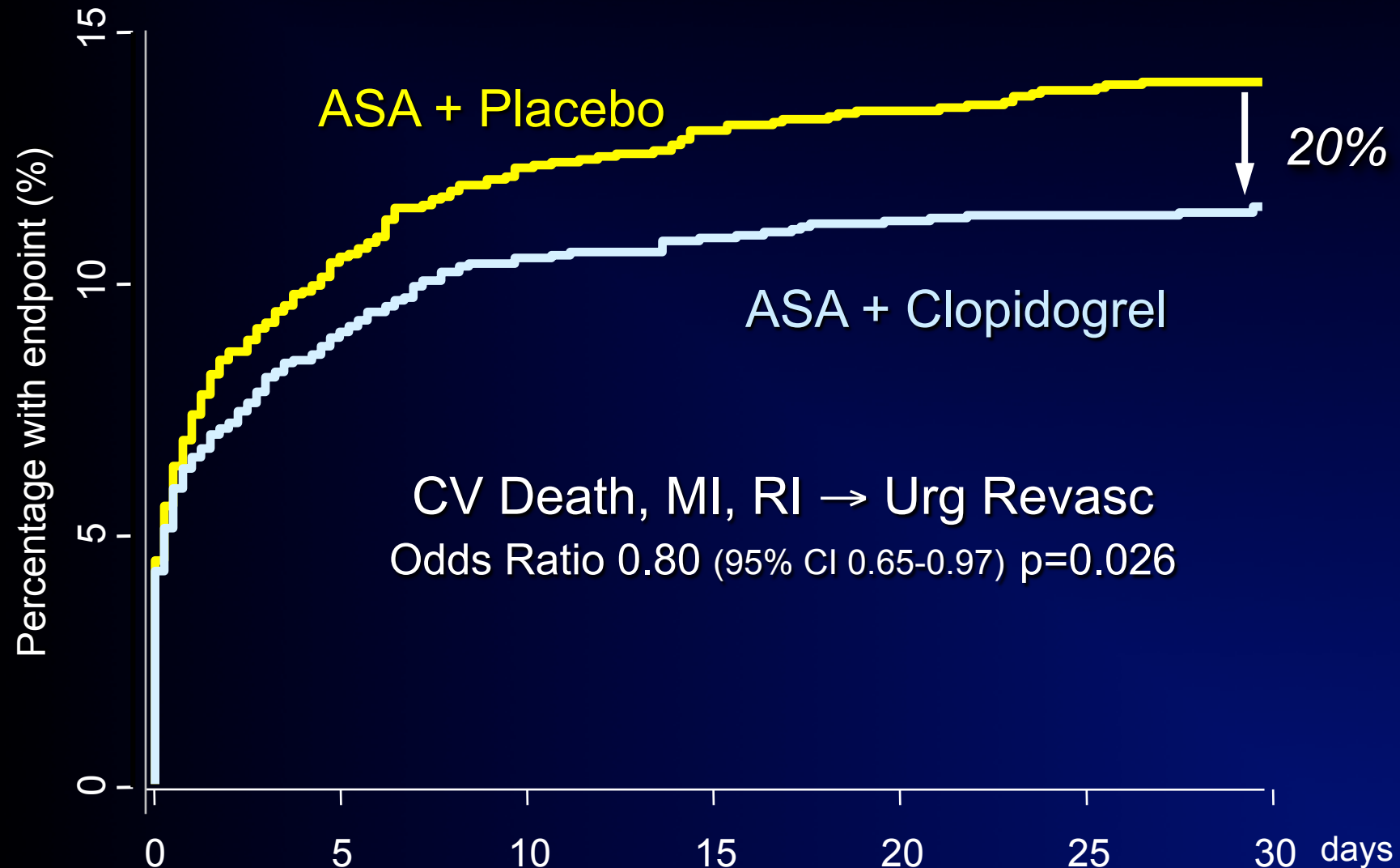
Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours





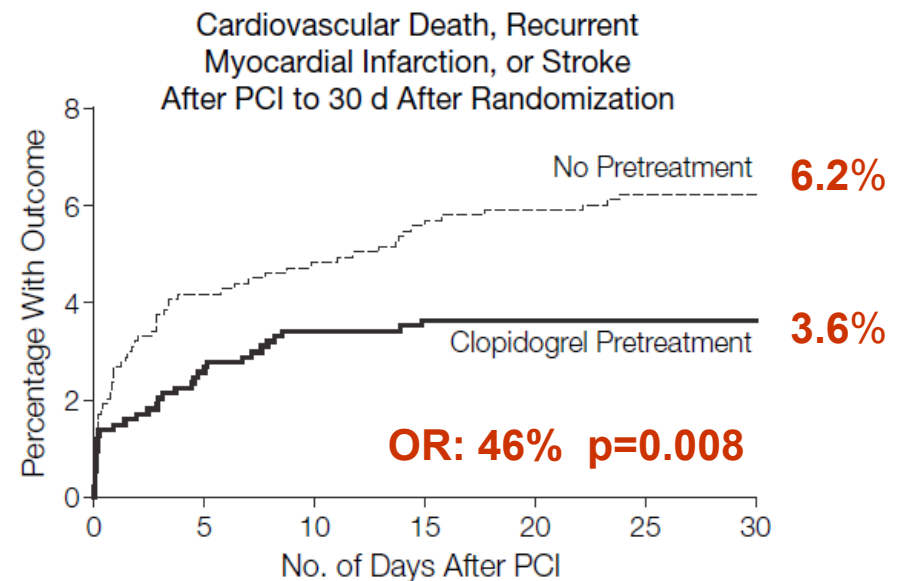
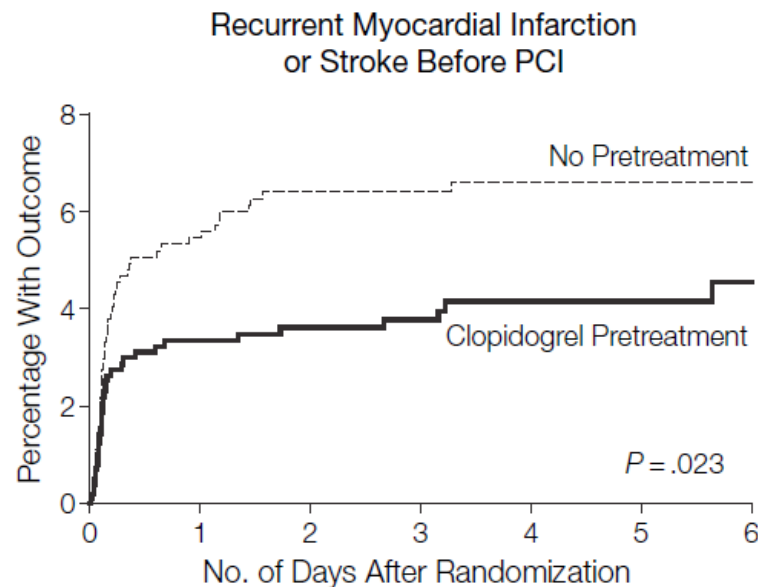
Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation.

Sabatine MS et al. *N Engl J Med.* 2005;352:1179-89.



Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics : the PCI-CLARITY study (1863 patients)

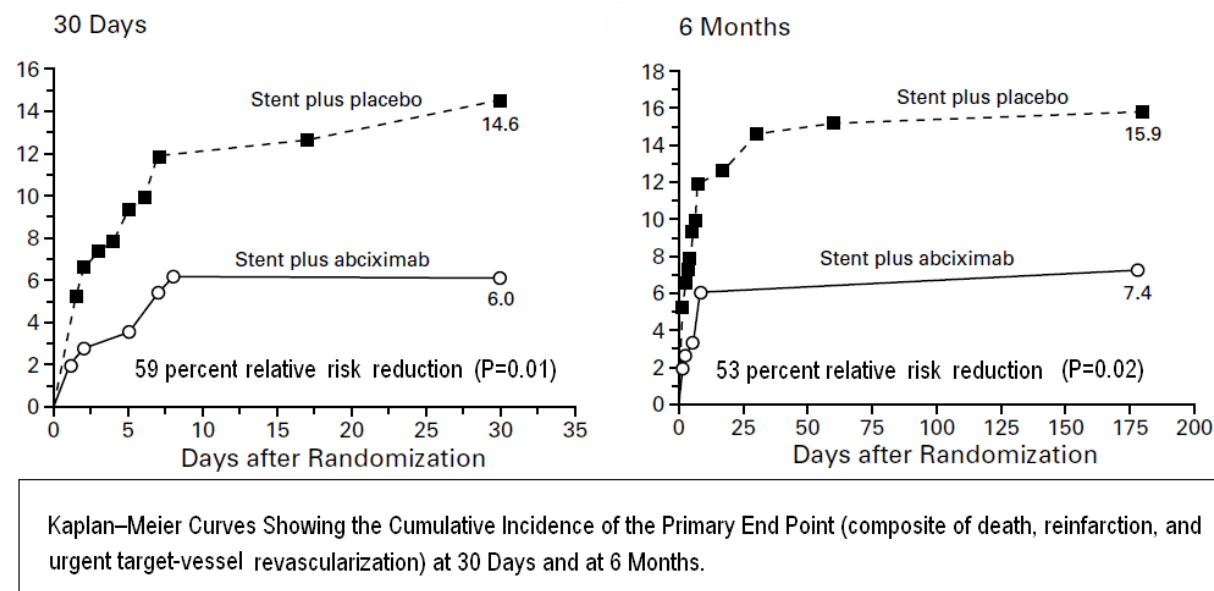
Sabatine MS, Cannon CP, Gibson CM, et al. JAMA 2005;294:1224-32.



Conclusions Clopidogrel pretreatment significantly reduces the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding.

ADMIRAL. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction.

Montalescot G, Barragan P, Wittenberg O, et al. N Engl J Med 2001;344:1895-903.

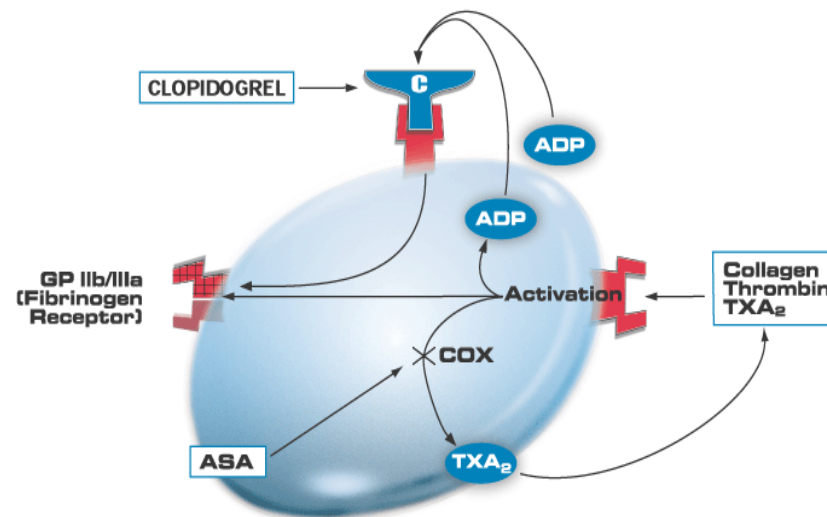


Abciximab vs placebo administration before stenting was associated with fewer occurrences of a composite primary end point of death, reinfarction, or urgent revascularization at 30 days (6.0% vs 14.6%) in 300 patients with AMI who underwent coronary angioplasty (p=0.01)

ST-elevation myocardial infarction: the role of adjunctive antiplatelet therapy[☆]

William E. Boden , James Hoekstra , Chadwick D. Miller

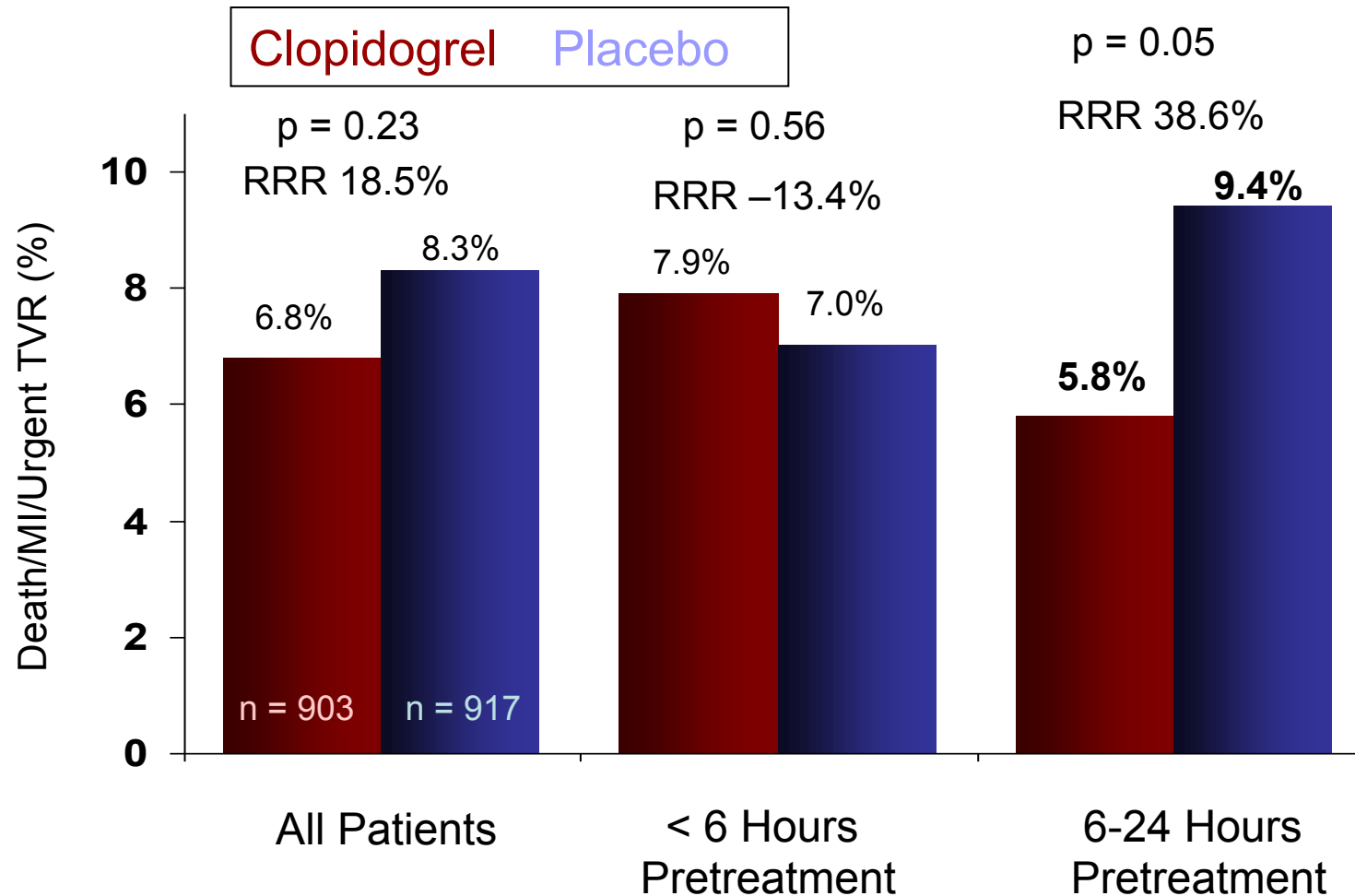
The
American Journal of
Emergency Medicine



Platelet inhibition represents an important target of treatment beyond pure mechanical intervention because patients with STEMI, in the context of high thrombotic and inflammatory activation, are at higher risk of ischemic events and may derive the greatest benefit from more intense platelet suppression»

Une thienopyridine doit-elle pour autant être administrée le plus tôt possible, avant l'arrivée en salle de cathétérisme, lorsque le patient est orienté vers une angioplastie primaire?

CREDO : Clopidogrel Pretreatment and Death/MI/ Urgent Target Vessel Revascularization by 28 Days



Effect of *Clopidogrel* Pretreatment on Angiographic and Clinical Outcomes in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Acute Myocardial Infarction

Lev El et al. Am J Cardiol 2008;101:435–9

- prospective registry of 292 consecutive patients treated with primary PCI for STEMI from march 2003 to June 2006 at the Rabin Medical center (Israel)
 - 165 received clopidogrel before PCI (in the emergency department or coronary care unit) and 127 immediately after PCI.
- TIMI Myocardial Perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group than in the no-pretreatment group (85% vs 71%, $p = 0.01$).
- The incidence of reinfarction at 30 days was lower in the pretreatment group (0% vs 3.2%, respectively, $p = 0.04$).
- **In conclusion**, these findings support the early use of clopidogrel in patients with STEMI who are treated with primary PCI.

Impact of Thienopyridine Administration Prior to Primary Stenting in Acute Myocardial Infarction

Rabbani LE et al. J Interv Cardiol 2009;22:378–384

*We examined the database from the **prospective, multicenter, controlled CADILLAC trial** in which 1036 patients were randomized to bare metal stenting with or without abciximab to determine whether patients who received a thienopyridine prior to bare metal stenting in AMI had superior clinical outcomes.*

Per operator discretion,

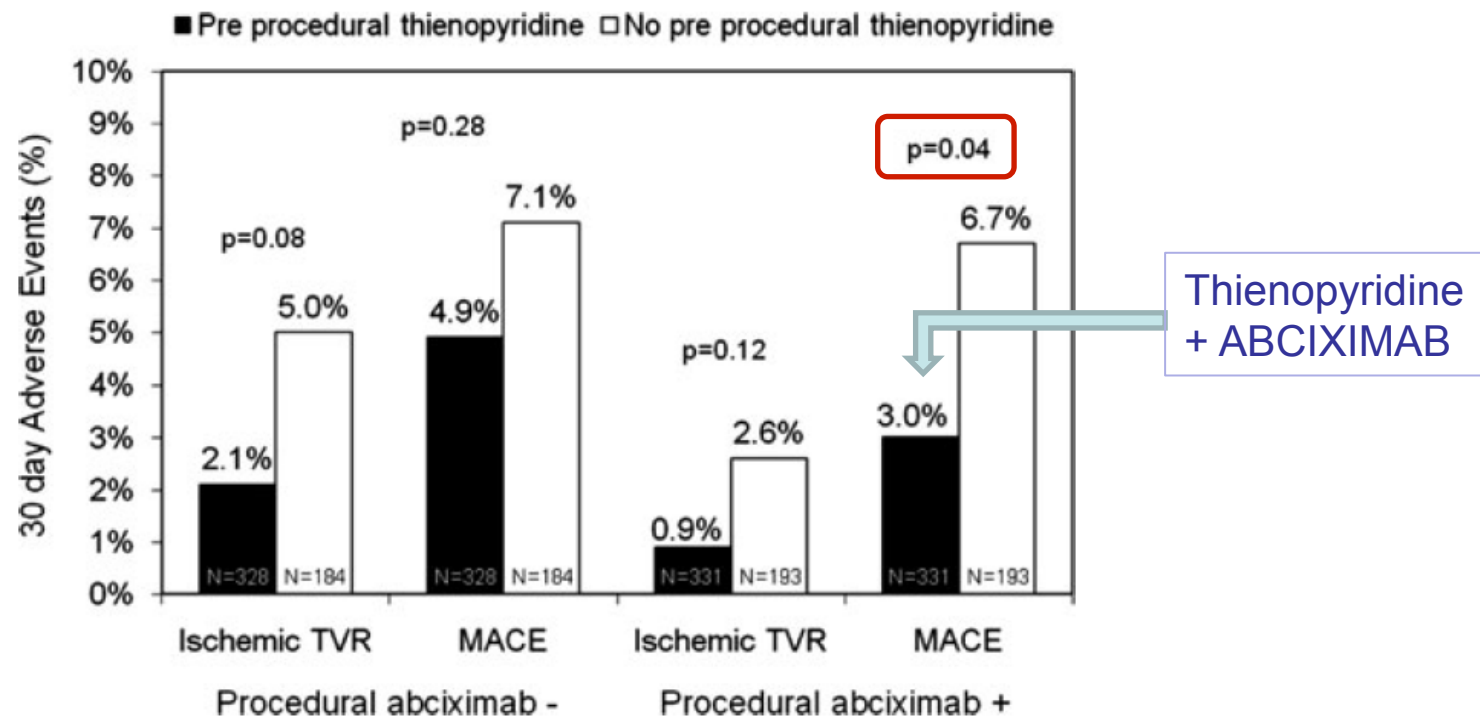
- ✓ 659 patients (63.6%; Th+) received either a **500 mg ticlopidine** loading dose (n=623) or a **300 mg clopidogrel** loading dose (n = 40), while
- ✓ 377 patients (36.4%; Th-) received no thienopyridine prior to stent implantation.

Baseline and procedural characteristics of the two groups, including abciximab use (52.5% vs 52.8%, P = 0.93) were well matched.

- ✓ **Th+ compared to Th- patients had lower rates of core lab assessed TIMI 0/1 flow post procedure (0.8% vs 2.7%, P = 0.01).**

Impact of Thienopyridine Administration Prior to Primary Stenting in Acute Myocardial Infarction

Rabbani LE et al. J Interven Cardiol 2009;22:378–384

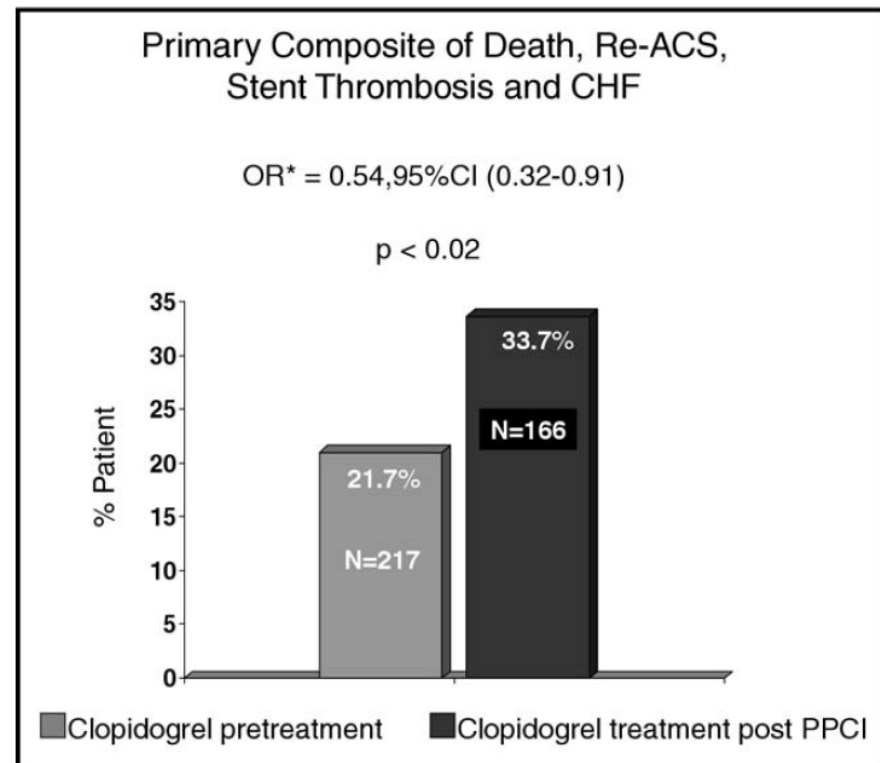


Thienopyridine pretreatment in patients with AMI undergoing primary bare metal stenting may improve angiographic and clinical outcomes at 30 days post procedure by improving postprocedure epicardial coronary flow rates and decreasing ischemic TVR and MACE.

Usefulness of Pretreatment With High-Dose Clopidogrel in Patients Undergoing Primary Angioplasty for ST-Elevation Myocardial Infarction

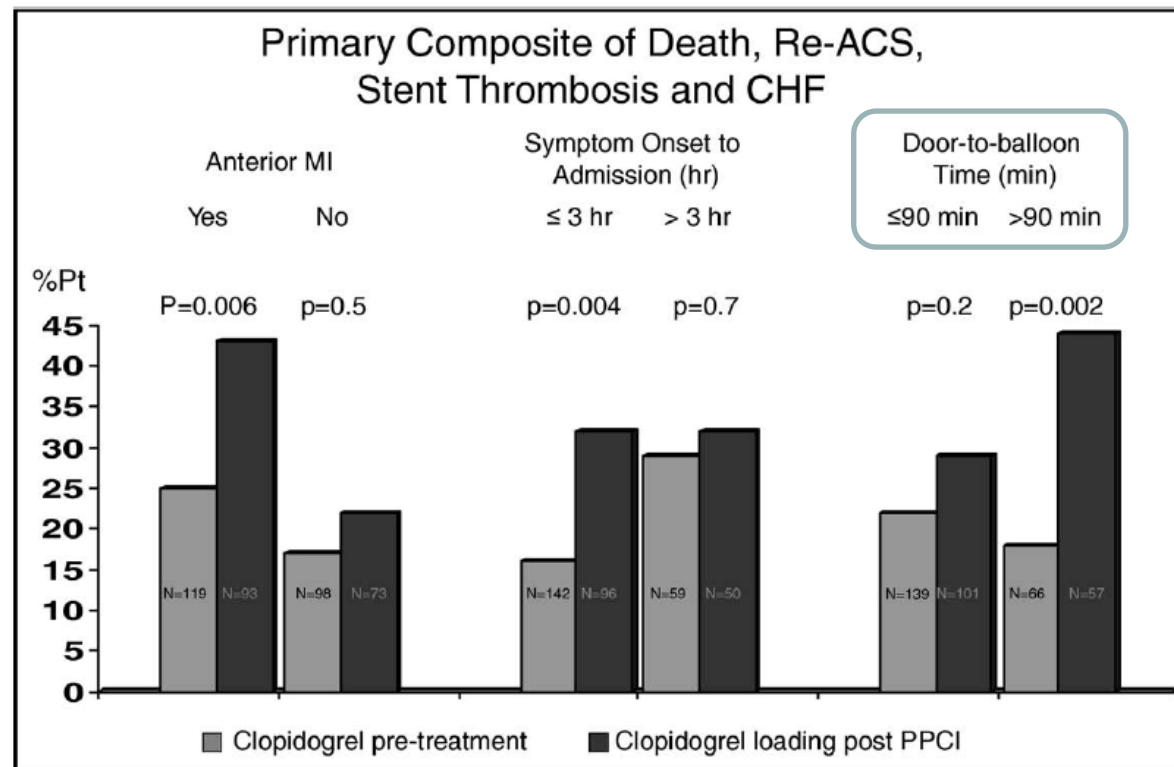
Fefer P et al. Am J Cardiol 2009;104:514 –8

- study including 383 consecutive patients with STEMI undergoing Primary PCI and prospectively followed up for a prespecified primary end point of recurrent acute coronary syndrome, stent thrombosis, congestive heart failure, and/or death at 30 days. Patients were derived from the Acute Coronary Syndrome Israeli Survey (ACSIS 2006), conducted during February and March 2006 in 25 coronary cardiac units
 - ✓ 217 (57%) received clopidogrel loading before and 166 (43%) after PPCI.
 - ✓ A similar number received low (300 mg) and high (600 mg) clopidogrel doses before and after PPCI.
 - ✓ When patients were further stratified into 4 groups according to the timing and dosage of clopidogrel loading, the incidence of the primary outcome was **16% and 27% in those receiving 600 and 300 mg before** and **28% and 39% in those receiving 600 and 300 mg after PPCI**, respectively ($p < 0.01$).



Usefulness of Pretreatment With High-Dose Clopidogrel in Patients Undergoing Primary Angioplasty for ST-Elevation Myocardial Infarction

Fefer P et al. Am J Cardiol 2009;104:514 –8



In conclusion,

- Both the timing and the dosage of clopidogrel loading are important and affect the outcome in patients with ST-elevation myocardial infarction undergoing PPCI.

Outcome Comparison of 600 and 300 mg Loading Doses of Clopidogrel in Patients Undergoing Primary PCI for STEMI.

Results From the ARMYDA-6 MI Randomized Study

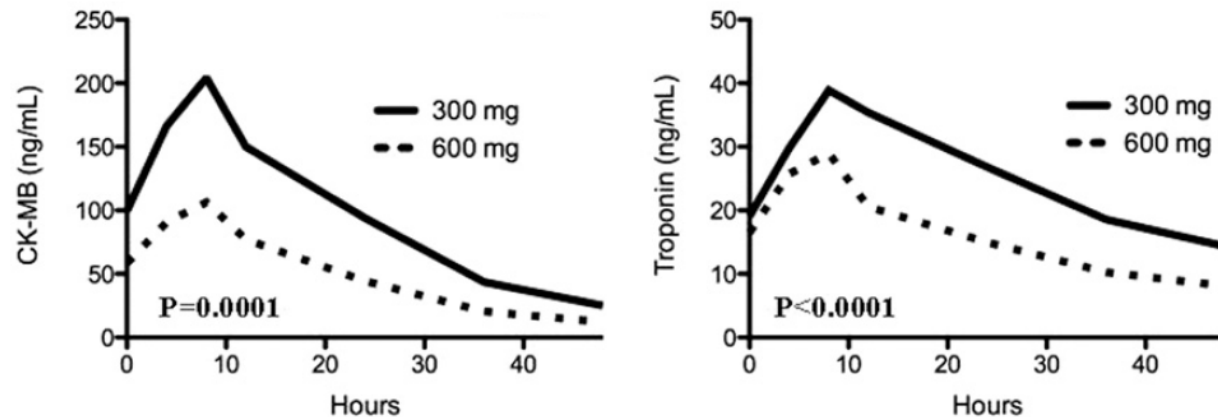
Patti G et al. J Am Coll Cardiol 2011;58:1592–9

Objectives

The purpose of this study was to compare 600- and 300-mg clopidogrel loading doses in patients with ST-segment elevation myocardial infarction (STEMI).

Methods

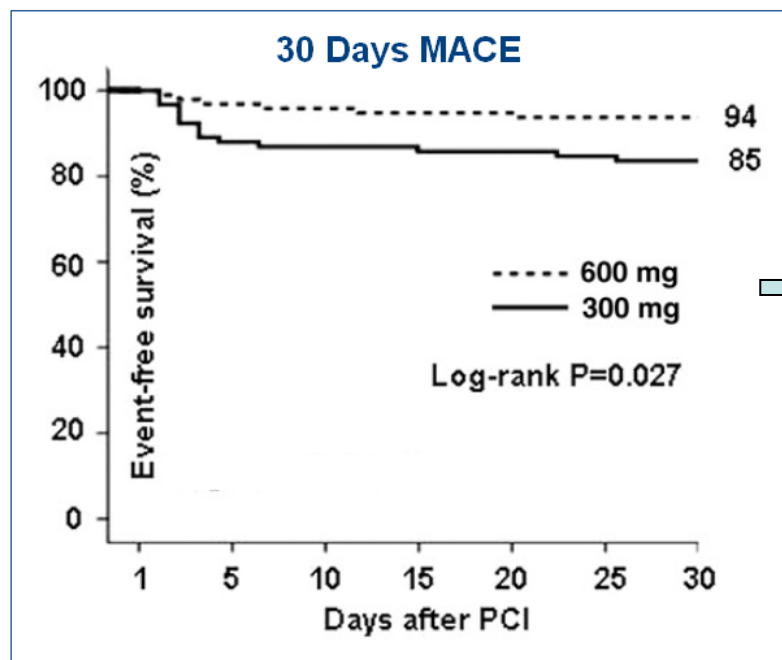
A total of 201 patients undergoing primary PCI for STEMI randomly received a 600-mg (n = 103) or 300-mg (n = 98) clopidogrel loading dose before the procedure. The primary endpoint was the evaluation of the infarct size, defined as the area under the curve of cardiac markers.



	600-mg (n = 103)	300-mg (n = 98)	p Value
TIMI flow pre-PCI >1	22 (21)	12 (12)	0.12
TIMI flow post-PCI <3	6 (6)	16 (16)	0.031

Outcome Comparison of 600 and 300 mg Loading Doses of Clopidogrel in Patients Undergoing Primary PCI for STEMI. Results From the ARMYDA-6 MI Randomized Study

Patti G et al. J Am Coll Cardiol 2011;58:1592–9



Values are n (%).	600-mg Clopidogrel (n = 103)	300-mg Clopidogrel (n = 98)	p Value
30-day MACE	6 (5.8)	15 (15.0)	0.049
Individual components			
Death	4 (3.9)	7 (7.1)	0.48
Reinfarction	1 (0.98)	5 (5.1)	0.19
TVR	1 (0.98)	7 (7.1)	0.06
Stroke	0	1 (1.0)	0.98
Death + reinfarction + TVR	6 (5.8)	14 (14.2)	0.08
Definite or probable stent thrombosis	1 (0.98)	4 (4.1)	0.34
Safety endpoint			
30-day major bleeding	2 (1.9)	2 (2.0)	0.65
30-day minor bleeding	8 (7.8)	6 (6.1)	0.86
Entry-site complications	3 (2.9)	3 (3.1)	0.72

Conclusions

In STEMI patients, pre-treatment with a 600-mg clopidogrel loading dose before primary PCI was associated with a reduction of the infarct size compared with a 300-mg loading dose, as well as with improvement of angiographic results, residual cardiac function, and 30-day major adverse cardiovascular events; further studies are warranted to evaluate impact of such strategy on survival.

A high loading dose of clopidogrel reduces myocardial infarct size in patients undergoing primary percutaneous coronary intervention : a magnetic resonance imaging study

Son YB et al (South Korea). Am Heart J 2012;163:500-7.

In 198 patients undergoing primary PCI for STEMI, contrast-enhanced magnetic resonance imaging was performed a median of 7 days after the index event. All patients received dual oral antiplatelet therapy with 300 mg aspirin and either 300 mg or 600 mg clopidogrel before PCI according to physician decision.

- The median infarct size was significantly smaller in the 600 mg group than in the 300 mg group (17.3% [8.9%-26.2%] vs 21.7% [12.9%-30.0%] $p = 0.03$).
- Myocardial salvage index ($[AAR - \text{infarct size}] \times 100/AAR$) was greater in the 600 mg group than in the 300-mg group (47.7 [33.7-60.9] vs 32 [23.6-51.5], $p < .01$).

Conclusions

In patients undergoing primary PCI for STEMI, a 600-mg loading dose of clopidogrel reduced myocardial infarct size and improved myocardial salvage compared with a 300-mg loading dose.

Clonidogrel pretreatment in ST-elevation myocardial infarction patients transferred for percutaneous coronary Intervention

David M. Larson, MD,^a Sue Duval, PhD,^{a,b} Scott S. Sharkey, MD,^a Christopher Solie, BS,^a Craig Tschautscher, BS,^a Daniel L. Lips, MD,^a M. Nicholas Burke, MD,^a Steven Steinhubl, MD,^c and Timothy D. Henry, MD^a
Minneapolis, MN; Zurich, Switzerland and Danville, PA

Am Heart J 2010;160:202-7.

clonidogrel 600 mg

- *Prospective data were analyzed from a regional STEMI system using rapid transfer for primary PCI in 30 community hospitals. Zone 1 community hospitals are <60 miles and Zone 2 hospitals are 60 to 210 miles away from the PCI hospital.*
- *Compared with 63 minutes in the PCI hospital, median door-to-balloon times were 94 minutes in Zone 1 and 123 minutes in Zone 2 hospitals.*
- All patients received aspirin, unfractionated heparin, and clonidogrel 600 mg in the emergency department of the presenting hospital within 15 minutes of diagnosis.

Results

- From April 2003 through December 2008, 2014 consecutive STEMI patients were pretreated with clonidogrel before PCI, with a median duration from pretreatment to PCI of 75 (58-93) minutes.
- Patients with pretreatment duration of >60 minutes before PCI had reduced 30-day reinfarction/reischemia (1.0% vs 2.9%, $p = 0.003$).
- Patients with longer pretreatment duration had significantly reduced stent thrombosis (Zone 1: 0.6%, Zone 2: 0.6% vs non transferred patients : 2.0%; $p = 0.04$).
- Similarly, There were no significant differences in mortality or major bleeding.

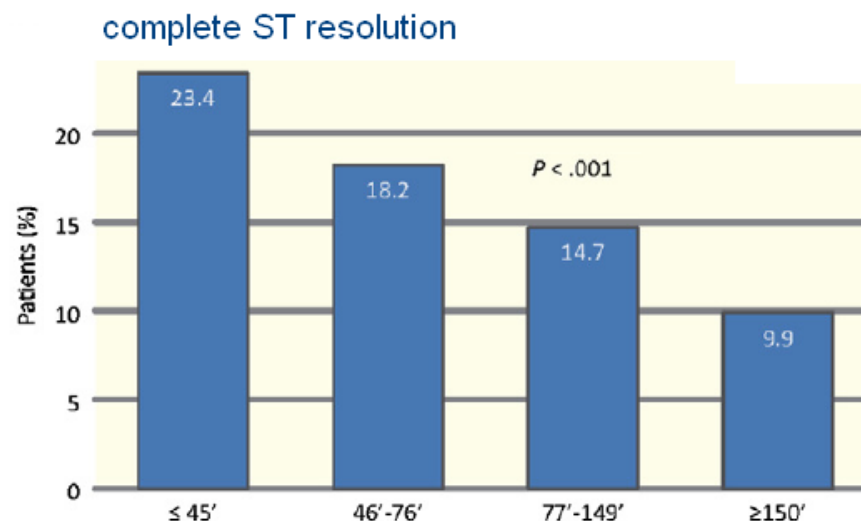
The golden hour of prehospital reperfusion with triple antiplatelet therapy

A sub-analysis from the Ongoing Tirofiban in Myocardial Evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy

Ton Heestertermans et al. Am Heart J 2010;160:1079-84.

clopidogrel 600 mg

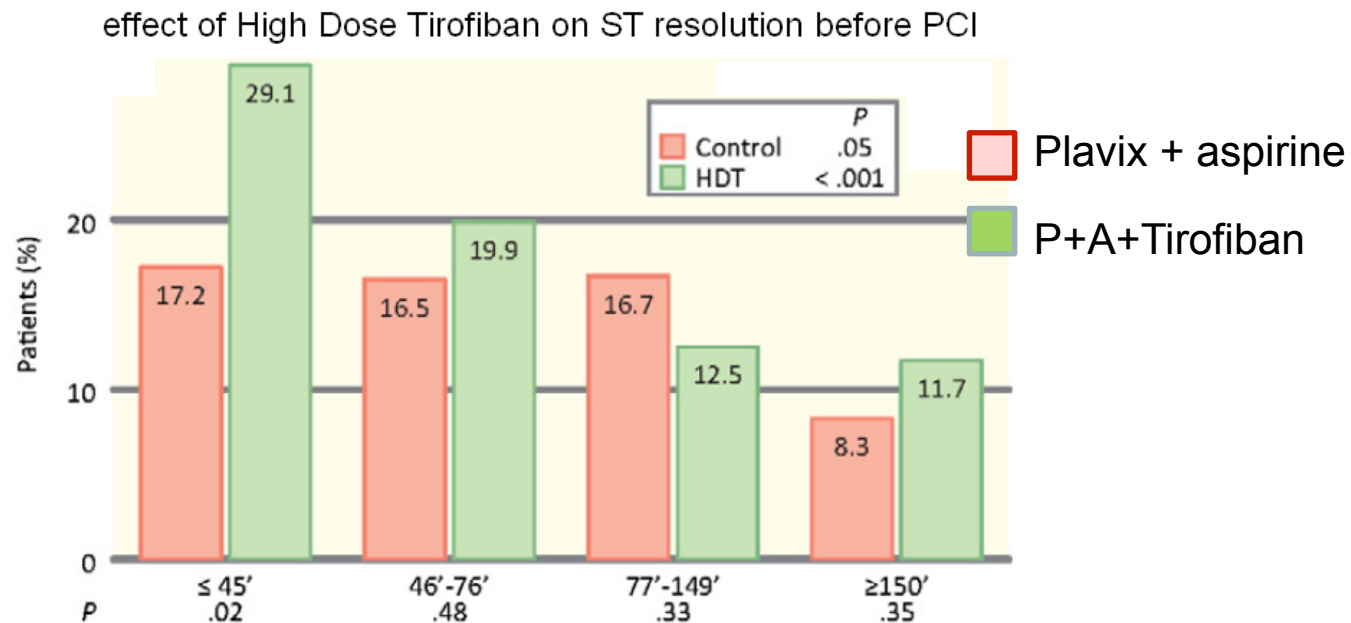
- 1398 consecutive STEMI patients referred for primary PCI, randomized to dual (500 mg aspirin and 600 mg clopidogrel) or triple antiplatelet (500 mg aspirin, 600 mg clopidogrel, and tirofiban 25 µg/kg bolus and 0.15 µg/kg per minute maintenance infusion for 18 hours) pretreatment in the ambulance.
- *Initial patency, ST segment Resolution before PCI, and the incidence of aborted myocardial infarction gradually increased with shorter time from symptom onset to first medical contact.*



The golden hour of prehospital reperfusion with triple antiplatelet therapy

A sub-analysis from the Ongoing Tirofiban in Myocardial Evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy

Ton Heestertermans et al. Am Heart J 2010;160:1079-84.



- This was largely driven by the effect of triple antiplatelet therapy, which further improved initial patency and STR and led to a significantly higher incidence of aborted myocardial infarction (13.2% vs 8.7%, $p = 0.01$), especially in the patients with short duration of symptoms.

Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction

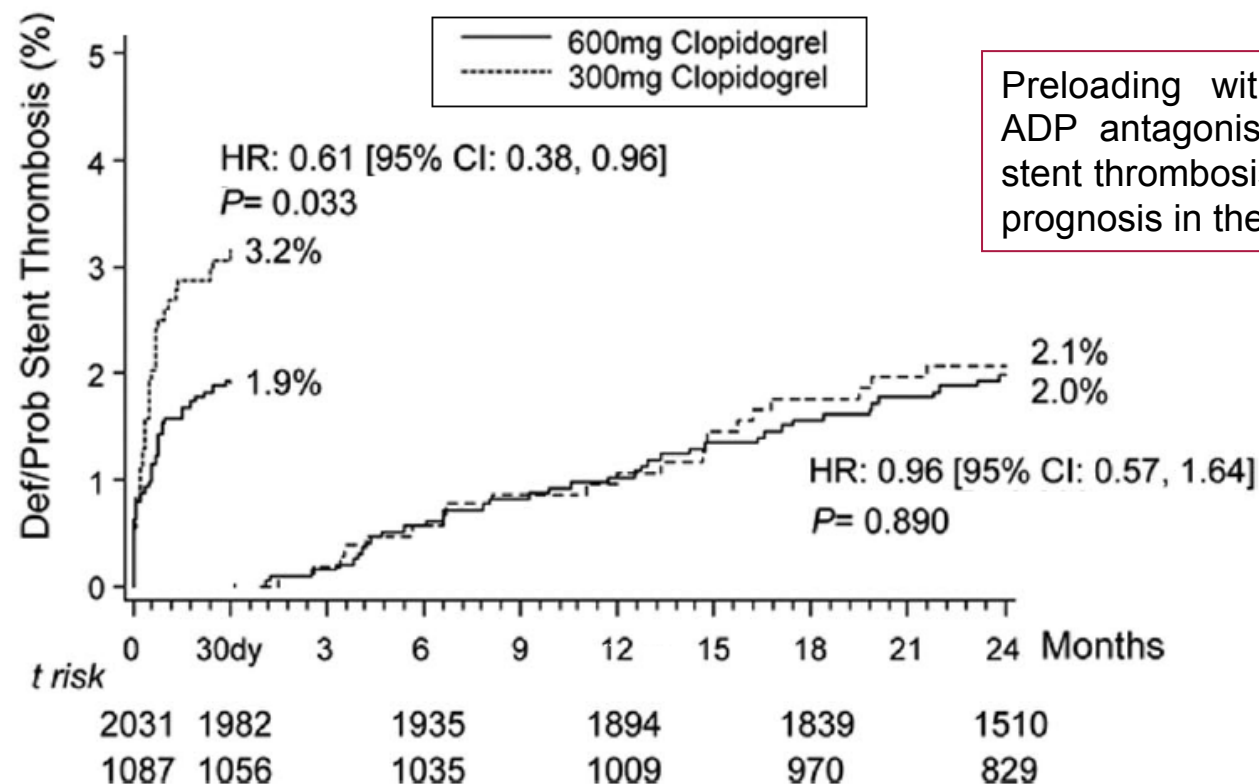
Dangas GD et al. Circulation. 2011;123:1745-56.

- The HORIZONS-AMI trial included 3602 patients with STEMI undergoing primary PCI who were randomized to heparin plus a glycoprotein IIb/IIIa inhibitor (n1802) versus bivalirudin monotherapy (n1800). Stents were implanted in 3202 patients, including 2261 who received DES and 861 who received only BMS.
- Aspirin 324 mg chewed or 500 mg intravenous was given in the emergency department, followed by 300 to 325 mg orally daily during the hospitalization and 75 to 81 mg daily indefinitely thereafter. A clopidogrel loading dose (either 300 or 600 mg per investigator discretion) was administered before catheterization, followed by 75 mg orally daily for at least 6 months; dual antiplatelet therapy was recommended for at least 1 year.
- Definite or probable stent thrombosis within 2 years occurred in 137 patients (4.4%), including 28 acute (0.9%), 49 subacute (1.6%), 32 late (1.0%), and 33 very late events (1.1%).
- The 2-year cumulative rates of stent thrombosis were 4.4% with both DES and BMS ($p=0.98$) and 4.3% versus 4.6% in patients randomized to bivalirudin monotherapy versus heparin plus a GPI, respectively ($p = 0.73$).
- Prerandomization heparin and a 600-mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis, respectively.

HORIZON-MI : Relationship between clopidogrel loading dose and stent thrombosis : 30-day landmark analyses.

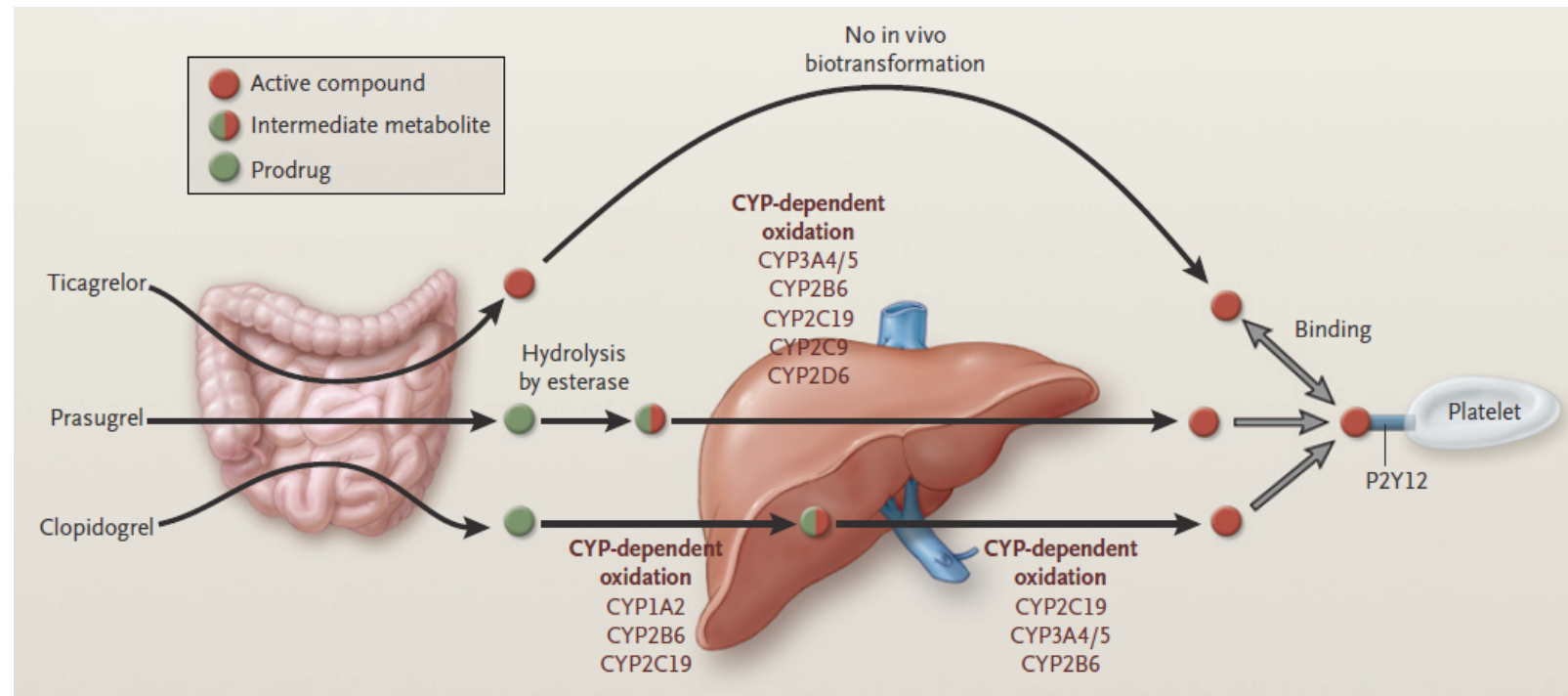
Dangas GD et al. Circulation. 2011;123:1745-56.

Definite/probable stent thrombosis



Preloading with a potent platelet ADP antagonist, may reduce early stent thrombosis and further improve prognosis in these high-risk patients.

Clopidogrel is an oral agent that requires first-pass hepatic metabolism to become active, so it would not be expected to lead to a rapid antiplatelet effect that could affect epicardial flow in the IRA before primary PCI; and it has been shown to achieve inconsistent levels of platelet inhibition.



The efficacy of clopidogrel is hampered by a modest and variable platelet inhibition favouring an increased risk of stent thrombosis and myocardial infarction in patients with a poor response.

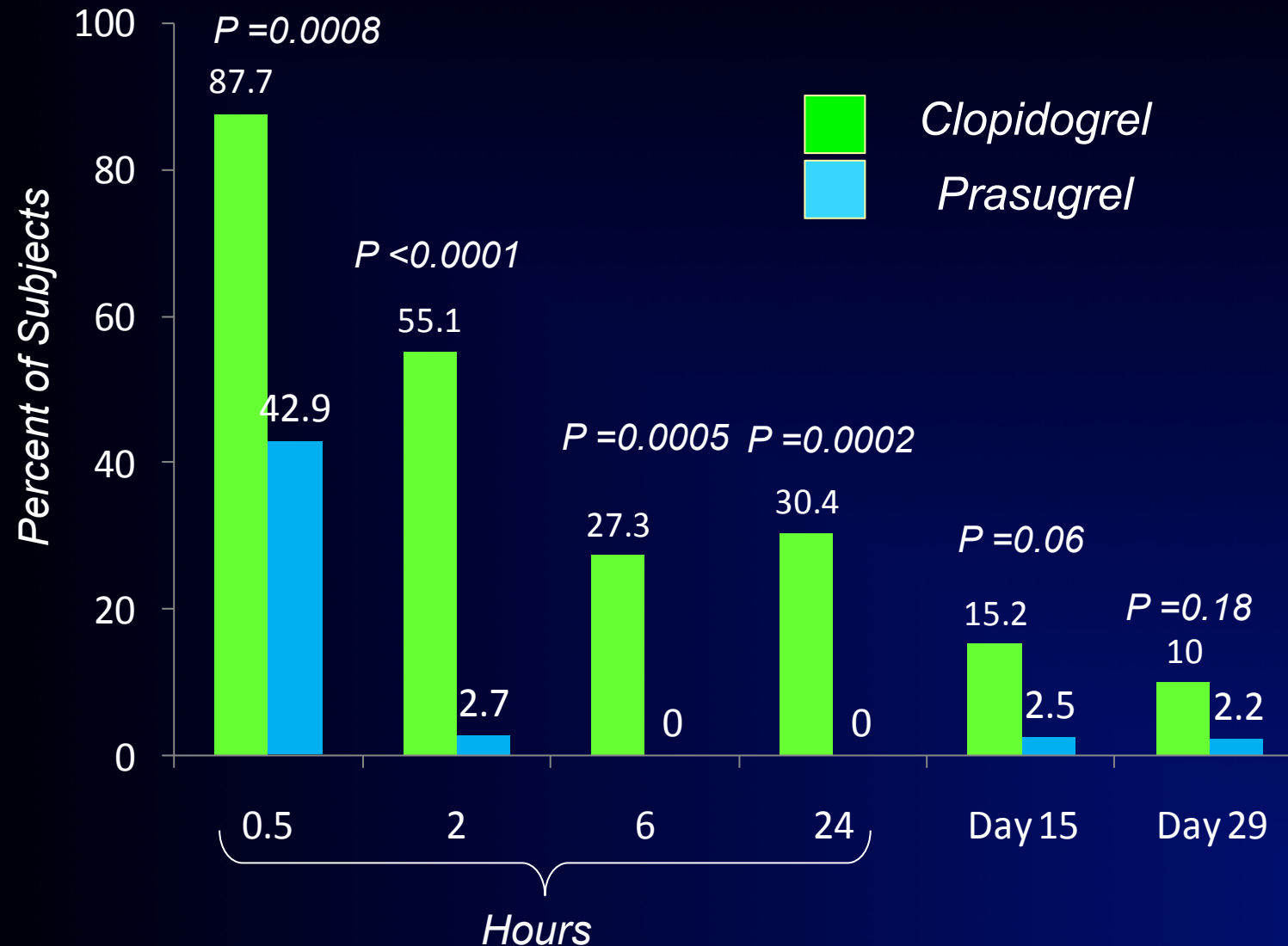


PRINCIPLE TIMI 44

Wiviott et al Circ 2007

Thienopyridine Hyporesponsiveness:

IPA 20 μ M ADP < 20%



The NEW ENGLAND
JOURNAL of MEDICINE

NEJM 2007 ; 357: 2001-15,
Prasugrel versus Clopidogrel in Patients
with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D.,
Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D.,
Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D.,
C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON-TIMI 38 Investigators*

ACS (STEMI or UA/NSTEMI) & Planned PCI

N= 13.600 ↓ ASA +

Double-blind

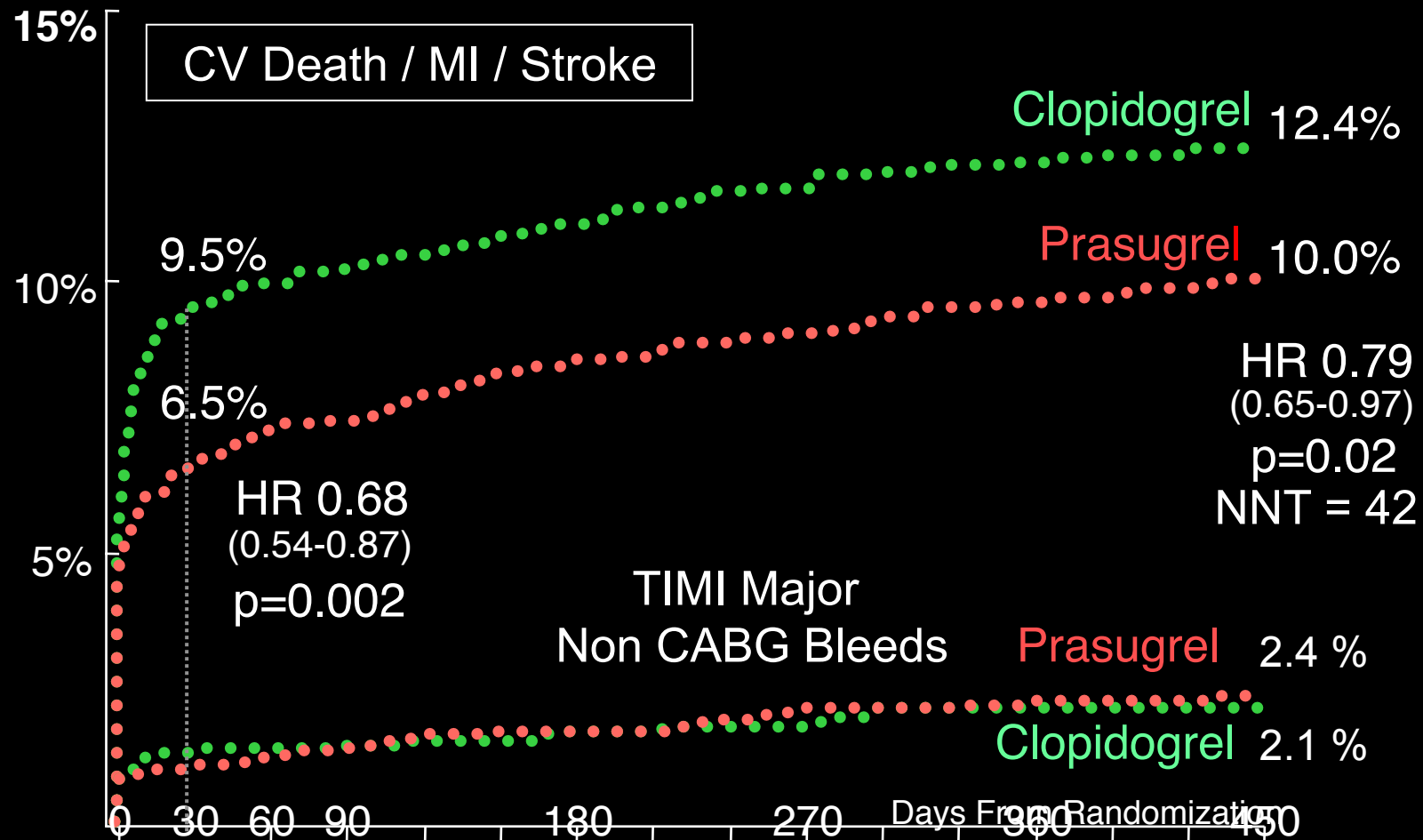
CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

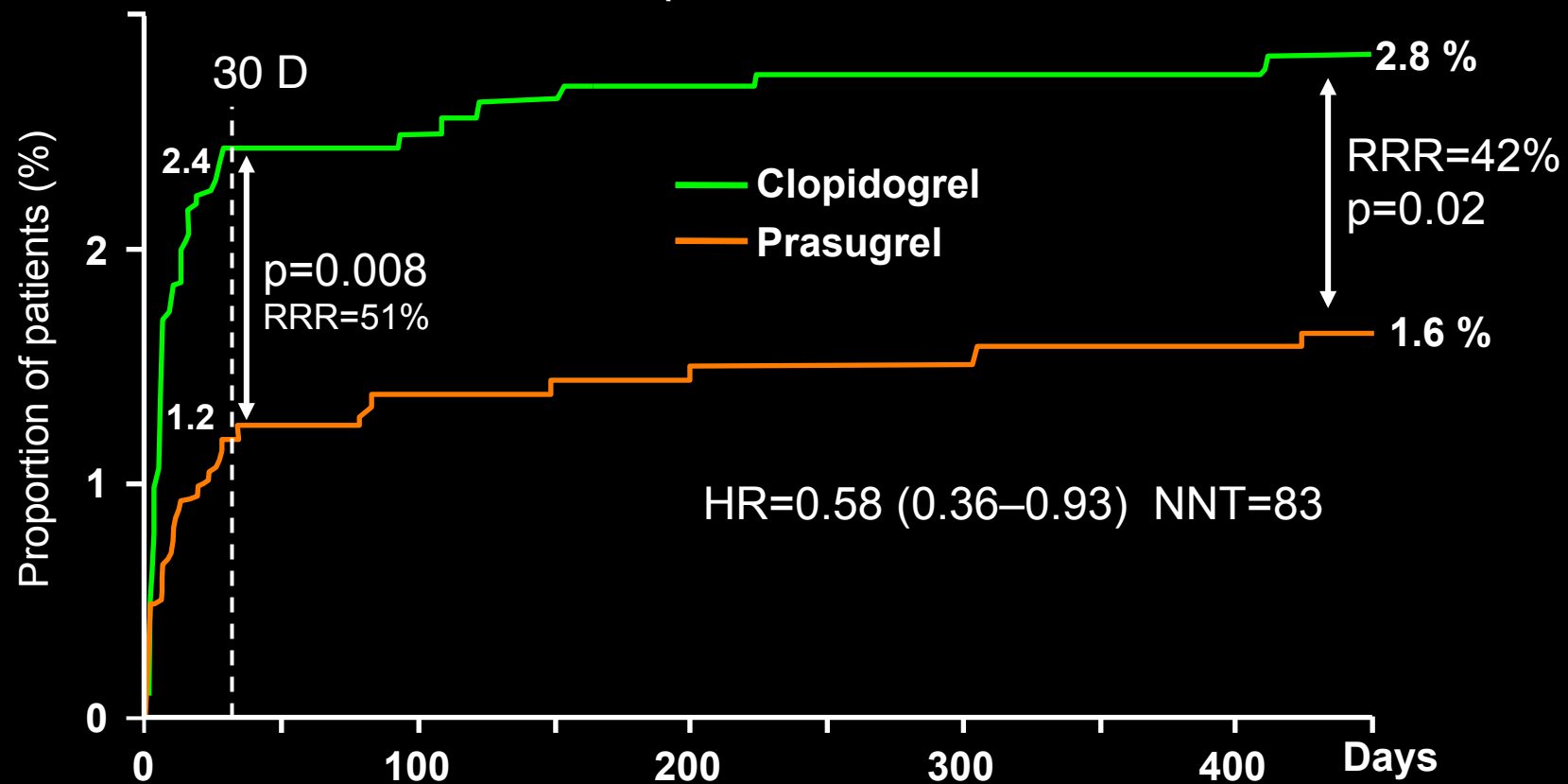


STEMI Cohort ; N=3534

Montalescot et al Lancet 2008.

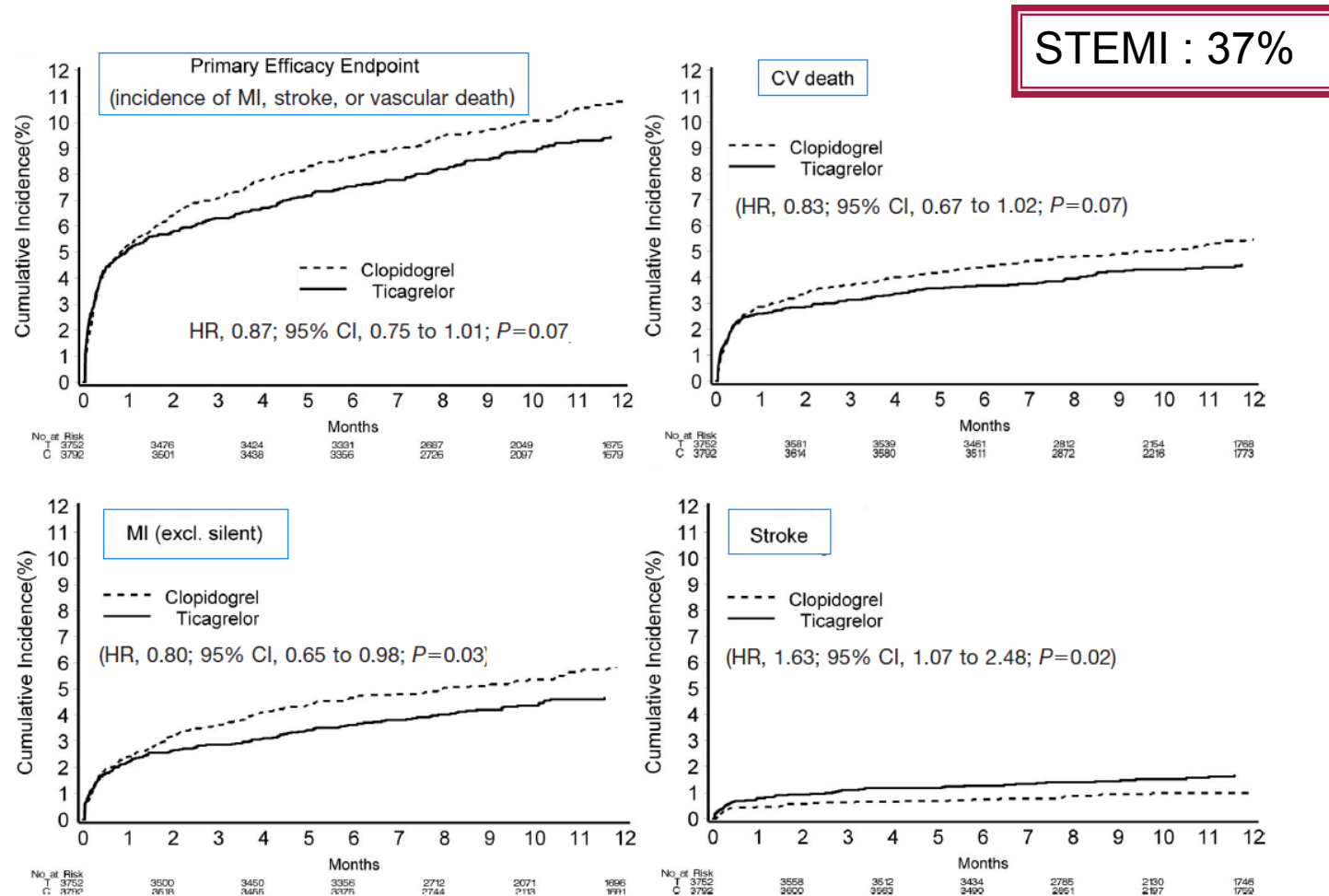


Stent thrombosis (ARC Definite/probable)



Ticagrelor Versus Clopidogrel in Patients With STEMI Intended for Reperfusion With Primary PCI. A PLATO Trial Subgroup Analysis

Steg PG et al. Circulation. 2010;122:2131-214.

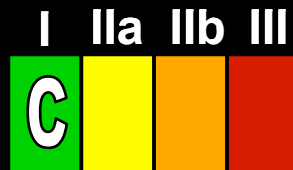


Ticagrelor reduced definite stent thrombosis ($HR, 0.66; p=0.03$).

Recommendations for the use of Thienopyridines

ACC/AHA 2009 Joint STEMI/PCI Guidelines Focused Update

MODIFIED
Recommendation



A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:

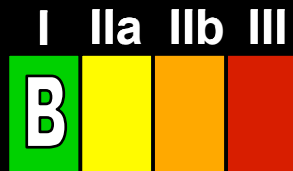
Clopidogrel at least 300 mg to 600mg* should be given as early as possible before or at the time of primary or non primary PCI.

- The necessity for giving a LD of clopidogrel prior to PCI is driven by the pharmacokinetics of clopidogrel where several hours are required to achieve desired levels of platelet inhibition.
- The optimum Loading Dose of clopidogrel has not been established. Randomized trials establishing its efficacy and providing data on bleeding risks used a LD of 300 mg orally followed by a daily oral dose of 75 mg. Higher oral LDs such as 600 mg or more than 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and safety of higher oral LDs have not been rigorously established.

Recommendations for the use of Thienopyridines

ACC/AHA 2009 Joint STEMI/PCI Guidelines Focused Update

MODIFIED
Recommendation



Prasugrel 60 mg should be given as soon as possible for primary PCI.

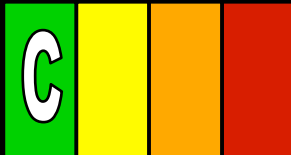
- ✓ Do not start prasugrel in patients likely to undergo urgent CABG
- ✓ Do not use prasugrel in patients with active bleeding or a history of TIA or stroke.
- ✓ In patients ≥ 75 years of age, prasugrel is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered.
- ✓ Additional risk factors for bleeding include: body weight < 60 kg; propensity to bleed; concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs]).

Recommendations for the use of Thienopyridines

ACC/AHA 2009 Joint STEMI/PCI Guidelines Focused Update

MODIFIED Recommendation

I IIa IIb III

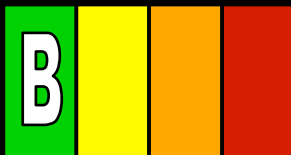


For STEMI patients undergoing ***non-primary*** PCI, the following regimens are recommended:

If the patient has received fibrinolytic therapy...

- a. ...and has been given clopidogrel, it should be continued as the thienopyridine of choice.
- b. ...without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice.

I IIa IIb III



If the patient did not receive fibrinolytic therapy...

- c. ...either a loading dose of 300-600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI.



Antithrombotic treatment options in myocardial revascularization

STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel ^f (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel ^d	I	B
	Ticagrelor ^d	I	B
	+ GPIIb–IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb–IIIa antagonists	III	B
Anticoagulation			
	Bivalirudin (monotherapy)	I	B
	UFH	I	C
	Fondaparinux	III	B

^dDepending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available. Long term follow-up is awaited for both drugs.

^fPrimarily if more efficient antiplatelet agents are contraindicated.

The controversial literature data and the beneficial effects of faster acting and more efficacious ADPreceptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GPIIb–IIIa inhibitors.

Conclusions

- L'activation des plaquettes joue un rôle déterminant dans l'infarctus
- L'introduction la plus précoce possible de produits d'action rapide et puissante bloquant l'activation et l'agrégation plaquettaire
 - augmente les chances de faire avorter l'infarctus par l'obtention d'une recanalisation au moins partielle du vaisseau obstrué,
 - facilite l'angioplastie primaire et diminue le risque de no reflow,
 - limite la taille de l'infarctus, sauvegarde la fonction gauche,
 - minore le risque de thrombose de stent,
 - diminue le taux d'évènements cardiaques majeurs à court et moyen terme...
- La question essentielle n'est plus de savoir s'il faut débiter l'administration des antiplaquettaires dès le premier contact médical* mais comment optimiser leur combinaison pour obtenir le meilleur ratio bénéfice/risque hémorragique...

**l'étude ATLANTIC répondra à la question*