



La storia del Clopidogrel e  
dei PPI: c'era una volta...

Dr. L. Mantovani

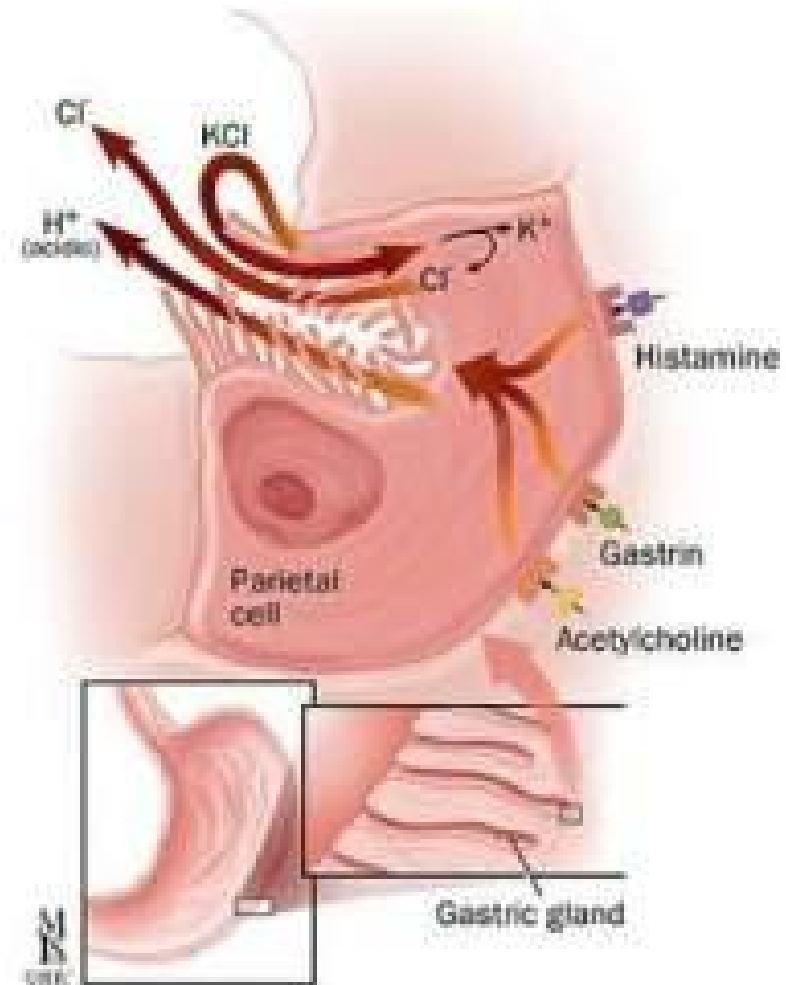
U.O. Gastroenterologia

S. Anna Ferrara

# Inibitori della pompa protonica (PPI)

Inibizione irreversibile della PP per 36 ore (emivita 2 ore)

- *Omeprazolo*
- *Esomeprazolo*
- *Lansoprazolo*
- *Rabeprazolo*
- *Pantoprazolo*

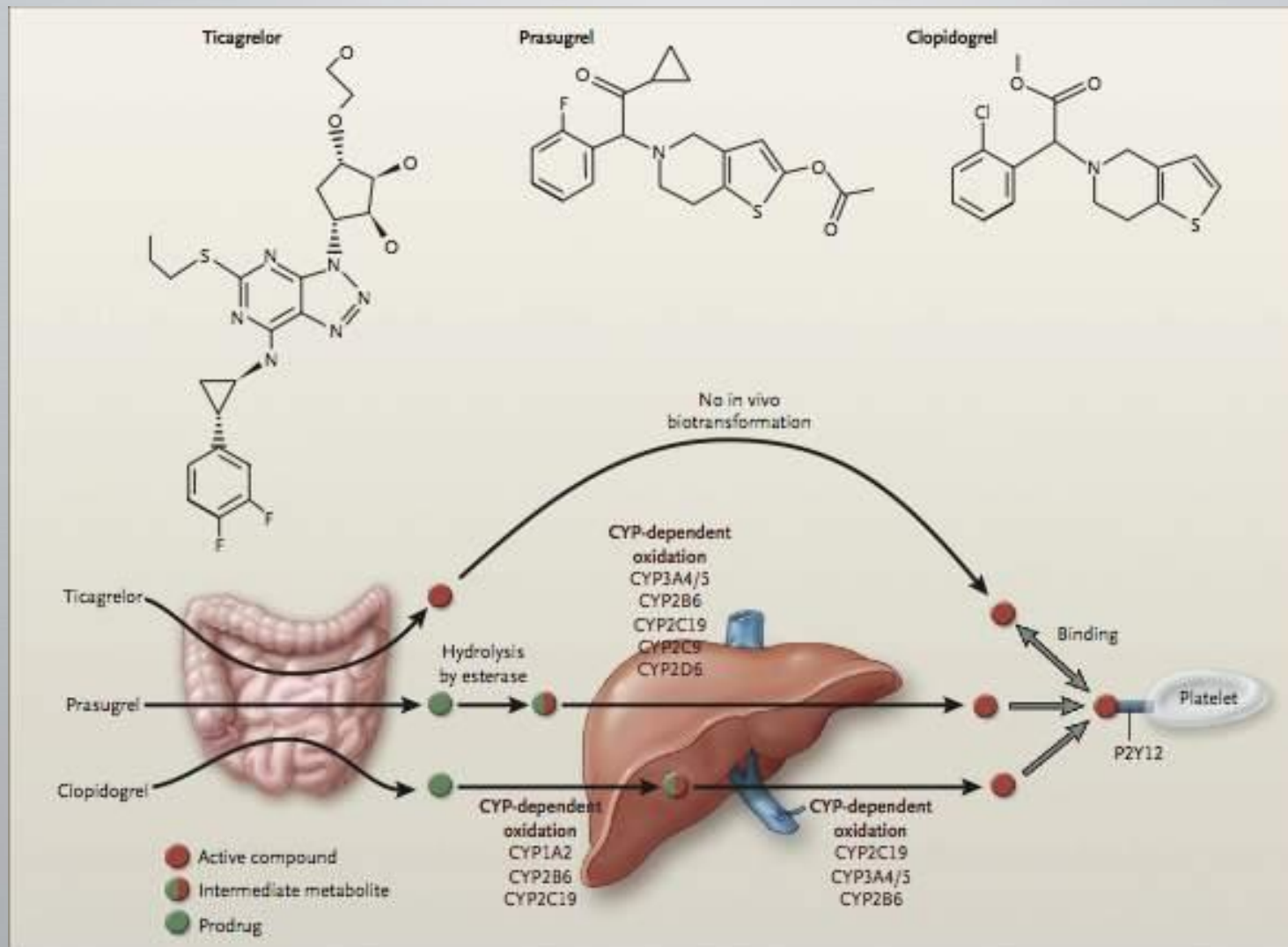


# Antiaggreganti piastrinici

*Clopidogrel* Profarmaco, dopo l'assorbimento intestinale necessita di 2 steps ossidativi epatici, dipendenti dal citocromo P450 (CYP2C19 e CYP3A4) per diventare un metabolita attivo e bloccare il recettore ADP P2Y12 sulle piastrine

*Prasugrel* Profarmaco che necessita, dopo l'assorbimento intestinale, di una idrolizzazione esterasi dipendente ed una ossidazione P450 (CYP2C19) dipendente per divenire un metabolita attivo

# Biotrasformazione e meccanismo d'azione di Clopidogrel, Prasugrel e Ticagrelor

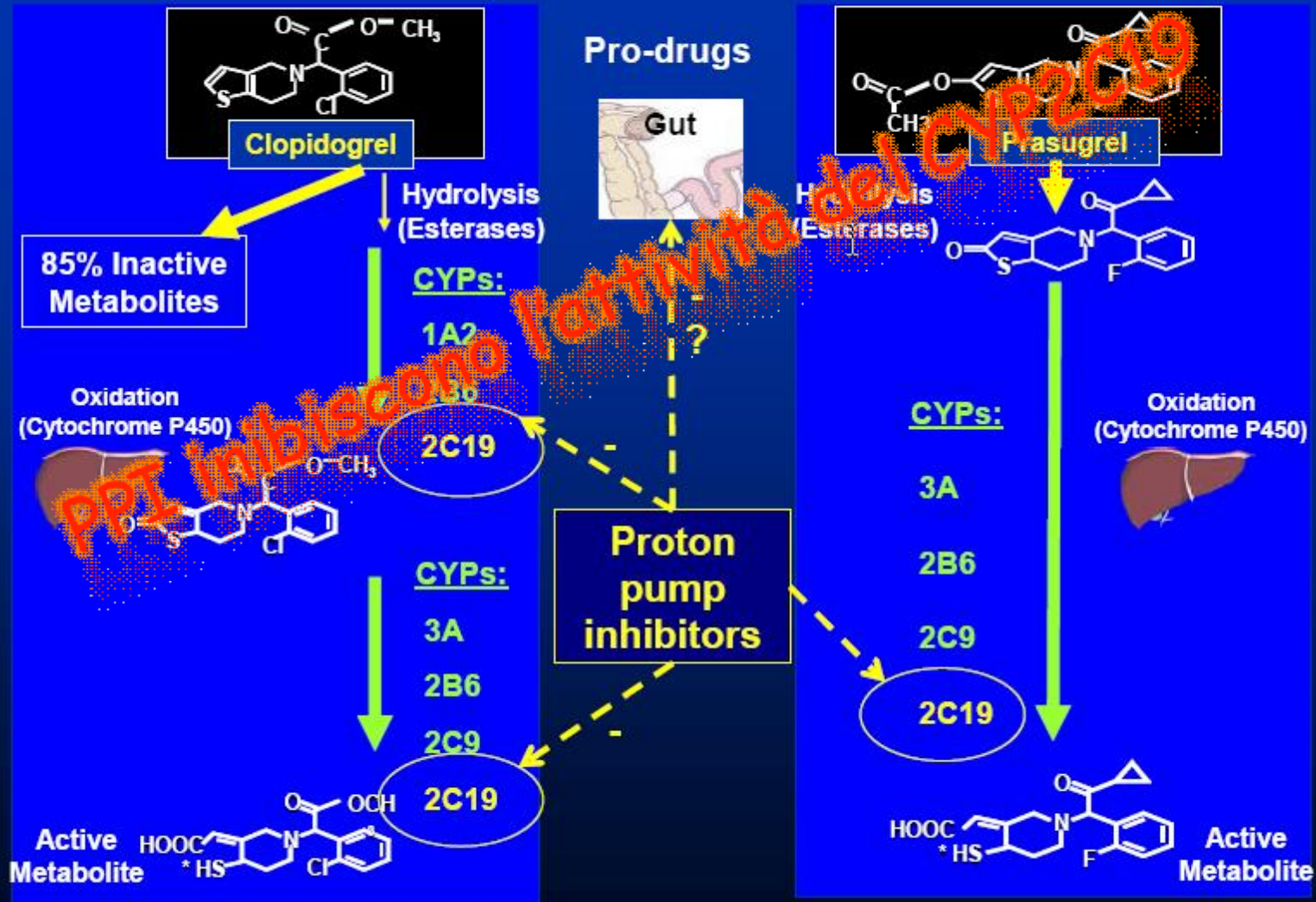


Schomig et al. N Engl J M 2009



The NEW ENGLAND  
JOURNAL of MEDICINE

# Thienopyridines: Formation of Active Metabolite



Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. J Am Coll Cardiol 2008; 51: 256-260

Gennaio 2008 Gilard e coll. nello studio randomizzato doppio cieco OCLA (Omeprazole CLopidogrel Aspirin) hanno per primi rivolto la loro attenzione all'interazione tra Clopidogrel e PPI. **PPI omeprazolo attenua significativamente l'attività antiaggregante del Clopidogrel**

Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008; 51: 256-260

Studi successivi hanno mostrato che **non è un problema che interessa tutta la classe farmacologica** dei PPI in egual misura. **Gli effetti di inibizione enzimatica interessano l'omeprazolo ma non il pantoprazolo o il rabeprazolo**

Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009; 101: 714-719.

Siller-Matula J, Spiel A, Lang I, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009; 157: 148.e1-148.e5.

Review article

## Inhibition of the antithrombotic effects of clopidogrel by proton pump inhibitors: Facts or fancies?

Maddalena Lettino\*

CCU- Department of Cardio-thoracic and Vascular diseases, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

Pharmacokinetic and pharmacodynamic properties of PPIs [13,14].

Drug, dose	$t_{max}$ (h)	Oral bioavailability (%)	$t_{1/2}$ (h)	Hepatic metabolism via cytochrome P450	CYP2C19 inhibition	Degree of acid inhibition* (h) [15]	Half-life of recovery of acid secretion (h)
Omeprazole, 20 mg	2	35-60	0.5-1.2	Yes	High	11.8	15
Esomeprazole, 20-40 mg	1-2	64-89	0.8-1.3	Yes	High	14	-
Lansoprazole, 30 mg	1.7	80-90	0.9-2.1	Yes	Very high	11.5	28
Pantoprazole, 20-40 mg	2.5	77	0.8-2.0	Yes	Very low	10.1	46
Rabeprazole, 20 mg	3.5	52	0.6-1.4	Yes	Low	12.1	-

$t_{max}$  = time to maximal plasma concentration;  $t_{1/2}$  = elimination half-life; \* = mean time (h) of intragastric pH >4 at day 5 (drug once daily).

Review article

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CCU- Department of Cardio-thoracic and Vascular diseases, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

Summary of the most important pharmacodynamic studies assessing the effect of PPIs on platelet inhibition in clopidogrel users.

Authors and study type	Population	Endpoint	Follow up	Comparison	Results
Gilard JL et al. [19] – OCLA study (double-blind, placebo-controlled, randomized trial)	124 pts undergoing PCI with stent implantation	VASP-PRI	Day 7	Omeprazole versus placebo	Omeprazole significantly interferes with clopidogrel antiplatelet activity
Cuisset T et al. [20] – PACA study (double-blind, randomized trial)	104 NSTEMI-ACS pts undergoing coronary stenting	VASP-PRI ADP-induced platelet aggregation	1 month	Pantoprazole versus omeprazole	Less poor clopidogrel responders in pantoprazole group (VASP-PRI); no differences in ADP-induced platelet aggregation
Siller Matula JM et al. [21] (cohort study)	300 pts with CAD undergoing PCI with stent implantation	VASP-PRI Aggregometry by Multiplate Analyzer	In the Cath-Lab	Pantoprazole or esomeprazole versus placebo	No association of PPIs with impaired response to clopidogrel
Sibbing D et al. [22] (cohort study)	1000 pts with prior coronary stent placement	ADP-induced platelet aggregation	Concomitantly with a control coronary angiography	PPIs (omeprazole, pantoprazole, esomeprazole) versus no PPIs	Less platelet inhibition with omeprazole compared with other PPIs or no PPI treatment
O'Donoghue ML et al. [23] – PRINCIPLE-TIMI44 (retrospective cohort study within a RCT)	201 pts undergoing PCI with stent implantation	ADP-induced platelet aggregation	Day 1, after the loading dose After two weeks	PPIs versus no PPIs in pts receiving clopidogrel or prasugrel	Mean platelet inhibition significantly lower in pts on clopidogrel receiving PPIs

Pts = patients; PCI = Percutaneous Coronary Intervention; VASP-PRI = Phosphorylated VASP – Platelet Reactivity Index; NSTEMI-ACS = Non-ST-Elevation Acute coronary syndrome; CAD = coronary artery disease; Cath-Lab = Catheterism Laboratory; RCT = randomized control trial.

# Studi sperimentali utilizzando test di reattività piastrinica

## Comparison of Omeprazole and Pantoprazole Influence on a High 150-mg Clopidogrel Maintenance Dose

The PACA (Proton Pump Inhibitors And Clopidogrel Association) Prospective Randomized Study

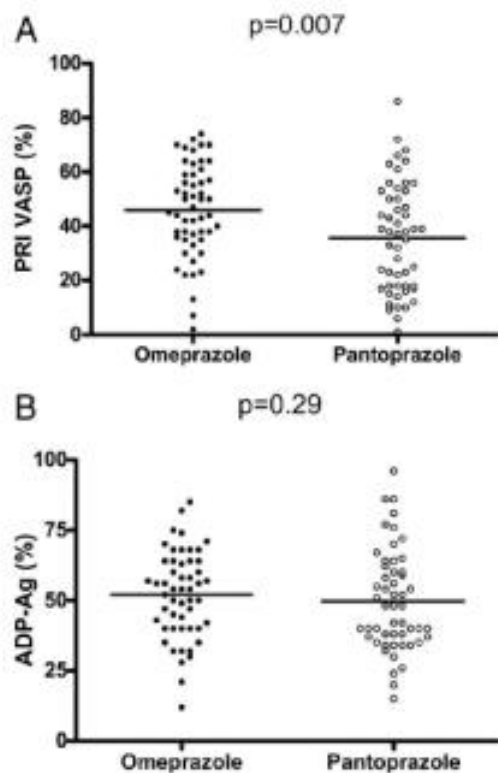


Figure 2 Platelet Parameters and According to Proton Pump Inhibitors

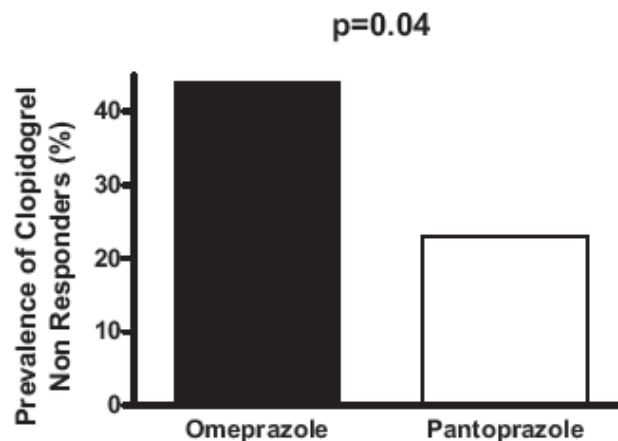


Figure 3 Prevalence of Clopidogrel Nonresponders

Prevalence of clopidogrel nonresponders (platelet reactivity index vasoactive stimulated phosphoprotein >50%) according to proton pump inhibitor treatment.

## Conclusions

The lack of negative effects of concomitant treatment with pantoprazole is an important finding because it may have an impact on clinical practice and suggests the preferential use of pantoprazole as PPI in patients receiving clopidogrel to avoid any potential negative interaction as described for omeprazole (13,19,20).

CLINICAL RESEARCH

Clinical Trials

## Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin

The Randomized, Double-Blind OCLA  
(Omeprazole CLopidogrel Aspirin) Study

Martine Gilard, MD,\* Bertrand Arnaud, PHARM.D,† Jean-Christophe Cornily, MD,\* Grégoire Le Gal, MD,§  
Karine Lacut, MD,‡ Geneviève Le Cabez, PHARM.D,† Jacques Mansourati, MD,\* Dominique Mottier, MD,§  
Jean-François Abgrall, MD,† Jacques Boschat, MD\*

*Brest, France*

### Results

Omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y<sub>12</sub> as assessed by VASP phosphorylation test. Aspirin-clopidogrel antiplatelet dual therapy is widely prescribed worldwide, with PPIs frequently associated to prevent gastrointestinal bleeding. The clinical impact of these results remains uncertain but merits further investigation. (OCLA: Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated to Aspirin; <http://www.clinicaltrials.gov/ct2/show/NCT00349661>; NCT00349661) (J Am Coll Cardiol 2008;51: 256-60) © 2008 by the American College of Cardiology Foundation

Review article

## Inhibition of the antithrombotic effects of clopidogrel by proton pump inhibitors: Facts or fancies?

Maddalena Lettino \*

CCU- Department of Cardio-thoracic and Vascular diseases, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

Clopidogrel and PPIs: clinical trials. A summary of the most important available studies.

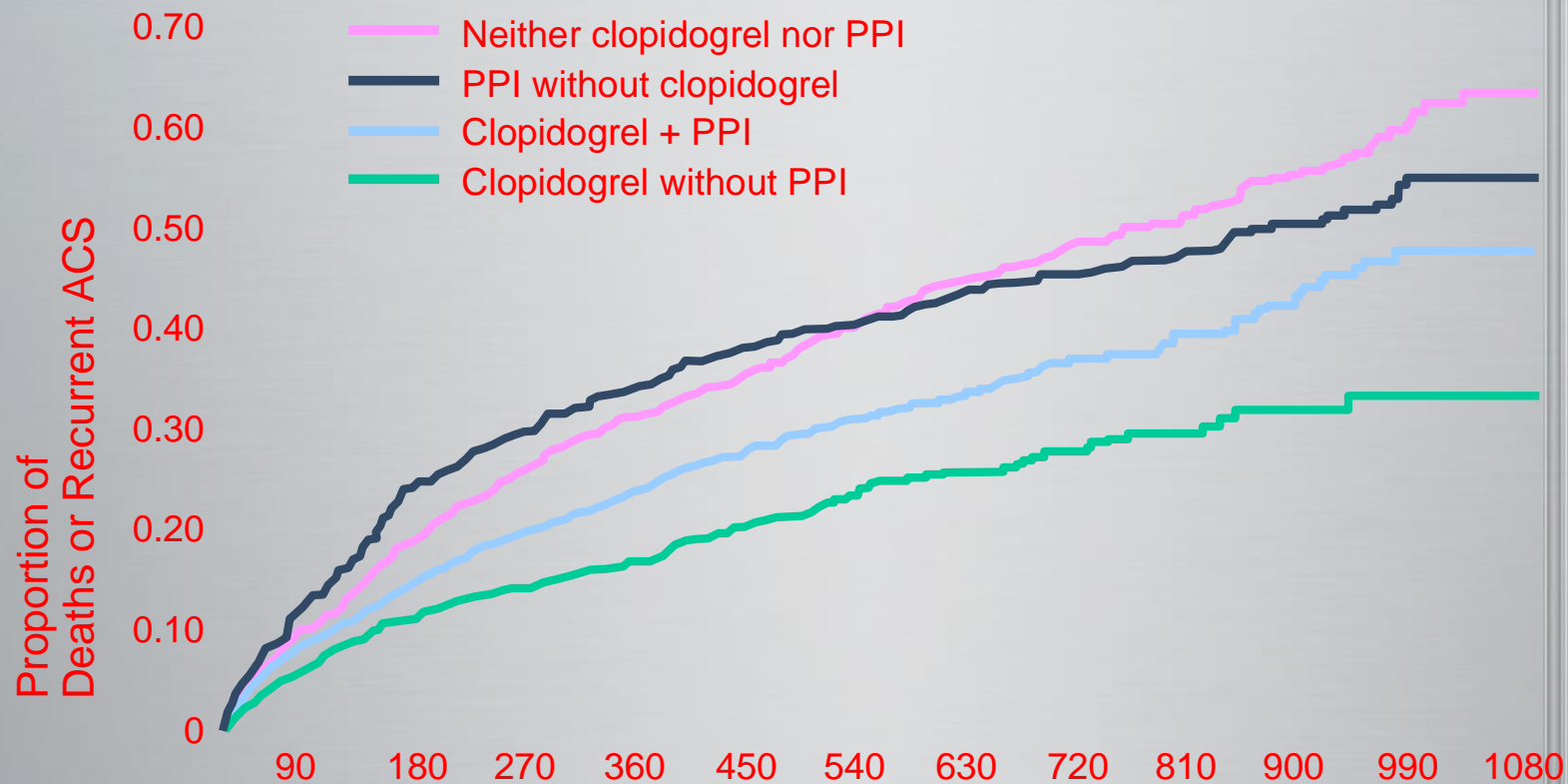
Author and study type	Population	Endpoint	Comparison	Follow up	Results
Juurlink DN et al. [24] [nested case-control study]	2790 post-MI pts	Death or new hospitalization for MI	PPIs versus no PPIs	90 days	Increased risk of reinfarction (OR 1.27) in PPI users, except for pantoprazole
Ho PM et al. [25] [Retrospective cohort study]	8205 pts discharged after acute MI or UA	Death or rehospitalization for ACS	PPIs (mainly omeprazole and rabeprazole) versus no PPIs	Mean 521 days	Increased risk of primary endpoint in PPI users (OR 1.25)
Stockl KM et al. [35] [Retrospective cohort study]	2066 pts discharged after acute MI or coronary stent implantation	Hospitalization for MI or coronary stent placement	PPIs versus no PPIs	360 days	Increased risk of rehospitalization for MI (OR 1.93); increased risk of rehospitalization for MI or stent placement (OR 1.64) in pts on PPIs
Rassen JA et al. [36] [Retrospective cohort study]	18565 pts with a previous PCI for ACS	Hospitalization for MI, death or revascularization	PPIs versus no PPIs	180 days	Trend toward a higher risk of the primary endpoint in pts on PPIs
Ray WA et al. [37] [Retrospective cohort study]	20596 pts hospitalized for MI, coronary revascularization or UA	MI, sudden death, cardiovascular death, stroke	PPIs (mainly pantoprazole) versus no PPIs	360 days	No differences between the two groups
O'Donoghue ML et al. – TRITON-TIMI39 [23] [Retrospective cohort within RCT]	13608 pts with ACS and a planned PCI	Cardiovascular death, non-fatal MI or stroke	PPIs versus no PPIs in pts receiving clopidogrel or prasugrel	6–15 months	No differences between the two groups
Bhatt DL. COGENT [17] [Prospective, double-blind RCT]	3600 pts with a previous NSTEMI-ACS, MI or stent implantation	Cardiovascular death, non-fatal MI, stroke, need for CABG or PCI	Omeprazole versus placebo	Mean 133 days (max 362)	No differences between the two groups

MI = post-myocardial infarction; pts = patients; UA = unstable angina; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; NSTEMI-ACS = Non-ST-elevation acute coronary syndrome; CABG = coronary artery bypass graft.

# COGENT: Conclusion

- COGENT is the first, randomized assessment of clopidogrel and PPIs on clinical events
- The data provide strong reassurance that there is no clinically relevant adverse cardiovascular interaction between clopidogrel and PPIs
- The results call into question the exact relationship between *ex vivo* platelet assays and clinical outcomes, especially with respect to assessing drug interactions
  - Platelet assays and observational data are not a substitute for RCT data
- Further research is needed to define the optimal strategy to reduce GI events in patients on antithrombotic therapy, though prophylactic PPIs seem very promising

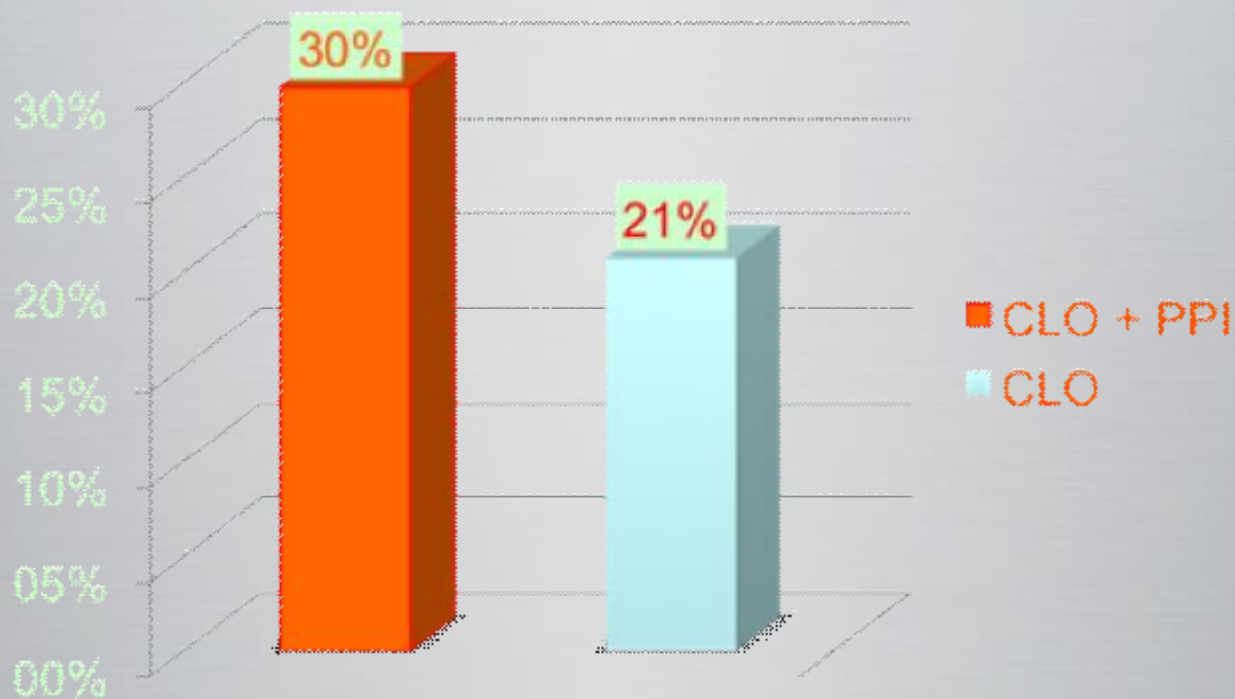
# Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome



Ho et al. JAMA 2009

# Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

morte o nuova ospedalizzazione



Ho et al. JAMA 2009

# Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials



Michelle L O'Donoghue, Eugene Braunwald, Elliott M Antman, Sabina A Murphy, Eric R Bates, Yoseph Rozenman, Alan D Michelson, Raymond W Hautvast, Peter N Ver Lee, Sandra L Close, Lei Shen, Jessica L Mega, Marc S Sabatine, Stephen D Wiviott

## Summary

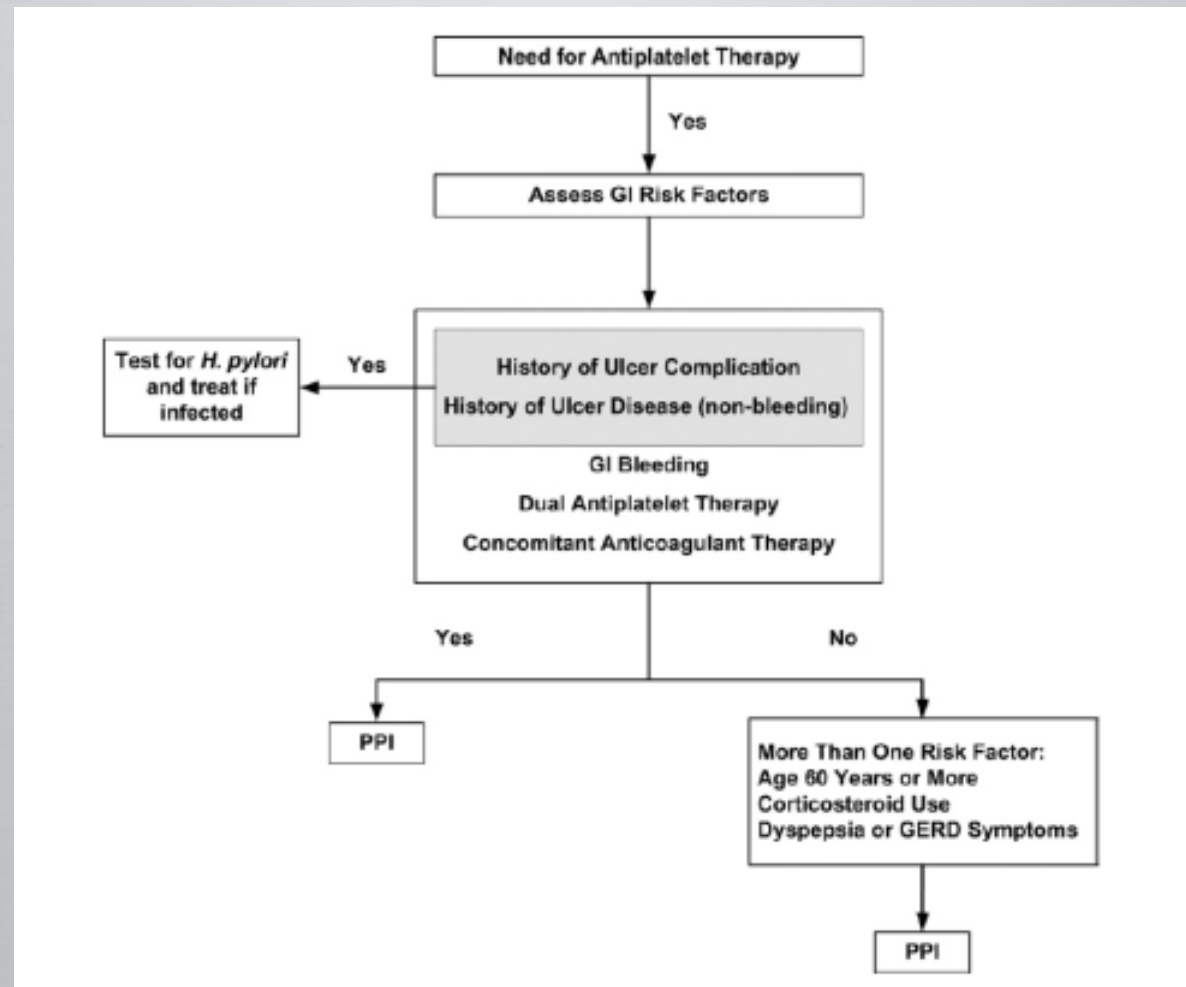
**Background** Proton-pump inhibitors (PPIs) are often prescribed in combination with thienopyridines. Conflicting data exist as to whether PPIs diminish the efficacy of clopidogrel. We assessed the association between PPI use, measures of platelet function, and clinical outcomes for patients treated with clopidogrel or prasugrel.

**Methods** In the PRINCIPLE-TIMI 44 trial, the primary outcome was inhibition of platelet aggregation at 6 h assessed by light-transmission aggregometry. In the TRITON-TIMI 38 trial, the primary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. In both studies, PPI use was at physician's discretion. We used a multivariable Cox model with propensity score to assess the association of PPI use with clinical outcomes.

*The current findings do not support the need to avoid concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel or prasugrel*

*The Lancet , 2009, 374, 9694 : 989 - 997*

# Flow chart per minimizzare il rischio di sanguinamento gastrointestinale



AHA/ACC Statement, Circulation 2008; 118:1894

**NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITÀ  
REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)**

**Potenziale interazione tra Inibitori di Pompa Protonica e farmaci a base di  
clopidogrel (Plavix®)**

Gentile Dottoressa, Egregio Dottore

L'uso concomitante di medicinali a base di clopidogrel e di Inibitori di Pompa Protonica\* (IPP) deve essere evitato a meno che non sia assolutamente necessario, in quanto Clopidogrel può essere meno efficace nei pazienti che assumono tale associazione di farmaci.

- non identifica quando si verifichi "l'assoluta" necessità dell'utilizzo dei farmaci PPI
- Non riporta alcuna distinzione tra i vari PPI

# Variant Alleles

- Extensive metabolism: CYP2C19\*1/\*1
- Intermediate metabolism:  
CYP2C19\*1/\*2 or \*1/\*3
- Poor metabolism:  
CYP2C19\*2/\*2, \*2/\*3 or \*3/\*3 (also \*4,\*5)
- Ultrarapid: CYP2C19\*17 /\*17

## Proton Pump Inhibitor and Clopidogrel Interaction: Fact or Fiction?

1. One PPI is NOT clearly different from another, so merely switching PPIs cannot be viewed as sufficient to avoid any potential risk.
2. The current evidence does not justify the conclusion that PPIs decrease the clinical efficacy of clopidogrel. Nonetheless, until further reliable data become available, wide separation of PPI and clopidogrel dosing should in theory minimize any potential, though unproven, clinical interaction between these two widely used medications.

## Poichè PPI e clopidogrel = 1 volta / die

- Poichè dopo 4-6 ore la concentrazione plasmatica di Clopidogrel sono non misurabili

How to deal with the interaction in practice? The following steps could be suggested to clinicians who take care of patients on clopidogrel for coronary artery disease:

1. First, evaluate the risk of gastrointestinal ulcers and bleeding in those who are administered dual antiplatelet therapy after an acute coronary syndrome or a percutaneous coronary intervention with stent implantation (dyspepsia, previous gastrointestinal bleeding, concomitant use of NSAID or oral anticoagulants)
2. Administer PPI in patients at high risk of peptic ulcer or gastrointestinal bleeding and in all patients who are symptomatic for dyspepsia
3. Among all PPIs available prefer pantoprazole or rabeprazole on the basis of their pharmacokinetic profile and their property to be weak inhibitors of CYP2C19. Moreover pantoprazole did not interfere with antiplatelet clopidogrel activity in mechanistic pharmacodynamic trials and could be considered the first choice proton pump inhibitor in patients on dual antiplatelet therapy.
4. Separate the administration of clopidogrel and the PPI by 12-15 hours: rapid metabolism of clopidogrel and transient inhibitory effect of the PPI on CYP2C19 make any interaction unrealistic if the dosing of the two medications are staggered.

- PPI prima di colazione
- CLOPIDOGREL prima di dormire



Grazie per l'attenzione