



מרכז רפואי רבין  
Rabin Medical Center

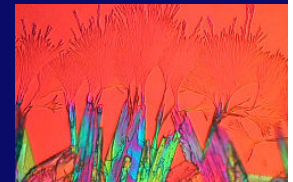


# Obstacles to Anti-Platelet Treatment in Patients Following PCI: Significant Interactions between Aspirin/Plavix and Other Medications

ICI Meeting, December 2008

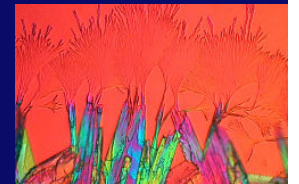
Tel-Aviv, Israel

Eli I. Lev, MD,  
Cardiology Department  
Rabin Medical Center



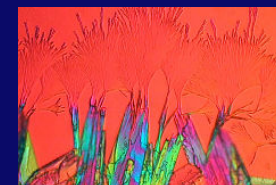
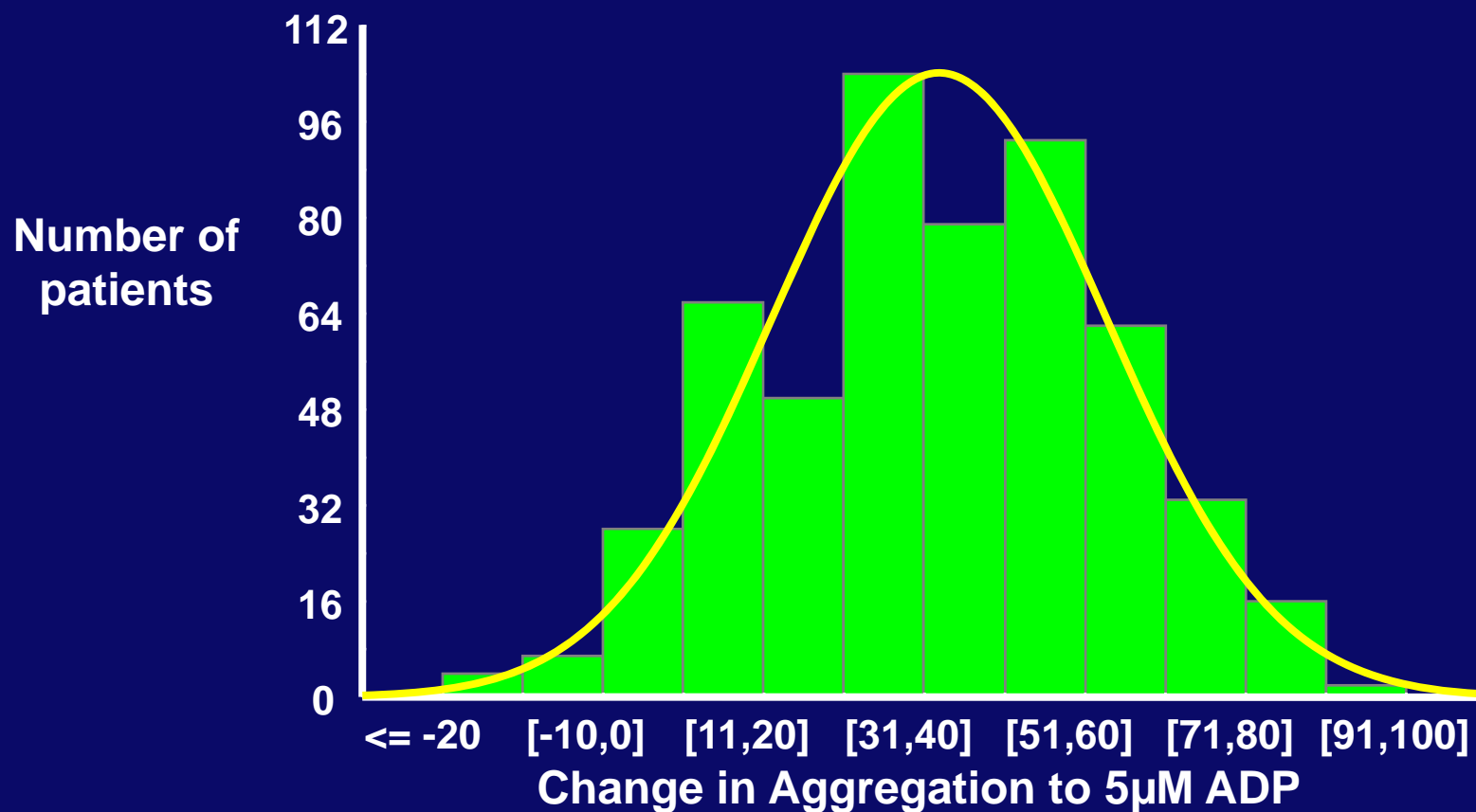
# Conflict of Interest

Research grants from Schering-Plough and  
Sanofi-Aventis

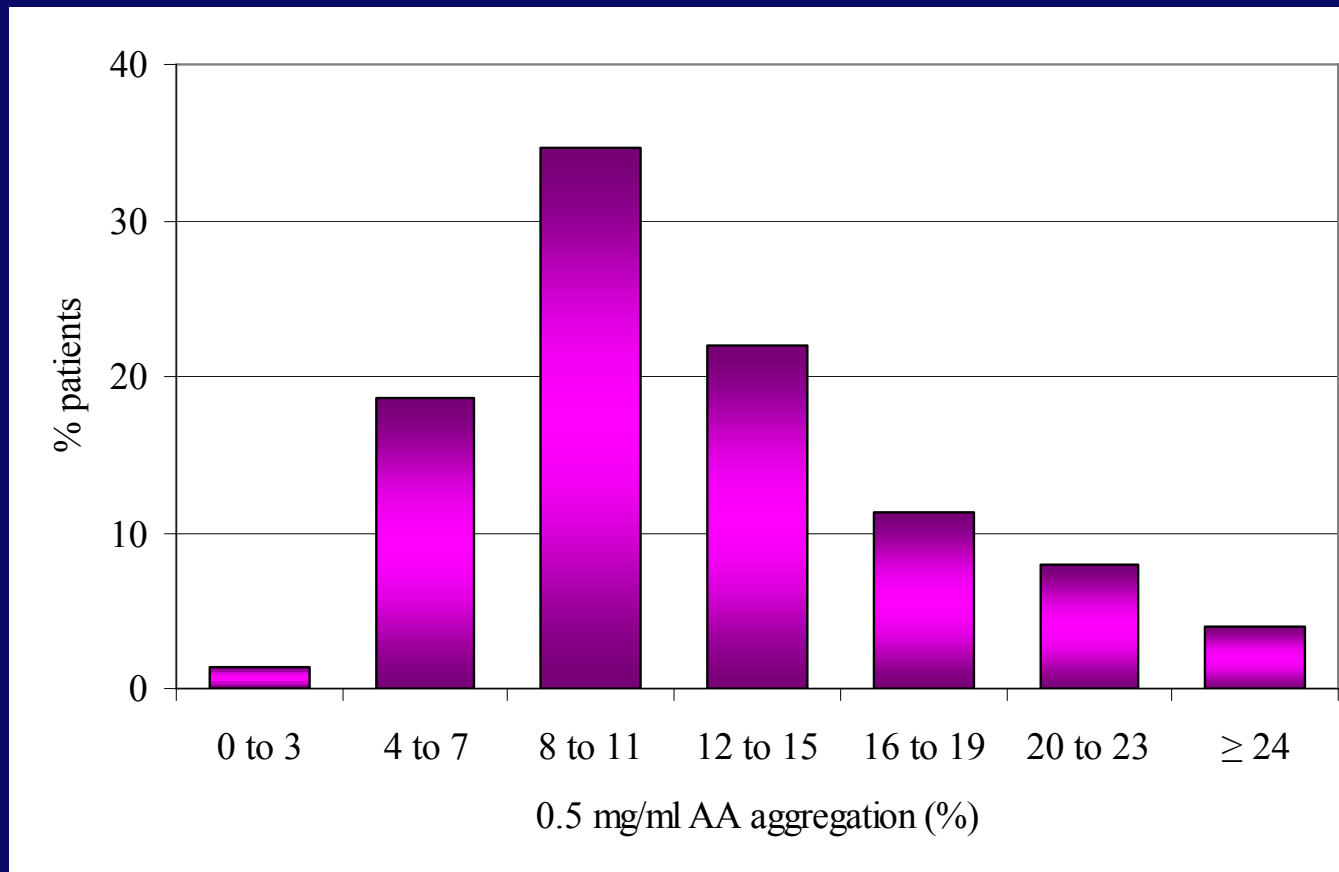


# Distribution of Responsiveness to Clopidogrel in 544 Individuals

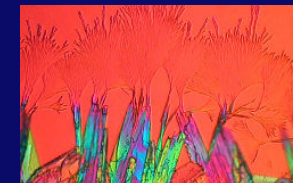
**A Normal Distribution: Consistent with a Poly-Genetic  
and Poly-Environmental Influence**



# Inter-patient Variability in Response to Aspirin (Platelet Aggregation)



150 pts undergoing elective PCI, *Lev E et al, J Am Coll Cardiol 2006*



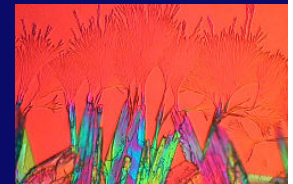
# The New York Times

## For Some, Aspirin May Not Help Hearts

By ANDREW POLLACK

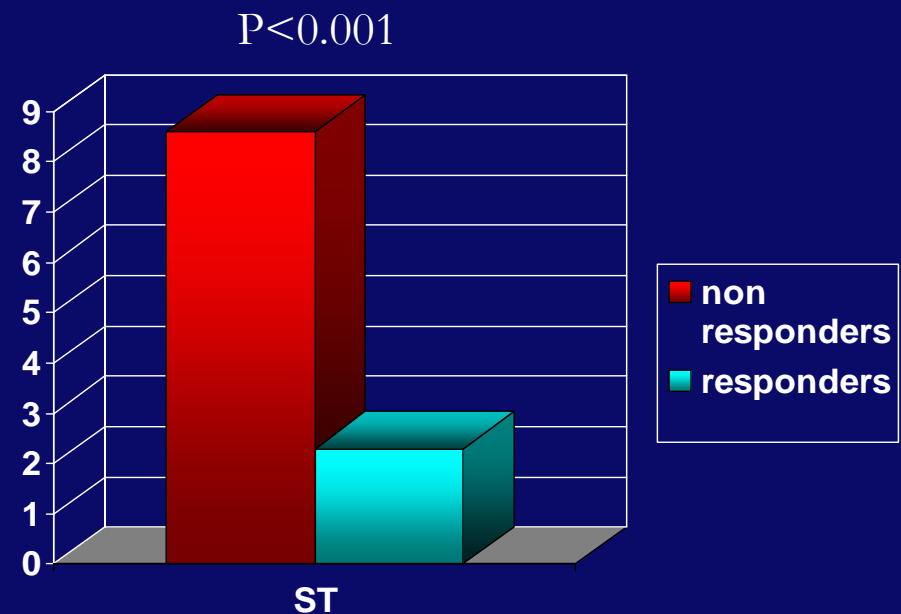
July 20, 2004

“More than 20 million Americans take aspirin regularly to help prevent heart attacks and strokes. But new evidence suggests that for many of them, the pills do little if any good. Recent studies have found that anywhere from 5 percent to more than 40 percent of aspirin users are "nonresponsive" or "resistant" to the medicine. That means that aspirin does not inhibit their blood from clotting, as it is supposed to.”

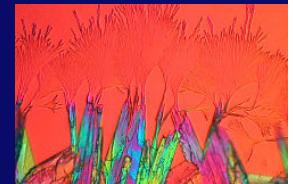


# Impact of Clopidogrel Response on Stent Thrombosis

- 804 pts who had successful PCI with DES implantation
- Loaded with 600 mg clopidogrel
- Platelet reactivity to ADP assessed 12-18 hrs after loading
- 105 pts (13%) not responsive to clopidogrel
- **ST incidence: 8.6% vs. 2.3%**
- Clopidogrel non response associated with HR of 3.1 (1.3-7.2) for ST

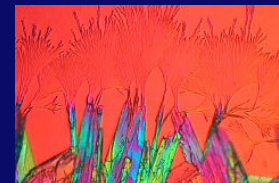


*Buonamici et al, JACC 2007*

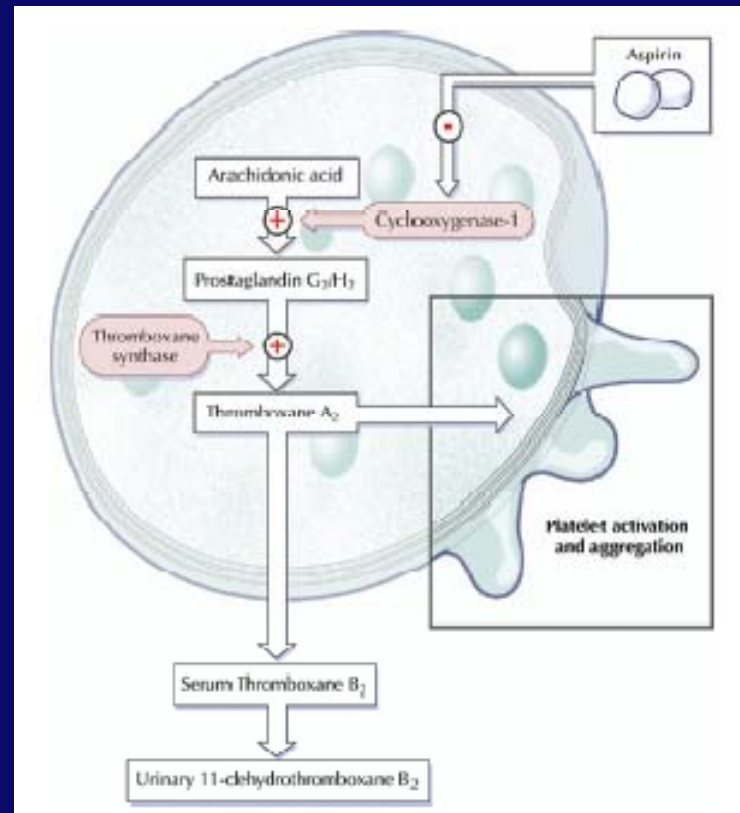


## Possible Drug Interaction Sites

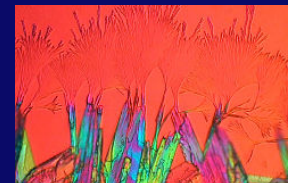
- Absorption
- Metabolism
- Bioavailability and distribution (protein binding and transport of the drug)
- Excretion and clearance – less relevant
- Target site (platelet COX-1 enzyme or platelet P2Y<sub>12</sub> receptor)



# Aspirin – Mechanism of Action

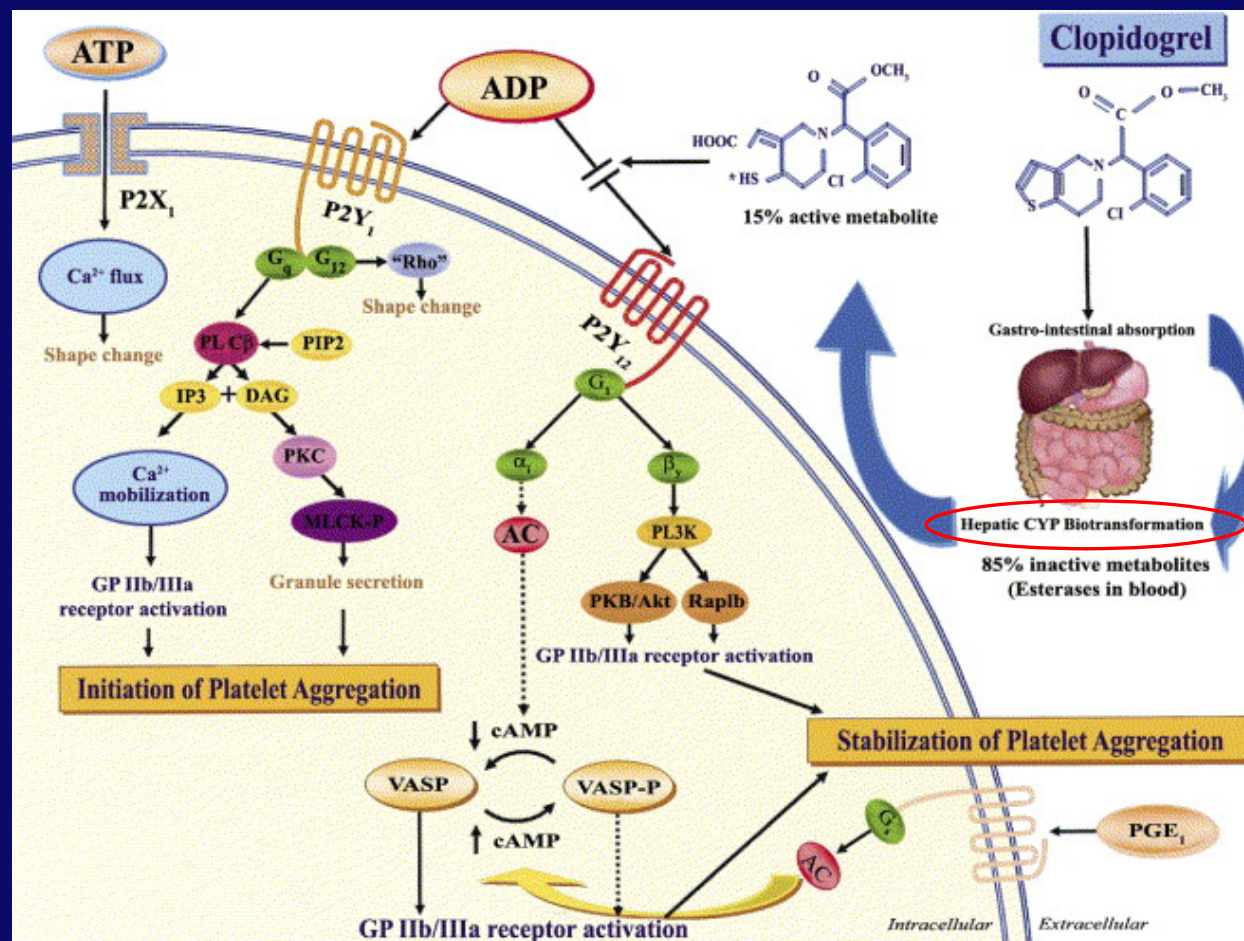


*Adapted from Gasparayan et al JACC 2008*

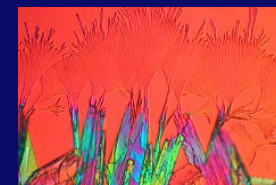


# Clopidogrel – Mechanism of Action

- Binding of ADP to the Gi-coupled P2Y<sub>12</sub> receptor results in stabilization of platelet aggregation.
- Inhibition of adenylyl cyclase reduces cAMP levels → this diminishes cAMP-mediated phosph. of vasodilator-stimulated phosphoprot. (VASP-P)
- The status of VASP-P modulates glycoprotein (GP) IIb/IIIa receptor activation



Adapted from Angiollillo D et al, JACC 2007



# Drug Interactions

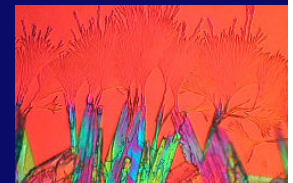


- NSAIDS
- H<sub>2</sub> Blockers

## Clopidogrel (plavix)

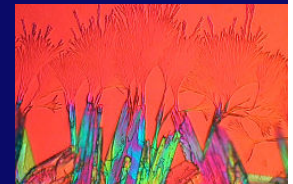


- Statins
- PPIs
- Ca Blockers
- Caffeine

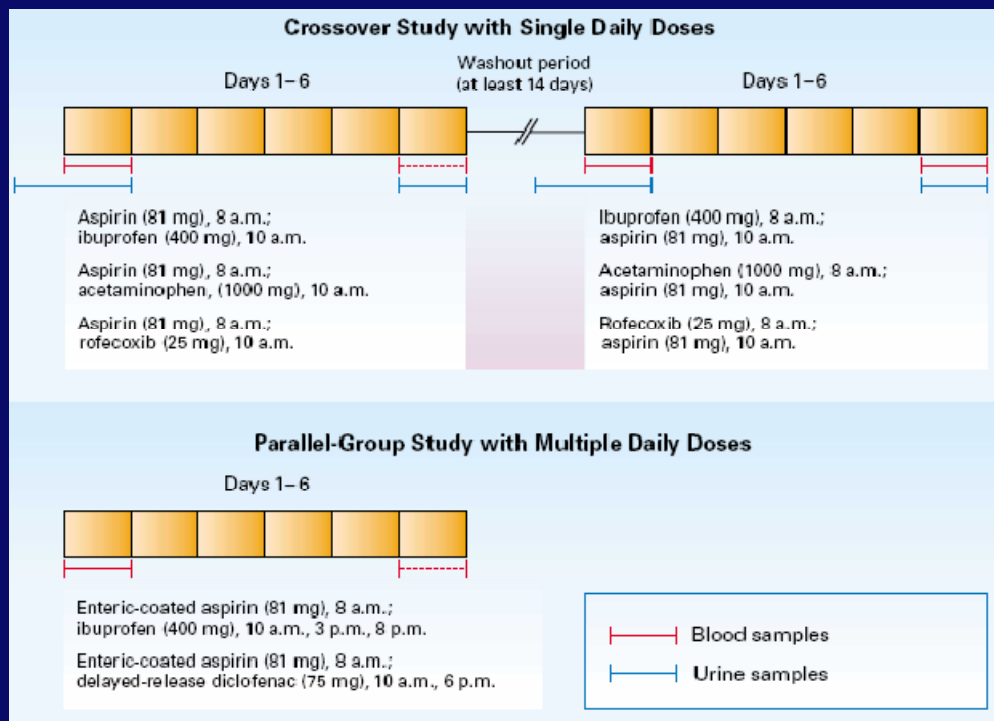


# ASPIRIN - NSAIDS

- Similar to aspirin, NSAIDs bind and inhibit platelet COX-1
- NSAIDs, unlike aspirin, bind **reversibly** at the enzyme active site, usually depressing platelet TXA<sub>2</sub> formation for only a portion of the dosing interval
- Both the aspirin- and the NSAID-binding sites lie within a narrow hydrophobic channel within the core of the enzyme → potential for a competitive interaction

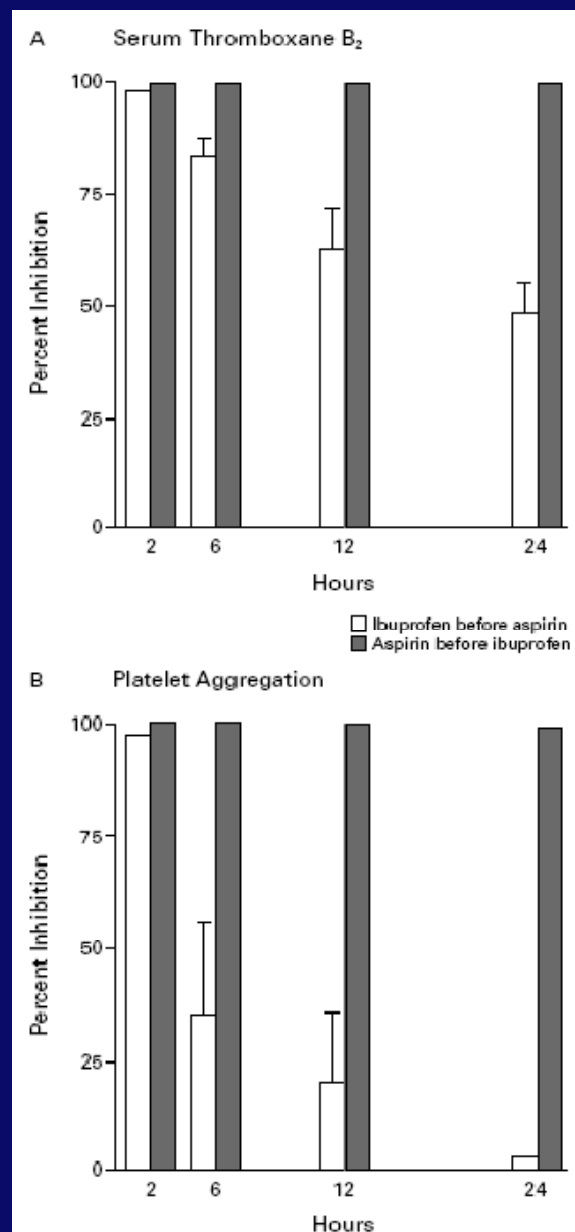


# ASPIRIN - NSAIDS



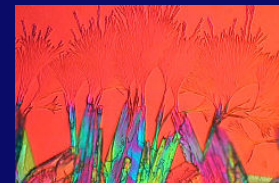
The concomitant administration of ibuprofen but not rofecoxib, acetaminophen, or diclofenac antagonizes platelet inhibition induced by aspirin !!

*Cattela-Lawson et al, NEJM 2001*



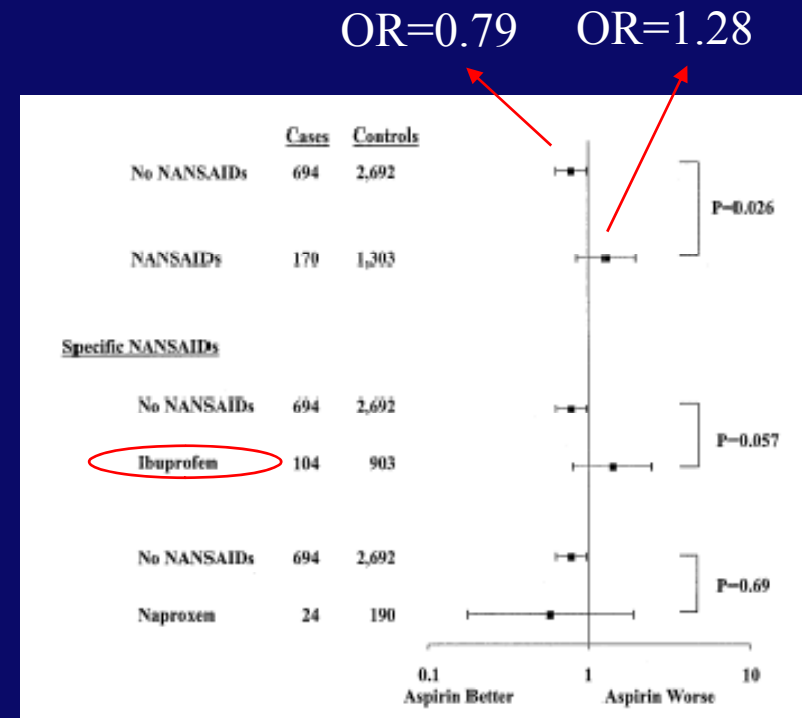
## ASPIRIN - NSAIDS

- In vitro: incubation of **naproxen** with platelets for 5 min before the addition of aspirin reduced the inhibition of TXB<sub>2</sub> production by aspirin
- Ex vivo (normal subjects): inhibition of serum TXB<sub>2</sub> production and platelet aggregation by ASA alone was not sig. altered by co-administration of naproxen **for > 1 week** (given either 2 h before or after ASA).
- Single dose of naproxen did inhibit the effect of a single dose of ASA



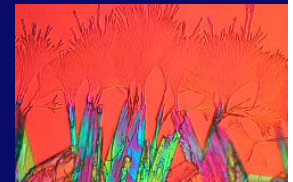
# ASPIRIN – NSAIDS, Clinical Significance?

- Case control study of first non-fatal MI (n=1,055) vs. controls (n=4,153)
- ASA alone was associated with ↓OR of MI in pts not also using NSAIDs (OR 0.79; 95% CI: 0.63-0.98)
- ASA was not associated with reduced OR of MI among pts who were also using NSAIDs (OR 1.28; 95% CI: 0.85-1.94)
- Among frequent (4 times per week) NSAID users, the OR of MI for ASA vs. no ASA was 2.04 (95% CI: 1.06-3.94).



Odds ratios of MI among aspirin users vs. nonusers of aspirin

*Kimmel SE et al, JACC 2004*

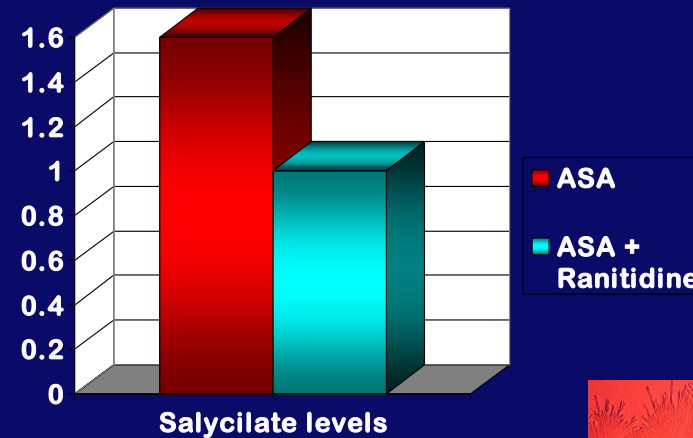
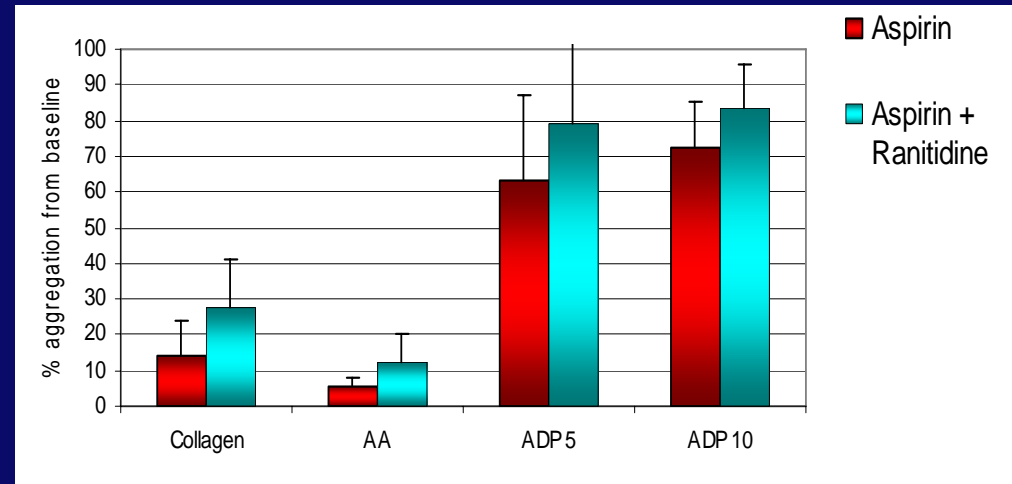


# ASPIRIN – H<sub>2</sub> Blockers

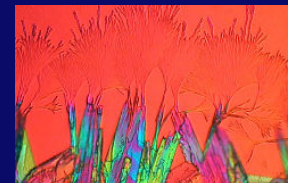
H<sub>2</sub> blockers cause an increase in gastric pH and may induce increased gastric emptying rate → effects that may reduce the relative amount of aspirin absorbed in the stomach.

In healthy volunteers ranitidine appears to attenuate the anti-platelet effects of aspirin.

P=0.03   P=0.07   P=0.04   P=0.02

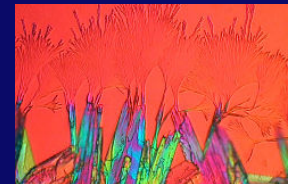


*Lev E et al, AJC 2007*



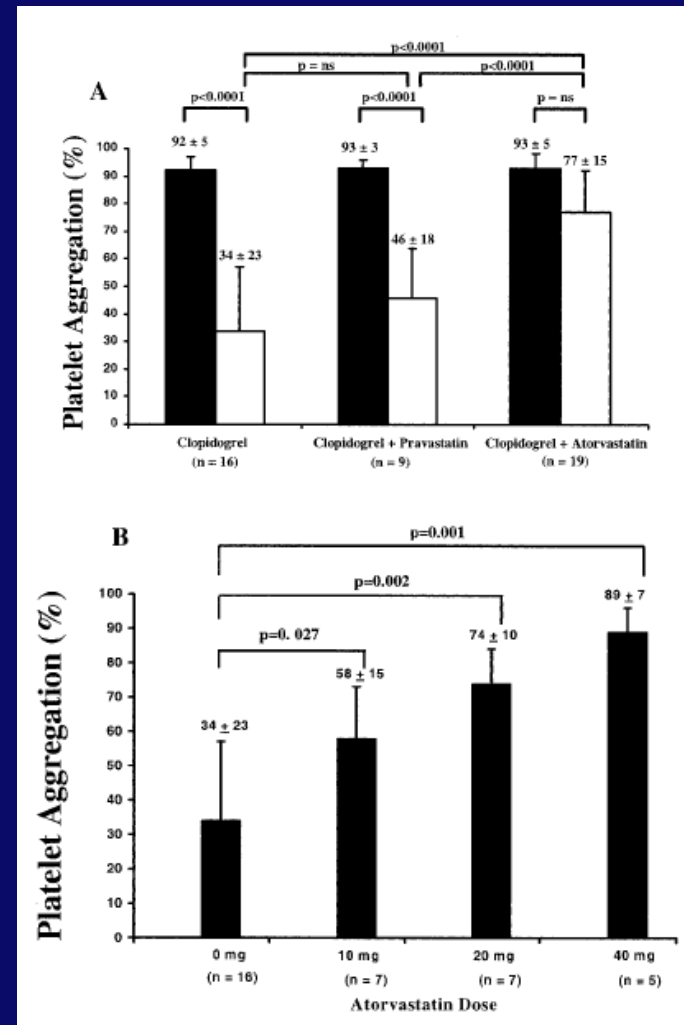
## Clopidogrel - Statins

- Clopidogrel is an inactive pro-drug that requires oxidation by the hepatic cytochrome P450 3A4 (CYP3A4) to generate an active metabolite
- Hepatic CYP3A4 is responsible for the metabolism of many other drugs including several lipophilic statins (e.g. atorvastatin), CA-blockers, erythromycin, etc.
- Possible attenuating interaction



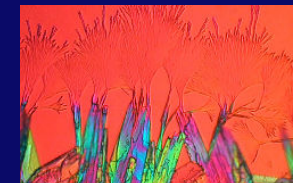
# Clopidogrel - Statins

- **Conclusions:**  
“Clopidogrel is less effective in inhibiting platelet aggregation when coadministered with atorvastatin, a CYP3A4 substrate”.
- “Atorvastatin inhibits CYP3A4 activity in a dose-dependent manner, and thereby decreases the metabolic conversion of clopidogrel to its pharmac. active form”.



Platelet aggregation before and 24 hrs after clopidogrel; pts undergoing PCI

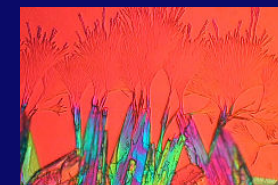
Escalating doses of atorvastatin



# Clopidogrel - Statins

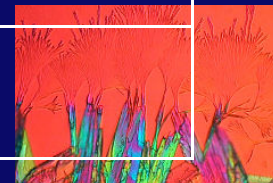
**Table I.** Ex vivo studies of clopidogrel-statin interaction

| Study                          | Patients | Clopidogrel dose              | Platelet function study        | Effect of CYP3A4 statin on clopidogrel's antiplatelet effect |
|--------------------------------|----------|-------------------------------|--------------------------------|--|
| Lau et al <sup>1</sup>         | 44       | 300 mg load, then 75 mg daily | WBSPC                          | Attenuates   |
| Neubauer et al <sup>4</sup>    | 47       | 300 mg load, then 75mg daily  | Flow cytometry                 | Attenuates   |
| Mach et al <sup>5</sup>        | 21       | 75 mg daily                   | LTA                            | No effect by atorvastatin, attenuated by simvastatin         |
| Hochholzer et al <sup>6</sup>  | 1397     | 600 mg load, then 75mg daily  | LTA                            | No effect  |
| Mitsios et al <sup>7</sup>     | 45       | 375 mg load, then 75 mg daily | Flow cytometry<br>LTA          | No effect  |
| Serebrany et al <sup>8</sup>   | 75       | 300 mg load, then 75 mg daily | Flow cytometry<br>LTA          | No effect  |
| Muller et al <sup>9</sup>      | 77       | 600 mg load                   | Flow cytometry<br>LTA          | No effect  |
| Gorchakova et al <sup>10</sup> | 180      | 600 mg load                   | LTA                            | No effect  |
| Smith et al <sup>11</sup>      | 58       | 300 mg load, then 75 mg daily | Flow cytometry<br>LTA<br>WBSPC | No effect  |
| Zsomboki et al <sup>12</sup>   | 48       | 300 mg load, then 75 mg daily | Ultegra<br>LTA                 | Increases  |
| Piorkowski et al <sup>13</sup> | 49       | 300 mg load, then 75 mg daily | Flow cytometry                 | Increases  |
| Vinholt et al <sup>14</sup>    | 66       | Chronic 75 mg daily           | LTA<br>PFA-100                 | Increases  |



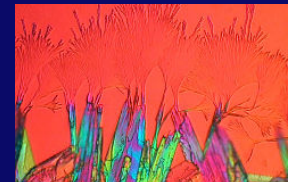
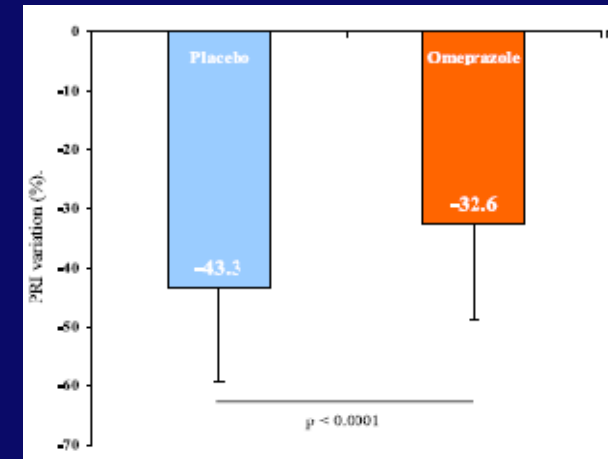
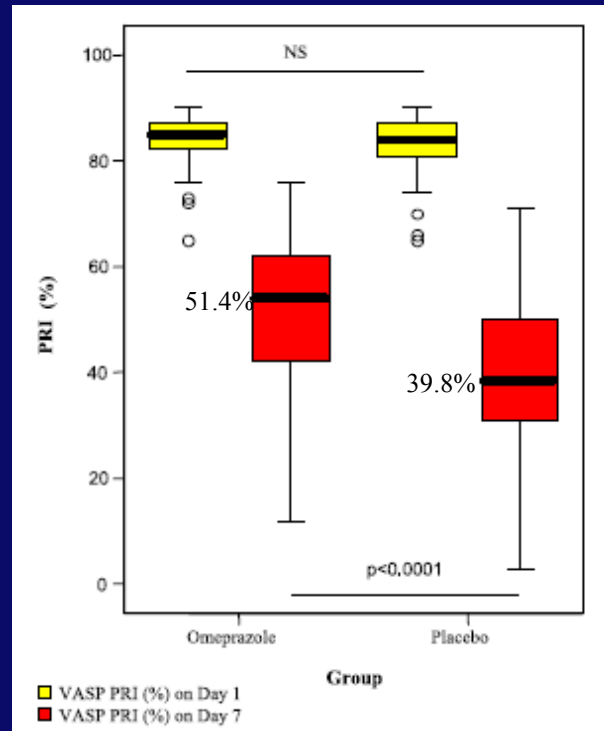
# Clopidogrel – Statins, clinical significance?

| Study            | Type of study                                 | Patients                              | Effect of statin on benefit from clopidogrel |
|------------------|---|---------------------------------------|--|
| Mukherjee et al  | Prospective single-center cohort              | 1651 with ACS                         | <b>None</b>                                  |
| CREDO            | Post hoc analysis                             | 2116 undergoing PCI                   | <b>None</b>                                  |
| MITRA PLUS       | Prospective multicenter registry              | 1576 with ACS                         | <b>None</b>                                  |
| GRACE            | Prospective multicenter registry              | 15693 with ACS                        | <b>Synergistic</b>                           |
| Brophy et al     | Retrospective analysis of population database | 2927 undergoing PCI                   | <b>Detrimental</b>                           |
| PROVE-IT TIMI 22 | Post hoc analysis                             | 4162 with ACS                         | <b>None</b>                                  |
| CHARISMA         | Post hoc analysis                             | 10078 with CV disease or risk factors | <b>None</b>                                  |



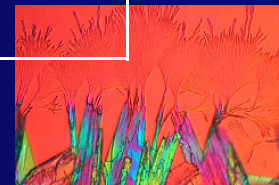
# Clopidogrel - PPI

- Hypothesis: PPIs reduce the biological action of clopidogrel, probably by competitive metabolic effects on CYP 2C19.
- Double-blind placebo-controlled trial, 124 pts undergoing PCI received ASA + clopidogrel and were randomized to receive either omeprazole or placebo for 7 days. Clopidogrel effect was tested by VASP-P
- Omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y<sub>12</sub>



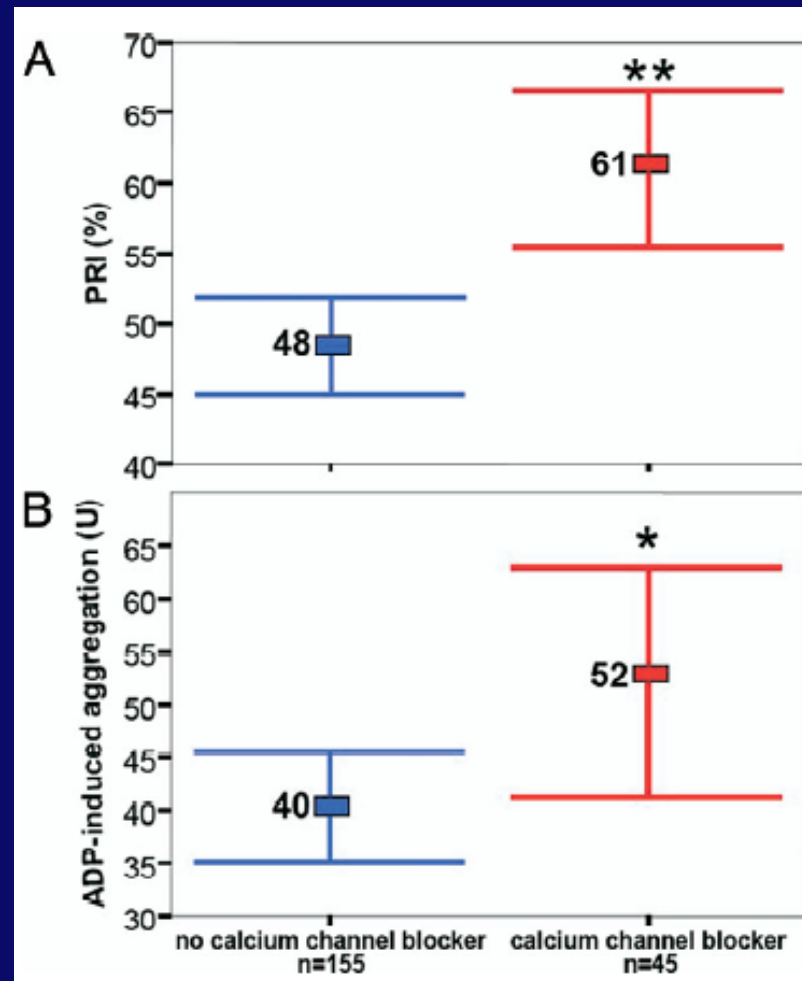
## Clopidogrel – PPI, Clinical significance?

| Study  | Patients                                     | Outcome                   | OR   |
|--|--|---------------------------|--|
| Pezalla et al<br>(JACC 2008,<br>letter) registry | 5,500 pts<br>receiving<br>clopidogrel ± PPIs | 1 year MI                 | RR for MI 337%<br>higher in ↑PPI<br>group than cntrl |
| Auber et al<br>(AHA 2008)<br>registry            | 14,383 pts who<br>underwent<br>stenting      | 1 year major CV<br>event  | 1.8 (1.6-1.97)<br>(higher with<br>PPI)               |
| Ho PM et al<br>(AHA 2008)<br>VA registry         | 3,311 ACS pts                                | >1 year death /<br>MI     | 1.3 (1.07-1.53)<br>(higher with<br>PPI)              |
| Dunn SP et al<br>(AHA 2008)<br>Post-hoc anal.    | 2,116 pts from<br>CREDO trial                | 1 year<br>death/MI/stroke | 1.5 (1.1-2.1)<br>(higher with<br>PPI)                |



# Clopidogrel – CA Channel Blockers

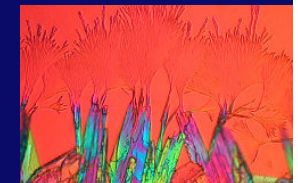
Non-randomized study  
200 pts undergoing  
PCI (155 received  
clopidogrel and 45  
received clopidogrel +  
CCB)



P=0.001

P=0.05

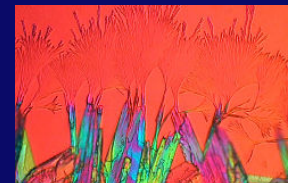
Siller-Matula et al, JACC 2008



# Clopidogrel - Caffeine



- Inhibition of the P2Y<sub>12</sub> receptor by clopidogrel prevents uncoupling of the G<sub>i2</sub> protein which ultimately leads to increased cAMP formation in the platelet
- Cyclic AMP is a key molecule in preventing and inhibiting platelet aggregation
- cAMP levels are affected by several other commonly used compounds – such as caffeine

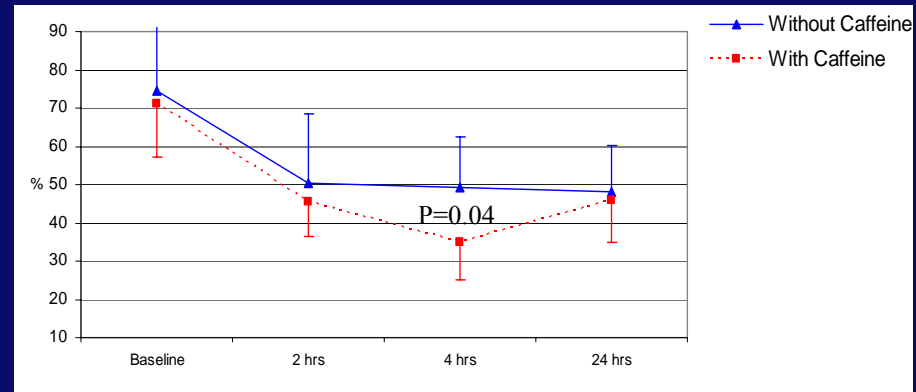


# Clopidogrel - Caffeine

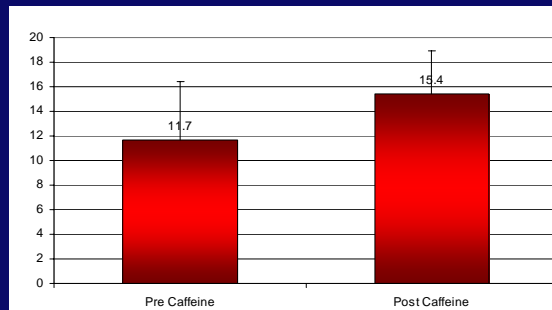


Crossover study, 12 healthy volunteers, 300 mg clopidogrel followed (30 min.) by 300 mg caffeine tablets

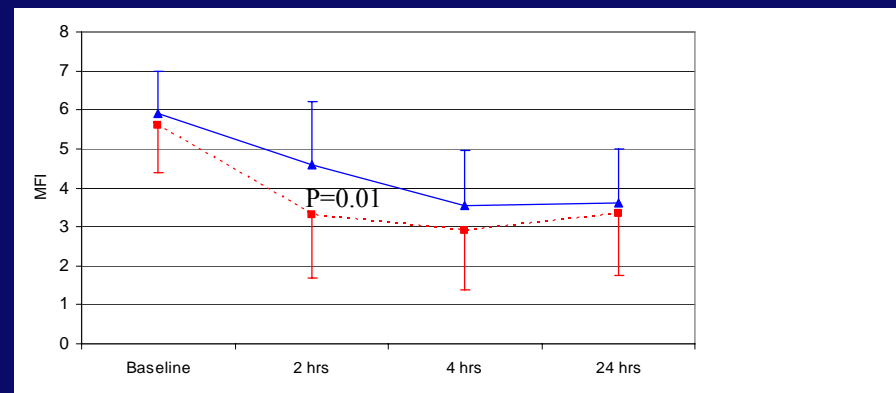
## Platelet Aggregation 5 MicroM ADP



## Plasma cAMP levels

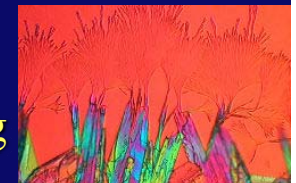


## PAC-1 binding, GP IIb/IIIa activation



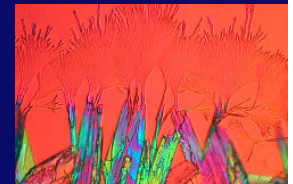
*Lev et al, AHJ 2007*

Caffeine administration was associated with  
↑ platelet inhibition 2-4 hrs after clop. loading



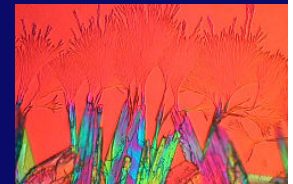
## SUMMARY

- Several drug interactions have been described for both aspirin and clopidogrel at the platelet level, may contribute to variability in response, but probably only few carry clinical significance for prolonged Rx
- Majority of data for aspirin → ibuprofen interaction, also a signal for clinical significance.
- Therefore, co-administration of aspirin with ibuprofen should probably be avoided if possible (other NSAIDS?)



## SUMMARY – cont.

- Clopidogrel – statin interaction not clinically sig.
- Clopidogrel – PPI interaction with a signal for clinical significance (switch to H<sub>2</sub> blockers?)
- Further studies to confirm clinical implications including risk of stent thrombosis as a result of attenuated clopidogrel action
- Prasugrel would resolve and “bypass” most interactions at the cytochrome P450 level
- Until then have your pts drink coffee !!



THANK YOU

