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# Aspirin and Clopidogrel Resistance

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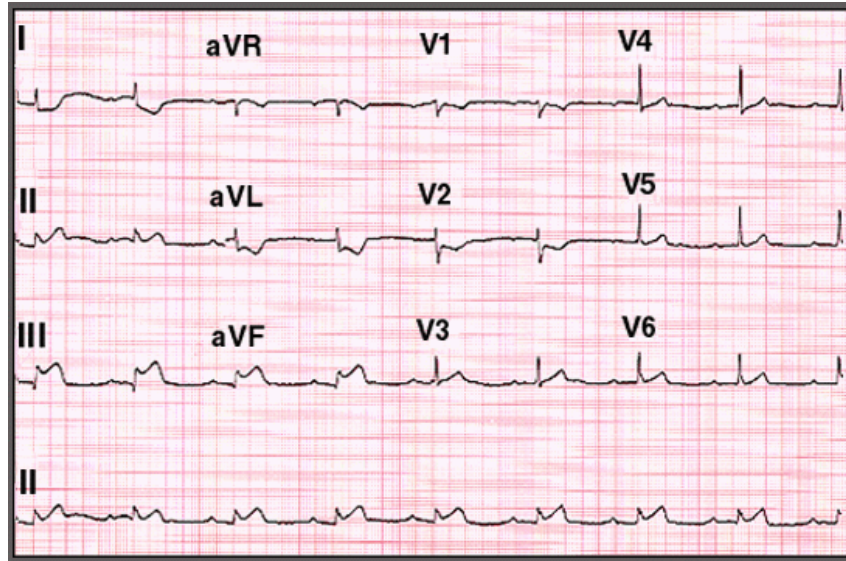
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# The Case of JS



- JS is a 52 year-old African-American male with a history of Crohn's disease, insulin-dependent diabetes mellitus, and hypertension who was ordered for a pharmacologic stress test as an outpatient for some vague left shoulder pain.
- Although chest pain free, the nuclear study suggested inferolateral ischemia with a preserved left ventricular ejection fraction.

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- Cardiac catheterization and coronary angiography demonstrated single-vessel right coronary artery (RCA) disease with an 80-90% mid to distal lesion.
  - Three overlapping bare metal stents were placed and post-PCI angiography demonstrated TIMI 3 flow with 0% residual obstruction.
  - The patient tolerated the procedure well and was discharged with aspirin 325mg and clopidogrel 75mg per day after completing 14 hours of eptifibatide
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- On day 2 after PCI, the patient went to his local emergency room with crushing substernal chest pain, nausea and left arm pain (his neck did not hurt) along with acute ST elevations in the inferior leads on EKG.
  - He was rushed back for catheterization and had an additional bare metal stent overlapping a prior stent as the clot was unable to be aspirated out.
  - The result was successful TIMI 3 flow restoration with 0% residual. At this point, the concern for clopidogrel resistance was considered and after discussion with the patient regarding potential adverse effects, the decision was made to double the clopidogrel dose to 75mg twice daily.
  - Resistance labs were sent.
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- Unfortunately, on day 5 after the initial catheterization, the patient had acute return of his thrombosis and had a repeat inferior myocardial infarction. Cardiac catheterization number 3 was performed and the thrombus was able to be dissolved and JS had resolution of his symptoms.
- In vitro labs demonstrated marked aspirin and clopidogrel “resistance”.



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# What do you do?

- The guy just had 2 big MIs and 8 cm of stent placed because of us. And, we didn't fix his neck pain.
  - He has a propensity to GI bleed (Crohn's)
  - Rare
  - No consensus on what to do
  - What does it even mean to be aspirin or clopidogrel resistant?
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# Goals of this Presentation



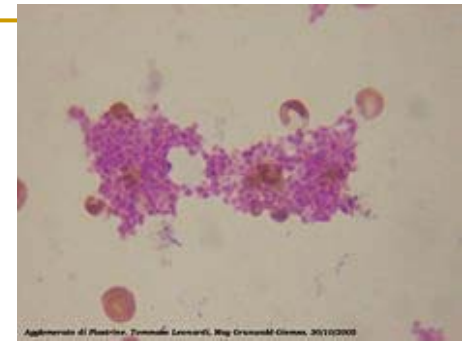
- Discuss aspirin resistance
  - Who might be at risk and what might be done to overcome this risk
  - Briefly comment on clopidogrel resistance post-PCI
  - Discuss methods to possibly overcome this resistance
  - Convince you that I do not want to be a cardiologist
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# Acetylsalicylic Acid (tradename Aspirin)

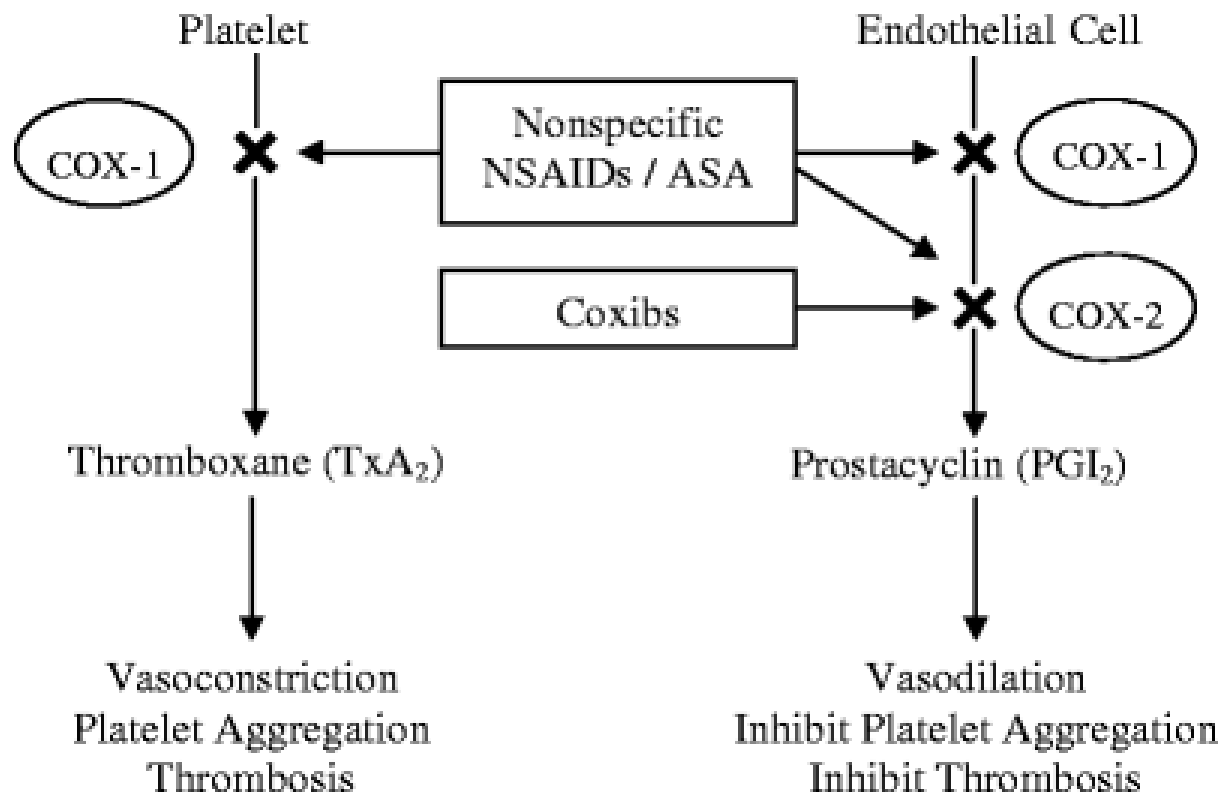
- First developed in 1897 at the Bayer Labs by Felix Hoffman
- Used as an analgesic and antipyretic
- Not until 1971 did John Vane discover that ASA suppresses thromboxane and prostaglandins, which earned him knighthood and a Nobel Prize in 1982.



# ASA



- Irreversibly inhibits cyclo-oxygenase (COX)-1 by acetylating a serine residue at position 530 and modifies the enzymatic activity of COX-2.
- Loss of platelet COX-1 leads to decreased synthesis of Thromboxane  $A_2$ , which is essential for full platelet aggregation
- Platelets are anucleate, so time of inhibition is the lifetime of the platelet (7-10 days).
- COX-1 is in most cells, COX-2 is virtually undetectable except at sites of inflammation



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# Antiplatelet Trialists' Collaboration

- Meta-analysis of 287 studies, 135,000 high risk patients randomized to antiplatelet therapy vs control or another antiplatelet agent ( $p < 0.00001$ ).

\*did not separate out for resistance\*

Receiving antiplatelet therapy vs control:

- Any serious vascular event      ↓ 25%
  - Non-fatal MI                              ↓ 33%
  - Non-fatal CVA                             ↓ 25%
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# What is the correct dose of aspirin for primary prevention?



- If you haven't had a heart attack, what you are taking is fine.
  - If you had a GI bleed, it is too much
  - If you had a heart attack or stroke, you need more
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# Dosing of ASA

- A single dose of 150mg ASA completely abolishes the platelet  $\text{TxA}_2$  as measured by its stable breakdown product  $\text{TxB}_2$ .
  - Once steady state, the same effect can be achieved with 30-50mg daily.
  - Recent clinical studies have not found evidence to support higher doses of aspirin for primary prevention of thromboembolic events
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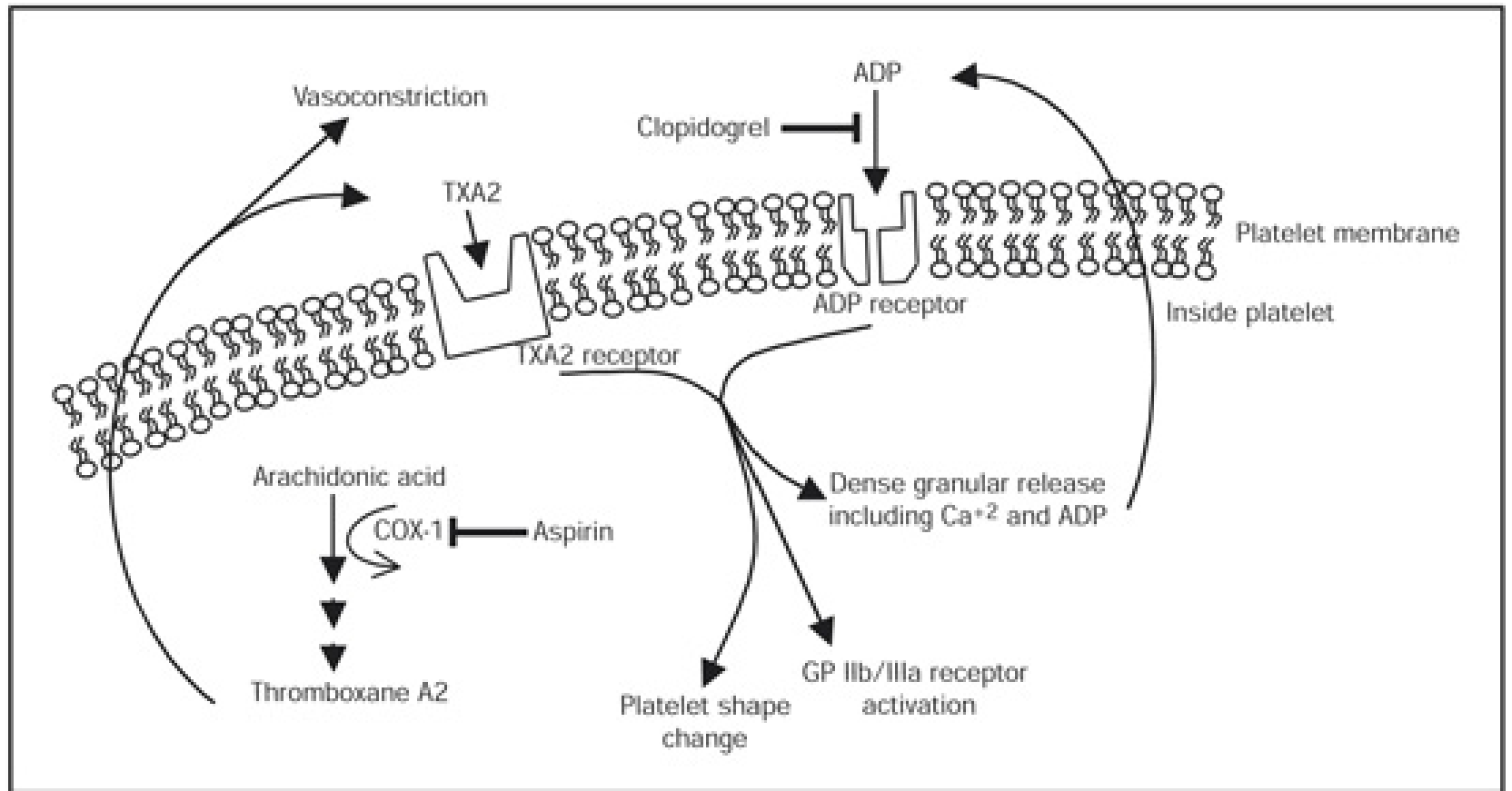
# What gets platelets going

Things that make platelets sticky

- ADP
- Thrombin
- Arachadonic Acid
- Collagen
- Epinephrine
- Thromboxane

Things that make them less sticky

- Prostacyclins
  - Anything that blocks things in the other column
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# Summary

1. Platelets make clots (thrombi in the bloodstream)
  2. ASA blocks COX-1 irreversibly to not allow thromboxane to activate platelet aggregation
  3. ASA has been proven to prevent thromboembolic events
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If ASA blocks platelet aggregation so well, why do people still get heart attacks and strokes?

- Obvious: there are multiple pathways, blocking COX-1 is just one way. Other things can overcome that pathway, such as thrombin and epinephrine (so you don't bleed to death with a paper cut)
  - Maybe less obvious: they are resistant to ASA.
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# Defining ASA Resistance

- Clinical “Resistance”: took ASA, still had a vascular event. Not resistance but a failed clinical goal. Treatment failure.
  - Laboratory Resistance: multiple assays available with normal values dependent on lab, those with above range aggregation while on ASA are resistant.
  - True Resistance: appropriate dosing and compliance of ASA with a failure to inhibit thromboxane A<sub>2</sub> production
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# Methods of Testing Platelet Aggregability

## Bleeding Time

- Involves inflating BP cuff to 40mmHg and inflicting a cut of 5-10mm length and 1mm depth on the volar surface of the forearm. The wound is gently blotted every 30 sec until bleeding stops.
- In vivo test, but lacks sensitivity- varies with skin thickness, temperature
- Highly inaccurate and poorly reproduced

## \*Platelet Function Analyser (PFA)-100

- Measures the time to cessation of flow (closure time) of blood through a capillary via a membrane coated with collagen and epinephrine or collagen and ADP. Like an in vitro bleeding time. Aspirin is expected to increase the closure time.
- Point of care method, reported to predict clinical ASA resistance
- Varies with VWF, platelet, RBC concentration

## Light Transmission Aggregometry

- Spectrophotometric technique which looks at the changes of optical density due to platelet aggregation, using platelet rich plasma and various concentrations of ADP and arachadonic acid

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# Methods of Testing Resistance (cont'd)

## VerifyNow/ Ultegra rapid platelet function assay

- Automated assay based on the ability of activated platelets to bind fibrinogen
- Point of care method; reported to predict clinical ASA resistance

## Serum Thromboxane B2

- Breakdown product of TXA2 → TXB2
- Very low concentration, difficult to assess change

## Urinary 11-dehydro thromboxane B2

- Breakdown product of TXA2 → TXB2 → 11DTB2
  - Not solely derived from platelet TXB2
  - Reported to predict clinical ASA resistance
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# PFA-100

- Simulates a damaged blood vessel to analyze the function of platelets in primary hemostasis
- Point of care testing- takes about 5 min
- Makes a great cup of coffee



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# PFA-100

- Uses cartridges of collagen and epinephrine (CEPI) or collagen and ADP (CADP) which coat the membrane
  - Test is measured in Closure Time (CT) or the time it takes for the 150 micrometer aperture to be occluded
  - CT CEPI >180 s; CADP <116 s - "Aspirin Effect": ASA only prolongs the CEPI cartridge, clopidogrel (stay tuned) only prolongs the CADP cartridge
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# Platelet Physiology Subcommittee of the International Society of Thrombosis and Haemostasis



- PFA-100 does not have sufficient sensitivity or specificity to be used as a screening tool.
- Affected by hematocrit, VWF concentration, platelet count
- Normal values are to be determined by each lab, but no “normal” blood sample is given
- Use should at best be restricted to research studies and prospective clinical trials

# Aspirin Resistance



A 2008 meta-analysis of 20 studies and 2920 patients with cardiovascular disease, using a variety of platelet assays, all on ASA 75-325mg daily; some on other antiplatelet agents found [18]:

- **28%** of patients were ASA resistant, and those patients did ***not*** appear to benefit from other antiplatelet agents
- This number is consistent with other studies, on average in this higher risk population

Of those ASA resistant:	# of Studies	# patients	Odds Ratio	P value
All Cerebro-vascular Events	20	2930	3.85	<0.001
Death	4	728	5.99	<0.003
ACS	9	1275	4.06	<0.001
75-100mg/ day	3	228	21.17	<0.003
>100- 325mg/ day	9	1309	2.81	<0.001
500mg TID	1	174	14.53	<0.001
All Doses	12	1710	3.28	<0.001

# ASPECT: An Analysis From the Aspirin-Induced Platelet Effect [19]



Are diabetics more likely to be ASA resistant?

- Examined the effect of ASA (81, 162, 325mg per day for 4 weeks on 120 stable diabetics and 90 non-diabetics, all with known CAD.
- Used light transmission aggregometry (LTA), VerifyNow, PFA-100, and urinary levels of 11-dehydro  $\text{TxB}_2$ .



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# ASPECT

- Diabetics taking 81mg/day demonstrated a significantly higher prevalence of ASA resistance:

□ LTA:	27% vs. 4%	P<0.001
□ VerifyNow	13% vs. 3%	P<0.005
□ PFA-100	not significant	
□ Urine dh TxB <sub>2</sub>	37% vs. 17%	P<0.03

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# ASPECT

- Increasing the dosing from 81mg to higher doses achieved similar rates of resistance and platelet function levels between groups
  - No resistance was seen in 325mg/ day groups
  - No comparison of glucose controlled vs uncontrolled
  - Maybe diabetics need more than 81mg??
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# Summary



- We have shown that high risk patients who are ASA resistant appear to have a increased cardiovascular risk and do not seem to benefit from other antiplatelet agents.
- Women are slightly more likely than men, and those with renal insufficiency are more likely to be ASA resistant according to the largest and most recent meta-analysis we have.
- Diabetics may need more than 81mg/ day
- We base these results on tests that are not proven or consistent

# Possible mechanisms of aspirin resistance:

## Bioavailability

- Non-compliance
- Underdosing
- Poor absorption (enteric coated aspirin)
- Interference: NSAID co-administration → competition for COX binding site

## Platelet function

- Incomplete suppression of thromboxane A<sub>2</sub> generation
- Accelerated platelet turnover, with introduction into bloodstream of newly formed, drug-unaffected platelets. ie. surgery, inflammation.
- Stress-induced COX-2 expression in platelets
- Increased platelet sensitivity to ADP and collagen

## Single nucleotide polymorphisms

- Receptors: GPIIb-IIIa, collagen receptor, thromboxane receptor, etc.
- Enzymes: COX-1, COX-2, thromboxane A<sub>2</sub> synthase, etc.

## Platelet interactions with other cells

- Endothelial cells and monocytes provide PGH<sub>2</sub> to platelets
- (bypassing COX-1) and also synthesize their own thromboxane A<sub>2</sub>

## Other factors

- Smoking, hypercholesterolemia, exercise, stress, etc.

# Ibuprofen/ Non-selective NSAIDs



- Inadequate inhibition by ASA due to non-selective inhibitors temporarily occupying the COX-1 receptor
  - Studies show that if you give ASA 2 hours prior to ibuprofen, the platelet aggregation is achieved.
  - ASA is **unable** to have its effect if ibuprofen is taken three times a day.
  - COX-2 inhibitors some of which were taken off the market, may cause increased thrombosis due to imbalance of the prostacyclin/ thromboxane balance
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## Play Along: how do we overcome aspirin resistance?

- Tirnakiz et al. found an improvement in PFA CT with the addition of 40mg atorvastatin ( $P < 0.0001$ ) over a 3 month period[10]. The authors speculated it was a class effect due to decreasing LDL which may be a platelet activator.
  - Clopidogrel? Most large studies did not find a benefit in adding it for prevention in those who are ASA resistant. It is speculated that if the ATC separated out resistant patients, the benefit to the ASA sensitive would be 50% (and not 25%)
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# Just add more *ASA*

- In theory, we could keep checking bloodwork and increasing the aspirin dose until we achieve a satisfactory closure time (good luck getting insurance to pay for that).
  - No convincing clinical correlation for doing this.
  - More studies are necessary
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# Clopidogrel

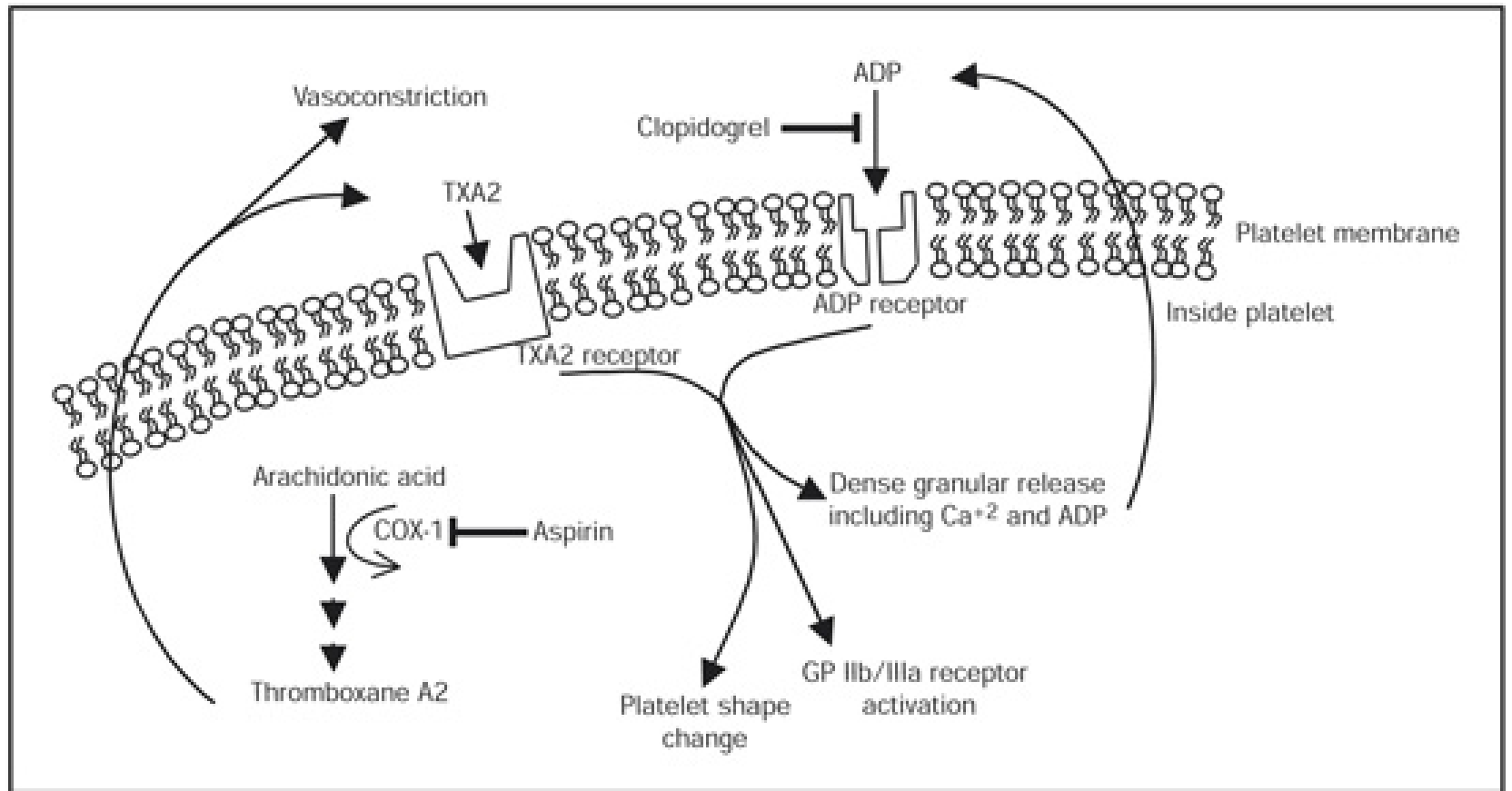


- Approved for (select) prevention of thrombotic events, as an adjunct with ASA in PCI, and in ACS.
- CREDO and PCI-CURE were both major prospective studies which demonstrated a 27-31% relative risk reduction with clopidogrel and aspirin vs. aspirin alone post-PCI.

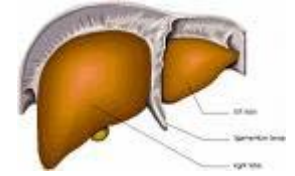
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# Clopidogrel Mechanism of Action

- Clopidogrel (and ticlopidine) are thienopyridines that irreversibly bind to the platelet surface P2Y<sub>12</sub> ADP receptor, inhibiting ADP-induced platelet activation.
  - Irreversible, so return of platelet function is with new platelets (~7 days; miraculously 5 if you need to get them to CT surgery)
  - Clopidogrel has proven more effective than ASA in some studies for prevention, but cost and NNT of 115 make it less than ideal.
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# Pharmacology of Clopidogrel



- There is a normal distribution of clopidogrel's effect, with an average of 40-50% platelet inhibition.
- A prodrug, clopidogrel must be converted to an active metabolite in the liver via the cytochrome P450 3A4 enzyme. The activity of this enzyme is variable in the population, and effect is unpredictable.
- Strong agonists such as thrombin are not affected by clopidogrel

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# Defining Clopidogrel Resistance

- In published studies, the prevalence of resistance is as high as 30-40%, generally using PFA-100 ADP or LTA.
  - Values for “normal” are somewhat arbitrary
  - Like for ASA, most likely not a true resistance but a decreased bioavailability.
    - Variability in CYP 3A4
    - Effect can be overcome by augmenting dose
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# Clopidogrel Resistance- Atorvastatin?

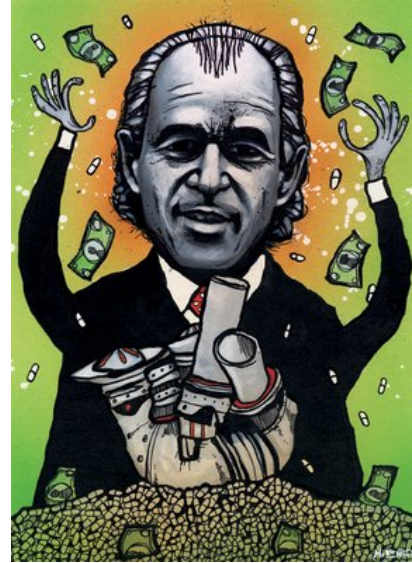


- In vitro studies show up to 90% decrease in clopidogrel activation when given at an equimolar dose
- A study of 44 patients post PCI on clopidogrel were randomized to atorvastatin (CYP 3A4 metabolized) vs. pravastatin (not CYP 3A4).
- Significant attenuation of platelet inhibition was noted in the atorvastatin group 77% vs 34% ( $p < 0.0001$ ).
- Subsequent studies have not shown this effect and many medications are also metabolized by this enzyme

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# Cytochrome P450 3A4 metabolized medications that JS was taking

- Prednisone (for a iodine contrast allergy)
- Amlodipine
- Glyburide
- Atorvastatin



Difficult to implicate one medication given that many medications are 3A4 metabolized

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## Class Effect?

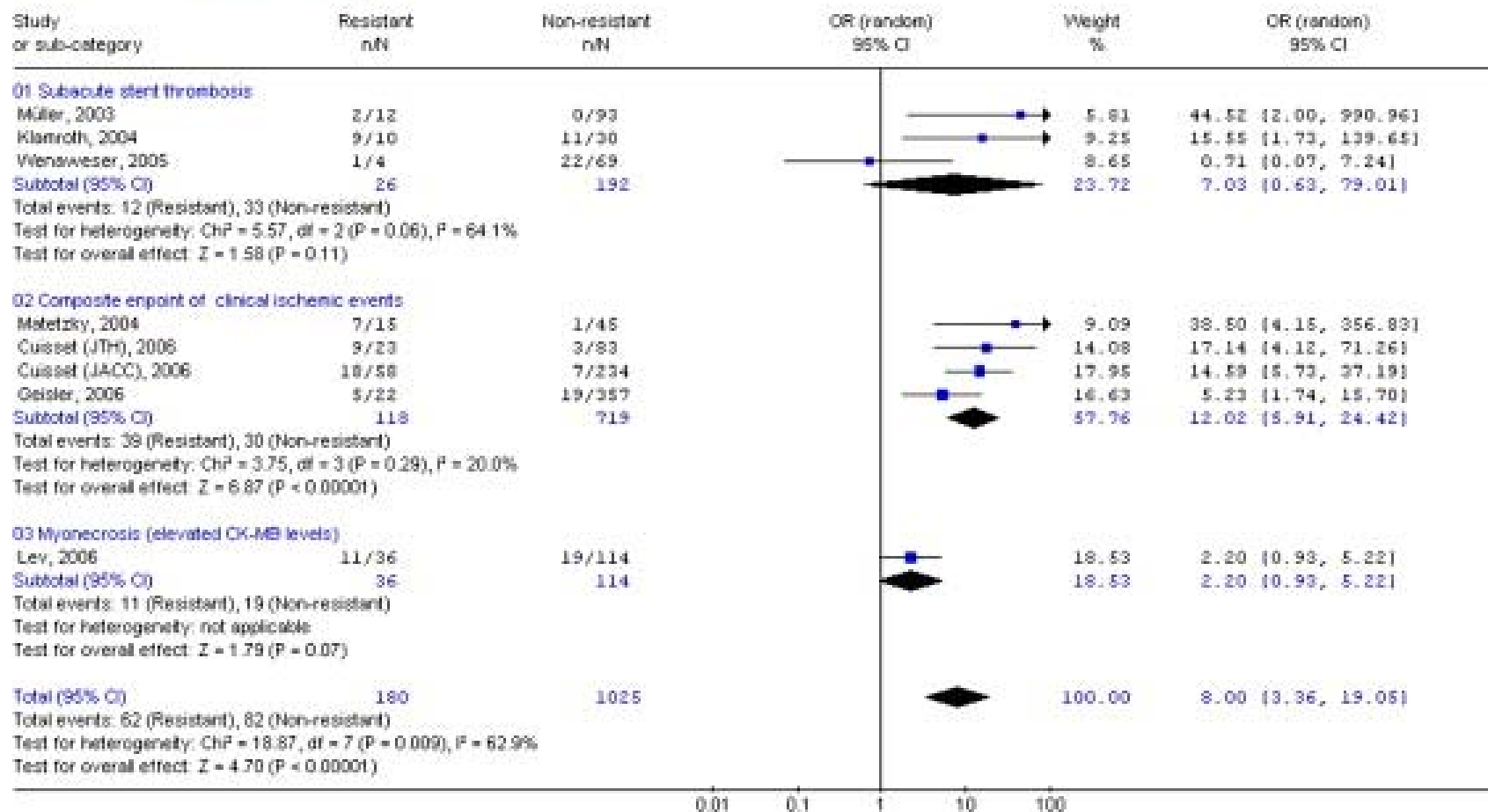
- 143 patients were in a clopidogrel to ticlopidine crossover study found that while poor responsiveness to either drug was common at steady state
  - 21% clopidogrel and 19% ticlopidine were nonresponders but only 3.5% were resistant to both by LTA
  - Suggests that this is not a class effect but may add to the idea of a reduced bioavailability since ticlopidine is CYP 2C9 metabolized.
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# Clinical Effect?

- A meta-analysis done in the Netherlands identified 25 studies comprising 3688 patients who were undergoing PCI [33].
  - 16 studies used a 600mg loading dose and 8 used a 300mg loading dose prior to PCI; maintenance dose of 75mg daily and ASA for all.
  - Labs were drawn (all methods of testing used)
    - 21% were clopidogrel nonresponders
    - They found an odds ratio for stent thrombosis, CV death, MI, CVA, revascularization of **8.0** (95% CI 3.4-19.0) in the nonresponders
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Review: Clopidogrel Resistance\_clinical consequences  
 Comparison: 01 Resistant vs. non-resistant patients  
 Outcome: 01 All cardiovascular endpoints



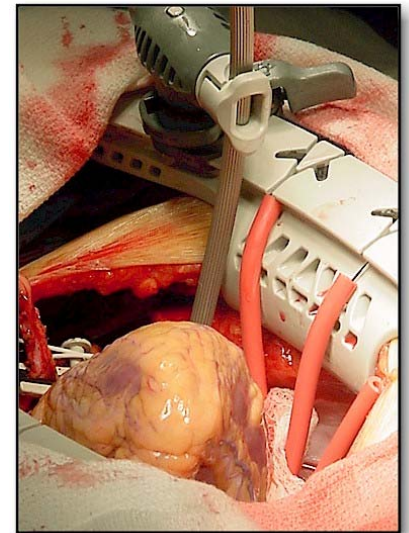
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# Findings:

- 300mg loading dose took 18-24 hours
  - 600mg loading dose took only 2-8 hours to reach peak effect
  - 900mg does not have any further benefit (ALBION study) beyond 600mg.
  - There is no increase in bleeding from 600 or 900mg
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# Clopidogrel Loading

- This meta-analysis found that those loaded with 300mg greater than 6 hours prior to PCI did better than those within 6 hours; No difference in the 600mg groups
- Why don't we use pre-PCI loading dose of 600mg?
  - Concern of the need for CABG
  - 300mg is the only FDA approved dose
  - Can be logistically more difficult
  - Tend to use short half-life GP IIB/IIIa inhibitors instead (eptifibatide, abciximab, tirofiban)



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# How about maintenance dosing of clopidogrel?

- The most recent American College of Cardiology/American Heart Association guidelines for percutaneous coronary intervention (PCI) recommend:
    - In patients in whom stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg/day if <50% platelet inhibition is demonstrated.
  - No randomized study data to support the recommendation, no lab test standardized.
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# Dual Drug Resistant

- Using a cohort of 150 patients undergoing elective PCI, Lev et al. found that those who were ASA resistant also had a reduced response to clopidogrel by in vitro studies [22].
  - Chen et al. found an increase in procedure related myonecrosis (by CK-MB) in those who were ASA resistant, despite pretreatment with clopidogrel.
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# Summary- Clopidogrel Resistance

- Evidence to support association with clopidogrel resistance and increased stent thrombosis. Increased risk with increased number of stents?
  - 600mg clopidogrel loading dose several hours prior to PCI is optimal
  - Check resistance labs and give 150mg per day maintenance dose if you “don’t think your patient could take a massive MI”. Huh?
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# Summary 2- Clopidogrel Resistance

- Still no gold standard lab test to indicate who is resistant. Testing is to be reserved for research.
  - There probably is an association with the non-responders and poorer outcomes, but no adjustment of treatment is known yet.
  - Might not be real:
    - Clopidogrel resistance is 30%, stent thrombosis is 1.2%.
    - Compliance often not checked in studies.
    - Would not expect higher bleeding rates if higher doses are needed to get the same effect.
    - Publication bias? More studies are needed...
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# New Medications/ Potential Treatments

## ■ Cilostazol

- Small trial with fewer adverse effects when given with ASA and clopidogrel

## ■ Prasugrel, Cangrelor, Ticagrelor

- New thienopyridines with a faster onset and 10 times more potent than clopidogrel
- Converted both hepatic and extrahepatically

## ■ Thrombin Inhibitors

- SCH 520348 being investigated
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# Back to JS

- A Polish group had nearly an identical patient: 2 consecutive MIs with suspicion for dual drug resistance. They did the following:
    - ❑ changed clopidogrel for ticlopidine (some evidence)
    - ❑ dose of ASA changed from 150mg to 300mg (some evidence)
    - ❑ added low molecular weight heparin.
    - ❑ They report that their patient did well several weeks out.
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# What we did

- Without a consensus on the proper management of a case as complicated and as rare as our patient, the therapeutic changes were speculative.
- By PFA-100 JS demonstrated aspirin resistance, and by VerifyNow there was evidence to support clopidogrel resistance.
- These were drawn both at the time of the third cardiac catheterization and confirmed one week later (he received eptifibatide).



# JS

- JS had aspirin discontinued (there is no evidence to support stopping this)
- Clopidogrel increased to 300mg/day (no evidence)
- Added low molecular weight heparin (no evidence to support this) for 6 weeks (the minimum duration of antiplatelet therapy for a bare metal stent) at a dose of 1mg/kg q12h.
- His situation was more concerning given his known Crohn's disease and the higher risk of gastrointestinal bleeding. Fortunately, he has remained infarction free at several months out and had no adverse effect from the additional anticoagulation.

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# Conclusions

- Aspirin and clopidogrel resistance are probably not true resistance but have variability in its bioavailability that we have not been able to account for.
  - The idea that a single dose would have the same effect for all is clearly not true
  - We need validation of the tests, large prospective trials and a better assortment of anti-platelet agents for patients whom we may be putting at risk with PCI
  - Until then, the routine use of these “resistance” tests are not warranted and decisions based on these tests are speculative at best.
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