THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin: The 1899 Wonder Drug

Monitoring Aspirin's Antiplatelet Property

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Aspirin Therapy; The Participant…

- Diagrams the biochemical pathways of aspirin's anti-platelet and anti-inflammatory effects.
- Employs aspirin to reduce risk of cardiovascular disease.
- Reviews effect of aspirin on platelet activation in inflammatory disease, cancer, and depression.
- Orders aspirin assays for compliance, efficacy, and dosage.

Please Silence Your Phone

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Felix Hoffman; 1897

- "Willow-bark Salix" appears in 1534 BC Egyptian papyri
- 1800s: Spirea (Meadowsweet) leaves
- 8/10/1897: Felix Hoffman synthesized pure, stable acetyl salicylic acid at Bayer Labs in Leverkusen, Germany
  - Aspirin: a = acetyl; spir = Spirea
- 1899: Bayer lab mixes ASA with starch: made the first tablet
- No scrip: 5 grains [~325 mg], WHO essential medicine list
- 2017: 40,000 tons of aspirin produced, 50,000,000 people
- Uruguayan stamp shows Hoffman, a willow branch, and his signature from the Bayer lab record.

Mann CC, Plummer ML. The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition. New York: Knopf 1991.

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Dr. Lawrence Craven: 1948

- California GP documented 400 men on aspirin had no MIs from 1948–50.
  - Recorded Aspergum related to post-T&A bleeding
  - Recommended an aspirin a day to reduce risk of heart attacks, was largely ignored
  - Extended studies to 8000 men
  - Died of a heart attack at age 74
- 1971: JB Smith demonstrated aspirin's inhibition of prostaglandin synthesis

Craven LL. Acetylsalicylic acid, possible preventive of coronary thrombosis. Ann Western Med 1950;4: 95–9.
Vane JN. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971;231:232–5.
Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nature 1971; 231: 235–7.

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Cyclooxygenase-1 Irreversible Acetylation

- Platelet membrane COX-1 acetylated at ser_{529}
  - Blocks arachidonic acid's access to reactive "tunnel"
  - Active site amino acid tyr_{385} unaffected but blocked
- Platelet loses COX-1 activation pathway
  - AKA *eicosanoid synthesis* pathway or *prostaglandin* pathway
  - Total function recovery ~10%/day as new platelets are produced
- Adhesion and shear-induced aggregation remain

Vane JR, Botting RM. Mechanism of action of aspirin-like drugs. Semin Arthr Rheum 1997; 25 Suppl I: 2-10.

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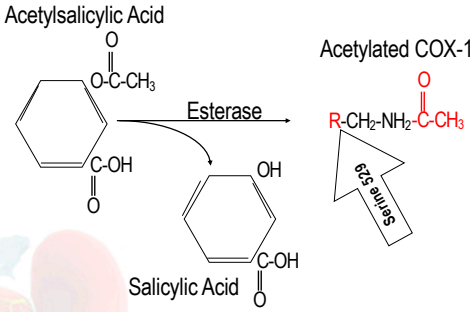
Acetylation of Cyclooxygenase-1



Pedersen AK, Fitzgerald GA. Dose-related kinetics of aspirin: Presystemic acetylation of platelet cyclooxygenase. New Engl J Med 1984; 311: 1206-11.

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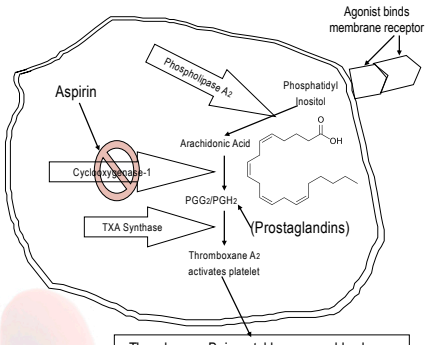
Aspirin acetylates COX-1 and reduces TXA_2 production



Thromboxane B_2 is a stable, measurable plasma product that is reduced in ASA therapy, converts to soluble urinary 11-dehydro TXB_2

8

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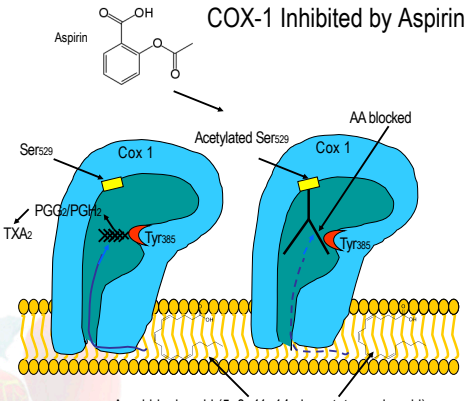
COX-1 Inhibited by Aspirin



9

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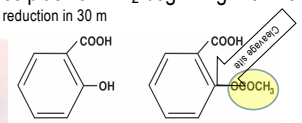
Aspirin Pharmacology

- 50% absorbed from stomach, duodenum
- Peak plasma levels at 15 minutes
- Hydrolyzed by esterase in gut, liver and RBCs
- Acetyl group hydrolyzed in 20–30 m, leave salicylic acid (salicylate)
  - Platelet COX-1 acetylation occurs in the pre-systemic (portal) circulation of gut and liver
- Reduces plasma TXB_2 beginning within 5 minutes
  - Max reduction in 30 m



10

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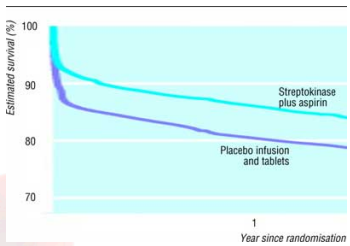
Aspirin Efficacy: ISIS-2

1988: ISIS-2 demonstrates a 0.78 incidence of death after MI with streptokinase + ASA vs SK + placebo, FDA clears ASA to reduce risk of secondary MI or a first MI in acute angina.



ISIS-2 Collaborative Group. Randomized trial of IV streptokinase, aspirin, both or neither among 17,187 cases of suspected AMI: ISIS-2. Lancet 1988; 2: 349–60.

11

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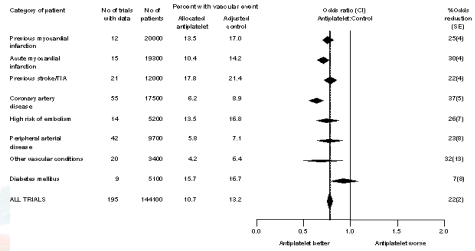
2002 Antiplatelet Trialists' Collaboration

Meta-analysis of 287 trials w/ 100,000 high-risk patients: composite 32% decrease in death, MI, ischemic stroke in vascular patients on 75–150 mg aspirin daily:



Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324: 71-86.

12

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Aspirin Dosage per Indication

- 75 mg (or baby aspirin—81 mg)
  - Primary and 2º MI and peripheral artery disease prevention, stroke prevention in atrial fibrillation, 2º prevention of TIA and stroke
  - Prevent pre-eclampsia, support fetal retention in primary antiphospholipid syndrome (with low MW heparin)

- 300 mg (or adult—325 mg) subsequent to:
  - MI, acute unstable angina, acute TIA, acute ischemic stroke

Navaratnam k, Alfirevic A, Alfirevic Z. Low dose aspirin and pregnancy: how important is aspirin resistance? BJOG 2016: 123: 1481–7.

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Aspirin in Primary Prevention

- Physician's Health Study 1982–96 (♂ only)
  - 1086 healthy ♂ physicians, 40–84
  - 325 mg aspirin on alternate days versus placebo
  - 44% reduction of fatal or nonfatal first MIs
  - Ethical termination at 60 months, 1987
  - ASA cleared in 1988 to prevent TIAs and strokes in healthy ♂s >50
- Women's Health Study 1991–2000 (♀ only)
  - 39,876 healthy health care ♀s over 45
  - 100 mg aspirin on alternate days versus placebo
  - 25% reduction in fatal or non-fatal first MIs
  - But 50% reduction in smokers, hypertensives, those with high cholesterol, greatest effect >65

Physician's health study: aspirin and primary prevention of coronary heart disease. N Engl J Med 1989; 321:129-35,183-5.

Gaziano JM, Skerrett PJ, Buring JE. Aspirin in the treatment and prevention of cardiovascular disease. Haemostasis 2000; 30:1-13S.

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2018: Weight-based ASA Dosages Affect Odds Ratio of Primary CAD

Mass	ASA mg/d	Primary CAD OR	Comment
50–69 kg	75–100	0.75 (P= .007)	>100 mg ASA *raises* CAD risk.
>70 kg	75–100	0.95 (non-sig)	75–100 mg *raises* CAD risk to 1.33 (P= .0082)!
	>325	↓ (P= .017)	OR not provided
Height data match weight, findings similar in men and women Worldwide, 80% of men and 50% of women are >70 kg In >70 YO, ASA *raised* 3Y cancer risk by OR 1.2 (P= .02)			

Rothwell PM, Cook NR, Gaziano JM, et al, Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018;392:387–99.

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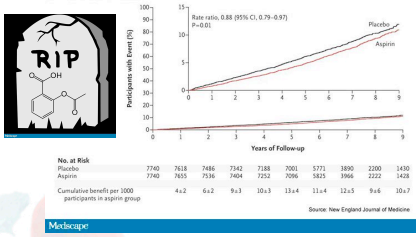
9/22/18: *ASA Offers No Protection*

- Measured vascular events: CAD, PAD, ischemic stroke
- Questionable protection for those with thrombotic risk factors
- No protection for those without cardiac indications
- Bleeding risk outweighs protection



Medscape

Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;22;392:1036–104.

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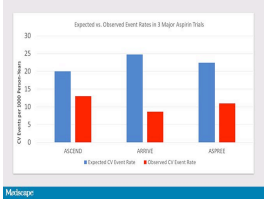
ASCEND, ARRIVE, and ASPREE Trials

- NEJM 9/16/18: 20,000 >70 in US & Australia
- Primary outcome composite of death, dementia, and disability—no effect
- ASA actually worse in…
  - All-cause mortality
  - Cancer-related death

Why?

- Modern CAD outcomes negate ASA value?
- CAD redefined?



Medscape

McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018;379:1499–1508.

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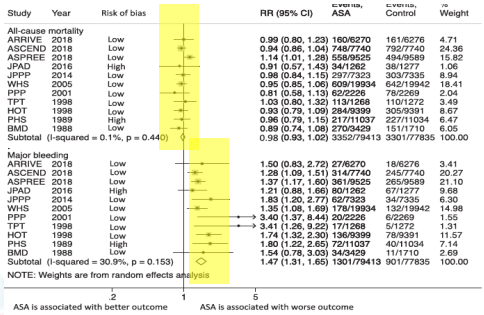
The Remarkable Story of a Wonder Drug, Which Now Comes to an End in the Primary Prevention Setting: Say Bye-bye to Aspirin!



Mahmoud AN, et al. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials European Heart Journal 2019;40, 607–17.

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What is Lacking in Aspirin Studies?

Labs!
Why?

- No national guideline for aspirin lab assay
- Lab assays are surrogates for outcomes
- VerifyNow and PFA-100 results not reproducible
- Lab assay platform results differ among patients
- But what if you dosed on lab results?

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Aspirin Monitoring

- Aspirin resistance
  - Laboratory phenomenon: suboptimal platelet function suppression
- Aspirin failure
  - Secondary stroke, MI, PAD while on aspirin therapy
  - Adverse thrombotic events such as fetal loss in antiphospholipid syndrome despite aspirin therapy

How to monitor aspirin?

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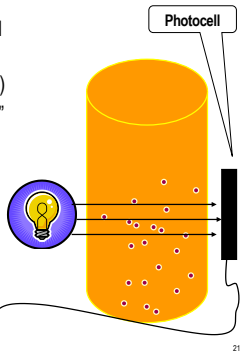
Light Transmittance Aggregometry (LTA) Specimen Preparation

- Collect 9–12 mL whole blood
  - 3–4 2.7 mL tubes + 0.3 citrate
- Centrifuge at 50×g 30" (PRP)
- Wait 30 m for "platelet shock"
- Dispense to cuvette
- Test within 4 hours
- Pipette agonist, record absorbance by photometry
- Attempt to record secretion by analyzing "lag phase"



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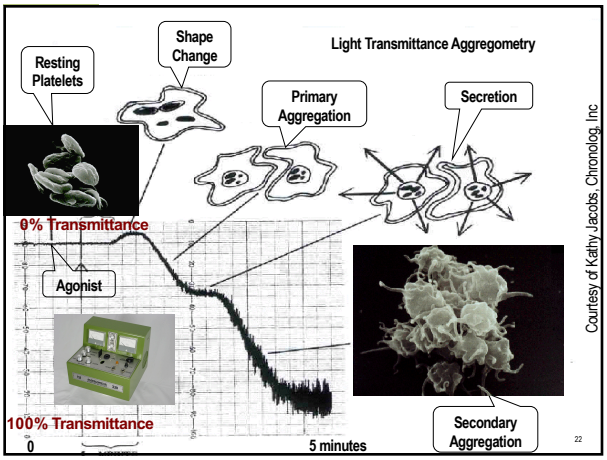

22

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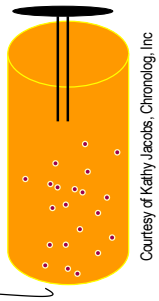
Impedance-based Whole Blood Aggregometry (WBA)

- Collect 9 mL blood, do not centrifuge
  - 3 tubes each 2.7 mL + 0.3 citrate
- Aliquot, dilute 1:1 with saline
- Pipette agonist, timer starts
- Electrodes lowered into suspension



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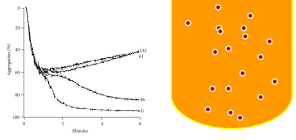
WBA: Impedance

- Aggregating platelets form layer on electrodes
- Platelet layer impedes current
  - Resistance in ohms (Ω)
  - 0 Ω = no aggregation
  - Aggregation proportional to Ω
  - Same pattern as LTA



Courtesy of Kathy Jacobs, Chronolog, Inc

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Aspirin Efficacy Agonists

- 0.5 mM arachidonic acid (AA)
  - Directly activates eicosanoid synthesis pathway to produce TXA_2
  - TXA_2 activates platelet by binding internal receptors TPα or TPβ
  - Response reduced by aspirin
- 1–5 µg/mL collagen
  - Binds receptors GP Ia/IIa (integrin $\alpha 2\beta 1$), GP IV, GP VI
  - Response reduced by aspirin
  - May bypass aspirin effect, aggregation via alternate pathways
- 5–10 µM ADP
  - ADP binds P_2Y_{12} receptor
  - Response reduced by thienopyridines like Plavix, Brilinta
  - May bypass aspirin effect, aggregation via alternate pathways

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Secretion Response Using The "Firefly" Reaction

Courtesy of Kathy Jacobs, Chronolog, Inc

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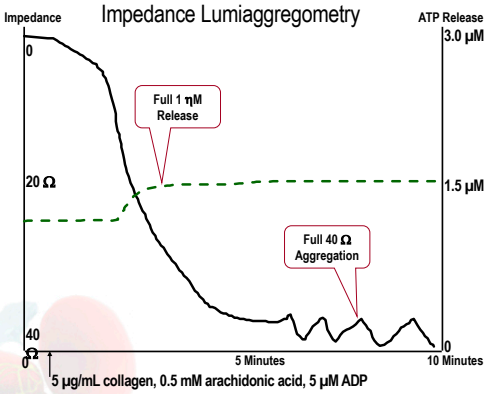
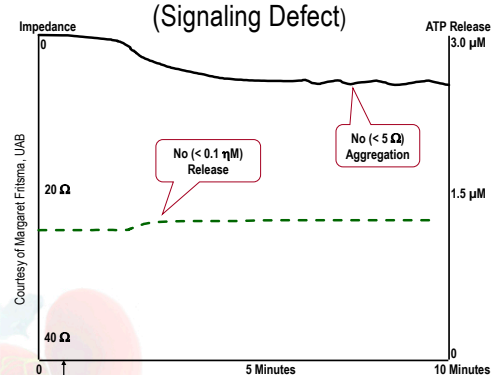
Normal Whole Blood Impedance Lumiaggregometry



The Fritsma Factor 27

Aspirin or "Aspirin-like Disorder" (Signaling Defect)



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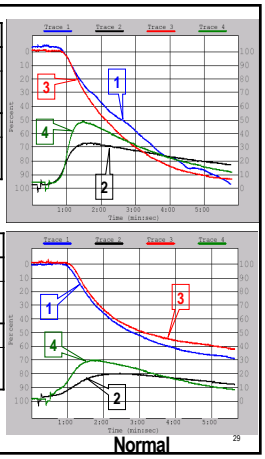
Agonist	Collagen 5 µg/mL	
Tracing	2-Control	4-Patient
Luminescence (Amplitude)	0.83ηm	0.81ηm
Tracing	1 Control	3-Patient
Aggregation (Impedance)	38Ω	37Ω

Agonist	Arachidonic Acid 0.5 mM	
Tracing	2-Control	4-Patient
Luminescence (Amplitude)	0.45ηm	0.45ηm
Tracing	1 Control	3-Patient
Aggregation (Impedance)	27Ω	25Ω



Courtesy of Patti Tichenor, UAB Coagulation; using AGGRO/LINK®

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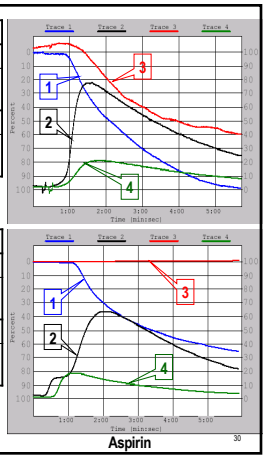
Normal 29

Agonist	Collagen 5 µg/mL	
Tracing	2-Control	4-Patient
Luminescence (Amplitude)	1.69ηm	0.57ηm
Tracing	1 Control	3-Patient
Aggregation (Impedance)	39Ω	26Ω

Agonist	Arachidonic Acid 0.5 mM	
Tracing	2-Control	4-Patient
Luminescence (Amplitude)	1.42ηm	0.57ηm
Tracing	1 Control	3-Patient
Aggregation (Impedance)	26Ω	0Ω



Courtesy of Laura Taylor, UAB Coagulation; using AGGRO/LINK®

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Aspirin 30

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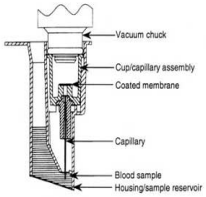
Siemens (Dade-Behring) PFA-100

- Transfer 800 µL citrated whole blood to each of two cartridges, load and run to closure time (CT)
  - Coated membrane: agonists
- Collagen and epinephrine (Col/Epi, CEPI)
  - "Weak:" normal CT 98–185 s
  - Initial cartridge
- Collagen and ADP (Col/ADP, CADP)
  - 50 µM ADP
  - "Strong:" normal CT 77–133 s
  - Confirmatory cartridge



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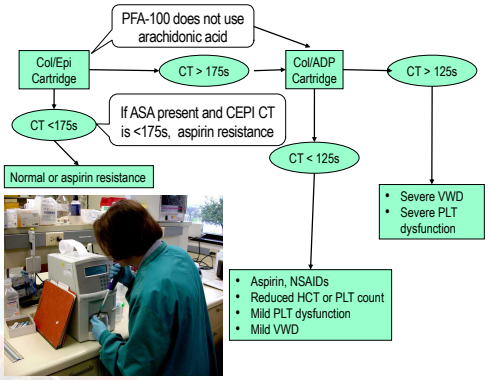
PFA-100 Aspirin Response Assay



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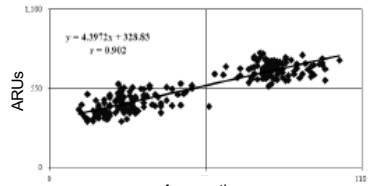
Werfen VerifyNow®
Aspirin Resistance Units (ARU)

Whole blood light transmittance rises as platelets aggregate to arachidonic acid. Aggregation suppressed by aspirin:

- ARUs <550: function inhibited = aspirin sensitive
- ARUs >550: function normal = aspirin resistance



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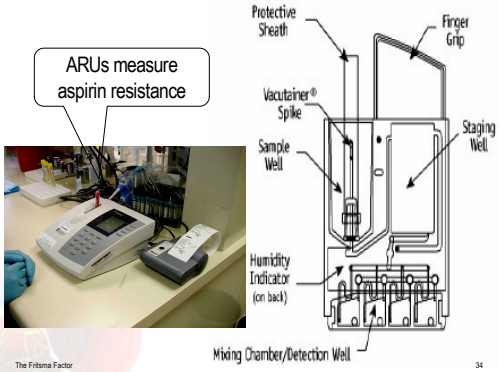
Werfen VerifyNow Reaction Chamber



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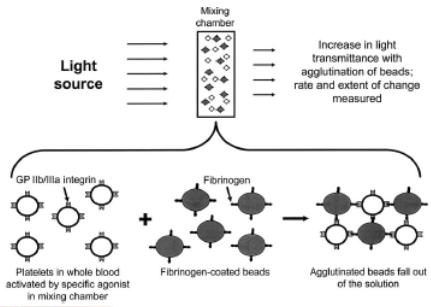
VerifyNow Principle



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Werfen VerifyNow and PFA-100 Limitations

- Cartridges ~$5.00 each
- Whole blood specimen volume 800 µL/assay
- Precision: CVs >10%, often requires duplication
- Must test whole blood within four hours
- Variable effects of…
  - von Willebrand factor, factor VIII, fibrinogen
  - Platelet count and hematocrit

McGlasson DL, Fritsma GA, Shah AD. Effects of elevated fibrinogen, factor VIII, von Willebrand antigen, and immunologic von Willebrand factor on the INNOVANCE® PFA P2Y cartridge. Poster, ISTH 2009

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AspirinWorks®
a division of Creative Clinical Concepts, Inc.

- Urinary 11-dehydrothromboxane B_2 (U 11-DHTB$_2$)
  - Liver-produce metabolite of plasma thromboxane B_2
- Platelet is the primary source for U11-DHTB$_2$
  - Also renal endothelial cells, monocytes
- Random urine specimen: store and ship
  - Normalized to urine creatinine: Pg U 11-DHTB$_2$ /mg creatinine
- Liver and renal disease limitations

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2002 HOPE Study: Aspirin Resistance

- Nested (quartile) retrospective case-control sample
  - 488 aspirin-treated CAD patients: end point was 5-yr 2º MI, stroke, or CV death
  - 488 age- and sex-matched controls taking aspirin who did not have an MI, stroke, or CV death
- In aspirin-treated CAD patients, U11-DHTB$_2$ predicts risk of MI or CV death: fourth quartile U11-DHTB$_2$ = OR 3.5 for CV death

Pg U11-DHTB$_2$/ mg creatinine	Quartile	Odds Ratio		
		MI	CV Death	Stroke
<134	1	1.0	1.0	1.0
134–193	2	1.3	2.0	2.5
194–298	3	1.5	2.5	0.6
>298	4	2.0	3.5	0.6

Eikelboom JW, Hirsh J, Weitz JI, et al. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002; 105: 1650–55

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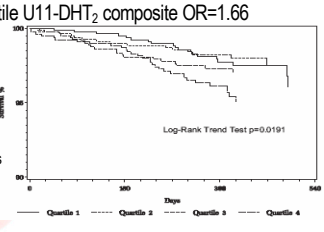
CHARISMA Trial: Dual Antiplatelet Therapy

- Randomized double-blind prospective trial of 3261 clopidogrel Vs. placebo in patients on aspirin at high risk of athero-thrombosis
  - Tested 1 month after starting clopidogrel, assigned quartiles
  - 144 with one-year stroke, MI, or CV death
  - 3117 with no adverse event
- Fourth quartile U11-DHT$_2$ composite OR=1.66

Kaplan–Meier curves for composite of stroke, MI, or CV death by quartiles



Eikelboom JW, Hankey GJ, Thom J, et al. Incomplete inhibition of thromboxane biosynthesis by acetylsalicylic acid: Determinants and effect on cardiovascular risk. Circulation 2008; 118: 1705–12

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CHARISMA Trial Conclusions

- Fourth quartile normal or elevated U11-DHTB$_2$
  - Age, ♀, PAD Hx, smoking, oral hypoglycemic Rx, ACE-inhibitor Rx
- Reduced U11-DHTB$_2$
  - Aspirin Rx >150 mg/d, NSAIDs, hypercholesterolemia, statin Rx
- Randomization to clopidogrel or placebo did not reduce risk ratio for CV events in patients in the fourth U11-DHTB$_2$ quartile
- U11-DHTB$_2$ level is potentially modifiable

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Aspirin Resistance Prevalence

Overall		27.1%
By definition	PFA-100	29.0%
	Ultegra VerifyNow	26.2%
	LTA	21.3%
By population	CAD	22.9%
	Stroke	32.1%
By dose	< 100 mg/d	35.6%
	101–299 mg/d	28.2%
	> 300 mg/d	18.6%

Hovens MMC, Snoep JD, Eikenboom CJ. Prevalence of persistent platelet reactivity despite use of aspirin: a systematic review. Am Heart J 2007;153:175–81.

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Aspirin Resistance and Adverse Events Review

Type	Percutaneous Intervention (Cath)		Stable CAD
N	151	106	315
% AR	19.2%		5.2%
Method	VerifyNow	Light Transmittance Aggregometry	
Results	Elevated creatine kinase and troponin I in AR	4th quartile ADP response associated with OR for CV events = 22.4	OR in AR Composite: 3.12 CV death: 2.98 MI: 1.91 CVA: 5.44
Ref	Chen WH, JACC 2004;43:1122	Cuisset T, J Thromb Haemost 2006;4:542	Gum PA, JACC 2003;41:961

AR= ASA resistance; CAD= coronary artery disease; OR= odds ratio; CV= cardiovascular; MI= myocardial infarction; CVA= cerebrovascular event

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Siemens PFA-100 and Aspirin Resistance

Gum PA, JACC 2003;41:961	9.5% aspirin resistance by CEPI closure time, low correlation with LTA
Hézard N, Thromb Res 2002;108:43	Poor aspirin resistance correlation among LTA, CEPI closure time, and flow
Sane DC. Thromb Haemost 2002;88:711	No CEPI closure time difference between aspirin resistance and aspirin sensitive
Ten Berg JM, Thromb Res 2002;105:385	CEPI closure time does not distinguish low dose from high dose aspirin
Grundmann K, J Neurol 2003;250:63	53 patients on aspirin for stroke prevention: CEPI closure time significantly shorter in 12/35 patients with recurrent stroke (p <0.01)
CEPI = collagen-epinephrine cartridge LTA = light transmittance aggregometry	

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Variation in Lab Detection of Aspirin Resistance

Assay	Aspirin Resistance %
Werfen VerifyNow Aspirin	17
Siemens PFA-100 CEPI	22
LTA	5
All tests abnormal per subject	2

Harrison P, Segal H, Blasbery K. Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry. Stroke 2005 36:1001–5.

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Seven Days of Aspirin
Comparison to Whole Blood Aggregometry

	Positive Predictive Value		Negative Predictive Value	
Dosage	81 mg	325 mg	81 mg	325 mg
AspirinWorks	74.3	82.1	40.2	0.0
PFA-100 CEPI	81.3	81.6	53.8	42.9
VerifyNow Aspirin	72.7	51.9	100	33.3

"Laboratory measures of PLT activity are suppressed by aspirin therapy, but are affected by the dosage and duration of therapy. Determinations of aspirin response should be made after at least 7 days of treatment. Laboratory test platform results do not closely reflect each other, thus application of laboratory platforms should be made consistently."

McGlasson DL, Fritsma GA. Comparison of four laboratory methods to assess aspirin sensitivity. Blood Coagul Fibrinolysis 2008;9:20–3

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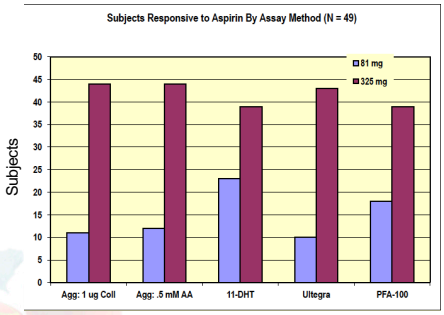
24-h Response to 81 & 325 mg



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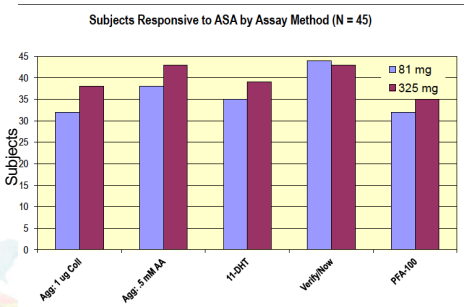
7-d Response to 81 & 325 mg



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Aspirin Resistance Study Limitations

- Inter-assay variation
- Biological variation over time
- Failure to adjust for race, age and sex
- Failure to confirm compliance
  - Serum salicylate?
  - Non-compliance and early withdrawal may account for most AR
- Failure to separate confounding conditions
  - Hypertension, diabetes, peripheral vascular disease, smoking, and inflammation may contribute to aspirin resistance, while independently raising vascular risk

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Proposed Mechanisms of Aspirin Resistance

- Increased platelet turnover: more than 10% per day
- Activation of alternate platelet pathways not blocked by aspirin
  - Diacylglycerol pathway activated through G-protein
  - Adhesion molecules: collagen (GP Ia/IIa) & VWF receptors (GP Ib/V/IX)
  - Activation by shear stress in atherosclerosis
- Aspirin-mediated reduction of PLT-inhibiting prostacyclins from vascular endothelial cells
- Elevated VWF, fibrinogen activity level
- Polypharmacy (> 4 drugs)

Goodman T, Sharma P, Ferro A. The genetics of aspirin resistance. Int J Clin Pract 2007;61:826–34
Kilanowska J, Favaloro EJ, Lippi G. Aspirin "responsiveness," "nonresponsiveness" or "resistance": a putative role for von Willebrand factor? Blood Coagul Fibrinolysis 2008;19:823–4

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More Proposed Mechanisms of Aspirin Resistance

- NSAIDs compete for Ser_{529} site
  - Naprosyn, ibuprofen
- COX-2 Induction
  - Non-constitutive, COX-2 response to cytokines and inflammation
  - COX-2 in megakaryocytes, monocytes, macrophages, vascular endothelial cells and newly released platelets
  - After bypass surgery, 16-fold increase of COX-2 causing transient aspirin resistance
  - Acetylation of COX-2 ser_{529} incompletely hinders arachidonic acid's access to reactive site
  - Smoking, diabetes, heart failure and hyperlipidemia

Weber AA, Zimmermann KC, Meyer-Kirchrath J, Schror K. Cyclooxygenase-2 in human platelets as a possible factor in aspirin resistance (letter). Lancet 1999; 353: 900.

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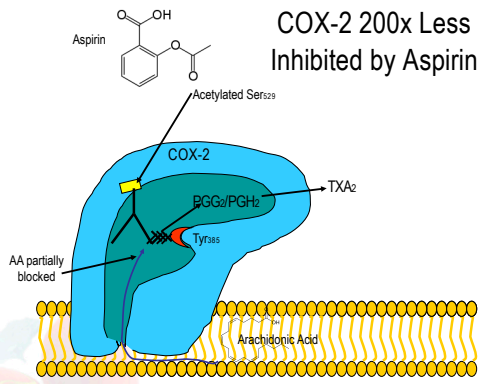
COX-2 200x Less Inhibited by Aspirin



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Dual Antiplatelet Therapy

- Aspirin, 81 or 325 mg + clopidogrel, 75 mg; or prasugrel, ticagrelor critical in stents, reduce repeat MI 20%
- Clopidogrel resistance 15–63% detected by molecular or phenotypic tests, predicts risk
- Little variability in response to prasugrel or ticagrelor
- Ticagrelor is more effective than clopidogrel in ACS with and without PCI. Similar rates of bleeding as clopidogrel
- Typical duration: aspirin indefinite, clopidogrel 1–2 y
- Triple therapy: aspirin and clopidogrel plus Coumadin or DOAC: benefit in mechanical heart valves, bleeding 43% higher but lowered overall mortality 57%

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Bridging Dual Antiplatelet Therapy During Surgery

- Discontinue: 20% incidence of ischemia
- Continue: 35% increased bleeding
- ACCP 2011 guidelines: D/C 7–10 days
  - Consider platelet function testing

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So, do we test for aspirin resistance?

W Check. Clot Knot; Unraveling Tests for Coag Disorders. CAP Today, December 2008.

Dr. Kristi Smock: "I think it is a problem of using different definitions for aspirin resistance and measuring it with tests that have different sensitivities and specificities."
"Moreover," she adds, "testing for this condition is not generally recommended because it is not known what the treatment changes would be. "

Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin–oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease a meta-analysis of randomized trials Arch Intern Med 2007;167:117–24.

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Response: Two Meta-Analyses

- *Snoep JD, Hovens MMC, Eikenboom JCJ, et al. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. Arch Intern Med 2007;167:1593-9:*
  Mean prevalence of laboratory aspirin resistance among all methods reviewed is 27%. Resistance predicts 3.8 OR for adverse cardiovascular outcomes. No concordance among methods.
- *Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. BMJ 2008; 336: 195-8.*
  20 studies totaling 2930 patients with cardiovascular disease. Classified 28% as aspirin resistant. Resistance confers a 3.85 OR for any adverse cardiovascular outcome including a 5.99 OR for death and a 2.96 OR for acute coronary syndrome. No concordance among methods.

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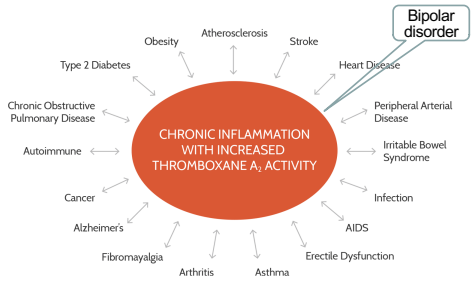
DISEASES OF CHRONIC INFLAMMATION



Savitz JB, Teague TK, Misaki M, et al. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2Â~2 double-blind, randomized, placebo controlled, phase IIA clinical trial. Translational Psychiatry2018;8

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Activated Platelets and Cancer

- Platelets are activated by tumor cells and generate TXA_2.
- Activated platelets raise activation potential of endothelium, attract WBCs to primary and metastatic tumor sites.
- Activated PLTs produce vascular endothelial growth factor, vascularize tumors.
- Activated platelets secrete and express inflammatory surface receptors that enhance cancer progression and metastasis.
- Activated platelets aid in metastasis by protecting circulating tumor cells from the immune system.
- COX-1 and 2 inhibition may enhance antitumor activity.
- U11-DHB_2 levels predict metastasis in relapsing breast cancer.
- U11-DHB_2 levels reflect activated platelets in colorectal cancer.
- Cancer progression is associated with thrombocytosis and platelet activity.

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Activated Platelets and Cancer References

1. Battinelli EM, Markens BA, Kulenthirarajan RA, et al. Anticoagulation inhibits tumor cell–mediated release of platelet angiogenic proteins and diminishes platelet angiogenic response. Blood 2014; 123:101–12.
2. Karachaliou N, Pilotto S, Bria E, Rosell R. *Platelets and their role in cancer evolution and immune system.* Translational Lung Cancer Research. 2015.
3. Olsson AK, Cedervall J. The pro-inflammatory role of platelets in cancer. Platelets. 2018.
4. Li N. Platelets in cancer metastasis: To help the "villain" to do evil. International Journal of Cancer. 2015.
5. Mitrugno A, Sylman J, Ngo A, Pang J, et al. Aspirin therapy reduces the ability of platelets to promote colon and pancreatic cancer cell proliferation: Implications for the oncoprotein c-MYC. The American Physiological Society. 2017.
6. Li H, Lee M, Liu K, Wang T, et al. Inhibiting breast cancer by targeting the thromboxane A2 pathway. Nature Partner Journals. 2017.

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Activated Platelets and Cancer References

6. Ferroni P, Santilli F, Cavaliere F, Simeone P, et al. Oxidant stress as a major determinant of platelet activation in invasive breast cancer. International Journal of Cancer. 2016.
7. Li H, Liu K, Boardman L, Zhao Y, et al. Circulating prostaglandin biosynthesis in colorectal cancer and potential clinical significance. EBioMedicine. 2014.
8. Cho M, Noh K, Haemmerie M, Li D, et al. Role of ADP receptors on platelets in the growth of ovarian cancer. Blood. 2017.
9. Wojtukiewicz M, Hempel D, Sierko E, Tucker S, et al. Antiplatelet agents for cancer treatment: a real perspective or just an echo from the past? Cancer Metastasis Review. 2017.
10. Dovizio M, Alberti S, Guillem-Llobat P, Patrignani P. Role of platelets in inflammation and cancer: novel therapeutic strategies. Nordic Pharmacological Society. 2013
11. Lopez L, Guyer K, De La Torre I, Pitts K, et al. Platelet thromboxane (11-dehydro-Thromboxane B2) and aspirin response in patients with diabetes and coronary artery disease. World Journal of Diabetes. 2014.

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