THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin: The 1899 Wonder Drug

Monitoring Antiplatelet Drugs

George A Fritsma MS, MLS
The Fritsma Factor, Your interactive Hemostasis Resource
Precision BioLogic Inc, Dartmouth, Nova Scotia
www.fritsmafactor.com

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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 in various indications.
- Orders aspirin laboratory assays for presence, efficacy, and dosage.

Please Silence Your Phone

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Felix Hoffman; 1897

- "Willow-bark Salix" appears in 1534 BC Egyptian papyri
- 8/10/1897: Felix Hoffman synthesized pure, stable acetyl salicylic acid at Bayer Labs in Leverkusen, Germany
- Aspirin: a = acetyl; spir = Spirea (meadowsweet)
- 1899: Bayer lab mixes aspirin with starch to make the first drug in tablet form
  - No prescription: 5 grains [~325 mg], WHO essential medicine list
  - 2017: 40,000 tons, 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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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 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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Cyclooxygenase-1 Acetylation

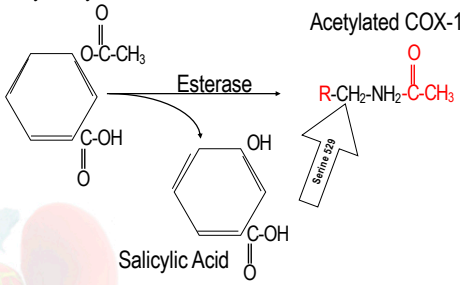
- Platelet membrane COX-1 acetylated at ser_{529}
  - Prevents arachidonic acid's access to reactive "tunnel"
  - Active site amino acid tyr_{385} unaffected but blocked
  - Irreversible
- Platelet loses COX-1 activation pathway
  - Total function recovery ~10%/day as new platelets are produced
  - Called the eicosanoid synthesis pathway or prostaglandin pathway
- 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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Acetylation of Cyclooxygenase-1

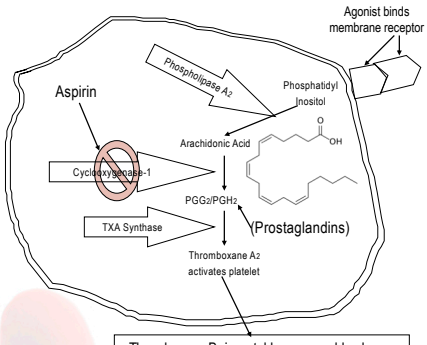
Acetylsalicylic Acid



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

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

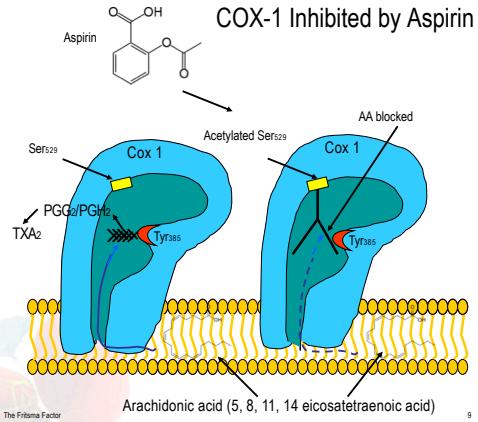
Aspirin acetylates COX-1 and reduces TXA_2 production



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

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

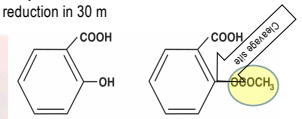
COX-1 Inhibited by Aspirin



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Pharmacology

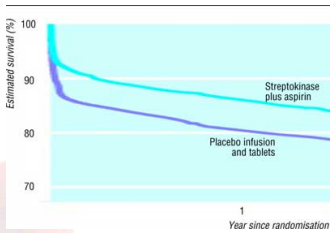
- 50% absorbed from stomach, duodenum
- Peak plasma levels at 15 minutes
- Hydrolyzed by esterase in gut, liver and RBCs
- Acetyl group hydrolyzed in 20–30 m, leave salicylic acid (salicylate)
  - Platelet COX-1 acetylation occurs in the pre-systemic (portal) circulation of gut and liver
- Reduces plasma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



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Efficacy: ISIS-2

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



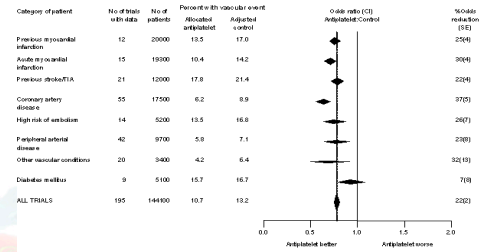
ISIS-2 Collaborative Group. Randomized trial of IV streptokinase, aspirin, both or neither among 17,187 cases of suspected AMI: ISIS-2. Lancet 1988; 2: 349–60.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

2002 Antiplatelet Trialists' Collaboration

Meta-analysis of 287 trials w/ 100,000 total subjects:

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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Dosage per Indication

- 75 mg (or baby aspirin—81 mg)
  - Primary and 2° MI and peripheral artery disease prevention, stroke prevention in atrial fibrillation, 2° 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)
  - 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.

The Fritsma Factor 13

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin in Primary Prevention

- Physician's Health Study 1982–96
  - 1086 healthy ♂ physicians, 40–84
  - 325 mg aspirin on alternate days versus placebo
  - 44% reduction of fatal or nonfatal first MIs was recorded
  - Ethical termination at 60 months
  - Aspirin cleared in 1988 to prevent TIAs and strokes in healthy males >50
- Women's Health Study 1991–2000
  - 39,876 healthy ♀ over 45
  - 100 mg aspirin on alternate days versus placebo
  - 25% reduction in fatal or non-fatal first MIs
  - 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.

The Fritsma Factor 14

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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

Kg	ASA mg/d	Primary CAD OR	Comment
50–69	75–100	0.75 (P= .007)	>100 mg ASA *raises* CAD risk.
>70		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)			

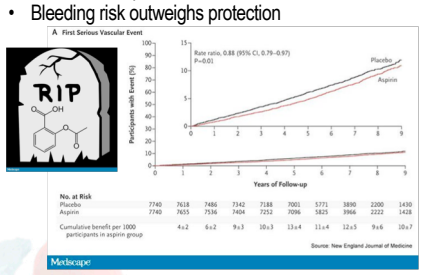
Rothwell PM, Cook NR, Gaziano JM, et al, Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018;392:387–99.

The Fritsma Factor

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Sept 22, 2018: *ASA No Protection*

- No protection for those without cardiac indications
- Questionable protection for those with risk factors
- Bleeding risk outweighs protection



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.

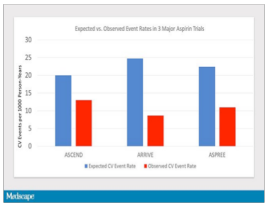
The Fritsma Factor

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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
- Better cardiac outcomes negate ASA value?

Why?



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.

The Fritsma Factor

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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?

The Fritsma Factor

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Monitoring

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

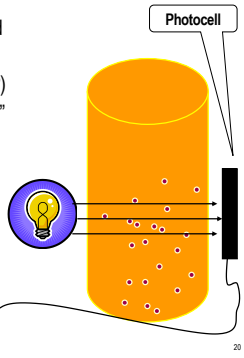
How to monitor aspirin?

The Fritsma Factor 19

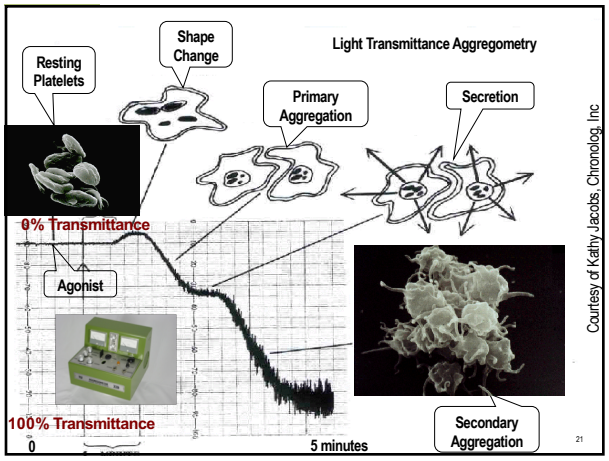
THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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"



The Fritsma Factor 20

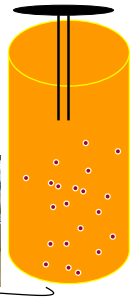


The Fritsma Factor 21

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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



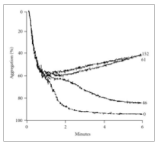
Courtesy of Kathy Jacobs, Chronolog, Inc

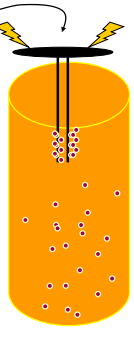
The Fritsma Factor 22

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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

The Fritsma Factor 23

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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 α2β1), 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

The Fritsma Factor 24

Secretion Response Using The "Firefly" Reaction

ATP → PPi

Luciferin → Luciferyl:AMP + O_2

Chromo-lume® firefly luciferase reagent

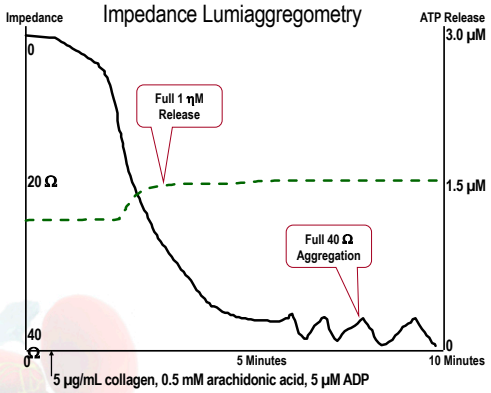
Luminescence

Proportional to ATP release in ηM

Oxyluciferin + AMP

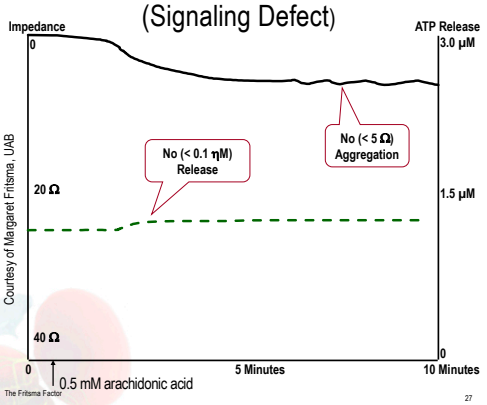
Courtesy of Kathy Jacobs, Chronolog, Inc

Normal Whole Blood Impedance Lumiaggregometry



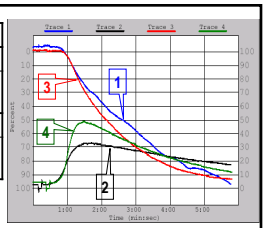
5 μg/mL collagen, 0.5 mM arachidonic acid, 5 μM ADP

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

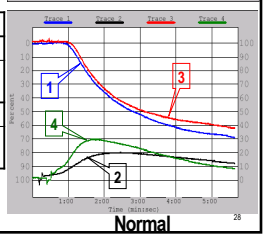


0.5 mM arachidonic acid

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



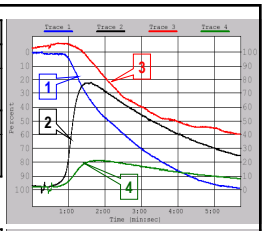
Agonist	Arachidonic Acid 0.5 mM	
Tracing	2-Control	4-Patient
Luminescence (Amplitude)	0.45ηm	0.45ηm
Tracing	1 Control	3-Patient
Aggregation (Impedance)	27Ω	25Ω



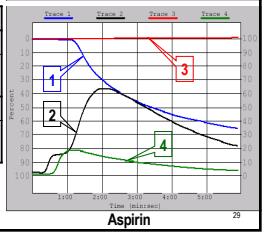
Courtesy of Patti Tichenor, UAB Coagulation; using AGGRO/LINK®

Normal

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

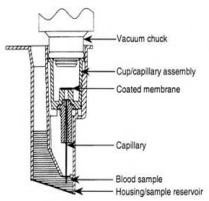


Courtesy of Laura Taylor, UAB Coagulation; using AGGRO/LINK®

Aspirin

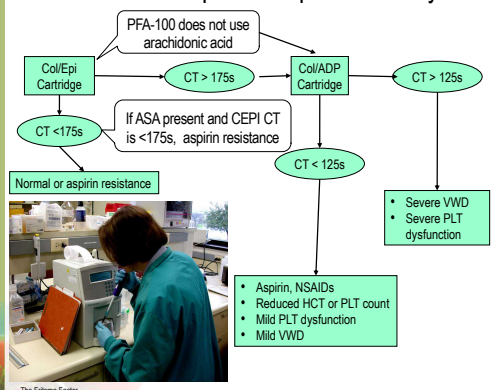
Siemens (Dade-Behring) PFA-100

- 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



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

PFA-100 Aspirin Response Assay

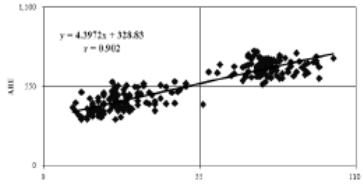


THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Werfen VerifyNow®
Aspirin Resistance Units (ARU)

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

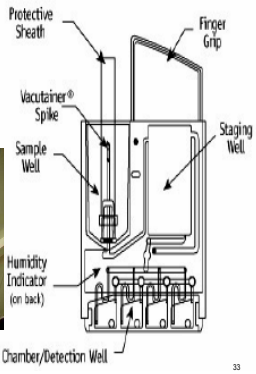
- ARUs <550: function inhibited = aspirin sensitive
- ARUs >550: function normal = aspirin resistance



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

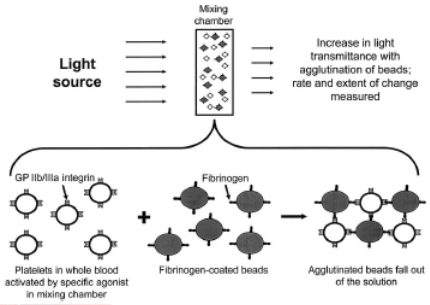
Werfen VerifyNow Reaction Chamber

ARUs define antiplatelet resistance to aspirin



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

VerifyNow Principle



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

AspirinWorks®

- Urinary 11-dehydrothromboxane B_2 ($UDHT_2$)
  - Liver-produce metabolite of plasma thromboxane B_2
- Platelet is the primary source for $UDHT_2$
  - Also renal endothelial cells, monocytes
- Random urine specimen: store and ship
  - Normalized to urine creatinine: Pg $UDHT_2$ /mg creatinine
- Liver and renal disease limitations

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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, $UDHT_2$ predicts risk of MI or CV death: fourth quartile $UDHT_2$ = OR 3.5 for CV death

Pg UDHT/ 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

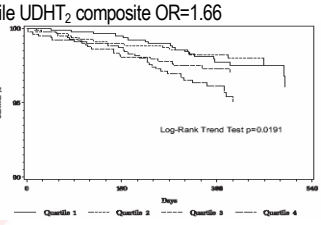
The Fritsma Factor 37

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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
  - 144 with stroke, MI, or CV death
  - 3117 with no adverse event
- Fourth quartile $UDHT_2$ composite OR=1.66

Kaplan–Meier curves for composite of stroke, MI, or CV death by $UDHT_2$ 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

The Fritsma Factor 38

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

CHARISMA Trial Conclusions

- Fourth quartile normal or elevated $UDHT_2$
  - Increasing age, ♀ sex, Hx of peripheral artery disease, smoking, oral hypoglycemic Rx, ACE-inhibitor Rx
- Reduced $UDHT_2$
  - 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 $UDHT_2$ quartile
- $UDHT_2$ is potentially modifiable

The Fritsma Factor 39

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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.

The Fritsma Factor 40

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Resistance and Adverse Events

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 = aspirin resistance; CAD = coronary artery disease; OR = odds ratio; CV = cardiovascular; MI = myocardial infarction; CVA = cerebrovascular event (stroke)

41

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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	

The Fritsma Factor 42

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Variation in Laboratory 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.

The Fritsma Factor 43

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Seven Days of Aspirin
Comparison to Whole Blood Aggregometry

Assay	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

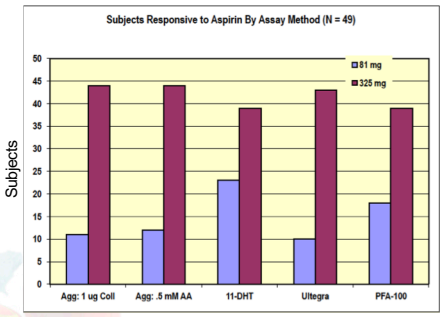
"Laboratory measures of PLT activity are suppressed by aspirin therapy, but are affected by the dosage and duration of therapy. Determinations of aspirin response should be made after at least 7 days of treatment. Laboratory test platform results do not closely reflect each other, thus application of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

The Fritsma Factor 44

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

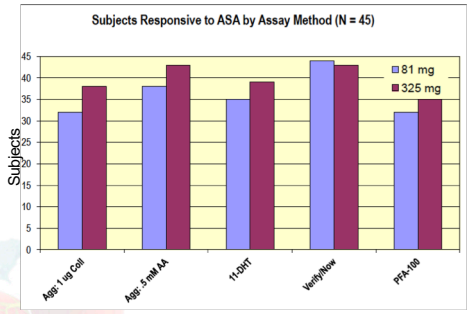
24-h Response to 81 & 325 mg



The Fritsma Factor 45

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

7-d Response to 81 & 325 mg



The Fritsma Factor 46

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Aspirin Resistance Study Limitations

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

The Fritsma Factor 47

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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) and von Willebrand factor receptors (GP Ib/V/IX)
  - Activation by shear stress in atherosclerosis
- Aspirin-mediated reduction of PLT-inhibiting prostacyclins from vascular endothelial cells
- Elevated von Willebrand factor, 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

The Fritsma Factor 48

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

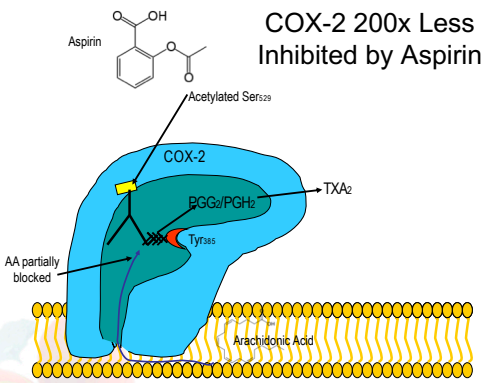
More Proposed Mechanisms of Aspirin Resistance

- NSAIDs compete for Ser_{529} site
  - Naprosyn, ibuprofen
- COX-2 Induction
  - Non-constitutive, 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.

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

COX-2 200x Less Inhibited by Aspirin



THE FRITSMA FACTOR Your Interactive Hemostasis Resource

Aspirin Failure Vs Resistance

- Variable antiplatelet efficacy=failure
  - Adverse events despite therapy: antiplatelet failure
  - Consider, 20% risk reduction, not 100%
- Laboratory testing for antiplatelet resistance
  - Light transmittance aggregometry (LTA)
  - Whole blood impedance lumiaggregometry (WBLA)
  - AspirinWorks®: Urine 11-dehydrothromboxane B_2 ($UDHT_2$) immunoassay
  - Werfen Accumetrics VerifyNow® Aspirin
  - Siemens PFA-100® CEP) and CADP cartridges

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

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: benefit in mechanical heart valves, bleeding 43% higher but lowered overall mortality 57%

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

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

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

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.

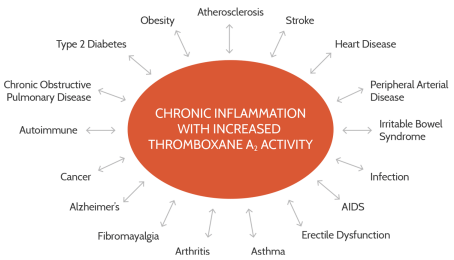
THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

DISEASES OF CHRONIC INFLAMMATION



THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Activated Platelets and Cancer

- Platelets are activated by tumor cells, generate TXA_2.
- Activated platelets raise activation potential of endothelium, attract WBCs to primary and metastatic tumor sites.
- 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.
- Breast cancer is associated with activation of TXA_2.
- COX-1 and 2 inhibition may enhance antitumor activity.
- $UDHB_2$ levels predict metastasis in relapsing breast cancer.
- $UDHB_2$ levels reflect activated platelets in colorectal cancer.
- Cancer progression is associated thrombocytosis and platelet activity.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Activated Platelets and Cancer References

1. Karachaliou N, Pilotto S, Bria E, Rosell R. *Platelets and their role in cancer evolution and immune system*. Translational Lung Cancer Research. 2015.
2. Olsson AK, Cedervall J. The pro-inflammatory role of platelets in cancer. Platelets. 2018.
3. Li N. Platelets in cancer metastasis: To help the "villain" to do evil. International Journal of Cancer. 2015.
4. 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.
5. Li H, Lee M, Liu K, Wang T, et al. Inhibiting breast cancer by targeting the thromboxane A2 pathway. Nature Partner Journals. 2017.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

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.

THE FRITSMA FACTOR
Your Interactive Hemostasis Resource