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Your Interactive Hemostasis Resource

Aspirin: The 1899 Wonder Drug

Monitoring Antiplatelet Drugs

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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.

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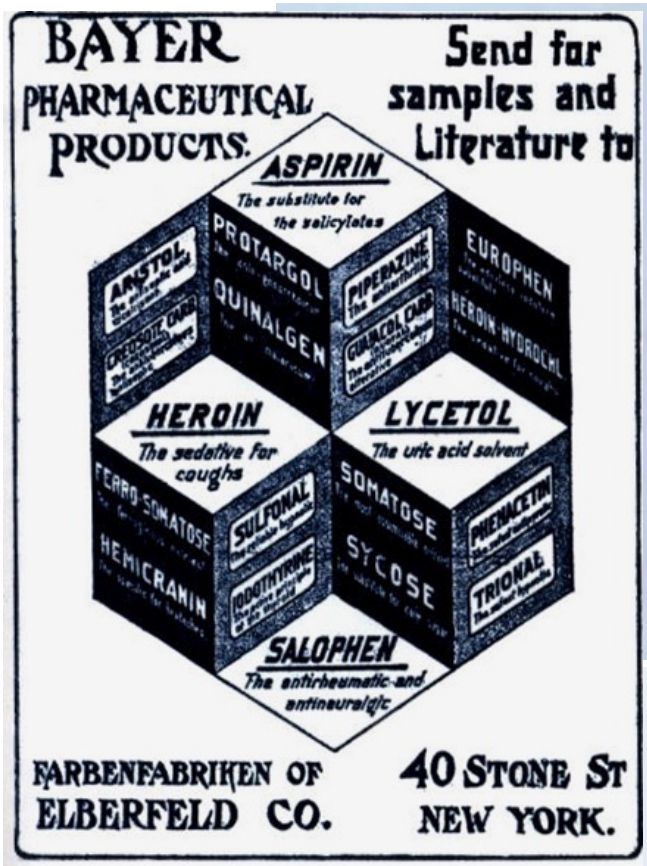
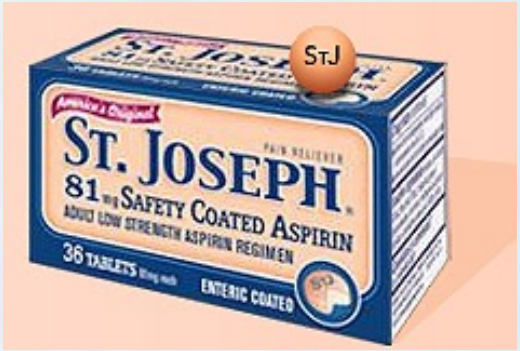


EL CORREO



ASPIRINA

Bayer

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.

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.

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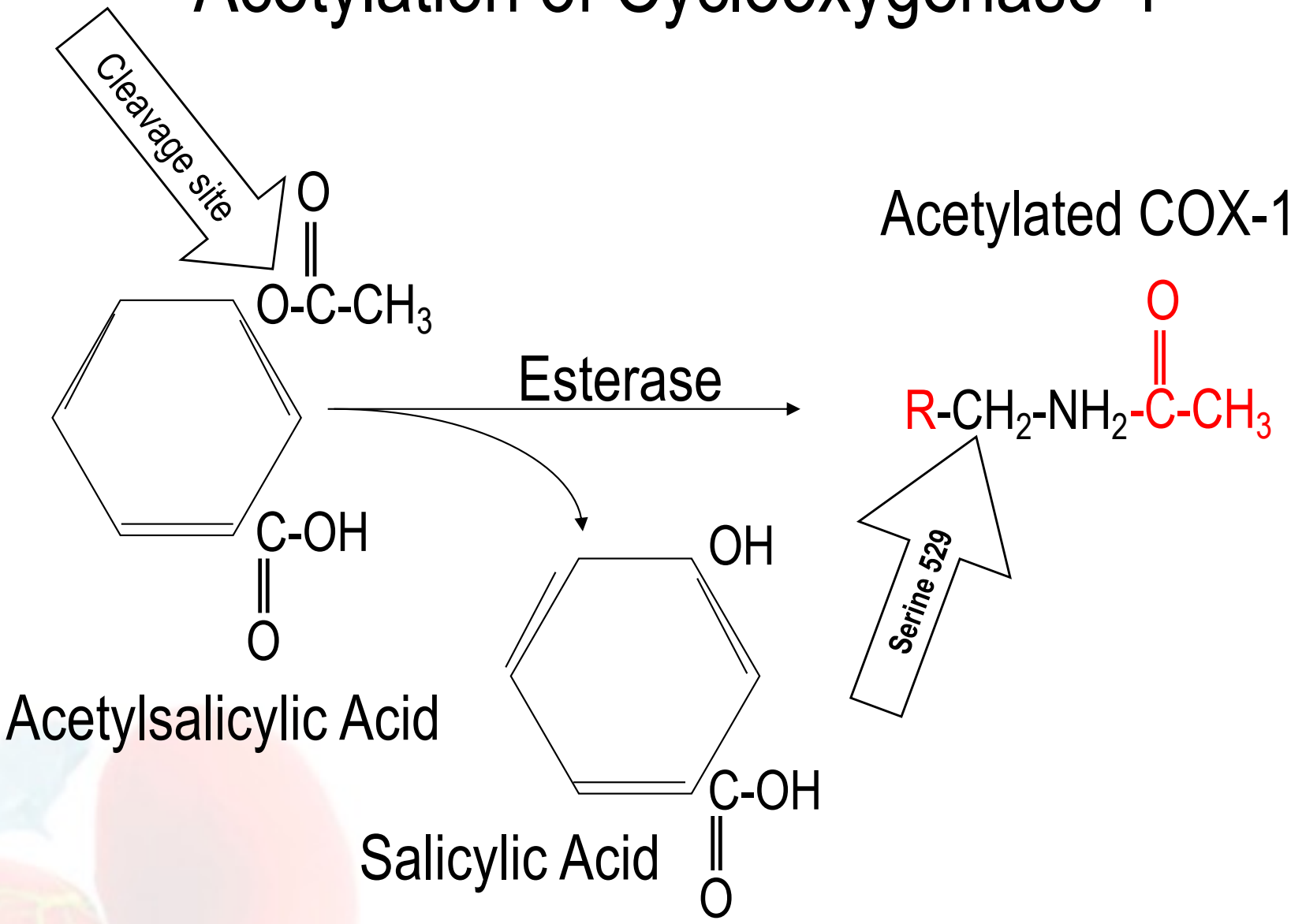
Acetylation of Cyclooxygenase-1



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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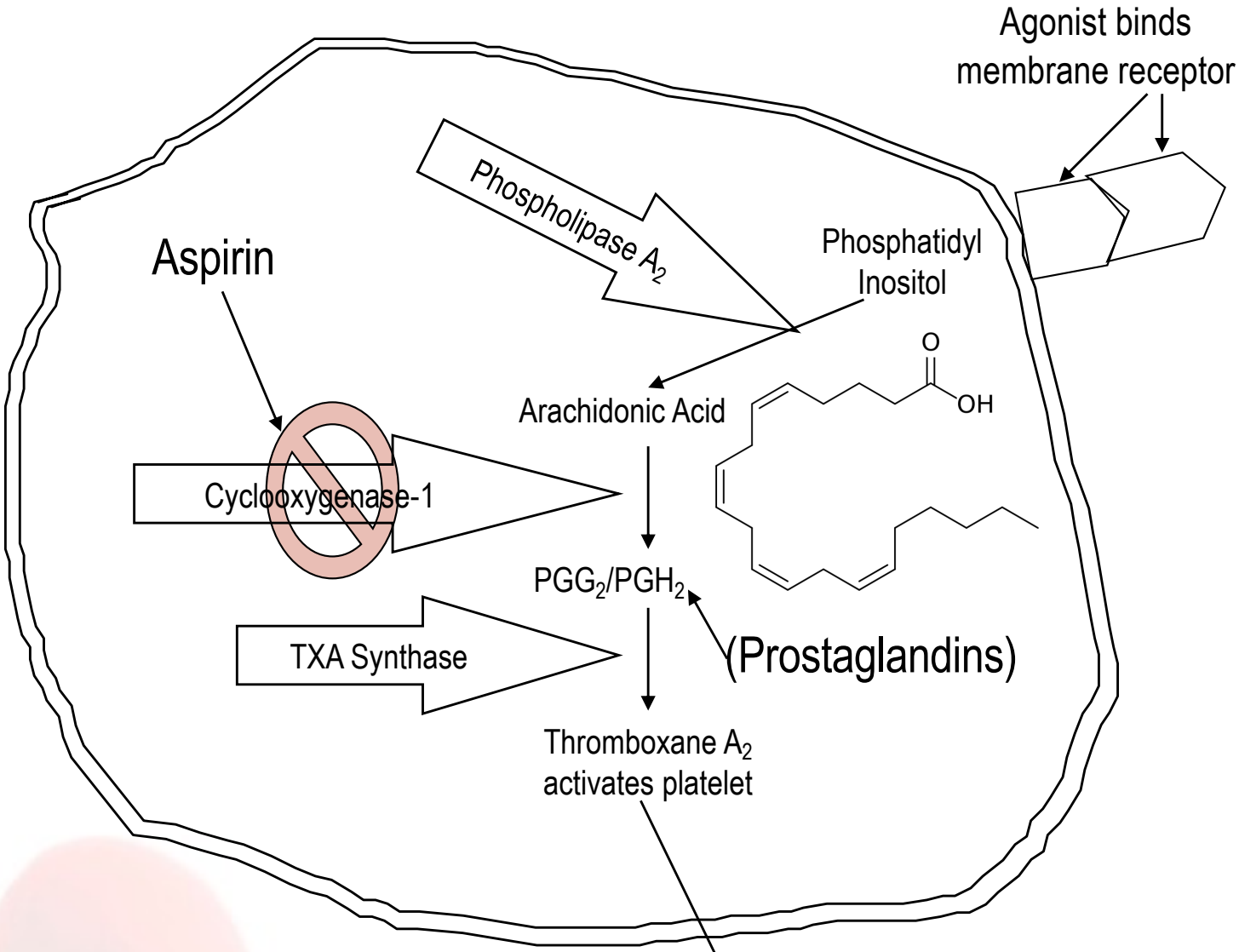
Aspirin acetylates COX-1 and reduces TXA_2 production



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

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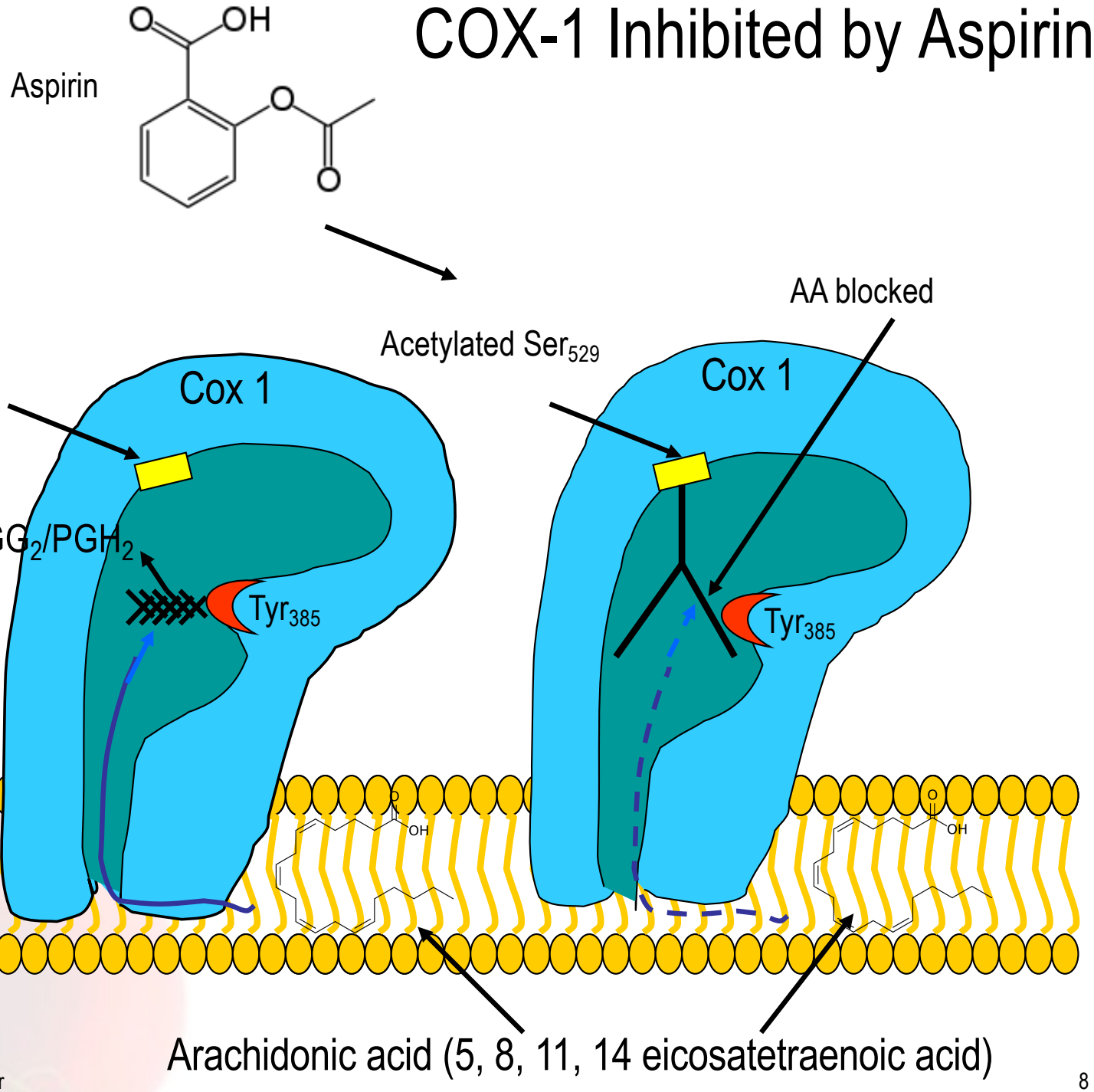
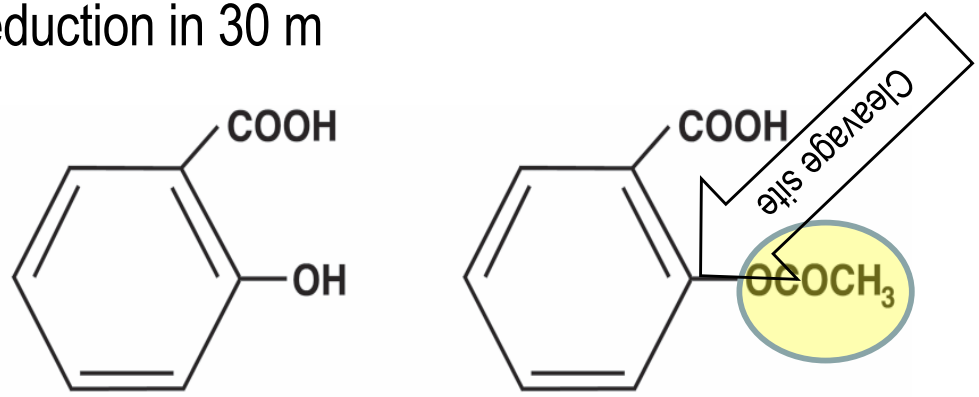
COX-1 Inhibited by Aspirin



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



Salicylic Acid Acetylsalicylic Acid (aspirin)

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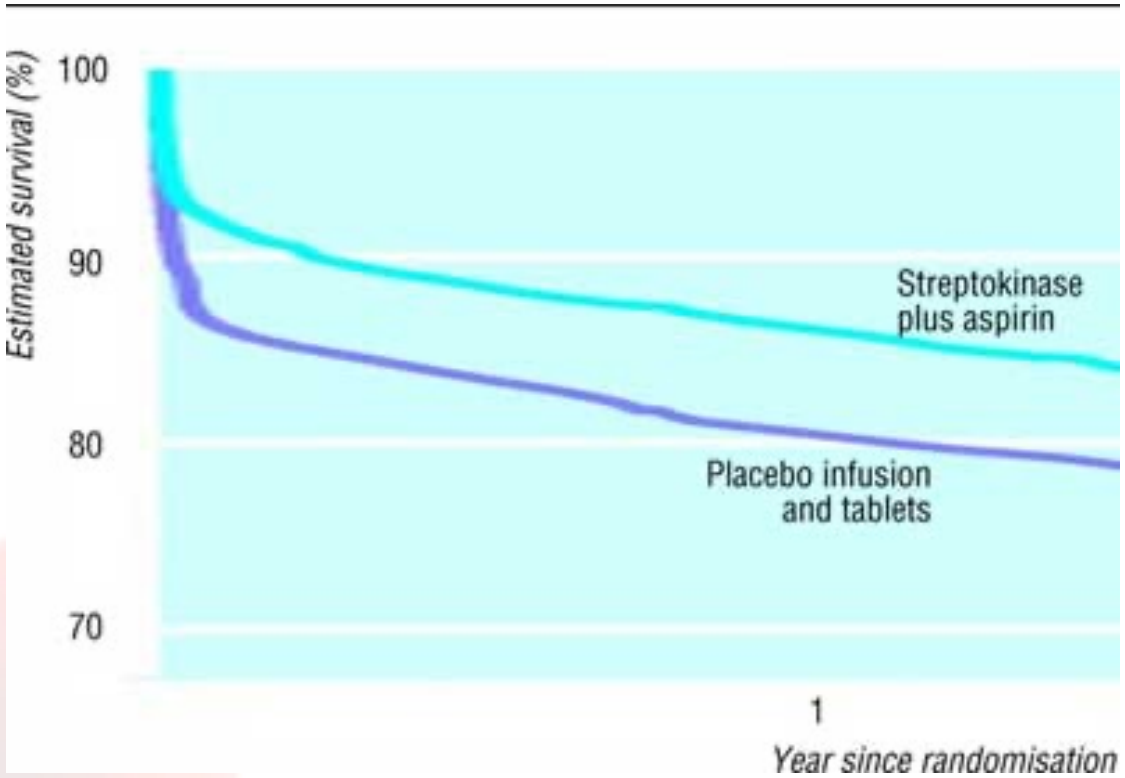
Aspirin Efficacy: ISIS-2

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.

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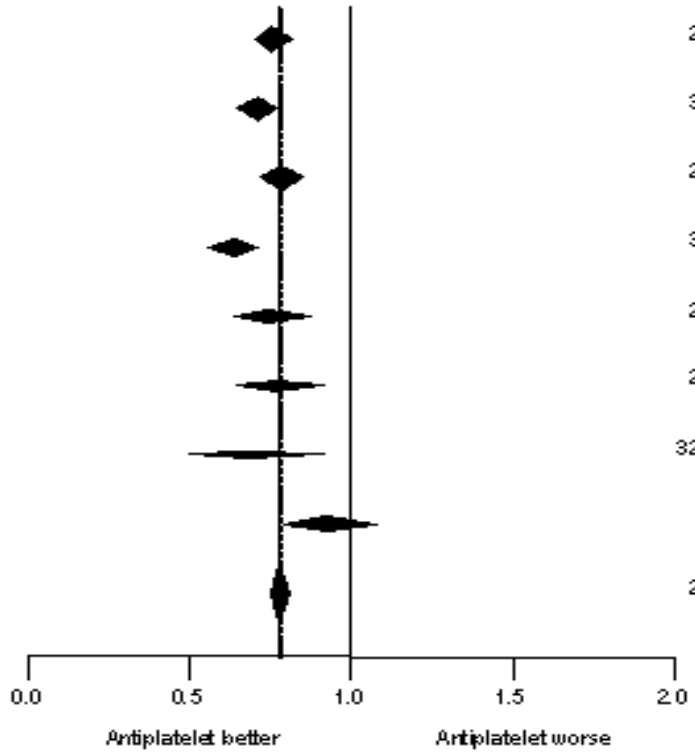
2002 Antiplatelet Trialists' Collaboration

Meta-analysis of 287 trials w/ 100,000 high-risk pats:

Composite 32% decrease in death, MI, ischemic stroke in vascular patients on 75–150 mg aspirin daily:

Category of patient	No of trials with data	No of patients	Percent with vascular event: Allocated antiplatelet	Percent with vascular event: Adjusted control	Odds ratio (CI) Antiplatelet:Control	%Odds reduction (SE)
Previous myocardial infarction	12	20000	13.5	17.0		25(4)
Acute myocardial infarction	15	19300	10.4	14.2		30(4)
Previous stroke/TIA	21	12000	17.8	21.4		22(4)
Coronary artery disease	55	17500	6.2	8.9		37(5)
High risk of embolism	14	5200	13.5	16.8		26(7)
Peripheral arterial disease	42	9700	5.8	7.1		23(8)
Other vascular conditions	20	3400	4.2	6.4		32(13)
Diabetes mellitus	9	5100	15.7	16.7		7(8)
ALL TRIALS	195	144100	10.7	13.2		22(2)



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.

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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)
  - 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 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 (♀ Only)
  - 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.

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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	75–100	0.95 (non-sig)	75–100 mg *raises* CAD risk to 1.33 (P= .0082) (How?)
>70	>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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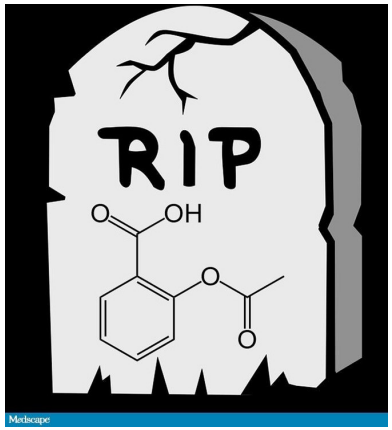
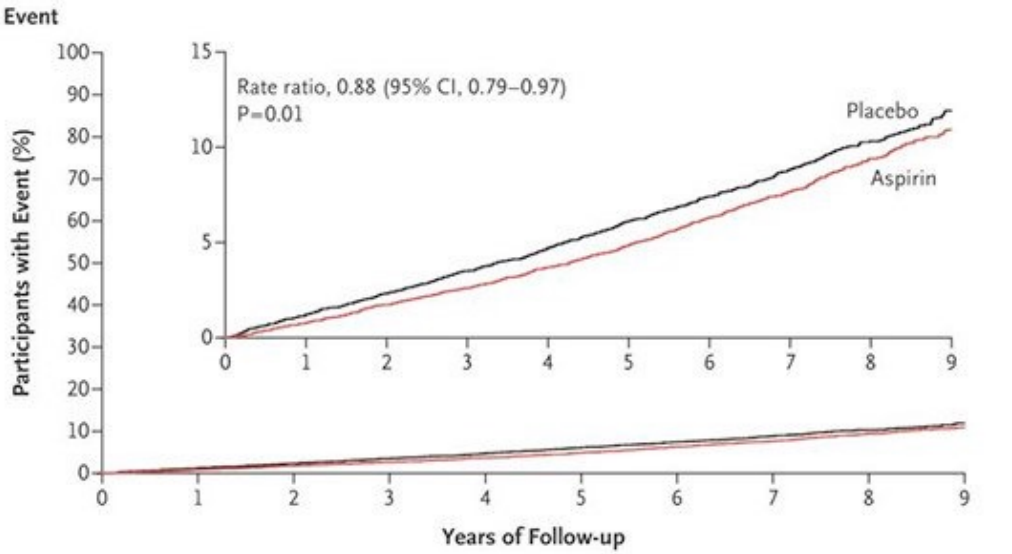
Sept 22, 2018: *ASA No Protection*

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





No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

Source: New England Journal of Medicine

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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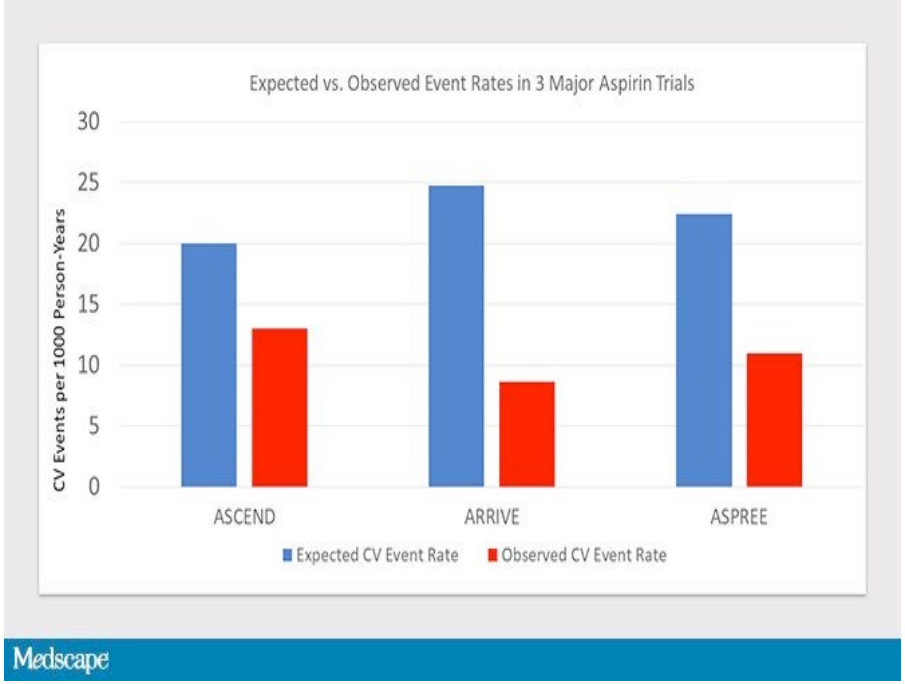
ASCEND, ARRIVE, and ASPREE Trials

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

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.

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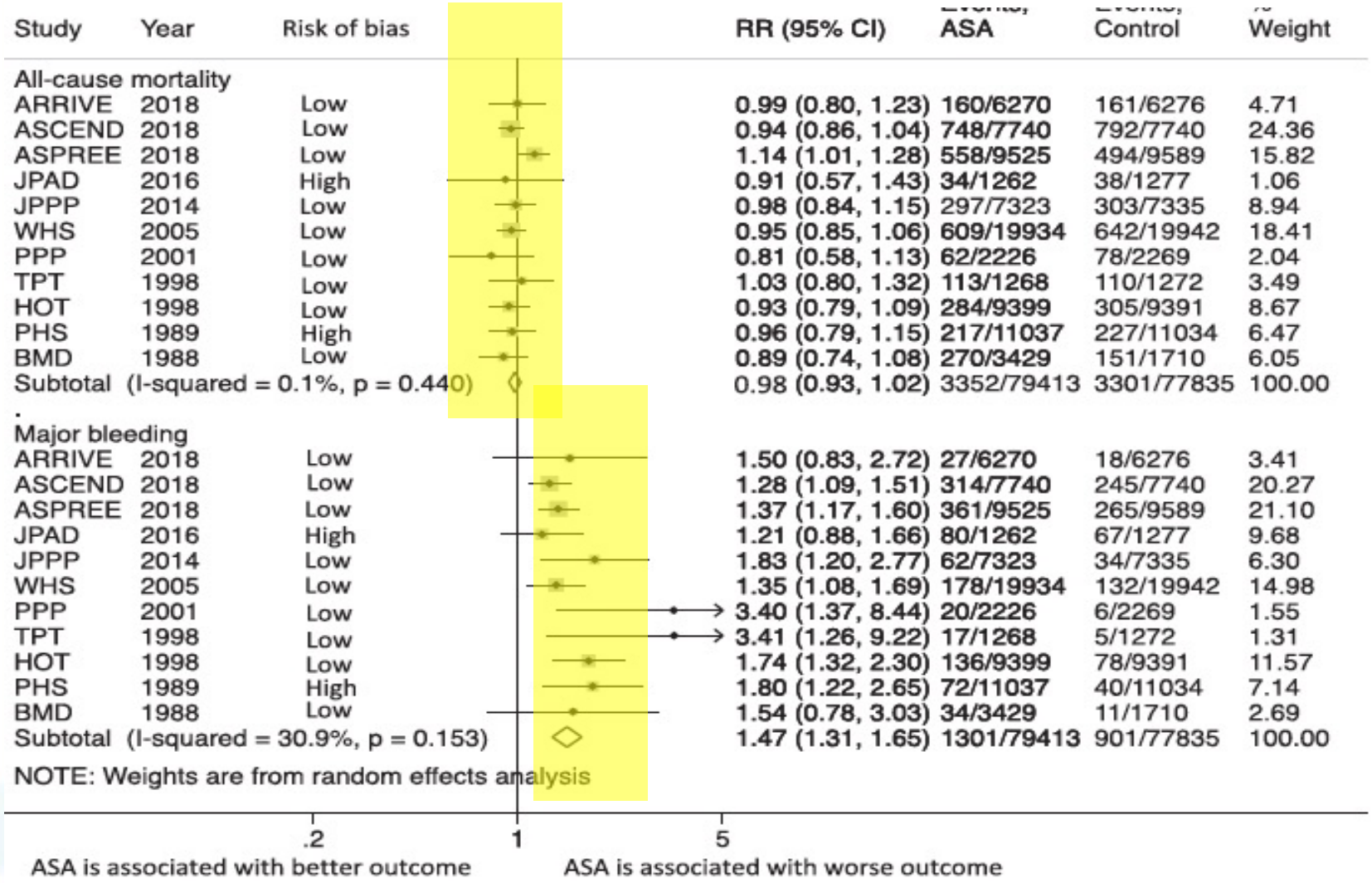
Slide Added 4-16-19

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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Proposed Mechanisms of Aspirin Resistance

- Alternate PLT pathways not blocked by aspirin
  - Diacylglycerol pathway activated through G-protein
  - Adhesion molecules: collagen (GP Ia/IIa) and VWF receptors (GP Ib/V/IX)
- Shear stress activation and turnover in atherosclerosis
- ASA-mediated reduction of PLT-inhibiting prostacyclins from vascular endothelial cells
- Elevated von Willebrand factor, fibrinogen activity level
- NSAIDs compete for Ser_{529} site: naprosyn, ibuprofen
- Polypharmacy (> 4 drugs)
- Lack of compliance

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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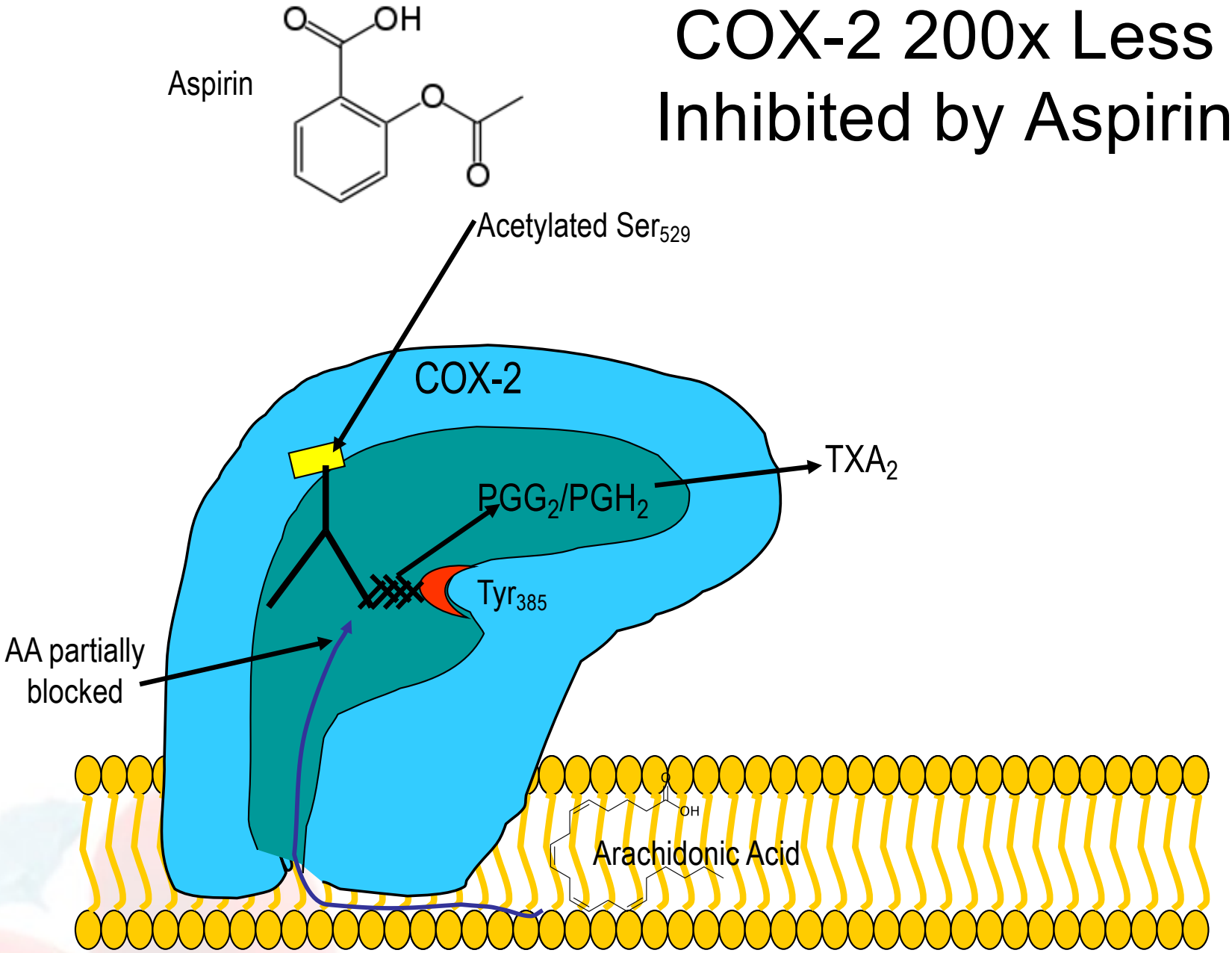
COX-2 Induction

- Increased PLT turnover: more than 10% per day
- Non-constitutive COX-2 , response to inflammatory cytokines
- COX-2 in megakaryocytes, monocytes, macrophages, vascular endothelial cells and newly released platelets
- Smoking, diabetes, congestive heart disease, obesity, hyperlipidemia
- After CABG, 16-fold increase of COX-2
- COX-2 ser_{529} acetylation incompletely hinders arachidonic acid's access to tyr_{385} reactive site

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.

COX-2 200x Less Inhibited by Aspirin



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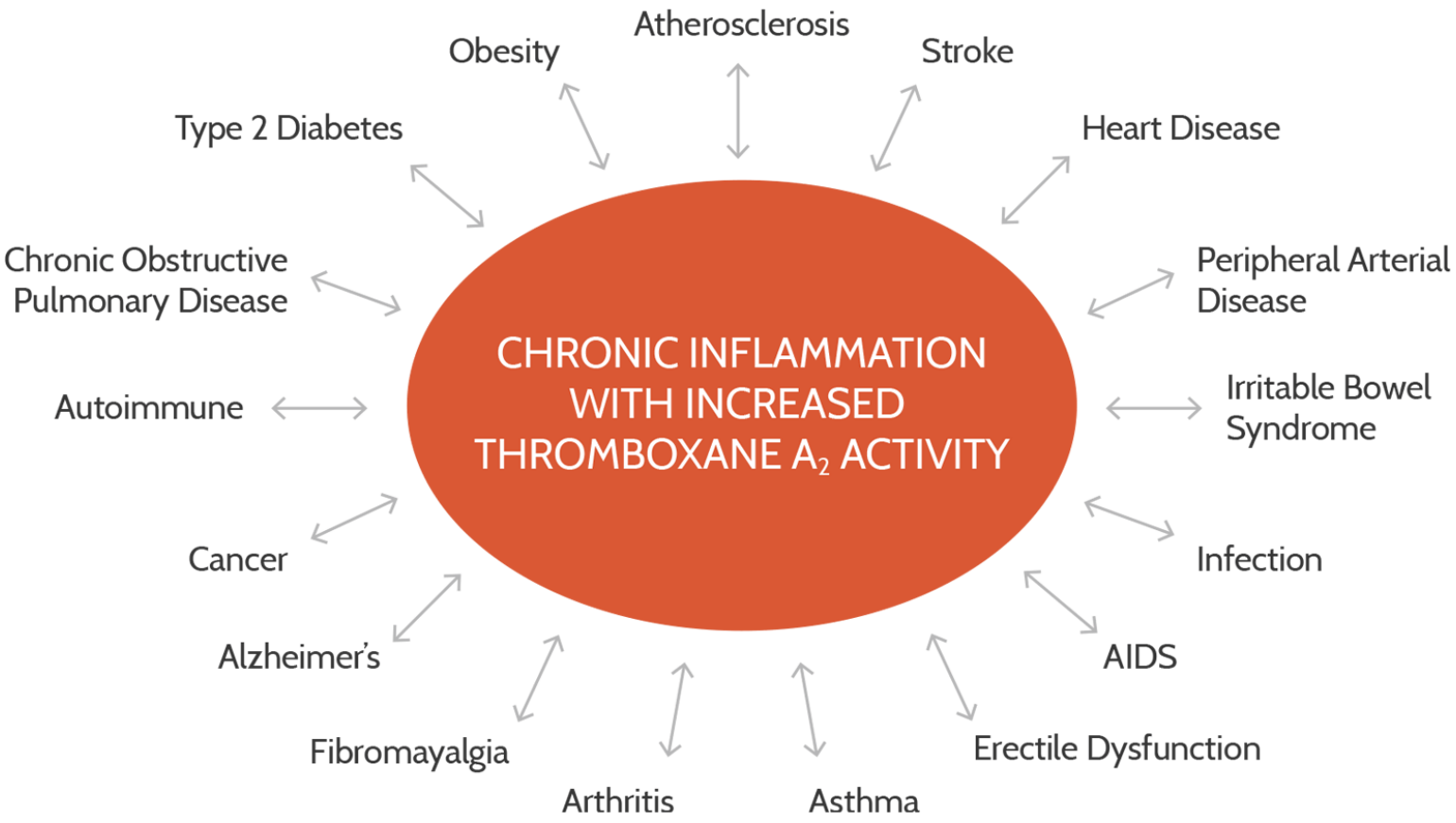
DISEASES OF CHRONIC INFLAMMATION



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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?