



ASPIRIN THERAPY IN 2022: NEW HORIZONS

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FACULTY DISCLOSURES -



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Present Research/Grant Funding (within the last year)

Ongoing: CSL Behring; Janssen Pharmaceuticals; Johnson & Johnson Corporation; SCAD Alliance;

Consulting

Amag Pharmaceuticals, Angel Medical Corporation, Anthos Therapeutics, AstraZeneca, Bayer Corporation, Boston Clinical Research Institute, Boston Scientific, Bristol-Myers Squibb, Caladrius Biosciences, Cardiovascular Research Foundation, CeleCor Therapeutics, CSL Behring, CytoSorbents Medical, Inc., DCRI, Eidos Therapeutics, EXCITE International (\$0 Received), Gilead Sciences, Inc., Janssen, Pharmaceuticals, Johnson & Johnson Corporation, MD Magazine, Medtelligence, Micodrop, LLC, Microport, MJHealth, NovoNordisk, Pfizer, PHRI, PLx Pharma Inc, SCAI, Smart Medics, Somahlution, Web MD

For Trials that Dr. Gibson actively serves as PI of and receives research grant support on an ongoing basis, there is less than \$25,000 per year in consulting monies received per the Harvard, BIDMC, Baim policies.

Equity

nference, Dyad Medical, Absolutys

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UpToDate in Cardiovascular Medicine

Spouse conflicts of interests (Employee of Boston Clinical Research Institute)

Amag Pharmaceuticals, Amarin, Angel Medical Corporation, Anthos Therapeutics, AstraZeneca, Bayer, Bioclinica, Boston Scientific, Caladrius Biosciences, Cardiovascular Clinical Science Foundation, Cardiovascular Research Foundation, CeleCor Therapeutics, CytoSorbents Medical, Inc., CSL Behring, DCRI, Eidos Therapeutics, EXCITE International (\$0 Received), Gilead Sciences, Inc., Inari, Janssen, Johnson and Johnson, MD Magazine, Medtelligence, MedImmune, MedTrace, Merck, Micodrop, LLC, Microport, NovoNordisk, Pfizer, PhaseBio, Paratek, PHRI, PLxPharma, Revance Therapeutics, SCAI, Smart Medics, Somahlution

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Consulting

MedCom

Consulting (non-paid)

AHA



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Ongoing: Alexion Pharmaceuticals, Heron Therapeutics, PhaseBio Pharmaceuticals

Consulting

Alexion Pharmaceuticals, Allergan Pharmaceuticals, Boehringer-Ingelheim, Pacira Biosciences, Pfizer, PhaseBio Pharmaceuticals, Vifor Pharma



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Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

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- a) Consulting fee or honorarium from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, and Sanofi
- b) Honorarium for participation in review activities (DSMB member) from NIH.
- c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member) and American College of Cardiology (Associate Editor JACC Cardiovasc Interventions)

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- a) Grant support industry: from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions.
- b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
- c) Federal agency: NIH

LEARNING OBJECTIVES



Upon completion of this activity, participants will:

- Have increased knowledge regarding the
 - Latest clinical guideline statements for the use of aspirin therapy in the setting of post procedural CAD, NSTEMI, STEMI.
 - Relevant data in secondary prevention of cardiovascular disease and differentiate primary and secondary prevention.
 - Tailoring of the aspirin formulation and dose for patients starting aspirin therapy or experiencing issues on therapy.
- Have greater competence related to
 - Evaluating the differences in available aspirin formulations
 - Recommending aspirin therapy and tailoring it the individual patient profile
 - Educating patients starting aspirin therapy on benefits, common side effects, and how to take it

ASPIRIN HISTORY

- Origins in herbal remedies dating back 4000 years to the Sumerians, who noted the pain remedies of the willow tree on early clay tablets. Aspirin was used to treat rheumatic disease, pain, fever
- Synthetic formulation made pharmaceutically available in 1899 by Bayer, registering the trade name of Aspirin
- Latter half of the 20th Century recognized in cardiovascular disease prevention and in urgent administration in acute cardiovascular events; The importance of aspirin was established in secondary prevention and post percutaneous or surgical revascularization and ischemic stroke
- Over 50 years ago, with patients reporting GI issues with plain immediate release aspirin, the delayed release enteric coated formulations were created. Enteric coated aspirin is the most used formulation in the U.S.
- With the more potent antiplatelet agents, P2Y₁₂ inhibitors, added to aspirin therapy for further reduction of CV events and preventing stent thrombosis- there was a need to reduce the risk of bleeding and balance CV protection. Low dose aspirin (75mg-100mg) is now what is recommended for post procedure and secondary prevention.

<https://www.sciencehistory.org/distillations/aspirin-turn-of-the-century-miracle-drug>
Desborough MJR. Brit J Haem 2017;177:674–683.

ASPIRIN TODAY



Aspirin landscape in 2022:

- Aspirin remains foundational therapy in *secondary prevention*.
- The United States Preventative Services Taskforce releasing the primary prevention aspirin statements, mirroring the 2019 ACC/AHA Prevention Guidelines limiting aspirin in *primary prevention* to high- risk patients.
- There have been studies published shortening DAPT in both CAD and post ACS patients. In late 2021, ACCF/AHA/SCAI released Revascularization Guidelines. The use of aspirin post procedure and in secondary prevention needs were reviewed.
- There is lack of awareness regarding the differences in aspirin formulations and there is a new FDA approved aspirin formulation available in the U.S.
- Our Physician, Advanced Practice Provider and Pharmacy Roundtables will offer discussion and pragmatic provider tips from practice.

USPSTF Taskforce. JAMA 2022;327:1577-1584.

Lawton JS, et al. JACC 2022;79(2):e21-e129.



PRIMARY PREVENTION VERSUS SECONDARY PREVENTION

Primary Prevention in ASCVD focuses on preventing major ischemic events and disease or **treating patients without known disease yet.**

Secondary Prevention refers to the effort to treat known, clinically significant ASCVD, and to prevent or delay the onset of disease manifestations or **to treat patients we know have ASCVD or other vascular disease to prevent another event.**

PRIMARY PREVENTION : USPSTF UPDATED RECOMMENDATION

Adults aged 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C
Adults 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older.	D

“Persons who are currently taking aspirin and have questions about why they are taking it, or whether they should continue or discontinue aspirin use, should discuss these questions with their clinician.

Persons who are taking aspirin should not discontinue using it without consulting their clinician.

For persons who are deciding with their clinician whether to continue or discontinue taking aspirin for primary prevention, clinicians may want to consider that person’s age, level of CVD risk and bleeding risk, preferences, and reasons for taking aspirin.”

PRIMARY PREVENTION : USPSTF UPDATED RECOMMENDATION

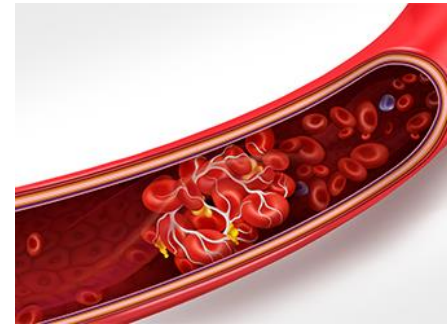
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"Persons who are currently taking aspirin and have not discussed with their clinician about why they are taking it, or whether they should continue or discontinue aspirin use, should discuss these questions with their clinician."

Persons who are taking aspirin should not discontinue using it without consulting their clinician."

"For persons who are not taking aspirin, clinicians may want to consider that person's age, level of CVD risk and bleeding risk, preferences, and reasons for taking aspirin."

CASE STUDY DISCUSSION



- 52 YO female with history of Type 2 Diabetes, HTN, and no past history of cardiovascular disease, but notable hysterectomy age 45 presented to the Cath lab directly by ambulance with ST elevation myocardial infarction.
- In the ambulance, the paramedics observed ST elevation in leads V2-4, applied 2L O₂ per nasal canula, administered 325mg chewable aspirin, SL NTG, and rushed the patient to a PCI center.
- CathLab: Pulse 90/min, RR 20/min, BP 130/78, Hb A1c 6.8, 110 KG (BMI 34); CathLab Team proceeded to immediate PCI to open the LAD and place DES.
- Post procedure and hospital course were uneventful. Discharged on prehospitalization medications losartan & dulaglutide, and DAPT.



THIS PATIENT SHOULD BE PLACED ON ASPIRIN THERAPY FOR?

- A) Primary Prevention
- B) Secondary Prevention

WHICH ANTIPLATELET REGIMEN WOULD YOU PLACE THE PATIENT ON?



- A) Immediate release/ plain aspirin 81 mg, clopidogrel 75 mg for 1 year
- B) Enteric coated aspirin 81 mg, clopidogrel 75 mg
- C) Enteric coated aspirin 81 mg, more potent P2Y12 prasugrel or ticagrelor
- D) PL-ASA 81 mg, clopidogrel
- E) PL-ASA 81 mg, more potent P2Y12 prasugrel or ticagrelor

AT ONE YEAR, WHAT ANTIPLATELET THERAPY WOULD YOU TRANSITION THE PATIENT TO?

- A. Enteric coated aspirin 81 mg
- B. PL-ASA 81 mg
- C. Clopidogrel 75 mg
- D. More potent P2Y₁₂ prasugrel or ticagrelor
- E. Continue DAPT

Eva Kline-Rogers MS, RN, NP.

University of Michigan

Cardiovascular Nurse Practitioner, Ann Harbor Michigan

and co-director for MCCRPP

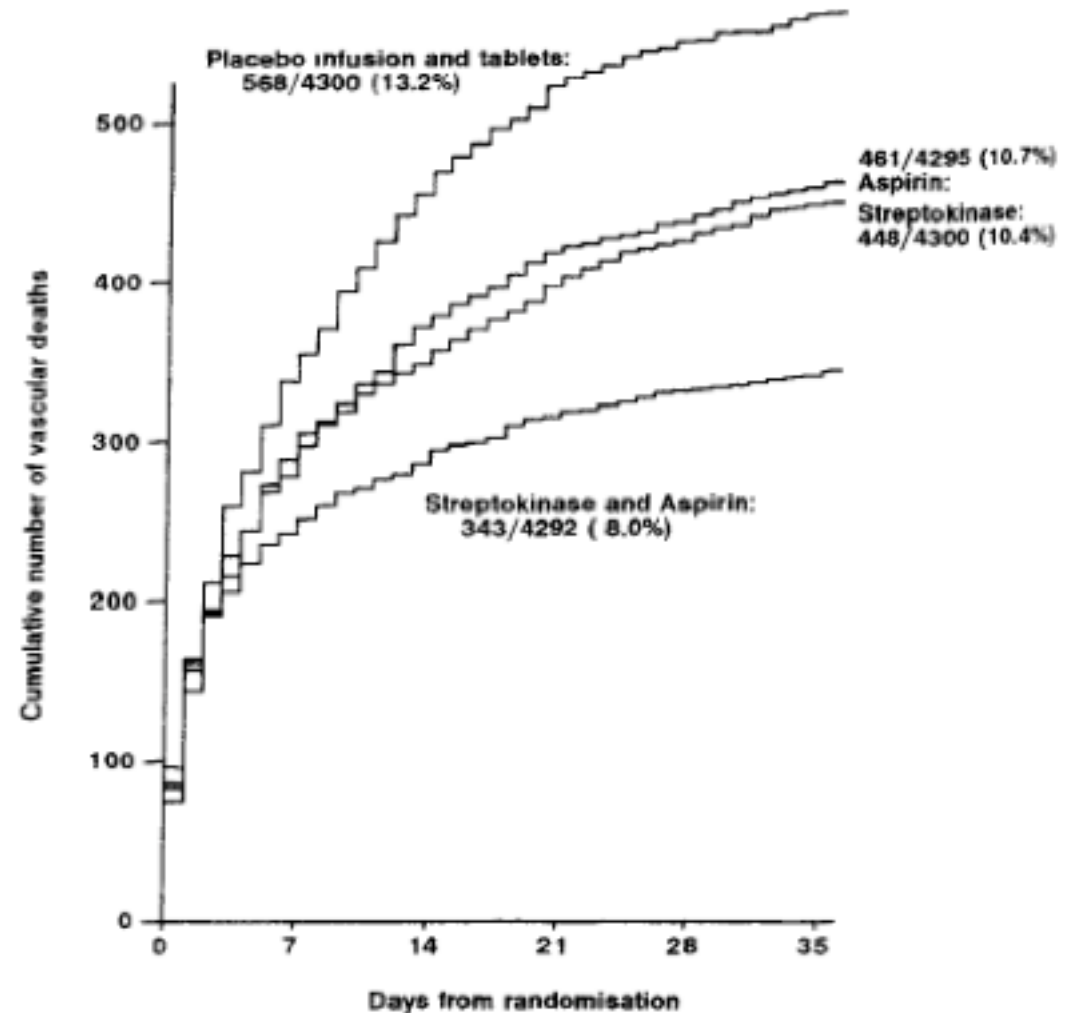
(Michigan Cardiovascular Outcomes Research and Reporting Program)



- Review briefly historical clinical studies and evidence on aspirin that led to practice changes
- How do we measure aspirin therapy and adherence
- Review the relevant Practice Guidelines for Aspirin

ISIS-2. Second International Study of Infarct Survival

- Cumulative mortality among 17,187 randomized pts
- Effects of aspirin and streptokinase(SK) were independent
- Aspirin reduced mortality whether pts received SK or placebo (reductions in the odds of death by aspirin: 25% (SD 6) and 21% (SD 6), respectively; each $p < 0.001$).
- **PRACTICE CHANGE = EMS/ED Nurses rushed to give 325 mg immediate release aspirin(chewable) for suspected MI**



Aspirin Evidence: Secondary Prevention

Aspirin reduces the risk of adverse cardiovascular events

Background:

Meta-analysis of randomized trials of antiplatelet therapy (majority with ASA)

Methods:

195 randomized trials, N= 135,640

Primary Endpoint:

Serious vascular event (SVE): Myocardial infarction, Stroke, or Vascular death

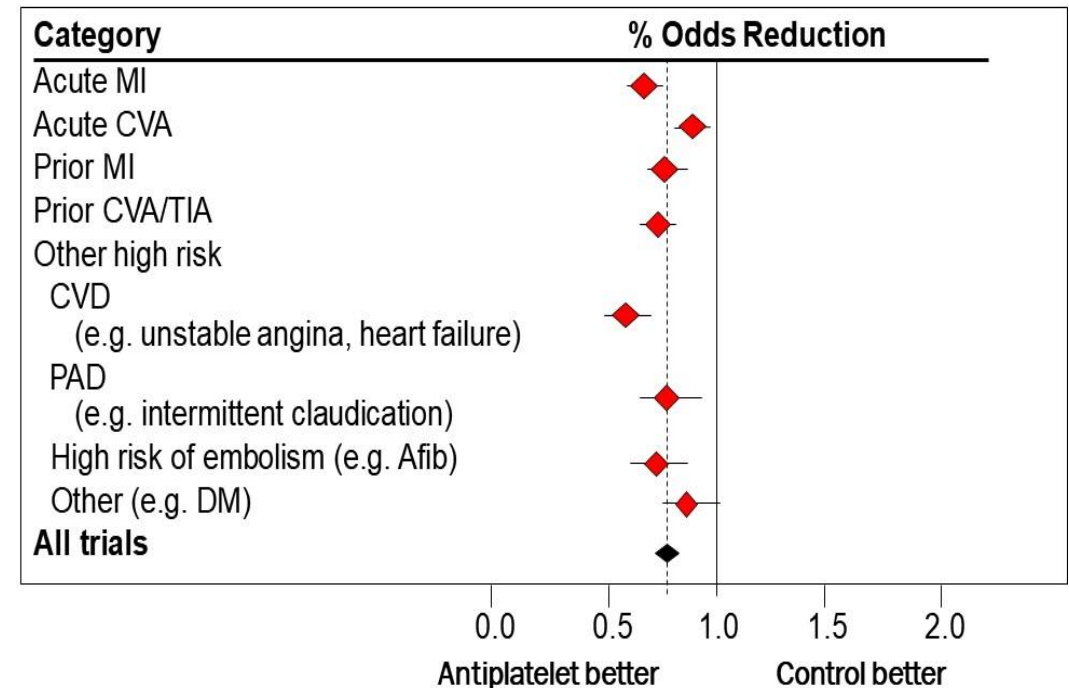
Results:

- **10.7%** SVE (7705/71 912) with antiplatelets vs **13.2%** (9502/72 139) controls ($P < 0.0001$)
- Reductions in SVE across all categories of high risk

PRACTICE CHANGE- Aspirin 325 mg was given to patients for secondary prevention

Antithrombotic Trialists Collaboration

Effect of antiplatelet treatment* on vascular events**



*Aspirin was the predominant antiplatelet agent studied

**Include MI, stroke, or death

Aspirin Evidence: Secondary Prevention

Aspirin increases the risk of major bleeding



Antithrombotic Trialists Collaboration

Number of Major bleeds/ # Patients (combined %)*				
Category of trial	Antiplatelet groups	Adj controls†	Stratified odds ratio (SE)	Adj absolute excess risk/1000 (SE)
Acute MI	28/9134 (0.31)	23/9136 (0.25)	1.2 (0.3)	0 (1)
Acute stroke	195/20 195 (0.97)	116/20 178 (0.57)	1.7 (0.1)	4 (1)§
Previous MI	3/672 (0.45)	3/668 (0.45)	—	—
Previous stroke/TIA	80/8276 (0.97)	39/8289 (0.47)	2.0 (0.3)	5 (2)‡
Other high risk	229/8881 (2.58)	152/8897 (1.71)	1.5 (0.1)	9 (3)‡
Total	535/47 158 (1.13)	333/47 168 (0.71)	1.6 (0.1)¶	
*Bleeds include fatal and nonfatal events, only trials with systematic recording of all major extracranial bleeds (and that recorded at least one such bleed) are include; Percentage adjusted for unbalanced randomization; ‡P<0.001; § P<0.0001; ¶ ÷ 2 for heterogeneity=2.6, df=4; NS. Adj=adjusted; SE= standard error'				

The practice change to recommend low dose (75-100 mg) aspirin for secondary prevention was to address the risk of bleeding along with introduction of P2Y12 inhibitors has now been generally accepted by the ESC and ACC/AHA in the U.S.

POST DISCHARGE USE OF ASPIRIN IN SECONDARY PREVENTION

- REACH Registry 2006: approximately 1/4 of US patients with vascular disease are not treated with aspirin for secondary prevention: 15% are not treated with any antithrombotic agent.
- Swedish prescription register 2005 to 2009: Outpatient use in 601,527 Swedish users of low-dose aspirin for primary or secondary prevention (long-term users):
 - discontinuation of low-dose aspirin (no major surgery or bleeding) was associated with a >30% increased risk of CV events and in pts discontinuing aspirin for secondary prevention
 - discontinuation rates led to a 46% higher rate in CV events.
- Issues/Concerns with Aspirin Use:
 - Post Discharge use of aspirin is difficult to track as it is OTC and it is not a prescription.
 - Tolerability based on GI issues and increased risk for bleeding based on concomitant use of other antiplatelets and anticoagulants
- HCPs should use the EHR to document aspirin formulation and use at subsequent visits
- Contemporary outpatient use studies are needed.

PRACTICE GUIDELINES



- The NSTEMI-ACS, STEMI and SIHD practice guidelines for aspirin therapy remains unchanged
- The recent 2021 ACCF/AHA/SCAI Revascularization Guidelines have updated the antiplatelet section for DAPT post revascularization to reflect recent studies to shorten DAPT for SIHD. This differs with post event ACS patients.
- Let us review the Guidelines in brief.
- Further discussion and questions will be answered in the roundtable discussion.

AHA/ACC GUIDELINES: ANTIPLATELET THERAPY FOR NSTEMI-ACS, STEMI, AND PCI



Summary of Recommendations for Initial Antiplatelet Therapy in Patients with Definite or Likely NSTEMI-ACS and PCI (Ref Table 7)¹

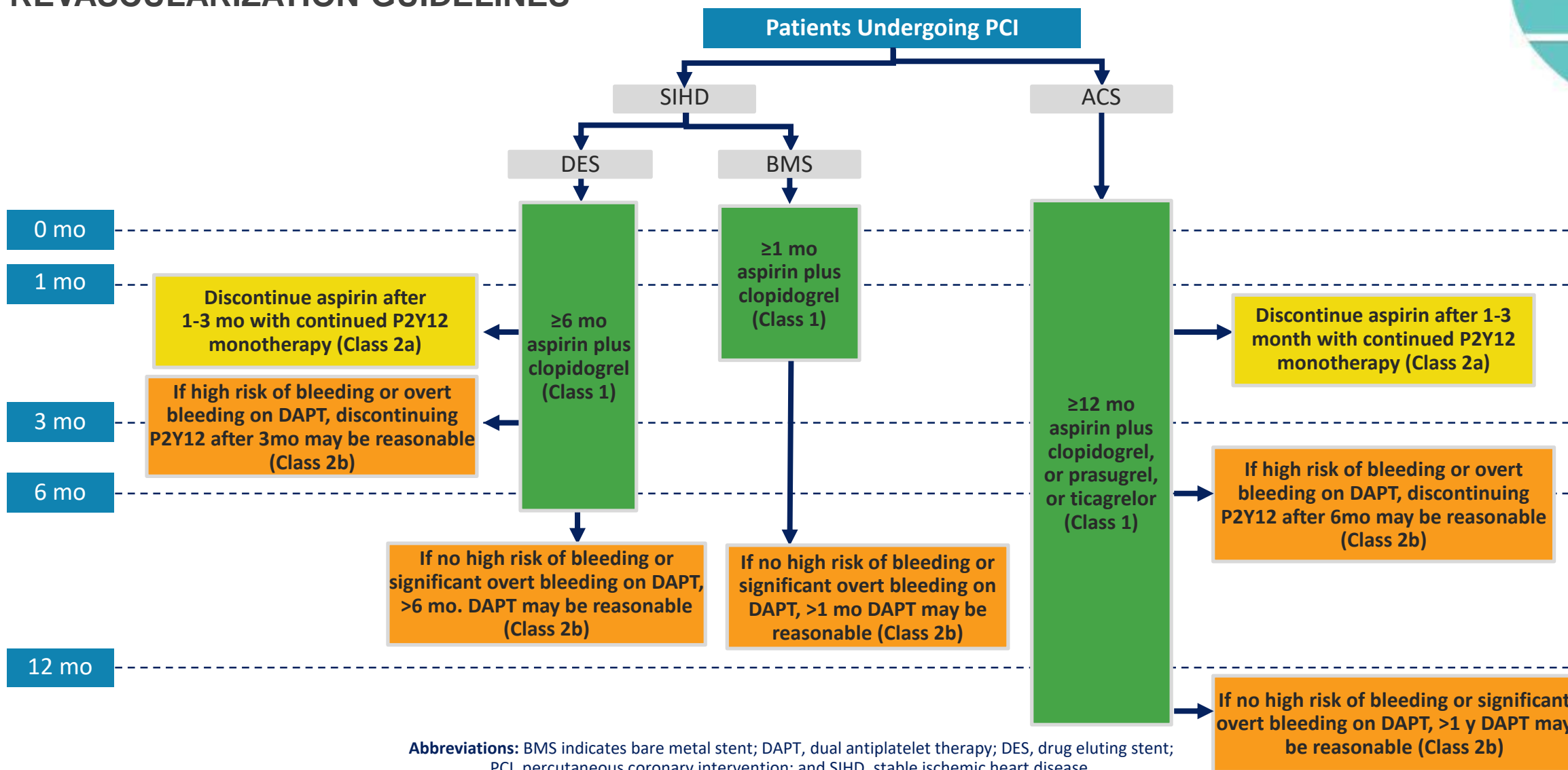
Recommendations	Dosing and Special Considerations	COR	LOE
Aspirin			
• Non-enteric coated aspirin to all patients promptly after presentation	162 mg-325 mg	I	A
• Aspirin maintenance dose continued indefinitely	81 mg/d 325 mg/d	I	A

Summary of Recommendations for Initial Antiplatelet Therapy in Patients with STEMI and PCI²

Recommendations	Dosing and Special Considerations	COR	LOE
Aspirin			
• Non-enteric coated aspirin to all patients promptly after presentation	162 mg-325 mg	I	B
• Aspirin maintenance dose continued indefinitely	81 mg/d 325 mg/d	I	A
• 81 mg daily is the preferred maintenance dose	81 mg	IIa	B

¹Amsterdam et al JACC 2014;64:e139-228. ²O'Gara et al JACC 2013; 61(4):e78-e140.

USE OF DAPT FOR PATIENTS AFTER PCI, ALGORITHM FROM ACC/AHA/SCAI REVASCULARIZATION GUIDELINES



Secondary prevention after DAPT: Aspirin or P2Y₁₂

Aspirin or a P2Y₁₂ inhibitor for monotherapy 2^o prevention?



Background:

What is the clinical implication of dropping the aspirin or P2Y₁₂ inhibitor after DAPT?

Methods:

Meta-analysis of 42,108 patients from 9 randomized trials

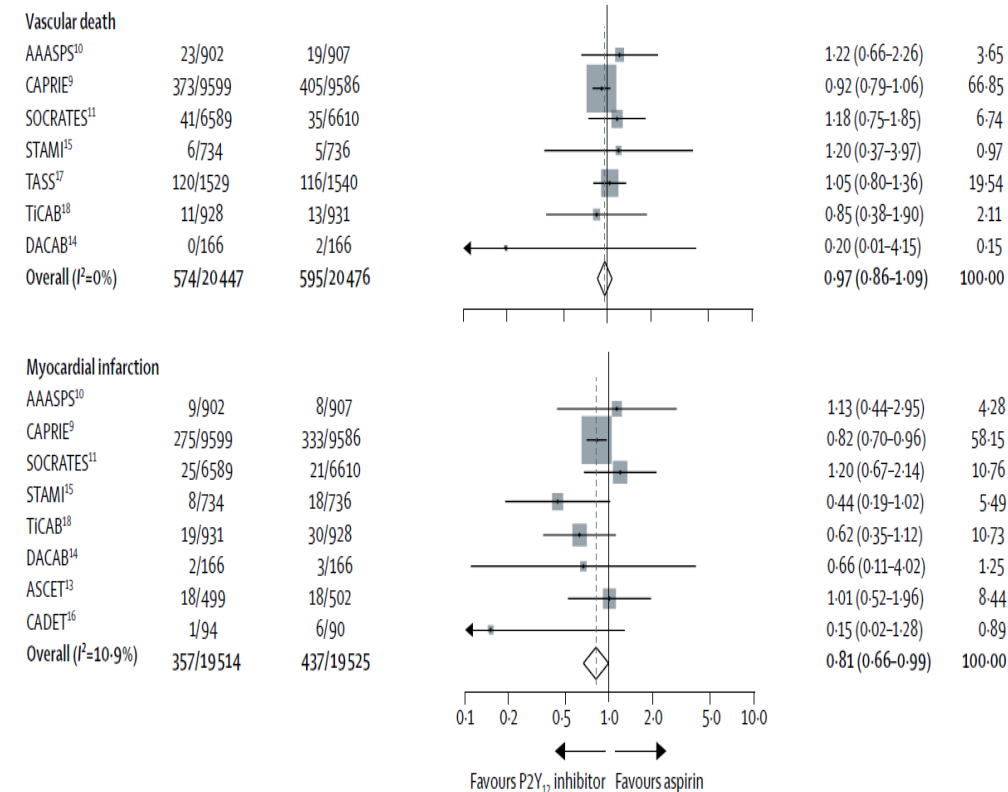
Results:

Compared to aspirin, a P2Y₁₂ inhibitor had

- Borderline reduction for the risk of MI (OR 0.81 [95% CI 0.66–0.99]); NNT =266
- No difference in risk of death, stroke or major bleeding (OR 0.90 [0.74–1.10])

Conclusions:

- The high NNT and no effect on death or bleeding questions the clinical relevance of the marginally lower risk of MI.
- The higher cost of novel P2Y₁₂ inhibitors vs aspirin, as well as different patient risk profiles should be considered.

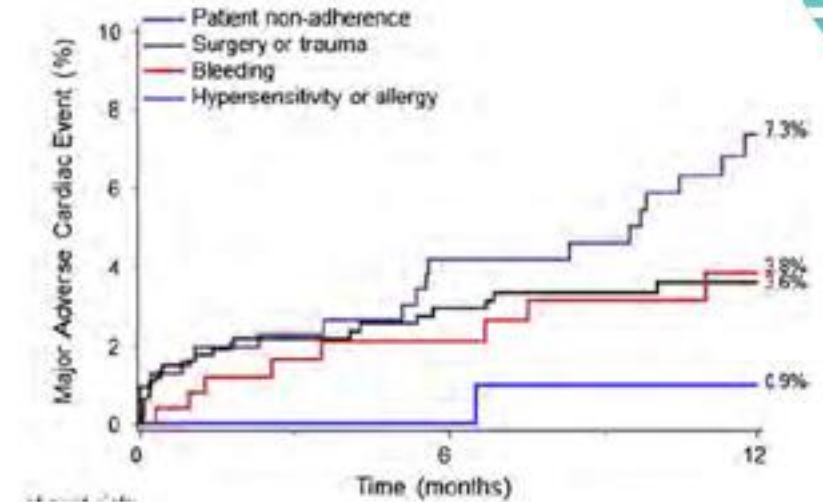
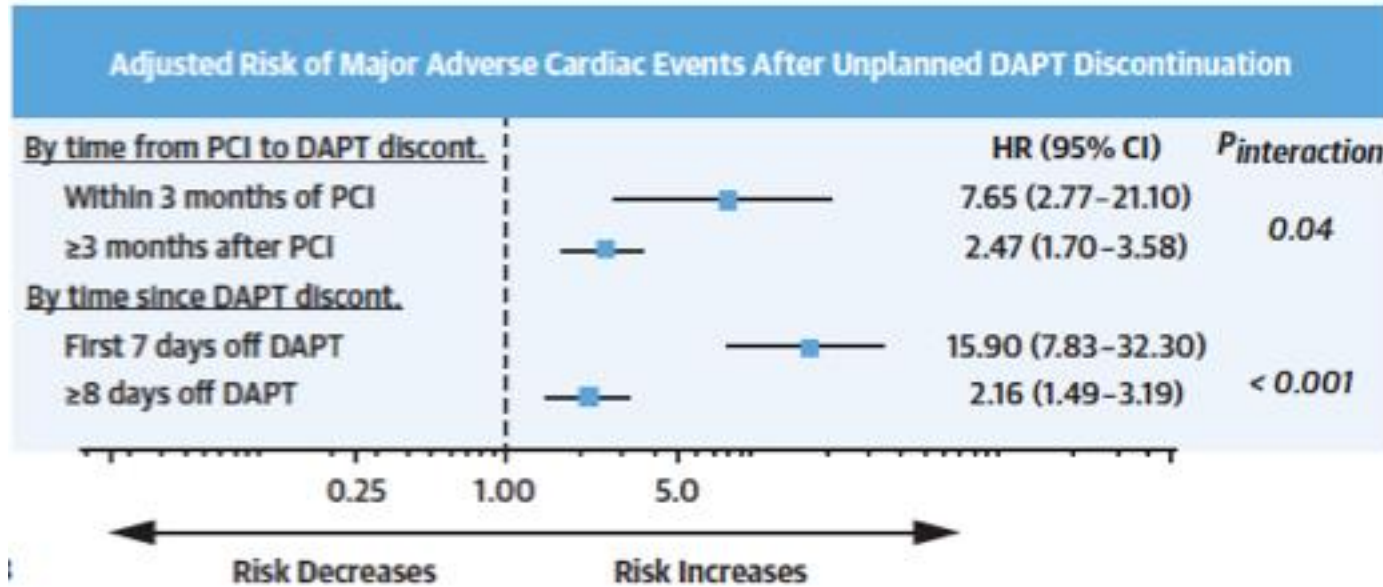


DAPT=dual antiplatelet therapy, NNT=number needed to treat;
MI=myocardial infarction; OR=odds ratio

PRACTICE : This is a vulnerable moment for the patient coming off DAPT.

The discussion from provider to patient regarding what antiplatelet to use for monotherapy or continuing DAPT should be made together tailored to the patient risk versus benefit

ADAPT-DES: CV Risk and Unplanned DAPT Discontinuation



- ADAPT-DES: Prospective, multicenter registry of 8,582 patients on clopidogrel +aspirin after PCI with stenting.
- Planned discontinuation of DAPT occurred in 37.3% of patients <2 years; in 18.3% of patients discontinuation was unplanned.
- Reasons for unplanned discontinuation included surgery or trauma (8.9%), nonadherence (3.7%), bleeding (3.1%) or drug allergy (1.3%).
- The risk of CV events was increased after unplanned (but not planned) discontinuation, with a 'particularly high' risk <1 week after discontinuation.

GUIDELINES IN ASCVD PATIENTS 2^o PREVENTION

ASCVD Type	Professional Association	Recommendation - Class	
CAD (SIHD)	2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease <small>Fihn SD et al. JACC 2012;60:e44–164</small>	Aspirin (75-162) Clopidogrel (if no ASA)	I A I B
PAD	2016 ACC/AHA Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease <small>Gernard-Herman MD, et al. JACC 2017;69:e71-e126</small>	Aspirin (75-325) or Clopidogrel	I A
Stroke/TIA	2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the management of patients with extracranial carotid and vertebral artery disease <small>Brott TG, et al. JACC 2011;57:e16–94</small>	Aspirin (75-325) Clopidogrel Aspirin + Dipyridamole	I A I B I B

RECOMMENDATIONS FOR ANTIPLATELET THERAPY FOR PATIENTS WITH DIABETES

ADA ^{1,2}	ACC/AHA + ADA Statement ³	EASD ⁴
<ul style="list-style-type: none"> • Consider for T2D or T2D with 10-y CVD risk >10% • Not recommended for adults with T2D at low CVD risk (<5%) or <50 years • Low-dose aspirin recommended for pregnant women with pre-existing T1D or T2D to lower risk of preeclampsia 	<ul style="list-style-type: none"> • Reasonable among those with a 10-year CVD risk \geq 10%, without an increased risk of bleeding • Reasonable in adults with diabetes and intermediate 10-year CVD risk (5% to 10%) 	<ul style="list-style-type: none"> • Antiplatelet therapy (i.e. with aspirin) is not recommended for people with diabetes who do not have ASCVD

¹ADA *Diabetes Care* 2016;39(suppl 1):S60-S71.

²ADA Website.

³Fox CS. *Circulation*;132:691-718.

⁴Piepoli MF *Eur Heart J*. 2016;37:2315-81.

Excellent reference on aspirin in primary prevention from a Montreal Heart Institute and University of Montreal

Del Bianco- Rondeau MD. et al. Thrombosis and Haemostasis. 2022 published online: <https://doi.org/10.1055/s-0042-1743469>

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- Aspirin professional prescribing
- MOA
- Formulations
- Cost and Considerations



PROFESSIONAL PRESCRIBING, MOA , & ASPIRIN FORMULATIONS

Aspirin OTC and Professional Prescribing Use

OTC Uses

For the temporary relief of minor aches and pains associated with:

- Headache
- Backache
- Muscular aches
- A cold
- Toothache
- Minor pain of arthritis
- Premenstrual and menstrual cramps

Temporarily reduces fever

Physician Prescribing information

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris):

Aspirin is indicated to: (1) Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy

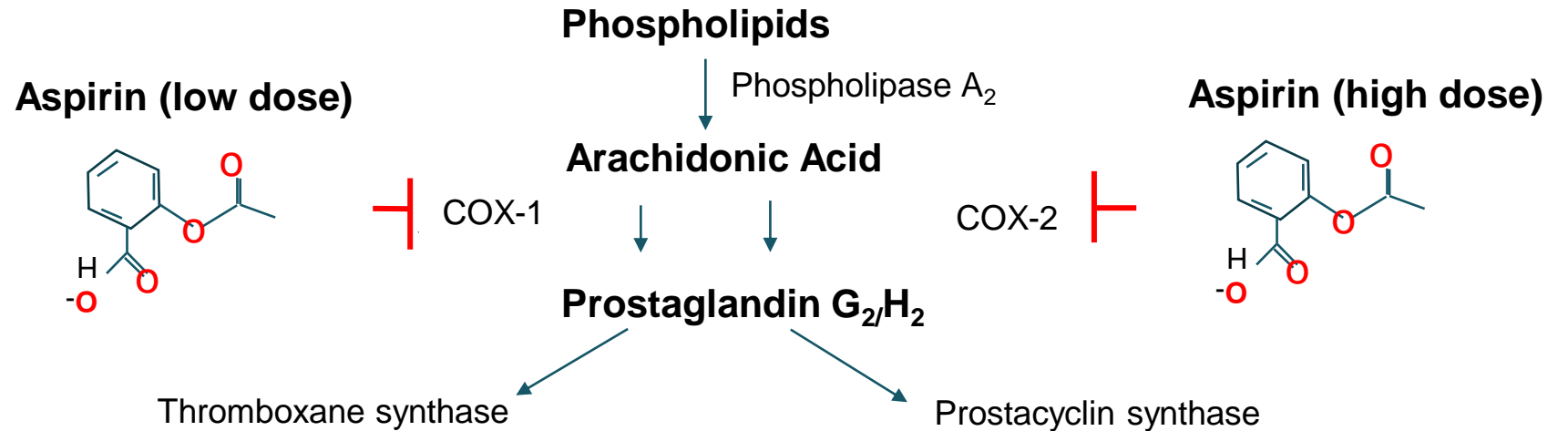
Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Disease Indications (Rheumatoid Arthritis (RA), Juvenile RA, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE))

Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

Mechanism of Action of Aspirin, and COX inhibition

- Prostaglandins (thromboxane and prostacyclin) are produced from arachidonic acid via the action of the COX-1 and COX-2 enzymes.



- Aspirin blocks both of these pathways by acetylating the COX enzyme

**Collagen,
ADP,
Thrombin**



Thromboxane A₂

- Induces platelet aggregation
- Potent vasoconstrictor
- Induces vascular smooth muscle cell proliferation
- Proatherogenic

Prostacyclin

- Inhibits platelet aggregation
- Induces vasodilation
- Inhibits vascular smooth muscle cell proliferation
- Antiatherogenic
- Gut protection
- Renal blood flow regulation

IMMEDIATE RELEASE-PLAIN ASPIRIN

- Considered the 'gold standard' by PK/PD effects of immediate thromboxane inhibition yielding fast and predictable antiplatelet effect
- Chewable formulation is most often used in emergency setting and new onset events.
- Plain tablet 81 mg is difficult to find in retail pharmacies. If the provider wants the patient on low dose immediate release, chewable 81 mg baby aspirin is available in most OTC retailers.
- The switch to delayed release or enteric coated aspirin went into effect over 50 years ago attempting to address GI issues from aspirin therapy.

DELAYED RELEASE OF ENTERIC COATED ASA *IN BRIEF*

- Quality evidence for reduced gastric injury is not clear^{1,2}
- Enteric coated aspirin formulations have 'erratic absorption' ^{3,4}
- Modified release formulations result in significantly variable antiplatelet effect⁵
- Platelet response to enteric aspirin may not be complete in patients with stable CV disease⁶
- Enteric coating or buffering may not lower Upper GI Bleeding rates⁷

¹Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Br J Clin Pharmacol 2001;52:563-571.;

²Kedir HM, Sisay EA, Abiye AA. Int J Gen Med 2021;14 4757–4763.

³FDA Professional label.; ⁴Bogentoft C. Eur J Clin Pharm 1978;14;351-355

⁵Cox D et al. Stroke 2006;348;1413-6.

⁶Maree AO, Curtin RJ, Fitzgerald D . JACC 2005;47;1258-1263

⁷Kelly JP. Lancet 1996;348;1413-6.

Is Enteric Coating Gastroprotective?

Quality evidence for reduced gastric injury is not consistent

Enteric coating is intended to resist disintegration in the stomach and reduce the risk of local injury in the stomach, allowing aspirin to be released in the less acidic environment of the duodenum.

Some studies suggest a reduction in gastric injury, other recent studies find no difference:

- In a systematic review of studies reporting serious upper GI complications with aspirin formulations the summary relative risk was 2.6 (95% CI: 2.3, 2.9) for plain, 5.3 (95% CI: 3.0, 9.2) for buffered, and 2.4 (95% CI: 1.9, 2.9) for enteric-coated aspirin formulations.¹
- A systematic review including 15,621 participants (N=9952 received enteric aspirin of different strengths from 81 mg to 325 mg. N= 5,669 received a placebo). Almost all studies found that enteric-coated aspirin treatment was not an effective mechanism against GI protection.²

¹Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Br J Clin Pharmacol 2001;52:563-571.;

²Kedir HM, Sisay EA, Abiye AA. Int J Gen Med 2021;14 4757–4763.

Enteric Coating and Absorption

Enteric coated aspirin formulations have 'erratic absorption'¹

Background:

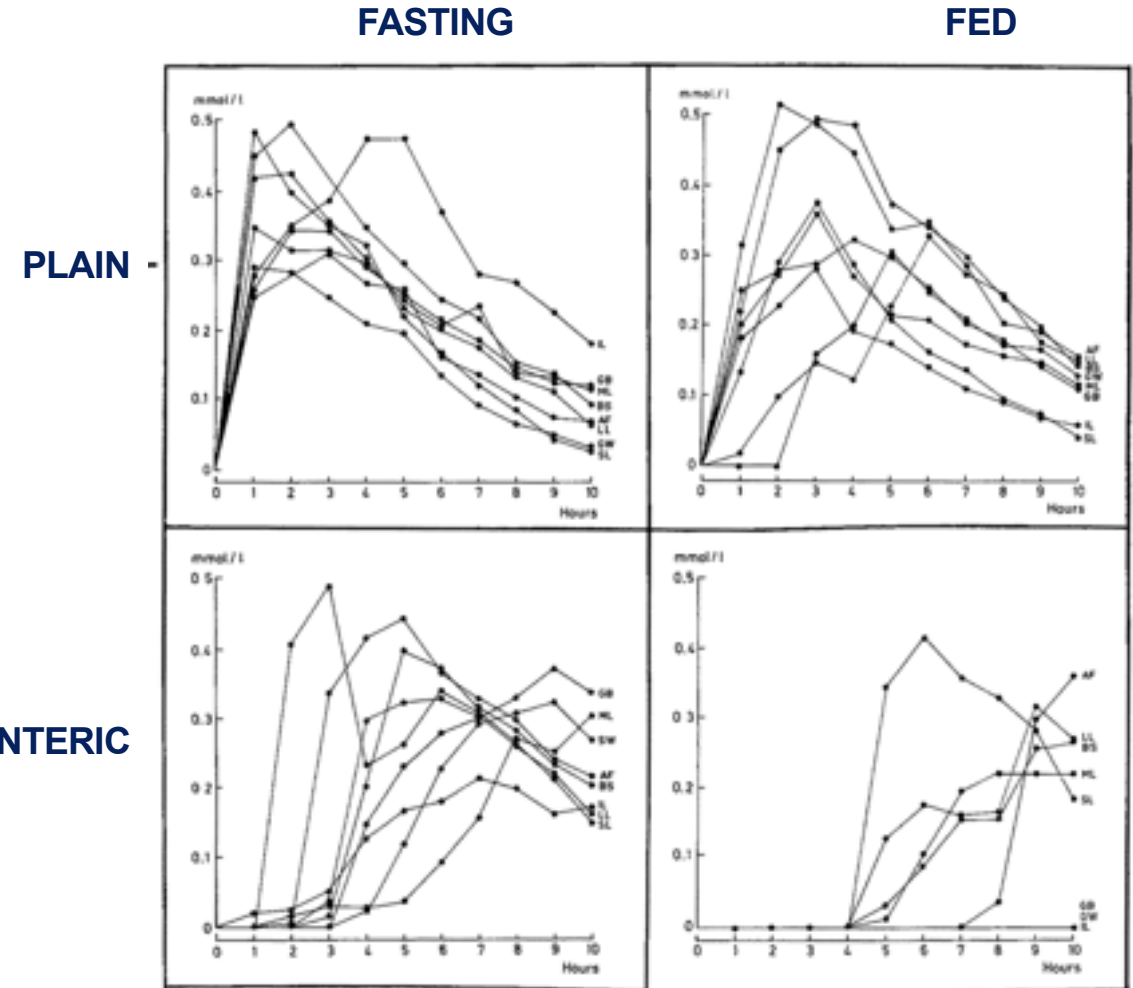
- Enteric formulations are known to have erratic absorption. Various factors affect absorption of enteric aspirin, including food

Methods:²

- 8 healthy volunteers, crossover design, plasma salicylic acid concentrations after plain and enteric formulations (1 g) assessed under fasting and fed conditions

Results:

- Compared to plain aspirin, enteric aspirin showed delayed and unpredictable absorption
- When taken with food absorption of enteric aspirin was greatly delayed; in 3 of 8 participants salicylate could not be detected in plasma after 10 hours.



¹FDA Professional label.

²Bogtoft C. *Eur J Clin Pharm* 1978;14;351-355.

Enteric Aspirin and Antiplatelet Activity

Modified release formulations result in variable antiplatelet effect

Background & Objectives:

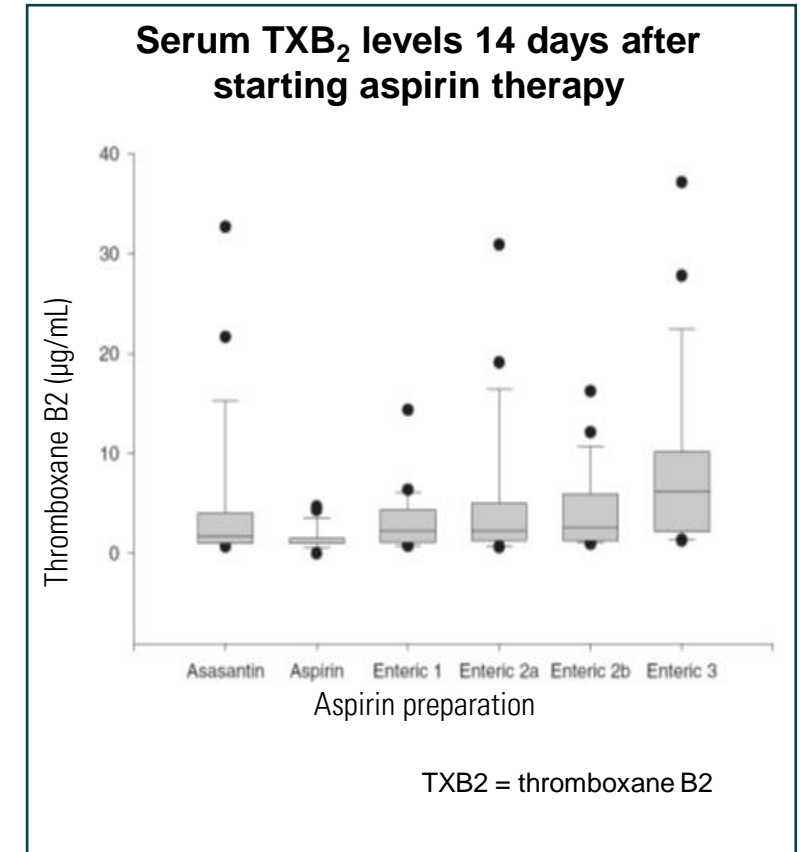
- Aspirin 'resistance' may have clinical implications. Enteric coating may be responsible for resistance
- Determine platelet activity with various aspirin formulations.

Methods:

- 71 healthy volunteers, 3 crossover studies w/ 5 aspirin types (3 enteric-coated, plain aspirin and asasantin), 75 mg.
- Serum TxB₂ measured before and after 14 days of treatment.

Results:

- Significant differences noted with all modified release forms.
- Incomplete platelet inhibition (<99% inhibition of TxB₂) was significantly higher with enteric vs dispersible aspirin (54.3% vs 8%).
- Equivalent doses of enteric aspirin were not as effective as plain aspirin, particularly in heavier patients.



Enteric Aspirin and Antiplatelet Activity

Platelet response to enteric aspirin may not be complete in patients with stable CV disease

Background & Objectives:

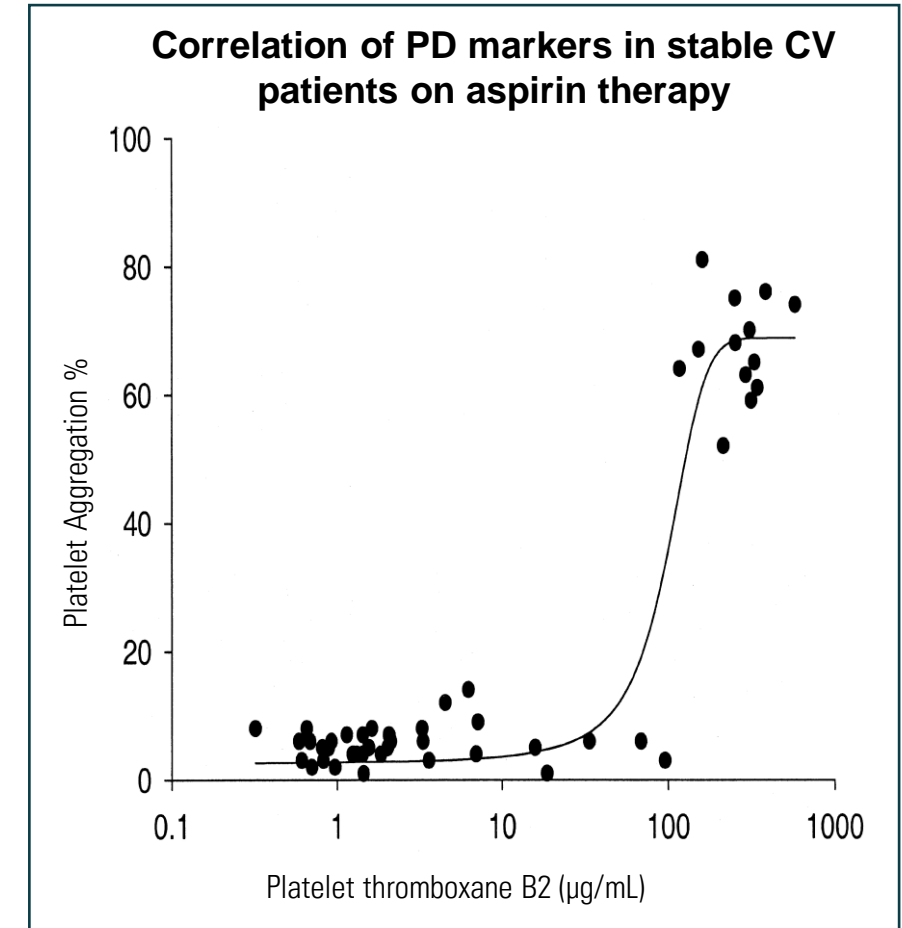
- There is variability in the way individuals respond to aspirin. Low response to aspirin is associated with CV events.

Methods:

- 131 patients with stable CV disease who were taking maintenance 75 mg enteric aspirin
- Serum TxB2 and arachidonic acid induced platelet aggregation measured during treatment.

Results:

- 44% of patients had elevated serum TxB2 (>2.2 ng/mL), indicating persistent uninhibited COX activity.
- In all cases addition of exogenous aspirin during the assay abolished platelet aggregation.
- Younger and heavier patients and those with prior MI were more likely to have an inadequate response to aspirin.



Risk of UGIB with Low-dose (< 325 mg) ASA Formulations

Enteric coating or buffering does not lower UGIB rates

Background:

Aspirin causes irritation and injury to gastric mucosa. Enteric-coated and buffered forms are thought to be less likely to cause major upper-gastrointestinal bleeding (UGIB).

Objectives:

Determine UGIB with aspirin formulations.

Methods:

550 cases of UGIB and 1202 controls queried about aspirin use <7 days before bleeding onset.

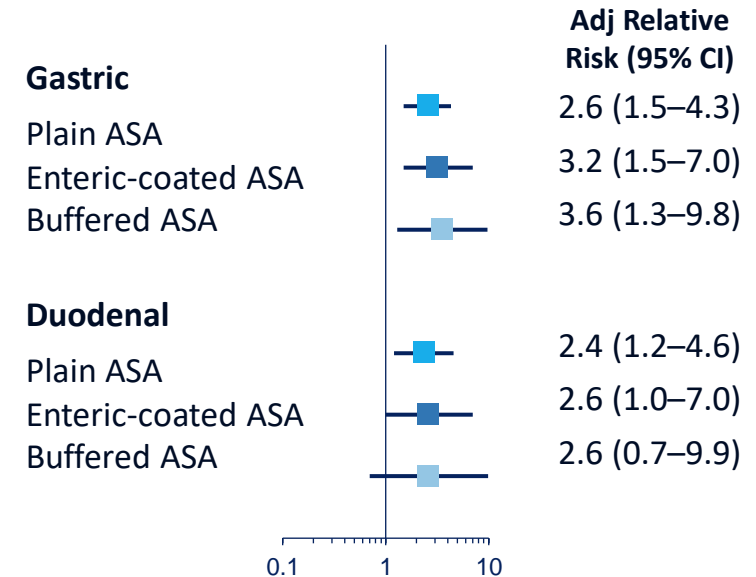
Primary Endpoint:

UGIB (melena or hematemesis) on admission, confirmed by endoscopy.

Results:

No significant difference in UGIB among aspirin formulations.

Regular use of aspirin products <7 days before index day according to bleeding site



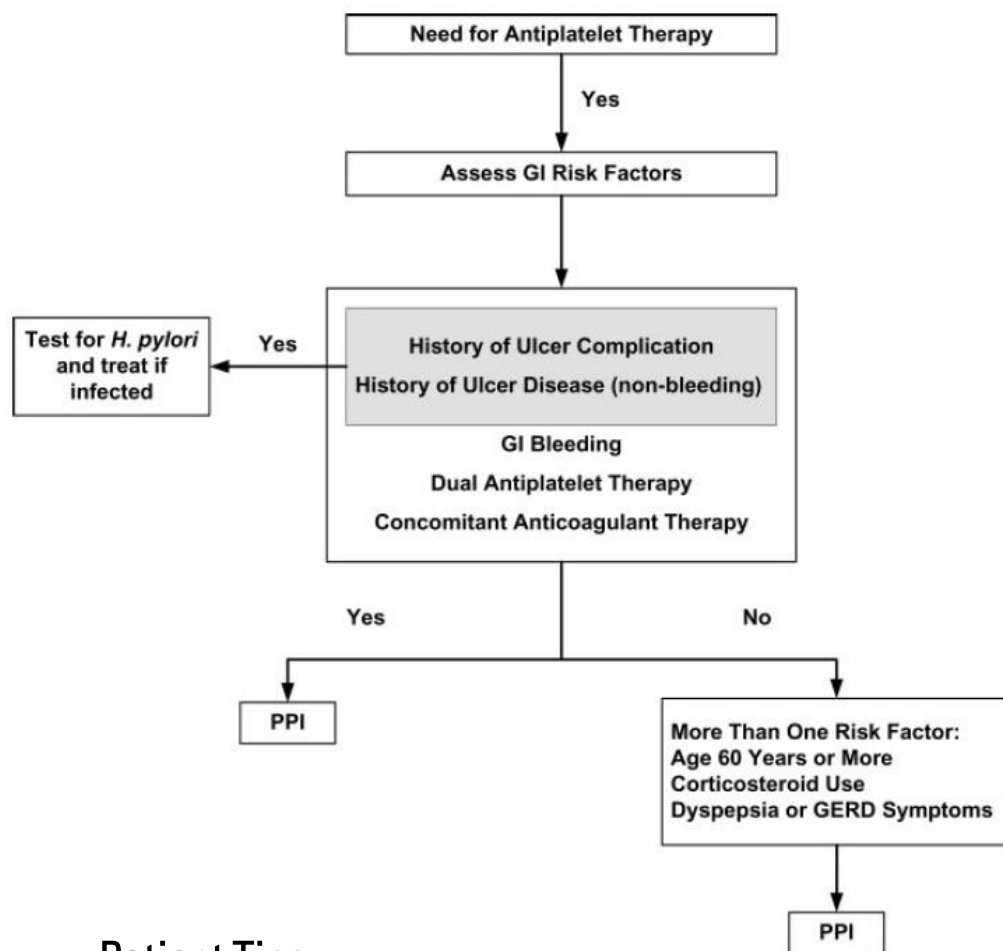
ASA = aspirin
All UGIB rates depicted occurred with aspirin <325 mg

Kelly JP. Lancet 1996;348;1413-6.

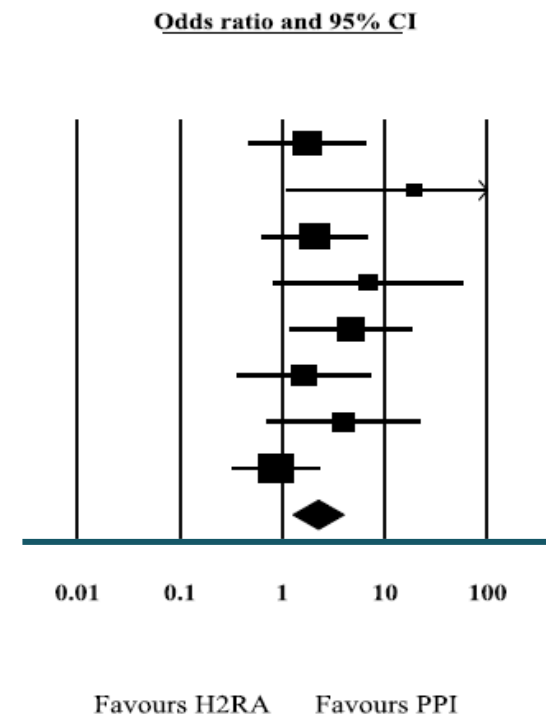
Solutions for GI Issues with Aspirin



PPIs were more effective than H2RAs in the prevention of GI bleeding and ulcer formation.



Study name	Outcome	Statistics for each study				Events / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	H2RA	PPI
Guo M et al. 2009	ulcer	1.765	0.472	6.603	0.399	5 / 22	6 / 42
NG FH et al. 2010	ulcer	19.365	1.094	342.940	0.043	8 / 65	0 / 65
Hu l et al. 2012	ulcer	2.077	0.642	6.721	0.223	9 / 48	5 / 50
NG FH et al. 2012	ulcer	6.845	0.814	57.540	0.077	6 / 148	1 / 163
Sun EE et. al 2012	ulcer	4.678	1.193	18.337	0.027	11 / 40	3 / 40
Wang J et al. 2012	ulcer	1.626	0.364	7.259	0.524	5 / 46	3 / 43
Wang YP et al. 2012	ulcer	3.938	0.700	22.153	0.120	6 / 22	2 / 23
Chan KL et al. 2016	ulcer	0.868	0.325	2.321	0.778	8 / 138	9 / 136
		2.257	1.277	3.989	0.005	58 / 529	29 / 562



Patient Tips:

Take medicines with food, or with a full glass of milk or water, which may reduce irritation.

Do not drink coffee or alcoholic beverages when taking these medicines.

Do not lie down right after eating.

Szabo IL. J Gastro intestine Liver Dis. 2017;26(4):395-402.

Bhatt DL. Circulation. 2008;118:1894-1909.

What about Cost?

- Aspirin is used by ~ 40 million Americans and the benefit of its benefit of cardioprotection is clear. The dosing of 81 mg is probably as good as 325 mg.

.....and it is readily available OTC in the U.S. and inexpensive in brand familiar names and a patient can buy it in bulk in generic store brands

- In patients requiring DAPT, the addition of the P2Y₁₂ does increase the cost. There are 2 generics- clopidogrel and prasugrel as once a day therapy and more expensive ticagrelor which is twice a day.
- As discussed earlier, aspirin is not a prescription drug making it more difficult to track, and we need contemporary post discharge studies.



Dominick Angiolillo, M.D., Ph.D., FACC
University of Florida College of Medicine
UF Health Cardiovascular Center - Jacksonville

- Potential Opportunities for Improving Aspirin
- Balancing Benefits and Risks of Aspirin Therapy
- Aspirin-Induced GI Toxicityand P2Y₁₂ injury
- New approved and investigational aspirin agents
- New FDA approved aspirin- PL-ASA, and the evidence
- Aspirin non responsiveness and weight considerations
- Aspirin considerations for HCPs

Potential Opportunities for Improving The Risk Benefit Profile of Aspirin



Effectiveness

- **Prompt:** Rapid absorption (i.e, PK) particularly in the acute setting
- **Potent:** High levels of inhibition (i.e, PD) needed
- **Predictable:** Need a consistent response and few non-responders / resistance and accurate, consistent dosing in high risk patients (obese, females, elderly, diabetes, chronic kidney disease)

Safety

- **Protective** against GI injury
 - Fewer erosions and ulcers
 - Improved tolerability | adherence (better efficacy)



BALANCING CV RISK REDUCTION AND BLEEDING

Strong **efficacy** evidence exists in favor of aspirin therapy in secondary prevention and the Practice Guidelines give aspirin therapy the strongest Class 1A recommendation.

HCPs however, are concerned about the **safety** side effects of GI intolerance, the effects of GI injury, and the significant adverse event (SAE), GI bleeding.

- Patients discontinue their aspirin due to GI symptoms from GI toxicity putting them at risk of thrombotic events
- 2 – 4 / 1000 patients have GI bleeding with aspirin, but the sheer volume of patient's taking aspirin make this an important SAE in terms of absolute numbers
- There are 2 pathways of injury to the gastroduodenal mucosa by aspirin— direct local damage and systemic effects

Moberg C et al. Patient 2011; 4 (2): 103-113 1178-1653.

Martín-Merino E et al. Pragmatic Observational Research. 2012;3:1-9.

Valkhoff VE et al. Can J Gastroenterol. 2013;27(3):159-167.

Kelly JP et al. Lancet. 1996;348(9039):1413-1416.

ASPIRIN-INDUCED GI TOXICITY

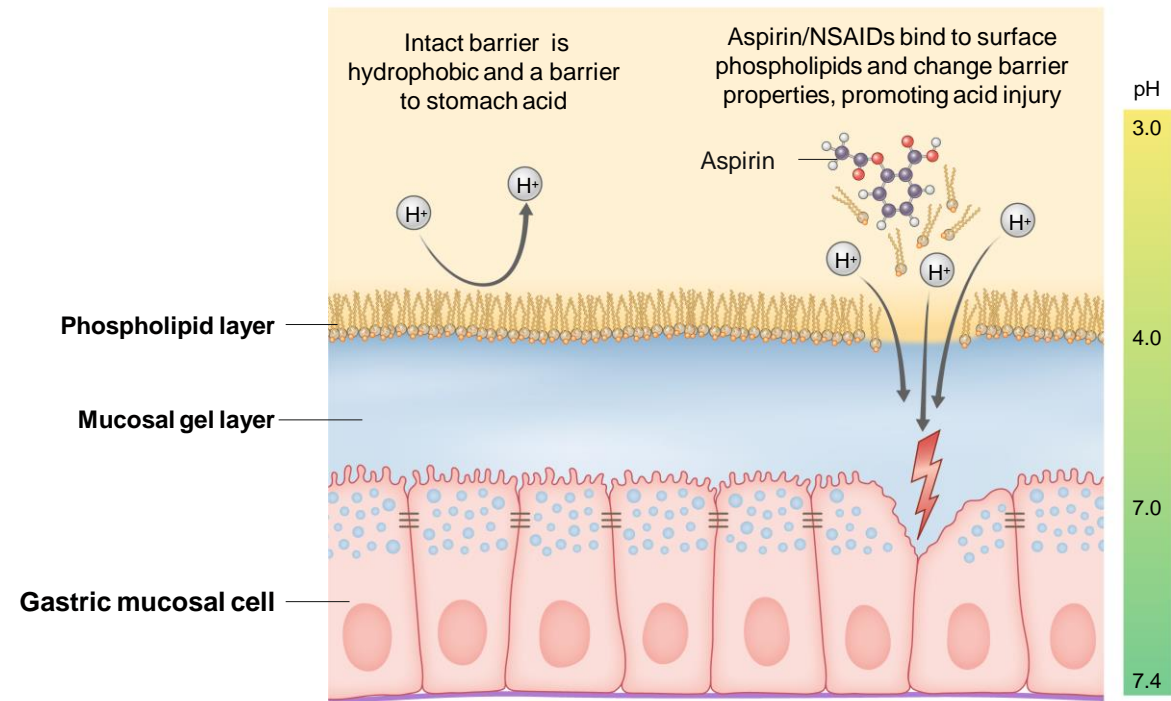
Aspirin-induced GI toxicity is mediated by three mechanisms including:

1. Impaired hemostatic function via antiplatelet effects (*systemic pathway*)
2. Inhibition of COX-derived prostaglandin (PG) production (locally and through systemic exposure), which is key in epithelial mucus production, microvascular mucosal perfusion and wound healing in the GI tract, (*systemic pathway*) and
3. Binding to the protective phospholipids in the gastric mucosa causing physical disruption of the protective gastric phospholipid barrier thereby allowing direct acid injury (*local pathway*)

Mechanism of Gastric Injury by NSAIDs (Aspirin)

Schematic model of the stomach's hydrophobic mucosal barrier and how it is compromised by aspirin, promoting the back-diffusion of luminal acid.

- The gastric epithelial layer of the stomach lumen has a hydrophobic phospholipid layer, protecting against acid injury.
- NSAIDs disrupt the protective layer by associating with the phospholipids, changing the hydrophobic properties of the layer.
- If the phospholipid layer is disrupted, the protective mechanism is compromised, allowing acid diffusion and injury to the epithelium.



Gastric Injury with Aspirin or P2Y₁₂ Inhibitor

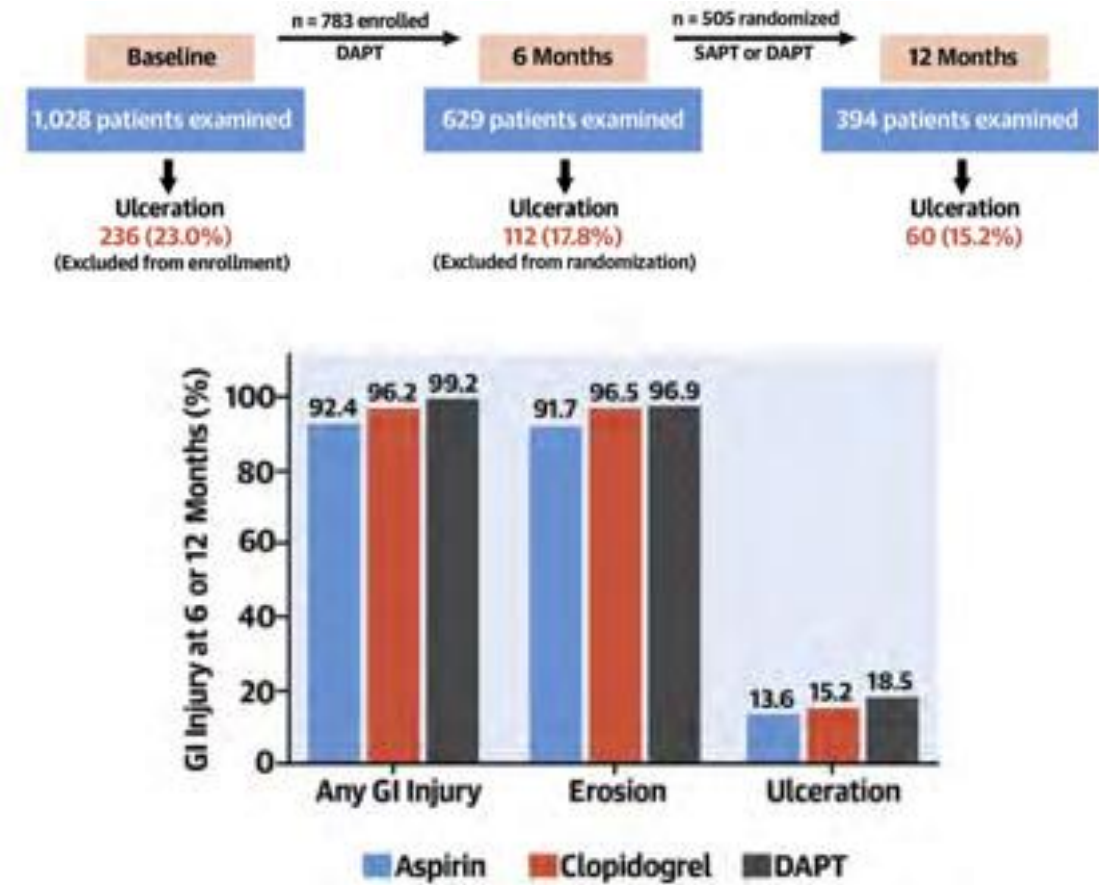
Gastric injury was similar with aspirin or clopidogrel after 12 months

Methods

- OPT-PEACE was a randomized double blind placebo-controlled trial in 28 Chinese centers
- Capsule endoscopy assessed gastric injury at baseline, after 6 months of DAPT and a further 6 months of SAPT (aspirin or clopidogrel)

Results

- Despite being at low risk of bleeding, nearly all patients receiving antiplatelet therapy developed GI injury, although overt bleeding was infrequent
- GI mucosal injury through 12 months was less with single antiplatelet therapy (SAPT) than with DAPT (94.3% vs 99.2%; P=0.02).
- Aspirin and clopidogrel monotherapy had similar effects.



OVERVIEW OF NEW FORMULATIONS OF ASPIRIN- APPROVED AND INVESTIGATIONAL

Approved in the U.S.

- PL-ASA (Vazalore, aspirin capsules)
 - Liquid filled aspirin capsule contains Phospholipid-Aspirin complex (81 mg, 325 mg)
 - Key studies involve 325 mg dosage, single day 81 mg PK/PD versus EC-ASA
 - PK/PD equivalence to plain immediate release aspirin¹; significantly reduced gastroduodenal ulcers and erosions versus plain immediate release aspirin in a 7- day endoscopy study²

• In Europe (dual agent w clopidogrel)

- Clopidogrel/Acetylsalicylic acid Zentiva, previously DuoCover³
 - Contains two active substances, clopidogrel and acetylsalicylic acid. It is available as tablets containing 75 mg clopidogrel, either with 75 mg or 100 mg acetylsalicylic acid.
 - CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone)

• Investigational Agents

- First In-Human Experience With Inhaled Acetylsalicylic Acid for Immediate Platelet Inhibition Comparison With Chewed and Swallowed Acetylsalicylic Acid--- An inhaled nanoparticle ASA preparation (I-ASA) , administered with a dry powder inhaler (Otitopic, Inc, Los Angeles, CA).⁴

¹Angiolillo DJ et al. J Thromb Thrombolysis. 2019;48:554–62.

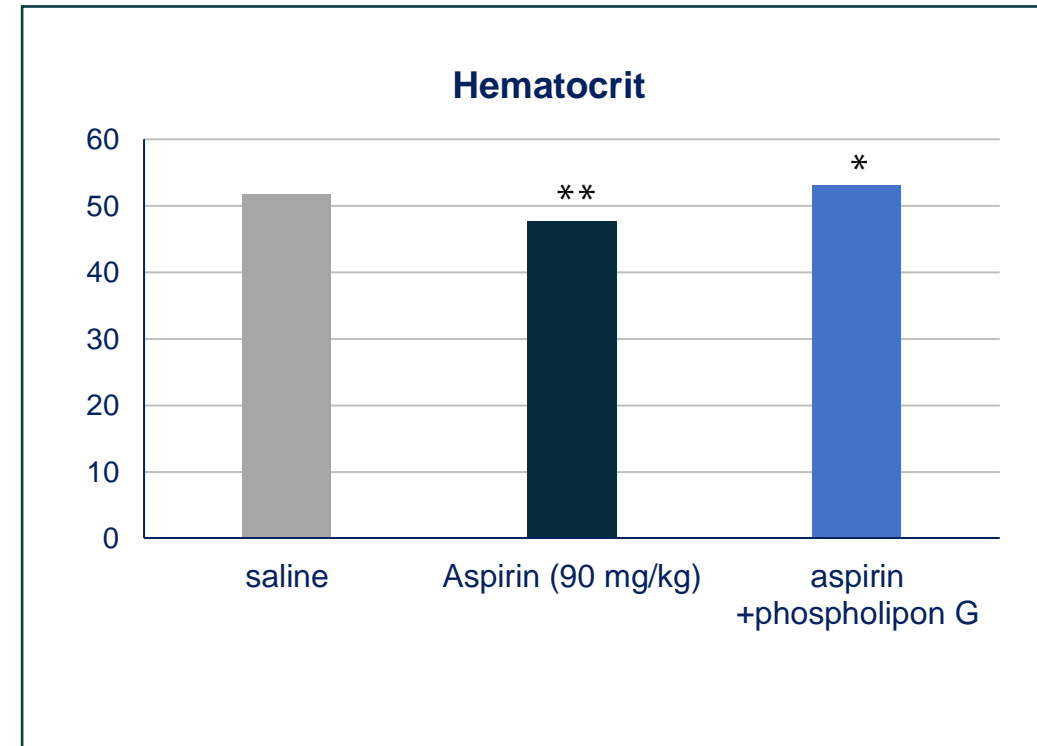
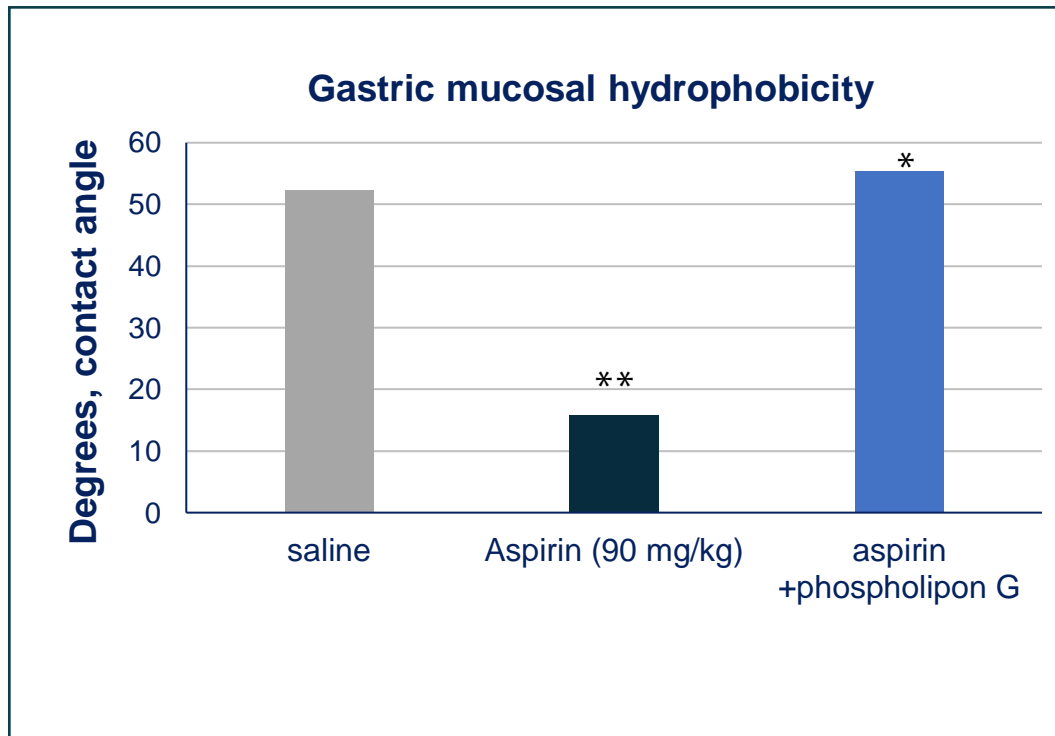
²Cryer B, Bhatt DL, Lanza FL, ...Marathi UK. Am J Gastroenterol 2011;106(2):272-7.

³https://www.ema.europa.eu/en/documents/product-information/clopidogrel/acetylsalicylic-acid-zentiva-previously-duocover-epar-product-information_en.pdf

⁴Gurbel PA. Circulation. 2020;142:1305–1307

ASPIRIN – PHOSPHOLIPID TO PRESERVE GASTRIC INTEGRITY

In animal models, pre-association of aspirin with phospholipids maintains gastric hydrophobicity and hematocrit

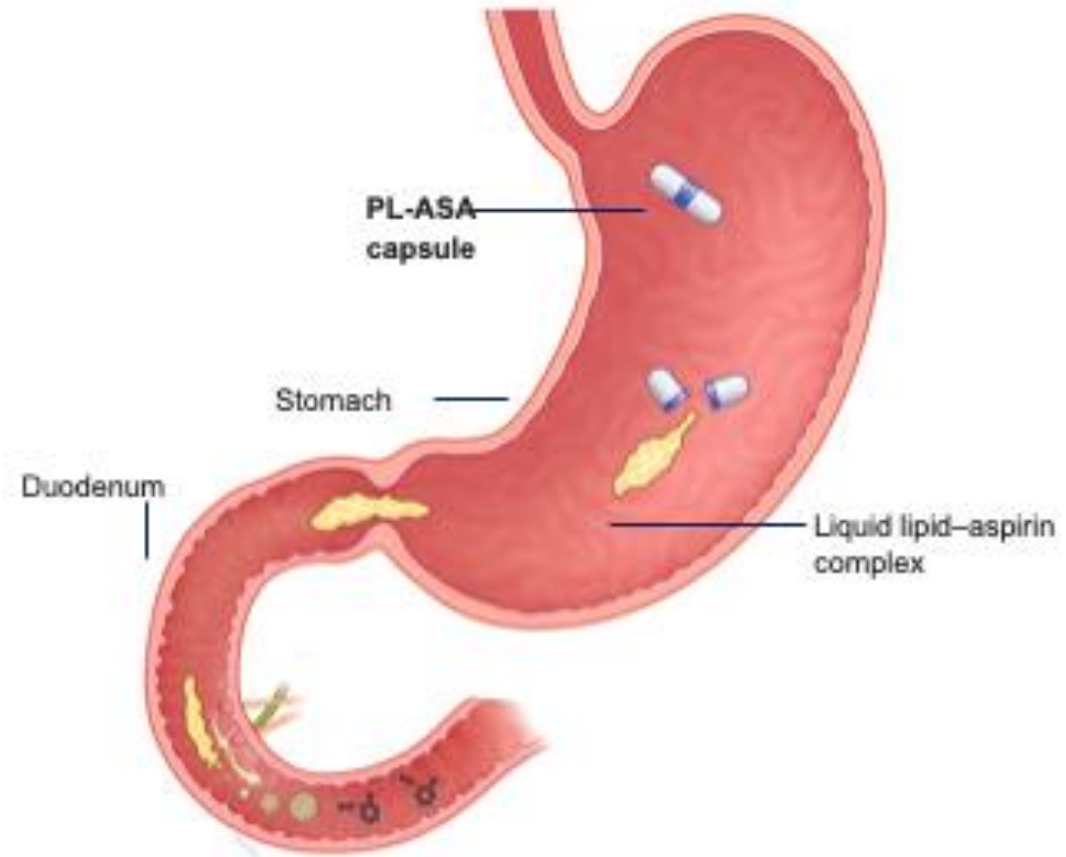


* $P < 0.05$ for comparison with aspirin treated rats, ** $p < 0.05$ for comparison to saline controls. N=6

Mechanism of Action of PL-ASA

Novel delivery system designed to help provide local protection with full bioavailability

- Phospholipid-aspirin complex (PL-ASA) is a novel aspirin formulation with a unique delivery mechanism intended to help provide protection while maintaining full aspirin bioavailability.
- Pre-association of the proprietary lipid complex with aspirin is specifically designed to limit direct contact of aspirin with the GI tract and reduce the risk of injury.
- The lipid complex remains intact in low pH environments, without limiting bioavailability.



ENDOSCOPIC ASSESSMENT OF ASPIRIN FORMULATIONS

PL-ASA reduces the risk for erosions and ulcers

Background & Objectives:

- Aspirin carries risk of gastric injury.
- Determine whether a lipid-aspirin formulation can reduce gastric erosions and ulcers.

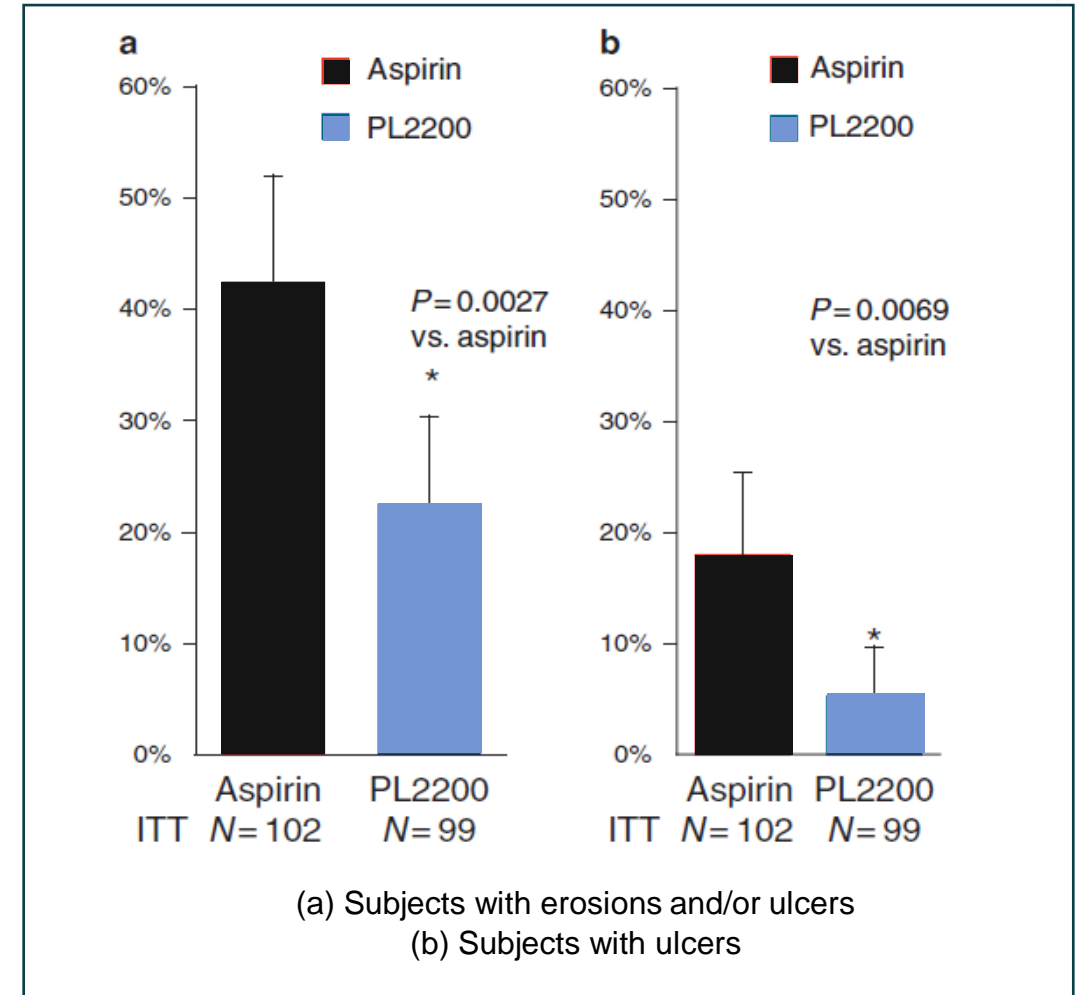
Methods:

Randomized, blinded study in 204 healthy volunteers:

- 7 days of either plain aspirin or PL-ASA 325mg
- Endoscopy performed at baseline and day 7
- Centralized, blinded endoscopic adjudication
- Primary endpoint: gastroduodenal erosions /ulcers at 7 days.

Results:

- 42.2% of aspirin-treated subjects vs 22.2% of PL-ASA treated subjects developed erosions or ulcers, $p=0.0027$
- Ulcers were seen in 17.6% (aspirin) vs 5.1% (PL-ASA), $p=0.0069$



PK Bioequivalence of Plain Aspirin and PL-ASA

PL-ASA is bioequivalent to plain aspirin, both are 'immediate release formulations'

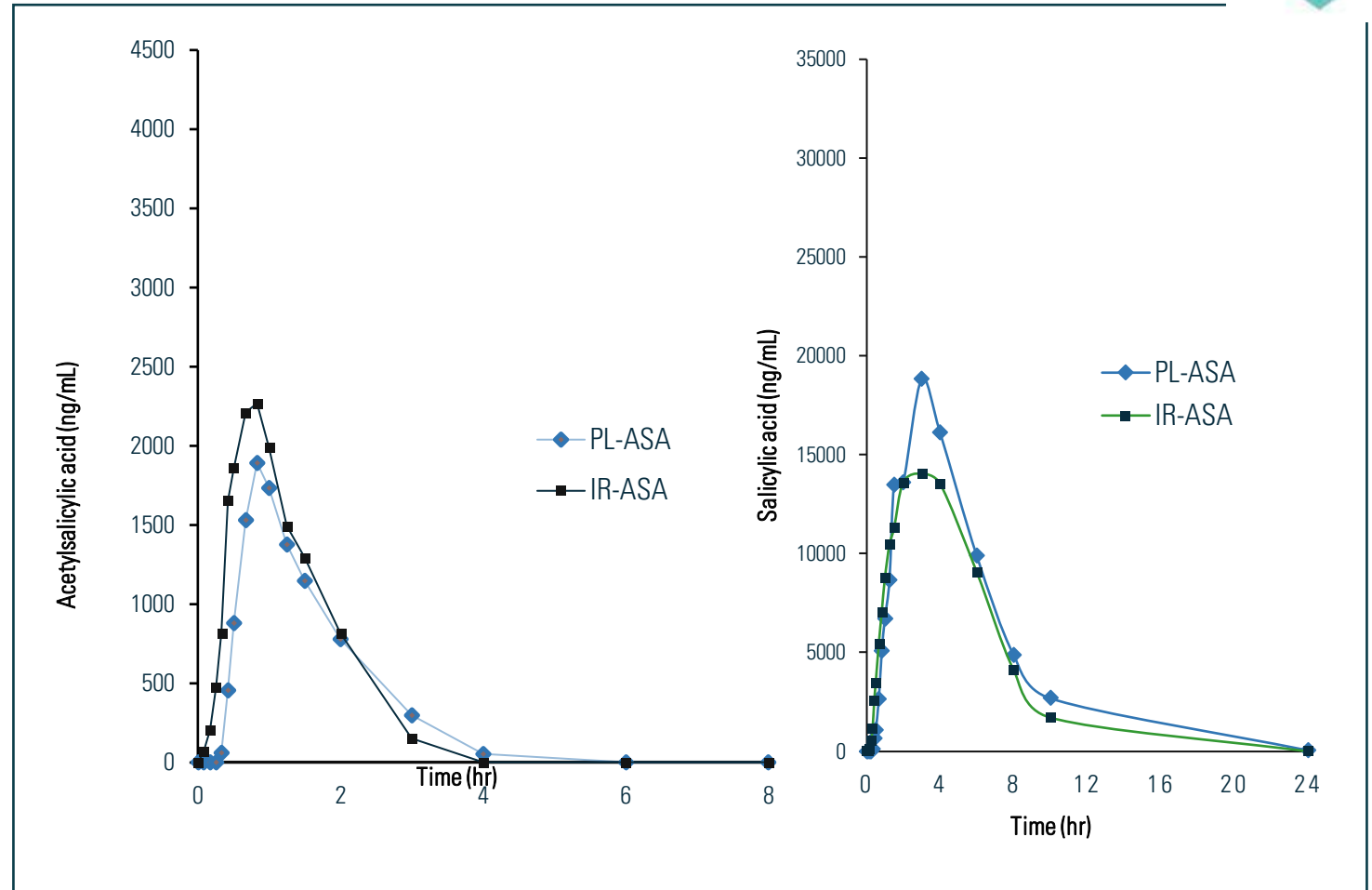


Methods:

- Randomized, active control, crossover study to assess bioequivalence of PL-ASA and plain aspirin.
- 32 healthy subjects randomized to 325 or 650 mg doses of either PL-ASA or plain aspirin.

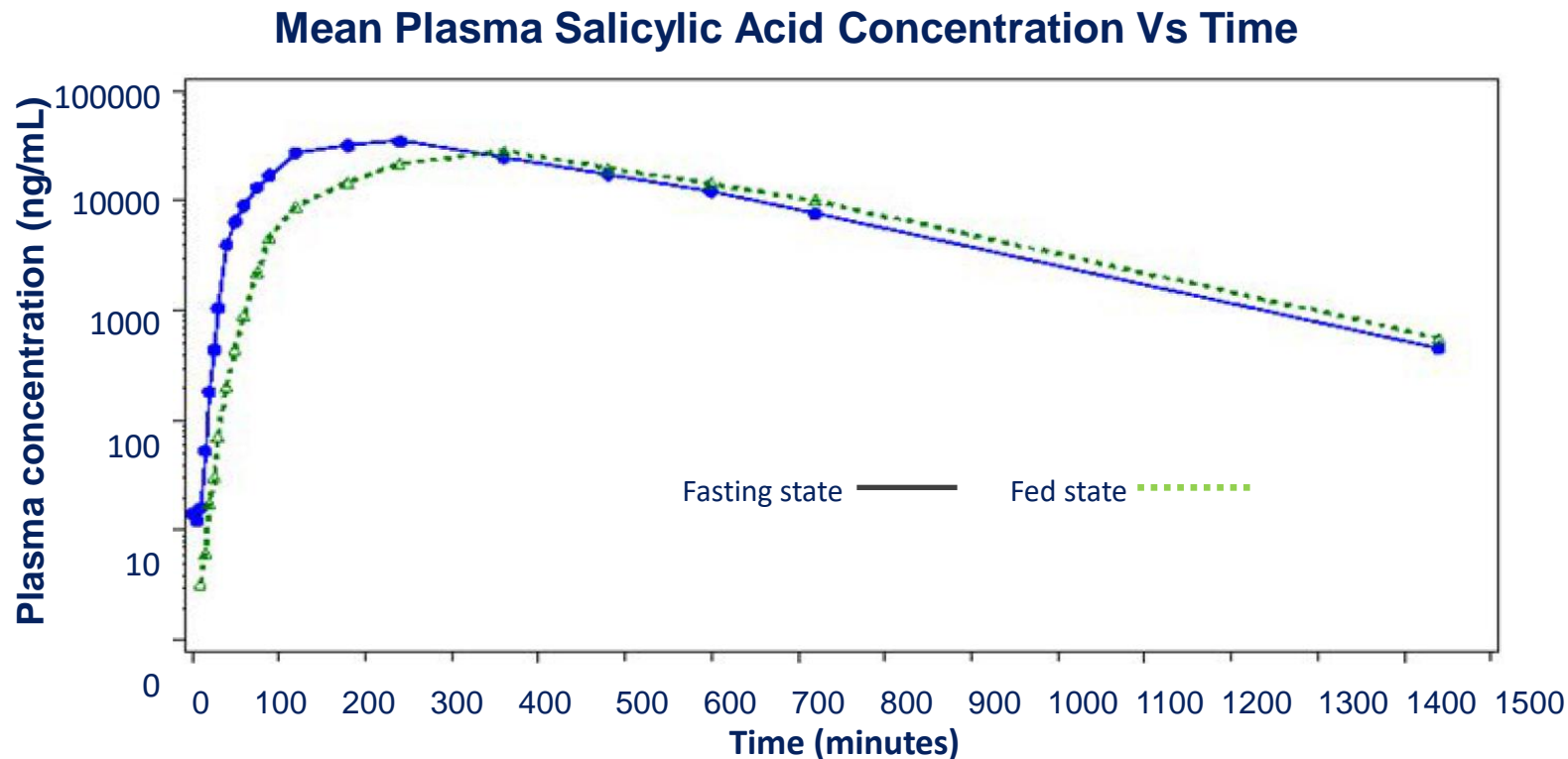
Results:

The study demonstrated the PK and PD bioequivalence of PL-ASA to IR-ASA, and supported the FDA approval of this novel liquid aspirin formulation.



Bioavailability of Aspirin in Fasted and Fed States of a Novel Pharmaceutical Lipid Aspirin Complex Formulation

- Curves in the fasted and fed states are similar.
- Mean peak SA concentration was 28.1% higher in the fasted state,
- Median time to maximum SA concentration occurred about 1.5 hours later in the fed state.



PK COMPARISON: PLAIN ASPIRIN, EC ASPIRIN & PL-ASA

Absorption of PL-ASA was similar to that of plain aspirin but 5X higher than enteric coated aspirin ($p < 0.0001$)



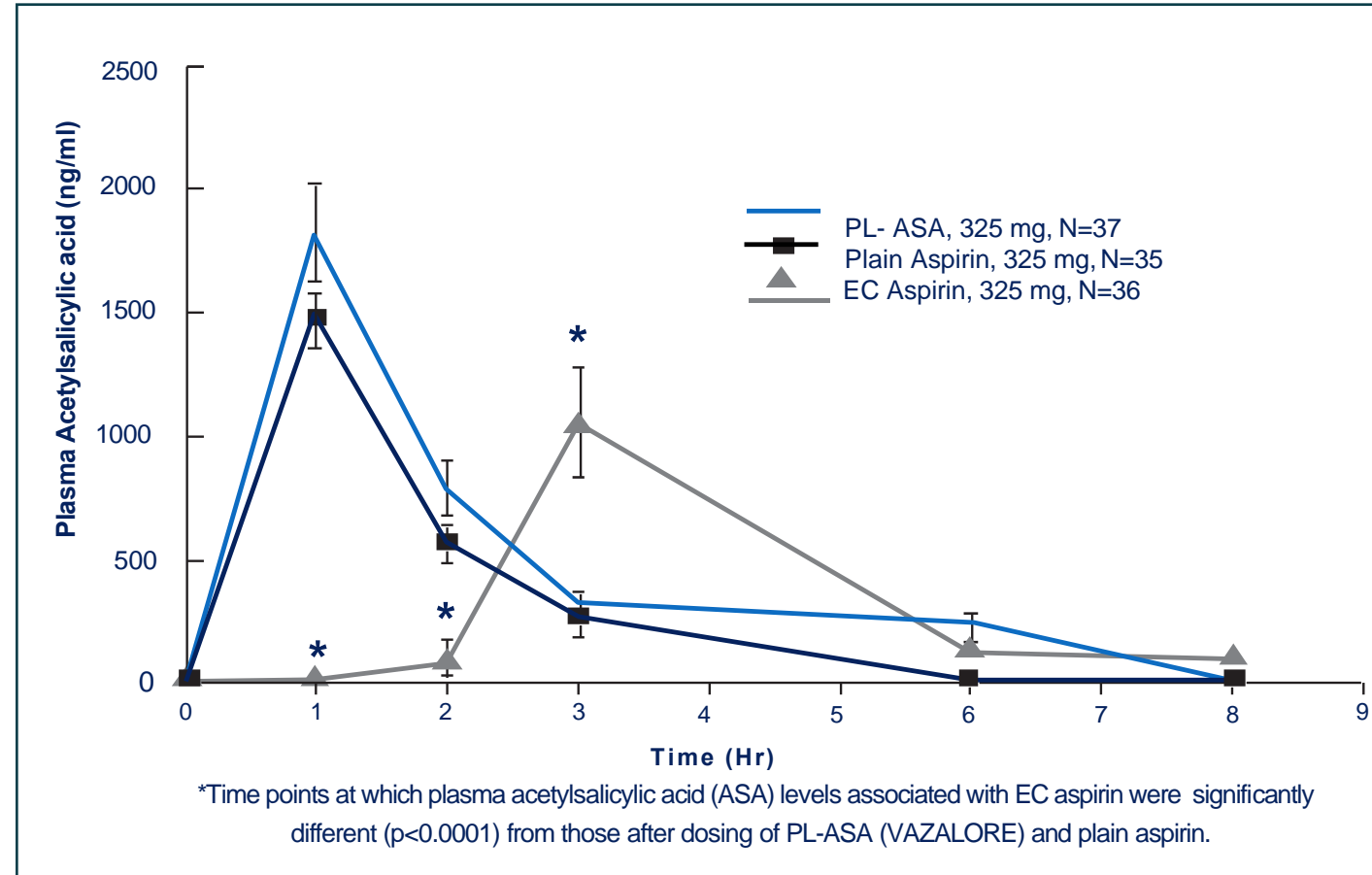
Background & Objectives:

- Some patients, particularly those with diabetes, may not have an optimal antiplatelet effect.
- Determine if oral bioavailability mediates aspirin non-responsiveness.

Methods:

Randomized study conducted in diabetic, obese subjects ($n=40$), 3 day dosing

- 3-way crossover: Plain aspirin, enteric-coated or PL-ASA 325mg



PD COMPARISON: PLAIN ASPIRIN, EC-ASPIRIN & PL-ASA



PL-ASA and plain aspirin exhibit faster time to complete aspirin effect ($\geq 99\%$ inhibition of thromboxane B2 generation)

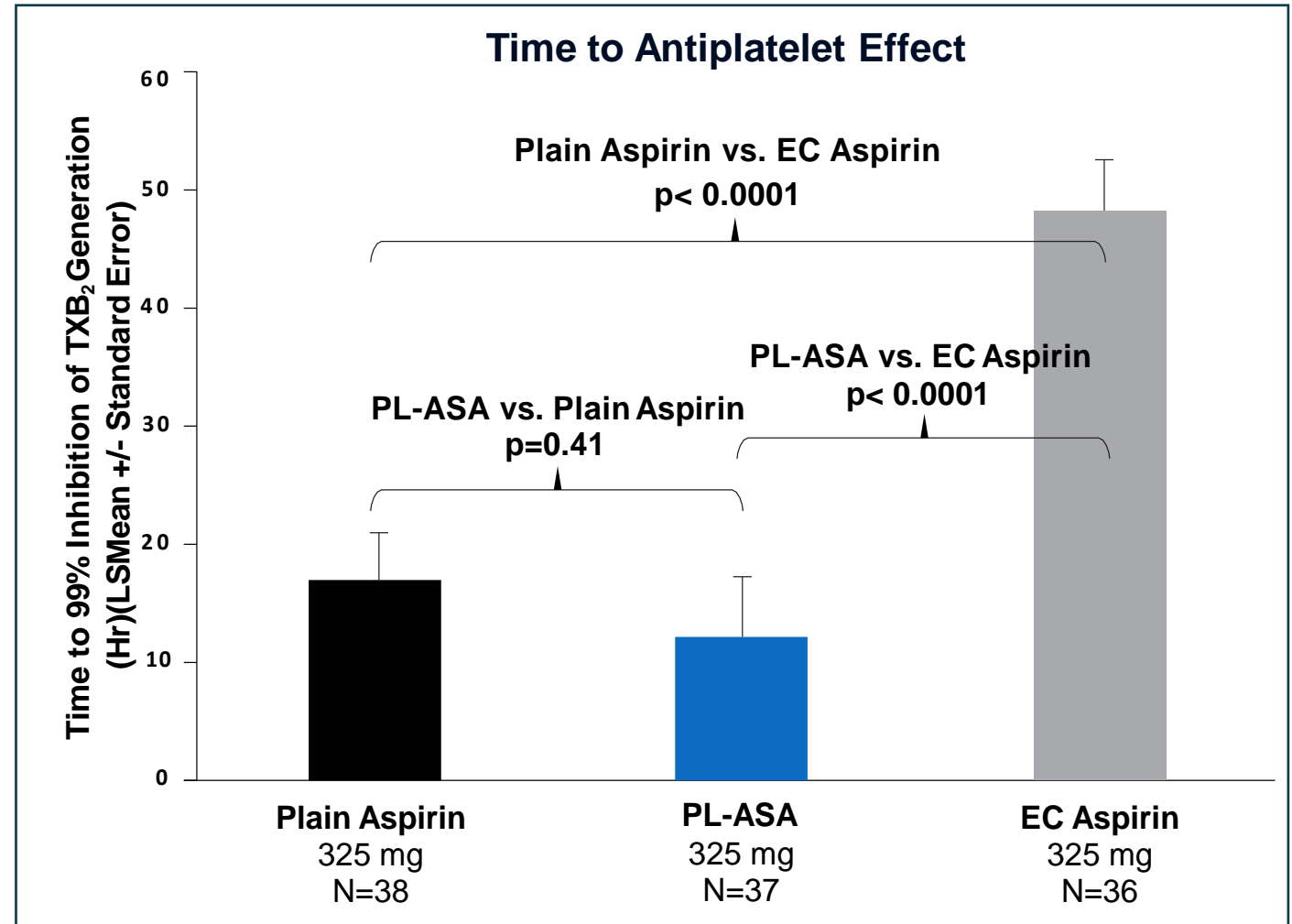
Background & Objectives:

- Some patients, particularly those with diabetes, may not have an optimal antiplatelet effect.
- Determine if oral bioavailability mediates aspirin non-responsiveness.

Methods:

Randomized study conducted in diabetic, obese subjects (n=40), 3- day dosing

- 3-way crossover: Plain aspirin, enteric-coated or PL-ASA 325mg



PD Comparison: Plain Aspirin, EC Aspirin & PL-ASA

Individual patient response varies with aspirin formulation

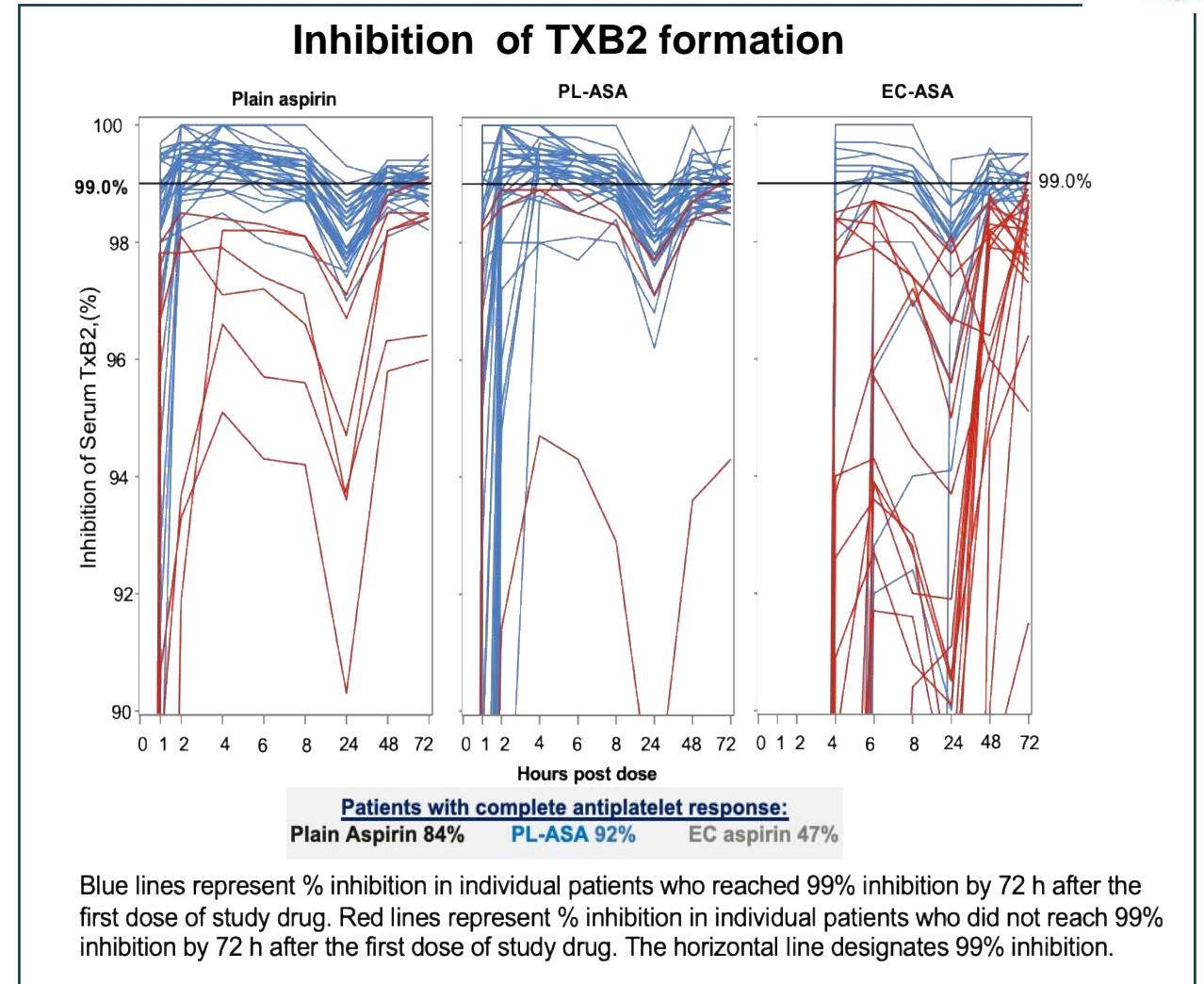
Methods:

Randomized study conducted in diabetic, obese subjects (n=40), 3 day dosing

- 3-way crossover: Plain aspirin, enteric-coated (EC) aspirin or PL-ASA 325mg

Results:

- PL-ASA provided complete antiplatelet effect ($\geq 99\%$ inhibition of TXB₂ generation) for almost 2x as many patients as EC aspirin by 72h.
- Inhibition of Tx_B2 generation was greater and less variable for PL-ASA or plain aspirin compared to EC aspirin.



PK/PD COMPARISON 81 MG OF ASA

PK: PL-ASA provides faster absorption and more complete bioavailability vs. EC Aspirin

PD: PL-ASA provides faster and more potent inhibition with lower levels of AA-induced platelet aggregation vs enteric coated (EC) aspirin

Objectives & Methods:

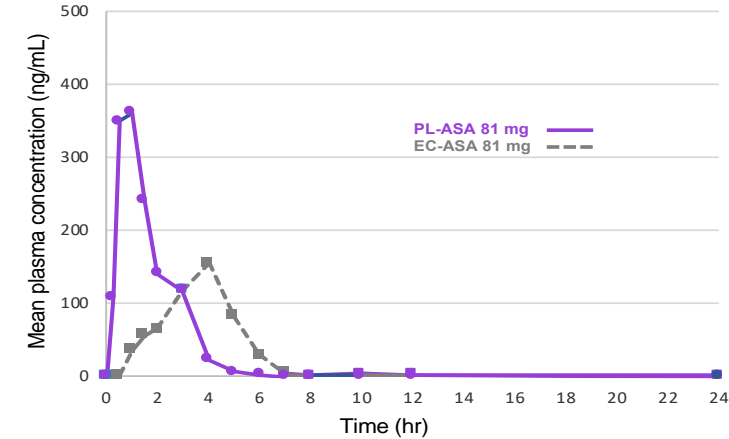
Randomized study conducted in subjects without CV disease (n=36)
- 2-way crossover, enteric aspirin or PL-ASA 81 mg

Results:

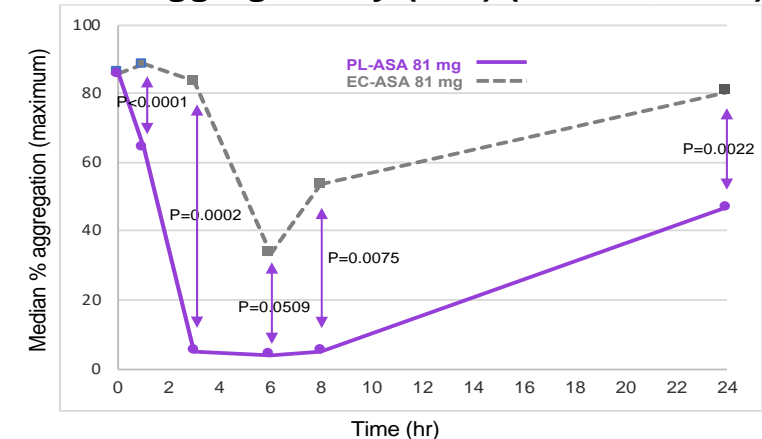
- PK and PD profile is consistent with 325mg
- PL-ASA provides rapid absorption with good bioavailability and platelet inhibition



Acetylsalicylic Acid Plasma Concentrations (mean, n=36)



Arachidonic Acid-Induced Light Transmission Aggregometry (LTA) (median, n=36)



Aspirin Weight Interaction: By Formulation



There is a lower aspirin response with increased weight which is dependent on type of aspirin formulation.

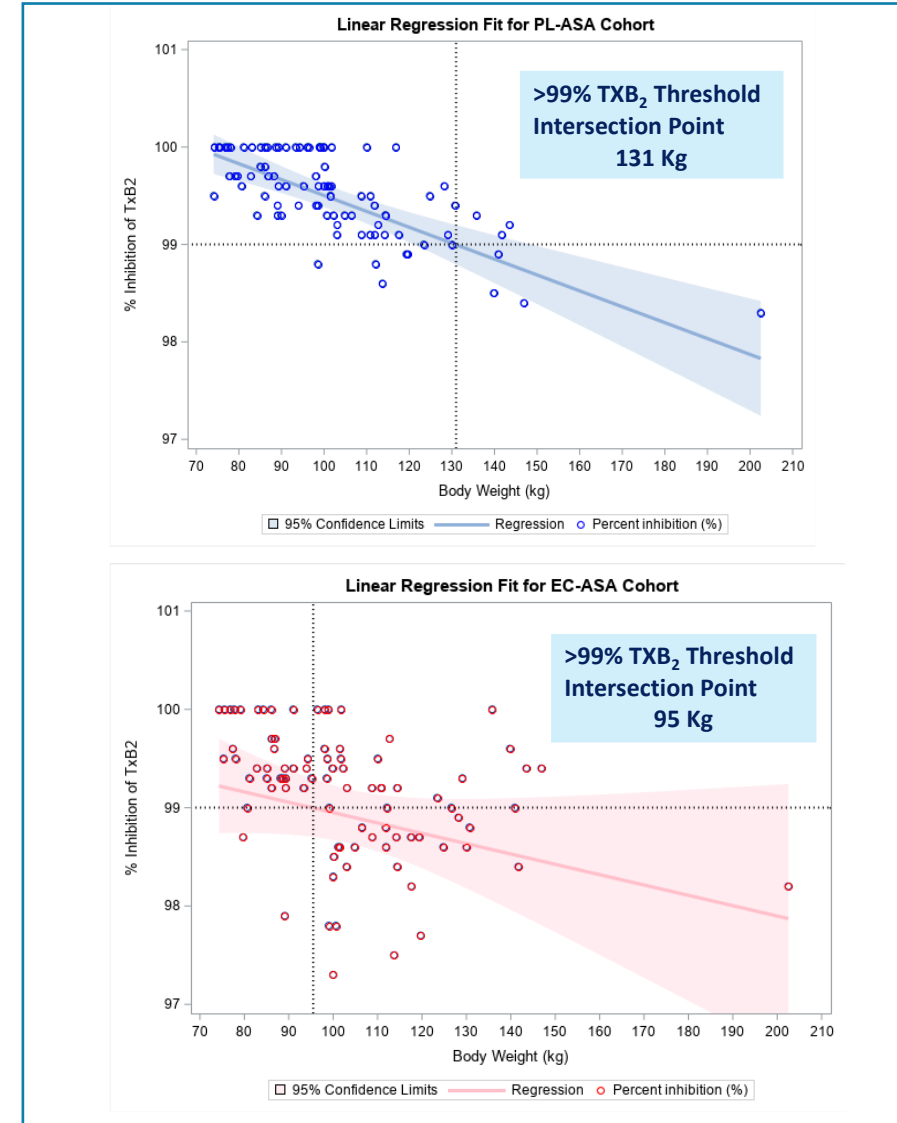
Methods:

- 2 randomized crossover studies in obese diabetic patients after 3 doses of 325 mg EC-ASA or PL-ASA were pooled at the patient level (n=183).
- Regression analysis determined the impact of weight on inhibition of thromboxane B2 (TXB2).

Results:

- There was a significantly earlier drop below the threshold of TXB2 inhibition with EC-ASA than PL-ASA (95 kg vs. 131 kg, $p < 0.001$).
- Lower aspirin response with increased weight is dependent on type of aspirin formulation.

Bhatt DL et al. JACC 2020;75:1344.



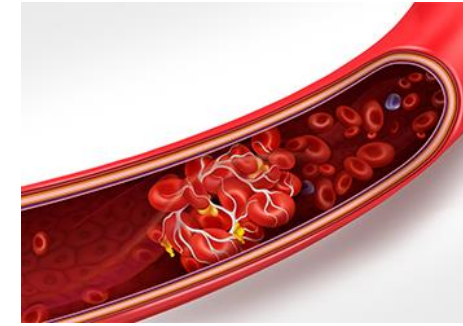
ASPIRIN CONSIDERATIONS FOR HEALTHCARE PROVIDERS

- Educate patient on importance of compliance
- Eliminate interfering substances (e.g., ibuprofen)
- Taking with full glass of water, without food, concomitant PPI(?)
- Accurate, tailored dosing (obese, females, elderly, DM, CKD)
- Formulations with reliable absorption/bioavailability (i.e., equivalent to immediate release formulation)
- Formulation with less GI injury (i.e., less bleeding; less need for PPI; less side effects; better adherence)

CONCLUSION

- Aspirin is a foundational therapy in secondary prevention and DAPT.
- Careful risk – benefit assessment tailored for each patient beginning aspirin therapy is warranted
- The duration of DAPT therapy is still debatable, but aspirin remains a Class IA indication for secondary prevention, indefinitely. The patient is vulnerable coming off of DAPT and shared decision making with provider and the patient is warranted.
- Immediate release aspirin has the best antiplatelet profile, especially for early ACS and special populations and is probably the better choice over enteric coated.
- Initiation of aspirin therapy requires education and reeducation with our patients

CASE STUDY ANOTHER LOOK AT YOUR ANSWERS, POST PROGRAM



- 52 YO female with history of Type 2 Diabetes, HTN, and no past history of cardiovascular disease, but notable hysterectomy age 45 presented to the Cath lab directly by ambulance with ST elevation myocardial infarction.
- In the ambulance, the paramedics observed ST elevation in leads V2-4, applied 2L O₂ per nasal canula, administered 325mg chewable aspirin, SL NTG, and rushed the patient to a PCI center.
- CathLab: Pulse 90/min, RR 20/min, BP 130/78, Hb A1c 6.8, 110 KG (BMI 34); CathLab Team proceeded to immediate PCI to open the LAD and place DES.
- Post procedure and hospital course were uneventful. Discharged on prehospitalization medications losartan & dulaglutide, and DAPT.

WHICH ANTIPLATELET REGIMEN WOULD YOU PLACE THE PATIENT ON?

- A) Immediate release/ plain aspirin 81 mg, clopidogrel 75 mg for 1 year
- B) Enteric coated aspirin 81 mg, clopidogrel 75 mg
- C) Enteric coated aspirin 81 mg, more potent P2Y₁₂ prasugrel or ticagrelor
- D) PL-ASA 81 mg, clopidogrel
- E) PL-ASA 81 mg, more potent P2Y₁₂ prasugrel or ticagrelor

AT ONE YEAR, WHAT ANTIPLATELET THERAPY WOULD YOU TRANSITION THE PATIENT TO?

- A) Enteric coated aspirin 81 mg
- B) PL-ASA 81 mg
- C) Clopidogrel 75 mg
- D) More potent P2Y₁₂ prasugrel or ticagrelor
- E) E) Continue DAPT

UNANSWERED QUESTIONS?

- Is Aspirin alone enough?
- Is P2Y12 monotherapy enough?
- Do antiplatelet needs based on new stent technologies?
- What is the best time to take aspirin ?
- Should you take aspirin with or without food?

FACULTY DISCLOSURE FOR M.D. ROUNDTABLE

JOINING DRS GIBSON AND ANGIOLILLO

Asif Ali, MD

**Clinical Assistant Professor, University of Texas Health Science Center
Cardiovascular & Preventive Medicine, Houston Cardiology Consultants**

Other:

PULS Cardiac Test. Regional Speaker 2021.

Jardiance: BI/ Lilly. Regional Speaker, 2018-Present.

Lifetest and HFAM: Zoll. Regional speaker, 2018-Present

Repatha: PCSK-9 Inhibitor. Regional Speaker, 2017-present

National Lipid Association (NLA) Regional Speaker for Texas, 2017-present

Thrive360: CMO, Board member

Cloudstream Medical Imaging: CMO

Curogram: Medical Advisor

LumiHealth: Medical Advisor

Preventric: CMO

ADDITIONAL FACULTY DISCLOSURE FOR PHARMACIST ROUNDTABLE

JOINING DRS GIBSON AND FANIKOS

Jennifer Goldman, R.Ph., PharmD, CDES, BC ADM, FCCP

Massachusetts College of Pharmacy & Health Science

Professor of Pharmacy Practice

Provider, Well Life Medical, Peabody, Mass

Consulting

NovoNordisk, Lilly, Amarin, Xeris, Abbott Diabetes, Bayer, Boehringer Ingelheim, Sanofi

FACULTY DISCLOSURES FOR ADVANCED PRACTICE PROVIDERS AND NURSES ROUNDTABLE *JOINING DR GIBSON AND MS. ROGERS*

Emilly Anjudar, APRN

Advanced Clinical Nurse Practitioner

Vascadio Heart & Vascular Institute, Hialeah, Florida

No relevant financial relationships to report

John Mulder, IV PA-C, AACN

Interventional Cardiology APP Leader

Spectrum Health Medical Group, Grand Rapids, MI

Speaker: Astra Zeneca, ABIOMED

Keri McGovern, RN

**Cardiac Catheterization Lab, Beth Israel Deaconess Medical Center,
Boston, MA**

No relevant financial relationships to report