Secondary Prevention with Aspirin and the Latest FDA Approved Aspirin Formulation

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Objectives

- At the completion of the webinar, the attendee will have a greater competence related to:
 - Understanding that current guidelines recommend aspirin as part of secondary prevention post ACS
 - Understanding the differences in available aspirin formulations including the latest FDA approved aspirin Formulation PL-ASA Vazalore- liquid filled aspirin capsule
 - Understanding the need to tailor aspirin therapy to the individual patient based upon the balance of risk and benefit

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.

Aspirin Evidence in 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

Antithrombotic Trialists Collaboration



*Aspirin was the predominant antiplatelet agent studied **Include MI, stroke, or death

AHA/ACC Guidelines: Antiplatelet Therapy for NSTE-ACS, STE-ACS and PCI

Summary of Recommendations for Initial Antiplatelet Therapy in Patients with Definite or Likely NSTE-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	1	A		
•	Aspirin maintenance dose continued indefinitely	81 mg/d 325 mg/d	1	A		

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

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Aspirin						
•	Non-enteric coated aspirin to all patients promptly after presentation	162 mg-325 mg	1	В		
•	Aspirin maintenance dose continued indefinitely	81 mg/d 325 mg/d		A		
•	81 mg daily is the preferred maintenance dose	81 mg	lla	В		

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



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.



Phospholipase A_2 Aspirin (low dose) **Arachidonic Acid** COX-1 COX-2 Η **Prostaglandin G₂**,H₂ Thromboxane synthase Prostacyclin synthase Prostacyclin Thromboxane A₂ Collagen, Inhibits platelet aggregation Induces platelet ADP, Induces vasodilation aggregation Thrombin Potent vasoconstrictor proliferation Induces vascular smooth muscle cell proliferation

Phospholipids

• Proatherogenic

Aspirin (high dose)

- Inhibits vascular smooth muscle cell
- Antiatherogenic
- Gut protection
- Renal blood flow regulation

What are the Concerns about Aspirin?

Main concern for decades has been GI toxicity

Dyspepsia GI bleeding

Mechanisms of GI toxicity

Direct Local Mechanism: Allows acid to come into contact with GI mucosa

Systemic: Reduces prostaglandins which protect the GI mucosa and is an antiplatelet

Mechanism of Direct Gastric Injury by NSAIDs (Aspirin)

- The stomach lumen has a protective hydrophobic layer, which does not allow acid entry.
- NSAIDs "associate" (don't covalently bind) with the phospholipids in the protective layer which in turn changes the hydrophobic properties of the layer.
- When the phospholipid layer is disrupted, the protective mechanism is compromised, and this allows acid to enter and injure the gastric mucosa cells.
- A new phospholipid formulation of aspirin comes already enclosed and shielded by phospholipids (PL-ASA) and this reduces gastric erosions.



Aspirin Formulations

- Immediate Release/Plain Aspirin
- Enteric- Coated Aspirin
- Latest FDA approved Immedicate Release/ Phospholipid- Aspirin (Vazalore)

Delayed Release- Enteric Coated ASA

- Developed over 50 years ago EC-ASA is a delayed release formulation
- Quality evidence for reduced gastric injury is not clear^{1,2}
- Enteric coating or buffering may not lower Upper GI Bleeding rates³
- Enteric coated aspirin formulations may have 'erratic absorption' 4,
- As a result, the antiplatelet effects of enteric aspirin may be erratic and incomplete in some patients with stable CV disease⁶

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. ³Kelly JP. Lancet 1996;348;1413-6. ⁴ FDA 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

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)

Phospholipid ASA- Vazalore

pH scale

4.0

7.4

3.0

The ASA molecules are pre-associated with and enclosed by phospholipids which mimics and minimizes the disruption of the phospholipid layer protecting the gastric mucosa minimizing erosions & ulcers

VAZALORE® IS SPECIALLY DESIGNED TO HELP REDUCE LOCAL GASTRIC INJURY WHILE MAINTAINING FULL ASPIRIN BIOAVAILABILITY

VAZALORE is a liquid-filled capsule containing aspirin preassociated with a unique phospholipid to prevent the aspirin from interacting with similar naturally occurring phospholipids in the gastric mucosal barrier, helping to avoid local gastric injury.

PL-ASA Reduces the risk of Erosions and Ulcers on Endoscopy

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



(a) Subjects with erosions and/or ulcers(b) Subjects with ulcers

Cryer B et al. Am J Gastroenterol 2011;106(2):272-7.

Slide by C. Michael Gibson MD

PL-ASA is Bioequivalent to Plain Aspirin as 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.



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

Absorption of PL-ASA is Similar to that of Plain Aspirin but Significantly 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, entericcoated or PL-ASA 325mg



PL-ASA and Plain Aspirin Exhibit Significantly Faster Time to Complete Aspirin Effect (≥99% inhibition of thromboxane B2 generation) than Enteric Coated ASA

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Methods:

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

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

Results:

- PL-ASA provided complete antiplatelet effect (≥99% inhibition of TXB2 generation) for almost 2x as many patients as EC aspirin by 72h.
- Inhibition of TxB2 generation was greater and less variable for PL-ASA or plain aspirin compared to EC aspirin.



Blue lines represent % inhibition in individual patients who reached 99% inhibition by 72 h after the first dose of study drug. Red lines represent % inhibition in individual patients who did not reach 99% inhibition by 72 h after the first dose of study drug. The horizontal line designates 99% inhibition.

PL-ASA and IR Immediate Release Plain Aspirin provide More Prompt and Predictable Platelet Inhibition vs. Enteric Coated (EC) Aspirin

Methods:

Randomized study conducted in diabetic,
obese subjects (n=40), 3 day dosing
- 3-way crossover: Plain aspirin, entericcoated (EC) or PL-ASA 325mg

Results:

- The aggregation response to AA for the 3 formulations was consistent with inhibition of TxB2 generation.
- The inhibition of aggregation response with PL-ASA or plain aspirin was similar and rapid compared to EC aspirin.
- The individual response to EC aspirin was individually variable.



Bhatt DL, Grosser T, Dong J-F,...Marathi UK. JACC 2017;69(6):603-12.

Methods:

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

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

True non-response (<99% txA inhibition) to aspirin is rare.



The p values were assessed by using McNemar's test. *The 2 subjects nonresponsive to all drugs are the same 2 subjects between PL-ASA and EC Aspirin, and between PL-ASA and Plain Aspirin, and part of the 5 between Plain Aspirin and EC Aspirin.

Co-Ingestion of ASA with Food Delays ASA Absorption and Makes Absorption More Erratic

Enteric coated aspirin formulations have 'erratic absorption¹

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.



Bioavailability of PL ASA in Fasted and Fed States

- 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.

Mean Plasma Salicylic Acid Concentration Vs Time



PK/PD Comparison 81 mg of PL ASA vs EC 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)



There is a Reduced Aspirin Response with Increased Body Weight which Varies by 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 patients on the importance of aspirin in secondary prevention and the importance of compliance
- Eliminate interfering substances (e.g., ibuprofen interferes with absorption)
- Take ASA with a full glass of water, without food
- Consider tailoring dose in high-risk patients (obese, DM)
- Consider formulations with reliable absorption/bioavailability (i.e., equivalent to immediate release ASA formulation)
- Consider formulation with less GI injury (i.e., less erosions, less ulcers)

Conclusions

- Aspirin is a foundational therapy in secondary prevention
- Careful risk benefit assessment tailored for each patient before beginning aspirin therapy is warranted
- The duration of DAPT therapy is still debatable, but aspirin remains a Class IA indication for secondary prevention, indefinitely.
- Immediate release aspirin has the best antiplatelet profile, especially for early ACS and special populations
- Initiation of aspirin therapy requires education and reeducation with our patients