Limitations of Enteric-Coated Aspirin Underscore the Need for a Next Generation, Safer and Effective Aspirin Formulation

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CARDIOVASCULAR DISEASE IS PREVALENT AND COSTLY

CARDIOVASCULAR (CV) DISEASE

- By 2035, ≈50% of the U.S. population is projected to have CV disease, many with atherosclerotic CV disease (ASCVD) [1]
- By 2035, CV medical costs are projected to skyrocket to $749 billion USD [1]

STROKE

- **Annual incidence of stroke:** 610,000 new attacks and 185,000 recurrent attacks; The majority are ischemic strokes due to ASCVD [1]
- In 2016, stroke accounted for ≈1 of every 19 deaths in the United States [1]
- Between 2015 and 2035, direct medical costs for stroke are projected to more than double, from $36.7 billion USD to $94.3 billion USD [1]

MYOCARDIAL INFARCTION (MI) AND CORONARY HEART DISEASE (CHD)

- **Annual incidence of MI:** 605,000 new attacks and 200,000 recurrent attacks all secondary to ASCVD [1]
- In 2013, MI ($12.1 billion USD) and CHD ($9.0 billion USD) were 2 of the 10 most expensive conditions treated in U.S. hospitals [1]
- Between 2015 and 2030, medical costs of CHD are projected to increase by ≈100% [1]

ASPIRIN IS A FOUNDATIONAL THERAPY FOR ASCVD

- Low-dose aspirin is effective in reducing the risk of recurrent events in patients with ASCVD
- ACC/AHA guidelines recommend aspirin use in patients with existing ASCVD for secondary prevention of CV events [1,2]
- Approximately 70% of ASCVD patients use aspirin daily [2]
- The Antithrombotic Trialist' Collaboration (ATC) showed that aspirin reduced serious vascular events by 20-30% in ASCVD patients [3]

ENTERIC-COATED ASPIRIN HAS TWO MAJOR LIMITATIONS: INCREASED GASTROINTESTINAL TOXICITY AND QUESTIONABLE EFFICACY

GASTROINTESTINAL (GI) TOXICITY IS THE MAJOR LIMITATION OF ASPIRIN THERAPY

- Aspirin use is associated with GI toxicity ranging from dyspepsia and heartburn to more serious complications such as ulcers and upper GI bleeding
- The risk of serious GI complications is at least 2-fold among patients on aspirin therapy [5]
- GI symptoms are difficult to tolerate and they frequently result in poor compliance | adherence (10-50%) or the need for proton-pump inhibitors [6-8]
- Patients who discontinue aspirin are at increased risk of CV events compared to those who remain compliant (HR 1.46, 95% CI: 1.41-1.51) [9]

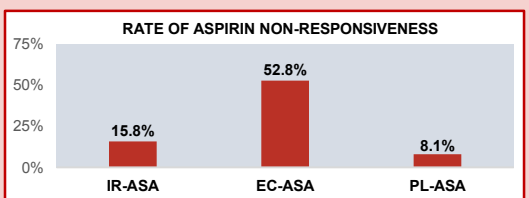
ASPIRIN FORMULATION	RELATIVE RISK FOR UGIC [95% CI]
IR-ASA	2.6 [95% CI: 2.3, 2.9]
EC-ASA	2.4 [95% CI: 1.9, 2.9]

Relative risk of UGIC associated with aspirin use vs no aspirin use (reference); UGIC defined as bleeding, perforation, or other serious upper GI event resulting in hospitalization or visit to specialist

- Enteric-coated aspirin (EC-ASA), designed to minimize GI toxicity and reduce GI complications, has been shown to carry the same risk for serious upper GI complications (UGIC) as immediate-release aspirin (IR-ASA) in large observational meta-analyses [5]

EC-ASA IS KNOWN TO HAVE DELAYED ABSOPTION WHICH LIMITS THE BIOAVAILABILITY AND RESULTS IN UNRELIABLE ANTIPLATELET ACTIVITY AND HIGH INCIDENCE RATE OF ASPIRIN NON-RESPONSIVENESS

- Pharmacokinetic and pharmacodynamic studies have clearly shown that the enteric coating on aspirin can impair bioavailability and result in slower and less predictable antiplatelet activity compared with IR-ASA [10-11]
- In a randomized study of 40 obese patients with diabetes, the rate of aspirin non-responsiveness was compared across three aspirin formulations: IR-ASA, EC-ASA and Vazalore™ (PLx Pharma, Sparta, NJ), which is a novel, pharmaceutical lipid-aspirin complex (PL-ASA) administered in liquid-filled capsules
- The rate of aspirin non-responsiveness was significantly higher amongst patients who received EC-ASA compared to IR-ASA and PL-ASA [11]



Aspirin non-responsiveness was defined as level of residual serum TXB_2 <99.0% inhibition or TXB_2 >3.1 ng/ml within 72 h after 3 daily aspirin doses

CLINICAL TRIAL DATA DO NOT CONCLUSIVELY SUPPORT THE EFFICACY OF EC-ASA

- Systematic reviews regarding the efficacy of aspirin for secondary prevention of CV events do not distinguish between different aspirin formulations
- Many trials included in the ATC review do not exclusively use EC-ASA nor do they specify the formulation of aspirin that was utilized in each trial – the weight of the analysis may be largely grounded on studies using non-EC-ASA
- This highlights the ambiguity regarding which formulation is informing our understanding of aspirin efficacy

A CALL FOR A SAFER ASPIRIN WITH UNCOMPROMISED EFFECTIVENESS

- EC-ASA failed to deliver on the promise of being safer, while jeopardizing the ability to reliably block platelets
- As such, a great unmet need remains for an alternative formulation with a safer GI profile and uncompromised antiplatelet activity
- Newer aspirin formulation, such as the liquid-filled capsule PL-ASA formulation, serve as a promising solution to this unmet need
- PL-ASA has been clinically shown to have faster absorption and more reliable platelet inhibition compared with enteric-coated aspirins [11]
- PL-ASA has also been clinically shown to have lower risk for stomach erosions and ulcers compared with IR-ASA [12]

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