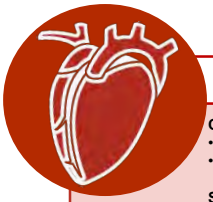
Limitations of Enteric Coated Aspirin Underscore the Need for a Next Generation, Safer and Effective Aspirin Formulation

Francine Chingcuanco[1], MHS; Jonothan Tierce[1,2], CPhil; Weihong Fan[3], MSc.; Efthymios N. Deliargyris[3], MD
1. Monument Analytics, Baltimore, MD; 2. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 3. PLx Pharma, Sparta NJ
Correspondence: Efthymios N. Deliargyris – edeliargyris@plxpharma.com



CARDIOVASCULAR DISEASE IS PREVALENT AND COSTLY

CARDIOVASCULAR (CV) DISEASE

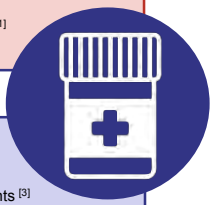
- By 2035, ≈50% of the U.S. population is projected to have CV disease, many with atherosclerotic CV disease (ASCVD) [1]
- By 2035, CV medical costs are projected to skyrocket to $749 billion USD [1]

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]

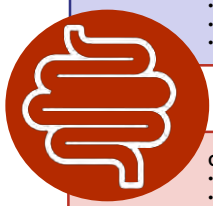
MYOCARDIAL INFARCTION (MI) AND CORONARY HEART DISEASE (CHD)

- **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]

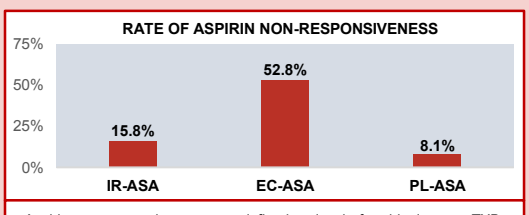
ASPIRIN FORMULATION	RELATIVE RISK FOR UGIC [95% CI]
IR-ASA	2.6 [95% CI: 2.3, 2.9]
EC-ASA	2.4 [95% CI: 1.9, 2.9]

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]

Reference [1] Benjamin EJ, Muntner P, Bittencourt MS. Heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation. 2019;139(10):e56-28. **[2] Gu Q, Dillon CF, Eberhardt MS, Wright JD, Burt VL. Preventive aspirin and other antiplatelet medication use among US adults aged≥ 40 years: data from the National Health and Nutrition Examination Survey, 2011–2012. Public Health Reports. 2015 Nov;130(6):643-54.** [3] Trialists'Collaboration A. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Bmj. 2002 Jan 12;324(7329):71-86. **[4] Carlton R, Coppolecchia R, Khalaf-Gillard K, Lennert B, Moradi A, Williamson T, Cameron J. Budget Impact of Appropriate Low-Dose Aspirin Use for Primary and Secondary Cardiovascular Event Prevention in the Managed Care Setting. Journal of managed care & specialty pharmacy. 2018 Nov;24(11):1102-11.** [5] Rodriguez LA, Sonia Hernández-Dí az, De Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. British journal of clinical pharmacology. 2001 Nov;52(5):563-71. **[6] Moberg C, Naesdal J, Svedberg LE, Duchateau D, Harte N. Impact of Gastrointestinal Problems on Adherence to Low-Dose Acetylsalicylic Acid. The Patient: Patient-Centered Outcomes Research. 2011 Jun 1;4(2):103-13.** [7] Pratt S, Thompson VJ, Elkin EP, Næsdal J, Sörstadius E. The impact of upper gastrointestinal symptoms on nonadherence to, and discontinuation of, low-dose acetylsalicylic acid in patients with cardiovascular risk. American journal of cardiovascular drugs. 2010 Oct 1;10(5):281-8. **[8] Herlitz J, Tóth PP, Næsdal J. Low-Dose Aspirin Therapy for Cardiovascular Prevention. American Journal of Cardiovascular Drugs. 2010 Apr 1;10(2):125-41.** [9] Sundström J, Hedberg J, Thuresson M, Aarskog P, Johannesen KM, Oldgren J. Low-dose aspirin discontinuation and risk of cardiovascular events: a Swedish nationwide, population-based cohort study. Circulation. 2017 Sep 26;136(13):1183-92. **[10] Haastrup PF, Grønlykke T, Jarbøl DE. Enteric Coating Can Lead to Reduced Antiplatelet Effect of Low-Dose Acetylsalicylic Acid. Basic & clinical pharmacology & toxicology. 2015 Mar;116(3):212-5.** [11] Bhatt DL, Grosser T, Dong JF, Logan D, Jeske W, Angiolillo DJ, Frelinger AL, Lei L, Liang J, Moore JE, Cryer B. Enteric coating and aspirin nonresponsiveness in patients with type 2 diabetes mellitus. Journal of the American College of Cardiology. 2017 Feb 6;69(6):603-12. **[12] Cryer B, Bhatt DL, Lanza FL, Dong JF, Lichtenberger LM, Marathi UK. Low-dose aspirin-induced ulceration is attenuated by aspirin–phosphatidylcholine: a randomized clinical trial. The American journal of gastroenterology. 2011 Feb;106(2):272.**