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ORIGINAL INVESTIGATIONS

Proton-Pump Inhibitors Reduce Gastrointestinal Events Regardless of Aspirin Dose in Patients Requiring Dual Antiplatelet Therapy

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ABSTRACT

BACKGROUND The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) showed that proton-pump inhibitors (PPIs) safely reduced rates of gastrointestinal (GI) events in patients requiring dual antiplatelet therapy (DAPT). However, utilization of appropriate prophylactic PPI therapy remains suboptimal, especially with low-dose aspirin.

OBJECTIVES The authors investigated the safety and efficacy of PPI therapy in patients receiving DAPT in low- and high-dose aspirin subsets.

METHODS Randomized patients with available aspirin dosing information in COGENT (N = 3,752) were divided into "low-dose" (≤100 mg) and "high-dose" (>100 mg) aspirin groups. The primary GI and cardiovascular endpoints were composite upper GI events and major adverse cardiac events, respectively. All events were adjudicated by independent, blinded gastroenterologists and cardiologists.

RESULTS Median duration of follow-up was 110 days. Low-dose aspirin users (n = 2,480; 66.1%) were more likely to be older, female, and have higher rates of peripheral artery disease, prior stroke, and hypertension, whereas high-dose aspirin users (n = 1,272; 33.9%) had higher rates of hyperlipidemia, smoking, a history of percutaneous coronary intervention, and were more than twice as likely to be enrolled from sites within the United States (80.4% vs. 39.8%). High-dose aspirin was associated with similar 180-day Kaplan-Meier estimates of adjudicated composite GI events (1.7% vs. 2.1%; adjusted hazard ratio: 0.88; 95% confidence interval: 0.46 to 1.66) and major adverse cardiac events (4.8% vs. 5.5%; adjusted hazard ratio: 0.73; 95% confidence interval: 0.48 to 1.11) compared with low-dose aspirin. Randomization to PPI therapy reduced 180-day Kaplan-Meier estimates of the primary GI endpoint in low-dose (1.2% vs. 3.1%) and high-dose aspirin subsets (0.9% vs. 2.6%; p for interaction = 0.80), and did not adversely affect the primary cardiovascular endpoint in either group.

CONCLUSIONS Gastroprotection with PPI therapy should be utilized in appropriately selected patients with coronary artery disease requiring DAPT, even if the patients are on low-dose aspirin. (Clopidogrel and the Optimization of Gastrointestinal Events Trial [COGENT]; NCT00557921) (J Am Coll Cardiol 2016;67:1661–71)

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

DAPT = dual antiplatelet therapy

GERD = gastroesophageal reflux disease

GI = gastrointestinal

HR = hazard ratios

IQR = interquartile range

NNT = number needed to treat

PCI = percutaneous coronary intervention

PPI = proton-pump inhibitor

SODA = Severity of Dyspepsia Assessment

Given similar antiplatelet inhibition and theoretically lower bleeding risk (1–3), lower-dose aspirin is generally preferred for secondary prevention of cardiovascular events compared with higher-dose aspirin (4), especially when used in combination with more potent $P2Y_{12}$ antagonists (5). Dual antiplatelet therapy (DAPT) poses significant risks of bleeding, particularly gastrointestinal (GI) bleeding, even with low-dose aspirin (6). GI bleeding in high-risk patients with coronary artery disease (CAD) is independently associated with poor prognosis (7), and on-treatment dyspepsia appears to be clinically important and may influence compliance with antiplatelet therapy (8). As such, safe and effective strategies limiting gastric toxicity are much needed.

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The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial; NCT00557921), despite being terminated prematurely due to loss of funding, demonstrated that omeprazole reduced rates of composite upper GI events (1.1% vs. 2.9%; $p < 0.001$) (9) and patient-reported dyspepsia (10) at 180 days compared with placebo in patients with CAD requiring DAPT, and achieved this without increasing rates of major adverse cardiac events (MACE) (9). Whether proton-pump inhibitor (PPI) use reduces GI risk consistently across aspirin doses has not definitively been established. Furthermore, utilization of appropriate prophylactic PPI therapy remains suboptimal, especially with low-dose aspirin (11). In this context, our post hoc analysis of the COGENT aimed to determine the overall GI and cardiovascular safety and efficacy of PPI therapy in patients on low-dose and high-dose aspirin.

METHODS

STUDY POPULATION. The study design and primary results of COGENT have been previously described (9). In brief, the COGENT was a global, prospective, phase III randomized, placebo-controlled, double-blind, double-dummy clinical trial of a fixed-combination of clopidogrel 75 mg and omeprazole 20 mg compared with clopidogrel 75 mg alone. Daily enteric-coated aspirin was administered to all study patients in open-label fashion, but specific dosing was left to the treating clinician. Patients older than 21 years of age requiring DAPT for at least 12 months, regardless of indication, were included as long as $P2Y_{12}$ therapy was initiated ≤21 days before

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