BRIEF OBSERVATION

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Efficacy and Safety of Proton-Pump Inhibitors in High-Risk Cardiovascular Subsets of the COGENT Trial

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ABSTRACT

BACKGROUND: Proton-pump inhibitors (PPIs) have been demonstrated to reduce rates of gastrointestinal events in patients requiring dual antiplatelet therapy (DAPT). Data are limited regarding the efficacy and safety of PPIs in high-risk cardiovascular subsets after acute coronary syndrome or percutaneous coronary intervention.

METHODS: All patients enrolled in COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) were initiated on DAPT (with aspirin and clopidogrel) for various indications within the prior 21 days. These post hoc analyses of the COGENT trial evaluated the efficacy and safety of omeprazole compared with placebo in subsets of patients requiring DAPT for the 2 most frequent indications: 1) patients undergoing percutaneous coronary intervention (for any indication) within 14 days of randomization (n = 2676; 71.2%); and 2) patients presenting with acute coronary syndrome managed with or without percutaneous coronary intervention (n = 1573; 41.8%). Unadjusted Cox proportional hazards models were used to estimate effect sizes through final follow-up.

RESULTS: Median follow-up duration was 110 days (interquartile range 55-167). In percutaneous coronary intervention-treated patients, omeprazole significantly reduced rates of composite gastrointestinal events at 180 days (1.2% vs 2.7%; hazard ratio [HR] 0.43; 95% confidence interval [CI], 0.22-0.85; $P = .02$) without increasing composite cardiovascular events (5.4% vs 6.3%; HR 1.00; 95% CI, 0.67-1.50; $P = 1.00$). Similarly, omeprazole lowered risk of the primary gastrointestinal endpoint at 180 days in patients presenting with acute coronary syndrome (1.1% vs 2.7%; HR 0.37; 95% CI, 0.13-1.01; $P = .05$) without a significant excess in cardiovascular events (5.6% vs 4.5%; HR 1.40; 95% CI, 0.77-2.53; $P = .27$).

CONCLUSIONS: PPI therapy attenuates gastrointestinal bleeding risk without significant excess in major cardiovascular events in high-risk cardiovascular subsets, regardless of indication for DAPT. Future studies will be needed to clarify optimal gastroprotective strategies for higher-intensity and longer durations of DAPT.

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KEYWORDS: Acute coronary syndrome; Bleeding; Clinical outcomes; Clinical trials; Coronary artery disease; Percutaneous coronary intervention; Proton-pump inhibitors

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Major gastrointestinal bleeding after acute coronary syndromes or in patients undergoing percutaneous coronary intervention is common and is associated with adverse prognosis.[1] The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial; ClinicalTrials.gov Identifier NCT00557921) trial demonstrated that omeprazole reduced rates of composite gastrointestinal events at 180 days[2] and patient-reported dyspepsia,[3] compared with placebo in patients with coronary artery disease requiring ≥12 months of dual antiplatelet therapy (DAPT) for any indication, without adversely influencing risk of major adverse cardiovascular events. Despite these data, safety concerns persist about the generalizability of this randomized experience to high-risk patients after acute coronary syndrome or percutaneous coronary intervention,[4-6] especially in the context of an adverse pharmacodynamic interaction between proton-pump inhibitors (PPIs) and clopidogrel.[7-10] Furthermore, although PPIs are often administered to hospitalized patients presenting with acute coronary syndrome or for percutaneous coronary intervention, continuation of PPI therapy postdischarge is a question faced by many outpatient clinicians. As such, we report the efficacy and safety of PPI therapy in high-risk, enriched subgroups after acute coronary syndrome or percutaneous coronary intervention in the COGENT trial.

CLINICAL SIGNIFICANCE

- These post hoc analyses of the COGENT trial evaluated the safety and efficacy of proton-pump inhibitor therapy in patients after acute coronary syndrome or requiring percutaneous coronary intervention.
- Proton-pump inhibitors consistently reduced rates of major gastrointestinal events at 180 days in these high-risk cardiovascular subsets.
- Proton-pump inhibitors did not significantly increase risk of major adverse cardiovascular events at 180 days without heterogeneity by indication for dual antiplatelet therapy.

METHODS

As previously described,[2] COGENT was a phase-3, multicenter, global, placebo-controlled, double-blind, double-dummy randomized controlled trial of a fixed combination of clopidogrel 75 mg and omeprazole 20 mg compared with clopidogrel 75 mg alone. Enteric-coated aspirin was provided to all study patients. Patients initiated on DAPT within the prior 21 days without use of recent gastroprotection, oral anticoagulation, or fibrinolytic therapy, were eligible for enrollment. The ethics committee and institutional review board of each individual site locally approved the study protocol, and all patients provided explicit informed consent for trial participation. The primary adjudicated composite gastrointestinal endpoint included overt upper gastrointestinal bleeding, bleeding of presumed gastrointestinal origin, symptomatic gastroduodenal ulcer, endoscopy-confirmed gastroduodenal erosions, obstruction, or perforation. The secondary adjudicated gastrointestinal endpoint for the present analysis was overt upper gastrointestinal bleeding (known or unknown origin). The primary adjudicated cardiovascular endpoint was the composite of cardiovascular death, nonfatal myocardial infarction, coronary revascularization, or ischemic stroke.

The number of patients who experienced events on or prior to 180 days and Kaplan-Meier estimates of event rates at 180 days are presented for patients with or without acute coronary syndrome and with or without percutaneous coronary intervention. Interaction analyses between treatment assignment (with PPI or placebo) and DAPT indication were performed using Breslow-Day tests. Effect sizes through final follow-up were estimated using unadjusted Cox proportional hazards models, expressed as hazard ratios (HR) and 95% confidence intervals (CI). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

COGENT was terminated early due to the sponsor filing for bankruptcy. In the final intention-to-treat population (n = 3759), risks of gastrointestinal and cardiovascular events were assessed in 2 non-mutually exclusive groups (the 2 most common indications for DAPT): 1) patients undergoing percutaneous coronary intervention within 14 days of randomization (n = 2676; 71.2%) and 2) patients presenting with acute coronary syndrome managed with or without percutaneous coronary intervention (n = 1573; 41.8%). Data regarding the status of percutaneous coronary intervention and acute coronary syndrome were missing in 36 and 38 patients, respectively. There were no major differences in baseline characteristics in patients randomized to omeprazole or placebo in either major subgroup (data not shown). As such, since the original randomization was preserved, no additional statistical adjustment was applied to these analyses. Median follow-up duration was 110 days (interquartile range 55-167). In percutaneous coronary intervention-treated patients, omeprazole significantly reduced rates of composite gastrointestinal events (1.2% vs 2.7%; HR 0.43; 95% CI, 0.22-0.85; P = .02) without increasing composite cardiovascular events (5.4% vs 6.3%; HR 1.00; 95% CI, 0.67-1.50; P = 1.00). Omeprazole lowered risk of the primary gastrointestinal event in patients presenting with acute coronary syndrome (1.1% vs 2.7%; HR 0.37; 95% CI, 0.13-1.01; P = .05) without a significant excess in cardiovascular events (5.6% vs 4.5%; HR 1.40; 95% CI, 0.77-2.53; P = .27). Similar trends were observed for the secondary gastrointestinal endpoint, overt upper gastrointestinal bleeding (**Table**).