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

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STRUCTURED ABSTRACT

Background: Proton-pump inhibitors (PPIs) have been demonstrated to reduce rates of gastrointestinal ~~(GI)~~ 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 ~~(ACS)~~ or percutaneous coronary intervention. ~~(PCI).~~

Methods: ~~These *post hoc* analyses of the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) trial evaluated the efficacy and safety of omeprazole compared with placebo in~~ 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 two most frequent indications: 1) ~~1)~~ patients undergoing ~~PCI~~ percutaneous coronary intervention (for any indication) within 14 days of randomization ~~and receiving DAPT~~ (n=2,676; 71.2%); and 2) patients who presented with ~~ACS and receiving DAPT~~acute coronary syndrome (n=1,573; 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 (IQR 55 to 167). In ~~PCI~~percutaneous coronary intervention-treated patients, omeprazole significantly reduced rates of composite ~~GI~~ gastrointestinal events at 180 days (1.2% vs. 2.7%; HR 0.43, 95% CI 0.22-0.85; p=0.02) 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 ~~GI~~ endpoint at 180 days in patients presenting with acute coronary syndrome ~~ACS~~ (1.1% vs. 2.7%; HR 0.37, 95% CI 0.13-1.01; p=0.05) without a significant excess in cardiovascular events (5.6% vs. 4.5%; HR 1.40, 95% CI 0.77-2.53; p=0.27).

Conclusions: PPI therapy attenuates gastrointestinal ~~GI~~ bleeding risk without a 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.

Major gastrointestinal ~~(GI)~~ bleeding after acute coronary syndromes ~~(ACS)~~ or in patients undergoing percutaneous coronary intervention ~~(PCI)~~ 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 ~~GI~~ events at 180 days[2] and patient-reported dyspepsia[3] compared with placebo in patients with coronary artery disease ~~(CAD)~~ 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 regarding the generalizability of this randomized experience to high-risk patients after acute coronary syndrome ~~ACS~~ or percutaneous coronary intervention~~PCI~~,[4-6] especially in the context of an adverse pharmacodynamic interaction between proton-pump inhibitors (PPIs) and clopidogrel.[7~~5~~-10~~8~~] Furthermore, although PPIs are often administered to hospitalized patients presenting with acute coronary syndrome ~~ACS~~ or for percutaneous coronary intervention~~PCI~~, continuation of PPI therapy post-discharge 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 ~~ACS~~ or percutaneous coronary intervention ~~PCI~~ in the COGENT trial.

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 75mg and omeprazole 20mg compared with clopidogrel 75mg 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 committees and institutional review boards of each individual site locally approved the study protocol and all patients provided explicit informed consent for trial participation. The primary adjudicated composite gastrointestinal ~~GI~~ endpoint included overt upper gastrointestinal ~~GI~~ bleeding, bleeding of presumed gastrointestinal ~~GI~~ origin, symptomatic gastroduodenal ulcer, endoscopy-confirmed gastroduodenal erosions, obstruction, or perforation. The secondary adjudicated gastrointestinal ~~GI~~ endpoint for the present analysis was overt upper gastrointestinal ~~GI~~ bleeding (known or unknown origin). The primary adjudicated cardiovascular endpoint was the composite of cardiovascular death, non-fatal myocardial infarction, coronary revascularization, or ischemic stroke.

Number of patients who experienced events on or before 180 days and Kaplan-Meier estimates of event rates at 180 days are presented for patients with or without acute coronary syndrome ~~ACS~~ and with or without percutaneous coronary intervention~~PCI~~. 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=3,759), risks of gastrointestinal ~~GI~~ and cardiovascular events were assessed in two non-mutually exclusive groups (the two most common indications for DAPT): 1) patients undergoing percutaneous coronary intervention ~~PCI~~ within 14 days of randomization (n=2,676; 71.2%) and 2) patients who presented with acute coronary syndrome ~~ACS~~ (n=1,573; 41.8%). Data regarding percutaneous coronary intervention ~~PCI~~ and acute coronary syndrome ~~ACS~~ status 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. ~~Despite differences in indications of DAPT utilization, baseline characteristics in the PPI and placebo groups were well-balanced across these subgroups.~~ Median follow-up duration was 110 days (IQR 55 to 167). In percutaneous coronary intervention~~PCI~~-treated patients, omeprazole significantly reduced rates of composite gastrointestinal ~~GI~~ events (1.2% vs. 2.7%; HR 0.43, 95% CI 0.22-0.85; p=0.02) 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 ~~GI~~ event in patients presenting with acute coronary syndrome

ACS (1.1% vs. 2.7%; HR 0.37, 95% CI 0.13-1.01; p=0.05) without a significant excess in cardiovascular events (5.6% vs. 4.5%; HR 1.40, 95% CI 0.77-2.53; p=0.27). Similar trends were observed for the secondary gastrointestinal GI endpoint, overt upper gastrointestinal GI bleeding (**Table**).

DISCUSSION

COGENT enrolled a high-risk cardiovascular cohort with over 70% of patients having undergone percutaneous coronary intervention PCI and over 40% presenting with acute coronary syndromeACS. Approximately 2-3% of patients experienced major gastrointestinal GI events during 6-months of DAPT after acute coronary syndrome ACS or percutaneous coronary interventionPCI. Consistent with the overall trial results,[2] this *post hoc* analysis demonstrates that PPI therapy safely attenuates this gastrointestinal GI risk without significant excess in major cardiovascular events at 180 days, regardless of initial indication for DAPT. The gastroprotective efficacy of PPIs in the post-acute coronary syndromeACS setting has recently been corroborated by real-world data from a large, nationwide cohort study.[119]

This study is subject to a number of limitations. The trial was prematurely terminated due to loss of funding prior to meeting target enrollment. However, sufficient follow-up was completed during the high-risk period after acute coronary syndrome ACS and percutaneous coronary interventionPCI. Our analyses did not account for multiple comparisons. The trial utilized a combination formulation of clopidogrel and omeprazole that is not commercially available, though it is unlikely this would affect the results. COGENT was significantly underpowered to detect differences in cardiovascular events

in individual subgroups, and some heterogeneity around the overall trial point estimate in cardiovascular risk was expected across the tested subsets. Future studies, including COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies; ClinicalTrials.gov Identifier NCT01776424), will shed further light on optimal gastroprotective strategies in high-risk ~~CAD~~ coronary artery disease patients requiring more potent antithrombotic combinations used for longer durations.[12~~0~~]

Despite high post-acute coronary syndrome~~ACS~~ and post-percutaneous coronary intervention ~~PCI~~ bleeding risk on contemporary DAPT regimens, PPI use remains suboptimal in appropriately-selected patients,[13~~1~~] perhaps related to underestimation of gastrointestinal ~~GI~~ bleeding risks[14~~2~~] or to concerns regarding a potentially adverse drug interaction between PPIs and clopidogrel.[4~~5~~-10~~8~~] These data from COGENT, the only large, randomized placebo-controlled trial evaluating effects of PPIs on clinical endpoints in patients requiring DAPT, provide reassurance regarding the safety of PPIs in high-risk cardiovascular subsets. At this juncture, use of prophylactic PPIs appears to be safe and represents a recommended strategy[15~~3~~-17~~5~~] for attenuating gastrointestinal ~~GI~~ bleeding risk in patients requiring DAPT, including after percutaneous coronary intervention ~~PCI~~ or acute coronary syndrome~~ACS~~.

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CONFLICTS OF INTEREST

Dr. Muthiah Vaduganathan has no relevant disclosures.

Dr. Christopher P. Cannon has served on advisory boards of Bristol-Myers Squibb, Lipimedix, and Pfizer; and has received research funding from Accumetrics, Arisaph, AstraZeneca, Boehringer-Ingelheim, CSL Behring, Essentialis, GlaxoSmithKline, Janssen, Merck Regeneron, Sanofi, and Takeda.

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Dr. Loren Laine has served on the Data Safety Monitoring Boards for studies sponsored by Bayer and Bristol-Myers Squibb.

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude

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