COGENT Study

By Brian Chou, 2014 PharmD Candidate; Michael E. Stuart, MD; and Sheri A. Strite

Introduction

The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) study was an international multi-centered, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, phase three trial. The trial ended prematurely due to insufficient financial sponsorship. The study was designed to determine the efficacy and safety of concomitant administration of dual anti-platelet therapy (clopidogrel plus aspirin) and PPIs (proton-pump inhibitors) in patients with coronary artery disease. There were both a primary efficacy endpoint for GI bleeding and a primary safety endpoint for CV events.

Many patients indicated for dual anti-platelet therapy experience symptoms of GI bleeding, pain and other complications. In spite of this, it is suspected that concomitant administration of clopidogrel and omeprazole, could decrease GI complications without becoming a drug-drug interaction that could affect CV safety.

Author's Results and Conclusion

Study population consisted of patients with elevated risk for death from cardiovascular causes. The number of events for the primary gastrointestinal end point was lower in the omeprazole group compared to the placebo group

Element	Criteria	Comments
Study Design Assessment	**Is the design appropriate to the research question? Is the research question useful?** • For **efficacy**, use of **experimental study design** (meaning study subjects and others were not allowed choice in determining interventions) • **Clinically significant area** for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable **definitions for clinical outcome such as response, treatment success or failure** • If **composite endpoints** used, reasonable combination used – and used for safety if used for efficacy	A double-blinded, double-dummy, placebo controlled, randomized controlled trial that assessed the GI efficacy and CV safety of concomitant dual anti-platelet therapy (clopidogrel plus aspirin) and PPIs.
Internal Validity Assessment	**Can bias, confounding or chance explain the study results?** • Ensure prespecified and **appropriate** 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance	The research question, population, outcomes, group assignment methods, analysis methods were appropriate. ***Threat:*** However, the trial ended prematurely, which leads to questionable levels of statistical significance discussed below. Other threats to internal validity are also discussed.
Selection Bias	• Groups are **appropriate** for study, of appropriate size, **concurrent** and **similar** in **prognostic variables** • Methods for generating the group assignment sequence are truly **random,** sequencing avoids potential for anyone **affecting assignment** to a study arm and **randomization remains intact** • **Concealment of allocation** strategies are employed to prevent anyone affecting assignment to a study arm	Baseline characteristics were evenly balanced between the omeprazole and placebo arms. Concealment and randomization of allocation was performed via a central voice-response system, and blinded study kits were distributed. ***Threat:*** No information on the generation of sequence.
Performance Bias	• **Double-blinding** methods employed (i.e., subject and all working with the subject or subject's data) and achieved • Reasonable **intervention** and reasonable **comparator** used (e.g., placebo) • **No bias or difference, except for what is under study, between groups during course of study** (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.)	***Threat:*** It was never stated how the investigators and data collectors were blinded, therefore potential bias may exist. ***Threat:*** Dual-antiplatelet administration of ASA varied between 75mg to 325mg doses. Varying ASA doses may produce variability in efficacy and safety outcomes. ***Threat:*** Loading doses for clopidogrel were not specified. Clopidogrel arm patients are clopidogrel-naïve due to exclusion criteria. Patients may or may not have been given loading dose and could potentially affect acute efficacy and safety outcomes. ***Threat:*** A single-pill formulation with release kinetics different from generic omeprazole was used. Different pharmacokinetics may affect outcomes. Co-interventions were not mentioned, but the baseline characteristics, adherence and exposure rates were relatively similar in both groups.

Element	Criteria	Comments
Attrition Bias	• Zero or minimal **missing data points** or loss from randomization (e.g., approximately 5 percent with differential loss, or approximately 10 percent without differential loss) unless good ITT analysis (see ITT below)	***Threat:*** There were no data pertaining to the duration the patients stayed in the trial, nor were the discontinuation rates of the trial specified. Overall, the experiment was limited by fewer events due to premature termination. ***Threat:*** 112 patients removed after the initial randomization and 4 GI events excluded from the data analysis were not accounted for. The exclusion of these patients may lead to a loss in randomization. ***Threat:*** Kaplan-Meier analysis was used, and a significant portion of the study population was censored, however details and data of who was censored were not specified.
Assessment Bias	• Assessors are **blinded** • Low likelihood of findings due to **chance, false positive and false negative outcomes** (judgment call on statistical significance, including **confidence intervals**) • **Non-significant findings** are reported, but the **confidence intervals include clinically meaningful differences** • **Intention-to-Treat Analysis (ITT)** performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) • Use of **modeling** only with use of reasonable assumptions	***Threat:*** The blinding of assessors was not specified, which may potentially lead to bias. ***Threat:*** No reference as to how frequent independent adjudicating committees were utilized. Authors stated that "there was also a significant reduction in the number of patients with investigator-defined gastrointestinal events." The investigator-defined parameters were not specified, nor did the author state which set of parameters were used in the data analysis. This missing information may result in bias of the results. ***Threat:*** The experiment was designed to end at 143 GI events, however, due to the premature termination, the experiment ended at 55 GI events. Kaplan-Meier analysis was not pre-specified to take place at that point (180 days). Therefore, the early assessment of data may pose a high risk that chance caused the difference in efficacy outcomes.
Usefulness Assessment	• **Clinically significant area + sufficient benefit size** = meaningful clinical benefit (consider efficacy vs. effectiveness)	***Threat:*** The NNT=55, meaning that for every 55 patients treated, omeprazole prevents 1 primary efficacy outcome. According to the data, omeprazole reduced the primary GI outcome relative to placebo with statistical significance (P<0.001), however, threats to internal validity may invalidate results. ***Threat:*** There was also not enough power to determine definitive safety outcomes. A wide confidence interval and high p-value (P=0.96) is not statistically significant, therefore more conclusive evidence and further testing is needed to establish the risk of CV events in concomitant therapy.
External Validity	**How likely are research results to be realized in the real world considering population and circumstances for care?** • Review n, inclusions, exclusions, baseline characteristics and intervention methods – this is a **judgment call**.	***Threat:*** The study population did not include patients indicated for clopidogrel due to non-CV causes, or those who have been taking clopidogrel and other thienopyridines for more than 21 days prior to randomization. Therefore, the study population is not representative of the real world usage of clopidogrel. ***Threat:*** Duration of clopidogrel therapy ranges from 9-12 months. Trial and analysis of data ended at 180 days. Data may not be representative of complete, long-term clopidogrel therapy. Overall, a controlled trial setting excludes extraneous variables that may provide different results than that of the real world setting.
Patient Perspective	• Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	-Concomitant therapy with omeprazole may decrease GI events. -Absence of CV events with concomitant therapy was inconclusive. -No data on long term usage.
Provider Perspective	• Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	-PPIs inhibit CYP2C19 metabolism of clopidogrel into its active metabolite, however, there was no statistically significant evidence suggesting that such a drug interaction affects CV events. Further studies are needed. -Other medications that are CYP2C19 inhibitors or inducers must be used with caution with this concomitant therapy. -No data beyond 180 days

**Chart taken from the Delfini Group,LLC. Short Critical Appraisal Checklist: Updated 02/19/08*

Delfini Evidence Grading Scale

Grade A Evidence: Useful
The evidence appears strong and sufficient to use in making health care decisions - no significant threats to validity were ascertained.

Grade B Evidence: Possibly Useful
The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified

Grade B-U Evidence: Possible to uncertain usefulness
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Health care decision-makers should be fully informed of the evidence quality.

Grade U Evidence: Uncertain
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions. Delfini does not use such information to inform clinical decisions regarding efficacy.

(1.1 percent vs. 2.9 percent, respectively; HR=0.34; 95 percent CI 0.18 to 0.63; P<0.001) at 180 days after randomization. The number of events for the primary cardiovascular end point between the omeprazole and placebo groups showed no difference between arms but was not statistically significant (4.9 percent vs. 5.7 percent, respectively; HR=0.99; 95 percent CI, 0.68 to 1.44; P=0.96). Stratification of study groups did not result in statistically significant data for interactions.

Authors of the study concluded that patients on concomitant dual-antiplatelet therapy with omeprazole showed significantly decreased rates of adverse gastrointestinal events compared to the placebo group. In addition, there was no clinically significant cardiovascular interaction between PPIs and clopidogrel.

Reviewer's Conclusion

Overall, the study design, clinical relevance, and endpoints were appropriate and useful; however, the results of the trial are inconclusive. The major limitation of this study was due to its premature termination. The data analysis ended with a maximum duration of 341 days with no details regarding the number of patients who remained in the trial for 341 days or the number of patients who discontinued the trial before the 341 days. The Kaplan Meier analysis censored a significant portion of the study population at 180 days after randomization; therefore, the statistically significant difference in primary outcomes may be due to chance. Safety CV outcomes were inconclusive because of a wide CI and high P-value. Furthermore, clopidogrel therapy ranges from 9-12 months for most CV indications. Data analysis of up to 6 months does not provide adequate long-term data. Results of long-term concomitant treatment are therefore unknown.

It was never stated how or whether or not the parties working on the data - including the academic steering committee, the academic principal investigator, or data collectors were blinded. If these parties were not blinded, then bias may result.

The dosing of aspirin was not controlled. Patients taking a lower dose of ASA could result in lower rates of bleeding compared to patients taking a higher dosed aspirin. The trial excluded patients who were taking clopidogrel and other thienopyridines for more than 21 days. This exclusion criterion is not representative of patients who take antiplatelet drug therapy on a regular basis. External validity may be limited.

The study showed that there is a clinically significant reduction in gastrointestinal bleeding with omeprazole compared to placebo. However, because of the diminished power, censoring, missing data, and threats to validity stated above, the reduction of gastrointestinal events may not be true. Moreover, the presence or absence of a CYP2C19 interaction between PPI's and clopidogrel was never definitively established. Further studies are necessary to establish both the effects of long-term therapy and a definitive cardiovascular effect from the interaction between PPI's and clopidogrel.

Overall Grade: U – No conclusive evidence for clinical practice

Reference

1. Deepak B, Cryer B, Contant C, et al. "Clopidogrel with or without Omeprazole in Coronary Artery Disease." *N Eng J Med* 363.20 (2011): 1909-1917

Delfini Comment

In one review of studies stopped early for benefit, most studies were of low quality and did not follow CONSORT guidelines.[1] Furthermore, in many trials stopped early, treatment effects appear to be inflated. Bassler et al[2] have pointed out the following problems in many studies stopped early for benefit:[2]

- A trial stopped early for benefit should usually be confirmed by subsequent studies because it may overestimate treatment effects. The reason for this is that, with early termination of trials, the reported difference in outcomes between groups is frequently due to chance.
- Even if the outcome difference is not due to chance and a stopping rule and independent monitoring group were utilized, the reported difference is likely to be exaggerated.

About the Author

Brian Chou is a 2014 PharmD Candidate at the University of Southern California School of Pharmacy. Guest Editors Michael E. Stuart, MD and Sheri A. Strite of Delfini Group are experts at systematic literature reviews. The chart template is adapted from "Delfini Group, LLC. Short Critical Appraisal Checklist: U."

References

1. Montori VM et al. Randomized trials stopped early for benefit: a systematic review. JAMA. 2005 Nov 2;294(17):2203-9. Review. PubMed PMID: 16264162.
2. Bassler D et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA. 2010 Mar 24;303(12):1180-7. PMID: 20332404