Project Title: **Gastrointestinal Safety of Antithrombotic Drug Regimens**

Grant Number: **5RO1HSO25402-04**

Principal Investigator: **Neena S. Abraham, MD**

Team Members:

Xiaoxi Yao, PhD

Nilay Shah, PhD

Peter Noseworthy, MD

Jeph Herrin, PhD

Jon Inselman, MSc

Project Period: 07/01/2017 – 04/30/2021; NCE 08/28/22

Grants Management Specialist: ANNA CAPONITI

Email: anna.caponiti@ahrq.hhs.gov Phone: (301) 427-1402 Fax: (301) 427-1341

Program Official: HAMID JALAL

Email: hamid.jalal@ahrq.hhs.gov Phone: (301) 427-1033

ABSTRACT

Background & Methods: Antithrombotic drugs (antiplatelet agents and oral anticoagulants) cause gastrointestinal bleeding (GIB). We quantified GIB risk in a large, geographically diverse cohort of elderly and nonelderly cardiac patients with atrial fibrillation, venous thromboembolism, or post-acute coronary syndrome using administrative data, studying heterogeneity of risks, and comparing machine learning (ML) methods for risk prediction.

Results: In all cardiovascular subgroups (under the age of 75), the GIB risk was similar (3.5%/year) if one agent was prescribed. Risk increased from 10%/year to 17.5%/year on combination therapy among patients ≥ 75 years, regardless of the cardiovascular indication. When compared with the HAS-BLED bleeding risk score, regularized Cox regression, random survival forest, and extreme gradient boosting demonstrated similar performance in identifying high-risk GIB patients. The HAS-BLED model had AUCs of 0.60 and 0.57 for predicting GIB at 6 and 12 months. The RegCox model performed the best, with AUCs of 0.67 at both 6 and 12 months; XGBoost was similar, with AUCs of 0.67 and 0.66, whereas RSF AUCs were 0.62 and 0.60. The most important variables in the RegCox model were prior GIB; having AF, IHD, and VTE combined; and using gastroprotective agents.

Conclusion: The risk of antithrombotic-related GIB is significant in elderly patients. We constructed a model with improved sensitivity and specificity using ML methods and demonstrated that the choice of method was not critical to the model performance. All

models were superior to the HAS-BLED model and could serve as the basis for a clinical risk assessment tool.

PURPOSE/STUDY OBJECTIVES

Aim 1: To determine how GIB risk (total-, upper- and lower-GIB risk) among patients post-acute coronary syndrome, with atrial fibrillation or venous thromboembolism, is influenced by different combinations of antithrombotic agents and medication use.

Aim 2: To quantify the incremental risk associated with advancing age, presence of renal and hepatic dysfunction, and multiple chronic conditions on GIB outcomes.

Aim 3: To derive and validate a highly sensitive algorithm for predicting antithrombotic-related GIB using machine learning activities.

SCOPE

Gastrointestinal bleeding (GIB) in cardiac patients is common, deadly, and on the rise due to an older population, antiplatelet and anticoagulant drugs used in combination, and the availability of new drugs with higher GIB risk than their predecessors. By 2040, 25 million Americans will be diagnosed with *at least* one cardiovascular condition requiring an antithrombotic agent such as aspirin (ASA), a non-ASA thienopyridine agent, or an anticoagulant for the prevention of cardioembolic events. Antithrombotic monotherapy is associated with a clinically significant risk of upper (165/100,000) and lower (27/100,000) gastrointestinal bleeding, contributing to >300,000 hospitalizations/year and a case-fatality rate of up to 10% at the cost of $2.5 billion/year. These are likely underestimates of the magnitude of risk, as antithrombotic drugs are increasingly prescribed in dual and triple combinations and as warfarin is being substituted for direct oral anticoagulants (DOACs); clinical impact has predominantly been limited to the assessment of upper gastrointestinal bleeding (upper GIB).

The real-world GIB risk of antithrombotic prescription regimens (ASA +/- thienopyridine antiplatelet agent, with or without warfarin or DOAC) remains poorly defined, and there are limited data regarding which cardiac patients are at the highest risk. Lack of data regarding the magnitude of GIB and limited knowledge of which patients are most at risk prevents accurate counseling regarding cardiac drug safety. To address these knowledge gaps, we proposed a series of interrelated aims using claims and electronic medical record data from a large, geographically diverse, national population of elderly and nonelderly adults. In this grant, we quantified risk, studied risk factors, and used machine learning techniques to derive and validate a clinical algorithm to predict at-risk

patients better. These data are necessary to advance our understanding of GIB in cardiac patients, facilitate risk-benefit consideration of treatment options, and challenge current clinical paradigms to predict the safety of prescribed antithrombotic regimens.

METHODS

In Aim #1, we examined GIB risk in a large, geographically diverse population of elderly and nonelderly privately insured individuals enrolled in Medicare Advantage in the United States. We quantified the risk of total-, lower- and upper-GIB in an incident cohort of patients prescribed an antiplatelet or an anticoagulant drug in dual and triple combinations by first identifying patients with overlapping drugs of interest defined as anticoagulant-antiplatelet [i.e., ACAP]; ASA-antiplatelet [i.e., ASAP]; and ASA-anticoagulant [i.e., ASAC] therapy and triple antithrombotic therapy strategies (anticoagulant-antiplatelet-ASA prescription). Drug combination subcohorts were stratified by cardiac conditions, including acute coronary syndrome, atrial fibrillation, or venous thromboembolism. Incidence rates (events/100 patient-years) and propensity-matched Cox proportional models (with 95% confidence intervals) estimated the outcome. For Aim #2, we used the sample to examine the heterogeneity of treatment effects related to age, multiple chronic comorbidities, and renal and hepatic dysfunction by specific regimens (ACAP, ASAP, ASAC, and TRIP). In Aim #3, we used machine learning techniques to derive and validate an antithrombotic-related GIB risk prediction algorithm that is generalizable and applicable in a diverse cardiac population.

For our science, assessing OTC ASA, NSAID, and gastroprotective agents was critical for accurately estimating GIB risk. We leveraged the electronic health record (EHR) data from Optum Labs Data Warehouse (OLDW) to enrich our dataset with estimates of these important pharmacological covariates. Estimates of OTC drug prevalence were obtained from the Natural Language Processing (NLP) information derived from the EHR, available from OLDW. We are experienced in obtaining this data using NLP and have used it in

other cardiac studies. OTC estimates were used to conduct multiple imputation methods to generate replicates of the original dataset, reflecting a 10%, 25%, and 50% misclassification. Estimates from models fit on different imputed datasets were combined using Robins' rule. We also examined underreporting of GIB risk in a one-way threshold sensitivity analysis of "worst-case scenarios."

RESULTS

A. In our manuscripts with *Clinical Gastroenterology and Hepatology,* we highlight the results of Aim 1 analysis and the age-related analysis proposed in Aim 2. A brief synopsis of these findings is presented below.

What is already known about this subject: Antithrombotic drugs (antiplatelets and anticoagulants) are prescribed to patients with atrial fibrillation, ischemic heart disease, and venous thromboembolism to prevent secondary cardiac events. Published studies tend to focus on a single cardiovascular risk group (i.e., nonvalvular atrial fibrillation patients) when studying drug safety. The safety of different antithrombotic strategies among patients with >1 indication for antithrombotic drugs is still unresolved, and prescribing clinicians tend to underestimate the risk of GI bleeding among this population.

What are the new findings: In this study, we comprehensively explore GI bleeding risk (i.e., safety) among patients with *more than one* cardiovascular condition in whom multiple drug strategies are efficacious. Among all cardiovascular subgroups (under the age of 75), the risk of bleeding was similar (3.5%/year) if only one agent was prescribed (i.e., monotherapy antiplatelet or anticoagulant). The risk of GI bleeds increases from 10%/year to 17.5%/year on combination therapy among patients ≥ 75 years, regardless of the cardiovascular indication for the drug.

How might our study impact clinical practice in the foreseeable future? By not limiting our investigation to one cardiovascular group, we successfully quantified the magnitude of risk of all commonly prescribed antithrombotic regimens among a broad

range of complex cardiovascular patients. This study quantifies the impact of going from single to combination therapy with higher risk estimates than previous studies examining only one at-risk patient population. It has been assumed previously that antiplatelets may be safer than anticoagulants among patients with moderate-to-high bleeding risk. Our study results demonstrate that these risks may be similar, and, in some individuals, the use of appropriately dosed anticoagulant monotherapy may be the most promising approach (i.e., in atrial fibrillation patients, with and without ischemic heart disease).

B. In our paper, published in JAMA Network Open, we compare the performance of three machine learning approaches for the prediction of gastrointestinal bleeding after initiation of antithrombotic drug therapy against the HAS-BLED risk score (hypertension, abnormal kidney and liver function, stroke, bleeding, labile international normalized ratio, older age, and drug or alcohol use).

What is already known about this subject: Physicians have long used prediction models to stratify patients according to their risk of adverse outcomes. Such risk stratification can promote better treatment decisions, more efficient monitoring, and implementation approaches to mitigate risk. One such outcome for which risk stratification is routinely used is related to the decision to prescribe cardiac patients antithrombotic medications (vitamin K antagonist and direct oral anticoagulants [DOACs]; thienopyridine antiplatelet agents). One of the key goals of this risk

stratification is to incorporate the risk of gastrointestinal bleeding (GIB) in the context of the treatment decision. Given the severity of this outcome and the widespread use of antithrombotics in this population, several risk models have been developed to predict bleeding, including the HAS-BLED, ATRIA, ORBIT, and HEMORR(2)HAGES models. HAS-BLED has demonstrated the best performance among these scores, with an AUC of 0.68 in a real-world population. However, the HAS-BLED score may not accurately reflect GIB risk in contemporary practice that has expanded to include DOACs and second-generation thienopyridine antiplatelet agents --- drugs often used in combination. The HAS-BLED model may also underestimate GIB in some patients, including older patients with multiple comorbidities, a group we have found to be at much higher risk of GIB in our published work related to this grant.

What are the new findings: The examined machine learning models (regularized Cox regression [RegCox], random survival forest [RSF], and extreme gradient boosting ([GBoost]) demonstrated similar performance in identifying high-risk GIB patients following prescription of antithrombotic agents. The HAS-BLED model had AUCs of 0.60 and 0.57 for predicting GIB at 6 and 12 months, respectively. The RegCox model performed the best, with AUCs of 0.67 at both 6 and 12 months; XGBoost was similar, with AUCs of 0.67 and 0.66, respectively, whereas respective RSF AUCs were 0.62 and 0.60. The most important variables in the RegCox model were prior GI bleed; having AF, IHD, and VTE combined; and using gastroprotective agents.

How might our study impact clinical practice in the foreseeable future? Although we could construct a model with improved sensitivity and specificity using machine learning methods, the choice of method was not critical to the model performance. The final models demonstrated improvement over the existing HAS-BLED model and could serve as the basis for a clinical risk assessment tool. A prospective evaluation of the RegCOX model compared with HAS-BLED may provide a better understanding of the clinical impact of improved performance.

C. In our manuscript in *Alimentary Pharmacology and Therapeutics,* we quantify the incremental GIB risk associated with clopidogrel or ticagrelor prescription versus prescription of ticagrelor following the percutaneous intervention.

What is already known about this subject: Following percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is used for up to 12 months to protect coronary arteries from re-stenosis. Traditionally, aspirin and a thienopyridine agent such as clopidogrel or prasugrel have been used during this period. However, combination antiplatelet therapy with these thienopyridine agents is associated with a high risk of GI bleeding (GIB). However, a new thienopyridine agent, ticagrelor, is now available; compared with clopidogrel and prasugrel, it lowers major adverse cardiac events in patients undergoing PCI for ACS with similar or possibly higher major bleeding events. The comparative GIB rates of these medications in real-world populations remain poorly understood.

What are the new findings: We performed a comparative safety analysis of these three thienopyridine agents, controlling for chronic comorbidities (as outlined in Aim 2), and found that ticagrelor was associated with a 25% and 24% relative reduction in GIB compared with clopidogrel and prasugrel, respectively. This is a new and novel finding.

How might our study impact clinical practice in the foreseeable future? In our analysis of national insurance and Medicare claims data of ACS patients following PCI, we discovered that ticagrelor was associated with a 25% relative risk reduction in GIB compared with clopidogrel or prasugrel. Prasugrel and clopidogrel had similar rates of GIB. Our data suggest that limiting ticagrelor due to bleeding concerns is not warranted.

D. In our abstract presented at the Annual Scientific Meeting of the American College of Gastroenterology, we quantified mortality following incident GIB among patients initiated on antithrombotic therapy to understand the mortality burden better.

What is already known about this subject: Although antithrombotic agents have been shown to decrease the risk of thromboembolism and major cardiac events, this benefit is tempered by the potential bleeding risk, suggesting the importance of major bleeding events in modulating overall mortality risk in this population. Patient- and medication-related risk factors for GIB have been identified in previous studies. However, the incidence of post-GIB mortality among cardiac patients and specific patient risk factors associated with increased mortality risk following incident GIB remains poorly described, especially in the post-DOAC era. We sought to address this knowledge gap by quantifying mortality following incident GIB in patients with atrial fibrillation (AFIB),

ischemic heart disease (IHD), and venous thromboembolism (VTE) on antithrombotic therapy, identifying risk factors predictive of post-GIB mortality.

What are the new findings: Among 24,044 patients (51.6% female, 62.7% White, mean age 72.9 [10.7] years), 4,605 (19.2%) died; 51.1% were prescribed anticoagulants, 43.7% were on antiplatelets, and 5.3% were on combination antithrombotic drugs at index GIB. Mortality was 6.5% (95% CI: 5.7%-6.5%) within 6 months and 8.8% (95% CI: 8.3%-9.2%) within 1 year of incident GIB. The groups at highest risk of mortality were patients ≥ 75 years (hazard ratio [HR] 3.0; 95% CI: 2.6-3.6) and those with a Charlson-Deyo score of 4+ (HR 3.5; 95% CI: 2.9-4.2).

How might our study impact clinical practice in the foreseeable future? The risk of early mortality following incident antithrombotic-related GIB is significant (8.8% in the first year following incident GIB) and more than a "nuisance side effect" of antithrombotic drug use. Advancing age and comorbidity burden are the most important risk factors associated with death following incident GIB among cardiac patients prescribed antithrombotic agents.

LIST OF PUBLICATIONS AND PRODUCTS

Publications

1. Telford JJ, Abraham NS. Management of Antiplatelet and Anticoagulant Agents before and after Polypectomy. Gastrointest Endosc Clin N Am. 2022 Apr;32(2):299-312. DOI: 10.1016/j.giec.2021.12.006. Review. PubMed PMID: 35361337; PubMed Central PMCID: PMC9169436.
2. Abraham NS, Huynh K. Ascending the Staircase of Periendoscopic Anticoagulant Knowledge. Clin Gastroenterol Hepatol. 2022 Mar;20(3):e357-e358. DOI: 10.1016/j.cgh.2021.01.034. Epub 2021 Jan 22. PubMed PMID: 33493700; PubMed Central PMCID: PMC8523091.
3. Herrin J, Abraham NS, Yao X, Noseworthy PA, Inselman J, Shah ND, Ngufor C. Comparative Effectiveness of Machine Learning Approaches for Predicting Gastrointestinal Bleeds in Patients Receiving Antithrombotic Treatment. JAMA Netw Open. 2021 May 3;4(5):e2110703. DOI: 10.1001/jamanetworkopen.2021.10703. PubMed PMID: 34019087; PubMed Central PMCID: PMC8140376.
4. Abraham NS, Yang EH, Noseworthy PA, Inselman J, Yao X, Herrin J, Sangaralingham LR, Ngufor C, Shah ND. Fewer gastrointestinal bleeds with ticagrelor and prasugrel compared with clopidogrel in patients with acute coronary syndrome following percutaneous coronary intervention. Aliment Pharmacol Ther. 2020 Aug;52(4):646-654. DOI: 10.1111/apt.15790. Epub 2020 Jul 13. PubMed PMID: 32657466; PubMed Central PMCID: PMC8183594.

5. Abraham NS. Antiplatelets, anticoagulants, and colonoscopic polypectomy. Gastrointest Endosc. 2020 Feb;91(2):257-265. DOI: 10.1016/j.gie.2019.09.033. Epub 2019 Oct 1. Review. PubMed PMID: 31585125; PubMed Central PMCID: PMC7386094.

6. Abraham NS, Noseworthy PA, Inselman J, Herrin J, Yao X, Sangaralingham LR, Cornish G, Ngufor C, Shah ND. Risk of Gastrointestinal Bleeding Increases With Combinations of Antithrombotic Agents and Patient Age. Clin Gastroenterol Hepatol. 2020 Feb;18(2):337-346.e19. DOI: 10.1016/j.cgh.2019.05.017. Epub 2019 May 18. PubMed PMID: 31108228; PubMed Central PMCID: PMC7386161.

Abstracts

Abraham NS, Inselman J, Yao X, Noseworthy PA, Herrin J, Ngufor C, Shah ND. Mortality and Associated Risk Factors After Antithrombotic-Related Gastrointestinal Bleeding. Am J Gastroenterol. 2021; 116:S305.