Anticoagulation with Enhanced Gastrointestinal Safety (AEGIS): A pragmatic randomized trial to evaluate clinician outreach to reduce upper gastrointestinal bleeding risk in patients taking warfarin and antiplatelet therapy

Protocol Number: 1.0
National Clinical Trial (NCT) Identified Number: TBD
Principal Investigator: Jacob E. Kurlander, MD, MS
Sponsor: NIDDK
Grant Title: Using Intervention Mapping and the Multiphase Optimization Strategy to Develop Multilevel Interventions to Prevent Upper GI Bleeding
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AMENDMENTS

Date	Version	Section(s)	Changes
8/4/2022	V.1.1	1.1 1.2 1.3 2.2 4 7.3 8.1 8.2 8.3 9.1 9.2 9.3 11.5	Updated trial timeline to reflect that CNNF follow-up will be delivered to non-responders 2 weeks rather than 4 weeks after delivery of the initial CNNF notification, and patient calls will thus be moved up from week 9-10 to week 7-8 to ensure patient recall of medication use will not be impacted due to too much time passing between delivery of the CNNF strategy and the phone assessment. The amendment also clarifies that CNNF will be delivered to up to 4 patients each week per anticoagulation nurse. While the total number of participants will not change, this may result in the randomized trial lasting for more than the originally stated 25 weeks.
10/27/2022	V.1.2	1.1 1.2 1.3 2.2 4 5.4 7.2 7.3 8.1 8.2 8.3 9.2 9.3 11.5	Updated trial timeline to reflect extension of timing for chart review and patient phone assessments from week 7-8 to week 7-9.
11/30/2022	V.1.3	1.1 1.2 1.3 2.2 4 5.4 7.2 7.3 8.1 8.2 8.3	Updated trial timeline to reflect extension of timing for chart review and patient phone assessments from week 7-9 to week 7-10.

		9.2 9.3 11.5	
12/13/2022	V.1.4	7.3	Updated protocol to reflect that while we will attempt to have blinded research staff conduct all patient phone calls, unblinded staff will assist with calls if necessary to complete all assessments within the specified time window of week 7-10 of study participation.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with research best practices, applicable United States Code of Federal Regulation, and the terms and conditions of the sponsor. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All research personnel involved in the conduct of this study have completed Human Subjects Protection and research best practices training.

1 PROTOCOL SUMMARY

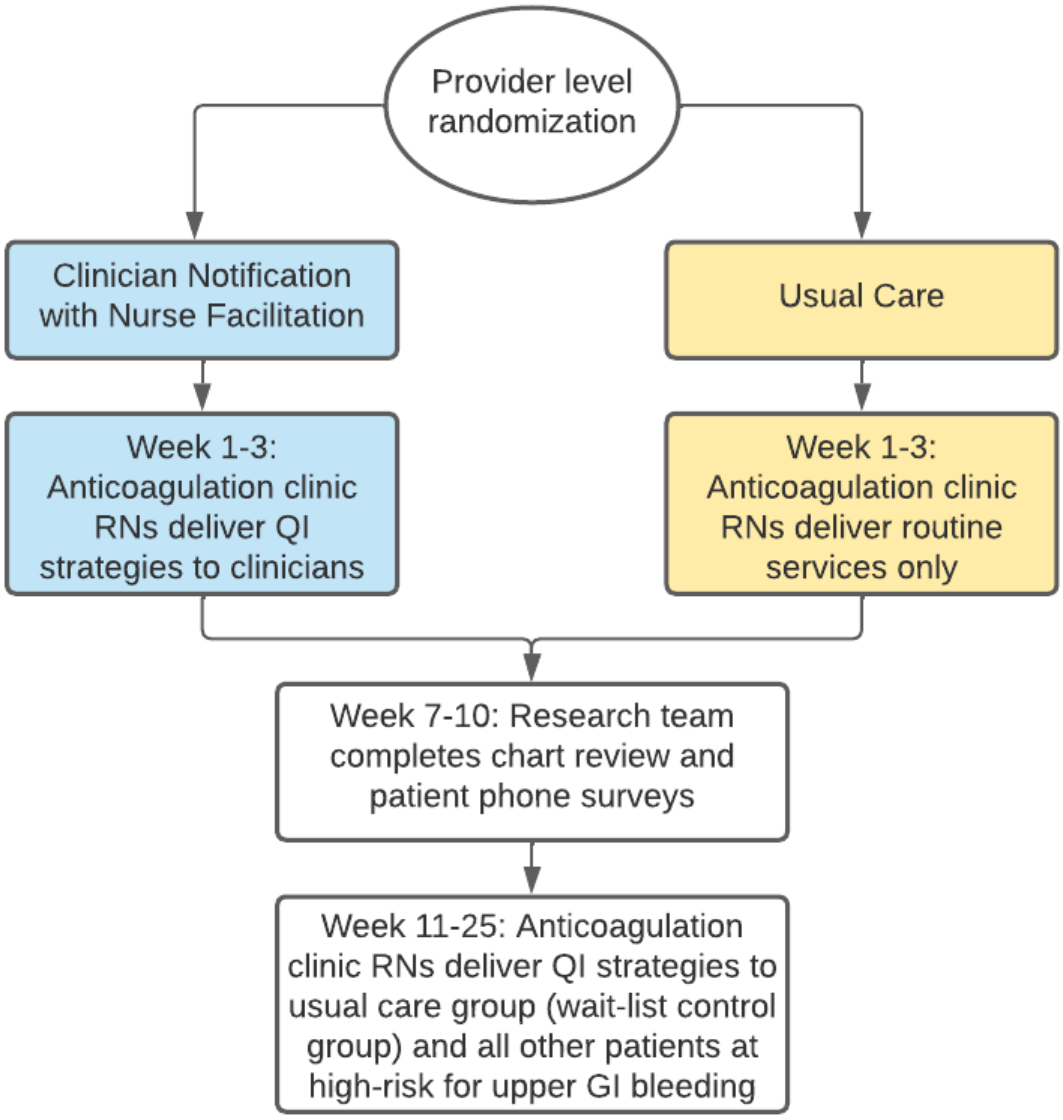
1.1 Synopsis

Title:	Anticoagulation with Enhanced Gastrointestinal Safety (AEGIS): A pragmatic randomized trial to evaluate clinician outreach to reduce upper gastrointestinal bleeding risk in patients taking warfarin and antiplatelet therapy
Grant Number:	K23 DK118179
Background	Patients who use an anticoagulant together with an antiplatelet drug (anticoagulant-antiplatelet therapy or AAT) are at increased risk for serious bleeding, which most commonly occurs in the gastrointestinal tract. For patients on AAT, there are two evidence-based medication optimization strategies to reduce upper gastrointestinal (GI) bleeding risk. Many of these patients may safely discontinue the antiplatelet drug. For patients who must continue the antiplatelet drug, proton pump inhibitors (PPIs) effectively reduce upper GI bleeding risk. Both strategies are underused. The aim of this trial is to evaluate the effectiveness of a novel clinician-facing quality improvement implementation strategy to optimize the use of antiplatelet therapy and PPI gastroprotection for patients who use warfarin and are followed by the Michigan Medicine anticoagulation monitoring service, as part of a quality improvement initiative.
Study Population:	Clinicians will be eligible for receipt of the implementation strategy if they care for patients who are enrolled with the anticoagulation monitoring service. Patients will be eligible for inclusion if they are prescribed warfarin and an antiplatelet drug without a PPI and are enrolled in the Michigan Medicine anticoagulation monitoring service. See section 6.1 for additional inclusion and exclusion criteria. We anticipate including 220 patients and 110 clinicians.

Study Description:	The study is designed as a pragmatic cluster randomized quality improvement trial. For each patient, a target clinician will be identified, defined as either a cardiologist at Michigan Medicine, if the patient has seen one in the past year, or else the patient's primary care provider if within Michigan Medicine, or else the clinician of record on file with the anticoagulation service. For each patient, assignment to receipt of the quality improvement strategy vs. usual care will be done at the cluster level according to the identity of the target clinician. Each clinician (cluster) will be randomized 1:1 to receive either clinician notification with nurse facilitation (CNNF), consisting of a notification message sent in the electronic health record, or to a usual care arm. Each clinician cluster will be limited to 4 or fewer patients. Following delivery of the quality improvement (QI) strategy to clinicians in the CNNF arm, the study team will conduct phone surveys with all patients whose clinicians received usual care or CNNF and perform chart review in the medical record to evaluate the effect of CNNF on reducing upper GI bleeding risk through discontinuation of all antiplatelet drugs or initiation of PPI co-therapy. **Primary Objective:** To determine the extent to which clinician notification with nurse facilitation (CNNF) versus usual care is associated with differences in the proportion of patients who have medication optimization (defined as either discontinuation of all antiplatelet drugs or initiation and adherence to a PPI) at week 7-10. **Secondary Objectives:** To determine the extent to which CNNF (vs usual care) is associated with differences in the proportion of patients who are recommended to have medication optimization based on chart review after 6 weeks.
Endpoints*:	**Primary Endpoint**: The proportion of patients who self-report either discontinuing all antiplatelet therapy (defined as none in the past 7 days) or initiation and adherence to a proton pump inhibitor (defined as use for at least 5 of the prior 7 days) at week 7-10. **Secondary Endpoints:** • The proportion of patients with a documented recommendation in the electronic health record to either discontinue all antiplatelet therapy or initiate a PPI
Phase or Stage:	Randomized quality improvement project with a wait-list control group

Description of Sites/Facilities Enrolling Participants:	Participants will be included from a single site (the Michigan Medicine anticoagulation monitoring service in Ann Arbor, Michigan, USA).
Description of Study Intervention/Experimental Manipulation:	1. **Clinician Notification with Nurse Facilitation:** A protocol-driven QI strategy in which an anticoagulation clinic nurse sends a templated message to the patient's target clinician that identifies the patient as high risk for upper GI bleeding and summarizes options for medication optimization. In addition, once clinicians decide on a medication optimization plan, the nurse will facilitate execution of the plan and communicate recommendations to the patient. 2. **Usual Care:** No additional education or clinical assistance outside of routine anticoagulation monitoring service care will be included.
Assessments	The only live patient assessment will be a phone survey at week 7-10. Endpoints will also be assessed by chart review.
Human subject's protection:	A waiver of informed consent will be sought for delivery of the clinician notifications, as well as for the patient phone survey, since they constitute minimal risk, the waiver will not adversely affect the rights or welfare of participants, and the research could not practically be carried out otherwise.
Study Duration:	~25 weeks
Participant Duration:	10 weeks

1.2 Schema



1.3 Schedule of Activities

It is anticipated that 110 clinicians will be included in the study, and 220 patients who are cared for by those clinicians. QI strategies will be delivered to clinicians of eligible patients by

anticoagulation clinic nursing staff. Up to 50-56 patients will enter the study each week for 5 weeks (or longer if fewer patients enter each week).

For informational purposes, whether the evaluation vs. the anticoagulation clinic staff performs the activity is indicated in bold. Failure of the anticoagulation clinic staff to follow the clinical protocols for delivery of the clinician- level QI strategies will not be considered study deviations.

Schedule of Activities

Activity	Screening and randomization	Week 1	Week 2-5	Week 7-10	Week 11-25
Eligibility determination of clinicians and patients **(research team)**	X				
Cluster randomization of patients to CNNF vs. usual care **(research team)**	X				
Clinician delivery of CNNF for patients randomized to receive it **(anticoagulation clinic staff)**		X	X		
Additional outreach, communication, or facilitation steps for patients and clinicians as per anticoagulation clinic protocol for CNNF recipients **(anticoagulation clinic staff)**		X	X		
Patient phone survey, with waiver of informed consent **(research team)**				X	
Chart review to ascertain exploratory outcomes **(research team)**	X	X		X	X

2 INTRODUCTION

2.1 Study Rationale & Background

Increasing numbers of patients in the United States are prescribed oral anticoagulants to treat or prevent a range of thromboembolic conditions [1]. The main risk with anticoagulants is major bleeding, most commonly from the gastrointestinal tract [2,3]. Many patients prescribed anticoagulants are co-prescribed an antiplatelet drug (aspirin or a thienopyridine), and these patients are at particularly high risk for major bleeding. In an observational study of patients prescribed warfarin, use of an antiplatelet drug increased the risk of major bleeding (5.7% vs. 3.3%), emergency department visits for bleeding (13.3% vs. 9.8%), and hospitalizations for bleeding (8.1% vs. 4.1%), but did not reduce the rate of thrombosis [4].

Medication optimization can substantially reduce bleeding risk for patients prescribed anticoagulant-antiplatelet therapy (AAT). One evidence-based practice is to discontinue antiplatelet therapy in patients for whom it is inappropriate. Based on recent clinical trial data, the indications for AAT are increasingly narrow, and most patients prescribed anticoagulants should only use antiplatelet drugs for a limited time after acute coronary syndrome, coronary stenting, or other vascular procedures [5]. A second evidence-based practice is the use of a proton pump inhibitor (PPI gastroprotection) for patients in whom AAT is truly indicated, a strategy recommended by professional guidelines [5,6]. A meta-analysis showed PPIs reduce the risk of UGIB by up to 79% in patients using aspirin or non-steroidal anti-inflammatory drugs [7]. Both of these evidence-based practices are underused [8]. In an observational study of six anticoagulation clinics, 45% of patients prescribed warfarin were co-prescribed an antiplatelet drug. Of these, 44% had no identifiable indication for antiplatelet therapy, and 36% were appropriately prescribed AAT but without a PPI [8].

There are multiple barriers to use of these evidence-based practices. Clinicians may lack knowledge of appropriate use of medication optimization strategies, have inadequate time or prioritization, or lack “ownership,” since many patients are co-managed by a PCP and a subspecialist (typically a cardiologist) [9]. In many cases, a clinician may be prepared to assess use of one of the evidence-based practices but not the other, which may lead to suboptimal care. Clinicians may also have concerns about provoking a cardiovascular event when deprescribing antiplatelet drugs, and about possible PPI adverse effects when initiating a PPI [10].

There is a critical need for implementation strategies to improve medication optimization for upper GI bleeding risk reduction in patients prescribed AAT. Importantly, to ensure the most appropriate care, any implementation strategy should simultaneously address both evidence-based practices, determining first the appropriateness of antiplatelet therapy, then of PPI gastroprotection. Previous one- or two- component clinician-facing interventions aimed at improving use of PPI gastroprotection (including decision support tools, electronic alerts, audit and feedback, and clinician education) have had limited success [11–13]. Several European studies that have tested multi-component interventions involving professional education, incentive payments, clinician feedback, and pharmacist support have effectively reduced the proportion of high-risk patients without gastroprotection (odds ratios 0.55-0.72) [14–16]. However, such

multicomponent strategies are resource intensive and challenging to implement in the fragmented US healthcare system.

As part of a quality improvement program through the Michigan Medicine anticoagulation service, a novel clinician-facing strategy has been identified to improve the safety of patients using AAT: clinician notification by electronic health record (EHR) message including a multi-faceted nurse facilitated process. The anticoagulation clinic has recently completed a pilot feasibility study that confirmed that delivery of the implementation strategy was feasible, that the strategy was acceptable to clinicians and patients, and that completing the necessary steps for the project did not impair the anticoagulation clinic nurses ability to perform other duties. In the pilot study, feedback was elicited from patient, clinician, and nursing staff participants through qualitative semi-structured phone questionnaires. The data from these interviews were used to optimize the implementation strategy and methodology described in this protocol. This protocol describes a randomized evaluation of a quality improvement initiative to determine the effectiveness of this novel clinician-facing approach to improve medication optimization.

2.2 Objectives

Primary Objective: To determine the extent to which clinician notification with nurse facilitation (CNNF) versus usual care is associated with differences in the proportion of patients who have medication optimization (defined as either discontinuation of all antiplatelet drugs or initiation and adherence to a PPI based on self-report) at week 7-10.

Secondary Objectives: To determine the extent to which CNNF (vs usual care) is associated with differences in the proportion of patients who are recommended to have medication optimization based on chart review after 6 weeks.

3 RISK/BENEFIT ASSESSMENT

3.1 Known Potential Risks to Patients

No novel therapeutic medications or devices are being tested in this study and participants are not required to discontinue an antiplatelet agent, initiate a PPI, or make any other medication changes as part of study participation. The risks and benefits discussed here relate to the implementation strategy and assessments of the implementation strategy, but not any possible medication changes undertaken by their clinicians, which are done as part of usual clinical care.

1. **Inconvenience.** Participants may feel inconvenienced by the attempts to reach them, or the time it takes to engage in study phone surveys.
2. **Breach of Data Confidentiality.** It is possible that the identity of the participant or protected health information (PHI) could be unintentionally revealed to persons outside of the research team. As this study does not deal with sensitive or stigmatized behavior

(i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.

3.2 Known Potential Risks to Clinicians

1. **Potential Psychological Discomfort due to Subject Content.** The clinician messages will deal with the topic of clinical care practices, including opportunities for clinical care improvement. This could cause clinicians to be upset or concerned. All efforts will be made to discuss these topics in a considerate manner.
2. **Inconvenience.** Clinician participants may feel inconvenienced by the attempts to reach them or the time it takes to engage with communications from anticoagulation clinic staff.
3. **Breach of Data Confidentiality.** It is possible that the identity of the participant could be unintentionally revealed to persons outside of the research team. However, no PHI will be sought from clinicians. As this study does not deal with sensitive or stigmatized behavior (i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.

3.3 Assessment of Potential Risks and Benefits

The risks to patients and clinicians are all minimal and justified by the value of the potential benefits and knowledge gained. Risks of confidentiality breach will be mitigated by separation of personal identifiers (enrollment forms) from data source documents. All data source documents and any personally identifying information for trial participants will be stored on a secure drive or in a locked file cabinet and will be accessible only to the study team.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To determine the extent to which clinician notification with nurse facilitation (CNNF) versus usual care is associated with differences in the proportion of patients who have medication optimization (defined as either discontinuation of all antiplatelet drugs or initiation and adherence to a PPI based on self-report) at week 7-10.	The proportion of patients who self-report either discontinuing all antiplatelet therapy (defined as none in the past 7 days) or initiating and adhering to a proton pump inhibitor (defined as use for at least 5 of the prior 7 days) at week 7-10.
Secondary	

To determine the extent to which CNNF (vs usual care) is associated with differences in the proportion of patients who are recommended to have medication optimization based on chart review after 6 weeks.	The proportion of patients with a documented recommendation in the electronic health record to either discontinue all antiplatelet therapy or initiate a PPI
Exploratory	
To determine how often the anticoagulation clinic nurse communicated the recommendation to either discontinue all antiplatelet therapy or start a PPI for patients who were randomized to receive CNNF.	The proportion of patients for whom an anticoagulation clinic RN documented communicating a recommendation to the patient to either discontinue all antiplatelet therapy or start a PPI based on chart review.
To determine how often the anticoagulation clinic nurse pended an order for a PPI for patients randomized to CNNF and recommended by their clinician to initiate PPI.	The proportion of patients for whom an anticoagulation clinic RN pended an order for a PPI among patients randomized to CNNF and recommended by their clinician to initiate PPI.
To explore why patients recommended to either discontinue an antiplatelet drug or initiate a PPI may choose not to make the medication change.	The reasons why patients who received a recommendation to make a medication change chose not to adhere to the recommendation according to patient self-report at week 7-10 (qualitative).
To explore the accuracy of the electronic health record's medication list for PPIs and antiplatelet drugs at baseline.	The proportion of patients who, retrospectively, report that they had been using antiplatelet therapy at baseline during the patient phone survey at week 7-10. The proportion of randomized patients who, retrospectively, report that they had been using PPI at baseline during the patient phone survey at week 7-10.
To explore the accuracy of the electronic health record's medication list for PPIs and antiplatelet drugs at week 7-10.	The accuracy of the EHR medication list at week 7-10 for antiplatelet drugs compared to self-report. The accuracy of the EHR medication list at week 7-10 for proton pump inhibitors compared to self-report.
To explore the appropriateness of antiplatelet therapy used by patients at the time of study entry.	The clinical appropriateness of baseline antiplatelet therapy as determined by a physician reviewing the medical record. Antiplatelet appropriateness will be categorized as probably guideline concordant, probably not guideline concordant, or uncertain in reference to

	practice recommendations (Appendix 1). Baseline antiplatelet therapy will be ascertained by self-report at week 7-10.
To explore the extent to which CNNF (vs. usual care) is associated with the appropriateness of antiplatelet therapy at week 7-10.	The clinical appropriateness of antiplatelet therapy at week 7-10 (relative to appropriateness assessment at the time of study entry, as determined by a physician reviewing the medical record). Antiplatelet appropriateness will be categorized as probably guideline concordant, probably not guideline concordant, or uncertain in reference to practice recommendations (Appendix 1). Antiplatelet therapy at week 7-10 will be determined by patient self-report. We will also evaluate this endpoint for the subset of patients who were recommended to make a medication change.
To explore fidelity to the CNNF vs. usual care	Fidelity to CNNF will be determined by performing a chart review on patients whose clinicians received the CNNF strategy, to confirm that it was delivered as intended. We will also perform chart review for patients randomized to usual care to ensure that they did not receive CNNF.
To explore patient and clinician factor associated with successful medication optimization.	Regression analysis will be used to identify patient and clinician factors associated with successful medication optimization.
To determine the extent to which CNNF (vs usual care) is associated with differences in the proportion of patients who exhibit PPI adherence, based on self-report, at week 7-10 among patients recommended to start a PPI.	Among patients recommended by a clinician to initiate a PPI (based on chart review at week 7-10), the proportion of days out of the prior 7 when a PPI was taken based on self-report

5 STUDY DESIGN

5.1 Overall Design

This is a pragmatic, single center randomized quality improvement trial to evaluate a clinician-facing implementation strategy to increase the use of evidence-based practices (EBPs) to reduce bleeding in patients who are using anticoagulant-antiplatelet therapy (AAT) and who are managed by the Michigan Medicine anticoagulation monitoring service. A clinician-level strategy will be evaluated and compared to usual care: clinician notification with nurse facilitation (CNNF) consists of an EHR message that identifies the patient as high-risk for upper GI bleeding and

suggests either discontinuing the antiplatelet agent or initiating a PPI and in which a nurse undertakes multiple steps to overcome barriers to medication optimization. Clinicians will be cluster randomized, such that up to 4 patients cared for by each clinician will receive the same clinician-level notification.

5.2 Scientific Rationale for Study Design

The current study is a quality improvement trial that will evaluate the effectiveness of a novel quality improvement strategy to reduce the risk of upper GI bleeding in patients using AAT.

Clinician notification is commonly used by the anticoagulation service as part of routine clinic practice to improve the safety of patients using warfarin. For example, the anticoagulation clinic previously undertook a quality improvement project that consisted of notifications to clinicians about the potential benefits of discontinuing aspirin in certain patients. However, even though these clinician-facing strategies are considered standard practices, it remains important for the clinic to understand the extent to which such strategies are effective, and whether they justify the significant resource investment of the anticoagulation clinic staff. This study will help to answer that question in the context of medication optimization to reduce upper GI bleeding.

The anticoagulation clinic eventually plans to use CNNF with all eligible patients. However, because deployment of CNNF requires additional effort by the nursing staff, only a limited number of patients (n=28) can be delivered CNNF each week. Therefore, we will use a “wait-listed design,” in which each week patients will be randomized to either have their clinicians receive CNNF or be included in wait-list control group. The patients in the wait list control group will serve as comparators to the patients who received CNNF, allowing for valid causal inference about the effect of CNNF compared to usual care. This design is often used to evaluate the effectiveness of interventions that are planned for a wider rollout because they are considered fair by patients in the setting of limited capacity to rollout the intervention all at once. At the completion of the study, the patients who were randomized to the wait-list control group will receive the quality improvement strategy.

5.3 Justification for Intervention

Upper GI bleeding is a serious risk to patients who use AAT. However, both medication optimization EBPs to reduce upper GI bleeding risk are underused.

This trial will rigorously evaluate a clinician outreach approach that is commonly used by the anticoagulation service to improve the safe use of warfarin.

5.4 End-of-Study Definition

Patients are considered to have completed the study after week 25.

Clinicians are considered to have completed the study 10 weeks after trial entry of the last patient within the clinicians' cluster.

6 STUDY POPULATION

6.1 Sample size

The target sample size for the study is 220 patients cared for by 110 target clinicians. See sample size determination (below) for a justification of the size.

6.2 Inclusion Criteria

For patients:

- Enrollment with the Michigan Medicine anticoagulation monitoring service
- Currently prescribed warfarin with anticipated use for ≥90 days on day 1 of trial enrollment, according to the MiChart documentation.
- Currently prescribed an antiplatelet drug (aspirin, clopidogrel, ticagrelor, or prasugrel) according to the MiChart medication list

For clinicians:

- Cardiologists at Michigan Medicine who in the prior year had a face-to-face or virtual visit with a patient who meets eligibility criteria
- Michigan Medicine primary care providers for patients who meet eligibility criteria
- Clinicians in any specialty who are designated as the clinician of record with the anticoagulation clinic for a patient who meets eligibility criteria

6.3 Exclusion Criteria

For patients:

- Age less than 18
- Currently prescribed a PPI
- Documented intolerance or allergy to PPI use
- Left ventricular assist device
- Heart transplant
- Participation in a previous pilot study of these QI strategies

For clinicians:

- Cardiologists specializing in electrophysiology or saw the patient for a clinic visit related to a TAVI procedure unless they are the clinician of record for a patient followed by the anticoagulation service who does not have a Michigan Medicine PCP.
- Participation in a previous pilot study of these QI strategies

6.4 Patient and Clinician Selection

Since this evaluation is part of a quality improvement initiative, we will include 220 patients who may benefit from medication optimization. These patients will be identified using a report developed in the EHR. The same report will identify the "target clinician" for each eligible patient. A patient's target clinician is defined as, in order of descending priority, either a (non-electrophysiologist) Michigan Medicine cardiologist (excluding TAVI visits) who has seen the patient in the prior year (if one exists), or else a Michigan Medicine PCP for the patient, or else the patient's clinician of record for the anticoagulation monitoring service.

All target clinicians will be randomized to receive CNNF or usual care. Eligibility will be determined based on information in the electronic health record. All participants will be screened for eligibility in the week prior to study entry.

6.5 Screen Failures

Patients who are ineligible for the study at the time of screening will not be included.

6.6 Strategies for Recruitment and Retention

This trial will be conducted as a pragmatic quality improvement initiative in partnership with the Michigan Medicine anticoagulation monitoring service. There will therefore not be a formal recruitment process. No strategies will be used for participant retention.

7 STUDY IMPLEMENTATION STRATEGIES

7.1 Quality Improvement Strategy Descriptions

The clinician notification process has been formalized as a clinical protocol approved by the anticoagulation clinic to address upper GI bleeding risk. As part of routine care, the QI strategy will be delivered by the anticoagulation nurses assigned to each of 7 anticoagulation clinic teams.

Clinician Notification (CNNF): An anticoagulation clinic nurse sends a templated message to the patient's target clinician that identifies the patient as high risk for upper GI bleeding, summarizes guidelines on appropriate antiplatelet drug use and PPI gastroprotection, and recommends that the clinician consider either discontinuing the patient's antiplatelet drug or initiating a PPI for gastroprotection. The nurse will also offer to pend the order for a PPI if the clinician wants to initiate a PPI and will provide education to the patient on any medication changes recommended by the clinician.

Usual care: With usual care, the anticoagulation clinic will not send the clinician notification letter or other project-specific materials to the clinician or patient.

7.2 Fidelity

7.2.1 Anticoagulation Nurse Training

Prior to commencing the quality improvement initiative, the anticoagulation clinic staff will attend an instructional meeting with a research team member on how and when to administer the QI strategy components and how to document delivery of strategies in the EHR. This training is anticipated to be 60 minutes long.

For anticoagulation clinic staff, the implementation strategies and how to perform them are additionally described in anticoagulation clinic protocol documents.

During week 1 of the trial, the research team will audit the charts of all patients randomized to CNNF and meet with the anticoagulation nurses to provide feedback if there were any discrepancies in delivery of the intervention. A similar meeting will recur in later weeks if discrepancies continue.

Fidelity will be assessed during the week 7-10 chart review for all patients to ensure that they received the QI strategy to which they were randomized.

7.2.2 Quality Improvement Strategy Delivery

Anticoagulation clinic nurses will have templated written materials to use as part of CNNF.

Nurses will also have an example script available to use when talking with patients about medication changes if the clinician requests that the nurse provide patient education.

7.2.3 Quality Improvement Strategy Receipt & Enactment

Chart review will be performed for patients whose clinicians were randomized to the clinician notification (CNNF) arm to ensure that the implementation strategy was delivered as intended and that the strategies had fidelity. A fidelity checklist will be used.

7.3 Measures to Minimize Bias: Randomization and Blinding

Assignment of clinicians to CNNF vs. usual care will be done at the cluster level according to the identity of the clinician to be contacted. Clinicians will be stratified by treating small vs. large numbers of patients eligible for the trial, and by procedural vs. non-procedural specialist. The cluster of patients cared for by each anticoagulation clinic target clinician will be randomized 1:1 to get either clinician notification with nurse facilitation (CNNF) or usual care. Randomization will be carried out by the study statistician. For each included clinician, up to 4 patients will be included in their cluster (see section 11.1 for justification). For clinicians with more than 4 eligible patients in their cluster, 4 patients will be selected at random.

Neither patients, clinicians, or anticoagulation staff can practically be blinded. We will attempt to blind the research staff who are making patient calls at week 7-10 to the randomization group of the patient by not providing them with any information that would allow them to infer the randomization group, by not having them enter MiChart for the patients, where such information could be obtained, and by excluding any information from the call script that might help identify the randomization group. However, if due to staffing or personnel issues, blinded research staff are unable to complete all calls within the specified time frame, unblinded research staff will assist with completing patient calls.

7.4 Concomitant Therapy

Patients in this study will continue to receive all other usual care through the anticoagulation clinic. They will not be prevented from seeking or being exposed to any other medications or information from other sources during the study period or from seeking care from other clinicians.

7.5 Rescue Therapy

N/A

8 END-OF-INTERVENTION/END-OF-STUDY

8.1 Discontinuation of Intervention

The QI strategies will not be delivered to patients who discontinue warfarin therapy or are closed to the anticoagulation monitoring service between the time of randomization and the

anticipated date of QI strategy delivery. Patients who discontinue warfarin therapy or are closed to the anticoagulation monitoring service after QI strategy delivery but before week 7-10 will not be assessed by phone at week 7-10, though chart review will still be completed for these patients. The QI strategies will additionally not be delivered to patients whose target clinician on the report changes between the time of randomization and the anticipated date of QI strategy delivery. However, patients whose target clinician changes after QI strategy delivery but before week 7-10 will still be assessed at week 7-10.

8.2 Participant Discontinuation/Withdrawal from the Study

Patients who wish not to participate in the phone survey at week 7-10 will have the phone survey discontinued.

8.3 Lost to Follow-Up

For patients unable to be reached for the phone survey at week 7-10, chart review will still be performed.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Eligibility Assessment

All eligible patients will be identified using a MiChart workbench report prior to the start of the study. Eligibility will be assessed based on information in the EHR. Each week, it is anticipated that 42 patients will be randomized to receive either CNNF or usual care, and that 21 will have CNNF directed at their target clinicians. Each anticoagulation nurses will deliver CNNF to up to 4 patients each week but may deliver CNNF to fewer some weeks depending on staffing. At the start of each week, eligibility will be re-assessed for patients anticipated to receive the QI strategy in the coming week.

Similarly, clinician eligibility will be determined at the start of the trial and at the beginning of each week to ensure that only actively practicing Michigan Medicine clinicians are included.

9.2 Assessment of the Primary Endpoint

The primary endpoint, defined as the proportion of patients for whom medication optimization was achieved (defined as either discontinuation of all antiplatelet therapy or initiation and

adherence to a proton pump inhibitor) will be determined by patient reported medication use at week 7-10. Up to three attempts will be made to contact patients by phone over the course of 4 weeks to assess the primary endpoint. The phone call is anticipated to take not more than 5 minutes. With calls 1 and 3, a brief message will be left stating the research assistant's name and affiliation with the anticoagulation clinic and asking the patient to call back at their earliest convenience. A script has been developed to guide the phone survey. If the patient self-reports any use or non-use of medications that contradicts the information in their MiChart medication list, the research assistant will send a message to the patient's anticoagulation clinic nurse so that the nurse can reconcile the chart. No remuneration will be offered with this patient assessment. We request a waiver of informed consent for this patient phone survey.

There will be no assessments that require physical exams, radiology, biological specimens or laboratory evaluations.

9.3 Assessment of the Secondary and Exploratory Endpoints

The secondary and exploratory endpoints outlined in section 4 of this protocol document will be determined based on chart review, as well as patient self-reported data from the week 7-10 phone survey.

10 ADVERSE EVENTS

Since this trial constitutes a quality improvement trial intended to improve the use of evidence-based practices to reduce bleeding in patients using AAT, and since all decisions regarding changes in drug treatment will be made by patients' own clinicians as part of usual care, the study will not proactively monitor for adverse events. No experimental drug is being investigated. However, any adverse events that are identified will be logged in an adverse event database.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

The study is powered to have 90% power to identify a difference between usual care and CNNF with a two-sided 5% type I error. We estimate that the rate of medication optimization will be 5% with usual care and 35% with CNNF. In the pilot study, we observed substantial variation at the clinician-level in whether clinicians responded to the notification messages at all. In our sample size estimates, we therefore assumed a high-level of correlation in the outcome for patients within clinician clusters (ICC=0.95). While our clinician population includes providers with 1-32 patients, if a clinician is selected to participate who has more than 4 patients (27/156), we will

randomly select 4 of their patients to participate in order to avoid overwhelming some clinicians with a large number of notifications in a short period of time. Therefore, capping the 27 providers who have more than 4 participants, there is a coefficient of variation=0.62 (calculated using preliminary data) of the number of patients per provider and an average of 2 participants per clinician. For 90% power to detect the 30% difference between interventions, we require 44 clinicians/arm and 176 total patient participants. We will assume a 20% dropout or ineligibility rate, so we plan to increase the N (176/0.8). This results in a final N of 220, equating to 110 participants and 55 clinicians per arm.

11.2 General Statistical Approach

For the primary and secondary endpoints, an intention-to-treat analysis approach will be used.

11.3 Descriptives

We will calculate descriptive statistics (means, standard deviations, range and proportions) for all patient variables for the sample in total, by main effect (CNNF vs usual care) with and without controlling for clinician.

11.4 Hypotheses

For the primary endpoint, we hypothesize that the CNNF compared to usual care will be associated with a higher probability of medication optimization.

11.5 Analysis of the Primary Endpoint(s)

We will use generalized linear mixed effects modeling (logit link) to estimate the odds of medication optimization at week 7-10. This model will include fixed effects for CNNF (vs. usual care), target provider specialty and size, and a random effect for clinician to account for the clustering of patients. We will report the odds ratios with corresponding confidence intervals for the main effect. The main effect will be tested at a two-sided 5% significance level. Sensitivity analyses will adjust for patient age, gender, comorbidities, antiplatelet drug at study entry, and clustering at the nurse level.

For patients who were unable to be contacted by phone for the week 7-10 phone call (lost to follow up), or who declined to participate, we will perform exploratory analyses to determine whether they differed (with respect to demographic characteristics, medical history, or target clinician specialty) from patients who were able to be reached. We will use multiple imputation to account for any missing data for the patients lost to follow up considering all demographic, medical history and target clinician specialty variables considering the data missing at random and combine results across imputation via Rubin’s rules. Best and worst case sensitivity

analyses will assess the robustness of the findings and provide the range of uncertainty of conclusions made. For patients who call back the research team after week 10, the survey will still be completed, but their outcome will be considered missing and imputed in primary analysis with a sensitivity analysis using the week 10 outcome.

Patients who reported at the week 7-10 phone call that they were either not using antiplatelet therapy at the start of the trial or were using a PPI will be included in the primary ITT analysis. We expect those who were not initially eligible to be balanced across the groups, thus the comparison of CNNF vs usual care will remain valid; however, for more accurate estimates, we will also conduct a per-protocol analysis where we exclude these individuals.

11.6 Analysis of the Secondary Endpoint(s)

The approach for analyzing the secondary endpoints will be similar to the approach for the primary endpoint, using mixed effects modelling with a random effect for clinician.

11.7 Exploratory Analyses

Exploratory analyses will mainly consist of descriptive analyses using cross-tabulations, means, standard deviations and proportions, as well as regressions using a similar approach as for the primary outcome.

11.8 Other Analyses

N/A

11.9 Safety Analyses

N/A

11.10 Planned Interim Analyses

None planned.

11.11 Subgroup Analyses

N/A

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 Informed Consent Process

12.1.1.1 Quality improvement strategy delivery

The type of quality improvement strategy (clinician notification) described in this document is routinely used by the anticoagulation clinic as part of clinical care to improve the safety of patients using warfarin. The quality improvement strategy used in this pilot trial was developed specifically for use as part of a quality improvement effort to promote the use of evidence-based practices and reduce bleeding risk among the anticoagulation clinic's patient population.

We request a waiver of informed consent for delivery of the clinician notifications. This is justified on the grounds that the study presents only minimal risk to participants (and is likely to be beneficial), the waiver does not adversely affect the rights and welfare of participants, and the research could not practically be carried out without the waiver. The study could not practicably be carried out if patients and clinicians are consented because the goals of this pragmatic quality improvement trial are to evaluate the effectiveness of these strategies when used as part of routine care for improving patient safety in the setting of upper GI bleeding risk reduction. The ethicality of this approach is further bolstered by the wait-listed control design, which will ensure that all participants will eventually receive the quality improvement strategies.

12.1.1.2 Patient phone survey

We request a waiver of informed consent for the conduct of the patient phone survey. The patient phone survey will consist of a one-time phone questionnaire anticipated to take 5 minutes (based on the duration of these calls in the pilot study). The survey will solely include questions that will allow the anticoagulation clinic to ensure that information in MiChart related to medications that influence bleeding risk are accurately documented in the patient's EHR both at baseline and at the time of the call and assess whether the patient made any medication changes during the study period. Accurate patient medication information in MiChart is necessary to correctly identify patients at high-risk for adverse events associated with warfarin use and knowledge of whether medication changes were made because of the study QI strategies or routine standard care is essential in assessing the impact of the strategy being tested and observing how often medication optimization occurs without CNNF, and as such these phone surveys are in-line with quality improvement efforts.

12.1.1.7 Chart Review for Randomized Participants

A waiver of informed consent will be sought for the chart review component of this study as it poses minimal risk to participants, does not adversely affect the risks and benefits of participation for the participant, and the study could not practically be completed without a waiver.

12.2 Confidentiality and Privacy

12.2.1 Future Use of Stored Specimens and Data

The data from this study may be used for future studies by the investigator team.

12.2.2 Data sharing

This study will be conducted in accordance with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will also comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested 3 years after the completion of the primary endpoint by contacting Dr. Kurlander.

12.3 Safety Oversight

This study will not have a Data and Safety Monitoring Board or Safety Monitoring committee since it constitutes quality improvement.

12.4 Key Roles and Study Governance

Principal Investigator
Jacob E. Kurlander, MD, MS Assistant Professor
Michigan Medicine
1500 E. Medical Center Drive, SPC 5362 Ann Arbor, MI 48109
(734) 660-4883

jkurland@umich.edu

12.5 Clinical Monitoring

N/A

12.6 Data Handling and Record Keeping

The source materials will include documentation of information collected during phone surveys and the results of chart review. Each study subject will be given a unique numeric identifier upon study entry. All individuals who wish to access the information system will need to pass through two levels of username and password authentication. All data will be stored on secured, password-protected UM computers. To access these data, approval must be obtained from the PI. These data will be kept only if specific use requires and then will be destroyed when all necessary linkages between data collection instruments have been accomplished.

Any paper records associated with this study will be stored at 2800 Plymouth Road, Ann Arbor MI in a locked cabinet.

12.7 Data Collection and Management Responsibilities

Data collection will be the responsibility of the research staff at the site under supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner or collected in digital form to ensure accurate interpretation of the data.

12.8 Study Records Retention

As this trial will involve collection of health-related data through interaction with participants, all study documents will be retained for at least 7 years after the trial is completed in accordance with the University of Michigan’s Human Research Protections Program (HRPP) Operations Manual Part 6.II.B.

12.9 Protocol Deviations

Deviations from the clinic protocol by anticoagulation clinic staff members when sending or delivering the implementation strategies as part of the quality improvement project will not constitute protocol deviations and will not be reported. This protocol defines a protocol deviation

as any noncompliance with the clinical trial protocol, related only to the research components. The noncompliance may be either on the part of the investigator, or research staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly. Any study design modifications that affect the risks and benefits of study participation will be submitted to the IRB at Michigan Medicine as study amendments and documented in the amendment section of this document.

All major protocol deviations or protocol amendments which affect the risks and benefits of participation will be reported to the IRB per the IRBMED reporting guidelines. It will be the responsibility of the site investigator to use continuous vigilance to identify and report major deviations or recurring minor deviations within 1 week of identification of the protocol deviation or deviation trend, or within 1 week of the scheduled protocol-required activity. Any protocol changes will be submitted to the IRB as a study amendment and will require IRB approval prior to implementation of the protocol change. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

13 DATA SAFETY MONITORING PLAN

As this trial constitutes a low-risk study with a small number of participants, participant safety will be monitored by the study PI and there will be no data safety monitoring board or independent safety monitor for this project. Any unanticipated adverse events associated with the implementation strategies tested in this study will be identified by the study team and PI through participant self-report during any of the study phone surveys. Adverse events related to any medication changes made by the patient's clinician will not be tracked or reported and the patient would be expected to discuss any such side effects with the clinician who initiated the medication change. The justification for not monitoring for adverse events related to a medication change is that participants in this study are not required to make a medication change as part of their participation and all medication changes will be made by the patient's clinician as part of usual care. Any unanticipated problems or adverse events self-reported by participants will be reported to the PI immediately and communicated to the IRB according to the policies described in the Human Research Protection Program Operations Manual. No individual stopping rules will apply to any participants as all patient-facing quality improvement strategies will be delivered one-time only. However, any participants who request to no longer be contacted by the study team for study assessments will not be contacted again and will be considered to have withdrawn from the study.

13.1 Study Leadership Roster

A study leadership roster is included herein. All CVs and licenses for investigators and staff members included on the roster will be filed in the essential document binder for this study.

Name	Study Team Role	Contact Information	Responsibilities
Jacob E. Kurlander	Principal Investigator (PI)	734-647-9252, jkurland@umich.edu	• Identification and enrollment of participants • Collection of study data through chart review, and patient surveys • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Geoffrey D. Barnes	Co-Principal Investigator (Co-PI)	734-763-0047, gbarnes@umich.edu	• Identification and enrollment of participants • Collection of study data through chart review, and patient surveys • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Danielle Helminski	Study Coordinator	734-615-3952, dhelmins@umich.edu	• Identification and enrollment of participants • Collection of study data through chart review, and patient surveys • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Kelley Kidwell	Statistician	734-764-6724, kidwell@umich.edu	• Develop randomization procedure • Assign participants to groups • Maintain the master randomization list • Notify PIs and study coordinator when participants have been randomized • Perform statistical analyses

Michael Lanham	Co-Investigator	934-936-1644, mlanham@umich.edu	• Develop randomization procedure • Assign participants to groups • Maintain the master randomization list • Notify PIs and study coordinator when participants have been randomized • Develop EMR tools to assist with identifying participants and sending quality improvement strategy components
Sameer D. Saini	Faculty Mentor	734-936-4785, sdsaini@umich.edu	• Provides expert advice on research conduct and study design • Monitor study progress to ensure completion of project
Caroline Richardson	Faculty Mentor	734-998-7120, caroli@umich.edu	• Provides expert advice on research conduct and study design • Monitor study progress to ensure completion of project
Sarah L. Krein	Faculty Mentor	734-845-3621, skrein@umich.edu	• Provides expert advice on research conduct and study design • Monitor study progress to ensure completion of project
Raymond De Vries	Faculty Mentor	734-936-1644, rdevries@umich.edu	• Provides expert advice on research conduct and study design • Monitor study progress to ensure completion of project

13.2 Protocol Amendment Procedures and Approvals

Protocol amendments require approval by both the PI and the Co-PI, Jacob E. Kurlander and Geoffrey D. Barnes, prior to submitting the amendment to the IRB. Written IRB approval of protocol amendments is required prior to implementation. Any amendment to the protocol will be adhered to by all study staff and will apply to all subjects.

13.3 Clinical Trial Registry and Publication Policy

Prior to subject enrollment, this clinical trial will be registered with clinicaltrials.gov by a University of Michigan's Michigan Institute for Clinical and Health Research (MICHR) representative. After the trial has been registered, the Co-PIs and study coordinator will be responsible for providing study updates and posting study results within 1 year of the primary completion date for the study on clinicaltrials.gov. Results from this trial will additionally be presented at cardiology or gastroenterology conferences and manuscripts of findings will be submitted for publication in relevant journals. As this study is being funded by the NIDDK through Dr. Kurlander's K23 award, all journal articles that arise from this study will be submitted to PubMed Central in accordance with NIH Public Access Policy.

14 APPENDICES

14.1 Appendix 1. Criteria for determining appropriateness of antiplatelet therapy.

Recommended duration of antiplatelet therapy for patients using anticoagulation, by indication.
Clinicians should use their judgment in applying these recommendations to patients depending on the specific clinical scenario.

Indication for antiplatelet drug		Recommended management of antiplatelet drug	Notes	Ref.
Primary prevention of coronary artery disease				
Primary prevention		Stop antiplatelet drug		[1]
Treatment of coronary artery disease with atrial fibrillation (AF)				
	PCI ≤ 6 months ago	Continue antiplatelet drug	-Clopidogrel preferred -Consider switch to aspirin 81mg	[1]

PCI for stable CAD	PCI >12 months ago	Antiplatelet therapy is typically stopped, but may still be appropriate in select patients at high risk for stent thrombosis		
CABG for stable CAD	CABG ≤12 months ago	Continue aspirin 81mg		
	CABG >12 months ago	Stop aspirin		
Acute Coronary Syndrome (ACS) +/- PCI	ACS +/- PCI ≤12 months ago	Continue antiplatelet drug	Clopidogrel preferred	
	ACS +/- PCI >12 months ago	Antiplatelet therapy is typically stopped, but may still be appropriate in select patients at high risk for stent thrombosis		
Treatment of coronary artery disease with venous thromboembolism (VTE)				
PCI for stable CAD	PCI ≤6 months ago	Continue antiplatelet drug	-Clopidogrel preferred -Consider stopping anticoagulant at 3 months if reversibly provoking risk factors	[1]
	PCI >6 months ago	Continue antiplatelet drug	-Consider switch to aspirin 81mg -Consider stopping anticoagulant if reversibly provoking risk factors	
	PCI >12 months ago	Antiplatelet therapy is typically stopped, but may still be appropriate in select patients at high risk for stent thrombosis	-Consider stopping anticoagulant if reversibly provoking risk factors	
CABG for stable CAD	CABG ≤12 months ago	Continue aspirin 81mg		
	CABG >12 months ago	Stop aspirin		
Acute coronary syndrome	ACS +/- PCI ≤3 months ago	Continue antiplatelet drug	Clopidogrel preferred	

(ACS) +/- PCI	ACS +/- PCI 3-12 months ago	Continue antiplatelet drug	-Consider switch to aspirin 81mg -Consider stopping anticoagulant if reversibly provoking risk factors	
	ACS +/- PCI >12 months ago	Antiplatelet therapy is typically stopped, but may still be appropriate in select patients at high risk for stent thrombosis	-Consider stopping anticoagulant if reversibly provoking risk factors	
Cerebrovascular disease				
History of TIA or CVA		Stop antiplatelet drug		1
History of CEA		Continue antiplatelet drug		
Carotid stent ≤ 3 months ago		Continue antiplatelet drug	Clopidogrel preferred	
Carotid stent > 3 months ago		Stop antiplatelet drug		
Peripheral arterial disease				
Without prior intervention		Stop antiplatelet drug		
Endovascular intervention		Continue antiplatelet drug	Clopidogrel preferred for the first 1-3 months	Institutional practice
Surgical repair / bypass		Continue antiplatelet drug		
Vascular graft		Continue antiplatelet drug		
Valve replacement				
Mechanical Heart Valve, excluding On-X valves		Stop antiplatelet drug unless another indication is present		2
Mechanical On-X Aortic Heart Valve		Continue aspirin 81mg		
Bioprosthetic Heart Valve ≤ 3 months ago		Continue aspirin 81mg only if high		

	thromboembolic risk		
Bioprosthetic Heart Valve > 3 months ago	Stop aspirin		
TAVR ≤ 3 months	Continue antiplatelet drug only if high thromboembolic risk		3
Venous Intervention (including IVC and Iliofemoral venoplasty/stenting)			
Venous procedure ≤2 months prior	Continue dual antiplatelet therapy		
Venous procedure >2 months prior	-Stop P2Y12 inhibitor -Continue aspirin 81mg indefinitely		
Anti-phospholipid Syndrome			
Anti-phospholipid syndrome	Antiplatelet therapy should be individualized and may be appropriate		4
Polycythemia vera, essential thrombocythemia, and other myeloproliferative neoplasms			
Polycythemia vera, essential thrombocythemia, and other myeloproliferative neoplasms	Antiplatelet therapy should be individualized and may be appropriate		Institutional practice

PCI=Percutaneous coronary intervention.

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15 ABBREVIATIONS AND SPECIAL TERMS

Abbreviation	Term
AAT	Anticoagulant-antiplatelet therapy
CFR	Code of Federal Regulations
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
NCT	National Clinical Trial

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCP	Primary Care Provider
PI	Principal Investigator
PPI	Proton Pump Inhibitor
PUD	Peptic Ulcer Disease
UGIB	Upper Gastrointestinal Bleeding
UM	University of Michigan
US	United States

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