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# Management of Antiplatelet Therapy Among Patients on Antiplatelet Therapy for Cerebrovascular or Peripheral Vascular Diseases Undergoing Elective Non-cardiac Surgery

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Prepared by:
Evidence-based Synthesis Program (ESP) Center
West Los Angeles VA Medical Center
Los Angeles, CA
Paul G. Shekelle, MD, PhD, Director

Investigators:

Principal Investigator:
Paul Shekelle, MD, PhD

Co-Investigators:
Melinda Maggard-Gibbons, MD, MSHS
Isomi M. Miake-Lye, PhD
Christopher P. Childers, MD
Sean M. O'Neill, MD, PhD

Contributing Investigators:
Selene Mak, PhDc
Roberta Shanman, MLS
Jessica M. Beroes, BS

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# PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for 4 ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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# EVIDENCE REPORT

## INTRODUCTION

The perioperative management of antiplatelet therapy (APT) for patients with coronary, cerebrovascular, or peripheral vascular stents remains unclear. After percutaneous coronary intervention, American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend delaying elective non-cardiac surgery, ideally 6 months following drug-eluting stent placement and 30 days after bare metal stent placement.[1] For patients on dual antiplatelet therapy (DAPT), ACC/AHA guidelines recommend continuing at least aspirin (ASA) throughout the perioperative period and restarting the $P2Y_{12}$ inhibitor as soon as possible following surgery. However, this latter recommendation is based on expert opinion and was the focus of a recent ESP report.[2] The conclusion of this report was that studies evaluating APT therapy in patients with coronary stents had significant methodologic limitations and that APT therapy likely has a small impact on perioperative bleeding and major adverse cardiac event (MACE) outcomes, compared to other clinical factors such as operative urgency and timing since stent implantation.

There are a number of indications for APT therapy beyond coronary stents, most notably peripheral vascular and cerebrovascular disease. All patients with symptomatic peripheral artery disease are recommended to be on APT, typically monotherapy with either aspirin or clopidogrel.[3] However, DAPT (typically with ASA and clopidogrel) is common, especially amongst the highest-risk patients – those following endovascular procedures for critical limb ischemia.[3] Duration of APT for vascular disease is typically lifelong, unless the patient develops a significant complication, such as a bleeding event. The perioperative management of APT in the setting of elective non-cardiac surgery, specifically the decision about whether to stop APT before surgery and for how long, requires balancing overall thrombotic risk against the risk of bleeding with surgery.

To help clinicians, patients, and policymakers with this important decision, we conducted a systematic review of the published literature to address the following questions. What are the risks and benefits of APT in the perioperative period for patients on APT for cerebrovascular or peripheral vascular disease? Do the risks and benefits vary by timing of discontinuation and resumption of APT? And do the risks and benefits vary by the type of procedure or the type of APT agent?

# METHODS

## TOPIC DEVELOPMENT

This topic was developed in response to a nomination by Dr. Arthur Wallace, Chief of Anesthesia at the San Francisco VAMC, and Dr. John Sum-Ping, Director of National Anesthesia Service. Key questions were then developed with input from the topic nominator, the ESP coordinating center, the review team, and the technical expert panel (TEP).

The Key Questions were:

1. Among patients on APT for cerebrovascular disease or peripheral vascular disease undergoing elective non-cardiac surgical procedures, including intraocular procedures, what are the benefits and harms of holding APT prior to surgery?

2. How does benefit/risk vary by the timing of discontinuation?

3. How does benefit/risk vary by type of surgical procedure, including intraocular procedures?

4. How does benefit/risk vary by type of APT?

5. How does benefit/risk vary by the timing of resuming APT?

The review was submitted to PROSPERO: CRD42017062522.

## SEARCH STRATEGY

We conducted searches in PubMed from inception to 10/18/2016 (see Appendix A for full search strategy). The search in PubMed used a broad set of terms relating to APT and non-cardiac surgery.

## STUDY SELECTION

Four team members, working in pairs, independently screened the titles of retrieved citations. Citations deemed relevant by at least one reviewer were then screened at the full-text level by 2 independent reviewers. Any disagreements were resolved by consensus decision after study team discussion. To be included, full texts needed to include: (1) The patients underwent elective, non-cardiac surgery, including endoscopy and minor procedures; (2) Patients were on dual antiplatelet therapy (DAPT) or single $P2Y_{12}$ inhibitor therapy in the great majority of cases (>70%); (3) The majority of patients were on APT for peripheral vascular or cerebrovascular stents; (4) Details regarding pre- and perioperative management of APT were described, with outcomes stratified by strategy; (5) The article presented original data (*eg*,, not a review, commentary, or duplicate publication using the same data as another included publication); (6) The article reported adverse events and/or bleeding outcomes; and (7) Published in the English language. We did not exclude studies based on the type of APT (*ie*,, all $P2Y_{12}$ agents were eligible).

Our initial full-text review was limited to studies where all or the great majority of patients had peripheral or cerebrovascular stents, in line with the previous ESP report that focused on

coronary stents.[2] Unfortunately, no studies were identified using these criteria. We then broadened the screen, allowing inclusion of studies where the majority of patients had indications for peripheral vascular or cerebrovascular disease, with or without stents. Again, no studies were identified. Finally, we allowed the search to include any study that did not focus exclusively on patients with coronary stents, which identified the 13 studies reported here.

The following PICOTS framework describes our inclusion criteria:

Participants/population: Patients undergoing elective non-cardiac surgery on preoperative DAPT or $P2Y_{12}$ inhibitor therapy for indications other than coronary stents.

Intervention(s): Stopping all or some APT, bridging therapy.

Comparators: Not stopping or stopping at different times relative to the surgical procedure, as well as by drug.

Outcomes: Bleeding outcomes, thrombotic outcomes, and other clinical outcomes.

Timing: There was no restriction on timing.

Setting: All patients were undergoing surgery, either in inpatient or outpatient/ambulatory arenas.

## DATA ABSTRACTION

Data extraction was completed in duplicate. All discrepancies were resolved with full-group discussion. We abstracted data on the following: study design, setting, number of sites, country of origin, sample size, surgical procedures, indications for APT, APT management including preoperative, perioperative, and postoperative (when available), and outcomes including major bleeding, thrombotic outcomes, and other clinical outcomes. Bleeding outcomes were reported variably, including estimates of blood loss, postoperative hemoglobin changes, need for transfusion intraoperatively or postoperatively, and need for repeat procedure or operation for bleeding. After consultation with 2 practicing surgeons, we included only clinically relevant bleeding outcomes such as need for transfusion, re-operation, or escalation of care. Minor bleeding, such as a wound hematoma, changes in estimated blood loss without the need for transfusion, or the application of topical antithrombotic agents were not included. We included the following thrombotic outcomes: deep vein thrombosis (DVT); pulmonary embolus (PE); major adverse cardiac event (MACE) including myocardial infarction (MI), sudden cardiac death, or stent thrombosis; ischemic strokes (IS) or transient ischemic attacks (TIA); and peripheral stent thrombosis. Additional outcomes deemed clinically relevant to the assessment of risks and benefits of APT, such as need for reoperation, readmission and mortality, were included under “other clinical outcomes.” Surgery-specific complications, such as surgical site infections, anastomotic leaks, as well as length of stay and utilization metrics, were not extracted.

## QUALITY ASSESSMENT

We had planned on assessing any randomized controlled trials with the Cochrane Risk of Bias tool.[4] However, we identified no trials. Cohort studies were assessed on design (*eg*,, retrospective

versus prospective), number of sites, representativeness of the enrolled subjects, and assessments of the exposure and outcome(s).

## DATA SYNTHESIS

Data were too heterogeneous to support statistical pooling, and due to heterogeneity both in the outcomes reported and the APT strategies, we were unable to graphically plot the data either. Data were synthesized in a narrative format only.

## RATING THE BODY OF EVIDENCE

Where possible a summary of findings and quality of evidence table was used to summarize the existing evidence. Based on the GRADE working group,[5] the quality of the evidence was categorized as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE evaluates the quality of the evidence across all identified studies contributing to the outcome of interest.

## PEER REVIEW

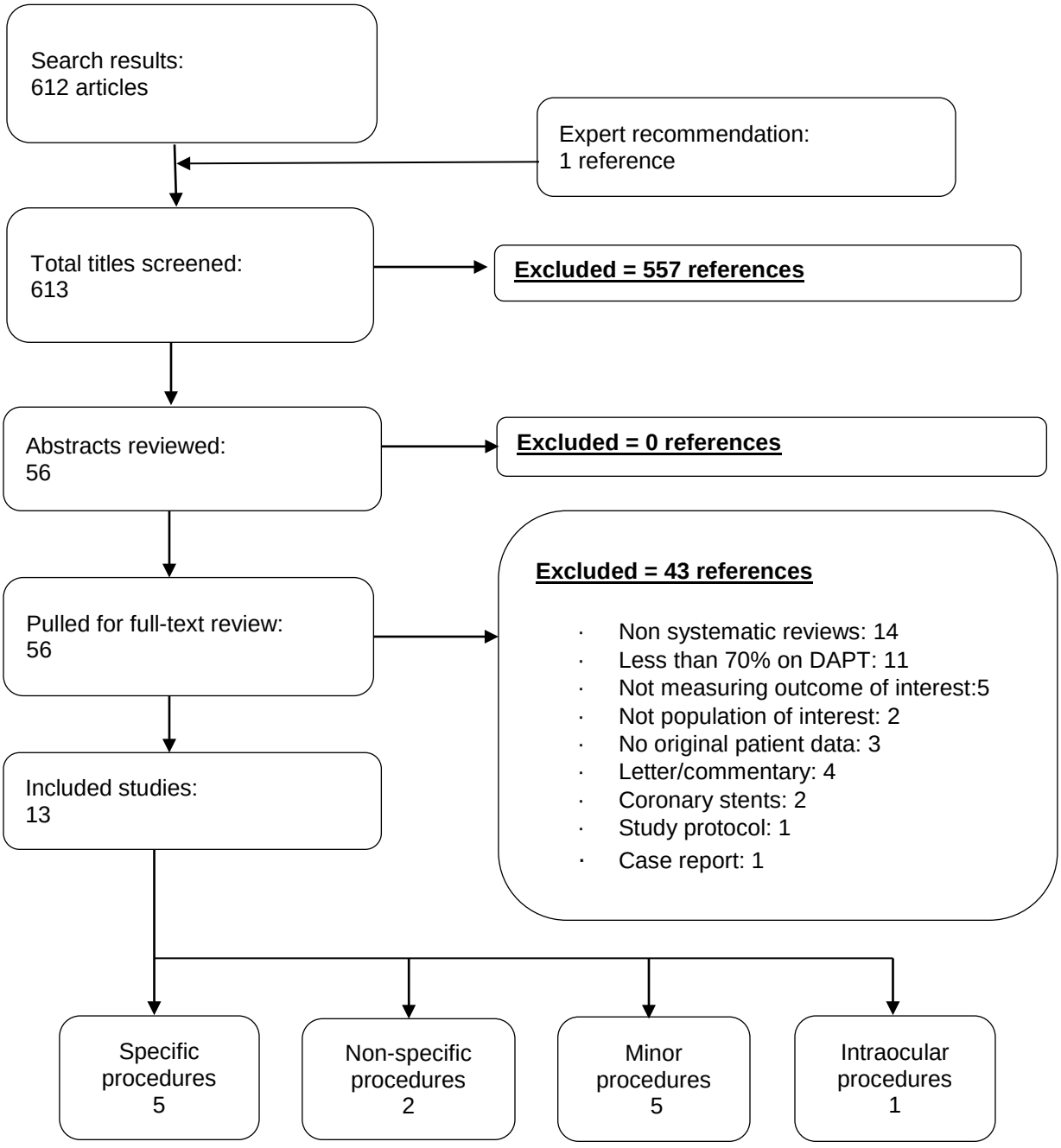
A draft version of the report will be reviewed by technical experts and clinical leadership. Reviewer comments and our response are documented in Appendix B.

# RESULTS

## LITERATURE FLOW

Our literature searches, expert recommendations, and reference mining identified 613 potentially relevant citations, of which 56 were included at the abstract screening. All 56 abstracts were included and obtained as full-text publications. Forty-three studies were excluded for the following reasons: non-systematic review (n=14), less than 70% of patients on DAPT (n=11), not measuring outcome of interest (n=5), did not present original data (n=3), not population of interest (n=2), exclusively coronary stents (n=2), letter or commentary (n=4), study protocol (n=1), or case report (n=1). A total of 13 publications were identified at full-text review as includes that contributed to our final sample. See Figure 1 for literature flow. Details of included studies are provided in Appendix C. A full list of these excluded studies from the full-text review is included in Appendix D.

**Figure 1. Literature Flow Chart**



## KEY QUESTION 1. Among patients on APT for cerebrovascular or peripheral vascular disease undergoing elective non-cardiac surgical procedures, including intraocular procedures, what are the benefits and harms of holding APT prior to surgery?

We identified 13 studies from full-text review. None were clinical trials. Twelve were cohort studies, of which 3 were prospective and 9 were retrospective. One additional study utilized a case-control design. Of the 13 studies, samples were generally small, with only one study reporting on over 1000 patients. Three studies included fewer than 100 patients, 5 reported 100-200 patients, and 4 reported 201-1000 patients. Eleven studies were conducted in an academic setting and 2 were conducted in a Veterans Affairs (VA) setting. Only 4 studies reported results from more than one site. Eight studies were conducted in the United States, with the remaining 5 studies coming from India, Ireland, the United Kingdom, and Canada.

The quality of studies was variable: most included all or a representative sample of eligible patients and used medical records to assess outcomes, and most were retrospective and single site. Methods for adjusting differences in other clinical variables were heterogeneous (Table 1).

Appendix C shows the evidence table for the 13 studies. An ideal study would provide the following data to assess the relationship between APT and postoperative outcomes: indication for APT (*eg*, peripheral vascular disease [PVD] with or without stent), the preoperative APT regimen (*ie*, the medications they were taking at baseline, before surgery was considered), and details about the perioperative management such as which agents were continued and which were held, and if held, for how many days preoperatively. Postoperative outcomes should be stratified based on these variables. As a hypothetical example, we would like to see postoperative bleeding rates only for those patients with a carotid stent, on preoperative DAPT, where the clopidogrel was held for 5 days preoperatively and the aspirin was continued. We did not identify any study that fulfilled all of these criteria.

Five of the included studies did not provide any information about indication for APT, preventing stratification along this important covariate. Adverse thrombotic events are therefore difficult to interpret for these studies. Of the 8 studies that did include some information about indication, the dominant indication for APT was a manifestation of coronary artery disease such as angina, post-myocardial infarction, post-coronary artery bypass, or post-percutaneous coronary intervention. Cerebrovascular and peripheral vascular indications were rare; for example, in the largest study, only 26 of 546 patients were on APT for history of an ischemic stroke (IS).[6] Only one study[7] had a significant proportion of individuals on APT for an indication of interest– this single-site retrospective review of 200 patients included 58 patients with a history of peripheral stent and 34 patients with a history of IS compared to 75 patients with an indication for coronary stent. However, outcome rates were not stratified by these indications, meaning only aggregate data are presented and we cannot attribute adverse outcomes to patients with peripheral stents, IS, etcetera. Further, most studies provided inadequate details about indication; for example, PVD would be listed as the indication but there would be no details about severity (*ie,* claudication versus critical limb ischemia), prior interventions (*ie,* whether or not surgery or endovascular intervention had been conducted), or any details about the interventions such as the complexity, presence or absence of stent, location of stent, etcetera.

All 13 studies provided some details about pre- and perioperative APT management. The 12 cohort studies typically adopted 1 of 2 study designs based on their labeling of individuals to intervention or control arms. The first design[6,8-13] labeled patients based on their preoperative APT (*eg*, clopidogrel, DAPT, *etc*) while the second design[7,14-17] labeled patients based on their perioperative management (*eg*, all patients in the study were on preoperative clopidogrel but interventions and controls were labeled based on whether the agent was successfully held perioperatively). For the cohort studies adopting the first design, the sample size of patients on $P2Y_{12}$ inhibitor or DAPT was generally very small. For example, one study of 454 patients only included 13 patients on clopidogrel while 369 patients served as "controls."[8] 3 cohort studies included agents that were not of interest for this report including coumadin and dipyridamole.[10,13,17] Further, study arms often suffered from significant contamination of APT agents. For example, studies often tried to compare those patients on a $P2Y_{12}$ inhibitor to those not on the $P2Y_{12}$ inhibitor; however, aspirin use was common, but disparate, between the 2 arms. Some studies did not comment on use of aspirin or other relevant APT/anticoagulant at all.

Of the 12 cohort studies, 9 did not find a difference in major bleeding outcome rates. Of the 3 studies that did show a difference, 2 evaluated small cohorts of patients on preoperative clopidogrel and compared those that did and did not receive a dose within 7 days of the procedure.[14,15] Both showed higher rates of intraoperative transfusions, and possibly increased bleeding postoperatively, although definitions were vague on this latter point. The third study compared patients on preoperative clopidogrel that was continued to those patients not on preoperative clopidogrel and found slightly higher rates of clinically significant delayed bleeding following endoscopic polypectomy (2.4% versus 0%).[11] 87% of patients in the clopidogrel group were also on aspirin while 40% of controls were also on aspirin, a potentially major confounder to consider when interpreting the results.

Seven of the cohort studies reported some type of thrombotic outcome in addition to major bleeding. All 7 found no statistical difference or reported no events in the 2 arms. Four studies reported on readmission and/or mortality rates with 3 finding no difference. One small retrospective cohort compared patients who received and did not received clopidogrel within 7 days of a general surgical procedure and found a higher 30-day mortality rate amongst those that received clopidogrel.[15] However, this study found no difference in thrombotic outcomes, and the etiology of the mortality was not elucidated.

The results of the one case-control study are reported here.[18] In this 2007 two-site Canadian study, confirmed cases of post-ERCP bleeding were compared to those without bleeding to assess risk factors. The researchers created a variable for APT exposure within 10 days of the procedure and included aspirin and $P2Y_{12}$ inhibitors as well as COX2 inhibitors and NSAIDs. Exposure to APT was not significantly associated with post-ERCP major bleeding. No thrombotic or other outcomes were reported.

**Table 1. Quality Assessment for Included Studies**

| | Study Design | Generalizability | Sample Representativeness | Assessment of Outcomes |
|---|---|---|---|---|
| Anderson, 2014 | - | - | + | + |
| Chernoguz, 2011 | - | - | + | + |
| Feagins, 2011 | - | - | + | + |
| Feagins, 2013 | + | + | + | + |
| Girotra, 2014 | + | - | ? | + |
| Hussain, 2007 | - | + | + | + |
| Jacob, 2014 | - | - | + | + |
| Mackinnon, 2008 | - | + | + | + |
| McCunniff, 2016 | - | - | + | + |
| Radovanovic, 2012 | - | - | ? | + |
| Ryan, 2013 | + | + | + | + |
| Strosberg, 2016 | - | - | + | + |
| Toepfer, 2013 | - | - | + | + |

Study Design: (+) Prospective, (-) Retrospective

Generalizability: (+) Multi site, (-) Single Site

Sample representativeness: (+) Consecutive or all patients (?) Unclear

Assessment of Outcomes: (+) Medical Chart Review

### Summary of Findings

Thirteen observational studies provided some detail regarding the pre- and perioperative management of APT and its relationship to bleeding and thrombotic outcomes. Studies were generally small and indications were both inadequately described and deviated substantially from our target population. The perioperative management of APT agents was heterogeneous with significant contamination issues. Only 3 of the 13 studies showed an adverse association between APT agent and bleeding outcomes, primarily a function of intraoperative need for transfusion. There was no consistent difference in thrombotic, readmission, or mortality outcomes based on pre- and perioperative management of APT.

### Quality of Evidence for Key Question 1

We judged the quality of evidence as insufficient to make conclusions.

## KEY QUESTION 2. How does benefit/risk vary by the timing of discontinuation?

The timing of discontinuation of APT cessation varied between studies and among individual patients within studies. Four studies compared patients based on timing of discontinuation of APT agents[7,14-16]; however, 2 studies used 7 days as a cutoff, 1 used 5 days as a cutoff, and 1

used 2 days as the cutoff. Two of these 4 studies included mostly patients with DAPT, one included patients on clopidogrel (with unknown ASA status), and one included patients predominantly on ASA alone. An additional layer of confounding is that some studies combined patients not on APT preoperatively with those *on* APT preoperatively *but* held therapy into a singular control group.

No included study systematically assessed the impact of timing of APT cessation on any clinical outcomes.

### Summary of Findings

Only a small subset of studies evaluated the timing of APT discontinuation, with significant intra- and inter-study variation, limiting our ability to draw conclusions.

### Quality of Evidence for Key Question 2

We judged the quality of evidence as insufficient regarding the timing of discontinuation of APT prior to surgery.

## KEY QUESTION 3. How does benefit/risk vary by type of surgical procedure, including intraocular procedures?

Studies were grouped into 4 categories based on the type of procedure – 4 studies addressed specific surgical procedures, such as laparoscopic cholecystectomy or total knee arthroplasty[9,10,14,17]; 2 studies were non-specific and included either major abdominal surgeries[15] or a mix of major abdominal, vascular, and thoracic procedures[7]; 5 studies only addressed minor procedures such as minor oral surgery or endoscopy[6,11,12,16-18]; one study addressed ophthalmology.[13] Despite categorization, there was significant variation within each category; for example, concern of bleeding in lumbar spine surgery is not equivalent to the risk in laparoscopic cholecystectomy or total knee arthroplasty. Only 2 studies explicitly evaluated "major abdominal surgery," with one finding no difference in bleeding rates, and one finding increased risk of transfusion, primarily driven by intraoperative transfusions. Neither found a difference in thrombotic events. Of the 5 studies that addressed minor procedures, only one found an increased risk of clinically significant delayed bleeding for patients who continued $P2Y_{12}$ therapy through endoscopic procedures.

Only one study of antiplatelet management and ocular procedures was identified.[13] This study prospectively studied 85 patients taking antiplatelet or anticoagulant therapy undergoing 107 vitreoretinal procedures. Patients were taking APT for a diversity of reasons with only 11 patients with the indication as cerebrovascular disease and 4 for peripheral vascular disease. Of the 107 cases, 72% were on ASA alone, 8% on clopidogrel alone, and 10% each on DAPT or coumadin. All patients continued therapy through the perioperative period. The primary outcome was intraoperative and postoperative bleeds, with no thrombotic or other clinical outcomes reported. On multivariate analysis there was no association between APT or anticoagulant type and intraoperative or postoperative bleeding. Further, there were no cases of catastrophic suprachoroidal hemorrhage leading to loss of vision across the entire study.

### Summary of Findings

Few studies reported results stratified by type of surgical procedure, and among those that did, there was no clear difference in outcomes depending on perioperative antiplatelet strategy.

### Quality of Evidence for Key Question 3

We judged the evidence as insufficient regarding the relationship between perioperative antiplatelet strategy and outcomes depending on the type of surgical procedure.

## KEY QUESTION 4. How does benefit/risk vary by type of APT?

In general, studies were either too small or did not include enough detail to compare APT agents to one another. The one study that enrolled over 1000 patients identified 310 patients on aspirin alone, 97 patients on clopidogrel alone, 139 patients on DAPT and 575 patients on neither ("controls").[6] All patients were undergoing minor oral surgical procedures and were continued on their preoperative regimen. They found no difference in transfusions postoperatively across the 4 cohorts. They did not evaluate thrombotic outcomes. Several studies included patients on multiple APT strategies, but did not stratify results based on these strategies. For example, one study evaluated 200 patients on clopidogrel preoperatively of which 143 were on DAPT.[7] Unfortunately, the results are not stratified by those on DAPT and those on clopidogrel.

### Summary of Findings

Studies were too small and did not include enough detail to associate outcomes with type of APT agent.

### Quality of Evidence for Key Question 4

We judged the evidence as insufficient regarding the association between the type of APT and outcomes.

## KEY QUESTION 5. How does benefit/risk vary by the timing of resuming APT?

No study reported the timing of resumption of APT.

No included study systematically assessed the impact of timing of resuming APT on any clinical outcomes.

### Summary of Findings

Evidence for the impact of timing of resuming APT was absent from the identified literature.

### Quality of Evidence for Key Question 5

We judged the evidence as insufficient regarding the timing of resumption of APT.

# SUMMARY AND DISCUSSION

The overarching finding from this systematic review is that the available evidence regarding perioperative antiplatelet management in patients with cerebrovascular or peripheral vascular disease undergoing non-cardiac, non-emergent surgery is insufficient to conclusively guide clinical practice. Study heterogeneity, specifically as it relates to the different aspects of APT – pre- and perioperative management, timing of cessation, restarting therapy, and type of APT – combined with small sample sizes, limits the ability to draw conclusions. Additionally, the varied range of invasiveness of the procedure likely contributes to the operative bleeding risk and thrombotic risk, yet many studies lack sufficient detail to assess the impact of procedure on outcomes. It is also likely that factors other than perioperative APT may be in part responsible for differences in bleeding and thrombotic outcomes.

## SUMMARY OF EVIDENCE BY KEY QUESTION

Thirteen observational studies provided some detail regarding the pre- and perioperative management of APT and its relationship to bleeding and thrombotic outcomes. Studies were generally small and indications were both inadequately described and deviated substantially from our target population. The perioperative management of APT agents was heterogeneous with significant contamination issues. Only 3 of the 13 studies showed an adverse association between APT agent and bleeding outcomes, primarily a function of intraoperative need for transfusion. There was no consistent difference in thrombotic, readmission, or mortality outcomes based on pre- and perioperative management of APT.

### Key Question 2

Only a small subset of studies evaluated the timing of APT discontinuation, with significant intra- and inter-study variation, limiting our ability to draw conclusions.

### Key Question 3

Few studies reported results stratified by type of surgical procedure, and among those that did, there was no clear difference in outcomes depending on perioperative antiplatelet strategy.

### Key Question 4

Studies were too small and did not include enough detail to associate outcomes with type of APT agent.

### Key Question 5

Evidence for the impact of timing for resuming APT was absent from the identified literature.

## LIMITATIONS

The primary limitation for this systematic review is the quantity and quality of the available evidence. Given the heterogeneity observed, the data suggest that variables other than the antiplatelet strategy play a role in determining perioperative bleeding or thrombotic outcome rates, and in most cases these other variables were not identified or not adequately able to be controlled for in these observational studies.

We theorize that several factors may work in conjunction and be associated with bleeding and thrombotic outcomes, but the data were too limited to help address this. For example, it is likely that the invasiveness of the procedure combined with the APT strategy may be associated with bleeding and thrombotic outcomes. However, studies often included multiple procedures with variable bleeding risk profiles. Further, APT management varied both within and between studies without stratified results. This prevented us from identifying whether one APT management, for a particular type of procedure or group of procedures, was protective or harmful. Indication for APT agent is likely a very important factor that was either absent from studies or was not used to stratify results. Patients with mild PVD are likely at much different thrombotic risk than a patient who required a complex endovascular intervention. Medical optimization was absent from the studies. Additionally, other perioperative management can also impact development of thrombotic events, such as perioperative anticoagulation and mobilization, which was not reported in the studies.

### Publication Bias

Publication bias is always a concern in any systematic review. We had too few studies to conduct statistical tests for the possible presence of publication bias, so we cannot provide a data-based estimate of its likelihood.

### Study Quality

Overall, the quality of the evidence was insufficient to support strong conclusions across the key questions.

### Heterogeneity

Heterogeneity is a major limitation of this systematic review, as the variation in reported bleeding and thrombotic outcomes between studies was large and did not suggest a pattern between perioperative antiplatelet management and outcomes.

### Applicability of Findings to the VA Population

Only 2 studies were conducted in a VA setting, both from the same system reporting on the same procedure (endoscopy with polypectomy). Even though the remaining studies were not in VA populations, we judged these results as being moderately or even strongly applicable to VA since the enrolled patients were very likely to moderately or strongly resemble VA patients, except with respect to gender.

## RESEARCH GAPS/FUTURE RESEARCH

There is obviously a very large research gap, as we were unable to find evidence sufficient to reach conclusions for any of the Key Questions. The evidence does suggest that differences in outcomes due to perioperative antiplatelet management are likely to be smaller than differences in outcomes due to other clinical factors. This suggests that observational studies are going to have difficulty identifying or balancing these other clinical factors, thus limiting their value in reaching strong conclusions about perioperative antiplatelet management strategies. Randomized studies would potentially balance these other clinical factors. Yet randomized studies present their own problem – namely sample size. Trying to detect small effects requires large samples. For example, if baseline rates of thrombotic outcomes are 5%, to detect a rate reduction of 2%

with 80% power would require a sample size of almost 1500 patients per arm. Similarly, if the rate of bleeding is 5% at baseline, then it would require more than 400 patients in each arm to have 80% power to detect a doubling of this to 10%. These study samples are much larger than any of the observational studies included in this review. Further, if any additional stratifying variables are included, such as indication of APT, invasiveness of surgery, or timing of APT stopping/resumption, this would greatly add to the needed sample size. Alternatively, if a randomized trial seems unlikely, a thoughtful and well-designed retrospective review may be helpful. A VA study conducted by Hawn et al evaluated perioperative MACE in patients undergoing non-coronary surgery after coronary stent placement.[19] This study found that, regardless of stent type, the optimal window for operating appears to be 6 months after implantation, a finding that was later incorporated into the American College of Cardiology (ACC) / American Heart Association (AHA) guidelines.[20] A study of similar design in patients with peripheral stents and/or cerebrovascular stents would be informative.

## CONCLUSIONS

Published studies of the association between perioperative APT management and outcomes in patients with cerebrovascular or peripheral vascular disease undergoing non-cardiac, non-emergent surgery have challenging methodologic limitations and heterogeneous results, and do not provide sufficient evidence to moderately or strongly support any clinical recommendation. The results suggest that clinical factors other than perioperative APT management may be more responsible for bleeding and thrombotic outcomes. It is likely that a clinical trial of large size would be needed to more definitely provide evidence about this clinical decision.

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