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Management of Antiplatelet Therapy among Patients on Antiplatelet Therapy for Coronary or Cerebrovascular Disease or with Prior Percutaneous Cardiac Interventions Undergoing Elective Surgery: A Systematic Review

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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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This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **West Los Angeles VA Medical Center, Los Angeles, CA**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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INTRODUCTION

The perioperative management of antiplatelet therapy for patients with coronary stents remains unclear. Patients who have coronary stents placed are at risk of stent thrombosis, and therefore are nearly all recommended to receive prolonged antiplatelet therapy: dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor) for a shorter time (such as 30 days, if a bare metal stent was placed) or a longer time (such as 6 months or a year or indefinitely, if a drug-eluting stent was placed); followed by indefinite single antiplatelet therapy (almost always aspirin). Historically, clopidogrel and aspirin has been prescribed. But use of newer agents such as ticagrelor and prasugrel are increasing. Patients undergoing non-cardiac surgery with prior history of percutaneous coronary intervention and placement of coronary stents or balloon angioplasty are at increased risk of perioperative cardiac events.[1] The risk of perioperative adverse events (*ie,* major adverse cardiac event, bleeding) is associated with time from percutaneous coronary intervention, operative urgency, and antiplatelet therapy.[2,3]

Current guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) published in 2014 recommend elective non-cardiac surgery be delayed one year after drug-eluting stent placement, and 30 days after bare metal stent placement.[4] When considering urgent non-cardiac operative intervention, ACC/AHA recommendations are to continue dual antiplatelet therapy in the perioperative period for 4 to 6 weeks after percutaneous coronary intervention, unless the risks of bleeding outweigh the risks of stent thrombosis.

To help clinicians, patients, and policymakers with this important decision, we conducted a systematic review of the published literature for the following questions. What are the risks and benefits of antiplatelet therapy in the perioperative period after percutaneous coronary intervention? Do the risks and benefits vary by timing of discontinuation and resumption of antiplatelet therapy? And do the risks and benefits vary by operative intervention, or do they vary by type of antiplatelet therapy?

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 by Dr. Christina Matadial of the Miami VAHCS. Key questions were then developed with input from the topic nominators, the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

The key questions were:

1. Among patients on antiplatelet therapy (APT) in conjunction with percutaneous coronary intervention (PCI) undergoing elective 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 registered in PROSPERO: CRD42016036607.

SEARCH STRATEGY

We conducted searches in PubMed, Web of Science, and Scopus from inception of each database to 12/17/2015 (see Appendix A for full search strategy). One of the searches in PubMed used a broad set of terms relating to APT, percutaneous coronary intervention (PCI), and discontinuing therapy. In addition, searches were run in all 3 databases looking for articles related to 3 key references.[5,6,7] We also reference mined key existing non-systematic review articles.[8]

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 abstract level by 2 independent reviewers. Any disagreements were resolved by consensus decision after study team discussion. To be included at the abstract stage, abstracts needed to include: 1.) That the patients underwent elective, non-cardiac surgery, either entirely or in the great majority of reported cases; 2.) That the patients were post-percutaneous coronary intervention with stent placement; 3.) That the article presented original data (*eg*, not a review, commentary, or duplicate publication using the same data as another included publication); 4.) That the article reported major adverse cardiac events (MACE) as a composite or any of the individual components (such as stent closure) or bleeding outcomes; and 5.) That the article was published in the English language. Any abstracts with ambiguity on these criteria were included for full-text review.

All included abstracts were then obtained as full text. Full-text publications were screened in duplicate against the same pre-specified eligibility criteria as for the abstract screen, as well as

the additional criteria that the publication could not report on a case series of under 10 patients, the stents being used had to be available in the US (which excluded studies of stents coated with endothelial progenitor cells[9] or carbofil coating,[10] and that the elective non-cardiac surgery outcomes had to be reported separately. At this stage, each article was carefully examined to make sure the details of the preoperative antiplatelet therapy and the perioperative antiplatelet management were described relative to the outcomes that were reported. We did not exclude studies based on the type of APT management (*ie,* all P2Y12 agents were eligible). Studies that did not report these details were excluded. So, for example, a hypothetical study that stated they assessed 100 patients who were on dual APT for a drug-eluting stent, and both antiplatelet agents were stopped 5 days prior to surgery "in 85% of cases, with the remainder continuing aspirin through surgery," and then reported major adverse cardiac events and serious bleeding, would be excluded since there was no way to know whether the adverse events happened in the patients who had both APT agents stopped or in the few patients who were continued on aspirin. Ergo, unless we could match the reported outcomes to the exact preoperative and perioperative APT, we were forced to exclude the study. Any disagreements were resolved by consensus decision after discussion with the study team.

The following PICOTS framework describes our inclusion criteria:

Participants/population: Patients on APT in conjunction with PCI undergoing elective surgical procedures including intraocular procedures and procedures requiring anesthesiologist (*eg,* some forms of endoscopy, but not dental procedures).

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

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

Outcomes: Thrombotic outcomes, hemorrhagic outcomes, death, disability, major adverse cardiac events (MACE).

Timing: There was no restriction on timing, but the majority of studies (10/13) included outcomes measured within 30 days of surgery.

Setting: All patients were hospitalized undergoing surgery.

DATA ABSTRACTION

Data extraction was completed in duplicate. All discrepancies were resolved with full group discussion. We abstracted data on the following: sample size, surgical procedures, number of centers included, cardiac stent types, preoperative antiplatelet management, antiplatelet management at surgery, APT cessation, whether bridging therapy was included, outcomes assessed and instruments used for outcomes, outcome follow-up time period, whether the study took place in an academic setting, country, mean age of patients, percent female patients, patient comorbidities, sampling method in retrospective studies, and whether the article addressed balancing for sample differences in cohort studies. MACE were usually defined as death, stent thrombosis, or myocardial infarction, and occasionally other outcome. If a study reported only one these outcomes (for example, stent thrombosis) we included it as MACE. Hemorrhagic outcomes were reported much more variably, from wound hematoma to blood loss requiring

transfusion of 1 or more units of blood. We did not include the former, but did include the latter, in our abstraction of hemorrhagic outcomes. Specifically, we abstracted bleeding events that the surgeons on the study team deemed clinically significant, which included the need for blood transfusion, re-operation, or blood loss leading to an escalation of care. Minor wound hematomas were not included, for example.

QUALITY ASSESSMENT

We had planned on assessing any randomized controlled trials with the Cochrane Risk of Bias tool.[11] However, we identified no trials. Cohort studies were assessed on design (*eg*, retrospective vs prospective), representativeness of the enrolled subjects, assessments of the exposure and outcome, follow-up rates, and statistical methods.

DATA SYNTHESIS

Data were too heterogeneous to support statistical pooling. We plotted MACE and bleeding outcomes by the preoperative APT and the perioperative management, and assessed for trends or patterns. We then assessed possible explanations for the observed heterogeneity by stratifying studies based on the types of surgical procedures included (major, such as thoracic surgery, versus minor, such as endoscopy, skin procedures), and by the duration of time between stent placement and surgery (using 6 months as the threshold, or the time closest to 6 months).

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,[12] 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: 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

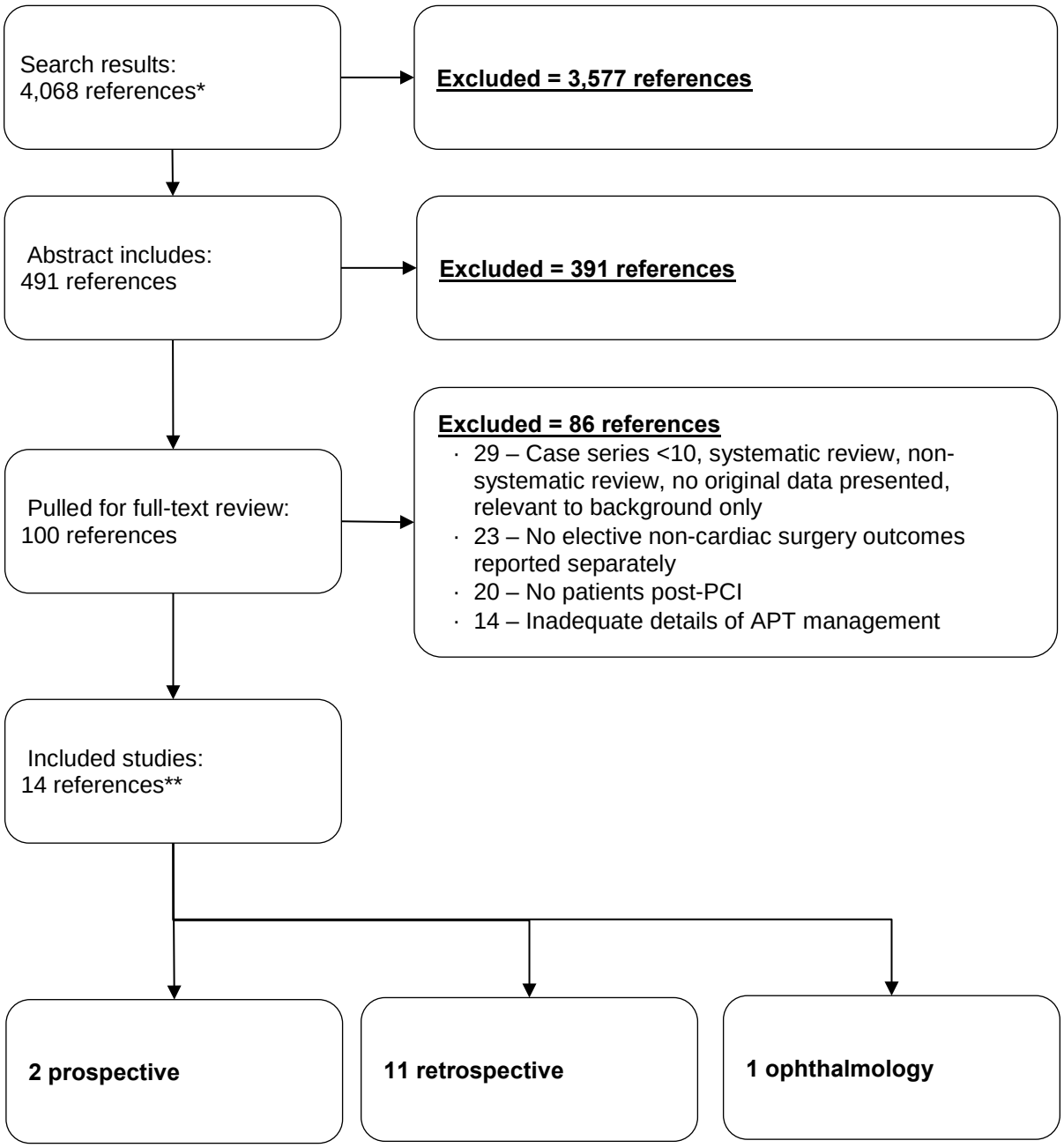
A draft version of the report was reviewed by technical experts and clinical leadership. Reviewer comments and our responses are documented in Appendix B.

RESULTS

LITERATURE FLOW

Our literature searches and reference mining identified 4,068 potentially relevant citations, of which 491 were included by at least one reviewer at the title screening. Of these, 100 abstracts were included and obtained as full-text publications. A total of 14 publications were identified that contributed as includes to our final sample. The 86 excluded studies from the full-text review were excluded for the following reasons: the study design was a case series less than 10, systematic review, non-systematic review, did not present original data, or was only relevant as background material (n = 29); no elective non-cardiac surgery outcomes were reported separately in the data (n = 23); no patients post-PCI were reported in the data (n = 20); or inadequate details were given on the APT management (n = 14). See Figure 1 for literature flow. Details of included studies are provided in Appendix C. A full list of those studies excluded from the full-text review is included in Appendix D.

Figure 1. Literature Flow Chart



* Search results were combined from Scopus, Web of Science, and PubMed. Reference mining identified 9 articles, also included in this number. See Appendix A for details.
** Manuscript reference list includes additional references cited for background and methods plus websites relevant to key questions.

KEY QUESTION 1. Among patients on APT in conjunction with PCI undergoing elective surgical procedures, including intraocular procedures, what are the benefits and harms of holding APT prior to surgery?

We identified 13 studies meeting all the eligibility requirements. None were clinical trials. Twelve of these were cohort studies, and of these 2 were prospective and 11 were retrospective. One study used a case control design and will be discussed separately. Among the cohort studies, most were small, with 5 reporting on fewer than 50 patients, another 4 reporting on 50-150 patients, and 3 studies reporting on more than 150 patients. The quality of studies was variable: most studies included all or a representative sample of eligible patients and used medical records to assess outcomes, but methods for assessing and adjusting for differences in other clinical variables were very heterogeneous (Table 1). We also included 1 study that did not meet all eligibility criteria, because it was the only identified study that assessed intraocular procedures.

Table 1. Quality Assessment for Included Studies

Author, year	Study design	Sample representativeness	Assessment of outcomes	Follow-up rate	Address balancing for sample differences	Statistical methods used
Alshawabkeh et al, 2013[13]	~	¢	¢	N/A	¿	N/A
Marcos et al, 2011[14]	~	¢	¢	N/A	¿	N/A
Yamamoto et al, 2014[15]	~	¢	¢	N/A	¿	N/A
Tanaka et al, 2014[16]	~	¢	¢	N/A	¿	N/A
Sonobe et al, 2011[17]	~	~	¿	N/A	¿	N/A
Cerfolio et al, 2010[18]	¢	N/A	¢	¢	¢	¢
Ryan et al, 2013[19]	¢	N/A	¢	¢	¢	¢
Capodanno et al, 2015[20]	~	¢	¢	N/A	¢	¢
Bolad et al, 2011[21]	~	¢	¢	N/A	¢	~
Hawn et al, 2013[22]	~	¢	¢	N/A	¢	¢
Assali et al, 2009[23]	~	¢	¢	N/A	~	~
Brotman et al, 2007[24]	~	¢	¢	N/A	¢	~
Choi et al, 2010[25]	¢	¢	¢	¢	¢	~
Conroy et al, 2007[26]	~	¢	¢	N/A	¿	¿

Study design: prospective = square, retrospective = circle
Sample representativeness: all patients/consecutive sample = square, not reported/unclear = circle
Assessment of outcomes: medical record review = square, administrative data = circle, unclear = diamond
Follow-up rate: > 80% = square, 60% - 80% = circle, < 60% = diamond
Address balancing of sample differences: yes = square, no = diamond
Statistical methods used: measurable methods = square, univariate methods = circle

Figure 2 presents the outcomes reported in the cohort studies, by the preoperative APT (dual, single, or none) and the perioperative management (stop both, stop one – which almost always meant stopping clopidogrel, stop one plus "bridge" the patient with another agent designed to reduce thrombosis (such as tirofiban), or continue both). In Figure 2, each study is given equal weight, regardless of sample size. Figure 3 presents the same results, but now the size of the mark for each study is proportional to the sample size, so that studies with larger samples are given more visual "weight." No clear pattern is apparent, as the reported outcomes vary as much across studies of "the same management" as across the different perioperative management choices. So, for example, 4 studies reported 0% MACE rates representing 3 different APT strategies. Further, among the studies that used DAPT pre-operatively, the study with the highest MACE event rate (21.4%) continued SAPT, whereas the studies that stopped both agents had less than half the MACE rates (11.1% and 2.3%). For bleeding, 3 studies reported 0% rates representing 3 different APT strategies. The highest rate (14.8%) was reported in a study where both agents were stopped perioperatively. Further complicating the interpretation is that almost all of these studies were small, with sample sizes within stratum of 17, 63, 51, 14, 10, and 27 and reporting very few events (actual numbers of MACE events reported were 2, 0, 2, 3, 2, and 3. Thus, from these data it is impossible to support a conclusion that a particular management strategy is associated with fewer MACE and bleeding outcomes compared to some other management strategy.

We next discuss here the case-control study, which is also the largest study and used sophisticated statistical techniques. [22] This study had 2 components. The first component was a retrospective cohort of 41,989 Veterans Affairs patients who underwent noncardiac surgery within 24 months of stent placement. Findings from an analysis of variables predicting MACE outcomes within 30 days showed that nonelective surgery, recent myocardial infarction (< 6 months), elevated cardiac risk index, the presence of heart failure, age, the presence of chronic kidney disease, and type of operation were all associated with increased risk. The second component of the study was focused on antiplatelet management and used a case-control design. Investigators abstracted from the medical records of 369 cases the specific details of preoperative and perioperative antiplatelet therapy management. A MACE occurred in 284 cases and did not occur in 85. There was no association of perioperative antiplatelet therapy and proportion of patients with a MACE. For example, in patients who were on dual antiplatelet therapy preoperatively there was no difference between persons who had a post-operative MACE and those that did not in the proportions who had all therapy continued (67.1% vs 64.6%), if only clopidogrel was held (9.4% vs 12.7%) or if both antiplatelet agents were held (19.4% vs 18.4%). Similar results were seen for patients who were on SAPT preoperatively, and whether therapy was or was not held for at least 5 days prior to surgery. These results are consistent with the results presented from the individual cohort studies that there is insufficient evidence to conclude that there is a strong or moderate relationship between perioperative antiplatelet management strategy and post-operative MACE.

Figure 2. Outcomes of observational studies of preoperative antiplatelet therapy, perioperative APT management, and outcomes (unweighted)

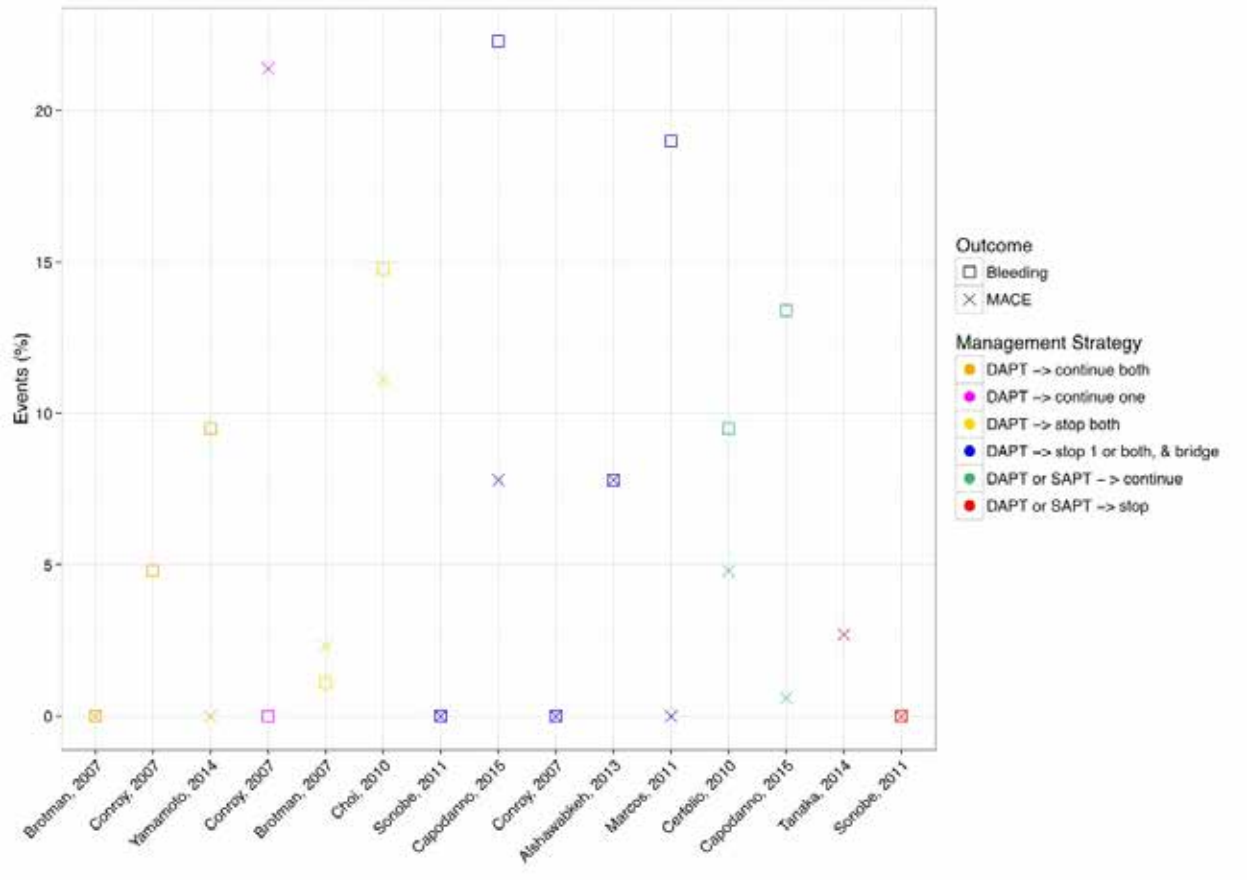
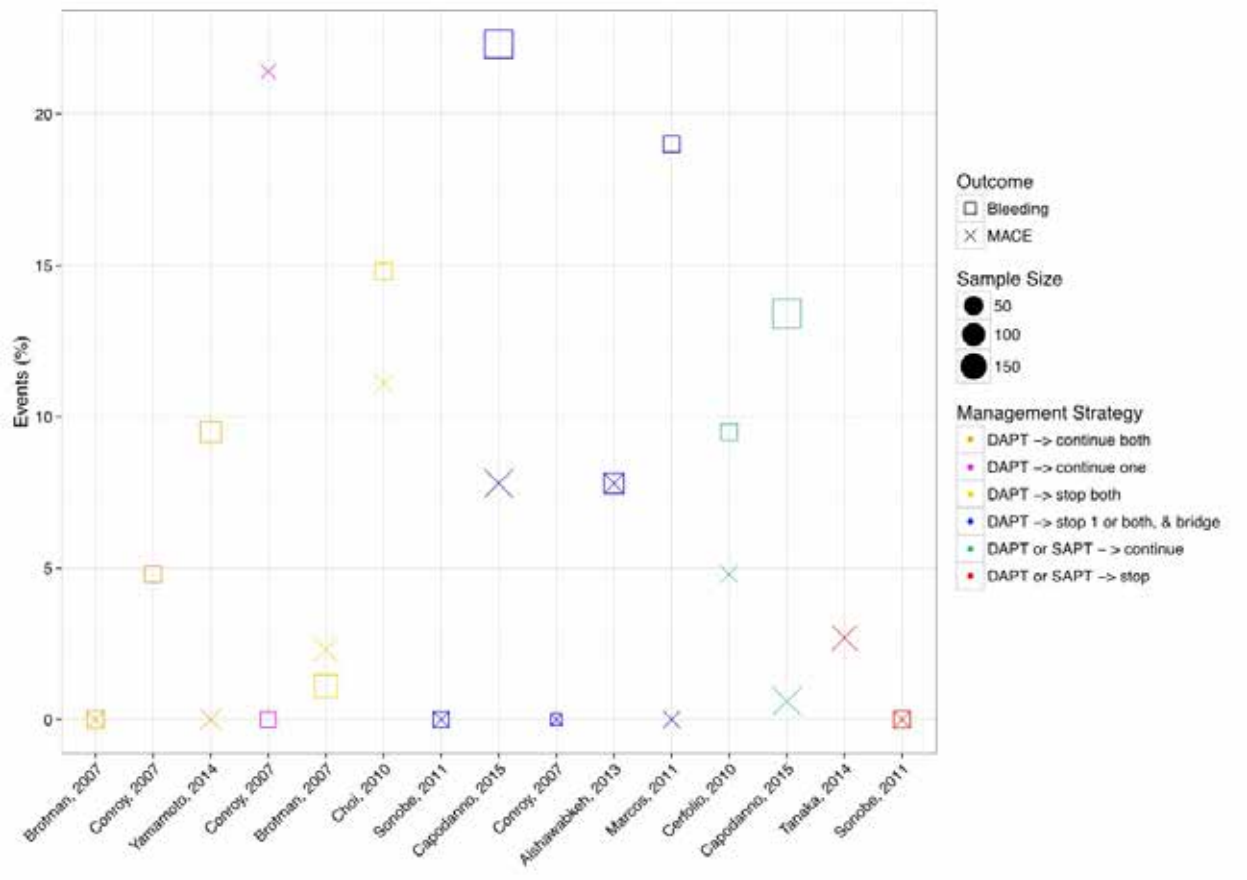


Figure 3. Outcomes of observational studies of preoperative antiplatelet therapy, perioperative APT management, and outcomes (weighted by sample size)



Summary of Findings

Thirteen observational studies reported the details of preoperative APT, perioperative APT management, and outcomes in sufficient detail to assess their association. The majority of studies were small, with fewer than 100 patients included, and the results were quite heterogeneous, with MACE rates and bleeding rates varying many-fold between studies reporting outcomes for the same combination of preoperative APT and perioperative management (such as preoperative DAPT, holding both prior to surgery). In general, within studies the bleeding outcomes were reported at higher rates than the MACE outcomes.

Quality of Evidence for Key Question 1

We judged the quality of evidence as insufficient in terms of specifying a particular preferred perioperative antiplatelet management that minimized MACE events and bleeding.

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. Most studies in which APT was discontinued preoperatively reported either a median or range of days of preoperative discontinuation. For the majority of these

studies, antiplatelet agents were discontinued between 3 and 10 days preoperatively, but no rationale for this timing was provided. One study did note that cardiologist recommendations influenced the duration of preoperative APT cessation.[17]

No included study systematically assessed the impact of timing of APT cessation on any clinical outcomes. Three studies provided limited case reports on a small subset of patients with MACE or bleeding outcomes,[17,23,24] but no trend was evident in any of these case reports for the impact of timing of APT cessation.

Summary of Findings

Evidence for the impact of timing of discontinuation of APT consists of very small case reports within larger studies, and demonstrated no identifiable trend. In the VA case-control study discussed above,[22] there was no association between stopping APT for at least 5 days versus some other strategy.

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?

Most studies included a mix of different types of surgical procedures, and did not stratify their outcome results by type of case and details of the antiplatelet management. We did identify 3 studies that were either about only cases our surgeon team members judged as all major or all minor, or which presented stratified results.[15,17,18]

Figure 4 and Figure 5 present the results of the MACE and bleeding outcomes in these studies. Figure 4 presents the results for each study with equal weight. Figure 5 presents the results for studies with the size of the mark proportion to the sample size, so that larger studies are given more visual "weight." No clear pattern is apparent. In the study by Yamamoto,[15] which was of major surgery, there were no MACE outcomes reported in any group defined by antiplatelet strategy, but there was higher reported bleeding if dual APT was continued or if the patient received bridging therapy. Another study of major surgery[17] also reported no MACE outcomes in patients who were on single antiplatelet therapy that was stopped prior to surgery. However, another study of patients on single APT prior to major surgery did report a nearly 5% rate of MACE, despite continuing the patients on antiplatelet therapy. The one study that included only patients with minor surgical procedures reported a MACE rate of about 2.5%, which occurred in patients on dual APT in which one agent was stopped. Thus, we could discern no pattern in these data to indicate whether the perioperative antiplatelet management strategy should vary depending on the type of surgical procedure.

Figure 4. Outcomes of observational studies of preoperative antiplatelet therapy, perioperative APT management, and outcomes by surgery risk category (unweighted)

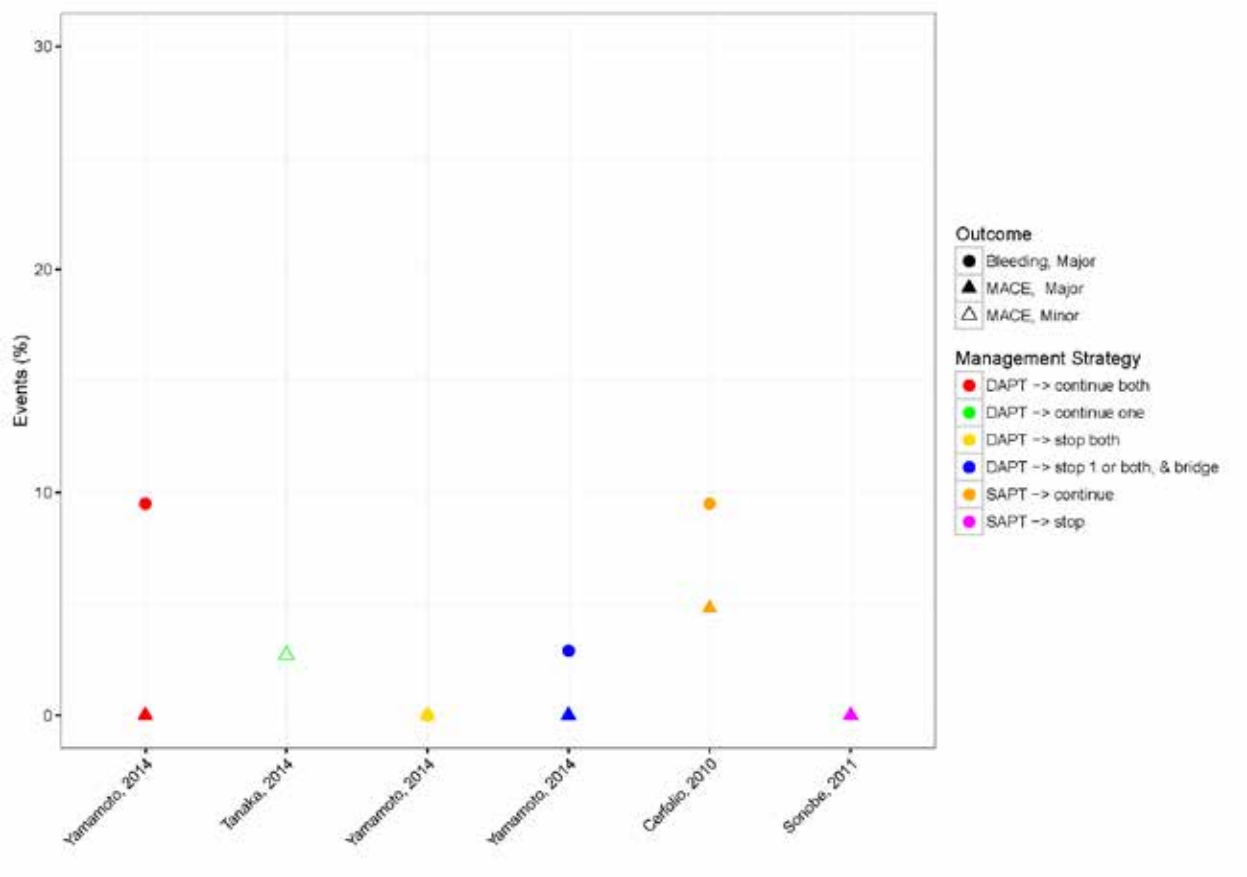
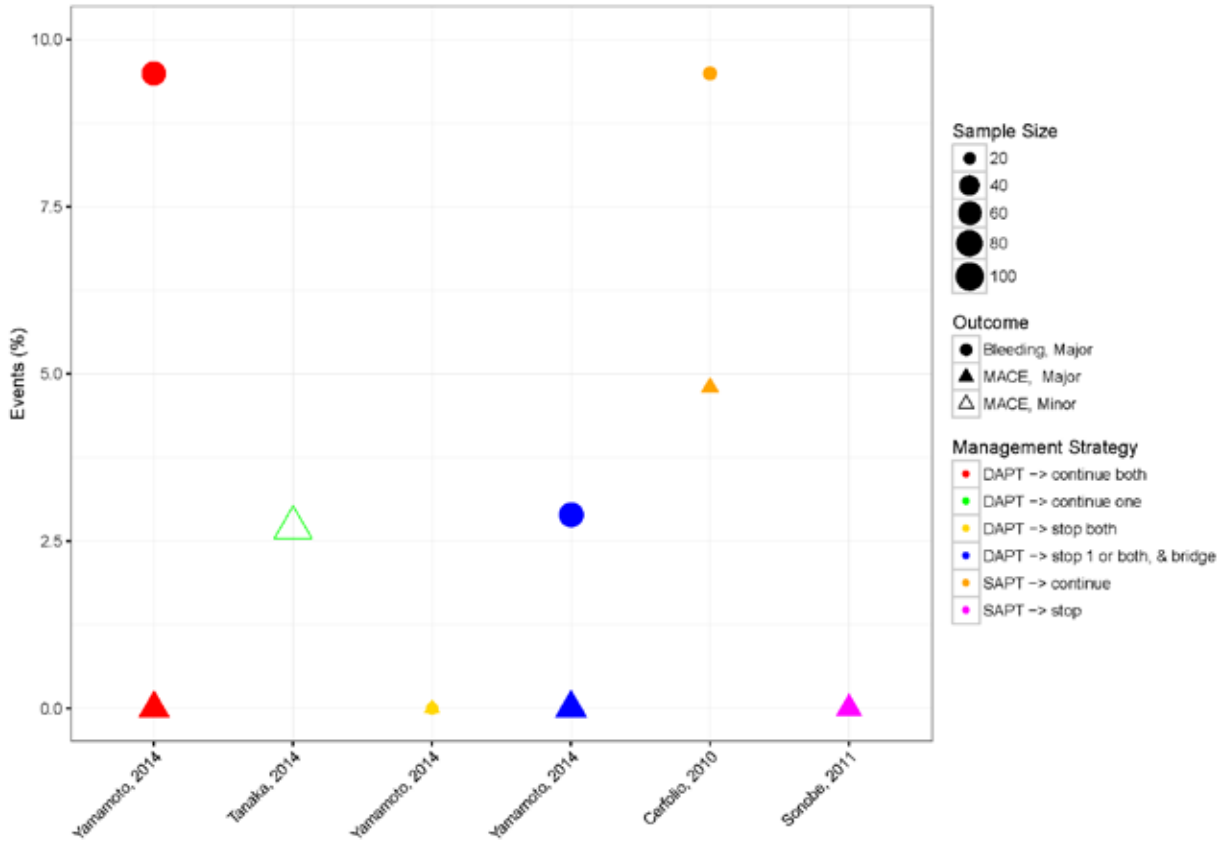


Figure 5. Outcomes of observational studies of preoperative antiplatelet therapy, perioperative APT management, and outcomes by surgery risk category (weighted by sample size)



There were no studies of ophthalmologic surgery that met inclusion criteria. The only study of antiplatelet management and ocular procedures that we identified was a prospective study of 85 patients taking antiplatelet or anticoagulant therapy and undergoing 107 vitreoretinal procedures (of which 88% of cases were vitrectomies).[19] Patients were taking antiplatelet or anticoagulant therapy for a diversity of reasons; only 13% of patients had cardiac stents. Thus, this study would have been excluded on the grounds of being the wrong patient population. Nevertheless, as it is the only study of ophthalmologic procedures we identified, we summarize the results here. Among the 107 cases, in 72% the patients were taking aspirin alone, in 8% taking clopidogrel alone, and in 10% each were taking aspirin and clopidogrel or warfarin. All patients had their antiplatelet or warfarin therapy continued during the perioperative period. The primary outcome was intraoperative or postoperative bleeding. No MACE outcomes were reported. There were 25 cases of intraoperative bleeding, of which 24 happened during vitrectomy. Of these 24, 22 were hemorrhage in the vitreous cavity, of which 20 were classified as “mild” and one each was classified as “moderate” and “dense.” There were 24 cases of post-operative bleeding, of which 22 followed vitrectomy and 2 followed scleral buckling. Among the vitrectomy cases, there were 12 cases of mild-to-moderate vitreous cavity hemorrhage, and 5 cases of dense hemorrhage. There were 4 cases of anterior chamber hemorrhage, and one choroidal hemorrhage. The 2 cases following scleral buckling consisted of one case each of a subretinal hemorrhage and a choirodal hemorrhage. There were no cases of catastrophic suprachoroidal hemorrhage leading to loss of

vision. The authors concluded that continuing these medications during the perioperative period is safe for vitreoretinal surgery.

Summary of Findings

Few studies reported results stratified by type of surgical procedure, and among those that did there was no clear signal of differences 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?

Among the 5 studies that included more than 100 patients, one was primarily focused on a bridging strategy,[20] 2 studies did not assess outcome differences by type of APT,[16,24] and one study only assessed differences between single antiplatelet therapy versus dual antiplatelet therapy.[15] Only the case-control study by Hawn and colleagues (done in a VA setting) assessed outcomes by particular type of antiplatelet management.[22] In that study, there was no statistically significant difference in the proportions of patients with and without MACE outcomes whether they had aspirin or clopidogrel both continued or both stopped perioperatively (for patients on DAPT), or one or the other held, or for patients on SAPT whether it was aspirin or clopidogrel and whether it was continued or stopped. Thus, there was no evidence that the type of antiplatelet therapy or its perioperative management was related to difference in MACE outcomes, although some categories included relatively few numbers of patients and therefore had relatively low statistical power to detect differences (such as only 33 patients who were taking only clopidogrel preoperatively, and only 14 patients who were on dual therapy that had only the aspirin held).

Summary of Findings

One large VA study did not find any evidence that the type of APT was associated with differences in MACE outcomes.

Quality of Evidence for Key Question 4

We judged the evidence as insufficient regarding the association between the type of APT and outcomes, as there is only a single study for MACE outcomes and no study that assessed bleeding outcomes.

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

The timing of resumption of APT after perioperative cessation varied between studies and among individual patients within studies. Most studies reported resuming APT as soon as possible after surgery. Cited rationales for timing of resuming APT therapy included clinical assessment of bleeding risk[14] and discretion of the surgical team.[13]

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 cardiac stents undergoing non-emergent surgery is insufficient to conclusively guide clinical practice. Study heterogeneity, combined with small sample sizes, limited the ability to assess the impact of the different aspects of APT – timing of cessation, bridging, restarting therapy, and type of APT. Additionally, the varied range of invasiveness of the procedure, from skin excisions to major thoracic cases, contributes to the operative bleeding risk and MACE, yet many studies lacks sufficient detail to assess the impact of procedure on the outcomes. It is also likely that factors other than perioperative APT may be in part responsible for differences in bleeding and MACE rates observed between studies.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1

Thirteen observational studies reported the details of preoperative APT, perioperative anti-platelet therapy management, and outcomes, in sufficient detail to assess their association. The majority of studies were small, with fewer than 100 patients included, and the results were quite heterogeneous, with MACE rates and bleeding rates varying many-fold between studies reporting outcomes for the same combination of preoperative APT and perioperative management (such as preoperative dual antiplatelet therapy, holding both prior to surgery). In general, within studies the bleeding outcomes were reported at higher rates than the MACE outcomes.

Key Question 2

Evidence for the impact of timing of discontinuation of APT consists of very small case reports within larger studies, and demonstrated no identifiable trend. In the VA case control study discussed above,[22] there was no association between stopping dual APT for at least 5 days versus some other strategy.

Key Question 3

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

Key Question 4

One large VA study did not find any evidence that the type of APT was associated with differences in MACE outcomes.

Key Question 5

Evidence for the impact of timing of 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. Numerous studies of APT in the perioperative period were excluded because details of

the antiplatelet therapy were not presented in sufficient detail. Given the heterogeneity observed, the data suggest that variables other than the antiplatelet strategy may play a role in determining perioperative bleeding or MACE rates, and in most cases these other variables were not identified or not adequately able to be controlled for in these observation studies.

We theorize that several factors may work in conjunction and be associated with bleeding and MACE events, but the data were too limited to help address this. For example, it is likely that the type of APT and the invasiveness of the operation combined may be associated with bleeding and MACE. However, the majority of studies included a wide range of procedures (skin excision through to thoracic surgery) and the APT management also varied between studies (timing, dual versus single preoperative, cessation versus continuing, and use of bridging). Additionally, the outcomes and APT management were often only reported for cases where an event occurred, thus the management of those without an event was unknown. This prevented us from identifying whether one APT management for a particular type of procedure, or group of procedures, was protective or harmful. Another possibility is that whether or not the patients' cardiac status was optimized or if they were satisfactorily cleared from a cardiac standpoint was absent from the studies. For example, we could not assess the adequacy of their level of beta blockade, functional status, or cardiac function at the time of surgery. Additionally, perioperative management can also impact development of MACE, such as fluid management, 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 4 key questions.

Heterogeneity

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

Applicability of Findings to the VA Population

Several studies specifically assessed Veterans, including the largest study. 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 with cardiac stents 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 in turn suggests that observational studies are going to have difficulty in identifying or balancing these other clinical factors, rendering additional observational studies of limited value in reaching strong conclusions about perioperative antiplatelet management strategies. Randomized studies would balance these other clinical factors, even if they could not be identified. Yet randomized studies present their own problem – namely sample size. Trying to detect small effects requires large samples. For example, if the rate of MACE outcomes is 5% if both dual antiplatelet agents are stopped, then in order for a clinical trial to have 80% power to detect a decrease in MACE outcomes to 3% if dual antiplatelet therapy is continued would require a sample size of almost 1500 patients in each arm. Similarly, if the rate of bleeding is 5% with all APT stopped, then it would require more than 400 patients in each arm to have 80% power to detect a doubling of this to 10% if dual antiplatelet therapy is continued. While these sample sizes are not unprecedented in cardiology research, they are nevertheless much larger than any of the observational studies included in this review (counting the case-control portion of the VA study by Hawn and colleagues). And if any additional stratifying variables are included, such as type of surgery, or timing of ATP stopping and resumption, this would greatly add to the needed sample size. Nevertheless, if stronger evidence is desired, rather than continue to conduct observational studies of limited ability to provide definitive conclusions, investing in a definitive RCT may be more cost-effective.

CONCLUSIONS

Published studies of the association between perioperative antiplatelet therapy management and outcomes in patients with coronary stents undergoing 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 MACE and bleeding 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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