Dual Antiplatelet Management in the Perioperative Period: A Systematic Review

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This report was prepared by the Evidence Synthesis Program Center located at the **VA Greater Los Angeles Healthcare System,** directed by Isomi Miake-Lye, PhD and Paul Shekelle, MD, PhD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. 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 program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the Surgical Quality Improvement Program in the National Surgery Office. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

The authors are grateful to the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Jason M. Johanning, MD, MS
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Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked

areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix F for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABBREVIATIONS TABLE

APT	Antiplatelet therapy
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BMS	Bare metal stent
CABG	Coronary artery bypass graft surgery
CDW	VA Corporate Data Warehouse
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MACE	Major adverse cardiac events
MALE	Major adverse limb events
MI	Myocardial infarction
NACE	Net adverse cardiovascular events
PCI	Percutaneous coronary intervention
ROBINS-I	Risk of Bias in Non-randomized Studies – of Interventions
STEMI	ST elevation myocardial infarction
TAVR	Transcatheter aortic valve replacement
TIMI	Thrombolysis in myocardial infarction
QUIP	VA Surgical Quality Improvement Program

EXECUTIVE SUMMARY

INTRODUCTION

Antiplatelet agents are central in the management of cardiovascular and cerebrovascular disease. Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 antagonist is protective against recurrent myocardial infarction, coronary stent thrombosis after percutaneous coronary intervention (PCI), and cerebrovascular ischemic events. The optimal perioperative management of antiplatelet agents for patients on DAPT is not clear. VA ESP reports in 2016 and 2017 found only observational studies that did not support strong conclusions. This review summarizes current evidence since that time regarding the occurrence of major adverse events associated with continuing, suspending, or varying DAPT in the perioperative period.

METHODS

Data Sources and Searches

We conducted broad searches using terms relating to *dual anti-platelet therapy* or *double anti-platelet* or *DAPT* and *general surgery* or *surgical procedures, operative*. To identify articles relevant to the key questions, a research librarian searched PubMed and Cochrane from 11/30/2015–5/16/2021 and Embase from 1/1/2016–5/17/22.

Study Selection

Studies were eligible if they compared 2 or more DAPT perioperative management strategies in patients already receiving DAPT.

***P**opulation:*	Adults on DAPT for any reason undergoing major elective, urgent, or emergent surgeries
***I**ntervention:*	Continued DAPT in the perioperative period
***C**omparator:*	Suspended or varied DAPT (*ie*, by drug or by timing) in the perioperative period
***O**utcomes:*	Occurrence of major adverse cardiac events (MACE and myocardial infarction [MI], stroke, cardiovascular death), major adverse limb events (MALE), all-cause death and major bleeding (standardized bleeding according to Thrombolysis in Myocardial Infarction [TIMI] or Bleeding Academic Research Consortium [BARC] scores, or transfusions or blood loss) and reoperation
***T**iming:*	2015–present
***S**etting:*	Any
***S**tudy Design:*	Original research studies of any design

Data Abstraction and Assessment

Data extraction was completed in duplicate. All discrepancies were resolved with full-group discussion.

Synthesis

As data were too heterogeneous in terms of different DAPT strategies and outcomes measured, no meta-analytic analysis was judged clinically sensible. Therefore, the synthesis is narrative, looking at different DAPT strategies, the types of surgical procedures (predominantly coronary artery bypass graft surgery [CABG]), and outcomes. In this report, we consider withdrawal or discontinuation of DAPT as stopping either aspirin or a P2Y12 inhibitor or both agents; continuation of DAPT indicates that both drugs were given in the specified timeframe.

RESULTS

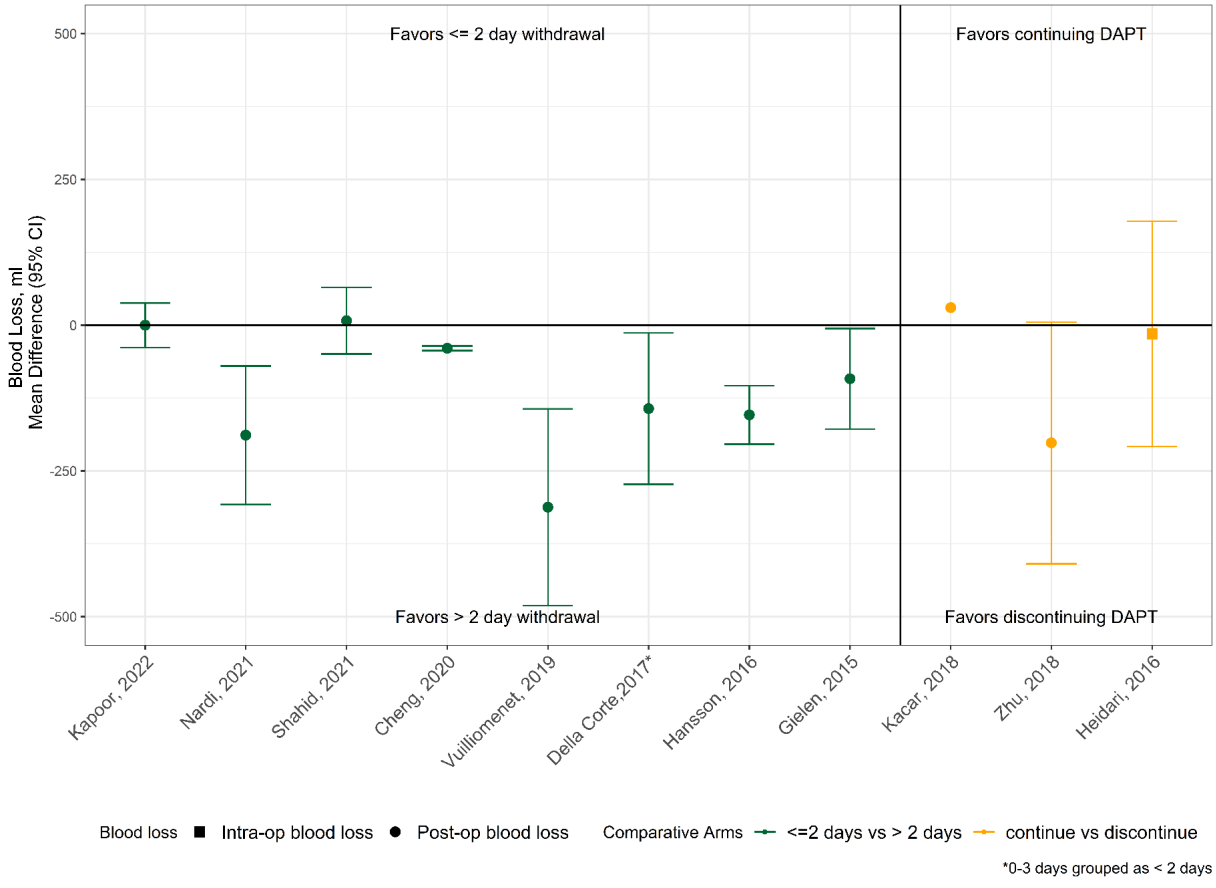
Results of Literature Search

The literature search identified 3,565 potentially relevant citations; 509 were included at the abstract screening level, 443 of which were excluded for various reasons. From the remaining 66 publications, 18 observational studies met inclusion criteria. No RCTs were identified and no studies were judged to be at low risk of bias.

Summary of Results for Key Questions

Among the 18 included studies, the majority involved CABG surgery and their reported outcomes were analyzed in aggregate when possible. Eleven observational CABG studies contained sufficient data on postoperative blood loss. See ES Figure 1 below.

ES Figure. Blood Loss Outcomes



The preponderance of these studies favor less blood loss with longer duration of suspension of DAPT therapy for more than 2 days. For transfusions, there appeared to be a slight trend favoring >2 days DAPT withdrawal or discontinuing DAPT. Surgical re-exploration data for CABG studies showed a similar pattern, with all of the point estimates favoring less re-exploration in patients with >2 days DAPT withdrawal, although in 2 of 5 studies this difference was not statistically significant. Two studies of DAPT discontinuation had no difference in re-exploration. Among 5 observational CABG studies, there were no statistically significant differences in patient death across DAPT management strategies. Few studies reported cardiac outcomes.

The remaining studies, which were about procedures other than exclusively CABG, included 1 combined analysis of cardiac and non-cardiac surgery and 5 studies about non-cardiac surgical procedures. Data from these studies demonstrated mixed findings with respect to DAPT strategy and bleeding and ischemic outcomes. No studies were found that reported limb outcomes.

DISCUSSION

Key Findings and Strength of Evidence

Perhaps the most important finding from this review is how thin the evidence base is for this consequential decision that must be taken many times every day at surgical centers around the country. We identified no RCTs that met inclusion criteria, meaning all the evidence comes from observational studies that have inherent methodologic limitations, chiefly concern for confounding in the patient selection for the different DAPT strategies. The strongest signal we could find, which was still low certainty evidence, was that suspension of DAPT therapy for more than 2 days was associated with less bleeding, transfusions, and re-explorations, and was limited to patients undergoing CABG. Data about other surgical procedures, other DAPT strategies, patients with non-cardiac stents, and other outcomes were either so thin that no conclusions could be drawn or absent entirely. In particular, while we found a signal that suspending DAPT therapy for greater than 2 days was associated with less bleeding in CABG surgery, the absolute differences in blood loss across strategies were modest and of uncertain clinical significance, and we were unable to find any conclusive evidence about that strategy's association with cardiac outcomes, leaving the knowledge about benefits and risks unbalanced.

Future Research

In the absence of randomized trials of different DAPT strategies, it is left to observational studies of sufficient size and rigor to help provide evidence about major adverse events associated with continuing, suspending, or varying DAPT in the perioperative period. The attributes of such an observational study would include: 1) a very large sample, to both facilitate risk adjusting and to support subgroup analyses of the kinds posed in Key Question 2; 2) periodic auditing of the accuracy of data collection, so that researchers can have confidence in the variables and values in the dataset; 3) multiple data sources from many institutions and surgical teams, to help avoid individual surgical team effects that may be confounded with DAPT strategy choice; and 4) the ability for the data collected to be used to create standardized composite endpoints such as BARC and MACE. One possible data source for such a study would be the VA Surgical Quality Improvement Program (QUIP). It would be worth an exploratory assessment of whether there is sufficient variation in DAPT strategies among patients in the VA QUIP database such that an analysis as outlined above is feasible. If the VA QUIP data is unable to provide clinically useful

conclusions regarding the above questions, then the VA Corporate Data Warehouse (CDW) could be evaluated as another potential data source for an adequately powered epidemiologic analysis, although this would likely require far more time in building and cleaning the data than VA QUIP.

Conclusions

The evidence base on the benefits and risks of different perioperative DAPT strategies for patient with stents is extremely thin. The strongest signal, which was still judged as low certainty evidence, is that suspension of DAPT for more than 2 days prior to CABG surgery is associated with less bleeding, transfusions, and re-explorations, but its association with other outcomes of interest, such as MACE, is uncertain.

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) is responding to a request from Jason Johanning, Medical Director, Surgical Quality Improvement Program in National Surgery Office, to review the evidence on the occurrence of major adverse events associated with continuing, suspending, or varying dual antiplatelet therapy (DAPT) in the perioperative period. Findings from this review will be used to inform guidance on the management of DAPT in the perioperative period for patients undergoing major elective, urgent, or emergent surgeries.

BACKGROUND

Antiplatelet agents are central in the management of cardiovascular and cerebrovascular disease. DAPT consisting of aspirin and a P2Y12 antagonist is protective against recurrent myocardial infarction, coronary stent thrombosis after percutaneous coronary intervention (PCI), and cerebrovascular ischemic events.[1-5] The benefits of DAPT in terms of thromboembolic prevention must be weighed against bleeding risk. This balance is especially critical in patients undergoing both cardiac and non-cardiac surgery. An estimated 5% of patients with coronary stents may need non-cardiac surgery within 1 year and up to 25% undergo surgery within 5 years.[6,7] A significant proportion of patients who are on DAPT may also require cardiac surgery.[8-10]

The optimal perioperative management of antiplatelet agents for patients on DAPT is not clear. Current international guidelines recommend delaying elective surgery for 1 to 6 months after stent placement and continuing aspirin through the perioperative period if the surgery cannot be delayed and when the procedure mandates discontinuation of a P2Y12 inhibitor.[9,10] However, there is limited evidence to guide decision-making involving urgent surgical intervention or patients with significant ischemic or bleeding risks. These situations pose a particular challenge to clinicians who must consider the consequence of delaying surgery, the hazard of periprocedural bleeding, and the risk of thrombotic events in patients with known cardiovascular disease.

In 2016 and 2017, the ESP produced 2 reports on antiplatelet therapy management for patients with stents undergoing elective surgery: 1 report focused on patients with cardiac stents[11] and the other on patients with peripheral vascular or cerebrovascular stents.[12] Both reports concluded that insufficient evidence was available at that time to offer clear guidance for clinical practice. In the intervening years, the urgency of the need for evidence for this clinical decision has grown, and thus ESP was engaged to search for current evidence since 2015 regarding the occurrence of major adverse events associated with continuing, suspending, or varying DAPT in the perioperative period.

METHODS

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ1: Among adults on DAPT undergoing major elective, urgent, or emergent surgeries, what is the occurrence of major adverse events when DAPT is continued versus suspended or varied perioperatively?

KQ2: Does occurrence of major adverse events vary across different patient subgroups (*eg*, indication for DAPT [*eg*, coronary artery disease, stroke, following stent placement], age, sex, comorbidity)?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number: CRD42022371032).

DATA SOURCES AND SEARCHES

We conducted broad searches using terms relating to *dual anti-platelet therapy* or *double anti-platelet* or *DAPT* and *general surgery* or *surgical procedures, operative*. To identify articles relevant to the key questions, a research librarian searched PubMed and Cochrane from 11/30/2015–5/16/2021 and Embase from 1/1/2016–5/17/22. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. See Appendix A for complete search strategy.

STUDY SELECTION

Four team members working independently screened the titles of retrieved citations. For titles deemed relevant by at least 1 person, abstracts were then screened independently by 2 team members. All disagreements were reconciled through group discussion. Full-text review was conducted in duplicate by independent team members with any disagreements resolved through discussion. Studies were included at the full-text level if they were original research studies of any design and had relevant outcome data presented for the patients that were on preoperative DAPT comparing at least 2 perioperative strategies.

The ESP included studies that met the following criteria:

***P**opulation:*	Adults on DAPT for any reason undergoing major elective, urgent, or emergent surgeries
***I**ntervention:*	Continued DAPT in the perioperative period
***C**omparator:*	Suspended or varied DAPT (*ie*, by drug or by timing) in the perioperative period

***O**utcomes:*	Occurrence of major adverse cardiac events (MACE and myocardial infarction [MI], stroke, cardiovascular death), major adverse limb events (MALE), all-cause death and major bleeding (standardized bleeding according to Thrombolysis in Myocardial Infarction [TIMI] or Bleeding Academic Research Consortium [BARC] scores, or transfusions or blood loss) and reoperation
***T**iming:*	2015–present
***S**etting:*	Any
***S**tudy Design:*	Original research studies of any design

DATA ABSTRACTION

Data extraction was completed in duplicate. All discrepancies were resolved with full-group discussion. At the abstract stage, information on the eligibility (whether patients were on preoperative DAPT, whether there was a comparison of patients on preoperative DAPT with at least 2 alterative preoperative or postoperative management groups, and whether there were postoperative outcomes included), sample size, and study design were collected. Articles meeting inclusion criteria underwent a second screening, and additional information was abstracted including categorization of comparison groups for each DAPT management strategy, patient characteristics, DAPT indication, and outcomes. Bleeding outcomes of interest were mean postoperative blood loss, reoperation for blood loss, red blood cell transfusions, platelet transfusions, and the occurrence of bleeding events classified by standardized criteria such as the TIMI and/or BARC systems. Cardiovascular outcomes of interest were myocardial infarction, stroke, revascularization, cardiovascular death, MACE (defined as the composite of total death, MI, stroke, hospitalization for heart failure, and revascularization), net adverse cardiovascular events (NACE, defined as MACE plus major bleeding), MALE (defined as severe limb ischemia leading to an intervention or major vascular amputation), and cardiovascular death. Data on all-cause mortality were also collected.

RISK OF BIAS ASSESSMENT

To assess the risk of bias, we used the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I).[13] We used ROBINS-I for observational studies. This tool requires an assessment of whether a study is at critical, serious, moderate, or low risk of bias (or no information) in 7 domains: confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result (see Appendix C for tool and Appendix D for table).

SYNTHESIS

Because studies differed significantly in DAPT strategies and outcomes measured, no meta-analytic analysis was judged clinically sensible. Therefore, the synthesis is narrative, looking at different DAPT strategies, the types of surgical procedures (predominantly coronary artery bypass graft surgery [CABG]), and outcomes. In this report, we consider withdrawal or discontinuation of DAPT as stopping either aspirin or a P2Y12 inhibitor or both agents; continuation of DAPT indicates that both drugs were given in the specified timeframe.

Continuous outcomes were analyzed by using the mean or median along with a measure of dispersion (standard deviation, interquartile range) to calculate the difference and 95% confidence intervals (CI) between arms. For binary outcomes, outcome counts were used to calculate risk differences and corresponding 95% CI. Risk differences were preferred because they allow for rare events and outcomes with zero events. When a study reported an eligible outcome only as an odds ratio, we converted outcome data from other studies to odds ratios. We created figures for outcomes with 3 or more studies and included all outcomes in Appendix E. Graphical representations of effect sizes (mean difference, risk difference, or odds ratio) and 95% CI were plotted when available or able to be estimated using counts and sample sizes using the *metafor* package in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

CERTAINTY OF EVIDENCE

We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[14] GRADE assesses the certainty of the evidence based on the assessment of the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. This results in the following categories:

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.

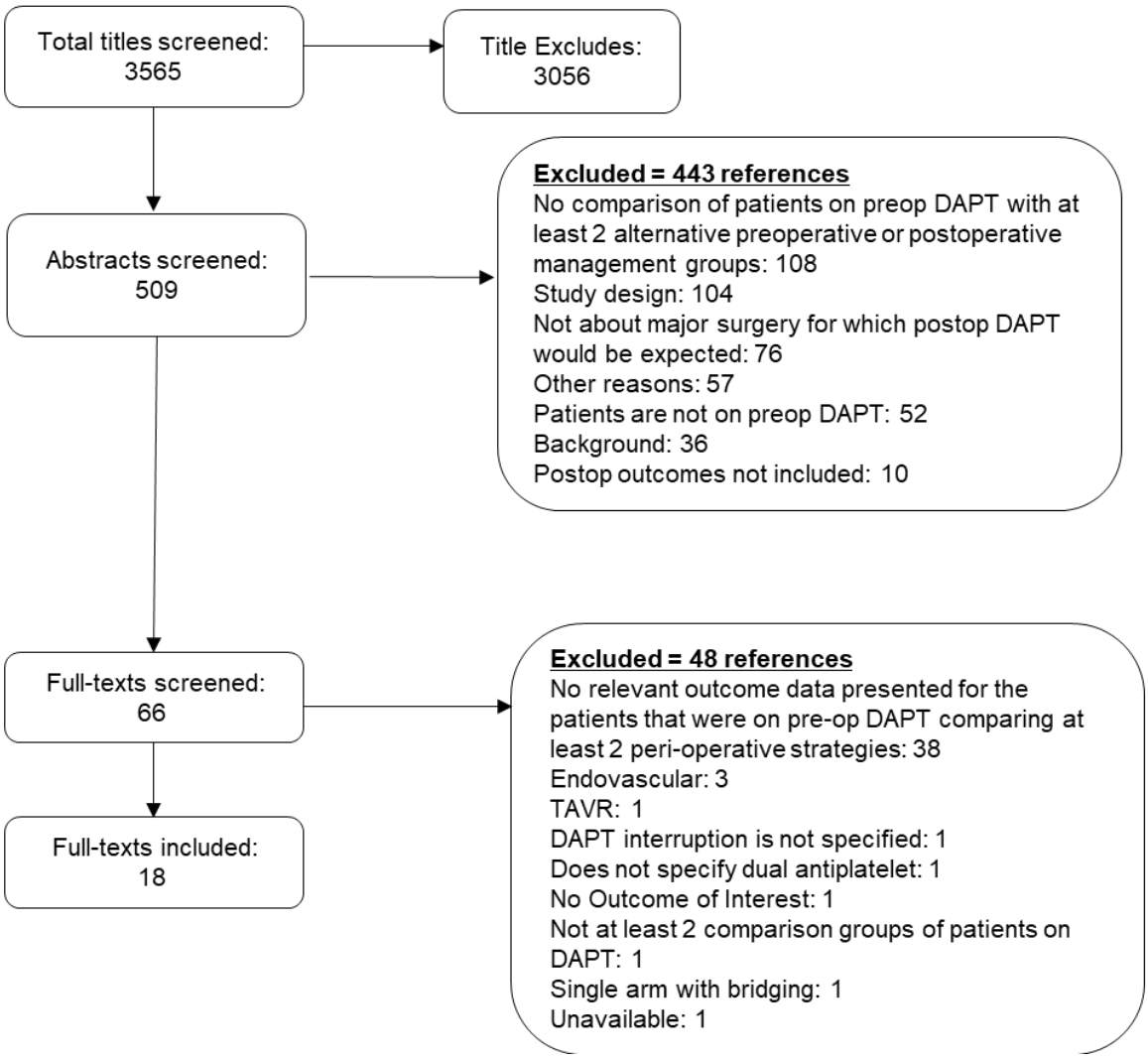
Very Low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (full list of excluded studies available in Appendix B).

Figure 1. Literature Flowchart



LITERATURE OVERVIEW

The literature search identified 3,565 potentially relevant citations, 509 of which were included at the abstract screening level. From these, a total of 443 abstracts were excluded for the following reasons: no comparison of patients on preoperative DAPT with at least 2 alternative preoperative or postoperative management groups ($N = 108$), study design ($N = 104$), not about major surgery for which postoperative DAPT would be expected ($N = 76$), other reasons ($N = 57$), patients are not on preoperative DAPT ($N = 52$), background ($N = 36$), and postoperative

outcomes not included (*N* = 10). This left 66 publications for full-text review, of which 48 publications were excluded for the following reasons: no relevant outcome data presented for the patients that were on preoperative DAPT comparing at least 2 perioperative strategies (*N* = 38), endovascular (*N* = 3), transcatheter aortic valve replacement (TAVR) (*N* = 1), DAPT interruption is not specified (*N* = 1), does not specify dual antiplatelet (*N* = 1), no outcome of interest (*N* = 1), not at least 2 comparison groups of patients on DAPT (*N* = 1), single arm with bridging (*N* = 1), and unavailable (*N* = 1). A full list of excluded studies from the full-text review is in Appendix B. A total of 18 publications were identified at full-text review as meeting initial inclusion criteria. Details of included publications are available in Appendix E.

DESCRIPTION OF THE EVIDENCE

We identified 18 publications that met the inclusion criteria. Of these 18 observational studies, 2[15,16] were propensity matched for patient and surgery characteristics (such as age, sex, comorbidities, severity of surgical disease, and surgical approach). Most studies were single-institution designs (*N* = 14). The majority of studies evaluated DAPT management at the time of CABG (*N* = 12), 3 studies evaluated varied groups of non-cardiac operations, and 1 study combined cardiac and non-cardiac surgery. Lastly, there was 1 study each evaluating hip fracture surgery and renal transplant outcomes. The strategies for perioperative management of DAPT varied: the most common approach compared different durations of time between stopping an antiplatelet agent and surgery (*N* = 11). Other comparisons included discontinuing 1 or both antiplatelet agents compared to continuing. One study compared a P2Y12 inhibitor discontinuation with IV tirofiban infusion (*N* = 1).

Risk of Bias

For the 18 observational studies, the quality of the studies was variable. Only 1 study was at low risk of confounding and the remainder were at medium or high risk. While most studies included a consecutive or full sample of patients from the specified operations, several did not and were considered moderate risk for selection bias (*N* = 10). There was overall low risk of bias in the classification of the interventions and deviation from these intended interventions (we judged retrospective chart review of drugs a patient received and the surgical procedure to be accurate). Missing data was not considered a significant source of bias given the use of retrospective chart reviews as the data source and the short term (perioperative) outcomes of most studies. Finally, several studies were at moderate or high risk of measurement bias, usually due to using unvalidated or non-standard measures of bleeding outcomes (*N* = 8). Several studies did not report cardiovascular outcomes and did provide a rationale for why clinically useful outcomes were not included. We felt that these may be at risk for reporting biases (*N* = 7).

KEY QUESTION 1: AMONG ADULTS ON DUAL ANTIPLATELET THERAPY (DAPT) UNDERGOING MAJOR ELECTIVE, URGENT, OR EMERGENT SURGERIES, WHAT IS THE OCCURRENCE OF MAJOR ADVERSE EVENTS WHEN DAPT IS CONTINUED VERSUS SUSPENDED OR VARIED PERIOPERATIVELY?

Our search identified 18 studies that met eligibility criteria. In these studies, dual antiplatelet therapy was defined as aspirin plus a P2Y12 inhibitor, often clopidogrel or an unspecified agent. Among these, 12 were studies about DAPT management in coronary artery bypass surgery

(CABG), 3 were studies involving non-cardiac surgery, 1 included both cardiac and non-cardiac surgery, 1 specifically included just hip operations, and 1 was only inclusive of renal transplant surgery. All included studies were observational; the majority were conducted at single centers, while 5 included patients from multiple institutions. Given the predominance of observational studies involving CABG, we present the results of these studies together in the following figures when possible. The others are discussed separately below.

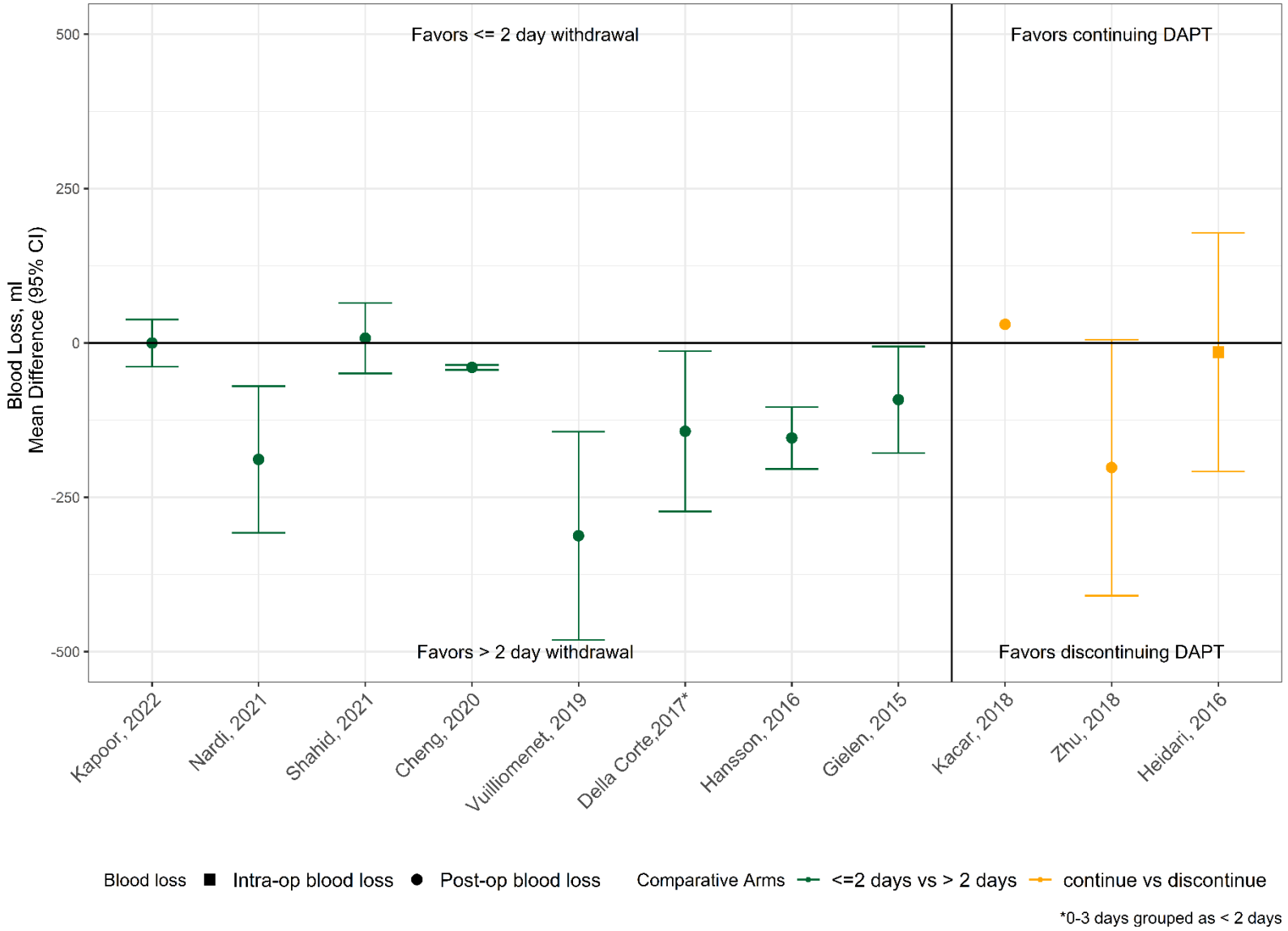
Patients on Preoperative DAPT and Undergoing CABG

Bleeding Outcomes

Blood loss

Eleven observational CABG studies contained sufficient data on postoperative blood loss to be presented collectively in Figure 2. Of these, 8 compared suspending DAPT (defined as holding P2Y12 inhibition with continuation of acetylsalicylic acid [ASA]) at various preoperative timepoints, which we dichotomized as ≤2 days withdrawal or >2 days withdrawal. Of note, 1 study that grouped 48–72 hours was placed in the >2 days withdrawal group.[17] A second study had comparison groups of 0–3 days and >4 days, which were reassigned to ≤2 and >2 withdrawal days , respectively.[18] The remaining 3 studies compared holding DAPT to continuing DAPT until surgery. In 6 of the 11 studies shown in Figure 2, mean blood loss was statistically lower in patients that either experienced withdrawal of DAPT >2 days preop or discontinuation of DAPT. The other 5 studies showed no significant differences in mean blood loss between DAPT management groups. Only 2 studies[19,20] reported higher blood loss in the DAPT-withheld or discontinued groups; however, these differences were minimal (≤30 mL) and nonsignificant. Longer duration of suspension of DAPT therapy (*ie*, for more than 2 days) favored less blood loss. However, while these studies demonstrated a statistically significant difference in postoperative blood loss between DAPT management strategies, the clinical significance of blood loss of this size (<300 mL) is uncertain.

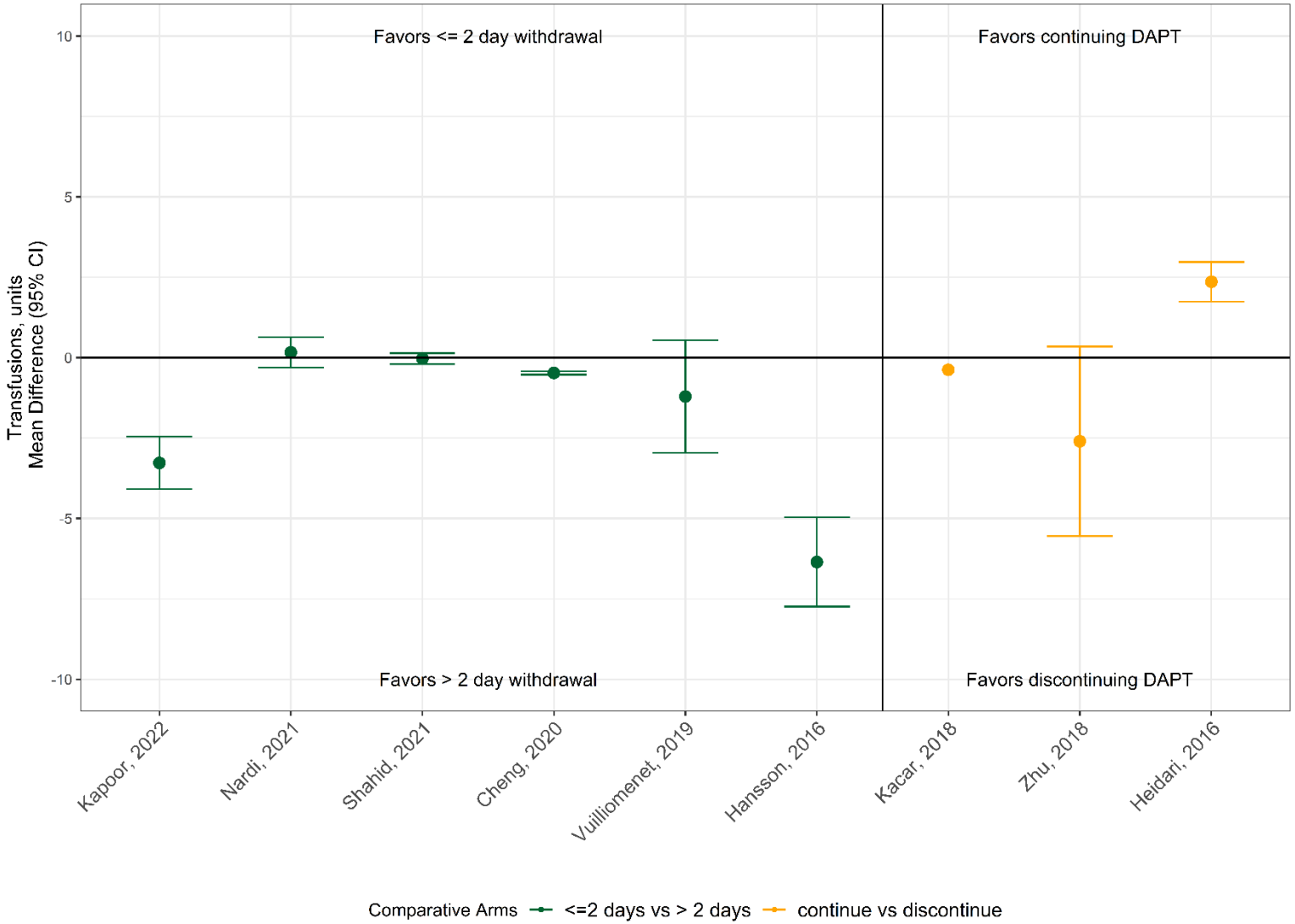
Figure 2. Blood Loss Outcomes



Transfusions

Differences in red blood cell transfusion requirements across DAPT strategies from the 9 observational CABG articles that reported transfusion outcomes are shown in Figure 3. Of the 9 available studies, 4 showed less transfusion requirements for >2 days DAPT withdrawal or discontinuing DAPT, 4 reported nonsignificant results (3 of which favored >2 days DAPT withdrawal or discontinuation), and only 1 study[21] reported statistically more transfusions in the DAPT discontinuation group.

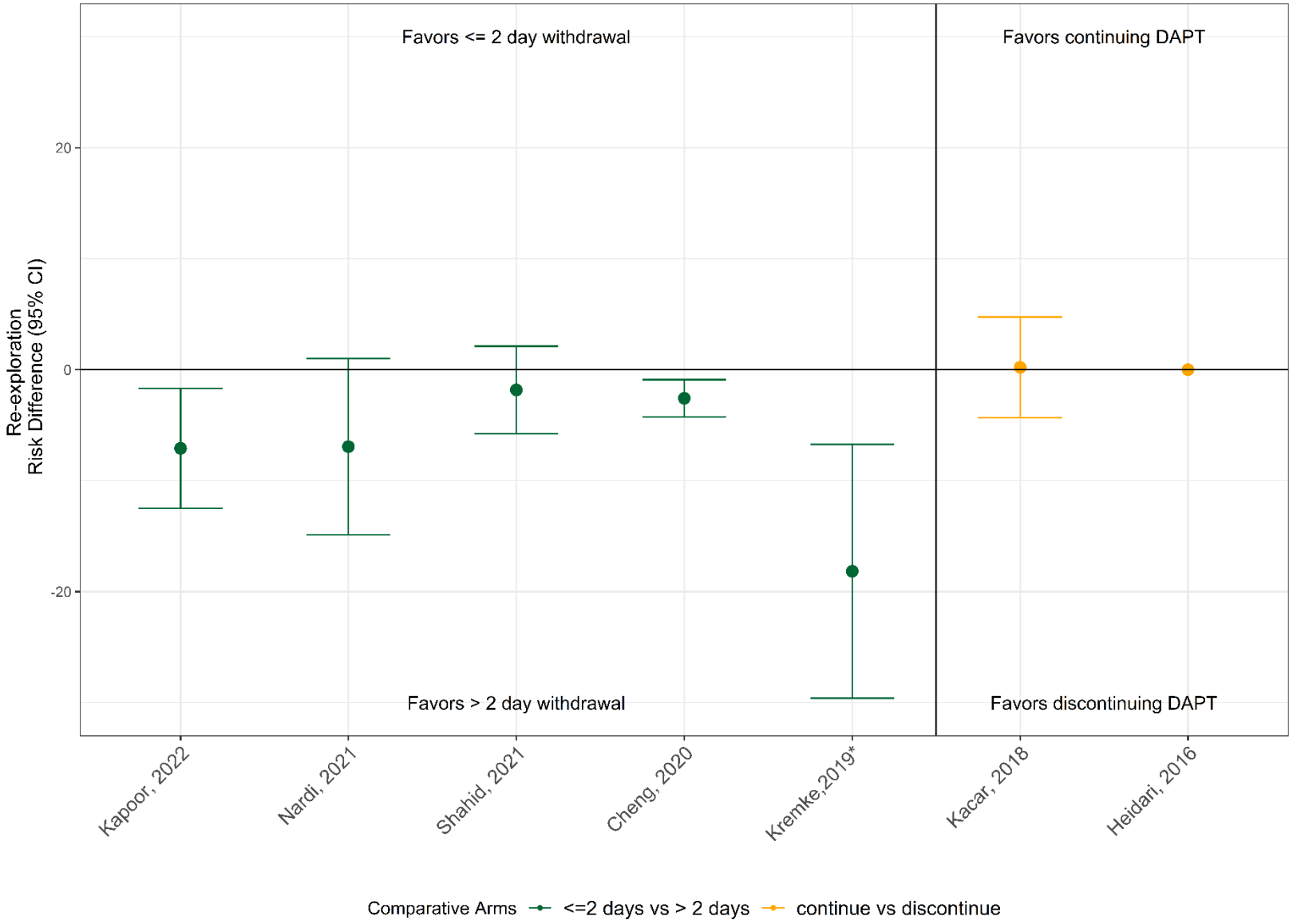
Figure 3. Transfusions Outcomes



Re-explorations

Surgical re-exploration data showed a similar pattern, with all the point estimates favoring less re-exploration in patients with >2 days DAPT withdrawal (in 2 of 5 studies this difference was not statistically significant). In contrast, the 2 studies of DAPT discontinuation found no difference in re-exploration (Figure 4).

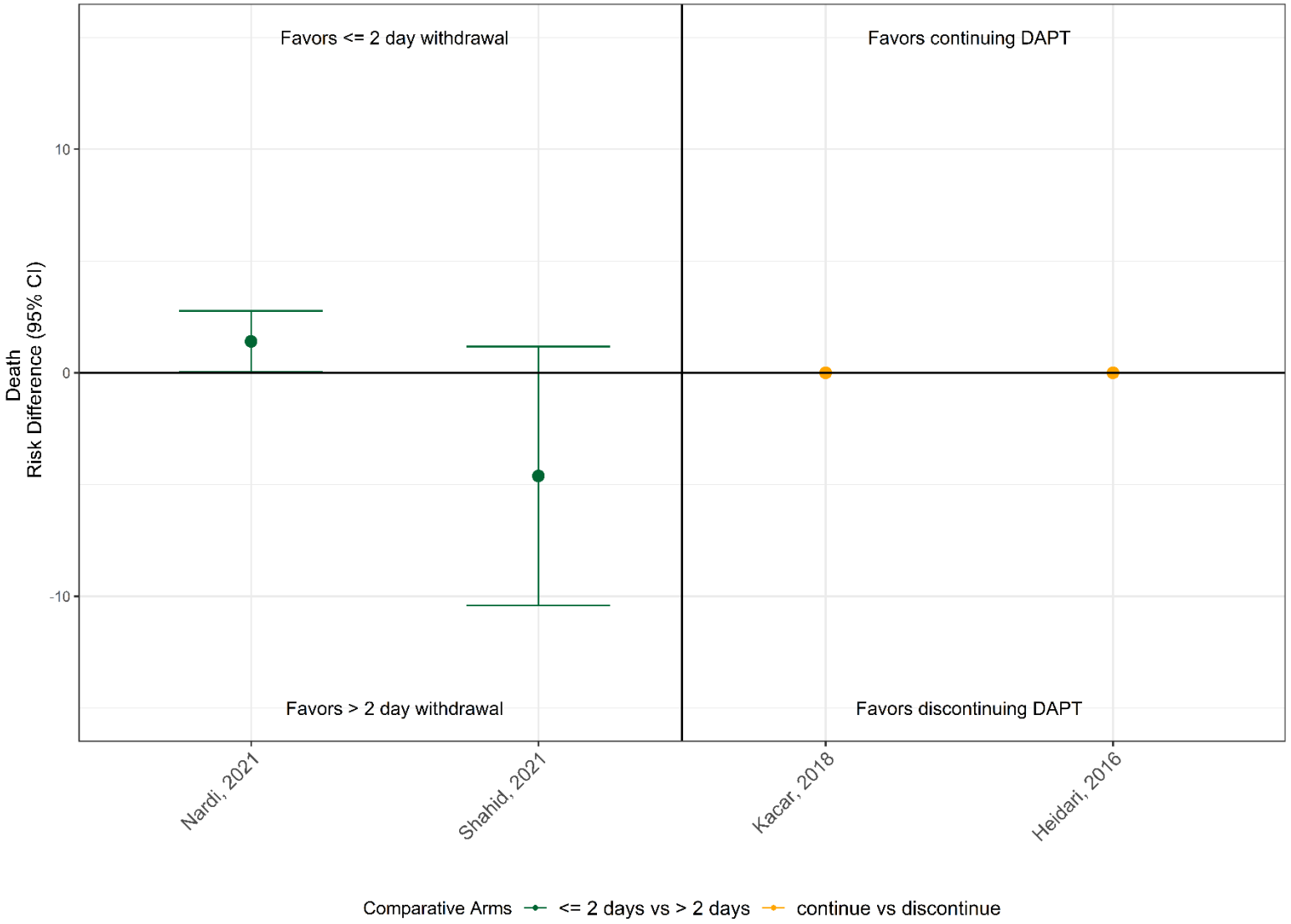
Figure 4. Re-exploration Outcomes



Perioperative Death

There were 4 observational CABG studies that reported mortality risk differences across comparison arms (shown in Figure 5) and 1 additional study[17] that reported mortality as odds ratios. None of these reported significant differences in patient death across DAPT management strategies.

Figure 5. Perioperative Death Outcomes



Cardiac Outcomes

There were too few CABG studies that reported similar cardiac outcomes to graph. Nardi and colleagues[17] observed no incidences of myocardial infarction for all DAPT management strategies, which included holding P2Y12 inhibition for 0 to 4 days prior to CABG. In a multicenter observational study of patients undergoing isolated CABG, Gielen et al found no significant association between last use of DAPT and MACE (odds ratio [OR] = 0.849, 95% CI [0.635, 1.135], $P = 0.27$).

Patients on Preoperative DAPT and Undergoing Non-cardiac Surgery

Three studies reported outcomes after non-cardiac surgery.[22-24] Each study had multiple types of surgeries, most commonly describing abdominal/gastrointestinal, vascular, ophthalmologic, and orthopedic surgeries. Because studies did not all report similar outcomes, it was not possible to create graphs as was done for the CABG studies. We discuss each study narratively below.

Irie and colleagues identified 133 patients on DAPT post-cardiac stenting who underwent emergency non-cardiac surgery (majority abdominal, 57.9%, followed by vascular, 9%) and determined predictors of life-threatening and major bleeding within 180 days of surgery ($N = 18$) compared to those who did not ($N = 115$).[22] There was no significant association between type of P2Y12 inhibitor and risk of bleeding (unadjusted). In addition, among the 18 patients who had major or life-threatening bleeding, 61% had restarted antiplatelet therapy less than 2 days after surgery compared to patients who did not develop these bleeding complications (61.1% vs 26.1%; unadjusted $P = 0.005$). After adjusting for potential confounders, overall survival did not significantly differ for patients with and without bleeding (180-day mortality: 4 [22.2%] in bleeding group vs 9 (7.8%) in no bleeding group; $P = 0.06$).

Cao and colleagues evaluated 747 patients who underwent non-cardiac surgery (mostly vascular, 33%, and gastrointestinal surgery, 23%) within 1 year of cardiac stenting and compared outcomes among those who interrupted antiplatelet therapy and those who did not.[23] There was no association between antiplatelet therapy management and MACE after adjusting for patient factors and procedure urgency (adjusted odds ratio [aOR] = 1.23, 95% CI [0.55, 2.74], $P = 0.62$) or death within 30 days (aOR = 1.21, 95% CI [0.49, 2.98]). However, there was an 83% increased odds of bleeding (defined as >2 units transfused) among patients with no interruption of antiplatelet agent (aOR = 1.83, 95% CI [1.11, 3.01], $P = 0.018$), which the authors note tended to occur sooner after cardiac stenting.

The third study of antiplatelet management after cardiac stenting by Kim and colleagues compared discontinuing ($N = 1750$) versus continuing 1 or both antiplatelet agents ($N = 1832$) for at least 1 day prior to non-cardiac surgery across 9 institutions.[24] Here, the most common types of surgeries that antiplatelet therapy was discontinued for included gynecologic, breast, head and neck, and intraabdominal surgeries, while other types such as vascular and ophthalmologic surgeries more often continued antiplatelet therapy. When comparing continuation versus discontinuation of antiplatelet therapy across all surgeries, the authors found no effect of antiplatelet discontinuation on MACE in a risk-adjusted Cox proportional hazards model (adjusted hazard ratio [HR] = 1.13, 95% CI [0.57, 2.24], $P = 0.721$) or in major bleeding when antiplatelet agents were discontinued (adjusted HR = 1.22, 95% CI [0.80, 1.87], $P = 0.349$). The authors also conclude that an optimal duration for discontinuing antiplatelet therapy

is 4–8 days, as this was associated with the lowest risk of MACE (unadjusted HR = 0.12; 95% CI [0.03, 0.52], *P* = 0.019).

Patients on Preoperative DAPT and Undergoing Surgery for Hip Fracture

We identified 1 retrospective study of 122 patients taking DAPT who sustained a hip fracture and require fixation or hip arthroplasty.[15] Patients were taking DAPT for a variety of reasons, the majority (61%) for ischemic heart disease. The authors assessed whether the duration of DAPT discontinuation (which was the number of days until surgery) was associated with clinical outcomes. They found a small increased adjusted odds of 30-day mortality for each day of operative delay (OR = 1.32, 95% CI [1.03, 1.68], *P* = 0.030) but no association with total units transfused among 11 patients requiring transfusion (incidence rate ratio = 1.00, 95% CI [0.87, 1.15], *P* = 0.968). The odds of major complications also varied across time to surgery, ranging from a small increased odds at 3.5 days (OR = 0.20, 95% CI [0.08, 0.53]), reflecting a U-shaped relationship, to a substantial increased odds at 7 days (OR = 7.91, 95% CI [2.50, 25.0], *P* = 0.001). The authors concluded that there was no benefit to surgical delay after hip fracture for older adults on DAPT. This study design precluded separating out the effects of DAPT washout from the effects of other reasons for the medical delay.

Patients on Preoperative DAPT and Undergoing Renal Transplant Surgery

Our search identified 1 study which compared antiplatelet interruption before renal transplantation in 106 patients with prior coronary stent placement.[25] This study uniquely characterized medication strategy in relation to time since DAPT indication, namely placement of a coronary stent, as well as stent type. Patients were divided into an early interruption group, defined as having transplant surgery 3 months from placement of a second-generation drug eluting stent (DES); a late interruption group, defined as having surgery 3–12 months from DES placement; and a bare metal stent (BMS) group, defined as having surgery at least 1 month from BMS placement. As opposed to the other studies included in our review that varied perioperative DAPT management across comparison groups, in this study both ASA and clopidogrel were held 5–7 days prior to transplantation for all patients. The primary finding of this study was that there were no significant differences in cardiovascular clinical outcomes, including stent thrombosis (*P* = 0.465), myocardial infarction (*P* = 0.840), MACE (*P* = 0.840), and death (*P* = 0.411), for early versus late DAPT interruption after second generation DES or BMS placement. The authors conclude that early interruption of DAPT after stent placement in preparation for renal transplant surgery was a safe strategy and did not lead to increased ischemic complications.

Major Adverse Limb Outcomes

We did not identify any studies reporting limb outcomes of any kind.

KEY QUESTION 2: DOES OCCURRENCE OF MAJOR ADVERSE EVENTS VARY ACROSS DIFFERENT PATIENT SUBGROUPS (*eg*, INDICATION FOR DAPT [*eg*, CORONARY ARTERY DISEASE, STROKE, FOLLOWING STENT PLACEMENT], AGE, SEX, COMORBIDITY)?

Among the studies in this systematic review, all but one included patients whose indication for DAPT was coronary artery disease, acute coronary syndrome, or percutaneous coronary intervention with stent placement. Tarrant et al, which investigated the effect of DAPT management following hip surgery, was the only study to include and specify multiple different indications for DAPT ($N = 122$, ischemic heart disease 61%, cerebrovascular disease 31%, peripheral vascular disease 5%, and other 3%). In this study, outcomes were not reported according to the different indications.

However, 2 studies analyzed the impact of time between surgery and prior coronary stent placement. Specifically, these studies sought to examine the safety of performing surgery and briefly suspending DAPT within the period of so-called mandatory antiplatelet therapy after stent placement. In contemporary PCI, this is considered to be 3 months following new generation DES placement and 1 month following BMS placement. In an investigation of risk factors associated with bleeding in emergency non-cardiac surgery, bleeding occurred more frequently in patients who underwent surgery within 3 months after DES, though this difference was nonsignificant (4 patients in the bleeding group vs 11 in the non-bleeding group, $P = 0.12$).[22] There was also no difference in bleeding for patients who underwent surgery within 30 days of BMS placement. The other article, by Dogan and colleagues, found that early interruption of DAPT 3 months from DES placement did not increase ischemic complications such as stent thrombosis, myocardial infarction, MACE, or death after renal transplantation. Outcomes were similar for patients treated with BMS. Notably, ST elevation myocardial infarction (STEMI) was excluded and the majority of these patients underwent PCI for stable angina, rather than acute coronary syndrome.

CERTAINTY OF EVIDENCE

The certainty of evidence for each of the outcomes and DAPT management strategies is shown in Table 1 below. In general, all outcomes were judged to have serious limitations due to study design and execution issues and there were no RCTs available. All outcomes were judged to have no limitations due to directness, as the outcomes measured were judged to be both sufficiently accurately assessed and the outcomes that matter to patients. All outcomes were judged to have limitations due to imprecision, even if the directionality of results was consistent. Some outcomes were judged to have inconsistent results across studies (bleeding, transfusions, re-explorations, *etc*), while some other outcomes were judged to be consistent, in part because there were so few studies (re-explorations, MACE outcomes), these latter all being judged as very low certainty evidence. In sum, there were no outcomes/DAPT strategy choices that were judged to be high or even moderate certainty of evidence. A few bleeding outcomes were judged to be low certainty evidence, and all other outcomes, including other possible interventions (bridging, other potential antiplatelet therapy [APT] variations) and all other outcomes (including limb outcomes), were judged to be very low certainty evidence since there was either a single observational study or no studies informing the decision.

Table 1. GRADE for Certainty of Evidence

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
Holding DAPT for More Than 2 Days vs Less Than ≤2 Days					
CABG Surgery					
Bleeding is less	Serious limitations	Inconsistent	Direct	Imprecise	Low
Transfusion is less	Serious limitations	Inconsistent	Direct	Imprecise	Low
Re-exploration is less	Serious limitations	Inconsistent	Direct	Imprecise	Low
Holding DAPT vs Continuing DAPT					
CABG Surgery					
No difference in bleeding	Serious limitations	Inconsistent	Direct	Imprecise	Very low
No difference in transfusions	Serious limitations	Inconsistent	Direct	Imprecise	Low
No difference in re-exploration	Serious limitations	Consistent	Direct	Imprecise	Very low
Non-cardiac Surgery					
Bleeding is less	Serious limitations	Inconsistent	Direct	Imprecise	Very low
No difference in MACE/cardiac outcomes	Serious limitations	Consistent	Direct	Imprecise	Very low

DISCUSSION

Perhaps the most important finding from this review is how little evidence is available for this consequential decision made many times every day at surgical centers around the country. We identified no RCTs, meaning all the evidence comes from observational studies with methodologic limitations, chiefly the concern for confounding in the patient selection for the different DAPT strategies. The strongest signal we could find, which was still low certainty evidence, was that the suspension of DAPT therapy greater than 2 days was associated with less bleeding, transfusions, and re-explorations, and limited to patients undergoing CABG. Data about other surgical procedures, other DAPT strategies, patients with non-cardiac stents, and other outcomes were either so limited that no conclusions could be drawn, or absent entirely. In particular, although we found a signal that suspending DAPT therapy for 3 days or greater was associated with less bleeding in CABG surgery, the clinical significance of this blood loss is uncertain, as the quantity of average blood loss across DAPT strategies amounted to <300 mL of blood. We were unable to find any conclusive evidence about that strategy's association with cardiac outcomes. Without this information, it is difficult to determine whether risks of suspending DAPT therapy outweigh its benefits.

Acknowledging these limitations, our findings pertaining to the possible benefits of holding DAPT greater than 2 days prior to CABG in terms of reduced bleeding risk are consistent with the 2021 ACC/AHA/SCAI guidelines for coronary artery revascularization and the 2017 European guidelines for dual antiplatelet therapy that recommend continuing aspirin perioperatively but holding clopidogrel for 5 days, ticagrelor for 3 days, and prasugrel for 7 days prior to elective CABG.[8,9] In our review, we considered DAPT discontinuation or withholding as stopping 1 or both antiplatelet agents, which most often entailed holding the P2Y12 agent. Similar DAPT advice is provided for non-cardiac surgery in the 2022 Chest guidelines, and the same preoperative P2Y12 withholding periods are also endorsed in current prescribing information from Sanofi-Aventis, AstraZeneca, and Eli Lily for clopidogrel, ticagrelor, and prasugrel, respectively.[26]

LIMITATIONS

This systematic review was limited by the quality of available evidence pertaining to the topic of antiplatelet management in the perioperative period. Had we limited our inclusion criteria to only RCTs, we would have been left without studies that addressed the key questions and met inclusion criteria. Thus, we needed to include observational studies, but doing so brings its own set of limitations. The majority of included observational studies were single-center experiences, and the attempts to control for confounding were uneven. Thus, our report includes no studies at low risk of bias.

Further hampering our ability to make cross-study comparisons was the inconsistency in comparison groups and reported outcomes. There was a wide range of observed antiplatelet strategies that included holding 1 or both agents for variable amounts of time preoperatively, bridging with intravenous antiplatelet medications, or using an entirely different medication or technique to prevent adverse bleeding outcomes. We attempt to summarize some of the data from CABG studies in the figures, with the caveat that, in dichotomizing the strategies as DAPT withdrawal for > or ≤2 days, some studies with prolonged DAPT withholding (*ie*, 7 days or more) are included in the >2 days withdrawal and may be skewing the results. We also recognize

that there are significant differences in the pharmacokinetic and pharmacodynamic profiles of available P2Y12 inhibitors, and that grouping them together risks oversimplifying any conclusions drawn from this review.

While some clinical outcomes such as reoperation and mortality were used by several studies, composite cardiovascular outcomes, such as MACE, and standardized bleeding outcomes were particularly disparate among the studies. For example, few studies used standardized bleeding outcomes such as BARC definitions, and instead we found a variety of reported lab values, quantities of transfused blood products, or blood loss at arbitrary postoperative time points.

Furthermore, nearly all the available data are about patients with stents (mostly cardiac stents) on preoperative DAPT who are undergoing CABG. This accounted for about 75% of included studies. No studies reported limb outcomes, such as MALE. Thus, the hypothetical case in the VA setting for which evidence was needed—that of a patient on DAPT for a lower limb stent who was now undergoing a renal operation—has no evidence available to inform the decision.

Lastly, there is always the issue of generalizability from the context of the published study to the clinical context where DAPT decisions must be made.

FUTURE RESEARCH

Clearly this field needs much future research. Such research should use well-established measures for both benefits (standardized measures of bleeding, such as BARC) and risks (standardized measures of cardiac events, such as MACE, or limb events, such as MALE). This will facilitate the comparison of results across studies, which was a major challenge with this review. Additionally, given the unique pharmacokinetic and pharmacodynamic properties of available P2Y12 agents, further research would ideally be able to yield recommendations for specific antiplatelet agents.

The best way to provide high-quality evidence on this topic would be with 1 or more well-designed RCTs, but such studies are challenging to mount, are resource intensive, and often do not yield conclusive findings for many years. Observational studies are appealing because they can be accomplished in less time and with fewer resources, but it is clear from the studies we found that better observational studies are needed. These studies should: 1) include data on potential confounders to facilitate risk adjustment; 2) use a sample large enough to provide sufficient statistical power for subgroup analyses like those posed in Key Question 2; 3) periodically audit the accuracy of data so that researchers can have confidence in the variables and values in the dataset; 4) employ data from multiple institutions and surgical teams to reduce the impact of site and surgical team effects that could obscure the effect of DAPT strategy choice; and 5) analyze and report outcomes as standardized composite endpoints such as BARC and MACE. The obvious possibility for a dataset that is sufficiently large and informative, and directly relevant to subjects and clinical practice within VA, is the VA Surgical Quality Improvement Program (QUIP) database. It would be worth an exploratory assessment of whether there is sufficient variation in DAPT strategies among patients in the VA QUIP database to allow for an analysis like the one outlined above. If the VA QUIP data are unable to provide clinically useful conclusions regarding the above questions, then the VA Corporate Data Warehouse (CDW) could evaluated as another potential data source for an adequately powered

epidemiologic analysis, although there will need to be more preparatory work if using CDW data than if using data from VA QUIP.

CONCLUSIONS

The evidence base on the benefits and risks of different perioperative DAPT strategies for patient with stents is extremely thin. The strongest signal, which was still based on low certainty evidence, is that suspension of DAPT for greater than 2 days prior to CABG surgery is associated with less bleeding, transfusions, and re-explorations. Different DAPT strategies' association with other outcomes of interest, such as MACE, remains uncertain.

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APPENDIX A. SEARCH STRATEGIES

PubMed
11/30/2015-5/16/22; English Language
"Dual Anti-Platelet Therapy"[Mesh] OR "dual antiplatelet*"[tiab] OR "dual anti-platelet*"[tiab] OR DAPT[tiab] OR "double antiplatelet*"[tiab] OR "double anti-platelet*"[tiab] OR (("Platelet Aggregation Inhibitors"[Mesh] OR "Factor Xa Inhibitors"[Mesh]) AND "Drug Therapy, Combination"[Mesh:NoExp])
AND
"General Surgery"[Mesh:NoExp] OR "Surgical procedures, operative"[mh] OR surgery[tiab] OR surgeries[tiab] OR surgical[tiab] OR operation[tiab] OR operations[tiab] OR amputat*[tiab] OR amputation[Mesh]
Results: 2597

Cochrane
11/30/2015-5/16/22; English Language
[mh "Dual Anti-Platelet Therapy"] OR (([mh "Platelet Aggregation Inhibitors"] OR [mh "Factor Xa Inhibitors"]) AND [mh ^"Drug Therapy, Combination"]) OR ("dual antiplatelet*" OR "dual anti-platelet*" OR DAPT OR "double antiplatelet*" OR "double anti-platelet*"):ti,ab
AND
[mh ^"General Surgery"] OR [mh "operative surgical procedures "] OR [mh amputation] OR (surgery OR surgeries OR surgical OR operation OR operations OR amputation*):ti,ab
Results: 278

Embase:
1/1/2016-5/17/22; English
'dual antiplatelet therapy'/exp OR ("dual antiplatelet*" OR "dual anti-platelet*" OR DAPT OR "double antiplatelet*" OR "double anti-platelet*"):ti,ab OR (('antithrombocytic agent'/exp OR 'blood clotting factor 10a inhibitor'/exp) AND 'combination drug therapy'/de)
AND
"General Surgery"/de OR 'amputation'/exp OR "operative surgical procedures"/de OR (surgery OR surgeries OR surgical OR operation OR operations OR amputat*):ti,ab
Results: 2215

APPENDIX B. EXCLUDED STUDIES

No Relevant Outcome Data Presented for the Patients that were on Preoperative DAPT Comparing at Least 2 Perioperative Strategies, *N* = 38

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APPENDIX C. RISK OF BIAS IN NON-RANDOMISED STUDIES – OF INTERVENTIONS (ROBINS-I)

Bias Domains Included in ROBINS-I

Pre-intervention	Risk of bias assessment is mainly distinct from assessments of randomized trials
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention
At intervention	Risk of bias assessment is mainly distinct from assessments of randomized trials
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias
Post-intervention	Risk of bias assessment has substantial overlap with assessments of randomized trials
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention)
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

APPENDIX D. QUALITY ASSESSMENT FOR INCLUDED OBSERVATIONAL STUDIES

Author, Year	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Results
Cao, 2022[23]	Moderate	Low	Low	Low	Low	Low	Low
Cheng, 2020[27]	Moderate	Low	Low	Low	Moderate	Low	Moderate
De Servi, 2016[28]	High	Low	Moderate	Low	Low	Low	Low
Della Corte, 2017[18]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Doğan, 2017[25]	Moderate	Moderate	Low	Low	Low	Low	Low
Gielen, 2015[29]	Moderate	Moderate	Low	Low	Low	Moderate	Low
Hansson, 2016[30]	Moderate	Low	Low	Low	Low	Low	Low
Heidari, 2016[21]	High	High	Low	Low	Low	Moderate	Moderate
Irie, 2019[22]	Moderate	Moderate	Low	Low	Low	Low	Low
Kacar, 2018[19]	Moderate	Low	Low	Low	Moderate	High	High
Kapoor, 2022[31]	High	Moderate	Low	Low	Low	Moderate	Low
Kim, 2020[24]	Moderate	Moderate	Low	Low	Low	Low	Low
Kremke, 2019[16]	Low	Moderate	Low	Low	Low	Low	Moderate
Nardi, 2021[17]	Moderate	Moderate	Low	Low	Low	Moderate	Low
Shahid, 2021[20]	High	Moderate	Low	Low	Low	High	Moderate
Tarrant, 2020[15]	Moderate	Moderate	Low	Low	Low	Moderate	Low
Vuilliomenet, 2019[32]	Moderate	Low	Low	Low	Low	Moderate	Moderate
Zhu, 2018[33]	High	Moderate	Low	Low	Low	Moderate	Moderate

APPENDIX E. EVIDENCE TABLE

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**			**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**			**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
				Continued DAPT (or DAPT held ≤ 2d)	Discontinued DAPT (or DAPT held > 2d)	Bridged / Other:	Continued DAPT (or DAPT held ≤ 2d)	Discontinued DAPT (or DAPT held > 2d)	Bridged / Other:		
Gielen, 2015[29] Observational 7 N	CABG	290 (27%) Groups: -DAPT held <2d before surgery (n=98) -DAPT held <1d before surgery (n=192)	Indication: Unclear, likely CAD Time:unclear Age: 65 (10) Gender: 83% male	Mean Blood Loss at 48 h: Day -2: 623 mL (IQR 485-913) vs Day -1: 715 mL, IQR (513-1078 mL) Plt transfusion: Day -2: 10% Day -1 : 41%				>2d, ASA+Clop MACE: OR, OR LCI, OR UCI: 0.849, 0.635, 1.135		Not propensity matched, Multiple linear regressions using the logarithm of 48-h blood loss as the dependent variable and the effect of the variable stop day was modelled.	MACCE data is not directly compared between DAPT and other groups. Linear regression using this group on only Median blood loss/Plt transfusion
Zhu, 2018[33] Observational 1 N	CABG	120/180 (66%) Groups: Treatment group: >1wk DAPT (n=60) Discontinuation: hx DAPT but dc'd >1wk before surgery (n=60) Control: no hx DAPT (n=60)	DAPT indication is CAD + PCI Age: (48.5±3.2) Male: 130/180	Cont DAPT at least 7 d before surgery Chest Tube Drainage (total, SD): 1456.8 mL, (680.3 mL) RBC Transfusion: 9.1, (11.2) Plt Transfusion: 0.5, (1.9)	Held DAPT at least 7 d before surgery (discontinue) Chest Tube Drainage (total, SD): 1254.8 mL (457 mL) RBC transfusion: 6.5 (3.2) Plt Transfusion 0.1 (0.6)					N	
Kapoor, 2022[31] Observational 1 N	CABG	1200 (100%) Discontinue >6 d (n=468) D/C 3-5 d (n=621) D/C <2 d (n=111)	"Ages 31-70, no significant diff in age between groups" No gender reported No time since indication reported	< 2 d RBC transfusion (packed cell volume mL, SD): 34.78, 3.89 CT Drainage (mL, SD): 283.682, 191.915 Re-operation: 10	3-5 d RBC transfusion (packed cell volume mL, SD): 35.05, 5.7 CT Drainage (total mL, SD): 216.475, 188.928 Re-operation (Count): 5 6 d RBC transfusion (packed cell volume mL, SD): 28.84, 6.61 CT Drainage (total mL, SD): 333.939, 258.845 Re-operation (Count): 16					No adjustment. Mean/std deviation, ANOVA, chi squared.	

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**		**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Nardi, 2021[17] Observational 1 N	CABG (on or off pump)	333 (100%) Group A: Discontinuing DAPT (ASA + Clopidogrel/Ticagrelor) > 72 hours or 3–4 days (n=159) Group B: Discontinuing Clopidogrel/Ticagrelor (maintaining ASA when possible) 48–72 hours or 2–3 days (n=126) Group C: Discontinuing Clopidogrel/Ticagrelor (maintaining ASA or both agents) < 24 hours or 0–1 days (n=48)	Indication: Coronary artery disease Time: Unspecified Age: A: 67 (8.5), B: 68 (9.8), C: 65 (11.4) Gender (%male): A: 89%, B: 83%, C: 90%	Group C Chest tube drainage (24hrs): 698mL (SD 409) RBC transfusions (total): 0.8u (SD 1.2) Plt transfusions (total): 4 (8.33%) Reoperation for bleeding: 4 (8.33%)	Group A Chest tube drainage (24hrs): 511mL (SD 254) RBC transfusions (total): 0.7u (SD 1.4) Plt transfusions (total): 4 (2.52%) Reoperation for bleeding: 2 (1.25%) Group B Chest tube drainage (24hrs): 507mL (SD 206) RBC transfusions (total): 1.3u (SD 4.6) Plt transfusions (total): 5 (3.97%) Reoperation for bleeding: 2 (1.59%)	Group C Acute MI: 0 All-cause death: 0	Group A Acute MI: 0 All-cause death: 3 (1.87%) Group B Acute MI: 0 All-cause death: 1 (0.79%)	Variables were compared in an unadjusted analysis. Separate univariate analysis and a logistic regression model were used for additional results not pertinent to the review and so not reported here.	
Tarrant, 2020[15] Observational 1 Y	Hip surgery (following low energy proximal femur fracture)	122 (100%) Compares day of operation after last antiplatelet agent dose (time as continuous variable, 0-9d) (n=122)	Indication: Ischemic heart disease (61%), cerebrovascular disease (31%), peripheral vasular disease (5%), other (3%) Time: Unspecified Age: 83.1 (66-98) Gender: 63% female	Results reported as OR for each day of operative delay after antiplatelet dose RBC transfusions: 1 (0.87-1.15)		OR for each day of operative delay after antiplatelet dose: All-cause death: 1.32 (1.03-1.68)		Y: propensity matched on age, sex, Charleston comorbidity index, Nottingham hip fracture score, procedure (arthroplasty: yes/no)	The results were reported as odds ratios of increased risk per day for relevant outcomes as opposed to quantity/ number of events per comparison groups.

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**	**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Cheng, 2020[27] Observational 1 N	CABG (off pump)	2012 (100%) Compares day of DAPT (ASA + Clopidogrel) discontinuation preoperation (time as continuous variable, 0-5d) 0d (n=220) 1d (n=240) 2d (n=360) 3d (n=332) 4d (n=428) 5d (n=432)	Indication: Coronary artery disease Time: Unspecified Age: 61.9 (9.1) Gender: 24.7% female	0 days Chest tube drainage (mL): 610 (50) RBC transfusions (units): 3.3 (0.4) Reoperation: 13 (5.9%) BARC 4 major bleeding event within 7d: 64 (29.1%) 1 day Chest tube drainage (mL): 660 (50) RBC transfusions (units): 3 (0.3) Reoperation: 9 (3.6%) BARC 4 major bleeding event within 7d: 59 (24.6%) 2 days Chest tube drainage (mL): 600 (40) RBC transfusions (units): 2.8 (0.9) Reoperation: 17 (4.7%) BARC 4 major bleeding event within 7d: 70 (19.4%)	3 days Chest tube drainage (mL): 595 (45) RBC transfusions (units): 2.5 (0.7) Reoperation: 6 (1.8%) BARC 4 major bleeding event within 7d: 43 (13%) 4 days Chest tube drainage (mL): 590 (40) RBC transfusions (units): 2.5 (0.5) Reoperation: 10 (2.3%) BARC 4 major bleeding event within 7d: 62 (14.5%) 5 days Chest tube drainage (mL): 560 (35) RBC transfusions (units): 2.6 (0.6) Reoperation: 10 (2.3%) BARC 4 major bleeding event within 7d: 56 (13%)		Y: Univariable associations between clinical outcomes and study variables were analyzed using binary logistic regression.	This study included a subgroup analysis of incidence of myocardial ischemia, however did not analyze ischemic outcome by DAPT use, so it was not relevant to this review.
Irie, 2019[22] Observational 1 N	Non-cardiac surgery (emergent, procedure performed within 24hrs of diagnosis)	133 (100%) Compares ASA + different P2Y12 inhibitors Groups: Clopidogrel (n=86) Ticlodipine (n=37) Prasugrel (n=10) *All patients received ASA < 5d and P2Y12 < 7d before emergent surgery	Indication: PCI (100%) Time: 982d (0-6433) Age: 74 (38-90) Gender: 73.7% male	Clopidogrel Life threatening or major bleed: 12 (14%) Ticlodipine Life threatening or major bleed: 3 (8.1%) Prasugrel Life threatening or major bleed: 3 (30%)		Restarting antiplatelet agents earlier than 2d postoperatively Life threatening or major bleed: 11 (8.3%)		Multiple methods: Kaplan-Meier method to describe survival until 180 days after surgery, log-rank test to compare survival between the groups. Multivariable logistic regression. Cox proportional hazard model and estimated hazard ratios (HRs). Covariates were also evaluated for collinearity.	The majority of the results in this study were not useful to our review because the authors' analysis comprised of factors associated with a bleeding and non-bleeding group as opposed to a comparison of DAPT strategies. Additionally,

Author Year Study design # Institutions: Propensity (Y/N)	Procedure(s)	Pre-op DAPT Sample: n (%) Comparison Groups	Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]	Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:	Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:	Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]	Comments
							patients received ASA and a P2Y12 inhibitor preop (given urgent nature of surgeries) and medication management consisted of P2Y12 type and restarting agents post op.

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**	**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Vuilliomenet, 2019[32] Observational 1 N	CABG (emergency or urgent)	262 (78%) Groups: Time of ticagrelor, prasugrel or clopidogrel d/c before surgery: <24h (n=101) 24-48h (n=92) 48-72h (n=21) >72h (n=48)	Indication: ACS (100%) Time: ACS within 10 days Age: Ticagrelor (65.1 (11.0)) Prasugrel (62.8(9.0)) Clopidogrel (67.7(10.9)) Gender: Ticagrelor (89% male) Prasugrel (85%) Clopidogrel (78%)	d/c ticagrelor <24h Chest tube drainage (cc): 1220 (1197.0) any transfusion (units): 2.5 (17.9) reoperation: d/c prasugrel <24h Chest tube drainage (cc): 1320 (1934.4) any transfusion (units): 2 (22.5) reoperation: d/c clopidogrel <24h Chest tube drainage (cc): 1190 (494.3) any transfusion (units): 1 (6.0) reoperation: d/c ticagrelor 24-48h Chest tube drainage (cc): 1220 (440.0) any transfusion (units): 1 (4.1) reoperation: d/c prasugrel 24-48h Chest tube drainage (cc): 1050 (742.5) any transfusion (units): 1 (5.2) reoperation: d/c clopidogrel 24-48h Chest tube drainage (cc): 830 (1319.0) any transfusion (units): 1 (10.6) reoperation:	d/c ticagrelor 48-72h Chest tube drainage (cc): 1100 (260.8) any transfusion (units): 1 (4.5) reoperation: d/c prasugrel 48-72h Chest tube drainage (cc): 1050 (0) any transfusion (units): 0 (0) reoperation: d/c clopidogrel 48-72h Chest tube drainage (cc): 820 (766.7) any transfusion (units): 1 (1.3) reoperation: d/c ticagrelor >72h Chest tube drainage (cc): 700 (350.7) any transfusion (units): 0 (1.63) reoperation: d/c prasugrel >72h Chest tube drainage (cc): 750 (587.8) any transfusion (units): 0 (3.1) reoperation: d/c clopidogrel >72h Chest tube drainage (cc): 900 (35.5) any transfusion (units): 0 (2.2) reoperation:	(note: mortality data not reported by time of discontinuation, only by type of DAPT agent, so not included as DAPT type was not varied)	multivariable linear regression only for predictors of 24h chest tube output	

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**		**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Kremke, 2018[16] Observational 3 Y	CABG and/or single valve surgery	90 (50%) Groups: Time of ticagrelor d/c before surgery compared to ASA control group: <72h (n=42) 72-120h (n=48)	Indication: not specified Time: not specified Age: DAPT: 68, control: 69 Gender: DAPT: 78% male, control: 80% male	d/c ticagrelor <72h major bleeding: 48% reoperation: 29%	d/c ticagrelor >72h major bleeding: 17% reoperation: 10%			Propensity score matching among DAPT group to ASA only control group (by sex, age insulin-dependent DM, COPD, PAD< CNS disease, prior cardiac surgery, critical preop state, unstable angina, reduced LVEF, recent MI, acute surgery, surgery type, ECMO time preop aprotinin use)	
Kacar, 2017[19] Observational 1 N	CABG (within 10d of ACS)	123 (100%) Groups: Clopidogrel discontinuation before surgery continued (clopidogrel held 1-4 days before surgery) (n=65) discontinued (clopid held 5-10d before surgery) (n=57)	Indication: PCI, 100% Time: Within 10 days Age: Continued: 61.8 (8.1), Discontinued: 60.8 (9.6) Gender: Continued: 68.4% male, Discontinued: 66.7% male	continued (clopidogrel held 1-4 days before surgery) Chest tube drainage (cc, total): 0.65L (in 48hrs) RBC transfusions (total): 0.64L Reoperation: 1	discontinued (clopid held 5-10d before surgery) (n=57) Chest tube drainage (cc, total): 0.68L (in 48hrs) RBC transfusions (total): 0.47L Reoperation: 1	continued (clopidogrel held 1-4 days before surgery) All-cause death: 0	discontinued (clopid held 5-10d before surgery) All-cause death: 0	no multivariable models for outcomes of interest reported	

Author **Year** **Study design** **# Institutions:** **Propensity (Y/N)**	**Procedure(s)**	**Pre-op DAPT Sample: n (%)** **Comparison Groups**	**Patient Characteristics** **Indication for DAPT, %** **Time Since Indication** **Age, Years Mean (SD)** **Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify]** **Chest tube Drainage (cc, Total):** **RBC Transfusions (Total):** **Plt Transfusions (Total):** **Intraop Blood Loss Volume (cc):** **Reoperation:** **Hematoma:** **TIMI-defined Bleeding:** **BARC Type:**	**Thrombotic/Cardiovascular Outcomes (30d or Specify)** **MACE:** **MALE:** **Acute MI:** **Stroke:** **Revascularization/Reintervention:** **Major Amputation:** **CV Death:** **All-cause Death:**	**Statistical Methods Adjustment?** **[If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Altun, 2017[34] RCT 1 N	CABG	Pre-Op DAPT: 54, 100% TnX-A (n = 18) TnX-A+Des (n = 16) Des (n = 10) Control (n = 10)	ACS, 100% Male TnX-A 84%, 65.8 ± 6.1 TnX-A+Des 88%, 65.6 ± 11.3 Des 90%, 66.4 ± 9.3 Control 90%, 57.9 ± 14.6	DAPT in all groups TnX-A Total Blood Loss (chest tube drainage mL, SD): 535, 116.8 RBC transfusion (erythro suspe mL): 125, 128.6 Platelet sus (mL): 0, 0 TnX-A + Des Total Blood Loss (chest tube drainage mL, SD): 574, 75.5 RBC transfusion (erythro suspe mL): 93.7, 125 Platelet sus (mL): 0, 0 Des alone Total Blood Loss (chest tube drainage mL, SD): 1430, 257.6 RBC transfusion (erythro suspe mL): 675, 237.1 Platelet sus (mL): 0, 0 Control (no drug) Total Blood Loss (chest tube drainage mL, SD): 1767.5, 293.2. RBC transfusion (erythro suspe mL): 900, 268.7 Platelet sus (mL): 120, 209.7		N	

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**	**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Doğan, 2017[25] Observational 1 N	Renal transplant	106 (100%) Compares groups with variable timing since stent placement interruption Groups: DES-Early 3mo from DES implantation (n=41) DES-Late- 3-12mo from DES implantation BMS- at least 1mo from BMS implantation *Interruption defined as holding ASA and Clopidogrel 5-7d before transplant	Indication: Stable angina, unstable angina, or NSTEMI Timing: Variable per group Age: BMS: 58.17 (5.4), DES-Early: 54.55 (6.6), DES-Late: 56.63 (6.9) Gender (%male): BMS: 75%, DES-Early: 65.9%, DES-Late: 65.9%			DES-Early MACE: 2 (4.9%) Acute MI: 1 (2.4%) CV Death: 0 All-Cause Death: 1 (2.4%) DES-Late MACE: 3 (7.3%) Acute MI: 2 (2.9%) CV Death: 0 All-Cause Death: 1 (2.4%) BMS MACE: 2 (8.3%) Acute MI: 1 (4.2% CV Death: 1 (4.2%) All-Cause Death: 2 (8.3%)	No adjustment	All patients had DAPT held 5-7 days prior to surgery. The timing since DAPT indication was varied.
Della Corte, 2017[18] Observational 1 N	CABG	226 (100%) Groups: time of d/c clopidogrel or ticagrelor 0-3 days (n=34) >3 days (n=192)	Indication: not specified Time: not specified Age: 63 (9) Gender: 80.5% male	d/c clopidogrel 0-3d Post-op blood loss: 700 (205.9) d/c ticagrelor 0-3d Post-op blood loss: 800 (577.8)	d/c clopidogrel >4d Post-op blood loss: 625 (264.4) d/c ticagrelor >4d Post-op blood loss: 560 (270.4)		multivariable logistic regression	Other outcomes (including transfusions, reexploration) only compared clopidogrel versus ticagrelor groups instead of comparing time to agent discontinuation so are not reported here

Author **Year** **Study design** **# Institutions:** **Propensity (Y/N)**	**Procedure(s)**	**Pre-op DAPT** **Sample: n (%)** **Comparison Groups**	**Patient Characteristics** **Indication for DAPT, %** **Time Since Indication** **Age, Years Mean (SD)** **Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify]** **Chest tube Drainage (cc, Total):** **RBC Transfusions (Total):** **Plt Transfusions (Total):** **Intraop Blood Loss Volume (cc):** **Reoperation:** **Hematoma:** **TIMI-defined Bleeding:** **BARC Type:**	**Thrombotic/Cardiovascular Outcomes (30d or Specify)** **MACE:** **MALE:** **Acute MI:** **Stroke:** **Revascularization/Reintervention:** **Major Amputation:** **CV Death:** **All-cause Death:**	**Statistical Methods** **Adjustment?** **[If Y: Propensity, Multivariable Regression, other?** **What Were Adjustment Variables?]**	**Comments**
De Servi, 2015[28] Observational 3 N	Cardiac/ Vascular/ Uro/ Abd/ Thoracic/ Ortho/ Other	Pre-Op DAPT: (100%) Bridge P2Y12 inhibitor with i.v. tirofiban.(n=87) Control (continue or d/c P2Y12 inhibitor without Bridge) (n=227)	DAPT Indication : PCI 6-12 months, 100% Time (days): Bridge: 104 [5–365]; control: 105 [0–360] Age: Bridge: 67.4 [25–83]; control: 69.2 [41–90] Gender: Bridge: 64 (73.6% male), Control: 180 (79.3% male)	Bridge TIMI major bleeding 5 (5.7%) Any transfusion 22 (25.9%) Control (no bridge) TIMI major bleeding: 36 (15.8%) Any transfusion: 76 (33.5%)	Bridge MACCE: 2 (2.3%) Stroke: 0 Death: 0 MI: 2 (2.34%) Control (no bridge) MACCE: 17 (7.5%) Stroke: 0 Death: 6 (2.6%) MI: 12 (5.3%)	multivariable logistic regression (only used for net adverse cardiac events which was not abstracted for consistency across studies) Nearest-neighbor matching, the bridge therapy did not show a statistically significant effect on overall MACE (4% lower in the treated sample, p = 0.199).	

Hansson, 2015 Observational 8 Y	CABG	Pre-Op DAPT Ticagrelor+ASA n = 1266 (56.4%) Clopidogrel+ASA n = 978, 43.5%	DAPT indication- ACS Time: Unspecified Clop+ASA Age: 68.4 +/- 9.5 Gender: 775/978 (79.2%) Tica + ASA Age: 67.8 +/- 9.4 Gender: 995/1266 (78.5%)	d/c clopidogrel 0-24 hours Blood Loss (mL, SD): 663, 627 RBC Transfusion (units, SD): 4.9, 6.8 Platelet Transfusion (units, SD): 1.5, 2.3 d/c clopidogrel 24-48 hours Post op blood loss (mL, SD): 714, 462 RBC Transfusion (units, SD): 3.4, 4.5 Platelet Transfusion (units, SD): 0.94, 1.5 d/c ticagrelor 0-24 hours Blood Loss (mL): 813, 478 RBC Transfusion (units, SD): 6.9, 9.8 Platelet Transfusion (units, SD): 3.2, 3.7 d/c ticagrelor 24-48 hours Post op blood loss (mL, SD): 641, 337 RBC Transfusion (units, SD): 4.4, 5.7 Platelet Transfusion (units, SD):1.6, 2.2	d/c clopidogrel 48-72 hours Post op blood loss (mL, SD): 659, 313 RBC Transfusion (units, SD): 2.8, 3.5 Platelet Transfusion (units, SD): 0.79,1.4 d/c clopidogrel 72-96 hours Post op blood loss (mL, SD): 682, 462 RBC Transfusion (units, SD): 3, 5.3 Platelet Transfusion (units, SD): 0.68, 1.4 d/c clopidogrel 96-120 hours Post op blood loss (mL, SD): 701, 454 RBC Transfusion (units, SD): 2.3, 2.9 Platelet Transfusion (units, SD): 0.51, 1 d/c clopidogrel >120 hours Post op blood loss (mL, SD): 555, 313 RBC Transfusion (units, SD): 1.7, 3 Platelet Transfusion (units, SD): 0.25, 0.84 d/c ticagrelor 48-72 hours Post op blood loss (mL, SD): 709, 707 RBC Transfusion (units, SD): 4, 9.9 Platelet Transfusion (units, SD): 1.8, 3.7 d/c ticagrelor 72-96 hours		Y: Multivariable logistic regression

Post op blood loss (mL, SD): 630, 541
RBC Transfusion (units, SD): 1.7, 3.2
Platelet Transfusion (units), SD: 0.44, 0.81

d/c ticagrelor 96-120 hours

Post op blood loss (mL, SD): 550, 296
RBC Transfusion (units), SD: 1.3, 2.1
Platelet Transfusion (units, SD): 0.32, 0.9

d/c ticagrelor >120 hours

Post op blood loss (mL, SD): 534, 363
RBC Transfusion (units, SD): 1.6, 3.2
Platelet Transfusion (units, SD): 0.24, 0.95

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**		**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Cao, 2021[23] Observational 1 N	Non-cardiac surgery	747 (81.7%) Groups: DAPT interruption (any kind) (n=297) No DAPT interruption (n=312) ASA + P2Y12 interruption (n=128) Only P2Y12 interruption (n=152)	Indication: PCI, 100% Time: <1yr since PCI Age: Not specified Gender: 67.6% male	No DAPT interruption Bleeding (defined as requiring >2u RBC transfusion): 26 (8.3%)	DAPT interruption (any kind) Bleeding (defined as requiring >2u RBC transfusion): 40 (13.5%) ASA + P2Y12 interruption Bleeding (defined as requiring >2u RBC transfusion): 25 (19.5%) Only P2Y12 interruption Bleeding (defined as requiring >2u RBC transfusion): 14 (9.3%)	No DAPT interruption: MACE: 11 (3.5%) Acute MI: 3 (1%) All-cause death: 8 (2.6%)	DAPT interruption (any kind) MACE: 8 (2.7%) Acute MI: 2 (0.7%) All-cause death: 6 (2%) ASA + P2Y12 interruption MACE: 5 (3.9%) Acute MI: 1 (0.8%) All-cause death: 4 (3.1%) Only P2Y12 interruption MACE: 2 (1.3%) Acute MI: 1 (0.7%) All-cause death: 1 (0.7%)	Y: Multivariable logistic regression. Variables for risk-adjustment: age, sex, urgent/emergent surgery, risk category (low, intermediate or high), and ASA-PS class.	
Shahid, 2021[20] Observational 1 N	CABG	192 (100%) Group A: d/c clopidogrel < 48h (n=102) Group B: d/c clopidogrel 48-120h before surgery (n=89)	ACS, 100% Male TnX-A group 84%, 65.8 ± 6.1 TnX-A+Des 88%, 65.6 ± 11.3 Des 90%, 66.4 ± 9.3 Control 90%, 57.9 ± 14.6	Group A: d/c clopidogrel < 48h Chest tube drainage (cc, total): 602.25 (200) Any transfusion: 33 (32%) Reoperation: 3 (2.9%)	Group B: d/c clopidogrel 48-120h Chest tube drainage (cc, total): 609.87 (200) Any transfusion 25 (28.1%) Reoperation: 1 (1.1%)	Group A: d/c clopidogrel < 48h All-cause death: 7 (6.8%)	Group B: d/c clopidogrel 48-120h All-cause death: 2 (2.2%)	N, all data are unadjusted	

Author Year Study design # Institutions: Propensity (Y/N)	**Procedure(s)**	**Pre-op DAPT Sample: n (%) Comparison Groups**	**Patient Characteristics Indication for DAPT, % Time Since Indication Age, Years Mean (SD) Gender [%Male or Female]**	**Bleeding Outcomes (Total or Specify) [Report N (%), Mean (SD) or Specify] Chest tube Drainage (cc, Total): RBC Transfusions (Total): Plt Transfusions (Total): Intraop Blood Loss Volume (cc): Reoperation: Hematoma: TIMI-defined Bleeding: BARC Type:**		**Thrombotic/Cardiovascular Outcomes (30d or Specify) MACE: MALE: Acute MI: Stroke: Revascularization/Reintervention: Major Amputation: CV Death: All-cause Death:**		**Statistical Methods Adjustment? [If Y: Propensity, Multivariable Regression, other? What Were Adjustment Variables?]**	**Comments**
Kim, 2020[24] Observational 9 N	Non-cardiac surgery	Total n=3582 Continue DAPT: n=984, (27.4%) Discontinue APT n=1750, (49%)	Indication for DAPT: PCI Time since indication, mean months (SD): not specified Age, years mean (SD): 69 (61-75) Gender, %male: 1282 (70)		HR: Incidence Major bleeding d/c 1-3 days OR, OR LIC, OR UCI: 1.54, 0.85, 2.8 d/c 4-8 days OR, OR LIC, OR UCI: 0.89, 0.55, 1.44 d/c: at least 9 days OR, OR LIC, OR UCI: 1.5, 0.76, 2.97	Continue DAPT MACE: 47 (4.8%)	Discontinue DAPT MACE (events): 36 (4.5%)	multivariate logistic regression model (Note: in an additional model looking at holding >8 days, they reported higher adjusted MACE compared to <8d (adjusted HR, 3.38; 95% CI, 1.36–8.38; P=0.009))	
Heidari 2016[21] Observational 1 N	CABG	100 (66%) Group A: DAPT continued, urgent CABG, experienced surgeon (n=50) Group C: DAPT held > 5d, elective CABG, experienced surgeon (n=50) (*Group B not relevant - does not vary DAPT)	Indication: ACS Time: not specified Age, years mean (SD): A: 59.5 (9.70), C: 57.9 (8.70) Gender, %male: A: 72, C: 66	DAPT continued (Group A) RBC transfusions (units): 0.78 (1.14) Intraop blood loss volume (cc): 987.9 (443) Reoperation: 0	DAPT held >5d (Group C) RBC transfusions (units): 3.14 (1.9) Intraop blood loss volume (cc): 973 (537.5) Reoperation: 0	DAPT continued (Group A) All-cause death: 0 (0%) [in-hospital]	DAPT held >5d (Group C) All-cause death: 0(0%) [in-hospital]	N, all data are unadjusted. (Group B was urgent CABG with DAPT continuation with empiric transfusions given and inexperienced surgeons. Given that the DAPT management did not vary, we determined A and C groups were the comparison of interest, and C was not randomized)	

Notes. Mean (SD) unless otherwise specified; median [IQR].
Abbreviations. ACS=acute coronary syndrome; CV=cardiovascular; d/c=discontinue; MACE=major adverse cardiovascular events; MACCE=all-cause death, myocardial infarction, definite stent thrombosis and stroke; MALE=major adverse limb; MI=myocardial infarction; ns=not significant; OR=odds ratio.

APPENDIX F. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	Thank you.
2	3	Yes	Thank you.
3	5	Yes	Thank you.
4	6	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
5	2	No	Thank you.
6	3	No	Thank you.
7	5	No	Thank you.
8	6	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
9	2	Yes - Grzegorz L. Kaluza MD, PhD, Jane Joseph, Joseph R. Lee MD, Michael E. Raizner MD and Albert E. Raizner MD, Catastrophic outcomes of noncardiac surgery soon after coronary stenting Catastrophic outcomes of noncardiac surgery soon after coronary stenting FACC 2000 25:5 1288-1294.	We reviewed this study and do not think it meets eligibility criteria, as it does not report the details on pre-op DAPT management or present different treatment strategies
10	3	No	Thank you.
11	5	No	Thank you.
12	6	Yes - Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025 Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370(16):1494-1503	We reviewed this study. It is a practice guideline and thus not primary evidence. We do cite it in the discussion. We reviewed this study, it is about ASA therapy and not about DAPT

Comment #	Reviewer #	Comment	Author Response
		Antolovic D, Reissfelder C, Rakow A, et al. A randomised controlled trial to evaluate and optimize the use of antiplatelet agents in the perioperative management in patients undergoing general and abdominal surgery--the APAP trial (ISRCTN45810007). BMC Surg. 2011;11:7. Published 2011 Mar 3.	We reviewed this study. This is the protocol for a study, and does not contain any study results
		Wang A, Wu A, Wojdyla D, et al. Dual antiplatelet therapy for perioperative myocardial infarction following CABG surgery. Am Heart J. 2018;199:150-155.	We reviewed this study. Not all of these patients are on pre-op DAPT and therefore it does not meet the inclusion criteria
		Burdess A, Nimmo AF, Garden OJ, et al. Randomized controlled trial of dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia. Ann Surg. 2010;252(1):37-42.	We reviewed this study. Not all of these patients are on pre-op DAPT and therefore it does not meet the inclusion criteria.
Additional suggestions or comments can be provided below.			
13	2	Note: I used the page numbers for the PDF not the page numbers on the pages in the PDF. So when I say Page 11 (from the PDF) that is page 8 of the report. Comments: Page 4&5: No anesthesia authors on review panel. Heavy surgical presence. No input from highest risk for DAPT surgical field, neurosurgery.	Lacking an anesthesiologist among our technical experts is a limitation we acknowledge. The lack of a neurosurgeon we don't consider a significant limitation since there were no eligible studies of neurosurgical procedures.
14	2	Page 12: With only 19 studies (1 RCT and 18 Observational Studies) review of literature is unlikely to find a result. I know it is against your charge but epidemiologic analysis of data from the VA CDW is likely to provide superior information to your review of the literature. On the time of NPO to scope ESP, there were no conclusions possible from the literature. Epidemiologic analysis of CDW data provided	Thank you. In our Future Research section, we suggest the VA QUIP database as a potential data source that could provide answers to our clinical questions. If the database has preoperative data on DAPT use and indication in addition to perioperative DAPT management, then analyzing this would benefit from the considerable existing work done to develop risk adjusting models.

Comment #	Reviewer #	Comment	Author Response
		meaningful results that were vastly more informative than the no conclusion possible from literature review.	We included your suggestion to also consider patient data from the CDW as another potential data source for analysis.
15	2	Page 12: CABG and cases that utilize cardiopulmonary bypass are fundamentally different from all non-cardiac surgery and should not be included with analysis from non-cardiac surgery.	In our draft report we did not lump together CABG and non-CABG cases, except for the one publication which did so. To make it more clear that we kept these separate we revised the wording in the Executive Summary to discuss CABG surgery and noncardiac surgery separately. We also present our findings for cardiac surgery separately from noncardiac surgery in the Results section of the Evidence Report.
16	2	Page 13 Line 3 "less blood less" I think you mean "loss". This paragraph is not interpretable for a very simple reason. If you lump cardiac surgery with non-cardiac surgery with neurosurgery, you will get meaningless results. All cardiac surgical cases, that use extracorporeal circulatory support, damage the coagulation system. They must be analyzed separately from surgical cases that do not use bypass. Vascular surgery cases have a lower risk of hemorrhage and a greater benefit from DAPT. They must be analyzed separately. Cases where hemorrhage will be lethal or cause profound neurologic injury such as neurosurgery, must be analyzed separately. You can't lump all these things together and then talk about blood loss, it is non-sensical. Blood loss of 1-2 liters is standard in CABG, a problem in vascular cases but not unexpected, and lethal in intracranial surgery. They must be analyzed separately to have any meaning.	Thank you. Please see the above comment. This paragraph is now referring only to studies involving CABG. The following paragraph discusses results from the single combined cardiac and noncardiac surgery and the remaining studies involving only noncardiac surgery.
17	2	Page 13 Line 22. When we did the ESP for GI NPO, I said and I quote "There is nothing in the literature that will indicate the risk from aspiration pneumonia and the risk of misdiagnosis because the sample sizes are too	We appreciate your insight. Please see Comment #14 above. We included your suggestion to perform an epidemiologic analysis using CDW data in the Future Research section, although if VA-QUIP has the data it would be far easier to do so with its

Comment #	Reviewer #	Comment	Author Response
		small, you must do epidemiologic analysis of data from the CDW." The published literature can't answer these questions. You must recognize this fault prior to doing an ESP, and do epidemiologic analysis of CDW data which will likely give you insight. This is the third ESP I have seen (two for DAPT and one for GI NPO) with no result that likely would have a result if you changed your mission statement to do epidemiologic analysis of VA CDW data when the literature has no chance to answering the question.	standardized data collection and risk-adjusting models already created.
18	2	Page 13 Line 40 Future Research: Absolutely, this can and should be done. ESP with no chance of success are a waste of time.	Thank you. Please see above.
19	2	Page 20 Line 21. The Turkish study is a comparison of four approaches to managing emergency patients all of whom are on DAPT (TXA, TXA+Desmopressin, Desmopressin, Nothing). This will only tell you if TXA or Desmopressin reduce risk of bleeding in patients on DAPT. It won't tell you what the effect of taking DAPT is versus not. What does this RCT, the only RCT in your ESP have to do with the risk of DAPT? There is no control group off DAPT.	Thank you; while we initially included this study because it tested a perioperative management strategy to mitigate the effect of DAPT, upon further review, we agree that it is outside the scope of our key questions since it did not vary or alter the DAPT itself. Thus, we excluded the article with subsequent alterations made in the report text.
20	2	Page 22 Line 43. How much less blood loss. 250 ml less blood loss, in the face of an average of 1-2 liters, is interesting but not clinically significant. A liter difference would be clinically significant difference. You need to know the difference that was detected to make this paragraph contributory. My guess from the graph is the average of all the studies is 125 ml, which is something you can write a paper about but is clinically not significant in CABG surgery.	We added information about the quantity of blood loss from the relevant studies. The question of whether or not this is clinically significant is raised in the Discussion section.

Comment #	Reviewer #	Comment	Author Response
21	2	Page 23 Line 38 Transfusion differences are clinically significant results. 4 of 9 fewer patients needing transfusion is interesting but 5 of 9 with no difference is consistent with the guess of 125 ml average additional blood loss.	Agreed. Thank you.
22	2	Page 24 Line 37 The requirement for surgical re-exploration after CABG for bleeding increases perioperative risk. Avoiding re-exploration requirements is important. Can you conclude there is less need for re-exploration if DAPT is discontinued more than 2 days before surgery? That would be an important conclusion. Figure 3 shows one study concluded a 20% reduction in the need for re-exploration,1 out of 5 at 20% reduction, likely isn't meaningful.	The data are not conclusive as 2 of the 5 studies comparing DAP withdrawal strategies prior to surgery were not significant. However, 3 of the studies do show statistically significant differences in reoperation risk and there is an overall trend in all these studies favoring withdrawal >2 days. We believe that this is clinically meaningful but acknowledge the limitations of the data in future sections of the report.
23	2	Page 26 Figure 4. My guess is a large epidemiologic analysis of CDW data would show an increase in mortality from DAPT. In the McSPI dataset, there was a 10 fold increased risk in patients who were on coumadin within 7 days of CABG. There is likely some additional risk from DAPT but you need to do a large epidemiologic analysis of CDW data to show it.	Thank you. We included your suggestion to perform an epidemiologic analysis using CDW data in the Future Research section.
24	2	Page 27 Line 30 Some discussion of how long the DAPT was discontinued would help make this section more interpretable. I would exclude all ophthalmic cases. Most of these are intraocular lens which doesn't cut through any blood vessels. The chance of bleeding is zero. Adding IOL cases into general surgery just confuses the results. Is this a week of discontinuation or 2 days? When did they restart the DAPT?	This study reports the ophthalmic cases grouped with all the other surgeries, so it cannot be excluded from analysis. However, we adjusted the paragraph to more clearly explain the study's findings. Information was added about how long DAPT was held preop, surgery types in which antiplatelet therapy was continued vs held, and DAPT duration.
25	2	Page 27 Line 35 This may be the most important study so far. There are two effects here. The first is the mortality effect of delaying	Thank you for the comment. We agree that they may be measuring increased risk from two phenomenon: the surgical delay after hip fracture and the impact of

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		ORIF in hip fractures. Each day of delay has an effect on mortality. The second effect is the increased risk from holding DAPT. These two risks are combined to get the OR 7.91 at one week. There are two risks here that are hard to separate.	holding DAPT. Since these factors were dependent on one another, we agree that they are hard to separate and added text to acknowledge this limitation.
26	2	Page 27 Line 51 This is an important study as it contradicts Grzegorz L. Kaluza MD, PhD, Jane Joseph, Joseph R. Lee MD, Michael E. Raizner MD and Albert E. Raizner MD, Catastrophic outcomes of noncardiac surgery soon after coronary stenting Catastrophic outcomes of noncardiac surgery soon after coronary stenting FACC 2000 25:5 1288-1294. I am surprised that they were really able to discontinue clopidogrel for 5-7 days. These must not be cadaveric transplants because there is rarely a 5-7 preoperative warning on a cadaveric transplant. Were these donor related transplants? If not, the results should be looked at carefully to see how they got a 5-7 preoperative time to hold DAPT for a cadaveric transplant.	Thank you for this interesting observation. We think there are several potential explanations as to why the Dogan study included in our analysis seems to contradict the article by Grzegorz et al. All patients in this study underwent renal transplant from living donors. Importantly, the Grzegorz study was published in the early PCI era, when only BMS or first-generation DES were available. The Dogan study is a more contemporary analysis that includes only second-generation DES and newer BMS, which have shown to be protective of cardiac ischemic complications. Finally, the average time from stent placement to surgery in the Gzregorz study was 13 days compared to 3 months in the early DES discontinuation group and 1 month in the BMS group in the Dogan study.
27	2	Page 31 Line 6 We need a large epidemiologic study of the VA CDW data to answer this question. I said this after the 2016 ESP concluded with a similar limitation.	Thank you. We have added this suggestion to the Future Research section.
28	2	Page 31 Line 32 You have an extra period. "Bias. .Further"	This has been corrected, thank you.
29	2	Page 31 Line 55 There are a number of clinical questions we face every day. 1. Patient for CABG, with prior PCI, on DAPT, how long do you discontinue the DAPT? 2. Patient for vascular surgery, like a AAA, with prior PCI, on DAPT, how long do you discontinue DAPT? 3. Same vascular surgery patient for Fem Distal. 4. Patient for general surgery, prior PCI, on DAPT, for exploratory laparotomy. Can we give	Please see additional comments which include your suggestion to consider the CDW as a potential source for an epidemiologic analysis.

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		ASA? Do we continue the clopidogrel? What is risk of MACE? We need an analysis of the CDW data to see the answers to these questions, ESP won't give us the answer.	
30	2	Page 32 Line 20. I guarantee the data is in the VA CDW to answer this question.	Thank you for this suggestion. We include this as a possible avenue for future research.
31	3	Balanced, thoughtful, and clear evaluation of available literature and clearly stated limitations. Did any studies look at continuing one agent rather than holding both agents? There is increasing interest/use of P2Y12i monotherapy in practice. Understand using >/< 2 days timeframe for DAPT DC, but noted some studies looked at significantly longer DC periods (e.g., 7 days) which could be expected to have different outcomes than shorter timeframes. Should this be evalauted or mentioned as a limitation? Suggest recognizing/addressing the 2021 ACC/AHA/SCAI revasc guideline recs for holding APT around CABG surgery (the most common setting studied) and how those fit with your findings. Suggest recognizing potential for differences in the PK/PD profiles of individual P2Y12i and possible need for different hold guidance rather than generic "class" guidance - e.g., how was this issue evaluated in the literature and what are future research needs. Last, the renal transplant study would not be generalizable or extrapolated to other settings - should this be stated?	Thank you. The majority of the studies compared dual antiplatelet therapy with single antiplatelet therapy given that current guidelines recommend continuing aspirin through the perioperative period when possible. In our analysis we considered holding either or both ASA or a P2Y12 inhibitor as discontinuing or withholding DAPT. This was clarified in our Methods section. We appreciate your point about prolonged DAPT withholding duration influencing the aggregate results. We added this as a limitation of our analysis. We added a reference to the 2021 ACC/AHA/SCAI revascularization guidelines and compare these to our results in the Discussion section. We also included the limitation you mention in grouping P2Y12 inhibitors together despite differences in PK/PD profiles. The generalizability of all studies is open to question, as surgical protocols and post-operative care may differ among hospitals, even for procedures given the same name, like “cholecystectomy”. We don’t think we need to call out this one study in specific for generalizability.
32	3	p19-l42 - typo and suggested reword - "point estimate favored less blood loss"	Thank you; this has been reworded.
33	3	p55-L19 - 2019 Irie study - is ticlopidine correct or is it ticagrelor?	Yes, Ticlopidine is correct.

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34	5	page iii - line 27, add 'the' before Surgical Quality Improvement Program	This has been corrected, thank you.
35	5	page 10, line 43 and page 29 line 9 - unclear wording of #1 - perhaps change to "to have a very large sample" or change first part of sentence to "The attributes of such an observational study would include:"	Thank you. We changed the wording here.
36	5	Figure 1 - please explain "Exclude:all else" or just label as "other reasons'	Thank you, this has been changed to “other reasons”.
37	5	page 48, citation of Nardi is cut off, so unable to see what Group C was. Consider reformatting table.	This appears to be fixed in our current version.
38	6	The manuscript sets out to discuss Dual Antiplatelet Management in the Perioperative Period but does not mention relevant clinical trials (presented in the comment box above), contemporary recommendations made by professional guidelines, or manufacturers. Please consider adding the following pertinent information:	We have added where relevant any published studies meeting the inclusion criteria, and in the Discussion have now mentioned the various guidelines and manufacturers information.
39	6	When possible, interrupt therapy with ticagrelor for five days prior to surgery that has a major risk of bleeding. Brilinta. Prescribing information. AstraZeneca; 2022.	Thank you. This has been added to the Discussion section.
40	6	When possible, discontinue prasugrel at least 7 days prior to any surgery. Effient. Prescribing information. Eli Lilly and Company; 2020. Discontinue [clopidogrel] 5 days prior to elective surgery that has a major risk of bleeding. Plavix. Prescribing information. Sanofi-Aventis; 2022. Stopping aspirin 3 or more days prior to surgery has been investigated in the POISE-2 trial <Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370(16):1494-1503.>	Thank you. This has been added to the Discussion section.

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41	6	CHEST guideline recommendations for P2y12 antagonists: Stop ticagrelor 3 to 5 days instead of 7 to 10 days before the surgery. Stop prasugrel 7 days instead of 7 to 10 days before the surgery. Stop clopidogrel 5 days instead of 7 to10 days before the surgery. <Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025>	Thank you. This has been added to the Discussion section.
42	6	In patients receiving aspirin who are undergoing elective non-cardiac surgery, CHEST guidelines suggest aspirin continuation over aspirin interruption. In those who require aspirin interruption, CHEST guidelines suggest stopping ASA 7 or less days instead of 7 to 10 days before the surgery. <Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025>	This is now cited in the Discussion.
43	6	DATA Sources page 13 lines 27-35: Other search term should include "Perioperative" Furthermore, search term should be Dual "antiplatelet" instead of "anti-platelet" as the former is widely recognized as the preferred spelling. For example, a PUBMED search using ((antiplatelet) AND (dual)) AND (perioperative) will yield significantly more results than if "antiplatelet" is replaced with "anti-platelet"	The spelling of “antiplatelet” is not an issue since in the search strategy both spellings are used, linked with an “OR”, meaning the search will identify either spelling. We added “peri-operative” and “perioperative” to our search and it only found 16 additional titles, none of which met eligibility criteria, and thus it is not a limitation of the original search to have not included these terms.

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44	6	Page 10; Lines 3-4 - please clarify sentence "The preponderance of point estimated favor less blood less with longer duration of suspension of DAPT therapy for at least 2 days." Did the authors intend to state "point estimates favor less blood loss"?	Yes, we meant to state “less blood loss.” This has been corrected.