Dual Antiplatelet Management in the Perioperative Period: A Systematic Review

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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
Medical Director
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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

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.

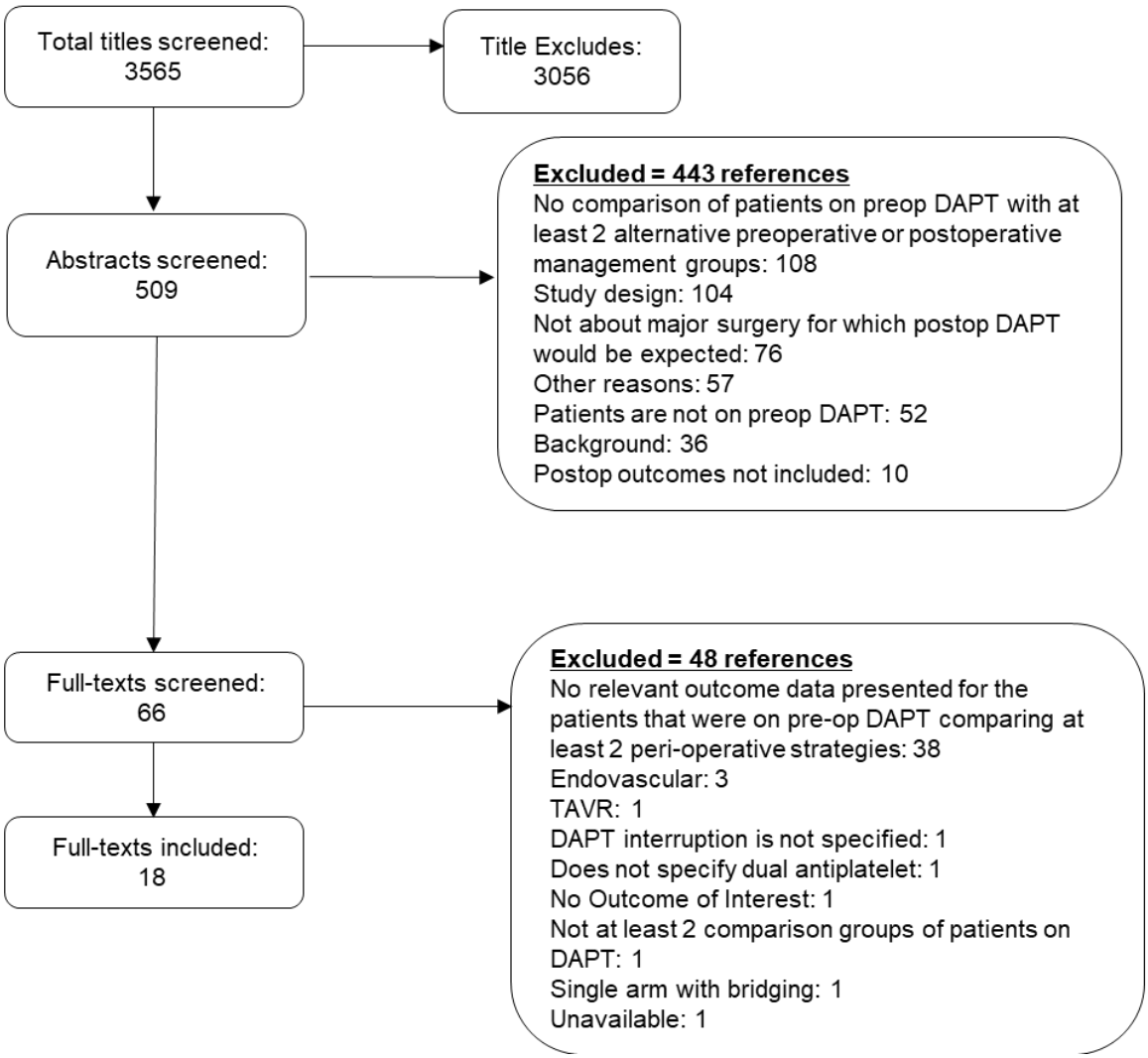
Very Low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

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.

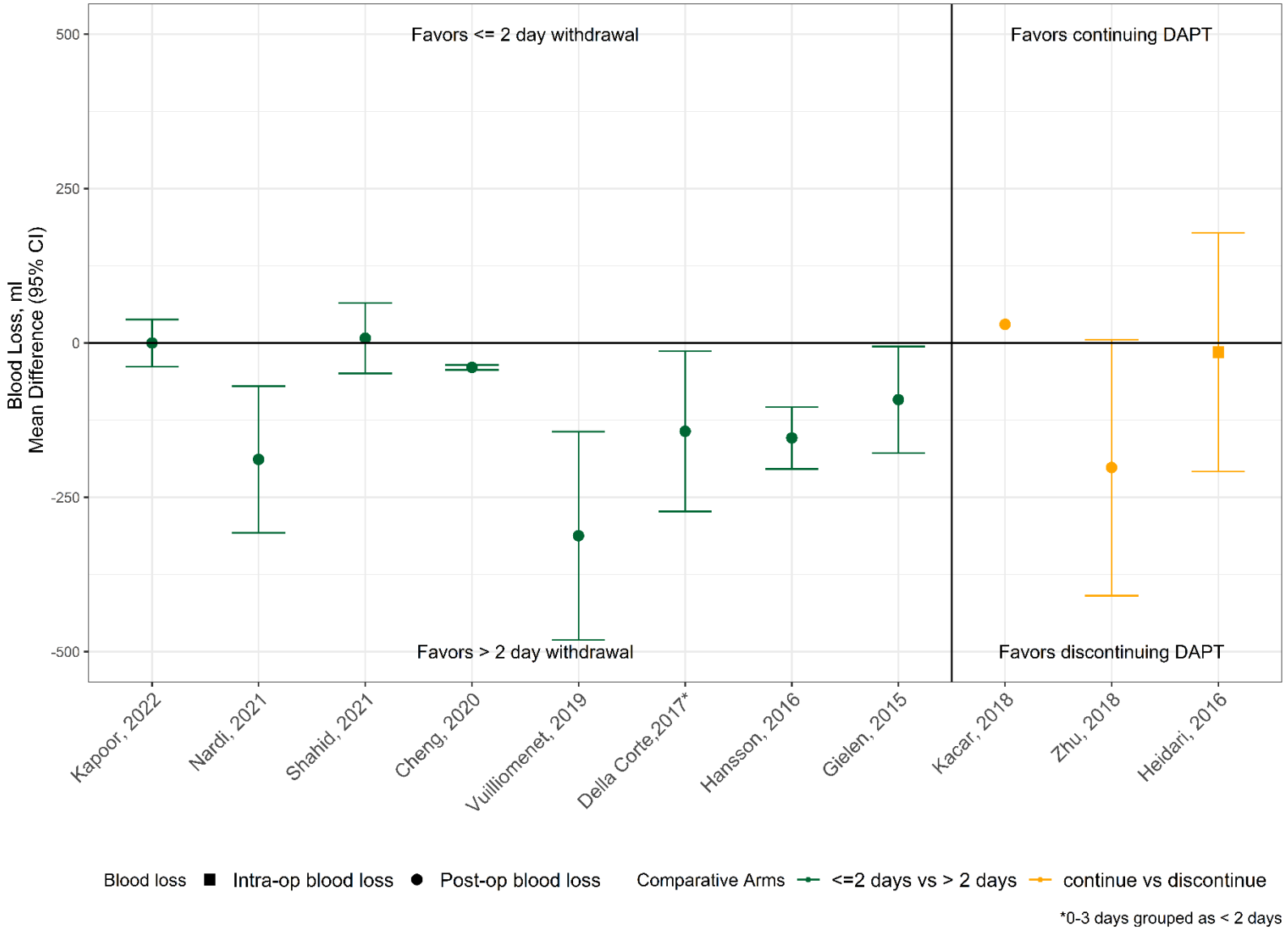
Patients on Preoperative DAPT and Undergoing CABG

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.

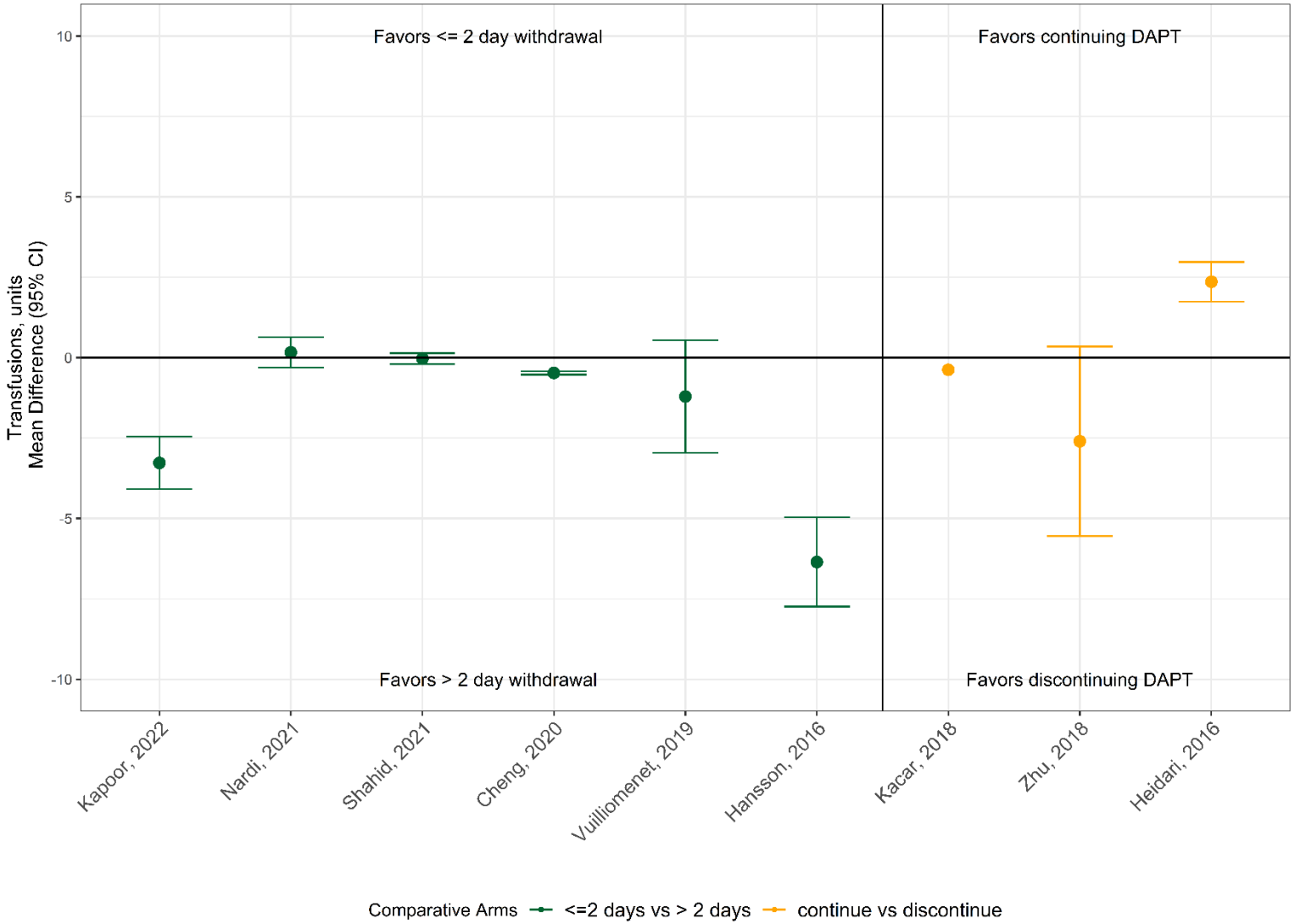
Figure 2. Blood Loss Outcomes



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.

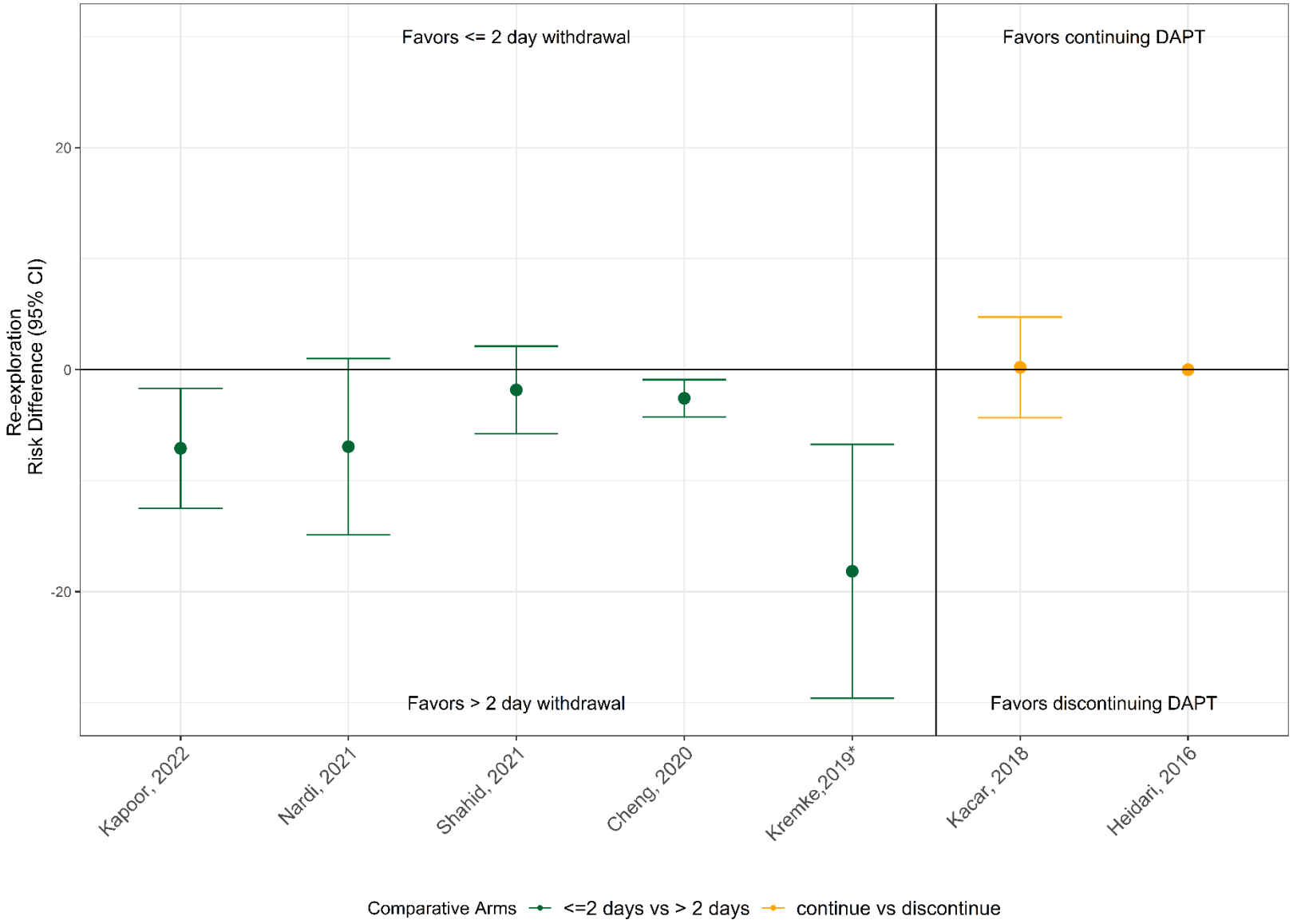
Figure 3. Transfusions Outcomes



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).

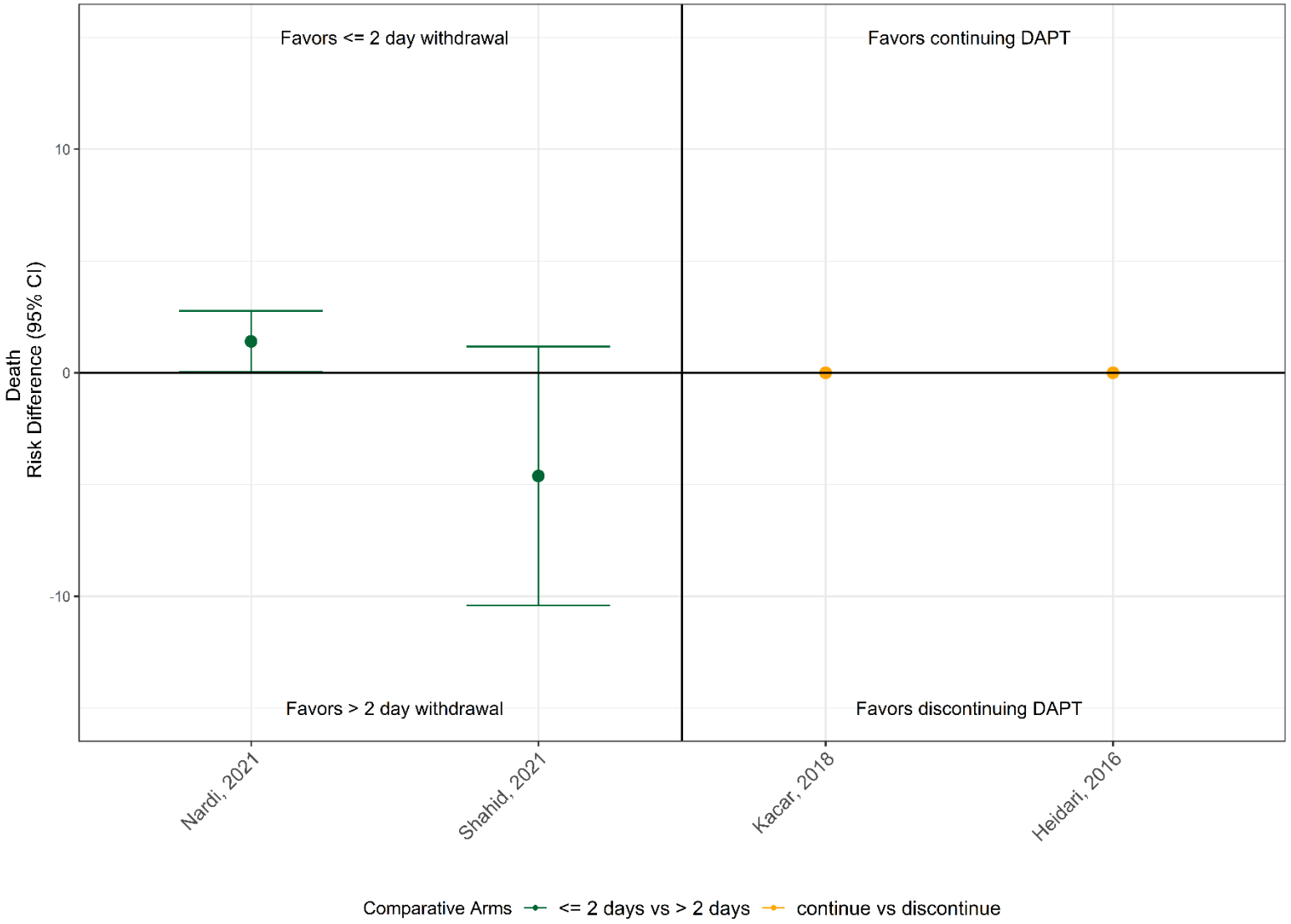
Figure 4. Re-exploration Outcomes



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.

REFERENCES

1. Desai NR, Bhatt DL. The state of periprocedural antiplatelet therapy after recent trials. *JACC Cardiovasc Interv*. Jun 2010;3(6):571-83. doi:10.1016/j.jcin.2010.04.008
2. Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. *Nat Rev Cardiol*. Jul 12 2011;8(10):547-59. doi:10.1038/nrcardio.2011.96
3. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. Nov 20 2002;288(19):2411-20. doi:10.1001/jama.288.19.2411
4. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. Aug 16 2001;345(7):494-502. doi:10.1056/NEJMoa010746
5. Bhatia K, Jain V, Aggarwal D, et al. Dual Antiplatelet Therapy Versus Aspirin in Patients With Stroke or Transient Ischemic Attack: Meta-Analysis of Randomized Controlled Trials. *Stroke*. Jun 2021;52(6):e217-e223. doi:10.1161/STROKEAHA.120.033033
6. Savonitto S, Caracciolo M, Cattaneo M, S DES. Management of patients with recently implanted coronary stents on dual antiplatelet therapy who need to undergo major surgery. *J Thromb Haemost*. Nov 2011;9(11):2133-42. doi:10.1111/j.1538-7836.2011.04456.x
7. Tokushige A, Shiomi H, Morimoto T, et al. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: a report from the CREDO-Kyoto PCI/CABG registry cohort-2. *Circ Cardiovasc Interv*. Apr 2012;5(2):237-46. doi:10.1161/CIRCINTERVENTIONS.111.963728
8. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Review. *Circulation*. 2022;145(3):E18-E114. doi:10.1161/CIR.0000000000001038
9. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. Jan 14 2018;39(3):213-260. doi:10.1093/eurheartj/ehx419
10. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Sep 6 2016;134(10):e123-55. doi:10.1161/cir.0000000000000404
11. Maggard Gibbons M, Ulloa JG, Macqueen IT, et al. Management of Antiplatelet Therapy Among Patients on Antiplatelet Therapy for Coronary or Cerebrovascular Disease or with Prior Percutaneous Cardiac Interventions Undergoing Elective Surgery: A Systematic Review. 2017. *VA Evidence-based Synthesis Program Reports*.
12. Childers CP, Mak S, Miake-Lye IM, et al. Management of Antiplatelet Therapy Among Patients on Antiplatelet Therapy for Cerebrovascular or Peripheral Vascular Diseases Undergoing Elective Non-Cardiac Surgery. 2017. *VA Evidence-based Synthesis Program Reports*.

13. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. Oct 12 2016;355:i4919. doi:10.1136/bmj.i4919
14. The Grading of Recommendations Assessment Development and Evalution. https://www.gradeworkinggroup.org/
15. Tarrant SM, Kim RG, McGregor KL, Palazzi K, Attia J, Balogh ZJ. Dual Antiplatelet Therapy and Surgical Timing in Geriatric Hip Fracture. *J Orthop Trauma*. Oct 2020;34(10):559-565. doi:10.1097/bot.0000000000001779
16. Kremke M, Gissel MS, Jensen MJ, Thomassen SA, Jakobsen CJ. The association between a three-day ticagrelor discontinuation and perioperative bleeding complications. *Eur J Cardiothorac Surg*. Apr 1 2019;55(4):714-720. doi:10.1093/ejcts/ezy355
17. Nardi P, Pisano C, Turturici M, et al. The impact of dual antiplatelet therapy administration on the risk of bleeding complications during coronary artery bypass surgery. *Kardiochir Torakochirurgia Pol*. Sep 2021;18(3):145-151. doi:10.5114/kitp.2021.109407
18. Della Corte A, Bancone C, Spadafora A, et al. Postoperative bleeding in coronary artery bypass patients on double antiplatelet therapy: predictive value of preoperative aggregometry. *Eur J Cardiothorac Surg*. Nov 1 2017;52(5):901-908. doi:10.1093/ejcts/ezx181
19. Kacar SM, Mikic A, Kačar MB. Postoperative Bleeding Following Preoperative Clopidogrel Administration in Patients with Haemoglobin Level Above 110 g/L Undergoing Urgent CABG. *Braz J Cardiovasc Surg*. Jan-Feb 2018;33(1):59-63. doi:10.21470/1678-9741-2017-0083
20. Shahid M, Islam MU, Ahmad I, et al. Post operative complications associated with preoperative use of clopidogrel in patients undergoning coronary artery bypass surgery. Article. *Pakistan Journal of Medical and Health Sciences*. 2021;15(10):3154-3156. doi:10.53350/pjmhs2115103154
21. Heidari A, Dezfouli FG, Tabatabi K, et al. Combined clopidogrel and aspirin treatment up to surgery dosen't increase the risk of postoperative blood loss and reoperation for bleeding in patients undergoing coronary artery bypass grafting. Article. *International Journal of Pharmaceutical Research and Allied Sciences*. 2016;5(3):164-167.
22. Irie H, Kawai K, Otake T, Shinjo Y, Kuriyama A, Yamashita S. Outcomes of patients on dual antiplatelet therapy post-coronary stenting following emergency noncardiac surgery. *Acta Anaesthesiol Scand*. Sep 2019;63(8):982-992. doi:10.1111/aas.13377
23. Cao D, Levin MA, Sartori S, et al. Perioperative risk and antiplatelet management in patients undergoing non-cardiac surgery within 1 year of PCI. Article. *Journal of Thrombosis and Thrombolysis*. 2022;53(2):380-389. doi:10.1007/s11239-021-02539-8
24. Kim C, Kim JS, Kim H, et al. Patterns of antiplatelet therapy during noncardiac surgery in patients with second-generation drug-eluting stents. Article. *Journal of the American Heart Association*. 2020;9(11)doi:10.1161/JAHA.119.016218
25. Doğan A, Özdemir E, Kahraman S, Açıl T, Saltan Y, Kurtoğlu N. Impact of early (3 months) dual antiplatelet treatment interruption prior to renal transplantation in patients with second-generation DES on perioperative stent thrombosis and MACEs. *Anatol J Cardiol*. Dec 2017;18(6):391-396. doi:10.14744/AnatolJCardiol.2017.7885
26. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. *Chest*. Nov 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025

27. Cheng Y, Liu X, Zhao Y, et al. Risk Factors for Postoperative Events in Patients on Antiplatelet Therapy Undergoing Off-Pump Coronary Artery Bypass Grafting Surgery. *Angiology*. Sep 2020;71(8):704-712. doi:10.1177/0003319720919319
28. De Servi S, Morici N, Boschetti E, et al. Bridge therapy or standard treatment for urgent surgery after coronary stent implantation: Analysis of 314 patients. *Vascul Pharmacol*. May 2016;80:85-90. doi:10.1016/j.vph.2015.11.085
29. Gielen CL, Bruggemans EF, Stijnen T, et al. Stopping antiplatelet medication before coronary artery bypass graft surgery: is there an optimal timing to minimize bleeding? Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't. *European journal of cardio-thoracic surgery*. 2015;48(4):e64-70. doi:10.1093/ejcts/ezv269
30. Hansson EC, Jidéus L, Åberg B, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. *Eur Heart J*. Jan 7 2016;37(2):189-97. doi:10.1093/eurheartj/ehv381
31. Kapoor S, Singh G, Arya RC, et al. Effect of anti-platelet therapy on peri-operative blood loss in patients undergoing off-pump coronary artery bypass grafting. Article. *Annals of Cardiac Anaesthesia*. 2022;25(2):182-187. doi:10.4103/aca.aca_12_22
32. Vuilliomenet T, Gebhard C, Bizzozero C, et al. Discontinuation of dual antiplatelet therapy and bleeding in intensive care in patients undergoing urgent coronary artery bypass grafting: a retrospective analysis. *Interact Cardiovasc Thorac Surg*. May 1 2019;28(5):665-673. doi:10.1093/icvts/ivy330
33. Murray M, Sundin D, Cope V. Supporting new graduate registered nurse transition for safety: A literature review update. *Collegian*. 2020;27(1):125-134. doi:10.1016/j.colegn.2019.04.007
34. Altun G, Hemşinli D, Pulathan Z, Civelek A. Emergency coronary bypass surgery in patients under the influence of dualantiplatelet therapy: effects of tranexamic acid and desmopressin acetate. *Turk J Med Sci*. Dec 19 2017;47(6)doi:10.3906/sag-1612-140