Dual Antiplatelet Management in the Perioperative Period: A Systematic Review

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Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

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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
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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.

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

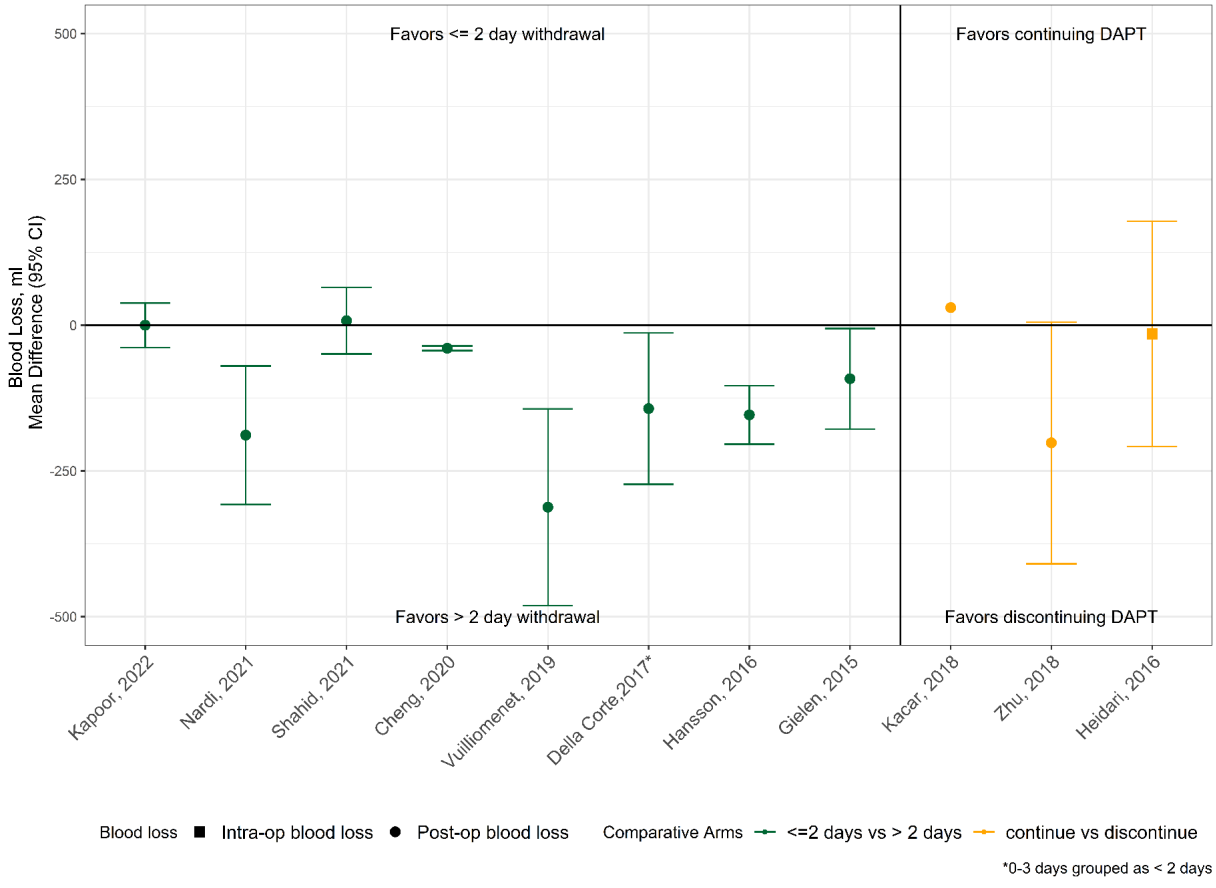
Results of Literature Search

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.