

Perioperative Management of Antiplatelet Therapy: A Systematic Review and Meta-analysis

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Abstract

Objective: To summarize the available evidence about the perioperative management of patients who are receiving long-term antiplatelet therapy and require elective surgery/procedures.

Methods: This systematic review supports the development of the American College of Chest Physicians guideline on the perioperative management of antiplatelet therapy. A literature search of MEDLINE, EMBASE, Scopus and Cochrane databases was conducted from each database's inception to July 16, 2020. Meta-analyses were conducted when possible.

Results: In patients receiving long-term antiplatelet therapy and undergoing elective noncardiac surgery, the available evidence did not show a significant difference in major bleeding between a shorter vs longer antiplatelet interruption, with low certainty of evidence (COE). Compared with patients who received placebo perioperatively, aspirin continuation was associated with increased risk of major bleeding (relative risk [RR], 1.31; 95% CI, 1.15-1.50; high COE) and lower risk of major thromboembolism (RR, 0.74; 95% CI, 0.58-0.94; moderate COE). During antiplatelet interruption, bridging with low-molecular-weight heparin was associated with increased risk of major bleeding compared with no bridging (RR, 1.86; 95% CI, 1.24-2.79; very low COE). Continuation of antiplatelets during minor dental and ophthalmologic procedures was not associated with a statistically significant difference in the risk of major bleeding (very low COE).

Conclusion: This systematic review summarizes the current evidence about the perioperative management of antiplatelet therapy and highlights the urgent need for further research, particularly with the increasing prevalence of patients taking 1 or more antiplatelet agents.

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Antiplatelet therapy is widely used for the secondary prevention of stroke, myocardial infarction (MI), and peripheral arterial disease, with such patients typically receiving single antiplatelet therapy with acetylsalicylic acid (ASA) or dual antiplatelet therapy with ASA and a P2Y₁₂ inhibitor such as clopidogrel or ticagrelor. Given this widespread use of antiplatelet therapy and that such patients, due to their advanced age, are also more likely to require a surgery/

procedure, it is not surprising that perioperative management is a frequently encountered clinical scenario. For example, the incidence of noncardiac surgery alone, even after excluding the more commonly needed nonsurgical procedures, after drug-eluting stent implantation was 7% at 1 year, 18% at 2 years, and 22% at 3 years.¹ Overall, the perioperative management of patients who are receiving antiplatelet therapy and need a surgery/procedure is a common clinical scenario.

Premature discontinuation of antiplatelet therapy has the potential to expose patients to an increased risk of perioperative acute coronary syndromes, with stent thrombosis being most feared because of its high associated morbidity and mortality. In the nonperioperative setting, premature cessation of antiplatelet therapy after MI confers a 3- to 5-fold increased risk of major adverse cardiac events. In a perioperative setting, a multicenter registry found that patients with a drug-eluting stent who discontinued P2Y₁₂ inhibitor therapy early had a higher risk of death and rehospitalization in the next 11 months.² In contrast, continuation of antiplatelet therapy without perioperative interruption exposes patients to an increased risk of bleeding, which, in turn, can increase the risk of adverse cardiovascular (CV) events. Therefore, the perioperative management of antiplatelet therapy requires balancing the risk of CV or thrombotic events against the risk of bleeding, the latter of which is driven by the surgery/procedure-related bleeding risk.

The American College of Chest Physicians (ACCP/CHEST) developed clinical practice guidelines³ in 2012 to address key clinical decisions in this context, including the management of antiplatelet therapy in settings such as coronary artery bypass graft (CABG) surgery, noncardiac surgery, minor procedures, and cardiac device implantation. Since the previous iteration of these guidelines, new antiplatelet drugs have emerged for clinical use alongside new evidence around perioperative antiplatelet management. This systematic review and meta-analysis was commissioned by ACCP/CHEST to support the development of the updated 2022 ACCP/CHEST guidelines.^{4,5} The aim of this review is to summarize and appraise the evidence base regarding prespecified clinical questions related to the perioperative management of patients who are receiving ASA, P2Y₁₂ inhibitors, or combined (dual) antiplatelet therapy. Findings from this systematic review have been incorporated in the guidelines, but this manuscript has not been published elsewhere.

METHODS

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Statement.⁶ The PRISMA checklist is provided in the appendix. The questions of this review and the inclusion and exclusion criteria were established by CHEST/ACCP guideline panel members in a nonregistered protocol using the patients—interventions—comparators—outcomes (PICO) format. The current review includes the direct evidence supporting PICO questions that addressed the perioperative management of antiplatelet therapy.

Data Source and Search Strategies

We searched MEDLINE and Epub ahead of print, in-process, and other nonindexed citations; EMBASE; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; and Scopus from each database's inception to July 16, 2020. The search strategy was designed and executed by a medical reference librarian (L.C.H.) with input from the investigators using controlled vocabulary supplemented with keywords without language restrictions. The search strategy also included anticoagulant therapies, which are presented in a separate manuscript. The details of the search are provided in [Supplemental Table 1](#) (available online at <http://www.mcpiqjournal.org>).

Study Selection

The titles and abstracts were screened by 2 independent reviewers. If considered eligible, full-text articles of the included abstracts were retrieved and reviewed by 2 independent reviewers. Conflicts were resolved by a third reviewer. The eligibility criteria included adult patients (≥ 18 years who (1) were receiving antiplatelet therapy and required an elective surgery/procedure; (2) were with or without coronary stents; (3) were undergoing noncardiac surgery or CABG; (4) were undergoing minor (dental, dermatologic, or ophthalmologic) procedures; and (5) reported an outcome of interest, including major and minor bleeding,⁷ arterial or venous thromboembolic events, including MI, stroke, systemic embolism, transient ischemic attack, deep vein thrombosis or pulmonary embolism, and mortality. Definitions of outcomes are provided in [Supplemental Table 2](#) (available online at <http://www.mcpiqjournal.org>).

Data Extraction and Risk of Bias Assessment

Data were extracted from the included studies by 2 independent reviewers using a standardized data extraction form. Disagreements were resolved by a third reviewer. The baseline characteristics of the included studies are shown in [Supplemental Table 3](#) (available online at <http://www.mcpiqjournal.org>). The risk of bias in the included studies was assessed by 2 independent reviewers. The Cochrane Collaboration's Risk of Bias 2 tool was used for randomized clinical trials (RCTs). This tool takes into consideration 6 domains: (1) the randomization process, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result, and (6) other sources of bias found, as shown in [Supplemental Table 4.1](#) (available online at <http://www.mcpiqjournal.org>). We summarized the risk of bias in all domains to produce an overall risk of bias for every RCT. For observational studies, we selected items from the Newcastle-Ottawa scale, with a focus on the representativeness of the exposed cohort, the selection of the nonexposed cohort, the ascertainment of exposure and outcomes, the comparability of cohorts, and adequacy of follow-up, as shown in [Supplemental Table 4.2](#) (available online at <http://www.mcpiqjournal.org>).

Statistical Analyses and Certainty of Evidence

Binary data from comparative studies (RCTs and cohort studies) were reported as a risk ratio (relative risk; RR) with associated 95% CIs. We pooled the outcomes across studies using the restricted maximum likelihood random-effects model and estimated heterogeneity using the Mantel-Haenszel model and the I^2 statistic where possible. Heterogeneity was deemed low, moderate, and high when I^2 values were <30%, 30%-60%, and >60%, respectively. All statistical analyses were conducted using R 4.2.0.⁸

To rate the certainty of evidence (COE) in the comparative estimates of direct evidence, the Grading of Recommendations, Assessments, Development and Evaluation approach was used.⁹ RCTs start at high certainty,

whereas non-RCTs start at low certainty. Certainty was rated down for risk of bias, imprecision, indirectness, inconsistency, and publication bias. Precision was judged on the basis of whether CIs crossed the null as a target of certainty.^{10,11}

RESULTS

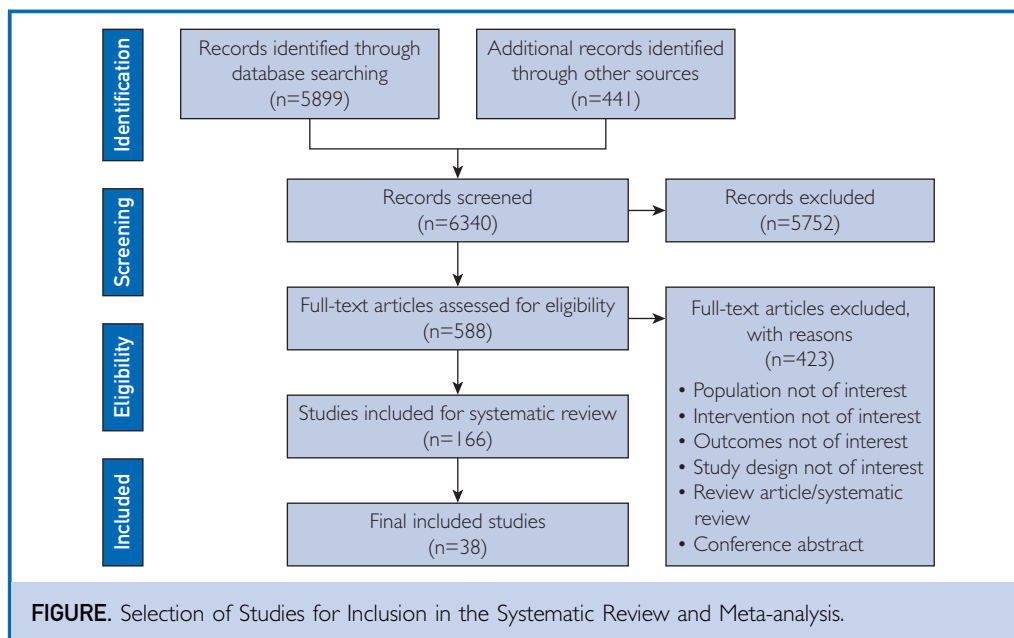
The study selection process is shown in the PRISMA flow diagram shown in the [Figure](#). A total of 38 studies were included that addressed 6 PICO questions.

Question 1. Stopping Antiplatelet Agents Before Elective Surgery/Procedure

Stopping ASA ≤ 7 days vs > 7 days. We included 1 RCT¹² and 1 cohort study¹³ that reported on 699 patients who stopped receiving ASA either ≤ 7 days or > 7 days before the surgery/procedure. The risk of bias for the cohort study and RCT was moderate. Compared with stopping ASA > 7 days, stopping ASA ≤ 7 days was not associated with a statistically significant difference in the risk of major bleeding, major thromboembolism (any outcomes: ischemic stroke, transient ischemic attack, MI, pulmonary embolism [PE], venous thromboembolism, or vascular death), and MI, as summarized in the [Table](#), with very low COE.

Continuing vs Stopping ASA ≤ 7 days. Another subset of studies compared stopping ASA within ≤ 7 days before surgery to continuing ASA throughout the elective surgery. We included 3 RCTs¹⁴⁻¹⁶ and 2 cohort studies^{17,18} that reported on 485 patients. The risk of bias for cohort studies and RCT was moderate. There was no statistically significant difference in the risk of major bleeding, as shown in [Supplemental Figure 1](#) (available online at <http://www.mcpiqjournal.org>), major thromboembolism, and MI, as summarized in the [Table](#), with very low COE.

Patients randomized to ASA perioperatively vs Placebo. Another subset of studies compared continuing ASA through elective surgery to placebo (not taking ASA) before surgery. We included 5 RCTs¹⁹⁻²³ that reported on 28,062 patients. The risk of bias for the RCTs was low. Compared with patients



who received placebo perioperatively, ASA continuation was associated with an increased risk of major bleeding (RR, 1.31; 95% CI, 1.15-1.50; high COE) and a lower risk of major thromboembolism (RR, 0.75; 95% CI, 0.59-0.95; high COE). There was no statistically significant difference in the risk of MI, stroke and mortality, with high COE for MI and stroke and low COE for mortality.

Question 2. Continuation vs Stopping Antiplatelet Agents in Patients With Coronary Stents at High Risk or Low-Moderate Risk for CV Events

We included 1 RCT²⁴ and 2 cohort studies^{25,26} that reported on 638 patients with coronary artery stents (mixed population; high risk or low-moderate risk for CV events) who continued antiplatelet agents perioperatively or stopped antiplatelet agents 7 to 10 days before the procedure/surgery. The risk of bias for the cohort studies was moderate and for the RCT was low.

Compared with stopping antiplatelet therapy, continuing antiplatelet therapy perioperatively was not associated with a statistically significant difference in the risk of major bleeding and major thromboembolism, as summarized in the Table, with low to very low COE for RCT and cohort studies, respectively.

Question 3. Bridging vs No Bridging in Patients with Coronary Stents and Receiving Antiplatelet Agents

We included 1 cohort study²⁷ that reported on 215 patients who received bridging with low-molecular-weight heparin (LMWH) compared with 264 patients with no bridging during interruption of antiplatelet agents. The risk of bias for the cohort study was moderate. Compared with no bridging during interruption, bridging with LMWH was associated with a statistically significant increase in the risk of major bleeding (RR, 1.86; 95% CI, 1.24-2.79) and thromboembolism (RR, 26.2; 95% CI, 1.56-441.6; very low COE).

Question 4. Continuation vs Stopping Antiplatelet Agents in Patients Undergoing CABG

We included 17 studies (5 RCTs²⁸⁻³² and 12 cohorts³³⁻⁴⁴) that reported on 12,621 patients. The risk of bias for RCTs and cohort studies was low-to-moderate and moderate-to-high, respectively. Compared with stopping of antiplatelet therapy, continuation of antiplatelet therapy was associated with a statistically significant increase in the risk of major bleeding in the 3 RCTs (RR, 1.68; 95% CI, 1.29-2.18), as shown in Supplemental Figure 2 (available online at <http://www.mcpiqjournal.org>), with moderate COE.

TABLE. Outcomes: Perioperative Management of Antiplatelet Therapy^a

Outcome	Findings, relative risk (95% CI)	Study design and sample size	Certainty of evidence ^b
Stopping ASA ≤ 7 d vs >7 d before elective surgery/procedure			
Major bleeding	0.78 (0.01-38.4) 0.81 (0.36-1.85)	1 RCT ¹⁰ ; 80 1 comparative observational ¹¹ ; 619	Very low ^{c,d} Very low ^{d,e}
Major thromboembolism	0.78 (0.01-38.5)	1 RCT ¹⁰ ; 80	Very low ^{c,d}
Myocardial infarction	0.26 (0.01-6.21)		Very low ^{c,d}
Continuing vs stopping ASA ≤ 7 d before elective surgery/procedure			
Major bleeding	0.87 (0.18-4.13) 0.95 (0.23-3.90)	3 RCTs ¹²⁻¹⁴ ; 179 2 comparative observational ^{15,16} ; 306	Very low ^{c,d} Very low ^{d,e}
Major thromboembolism	1.00 (0.02-48.6) 0.62 (0.05-7.37)	1 RCT ¹² ; 52 2 comparative observational ^{15,16} ; 306	Very low ^{c,d} Very low ^{c,d}
Myocardial infarction	1.96 (0.13-30.25) 0.95 (0.06-14.8)	2 comparative observational ^{15,16} ; 83 2 RCTs ^{12,14} ; 109	Very low ^{d,e} Very low ^{c,d}
Continuing ASA vs placebo before elective surgery/procedure			
Major bleeding	1.31 (1.15-1.50)	5 RCTs ¹⁷⁻²¹ ; 28,062	High
Stroke	1.00 (0.7-1.44)	5 RCTs ¹⁷⁻²¹ ; 28,062	High
Major thromboembolism	0.75 (0.59-0.95)	3 RCTs ¹⁹⁻²¹ ; 17,832	High
Myocardial infarction	1.05 (0.63-1.77)	3 RCTs ¹⁷⁻¹⁹ ; 27,674	High
Mortality	1.01 (0.14-7.05)	1 RCT ²¹ ; 291	Low ^d
Continuing vs stopping antiplatelet agents in patients with coronary stents at high risk or low-moderate risk for cardiovascular events			
Major bleeding	0.96 (0.02-46.05) 0.58 (0.19-1.83)	1 RCT ²² ; 43 1 comparative observational ²³ ; 27	Low ^d Very low ^{d,e}
Major thromboembolism	0.96 (0.02-46.05) 1.07 (0.88-1.31)	1 RCT ²² ; 43 1 comparative observational ^{23,24} ; 568	Low ^d Very low ^{d,e}
Continuing vs stopping antiplatelet agents in patients undergoing coronary artery bypass graft			
Major bleeding	1.68 (1.29-2.18) 1.10 (0.93-1.30)	3 RCTs ²⁶⁻²⁸ ; 1073 12 comparatives observational ³¹⁻⁴² ; 11,466	Moderate ^d Low
Arterial thromboembolism	1.20 (1.00-1.44) 1.29 (0.41-4.02)	2 comparatives observational ^{35,38} ; 3525 2 RCTs ^{26,30} ; 831	Low Low ^d

Continued on next page

TABLE. Continued

Outcome	Findings, relative risk (95% CI)	Study design and sample size	Certainty of evidence ^b
Mortality	1.20 (0.47-3.01) 0.79 (0.49-1.28)	5 RCTs ²⁶⁻³⁰ ; 1186 10 comparatives observational ^{31-34,36-41} ; 8676	Low ^d Very low ^d
Management of antiplatelet agents around minor procedures (dental)			
Major bleeding	0.95 (0.27-3.38)	3 RCTs ⁴³⁻⁴⁵ ; 155	Very low ^{c,d}
Minor bleeding	2.1 (0.88-5.00)	1 RCT ⁴³ ; 39	Very low ^{c,d}
Management of antiplatelet agents around minor procedures (ophthalmological)			
Major bleeding	0.65 (0.15-2.90)	1 RCT ⁴⁶ ; 39	Low ^{c,d}
Major thromboembolism	0.67 (0.01-32.25)		Very low ^{c,d}
Minor bleeding	1.45 (0.07-30.25)	1 comparative observational ⁴⁷ ; 4340	Very low ^{d,e}
Stroke	0.29 (0.02-4.64)		Very low ^{d,e}
Myocardial Infarction	2.00 (0.1-39.4)		Very low ^{d,e}

^aASA, acetylsalicylic acid; RCT, Randomized clinical trial.
^bWhen the number of events was very low (<10), we considered rating down by 2-3 levels unless the sample size was large (>2000-4000). An arbitrary cutoff of the relative risk reduction of 25% was used as a cutoff for lowering certainty in precision by 2 levels. RCTs start at high certainty, whereas non-RCTs start at low certainty. Certainty was rated down for risk of bias, imprecision, indirectness, inconsistency, and publication bias. Precision was judged on the basis of whether confidence intervals crossed the null as a target of certainty. **Certainty of evidence**
^cSee Cochrane Risk of Bias Tool table.
^dwide CI, including substantial benefits and harms and/or small sample size.
^eSee the Newcastle-Ottawa risk of bias table.
Major thromboembolism: any outcomes: ischemic stroke, transient ischemic attack, myocardial infarction, peripheral embolism, venous thromboembolism, or vascular death. Major bleeding defined following the International Society on Thrombosis and Haemostasis standards as having a symptomatic presentation and fatal bleeding and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of 2 or more units of whole blood or red blood cells.

There was no statistically significant difference in the risk of arterial thromboembolism (ATE) events, summarized in the Table, and mortality, as shown in Supplemental Figure 3 (available online at <http://www.mcpiqjournal.org>). The COE was low for mortality.

Question 5. Management of Antiplatelet Agents Around Minor (Dental) Procedures

We included 3 RCTs⁴⁵⁻⁴⁷ that reported on 155 patients who were undergoing minor dental procedures. The risk of bias in these RCTs was moderate. Compared with stopping antiplatelet therapy between 7 and 10 days before the procedure/surgery, continuation of antiplatelet therapy was not associated with a statistically significant difference in the risk of major bleeding, as shown in Supplemental Figure 4 (available online at <http://www.mcpiqjournal.org>), and minor bleeding, summarized in the Table, with very low COE.

[mcpiqjournal.org](http://www.mcpiqjournal.org)), and minor bleeding, summarized in the Table, with very low COE.

Question 6. Management of Antiplatelet Agents Around Minor (Ophthalmological) Procedures

We included 1 RCT⁴⁸ and 1 cohort study⁴⁹ that reported on 4382 patients. The risk of bias for these cohort studies and the RCT was high to moderate. Compared with stopping, continuation of antiplatelet therapy was not associated with a statistically significant difference in the risk of major bleeding, stroke, MI, and other major thromboembolism events, as summarized in the Table, with low to very low COE.

DISCUSSION

We conducted a systematic review and meta-analysis to support the development of the

ACCP/CHEST clinical practice guidelines. The current review summarizes the evidence from 38 studies addressing 6 PICO questions relating to the perioperative management of antiplatelet therapy. Overall, although there have been considerable advances in knowledge, especially pertaining to the perioperative management of ASA in noncardiac surgery and CABG, data remained limited as was the certainty in the various outcomes. This precluded the development of strong practice recommendations relating to perioperative management of antiplatelet therapy.

In patients receiving single antiplatelet therapy with ASA alone, the available literature suggested no difference between perioperative continuation or interruption of ASA in terms of major bleeding and thromboembolic events. The Pulmonary Embolism Prevention (PEP) trial that included patients requiring hip fracture repair or joint replacement who were randomized to receive ASA started preoperatively or placebo found a reduction in the risk for venous thromboembolism but an increased risk of major bleeding and no effect on MI.²¹ The Perioperative Ischemic Evaluation 2 (POISE-2) randomized trial conducted in patients at risk for coronary artery diseases undergoing noncardiac surgery found that continuing ASA or starting it preoperatively decreased the risk of major thromboembolism but increased the risk of major bleeding, with no significant effect on CV events, including MI.¹⁹ No direct evidence was available about the perioperative management of clopidogrel, prasugrel, or ticagrelor in noncardiac surgery.

No prospective studies have assessed perioperative management of clopidogrel, prasugrel, or ticagrelor in noncardiac surgery. Retrospective cohort studies of clopidogrel suggest an increased risk of bleeding with perioperative clopidogrel continuation. Thus, making decisions in this context relies on indirect evidence. For example, a retrospective cohort analysis of patients undergoing coronary artery bypass or single-valve surgery has found that ticagrelor exposure 0-72 hours before cardiac surgery was associated with an increased risk of major bleeding complications. On the other hand, ticagrelor exposure 72-120 hours before surgery was not associated with a clinically relevant increase in major bleeding complications.⁵⁰

In terms of heparin bridging in patients with coronary stents who are on antiplatelet agents and required treatment interruption before elective surgery, bridging with LMWH was associated with increased bleeding risk and no difference in the risk of ATE. Therefore, a rationale for bridging may only exist in selected high-risk patients, for example, in those with 3 months of coronary stent. There is limited evidence overall on a bridging approach in patients with coronary stents at low or moderate-high risk of CV events.

An analysis of 5 RCTs²⁸⁻³² and 12 cohort studies³³⁻⁴⁴ that evaluated patients undergoing CABG surgery found an increased risk of major bleeding in patients who continued antiplatelet agents, although the bleeding outcomes assessed varied and results were not always presented according to antiplatelet drug type. The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS)⁵¹ trial, which assessed perioperative initiation of ASA against no initiation found no increased risk for surgical-site bleeding. When considering the postoperative complications of antiplatelet agents, the timing of cessation before CABG surgery was deemed an important determinant of bleeding risk. A meta-analysis evaluating clopidogrel interruption before CABG reported that a shorter period (<5 days) of clopidogrel interruption was associated with less CV events and a lower bleeding risk compared with a longer period of interruptions (>5 days).⁵² Despite the widespread prescription of antiplatelets in the clinical setting, it was surprising to find very limited data about this clinical scenario.

In settings of minor procedures, such as dental, ophthalmologic, or dermatologic procedures in which patients are receiving antiplatelet therapy, the available literature suggests no major risk of bleeding or ATE events with periprocedural ASA continuation. In dermatologic procedures, 1 meta-analysis of RCTs and observational studies found no greater risk of hemorrhagic complications with continuation of ASA and no evidence of long-term morbidity.⁵³ Data on the rate of complications of clopidogrel appear to be low. However, data on ASA continuation in patients undergoing cataract surgery suggested a low incidence of major bleeding, supporting the continued use of ASA.⁴⁹ Similarly, data on stopping ASA before vitreoretinal surgery

indicated no difference in terms of hemorrhagic complications.⁵⁴

This review has 2 major limitations. First, firm conclusions were precluded by the limited evidence base, as reflected by the small number of high-quality studies directly addressing the perioperative management of antiplatelet therapy. Second, certainty in the estimates of effect was low for many PICO questions and associated outcomes, thereby requiring greater reliance on indirect evidence from nonrandomized studies or other clinical contexts to develop practice recommendations. These limitations are consistent with what others have described in this field. A systematic evaluation of 10 guidelines for perioperative management of dual antiplatelet therapy has demonstrated limited rigor and lack of evidence and consensus.⁵⁵ The strengths of this systematic review relate to the close working relationship with experts from CHEST/ACCP who developed *a priori* clinical question and inclusion criteria and. A panel from CHEST/ACCP will use this evidence along with other contextual and implementation factors, such as patients' values and preferences, feasibility, and acceptability, to develop practical advice for clinicians.

CONCLUSION

Although the perioperative management of patients who are receiving antiplatelet therapy is a common clinical occurrence, there is a relative dearth of high-quality studies that directly address whether to continue or interrupt antiplatelet therapy, the timing of interruption, and the role of bridging therapy. The current best available evidence is derived from a few randomized trials with methodological limitations that only address perioperative continuation or interruption before noncardiac and CABG surgery. For all other clinical scenarios, including the management of patients who are receiving non-ASA single antiplatelet therapy or dual antiplatelet agents, and for those who require minor (nonsurgical) procedures, there is only nonrandomized evidence or indirect evidence to inform practice recommendations. It is, therefore, not surprising that strong recommendations are lacking in the area of perioperative antiplatelet management. This review highlights the urgent need for further research to address these gaps in knowledge,

especially as the prevalence of patients taking one or more antiplatelet agents is increasing with an ageing population and such patients are most likely to require a surgery/procedure.

POTENTIAL COMPETING INTERESTS

Dr James Douketis reported consulting fees and honoraria from Up-to-Date, Merck Manual, Pfizer, Leo Pharma, Sanofi, Janssen, Servier, and PhaseBio. The other authors report no competing interests.

AUTHOR CONTRIBUTIONS

Conception and design: S.S., M.H.M.; analysis and interpretation: S.S., T.N., M.H.M.; data collection: S.S., M.U., M.F., B.H., T.N., S.S., D.N.F., A.N., R.A., M.O.S., N.R., L.C.H.; writing the article: S.S., A.C.S., J.D.D., M.H.M.; critical revision of the article: S.S., M.U., M.F., B.H., T.N., S.S., D.N.F., M.S., A.N., R.A., N.R., L.C.H., M.O.S.; final approval of the article: S.S., M.U., M.F., M.S., B.H., T.N., S.S., D.N.F., A.N., R.A., M.O.S., N.R., L.C.H.; obtaining funding: M.H.M.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: ACCP/CHEST, American College of Chest Physicians; ASA, acetylsalicylic acid; ATE, arterial thromboembolism; CABG, coronary artery bypass graft; COE, certainty of evidence; CV, cardiovascular; DES, drug-eluting stent; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PE, pulmonary embolism; PICO, patients—interventions—comparators—outcomes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risk; RCT, randomized clinical trial

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