CHEST

Original Research

CARDIOVASCULAR DISEASE

Perioperative Management of Antiplatelet Therapy in Patients With a Coronary Stent Who Need Noncardiac Surgery

A Systematic Review of Clinical Practice Guidelines

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Background: **It is unclear how to appropriately manage discontinuation and resumption of antiplatelet therapy in patients with coronary stents who need noncardiac surgery. We undertook a systematic review of the literature to identify practice guideline statements regarding antiplatelet therapy in patients with coronary stents undergoing noncardiac surgery.**

Methods: **We used six search strategies to identify practice guideline statements that comment on perioperative antiplatelet management for patients with coronary stents undergoing noncardiac surgery. Two independent reviewers assessed study eligibility, abstracted data, and completed quality assessment.**

Results: **We identified 11 practice guidelines that met the eligibility criteria; these were included in the review. These guidelines advised that elective noncardiac surgery be delayed for at least 4 weeks after bare-metal stent implantation and at least 6 months after drug-eluting stent implantation. For elective surgery, all guidelines advised continuing acetylsalicylic acid (ASA) therapy whenever possible. If interruption of antiplatelet therapy was required, four guidelines advised to discontinue ASA/clopidogrel at least 5 days before surgery, while two guidelines advised to discontinue 7 to 10 days before surgery. Five guidelines provided varying guidance for the use of perioperative bridging during antiplatelet therapy interruption.**

Conclusions: **Most current recommendations are based on expert opinion. This review highlights the need for well-designed prospective studies to identify optimal management strategies in patients with coronary stents who are on antiplatelet therapy and who need noncardiac surgery.**

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Abbreviations: AGREE = Appraisal of Guidelines Research and Evaluation; ASA = acetylsalicylic acid; BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; MACE = major adverse cardiovascular event; ST = stent thrombosis

Major perioperative cardiovascular complications such as nonfatal myocardial infarction, nonfatal stroke, and death occur in nearly 10 million patients annually.[1] This number is expected to rise due to the increase in noncardiac surgery and other procedures performed in an aging population. The perioperative management of patients with coronary artery stents is particularly challenging and is becoming more common, as 900,000 patients receive coronary stents in the United States annually.[2] Coronary stents consist of bare-metal stents (BMSs) or, in the majority of cases in the United States, drug-eluting stents (DESs). After stent implantation, it is recommended that patients receive 6 weeks to 12 months of dual antiplatelet therapy (DAPT),[3,4] typically consisting of acetylsalicylic acid (ASA) combined with clopidogrel, although DAPT often is continued beyond this time frame. Within 1 year of stent implantation, 4% to 5% (36,000-45,000 patients) of such patients will require surgery, a number that rises to 11% (99,000 patients) within 2 years of stenting.[5] It is anticipated that a much higher number of stented patients will require nonsurgical procedures such as colonoscopy.

There are no established management strategies for patients with coronary stents who are receiving DAPT and require elective surgery. Clinicians balance

the perceived risk for major adverse cardiovascular events (MACEs) and stent thrombosis (ST) associated with perioperative antiplatelet drug interruption against the risk of bleeding associated with drug continuation. Patients with coronary stents have an 8% to 10% risk of developing MACE and ST after elective noncardiac surgery,[6,7] which exceeds the 1% to 5% risk for MACE in nonstented patients having noncardiac surgery.[8] Given that fatality from ST ranges from 40% to 60%, this represents a significant clinical problem.[9,10] Patients are at highest risk for ST during the time between stent implantation and re-endothelialization at the stent site. This process takes 4 to 6 weeks in patients with a BMS and 6 to 12 months in patients with a DES.[11] Premature withdrawal of DAPT is the strongest predictor of ST, with the majority of drug withdrawals occurring in the perioperative setting.[12] The risk for MACE and ST diminishes as the interval between stent implantation and surgery increases, irrespective of the stent type, but remains at 5% to 10% if surgery is done > 2 years after stenting.[13,14]

There are few well-designed studies to inform perioperative management of stented patients who need elective surgery, specifically about when to interrupt and resume DAPT and whether one or both antiplatelet drugs should be continued or stopped. Thus, although one observational study found that stopping both antiplatelet drugs > 5 days before surgery conferred a 2.1-fold increased risk for MACE, an optimal management was not identified.[15] Similarly, the risk of bleeding if antiplatelet therapy is continued perioperatively is uncertain,[15] and although continuing ASA appears to increase the risk for major bleeding (from 1% to 2%), this estimate is imprecise as the definition of bleeding was not standardized.[16]

Given the paucity of well-designed studies to inform practice, clinicians may rely on practice guidelines to assist with decisions regarding perioperative antiplatelet management in patients with coronary stents who need noncardiac surgery. While such guidelines are available, they appear to vary according to methodological approaches and recommendations. We undertook a systematic review of the literature aiming to evaluate and synthesize guideline statements regarding perioperative antiplatelet therapy focusing on the following clinical questions:

1. When should elective noncardiac surgery be done in patients with a coronary stent?
2. Which antiplatelet agents should be stopped or continued around the time of surgery?
3. When should antiplatelet therapy be stopped and resumed before and after surgery?
4. Is bridging with an anticoagulant or antiplatelet agent needed around the time of surgery?

Materials and Methods

Study Eligibility Criteria

We included clinical practice guidelines that comment on perioperative antiplatelet management strategies for patients with coronary stents who are having noncardiac surgery. Studies were eligible regardless of their language, publication status, primary objective, or size and scope of the practice guideline group. We excluded studies that were not deemed to be guideline statements, duplicate publications, copies or summaries of previous guidelines, and guidelines that did not provide recommendations or statements pertaining to any of the aforementioned clinical questions.

Study Identification and Search Strategy

We used the following strategies to identify eligible studies: electronic search of databases, including the National Guideline Clearinghouse website (http://www.guideline.gov, accessed January 2013), MEDLINE (1946 to January, week 1, 2013), EMBASE (1974 to 2012, week 52), AMED (1985 to December 2012), and Cochrane Library (until December 2012); consultation with experts in perioperative medicine; review of reference lists from retrieved articles fulfilling eligibility criteria; use of the "see related articles" for key publications in PubMed (until January 2013); and search of SciSearch (until January 2013) for publications that cited key publications.

Study Selection

Search results were merged using reference management software (RefWorks), and duplicate records were removed. All titles and abstracts of identified articles were independently screened by two authors (S. D.-K., M. G.). If either reviewer considered that a citation contained a guideline of interest, the citation was selected for full review. After retrieving the full text of citations selected for full review, the same two authors independently assessed eligibility. A κ statistic was used to quantify interobserver agreement. Any disagreements were resolved by discussion among the two reviewers. An independent third author (M. M.) resolved any outstanding disagreements. If there were questions regarding the methods of a reviewed article, we contacted the study authors for clarification.

The eligibility criteria for each article were assessed in a predetermined order and the first criterion not met was used as the reason for exclusion. The order was as follows: guideline statements, involved patients having noncardiac surgery, comments specifically

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on patients with coronary stents, and provides statements regarding perioperative antiplatelet management.

Data Collection and Study Quality Assessment

Using a standardized data collection form, two authors (S. D.-K., M. G.) independently abstracted data from all guidelines that fulfilled our eligibility criteria. A κ statistic was used to assess agreement in data abstraction, and any discrepancies were resolved using the consensus process outlined previously. We abstracted the following descriptive data from all eligible practice guidelines: year of publication, primary disease/condition(s), target population, major outcomes considered, and rating scheme for the strength of the recommendation. The quality of the clinical practice guidelines was appraised by applying the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument to all eligible papers. The AGREE II instrument is designed to assess quality of clinical practice guidelines based on six factors: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity and presentation, (5) applicability, and (6) editorial independence. We also abstracted the recommendations and associated grade and/or level of evidence from each guideline pertaining to our four prespecified clinical questions.

For consistency and clarity, we adopted three conventions for this review. First, we avoided the terms "recommend" or "suggest" when describing the wording of a practice guideline. This was done because the term "recommend" may imply a strong guidance statement that is typically (but not uniformly) supported by well-designed randomized trial data, whereas use of "suggest" may imply a weak guidance statement that is typically (but not uniformly) supported by weaker, observational study data. Moreover, some guidelines may use the term "recommend" when it pertains to expert opinion, whereas other guidelines restrict the use of this term to reflect high-quality evidence. We use generic terms such as "advised" or "guidance" to describe the expression of intent of the included practice guideline. Second, the use of DAPT herein refers to ASA and clopidogrel, since all but one guideline reviewed do not refer to other $P2Y_{12}$ inhibitors (prasugrel, ticagrelor), which can be combined with ASA . Third, although we mention the grade and/or level of evidence ascribed to guideline statements and the system and/or nomenclature of each guideline group, we recognized that there is no universally accepted format used for guidance statements. For example, although the American College of Chest Physicians has adopted the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) convention, this was not adopted by other guideline groups, thereby limiting across-guideline comparisons.

Results

Included Studies and Quality Assessment

We identified and evaluated for inclusion 2,766 potentially relevant articles, of which 254 were identified for full review. From these articles, 164 guideline statements were excluded, as they did not comment on antiplatelet therapy or involve patients with coronary stents undergoing noncardiac surgery. Of these 164 guideline statements, two articles discussed overall medical management of patients during the perioperative period but were deemed nonrelevant for this review. Overall, 11 practice guidelines fulfilled the eligibility criteria and were included in our review ($\kappa = 0.93$).[4,17-26] Figure 1 illustrates our systematic review process. The guidance statements from each guideline group pertaining to our four prespecified clinical questions are summarized in Table 1.

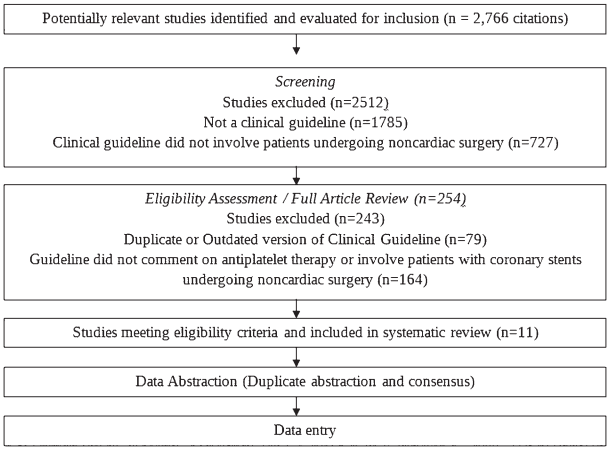

Figure 1. Systematic review process.

The AGREE II instrument was applied to the 11 practice guidelines to assess methodological rigor, with the composite domain scores for each guideline shown in Table 2 (κ=0.91). Overall, there was considerable variability in domain scores across guidelines and indicators of methodological limitation in most guidelines. Thus, of a possible maximum 161 domain score points, six guidelines had $<$100 points, and only two guidelines had $>$128 points (80% mark). In the six guidelines scoring $<$100 points, the predominant domains with methodological limitations that impaired overall quality were rigor of development, applicability, and editorial independence.

Level of Evidence and Grade of Recommendations Associated With Guideline Statements

As shown in Table 1, there were no practice guidelines that conferred a strong recommendation that was associated with high- or moderate-quality evidence (eg, Grade 1A or 1B) for the perioperative management of antiplatelet therapy in patients with coronary stents. Some guidelines conferred strong recommendations as to the timing of elective surgery after BMS and DES implantation, but the associated level of evidence was low. For questions relating to which antiplatelet drugs should be stopped and the timing of discontinuation and resumption, no practice guideline conferred a strong recommendation regarding such practices, and for many guidelines there was only a narrative commentary without an associated strength of recommendation/level of evidence.

Clinical Questions

When Should Elective Noncardiac Surgery Be Done in Patients With a Coronary Stent? In patients with

Table 1—*Practice Guidelines for Perioperative Antiplatelet Management of Patients With a Coronary Stent Who Need Elective Noncardiac Surgery*

Guideline	When Should Elective Noncardiac Surgery Be Done in Patients With a Coronary Stent?	Which Antiplatelet Agents Should Be Stopped or Continued Around the Time of Surgery?	When Should Antiplatelet Therapy Be Stopped and Resumed Before and After Surgery?	Is Bridging Needed Around the Time of Surgery?
Cardiac Society of Australia/New Zealand[17]	BMS: Delay elective surgery for at least 6 wk, and ideally 3 mo (LOE III-3; grade A).[a] DES: Delay elective surgery for 12 mo (LOE IV; grade B).[a]	Continuation of DAPT is recommended for patients at low risk for ST unless undergoing spinal, intracranial, extraocular, urologic, or major plastic reconstructive procedures. (LOE: IV; grade A)[a] Antiplatelet therapy should be continued wherever possible in high-risk patients (LOE: III-3; grade B).[a]	Stop ASA and/or clopidogrel 5 d preoperatively. No recommendation regarding resumption after surgery.[b]	For patients at high risk for ST who stop DAPT, bridging with heparin and/or GPIIb/IIIa antagonist should be considered. (LOE: IV; grade B)[a]
Austrian Society for Anesthesiology/European Society of Cardiology[18]	BMS: Delay elective surgery for 4-6 wk.[b] DES: Delay elective surgery for a minimum of 12 mo.[b]	Semi-urgent surgery: Continue ASA and consider discontinuing clopidogrel. Urgent surgery: Continue ASA and clopidogrel. In patients undergoing closed space surgery (eg, intracranial, intraspinal) or other high-bleed risk surgery, clopidogrel should be discontinued while continuing ASA therapy.[b]	Discontinue ASA/clopidogrel 5 d before elective surgery. Resume within 24 h of surgery if adequate hemostasis.[b]	Consider bridging in patients at high risk for ST up to a few hours before surgery with short-acting GPIIb/IIIa antagonists.[b]
American College of Chest Physicians[19]	BMS: Delay elective surgery for at least 6 wk. DES: Delay elective surgery for at least 6 mo (both grade 1C).[c]	In patients who need surgery within 6 wk of BMS or within 6 mo of DES implantation, continue DAPT around the time of surgery instead, stopping DAPT 7-10 d before surgery (grade 2C).[c]	If DAPT is discontinued, it should be done 7-10 d before surgery and resumed 24 h after surgery if possible.[b]	Routine use of bridging is not recommended.[b]
American Heart Association/American College of Cardiology[20]	BMS: Delay elective surgery for at least 1 mo. DES: Delay elective surgery for at least 12 mo.[b]	ASA should be continued if possible and thienopyridines should be resumed as early as possible after surgery.[b]	No statement	No statement
Canadian Cardiovascular Society[4]	BMS: Delay surgery for at least 6 wk. DES: Delay surgery for at least 12 mo (both class 1, level B).[d]	If urgent surgery needed within 6 wk of BMS or 1 yr of DES implantation, continue DAPT if possible during perioperative period (class 1, level B).[d] For elective procedures, if the risk for cardiovascular events is high, continue ASA (class IIa, level C)[d] but discontinue clopidogrel (class IIb, level C).[d]	If interruption required, stop ASA and clopidogrel 7-10 d before surgery (class IIa/b, level C),[d] restart 24 h after surgery.	No statement
French Task Force[21]	BMS: No recommendation. DES: Delay elective surgery for 6-12 mo.[b]	ASA therapy should be continued in most scenarios.[b]	If interruption required, ASA/clopidogrel should be discontinued 5 d prior to surgery. Resume treatment as soon as possible after surgery.[b]	Consider 300 mg clopidogrel loading dose after surgery. Bridging with a nonsteroidal antiinflammatory or low-molecular-weight heparin can be considered.[b]

(Continued)

Table 1—*Continued*

Guideline	When Should Elective Noncardiac Surgery Be Done in Patients With a Coronary Stent?	Which Antiplatelet Agents Should Be Stopped or Continued Around the Time of Surgery?	When Should Antiplatelet Therapy Be Stopped and Resumed Before and After Surgery?	Is Bridging Needed Around the Time of Surgery?
European Society of Cardiology[22]	BMS: Delay elective surgery for at least 6 wk, and optimally 3 mo. DES: Delay elective surgery for 12 mo (both class 1, level B).[d]	Continue ASA if possible, consider discontinuing ASA if difficult hemostasis is anticipated (class IIa, level B).[d]	No statement	No statement
American College of Cardiology/American Heart Association[23]	BMS: Delay elective surgery for 4-6 wk. DES: Delay elective surgery for 12 mo (both LOE: B, class 3).[d]	ASA should be continued for elective surgery in most cases. In patients with DES requiring urgent surgery, continue ASA if possible; thienopyridine can be discontinued if needed (LOE: C, class IIa).[d]	Resume thienopyridine as soon as possible after surgery (LOE: C, class IIa).[d]	No statement
Japanese Circulation Society[24]	BMS: Delay elective surgery for at least 4 wk.[b] DES: Delay elective surgery for at least 12 mo.[b]	If thienopyridine therapy is discontinued for patients with DES, continue ASA when possible.[b]	Resume thienopyridine promptly after surgery.[b]	Bridging with heparin can be considered if both DAPT are discontinued.[b]
Institute for Clinical Systems Improvement[25]	BMS: Delay elective surgery for at least 4 wk. DES: Delay elective surgery for at least 12 mo (both low-quality evidence, strong recommendation).[c]	In patients who require surgery within 4 wk of BMS or within 12 mo of DES implantation, DAPT should be continued except in procedures with high risk for bleeding; if need to discontinue clopidogrel, prasugrel, or ticlopidine, continue ASA if possible (both low quality evidence, strong recommendation).[c]	Resume antiplatelet therapy as soon as possible after surgery.[b]	No statement
Brazilian Society of Cardiology[26]	BMS: Delay elective surgery for at least 2 wk (class 1, level C)[d] and ideally ≥ 6 wk (class 1, level B).[d] DES: Delay elective surgery for at least 12 mo (class 1, level B).[d]	Patients on DAPT: Continue DAPT in surgery with low bleeding risk (class IIa, level C)[d]; in other procedures, continue ASA and discontinue thienopyridine (class 1, level C).[d] Patients on thienopyridine only: Continue therapy if low bleeding risk (class IIa, level C).[d]	If interruption required, stop thienopyridine 5 d before surgery; resume as soon as possible after surgery (class 1, level C).[d]	No statement

ASA = acetylsalicylic acid; BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; LOE = level of evidence; RCT = randomized controlled trial; ST = stent thrombosis.

[a]Strength of recommendation: grade A: judgment most well-informed people would make; grade B: judgment majority of well-informed people would make but that a substantial minority would not. Level of evidence: 1: systematic review of all relevant RCTs; 2: at least one RCT; 3-1: pseudo-RCT; 3-2: comparative studies with concurrent controls; 3-3: comparative studies without concurrent controls; 4: case series.

[b]Strength of recommendation and level of evidence not stated.

[c]Strength of recommendation: grade 1: strong recommendation; grade 2: weak recommendation. Level of evidence: A: high-quality evidence; B: moderate quality of evidence; C: low or very low quality of evidence.

[d]Strength of recommendation: class I: procedure/treatment strongly recommended; class IIa: procedure/treatment is reasonable; class IIb: procedure/treatment may be considered; class III: procedure/treatment is NOT recommended and may be harmful. Level of evidence: A: data from multiple RCT or meta-analyses; B: single RCT or nonrandomized studies; C: consensus opinion of experts, case studies, or standard of care.

Table 2—*Composite Domain Scores for Practice Guidelines Assessed With AGREE II Instrument*

Clinical Practice Guideline	Scope and Purpose[a]	Stakeholder Involvement[b]	Rigor of Development[c]	Clarity and Presentation[d]	Applicability[e]	Editorial Independence[f]	Total Score (161)
Cardiac Society of Australia/New Zealand[17]	19/21	14/21	28/56	16/21	8/28	4/14	89
Austrian Society for Anesthesiology/European Society of Cardiology[18]	19/21	12/21	13/56	17/21	4/28	3/14	68
American College of Chest Physicians[19]	21/21	21/21	55/56	17/21	24/28	14/14	152
American Heart Association/American College of Cardiology[20]	13/21	7/21	20/56	13/21	6/28	14/14	79
Canadian Cardiovascular Society[4]	21/21	12/21	50/56	18/21	20/28	14/21	135
French Task Force[21]	12/21	5/21	10/56	13/21	4/28	2/21	46
European Society of Cardiology[22]	20/21	14/21	35/56	17/21	18/28	12/14	116
American College of Cardiology/American Heart Association[23]	19/21	15/21	42/56	18/21	15/28	14/14	123
Japanese Circulation Society[24]	18/21	8/21	10/56	13/21	4/28	2/28	55
Institute for Clinical Systems Improvement[25]	21/21	14/21	30/56	17/21	18/28	12/14	112
Brazilian Society of Cardiology[26]	19/21	10/21	21/56	14/21	6/28	5/14	75

AGREE = Appraisal of Guidelines Research and Evaluation.
[a]Assesses the overall aim of the guideline, the specific clinical questions, and the target patient population.
[b]Focuses on the extent to which the guideline represents the views of its intended users.
[c]Relates to the process used to gather and synthesize the evidence and the methods to formulate the recommendations and to update them.
[d]Pertains to the language and format of the guidelines.
[e]Pertains to the likely organizational, behavioral, and cost implications of applying the guidelines.
[f]Assesses the independence of the recommendations and acknowledgments of possible conflict of interest.

a BMS, four practice guidelines advised delaying elective noncardiac surgery for at least 6 weeks after stent implantation.[4,17,19,22] Five guidelines advised at least a 4-week interval,[18,20,23-25] and one guideline advised at least a 2-week interval between stent implantation and surgery.[26] In addition, one guideline advised that, optimally, surgery should be delayed for 3 months after BMS implantation.[22] In patients with a DES, nine guidelines advised delaying an elective noncardiac surgery for 12 months after stent implantation,[4,17,18,20,22-26] and two guidelines advised a minimum interval of 6 months.[19,21]

Which Antiplatelet Agents Should Be Stopped or Continued Around the Time of Surgery? All practice guidelines advised continuing ASA therapy around the time of noncardiac surgery whenever possible.[4,17-26] In patients having surgery with high bleeding risk, such as spinal, intracranial, extraocular, urologic, or major reconstructive procedures, one guideline advised discontinuing both ASA and clopidogrel,[17] whereas another guideline advised discontinuing clopidogrel only.[18] In the setting of urgent surgery, six guidelines advised continuing DAPT whenever possible.[4,18,19,23,25,26] If discontinuation of clopidogrel was deemed clinically necessary due to an increased perioperative bleeding risk, eight guidelines advised perioperative continuation of ASA therapy.[4,18,20,22-26]

When Should Antiplatelet Therapy Be Stopped and Resumed Before and After Surgery? If interruption of antiplatelet therapy was required, four guidelines advised that ASA/clopidogrel be discontinued a minimum of 5 days prior to surgery[17,18,21,26] while two guidelines advised discontinuation 7 to 10 days before surgery.[4,19] The prompt resumption of antiplatelet therapy was advised by eight guidelines,[4,18,19,21,23-26] with three guideline groups advising that this be done 24 h after surgery.[4,18,19] Three other guideline groups did not provide any guidance regarding the resumption of antiplatelet therapy after surgery.[17,20,22]

Is Bridging With an Anticoagulant or Antiplatelet Agent Needed Around the Time of Surgery? There were five practice guidelines that provided clinical advice for the use of a bridging agent, comprising low-molecular-weight heparins, direct thrombin inhibitors (eg, hirudin, lepirudin), or glycoprotein IIb/IIIa inhibitors (eg, eptifibatide), during the perioperative period.[17-19,21,24] The Cardiac Society of Australia/New Zealand states that bridging with a glycoprotein IIb/IIIa inhibitor or heparin may be considered, while the French Task Force advises bridging with a low-molecular-weight heparin or nonsteroidal inflammatory agent in patients at high risk for ST after interruption of DAPT.[17,21] The Austrian Society for Anesthesiology advises that bridging can be considered in patients at

high risk for ST with the use of short-acting glycoprotein IIb/IIIa antagonists administered in the immediate perioperative period.[18] The Japanese Circulation Society advises bridging with heparin if DAPT therapy is discontinued perioperatively.[24] The American College of Chest Physicians advises against the routine use of bridging in patients who are receiving DAPT and require surgery.[19]

Discussion

The aim of this review was to evaluate and synthesize guidance from 11 clinical practice guidelines addressing the perioperative management of antiplatelet therapy in patients with coronary stents who need elective noncardiac surgery. Overall, we found considerable variability in clinical guidance and low levels of evidence (eg, Grade 2C) associated with these guidance statements.

Despite a lack of strong guidance statements based on high-quality evidence (eg, commensurate with Grade 1A or 1B recommendations), there are several noteworthy points from these guidelines. First, there appeared to be a consistent guidance to defer surgery for at least 4 to 12 weeks (6 weeks was dominant) after BMS implantation, and for at least 6 to 12 months (12 months was dominant) after DES implantation. Second, there appeared to be consensus to continue ASA perioperatively and, when possible, to continue DAPT in patients at high risk for MACE/ST, unless this was precluded by the surgery-associated bleeding risk. Third, consensus was lacking as to the timing of antiplatelet therapy interruption; moreover, there was limited guidance on the postoperative resumption of such treatment. Finally, the greatest variability in clinical guidance related to use of bridging therapy with a heparin or glycoprotein IIb/IIIa inhibitor during perioperative antiplatelet interruption. Of note, the consistency of guidance statements did not appear to be related to the date of publication of the studies, despite their inclusion of the most recent evidence pertaining to this topic.

Strengths and Weaknesses

Our systematic review has several strengths. Our search was comprehensive and used six search strategies to identify eligible studies. Screening, eligibility assessment, and data abstraction were conducted in duplicate with a high degree of agreement between reviewers. Additionally, we provided an estimate of the quality of the various clinical practice guidelines using the AGREE II instrument. Our review is limited by the lack of high-quality evidence in the field, which is reflected in the grades of recommendations and levels of evidence associated with the guideline statements. Most practice guideline statements are based on low-quality evidence (ie, observational studies with limitations) or expert opinion alone. This review is also limited in its ability to make comparisons regarding guidance statements across guidelines, as different grading systems and nomenclature were used by each writing group. As standard of practice has changed over the years, it is possible that the differences in advice provided by the guidelines are affected by this variable. We aimed to limit this by only including the most recent updated versions of a guideline.

Relation to Other Systematic Reviews

To our knowledge, this the first systematic and comprehensive review of clinical practice guidelines regarding the perioperative management of antiplatelet therapy in patients with coronary stents who need noncardiac surgery. Our review highlights current guidance for prespecified clinical questions and provides an estimate of their quality using the AGREE II instrument.

Clinical Implications

Patients undergoing noncardiac surgery who are receiving single or DAPT for a coronary stent represent a common problem for clinicians. Patients with a BMS or DES on antiplatelet therapy face risks for perioperative ST and bleeding, which must be balanced by both the clinician and patient. The scope of this problem is considerable. Thus, the Evaluation of Drug-Eluting Stents and Ischemic Event Registry in the United States demonstrated that in 4,367 patients with DES implantation, 4.4% had noncardiac surgery within 1 year of stent placement, with a 1.9% event rate for myocardial infarction, death, or ST.[27] Moreover, the Scottish Coronary Revascularization Registry of 17,797 patients with a BMS or DES demonstrated that the perioperative rate for MACEs was higher in patients with surgery done $\leq$42 days after stent implantation compared with $>$42 days after stent implantation (42.4% vs 12.8%, $P < .01$).[3]

Despite the lack of high-quality evidence, most guidelines advised to continue ASA perioperatively in most patients and to continue DAPT in patients at highest risk for ST, unless this was limited by the bleeding risk associated with the planned surgery. Such guidance is based on studies that have evaluated the perioperative stopping or continuation or ASA. Thus, Mantz et al[28] randomized 290 patients who were receiving an antiplatelet agent for the secondary prevention for coronary artery disease to ASA (75 mg daily) or placebo, starting 10 days before intermediate-risk or high-risk noncardiac surgery, and there was no difference in thrombotic or bleeding events within the first few days after surgery. Indirect evidence from

the Pulmonary Embolism Prevention trial, which compared low-dose ASA with placebo in 17,444 patients undergoing hip fracture or joint replacement surgery with continuation for 35 days after surgery, showed that ASA use reduced the incidence of postoperative venous thromboembolism but with a small increase in the risk for major bleeding (2.9% vs 2.4%, $P = .04$).[16] Similarly, a meta-analysis of $>49{,}000$ patients undergoing noncardiac surgery found that perioperative continuation of ASA increased the overall risk for bleeding by a factor of 1.5.[29] For patients receiving DAPT, one study demonstrated that in patients requiring surgery within 2 months of stent placement, continuing ASA and clopidogrel increased the proportion of patients needing transfusion (eg, 42.6% vs 38.5%; $P < .05$), but there was no difference in major bleeding.[30] There appears to be no uniform consensus regarding the timing of antiplatelet therapy interruption and postoperative resumption of treatment. This result is not unexpected given the lack of relevant high-quality evidence. Although the Multicenter, Prospective Cohort of Patient With Coronary Stents Undergoing Noncardiac Surgery or Invasive Procedures (RECO) study, a multicenter observational study assessing patients on single or DAPT who needed surgery, showed no increase in bleeding if antiplatelet therapy was stopped ≤ 5 days before surgery (OR = 0.72; 95% CI, 0.35-1.5) or >5 days before surgery (OR = 0.93; 95% CI, 0.48-1.8), this study did not specify outcomes based on whether only clopidogrel or only ASA was interrupted perioperatively.[15] Finally, the lack of consensus (or absence of guidance statements) regarding bridging therapy during perioperative DAPT interruption reflects the low quality of associated evidence that is based on case reports alone.

In summary, our review highlights the lack of high-quality evidence to inform perioperative antiplatelet management for patients with coronary stents who are undergoing noncardiac surgery. Further analysis of existing data may help to answer some questions, such as whether the total duration of time off DAPT prior to surgery affects the incidence of postoperative MACEs. Ultimately, given the scope and importance of this clinical problem, there is a need for high-quality prospective studies assessing different management strategies in stented patients on antiplatelet therapy who require noncardiac surgery. Currently, one prospective cohort study is beginning enrollment to evaluate the efficacy and safety of a standardized, perioperative antiplatelet management strategy for patients with a coronary stent who require an elective or urgent surgery/procedure. Patients will be stratified according to their two-tiered risk (high, nonhigh) for MACEs and bleeding (high, nonhigh) to a standardized management strategy and assessed for outcomes such as death, bleeding, and major cardiovascular events. Given the lack of consensus regarding current standard of care for patients with coronary stents undergoing noncardiac surgery, a cohort study will provide important baseline information that can be used to design subsequent randomized controlled trials. Additionally, a randomized controlled trial design would be difficult given the lack of a reliable estimate of the incidence of postoperative events in this patient population. The results of this study will help to define future management strategies for patients with coronary stents who are undergoing noncardiac surgery.

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