Oral antithrombotics and dentistry: Current state of affairs and guideline proposal
van Diermen, D.E.

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Chapter 4

Review of postoperative bleeding risk in dental patients on antiplatelet therapy

Joel Napeñas
Floor Oost
Annika de Groot
Bridget Loven
Catherine Hong
Michael Brennan
Peter Lockhart
Denise van Diermen

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Chapter 4

ABSTRACT

Objective. We conducted a review of the literature to assess risk for oral bleeding complications after dental procedures in patients on antiplatelet therapy.

Study Design. We conducted a search in the Medline, Embase, and National Guideline Clearinghouse databases for studies involving patients on single and dual antiplatelet therapy that had invasive dental procedures or manipulations that induce oral bleeding.

Results. The literature search yielded 15 studies that met inclusion criteria. There is a trend toward increased occurrence of immediate postoperative bleeding for dual antiplatelet therapy, but there is no increase in the occurrence of intra- or late postoperative bleeding complications.

Conclusions. We found no clinically significant increased risk of postoperative bleeding complications from invasive dental procedures in patients on either single or dual antiplatelet therapy. These findings support the recommendation that there is no indication to alter or stop these drugs, and that local hemostatic measures are sufficient to control bleeding.
INTRODUCTION

Antithrombotics can be divided into 2 entirely different groups of drugs: those that affect platelet aggregation (e.g., acetylsalicylic acid [ASA] and clopidogrel), and those that affect clot formation and maintenance (e.g., coumarin derivatives). Antiplatelet agents are used for the secondary prevention of cardiac and cerebrovascular diseases, specifically for the prevention of arterial and venous thrombosis in patients with conditions such as ischemic heart disease, prosthetic heart valves, and coronary artery stents and those at risk for ischemic cerebrovascular accidents.

Antiplatelet agents can be classified by their mode of action in prevention of platelet activation and aggregation. ASA and triflusal work through inactivation of the enzyme cyclooxygenase, which converts arachidonic acid to the prostaglandin thromboxane A2, a key factor in platelet activation and aggregation. Inhibiting thromboxane A2 prevents clot formation for the lifetime of the platelet, which is 9-11 days\(^1\). Thienopyridines (e.g., clopidogrel, ticlopidine, and prasugrel) irreversibly inhibit adenosine diphosphate, which is necessary for the activation of the receptor GPIIb/IIIa complex in platelet aggregation\(^3\). Drugs targeted directly to the GPIIb/IIIa complex include tirofiban, eptifibatide, and abciximab. Dipyridamole and cilostazol are phosphodiesterase inhibitors that decrease platelet aggregability. In addition, \(\alpha\)-tocopherol (vitamin E) has been shown to inhibit platelet adhesion to the adhesive proteins collagen, fibrinogen, and fibronectin\(^4\).

Of concern to dental practitioners is the risk of excessive oral bleeding during or after invasive dental procedures. Although there is an abundance of literature pertaining to the effects of coumarin derivatives on patients having invasive dental procedures\(^5\), there is far less information on antiplatelet drugs. Although there have been strong warnings from some authors and organizations\(^6\) that the risks from altering dosage of or stopping antiplatelet drugs far outweigh any benefit\(^6\) there remains a prevailing practice of stopping these drugs before invasive dental procedures. There is no definitive prospective study of patients on antiplatelet therapy, and it is highly unlikely that one will ever be done. The purpose of the present paper was to review the existing literature for oral bleeding complications after dental procedures in patients on antiplatelet therapy.
Chapter 4

MATERIALS AND METHODS

We performed a search for relevant literature on the Medline (1948 to September 2011) and Embase databases (1978 to September 2011) and the National Guideline Clearinghouse. The searches were limited to English-language studies on humans pertaining to antithrombotic therapy and dental practice. Initial screening was done by 1 author (B.L.), and final selection was done independently by 3 reviewers (J.J.N., F.O., A.D.G.) by reviewing the titles and abstracts of the articles. In addition, the reference lists of retrieved articles on the subject were reviewed, and more recent additional articles were retrieved via correspondence with content experts. For studies to meet eligibility, they had to have at least 1 group of patients on at least 1 antiplatelet agent and there had to be a measurement of bleeding outcomes after invasive dental treatment (e.g., tooth extractions) or other oral manipulations (e.g., periodontal probing). Studies were required to be one of the following: randomized controlled trials, cohort studies, or case-control studies, either prospective or retrospective. We excluded case reports, reviews, guidelines, and expert opinions. In cases of multiple articles from the same group that were thought to use the same data, only the more recent were included. For each study, data were extracted regarding study design, patient characteristics, type of antiplatelet regimen, dental intervention or manipulation, and perioperative and postoperative clinical and laboratory outcomes for bleeding.

RESULTS

Study identification, selection, characteristics, and outcome variables

The results of the search on Medline and Embase yielded totals of 3,377 and 498 potentially relevant studies, respectively, and the search on National Guideline Clearinghouse yielded 1 additional publication. After the authors screened the titles and abstracts, 14 articles met inclusion criteria for the review. However, 2 of the studies from the same group seemed to be reporting the same data, so only the more recent study was included in this review. Two additional articles were discovered through correspondence and through review of reference lists, giving a total number
Review of postoperative bleeding risk in dental patients on antiplatelet therapy

of eligible studies of 15 (Table I). Of these, 3 were randomized controlled trials, 9 were prospective cohort studies, and 3 were retrospective cohort studies. There were a total of 2,428 patients, with enrollment cohorts ranging from 36 to 643 patients in each study. All studies involved antiplatelet therapy with ASA, 9 of which also involved non-ASA–based antiplatelet medications (α-tocopherol, clopidogrel, cilostazol, dipyridamole, ticlodipine, and triflusal) and 2 included patients on warfarin therapy. Nine studies had control groups, with 3 studies having a placebo group, 1 having a group that stopped antiplatelet therapy, 4 having groups that were never on antiplatelet drugs, and 1 having 2 control groups (stopped antiplatelet therapy and never on antiplatelet drugs). Demographics were reported for all but 3 studies. Invasive dental procedures included tooth extractions (single and/or multiple, including third molar extractions), alveoloplasty, apicoectomy, implant placement, torus removal, excisional biopsies, flap surgery, periodontal surgery, and deep scaling and root planing. Three studies, did not involve a dental procedure, but used periodontal probing to assess the presence of bleeding on probing (BOP). Because there is no universally accepted standardized definition of bleeding in patients undergoing surgical procedures, the postoperative bleeding outcome variables were grouped in the following manner: provider-monitored intra- and postoperative bleeding (quantitative and qualitative measures), telephone follow-up surveys and patient return visits (scheduled and unscheduled), and postoperative time at which the patient was monitored, seen, and/or contacted for follow-up. Eight studies indicated that they had examined laboratory variables, but only 5 reported this information. Four studies attempted to quantify the degree of intraoperative blood loss, 3 reported the results as occurrence of excessive blood loss, and 1 reported actual degree of blood loss per surgical unit.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Dental procedure(s)*</th>
<th>No. of patients</th>
<th>Control/placebo group(s)</th>
<th>Intervention group(s)†</th>
<th>Bleeding outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardekian et al.¹³</td>
<td>Cohort (prospective)</td>
<td>Extractions (single and multiple)</td>
<td>39</td>
<td>Stopped ASA therapy 7 d before (n = 20)</td>
<td>Daily ASA therapy (75-150 mg) (n = 19)</td>
<td>Intraoperative bleeding (quantity)Patient report of postoperative bleedingCutaneous BT</td>
</tr>
<tr>
<td>Brennan et al.¹⁴</td>
<td>RCT (double-blind placebo controlled)</td>
<td>Extractions (single)</td>
<td>36</td>
<td>Placebo 2 d before and 2 d after (n = 19)</td>
<td>Daily ASA therapy (325 mg) 2 d before and 2 d after (n = 17)</td>
<td>Oral BTPatient report of bleeding at 30 min, 3-7 h, and 40-55 h after extractionCutaneous BT</td>
</tr>
<tr>
<td>Cañigral et al.⁹</td>
<td>Cohort (prospective)</td>
<td>Extractions (single and multiple)</td>
<td>99</td>
<td>None</td>
<td>ASA (dose not specified; n = 17) Clopidogrel (n = 10) ASA and clopidogrel (n = 9) Oral anticoagulants (not specified; n = 19) LMWH (n = 20) NSAIDs (unspecified; n = 15) [As reported, numbers do not add up to total participants]</td>
<td>Degree of postoperative bleeding based on duration (&lt;10 min, &lt;60 min, &gt;60 min)Laboratory values: CBC, quick index, INR, aPTT, fibrinogen, platelet function tests</td>
</tr>
</tbody>
</table>
### Review of postoperative bleeding risk in dental patients on antiplatelet therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Dental procedure(s)*</th>
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<th>Bleeding outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardona-Tortajada et al.</td>
<td>Cohort</td>
<td>Extractions (single and multiple)</td>
<td>155</td>
<td>None (though 22 patients reported interruption of therapy before extraction)</td>
<td>ASA therapy (100-300 mg; n = 118) Clopidogrel (75 mg; n = 20) Ticlopidine (250 mg; n = 2) Triflusal (n = 15)</td>
<td>Postoperative bleeding at 10 min Patient report of bleeding at 24 h after extraction</td>
</tr>
<tr>
<td>Krishnan et al.</td>
<td>Cohort</td>
<td>Extractions (single and multiple)</td>
<td>82</td>
<td>Patients never having received any antiplatelet therapy (n = 25) Stopped daily ASA therapy (75-100 mg) before (time not specified; n = 25)</td>
<td>Continued daily ASA therapy (75-100 mg; n = 25)</td>
<td>Cutaneous BT Clotting time Postoperative bleeding: patient report 12 h after; patient phone call; return to clinic or ED; large hematoma; blood transfusion Percentage of sites with bleeding on probing</td>
</tr>
<tr>
<td>Liede et al.</td>
<td>Cohort</td>
<td>Periodontal probing</td>
<td>409</td>
<td>Patients taking neither ASA or α-tocopherol (n = 192)</td>
<td>Daily ASA therapy (100-3,200 mg; n = 26) Daily ASA therapy and α-tocopherol (50 mg/d; n = 30) α-Tocopherol (n = 161)</td>
<td></td>
</tr>
<tr>
<td>Madan et al.</td>
<td>Cohort</td>
<td>Extractions (single and multiple)</td>
<td>51</td>
<td>None</td>
<td>Daily ASA therapy (75-100 mg; n = 51)</td>
<td>Cutaneous BT Platelet count Intraoperative blood loss Postoperative bleeding at 30 min, 24 h, 48 h, 72 h, 1 wk, 2 wk</td>
</tr>
</tbody>
</table>

*Study type: Cohort (prospective)*

†Intervention group(s): ASA therapy (100-300 mg; n = 118) Clopidogrel (75 mg; n = 20) Ticlopidine (250 mg; n = 2) Triflusal (n = 15)
<table>
<thead>
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<th>Study</th>
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<th>Intervention group(s)†</th>
<th>Bleeding outcomes assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lillis et al.</td>
<td>Cohort</td>
<td>Simple extractions (single and multiple)</td>
<td>643</td>
<td>Patients never having received any antiplatelet therapy (n = 532)</td>
<td>ASA (n = 42)</td>
<td>Postoperative bleeding at 30 min</td>
</tr>
<tr>
<td></td>
<td>(prospective)</td>
<td></td>
<td></td>
<td>Clopidogrel (n = 36)</td>
<td>ASA and clopidogrel (n = 33)</td>
<td>Late postoperative bleeding &gt;12 h; patient phone call; return to clinic or ED; hematoma or ecchymosis; blood transfusion</td>
</tr>
<tr>
<td>Morimoto et al.</td>
<td>Cohort</td>
<td>Periodontal probing</td>
<td>139</td>
<td>None</td>
<td>Antiplatelet therapy</td>
<td>Postoperative bleeding: patient report by phone within 24 h; follow up within 1 wk</td>
</tr>
<tr>
<td></td>
<td>(retrospective)</td>
<td>Scaling Superficial and subgingival scaling and root planing Flap operation Gingivectomy and alveoloplasty</td>
<td></td>
<td>(single or dual ASA, ticlopidine, cilostazol; n = 87)</td>
<td>Warfarin and antiplatelet therapy (ASA and other; n = 49)</td>
<td>Laboratory values: INR, platelet counts</td>
</tr>
<tr>
<td>Morimoto et al.</td>
<td>Cohort</td>
<td>Extractions (single and multiple)</td>
<td>382</td>
<td>None</td>
<td>Antiplatelet therapy</td>
<td>Postoperative bleeding: patient report by phone within 24 h; follow up within 1 wk</td>
</tr>
<tr>
<td></td>
<td>(retrospective)</td>
<td></td>
<td></td>
<td>(single or dual ASA, ticlopidine, cilostazol; n = 128)</td>
<td>Warfarin and antiplatelet therapy (ASA and other; n = 66)</td>
<td>Laboratory values: INR, platelet counts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warfarin therapy (n = 188)</td>
<td></td>
</tr>
<tr>
<td>Napeñas et al.</td>
<td>Cohort</td>
<td>Deep subgingival scaling and root planing Extractions (single and multiple) Periodontal surgery</td>
<td>43</td>
<td>None</td>
<td>Single antiplatelet therapy (non-ASA based; n = 14)</td>
<td>Postoperative bleeding: patient phone call; return to clinic or ED; inpatient documentation of bleeding; blood transfusion</td>
</tr>
<tr>
<td></td>
<td>(retrospective)</td>
<td></td>
<td></td>
<td></td>
<td>Dual antiplatelet therapy (ASA and 1 other drug; n = 29)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study type</td>
<td>Dental procedure(s)*</td>
<td>No. of patients</td>
<td>Control/placebo group(s)</td>
<td>Intervention group(s)†</td>
<td>Bleeding outcomes assessed</td>
</tr>
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<tr>
<td>Park et al.</td>
<td>Cohort (prospective)</td>
<td>Extractions (single and multiple)</td>
<td>200</td>
<td>Patients never having received any antiplatelet therapy—matched control subjects (n = 100)</td>
<td>Daily ASA (100-200 mg) and clopidogrel (75 mg; n = 59) Daily ASA (100-200 mg), clopidogrel (75 mg) and cilostazol (100 mg; n = 41)</td>
<td>Perioperative blood loss: total Postoperative: blood transfusion, rehospitalization due to bleeding Laboratory values: platelet count, PT, aPTT</td>
</tr>
<tr>
<td>Partridge et al.</td>
<td>Cohort (prospective)</td>
<td>Extractions (single and multiple) Biopsy Alveoloplasty</td>
<td>50</td>
<td>Patients never having received any antiplatelet therapy for ≥10 d before (n = 23)</td>
<td>ASA therapy (n = 13) Clopidogrel bisulfate (n = 2) NSAIDs (n = 12)</td>
<td>Perioperative blood loss: total; mean per surgical unit Postoperative bleeding: patient phone call</td>
</tr>
<tr>
<td>Royzman et al.</td>
<td>RCT (double-blind placebo controlled)</td>
<td>Periodontal probing</td>
<td>54</td>
<td>Placebo 7 consecutive days (n = 17)</td>
<td>Daily ASA therapy (81 mg) 7 consecutive days (n = 17) Daily ASA therapy (325 mg) 7 consecutive days (n = 20)</td>
<td>Percentage of sites with bleeding on probing</td>
</tr>
<tr>
<td>Schrodi et al.</td>
<td>RCT (double-blind placebo controlled)</td>
<td>Periodontal probing</td>
<td>46</td>
<td>Placebo 7 consecutive days (n = 17)</td>
<td>Daily ASA therapy (81 mg) 7 consecutive days (n = 17) Daily ASA therapy (325 mg) 7 consecutive days (n = 20)</td>
<td>Percentage of sites with bleeding on probing</td>
</tr>
</tbody>
</table>

aPTT, Activated partial thromboplastin time; ASA, acetylsalicylic acid; BT, bleeding time; CBC, complete blood count; ED, emergency department; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time; RCT, randomized controlled trial.

* Includes only those procedures actually performed among enrolled patients.
† Dosages are not specified in study unless indicated.
Intraoperative and postoperative bleeding

Intraoperative bleeding and quantitative measures of blood loss (Table II). Three studies reported the occurrence of excessive blood loss. Ardekian et al. defined severe bleeding as blood loss of >50 mL during dental extractions, which occurred in 10% (2/19) of patients taking ASA (75-100 mg) and 20% (4/20) of control patients who had discontinued ASA 7 days prior to oral surgery. This study also further subdivided the ASA and control groups into 3 groups based on surgical difficulty. In doing so, they found that more intraoperative bleeding occurred when extractions were more complicated in both groups, though there were no differences between groups. Madan et al. and Park et al. defined severe bleeding as blood loss of >30 mL during extractions. Between both studies, there was a 1.9% (3/151) occurrence of excessive blood loss in antiplatelet patients, and a 1% (1/100) occurrence in controls. Partridge et al. compared intraoperative mean blood loss per ‘surgical unit’ for a variety of oral surgical procedures, with higher surgical unit values assigned to extraction of multirooted teeth and alveoloplasty, and lower surgical unit values assigned to extraction of single-rooted teeth. There were no significant differences in mean blood loss between patients on ASA, clopidogrel and NSAIDs.

Postoperative bleeding

Immediate postoperative bleeding (i.e., <60 minutes after surgery) (Tables II and III). Lillis et al. reported a 66.7% occurrence of bleeding within 30 minutes for patients on dual antiplatelet therapy, compared with 2.6% for single antiplatelet and 0.4% in control subjects, differences which were statistically significant. A similar difference was observed by Cañigral et al. between dual antiplatelet (ASA and clopidogrel, 40%) and single antiplatelet therapy groups (ASA, 6%; clopidogrel, 0%; nonsteroidal antiinflammatory drugs (NSAIDs), 30%; low-molecular-weight heparin (LMWH), 15%; and oral anticoagulants, 5%) within 60 minutes. However, they reported a 0% occurrence of postoperative bleeding after 60 minutes for all groups. Cardona-Tortajada et al. reported a 0.6% occurrence of postoperative bleeding among single and dual antiplatelet patients after 10 minutes, and Madan et al. reported a 0% occurrence for patients on ASA after 30 minutes. Brennan et al. reported that 93% of ASA patients, and 79% of placebo control subjects reported bleeding after leaving their appointment, when surveyed by telephone.
Table II. Provider-monitored intraoperative and postoperative bleeding outcomes

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Reported occurrence by study, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiplatelet ± other antithrombotics</td>
</tr>
<tr>
<td><strong>Quantitative intraoperative bleeding measure</strong></td>
<td></td>
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<tr>
<td>Excessive intraoperative blood loss (% incidence)</td>
<td></td>
</tr>
<tr>
<td>Ardekian et al.\textsuperscript{13} \ (&gt;50 mL loss)</td>
<td>Ardekian et al.\textsuperscript{13} \ (&gt;50 mL loss)</td>
</tr>
<tr>
<td>ASA: 10% (2/19)</td>
<td>Stopped ASA: 20% (4/20)</td>
</tr>
<tr>
<td>Madan et al.\textsuperscript{15} (&gt;30 mL loss)</td>
<td>Park et al.\textsuperscript{12} (&gt;30 mL loss)</td>
</tr>
<tr>
<td>ASA: 2% (1/51)</td>
<td>Control: 1% (1/100)</td>
</tr>
<tr>
<td>Park et al.\textsuperscript{12} (&gt;30 mL loss)</td>
<td></td>
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<tr>
<td>ASA and clopidogrel: 1.7% (1/59)</td>
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<tr>
<td>ASA, clopidogrel, and cilostazol: 2.4% (1/41)</td>
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<tr>
<td><strong>Qualitative bleeding measures</strong></td>
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<tr>
<td>(monitored or documented by providers)</td>
<td></td>
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<tr>
<td>Postoperative bleeding at 10-30 min</td>
<td></td>
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<tr>
<td>Lillis et al.\textsuperscript{16}</td>
<td></td>
</tr>
<tr>
<td>ASA: 2.4% (1/42)</td>
<td>Lillis et al.\textsuperscript{16}</td>
</tr>
<tr>
<td>Clopidogrel: 2.8% (1/36)</td>
<td>Control: 0.4% (2/532)</td>
</tr>
<tr>
<td>ASA and clopidogrel: 66.7% (22/33)</td>
<td></td>
</tr>
<tr>
<td>Cardona-Tortajada et al.\textsuperscript{17}</td>
<td></td>
</tr>
<tr>
<td>Single/dual antiplatelet: 0.6% (1/155)</td>
<td></td>
</tr>
<tr>
<td>Madan et al.\textsuperscript{15}</td>
<td></td>
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<tr>
<td>ASA: 0% (0/51)</td>
<td></td>
</tr>
<tr>
<td>Postoperative bleeding &lt;60 min with local hemostatic measures</td>
<td>Cañigral et al.\textsuperscript{9}</td>
</tr>
<tr>
<td>ASA: 6% (1/17)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel: 0% (0/10)</td>
<td></td>
</tr>
<tr>
<td>ASA and clopidogrel: 40% (4/10)</td>
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<tr>
<td>NSAIDs: 13% (2/15)</td>
<td></td>
</tr>
<tr>
<td>LMWH: 15% (3/20)</td>
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<tr>
<td>Oral anticoagulants (not specified): 5% (1/19)</td>
<td></td>
</tr>
<tr>
<td>Postoperative bleeding &gt;60 min requiring medical or surgical management</td>
<td>Cañigral et al.\textsuperscript{9}</td>
</tr>
<tr>
<td>ASA: 0% (0/17)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel: 0% (0/10)</td>
<td></td>
</tr>
<tr>
<td>ASA and clopidogrel: 0% (0/10)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs: 0% (0/15)</td>
<td></td>
</tr>
<tr>
<td>Measures of blood loss</td>
<td>Partridge et al.\textsuperscript{8}</td>
</tr>
<tr>
<td>Mean blood loss per surgical unit (g ± SD)</td>
<td>ASA (n = 13)-1.97 ± 1.48</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel (n = 2): 0.43 ± 0.18</td>
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<td></td>
<td>NSAIDs (n = 12)-1.80 ± 1.28</td>
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</tbody>
</table>

Abbreviations as in Table I.
Late postoperative bleeding (Table III). Through follow-up phone calls 3-7 hours after surgery, Brennan et al. reported bleeding occurrences of 27% among ASA patients, compared with 32% among control subjects. At follow-up phone calls 40-55 hours after surgery, 0% in both groups reported bleeding. Through follow-up phone calls after 24 hours, Cardona-Tortajada et al. reported bleeding occurrences of 18% (22/118), 100% (2/2), and 13% (2/15) of ASA, clopidogrel, and triflusal patients, respectively. Two studies observed 0% occurrences of postoperative bleeding among patients on ASA and clopidogrel and among control subjects.

Six studies did not specify or had a wide time range for reported follow-up visits (e.g., clinic or emergency department visits) or phone calls. Among them, 4 reported a 0% occurrence of postoperative bleeding in all patients, including those taking ASA, clopidogrel, dipyridamole, and ticlopidine, control groups, and those who had stopped taking ASA. Morimoto et al. reported postoperative bleeding of 1.4% for single or dual antiplatelet therapy, 4.1% for warfarin, and 8.2% for combined warfarin and antiplatelet therapy after teeth extractions. The same group performed a similar study involving periodontal therapy (e.g., scaling and root planing, periodontal surgery), with postoperative bleeding occurrences of 0%, 1.4%, and 3.4% for antiplatelet therapy, warfarin, and combined warfarin and antiplatelet therapy, respectively.

Hemostatic measures

Three studies reported occurrences of postoperative hemostatic measures, which included: gauze pressure, use of a splint, removal of hematoma, placement of oxidized cellulose, resuturing, and electrocautery. Morimoto et al. reported that 1.5% (2/128) of single or dual antiplatelet patients required gauze pressure after teeth extractions. Postoperative measures were 6.8% (5/73) for warfarin in combination with single or dual antiplatelet therapy and 4.5% (10/219) for warfarin therapy. The same group published another study evaluating bleeding outcomes after periodontal therapy and reported that 1.3% (2/155) of antiplatelet patients required local hemostatic measures. Through follow-up phone calls, Brennan et al. reported that 93% (14/15) of ASA patients and 74% (14/19) of control subjects replaced gauze at 3-7 hours after extraction. At 40-55 hours after extraction, 14% (2/14) of ASA patients and 29% (5/17) of control subjects replaced gauze.
Table III. Patient-reported (i.e., by return visit or telephone follow-up) intra- and postoperative bleeding outcomes

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Reported occurrence by study (%, n)</th>
</tr>
</thead>
</table>
| Immediate postoperative bleeding (≤30 min)   | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |
| Postoperative bleeding (follow-up ≤24 h)     | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |
| Postoperative bleeding (follow-up at 24-72 h) | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |
| Postoperative bleeding (follow-up at 1-2 wk)  | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |
| Postoperative bleeding (follow-up time not specified or wide range) | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |
| Return visit to dental clinic or ED for postoperative bleeding | Brennan et al.14  
ASA: 93% (14/15)  
Brennan et al.14  
ASA: 27% (4/15)  
Cardona-Tortajada et al.17  
ASA: 18% (22/118)  
Clopidogrel: 100% (2/2)  
Triflusal: 13% (2/15)  
Partridge et al.8  
NSAIDs: 0% (0/12)  
ASA: 0% (0/3)  
Clopidogrel: 0% (0/2)  
  | Brennan et al.14  
Placebo: 79% (15/19)  
Brennan et al.14  
Placebo: 32% (6/19)  
Partridge et al.8  
Control: 0% (0/23)  
  |

Abbreviations as in Table I.
Bleeding on periodontal probing

Three studies (2 of which were conducted by the same group) reported BOP as their primary outcome variable⁴,¹⁰,¹¹. One study involved patients with gingivitis and compared percentage of sites with BOP before and after exposure to 3 regimens; placebo, 81 mg ASA and 325 mg ASA¹⁰. There were statistically significant increases in mean percentage of sites that exhibited BOP in patients on both ASA regimens, which was not observed in the placebo group. The other study by the same group had a similar protocol but involved periodontally healthy patients¹¹. The only subgroup that exhibited significant increases in mean percentage of sites with BOP were those taking 325 mg ASA. Liede et al. compared the effects of α-tocopherol, both alone and in combination with ASA therapy, in a population of smokers⁴. Mean percentage of sites that exhibited BOP were 34% in the combination therapy group, 25.8% in those who had taken neither α-tocopherol or ASA, and 25.95% in those who took ASA alone (P < .001).

Laboratory variables

Cutaneous bleeding time test was measured in 4 studies, with variations of the Ivy method used in 2 studies¹³,¹⁴, the Duke method in 1⁷, and 1 study not specifying their method¹⁵. Among all of the studies, there were no significant differences between antiplatelet therapy and control groups. Oral bleeding time (OBT) was measured in 1 study¹⁴, which involved observation of the extraction site without gauze in place, for blood extending beyond the crest of the tooth socket within 1 minute after blotting the socket at set time intervals after tooth extraction (i.e., 2, 5, 8, 11, 14, and 20 minutes). Mean OBT was 7.2 minutes (SD 5.9) for patients on 325 mg ASA and 5.8 minutes (SD 6.2) for the placebo group (P = .51).

Krishnan et al. reported no differences between ASA and control groups in clotting time, using the slide method⁷. Brennan et al. measured whole-blood platelet aggregation and found significant differences between the ASA and control groups¹⁴. Park et al. reported platelet counts to be significantly lower in patients on antiplatelet therapy than in healthy control subjects, with mean values of 126 (SD 42) x 10³/µL and 235 (SD 56) x 10³/µL, respectively (P < .001)¹². That study also reported a number of other laboratory parameters, including hemoglobin, prothrombin time, partial
thromboplastin time, hemoglobin A1c, fasting blood sugar, creatinine, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, ejection fraction, and uric acid. There were no significant differences between groups.

Cañigral et al. indicated that they obtained multiple laboratory studies that included complete blood count, international normalized ratio (INR), activated partial thromboplastin time, fibrinogen, and various platelet function tests. Although they did not report the results, they reported that none of the parameters was associated with postoperative bleeding risk.

**DISCUSSION**

Discontinuation of chronic antiplatelet therapy in patients with coronary artery disease poses a significant risk for acute coronary events that can result in death. It is recommended that patients with drug-eluting coronary artery stents be on dual antiplatelet therapy continuously for 12 months and that elective procedures where there is high risk of bleeding should be deferred until this course of antiplatelet therapy is completed. Long-standing dogma concerning the exaggerated risk for bleeding during and after dental procedures results in a standard of care that often results in stopping these medications before a procedure or in unnecessary deferral of dental care. This practice persists despite published recommendations to the contrary. Among patients with drug-eluting stents, 1 in 10 prematurely discontinue antiplatelet drugs within the first year, in many cases owing to dental procedures, leading to increased cardiovascular events, including myocardial infarction and death.

Because of the paucity of literature on this subject, we embarked on this review to assess the risks that are of concern to the dental practitioner, specifically excessive intraoperative, immediate postoperative, and late postoperative bleeding complications. We also included studies that involved the diagnostic exercise of periodontal probing in patients on antiplatelet therapy, because it was a manipulation that can induce oral bleeding and had measurable objective data. The studies involved various types of invasive procedures, ranging from periodontal probing to
multiple teeth extractions and alveoloplasty. The outcome measures and grouping of patients varied significantly among all of the studies, which prevented combination of the data, leaving us to narratively compare the outcomes of individual studies.

For intraoperative bleeding, the reviewed studies showed no significant differences in the occurrence or degree of excessive blood loss between patients on single or dual antiplatelet therapy and control subjects. However, there appeared to be an increase in occurrence of immediate postoperative bleeding (i.e., <60 minutes) in patients on dual antiplatelet therapy compared with single antiplatelet therapy and control subjects, but no differences between single antiplatelet therapy compared with control subjects. For later post-operative bleeding, from 3 hours to 1 week, 7 studies reported a 0% occurrence among all patients on antiplatelet therapy.

Morimoto et al. found that occurrences of postoperative bleeding after teeth extractions and periodontal surgery for those on single or dual antiplatelet therapy were significantly lower than for those on antiplatelet/warfarin therapy and warfarin therapy alone. Collectively, these 2 studies suggest that the risk for postoperative bleeding complications is greater with warfarin, either alone or in combination with antiplatelet medications, than antiplatelet medications alone. The prevailing standard of care is that warfarin therapy not be altered for routine dental extractions if the therapeutic target is at or below an INR of 3.5 before invasive dental procedures.

One can apply the same standard to the lower-risk antiplatelet medications, but more caution may be exercised for those on combined warfarin/antiplatelet therapy. Two randomized controlled trials by the same group determined the effects of ASA on the clinical measure of BOP. Both studies found that ASA had an effect on BOP only in patients with some degree of periodontal inflammation or disease. This was in agreement with a cohort study that also looked at BOP, because differences were observed in patients with higher amount of plaque in patients on both ASA and α-tocopherol. Collectively, these studies show that antiplatelet drugs may distort periodontal patients’ clinical measures of disease activity and response to therapy for their periodontal condition.

The data on laboratory variables among the studies show the lack of indication for the use of the surrogate measures of cutaneous bleeding time and clotting time in the overall risk assessment of patients on antiplatelet therapy. Our group has
previously shown that cutaneous bleeding time does not correlate with postoperative bleeding\textsuperscript{37}. However, there was an observed effect of antiplatelet medications in decreasing platelet counts in one study\textsuperscript{12}, albeit not at clinically significant levels that would alter planned invasive treatment.

This review examined the available data in the literature concerning invasive procedures on patients on antiplatelet therapy and found only 3 randomized controlled trials, with only 1 involving an actual invasive dental procedure\textsuperscript{14}. The lack of randomized controlled trials may be attributed to the ethical dilemma of the potential for patients, who otherwise have no clinical indication for the study drug, to be randomized to the medications and be at risk for adverse effects. This especially applies to the non-ASA antiplatelet medications (e.g., clopidogrel) and likely precludes the future prospects of further larger randomized controlled trials on these medications.

**SUMMARY AND CONCLUSION**

There is limited literature on intraoperative bleeding in patients on antiplatelet therapy, with even fewer data on non-ASA–based antiplatelet regimens or dual antiplatelet therapy. From the existing data, there appears to be an increased occurrence of minor immediate postoperative bleeding, but there is no clinically significant increase in the degree or occurrence of intra- or late postoperative bleeding complications. For immediate postoperative bleeding, or in the rare event of prolonged postoperative bleeding, local hemostatic measures are sufficient to address this problem. The results of this review suggest that there is no indication to alter or discontinue antiplatelet therapy before invasive dental procedures and that, in the rare event of postoperative bleeding, local hemostatic measures are effective. However, patients on combined anticoagulant and antiplatelet therapy appear to be at increased risk for postoperative bleeding complications, and their management warrants added consideration.
REFERENCES

Review of postoperative bleeding risk in dental patients on antiplatelet therapy