ADA CE Program ARTICLE 2

An evidence summary of the management of the care of patients taking novel oral antiplatelet drugs undergoing dental surgery

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ABSTRACT

Background. Novel oral antiplatelet (NOAP) drugs (prasugrel and ticagrelor) have emerged in the past decade to overcome some of the drawbacks of existing medications. Little is known, however, regarding the management of the dental care of patients taking these drugs. The author of this study reviewed the available literature to assess the evidence for the management of the care of patients undergoing dental surgery while taking these medications.

Methods. The author used a rapid review approach to identify clinical and scientific research related to dental surgery performed in patients taking NOAP drugs to produce an evidence summary.

Results. The author did not identify any dental-related systematic reviews or randomized controlled trials of prasugrel and ticagrelor and found the overall quality of evidence to be poor. Most of the literature consisted of nonstructured review articles and guidance documents based on assumptions from nondental data and expert opinion; recommendations on best practice varied throughout.

Conclusions. The findings from the review of the literature on NOAP drugs varied considerably. Recommendations are based on poor-quality scientific data, and clinical trials are required to establish best evidence–based practice guidance.

Practical Implications. Owing to the lack of evidence on NOAP drugs for dental procedures, clinicians should base their decisions to prescribe prasugrel and ticagrelor knowing recommendations provided in the literature are either unlikely to have sound scientific backing or may have been derived from extrapolation from other surgical specialties. Clinicians should tread carefully when managing the care of dental patients taking NOAP drugs.

Key Words. Novel oral antiplatelet; NOAP; prasugrel; ticagrelor.

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Many dental procedures carry a risk of perioperative bleeding. Knowing factors that compound this risk helps clinicians prevent and control bleeding during procedures and postoperatively. One factor that can place the patient at increased risk of perioperative bleeding is the use of antiplatelet medication. Since 2009, new antiplatelet drugs have been available for prescribing; however, the implications for dental surgery are unclear.

HEMOSTASIS AND DRUG MECHANISMS

In a healthy person, the components of coagulation reside within the bloodstream and remain inactivated until a trigger occurs. When the endothelium of a blood vessel is breached, vasoconstriction (the vascular component of hemostasis) ensues to reduce blood loss but also to assist in platelet adhesion. Platelets then become activated, which causes changes in cell morphology and the release of platelet agonists such as adenosine diphosphate (ADP) and thromboxane A_2. The platelets are then cross-linked with fibrinogen in a process called platelet aggregation that forms the primary platelet plug and thus completes primary hemostasis.[1] The 2 most common antiplatelet drugs act by reducing platelet aggregation via different mechanisms of action; aspirin irreversibly inhibits the cyclooxygenase enzyme, which in turn reduces thromboxane A_2 production,[2] and clopidogrel inhibits the $P2Y_{12}$ platelet receptor, a subtype of ADP receptor.[3]

NOVEL ORAL ANTIPLATELET MEDICATION

Novel oral antiplatelet (NOAP) medications have been developed. Prasugrel (Effient) is a new oral

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thienopyridine—similar to clopidogrel—that binds irreversibly to the $P2Y_{12}$ platelet receptor. It has a faster onset with more potent antiplatelet effect and reduced variability and has fewer drug interactions compared with clopidogrel.[4] Wiviott and colleagues[5] studied more than 13,000 patients in a randomized controlled trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38) comparing prasugrel with clopidogrel. They found that although prasugrel reduced the risk of experiencing ischemic events, it was associated with a higher risk of experiencing major bleeding.[5]

In another randomized controlled trial of 7,243 patients conducted by Roe and colleagues[6] as part of the TaRgeted platelet Inhibition to cLarify the Optimal strategy to medically manage Acute Coronary Syndromes study group, no difference was detected in overall clinical effectiveness, or major bleeding between prasugrel and clopidogrel, but prasugrel did reduce the risk of multiple ischemic events. The latter study by Roe and colleagues[6] was of superior methodological quality to that of Wiviott and colleagues,[5] being of a double-masked and double-dummy design.

The second NOAP drug to have emerged is ticagrelor (Brilique), which also acts on the $P2Y_{12}$ platelet receptor but in a reversible fashion, allowing a more rapid mechanism of action.[4] Wallentin and colleagues[7] conducted the landmark PLATelet inhibition and patient Outcomes multicenter double-masked clinical trial of over 18,000 patients in which ticagrelor showed reduced death rate from myocardial infarction (MI), stroke, or vascular causes compared with clopidogrel, without an increase in bleeding events.

Guidance produced in the United Kingdom by the National Institute for Health and Care Excellence recommends prasugrel or ticagrelor in combination with aspirin in the management of the care of a subset of patients with acute coronary syndromes.[8,9] Although these NOAP drugs are encountered infrequently, their use is likely to increase in time with increased awareness and clinical trials of other indications.

In 2014, vorapaxar (Zontivity), an antiplatelet agent with a new mechanism of action (protease-activated receptor-1 inhibition), was developed for the prevention of cardiovascular events in patients who have experienced MI. It has been approved for use by the US Food and Drug Administration (FDA) and has been given marketing authorization by the European Committee for Medicinal Products for Human Use.[10,11] I do not discuss Vorapaxar further in this study, as it appears that there is little scientific information available pertaining to dental surgery in patients taking the drug.

The aim of this review was to assess the evidence for the management of the care of patients undergoing dental surgery while taking the NOAP drugs prasugrel or ticagrelor.

METHODS

I conducted a literature review adopting an *evidence summary* approach to make the process more efficient at identifying the available evidence in a relatively short time, while maintaining good-quality information. The Knowledge to Action research program at the Ottawa Hospital Research Institute, Ontario, Canada, developed evidence summaries from the rapid review approach which in turn was developed to avoid some of the disadvantages of full systematic review.[12] Although this approach was designed to inform health care decision makers on a topic in a cost-effective and timely fashion, it has been adapted in this study. In this study, I used the rapid review approach as a means of gathering relevant scientific information on dental patients taking 1 of the NOAP drugs valuable to the end user.

Systematic reviews can take 6 to 24 months to carry out, compared with less than 5 weeks for a rapid review in which the objective is to speedily produce a user-friendly summary of the evidence. Although rapid review encompasses a smaller volume of information, the strategy for obtaining the evidence is well defined and involves selection of reports from a wide range of sources. Watt and colleagues[13] suggested that there is little difference in the overall findings of rapid review when compared with systematic review; however, it is acknowledged that results should still be interpreted with a degree of caution given the less rigorous methods used.

During April and May 2015, I searched the Web of Science database for each of the generic and proprietary drug names against information specific to dental surgery using a comprehensive list of terms. I performed a second similar search using PubMed to reduce the risk of omitting important studies. The search terms used are outlined in Table 1.

On first pass, I studied abstracts and included any that referenced either prasugrel or ticagrelor and also any type of surgical procedures in the next stage. Then, I examined the full text of each remaining article for information specific to the management of the care of and outcomes of any form of dental surgery in patients taking these drugs—the main inclusion criteria. For potentially relevant citations identified within these articles that were not identified in the database searches, I pursued and assessed these in the same fashion described above. I only included English-language and human studies. For

ABBREVIATION KEY. **ADP:** Adenosine diphosphate. **CASP:** Critical Appraisal Skills Programme. **FDA:** Food and Drug Administration. **MI:** Myocardial infarction. **NOAP:** Novel oral antiplatelet. **SDCEP:** Scottish Dental Clinical Effectiveness Programme.