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### Oral antithrombotics and dentistry: Current state of affairs and guideline proposal

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# Chapter 2

## Invasive dental surgery in patients on antithrombotic drugs: new insights

Denise van Diermen

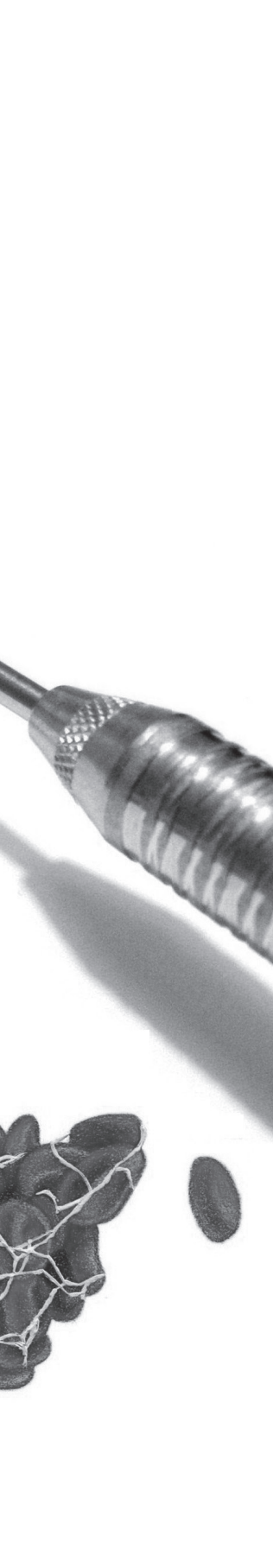
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## **ABSTRACT**

What should a practitioner do if a patient taking antithrombotic drugs needs to undergo invasive dental surgery? Should the patient stop taking the medication before the surgery at the risk of developing thrombotic complications, or should the procedure be carried out without any adjustment to the medication? What is the risk of continued bleeding? It appears from recent research that temporarily discontinuing the use of antithrombotic drugs is unnecessary in many cases and that it may even harm the patient. Dentists have received inconsistent recommendations during the last few decades. This article summarises and discusses new studies on the subject. The authors advocate the development of clinical, evidence-based practice guidelines.

## INTRODUCTION

In the Netherlands, over four million prescriptions were issued in 2005 for acetylsalicylic acid (Aspirin®) and carbasalate calcium (Ascal®), both drugs that affect the blood platelet function (Tab. 1). As a result, these drugs occupied the fifth and seventh positions in the top ten list of the most frequently prescribed drugs in the Netherlands in 2006 (Foundation for Pharmaceutical Statistics, 2006). The use of oral anticoagulants, such as acenocoumarol and fenprocoumon, increases year upon year too: in 2004, the 63 thrombosis centres in our country monitored approximately 342,000 patients in connection with the use of anticoagulants (Federation of Dutch Thrombosis Services, 2006). A third drug is clopidogrel (Plavix®), a thrombocyte aggregation inhibitor that is prescribed with increasing frequency in combination with acetylsalicylic acid after cardiac surgery. These numbers imply that a significant proportion of people visiting a dentist are likely to be using one of these drugs.

**Table 1.** Top 10 of prescribed drugs in 2005<sup>30</sup>

	<b>Substance name</b>	<b>Brand name</b>	<b>Type of drug</b>	<b>Prescriptions</b>
1	Metoprolol	Lopresor® Selokeen®	Anti-hypertensive For angina pectoris and raised blood pressure	2,984,000
2	Oxazepam	Seresta®	Sedative	2,860,000
3	Temazepam	Normison®	Sleeping pill	2,487,000
4	Diclofenac	Voltaren®	Analgesic	2,307,000
5	Acetylsalicylic acid	Aspirin®	Blood platelet aggregation inhibitor	2,294,000
6	Omeprazol	Losec®	Inhibits gastric acid production	2,185,000
7	Carbasalate calcium	Ascal®	Blood platelet aggregation inhibitor	1,893,000
8	Simvastatin	Zocor®	Lowers cholesterol	1,815,000
9	Metformin	Glucophage®	Lowers blood sugar	1,693,000
10	Levothyroxine	Thyrax®	For hypoactive thyroid	1,577,000

Ever since these drugs were first used by patients, there has been much discussion around the question of whether in the case of invasive surgery, including dental surgery, medication needs to be adjusted prior to a procedure in order to limit the risk of bleeding during and after surgery. This journal has also published other contributions, including in 2004 and 2006, which discussed this subject directly

or indirectly<sup>1-3</sup>. Recent international publications further justify the subject being discussed in greater detail<sup>4-6</sup>.

The objective of this contribution is to give an overview of the most recent insights in this area and on the other hand, to emphasise how important it is to develop clinical guidelines.

### **Inhibiting thrombocytes or the clotting process?**

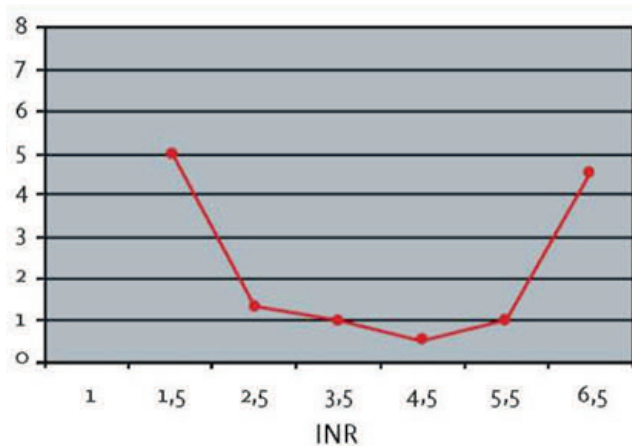
Antithrombotic drugs, making the blood less coagulable, are prescribed to reduce the risk of unwanted coagulation of the blood (thrombosis). Below, we will discuss the drugs that are often prescribed and the way they operate.

Firstly, it is possible to intervene early in the blood clotting process by inhibiting the thrombocyte aggregation with an aspirin-like substance. As soon as this drug is absorbed into the blood, the aggregation of all thrombocytes circulating at that time is irreversibly inhibited and the patient will have an increased tendency to bleed. This is clinically noticeable if a patient continues to bleed for longer after sustaining injuries. Within five to ten days, this tendency to bleed will disappear due to the generation of new thrombocytes from the bone marrow. The aggregation inhibiting effect of aspirin and related chemical substances, such as carbasalate calcium, is used in patients who have suffered from a myocardial infarction, a transient ischemic attack (TIA), or a cerebrovascular accident (CVA), in order to prevent a reoccurrence (secondary prevention). Also, patients running a greater risk of suffering from these complaints will be prescribed acetylsalicylic acid as primary prevention<sup>7</sup>. Acetylsalicylic acid is prescribed as a fixed, low daily dose varying from 30 to 120 mg depending on the medical indications. The extent of the tendency to bleed is nevertheless not dependent on the dosage. It is therefore not necessary to control the disposition or extent of the tendency to bleed in patients using thrombocyte aggregation inhibitors.

Another drug used in tackling platelet aggregation is clopidogrel (Plavix®). This substance is sometimes prescribed to patients with an allergy to aspirin, though it is far more costly. Plavix® is also prescribed in combination with acetylsalicylic acid to patients with an acute myocardial infarction, threat of myocardial infarction, or after a percutaneous coronary intervention (PCI or coronary angioplasty) involving a metal tube (stent) being implanted in one or more of the coronary arteries. This dual therapy is frequently recommended by the American College of Cardiology<sup>8-9</sup>, and also by Dutch cardiologists<sup>10</sup> to prevent a new stent thrombosis and possibly a new myocardial infarction. As a general rule, the tendency to bleed does not need to be monitored when a patient is using clopidogrel.

A third way to treat or prevent thrombosis is to intervene in the blood clotting system. Oral anti-clotting drugs are drugs that intervene in the synthesis of clotting agents in the liver. Components of the drug resembling vitamin K are built into clotting factors II, V, VII and IX, making them less active. Drugs that can achieve this are the frequently used acenocoumarol and longer-acting fenprocoumon (Marcoumar®), which are coumarin derivatives. Contrary to acetylsalicylic acid and clopidogrel, the clotting level does depend on the dosage, as far as coumarin derivatives are concerned. As the individual dosage depends on patient-related and environmental factors, each patient must be considered individually. In the Netherlands, there are thrombosis centres for the purpose of checking and monitoring individual dosage levels in patients. Once a medical specialist has found medical grounds for prescribing anti-coagulant drugs, the patient is referred to their local thrombosis centre. Here, a dosage schedule is agreed with the patient, who is checked every three to four weeks. The patient is checked against the International Normalised Ratio (INR), to determine whether they have been given too little or too much anticoagulant. The INR is a measure of the time it takes for blood to clot, which is referred to as the prothrombin time. The INR has been developed as a standard in order to compare the various commercially available blood tests, since each of those produce their own results. The INR is 1.0 if the blood clotting system functions normally. After taking oral anti-coagulant drugs, the INR increases, which means that the blood clots less readily. If the INR is 3.0, it will take three times as long for the blood to clot in

comparison with an INR of 1.0. The preferred INR value depends on the medical indications for prescribing anti-clotting drugs; the therapeutic scale can vary from 2.5 to 3.5 for the treatment of deep venous thrombosis and from 3.0 to 4.0 for a patient with a heart valve prosthesis. An INR of 5.5 or higher may lead to spontaneous bleeds, also without (dental) trauma. If the INR becomes too low, there is a risk of complications due to thrombosis (Fig. 1).



**Figure 1.** Relationship between anti-clotting level and risk of complications. For an INR of 2.5 or lower, there is a greater risk of complications caused by thrombosis. An INR of 5.5 or higher may lead to spontaneous bleeding-related complications, also without dental trauma<sup>31</sup>. (Y-axis: Odds ratio for complications)

### To cease or continue taking antithrombotic drugs

Until a few years ago, patients due to undergo dental surgery were advised to temporarily stop or reduce taking all drugs affecting the thrombocytes or clotting system several days before undergoing a procedure<sup>11</sup>. It was assumed that surgery would involve an excessive risk of bleeding, leading to dangerous complications. A case report is cited of a dentist in the Netherlands facing charges after her patient died. The patient concerned, who had not been instructed to discontinue taking fenprocoumon, continued to bleed after a tooth extraction. One of the accusations levelled against the dentist was that she had not approached the patient's general practitioner or thrombosis centre, and that she had given the patient insufficient

information prior to the surgery<sup>12</sup>. This case report generated a lot of discussion in the Netherlands<sup>13-14</sup>.

It is important for the dentist to assess what constitutes the greatest risk to the patient. Is this the risk of continued bleeding after dental surgery while using antithrombotic drugs, or rather the risk of (another) thrombosis caused by the temporary decrease of the dosage of antithrombotic drugs? Below, we will describe the various studies found in medical literature on whether to suspend or continue taking antithrombotic drugs at a time of oral surgery. We will discuss the risks of the different options available.

#### **Risk of thrombosis upon temporary suspension of taking acetylsalicylic acid**

A meta-analysis published in 2006 evaluated the results of six clinical studies. The temporary discontinuation of acetylsalicylic acid in patients with coronary heart conditions led to a three-fold increase in the risk of serious cardiovascular problems. The risk was even higher in patients that were also given a coronary stent<sup>15</sup>.

#### **Risk of bleeding in the event of dentoalveolar surgery with the continued use of acetylsalicylic acid**

About ten years ago, the view arose that acetylsalicylic acid does not cause a high risk of bleeding during surgery, including dental surgery. Discontinuing the use of these drugs was not thought to outweigh the risk of thrombosis. In 2003, a systematic literature search was published in the *Nederlands Tijdschrift voor Geneeskunde* (Dutch Journal of Medicine) of studies investigating the need to suspend the use of aspirin before surgery<sup>16</sup>. The survey evaluated 30 studies that had examined blood loss during various procedures performed on patients taking aspirin. The authors found that no clinically significant bleeds were observed during cardiovascular, vascular and orthopaedic operations. They nevertheless found an increase in clinically irrelevant continued bleeding caused by acetylsalicylic acid. Their conclusion was that suspending the use of acetylsalicylic acid for five to ten days before surgery is only necessary for procedures during which a minimal bleed can have serious consequences, such as brain surgery or surgery on patients with an underlying



clotting disorder. As far as dental surgery is concerned, insufficient information was available in literature to draw conclusions at that time. Partly as a result of this, an article was published in this journal in 2004 by Allard et al.<sup>1</sup> These authors also recommended that the use of acetylsalicylic acid should not be suspended for single dental operations. A meta-analysis in 2005 arrived at the same conclusions<sup>17</sup>.

#### **Risk of thrombosis and continued bleeding if clopidogrel is temporarily suspended**

A very recent publication from the American Heart Association contains a warning of an increased risk of stent thrombosis among patients who have undergone coronary angioplasty with stent insertion and who discontinued the dual therapy of aspirin with clopidogrel prematurely (i.e. within one year of the stent being fitted)<sup>5</sup>. The discontinuation of clopidogrel is said to significantly increase the risk of stent thrombosis, which may result in a (fatal) myocardial infarction. The risk of significant continued bleeding after dental surgery is not thought to outweigh the risk of serious cardiac problems<sup>18</sup>. No studies have been published so far about the risk of post-operative bleeding in patients using clopidogrel<sup>4</sup>.

#### **Risk of thrombosis in cases of temporary suspension of coumarin derivatives for dentoalveolar surgery**

A 1998 study concluded that several cases have been recorded with a fatal outcome after the (temporary) suspension of coumarin derivatives for invasive dental surgery<sup>19</sup>. Discontinuing coumarin derivatives was thought to cause an eight-fold increase in the risk of thrombosis<sup>20-21</sup>.

#### **Risk of bleeding in cases of dentoalveolar surgery with the continued use of coumarin derivatives**

In the 1980s, the first studies appeared on the option of performing invasive dental procedures without altering the level of oral anticoagulants<sup>19,22</sup>. The first meta-analysis on this group of drugs was published in 2003<sup>23</sup>. It was concluded that it is usually unnecessary to suspend the use of coumarin derivatives prior to surgery, including invasive dental treatments, but that further research is necessary to substantiate this decision. The controversy surrounding invasive interventions on

patients using oral anticoagulant drugs regularly flared up in the following years<sup>24-26</sup> and primarily focused on continued bleeding, until the first systematic literature study concentrating on dental surgery was published in 2007<sup>4</sup>. The conclusion of that literature study was that no clinically significant instances of continued bleeding during invasive dental surgery were found in patients who continued to take acenocoumarol or fenprocoumon, even if several teeth were removed at once. Further to this study, Aframian et al.<sup>4</sup> proposed the following recommendations: simple dental extractions can be carried out without discontinuing acenocoumarol or fenprocoumon if the INR is less than or equal to 3.5. The researchers nevertheless emphasised that “clinical experience, training and the accessibility of after-care in the event of continued bleeding are important components in the decision to proceed with treatment”, but without specifying precisely what knowledge is needed to perform treatment safely. If the INR is higher than 3.5, they propose referring the patient to their doctor to examine whether the dosage could be adjusted prior to invasive surgery. Lastly, they recommended prescribing a two-day course of 4.8% tranexamic acid mouth rinse after the operation, since this preserves the coagulum in patients who have undergone oral surgery, and continuing the use of acenocoumarol or fenprocoumon. A guideline issued to English practices in May 2007 supports the above recommendations<sup>6</sup>.

### **Day-to-day practice**

A few Dutch publications have made numerous recommendations over the last few years with regard to the management by dentists and general medical practitioners in respect of patients using antithrombotic drugs<sup>1,3,11,27</sup>. However, many dentists still seem to be somewhat in the dark about the policy to be adopted. The Feedback service of the Academic Centre of Dentistry Amsterdam (ACTA) gives some insight into the sticking points for dentists (Unpublished data of D. van Diermen). The Feedback service is an information point for dentists, who can submit medical questions in writing and by telephone or email. Between 2000 and 2006, it received 22 questions relating to antithrombotics and dental surgery. It emerged from those questions and interviews with dentists and general medical practitioners from the Amsterdam region that dentists still receive variable recommendations from doctors,

which may lead to confusion, lack of clarity, and probably to a harmful policy. To date, recommendations from previous publications have not yet led to clinical guidelines for dental practitioners in the Netherlands. Earlier clinical practice guidelines developed in other countries, such as the aforementioned American clinical practice guideline<sup>4</sup> and the English clinical practice guideline<sup>6</sup> cannot usually be directly copied<sup>28</sup>. Such clinical practice guidelines must first be appraised on scientific value, for example with what is known as the AGREE instrument<sup>29</sup>. Next, clinical practice guidelines can be adjusted to the specific Dutch context, if necessary. There is consequently an urgent need in the Netherlands for a widely supported, unambiguous, preferably evidence-based clinical practice guideline for the dental profession. Its content must be drawn up in the Netherlands in collaboration with general dental practitioners and medical consultants who prescribe to their patients the medication concerned.

The clinical practice guidelines referred to are currently being developed by the ACTA. The objective of these practice guidelines, which will be supported by empirical evidence, is to obtain a clear, uniform policy among all the medical professions, and eventually to achieve a qualitative improvement in patient care. Only then will it also be possible to give responsible advice with regard to how dentists should deal with patients using antithrombotic drugs.

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