

# Anticoagulants, Anti-platelets and Their Implications in Surgery: A Literature Review

Usama Faris Taha Al-Ani<sup>1\*</sup>, Mohammed Ali Hamdi<sup>1</sup> and Raghad Adel Mohamed<sup>2</sup>

<sup>1</sup>Department of Surgery, Abu Ghraib General Hospital, Baghdad Alkarkh Health Directorate, Ministry of Health/Environment, Baghdad, Iraq

<sup>2</sup>Abu Ghraib General Hospital, Baghdad Alkarkh Health Directorate, Ministry of Health/Environment, Baghdad, Iraq

## Abstract

All health care providers should be aware of the impact of bleeding disorders on their patients during any surgical procedures. The knowledge of the mechanisms of hemostasis and optimized management are very important. Initial recognition of a bleeding disorder, in such patients with a systemic pathologic process, may occur in surgical practice. The surgical treatment of those patients might be complicated during the surgery due to the use of anticoagulant and/or antiplatelet medications raises a challenge in the daily practice of surgical professionals. Adequate hemostasis is critical for the success of any surgical procedure because bleeding problems can give rise to complications associated with important morbidity-mortality. Besides, prophylactic, restorative, and surgical care of patients with any bleeding disorders is handled skillfully by practitioners who are well educated regarding the pathology, complications which could arise, and surgical options associated with these conditions. The purpose of this paper is to review common bleeding disorders and their effects on the surgical aspect. Many authors consider that patient medication indicated for the treatment of background disease should not be altered or suspended unless so indicated by the prescribing physician. Local hemostatic measures have been shown to suffice for controlling possible bleeding problems resulting from surgery.

**Keywords:** Surgery; Hemostasis; Platelet Aggregation Inhibitors; Antiplatelet; Anticoagulants

\***Correspondence to:** Usama Faris Taha Al-Ani, Department of Surgery, Abu Ghraib General Hospital, Baghdad Alkarkh Health Directorate, Ministry of Health/Environment, Baghdad, Iraq; Tel: +7733962400; E-mail: Medicalresearch82@yahoo.com

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## Introduction

Hemostasis is a defense mechanism that consists of a series of independent biological systems that aim to preserve vascular integrity and avoid blood losses [1,2]. Hemostatic dysfunctional causes, including deficiency states, hereditary and metabolic alterations, traumatic, idiopathic, iatrogenic, and cancers [2,3]. Now a day, the most frequent cause of blood coagulation disorders in developed countries is the use of medications [3]. Tissue damage is generally associated with vascular injuries resulting in more or less profuse bleeding [2].

Vascular endothelial rupture exposes different proteins of the subendothelial tissue layer to the bloodstream, triggering three different hemostatic mechanisms. Vascular or vasoconstriction phase, which is started by vasoconstriction of the damaged blood vessel occurs immediately after vascular injury, mediated by the vascular smooth muscle, and reduces blood loss from the damaged vessel and lasts for about 20 min [2]. The vasoconstrictive response alone is not sufficient to stop bleeding, but it does have two important effects: it reduces blood loss and triggers the second phase, facilitating platelet adhesion secondary to exposure of the subendothelial collagen fibers and basal membrane of the damaged blood vessel wall [2-5]. The two major factors which cause the blood clot normally in our body are platelets which clump together at the wound to form a plug which slows the flow of blood through the vessel and forms a matrix and coagulation

where proteins in the blood interact with each other to fill in the spaces between the platelets, stabilize the clot, and make it more solid until bleeding stops [8].

Surgeons must be familiar with the impact of bleeding disorders on the management of their patients. Proper surgical and medical evaluation of patients is therefore necessary before starting any invasive treatment. Based on this inspiration we aim to study the present antiplatelet drugs and anticoagulant drugs used for the treatment of these illnesses and also to establish guidelines for the approach of patients treated with antiplatelet drugs and anticoagulant drugs who are going to be treated with surgical procedures.

## Patients and Methods

### History

Patients should be evaluated carefully and full history should begin with standard medical questionnaires regarding the patient's systemic health condition [5]. Several bleeding disorders, such as hemophilia and von Willebrand's disease, run in families; therefore, a family history of bleeding disorders should be carefully elicited [6]. Patients should be queried about any previous unusual bleeding episode after surgery or trauma, spontaneous bleeding, and easy or frequent bruising [5]. A history of nasal or oral bleeding should be recorded [4]. Complete drug history is important. In addition, when a patient is taking anticoagulant

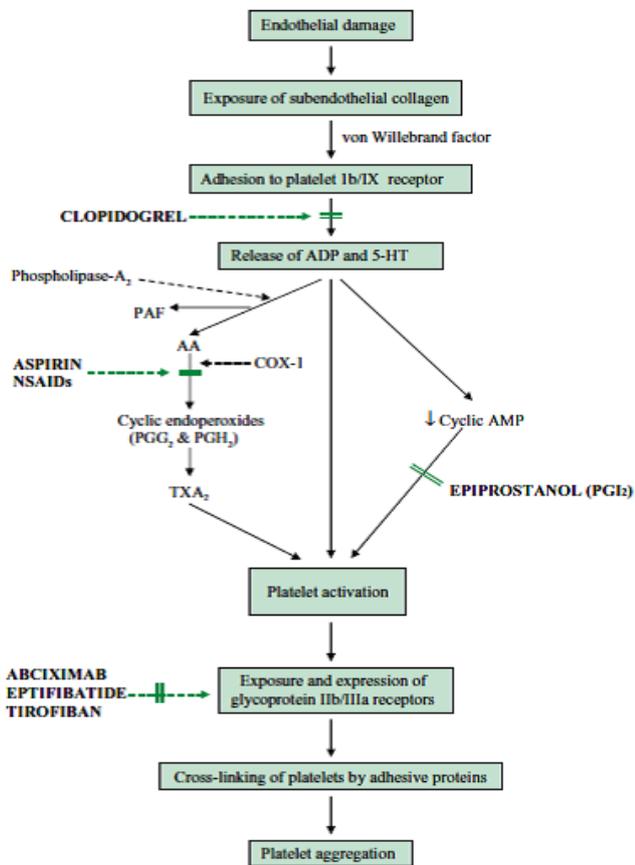


Figure 1: Platelet adhesion, activation, and aggregation, and its modification by antiplatelet drugs [9].

drugs, it will be important to consult his or her physician before any major surgical procedure [5]. Besides, several medications and drugs of abuse may interfere with hemostasis and prolong bleeding like alcohol or heroin, which may also cause excess bleeding by causing liver damage resulting in altered production of coagulation factors [6]. The patient should be asked for any history of significant and prolonged bleeding after dental extraction or bleeding from gingiva [7].

### Examination

A general examination of the patient might indicate a tendency to bleed, including Multiple purpurae of the skin, bleeding wounds, evident hematomas, or/ and swollen joints may be evident in patients with severe bleeding defects. Also, evidence of petechiae, ecchymoses, hematomas, or excessive gingival bleeding should direct the practitioner's attention toward a possible underlying bleeding disorder.

Patients may show signs of underlying systemic disease like liver diseases, cardiovascular diseases, renal disorders, and other syndromes [7]. Patients with liver disease may have jaundice, spider nevi, ascites, and other signs of impaired hepatic function. A cardiac patient can show tachycardia or hypertension, which may make hemostasis more difficult to achieve [3-6].

### Diagnosis

Blood counts and clotting studies should be carried out. Preoperative laboratory tests of the hemostatic system [1,2] are:

1. Bleeding time to determine platelet function (normal range:

2-7 minutes).

2. Activated partial thromboplastin time to evaluate the intrinsic coagulation pathway (normal range:  $25 \pm 10$  seconds).
3. International normalized ratio to measure the extrinsic pathway (normal range: 1.0).
4. Platelet count to quantify platelet function (normal range: 150,000-450,000/ $\mu$ L).

Patients are administered with a blood thinner for various reasons such as for the treatment or prevention of formation of potentially harmful blood clots which leads to stroke, heart attack, deep vein thrombosis (DVT), or pulmonary embolism (PE). However, these medications interfere with the body's normal clotting mechanism to stop blood flow at a site of tissue injury, which needs to be taken under consideration by the dentist.

### Anti-platelets

An antiplatelet agent is a drug whose main function is to inhibit the aggregation of thrombocytes and, therefore, the formation of a thrombus or clot inside the arteriovenous system. Any invasive or surgical procedure involves intra and postoperative hemorrhage, being one of the most frequent emergencies for a surgeon [8]. This way, patients undergoing antithrombotic therapy have a higher hemorrhagic risk [8]. One treatment option is the interruption of the antithrombotic therapy eliminating this way the hemorrhage risk, nevertheless, the interruption implies an increased risk of cerebrovascular or cardiac thromboembolism [8]. So, it is necessary to manage patients undergoing these types of pharmacological treatments to minimize hemorrhagic as well as thromboembolism risks [8]. These medications target the first phase of clot formation by preventing platelets from sticking to each other and the blood vessel walls. Aspirin does this by creating permanent changes in the platelets which last throughout the lifetime of the platelet (7-10 days), which can only be reversed as the body produces new platelets that have not been exposed to the medication [8] (Table 1).

Table 1: Different antiplatelet and anticoagulant agents [8-11].

Antiplatelet agents	Direct-acting anticoagulants
<ul style="list-style-type: none"> <li>▪ clopidogrel (Plavix®)</li> <li>▪ ticlopidine (Ticlid®)</li> <li>▪ prasugrel (Effient®)</li> <li>▪ ticagrelor (Brilinta®)</li> <li>▪ aspirin</li> <li>▪ non-selective NSAIDs</li> <li>▪ Epoprostenol</li> <li>▪ Dipyridamole</li> <li>▪ Abciximab</li> <li>▪ Eptifibatide</li> <li>▪ Tirofiban</li> <li>▪ Etamsylate</li> <li>▪ Dextrans</li> </ul>	<ul style="list-style-type: none"> <li>▪ Heparin</li> <li>▪ low molecular weight heparins (LMWHs)                             <ul style="list-style-type: none"> <li>• Bemiparin</li> <li>• Dalteparin</li> <li>• Enoxaparin</li> <li>• Reviparin</li> <li>• Tinzaparin</li> </ul> </li> <li>▪ heparinoids (Danaparoid)</li> <li>▪ hirudins (Bivalirudin, Lepirudin)</li> <li>▪ Fondaparinux</li> <li>▪ warfarin (Coumadin®)</li> <li>▪ dabigatran (Pradaxa®)</li> <li>▪ rivaroxaban (Xarelto®)</li> <li>▪ apixaban (Eliquis®)</li> <li>▪ edoxaban (Savaysa® [Lixiana®])</li> <li>▪ Phytomenadione (Vitamin K)</li> <li>▪ Menadione (vitamin K3)</li> </ul>

### Anti-platelets and its Implications in Surgery

There is a general agreement that treatment regimens with these older antiplatelet agents should not be altered before surgical procedures [12-14]. In an article published in the year 2007, the American Heart



Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association published their consensus opinion about drug-eluting stents and antiplatelet therapy (e.g., aspirin, clopidogrel, ticlopidine). The consensus opinion states that healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding should contact the patient's cardiologist regarding the patient's antiplatelet regimen and discuss optimal patient management, before discontinuing the antiplatelet medications. Given the importance of antiplatelet medications post-stent implantation in minimizing the risk of stent thrombosis, the medications should not be discontinued prematurely [15]. In 2009, a systematic review and meta-analysis found that there is no increased risk of bleeding associated with continuing regular doses of warfarin in comparison with discontinuing or modifying the dose for patients undergoing surgery [16].

### Anticoagulants

Anticoagulation therapy is required by a lot of patients to prevent, treat or reduce the risk of thromboembolism in atrial fibrillation, treatment of venous thromboembolism, cerebrovascular accidents, ischaemic heart disease, myocardial infarction, pulmonary embolism, and in the prevention of thromboembolism after hip and knee replacement or stent placement, bypass surgery and prosthetic heart valve placement [17,18]. Historically, vitamin K antagonists such as warfarin and acenocoumarol, have been the oral anticoagulants of choice [19]. However, they have some disadvantages such as low therapeutic index, delayed onset of action, many drug and food interactions, and difficult pharmacological management since they require regular monitoring and adjustment [20]. In recent years, Direct Oral Anticoagulants (DOACs) have been introduced to eliminate some of these disadvantages. The first four DOACs are dabigatran, rivaroxaban, apixaban, and edoxaban. These novel agents target specific proteins or proteases of the coagulation cascade such as thrombin or activated factor Xa [21]. They have an immediate onset of action, more predictable pharmacokinetics, fewer drug interactions than warfarin, and a short half-life [22] (Table 1).

### Anticoagulants and its Implications in Surgery

Anticoagulant medications inhibit the second phase of clotting by blocking the production or the function of proteins that stabilize the clot [8,12]. For example warfarin, it takes several days after the starting of medication to reach full anticoagulation effect, and several days after the medication is stopped for the anticoagulation to stop. Also, many foods and other medications can affect warfarin by either increasing or decreasing activity, therefore the physician needs to frequently monitor the patients [8].

Our review has shown that the first option is the best in most of the surgical procedures, with none of the 10 studies recommending the remaining two options since no statistically significant difference in postoperative bleeding existed between most groups continuing and interrupting oral anticoagulation [12,13].

Other studies have also come to the same conclusion: if INR is acceptable and local hemostatic measures adopted properly during the procedure, then there will be no adverse outcome for continuing oral anticoagulation in surgical procedures [23,24], provide according to recent literature normal INR values should be 1.1 or less for normal individuals, and patients on anticoagulant therapy should be within 2.0 to 3.0 to carry out surgical procedures [23]. It was recommended

that vitamin K antagonists must be continued in all surgical procedures if INR is within the therapeutic range [8]. As for novel oral anticoagulants, they must also be maintained in most procedures. Local hemostatic agents are mostly needed in both cases [8,12]. Special measures were taken in most studies to handle the risk of bleeding, like reducing soft tissue and bone injuries and minimizing the need to raise a mucoperiosteal flap during the procedures [23].

In contrast to previous studies conducted by Cannon and Dharmar [25] and in line with others [26], a short interruption of oral anticoagulation did not seem to increase the risk of thromboembolic events in the 10 trials. However, the follow-up period, extending from one day to one month, was relatively small, and the thromboembolic risk could not be fully assessed based on these trials [23].

Some patients who are taking one or multiple anticoagulant medications may have additional medical conditions that can increase the risk of prolonged bleeding, including liver impairment or alcoholism; kidney failure; thrombocytopenia, hemophilia, or other hematologic disorders; or maybe currently receiving a course of cytotoxic medication (e.g., chemotherapy and/ or target therapy). In these situations, surgeons have to consult the patient's physician [27].

Any suggested modification to the medication regimen prior to surgery should be done in consultation with and on the advice of the patient's physician [28,29]. In brief, there is an immense need for cooperation between physicians and surgeons [30-32].

### Conclusions

This review gives a clear picture of the bleeding disorder and knowledge of anticoagulants for surgeons. Multiple measures are proposed for better cooperation, like having common classes in schools and establishing guidelines together. If a physician referral is necessary before a surgical procedure, the surgeon should inform the physician that major bleeding is less likely in most procedures and that most guidelines recommend the continuation of anticoagulation, since physicians tend to overestimate the risk of bleeding.

### References

1. Romney G, Glick M (2009) An updated concept of coagulation with clinical implications. *J Am Dent Assoc* 140: 567-574. <https://doi.org/10.14219/jada.archive.2009.0227>
2. Williams NS, O'Connell PR, McCaskie A, editors (2018) *Bailey & Love's short practice of surgery: the collector's edition*. CRC press, Taylor and Francis Group, London, United Kingdom.
3. Parada EQ, Recolons MMS, Kustner EC, López JL (2004) Hemostasia y tratamiento odontológico. *Av Odontostomatol* 20: 247-261.
4. Sweta VR, Abhinav RP, Ramesh A (2019) Role of virtual reality in pain perception of patients following the administration of local anesthesia. *Ann Maxillofac Surg* 9: 110-113. [https://dx.doi.org/10.4103/ams.ams\\_263\\_18](https://dx.doi.org/10.4103/ams.ams_263_18)
5. Cañigral A, Silvestre FJ, Cañigral G, Alós M, Garcia-Herrera A, et al. (2010) Evaluation of bleeding risk and measurement methods in dental patients. *Med Oral Patol Oral Cir Bucal* 15: e863-e868. <https://doi.org/10.4317/medoral.15.e863>
6. Wahab PA, Nathan PS, Madhulaxmi M, Muthusekhar MR, Loong SC, et al. (2017) Risk factors for post-operative infection following single piece osteotomy. *J Maxillofac Oral Surg* 16: 328-332. <https://doi.org/10.1007/s12663-016-0983-6>
7. Hirsh J (1991) Heparin. *New Engl J Med* 324: 1565-1574. <https://doi.org/10.1056/NEJM199105303242206>
8. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, et al. (2008) The perioperative management of antithrombotic therapy: American college of chest physicians evidence-based clinical practice guidelines (8th Edition). *Chest* 133: 299S-339S. <https://doi.org/10.1378/chest.08-0675>
9. Collins R, Peto R, Baigent C, Sleight P (1997) Aspirin, heparin and thrombolytic



- therapy in suspected acute myocardial infarction. *New Engl J Med* 336: 847-860. <https://doi.org/10.1056/NEJM199703203361207>
10. Hirsh J, Levine MN (1992) Low molecular weight heparin. *Blood* 79: 1-17.
  11. Kaplan K, Francis C (1999) Heparin-induced thrombocytopenia. *Blood Rev* 13: 1-7. [https://doi.org/10.1016/s0268-960x\(99\)90018-8](https://doi.org/10.1016/s0268-960x(99)90018-8)
  12. Armstrong MJ, Gronseth G, Anderson DC, Biller J, Cucchiara B, et al. (2013) Summary of evidence-based guideline: perioperative management of antithrombotic medications in patients with ischemic cerebrovascular disease: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 80: 2065-2069. <https://doi.org/10.1212/WNL.0b013e318294b32d>
  13. Perry DJ, Noakes TJC, Helliwell PS (2007) Guidelines for the management of patients on oral anticoagulants requiring dental surgery. *Br Dent J* 203: 389-393. <https://doi.org/10.1038/bdj.2007.892>
  14. Institute of Medicine (2007) Preventing Medication Errors. National Academies Press, Washington DC, United States. <https://doi.org/10.17226/11623>
  15. Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, et al. (2007) Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol* 49: 734-739.
  16. Sherman DG, Dyken ML, Gent M, Harrison MJ, Hart RG, et al. (1995) Antithrombotic therapy for cerebrovascular disorders: an update. *Chest* 108: 444S-456S. [https://doi.org/10.1378/chest.108.4\\_Supplement.444S](https://doi.org/10.1378/chest.108.4_Supplement.444S)
  17. Decker SH, Pyrooz DC (2015) The handbook of gangs. John Wiley & Sons, New York, United States. <https://doi.org/10.1002/9781118726822>
  18. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, et al. (2007) European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 28: 2375-2414. <https://doi.org/10.1093/eurheartj/ehm316>
  19. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6: e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
  20. Harbour R, Miller J (2001) A new system for grading recommendations in evidence based guidelines. *BMJ* 323: 334-336. <https://doi.org/10.1136/bmj.323.7308.334>
  21. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, et al. (2011) Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 342: d124. <https://doi.org/10.1136/bmj.d124>
  22. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, et al. (2010) Guías de práctica clínica para el manejo de la fibrilación auricular. *Rev Esp Cardiol* 63: 1483-e1-e83. [https://doi.org/10.1016/S0300-8932\(10\)70275-X](https://doi.org/10.1016/S0300-8932(10)70275-X)
  23. Jimson S, Amaldhas J, Jimson S, Kannan I, Parthiban J (2015) Assessment of bleeding during minor oral surgical procedures and extraction in patients on anticoagulant therapy. *J Pharm Bioallied Sci* 7: S134-S137. <https://dx.doi.org/10.4103/0975-7406.155862>
  24. Napeñas JJ, Hong CH, Brennan MT, Furney SL, Fox PC, et al. (2009) The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. *J Am Dent Assoc* 140: 690-695. <https://doi.org/10.14219/jada.archive.2009.0255>
  25. Cannon PD, Dharmar VT (2003) Minor oral surgical procedures in patients on oral anticoagulants a controlled study. *Aust Dent J* 48: 115-118. <https://doi.org/10.1111/j.1834-7819.2003.tb00019.x>
  26. Bajkin BV, Popovic SL, Selakovic SDJ (2009) Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. *J Oral Maxillofac Surg* 67: 990-995. <https://doi.org/10.1016/j.joms.2008.12.027>
  27. Souto JC, Oliver A, Zuazu-Jausoro I, Vives A, Fontcuberta J (1996) Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: A prospective randomized study. *J Oral Maxillofac Surg* 54: 27-32.
  28. Raunso J, Selmer C, Olesen JB, Charlott MG, Olsen AM, et al. (2012) Increased short-term risk of thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 33: 1886-1892. <https://doi.org/10.1093/eurheartj/ehr454>
  29. Akopov SE, Suzuki S, Fredieu A, Kidwell CS, Saver JL, et al. (2005) Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines?. *Cerebrovasc Dis* 19: 337-342. <https://doi.org/10.1159/000085027>
  30. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, et al. (2008) Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 168: 63-69. <https://doi.org/10.1001/archinternmed.2007.23>
  31. Russo G, Dal Corso L, Biasiolo A, Berengo M, Pengo V (2000) Simple and safe method to prepare patients with prosthetic heart valves for surgical dental procedures. *Clin Appl Thromb Hemost* 6: 90-93. <https://doi.org/10.1177/10760296000600208>
  32. Hupp WS (2015) Cardiovascular diseases. *ADA Pract Guide Pat Med Cond* 19: 25-42. <https://doi.org/10.1002/9781119121039.ch2>