Review

Dental implants and bleeding disorders: review and clinical indications

Christian Bacci *, Claudia Schiazzano , Ezio Zanon , Edoardo Stellini , Luca Sbricoli

Posted Date: 26 June 2023

doi: 10.20944/preprints202306.1835.v1

Keywords: Dental implants; bleeding disorders; haemophilia; von Willebrand disease.

Review

Dental Implants and Bleeding Disorders: Review and Clinical Indications

Christian Bacci [1]*, Claudia Schiazzano [1], Ezio Zanon [2], Edoardo Stellini [1] and Luca Sbricoli [1]

[1] Department of Neurosciences, School of Dentistry, University of Padua, 35128 Padua, Italy; christian.bacci@unipd.it ; claudiaschiazzano95@gmail.com ; edoardo.stellini@unipd.it ; luca.sbricoli@unipd.it

[2] Haemophilia Centre, General Medicine, Padua University Hospital, Padua, Italy; ezio.zanon@unipd.it

* Correspondence: christian.bacci@unipd.it

Abstract: Background: Bleeding disorders can be divided into three categories: congenital coagulation disorders (CCDs), antiplatelet induced bleeding disorders (APBDs) and anticoagulant induced bleeding disorders (ACBDs). Implant placement can be challenging in this kind of patients. The aim of this study is to provide evidence on implant surgery in patient with bleeding disorders and to generate some practical recommendations for clinicians. Material & Methods: Pubmed/MEDLINE, Scopus, Web of Science and Cochrane Library databases were screened. The latest search was performed in July 2022. Case Reports, Case Series, Cohort Studies, Cross-Sectional Studies, Case Control Studies, Reviews, Consensus Reports, Surveys and Animal Studies were included in the analysis. Results: Seventeen articles on CCDs were found, fourteen on APBDs, twenty-six on ACBDs. Most of these articles were case report or case series. Patients with CCDs can be treated after the infusion of the missing coagulation factor. Patients with APBDs can be treated without withdrawing the therapy. Patients with ACBDs should be treated depending on the anti-coagulative medication. Conclusion: Despite the low level of evidence, dental implants can be safely placed in patients with bleeding disorders. However, careful preoperative evaluation and the adoption of local and post-operative bleeding control measures are mandatory.

Keywords: Dental implants; bleeding disorders; haemophilia; von Willebrand disease.

1. Introduction

Bleeding disorders are a group of conditions when blood cannot clot properly. They can be congenital or acquired. The congenital ones are inherited and are quite rare. The acquired ones can develop from a pathological condition or can be caused by the intake of drugs belonging to the category of anti-platelet or to the inhibitors of coagulation factors.

Among congenital bleeding disorders the most common is Von Willebrand's disease, caused by diminished quantity or by a structural defect of the von Willebrand factor [1]. Von Willebrand disease is primarily a hereditary disease, but an acquired variant of von Willebrand disease has also been observed (4). The most famous classification of the disease distinguishes three inherited types: classes 1 and 3 include quantitative factor deficits, while class 2 includes qualitative defects [1, 2].

The second most common congenital bleeding disorder is haemophilia, a class of hereditary diseases whose etiopathogenetic mechanism is based on defects of the proteins involved in the coagulation process. It was once called "the royal disease" due to its presence in European royal families in the 19th and 20th centuries. Queen Victoria of England (1818-1901) was an asymptomatic carrier and her descendants in turn transmitted the mutation in various royal houses across Europe [3–5].

Anti-platelet drugs, also called "antiaggregant", interfere with the platelet plug formation. Acetylsalicylic acid (aspirin) and clopidogrel are the most commonly prescribed. They are used both in acute treatment and in the prevention of coronary artery disorders and stroke; they are also used for prevention of venous thromboembolism after orthopedic surgery, in generic vascular diseases, unstable angina and in patients who have undergone percutaneous coronary artery surgery and cardiac surgery [6].

Coagulation inhibitors selectively act on certain clotting factors, hindering the clot formation process. These drugs are indicated for deep venous thrombosis, venous and arterial thromboembolic disease, pulmonary embolism, atrial fibrillation with risk of embolization, mechanical heart valve prostheses (to prevent thrombus formation on valves), myocardial infarction, recent heart attack to prevent the onset of new cardiovascular events (another heart attack, stroke, etc.), unstable angina, acute peripheral arterial occlusion and unstable coronary syndromes.[7] Anticoagulant medicines that have been most used over the years are vitamin K-dependent inhibitor drugs Warfarin[8] and Acenocumarol [9]. Recently, to overcome the limits of these kind of anticoagulants, direct thrombin inhibitors and activated Factor X inhibitors have been proposed [10].

Another anticoagulant worth mentioning is heparin, although most often used as short-term therapy or to overlap a long-term therapy when a suspension is required [11]. Thrombocytopenia goes beyond the boundaries of the above classification, as it can be due to a congenital disorder or medically induced. By definition, thrombocytopenia is observed when the platelet count is below 150,000 / μL. The reasons why a platelet count may be below the normal range can be many and varied (4).

Nowadays, clinicians are reluctant to perform dental implants in this type of patients with bleeding disorders and prefer to send the patient to hospital facilities or choose other prosthetic solutions. Moreover, randomized controlled clinical trials cannot be conducted for security and ethical reasons. Therefore, the management of these patients are often demanded to expert opinions and practical guidelines that differs between countries. The aim of this paper is to perform a literature review about dental implants inserted in patients with bleeding disorders and to provide indications for clinicians to help them dealing with these patients.

2. Materials and Methods

Bibliographic electronic search was performed on Pubmed/MEDLINE, Scopus, Web of Science and Cochrane Library databases. The latest research was performed in July 2022. Only article in English were considered.

The keywords “oral implant”, “dental implant(s)”, implantology and implant(s) were searched in combination with the following terms: haemophilia, von Willebrand Desease, thrombocytopenia, bleeding disorder(s), aspirin, clopidogrel, prasugrel, ticagrelor, anti-platelet, antiaggregant, warfarin, sintrom, heparin, dabigatran, rivaroxaban, apixaban, edoxaban, anticoagulant, NOAC, DOAC, novel anticoagulant, direct anticoagulant.

Randomized controlled trials, , cohort studies, cross-sectional studies, case-control studies, review, case series, case reports and animal studies were included in the analysis. Letters to the Editor, expert opinion and article evaluations were excluded.

3. Results

Among the articles found on PubMed and Scopus seventeen were selected for the first section, fourteen for the second one and twenty-six for the third.

Six articles considered both patients with either anticoagulant or anti-platelet therapy. Therefore, they were considered for analysis in both the second and the third categories. Articles retrieved from the electronic search are reported in table 1, 2 and 3. Literature reviews were not reported. Results are divided into three sections, one for each of the different bleeding disorder.

3.1. Congenital Coagulation Disorders (CCDs)

Among seventeen articles, twelve were case reports and five reviews. Seven articles considered patients with haemophilia [12–18], seven considered patients with Von Willebrand Disease [19–22], one considered patients with Idiopatic Trombocitopenic Purpura [23]. Five articles performed the surgery flapless [12, 18–21], three articles did not [13, 14, 17] and four articles did not specify [15, 16, 22, 23]. One article did not report on post-operative complications [22], one article reported mild post-operative bleeding complication [18] and one article reported a severe bleeding complication, which

 doi:10.20944/preprints202306.1835.v1

required an emergency tracheotomy and hospitalization of the patient [23]. The remaining articles reported no complications [12–17, 19–21].

Literature reviews considered the safety of oral surgery in general and not specifically the implant surgery. Four out of five reviews concluded that there is no contraindication to implant surgery in this type of patient [24–27]. The remaining article recommended not to perform implant surgery in all patients with coagulation disorders [28].

3.2. Antiplatelet induced bleeding disorders (APBDs)

Among fourteen articles included: one case report [29], one case-cross-over study [30], two cohort studies [31, 32], four case-control studies [33–36] , two animal studies [37, 38] and four reviews [39–42]. In almost all clinical studies related to this section, implant surgeries took place without interruption of the anti-aggregative therapy [29, 31–36]. Only two studies reported a change in drug therapy [30, 31]. This occurred in patient with dual antiaggregant therapy or when an anticoagulant was used in addition. Few hemorrhagic complications were observed, with a range between 1% and 15% of the surgeries. Most of the studies agreed on compressive hemostasis after surgery, with or without the association of tranexamic acid. Literature reviews agree on not suspending the antiaggregant therapy before implant surgery [39–42].

3.3. Anticoagulant induced bleeding disorders (ACBD).

Among twenty-six articles: four were case reports [43–46], one was a case series [47], six were cohort studies[8, 31, 48–51], eight were case control studies [33–36, 52–55], six were reviews [40, 56–60] and one was an animal study.

Considering the clinical studies, five authors treated patients undergoing conventional anticoagulant drugs [8, 44, 45, 48, 53]; six treated patients using DOAC [43, 47, 49, 51, 54, 55] and in the remaining articles the sample considered used both medications [31, 33–36, 52].

Case-control studies showed no significant differences in hemorrhagic complications after implant surgery between patients in the test and in the control group.

However, in every clinical study, where a haemorrhagic complication occurred, it was always solved with the only help of local hemostatic measurements [33, 34, 36, 43, 48, 49, 51–55]. The only animal study investigated the effects of Rivaroxaban on osteointegration and it showed that it did not effect it. The results emerged from the evaluation of the clinical studies are in accordance with the evidence found in the reviews [56–60].

4. Discussion

The present review addressed implant rehabilitation of patients with bleeding disorders. The information obtained from the analysis of the clinical studies was rather heterogeneous, and thus difficult to compare with each other.

As regard the Section I, in almost all the Case Reports local hemostatic measures and pre-medication with missing factor or desmopressin were implemented. It didn't happen in the Case Report concerning the patient with idiopathic thrombocytopenic purpura. It may not be a coincidence that this Case Report is the only one in which the patient developed complication not manageable by only local hemostatic measures or the simple administration of tranexamic acid.

In the II and III Sections, the trend observed is to not interrupt the anticoagulant therapy before the implant surgery, as recommended by the European Guidelines.

5. Clinical indications

The following clinical indications should be considered when treating patients with bleeding disorders. The evidence cannot be considered strong, since these recommendations are based on case reports, case series, few cohort studies, some reviews. Stronger scientific evidence is not available now.

 doi:10.20944/preprints202306.1835.v1

1. Consulting the physician who treat the patient for his bleeding disorder before implant surgery;
2. Administer deficiency factor or desmopressin before the surgery in patients with congenital hemostasis disease;
3. Do not withdraw anti-aggregative therapy for implant surgery, even if dual;
4. Do not interrupt therapy with dicumarolics. On the contrary, clinicians should check the INR value before implant surgery;
5. When dealing with direct anticoagulants (DAOC) skip only one dose of the drug, the day before;
6. Choose the minimally invasive or even a flapless approach, if reasonable. A thorough clinical and radiographic evaluation should be performed, respecting bone thickness and the lingual cortical wall;
7. Adopt local hemostatic measures at the end of the procedure and in case of postoperative bleeding: compressive hemostasis with gauze soaked in Tranexamic Acid showed excellent results in both situations;
8. Instruct the patient about the appropriate post-operative measures: soft and cold diet for 2-3 days, avoiding vigorous rinses, physical effort and supine position, applying a gauze for 5 minutes in case of bleeding. If not enough, repeat the application of the gauze soaking with tranexamic acid.

Author Contributions: C.B. and L.S. designed the research study; C.S. performed the research; L.S. and C.S. wrote the paper; E.S. and E.Z. revised critically the paper; all authors read and approved the final draft.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

Appendix A

TABLES WITH LEGENDS:

Table 1. Published evidence about dental implants performed in patients with CCDs.

	Study Type	Underlying blood disease	No. of implants inserted for intervention	Flapless	Prophylaxis	Additional drug administered after the procedure	Local haemostatic measurements	Bleeding complications
Gornitisky et al. 2005	Case Report	Moderate haemophilia A	3; 2; 1	Unspecified	Factor VIII; Tranexamic acid per os	Factor VIII; Tranexamic acid per os	Suture	no
Rosen et al. 2005	Case Report	Moderate haemophilia A	3; 2; 1	Unspecified	Unspecified	Unspecified	Unspecified	no
Neskoromna-Jędrzejczak et al. 2005	Case Report	Severe haemophilia B	2; 2	no	Recombinant Factor IX	Recombinant Factor IX	Suture	no
Castellanos-Cosano et al. 2014	Case Report	Severe haemophilia A; HIV; HCV	3; 2	no	Antibiotic; Factor VIII (FVIII), Tranexamic acid per os	Antibiotic; Factor VIII (FVIII), Tranexamic acid per os	Unspecified	no
Fénelon et al. 2017	Case Report	Von Willebrand Desease	1	Yes	Von Willebrand Factor (vWF)	Von Willebrand Factor (vWF); Antibiotic	Suture; fibrin glue	no
Kang et al. 2018	Case Report	Von Willebrand Desease	1	Yes	Desmopressin	none	Unspecified	no
Sung-Tak Lee et al. 2018	Case Report	Porpora thrombocitopenica idiopatica	1	Presumably not	none	none	Unspecified	Severe
Calvo-Guirado et al. 2019	Case Report	Severe haemophilia B	1	no	Antibiotic; Factor IX;	Factor IX;	Suture; particulate bone graft	no

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

					Tranexamic acid per os	Tranexamic acid per os and rinses	and collagen membrane soaked in tranexamic acid; compressive hemostasis with gauze soaked in tranexamic acid	
Bacci et al. 2020	Case Report	Von Willebrand Desease type 2B	5	Yes	Factor VIII + VWF; tranexamic acid	tranexamic acid per os;	Unspecified	no
Bacci et al. 2021	Case Report	Mild haemophilia A	1	Yes	Factor VIII; tranexamic acid	Unspecified	Unspecified	no
Takashima et al. 2021	Case Report	Von Willebrand Desease type 1	6	Unspecified	Factor VIII + VWF	Unspecified	Unspecified	Unspecified
Kinalsky et al. 2021	Case Report	Haemophilia A	3; 3	Yes	Factor VIII; tranexamic acid	no	Suture	Mild

Table 2. Published evidence about dental implants performed in patients with APBDs.

	Study Type	**Antithrombotic treatment**	**Discontinuation of the pharmacological therapy**	**N. of procedures**	**Post-operative bleeding complications**	**Management of complications**
Flanagan et al. 2015	Case Report	Clopidogrel + ASA	No	1	1	Compressive hemostasis with sponge soaked in tranexamic acid

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

Clemm et al. 2015	Case-control study	Dicumarols (32) / bridging with LMWH (8) / Dabigatran (6) / Rivaroxaban (8) / Apixaban (2) / Antiaggregants (61)	No	61 (antiaggregants)	4 (1 antiaggregant; 2 dicumarols e 1 dicumarols bridged with LMWH)	Compressive hemostasis with gauze soaked in tranexamic acid/Compressive hemostasis with gauze soaked in tranexamic acid + additional suture/revision of the wound and electrocoagulation
Tabrizi et al. 2018	Case-crossover study	Clopidogrel / ASA	Only in the second session of the study	41	/	/
Rubino et al. 2019	Retrospective cohort study	ASA / Clopidogrel / Warfarin / DOAC / ASA + clopidogrel / Clopidogrel + warfarin / ASA + clopidogrel + warfarin / ASA + clopidogrel + DOAC / ASA + DOAC / ASA + warfarin + DOAC	Only in 4 cases, after consulting the physician	218	2 (1 in ASA + warfarin; 1 in warfarin)	Cauterization and infiltration with lidocaine
Kaura et al. 2021	Prospective cohort study	Clopidogrel / ASA / Clopidogrel + ASA	No	65	1 (in dual therapy)	/
Manor et al. 2021	Case-control study	Clopidogrel / ASA / DOAC / Warfarin / Combinations	No	72 (+ *121 control group)*	4 (1 warfarin+DOAC; 2 Clopidogrel+ ASA; 1 warfarin+clopidogrel); + *7 control group*	Suture / Suture + Compressive hemostasis with sponge gauze in tranexamic acid

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

Broekema et al. 2021	Case-control study	Antiaggregants / Dicumarols	No	8 (+ *7 control group*)	0	/
Buchbender et al. 2021	Case-control study	Antiaggregants / Dicumarols / DOACs	No	95 (+100 control group)	15	Compressive hemostasis with gauze soaked in tranexamic acid

Table 3. Published evidence about dental implants performed in patients with ACBDs.

	Study Type	***Anticoagulant therapy***	***N. of patients in the study***	***N. of implants***	***Discontinuation of the pharmacological therapy***	***Flapless***	***Local hemostatic measures***	***Bleeding complications***	***Management of complications***
Ferrieri et al. 2007	Cohort Study	warfarin	3	7	no	no	Suture + Compressive hemostasis for 30 minutes with gauzed soaked in saline	no	/
Bacci et al. 2010	Case-control study	Warfarin	50	159	no	no	Suture + Compressive hemostasis with gauze	2	Compressive hemostasis with gauze soaked

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

							soaked in tranex-amic acid for 30-60 minutes		in tranex-amic acid for 1 hour
Miranda et al. 2011	Case Report	Warfarin	1	4	bridged with Heparin	no	unspecified	no	/
Hong et al. 2012	Cohort Study	Warfarin	1	2	no	unspecified	"Poncho" of gingival former soaked with tramexamic acid	1	local hemostatic measures and reinforcement of home care instructions
Broekema et al. 2014	Case-control study	Anti-aggregants / Dicumarols	7	Unspecified	no	no	Unspecified	0	/
Clemm et al. 2015	Case-control study	Dicumarolici (32) / bridging with LMWH (8) / Dabigatran (6) / Rivaroxaban (8) / Apixaban (2) / Anti-aggregants (61)	117 (among them, 61 in therapy with anti-aggregants)	Unspecified	no	no	suture; electrocoagulation	4 (1 anti-aggreganti; 2 dicumarolici e 1 dicumarolici embricato con LMWH)	Compressive hemostasis with gauze soaked in tranex-amic acid/Compressive hemostasis with gauze soaked in tranex-amic acid +

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

									additional suture/revision of the wound and electrocoagulation
Gomez-Moreno 2015	Case-control study	Rivaroxaban	18	43	no	no	suture + Compressive hemostasis with gauze soaked in tranexamic acid	1	Compressive hemostasis with gauze soaked in tranexamic acid
Romero-Ruiz et al 2015 Caso 3	Case Report	Acenocumarolo	1	12	no	yes	unspecified	no	/
Gomez-Moreno 2016	Case-control study	Dabigatran	29	67	yes	no	suture + Compressive hemostasis with gauze soaked in tranexamic acid for 30-60 minutes	2	Compressive hemostasis with gauze soaked in tranexamic acid
Kim et al. 2017	Case Report	Rivaroxaban	1	2	yes	no	Suture + Compressive	yes (3)	Compressive hemostasis with gauze +

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

							hemostasis for 1 hour		applying oxidized regenerated cellulose
Okamoto et al. 2018	Cohort Study	non specificato	289	unspecified	no	unspecified	unspecified	0	/
Gandhi et al 2019	Case Serie	Rivaroxaban (3); Apixaban (1); Dabigatran (1)	6	18	no	yes	unspecified	no	/
Rubino et al. 2019	Cohort Study	Anti-aggrant / Warfarin / DOAC / combinations	176	218	Only in 4 cases	unspecified	unspecified	2 (1 in ASA + warfarin; 1 in warfarin)	local hemostatic measures
Kwak et al. 2019	Cohort Study	Dabigatran (3); Rivaroxaban (3); Apixaban (3)	8	unspecified	yes: for 24 hours in 8 case; 48 hours for 1 case	no	Suture + Compressive hemostasis for 1 hour	3	Compressive hemostasis
Al Zoman et al. 2020	Case Report	Warfarin	1	1; 1	no	yes	Compressive hemostasis	no	/
Sannino et al. 2020	Case-control study	warfarin (40) e rivaroxaban (40)	80	320	no	no	bone wax and spongostan in the extraction site + Compressive	Gruppo warfarin: 29 mild, 11 moderate; Gruppo rivaroxavan: 37 mild, 3 moderate	Mild: Compressive hemostasis with gauze ; moderate: unspecified

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 June 2023 doi:10.20944/preprints202306.1835.v1

						hemostasis with gauze soaked in tranexamic acid		
Galletti et al. 2020	Cohort Study	Rivaroxaban	12	57	yes (for 24 hours)	no	Suture + Compressive hemostasis for 30 minutes (+ compressive hemostatis with gauze soaked with tranexamic acid for other 30 minutes if needed)	3	Compressive hemostasis with gauze soaked in tranexamic acid (+ electrocauterization and additional sutures, if necessary)
Manor et al. 2021	Case-control study	Clopidogrel / ASA / DOAC / Warfarin / Combinations	72	Unspecified	no	no	suture + gelatin sponge + Compressive hemostasis with gauze soaked in	4 (1 warfarin+DOAC; 2 Clopidogrel+ ASA; 1 warfarin+clopidogrel); *+ 7 controlli*	Suture / Suture + Compressive hemostasis with gauze soaked in tranexamic acid

 doi:10.20944/preprints202306.1835.v1

						tranex-amic acid for 20-30 minute s		
Buchbend er et al. 2021	Case-control study	Anti-aggre-gants / Dicuma-rols / DO-ACs	95	Un-spec-ified	no	Un-spec ified	suture + Com-pres-sive he-mosta-sis with gauze soaked in tranex-amic acid	1	Com-pressive hemo-stasis with gauze soaked in tranex-amic acid

References

1. Federici AB (2009) Classification of inherited von Willebrand disease and implications in clinical practice. Thrombosis Research 124:S2. https://doi.org/10.1016/S0049-3848(09)70150-1
2. Mazzeffi MA, Stone ME (2011) Perioperative management of von Willebrand disease: A review for the anesthesiologist. Journal of Clinical Anesthesia 23:418–426. https://doi.org/10.1016/j.jclinane.2011.02.003
3. Peyvandi F, Garagiola I, Young G (2016) The past and future of haemophilia: diagnosis, treatments, and its complications. The Lancet 388:187–197. https://doi.org/10.1016/S0140-6736(15)01123-X
4. Sacco R, Sacco M, Carpenedo M, Mannucci PM (2007) Oral surgery in patients on oral anticoagulant therapy: a randomized comparison of different intensity targets. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology 104:18–21. https://doi.org/10.1016/j.tripleo.2006.12.035
5. Zimmerman B, Valentino LA (2013) Hemophilia: In review. Pediatrics in Review 34:289–295. https://doi.org/10.1542/pir.34-7-289
6. Baron TH, Kamath PS, McBane RD (2013) Management of Antithrombotic Therapy in Patients Undergoing Invasive Procedures. New England Journal of Medicine 368:2113–2124. https://doi.org/10.1056/nejmra1206531
7. J.K. S How to choose appropriate direct oral anticoagulant for patient with nonvavular atrial fibrillation.pdf
8. Ferrieri GB, Castiglioni S, Carmagnola D, et al (2007) Oral Surgery in Patients on Anticoagulant Treatment Without Therapy Interruption. Journal of Oral and Maxillofacial Surgery 65:1149–1154. https://doi.org/10.1016/j.joms.2006.11.015
9. Leaflet P, For I, User THE, et al To request a copy of this leaflet in Braille , large print or. 10–11
10. Schulman Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism.pdf
11. Szumita PM, Szumita RP (2018) Hemostasis in Dentistry
12. Bacci C, Zanon E (2021) Regenerative Surgery with Dental Implant Rehabilitation in a Haemophiliac Patient. 104–106
13. Castellanos-Cosano L, Núñez-Vázquez RJ, Segura-Egea JJ, et al (2014) Protocol for oral implant rehabilitation in a hemophilic HIV-positive patient with type C hepatitis. Implant Dentistry 23:622–625. https://doi.org/10.1097/ID.0000000000000145
14. Calvo-Guirado JL, Romanos GE, Delgado-Ruiz RA (2019) Infected tooth extraction, bone grafting, immediate implant placement and immediate temporary crown insertion in a patient with severe type-b hemophilia. BMJ Case Reports 12:10–15. https://doi.org/10.1136/bcr-2019-229204

15. Rosen H, Gornitsky M (2004) Cementable implant-supported prosthesis, serial extraction, and serial implant installation: Case report. Implant Dentistry 13:322–327. https://doi.org/10.1097/01.id.0000144511.43654.d3
16. Gornitsky M, Hammouda W, Rosen H (2005) Rehabilitation of a hemophiliac with implants: A medical perspective and case report. Journal of Oral and Maxillofacial Surgery 63:592–597. https://doi.org/10.1016/j.joms.2005.01.009
17. Neskoromna-Jędrzejczak A, Bogusiak K, Chojnowski K, et al (2018) Implantoprosthetic rehabilitation of a patient with severe form of hemophilia B: A case report. Acta Haematologica Polonica 49:33–36. https://doi.org/10.2478/ahp-2018-0006
18. Kinalski M de A (2021) Delayed bleeding in a hemophilic patient after sinus floor elevation and multiple implant placements. The Journal of oral implantology 6
19. Kang M, Kang P (2018) Dental implant therapy on a patient with von willebrand disease: A case study. Implant Dentistry 27:599–601. https://doi.org/10.1097/ID.0000000000000821
20. Fénelon M, Castet S, Fricain J-C, Catros S (2018) Guided Implant Surgery to Reduce Morbidity in Von Willebrand Disease Patients: A Case Report. The Open Dentistry Journal 12:80–86. https://doi.org/10.2174/1874210601812010080
21. Christian Bacci E, Zanon, Alessia Cerrato, Gastone Zanette, Ludovica Pampaloni AG (2020) Riabilitazione implantare nel morbo di Von Willebrand : un caso resistente alla desmopressina. 89:632–640. https://doi.org/10.19256/d.cadmos.08.2021.08
22. Takashima Perioperative management of von willebrand patients at the time of implant placement: case report .pdf
23. Lee S-T, Kim J-W, Kwon T-G (2018) Life-threating outcomes after dental implantation in patient with idiopathic thrombocytopenic purpura: a case report and review of literature. Maxillofacial Plastic and Reconstructive Surgery 40:0–6. https://doi.org/10.1186/s40902-018-0178-9
24. Donos N, Calciolari E (2014) Dental implants in patients affected by systemic diseases. British Dental Journal 217:425–430. https://doi.org/10.1038/sj.bdj.2014.911
25. Diz P, Scully C, Sanz M (2013) Dental implants in the medically compromised patient. Journal of Dentistry 41:195–206. https://doi.org/10.1016/j.jdent.2012.12.008
26. Scully C, Hobkirk J, Dios PD (2007) Dental endosseous implants in the medically compromised patient. Journal of Oral Rehabilitation 34:590–599. https://doi.org/10.1111/j.1365-2842.2007.01755.x
27. Hewson ID, Daly J, Hallett KB, et al (2011) Consensus statement by hospital based dentists providing dental treatment for patients with inherited bleeding disorders. Australian Dental Journal 56:221–226. https://doi.org/10.1111/j.1834-7819.2011.01328.x
28. Hwang D, Wang HL (2006) Medical contraindications to implant therapy: Part I: Absolute contraindications. Implant Dentistry 15:353–360. https://doi.org/10.1097/01.id.0000247855.75691.03
29. Flanagan D (2015) Tranexamic acid tamponade to control postoperative surgical hemorrhage. Journal of Oral Implantology 41:e82–e89. https://doi.org/10.1563/AAID-JOI-D-13-00158
30. Tabrizi R, Khaheshi I, Hoseinzadeh A, et al (2018) Do Antiplatelet Drugs Increase the Risk of Bleeding After Dental Implant Surgery? A Case-and-Crossover Study. Journal of Oral and Maxillofacial Surgery 76:2092–2096. https://doi.org/10.1016/j.joms.2018.04.036
31. Rubino RT, Dawson DR, Kryscio RJ, et al (2019) Postoperative bleeding associated with antiplatelet and anticoagulant drugs: A retrospective study. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 128:243–249. https://doi.org/10.1016/j.oooo.2019.04.005
32. Kaura S, Rai R, Satia G, et al (2021) Assessment of Bleeding in Patients on Antiplatelets Undergoing Dental Implants. Journal of Maxillofacial and Oral Surgery. https://doi.org/10.1007/s12663-021-01510-7
33. Clemm R, Neukam FW, Rusche B, et al (2016) Management of anticoagulated patients in implant therapy: a clinical comparative study. Clinical oral implants research 27:1274–1282. https://doi.org/10.1111/clr.12732
34. Manor Y, Peleg O, Mijiritsky E, et al (2020) A retrospective analysis of dental implantation under anticoagulant treatment. Clinical Oral Investigations. https://doi.org/10.1007/s00784-020-03389-z
35. Broekema FI, Van Minnen B, Jansma J, Bos RRM (2014) Risk of bleeding after dentoalveolar surgery in patients taking anticoagulants. British Journal of Oral and Maxillofacial Surgery 52:e15–e19. https://doi.org/10.1016/j.bjoms.2014.01.006

36. Buchbender M, Schlee N, Kesting MR, et al (2021) A prospective comparative study to assess the risk of postoperative bleeding after dental surgery while on medication with direct oral anticoagulants , antiplatelet agents , or vitamin K antagonists. BMC Oral Health 1–9. https://doi.org/10.1186/s12903-021-01868-7
37. Lillis T, Veis A, Sakellaridis N, et al (2019) Effect of clopidogrel in bone healing-experimental study in rabbits. World Journal of Orthopaedics 10:434–445. https://doi.org/10.5312/wjo.v10.i12.434
38. Lupepsa AC, Vargas-Sanchez P, Moro MG, et al (2021) Effects of low-dose aspirin on the osseointegration process in rats. International Journal of Implant Dentistry 7:3–8. https://doi.org/10.1186/s40729-020-00283-x
39. Bajkin B V., Wahl MJ, Miller CS (2020) Dental implant surgery and risk of bleeding in patients on antithrombotic medications: A review of the literature. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 130:522–532. https://doi.org/10.1016/j.oooo.2020.07.012
40. Nascimento (2021) Risk of bleeding during implant surgery in patients taking antithrombotics: A Systematic Review.pdf
41. Cervino G, Fiorillo L, Monte IP, et al (2019) Advances in antiplatelet therapy for dentofacial surgery patients: Focus on past and present strategies. Materials 12:. https://doi.org/10.3390/ma12091524
42. Apostu D, Lucaciu O, Lucaciu GDO, et al (2017) Systemic drugs that influence titanium implant osseointegration. Drug Metabolism Reviews 49:92–104. https://doi.org/10.1080/03602532.2016.1277737
43. Kim C, Dam C, Jeong J, et al (2017) Delayed bleeding after implant surgery in patients taking novel oral anticoagulants: a case report. Journal of Dental Anesthesia and Pain Medicine 17:143. https://doi.org/10.17245/jdapm.2017.17.2.143
44. Al Zoman H, Al Jetaily S, Robert AA, et al (2013) Flapless dental implant surgery for patients on oral anticoagulants - The "warLess Procedure": A report of 2 cases. Journal of Oral Implantology 39:264–270. https://doi.org/10.1563/AAID-JOI-D-11-00105
45. Miranda M, Bollero P, D'Ovidio N, et al (2014) Implant surgery and oral anticoagulant therapy: Case report. ORAL and Implantology 7:51–56. https://doi.org/10.11138/orl/2014.7.2.051
46. Romero-Ruiz MM, Mosquera-Perez R, Gutierrez-Perez JL, Torres-Lagares D (2015) Flapless implant surgery: A review of the literature and 3 case reports. Journal of Clinical and Experimental Dentistry 7:e146–e152. https://doi.org/10.4317/jced.51985
47. Gandhi Y, Bhatavdekar N (2019) MIDAS (Minimally Invasive Drilling And Styptic)protocol - A modified approach to treating patients under therapeutic anticoagulants. Journal of Oral Biology and Craniofacial Research 9:208–211. https://doi.org/10.1016/j.jobcr.2019.04.006
48. Hong C, Napenas JJ, Brennan M, et al (2012) Risk of postoperative bleeding after dental procedures in patients on warfarin: A retrospective study. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 114:464–468. https://doi.org/10.1016/j.oooo.2012.04.017
49. Galletti G, Alfonsi F, Raffaele A, et al (2020) Implant placement in patients under treatment with rivaroxaban: A retrospective clinical study. International Journal of Environmental Research and Public Health 17:1–13. https://doi.org/10.3390/ijerph17124607
50. Okamoto T, Hoshi K, Fukada K, et al (2018) Factors Affecting the Occurrence of Complications in the Early Stages After Dental Implant Placement. Implant Dentistry 1. https://doi.org/10.1097/id.0000000000000753
51. Kwak EJ, Nam S, Park K mee, et al (2019) Bleeding related to dental treatment in patients taking novel oral anticoagulants (NOACs): a retrospective study. Clinical Oral Investigations 23:477–484. https://doi.org/10.1007/s00784-018-2458-2
52. Sannino G, Capparé P, Montemezzi P, et al (2020) Postoperative bleeding in patients taking oral anticoagulation therapy after "All-on-four" rehabilitation: A case-control study. International journal of oral implantology (New Malden, London, England) 13:77–87
53. Bacci C, Berengo M, Favero L, Zanon E (2011) Safety of dental implant surgery in patients undergoing anticoagulation therapy: A prospective case-control study. Clinical Oral Implants Research 22:151–156. https://doi.org/10.1111/j.1600-0501.2010.01963.x
54. Gómez-Moreno G, Aguilar-Salvatierra A, Fernández-Cejas E, et al (2016) Dental implant surgery in patients in treatment with the anticoagulant oral rivaroxaban. Clinical Oral Implants Research 27:730–733. https://doi.org/10.1111/clr.12653
55. Gómez-Moreno G, Fernández-Cejas E, Aguilar-Salvatierra A, et al (2018) Dental implant surgery in patients in treatment by dabigatran. Clinical Oral Implants Research 29:644–648. https://doi.org/10.1111/clr.12785

56. Madrid C, Sanz M (2009) What influence do anticoagulants have on oral implant therapy? A systematic review. Clinical Oral Implants Research 20:96–106. https://doi.org/10.1111/j.1600-0501.2009.01770.x
57. Sivolella S, De Biagi M, Brunello G, et al (2015) Managing dentoalveolar surgical procedures in patients taking new oral anticoagulants. Odontology 103:258–263. https://doi.org/10.1007/s10266-015-0195-4
58. Pirlog CD, Pirlog AM, Maghiar T (2019) A systematic review of hemorrhage risk in patients on the new oral anticoagulant therapy postdental implant placement. World Journal of Dentistry 10:154–157. https://doi.org/10.5005/jp-journals-10015-1623
59. Fortier K, Shroff D, Reebye UN (2018) Review: An overview and analysis of novel oral anticoagulants and their dental implications. Gerodontology 35:78–86. https://doi.org/10.1111/ger.12327
60. Shi Q, Xu J, Zhang T, et al (2017) Post-operative bleeding risk in dental surgery for patients on oral anticoagulant therapy: A meta-analysis of observational studies. Frontiers in Pharmacology 8:1–11. https://doi.org/10.3389/fphar.2017.00058