Assessment of bleeding complications with oral anticoagulants in total hip or knee arthroplasty: retrospective analysis

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Baptiste Compagnon[1], Matthieu Breton[1], Edmundo Pereira de Souza Neto[1,2*], Remi Bouquerel[1], Benjamin Le Gaillard[1], Antoine Strzelecki[1], Christophe Pelletier[1], Mireille Houadec [1], Gorka Usandizaga [3].

1- Anesthesia Department, Montauban Hospital, 100 rue Léon Cladel, 82013 Montauban, France

2 - Hôpital d'instruction des armées Robert Picqué, 351, route de Toulouse, 33882 Villenave d'Ornon, France

3 - Surgery Orthopedic and Traumatology Department, Montauban Hospital, 100 rue Léon Cladel, 82013 Montauban, France

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* **Corresponding author**:

Edmundo Pereira de Souza Neto

Telephone number: **33.7.70.01.72.59** / E-mail: **edmundo.pereira-de-souza@hotmail.fr**

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Assessment of Bleeding Complications with Oral Anticoagulants in Total Hip or Knee Arthroplasty: Retrospective Analysis

Abstract

Introduction: Direct oral anticoagulants (DOACs) have been widely used for the prevention and treatment of thromboembolic disease. However, the bleeding risk in patients with DOACs in orthopedic surgery has been poorly studied. The objective of this study is to compare the bleeding complications rate in total hip arthroplasty (THA) or total knee arthroplasty (TKA) surgery between patients with and without DOACs.

Method: In a retrospective unicentric study, we included adult patients who have had surgery for THA or TKA. We excluded patients under the age of 18 years, secondary arthroplasty and patients treated by anti-vitamin K or heparin.

Results: One thousand two hundred and fifty - eight files of operated patients for scheduled THA (530 patients) or TKA (728 patients) surgery were analyzed. Among THA patients, 31% in the DOACs group and 11.5% in the no-DOACs group had at least one bleeding complication. Among TKA, 13.4% in the DOACs group and 11.8% in the no-DOACs group, had at least one bleeding complication.

Otherwise, we didn't find any overdose in the DOACs specific dosages despite discontinuing between 3 to 5 days.

Conclusions: Our study did not find differences concerning hematoma between patients with no-DOACs and with DOACs after THA or TKA surgery. However, the TKA patients with DOACs received more transfusions compared to TKA patients with no-DOACs. More research will be necessary to explore the inter-individual variability of DOACs elimination.

Keywords: Blood transfusion, anticoagulants, hip replacement surgery, knee replacement.

Introduction

Direct oral anticoagulants (DOACs) are medicines often-used by the general public and more particularly by elderly people. It is known that 10 to 15% of the population with anticoagulants require surgery or invasive procedures.[1-3] Bleeding and transfusion in perioperative orthopedic surgery both increase mortality and also the time needed to discontinue DOACs before surgery, to eliminate the bleeding risks.[4] However, DOACs use is very complex: it is a heterogeneous drug class with different international guidelines and variable pharmacological profiles. Indeed, DOACs are administrated with only one dosage without concentration monitoring.[1, 5, 6] However, for some population subgroups or certain clinical circumstances, monitoring DOACs' concentration can be useful, for example when there is an overdose suspicion, bleeding complication, acute kidney failure, or before an emergency surgery.[6, 7]

The French Society of Anesthesia and Intensive Care (SFAR) doesn't propose any clear guidelines for preoperative DOACs management and follows only the French Working Group on Perioperative Hemostasis (GIHP) propositions.[2] The American Society of Regional Anesthesia (ASRA) guidelines suggest a different discontinue time for DOACs management, especially before spinal anesthesia, thus opening the discussion.[8]

We tested the hypothesis that interruption of the use of DOACs before major orthopedic surgery is not associated with an increased risk of bleeding complications.

Method

In the Centre Hospitalier de Montauban (Tarn et Garonne, France), we analyzed retrospective adult patients scheduled for total hip (THA) or knee (TKA) replacement between 1st January 2017 and 31th December 2021. All the patient data were extracted from the M-CrossWay software (Maincare Solutions®, Canejan, Cestas, France). We had to start our inclusion from January 1st 2017 due to a lack of systematic computerization of anesthesia files before this date.

We started data collection after appropriate ethical clearance (Ethics committee of the University Hospital of Bordeaux, reference GP - CE2020 - 47).

We excluded patients under the age of 18 years, secondary arthroplasty patients and patients treated by anti-vitamin K or heparin. In our study, the same orthopedic surgeon operated on all patients (Figure 1).

We separated our population study between subjects operated for THA and TKA. Secondarily, we distinguished patients with DOACs treatment and patients without DOACs treatment. The primary endpoint is defined as the bleeding complications rates during two postoperative months in patients operated for THA or TKA between groups with and without DOACs.

We consider bleeding complication rates according to the International Society on Thrombosis and Haemostasis bleeding scale: [9]

1 - Surgical site bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of red cells, and/or

2 - Surgical site bleeding that requires a second intervention or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection.

Evidence of transfusion, type of blood products and number of units transfused were identified based on information on interventions in the study database. Pre- and post-bleeding

hemoglobin values were ascertained from daily hemoglobin laboratory values dated immediately prior to and subsequent to the date of the bleeding event.

Re-operation due to bleeding were requested in the study database looking for events labeled “return to operating room” due to bleeding during the postoperative period, or one or more of the following procedure codes: drainage of hematoma, hip replacement or knee surgery.

For each patient, the demographic data we collected were: age, weight, height, Body Mass Index (BMI), sex, American Society of Anesthesiologist (ASA) classification, the anesthesia performed (general or regional), THA or TKA surgery, estimation of clearance creatinine with glomerular filtration rate (GFR) by the CKD-EPI algorithm [8], initial hemoglobin, medical disease, the discontinue time without DOACs and the DOACs specific dosage if they were carried out.

The hemoglobin rate variation was analysed in different moments during the hospital stay: initially, postoperative day one, minimal, and the last day before release. These characteristics were compared between THA and TKA patients and in each group THA or TKA patients between those with and without DOACs.

For transfusion savings, the patients with anemia (man <13g/dl and woman <12g/dl) caused by iron deficiency received an intravenous iron injection with an erythropoietin infusion before surgery.

To prevent bleeding risk, all patients, with no major contraindications, benefited from a protocol by tranexamic acid 15mg/kg (1g maximum) just before surgery and repeated at 6th and 12th hours after the firste dose.

All patients benefited from a hemoglobin control plasma dosage during all the hospitalization stay. In the postoperative period, preventive anticoagulation treatment with low molecular weight heparin was administrated for patients in the no-DOACs group during 35 days, according to the French guidelines.[10] For patients with DOACs, a thromboembolism prophylaxis with low-molecular-weight heparin was administered for 48 heures after surgery. Then curative doses with low-molecular-weight heparin were given between seven to fifteen days after surgery according to medical decision.

Part of this study has been published elsewhere. [11]

Statistical analysis

The quantitative variables were carried out by the Mann-Whitney test and the qualitative variables were compared by Fisher's test.

The Mann-Whitney U test was performed to compare quantitative variables (age, weight, and body mass index). Qualitative variables were compared by the exact Fischer test. The non-parametric Kruskal-Wallis test, associated with the Mann-Whitney test, was used to compare values of hemoglobin between groups in the different periods (baseline, postoperative day 1, minimal value and before leaving the hospital).

The non-parametric Friedman test, associated with the Wilcoxon matched-pairs test corrected for multiple comparisons, was used to compare changes in hemoglobin between successive periods within each group in the different periods (baseline, postoperative day 1, minimal value and before leave the hospital).

P-values lower than the chosen level of 0.05 are regarded as statistically significant.

The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.[12] The median absolute deviation is a variation of the average absolute deviation that is even less affected by values in the top and bottom quartiles.[12] In general, for data with extreme values, the median absolute deviation or inter-quartile range can provide a more stable estimate or variability than the standard deviation.[12]

Statistical analyses had performed using StatView TM software for Windows (Abacus Concepts Inc, Berkeley, CA, USA, 1996, version 4.57).

Results

One thousand two hundred fifty-eight files of operated patients for scheduled THA (530 patients) or TKA (728 patients) surgery were analyzed (Figure 1). Table 1 compares the patients' characteristics with bleeding complication without and with DOACs between the THA and TKA groups.

The hematoma rates were more frequent in the TKA group. However, the transfusion rates were more frequent in the THA group. All the THA patients received general anesthesia according to a local protocol. The majority of patients in the TKA group received spinal anesthesia. Regarding sex, age, GFR and ASA score, the number of DOACs subjects, no differences were found between THA and TKA groups. Due to this, we performed our analyses in each group, THA and TKA, to avoid possible bias.

In the 68 patients who had surgical site bleeding complications up to two months after THA, eleven patients received DOACs treatment (Table 2).

We didn't find any significant difference between the groups with and without DOACs on the following data: sex, age, GFR, ASA score distribution, anesthesia, hemoglobin variations during hospitalization, hematoma on the surgical site, and transfusion rates. However, there was a significant difference with higher BMI in the no-DOACs group (Table 2). It should be noted that two patients in the group no-DOACs presented simultaneously a hematoma on the site operating and blood transfusion.

In the 87 patients who had surgical site bleeding complications up to two months after TKA, seven patients received DOACs treatment (Table 3). We did not find any significant difference in the following characteristics: sex, BMI, GFR, and the hematoma rate. However, the patients who had bleeding complications in the DOACs group were significantly older than those no-DOACs (Table 3). We found significantly more patients classified ASA III in the DOACs group than those no-DOACs. Subjects with DOACs received more general anesthesia. In effect, the anesthesia technique was left to the anesthesiologist decision on the surgery day depending on the risk benefit balance. No difference was found for hemoglobin levels between the two

groups. The transfusion rate in patients with DOAC was significantly higher than in patients with no-DOACs (57% and 20%) while there was no difference in the hematoma rate between the two groups. It should be noted that two subjects in the group without DOACs and one subject in the DOACs group presented simultaneously a hematoma and a blood transfusion during the stay in the hospital.

In our study population, 51 specific DOACs dosages were performed among the 87 DOACs patients (59%). Among the 51 dosages analysed, all presented undetectable values below the concentration of 30ng/ml. This value authorizes any surgical or anesthesia procedure.[13] The delay without DOACs decided during anesthesia consultation varied between three, four, or five days (Table 4).

During the two month data analysis follow-up, no patients included in this study had a symptomatic thromboembolic event or deep surgical site infection.

Discussion

We did not find any differences concerning hematoma between patients with no-DOACs and with DOACs after THA or TKA surgery. However, the TKA patients with DOACs received more transfusions compared to TKA patients with no-DOACs.

In the postoperative period of orthopedic surgery, DOACs are used to prevent venous thromboembolic disease. Some studies are interested in bleeding complications occurring in postoperative orthopedic surgery following the introduction of DOAsCs for the venous thromboembolic diseases. Among them, a meta-analysis did not find any significant difference for bleeding postoperative complication rates between subjects with DOACs and subjects with preventive heparin.[14] To our knowledge, we did not find any study which analyzed the postoperative bleeding complications on orthopedic surgery in patients already receiving DOACs treatment over a long term. Furthermore, bleeding complications in orthopedic surgery are clinically and economically relevant because they are associated with significantly longer stays in hospital, and higher costs of inpatient care. In our patients who developed postoperative bleeding spent an additional 3 days in hospital compared with those without this complication. Our results are consistent with previous studies.[9,15]

Regarding our main objective, our results did not seem to show any increased hematoma risk after THA and TKA surgery, nor transfusion risk after THA associated with the DOACs.

In THA subjects, the only difference found between patients in the DOACs group and with no-DOACs was a higher BMI. To date, it has not been proven that obesity was a risk factor for postoperative bleeding complications in orthopedic surgery.[16, 17]

The subjects operated for TKA with DOACs were older than those with no-DOACs. In fact, with age, patients develop rhythmic heart disease more easily, which may be the cause of thromboembolic disease, and leading to the use of DOACs.[18] This elderly population is, therefore, exposed to more pathologies, which may explain why the majority of subjects classified ASA III compared to subjects with no-DOACs.

Regarding our secondary objective, the transfusion rate in TKA operated patients with DOACs was significantly higher than with no-DOACs. Age and ASA III scores were higher and may explain the higher transfusion rate. Indeed, because of the pathologies reflected by the high ASA score, the transfusion threshold in the DOACs group would potentially be lower than patients without DOACs.[19,20] Also, the elderly population is more exposed to osteoporosis responsible for bone fragility.[20] Furthermore, this older population has more exposure to undernutrition, responsible for vitamin deficiencies, delayed bone marrow regeneration and anemia, and therefore more risk transfusion.[21]

The choice for general anesthesia compared to spinal anesthesia was significantly higher in the TKA group with DOACs. This could simply be the consequence of anesthesiologist' fear of neuraxial hematoma during spinal anesthesia, despite stopping the DOAC. This fear would reflect that carrying out this action with DOAC was not without risk, despite the GIHP propositions. [2] In the THA group, no significant difference was found when we analyzed separately hematoma on the surgical site or transfusion rate.

In comparison to other studies, our transfusion rate is much lower, around 6.6% in THA surgery and 7.1% in TKA surgery. A study reports a transfusion rate of 22.2% in THA and 18.3% in TKA surgery in their population.[20] Unfortunately, the surgical technique has not been specified, for example the perioperative transfusion-saving measures employed, such as tranexamic acid. Indeed, its use reduces the need for transfusion in orthopedic prosthesis surgery, and may explain the difference between our two studies.[22-24] They significantly find transfusion risk factors such as age, ASA score ≥ II, BMI <30kg/m^2, preoperative anemia, and among females. However, these results are not completely comparable with our population because these studies don't mention the patients treated with anticoagulants and anti-aggregants. Another study assessed the transfusion rate and blood lost in planned THA and TKA surgery. They obtained a transfusion rate of 18% in THA group and 11% in TKA group.[25] These results are also higher than those found in our work. The significant transfusion risk factor was preoperative anemia for the THA and TKA groups and a low BMI and the surgery duration only for the TKA

group. All patients benefited from transfusion saving measure by tranexamic acid preoperative administration.

All of our patients treated with DOACs and having undergone spinal anesthesia for TKA surgery did not present an epidural hematoma. This hemorrhagic complication is exceptional, and the literature is poor about DOACs patients. The GIHP, for preoperative DOACs management, suggests five days' discontinuation before spinal anesthesia procedure.[2] Other international guidelines propose to shorten the interruption period to three days.[8] Our results, because of our small population and the lak of data in the literature, do not allow certainty about the delay for DOACs interruption before a spinal anesthesia procedure.

Concerning the limitations of the study, the first concerns the retrospective and observational characteristics, leading different DOACs interruption delay between three and five days. This made our DOACs group heterogeneous. The second limit is the small number of patients with DOACs, exposing our results to possible bias and decrease power. The third limit is the absence of spinal anesthesia in THA patients with DOACs due to the surgical technique, limiting the DOACs exposure in this procedure. The fourth limit is the absence of information about the factors that could influence the specific DOAC dosage such as inducing or inhibiting drugs like cytochrome P450 3A4 or P-glycoprotein, about the renal function by clearance calculated and not measured clearance. Our last limit is the low DOAC dosage number performed. In this context, we cannot eliminate a potential residual concentration on the surgery day. This limit is independent of our desire due to the retrospective character of our study.

Conclusion

In our retrospective report, we did not find any differences concerning hematoma between patients with no-DOACs and with DOACs after THA or TKA surgery. However, the TKA patients with DOACs received more transfusions compared to TKA patients with no-DOACs. Some biases make the interpretation results difficult, in particular the transfusion risk. Further studies, with a bigger population, will be necessary to explore some unknown areas of DOAC: the inter-individual variability elimination and the neuraxial hematoma incidence after spinal anesthesia. This research will help answer many questions and, maybe, lead scientific societies to propose new strategies for DOAC preoperative management.

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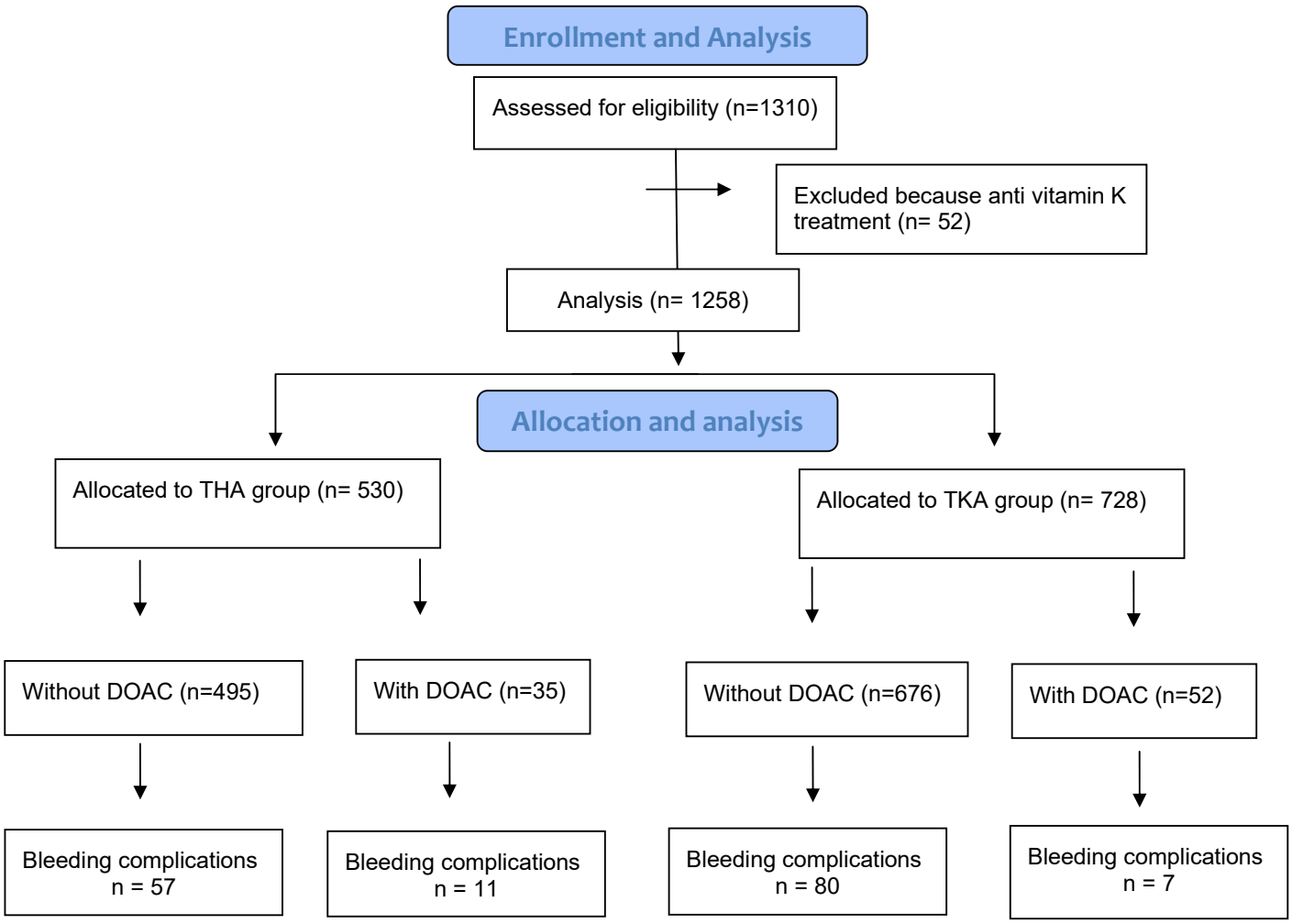
Figure 1: Patients scheduled for elective orthopedic surgery between the 1st January 2017 and the 31th of December 2021.



DOAC: Direct Oral Anticoagulant, **n**: patients number **n**: patients number, **THA**: Total Hip Arthroplasty, **TKA**: Total Knee Arthroplasty.

Table 1: Comparative table of characteristics patients with bleeding complications, with and without DOACs, between THA and TKA group.

	THA with/without DOAC n= 68	TKA with/without DOAC n= 87	P value
Sex: n (%)	Man 27 (40) Woman 41 (60)	Man 35 (40) Woman 52 (60)	0.9 0.9
Age (year):	78 (8)	74 (7)	0.59
BMI (kg.m$^{-2)}$	26 (3)	30 (4)	0.60
GFR (ml.min^{1}.1.73m^{-2})	80 (10)	78 (12)	0.92
ASA score n (%)	ASA I 7 (10) ASA II 39 (58) ASA III 22 (32)	ASA I 7 (8) ASA II 58 (67) ASA III 22 (25)	0.46 0.60 0.94
Anesthesia n (%)	GA 68 (100) SA 0 (0)	GA 19 (22) SA 68 (78)	**<0.001** **<0.001**
DOAC n (%)	11 (16)	7 (8)	1
Hematoma n	45 (66)	68 (78)	**0.033**
Transfusion n	23 (34)	19 (22)	**0.037**

THA: Total Hip Arthroplasty, **TKA**: Total Knee Arthroplasty, **DOAC**: Direct Oral Anticoagulant, **BMI**: Body Mass Index, **GFR**: Glomerular Filtration Rate, **ASA**: American Society of Anesthesiologists, **GA**: General Anesthesia, **SA**: Spinal Anesthesia, **n**: patients number. The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Table 2: Comparative table of characteristics and bleeding complications in THA patients between subjects with and without DOAC.

	THA without DOAC n = 57	THA with DOAC n = 11	P value
Sex n (%)	Man 22 (38) Woman 35 (62)	Man 5 (45) Woman 6 (55)	0.63 0.63
Age (year)	76 (7)	84 (2)	0.09
BMI ($kg.m^{-2}$)	27 (3)	25 (4)	**0.04**
GFR ($ml.min^{-1}.1.73m^{-2}$)	83 (11)	71 (8)	0.16
ASA score n (%)	ASA I 5 (9) ASA II 36 (63) ASA III 16 (28)	ASA I 0 (0) ASA II 3 (27) ASA III 8 (73)	1 0.24 0.08
Anesthesia n (%)	GA 57 (100) SA 0 (0)	GA 11 (100) SA 0 (0)	1 1
Hemoglobin (g/dl)			
- Baseline	13 (2)	13 (3)	0.34
- Postoperative day 1	11 (2)	11 (2)	0.32
- Minimal	10 (2)	9 (2)	0.29
- Before discharge	11 (2)	10 (1)	0.09
Hematoma n (%)	37 (66)	3 (28)	0.24
Transfusion n (%)	20 (34)	8 (72)	0.17

THA: Total Hip Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **BMI:** Body Mass Index, **GFR:** Glomerular Filtration Rate, **ASA:** American Society of Anesthesiologists, **GA:** General Anesthesia, **SA:** Spinal Anesthesia, **n:** patients number. The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Table 3: Comparative table of characteristics and bleeding complications in TKA patients between subjects with and without DOAC.

	TKA without DOAC n = 80	TKA with DOAC n = 7	P value
Sex n (%)	Man 31 (39) Woman 49 (61)	Man 3 (43) Woman 4 (57)	1 1
Age (years)	73 (7)	83 (3)	0.04
BMI ($kg.m^{-2}$)	29 (3)	35 (3)	0.54
GFR ($ml.min^{-1}.1.73m^{-2}$)	79 (12)	73 (11)	0.23
ASA score n (%)	ASA I 4 (5) ASA II 60 (75) ASA III 16 (20)	ASA I 0 (0) ASA II 1 (14) ASA III 6 (86)	1 **0.01** **0.02**
Anesthesia n (%)	GA 17 (21) SA 63 (79)	GA 5 (71) SA 2 (29)	0.06 0.30
Hemoglobin (g/dl)			
- Initial	14 (2)	13 (1)	0.30
- Postoperative day 1	12 (2)	12 (1)	0.52
- Minimal	10 (2)	9 (1)	0.30
- Before discharge	11 (2)	11 (1)	0.52
Hematoma n (%)	64 (80)	4 (57)	0.06
Transfusion n (%)	16 (20)	4 (57)	**0.02**

TKA: Total Knee Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **BMI:** Body Mass Index, **GFR:** Glomerular Filtration Rate, **ASA:** American Society of Anesthesiologists, **GA:** General Anesthesia, **SA:** Spinal Anesthesia, **n:** patients number.

The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

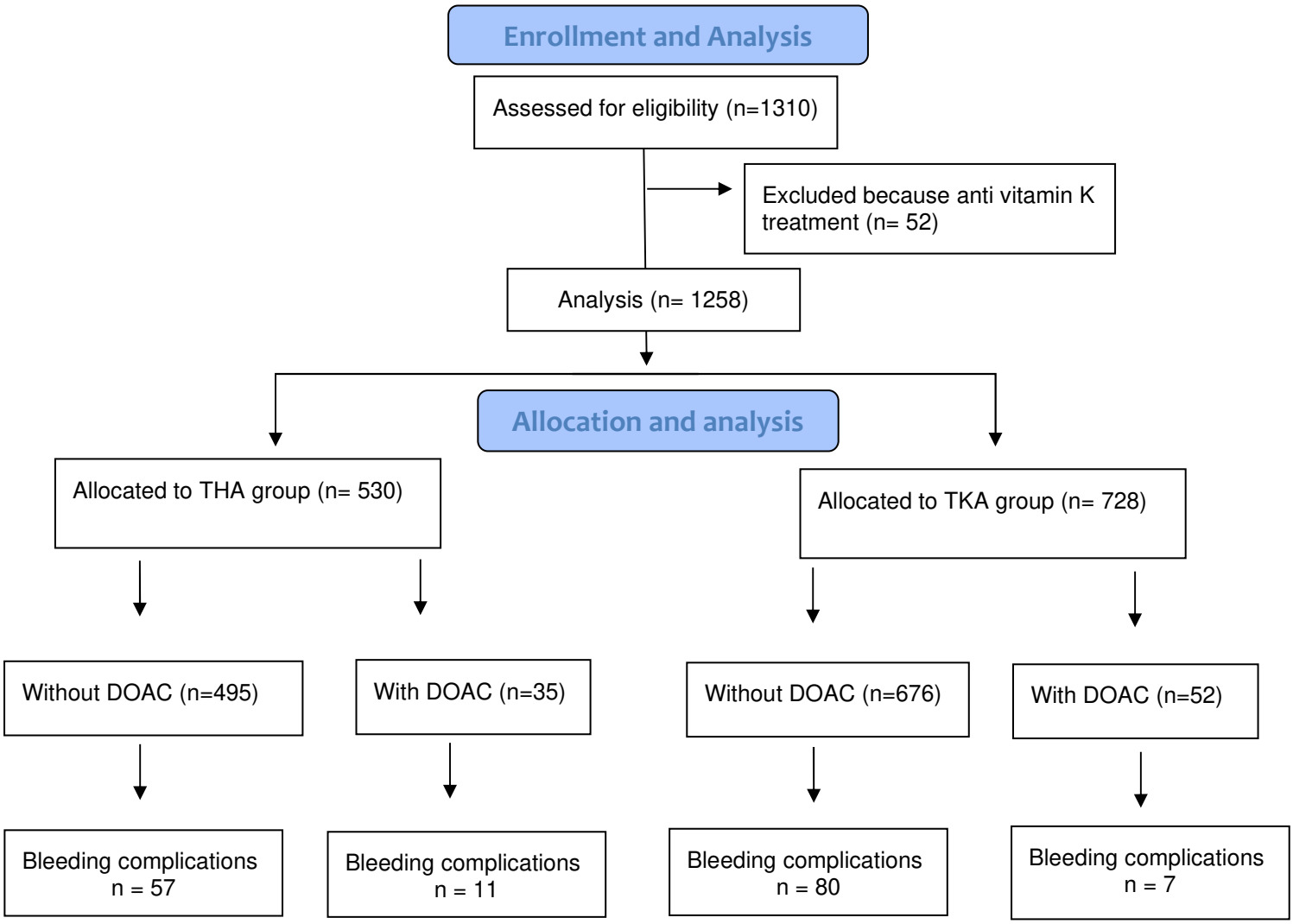
Table 4: DOAC related data from THA or TKA patients with or without bleeding complications

	THA with DOAC n= 35	TKA with DOAC n= 52
DOAC, n (%)	Rivaroxaban: 15 (43) Apixaban: 20 (57) Dabigatran: 0	Rivaroxaban: 25 (48) Apixaban: 23 (44) Dabigatran: 4 (8)
Patients distribution according to the days number discontinue DOAC, n (%)	3 days: 21 (60) 4 days: 9 (26) 5 days: 5 (14)	3 days: 18 (35) 4 days: 18 (35) 5 days: 16 (30)
Dosage specific DOAC number, n (%)	22 (63)	29 (56)
Dosage <30ng.ml^{-1}, n (%)	22 (100)	29 (100)

THA: Total Hip Arthroplasty, **TKA:** Total Knee Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **n:** patients number.

The median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Figure 1: Patients scheduled for elective orthopedic surgery between the 1st January 2017 and the 31th of December 2021.



DOAC: Direct Oral Anticoagulant, **n**: patients number **n**: patients number, **THA**: Total Hip Arthroplasty, **TKA**: Total Knee Arthroplasty.

Table 1: Comparative table of characteristics patients with bleeding complications, with and without DOACs, between THA and TKA group.

	THA with/without DOAC n= 68	**TKA with/without DOAC n= 87**	**P value**
Sex: n (%)	Man 27 (40) Woman 41 (60)	Man 35 (40) Woman 52 (60)	0.9 0.9
Age (year):	78 (8)	74 (7)	0.59
BMI ($kg.m^{-2)}$	26 (3)	30 (4)	0.60
GFR ($ml.min^{1}.1.73m^{-2}$)	80 (10)	78 (12)	0.92
ASA score n (%)	ASA I 7 (10) ASA II 39 (58) ASA III 22 (32)	ASA I 7 (8) ASA II 58 (67) ASA III 22 (25)	0.46 0.60 0.94
Anesthesia n (%)	GA 68 (100) SA 0 (0)	GA 19 (22) SA 68 (78)	**<0.001** **<0.001**
DOAC n (%)	11 (16)	7 (8)	1
Hematoma n	45 (66)	68 (78)	**0.033**
Transfusion n	23 (34)	19 (22)	**0.037**

THA: Total Hip Arthroplasty, **TKA**: Total Knee Arthroplasty, **DOAC**: Direct Oral Anticoagulant, **BMI**: Body Mass Index, **GFR**: Glomerular Filtration Rate, **ASA**: American Society of Anesthesiologists, **GA**: General Anesthesia, **SA**: Spinal Anesthesia, **n**: patients number. The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Table 2: Comparative table of characteristics and bleeding complications in THA patients between subjects with and without DOAC.

	THA without DOAC n = 57	THA with DOAC n = 11	P value
Sex n (%)	Man 22 (38) Woman 35 (62)	Man 5 (45) Woman 6 (55)	0.63 0.63
Age (year)	76 (7)	84 (2)	0.09
BMI (kg.m^{-2})	27 (3)	25 (4)	**0.04**
GFR (ml.min^{-1}.1.73m^{-2})	83 (11)	71 (8)	0.16
ASA score n (%)	ASA I 5 (9) ASA II 36 (63) ASA III 16 (28)	ASA I 0 (0) ASA II 3 (27) ASA III 8 (73)	1 0.24 0.08
Anesthesia n (%)	GA 57 (100) SA 0 (0)	GA 11 (100) SA 0 (0)	1 1
Hemoglobin (g/dl)			
- Baseline	13 (2)	13 (3)	0.34
- Postoperative day 1	11 (2)	11 (2)	0.32
- Minimal	10 (2)	9 (2)	0.29
- Before discharge	11 (2)	10 (1)	0.09
Hematoma n (%)	37 (66)	3 (28)	0.24
Transfusion n (%)	20 (34)	8 (72)	0.17

THA: Total Hip Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **BMI:** Body Mass Index, **GFR:** Glomerular Filtration Rate, **ASA:** American Society of Anesthesiologists, **GA:** General Anesthesia, **SA:** Spinal Anesthesia, **n:** patients number. The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Table 3: Comparative table of characteristics and bleeding complications in TKA patients between subjects with and without DOAC.

	TKA without DOAC n = 80	TKA with DOAC n = 7	P value
Sex n (%)	Man 31 (39) Woman 49 (61)	Man 3 (43) Woman 4 (57)	1 1
Age (years)	73 (7)	83 (3)	0.04
BMI ($kg.m^{-2}$)	29 (3)	35 (3)	0.54
GFR ($ml.min^{-1}.1.73m^{-2}$)	79 (12)	73 (11)	0.23
ASA score n (%)	ASA I 4 (5) ASA II 60 (75) ASA III 16 (20)	ASA I 0 (0) ASA II 1 (14) ASA III 6 (86)	1 **0.01** **0.02**
Anesthesia n (%)	GA 17 (21) SA 63 (79)	GA 5 (71) SA 2 (29)	0.06 0.30
Hemoglobin (g/dl)			
- Initial	14 (2)	13 (1)	0.30
- Postoperative day 1	12 (2)	12 (1)	0.52
- Minimal	10 (2)	9 (1)	0.30
- Before discharge	11 (2)	11 (1)	0.52
Hematoma n (%)	64 (80)	4 (57)	0.06
Transfusion n (%)	16 (20)	4 (57)	**0.02**

TKA: Total Knee Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **BMI:** Body Mass Index, **GFR:** Glomerular Filtration Rate, **ASA:** American Society of Anesthesiologists, **GA:** General Anesthesia, **SA:** Spinal Anesthesia, **n:** patients number.

The results were expressed as the median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.

Table 4: DOAC related data from THA or TKA patients with or without bleeding complications

	THA with DOAC n= 35	**TKA with DOAC n= 52**
DOAC, n (%)	Rivaroxaban: 15 (43) Apixaban: 20 (57) Dabigatran: 0	Rivaroxaban: 25 (48) Apixaban: 23 (44) Dabigatran: 4 (8)
Patients distribution according to the days number discontinue DOAC, n (%)	3 days: 21 (60) 4 days: 9 (26) 5 days: 5 (14)	3 days: 18 (35) 4 days: 18 (35) 5 days: 16 (30)
Dosage specific DOAC number, n (%)	22 (63)	29 (56)
Dosage <30ng.ml^{-1}, n (%)	22 (100)	29 (100)

THA: Total Hip Arthroplasty, **TKA:** Total Knee Arthroplasty, **DOAC:** Direct Oral Anticoagulant, **n:** patients number.

The median ± absolute deviation from the median for the quantitative variables and as the number (percentage) for the qualitative variables.