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RESEARCH ARTICLE

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Intra-operative blood transfusion in elderly patients on antithrombotic therapy

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Abstract

Background: Many elderly patients are receiving antithrombotics, which may increase intra-operative blood loss. We aimed to assess whether chronic antithrombotic therapy was associated with intra-operative transfusion of packed red blood cells in patients at least 80 years of age undergoing elective procedures.

Methods: We performed a secondary analysis of the prospective, observational European multicentre study entitled POSE (peri-interventional outcome study in the elderly) including 9497 surgical patients aged 80 years and older in 177 centres from October 2017 to December 2018. In this secondary analysis we included POSE patients who underwent elective procedures and with available data on chronic antithrombotic therapy. The primary outcome was intra-operative transfusion of packed red blood cells and results were analysed using multiple logistic regression model. We adjusted for the following predetermined explanatory variables: Age, sex, body mass index, American Society of Anaesthesiologists Physical Status Classification System, baseline haemoglobin concentration, disseminated cancer, and type and severity of surgery.

Results: A total of 7174 patients were included of whom 4073 (56.8%) were on antithrombotic therapy. Among patients on antithrombotic therapy 191 (4.7%) received intra-operative blood transfusion compared with 98 (3.2%) of patients not on chronic antithrombotic therapy (crude odds ratio: 1.51, 95% CI 1.18–1.94). Following multiple logistic regression analysis, the adjusted odds ratio was 0.98; 0.73–1.32.

We found that chronic antithrombotic therapy was associated with intra-operative transfusion of packed red blood cells in elderly patients undergoing elective procedures in an unadjusted analysis, but not in a multivariate adjusted model.

Editorial Comment

This is a pre-planned substudy of the POSE observational multicenter trial focusing on blood transfusion in patients >80 years and above of age undergoing elective surgery. The authors report unadjusted analysis where pre-operative antithrombotic therapy had an association with more blood transfusion, though this association disappeared when the analysis was adjusted for

relevant patient factors. Elective surgery in this high-risk patient group was generally safe regardless of antithrombotic therapy, and the findings of this study should prompt prospective studies evaluating the effect of anticoagulation in elderly patients.

1 | INTRODUCTION

Antithrombotic therapy is frequently used to prevent and treat thromboembolic diseases, especially among the continuously increasing elderly population. Despite its clinical benefits in reducing thrombosis and haemostasis, antithrombotics may increase bleeding complications, including intra-operative bleeding, as indicated by several studies.[1–7] Nevertheless, one study concluded that patients undergoing commonly performed elective general surgeries can be safely maintained on clopidogrel without increased risk of peri-operative bleeding.[8] Likewise, another study found no association between intra-operative blood loss and blood transfusion rate and peri-operative continuation of aspirin, oral anticoagulants or bridging with therapeutic low molecular weight heparin in cystectomy patients.[9] Of note, most data on this topic is limited to either specific high-risk patients, for example, patients with cardiovascular disease, specific types of surgeries and predominantly includes middle-aged patients rather than the specific elderly population aged 80 years and older.[1–13]

The premise of this study was that clinically important information on chronic antithrombotic therapy and intra-operative transfusion of packed red blood cells (PRBC) in the elderly population could be obtained by accessing the database of the prospective, observational European multicenter study entitled POSE (Peri-interventional outcome study in the elderly), which previously aimed to determine the peri-interventional (surgical and non-surgical interventional) all-cause mortality rate on day 30.[10] In this secondary analysis we aimed to assess the risk of receiving intra-operative blood transfusion during elective procedures in elderly patients receiving chronic antithrombotic therapy.

2 | METHODS

2.1 | Study design, setting, and participants

This study was a secondary analysis of the POSE study.[10] In brief, the POSE study included 9497 surgical and non-surgical patients 80 years of age and older in 177 European centres from October 2017 to December 2018. The patients were followed for 30 days from the day they were anaesthetised. In this secondary analysis we included POSE patients who underwent elective procedures, including both surgical and non-surgical interventions (radiological, neuroradiological, cardiological, gastroenterological) requiring anaesthesia care performed by an anaesthetist. We included both in- and outpatient interventions defined as procedures where the patient remained either in hospital for at least one night after intervention or was discharged on the day of intervention. Furthermore, we included only POSE patients with available data on chronic antithrombotic therapy defined as intake of anticoagulants (e.g., heparin, warfarin, and new oral anticoagulants (NOACs)) and/or antiplatelets (e.g., acetylsalicylic acid, and clopidogrel) until at least 7 days before intervention. Patients were included regardless of pre-operative functional status.

2.2 | Ethics

The original POSE study was either approved by a research ethics board (REB) or a waiver was granted at each centre. Initial REB approval was received from the institutional REB of the University Hospital RWTH Aachen, Germany (EK 162/17) on the 18th of august 2017 (chairperson: Prof. G. Schmalzing). The POSE study was registered at ClinicalTrials.gov (NCT03152734). This non-interventional secondary analysis was approved by the Steering Committee of the POSE study and no additional approval was needed. The study protocol was published on the POSE-trial.org website (https://pose-trial.org/secondary-analyses/) before data transfer agreement was made with the University Hospital RWTH Aachen, Germany and before gaining access to data. This study was reported according to the STROBE guidelines.[11]

2.3 | Variables and data

Pre-operative data included demographical data (age, sex, height, and weight), functional status within 30 days before assessment of independency (patient did not require assistance from another person for activities of daily living), partial dependency (the patient required some assistance from another person), and total dependency (the patient required total assistance for all activities of daily living) were included in the study, American Society of Anesthesiologists (ASA) Physical Status Classification System dichotomised to ASA score I–II or ASA score III–V, most recent (within 1 month) pre-interventional blood results including baseline haematocrit and baseline concentrations of haemoglobin, creatinine, and albumin, and only when done as part of the clinical routine. Furthermore, we included medical history of current smoking status (less than 1 year prior to intervention; excluding pipes, cigars and chewing tobacco), diabetes mellitus requiring oral or insulin treatment, severe chronic obstructive pulmonary disease (COPD) defined as functional disability or chronic bronchodilator therapy or past hospitalisation or forced expiratory volume in 1 s of <75%, hypertension requiring medication (<30 days prior to intervention), congestive heart failure (<30 days prior to intervention, acute or chronic, and with symptoms), and disseminated cancer including acute lymphoid leukaemia, acute myeloid leukaemia, lymphoma grade IV; excluding chronic lymphoid leukaemia, chronic

myeloid leukaemia and lymphoma grade I–III.[10] Intra-operative data included severity of surgery classified as minor (e.g., skin-lesions or small skin tumours, biopsies, draining breast abscess, brief diagnostic and therapeutic procedures like arthroscopy without intervention), intermediate (primary repair of inguinal hernia, excising varicose veins in the leg, tonsillectomy or adeno-tonsillectomy, knee arthroscopy, cataract surgery, uvuloplasty, minimally invasive repair of vaginal prolapse, vaginal hysterectomy, tendon repair of hand etc.), or major (total abdominal hysterectomy, endoscopic resection of prostate, lumbar discectomy, thyroidectomy, total joint replacement, lung operations, colon resection, radical neck dissection etc.). Furthermore, we included type of surgery distributed into seven categories including orthopaedic, gynaecologic, vascular, abdominal, cardiothoracic, neurosurgical and other (Ear, nose and throat, plastics, ophthalmologic etc.) (See Table S1, which demonstrates the distribution of surgical categories) a intra-operative transfusion of PRBC as well as plasma and/or platelets each defined as ≥1 units received. Post-operative data included hospital length of stay (including the day of intervention, excluding the day of discharge, if still in hospital at day 30, hospital length of stay was 31 days), all cause 30-day mortality, and complications in and out of hospital within 30 days including venous thromboembolism, stroke and/or re-operation. No data on post-operative bleeding was available from the original POSE study.

2.4 | Primary outcome measure

The primary outcome was intra-operative blood transfusion dichotomised to transfusion or not. Receiving intra-operative blood transfusion was defined as transfusion of one or more units of PRBC given intra-operatively.

2.5 | Secondary outcome measure

Secondary outcomes were dichotomised intra-operative transfusion of platelets and/or fresh frozen plasma (≥1 units received), frequency of complications in and out of hospital within 30 days defined as a combined outcome including venous thromboembolism, stroke, and re-operation and separate outcomes including hospital length of stay, and all cause 30-day mortality.

2.6 | Statistics

All statistical analyses were carried out using the statistical software R.[12] Categorical values were presented as frequencies and continues data as median and interquartile range.

The primary outcome was analysed using multiple logistic regression model adjusted for age and sex as well as predetermined variables that could potentially be explanatory variables for intra-operative blood transfusion based on previous literature, including ASA score, body mass index (BMI), baseline haemoglobin concentration, disseminated cancer and type and severity of surgery.[13–26] BMI was calculated using the variables weight and height and categorised into three levels: Underweight (<18.5 kg/m^2), Normal weight (18.5–24.9 kg/m^2) and Overweight/obesity (≥25.0 kg/m^2). As a secondary analysis we planned to perform backward elimination model with the same predetermined explanatory variables as written in the published protocol. However, this analysis was omitted in the peer-review process. Outcome was dichotomised intra-operative transfusion of PRBC (≥1 units given intra-operatively) with odds ratio (OR) and 95% confidence interval (CI) for chronic antithrombotic therapy (anticoagulants and/or antiplatelets). Similar methods were used for secondary outcomes except hospital length of stay, which was analysed using non-parametric statistics including Mann–Whitney-*U*-test. A *p*-value <.05 was considered statistically significant.

According to the protocol we planned to use multiple imputation to handle missing data.

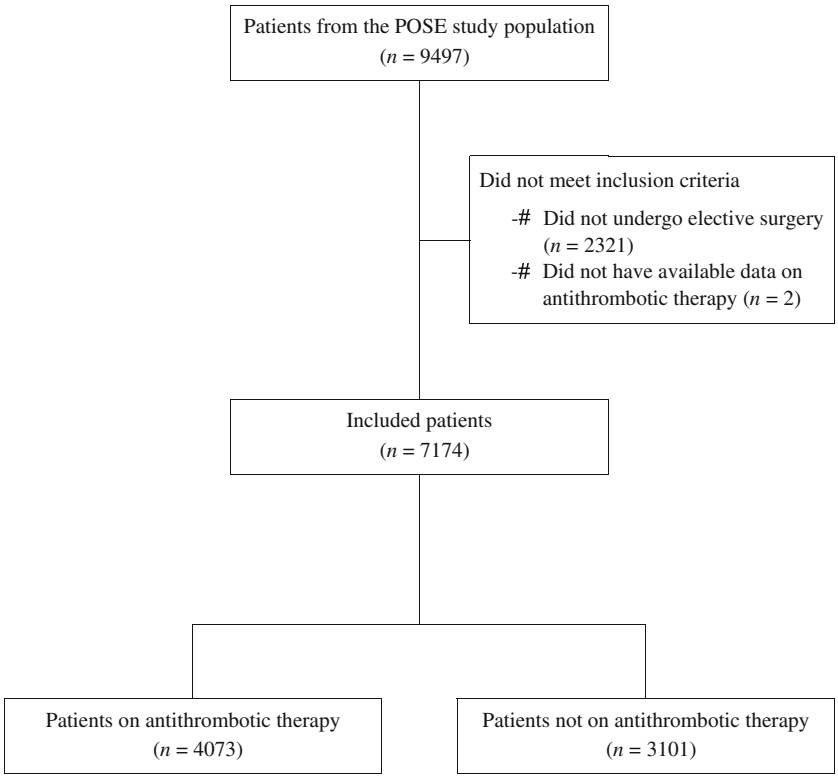
2.7 | Study size

All POSE patients undergoing elective procedures and with available data on antithrombotic therapy (yes/no) were included in this study. The rationale behind our analysis was that one third of an estimated 7100 elective surgical POSE patients received antiplatelets. Hence, we would be able to detect a difference of PRBC transfusion incidence of 7% versus 5% in POSE patients undergoing elective procedures with or without antiplatelets before surgery with a power of 90% at the 0.05 significance level.

3 | RESULTS

A total of 7176 POSE patients underwent elective surgery or elective non-surgical interventions. Two patients did not have available data on antithrombotic therapy resulting in inclusion of 7174 patients in this study (Figure 1). Of those 4073 (56.8%) patients were treated with antithrombotics and 3101 (43.2%) patients were not (Table 1). Of the 4073 (56.8%) patients receiving chronic antithrombotic therapy, 1347 (33%) patients received only anticoagulants, 2310 (56.7%) patients received only antiplatelets, 415 (10.2%) patients received both anticoagulants and antiplatelets, and one patient had missing data on anticoagulants but received antiplatelets (Table 2). More patients receiving chronic antithrombotic therapy were male and had a higher ASA score as well as more comorbidities and underwent vascular and cardiothoracic surgeries more frequently. The proportion of missing values was only 5.8% for the entire dataset, hence we did not find the multiple imputation rational. Although a limited amount of data was generally missing, we found a higher proportion of missing data for specific laboratory values: the baseline haemoglobin concentration was missing in 25%, baseline haematocrit level in 32%, baseline creatinine concentration in 28%, and baseline albumin concentration had 80% missing data.

FIGURE 1 Study flow chart



3.1 | Intra-operative blood transfusion

Data on intra-operative transfusion of PRBC was missing in two patients both treated with antithrombotics. Of those on chronic antithrombotic therapy 191 patients received intra-operative blood transfusion (4.7%) compared with 98 patients not on antithrombotics (3.2%) revealing increased crude OR of 1.51 (95% CI 1.18–1.94) for receiving intra-operative blood transfusion when treated with chronic antithrombotic therapy. However, when adjusted for age, sex, BMI, ASA score, baseline haemoglobin concentration, disseminated cancer as well as type and severity of surgery the OR was 0.98 (95% CI 0.73–1.32) (Table 3). Similarly, we found no statistically significant association between treatment of antithrombotics and intra-operative transfusion of plasma and/or platelets when adjusting (adjusted OR 0.80; 95% CI 0.50–1.28) as shown in Table 4, however, the crude OR was 1.58 with 95% CI 1.05–2.41. From our multiple logistic regression analysis, we found baseline haemoglobin concentration as well as undergoing major surgery to be the strongest explanatory variables for intra-operative blood transfusion (Table 5).

3.2 | Frequency of complications, length of stay, and all-cause mortality

Although the frequency of complications appeared to be higher among patients on chronic antithrombotic therapy (5.1%) with increased crude OR of 1.63 (95% CI 1.28–2.09) we found no statistically significant association when adjusting for our predetermined explanatory variables (adjusted OR 1.04; 95% CI 0.79–1.37) (Table 4). Similarly, the odds of all cause 30-day mortality were attenuated after adjustment (crude OR 1.94; 95% CI 1.36–2.81, adjusted OR 1.19; 95% CI 0.80–1.79) (Table 4). However, treatment of antithrombotic therapy was associated with a longer hospital stay ($p < .001$) in the univariate analysis.

4 | DISCUSSION

In this secondary analysis of the POSE study including more than 7000 elderly patients aged 80 years and older undergoing elective procedures, we found a higher rate of intra-operative transfusion of PRBC in patients receiving chronic antithrombotic therapy. In the adjusted analysis, however, we were not able to show an association between chronic antithrombotic therapy and intra-operative transfusion of PRBC. The transfusion rate was low in this population.

The primary strength of the study is the large sample with a high number of elderly patients who received chronic antithrombotic therapy. The broad inclusion criteria reduce the risk of selection bias as the original POSE study included various types of procedures, multiple centres across Europe, and legally incompetent patients. In addition, we applied no exclusion criteria, further strengthening the generalisability of our data. Besides, the prospective collection of data with few missing values increases the clinical relevance and validity.

The performance of a secondary analysis, however, may be a limitation of this study. The original POSE study primarily aimed to assess the peri-interventional (surgical and non-surgical interventional) all-

TABLE 1 Characteristics and outcomes of elderly patients included, according to antithrombotic therapy

Characteristic	Antithrombotic therapy[c] $n = 4073$	No antithrombotic therapy $n = 3101$	p-value[a]
Age, median (IQR), years	83.00 (81.00–86.00)	83.00 (81.00–85.00)	<.001
Sex, no. (%)			
Male	2285 (56)	1341 (43)	<.001
Body mass index, no. (%)	$n = 4029$[b]	$n = 3080$[b]	.002
Underweight (<18.5 kg/m^2)	0 (0)	0 (0)	
Normal weight (18.5–24.9 kg/m^2)	1603 (40)	1336 (43)	
Overweight/obesity (≥25.0 kg/m^2)	2426 (60)	1744 (57)	
Baseline haematocrit[c], median (IQR), %	$n = 2846$[b] 38.00 (34.00–41.10)	$n = 2023$[b] 38.90 (35.00–42.00)	<.001
Baseline haemoglobin concentration[c], median (IQR), g dl^{-1}	$n = 3123$[b] 12.60 (11.20–13.80)	$n = 2264$[b] 12.80 (11.60–14.00)	<.001
Baseline creatinine concentration[c], median (IQR), mg dl^{-1}	$n = 3045$[b] 1.00 (0.82–1.31)	$n = 2145$[b] 0.90 (0.75–1.11)	<.001
Baseline albumin concentration[c], median (IQR), g dl^{-1}	$n = 840$[b] 3.70 (3.20–4.20)	$n = 602$[b] 3.80 (3.34–4.20)	.03
ASA[a] score, no. (%)	$n = 4069$[b]		<.001
I–II	1110 (27)	1927 (62)	
III–V	2959 (73)	1174 (38)	
Functional status[c], no. (%)	$n = 4071$[b]	$n = 3101$[b]	<.001
Independent	2592 (64)	2273 (73)	
Partially dependent	1223 (30)	685 (22)	
Totally dependent	256 (6.3)	143 (4.6)	
Currently smoking[c], no. (%)	$n = 4072$[b] 225 (5.5)	$n = 3100$[b] 169 (5.5)	.89
Diabetes mellitus[c], no. (%)	1003 (25)	465 (15)	<.001
Severe COPD[c], no. (%)	360 (8.8)	190 (6.1)	<.001
Hypertension requiring medication[c], no. (%)	3383 (83)	1985 (64)	<.001
Congestive heart failure[c], no. (%)	841 (21)	162 (5.2)	<.001
Disseminated cancer[c], no. (%)	$n = 4071$[b] 210 (5.2)	$n = 3100$[b] 172 (5.5)	.47
Severity of surgery[d], no. (%)			<.001
Minor	969 (24)	726 (23)	
Intermediate	1517 (37)	1339 (43)	
Major	1587 (39)	1036 (33)	
Planned type of intervention, no. (%)			<.001
Inpatient intervention	3124 (77)	2160 (70)	
Outpatient intervention	949 (23)	941 (30)	
Type of surgery, no. (%)			<.001
Orthopaedic	643 (16)	593 (19)	
Gynaecologic	122 (3.0)	162 (5.2)	
Vascular	355 (8.7)	78 (2.5)	
Abdominal	1265 (31)	1083 (35)	
Cardiothoracic	565 (14)	120 (3.9)	
Neurosurgical	71 (1.7)	62 (2.0)	
Other	1052 (26)	1003 (32)	
Intra-operative transfusion of packed red blood cells[d], no. (%)	$n = 4071$[b] 191 (4.7)	98 (3.2)	.001

TABLE 1 (Continued)

Characteristic	Antithrombotic therapy[c] $n = 4073$	No antithrombotic therapy $n = 3101$	p-value[a]
Intra-operative transfusion of plasma and/or platelets[d], no. (%)	$n = 4072$[b] 70 (1.7)	34 (1.1)	.03
Hospital length of stay[e], median (IQR), days	3.00 (1.00–7.00)	2.00 (0.00–5.00)	<.001
Complications in and out of hospital within 30 days[e], No. (%)	$n = 4071$[b] 208 (5.1)	99 (3.2)	<.001
All cause 30-day mortality, no. (%)	$n = 3960$[b] 104 (2.6)	$n = 3060$[b] 42 (1.4)	<.001

[a]Wilcoxon rank sum test; Pearson's χ^2-test; ASA: American Society of Anesthesiologists (ASA) physical status classification system.
[b]Number of patients with available data.
[c]Pre-operative data: laboratory values including baseline haematocrit and concentrations of haemoglobin, creatinine and albumin (within 1 month), pre-interventional blood results if part of clinical routine, functional status within 30 days before assessment: independent (patients does not require assistance from another person for activities of daily living), partially dependent (the patient requires some assistance from another person), totally dependent (the patient requires total assistance for all activities of daily living), medical history: currently smoking status (less than 1 year prior to intervention), diabetes mellitus (requiring oral or insulin treatment), severe COPD (functional disability or chronic bronchodilator therapy or past hospitalisation or forced expiratory volume in 1 s of <75%), hypertension requiring medicine (<30 days prior to intervention), congestive heart failure (<30 days prior to intervention, acute or chronic, and with symptoms) and disseminated cancer (acute lymphoid or myeloid leukaemia, lymphoma grade IV; excluding chronic lymphoid or myeloid leukaemia), antithrombotic therapy (receiving anticoagulants e.g., heparin, warfarin and new oral anticoagulants and/or antiplatelets e.g., acetylsalicylic acid and clopidogrel until at least 7 days before intervention).
[d]Intra-operative data: planned kind of intervention: inpatient intervention (patient remains in the hospital for at least one night after intervention) and outpatient intervention (patient is discharged the day of intervention), Severity of surgery: minor (e.g., small skin tumours, biopsies, brief diagnostic and therapeutic procedures like arthroscopy without intervention), intermediate (primary repair of inguinal hernia, excising varicose veins in the leg, tonsillectomy, knee arthroscopy, cataract surgery, etc.) and major (total abdominal hysterectomy, resection of prostate, lumbar discectomy, total joint replacement, etc.), type og surgery: orthopaedic (arthroplasty and spine, trauma, other), gynaecologic, vascular, abdominal (endoscopic digestive, gastrointestinal, hepatic, urologic, renal transplant), cardiothoracic (intervention cardiology e.g., Transcatheter Aortic Valve Implantation, thoracic, cardiac), neurosurgical (intervention neuroradiology) and other (ear, nose and throat, ophthalmologic, plastic, transplant, multiple trauma related, other), transfusions of packed red blood cells and plasma and/or platelets (one or more units received intra-operatively).
[e]Post-operative data: hospital length of stay (including the day of intervention, excluding the day of discharge, if still in hospital at day 30, hospital length of stay was 31 days), complications in and out of hospital within 30 days (venous thromboembolism, stroke and/or re-operation).

TABLE 2 Distribution of patients, according to type of antithrombotic therapy

	Antithrombotic therapy[a] $n = 4073$	No antithrombotic therapy $n = 3101$
Anticoagulants only[b], no. (%)	1347 (33)	
Antiplatelets only[c], no. (%)	2310 (56.7)	
Both anticoagulants and antiplatelets, no. (%)	415 (10.2)	
Missing data on anticoagulants but received antiplatelets, no. (%)	1 (0)	

[a]Antithrombotic therapy was defined as receiving anticoagulants and/or antiplatelets until at least 7 days before intervention.
[b]Types of anticoagulants included, for example, heparin, Warfarin, and new oral anticoagulants.
[c]Types of antiplatelets included, for example, acetylsalicylic acid, and Clopidogrel.

cause 30-day mortality rate rather than the association between antithrombotic therapy and intra-operative blood transfusion. This might have resulted in a lack of more detailed information on antithrombotic therapy and intra-operative transfusion of PRBC, including data on specific types and doses of antithrombotics, and no information about intra-operative and post-operative bleeding volume. Similarly, the discontinuation strategy for antithrombotic therapy and the doses and types of antithrombotic therapy given in each centre will not be uniform. This also applies to the guidelines for transfusion criteria. Conversely, the external validity is improved as nearly 200 different European centres were involved. Furthermore, it is a limitation that we do not have data on the median number of days before intervention the antithrombotic therapy was withheld, and therefore we cannot exclude an uncertainty in intake and withdrawal of this medication during the 7 days before intervention. We assumed that the discontinuation guidelines depended on the standard management of antithrombotic therapy before intervention in each country and centre taking into account each patient's individual risk for bleeding or thrombosis, and type and severity of intervention. The opportunity to withhold antithrombotic therapy before an elective procedure should theoretically not lead to a higher risk of receiving intra-operative blood transfusion in patients on chronic antithrombotic therapy compared to patients without. However, we hypothesised that receiving chronic antithrombotic therapy would still increase the risk of receiving intra-operative blood transfusion compared with patients not on chronic antithrombotic therapy, which was the rational for including only patients undergoing elective procedures. Regarding intra-operative transfusion of PRBC, we dichotomised the amount of blood transfused intra-operatively (≥1 units), thereby not

considering the number of units transfused. This is as well a limitation due to the lack of information on the severity of intra-operative bleeding. However, intra-operative bleedings that result in blood transfusion compared with minor intra-operative bleedings that do not, may be considered more severe bleeding complications which could more potentially be a life-threatening condition for the patient. Therefore, intra-operative blood transfusion may be a more clinically relevant measurement than intra-operative bleeding itself.

All observational studies have an imbedded risk of known and unknown residual confounding. In our multiple logistic regression model, we adjusted for age, sex, ASA score, BMI, baseline haemoglobin concentration, disseminated cancer and type and severity of surgery. The selection of variables was restricted by the original POSE study, and we acknowledge that several other variables have been associated with an increased bleeding risk, and that residual confounding cannot be excluded in our study. Nevertheless, previous studies have shown that higher ASA scores are associated with increased risk of bleeding.[17–19] Furthermore, receiving antithrombotic therapy is more common in patients with higher ASA scores due to the presence of more co-morbidity (e.g., cardiac disease) in this group of patients. In regard to BMI, being both underweight and overweight have been associated with a higher risk of bleeding as well as patients on antithrombotic therapy with a lower BMI seem to have more bleeding complications.[15,20–24] In our study we did not find any patients with a BMI less than 18.5 kg/m^2 which was unexpected since many elderly patients, especially women might be malnutritioned leading to osteoporosis, fractures and surgery. The lack of underweight patients in the study might have influenced our results. In addition, both cancer and low baseline haemoglobin concentration may increase the risk of bleeding and intra-operative transfusion.[16,25,26]

Last, the findings in this study concern the specific elderly population aged 80 years and older undergoing elective surgical and elective non-surgical interventions and cannot be generalised to other populations, including those who do not undergo interventions requiring anaesthetic care, or any urgent and emergency surgeries. Thus, these results cannot be used to address the controversy concerning interruption and bridging strategies as well as the safety of continuing antithrombotic therapy during surgery, since we do not have detailed information on this.

Chronic antithrombotic therapy may increase surgical blood loss, which has been shown to cause a higher mortality,[26] which could especially be disadvantageous in vulnerable patients such as the elderly population aged 80 years and older. Furthermore, as the life expectancy in the population is continuously increasing, more elderly patients may be scheduled for surgery as well as require treatment with antithrombotic therapy in the future. This will potentially leave a

TABLE 3 Odds Ratio for the association of intra-operative blood transfusion and antithrombotic therapy

Variable	OR	95% CI	*p*-value
Transfusion of packed red blood cells			
Not on antithrombotic therapy	-	-	-
Antithrombotic therapy[a]	0.98	0.73–1.32	1.0

Note: Table adjusted for age, sex, body mass index, American Society of Anesthesiologists (ASA) physical status classification system, baseline haemoglobin concentration, disseminated cancer, type and severity of surgery. Elderly patients undergoing elective procedures.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Antithrombotic therapy was defined as receiving anticoagulants (e.g., heparin, warfarin, new oral anticoagulants) and/or antiplatelets (e.g., acetylsalicylic acid, clopidogrel) until at least 7 days before intervention.

TABLE 4 Odds Ratios for plasma and/or platelet transfusion, peri-operative complications, and all cause 30-day mortality

Variable	OR	95% CI	*p*-value
Transfusion of plasma and/or platelets[a]			
Not on antithrombotic therapy	-	-	-
Antithrombotic therapy[b]	0.80	0.50–1.28	.3
Complications in and out of hospital within 30 days[a]			
Not on antithrombotic therapy	-	-	-
Antithrombotic therapy[b]	1.04	0.79–1.37	.8
All cause 30-day mortality			
Not on antithrombotic therapy	-	-	-
Antithrombotic therapy[b]	1.19	0.80–1.79	.4

Note: Model adjusted for age, sex, body mass index, American Society of Anesthesiologists (ASA) physical status classification system, baseline haemoglobin concentration, disseminated cancer, type and severity of surgery. Elderly patients undergoing elective procedures.
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Transfusion of plasma and/or platelets defined as receiving one or more units of fresh frozen plasma and/or platelets, complications in and out of hospital within 30 days including venous thromboembolism, stroke and/or re-operation.
[b]Antithrombotic therapy was defined as receiving anticoagulants (e.g., heparin, warfarin, new oral anticoagulants) and/or antiplatelets (e.g., acetylsalicylic acid, clopidogrel) until at least 7 days before intervention.

TABLE 5 Explanatory variables for intra-operative blood transfusion in elderly patients undergoing elective procedures

Variable	OR	95% CI	*p*-value
Antithrombotic therapy[b]			
No (reference)	-	-	
Yes	0.98	0.73–1.32	1.0
Age, increment = 1 year	0.94	0.90–0.97	.001
Sex			
Female (reference)	-	-	
Male	0.79	0.60–1.04	.09
Body mass index			
Underweight[a]	-	-	
Normal weight (reference)	-	-	
Overweight/obesity	1.01	0.78–1.32	1.0
ASA[a] score			
I–II (reference)	-	-	
III–V	1.33	0.95–1.88	.1
Baseline haemoglobin concentration[b], increment = 0.1 g dl^{-1}	0.62	0.57–0.67	<.001
Disseminated cancer[b]			
No (reference)	-	-	
Yes	1.10	0.64–1.81	.7
Severity of surgery[c]			
Minor (reference)	-	-	
Intermediate	14.6	3.02–263	.01
Major	127	28.30–2244	<.001
Type of surgery[c]			
Orthopaedic (reference)	-	-	
Gynaecologic	1.15	0.56–2.19	.7
Vascular	1.00	0.58–1.70	1.0
Abdominal	0.70	0.49–1.01	.06
Cardiothoracic	1.76	1.20–2.58	.004
Neurosurgical	0.73	0.21–1.87	.6
Other	0.23	0.07–0.59	.006

Abbreviations: ASA, American Society of Anesthesiologists (ASA) physical status classification system; CI, confidence interval; OR, odds ratio.

[a]No underweight patients in the study.

[b]Pre-operative data: Baseline haemoglobin concentration: most recent (within 1 month) pre-interventional blood result and if part of clinical routine, (acute lymphoid or myeloid leukaemia, lymphoma grade IV; excluding chronic lymphoid or myeloid leukaemia), antithrombotic therapy (receiving anticoagulants e.g., heparin, warfarin and new oral anticoagulants and/or antiplatelets e.g., acetylsalicylic acid and clopidogrel until at least 7 days before intervention).

[c]Intra-operative data: Severity of surgery: minor (e.g., small skin tumours, biopsies, brief diagnostic and therapeutic procedures like arthroscopy without intervention), intermediate (primary repair of inguinal hernia, excising varicose veins in the leg, tonsillectomy, knee arthroscopy, cataract surgery, etc.) and major (total abdominal hysterectomy, resection of prostate, lumbar discectomy, total joint replacement, etc.), type og surgery: orthopaedic (arthroplasty and spine, trauma, other), gynaecologic, vascular, abdominal (endoscopic digestive, gastrointestinal, hepatic, urologic, renal transplant), cardiothoracic (intervention cardiology e.g., Transcatheter Aortic Valve Implantation, thoracic, cardiac), neurosurgical (intervention neuroradiology) and other (ear, nose and throat, ophthalmologic, plastic, transplant, multiple trauma related, other).

greater proportion of those patients at risk of additional intra-operative blood loss. However, it can be a difficult balance as discontinuation of chronic antithrombotic therapy prior to surgery may put the patients at increased risk of thromboembolic complications, including myocardial infarction, stroke, and venous and pulmonary thromboembolism, which may as well be life threatening. According

to the adjusted OR in our current study we found no association between chronic antithrombotic therapy and intra-operative blood transfusion as well as chronic antithrombotic therapy was not associated with either intra-operative transfusion of plasma and/or platelets, complications in and out of hospital, including venous thromboembolism, stroke and return to operating room nor all-cause 30-day mortality. Several other studies have found that chronic antithrombotic therapy may not increase the risk of clinically significant surgical bleeding or peri-operative complications.[8,9,28-31] Contrary some previous studies have shown that patients who recently withdrew their antithrombotic therapy, or prior users of this medication were at increased bleeding risk, and were more common to receive post-operative blood transfusion, or return to operating room due to post-operative haemorrhage compared with nonusers. Of note, these studies only included heart disease patients with a high number of the patients not undergoing surgery, or exclusively looked at post-operative bleeding complications.[1-6]

Our findings should, thus, be interpreted with caution due to the before mentioned limitations as well as inclusion of patients undergoing elective non-surgical interventions with minimal bleeding risk lowering the transfusion rate, which may have underestimated the risk of bleeding for high bleeding risk patients receiving antithrombotic therapy. This may be reflected in the relatively wide CI of 0.73–1.32 despite an OR of 0.98. Additionally, the transfusion rates were lower than the anticipated 7% versus 5%. Furthermore, we adjusted for baseline haemoglobin concentration which was only available in 75% of the population due to collection of this variable as part of usual care in the original POSE study. This might have biased our results since we would expect that patients without a baseline haemoglobin concentration might represent a population with less comorbidity and lower ASA scores who undergo more minor-intermediate interventions as compared with patients with measured baseline haemoglobin concentration. Similarly, most patients with available data on haemoglobin could potentially be patients with anaemia, and therefore be at a higher a priori risk of intra-operative transfusion of PRBC. Thus, we cannot completely exclude an increased risk of receiving intra-operative blood transfusion when on antithrombotic therapy. However, patients without a baseline haemoglobin concentration might not have contributed as much to the events, and likewise it is most likely that patients who were at particularly increased risk of major bleeding may have had their antithrombotic therapy interrupted during the 7 days up until intervention since current guidelines recommend such individual risk assessment.[32] Therefore, our study may reflect standard practices, and our results thereby indicating adequate guidelines on this area, also when it comes to the very elderly and vulnerable population.

5 | CONCLUSION

This study concludes that the risk of receiving intra-operative transfusion of PRBC is low for this specific elderly population aged 80 years and older undergoing a wide range of elective procedures. Furthermore, in this patient population, receiving chronic antithrombotic therapy does not seem to result in a higher risk of receiving intra-operative blood transfusion compared to not receiving chronic antithrombotic therapy. However, this finding is based on our adjusted analysis including age, sex, BMI, American Society of Anesthesiologists Physical Status Classification System, baseline haemoglobin concentration, disseminated cancer and type and severity of surgery. The unadjusted analysis indicates an opposed result, thus, we cannot exclude an increased risk of bleeding for this specific elderly population on chronic antithrombotic therapy when undergoing elective procedures.

AUTHORS' CONTRIBUTIONS

Caroline Hjelmdal conceived and designed the analysis, performed the analysis, wrote the study protocol and the manuscript, and reviewed the paper. Christina Draegert and Morten Vester-Andersen collected the data and reviewed the manuscript. Ana Kowark conceived and designed the analysis, collected the data, performed and wrote the original POSE-study and reviewed this secondary analysis. Mark Coburn conceived and designed the analysis, collected the data, reviewed the manuscript and performed and was the national coordinator in Germany on the original POSE-study. Lars S. Rasmussen conceived and designed the analysis and reviewed the manuscript. Lars H. Lundstrøm conceived and designed the analysis, collected the data, reviewed the manuscript and was the national coordinator in Denmark on the original POSE-study. Jacob Steinmetz conceived and designed the analysis, collected the data, reviewed the manuscript and was a part of the POSE-trial Steering Committee as well as investigator on the original POSEstudy

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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