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Gender Disparities in the Use of Blood Transfusion in Elective Surgery Warrant a Practice Change

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Abstract

Objectives: A post hoc gender comparison of transfusion-related modifiable risk factors among patients undergoing elective surgery.

Settings: 23 Austrian centres randomly selected and stratified by region and level of care.

Participants: We consecutively enrolled in total 6530 patients (3465 women and 3065 men); 1491 underwent coronary artery bypass graft (CABG) surgery, 2570 primary unilateral total hip replacement (THR), and 2469 primary unilateral total knee replacement (TKR).

Main outcome measures: The primary outcome variables were perioperative blood loss and the volume of red blood cells (RBC) transfused in relation to the preoperative circulating RBC volume. The secondary outcome variables were the number of RBC units transfused, the perioperative haemoglobin values and the prevalence of preoperative anaemia.

Results: In all surgical groups, the transfusion rate was significantly higher in women than in men (CABG 81 vs. 49%, THR 46 vs. 24%, TKR 37 vs. 23%). In *transfused* patients, the absolute blood loss was higher among men in all surgical categories while the relative blood loss was higher among women in the CABG group (52.8 vs. 47.8%) but comparable in orthopaedic surgery. The relative RBC volume transfused was significantly higher among women in all categories (CABG 40.0 vs. 22.3; TKR 25.2 vs. 20.2; THR 26.4 vs. 20.8%). On postoperative day 5 the relative haemoglobin values and the relative circulating RBC volume were higher in women in all surgical categories.

Conclusions: The higher transfusion rate and volume in women as compared with men in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender. This, together with the common use of a liberal transfusion strategy leads to further over-transfusion in women.

Trial registration: Ethical approval: Ethikkomission des Landes Oberösterreich, 15 July 2009

Data sharing statement: No additional data are available

Strengths and limitations of this study

- After surgery, women have a higher risk for adverse outcomes and death, which may be at least partially attributable to a higher allogeneic transfusion rate. The latter phenomenon, together with the occurrence of perioperative blood loss and anaemia, may even worsen their postoperative outcome.
- Therefore, identifying the underlying causes of the higher RBC transfusion rate in women might be of critical importance.
- The study's great strength is the calculation of perioperative blood loss including the so-called hidden blood loss. Moreover, we compared not only absolute transfusion-related data but also relative values in relation to the WHO's cut-off values. This enabled a fair gender comparison since baseline differences between men and women were eliminated.
- The findings that women have a higher postoperative RBC volume in all surgical groups and higher intra- and postoperative haemoglobin levels, together with a higher relative RBC volume transfused, clearly indicate that the transfusion strategies applied in women were too liberal in elective CABG and orthopaedic surgery despite relevant guidelines.
- The higher transfusion rate and volume in women as compared with men in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender despite the fact that women have a lower baseline RBC volume. Given the possibility to pre-empt transfusions through the treatment of modifiable risk factors by applying the patient blood management concept, a beneficial change in practice is warranted.

Introduction

Women tend to live longer than men but typically experience more stress, poorer health, and more years with disabilities along the way [1 2]. Furthermore, in clinical decision-making and therapeutic interventions gender disparities are common. Women are less likely to receive coronary angiography and coronary interventions [3-5], implantable cardioverter defibrillators [6], dialysis and renal transplants [7 8], or arthroplasties [9]. Also, after surgical treatment, women have a higher risk for adverse outcomes and death, which may be at least partially attributable to a higher allogeneic transfusion rate [9-13].

It is a matter of fact that women have a higher bleeding tendency [14 15] and are more likely to be transfused than men [11-13 16-22]. The latter phenomenon, together with the occurrence of perioperative blood loss and anaemia, may worsen their postoperative outcome. However, in contrast to other preoperative risk factors, these factors can be mitigated by adequate and timely prevention and treatment.

In the last years, the modern concept of patient blood management has been developed by international experts and implemented worldwide [23-25]. Its aim is to manage and preserve a patient's own blood by reducing the above mentioned transfusion related risk factors – anaemia, blood loss, and red blood cell (RBC) transfusion – with the ultimate goal of improving the patient's outcome and safety [26]. Therefor, identifying the underlying causes of the higher RBC transfusion rate in women and – as a consequence - to enable adequate and timely prevention and treatment might be of critical importance.

The aim of our study was a gender comparison in patients undergoing elective surgery with special attention to differences in transfusion-related modifiable risk factors for an adverse outcome [26].

Methods

The present analysis included data from patients enrolled in two Austrian benchmark studies on blood use in elective surgery [18 20]. Both studies were prospective, observational multicentre studies with 23 participating centres, which were randomly selected and stratified by region and level of care. The study design, selection and recruitment of the centres, patient selection, data collection, quality management, and first-line data analysis were similar in the two studies. The first study was conducted from April 2004 through February 2005, the second study from July 2009 through August 2010.

In the two studies, we collected data from patients undergoing primary unilateral cemented or non-cemented total hip replacement (THR), primary unilateral non-cemented total knee replacement (TKR), or coronary artery bypass graft (CABG) surgery. Based on the Austrian Data Protection Commission's review, informed consent from individual patients was not necessary because only de-identified data were collected and complete patient confidentiality was maintained. After obtaining approval from the local ethics committee (Ethikkomission des Landes Oberösterreich, 15 July 2009), we consecutively enrolled all eligible patients aged 18 years or older. Our exclusion criteria were: any other concomitant surgery, emergency surgery, and an underlying coagulopathy documented by a history of bleeding and/or laboratory testing (international normalized ratio >1.5 or activated partial thromboplastin time >35 seconds).

We collected the following demographic and clinical data from the hospital records: patient age, body weight and height, preoperative use of platelet inhibitors or anticoagulants, type of anaesthesia, duration of surgery, use of a cell saver, and length of hospital stay. In addition, we obtained routinely measured perioperative haemoglobin and haematocrit values and the number of RBC concentrates transfused. To account for gender differences, we presented the haemoglobin values as percentages of the anaemia cut-off values given by the World Health Organization (WHO; women 120 g/L, men 130 g/L)[27] (Figure 1). The body surface area was calculated using the Du Bois formula [28]. The Nadler et al. formula was used to calculate the patients' blood volume [29]. The total RBC volume was derived by multiplying the calculated blood volume with the corresponding haematocrit level. A factor of 0.91 was applied to correct the haematocrit value for peripheral blood sampling [30]. The overall perioperative RBC loss was calculated by subtracting the RBC volume on postoperative day 5 from the preoperative RBC volume and by adding the total RBC volume transfused. Differences in the average haematocrit (range 56–65%) and volume (range 250–316.7 mL) of RBC units from different blood banks were accounted for by multiplying the volume by the mean haematocrit of the respective unit. To calculate the salvaged, washed, and returned RBC volume during cell saver use, we assumed a haematocrit level of 60% [31]. To adjust for baseline differences in the total RBC volume, the lost and transfused RBC volumes were analysed as percentages of the patient's total circulating baseline RBC volume (relative RBC volume).

The primary outcome variables were the perioperative blood loss, the volume of RBCs transfused and the blood volume on postoperative day 5 in relation to the preoperative baseline RBC volume. The secondary outcome variables were the number of RBC units transfused (transfusion rate), the prevalence of preoperative anaemia, and the perioperative haemoglobin values.

Descriptive statistics for the data were presented as median and interquartile range, or absolute and relative frequencies (%). Differences between women and men were tested for statistical significance using the Mann–Whitney *U* test for continuous variables and the chi-square test for frequencies, respectively. We used Matlab, release 2015a (The MathWorks Inc, Natick, MA) for the statistical analysis. Box plots, bar charts, and line diagrams were used to present the data graphically. $p < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics and perioperative data

The present analysis included 6530 patients (3465 women and 3065 men) (Table 1), with 1491 patients (350 women and 1141 men) undergoing CABG surgery, 2570 patients (1424 women and 1146 men) undergoing THR, and 2469 patients (1691 women and 778 men) undergoing TKR. Table 2 gives an overview of the demographic characteristics and perioperative parameters. Men were younger (except for those undergoing TKR) and taller than women, and they had a higher body surface area and a higher body weight. There were no gender differences in the body mass index and the patients' overall health (American Society of Anesthesiologists score). The prevalence of anaemia was also similar in both genders with the exception of patients undergoing CABG surgery; in this subgroup, preoperative anaemia was more common among women than among men. Women in the CABG group also had a significantly higher surgical risk of death (euroSCORE) than men. Tranexamic acid was the main antifibrinolytic agent used in the second benchmark study, aprotinin the one used in the first benchmark study.

Primary outcome variables

The absolute blood loss among patients undergoing CABG was comparable in both genders, and that among patients undergoing orthopaedic surgery was slightly lower in women than in men. By contrast, the relative blood loss among patients undergoing CABG surgery was considerably higher in women than in men; it was also slightly higher in women in the THR group, whereas it was similar in both genders in the TKR group (Table 3). The absolute RBC volume transfused was higher in women than in men among patients undergoing CABG surgery and equal in both genders among orthopaedic patients, whereas the relative RBC volume transfused was twice as high in women compared with men in the CABG group, and it was also elevated in women undergoing orthopaedic surgery. On postoperative day 5 *absolute* circulating blood volumes were significantly higher in men whereas *relative* blood volume were significantly higher in women in all categories (Table 3).

In ***transfused*** patients, the absolute RBC loss was lower in women than in men in all surgical categories, but the relative RBC loss was higher in women than in men in CABG surgery (52.8% vs. 47.8%, $p < 0.0001$) and comparable in both genders in orthopaedic surgery. The absolute RBC volume transfused was slightly higher in men. However, the relative RBC volume transfused was significantly higher in women than in men (26.4% vs. 20.8%; $p < 0.0001$) (Table 4) (Figure 2). The absolute preoperative RBC volume was about 30% higher in men than in women and the RBC volume on postoperative day 5 was approximately 20% higher in men. On the other hand, on postoperative day 5 the relative RBC volumes were elevated (by about 5%) in women in all surgical subgroups when compared with men.

Secondary outcome variables

In all subgroups, the transfusion rate was significantly higher in women than in men (CABG 81% vs. 49%, THR 46% vs. 24%, TKR 37% vs. 23%) (Figure 3). Also women received one or two RBC units more often than men (Figure 4).

No gender difference in the prevalence of preoperative anaemia could be detected in patients undergoing orthopaedic surgery. In patients undergoing CABG surgery, the prevalence and severity of preoperative anaemia was higher among women (prevalence in women, 30.3%; prevalence in men, 23.7%). In younger patients below the age of 60, anaemia was more common in women, whereas at ages 70 years and older, anaemia was more common in men. Figure 5 shows the percentages of the transfused patients for the different surgical interventions, both for patients with (left) and for those without (right) preoperative anaemia. Overall, the transfusion rates were significantly higher in patients with preoperative anaemia than in non-anaemic patients (total population: women 75% vs. 38%, men 66% vs. 25%; CABG: women 93.4% vs. 75.4%, men 76.3% vs. 40.0%; THR: women 77.0% vs. 37.8%, men 60.7% vs. 17.7%; TKR: women 65.4% vs. 31.5%, men 51.8% vs. 16.9%).

In transfused patients the absolute preoperative haemoglobin values were generally lower in women, relative haemoglobin values were comparable except for the in the TKR subgroup. The lowest measured haemoglobin (nadir haemoglobin) value was slightly lower in women than in men in orthopaedic surgery, whereas the relative values were higher in women than in men among those undergoing CABG surgery. On postoperative day 5, the absolute haemoglobin values were slightly higher in men (except for CABG patients). By comparison, the relative haemoglobin values on postoperative day 5 were elevated in women in all surgical categories (Table 4).

Discussion

The present study identified a higher transfusion rate in women compared with men in three surgical categories. Other findings of this study are:

1. Although the absolute perioperative blood loss was higher in men in all subgroups, the relative blood loss was comparable between the genders in orthopaedic surgery, and in the CABG subgroup it was higher in women.

2. Furthermore, the relative RBC volume transfused was significantly higher in women in all surgical categories, especially in CABG surgery.
3. This was accompanied by a higher relative nadir haemoglobin value and a higher haemoglobin value on postoperative day 5 in women.
4. In addition, the calculated relative postoperative RBC volume in women was approximately 5% higher than that in men across all surgical groups.
5. There was no gender difference in the overall prevalence of preoperative anaemia as defined by the gender-specific WHO cut-off values.

Anaemia, blood loss, and transfusion constitute a triad of risk factors for adverse patient outcomes [26 32-36]. Each of these three parameters represents a risk factor in itself and their combination may further potentiate the risk of an adverse outcome [37]. Within this triad, a vicious cycle is set in motion: blood loss and bleeding induce anaemia or exacerbate pre-existing anaemia. Anaemia triggers transfusion, and transfusion – besides having many other adverse effects – increases the risk of re-bleeding, potentially leading to additional blood loss, as shown in several studies [36 38-41]. The intention of breaking this vicious cycle by modifying these risk factors has led to the development of the concept of patient blood management, which is based on three pillars: optimization of the patient's endogenous RBC mass; minimization of diagnostic, interventional, and surgical blood loss; and optimization of the patient's tolerance of anaemia [24 42]. In most clinical scenarios, application of just the first two pillars is sufficient to address all three risks of the triad. Optimization of the RBC mass and the reduction of blood loss keep the haemoglobin levels of most patients above a level where transfusion might be considered. However, addition of the third pillar can further reduce transfusion rates [43].

With regard to the optimization of the patient's endogenous RBC mass (first pillar), women generally seem to be less susceptible to anaemia-induced adverse events than men. For example, in normal life, the lowest risk for mortality occurs at haemoglobin values between 130 and 150 g/L in women and between 140 and 170 g/L in men [44-47]. In a cohort of 6880 elderly patients without severe comorbidities, mild and moderate anaemia was significantly associated with a higher mortality in men but not in women [34 48]. In a recent publication focusing on non-emergent CABG surgery, a low haematocrit and blood transfusion were significant predictors for major morbidity in men, whereas in women blood transfusion was the only predictor of major morbidity [34]. In non-cardiac surgery, the mortality was higher in men than in women at similar haemoglobin levels.

The prevalence of preoperative anaemia in the present study was similar in both genders, so this factor cannot explain the higher transfusion rates in women. The fact that the prevalence of anaemia among women was similar to that among men might be attributable to the higher age of the patients included in the study [49], because the higher prevalence of low haemoglobin values observed in younger women disappears with increasing age. After the age of 75 years, men have in fact a higher prevalence of anaemia than women, with the prevalence among men being highest at age 85 years and older [50 51].

The observation that anaemia is associated with a poor prognosis in many disorders is not a sufficient reason to assume a cause-and-effect relationship. Anaemia of chronic disease in particular may be associated with an adaptive physiological response [52 53]. The treatment of mild to moderate anaemia of chronic disease may therefore not always bring the desired improvement or may even increase the mortality in some cases [54]. Nevertheless, optimization of the preoperative blood volume up to the WHO cut-off values should be an integral strategy to reduce the transfusion requirements in both genders [55 56].

The amount of perioperative blood loss (second pillar) depends on the surgical technique, the management of perioperative coagulation, and the blood conservation techniques used. The degree of acute blood loss that patients can safely tolerate is inversely related to their baseline haemoglobin concentration and the decrease of their RBC volume [57]. A decrease of at least 50% from the preoperative haemoglobin level during cardiac surgery is associated with adverse outcomes even if the absolute haemoglobin level remains above the commonly used transfusion threshold of 7.0 g/dL [58].

In the present study, the absolute blood loss was smaller among women than among men in all-surgical subgroups, but the relative perioperative blood loss was 5% higher among women than among men in the CABG subgroup and it was comparable between men and women in the orthopaedic surgery subgroups. The higher blood loss among women undergoing CABG surgery may be attributable to the extreme haemodilution associated with extracorporeal circulation. As women have a lower body mass index than men, their haemodilution during the operation is more profound, and women therefore tend to receive more transfusions during and after the CABG operation[19]. Nevertheless, the differences in blood loss alone cannot explain why the RBC volume transfused among women was twice that among men in the CABG group and 25% higher than that among men in the orthopaedic surgery groups (Table 4).

With regard to the tolerance of anaemia (third pillar), it is possible that the ability to compensate for low haemoglobin values differs by gender. Moreover, to our knowledge neither cut-off values nor transfusion guidelines exist for postmenopausal women [59 60]. Several authors have suggested that anaemia in women beyond menopause should be defined by a higher haemoglobin threshold, similar to that used for men [45 61 62]. Current transfusion guidelines revolve around absolute haemoglobin values and do not account for this phenomenon, nor do they consider the special needs of women in general [60 63-65]. In fact, in routine clinical practice similar transfusion triggers are applied in both genders[66].

The present study has several limitations. First, it is a post hoc analysis that uses data from two similar consecutive benchmark studies [18 20]. Second, because financial resources were limited, postoperative outcomes could not be studied. Third, because of the observational character of the two benchmark studies only routine parameters could be collected. Therefore, several aspects of interest such as the causes of preoperative anaemia could not be investigated.

A main strength of the study is the fact that the perioperative blood loss was calculated and the so-called hidden blood loss is therefore included in the analysis. Moreover, we compared not only absolute transfusion-related data but also relative values (in relation to the WHO cut-off values [27]). This enabled a fair gender comparison because baseline differences between men and women were eliminated.

The present findings—that women had a higher postoperative RBC volume in all surgical groups and higher intra- and postoperative haemoglobin levels, together with a higher relative RBC volume transfused—are clear indicators that the transfusion strategies applied in women were too liberal. These results could have an enormous impact on clinical treatment and eventually lead to improvements in outcome and patient safety. Once clinicians are aware of the fact that women tend to be over-transfused, measures can be taken to address this matter. These include the correction of preoperative anaemia, the reduction of perioperative blood loss by optimizing the surgical technique, the reduction of the transfusion volume (e.g. by implementing a single-unit strategy), and the use of lower haemoglobin values as transfusion triggers. Such strategies may dramatically reduce the transfusion rate among women while improving outcome and patient safety.

Conclusion

The higher transfusion rate and volume in women, compared with men, in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender even though women have a lower baseline RBC volume. This, together with the common use of a liberal transfusion strategy in elective CABG and orthopaedic surgery despite the recommendations in relevant guidelines, leads to over-transfusion in women. Given the possibility to pre-empt transfusions through the treatment of modifiable risk factors by applying the patient blood management concept, a beneficial change in practice is warranted.

Table 1 Patients included

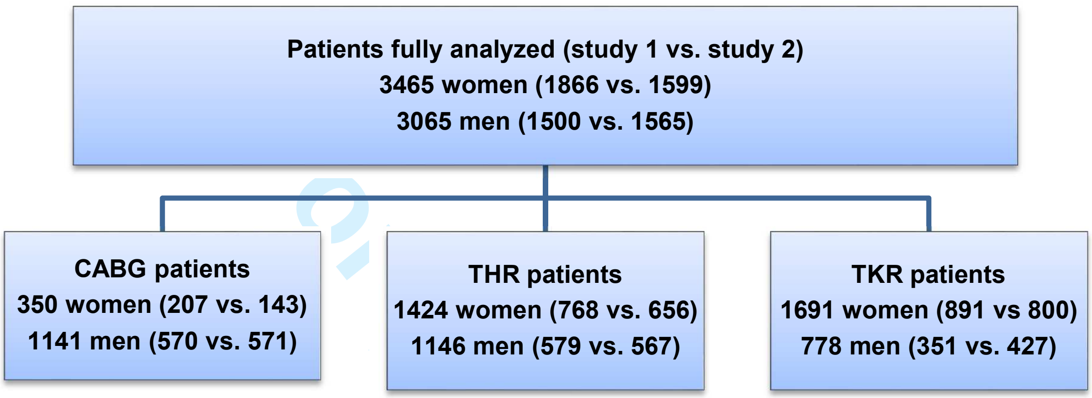

Table 2: Demographic Data

		Women	Men	p value
Age	**All**	70/14	67/14	**< 0.0001**
	CABG	71/13	66/13	**< 0.0001**
	THR	69/15	66/15	**< 0.0001**
	TKR	71/12	70/12	0.0017
Body Weight (kg)	**All**	74/19	84/18	**< 0.0001**
	CABG	70/16	82/18	**< 0.0001**
	THR	72/17	84/19	**< 0.0001**
	TKR	78/20	87/18	**< 0.0001**
Body Height (m^2)	**All**	162/8	174/9	**< 0.0001**
	CABG	160/9	173/8	**< 0.0001**
	THR	162/9	175/10	**< 0.0001**
	TKR	162/7	174/8	**< 0.0001**
BSA (m^2)	**All**	1.79/0.23	1.99/0.23	**< 0.0001**
	CABG	1.74/0.22	1.96/0.22	**< 0.0001**
	THR	1.77/0.22	1.99/0.25	**< 0.0001**
	TKR	1.82/0.23	2.02/0.24	**< 0.0001**
ASA Score	**All**	2/1	3/1	**< 0.0001**
	CABG	3/0	3/0	0.2332
	THR	2/1	2/1	0.7003
	TKR	2/1	2/1	0.9099
Euro Score	**CABG**	5/4	4/3	**< 0.0001**
Preop. Anemia (number yes (%))	**All**	629 (18.2)	582 (19.0)	0.3859
	CABG	106 (30.3)	270 (23.7)	0.0126
	THR	243 (17.1)	173 (15.1)	0.1780
	TKR	280 (16.6)	139 (17.9)	0.4212
Platelet Inhibitors (preop.) (number yes (%))	**All**	332 (9.6)	730 (23.8)	**< 0.0001**
	CABG	159 (45.4)	567 (49.7)	0.1626
	THR	70 (4.9)	87 (7.6)	**0.0049**
	TKR	103 (6.1)	76 (9.8)	**0.0011**
Regional anesthesia (number yes (%))	**All**	1777 (51.3)	1140 (37.2)	**< 0.0001**
	THR	777 (54,6)	649 (56,6)	0.2946
	TKR	1000 (59,1)	490 (63,0)	0.0696
Minimal invasive surgery (number yes (%))	**All**	59 (1.70)	71 (2.32)	0.0764
	CABG	2 (0.57)	14 (1,23)	0.2977
	THR	56 (3,93)	56 (4,89)	0.2390
	TKR	1 (0,06)	1 (0,13)	0.5734
Duration of Surgery (min)	**All**	80/45	105/122	**< 0.0001**
	CABG	216/92	220 /97	0.4573
	THR	70/32	72 /30	**0.0012**
	TKR	84 /39	90 /46	**< 0.0001**
Duration of extracorporeal Circulation (min)	**CABG**	88/39	90/44	0.458
Use of aprotinin or tranexamic acid† (number yes (%))	**CABG**	336 (96)	1103 (96.7)	0.5503
Use of Cell Saver (number yes (%))	**All**	1694 (48.9)	1478 (48.2)	0.5904
	CABG	152 (43.4)	504 (44.2)	0.8064
	THR	750 (52.7)	589 (51.4)	0.5210
	TKR	792 (46.8)	385 (49.5)	0.2207
Length of stay (days)	**All**	12/4	11 /4	**< 0.0001**
	CABG	10 /6	10 /5	0.1753
	THR	12 /4	11 /3	**< 0.0001**
	TKR	12 /3	12 /4	**0.0015**

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables.
The percentages are calculated based on the total applicable population for each variable.
Presented p values correspond to Man-Whitney U test, or Chi^2 test, respectively.
† Aprotinin was used in the first study and tranexamic acid was used in the second study only.

Table 3 Transfusion related variables (all patients) Values are presented as median/IQR for measured values and frequencies (%) for categorical variables. The percentages are calculated as the fraction of the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	men	p value	women	men	p value
Hb preop (g/L)	All	131/16	143/18	**< 0.0001**	109/13.3	110/13.8	0.1424
	CABG	127/17	141/20	**< 0.0001**	105.83/14.17	108.46/15.38	**< 0.0001**
	THR	131/16	144/16	**< 0.0001**	109.17/13.33	110.77/12.31	**0.0004**
	TKR	132/16	143/18	**< 0.0001**	110.00/13.33	110.00/13.85	0.8485
Hb POD5 (g/L)	All	100/15	105/1.8	**< 0.0001**	83.3/12.5	80.8/13.8	**< 0.0001**
	CABG	104/17	106/1.8	0.2730	86.88/14.17	81.15/13.85	**< 0.0001**
	THR	100/15	105/1.7	**< 0.0001**	83.33/12.50	80.96/13.08	**< 0.0001**
	TKR	100/15	103/1.9	**< 0.0001**	83.33/12.71	79.23/14.62	**< 0.0001**
Hb nadir(g/L)	All	97/16	102/1.8	**< 0.0001**	80.8/13.3	78.5/13.8	**< 0.0001**
	CABG	98/17	99/16	0.0729	81.67/14.17	76.15/12.31	**< 0.0001**
	THR	97/15	105/19	**< 0.0001**	80.83/12.50	80.77/14.62	0.4955
	TKR	97/16	102/.0	**< 0.0001**	80.83/13.33	78.46/15.38	0.0024
RBC volume preop	All	1455/336	2007/428	**< 0.0001**	---	---	---
	CABG	1339/291	1950/415	**< 0.0001**	---	---	---
	THR	1435/319	2037/435	**< 0.0001**	---	---	---
	TKR	1494/343	2028/434	**< 0.0001**	---	---	---
RBC volume POD5	All	1127/267	1477/352	**< 0.0001**	76.6 /13.2	74.3 /13.0	**< 0.0001**
	CABG	1126/248	1468/346	**< 0.0001**	82.8 /16.0	75.4 /14.0	**< 0.0001**
	THR	1110/261	1487/353	**< 0.0001**	76.0/12.9	73.4 /12.5	**< 0.0001**
	TKR	1148/289	1477/366	**< 0.0001**	76.0/12.6	73.4 /13.4	**< 0.0001**
RBC volume lost	All	488/290	628/347	**< 0.0001**	32.1/21.3	30.7/17.2	**< 0.0001**
	CABG	619/465	655/438	0.3945	46.5/36.3	33.1/22.9	**< 0.0001**
	THR	479/277	620/311	**< 0.0001**	32.4/20.9	29.3/15.0	**< 0.0001**
	TKR	471/270	615/296	**< 0.0001**	30.2/18.2	29.9/14.5	0.1345
RBC units transfused (number yes (%))	All	1545 (44.6)	1011 (32.9)	**< 0.0001**	---	---	---
	CABG	283 (80.9)	554 (48.6)	**< 0.0001**	---	---	---
	THR	634 (44.5)	277 (24.2)	**< 0.0001**	---	---	---
	TKR	628 (37.1)	180 (23.1)	**< 0.0001**	---	---	---

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Table 4 Transfusion related variables (transfused patients only)

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables. The percentages are calculated based on the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	men	p value	women	men	p value
Hb preop (only transfused patients)	**All**	126/17	134/19	**< 0.0001**	105/14.2	103/14.6	**< 0.0001**
	CABG	124/17	135/20	**< 0.0001**	103/14.0	104/15.4	0.6925
	THR	126/17	135/17	**< 0.0001**	105/14.2	104/13.3	**0.0120**
	TKR	127/17	133/20	**< 0.0001**	106/14.2	102/15.4	**0.0003**
Hb POD5 (only transfused patients)	**All**	102/17	101/18	0.9279	85.0/14.2	77.7/13.7	**< 0.0001**
	CABG	105/17	102/18	0.0485	87.5/14.0	78.5/13.8	**< 0.0001**
	THR	101/16	101/.9	0.4562	84.2/13.3	77.7/14.6	**< 0.0001**
	TKR	101/16	100/17	0.4262	84.2/13.7	76.9/13.1	**< 0.0001**
Hb nadir (only transfused patients)	**All**	93/16	94/16	0.5446	77.5/13.3	72.3/12.3	**< 0.0001**
	CABG	97/18	94/14	0.0173	80.8/15.0	72.3/10.8	**< 0.0001**
	THR	93/15	93/18	0.4170	77.5/12.5	71.5/13.8	**< 0.0001**
	TKR	92/16	93/16	0.4918	76.7/13.3	71.5/12.3	**< 0.0001**
RBC volume preop (only transfused patients)	**All**	1370/290	1830/398	**< 0.0001**	---	---	---
	CABG	1320/256	1830/405	**< 0.0001**	---	---	---
	THR	1360/279	1830/409	**< 0.0001**	---	---	---
	TKR	1413/303	1850/414	**< 0.0001**	---	---	---
RBC volume POD5 (only transfused patients)	**All**	1110/256	1400/316	**< 0.0001**	80.9 /16	76.9 /15.7	**< 0.0001**
	CABG	1120/243	1410/314	**< 0.0001**	84.4/16.4	77.3/16.2	**< 0.0001**
	THR	1090/252	1390/347	**< 0.0001**	80.2/15.6	76.2/14.0	**< 0.0001**
	TKR	1120/262	1380/320	**< 0.0001**	79.6/15.4	77.6/16.5	**< 0.0001**
RBC volume lost (only transfused patients)	**All**	653/292	871/441	**< 0.0001**	47/18.9	47.4/20.7	0.9313
	CABG	703/415	882/498	**< 0.0001**	52.8/32.6	47.8/24.1	**0.0001**
	THR	635/280	863/389	**< 0.0001**	47.0/18.2	47.1/17.4	0.7359
	TKR	657/266	869/415	**< 0.0001**	45.9/15.8	45.6/18.2	0.7754
RBC volume transfused (only transfused patients)	**All**	363/133	365/284	**< 0.0001**	26.4/14.7	20.8/18.5	**< 0.0001**
	CABG	539/417	380/376	**0.0051**	40.0/36.3	22.3/22.9	**< 0.0001**
	THR	363/89.1	363/219	**0.0041**	26.3/12.2	20.1/11.4	**< 0.0001**
	TKR	363/72.8	363/144	**0.0226**	25.2/10.8	20.2/14.0	**< 0.0001**

Contributors: HG initiated and implemented both benchmark studies, designed data collection tools, and wrote and revised the paper. He is guarantor. GS wrote the statistical analysis plan, analysed the data and revised the drafted paper. SN cleaned and analysed the data. PK monitored data collection for both trials, drafted and revised the paper. AH implemented both benchmark studies and revised the drafted paper.

Conflict of interest None of the authores except AH has any conflict of interests
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Figure 1. Boxplots for absolute versus relative haemoglobin values. The significant gender difference in haemoglobin values (left) disappears by using relative values according the WHO guidelines[24] (right).

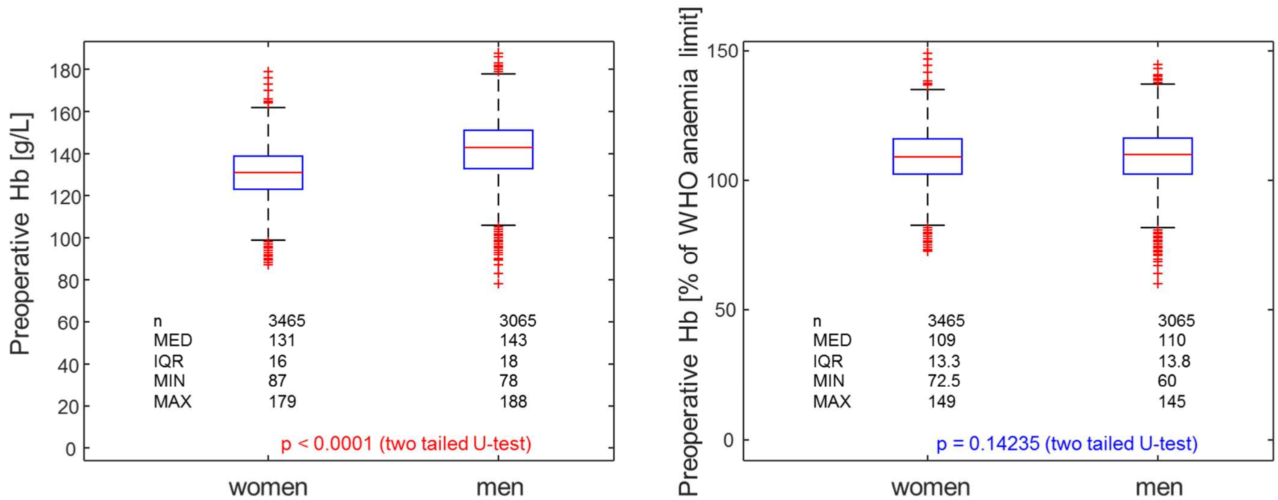


Figure 2: Boxplots for absolute and relative RBC volumes: lost (left) and transfused (right) for CABG (top), THR (middle), TKR (bottom) – women versus men **for transfused patients only**.

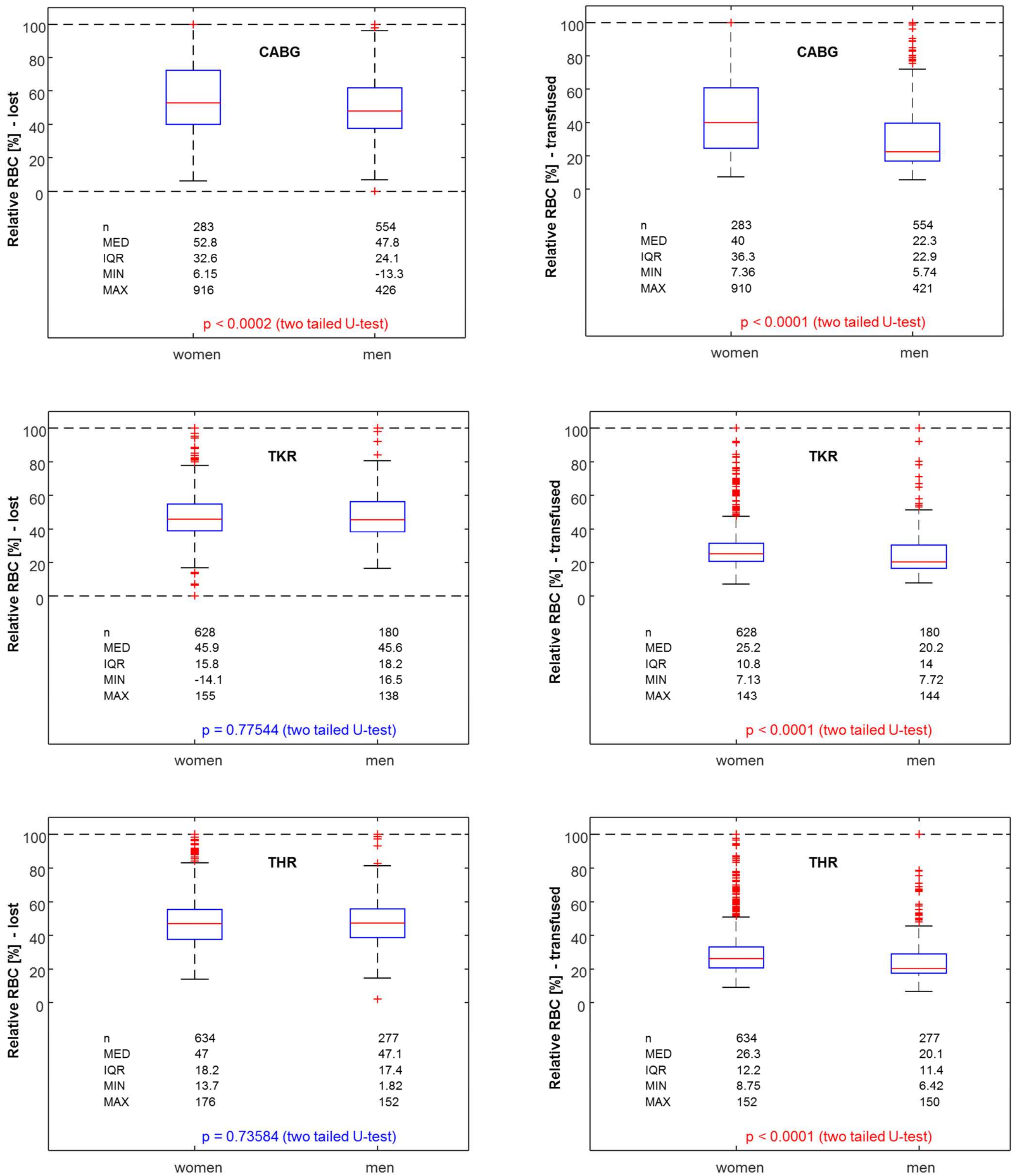


Figure 3. Type of surgery and percentage of all patients transfused

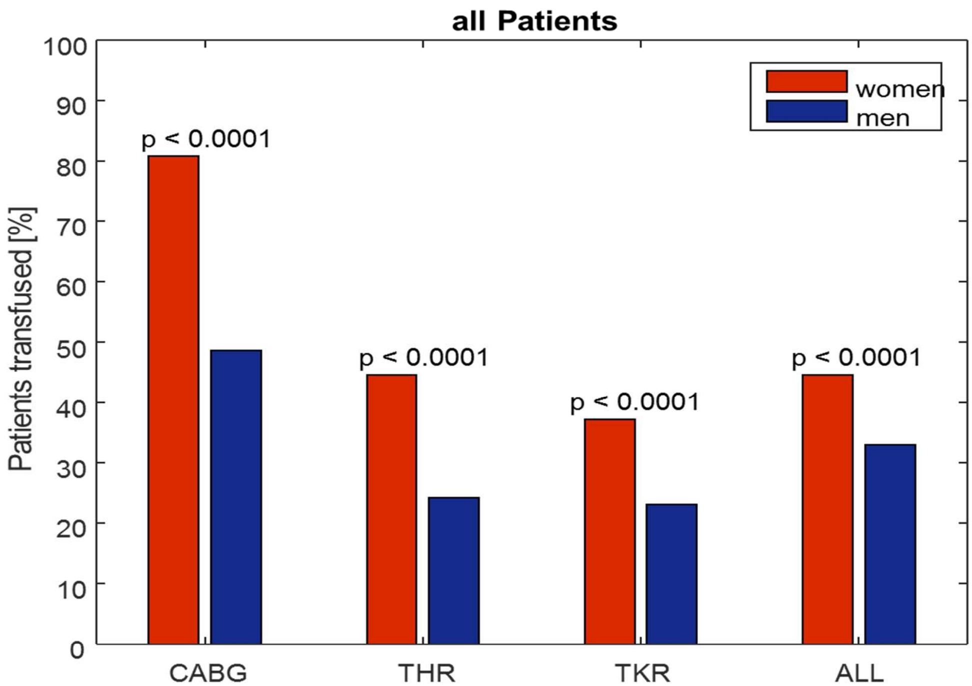


Figure 4 Percentage of patients receiving a given number of RBC units (indicating that women received one or two RBC units more often as men do, mostly at the expense of the percentage of patients who did not receive any transfusion.

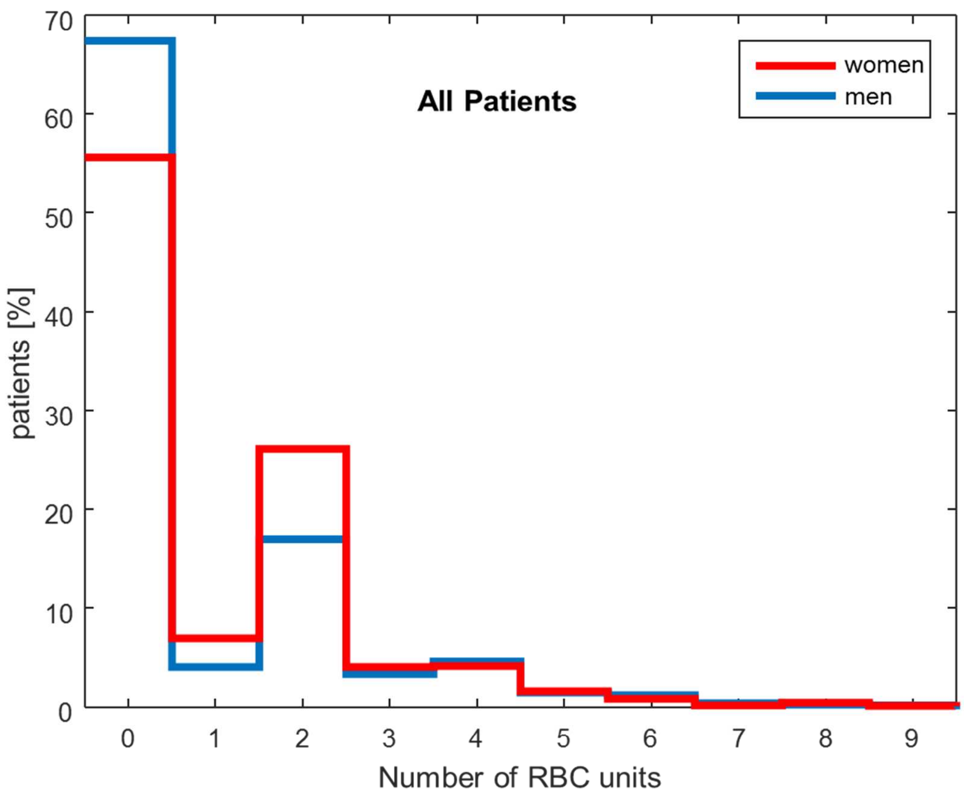
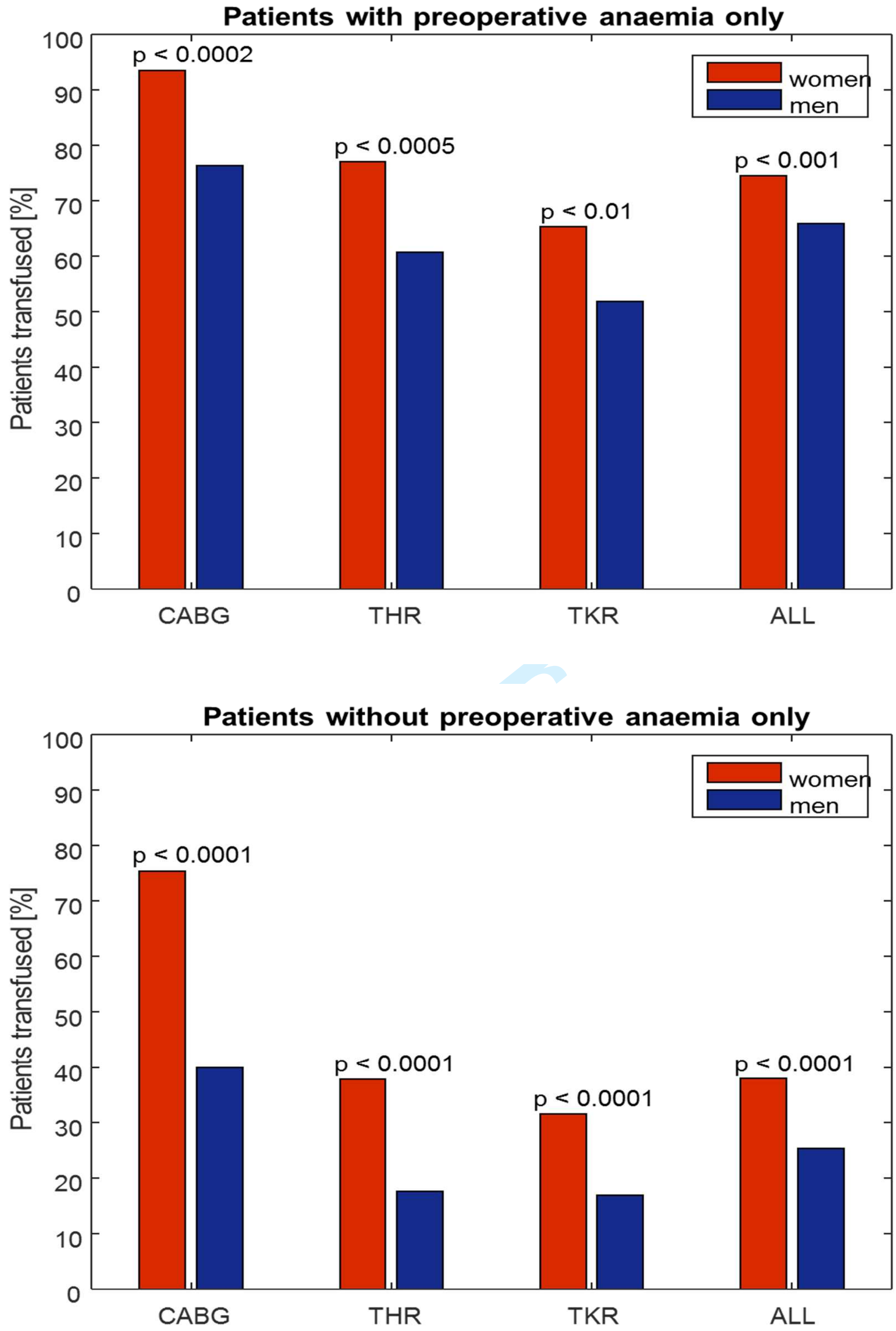


Figure 5: Transfusion rate in anemic (top) and non-anemic (bottom) patients.



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Gender Disparities in the Use of Blood Transfusion in Elective Surgery Warrant a Practice Change

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Abstract

Objectives: A post hoc gender comparison of transfusion-related modifiable risk factors among patients undergoing elective surgery.

Settings: 23 Austrian centres randomly selected and stratified by region and level of care.

Participants: We consecutively enrolled in total 6530 patients (3465 women and 3065 men); 1491 underwent coronary artery bypass graft (CABG) surgery, 2570 primary unilateral total hip replacement (THR), and 2469 primary unilateral total knee replacement (TKR).

Main outcome measures: Primary outcome measures were the number of allogeneic and autologous RBC units transfused (postoperative day 5 included) and differences in intra- and postoperative transfusion rate between men and women. Secondary outcomes included perioperative blood loss in transfused and non-transfused patients, volume of RBCs transfused, perioperative haemoglobin values and circulating red blood volume on postoperative day 5.

Results: In all surgical groups, the transfusion rate was significantly higher in women than in men (CABG 81 vs. 49%, THR 46 vs. 24%, TKR 37 vs. 23%). In *transfused* patients, the absolute blood loss was higher among men in all surgical categories while the relative blood loss was higher among women in the CABG group (52.8 vs. 47.8%) but comparable in orthopaedic surgery. The relative RBC volume transfused was significantly higher among women in all categories (CABG 40.0 vs. 22.3; TKR 25.2 vs. 20.2; THR 26.4 vs. 20.8%). On postoperative day 5 the relative haemoglobin values and the relative circulating RBC volume were higher in women in all surgical categories.

Conclusions: The higher transfusion rate and volume in women as compared with men in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender. This, together with the common use of a liberal transfusion strategy leads to further over-transfusion in women.

Trial registration: Ethical approval: Ethikkomission des Landes Oberösterreich, 15 July 2009

Data sharing statement: No additional data are available

Strengths and limitations of this study

It is a post hoc analysis using prospectively collected data from two similar and consecutive benchmark studies including 6530 patients undergoing elective surgery in 23 centres.

The main focus was the gender differences of the transfusion-related modifiable risk factors: anaemia, blood loss and transfusion (triad of adverse outcome).

Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values enabled a fair gender comparison with baseline differences between men and women being eliminated.

Perioperative blood loss including the so-called hidden blood loss and RBC volume transfused were precisely calculated.

Due to the observational character of the two benchmark studies only routine parameters could be collected. As a consequence, several aspects of interest such as the causes of preoperative anaemia, cardiac co-morbidities and data on transfusion outcomes could not be investigated.

Introduction

Women tend to live longer than men but typically experience more stress, poorer health, and more years with disabilities along the way [1 2]. Furthermore, in clinical decision-making and therapeutic interventions gender disparities are common. Women are less likely to receive coronary angiography and coronary interventions [3-5], implantable cardioverter defibrillators [6], dialysis and renal transplants [7 8], or arthroplasties [9]. Also, after surgical treatment, women have a higher risk for adverse outcomes and death, which may be at least partially attributable to a higher allogeneic transfusion rate [9-13].

It is a matter of fact that women have a higher bleeding tendency [14 15] and are more likely to be transfused than men [11-13 16-21]. The latter phenomenon, together with the occurrence of perioperative blood loss and anaemia, may worsen their postoperative outcome. However, in contrast to other preoperative risk factors, these factors can be mitigated by adequate and timely prevention and treatment.

In the last years, the modern concept of patient blood management has been developed by international experts and implemented worldwide [22 23]. Its aim is to manage and preserve a patient's own blood by reducing the above mentioned transfusion related risk factors – anaemia, blood loss, and red blood cell (RBC) transfusion – with the ultimate goal of improving the patient's outcome and safety [24]. Therefor, identifying the underlying causes of the higher RBC transfusion rate in women and – as a consequence - to enable adequate and timely prevention and treatment might be of critical importance.

The aim of our study was a gender comparison in patients undergoing elective surgery with special attention to differences in transfusion-related modifiable risk factors for an adverse outcome [24].

Methods

The present analysis included data from patients enrolled in two Austrian benchmark studies on blood use in elective surgery [20 21]. Both studies were prospective, observational multicentre studies with 23 participating centres, which were randomly selected and stratified by region and level of care. The study design, selection and recruitment of the centres, patient selection, data collection, quality management, and first-line data analysis were similar in the two studies. The first study was conducted from April 2004 through February 2005, the second study from July 2009 through August 2010.

In the two studies, we collected data from patients undergoing primary unilateral cemented or non-cemented total hip replacement (THR), primary unilateral non-cemented total knee replacement (TKR), or coronary artery bypass graft (CABG) surgery. Based on the Austrian Data Protection Commission's review, informed consent from individual patients was not necessary because only de-identified data were collected and complete patient confidentiality was maintained. After obtaining approval from the local ethics committee (Ethikkomission des Landes Oberösterreich, 15 July 2009), we consecutively enrolled all eligible patients aged 18 years or older. Our exclusion criteria were: any other concomitant surgery, emergency surgery, and an underlying coagulopathy documented by a history of bleeding and/or laboratory testing (international normalized ratio >1.5 or activated partial thromboplastin time >35 seconds).

Primary outcome measures were the number of intra- postoperatively allogeneic and autologous RBC units transfused and differences in transfusion rate between men and women (until postoperative day 5). Secondary outcomes included perioperative blood loss in transfused and non-transfused patients, volume of RBCs transfused, perioperative haemoglobin values and circulating red blood volume on postoperative day 5.

We collected the following demographic and clinical data from the hospital records: patient age, body weight and height, preoperative use of platelet inhibitors or anticoagulants, type of anaesthesia, duration of surgery, use of a cell saver, and length of hospital stay. In addition, we obtained routinely measured perioperative haemoglobin and haematocrit values and the number of RBC concentrates transfused. To account for gender differences, we presented the haemoglobin values as percentages of the anaemia cut-off values given by the World Health Organization (Figure 1). Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values (WHO; women 120 g/L, men 130 g/L)[25] enabled a fair gender comparison with baseline differences between men and women being eliminated.

The body surface area was calculated using the Du Bois formula [26]. The Nadler et al. formula was used to calculate the patients' blood volume [27]. The total RBC volume was derived by multiplying the calculated blood volume with the corresponding haematocrit level. A factor of 0.91 was applied to correct the haematocrit value for peripheral blood sampling [28]. The overall perioperative RBC loss was calculated by subtracting the RBC volume on postoperative day 5 from the preoperative RBC volume and by adding the total RBC volume transfused. Differences in the average haematocrit (range 56–65%) and volume (range 250–316.7 mL) of RBC units from different blood banks were accounted for by multiplying the volume by the mean haematocrit of the respective unit. To calculate the salvaged, washed, and returned RBC volume during cell saver use, we assumed a haematocrit level of 60% [29]. To adjust for baseline differences in the total RBC volume, the lost and transfused RBC volumes were analysed as percentages of the patient's total circulating baseline RBC volume (relative RBC volume).

We provided a Web-based electronic data capture system for data acquisition with a training program included. During the initiation visit, the study physicians—mainly members of anaesthesia departments—received special training on the system. Data were recorded directly into the study database. The system provided login names and passwords dedicated for registration of patients, monitoring of recruiting progress, query management, and source data verification as well as an internal communication platform. Automatic data entry plausibility checks and mandatory data items enforced high data quality. On-site CRO monitoring on a regular basis (at least twice during the study period per centre) was performed with special focus on continuity of enrolment and patient selection criteria [21].

Descriptive statistics for the data were presented as median and interquartile range, or absolute and relative frequencies (%). Differences between women and men were tested for statistical significance using the Mann–Whitney *U* test for continuous variables and the chi-square test for frequencies, respectively.

Multivariate analysis was already done in the two previous studies using logistic regression with RBC transfusion and multiple linear regression analysis with the relative volume of RBCs transfused (relative to the patient's estimated RBC volume) as the dependent variables. The independent variables included age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) physical status classification score, preoperative and lowest perioperative haemoglobin, type of anaesthesia, duration of surgery, usage of intraoperative cell salvage, infusion of washed versus unwashed shed blood, treatment with platelet (PLT) aggregation inhibitors and relative lost RBC volume. In CABG procedures, the number of bypasses, use of extracorporeal circulation, and use of tranexamic acid were additional independent variables. Given the nature of the study, no formal sample size estimation was deemed necessary [20 21]. In the current study, however, we conducted additional multivariate analyses on gender disparity and found only negligible differences.

We used Matlab, release 2015a (The MathWorks Inc, Natick, MA) for the statistical analysis. Box plots, bar charts, and line diagrams were used to present the data graphically. $p < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics and perioperative data

The present analysis included 6530 patients (3465 women and 3065 men) **(Table 1)**, with 1491 patients (350 women and 1141 men) undergoing CABG surgery, 2570 patients (1424 women and 1146 men) undergoing THR, and 2469 patients (1691 women and 778 men) undergoing TKR. **Table 2** gives an overview of the demographic characteristics and perioperative parameters. Men were younger (except for those undergoing TKR) and taller than women, and they had a higher body surface area and a higher body weight. There were no gender differences in the body mass index and the patients' overall health (American Society of Anesthesiologists score). Women in the CABG group also had a significantly higher surgical risk of death (euroSCORE) than men. Tranexamic acid was the main antifibrinolytic agent used in the second benchmark study, aprotinin the one used in the first benchmark study. The prevalence of anaemia was also similar in both genders with the exception of patients undergoing CABG surgery; in this subgroup, preoperative anaemia was more common among women than among men (prevalence in women, 30.3%; prevalence in men, 23.7%). In younger patients below the age of 60, anaemia was more common in women, whereas at ages 70 years and older, anaemia was more common in men.

Primary outcome variables

In all subgroups, the transfusion rate was significantly higher in women than in men (CABG 81% vs. 49%, THR 46% vs. 24%, TKR 37% vs. 23%) (Figure 2). Also women received one or two RBC units more often than men (Figure 3). Overall, the transfusion rates were significantly higher in patients with preoperative anaemia than in non-anaemic patients (total population: women 75% vs. 38%, men 66% vs. 25%; CABG: women 93.4% vs. 75.4%, men 76.3% vs. 40.0%; THR: women 77.0% vs. 37.8%, men 60.7% vs. 17.7%; TKR: women 65.4% vs. 31.5%, men 51.8% vs. 16.9%). Figure 4 (a-b) shows the percentages of the transfused patients for the different surgical interventions, both for patients with (top) and for those without (bottom) preoperative anaemia. Compared with the first study, the overall percentage of transfused patients and mean number of RBC units transfused in the second study decreased in THR and TKR, but remained relatively unchanged in CABG surgery. Among the patients who received transfusions, there was no difference in the RBC volume as well as the number of units transfused between the studies. Usage of pre-donation of autologous blood in CABG procedures was negligible in the first (0.5%) and second studies (0.4%), and there was a substantial decrease of usage of pre-donation in orthopaedic patients from the first to the second study (THR, 11% to 4%; TKR, 8%-3%, respectively) .

Secondary outcome variables

The absolute blood loss among patients undergoing CABG was comparable in both genders, and that among patients undergoing orthopaedic surgery was slightly lower in women than in men. By contrast, the relative blood loss among patients undergoing CABG surgery was considerably higher in women than in men; it was also slightly higher in women in the THR group, whereas it was similar in both genders in the TKR group. The absolute RBC volume transfused was higher in women than in men among patients undergoing CABG surgery and equal in both genders among orthopaedic patients, whereas the relative RBC volume transfused was twice as high in women compared with men in the CABG group, and it was also elevated in women undergoing orthopaedic surgery. On postoperative day 5 *absolute* circulating blood volumes were significantly higher in men whereas *relative* blood volume were significantly higher in women in all categories **(Table 3).**

In ***transfused*** patients, the absolute RBC loss was lower in women than in men in all surgical categories, but the relative RBC loss was higher in women than in men in CABG surgery (52.8% vs. 47.8%, $p < 0.0001$) and comparable in both genders in orthopaedic surgery. The absolute RBC volume transfused was slightly higher in men. However, the relative RBC volume transfused was significantly higher in women than in men (26.4% vs. 20.8%; $p < 0.0001$) **(Table 4)** (Figure 5 a-c). The absolute preoperative RBC volume was about 30% higher in men than in women and the RBC volume on postoperative day 5 was approximately 20% higher in men. On the other hand, on postoperative day 5 the relative RBC volumes were elevated (by about 5%) in women in all surgical subgroups when compared with men.

In transfused patients the absolute preoperative haemoglobin values were generally lower in women, relative haemoglobin values were comparable except for the in the TKR subgroup. The lowest measured haemoglobin (nadir haemoglobin) value was slightly lower in women than in men in orthopaedic surgery, whereas the relative values were higher in women than in men among those undergoing CABG surgery. On postoperative day 5, the absolute haemoglobin values were slightly higher in men (except for CABG patients). By comparison, the relative haemoglobin values on postoperative day 5 were elevated in women in all surgical categories **(Table 4).**

Predictors of Transfusion

Apart from female sex the relative lost RBC volume; relative preoperative haemoglobin and the lowest relative postoperative haemoglobin are strongest and independent predictors for RBC transfusion in all procedures **(Table 5).** Regional anaesthesia was a significant factor in THR, ASA score was significant in TKR, and BMI and PLT inhibitors were significant predictors for transfusion in CABG.

First vs. second study

Compared with the first study, in the second study the overall percentage of transfused patients and mean number of RBC units transfused decreased in THR and TKR, but remained relatively unchanged in CABG surgery. Among the patients who received transfusions, there was no difference in the RBC volume as well as the number of units transfused between the studies.

Transfusion rate in THR procedures decreased in seven centres while it increased in one centre compared with the first study. Eight centres had decreased transfusion rates in TKR. In CABG, transfusion rate significantly increased in one centre and decreased in another centre compared with the first study. Usage of pre-donation of autologous blood in CABG procedures was negligible in the first (0.5%) and second studies (0.4%), and there was a substantial decrease of usage of pre-donation in orthopaedic patients from the first to the second study (THR, 11% to 4%; TKR, 8%-3%, respectively) [20 21].

Discussion

The present study identified a higher transfusion rate in women compared with men in three surgical categories. Other findings of this study are:

1. Although the absolute perioperative blood loss was higher in men in all subgroups, the relative blood loss was comparable between the genders in orthopaedic surgery, and in the CABG subgroup it was higher in women.
2. Furthermore, the relative RBC volume transfused was significantly higher in women in all surgical categories, especially in CABG surgery.
3. This was accompanied by a higher relative nadir haemoglobin value and a higher haemoglobin value on postoperative day 5 in women.
4. In addition, the calculated relative postoperative RBC volume in women was approximately 5% higher than that in men across all surgical groups.

5. There was no gender difference in the overall prevalence of preoperative anaemia as defined by the gender-specific WHO cut-off values.

Anaemia, blood loss, and transfusion constitute a triad of risk factors for adverse patient outcomes [24 30-35]. Each of these three parameters represents a risk factor in itself and their combination may further potentiate the risk of an adverse outcome [36]. Within this triad, a vicious cycle is set in motion: blood loss and bleeding induce anaemia or exacerbate pre-existing anaemia. Anaemia triggers transfusion, and transfusion – besides having many other adverse effects – increases the risk of re-bleeding, potentially leading to additional blood loss, as shown in several studies [34 37-40]. The intention of breaking this vicious cycle by modifying these risk factors has led to the development of the concept of patient blood management, which is based on three pillars: optimization of the patient's endogenous RBC mass; minimization of diagnostic, interventional, and surgical blood loss; and optimization of the patient's tolerance of anaemia [22 41]. In most clinical scenarios, application of just the first two pillars is sufficient to address all three risks of the triad. Optimization of the RBC mass and the reduction of blood loss keep the haemoglobin levels of most patients above a level where transfusion might be considered. However, addition of the third pillar can further reduce transfusion rates [42].

With regard to the optimization of the patient's endogenous RBC mass (first pillar), women generally seem to be less susceptible to anaemia-induced adverse events than men. For example, in normal life, the lowest risk for mortality occurs at haemoglobin values between 130 and 150 g/L in women and between 140 and 170 g/L in men [43-46]. In a cohort of 6880 elderly patients without severe comorbidities, mild and moderate anaemia was significantly associated with a higher mortality in men but not in women [32 47]. In a recent publication focusing on non-emergent CABG surgery, a low haematocrit and blood transfusion were significant predictors for major morbidity in men, whereas in women blood transfusion was the only predictor of major morbidity [32]. In non-cardiac surgery, the mortality was higher in men than in women at similar haemoglobin levels.

The prevalence of preoperative anaemia in the present study was similar in both genders, so this factor cannot explain the higher transfusion rates in women. The fact that the prevalence of anaemia among women was similar to that among men might be attributable to the higher age of the patients included in the study [48], because the higher prevalence of low haemoglobin values observed in younger women disappears with increasing age. After the age of 75 years, men have in fact a higher prevalence of anaemia than women, with the prevalence among men being highest at age 85 years and older [49 50].

The observation that anaemia is associated with a poor prognosis in many disorders is not a sufficient reason to assume a cause-and-effect relationship. Anaemia of chronic disease in particular may be associated with an adaptive physiological response [51 52]. The treatment of mild to moderate anaemia of chronic disease may therefore not always bring the desired improvement or may even increase the mortality in some cases [53]. Nevertheless, optimization of the preoperative blood volume up to the WHO cut-off values should be an integral strategy to reduce the transfusion requirements in both genders [54 55].

The amount of perioperative blood loss (second pillar) depends on the surgical technique, the management of perioperative coagulation, and the blood conservation techniques used. The degree of acute blood loss that patients can safely tolerate is inversely related to their baseline haemoglobin concentration and the decrease of their RBC volume [56]. A decrease of at least 50% from the preoperative haemoglobin level during cardiac surgery is associated with adverse outcomes even if the absolute haemoglobin level remains above the commonly used transfusion threshold of 7.0 g/dL [57].

In the present study, the absolute blood loss was smaller among women than among men in all-surgical subgroups, but the relative perioperative blood loss was 5% higher among women than among men in the CABG subgroup and it was comparable between men and women in the orthopaedic surgery subgroups. The higher blood loss among women undergoing CABG surgery may be attributable to the extreme haemodilution associated with extracorporeal circulation. As women have a lower body mass index than men, their haemodilution during the operation is more profound, and women therefore tend to receive more transfusions during and after the CABG operation[18]. Nevertheless, the differences in blood loss alone cannot explain why the RBC volume transfused among women was twice that among men in the CABG group and 25% higher than that among men in the orthopaedic surgery groups (Table 4).

With regard to the tolerance of anaemia (third pillar), it is possible that the ability to compensate for low haemoglobin values differs by gender. Moreover, to our knowledge neither cut-off values nor transfusion guidelines exist for postmenopausal women [58 59]. Several authors have suggested that anaemia in women beyond menopause should be defined by a higher haemoglobin threshold, similar to that used for men [44 60 61]. Current transfusion guidelines revolve around absolute haemoglobin values and do not account for this phenomenon, nor do they consider the special needs of women in general [59 62-64]. In fact, in routine clinical practice similar transfusion triggers are applied in both genders[65].

The present study has several limitations. First, it is a post hoc analysis that uses data from two similar consecutive benchmark studies [20 21]. Second, because financial resources were limited, postoperative outcomes could not be studied. Third, because of the observational character of the two benchmark studies only routine parameters could be collected. Therefore, several aspects of interest such as the causes of preoperative anaemia could not be investigated.

A main strength of the study is the fact that the perioperative blood loss was calculated and the so-called hidden blood loss is therefore included in the analysis. Moreover, we compared not only absolute transfusion-related data but also relative values (in relation to the WHO cut-off values [25]). This enabled a fair gender comparison because baseline differences between men and women were eliminated.

The present findings—that women had a higher postoperative RBC volume in all surgical groups and higher intra- and postoperative haemoglobin levels, together with a higher relative RBC volume transfused—are clear indicators that the transfusion strategies applied in women were too liberal. These results could have a significant impact on blood utilisation levels and possibly lead to improvements in outcome and patient safety. Once clinicians are aware of the fact that women tend to be over-transfused, measures can be taken to address this matter. These include the correction of preoperative anaemia, the reduction of perioperative blood loss by optimizing the surgical technique, the reduction of the transfusion volume (e.g. by implementing a single-unit strategy), and the use of lower haemoglobin values as transfusion triggers. Such strategies may dramatically reduce the transfusion rate among women while improving outcome and patient safety.

Conclusion

The higher transfusion rate and volume in women, compared with men, in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender even though women have a lower baseline RBC volume. This, together with the common use of a liberal transfusion strategy in elective CABG and orthopaedic surgery despite the recommendations in relevant guidelines, leads to over-transfusion in women. Given the possibility to pre-empt transfusions through the treatment of modifiable risk factors by applying the patient blood management concept, a beneficial change in practice is warranted. Given the accumulating evidence on transfusion outcomes from meta-analyses of RCTs[66-69] comparing liberal vs. restrictive transfusion thresholds, a prospective RCT comparing gender-specific transfusion thresholds and targets with current standard of care is warranted.

Table 1 Patients included

Total = Study I + Study II	Women	Men	Sum
CABG	350 = 207 + 143	1141 = 570 + 571	1491 = 777 + 714
THR	1424 = 768 + 656	1146 = 579 + 567	2057 = 1347 + 1223
TKR	1691 = 891 + 800	778 = 351 + 427	2469 = 1242 + 1227
Sum	3465 = 1866 + 1599	3065 = 1500 + 1565	6530 = 3366 + 3164

Table 2: Demographic Data

		Women	Men	p value
Age	**All**	70/14	67/14	**< 0.0001**
	CABG	71/13	66/13	**< 0.0001**
	THR	69/15	66/15	**< 0.0001**
	TKR	71/12	70/12	0.0017
Body Weight (kg)	**All**	74/19	84/18	**< 0.0001**
	CABG	70/16	82/18	**< 0.0001**
	THR	72/17	84/19	**< 0.0001**
	TKR	78/20	87/18	**< 0.0001**
Body Height (m^2)	**All**	162/8	174/9	**< 0.0001**
	CABG	160/9	173/8	**< 0.0001**
	THR	162/9	175/10	**< 0.0001**
	TKR	162/7	174/8	**< 0.0001**
BSA (m^2)	**All**	1.79/0.23	1.99/0.23	**< 0.0001**
	CABG	1.74/0.22	1.96/0.22	**< 0.0001**
	THR	1.77/0.22	1.99/0.25	**< 0.0001**
	TKR	1.82/0.23	2.02/0.24	**< 0.0001**
ASA Score	**All**	2/1	3/1	**< 0.0001**
	CABG	3/0	3/0	0.2332
	THR	2/1	2/1	0.7003
	TKR	2/1	2/1	0.9099
Euro Score	**CABG**	5/4	4/3	**< 0.0001**
Preop. Anemia (number yes (%))	**All**	629 (18.2)	582 (19.0)	0.3859
	CABG	106 (30.3)	270 (23.7)	0.0126
	THR	243 (17.1)	173 (15.1)	0.1780
	TKR	280 (16.6)	139 (17.9)	0.4212
Platelet Inhibitors (preop.) (number yes (%))	**All**	332 (9.6)	730 (23.8)	**< 0.0001**
	CABG	159 (45.4)	567 (49.7)	0.1626
	THR	70 (4.9)	87 (7.6)	**0.0049**
	TKR	103 (6.1)	76 (9.8)	**0.0011**
Regional anesthesia (number yes (%))	**All**	1777 (51.3)	1140 (37.2)	**< 0.0001**
	THR	777 (54,6)	649 (56,6)	0.2946
	TKR	1000 (59,1)	490 (63,0)	0.0696
Minimal invasive surgery (number yes (%))	**All**	59 (1.70)	71 (2.32)	0.0764
	CABG	2 (0.57)	14 (1,23)	0.2977
	THR	56 (3,93)	56 (4,89)	0.2390
	TKR	1 (0,06)	1 (0,13)	0.5734
Duration of Surgery (min)	**All**	80/45	105/122	**< 0.0001**
	CABG	216/92	220 /97	0.4573
	THR	70/32	72 /30	**0.0012**
	TKR	84 /39	90 /46	**< 0.0001**
Duration of extracorporeal Circulation (min)	**CABG**	88/39	90/44	0.458
Use of aprotinin or tranexamic acid† (number yes (%))	**CABG**	336 (96)	1103 (96.7)	0.5503
Use of Cell Saver (number yes (%))	**All**	1694 (48.9)	1478 (48.2)	0.5904
	CABG	152 (43.4)	504 (44.2)	0.8064
	THR	750 (52.7)	589 (51.4)	0.5210
	TKR	792 (46.8)	385 (49.5)	0.2207
Length of stay (days)	**All**	12/4	11 /4	**< 0.0001**
	CABG	10 /6	10 /5	0.1753
	THR	12 /4	11 /3	**< 0.0001**
	TKR	12 /3	12 /4	**0.0015**

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables.
The percentages are calculated based on the total applicable population for each variable.
Presented p values correspond to Man-Whitney U test, or Chi^2 test, respectively.
† Aprotinin was used in the first study and tranexamic acid was used in the second study only.

Table 3 Transfusion related variables (all patients) Values are presented as median/IQR for measured values and frequencies (%) for categorical variables. The percentages are calculated as the fraction of the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	men	p value	women	men	p value
Hb preop (g/L)	All	131/16	143/18	< 0.0001	109/13.3	110/13.8	0.1424
	CABG	127/17	141/20	< 0.0001	105.83/14.17	108.46/15.38	< 0.0001
	THR	131/16	144/16	< 0.0001	109.17/13.33	110.77/12.31	0.0004
	TKR	132/16	143/18	< 0.0001	110.00/13.33	110.00/13.85	0.8485
Hb POD5 (g/L)	All	100/15	105/1.8	< 0.0001	83.3/12.5	80.8/13.8	< 0.0001
	CABG	104/17	106/1.8	0.2730	86.88/14.17	81.15/13.85	< 0.0001
	THR	100/15	105/1.7	< 0.0001	83.33/12.50	80.96/13.08	< 0.0001
	TKR	100/15	103/1.9	< 0.0001	83.33/12.71	79.23/14.62	< 0.0001
Hb nadir(g/L)	All	97/16	102/1.8	< 0.0001	80.8/13.3	78.5/13.8	< 0.0001
	CABG	98/17	99/16	0.0729	81.67/14.17	76.15/12.31	< 0.0001
	THR	97/15	105/19	< 0.0001	80.83/12.50	80.77/14.62	0.4955
	TKR	97/16	102/.0	< 0.0001	80.83/13.33	78.46/15.38	0.0024
RBC volume preop	All	1455/336	2007/428	< 0.0001	---	---	---
	CABG	1339/291	1950/415	< 0.0001	---	---	---
	THR	1435/319	2037/435	< 0.0001	---	---	---
	TKR	1494/343	2028/434	< 0.0001	---	---	---
RBC volume POD5	All	1127/267	1477/352	< 0.0001	76.6 /13.2	74.3 /13.0	< 0.0001
	CABG	1126/248	1468/346	< 0.0001	82.8 /16.0	75.4 /14.0	< 0.0001
	THR	1110/261	1487/353	< 0.0001	76.0/12.9	73.4 /12.5	< 0.0001
	TKR	1148/289	1477/366	< 0.0001	76.0/12.6	73.4 /13.4	< 0.0001
RBC volume lost	All	488/290	628/347	< 0.0001	32.1/21.3	30.7/17.2	< 0.0001
	CABG	619/465	655/438	0.3945	46.5/36.3	33.1/22.9	< 0.0001
	THR	479/277	620/311	< 0.0001	32.4/20.9	29.3/15.0	< 0.0001
	TKR	471/270	615/296	< 0.0001	30.2/18.2	29.9/14.5	0.1345
RBC units transfused (number yes (%))	All	1545 (44.6)	1011 (32.9)	< 0.0001	---	---	---
	CABG	283 (80.9)	554 (48.6)	< 0.0001	---	---	---
	THR	634 (44.5)	277 (24.2)	< 0.0001	---	---	---
	TKR	628 (37.1)	180 (23.1)	< 0.0001	---	---	---

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Table 4 Transfusion related variables (transfused patients only)

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables. The percentages are calculated based on the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	men	p value	women	men	p value
Hb preop (only transfused patients)	**All**	126/17	134/19	**< 0.0001**	105/14.2	103/14.6	**< 0.0001**
	CABG	124/17	135/20	**< 0.0001**	103/14.0	104/15.4	0.6925
	THR	126/17	135/17	**< 0.0001**	105/14.2	104/13.3	**0.0120**
	TKR	127/17	133/20	**< 0.0001**	106/14.2	102/15.4	**0.0003**
Hb POD5 (only transfused patients)	**All**	102/17	101/18	0.9279	85.0/14.2	77.7/13.7	**< 0.0001**
	CABG	105/17	102/18	0.0485	87.5/14.0	78.5/13.8	**< 0.0001**
	THR	101/16	101/.9	0.4562	84.2/13.3	77.7/14.6	**< 0.0001**
	TKR	101/16	100/17	0.4262	84.2/13.7	76.9/13.1	**< 0.0001**
Hb nadir (only transfused patients)	**All**	93/16	94/16	0.5446	77.5/13.3	72.3/12.3	**< 0.0001**
	CABG	97/18	94/14	0.0173	80.8/15.0	72.3/10.8	**< 0.0001**
	THR	93/15	93/18	0.4170	77.5/12.5	71.5/13.8	**< 0.0001**
	TKR	92/16	93/16	0.4918	76.7/13.3	71.5/12.3	**< 0.0001**
RBC volume preop (only transfused patients)	**All**	1370/290	1830/398	**< 0.0001**	---	---	---
	CABG	1320/256	1830/405	**< 0.0001**	---	---	---
	THR	1360/279	1830/409	**< 0.0001**	---	---	---
	TKR	1413/303	1850/414	**< 0.0001**	---	---	---
RBC volume POD5 (only transfused patients)	**All**	1110/256	1400/316	**< 0.0001**	80.9 /16	76.9 /15.7	**< 0.0001**
	CABG	1120/243	1410/314	**< 0.0001**	84.4/16.4	77.3/16.2	**< 0.0001**
	THR	1090/252	1390/347	**< 0.0001**	80.2/15.6	76.2/14.0	**< 0.0001**
	TKR	1120/262	1380/320	**< 0.0001**	79.6/15.4	77.6/16.5	**< 0.0001**
RBC volume lost (only transfused patients)	**All**	653/292	871/441	**< 0.0001**	47/18.9	47.4/20.7	0.9313
	CABG	703/415	882/498	**< 0.0001**	52.8/32.6	47.8/24.1	**0.0001**
	THR	635/280	863/389	**< 0.0001**	47.0/18.2	47.1/17.4	0.7359
	TKR	657/266	869/415	**< 0.0001**	45.9/15.8	45.6/18.2	0.7754
RBC volume transfused (only transfused patients)	**All**	363/133	365/284	**< 0.0001**	26.4/14.7	20.8/18.5	**< 0.0001**
	CABG	539/417	380/376	**0.0051**	40.0/36.3	22.3/22.9	**< 0.0001**
	THR	363/89.1	363/219	**0.0041**	26.3/12.2	20.1/11.4	**< 0.0001**
	TKR	363/72.8	363/144	**0.0226**	25.2/10.8	20.2/14.0	**< 0.0001**

Table 5 Predictors of transfusion

Independent predictors of RBC transfusions by gender

	CABG		THR		TKR	
Independent variable	**Regression coefficient**	**OR (95% CI)**	**Regression coefficient**	**OR (95% CI)**	**Regression coefficient**	**OR (95% CI)**
Women						
Preoperative Hb (%)*	- 0.304	0.74 (0.67-0.83)	– 0.304	0.74 (0.71–0.77)	– 0.279	0.76 .73–0.79)
Lowest postoperative Hb (%)*	0.197	1.22 (1.10-1.35)	0.194	1.22 (1.17–1.26)	0.209	1.23 .19–1.28)
Lost RBC volume (%)†	0.402	1.50 (1.30-1.71)	0.405	1.50 (1.42–1.58)	0.437	1.55 .47–1.63)
Cases correctly classified (%)		94.3 %		93.5		93.6
R squared		0.864		0.857		0.853
Men						
Preoperative Hb (%)*	- 0.225	0.80 (0.77-0.83)	– 0.248	0.78 (0.74–0.82)	– 0.248	0.78 .74–0.82)
Lowest postoperative Hb (%)*	0.153	1.17 (1.12-1.21)	0.154	1.17 (1.12–1.22)	0.154	1.17 .12–1.22)
Lost RBC volume (%)†	0.301	1.35 (1.30-1.41)	0.359	1.43 (1.34–1.53)	0.359	1.43 .34–1.53)
Cases correctly classified (%)		91.4 %		94.7		93.4
R squared		0.800		0.802		0.786

* Percentages of the anemia cutoff values given by the WHO (women 120 g/L; men 130 g/L).

Percentage of the preoperatively circulating RBC volume.

Only significant predictors are presented.

Contributors: HG initiated and implemented both benchmark studies, designed data collection tools, and wrote and revised the paper. He is guarantor. GS wrote the statistical analysis plan, analysed the data and revised the drafted paper. SN cleaned and analysed the data. PK monitored data collection for both trials, drafted and revised the paper. AH implemented both benchmark studies and revised the drafted paper.

Conflict of interest None of the authores except AH has any conflict of interests
A. H: Lectures for Vifor Pharma

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Legends

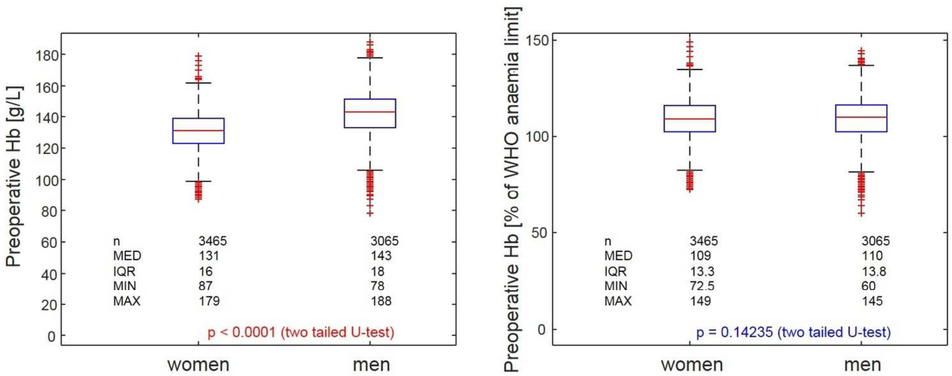
Figure 1. Boxplots for absolute versus relative haemoglobin values. The significant gender difference in haemoglobin values (left) disappears by using relative values according the WHO guidelines[25] (right).

Figure 2. Type of surgery and percentage of patients transfused

Figure 3 Percentage of patients receiving a given number of RBC units (indicating that women received one or two RBC units more often as men do, mostly at the expense of the percentage of patients who did not receive any transfusion.

Figure 4 (a-b): Transfusion rate in anemic (top) and non-anemic (bottom) patients.

Figure 5 a-c: Boxplots for absolute and relative RBC volumes: lost (left) and transfused (right) for CABG (top), THR (middle), TKR (bottom) – women versus men **for transfused patients only**.



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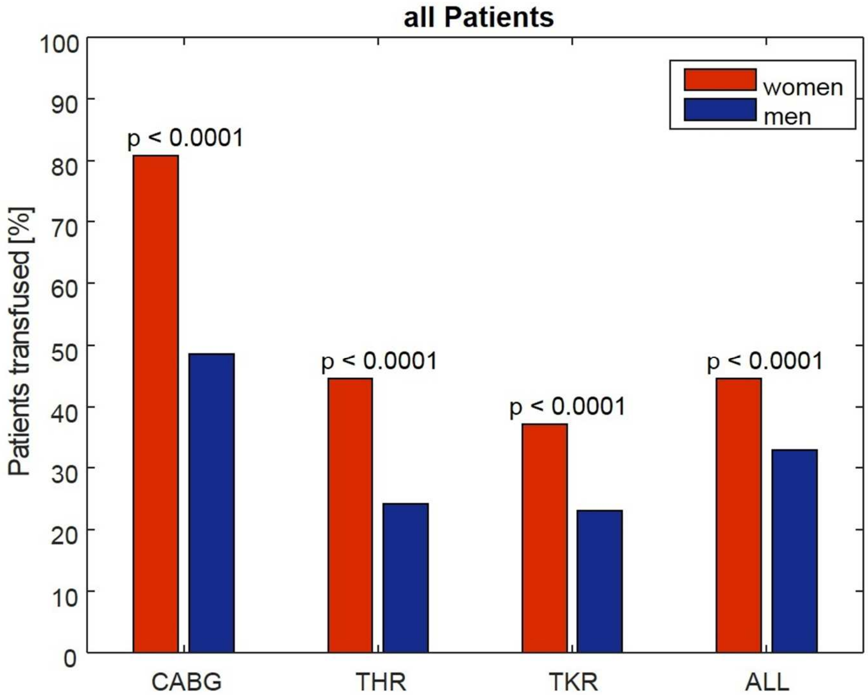

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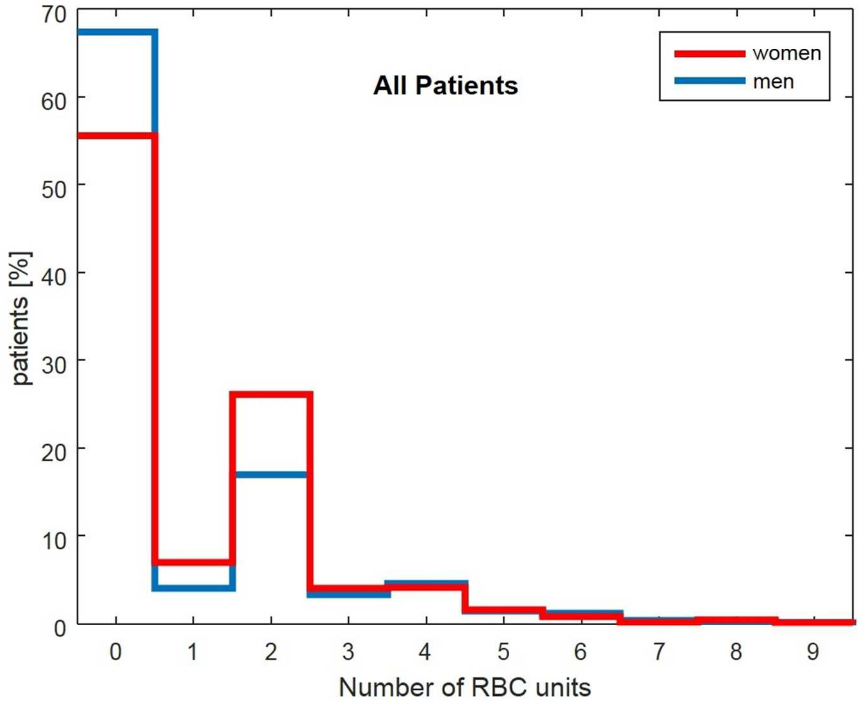

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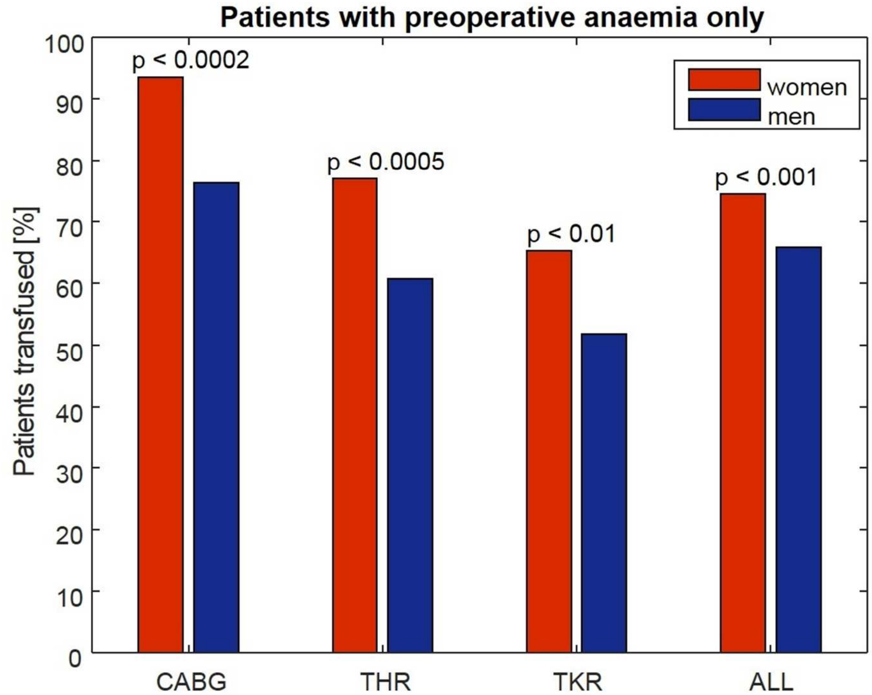

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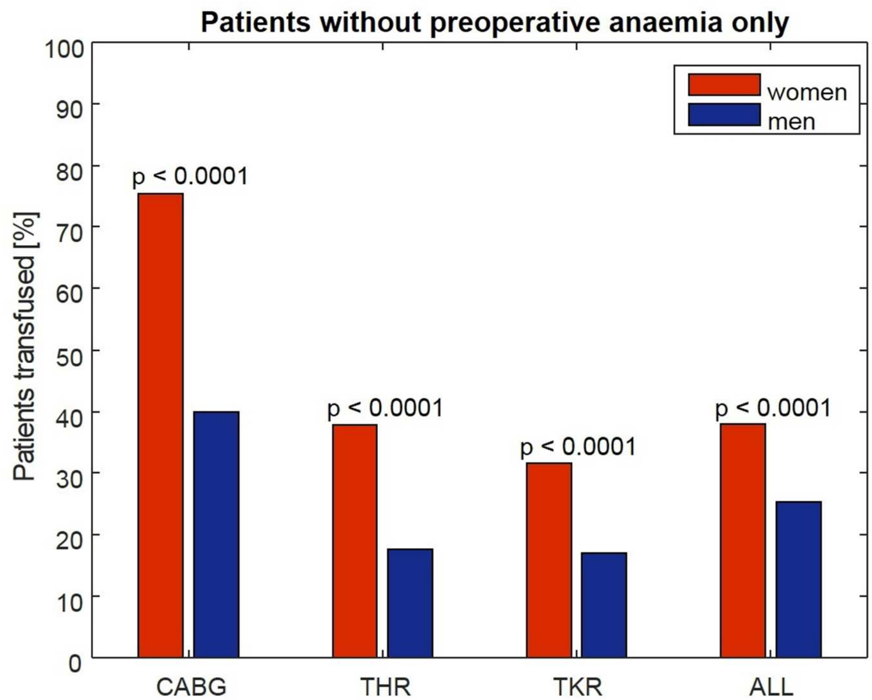

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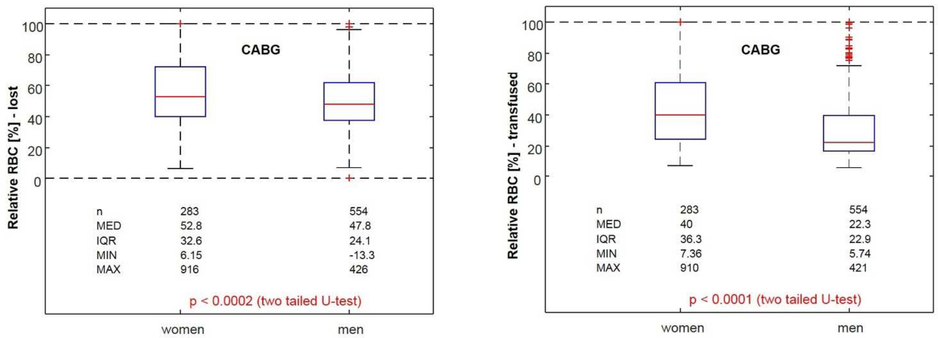

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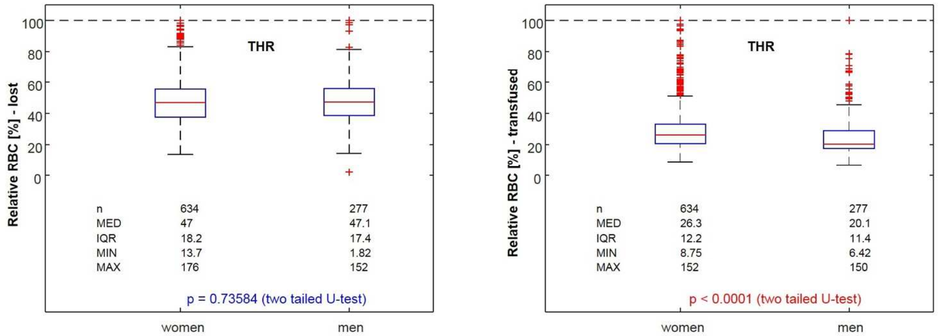

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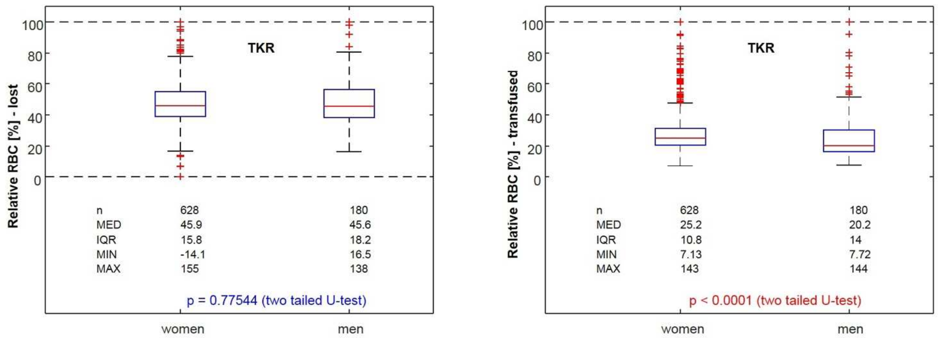

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STROBE Statement—checklist of items that should be included in reports of observational studies

Gender Disparities in the Use of Blood Transfusion in Elective Surgery. A Prospective Multicenter Cohort Study.

	Item No	Recommendation
Pg. Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4, pg 1 and 2**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4, pg 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, pg 3, Page 5, pg 2**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 5, pg 1**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 5, pg 2-4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 5 last pg, Page 6 1st pg**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 6, 1st pg**
Bias	9	Describe any efforts to address potential sources of bias **Page 6, 2nd pg**
Study size	10	Explain how the study size was arrived at **Page 5, 1st pg**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **page 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 6, pg 3,4, Page 7 pg1**
		(*b*) Describe any methods used to examine subgroups and interactions ---
		(*c*) Explain how missing data were addressed ---
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Table 2,3,4**
		(b) Give reasons for non-participation at each stage ---
		(c) Consider use of a flow diagram **Table 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest ---
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) no follow up
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 3,4,**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 9, last pg, Table 5**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ---
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 10,**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11 and 12**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based no fnding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Gender disparities in red blood cell transfusion in elective surgery. A post hoc multicenter cohort study.

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Gender disparities in red blood cell transfusion in elective surgery. A post hoc multicenter cohort study.

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Keywords: gender disparity, anaemia, blood loss, patient blood management, patient safety

Abstract

Objectives: A post hoc gender comparison of transfusion-related modifiable risk factors among patients undergoing elective surgery.

Settings: 23 Austrian centres randomly selected and stratified by region and level of care.

Participants: We consecutively enrolled in total 6530 patients (3465 women and 3065 men); 1491 underwent coronary artery bypass graft (CABG) surgery, 2570 primary unilateral total hip replacement (THR), and 2469 primary unilateral total knee replacement (TKR).

Main outcome measures: Primary outcome measures were the number of allogeneic and autologous RBC units transfused (postoperative day 5 included) and differences in intra- and postoperative transfusion rate between men and women. Secondary outcomes included perioperative blood loss in transfused and non-transfused patients, volume of RBCs transfused, perioperative haemoglobin values and circulating red blood volume on postoperative day 5.

Results: In all surgical groups, the transfusion rate was significantly higher in women than in men (CABG 81 vs. 49%, THR 46 vs. 24%, TKR 37 vs. 23%). In *transfused* patients, the absolute blood loss was higher among men in all surgical categories while the relative blood loss was higher among women in the CABG group (52.8 vs. 47.8%) but comparable in orthopaedic surgery. The relative RBC volume transfused was significantly higher among women in all categories (CABG 40.0 vs. 22.3; TKR 25.2 vs. 20.2; THR 26.4 vs. 20.8%). On postoperative day 5 the relative haemoglobin values and the relative circulating RBC volume were higher in women in all surgical categories.

Conclusions: The higher transfusion rate and volume in women as compared with men in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender. This, together with the common use of a liberal transfusion strategy leads to further over-transfusion in women.

Trial registration: Ethical approval: Ethikkomission des Landes Oberösterreich, 15 July 2009

Data sharing statement: No additional data are available

Strengths and limitations of this study

It is a post hoc analysis using prospectively collected data from two similar and consecutive benchmark studies including 6530 patients undergoing elective surgery in 23 centres.

The main focus was the gender differences of the transfusion-related modifiable risk factors: anaemia, blood loss and transfusion of red blood cells (triad of adverse outcome).

Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values enabled a fair gender comparison with baseline differences between men and women being eliminated.

Perioperative blood loss including the so-called hidden blood loss and RBC volume transfused were precisely calculated.

Due to the observational character of the two benchmark studies only routine parameters could be collected. As a consequence, several aspects of interest such as the causes of preoperative anaemia, cardiac co-morbidities and data on transfusion outcomes could not be investigated.

Introduction

Women tend to live longer than men but typically experience more stress, poorer health, and more years with disabilities along the way [1 2]. Furthermore, in clinical decision-making and therapeutic interventions gender disparities are common. Women are less likely to receive coronary angiography and coronary interventions [3-5], implantable cardioverter defibrillators [6], dialysis and renal transplants [7 8], or arthroplasties [9]. Also, after surgical treatment, women have a higher risk for adverse outcomes and death, which may be at least partially attributable to a higher allogeneic transfusion rate [9-13].

It is a matter of fact that women have a higher bleeding tendency [14 15] and are more likely to be transfused than men [11-13 16-21]. The latter phenomenon, together with the occurrence of perioperative blood loss and anaemia, may worsen their postoperative outcome. However, in contrast to other preoperative risk factors, these factors can be mitigated by adequate and timely prevention and treatment.

In the last years, the modern concept of patient blood management has been developed by international experts and implemented worldwide [22 23]. Its aim is to manage and preserve a patient's own blood by reducing the above mentioned transfusion related risk factors – anaemia, blood loss, and red blood cell (RBC) transfusion – with the ultimate goal of improving the patient's outcome and safety [24]. Therefor, identifying the underlying causes of the higher RBC transfusion rate in women and – as a consequence - to enable adequate and timely prevention and treatment might be of critical importance.

The aim of our study was a gender comparison in patients undergoing elective surgery with special attention to differences in transfusion-related modifiable risk factors for an adverse outcome [24].

Methods

The present analysis included data from patients enrolled in two Austrian benchmark studies on blood use in elective surgery [20 21]. Both studies were prospective, observational multicentre studies with 23 participating centres, which were randomly selected and stratified by region and level of care. The study design, selection and recruitment of the centres, patient selection, data collection, quality management, and first-line data analysis were similar in the two studies. The first study was conducted from April 2004 through February 2005, the second study from July 2009 through August 2010. The present post hoc analysis was conducted without funding (whereas the original two studies on which the post hoc analysis is based were exclusively funded by the Austrian Ministry of Health).

In the two studies, we collected data from patients undergoing primary unilateral cemented or non-cemented total hip replacement (THR), primary unilateral non-cemented total knee replacement (TKR), or coronary artery bypass graft (CABG) surgery. Based on the Austrian Data Protection Commission's review, informed consent from individual patients was not necessary because only de-identified data were collected and complete patient confidentiality was maintained. After obtaining approval from the local ethics committee (Ethikkomission des Landes Oberösterreich, 15 July 2009), we consecutively enrolled all eligible patients aged 18 years or older. Our exclusion criteria were: any other concomitant surgery, emergency surgery, and an underlying coagulopathy documented by a history of bleeding and/or laboratory testing (international normalized ratio >1.5 or activated partial thromboplastin time >35 seconds).

Primary outcome measures were the number of intra- and postoperatively allogeneic and autologous RBC units transfused and differences in transfusion rate between men and women (until postoperative day 5). Secondary outcomes included perioperative blood loss in transfused and non-transfused patients, volume of RBCs transfused, perioperative haemoglobin values and circulating red blood volume on postoperative day 5.

We collected the following demographic and clinical data from the hospital records: patient age, body weight and height, preoperative use of platelet inhibitors or anticoagulants, type of anaesthesia, duration of surgery, use of a cell saver, and length of hospital stay. In addition, we obtained routinely measured perioperative haemoglobin and haematocrit values and the number of RBC concentrates transfused. To account for gender differences, we presented the haemoglobin values as percentages of the anaemia cut-off values given by the World Health Organization (Figure 1). Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values (WHO; women 120 g/L, men 130 g/L)[25] enabled a fair gender comparison with baseline differences between men and women being eliminated.

The body surface area was calculated using the Du Bois formula [26]. The Nadler et al. formula was used to calculate the patients' blood volume [27]. The total RBC volume was derived by multiplying the calculated blood volume with the corresponding haematocrit level. A factor of 0.91 was applied to correct the haematocrit value for peripheral blood sampling [28]. The overall perioperative RBC loss was calculated by subtracting the RBC volume on postoperative day 5 from the preoperative RBC volume and by adding the total RBC volume transfused. Differences in the average haematocrit (range 56–65%) and volume (range 250–316.7 mL) of RBC units from different blood banks were accounted for by multiplying the volume by the mean haematocrit of the respective unit. To calculate the salvaged, washed, and returned RBC volume during cell saver use, we assumed a haematocrit level of 60% [29]. To adjust for baseline differences in the total RBC volume, the lost and transfused RBC volumes were analysed as percentages of the patient's total circulating baseline RBC volume (relative RBC volume).

We provided a Web-based electronic data capture system for data acquisition with a training program included. During the initiation visit, the study physicians—mainly members of anaesthesia departments—received special training on the system. Data were recorded directly into the study database. The system provided login names and passwords dedicated for registration of patients, monitoring of recruiting progress, query management, and source data verification as well as an internal communication platform. Automatic data entry plausibility checks and mandatory data items enforced high data quality and completeness. On-site CRO monitoring on a regular basis (at least twice during the study period per centre) was performed with special focus on continuity of enrolment and patient selection criteria [21].

Descriptive statistics for the data were presented as median and interquartile range, or absolute and relative frequencies (%). Differences between women and men were tested for statistical significance using the Mann–Whitney *U* test for continuous variables and the chi-square test for frequencies, respectively.

Multivariate analysis was already done in the two previous studies using logistic regression with RBC transfusion and multiple linear regression analysis with the relative volume of RBCs transfused (relative to the patient's estimated RBC volume) as the dependent variables. The independent variables included age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) physical status classification score, preoperative and lowest perioperative haemoglobin, type of anaesthesia, duration of surgery, usage of intraoperative cell salvage, infusion of washed versus unwashed shed blood, treatment with platelet (PLT) aggregation inhibitors and relative lost RBC volume. In CABG procedures, the number of bypasses, use of extracorporeal circulation, and use of tranexamic acid were additional independent variables. Given the nature of the study, no formal sample size estimation was deemed necessary [20 21]. In the current study, however, we conducted additional multivariate analyses on gender disparity and found only negligible differences.

We used Matlab, release 2015a (The MathWorks Inc, Natick, MA) for the statistical analysis. Box plots, bar charts, and line diagrams were used to present the data graphically. $p < 0.05$ was considered to indicate statistical significance.

Minimizing the risk of bias

Participating centers were randomly selected and stratified according to region and level of care. Patients in each center were enrolled consecutively. To ensure correct enrollment and adherence to patient selection criteria, onsite monitoring was regularly performed (twice per center). During the initiation visit, the study physicians—mainly members of anaesthesia departments—received special training on the remote data entry system. Data were recorded directly into the study database.

Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values enabled a fair gender comparison with baseline differences between men and women being eliminated. Differences in the average haematocrit and volume of RBC units from different blood banks were accounted for by multiplying the volume by the mean haematocrit of the respective blood bank.

Results

Patient characteristics and perioperative data

The present analysis included 6530 patients (3465 women and 3065 men) **(Table 1)**, with 1491 patients (350 women and 1141 men) undergoing CABG surgery, 2570 patients (1424 women and 1146 men) undergoing THR, and 2469 patients (1691 women and 778 men) undergoing TKR. **Table 2** gives an overview of the demographic characteristics and perioperative parameters. Men were younger (except for those undergoing TKR) and taller than women, and they had a higher body surface area and a higher body weight. There were no gender differences in the body mass index and the patients' overall health (American Society of Anesthesiologists score). Women in the CABG group also had a significantly higher surgical risk of death (euroSCORE) than men. Tranexamic acid was the main antifibrinolytic agent used in the second benchmark study, aprotinin the one used in the first benchmark study. The prevalence of anaemia was also similar in both genders with the exception of patients undergoing CABG surgery; in this subgroup, preoperative anaemia was more common among women than among men (prevalence in women, 30.3%; prevalence in men, 23.7%). In younger patients below the age of 60, anaemia was more common in women, whereas at ages 70 years and older, anaemia was more common in men.

Primary outcome variables

In all subgroups, the transfusion rate was significantly higher in women than in men (CABG 81% vs. 49%, THR 46% vs. 24%, TKR 37% vs. 23%) (Figure 2). Also women received one or two RBC units more often than men (Figure 3). Overall, the transfusion rates were significantly higher in patients with preoperative anaemia than in non-anaemic patients (total population: women 75% vs. 38%, men 66% vs. 25%; CABG: women 93.4% vs. 75.4%, men 76.3% vs. 40.0%; THR: women 77.0% vs. 37.8%, men 60.7% vs. 17.7%; TKR: women 65.4% vs. 31.5%, men 51.8% vs. 16.9%). Figure 4 (a-b) shows the percentages of the transfused patients for the different surgical interventions, both for patients with (top) and for those without (bottom) preoperative anaemia. Compared with the first study, the overall percentage of transfused patients and mean number of RBC units transfused in the second study decreased in THR and TKR, but remained relatively unchanged in CABG surgery. Among the patients who received transfusions, there was no difference in the RBC volume as well as the number of units transfused between the studies. Usage of pre-donation of autologous blood in CABG procedures was negligible in the first (0.5%) and second studies (0.4%), and there was a substantial decrease of usage of pre-donation in orthopaedic patients from the first to the second study (THR, 11% to 4%; TKR, 8%-3%, respectively) .

Secondary outcome variables

The absolute blood loss among patients undergoing CABG was comparable in both genders, and that among patients undergoing orthopaedic surgery was slightly lower in women than in men. By contrast, the relative blood loss among patients undergoing CABG surgery was considerably higher in women than in men; it was also slightly higher in women in the THR group, whereas it was similar in both genders in the TKR group. The absolute RBC volume transfused was higher in women than in men among patients undergoing CABG surgery and equal in both genders among orthopaedic patients, whereas the relative RBC volume transfused was twice as high in women compared with men in the CABG group, and it was also elevated in women undergoing orthopaedic surgery. On postoperative day 5 *absolute* circulating blood volumes were significantly higher in men whereas *relative* blood volume were significantly higher in women in all categories **(Table 3).**

In ***transfused*** patients, the absolute RBC loss was lower in women than in men in all surgical categories, but the relative RBC loss was higher in women than in men in CABG surgery (52.8% vs. 47.8%, $p < 0.0001$) and comparable in both genders in orthopaedic surgery. The absolute RBC volume transfused was slightly higher in men. However, the relative RBC volume transfused was significantly higher in women than in men (26.4% vs. 20.8%; $p < 0.0001$) **(Table 4)** (Figure 5 a-c). The absolute preoperative RBC volume was about 30% higher in men than in women and the RBC volume on postoperative day 5 was approximately 20% higher in men. On the other hand, on postoperative day 5 the relative RBC volumes were elevated (by about 5%) in women in all surgical subgroups when compared with men.

In transfused patients the absolute preoperative haemoglobin values were generally lower in women, relative haemoglobin values were comparable except for the in the TKR subgroup. The lowest measured haemoglobin (nadir haemoglobin) value was slightly lower in women than in men in orthopaedic surgery, whereas the relative values were higher in women than in men among those undergoing CABG surgery. On postoperative day 5, the absolute haemoglobin values were slightly higher in men (except for CABG patients). By comparison, the relative haemoglobin values on postoperative day 5 were elevated in women in all surgical categories **(Table 4).**

Predictors of Transfusion

Apart from female sex the relative lost RBC volume; relative preoperative haemoglobin and the lowest relative postoperative haemoglobin are strongest and independent predictors for RBC transfusion in all procedures **(Table 5).** Regional anaesthesia was a significant factor in THR, ASA score was significant in TKR, and BMI and PLT inhibitors were significant predictors for transfusion in CABG.

First vs. second study

Compared with the first study, in the second study the overall percentage of transfused patients and mean number of RBC units transfused decreased in THR and TKR, but remained relatively unchanged in CABG surgery. Among the patients who received transfusions, there was no difference in the RBC volume as well as the number of units transfused between the studies.

Transfusion rate in THR procedures decreased in seven centres while it increased in one centre compared with the first study. Eight centres had decreased transfusion rates in TKR. In CABG, transfusion rate significantly increased in one centre and decreased in another centre compared with the first study. Usage of pre-donation of autologous blood in CABG procedures was negligible in the first (0.5%) and second studies (0.4%), and there was a substantial decrease of usage of pre-donation in orthopaedic patients from the first to the second study (THR, 11% to 4%; TKR, 8%-3%, respectively) [20 21].

Discussion

The present study identified a higher transfusion rate in women compared with men in three surgical categories. Other findings of this study are:

1. Although the absolute perioperative blood loss was higher in men in all subgroups, the relative blood loss was comparable between the genders in orthopaedic surgery, and in the CABG subgroup it was higher in women.
2. Furthermore, the relative RBC volume transfused was significantly higher in women in all surgical categories, especially in CABG surgery.
3. This was accompanied by a higher relative nadir haemoglobin value and a higher haemoglobin value on postoperative day 5 in women.
4. In addition, the calculated relative postoperative RBC volume in women was approximately 5% higher than that in men across all surgical groups.
5. There was no gender difference in the overall prevalence of preoperative anaemia as defined by the gender-specific WHO cut-off values.

Anaemia, blood loss, and transfusion of red blood cells constitute a triad of risk factors for adverse patient outcomes [24 30-35]. Each of these three parameters represents a risk factor in itself and their combination may further potentiate the risk of an adverse outcome [36]. Within this triad, a vicious cycle is set in motion: blood loss and bleeding induce anaemia or exacerbate pre-existing anaemia. Anaemia triggers transfusion, and transfusion – besides having many other adverse effects – increases the risk of re-bleeding, potentially leading to additional blood loss, as shown in several studies [34 37-40]. The intention of breaking this vicious cycle by modifying these risk factors has led to the development of the concept of patient blood management, which is based on three pillars: optimization of the patient's endogenous RBC mass; minimization of diagnostic, interventional, and surgical blood loss; and optimization of the patient's tolerance of anaemia [22 41]. In most clinical scenarios, application of just the first two pillars is sufficient to address all three risks of the triad. Optimization of the RBC mass and the reduction of blood loss keep the haemoglobin levels of most patients above a level where transfusion might be considered. However, addition of the third pillar can further reduce transfusion rates [42].

With regard to the optimization of the patient's endogenous RBC mass (first pillar), women generally seem to be less susceptible to anaemia-induced adverse events than men. For example, in normal life, the lowest risk for mortality occurs at haemoglobin values between 130 and 150 g/L in women and between 140 and 170 g/L in men [43-46]. In a cohort of 6880 elderly patients without severe comorbidities, mild and moderate anaemia was significantly associated with a higher mortality in men but not in women [32 47]. In a recent publication focusing on non-emergent CABG surgery, a low haematocrit and blood transfusion were significant predictors for major morbidity in men, whereas in women blood transfusion was the only predictor of major morbidity [32]. In non-cardiac surgery, the mortality was higher in men than in women at similar haemoglobin levels.

The prevalence of preoperative anaemia in the present study was similar in both genders, so this factor cannot explain the higher transfusion rates in women. The fact that the prevalence of anaemia among women was similar to that among men might be attributable to the higher age of the patients included in the study [48], because the higher prevalence of low haemoglobin values observed in younger women disappears with increasing age. After the age of 75 years, men have in fact a higher prevalence of anaemia than women, with the prevalence among men being highest at age 85 years and older [49 50].

The observation that anaemia is associated with a poor prognosis in many disorders is not a sufficient reason to assume a cause-and-effect relationship. Anaemia of chronic disease in particular may be associated with an adaptive physiological response [51 52]. The treatment of mild to moderate anaemia of chronic disease may therefore not always bring the desired improvement or may even increase the mortality in some cases [53]. Nevertheless, optimization of the preoperative blood volume up to the WHO cut-off values should be an integral strategy to reduce the transfusion requirements in both genders [54 55].

The amount of perioperative blood loss (second pillar) depends on the surgical technique, the management of perioperative coagulation, and the blood conservation techniques used. The degree of acute blood loss that patients can safely tolerate is inversely related to their baseline haemoglobin concentration and the decrease of their RBC volume [56]. A decrease of at least 50% from the preoperative haemoglobin level during cardiac surgery is associated with adverse outcomes even if the absolute haemoglobin level remains above the commonly used transfusion threshold of 7.0 g/dL [57].

In the present study, the absolute blood loss was smaller among women than among men in all-surgical subgroups, but the relative perioperative blood loss was 5% higher among women than among men in the CABG subgroup and it was comparable between men and women in the orthopaedic surgery subgroups. The higher blood loss among women undergoing CABG surgery may be attributable to the extreme haemodilution associated with extracorporeal circulation. As women have a lower body mass index than men, their haemodilution during the operation is more profound, and women therefore tend to receive more transfusions during and after the CABG operation[18]. Nevertheless, the differences in blood loss alone cannot explain why the RBC volume transfused among women was twice that among men in the CABG group and 25% higher than that among men in the orthopaedic surgery groups (Table 4).

With regard to the tolerance of anaemia (third pillar), it is possible that the ability to compensate for low haemoglobin values differs by gender. Moreover, to our knowledge neither cut-off values nor transfusion guidelines exist for postmenopausal women [58 59]. Several authors have suggested that anaemia in women beyond menopause should be defined by a higher haemoglobin threshold, similar to that used for men [44 60 61]. Current transfusion guidelines revolve around absolute haemoglobin values and do not account for this phenomenon, nor do they consider the special needs of women in general [59 62-64]. In fact, in routine clinical practice similar transfusion triggers are applied in both genders[65].

The present study has several limitations. First, it is a post hoc analysis that uses data from two similar consecutive benchmark studies [20 21]. Second, because financial resources were limited, postoperative outcomes could not be studied. Third, because of the observational character of the two benchmark studies only routine parameters could be collected. Therefore, several aspects of interest such as the causes of preoperative anaemia could not be investigated.

A main strength of the study is the fact that the perioperative blood loss was calculated and the so-called hidden blood loss is therefore included in the analysis. Moreover, we compared not only absolute transfusion-related data but also relative values (in relation to the WHO cut-off values [25]). This enabled a fair gender comparison because baseline differences between men and women were eliminated.

The present findings—that women had a higher postoperative RBC volume in all surgical groups and higher intra- and postoperative haemoglobin levels, together with a higher relative RBC volume transfused—are clear indicators that the transfusion strategies applied in women were too liberal. These results could have a significant impact on blood utilisation levels and possibly lead to improvements in outcome and patient safety. Gender specific transfusion thresholds and dosing are neither recommended by guidelines nor common in clinical practice. Therefore the findings of this study might be generalizable across most transfused populations. Once clinicians are aware of the fact that women tend to be over-transfused, measures can be taken to address this matter. These include the correction of preoperative anaemia, the reduction of perioperative blood loss by optimizing the surgical technique, the reduction of the transfusion volume (e.g. by implementing a single-unit strategy), and the use of lower haemoglobin values as transfusion triggers. Such strategies may dramatically reduce the transfusion rate among women while improving outcome and patient safety.

Conclusion

The higher transfusion rate and volume in women, compared with men, in elective surgery can be explained by clinicians applying the same absolute transfusion thresholds irrespective of a patient's gender even though women have a lower baseline RBC volume. This, together with the common use of a liberal transfusion strategy in elective CABG and orthopaedic surgery despite the recommendations in relevant guidelines, leads to over-transfusion in women. Given the possibility to pre-empt transfusions through the treatment of modifiable risk factors by applying the patient blood management concept, a beneficial change in practice is warranted. Given the accumulating evidence on transfusion outcomes from meta-analyses of RCTs[66-69] comparing liberal vs. restrictive transfusion thresholds, a prospective RCT comparing gender-specific transfusion thresholds and targets with current standard of care is warranted.

Table 1 Patients included

Total = Study I + Study II	Women	Men	Sum
CABG	350 = 207 + 143	1141 = 570 + 571	1491 = 777 + 714
THR	1424 = 768 + 656	1146 = 579 + 567	2057 = 1347 + 1223
TKR	1691 = 891 + 800	778 = 351 + 427	2469 = 1242 + 1227
Sum	3465 = 1866 + 1599	3065 = 1500 + 1565	6530 = 3366 + 3164

Table 2: Demographic Data

		Women	Men	p value
Age	**All**	70/14	67/14	**< 0.0001**
	CABG	71/13	66/13	**< 0.0001**
	THR	69/15	66/15	**< 0.0001**
	TKR	71/12	70/12	0.0017
Body Weight (kg)	**All**	74/19	84/18	**< 0.0001**
	CABG	70/16	82/18	**< 0.0001**
	THR	72/17	84/19	**< 0.0001**
	TKR	78/20	87/18	**< 0.0001**
Body Height (m^2)	**All**	162/8	174/9	**< 0.0001**
	CABG	160/9	173/8	**< 0.0001**
	THR	162/9	175/10	**< 0.0001**
	TKR	162/7	174/8	**< 0.0001**
BSA (m^2)	**All**	1.79/0.23	1.99/0.23	**< 0.0001**
	CABG	1.74/0.22	1.96/0.22	**< 0.0001**
	THR	1.77/0.22	1.99/0.25	**< 0.0001**
	TKR	1.82/0.23	2.02/0.24	**< 0.0001**
ASA Score	**All**	2/1	3/1	**< 0.0001**
	CABG	3/0	3/0	0.2332
	THR	2/1	2/1	0.7003
	TKR	2/1	2/1	0.9099
Euro Score	**CABG**	5/4	4/3	**< 0.0001**
Preop. Anemia (number yes (%))	**All**	629 (18.2)	582 (19.0)	0.3859
	CABG	106 (30.3)	270 (23.7)	0.0126
	THR	243 (17.1)	173 (15.1)	0.1780
	TKR	280 (16.6)	139 (17.9)	0.4212
Platelet Inhibitors (preop.) (number yes (%))	**All**	332 (9.6)	730 (23.8)	**< 0.0001**
	CABG	159 (45.4)	567 (49.7)	0.1626
	THR	70 (4.9)	87 (7.6)	**0.0049**
	TKR	103 (6.1)	76 (9.8)	**0.0011**
Regional anesthesia (number yes (%))	**All**	1777 (51.3)	1140 (37.2)	**< 0.0001**
	THR	777 (54,6)	649 (56,6)	0.2946
	TKR	1000 (59,1)	490 (63,0)	0.0696
Minimal invasive surgery (number yes (%))	**All**	59 (1.70)	71 (2.32)	0.0764
	CABG	2 (0.57)	14 (1,23)	0.2977
	THR	56 (3,93)	56 (4,89)	0.2390
	TKR	1 (0,06)	1 (0,13)	0.5734

Duration of Surgery (min)	**All**	80/45	105/122	**< 0.0001**
	CABG	216/92	220 /97	0.4573
	THR	70/32	72 /30	**0.0012**
	TKR	84 /39	90 /46	**< 0.0001**
Duration of extracorporeal Circulation (min)	**CABG**	88/39	90/44	0.458
Use of aprotinin or tranexamic acid† (number yes (%))	**CABG**	336 (96)	1103 (96.7)	0.5503
Use of Cell Saver (number yes (%))	**All**	1694 (48.9)	1478 (48.2)	0.5904
	CABG	152 (43.4)	504 (44.2)	0.8064
	THR	750 (52.7)	589 (51.4)	0.5210
	TKR	792 (46.8)	385 (49.5)	0.2207
Length of stay (days)	**All**	12/4	11 /4	**< 0.0001**
	CABG	10 /6	10 /5	0.1753
	THR	12 /4	11 /3	**< 0.0001**
	TKR	12 /3	12 /4	**0.0015**

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables.
The percentages are calculated based on the total applicable population for each variable.
Presented p values correspond to Man-Whitney U test, or Chi^2 test, respectively.
† Aprotinin was used in the first study and tranexamic acid was used in the second study only.

Table 3 Transfusion related variables (all patients) Values are presented as median/IQR for measured values and frequencies (%) for categorical variables. The percentages are calculated as the fraction of the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	**men**	**p value**	**women**	**men**	**p value**
Hb preop (g/L)	**All**	131/16	143/18	**< 0.0001**	109/13.3	110/13.8	0.1424
	CABG	127/17	141/20	**< 0.0001**	105.83/14.17	108.46/15.38	**< 0.0001**
	THR	131/16	144/16	**< 0.0001**	109.17/13.33	110.77/12.31	**0.0004**
	TKR	132/16	143/18	**< 0.0001**	110.00/13.33	110.00/13.85	0.8485
Hb POD5 (g/L)	**All**	100/15	105/1.8	**< 0.0001**	83.3/12.5	80.8/13.8	**< 0.0001**
	CABG	104/17	106/1.8	0.2730	86.88/14.17	81.15/13.85	**< 0.0001**
	THR	100/15	105/1.7	**< 0.0001**	83.33/12.50	80.96/13.08	**< 0.0001**
	TKR	100/15	103/1.9	**< 0.0001**	83.33/12.71	79.23/14.62	**< 0.0001**
Hb nadir(g/L)	**All**	97/16	102/1.8	**< 0.0001**	80.8/13.3	78.5/13.8	**< 0.0001**
	CABG	98/17	99/16	0.0729	81.67/14.17	76.15/12.31	**< 0.0001**
	THR	97/15	105/19	**< 0.0001**	80.83/12.50	80.77/14.62	0.4955
	TKR	97/16	102/.0	**< 0.0001**	80.83/13.33	78.46/15.38	0.0024
RBC volume preop	**All**	1455/336	2007/428	**< 0.0001**	---	---	---
	CABG	1339/291	1950/415	**< 0.0001**	---	---	---
	THR	1435/319	2037/435	**< 0.0001**	---	---	---
	TKR	1494/343	2028/434	**< 0.0001**	---	---	---
RBC volume POD5	**All**	1127/267	1477/352	**< 0.0001**	76.6 /13.2	74.3 /13.0	**< 0.0001**
	CABG	1126/248	1468/346	**< 0.0001**	82.8 /16.0	75.4 /14.0	**< 0.0001**
	THR	1110/261	1487/353	**< 0.0001**	76.0/12.9	73.4 /12.5	**< 0.0001**
	TKR	1148/289	1477/366	**< 0.0001**	76.0/12.6	73.4 /13.4	**< 0.0001**
RBC volume lost	**All**	488/290	628/347	**< 0.0001**	32.1/21.3	30.7/17.2	**< 0.0001**
	CABG	619/465	655/438	0.3945	46.5/36.3	33.1/22.9	<

							0.0001
	THR	479/277	620/311	**< 0.0001**	32.4/20.9	29.3/15.0	**< 0.0001**
	TKR	471/270	615/296	**< 0.0001**	30.2/18.2	29.9/14.5	0.1345
RBC units transfused (number yes (%))	**All**	1545 (44.6)	1011 (32.9)	**< 0.0001**	---	---	---
	CABG	283 (80.9)	554 (48.6)	**< 0.0001**	---	---	---
	THR	634 (44.5)	277 (24.2)	**< 0.0001**	---	---	---
	TKR	628 (37.1)	180 (23.1)	**< 0.0001**	---	---	---

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Table 4 Transfusion related variables (transfused patients only)

Values are presented as median/IQR for non-normally distributed variables, or number (%) for categorical variables. The percentages are calculated based on the total applicable population for each variable.

		absolute (g/L, ml)			relative (%)		
		women	men	p value	women	men	p value
Hb preop (only transfused	**All**	126/17	134/19	**< 0.0001**	105/14.2	103/14.6	**< 0.0001**
	CABG	124/17	135/20	**< 0.0001**	103/14.0	104/15.4	0.6925
	THR	126/17	135/17	**< 0.0001**	105/14.2	104/13.3	**0.0120**
	TKR	127/17	133/20	**< 0.0001**	106/14.2	102/15.4	**0.0003**
Hb POD5 (only transfused patients)	**All**	102/17	101/18	0.9279	85.0/14.2	77.7/13.7	**< 0.0001**
	CABG	105/17	102/18	0.0485	87.5/14.0	78.5/13.8	**< 0.0001**
	THR	101/16	101/.9	0.4562	84.2/13.3	77.7/14.6	**< 0.0001**
	TKR	101/16	100/17	0.4262	84.2/13.7	76.9/13.1	**< 0.0001**
Hb nadir (only transfused patients)	**All**	93/16	94/16	0.5446	77.5/13.3	72.3/12.3	**< 0.0001**
	CABG	97/18	94/14	0.0173	80.8/15.0	72.3/10.8	**< 0.0001**
	THR	93/15	93/18	0.4170	77.5/12.5	71.5/13.8	**< 0.0001**
	TKR	92/16	93/16	0.4918	76.7/13.3	71.5/12.3	**< 0.0001**
RBC volume preop (only transfused patients)	**All**	1370/290	1830/398	**< 0.0001**	---	---	---
	CABG	1320/256	1830/405	**< 0.0001**	---	---	---
	THR	1360/279	1830/409	**< 0.0001**	---	---	---
	TKR	1413/303	1850/414	**< 0.0001**	---	---	---
RBC volume POD5 (only transfused patients)	**All**	1110/256	1400/316	**< 0.0001**	80.9 /16	76.9 /15.7	**< 0.0001**
	CABG	1120/243	1410/314	**< 0.0001**	84.4/16.4	77.3/16.2	**< 0.0001**
	THR	1090/252	1390/347	**< 0.0001**	80.2/15.6	76.2/14.0	**< 0.0001**

	TKR	1120/262	1380/320	**< 0.0001**	79.6/15.4	77.6/16.5	**< 0.0001**
RBC volume lost (only transfused patients)	**All**	653/292	871/441	**< 0.0001**	47/18.9	47.4/20.7	0.9313
	CABG	703/415	882/498	**< 0.0001**	52.8/32.6	47.8/24.1	**0.0001**
	THR	635/280	863/389	**< 0.0001**	47.0/18.2	47.1/17.4	0.7359
	TKR	657/266	869/415	**< 0.0001**	45.9/15.8	45.6/18.2	0.7754
RBC volume transfused (only transfused patients)	**All**	363/133	365/284	**< 0.0001**	26.4/14.7	20.8/18.5	**< 0.0001**
	CABG	539/417	380/376	**0.0051**	40.0/36.3	22.3/22.9	**< 0.0001**
	THR	363/89.1	363/219	**0.0041**	26.3/12.2	20.1/11.4	**< 0.0001**
	TKR	363/72.8	363/144	**0.0226**	25.2/10.8	20.2/14.0	**< 0.0001**

Table 5 Predictors of transfusion

Independent predictors of RBC transfusions by gender						
	CABG		THR		TKR	
Independent variable	**Regression coefficient**	**OR (95% CI)**	**Regression coefficient**	**OR (95% CI)**	**Regression coefficient**	**OR (95% CI)**
Women						
Preoperative Hb (%)*	- 0.304	0.74 (0.67-0.83)	– 0.304	0.74 (0.71–0.77)	– 0.279	0.76 .73–0.79)
Lowest postoperative Hb (%)*	0.197	1.22 (1.10-1.35)	0.194	1.22 (1.17–1.26)	0.209	1.23 ..19–1.28)
Lost RBC volume (%)†	0.402	1.50 (1.30-1.71)	0.405	1.50 (1.42–1.58)	0.437	1.55 ..47–1.63)
Cases correctly classified (%)		94.3 %		93.5		93.6
R squared		0.864		0.857		0.853
Men						
Preoperative Hb (%)*	- 0.225	0.80 (0.77-0.83)	– 0.248	0.78 (0.74–0.82)	– 0.248	0.78 .74–0.82)
Lowest postoperative Hb (%)*	0.153	1.17 (1.12-1.21)	0.154	1.17 (1.12–1.22)	0.154	1.17 ..12–1.22)
Lost RBC volume (%)†	0.301	1.35 (1.30-1.41)	0.359	1.43 (1.34–1.53)	0.359	1.43 ..34–1.53)
Cases correctly classified (%)		91.4 %		94.7		93.4
R squared		0.800		0.802		0.786

* Percentages of the anemia cutoff values given by the WHO (women 120 g/L; men 130 g/L).

Percentage of the preoperatively circulating RBC volume.

Only significant predictors are presented.

Contributors: HG initiated and implemented both benchmark studies, designed data collection tools, and wrote and revised the paper. He is guarantor. GS wrote the statistical analysis plan, analysed the data and revised the drafted paper. SN cleaned and analysed the data. PK monitored data collection for both trials, drafted and revised the paper. AH implemented both benchmark studies and revised the drafted paper.

Conflict of interest None of the authors except AH has any conflict of interests
A. H: Lectures for Vifor Pharma and TEM international

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Legends

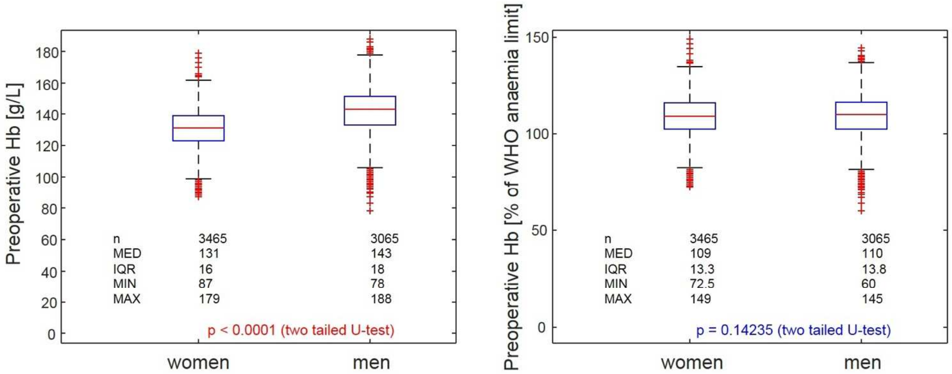
Figure 1. Boxplots for absolute versus relative haemoglobin values. The significant gender difference in haemoglobin values (left) disappears by using relative values according the WHO guidelines[25] (right).

Figure 2. Type of surgery and percentage of patients transfused

Figure 3 Percentage of patients receiving a given number of RBC units (indicating that women received one or two RBC units more often as men do, mostly at the expense of the percentage of patients who did not receive any transfusion.

Figure 4 (a-b): Transfusion rate in anaemic (top) and non-anaemic (bottom) patients.

Figure 5 a-c: Boxplots for absolute and relative RBC volumes: lost (left) and transfused (right) for CABG (top), THR (middle), TKR (bottom) – women versus men **for transfused patients only**.



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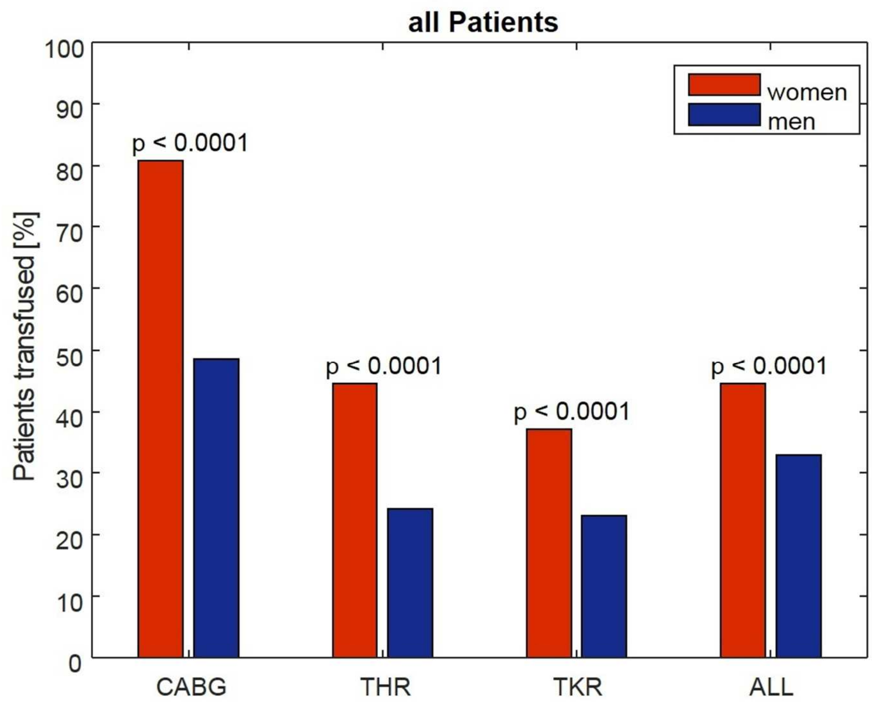

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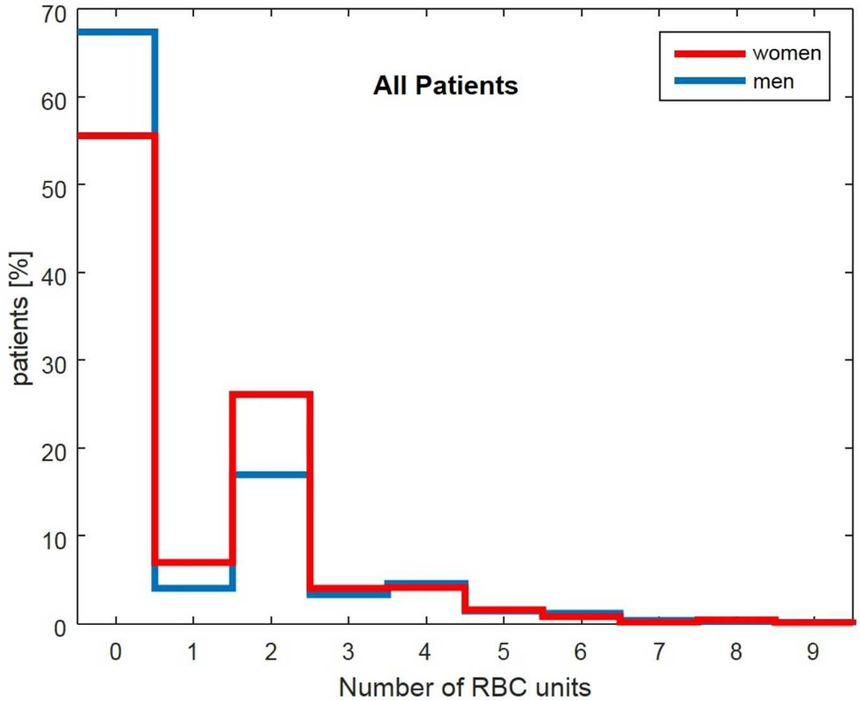

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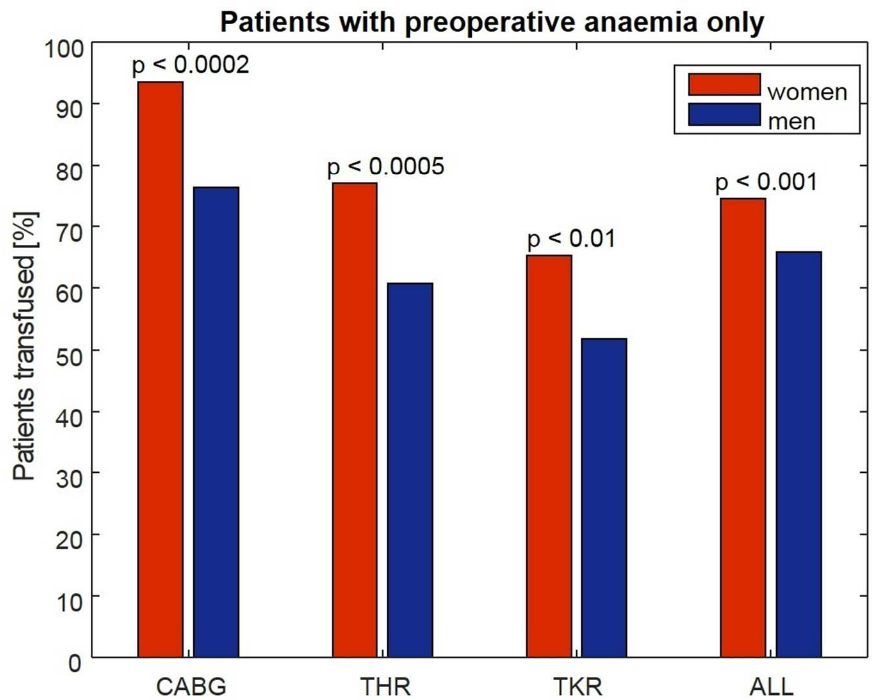

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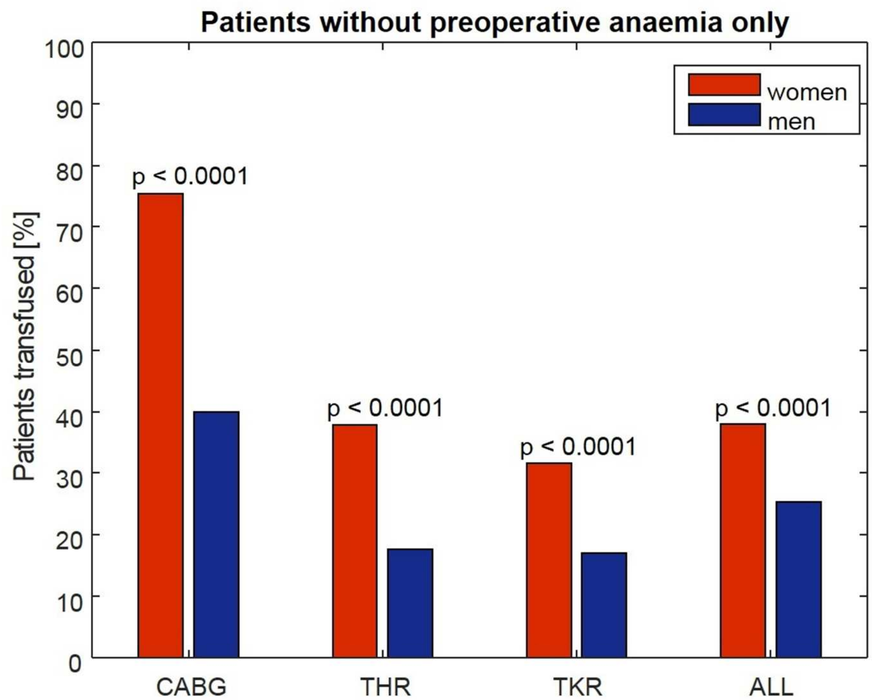

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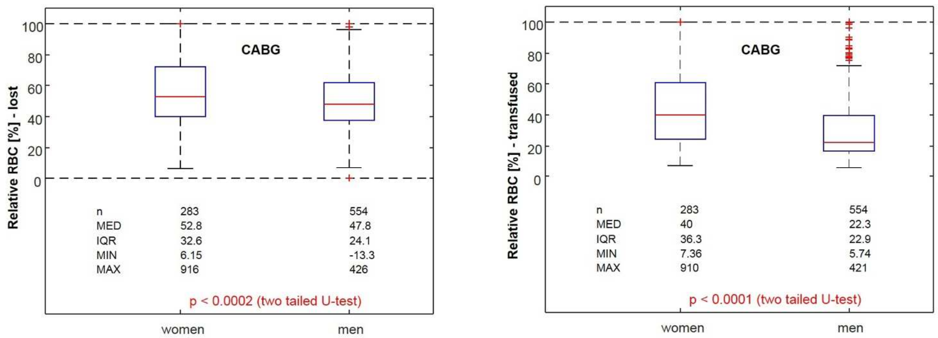

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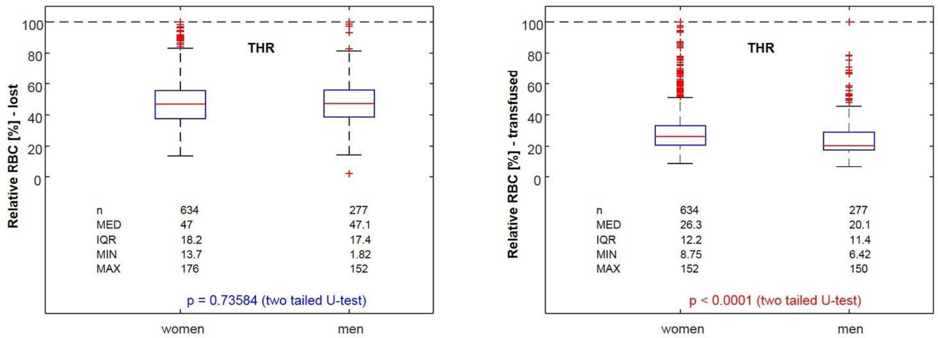

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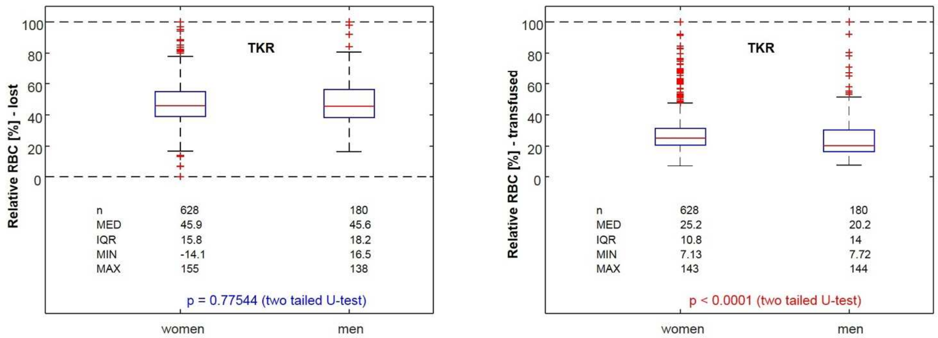

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Gender disparities in red blood cell transfusion in elective surgery. A post hoc multicenter cohort study.

	Item No	Recommendation
Pg. Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4, pg 1 and 2**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4, pg 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4, pg 3, Page 5, pg 2**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 5, pg 1**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 5, pg 2-4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 5 last pg, Page 6 1st pg**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 6, 1st pg**
Bias	9	Describe any efforts to address potential sources of bias **Page 7, 2nd pg**
Study size	10	Explain how the study size was arrived at **Page 5, 1st pg**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **page 6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		Page 6, pg 3,4, Page 7 pg1
		(*b*) Describe any methods used to examine subgroups and interactions ---
		(*c*) Explain how missing data were addressed ---
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Table 2,3,4**
		(b) Give reasons for non-participation at each stage ---
		(c) Consider use of a flow diagram **Table 1**
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Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 3,4,**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 9, last pg, Table 5**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ---
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 10,**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11 and 12**
Generalisability	21	Discuss the generalisability (external validity) of the study results Page **13, pg 2**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based no fnding **page 5, pg1**

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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

STROBE Statement—checklist of items that should be included in reports of observational studies

Gender Disparities in the Use of Blood Transfusion in Elective Surgery. A Prospective Multicenter Cohort Study.

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Continued on next page

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Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based no fnding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.