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Gender disparities in red blood cell transfusion in elective surgery: a post hoc multicentre cohort study

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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 red blood cell (RBC) units transfused (postoperative day 5 included) and differences in intraoperative 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% and 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 when 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 overtransfusion in women.

INTRODUCTION

Women tend to live longer than men, but typically experience more stress, poorer

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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 in the transfusion-related modifiable risk factors such as 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 red blood cell volume transfused were precisely calculated.
- Owing 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 comorbidities and data on transfusion outcomes could not be investigated.

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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 few 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] Therefore, identifying the underlying causes of the higher RBC transfusion rate in women and—as a consequence—enabling 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 to February 2005, and the second study from July 2009 to 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 deidentified data were collected and complete patient confidentiality was maintained. After obtaining approval from the local ethics committee (Ethikkommission 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 normalised ratio >1.5 or activated partial thromboplastin time >35 s).

Primary outcome measures were the number of intraoperatively 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 WHO (figure 1). Comparing absolute transfusion-related data and relative values in relation to the WHO's cut-off values (WHO; women 120 g/L and 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*[27] formula was used to calculate the patients' blood volume. The total RBC volume was derived by multiplying the calculated blood volume with the corresponding haematocrit level. A
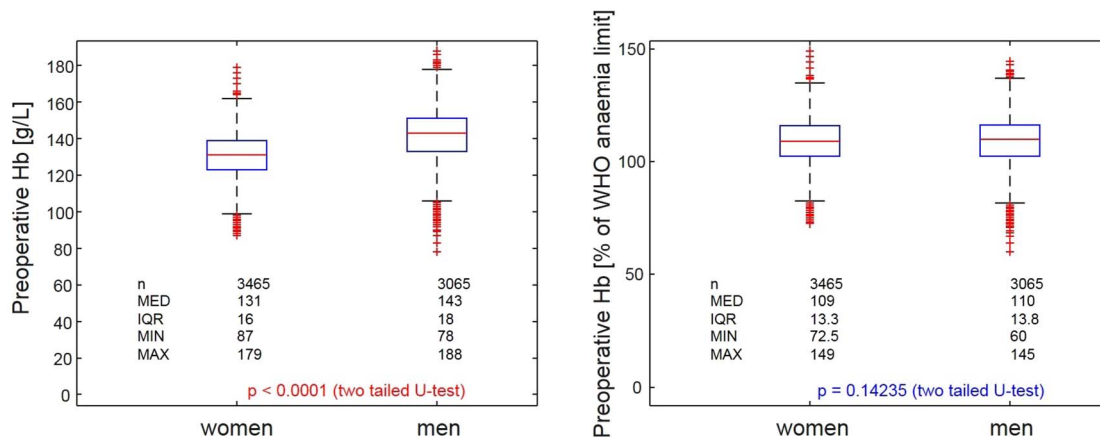
Figure 1 Boxplots for absolute versus relative haemoglobin values. The significant gender difference in haemoglobin values (left) disappears by using relative values according the WHO guidelines[25] (right). Hb, haemoglobin.

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 programme 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 Contract Research Organisation (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 IQR, 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 χ^2 test for frequencies, respectively.

Multivariate analysis was already performed 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 Anaesthesiology (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, Natick, Massachusetts, USA) for the statistical analysis. Box plots, bar charts and line diagrams were used to present the data graphically. A value of p<0.05 was considered to indicate statistical significance.

Minimising the risk of bias
Participating centres were randomly selected and stratified by region and level of care. Patients in each centre were enrolled consecutively. To ensure correct enrolment and adherence to patient selection criteria, onsite monitoring was regularly performed (twice per centre). 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

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

CABG, coronary artery bypass graft; THR, total hip replacement; TKR, total knee replacement.

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
EuroSCORE			
CABG	5/4	4/3	**<0.0001**
Preoperative anaemia (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 (preoperative) (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 anaesthesia (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
			Continued

Table 2 Continued

	Women	Men	p Value
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**

Bold values indicate p Values <0.05.
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 Mann-Whitney U test, or χ^2 test, respectively.
*Aprotinin was used in the first study and tranexamic acid was used in the second study only.
ASA, American Society of Anaesthesiology; CABG, coronary artery bypass graft; THR, total hip replacement; TKR, total knee replacement.

differences in the BMI and the patients' overall health (American Society of Anaesthesiologists 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, and aprotinin was 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% and 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% and 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 those with non-anaemia (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 4A, B shows the percentages of the transfused patients for the different surgical interventions, for patients with (top) and for those without (bottom) preoperative anaemia. Compared with the first study, the overall percentage of transfused patients and the 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
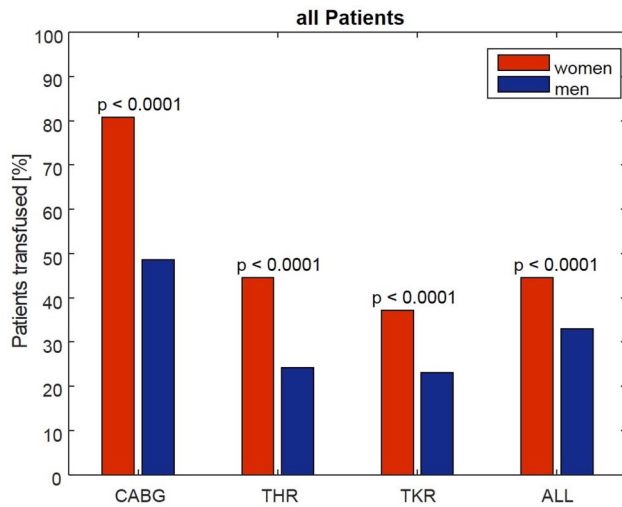
Figure 2 Type of surgery and percentage of patients transfused. CABG, coronary artery bypass graft; THR, total hip replacement; TKR, total knee replacement.
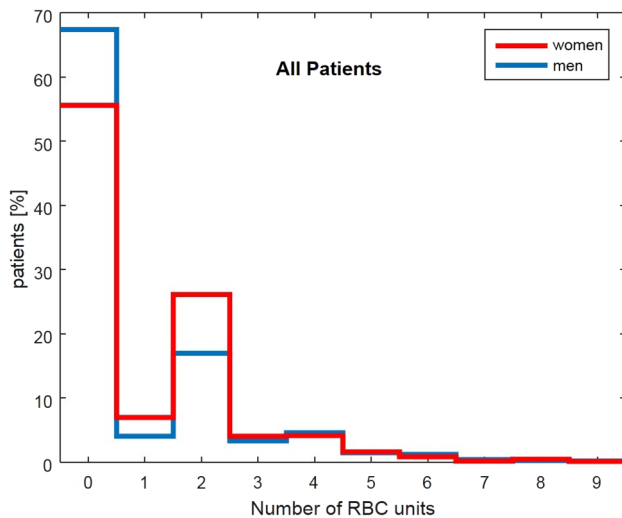

Figure 3 Percentage of patients receiving a given number of RBC units (indicating that women received one or two RBC units more often as men do, mostly at the expense of the percentage of patients who did not receive any transfusion. RBC, red blood cell.

transfused between the studies. Usage of predonation 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 predonation 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. In contrast, the relative blood loss among patients undergoing CABG surgery was considerably higher in women than in men; it was
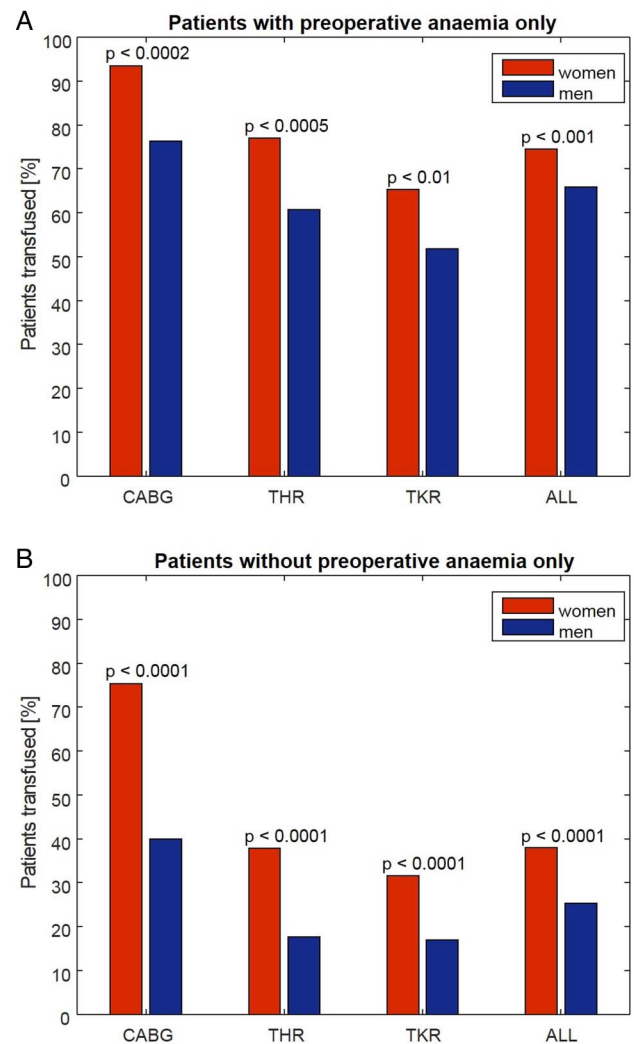
Figure 4 (A and B) Transfusion rate in patients with anaemia (top) and non-anaemia (bottom). CABG, coronary artery bypass graft; THR, total hip replacement; TKR, total knee replacement.

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 volumes 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 3 Transfusion-related variables (all patients)

	Absolute (g/L, mL)			Relative (%)		
	Women	Men	p Value	Women	Men	p Value
Hb preoperative (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 preoperative						
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**	–	–	–

Bold values indicate p Values <0.05
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.
CABG, coronary artery bypass graft; Hb, haemoglobin; POD5, post-operative day 5; RBC, red blood cell; THR, total hip replacement; TKR, total knee replacement.

table 4 and figure 5A–C). The absolute preoperative RBC volume was ~30% higher in men than in women, and the RBC volume on postoperative day 5 was ~20% higher in men. On the other hand, on postoperative day 5, the relative RBC volumes were elevated (by ~5%) in women in all surgical subgroups when compared with men.

In transfused patients, the absolute preoperative haemoglobin values were generally lower in women, and relative haemoglobin values were comparable except for 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). In 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 versus second study

Compared with the first study, in the second study the overall percentage of transfused patients and the mean number of RBC units transfused decreased in THR and

Table 4 Transfusion-related variables (transfused patients only)

	Absolute (g/L, mL)			Relative (%)		
	Women	Men	p Value	Women	Men	p Value
Hb preoperative (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 preoperative (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**

Bold values indicate p Values <0.05.
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.
CABG, coronary artery bypass graft; Hb, haemoglobin; RBC, red blood cell; THR, total hip replacement; TKR, total knee replacement.

TKR, but remained relatively unchanged in CABG surgery. Among the patients who received transfusions, there was no difference in the RBC volume and 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 predonation 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 predonation in orthopaedic patients from the first to the second study (THR, 11% to 4%; TKR, 8% to 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:

▶ 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.
▶ Furthermore, the relative RBC volume transfused was significantly higher in women in all surgical categories, especially in CABG surgery.
▶ This was accompanied by a higher relative nadir haemoglobin value and a higher haemoglobin value on postoperative day 5 in women.
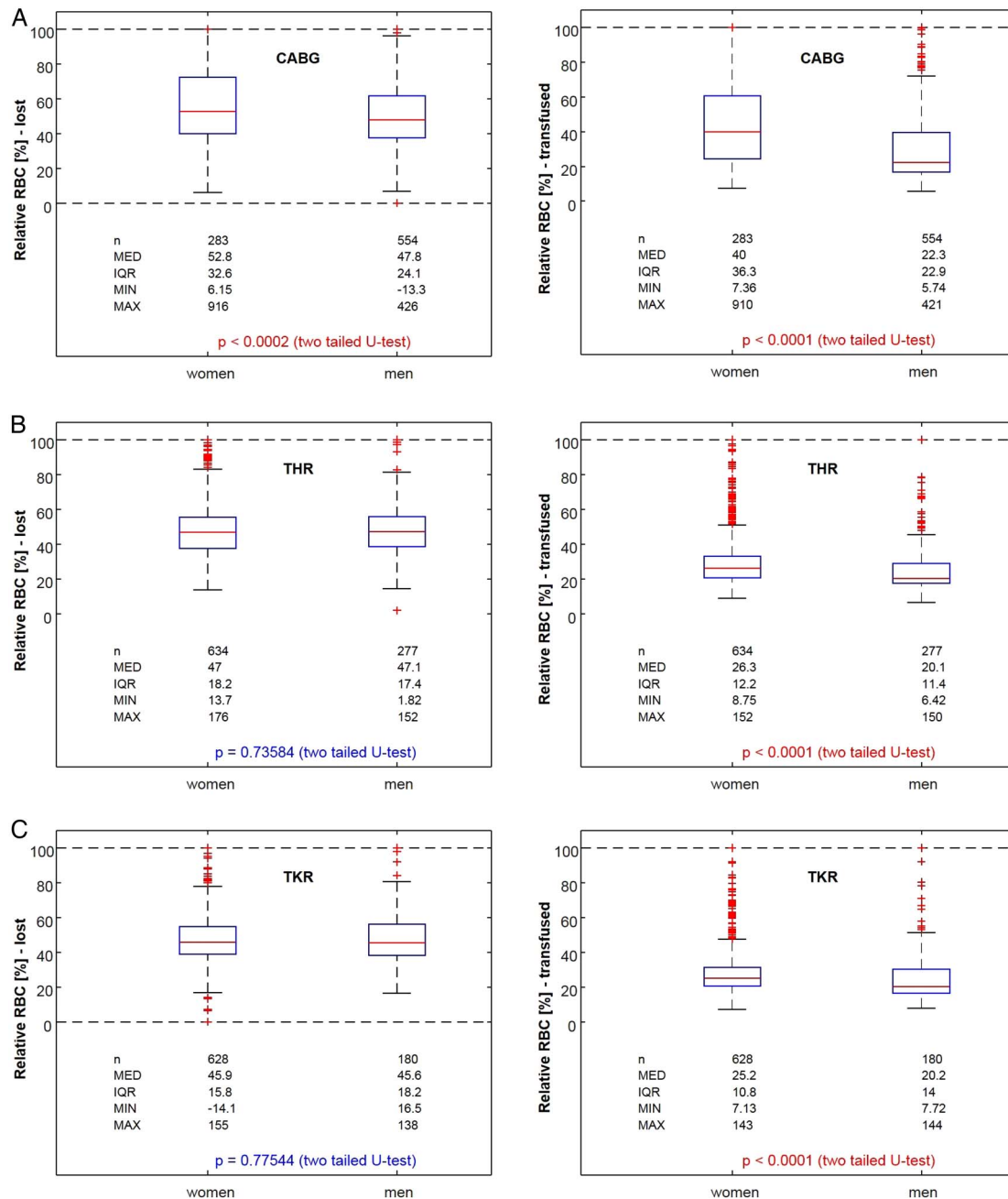
Figure 5 (A–C) Boxplots for absolute and relative RBC volumes: lost (left) and transfused (right) for CABG (top), THR (middle), TKR (bottom)—women versus men for transfused patients only. CABG, coronary artery bypass graft; RBC, red blood cell; THR, total hip replacement; TKR, total knee replacement.

▶ In addition, the calculated relative postoperative RBC volume in women was ~5% higher than that in men across all surgical groups.

▶ 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 RBCs 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: optimisation of the patient's endogenous RBC mass; minimisation of diagnostic, interventional and surgical blood loss and optimisation of the patient's tolerance of anaemia.[22] [41] In most clinical scenarios,

Table 5 Predictors of transfusion

Independent predictors of RBC transfusions by gender

Independent variable	CABG		THR		TKR	
	Regression coefficient	OR (95% CI)	Regression coefficient	OR (95% CI)	Regression coefficient	OR (95% CI)
Women						
Preoperative Hb (%)*	−0.304	0.74 (0.67 to 0.83)	−0.304	0.74 (0.71 to 0.77)	−0.279	0.76 (0.73 to 0.79)
Lowest postoperative Hb (%)*	0.197	1.22 (1.10 to 1.35)	0.194	1.22 (1.17 to 1.26)	0.209	1.23 (1.19 to 1.28)
Lost RBC volume (%)†	0.402	1.50 (1.30 to 1.71)	0.405	1.50 (1.42 to 1.58)	0.437	1.55 (1.47 to 1.63)
Cases correctly classified (%)		94.3		93.5		93.6
R^2		0.864		0.857		0.853
Men						
Preoperative Hb (%)*	−0.225	0.80 (0.77 to 0.83)	−0.248	0.78 (0.74 to 0.82)	−0.248	0.78 (0.74 to 0.82)
Lowest postoperative Hb (%)*	0.153	1.17 (1.12 to 1.21)	0.154	1.17 (1.12 to 1.22)	0.154	1.17 (1.12 to 1.22)
Lost RBC volume (%)†	0.301	1.35 (1.30 to 1.41)	0.359	1.43 (1.34 to 1.53)	0.359	1.43 (1.34 to 1.53)
Cases correctly classified (%)		91.4		94.7		93.4
R^2		0.800		0.802		0.786

Percentage of the preoperatively circulating RBC volume.
Only significant predictors are presented.
*Percentages of the anaemia cut-off values given by the WHO (women 120 g/L and men 130 g/L).
†Percentages of pre-operative RBC volume.
CABG, coronary artery bypass graft; Hb, haemoglobin; RBC, red blood cell; THR, total hip replacement; TKR, total knee replacement.

application of just the first two pillars is sufficient to address all three risks of the triad. Optimisation 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 optimisation 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, optimisation of the pre-operative 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 BMI 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 the best of 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 absolute transfusion-related data and 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 intraoperative 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 usage 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 generalisable across most transfused populations. Once clinicians are aware of the fact that women tend to be overtransfused, measures can be taken to address this matter. These include the correction of preoperative anaemia, the reduction of perioperative blood loss by optimising the surgical technique, the reduction of the transfusion volume (eg, 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 overtransfusion 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 versus restrictive transfusion thresholds, a prospective randomised controlled trial (RCT) comparing gender-specific transfusion thresholds and targets with current standard of care is warranted.

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REFERENCES

1. Wang H, Dwyer-Lindgren L, Lofgren KT, *et al*. Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2071–94.
2. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
3. Blomkalns AL, Chen AY, Hochman JS, *et al*. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;45:832–7.
4. Tavris D, Shoaibi A, Chen AY, *et al*. Gender differences in the treatment of non-ST-segment elevation myocardial infarction. *Clin Cardiol* 2010;33:99–103.
5. Gnavi R, Rusciani R, Dalmasso M, *et al*. Gender, socioeconomic position, revascularization procedures and mortality in patients presenting with STEMI and NSTEMI in the era of primary PCI. Differences or inequities? *Int J Cardiol* 2014;176:724–30.
6. Hernandez AF, Fonarow GC, Liang L, *et al*. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. *JAMA* 2007;298:1525–32.
7. Garg PP, Furth SL, Fivush BA, *et al*. Impact of gender on access to the renal transplant waiting list for pediatric and adult patients. *J Am Soc Nephrol* 2000;11:958–64.
8. Couchoud C, Bayat S, Villar E, *et al*. A new approach for measuring gender disparity in access to renal transplantation waiting lists. *Transplantation* 2012;94:513–19.
9. Hawker GA, Wright JG, Coyte PC, *et al*. Differences between men and women in the rate of use of hip and knee arthroplasty. *N Engl J Med* 2000;342:1016–22.
10. Aldea GS, Gaudiani JM, Shapira OM, *et al*. Effect of gender on postoperative outcomes and hospital stays after coronary artery bypass grafting. *Ann Thorac Surg* 1999;67:1097–103.
11. Koch CG, Weng YS, Zhou SX, *et al*. Prevalence of risk factors, and not gender per se, determines short- and long-term survival after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2003;17:585–93.
12. Rogers MA, Blumberg N, Heal JM, *et al*. Increased risk of infection and mortality in women after cardiac surgery related to allogeneic blood transfusion. *J Womens Health (Larchmt)* 2007;16:1412–20.
13. Ried M, Lunz D, Kobuch R, *et al*. Gender's impact on outcome in coronary surgery with minimized extracorporeal circulation. *Clin Res Cardiol* 2012;101:437–44.
14. Othman H, Khambatta S, Seth M, *et al*. Differences in sex-related bleeding and outcomes after percutaneous coronary intervention: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) registry. *Am Heart J* 2014;168:552–9.
15. Yu J, Mehran R, Grinfeld L, *et al*. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. *Catheter Cardiovasc Interv* 2015;85:359–68.
16. Stehling L. Gender-related variation in transfusion practices. *Transfusion* 1998;38:392–9.
17. Rogers MA, Blumberg N, Saint SK, *et al*. Allogeneic blood transfusions explain increased mortality in women after coronary artery bypass graft surgery. *Am Heart J* 2006;152:1028–34.
18. Ranucci M, Pazzaglia A, Bianchini C, *et al*. Body size, gender, and transfusions as determinants of outcome after coronary operations. *Ann Thorac Surg* 2008;85:481–6.
19. Desai SJ, Wood KS, Marsh J, *et al*. Factors affecting transfusion requirement after hip fracture: can we reduce the need for blood? *Can J Surg* 2014;57:342–8.
20. Gombotz H, Rehak PH, Shander A, *et al*. The second Austrian benchmark study for blood use in elective surgery: results and practice change. *Transfusion* 2014;54(Pt 2):2646–57.
21. Gombotz H, Rehak PH, Shander A, *et al*. Blood use in elective surgery: the Austrian benchmark study. *Transfusion* 2007;47:1468–80.
22. Gombotz H, Zacharowski K, Spahn D. *Patient blood management*. Stuttgart, New York, Delhi, Rio de Janeiro: Thieme, 2016.
23. Shander A, Isbister J, Gombotz H. Patient blood management: the global view. *Transfusion* 2016;56(Suppl 1):S94–102.
24. Ranucci M, Baryshnikova E, Castelvecchio S, *et al*. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. *Ann Thorac Surg* 2013;96:478–85.
25. World Health Organization. Nutritional anaemias. Report of a WHO Scientific Group. Technical Report Series, 1968;405.
26. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;5:303–11; discussion 12-3.
27. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962;51:224–32.
28. Chaplin H Jr, Mollison PL, Vetter H. The body/venous hematocrit ratio: its constancy over a wide hematocrit range. *J Clin Invest* 1953;32:1309–16.
29. Serrick CJ, Scholz M, Melo A, *et al*. Quality of red blood cells using autotransfusion devices: a comparative analysis. *J Extra Corpor Technol* 2003;35:28–34.
30. Loor G, Rajeswaran J, Li L, *et al*. The least of 3 evils: exposure to red blood cell transfusion, anemia, or both? *J Thorac Cardiovasc Surg* 2013;146:1480–7.e6.
31. Gupta PK, Sundaram A, Mactaggart JN, *et al*. Preoperative anemia is an independent predictor of postoperative mortality and adverse cardiac events in elderly patients undergoing elective vascular operations. *Ann Surg* 2013;258:1096–102.
32. Ad N, Holmes SD, Massimiano PS, *et al*. Operative risk and preoperative hematocrit in bypass graft surgery: role of gender and blood transfusion. *Cardiovasc Revasc Med* 2015;16:397–400.
33. Spiegelstein D, Holmes SD, Pritchard G, *et al*. Preoperative hematocrit as a predictor of perioperative morbidities following nonemergent coronary artery bypass surgery. *J Card Surg* 2015;30:20–6.
34. Hollis RH, Singletary BA, McMurtrie JT, *et al*. Blood transfusion and 30-day mortality in patients with coronary artery disease and anemia following noncardiac surgery. *JAMA Surg* 2016;151:139–45.
35. von Heymann C, Kaufner L, Sander M, *et al*. Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? *J Thorac Cardiovasc Surg* 2016;152:1412–20.
36. Engoren M, Schwann TA, Habib RH, *et al*. The independent effects of anemia and transfusion on mortality after coronary artery bypass. *Ann Thorac Surg* 2014;97:514–20.
37. Hearnshaw SA, Logan RF, Palmer KR, *et al*. Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2010;32:215–24.
38. Jairath V, Hearnshaw S, Brunskill SJ, *et al*. Red cell transfusion for the management of upper gastrointestinal haemorrhage. *Cochrane Database Syst Rev* 2010;Cd006613.
39. Restellini S, Kherad O, Jairath V, *et al*. Red blood cell transfusion is associated with increased rebleeding in patients with nonvariceal upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2013;37:316–22.
40. Valeri CR, Cassidy G, Pivacek LE, *et al*. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. *Transfusion* 2001;41:977–83.
41. Shander A, Hofmann A, Isbister J, *et al*. Patient blood management—the new frontier. *Best Pract Res Clin Anaesthesiol* 2013;27:5–10.
42. Meier J, Gombotz H. Pillar III—optimisation of anaemia tolerance. *Best Pract Res Clin Anaesthesiol* 2013;27:111–19.
43. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA* 1999;281:1714–17.
44. Chaves PH, Xue QL, Guralnik JM, *et al*. What constitutes normal hemoglobin concentration in community-dwelling disabled older women? *J Am Geriatr Soc* 2004;52:1811–16.
45. Culleton BF, Manns BJ, Zhang J, *et al*. Impact of anemia on hospitalization and mortality in older adults. *Blood* 2006;107:3841–6.
46. Martinsson A, Andersson C, Andell P, *et al*. Anemia in the general population: prevalence, clinical correlates and prognostic impact. *Eur J Epidemiol* 2014;29:489–98.
47. Endres HG, Wedding U, Pittrow D, *et al*. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. *Curr Med Res Opin* 2009;25:1143–58.
48. Anía BJ, Suman VJ, Fairbanks VF, *et al*. Prevalence of anemia in medical practice: community versus referral patients. *Mayo Clin Proc* 1994;69:730–5.
49. Anía BJ, Suman VJ, Fairbanks VF, *et al*. Incidence of anemia in older people: an epidemiologic study in a well defined population. *J Am Geriatr Soc* 1997;45:825–31.
50. Guralnik JM, Eisenstaedt RS, Ferrucci L, *et al*. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004;104:2263–8.
51. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation* 2006;113:2454–61.

52. Zarychanski R, Houston DS. Anemia of chronic disease: a harmful disorder or an adaptive, beneficial response? *CMAJ* 2008;179:333–7.

53. Maurer MS, Teruya S, Chakraborty B, *et al*. Treating anemia in older adults with heart failure with a preserved ejection fraction with epoetin alfa: single-blind randomized clinical trial of safety and efficacy. *Circ Heart Fail* 2013;6:254–63.

54. Na HS, Shin SY, Hwang JY, *et al*. Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. *Transfusion* 2011;51:118–24.

55. Goodnough LT, Maniatis A, Earnshaw P, *et al*. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth* 2011;106:13–22.

56. Karkouti K, Wijeysundera DN, Yau TM, *et al*. The influence of baseline hemoglobin concentration on tolerance of anemia in cardiac surgery. *Transfusion* 2008;48:666–72.

57. Hogervorst E, Rosseel P, van der Bom J, *et al*. Tolerance of intraoperative hemoglobin decrease during cardiac surgery. *Transfusion* 2014;54(Pt 2):2696–704.

58. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American society of Anesthesiologists task force on perioperative blood management. *Anesthesiology* 2015;122:241–75.

59. Napolitano LM, Kurek S, Luchette FA, *et al*. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009;37:3124–57.

60. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood* 2006;107:1747–50.

61. Patel KV. Epidemiology of anemia in older adults. *Semin Hematol* 2008;45:210–17.

62. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006;105:198–208.

63. Ferraris VA, Brown JR, Despotis GJ, *et al*., Society of Thoracic Surgeons Blood Conservation Guideline Task Force. 2011 update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011;91:944–82.

64. Carson JL, Grossman BJ, Kleinman S, *et al*. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2012;157:49–58.

65. Meier J, Filipescu D, Kozek-Langenecker S, *et al*., ETPOS collaborators. Intraoperative transfusion practices in Europe. *Br J Anaesth* 2016;116:255–61.

66. Holst LB, Haase N, Wetterslev J, *et al*., TRISS Trial Group; Scandinavian Critical Care Trials Group. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014;371:1381–91.

67. Carson JL, Brooks MM, Abbott JD, *et al*. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013;165:964–71.

68. Rohde JM, Dimcheff DE, Blumberg N, *et al*. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA* 2014;311:1317–26.

69. Salpeter SR, Buckley JS, Chatterjee S. Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review. *Am J Med* 2014;127:124–31.e3.