Introduction of national guidelines for restrictive blood transfusion threshold for hip fracture patients
a consecutive cohort study based on complete follow-up in national databases

Viberg, Bjarke; Gundtoft, Per Hviid; Schønnemann, Jesper; Pedersen, Lasse; Andersen, Lis Røhl; Titlestad, Kjell; Madsen, Carsten Fladmose; Lauritsen, Jens; Overgaard, Søren

Published in:
Journal of Orthopaedic Surgery and Research

DOI:
10.1186/s13018-018-0828-8

Publication date:
2018

Document version
Final published version

Document license
CC BY

Citation for published version (APA):
Viberg, B., Gundtoft, P. H., Schønnemann, J., Pedersen, L., Andersen, L. R., Titlestad, K., Madsen, C. F., Lauritsen, J., & Overgaard, S. (2018). Introduction of national guidelines for restrictive blood transfusion threshold for hip fracture patients: a consecutive cohort study based on complete follow-up in national databases. Journal of Orthopaedic Surgery and Research, 13, [116]. https://doi.org/10.1186/s13018-018-0828-8

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 27. Jan. 2021
Introduction of national guidelines for restrictive blood transfusion threshold for hip fracture patients—a consecutive cohort study based on complete follow-up in national databases

Bjarke Viberg1,2,3,4*, Per Hviid Gundtoft1, Jesper Schønnemann5, Lasse Pedersen6, Lis Røhl Andersen1, Kjell Titlestad7, Carsten Fladmose Madsen2, Jens Lauritsen2,3 and Søren Overgaard2,3

Abstract

Background: Randomized controlled trials have demonstrated that a restrictive red blood cell (RBC) transfusion strategy lowers transfusion frequency without affecting mortality. However, the external validity of these trials has not been tested in a large cohort. The purpose was to estimate the effect of introducing a National Clinical Guideline (NCG) for a restrictive hemoglobin transfusion threshold on transfusion frequency and mortality in hip fracture patients > 65 years old.

Methods: A consecutive cohort study of hip fracture patients > 65 years old residing in the southern region of Denmark was conducted using prospectively gathered data from registers during two separate 1-year time periods. The first period from October 1, 2012, to September 30, 2013, included 1494 patients and used a liberal transfusion threshold, whereas the second period from October 1, 2015, to September 30, 2016, including 1414 participants used a restrictive threshold from the NCG. Participant data for age, sex, body mass index, Charlson Comorbidity Index, time to surgery, and death were retrieved from the Danish Interdisciplinary Registry of Hip Fractures and were merged with RBC transfusion and medication data extracted from the Danish Transfusion and Odense Pharmacoepidemiological Databases, respectively. Cox proportional hazards models were used to test relative mortality risk for the restrictive group compared with the liberal group at 30 and 90 days.

Results: Overall RBC transfusions decreased from 42 to 30% (p < 0.001). The 30-day mortality rate (95% CI) was 9% (8;11) in the restrictive group and 13% (11;14) in the liberal group (p < 0.008), whereas the adjusted relative mortality risk was 0.72 (0.57;0.91). The 90-day mortality rate was 15% (13;17) in the restrictive group and 19% (17;21) in the liberal group, whereas the adjusted relative mortality risk was 0.78 (0.65;0.94).

Conclusion: These data suggest that the introduction of an NCG on restrictive blood transfusion leads to lower transfusion frequency in hip fracture patients > 65 years old. Even though this reduction is associated with decreased mortality at both 30 and 90 days, it may be explained by other issues than restrictive transfusion strategy. There has been an improvement in the mortality of hip fracture patients in Denmark, and we suggest that a restrictive transfusion strategy does not lead to increased mortality.

Keywords: Hip fracture, Transfusion, Restrictive, Liberal, Mortality

* Correspondence: Bjarke.viberg@rsyd.dk
1Department of Orthopaedic Surgery and Traumatology, Kolding Hospital – part of Hospital Lillebaelt, Sygehusvej 24, 6000 Kolding, Denmark
2Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense C, Denmark
Full list of author information is available at the end of the article

© The Author(s). 2018 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
Blood loss leading to anemia commonly occurs in hip fracture patients, resulting in approximately half of them receiving RBC transfusions [1, 2]. RBC transfusions are associated with complications such as transfusion-associated circulatory overload, acute hemolysis, and acute lung injury. Importantly, these and other events increase patient morbidity and mortality [3].

Accordingly, in attempts to avoid transfusion-associated complications, a restrictive RBC transfusion strategy has been introduced using a hemoglobin threshold of 8 g/dL as opposed to the liberal 10 g/dL. It is claimed that this approach does not affect mortality, functional recovery, or postoperative morbidity in hip fracture patients [4]. Nevertheless, the previous Cochrane review [4] on this topic demonstrated low-quality evidence specific to hip fracture patients, whereas a more recent Cochrane review [5] referencing a broader range of clinical specialties found that compared with the liberal transfusion threshold, a restrictive hemoglobin threshold of 7 to 8 g/dL decreased the RBC proportion by 43% while also demonstrating evidence supporting no significant impact on 30-day mortality or morbidity. A recent systematic review [6] also suggests that patients with cardiovascular disease undergoing non-cardiac surgery should be set at a threshold of 8 g/dL since a lower threshold may not be safe.

While the National Institute for Health and Care Excellence (NICE) guidelines from 2015 [7] recommend a restrictive transfusion threshold, it is important to note that this is based on very low- to low-quality evidence. Because the NICE guidelines are based exclusively on randomized controlled trials (RCT), there is an additional need for data based on pragmatic trials such as those involving population studies without exclusion of individuals. Therefore, this study aimed to estimate the effect of introducing an NCG for a restrictive hemoglobin transfusion threshold on transfusion frequency and mortality in individuals > 65 years of age with a hip fracture.

Methods
Study design
This consecutive cohort study included patients demonstrating a hip fracture within two separate 1-year time periods, prior to and following the introduction of the NCG. The first time period was between October 1, 2012, and September 30, 2013, which was the control period (hereafter referred to as the liberal group). The second time period was between October 1, 2015, and September 30, 2016, which was the intervention period adhering to the Danish NCG [8] for blood component transfusion indications (hereafter referred to as the restrictive group). Reporting of data is performed according to the RECORD extension to the STROBE guidelines [9].

Setting
The present study was performed in four independent public hospitals in the Southern Region of Denmark, encompassing the entire territory consisting of 1.22 million inhabitants. The Danish National Health Service provides tax-supported free healthcare and general hospital care for all Danish citizens [10]. Since it is not typical for acute hip fracture patients to be treated in the few remaining private hospital clinics, but when this does occur, reporting is mandatory, patients included in this study comprise a consecutive and complete series. Prior to the introduction of the NCG in 2014, the blood transfusion limit was 7.2 g/dL for healthy individuals, with a level of 9.7 g/dL used for individual assessment (e.g., age, rate of anemia, clinical condition, and type of anemia) [11]. The NCG from 2014 references 7.0 g/dL as the lowest transfusion limit for any patient or those demonstrating symptoms of anemia and 8.0 g/dL if the patient has chronic heart disease [8]. This is illustrated in Table 1. In addition, the NCG from 2014 also set a limit of 9.0 g/dL for patients demonstrating an acute coronary syndrome.

Participants
The Danish Interdisciplinary Registry of Hip Fracture database was used to identify the study population. This included all patients admitted with a hip fracture (ICD-10 codes DS720, DS721, and DS722) to one of the four public hospitals in the Southern Region of Denmark. Procedure codes [12] were used to categorize the type of surgery.

Variables
Participant information for age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI) [13], time to surgery, and death were retrieved from the Danish Interdisciplinary Registry of Hip Fractures. The CCI is calculated by using diagnoses reported to the Danish National Patient Register up to 10 years prior to a hip fracture operation. Patient data regarding hemoglobin was retrieved from the department of Clinical Biochemistry and Pharmacology at the Odense University Hospital, which is able to retrieve data from the whole region. Data regarding transfusion with red blood cells (RBC) was retrieved from the Danish Transfusion Database [14]. Data on patient medication, if reimbursed within 100 days prior to admission to hospital, was retrieved from the Odense Pharmacoepidemiological Database [15].

Table 1: Transfusion thresholds for the liberal and restrictive guidelines

|                        | Liberal | Restrictive |
|------------------------|---------|-------------|
| Healthy patients       | 7.2     | 7.0         |
| Patients with chronic heart disease | 9.7*    | 8.0         |

*Individual assessment was applied using age, rate of anemia, clinical condition, and type of anemia instead of chronic heart disease
Data sources
The Danish Interdisciplinary Registry of Hip Fractures is a population-based clinical quality database established in 2003 and includes data on all hip fracture patients aged 65 or older. Reporting of hip fractures is mandatory for all hospital units, and a number of pre- and peri-operative data are prospectively collected, which includes data on quality of patient care [16]. The Danish Interdisciplinary Registry of Hip Fractures database was linked to the Danish National Patient Registry database in order to extract patient information for BMI, CCI, and reoperations [17].

The Danish National Patient Registry database contains data for all hospital admissions since 1977, which includes dates of admission and discharge, diagnoses (ICD 8 1977-1993, ICD 10 1994 onwards) at discharge and surgical procedure dates and codes according to the Nordic Medico-Statistical Committee (NOMESCO) classification [12]. The Danish Interdisciplinary Registry of Hip Fractures database is also linked to the Danish Civil Registration System database containing information on changes in vital status (e.g., death, new civil registration number, lost, no residence) and migration for the entire Danish population dating back to 1968 [10].

The Danish Transfusion Database is also a population-based clinical quality database maintained since 2006 and linked to the Danish National Patient Registry database. The Danish Transfusion Database contains data from blood bank registries, patient administrative systems, and clinical-biochemical registries. The Odense Pharmacoepidemiological Database is a region-specific prescription database, which covers all inhabitants in the Southern Region of Denmark since 2007. The Odense Pharmacoepidemiological Database contains data for any drug prescription written by hospital staff or general practitioners. However, drug records do not include benzodiazepines, other hypnotics, drugs used to promote weight loss or tobacco abstinence, oral contraceptives, certain antibiotics (e.g., quinolones, tetracyclines), and those that are dispensed over the counter.

Bias
For this study, data has been included for medication as well as comorbidities in attempts to minimize biases by indication. However, we acknowledge that we are not able to include information on clinical condition nor rate and type of anemia, which are potentially relevant data omissions in terms of RBC transfusion.

Study size
The survival sample size for finding a reduction of RBC transfusion events yielded 1112 patients for each group. Event for RBC transfusion was set to 50% [1], censoring including death was set to 15%, and minimal clinical difference was set to a hazard ratio of 1.2.

Quantitative variables
Age was categorized as 65–74, 75–84, and ≥85 years old. Three comorbidity levels were defined: a score of 0 (low) was given to patients with no previous record of diseases included in the CCI, a score of 1–2 (medium), and a score of 3 or more (high). Pharmacotherapy use was categorized using dichotomous values (yes/no) for NSAIDs, antihypertensives, glucocorticoids, antidepressants, statins, anticoagulants, and immunosuppressants.

Statistics
The study population was divided into two comparison groups: group 1 was the restrictive transfusion group following implementation of the NCG (time period October 1, 2015–September 30, 2016), and group 2 was the control group defined as the liberal transfusion group (time period October 1, 2012–September 30, 2013). The statistician was blinded to the groups’ time periods. We described the study population according to the distribution of patients’ characteristics, tabulating the numbers and percentages of patients. Fisher’s exact test was used to evaluate differences between groups for variables of interest. Two-tailed significance was determined using an alpha level set at 0.05.

Mortality at 30 and 90 days was assessed using Kaplan–Meier analyses, with all patients followed until death, emigration, or end of the follow-up period. Relative mortality risk for the intervention group compared with the control group at 30 and 90 days was estimated using Cox proportional hazards modeling. The proportional hazard assumption was tested via log-minus-log plots and was not violated. We adjusted models for age (i.e., 65–74; 75–84, ≥85 years), sex, CCI (i.e., 0, 1–2, ≥3), and type of surgery (e.g., cannulated screws, sliding hip screw, intramedullary nail, and hip arthroplasty). All outcomes were estimated with a 95% confidence interval (CI).

Data access, linkage, and cleaning methods
The authors had complete access to aggregated data from the Danish Interdisciplinary Registry of Hip Fractures, Danish Transfusion Database, and Odense Pharmacoepidemiological Database. The civil registration system contains data for individual unique and unchangeable civil registration numbers, which are assigned to all Danish citizens at date of birth or immigration. The civil registration number is recorded in all Danish registers, which allows for unambiguous linkage between registers on an individual basis. Furthermore, the civil registration systems hold information on date of birth, sex, emigration, and death. The prevalence of disappearing persons is 0.3%, which allows for almost complete follow-up for all patients [10].

Results
The dataset from the Danish Interdisciplinary Registry of Hip Fractures yielded 1494 patients stratified to the liberal group and 1414 for the restrictive group (Table 2). The two
Table 2 Demographic data of the study population and divided by the two cohorts

|                  | Study population | Liberal group | Restrictive group | p <  
|------------------|------------------|---------------|-------------------|------
|                  | n | % | n | % | n | % |      |
| **Total**        | 2908 | 100 | 1494 | 100 | 1414 | 100 |      |
| **Age**          |    |   |    |   |    |   |      |
| 65–74            | 590 | 20 | 308 | 21 | 282 | 20 | 0.766 |
| 75–84            | 1018 | 35 | 514 | 34 | 504 | 36 |      |
| ≥ 85             | 1300 | 45 | 672 | 45 | 628 | 44 |      |
| **Sex**          |    |   |    |   |    |   |      |
| Female           | 2014 | 69 | 1065 | 71 | 949 | 67 | 0.015 |
| Male             | 894 | 31 | 429 | 29 | 465 | 33 |      |
| **CCI**          |    |   |    |   |    |   |      |
| None (0)         | 1019 | 35 | 526 | 35 | 493 | 35 | 0.800 |
| Low (1–2)        | 1238 | 43 | 641 | 43 | 597 | 42 |      |
| High (≥ 3)       | 651 | 22 | 327 | 22 | 324 | 23 |      |
| **BMI**          |    |   |    |   |    |   |      |
| < 18.5           | 278 | 10 | 153 | 10 | 125 | 9 |      |
| 18.5–24.9        | 1269 | 44 | 645 | 43 | 624 | 44 |      |
| 25–29.9          | 686 | 24 | 341 | 23 | 345 | 24 | 0.433 |
| ≥ 30             | 210 | 7  | 102 | 7  | 108 | 8  |      |
| Missing          | 465 | 16 | 253 | 17 | 212 | 15 |      |
| **Prescription medicine** |    |   |    |   |    |   |      |
| NSAID            | 223 | 8  | 137 | 9  | 86  | 6  | 0.002 |
| Diabetes         | 330 | 11 | 166 | 11 | 164 | 11 | 0.66  |
| Anticoagulant    | 1191 | 41 | 620 | 42 | 571 | 41 | 0.58  |
| Antihypertensive | 1457 | 50 | 757 | 51 | 700 | 49 | 0.58  |
| Statin           | 720 | 25 | 356 | 24 | 364 | 26 | 0.22  |
| Glucocorticoid   | 172 | 6  | 89  | 6  | 83  | 6  | 0.94  |
| Depression medicine | 888 | 31 | 486 | 33 | 402 | 29 | 0.02  |
| COPD medicine    | 399 | 14 | 209 | 14 | 190 | 13 | 0.69  |
| **Type of fracture** |    |   |    |   |    |   |      |
| Femoral neck     | 1693 | 59 | 875 | 59 | 818 | 58 | 0.851 |
| Pertrochanteric  | 948 | 32 | 480 | 33 | 468 | 33 |      |
| Subtrochanteric  | 267 | 9  | 139 | 9  | 128 | 9  |      |
| **Type of surgery** |    |   |    |   |    |   |      |
| Cannulated screws | 383 | 13 | 206 | 14 | 177 | 13 | 0.001 |
| Sliding hip screw | 677 | 23 | 404 | 27 | 273 | 19 |      |
| Intramedullary nail | 787 | 27 | 357 | 24 | 431 | 30 |      |
| Arthroplasty     | 1018 | 35 | 506 | 34 | 512 | 36 |      |
| Miscellaneous    | 42  | 1  | 21  | 1  | 21  | 1  |      |
| **Time to surgery** |    |   |    |   |    |   |      |
| < 24 h           | 2050 | 72 | 1104 | 74 | 946 | 69 |      |
| 24–48 h          | 636 | 22 | 317 | 21 | 319 | 23 | 0.001 |
| > 48 h           | 180 | 6  | 65  | 4  | 115 | 8  |      |

NSAID nonsteroidal anti-inflammatory drug, COPD chronic obstructive pulmonary disease
groups did not differ for age ($p < 0.766$), whereas there were more males in the restrictive group ($p < 0.015$). There were no group differences for comorbidities ($p < 0.80$) or type of fracture ($p < 0.851$), whereas more intramedullary nails were used in the restrictive group ($p < 0.001$). The surgical delay was also longer for the restrictive compared with the control group ($p < 0.001$).

In the period following the introduction of the NCG, overall RBC transfusion proportion was reduced from 42 to 30% ($p < 0.001$) (Table 3). One hospital decreased transfusion rates from 43 to 19%, whereas another hospital did not lower it at all. The mean hemoglobin level at admission was 12.3 (12.2;12.3), with no group differences ($p < 0.540$) (Table 4). At the time of first transfusion, the liberal group demonstrated a mean (95% CI) hemoglobin level equal to 9.1 (9.0;9.2), which was compared with the restrictive group at 8.5 (8.2;8.4) ($p < 0.001$). The transfusion threshold differed between the two periods, as 19% of the RBC transfusion was given at a hemoglobin level < 8.0 g/dL in the liberal period compared with 47% in the restrictive period (Table 5).

In a subgroup analysis for patients demonstrating a hemoglobin level between 7.0 and 8.9 g/dL ($n = 1101$), which constituted patients with a possible indication for RBC transfusion, 80.7% received an RBC transfusion in the liberal group compared with 58.6% for the restrictive group.

Overall, 30-day mortality was 11% (10;12); in the restrictive group, it was 9% (8;11), and in the liberal group, it was 13% (11;14) ($p < 0.008$). The crude relative mortality risk at 30 days was 0.80 (0.56;1.12) for the restrictive group compared with the liberal group. However, after adjusting for age, sex, CCI, medication, time to surgery, and type of surgery, the relative mortality risk was 0.72 (0.57;0.91). Overall, 90-day mortality was 17% (16;10); in the restrictive group, it was 15% (13;17), and in the liberal group, it was 19% (17;21). Comparing the restrictive to the liberal group, the crude relative mortality risk was 0.91 (0.69;1.19), whereas the adjusted relative mortality risk was 0.78 (0.65;0.94).

In the subgroup analysis for patients demonstrating a hemoglobin level between 7.0 and 8.9 g/dL ($n = 1101$), there was a 30-day mortality proportion equal to 13% (0.10;0.16) in the restrictive period compared with 10% (0.08;0.13) for the liberal period.

## Discussion

Using a population-based study design of hip fracture patients, the present study reported on transfusion frequency and mortality following the introduction of the NCG on restrictive blood transfusion. These data suggest that the lower hemoglobin threshold for RBC transfusion does not increase mortality for older patients with a hip fracture. This observation is consistent with the current literature suggesting there is no difference in patient outcomes between restrictive and liberal treatment strategies [4]. One RCT [18], however, has demonstrated a higher mortality with the restrictive treatment strategy, but this was only for nursing home patients and only per protocol analysis, not the intention-to-treat analysis. This particular RCT is therefore restricted to a small subgroup of hip fracture patients. In contrast, we found a decreased mortality in the restrictive period, which was for all patients, including those with a hemoglobin > 9.0 g/dL. In our data, we see a baseline difference in time to surgery, which is longer in the restrictive group. This may be due to the introduction of new oral anticoagulants (NOAC), which is usually equivalent to a 2-day postponement of surgery to reduce operative bleeding [19]. An increased time to surgery is associated with an increased mortality risk [20], which therefore could lead to an increased risk of mortality in the restrictive group. However, an important bias for mortality is the continuous work for improvement in mortality, and the lowered mortality may therefore lie in

### Table 3

Patients admitted and receiving red blood cell transfusion divided by hospital and group

|                  | Liberal group |                    | Restrictive group |                    | $p <$ for transfusion % |
|------------------|---------------|--------------------|-------------------|--------------------|-------------------------|
|                  | Admitted Transfused n Transfused % (95% CI) | Admitted Transfused n Transfused % (95% CI) |                  |                    |                         |
| Total            | 1494 628 42 (40.45) | 1414 430 30 (28.33) | 0.001             |                    |                         |
| Hospital 1       | 640 268 42 (38.46) | 577 145 25 (21.29) | 0.001             |                    |                         |
| Hospital 2       | 312 135 43 (38.49) | 283 99 35 (29.41) | 0.039             |                    |                         |
| Hospital 3       | 263 113 43 (37.49) | 233 44 19 (14.24) | 0.001             |                    |                         |
| Hospital 4       | 279 112 40 (34.46) | 321 142 44 (39.50) | 0.311             |                    |                         |

### Table 4

Mean hemoglobin level (g/dl) at admission and prior to first red blood cell transfusion by group

|                  | All patients | Liberal group | Restrictive group | $p<$ |
|------------------|--------------|---------------|-------------------|------|
|                  | Mean (95% CI)| Mean (95% CI) | Mean (95% CI)     |      |
| Total, admission | 12.3 (12.2;12.3) | 12.3 (12.2;12.4) | 12.3 (12.2;12.4) | 0.54 |
| Total, first transfusion | 8.8 (8.7;8.9) | 9.1 (9.0;9.2) | 8.5 (8.2;8.4) | 0.001 |
other unmeasured aspects since the mortality for hip fracture patients has improved over the last 35 years [21]. An important factor in improving the mortality for hip fracture patients is a multidisciplinary approach [22], and especially an integrated orthogeriatric care [23]. We therefore not interpret the demonstrated decreased mortality as a direct cause to the introduction of a restrictive transfusion strategy.

Being a cohort study, there may be uncontrolled bias. There are several baseline differences which could constitute significant biases. One is the slightly higher proportion of females in the restrictive group, with two retrospective cohort studies [24, 25] finding an odds ratio of 1.5 for females receiving RBC transfusion compared to males. In contrast, Johnston et al. [26] demonstrated in a cohort study of 3625 patients that males had a hazard ratio of 1.8 upon receiving an RBC transfusion compared with females, whereas three other studies did not observe any difference in risk associated with receiving RBC transfusions between males and females [27–29]. Therefore, we suggest that differences between the male and female proportion in this study does not constitute meaningful bias. A second baseline difference is a higher proportion of intramedullary nails in the restrictive group. A shift from sliding hip to intramedullary nails are also seen in other Scandinavian countries [30, 31] resulting in a lower reoperation for complex pertrochanteric fractures [32]. A higher use of intramedullary nails in the restrictive group may increase the likelihood of having a transfusion [24, 25, 28, 33]. This would potentially lead to a slightly higher transfusion proportion in the restrictive group. Accordingly, while the difference in transfusion proportion between the groups could be due to different baselines, we are certain that the reason for a lower RBC transfusion proportion in the restrictive group is due to the lower hemoglobin threshold.

Our large cohort study confirms that a restrictive RBC transfusion threshold does not affect mortality and even though the included studies are of low-quality, a meta-analysis demonstrates no difference in functional recovery or postoperative morbidity in hip fracture patients when comparing restrictive and liberal transfusion thresholds [4]. So why hold on to a liberal transfusion threshold? RBC transfusions are not without complications and specific complications such as transfusion-associated circulatory overload (TACO), acute hemolysis, and transfusion-related acute lung injury (TRALI) can all cause further morbidity and mortality [3]. There may even be a higher association with infections when treated with RBC transfusion [34]. These considerations in combination with our findings should lead to a restrictive transfusion threshold for hip fracture patients.

This study has prospectively collected data from several databases and has precise longitudinal follow-up data due to unique civil registration numbers. This is a major strength since the study is performed on all hip fracture patients and therefore reflects the true clinical value of a restrictive RBC transfusion strategy.

### Conclusion

These data suggest that the introduction of an NCG on restrictive blood transfusion leads to lower transfusion frequency in hip fracture patients > 65 years old. Even though this reduction is associated with decreased mortality at both 30 and 90 days, it may be explained by other issues than restrictive transfusion strategy. There has been an improvement in the mortality of hip fracture patients in Denmark, and we suggest that a restrictive transfusion strategy does not lead to increased mortality.

### Abbreviations

BMI: Body mass index; CCI: Charlson Comorbidity Index; CI: Confidence interval; NCG: National Clinical Guideline; RBC: Red blood cell; RCT: Randomized controlled trial

### Acknowledgements

The Danish Interdisciplinary Registry of Hip Fractures and Odense Pharmacoepidemiological Database kindly delivered data free of charge.

### Funding

We received 150,000 dKr from the Region of Southern Denmark’s Research Fund that seeks to promote health research. The Regional Council each year grants 45 million dKr for research conducted by researchers in the Region of Southern Denmark. The grant given covered data extraction and analysis fees for three research papers. The Research Fund had no direct involvement.

| Table 5 Hemoglobin level at time of first red blood cell transfusion by group |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Hemoglobin level | Overall | 30-day mortality | Liberal group | Restrictive group | p|< |
| g/dL n % | n % (95% CI) | n % (95% CI) | n % (95% CI) |
| < 7.0 64 6 | 19 3 (2;4) | 45 10 (8;13) | 0.001 |
| 7.0–7.9 260 25 | 103 16 (13;19) | 157 37 (32;41) |
| 8.0–8.9 339 32 | 207 33 (29;37) | 132 31 (26;35) |
| > 9.0 345 33 | 254 40 (37;44) | 91 21 (17;25) |
| Missing 50 5 | 45 7 | 5 1 |
| Total 1058 100 | 628 100 | 428 100 |

Viberg et al. Journal of Orthopaedic Surgery and Research (2018) 13:116
in this paper in any form. The researchers were therefore completely independent from the Research Fund.

Availability of data and materials
Due to Danish legislation, the data are not publicly available. However, the corresponding author would be happy to answer any question about data.

License agreement
In submitting an article to any of the journals published by BioMed Central, I certify that;

1. I am authorized by my co-authors to enter into these arrangements.
2. I warrant, on behalf of myself and my co-authors, that:
   - The article is original, has not been formally published in any other peer-reviewed journal, is not under consideration by any other journal and does not infringe any existing copyright or any other third party rights;
   - I/we have taken due care to ensure the integrity of the article. To our—and currently accepted scientific—knowledge, all statements contained in it purporting to be facts are true and any formula or instruction contained in the article will not, if followed accurately, cause any injury, illness, or damage to the user.
3. I, and all co-authors, agree that the article, if editorially accepted for publication, shall be licensed under the Creative Commons Attribution License 4.0. In line with BioMed Central’s Open Data Policy, data included in the article shall be made available under the Creative Commons 1.0 Public Domain Dedication waiver, unless otherwise stated. If the law requires that the article be published in the public domain, I/we will notify BioMed Central at the time of submission, and in such cases, not only the data but also the article shall be released under the Creative Commons 1.0 Public Domain Dedication waiver. For the avoidance of doubt, it is stated that sections 1 and 2 of this license agreement shall apply and prevail regardless of whether the article is published under Creative Commons Attribution License 4.0 or the Creative Commons 1.0 Public Domain Dedication waiver.

Authors’ contributions
BV, SO, and JL contributed to the conception or design of the work. BV, LP, LA, JS, CM, and KT drafted the work or revised it critically for important intellectual content. All authors approved of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Register studies in Denmark do not have ethical approval or consent for participants since it is routinely collected data. All aspects of the present study were reviewed and approved by the Danish Data Protection Agency (case number 16/10091) and the Danish Patient Safety Authority (case number 3-3013-1709/1).

Competing interests
The following authors declare that they have no competing interests: BV, PG, JS, LP, LA, KT, CM, JL. Professor SO has received grants from Biomet Denmark and Biomet Inc, DePuy and Protekompagniet, and Zimmer. He has a board membership in Mundipharma International Ltd, and he is also on the advisory board for Eli Lilly (Fostero) and MSD (NSAID). He is investigator for Sanofi-aventis Denmark A/S.

References
1. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Steering Committee of the Pentasaccharide in Hip-Fracture Surgery S: Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345(18):1298–304.
2. Pedersen AB, Cronin Fenton D, Norgaard M, Kristensen NR, Kuno Moller B, Erikstrup C. Body mass index, risk of alloageneic red blood cell transfusion, and mortality in elderly patients undergoing hip fracture surgery. Osteoporos Int. 2016;27(9):2765–75.
3. Willett LR, Garson JL. Management of postoperative complications: anemia. Clin Geriatr Med. 2014;30(2):279–84.
4. Brunsbjerg SJ, Millette SL, Shokoohi A, Pullford EC, Doree C, Murphy MF, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev. 2015;4:CD009699.
5. Canson JL, Stansworth JL, Roubinian N, Ferguson DA, Trulsd D, Doree C, et al. Transfusion thresholds and other strategies for guiding alloageneic red blood cell transfusion. Cochrane Database Syst Rev. 2016;10:CD002042.
6. Docherty AB, O’Donnell R, Brunsbjerg SJ, Trivella M, Doree C, Holst L, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. BMJ. 2016;352:i3351.
7. National Institute for Health and Care Excellence. Transfusion: NICE guideline NG24. In: 2015.
8. Danish Health Authority: National Clinical Guideline on the Indication for Blood Component Transfusion. In: 2014.
9. Benchimol EI, Smeeth L, Gormann A, Haron K, Moher D, Petersen I, et al. The Repporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
10. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):341–9.
11. Danish Health Authority: Guidance on Blood Transfusion [Vejledning om blodtransfusion]. In: 2007.
12. The Nordic Medico-Statistical Committee: NOMESCO Classification of Surgical Procedures; 2012.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
14. Danish Society of Clinical Immunology: Danish Transfusion Database - National Annual Report. In: Regions of Denmark; 2016.
15. Hallas J, Hofftjdzsch M, Rix M, Olesen M, Reikv M, Pottegard A. Odense Pharacopeiiodemical Database: a review of use and content. Basic Clin Pharmacol Toxicol. 2017;120(3):419–25.
16. Mainz K, Krog BR, Bjornshaw B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. Int J Qual Health Care. 2004;16(Suppl 1):145–50.
17. Schmidt M, Schmidt SA, Sandegaard JL, Ehrensen V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:949–90.
18. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. Acta Orthop. 2015;86(3):363–72.

19. Danish Society of Thrombosis and Hemostasis: [perioperative regulation of antithrombotic treatment]. In.; 2016.

20. Nyholm AM, Gromov K, Palm H, Brix M, Kallenrose T, Troelsen A, et al. Time to surgery is associated with thirty-day and ninety-day mortality after proximal femoral fracture: a retrospective observational study on prospectively collected data from the Danish Fracture Database Collaborators. J Bone Joint Surg Am. 2015;97(16):1333–9.

21. Pedersen AB, Ehrenstein V, Szepligeti SK, Lunde A, Lagenros YT, Westerlund A, et al. Thirty-five-year trends in first-time hospitalization for hip fracture, 1-year mortality, and the prognostic impact of comorbidity: a Danish Nationwide Cohort Study, 1980-2014. Epidemiology. 2017;28(6):898–905.

22. Shenuouda M, Silk Z, Radha S, Bouanem E, Radford W. The introduction of a multidisciplinary hip fracture pathway to optimise patient care and reduce mortality: a prospective audit of 161 patients. Open Orthop J. 2017;11:309–15.

23. Middleton M, Wan B, da Arsalncaco R. Improving hip fracture outcomes with integrated orthogeriatric care: a comparison between two accepted orthogeriatric models. Age Ageing. 2017;46(3):465–70.

24. Kadar A, Chechik O, Steinberg E, Reider E, Sternheim A. Predicting the need for blood transfusion in patients with hip fractures. Int Orthop. 2013;37(6):693–700.

25. Desai SJ, Wood KS, Marsh J, Bryant D, Abdo H, Lawwedy AR, et al. Factors affecting transfusion requirement after hip fracture: can we reduce the need for blood? Can J Surg. 2014;57(5):342–8.

26. Johnston P, Wyn-Jones H, Chakravarty D, Boyle A, Parker MJ. Is perioperative blood transfusion a risk factor for mortality or infection after hip fracture? J Orthop Trauma. 2006;20(10):675–9.

27. Martinsen M, Valland H, Solheim LF, Holvik K, Ranhoff A. A restrictive policy for red blood cell transfusion in older hip fracture patients: experiences from a patient register. BMC Res Notes. 2016;9:75.

28. Madsen CM, Jorgensen HL, Norgaard A, Ris T, Jantzen C, Pedersen OB, et al. Preoperative factors associated with red blood cell transfusion in hip fracture patients. Arch Orthop Trauma Surg. 2014;134(3):375–82.

29. Shokoohi A, Stanworth S, Mistry D, Lamb S, Staves J, Murphy MF. The risks of red cell transfusion for hip fracture surgery in the elderly. Vox Sang. 2012;103(1):22–30.

30. Norwegian Hip Fracture Register: annual report. In.; 2016.

31. Rikshoï: annual report. 2016.

32. Matre K, Havelin LI, Gjertsen JE, Vinje T, Espehaug B, Fevang J. Sliding hip screw versus IM nail in reverse oblique trochanteric and subtrochanteric fractures. A study of 2716 patients in the Norwegian Hip Fracture Register. Injury. 2013;44(6):735–42.

33. Morris R, Rethnam LI, Russ B, Topliss C. Assessing the impact of fracture pattern on transfusion requirements in hip fractures. Eur J Trauma Emerg Surg. 2017;43(3):337–42.

34. Carson JL, Altman DG, Duff A, Noveck H, Weinstein MP, Sonnenberg FA, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. Transfusion. 1999;39(7):694–700.