UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Patient blood management in elective fast-track hip-and knee arthroplasty – clinical and epidemiological studies

Doctoral Thesis

Øivind Jans

The Section for Surgical Pathophysiology, The Department of clinical Immunology and The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement

Rigshospitalet, Copenhagen, Denmark
2021

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defence for the doctoral degree in medical science.
Copenhagen, 14 December 2021

Ulla Wewer, Head of Faculty

The public defence will take place at Rigshospitalet, Auditorium 2.
May 6th 2022 at 2pm.

Title page: Samuel van Hoogstraten “The anemic Lady”, 1660 - 1678
Rijksmuseum, Amsterdam, The Netherlands
Published in the public Domain

ISBN 978-87-973837-0-4

Acknowledgements

The foundation for this thesis was laid during my position as a research fellow at the Section for Surgical Pathophysiology, Rigshospitalet and The Lundbeck Foundation Centre for fast-track hip and knee Replacement (LFHKR) from 2009 to 2013 and with further studies conducted in the following years during my training and clinical positions as an anaesthesiologist. The work has been made possible with the financial support from The Lundbeck Foundation, Dr. Fritz Karners and Wife Edith Karners Foundation, and Edgar Schnohr and wife Gilberte Schnohr's Foundation.

Foremost, I must express my deepest gratitude to my academic supervisors Prof. Henrik Kehlet and Prof. Pär I. Johansson who have both provided excellent supervision, patience and support for more than 10 years, both in good times and when progress was slow or personal obstacles piling up. Professor Niels H. Secher led me into research and anesthesiology for which I am him forever thankful.

This work would not have been possible without the help and support from numerous patients, surgeons, anesthesiologists and nurses within the LFHKR collaboration. Dr. Henrik Husted has been a longstanding support and has provided invaluable expert knowledge into the field of orthopaedic surgery. Prof. Thomas Bandholm has been a great sparring partner and expert in all things related to functional outcome measures. In addition, Drs. Christian Skovgaard-Nielsen, Kirill Gromov and prof. Anders Troelsen are to be thanked for great collaboration with the studies conducted at Hvidovre Hospital.

Furthermore, Anesthesiologists Ulrik Grevstad and Hans Mandøe have been invaluable in planning and carrying out the epinephrine RCT, while research nurses Stina Bogø, Heidi R. Wede, Susanne Jung and Charlotte Troldborg have put in countless hours into patient inclusion and data collection, I cannot thank you enough.

I must also thank Dr. Carsten Tollund for being a great friend and clinical mentor, and Drs. Christian Selmer, Martin Blomberg Jensen, Troels Haxholdt Lunn and Lars Broksø Holst for support, sparring and friendship.

Finally, I am deeply grateful to my wife Eva for her love and support and to my 2 children Erik and Karen for making me happy every day.

This thesis is written in the loving memory of Ellen Kristine Charlotte Jans – my mother and first academic mentor.

Table of contents

Abbreviations

6MWT	Six-minute walk-test
CAS	Cumulated ambulation score
FCM	Ferric Carboxymaltose
FFP	Fresh frozen plasma
FIM	Functional independence motor score
Hb	Hemoglobin
ID	Iron deficiency
IDA	Iron deficiency anemia
IV	Intravenous
LFHKR	Lundbeck Foundation Centre for Fast-Track Hip- and Knee Replacement
LOS	Length of stay
PAM	Preoperative anemia management
PBM	Patient Blood Management
OH	Orthostatic hypotension
OI	Orthostatic intolerance
QOL	Quality of Life
RBC	Red blood cells
RCT	Randomized controlled trial
SSI	Surgical site infection
SVR	Systemic vascular resistance
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TUG	Timed up-and-go test
TXA	Tranexamic acid
UK	United Kingdom
US	United States
WHO	World Health Organization

List of papers

This thesis is based on the following original papers:

I. **Jans Ø**, Jørgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion. 2014; **54**:717–26. [1]

II. Jørgensen CC, **Jans Ø**, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Preoperative anaemia and newly diagnosed cancer 1 year after elective total hip and knee arthroplasty. Vox Sang. 2015; **109**:62–70. [2]

III. **Jans Ø**, Nielsen CS, Khan N, Gromov K, Troelsen A, Husted H. Iron deficiency and preoperative anaemia in patients scheduled for elective hip- and knee arthroplasty - an observational study. Vox Sang. 2018; **113**:260–7. [3]

IV. **Jans Ø**, Kehlet H, Hussain Z, Johansson PI. Transfusion practice in hip arthroplasty--a nationwide study. Vox Sang. 2011; **100**:374–80. [4]

V. **Jans Ø**, Kehlet H, Johansson PI. Transfusion-related mortality after primary hip arthroplasty - an analysis of mechanisms and confounders. Vox Sang. 2012; **103**:301–8. [5]

VI. **Jans Ø**, Grevstad U, Mandøe H, Kehlet H, Johansson PI. A randomized trial of the effect of low dose epinephrine infusion in addition to tranexamic acid on blood loss during total hip arthroplasty. Br J Anaesth. 2016; **116**:357–62. [6]

VII. Nielsen CS, **Jans Ø**, Ørsnes T, Foss NB, Troelsen A, Husted H. Combined Intra-Articular and Intravenous Tranexamic Acid Reduces Blood Loss in Total Knee Arthroplasty. J Bone Jt Surg. 2016; **98**:835–41. [7]

VIII. **Jans Ø**, Bandholm T, Kurbegovic S, Solgaard S, Kjærsgaard-Andersen P, Johansson PI, Kehlet H. Postoperative anemia and early functional outcomes after fast-track hip arthroplasty: a prospective cohort study. Transfusion. 2016; **56**:917–25. [8]

1. Introduction

Patients undergoing elective hip- (THA) and knee (TKA) arthroplasty experience substantial perioperative blood loss resulting in various degrees of postoperative anemia, but anemia may also be present preoperatively in 15 to 39 % of patients. [9] Although anemia tolerance may differ between patients, severe anemia can cause organ dysfunction and even moderate postoperative anemia may delay early recovery due to anemia related symptoms such as fatigue and dizziness.[10] The transfusion of red blood cells (RBC) corrects anemia by increasing the hemoglobin (Hb) concentration and thus the oxygen carrying capacity of the blood, but carries inherent risks of complications and has been associated with increased postoperative morbidity and mortality.[11] It is estimated that orthopedic surgery accounts for approximately 10% of all transfused red cell units in the UK,[12] and hip- and knee surgery were both among the top 10 most RBC transfusion consuming procedures in Denmark in 2012. [13] Together with an increased awareness of the risks of allogeneic blood transfusion, the focus on measures to reduce anemia and surgical blood loss and recent evidence suggesting the safety of a restrictive approach to RBC transfusion in most patients, [14–16] allogeneic RBC transfusion rates in elective THA and TKA have decreased dramatically. This has been demonstrated both among Danish- and European centres but also recently in the US.[17–19] However transfusion rates are still highly variable for the same procedure across different orthopedic departments, despite existing national and international guidelines, suggesting a high variation in actual transfusion practice.[4 17 20–22] Strategies to minimize the risk of exposure to allogeneic RBC transfusion have been introduced in the concept of perioperative "Patient Blood Management" (PBM) which is a multimodal three pillar strategy. This includes the assessment and treatment of preoperative anemia (Pillar I), measures to reduce perioperative blood loss (Pillar II), and a rational approach to managing postoperative anemia (Pillar III). [14] The introduction of PBM programmes in orthopedic surgery has resulted in decreasing transfusion rates, but wide and systematic implementation among orthopedic departments has yet to be established.[23–25] Most evidence regarding management of perioperative anemia and blood loss in elective joint arthroplasty is derived from traditional surgical regimens and has

not previously been evaluated in the context of fast-track THA / TKA patients with early mobilization and discharge with a short median length of hospital stay (LOS) of 1-3 days.

Thus, the aim of this thesis was to examine aspects related to all 3 pillars of perioperative blood management by both epidemiological and clinical studies in a Danish elective joint arthroplasty cohort with most of the included studies performed within a fast-track context,[1–3 6–8] while the remaining 2 where carried out in a nationwide Danish context.[4 5] Topics covered were the prevalence, causes and impact of preoperative anemia, current transfusion practice in Denmark, possible postoperative mortality related to transfusion, measures to reduce perioperative blood loss and the role of postoperative anemia for early functional outcomes after THA in the context of a fast-track regimen with early mobilization and short LOS.

2. Specific aims of studies included in this thesis

- To evaluate the prevalence of preoperative anemia in patients presenting for primary elective fast-track THA/TKA and to evaluate a possible association between preoperative anemia and postoperative morbidity (Study 1).[1]
- To determine if patients with preoperative anemia prior to primary elective fast-track THA/TKA had a higher risk of being diagnosed with cancer 1 year following surgery, compared to non-anemic patients (Study 2).[2]
- To evaluate the prevalence of iron deficiency prior to fast-track THA/TKA in preoperatively anemic patients according to the World Health Organization (WHO) anemia definition and in all patients with a preoperative Hb < 13 g/dl (Study 3).[3]
- To evaluate RBC transfusion practice, variation in transfusion rates and timing of RBC transfusion in relation to surgery in a nationwide study of patients undergoing elective primary and revision THA in Denmark (Study 4).[4]
- To evaluate cases of mortality with a possible relationship to RBC transfusion in elective primary THA in a mechanistic study using patient chart review (Study 5).[5]
- To evaluate whether intraoperative low-dose epinephrine infusion, in addition to IV TXA administration, reduced perioperative blood loss compared to placebo and IV TXA in elective fast-track THA (Study 6).[6]
- To evaluate whether the combined administration of IV + intra-articular (IA) tranexamic acid (TXA) reduced perioperative blood loss compared to IV TXA + IA placebo in elective fast-track TKA (Study 7).[7]
- To evaluate whether postoperative Hb level at discharge was associated with functional recovery and quality of life during the first 2 weeks after fast-track THA in patients > 65 years of age (Study 8).[8]

3. Foundation

The studies forming the foundation for this thesis were conducted in the years 2008 to 2018, spanning 10 years. Studies were conducted within the Lundbeck Foundation Centre for Fast-Track Hip- and Knee Replacement (LFHKR), which was founded in 2009 and is a research collaboration between 9 Danish- and 1 Swedish high-volume orthopedic centres adhering to the fast-track concept. The participating centres co-ordinates research activities, register all patient demographics, specific co-morbidities and preoperative Hb in a shared study database which can be linked to other national health related databases to provide insight into individual patient trajectories following surgery in epidemiological studies. In addition, observational- and interventional clinical studies are conducted within the framework of LFHKR, either as single- or multicentre studies.

4. Scope, delimitation and weighting

The topic of PBM is broad, interventions are multimodal, and the underlying body of evidence is huge and rapidly growing. The studies forming the basis for this thesis represents elements from all three pillars in PBM but far from covers all individual topics within each of these pillars. This is also reflected in the present narrative review, which should not be considered an exhaustive systematic review of all possible PBM issues in orthopedic surgery, but rather the topics covered by the 8 included studies have the main focus. Therefore, interventions such as intra- and postoperative cell-salvage, preoperative autologous blood donation and deliberate hypotensive anesthesia are given less attention, as these were not covered in the included studies and are also not routinely practiced among Danish orthopedic- and anesthesia departments performing primary fast-track hip- and knee arthroplasty. In contrast, special attention is given to the issues related to early functional recovery with a short LOS, as this is inherent to the fast-track concept.

Of the 8 included studies, 6 were carried out in a fast-track THA/TKA cohort within the LFHKR centres.[1–3 6–8] However, 2 of the 5 epidemiological studies in

this thesis used a nationwide approach, and thus included patients from both fast-track and non fast-track centres.[4 5] Furthermore, studies were conducted in the same 10 year period (2008 – 2018) as when transfusion rates in THA/TKA were drastically reduced and this is essential to consider when interpreting the results from the individual studies included in this thesis.

Finally, although this thesis covers both THA and TKA, the included studies are skewed towards inclusion of THA patients (included in 7 of 8 studies) at the expense of TKA patients (included in 4 of 8 studies). The reason for not including TKA patients in some studies was partly due to the view that the need for transfusion was a larger issue in THA than in TKA, and partly due to efforts of standardization,[4 5] the problems posed with the use of tourniquet in evaluating intraoperative blood loss,[6] and the view that early recovery impaired by pain was a larger problem in TKA than in THA.[8] However, the thesis as a whole and the following narrative review covers both surgical procedures.

5. The concept of fast-track hip and knee arthroplasty.

The term "fast-track surgery" refers to implementation of a wide range of evidence-based pre-, intra- and postoperative measures with the ultimate goal to enhance early recovery and decrease postoperative morbidity.[26] In this multimodal concept several perioperative interventions related to anesthetic and surgical techniques, optimized fluid therapy, multimodal opioid sparing analgesia, preoperative patient education, early oral nutrition, early postoperative mobilization and discharge to home using functional discharge criteria have been implemented.[27] Fast-track protocols were at first developed and implemented in abdominal surgery but have now been established among many Danish orthopedic departments in unselected patients undergoing elective THA and TKA. Thus, the implementation of fast-track protocols has been associated with a decrease in postoperative morbidity and in LOS from 7-10 days to median 2-3 days, with some centres now evaluating THA/TKA as an ambulatory procedure in selected patients.[28–31]. However, several questions and future challenges remain to be solved in fast-track THA/TKA including optimal pain-management, postoperative orthostatic intolerance, postoperative cognitive dysfunction and sleep disturbances, further reduction in postoperative

morbidity and finally issues related to transfusion and pre- and postoperative anemia.[32] Although, specific interventions, to reduce blood loss such as the routine use of tranexamic acid (TXA) and avoidance of postoperative drainage have now been implement among Danish fast-track THA/TKA centres,[33] several other aspects related to blood loss, anemia and transfusion need further study. Postoperative mobilization occurs already on the day of surgery and extensively in the following days prior to discharge but may potentially be impaired by anemia symptoms or the need for RBC transfusion.[34] Furthermore, due to early discharge and a short a LOS of 2-3 days in fast-track patients, the time and consequences of nadir Hb may occur at home after discharge, in contrast to patients with a longer LOS where anemia related symptoms can be readily identified and addressed during hospital admission.

6. Patient blood management – an overview

Patient blood management (PBM) is defined by the Society for Advancement of Blood Management (SABM) as "The timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome".[35]

In a surgical context, PBM should be viewed as a bundle of interventions organized into a three pillar strategy aiming for the appropriate use of blood products by avoiding unnecessary allogeneic transfusion.[14]. The first pillar of PBM consists of pre- and postoperative optimization of hematopoiesis, with a focus on assessment and treatment of preoperative anemia, by biochemical screening and correction of iron- or other nutritional deficiencies and by the use of erythropoiesis stimulating agents (ESA) in some patients.[36 37] The second pillar aims at minimizing perioperative blood loss by application of minimally invasive surgical techniques, avoidance of unnecessary blood sampling, the use of systemic pharmacologic agents such as antifibrinolytics,[38] the application of local hemostatic agents,[39] and the use of intra- or postoperative cell-salvage techniques in appropriate procedures. The third pillar consists of a rational management of perioperative anemia by providing supportive measures and harness the individual patients tolerance to anemia and by the use of evidence based restrictive transfusion triggers, thus minimizing the need for RBC transfusion.[40] The different PBM components and their efficacy in the perioperative period have recently been reviewed.[41]

It is emphasized that PBM is a multimodal and multidisciplinary strategy that should be tailored to the specific surgical procedure and the needs of the individual patient. Therefore, health personnel across several specialities such as surgeons, anesthesiologists and blood bankers may be involved in order to secure successful implementation of PBM programmes.

In 2008 PBM was launched as a state-wide initiative by the Western Australia department of Health,[42] and has since been adopted by the World Health organization (WHO) in 2010.[43] The formation of national PBM programmes is now endorsed by The European Commission (EC). Furthermore, several blood management components, including preoperative anemia management and the

use of tranexamic acid, are now recommended in the UK NICE guidelines under the British National Health Service (NHS).[44] Introduction of various PBM measures has successfully led to reduced transfusion rates, improved clinical outcomes and reduced cost,[45] in reports spanning several countries and surgical specialties, including cardiac,[46] abdominal,[47] and major orthopedic surgery.[24 48–56] Most, but not all,[54] of these protocols addressed preoperative anemia (Pillar 1) but differed substantially in both scope and the implemented measures and the majority did not consider all 3 pillars of PBM. However, a recent systematic review and meta-analysis, including 17 studies that implemented at least 1 measure from each of the 3 PBM pillars, demonstrated significant reductions in allogeneic RBC transfusion rate, (RR 0.61, 95% CI 0.55 – 0.68), but also a reduction in the total number of complications (RR 0.88, 95% CI 0.74 – 0.88) and in mortality (RR 0.89, 95% CI 0.80 – 0.98).[57] Importantly, the largest blood sparing effect was noted among patients undergoing orthopedic surgery (13 studies; RR 0.45, 95% CI 0.35 – 0.59).[57]

Although a recent study reported increased knowledge and implementation of PBM measures among UK hospitals,[58] wider implementation of systematic PBM protocols are variable and seems to be lacking in many countries. [23–25 59 60] Furthermore, apart from the routine use of TXA and the adherence to restrictive transfusion thresholds, systematic PBM protocols and especially preoperative anemia management, are not yet a part of routine care among the majority of Danish orthopedic departments.[1]

There may be several barriers for the successful implementation of PBM protocols, including perceived cost or logistical challenges. Therefore, in an attempt to overcome the barriers in adopting PBM into clinical practice, several guidelines and bundles to support PBM implementation have recently been published.[61 62]

7. Patient blood management - Issues in hip- and knee arthroplasty

Although many PBM measures are similar across surgical specialities, a prerequisite for the successful implementation of PBM protocols is that all 3 pillars of the PBM approach are tailored to the specific perioperative challenges posed by the individual type of surgery – a procedure specific approach. In the following sections, general issues in PBM are discussed but with a specific focus on PBM components with relevance for elective THA/TKA.

7.1 Preoperative anemia

7.1.1 Prevalence and classification

Most patients undergoing elective THA or TKA are elderly and some may be anemic already prior to surgery. Several studies, spanning different countries have evaluated the prevalence of preoperative anemia in THA and TKA. A systematic review published in 2010 which included 5 studies reporting the prevalence of preoperative anemia in elective THA/TKA found that the proportion of patients that were anemic preoperatively ranged from 15 to 39%.[9] However, anemia definition was variable and did not follow the definition by the World Health Organization (Hb < 12 g/dl in females and < 13 g/dl in males).[63] Thus some studies considered patients with Hb < 13 g/dl anemic regardless of gender,[64 65] and one study used a hematocrit < 30% as anemia cut-off.[66] More recent studies have reported a lower preoperative anemia prevalence in the range of 10 to 17%,[17 24 67–69] and this is consistent with our findings from a Danish fast-track THA/TKA cohort, where the prevalence of preoperative anemia was 13% and ranged between 10 and 15% across the included 6 high-volume orthopedic centres.[1] As women in general have a lower circulating red cell mass and a higher risk of transfusion, it has recently been proposed that the definition of preoperative anemia and the target for Hb optimization should be changed to 13 g/dl for both genders.[70–72] However, this will substantially increase the number of patients requiring preoperative anemia management and may pose logistical challenges in some centres. Thus, in a recent study in fast-track THA/TKA we found that the proportion of patients in need of preoperative

anemia management increased from 11 to 28 % of all patients with a change in preoperative anemia definition from the WHO criteria to 13 g/dl regardless of gender.[3]

When evaluating the type of preoperative anemia, investigation of the patients iron status is a key initial step, as iron deficiency (ID) is the most common and reversible cause of anemia in the elderly.[36 73] However, the classification of anemia and identification of ID is not straightforward, as the different anemia types may overlap in "mixed anemia" and readily available markers of iron stores such as ferritin is elevated in the presence of inflammation.[74] In this situation, other biochemical markers such as the serum transferrin receptor level, reticulocyte hemoglobin content or hepcidin assays may aid in diagnosing iron deficiency but may not be available in most surgical centres.[75] However, point-of-care tests based on either soluble transferrin receptor levels or non-invase measurement of Zinc protoporphyrin are being developed and may be used in a clinical setting to diagnose iron deficiency anemia (IDA) in the future.[76 77] A distinction needs to be made between absolute iron deficiency (low body iron stores), iron sequestration (decreased mobilization of iron and low availability to hematopoietic tissue due to inflammation and hepcidin upregulation) or functional iron deficiency (insufficient mobilization of iron despite normal / elevated iron stores due to increased demand).[70] Until recently, a clear consensus regarding the criteria for identification of absolute- and functional iron deficiency in the context of preoperative anemia was lacking, but is now available.[70 74]

A recent large study in a cohort of 3342 patients undergoing mixed non-cardiac surgery reported an overall ID prevalence of 62 % in patients with a Hb < 13 g/dl and a ID prevalence of ~55% of patients undergoing major orthopedic surgery (THA, TKA and spine surgery).[78] However, only few studies have evaluated the type of preoperative anemia by assessment of iron status and other biochemical markers in the specific context of elective THA/TKA.[3 65 67 79 80] Moreover, these studies used different criteria for the diagnosis of anemia and used different biochemical markers for the diagnosis of ID. Two studies using hypochromic indices (low mean corpuscular hemoglobin concentration, only defined in 1 study) as a criterion for ID, reported a prevalence of ID in 23 % and 60 % of

preoperatively anemic patients, respectively.[79 80] One study used an elevated soluble transferrin receptor (sTfR) to identify patients with "functional iron deficiency" and found that 45% of preoperatively anemic patients had an elevated sTfR.[65] Only three studies used the ferritin level in the diagnosis of ID.[3 67] One study included 75 anemic THA/TKA patients and found that ID defined as a ferritin level < 30 ug/L was prevalent in 30% of anemic patients before surgery, while "anemia of chronic disease" accounted for 31% and a further 14% had mixed causes of anemia.[67] In a Danish single-centre cohort including 882 fast-track THA/TKA patients, we defined ID as a ferritin level < 30 ug/L or a ferritin level between 30-100 ug/L with a concomitant transferrin saturation (TSAT) < 20 %. In this study, which included 95 anemic patients (WHO definition), ID was prevalent in 41% of anemic patients with a further 20 % having iron sequestration.[3] In the same study, ID in non-anemic patients presenting for surgery was found in 18 % which is somewhat comparable to the 13% reported in a previous study.[3 67]

Although the range reported varies between studies, it can be concluded from the above that preoperative anemia is common in elective THA/TKA and that ID is a major cause of anemia prior to elective THA/TKA and ID may also be present in patients without preoperative anemia.

7.1.2 Consequences of preoperative anemia

In a wide range of observational studies across several surgical specialities, the presence of preoperative anemia has been associated with an increased risk of postoperative morbidity and mortality, in addition to a markedly increased risk of receiving allogeneic RBC transfusion.[9 81–83] However, the prevalence of anemia increases with age and anemia is associated with a wide range of comorbidities which in themselves may negatively affect outcome.[84] Thus, the well-established association between preoperative anemia and poor outcome may relate to one or more of the following underlying mechanisms:

1) anemia *per-se* has a causal negative effect (organ dysfunction, fatigue etc.)
2) negative effect mediated through the higher risk of receiving allogeneic blood transfusion (higher risk of infection through immunomodulation or other transfusion related side-effects or complications causing morbidity)

3) residual confounding (higher degree of comorbidity and frailty in anemic patients not accounted for in observational studies).

All of the 3 above factors may contribute to the observed anemia related morbidity and mortality, but the extent has not been elucidated and may differ with different surgical settings, patient populations, transfusion policies (restrictive/liberal), and the research methodology used, including the choice of confounding factors in adjusted analyses. One hypothesis regards the problem as a "double-hit" situation, where a patient may start out as vulnerable due to preoperative anemia "first hit" and frailty but a "second hit" is added with surgical blood loss resulting in aggravation of anemia and subsequent allogeneic RBC transfusion. Nevertheless, the negative association between preoperative anemia and outcome has been demonstrated in several large observational studies in cardiac surgery,[85] and mixed non-cardiac surgery including patients scheduled for major orthopedic surgery.[82 83 86–88] However, only few studies have been conducted specifically addressing elective THA and TKA and these tended to focus on specific outcomes such as surgical site infection or myocardial infarction.[79 89–91] Moreover, the majority of these studies differ in exact methodology and do not account for, or standardize, key perioperative care elements which may also influence postoperative morbidity. One small study including 225 THA patients reported a higher proportion of urinary tract infections among preoperatively anemic patients but failed to adjust for any confounding factor related to anemia.[79] A retrospective study of 15222 THA/TKA patients found preoperative anemia to be associated with increased risk of periprosthetic joint infection but not increased risk of 30- or 60- day mortality, after adjustment for confounders.[90] A case-control study spanning a 20 year period included 391 THA patients that had a myocardial infarction or died within 30 days of surgery and found no increased risk of these events in preoperatively anemic patients after adjusting for pre-existing comorbidity.[89]

In the context of elective fast-track THA/TKA with a standardized perioperative setup and a short LOS, we found preoperative anemia to be an independent predictor for risk of transfusion (OR 4.7; 95% CI 3.8-5.8), prolonged length of stay (OR, 2.5; 95% CI, 1.9-3.4), and readmission < 90 days (OR, 1.4; 95% CI, 1.1-1.9) in a cohort of 5175 THA/TKA procedures from 6 high-volume Danish

orthopedic departments.[1] In this study, the association between anemia and postoperative morbidity was retained even when accounting for whether patients were transfused or not, suggesting that at least some of the observed negative impact of preoperative anemia is unrelated to RBC transfusion.[1] Furthermore, a recent Danish observational study in 24862 fast-track THA/TKA procedures found preoperative anemia to be a borderline significant independent predictor for postoperative stroke at day 30 (OR 2.1; 95% CI, 0.98-4.6, P = .055).[92] Although the exact mechanisms for the deleterious effects of preoperative anemia in elective surgery, including elective THA/TKA, are not clear, it is now well established that anemia prior to surgery is an independent risk factor for worsened outcome after surgery. Therefore, preoperative anemia should be properly investigated and treated prior to the surgical procedure.

7.1.3 Preoperative anemia management – recommendations and treatment

Elective surgery allows for preoperative planning of the surgical procedure but also for individualized optimization of the patient. In this context several guidelines have been published on how to assess and treat preoperative anemia in the elective orthopedic patient with the aim of optimizing Hb prior to surgery and reduce the need for RBC transfusion in the perioperative period.[36 37 70 73 93 94] The key factor in such recommendations is a timely identification of a low Hb and further biochemical tests to allow for anemia classification, ideally no less than 4 weeks prior to surgery.[36] Measures to optimize Hb depend on the underlying cause but include the correction of hematinic deficiencies by the use of oral- or intravenous iron and vitamin supplements (B12 and folic acid). In addition, the use of erythropoiesis stimulating agents (ESA) in selected cases, i.e. renal or other chronic disease and if inflammation may be considered the underlying cause of anemia, is recommended by most guidelines although with some variation in the exact indication.[36 70 73 93 94]

Correcting ID anemia with the use of either oral- or IV iron supplements seems straightforward and with documented efficacy in various non-surgical conditions. [95] However, a recently published Cochrane review identified only 6 RCT´s with a total of 372 patients evaluating the effect of isolated iron therapy (both oral and IV) in the context of preoperative anemia.[96] From the 4 small

studies (total 200 patients) evaluating iron therapy vs. placbo, preoperative iron therapy did not significantly reduce the number of transfused patients (RR 1.21 95% CI 0.87 – 1.70).[96] However, a large scale randomized trial investigating the preoperative use of IV iron (Ferric carbomaltose) in preoperatively anemic abdominal surgery patients is soon to be published and should hopefully add significantly to the evidence quality regarding preoperative iron therapy.[97] Nevertheless, none of the available RCT´s were carried out in the elective THA/TKA setting where data from non-randomized interventional studies needs to be considered. Thus, in elective THA/TKA several reports have evaluated the use of iron (oral, IV or both) supplementation to manage preoperative anemia, either alone or as one of several measures in the implementation of a PBM strategy.[98] Two smaller non-randomized studies including, 20 and 63 anemic THA/TKA patients demonstrated a mean Hb increase of 1.0 and 1.8 g/dl, respectively by IV administration of either iron sucrose or iron maltodextrose prior to surgery. [99] [100] In one of these studies, a response rate defined as an Hb increase > 1.5 g/dl or a final Hb > 13 g/dl, was reported to be 67-69%. [100] Likewise, other more recent studies including THA/TKA patients, where preoperative anemia treatment with IV- or oral iron was a part of a wider blood management strategy, showed decreasing transfusion rates with PBM implementation.[50] [55] [56]

Besides Hb correction and decreased transfusion rates, it was not until recently reported whether treatment of preoperative anemia with iron therapy would translate into improvements in “hard” clinical end-points, such as postoperative morbidity and mortality. However a recent British large prospective observational study compared 1814 THA/TKA patients before- with 1622 patients after the implementation of preoperative anemia management with oral or IV iron, respectively. This study demonstrated a significantly reduced transfusion rate with anemia management (4% vs. 6%), but more interestingly also showed decreased postoperative morbidity as reduced readmission- and critical care admission rates (2.3 vs. 4.5 %) and (0.5 vs. 1.3 %) respectively together with a slightly reduced LOS (3.6 vs. 3.9 days).[68] Although the pre-PBM transfusion rate was already low, this study clearly supports routine preoperative anemia management in elective THA/TKA.

Besides correcting iron- and other nutritional deficiencies, preoperative Hb optimization may also be achieved using ESA´s, typically in combination with iron therapy. Thus, guidelines published by the Network for Advancement of Transfusion Alternatives (NATA) recommend the use of ESA´s for correcting preoperative anemia in those patients where "nutritional deficiencies has either been treated / ruled out or both".[36] However, concerns regarding increased risk of deep venous thrombosis, myocardial infarction and other side effects of ESA have been raised.[101 102] Thus, the British committee for standards in haematology recommends the use of preoperative ESA "only in patients where transfusion avoidance is clearly beneficial (i.e. patients refusing transfusions or patients with complex alloimmunization)".[73]

In cardiac surgery, a recent large scale RCT found decreased RBC transfusion and a higher postoperative Hb with a combination of ESA, IV iron, B12 and folate administered the day before surgery compared to placebo.[103] Furthermore, in patients scheduled for THA/TKA, the efficacy of ESA therapy for raising Hb and decreasing transfusion rates in has been well demonstrated in a recent meta-analysis consisting of 25 RCT´s including 4159 patients. [104] However, the included RCTs compared ESA´s to either placebo or a strategy involving preoperative autologous blood donation (PABD), were heterogeneous regarding ESA dose and timing, and many did not restrict treatment to patients with preoperative anemia. Nevertheless, when studies involving PABD were excluded in a similar meta-analysis, ESA use was found to reduce the exposure to RBC transfusion by 55 and 62 % in THA and TKA, respectively.[105] Both meta-analyses considered ESA use to be safe and reported a non-significant increase in the risk of thromboembolic events (RR 1.40; 95% CI 0.87 – 2.26)[104] and (RR 1.14; 95% CI 0.71 – 1.84),[105] respectively. However, the overall number of reported events were small and thus even these meta-analyses may suffer from insufficient statistical power to detect an increased risk with ESA use.

Considering preoperatively anemic patients, a recent RCT with a factorial design in THA/TKA patients with a preoperative Hb ranging from 10 to 13 g/dl compared placebo to the use of a weekly EPO dose (40.000 U) started 3 weeks prior to surgery. [106] Patients were concomitantly randomized to no or 2 different cell salvage strategies. The authors concluded that the use of preoperative ESA,

regardless of the cell salvage strategy used, reduced the exposure to allogeneic RBC by 55% (OR 0.45; 95% CI 0.28 – 0.69). However, in an economic analysis the use of ESA to optimize preoperative Hb was not found to be cost effective and the study was not powered to evaluate the safety aspect of preoperative ESA use.[106] Thus, in the context of THA/TKA there is a still a need for large-scale studies investigating both the safety and optimal patient selection criteria for correcting preoperative anemia with ESA therapy.

Finally, the organizational aspects regarding preoperative anemia assessment and treatment have only been sparsely covered in the available literature. Although this is probably country and centre specific, clear logistic pathways for the flow and responsibility for preoperative anemia management are not always clear which may hinder implementation.[40] Some centres have successfully initiated special "preoperative anemia clinics",[107–109] but other key partners such as the general physician, a hospital medical department, the blood bank, or the surgical or anesthesia departments themselves may also be responsible for or involved in preoperative anemia management.

7.2 Red cell transfusion in THA / TKA

7.2.1 Allogeneic RBC transfusion – current practice in elective THA/TKA

RBC transfusion to correct anemia may be administered preoperatively, during surgery or in the postoperative period and RBC may be given as either autologous or allogeneic transfusion.

Allogeneic RBC transfusion rates in THA/TKA have been documented for more than 25 years.[110] Thus, several studies have evaluated the use of allogeneic blood in primary and revision THA/TKA in both North American,[21 111–114] European,[17 20 24 64 115–117] and Danish settings.[4 118] In a report from 2003 which was conducted among 225 orthopedic centres from 6 different European countries the overall transfusion rate in THA and TKA (both allogeneic, autologous or both) was as high as 69%.[64] However, the overall transfusion rate has decreased considerably in recent years, both in Denmark and other European countries. Thus, in elective primary THA the overall allogeneic RBC transfusion rate in Denmark was more

than halved from 55% in 1999 to 21% in 2006 and with a further reduction in the following ten years to 3.5% in 2017.[4 118 119] A similar decrease has been observed for primary TKAs in Denmark where the transfusion rate was halved from 10 to 5% in the years 2011 to 2015.[18] Likewise, 2 benchmark studies carried out in 15 Austrian orthopedic departments in 2004-2005 and again in 2009-2010 reported a decrease in transfusion rate from 41 to 30 % and 41% to 25 % in THA and TKA, respectively.[17 20] A large study, performed in 2010-2011 across seven European countries and including both THA/TKA and spine surgery patients found a 38% overall transfusion rate (17% allogeneic, 11% autologous) while a recent Dutch study reported mean allogeneic transfusion rates as low 7 and 4 % in THA and TKA, respectively,[22] which is in line with current Danish practice.

Until recently it was reported that transfusion rates in THA/TKA in the US did not follow the same decreasing trend as observed in Europe and some studies even reported increasing allogeneic transfusion rates in the years 2000 - 2009.[111 112 120] Moreover, reports on THA/TKA in the US and Canada have until recently found significantly higher transfusion rates among US hospitals compared to Canadian hospitals for both THA 19 vs. 10 % and TKA 16 vs. 10 %.[114] However, an overall decrease in RBC usage in has been observed in the US since 2011, including a reduction in transfusion rate to 9 and 4 % in 2015 for THA and TKA, respectively. [19 121] In contrast, transfusion rates remains remarkably high in other countries with a recent Korean study reporting a transfusion rate as high as 80% in primary THA with almost no reduction from 2007 to 2015.[122]

Despite the decrease in overall transfusion rate, a remarkable consistent finding in the available literature is a highly variable transfusion rate in THA/TKA across surgical centres, both within and between countries.[4 21 23] Thus, in a Danish nationwide context we analysed transfusion data from the year 2008 and found transfusion rates ranging from 7 to 71% among Danish THA centres performing more than 50 procedures per year.[4] This is consistent with both older Danish transfusion data (1999-2006), where THA transfusion rates ranged between 16 and 64%,[118] and consistent with other European and US studies.[17 21 22 24]

Importantly, the high variation in transfusion rates among THA/TKA centres

remains when adjusting for patient related factors, and may rather be explained by hospital related factors such as different transfusion policies and the implementation of PBM measures, or the lack thereof. [21 24 118]

In conclusion, transfusion rates in THA/TKA have declined dramatically in recent years to well below 10% in Denmark but with a remaining high variability between centres, which seems related to the use of PBM measures rather than the case-mix. Thus, there is a considerable potential for a further reduction in RBC usage by implementing PBM in a large number of surgical centres worldwide and in Denmark.

7.2.2 Transfusion thresholds – Current guidelines and evidence from RCT´s

When deciding whether to transfuse a patient one has to balance the potential harmful effects of anemia and the potential benefit of RBC transfusion (increased oxygen carrying capacity of the blood and volume substitution) with the inherent risks and complications of transfusion. Although rigorous screening procedures have rendered transfused blood safe when it comes to most transmissible diseases,[123] the transfusion of allogeneic blood products carries other risks such as alloimmunisation, febrile reaction, immunomodulation, cardiac overload (TACO) and transfusion associated lung injury (TRALI).[124 125] Several guidelines on transfusion thresholds have been published in recent years by the American Association of Blood Bankers (AABB), [126] the Americans Society of Anesthesia (ASA), [127] the British Committee for Standards in Hematology,[128] and in a Danish context by the Danish national board of health,[129] all promoting a restrictive transfusion Hb trigger of 7-8 g/dl compared to a more liberal transfusion trigger of 9-10 g/dl.

The evidence base for these guidelines has increased significantly in the last 10 years with the addition of several high quality large RCT´s comparing liberal vs. restrictive transfusion thresholds in various patient populations, but mostly including critical care,[130] hip fracture,[131] and cardiac surgery.[132 133] The latest guideline from the AABB recommends transfusion in hemodynamic stable adult patients if the Hb decreases below 7 g/dl.[126] However, in patients undergoing orthopedic- or cardiac surgery, or patients with pre-existing cardiovascular

disease a transfusion threshold of 8 g/dl is recommended (strong recommendation but moderate quality evidence).[126]

Among the 12587 patients randomized in the 31 transfusion trigger RCT´s identified in the latest 2016 Cochrane review,[16] a total of 1217 patients undergoing elective joint arthroplasty were included from 5 studies conducted in the years 1999-2014 (Table 1).[134–138] A more recent meta-analysis published in 2018 identified 37 RCT´s comparing different RBC transfusion thresholds and included a total of 19049 patients, but with no additional studies from elective THA/TKA.[139] Both meta-analyses concluded that a restrictive transfusion threshold of 7-8 g/dl is safe and decreases RBC use but that more trials are needed in patients with acute myocardial infarction.[16 139] Moreover, a meta-analysis focusing entirely on patients with cardiovascular disease undergoing non-cardiac surgery found no difference in overall mortality between a liberal or restrictive transfusion trigger but the risk of acute coronary syndrome was increased with a restrictive trigger.[140]

Nevertheless, the majority of the available evidence regarding transfusion thresholds is derived from contexts other than orthopedic surgery such as critical care and cardiac surgery. However, the FOCUS trial, including more than 2000 hip-fracture patients, is the largest RCT carried out in the context of orthopedic surgery, although in a non-elective setting.[131] In this study, patients were randomized to a transfusion threshold of either 10 g/dl (liberal) or 8 g/dl (restrictive). There was no difference in the primary outcome, which was a composite of death or the inability to walk 3 m across a room 60 days after surgery (OR 1.01; 95% CI 0.84 – 1.22).[131] This is in agreement with other large RCT´s conducted in critical care settings that likewise found no difference in mortality when comparing restrictive and liberal transfusion thresholds.[130 141] In contrast, one smaller Danish RCT in 284 frail elderly with hip fracture found an increase in 30 day mortality with a “restrictive” (Hb < 9.7 g/dl) postoperative transfusion threshold (HR 2.4; 95% CI 1.1 – 5.2) compared to a liberal threshold (Hb < 11.3 g/dl).[142] However, the definition of a restrictive threshold in this study is comparable to the liberal threshold in the majority of other transfusion trigger RCT´s.[16]

In the context of elective joint arthroplasty, the largest of the 5 available RCT´s randomized 619 THA/TKA patients to either a restrictive risk based transfusion threshold or standard transfusion practice.[136] However, there was substantial heterogeneity regarding the standard transfusion practice arm among the 3 participating hospitals, which in one hospital was more restrictive than the studied restrictive threshold. Therefore, the trial did not achieve separation of treatment groups regarding both the proportion of patients transfused and the achieved postoperative Hb concentration, thus rendering interpretation difficult.[136] A smaller RCT, dating back to 1999, randomized 152 TKA patients to receive either 2 units of predonated autologous RBC immediately following surgery (liberal) or RBC transfusion (both autologous and allogeneic) if the Hb decreased below 9 g/dl (restrictive). A decreased occurrence of non-surgical complications (5 vs. 16 events) was found among patients in the liberal group compared to the restrictive transfusion group.[134] Another study evaluated if a restrictive transfusion trigger of 8 g/dl would increase the incidence of postoperative silent myocardial infarction (SMI) compared to a liberal trigger of 10 g/dl. No difference in the SMI incidence was found between treatment groups but the authors only managed to enrol 260 of the planned THA/TKA 660 patients in the study prior to analysis.[135] A more recent study conducted in 192 THA patients focusing of postoperative delirium (POD) found no difference in the incidence of POD (21.3 vs. 23.9 %; P=0.7) in patients randomized to a restrictive threshold of Hb 8 g/dl vs. a liberal threshold of Hb 10 g/dl, respectively.[138] However, in this study one third of all patients also received concomitant transfusion of fresh frozen plasma (FFP). Another study conducted in 66 patients undergoing hip revision surgery focused on postoperative ambulation by comparing a liberal transfusion trigger of 8.9 g/dl to a restrictive trigger of 7.3 g/dl. A mean difference of 14.5 seconds in the timed up and go (TUG) test was found with better performance in the liberal group. However, the study failed to separate the Hb concentration between treatment groups at the day of testing. [137]

Thus, it can be concluded that the 5 available transfusion trigger RCTs conducted in elective joint arthroplasty suffers from methodological flaws and are characterized by a wide variation in the outcomes studied and a large

heterogeneity in the definition of a liberal/restrictive transfusion threshold. Moreover, none of the included studies were conducted in a fast-track setting with early mobilization and a short LOS.

Considering the lack of high quality transfusion trigger RCT´s in elective THA/TKA, higher quality evidence to guide the transfusion decision can be derived from RCT´s like the FOCUS study.[131] However, it must be and has been debated whether only considering a single Hb value serves as the most appropriate transfusion trigger in a clinical context.[143] In this context, the relative decrease in Hb reflecting the acute red cell mass reduction due to perioperative blood loss may also be important, but remains largely unexplored as a transfusion trigger. Furthermore, the occurrence of acute anemia symptoms may also be considered. This is reflected in a good clinical practice statement found in the latest AABB recommendations listing the following variables to be taken into consideration: "the rate of decline in hemoglobin level, intravascular volume status, shortness of breath, exercise tolerance, light- headedness, chest pain thought to be cardiac in origin, hypotension or tachycardia unresponsive to fluid challenge, and patient preferences".[126] However, such "symptomatic transfusion triggers" were in combination with a Hb threshold part of transfusion criteria evaluated in some,[131 144 145] but far from all RCT´s conducted in orthopedic surgery (Table 1). Nevertheless, there is today no high-quality transfusion trigger RCT´s of a substantial size available that evaluates elective THA/TKA. The feasibility of carrying out such a study in all THA/TKA patients is also questionable, as transfusion rates have decreased to very low rates in many countries, including Denmark. However, there is a need for further studies evaluating the optimal transfusion trigger in frail or very elderly patients scheduled for elective THA/TKA, as it is still not clear if a restrictive transfusion threshold is safe and well tolerated in this subgroup of patients. In this context, a future RCT specifically targeting elderly > 70 years undergoing non-cardiac surgery and evaluating a liberal vs. a restrictive transfusion threshold may provide new knowledge.[146]

7.2.3 Allogeneic RBC transfusion and outcome in THA/TKA – observational data

A numerous and growing body of evidence from observational studies has established a robust association between allogeneic RBC transfusion and increased morbidity and mortality both in cardiac and non-cardiac surgery. [11 147–149] Direct adverse effects of allogeneic RBC transfusion may be due to both direct hemolytic or non-haemolytic transfusion reactions, transfusion related lung injury (TRALI) or transfusion related cardiac overload (TACO) but also transfusion related immunomodulation (TRIM), which has several potential underlying mechanisms. [125 150] TRIM may increase the risk of postoperative infections, although leukoreduction of blood may partly reduce this risk. [151] In THA/TKA, postoperative infections, including surgical site infection (SSI) is a considerable concern. Although deep prosthesis joint infection requiring revision surgery is rare,[152] it has been reported to increase postoperative mortality after THA.[153] Several observational studies have evaluated this, but with conflicting results.[64 113 154–160] A recent meta-analysis of observational studies focusing on SSI included 21770 patients from 6 studies and concluded that RBC transfusion was a risk factor for surgical site infection,[161] but no adjustments for anemia, blood loss or any other confounders were performed, therefore rendering interpretation difficult. Another meta-analysis focusing on infection data derived from secondary endpoints in 21 transfusion trigger RCT´s found a significant risk reduction in serious infections (not only SSI) with a restrictive transfusion threshold, both overall and when considering the 4 available studies in orthopedic surgery alone,[131 135 144 162] (RR 0.72 95% CI 0.53 – 0.97).[163] Among these 4 studies, only 1 was performed in elective THA/TKA and contributed with as little as 10% of the analysed patients while the remaining were hip fracture studies.[135] Nevertheless, these results raise serious concern regarding increased risk of infection with allogeneic RBC transfusion in relation to surgery. Establishing causation between transfusion and poor outcome is difficult due to the observational nature of the available studies and.[164] Some authors have questioned whether the true risk of transfusion is attributable to other patient- or surgically related factors and that the observed association is due to "confounding by indication".[165–167] In addition, there is a discrepancy between observational data showing adverse outcomes with transfusion and the results

from the available large RCT´s comparing liberal and restrictive transfusion thresholds where no benefit, but also no increased mortality, was found with a liberal transfusion strategy.[16]

Therefore, the observed association might be due to adverse effects of transfusion *per-se* but also due to other unmeasured or unknown confounders including preoperative anemia, patient comorbidity or surgical blood loss and complexity not sufficiently controlled for, in at least some of the available studies. In the context of Danish elective THA we performed an exploratory study with a nationwide detailed mortality analysis in an attempt to elucidate the mechanisms behind the observed association between transfusion and increased postoperative mortality. In this study we found that the few mortalities with a possible relation to transfusion were just as likely to be caused by massive bleeding or delayed transfusion in severely anemic patients causing type-2 myocardial infarction, than by possible complications to RBC transfusion.[5]

Nevertheless and despite obvious methodological weaknesses, the evidence base from observational studies showing adverse outcomes linked to transfusion should trigger caution in clinicians and the lack of benefit of a liberal transfusion strategy in almost all of the available RCT´s clearly argues for a restrictive threshold for RBC transfusion in in the vast majority of elective THA/TKA patients, whom overall carry a low comorbidity burden.[168]

7.3 Measures to reduce perioperative blood loss

The second pillar of PBM aims to minimize blood loss. This begins already preoperatively where patient related bleeding risks should be considered, including family history of increased bleeding tendency and the use of antiplatelet and anticoagulation therapy.[169] In the perioperative phase several pharmacological and non-pharmacological measures to reduce blood loss have been evaluated. These include the use of tranexamic acid (TXA) or topical hemostatic agents and various surgical and anesthetic techniques including minimal invasive surgical techniques, meticulous hemostasis, neuro-axial blockade, acute normovolemic hemodilution and different cell-salvage techniques. However, the measures used should be tailored to the specific

procedure / patient population and thus the following section will primarily discuss those relevant to elective hip- and knee arthroplasty today and with a focus on pharmacological interventions.

7.3.1 Blood loss in elective THA and TKA

A systematic review published in 2010, summarizing the available evidence regarding anemia and PBM in joint arthroplasty, found a weighted mean total blood loss of 1004 (± 302) ml.[9] This number is consistent with later findings both in THA and TKA,[117] including recent studies conducted in Danish fast-track arthroplasty,[6 7 170] but contrasts an older landmark study evaluating blood loss and transfusion in orthopedic surgery.[64] In this study a total blood loss of approximately 1900 ml in primary THA/TKA was reported.[64] In 2 serial Austrian benchmark studies, with data collected in 2004-2005 and again in 2009-2010, the relative RBC mass lost were significantly reduced from 39 to 32 % and from 35 to 31 %, in THA and TKA respectively.[17 20] However, there was a wide variation in the total lost RBC mass between the participating orthopedic departments. Furthermore, it is important to note that intraoperative blood loss accounts for only a minor fraction of total blood loss, as up to two-thirds consists of "hidden blood loss" due to postoperative oozing. However, the exact proportion may vary between THA and TKA, and with or without postoperative drainage and the use of a tourniquet in TKA.[170–172]

7.3.2 Tranexamic acid and other antifibrinolytics

Tranexamic acid (TXA), is a lysine analogue which acts as an antifibrinolytic by binding to plasminogen which prevents the binding of fibrin to the plasminogen-plasmin tissue activator complex.[173] TXA has been evaluated for well over 20 years to reduce blood loss in orthopedic surgery,[174] and is now considered a "game changer" when it comes to reducing perioperative blood loss in major joint arthroplasty.[175] TXA can be administered systemically (oral or IV), topically at the surgical site, or by combined systemic and topical administration. The body of literature supporting the efficacy of TXA to reduce blood loss and decrease RBC transfusion rates in elective THA/TKA is vast, rapidly growing, and includes numerous RCT´s and subsequent meta-analyses.[38 176–179]. As an

example, in the previous two years alone more than 30 systematic reviews and meta-analyses have been published on TXA in joint arthroplasty.
Two recent meta-analyses estimated that IV and topical TXA administration decreased the risk of transfusion by 60 and 71 %, in TKA and by 75% and 66% in THA, respectively. [178 179] Thus, the routine use of TXA in arthroplasty is recommended by both Danish- and American orthopedic societies, the American Society of Regional Anesthesia and is supported by UK National Institute for Health and Care Excellence (NICE) guidelines when a blood loss > 500 ml is expected. [44 180–182] However, there is no clear consensus regarding the optimal dosing, timing and route of TXA administration which is reflected both in the available trials and in a wide variation in clinical practice.[175] Moreover, in recent years the additional benefit of combining topical (intra-articular) and IV TXA administration has been evaluated. In a Danish fast-track context we conducted a single centre RCT where 60 TKA patients were randomized to receive either 1g IV TXA combined with 3g intra-articular TXA or 1g IV TXA alone. We found a significant 37% reduction in calculated blood loss 24h postoperatively and on the 2nd postoperative day (277 and 373 ml reduction), respectively, compared to the IV TXA group.[7] No adverse events were noted and only one patient received transfusion. Two recent network meta-analyses evaluated the efficacy of TXA, and included 34 and 67 RCT´s in THA and TKA, respectively.[178 179] Mixed models were used to compare different doses and routes of TXA administration and found no significant difference between IV and topical TXA administration or IV and combined IV/topical administration with regards to blood loss. However, in THA combined IV/topical administration was found to reduce transfusion exposure when compared to both IV- or topical administration alone in THA and to low dose IV TXA in TKA.[178 179]. A recent meta-analysis including 7 RCT´s with a total of 701 unilateral TKA patients has confirmed the efficacy of combined topical/IV TXA administration to reduce blood loss compared to IV TXA alone (mean reduction 156 ml; 95% CI 71 – 242 ml).[183] However, the included studies differed regarding topical TXA dose and in the use of tourniquet and postoperative drains. Likewise, in primary THA a meta analysis of 7 RCT´s including 1346 patients found a significant reduction in total blood loss with combined TXA administration compared to topical (mean reduction 163 ml;

95% CI 60 – 265 ml) or IV administration alone (mean reduction 154 ml; 95% CI 105 – 202 ml).[184] The most recent meta-analysis published in 2019 has confirmed the superiority of combined administration compared to single route TXA in reducing both blood loss and transfusion rates in THA and TKA.[185]
Despite the compelling evidence regarding the efficacy of TXA for reducing blood loss and transfusion, due to its antifibrinolytic properties, safety concerns have been raised regarding the risk of thromboembolic complications, and this may hinder implementation in some centres. However, several meta-analysis and large observational studies did not find increased risk of arterial- or venous thromboembolic events with TXA administration compared to placebo.[186–189] In a Danish context, a recent a large nationwide retrospective cohort study in THA comparing 38586 patients that received TXA to 6704 who did not in the years 2006 to 2013 found no evidence of increased cardiovascular events with TXA use after controlling for patient comorbidity.[190] Although data suggest the safety of TXA in most patients scheduled for THA/TKA, concerns still remain regarding patients with a high risk of thromboembolism, including patients with previous or recurrent venous- or arterial thrombotic events or patients with vascular stents, as these patients are often excluded from the available RCT´s. However, one smaller observational study focusing on patients with a history of venous thromboembolism (VTE) did not find increased VTE rates with TXA use but the number of events was small.[191] It is also noteworthy that a large RCT in patients undergoing coronary artery bypass grafting (CABG) which randomized patients to an intraoperative high TXA dose (100 mg/kg) or placebo, found no increased thromboembolic complications within 30 days postoperatively in the TXA group although a higher seizure rate was found with TXA use.[192]
Epsilon aminocaproic acid (EACA) and aprotinin are two other antifibrinolytic agents that have also been used to reduce surgical blood loss. However, aprotinin was withdrawn in 2007 due to an observed association with postoperative morbidity, including myocardial infarction and renal failure after cardiac surgery.[193] EACA has been suggested as an alternative to TXA, offering lower cost and fewer side-effects, together with reduced blood loss and transfusion rates compared to patients without antifibrinolytics in a recent retrospective study.[194] However EACA is not routinely used in Danish orthopedic centres, has a shorter

half-life than TXA that may require repeated dosing or infusion, and has only been sparsely studied in THA/TKA. Thus in TKA a higher blood loss compared to TXA was found in 1 of 2 small RCT´s and in one larger observational study performed in TKA.[195–197]

From the above it can be concluded that TXA administration is highly efficient in reducing blood loss and RBC transfusion and TXA should be standard of care in THA and TKA. In addition, recent evidence suggests additional effect with combined IV/topical administration in both THA and TKA, but there is still no consensus regarding the optimal TXA dosing regimen. Moreover, some safety concerns remains regarding the use of TXA in patients with a high thromboembolic risk.

7.3.3 Epinephrine

Epinephrine (EPI) when administered locally may decrease blood loss, both by a direct vasoconstrictor effect and indirectly by reducing uptake of locally administered TXA. Administered systemically EPI has pro-coagulant potential as it causes an instant 20-30% increase in platelet count and activates several coagulation factors.[198] This effect has been know for many years but had not previously been evaluated for reducing blood loss in THA/TKA. Therefore, we performed a RCT comparing intraoperative low dose EPI infusion (0.05 ug/kg/min) + IV TXA with IV TXA alone and found a significantly reduced total blood loss (treatment effect 180 ml; 95% CI 10 – 350 ml) in the EPI group. This finding has recently been confirmed in a 3-arm RCT in 195 THA patients comparing low dose EPI infusion and topical EPI administration to a control group IV placebo + topical placebo. In this study IV 10 mg/kg + topical TXA 4 g was also administered in all 3 allocation groups.[199] Compared to the control group low dose IV EPI and topical EPI decreased total blood loss by 194 ml (95 % CI 147 – 242 ml) and 65 ml (95% CI 17 – 112 ml), respectively. Interestingly, this study also measured coagulation by viscoelastic whole blood assays and found an improved coagulation competence (reduced reaction time and higher clot strength) with low dose EPI infusion.[199] The same author group conducted an identical RCT, using the same 3-arm intervention protocol in 179 TKA patients and found similar results.[200] Thus total blood loss and transfusion rate

were reduced in the IV EPI group compared to both the topical- and placebo group. Moreover, coagulation competence was increased in the IV EPI group as measured by viscoelastic assays. [200]

However, low dose EPI infusion is not used routinely in THA/TKA but may be useful as an adjuvant to TXA in selected cases where a higher risk of bleeding is expected, i.e. in bilateral procedures or revision surgery. However, despite these initial positive findings, further studies are needed to evaluate the efficacy and safety of low dose EPI infusion in these settings.[201]

7.3.4 Topical hemostatic agents

Apart from topical TXA administration which has been discussed above, a large variety of other topical pharmacologic agents are available for reducing surgical blood loss.[39] These include collagen, various types of thrombin, platelet rich plasma, and different types of fibrin sealants. There is a large variety in formulation and application technique and the cost of these products can be substantial.[39] Some of these agents have been evaluated for reducing blood loss in THA/TKA. Thus, a recent meta-analysis including 6 RCT´s in THA and 12 in TKA with a total of 1489 patients, concluded that the use of a fibrin sealer reduced the need for RBC transfusion and reduced total blood loss for both THA and TKA patients.[202] However, there was considerable heterogeneity regarding efficacy, the type of fibrin sealant and the use of drains. Moreover, IV TXA was found to be superior to the use of a fibrin sealer in reducing transfusion rates and resulted in higher postoperative Hb levels.[203] Another hemostatic agent (Floseal ®) based on collagen/thrombin has been evaluated in TKA. Although a meta-analysis found a overall blood sparing effect, results from the available RCT´s are conflicting and TXA was not used.[204] [205] Thus, it is unclear whether the use of fibrin sealants or other topical agents reduces blood loss when used in addition to IV, topical or combined use of TXA. In fact, some types of fibrin sealants contains TXA which may, at least partly, explain the observed blood sparing effect.[202] In a Danish context, 2 studies, in THA and bilateral TKA found no effect of a fibrin sealant regarding blood loss or RBC transfusion and fibrin sealant is not used routinely in THA/TKA in Denmark.[206] [207]

7.3.5 Cell-Saver and postoperative reinfusion drains

Previously, preoperative autologous blood donation (PABD) was used in many centres as a measure to reduce exposure to allogeneic blood in elective surgery, including THA/TKA.[208] However, after the implementation of other blood sparing measures, the cost-effectiveness of PABD has been questioned and its use has declined significantly,[209] and PABD it is not used routinely among Danish THA/TKA centres today. As an intra- or postoperative measure, the use of a cell-saver or reinfusion drains to re-infuse autologous blood during or after the procedure has been proposed as one of several PBM measures to reduce blood loss (Pillar-II).[14] Cell salvage in THA/TKA has become widespread in some countries with a Dutch survey reporting frequent use of cell-saver and postoperative reinfusion drainage among 31% and 69 % of the included departments, respectively.[210] Reinfusion has been extensively studied and has been reported to reduce the need for ABT in THA (RR 0.66; 95% CI 0.51 – 0.85) and TKA (RR 0.51; 95% CI 0.39 – 0.68). [211] However, the re-infused volume may be small in THA/TKA, with a median re-infused volume in THA of only 135 ml.[212] Also, more recent literature has questioned the efficacy and cost effectiveness of cell-salvage in elective THA/TKA due to the implementation of other PBM measures such as restrictive transfusion thresholds and the use of TXA. [211 213 214] Some authors have even argued for de-implementation of cell-salvage in most THA/TKA cases.[215] Among Danish orthopedic departments, intra- and postoperative cell-salvage and re-infusion is not used routinely for primary THA/TKA. However, selected patients or procedures (such as revision surgery) may still benefit from perioperative cell-salvage.

7.3.6 Surgical measures

There is considerable variation regarding surgical practices in THA/TKA, some of which may substantially influence blood loss and the need for transfusion.[33] The use of postoperative closed suction drain to avoid hematoma formation is practiced in some centres. However, several RCT´s and meta-analysis have reported higher blood loss and need for allogeneic transfusion with the use of drains, both in THA and TKA.[216 217] In TKA, a tourniquet is used in many centres to reduce intraoperative blood loss and improve surgical field conditions.

Although the use of tourniquet reduces intraoperative blood loss, the available literature is conflicting regarding the effect on postoperative blood loss, total blood loss and transfusion rates. [218] Furthermore, the benefits of tourniquet use may be less with an optimal perioperative TXA strategy, and the use of tourniquet may decrease postoperative range of motion and increase swelling and venous thrombus formation. [219 220]

In conclusion, today several measures to reduced blood loss in THA/TKA exist, with TXA administration being standard of care in many countries, including Denmark, due to demonstrated efficacy and safety but with considerable variation in dosing regimens. Other pharmacologic agents, including low dose epinephrine infusion may also be beneficial in selected cases and warrants further investigation. Autologous reinfusion using cell-saver or drains may play a role in individual cases but the routine use in primary THA/TKA have been questioned.

7.4 Postoperative anemia in THA / TKA

Postoperative anemia is highly prevalent after elective THA and TKA due to surgical blood loss, preoperative anemia or both. The prevalence of postoperative anemia may be up to 90% after major surgery, depending on the definition used. A review found a weighted mean perioperative Hb decrease from 13.6(±0.4) to 10.6 (±0.8) g/dl among 6626 THA/TKA patients from 5 different studies.[9] In contrast, the recovery of anemia after THA/TKA is less studied. Thus, a small but detailed study in 30 THA patients reported incomplete recovery of the Hb as late as day 56 after surgery with a mean 68% recovery of the perioperative Hb decrease.[221]

Postoperative anemia may have significant consequences in fast-track joint arthroplasty where patients are mobilized early and discharged on postoperative day 1 or 2, thus leaving hospital before nadir Hb is reached.[222] Although blood loss in THA/TKA patients have been reduced, the implementation of more restrictive transfusion triggers a larger proportion of patients being discharged with moderate anemia, and some patients may be

discharged with more pronounced anemia than previously accepted. However, the clinical impact of postoperative anemia, concerning postoperative morbidity and functional recovery after joint arthroplasty, has only been sparsely studied with a wide variation in methodology and in the definition of postoperative anemia.

7.4.1 Postoperative anemia and morbidity

In contrast to preoperative anemia, the consequences of postoperative anemia has been less studied. Also, untreated preoperative anemia is inherently linked too the magnitude of postoperative anemia and increased risk of morbidity. Therefore, isolating the effects of postoperative anemia regarding postoperative morbidity in preoperatively anemic patients may pose problems.

A recent large retrospective analysis, including almost half a million adult hospitalizations, reported that the prevalence of moderate anemia at discharge (Hb between 7 and 10 g/dl) had increased from 20 to 25% from 2010 to 2014 and with decreasing anemia recovery 6 months post discharge.[223] Another study including 152.757 surgical and non-surgical hospitalizations, found that the magnitude of discharge anemia was associated with the risk of 30 day readmission after adjusting for comorbidity.[224] However, when isolating the surgical setting, a lower discharge Hb level < 10 g/dl was not associated with increased readmission risk in cardiac surgery compared to a discharge Hb between 10 and 12 g/dl. However, no comparisons to non-anemic patients were made.[225] This finding is contrasted by a recent large retrospective study, including 142.510 major vascular and general surgery procedures, where 2 weeks postoperative anemia (Hb < 10 g/dl) was the strongest independent predictor for postoperative mortality and major morbidity and the effect of postoperative anemia increased significantly with increasing cardiac risk class.[226] Importantly, the authors accounted for blood loss (delta Hb) and the number of perioperative RBC transfusions in the multivariate model. In the specific context of elective THA and TKA, several observational studies have associated postoperative anemia with postoperative morbidity, but only one of these evaluated the Hb at the day of discharge.[227–231] Thus, in a retrospective cohort of 2467 THA patients, patients with a postoperative Hb < 10 g/dl had a

higher risk of acute kidney injury (OR 2.0; 95% CI 1.4 – 3.0) compared to patients with Hb > 10 g/dl. However, this study used Hb measured 2 hour postop and not discharge Hb for classification and preoperative anemia was not controlled for in the multivariate analysis.[227] Two studies, based on the Lundbeck Center Database and review of medical charts, which was conducted among 3202 and 8288 Danish fast-track THA/TKA patients, respectively, found anemia requiring RBC transfusion to be the direct cause in 12% and 8% 30 day readmissions related to medical reasons, respectively.[228 229] A similar study in a Danish fast-track cohort of 549 THA/TKA patients aged > 85 years, postoperative anemia requiring transfusion was the most common cause (27%) of a LOS > 4 days. However, anemia was an uncommon (4%) direct reason for being readmitted within 30 days.[230] Another study focusing on postoperative myocardial infarction (MI) found MI in 31 (0.12%) of 24862 THA/TKA procedures within 30 days of after surgery. 27 (87%) of MI patients had postoperative anemia (defined as Hb < 13 g/dl) with a mean postoperative Hb of 9.9 (SD 1.7) g/dl and a large mean reduction from the preoperative Hb of 3.6 (95% CI; 2.8 – 4.3) g/dl.[231] However, this study did not explore postoperative Hb as an independent factor for developing postoperative MI.
Although the caveats of the above observational studies should be accounted for and the exact mechanism remains to be elucidated, the evidence suggests that postoperative anemia is associated with postsurgical morbidity especially in patients with a high comorbidity burden. Thus the treatment strategy for postoperative anemia in high-risk patients, including those scheduled for THA/TKA, should be evaluated further.

7.4.2 Postoperative anemia and functional recovery

Postoperative functional capacity may be impaired by factors such as pain and post-surgical inflammation.[26] In addition, surgical blood loss causing acute postoperative anemia may also impede functional recovery due to the well known anemia related symptoms such as fatigue and dizziness,[10] which may potentially have an impact on recovery from the initial postoperative mobilization attempt to functional capacity days and weeks following surgery.[232] In a fast-track THA/TKA setting, with an intended short LOS, delayed

mobilization and impaired functional recovery due to anemia is especially detrimental as patients are expected to be mobilized already on the day of surgery, and discharged to home within few days following surgery, often before the nadir Hb occurs. Thus, the consequences of a low, but unmeasured Hb may impair initial recovery at home in the days following discharge. When patients are mobilised on the day of surgery, it has been established that up to 42% of patients experience orthostatic intolerance (dizziness and other presyncopal symptoms) during the initial mobilization attempt.[233] This could trigger the decision to transfuse in some patients as orthostatic hypotension and dizziness have been proposed as symptomatic transfusion triggers.[126] However, we have previously established that OI in the early postoperative period may be caused by impaired hemodynamic regulation and autonomic dysfunction rather than symptoms of acute anemia. [234–236]

Besides the initial mobilization procedures, as conducted in fast-track THA/TKA, several studies have tried to elucidate whether postoperative anemia has any clinical impact on functional recovery in the days, weeks and months following both hip fracture and elective THA / TKA (Table 2). However, the majority have been conducted in more traditional care pathways with longer LOS and with a huge variation in perioperative care, functional outcome measures used and the timing of assessments in relation to surgery and Hb measurements.

Most evidence supporting the negative effects of postoperative anemia on functional recovery originates from patients with hip-fracture (Table 2).[237 238] Thus, a large retrospective study in 5793 hip fracture patients reported a correlation between postoperative Hb and the distance walked at discharge.[237] A Danish prospective single centre study included 487 hip-fracture patients and found that the cumulated ambulation score correlated with Hb during the first 3 postoperative days and that anemia defined as a Hb < 10 g/dl was, independently associated with the inability to walk on POD 3.[238] In contrast, a third hip-fracture study found no correlation between the postoperative Hb and the functional independence motor (FIM) score.[239]

However, one important limitation to studies in an acute setting such as hip-fracture is the lack of measurements of preoperative functional capacity and pre fracture Hb levels. Thus, in this population a low postoperative Hb may partly

reflect a high degree of comorbidity, frailty, preoperative anemia or a larger fracture / tissue trauma - factors that may all be associated with poor functional capacity. Furthermore, as previously discussed, it is important to note that the 8 existing transfusion trigger RCT´s in orthopedic surgery that included functional outcome measures showed no benefit of a liberal transfusion strategy on functional recovery, (Table 1) although most were conducted in hip-fracture patients and with a high variation in functional measures and timing of assessment.

Within the context of elective THA/TKA, 8 observational studies, which included between 30 and 603 patients and spanning the last 15 years, have evaluated a possible association between postoperative anemia and functional recovery (Table 2) and these will be discussed in detail below. Three studies evaluated only subjective quality of life (QOL) measures,[221 240 241] another 3 studies evaluated only objective measures or physiotherapy scores,[242–244] while the remaining 2 studies included both subjective and objective measures of functional outcome.[8 245]

7.4.2.1 Quality of life measures

The first study to address the question whether a low postoperative Hb impairs QOL after elective arthroplasty was published in 2005 and included only 30 THA patients. This study focused on Hb recovery characteristics after surgery but also measured QOL using the Short Form 36 (SF-36) questionnaire. No correlation between postop Hb and SF-36, was found, even when the physical well-being part of the SF-36 were analysed separately, but changes in QOL scores from pre- to postoperatively were not considered. [221] In contrast, one study conducted in 87 THA and TKA patients reported a significant correlation between Hb at POD 8 and changes in QOL from pre- to 2 months postoperatively, as measured by both the SF-36 and the Functional assessment of Cancer Therapy Anemia subscale (FACT-Anemia). However no correlation between postop Hb and absolute values was identified.[240] Furthermore, 3 more recent (2011 – 2016) and larger studies including a total of 1029 THA and TKA patients found no or only very weak correlations between postoperative Hb and QOL scores.[8 241 245] One study, which

was a secondary analysis of an earlier transfusion trigger RCT included 603 patients, and evaluated 3 different QOL measures. No clinical significant correlations to Hb were identified, both when considering absolute values and changes in Hb and QOL scores, or when considering patients aged more than 65 years separately.[241] Likewise, in a prospective study including 305 THA/TKA patients, SF-36 scores were not different between patients grouped by postoperative Hb and did not correlate with postoperative Hb both when absolute values and changes in SF-36 compared to preoperatively were considered.[245] The most recent study, published in 2016, is the only one which has been conducted within the context of fast-track arthroplasty. In this study we included 122 THA patients and evaluated QOL preoperatively and on day 7 following discharge using the FACT-Anemia scale.[8] However, we found no correlation between QOL scores and Hb at discharge or the decrease in Hb from preoperatively.[8]

Thus, from the above it seems that moderate postoperative anemia may not have an impact on QOL scores after THA/TKA. However, this could be due to the fact that in the majority of patients, moderate postoperative anemia may not affect well being or that QOL is affected to a much greater extent by the changes caused by the joint replacement itself (pain etc.) thus masking any effects of anemia.

7.4.2.2 Objectively assessed functional capacity

In a small study including 49 TKA patients the Hb at admission to rehabilitation ward (post surgery) correlated with rehabilitation admission functional independence measure (FIM) score but not with improvement in FIM during the rehabilitation stay.[242] This finding was confirmed using the 6-minute walk test (6MWT) in a similar study including 104 THA/TKA patients also admitted to a postoperative rehabilitation ward.[243] In this study, the postoperative Hb correlated with the 6MWT at admission but not with improvement in the 6MWT during rehabilitation.[243] A study, including 305 THA/TKA patients, evaluated both the 6MWT and maximal dominant hand strength (MHS) before surgery and in the days following surgery prior to discharge (not standardized).[245] Objective functional outcomes did not differ between patients when grouped by

postoperative Hb but less than 7 % of the included patients had a Hb < 8 g/dl at the day of testing. In the same study, a correlation analysis showed a weak correlation between the decrease in Hb and the change in 6MWT from pre- to postoperatively. However in a multivariate regression analysis the Hb decrease only explained 1.9 % of the variation in 6MWT performance while other demographic variables explained up to 28 % of the variation.[245] In a population of 122 fast-track THA patients with a short LOS of 2 days, we related the postoperative Hb and the perioperative Hb decrease to several objective measures of functional capacity.[8] The 6MWT and the TUG-test were assessed preoperatively, the day of discharge and at 2 weeks following surgery. In addition and in contrast to other studies, objective measures of mobility at home was also evaluated the first 6 days following discharge by using wearable activity monitors quantifying the number of steps walked, transitions from supine to upright and the time spent upright. In line with previous studies, we found only weak correlations between postoperative Hb and the 6MWT and number of steps walked on day 1-6 following surgery, respectively. All other measures of physical function were not correlated to postoperative Hb or the perioperative Hb decrease.[8] However, as in other studies, one important limitation was the lack of patients with more severe anemia as only 20% of the included patients had a Hb < 10 g/dl on the day of discharge.[8] The most recent study from 2018, evaluated hip muscle strength and the improvement from pre- to 2 months postoperatively in 82 women undergoing THA. An effect of postoperative Hb was evaluated by grouping patients according to whether the ratio between Hb at POD 10 and the preoperative Hb was above or below 85%. A small statistical difference in straight leg raise strength was found, but the magnitude was not reported and the overall Hb decrease was small (mean 1.1 g/dl) due to the use of intraoperative cell salvage. [244]

From the above review it can be concluded that although some studies have demonstrated a correlation between postoperative anemia and objective measures of physical function, this is not a consistent finding. Furthermore, the effects found in relation to a low postoperative Hb or a large Hb decrease were small and may be clinically irrelevant, at least in the majority of patients. Thus, it seems that moderate postoperative anemia after elective THA/TKA has limited

impact on functional recovery. However, although many of the functional outcome measures were identical in the available studies, it must be noted that there was a large heterogeneity regarding the timing of outcome assessments, which varied from a few days to several months following surgery but also in postoperative care including physiotherapy regimens etc. The most important limitation, however, is the apparent lack of patients with more severe postoperative anemia, i.e. Hb < 7-8 g/dl and patients undergoing procedures with higher blood loss such as revision surgeries or bilateral procedures. Furthermore, studies evaluating the very elderly and frail patients are lacking. Therefore, it remains unknown whether anemia impairs functional recovery in these settings and patient populations.

7.4.3 Postoperative anemia – management and recommendations

When correcting a low postoperative Hb due to blood loss or existing anemia, options such as iron supplementation or the use of ESA´s may be considered to avoid transfusion. However, compared to preoperative anemia, the evidence concerning how to manage postoperative anemia is sparse.[98] Although oral iron is recommended by NICE guidelines for postoperative IDA, oral iron may not be efficient for restoring Hb after surgery due to inflammation.[222] Furthermore, a recent international consensus statement recommends IV iron formulations for the treatment of postoperative IDA while the use of ESAs is suggested only in non-cancer patients with severe postoperative anemia or patients refusing blood transfusion.[222] A recent systematic review evaluating postoperative iron therapy identified 15 studies with 8 of them including orthopedic patients (acute and elective) and found no evidence to support routine postoperative iron treatment.[246] However, many of the included studies evaluated oral iron only and excluded patients with preoperative anemia. Another recent review identified 5 studies, including 1008 patients (3 RCT´s, 2 observational trials) evaluating postoperative IV iron in elective THA/TKA patients.[247] One RCT randomized 122 TKA patients with a postoperative Hb < 12 g/dl to receive either 700-1000 mg IV ferric carboxymaltose (FCM) on POD 1 or oral iron from POD 7 and reported a higher Hb recovery rate (Hb > 12 g/dl at POD 30) in the IV FCM vs. the oral iron group (42.3 vs. 23.5 %; P=0.04).[248] There were no overall

differences in postoperative function scores between treatment groups but better postoperative QOL scores in the IV FCM groups when considering patients with preoperative iron deficiency or severe postoperative anemia (Hb < 10 g/dl).[248] Another RCT, wherein 156 (78%) of the study population consisted of elective THA, TKA or spine surgery patients with IDA, randomized patients to either 1g IV FCM at POD1 or standard care. At 4 weeks postoperatively Hb was higher in the IV FCM group with a small but statistically significant difference (0.78 g/dl 95% CI 0.37 – 1.19; P < 0.0001). In contrast, a small 3-arm RCT including only 31 patients (13 cardiac and 18 THA, TKA or spine surgery patients) randomized patients to either placebo, IV iron sucrose or IV iron sucrose + EPO.[249] No differences in postoperative Hb recovery or QOL measures were found, but the study lacked statistical power and excluded patients with preoperative anemia or significant comorbidities.[249] Of the 2 available observational studies, one reported a reduced allogeneic transfusion rate (12 vs. 26 %) and a higher postoperative Hb in 182 THA/TKA patients treated with IV iron (FCM or iron sucrose) compared to matched patients receiving either oral- or no iron supplements.[250] Another study compared 150 THA patients with 150 propensity matched controls before and after introduction of a blood saving protocol consisting of 1) postoperative 1g IV FCM administration in patients with a Hb < 10 g/dl or a perioperative decrease > 3 g/dl and 2) the introduction of a restrictive transfusion trigger. [251] The allogeneic transfusion rate was lower (47 vs. 61 %) and the increase in postoperative Hb was higher in the IV FCM group compared to matched control group. However, the study also included hip fracture patients and bilateral procedures and it is difficult to separate the effects of IV FCM and the changed transfusion policy regarding the observed transfusion rates.[251]

In conclusion, postoperative IV iron with or without EPO improves postoperative haematopoiesis after THA/TKA and may improve postoperative outcome. However, the available evidence is of low to moderate quality and there is a clear need for larger high quality studies to establish the optimal patient selection, dosing regimens and efficacy regarding clinical postoperative outcomes. In addition, the role of IV iron in treating postoperative iron deficiency without anemia needs to be evaluated.

8. Conclusions and future perspectives

8.1 Specific thesis conclusions from the included papers

- Preoperative anemia, as defined by the WHO definition, had a prevalence of 13% in a Danish multicentre fast-track THA/TKA population and preoperative anemia was independently associated with both increased risk of allogeneic RBC transfusion and increased readmission rates up to 90 days following surgery (Paper 1).[1]
- Preoperative anemia was not associated with a significantly increased occurrence of any cancer, or gastrointestinal cancers specifically, 1 year following fast-track THA/TKA surgery after adjusting for patient related factors. Consequently, the optimal criteria for referral to cancer screening in preoperatively anemic patients prior to THA/TKA surgery need further evaluation (Paper 2).[2]
- In a single centre fast-track THA/TKA cohort study, iron deficiency was the cause in 41% of patients with preoperative anemia (WHO definition) and in 33% of patients with a preoperative Hb < 13 g/dl. A further 20% of anemic patients had evidence of iron sequestration. Thus, there is a significant unmet need for reversal of preoperative anemia with iron therapy prior to fast-track THA/TKA (Paper 3).[3]
- In a nationwide study of all Danish surgical departments performing elective THA in 2008, transfusion practice was highly variable with a difference in RBC transfusion rates ranging from 7 to 71% among departments. The overall transfusion rate was 24%. For revision THA, the overall transfusion rate was 61 % and ranged from 26 to 85% (Paper 4).[4]
- In a detailed case analysis of possible transfusion related mortalities after THA, we found that major bleeding or severe anemia was associated with mortality in a subgroup of transfused patients, rather than possible deleterious effects of transfusion *per-se.* Thus, surgical blood loss and pre-transfusion Hb should be accounted for in observational studies reporting associations between transfusion and mortality (Paper 5).
- In a RCT conducted in 2 different orthopedic departments. Intraoperative low-dose epinephrine infusion had no effect on intraoperative blood loss

but decreased total 24 h calculated blood loss in fast-track THA compared to placebo. The pro-coagulant effects and safety of low dose epinephrine infusion needs to be evaluated in procedures with a higher perioperative blood loss (Paper 6).[6]

- In a single centre RCT the administration of combined IV and intra-articular (IA) administration of tranexamic acid in TKA, without the use of a tourniquet, decreased 24 and 48 h calculated total blood loss by approximately 37% compared to IV TXA + IA placebo (Paper 7).[7]
- Although the postoperative Hb concentration was statistically associated with objective measures of early postoperative recovery, no clinical significant effects of moderate postoperative anemia was identified after fast-track THA. However, functional impairment in more severely anemic patients could not be evaluated (Paper 8).[8]

8.2 General conclusions and future research implications

The present narrative review and associated original studies sought to provide an overview of specific aspects of PBM relevant to elective THA and TKA with a focus on fast-track surgery. Thus, the following conclusions are presented grouped according to the three pillars in PBM. In addition, suggestions for future research topics in relation to PBM in elective arthroplasty are presented in the text and in Table 3.

In the first pillar of PBM (optimizing hematopoiesis), preoperative anemia remains of considerable concern. Despite published algorithms, guidelines and demonstrated benefits regarding decreased transfusion rates and postoperative morbidity, implementation of preoperative anemia management (PAM) seems to be lacking in many orthopedic departments. This is also the case in most Danish departments performing elective THA and TKA. However, several aspects of PAM need to be studied further. It is straightforward that patients with iron deficiency should be managed with iron therapy. However, other- or mixed forms of anemia may not respond to iron alone: Although ESA´s are proposed in this setting in some guidelines and countries, the role of ESA´s to correct anemia in these patients, including patient selection and safety issues, needs further

clarification. Furthermore, the longstanding WHO cut-off for preoperative anemia has been debated in recent literature with the proposal of a preoperative Hb target of > 13 g/dl in both male and females. Although females with a Hb between 12 and 13 g/dl have a higher risk of transfusion than those with Hb > 13 g/dl, a substantial larger number of patients need preoperative anemia management with this cut-off. Thus, further research regarding the logistics and benefits of PAM with a Hb cut-off of 13 g/dl in both genders compared to the WHO cut-off is needed.

Regarding the second pillar of PBM (minimizing perioperative blood loss), there is now compelling evidence that TXA significantly reduces blood loss in elective THA and TKA. Therefore, TXA administration should be standard of care unless clearly contraindicated. However, there is still no clear gold-standard in THA/TKA regarding TXA dosing, timing and routes of administration. However, combined IV and topical administration seems to provide additional blood loss reduction compared to IV administration alone. Alternative antifibrinolytics such Epsilon aminocaproic acid (EACA) may also be beneficial but the available literature in THA/TKA is sparse and further evaluation of the efficacy and safety as compared to TXA is needed. In addition, other pharmacological agents such as low dose epinephrine and topical hemostatic agents may further reduce blood loss as an adjuvant to TXA in some patients, especially when larger blood loss is expected. However, issues such as optimal patient selection, duration and timing of administration and safety issues have not yet been elucidated.

Cell salvage and autologous reinfusion drains, have been, and are still being used in elective primary THA/TKA in some centres. However, recent evidence questions the efficacy of these measures when other PBM measures to reduce blood loss and transfusion have been implemented. Thus, cell salvage and postoperative autologous reinfusion drains should probably be reserved for cases with larger blood loss, such as some types of revision surgery, or cases where antifibrinolytics such as TXA are contraindicated. Furthermore, the routine use of low-vacuum postoperative drains is questionable and may increase total blood loss.

The third PBM pillar concerns a rational approach to postoperative anemia management including transfusion practice based on the implementation of

evidence based transfusion triggers. In most centres, transfusion rates in THA and TKA have decreased dramatically during the last 10 years. In the same time period, several high quality large RCT´s have been published with the vast majority demonstrating the safety of a restrictive transfusion threshold. Although, none of the high quality RCT´s have been conducted in elective arthroplasty and the available RCT´s in THA/TKA unfortunately have considerable methodological flaws, a restrictive transfusion threshold of 7-8 g/dl seems safe in the majority of elective THA/TKA patients. However, evidence is still lacking on how to manage anemia in high-risk THA/TKA patients, such as the very elderly or frail, or patients with a high co-morbidity burden. Furthermore, early functional recovery after THA/TKA, which is important and one of the primary goals within a fast-track context, may not be impaired by moderate postoperative anemia in most patients. However, this needs further research in high-risk patients, or patients with more severe anemia or a higher relative blood loss, than those included in the available studies. Also, more studies evaluating the consequences of postoperative anemia should be carried out in the context of highly standardized perioperative care regimens with a short LOS, which was not the case in the majority of studies. Finally, there is a need for studies evaluating postoperative anemia management by other means than RBC transfusion in patients where pre- and intraoperative measures have failed or were insufficient to ensure sufficient red cell mass. Such interventions could include postoperative IV iron or ESA therapy, which may improve Hb recovery and outcome but are only sparsely studied in the postoperative setting.

9. Methodological considerations

The 8 included studies in this thesis consist of 5 epidemiological studies, 1 prospective observational clinical study and 2 double-blinded randomized controlled trials (RCT´s). These represents various methodological research approaches and spans the evidence ladder from a case-series analysis (Level 4) to up to the 2 RCT´s considered to have a low risk of bias (Level 1b). The included epidemiological studies were based on several clinical databases, which were cross-linked on an individual level. Thus, The Danish National Patient Registry (DNPR) formed the basis for 4 of the 5 epidemiological studies. The

DNPR was established in 1977 and has provided clinical and administrative data for all patients discharged from all Danish hospitals since 2007.[252] It has a high validity regarding registration of surgical procedures, but diagnosis of various diseases may be less valid.[253] Therefore, patient demographics, preoperative Hb and existing co-morbidity were registered using a preoperative questionnaire for all patients scheduled for surgery in the participating fast-track departments.[228] Hospital readmissions following surgery were also identified in the DNPR but to increase validity, all were crosschecked using electronic discharge summaries or individual patient charts. Although various multivariate methods to adjust for confounders were used in the included epidemiological studies, these may still suffer from residual confounding as is true of the vast majority of the published literature regarding the impact of anemia and transfusion in THA and TKA. Both of the included RCT´s were monitored by the local Good clinical Practice (GCP) committee and reported according to the CONSORT statement.

For specific strengths and limitations of each study, the reader is kindly referred to the individual publications.

10. Summary

Total hip- (THA) and knee arthroplasty (TKA) for the treatment of osteoarthritis are two of the most common major elective procedures performed in developed countries with numbers expected to increase due to an increased elderly population. The implementation of fast-track THA/TKA protocols with a multimodal evidence based approach, including early ambulation and discharge has improved patient outcome and decreased length of stay. However THA/TKA is complicated by blood loss, perioperative anemia and the need for transfusion in some patients. Patient Blood Management (PBM) is a concept to improve patient outcome using a 3-pillar strategy aiming to optimize haematopoiesis (pillar-1), reduce blood loss (Pillar-2) and rationally manage perioperative anemia harnessing the individuals tolerance of anemia (pillar-3).

This thesis consists of 8 original papers and a narrative review and aims to evaluate aspects from all 3 PBM pillars in the context of fast-track THA/TKA in Denmark. The main findings from the included papers were: Preoperative anemia (PA) was prevalent (13%) among Danish fast-track THA/TKA patients and was independently associated with increased risk of transfusion and readmission (Paper 1) but not associated with an increased risk of cancer 1 year following surgery (Paper 2). Iron deficiency was found to be the major cause of preoperative anemia (Paper 3). In 2008 the Danish nationwide red cell transfusion rate in elective THA was 24% but with a very high variation (7% - 71%) between surgical centres (Paper 4). Postoperative mortalities in transfused THA patients were related to severe blood loss and acute anemia rather than possible complications to RBC transfusion (Paper 5). Intraoperative low-dose epinephrine infusion decreased total 24 h calculated blood loss but not intraoperative blood loss in fast-track THA (Paper 6). In TKA without the use of a tourniquet, combined administration of intra-articular and intravenous (IV) tranexamic acid (TXA) reduced total calculated blood loss by 37% compared to IV TXA alone (Paper 7). Moderate postoperative anemia had only very limited negative impact on early functional recovery in fast-track THA (Paper 8).
From the narrative review it was concluded that preoperative anemia is common in THA/TKA, is associated with increased transfusion risk and postoperative

morbidity and that PA can effectively be managed by IV-iron in the majority of patients while erythropoietin stimulating agents are also effective but is usually reserved for select cases. The administration of antifibrinolytics such as tranexamic acid (TXA) has proven to be highly effective in reducing blood loss and transfusion rates in THA/TKA. Although combined topical and systemic administration may be most effective, consensus regarding the optimal dosage, timing and route of administration is still lacking. Other antifibrinolytics or the use administration of low dose epinephrine may also reduce blood loss but needs further evaluation. The overall transfusion rate in THA/TKA has been reduced dramatically to single digit percentages during the last 15 years in most countries but with a remaining high inter centre variation. Restrictive transfusion triggers seem safe in most THA/TKA patients and have been adopted by many centres, but the evidence for the optimal transfusion trigger in THA/TKA is mainly derived from large scale RCT´s conducted in other patient populations. Thus there is still uncertainty regarding the optimal transfusion trigger in the most frail and elderly patients undergoing THA/TKA. It has also been debated if postoperative anemia impedes functional recovery and early ambulation, which is a corner stone in fast-track protocols. The available evidence is sparse but points to very limited impact of moderate postoperative anemia on functional recovery. However, data from frail patients and patients with more severe anemia are lacking.

To improve the available evidence, it is suggested that PBM research efforts in THA/TKA should generally focus on high-risk and frail patients. Other issues such as the optimal Hb threshold for preoperative anemia management, the use of combined systemic and topical antifibrinolytics or other adjuvants to reduce blood loss, and the potential for postoperative Hb optimization also warrant further research.

11. Resumé (Danish summary)

Total hofte (THA) og knæalloplastik (TKA) til behandling af slidgigt er to af de hyppigst udførte kirurgiske procedurer i den vestlige verden med en forventet betydelig øgning i antallet af indgreb pga. et stigende antal ældre i samfundet. Implementeringen af fast-track THA/TKA protokoller baseret på flere multimodale evidensbaserede interventioner, herunder tidlig mobilisering og udskrivelse har ført til en betydelig reduktion i liggetid samt bedring i patient outcome. THA/TKA er dog forbundet med blodtab, perioperativ anæmi og behov for blodtransfusion hos nogle patienter. Patient Blood Management (PBM) adresserer disse problemstillinger gennem en multimodal strategi baseret på 3 søjler der søger at optimere hæmatopoiesen (søjle 1), minimere perioperativt blodtab (søjle 2) og indføre en rationel håndtering af perioperativ anæmi (søjle 3).

Denne afhandling består af 8 publicerede originalarbejder samt et narrativt review og har til formål at afdække aspekter fra alle 3 PBM søjler indenfor fast-track THA og TKA i Danmark. Hovedfundende i de inkluderede arbejder var: Præoperativ anæmi (PA) var hyppigt forekommende (13%) hos danske fast-track THA/TKA patienter og var associeret med øget risiko for blodtransfusion og genindlæggelse (studie 1) men var ikke associeret med signifikant øget cancerrisiko 1 år efter kirurgi (studie 2). Jernmangel var den hyppigste årsag til præoperativ anæmi (studie 3). I 2008 var den samlede transfusionsrate ved THA i Danmark 24% men med en udtalt variation (7% - 71%) mellem kirurgiske afdelinger (studie 4). Postoperativ 90 dages mortalitet blandt transfunderede THA patienter var relateret til alvorligt blodtab og akut anæmi i højere grad end til mulige transfusionskomplikationer (Studie 5). Intraoperativt administreret lavdosis adrenalininfusion reducerede 24 timer totalt beregnet blodtab men ikke intraoperativt blodtab i fast-trak THA (Studie 6). Ved TKA reducerede kombineret intraartikulært og intravenøst (IV) administreret tranexamsyre (TXA) det totale beregnede blodtab med 37% sammenlignet med IV administration af TXA alene (Studie 7). Moderat postoperativ anæmi havde kun en begrænset og klinisk insignifikant betydning for tidlige postoperative funktionelle endemål hos fast-track THA patienter (studie 8).

Fra det narrative review kan det konkluderes at præoperativ anæmi er hyppigt forekommende ved THA/TKA, er associeret med øget transfusionsrisiko og postoperativ morbiditet og at PA kan behandles med IV-jern hos størstedelen af patienterne. Erythropoetin stimulerende stoffer er også effektive til at normalisere præoperativ Hb men brugen er kun udbredt i nogle lande og begrænset til selekterede patienter. Antifibrinolytika så som TXA har vist sig højeffektive til at reducere blodtabet og transfusionsbehovet ved THA/TKA. Selvom kombineret lokal og systemisk administration af TXA ser ud til at være mest effektivt, er det endnu ikke konsensus om den optimale dosis, timing og administrationsmåde for TXA. Andre antifibrinolytika, samt administration af lavdosis adrenalin, reducerer også blodtab men der er behov for flere højkvalitetsstudier vedr. effekt, sikkerhed og optimal patientselektion. Den samlede transfusionsrate for THA/TKA er blevet reduceret dramatisk over de sidste 15 år i til under 10% i mange lande men der er forstsat en meget høj variation mellem de enkelte kirurgiske afdelinger. En af årsagerne til reduktionen i transfusionsrater er implementeringen af restriktive transfusionsgrænser i mange afdelinger. Selvom en restriktiv transfusionsstrategi ser ud til at være sikker hos de fleste patienter, er det meste evidens baseret på store randomiserede studier udført i andre patientpopulationer end THA/TKA. Der er især usikkerhed omkring den optimale transfusionsstrategi hos de meste syge, ældre og skrøbelige patienter der får foretaget THA/TKA. Det har været debatteret hvorvidt postoperativ anæmi hæmmer evnen til tidlig mobilisering og genvindelse af fysisk funktionsevne, hvilket er essentielle elementer i fast-track protokoller. Den nuværende evidens er sparsom og tyder på moderat postoperativ anæmi har en meget begrænset indvirkning på tidlige funktionelle endemål, men der mangler data fra skrøbelige patienter og patienter med mere udtalt anæmi.
For at øge kvaliteten af den foreliggende evidens foreslås det at fremtidig PBM forskning inden for THA/TKA generelt fokuserer på højrisiko patienter så som de ældste og skrøbelige der gennemgår THA/TKA. Andre områder der bør belyses yderligere er: Den optimale Hb grænse for præoperativ anæmibehandling, brugen af kombineret topikal / systemisk antifibrinolytika

eller anden adjuverende behandling til at reducere blodtabet samt potentialet for postoperativ Hb optimering med jernbehandling og andre farmaka.

.

12. References

1. Jans Ø, Jørgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion. 2014; **54**:717–26.
2. Jørgensen CC, Jans Ø, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Preoperative anaemia and newly diagnosed cancer 1 year after elective total hip and knee arthroplasty. Vox Sang. 2015; **109**:62–70.
3. Jans Ø, Nielsen CS, Khan N, Gromov K, Troelsen A, Husted H. Iron deficiency and preoperative anaemia in patients scheduled for elective hip- and knee arthroplasty - an observational study. Vox Sang. 2018; **113**:260–7.
4. Jans Ø, Kehlet H, Hussain Z, Johansson PI. Transfusion practice in hip arthroplasty--a nationwide study. Vox Sang. 2011; **100**:374–80.
5. Jans O, Kehlet H, Johansson PI. Transfusion-related mortality after primary hip arthroplasty - an analysis of mechanisms and confounders. Vox Sang. 2012; **103**:301–8.
6. Jans Ø, Grevstad U, Mandøe H, Kehlet H, Johansson PII. A randomized trial of the effect of low dose epinephrine infusion in addition to tranexamic acid on blood loss during total hip arthroplasty. Br J Anaesth. 2016; **116**:357–62.
7. Nielsen CS, Jans Ø, Ørsnes T, Foss NB, Troelsen A, Husted H. Combined Intra-Articular and Intravenous Tranexamic Acid Reduces Blood Loss in Total Knee Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial. J Bone Joint Surg Am. 2016; **98**:835–41.
8. Jans Ø, Bandholm T, Kurbegovic S, et al. Postoperative anemia and early functional outcomes after fast-track hip arthroplasty: a prospective cohort study. Transfusion. 2016; **56**:917–25.
9. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010; **113**:482–95.
10. Ludwig H, Strasser K. Symptomatology of anemia. Semin Oncol. 2001; **28**:7–14.
11. Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011; **114**:283–92.
12. Stanworth SJ, Cockburn HAC, Boralessa H, Contreras M. Which groups of patients are transfused? A study of red cell usage in London and southeast England. Vox Sang. 2002; **83**:352–7.
13. Danish Transfusion Database (DTDB) annual report 2013 [Internet]. 2014. Available from: https://www.sundhed.dk/content/cms/13/4713_dtbd_årsrapport2013_111102013_final.pdf

14. Goodnough LT, Shander A. Patient blood management. Anesthesiology. 2012; **116**:1367–76.

15. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ. 2015; **350**:h1354.

16. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Carson JL, editor. Cochrane database Syst Rev. Chichester, UK; 2016; **10**:CD002042.

17. Gombotz H, Rehak PH, Shander A, Hofmann A. The second Austrian benchmark study for blood use in elective surgery: results and practice change. Transfusion. 2014; **54**:2646–57.

18. Danish Transfusion Database (DTDB) annual report 2015 [Internet]. 2016. Available from: https://www.sundhed.dk/content/cms/13/4713_2016-09-18-årsrapport-2015_v5_dansk_transfusionsdatabase.pdf

19. Bedard NA, Pugely AJ, Lux NR, Liu SS, Gao Y, Callaghan JJ. Recent Trends in Blood Utilization After Primary Hip and Knee Arthroplasty. J Arthroplasty. 2017; **32**:724–7.

20. Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. Transfusion. 2007; **47**:1468–80.

21. Menendez ME, Lu N, Huybrechts KF, et al. Variation in Use of Blood Transfusion in Primary Total Hip and Knee Arthroplasties. J Arthroplasty. 2016; **31**:2757-2763.e2.

22. Voorn VMA, Marang-van de Mheen PJ, van der Hout A, et al. Hospital variation in allogeneic transfusion and extended length of stay in primary elective hip and knee arthroplasty: a cross-sectional study. BMJ Open. 2017; **7**:e014143.

23. Shander A, Van Aken H, Colomina MJ, et al. Patient blood management in Europe. Br J Anaesth. 2012; **109**:55–68.

24. Lasocki S, Krauspe R, von Heymann C, Mezzacasa A, Chainey S, Spahn DR. PREPARE: the prevalence of perioperative anaemia and need for patient blood management in elective orthopaedic surgery: a multicentre, observational study. Eur J Anaesthesiol. 2015; **32**:160–7.

25. Van der Linden P, Hardy J-F. Implementation of patient blood management remains extremely variable in Europe and Canada. Eur J Anaesthesiol. 2016; **33**:913–21.

26. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008; **248**:189–98.

27. Kehlet H. Fast-track surgery-an update on physiological care principles to enhance recovery. Langenbecks Arch Surg Dtsch Gesellschaft fur Chir. 2011; **396**:585–90.

28. Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from

research to implementation. Arch Orthop Trauma Surg. 2012; **132**:101–4.

29. Kehlet H. Fast track hip and knee arthroplasty. Lancet. 2013; **381**:1600–2.
30. Gromov K, Kristensen BB, Jørgensen CC, Hansen TB, Kehlet H, Husted H. [Fast-track total knee arthroplasty]. Ugeskr Laeger. 2017; **179**.
31. Vehmeijer SBW, Husted H, Kehlet H. Outpatient total hip and knee arthroplasty. Acta Orthop. 2018; **89**:141–4.
32. Wainwright TW, Kehlet H. Fast-track hip and knee arthroplasty – have we reached the goal? Acta Orthop. 2019; **90**:3–5.
33. Husted H, Gromov K, Malchau H, Freiberg A, Gebuhr P, Troelsen A. Traditions and myths in hip and knee arthroplasty. Acta Orthop. 2014; **85**:548–55.
34. Husted H, Solgaard S, Hansen TB, Søballe K, Kehlet H. Care principles at four fast-track arthroplasty departments in Denmark. Dan Med Bull. 2010; **57**:A4166.
35. The Society for Advancement of Blood Management [Internet].

    Available from: https://www.sabm.org/
36. 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.
37. Beris P, Muñoz M, García-Erce J a, Thomas D, Maniatis a, Van Der Linden P. Perioperative anaemia management: consensus statement on the role of intravenous iron. Br J Anaesth. 2008; **100**:599–604.
38. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane database Syst Rev. 2011; :CD001886.
39. Shander A, Kaplan LJ, Harris MT, et al. Topical hemostatic therapy in surgery: bridging the knowledge and practice gap. J Am Coll Surg. 2014; **219**:570-9.e4.
40. Desai N, Schofield N, Richards T. Perioperative Patient Blood Management to Improve Outcomes. Anesth Analg. 2018; **127**:1211–20.
41. Spahn D, Muñoz M, Klein A, Levy J, Zacharowski K. Patient Blood Management: Effectiveness and Future Potential. Anesthesiology. 2020; **133**:212–22.
42. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion. 2017; **57**:1347–58.
43. WHO. Word Health Assembly. Availability, safety and quality of blood products [Internet]. 2010. Available from: http://apps.who.int/medicinedocs/documents/s19998en/s19998en.pdf
44. Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF, Guideline Development Group. Blood transfusion: summary of NICE guidance. BMJ. 2015; **351**:h5832.

45. Kaserer A, Rössler J, Braun J, et al. Impact of a Patient Blood Management monitoring and feedback programme on allogeneic blood transfusions and related costs. Anaesthesia. 2019; **74**:1534–41.

46. Gross I, Seifert B, Hofmann A, Spahn DR. Patient blood management in cardiac surgery results in fewer transfusions and better outcome. Transfusion. 2015; **55**:1075–81.

47. Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. Ann Surg. 2016; **264**:41–6.

48. Martinez V, Monsaingeon-Lion A, Cherif K, Judet T, Chauvin M, Fletcher D. Transfusion strategy for primary knee and hip arthroplasty: impact of an algorithm to lower transfusion rates and hospital costs. Br J Anaesth. 2007; **99**:794–800.

49. Wong CJ, Vandervoort MK, Vandervoort SL, et al. A cluster-randomized controlled trial of a blood conservation algorithm in patients undergoing total hip joint arthroplasty. Transfusion. 2007; **47**:832–41.

50. Kotzé A, Carter LA, Scally AJ. Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle. Br J Anaesth. 2012; **108**:943–52.

51. Moráis S, Ortega-Andreu M, Rodríguez-Merchán EC, et al. Blood transfusion after primary total knee arthroplasty can be significantly minimised through a multimodal blood-loss prevention approach. Int Orthop. 2014; **38**:347–54.

52. Kopanidis P, Hardidge A, McNicol L, Tay S, McCall P, Weinberg L. Perioperative blood management programme reduces the use of allogenic blood transfusion in patients undergoing total hip and knee arthroplasty. J Orthop Surg Res. 2016; **11**:28.

53. Rineau E, Chaudet A, Chassier C, Bizot P, Lasocki S. Implementing a blood management protocol during the entire perioperative period allows a reduction in transfusion rate in major orthopedic surgery: a before-after study. Transfusion. 2016; **56**:673–81.

54. Gupta PB, DeMario VM, Amin RM, et al. Patient Blood Management Program Improves Blood Use and Clinical Outcomes in Orthopedic Surgery. Anesthesiology. 2018; **129**:1082–91.

55. Polanco-García M, Capielo AM, Miret X, et al. Effectiveness of a patient blood management protocol on reduction of allogeneic red blood cell transfusions in orthopedic surgery. Med Clin (Barc). 2019; **152**:90–7.

56. Albinarrate A, López-Picado A, Oiartzabal I, López-Ariznabarreta C, Molano J, Barrachina B. Assessment of the introduction of a blood management program in orthopaedic surgery. Rev Esp Anestesiol Reanim. 2015; **62**:443–9.

57. Althoff FC, Neb H, Herrmann E, et al. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic

Review and Meta-analysis. Ann Surg. 2019; **269**:794–804.

58. Sherliker L, Pendry K, Hockley B. Patient blood management: how is implementation going?: A report comparing the 2015 survey with the 2013 survey of PBM in England. Transfus Med. 2018; **28**:92–7.

59. Bruun MT, Pendry K, Georgsen J, et al. Patient Blood Management in Europe: surveys on top indications for red blood cell use and Patient Blood Management organization and activities in seven European university hospitals. Vox Sang. 2016; **111**:391–8.

60. Manzini PM, Dall'Omo AM, D'Antico S, et al. Patient blood management knowledge and practice among clinicians from seven European university hospitals: a multicentre survey. Vox Sang. 2018; **113**:60–71.

61. Meybohm P, Richards T, Isbister J, et al. Patient Blood Management Bundles to Facilitate Implementation. Transfus Med Rev. 2017; **31**:62–71.

62. Meybohm P, Froessler B, Goodnough LT, et al. "Simplified International Recommendations for the Implementation of Patient Blood Management" (SIR4PBM). Perioper Med. 2017; **6**:5.

63. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968; **405**:5–37.

64. Rosencher N, Kerkkamp HEM, Macheras G, et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion. 2003; **43**:459–69.

65. Basora M, Deulofeu R, Salazar F, Quinto L, Gomar C. Improved preoperative iron status assessment by soluble transferrin receptor in elderly patients undergoing knee and hip replacement. Clin Lab Haematol. 2006; **28**:370–5.

66. Hasley PB, Lave JR, Hanusa BH, et al. Variation in the use of red blood cell transfusions. A study of four common medical and surgical conditions. Med Care. 1995; **33**:1145–60.

67. Bisbe E, Castillo J, Sáez M, Santiveri X, Ruíz A, Muñoz M. Prevalence of preoperative anemia and hematinic deficiencies in patients scheduled for elective major orthopedic surgery. Transfus Altern Transfus Med. 2008; **10**:166–73.

68. Pujol-Nicolas A, Morrison R, Casson C, et al. Preoperative screening and intervention for mild anemia with low iron stores in elective hip and knee arthroplasty. Transfusion. 2017; **57**:3049–57.

69. Meybohm P, Kohlhof H, Wirtz DC, et al. Preoperative Anaemia in Primary Hip and Knee Arthroplasty. Z Orthop Unfall. 2020; **158**:194–200.

70. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia. 2017; **72**:233–47.

71. Butcher A, Richards T, Stanworth SJ, Klein AA. Diagnostic criteria for pre-operative anaemia-time to end sex discrimination. Anaesthesia. 2017; **72**:811–4.

72. Klement MR, Peres-Da-Silva A, Nickel BT, et al. What Should Define Preoperative Anemia in Primary THA? Clin Orthop Relat Res. 2017; **475**:2683–91.

73. Kotzé A, Harris A, Baker C, et al. British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia. Br J Haematol. 2015; **171**:322–31.

74. Clevenger B, Richards T. Pre-operative anaemia. Anaesthesia. 2015; **70 Suppl 1**:20–8, e6-8.

75. Muñoz M, García-Erce JA, Remacha ÁF. Disorders of iron metabolism. Part II: iron deficiency and iron overload. J Clin Pathol. 2011; **64**:287–96.

76. Füllenbach C, Stein P, Glaser P, et al. Screening for iron deficiency in surgical patients based on noninvasive zinc protoporphyrin measurements. Transfusion. 2020; **60**:62–72.

77. Meybohm P. The future of iron deficiency diagnostics - Rapid home-use point-of-care test kits. EBioMedicine. 2019; **42**:28–9.

78. Muñoz M, Laso-Morales MJ, Gómez-Ramírez S, Cadellas M, Núñez-Matas MJ, García-Erce JA. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia. 2017; **72**:826–34.

79. Myers E, O'Grady P, Grady PO, Dolan AM. The influence of preclinical anaemia on outcome following total hip replacement. ArchOrthopTrauma Surg. 2004; **124**:699–701.

80. Saleh E, McClelland DBL, Hay a, Semple D, Walsh TS. Prevalence of anaemia before major joint arthroplasty and the potential impact of preoperative investigation and correction on perioperative blood transfusions. Br J Anaesth. 2007; **99**:801–8.

81. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet. 1996; **348**:1055–60.

82. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet. 2011; **378**:1396–407.

83. Wu W-C, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA. 2007; **297**:2481–8.

84. Wallis JP. Disentangling anemia and transfusion. Transfusion. 2011; **51**:8–10.

85. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation. 2008; **117**:478–84.

86. Beattie WS, Karkouti K, Wijeysundera DN, Tait G. Risk Associated with Preoperative Anemia in Noncardiac Surgery. Anesthesiology. 2009; **110**:574–81.

87. Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J

Anaesth. 2014; **113**:416–23.

88. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015; **102**:1314–24.

89. Mantilla CB, Wass CT, Goodrich K a, et al. Risk for perioperative myocardial infarction and mortality in patients undergoing hip or knee arthroplasty: The role of anemia. Transfusion. 2011; **51**:82–91.

90. Greenky M, Gandhi K, Pulido L, Restrepo C, Parvizi J. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res. 2012; **470**:2695–701.

91. Bozic KJ, Lau E, Kurtz S, et al. Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am. 2012; **94**:794–800.

92. Petersen PB, Kehlet H, Jørgensen CC, et al. Incidence and Risk Factors for Stroke in Fast-Track Hip and Knee Arthroplasty—A Clinical Registry Study of 24,862 Procedures. J Arthroplasty. 2019; **34**:743-749.e2.

93. Leal-Noval SR, Muñoz M, Asuero M, et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the 'Seville Document'. Blood Transfus. 2013; **11**:585–610.

94. Bisbe E, Basora M, Colomina MJ, Spanish Best Practice in Peri-operative Anaemia Optimisation Panel. Peri-operative treatment of anaemia in major orthopaedic surgery: a practical approach from Spain. Blood Transfus. 2017; **15**:296–306.

95. Clevenger B, Gurusamy K, Klein AA, Murphy GJ, Anker SD, Richards T. Systematic review and meta-analysis of iron therapy in anaemic adults without chronic kidney disease: updated and abridged Cochrane review. Eur J Heart Fail. 2016; **18**:774–85.

96. Ng O, Keeler BD, Mishra A, et al. Iron therapy for preoperative anaemia. Cochrane database Syst Rev. 2019; **12**:CD011588.

97. Richards T, Clevenger B, Keidan J, et al. PREVENTT: preoperative intravenous iron to treat anaemia in major surgery: study protocol for a randomised controlled trial. Trials. 2015; **16**:254.

98. Peters F, Ellermann I, Steinbicker AU. Intravenous Iron for Treatment of Anemia in the 3 Perisurgical Phases. Anesth Analg. 2018; **126**:1268–82.

99. Theusinger OM, Leyvraz P-F, Schanz U, Seifert B, Spahn DR. Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits: a prospective study. Anesthesiology. 2007; **107**:923–7.

100. Bisbe E, García-Erce JA, Díez-Lobo AI, Muñoz M, Anaemia Working Group España. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. Br J Anaesth. 2011; **107**:477–8.

101. Stowell CP, Jones SC, Enny C, Langholff W, Leitz G. An open-label, randomized, parallel-group study of perioperative epoetin alfa versus

standard of care for blood conservation in major elective spinal surgery: safety analysis. Spine (Phila Pa 1976). 2009; **34**:2479–85.

102. Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents--time for a reevaluation. N Engl J Med. 2010; **362**:189–92.
103. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet. 2019; **393**:2201–12.
104. Li Y, Yin P, Lv H, Meng Y, Zhang L, Tang P. A meta-analysis and systematic review evaluating the use of erythropoietin in total hip and knee arthroplasty. Ther Clin Risk Manag. 2018; **14**:1191–204.
105. Voorn VMA, van der Hout A, So-Osman C, et al. Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty. Vox Sang. 2016; **111**:219–25.
106. So-Osman C, Nelissen RGHH, Koopman-van Gemert AWMM, et al. Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 1). Anesthesiology. 2014; **120**:839–51.
107. Guinn NR, Guercio JR, Hopkins TJ, et al. How do we develop and implement a preoperative anemia clinic designed to improve perioperative outcomes and reduce cost? Transfusion. 2016; **56**:297–303.
108. Meybohm P, Goehring MH, Choorapoikayil S, et al. Feasibility and efficiency of a preoperative anaemia walk-in clinic: secondary data from a prospective observational trial. Br J Anaesth. 2017; **118**:625–6.
109. Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth. 2020; **124**:243–50.
110. Surgenor DM, Wallace EL, Churchill WH, Hao SH, Chapman RH, Poss R. Red cell transfusions in total knee and total hip replacement surgery. Transfusion. 1991; **31**:531–7.
111. Browne JA, Adib F, Brown TE, Novicoff WM. Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. J Arthroplasty. 2013; **28**:34–7.
112. Yoshihara H, Yoneoka D. National Trends in the Utilization of Blood Transfusions in Total Hip and Knee Arthroplasty. J Arthroplasty. 2014; **29**:1932–7.
113. Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty-day complication rates. J Bone Joint Surg Am. 2014; **96**:1945–51.
114. Hart A, Bergeron SG, Epure L, Huk O, Zukor D, Antoniou J. Comparison of US and Canadian Perioperative Outcomes and Hospital Efficiency After Total Hip and Knee Arthroplasty. JAMA Surg. 2015; **150**:990–8.
115. Capraro L. Transfusion practices in primary total joint replacements in Finland. Vox Sang. 1998; **75**:1–6.
116. Boralessa H, Goldhill DR, Tucker K, Mortimer AJ, Grant-Casey J. National comparative audit of blood use in elective primary unilateral total hip

replacement surgery in the UK. Ann R Coll Surg Engl. 2009; **91**:599–605.

117. Carling MS, Jeppsson A, Eriksson BI, Brisby H. Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study. J Orthop Surg Res. 2015; **10**:48.
118. Pedersen AB, Mehnert F, Overgaard S, Møller B, Johnsen SP. [Transfusion practice in total hip arthroplasty in Danish departments of orthopaedic surgery]. Ugeskr Laeger. 2009; **171**:973–7.
119. Danish Hip Arthroplasty Registry 'Annual report 2019' [Internet]. 2019. Available from: http://danskhoftealloplastikregister.dk/wp-content/uploads/2019/09/DHR-årsrapport-2019_til-offentliggørelse.pdf
120. Saleh A, Small T, Chandran Pillai ALP, Schiltz NK, Klika AK, Barsoum WK. Allogenic blood transfusion following total hip arthroplasty: results from the nationwide inpatient sample, 2000 to 2009. J Bone Joint Surg Am. 2014; **96**:e155.
121. Goel R, Chappidi MR, Patel EU, et al. Trends in Red Blood Cell, Plasma, and Platelet Transfusions in the United States, 1993-2014. JAMA. 2018; **319**:825.
122. Suh Y, Lee JJ, Nho J, Lee J, Won SH, Yang H. Transfusion trends in hip arthroplasty in Korea: a nationwide study by the Korean National Health Insurance Service. Transfusion. 2019; **59**:2324–33.
123. Shander A, Lobel GP, Javidroozi M. Transfusion practices and infectious risks. Expert Rev Hematol. 2016; **9**:597–605.
124. Politis C, Wiersum JC, Richardson C, et al. The International Haemovigilance Network Database for the Surveillance of Adverse Reactions and Events in Donors and Recipients of Blood Components: technical issues and results. Vox Sang. 2016; **111**:409–17.
125. Remy KE, Hall MW, Cholette J, et al. Mechanisms of red blood cell transfusion-related immunomodulation. Transfusion. 2018; **58**:804–15.
126. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016; **316**:2025–35.
127. Transfusion PB, Therapies A. Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006; **105**:198–208.
128. Retter A, Wyncoll D, Pearse R, et al. Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. Br J Haematol. 2013; **160**:445–64.
129. Danish Board of Health. 'Vejledning om blodtransfusion' [Internet]. 2015. Available from: https://stps.dk/da/udgivelser/2015/vejledning-om-blodtransfusion/~/media/8147748CEC6140FF9112674B5EF1307B.ashx
130. Holst LB, Haase N, Wetterslev J, et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. N Engl J Med. 2014; **371**:1381–91.
131. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011; **365**:2453–62.

132. Murphy GJ, Pike K, Rogers CA, et al. Liberal or Restrictive Transfusion after Cardiac Surgery. N Engl J Med. 2015; **372**:997–1008.

133. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med. 2017; **377**:2133–44.

134. Lotke PA, Barth P, Garino JP, Cook EF. Predonated autologous blood transfusions after total knee arthroplasty: immediate versus delayed administration. J Arthroplasty. 1999; **14**:647–50.

135. Grover M, Talwalkar S, Casbard A, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang. 2006; **90**:105–12.

136. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang. 2010; **98**:56–64.

137. Nielsen K, Johansson PI, Dahl B, et al. Perioperative transfusion threshold and ambulation after hip revision surgery--a randomized trial. BMC Anesthesiol. 2014; **14**:89.

138. Fan Y-X, Liu F-F, Jia M, et al. Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: A preliminary study. Arch Gerontol Geriatr. 2014; **59**:181–5.

139. Carson JL, Stanworth SJ, Alexander JH, et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J. 2018; **200**:96–101.

140. Docherty AB, O'Donnell R, Brunskill S, 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**:i1351.

141. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; **340**:409–17.

142. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture. Acta Orthop. 2015; **86**:363–72.

143. Wang JK, Klein HG. Red blood cell transfusion in the treatment and management of anaemia: the search for the elusive transfusion trigger. Vox Sang. 2010; **98**:2–11.

144. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion. 1998; **38**:522–9.

145. Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. Injury. 2013; **44**:1916–8.

146. Meybohm P, Lindau S, Treskatsch S, et al. Liberal transfusion strategy to prevent mortality and anaemia-associated, ischaemic events in elderly non-cardiac surgical patients – the study design of the LIBERAL-Trial. Trials. 2019; **20**:101.

147. Koch CG, Li L, Duncan AI, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg. 2006; **58**:1650–7.

148. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation. 2007; **116**:2544–52.

149. Reeves BC, Murphy GJ. Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery. Curr Opin Anaesthesiol. 2008; **21**:669–73.

150. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev. 2007; **21**:327–48.

151. Lannan KL, Sahler J, Spinelli SL, Phipps RP, Blumberg N. Transfusion immunomodulation--the case for leukoreduced and (perhaps) washed transfusions. Blood Cells Mol Dis. 2013; **50**:61–8.

152. Gundtoft PH, Pedersen AB, Schønheyder HC, Møller JK, Overgaard S. One-year incidence of prosthetic joint infection in total hip arthroplasty: a cohort study with linkage of the Danish Hip Arthroplasty Register and Danish Microbiology Databases. Osteoarthr Cartil. 2017; **25**:685–93.

153. Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. Increased Mortality After Prosthetic Joint Infection in Primary THA. Clin Orthop Relat Res. 2017; **475**:2623–31.

154. Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion. 2005; **45**:103–10.

155. Dowsey MM, Choong PFM. Obesity is a Major Risk Factor for Prosthetic Infection after Primary Hip Arthroplasty. Clin Orthop Relat Res. 2008; **466**:153–8.

156. Basora M, Pereira a, Soriano a, et al. Allogeneic blood transfusion does not increase the risk of wound infection in total knee arthroplasty. Vox Sang. 2010; **98**:124–9.

157. Friedman R, Homering M, Holberg G, Berkowitz SD. Allogeneic Blood Transfusions and Postoperative Infections After Total Hip or Knee Arthroplasty. J Bone Jt Surg. 2014; **96**:272–8.

158. Newman ET, Watters TS, Lewis JS, et al. Impact of Perioperative Allogeneic and Autologous Blood Transfusion on Acute Wound Infection Following Total Knee and Total Hip Arthroplasty. J Bone Jt Surg. 2014; **96**:279–84.

159. Klasan A, Dworschak P, Heyse TJ, et al. Transfusions increase complications and infections after hip and knee arthroplasty: An analysis

of 2760 cases. Technol Heal Care. 2018; **26**:825–32.

160. Almustafa MA, Ewen AM, Deakin AH, Picard F, Clarke J V, Mahmood FF. Risk Factors for Surgical Site Infection Following Lower Limb Arthroplasty: A Retrospective Cohort Analysis of 3932 Lower Limb Arthroplasty Procedures in a High Volume Arthroplasty Unit. J Arthroplasty. 2018; **33**:1861–7.
161. Kim JL, Park J-H, Han S-B, Cho IY, Jang K-M. Allogeneic Blood Transfusion Is a Significant Risk Factor for Surgical-Site Infection Following Total Hip and Knee Arthroplasty: A Meta-Analysis. J Arthroplasty. 2017; **32**:320–5.
162. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion. 2009; **49**:227–34.
163. 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.
164. Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev. 2011; **25**:89–101.
165. Karkouti K, Stukel TA, Beattie WS, et al. Relationship of erythrocyte transfusion with short- and long-term mortality in a population-based surgical cohort. Anesthesiology. 2012; **117**:1175–83.
166. Dardashti a, Ederoth P, Algotsson L, Brondén B, Lührs C, Bjursten H. Blood transfusion after cardiac surgery: is it the patient or the transfusion that carries the risk? Acta Anaesthesiol Scand. 2011; **55**:952–61.
167. Middelburg R a, van de Watering LMG, van der Bom JG. Blood transfusions: good or bad? Confounding by indication, an underestimated problem in clinical transfusion research. Transfusion. 2010; **50**:1181–3.
168. Pedersen AB, Baron J, Overgaard S, Johnsen S. Short- and long-term mortality following primary total hip replacement for osteoarthritis: a Danish nationwide epidemiological study. J Bone Joint Surg Br. 2011; **93**:172–7.
169. Bisbe E, Moltó L. Pillar 2: minimising bleeding and blood loss. Best Pract Res Clin Anaesthesiol. 2013; **27**:99–110.
170. Giral T, Tesniere A, Bellamy L, Ozier Y, Samama CM, Rosencher N. Bleeding Kinetics after Total Hip or Knee Replacement: A Prospective Observational Study. J Anesth Clin Res. 2013; **4**:1–5.
171. Liu X, Zhang X, Chen Y, Wang Q, Jiang Y, Zeng B. Hidden blood loss after total hip arthroplasty. J Arthroplasty. 2011; **26**:1100-5.e1.
172. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br. 2004; **86**:561–5.
173. Kim C, Park SS-H, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. J Blood Med. 2015; **6**:239–44.

174. Benoni G, Carlsson A, Petersson C, Fredin H. Does tranexamic acid reduce blood loss in knee arthroplasty? Am J Knee Surg. 1995; **8**:88–92.

175. Goobie SM, Frank SM. Tranexamic Acid. Anesthesiology. 2017; **127**:405–7.

176. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011; **93**:1577–85.

177. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J bone Jt Surg Br Vol. 2011; **93**:39–46.

178. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. J Arthroplasty. 2018; **33**:3090-3098.e1.

179. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis. J Arthroplasty. 2018; **33**:3083-3089.e4.

180. Danish orthopedic Society and Danish Society for hip- and knee Arthroplasty. 'Referenceprogram - Total Hoftealloplastik' [Internet]. 2006. Available from: https://www.ortopaedi.dk/fileadmin/Guidelines/Referenceprogrammer/THA-referenceprogram.pdf

181. Danish orthopedic Society and Danish Society for hip- and knee Arthroplasty. Referenceprogram - Knænær osteotomi og Total Knæalloplastik [Internet]. 2004. Available from: https://www.ortopaedi.dk/fileadmin/Guidelines/Referenceprogrammer/Osteotomi_og_TKA.pdf

182. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. Tranexamic Acid Use in Total Joint Arthroplasty: The Clinical Practice Guidelines Endorsed by the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Socie. J Arthroplasty. 2018; **33**:3065–9.

183. Xiong H, Liu Y, Zeng Y, Wu Y, Shen B. The efficacy and safety of combined administration of intravenous and topical tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord. 2018; **19**:321.

184. Zhang P, Liang Y, Chen P, Fang Y, He J, Wang J. Combined application versus topical and intravenous application of tranexamic acid following primary total hip arthroplasty: a meta-analysis. BMC Musculoskelet Disord. 2017; **18**:90.

185. Sun Q, Li J, Chen J, Zheng C, Liu C, Jia Y. Comparison of intravenous, topical or combined routes of tranexamic acid administration in patients undergoing total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. BMJ Open. 2019; **9**:e024350.

186. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ.

2014; **349**:g4829–g4829.

187. Duncan CM, Gillette BP, Jacob AK, Sierra RJ, Sanchez-Sotelo J, Smith HM. Venous Thromboembolism and Mortality Associated With Tranexamic Acid Use During Total Hip and Knee Arthroplasty. J Arthroplasty. 2015; **30**:272–6.
188. Franchini M, Mengoli C, Marietta M, et al. Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: a meta-analysis of randomised controlled trials. Blood Transfus. 2018; **16**:36–43.
189. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis. J Arthroplasty. 2018; **33**:3070-3082.e1.
190. Dastrup A, Pottegård A, Hallas J, Overgaard S. Perioperative Tranexamic Acid Treatment and Risk of Cardiovascular Events or Death After Total Hip Arthroplasty. J Bone Jt Surg. 2018; **100**:1742–9.
191. Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW. Tranexamic Acid Was Safe in Arthroplasty Patients With a History of Venous Thromboembolism: A Matched Outcome Study. J Arthroplasty. 2017; **32**:S246–50.
192. Myles PS, Smith JA, Forbes A, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. N Engl J Med. 2017; **376**:136–48.
193. Ortmann E, Besser MW, Klein AA. Antifibrinolytic agents in current anaesthetic practice. Br J Anaesth. 2013; **111**:549–63.
194. Hobbs JC, Welsby IJ, Green CL, Dhakal IB, Wellman SS. Epsilon Aminocaproic Acid to Reduce Blood Loss and Transfusion After Total Hip and Total Knee Arthroplasty. J Arthroplasty. 2018; **33**:55–60.
195. Boese CK, Centeno L, Walters RW. Blood Conservation Using Tranexamic Acid Is Not Superior to Epsilon-Aminocaproic Acid After Total Knee Arthroplasty. J Bone Joint Surg Am. 2017; **99**:1621–8.
196. Camarasa MA, Ollé G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth. 2006; **96**:576–82.
197. Churchill J, Puca K, Meyer E, Carleton M, Anderson M. Comparing ε-Aminocaproic Acid and Tranexamic Acid in Reducing Postoperative Transfusions in Total Knee Arthroplasty. J Knee Surg. 2017; **30**:460–6.
198. von Känel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol. 2000; **65**:357–69.
199. Liu JL, Zeng WN, Wang FY, et al. Effects of low-dose epinephrine on perioperative hemostasis and inflammatory reaction in major surgical operations: a randomized clinical trial. J Thromb Haemost. 2018; **16**:74–82.
200. Zeng W-N, Liu J-L, Wang F-Y, Chen C, Zhou Q, Yang L. Low-Dose Epinephrine Plus Tranexamic Acid Reduces Early Postoperative Blood Loss and Inflammatory Response. J Bone Jt Surg. 2018; **100**:295–304.
201. Sierra RJ, Smith HM. Low-Dose Epinephrine Infusions and Tranexamic

Acid During Lower-Extremity Total Joint Arthroplasty: Commentary on an article by Wei-Nan Zeng, MD, et al.: "Low-Dose Epinephrine Plus Tranexamic Acid Reduces Early Postoperative Blood Loss and Inflammato. J Bone Joint Surg Am. 2018; **100**:e23.

202. Li J, Li H, Zhai X, Qin-lei, Jiang X, Zhang Z. Topical use of topical fibrin sealant can reduce the need for transfusion, total blood loss and the volume of drainage in total knee and hip arthroplasty: A systematic review and meta-analysis of 1489 patients. Int J Surg. 2016; **36**:127–37.
203. Gao F, Ma J, Sun W, Guo W, Li Z, Wang W. Topical fibrin sealant versus intravenous tranexamic acid for reducing blood loss following total knee arthroplasty: A systematic review and meta-analysis. Int J Surg. 2016; **32**:31–7.
204. Kim HJ, Fraser MR, Kahn B, Lyman S, Figgie MP. The efficacy of a thrombin-based hemostatic agent in unilateral total knee arthroplasty: a randomized controlled trial. J Bone Joint Surg Am. 2012; **94**:1160–5.
205. Wang C, Han Z, Zhang T, et al. The efficacy of a thrombin-based hemostatic agent in primary total knee arthroplasty: a meta-analysis. J Orthop Surg Res. 2014; **9**:90.
206. Lassen MR, Solgaard S, Kjersgaard AG, et al. A pilot study of the effects of Vivostat patient-derived fibrin sealant in reducing blood loss in primary hip arthroplasty. Clin Appl Thromb Hemost. 2006; **12**:352–7.
207. Skovgaard C, Holm B, Troelsen A, et al. No effect of fibrin sealant on drain output or functional recovery following simultaneous bilateral total knee arthroplasty: a randomized, double-blind, placebo-controlled study. Acta Orthop. 2013; **84**:153–8.
208. Themistoklis T, Theodosia V, Konstantinos K, Georgios DI. Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now? World J Orthop. 2017; **8**:441–54.
209. Vassallo R, Goldman M, Germain M, Lozano M, BEST Collaborative. Preoperative Autologous Blood Donation: Waning Indications in an Era of Improved Blood Safety. Transfus Med Rev. 2015; **29**:268–75.
210. Voorn VM, Marang-van de Mheen PJ, Wentink MM, et al. Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey. BMC Musculoskelet Disord. 2013; **14**:230.
211. van Bodegom-Vos L, Voorn VM, So-Osman C, et al. Cell Salvage in Hip and Knee Arthroplasty. J Bone Jt Surgery-American Vol. 2015; **97**:1012–21.
212. Waters JH, Dyga RM, Waters JFR, Yazer MH. The volume of returned red blood cells in a large blood salvage program: where does it all go? (CME). Transfusion. 2011; **51**:2126–32.
213. So-Osman C, Nelissen RGHH, Koopman-van Gemert AWMM, et al. Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 2). Anesthesiology. 2014; **120**:852–60.
214. Muñoz M, Cobos A, Campos A. Low vacuum re-infusion drains after total knee arthroplasty: is there a real benefit? Blood Transfus. 2014; **12 Suppl**

1:s173-5.

215. Voorn VMA, Marang-van de Mheen PJ, van der Hout A, et al. The effectiveness of a de-implementation strategy to reduce low-value blood management techniques in primary hip and knee arthroplasty: a pragmatic cluster-randomized controlled trial. Implement Sci. 2017; **12**:72.
216. Zhang Q, Liu L, Sun W, et al. Are closed suction drains necessary for primary total knee arthroplasty? Medicine (Baltimore). 2018; **97**:e11290.
217. Kelly EG, Cashman JP, Imran FH, Conroy R, O'Byrne J. Systematic Review and Meta-analysis of Closed Suction Drainage Versus Non-drainage in Primary Hip Arthroplasty. Surg Technol Int. 2014; **24**:295–301.
218. Zhang W, Li N, Chen S, Tan Y, Al-Aidaros M, Chen L. The effects of a tourniquet used in total knee arthroplasty: a meta-analysis. J Orthop Surg Res. 2014; **9**:13.
219. Brusalis CM, Bostrom MPG, Richardson SS. Has Tranexamic Acid in Total Knee Arthroplasty Made Tourniquet Use Obsolete? HSS J. 2018; **14**:338–40.
220. Huang Z, Xie X, Li L, et al. Intravenous and Topical Tranexamic Acid Alone Are Superior to Tourniquet Use for Primary Total Knee Arthroplasty. J Bone Jt Surg. 2017; **99**:2053–61.
221. Wallis JP, Wells a W, Whitehead S, Brewster N. Recovery from post-operative anaemia. Transfus Med Oxford Engl. 2005; **15**:413–8.
222. Muñoz M, Acheson AG, Bisbe E, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia. 2018; **73**:1418–31.
223. Roubinian NH, Murphy EL, Mark DG, et al. Long-Term Outcomes Among Patients Discharged From the Hospital With Moderate Anemia. Ann Intern Med. 2019; **170**:81.
224. Koch CG, Li L, Sun Z, et al. Magnitude of Anemia at Discharge Increases 30-Day Hospital Readmissions. J Patient Saf. 2017; **13**:202–6.
225. Shehata N, Forster A, Li L, et al. Does anemia impact hospital readmissions after coronary artery bypass surgery? Transfusion. 2013; **53**:1688–97.
226. Kougias P, Sharath S, Mi Z, Biswas K, Mills JL. Effect of Postoperative Permissive Anemia and Cardiovascular Risk Status on Outcomes After Major General and Vascular Surgery Operative Interventions. Ann Surg. 2019; **270**:602–11.
227. Choi YJ, Kim S-O, Sim JH, Hahm K-D. Postoperative Anemia Is Associated with Acute Kidney Injury in Patients Undergoing Total Hip Replacement Arthroplasty. Anesth Analg. 2016; **122**:1923–8.
228. Jørgensen CCC, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of patient characteristics for fast-track hip and knee arthroplasty. Br J Anaesth. 2013; **110**:972–80.
229. Jørgensen CC, Petersen MA, Kehlet H, Lundbeck Foundation Centre for Fast-Track Hip and Knee Replacement Collaborative Group. Preoperative

prediction of potentially preventable morbidity after fast-track hip and knee arthroplasty: a detailed descriptive cohort study. BMJ Open. 2016; **6**:e009813.

230. Pitter FT, Jørgensen CC, Lindberg-Larsen M, Kehlet H, Lundbeck Foundation Center for Fast-track Hip and Knee Replacement Collaborative Group. Postoperative Morbidity and Discharge Destinations After Fast-Track Hip and Knee Arthroplasty in Patients Older Than 85 Years. Anesth Analg. 2016; **122**:1807–15.
231. Petersen PB, Kehlet H, Jørgensen CC, Lundbeck Foundation Center for Fast-track Hip and Knee Replacement Collaborative Group. Myocardial infarction following fast-track total hip and knee arthroplasty-incidence, time course, and risk factors: a prospective cohort study of 24,862 procedures. Acta Orthop. 2018; **89**:603–9.
232. Diamond PT. Severe anaemia: implications for functional recovery during rehabilitation. Disabil Rehabil. 2000; **22**:574–6.
233. Jans Ø, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H. Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. Br J Anaesth. 2012; **108**:436–43.
234. Jans Ø, Kehlet H. Postoperative orthostatic intolerance: a common perioperative problem with few available solutions. Can J Anesth. 2017; **64**.
235. Jans Ø, Mehlsen J, Kjærsgaard-Andersen P, et al. Oral Midodrine Hydrochloride for Prevention of Orthostatic Hypotension during Early Mobilization after Hip Arthroplasty: A Randomized, Double-blind, Placebo-controlled Trial. Anesthesiology. 2015; **123**:1292–300.
236. Jans Ø, Brinth L, Kehlet H, Mehlsen J. Decreased heart rate variability responses during early postoperative mobilization - an observational study. BMC Anesthesiol. 2015; **15**:120.
237. Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL. Higher Hb level is associated with better early functional recovery after hip fracture repair. Transfusion. 2003; **43**:1717–22.
238. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. Age Ageing. 2008; **37**:173–8.
239. Halm EA, Wang JJ, Boockvar K, et al. The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. J Orthop Trauma. 2004; **18**:369–74.
240. Conlon NP, Bale EP, Herbison GP, McCarroll M. Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. Anesth Analg. 2008; **106**:1056–61.
241. So-Osman C, Nelissen R, Brand R, Brand A, Stiggelbout AM. Postoperative anemia after joint replacement surgery is not related to quality of life during the first two weeks postoperatively. Transfusion. 2011; **51**:71–81.
242. Wang X, Rintala DH, Garber SL, Henson HK. Association of hemoglobin levels, acute hemoglobin decrease, age, and co-morbidities with

rehabilitation outcomes after total knee replacement. Am J Phys Med Rehabil Assoc Acad Physiatr. 2005; **84**:451–6.

243. Cavenaghi F, Cerri C, Panella L. Association of hemoglobin levels, acute hemoglobin decrease and age with Rehabilitation outcomes after total hip and knee replacement. Eur J Phys Rehabil Med. 2009; **45**:319–25.
244. Maezawa K, Nozawa M, Yuasa T, et al. Postoperative hemoglobin and recovery of hip muscle strength after total hip arthroplasty. J Orthop. 2018; **15**:886–8.
245. Vuille-Lessard E, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy J-F. Postoperative anemia does not impede functional outcome and quality of life early after hip and knee arthroplasties. Transfusion. 2012; **52**:261–70.
246. Perelman I, Winter R, Sikora L, Martel G, Saidenberg E, Fergusson D. The Efficacy of Postoperative Iron Therapy in Improving Clinical and Patient-Centered Outcomes Following Surgery: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2018; **32**:89–101.
247. Gómez-Ramírez S, Maldonado-Ruiz MÁ, Campos-Garrigues A, Herrera A, Muñoz M. Short-term perioperative iron in major orthopedic surgery: state of the art. Vox Sang. 2019; **114**:3–16.
248. Bisbe E, Moltó L, Arroyo R, Muniesa JM, Tejero M. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. Br J Anaesth. 2014; **113**:402–9.
249. Karkouti K, McCluskey SA, Ghannam M, Salpeter MJ, Quirt I, Yau TM. Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. Can J Anesth. 2006; **53**:11–9.
250. Muñoz M, Gómez-Ramírez S, Martín-Montañez E, Naveira E, Seara J, Pavía J. Cost of post-operative intravenous iron therapy in total lower limb Arthroplasty: A retrospective, matched cohort study. Blood Transfus. 2014; **12**:40–9.
251. Kim SK, Seo WY, Kim HJ, Yoo JJ. Postoperative intravenous ferric carboxymaltose reduces transfusion amounts after orthopedic hip surgery. CiOS Clin Orthop Surg. 2018; **10**:20–5.
252. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011; **39**:30–3.
253. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015; **7**:449.

13. Tables

Table 1. Overview of published interventional trials comparing different transfusion strategies in major joint surgery.

Author & publication year	Patient group	n	Transfusion thresholds (liberal vs. restrictive)	Outcomes	Includes functional outcome(s)	Major limitations
Carson et. al. 1998	Hip fracture	80	Hb based (10 g/dl) vs. symptomatic or Hb based (8 g/dl)	- Reduced transfusion in symptomatic group. - No difference mortality or ability to walk 10-feet day 60 postop	Y	-Pilot study
Lotke et. al. 1999	TKA	152	Immediate postoperative transfusion of 2 units PAB vs. Hb based (9 g/dl)	- Reduced transfusion and increased nonsurgical complications in the Hb based group. -Increased physiotherapy score in immediate group on post-op day 3.	Y	- Statistical methods not stated. - Inclusion of 25 non-PAB patients in the Hb based group, of which 26% received allogeneic transfusion.
Pilot et al., 2006	THA	36	Postoperative autologous transfusion vs. matched controls	- Increased maximum power output (bicycle ergometer) day 4 but not on day 23 and 39	Y	No randomization regarding interventional factor.
Grover et al. 2006	THA & TKA	260	Hb based (10 g/dl) vs. Hb based (8 g/dl)	- No difference in silent myocardial infarction (SMI)	N	Did not include all planned patients.
Foss et. al. 2009	Hip fracture	120	Hb based (10 g/dl) vs. Hb based (8 g/dl)	-Reduced transfusion in restrictive group. - No difference in post-op mobilization.- Increased mortality and cardiovascular complications in restrictive group.	Y (Primary)	-Unequal distribution of surgery type between groups. - Study not initially powered to detect differences in mortality.

Carson et al. 2011	Hip Fracture	2016	Hb based (10 g/dl) vs. Symptomatic or Hb-based (8 g/dl)	-Reduced transfusion in restrictive group. -No difference in primary outcome (death or inability to walk 10ft at day 60) -No difference in ADL at day 30 and 60 (telephone based assessment)	Y	-No clear definition of anemia symptoms. -recruitment up to 3 days postop. -Excluded patients with symptoms at the time of screening.
So-Osmann et al. 2013	THA	603	Standard care vs. Restrictive Hb based (Hb 6.4 – 9.7 g/dl; risk stratified)	- No difference in RBC usage, mobilization delay, complications or LOS	Y	- No separation in Hb between allocation group -Standard transfusion care and mobilization regimens differed between centres
Parker et al. 2013	Hip Fracture	200	Hb based (10 g/dl) vs. Symptomatic	-No difference in mortality or LOS -No difference in mobility score at 6 weeks postop	Y	-Primary outcome not stated -9 year inclusion period -no sample size calculation
Fan et al. 2014	THA	186	Hb based (10 g/dl) vs. Hb based (8 g/dl)	- No difference in postoperative delirium (POD) -Reduced RBC and FFP transfusion in restrictive group -Increased IL-8 in liberal group	N	
Nielsen et al. 2014	RTHA	66	Hb based (10 g/dl) vs. Hb based (8 g/dl	- TUG test 6 sec faster in liberal group - No difference in postop complications	Y (Primary)	Did not achieve separation in Hb between allocation groups at the day of testing
Gregersen et al. 2015	Hip Fracture	284	Hb based (11.3 g/dl) vs. Hb based (9.7 g/dl	- No difference in recovery of disabilities (ADL, new mobility score and CAS)- Higher 90 day mortality for nursing home residents in restrictive group	Y (Primary)	- intervention continued up to 30 days postop

Table. 2. Overview of published observational trials evaluating the effect of postoperative anemia on functional outcomes in major joint surgery

Author & publication year	Patient group	n	Study	QOL / objective	Functional outcome measures	Postop anemia magnitude	Outcomes
Halm et al., 2004	Hip fracture	550	Prospective	Objective	FIM	Mean postop Hb 9.5 (±1.5) g/dL Low Postop Hb < 10 g/dl in 65% Low Postop Hb < 8 g/dl in 11%	- Lowest postop Hb correlated with FIM scores unadjusted but not in adjusted analysis
Lawrence et. Al., 2003	Hip fracture	5793	Retrospective	Objective	Distance walked at time of discharge	Mean postop Hb 10.5 (±1.9) g/dL Postop Hb < 10 g/dl in 37 % Postop Hb < 8 g/dl in 0.5 %	- The distance walked at discharge increased with higher Hb levels.
Wallis et al., 2005	THA and TKA	30	Prospective	QoL	SF-36	Mean postop Hb 10.6 (±1.5) g/dL	- The QoL scores used did not show any relationship with Hb.
Wang et al., 2005	TKA	49	Retrospective	Objective	FIM	Mean postop Hb 10.1 (±1.4) g/dl Postop Hb < 10 g/dl in 53 %	- Patients who had higher haemoglobin levels at admission at rehabilitation ward had higher admission motor FIM scores.
Foss et al., 2008	Hip fracture	487	Prospective	Objective	CAS	Postop (POD1) Hb < 10 g/dl in 38 %	- Hb < 10 g/dl predictor of inability to walk independently at day 3, - Correlation between CAS and Hb level at each postop. day.
Conlon et al., 2008	THA and TKA	87	Prospective	QoL	SF-36 FACT-anemia	Mean postop Hb 9.7 g/dl Postop Hb < 10 g/dl in 57 % Postop Hb < 8 g/dl in 9 %	- Hb-levels on discharge associated with change in QoL scores from pre- to postoperatively.
Cavenaghi et al., 2009	THA and TKA	104	Prospective	Objective	6MWT	Mean rehab admission Hb 9.9 (±1.3) g/dl	- 6MWT at admission to rehab. ward correlated with postoperative Hb. -No correlation between Hb and 6MWT at discharge from rehab.

So-Osman et al., 2011	THA and TKA	603	Secondary analysis of RCT	QoL	FSI VAS-fatigue score FACT-anemia	Mean postop Hb 10.5 (±1.1) g/dl Postop Hb < 10 g/dl in 63 % Postop Hb < 8 g/dl in 1.3 %	- No correlation existed between postoperative Hb levels or acute postoperative decline in Hb values and QoL scores (FSI, VAS-Fatigue or FACT-Anemia).
Vuille-Lesard et al. 2011	THA and TKA	305	Prospective	QoL Objective	SF-36 6MWT Hand grip strength	Postop Hb < 8 g/dl in 7 %	- No differences between Hb groups with regards to functional outcomes. - Weak correlation between 6MWT and postop Hb
Jans et al., 2016	THA	122	Prospective	QoI Objective	6MWT TUG BORG Mobility measures FACT-Anemia	Mean postop Hb 11.1 (±1.4) g/dl Postop Hb < 10 g/dl in 20.5 %	- Weak correlation between 6MWT and postop Hb - No correlation between postop Hb and other functional outcomes
Maezawa et al., 2018	THA	82	Prospective	Objective	Hip muscle strength	Mean postop Hb 11.6 g/dl	- Straight leg raise strength different between patients with Hb at above or below 85% of preoperative Hb level. - no difference in abduction strength

Table. 3. Suggestions for further PBM studies in elective THA/TKA

PBM Pillar	Topic	
Pillar – 1 Optimization of haemotopoesis	-	Preoperative anemia management using Hb < 13 g/dl cutoff in both genders *Logistics, efficacy and cost-efficiency*
	-	The role of ESA´s in PAM *Optimal patient selection and safety issues*
	-	Postoperative anemia management, *Recovery of anemia and postop iron deficiency,* *Role of IV iron and ESA´s.* *Optimal patient selection and treatment algorithms* *Effects on clinical outcomes*
Pillar 2 – Measures to reduce blood loss	-	TXA optimal dosing, timing and route of administration in THA & TKA *Maximal efficacy with minimal side-effects* *TXA in patients with high risk of thromboembolism?*
	-	TXA Combined (IV & topical) administration *Patient selection, safety issues*
	-	Epsilon aminocaproic acid (EACA) Efficacy vs. TXA, dosing, patient selection
	-	Low dose epinephrine infusion *Which procedures / patients?* *Efficacy and safety*
Pillar 3 – Tolerance of anemia	-	Restrictive transfusion thresholds in high risk patients *Safety in very elderly / frail pts? Ie. Age > 80*
	-	Postoperative anemia. *Impact on morbidity and functional recovery in high-risk patients*

ISBN 978-87-973837-0-4