Postoperative morbidity and associated risk-factors in fast-track total hip and knee arthroplasty

Painting by T. Cooper https://fineartamerica.com/featured/surgery-1900-todd-cooper.html

Christoffer C Jørgensen M.D.
Section for Surgical Pathophysiology Rigshospitalet Copenhagen University Hospital and The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement, Copenhagen, Denmark

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defence for the doctoral degree in medicine. Copenhagen, 3 February 2022.

Ulla Wever, Head of Faculty

The public defence will take place in the Auditorium at the Hospital of Northern Seeland Hillerød the 26th of August 2022 at 2 pm.

ISBN 978-87-974004-0-1

Preface

The studies of this thesis were made during my time as a Research Fellow at the Section for Surgical Pathophysiology, Rigshospitalet and the Lundbeck Foundation Centre for Fast-track hip and knee Replacement. The studies and thesis were supported by the Lundbeck Foundation and a 3-year research grant from the University of Copenhagen.

None of the studies would have been possible without the support from the initiators of the Lundbeck Foundation Centre for Fast-track hip and knee replacement, Professors Torben B. Hansen, Kjeld Søballe and in particular, Henrik Kehlet.

First and foremost, I am grateful to Professor Kehlet for long and enjoyable discussions on all aspects of perioperative care and postoperative complications and for giving me the opportunity to present the results of our works in major international forums. Finally, I am especially grateful to Professor Kehlet for never giving me reasons to doubt his interest and support, whether it being professionally or personally.

I would also like to thank the many co-authors of our studies for their expertise and insights: Professor Sten Madsbad, Professor Merete Nordentoft, Dr. Joakim Knop, Dr. Michael K Jacobsen, and Mr. Morten Aa. Pedersen. A special thanks to Dr. Øivind Jans for teaching me how to use Microsoft Access and do sophisticated statistics, to Dr. Martin Lindberg-Larsen for enjoyable times and many discussions on study designs in the office or on the phone, to Dr. Frederik Pitter for his energy and stamina when acquiring data and last but not least, to Dr. Pelle Petersen for continuing the work when I became a clinician again. Thank you to Drs Henrik Husted, Søren Solgaard, Per Kjærsgaard-Andersen, Lars T. Hansen, Mogens B. Laursen, Niels H. Krarup, Jens Bagger and Lars-Peter Jorn of the Lundbeck Foundation Centre Collaborative group who all have introduced our database at their institutions and contributed with everything from operating the patients to co-authoring the manuscripts. Thanks to Professor Lars Pedersen from the Department of Clinical Epidemiology Aarhus University Hospital and the Danish National Database for Reimbursed Prescriptions. Furthermore, a very special thanks goes out to Lene Lütken, Charlotte Stilling, Charlotte Troldborg, Susanne Jung, Marianne Woller, Andrea Søe-Larsen, Heidi Raahauge, Aneta Møller, Ulla Hornum and all the other research nurses and secretaries who have done a tremendous work when sending me tons of paper or pdf files on hospital admissions. This could never have been done without you. Also, thanks to all the guys and girls at the Section for Surgical Pathophysiology and the Section for Palliative care for both fun and boring days at the office. Last but most important, thank you to my wife Camilla Damstrup, for still having patience when listening to me rambling about difficulties of research or on the acquirement of data and other boring things. But mostly for giving me the privilege of becoming the father of two wonderful boys at a time in my life when there were no night-shifts, and yet a third at a time when nightshifts provided more sleep than being at home. I love you all.

Christoffer C. Jørgensen.
Hillerød, November 2020.

Contents

List of abbreviations

(alphabetical order)

ATC: Anatomical Therapeutic Chemical Classification System

APGAR: Appearance, Pulse, Grimace, Activity, Respiration. A score originally developed to quantify the effects of obstetric anaesthesia in new-borns

ASA: American Society of Anesthesiologists

BMI: Body mass index**:** Pharmacologically treated cardiac disease

CCI: Charlson Comorbidity Index

CI: 95% Confidence interval

COPD: Chronic obstructive pulmonary disease

CPD: Pharmacologically treated cardiopulmonary disease

CT-scan: Computer tomography scan

DM: Diabetes Mellitus

DNDRP: The Danish National Database of Reimbursed Prescriptions

DNPR: The Danish National Patient Registry

DOAC: Dual oral anticoagulants

DVT: Deep venous thrombosis

EPCO: European perioperative clinical outcome

ERAS: Enhanced Recovery After Surgery

ESA: The European Society of Anaesthesiology

IDDM: Insulin dependent diabetes mellitus

LCDB: The Lundbeck foundation Centre for Hip and Knee Replacement Database

LOS: Length of hospital stay

MI: Myocardial infarction

MINS: Myocardial infarction after non-cardiac surgery

MPEH: Medical predictors excluding hypertension

MUA: Manipulation under anaesthesia

NIDDM: non-insulin dependent diabetes mellitus

NIS: National Inpatient Sample (U.S.)

NSQUIP: The National Surgical Quality Indicator Program (U.S.)

OR: Odds ratio

PE: Pulmonary embolism

PsD: Pharmacologically treated psychiatric disorder

RADS: Danish Council for use of expensive hospital medication (Rådet for Anvendelse af Dyr Sygehusmedicin)

RCT: Randomized controlled trial

RR: Relative Risk

SSRI: Selective serotonin reuptake inhibitors

Surgical-APGAR: A score from 0-10 calculated after major surgery and based on estimated blood loss, lowest mean arterial pressure and lowest heart rate. Has been found to correlate with the risk of postoperative complications and death.

T1D: Type 1 diabetes

T2D: Type 2 diabetes

THA: Total hip arthroplasty

TKA: Total knee arthroplasty

TTE: Thromboembolic event

VKA: Vitamin-K antagonists

VTE: Venous thromboembolic events

Papers upon which this thesis is based

I. **Jorgensen CC, Kehlet H.** Role of patient characteristics for fast-track hip and knee arthroplasty. *Br J Anaesth* 2013; 110: 972-80

II. **Jorgensen CC, Kehlet H.** Fall-related admissions after fast-track total hip and knee arthroplasty - cause of concern or consequence of success? *Clin Interv Aging* 2013; 8: 1569-77

III. **Jorgensen CC, Jacobsen MK, Soeballe K, Hansen TB, Husted H, Kjaersgaard-Andersen P, Hansen LT, Laursen MB, Kehlet H.** Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. *BMJ Open* 2013;3:e003965.

IV. **Jorgensen CC, Madsbad S, Kehlet H.** Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. *Anesth Analg* 2015; 120: 230-8

V. **Jorgensen CC, Knop J, Nordentoft M, Kehlet H.** Psychiatric disorders and psychopharmacologic treatment as risk factors in elective fast-track total hip and knee arthroplasty. *Anesthesiology* 2015; 123: 1281-91

VI. **Jorgensen CC, Kehlet H**, Early thromboembolic events <=1week after fast-track total hip and knee arthroplasty *Thromb Res.* 2016; 138:37-42

VII. **Pitter FP, Jorgensen CC, Lindberg-Larsen M, Kehlet H**, Postoperative morbidity and discharge destinations after fast-track hip and knee arthroplasty in patients older than 85 years. *Anesth Analg* 2016;122:1807-15

VIII. **Jorgensen CC, Pedersen MA, Kehlet H**, Preoperative prediction of potentially preventable morbidity after fast-track hip and knee arthroplasty: a detailed descriptive cohort study *BMJ-Open* 2016;6:e009813

IX. **Jorgensen CC, Kehlet H**, Time course and reasons for 90-day mortality in fast-track hip and knee arthroplasty. *Acta Anaesthesiol.Scand.* 2017; 61: 436-444

X. **Petersen PB, Kehlet H, Jorgensen CC.** Safety of In-Hospital Only Thromboprophylaxis after Fast-Track Total Hip and Knee Arthroplasty: A Prospective Follow-Up Study in 17,582 Procedures. *Thromb Haemost.* 2018; 118:2152-2161

XI. **Petersen PB, Kehlet H, Jorgensen CC.** Improvement in fast-track hip and knee arthroplasty- a prospective multicentre study of 36,935 procedures from 2010-2017. *Scientific Reports:* 2020; **10**:21233

Introduction

Throughout the last decades, the introduction of enhanced recovery protocols, or so called fast-track surgery, has been shown to improve surgical outcomes across various surgical specialties including total hip (THA) and knee arthroplasty (TKA).[1-3] Fast-track protocols focus on optimizing all aspects of peri-, intra- and postoperative care through the use of best evidence-based clinical practice in order to reduce the surgical stress response and have challenged traditional surgical care principles such as use of drains, nasogastric tubes and prolonged use of urinary catheters.[4] This has resulted in a reduced need for postoperative convalescence and length of hospital stay (LOS) without increase in readmissions,[2-4] making the use of fast-track protocols a potential means for improving postoperative outcomes[5]

While the initial focus of fast-track THA and TKA has mainly been on LOS and early recovery, less attention has been given to the initial 30 to 90 days after surgery. Furthermore most studies are case series from single institutions,[6-9] often either in selected patients[10, 11] or including a time while the fast-track protocol was still being implemented.[12-14] At the time of writing there were less than 10 studies in THA and TKA with >1000 procedures using well-documented fast-track protocols with a median LOS of 3-4 days or less and follow-up >80% (table 1). Of these, only one was published prior to the initial study of this thesis.[15]
Furthermore, most of the large observational studies on postoperative morbidity from the U.S., are based on large registries using diagnostic codes or administrative claims data to classify types of complications, but without considering data accuracy/completeness[16] or whether the registered complication was due to other unregistered complications. While incomplete or inaccurate follow-up is obviously problematic, the lack of consideration on "what came first" has not previously received much focus. However, this may be problematic as a registered "surgical" complication may have been preceded by a "medical" complications and vice versa.[17]
When discussing prevention of postoperative complications, one also need to consider the presence of associated risk-factors. Formalized preoperative risk assessment has been a part of the surgical setup since 1941 where the American Society of Anesthesiologists Physical Status Classification system (ASA-score) was introduced.[18] The ASA-score has since been followed by numerous other

perioperative risk and comorbidity indexes including the Revised Cardiac Risk index,[19] the Charlson Comorbidity Index (CCI),[20] the Surgical APGAR score,[21] and more recently, a wide range of internet-based risk calculators.[22, 23] Interestingly, most studies on preoperative risk-factors and perioperative risk-stratification tools are based on large databases with little information on perioperative care[21-29] or with lengths of hospitalization indicating absence of well-established fast-track protocols.[19, 30-32]

Fast-track protocols include preoperative assessment, adequate patient information, planning of postoperative pain relief, risk-assessment followed by optimization of potential organ-dysfunction etc.[4] When combined with procedure-specific intra- and postoperative attempts at reducing the surgical stress-response, there are various ways in which fast-track protocols may affect the influence of traditional preoperative risk factors. In example reduction of the surgical stress-response leading to reduced postoperative insulin resistance[33] and cortisol levels[34] may potentially lead to fewer infections,[33] thus affecting the importance of preoperative diabetes. Another example is early mobilization, which may improve postoperative pulmonary function[17, 35] and arterial oxygenation.[36] Thus, early mobilization could be of additional benefit in smokers or patients with preoperative pulmonary disease who traditionally are considered at increased risk of pulmonary complications or tissue-hypoxia related infections.[37] Furthermore, a reduction in venous thromboembolic events (VTE) with early mobilization,[38] could influence baseline risk of VTE and consequently, the need for prolonged postoperative thromboprophylaxis.[14]

In conclusion, the limited detailed data on postoperative complications and associated risk-factors within a well-established fast-track protocol has been problematic[17] as it may lead to inclusion of unproven treatments[39, 40] and difficulties in identification of potential high-risk patients.[17, 40] Consequently, this thesis aims at providing an update on postoperative morbidity and associated preoperative risk-factors leading to prolonged LOS, readmissions or mortality after primary elective unilateral fast-track THA and TKA, focusing on information from detailed observational studies conducted throughout the last 10 years within a well-established fast-track multicentre collaboration.

Study	$N_{fast-track}$ (THA/TKA)	Inclusion criteria	Follow-up duration/method	LOS	Outcomes
Malviya et al. 2011[15]	1500 (630/680)	2008-2009 Primary proc. Unit 1: ASA I/II Unit 2: unselected	90-days/ National registry w. diagnostic codes.	3.0 median	LOS, complications, readmissions, mortality
Saveridas et al. 2013[44]	1500[1] (630/680)	2008-2009 Primary proc. Unit 1: ASA I/II Unit 2: unselected	2 years/ National registry codes and hospital notes	3.0 median	Mortality and causes of death
Khan et al. 2014[43]	3000[2] (1256/1744)	2008-2011 Primary proc. Unit 1: ASA I/II Unit 2: unselected	30,60 and 90 days/ National registry w. diagnostic codes	3.0 median	LOS, surgical endpoint, medical complications, mortality
Winther et al. 2015[42]	1069 (673/396) (82 rev.)	2010-2012: Elective primary proc. due to osteoarthritis May 2012: All elective primary and revision procedures.	1 year/ Primary admission: registry data Readmissions: N/R PROM: Visit/questionnaire	3.1 mean (4.2 rev)	LOS, time to mobilization, % home discharge, readmissions, PROM (function/satisfaction)
Berg et al. 2018[41]	7345 (3915/3430)	2012-2014: Elective primary proc. due to osteoarthritis	90-days/ National and regional registries w. diagnostic codes	3.0 mean	30 and 90-days readmissions and adverse events
Pamillo et al.[8, 9] 2018	1061 (437/624)	2012-2013 Primary proc. no diagnostic codes of RA, transplantation sequalae, connective tissue disease, dialysis	42-days/ National registries w. diagnostic codes.	2.0 THA 3.0 TKA median	LOS, length of uninterrupted institutional care, readmissions

Table 1. Other published studies of >1000 fast-track procedures with LOS 3-4 days and >80% follow-up, excluding U.S. databasestudies without information on perioperative care. THA: total hip arthroplasty, TKA total knee arthroplasty LOS: length of stay (days) N/R: not reported. RA: Rheumatiod Arthritis [1]same cohort as in reference 41 [2]expanded cohort from reference 41

Aim and hypothesis

In order to facilitate the overall aim of evaluating the incidence of postoperative complications and associated risk-factors leading to prolonged LOS, readmissions or mortality the following hypotheses were formulated:

- The distribution of postoperative morbidity and consequently, the influence of conventional preoperative risk factors, may be different in fast-track THA and TKA compared to previous studies without fast-track protocols.
- When investigating potential preoperative risk-factors for postoperative morbidity there is a need to separate between “medical” and “surgical” complications.
- The incidence of thromboembolic events up to 90 days after surgery in fast-track THA and TKA is reduced and consequently, in-hospital thromboprophylaxis only after fast-track THA and TKA may be safe in patients with LOS ≤5 days.
- A short LOS may not dispose to an increased risk of readmissions.
- LOS and readmissions may be further reduced within a scientific and clinical multicenter collaboration dedicated to further refinements of the fast-track protocol.

The studies included in the thesis attempted to explore these hypotheses by answering the following study questions:

1. What is the distribution and pathogenesis of complications leading to a LOS of >4 days, 90-days readmissions or mortality in fast-track THA and TKA ? (**Study I, IV, V, VII, VII, X and XI**)
2. What is the proportion of “medical” vs. “surgical” complications in fast-track THA and TKA (**Study I, VII, VIII and XI**), and how do they correlate with preoperative risk factors? (**Study V, VII, VIII**)
3. What is the incidence and disposing factors for thromboembolic complications after fast-track THA and TKA with only in-hospital thromboprophylaxis when LOS ≤5 days? **(Study III, VI and X)**

4. What is the incidence, mechanisms and disposing factors for admission due to falls 90-days after fast-track THA and TKA? (**Study II**)
5. Is a further reduction in the fraction of THA and TKA patients with LOS >4 days, readmissions or mortality in departments with all-ready well established fast-track protocols possible? (**Study XI**)
6. What is the influence of preoperative risk factors on prolonged hospitalization with a LOS >4 days, 90-days readmissions and mortality in fast-track THA and TKA? (**Study I, IV, V, VII, VIII and IX**)
7. Is it possible to construct a simple, yet clinically relevant preoperative risk-score specifically for fast-track THA and TKA? (**Study VIII**)

The thesis attempts to put the results from fast-track THA and TKA into perspective by comparing with other national and international data, and to provide suggestions for future efforts for the improvement of perioperative care and reduction of postoperative morbidity.

Study methods

The included studies all used a prospective observational cohort design with follow-up through evaluation of discharge summaries and complete electronical health records. The continuously expanding cohort included all patients having primary elective unilateral THA and TKA in dedicated fast-track arthroplasty departments participating in the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaboration. From 2011 to 2015 several studies (of which only some are included in this thesis) focusing on a variety of safety aspects were conducted in a having (*Table 2*). The studies were based on the prospective Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Database (LCDB) on preoperative patient characteristics, and the Danish National Patient Registry (DNPR) followed by review of discharge summaries and, if necessary, the complete electronical health records. However, information was also acquired from other sources such as death certificates, clinical databases, by contacting general practitioners etc., depending on each specific study question.
An observational study design was chosen as this is an efficient and relatively fast method for collecting outcome data on rare conditions and complications,[45] especially, when including prospectively collected data and prespecified outcomes.[45, 46] Thus, although randomized controlled trials are the gold standard study design for investigating causality and are superior for minimizing bias and reverse causation,[47, 48] it may be difficult to achieve sufficient power within a reasonable time-frame.[49, 50] Consequently, the contributions of large well designed cohort studies in medical science in general, and perioperative medicine specifically,[50, 51] have become increasingly recognized in the last decade.[45, 48, 52-55]

Table 2 Published studies using LCDB data from 2010-2012

Cohort	January 2010-May 2011 n:3112	January 2010-December 2011 n: 5200	January 2010-November 2012 n: 8804
Studies (n)	2[56, 57]	5[58-62]	7[63-69]
Risk-factors / dispositions	Age, walking aids, living alone, CPD, smoking, alcohol use.	Preop. anaemia. fall and hip-dislocations	PsD, psychiatric diagnosis, T2DM, MUA
Outcomes	LOS>4 days, readmissions, " surgical" and " medical" readm, smoking/alcohol-related readm	LOS >5 days, readm, cancer risk 1 year post op. TEE and VTE with only in-hospital prophylaxis.	LOS>4 days, read surgical" and " medical " , readm, " diabetes" related morbidity,
Other objectives		Timing, mechanism and consequences of falls. Timing and mechanism of hip-dislocations	Risk-score for potentially preventable morbidity. Renal/urological complications Transfusions with PsD MUA incidence

N: number of patients/studies CPD: cardiopulmonary disease PsD: Psychiatric disorder T2DM: Type 2 diabetes mellitus readm: readmissions LOS: Length of hospital stay MUA: manipulation under anaesthesia TEE: thromboembolic events VTE: Venous thromboembolic events

Table 2 (continued) Published studies using based on LCDB data from 2010-2017

Cohort	January 2010-November 2013 n:13775	January 2010-October 2015 n: 24862	January 2010-August 2017 n:36935
Studies (n)	8[70-77]	4[78-82]	5[83-87]
Risk-factors / dispositions	BMI, Risk-factors in patients ≥85 years, delirium in patients >≥60 years, early TEE.	Stroke, MI, VTE	
Outcomes	LOS Z days, readm, and discharge destination ≥85 years. Trends in post-op analgesic consumptions	Stroke incidence MI incidence Safety of high-dose methylprednisolone	LOS >4 days, readm,, " surgical" and " medical" morbidity, mortality, outcomes +/- cement in THA. VTE incidence despite prpohylaxis Safety of same day THA/TKA
Other objectives	Surgery related mortality, early TEE Perioperative management and outcomes with preop. anticoagulants. Delirium incidence, periprosthetic fracture	VTE incidence with only in-hospital prophylaxis Days alive and out of hospital	Temporal trends in LOS and readmissions, temporal trends in "medical" , " surgical" and specific morbidity, temporal trends in patients ≥85 years

n: number of patients/studies BMI: body mass index readm: readmissions LOS: Length of hospital stay TEE: thromboembolic events VTE: Venous thromboembolic events MI: Myocardial infarction THA: total hip arthroplasty TKA: total knee arthroplasty

The Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Database

The LCDB was constructed in 2010 and is a prospective database on preoperative patient characteristics. The LCDB was launched in cohesion with a prospective observational study on thromboprophylaxis (study III) in 2010 and registered as an observational study register on ClinicalTrials.gov in January 2012 (ID: NCT01515670). The database is based upon a questionnaire initially containing 19 patient completed items and 5 items completed by attending staff. The questionnaire underwent minor modifications in May 2013, namely by the inclusion of questions on renal disease and cancer and exclusion of d-dimer levels. (Appendix 1) The majority of departments have staff available to assist the patients completing the questionnaire if necessary. The number of dedicated Danish fast-track arthroplasty departments reporting to the LCDB has increased from 5 in 2010 to 9 (7 of which are university hospitals and the remaining being regional hospitals with dedicated arthroplasty departments) in 2016, and the number of included procedures increased from 2467 in 2010 to a cumulated number of >75.000 at the end of 2020. During this period the participating departments accounted for 30-50% of all performed primary procedures in Denmark.[88, 89] All departments use similar fast-track protocols with focus on spinal anesthesia (about 90% of procedures[90]), in-hospital thromboprophylaxis only if LOS ≤5 days, multimodal opioid sparing analgesia, early mobilization, functional discharge criteria and discharge to own home.[91] From October 2013 the multimodal analgesic protocol included high-dose (125 mg) methylprednisolone in TKA and allowed for use in THA as well,[81, 92] while gabapentin was removed from the protocol in 2014 based on the results of a RCT.[93] Finally, most departments increased their thresholds for urinary catherization to 800 ml in 2015,[94] the same year as introduction of outpatient surgery began in two departments[95] Peripheral nerve blocks are not standard part of the multimodal pain management, but are used on indication in some departments. Thus, the used fast-track protocol reflects the current recommendations from the ERAS-society recommendations,[96] which are based on several of the studies performed within the Lundbeck Foundation Centre for fast-track Hip and Knee Arthroplasty.

Data completeness and consistency between the LDCB and the electronic health care records

Several analyses on data completeness and outcomes in the few patients unregistered in the LCDB have been conducted to ascertain that selection bias is not issue an issue within the database. In January 2011 a random sample-audit was performed on 50 randomly selected THA or TKA patients from each of 5 the departments participating at the time, of which all were registered in the database.[62] Subsequently, the number of procedures reported to the DNPR, but without a completed questionnaire in the LCDB, consistently remained at 3.4-3.5% between 2010 and 2013.[56, 61, 68] Furthermore, in study I a sub-analysis on 110 procedures without a completed questionnaire, and in whom it was not possible to retrospectively gather the required preoperative information from the admission notes, did not find any differences in postoperative outcomes.[56]

Finally, a consistency analysis evaluating the data quality of the LCDB was done in study VII on 516 patients ≥85 years having surgery between 2010 and 2013.[75] The analysis evaluated 4 items which were completely based on the preoperative questionnaire (use of walking aid, living alone, pharmacologically treated cardiac disease (CD), pharmacologically treated pulmonary disease (PD)) and one (pharmacologically treated psychiatric disorder (PsD)) based on information in the LCDB as well as information from the Danish National Database on Reimbursed Prescriptions.[97] The analysis found that 78.2% of questionnaires had no inconsistencies compared to information in the medical records and consistency was >91% for each of the individual items (table 3). The κ-coefficient, used to grade relative agreement strength,[98] was ≥0.82 indicating almost perfect agreement in all items except for CD where it was 0.77 (substantial agreement). Consequently, it can be concluded that in patients ≥85 years the LCDB has a high degree of agreement with the medical records in these 5 investigated items, and even superseding previous reports in THA and TKA,[99] as well as in Veterans Affairs NSQUIP data regarding pulmonary disease.[100] Whether there is the same high consistency in other age-groups or regarding other items from the preoperative questionnaire is uncertain as no such analysis has been performed.

Table 3. Results of consistency analysis from study 4. Reporting of the κ-coefficient was not originally included.

Characteristic	" yes" in questionnaire and medical records	" no" in questionnaire and medical records	" yes" in medical records	" no" in medical records	Consistency % (95%CI)	Sensitivity	Specificity	κ (95%CI)
Living alone/institution	324	104	10	13	94.9 (92.2-96.6)	97.0	88.9	0.87 (0.81-9.20)
Use of walking aid	314	104	27	1	97.4 (95.5-98.6)	92.1	96.3	0.84 (0.78-0.90)
Pharmacologically treated cardiac	93	377	26	14	92.0 (89.5-94.2)	78.2	96.4	0.77 (0.71-0.84)
Pharmacologically treated pulmonary	36	464	9	1	98.0 (96.4-98.9)	80.0	99,8	0.87 (0.79-0.95)
Pharmacologically treated psychiatric	71	415	2	23	91.2 (88.4-93.3)	97.3	94.8	0.82 (0.75-0.89)

Analysis was conducted on 516 (94%) procedures, due to missing data the total for each characteristic may vary. CI: 95% confidence interval. Modified from Pitter et al. *Anaesth Analg* 2016[75]

Merging of the LCDB with other datasources

The Danish National Patient Registry and electronic health care records

The LCDB is merged with data from the DNPR for information on index admission and all hospital-admissions 90 days after surgery. The DNPR is a valuable source of information on somatic admissions in Denmark and with a completeness of >99%, due to reporting being mandatory in order to receive reimbursement.[101] As diagnostic coding in the DNPR may be inaccurate,[102] information on reasons for a LOS >4 days during primary admission or admissions within 90-days after surgery are manually extracted from the discharge summary and an evaluation on potential relation with THA/TKA is performed. A cut-off LOS of >4 days was chosen based on a median LOS of 3 days in 2010.[56]

From 2010 to September 2013 the primary screening was done by Dr. Jorgensen. From October 2013 to present the primary screening was done by Dr. Petersen, supervised by Dr. Jorgensen. In this evaluation admissions within 90-days postoperatively are excluded if obviously unrelated to surgery or surgery related organ dysfunction (eye surgery, newly discovered cancer, other elective admissions, etc.) Furthermore, uncomplicated urinary tract infection and dizziness are excluded if occurring more than 30 days after surgery.

In case of inconclusive discharge summary information for assigning a primary reason for a LOS >4 days or readmission, the complete electronic health records are evaluated and a third reviewer (Prof. Kehlet) is also included in deciding the relevance of complications. Additionally, in case of mortality within 90-days of surgery the complete electronic health records of index- and readmissions are always evaluated regarding cause of death and relation to THA/TKA.

Using this combination of the unique Danish registers with detailed information from the medical records may yield "micro-data" not available in most classic BIG-DATA studies depending on diagnostic codes or other coded variables.[103]

Naturally this method has it weaknesses as it may be considered subjective, why review by at least 3, preferably independent, reviewers or use of a standardized tool for evaluation of adverse events to minimize bias has been proposed.[104, 105] However, the inclusion of initially two and later three reviewers in case of doubts, as well as the ability to acquire further clinical information when necessary is an improvement compared to most other studies using chart reviews and has been shown to increase the number of relevant readmissions compared to use of diagnostic coding alone.[106, 107] Finally, the sole use of diagnostic coding or administrative data has often found to be insufficient for registering complications,[108, 109] with conflicting results between datasources[110, 111] and uncertain quality[16]

The Danish National Database of Reimbursed Prescriptions (DNDRP)

The LCDB has also been merged with information from the DNDRP. The DNDRP contains information on prescriptions which qualifies for reimbursement dispensed in Danish pharmacies, including hospital-based outpatient pharmacies (nursing homes etc.).[97] The database does not contain information on in-hospital prescriptions or over-the-counter medicine, but due to the extensive drug reimbursement plan in Denmark, the DNDRP has been demonstrated to include between 85 and 99% of the total number of dispensed prescriptions depending on the Anatomical Therapeutic Chemical classification system code.[97] A major advantage of the DNDRP, is that it includes the Central Personal Registration number which enables combination with the LCDB. This is not available from the Danish National Prescription Registry run by Statistics Denmark (http://www.dst.dk/da/Statistik).
As a completeness of 85% may be considered insufficient, the specific types of drugs investigated using DNDRP data (antipsychotics, antidepressants, anticoagulants) were further investigated regarding the fraction of sold packages with reimbursement for each study period. These data can be found using http://medstat.dk/ supplied by the Danish National Board of Health Data and documents that the fraction of sold relevant drugs receiving reimbursement was about >98% from 2010-2014 (*table 4*).

Table 4. Number of sold drug packages with and without reimbursement from 2010-2014 according to the Danish National Board of Health data (http://medstat.dk/)

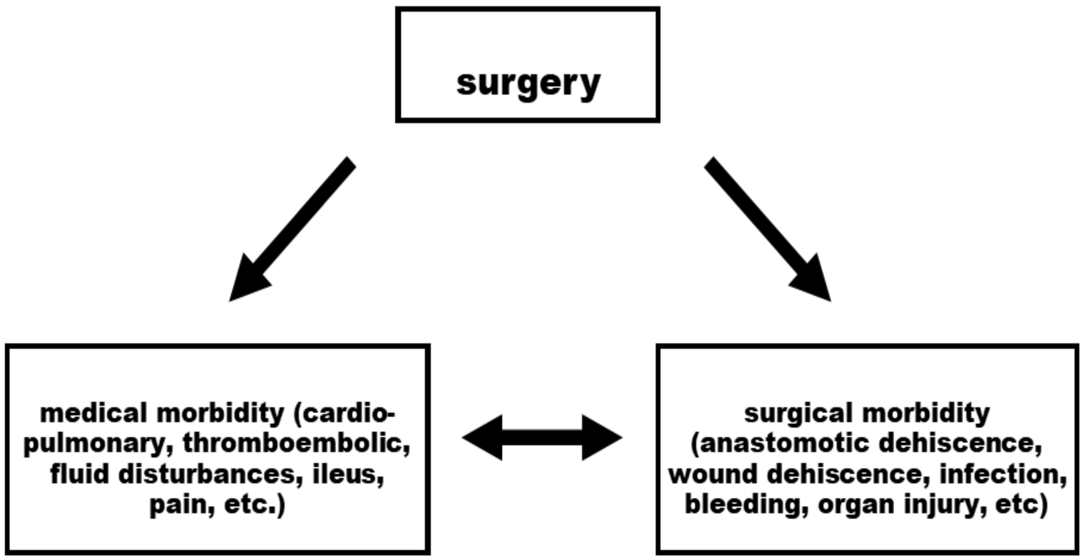
Drug (ATC-code)	2010	2011	2012	2013	2014	Average % with reimbursement 2010-2014
Antipsychotics (N05A)	1196.5/1185.0 (99.0%)	1212.0/1199.2 (98.9%)	1227.3/1211.3 (98.7%)	1179.0/1164 .5 (98.8%)	1141.3/1128.4 (98.9%)	98.9%
Antidepressants (N06A)	2516.0/2499.9 (99.4%)	2404.6/2386.2 (99.2%)	2378.2/2334.7 (98.2%)	2226.1/2187 .1 (98.2%)	2123.9/2090.0 (98.4%)	98.8%
Anticoagulants (B01A[1])	523.8/522.3 (99.7%)	563.7/562.4 (99.8%)	655.4/654.2 (99.8%)	729.3/727.9 (99.8%)	798.8/797.8 (99.9%)	99.8%

Number*1000 packages total/with reimbursement (% with reimbursement)
ATC: Anatomical Therapeutic Chemical classification system
[1]only: B01AA03 (Warfarin), B01AA04 (Phenprocoumon), B01AB01 (Heparin), B01AB04 (Dalteparin), B01AB05 (Enoxaparin), B01AE07 (Dabigatranetexilat), B01AF01 (Rivaroxaban), B01AF02 (Apixaban), B01AF03 (Edoxaban), B01AX05 (Fondaparinux)

Classification of postoperative morbidity and complications

There have been numerous attempts at developing different scoring systems or categories of postoperative morbidity. The most widely used is probably the Clavien-Dindo index where the newest edition is scaled from I-V with several subcategories and depending on the most severe complication.[112] The same group has later proposed the Comprehensive Complications Index, which not only converts the most severe complication but also the total complication burden, into a score running from 0 (no complication) to 100 (death).[113] Furthermore, the system was developed by using the opinions of both healthcare professionals as well as patients, making it more patient focused than the Clavien-Dindo system.

Figure 1



The potential relationship between postoperative “medical” and “surgical” morbidity. A surgical procedure may lead to both “medical” or “surgical” complications, but a “medical” complication may also lead to further “surgical” complications and vice versa. Adapted with permission from prof. H. Kehlet.

The main weakness of the Comprehensive Complications Index is the lack of information on what came first, which may limit the potential for devising interventional strategies. Thus, a surgical complication may be followed by medical complications and vice versa (figure 1).[17] Such information may be of value when evaluating whether focus should be on surgical technique or perioperative care.

Consequently, within the studies from the LCDB, complications leading to LOS >4 days or readmissions were categorized according to the initial type of complication and subdivided into “medical” and “surgical” morbidity.

The term “surgical” morbidity is used for complications requiring further refinement of surgical technique (minimally invasive surgery, prosthetic materials, surgical approach, improved antibiotic regimens etc.), while “medical” morbidity (myocardial infarctions, pneumonia, renal failure, pain management etc.) covers areas requiring further improvements in perioperative care and the fast-track protocol (table 5).[56, 114] This approach has subsequently become more accepted[115-122] and hopefully may provide additional insights into which measures are needed to further reduce postoperative morbidity.

Table 5. Classification of complications in the majority of studies using the LCDB.

“Surgical” complication:	
	Prosthetic infections
	Wound complications
	Fracture without trauma
	Other revision surgery
	Knee manipulation
	Hip dislocation
“Medical” complication:	
	Cardiac
	Gastrointestinal
	Anaemia
	Medication/Mobilization
	Falls
	Urological
	Pulmonary
	Cerebral
	Pain
	Renal
	Other
“Other” complications:	
	No recorded morbidity but LOS >4 days
	Suspected but disproven venous thromboembolism
	Suspected but disproven prosthetic infection
	Suspected but disproven myocardial Infarction

LOS: length of hospital stay at primary admission

Potential weaknesses of the included studies

Patients with multiple procedures

As in all large databases spanning several years, some patients had more than 1 procedure during the study period. In case of < 90 days between procedures, patients were excluded as it would be impossible to assign a potential complication to a specific procedure. In contrast, patients with > 90 days between procedures were not excluded although this can introduce statistical bias by compromising the concept of statistical independence within the dataset.[123] However, it has also been argued that excluding patients with multiple procedures will exclude a large and clinically relevant number of procedures. Thus, excluding the second procedure in patients with a successful first procedure may introduce a "negative" selection bias with overestimation of surgical risk.[124] In this context, the number of patients with >1 procedure was limited to about 3% in the smallest[56] but increasing to 15% in the largest cohort.[71] Importantly, all patients completed a new preoperative questionnaire before each procedure why changes in preoperative risk profile, i.e. due to a postoperative complication after the first procedure, would be registered. Furthermore, in study III and X where patients using anticoagulants were excluded, there is a potential risk of selection bias if a large fraction of patients who developed VTE were subsequently excluded when having their second procedure due to use of anticoagulants. However, given the scarcity of VTE in both studies (about 0.4%)[62] the influence seems minimal.

Patients with missing data

Another potential problem was the handling of patients with missing data in the LCDB. Patients missing data on specific variables in the preoperative questionnaire were consequently excluded from statistic models including these variables. It could be argued that this should have been dealt by using multiple imputations in order to minimize the risk of bias.[125] However, the amount of missing data on specific variables in the included studies was rarely >4% which argues for using only complete data[65] and multiple imputations may by itself introduce bias if the imputation model is insufficient or if there is a substantial number of missing variables.[126]

Overlapping time periods

The conducted studies used different datasets but with overlapping time-periods and thus, some of the same patients were included in several different analysis. This may introduce a risk of statistical bias in the regression models of the conducted studies.[127, 128] There have been several proposals on which statistical tests to use when conducting regression analysis on overlapping data,[127] especially within the field of economics.[128] However, none of the studies using logistic regression in this thesis focused on the same outcome, thus not introducing hypothesis bias due to repeated measurements using the same data. It may be more problematic when analysing overlapping outcomes as in studies III [62] and VI.[74] Thus, it could be argued that these studies are a repetition of the same data. However, study VI was a detailed analysis on early thromboembolic events of which 70% occurred while in hospital[74] consequently resulting in a LOS of >5 days and exclusion from the "successful early discharge cohort" with only in-hospital prophylaxis which was the focus of study I.[62]

Postoperative morbidity and mortality

Thromboprophylaxis and thromboembolic events

Safety of only in-hospital thromboprophylaxis in patients with LOS ≤5 days

THA and TKA have traditionally been considered "high-risk" procedures for VTE, with an in-hospital occurrence of about 0.5 and 1.0 % in THA and TKA, respectively.[129] Consequently, thromboprophylaxis from 14 to 35 days postoperatively has been recommended.[130, 131] However, these recommendations are based on randomized clinical trials with a mean LOS of 7-8 days,[132-136]about 2-3 times as long as when applying a fast-track protocol.[137] This suggests that a considerable fraction of the procedures included in the randomized trials were not treated according to fast-track principles such as spinal anaesthesia and early mobilization,

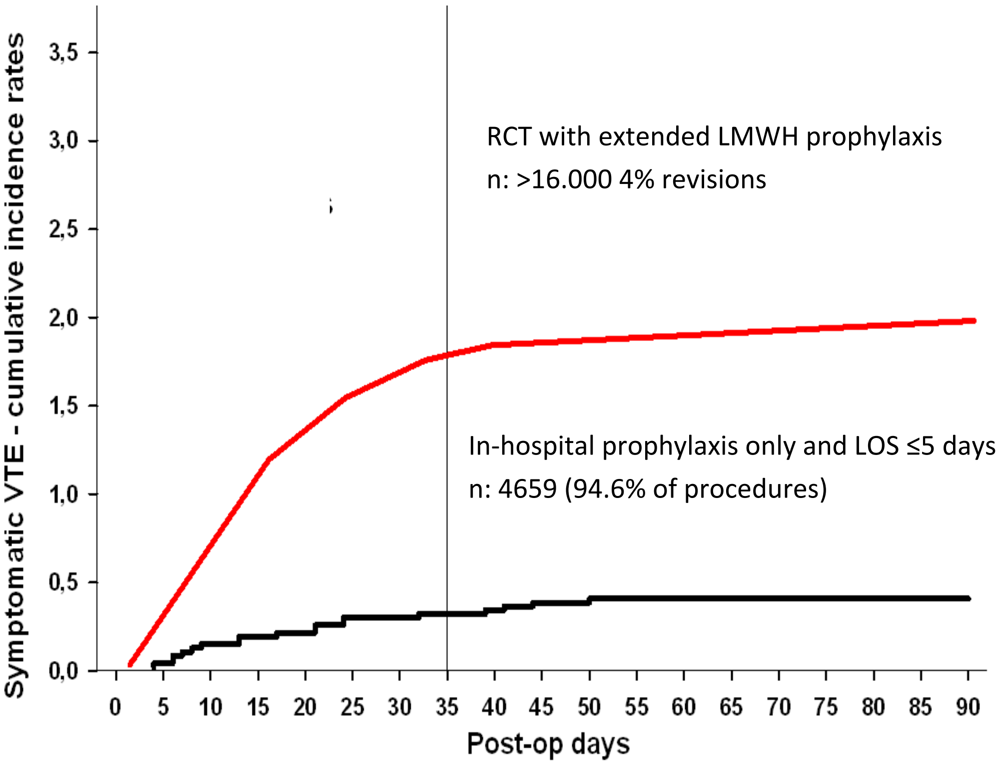


Figure 2 modified from Falck-Ytter et al *Chest* 2012[130] and from Jørgensen et al. *BMJ-Open* 2013[62]

both of which may be associated with fewer venous thromboembolic events (VTE).[38, 138] Such aspects have rarely been considered in the randomized trials with symptomatic VTE rates of about 1.7% at 35 days,[130] as opposed to reported VTE rates of < 0.5 % after fast-track THA and

TKA with thromboprophylaxis only during hospitalization and LOS ≤5 days.[62, 139] Furthermore, the RCTs often included asymptomatic DVT as primary outcome, despite the clinical relevance of these may be debatable.[140] Consequently, several studies have questioned the benefits of prolonged thromboprophylaxis,[141-146] including in fast-track THA and TKA.[147] Finally, there remains the problem of patient selection in published RCTs, which often exclude the elderly and the very sick. In example, a review on the benefits of prolonged prophylaxis found that in some studies the number of obese patients was as low as 8%.[148] In contrast, patients with a BMI >30 in the studies of this thesis was consistently >30%.

Study III, was a prospective observational multicentre study in unselected consecutive fast-track THA and TKA patients having thromboprophylaxis with low molecular weight heparin (LMWH) or rivaroxaban only during hospitalization if LOS ≤5 days.[62] Both LMWH and rivaroxaban are recommended as first choice of thromboprophylaxis after major arthroplasty,[130] and a clinically relevant superiority of one above the other remains controversial.[149] The study was protocolled and registered on ClinicalTrials.gov (NCT01557725), and all outcomes were pre-defined. Thus, occurrence of deep venous thrombosis (DVT) had to be confirmed by ultrasound and pulmonary embolism (PE) by lung scintigraphy, computer tomography (CT) or removal of embolus. For arterial thromboembolic events MI was predefined as rise in biomarkers and ischemic symptoms or diagnostic electrocardiogram changes with primary coronary intervention or a coronary bypass graft. Ischemic stroke was defined as neurological symptoms lasting >24 hours and a positive CT-scan, and a transient ischemic attack was defined as a neurological symptom lasting <24 hours and with no new changes on CT-scan. The only excluded patients were those <18 years old, those without Danish social security numbers or those with preoperative continuous oral anticoagulant treatment with vitamin-K antagonists or direct oral anticoagulants. The study demonstrated that about 95% of 4924 procedures had LOS ≤ 5 days and consequently, thromboprophylaxis only during hospitalization. Median LOS in these patients was 2 days resulting in 75% of patients having thromboprophylaxis for 3 days or less. The incidence of VTE was < 0.3% at 30 and < 0.5% at 90 days, and even when including deaths of unknown causes, the 90-days incidence was only about 0.5%. In contrast, 5% of patients with a LOS >5 days had VTE rates of > 2.5% at 90-days postoperatively, with half occurring during index hospitalization and despite prophylaxis after discharge.[62] (*figure 2*) A limitation of the study was lack of individual patient data on duration of prophylaxis and, although less likely, that VTEs during hospitalization but without a LOS of ≥5 days were overlooked.

The results of study III are not the only ones with fewer registered VTE's compared to the older RCTs. Thus, the XAMOS-study, an open label study on rivaroxaban vs. other types of prophylaxis found symptomatic 60-day VTE rates of 0.83%, but with prophylaxis for about 3 months.[150] However, the XAMOS-study provided no information on LOS and no objective criteria were required for diagnosis of VTE, potentially influencing the results.[150] In contrast, a different phase IV-study on rivaroxaban in a real world setting found 90-days VTE rates of 1.2% in primary THA and TKA, with 15 days of treatment.[151] The authors argued that increasing the treatment period to 35 days in all THA patients could theoretically have prevented 1-3 DVTs occurring on postoperative days 34 and 36. However, 82% of DVTs in THA occurred after day 35 and there was no information on LOS or use of early mobilization.[151]

A low incidence of VTE in fast-track THA and TKA was also demonstrated by Glassou and colleagues who found that the relative risk of readmissions due to thromboembolic events between 2010 and 2011 was 0.7 (CI 0.6-0.9) or about a 27% reduced compared to other Danish national data.[152] Limitations on this study included lack of knowledge about use of fast-track protocols in the control cohort, the use of diagnostic codes with varying accuracy for VTE detection[102] and no information on duration of thromboprophylaxis.[152] Especially the first point may be of significance as fast-track protocols appeared to be widely, but not universally implemented in Denmark during the time period.[153] Furthermore, two studies using national data from Denmark and Norway found no clinically relevant differences in 90-days occurrence of VTE after THA regardless of receiving "short", "standard" or "extended" thromboprophylaxis.[154, 155] However, there was an unexplained increased risk of 90-days mortality in the "short" treatment group.[155] In this context, a Norwegian study found that introduction of prolonged prophylaxis in 2003 was associated with a sudden drop in VTE rates compared to 7-10 days of prophylaxis.[156] However, the study was a single centre study comparing surgeries from 1989-1999 vs. 2003-2011 and with no information on LOS or use of fast-track protocols.

The results of Study III contributed to a revision of the Danish recommendations for postoperative thromboprophylaxis, where thromboprophylaxis only during hospitalization is now considered a viable option in fast-track THA and TKA patients with a LOS of ≤5 days.[a] This strategy has now also been recognized as an option in the European Society of Anaesthesiology (ESA) Guideline on Day and Fast-track surgery.[157]

Unfortunately, no other institutions attempted to confirm the results of study III, why in 2018, Study X was conducted as a follow-up study in an additional >17.000 procedures and using the same methods. Study X confirmed the previous results of 90-day VTE rates of about 0.4%, but

---

[a] The Counsel for use of expensive hospital medication (RADS) treatment recommendation (in Danish): http://www.regioner.dk/medicinsite/rads/behandlingsvejledninger/~/media/EA98DB295B7E450E9CE2A8AF5D2A60D3.ashx

was also able to provide a much needed risk-factor analysis on associated pre-operative risk factors for VTE with only in-hospital prophylaxis.[139] (table 6) The study found that the thresholds for association between age and BMI with VTE were increased compared to those used by the Caprini-score recommended for preoperative risk-evaluation by the ESA.[157]

Table 6. Multiple logistic regression analysis on risk-factors for VTE within 90 days of surgery. From *Petersen et al. Thromb Harmost. 2018*[139]

Variable	OR (95% CI)	p-value
Age (years)		
< 50	1.04 (0.29-.376)	0.952
50-60	0.72 (0.28-1.87)	0.498
61-65	1.36 (0.59-3.16)	0.469
66-70	1	Reference
71-75	0.85 (0.34-2.11)	0.720
76-80	1.66 (0.71-3.88)	0.238
8-85	1.76 (0.60-5.15)	0.304
>85	*3.74 (1.15-12.14)*	*0.028*
BMI		
< 18.5	NA	NA
18.5-24.9	1	Reference
25.0-29.9	1.10 (0.55-2.17)	0.791
30.0-34.9	1.28 (0.59-2.79)	0.534
35.0-39.9	*2.55 (1.02-6.35)*	*0.045*
>39.9	*3.28 (1.02-10.56)*	*0.046*
IDDM	NA	NA
NIDDM	1.47 (0.68-3.19)	0.329
Cardiac disease	1.49 (0.72-3.09)	0.281
Pulmonary disease	0.84 (0.33-2.11)	0.706
History of VTE	2.04 (0.94-4.44)	0.073
Hereditary VTE	1.62 (0.86-3.06)	0.139

Per protocol analysis of 17.582 procedures. OR: odds ratio. CI: confidence interval.
BMI: body mass index. NA: not available due to lack of data.
IDDM: insulin dependent diabetes mellitus. NIDDM: non-insulin dependent diabetes mellitus VTE venous thromboembolic event.

Considering that the usefulness of the Caprini-score in THA and TKA remains undecided,[158-160] and that more individualized thromboprophylaxis strategies based on thromboembolic risk-stratification are being advocated,[160-162] further evaluation within fast-track THA and TKA seems justified. In conclusion, in-hospital thromboprophylaxis in fast-track THA and TKA with LOS ≤5 days seems acceptable. However, the topic of postoperative thromboprophylaxis, not only with regards to risk-stratification but also with regards to choice and duration of drugs (e.g. aspirin vs. LMWH or rivaroxaban, in-hospital only vs. after discharge) remains controversial with several differences in published guidelines and recommendations.[163-166]

"Early" and in-hospital venous thromboembolic events

In study III, 5 of 7 VTEs in the patients with LOS >5 days and prophylaxis after discharge occurred in-hospital or within the first 14 days, likely while patients were receiving recommended prophylaxis.[62] That the majority of VTEs in fast-track THA and TKA patients with prophylaxis occur while patients are in-hospital was also confirmed in study X where 12 of 18 VTEs were in-hospital.[139] This further suggests that a subgroup of patients need alternative or more aggressive antithrombotic strategies rather than simply extending the treatment period. Similar findings have been done in colorectal surgery where 92% of VTEs occurred while patients received appropriate prophylaxis.[167] Study VI was the first to provide a detailed description on occurrences of "early" VTE (in-hospital or within the first 7 days after surgery), as well as focusing on 30-day incidences in fast-track THA and TKA.[74] The study was conducted in 13775 procedures, and found that the "early" VTE rate was <0.2 %, with the majority of PE's occurring after TKA. In contrast, the study by Gomez et al. investigating the effectiveness of rivaroxaban for 15 days postoperatively found the incidence of VTE within the first week to be 0.35%, of which the majority were PEs and with 10 of 12 being in TKA.[151] Furthermore, a subsequent analysis on a larger dataset from the LCDB found that in-hospital VTEs despite ongoing thromboprophylaxis contributed about 22% of all VTEs during the initial 90 postoperative days with an incidence of 0.09%.[78] These reports contrast with a previous systematic review of older randomized clinical trials with in-hospital VTE rates of about 1% in TKA and 0.5% in THA.[129] While it is logical to assume that reducing LOS will also reduce number of in-hospital VTEs, there was no registered increase in readmissions due to VTE in the mentioned studies.

Interestingly, about 80% of VTE patients in study VI had one or more pre-(BMI >30, previous VTE, ischemic cardiac disease etc.) or perioperative (postoperative immobilization, infection etc.) dispositions.[74] Furthermore, although identification of specific risk factors for VTE despite ongoing prophylaxis was possible in the follow-up study in >34.000 procedures , 78% occurred without any identifiable disposing complication.[78] That standard thromboembolic regimes may be insufficient in some patients has been suggested after knee arthroscopy,[168] in intensive care[169] and in other critically ill patients.[170] However, no specific drug has yet shown superiority in preventing symptomatic VTE in major arthroplasty[149, 171] and the use of risk-stratification and increased dosing remains controversial.[162] Consequently, how to identify and treat patients in high-risk of VTE despite standard thromboprophylaxis and the use of a fast-track protocol remains an important area of investigation in THA and TKA.

Myocardial infarction and ischemic stroke

The use of thromboprophylaxis should ideally also effect arterial thromboembolic events such as MI and ischemic stroke.[172] However, the reported incidences of in-hospital myocardial infarction or ischemic stroke after THA and TKA remains about 0.2%[173, 174] despite recommendations of chemical thromboprophylaxis. Furthermore, there may be a substantial number of patients in which the myocardial damage or stroke is "silent".[175, 176] Recently, an asymptomatic rise in biomarkers of myocardial injury after noncardiac surgery (MINS) has received increasing attention due to associations with perioperative and long-term mortality,[177-179] including after THA and TKA.[180] However, so far attempts at identifying which patients may benefit from such tests and how to reduce the occurrence of MINS remains controversial.[178, 181-183] Consequently, the studies in this thesis have focused on symptomatic MI and ischemic stroke. The overall occurrence of these complications was 0.49% in study III, but with 3 in the 265 patients with LOS >5 days (1.1%).[62] Study VI, which expanded the study cohort with about 8000 patients, confirmed an overall low in-hospital/7-days occurrence of symptomatic myocardial infarction or ischemic stroke (0.07%). Furthermore, the 30-day rates were also much lower than previously described (0.10% and 0.11% for MI and ischemic stroke, respectively).[74] Thus, Singh et al. used data from the Mayo Clinic to report on in-hospital and 30-days MI and ischemic stroke. They found 7-day MI occurrences of 0.18%, increasing to 0.9% at 30 days.[184] Belmont et al. found 30-day rates of 0.33% using NSQUIP data,[26] and two Danish studies using national data from 1998-2007 and 1997-2011 found MI rates of about 0.4[185] and 0.36%,[186] respectively. Finally Khan et al. reported significant reductions in MI from 0.9% to 0.4% after introducing fast-track principles.[43] As in most of the previous studies, study VI found that that the majority of myocardial infarctions occurred after THA, despite a higher burden of preoperative comorbidity in TKA patients.[74] Interestingly, 5 of 9 patients with myocardial infarction had severe postoperative anaemia, as well as preoperative cardiac risk factors.[129] That the presence of postoperative anaemia in patients with cardiac disease may be of particular importance was later confirmed in a larger population from the LCDB where 27 of 28 patients with MI ≤30 days had postoperative anaemia according to WHO definitions.[80] Regarding postoperative stroke, Pedersen et al. found that similar occurrence of 30-day ischemic stroke after THA (0.4%) and TKA (0.3%) using Danish national data (but not considering use of fast-track protocols) from 1997 to 2011. There was no difference in relative risk (RR) between 1997 and 2011 (RR: 0.9 (CI:0.5-1.7) in 1997 vs 2011 although the risk of and no differences between procedures.[186] In contrast, a study using the U.S. National Inpatient Sample data and relying on diagnostic coding, found a significant decline in in-hospital stroke between 2002 (0.17%) and 2011 (0.14%) but also with no information on fast-track protocol and no differentiation between THA and TKA.[187] That use of a fast-track protocol may reduce

the incidence of stroke was supported by Kahn et al. who a clinically relevant, albeit statistically insignificant reduction in 30-days ischemic stroke in THA and TKA after introduction of a fast-track protocol (0.2 % vs. 0.5 %).[43] In study VI, the occurrence of in-hospital/7-days symptomatic "early" ischemic stroke was only 0.07 %, but significantly increased in THA (0.17%) vs. TKA (0.05%) at 30-days. Thus, the overall 30-day occurrence of stroke was only 0.11% but without a control group, conclusions on direct benefits of a fast-track protocol cannot be drawn. Noticeably, a subsequent study using the LCDB found similar stroke rates from 30 to 90-days postoperatively as in the Danish background population.[79] This is in contrast to a previous Danish national study which, in addition to finding a >4 fold increased risk of stroke within the initial 2 weeks after THA, found the risk to remain increased for up to 6 weeks for ischemic and 12 weeks for haemorrhagic stroke compared to in matched controls.[188]
Regarding potential prevention of the strokes that did occur, most of the patients in study VI who experienced postoperative strokes, had irreversible dispositions (age > 70 years, previous stroke, cardiac disease etc.),[74] and even potentially modifiable risk factors like smoking and BMI, may be difficult to modify. Furthermore, spinal anaesthesia, which may reduce the occurrence of stroke,[138] is all-ready implemented in the fast-track protocol.
In summary, the incidence of "early" and 30-day myocardial infarctions and cerebral strokes seems reduced in fast-track THA and TKA compared to without a fast-track protocol. Postoperative myocardial infarction may be prevented by avoiding postoperative anaemia while further reduction in incidence of cerebral stroke may be more problematic.

Postoperative falls, cause of concern or consequence of success?

The risk of falling has gained increasing attention both as a serious occurrence in community and hospital settings,[189-191] and as an independent preoperative risk factor of postoperative complications.[192, 193] Although there are several studies on risk factors and preventions of in-patient falls,[194-196] most studies in THA and TKA have focused on the role of postoperative peripheral nerve blocks.[197, 198] Thus, fall-incidences of about 7% within the first 4 days with femoral nerve blocks have been reported[199] although large scale data have been unable to demonstrate an association with peripheral nerve blocks in general.[198] Nevertheless, the use of continuous femoral nerve blocks which may impair motor function is not ideal when using a fast-track protocol with early mobilization.[200, 201] Instead blocks which do not target the motor nerves e.g. the adductor canal block, are a potential better choice,[202, 203] but with uncertain effect on LOS, recovery and post-operative opioid consumption.[204, 205]

TKA and THA per se may also increase the risk of falling,[206, 207] likely due to reductions in muscle strength of 40-80%.[208, 209] Thus, fall-rates of about 12% within the first 3 postoperative months have been reported,[206] with even higher risk in those with falls prior to surgery.[192, 210]

As fast-track surgery aims at enhancing postoperative recovery, it could be speculated that there would be a decreased risk of falling due to improved physical function, but on the contrary, early discharge and return to daily activities could also increase the risk of falling within the early postoperative period. However, a recent review found some evidence for use of fast-track protocols to improve in-patient functional recovery after TKA.[211] This is despite that although initiation of progressive strength training immediately after surgery is feasible,[212] the effect on functional performance has been negligible.[213]

Study II provided the first detailed analysis on the incidence, circumstances and consequences of falls after discharge resulting in hospital or emergency-room admission 90 days after THA/TKA.[61] It was found that about 1.6% of patients were admitted to hospital within 90 days after fast-track THA and TKA due to falling, of which about half required hospital admittance for 1 day or more. Furthermore, falls linked to postoperative weakness or balance problems comprised 73.5% of all falls, while 7 (8.4%) falls occurred during bathroom visits.[61] However, analysis on circumstances of falls were limited by almost half of the surgery-related falls having insufficient information in their medical records.

When analysing surgery-related vs. other falls, surgery-related falls occurred significantly earlier than those related to a high level of physical activity or extrinsic factors, with about half occurring within the first month of discharge. (*figure 3a*) In contrast, almost 1/3 of the falls between postoperative days 31 and 90 were due to either a high level of activity or extrinsic factors. There were no typical reasons for these types of falls which included falling from heights, moving vehicles, slipping on ice, and being intoxicated or pushed.

figure 3a

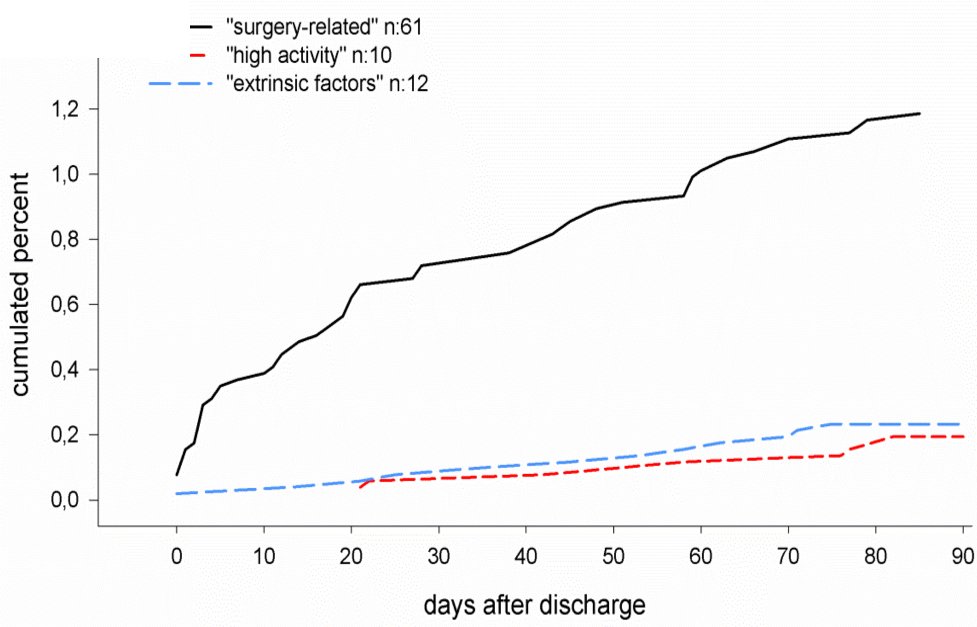
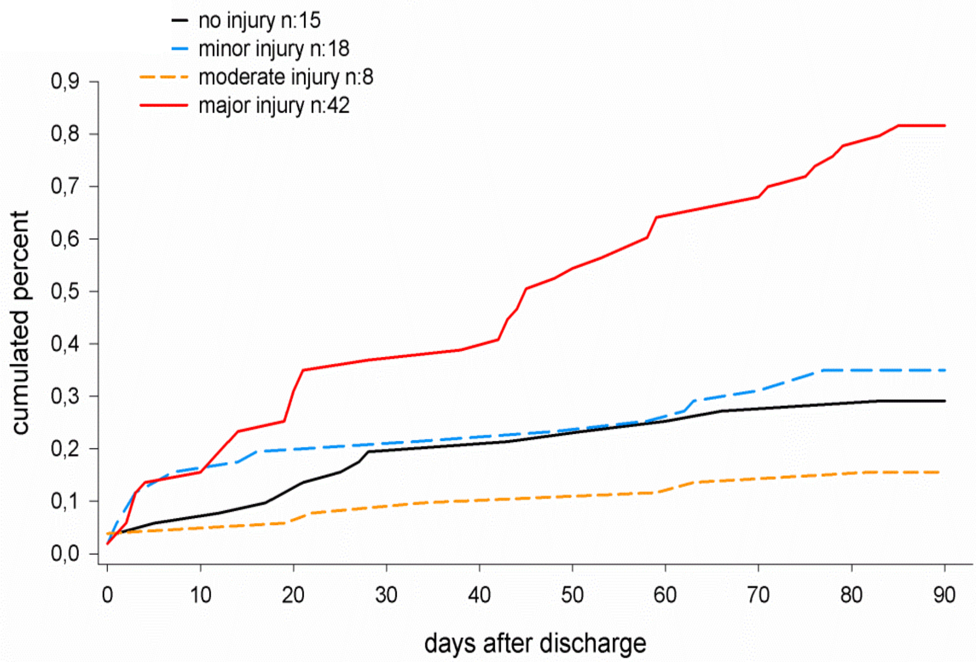


Figure 3b



From Jørgensen & Kehlet *Clin Interv Aging 2013*[61]

When considering the severity of injury, the fraction of falls leading to minor injuries was largest during the first postoperative week (*figure 3b*) and with about 50% of all falls resulting in major injuries, often requiring return to surgery. Finally, analysis on risk-factors related to admissions due to falling found that age/year (OR: 1.05 CI:1.02–1.08) PsD (OR: 2.80 CI:1.42–5.50) and living alone (OR: 2.09 CI:1.20–3.62), but not a LOS ≤4 days (1.19 (CI:0.52-1.28) were independently associated with admission due to falling.[61]
There is still very limited information regarding falls leading to readmissions after fast-track THA and TKA. However, it seems that the mechanisms of falling after discharge may assimilate what has been found in community dwelling individuals rather than in in-patients. Thus, Campbell et al. reported that 20% of falls in rural dwelling subjects >70 years were due to tripping and slipping while going about daily activities..[214] Also, Robbinovitch et al. were able to use video material to document that the majority of falls in elderly people in long term care are due to incorrect weight shifting or stumbling. [215] In contrast, the incidence of bathroom-related falls has been reported to be 45% of in-patients falls after mixed elective orthopaedic surgery[216] increasing to 60% specifically after TKA.[217] However, these studies were not performed within a fast-track set-up, did not consider falls after discharge, and with a considerable number of patients having either a femoral nerve catheter[217] or other patient controlled analgesia.[216] Interestingly, the study on mixed orthopaedic procedures by Mandl et al. reported only 3.3 % of falls resulting in major injury, while the study in TKA reported only 23% resulting in morbidity, return to theatre or new fractures.[217] This may be due to registration of a considerable number of less severe falls, but could also support that falls without major injuries are more common in the early postoperative phase.
In contrast, studies on post-discharge falls after THA and TKA are conflicting. Thus, a small study in only 269 arthroplasty patients, found similar risk of falling, but up to 65% reduced 1-year risk of fall-related fractures in THA patients vs. controls.[218] Contradicting data were reported in two Japanese studies with even fewer patients and finding increased risk of falling within the 1.st year after THA (30% vs 13%)[207] and TKA (38% vs 24%),[219] respectively. Interestingly, both studies found low 1-year incidences in fall-related fractures of 5.7-6.2%,[207, 219] but they included falls not requiring admission to hospital. Unfortunately study II had no control group, prohibiting conclusions on whether patients having fast-track THA and TKA are at increased risk of falls compared to controls not having surgery.
As a consequence of such heterogeneity in available studies a recent review on postoperative falls in THA and TKA concluded that the incidence of postoperative falls ranges from 0.8% - 2.7% within the first few days after surgery and between 3.1% and 51.8% up to 24 months after.[220] This was despite that the authors were able to include 12 studies with a total of about 1.3 million patients.[220] They also found moderate evidence for PsD, and living alone to increase

the risk of falls after discharge, but only low-level evidence for age being a risk factor specifically in THA and TKA.[220] Unfortunately, no other studies apart from study II, were conducted within a well-defined fast-track setup, prohibiting conclusions on potential benefits of the fast-track protocol per se on the risk of falling after THA and TKA.

In conclusion, the incidence of admissions due to postoperative falls in fast-track THA and TKA is less than 2%. Furthermore, about 25% of fall-related admissions may not be related to surgery-induced muscle weakness or balance problems, but rather to a return to normal life and activity levels. However, >50% of falls resulted in major injuries why specific considerations on postoperative fall-risk may be relevant for elderly patients, those living alone and those using psychotropic drugs. Nonetheless, it seems reasonable to conclude that an overall increase in fall-related admissions due to short LOS and early mobilisation is not a cause of concern in fast-track THA and TKA.

Postoperative mortality and relation to surgery

Although postoperative mortality has declined steadily in developed countries, it remains of considerable interest in many surgical outcome studies.[221-225] Recently, there have been reported associations with symptom-free increase in biomarkers, e.g. troponin-T, and mortality up to 30 days postoperatively,[226] as well as increased 1 year mortality compared to persons who did not receive surgery.[224] Furthermore, the European Surgical Outcomes Study (ESOS) reported major variations in 7 days postoperative mortality from 1.2 to 21.5% between European countries.[225] Mortality in the Scandinavian countries was generally low in this study, potentially attributable to well driven perioperative teams, post-anaesthesia care units and a strong tradition for enhanced recovery or fast-track protocols.[227] Currently, the European Perioperative Clinical Outcome (EPCO) definitions state that mortality should be reported at a minimum of 90 days and ideally 1 year after surgery.[228] However, existing studies have rarely attempted to analyse the exact cause of events leading to mortality after surgery in order to evaluate the likely relation to the surgical procedure. Furthermore, studies seldom consider whether death is due to direct surgical complications, e.g. major intraoperative bleeding, or surgery induced organ dysfunction such as postoperative pneumonia or venous thromboembolic events. This may be due to the nature of the studies which often use large database relying solely on diagnostic codes.[224, 229-231] Nonetheless, such details may be important for developing appropriate interventional strategies by identifying which complications came first.

In THA and TKA 90-days mortality is reported to be about 0.3%,[222, 229] and adhering to a fast-track protocol may be associated with a further reduction.[43, 44] The low mortality following these procedures may be due to surgical selection prior to elective procedures as THA and TKA patients often have lower short[232] and long-term mortality[233] compared to the background population.

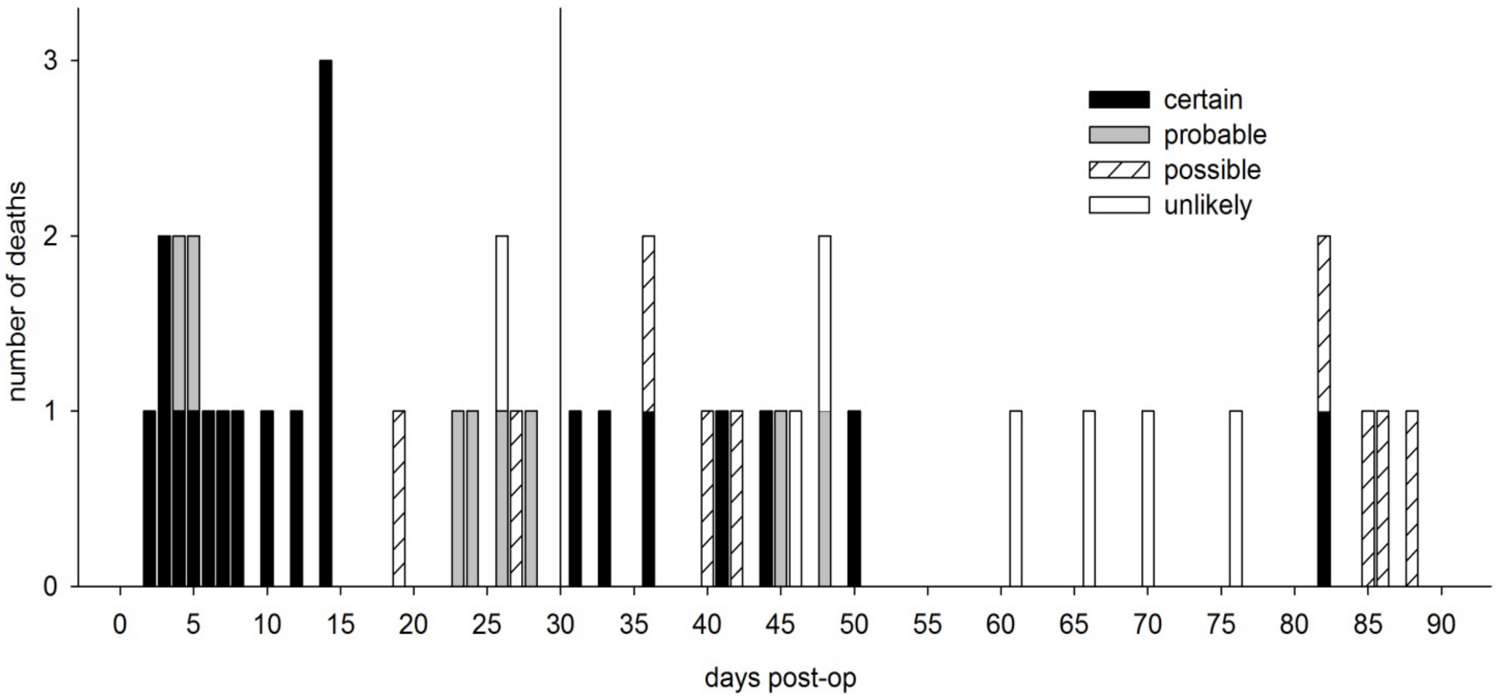


figure 4 Jørgensen and Kehlet 2017 *Acta Anaesthesiol.Scand.*[71]

Although a few studies have attempted to provide disease-specific data on cause of death,[144, 231] information on what actually happened is rare. Study IX included a detailed evaluation of all available information on the patients who died within 90-days after THA and TKA. In case of death in own home the patients' general practitioner was contacted to establish whether any complications had occurred outside of hospital after discharge.[71] All-cause mortality was 0.3%, of which 0.2% were likely to be surgery-related. In this context, the average 90-days death-rate in Danish citizens aged 67 years (the median age of THA and TKA patients) was about 0.4% during the same period.[b] Of a total of 44 deaths, 7 were unlikely to be related to the surgical procedure, accounting for 16% of fatalities within the first 90-days. Also, about two thirds of the surgery-related deaths occurred within the first 30-days of surgery, while deaths with less certain relation to surgery were much more common after day 30 *(figure 4).* Death was also rarely a consequence of direct surgical complications such as fatal intraoperative bleeding or prosthetic infection, but mostly due to surgically-induced organ dysfunction such as pneumonia, stroke or bowel dysfunction. Importantly, several patients had initial organ dysfunction resulting in subsequent treatment/surgical procedures followed by new complications from different organ systems leading to mortality (*figure 5*).[71]

That postoperative complications are predictors for mortality has been described previously in major surgery.[234, 235] An analysis of > 2 million patients from the NSQUP database found that about two thirds of patients developed more than one postoperative complication and typically 6-9 days prior to death.[234] However, there was no subgroup analysis or information on the number of individual procedures consequently prohibiting extrapolation to THA and TKA. The results of Study IX emphasizes the importance of procedure-specific studies focusing on what came first when discussing strategies for reducing postoperative mortality as the pattern of postoperative complications after THA and TKA was much different from the NSQUIP analysis which found the majority of complications to be reoperations due to bleeding.[234]

When investigating mortality in THA and TKA after postoperative day 30, a considerable number of deaths have been demonstrated to be due to cancer or other conditions unrelated to the surgical procedure.[43, 145, 232] Thus, Jones et al. were unable to demonstrate any excess mortality in THA after 90 postoperative days,[236] while a Norwegian study in both THA and TKA found excess mortality only during the initial 26 postoperative days.[237]

Finally, Cusick and Beverland investigated >4000 arthroplasties, and found that 3 of 6 deaths between the 30th and 90th postoperative day were due to duodenal ulcer, carcinoma and ruptured aortic aneurism respectively.[145] This could indicate that adhering to the EPCO

---

[b] Ref. Danish Statistics internet ressource: https://www.statistikbanken.dk

recommendations of 1-year follow-up on mortality will lead to inclusion of a number of deaths without relation to the surgical procedure. In conclusion, all-cause mortality in fast-track THA and TKA is comparable to or lower than previously reported, and often preceded by other organ dysfunctions than the immediate cause of death. Consequently, reporting all-cause mortality or immediate cause of death may be insufficient for determining surgical quality in fast-track THA and TKA as it is often unrelated to the surgical procedure.

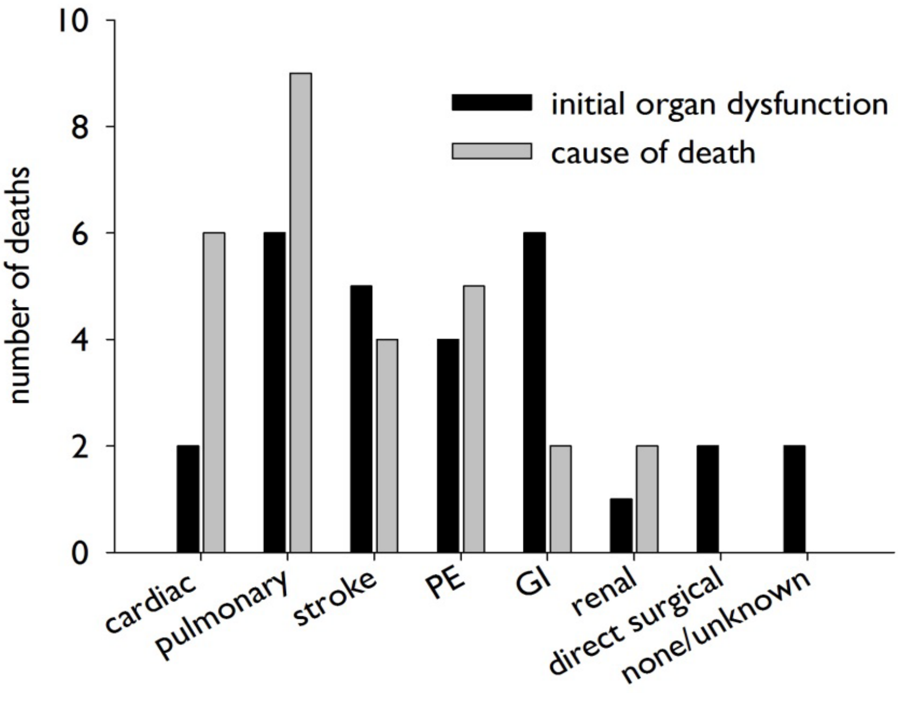


Figure 5 Initial organ dysfunction and cause of death, GI: gastrointestinal PE: pulmonary embolism "surgery-related deaths (n:28). Jørgensen and Kehlet 2017 *Acta Anaesthesiol.Scand*[71]

Incidences and distributions of postoperative morbidity over time.

Despite most evidence pointing at considerable benefits of a fast-track protocol,[9, 42, 43] there has been few studies investigating time related changes in LOS and readmissions within a well-established fast-track setup. That the incidence of complications may change with the introduction of new surgical techniques, pain management, different types of rehabilitation and changes in antibiotic or thromboprophylaxis strategies in THA and TKA is possible.[156, 238] Thus, a British study found that between 2005 and 2014 there was a drop in reported complications from 3.3% to 2.8%, but an increase in occurrence of lower respiratory tract infections and renal failure (0.54% to 0.84% and 0.21% to 1.09%, respectively).[238] An increase in renal failure from >4% to >8% between 2006 to 2016 has also been reported from the U.S. using the Premier Healthcare Database.[239] In Denmark, Husted et al. evaluated the effect of fast-track implementation on national LOS between 2000-2009, and found a drop in median LOS from about 11 to 4 days within this period.[153] However, this was in the beginning of fast-track implantation in Denmark and no further detailed evaluations on the effects of continuous refining of a well-established fast-track protocol has been conducted.
As fast-track protocols comprise many aspects of perioperative care, the lack of such time-related data evaluating outcomes in fast-track THA and TKA may be problematic. In 2019 two national registry based studies from the U.K. were unable to find time-independent reductions in LOS after what they defined as "national implementation" of enhanced recovery after surgery (ERAS) protocols in TKA[240] and THA.[241] Surprisingly, it was found that the introduction of ERAS maintained or even slowed the pre-existing secular trends of both decreasing LOS and complications. However, there was no clear definition of what comprised an ERAS-protocol and mean LOS at study start was about 6 days with a reduction of only 2 days during the 8-year period. Furthermore, LOS in patients >85 years was even considerably longer than reported by Starks et al. in selected patients from the U.K. from 2007-2009.[11] Interestingly, in TKA, the 6-month complication rate declined from about 4% at the start of ERAS implementation to 2% at the end, but not attributable to ERAS implementation in the secular analysis. As further reductions in complications after ERAS introduction were limited, the authors concluded that 6-month complication rates were stable.[240] In THA complications appeared to increase on a monthly basis during ERAS implementation but ultimately stabilized. Nonetheless, the proportion of 6-month complications in THA was reduced from 4.1% to 1.7% at the end of protocol or on time of implementation. Such weaknesses, combined with a very low total complication rate of only 1.6%, likely due to use of a limited number of diagnostic codes, and lack of details on follow-up completeness[240, 241] further complicates data interpretation. Also, the lack of a clear definition of the used ERAS protocol is problematic, especially considering

that an audit by the U.K. Department of Health Enhanced Recovery Partnership Program found an association between compliance with individual components and reductions in LOS.[242] The same findings have been made in Spain, where increased overall adherence to ERAS protocols

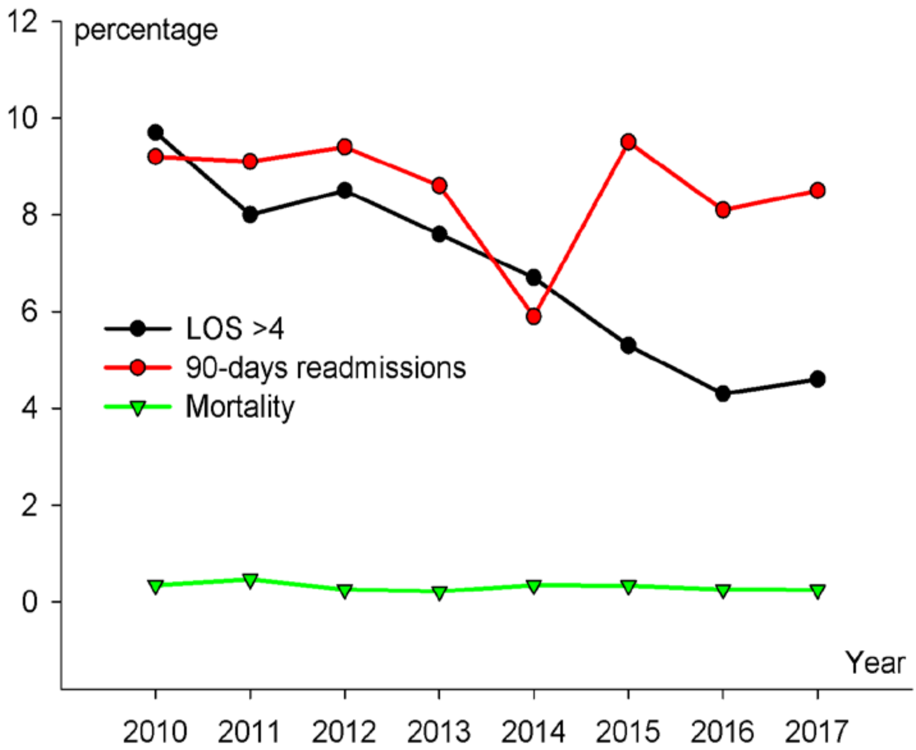


Figure 6. Changes in LOS, readmissions and mortality from 2010-2017 in 9 dedicated fast-track departements. Adapted from Pedersen et al. *Scientific Reports;* 2020[87]

was associated with improved the study period.[241]
Unfortunately, both studies excluded patients with a LOS >15 days, had no information on the implemented components of the ERAS postoperative outcomes after THA and TKA. However an association could only be documented in few individual components.[243] Another large retrospective study using the Premier Database from the U.S. which also investigated the utilization of ERAS components and their effect on complications.[244] found that the number of included ERAS components increased from 2006 to 2016, and supported that reduction in postoperative complications, as well as a reduction in LOS from 3 to 2 days, was related to ERAS protocol adherence.[244]
Study XI of this thesis evaluated the time-related trends in LOS, readmissions and specific types of morbidity within the LCDB where all departments have well-established fast-track protocols and with a continued focus on further refinement of these.[245] The study found a continuous reduction in LOS from median 3 days in 2010 to 1 day in 2017, but no changes in readmissions

and mortality (figure 6).
"Medical" readmissions decreased slightly from 4.3% to 3.2%, while "surgical" readmissions increased slightly from 2.7% to 3.6%. (figure 7). The reduction in LOS >4 days was primarily due to fewer patients having a LOS >4 days with no recorded morbidity but also due to a reduction

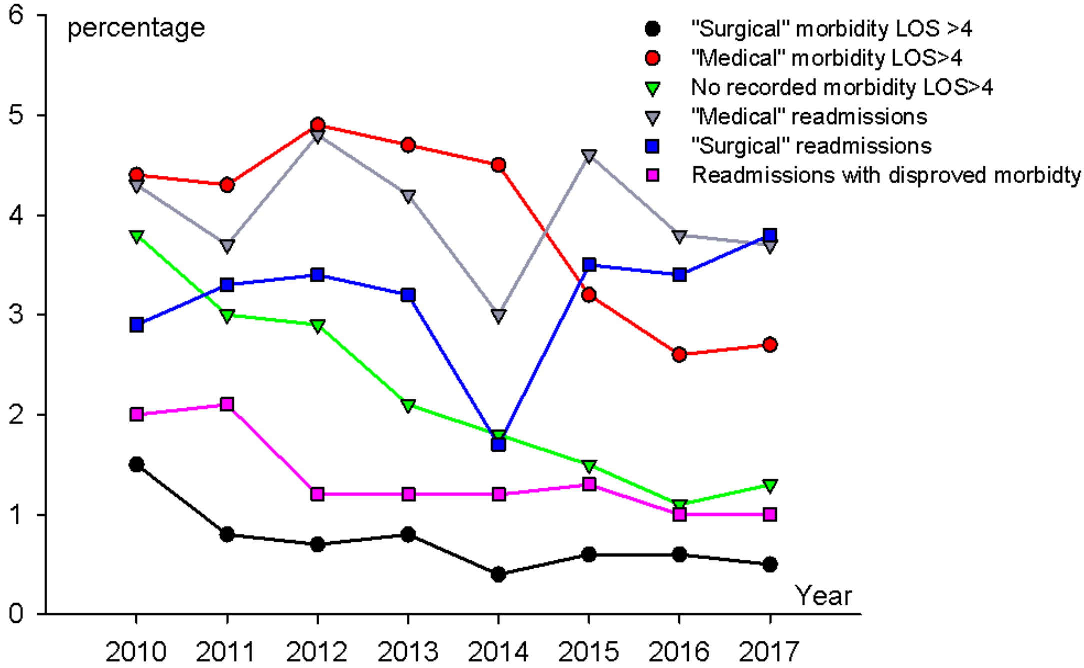


Figure 7. Distribution of morbidity resulting in LOS >4 days or readmissions. Adapted from Pedersen et al. *Scientific Reports;* 2020[87]

in "medical" complications. Interestingly, the reduction of patients with LOS >4 days but no recorded morbidity was monotonic throughout the time-period (figure 7). In contrast, the drop in LOS >4 days due to "medical" complications began in 2014 and onwards (figure 7+8), coincident with the introduction of preoperative high- dose methylprednisolone.[81]
It is not surprising that the drop in LOS did not continue at the initial pace found by Husted et al.,[153] as most of the "low-hanging" fruits would have been identified after a decade of implementation. However, the results suggest a continuous logistic improvement and reduction in both minor complications not mentioned in the discharge records, as well as in medical morbidity during admission. A weakness of the study is the lack of data before fast-track implementation or on other Danish arthroplasty departments outside of the LCDB.

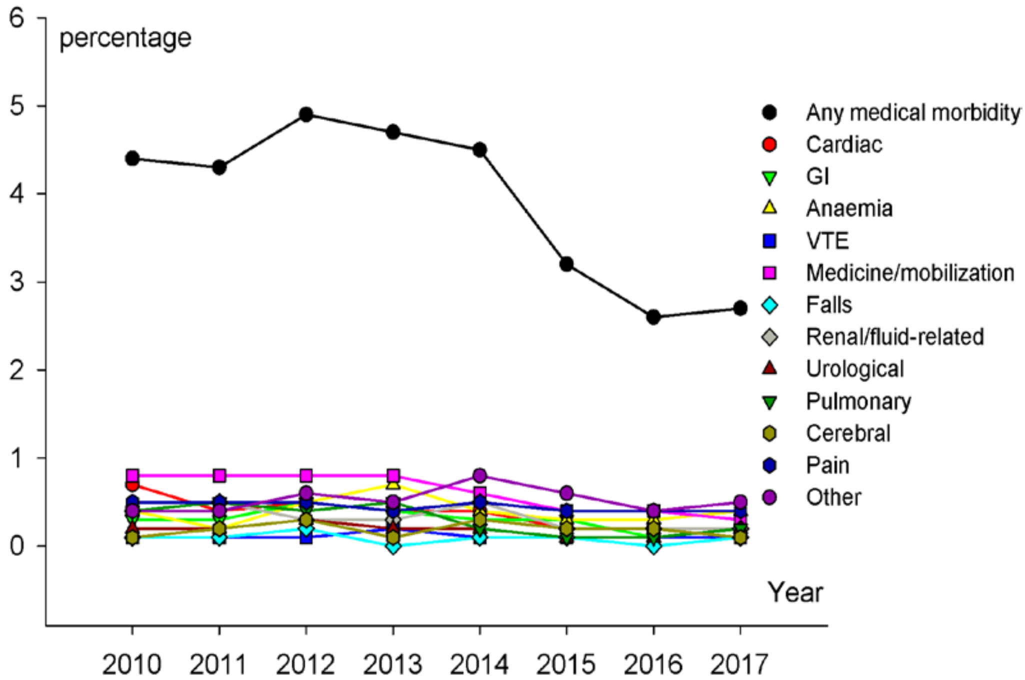


Figure 8. Distribution of individual types of "medical" morbidity leading to LOS >4 days. GI: Gastrointestinal VTE: venous thromboembolic event. Modified from Pedersen et al. *Scientific Reports;* 2020[87]

Thus, the study cannot conclude whether these changes would have happened regardless of participation in the LCDB or implementation of fast-track protocols. However, as many concepts of fast-track protocols are now considered "standard of care" e.g. limiting period of fasting prior to surgery, use of opioid sparing analgesia, prophylactic antibiotics and avoidance of hypothermia, the discussion of whether to adhere to such principles seems affluent. Finally, the reports from both Spain, the U.K. and the U.S. suggest that there are differences with regards to postoperative outcomes, depending on adherence to ERAS-protocols, and that mainly the use of early mobilization may influence postoperative morbidity[242-244]Consequently, the key message of study XI is that the continuous use and refinement of fast-track protocols, including introduction of high-dose methylprednisolone,[81] reduced utilisation of urinary catheters[94] and increased focus on specific risk-patients (e.g. blood-management in anaemics[58], avoidance of NSAIDs in patients with impaired renal function[64]) through continuous scientific collaboration and evaluation of outcome data[114] may lead to further reductions in LOS and morbidity even several years after successful implementation of a fast-track protocol. However, readmissions remain an unsolved challenge.

Preoperative risk factors

It has been estimated that about 10-20% of mixed surgical patients account for about 80-90% of all postoperative deaths.[234, 246] Although mortality after THA and TKA is low compared to other procedures and with a substantial decrease through the last decades,[229-231, 247] numerous studies in THA and TKA have linked comorbidity burden with risk of early death.[247, 248] Consequently, much effort has been done to identify patient-related characteristics associated not only with mortality,[25, 184, 246, 249-252] but also with increased LOS and readmissions.[32, 120, 253-256] However, a substantial amount of the current evidence is based on data gathered 10-20 years ago,[25, 32, 184, 222, 252, 253, 257, 258] and the results may therefore not necessarily apply to modern clinical practice. Furthermore, in THA and TKA specifically, there are numerous large American database studies on preoperative risk-factors and with reported mean LOS of 2-3 days. However, 30-70 % of patients having surgery in the U.S. are typically discharged to skilled in- or out-hospital nursing facilities,[259, 260] which is conflicting with the fast-track concept of functional discharge criteria and severely limiting generalizability of results to other countries and health-care systems.

Age

The number of surgical procedures which elderly patients have been offered has increased with the introduction of less invasive procedures and improved postoperative care.[261] However, combined with a reluctance to include elderly patients in clinical trials, there has been a scarcity of data on elderly patients with regards to postoperative interventions and outcomes.[262, 263] Regardless, age has repeatedly been found to be an independent risk factor for prolonged LOS and readmission in various types of surgery[264, 265] including THA and TKA.[118, 266-269] Reasons for increased LOS in elderly surgical patients may be related to both increased comorbidity and decreased physiological reserves,[270, 271] leading to increased convalescence[272, 273] and discharge to skilled nursing facilities.[274-276] However, the cut-off for patients being considered too old for surgery has increased throughout the last decades,[261, 277] which is reflected in an increasing number of studies focusing on THA and TKA in patients aged >90 years.[278-280] Furthermore, despite an increased risk of prolonged LOS and complications, the functional outcome and/or satisfaction after THA and TKA in the elderly is comparable to in younger patients.[30, 281]

In study I of this thesis it was found that age > 75 years was an independent predictor of a LOS >4 days (OR: 1.09 to OR: 4.10).[56] However, median LOS was 2-3 days until age >85 years and more than 75% of patients aged >80 years had a LOS ≤4 days.[56] That increasing age may be an independent risk factor for increased LOS has previously been documented in THA and TKA,[30, [117, 266] but not specifically within a fast-track protocol. Furthermore, in study I the quantitatively largest reduction in LOS was in patients >85 years (> 8 days vs. ≈ 5 days), when comparing to a previous study investigating outcomes in THA and TKA patients >80 years without a fast-track protocol.[266] But, despite the inclusion of consecutive procedures, the limited information on comorbidity and standard of care prohibit direct comparisons.[266]

That the benefits of a fast-track protocol in THA and TKA may be more pronounced in elderly patients was also suggested by Starks and colleagues in 116 selected patients ≥85 years having THA and TKA within an enhanced recovery protocol between 2007 and 2009.[11] They found a reduction in median LOS from 8 to 5 days within their own institution and with no increase in emergency readmissions after introducing an enhanced recovery protocol. Furthermore, the decrease in LOS was even larger when compared to national British data from the same period,[11] and their LOS was even comparable to national British data about 10 years later.[240, 241] However, the study was limited by being a single institution with few patients and several selection criteria for being included in the fast-track protocol.[11]

Study VII specifically focused on outcomes in fast-track THA and TKA patients ≥85 years and found a median LOS of 3 days and that 93% were discharged to home.[75] Of those who stayed >4 days about 25% had postoperative anaemia or unsatisfactory mobilization,[75] however, the distribution between "medical" and "surgical" reasons for LOS >4 days was no different from those < 85 years (figure 9). That focus on perioperative blood management and preoperative anaemia may be of increased importance in elderly patients was further supported by about 25% of patients with LOS >4 days remaining in hospital due to a need for blood transfusions.[75] This is in accordance with a small study in 112 TKA patients >75 years showing that "prolonged" LOS was associated with use of walking aids and low perioperative haemoglobin levels, albeit with a mean LOS of 6.25 days.[282] However, current evidence on transfusion thresholds does not support a more liberal transfusion policy[283] including in elderly patients.[284]

That patients should not be discharged until they fulfil strict functional discharge criteria is of major importance in fast-track surgery, but little data exist to confirm that this is always the case. Thus, the findings of 93% discharge to home is encouraging and in contrast to reports from the U.S. where between 30% and 70% of patients are discharged to skilled nursing facilities or in-hospital rehabilitation units,[221, 259, 260] despite very limited evidence on improved outcomes.[285, 286 285] Thus, one study from 2014 reported increased readmission rates in patients discharged to in-hospital rehabilitation,[287] while another reported impaired functional measures but higher ASA-scores.[288] Furthermore, it has been shown that patients requiring critical care services in the U.S., are also more likely to be discharged to rehabilitation units.[275]

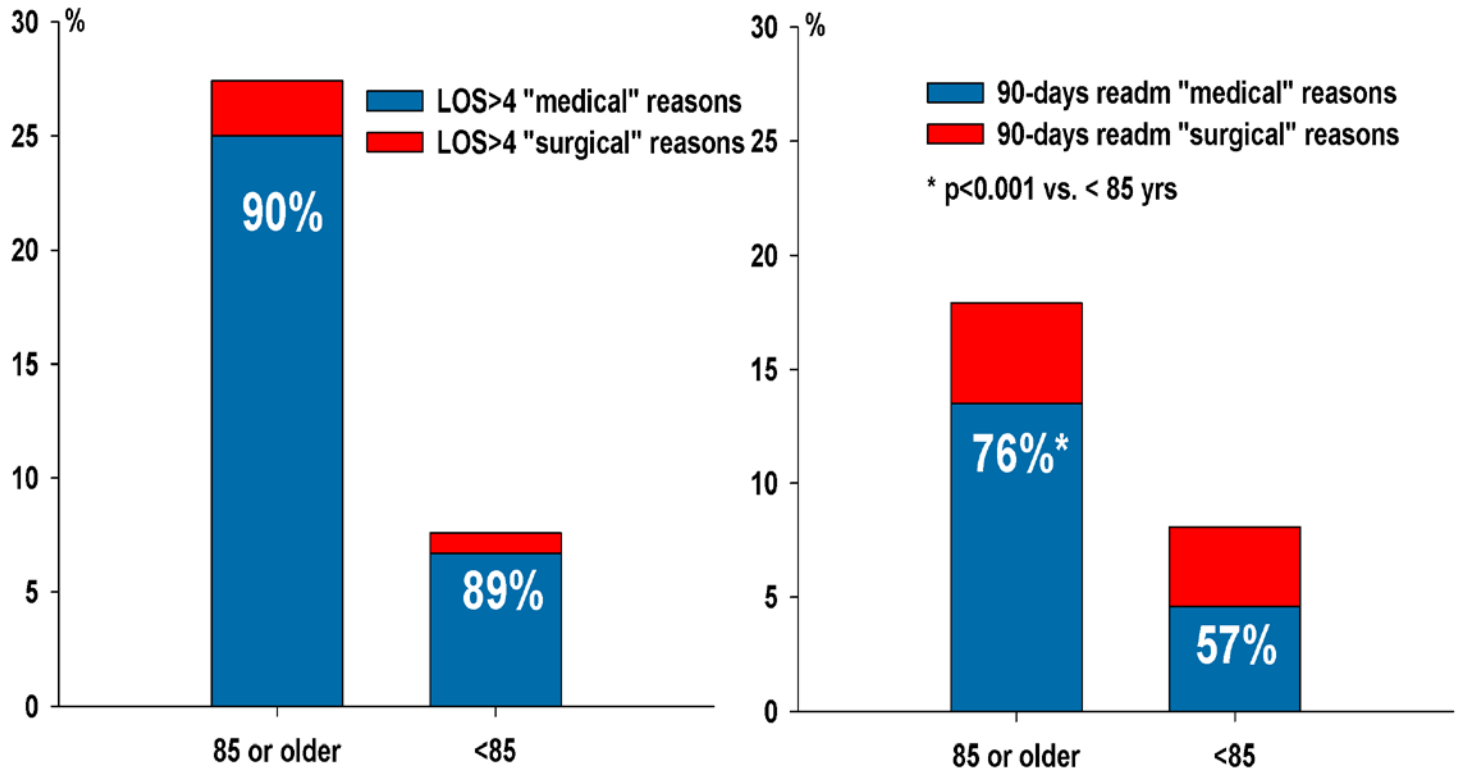


Figure 9. Distribution of ”medical” and ”surgical” reasons for LOS >4 days or 90-days readmissions in 13775 procedures of which 549 were 85 years or older. Unpublished data based on study I[56] and VII[75]

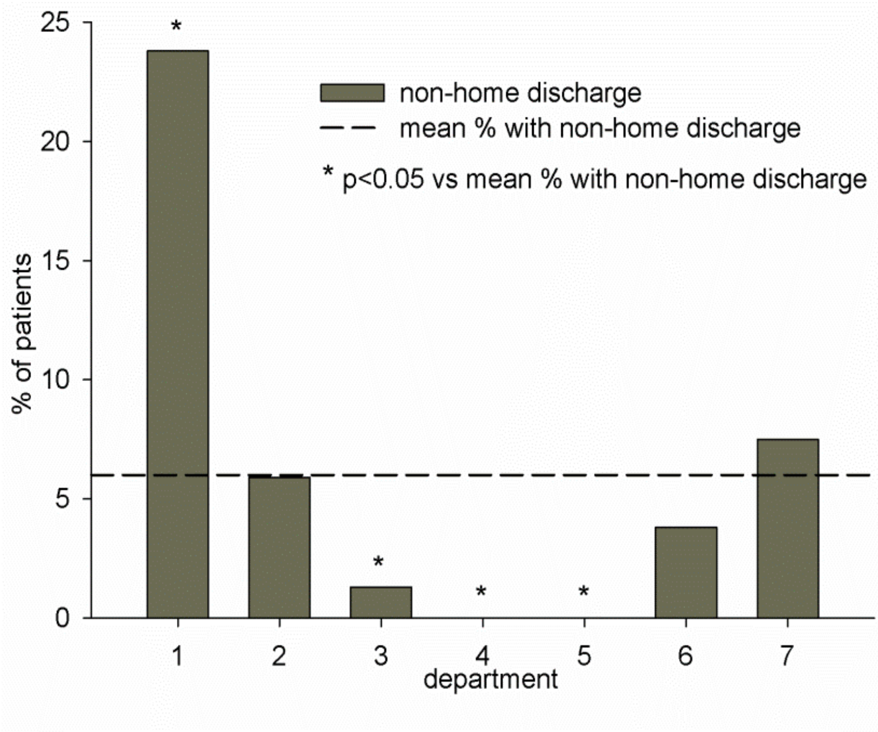


Figure 10 From Pitter et al. *Anesth & Analg* 2016[75]

However, in study VII, one department accounted for more than half of the 7% of patients discharged to a care-facility and with no difference in comorbidity or readmissions between patients with and without home discharge (*figure 10*).[75] This calls for further assessment on the indication for discharge to rehabilitation units within a fast-track protocol.

Study I also found that an age ≥85 years was independently associated with 90-days readmissions[56] and study VII found 30-day readmission rate of about 14%,[75] considerably higher than the 6-7% in fast-track cohorts including all ages.[56, 58] However, these numbers appear consistent with a large database study on TKA in nonagenarians with readmission rates of 10-12%.[278] Unsurprisingly, the fraction of "medical" complications leading to readmission increased in patients aged ≥85 years to about 75%[75] vs. 60% in the those <85 years (figure 9). Furthermore, examination of the causes of readmissions revealed that the majority of "medical" causes were falls, disproved VTE and cardiac problems.[75] In contrast, postoperative delirium seems to be a minor problem in elderly patients having fast-track THA and TKA, as it is the cause of a LOS >4 day in only about 0,7% of patients >70 years.[72] The findings of Study VII were reinvestigated in a subsequent study from the LCDB with an expanded cohort of 1427 procedures in patients aged ≥85 years finding.[85] In this study, the median LOS as well as the number of patients with LOS >4 years decreased by about 1 day and from 32% to 18%

between 2010 and 2017, respectively.[85] However readmission rates and mortality remained stable, much reflecting the results of study XI.

In conclusion, fast-track THA and TKA in elderly patients is feasible and may yield a large reduction in LOS. However, issues remain regarding specific medical complications and readmissions. Thus, patients ≥85 years may benefit from further focus on preoperative optimization of haemoglobin and postoperative fall prevention, in example by perioperative blood management,[289] pre and postoperative conditioning[290] and de-prescription to avoid polypharmacy[291-293] and unnecessary use of psychotropics.[294]

Living alone

There is conflicting evidence regarding the importance of living alone with regards to LOS and readmissions. Thus, outside of a fast-track setup Macdonald and colleagues found that patients who were living alone had up to 3 times higher risk of LOS >7 days after THA and TKA.[295] In contrast, Raut et al. did not find any association between marital status and LOS,[282] while Keeney and colleagues only found a trend towards increased risk of LOS >3 days specifically after TKA.[296] However, neither study provided information on the use of fast-track protocols. Also, the study by Raut et al. only included 112 patients preventing adjusted analysis,[282] while in the study by Keeney et al. about 38% of patients were discharged to other facilities. Furthermore, in the Keeney study, there was a significant number of missing data on patient characteristics, including whether living alone.[296] An early Danish fast-track study from 2005-2008 found that patients living alone had 25% increased probability of staying for more than 3 days, but no analysis was made with regards to readmissions.[13] Two Dutch fast-track studies from in 879 and 477 consecutive TKA and THA patients reported that living alone was associated with increased LOS and risk of LOS >2 nights, respectively.[297, 298] However, both studies were small single-centre studies with limited adjustments for comorbidities.

Study I investigated the association between living alone, LOS and readmissions in 3112 consecutive unselected patients having fast-track THA and TKA between 2010 and 2011 in 5 dedicated fast-track departments. It was possible to adjust for several characteristics and missing data was only about 7%. Median LOS when living alone remained at 2-3 days, regardless of age (figure 11) and with 85% of patients being discharged ≤4 days.[56] However, living alone was associated with increased risk of LOS >4 days (OR:1.86 CI:1.40–2.46) in an adjusted analysis.

It could be speculated that patients who live alone more often stay in hospital due to logistical problems regarding home arrangements after discharge, despite fulfilling the functional discharge criteria. Another possibility is that patients feel unsecure about being alone, and consequently either await home-care or temporary rehabilitation placement. Thus, the French clinical guidelines from 2007 on who to transfer to rehabilitation wards after THA and TKA advocate for this being dependent mainly on demographic criteria such as age, gender and whether living alone, but acknowledging the urgent need for more and better studies.[299]

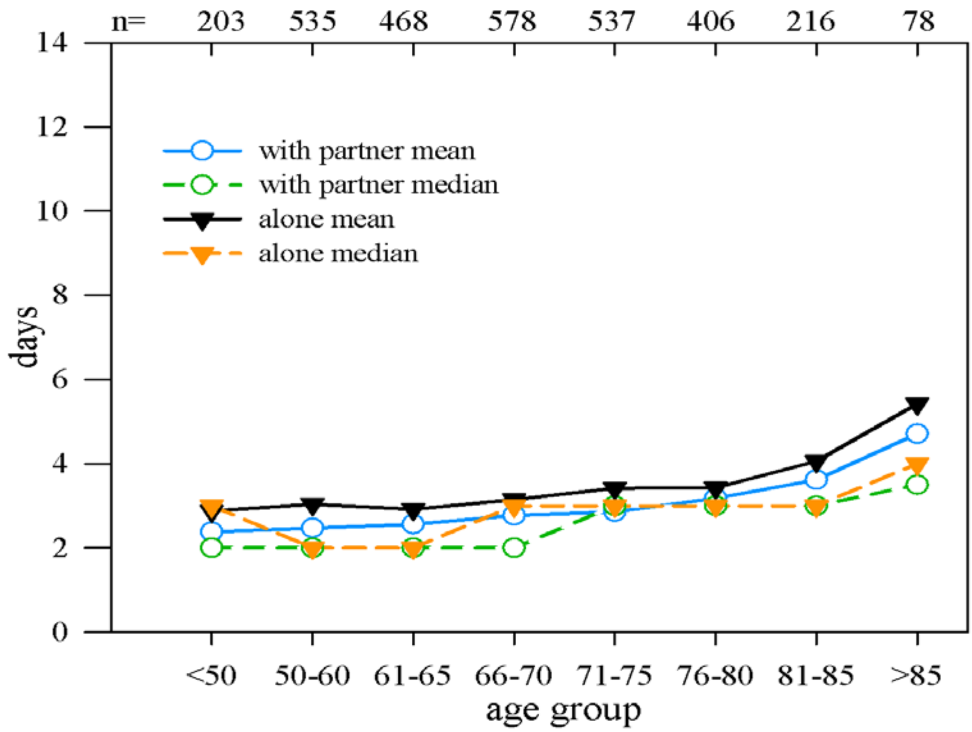


Figure 11. Association between living alone and LOS in different age-groups. Modified from Jørgensen and Kehlet *British Journal of Anaesthesia* 2013[56]

That logistics may be partly influencing a LOS >4 days in patients living alone was supported by living alone not being associated with 90-days readmissions (OR:1.18 CI:0.90–1.55),[56] although an association specifically with fall-related admissions was found in study VII (OR: 2.09 CI:1.20–3.62).[61] Consequently, living alone does seem not dispose towards specific morbidity leading to prolonged LOS or with overall risk of readmissions after fast-track THA and TKA. However, it may be justified to provide an individualized evaluation of both social network and clinical recovery prior to discharge in order to prevent readmissions due falls or insecurity when at home, potentially resulting in a slightly prolonged LOS.

Use of walking aids

Preoperative use of walking aids has previously been found to influence LOS after THA and TKA in smaller cohorts without fast-track protocols,[32, 256, 282] and a recent metanalysis on preoperative factors affecting LOS after TKA, found that of the four studies assessing use of assistive devices, all reported an association with increased LOS.[282] However, none reported the use of fast-track protocols and in the only two studies with > 1000 patients mean LOS was 5 and 9.4 days, respectively.[32, 300]

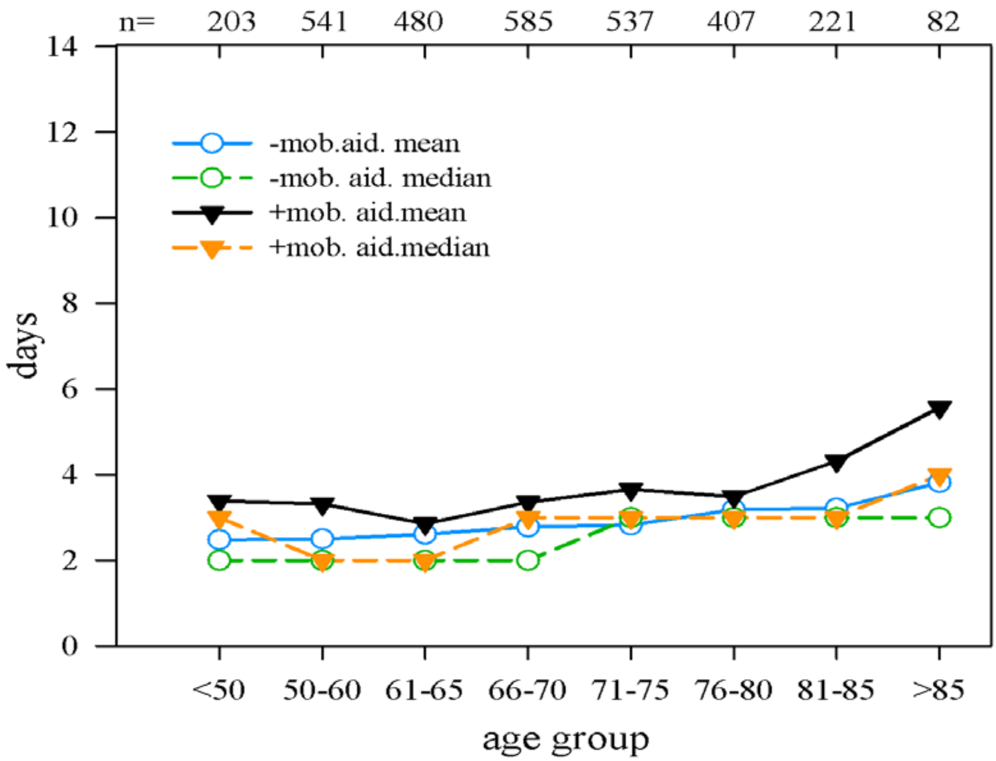


Figure 12. Association between use of mobility aids and LOS in different age-groups. Modified from Jørgensen and Kehlet *British Journal of Anaesthesia* 2013[56]

Furthermore, the study by Ong and Pua included uni-compartmental procedures and with wide use of opioid-based postoperative analgesia.[300]
Raut et al. investigated 112 TKA patients aged ≥75 years and found an increase in mean LOS from 4,9 without any walking aids to 6,1 day when using a walking stick and 6,9 day when using crutches.[282] However, apart from the low number of patients preventing adjusted analysis, these data are further difficult to interpret in a fast-track context as 34% of patients received femoral nerve blocks which may impair postoperative mobility and potentially increase LOS.[203]

In fast-track THA and TKA, study in 712 patients having surgery between 2003 and 2005 found that use of walking aids increased the probability of a LOS >3 days by 40%. However, this was a single centre study from the early days of fast-track arthroplasty with a total mean LOS of 3.8 days.[13]

Study I found about 80% of patients with preoperative use of a walking aids had a LOS of ≤4 days (figure 12).[56] However, use of walking aids was associated with LOS >4 days (OR: 1.96 CI:1.47–2.62) and 90-days readmissions (OR: 1.54 CI:1.13–2.10) when adjusting for other characteristics.[56] The association between preoperative use of walking aids and LOS >4 days was found to be even more accentuated in patients ≥85 years (OR: 1.99 CI:1.26–3.15) in study VII,[75] and was also found when analysing potentially preventable medical morbidity in study VIII.[65] However, it has not been possible to demonstrate any association between use of walking aids and hip dislocations in fast-track THA or with fall-related readmissions in study II.[60, 61]

A reason for why the use of walking aids may be associated with increased LOS could be that it is a surrogate measure for physical capacity and frailty. The frailty syndrome has been associated with impaired surgical outcomes and is especially important in elderly patients,[301] but has also been found in about 1 of 5 patients between 40 and 50 years scheduled for general surgery.[302] Currently, there is limited knowledge on the use of frailty indices and surgical outcomes in fast-track THA and TKA. Consequently, information on physical capacity, i.e. by objective measures,[303, 304] detailed evaluation on preoperative falls[192, 193] or physical impairment[305] deserve further investigation within a fast-track protocol, especially in relation to preoperative conditioning and postoperative physiotherapy. However, the effect of such interventions so far remains uncertain.[306]

Cardiopulmonary disease

Both cardiac and pulmonary disease has repeatedly been associated with impaired postoperative outcome after THA and TKA without fast-track protocols[26, 117, 118, 249] and may complicate both anaesthesia and postoperative convalescence.[307-309] Furthermore, the consequences of intraoperative cardiopulmonary events i.e. hypotension may be exaggerated in patients with pre-existing cardiopulmonary disease.[307, 308, 310]

Higuerra et al. investigated 198 THA and 256 TKA patients >65 years and found that COPD, as well as chronic heart failure, were the only specific characteristics associated with increased LOS, but with no information on mean LOS and discharge destination.[311] Yakubek et al. used NSQUIP data with 25-30% non-home discharges, and found increased LOS and complications, specifically pneumonia, reintubation and prolonged mechanical ventilation in COPD patients having THA and TKA.[312, 313] In THA Belmont et al. investigated 17.640 patients using NSQUIP data from 2006-2011. They found that 4.9% of patients had perioperative complications and that cardiac issues and chronic obstructive pulmonary disease (COPD) were related to a LOS of ≥4 days.[117] Furthermore, COPD was the second most important risk-factor for minor complications. However, about 30% of patients had a LOS of ≥4 days and 31% were discharged to skilled nursing facilities. Yohe et al. analysed 7730 patients >80 years from the NSQUIP database having THA between 2008 and 2014. They found that chronic heart failure was predictive for major complications while COPD was associated with unplanned readmissions within 30 days of surgery.[314] However, there was no reporting of LOS or discharge destinations. Pugely et al. used administrative data from the NIS-database and found that pulmonary-circulatory disorders were associated with increased resource use and about 1.3 days increase in LOS after TKA, but with only 25% of patients having routine discharge to own home.[315]

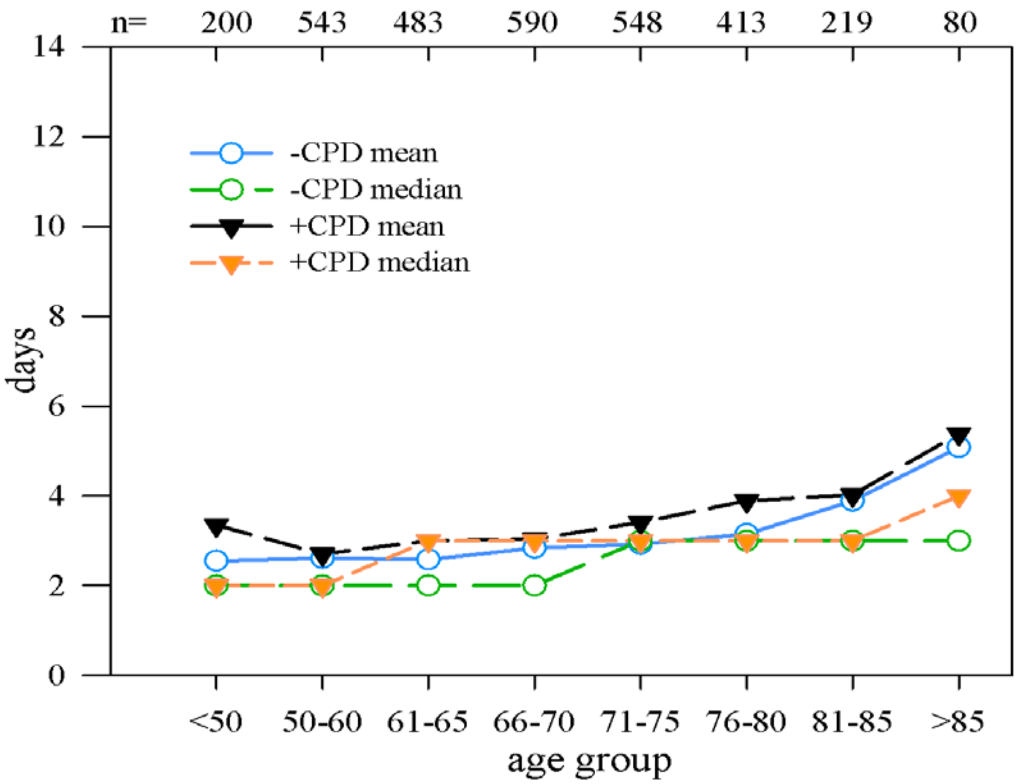


Figure 13. Association between cardiopulmonary disease and LOS in different age-groups. Modified from Jørgensen and Kehlet *British Journal of Anaesthesia* 2013[56]

In TKA, Easterlin et al. analysed NSQUIP-data between 2005 and 2009 and found that dyspnoea, but not COPD, was related to return to the operating room in multiple regression analysis. Neither characteristic was related with complications or extended LOS.[316] Finally, they found that recently diagnosed chronic heart failure was the strongest predictor for extended LOS. However, extended LOS was defined as LOS >7 days and occurred in 3.3% of patients,[316] preventing any conclusions when using a fast-track protocol. Curtis et al. also used NSQUIP data to analyse patients with heart failure having TKA, and found increased LOS, readmissions, reoperations and MI's than controls.
However, only 251 of 111,634 (0.2%) patients were registered as having heart failure and non-home discharge occurred in about 30 % of all patients.[317] In this context, the limited number of patients with heart failure is unsurprising as newly discovered or over heart failure is usually considered a contraindication in non-malignant elective non-cardiac surgery. Consequently, the results of these, mainly NSQUIP based, large register studies may not simply be applied to fast-track surgery with intended discharge to own home and limited use of general anaesthesia.
Study I was the first study to investigate the influence of pharmacologically treated cardiopulmonary disease (CPD) on LOS and 90-days readmissions within an established fast-track setup with discharge to own home. It was found that 87% of the patients with CPD had a LOS <4 days, and median LOS remained 2-3 days regardless of age group (Figure 13).[56] Nonetheless, the OR for a LOS >4 days with CPD was 1.40 (1.03–1.91) and 2.00 (1.45–2.66) for 90-days readmissions.[56] The importance of CPD may primarily be due to pulmonary disease, which was found associated with potentially preventable medical morbidity in study VIII.[65] In contrast, a subsequent Dutch single centre fast-track study in 879 TKAs, was unable to demonstrate any association between pulmonary or cardiovascular disease and increased LOS.[298] Nonetheless, It has been observed that patients with pre-existing cardiac disease have a greater risk of cardiac complications,[318] including after fast-track THA and TKA.[74, 80] Regardless, the low incidences of MI and cardiac arrest in fast-track THA and TKA[74] may partially explain why the influence of pre-existing cardiac disease on overall morbidity in fast-track THA and TKA is low. In conclusion, although CPD may influence LOS and readmission in fast-track THA and TKA, most patients with these comorbidities can be discharged within 4 days after surgery. However, a considerable number of patients with CPD are readmitted within 90-days of surgery, often due to cardiac complications.

Type-2 diabetes

Diabetes Mellitus (DM) is one of the classical preoperative risk-factors and is incorporated into numerous comorbidity scores such as the Charlson Comorbidity index[20] and the ASA-score.[18] The diabetic patient imposes several problems in the perioperative phase such as management of oral antidiabetics,[293, 319] management of blood glucose,[320] renal[321, 322] and neurological organ dysfunction[293] and cardiac disease.[319] Furthermore, an association between long-term blood glucose control defined as haemoglobin in THA and TKA A1c < 7% and postoperative complications after THA and TKA has been found when using NIS,[320] but not Kaiser Permanente Registry data.[322, 323] Finally, the influence of diabetes on postoperative outcomes is further complicated by a potentially increased risk of postoperative infections due to elevated blood glucose per se in both diabetic[325, 326] and non-diabetic patients.[327] Consequently, perioperative management of diabetic surgical patients has focused on strict control of blood glucose,[328, 329] despite concerns about hypoglycaemia and uncertain effect on postoperative outcomes.[330-332] Increased risk of postoperative complications and prolonged LOS in diabetics having THA and TKA has been found in most[28, 333, 334] but not all studies.[335, 336] In the study by Bolognesi at al. using NIS data from 1988-2003, the authors found an increased number of complications in diabetic patients except for MI. Strangely, mean LOS was slightly increased in non-diabetics but was 5-6 days in both groups, and discharge to own home only occurred in about 30% of patients.[28] Two Spanish studies using Spanish National Health Database data from 2001-2008 and 2010-2014, found increased risk of prolonged LOS, mortality and in-hospital complications in THA and TKA patients with type-2 diabetes (T2D), but without use of a fast track protocol and a mean LOS of > 7 days.[333, 337] Two more recent studies using NSQUIP data from 2005 to 2014 but again without mention of fast-track protocols, also found greater risks of postoperative adverse events and extended LOS (>5 days),[338] and 30-days readmissions, mortality and "medical" but not "surgical" complications in patients with insulin dependent vs. patients with non-insulin dependent diabetic mellitus.[339] Finally, in a secondary analysis of data from the APEX trial, Lenguerrand et al. did not find any relationship between diabetes, haemoglobin A1c and increased LOS after adjusting for confounders.[340] However, the APEX trial which investigated the effect of local infiltration analgesia on chronic postoperative pain used femoral nerve-blocks in all patients, had a median LOS of 5 days and only included 64 patients with diabetes.[341]

Thus, few studies in THA and TKA have focused on adherence to fast-track principles, despite various components of the fast-track protocol may reduce postoperative insulin resistance, hyperglycaemia and the catabolic response.[33, 319, 342] These modifications may be especially important in diabetic patients and it seems plausible that the implementation of fast-track

principles could reduce the importance of DM as a preoperative risk factor.
Study IX, focused on postoperative outcomes in patients T2D which comprise the largest group of diabetic patients presenting for THA and TKA. There was no association between T2D and LOS >4 days, 30 or 90-days readmissions or with specific types of "diabetes-related" morbidity resulting in LOS >4 days or readmissions after adjusting for other preoperative characteristics (figure 14).[67]

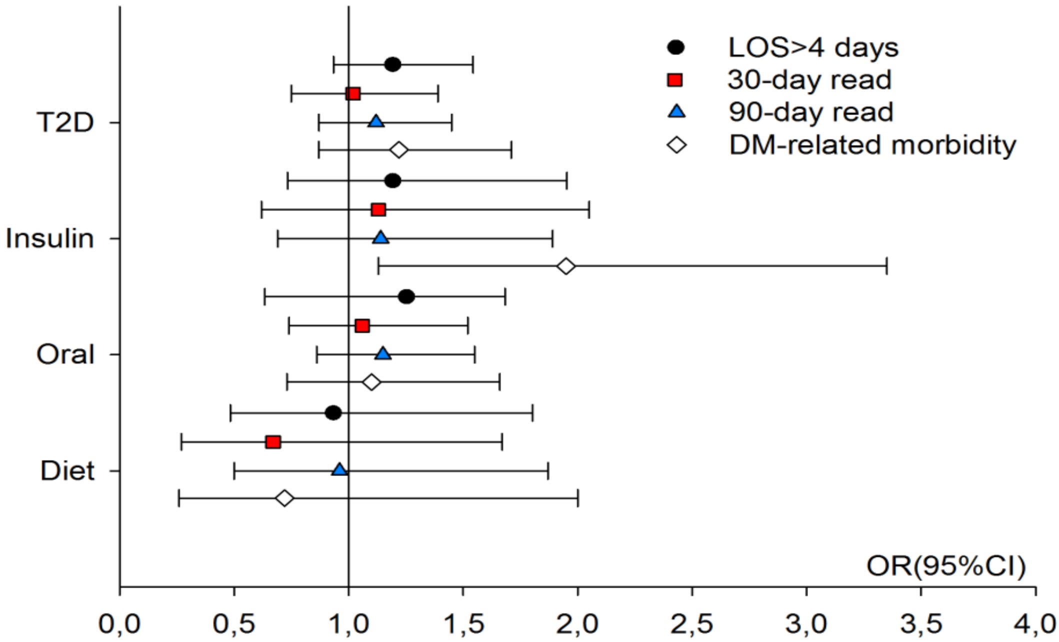


Figure 14 Adapted from Jørgensen et al. *Anesth & Analg* 2015[67] read: readmissions
DM: diabetes mellitus

That T2D *per se* may have less influence on postoperative outcomes in fast-track THA and TKA was further illustrated by a statistically insignificant adjusted "number needed to harm"[343] of 78 for one additional occurrence of a LOS >4 days due to the presence of T2D, increasing to 957 and 115 for one additional readmission at 30 and 90-days respectively.[67] Importantly, amongst the 174 type-2 diabetics who needed insulin treatment there was an association with "diabetes-related" morbidity and sub-analysis of the few patients with type-1 diabetes found 21% with LOS >4 days and 18% with 90-days readmissions.[67] Consequently, a follow-up study including >4000 patients with both T1D and T2D, but divided by antihyperglycemic treatment was designed within the LCDB.[344] This larger cohort confirmed found that insulin-treatment but also oral antihyperglycemic treatment increased the risk of LOS >4 days. However, oral antihyperglycemic treatment was only just statistically significant (OR 1.2 CI 1.00-1.4). The reason for this was mainly due to more cases of renal, mobilisation and miscellaneous medical

issues, mainly in those with insulin treatment which was also associated with increased 30 and 90-days readmissions.[344]
In conclusion, the role of T2D *per se* as a preoperative risk-factor for increased LOS or readmissions may be reduced in fast-track THA and TKA. However, considerations on antihyperglycemic treatment may be relevant for preoperative risk-stratification and potential reduction of "medical" complications related to blood-glucose levels, as the introduction a considerable number of novel combinations of insulins and antihyperglycemics have made the optimal perioperative regimens increasingly complex.[345, 346] Finally, the perioperative blood-glucose level which is most efficient at preventing both hypo- and hyperglycaemia, and how best to achieve this has yet to be found.[346, 347]

Psychiatric disorder and psychopharmacological treatment

Recently there has been increasing interest in the role of psychiatric disorders and psychopharmacological treatment in relation to surgical outcomes.[348, 349] Although it is well established that psychiatric conditions may influence long-term functional outcomes in THA[350] and TKA,[351, 352] the influence of pre-existing psychiatric conditions upon postoperative length of hospital stay and complications is less well described. However, there is growing evidence that psychiatric disorders and psychopharmacological treatment may be significant preoperative risk factors for postoperative morbidity and mortality, both in mixed surgery[353, 354] and THA and TKA specifically.[348, 355-357] This effect may be linked to differences regarding other comorbidities, side effects of psychopharmacological treatment and impaired access to and quality of health care.[358-360] However, most studies are limited by lack of adjustments for relevant preoperative characteristics,[361, 362] inclusion of mixed surgical procedures,[354] dependence on diagnostic coding or hospital encounters[354-356, 361, 363, 364] and limited follow-up.[361, 363]
Currently, an association between the SSRIs and increased surgical bleeding and transfusions is now well described in several studies and meta-analyses,[349, 365-367] with an increased bleeding risk between 12 and 64% according to some authors.[366] This is most likely explained by inhibition of several pathways for aggregation and clot-formation of thrombocytes,[368] as well as a reduction in the number of coated platelets.[369]In one of the largest studies of more than 500.000 patients having mixed major surgery, Auerbach and colleagues found that perioperative use of selective serotonin reuptake inhibitors (SSRI) significantly increased the likelihood of mortality, bleeding and 30-days readmission. This effect was present, regardless of differentiating between those with SSRI the day before surgery and those with only postoperative use.[370] However, as the effect of SSRIs was attenuated amongst patients with a diagnostic code of depression, conclusions on whether the results were due to the psychiatric disorder or SSRIs per se were limited. In THA and TKA, Klement et al. used Medicare data and

Table 7. From Jørgensen et al. *Anesthesiology* 2015[68]
Multiple logistic regression analyses on postoperative outcomes in 8,145 total hip and knee arthroplasties.[a]

	LOS>4		30-days readmissions		90-days readmissions	
Variable	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
PsD overall (n:911)	1.90 (1.52-2.37)	<0.001	1.93 (1.49-2.49)	<0.001	1.68 (1.34-2.10)	<0.001
"potential" PsD[b] (n:331)	2.00 (1.43-2.81)	<0.001	1.30 (0.84-2.02)	0.238	1.50 (1.05-2.14)	0.024
Age (yrs)						
<50	1.29 (0.83-2.01)	0.251	0.60 (0.34-1.08)	0.087	0.83 (0.54-1.27)	0.387
50-60	0.68 (0.47-0.99)	0.043	0.88 (0.61-1.27)	0.491	0.85 (0.63-1.14)	0.274
61-65	0.71 (0.49-1.03)	0.068	0.80 (0.55-1.17)	0.251	0.73 (0.53-1.00)	0.048
66-70	1	Ref	1	Ref	1	Ref
71-75	1.46 (1.08-1.96)	0.013	1.42 (1.03-1.96)	0.033	1.28 (0.98-1.66)	0.073
76-80	2.18 (1.62-2.93)	<0.001	1.48 (1.05-2.08)	0.025	1.21 (0.91-1.62)	0.192
81-85	2.94 (2.13-4.07)	<0.001	1.57 (1.06-2.34)	0.024	1.44 (1.04-2.01)	0.029
<85	4.15 (2.78-6.18)	<0.001	2.49 (1.55-4.03)	<0.001	1.97 (1.30-3.00)	0.001
BMI						
<18.5	1.34 (0.61-2.94)	0.471	0.53 (0.16-1.77)	0.297	0.54 (0.19-1.54)	0.248
18.5-24.9	1	Ref	1	Ref	1	Ref
25.0-29.9	0.95 (0.77-1.17)	0.618	0.86 (0.67-1.09)	0.213	0.92 (0.75-1.13)	0.431
30.0-34.9	1.06 (0.83-1.37)	0.644	1.04 (0.79-1.37)	0.794	0.98 (0.77-1.25)	0.889
35.0-39.9	1.56 (1.12-2.18)	0.009	1.07 (0.71-1.59)	0.757	1.07 (0.76-1.49)	0.814
>39.9	1.29 (0.75-2.23)	0.361	0.53 (0.23-1.24)	0.143	0.44 (0.21-0.92)	0.030
Male vs Female	0.88 (0.73-1.06)	0.185	1.29 (1.04-1.59)	0.019	1.20 (1.00-1.44)	0.045
TKA v THA	1.25 (1.05-1.48)	0.013	0.95 (0.78-1.16)	0.609	0.94 (0.80-1.12)	0.507
Living with others	1	Ref	1	Ref	1	Ref
Living alone	1.54 (1.28-1.85)	<0.001	1.14 (0.92-1.41)	0.241	1.03 (0.86-1.24)	0.735
Living in institution	1.50 (0.71-3.20)	0.291	1.44 (0.59-3.54)	0.422	1.49 (0.70-3.19)	0.301
Use of walking aids	2.13 (1.77-2.56)	<0.001	1.53 (1.23-1.91)	<0.001	1.64 (1.37-1.93)	<0.001
Smoking	1.19 (0.93-1.53)	0.165	1.61 (1.25-2.07)	<0.001	1.24 (0.99-1.55)	0.065
Alcohol >2 units a day	0.87 (0.59-1.27)	0.468	0.76 (0.50-1.14)	0.187	0.83 (0.59-1.16)	0.277
Pulmonary disease	1.41 (1.08-1.85)	0.012	1.46 (1.07-1.98)	0.017	1.48 (1.14-1.92)	0.004
Cardiovascular disease	1.48 (1.21-1.80)	<0.001	1.39 (1.10-1.75)	0.004	1.43 (1.18-1.74)	<0.001
Type-1 diabetes	2.69 (1.19-6.12)	0.018	1.97 (0.75-5.18)	0.171	2.37 (1.06-5.28)	0.035
Type-2 diabetes	1.27 (0.99-1.63)	0.061	0.97 (0.71-1.33)	0.859	1.15 (0.89-1.48)	0.290
Preoperative anemia	1.92 (1.57-2.35)	<0.001	1.43 (1.11-1.83)	0.005	1.33 (1.07-1.65)	0.010
PsD stratified by psychopharmacological treatment[a,b]						
SSRI (n:394)	2.19 (1.62-2.97)	<0.001	1.97 (1.38-2.82)	<0.001	1.77 (1.29-2.43)	<0.001
Other antidepressants (n:291)	1.81 (1.25-2.61)	0.002	2.24 (1.51-3.31)	<0.001	1.82 (1.27-2.61)	0.001
SSRI+other antidepressants (n:73)	1.05 (0.49-2.27)	0.893	0.88 (0.31-2.47)	0.803	0.91 (0.38-2.16)	0.829
Antipsychotics (n:153)	1.90 (1.62-3.16)	0.013	1.85 (1.03-3.31)	0.040	1.49 (0.88-2.55)	0.141

Number of patients included in analysis differs from the total number of patients due to missing data. All covariates were defined a priori. [a] The stratified analysis was adjusted for the above confounders, but excluding the "potential PsD patients. [b] Patients without PsD used as referenceBMI: body mass index CI: confidence interval LOS: length of hospital stay OR: odds ratio PsD: psychiatric disorder SSRI: selective serotonin inhibitors THA: total hip arthroplasty TKA: total knee arthroplasty found increased 30-day occurrence in about 80% of "medical" and 90% of "surgical" complications, including bleeding in patients with psychiatric diagnoses. But both studies lacked information psychopharmacological treatment, fast-track protocols or discharge destination,[355, 356] precluding conclusions on the effect of psychotropic treatment or relevance within fast-track surgery.

Table 8. From Jørgensen et al *Anaesthesiology* 2015[68]
Influence of an unmeasured confounder with odds ratio of 2.0 on length of hospital stay >4 days

	P_c					
P_{PsD}	0	0.1	0.2	0.3	0.4	0.5
0	1.90 (1.52-2.37)					
0.1	1.73 (1.38-2.15)	1.90 (1.52-2.37)				
0.2	1.58 (1.27-1.98)	1.74 (1.39-2.17)	1.90 (1.52-2.37)			
0.3	1.46 (1.17-1.82)	1.61 (1.29-2.01)	1.75 (1.40-2.19)	1.90 (1.52-2.37)		
0.4	1.36 (1.09-1.69)	1.49 (1.19-1.86)	1.63 (1.30-2.03)	1.76 (1.41-2.20)	1.90 (1.52-2.37)	
0.5	1.27 (1.01-1.58)	1.39 (1.11-1.74)	1.52 (1.22-1.90)	1.65 (1.30-2.05)	1.77 (1.42-2.21)	1.90 (1.52-2.37)
0.6	1.19 (0.95-1.48)	1.31 (1.05-1.63)	1.43 (1.14-1.78)	1.54 (1.24-1.93)	1.66 (1.33-2.07)	1.78 (1.43-2.22)
0.7	1.12 (0.89-1.39)	1.23 (0.98-1.53)	1.34 (1.07-1.67)	1.45 (1.16-1.81)	1.56 (1.25-1.95)	1.68 (1.34-2.09)
0.8	1.06 (0.84-1.32)	1.16 (0.93-1.45)	1.27 (1.01-1.58)	1.37 (1.10-1.71)	1.48 (1.18-1.84)	1.58 (1.27-1-98)
0.9	1.00 (0.80-1.25)	1.10 (0.88-1.37)	1.20 (0.96-1.50)	1.30 (1.04-1.62)	1.40 (1.12-1.75)	1.50 (1.20-1.87)
1	0.95 (0.76-1.19)	0.52 (0.42-1.30)	1.14 (0.91-1,42)	1.24 (0.99-1.54)	1.33 (1.06-1.66)	1.43 (1.14-1.78)

P_{PsD}: Prevalence of unmeasured confounder in patients with psychiatric disorder (PsD) P_c: Prevalence of unmeasured confounder in controls. Results are the new odds ratio with 95% confidence intervals for PsD. Bold line marks cut-off for no significance for PsD, blanks are where odds ratio for PsD would have increased.

Study V was the first to investigate the influence of psychiatric disorder with psychotropic treatment (PsD), defined as reimbursed prescriptions on psychopharmacological treatment with sufficient doses to include day of surgery) on LOS, readmissions and mortality within a well-defined fast-track protocol. It found a pronounced increased risk of LOS >4 days, 30 and 90-days readmissions amongst the 11% of patients with PsD [68] Interestingly, this applied to all patients regardless of prescriptions on SSRIs, other antidepressants or antipsychotics and after adjusting for comorbidity and lifestyle related characterstics.[68] The results were also largely

similar in 365 patients with suspected psychiatric disorder, but potentially insufficient doses of psychopharmacological drugs to include day of surgery (table 7). An accompanying robustness analysis found that to negate the influence of PsD the risk of LOS >4 days, an unmeasured confounder with an independent OR of 2.0 would have to be present in 50% of the patients with PsD and in none of those without (table 8). That PsD is an important risk-factor in fast-track THA and TKA was further supported by the association between PsD and potentially preventable medical morbidity demonstrated in study VII.[65] Furthermore, study II focusing on post-discharge falls as well as an additional LCDB study on hip dislocations with details on type of prosthesis, complete and detailed follow-up and adjusting for several preoperative characteristics, found significant associations with preoperative PsD.[60, 61] In this context, one of the main questions is whether this is due to PsD per se or the psychotropic treatment?
That the use of psychotropic drugs may despise towards impaired balance and increased risk of falling is well known from studies in hospitalized patients not having surgery,[190, 195, 371] as well on community dwellers,[372] possibly related to side-effects such as sedation, impaired reflexes and increased reaction time[294] Consequently, further studies based on the LCDB in patients with PsD outside of this thesis were conducted. Thus, a follow-up study on the same cohort but including data on postoperative transfusions from the Danish regional transfusion databases, found that although the risk of transfusion were almost doubled in patients using SSRIs, there was also a significantly increased risk of blood transfusions with other types of psychopharmacological treatment.[69] Importantly, another follow-up study explored whether PsD patients having been in contact with any Danish psychiatric hospital had worse 90-days outcomes, compared to those being treated in private practice or by their general practitioner. This study did not find an increased risk of LOS >4 days or readmissions in patients with, presumably more severe psychiatric disorder needing in-hospital psychiatric treatment,[63] further supporting that psychotropic treatment may be the more important risk-factor. Finally, a prospective study on psychiatric characteristics in 2183 fast-track THA and TKA patients, was unable to find significant differences in psychiatric symptoms when compared to a Danish background population.[373] Thus, the PsD associated risk seems less likely to be due to specific psychiatric characteristics in the THA and TKA population but rather related with the psychotropic treatment per se.
In conclusion, the presence of preoperative PsD is an important preoperative risk-factor in fast-track THA and TKA. Currently this seems to be primarily related to the use of psychotropics and not the PsD per se. However, despite previous suggestions on pre- and perioperative anesthetic risk-stratification[367, 374] and handling of psychopharmacological treatment,[349, 367, 375] the effect and safety of withholding or reducing psychotropic drugs prior to surgery remains undecided.[348, 376, 377]

LOS ≤4 days, an independent risk factor for readmissions?

A common concern of reducing LOS after THA and TKA is the potential increase in readmission rates or that patients are unable to manage upon returning to their homes. It is difficult to argue against the benefits of being in hospital if a life-threatening complication occurs, which was why Parvizi and colleagues cautioned against a LOS of <2 days after finding that >90% of potentially fatal complications in a non-fast-track setting, occurred within the four initial postoperative days.[378] However, the occurrence of potentially fatal complications such as myocardial infarctions and thromboembolic events within the first postoperative week has been found to be only about 0.3% in fast-track THA and TKA,[62, 80, 379] as opposed to about 2% in the Parvizi study.[378] Furthermore, mortality within the first week in discharged patients was almost negligible,[71] likely due the need for fulfilling the functional discharge criteria prior to discharge. Whether a short LOS increases the risk of readmissions has been investigated in several of fast-track studies, including several in this thesis. Thus, in study I the OR for 90-days readmissions with a LOS ≤4 was 0.78 (CI:0.52–1.19)[56] while OR for readmission due to falls in study II was 1.19 (CI:0.52-1.28).[61] Also, in selected patients Starks et al. found a 45% reduction in readmissions despite a reduction in LOS from median 8 to 5 days.[11] The same findings of no increase in readmissions despite reductions in LOS has been reported from other institutions with fast-track protocols in the U.K.[43, 380] Norway,[42] and the Netherlands.[12] Finally, a single-centre study from the U.S with a mean LOS of about 5 days, found no increase in readmissions specifically due to “failure to cope” after discharge in patients with a LOS of ≤ 3 days.[381]

In the context of a short LOS, there has been an increase in reports of THA and TKA as outpatient procedures in selected patients with limited comorbidities and a functioning social network.[382-385] However, data of the fraction of patients eligible for outpatient procedures in an unselected population are limited,[386] but may be as high as 30-50%.[95] Currently, some authors have found an increased risk of postoperative complications and readmissions in patients having outpatient surgery,[380, 387] including cardiac and pulmonary complications.[388] However, whether this would also apply to outpatient surgery with dedicated fast-track protocols is uncertain,[389] and a small propensity matched cohort in fast-track THA and TKA found no readmissions within 48 hours of discharge or relation to surgery and only slightly increased 90-days readmission rates (6% vs 4%).[86]

Nonetheless, some authors have suggested that like in outpatient surgery, fast-track protocols should only be applied to selected patients deemed “fit” enough.[10, 389, 390] However, the reduction in LOS should not be a goal by itself but rather a result of supplying the best possible level of care with a “first better, then faster” approach.[386] In this context, it seems counterintuitive not to provide the best evidence-based care to patients with high age or comorbidity. In conclusion, while selection criteria of some sort are necessary for safe outpatient surgery,[391] the use of fast-track protocols but with a consideration on relevant patient-comorbidities in unselected populations is a different matter.

The construction of a preoperative risk-score for potentially preventable "medical" complications.

Identification of preoperative risk factors is merely the first step in establishing why the surgical high-risk patient is at risk. The second step is to identify how to prevent postoperative complications either through preoperative optimization, postoperative intervention or both. Preoperative optimization in THA and TKA is potentially problematic due to limited modifiable risk-factors, mainly smoking, alcohol use and BMI, all which have shown limited relevance in a fast-track setup.[57, 73] Nonetheless, a recent review in THA and TKA found decreased LOS and readmissions, especially surgical site infections, with use of preoperative screening protocols.[392] However, of the eight included studies, none had fast-track protocols and there was a wide variation in definitions of successful preoperative screening. Thus, some studies considered referral to appropriate specialties to be sufficient while others required actual attempts at intervention.[392]

Postoperatively, rounds by anaesthesiologists may improve outcomes after hip fractures,[393] just as rounds by medicine physicians after colectomies[394] and workouts by geriatric services in mixed elective procedures.[395, 396] However, the necessary interventions may be highly procedure specific and no such data exist after fast-track THA and TKA. In this context, the Association of Anaesthetists of Great Britain and Ireland now support the expanded role of senior geriatricians in coordinating perioperative care in all elderly surgical patients, supported by senior anaesthesiologists and surgeons.[271] Interestingly, the guideline provide no details about what this expanded role should include as the focus is mainly on choice of anaesthesia, hemodynamic management and immediate postoperative care.[271] Correspondingly, the ASA have launched an initiative called the Perioperative Surgical Home, with the intention of anaesthesiologists having a central role in coordinating the entire surgical course, from preoperative workout to after discharge.[397, 398] Noteworthy, the lack of mentioning of other staff, e.g. surgeons, nurses, physiotherapists etc.[398] prompted immediate response from several surgeons.[399]

Finally, as demonstrated in the study on fall-related admissions, not all readmissions after THA and TKA are necessarily preventable. In a meta-analysis on studies in surgical, medical and geriatric patients, in which an evaluation on preventability had been performed, Walraven and colleagues found that less than one of four urgent readmissions within 30 days of hospitalization were deemed avoidable.[105] This number has been shown to vary with the teaching status of the hospital and the number of reviewers evaluating preventability.[107]

Furthermore, differences in criteria for avoidable readmissions (e.g. predefined diagnostic codes vs. evaluation of patient records) and limitations on available data may also influence evaluation of preventability.[105, 106]

Most existing risk-scores and indices are not based upon fast-track care and without an evaluation of preventability,[18-21] perhaps contributing to the lack of demonstrated benefits of preoperative risk-stratification tools.[400] A study using NSQUIP data on THA and TKA between 2011 and 2012, but without information on use of fast-track protocols, LOS or discharge destination, investigated the association between reoperations, readmissions, mortality, “medical” and “surgical” complications and the CCI, the ASA-score and specific patient characteristics. They found that only the ASA-score was significantly associated with four of five ouctomes, but although it was more reliable than the CCI, it was insufficient as a risk-stratification tool by itself.[120] However, due to strict criteria for relevant readmissions and a follow-up of only 30 days, no more than 5 % of all patients had registered adverse events.[120] Interestingly, the ASA-score was never designed to predict surgical risk, but rather to provide a common reference point when comparing the health of patients,[18] potentially explaining why it may be insufficient for clinically relevant risk-prediction in THA and TKA. Using the State Inpatient Database, Siracuse et. al developed a prediction scale for 30-days readmissions after THA.[401] Based on various preoperative and procedure-related characteristics they developed a score from 0-40 points demonstrating a 0.36% increase readmission risk for each point. However, the study mixed primary and revision procdures, and did not consider whether readmissions were “surgical” or “medical”. Furthermore, only 20% of patients were discharged to own home, 20% had a LOS >4 days, and 30-days readmission rates due to VTE was 2%,[401] considerably different from when using a fast-track protocol.

Consequently, Study VIII is the first study attempting to construct a preoperative risk-score for “preventable” morbidity resulting in either LOS >4 days or readmissions in fast-track THA and TKA.[65] It was found that defining a high-risk population using a cut-off of ≥2 of 6 relevant preoperative risk-factors (age >80 years, use of walking aids, use of anticoagulants, anaemia, pulmonary disease or PsD) was statistically possible. Using this definition for the “high-risk fast-track THA and TKA patient” would include about 20% of all patients who in turn accounted for about 60% of all “potentially preventable medical complications” (figure 15).[65] However, the total incidence of preventable complications in the cohort was 6.4% and only 4.2% were “medical”. Furthermore, even a 50% reduction in “preventable medical complications” would result in only 91 avoided complications in the 1530 “high-risk” patients.[65]

Using the same method, it was found that the incidence of “potentially preventable” “surgical” morbidity was 2.2% and associated with only 3 preoperative characteristics, one of which was having THA rather than TKA. Consequently, it was not possible to make a meaningful risk prediction model for "surgical" morbidity.[65] The study also demonstrated that the type of "medical" complications include all organ systems, also in the high-risk

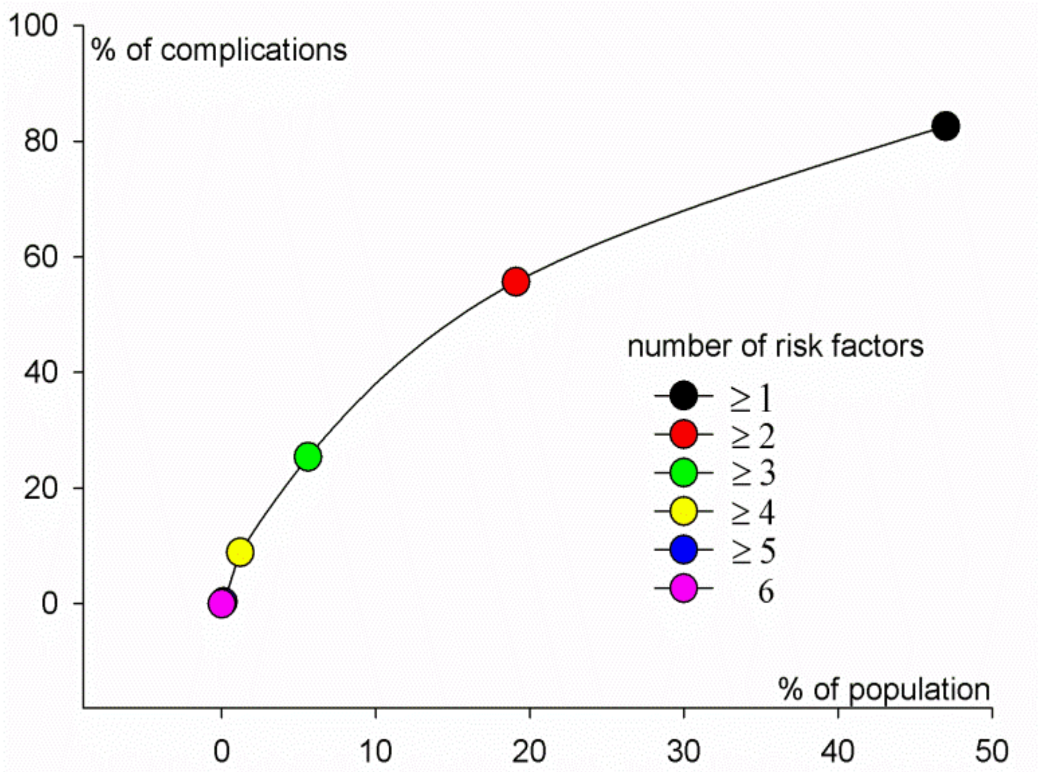


Figure 15 Number of risk factors and corresponding proportion of "potentially preventable medical complications". Adapted from Jørgensen et al. *BMJ-Open* 2016[65]

patients (figure 16).[65] This is unfortunate, as it suggests that the effect of a single intervention targeting a specific complication may be limited, supporting the need for more multifactorial interventions. In contrast, there was only a limited number of types of "surgical" complications (figure 17), partly due to our definition of "preventability". Interestingly were no cases of manipulation under anaesthesia (MUA) after TKA in "high-risk" patients. This is in accordance with a previous study investigating disposing factors for MUA, where younger age and no use of walking aids increased risk of having MUA within 90 days after surgery, probably due to these patients having higher levels of activity and maybe also higher functional expectations.[66] In the "high-risk" patients >50% of complications were caused by hip dislocations. An association with use of walking aids, increased age and PsD was also previously found in fast-track THA.[60] Unfortunately, no correlation with size or placement of the prosthesis could found, and the benefits of i.e. dual mobility cups compared to increased complication risk is not yet well established.[402] However, as there was a considerable number of dislocations in one department with no use of postoperative restrictions and the primary mechanism of dislocation was found associated with squatting or sitting, it could be speculated that “high-risk” THA patients may benefit from some use of postoperative restrictions. Finally, although periprosthetic fracture was not included as “potentially preventable” “surgical” complications, a recent fast-track study on the use of cement in THA found a strong association between age >70 years, use of uncemented stems and periprosthetic fracture.[76] Thus, this type of complication may be prevented by increased use of cemented stems in elderly patients with reduced bone quality.[76, 403]

In summary the “high-risk” patient in fast-track THA and TKA may be defined by ≥2 of the following 6 preoperative risk-factors: age >80 years, use of walking aids, anaemia, pulmonary disease, use of anticoagulants and PsD. However, this only applies to “medical” and not “surgical” complications. Finally, the need for multimodal interventional strategies due to the wide range different of medical complications, limits current clinical relevance as data on effect of potential interventions are sparse.

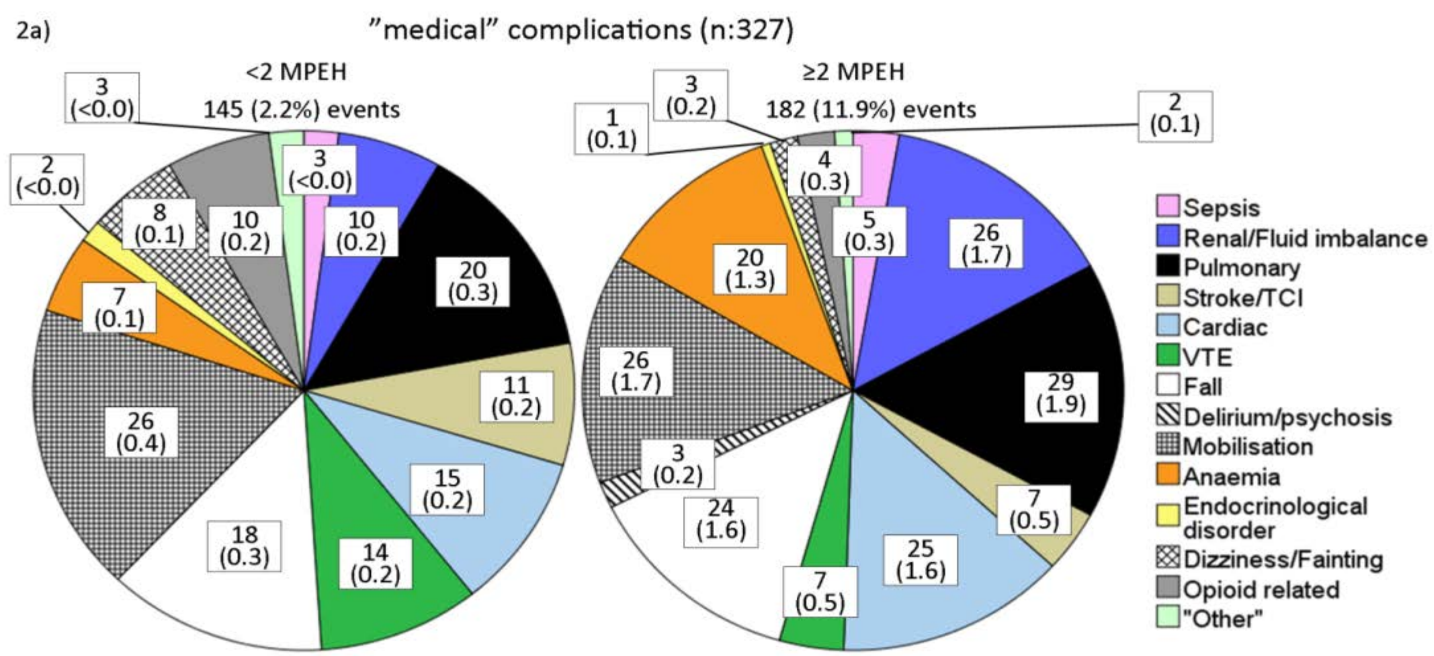


Figure 16. distribution of potentially preventable "medical" complications in high risk (≥2MPEH) vs. low risk patients (<2 MPEH) MPEH: medical predictors excluding hypertension. From Jørgensen et al. *BMJ-OPEN* 2016[65]

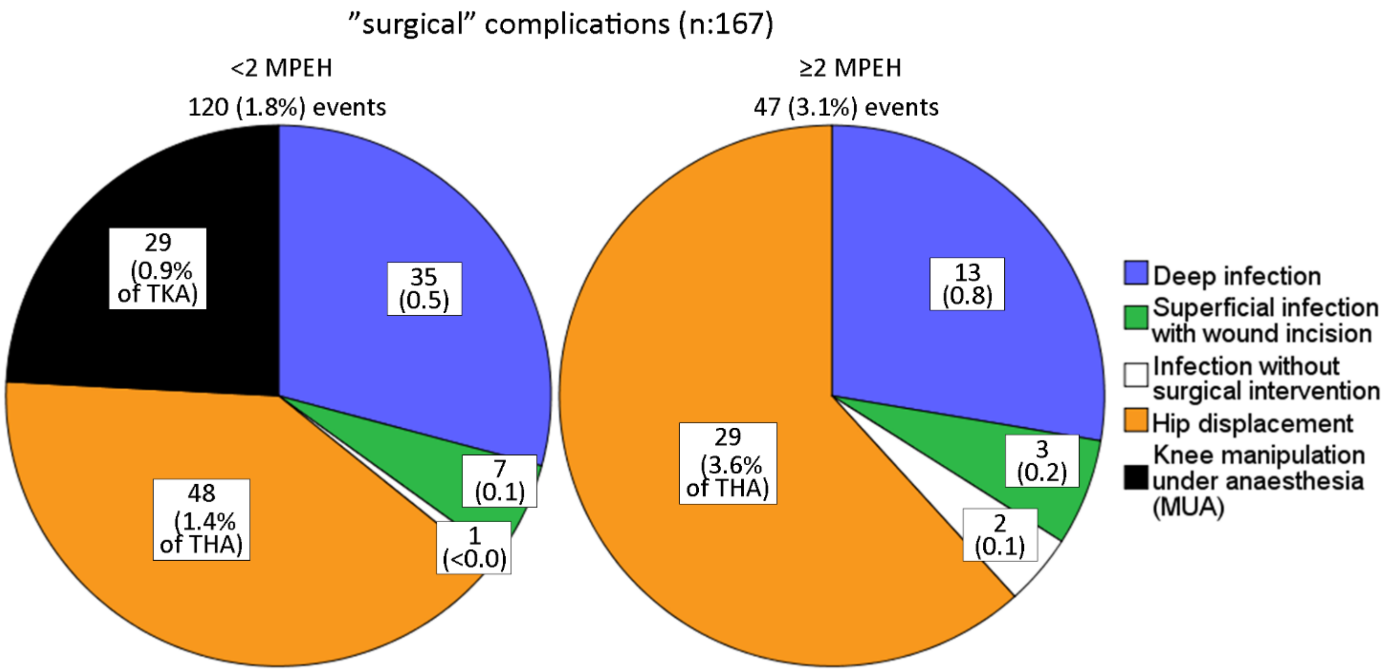


Figure 17. distribution of potentially preventable “surgicall” complications in high risk (≥2MPEH) vs. low risk patients (<2 MPEH) MPEH: medical predictors excluding hypertension. From Jørgensen et al. *BMJ-OPEN 2016*[65]

Future directions

The studies in this thesis have focused on which, when and in whom postoperative complications occur after fast-track THA and TKA. Thus, for the first time it has been possible to provide complete highly detailed 90-days follow-up data on complications leading to LOS >4 days, readmissions and mortality in unselected patients having fast-track THA and TKA on a multicentre level within a socialized health-care system. Hopefully these data will serve to qualify argumentations on when and how to focus interventions in future RCT's or detailed observational studies specifically in "high-risk" patients having fast-track THA and TKA. While RCT's are the gold standard for evaluation of well-defined interventions, large detailed prospective observational studies have the advantage of being better suited for investigating rare adverse events and intervention effects.[52] Thus, the ideal way forward may be an initial well-defined cohort study within a mandatory fast-track protocol, followed by a well-defined RCT and then continued monitoring through large scale detailed prospective observational studies.[50]

Although the construction of a preoperative risk-score was possible the diversity of complications limited its immediate clinical value. Some of this may be addressed by inclusion of factors which have not been considered in the present studies. Thus, this thesis has not focused on risk-factors related to the THA and TKA procedure, such as surgeon volume,[404] surgical approach[405] and type of prosthesis.[406] Furthermore, postoperative risk-scores such as the Surgical APGAR-score[21] or PostOperative Morbidity Survey (POMS)[407] have shown a correlation with postoperative mortality and morbidity. However, neither the Surgical APGAR-score or POMS have been validated in fast-track THA and TKA, and both mortality and POMS related morbidity in orthopaedic surgery is low. Other promising approaches include the use of preoperative blood samples to identify patients with increased inflammatory responses to surgical stress and consequently delayed recovery.[408] Another limitation to the proposed risk-score for fast-track THA and TKA is the lack of an independent validation. However, the risk score did correlate with reduced number of "days alive and out of hospital" compared to "low-risk patients, [82] although whether this outcome parameter adds to the all-ready established knowledge remains questionable. Furthermore, a recent study from the LCDB in patients having surgery between 2016-2017 found mostly the same risk-factors to predict a LOS >2 days.[409]

The next logical step for improvement is appropriate interventions in "high-risk" patients. In this context, both pre- and postoperative anaemia have consistently been demonstrated to be significant risk-factors for postoperative morbidity leading to increased LOS and readmissions after fast-track THA and TKA.[58, 74, 80] As the benefits of perioperative blood-management and

correction of both pre and postoperative anaemia are already recognized strategies for improving postoperative outcomes,[289, 410] this is an obvious area of interest.
The use of preoperative glucocorticoids may provide other benefits than pain reduction,[92, 411] as it is associated with a reduction in inflammatory markers after surgery.[412] Consequently, it could be speculated that these may provide general benefits on the broad spectrum of medical morbidity, as suggested by study XI of this thesis. Importantly, concerns about increased number of prosthetic infections with a single dose has not been confirmed.[81] Other potential strategies include de-prescription in elderly patients to reduce risk of falling[293] or adverse events due to polypharmacy,[291] and attempts to optimize pre-[189] and postoperative[290] balance function. As pointed out in several studies, preoperative use of psychotropic drugs pose a potential due to increased fall-episodes[61, 68, 190] and bleeding.[69, 370] However, SSRIs may have a role in the analgesic treatment of high-pain responders.[411]
Finally, the use of anaesthesiologists, geriatricians or medical internists in the immediate postoperative period is sporadic,[231,233] despite initial promising results across different surgical specialties.[242,243] Thus, studies with a systematic approach towards involvement of other specialties and focusing on the “high-risk” patients are needed. However, it is crucial that such studies are performed within an updated evidence fast-track protocol.[114]
The use of thromboprophylaxis also remains an area of important future work. Although it seems justifiable to conclude that there is no increased risk of VTEs with in-hospital thromboprophylaxis only when LOS is ≤ 5 days, the continued reduction in LOS as well as increasing use of outpatient procedures and consequently only 1-2 doses of thromboprophylaxis[62, 139] questions whether thromboprophylaxis is needed at all.[147, 164] Furthermore, there is a current shift in Europe towards increased recognition of aspirin as thromboprophylaxis,[157, 413] but with a lack of studies in fast-track THA and TKA. The same goes for revision and simultaneous bilateral procedures, where there are only a few detailed studies on risk of VTE within a fast-track protocol.[414-417] However, based on the findings of the present thesis within primary unilateral fast-track THA and TKA, focus should now be on preoperative identification of patients with increased risk of thromboembolic events,[74] in whom standard prophylactic regimens may be inadequate.[62, 74]
In summary, much has been achieved with regards to describing and understanding postoperative morbidity and preoperative risk-factors in fast-track THA and TKA. At the same time, there has been an encouraging continuous decline in LOS without increase in readmissions or mortality. However, we now face a need to look back into the pathophysiology of recovery and use the gained knowledge to devise rational strategies for pre- and postoperative interventions aimed at reducing readmissions in selected “high-risk” patients.[418]

English Summary

This thesis on postoperative morbidity and associated risk-factors in fast-track total hip (THA) and knee arthroplasty (TKA) is based on a continuously expanding cohort of fast-track THA and TKA patients from a multicentre collaboration with prospective data on patient characteristics, prescription data from the Danish National Database on Reimbursed Prescriptions and complete follow-up through the Danish National Patient Registry and review of medical records. Although there are limitations associated with the use of this type of observational design, (e.g. subjective evaluation of medical records,[107] unmeasured confounding,[45] missing data[45] and overlapping study periods[128]), such an approach may also provide valuable "real life" data not available in randomized controlled trials.[45, 52, 53] Thus, the use of detailed individual "micro" data from the medical records may contribute with details unavailable in BIG-DATA studies.[103] This is especially relevant in THA and TKA where postoperative morbidity is generally low.

By analysing detailed information on the causes of length of stay (LOS) >4 days and readmissions it was found that the majority of complications are a result of organ dysfunction related to the surgical stress-response rather than direct surgical complications,[56, 65, 245] and most pronounced in patients ≥85 years.[75] It was found that the total 90-day incidence of postoperative thromboembolic events is about 1%, and with about 0.4% venous thromboembolisms despite only in-hospital thromboprophylaxis when LOS is ≤ 5 days and excluding the about 4% of patients with preoperative anitcoagulants.[62, 139] Furthermore, the occurrence of myocardial infarction and cerebral stroke within the first month of surgery was 0.1%,[74] which is about half of previously reported.[26, 186] When investigating falls after discharge it was found that these occurred in 1.6% of patients, but about 40% of falls after the first postoperative month appear unrelated to surgery as they are due to physical activity or intrinsic factors.[61] Compared to reported fall-rates of up to 2.7% within the first few postoperative days,[220] there does not appear to be an increased number of fall-related admissions after fast-track THA and TKA. Total 90-days mortality was found to be about 0.3%, but only about 0.2% considered related to surgery.[71] Also, initial organ dysfunction leading to mortality was mostly from different organ systems than the organ-related immediate cause of death.[71]

When evaluating the distributions and developments in LOS, readmissions and mortality over time, there was a continuous reduction in median LOS from 3 days in 2010 to 1 day in 2017.[245] This was mainly driven by a reduction in patients with LOS > 4 days and no recorded morbidity. However, there was also fewer "medical" complications from 2014 and onwards, coinciding with the introduction of high-dose methylprednisolone as part of the fast-track protocol.[81] Despite the reduction in patients with LOS >4 days, no certain reductions were found with regards to 90-days readmissions or mortality which remained stable around 8.5% and 0.2%, respectively.[245]

When investigating preoperative risk factors associated with increased LOS or readmissions, it was found that conventional risk factors such as age, diabetes and cardiac disease may have less influence when using a fast-track protocol than in a conventional surgical setting[56, 65, 67] and that other characteristics such as psychiatric disorder with psychopharmacological medication

(PsD)[68] and anaemia[58, 65] may be of more importance. PsD in particular was associated with increased risk of having LOS >4 days, readmissions and potentially even surgery-related mortality.[68] However, increased focus on patients ≥85 years is also needed as about 25% were readmitted within 90-days and in-hospital mortality was about 1%.[75] Consequently, patients ≥85 years may be considered "high-risk" despite most having short LOS and with discharge to own home. Future studies, especially on fall-prevention and perioperative blood management are needed in this particular population, which often has been neglected from randomized trials.[262] It was also demonstrated that a short LOS does not increase the risk of readmissions within 90-days of surgery[56, 61] and that the use of a fast-track protocol is feasible and safe in unselected patients regardless of age and comorbidity.

Finally, in an attempt to define the "high-risk" population for potentially preventable medical complications, it was found that patients having two or more of the following: age >80 years, use of walking aids, use of anticoagulants, anaemia, pulmonary disease or PsD, accounted for about 60% of complications, but only present in about 20% of patients.[65] However, the diversity of complications necessitates multimodal rather than singular interventions, i.e. postoperative rounds by anaesthetists, geriatricians or other relevant specialties.

In conclusion, the studies of this thesis were the first to provide a detailed evaluation of postoperative complications after fast-track THA and TKA. Furthermore, it was possible to document a continued reduction in LOS, but not readmissions over time. Finally, although it was found that the importance of several conventional risk factors may be reduced, patients with specific combinations of risk-factors remain a challenge. These patients are especially vulnerable with regards to "medical" morbidity caused by surgery-induced organ dysfunction, needing focused multimodal perioperative interventions potentially requiring a combination of detailed observational and pragmatic randomized clinical trials.[50]

Danish summary

Denne afhandling omhandlende postoperativ morbiditet og associerede risikofaktorer efter fast-track total hofte- (THA) og knæalloplastik (TKA), er baseret på en kontinuerligt voksende kohorte af fast-track THA or TKA patienter fra et multicenter samarbejde med prospektive data ang. patient karakteristika, recept data fra Dansk National Database for Tilskudsberettigede Recepter og komplet follow-up gennem Landspatient Registret og journal gennemgang. På trods af begrænsningerne ved denne type observationelt design (f.eks. subjektiv vurdering af journaler,[107] umålt confounding,[45] manglende data[45] og overlappende studie perioder[128]), kan en sådan tilgang også give værdifulde "real life" data som ikke kan fås gennem randomiserede kontrollerede undersøgelser.[45, 52, 53] Således kan brugen af detaljerede individuelle "mikro" data gennem journalopslag bidrage med detaljer som ikke er tilgængelige i BIG-DATA studier.[103]
Dette er særlig relevant ved THA og TKA hvor den postoperative morbiditet generelt er lav.
Ved at analysere detaljeret information om årsager til indlæggelses tid (LOS) >4 dage og genindlæggelser, blev det fundet at størstedelen af komplikationer opstår på baggrund af organdysfunktion relateret til det kirurgiske stress-respons snarere end pga. direkte kirurgiske komplikationer,[56, 65, 245] og at dette er mest udtalt hos patienter ældre end 85 år.[75] Det blev fundet at 90-dags incidensen for postoperative thromboemboliske events generelt er omkring 1%, og med kun 0.4% venøse thromboembolier på trods af thromoboseprofylakse kun under indlæggelse når LOS er ≤ 5 dage og ekskluderende de ca. 4% af patienter med præoperativ brug af antikoagulantia.[62, 139] Yderligere opstår myokardieinfarkt og cerebralt stroke kun hos 0,1% inden for den første postoperative måned,[74] hvilket er omtrent halvdelen af tidligere rapporteret.[26, 186] Da man undersøgte fald efter udskrivelse fandt man at dette skete for 1.6% af patienterne, men omkring 40% af fald efter den første postoperative måned lader ikke til at være relaterede til kirurgien da de opstår pga. fysisk aktivitet eller udefrakommende faktorer.[61]
Sammenlignet med rapporterede fald-rater på op til 2.7% inde for de første få postoperative dage,[220] lader der ikke til at være et øget antal fald-relaterede indlæggelser efter fast-track THA og TKA. Total 90-dages mortalitet var omkring 0.3 % men kun 0.2% må betragtes som sikkert relateret til operationen.[71] Yderligere fandtes det at initial organ-dysfunktion ofte var fra et andet organsystem end den organ-relaterede umiddelbare primære dødsårsag.[71]
Ved at evaluerer distribution og udvikling for hhv. LOS, genindlæggelser og mortalitet over tid, fandtes en kontinuerlig reduktion i LOS fra median 3 dage i 2010 til 1 dag i 2017.[245] Dette var primært grundet en reduktion af patienter med LOS > 4 dage og uden beskrevet morbiditet. Dog var der også færre "medicinske" komplikationer fra 2014 og frem, sammenfaldende med introduktionen af høj-dosis steroid som en del af fast-track protokollen.[81] Trods færre patienter med LOS >4 days, var der ingen sikker reduktion mht. 90-dages genindlæggelser eller mortalitet som lå stabilt omkring hhv. 8.5% og 0.3%.[245]
Ved undersøgelse af præoperative risikofaktorer associerede til øget indlæggelsestid og genindlæggelser, blev det fundet at konventionelle risikofaktorer såsom alder, diabetes og hjertesygdom, muligvis har mindre betydning i et fast-track setup end ved konventionel kirurgisk behandling,[56, 65, 67] og at andre karakteristika såsom psykiatrisk sygdom med farmakologisk behandling (PsD)[68] og anæmi[58, 65] er af større betydning. Særlig PsD var associeret med øget risiko for LOS >4 dage, genindlæggelser og potentielt endda kirurgi-

relateret mortalitet.[68] Dog er øget fokus på patienter ≥85 år også nødvendigt, da omkring 25% blev genindlagt inden for 90 dage og hospitals mortaliteten er omkring 1%.[75] Således kan patienter ≥85 år betragtes som "høj-risiko", trods at de fleste har kort LOS og bliver udskrevet til eget hjem. Fremtidige undersøgelser, især mhp. fald-forebyggelse og perioperativ blod management er nødvendige for denne særlige gruppe, som ofte er blevet udelukket fra randomiserede studier.[262] Det blev også demonstreret at kort LOS ikke øget risikoen for genindlæggelse inde for 90-dage efter kirurgi.[56, 61] og at brugen af en fast-track protokol er mulig og sikker hos uselekteretede patienter, uagtet alder eller komorbiditet.

Endelig, blev det i et forsøg på at definere "høj-risiko" populationen for potentielt undgåelige medicinske komplikationer, fundet at patienter med to eller flere af flg. : alder >80 år, brug af gangredskab, behandling med antikoagulantia, anæmi, behandlet lungesygdom eller PsD udgjorde omkring 60% af disse.[65] Men, variationen af komplikationer nødvendiggør snarere multimodale end enkelt interventioner, f.eks. postoperative stuegang v. anæstesiolog, geriater eller andre relevante specialer.

Som konklusion kan siges at studierne i denne tese var de første til at give en detaljeret oversigt over postoperativ morbiditet efter fast-track THA and TKA. Herudover var det muligt at dokumentere en kontinuerlig reduktion i indlæggelsestid, men ikke genindlæggelser over tid. Slutteligt må nævnes at selvom vigtigheden af flere konventionelle risikofaktorer lader til at være reduceret, er patienter med specifikke kombinationer af risikofaktorer fortsat en udfordring. Disse patienter er særlig sårbare mht. "medicinsk" morbiditet forårsaget af kirurgi-induceret organ dysfunktion med behov for fokuserede multimodale perioperative interventioner hvilket kan nødvendiggøre en kombination af detaljerede observationelle og pragmatiske randomiserede kliniske studier.

References

references

1 Kehlet H. Fast-track hip and knee arthroplasty. *Lancet* 2013; **381**: 1600-2
2 Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *The British journal of surgery* 2014; **101**: 172-88
3 Hu ZC, He LJ, Chen D, et al. An enhanced recovery after surgery program in orthopedic surgery: a systematic review and meta-analysis. *Journal of orthopaedic surgery and research* 2019; **14**: 77
4 Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *AnnSurg* 2008; **248**: 189-98
5 Pearse RM, Holt PJ, Grocott MP. Managing perioperative risk in patients undergoing elective non-cardiac surgery. *BMJ* 2011; **343**: d5759
6 Klapwijk LCM, Mathijssen NMC, van Egmond JC, Verbeek BM, Vehmeijer SBW. The first 6 weeks of recovery after primary total hip arthroplasty with fast track. *Acta orthopaedica* 2018; **89**: 140
7 Amlie E, Lerdal A, Gay CL, Hovik O, Nordsletten L, Dimmen S. A Trend for Increased Risk of Revision Surgery due to Deep Infection following Fast-Track Hip Arthroplasty. *Advances in orthopedics* 2016; **2016**: 7901953
8 Pamilo KJ, Torkki P, Peltola M, Pesola M, Remes V, Paloneva J. Fast-tracking for total knee replacement reduces use of institutional care without compromising quality. *Acta orthopaedica* 2018; **89**: 184-9
9 Pamilo KJ, Torkki P, Peltola M, Pesola M, Remes V, Paloneva J. Reduced length of uninterrupted institutional stay after implementing a fast-track protocol for primary total hip replacement. *Acta orthopaedica* 2018; **89**: 10-6
10 Raphael M, Jaeger M, van VJ. Easily adoptable total joint arthroplasty program allows discharge home in two days. *CanJAnaesth* 2011; **58**: 902-10
11 Starks I, Wainwright TW, Lewis J, Lloyd J, Middleton RG. Older patients have the most to gain from orthopaedic enhanced recovery programmes. *Age Ageing* 2014; **43**: 642-8
12 den Hartog YM, Mathijssen NM, Vehmeijer SB. Reduced length of hospital stay after the introduction of a rapid recovery protocol for primary THA procedures. *Acta Orthop* 2013; **84**: 444-7
13 Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. *Acta Orthop* 2008; **79**: 168-73
14 Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. *Acta Orthop* 2010; **81**: 599-605
15 Malviya A, Martin K, Harper I, et al. Enhanced recovery program for hip and knee replacement reduces death rate. *Acta Orthop* 2011; **82**: 577-81
16 van WC, Bennett C, Forster AJ. Administrative database research infrequently used validated diagnostic or procedural codes. *JClinEpidemiol* 2011; **64**: 1054-9

17 Kehlet H, Mythen M. Why is the surgical high-risk patient still at risk? *BrJAnaesth* 2011; **106**: 289-91
18 Keats AS. The ASA classification of physical status--a recapitulation. *Anesthesiology* 1978; **49**: 233-6
19 Ackland GL, Harris S, Ziabari Y, Grocott M, Mythen M, Investigators SO. Revised cardiac risk index and postoperative morbidity after elective orthopaedic surgery: a prospective cohort study. *Br J Anaesth* 2010; **105**: 744-52
20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *JChronicDis* 1987; **40**: 373-83
21 Reynolds PQ, Sanders NW, Schildcrout JS, Mercaldo ND, St Jacques PJ. Expansion of the surgical Apgar score across all surgical subspecialties as a means to predict postoperative mortality. *Anesthesiology* 2011; **114**: 1305-12
22 Hyder JA, Wakeam E, Habermann EB, Hess EP, Cima RR, Nguyen LL. Derivation and validation of a simple calculator to predict home discharge after surgery. *JAmCollSurg* 2014; **218**: 226-36
23 Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *JAmCollSurg* 2013; **217**: 833-42
24 Hammill BG, Curtis LH, nett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008; **108**: 559-67
25 Memtsoudis SG, la Valle AG, Besculides MC, Esposito M, Koulouvaris P, Salvati EA. Risk factors for perioperative mortality after lower extremity arthroplasty: a population-based study of 6,901,324 patient discharges. *JArthroplasty* 2010; **25**: 19-26
26 Belmont PJ, Jr., Goodman GP, Kusnezov NA, et al. Postoperative myocardial infarction and cardiac arrest following primary total knee and hip arthroplasty: rates, risk factors, and time of occurrence. *JBone Joint SurgAm* 2014; **96**: 2025-31
27 de Wit M, Goldberg S, Hussein E, Neifeld JP. Health care-associated infections in surgical patients undergoing elective surgery: are alcohol use disorders a risk factor? *JAmCollSurg* 2012; **215**: 229-36
28 Bolognesi MP, Marchant MH, Jr., Viens NA, Cook C, Pietrobon R, Vail TP. The impact of diabetes on perioperative patient outcomes after total hip and total knee arthroplasty in the United States. *J Arthroplasty* 2008; **23**: 92-8
29 Rubinsky AD, Sun H, Blough DK, et al. AUDIT-C alcohol screening results and postoperative inpatient health care use. *J AmCollSurg* 2012; **214**: 296-305
30 Maempel JF, Riddoch F, Calleja N, Brenkel IJ. Longer hospital stay, more complications, and increased mortality but substantially improved function after knee replacement in older patients. *Acta orthopaedica* 2015; **86**: 451-6
31 Moller AM, Villebro N, Pedersen T, Tonnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 2002; **359**: 114-7
32 Smith ID, Elton R, Ballantyne JA, Brenkel IJ. Pre-operative predictors of the length of hospital stay in total knee replacement. *JBone Joint SurgBr* 2008; **90**: 1435-40
33 Ljungqvist O. Jonathan E. Rhoads lecture 2011: Insulin resistance and enhanced recovery after surgery. *J ParenterEnteral Nutr* 2012; **36**: 389-98

34 Ren L, Zhu D, Wei Y, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. *World journal of surgery* 2012; **36**: 407-14
35 Scheidegger D, Bentz L, Piolino G, Pusterla C, Gigon JP. Influence of early mobilisation of pulmonary function in surgical patients. *EurJ Intensive Care Med* 1976; **2**: 35-40
36 Mynster T, Jensen LM, Jensen FG, Kehlet H, Rosenberg J. The effect of posture on late postoperative oxygenation. *Anaesthesia* 1996; **51**: 225-7
37 Khullar D, Maa J. The impact of smoking on surgical outcomes. *J AmCollSurg* 2012; **215**: 418-26
38 Pearse EO, Caldwell BF, Lockwood RJ, Hollard J. Early mobilisation after conventional knee replacement may reduce the risk of postoperative venous thromboembolism. *JBone Joint SurgBr* 2007; **89**: 316-22
39 Memtsoudis SG, Poeran J, Kehlet H. Enhanced Recovery After Surgery in the United States: From Evidence-Based Practice to Uncertain Science? *JAMA* 2019; **321**: 1049-50
40 Sessler DI. Implications of Practice Variability. *Anesthesiology* 2020; **132**: 606-8
41 Berg U, BuLow E, Sundberg M, Rolfson O. No increase in readmissions or adverse events after implementation of fast-track program in total hip and knee replacement at 8 Swedish hospitals: An observational before-and-after study of 14,148 total joint replacements 2011-2015. *Acta orthopaedica* 2018; **89**: 522-7
42 Winther SB, Foss OA, Wik TS, et al. 1-year follow-up of 920 hip and knee arthroplasty patients after implementing fast-track. *Acta Orthop* 2015; **86**: 78-85
43 Khan SK, Malviya A, Muller SD, et al. Reduced short-term complications and mortality following Enhanced Recovery primary hip and knee arthroplasty: results from 6,000 consecutive procedures. *Acta Orthop* 2014; **85**: 26-31
44 Savaridas T, Serrano-Pedraza I, Khan SK, Martin K, Malviya A, Reed MR. Reduced medium-term mortality following primary total hip and knee arthroplasty with an enhanced recovery program. *Acta Orthop* 2013; **84**: 40-3
45 Sessler DI, Imrey PB. Clinical Research Methodology 2: Observational Clinical Research. *AnesthAnalg* 2015; **121**: 1043-51
46 Thomas L, Peterson ED. The value of statistical analysis plans in observational research: defining high-quality research from the start. *Jama* 2012; **308**: 773-4
47 Sessler DI, Imrey PB. Clinical Research Methodology 3: Randomized Controlled Trials. *Anesthesia and analgesia* 2015; **121**: 1052-64
48 Jones DS, Podolsky SH. The history and fate of the gold standard. *Lancet* 2015; **385**: 1502-3
49 Sessler DI. Negative Trials, and What to Do with Them?: First, Stop Calling Them "Negative". *Anesthesiology* 2020; **132**: 221-4
50 Joshi GP, Alexander JC, Kehlet H. Large pragmatic randomised controlled trials in peri-operative decision making: are they really the gold standard? *Anaesthesia* 2018; **73**: 799-803
51 Boney O, Moonesinghe SR, Myles PS, Grocott MP. Standardizing endpoints in perioperative research. *CanJAnaesth* 2016; **63**: 159-68
52 Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. *The New England journal of medicine* 2017; **377**: 465-75
53 Berwick DM. The science of improvement. *JAMA* 2008; **299**: 1182-4

54 Merkow RP, Ko CY. Evidence-based medicine in surgery: the importance of both experimental and observational study designs. *JAMA* 2011; **306**: 436-7
55 McIsaac DI. Real-world evaluation of enhanced recovery after surgery: big data under the microscope. *Br J Anaesth* 2020; **124**: 510-2
56 Jorgensen CC, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. *BrJ Anaesth* 2013; **110**: 972-80
57 Jorgensen CC, Kehlet H. Outcomes in smokers and alcohol users after fast-track hip and knee arthroplasty. *Acta AnaesthesiolScand* 2013; **57**: 631-8
58 Jans O, Jorgensen C, Kehlet H, Johansson PI. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. *Transfusion* 2014; **54**: 717-26
59 Jorgensen CC, Jans O, Kehlet H. Preoperative anaemia and newly diagnosed cancer 1 year after elective total hip and knee arthroplasty. *Vox sanguinis* 2015; **109**: 62-70
60 Jorgensen CC, Kjaersgaard-Andersen P, Solgaard S, Kehlet H. Hip dislocations after 2,734 elective unilateral fast-track total hip arthroplasties: incidence, circumstances and predisposing factors. *ArchOrthopTrauma Surg* 2014; **134**: 1615-22
61 Jorgensen CC, Kehlet H. Fall-related admissions after fast-track total hip and knee arthroplasty - cause of concern or consequence of success? *Clin IntervAging* 2013; **8**: 1569-77
62 Jorgensen CC, Jacobsen MK, Soeballe K, et al. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. *BMJ Open* 2013; **3**: e003965
63 Gylvin SH, Jorgensen CC, Fink-Jensen A, Gislason GH, Kehlet H. The Role of Psychiatric Diagnoses for Outcome After Hip and Knee Arthroplasty. *J Arthroplasty* 2017; **32**: 3611-5
64 Bjerregaard LS, Jorgensen CC, Kehlet H. Serious renal and urological complications in fast-track primary total hip and knee arthroplasty; a detailed observational cohort study. *Minerva Anestesiol* 2016
65 Jorgensen CC, Petersen MA, Kehlet H. Preoperative prediction of potentially preventable morbidity after fast-track hip and knee arthroplasty: a detailed descriptive cohort study. *BMJ Open* 2016; **6**: e009813
66 Husted H, Jorgensen CC, Gromov K, Troelsen A. Low manipulation prevalence following fast-track total knee arthroplasty. *Acta Orthop* 2015; **86**: 86-91
67 Jorgensen CC, Madsbad S, Kehlet H. Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. *AnesthAnalg* 2015; **120**: 230-8
68 Jorgensen CC, Knop J, Nordentoft M, Kehlet H. Psychiatric Disorders and Psychopharmacologic Treatment as Risk Factors in Elective Fast-track Total Hip and Knee Arthroplasty. *Anesthesiology* 2015; **123**: 1281-91
69 Gylvin SH, J›rgensen CC, Johansson PI, Kehlet H. Psychopharmacological treatment and blood transfusion in fast-track total hip and knee arthroplasty. *Transfusion* 2017
70 Jorgensen CC, Kehlet H, Lundbeck Foundation Center for Fast-Track H, Knee Replacement Collaborative G. Thromboembolic and major bleeding events in relation to perioperative bridging of vitamin K antagonists in 649 fast-track total hip and knee arthroplasties. *Acta orthopaedica* 2017; **88**: 55-61

71 Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative g. Time course and reasons for 90-day mortality in fast-track hip and knee arthroplasty. *Acta Anaesthesiol Scand* 2017; **61**: 436-44
72 Petersen PB, Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Delirium after fast-track hip and knee arthroplasty - a cohort study of 6331 elderly patients. *Acta Anaesthesiol Scand* 2017; **61**: 767-72
73 Husted H, Jorgensen CC, Gromov K, Kehlet H. Does BMI influence hospital stay and morbidity after fast-track hip and knee arthroplasty? *Acta Orthop* 2016; **87**: 466-72
74 Jorgensen CC, Kehlet H. Early thromboembolic events <=1week after fast-track total hip and knee arthroplasty. *ThrombRes* 2016; **138**: 37-42
75 Pitter FT, Jorgensen CC, Lindberg-Larsen M, Kehlet H. Postoperative morbidity and discharge destinations after fast-track hip and knee arthroplasty in patients older than 85 years. *AnesthAnalg* 2016; **122**: 1807-15
76 Lindberg-Larsen M, Jorgensen CC, Solgaard S, et al. Increased risk of intraoperative and early postoperative periprosthetic femoral fracture with uncemented stems. *Acta orthopaedica* 2017; **88**: 390-4
77 Jorgensen CC, Petersen M, Kehlet H, Aasvang EK. Analgesic consumption trajectories in 8975 patients 1 year after fast-track total hip or knee arthroplasty. *European journal of pain (London, England)* 2018
78 Petersen PB, Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip Knee Replacement Collaborative G. Venous Thromboembolism despite Ongoing Prophylaxis after Fast-Track Hip and Knee Arthroplasty: A Prospective Multicenter Study of 34,397 Procedures. *Thrombosis and haemostasis* 2019; **119**: 1877-85
79 Petersen PB, Kehlet H, Jorgensen CC, Lundbeck Foundation Center for Fast-Track H, Knee Replacement Collaborative G. 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**: 743-9 e2
80 Petersen PB, Kehlet H, Jorgensen CC, Lundbeck Foundation Center for Fast-track H, Knee Replacement Collaborative G. 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 orthopaedica* 2018; **89**: 603-9
81 Jorgensen CC, Pitter FT, Kehlet H, Lundbeck Foundation Center for Fast-track H, Knee Replacement Collaborative G. Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement. *Br J Anaesth* 2017; **119**: 267-75
82 Jorgensen CC, Petersen PB, Kehlet H, Lundbeck Foundation Center for Fast-track H, Knee Replacement Collaborative G. Days alive and out of hospital after fast-track total hip and knee arthroplasty: an observational cohort study in 16 137 patients. *Br J Anaesth* 2019; **123**: 671-8
83 Lindberg-Larsen M, Petersen PB, Jorgensen CC, et al. Postoperative 30-day complications after cemented/hybrid versus cementless total hip arthroplasty in osteoarthritis patients > 70 years. *Acta orthopaedica* 2020; **91**: 286-92
84 Petersen PB, Jorgensen CC, Kehlet H, Lundbeck Foundation Center for Fast-track H, Knee Replacement collaborative g. Temporal trends in length of stay and readmissions after fast-track hip and knee arthroplasty. *Danish medical journal* 2019; **66**

85 Petersen PB, Jorgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Fast-track hip and knee arthroplasty in older adults-a prospective cohort of 1,427 procedures in patients >/=85 years. *Age Ageing* 2020; **49**: 425-31
86 Gromov K, Jorgensen CC, Petersen PB, et al. Complications and readmissions following outpatient total hip and knee arthroplasty: a prospective 2-center study with matched controls. *Acta orthopaedica* 2019; **90**: 281-5
87 Petersen PB, Kehlet H, Jorgensen CC, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Improvement in fast-track hip and knee arthroplasty: a prospective multicentre study of 36,935 procedures from 2010 to 2017. *Scientific reports* 2020; **10**: 21233
88 The Danish Knee R. Annual Report 2013. *https://wwwkneedk/groups/dkr/pdf/DKR_2013pdf* 2015
89 The Danish Hip Arthroplasty R. Danish Hip Arthroplasty Registry, annual report 2013. 2013.
90 Bjerregaard LS, Bogo S, Raaschou S, et al. Incidence of and risk factors for postoperative urinary retention in fast-track hip and knee arthroplasty. *Acta orthopaedica* 2015; **86**: 183-8
91 Husted H, Solgaard S, Hansen TB, Soballe K, Kehlet H. Care principles at four fast-track arthroplasty departments in Denmark. *DanMedBull* 2010; **57**: A4166
92 Lunn TH, Kristensen BB, Andersen LO, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. *BrJAnaesth* 2011; **106**: 230-8
93 Lunn TH, Husted H, Laursen MB, Hansen LT, Kehlet H. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: a randomized, double-blind, placebo-controlled dose-finding study. *Pain* 2015; **156**: 2438-48
94 Bjerregaard LS, Hornum U, Troldborg C, Bogoe S, Bagi P, Kehlet H. Postoperative Urinary Catheterization Thresholds of 500 versus 800 ml after Fast-track Total Hip and Knee Arthroplasty: A Randomized, Open-label, Controlled Trial. *Anesthesiology* 2016; **124**: 1256-64
95 Gromov K, Kjaersgaard-Andersen P, Revald P, Kehlet H, Husted H. Feasibility of outpatient total hip and knee arthroplasty in unselected patients - a prospective two-center study. *Acta Orthop* 2017
96 Wainwright TW, Gill M, McDonald DA, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. *Acta orthopaedica* 2020; **91**: 3-19
97 Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *ClinEpidemiol* 2012; **4**: 303-13
98 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159-74
99 Gad BV, Higuera CA, Klika AK, Elsharkawy KA, Barsoum WK. Validity of patient-reported comorbidities before total knee and hip arthroplasty in patients older than 65 years. *J Arthroplasty* 2012; **27**: 1750-6
100 Davis CL, Pierce JR, Henderson W, et al. Assessment of the reliability of data collected for the Department of Veterans Affairs national surgical quality improvement program. *J AmCollSurg* 2007; **204**: 550-60

101 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical epidemiology* 2015; **7**: 449-90
102 Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjonneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol* 2010; **63**: 223-8
103 Moonesinghe SR. Innovation good ... evaluation essential A plea for formal evaluation of new pathways of care and ways of working. *BrJAnaesth* 2016; **116**: 151-3
104 Griffin FA RR. IHI Global Trigger Tool for Measuring Adverse Events. *IHI Innovation Series white paper* 2009:
105 van WC, Jennings A, Taljaard M, et al. Incidence of potentially avoidable urgent readmissions and their relation to all-cause urgent readmissions. *CMAJ* 2011; **183**: E1067-E72
106 van WC, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. *CMAJ* 2011; **183**: E391-E402
107 van WC, Jennings A, Forster AJ. A meta-analysis of hospital 30-day avoidable readmission rates. *JEvalClinPract* 2012; **18**: 1211-8
108 Magneli M, Unbeck M, Rogmark C, et al. Validation of adverse events after hip arthroplasty: a Swedish multi-centre cohort study. *BMJ open* 2019; **9**: e023773
109 Dalsgaard EM, Witte DR, Charles M, Jorgensen ME, Lauritzen T, Sandbaek A. Validity of Danish register diagnoses of myocardial infarction and stroke against experts in people with screen-detected diabetes. *BMC public health* 2019; **19**: 228
110 Sebastian AS, Polites SF, Glasgow AE, Habermann EB, Cima RR, Kakar S. Current Quality Measurement Tools Are Insufficient to Assess Complications in Orthopedic Surgery. *The Journal of hand surgery* 2017; **42**: 10-5 e1
111 Lawson EH, Louie R, Zingmond DS, et al. A comparison of clinical registry versus administrative claims data for reporting of 30-day surgical complications. *Annals of surgery* 2012; **256**: 973-81
112 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *AnnSurg* 2004; **240**: 205-13
113 Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *AnnSurg* 2014; **260**: 757-62
114 Kehlet H, Jorgensen CC. Advancing Surgical Outcomes Research and Quality Improvement Within an Enhanced Recovery Program Framework. *AnnSurg* 2016; **264**: 237-8
115 Merkow RP, Ju MH, Chung JW, et al. Underlying reasons associated with hospital readmission following surgery in the United States. *Jama* 2015; **313**: 483-95
116 Schairer WW, Sing DC, Vail TP, Bozic KJ. Causes and frequency of unplanned hospital readmission after total hip arthroplasty. *ClinOrthopRelat Res* 2014; **472**: 464-70
117 Belmont PJ, Jr., Goodman GP, Hamilton W, Waterman BR, Bader JO, Schoenfeld AJ. Morbidity and mortality in the thirty-day period following total hip arthroplasty: risk factors and incidence. *JArthroplasty* 2014; **29**: 2025-30

118 Belmont PJ, Jr., Goodman GP, Waterman BR, Bader JO, Schoenfeld AJ. Thirty-day postoperative complications and mortality following total knee arthroplasty: incidence and risk factors among a national sample of 15,321 patients. *JBone Joint SurgAm* 2014; **96**: 20-6
119 O'Malley NT, Fleming FJ, Gunzler DD, Messing SP, Kates SL. Factors independently associated with complications and length of stay after hip arthroplasty: analysis of the National Surgical Quality Improvement Program. *JArthroplasty* 2012; **27**: 1832-7
120 Gronbeck C, Cote MP, Lieberman JR, Halawi MJ. Risk stratification in primary total joint arthroplasty: the current state of knowledge. *Arthroplasty today* 2019; **5**: 126-31
121 Sahota S, Lovecchio F, Harold RE, Beal MD, Manning DW. The Effect of Smoking on Thirty-Day Postoperative Complications After Total Joint Arthroplasty: A Propensity Score-Matched Analysis. *J Arthroplasty* 2018; **33**: 30-5
122 Kurtz SM, Lau EC, Ong KL, Adler EM, Kolisek FR, Manley MT. Which Clinical and Patient Factors Influence the National Economic Burden of Hospital Readmissions After Total Joint Arthroplasty? *Clinical orthopaedics and related research* 2017; **475**: 2926-37
123 Bryant D, Havey TC, Roberts R, Guyatt G. How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. *The Journal of bone and joint surgery American volume* 2006; **88**: 41-5
124 Ravi B, Croxford R, Hawker G. Exclusion of patients with sequential primary total joint arthroplasties from arthroplasty outcome studies biases outcome estimates: a retrospective cohort study. *Osteoarthritis and cartilage* 2013; **21**: 1841-8
125 Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; **59**: 1087-91
126 Lee KJ, Carlin JB. Recovery of information from multiple imputation: a simulation study. *Emerging themes in epidemiology* 2012; **9**: 3
127 Albert AA, J. A. On the Existence of Maximum Likelihood Estimates in Logistic Regression Models. *Biometrika* 1984; **71**: 1-10
128 Harriri A. BB, W. The Overlapping Data Problem. *Quantitative and Qualitative Analysis in Social Sciences* 2009; **3**: 78-115
129 Januel JM, Chen G, Ruffieux C, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. *JAMA* 2012; **307**: 294-303
130 Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e278S-e325S
131 NICE. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital Appendices E – I. 2010. Available from https://www.nice.org.uk/guidance/cg92/evidence/appendices-ei-pdf-243920127 (accessed 12-12 2012)
132 Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *NEnglJ Med* 2010; **363**: 2487-98
133 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010; **375**: 807-15

134 Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009; **373**: 1673-80
135 Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *NEnglJ Med* 2008; **358**: 2765-75
136 Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; **372**: 31-9
137 Kehlet H, Thienpont E. Fast-track knee arthroplasty -- status and future challenges. *Knee* 2013; **20 Suppl 1**: S29-S33
138 Memtsoudis SG, Sun X, Chiu YL, et al. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology* 2013; **118**: 1046-58
139 Petersen PB, Kehlet H, Jorgensen CC, Lundbeck Foundation Centre for Fast-track H, Knee Replacement Collaborative G. Safety of In-Hospital Only Thromboprophylaxis after Fast-Track Total Hip and Knee Arthroplasty: A Prospective Follow-Up Study in 17,582 Procedures. *Thrombosis and haemostasis* 2018; **118**: 2152-61
140 Alatri A, Iorio A, Agnelli G. Choice of end-points in assessing the efficacy of post-discharge prophylaxis for venous thromboembolism. *Thrombosis and haemostasis* 1998; **79**: 234
141 Jameson SS, Bottle A, Malviya A, Muller SD, Reed MR. The impact of national guidelines for the prophylaxis of venous thromboembolism on the complications of arthroplasty of the lower limb. *J Bone Joint SurgBr* 2010; **92**: 123-9
142 Jameson SS, Rymaszewska M, Hui AC, James P, Serrano-Pedraza I, Muller SD. Wound complications following rivaroxaban administration: a multicenter comparison with low-molecular-weight heparins for thromboprophylaxis in lower limb arthroplasty. *J Bone Joint SurgAm* 2012; **94**: 1554-8
143 Qadan M, Polk HC, Jr., Hohmann SF, Fry DE. A reassessment of needs and practice patterns in pharmacologic prophylaxis of venous thromboembolism following elective major surgery. *AnnSurg* 2011; **253**: 215-20
144 Poultsides LA, Gonzalez DV, Memtsoudis SG, et al. Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. *J Bone Joint SurgBr* 2012; **94**: 113-21
145 Cusick LA, Beverland DE. The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. *JBone Joint SurgBr* 2009; **91**: 645-8
146 Wood RC, 3rd, Stewart DW, Slusher L, et al. Retrospective Evaluation of Postoperative Bleeding Events in Patients Receiving Rivaroxaban After Undergoing Total Hip and Total Knee Arthroplasty: Comparison with Clinical Trial Data. *Pharmacotherapy* 2015; **35**: 663-9
147 Kjaersgaard-Andersen P, Kehlet H. Should deep venous thrombosis prophylaxis be used in fast-track hip and knee replacement? *Acta Orthop* 2012; **83**: 105-6
148 Sobieraj DM, Lee S, Coleman CI, et al. Prolonged versus standard-duration venous thromboprophylaxis in major orthopedic surgery: a systematic review. *AnnInternMed* 2012; **156**: 720-7

149 Sun G, Wu J, Wang Q, et al. Factor Xa Inhibitors and Direct Thrombin Inhibitors Versus Low-Molecular-Weight Heparin for Thromboprophylaxis After Total Hip or Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. *J Arthroplasty* 2019; **34**: 789-800 e6
150 Turpie AG, Haas S, Kreutz R, et al. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *ThrombHaemost* 2014; **111**: 94-102
151 Gomez D, Razmjou H, Donovan A, Bansal VB, Gollish JD, Murnaghan JJ. A Phase IV Study of Thromboembolic and Bleeding Events Following Hip and Knee Arthroplasty Using Oral Factor Xa Inhibitor. *J Arthroplasty* 2017; **32**: 958-64
152 Glassou EN, Pedersen AB, Hansen TB. Risk of re-admission, reoperation, and mortality within 90 days of total hip and knee arthroplasty in fast-track departments in Denmark from 2005 to 2011. *Acta Orthop* 2014; **85**: 493-500
153 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. *ArchOrthopTrauma Surg* 2012; **132**: 101-4
154 Pedersen AB, Sorensen HT, Mehnert F, Johnsen SP, Overgaard S. Effectiveness and safety of different duration of thromboprophylaxis in 16,865 hip replacement patients--a real-word, prospective observational study. *ThrombRes* 2015; **135**: 322-8
155 Pedersen AB, Andersen IT, Overgaard S, et al. Optimal duration of anticoagulant thromboprophylaxis in total hip arthroplasty: new evidence in 55,540 patients with osteoarthritis from the Nordic Arthroplasty Register Association (NARA) group. *Acta orthopaedica* 2019; **90**: 298-305
156 Dahl OE, Gudmundsen TE, Pripp AH, Aanesen JJ. Clinical venous thromboembolism following joint surgery: effect of extended thromboprophylaxis on its annual frequency and postoperative pattern over 22 years. *ClinApplThrombHemost* 2014; **20**: 117-23
157 Venclauskas L, Llau JV, Jenny JY, Kjaersgaard-Andersen P, Jans O. European guidelines on perioperative venous thromboembolism prophylaxis: Day surgery and fast-track surgery. *EurJ Anaesthesiol* 2017
158 Bateman DK, Dow RW, Brzezinski A, Bar-Eli HY, Kayiaros ST. Correlation of the Caprini Score and Venous Thromboembolism Incidence Following Primary Total Joint Arthroplasty-Results of a Single-Institution Protocol. *J Arthroplasty* 2017; **32**: 3735-41
159 Cassidy MR, Rosenkranz P, McAneny D. Reducing postoperative venous thromboembolism complications with a standardized risk-stratified prophylaxis protocol and mobilization program. *JAmCollSurg* 2014; **218**: 1095-104
160 Kunutsor SK, Beswick AD, Whitehouse MR, Blom AW. Systematic review of risk prediction scores for venous thromboembolism following joint replacement. *Thrombosis research* 2018; **168**: 148-55
161 Nemeth B, Cannegieter SC. Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy. *Thrombosis research* 2019; **174**: 62-75
162 Nemeth B, Nelissen R, Arya R, Cannegieter S. Preventing VTE following total hip and knee arthroplasty: Is prediction the future? *Journal of thrombosis and haemostasis : JTH* 2021; **19**: 41-5

163 Jorgensen CC, Petersen PB, Reed M, Kehlet H. Recommendations on thromboprophylaxis in major joint arthroplasty - many guidelines, little consensus? *Journal of thrombosis and haemostasis : JTH* 2019; **17**: 250-3
164 Samama CM. Fast-Track Procedures in Major Orthopaedic Surgery: Is Venous Thromboembolism Prophylaxis Still Mandatory? *Thrombosis and haemostasis* 2019; **119**: 3-5
165 Dahl OE, Borris LC. Thromboembolism in major joint prosthetic surgery: False or fact. *Journal of thrombosis and haemostasis : JTH* 2019; **17**: 1623-5
166 Azboy I, Barrack R, Thomas AM, Haddad FS, Parvizi J. Aspirin and the prevention of venous thromboembolism following total joint arthroplasty: commonly asked questions. *Bone Joint J* 2017; **99-B**: 1420-30
167 Monn MF, Haut ER, Lau BD, et al. Is venous thromboembolism in colorectal surgery patients preventable or inevitable? One institution's experience. *JAmCollSurg* 2013; **216**: 395-401
168 Moll S. After the Fall - Prophylaxis for All? *The New England journal of medicine* 2017; **376**: 576-7
169 Lim W, Meade M, Lauzier F, et al. Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients*. *Critical care medicine* 2015; **43**: 401-10
170 Nemeth B, Lijfering WM, Cannegieter SC. Thromboprophylaxis after hospital discharge in acutely ill medical patients: need for trials in patients who are at high risk of venous thrombosis. *Journal of thoracic disease* 2017; **9**: 950-2
171 Cafri G, Paxton EW, Chen Y, et al. Comparative Effectiveness and Safety of Drug Prophylaxis for Prevention of Venous Thromboembolism After Total Knee Arthroplasty. *J Arthroplasty* 2017; **32**: 3524-8.e1
172 Warwick D, Dahl OE, Fisher WD. Orthopaedic thromboprophylaxis: limitations of current guidelines. *The Journal of bone and joint surgery British volume* 2008; **90**: 127-32
173 Mortazavi SM, Kakli H, Bican O, Moussouttas M, Parvizi J, Rothman RH. Perioperative stroke after total joint arthroplasty: prevalence, predictors, and outcome. *JBone Joint SurgAm* 2010; **92**: 2095-101
174 Menendez ME, Memtsoudis SG, Opperer M, Boettner F, Gonzalez DV. A nationwide analysis of risk factors for in-hospital myocardial infarction after total joint arthroplasty. *IntOrthop* 2015; **39**: 777-86
175 Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *AnnInternMed* 2011; **154**: 523-8
176 Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology* 2009; **110**: 231-8
177 Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120**: 564-78
178 Smilowitz NR, Redel-Traub G, Hausvater A, et al. Myocardial Injury After Noncardiac Surgery: A Systematic Review and Meta-Analysis. *Cardiology in review* 2019; **27**: 267-73

179 Thomas S, Borges F, Bhandari M, et al. Association Between Myocardial Injury and Cardiovascular Outcomes of Orthopaedic Surgery: A Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Substudy. *The Journal of bone and joint surgery American volume* 2020; **102**: 880-8
180 Van Zyl RD, Burger MC, Jordaan JD. Prevalence of a postoperative troponin leak in patients with cardiac risk factors undergoing knee and hip arthroplasty in a South African population. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2020; **110**: 320-6
181 Gerstein NS, Carey MC, Cigarroa JE, Schulman PM. Perioperative aspirin management after POISE-2: some answers, but questions remain. *Anesthesia and analgesia* 2015; **120**: 570-5
182 Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet* 2018; **391**: 2325-34
183 Sharma V, Sessler DI, Hausenloy DJ. The role of routine postoperative troponin measurement in the diagnosis and management of myocardial injury after non-cardiac surgery. *Anaesthesia* 2021; **76**: 11-4
184 Singh JA, Jensen MR, Harmsen WS, Gabriel SE, Lewallen DG. Cardiac and thromboembolic complications and mortality in patients undergoing total hip and total knee arthroplasty. *AnnRheumDis* 2011; **70**: 2082-8
185 Lalmohamed A, Vestergaard P, Klop C, et al. Timing of acute myocardial infarction in patients undergoing total hip or knee replacement: a nationwide cohort study. *ArchInternMed* 2012; **172**: 1229-35
186 Pedersen AB, Mehnert F, Sorensen HT, Emmeluth C, Overgaard S, Johnsen SP. The risk of venous thromboembolism, myocardial infarction, stroke, major bleeding and death in patients undergoing total hip and knee replacement: a 15-year retrospective cohort study of routine clinical practice. *Bone Joint J* 2014; **96-B**: 479-85
187 Rasouli MR, Tabatabaee RM, Maltenfort MG, Chen AF. Acute stroke after total joint arthroplasty: a population-based trend analysis. *Journal of clinical anesthesia* 2016; **34**: 15-20
188 Lalmohamed A, Vestergaard P, Cooper C, et al. Timing of stroke in patients undergoing total hip replacement and matched controls: a nationwide cohort study. *Stroke* 2012; **43**: 3225-9
189 Clemson L, Fiatarone Singh MA, Bundy A, et al. Integration of balance and strength training into daily life activity to reduce rate of falls in older people (the LiFE study): randomised parallel trial. *BMJ* 2012; **345**: e4547
190 Mion LC, Chandler AM, Waters TM, et al. Is it possible to identify risks for injurious falls in hospitalized patients? *JtComm J QualPatientSaf* 2012; **38**: 408-13
191 Fleming J, Brayne C. Inability to get up after falling, subsequent time on floor, and summoning help: prospective cohort study in people over 90. *BMJ* 2008; **337**: a2227
192 Kronzer VL, Jerry MR, Ben AA, et al. Preoperative Falls Predict Postoperative Falls, Functional Decline, and Surgical Complications. *EBioMedicine* 2016
193 Jones TS, Dunn CL, Wu DS, Cleveland JC, Jr., Kile D, Robinson TN. Relationship between asking an older adult about falls and surgical outcomes. *JAMA Surg* 2013; **148**: 1132-8
194 Ackerman DB, Trousdale RT, Bieber P, Henely J, Pagnano MW, Berry DJ. Postoperative patient falls on an orthopedic inpatient unit. *J Arthroplasty* 2010; **25**: 10-4

195 Fischer ID, Krauss MJ, Dunagan WC, et al. Patterns and predictors of inpatient falls and fall-related injuries in a large academic hospital. *InfectControl HospEpidemiol* 2005; **26**: 822-7
196 Schwendimann R, Buhler H, De GS, Milisen K. Characteristics of hospital inpatient falls across clinical departments. *Gerontology* 2008; **54**: 342-8
197 Johnson RL, Kopp SL, Hebl JR, Erwin PJ, Mantilla CB. Falls and major orthopaedic surgery with peripheral nerve blockade: a systematic review and meta-analysis. *BrJ Anaesth* 2013; **110**: 518-28
198 Memtsoudis SG, Danninger T, Rasul R, et al. Inpatient falls after total knee arthroplasty: the role of anesthesia type and peripheral nerve blocks. *Anesthesiology* 2014; **120**: 551-63
199 Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. *AnesthAnalg* 2010; **111**: 1552-4
200 Finn DM, Agarwal RR, Ilfeld BM, et al. Fall Risk Associated with Continuous Peripheral Nerve Blocks Following Knee and Hip Arthroplasty. *Medsurg nursing : official journal of the Academy of Medical-Surgical Nurses* 2016; **25**: 25-30, 49
201 McIsaac DI, McCartney CJ, Walraven CV. Peripheral Nerve Blockade for Primary Total Knee Arthroplasty: A Population-based Cohort Study of Outcomes and Resource Utilization. *Anesthesiology* 2017; **126**: 312-20
202 Ilfeld BM. Continuous Peripheral Nerve Blocks: An Update of the Published Evidence and Comparison With Novel, Alternative Analgesic Modalities. *Anesthesia and analgesia* 2017; **124**: 308-35
203 Kopp SL, Borglum J, Buvanendran A, et al. Anesthesia and Analgesia Practice Pathway Options for Total Knee Arthroplasty: An Evidence-Based Review by the American and European Societies of Regional Anesthesia and Pain Medicine. *Regional anesthesia and pain medicine* 2017; **42**: 683-97
204 Jaeger P, Grevstad U, Henningsen MH, Gottschau B, Mathiesen O, Dahl JB. Effect of adductor-canal-blockade on established, severe post-operative pain after total knee arthroplasty: a randomised study. *Acta Anaesthesiol Scand* 2012; **56**: 1013-9
205 van der Merwe JM, Mastel MS. Controversial Topics in Total Knee Arthroplasty: A 5-Year Update (Part 1). *Journal of the American Academy of Orthopaedic Surgeons Global research & reviews* 2020; **4**: e1900047
206 Swinkels A, Newman JH, Allain TJ. A prospective observational study of falling before and after knee replacement surgery. *Age Ageing* 2009; **38**: 175-81
207 Ikutomo H, Nagai K, Tagomori K, Miura N, Nakagawa N, Masuhara K. Incidence and Circumstances of Falls in Women Before and After Total Hip Arthroplasty: A Prospective Cohort Study. *J Arthroplasty* 2018; **33**: 2268-72
208 Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. *ArchPhysMedRehabil* 2010; **91**: 1770-6
209 Holm B, Thorborg K, Husted H, Kehlet H, Bandholm T. Surgery-induced changes and early recovery of hip-muscle strength, leg-press power, and functional performance after fast-track total hip arthroplasty: a prospective cohort study. *PLoSOne* 2013; **8**: e62109

210 Swinkels A, Allain TJ. Physical performance tests, self-reported outcomes, and accidental falls before and after total knee arthroplasty: an exploratory study. *PhysiotherTheoryPract* 2013; **29**: 432-42
211 Hewlett-Smith N, Pope R, Furness J, Simas V, Hing W. Prognostic factors for inpatient functional recovery following total hip and knee arthroplasty: a systematic review. *Acta orthopaedica* 2020; **91**: 313-8
212 Jakobsen TL, Husted H, Kehlet H, Bandholm T. Progressive strength training (10 RM) commenced immediately after fast-track total knee arthroplasty: is it feasible? *DisabilRehabil* 2012; **34**: 1034-40
213 Jakobsen TL, Kehlet H, Husted H, Petersen J, Bandholm T. Early progressive strength training to enhance recovery after fast-track total knee arthroplasty: a randomized controlled trial. *Arthritis care & research* 2014; **66**: 1856-66
214 Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. *Age Ageing* 1990; **19**: 136-41
215 Robinovitch SN, Feldman F, Yang Y, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* 2013; **381**: 47-54
216 Mandl LA, Lyman S, Quinlan P, Bailey T, Katz J, Magid SK. Falls among patients who had elective orthopaedic surgery: a decade of experience from a musculoskeletal specialty hospital. *J OrthopSports PhysTher* 2013; **43**: 91-6
217 Johnson RL, Duncan CM, Ahn KS, Schroeder DR, Horlocker TT, Kopp SL. Fall-prevention strategies and patient characteristics that impact fall rates after total knee arthroplasty. *AnesthAnalg* 2014; **119**: 1113-8
218 Smith TO, Pearson M, Latham SK. Are people following hip and knee arthroplasty at greater risk of experiencing a fall and fracture? Data from the Osteoarthritis Initiative. *Archives of orthopaedic and trauma surgery* 2016; **136**: 865-72
219 Matsumoto H, Okuno M, Nakamura T, Yamamoto K, Osaki M, Hagino H. Incidence and risk factors for falling in patients after total knee arthroplasty compared to healthy elderly individuals. *Yonago acta medica* 2014; **57**: 137-45
220 Lo CWT, Tsang WWN, Yan CH, Lord SR, Hill KD, Wong AYL. Risk factors for falls in patients with total hip arthroplasty and total knee arthroplasty: a systematic review and meta-analysis. *Osteoarthritis and cartilage* 2019; **27**: 979-93
221 Cram P, Lu X, Kaboli PJ, et al. Clinical characteristics and outcomes of Medicare patients undergoing total hip arthroplasty, 1991-2008. *JAMA* 2011; **305**: 1560-7
222 Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991-2010. *JAMA* 2012; **308**: 1227-36
223 Yu P, Chang DC, Osen HB, Talamini MA. NSQIP reveals significant incidence of death following discharge. *JSurgRes* 2011; **170**: e217-e24
224 Jawad M, Baigi A, Oldner A, et al. Swedish surgical outcomes study (SweSOS): An observational study on 30-day and 1-year mortality after surgery. *EurJ Anaesthesiol* 2016; **33**: 317-25
225 Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**: 1059-65

226 Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295-304
227 Soreide K, Story DA, Walder B. Perioperative medicine and mortality after elective and emergency surgery. *European journal of anaesthesiology* 2016; **33**: 314-6
228 Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *EurJAnaesthesiol* 2015; **32**: 88-105
229 Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409,096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *Lancet* 2013; **382**: 1097-104
230 Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467,779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. *Lancet* 2014; **384**: 1429-36
231 Lalmohamed A, Vestergaard P, de BA, Leufkens HG, van Staa TP, de VF. Changes in mortality patterns following total hip or knee arthroplasty over the past two decades: a nationwide cohort study. *Arthritis Rheumatol* 2014; **66**: 311-8
232 Pedersen AB, Baron JA, Overgaard S, Johnsen SP. Short- and long-term mortality following primary total hip replacement for osteoarthritis: a Danish nationwide epidemiological study. *JBone Joint SurgBr* 2011; **93**: 172-7
233 Kjellberg J, Kehlet H. A nationwide analysis of socioeconomic outcomes after hip and knee replacement. *DanMedJ* 2016; **63**: A5257
234 Ferraris VA, Bolanos M, Martin JT, Mahan A, Saha SP. Identification of patients with postoperative complications who are at risk for failure to rescue. *JAMA Surg* 2014; **149**: 1103-8
235 Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *AnnSurg* 2005; **242**: 326-41
236 Jones MD, Parry MC, Whitehouse MR, Blom AW. Early death following primary total hip arthroplasty. *JArthroplasty* 2014; **29**: 1625-8
237 Lie SA, Pratt N, Ryan P, et al. Duration of the increase in early postoperative mortality after elective hip and knee replacement. *JBone Joint SurgAm* 2010; **92**: 58-63
238 Partridge T, Jameson S, Baker P, Deehan D, Mason J, Reed MR. Ten-Year Trends in Medical Complications Following 540,623 Primary Total Hip Replacements from a National Database. *The Journal of bone and joint surgery American volume* 2018; **100**: 360-7
239 Liu J, Wilson L, Poeran J, et al. Trends in total knee and hip arthroplasty recipients: a retrospective cohort study. *Regional anesthesia and pain medicine* 2019; **44**: 854-9
240 Garriga C, Murphy J, Leal J, et al. Impact of a national enhanced recovery after surgery programme on patient outcomes of primary total knee replacement: an interrupted time series analysis from "The National Joint Registry of England, Wales, Northern Ireland and the Isle of Man". *Osteoarthritis and cartilage* 2019; **27**: 1280-93

241 Garriga C, Murphy J, Leal J, et al. Assessment on patient outcomes of primary hip replacement: an interrupted time series analysis from 'The National Joint Registry of England and Wales'. *BMJ open* 2019; **9**: e031599
242 Simpson JC, Moonesinghe SR, Grocott MP, et al. Enhanced recovery from surgery in the UK: an audit of the enhanced recovery partnership programme 2009-2012. *BrJAnaesth* 2015; **115**: 560-8
243 Ripolles-Melchor J, Abad-Motos A, Diez-Remesal Y, et al. Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Total Hip and Knee Arthroplasty in the Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol in Elective Total Hip and Knee Arthroplasty Study (POWER2). *JAMA surgery* 2020; **155**: e196024
244 Memtsoudis SG, Fiasconaro M, Soffin EM, et al. Enhanced recovery after surgery components and perioperative outcomes: a nationwide observational study. *Br J Anaesth* 2020; **124**: 638-47
245 Petersen PB, Kehlet H, Jorgensen CC. Improvements in fast-track hip and knee arthroplasty – a prospective multicentre study of 36,935 procedures from 2010-2017. *SciRep* 2020; **in press**
246 Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care* 2006; **10**: R81
247 Berstock JR, Beswick AD, Lenguerrand E, Whitehouse MR, Blom AW. Mortality after total hip replacement surgery: A systematic review. *Bone Joint Res* 2014; **3**: 175-82
248 Aynardi M, Jacovides CL, Huang R, Mortazavi SM, Parvizi J. Risk factors for early mortality following modern total hip arthroplasty. *JArthroplasty* 2013; **28**: 517-20
249 Memtsoudis SG, Ma Y, Chiu YL, Walz JM, Voswinckel R, Mazumdar M. Perioperative mortality in patients with pulmonary hypertension undergoing major joint replacement. *Anesthesia and analgesia* 2010; **111**: 1110-6
250 Singh JA, Kundukulam J, Riddle DL, Strand V, Tugwell P. Early postoperative mortality following joint arthroplasty: a systematic review. *JRheumatol* 2011; **38**: 1507-13
251 Singh JA, Lewallen DG. Ninety-day mortality in patients undergoing elective total hip or total knee arthroplasty. *JArthroplasty* 2012; **27**: 1417-22
252 Turan A, Mascha EJ, Roberman D, et al. Smoking and perioperative outcomes. *Anesthesiology* 2011; **114**: 837-46
253 Soohoo NF, Farng E, Lieberman JR, Chambers L, Zingmond DS. Factors that predict short-term complication rates after total hip arthroplasty. *ClinOrthopRelat Res* 2010; **468**: 2363-71
254 Vorhies JS, Wang Y, Herndon J, Maloney WJ, Huddleston JI. Readmission and length of stay after total hip arthroplasty in a national Medicare sample. *J Arthroplasty* 2011; **26**: 119-23
255 Jimenez-Garcia R, Villanueva-Martinez M, Fernandez-de-Las-Penas C, et al. Trends in primary total hip arthroplasty in Spain from 2001 to 2008: evaluating changes in demographics, comorbidity, incidence rates, length of stay, costs and mortality. *BMCMusculoskeletDisord* 2011; **12**: 43
256 Dall GF, Ohly NE, Ballantyne JA, Brenkel IJ. The influence of pre-operative factors on the length of in-patient stay following primary total hip replacement for osteoarthritis: a multivariate analysis of 2302 patients. *JBone Joint SurgBr* 2009; **91**: 434-40

257 Moller AM, Pedersen T, Villebro N, Munksgaard A. Effect of smoking on early complications after elective orthopaedic surgery. *J Bone Joint SurgBr* 2003; **85**: 178-81
258 Huddleston JI, Maloney WJ, Wang Y, Verzier N, Hunt DR, Herndon JH. Adverse events after total knee arthroplasty: a national Medicare study. *J Arthroplasty* 2009; **24**: 95-100
259 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
260 Kirksey M, Chiu YL, Ma Y, et al. Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998-2008. *AnesthAnalg* 2012; **115**: 321-7
261 Oksuzyan A, Jeune B, Juel K, Vaupel JW, Christensen K. Changes in hospitalisation and surgical procedures among the oldest-old: a follow-up study of the entire Danish 1895 and 1905 cohorts from ages 85 to 99 years. *Age Ageing* 2013; **42**: 476-81
262 White SM. Including the very elderly in clinical trials. *Anaesthesia* 2010; **65**: 778-80
263 McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. *BMJ* 2005; **331**: 1036-7
264 Neuman HB, Weiss JM, Leverson G, et al. Predictors of short-term postoperative survival after elective colectomy in colon cancer patients >/= 80 years of age. *Annals of surgical oncology* 2013; **20**: 1427-35
265 Story DA, Fink M, Leslie K, et al. Perioperative mortality risk score using pre- and postoperative risk factors in older patients. *AnaesthIntensive Care* 2009; **37**: 392-8
266 Clement ND, MacDonald D, Howie CR, Biant LC. The outcome of primary total hip and knee arthroplasty in patients aged 80 years or more. *JBone Joint SurgBr* 2011; **93**: 1265-70
267 Kuo FC, Hsu CH, Chen WS, Wang JW. Total knee arthroplasty in carefully selected patients aged 80 years or older. *Journal of orthopaedic surgery and research* 2014; **9**: 61
268 Jonas SC, Smith HK, Blair PS, Dacombe P, Weale AE. Factors influencing length of stay following primary total knee replacement in a UK specialist orthopaedic centre. *The Knee* 2013; **20**: 310-5
269 Winemaker M, Petruccelli D, Kabali C, de Beer J. Not all total joint replacement patients are created equal: preoperative factors and length of stay in hospital. *Canadian journal of surgery Journal canadien de chirurgie* 2015; **58**: 160-6
270 Rasmussen LS, Jorgensen CC, Kehlet H. Enhanced recovery programmes for the elderly. *European journal of anaesthesiology* 2016; **33**: 391-2
271 Griffiths R, Beech F, Brown A, et al. Peri-operative care of the elderly. *Anaesthesia* 2014; **69 Suppl 1**: 81-98
272 Bouras AF. Hospital discharge of elderly patients after surgery: fast-track recovery versus the need for convalescence. *Journal of visceral surgery* 2014; **151**: 89-90
273 Opperer M, Danninger T, Stundner O, Memtsoudis SG. Perioperative outcomes and type of anesthesia in hip surgical patients: An evidence based review. *World journal of orthopedics* 2014; **5**: 336-43
274 Sikora-Klak J, Zarling B, Bergum C, Flynn JC, Markel DC. The Effect of Comorbidities on Discharge Disposition and Readmission for Total Joint Arthroplasty Patients. *J Arthroplasty* 2017; **32**: 1414-7

275 Memtsoudis SG, Sun X, Chiu YL, et al. Utilization of critical care services among patients undergoing total hip and knee arthroplasty: epidemiology and risk factors. *Anesthesiology* 2012; **117**: 107-16
276 Sacks GD, Lawson EH, Dawes AJ, Gibbons MM, Zingmond DS, Ko CY. Which Patients Require More Care after Hospital Discharge? An Analysis of Post-Acute Care Use among Elderly Patients Undergoing Elective Surgery. *Journal of the American College of Surgeons* 2015; **220**: 1113-21.e2
277 Etzioni DA, Liu JH, Maggard MA, Ko CY. The aging population and its impact on the surgery workforce. *AnnSurg* 2003; **238**: 170-7
278 Miric A, Inacio MC, Kelly MP, Namba RS. Can total knee arthroplasty be safely performed among nonagenarians? An evaluation of morbidity and mortality within a total joint replacement registry. *JArthroplasty* 2014; **29**: 1635-8
279 Nanjayan SK, Swamy GN, Yellu S, Yallappa S, Abuzakuk T, Straw R. In-hospital complications following primary total hip and knee arthroplasty in octogenarian and nonagenarian patients. *Journal of orthopaedics and traumatology : official journal of the Italian Society of Orthopaedics and Traumatology* 2014; **15**: 29-33
280 D'Apuzzo MR, Pao AW, Novicoff WM, Browne JA. Age as an independent risk factor for postoperative morbidity and mortality after total joint arthroplasty in patients 90 years of age or older. *JArthroplasty* 2014; **29**: 477-80
281 Hamel MB, Toth M, Legedza A, Rosen MP. Joint replacement surgery in elderly patients with severe osteoarthritis of the hip or knee: decision making, postoperative recovery, and clinical outcomes. *Archives of internal medicine* 2008; **168**: 1430-40
282 Raut S, Mertes SC, Muniz-Terrera G, Khanduja V. Factors associated with prolonged length of stay following a total knee replacement in patients aged over 75. *IntOrthop* 2012; **36**: 1601-8
283 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
284 Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *AmJHematol* 2014; **89**: 88-96
285 Hakkarainen TW, Ayoung-Chee P, Alfonso R, Arbabi S, Flum DR. Structure, process, and outcomes in skilled nursing facilities: understanding what happens to surgical patients when they cannot go home. A systematic review. *JSurgRes* 2015; **193**: 772-80
286 Tian W, Dejong G, Munin MC, Smout R. Patterns of rehabilitation after hip arthroplasty and the association with outcomes: an episode of care view. *AmJPhysMedRehabil* 2010; **89**: 905-18
287 Ramos NL, Karia RJ, Hutzler LH, Brandt AM, Slover JD, Bosco JA. The effect of discharge disposition on 30-day readmission rates after total joint arthroplasty. *JArthroplasty* 2014; **29**: 674-7
288 Sharareh B, Le NB, Hoang MT, Schwarzkopf R. Factors determining discharge destination for patients undergoing total joint arthroplasty. *JArthroplasty* 2014; **29**: 1355-8
289 Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *BrJ Anaesth* 2011; **106**: 13-22

290 Vogler CM, Menant JC, Sherrington C, Ogle SJ, Lord SR. Evidence of detraining after 12-week home-based exercise programs designed to reduce fall-risk factors in older people recently discharged from hospital. *ArchPhysMedRehabil* 2012; **93**: 1685-91
291 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA InternMed* 2015; **175**: 827-34
292 Samuelsson KS, Egenvall M, Klarin I, Lokk J, Gunnarsson U. Inappropriate drug use in elderly patients is associated with prolonged hospital stay and increased postoperative mortality after colorectal cancer surgery: a population-based study. *Colorectal Dis* 2016; **18**: 155-62
293 Roman de Mettelinge T, Cambier D, Calders P, Van Den Noortgate N, Delbaere K. Understanding the relationship between type 2 diabetes mellitus and falls in older adults: a prospective cohort study. *PloS one* 2013; **8**: e67055
294 Darowski A, Chambers SA, Chambers DJ. Antidepressants and falls in the elderly. *Drugs Aging* 2009; **26**: 381-94
295 Macdonald V, Ottem P, Wasdell M, Spiwak P. Predictors of prolonged hospital stays following hip and knee arthroplasty *Intl J Ortho Trauma Nursing* 2010; **14**: 198-205
296 Keeney BJ, Koenig KM, Paddock NG, Moschetti WE, Sparks MB, Jevsevar DS. Do Aggregate Socioeconomic Status Factors Predict Outcomes for Total Knee Arthroplasty in a Rural Population? *J Arthroplasty* 2017; **32**: 3583-90
297 den Hartog YM, Mathijssen NM, Hannink G, Vehmeijer SB. Which patient characteristics influence length of hospital stay after primary total hip arthroplasty in a 'fast-track' setting? *Bone Joint J* 2015; **97-B**: 19-23
298 Mathijssen NM, Verburg H, van Leeuwen CC, Molenaar TL, Hannink G. Factors influencing length of hospital stay after primary total knee arthroplasty in a fast-track setting. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2016; **24**: 2692-6
299 Coudeyre E, Lefevre-Colau MM, Griffon A, et al. Is there predictive criteria for transfer of patients to a rehabilitation ward after hip and knee total arthroplasty? Elaboration of French clinical practice guidelines. *Annales de readaptation et de medecine physique : revue scientifique de la Societe francaise de reeducation fonctionnelle de readaptation et de medecine physique* 2007; **50**: 327-36; 17-26
300 Ong PH, Pua YH. A prediction model for length of stay after total and unicompartmental knee replacement. *Bone Joint J* 2013; **95-b**: 1490-6
301 Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. *Age Ageing* 2012; **41**: 142-7
302 Revenig LM, Canter DJ, Kim S, et al. Report of a Simplified Frailty Score Predictive of Short-Term Postoperative Morbidity and Mortality. *Journal of the American College of Surgeons* 2015; **220**: 904-11.e1
303 Sultan P, Hamilton MA, Ackland GL. Preoperative muscle weakness as defined by handgrip strength and postoperative outcomes: a systematic review. *BMC anesthesiology* 2012; **12**: 1
304 de Mettelinge TR, Calders P, Palmans T, Vanden Bossche L, Van Den Noortgate N, Cambier D. Vibration perception threshold in relation to postural control and fall risk assessment in elderly. *Disability and rehabilitation* 2013; **35**: 1712-7

305 Greysen SR, Stijacic Cenzer I, Auerbach AD, Covinsky KE. Functional impairment and hospital readmission in Medicare seniors. *JAMA internal medicine* 2015; **175**: 559-65
306 Bandholm T, Wainwright TW, Kehlet H. Rehabilitation strategies for optimisation of functional recovery after major joint replacement. *Journal of experimental orthopaedics* 2018; **5**: 44
307 Goodman SM, Krauser D, Mackenzie CR, Memtsoudis S. Cardiac Arrest during Total Hip Arthroplasty in a Patient on an Angiotensin Receptor Antagonist. *HSS journal : the musculoskeletal journal of Hospital for Special Surgery* 2012; **8**: 175-83
308 Calloway JJ, Memtsoudis SG, Krauser DG, Ma Y, Russell LA, Goodman SM. Hemodynamic effects of angiotensin inhibitors in elderly hypertensives undergoing total knee arthroplasty under regional anesthesia. *Journal of the American Society of Hypertension : JASH* 2014; **8**: 644-51
309 Brilakis ES, Banerjee S. Patient with coronary stents needs surgery: what to do? *Jama* 2013; **310**: 1451-2
310 Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent Associations between Hypotension during and for Four Days after Noncardiac Surgery and a Composite of Myocardial Infarction and Death: A Substudy of the POISE-2 Trial. *Anesthesiology* 2018; **128**: 317-27
311 Higuera CA, Elsharkawy K, Klika AK, Brocone M, Barsoum WK. 2010 Mid-America Orthopaedic Association Physician in Training Award: predictors of early adverse outcomes after knee and hip arthroplasty in geriatric patients. *Clinical orthopaedics and related research* 2011; **469**: 1391-400
312 Yakubek GA, Curtis GL, Khlopas A, et al. Chronic Obstructive Pulmonary Disease Is Associated With Short-Term Complications Following Total Knee Arthroplasty. *J Arthroplasty* 2018; **33**: 2623-6
313 Yakubek GA, Curtis GL, Sodhi N, et al. Chronic Obstructive Pulmonary Disease Is Associated With Short-Term Complications Following Total Hip Arthroplasty. *J Arthroplasty* 2018; **33**: 1926-9
314 Yohe N, Weisberg MD, Ciminero M, Mannino A, Erez O, Saleh A. Complications and Readmissions After Total Hip Replacement in Octogenarians and Nonagenarians. *Geriatric orthopaedic surgery & rehabilitation* 2020; **11**: 2151459320940959
315 Pugely AJ, Martin CT, Gao Y, Belatti DA, Callaghan JJ. Comorbidities in patients undergoing total knee arthroplasty: do they influence hospital costs and length of stay? *Clinical orthopaedics and related research* 2014; **472**: 3943-50
316 Easterlin MC, Chang DG, Talamini M, Chang DC. Older age increases short-term surgical complications after primary knee arthroplasty. *Clinical orthopaedics and related research* 2013; **471**: 2611-20
317 Curtis GL, Newman JM, George J, Klika AK, Barsoum WK, Higuera CA. Perioperative Outcomes and Complications in Patients With Heart Failure Following Total Knee Arthroplasty. *J Arthroplasty* 2018; **33**: 36-40
318 Elsiwy Y, Jovanovic I, Doma K, Hazratwala K, Letson H. Risk factors associated with cardiac complication after total joint arthroplasty of the hip and knee: a systematic review. *Journal of orthopaedic surgery and research* 2019; **14**: 15

319 Duggan EW, Carlson K, Umpierrez GE. Perioperative Hyperglycemia Management: An Update. *Anesthesiology* 2017; **126**: 547-60
320 Marchant MH, Jr., Viens NA, Cook C, Vail TP, Bolognesi MP. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. *JBone Joint SurgAm* 2009; **91**: 1621-9
321 Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009; **110**: 505-15
322 Adams AL, Paxton EW, Wang JQ, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. *J Bone Joint SurgAm* 2013; **95**: 481-7
323 Namba RS, Inacio MC, Paxton EW. Risk factors associated with surgical site infection in 30 491 primary total hip replacements. *J Bone Joint SurgBr* 2012; **94**: 1330-8
324 Galat DD, McGovern SC, Larson DR, Harrington JR, Hanssen AD, Clarke HD. Surgical treatment of early wound complications following primary total knee arthroplasty. *J Bone Joint SurgAm* 2009; **91**: 48-54
325 Iorio R, Williams KM, Marcantonio AJ, Specht LM, Tilzey JF, Healy WL. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. *J Arthroplasty* 2012; **27**: 726-9
326 Jamsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. *J Bone Joint SurgAm* 2012; **94**: e101
327 Stryker LS, Abdel MP, Morrey ME, Morrow MM, Kor DJ, Morrey BF. Elevated postoperative blood glucose and preoperative hemoglobin A1C are associated with increased wound complications following total joint arthroplasty. *JBone Joint SurgAm* 2013; **95**: 808-2
328 Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *AnnSurg* 2013; **257**: 8-14
329 Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. *ArchSurg* 2010; **145**: 858-64
330 Webster NR, Galley HF. Does strict glucose control improve outcome? *BrJ Anaesth* 2009; **103**: 331-4
331 Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of the critically ill? *Diabetologia* 2006; **49**: 1722-5
332 Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010; **33**: 1783-8
333 Martinez-Huedo MA, Villanueva M, de Andres AL, et al. Trends 2001 to 2008 in incidence and immediate postoperative outcomes for major joint replacement among Spanish adults suffering diabetes. *EurJ OrthopSurgTraumatol* 2013; **23**: 53-9
334 Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. *Bone Joint J* 2014; **96-B**: 1637-43

335 Ojemolon PE, Shaka H, Edigin E, et al. Impact of Diabetes Mellitus on Outcomes of Patients With Knee Osteoarthritis Who Underwent Knee Arthroplasty: An Analysis of the Nationwide Inpatient Sample. *Cureus* 2020; **12**: e8902
336 Shah A, Memon M, Kay J, et al. Preoperative Patient Factors Affecting Length of Stay following Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. *J Arthroplasty* 2019; **34**: 2124-65 e1
337 Martinez-Huedo MA, Jimenez-Garcia R, Jimenez-Trujillo I, Hernandez-Barrera V, Del Rio Lopez B, Lopez-de-Andres A. Effect of Type 2 Diabetes on In-Hospital Postoperative Complications and Mortality After Primary Total Hip and Knee Arthroplasty. *J Arthroplasty* 2017; **32**: 3729-34 e2
338 Webb ML, Golinvaux NS, Ibe IK, Bovonratwet P, Ellman MS, Grauer JN. Comparison of Perioperative Adverse Event Rates After Total Knee Arthroplasty in Patients With Diabetes: Insulin Dependence Makes a Difference. *J Arthroplasty* 2017; **32**: 2947-51
339 Lovecchio F, Beal M, Kwasny M, Manning D. Do patients with insulin-dependent and noninsulin-dependent diabetes have different risks for complications after arthroplasty? *Clinical orthopaedics and related research* 2014; **472**: 3570-5
340 Lenguerrand E, Beswick AD, Whitehouse MR, Wylde V, Blom AW. Outcomes following hip and knee replacement in diabetic versus nondiabetic patients and well versus poorly controlled diabetic patients: a prospective cohort study. *Acta orthopaedica* 2018; **89**: 399-405
341 Wylde V, Lenguerrand E, Gooberman-Hill R, et al. Effect of local anaesthetic infiltration on chronic postsurgical pain after total hip and knee replacement: the APEX randomised controlled trials. *Pain* 2015; **156**: 1161-70
342 Yang DJ, Zhang S, He WL, et al. Fast track surgery accelerates the recovery of postoperative insulin sensitivity. *Chinese medical journal* 2012; **125**: 3261-5
343 Bender R, Kuss O, Hildebrandt M, Gehrmann U. Estimating adjusted NNT measures in logistic regression analysis. *StatMed* 2007; **26**: 5586-95
344 Ortved M, Petersen PB, Jorgensen CC, Kehlet H. Postoperative morbidity and mortality in diabetic patients after fast-track hip and knee arthroplasty – a prospective follow-up cohort of 36,762 procedures. *Anesthesia Analgesia* 2020; **in press**
345 Preiser JC, Provenzano B, Mongkolpun W, Halenarova K, Cnop M. Perioperative Management of Oral Glucose-lowering Drugs in the Patient with Type 2 Diabetes. *Anesthesiology* 2020; **133**: 430-8
346 Duggan E, Chen Y. Glycemic Management in the Operating Room: Screening, Monitoring, Oral Hypoglycemics, and Insulin Therapy. *Current diabetes reports* 2019; **19**: 134
347 Rudy MD, Ahuja NK, Aaronson AJ. Diabetes and Hyperglycemia in Lower-Extremity Total Joint Arthroplasty: Clinical Epidemiology, Outcomes, and Management. *JBJS reviews* 2018; **6**: e10
348 Gylvin SH, Jorgensen CC, Fink-Jensen A, Kehlet H. Psychiatric disease as a risk factor in fast-track hip and knee replacement. *Acta Orthop* 2016: 1-5
349 Shepherd SJ, Fiandeiro C, Sanders RD. Selective serotonin reuptake inhibitors: depressing perioperative outcomes? *Br J Anaesth* 2015; **115**: 5-7
350 Singh JA, Lewallen DG. Predictors of activity limitation and dependence on walking aids after primary total hip arthroplasty. *JAmGeriatrSoc* 2010; **58**: 2387-93

351 Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. *Rheumatology(Oxford)* 2013; **52**: 916-23
352 Ellis HB, Howard KJ, Khaleel MA, Bucholz R. Effect of psychopathology on patient-perceived outcomes of total knee arthroplasty within an indigent population. *J Bone Joint SurgAm* 2012; **94**: e84
353 Copeland LA, Zeber JE, Pugh MJ, Mortensen EM, Restrepo MI, Lawrence VA. Postoperative complications in the seriously mentally ill: a systematic review of the literature. *AnnSurg* 2008; **248**: 31-8
354 Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Influence of psychiatric comorbidity on surgical mortality. *ArchSurg* 2010; **145**: 947-53
355 Klement MR, Bala A, Blizzard DJ, Wellman SS, Bolognesi MP, Seyler TM. Should We Think Twice About Psychiatric Disease in Total Hip Arthroplasty? *JArthroplasty* 2016
356 Klement MR, Nickel BT, Penrose CT, et al. Psychiatric disorders increase complication rate after primary total knee arthroplasty. *Knee* 2016
357 Vakharia RM, Ehiorobo JO, Sodhi N, Swiggett SJ, Mont MA, Roche MW. Effects of Depressive Disorders on Patients Undergoing Primary Total Knee Arthroplasty: A Matched-Control Analysis. *J Arthroplasty* 2020; **35**: 1247-51
358 De HM, Cohen D, Bobes J, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry* 2011; **10**: 138-51
359 De HM, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry* 2011; **10**: 52-77
360 Laursen TM, Munk-Olsen T, Agerbo E, Gasse C, Mortensen PB. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *ArchGenPsychiatry* 2009; **66**: 713-20
361 Sutherland AM, Katznelson R, Clarke HA, Tait G, Beattie WS. Use of preoperative antidepressants is not associated with postoperative hospital length of stay. *CanJAnaesth* 2014; **61**: 27-31
362 Stundner O, Kirksey M, Chiu YL, et al. Demographics and perioperative outcome in patients with depression and anxiety undergoing total joint arthroplasty: a population-based study. *Psychosomatics* 2013; **54**: 149-57
363 Bot AG, Menendez ME, Neuhaus V, Ring D. The influence of psychiatric comorbidity on perioperative outcomes after shoulder arthroplasty. *JShoulderElbowSurg* 2014; **23**: 519-27
364 Buller LT, Best MJ, Klika AK, Barsoum WK. The influence of psychiatric comorbidity on perioperative outcomes following primary total hip and knee arthroplasty; a 17-year analysis of the National Hospital Discharge Survey database. *JArthroplasty* 2015; **30**: 165-70
365 Jeong BO, Kim SW, Kim SY, Kim JM, Shin IS, Yoon JS. Use of serotonergic antidepressants and bleeding risk in patients undergoing surgery. *Psychosomatics* 2014; **55**: 213-20
366 Laporte S, Chapelle C, Caillet P, et al. Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: A meta-analysis of observational studies. *Pharmacological research* 2017; **118**: 19-32

367 Roose SP, Rutherford BR. Selective Serotonin Reuptake Inhibitors and Operative Bleeding Risk: A Review of the Literature. *Journal of clinical psychopharmacology* 2016; **36**: 704-9
368 de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; **28**: 345-67
369 Prodan CI, Joseph PM, Vincent AS, Dale GL. Coated-platelet levels are influenced by smoking, aspirin, and selective serotonin reuptake inhibitors. *Journal of thrombosis and haemostasis : JTH* 2007; **5**: 2149-51
370 Auerbach AD, Vittinghoff E, Maselli J, Pekow PS, Young JQ, Lindenauer PK. Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA InternMed* 2013; **173**: 1075-81
371 Mahoney JE, Palta M, Johnson J, et al. Temporal association between hospitalization and rate of falls after discharge. *ArchInternMed* 2000; **160**: 2788-95
372 Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011; **343**: d4551
373 Gylvin SH, Fink-Jensen A, Kehlet H, et al. Prospective psychometric characterization of hip and knee arthroplasty patients. *Nordic journal of psychiatry* 2018; **72**: 39-44
374 Bryson EO, Kellner CH. Psychiatric diagnosis counts as severe systemic illness in the American Society of Anesthesiologists (ASA) physical status classification system. *Medical hypotheses* 2014; **83**: 423-4
375 Huyse FJ, Touw DJ, van Schijndel RS, de Lange JJ, Slaets JP. Psychotropic drugs and the perioperative period: a proposal for a guideline in elective surgery. *Psychosomatics* 2006; **47**: 8-22
376 Mrkobrada M, Hackam DG. Selective serotonin reuptake inhibitors and surgery: to hold or not to hold, that is the question: comment on "Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery". *JAMA InternMed* 2013; **173**: 1082-3
377 Raeder J. Hip and knee replacement-do we need to bother about psychiatry? *Acta Orthop* 2016; **87**: 437-8
378 Parvizi J, Mui A, Purtill JJ, Sharkey PF, Hozack WJ, Rothman RH. Total joint arthroplasty: When do fatal or near-fatal complications occur? *JBone Joint SurgAm* 2007; **89**: 27-32
379 Petersen PB, Kehlet H, Jorgensen CC. Safety of In-Hospital Only Thromboprophylaxis after Fast-Track Total Hip and Knee Arthroplasty: A Prospective Follow-Up Study in 17,582 Procedures. *Thrombosis and haemostasis* 2018
380 Nowak LL, Schemitsch EH. Same-day and delayed hospital discharge are associated with worse outcomes following total knee arthroplasty. *Bone Joint J* 2019; **101-B**: 70-6
381 Avram V, Petruccelli D, Winemaker M, de BJ. Total joint arthroplasty readmission rates and reasons for 30-day hospital readmission. *JArthroplasty* 2014; **29**: 465-8
382 Kort NP, Bemelmans YF, Schotanus MG. Outpatient surgery for unicompartmental knee arthroplasty is effective and safe. *KneeSurgSports TraumatolArthrosc* 2015
383 Goyal N, Chen AF, Padgett SE, et al. Otto Aufranc Award: A Multicenter, Randomized Study of Outpatient versus Inpatient Total Hip Arthroplasty. *ClinOrthopRelat Res* 2016

384 Hartog YM, Mathijssen NM, Vehmeijer SB. Total hip arthroplasty in an outpatient setting in 27 selected patients. *Acta Orthop* 2015; **86**: 667-70
385 Rolighed LJ, Skovgaard B, Pryno T, et al. Feasibility of day-case total hip arthroplasty: a single-centre observational study. *HipInt* 2016: 0
386 Thienpont E, Lavand'homme P, Kehlet H. The constraints on day-case total knee arthroplasty: the fastest fast track. *Bone Joint J* 2015; **97-B**: 40-4
387 Otero JE, Gholson JJ, Pugely AJ, Gao Y, Bedard NA, Callaghan JJ. Length of Hospitalization After Joint Arthroplasty: Does Early Discharge Affect Complications and Readmission Rates? *J Arthroplasty* 2016; **31**: 2714-25
388 Liu J, Elkassabany N, Poeran J, et al. Association between same day discharge total knee and total hip arthroplasty and risks of cardiac/pulmonary complications and readmission: a population-based observational study. *BMJ open* 2019; **9**: e031260
389 Lovecchio F, Alvi H, Sahota S, Beal M, Manning D. Is Outpatient Arthroplasty as Safe as Fast-Track Inpatient Arthroplasty? A Propensity Score Matched Analysis. *J Arthroplasty* 2016; **31**: 197-201
390 Callaghan JJ, Pugely A, Liu S, Noiseux N, Willenborg M, Peck D. Measuring rapid recovery program outcomes: are all patients candidates for rapid recovery. *JArthroplasty* 2015; **30**: 531-2
391 Jaibaji M, Volpin A, Haddad FS, Konan S. Is Outpatient Arthroplasty Safe? A Systematic Review. *J Arthroplasty* 2020; **35**: 1941-9
392 Johns WL, Layon D, Golladay GJ, Kates SL, Scott M, Patel NK. Preoperative Risk Factor Screening Protocols in Total Joint Arthroplasty: A Systematic Review. *J Arthroplasty* 2020; **35**: 3353-63
393 Foss NB, Christensen DS, Krasheninnikoff M, Kristensen BB, Kehlet H. Post-operative rounds by anaesthesiologists after hip fracture surgery: a pilot study. *Acta AnaesthesiolScand* 2006; **50**: 437-42
394 Chen LM, Wilk AS, Thumma JR, Birkmeyer JD, Banerjee M. Use of medical consultants for hospitalized surgical patients: an observational cohort study. *JAMA InternMed* 2014; **174**: 1470-7
395 Partridge JS, Collingridge G, Gordon AL, Martin FC, Harari D, Dhesi JK. Where are we in perioperative medicine for older surgical patients? A UK survey of geriatric medicine delivered services in surgery. *Age Ageing* 2014; **43**: 721-4
396 Harari D, Hopper A, Dhesi J, Babic-Illman G, Lockwood L, Martin F. Proactive care of older people undergoing surgery ('POPS'): designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. *Age Ageing* 2007; **36**: 190-6
397 Vetter TR, Barman J, Hunter JM, Jr., Jones KA, Pittet JF. The Effect of Implementation of Preoperative and Postoperative Care Elements of a Perioperative Surgical Home Model on Outcomes in Patients Undergoing Hip Arthroplasty or Knee Arthroplasty. *Anesthesia and analgesia* 2017; **124**: 1450-8
398 Cannesson M, Ani F, Mythen MM, Kain Z. Anaesthesiology and perioperative medicine around the world: different names, same goals. *BrJAnaesth* 2015; **114**: 8-9

399 Kehlet H, Delaney CP, Hill AG. Perioperative medicine--the second round will need a change of tactics. *Br J Anaesth* 2015; **115**: 13-4
400 Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MP. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. *Anesthesiology* 2013; **119**: 959-81
401 Siracuse BL, Chamberlain RS. A Preoperative Scale for Determining Surgical Readmission Risk After Total Hip Replacement. *JAMA Surg* 2016; **151**: 701-9
402 Young JR, O'Connor CM, Anoushiravani AA, DiCaprio MR. The Use of Dual Mobility Implants in Patients Who Are at High Risk for Dislocation After Primary Total Hip Arthroplasty. *JBJS reviews* 2020; **8**: e20 00028
403 Gromov K, Bersang A, Nielsen CS, Kallemose T, Husted H, Troelsen A. Risk factors for post-operative periprosthetic fractures following primary total hip arthroplasty with a proximally coated double-tapered cementless femoral component. *Bone Joint J* 2017; **99-b**: 451-7
404 Ravi B, Jenkinson R, Austin PC, et al. Relation between surgeon volume and risk of complications after total hip arthroplasty: propensity score matched cohort study. *BMJ* 2014; **348**: g3284
405 Kwon MS, Kuskowski M, Mulhall KJ, Macaulay W, Brown TE, Saleh KJ. Does surgical approach affect total hip arthroplasty dislocation rates? *Clin OrthopRelat Res* 2006; **447**: 34-8
406 Makela KT, Matilainen M, Pulkkinen P, et al. Failure rate of cemented and uncemented total hip replacements: register study of combined Nordic database of four nations. *BMJ* 2014; **348**: f7592
407 Grocott MP, Browne JP, Van der MJ, et al. The postoperative morbidity survey was validated and used to describe morbidity after major surgery. *JClinEpidemiol* 2007; **60**: 919-28
408 Gaudilliere B, Fragiadakis GK, Bruggner RV, et al. Clinical recovery from surgery correlates with single-cell immune signatures. *SciTranslMed* 2014; **6**: 255ra131
409 Jorgensen CC, Gromov K, Petersen PB, Kehlet H. Influence of day of surgery and prediction of LOS > 2 days after fast-track hip and knee replacement. *Acta orthopaedica* 2021; **92**: 170-5
410 Munoz M, Gomez-Ramirez S, Kozek-Langeneker S, et al. 'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients. *BrJ Anaesth* 2015; **115**: 15-24
411 Lunn TH, Frokjaer VG, Hansen TB, Kristensen PW, Lind T, Kehlet H. Analgesic effect of perioperative escitalopram in high pain catastrophizing patients after total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Anesthesiology* 2015; **122**: 884-94
412 de la Motte L, Kehlet H, Vogt K, et al. Preoperative methylprednisolone enhances recovery after endovascular aortic repair: a randomized, double-blind, placebo-controlled clinical trial. *AnnSurg* 2014; **260**: 540-8
413 NICE. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018. Available from https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0795 (accessed 17-04 2018)
414 Lindberg-Larsen M, Joergensen CC, Husted H, Kehlet H. Simultaneous and staged bilateral total hip arthroplasty: a Danish nationwide study. *ArchOrthopTrauma Surg* 2013; **133**: 1601-5
415 Lindberg-Larsen M, Jorgensen CC, Baek HT, Solgaard S, Odgaard A, Kehlet H. Re-admissions, re-operations and length of stay in hospital after aseptic revision knee replacement in Denmark: a two-year nationwide study. *Bone Joint J* 2014; **96-B**: 1649-56

416 Lindberg-Larsen M, Jorgensen CC, Hansen TB, Solgaard S, Kehlet H. Early morbidity after aseptic revision hip arthroplasty in Denmark: a two-year nationwide study. *Bone Joint J* 2014; **96-B**: 1464-71
417 Lindberg-Larsen M, Jorgensen CC, Husted H, Kehlet H. Early morbidity after simultaneous and staged bilateral total knee arthroplasty. *KneeSurgSports TraumatolArthrosc* 2015; **23**: 831-7
418 Wainwright TW, Kehlet H. Fast-track hip and knee arthroplasty - have we reached the goal? *Acta orthopaedica* 2019; **90**: 3-5

Appendix 1 The LCDB questionnaire

Database - Lundbeckfondcenter for fast track hofte og knæ-kirurgi v.8

Social security number ________-_____

Date of surgery ____________

Joint

- ☐ Knee
- ☐ Hip

Type of surgery (completed by the hospital):

- ☐ Primary
- ☐ Revision
- ☐ Uniknee
- ☐ Bilateral procedure

Bloodpercentage (Hb) _______ mmol/l (max three months previously – completed by the hospital)

Heigt: _______ cm

Weight: ________kg

Civil status

- ☐ Living with others
- ☐ Living alone
- ☐ Other (nursing home etc)

Daily smoking?

- ☐ Yes
- ☐ No

Alchohol : Do you drink more than 2 units daily?

- ☐ Yes
- ☐ No

Do you regularly use walking aids outside of home
(Cane/walker or wheelchair)

- ☐ Yes
- ☐ No

Do you feel rested in the morning

- ☐ Yes
- ☐ No

Do you often snore loudly

- ☐ Yes
- ☐ No
- ☐ Do not know

Do you have type-1 diabetes
(treated with insulin just after diagnosis)

- ☐ Yes
- ☐ No

Do you have type-2 diabetes
(often treated with diet, tablets or insulin)

- ☐ Yes
- ☐ No

Do you recieve treatment for hypercholesterolemia

- ☐ Yes
- ☐ No

Do you receive treatment for high blood pressure

- ☐ Yes
- ☐ No

TURN

Do you receive treatment for cardiac disease* (use of medication)

- ☐ Yes
- ☐ No

**E.g. irregular heartrythem, chestpain valvular disease, heart failure etc.*

Do you receive treatment for pulmonary disease* (use of medication)

- ☐ Yes
- ☐ No

**E.g. COPD, Asthma, Cystic fibrosis, Sarcoidosis, systemisc lupus erythematosus, pulmonary oedema etc.*

Do you receive treatment for psychiatric disorder* (use of medication)

- ☐ Yes
- ☐ No

** E.g. Depression, Bipolar (manio-depressive illness), Schizofrenia OCD, Personality disorder, Anxiety, ADHD, congenitive disorders such as Aspergers syndrome etc.*

Have you suffered from a cerebral stroke or bleeding

- ☐ Yes
- ☐ No

Do you have any type of cancer

- ☐ Yes
- ☐ No
- ☐ I have had cancer but have been cured

Do you suffer from renal disease*

- ☐ Yes
- ☐ No

E.g. chronic kidney disease, kidney cysts, diabetic nephropathy etc.
NB. kidneystones, urinary tract infection etc. are ***NOT*** *considered as renal diseases*

Do you use anticaoauglants such as Warfarin, Pradaxa, Xarelto Eliquis etc?
(If you use ASA, clopidogrel or Dipyradimol answer no to this question, if in doubt ask the staff)

- ☐ Yes
- ☐ No

Have you ever had phlebitis or thrombosis in the leg, lung or eye?*

- ☐ Yes
- ☐ No

** Previous venous thromboembolic event: deep venous thrombosis, pulmonary embolism, thrombosis in the eye (Retinal venous occlusion)*

Have your parents/siblings/children experienced phlebitis or thrombosis in the leg, lung or eye

- ☐ Yes
- ☐ No