Title page

Increasing risk of hospital-treated infections and community-based antibiotic use after hip fracture surgery: A nationwide study 2005-2016

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Supplemental data is included with the submission.

Disclosure page

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Increasing risk of hospital-treated infections and community-based antibiotic use after hip fracture surgery: A nationwide study 2005-2016

Abstract:

We aimed to examine trends in the incidence of treated infections following hip fracture surgery in Denmark from 2005 to 2016. We conducted a nationwide cohort study using individual-level linked data from Danish population-based registries. We calculated cumulative incidence considering death as competing risk and, based on the pseudo-observation method, risk ratios (RRs) with 95% confidence interval (CI) using the period 2005-2006 as a reference. RRs were adjusted for age, sex and comorbidity. A total of 74,771 patients aged 65 years or older with first time hip fracture surgery were included. The risk of postoperative (at 15, 30, 90, and 365 days) infections increased during 2005-2016. The 30 days cumulative incidence of all hospital-treated infections increased from 10.8 % (95 % CI: 10.2-11.3) in 2005-2006 to 14.3% (95 % CI: 13.7-15.0) in 2015-2016 [adjusted RR: 1.32 (95% CI: 1.23-1.42)]. Adjusted RR for 30 days hospital-treated pneumonia was 1.70 (95% CI: 1.49-1.92). The 30 days cumulative incidence of redeeming community-based antibiotic prescriptions increased from 17.5 % (95 % CI: 16.8-18.2) in 2005-2006 to 27.1 % (95 % CI: 26.3-27.9) in 2015-2016 [adjusted RR: 1.54 (95 % CI: 1.47-1.62)]. The largest increase was observed for broad-spectrum antibiotic use [adjusted RR: 1.79 (95 % CI: 1.68-1.90**)]**. During 2005-2016, risk of infections was substantially higher in hip fracture patients than in the general population. The risk of hospital-treated pneumonia and antibiotic prescriptions increased more over time among hip fracture patients. We found increased risks of postoperative treated infections following hip fracture surgery during the 12-year study period, which could not entirely be explained by similar infection trends in the general population. Given the high mortality following infections in the elderly, further research is needed to identify patients at increased risk to target preventive treatment and potentially reduce complications and mortality in hip fracture patients.

JBMR Key words: Hip Fracture, Infections, Osteoporosis, Epidemiology, Trends

Introduction

Hip fractures constitute a major clinical and financial burden to the health care system [1, 2], and is the most severe outcome of osteoporosis [3]. Scandinavia, and especially Denmark, has the highest incidence rate of hip fracture worldwide[1, 4], with a standardized incidence rate of 4.23 pr. 1000 person-years in 2014 [5]. Due to ageing populations, the burden of osteoporosis is expected to increase [6], and the annual number of hip fracture is estimated to rise to over six million by the year of 2050 worldwide [7]. Although 1-year mortality decreased by 40% from 1980 through 2014 [5], despite increase in the proportion of patients with severe comorbidity, hip fracture is still associated with a 10% mortality within 30 days and up to 30 % within 1 year of surgery [5, 8].

About 9 %-11 % of hip fracture patients has been reported to develop hospital-acquired pneumonia and 4 %-17.9% to develop urinary tract infection [8, 9, 10, 11], within a varying follow-up time window spanning from during admission to six months follow-up. Pneumonia is a leading cause of death among hip fracture patients [12, 13], and is associated with an excess mortality risk among hip fracture patients [8, 14, 15] . It has been suggested that the decrease in mortality among hip fracture patients over the last 20 years could be explained by improvement in both perioperative and postoperative patient care [5]. Hence, the decrease in mortality in hip fracture patients could be related to a decrease in incidence of infections. We hypothesized that there has been a decrease in the risk of both hospital-treated and community acquired infections over time. No previous studies have examined the change in risk of hospital-treated infections after hip fracture surgery over time in population-based settings; neither have looked at antibiotics use after discharge from the hospital. We therefore conducted a nationwide cohort study to examine temporal trends in the incidence of infections following hip fracture surgery, including hospital-treated infections and community-based antibiotic prescriptions in Denmark from 2005 to 2016. Furthermore, we compared the trends of infections in hip fracture patients with a trend in the general population cohort.

Methods

Setting

We conducted this population-based cohort study within the Danish registers and databases [16]. Denmark is a country of approximately 5.6 million inhabitants with tax-supported universal and free access to healthcare.

The study is reported according to the RECORD guidelines [17].

Data sources

We collected data from The Danish Multidisciplinary Hip Fracture Registry (DMHFR), The Danish National Patient Registry (DNPR), The Danish National Health Service Prescription Database (DNHSPD), and the Danish Civil Registration System (DCRS*).*

DMHFR is a nationwide clinical-quality database on all hip fracture patients age 65 years or older undergoing surgery for an medial, pertrochanteric or subtrochanteric femoral fracture [18]. The database was established in 2003 with the intention to improve the quality of treatment and care of hip fracture patients.

DNPR was established in 1977, and has registered all non-psychiatric hospital admissions since 1977 and all hospital outpatient and emergency visits since 1995 [19]. It includes dates of admission and discharge, main diagnoses, and up to 20 secondary discharge diagnosis codes according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter.

DNHSP contains complete data on all reimbursed prescriptions dispensed from community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 [20]. The drugs are coded according to the Anatomical Therapeutic Chemical classification system.

The DCRS was established in 1968 and contains electronic records on vital status (date of death or emigration) for the entire Danish population and is updated daily. The DCRS assigns unique civil register number to every Danish citizen, which goes through all Danish registers allowing for unambiguous linkage between registers on individual level.

Study participants

DMHFR was used to identify all patients aged 65 years and older who sustained a first-time hip fracture surgery between January 1 2005 and December 31 2016. Patients were included if they were coded with hip fracture as either a primary or secondary inpatient diagnosis. In addition, all included patients had undergone surgery including insertion of a primary hip replacement or open reduction and internal fixation. Patients that emigrated (n=19) or disappeared (n=1) were lost to follow-up and therefore excluded. The total cohort included 74,771 hip fracture patients. Hip fracture surgery date was index date. By using CRS, for each hip fracture patient, we identified up to 5 persons from the general population without hip fracture, alive at the index date, matching on year of birth and gender at the index date. The purpose of the general population comparison cohort was to examine if the infection trends among hip fracture patients differed from infection trends in general. A total of 373,429 persons were included in analysis of the general population comparison cohort.

Outcomes

We examined time to the following outcomes: 1) any hospital-treated infection, and 2) any community-based antibiotic prescriptions in the post-operative period. Using the DNPR, hospital-treated infection was defined as any first time hospital admission or outpatient clinic visit with an infection at a private or a public hospital, after the hip fracture surgery date (ICD-10 codes are listed in Supplementary). Community-based antibiotic prescription was defined as any redeemed first-time antibiotic prescription recorded in the DNHSPD after the surgery date (ATC-codes are listed in Supplementary). Data on in-hospital antibiotic treatment was not available. The outcomes were examined 15-, 30-, 90-, and 365 days after the surgery index.

In addition, we examined specific infections, including hospital-treated pneumonia and hospital-treated urinary tract infections (UTIs), as well as specific subgroups of antibiotics, including broad-spectrum and narrow-spectrum antibiotics.

Covariates

We assessed the following covariates at the date of surgery from the DMHFD: age (65-70, 70-74, 75-79, 80-84, 85-90 and ≥ 90), sex, fracture type (femoral neck and per/subtrochanter fracture), operation type (osteosynthesis and total/hemi arthroplasty), and surgery delay (<24, 24-36, >36 hours, and unknown). Further, we obtained information on body weight and height from the DMHFD to calculate body mass index (BMI) [weight in kilograms (kg) divided by the square of height in meters (m)]. Patients were categorized as underweight (BMI was <18.5 kg/m^2), normal weight (BMI was 18.5- 24.9 kg/m^2), overweight (BMI was 25-29.9 kg/m^2), and obese (BMI was ≥30 kg/m^2).

We collected information on the comorbidities from DNPR ten years prior to hip fracture surgery. As a measure of overall comorbidity, we used the Charlson Comorbidity Index (CCI) score [21, 22]. We defined three comorbidity levels: a score of 0 (low), given to individuals with no previous record of diseases included in the CCI; a score of 1-2 (medium); and a score of 3 or more (high) [23]. In addition, information on specific comorbidities related to risk of infection, such as presence of alcoholism-related disorders, was retrieved from DNRP using ICD-10 codes.

Furthermore, we included use of anti-osteoporotic medication, statins and systemic corticosteroids as reflected by at least one redeemed prescription within one year prior surgery date from DNHSPD, due to potential association between these drugs and infection risk.

Statistical analysis

The study population was followed from the hip fracture surgery date (index date for the general population members) until occurrence of the first infection (or first redeemed antibiotic prescription), death or study end-date. We described characteristics of the hip fracture cohort as the number and percent of patients overall and by calendar period of hip fracture surgery (2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016).

We computed cumulative incidences by calendar year for the hip fracture cohort, considering death as competing risk [24, 25]. Competing risk analysis was chosen instead of Kaplan-Meier in order to avoid a potential overestimation of infections risk [26]. The overall cumulative incidences were calculated within 15, 30, 90 and 365 days of surgery date. For the hip fracture cohort, we calculated overall 30-days incidence rates (IRs) as the number of hip fracture patients with hospital-treated infection during each calendar year (or biennial) divided by the total of risk-time during the same time period following the hip fracture admission, expressed per 1,000 person-years.. The IRs were stratified by sex, age and CCI-score. Based on the pseudo-observation method, 15,30,90 and 365 days cumulative risk ratios (RR) and risk differences (RD) with 95% confidence interval (CI) were calculated using calendar period 2005-2006 as a reference. We estimated both crude and adjusted estimates after accounting for sex, age group and CCI score.

For the general population cohort, we calculated 30-days cumulative incidence of any hospital-treated infection and any community-based antibiotic prescriptions considering death as competing risk. We used Cox Proportional Hazard Regression to compute 30-days Hazards Ratio (HR) with 95

% CI adjusted for CCI, comparing the hip fracture cohort to the matched cohort from the general population in each calendar period. Assumptions for proportional hazard were analyzed by log-minus-log plot, and found acceptable.

All analyses were performed using Stata Version 15.0 (Stata Corp, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency (Region of Central Denmark journal number 1-16-02-444-15). Codes for all study variables are listed in the Supplementary.

Results

Patient characteristics

We identified 74,771 patients with hip fracture surgery from January 1 2005 to December 31 2016. The number of patients per year was stable over the study period. The proportion of females decreased by 4% in 2015-2016 compared to 2005-2006 (Table 1). Age at hip fracture surgery slightly changed over time, and the proportion of patients aged 90 years or older increased from 18 % to 21 % over the study period. The proportion of patients with severe comorbidities (CCI score 3+) increased from 17 % in 2005-2006 to 22 % in 2015-2016. The proportion of patients operated within 24 hours increased from 57 % to 71 % over time. Type of surgery has slightly changed over the study period (Table 1). There were no temporal changes in medication use.

Risk of hospital-treated infection

The cumulative incidences of hospital-treated infections increased from 2005-2006 to 2015-2016 (Table 2). The adjusted RRs were 1.28 (95% CI: 1.18-1.39) for 15-day, 1.32 (95% CI: 1.23-1.42) for 30-day, 1.27 (95 % CI: 1.20-1.35) for 90-day, and 1.23 (95% CI: 1.17-1.30) for 365-day post-operative infections in 2015-2016 compared with 2005-2006 (Table 2). The corresponding risk differences were 2.2% (95% CI: 1.4-3.0), 3.3% (95 % CI: 2.4-4.1), 3.8% (95% CI: 2.8-4.7), and 4.8% (95% CI: 3.4-6.1), respectively.

Patients who underwent surgery in 2015-2016 had an adjusted RR for hospital-treated pneumonia of 1.70 (95 % CI: 1.49-1.92) within 30 days compared with period 2005-2006. In contrast, the adjusted RR for hospital treated UTIs within 30 days was 0.99 (95 % CI: 0.89-1.10) comparing the same periods. Cumulative incidences for pneumonia and UTIs are presented in Table 3.

Risk of community-based antibiotic prescriptions

The cumulative incidences and RRs of community-based antibiotic prescriptions increased continuously during the study period (Table 3). The RRs were highest within 15 days follow-up (Table 3). For patients who underwent surgery in 2015-2016, the adjusted RRs were 2.03 (95% CI: 1.89-2.18) within 15 days, 1.54 (95 % CI: 1.47-62) within 30 days, 1.23 (95 % CI: 1.18-1.28) within 90 days, and 1.06 (95% CI: 1.03-1.09) within 365 days of surgery compared with period 2005-2006. The corresponding adjusted risk differences were 8.7% (95 % CI: 7.9-9.6), 9.6 % (95 % CI: 8.5-10.7), 7.5 % (95 % CI: 6.0-9.0) and 3.1% (95 % CI: 1.5-4.6), respectively. The adjusted RR of broad-spectrum antibiotic prescriptions was 1.79 (95 % CI: 1.68-1.90**)** within 30 days follow up for patients who underwent surgery in 2015-2016 compared with 2005-2006. The adjusted RR of narrow-spectrum antibiotic prescriptions was 1.25 (95 % CI: 1.14-1.38) over the same study period.

Stratified analyses

The 30-day IRs of hospital-treated infections, stratified by sex, age groups and CCI score are presented in *Table 1 A and 1B in Supplementary.* In addition, risk ratios by the same subgroups looking at trend over time are presented in Table 2A and 2B in Supplementary.

The risk of hospital-treated infections within 30 days increased irrespective of sex, age group, and CCI score during the study period. We observed both the highest absolute and relative increase over time among patients older than 85 years and patients with high CCI score.

Changing the reference group from 2005-2006 to 2007-2008 did not essentially change any of study estimates or study conclusions.

In comparison to the matched general population

The 30-days cumulative incidences of both hospital-treated infections and community-based antibiotics were substantially higher in hip fracture patients than in the background population over the entire study period (Figure 2A and 2B). Hip fracture patients had a 13.70 (95% CI: 12.30-15.27) times higher risk of any hospital-treated infection in 2005-2006 and 13.45 (95% CI: 12.19-14.83) times higher risk in 2015-2016, compared with the matched general population (Figure 3A, Supplemental Table 3). Similarly, the risk of hospital-treated pneumonia was 11.28 (95% CI: 9.49-13.41) in 2005-2006 increasing to 16.24 (95% CI: 13.89-19.00) in 2015-2016 for hip fracture patients compared with the general population (Figure 3A). Compared to the background population, hip fracture patients had aHR for community-based antibiotics prescription of 2.70 (95% CI: 2.56-2.85) in 2005-2006 increasing to 4.15 (95% CI: 3.95-4.36) in 2015-2016 (Figure 3B,Supplemental Table 3).

Discussion

In this nationwide cohort study, we found a significant increased risk of both hospital-treated infections and community-based antibiotic prescriptions, following hip fracture surgery during the 12-year study period. The increased risk of treated infections was observed irrespective of patient's age, sex and CCI score. Risk of treated infections in hip fracture patients was substantially higher during the entire study period compared with the risk in the background population.

Methodological considerations

This study is strengthened by its large sample-size with complete follow-up, involving 74,771 patients undergoing hip fracture surgery. Additional strengths include use of a population-based design with nationwide individual-level collected data, eluding potential sampling bias. We identified hospital-treated infections relying on ICD-10 codes from DNPR. Validation studies have indicated a high accuracy, i.e., the positive predictive value (PPV) of any infection diagnosis in the DNPR has been reported to be 98 % among cancer patients between 2006-2010 [(27)]. Furthermore, the PPV of hospitalized pneumonia was 90 % in 1994-2004 in general [(28)] and 93 % in 2006-2010 among cancer patients [(27)]. However, we do not know if the PPV and sensitivity of the infection diagnoses has changed during the study period among hip fracture patients. Diagnostic tools has presumably improved [(19)], leading to a higher probability of detecting a hospital-treated infection over time. An increasing PPV and sensitivity of ICD-10 infection codes among hip fracture patients would potentially lead to differentiated misclassifications and an overestimation of the relative risk estimates. In addition, we cannot eliminate the possibility of residual confounding, and adjustment for CCI might not be sufficient since registration and diagnostic workout for some comorbid conditions included in CCI score most likely improved over time.

Comparison with previous studies

The yearly incidences of pneumonia or UTIs in our study are lower compared to previous studies (in exception of UTI in one study [8,]), evaluating the risk after hip fracture surgery [(8, 9, 10, 11)]. However, these studies have several limitations; including only descriptive analysis and small study populations [(8, 9, 10, 11)] , measuring outcome as patient-reported [(11)], or is restricted to patients treated at a single institution or a selected university hospital [(8, 9, 11)]. We extended the knowledge by including community-based infections, evaluating trends over time, and considered death as competing risk to minimize potential bias.

In the general population, the incidence of common hospital-treated infections, like pneumonia, has increased during 1998-2014 period in UK[(29)]. The total of pneumonia-related hospitalization increased by 63 % from 1997-2011 in the general population in Denmark, and the proportion of pneumonia after any surgical procedure increased from 5.5-6.6% among first-time pneumonia hospitalization in period 2002-2011[(30)].This corresponds to our findings of increased risk of hospital-treated infection in both hip fracture patients and general population. However, increased risk of infections has not been observed in all countries, and a decreased risk of pneumonia was reported in U.S general population during 2003-2009, with the largest decrease among patients >85 years old [(31)]. In contrast, UTIs hospitalization increased by 52 % from 1998 to 2011 in the U.S general population [(32)], but we observed consistent risk among hip fracture patients in our study. Increase in pneumonia risk was also observed among elective total hip arthroplasty between 2000 and 2013, although the absolute estimates were considerable lower in elective arthroplasty compared with hip fracture patients [(33)]. The risk of UTIs in elective hip patients remained unchanged over the same period [(33)]. In addition, some cohort studies reports an increased risk of revision due to prosthetic joint infection after total hip arthroplasty over time (1995-2009 [(34)], 2003-2015 [(35)]). However, results are conflicting (2005-2014 [(36)]), probably related to discrepancy of registration of joint infections in the arthroplasty registers. None of the studies on prosthetic infection was based solely on hip fracture patients.

Possible explanations and underlying mechanisms

The innate and adaptive immune response attenuate with age (immunosenescence) [(37)], resulting in increased risk of infection. The innate response decreases to an even larger extend after hip fracture surgery [(38)], leaving hip fracture patients vulnerable to bacterial infections. However, we did not expect increased infections-risk over time because the quality of in-hospital care has increased among hip fracture patients in Denmark, including increase in patients receiving preoperative optimization before surgery by geriatricians and anaesthesiologists, mobilization within 24 hours of surgery, and assessment of nutritional risk, as well as reduction in surgery delay over time [18]. Furthermore, guidelines for pre- and perioperative prophylactic antibiotics has remained unchanged in hip fracture surgery patients over the study period [39, 40] . However, changes in types of surgery and surgical technique, and blood transfusion practice [41] could have explained our results. Further, we do not know much about quality of rehabilitation of hip fracture patients after discharge from the hospital. Finally, survived patients could be more fragile over time and thereby susceptible for infections. Increasing risk of hospital-treated pneumonia in hip fracture patients could not be explained by increase seen in the general population, because we observed a higher increase among hip fracture patients over the study period.

In addition, hospital-treated infections constitute only small part of infections in general, not capturing infections treated by general practitioners (GPs). Our data suggest that problems with infections in hip fracture patients are even larger than anticipated after including also less serious infections treated by GPs. The total use of antibiotics has generally expanded over the last decades, especially due to the an increased use of broad-spectrum antibiotics [42]. However, the overall use in primary sector, (representing 90 % of the total use of antibiotics,) has been stabilized in Denmark since 2011 [43]. This deviates from the increased risk of antibiotic use among hip fracture patients. As we found higher increase of community-based antibiotic use among hip fracture patients compared to the age-and gender-match cohort, the increase among hip fracture patients is not explained by similar antibiotics trends in general. If the increase of antibiotic treatment was related to a general higher antibiotic availability or changes in antibiotic prescribing over the study period, we would have expected to see similar patterns in the general population.

Clinical implications

Our observed increasing incidence of infections could potentially raise concern. Inappropriate antibiotic use, and especially use of broad-spectrum antibiotics, contributes to antimicrobial resistance [44, 45]. National recommendations (2017) [43] highlights the importance of reducing broad-spectrum antibiotic use in general. Hip fracture patients represent a large patient group, and the increase of broad-spectrum antibiotic use should get attention. Given the high mortality following infections in elderly persons, reducing infections will not only improve post-operative care, but potentially reduce mortality as well. It is clinical important that future studies identify patients at higher risk of infections and that these factors are more than ever considered in individual patient clinical care.

Conclusion

We found evidence of increasing trends in hospital-treated infections and community-based antibiotic use up to one year after hip fracture surgery, from 2005 through 2016. This could not entirely be explained by increase seen in the background population. Given the high mortality following infections in elderly persons, it is clinically important that future studies identify patients at increased risk to target preventive treatment and reduce the risk of infections in hip fracture patients.

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TABLE 1: BASELINE CHARACTERISTICS OF THE HIP FRACTURE STUDY POPULATION, DENMARK 2005-2016

	Calendar Period Of hip fracture diagnosis						**Total**
Patient characteristics	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2005-2016
No. of patients	12,453	13,236	12,724	12,706	12,285	11,367	74,771
Age, years							
65-69	884 (7)	895 (7)	986 (8)	1,133 (9)	1,108 (9)	1,045 (9)	6,051 (8)
70-74	1,334 (11)	1,372 (10)	1,426 (11)	1,402 (11)	1,418 (12)	1,399 (12)	8,351 (11)
75-79	2,196 (18)	2,140 (16)	2,027 (16)	2,082 (16)	1,947 (16)	1,793 (16)	12,185 (16)
80-84	3,087(25)	3,163 (24)	2,882 (23)	2,632 (21)	2,507 (20)	2,285 (20)	16,556 (22)
85-89	2,753 (22)	3,205 (24)	3,114 (24)	3,065 (24)	2,827 (23)	2,500 (22)	17,464 (23)
≥90	2,199 (18)	2,461 (19)	2,289 (18)	2,392 (19)	2,478 (20)	2,345 (21)	14,164 (19)
Sex							
Female	9,128(73)	9,628 (73)	9,151(72)	8,919 (70)	8,662 (71)	7,858 (69)	53,346 (71)
Male	3,325 (27)	3,608 (27)	3,573 (28)	3,787 (30)	3,623 (29)	3,509 (31)	21,425 (29)
Charlson Comorbidity Index score							
- 0 (No comorbidity)	5,427 (44)	5,473 (41)	5,140 (40)	5,032 (40)	4,673 (38)	4,354 (38)	30,111 (40)
- 1-2 (Medium)	4,969 (40)	5,383 (41)	5,202 (41)	5,123 (40)	5,006 (41)	4,562 (40)	30,251 (40)
- 3+ (High)	2,057 (17)	2,380 (18)	2,382 (19)	2,551 (20)	2,606 (21)	2,451 (22)	14,429 (19)
Alcohol-related conditions*							
None	12,179 (98)	12,841(97)	12,289 (97)	12,238 (96)	11,766 (96)	10,821 (95)	72,134 (96)
1 or more	274 (2)	395 (3)	435 (3)	468 (4)	519 (4)	546 (5)	2,637 (4)
Body Mass Index, kg/m2							
Underweight <18.5	1,002 (8)	1,274 (10)	1,124 (9)	1,109 (9)	1,088 (9)	857 (8)	6,454 (9)

Normal weight 18.5- 24.9	5,126 (41)	6,179 (47)	5,713 (45)	5,897 (46)	5,926 (48)	5,140 (45)	33,981 (45)
Overweight 25-29.9	1,974 (16)	2,355 (18)	2,328 (18)	2,739 (22)	2,724 (22)	2,568 (23)	14,688 (20)
Obese ≥30	541 (4)	617 (5)	624 (5)	763 (6)	770 (6)	788 (7)	4,103 (5)
Unknown	3,810 (31)	2,811 (21)	2,935 (23)	2,198 (17)	1,777 (14)	2,014 (18)	15,545 (21)
Medication use (yes)							
Anti-Osteoporotic drugs	843 (7)	964 (7)	986 (8)	1,007 (8)	925 (8)	795 (7)	5,520 (7)
Systemic corticosteroids	875 (7)	835 (6)	798 (6)	771 (6)	682 (6)	645 (6)	4,606 (6)
Statins	1,096 (9)	1,825 (18)	2,376 (19)	2,761 (22)	2,832 (23)	2,650 (23)	13,540 (18)
Surgery delay							
<24 hours	7,130 (57)	7,563 (57)	7,614 (60)	8,251 (65)	8,630 (70)	8,097 (71)	47,285 (63)
24-35 hours	1,965 (16)	2,104 (16)	2,035 (16)	1,990 (16)	1,738 (14)	1,547 (14)	11,379 (15)
>36 hours	3,263 (26)	3,496 (26)	3,074 (24)	2,464 (19)	1,917 (16)	1,723(15)	15,937 (21)
Unknown	95 (1)	73 (1)	1 (0)	1 (0)	0 (0)	0 (0)	170 (0)
Fracture type							
Fracture of femoral neck	6,423 (52)	6,736 (51)	6,552 (51)	6,714 (53)	6,821 (56)	6,352 (56)	6,423 (52)
Per and Sub-trochanter fractures	6,030 (48)	6,500 (49)	6,172 (49)	5,992 (47)	5,464 (44)	5,015 (44)	6,030 (48)
Operation type							
Osteosyntheses	9,341 (75)	9,669 (73)	8,830 (69)	8,422 (66)	7,962 (65)	7,312 (64)	51,536 (69)
Total and hemi hip arthroplasty	3,112 (25)	3,567 (27)	3,894 (31)	4,284 (34)	4,323 (35)	4,055 (36)	23,235 (31)

* Not included in the Charlson Comorbidity Index score

TABLE 2*: CUMULATIVE INCIDENCE, CUMULATIVE RISK DIFFERENCE AND CUMULATIVE RISK RATIO FOR HOSPITAL-TREATED INFECTION AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

		0-15 Days of surgery					**0-30 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Infections	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Cumulative Risk Ratio (RR) (95 % CI) Adjusted**	No. Of Infections	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Cumulative Risk Ratio (RR) (95 % CI) Adjusted**
2005-2006	12,453	1,043	8.4 (7.9-8.9)	Reference	Reference	Reference	1,339	10,8 (10.2-11.3)	Reference	Reference	Reference
2007-2008	13,236	1,134	8.6 (8.1-9.1)	0.0 (-0.6 -0.7)	1.02 (0.94-1.11)	1.01 (0.93-1.10)	1,482	11.2 (10.7-11.7)	0.2 (-0.5-0.9)	1.04 (0.97-1.11)	1.03 (0.96-1.10)
2009-2010	12,724	1,296	10.2 (9.7-10.7)	1.6 (0.9- 2.3)	1.21 (1.12-1.31)	1.21 (1.11-1.31)	1,679	13.2 (12.6-13.8)	2.2 (1.4-3.0)	1.22 (1.14-1.31)	1.21 (1.13-1.30)
2011-2012	12,706	1,242	9.8 (9.3-10.3)	1.2 (0.5-1.9)	1.16 (1.08-1.26)	1.16 (1.07-1.25)	1,690	13.3 (12.7-13.9)	2.3 (1.5-3.1)	1.23 (1.15-1.32)	1.22 (1.14-1.31)
2013-2014	12,285	1,304	10.6 (10.1-11.2)	2.0 (1.3-2.7)	1.27 (1.17-1.36)	1.25 (1.16-1.36)	1,771	14.4 (13.8-15.0)	3.3 (2.5-4.1)	1.34 (1.25-1.43)	1.32 (1.23-1.41)
2015-2016	11,367	1,229	10.8 (10.2-11.4)	2.2 (1.4-3.0)	1.29 (1.19-1.40)	1.28 (1.18-1.39)	1,631	14.3 (13.7-15.0)	3.3 (2.4-4.1)	1.33 (1.25-1.43)	1.32 (1.23-1.42)
		0-90 Days of surgery					**0-365 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Infections	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Cumulative Risk Ratio (RR) (95 % CI) Adjusted**	No. Of Infections	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Cumulative Risk Ratio (RR) (95 % CI) Adjusted**
2005-2006	12,453	1,841	14.8 (14.2-15.4)	Reference	Reference	Reference	2,706	21.8 (21.0-22.4)	Reference	Reference	Reference
2007-2008	13,236	2,112	16.0 (15.3-16.6)	0.8 (-0.0-1.7)	1.08 (1.02-1.14)	1.06 (1.00-1.12)	3,112	23.6(22.9-24.3)	1.4 (0.4-2.4)	1.08 (1.04-1.13)	1.07 (1.02-1.12)
2009-2010	12,724	2,263	17.8 (17.1-18.5)	2.6 (1.7-3.5)	1.20 (1.13-1.27)	1.18 (1.12-1.26)	3,212	25.2 (24.5-26.0)	3.0 (2.0-4.0)	1.16 (1.11-1.21)	1.14 (1.09-1.20)
2011-2012	12,706	2,325	18.3 (17.6-19.0)	3.1 (2.2-4.0)	1.23 (1.17-1.30)	1.22 (1.15-1.29)	3,287	25.9(25.1-26.6)	3.5 (2.5-4.6)	1.19 (1.14-1.24)	1.17 (1.12-1.23)
2013-2014	12,285	2,387	19.4 (18.7-20.1)	4.1 (3.2-5.1)	1.31 (1.24-1.38)	1.29 (1.22-1.37)	3,387	27.6 (26.8-28.3)	5.1 (4.0-6.2)	1.27 (1.21-1.32)	1.24 (1.19-1.30)
2015-2016	11,367	2,167	19.1 (18.3-19.8)	3.8 (2.8-4.7)	1.29 (1.22-1.36)	1.27 (1.20-1.35)	1,614 ***	27.2 (26.1-28.3) ***	4.8 (3.4-6.1) ***	1.25 (1.18-1.32) ***	1.23 (1.17-1.30) ***

* Considering death as competing risk, **Adjusted for age, sex and comorbidity (Charlson Comorbidity Index score), ***Only patients operated in 2015 (not 365 days follow-up time in 2016)

TABLE 3*: CUMULATIVE INCIDENCE AND CUMULATIVE RISK RATIO OF SPECIFIK INFECTIONS AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

0-30 Days Risk Of Pneumonia and Urinary Tract Infection				
	PNEUMONIA		URINARY TRACT INFECTION (UTI)	
Calendar period of hip fracture diagnosis	Cumulative Incidence- % (95 % CI)	Cumulative Risk Ratio(RR)** (95 % CI)	Cumulative Incidence- % (95 % CI)	Cumulative Risk Ratio(RR)** (95 % CI)
2005-2006	3.7 (3.4-4.0)	Reference	5.7 (5.3-6.1)	Reference
2007-2008	4.2 (3.8-4.5)	1.10 (0.96-1.26)	5.5 (5.1-5.9)	0.94 (0.85-1.04)
2009-2010	5.3 (4.9-5.7)	1.37 (1.20-1.56)	6.0 (5.6-6.4)	1.05 (0.95-1.16)
2011-2012	5.5 (5.1-5.9)	1.42 (1.25-1.61)	5.8 (5.4-6.2)	1.01 (0.91-1.12)
2013-2014	6.5 (6.1-7.0)	1.70 (1.50-1.92)	6.0 (5.5-6.4)	1.02 (0.92-1.13)
2015-2016	6.6 (6.1-7.0)	1.70 (1.49-1.92)	5.7 (5.3-6.1)	0.99 (0.89-1.10)

*Considering death as competing risk ** Adjusted for age, sex and comorbidity Charlson Comorbidity Index score)

TABLE 4*: CUMULATIVE INCIDENCE, CUMULATIVE RISK DIFFERENCE AND CUMULATIVE RISK RATIO FOR COMMUNITY-BASED ANTIBIOTIC PRESCIPRTIONS AFTER HIP FRACTURE SURGERY, DENMARK, 2005-2016

		0-15 Days of surgery					**0-30 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**
2005-2006	12,453	1,047	8.4 (7.9-8.3)	Reference	Reference	Reference	2,179	17.5 (16.8-18.2)	Reference	Reference	Reference
2007-2008	13,236	1,244	9.4 (8.9-9.9)	0.8 (0.1-1.4)	1.11 (1.03-1.19)	1.10 (1.02-1.19)	2,472	18.7 (18.0-19.3)	0.8 (-0.0-1.7)	1.06 (1.01-1.12)	1.05 (1.00-1.11)
2009-2010	12,724	1,423	11.2 (10.6-11.7)	2.5 (1.8-3.3)	1.30 (1.21-1.40)	1.32 (1.23-1.43)	2,702	21.2 (20.5-22.0)	3.4 (2.5-4.4)	1.20 (1.14-1.26)	1.21 (1.15-1.27)
2011-2012	12,706	1,719	13.5 (12.9-14.1)	4.9 (4.2-5.7)	1.58 (1.47-1.69)	1.58 (1.47-1.70)	3,023	23.8 (23.1-24.5)	6.1 (5.1-7.1)	1.35 (1.28-1.41)	1.35 (1.28-1.41)
2013-2014	12,285	1,940	15.8 (15.1-16.4)	7.2 (6.4-8.1)	1.85 (1.73-1.98)	1.86 (1.73-2.00)	3,187	25.9 (25.2-26.7)	8.2 (7.2-9.3)	1.47 (1.40-1.54)	1.47 (1.40-1.55)
2015-2016	11,367	1,945	17.1 (16.4-17.8)	8.7 (7.9-9.6)	2.02 (1.89-2.16)	2.03 (1.89-2.18)	3,082	27.1 (26.3-27.9)	9.6 (8.5-10.7)	1.55 (1.47-1.62)	1.54 (1.47-1.62)

		0-90 Days of surgery					**0-365 Days of surgery**				
Calendar Period of Diagnosis	No. Of Patients	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-%** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**	No. Of Prescriptions	Cumulative Incidence- % (95 % CI)	Cumulative Risk Difference-% ** (95 % CI)	Cumulative Risk Ratio (RR) (95 % CI) Crude	Adjusted**
2005-2006	12,453	4,067	32.7 (31.8-33.5)	Reference	Reference	Reference	6,656	53.4 (52.6-54.3)	Reference	Reference	Reference
2007-2008	13,236	4,484	33.9 (33.07-34.7)	0.7 (-0.0-1.8)	1.03 (1.00-1.07)	1.02 (0.99-1.06)	7,093	53.6 (52.7-54.4)	-0.2 (-1.4- 1.0)	1.00 (0.98-1.02)	0.99 (0.97-1.02)
2009-2010	12,724	4,558	35.8 (35.0-36.7)	2.3 (1.6-3.9)	1.09 (1.06-1.13)	1.09 (1.05-1.12)	6,961	54.7 (53.8-55.6)	1.0 (-0.2-2.3)	1.02 (1.00-1.05)	1.02 (1.00-1.04)
2011-2012	12,706	4,862	38.3 (37.4-39.1)	5.3 (4.2-6.5)	1.17 (1.19-1.21)	1.16 (1.12-1.20)	7,085	55.8 (54.9-56.6)	2.3 (1.0-3.5)	1.04 (1.02-1.07)	1.04 (1.02-1.07)
2013-2014	12,285	4,966	40.4 (39.3-41.2)	7.5 (6.3-8.7)	1.23 (1.19-1.28)	1.23 (1.19-1.27)	7,079	57.6 (56.7-58.5)	4.1 (2.8-5.3)	1.08 (1.05-1.10)	1.08 (1.05-1.10)
2015-2016	11,367	4,576	40.4 (39.2-41.7) ***	7.5 (6.0-9.0) ***	1.23 (1.19-1.28) ***	1.23 (1.18-1.28) ***	3409 ***	56.5 (52.8-54.7) ***	3.1 (1.5-4.6) ***	1.06 (1.03-1.09) ***	1.06 (1.03-1.09) ***

* Considering death as competing risk, **Adjusted for age, sex and comorbidity (Charlson Comorbidity Index score), ***Only patients operated in 2015 (not 365 days follow-up time in 2016)

Figure legends

FIGURE 1: Adjusted cumulative risk ratio of community-based antibiotic prescriptions within 30 days of hip fracture surgery for periods 2007-2008, 2009-2010, 2011-2012, 2013-2014 and 2015-2016 compared with 2005-2006 as reference

FIGURE 2 (A and B): 30-Days Cumulative incidence of infection in hip fracture patients and general population, 2005-2016

FIGURE 3A: Time trends of 30-Days adjusted hazard ratio (aHR) of hospital-treated infections in hip fracture patients, compared to a matched cohort from the general population, 2005-2016

FIGURE 3B: Time trends of 30-Days adjusted hazard ratio (aHR) of community-based antibiotics in hip fracture patients, compared to a matched cohort from the general population, 2005-2016