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Research Article

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The association between initial opioid type and long-term opioid use after hip fracture surgery in elderly opioid-naïve patients

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Abstract

Objectives: Long-term opioid use after hip fracture surgery has been demonstrated in previously opioid-naïve elderly patients. It is unknown if the opioid type redeemed after hip surgery is associated with long-term opioid use. The aim of this study was to examine the association between the opioid type redeemed within the first three months after hip fracture surgery and opioid use 3–12 months after the surgery.

Methods: A nationwide population-based cohort study was conducted using data from Danish health registries (2005–2015). Previously opioid-naïve patients registered in the Danish Multidisciplinary Hip Fracture Registry, aged ≥ 65 years, who redeemed ≥ 1 opioid prescription within three months after the surgery, were included. Long-term opioid use was defined as ≥ 1 redeemed prescription within each of three three-month periods within the year after hip fracture surgery. The proportion with long-term opioid use after surgery, conditioned on nine-month survival, was calculated according to opioid types

within three months after surgery. Adjusted odds ratios (aOR) for different opioid types were computed by logistic regression analyses with 95% confidence intervals (CI) using morphine as reference. Subgroup analyses were performed according to age, comorbidity and calendar time before and after 2010.

Results: The study included 26,790 elderly, opioid-naïve patients with opioid use within three months after hip fracture surgery. Of these patients, 21% died within nine months after the surgery. Among the 21,255 patients alive nine months after surgery, 15% became long-term opioid users. Certain opioid types used within the first three months after surgery were associated with long-term opioid use compared to morphine (9%), including oxycodone (14%, aOR; 1.76, 95% CI 1.52–2.03), fentanyl (29%, aOR; 4.37, 95% CI 3.12–6.12), codeine (13%, aOR; 1.55, 95% CI 1.14–2.09), tramadol (13%, aOR; 1.56, 95% CI 1.35–1.80), buprenorphine (33%, aOR; 5.37, 95% CI 4.14–6.94), and >1 opioid type (27%, aOR; 3.83, 95% CI 3.31–4.44). The proportion of long-term opioid users decreased from 18% before 2010 to 13% after 2010.

Conclusions: The findings suggest that use of certain opioid types after hip fracture surgery is more associated with long-term opioid use than morphine and the proportion initiating long-term opioid use decreased after 2010. The findings suggest that some elderly, opioid-naïve patients appear to be presented with untreated pain conditions when seen in the hospital for a hip fracture surgery. Decisions regarding the opioid type prescribed after hospitalization for hip fracture surgery may be linked to different indication for pain treatment, emphasizing the likelihood of careful and conscientious opioid prescribing behavior.

Keywords: hip fracture surgery; opioid; opioid cessation.

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Introduction

Hip fracture surgery is frequent in the elderly population with an incidence rate of up to four cases per 1,000

person-years in Denmark [1]. Despite age-standardized incidence rates seem decreasing in most countries; the decrease in rates is exceeded by an increase in absolute numbers due to the aging of the populations [2]. Hip fracture patients are typically fragile and often present with comorbidity and polypharmacy making them more vulnerable to drug interactions and adverse events [3]. Lindestrand et al. (2015) found that 95% of 416 admitted hip fracture patients received opioids for acute pain management during the hospital admission and 3% of 416 admitted hip fracture patients were opioid users after six months [4]. Another study has shown that 17% of previously opioid-naïve patients redeemed opioid prescriptions within 9–12 months after hip fracture surgery, and 8% of previously opioid-naïve patients continued redeeming opioid prescriptions in all four quarters after the surgery [5].

Opioid use both in Denmark and worldwide seems closely linked to the level of pain and aging in the population [6]. Poor assessment of pain in elderly patients and concerns of polypharmacy, tolerance, physical dependence, addiction and adverse effects results in underutilization of opioids and poor pain management in elderly patients [7]. Underutilized pain management may generally result in readmissions, delayed recovery, morbidity, mortality, and possibly chronic pain [8]. Although evidence supporting the choice of one specific opioid type over another is lacking, recommendations exist regarding considerations of specific patient factors [9]. There has been a global shift in patterns of prescription opioid use, specifically the types of opioid prescribed [10–12], but the total number of opioid users in Denmark has stabilized from 2011 to 2012 up to 2017 [10, 12]. A study across multiple pain etiologies, including surgery, determined that higher doses, longer durations, slow-release formulations and prescribing of tramadol at initiation were associated with long-term opioid use [13]. However, the indication for opioid initiation was chronic pain for the majority of the patients [13]. The prevalence of self-reported chronic non-malignant pain in Denmark affected almost 27% of the adult population in 2010, and the tendency to treat with opioids increased from 2005 to 2013 and was highest among elderly women [14]. The present study hypothesize that the prescribers behavior and choice of opioid types after hip fracture surgery in elderly patients, is linked to the need of opioid therapy the year after surgery for the individual patients, and opioid prescribing behavior have changed as the public focus on misuse, addiction, and withdrawal has increased.

The aim of this Danish nationwide cohort study was to examine the association between the type of opioid

redeemed within three months after surgery and long-term opioid use 3–12 months after surgery in opioid-naïve elderly hip fracture patients from 2005 until 2015.

Methods

Study design and settings

This population-based cohort study was conducted in Denmark (source population aged ≥ 65 ~1.07 million in 2015 [15]), using prospectively collected data from a nationwide clinical quality database [16] and administrative data from national health registries, which cover all contacts to the health-care sector [17]. Universal healthcare for all Danish citizens is tax-supported and free [18]. This study was approved by the Danish Data Protection Agency (Central Denmark Region record number: 1-16-02-467-15).

Data sources

The study population was identified from the Danish Multidisciplinary Hip Fracture Database and linked to additional data from the Danish National Patient Registry (DNPR), the Danish National Health Service Prescription Database, and the Danish Civil Registration System. A complete list of the included codes for registry diagnoses, procedures, and drugs is available in the supplemental (Appendix E1).

The Danish Multidisciplinary Hip Fracture Registry is a nationwide clinical registry of population-based pre-, peri-, and post-operative data on all patients aged 65 or more who underwent surgical treatment (osteosynthesis or total/partial hip replacement) for a primary hip fracture (fracture of femoral neck, per-, or sub-trochanter fracture) in Denmark since 2003 (Table E1.1) [16]. Between 2004 and 2010, the registry was based on an online independent registration system, but since 2010, the registry uses data directly reported to DNPR. A number of new diagnostic and treatment codes have been created in DNPR in order to transform all data from the Danish Multidisciplinary Hip Fracture Registry registration platform to DNPR. The primary data source in the present study is the Danish Multidisciplinary Hip Fracture Registry. Although majority of clinical data is pooled from DNPR, this is recommended by clinicians and The Danish Clinical Quality Program, National Clinical Registries in order to maintain and further improve the continuously registration of codes specifically established for this database in the DNPR [16]. However, not all data are available in this database e.g. data on comorbidity and prescriptions. The ability to identify hip fracture patients using administrative databases is high because hip fracture surgery is an acute hospital-based procedure and because of reimbursement policy for both diagnosis and surgery codes [19].

Additionally, the DNPR holds records on all inpatient admissions to Danish somatic hospitals since 1977 and outpatient discharges and emergency room visits since 1995. Diagnoses are coded according to the International Classification of Diseases, Eight Revision (ICD-8) from 1977 to 1993 and according to International Classification of Diseases, 10th Revision (ICD-10) thereafter [20]. All somatic diagnoses 10 years before surgery (thus, until 1995) were identified based on ICD-10.

The Danish National Health Service Prescription Database holds information on all prescription drugs distributed by Danish

pharmacies after 2004, identified by the Anatomical Therapeutic Chemical classification system codes (ATC codes) [21]. The Danish Civil Registration System holds data on date of birth, age, gender, and vital status (daily updated). Furthermore, the registry holds 10-digit personal identification numbers, which permit database-linkage on individual patient-level [22].

Study population

First, all patients aged 65 years or older undergoing primary hip fracture surgery in Denmark from 1st of January 2005 to 31st of December 2015 and registered in the Danish Multidisciplinary Hip Fracture Registry were identified. Only patients who were opioid-naïve at the time of surgery (defined as no opioid dispensing six months before surgery) and those with at least one opioid dispensing within eight days to three months after surgery were included in the final study population. Furthermore, only patients who were alive nine months after the surgery were included in analyses on long-term opioid use. Age above 65 years was chosen because the primary data source for this study was based on the Danish Multidisciplinary Hip Fracture Registry, which collects clinical data on all hip fracture in patients above 65 years of age.

Opioid use within three months after surgery and long-term use

Opioid use was identified from the Danish National Health Service Prescription Database. Opioid dispensing was collected from six months before the date of surgery until a year after surgery. Opioid dispensing in community pharmacies within a seven-day period before and after the hip fracture surgery date was not included because data on in-hospital opioid use, directly dispensed by healthcare providers, are not available from the Danish National Health Service Prescription Database, and all included patients were hospitalized within at least part of this period.

The opioids were classified into eight types according to ATC codes and number of users (Table 1). The opioid types included in the analyses were: morphine, oxycodone, fentanyl, codeine, tramadol, buprenorphine, “other opioids” (nicomorphine, oxycodone combined with naloxone, pethidine, ketobemidone, methadone, and tapentadol), and >1 opioid type. Patients were identified as users of a specific opioid type based on one or more redeemed prescription of the specific opioid types within the period. The category “Other opioids” was defined based on opioid types with > 1,000 prescriptions redeemed in total within the first three months after surgery. If patients redeemed more than one opioid type within three months after surgery, they were defined within the >1 opioid type group; thus, not counted within any specific opioid type group in the analyses.

Long-term opioid use has previously been defined based on different patterns of repeated prescription redeeming and continuation of opioid therapy for more than 90 days [23, 24]. In the present study, long-term opioid use up to a year after surgery was defined as one or more redeemed opioid prescriptions within each of three time periods the year after hip fracture surgery. The three periods include 3–6 months, 6–9 months, and 9–12 months after hip fracture surgery. Thus, the overall opioid use (beyond the three months inclusion criteria) starts within six months after hip fracture surgery and that it

Table 1: Opioids. The table illustrates the included and analyzed opioids, ATC codes, administration forms for prescription drugs in pharmacies, and number of users of each opioid type in total within eight days to three months after hip fracture surgery in the opioid-naïve hip fracture population with opioid use after the surgery (n=26,790). The number of users of each opioid type indicates a high amount of users of more than one opioid type within the period. ATC: Anatomical Therapeutic Chemical Classification System code, PO: Per Oral, N: Number of patients.

Opioid	ATC	Administration	n, within first three month:
Agonists			16,681
Morphine	N02AA01	PO, Rectal	5,871
Nicomorphine	N02AA04	PO	189
Oxycodone	N02AA05	PO, Rectal	9,333
Oxycodone + naloxone	N02AA55	PO	≤5
Pethidine	N02AB02	PO, Rectal	124
Fentanyl	N02AB03	Transdermal, Buccal	1,433
Ketobemidone	N02AG02	PO, Rectal	603
Codeine	N02AI06	PO	1,095
Methadone	N07BC02	PO	17
Dual action agonists:			12,244
Tramadol	N02AX02	PO	12,239
Tapentadol	N02AX06	PO	8
Partial agonists:			1,602
Buprenorphine	N02AE01	Transdermal, Buccal	1,602

spans for more than three months; although, redemption-free periods may appear. No information on doses or days' supply was included in the definition.

Covariates

The following covariates were assessed from the Danish Multidisciplinary Hip Fracture Registry at the day of surgery: age (in categories 65–74, 75–84 and ≥85 years), gender, fracture type (femoral neck or per-/sub-trochanter fracture), and surgery type (osteosynthesis or total/partial hip replacement). Additionally, comorbidity was identified from the DNPR and summarized using the Charlson Comorbidity Index (CCI) score, including both primary and secondary somatic diagnoses from any in- and outpatient contact 10 years preceding the date of hip fracture surgery [25, 26]. In the absence of good reference for look-back period relevant for opioid use, 10 years look-back period was chosen, since CCI based on DNPR 10 years before submission was found to account for the most predictive ability of one-year mortality in patients with admission for Myocardial Infarction in Denmark from 2009 to 2011 [27]. However, the strength of the association between time of diagnosis and mortality may to some extent be disease dependent [28]. The CCI scores were classified as ‘no comorbidity’ (CCI score 0), ‘medium comorbidity’ (CCI score 1–2) or ‘severe comorbidity’ (CCI score ≥3) (Table E1.2).

Statistics

Baseline characteristics of the hip fracture cohort were described as median age and interquartile range (IQR) and proportions (numbers and percentages) overall and stratified according to opioid types used within three months after surgery. Additionally, three-, nine-, and 12-month cumulative mortality risk after hip fracture surgery was reported and the three- and nine-month cumulative risk were presented according to opioid types used within three months after surgery. The proportion of long-term opioid users conditioned on nine-month survival was calculated for each opioid type. Uni- and multivariable logistic regression analyses conditioned on nine-month survival were performed in order to identify the odds ratios (OR) and adjusted odds ratios (aOR) for long-term opioid use according to opioid type after hip fracture surgery compared with morphine as reference group. The multivariable analyses were adjusted for age, gender, fracture- and surgery type, and comorbidity level. Corresponding subgroup logistic regression analyses according to time of surgery (before and after 2010), age, and comorbidity levels were executed. Confidence levels were set at 95%. Statistical analyses were performed in STATA version 15 (StataCorp, TX, USA).

Results

Patient characteristics

A total of 69,456 patients had primary hip fracture surgery in Denmark from the 1st of January 2005 to the 31st of December 2015, of whom 27% used opioids within six months prior to

surgery. Additionally, 3% of the hip fracture patients were opioid-naïve but died within seven days after the surgery and 32% were opioid-naïve but without opioid use within eight days to three months after the surgery. Thus, 26,790 patients were included in the study population corresponding to 39% of the basis population. A study population flowchart is presented in Figure 1. Median age for these patients at surgery was 83 years (IQR 77–88), and 19,094 (71%) of the patients were women. Baseline characteristics of the patients according to use of different opioid types within three months after hip fracture surgery as well as number and proportion of users of the opioids within the period are presented in Table 2, along with numbers and proportions of patients with use of each opioid, overall and before and after 2010. This revealed large differences in prescribing habits in regard to baseline patient characteristics within the population. Among the patients included in the study population, 5,535 (21%) died within eight days to nine months after surgery. Consequently, only 21,255 patients were alive nine months after hip fracture surgery, and thus, were at-risk of long-term opioid use. This corresponds to 31% of the basis population.

Mortality according to opioid type

Within the period of eight days to three months after hip fracture surgery, 3,204 (12%) of the 26,790 included hip

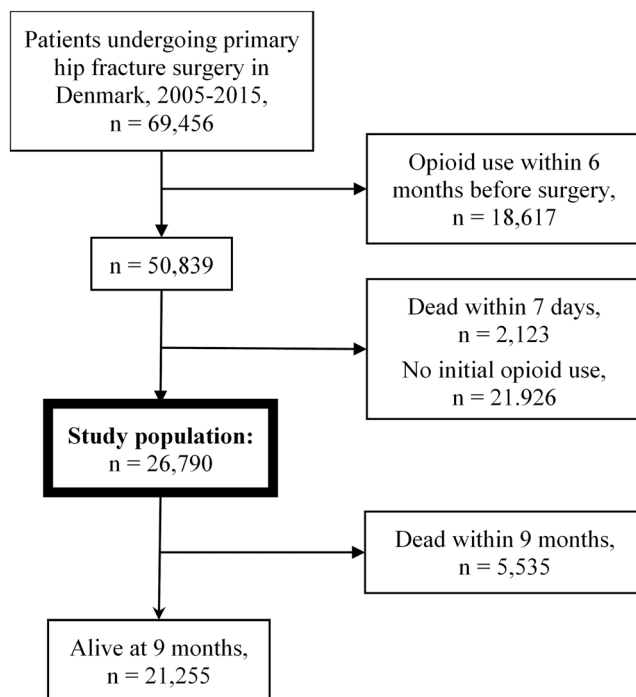


Figure 1: Flowchart. Flowchart on the formation of the study population. Proportions and regression analysis were conditioned on nine-month survival.

Table 2: Baseline characteristics. Baseline characteristics of the hip fracture cohort according to opioid type used within three months after surgery, Denmark, 2005–2015, presented according to age, gender, fracture- and surgery type, and comorbidity level. Additionally, the numbers and proportions of users of the different opioid types within the first three months after hip fracture surgery are presented for two time intervals for the surgery 2005–2009 and 2010–2015. n: Number of patients, CCI: Charlsons Comorbidity Index.

	All patients						Patients with initial use of:			
	Morphine	Oxycodone	Fentanyl	Codeine	Tramadol	Buprenorphine	Other	>1 type		
Total	26,790 (100%)	6,865 (26%)	448 (2%)	547 (2%)	9,180 (34%)	595 (2%)	322 (1%)	4,969 (19%)		
Age										
65–74	942 (24%)	1,508 (22%)	29 (6%)	82 (15%)	1,873 (20%)	33 (6%)	38 (12%)	861 (17%)		
75–84	1,408 (36%)	2,698 (39%)	126(28%)	207 (38%)	3,701 (40%)	188 (32%)	93 (29%)	1,804 (36%)		
≥85	1,514 (39%)	2,659 (39%)	293(65%)	258 (47%)	3,701 (39%)	374 (63%)	191 (59%)	2,304 (46%)		
Gender										
Male	1,246 (32%)	1,937 (28%)	130 (29%)	123 (22%)	2,609 (28%)	147 (25%)	93 (29%)	1,411 (28%)		
Female	2,618 (68%)	4,928 (72%)	318 (71%)	424 (78%)	6,571 (72%)	448 (75%)	229 (71%)	3,558 (72%)		
Fracture type										
Femoral neck	1,877 (49%)	3,203 (47%)	215 (48%)	281 (51%)	4,623 (50%)	287 (48%)	152 (47%)	2,313 (47%)		
Per-/sub-trochanter	1,987 (51%)	3,662 (53%)	233 (52%)	266 (49%)	4,557 (50%)	308 (52%)	170 (53%)	2,656 (53%)		
Surgery type										
Osteosynthesis	2,691 (70%)	5,110 (74%)	322 (72%)	401 (73%)	6,668 (73%)	435 (73%)	242 (75%)	3,841 (77%)		
Primary hip replacement	1,173 (30%)	1,755 (26%)	126 (28%)	146 (27%)	2,512 (27%)	160 (27%)	80 (25%)	1,128 (23%)		
CCI										
No comorbidity (0)	1,649 (43%)	3,068 (45%)	158 (35%)	238 (43%)	4,141 (45%)	251 (42%)	128 (40%)	1,958 (39%)		
Medium comorbidity (1–2)	1,580 (41%)	2,702 (39%)	210 (47%)	217 (40%)	3,658 (40%)	247 (42%)	141 (44%)	2,068 (42%)		
Severe comorbidity (≥3)	635 (16%)	1,095 (16%)	80 (18%)	92 (17%)	1,381 (15%)	97 (16%)	53 (16%)	943 (19%)		
Sub population										
All patients										
Morphine										
2005–2009	255 (2%)	3,784 (31%)	169 (1%)	268 (2%)	4,963 (41%)	306 (3%)	223 (2%)	2,089 (17%)		
2010–2015	3,609 (24%)	3,081 (21%)	279 (2%)	279 (2%)	4,217 (29%)	289 (2%)	99 (0.7%)	2,880 (20%)		

Table 3: Mortality. Three and nine month mortality in the patients with use of different opioid types within three and nine months after hip fracture surgery, ranked from the lowest to highest mortality. n: Number of patients. n=26,790.

Opioid type	Number of users	eight days to three month	eight days to nine months
	n	n, %	n, %
Oxycodone	6,865	397 (6%)	872 (13%)
Tramadol	9,180	648 (7%)	1,390 (15%)
Codeine	547	40 (7%)	85 (16%)
Morphine	3,864	417 (11%)	694 (18%)
>1 type	4,969	1,164 (23%)	1,778 (36%)
Buprenorphine	595	156 (26%)	251 (42%)
Fentanyl	448	203 (45%)	258 (58%)
Other opioids	322	179 (56%)	198 (62%)

fracture patients died. The mortality in this period varied significantly in association with the type of opioid use (Table 3). Within eight days to nine months after hip fracture surgery, 5,526 (21%) of the 26,790 hip fracture patients died. The nine-month mortality also varied in association with the type of opioid use (Table 3). Within eight days to 12 months after hip fracture surgery, 6,274 (23%) of the 26,790 hip fracture patients died in total; 739 (3%) of the 21,255 patients who survived nine months after hip fracture surgery died within 9–12 months.

In the basis population with 69,456 hip fractures in Denmark from 2005 to 2015, 2,969 (4%) died within seven days after the surgery, 9,374 (13%) died within eight days to three month, 15,140 (22%) within eight days to nine month, and 17,104 (25%) within eight days to 12 month.

Opioid type and long-term use

Long-term opioid use was observed in 3,213 (15%) of the 21,255 nine-month survivors who were opioid-naïve prior to surgery and redeemed at least one opioid prescription in the interval from eight days to three months after hip fracture surgery.

Use of any opioid type within three months after hip fracture surgery (except the grouped “other opioids”) was associated with higher odds of long-term opioid use after hip fracture surgery compared to use of morphine when looking at the entire study period. Proportion, ORs, and confidence intervals (CI) for long-term opioid use after hip fracture surgery, conditioned on nine-month survival, according to opioid type used within three months after the surgery are presented in Table 4, both overall and according to calendar time subpopulations. The proportion of long-term opioid users changed from 18% in the

period before 2010 to 13% in the period after 2010. There are minimal differences between the crude ORs and the adjusted ORs. Additionally, ORs and CI for the subgroup analysis according to age and comorbidity are provided in Table 5.

Discussion

In this nationwide cohort study 15% of the opioid-naïve patients who redeemed a prescription opioid in the first three months after surgery met our definition for long-term opioid use. Use of oxycodone, fentanyl, codeine, tramadol, buprenorphine, or more than one type within three months after hip fracture surgery was associated with opioid prescriptions three to 12 months after surgery compared to morphine. However, baseline characteristics differed according to prescriptions and prescription patterns changes remarkably around 2010.

Interpretation

The present study used person-based linkage between nationwide registries to explore opioid use among elderly opioid-naïve patients who underwent hip fracture surgery and subsequently redeemed opioid prescriptions. The present study identified that use of a variety of opioid types after hip fracture surgery, of which some are regularly prescribed, were associated with long-term opioid use compared to morphine. However, the association may be affected by uncontrolled confounding by indication of the opioid prescriptions. The present study surprisingly only found minimal differences between the crude and the adjusted ORs for long-term opioid use after hip fracture surgery, despite differences in baseline characteristics e.g., the number of users of fentanyl, buprenorphine, codeine, and other opioids aged ≥ 85 years were higher compared to users of morphine, oxycodone, tramadol, and more than one type, which is the primary finding in this study. This suggests, these patients have other indications for opioid use than undergoing a hip fracture surgery. This expectation strengthens when looking at the mortality distribution, since the proportions of survivors are lower among users of fentanyl, buprenorphine, other opioids, and more than one type. Particularly among users of fentanyl and buprenorphine, the subgroup analysis revealed that ORs for long-term opioid use differ between the lowest and highest age and comorbidity group. As the study was conditioned on redeemed opioid

Table 4: Long-term opioid use. Proportion, ORs and confidence intervals for long-term opioid use after hip fracture surgery conditioned on nine-month survival (n=21,255), according to opioid type used within three months after the surgery. Additionally, the data have been presented for sub populations for the time period before and after 2010. Numbers and proportions for users of “other opioids” have not been included in the subpopulations, due to very few cases (n=21,245). aOR: adjusted odds ratio, CI: Confidence interval, N: Number of patients OR: odds ratio, Ref: Reference value.

Opioid type	Proportion with long-term opioid use		Univariable analysis		Multivariable analysis	
	n, %		OR	95% CI	aOR	95% CI
2005–2015 (n=21,255)						
Morphine	270 (9%)		Ref	Ref	Ref	Ref
Oxycodone	852 (14%)		1.78	[1.54–2.05]	1.76	[1.52–2.03]
Fentanyl	56 (29%)		4.48	[3.20–6.27]	4.37	[3.12–6.12]
Codeine	59 (13%)		1.57	[1.16–2.12]	1.55	[1.14–2.09]
Tramadol	994 (13%)		1.57	[1.36–1.81]	1.56	[1.35–1.80]
Buprenorphine	115 (33%)		5.39	[4.17–6.96]	5.36	[4.14–6.94]
Other opioids	10 (8%)		0.86	[0.49–1.82]	0.93	[0.48–1.80]
>1 type	857 (27%)		3.94	[3.40–4.57]	3.83	[3.31–4.44]
Subpopulation: 2005–2009 (n=9,515)						
Morphine	30 (18%)		Ref	Ref	Ref	Ref
Oxycodone	571 (17%)		0.95	[0.63–1.42]	0.96	[0.64–1.44]
Fentanyl	22 (30%)		1.93	[1.02–3.65]	1.96	[1.03–3.71]
Codeine	34 (15%)		0.83	[0.49–1.43]	0.83	[0.49–1.43]
Tramadol	637 (15%)		0.81	[0.54–1.22]	0.83	[0.55–1.24]
Buprenorphine	60 (32%)		2.16	[1.31–3.56]	2.20	[1.33–3.64]
Other opioids	–		0.43	[0.18–1.03]	0.43	[0.18–1.04]
>1 type	378 (30%)		1.98	[1.31–3.00]	1.97	[1.30–2.98]
Subpopulation: 2010–2015 (n=11,730)						
Morphine	240 (8%)		Ref	Ref	Ref	Ref
Oxycodone	281 (11%)		1.36	[1.13–1.62]	1.34	[1.12–1.61]
Fentanyl	34 (29%)		4.77	[3.13–7.26]	4.65	[3.04–7.10]
Codeine	25 (10%)		1.32	[0.86–2.05]	1.32	[0.85–2.04]
Tramadol	357 (10%)		1.28	[1.08–1.52]	1.28	[1.07–1.51]
Buprenorphine	55 (35%)		6.20	[4.35–8.83]	6.23	[4.36–8.90]
Other opioids	–		0.86	[0.26–2.81]	0.86	[0.26–2.80]
>1 type	479 (25%)		3.77	[3.19–4.46]	3.69	[3.12–4.36]

prescriptions after hospital discharge, the mortality in the basis population was higher than in the study population. Overall, findings indicate that different opioid types are used for different indications among elderly previously opioid-naïve hip fracture patients.

Opioid type and long-term use

The morphine users in the present study were least likely to have a long-term opioid use after hip fracture surgery in the whole study period and especially after 2010. Prescribed opioid types have changed over time and the Danish national recommendations are to prescribe morphine as first choice [6, 29]. It is clear from the results that the choice of opioids other than morphine after hip fracture surgery is not random. The use of prescription medication in the

population is affected by changes in society and therapeutic indication for prescriptions [29]. Thus, prescribing behavior appears to be related to other conditions than hip fracture surgery, and patient awareness of addictive properties of morphine may also ensure attention to withdrawal.

Patients with use of oxycodone had 1.8-fold higher odds of long-term opioid use, than patients with morphine use in the entire study period. However, in the period before 2010, the odds for long-term opioid use were no higher (odds 1.0) than for morphine but increased in the following period. However, the change in odds according to calendar time in this study reflects a major change in prescription of morphine in the two periods. The patients with oxycodone use had a low CCI before surgery and the lowest nine-month mortality; thus, the patients seemed less fragile. However, the odds for long-term opioid use

Table 5: Long-term opioid use in subgroups. ORs and confidence intervals for long-term opioid use after hip fracture surgery in subgroups according to age and comorbidity, conditioned on nine-month survival (n=21,255), depending on opioid type used within three months after the surgery. CI: Confidence interval, N: Number of patients OR: odds ratio, Ref: Reference value.

Univariable analysis	Age				CCI			
	65–74 (n=4,888)		≥85 (n=7,783)		No comorbidity (n=9,763)		Severe comorbidity (n=3,049)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Morphine	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Oxycodone	1.86	[1.40–2.47]	1.64	[1.28–2.10]	1.76	[1.39–2.22]	1.93	[1.36–2.75]
Fentanyl	7.65	[2.83–20.71]	4.12	[2.59–6.56]	4.96	[2.78–8.83]	1.50	[0.50–4.51]
Codeine	1.25	[0.58–2.70]	1.86	[1.20–2.90]	2.06	[1.32–3.23]	1.37	[0.64–2.95]
Tramadol	1.67	[1.27–2.21]	1.50	[1.18–1.91]	1.75	[1.40–2.20]	1.77	[1.25–2.51]
Buprenorphine	2.73	[0.89–8.39]	6.56	[4.62–9.32]	6.32	[4.29–9.31]	5.69	[2.96–10.91]
Other opioids	0.36	[0.49–2.71]	1.11	[0.43–2.85]	1.00	[0.35–2.82]	1.06	[0.24–4.72]
>1 type	3.68	[2.75–4.94]	3.87	[3.02–4.96]	4.91	[3.88–6.22]	4.41	[3.08–6.31]

compared to morphine seemed similar within age and comorbidity subgroups. The association with use of oxycodone and long-term opioid use is noticeable as it affects a large proportion, i.e., overall 26% in this study, 31% before 2010 and 21% after.

Tramadol was the most prevalent opioid in this study used among 34% of the opioid users within three months after the surgery; however, the number of users decreased noticeably from 41% in the period before 2010 to 27% in the period after. This correspond to studies in other patient populations, who found that the number of tramadol users in Denmark increased by 70% from 2001 to 2013 but have decreased by more than 25% from 2016 to 2018 [30, 31].

The present study found that use of fentanyl or buprenorphine was associated with 4–5 fold higher odds for long-term opioid use than morphine. However, only 4% of the patients in this study used buprenorphine or fentanyl after the surgery and odds for long-term opioid use varied within the age and comorbidity subgroups. Patients with use of fentanyl or buprenorphine were mainly aged 85 years or older and suffered a high mortality within three months (26–45%) and nine months (42–58%) after the surgery. This is in compliance with the context that indication for buprenorphine would commonly be chronic pain, especially in elderly patients [32, 33]. Nevertheless, this clearly indicates that prescribing behavior appears not to be related to hip fracture surgery but other circumstances which would affect long-term opioid use.

The 3.8 OR of long-term opioid use among users of more than one opioid type compared to morphine may be explained by comorbidity and chronic pain among these patients, which is a strong predictor of long-term opioid use [13]. In this study, the comorbidity level was higher in patients

with more than one opioid type than other patients, but the odds did not vary considerably in the subgroup analysis. The multivariable analysis was adjusted for CCI level, which summarize the morbidity burden before the surgery. Nevertheless, switching between opioids suggests periods of insufficient pain management or unacceptable side effects, possibly related to more complicated conditions not related to the hip fracture surgery.

Methodological considerations and limitations

Methodological strengths of the study include the population-based nationwide design with complete access to healthcare for all citizens and follow-up through patient-leveled data-linkage. The positive predictive value of the hip fracture diagnosis is up to 98% [34, 19]. Thus, the risk of selection bias due to registration failure is low. However, the analysis was limited to prescriptions redeemed in the Danish pharmacies as information on medications dispensed during hospitalization was not accessed in the present study. Potentially, patients receive a few days' opioid supply at discharge and the most fragile patients have longer hospital stays. Opioid prescriptions from pharmacies were consequently redeemed later among these patients; thus, initial opioid use may be underestimated and the included opioid type was not the first used after hip fracture surgery which could imply information bias. To manage this, all opioids redeemed within seven days after surgery were excluded. Studies found that long-term opioid use was associated with opioid dose after orthopedic surgery [35], or days' supply on the first

prescription across multiple pain etiologies, rather than opioid type [13]. Unfortunately, information on dose and days' supply was not available in the present study.

The definition of long-term opioid use, in the present study (opioids redeemed within all three-month periods the year after surgery) allow patients to have redemption-free periods up to almost six months. Thus, new pain conditions the year following surgery may be observed as long-term opioid use after hip fracture surgery in some patients. The analyses were restricted to opioid-naïve patients six months before surgery who redeem opioids within three months after the surgery. However, since the present study was based on opioid dispensing data unable to account for prescription compliance, opioid use may be overestimated if patients were prescribed opioids without using them. The Danish National Health Service Prescription Database is considered a good predictor of medication use [21, 36]. However, lacking knowledge on indications and contraindications for opioid treatment, pain level and etiology, personal preferences of patients and prescribers' habits, doses, and benefit from medications, implies that the results may be confounded by opioid indication. Thus, comorbidities, e.g., cancer, probably correlate with both opioid type and long-term use. To oblige this challenge the multivariate analysis was adjusted for potential confounders, including comorbidity. However, given the study design, casual relations between opioid type and long-term opioid use after hip fracture surgery could not be identified due to unknown characteristics such as pain or reasons for opioid choice. Additionally, the study was confounded by competing risk of death. The mortality is high in the hip fracture population and varied within recipients of different opioid types.

Conclusions

Results from this study demonstrate that use of certain opioid types after hip fracture surgery including the most commonly prescribed opioids, tramadol and oxycodone, were associated with a higher likelihood of long-term opioid use compared to morphine. However, the proportion of patients initiating a long-term opioid use decreased after 2010. The findings suggest that some elderly, opioid-naïve, patients have untreated pain conditions before hip fracture surgery and the hospitalization could be an opportunity to start a relevant pain treatment. Additionally, the decrease in long-term users emphasizes the likelihood of careful and conscientious opioid prescribing behavior. Studies with prospectively collected data on indication for the opioid prescriptions are still warranted.

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