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Original Article

Effect of acetylcholinesterase inhibitors on post-surgical complications and mortality following a hip fracture: a cohort study

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Abstract

There is increasing evidence suggesting that the use of acetylcholinesterase inhibitors may have beneficial effects on bone. Data on the potential post-surgical effects of these medications on orthopedic interventions are very limited. This study was designed to determine whether the use of acetylcholinesterase inhibitors is associated with a decrease in post-surgical mortality and complications in hip fracture patients with Alzheimer's disease. To accomplish this objective, a retrospective cohort study was performed using data from the Clinical Practice Research Database, UK. The study included 532 Alzheimer's disease patients of age 65 years and older, who sustained a hip fracture between 1998 and 2012. During the follow-up period, 34% of the patients died (n=182), 22% sustained a second hip fracture (n=118) and 5% (n=29) required reintervention. The users of acetylcholinesterase inhibitors had a 56% reduction in all-cause mortality (HR= 0.44, 95% CI 0.30-0.63) and a 41% reduction in second hip fracture incidence during a year of post-surgical follow-up (HR= 0.59, 95% CI 0.38-0.94) after adjusting for potential confounders. Our results show that acetylcholinesterase inhibitors may have the potential to reduce all-cause mortality and the risk of suffering a second hip fracture during the first year after surgery.

Keywords: Hip Fracture, Acetylcholinesterase Inhibitors, Alzheimer's Disease, Mortality, Second Fracture

Introduction

Hip fractures are becoming a major health and economic problem in many countries. More than 1.6 million people worldwide suffer from hip fractures each year, and this incidence continues to increase along with the aging world population[1]. These fractures usually occur in elderly individuals with multiple comorbidities and are associated with high mortality and morbidity[2]. Approximately 21.9% of the patients in the US will die within one year after a hip fracture[3]; and the higher mortality risk of these patients may persist for several years after the fracture[4].

Hip fractures are classified into two main categories according to their anatomic location: intracapsular and extracapsular[5]. The former can be treated either by osteosynthesis or joint replacement[6], whereas the later usually preserve the blood supply of the femoral neck and are treated by osteosynthesis[7]. Certain surgical complications such as nonunion, avascular necrosis, dislocation, and infection are directly related to the type of treatment used[8]. These complications may delay functional recovery and contribute to mortality[9]. Therefore, there is great need to discover and develop new treatment modalities to speed up the recovery process[10].

Recent *in vivo* studies have reported a relation between cholinergic receptor activity, and bone turnover[11-14].

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Indeed, subtype α2 nicotinic receptor knockout mice are osteoporotic due to osteoclast up-regulation, whereas the stimulation of nicotinic receptors in wild type mice increased the bone mass due to osteoclast apoptosis[14]. Moreover, M3 muscarinic receptors favor bone formation and decrease bone resorption. M3 receptors knockout mice are osteoporotic due to an increase in the number of osteoclasts and a decrease in the number of osteoblasts. The stimulation of muscarinic receptors with cholinergic agonists *in vitro* increased osteoblast proliferation[12,15,16]. Altogether, the available literature seems to indicate that the inhibition of the AChR at the bone level seems to cause a reduction in bone turnover.

Acetylcholinesterase inhibitors (AChEIs) are a group of medications that stimulate the cholinergic receptors by inhibiting the action of acetylcholinesterase and increasing the synaptic levels of acetylcholine thus activating M1-M5 receptors[15,17]. However, these drugs may have different mechanisms of action, for example, the therapeutic action of galantamine is mainly mediated by an allosteric stimulation of the nAChRs rather than by general cholinergic enhancement due to cholinesterase inhibition[18], whereas rivastigmine and donepezil appear to increase the cholinergic activity of both muscarinic and nicotinic receptors[19,20]. These medications have been widely used in the treatment of Alzheimer's disease (AD) since the mid-1990s[21]. Recent reports have observed that the use of AChEIs could decrease the hip fracture risk in AD patients[22]. Moreover, the use of AChEIs in elderly AD patients has been associated with enhanced hip fracture consolidation, better bone density, and fewer healing complications[23]. The mechanism by which these drugs regulate bone remodeling is not well understood. Our research team has recently reported that the body and visceral fat weights as well as serum leptin level were increased in donepezil-treated mice compared to controls. In addition, donepezil-treated mice had better bone density than controls due to a decrease in the osteoclast numbers. These results indicate that donepezil has a systemic effect on body energy metabolism and favors bone mass[24]. However, the potential post-surgical effects of these medications in patients with hip fractures have not yet been explored. We hypothesize that the use of AChEIs decreases the risk of post-surgical complications and therefore of death in patients with hip fractures. In order to test this hypothesis, we designed and carried out a retrospective cohort study in AD patients who suffered a hip fracture and underwent a surgical procedure for it.

Materials and methods

Study type and level of evidence: Retrospective cohort, level III

Regulatory approval

The study was approved by the Scientific and Ethical Advisory Group of the Clinical Practice Research Database (CPRD)[25], and the ethics review board of the McGill University Health Centre.

Data sources

We conducted a population-based retrospective cohort study using data from the CPRD, Hospital Episode Statistics (HES) database, and Office of National Statistics (ONS). The CPRD is the world's largest computerized database of longitudinal records from primary care[25]. It contains medical records of more than 650 general practices across the UK and primary-care medical records of approximately 14 million UK inhabitants[26]. Clinical data collection was done using the Oxford Medical Information System (OXMIS) and disease read codes that are cross referenced to the International Classification of Diseases - 10th revision (ICD-10). Information on specific procedures was collected using the Office of Population Census and Surveys Coding System version 4 (OPCS4).

Cohort definition

First, we identified patients of age 65 years or above with a first-time diagnosis of AD according to the ICD-10 and OXMIS coding systems, who were registered in the computerized database between January 1998 and December 2012. To increase the probability of including only well-defined AD patients in the study population, we used an algorithm previously described by Imfeld et al[27], which was applied to all potential cases with a first-time diagnosis of AD. To be eligible for the study AD patients had to have at least one of the following: 1) a diagnosis of AD followed by at least one prescription for an AD specific medication or vice versa; 2) two prescriptions for an AD specific medication; 3) at least two recordings of an AD diagnosis; 4) an AD diagnosis after a specific dementia test (e.g., Clock Drawing Test, Mini Mental State Examination or Abbreviated Mental Test), a referral to a specialist (e.g., geriatrician, neurologist or psycho-geriatrician), or an evaluation based on a neuroimaging technique (e.g., magnetic resonance imaging, computed tomography, or single photon emission computed tomography); or 5) an AD diagnosis preceded or followed by any registered dementia symptoms (e.g., memory impairment, aphasia, apraxia, or agnosia).27 All the selected patients had at least one year of up-to-standard follow-up in the CPRD records before the diagnosis of AD.

Second, from the identified AD patients, we selected individuals who had a specific record of hip fracture according to the ICD-10 and OXMIS coding systems, followed by an OPCS4 code for a surgical procedure of the affected hip (e.g., joint replacement and osteosynthesis) within 7 days of the fracture. The date of the surgical procedure was designated as the index date. The proportion of patients recorded in the CPRD with fractures secondary to severe polytrauma is low (0.5-1%)[28]. Thus, we decided to include patients with fractures regardless of the causes identified in the computerized database.

Patients diagnosed with diseases or conditions known to substantially affect bone metabolism (i.e., osteomalacia, Paget's disease, cancer (excluding non-melanoma skin cancer), human immunodeficiency virus (HIV), rheumatoid

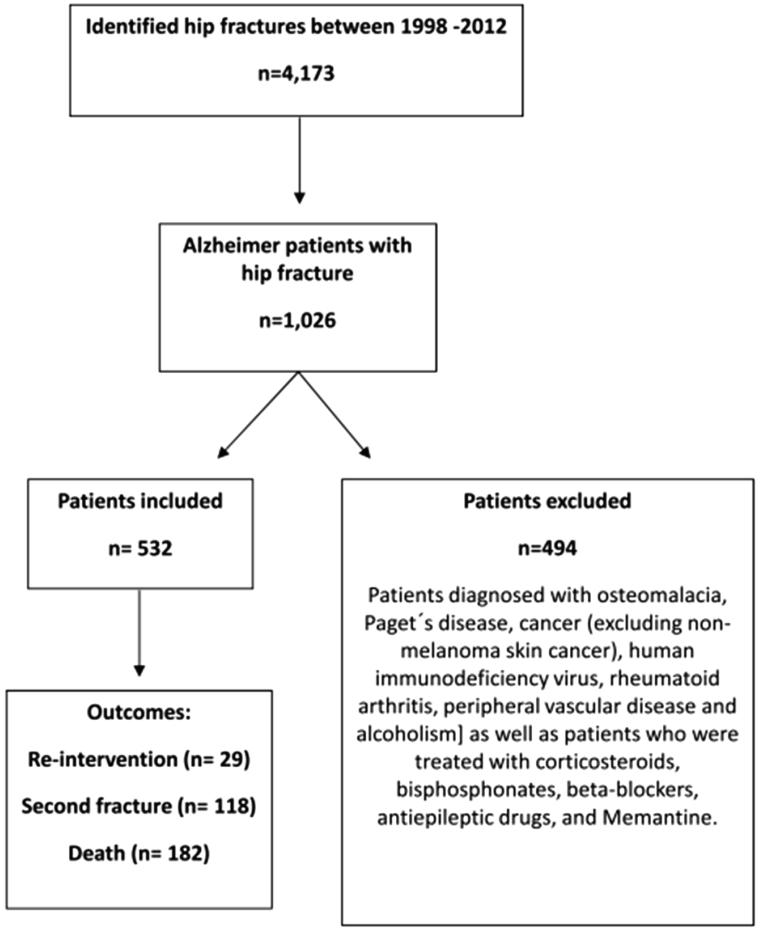

Figure 1. Flow chart of patients that met the inclusion / exclusion criteria for the study.

arthritis, peripheral vascular disease and alcoholism] as well as patients who used medications known to affect bone metabolism (i.e., corticosteroids, bisphosphonates, beta-blockers, and antiepileptic drugs) prior to the index date were excluded. Memantine can be an alternative option for the treatment of AD, and may also reduce the risk of fracture in these patients[29]. Thus, we decided to exclude from the study cohort all the patients who were treated with memantine any time before or after the index date (Figure 1).

Exposure assessment

A detailed history of exposure to prescribed AChEIs (namely, rivastigmine, donepezil, and galantamine) was obtained from the Medicines and Healthcare Products Regulatory Agency and CPRD for the period between one year before the index date and the end of follow-up. An approach similar to intention-to-treat analysis was used to define exposure status, where patients who had at least one prescription for any type of AChEIs during the post-surgical follow-up period was considered as exposed.

Study outcomes and follow-up

Three study outcomes were used: reintervention (i.e., revision surgery, extraction of implanted material, re-fixation, or conversion to hip replacement), post-baseline hip fracture, and death. The outcomes were identified using data from the CPRD, HES and ONS and were analyzed independently. Patients in the study cohort were followed from the index date until death from any cause, loss to follow-up, one-year of follow-up from index date, or December 31st, 2013 whichever came first.

Potential confounders

Information on age, sex, body mass index (BMI), smoking status, duration of AD, type of surgical treatment, medical conditions associated with an increased fracture risk, institutionalization status, mobility status, and exposure to drugs that could increase the fracture risk was also collected from the CPRD (Table 1)[30,31]. The patients' histories in respect to the disease at issue were ascertained at the index date. The use of the medications under the study was ascertained

Table 1. Selected baseline characteristics of users and nonuser sub-cohorts.

Characteristics	Users of AChEIs (n = 223)	Nonusers (n=309)	*P*-value [b]
Age in years			
Mean ± SD	84.0 ± 7.0	84.6 ± 6.4	0.25
Sex			
Men	21.5	26.2	0.21
Women	78.5	73.8	
Years in the GPRD			
Mean ± SD	5.5 ± 4.4	6.1 ± 4.0	0.07
Median (IQR)	3.6 (1.7 - 9.4)	5.5 (2.5 - 9.0)	0.02
Smoking status			
Never	51.6	50.2	
Current	1.8	1.9	0.93
Ex-smoker	4.9	5.5	
Missing	41.7	42.4	
Body mass index [a]			
<20	16.6	17.5	
20-24	29.2	33.0	
25-29	12.1	14.2	0.59
≥30	4.0	2.9	
Unknown	38.1	32.4	
Duration of Alzheimer disease			
<2	47.1	35.9	
2-6	46.6	54.1	0.02
≥6	6.3	10.0	
Surgical treatment			
Joint replacement	56.5	45.0	0.009
Osteosynthesis	43.5	55.0	
Comorbidity factors			
Chronic pulmonary disease	14.4	18.5	0.21
Diabetes	9.4	6.5	0.21
Cerebrovascular disease	9.9	13.9	0.16
Chronic liver disease	0.5	0.3	0.49
Ischemic heart disease	83.0	86.1	0.32
Peptic ulcer	5.4	10.0	0.05
Renal diseases	2.2	3.2	0.49
Known Osteoporosis	3.1	2.6	0.71
History of falls	37.7	42.1	0.31
Institutionalization	21.1	12.3	0.006
Mobility			
Walks without aid	93.7	95.2	
Poor mobility	2.2	3.2	
Very Poor mobility	0.3	0.9	0.34
Use of wheelchair	0.0	0.0	
Bedridden	3.1	1.3	
Use of medication			
PPI	21.5	18.8	0.43
Statins	19.3	12.3	0.02
SSRI	25.6	20.4	0.16
Hypnotics	39.5	38.8	0.88
Diuretics	13.5	15.5	0.50
ACE inhibitors	17.5	10.4	0.02
Pre-baseline use of AChEIs	91.3	40.8	<0.001

Abbreviations: CI, confidence interval, PPI-proton pump inhibitors; SSRI- selective serotonin reuptake; ACE-Angiotensin converting enzyme, AChEIs - acetylcholinesterase inhibitors.

[a] *Measured as weight in kilograms divided by the square of height in meters*.*

[b] *Nonparametric median test and Chi2 test for homogeneity.*

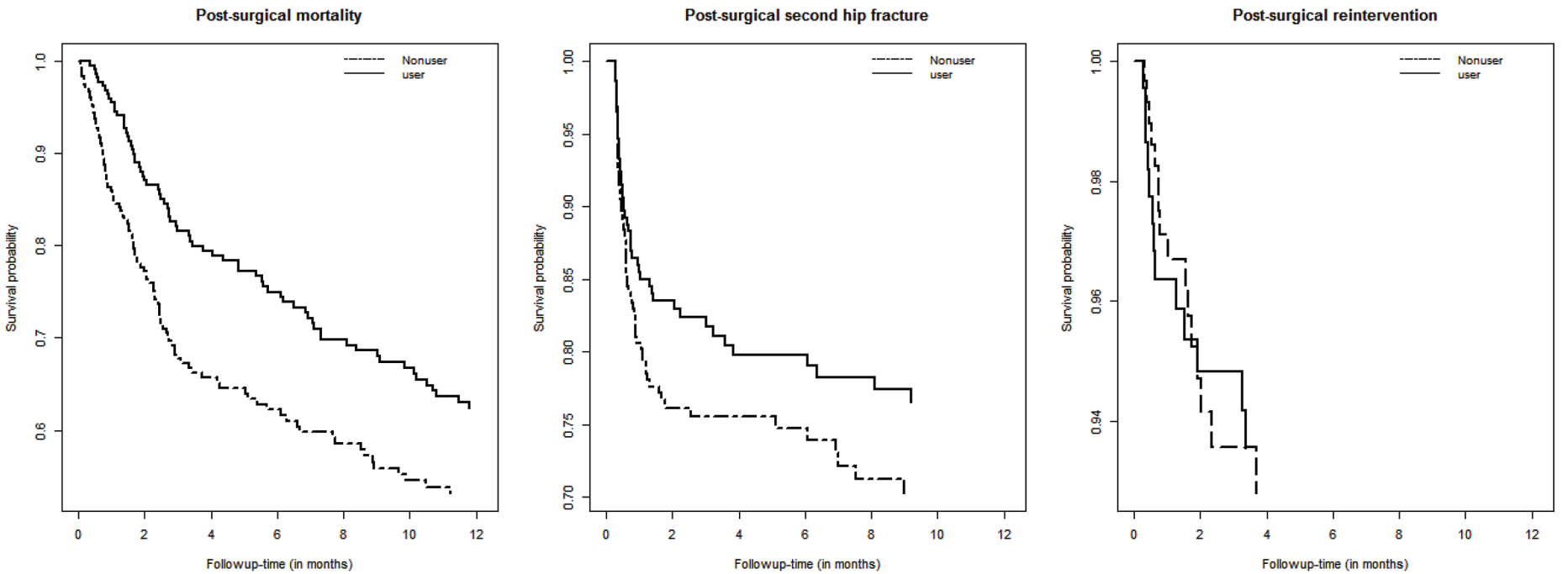

Figure 2. Kaplan-Meier survival curves for all-cause mortality, second hip fracture and ipsilateral reintervention according to AChEI use.

for the time period within one year before the index date and dichotomized as users and non-users. In order to reduce the possibility of confounding by myriad factor, three directed acyclic graphs (using the Dagitty 2.2 software[32]) were used to identify the confounders requiring control for each of the three different study outcomes. The following set of confounders was identified for each outcome: age, diabetes, duration of AD, ischemic heart disease, renal disease, and use of ACEIs, diuretics, SSRI, PPI, statins, and hypnotics.

Sample size consideration

Previous studies have shown that 53% of AD patients with a hip fracture were AChEI users[22] and post-surgical mortality rate is approximately 21.9% among this population[3]. Based on this information our study required a sample size of 517 participants to detect a hazard ratio of 0.59 or below with a power of 80% at a significance level of 0.05.

Statistical analysis

The distributions of relevant patient-characteristics were examined and compared between the study groups. Kaplan-Meier estimators were plotted to explore the survival function according to the use of the drug for each outcome. Cox's proportional hazard model was used to estimate the association between AChEI use and post-surgical complications and mortality.

Crude and adjusted hazard-ratios (HR) for death and the complications were estimated along with the accompanying 95% confidence intervals (CIs). All analyses were carried out at a significance level of 5% using SAS version 9.3 (SAS

Table 2. Association between use of Acetylcholinesterase Inhibitors and all-cause mortality.

AChEIs use	Post-surgical outcomes		Crude HR (95% CI)	Adjusted HR[a] (95% CI)
	Second hip fracture			
	No (n=414)	Yes (n=118)		
Non-user	237 (57.3)	72 (61.0)	1	1
User	177 (42.7)	46 (39.0)	0.74 (0.51,1.08)	0.59 (0.38-0.94)
	Ipsilateral hip reintervention			
	No (n=503)	Yes (n=29)		
Non-user	293 (58.3)	16 (55.2)	1	1
User	210 (41.7)	13 (44.8)	0.94 (0.47-1.96)	0.72 (0.27-1.92)
	All-cause mortality			
	Alive (n=350)	Dead (n=182)		
Non-user	199 (56.9)	110 (60.0)	1	1
User	151 (43.1)	72 (40.0)	0.65 (0.48,0.88)	0.44 (0.30-0.63)

[a] Adjusted for: age, diabetes, ischemic heart disease, renal disease, duration of Alzheimer's disease (<2, 2-6, >6 years) and use of selective serotonin reuptake inhibitors, hypnotics, proton pump inhibitors, diuretics, statins, history of falls and pre-baseline use of acetylcholinesterase Inhibitors.
Abbreviations: AChEIs - acetylcholinesterase inhibitors, HR - hazard ratio, Ci - confidence interval.

Institute Inc. Cary NC). Missing data were represented as a separate category and patients who were lost to follow up considered as censored.

Results

After applying our inclusion and exclusion criteria, we identified a total of 532 patients diagnosed with AD who sustained a hip fracture during the study period. During the follow-up period, 34% of the patients died (n=182), 22% suffered a second hip fracture (n=118) and 5% (n=29) underwent reintervention; this added up to 328 outcomes (Figure 1). A total of 223 individuals were classified as users of AChEIs and 309 as non-users. The distributions of users and non-users of AChEIs by age, gender, years of registration in the CPRD, smoking status, BMI, duration of AD, treatment type, and comorbidity factors are presented in Table 1. The duration of AD differed between the two groups as non-users suffered from the disease for a longer time. The majority of AChEIs users (91.3%) had at least one prescription during the year prior to the index date of surgery compared to less than half of non-users (40.8%). Although non-users had been registered in the CPRD records for longer, the distributions of comorbidities were similar between users and non-users of AChEIs. There were no differences in the history of fall between the groups and more than 90% of both groups did not have any mobility concerns. However, 56.5% of AChEIs users had a joint replacement surgery compared to 45% of non-users. In addition, the use of ACE inhibitors and statins was more frequent in users than in non-users of AChEIs (Table 1). No differences were observed between the two groups regarding distributions of age, gender, smoking status, and BMI (Table 1). Figure 2 presents the Kaplan-Meier survival estimators for the three outcomes according to AChEI use.

Multivariate Cox's proportional hazard model results suggest that compared to non-users, users of AChEIs had a 56% reduction in all-cause mortality during a period of one year following surgery (HR=0.44, 95%CI=0.30-0.63), after adjusting for pre-baseline use of the drug and other potential confounders (Table 2). The users showed a 41% reduction in second hip-fracture during the follow-up period (HR=0.59, 95%CI=0.38-0.94). No association was found between use of AChEIs and the risk of ipsilateral post-surgical reintervention (HR=0.72, 95%CI=0.27-1.92) (Table 2).

Discussion

In this study, the one-year mortality rates in AD patients after suffering a hip fracture were lower in users than in non-users of AChEIs. Patients with hip fractures are subject to potentially multiple medical and surgical complications that can eventually lead to reintervention or death[33,34]. Previous reports estimate that the one-year mortality rate after suffering a hip fracture to range from 14% to 37%[3,35,36], and that the risk of death may remain high for up to 6 years after the fracture[37]. On the other hand, AD is also a significant cause of morbidity and mortality in elderly patients and is a risk factor for hip fractures[38]. In this study, the one-year mortality rate in AD patients after suffering a hip fracture was the upper limit of values previously reported in the literature[3,35,36].

We also observed that the second hip fracture rates were lower for AChEIs users compared to non-users. Suffering a second hip fracture can be a particularly serious complication in elderly individuals; however, little research has been conducted on the potential consequences of this condition. Nevertheless, the second hip fracture rate has been estimated

to range between 2% and 11 % in the general population[39,40]. Accordingly, our results indicate that AD patients may have a considerably higher risk of suffering a second hip fracture compared to the general population (i.e., 2-4 folds).

Previous studies have shown that cholinergic activity may be positively related to osteoblastic proliferation and differentiation in bone[15,16,41]. Moreover, AChEIs are known to increase synaptic acetylcholine levels in the organism[17]; therefore, our results could be partially explained by a rise in osteoblastic proliferation and differentiation caused by an AChEIs-mediated increase in the cholinergic activity[16,41]. Furthermore, the use of AChEIs in elderly AD patients has been associated with a lower hip fracture risk, enhanced hip fracture consolidation, better bone density and fewer healing complications[22,23]. Nevertheless, the use AChEIs has also been associated with a risk of orthostatic hypotension[42] and syncope related-falls[43], which could eventually increase the hip fracture risk. In our study we found a reduction in second hip fracture risk among AChEI users. Even though we did not investigate the specific cause of these second hip fractures we could hypothesize that perhaps the effects of AChEIs on bone accrual seem to have outweighed the potential increase in the risk of syncope-related fractures.

The British national guidelines for the treatment of AD recommend the use of AChEIs (e.i., donepezil, galantamine and rivastigmine) in mild to moderately severe disease[44]. The presence of a hip fracture is not considered a reason for the modification of the treatment with AChEIs[44]. In this study, the data quality on the degree of AD was not optimal; therefore, AD patients were instead categorized according to duration of AD. Some differences were observed between the two groups at the baseline regarding the duration of AD, type of surgical treatment, and intake of ACEIs and statins. These variables could influence the mortality rates of the studied population; however, our results were significant after adjustment for these potential confounders.

The reintervention rates in hip fractures may depend on several factors such as the fracture type, the selected surgical procedure and the prosthetic implant[45,46]. In this study, the reintervention rates during the first year of follow-up did not differ significantly between users and non-users of AChEIs. This study was designed to analyze the effect of AChEIs in AD patients with hip fractures, thus our results cannot be extrapolated into the general population, and new studies should be designed to assess the potential effects of these drugs in elderly patients with hip fractures.

Our study has several strengths and limitation. First, it has a small sample size due to stringent criteria to defined AD patients. While this may have affected the precision of our results, we followed an algorithm that has been previously validated[27]. Moreover, previous studies have validated the accuracy of the CPRD in the ascertainment of patients with AD or fractures[47,48]. Furthermore, we used a high quality population-based database that covers a well-defined population with a low likelihood of selection bias. A second limitation is the definition of exposure (users and non-users of AChEIs) according to the follow-up period; this design could make the results prone to the immortal-time bias, making the medication look beneficial or at least more beneficial than it really is[49]. One of the suggested analytical strategies to address immortal-time bias is time-dependent modeling of the exposure. However, only the day of prescription is available in CPRD and not the day of dispensing of the drug. The variable may have large measurement errors which in turn may render results from complex modeling of exposure less valid.

Third, although we adjusted for a range of potential confounding factors, residual confounding caused by unrecorded or incomplete data cannot be ruled out. However, we adjusted for a number of relevant risk factors which were selected using a DAG model. The latter avoids over-adjustment bias and unnecessary adjustment[50].

Following a hip fracture, AD patients seem to have a very high risk of mortality and second fracture. However, our results suggest that AD patients who had at least one post-surgical prescription for AChEIs may have a reduced risk of all-cause mortality and second hip fracture during the year following surgery when adjusting for pre-baseline use of the drug. Patients with AD could potentially benefit from the positive effects AChEIs have on bone. However, whether these effects could apply to the general elderly population remains unknown, and future clinical trials and prospective cohort studies should be performed to answer this question.

Author's contribution

Abbas Kezouh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tamimi Iskandar, Nicolau Belinda, Karp Igor, Tamimi Faleh. Acquisition, analysis, or interpretation of data: Tamimi Iskandar, Madathil Sreenath Arekunnath, Kezouh Abbas, Nicolau Belinda, Karp Igor, Tamimi Faleh. Drafting of the manuscript: Tamimi Iskandar, Madathil Sreenath Arekunnath, Nicolau Belinda, Karp Igor, Tamimi Faleh. Critical revision of manuscript for important intellectual content: Tamimi Iskandar, Madathil Sreenath Arekunnath, Nicolau Belinda, Karp Igor, Tamimi Faleh. Administrative, technical, or material support: Tamimi Faleh, Kezouh Abbas.

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