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Original Article

Drugs with Anticholinergic Properties and Association with Hip Fractures in Older Patients: A Danish Nationwide Cohort-Study

Rebekka Vedelsbøl[1,2], Pavithra Laxsen Anru[3], Jesper Ryg[1,2]

[1]Department of Geriatric Medicine, Odense University Hospital, Odense, Denmark;
[2]Geriatric Research Unit, Department of Clinical Research, University of Southern Denmark, Odense, Denmark;
[3]Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

Abstract

Objectives: Hip fractures (HFx) resulting from falls are a significant health concern, and drugs with anticholinergic properties (DAP) increase the risk of falls. This study aimed to assess the association between use of DAP at hospital admission and HFx risk in older patients. **Methods**: This nationwide population-based study included all patients ≥65 years admitted to Danish geriatric wards during 2005-2014. Outcome of interest was first HFx within 2-years follow-up. The Anticholinergic Cognitive Burden (ACB) scale quantified DAP use. Cox regression analysis of data from four national registries was adjusted for activities of daily living, age, marital status, admission year, BMI, fracture history, previous admissions, dementia, anti-osteoporotic drugs, and Charlson comorbidity index. **Results**: 74,589 patients (62.8% female) were included, 45,463 (60.9%) received DAP at index, and 7,861 HFx occurred during follow-up. Cumulative 2-year HFx hazard was highest for ACB=0 (15.3%). Higher ACB-score was not associated with increased HFx risk in univariable nor multivariable analyses. In sensitivity analysis, use of DAP with high anticholinergic burden (≥2) did not alter results. **Conclusions**: In this high-incidence national cohort, higher ACB-score was not associated with increased HFx risk. Our results call for further research on association between specific DAP and risk of HFx.

Keywords: Anticholinergic drugs, Cohort study, Falls, Geriatric, Hip fractures

Introduction

From the age of 50, the risk of hip fractures increases exponentially[1]. As a result of a global increase in older people[2], the number of hip fractures are predicted to grow substantially in the coming decades[3]. Hip fractures have major consequences for the individual patient as well as for the society in general[4], since they cause substantial functional disability, loss of independency, decreased quality of life, and have a high mortality[5]. It is therefore of much importance to assess factors potentially associated with hip fractures.

The majority of hip fractures in older adults are caused by a fall[6]. The risk of fall related injury is multifactorial and, in some cases, reducible. An important risk factor is the intake of Fall Risk Increasing Drugs (FRIDs). The recent published World guidelines for falls prevention and management for older adults highlight the importance of conducting a medication review for FRIDs as part of the multifactorial approach, issuing strong recommendations to health care workers assessing older patients. In the newly developed STOPPFall tool, several medication classes are

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Corresponding author: *Rebekka Vedelsbøl, Department of Geriatric Medicine, Odense University Hospital, J.B. Winsløwsvej 4, 5000 Odense C*

E-mail: *rebekka.s.d.vedelsbol@rsyd.dk*

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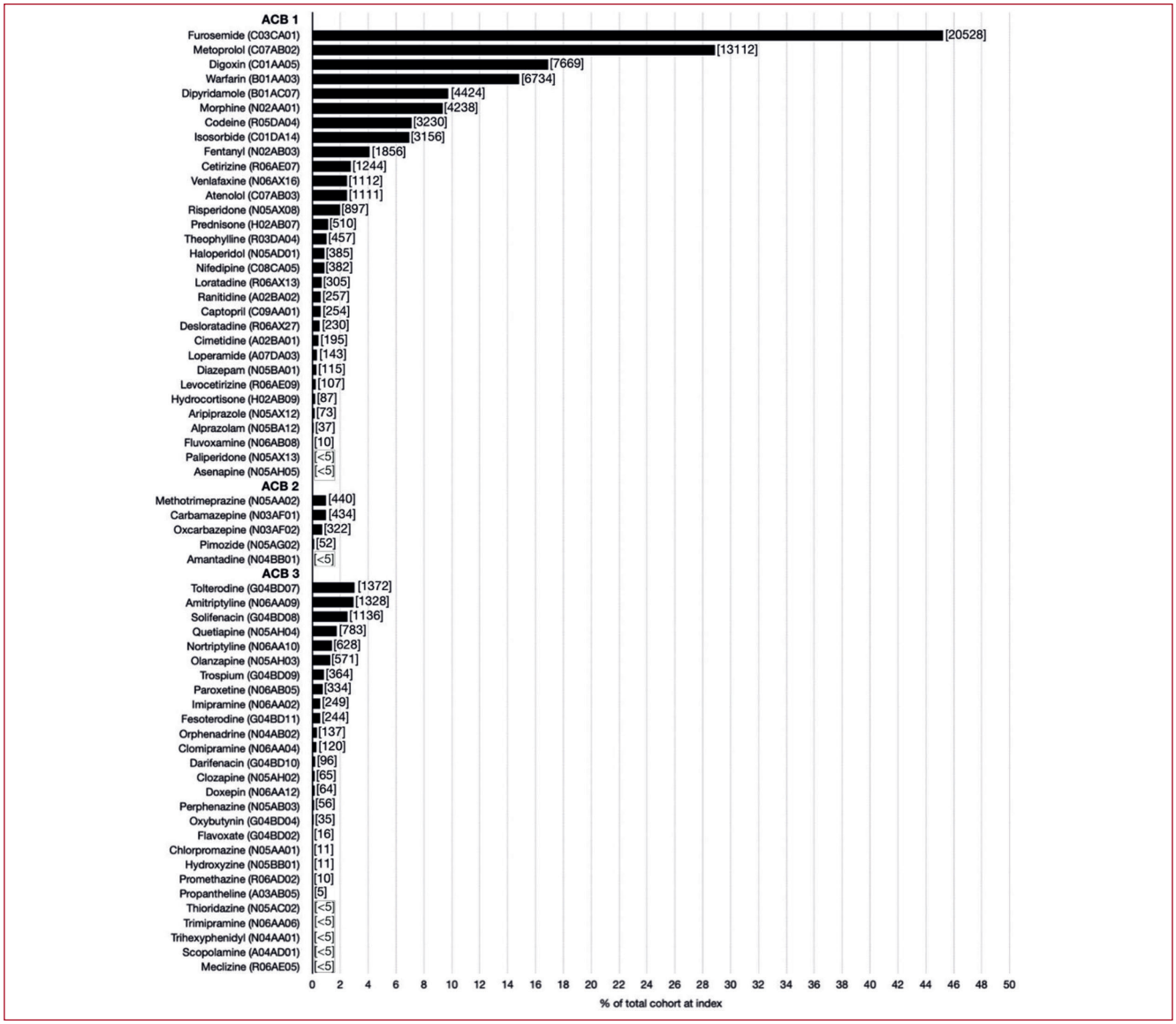

Figure 1. Anticholinergic drugs prescribed in the cohort. Data extracted from the Danish National Database of Reimbursed Prescriptions. [] = Number of patients; () = Anatomical Therapeutic Chemical (ATC) code. Abbreviations: ACB, Anticholinergic Cognitive Burden.

listed as FRIDs, one of them being drugs with anticholinergic properties (DAP)[7,8].

Potential adverse effects of DAP include increased heartrate, blurred vison, sedation, confusion, and delirium[9]. Consequently, use of DAP in older patients may be associated with negative outcomes such as falls[10] and fall-related fractures[11]. Age related change in pharmacokinetics is suspected to cause this apparent vulnerability. However, treatment of common geriatric conditions often relies on DAP[12], adding to the importance of further studies on the adverse effects in this specific age group. Prior studies have shown that the Anticholinergic Cognitive Burden (ACB) scale is a feasible tool to assess the cumulative effect of DAP systematically[13].

Studies on falls and fall-related injuries such as hip fractures in older patients are complicated by the presence of multiple co-risk factors including but not limited to age, osteoporosis, polypharmacy in general and FRIDs specifically, comorbidity, mobility, and functional level[7]. Often, data on all factors are not available in the same dataset e.g. due to either lack of relevant registers to assess data on medications or morbidity or due to lack of objective measurements like functional level[14]. One way to assess daily function is by assessing Activities of Daily Living (ADL).

ADL has a non-linear association with increased risk of falls, fall-related fractures, and mortality in geriatric patients[15-17], yet only a small number of studies on DAP have adjusted for this in their analysis[10,14,18]. When older patients are admitted to a geriatric department in Denmark, ADL is addressed routinely upon admission[17]. Furthermore, Denmark is well known for its high standard national registers including data on medications and comorbidities[19] and in addition holds some of the highest rates of hip-fractures internationally[20], which makes it an ideal place to study risk factors for hip fractures.

The aim of this study was to examine if the use of DAP according to ACB-score was associated with an increased future hip fracture risk in acutely hospitalized Danish geriatric patients while adjusting for relevant confounders including ADL.

Methods

Data sources, Study population, and Variables of interest

This was a nationwide register-based cohort study. The study setting and design have been described in detail previously[17]. In brief summary, this study analyses data from four Danish population based health registries: The Danish National Database of Geriatrics[21], The Danish Civil Registration System[22], The Danish National Patient Registry[23], and The Danish National Database of Reimbursed Prescriptions[24]. The ten-digit social security number given to citizens at birth or immigration was used to link data across registers.

The study population included all patients ≥65 years of age registered in the Danish National Database of Geriatrics[21] due to geriatric ward admission between January 2005 and December 2014. Primary outcome of interest was first hip fracture within 2 years after index admission (ICD10 codes: S72.0, S72.1, or S72.2). Patients were followed 2 years from time of admission, and were censored after either death, emigration, or hip fracture.

Height, weight, and admission assessment of ADL were gathered from the Danish National Database of Geriatrics. Barthel Index-100 is utilized routinely in Danish geriatric departments to summarize ADL of older patients. We calculated body mass index (BMI) as weight in kilograms divided with height in meters squared. Vital-, civil-, and residency status was obtained from the Danish Civil Registration System, along with birthdate and –sex. Hospital admissions and ICD-10 diagnoses 10 years prior to index were collected from the Danish National Patient Registry, including fractures and chronic illnesses. Individual Charlson Comorbidity Index (CCI) scores were calculated from data on 19 different comorbid diseases[25]. Fractures prior to index admission and current fractures at index were included using the following ICD-10 codes: S22.x (fracture of rib, sternum, and thoracic spine), T08.x (fracture of spine, level unspecified), S42.x (fracture of shoulder and upper arm), S52.x (fracture of forearm), and S72.x (fracture of femur/hip). Data on all redeemed prescriptions of reimbursed medication, including prescribed DAP, were extracted from the Danish National Database of Reimbursed Prescriptions. The ACB scale assigns individual DAP a score of 1, 2, or 3. A score of 1 indicates a possible anticholinergic effect, whereas 2 and 3 indicate a definite anticholinergic effect[26]. Data on DAP were extracted from the Danish National Database of Reimbursed Prescriptions, and drugs were identified by their ATC code (See Figure 1 for list of medications).

Additionally, data on prior anti-osteoporotic treatment was deduced from the following redeemed prescriptions using Anatomical Therapeutic Chemical (ATC) codes: M05BA08 (zoledronic acid) (prior 12 months); M05BX04 (Denosumab), and M05BX06 (Romosozumab) (prior six months); and G03XC01 (Raloxifene), H05AA02 (Teriparatide), H05AA03 (Preotact), M05BA (Bisphosphonates: Etidronate, Clodronate, Pamidronate, Alendronate, Tiludronate, Ibandronate, or Risedronate), M05BB (Bisphosphonate combinations: Etidronate & calcium, Risedronate & calcium, Alendronate & colecalciferol, Risedronate & colecalciferol, Alendronate & calcium & colecalciferol, Alendronate & alfacalciferol, Risedronate & colecalciferol, or Zoledronate & calcium & colecalciferol), or M05BX (Strontiumranelat or Strontiumranelat & colecalciferol) (prior four months).

Data are reported according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines[28].

Statistical analysis

Descriptive statistics are reported as mean or median including standard deviations (SD) or interquartile range (IQR) as appropriate, depending on normal or skewed distribution inspected graphically. Univariable and multivariable analyses was performed using Cox regression. The multivariable model 1 adjusted for Barthel Index, age, marital status, year of admission, BMI, prior or current fracture, number of previous admissions, dementia, and anti-osteoporotic medicine. Model 2 adjusted for variables in Model 1 and Charlson Comorbidity Index (CCI). These covariates were selected based on clinical reasoning and well-stablished associations with falls- or hip fracture risk in older people (ADL measured by Barthel, age, marital status, BMI, fracture history, dementia, and anti-osteoporotic medications). Also, a marker for vulnerability not addressed in the other variables but available in the registries were included (number of previous admissions) as well as a factor taking potential time trend into account (year of admission). Finally, since DAP are prescribed to treat relevant diseases CCI was included in the final model to address potential impact of comorbidity. Quantitative variables (age, BMI, BI, ACB, CCI, and hospital admissions) were treated as continuous variables in the analysis and results reported as hazard ratios (HR), including corresponding 95% confidence intervals. Imputation methods were not used[27]. If patients

	Total cohort N=74,589	Women N=46,815	Men N=27,774
Age (years), median (IQR)	83 (77-88)	84 (79-89)	81 (76-86)
Any medication, median (IQR)	6 (4-9)	6 (4-9)	6 (3-9)
ACB-score, median (IQR)‡	1 (0-2)	1 (0-2)	1 (0-2)
0, n (%)	27,971 (37.5)	17,744 (37.9)	10,227 (36.8)
1, n (%)	19,791 (26.5)	12,431 (26.6)	7,360 (26.5)
2, n (%)	11,201 (15.0)	6,874 (14.7)	4,327 (15.6)
3, n (%)	7,384 (9.9)	4,612 (9.8)	2,772 (10.0)
4, n (%)	3,908 (5.2)	2,473 (5.3)	1,435 (5.2)
≥5, n (%)	3,125 (4.2)	2,010 (4.3)	1,115 (4.0)
Missing, n (%)	1,209 (1.6)	671 (1.4)	538 (1.9)
Barthel Index, median (IQR)	54 (29-77)	55 (30-77)	52 (26-77)
BMI (kg/m^2), mean (SD)	23.9 (5.1)	23.6 (5.3)	24.5 (4.7)
CCI, median (IQR) *	2 (1-3)	2 (1-3)	2 (1-4)
Hospital admissions past year (IQR)	0 (0-1)	0 (0-1)	1 (0-2)
Fracture past 10 years, n (%)	28,988 (33.2)	18,654 (39.8)	6,142 (22.1)
Current fracture, n (%)	3,271 (4.4)	2,225 (4.8)	1,046 (3.8)
Marital status			
Unmarried, n (%)	4,851 (6.5)	2,733 (5.8)	2,118 (7.6)
Married, n (%)	21,639 (29.0)	8,268 (17.7)	13,371 (48.1)
Divorced, n (%)	9,204 (12.3)	5,763 (12.3)	3,441 (12.4)
Widowed, n (%)	38,881 (52.1)	30,044 (64.2)	8,837 (31.8)
Missing, n (%)	14 (0.0)	7 (0.0)	7 (0.0)

*Notes: ‡ All redeemed prescriptions were included, except from the following ATC codes: B05x (Blood substitutes and perfusion solutions), B06x (Other hematological agents), D09x (Medicated dressings), J07x (Vaccines), N01x (Anesthetics) and Vx (Various). ACB-score calculated according to Figure 1. * The CCI were calculated based on hospital discharge diagnoses during 10 years before baseline. Normal distributed data are presented with mean SD. Abbreviations: ACB, Anticholinergic Cognitive Burden; ATC, Anatomical Therapeutic Chemical; BI, Barthel Index; BMI, Body mass index; CCI, Charlson Comorbidity Index; DAP, Drugs with Anticholinergic Properties; IQR, Interquartile Range; SD, Standard Deviation.*

Table 1. Baseline characteristics of included patients (n = 74,589).

ACB-score	Total cohort, IR (95% CI)	Women, IR (95% CI)	Men, IR (95% CI)
0	90.8 (87.8-93.9)	104.3 (100.2-108.4)	66.3 (62.0-70.8)
1	82.4 (78.9-86.0)	90.0 (85.5-94.8)	68.0 (62.7-73.7)
2	75.1 (70.6-79.8)	83.2 (77.4-89.6)	60.5 (53.9-67.8)
3	74.0 (68.6-79.9)	81.0 (74.0-88.7)	61.1 (53.1-70.4)
4	73.8 (66.5-81.9)	76.3 (67.3-86.5)	68.9 (57.1-83.1)
≥5	71.9 (63.9-80.9)	78.7 (68.5-90.3)	58.7 (46.9-73.5)

Abbreviations: ACB, Anticholinergic Cognitive Burden; CI, Confidence Interval; IR, Incidence Rate.

Table 2. Incidence rates of hip fractures per 1,000 person years according to ACB-score.

had missing data on one or more of the included variables in the multivariable models they were excluded. In this way, the multivariable analyses were conducted as complete case analyses. Analyses were stratified by sex at birth according to the health registers. Analyses was performed using STATA (Stata, OP, College Station, TX, USA). A p-value of 0.05 indicated statistical significance.

Results

A total of 74,589 patients were included (62.8% women) with a median (IQR) age of 83 (77-88) years. Table 1 summarizes the baseline demographic characteristics of the study population. At baseline, 33.2% of the population had experienced a prior fracture and 4.4% of patients were admitted with a fracture on index date. Multi-complexity was prevalent among the study population with 82% of patients living with ≥1 co-morbidity condition, median CCI of 2, and a median (IQR) number of prescribed medications of 6 (4-9) with 19.9% of patients receiving ≥10 medications (Table 1).

The mean ACB-score at baseline was 1.3 with 63.5% of patients (n = 46,618) receiving ≥1 DAP. The majority (89%) of anticholinergic medications prescribed to the studied population scored 1 on the ACB scale (Figure 1). Of these patients, 45% received Furosemide (ACB = 1), 29% Metoprolol (ACB = 1), and 17% Digoxin (ACB = 1).

Hip fractures during follow-up

The 2-years follow-up resulted in 94,513 person-years. At the end of the study, 7,861 patients (72% women) had experienced a hip fracture, 31,351 patients had died, and 38,263 patients were alive with no hip fracture. In the total cohort, the incidence rates (IR) per 1,000 person years in the 2-year follow-up period was highest when ACB = 0 (IR 90.8; 95% CI 87.8-93.9) and decreased with increasing ACB-score in both sexes with the most prominent decrease seen in women (Table 2). The cumulative hazard for 2-year hip fracture according to ACB-score was between 15.3% (ACB = 0) and 11.7% (ACB ≥ 5) in the total cohort. The highest cumulative hazard of 17.8% was seen for ACB = 0 in women and the lowest cumulative hazard of 9.2% for ACB ≥ 5 in men (Figure 2).

Association between drugs with anticholinergic properties and hip fracture

Data on the regression coefficients, HR (95% CI), and statistical significance for each of the included covariates in relation to hip fractures are shown in Supplementary Table 1. Use of DAP was not associated with an increased risk of hip fractures. This was true for the total cohort in both the univariable and the multivariable analysis and when assessing women and men separately (Table 3). In the univariable analysis, increasing ACB-score was associated with lower hip fracture risk (HR (95% CI)) in the total cohort with the lowest risk seen in the category ACB ≥ 5 (HR 0.76

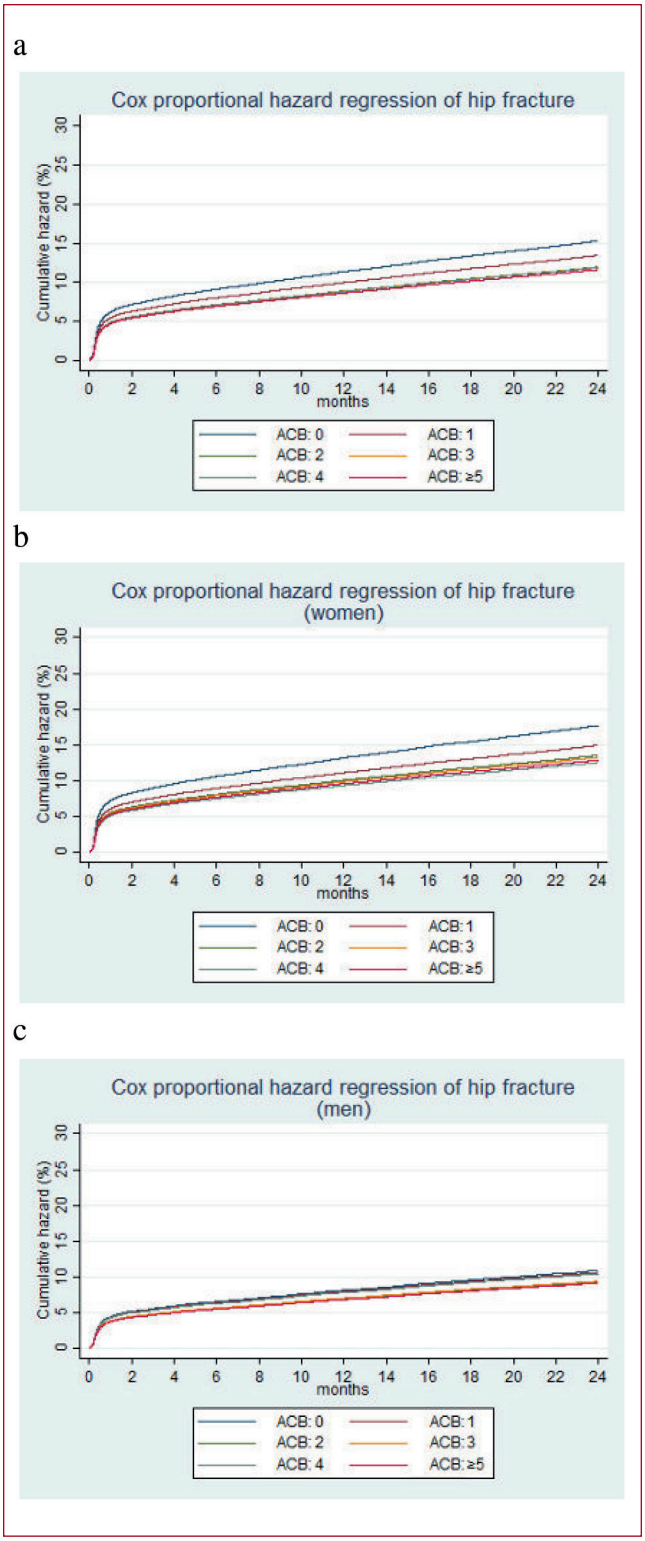

Figure 2. Cumulative hazard for 2-year hip fracture according to ACB-score in a) Total cohort, b) Women, and c) Men. Abbreviations: ACB, Anticholinergic Cognitive Burden.

Total cohort			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
1	0.88 (0.83-0.93)	0.91 (0.86-0.97)	0.94 (0.88-1.00)
2	0.78 (0.73-0.84)	0.88 (0.81-0.95)	0.92 (0.85-1.00)
3	0.78 (0.72-0.85)	0.84 (0.76-0.92)	0.86 (0.79-0.95)
4	0.78 (0.70-0.87)	0.82 (0.72-0.93)	0.85 (0.75-0.96)
≥5	0.76 (0.67-0.86)	0.80 (0.70-0.92)	0.83 (0.73-0.96)
Women			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
1	0.84 (0.79-0.90)	0.87 (0.81-0.93)	0.89 (0.83-0.96)
2	0.77 (0.70-0.83)	0.85 (0.78-0.93)	0.88 (0.81-0.97)
3	0.75 (0.68-0.83)	0.78 (0.70-0.87)	0.80 (0.72-0.90)
4	0.71 (0.62-0.81)	0.76 (0.66-0.88)	0.79 (0.68-0.91)
≥5	0.73 (0.63-0.84)	0.74 (0.63-0.87)	0.77 (0.65-0.90)
Men			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
1	0.98 (0.88-1.09)	1.05 (0.93-1.19)	1.09 (0.96-1.23)
2	0.85 (0.74-0.97)	0.99 (0.85-1.15)	1.03 (0.89-1.20)
3	0.87 (0.74-1.01)	1.01 (0.85-1.21)	1.05 (0.88-1.25)
4	0.96 (0.79-1.17)	1.00 (0.79-1.27)	1.04 (0.82-1.32)
≥5	0.84 (0.67-1.06)	0.98 (0.76-1.27)	1.01 (0.78-1.31)

Notes: Model 1: Barthel Index, age, marital status, year of admission, BMI, prior or current fracture, number of previous admissions, dementia, osteoporotic medicine. Model 2: Model 1 + Charlson Comorbidity Index. Abbreviations: ACB, Anticholinergic Cognitive Burden; CI, Confidence Interval; HR, Hazard Ratio.

Table 3. Univariable and multivariable HRs (95% CI) for hip fracture using Cox regression analysis according to ACB-score. Data are reported for total cohort, women, and men separately.

(0.67-0.86)). This was driven by a lower risk seen in women (ACB ≥ 5 (HR 0.73 (0.63-0.84) whereas a non-significant association was found in men with the highest ACB-score (ACB ≥ 5 (HR 0.84 (0.67-1.06). In the multivariable analysis, the trend remained the same in both models. In the fully adjusted model, the association with hip fracture was slightly smaller in both the total cohort (ACB ≥ 5 (HR 0.83 (0.73-0.66) and in women (ACB ≥ 5 (HR 0.77 (0.65-0.90). In men, there was a slightly non-significant increased risk of hip fracture for all ACB categories (Table 3).

Sensitivity analysis

In a sensitivity analysis, dichotomizing patients into whether they received no DAP (ACB-score = 0 (reference)) or DAP with an individual score of ≥2 points showed that the association with 2-year hip fracture risk (HR (95% CI)) in the multivariable analysis got attenuated in the total cohort (0.91 (0.84-0.99)) and in women (0.88 (0.80-0.97)) whereas no association was found in men (0.98 (0.84-1.14)) (Supplementary Table 2). In further analysis, dichotomizing patients into whether they received no DAP or DAP with an individual score of 3 points showed that the association got even less in the total cohort (0.92 (0.84-1.00)) and women (0.87 (0.79-0.97)) and stayed non-significant in men (1.04 (0.88-122)) (Supplementary Table 3).

Discussion

In this national register-based study of older geriatric patients, increasing ACB-score at time of hospital admission was not significantly associated with an increased risk of hip fracture during 2-years follow-up.

In general, ACB-score is associated with several adverse outcomes in older people[29] including mortality that was revealed in a recent study on the same cohort as our current study showing a dose-response relationship between higher ACB-score at hospital admission and mortality[30]. However, when it comes to the association between ACB-score and hip fractures data seems more divergent. A prior meta-analysis reported an association between ACB-score and fracture-risk[11] but these data are in contrast with our results. A partial explanation for that is the opportunity to adjust for several important confounders in our study including fracture comorbidities and objective measurements like BMI and ADL whereas the meta-analysis reported high heterogeneity and lacked adjustment for fracture-history. Furthermore, a study on community-dwelling older Canadians showed initial fracture-risk increase with use of DAP but this was no longer present after adjusting for frailty and bone mineral density[31]. In our study, less fall related hip fractures according to higher ACB-score was seen in women. This is in line with another study, which addressed the association between use of DAP and self-reported falls and found an increased risk in men only[32].The underlying mechanism of this is unclear and further research is needed to address this sex-specific difference to guide preventive measures most efficiently.

Authors of the original ACB scale define a sum of ≥3 as clinically relevant[26], but when it comes to hip fracture risk the cutoff is less well established. In our cohort, 89% of DAP prescribed had an ACB-score = 1 and as such, only qualified as 'possible' anticholinergic. In the few patients with an ACB-score ≥3 we were not able to find any increased hip fracture risk including our sensitivity analysis only including drugs with high ACB-score. Also, in a recent large Taiwanese register-based study on ACB-score and clinical outcomes for geriatric patients they assessed fracture-specific hospital admissions and found that data on cumulative ACB-score was inconsistent: Patients receiving one drug with ACB-score = 2 had higher risk of fracture than patients receiving two drugs with ACB-score = 1 or even one drug with ACB-score = 3 [14]. Similarly, a retrospective cohort study of older adults with mild cognitive impairment reported that the combination of one drug with ACB-score = 2 and one drug with ACB-score = 3 was the most potent FRID-prescription[33].

Implication

Fall prevention guidelines recommend considering deprescribing anticholinergic medication in general[7]. As of now, most studies have used ACB-score when assessing DAP. However, the mentioned prior research on the association between cumulative ACB-score and hip fractures combined with data from our study implies that maybe more focus should be applied on the individual specific anticholinergic drug and/or specific combinations of DAP when assessing hip fracture risk in geriatric patients. Furthermore, DAP is a cornerstone in the treatment of multiple comorbidities seen in older people. This suggests an important area of future research with the aim of developing an anticholinergic burden score specifically aimed at fall related fractures, which needs to take into account the pro's and cons' of prescribing/deprescribing DAP to older patients using shared decision making.

Strengths and limitations

Our study had several strengths. This was a nationwide cohort study in which we were able to combine data from many national Danish health registers, all known for their high standard and reliability[19]. This allowed us to adjust for a wide array of confounding risk factors, including ADL. Also, since no patients were lost to follow-up this further increase the validity of our results.

Our study also had some limitations. First, our dataset did not hold information on important co-factors that contribute to the risk of falls and hip fractures such as over-the-counter DAP, frailty, bone mineral density, smoking, or muscle mass. In this way, we were not able to account for these factors in our analyses. Conversely, all of the covariates that was included in the analyses (Barthel Index, age, marital status, year of admission, BMI, prior or current fracture, number of previous admissions, dementia, and anti-osteoporotic medicine) were associated with hip fractures. Not surprisingly, prior fracture history was the single factor with the highest HR. However, we did not explore these individual covariates further, since this was outside the scope of the current paper. Second, our data on DAP originates from the time of admission to a geriatric ward. Since DAP are known to have several negative outcomes important for older patients[9] geriatricians in charge of patients might have performed DAP deprescribing as part of their general medication review or as part of identification of potential FRIDs. Consequently, the index admission to a Danish geriatric ward may have acted as an intervention for specific patients – possibly the patients at the highest risk of injurious falls. However, our dataset holds no information on changes in medication during hospitalization and we can therefore not assess the potential impact of this. Furthermore, prior studies using the same cohort as in our study have demonstrated associations between admission data (ADL, DAP, or polypharmacy) and mortality[30,34,35], despite being subjected to the same intervening. Third, the ACB-score was not adapted to the medications used in a Danish setting since no validated Danish lists of DAP exists. Finally, prior studies in older people have shown that some of the drugs included on the ACB list have a specific association with decreased fracture risk like digoxin[36] or reduced risk of falls like selective beta-blocker metoprolol[37] representing 17% and 29% of DAP prescribed in our cohort, respectively. In this way, including these prevalent potentially preventive hip fracture drugs in the cumulative ACB-score might have diminished any positive associations.

Conclusion

Increasing cumulative anticholinergic burden assessed by ACB-score was not associated with an increased risk of hip fractures in this nationwide register-based cohort study of geriatric patients. Additional analysis of the impact of DAP with the highest anticholinergic burden did not alter the results. Our study emphasizes the importance of further research on the impact of individual DAP on hip fracture risk and development of anticholinergic burden scores specifically aimed at fall related fractures to support evidence-based recommendations in clinical practice.

Ethics approval

The Danish Data Protection Agency approved the study (2012-58-0018, J.nr. 16/23359). Consent to participate

Informed consent is not necessary in register-based studies according to Danish law on medical ethics.

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Authors' contributions

All authors (RV, PLA, JR) participated in the design of the study. PLA performed the statistical analyzes in dialogue with RV and JR. All authors (RV, PLA, JR) were involved in the interpretation of data. RV wrote the first manuscript draft, and all authors (RV, PLA, JR) were involved in the critical revision of the manuscript. RV had the primary responsibility for the final content, but all authors (RV, PLA, JR) are accountable for the aspects of the work. All authors (RV, PLA, JR) read and approved the final manuscript.

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ChatGPT was used during the writing process of the first draft to enhance readability and ensure grammatical correctness. ChatGPT was not employed for scientific insights, data interpretation, or drawing scientific conclusions. Use of ChatCGPT was carried out with oversight and control from the authors, who take responsibility for the originality, accuracy, and integrity of the work.

References

1. Pasco JA, Lane SE, Brennan-Olsen SL, Holloway KL, Timney EN, Bucki-Smith G, et al. The Epidemiology of Incident Fracture from Cradle to Senescence. Calcif Tissue Int 2015;97(6):568-76.
2. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2022: Summary of Results; UN DESA/POP/2022/TR/NO. 3.
3. Chen IJ, Chiang CY, Li YH, Chang CH, Hu CC, Chen DW, et al. Nationwide cohort study of hip fractures: time trends in the incidence rates and projections up to 2035. Osteoporos Int 2015;26(2):681-8.
4. Lozano-Ortega G, Schermer CR, Walker DR, Szabo SM, Rogula B, Deighton AM, et al. Fall/Fracture-Related Healthcare Costs and Their Association with Cumulative Anticholinergic Burden in People with Overactive Bladder. Pharmacoecon Open 2021;5(1):45-55.
5. Collaborators GBDF. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Healthy Longev 2021;2(9):e580-e92.
6. Parkkari J, Kannus P, Palvanen M, Natri A, Vainio J, Aho H, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. Calcif Tissue Int 1999; 65(3):183-7.
7. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing 2022 2;51(9):afac205.
8. Seppala LJ, Petrovic M, Ryg J, Bahat G, Topinkova E, Szczerbinska K, et al. STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk): a Delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age Ageing 2021; 50(4):1189-99.
9. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62 Suppl 21:11-4.
10. Stewart C, Taylor-Rowan M, Soiza RL, Quinn TJ, Loke YK, Myint PK. Anticholinergic burden measures and older people's falls risk: a systematic prognostic review. Ther Adv Drug Saf 2021; 12:20420986211016645.
11. Ogawa Y, Hirai T, Mihara K. A meta-analysis of observational studies on anticholinergic burden and fracture risk: evaluation of conventional burden scales. J Pharm Health Care Sci 2021;7(1):30.
12. Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. Expert Opin Drug Saf 2011;10(5):751-65.
13. Lisibach A, Benelli V, Ceppi MG, Waldner-Knogler K, Csajka C, Lutters M. Quality of anticholinergic burden scales and their impact on clinical outcomes: a systematic review. Eur J Clin Pharmacol 2021; 77(2):147-62.
14. Hsu WH, Huang ST, Lu WH, Wen YW, Chen LK, Hsiao FY. Impact of Multiple Prescriptions With Anticholinergic Properties on Adverse Clinical Outcomes in the Elderly: A Longitudinal Cohort Study in Taiwan. Clin Pharmacol Ther 2021;110(4):966-74.
15. Mamikonian-Zarpas A, Lagana L. The Relationship between Older Adults' Risk for a Future Fall and Difficulty Performing Activities of Daily Living. J Aging Gerontol 2015;3(1):8-16.
16. Lobo E, Marcos G, Santabarbara J, Salvador-Roses H, Lobo-Escolar L, De la Camara C, et al. Gender differences in the incidence of and risk factors for hip fracture: A 16-year longitudinal study in a southern European population. Maturitas 2017;97:38-43.
17. Ryg J, Engberg H, Mariadas P, Pedersen SGH, Jorgensen MG, Vinding KL, et al. Barthel Index at hospital admission is associated with mortality in geriatric patients: a Danish nationwide population-based cohort study. Clin Epidemiol 2018;10:1789-800.
18. Graves-Morris K, Stewart C, Soiza RL, Taylor-Rowan M, Quinn TJ, Loke YK, et al. The Prognostic Value of Anticholinergic Burden Measures in Relation to Mortality in Older Individuals: A Systematic Review and Meta-Analysis. Front Pharmacol 2020;11:570.
19. Frank L. Epidemiology. When an entire country is a cohort. Science 2000;287(5462):2398-9.
20. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C,

et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 2012;23(9):2239-56.
21. Kannegaard PN, Vinding KL, Hare-Bruun H. National Database of Geriatrics. Clin Epidemiol 2016;8:731-5.
22. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014; 29(8):541-9.
23. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90.
24. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 2012;4:303-13.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.
26. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health 2008;4(3):311–20.
27. Bennett DA. How can I deal with missing data in my study? Aust N Z J Public Health. 2001 Oct;25(5):464-9.
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370(9596):1453-7.
29. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr 2015;15:31.
30. Sorensen SR, Frederiksen JD, Anru PL, Masud T, Petrovic M, Rosholm JU, et al. Use of Drugs with Anticholinergic Properties at Hospital Admission Associated with Mortality in Older Patients: A Danish Nationwide Register-Based Cohort Study. Drugs Real World Outcomes 2022;9(1):129-40.
31. Fraser LA, Adachi JD, Leslie WD, Goltzman D, Josse R, Prior J, et al. Effect of Anticholinergic Medications on Falls, Fracture Risk, and Bone Mineral Density Over a 10-Year Period. Ann Pharmacother 2014; 48(8):954-61.
32. Richardson K, Bennett K, Maidment ID, Fox C, Smithard D, Kenny RA. Use of Medications with Anticholinergic Activity and Self-Reported Injurious Falls in Older Community-Dwelling Adults. J Am Geriatr Soc 2015;63(8):1561-9.
33. Green AR, Reifler LM, Bayliss EA, Weffald LA, Boyd CM. Drugs Contributing to Anticholinergic Burden and Risk of Fall or Fall-Related Injury among Older Adults with Mild Cognitive Impairment, Dementia and Multiple Chronic Conditions: A Retrospective Cohort Study. Drugs Aging 2019;36(3):289-97.
34. Ryg J, Engberg H, Anru PL, Pedersen SGH, Jorgensen MG, Vinding KL, et al. Activities of daily living at hospital admission and estimated survival time of older patients. Age Ageing 2021;50(4):1200-7.
35. Brockhattingen KK, Anru PL, Masud T, Petrovic M, Ryg J. Association between number of medications and mortality in geriatric inpatients: a Danish nationwide register-based cohort study. Eur Geriatr Med 2020;11(6):1063-71.
36. Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56(7):1333-41.
37. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. J Am Med Dir Assoc 2018;19(4):371 e1- e9.

Supplementary Table 1. Univariable hazard ratios (95% CI) for hip fracture in the total cohort using separate Cox regression analysis for each covariate and multivariable hazard ratios (95% CI) using Cox regression analysis incorporating all covariates besides comorbidity in model 1 and all covariates including comorbidity in model 2.

Covariate	Univariable model				Multivariable model 1				Multivariable model 2			
	Coefficient (b)	HR [exp(b)]	95% CI	P-value	Coefficient (b)	HR [exp(b)]	95% CI	P-value	Coefficient (b)	HR [exp(b)]	95% CI	P-value
ACB-score												
0	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A
1	-0.128	0.88	(0.83-0.93)	<0.001	-0.091	0.91	(0.86-0.97)	0.004	-0.064	0.94	(0.88-1.00)	0.044
2	-0.243	0.78	(0.73-0.84)	<0.001	-0.126	0.88	(0.81-0.95)	0.002	-0.082	0.92	(0.85-1.00)	0.043
3	-0.248	0.78	(0.72-0.85)	<0.001	-0.177	0.84	(0.76-0.92)	<.001	-0.145	0.87	(0.79-0.95)	0.003
4	-0.252	0.78	(0.70-0.87)	<0.001	-0.200	0.82	(0.72-0.93)	0.002	-0.163	0.85	(0.75-0.96)	0.011
≥5	-0.272	0.76	(0.67-0.86)	<0.001	-0.217	0.81	(0.70-0.92)	0.002	-0.182	0.83	(0.73-0.96)	0.010
Barthel Index	-0.012	0.99	(0.99-0.99)	<0.001	-0.010	0.99	(0.99-0.99)	<0.001	-0.011	0.99	(0.99-0.99)	<0.001
Age	0.015	1.01	(1.01-1.02)	<0.001	0	1	(1.00-1.00)	0.859	-0.001	1	(0.99-1.00)	0.453
Marital status												
Married	0.119	1.13	(1.02-1.24)	0.015	-0.026	0.97	(0.87-1.09)	0.636	-0.042	0.96	(0.86-1.07)	0.461
Unmarried	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A
Divorced	0.001	1	(0.93-1.08)	0.982	-0.067	0.94	(0.86-1.02)	0.134	-0.073	0.93	(0.85-1.02)	0.104
Widow	0.154	1.17	(1.11-1.23)	<0.001	0.023	1.02	(0.96-1.09)	0.476	0.013	1.01	(0.95-1.08)	0.683
Year of admission	0.029	1.03	(1.02-1.04)	<0.001	0.041	1.04	(1.03-1.05)	<0.001	0.042	1.04	(1.03-1.05)	<0.001
BMI	-0.044	0.96	(0.95-0.96)	<0.001	-0.029	0.97	(0.97-0.98)	<0.001	-0.028	0.97	(0.97-0.98)	<0.001
Prior/current fracture												
No	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A
Yes	1.337	3.81	(3.63-3.99)	<0.001	1.303	3.68	(3.48-3.89)	<0.001	1.292	3.64	(3.45-3.85)	<0.001
Previous admissions	-0.079	0.92	(0.91-0.94)	<0.001	-0.076	0.93	(0.91-0.95)	<0.001	-0.061	0.94	(0.92-0.96)	<0.001
Dementia												
No	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A
Yes	0.213	1.24	(1.15-1.33)	<0.001	-0.003	1	(0.91-1.09)	0.953	0.029	1.03	(0.94-1.12)	0.516
AOM												
No	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A	(0.000)	(1.00)	N/A	N/A
Yes	0.128	1.14	(1.05-1.23)	0.001	-0.145	0.87	(0.80-0.94)	0.001	-0.147	0.86	(0.79-0.94)	0.001
CCI	-0.079	0.92	(0.91-0.94)	<0.001	N/A	N/A	N/A	N/A	-0.051	0.95	(0.94-0.96)	<0.001

Abbreviations: ACB, Anticholinergic Cognitive Burden; AOM, Anti-osteoporotic medicine; BMI, Body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; N/A, not applicable

Total cohort			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
≥2	0.93 (0.87-1.01)	0.91 (0.84-0.99)	0.91 (0.84-0.99)
Women			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
≥2	0.89 (0.82-0.97)	0.88 (0.80-0.97)	0.88 (0.80-0.97)
Men			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
≥2	1.03 (0.90-1.18)	0.98 (0.84-1.15)	0.98 (0.84-1.14)

Model 1: Barthel Index, age, marital status, year of admission, BMI, prior or current fracture, number of previous admissions, dementia, osteoporotic medicine. Model 2: Model 1 + Charlson Comorbidity Index (CCI).

Supplementary Table 2. Univariable and multivariable HRs (95% CI) for hip fracture using Cox regression analysis after dichotomizing patients into whether they received individual drugs with anticholinergic properties with a score of 0 (reference) or ≥2 points. Data are reported for total cohort, women, and men separately.

Total cohort			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
3	0.93 (0.86-1.00)	0.92 (0.85-1.01)	0.92 (0.84-1.00)
Women			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
3	0.88 (0.80-0.96)	0.87 (0.79-0.97)	0.87 (0.79-0.97)
Men			
ACB	Univariable model, HR (95% CI)	Multivariable model 1, HR (95% CI)	Multivariable model 2, HR (95% CI)
0	1.00	1.00	1.00
3	1.04 (0.90-1.20)	1.04 (0.89-1.23)	1.04 (0.88-1.22)

Model 1: Barthel Index, age, marital status, year of admission, BMI, prior or current fracture, number of previous admissions, dementia, osteoporotic medicine. Model 2: Model 1 + Charlson Comorbidity Index (CCI).

Supplementary Table 3. Univariable and multivariable HRs (95% CI) for hip fracture using Cox regression analysis after dichotomizing patients into whether they received individual drugs with anticholinergic properties with a score of 0 (reference) or 3 points. Data are reported for total cohort, women, and men separately.