Use of Drugs with Anticholinergic Properties at Hospital Admission Associated with Mortality in Older Patients: A Danish Nationwide Register-Based Cohort Study

Søren Ramsdal Sørensen1,2, Jeppe Dalskov Frederiksen1,2, Pavithra Laxsen Anru3,4, Tahir Masud1,2,5, Mirko Petrovic6, Jens-Ulrik Rosholm1,2, Jesper Ryg1,2

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Abstract

Background Use of drugs with anticholinergic properties (DAP) has a negative impact on older people.

Objective Our aim was to examine the association between DAP at hospital admission and mortality in older patients.

Patients and Methods We performed a nationwide population-based cohort study including patients aged ≥ 65 years admitted to Danish geriatric medicine departments during 2005–2014. National health registers were used to link with individual-level data. Patients were followed to emigration, death, or study termination (31 December 2015). DAP was defined as medications included in the anticholinergic cognitive burden (ACB) scale, which assigns each DAP a score between 1 and 3. The individual ACB score was calculated and the number of DAP counted. We used Cox proportional-hazard regressions to estimate the crude and adjusted hazard ratios adjusting for age, activities of daily living, marital status, index admission period, BMI, and prior hospitalizations (model 1), and additionally Charlson Comorbidity Index (model 2).

Results We included 74,589 patients aged (median [IQR]) 83 (77–88) years. Use of one or more DAP (62.5%) was associated with increased mortality compared with those with no use (p < 0.001). In the fully adjusted model 2, compared with no use, higher mortality risks (HR [95% CI]) were seen with ACB score of 2 and number of DAP ≥ 5 for 30-day (1.46 [1.32–1.61] and 1.46 [1.09–1.95]), 1-year (1.34 [1.28–1.41] and 1.48 [1.29–1.70]), and overall mortality (1.27 [1.23–1.31] and 1.44 [1.31–1.59]), respectively.

Conclusions Use of DAP at hospital admission is associated with short- and long-term mortality in geriatric patients. Deprescribing studies are warranted to study whether the impact on mortality can be attenuated.
Key Points

Our study found a dose–response association between increased anticholinergic cognitive burden score as well as increased number of drugs with anticholinergic properties (DAP) at hospital admission and mortality in older patients.

The use of DAP was significantly associated with all-cause mortality even when adjusting for important confounders including comorbidities and activities of daily living.

In terms of mortality, our findings suggest that counting the number of DAP might be as relevant as calculating the anticholinergic cognitive burden score.

1 Introduction

Current demographic trends mean that the proportion of older people will increase substantially over the next 30 years [1]. Moreover, the prevalence of multimorbidity and disability is increasing with age [2]. The use of medications is consequently also on the rise and polypharmacy has become a major issue in the older population [3, 4]. Older people are more exposed to the negative effects of polypharmacy, in part because of multimorbidity and age-related changes in pharmacokinetics and pharmacodynamics [4, 5]. One of the major groups of medications contributing to polypharmacy in the older population are drugs with anticholinergic properties (DAP) [6]. Accordingly, research is beginning to focus on deprescribing DAP and the impact on outcomes in older people [7, 8].

DAP act on acetylcholine receptors in the central and peripheral nerve systems causing various adverse effects, and therefore must be used judiciously. These adverse effects are both cognitive and physical in nature and include delirium, constipation, urinary retention, dry mouth, acute glaucoma precipitation, falls, and cardiovascular outcomes [9–13].

Several scales have been used to quantify the burden of DAP. The most widely used scales include the Drug Burden Index, the Anticholinergic Drug Scale, the Anticholinergic Risk Scale, and the anticholinergic cognitive burden (ACB) scale [14–17]. The ACB scale is one of the oldest and most validated scales [18, 19], and some researchers suggest an association between ACB score and mortality [10, 20–25], whilst others find no association [11, 26]. However, even with multiple studies showing an association between ACB score and mortality, there is no clear dose–response relationship.

Several other factors are associated with mortality in older people. Among important factors are multimorbidity and the individuals’ functional level expressed as activities of daily living (ADL) [27–30]. The aim of the present study was to examine the association between use of DAP at hospital admission and mortality in a nationwide cohort of acutely admitted geriatric patients when taking comorbidities and ADL into account.

2 Methods

This was a nationwide register-based longitudinal cohort study in acutely hospitalized geriatric patients. Our primary outcome of interest was all-cause mortality.

2.1 Data Sources, Study Population, and Variables

Setting and participants have previously been described in detail elsewhere [27]. In short, the study combines data from four different Danish national registers: the Danish Civil Registry System [31], the Danish National Database of Reimbursed Prescriptions [32], the Danish National Database of Geriatrics [33], and the Danish National Patient Register [34]. Data was linked on an individual level using the unique social security number given to all persons in Denmark at birth or upon immigration. The study population was identified through the Danish National Database of Geriatrics and included all patients aged ≥ 65 years with their first registered hospitalization at a Danish geriatric department from the start of 2005 to the end of 2014. Patients were followed up until death, emigration, or the end of the study on December 31, 2015. Data on marital status, emigration, and death were extracted from the Danish Civil Registry System whereas prior hospitalizations and diseases were extracted from the Danish National Patient Register. We used the Charlson Comorbidity Index (CCI) to report data on comorbidity. CCI is associated with mortality and takes comorbidity into account by scoring 19 chronic diseases according to the number and severity of disease [35]. We calculated CCI using ICD-10 codes from 10 years prior to individual index admission and reported it in categories of 0, 1, 2, 3, 4, or ≥ 5 points. Data on patient’s functional level and body mass index (BMI), which are other covariates known to impact mortality, were also included.

One way to describe functional level is to evaluate ADL. The Danish National Database of Geriatrics holds data on Barthel Index (BI), which is scored routinely upon hospital admission and used to measure patients’ ADLs [36]. Ten different aspects of ADL are assessed and scored numerically with a combined score ranging from 0 (completely...
medications’ in the baseline characteristics shown in Table 1. Chemical (ATC) codes. Medications in the variable ‘all bursed Prescriptions [32] using Anatomical Therapeutic packages [38]. Information about redeemed prescriptions long-term treatment in Denmark are administered in 100-pill cut-off was chosen since most medications given for medications purchased up to 120 days prior to the index date. This cut-off was chosen since most medications given for the ACB-listed medications.

2.2 Statistics

Descriptive statistics were reported in contingency tables as mean and standard deviation (SD) for normally distributed data and as median and interquartile range (IQR) for skewed data. Follow-up started from the patient’s first registration of hospital admission at a geriatric department to the date of emigration, death, or end of the follow-up period (31 December 2015), whichever came first. We used Cox proportional-hazard regressions to estimate the crude and adjusted hazard ratios with corresponding 95% confidence interval (95% CI) for the following outcomes: overall mortality, 30-day mortality, and 1-year mortality. The multivariable models were adjusted for age, BI, marital status, period of index admission, BMI, prior hospital admission 1 year prior to index admission in model 1 and CCI was further added as confounder in model 2. All univariable and multivariable analyses were performed on the total cohort and further stratified on gender at birth. We used the Wald statistics to test the statistical significance of the categorical variables included in the multivariable Cox regression models. For each model, where the variables of interest were ACB score or number of DAP, we computed receiver operating characteristic (ROC) curves and their area under the curve (AUC) with 95% CIs for the fully adjusted model 2. Furthermore, a graphical presentation of the variable of interest was presented, where the ACB score or number of DAP was plotted as a continuous variable against the risk of overall mortality. P values < 0.05 indicated the statistical significance, and all analyses were performed using STATA version 14.2 (StataCorp, College Station, TX, USA).

2.3 Ethics

This study was approved by the Danish data protection agency (2012580018, J.nr. 16/23359). Informed consent was not necessary according to Danish legislation on medical ethics due to the register-based study design. Data are reported according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines [40].

3 Results

We included a total of 74,589 patients, consisting of 46,815 women and 27,774 men with a median (IQR) age of 83 (77–88) years. The mean ± SD number of all prescribed medications was 6.4 ± 3.9 in the total cohort, whereas the mean ± SD number of DAP was 1.1 ± 1.2 and the mean ± SD ACB score was 1.3 ± 1.5. The baseline characteristics of the study population are summarized in Table 1. The median follow-up time of the total cohort was 2 years. During follow-up, a total of 51,197 participants died with a median survival (95% CI) of 3.1 (3.1–3.2) years in women and 2.1 (2.0–2.1) years in men.

The majority of patients (62.5%) received DAP. Few patients received medications with an ACB score of two or three while a score of one accounted for 88.1% of the overall anticholinergic intake. The three most used DAP in the cohort (furosemide, metoprolol, and digoxin) accounted for 55.4% of the overall anticholinergic intake and the ten most used DAP (furosemide, metoprolol, digoxin, warfarin, dipyridamole, morphine, codeine, isosorbide, fentanyl, and tolterodine) for 88.9% (Supplementary Table 1, see ESM).

Table 2 illustrates risk of overall, 30-day, and 1-year mortality with increasing ACB score for the total cohort, whereas Supplementary Table 2 (see ESM) illustrates the risks for women and men separately. Patients prescribed DAP (62.5%) had increased mortality compared with those who were not prescribed any (37.5%) (p < 0.001). The univariable analysis showed an increasing risk of overall mortality (HR [95% CI]) in the total cohort with an ACB score.
Table 1  Baseline characteristics of the study population

|                           | Total cohort | Women | Men |
|----------------------------|--------------|-------|-----|
|                            | $N = 74,589$ | $N = 46,815$ | $N = 27,774$ |
| **ACB score**             |              |       |     |
| Mean ± SD                  | 1.3 ± 1.5    | 1.3 ± 1.6 | 1.3 ± 1.5 |
| Median (IQR)               | 1 (0–2)      | 1 (0–2)  | 1 (0–2)   |
| 0                          | 27,971 (37.50) | 17,744 (37.90) | 10,227 (36.82) |
| 1                          | 19,791 (26.53) | 12,431 (26.55) | 7360 (26.50) |
| 2                          | 11,201 (15.02) | 6874 (14.68)  | 4327 (15.58) |
| 3                          | 7384 (9.90)   | 4612 (9.85)  | 2772 (9.98)  |
| 4                          | 3908 (5.24)   | 2473 (5.28)  | 1435 (5.17)  |
| ≥ 5                        | 3125 (4.19)   | 2010 (4.29)  | 1115 (4.01)  |
| Missing, n (%)             | 1209 (1.63)   | 671 (1.43)   | 538 (1.94)   |
| **No. of DAPs**            |              |       |     |
| Mean ± SD                  | 1.1 ± 1.2     | 1.1 ± 1.2  | 1.1 ± 1.2   |
| Median (IQR)               | 1 (0–2)       | 1 (0–2)    | 1 (0–2)     |
| 0                          | 27,971 (37.50) | 17,744 (37.90) | 10,227 (36.82) |
| 1                          | 22,461 (30.11) | 14,153 (30.23) | 8308 (29.91) |
| 2                          | 13,519 (18.12) | 8369 (17.88) | 5150 (18.54) |
| 3                          | 6338 (8.50)   | 3917 (8.37)  | 2421 (8.72)  |
| 4                          | 2375 (3.18)   | 1481 (3.16)  | 894 (3.22)   |
| ≥ 5                        | 716 (0.96)    | 480 (1.03)   | 236 (0.85)   |
| Missing, n (%)             | 1209 (1.63)   | 671 (1.43)   | 538 (1.94)   |
| **All medications**        |              |       |     |
| Mean ± SD                  | 6.4 ± 3.9     | 6.5 ± 3.9  | 6.3 ± 3.9  |
| Median (IQR)               | 6 (4–9)       | 6 (4–9)    | 6 (3–9)     |
| 0                          | 2856 (3.83)   | 1621 (3.46) | 1235 (4.45) |
| 1                          | 3847 (5.16)   | 2291 (4.89) | 1556 (5.60) |
| 2                          | 5066 (6.79)   | 3065 (6.55) | 2001 (7.20) |
| 3                          | 6316 (8.47)   | 3926 (8.39) | 2390 (8.61) |
| 4                          | 7210 (9.67)   | 4465 (9.54) | 2745 (9.88) |
| 5                          | 7580 (10.16)  | 4780 (10.21) | 2800 (10.08) |
| 6                          | 7494 (10.05)  | 4830 (10.32) | 2664 (9.59) |
| 7                          | 6901 (9.25)   | 4352 (9.30) | 2549 (9.18) |
| 8                          | 6120 (8.20)   | 3973 (8.49) | 2147 (7.73) |
| 9                          | 5155 (6.91)   | 3363 (7.18) | 1792 (6.45) |
| ≥ 10                       | 14,835 (19.89)| 9478 (20.25) | 5357 (19.29) |
| Missing                    | 1209 (1.63)   | 671 (1.43)  | 538 (1.94)  |
| **Barthel Index, median [IQR]** |         |       |     |
| 80–100, n (%)              | 15,801 (21.18)| 9969 (21.29) | 5832 (21.00) |
| 50–79, n (%)               | 22,509 (30.18)| 14,681 (31.36) | 7828 (28.18) |
| 25–49, n (%)               | 16,479 (22.09)| 10,375 (22.16) | 6104 (21.98) |
| 0–24, n (%)                | 15,170 (20.34)| 8799 (19.18) | 6191 (22.29) |
| Missing                    | 4630 (6.21)   | 2811 (6.00)  | 1819 (6.55) |
| **Age (years), median [IQR]** |         |       |     |
| 65–74, n (%)               | 12,076 (16.19)| 6117 (13.07) | 5959 (21.46) |
| 75–84, n (%)               | 30,603 (41.03)| 18,361 (39.22) | 12,242 (44.08) |
| 85–94, n (%)               | 28,988 (38.86)| 20,092 (42.92) | 8896 (32.03) |
| ≥ 95, n (%)                | 2922 (3.92)   | 2245 (4.80)  | 677 (2.44)  |
| **Marital status, n (%)**  |              |       |     |
| Unmarried                  | 4851 (6.50)   | 2733 (5.84)  | 2118 (7.63)  |
| Married                    | 21,639 (29.01)| 8268 (17.66) | 13,371 (48.14)|
of 1 (1.23 [1.20–1.25]) and a score of 2 (1.40 [1.37–1.44]).

The risk was still increased but did not increase further with scores of 3 (1.36 [1.32–1.40]), 4 (1.36 [1.32–1.41]), or ≥ 5 (1.32 [1.26–1.38]) (Table 2). ACB score was associated with both increased short- and long-term mortality. The highest risk of mortality (HR [95% CI]) was found at 30 days in patients with an ACB score of 2 (1.64 [1.52–1.77]) (Table 2).

In women, the highest overall mortality risk (HR [95% CI]) was seen with an ACB score of ≥ 5: model 1 (1.41 [1.35–1.45]) and for men the highest risk was seen with an ACB score of 4 (1.50 [1.40–1.59]) (Supplementary Table 2a and 2b, see ESM).

In the multivariable analysis, the ACB score remained significantly associated with increased risk of overall mortality. The risk increased with an increasing ACB score up to 2 and remained increased but levelled off with ACB scores ≥ 3. Risk of overall mortality (HR [95% CI]) for model 2 were ACB 1 (1.14 [1.11–1.17]), ACB 2 (1.27 [1.23–1.31]), ACB 3 (1.24 [1.20–1.28]), ACB 4 (1.23 [1.17–1.29], and ACB ≥ 5 (1.24 [1.18–1.31]), respectively (Table 2). Figure 1a shows a ROC curve of model 2 overall mortality with an AUC of 0.7884. Including both models, ACB score was also associated with increased mortality, both short and long term. The strongest association was seen after 30 days with a decreasing trend towards 1 year. The highest risk of mortality (HR [95% CI]) was found with a score of 2 in model 1 (1.65 [1.50–1.82]) after 30 days (Table 2). For women, the highest overall risk of mortality (HR [95% CI]) in both models was seen with an ACB score of ≥ 5: model 1 (1.41 [1.35–1.45]) and model 2 (1.27 [1.23–1.31]).
Table 2 Univariable and multivariable hazard ratios and corresponding 95% confidence intervals for overall, 30-day, and 1-year mortality according to the anticholinergic cognitive burden (ACB) score in the total cohort

|                | Univariable HR (95% CI) | Multivariable HR (95% CI) |
|----------------|-------------------------|---------------------------|
|                | Model 1 | Model 2 | Model 1 | Model 2 | Model 1 | Model 2 |
| Overall mortality |         |         |         |         |         |         |
| ACB score       |         |         |         |         |         |         |
| 0               | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| 1               | 1.23 (1.20–1.25) | 1.21 (1.18–1.24) | 1.14 (1.11–1.17) | 1.21 (1.18–1.24) | 1.14 (1.11–1.17) | 1.21 (1.18–1.24) |
| 2               | 1.40 (1.37–1.44) | 1.39 (1.35–1.43) | 1.27 (1.23–1.31) | 1.39 (1.35–1.43) | 1.27 (1.23–1.31) | 1.39 (1.35–1.43) |
| 3               | 1.36 (1.32–1.40) | 1.33 (1.29–1.38) | 1.24 (1.20–1.28) | 1.33 (1.29–1.38) | 1.24 (1.20–1.28) | 1.33 (1.29–1.38) |
| 4               | 1.36 (1.31–1.41) | 1.34 (1.28–1.40) | 1.23 (1.17–1.29) | 1.34 (1.28–1.40) | 1.23 (1.17–1.29) | 1.34 (1.28–1.40) |
| ≥5              | 1.32 (1.26–1.38) | 1.35 (1.28–1.42) | 1.24 (1.18–1.31) | 1.35 (1.28–1.42) | 1.24 (1.18–1.31) | 1.35 (1.28–1.42) |
| 30-day mortality |         |         |         |         |         |         |
| ACB score       |         |         |         |         |         |         |
| 0               | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| 1               | 1.42 (1.33–1.52) | 1.38 (1.27–1.51) | 1.28 (1.17–1.39) | 1.38 (1.27–1.51) | 1.28 (1.17–1.39) | 1.38 (1.27–1.51) |
| 2               | 1.64 (1.52–1.77) | 1.65 (1.50–1.82) | 1.46 (1.32–1.61) | 1.65 (1.50–1.82) | 1.46 (1.32–1.61) | 1.65 (1.50–1.82) |
| 3               | 1.50 (1.38–1.64) | 1.60 (1.43–1.80) | 1.44 (1.28–1.61) | 1.60 (1.43–1.80) | 1.44 (1.28–1.61) | 1.60 (1.43–1.80) |
| 4               | 1.51 (1.35–1.69) | 1.38 (1.19–1.61) | 1.23 (1.06–1.43) | 1.38 (1.19–1.61) | 1.23 (1.06–1.43) | 1.38 (1.19–1.61) |
| ≥5              | 1.51 (1.33–1.71) | 1.49 (1.26–1.76) | 1.32 (1.12–1.56) | 1.49 (1.26–1.76) | 1.32 (1.12–1.56) | 1.49 (1.26–1.76) |
| 1-year mortality |         |         |         |         |         |         |
| ACB score       |         |         |         |         |         |         |
| 0               | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| 1               | 1.31 (1.27–1.36) | 1.28 (1.23–1.33) | 1.19 (1.14–1.24) | 1.28 (1.23–1.33) | 1.19 (1.14–1.24) | 1.28 (1.23–1.33) |
| 2               | 1.52 (1.47–1.58) | 1.50 (1.43–1.57) | 1.34 (1.28–1.41) | 1.50 (1.43–1.57) | 1.34 (1.28–1.41) | 1.50 (1.43–1.57) |
| 3               | 1.44 (1.38–1.51) | 1.40 (1.32–1.47) | 1.27 (1.20–1.34) | 1.40 (1.32–1.47) | 1.27 (1.20–1.34) | 1.40 (1.32–1.47) |
| 4               | 1.45 (1.37–1.54) | 1.37 (1.27–1.46) | 1.23 (1.15–1.32) | 1.37 (1.27–1.46) | 1.23 (1.15–1.32) | 1.37 (1.27–1.46) |
| ≥5              | 1.41 (1.33–1.51) | 1.38 (1.28–1.49) | 1.25 (1.16–1.35) | 1.38 (1.28–1.49) | 1.25 (1.16–1.35) | 1.38 (1.28–1.49) |

Model 1: adjusted for Barthel Index, age, marital status, period of index admission, BMI, and hospital admissions 1 year prior to index date. Model 2: adjusted for Barthel Index, age, marital status, period of index admission, BMI, hospital admissions 1 year prior to index date, and Charlson comorbidity index

N = 56,564

ACB Anticholinergic cognitive burden, BMI body mass index, CI confidence interval, HR hazard ratio

[1.32–1.50]) and model 2 (1.29 [1.21–1.38]) (Supplementary Table 2a, see ESM). For men, the highest overall risk of mortality (HR [95% CI]) in both models was seen with an ACB score of 4: model 1 (1.49 [1.39–1.61]) and model 2 (1.39 [1.30–1.50]) (Supplementary Table 2b, see ESM). Figure 2 shows the relationship between the ACB score and risk of mortality in model 2 with a significant dose–response relationship before levelling off when a score of 2 is reached.

When assessing the total number of DAP, a significant increase in overall mortality was also seen in both the univariable and multivariable analyses (Table 3; Supplementary Table 3a and 3b, see ESM). Figure 3 shows the relationship between the number of DAP and risk of mortality with a significant dose–response relationship with increasing number of anticholinergic medications before levelling off when number of medications reaches 4. Figure 1b shows a ROC curve of model 2 overall mortality for number of DAP in the total cohort with an AUC of 0.7888. No clinically relevant difference was seen between the ROC curves assessing either ACB score or number of DAP (AUC 0.7884 vs AUC 0.7888).

4 Discussion

In the present study, we found that the use of DAP at hospital admission is significantly associated with both short- and long-term mortality in older geriatric patients when taking comorbidities and ADL into account. This was seen both when using the ACB score and counting the number of DAP. The ACB score shows a dose–response relationship until a score of two, whilst the number of DAP shows a dose–response relationship with increasing number of medications.

4.1 Context

4.1.1 Quantifying Anticholinergic Drug Burden

In this study, we used the ACB score to quantify the anticholinergic drug burden. Several other scales have been developed with varying rationale and use. They differ in association between anticholinergic burden and adverse outcomes [12]. A recent study assessed the different scales, with the ACB score considered to be the scale of the best quality [41]. Also, another recent study found that out of eight anticholinergic-specific measures, the ACB score was the best for assessing the association between DAP and mortality in older people [42].

Existing literature has examined the association between ACB score and mortality in different settings and with mixed results. The settings include general population [10], community-dwellings [25], nursing homes [22], patients with dementia [24], and older patients admitted to hospital [11, 20, 21, 23, 26]. Generally, studies with follow-up longer than a year were successful in demonstrating the association between ACB score and mortality [10, 20–25]. One study examining the association on 3- and 7-day in-hospital mortality [26] and another examining this association 12 months following hospital discharge [11] did not demonstrate a relationship. In our study, we demonstrated a significant relationship between ACB score and mortality after

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In studies demonstrating increased mortality, only limited data on a potential dose–response relationship were available. Most studies included hazard ratios for ACB cognitive burden score (a) and number of drugs with anticholinergic properties (b).

Fig. 1 Receiver operating characteristic curve for the association between drugs with anticholinergic properties and mortality for the fully adjusted model 2* illustrated separately for the anticholinergic cognitive burden score (a) and number of drugs with anticholinergic properties (b).

both 30 days and 1 year after hospitalization, and is to our knowledge the first to do so using the ACB score.
scores of 1 and ≥ 2 compared with ACB score of 0 [20, 22–24]. One study categorized the scores into 1, 2–3, and ≥ 4 [10] and yet another only showed hazard ratios for increasing ACB score by one unit [25]. In this study, we included hazard ratios for both ACB score and number of DAP with categorizations from 0 to ≥ 5. Counting the number of DAP showed a similar dose–response relationship as when using the ACB score and none of the measures had a continuous dose–response relationship. One other study addressed the total number of DAP and impact on mortality among long-term care facility residents [43]. The study used three different approaches to identify anticholinergic drugs and found a similar tendency with number of DAP associated with mortality. To our knowledge, no other studies so far have looked at the association between anticholinergic polypharmacy and mortality using ACB score in hospitalized patients. The association found in the present study cannot be explained by polypharmacy alone. In a prior study using data from the same cohort as the current study, the association between number of total medications and mortality was assessed [44]. The study found an increased risk of mortality with five or more medications prescribed whereas the use of one to four medications was not significantly associated with mortality. An Australian study assessing older men also reported that the use of five or more medications was associated with mortality [45]. In the current study, the number of DAP was significantly associated with mortality even with only one medication prescribed. This suggests an important anticholinergic component when assessing the association between polypharmacy in general and mortality.

4.1.2 Independent Association Between the Use of DAP and Mortality

In the present study, we found an independent association between the use of DAP at hospital admission and mortality, even when adjusting for several important risk factors in the multivariable analyses including ADL and different ways of expressing comorbidity. We have no data to explore the specific mechanism behind why DAP affect mortality in older people. However, several other studies have explored this. Changes in the permeability of the blood–brain barrier as well as changes in pharmacokinetics and pharmacodynamics with increasing age make older people more susceptible to unfavorable effects from DAP [5]. These adverse effects vary widely. Some studies found an association between the use of DAP in older people and neurological symptoms such as confusion, agitation, and coma [46]. Some evidence suggests that DAP may contribute to cardiovascular events via their ability to decrease the heart rate variability [46, 47], their inhibition of the parasympathetic control of the heart [48], or their pro-arrhythmic and pro-ischemic effect [49]. Other
Table 3  Univariable and multivariable hazard ratios and corresponding 95% confidence intervals for overall, 30-day, and 1-year mortality according to the number of drugs with anticholinergic properties in the total cohort

| No. of DAP | Overall mortality | 30-day mortality | 1-year mortality |
|------------|------------------|------------------|------------------|
|            | Univariable HR (95% CI) | Multivariable HR (95% CI) | Univariable HR (95% CI) | Multivariable HR (95% CI) |
| 0          | 1 (reference)     | 1 (reference)    | 1 (reference)    | 1 (reference)  |
| 1          | 1.19 (1.17–1.22)  | 1.18 (1.15–1.21) | 1.12 (1.09–1.15) | 1.18 (1.15–1.21) |
| 2          | 1.37 (1.34–1.41)  | 1.37 (1.33–1.40) | 1.25 (1.22–1.29) | 1.37 (1.33–1.40) |
| 3          | 1.50 (1.45–1.55)  | 1.49 (1.43–1.55) | 1.35 (1.30–1.40) | 1.49 (1.43–1.55) |
| 4          | 1.57 (1.49–1.65)  | 1.57 (1.48–1.66) | 1.39 (1.32–1.47) | 1.57 (1.48–1.66) |
| ≥5         | 1.57 (1.44–1.71)  | 1.64 (1.48–1.81) | 1.44 (1.31–1.59) | 1.64 (1.48–1.81) |

Model 1: adjusted for Barthel Index, age, marital status, period of index admission, BMI, and hospital admissions 1 year prior to index date. Model 2: adjusted for Barthel Index, age, marital status, period of index admission, BMI, hospital admissions 1 year prior to index date, and Charlson comorbidity index

N = 56,564

*BMI* body mass index, *CI* confidence interval, *DAP* drugs with anticholinergic properties, *HR* hazard ratio

The present study has various strengths. To our knowledge, this is the first nationwide longitudinal cohort study to assess the association between DAP and mortality taking into account several important risk factors including ADL. Furthermore, the study allowed a long follow-up of 11 years. The validity of the results was increased due to no patients lost to follow-up throughout the study period. This was attained via accurate linkage at the personal level between the many nationwide population-based Danish health registers.

The present study also has several limitations. First, the ACB score is not customized to Danish medicine. This means that some DAP used in Denmark may not be considered. Second, we have no data either on comorbidities or DAP (including dose, duration, or number) after index date. In this way, potential development of additional comorbidities or changes in use of medications following discharge might not have been captured. However, the association with use of DAP upon admission was still associated with both short- and long-term mortality. Third, the CCI in our study is calculated using prior ICD-10 diagnoses. These diagnoses are obtained from the health registers and based on data from hospital discharge, which may have introduced information bias. However, the use of Danish national health registers to calculate CCI have shown high validity in a prior study [51]. Fourth, due to our observational design it is difficult to explore whether DAP are associated with mortality or serve as a proxy for severity of diseases and we cannot rule out the risk of confounding by indication. However, the vast majority of DAP used among patients was given due to heart diseases. In our fully adjusted model we included CCI, which takes both several heart diseases and their severity into account and still found a persistent association between the use of DAP and mortality. Despite these efforts, residual effects might, however, still be present. Also, we cannot rule out that some of DAP are prescribed to manage symptoms in end of life and in this context can even be considered appropriate. Finally, there is no gold standard for quantifying anticholinergic burden and the use of other scales might not have shown similar results. However, prior evidence shows that the ACB score is of most value when assessing the association between DAP and mortality in older people [42].
Conclusion and Implications

This study demonstrated a significant association between the use of DAP at hospital admission and all-cause mortality in older geriatric patients even when adjusting for other important variables such as comorbidity and ADL. Assessing either ACB score or the number of DAP showed similar dose–response relationships. This reveals that in terms of mortality, the simple counting of the number of DAP might be just as important as calculating the ACB score. Our study may ease the feasibility of deprescribing for clinicians, as a simple cumulative count of DAP is easier to administer than calculating an ACB score. Reduction of the use of DAP is feasible but challenging in a real-life setting [52] and a gap still exists in the literature on the effects on mortality of reducing the use of DAP prescribed for older adults. While awaiting RCT studies on deprescribing, initiation of pragmatic studies with focus on the effect of stopping these medications on both clinical and implementation outcomes should be encouraged as well as further analyses of observational data in order to better understand which harmful effects or adverse drug events in general might potentially be reversed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-021-00270-7.

Declarations

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Conflict of interest Dr. Ryg reports an unrestricted research grant from Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation, during the conduct of the study [Grant number: R3-017]. All authors declare no personal conflict of interest regarding the present study.

Ethics approval Approval from an ethical committee was not needed according to Danish legislation due to the epidemiological study design.

Consent to participate According to Danish legislation, informed consent was not needed from patients due to the retrospective cohort design.

Consent for publication Not applicable.

Availability of data and material According to the Danish Law on personal data, it is not allowed to make the dataset publicly available. Access to data from the Danish Health Data Authority requires association with a Danish research unit and approval from the Danish Data Protection Agency (http://www.datatilsynet.dk/english/) and the National Health Service Register (http://www.sundhedsdatastyrelsen.dk/da/forskerservice [in Danish]).

Code availability Not applicable.
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Author contributions JR and PLA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SRS, JDF, TM, PM, and JR designed the study. PLA performed the statistical analyses in dialog with SRS, JDF, and JR. All authors (SRS, JDF, PLA, TM, MP, JUR, JR) were involved in the interpretation of data. SRS and JDF wrote the first manuscript draft and all authors (SRS, JDF, PLA, TM, MP, JUR, JR) were involved in the critical revision of the manuscript. JR had the primary responsibility for the final content but all authors (SRS, JDF, PLA, TM, MP, JUR, JR) are accountable for the aspects of the work. All authors (SRS, JDF, PLA, TM, MP, JUR, JR) read and approved the final manuscript.

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