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Brief Report

Anticholinergic Medication Burden and 5-Year Risk of Hospitalization and Death in Nursing Home Elderly Residents With Coronary Artery Disease

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A B S T R A C T

Objectives: To assess the association of the anticholinergic medication burden with hospitalization and mortality in nursing home elderly patients and to investigate the role of coronary artery disease (CAD).
Design: Longitudinal (5-year) retrospective observational study.
Setting: Nursing homes in Italy.
Participants: A total of 3761 nursing home older residents.
Measurements: A comprehensive clinical and functional assessment was carried out through the interRAI long-term care facility instrument. The anticholinergic burden was assessed through the anticholinergic cognitive burden (ACB) scale. Occurrence of hospitalization/all-cause mortality was the primary composite outcome. First hospitalization and all-cause mortality were the secondary outcomes of the study. Hazard ratios (HRs) and subdistribution HRs were obtained through Cox and competing risk (death as competing event for hospitalization) models.
Results: Within the sample (mean age 83 ± 7 years; 72% females) the incidence rate of the primary outcome was 10/100 person-year. After adjusting for potential confounders and compared with participants with an ACB of 0, those with an ACB of 1 [HR 1.46; 95% confidence interval (CI) 1.12−1.90] and ABC of 2+ (HR 1.41; 95% CI 1.11−1.79) presented an increased risk of developing the primary outcome. After stratification, the risk for the primary outcome increased along with the anticholinergic burden, only for participants affected by CAD (HR 1.53; 95% CI 0.94−2.50 and HR 1.71; 95% CI 1.09−2.68 for the ACB of 1 and ACB of 2+ groups). An ACB score of 2+ was marginally associated with first hospitalization, considering death as a competing risk, only for those with CAD (subdistribution HR 3.47; 95% CI 0.99−12.3).
Conclusions: Anticholinergic medication burden is associated to hospitalization and all-cause mortality in institutionalized older adults. CAD increases such risk. The effectiveness and safety profile of complex drug regimens should be reconsidered in this population.

Among the elderly, nursing home (NH) residents are the frailest group, characterized by high rates of chronic multimorbidity and polypharmacy.[1,2] As a consequence, the chance of being prescribed with potentially inappropriate drugs increases, resulting in higher risk of negative events and health services use.[3]

The authors declare no conflicts of interest.

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Anticholinergics have recently been pointed out as potentially harmful for the elders. They include drugs used by purpose for their anticholinergic action (eg, bronchodilators, antiparkinsonians) and drugs that explicate anticholinergic properties as a side effect (eg, antidepressants, antipsychotics). Several concerns orbit around their neurologic and systemic action, and their proved negative impact on hospitalization, cardiovascular events and death.[4] It was reported that 1 out of 3 NH residents takes more than 2 anticholinergic drugs, and 5 out of 10 take more than 5.[5,6]

Sparse evidence suggests a higher risk of negative outcomes related to anticholinergics use among elders affected by heart diseases. Namely, in older adults with cardiovascular disease, a higher anticholinergic burden was associated with an increased risk of hospitalization, length of hospital stay, and marginally, with mortality.[7,8] Moreover, coronary artery disease (CAD) might represent a favorable substrate for the pro-arrhythmic effect of anticholinergics. Indeed, both pro-arrhythmic and pro-ischemic properties have been described for anticholinergics.[9,10]

The aim of the present study was to assess the 5-year association of the anticholinergic medication burden with hospitalization and mortality in NH elderly patients. The role of CAD was also investigated.

Methods

Sample and Data Sources

We analyzed a random sample of 3761 NH residents in the Italian region of Umbria, with at least 2 evaluations during the period from January 2010 to January 2015. Evaluations were carried out through the multidimensional assessment instrument interRAI long-term care facility (LTCF). This tool includes over 350 data elements (ie, sociodemographics, clinical information, physical function, and cognition), and it is currently used in several Italian regions for administrative and clinical purposes. InterRAI LTCF is a reliable instrument that enables the creation of databases that can be used to assess and compare characteristics of NH residents across countries, languages, and cultures.[11–13] Health professionals using interRAI LTCF are trained to use a variety of information sources, such as direct observation, interviews with the person under care, family, friends, or formal service providers, and review clinical records, both medical and nursing. This is an observational, retrospective, noninterventional study. According to a by-law on the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency (an entity belonging to the Italian Ministry of Health), the present study does not require approval by an Ethics Committee (Italian Drug Agency note of August 3, 2007).

Assessment of Drug Use and Anticholinergic Burden

All the drugs used by the participants in the 3 days prior to the assessment were collected and registered according to their anatomic therapeutic and chemical code. The anticholinergic medication burden was evaluated through the anticholinergic burden scale (ACB). The ACB assesses the anticholinergic cognitive impact of any drug based on review of the literature. According to the ACB scale, a score of 0, 1, 2, or 3 is given to each drug as elsewhere described.[14] According to a recent review by Cardwell et al,[15] the ACB score is proposed as a reliable instrument for longitudinal research in the oldest old. According to another review, ACB score was reported to be the most frequently validated tool to address the effect of anticholinergic drugs on negative outcomes.[16] For our purposes, we categorized the ACB scale in 3 groups: 0, 1, and 2+.

Study Outcomes

The primary outcome of the study was the composite occurrence of overall mortality/first hospitalization. Study participants were followed-up until the occurrence of one of the above mentioned events or until the maximum period of observation, defined as the time span (years) between the first and the last available assessment. Death and hospitalization were the secondary outcomes.

Independent Variables

The demographic variables included age and sex. The 7-point Minimum Data Set activities of daily living hierarchy scale was used as functional assessment. This scale ranges from 0 (no impairment) to 6 (total dependence); lower values mean less impairment. Cognition was evaluated through the Cognitive Performance Scale. Such instrument combines information on memory impairment, level of consciousness, and executive function, with scores ranging from 0 (intact) to 6 (very severe impairment). Depressing symptoms were assessed through the Depression Rating Scale. This scale was found to be reliable for detecting depression among older adults, and, when tested against diagnoses of major or non-major depression, sensitivity was 91%, and specificity was 69%.[17] All the comorbidities were gathered through specific interRAI LTCF items.

Statistical Analysis

Analysis of the variance and χ^2 test were used, as appropriate, to compare participants' baseline characteristics across different ACB scores. Survival estimations were computed through Kaplan-Meier curves and significance obtained through the log-rank test. Adjusted proportional hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary outcome and overall mortality were obtained through Cox regression models. Adjusted subdistribution HRs (sHR) were calculated for the first hospitalization since baseline evaluation and competing risk mortality. Variables differently distributed at the univariate at a P level of $<.05$ were considered potential confounders. Analyses were finally stratified by presence of CAD. A P value of $<.05$ has been considered statistical significant for all the analyses. All analyses have been done with the statistical software Stata v 14.0 (StataCorp, College Station, TX).

Results

The study participants (mean age 83 ± 7 years; 72% females) were observed for a mean follow-up period of 1.4 years (max. follow up 5 years). Sample characteristics are shown in Table 1. During the observation time, 91 participants were hospitalized (incident rate 2/100 person-year), and 386 died (incidence rate 8/100 person-year). Figure 1 shows the survival curves for the primary outcomes by anticholinergic burden exposition. As shown in Figure 2, after adjusting for potential confounders, participants with an ACB score of 1 (HR 1.46; 95% CI 1.12–1.90) and an ACB score of 2+ (HR 1.41; 95% CI 1.11–1.79) presented an increased risk to develop the primary outcome as compared with the others. After stratification, the risk for the primary outcome increased along with the anticholinergic burden only for participants affected by CAD (HR 1.53; 95% CI 0.94–2.50 and HR 1.71; 95% CI 1.09–2.68 for the ACB 1 and ACB 2+ groups). No association arose between ACB score and mortality either in the whole sample or after stratification for CAD. An ACB score 2+ was marginally associated with first hospitalization, considering death as a competing risk, in participants affected by CAD (sHR 3.47; 95% CI 0.99–12.3).