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Original Study

Renin-Angiotensin System Blockers and Statins Are Associated With Lower In-Hospital Mortality in Very Elderly Hypertensives

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A B S T R A C T

Objectives: Cardiovascular diseases are mainly related to hypertension and dyslipidemia and increase with aging because of the larger time span for these risk factors to damage arterial blood vessels. The impact of cardiovascular drug therapy on outcomes in the very elderly hospitalized is still not well established. The aim of our study was to evaluate the associations between cardiovascular therapy and in-hospital mortality in very elderly hypertensives.
Design: Prospective observational study.
Setting: Hospital assessment.
Participants: 310 very elderly hypertensive patients admitted to our Internal Medicine and Geriatrics Department for medical conditions.
Measurements: Main comorbidities, laboratory parameters, and cardiovascular drug therapy taken before admission were considered for the analyses.
Results: The mean age was 88.1 ± 5.1 years, with female prevalence of 57.4%. Among cardiovascular drugs taken before admission, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers and statins were those associated with lower in-hospital mortality, even after adjusting for covariates (age, hemoglobin, albumin, acute kidney injury, ADL Hierarchy Scale, NT-proBNP levels) [odds ratio (OR) = 0.46, $P = .045$, and OR = 0.21, $P = .008$, respectively]. No difference regarding in-hospital mortality was found between ACE inhibitors and angiotensin receptor blockers ($P = .414$).
Conclusion: ACE inhibitors/angiotensin receptor blockers and statins, through their beneficial effects on the cardiovascular system, have a positive impact on survival in very elderly hospitalized patients. Our data confirm the important role of such drugs even in this particular population with a mean age higher than 88 years, where scientific evidence is still scanty.

Life expectancy has increased over the past century in industrialized countries. Italy has one of the highest life expectancy rates worldwide. According to the latest WHO data published in 2015, life expectancy in Italy was 80.5 years for men and 84.8 years for women, and the total life expectancy was 82.7 years.[1] Cardiovascular diseases (CVD), mainly related to hypertension and dyslipidemia, are the leading causes of disability and death worldwide and we are facing a true pandemic of older adults with CVD, as a result of longevity.[2] Indeed, aging increases the time span for the deleterious effects of these risk factors on the vessel walls. Despite the prevalence of older individuals with CVD and other comorbidities in the real world, randomized controlled trials (RCTs) on cardiovascular (CV) drugs are generally focused on younger individuals, without such comorbidities and polypharmacy, common conditions among elderly, resulting in important gaps in published evidence.[2] Hypertension is one of the main CV risk factors for morbidity and mortality, particularly in the elderly. Hypertension, defined by arterial blood pressure (BP) ≥140/90 mm Hg, is present in approximately 70% of men and 80% of women aged 70 years or

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older.[3] European hypertension guidelines, mainly based on RCTs, do not favor a specific antihypertensive drug class in the very elderly.[4] HYVET (Hypertension in the Very Elderly Trial) and SPRINT (Systolic Blood Pressure Intervention Trial) are the only 2 RCTs focused on older hypertensives,[5,6] but they are still poorly representative of the very elderly population encountered in "real life" clinical practice.[7] Moreover, very elderly hypertensives often receive statin therapy, because of dyslipidemia and/or previous CV events. Given the increase in the elderly population and the rising incidence of hospitalization with aging, there are more and more elderly patients with CVD admitted to internal medicine and geriatrics departments.[8] The impact of previous CV therapy on in-hospital outcome is largely unknown in this particular population. Therefore, the aim of our prospective observational study was to evaluate the associations between CV drug therapy taken before hospitalization and in-hospital mortality in a very elderly hypertensive population, hospitalized for medical conditions.

Methods

Study Design and Population

Prospective observational study on 310 very elderly hypertensive patients, consecutively admitted to an Internal Medicine and Geriatrics Department, from January 2015 to December 2016. Inclusion criteria were as follows: age ≥80 years, history of treated hypertension, admission for medical conditions, no conditions with a life expectancy of less than 1 year (end-stage renal disease, decompensated cirrhosis or advanced cancer). An admission diagnosis of heart failure (HF) confirmed by a cardiologist was considered an exclusion criterion. We considered hypertensives those very elderly with a documented history of hypertension treated with at least 1 antihypertensive drug.

Clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. Data were collected and analyzed anonymously, so it was not necessary to obtain informed consent from each patient. This observational study of a "best clinical practice" experience was approved by the local institutional ethics committee. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Laboratory Parameters

We considered the following laboratory parameters: hemoglobin (Hgb), white blood cell count, creatinine, estimated glomerular filtration rate (eGFR), serum sodium and potassium, NT-proBNP, glycemia, C reactive protein, albumin, total cholesterol. Creatinine was determined in serum or plasma using a "Creatinine Jaffé of second generation in a Cobas c 501 Roche analyzer" and the eGFR was estimated using the CKD-EPI equation.[9] Age-adjusted N-terminal pro-B-type natriuretic peptide (NT-proBNP) cut-off of 1800 pg/mL, proposed by Januzzi et al, was considered for diagnosis of HF. This age-adjusted threshold does not require further adjustment for renal function and remains useful for the diagnostic evaluation of patients with conditions such as chronic kidney disease and atrial fibrillation, that are particularly frequent in very elderly.[10] In all patients with NT-proBNP values higher than 1800 pg/mL, an echocardiographic confirmation of the presence of features compatible with HF was performed.

Geriatric Comprehensive Assessment and Drug Therapy

To evaluate patients' functional status, the 7-point MDS Activities of Daily Living (ADL) Hierarchy scale was used.[11] The ADL Hierarchy scale groups activities of daily living according to the stage of the disablement process in which they occur. The ADL Hierarchy Scale ranges from 0 (no dependence) to 6 (total dependence). ADL disability was categorized as follows: no impairment (ADL Hierarchy Scale score <2), assistance required (ADL Hierarchy Scale score 2-4), and dependence (ADL Hierarchy Scale score ≥5). The Mini-Cog, which combines 2 simple cognitive tasks (3-item word memory and clock drawing) with an empirical algorithm for scoring, was performed to evaluate cognitive impairment.[12] The Geriatric Index of Comorbidity (GIC) was used to determine the burden of comorbidities[13] and it was categorized as low comorbidity (GIC classes 1 or 2) and high comorbidity (GIC classes 3 or 4). Polypharmacy was defined as the use of 5 or more drugs.

The following cardiovascular drug classes were considered: angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), β-blockers, calcium antagonists, diuretics, mineralocorticoid receptor antagonists, statins, antiplatelets, anticoagulants.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Science version 13 (SPSS, Chicago, IL). A value of $P < .05$ was defined as statistically significant. Continuous variables were checked for normality and were expressed as mean ± standard deviation or as median and interquartile range for the variables markedly skewed. Categorical variables were expressed as absolute number and percentage. The χ^2 test was used to analyze the differences between categorical variables. Unpaired *t* test and Mann-Whitney test were used to compare quantitative variables. Logistic regression analyses were used to create adjusted models.

Results

General characteristics of the studied population are summarized in Table 1. Mean age was 88.1 ± 5.1 years, with female prevalence (57.4%). A high prevalence of comorbidities and polypharmacy was found in our patients. All patients had a history of hypertension, but mean BP values on admission were not elevated. Although an admission diagnosis of HF was considered an exclusion criterion, we found NT-proBNP levels ≥1800 pg/mL, compatible with an underlying HF, in 183 patients (59%). Only 62 patients (20%) had a previous history of HF. Anemia (defined as Hgb levels < 12 g/dL) was also very common (169 patients, 54.7%). ACE-Is/ARBs and diuretics were the most common antihypertensive drugs taken before admission.

In-Hospital Mortality

Forty-seven patients (15.2%) died during hospitalization. Table 2 summarizes the risk factors associated with in-hospital mortality. Deceased patients were older than survivors. Cognitive impairment [odds ratio (OR) 2.06, 95% confidence interval (CI) 1.10-3.87], high comorbidity (OR 1.21, 95% CI 1.15-1.28), and dependence in ADL were associated with poor outcome. Regarding admission diagnosis, patients hospitalized for acute kidney injury showed a 2-fold higher risk of dying (OR 2.11, 95% CI 1.04-4.27). HF, according to NT-proBNP levels ≥1800 pg/mL, showed a positive association with in-hospital mortality (OR 2.58, 95% CI 1.26-5.29). No difference in admission BP values was found between survivors and the deceased. On the contrary, deceased patients showed a higher heart rate compared to survivors (Table 2). Deceased patients showed higher admission white blood cell count, higher NT-proBNP, lower Hgb, lower albumin, higher serum potassium, higher glycemia, and higher C reactive protein levels. History of coronary artery disease and stroke/TIA did not affect in-hospital mortality ($P = .536$ and $P = .280$, respectively). Analyzing CV drug therapy, patients who were taking ACE-Is/ARBs, antiplatelets and