# Statins, ACE/ARBs drug use and risk of pneumonia in hospitalized older patients: a retrospective cohort study

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# Abstract

**Aims:** To evaluate the association between angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARBs) and/or statin use with the risk of pneumonia, and with in-hospital and short-term outpatient mortality in hospitalized older patients with pneumonia.

**Methods:** Patients aged 65 years or older hospitalized in internal medicine and/or geriatric wards throughout Italy and enrolled in the REPOSI (REgistro POliterapuie SIMI - Società Italiana di Medicina Interna) register from 2010 to 2019 were screened to assess diagnosis of pneumonia and classified on whether or not they were prescribed with at least one drug among ACE-I, ARBs and/or statins. Further study outcomes were mortality during hospital stay and at 3 months after hospital discharge.

**Results**: Among 5717 cases included (of whom 18.0% with pneumonia), 2,915 (51.0%) were prescribed at least one drug among ACE-I, ARBs and statins. An inverse association was found between treatment with ACE-I or ARBs and pneumonia (OR= 0.79, 95%CI: 0.65-0.95). A higher effect was found among patients treated with ACE-I or ARBs in combination with statins (OR=0.67, 95% CI: 0.52-0.85).

**Conclusion**: This study confirmed in the real-world setting that these largely used medications may reduce the risk of pneumonia in older people, who chronically take them for cardiovascular conditions.


# Introduction

Pneumonia is one of the most common infectious diseases in clinical practice and a leading cause of morbidity and mortality [1]. In adults, pneumonia disproportionally affects older individuals, comorbidities, weakened immunity, diminished cough reflex, and poor functional status being the major risk factors contributing to the increased incidence of pneumonia in older adults [1].

People older than 65 years old are a rapidly expanding cohort, with rates in the European countries growing from 90.5 millions at the start of 2019 to expected 129.8 million by 2050 [2]. With this expected increase, the burden of pneumonia will become even more significant in the coming years.

The chronic use of cardiovascular drugs such as angiotensin converting enzyme (ACE) inhibitors has been shown to lower the risk of pneumonia [3–5]. ACE inhibitors (ACEi) have known effects on the respiratory system, in particular ACE is an enzyme that metabolizes not only angiotensin but also substance P and bradykinin, which are two inflammatory peptides that sensitise the sensory nerves of the airways thus enhancing the cough reflex [6, 7]. The underlying mechanisms of the protective role of ACEi on the risk of pneumonia may be an enhanced cough reflex, that in turn reduces the risk of aspiration. Even patients treated with angiotensin receptor blockers (ARBs) have been shown to less likely experience respiratory adverse events and these medications may have a protective role, even if results are contrasting and these drugs are not associated with increased coughing [8–10]. Anyway, ARBs might exert anti-inflammatory effects thus contributing to fewer lung injuries [11]. Furthermore, statins have anti-inflammatory properties which may impact the risk of severe pneumonia, as suggested by a report

showing that statins reduce the risk of hospitalization for pneumonia in myocardial infarction patients [12]. Furthermore, in the frame of a large population-based case–control study, exposure to statins was associated with a reduced risk of pneumonia [13]. To our knowledge, a paucity of studies analysed the synergistic effects of the combination of ACEIs/ARBs with statins on infectious diseases, showing contrasting results [14, 15].

With this background, the aims of this study carried out in a large cohort of acutely hospitalized older patients enrolled in REPOSI (REGISTRO POliterapie SIMI – Società Italiana di Medicina Interna - register) were: 1) to evaluate the association between ACE-I, ARBs and/or statin dispensation with the risk of pneumonia, and 2) the association between ACE-I, ARBs and/or statin use with in-hospital and short-term outpatient mortality in patients with pneumonia.

# Methods

# Setting

The REPOSI register is a multicenter, prospective register promoted by the Italian Society of Internal Medicine (SIMI), the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Milan that involves about 100 internal medicine and geriatrics hospital wards throughout Italy.

REPOSI started in 2008, continued in 2010, 2012, 2014, 2016 and yearly thereafter and enrolled 65 years or older patients consecutively admitted to the participating wards during 4 index weeks, one in each season, with the goal to investigate the pattern of multimorbidity and polypharmacy in acutely hospitalized older patients along with clinical and therapeutic correlates. After discharge, follow-up data were obtained via telephone calls at 3 months [16, 17].

The database of the register collects information on socio-demographic characteristics, activities of daily living according to the Barthel Index [18], co-morbidities according to the Cumulative Illness Rating Scale (CIRS) [19], cognitive status according the Short-Blessed Test (SBT) [20], laboratory parameters and drugs prescribed at admission, during hospitalization and at discharge. All medical conditions were coded according to the International Classification of Diseases – Ninth Revision (ICD-9-CM) and all drugs according to the Anatomic Therapeutic Chemical Classification (ATC).

REPOSI was approved by the Ethics Committee of the IRCCS Fondazione Ca’ Granda Ospedale Maggiore Policlinico and then by the local committee of each participating ward. This study was conducted following Good Clinical Practices and the Declaration of Helsinki. All patients enrolled in the study provided signed informed consent.

# Outcome variables

Patients participating in the REPOSI register from 2010 to 2019 were scrutinized to identify those with a diagnosis of pneumonia both at hospital admission or occurring during hospital stay. Pneumonia cases

were identified from the reason for hospitalization, the CIRS completed at hospital admission, intercurrent clinical events and drugs prescribed at hospital admission and/or during hospital stay. Diagnoses of pneumonia were established by ICD-9 codes 480–487.0 and 507. Pneumonia cases were further classified as 1) community acquired pneumonia (CAP) when the onset of symptoms did occur before hospital admission or within 48 hours, and 2) hospital acquired pneumonia (HAP) if diagnosed after 48 hours from hospitalization (when available, the date of access to emergency service was used to calculate the time of symptom onset). Further study outcomes were in-hospital mortality and at 3 months after hospital discharge.

# Exposure variables

Patients were further classified on whether or not they were prescribed with at least one drug among angiotensin-converting enzyme inhibitors (ACE-I) (ATC: C09A*/C09B*), angiotensin II receptor blockers (ARBs) (ATC:C09C*/C09D*) and/or statins (ATC:C10AA*). Patients with treatment duration less than one month were excluded from the analyses.

# Statistical analysis

Characteristics of patients were summarized as frequencies and percentages (%), means and standard deviations (st.dev) or medians and interquartile ranges (IQR) as appropriate.

The association between pneumonia and type of treatment (classified: none, statin only, ACE-I and/or ARBs only, ACE-I and/or ARBs plus statin) was assessed by three hierarchical logistic regression models: model 1 adjusted for age, sex, year of enrollment and smoking habit; model 2, adjusted for the variables included in model 1 plus Barthel and SBT score; model 3, adjusted for the variables included in model 2 plus CIRS severity index and total number of drugs. Multinomial logistic regression models were used to evaluate the association between type of treatment and type of pneumonia. Effect of type of treatment on in-hospital and 3-month mortality was assessed by means of the three logistic regression models described above.

Statistical analyses were conducted using SAS/STAT software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

# Study population

Figure 1 shows the flow-chart of patients included in the study. From 2010 to 2019, 7085 patients were enrolled in the register. Among them, 173 were excluded because of incomplete data on vital status at hospital discharge, leaving 6912 cases. Of them, 1144 were further excluded because the duration of treatment was not available and 51 because prescribed for less than one month. Ultimately, 5717 cases with or without pneumonia were included in the analyses. Among them 1031 (18.0%) were diagnosed with pneumonia, 748 (72.5%) with CAP and 283 (27.5%) with HAP.

Table 1 reports main sociodemographic characteristics and comorbidities of the whole 5717 analyzed cases and according to pneumonia diagnosis. Compared to those without pneumonia, cases with pneumonia were more frequently male (52.3% vs 49.1%), slightly older - with a mean (st.dev) age of 81.2 (7.7) vs 79.1 (7.6) -, and with a higher rate of multimorbidity.

Table 1
Characteristics of 5717 patients admitted to hospital from 2010 to 2019

| Characteristics | Hospitalized with pneumonia (N = 1031) | Hospitalized without pneumonia (N = 4686) | Missing values | Total hospitalized patients N = 5717 |
|---|---|---|---|---|
| **Year of enrollment, n (%)** | | | - | |
| 2010 | 84 (8.2) | 456 (9.7) | | 540 (9.5) |
| 2012 | 187 (18.1) | 1049 (22.4) | | 1236 (21.6) |
| 2014 | 150 (14.5) | 816 (17.4) | | 966 (16.9) |
| 2016 | 120 (11.6) | 567 (12.1) | | 687 (12.0) |
| 2017 | 175 (17.0) | 667 (14.3) | | 842 (14.7) |
| 2018 | 154 (14.9) | 531 (11.3) | | 685 (12.0) |
| 2019 | 161 (15.7) | 600 (12.8) | | 761 (13.3) |
| **Age, years, mean (SD)** | 81.2 (7.7) | 79.1 (7.6) | - | 79.5 (7.7) |
| 65–74 | 221 (21.4) | 1434 (30.6) | | 1655 (28.9) |
| 75–84 | 418 (40.6) | 2009 (42.9) | | 2427 (42.5) |
| 85+ | 392 (38.0) | 1243 (26.5) | | 1635 (28.6) |
| **Sex** | | | 2 | |
| Female | 492 (47.7) | 2419 (51.6) | | 2911 (50.9) |
| Male | 539 (52.3) | 2265 (48.4) | | 2804 (49.1) |
| **BMI** | | | 873 | |
| Underweight (< 18.5) | 59 (6.9) | 182 (4.6) | | 241 (5.0) |
| Normal weight (18.5–24.9) | 390 (45.7) | 1709 (42.8) | | 2099 (43.3) |
| Overweight (25-29.9) | 278 (32.6) | 1416 (35.5) | | 1694 (35.0) |
| Obesity (≥ 30) | 127 (14.8) | 683 (17.1) | | 810 (16.7) |
| **Smoke** | | | 200 | |

BMI: Body Mass Index; CIRS: Cumulative Index Rating Scale; SD; standard deviation, IQR: Inter-Quartile Range, COPD: Chronic Obstructive Pneumopathy Disease

ICD-9-CM code for assessing main diagnosis: Hypertension: 401 (CIRS item 2); Ischemic heart disease: 410–414; CKD: 585; Atrial fibrillation: 427; Heart failure: 428, 402.11; Stroke or TIA: 430–438; Peripheral arterial disease: 440–441; Dyslipidemia: 272; Chronic Obstructive Pulmonary Disease: 491; Dementia (ICD-9: 290 / 294 / 310 / 331)

| Characteristics | Hospitalized with pneumonia (N = 1031) | Hospitalized without pneumonia (N = 4686) | Missing values | Total hospitalized patients N = 5717 |
|---|---|---|---|---|
| Never | 515 (51.8) | 2533 (56.0) | | 3048 (55.3) |
| Ex-smoker | 404 (40.6) | 1557 (34.4) | | 1961 (35.5) |
| Smoker | 76 (7.6) | 432 (9.6) | | 508 (9.2) |
| **Alcohol** | | | 231 | |
| Never | 571 (58.5) | 2592 (57.5) | | 3163 (57.7) |
| Ex drinker | 68 (7.0) | 390 (8.7) | | 458 (8.4) |
| Drinker | 133 (13.6) | 631 (14.0) | | 764 (13.9) |
| Social drinker | 204 (20.9) | 897 (19.8) | | 1101 (20.0) |
| **Barthel Index** | | | 683 | |
| No or negligible dependence (91–100) | 375 (40.8) | 2155 (52.4) | | 2530 (50.3) |
| Mild dependence (75–90) | 169 (18.4) | 813 (19.8) | | 982 (19.5) |
| Moderate dependence (50–74) | 136 (14.8) | 560 (13.6) | | 696 (13.8) |
| Severe dependence (25–49) | 96 (10.5) | 282 (6.8) | | 378 (7.5) |
| Total dependence (0–24) | 143 (15.5) | 305 (7.4) | | 448 (8.9) |
| **SBT** | | | 595 | |
| Normal (0–4) | 322 (35.5) | 1709 (40.6) | | 2031 (39.7) |
| Possible cognitive impairment (5–9) | 127 (14.0) | 735 (17.4) | | 862 (16.8) |
| Moderate-severe cognitive impairment (10+) | 459 (50.5) | 1770 (42.0) | | 2229 (43.5) |
| **CIRS - Comorbidity index, mean (SD)** | 3.1 (2.0) | 2.9 (1.9) | 9 | 3.0 (1.9) |

BMI: Body Mass Index; CIRS: Cumulative Index Rating Scale; SD; standard deviation, IQR: Inter-Quartile Range, COPD: Chronic Obstructive Pneumopathy Disease

ICD-9-CM code for assessing main diagnosis: Hypertension: 401 (CIRS item 2); Ischemic heart disease: 410–414; CKD: 585; Atrial fibrillation: 427; Heart failure: 428, 402.11; Stroke or TIA: 430–438; Peripheral arterial disease: 440–441; Dyslipidemia: 272; Chronic Obstructive Pulmonary Disease: 491; Dementia (ICD-9: 290 / 294 / 310 / 331)

| Characteristics | Hospitalized with pneumonia (N = 1031) | Hospitalized without pneumonia (N = 4686) | Missing values | Total hospitalized patients N = 5717 |
|---|---|---|---|---|
| **CIRS - Severity index, mean (SD)** | 1.7 (0.3) | 1.6 (0.3) | 9 | 1.6 (0.3) |
| **Previous hospitalization, n (%)** | 491 (47.6) | 1964 (41.9) | - | 2455 (42.9) |
| **Number of drugs at admission, median (IQR)** | 5 (3–7) | 4 (3–6) | | 4 (3–6) |
| 0–1 | 106 (10.3) | 608 (13.0) | - | 714 (12.5) |
| 2–4 | 374 (36.3) | 1830 (39.1) | | 2204 (38.6) |
| 5+ | 551 (53.4) | 2248 (47.9) | | 2799 (48.9) |
| **Laboratory values and other clinical parameters, mean (SD)** | | | | |
| White blood cells | 11.1 (12.9) | 9.1 (7.1) | 58 | 9.5 (7.5) |
| Platelets | 239.5 (112.5) | 228.9 (103.7) | 66 | 230.8 (105.4) |
| Hemoglobin | 11.7 (2.2) | 11.7 (2.4) | 47 | 11.7 (2.3) |
| Glucose | 131.0 (66.3) | 124.2 (57.2) | 249 | 125.4 (58.9) |
| Creatinine | 1.3 (0.9) | 1.3 (0.9) | 82 | 1.3 (0.9) |
| **Co-morbidities** | | | | |
| Diabetes | 276 (26.8) | 1357 (29.0) | - | 1633 (28.6) |
| Hypertension | 640 (62.1) | 3005 (64.1) | | 3645 (63.8) |
| Ischemic heart disease | 247 (24.0) | 953 (20.3) | | 1361 (23.8) |
| CKD | 246 (23.9) | 953 (20.3) | | 1199 (21.0) |
| Atrial fibrillation | 354 (34.3) | 1284 (27.4) | | 1638 (28.6) |
| Heart Failure | 235 (22.8) | 930 (19.9) | | 1165 (20.4) |
| Stroke/TIA | 241 (23.4) | 995 (21.2) | | 1236 (21.6) |

BMI: Body Mass Index; CIRS: Cumulative Index Rating Scale; SD; standard deviation, IQR: Inter-Quartile Range, COPD: Chronic Obstructive Pneumopathy Disease

ICD-9-CM code for assessing main diagnosis: Hypertension: 401 (CIRS item 2); Ischemic heart disease: 410–414; CKD: 585; Atrial fibrillation: 427; Heart failure: 428, 402.11; Stroke or TIA: 430–438; Peripheral arterial disease: 440–441; Dyslipidemia: 272; Chronic Obstructive Pulmonary Disease: 491; Dementia (ICD-9: 290 / 294 / 310 / 331)

| Characteristics | Hospitalized with pneumonia (N = 1031) | Hospitalized without pneumonia (N = 4686) | Missing values | Total hospitalized patients N = 5717 |
|---|---|---|---|---|
| Peripheral arterial disease | 147 (14.3) | 601 (12.8) | | 748 (13.1) |
| Dyslipidemia | 77 (7.5) | 430 (9.2) | | 507 (8.9) |
| COPD | 288 (27.9) | 895 (19.1) | | 1183 (20.7) |
| Dementia | 189 (18.3) | 491 (10.5) | | 680 (11.9) |
| BMI: Body Mass Index; CIRS: Cumulative Index Rating Scale; SD; standard deviation, IQR: Inter-Quartile Range, COPD: Chronic Obstructive Pneumopathy Disease | | | | |
| ICD-9-CM code for assessing main diagnosis: Hypertension: 401 (CIRS item 2); Ischemic heart disease: 410–414; CKD: 585; Atrial fibrillation: 427; Heart failure: 428, 402.11; Stroke or TIA: 430–438; Peripheral arterial disease: 440–441; Dyslipidemia: 272; Chronic Obstructive Pulmonary Disease: 491; Dementia (ICD-9: 290 / 294 / 310 / 331) | | | | |

# Prevalence of ACE-I, ARBs and/or statin users

Table 2 reports the prevalence of cases prescribed or not with ACE-I, ARBs and statins according to pneumonia diagnosis. Among the 5717 cases ultimately included in the study, 2,915 (51.0%) were prescribed at least one drug among ACE-I, ARBs and statins. Among 1031 patients with a diagnosis of pneumonia, 479 (46.5%) were prescribed at least one of these drugs. In particular, 118 (24.6%) were prescribed ACE-I and/or ARB in combination with a statin. Among the 4686 patients without pneumonia, 2436 (52.0%) were prescribed at least one drug and 691 (28.4%) the combination an antihypertensive medication and statin. Antihypertensive drugs were considered as a whole category because no significant association was found when each of them was considered separately.

Table 2
Prevalence of angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARBs) and statin users

| Variable | Hospitalized with pneumonia (N = 1031) | Hospitalized without pneumonia (N = 4686) | Total hospitalized patients (N = 5717) |
|---|---|---|---|
| No ACE-I, ARBs or statin | 552 (53.5) | 2250 (48.0) | 2802 (49.0) |
| At least one among ACE-I, ARBs or statin | 479 (46.5) | 2436 (52.0) | 2915 (51.0) |
| Statin only | 91 (19.0) | 375 (15.4) | 466 (15.9) |
| ACE-I or ARBs only | 270 (56.4) | 1370 (56.2) | 1640 (56.3) |
| ACE-I or ARBs and statin | 118 (24.6) | 691 (28.4) | 809 (27.8) |
| ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker | | | |

# Outcomes

# Risk of pneumonia

Table 3 reports the results of multivariate logistic regression models for the association between prescription of ACE-I, ARBs and/or statin and risk of pneumonia. Treatment with statins only was not associated with pneumonia in all the regression logistic models, and an inverse association was found between treatment with ACE-I or ARBs and pneumonia (OR = 0.79, 95%CI: 0.65–0.95). As stronger inverse association was found among patients treated with ACE-I or ARBs in combination with statins according to all the three logistic regression models (OR = 0.67, 95% CI: 0.52–0.85).

Table 3
Risk factors for pneumonia: results from adjusted logistic regression models

| | OR (95% CI) | | |
|---|---|---|---|
| **Variables** | **Model 1** | **Model 2** | **Model 3** |
| None | 1.00 | 1.00 | 1.00 |
| Statin only | 0.88 (0.68–1.14) | 0.94 (0.71–1.23) | 0.89 (0.68–1.17) |
| ACE-I/ARBs only | 0.77 (0.66–0.91) | 0.79 (0.66–0.95) | 0.79 (0.65–0.95) |
| ACE-I/ARBs and statin | 0.66 (0.53–0.83) | 0.70 (0.55–0.90) | 0.67 (0.52–0.85) |
| ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker, SBT:short blessed test | | | |
| Model 1: adjusted for age, sex, year of enrollment, smoke (N Observations 5,515; Pneumonia cases N = 995; No Pneumonia cases N = 4520) | | | |
| Model 2: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT (N Observations 4399; Pneumonia cases N = 794; No Pneumonia cases N = 3605) | | | |
| Model 3: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT, CIRS-IS, number of drugs (N Observations 4395; Pneumonia cases N = 794; No Pneumonia cases N = 3601) | | | |

Table 4
A. Regression logistic models for in-hospital mortality in patients with pneumonia

| **Variables** | **OR (95% CI)[1]** | **OR (95% CI)[2]** | **OR (95% CI)[3]** |
|---|---|---|---|
| None | 1.00 | 1.00 | 1.00 |
| Statin only | 0.71 (0.29–1.74) | 1.29 (0.45–3.70) | 1.16 (0.40–3.36) |
| ACE-I/ARBs only | 0.37 (0.18–0.75) | 0.65 (0.27–1.60) | 0.64 (0.26–1.56) |
| ACE-I/ARBs and statin | 0.68 (0.30–1.57) | 1.34 (0.47–3.86) | 1.13 (0.38–3.35) |
| ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; SBT: Short Blessed Test | | | |
| Model 1: adjusted for age, sex, year of enrollment, smoke (N Observations: N = 995; Death N = 75) | | | |
| Model 2: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT (N Observations: N = 794; Death N = 37) | | | |
| Model 3: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT, CIRS-IS, number of drugs (N Observations: N = 794; Death N = 37) | | | |

Table 4

B. Regression logistic models for short-term mortality (3 months) in patients with pneumonia

| Variables | OR (95% CI)[1] | OR (95% CI)[2] | OR (95% CI)[3] |
|---|---|---|---|
| None | 1.00 | 1.00 | 1.00 |
| Statin only | 0.74 (0.33–1.63) | 0.78 (0.33–1.85) | 0.80 (0.33–1.92) |
| ACE-I/ARBs only | 0.71 (0.41–1.23) | 0.75 (0.40–1.43) | 0.76 (0.40–1.44) |
| ACE-I/ARBs and statin | 0.41 (0.16–1.01) | 0.48 (0.17–1.32) | 0.49 (0.17–1.39) |
| ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; SBT: Short Blessed Test | | | |
| Model 1: adjusted for age, sex, year of enrollment, smoke (N Observations: N = 598; Death N = 96) | | | |
| Model 2: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT (N Observations: N = 501; Death N = 69) | | | |
| Model 3: adjusted for age, sex, year of enrollment, smoke, Barthel, SBT, CIRS-IS, number of drugs (N Observations: N = 501; Death N = 69) | | | |

When investigating the association with the type of pneumonia, similar results were obtained. An inverse association of ACE-I or ARBs (OR = 0.78, 95%CI: 0.63–0.96) and ACE-I or ARBs in combination with statins (OR = 0.64, 95%CI: 0.48–0.85) was seen in patients with CAP compared to those without pneumonia, whereas there was no significant association for patients with HAP compared to those without (Table S1).

# In-hospital mortality

Among the 5717 patients included in the analyses, 4981 (87.1%) were discharged from the hospital, 491 (8.6%) were transferred to another hospital ward and 245 (4.3%) died during hospital stay. Among 1031 cases with pneumonia 79 (7.7%) died. Those prescribed with ACE-I or ARBs showed a lower risk of in-hospital mortality than those not treated in model 1 (OR = 0.37, 95%CI: 0.18–0.75), but this effect weakened and was no longer statistically significant after adjustment for health-related risk factors in model 3 (Table 4A).

# Post-discharge mortality

Among the 4981 cases discharged from hospital information on vital status at 3 months was available for 3408 of them. In particular, follow-up was available for 562 of the 855 patients with pneumonia (59.0%) who were discharged. Among them 79 died during the next 3 months. Treatment with ACE-I or ARBs and statins in patients with pneumonia was negatively associated with short-term mortality (ORs between 0.41 in model 1 to 0.49 in the fully adjusted model 3), but these results were not statistically significant (Table 4B).

# Discussion

This retrospective cohort study based upon data stemming over a period of 9 years (from 2010 to 2019) from a nationwide register found that, among 5717 older people acutely admitted to hospital medical wards, approximately half had a diagnosis of pneumonia. When the cases with pneumonia were compared with those without this diagnosis, it was shown that being prescribed with such antihypertensive drugs as ACE-I or ARB had a protective role on the odds of developing pneumonia. This association with a diagnosis of pneumonia was observed when the cases were taking either antihypertensive drug but much more emphasized in patients also co-prescribed with statins, albeit statins alone were not associated with the diagnosis of pneumonia. Most importantly, the cases with pneumonia prescribed with ACE-I or ARB had a lower risk of death in hospital or also during a short-term follow-up of 3 months after hospital discharge.

The views that antihypertensive drugs acting upon the angiotensin signaling pathway may decrease the risk of pneumonia and its outcome has been a cogent topic following several reports in the last two decades [3–5, 10], but data on older acutely hospitalized patients are scanty. The mechanisms of the decreased risk of pneumonia are not clear cut, at least for ARB that, at variance with ACE-I, do not increase coughing, because they lack the airway sensor nerve stimulation evoked by bradykinin. A role in improving endothelial and mitochondrial dysfunction and in reducing reactive oxygen species is also demonstrated for ACEi, ARBs and statins [21].

Other cardiovascular drugs unrelated to angiotensin such as statins have been associated to a reduced risk of pneumonia requiring hospital admission. The potential mechanism associated with this effect may be related to the well-established anti-inflammatory properties of statins, but the available clinical data are few and inconsistent [12–13]. Our study did not establish a protective effect of statins alone on the risk of pneumonia, but it pointed out that these drugs widely used for primary and secondary cardiovascular prevention, act synergistically with ACEi and/or ARBs in reducing the risk of pneumonia.

With this background and gaps of knowledge, the present study was designed to tackle these controversies and related unknowns in a large population of older people who were admitted to hospital wards with a high prevalence of both the main types of pneumonia. Statin intake alone had no influence on the odds of being diagnosed with pneumonia, but when they were taken in association with ACE-I or ARB the effects of both these drugs acting mechanistically on angiotensin was magnified. The design of our study makes impossible to understand the mechanism of such synergism but helps to confirm in a

real-word situation that these largely used medications may reduce the risk of pneumonia in older people when their chronic intake is dictated and justified by cardiovascular conditions. These drugs have been also shown to regulate the immune response of the host and the endothelial dysfunction contributing to decrease systemic inflammation that could lead to organ damage.

This study has limitations. The retrospective study design precludes any causal inference. However, it has several strengths, the first one being the very large sample size and the real-world setting. Furthermore, REPOSI was initially designed to evaluate the pattern of drug use and drug-drug interactions in older hospitalized people, so that the present study is consistent with the goals of the register.

In conclusion, this study provides evidence to support existing literature that drugs widely used in older people for cardiovascular purposes, such as antihypertensive and statins, may help to decrease the risk of such a condition as pneumonia typically associated with aging.

## Declarations

# Conflict of interests

The authors declare that they have no known competing financial interests.

# Author contributions

Conceptualization, CF, IA, RR. Methodology, IA. Formal analysis, SM. Writing — original draft preparation, CF, IA, RR, PMM. Writing - review and editing, CF, IA, RR, PMM, SM, AN, FP. All authors have read and agreed to the published version of the manuscript.

# Data Availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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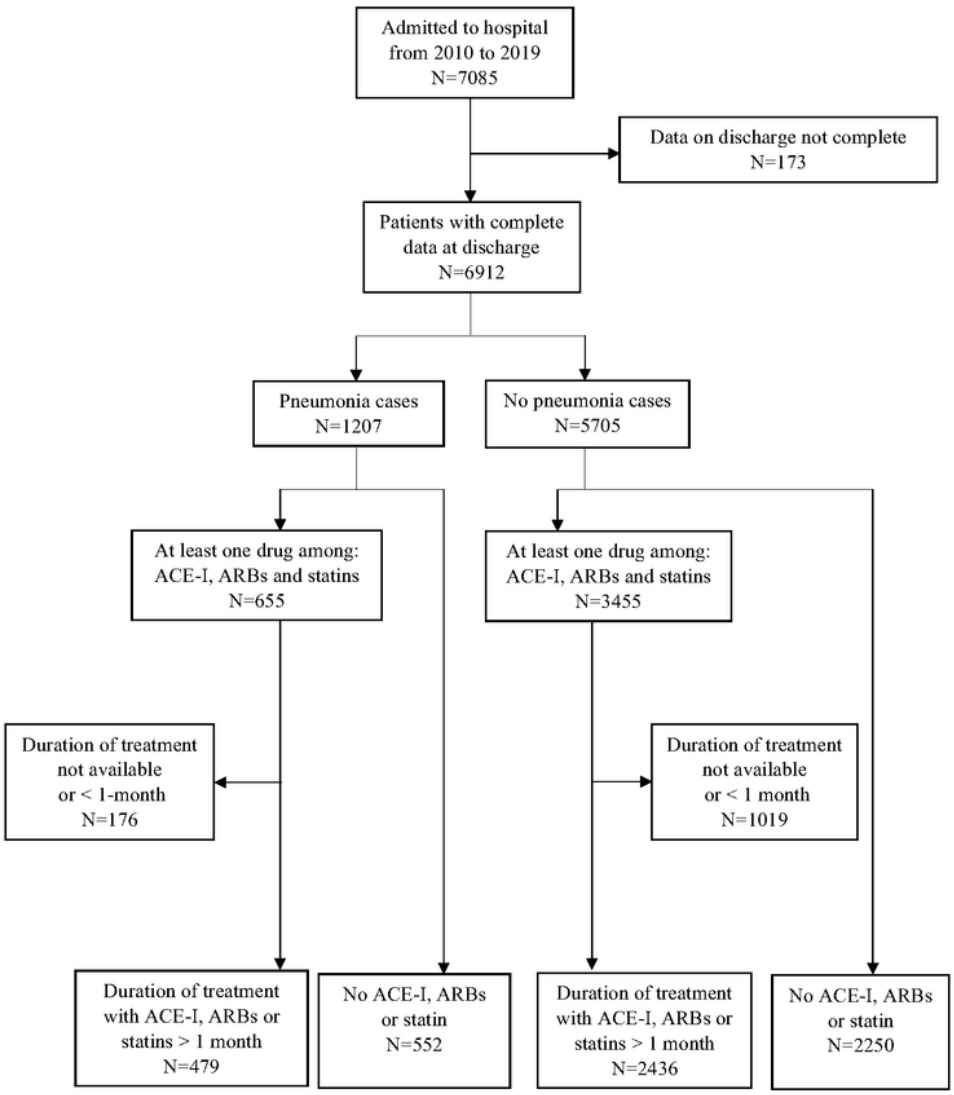
# Figures

Figure 1: Flow-chart of patients' inclusion




Abbreviations: ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker
Details on patients excluded due to Duration of treatment:
Pneumonia: Tine on treatment N/A N = 161, < 1 week N =2, < 1 month N =13.
No Pneumonia: time on treatment N/A N=983, < 1 week N = 7, 1 month N = 29

**Figure 1**

Flow-chart of patients' inclusion

# Supplementary Files

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