ORIGINAL RESEARCH

Lower Mortality Rate in Elderly Patients With Community-Onset Pneumonia on Treatment With Aspirin

Marco Falcone, MD; Alessandro Russo, MD; Roberto Cangemi, MD; Alessio Farcomeni, PhD; Camilla Calvieri, MD; Francesco Barillà, MD; Maria Gabriella Scarpellini, MD; Giuliano Bertazzoni, MD; Paolo Palange, MD; Gloria Taliani, MD; Mario Venditti, MD; Francesco Violi, MD

***Background*—**Pneumonia is complicated by high rate of mortality and cardiovascular events (CVEs). The potential benefit of aspirin, which lowers platelet aggregation by inhibition of thromboxane A2 production, is still unclear. The aim of the study was to assess the impact of aspirin on mortality in patients with pneumonia.

***Methods and Results*—**Consecutive patients admitted to the University-Hospital Policlinico Umberto I (Rome, Italy) with community-onset pneumonia were recruited and prospectively followed up until discharge or death. The primary end point was the occurrence of death up to 30 days after admission; the secondary end point was the intrahospital incidence of nonfatal myocardial infarction and ischemic stroke. One thousand and five patients (age, 74.7±15.1 years) were included in the study: 390 were receiving aspirin (100 mg/day) at the time of hospitalization, whereas 615 patients were aspirin free. During the follow-up, 16.2% of patients died; among these, 19 (4.9%) were aspirin users and 144 (23.4%; $P<0.001$) were aspirin nonusers. Overall, nonfatal CVEs occurred in 7% of patients, 8.3% in nonaspirin users, and 4.9% in aspirin users (odds ratio, 1.77; 95% confidence interval, 1.03 to 3.04; $P=0.040$). The Cox regression analysis showed that pneumonia severity index (PSI), severe sepsis, pleural effusion, and PaO_2/FiO_2 ratio <300 negatively influenced survival, whereas aspirin therapy was associated with improved survival. Compared to patients receiving aspirin, the propensity score adjusted analysis confirmed that patients not taking aspirin had a hazard ratio of 2.07 (1.08 to 3.98; $P=0.029$) for total mortality.

***Conclusions*—**This study shows that chronic aspirin use is associated with lower mortality rate within 30 days after hospital admission in a large cohort of patients with pneumonia. **(*J Am Heart Assoc*. 2015;4:e001595 doi: 10.1161/JAHA.114.001595)**

Key Words: aspirin • pneumonia • septic shock • severe sepsis

Community-onset pneumonia, including the epidemiological definitions of community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP), is the most common infection leading to hospitalization in intensive care units and the most common cause of death associated with infectious diseases.[1,2] Among the causes of poor survival, acute cardiovascular (CV) events (CVEs), which complicate the clinical course of pneumonia, may play a relevant role; thus, respiratory tract infections are associated with an increased risk for vascular disease, such as myocardial infarction (MI) and stroke, which usually occur in the early phase of pneumonia.[3–8]

Aspirin is an anti-inflammatory drug, which significantly lowered the rate of MI and stroke in primary and secondary intervention trials by irreversible acetylation of cyclooxygenase 1 (COX1) and ensuing impaired formation of thromboxane A2.[9,10] Previous studies found increased platelet activation in patients affected by viral upper respiratory tract infection or pneumonia,[11,12] suggesting that lung infection could be a trigger for platelet activation, but the impact of such changes on survival in patients with pneumonia is still unclear. Thus, data regarding the impact of aspirin on survival after pneumonia are few and equivocal.[13,14] Furthermore, no data on the association between aspirin use and CVEs have been reported thus far in patients with pneumonia. In this prospective, observational study, we investigated whether aspirin use affects early (within 30 days) mortality and CVEs in patients with community-onset pneumonia during follow-up.

From the Departments of Public Health and Infectious Diseases (M.F., A.R., A.F., P.P., M.V.), Internal Medicine and Medical Specialties (R.C., C.C., F.B., F.V.), Emergency Medicine (M.G.S., G.B.), and Clinical Medicine (G.T.), Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy.

Correspondence to: Francesco Violi, MD, Department of Internal Medicine and Medical Specialties, Policlinico Umberto I, "Sapienza" University of Rome, Viale dell'Università 37, 00161 Rome, Italy.
E-mail: francesco.violi@uniroma1.it
Marco Falcone, MD, Department of Public Health and Infectious Diseases, Policlinico Umberto I, "Sapienza" University of Rome, Viale dell'Università 37, 00161 Rome, Italy. E-mail: marco.falcone@uniroma1.it

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Patients and Methods

Study Design and Patient Selection

The study was conducted at the University-Hospital Policlinico Umberto I (Rome, Italy). All patients admitted to medical wards with diagnosis of community-onset pneumonia through the emergency department (ED) from January 2011 to December 2013 were consecutively recruited and prospectively followed up. Patients who fulfilled the following criteria were enrolled in the study after giving written informed consent: (1) age 18 years or over; (2) clinical presentation of an acute illness with 1 or more of the following signs or symptoms suggesting pneumonia: presence of rales, rhonchi, bronchial breath sounds, fever (>38.0°C), tachycardia, chills, dyspnea, coughing (with or without sputum), or chest pain; and (3) presence of new consolidation(s) on chest X-ray. Pneumonia was considered as CAP if it was diagnosed upon hospitalization and the patient had not been discharged from an acute care facility within 14 days preceding the clinical presentation. We classified patients as having HCAP if they had attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the past 30 days, had been admitted to an acute-care hospital for at least 2 days or had surgery in the past 90 days, or resided in a nursing home or long-term care facility.[15] We classified patients as having hospital-acquired pneumonia (HAP) if they received their diagnosis after being hospitalized for more than 72 hours or within 10 days of leaving the hospital.

Patients were excluded from the study if 1 of the following criteria was applied: radiographic evidence of a preexisting infiltrates, criteria for HAP, pregnancy or breastfeeding, documented severe allergy to antibiotics, or refusal to sign informed consent. All patients were followed up during hospitalization and for 30 days after admission or until death. The present study was conducted according to the principles stated in the Declaration of Helsinki. The institutional review board approved this prospective, observational study.

Baseline Assessment and Follow-up

Data on demographic characteristics, comorbidities, and antibiotic and concomitant therapy were collected; severity of illness at presentation was quantified by the pneumonia severity index (PSI) and CURB-65 score.[16]

Type-2 diabetes mellitus, hypertension, history of coronary heart disease, dyslipidemia, peripheral arterial disease, and chronic obstructive pulmonary disease (COPD) were defined as previously described.[17,18] Baseline treatments were defined according to the patients' pharmacological history. Severe sepsis was defined as sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion (manifesting as hypotension, elevated lactate, or decreased urine output) and septic shock as severe sepsis plus persistently low blood pressure following the administration of intravenous fluids.[19]

Patient status was assessed by the Sequential Organ Failure Assessment (SOFA) score.[20] Antibiotic therapy was initiated in the ED in accord with the hospital guidelines and/or consultation of an infectious diseases specialist. Patients were followed up for 30 days from hospital admission or until death.

Study End Points

The primary study end point was the occurrence of death up to 30 days after hospital admission.

Secondary end points were the in-hospital occurrence of a nonfatal ischemic CVE (including MI and ischemic stroke).

MI criteria were those of the "Third Universal Definition of Myocardial Infarction": the detection of a rise of cardiac troponin with at least 1 value above the 99th percentile upper reference limit was associated with at least 1 of the following: (1) chest pain; (2) detection of new or presumably new significant ST-segment–T wave changes or new left bundle branch block (LBBB); (3) development of pathological Q waves in the electrocardiogram (ECG); (4) de novo imaging evidence of viable myocardium loss or regional wall motion abnormality; (5) identification of an intracoronary thrombus by angiography or autopsy; and (6) cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB. ST elevation MI and non-ST elevation MI were defined as previously reported.[21]

The occurrence of stroke was determined based on clinical manifestations and confirmed by computed tomography scan. Blind adjudication of the events was performed by 2 independent cardiologists (C.C. and F.B.), who did not participate in the patients' recruitment and follow-up.

Aspirin Treatment

The population was divided in 2 groups: patients taking aspirin before and during hospitalization (aspirin group) and patients not taking aspirin before and during hospitalization (nonaspirin group). Compliance with aspirin and the other drugs was daily monitored.

Statistical Analysis

The results obtained were analyzed using commercially available statistical software packages (SPSS, version 20.0; SPSS, Inc., Chicago, IL and R, version 3.0.2; R development core team, Vienna, Austria).

The sample size was planned using a log-rank test for comparing mortality rate in patients receiving or not the

aspirin. With a minimum follow-up time of 30 days, assuming a 1.5 to 1 ratio for number of controls versus treated, an incidence rate of mortality in the control group of 18%,[22] and a reduction of mortality by aspirin of at least 5.5% (corresponding to a hazard ratio [HR] of 0.82 and a relative reduction of approximately 30%), we planned a sample size of 975 patients. This guarantees a power of at least 80% at a fixed a type I error rate of 5%.

To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables and the 2-tailed *t* test or Mann-Whitney test for continuous variables, when appropriate. Survival curves for time-to-event variables were constructed with the use of Kaplan–Meier estimates based on all available data and were compared with the use of the log-rank test. In a multivariate analysis of survival, the Cox regression model was used to determine the effects of different variables on overall survival. The bivariate effect of aspirin treatment on the secondary end point (in hospital nonfatal CVEs) was assessed by means of a logistic regression model. Wald confidence intervals (CIs) and tests for odds ratios (ORs) were computed based on the estimated standard errors. The proportionality of hazards assumption for the Cox model has been checked using plots of Schoenfeld residuals.

Finally, in order to correct for possible bias arising from the observational nature of the experiment, we corrected all relevant effect estimates and *P* values with the propensity score estimated using all prehospitalization variables (age, gender, previous therapies, comorbidities, signs, and symptoms at hospitalization). In detail, we built the propensity scores by considering all variables for possible prediction of the treatment indicator and performing forward step-wise selection for parsimony. After, the estimated propensity score has been used as a predictor in multivariate models assessing the relationship between treatment and outcomes. The balancing properties of the propensity score have been assessed by evaluating the propensity score adjusted summaries within each treatment group. Propensity score adjusted estimates can be expected to be close to the estimates that would be obtained had the treatment been randomized.[23] Statistical significance was established at $\leq$0.05. All reported *P* values are 2-tailed.

Results

During the study period, a total of 1452 patients were assessed for eligibility, and 1005 were finally included in the study. A consort diagram describing the study flow is presented in Figure 1.

Among the patients included in the study, 390 were analyzed as the "aspirin group" (100 mg/day) and 615 as the "nonaspirin group." Comparison of demographics and clinical features of patients included in the aspirin and nonaspirin groups are summarized in Table 1. Comparison between aspirin and nonaspirin groups after propensity score adjustment, showing the balance between the 2 study groups with respect to baseline characteristics, is reported in Table 2.

No differences in demographic characteristics were recorded between the 2 study groups, but patients included

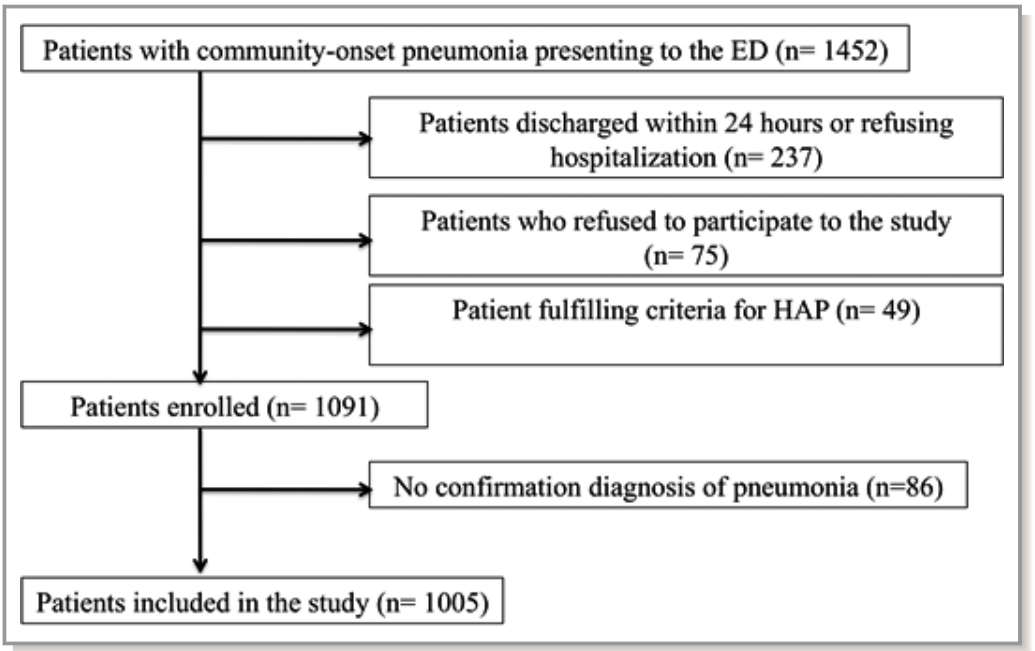

Figure 1. Study flow diagram. ED indicates emergency department; HAP, hospital-acquired pneumonia.

Table 1. Clinical Characteristics of Aspirin- Versus Non-Aspirin-Treated Patients

Variables	Aspirin Group n=390 Patients	Nonaspirin Group n=615 Patients	*P* Value
Age, y	73.6±17.4	75.3±12.8	0.08
Male sex	215 (55.1%)	375 (61.0%)	0.067
PSI II to III classes	130 (33.3%)	58 (9.4%)	<0.001
PSI IV class	206 (52.8%)	299 (48.6%)	0.194
PSI V class	54 (13.8%)	258 (42.0%)	<0.001
CURB-65 I class	195 (50%)	219 (35.6%)	<0.001
CURB-65 II class	153 (39.2%)	211 (34.3%)	0.1
CURB-65 III class	42 (10.7%)	185 (30.1%)	<0.001
Chronic heart disease	175 (44.9%)	134 (21.7%)	<0.01
Chronic hepatitis	31 (7.9%)	61 (9.9%)	0.8
Diabetes	41 (10.5%)	151 (24.5%)	<0.001
Renal failure	62 (16%)	131 (21.3%)	0.1
COPD	128 (32.8%)	198 (32.2%)	0.8
CAP	271 (69.4%)	356 (57.8%)	0.02
HCAP	119 (30.5%)	259 (42.2%)	0.03
Neoplasm	50 (12.9%)	179 (29.1%)	<0.001
Pleural effusion	86 (22.1%)	338 (54.9%)	<0.001
Immunosuppressive therapy	52 (13.3%)	84 (13.6%)	0.5
Fever >38°C	224 (57.4%)	330 (53.6%)	0.5
PaO_2/FiO_2 ratio <300	26 (6.6%)	156 (25.3%)	<0.001
NIV	2 (0.5%)	29 (4.7%)	<0.001
SOFA score >2	142 (36.4%)	503 (81.8%)	<0.001
Severe sepsis or septic shock	18 (4.6%)	71 (11.5%)	<0.001
Nonfatal cardiovascular events	19 (4.9%)	51 (8.3%)	0.03

CAP indicates community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NIV, noninvasive ventilation; PSI, pneumonia severity index; SOFA, Sequential Organ Failure Assessment.

in the aspirin group showed a higher frequency of chronic heart failure and belonged to the lower-severity classes of PSI and CURB-65 scores. Compared to the nonaspirin group, patients on aspirin showed a lower incidence of pleural effusion and a minor degree of respiratory impairment; they also had a lower median SOFA score (1.8 vs. 2.5; P=0.02). Moreover, patients on aspirin had a lower incidence of severe sepsis or septic shock (4.6% vs. 11.5%; P<0.001).

During the follow-up, 163 patients (16.2%) died; demographics and clinical features of survivors and nonsurvivors are reported in Table 3. Patients who died were older, had a higher incidence of comorbidities, and a greater severity of pneumonia according to PSI and CURB-65 scoring systems. Furthermore, nonsurvivors had a higher median SOFA score (3.9 vs. 2.1; P<0.001) and higher incidence of severe sepsis or septic shock (23.9% vs. 5.9%; P<0.001). Finally, patients who died were less frequently on aspirin therapy (11.7% vs. 44.1%; P<0.001).

Compared to the nonaspirin group, patients on aspirin showed a lower incidence of in-hospital 30-day mortality (23.4% vs. 4.9%; P<0.001). Intrahospital nonfatal CVEs occurred in 70 patients (7.0%); 8.3% of patients in the nonaspirin group and in 4.9% of patients in the aspirin group, showing an increased risk for patients not taking aspirin (OR, 1.77; 95% CI, 1.03 to 3.04; P=0.040).

As shown in Figure 2, Kaplan–Meier analysis on estimated survival during hospitalization showed improved survival of the aspirin group, compared to the nonaspirin group (P<0.001). Table 4 describes Cox regression analysis about effects of different variables on overall survival during follow-up. Whereas a PSI V class, severe sepsis or septic shock, pleural effusion, and PaO_2/FiO_2 ratio <300 negatively

Table 2. Clinical Characteristics of Aspirin- Versus Non-Aspirin-Treated Patients After Propensity Score Adjustment

Variables	Aspirin Group n=390 Patients	Nonaspirin Group n=615 Patients	SD
Age, y	71.99±16.11	73.51±16.52	0.092
Male sex	53.9%	63.5%	0.097
PSI II to III classes	22.8%	17.0%	0.072
PSI IV class	58.6%	62.0%	0.035
PSI V class	18.6%	21.0%	0.030
CURB-65 I class	30.5%	32.8%	0.025
CURB-65 II class	32.4%	40.2%	0.081
CURB-65 III class	16.7%	19.7%	0.039
Chronic heart disease	21.3%	28.9%	0.088
Chronic hepatitis	8.6%	8.0%	0.030
Diabetes	12.6%	15.2%	0.038
Renal failure	11.6%	13.8%	0.033
COPD	29.4%	30.2%	0.009
CAP	18.4%	21.9%	0.044
HCAP	81.6%	78.1%	0.044
Neoplasm	13.7%	17.0%	0.046
Pleural effusion	25.5%	33.2%	0.085
Immunosuppressive therapy	11.0%	14.6%	0.054
Fever >38°C	57.4%	51.8%	0.056
PaO_2/FiO_2 ratio <300	4.5%	5.0%	0.012
NIV	0.6%	3.5%	0.103
SOFA score >2	57.1%	55.6%	0.015
Severe sepsis or septic shock	5.6%	5.4%	0.004
Nonfatal cardiovascular events	6.2%	3.3%	0.068

SD <10% indicates balance. CAP indicates community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NIV, noninvasive ventilation; PSI, pneumonia severity index; SOFA, Sequential Organ Failure Assessment.

influenced survival, aspirin therapy was associated with lower mortality rate. This finding was confirmed by the propensity score adjusted estimates, given that patients of the nonaspirin group had an HR of 2.07 (95% CI, 1.08 to 3.98; *P*=0.029), compared to patients receiving aspirin.

Discussion

The relevant finding of our prospective, observational study is that patients with community-onset pneumonia on chronic treatment with aspirin have a lower 30-day mortality rate, compared to those not receiving aspirin.

The overall mortality rate observed in our population (16.2%) is comparable to that previously reported by Ruhnke et al.,[24] who observed, in hospitalized patients with CAP in the United States, a short-term morality rate ranging from 11.7% in 65- to 69-year-old patients to 25.2% in patients >85; this finding was confirmed in a recent world-wide perspective study in which the 30-day mortality of CAP was approximately 18%.[21]

In the present study, we aimed at investigating whether aspirin treatment affects mortality in patients with community-onset pneumonia. Thus far, very few clinical studies analyzed the clinical impact of antiplatelet drugs on clinical outcomes in patients with pneumonia. A retrospective study in elderly patients hospitalized for CAP showed a significant association between the use of antiplatelet drugs (low-dose aspirin or thienopyridines) and reduced need for intensive care and hospital stay.[13] In our population, approximately 40% of patients were treated with aspirin during the intrahospital stay. Whereas age and sex were equally distributed between aspirin and nonaspirin users, patients on aspirin had a significantly more-prevalent history of CVD, less prevalence of

Table 3. Clinical Characteristics of Survived Versus Nonsurvived Patients

Variables	Survived n=842 Patients	Nonsurvived n=163 Patients	*P* Value
Age (mean)	74.1±15.7	77.9±11.1	<0.001
Male sex	507 (60.2%)	83 (50.1%)	0.027
PSI II to III classes	185 (22.0%)	3 (1.8%)	<0.001
PSI IV class	424 (50.4%)	81 (49.7%)	0.877
PSI V class	233 (27.7%)	79 (48.5%)	<0.001
CURB-65 I class	373 (44.3%)	44 (27.0%)	<0.001
CURB-65 II class	290 (34.4%)	66 (40.5%)	0.139
CURB-65 III class	179 (21.3%)	53 (32.5%)	0.002
Chronic heart disease	235 (27.9%)	54 (33.1%)	0.178
Chronic hepatitis	63 (7.5%)	32 (19.6%)	<0.001
Diabetes	164 19.5%)	31 (19.0%)	0.892
Renal failure	142 (16.9%)	52 (31.9%)	<0.001
COPD	284 (33.7%)	39 (23.9%)	0.014
CAP	576 (70.2%)	51 (27.5%)	<0.001
Neoplasm	186 (22.1%)	47 (28.8%)	0.062
Pleural effusion	340 (40.6%)	94 (57.7%)	<0.001
Immunosuppressive therapy	106 (12.9%)	30 (16.2%)	0.27
Aspin use	371 (44.1%)	19 (11.7%)	<0.001
Fever >38°C	457 (54.3%)	91 (55.8%)	0.716
PaO_2/FiO_2 ratio <300	279 (33.1%)	103 (63.2%)	<0.001
NIV	14 (1.7%)	17 (9.2%)	<0.001
SOFA score (median)	2.1	3.9	<0.001
Severe sepsis or septic shock	50 (5.9%)	39 (23.9%)	<0.001

CAP indicates community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HCAP, healthcare-associated pneumonia; NIV, noninvasive ventilation; PSI, pneumonia severity index; SOFA, Sequential Organ Failure Assessment.

diabetes, and lower pneumonia severity, as assessed by PSI and CURB-65 scores; conversely, nonaspirin users had more-prevalent neoplasm, which, however, was not significantly associated with intrahospital mortality at Cox regression analysis.

The novelty of the present study is that patients with pneumonia receiving aspirin had significantly lower total 30-day mortality rate (4.9%), compared to nonaspirin users (23.4%), and aspirin therapy was a factor independently associated with improved survival. This finding is apparently in contrast with a previous prospective observational study of 1007 patients admitted to the hospital with CAP, of whom approximately 30% were on aspirin treatment; Chalmers et al.[13] found an approximate 35% risk reduction of mortality, which, however, did not reach significance. Given that the population included by Chalmers et al.,[13] compared to our population, was younger and had less-severe pneumonia, as suggested by the 2-fold lower incidence of mortality, we cannot exclude that the benefit of aspirin is observed more prevalently in elderly patients with severe pneumonia and high mortality rate.

Several mechanisms may account for lower mortality rate in our pneumonia population. A previous study by Corrales-Medina et al.[25] demonstrated that the early phase of pneumonia might be complicated by MI, which may worsen the illness prognosis. Accordingly, we found a high rate of CV complications, such as MI and stroke, which were significantly reduced in aspirin users, compared to nonusers. This is consistent with our recent study showing a significant association between platelet activation and thromboxane A2 production and MI, suggesting a role for COX1 activation as a trigger for MI in patients with pneumonia.[12] However, the interplay among platelet activation, aspirin use, and CV outcomes needs to be further elucidated owing to the fact that low-dose aspirin is able to only partly inhibit platelet activation and COX1 in patients with pneumonia.[12]

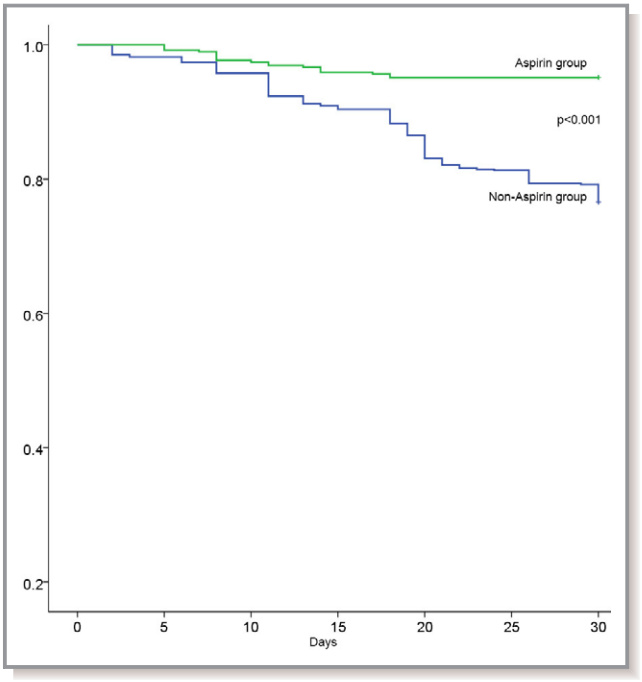

Figure 2. Estimated survival during hospitalization of the aspirin group, compared to the nonaspirin group, using Kaplan–Meier survival analysis.

An alternative mechanism, unrelated to the reduced cardiac complications, could also be implicated in lower mortality rate by aspirin. Thus, experimental and clinical studies demonstrated that platelet activation is associated with severity of sepsis and contributes to organ failure.[26–29] There is also evidence from observational studies that aspirin treatment is associated with less-severe sepsis and lower mortality, which is consistent with animal studies showing that aspirin attenuates sepsis severity.[30–32] Consistently with these reports, sepsis rate was significantly reduced in aspirin-treated patients, suggesting that aspirin use may protect against systemic inflammation and organ failure and eventually lower mortality rate. In agreement with this hypothesis, patients on aspirin treatment had significantly lower PSI and CURB-65 scores, compared to nonaspirin users.

The study has limitations and implications. The observational nature of the study is an intrinsic limitation because the lack of randomization precludes a definite analysis of aspirin benefit. Therefore, we believe that these findings cannot be transferred to clinical practice until an interventional study with aspirin has been done. An interventional study with aspirin is also necessary to establish the real impact of aspirin on total mortality, whose reduction is even higher than that observed in patients with acute coronary syndrome[33] and needs to be confirmed in further studies. The strength of the study is, however, the analysis of pneumonia in the real world, which suggests that aspirin may have a positive impact on mortality independently from other confounding factors. In particular, aspirin and nonaspirin users were well balanced in terms of demographic and clinical characteristics and had no difference in concomitant diseases, which could bias the results, with the exception of previous CVD and neoplasm, which were more frequent in aspirin and nonaspirin users, respectively. It is possible that aspirin benefit may be detected in an old population, as depicted by the present study, and therefore our data cannot be extrapolated to a younger population affected by pneumonia. This should be carefully considered when planning future randomized trials to further explore the efficacy of aspirin in this setting.

In conclusion, we provide the first evidence that, in an old population affected by pneumonia, aspirin treatment, though prevalently used by patients with higher CV risk, is associated with a lower mortality rate within 30 days from hospital admission. Owing to the observational methodology of the study, randomized, clinical trials are warranted to support this finding.

Appendix

The SIXTUS study group who collaborated to the study: Fabiana Albanese, Elisa Biliotti, Tommaso Bucci, Cinzia Myriam Calabrese, Roberto Carnevale, Marco Casciaro, Andrea Celes-

Table 4. Cox Regression Analysis About Effects of Different Variables on Overall Survival During Hospitalization

Variables	HR	95% CI	*P* Value
Aspirin use	0.43	0.25 to 0.75	0.003
PSI V class	1.41	1.03 to 1.93	0.035
Severe sepsis or septic shock	3.44	2.39 to 4.96	<0.001
Pleural effusion	1.53	1.10 to 213	0.011
PaO_2/FiO_2 ratio <300	2.27	1.58 to 3.26	<0.001

CI indicates confidence interval; HR, hazard ratio; PSI, pneumonia severity index.

tini, Paolo de Marzio, Rozenn Esvan, Lucia Fazi, Maria Cristina Gentile, Stefania Grieco, Sergio Morelli, Laura Napoleone, Michela Palumbo, Daniele Pastori, Ludovica Perri, Pasquale Pignatelli, Elisabetta Rossi, Roberta Russo, and Ines Ullo.

Disclosures

None.

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