HHS Public Access

Author manuscript

JAMA Intern Med. Author manuscript; available in PMC 2018 September 04.

Published in final edited form as:

JAMA Intern Med. 2013 April 08; 173(7): 518–523. doi:10.1001/jamainternmed.2013.2851.

Proton Pump Inhibitors and Risk of 1-Year Mortality and Rehospitalization in Older Patients Discharged From Acute Care Hospitals

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Conflict of Interest Disclosures: None reported.

Additional Information: A complete list of participating centers has been previously published.[17]

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Abstract

Importance: The use of proton pump inhibitors (PPIs) has rapidly increased during the past several years. However, concern remains about risks associated with their long-term use in older populations.

Objective: To investigate the relationship between the use of PPIs and the risk of death or the combined end point of death or rehospitalization in older patients discharged from acute care hospitals.

Design: We investigated the relationship between PPI use and study outcomes using time-dependent Cox proportional hazards regression in patients 65 years or older discharged from acute care medical wards from April 1 to June 30, 2007.

Setting: Eleven acute care medical wards.

Participants: Four hundred ninety-one patients (mean [SD] age, 80.0 [5.9] years).

Main Outcome Measures: Mortality and the combined end point of death or rehospitalization.

Results: The use of PPIs was independently associated with mortality (hazard ratio, 1.51 [95% CI, 1.03–2.77]) but not with the combined end point (1.49 [0.982.17]). An increased risk of mortality was observed among patients exposed to high-dose PPIs vs none (hazard ratio, 2.59 [95% CI, 1.22–7.16]).

Conclusions and Relevance: In older patients discharged from acute care hospitals, the use of high-dose PPIs is associated with increased 1-year mortality. Randomized controlled studies including older frail patients are needed. In the meantime, physicians need to use caution and balance benefits and harms in longterm prescription of high-dose PPIs.

THE USE OF PROTON PUMP INhibitors (PPIs) has increased rapidly during the past 2 decades, especially in older people.[1] Proton pump inhibitors are superior to histamine receptor antagonists in treating gastroesophageal reflux disease (GERD) and peptic ulcers, which are often more critical even if less symptomatic in older patients than in younger adults.[2,3]

However, recent studies raised concerns about the potential increased risk of fractures,[4,5] *Clostridium difficile* infections,[6] and community-acquired pneumonia[7] associated with long-term use of PPIs.[1] In addition, recent findings suggest that PPIs may be inappropriately prescribed in 50% to 80% of patients admitted to geriatric and internal medicine wards in acute care hospitals.[8,9]

Because of their mechanism of action, PPIs may interfere with the absorption of nutrients, exacerbating the risk of malnutrition commonly observed in older patients.[10] Moreover, shared metabolic pathways with other drugs may also explain why long-term use of PPIs may reduce the efficacy of nonsteroidal anti-inflammatory drugs, antithrombotics, and

bisphosphonates.[11–13] Older hospitalized patients might be more susceptible to adverse effects during long-term PPI use because of their poor nutritional status, comorbidities, and polypharmacotherapy. Moreover, given the widespread use of antithrombotics in older patients, the inappropriate prescription of high-dose PPIs during or after hospitalization is particularly frequent.[14] The dosage and duration of PPI treatment have been rarely monitored in previous studies, and little is known about the effects of these drugs on mortality in older patients discharged from acute care hospitals. Two recent studies showed that the use of PPIs could be associated with increased mortality in institutionalized older people[15] and in patients discharged from hospitals.[16]

Therefore, we investigated whether the use of PPIs was associated with mortality or with the combined end point of death or rehospitalization in a population of elderly patients discharged from acute care hospitals during a 1-year follow-up. To test our hypotheses, we used data from the Italian observational study Pharmacosurveillance in the Elderly Care.[17,18]

METHODS

The methods of the Pharmacosurveillance in the Elderly Care study have been described previously.[17,18] Briefly, all patients 65 years or older consecutively admitted to participating wards (11 acute care medical wards and 3 long-term care/ rehabilitation units) from April 1 through June 30, 2007, were asked to participate in the study.

Overall, 762 patients underwent screening in the survey period, but 72 (9.4%) refused to participate. Patients who died during their hospital stay (n = 25) or who were enrolled in longterm care/rehabilitationunits (n=159) were excluded from the present study. We initially planned to consider histamine receptor antagonists as an active comparator. However, the number of histamine receptor antagonist users (n=15) was too small to obtain reliable results and they were excluded. Thus, our study sample consisted of 491 patients with complete baseline and follow-up data for study analyses.

After obtaining written informed consent, a study-experienced physician team completed a questionnaire for each patient at the time of hospital admission. The questionnaire was continuously updated on a daily basis until the time of discharge. Data collection included demographic, socioeconomic, and clinical data, with a special emphasis on pharmacological therapy and comprehensive geriatric assessment. Once discharged, patients underwent follow-up visits every 3 months for 1 year. All patients and/or their relative/ caregiver were contacted by telephone to schedule the follow-up visit. At each follow-up visit, information regarding vital status, functional status (activities of daily living [ADLs]), occurrence of adverse drug reactions, and changes in drug prescriptions (date of start or withdrawal for each drug regimen) was collected. The study protocol was approved by the Ethical Committee of the Italian National Research Center on Aging.

OUTCOMES

We considered the following 2 main outcomes: 1-year survival of patients discharged from participating acute care medical wards and the combined end point of death or rehospitalization. For patients who died during the follow-up period, information about the

date, place, and cause of death was collected from death certificates provided by relatives or care-givers. City or town registers were consulted to retrieve information about death when relatives and caregivers could not be contacted (n=7). Information on a short-term hospitalization during the follow-up period was confirmed by discharge documents provided by patients and/or caregivers during the follow-up visits. For statistical purposes, we considered the first hospitalization during follow-up in patients who had experienced more than one.

USE OF PPIs

Drugs were coded using the Anatomical and Therapeutic Classification system.[19] For each prescription, we recorded the dates of start and withdrawal, drug type, and dosage. Patients receiving PPIs were identified by means of the Anatomical and Therapeutic Classification code A02BC. Users of PPIs were defined by the first prescription recorded starting from the date of discharge (ie, at the end of the index hospitalization). On this basis, the exposure started at the time of prescription, and current use was defined as the period from the recorded prescription date to withdrawal or the end of follow-up.

The type of PPI was defined by Anatomical and Therapeutic Classification codes (A02BC-01 for omeprazole magnesium, A02BC-02 for pantoprazole sodium, A02BC-03 for lansoprazole, A02BC-04 for rabeprazole sodium, and A02BC-05 for esomeprazole magnesium) and considered in the analysis. An analytic variable was also created to investigate the relationship between the PPI dosage and study outcomes. To address this aim, patients receiving dosages of 10 to 20 mg/d for omeprazole magnesium, 10 to 20 mg/d for pantoprazole sodium, 15 mg/d for lansoprazole, 10 mg/d for rabeprazole sodium, or 20 mg/d for esomeprazole magnesium were classified as receiving low-dose PPIs. Patients receiving dosages of 40 mg/d for omeprazole magnesium, 40 mg/d for pantoprazole sodium, 30 mg/d for lansoprazole, 20 mg/d for rabeprazole sodium, or 40 mg/d for esomeprazole magnesium were classified as receiving high-dose PPIs.

COVARIATES

Variables considered in the analyses included the following factors known to affect the prognosis in elderly populations: age, sex, cognitive impairment (age- and education-adjusted Mini-Mental State Examination score <24),[20] depression (Geriatric Depression Scale score >5),[21] dependency in basic ADLs (independent in all 5 ADLs, dependent in 1–4 ADLs, or dependent in all 5 ADL),[22] nutritional status (body mass index [calculated as weight in kilograms divided by height in meters squared] <20; serum albumin level, <3.5 g/dL [to convert to grams per liter, multiply by 10]), and overall comorbidity (Cumulative Illness Rating Scale comorbidity score).[23] The number of drugs prescribed at discharge and discharge prescriptions of antithrombotics and nonsteroidal anti-inflammatory drugs were also included in the analysis. Finally, cardiovascular diseases (ie, heart failure, coronary artery disease, carotid and peripheral artery disease, atrial fibrillation, venous thrombosis, and pulmonary embolism), GERD, peptic ulcer, diarrhea, infections, and fractures were also considered potential confounders.

ANALYTIC APPROACH

For the statistical analysis, we first compared baseline users and nonusers of PPIs with regard to study variables. We used the χ^2 test or the 1-way analysis of variance when appropriate. We also calculated the incidence rates of study outcomes in relation to the use of PPIs at the baseline.

Therefore, we built Cox proportional hazards regression models to derive hazard ratios and 95% confidence intervals. The time from hospital discharge through the day of death (or rehospitalization when considering the combined end point) was used as the time-to-failure variable for the model. Survivors (or patients who were not rehospitalized) were censored on the day of the last follow-up visit. We adjusted the models for age, sex, variables that were associated with the use of PPIs and study outcomes in preliminary analyses and for confounders known to increase the risk of adverse outcomes in older populations.[24,25] The prescription of nonsteroidal antiinflammatory drugs and/or antithrombotics at discharge was considered an additional potential confounder. Finally, cardiovascular diseases, GERD, peptic ulcer, diarrhea, infections, and fractures were also included in the analysis. Use of PPIs was included in the multivariable models as a time-dependent covariate.

We performed a sensitivity analysis using a negative control drug class; we therefore compared angiotensinconverting enzyme (ACE) inhibitor users not taking PPIs (n=94) with PPI users who were not taking ACE inhibitors (n=118). We resolved to use ACE inhibitors as a control drug because, on the basis of the well-known properties of these drugs,[26] a reduced mortality would be expected among users of ACE inhibitors in a population of older patients with a high prevalence of cardiovascular diseases, as in our study. Thus, the comparison between users of PPIs and ACE inhibitors would have maximized the difference in terms of mortality. We performed time-dependent Cox proportional hazards regression analysis to estimate the risk associated with the use of PPIs vs ACE inhibitors. All analyses were performed using commercially available software (SPSS Statistical Software Package for Windows; SPSS, Inc).

RESULTS

Baseline characteristics of the patients studied are reported in Table 1. Patients using PPIs showed greater prevalence of cognitive impairment, had a greater overall comorbidity, and received more prescription drugs compared with nonusers. The prevalence of cardiovascular diseases, peptic ulcer, GERD, diarrhea, and antithrombotic use was higher in PPI users (Table 1). Twenty-eight of 317 patients who were PPI nonusers at the baseline received a prescription for PPIs during follow-up.

Overall, 10.4% of patients not receiving PPIs at baseline and 18.4% of patients receiving PPIs died during the 1-year follow-up. Similar findings were obtained when the combined end point was considered: 18.6% of nonusers at baseline and 30.5% of PPI users died or were rehospitalized during the follow-up period. Incidence rates for mortality or the combined end point were higher in PPI users compared with nonusers (Table 2).

The use of PPIs was significantly associated with mortality in time-dependent multivariable analysis (Table 2). Age, hypoalbuminemia, being completely dependent in ADLs, and overall comorbidity also qualified as significant predictors of mortality, whereas the use of antithrombotics was associated with reduced mortality (Table 3).

The use of PPIs was no longer significantly associated with an increased risk of the combined end point of death or rehospitalization after adjusting for potential confounders (Table 2). Hypoalbuminemia, complete dependency in ADLs, and overall comorbidity were significant predictors of this outcome (Table 3). Patients exposed to high-dose PPIs had a significantly increased risk of death (Table 4), whereas such an association could not be observed when considering the combined end point (data not shown).

Of the 174 patients receiving PPIs at baseline, 18 patients received omeprazole; 18, pantoprazole; 75, lansoprazole; 10, rabeprazole; and 53, esomeprazole. Because the groups taking omeprazole, pantoprazole, and rabeprazole were too small to generate reliable results, the study of the association between type of PPI and mortality was limited to patients taking lansoprazole or esome0prazole. In time-dependent multivariable analysis, the use of esomeprazole (hazard ratio, 2.51 [95% CI, 1.20–5.22]) and lansoprazole (1.75 [95% CI, 0.90–3.40]) was associated with mortality. The type of PPI was not significantly associated with the combined end point (data not shown).

Finally, when we compared mortality among users of ACE inhibitors not taking PPIs with that observed among users of PPIs not taking ACE inhibitors, the time-dependent hazard ratio for the use of PPIs was 2.57 (95% CI, 1.05–6.28).

COMMENT

Our study showed that the use of PPIs is associated with an increased risk of all-cause death but not our combined end-point outcome in older patients discharged from acute care hospitals. The association between the use of PPIs and mortality remained significant after adjusting for well-known predictors of adverse outcomes in older populations, including age, cognitive impairment, disability, comorbidities, the use of drugs known to affect the prescription of PPIs, the number of drugs, and nutritional status. Our data are consistent with recent findings showing that PPI use is independently associated with all-cause mortality in 2 cohorts of institutionalized older people[15] and in a group of patients discharged from acute care hospitals.[16]

The relationship between the use of PPIs and the risk of death can imply many potential mechanisms. The suppression of gastric acidity and the alteration in gut bacterial flora may explain the higher prevalence of *C difficile* infections[6] and community-acquired pneumonia observed in long-term PPI users.[7] Frail older patients seem to be even more susceptible to such infections. Unfortunately, although the information regarding the cause of death or hospitalization was available in our data set, the number of specific events for each cause of death was too small to obtain a reliable estimate of the association between the use of PPIs and infection-related death and hospitalization.

An increased risk of cardiovascular events and deaths has also been reported in older patients receiving longterm PPI therapy.[12,15,16,27] In addition, PPIs may blunt the antiplatelet benefits of clopidogrel bisulfate and aspirin.[12,13] However, in accordance with Charlot et al,[12] our results did not vary substantially after adjusting for the concurrent use of antithrombotics, suggesting that antithrombotic antagonism is unlikely to represent the primary mechanism by which long-term use of PPIs increases the risk of mortality.

Proton pump inhibitors may also interfere with nutritional status. Indeed, suppression of acid production may affect the absorption of nutrients, exacerbating the risk of malnutrition commonly observed in older patients.[1] Serum albumin levels were not different in PPI users and nonusers in our study; even after adjusting for hypoalbuminemia, the association between PPIs and mortality did not change. However, our database did not include information on reliable instruments and markers of nutritional assessments other than the measurement of albumin levels, which could have provided more insight into a potential role of PPI on malnutrition in older frail individuals.

Finally, the use of PPIs has been associated with an increased risk of bone fractures in older people[4,5] and can blunt the antifracture efficacy of alendronate sodium.[11] Reduced efficacy is of particular concern in frail people, in whom these 2 treatments are often coadministered.

The use of PPIs was not associated with the combined end point in our study. Rehospitalization cannot be considered an easily predictable outcome in geriatric populations because it largely depends on other factors, such as the availability of health and social care facilities and informal support.[28] For instance, the use of hospital resources in the year preceding death was reduced in the very old despite high comorbidity and disability.[29] This finding likely contributes to the reasons we failed to find a significant association between PPI use and the combined end point.

Because of the observational design of our study, we can only speculate on potential mechanisms linking the use of PPIs to negative outcomes. However, our data are of particular concern in older patients, in whom complex medication regimens are often necessary for treating multiple chronic conditions,[30] and hospitalization itself may contribute to an increased number of prescribed drugs.[31] Indeed, users of PPIs had a greater overall comorbidity and number of drugs prescribed at discharge with respect to nonusers in our study, and similar findings have been recently reported in older nursing home residents.[32] Considering the rise in the number of older frail patients, any effort should be made to reduce unnecessary polypharmacy and to improve the appropriateness of prescription. Our findings suggest the need for greater attention to indications for long-term use of PPIs in the hospital setting.

Our results should be interpreted with caution because of several limitations. Because cardiovascular disease, GERD, and peptic ulcer were more prevalent in PPI users at baseline, confounding by indication is a concern in our study. Residual confounding due to unmeasured factors might also affect results. For example, given that PPIs may affect nutritional status[1] and that malnutrition is known to worsen prognosis in older patients,[10] the lack of more detailed information about malnutrition (eg, Mini Nutritional Assessment)[33] in

our study also represents a potential source of residual confounding. The duration of exposure to PPIs before the index hospitalization was not available, and we could not explore the association between the use of PPIs and specific causes of death. Our study may lack precision in estimating the observed associations owing to its limited power. Although an increased risk of mortality in relation to the use of PPIs has been observed in a similar number of older patients (n = 425) discharged from hospitals,[16] limited statistical power could be particularly relevant when investigating subgroups based on the type of PPI. We could only speculate about a cause- and-effect relationship between the use of PPIs and mortality, which should be addressed in a randomized clinical trial including a substantial proportion of frail older patients. The 1-year follow-up and the related mortality did not allow the optimal exploration of the prognostic impact of PPIs. Finally, adherence to medication regimens during follow-up was not addressed in our study.

Nevertheless, our study adds to the present knowledge by addressing the relationship between PPIs and mortality in a well-characterized population of older patients discharged from acute care hospitals. In addition, we account for data on the dosage of PPIs, which has not been evaluated in previous studies.[15,16] Furthermore, we considered several specific sources of confounding, and we used time-dependent analysis and sensitivity analysis of PPIs vs a negative control drug class to increase the robustness of our observation.

CONCLUSIONS

Our results together with recent findings[12,15,16] suggest that use of PPIs is associated with an excess mortality risk in older patients discharged from acute care hospitals. Such findings need to be replicated using a randomized controlled design. In the meantime, physicians should balance benefits and harms in the long-term prescription of high-dose PPIs to older people with high comorbidity and polypharmacy and should periodically review the indications for PPI treatment to avoid unnecessary long-term prescriptions. Because hospitalization may not contribute to improving the appropriateness of PPI prescription,[34] this issue should be also addressed by hospital physicians.

Acknowledgments

Funding/Support: This study was supported in part by grant RF-INR-2005–127640 from the Italian Ministry of Health (Pharmacosurveillance in the Elderly Care study) and by grant RF-2010–2312659 from the Italian Ministry of Health and Emilia Romagna Region.

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Table 1.

General Characteristics of the Study Population[a]

Characteristic	All (n = 491)	Baseline		*P* Value
		Nonusers (n = 317)	PPI Users (n = 174)	
Age, mean (SD), y	80.0 (5.9)	79.9 (5.9)	80.2 (5.9)	.54
Male sex	226 (46.0)	144 (45.4)	82 (47.1)	.72
Current smokers	27 (5.5)	18 (5.7)	9(5.2)	.81
BMI <20	41 (8.4)	25 (7.9)	16(9.2)	.62
Albumin level <3.5 g/dL	220 (44.8)	143 (45.1)	77 (44.3)	.86
MMSE score <24	247 (50.3)	138 (43.5)	109 (62.6)	.001
GDS score >5	194 (39.5)	120 (37.9)	74 (42.5)	.31
No. of lost ADLs at discharge				
0	366 (74.5)	243 (76.7)	123 (70.7)	
1–4	71 (14.5)	41 (12.9)	30 (17.2)	.32
5	54 (11.0)	33 (10.4)	21 (12.1)	
CIRS comorbidity score, mean (SD)	3.7 (1.9)	3.4 (1.8)	4.2 (1.9)	.001
Cardiovascular disease	315 (64.2)	193 (60.9)	122 (70.1)	.04
Peptic ulcer	14 (2.9)	4(1.3)	10(5.7)	.004
GERD	46 (9.4)	22 (6.9)	24 (13.8)	.01
Diarrhea	7(1.4)	2 (0.6)	5(2.9)	.045
Infectious disease	58 (11.8)	37 (11.7)	21 (12.1)	.90
Fracture	5(1.0)	3 (0.9)	2(1.1)	.83
No. of drugs prescribed at discharge, mean (SD)	6.9 (2.9)	6.2 (2.7)	8.3 (2.8)	.001
Antithrombotic use (including aspirin)	320 (65.2)	189 (59.6)	131 (75.3)	.001
NSAID use	17 (3.5)	12 (3.8)	5(2.9)	.60
Length of stay, mean (SD), d	11.7 (6.9)	11.6 (7.1)	12.0(6.7)	.53

Abbreviations: ADLs, activities of daily living; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale; GDS, Geriatric Depression Scale; GERD, gastroesophageal reflux disease; MMSE, Mini-Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

SI conversion factor: To convert albumin to grams per liter, multiply by 10.

[a]Unless otherwise indicated, data are expressed in number (percentage) of patients.

Table 2.

Relationship Between Use of PPIs (Predictor) and Outcomes[a]

	Incidence Rates, Person-years (95% CI)				
Outcome	**PPI Nonusers**	**PPI Users**	***P* Value**	**Adjusted HR (95% CI)[b]**	***P* Value**
Mortality	12.0 (5.2–18.8)	21.5(11.8–31.2)	.009	1.51 (1.03–2.77)	.03
Combined end point	22.9 (13.5–32.3)	39.8 (27.4–52.2)	.003	1.49 (0.98–2.17)	.11

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a]Includes mortality and the combined end point of death or rehospitalization, as outcomes.

[b]Indicates time-dependent Cox proportional hazards regression HRs adjusted forage, sex, body mass index, hypoalbuminemia, cognitive impairment, dependency in activities of daily living, gastroesophageal reflux disease, peptic ulcer, diarrhea, infectious disease, fracture, the number of drugs at discharge, antithrombotic use, and nonsteroidal anti-inflammatory drug use.

Table 3.

Associations Between Predictors Other Than Exposure to Proton Pump Inhibitors and Study Outcomes

	Outcome, HR (95% CI)	
Predictor	**Death**	**Death or Rehospitalization**
Age	1.06(1.01–1.11)	1.00 (0.95–1.03)
Sex	0.72 (0.42–1.22)	1.00 (0.66–1.50)
BMI <20	1.01 (0.96–1.07)	1.01 (0.97–1.06)
Hypoalbuminemia	2.36 (1.31–4.25)	1.65 (1.10–2.46)
MMSE score <24	1.04 (0.52–2.05)	1.06 (0.66–1.70)
Complete dependency in ADLs	7.41 (3.64–15.10)	4.51 (2.58–7.90)
CIRS comorbidity score	1.10 (1.03–1.24)	1.16 (1.04–1.30)
Cardiovascular disease	1.77 (0.42–2.43)	1.67 (0.62–3.06)
GERD	1.62 (0.70–3.72)	1.55 (0.87–2.78)
Peptic ulcer	1.98 (0.83–6.60)	1.84 (0.79–5.57)
Diarrhea	1.80 (0.40–8.18)	2.32 (0.54–9.98)
Infectious disease	1.66 (0.33–2.30)	1.87 (0.50–3.53)
Fracture	1.77 (0.11–6.98)	1.60 (0.40–3.56)
No. of drugs prescribed at discharge	0.98 (0.88–1.07)	1.04 (0.96–1.12)
Antithrombotic use	0.59 (0.33–0.99)	0.70 (0.43–1.03)
NSAID use	0.90 (0.19–3.77)	0.97 (0.37–2.90)

Abbreviations: ADLs, activities of daily living; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIRS, Cumulative Illness Rating Scale; GERD, gastroesophageal reflux disease; HR, hazard ratio; MMSE, Mini-Mental State Examination; NSAID, nonsteroidal anti-inflammatory drugs.

Table 4.

Relationship Between PPI Dose (Predictor) and 1-Year Mortality (Outcome)

PPI Use[a]	No. of Patients	HR (95% CI)[b]	*P* Value
None	317	1 [Reference]	
Low-dose PPIs	146	1.34 (0.73–2.69)	.77
High-dose PPIs	28	2.59 (1.22–7.16)	.007

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.

[a]Patients receiving dosages of 10 to 20 mg/d for omeprazole magnesium, 10 to 20 mg/d for pantoprazole sodium, 15 mg/d for lansoprazole, 10 mg/d for rabeprazole sodium, or 20 mg/d for esomeprazole magnesium were classified as receiving low-dose PPIs. Those receiving dosages of 40 mg/d for omeprazole magnesium, 40 mg/d for pantoprazole sodium, 30 mg/d for lansoprazole, 20 mg/d for rabeprazole sodium, or 40 mg/d for esomeprazole magnesium were classified as receiving high-dose PPIs.

[b]Indicates time-dependent Cox proportional hazards regression adjusted for age, sex, body mass index, hypoalbuminemia, cognitive impairment, depression, dependency in activities of daily living, Cumulative Illness Rating Scale comorbidity score, cardiovascular diseases, gastroesophageal reflux disease, peptic ulcer, diarrhea, infectious disease, fracture, the number of drugs at discharge, antithrombotic use, and nonsteroidal anti-inflammatory drug use.