Evidence is accumulating in relation to adverse events associated with proton pump inhibitors (PPIs). Reports in the Archives have demonstrated an association with fractures,\(^1\) Clostridium difficile infections,\(^2\) and community-acquired pneumonia.\(^3\) Proton pump inhibitors may also attenuate the antiplatelet benefits of clopidogrel.\(^4\) Because frail older people often use PPIs and may be especially vulnerable, we investigated the association between PPIs and all-cause mortality in 2 cohorts of institutionalized people.

**Methods.** We conducted post hoc analyses of data from 2 prospective cohort studies in Helsinki, Finland, that included (1) 1004 residents from 53 long-term care wards in September 2003\(^3\) and (2) 425 residents 70 years or older in acute geriatric wards (n=230) and in nursing homes (n=195) in 1999-2000.\(^5\) Data were extracted by trained nurses and geriatricians (J.V.L. and K.H.P.). Only regular medication was included in the analyses. Mortality was extracted from national registers. Statistical analyses were performed using NCSS 2004 software (NCSS, Kaysville, Utah). \(^6\) Tests and Cox proportional hazards models (hazard ratios [HRs] and 95% confidence intervals [CIs]) were used to investigate the association between PPIs and mortality.

**Results.** In the first cohort, the mean (SD) age of the 1004 residents was 81.3 (10.9) years, and 755 (75.2%) were female. Of the 1004 residents, 231 (23.0%) used a PPI at baseline and 283 (28.2%) died during the 12-month follow-up. The mortality rate was 33.3% (n=77) and 26.6% (n=206) among users and nonusers of PPIs, respectively (P=.048). After adjusting for age, sex, comorbidity, and malnutrition, PPIs were associated with a 37% increased mortality (HR, 1.37; 95% CI, 1.05-1.78) (Table). In the second cohort, the mean (SD) age of the 425 residents was 86.1 (7.0) years, and 347 residents (81.6%) were female. Of the 425 residents, 91 (21.4%) used a PPI at baseline and 106 (24.9%) died during the 12-month follow-up. The mortality rate was 36.3% (n=33) and 21.9% (n=73) among users and nonusers of PPIs, respectively (P=.005). After adjusting for age, sex, comorbidity, and delirium, PPIs were associated with an 82% increased mortality (HR, 1.82; 95% CI, 1.20-2.78).

In the first cohort, use of NSAIDs and low-dose aspirin were similar among users and nonusers of PPIs (4.3% vs 3.2%; P=.43) and (32.0% vs 37.5%; P=.13), respectively. Users of PPIs were more likely to use a selective serotonin reuptake inhibitor (SSRI) (38.1% vs 24.7%; P<.001). However, there were no differences in mortality among users and nonusers of NSAIDs (20.0% vs 28.5%; P=.27), low-dose aspirin (28.3% vs 28.1%; P=.95), or SSRIs (28.0% vs 28.3%; P=.92). In the second cohort, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was similar among users and nonusers of PPIs (8.8% vs 7.5%; P=.68). Users of PPIs were less likely to use low-dose aspirin (34.1% vs 52.4%; P=.002) and SSRIs (15.4% vs 29.9%; P=.005). There were no significant differences in mortality among users and nonusers of low-dose aspirin (27.7% vs 22.4%; P=.21), NSAIDs (12.1% vs 26.0%; P=.08), or SSRIs (19.3% vs 27.0%; P=.10).

**Table.** Risk of Death During 12 Months of Follow-up Associated With Baseline Use of Proton Pump Inhibitors (PPIs)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Model 1, HR (95% CI)</th>
<th>Model 2, HR (95% CI)</th>
<th>Model 3, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPI use</td>
<td>Age</td>
<td>Male sex</td>
</tr>
<tr>
<td>Cohort 1: residents of long-term care facilities in Helsinki (n=1004)</td>
<td>1.30 (1.00-1.68)</td>
<td>1.03 (1.02-1.05)</td>
<td>1.39 (1.04-1.85)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.05)</td>
<td>1.03 (1.01-1.04)</td>
<td>1.44 (1.08-1.91)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.39 (1.04-1.85)</td>
<td>1.44 (1.08-1.91)</td>
<td>1.07 (1.00-1.15)</td>
</tr>
<tr>
<td>CCI</td>
<td>1.30 (1.00-1.68)</td>
<td>1.03 (1.02-1.05)</td>
<td>1.44 (1.08-1.91)</td>
</tr>
<tr>
<td>Malnutrition(^a)</td>
<td>2.28 (1.75-2.97)</td>
<td>1.30 (1.00-1.68)</td>
<td>1.03 (1.02-1.05)</td>
</tr>
<tr>
<td>Delirium(^b)</td>
<td>1.48 (0.98-2.23)</td>
<td>1.07 (1.00-1.15)</td>
<td>2.28 (1.75-2.97)</td>
</tr>
</tbody>
</table>

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio.

\(^a\) Defined as Mini-Nutritional Assessment score less than 17.

\(^b\) Determined according to operationalized Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria.
Our main finding was that baseline PPI use was associated with all-cause mortality in 2 cohorts of institutionalized older people. These people may be at high risk of death due to infections, hip fractures, and vascular complications—adverse events that have been associated with PPIs. However, our unpublished analyses revealed no association between PPIs and 3-year mortality in 400 home-dwelling cardiovascular patients 75 years or older in the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study conducted in Helsinki from 2000 to 2003. As with all observational studies there is the possibility of confounding. Proton pump inhibitors may be prescribed for gastrointestinal protection in users of low-dose aspirin, NSAIDs, and SSRIs. However, these drugs were not associated with mortality. Our data highlight the need for urgent research into the risks vs benefits of routinely prescribing PPIs to older people in long-term care.

J. Simon Bell, PhD
Timo E. Strandberg, MD, PhD
Mariko Teramura-Gronblad, MD
Jouko V. Laurila, MD, PhD
Reijo S. Tilvis, MD, PhD
Kaisu H. Pitkälä, MD, PhD

Author Affiliations: Kuopio Research Centre of Geriatric Care and Clinical Pharmacology and Geriatric Pharmacotherapy Unit, School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio (Dr Bell); Department of Health Sciences/Geriatrics, University of Oulu, and Oulu City Hospital, Oulu, Finland (Dr Strandberg); Unit of General Practice (Drs Teramura-Gronblad and Pitkälä) and Clinics of General Internal Medicine and Geriatrics (Drs Laurila and Tilvis), Helsinki University Central Hospital, Helsinki, Finland; and Home Nursing Services, Helsinki City Health Center, Helsinki (Dr Teramura-Gronblad).

Correspondence: Dr Pitkälä, Unit of General Practice, Helsinki University Central Hospital, PO Box 20, 00014 Helsinki, Finland (kaisu.pitkal@helsinki.fi).

Author Contributions: Dr Pitkälä had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is the guarantor. Study concept and design: Bell, Strandberg, Teramura-Gronblad, Laurila, Tilvis, and Pitkälä. Acquisition of data: Strandberg, Laurila, and Pitkälä. Analysis and interpretation of data: Bell and Pitkälä. Drafting of the manuscript: Bell, Strandberg, Laurila, and Pitkälä. Critical revision of the manuscript for important intellectual content: Teramura-Gronblad, Tilvis, and Pitkälä. Statistical analysis: Pitkälä. Obtained funding: Laurila and Pitkälä. Administrative, technical, and material support: Bell, Strandberg, Tilvis, and Pitkälä. Study supervision: Pitkälä.

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Combined Influence of Health Behaviors on Total and Cause-Specific Mortality

A recent article in the Archives prospectively examined the individual and collective influence of 4 risk factors (physical activity, diet, smoking, and alcohol consumption) on total and cause-specific mortality. In the Health and Lifestyle Survey (HALS), adjusted hazard ratios and 95% confidence intervals (CIs) for total mortality associated with 1, 2, 3, and 4 poor health behaviors compared with none were 1.85 (95% CI, 1.28-2.68), 2.23 (95% CI, 1.55-3.20), 2.76 (95% CI, 1.91-3.99), and 3.49 (95% CI, 2.31-5.26), respectively (P value for trend, <.001). Only a handful of population-based studies have examined the combi-