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ORIGINAL RESEARCH

Proton Pump Inhibitor Use and Incident Hypertension in Menopausal Women

Ahmed I. Soliman, PharmD; Jean Wactawski-Wende, PhD; Amy E. Millen, PhD; Shelly L. Gray, PharmD, MS; Charles B. Eaton, MD, MS; Kathleen M. Hovey, MS; Macarius Donneyong, PhD, MPH; Nazmus Saquib, MBBS, MPH, PhD; Charles P. Mouton, MD; Deepika Laddu, PhD; Simin Liu, MD, ScD; Daichi Shimbo, MD; Sylvia Wassertheil-Smoller, PhD; Michael J. LaMonte, PhD, MPH

BACKGROUND: Proton pump inhibitors (PPIs) could affect blood pressure regulation by suppressing gastric acid required for the conversion of oral nitrite into nitric oxide. Whether PPI use is associated with incident hypertension remains unknown.

METHODS: We included 64 720 menopausal women who were free from cardiovascular disease and hypertension at enrollment in the Women's Health Initiative Observational Study (1993–1998). Baseline PPI use and duration were determined using medication inventories. The outcome was physician diagnosed/treated incident hypertension, assessed by self-report on annual questionnaires. Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazard models for incident hypertension according to baseline PPI use (no/yes) and duration (<1 year, 1–3 years, >3 years). The association between PPI use and 3-year changes in measured blood pressure was examined using linear regression.

RESULTS: There were 28 951 cases of incident hypertension after a mean follow-up of 8.7 years. PPI use was associated with 17% higher risk of hypertension compared with nonuse in the fully adjusted model (HR, 1.17 [95% CI, 1.08–1.27]). Longer PPI use durations were significantly associated with incrementally higher risk of hypertension (HR, 1.13, 1.17, 1.28, respectively; trend $P<0.001$). The 3-year change in multivariable-adjusted mean systolic blood pressure increased significantly for PPI new users (+3.39 mm Hg, $P=0.049$) compared with never users.

CONCLUSIONS: PPI use was associated with higher risk of diagnosed hypertension in menopausal women, and the risk showed a significant trend according to longer duration of use. Further studies are needed to confirm these findings.

Key Words: blood pressure ■ hypertension ■ menopause ■ proton pump inhibitors ■ women

Proton pump inhibitors (PPIs) are the treatment of choice for conditions such as esophagitis and peptic ulcer disease.[1] Due to their high efficacy, PPIs are among the most prescribed medications in the United States.[1] PPI use more than doubled from 2002 to 2009 (4% and 9%, respectively).[2] In 2016, one of the PPIs was dispensed more than 70 million times in the United States.[3] Inappropriate PPI use either due to prolonged use or lacking an appropriate indication has been linked with several adverse events such as bone fractures, pneumonia, and kidney damage, especially in older people.[4–6]

Nitric oxide (NO) is a potent vasodilator that plays a critical role in blood pressure (BP) regulation.[7] Recent studies have shown the importance of the nitrate–nitrite–NO pathway in the production of NO.[8,9] The conversion of nitrite to NO in the stomach is dependent on the presence of gastric acid.[8] PPIs are highly effective in suppressing gastric acid secretion and are hypothesized to affect NO production from nitrate/nitrites.[10]

Correspondence to: Ahmed I. Soliman, PharmD, Department of Epidemiology and Environmental Health, University at Buffalo, 265 Farber Hall, 3435 Main St. Buffalo, NY 14214. Email: asoliman@buffalo.edu

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CLINICAL PERSPECTIVES

What Is New?

- This is the first large-scale epidemiological study to assess whether proton pump inhibitor use is associated with incident hypertension, and how long-term use could affect hypertension risk.

What Are the Clinical Implications?

- Long-term proton pump inhibitor use (≥1 year) was associated with higher risk of hypertension.
- New users and continued users of proton pump inhibitors had a higher risk of hypertension whereas former users had no significant association.

Nonstandard Abbreviations and Acronyms

NO	nitric oxide
WHI-OS	Women's Health Initiative Observational Study

This hypothesis was tested in a randomized trial on 15 participants with normal BP where an oral nitrite produced an acute lowering of systolic BP (SBP) (lowest mean=−6 mm Hg) when participants were given a placebo.[11] However, the oral nitrite produced no significant change in SBP when the participants were given a PPI. Whether prolonged PPI use could be associated with clinical hypertension remains unknown.

The primary aim of this study was to evaluate the association between PPI use and incident hypertension in menopausal women enrolled in the WHI-OS (Women's Health Initiative Observational Study).[12,13] The secondary aim was to examine the association between PPI use and 3-year changes in BP measured in the clinical setting. We hypothesized that PPI use would be associated with higher risk of incident hypertension and positive 3-year changes in measured BP.

METHODS

The data that support the findings of this study are available from WHI at helpdesk@whi.org. Further information is available from the corresponding author with the permission of WHI.

Study Design and Participants

The WHI enrolled 161 808 menopausal women aged 50 to 79 across 40 clinical centers in the United States between 1993 and 1998. Details on the design and recruitment have been described elsewhere.[13,14] Women were recruited to either the clinical trials (n=68 132) or observational study (n=93 676). The current analysis included only women in the WHI-OS who had information on PPI use and relevant covariates collected at baseline and year-3 clinic visits. We excluded women with a history of hypertension (n=23 464), antihypertensive use (10 247), history of cardiovascular disease (myocardial infarction, stroke, heart failure, or atrial fibrillation) at baseline (n=7741), missing information on PPI use (n=1), or missing follow-up information (n=627). The final analytic cohort was 64 720 women (Figure S1). Institutional review board approval and participant informed consent were obtained at all WHI clinical centers.

PPI Use Assessment

Women enrolled in the WHI-OS were asked to bring all their current medications (prescription and over the counter) to the baseline and year-3 clinic visits. Clinic interviewers conducted a medication inventory by reviewing the labels of each medication and entering the medication name into a database using Medi-Span software.[14] Duration of use for each medication was also documented. PPIs were available by prescription only at the time of the WHI clinic visits and included omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. The primary exposure for our analysis was PPI use (no/yes) according to the baseline visit. Duration of use was categorized as <1 year, 1 to 3 years, and >3 years, similar to previous studies in WHI that evaluated PPI use duration.[15–17] PPI use (no/yes) was also modeled as a time-varying exposure using data from baseline and year-3 visits. To examine the impact of change in PPI use between visits on hypertension, we completed another analysis in which we used the year-3 visit as the start of follow-up, and participants were classified into 4 groups based on their baseline and year-3 PPI use as never users (no use at both visits), former users (use at baseline but not at year 3), new users (no use at baseline but use at year 3), and continued users (use at both visits).

Hypertension Ascertainment

Incident hypertension was based on self-reported newly physician-diagnosed hypertension treated with medication documented on annual health update questionnaire. Participants were asked "Since the date given on the front of this form, has a doctor prescribed pills for high blood pressure or hypertension?"[18] Self-reported hypertension has high reproducibility (κ=0.86) for repeated assessments 3 months apart at WHI-OS enrollment and was found to agree strongly with Centers for Medicare & Medicaid Services medical claims data (κ=0.84).[18] In an ancillary study to WHI, self-reported hypertension compared with medication

inventories at a subsequent clinic visit had a sensitivity, specificity, and κ of 0.58, 0.98, and 0.64, respectively.[19]

BP change was based on measurements conducted at WHI clinics at both baseline and year-3 visits.[12] Trained staff took measurements by auscultation in the right arm using a calibrated mercury sphygmomanometer and appropriately sized cuff based on arm circumference. Participants were seated and rested for 5 minutes in a straightback chair, legs uncrossed. BP was measured twice at each visit, and we used the average of the 2 measurements in our analysis. We conducted a separate analysis for systolic and diastolic BP (DBP).

Covariates Assessment

Information on demographic, lifestyle, and clinical variables was collected from participants using clinical measurements and self-report using standardized questionnaires. Demographic variables included age, self-identified race and ethnicity, education, and annual household income. Lifestyle variables included dietary intake, smoking history (never, former, current), lifetime smoking pack-years, alcohol intake (servings/week), usual sleep duration (hours/night), and physical activity (metabolic equivalent hours/week). The Dietary Approaches to Stop Hypertension diet score was calculated from food frequency questionnaires.[20] Clinical variables included body mass index (BMI), history of treated diabetes, treated hypercholesterolemia, family history of cardiovascular disease, and medication use that could be associated with BP (acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, hormone therapy, and corticosteroids). For example, participants were asked "Has a doctor told you that you have high cholesterol requiring pills?" BMI was calculated (kg/m^2) using height and weight measured at the clinic. Most of the self-reported information collected from participants has shown high reliability (κ >0.75).[13]

Statistical Analysis

Baseline characteristics were compared according to PPI use (no/yes) using χ^2 test for categorical variables and *t* test for continuous variables. Kaplan–Meier curves were used to visualize the unadjusted annualized hypertension incidence according to baseline PPI use (no/yes) and duration of use (nonuser, <1 year, 1–3 years, >3 years), and log-rank tests were used to determine statistical significance.

Cox proportional hazard regression was used to estimate hazard ratios (HRsy) and 95% CIs for incident hypertension comparing PPI users with nonusers. The proportional hazards assumption was evaluated graphically using log–log survival curves, and no appreciable violations were found. Follow-up time was defined as years from enrollment in the WHI-OS to the time of the questionnaire on which hypertension diagnosis was reported, loss to follow-up, or end of follow-up on September 17, 2010, whichever came first. We ended follow-up in 2010 to minimize the possibility of exposure misclassification as PPIs were by prescription only until the mid-2000s, after which PPIs became over the counter, making indication for use less certain. To account for potential competing risk by death, we estimated the cumulative incidence function of hypertension while taking overall mortality into account using Gray's test.[21] The Fine–Gray subdistribution hazard model was used to examine the results of the fully adjusted model in the presence of death as a competing risk.[21]

Multivariable-adjusted Cox models were fitted to account progressively for potential confounders, starting with model 1 adjusted for age, then adding demographic variables (education, income, race, ethnicity) as model 2, lifestyle variables (smoking history, smoking pack years, alcohol intake, Dietary Approaches to Stop Hypertension diet score, physical activity, and sleep duration) as model 3, and clinical risk factors (family history of cardiovascular disease, BMI, treated diabetes, treated hypercholesterolemia, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, corticosteroids, and hormone therapy) as model 4. The fully adjusted model included all variables in the previous models. Linearity for continuous variables was checked by plotting the cumulative martingale residuals against each continuous variable, and no appreciable deviations were observed. Similar multivariable-adjusted Cox models were fitted using PPI duration use categories (nonuser, <1 year, 1–3 years, >3 years) to examine the impact of duration of PPI use on hypertension risk. Furthermore, time-varying Cox models were also fitted in which PPI use (no/yes) and covariate data for participants were allowed to vary based on data from baseline and year-3 clinic visits. We determined potential confounders based on clinical relevance and previous literature.[22,23] We used an unknown/missing indicator variable for missing information on categorical variables, and complete case analysis was used for continuous variables (3.6% missing). No appreciable difference in the missing pattern was found between PPI users and nonusers. Moreover, imputation methods using mean or median imputation did not affect the overall findings.[24]

As a sensitivity analysis, the consistency of an association between PPI use and hypertension across baseline subgroups were explored using stratification by age (50–59, 60–69, 70 and above), BMI (<30 kg/m^2, ≥30 kg/m^2), BP groups (SBP < 120 and DBP <80, SBP=120–139 or DBP=80–89, SBP ≥140 or DBP ≥90 mm Hg), and treated diabetes (no/yes). Statistical tests for interactions were conducted by adding a cross-product term between each of the categories

of age, BMI, or BP and PPI use (no/yes) in the fully adjusted model. The Wald χ^2 test was used to assess the statistical significance of the interaction term, and the Akaike information criterion was used to assess each model fit. Other sensitivity analyses included using the fully adjusted model excluding women with high measured BP at baseline (SBP ≥140 or DBP ≥90 mm Hg) to examine the impact of undiagnosed hypertension on the association, another model excluding women with prevalent cardiovascular risk factors at baseline (current smokers, treated diabetes, treated hypercholesteremia, and high measured BP), and adjusting for interaction between covariates such as BMI*smoking, BMI*treated diabetes, and BMI*treated hypercholesterolemia.

We used propensity score adjusted models to further control for residual confounding.[25] Logistic regression models were fitted to determine the propensity score predicting PPI use based on age, demographic, lifestyle, and clinical risk factors. We then trimmed the propensity score at the fifth percentile in the PPI users as a lower cut point and the 95th percentile in the nonusers as a higher cut point as recommended by Stürmer et al.[26] Inverse probability weighting was then used to fit the Cox proportional hazards model.[26]

Linear regression models were used to determine least square means and standard errors for SBP and DBP change according to 4 PPI use categories (never user, new user, continued user, former user) determined based on baseline and year-3 clinic visits. A change score representing the difference between the year-3 and baseline measured BP was used as the outcome variable. We adjusted for age, demographic, lifestyle, and clinical variables as in the Cox models.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values were 2 sided at an α of 0.05 to determine statistical significance.

RESULTS

The cohort at baseline had 64 720 participants, 1162 of whom (1.8%) were PPI users, and 63 558 (98.2%) were nonusers. Table 1 shows baseline characteristics overall and according to PPI use. On average, participants were aged 63 years, had a BMI of 27 kg/m^2, SBP of 123 mm Hg, DBP of 74 mm Hg, were educated beyond high school, and were predominantly non-Hispanic White. Baseline prevalence of former smokers was 42%, 6% were current smokers, 64% had a family history of cardiovascular disease, 20% were current acetylsalicylic acid users, 18% were current nonsteroidal anti-inflammatory drug users, 46% were current hormone therapy users, 1% were current corticosteroid users, 2% were being treated for diabetes, and 11% were being treated for hypercholesterolemia. All baseline characteristics were statistically different between PPI users and nonusers (*P*<0.05) except for DBP (*P*=0.52), ethnicity (*P*=0.45), and acetylsalicylic acid use (*P*=0.35). PPI users were older, had a higher BMI, higher smoking pack-years, higher SBP, and lower physical activity, Dietary Approaches to Stop Hypertension diet score, and alcohol consumption (Table 1). PPI users were more likely to have high school or less education, have a family income of <$20 000, be former smokers, have a family history of cardiovascular disease, report treated diabetes, report shorter sleep duration, report treated hypercholesterolemia, more current hypertension medication, nonsteroidal anti-inflammatory drugs use, and corticosteroid use. Baseline characteristics according to incident hypertension status (no/yes) are shown in Table S1. All baseline characteristics differed significantly (*P*<0.05) according to incident hypertension status except for corticosteroid use (*P*=0.28).

Hypertension Risk by Baseline PPI Use

We identified 28 951 (44.7%) cases of incident hypertension over a mean follow-up of 8.7 years. PPI users had a crude incidence rate (per 1000 person-years) of 71, whereas the rate among nonusers was 51. Kaplan–Meier plot showed significantly higher annualized hypertension incidence in PPI users compared with non-sers over the follow-up time (log-rank *P*<0.0001; Figure S2). Crude incidence rates (per 1000 person-years) were progressively higher according to PPI use duration categories (<1 year: 66, 1–3 years: 73, >3 years: 83) compared with nonusers for whom the rate was 51. There was a significantly higher annualized hypertension incidence in longer PPI use durations compared with nonusers over the follow-up time (log-rank *P*<0.0001; Figure S3).

PPI users had a significant 38% higher risk of hypertension compared with nonusers in the age-adjusted model (HR, 1.38 [95% CI, 1.27–1.49]; Table 2). The association persisted after further adjustment for demographics (model 2), lifestyle (model 3), and clinical risk factors (model 4). PPI use was associated with a significant 17% higher risk of hypertension in the fully adjusted model (HR, 1.17 [95% CI, 1.08–1.27]). The association remained significant after propensity score adjustment to better control for residual confounding (HR, 1.17 [95% CI, 1.15–1.19]). Moreover, excluding women with high measured BP at baseline (SBP ≥140 or DBP ≥90 mm Hg) or prevalent cardiovascular risk factors did not appreciably change the results of the fully adjusted model (HR, 1.24 [95% CI, 1.12–1.36], HR, 1.19 [95% CI, 1.06–1.34], respectively). Competing risk analysis showed no noticeable deviations from the main results (Gray's test *P*<0.0001), subdistribution

Table 1. Characteristics of Participants, Overall and According to Baseline PPI Use

Characteristic	Overall (n=64 720)	PPI nonuser n=63 558 (98.2%)	PPI user n=1162 (1.8%)	*P* value
Age, y	62.7 (7.3)	62.7 (7.3)	63.7 (7.3)	<0.0001
Body mass index, kg/m^2	26.5 (5.4)	26.4 (5.4)	28.7 (5.7)	<0.0001
Physical activity, metabolic equivalent h/wk	14.7 (14.9)	14.7 (14.9)	11.1 (12.8)	<0.0001
Dietary Approaches to Stop Hypertension diet score	25.5 (4.9)	25.5 (4.9)	24.3 (4.8)	<0.0001
Alcohol, servings/wk	2.6 (5.2)	2.7 (5.2)	1.6 (3.8)	<0.0001
Smoking, pack years	9.6 (18.0)	9.6 (18.0)	11.2 (18.9)	0.004
Systolic BP, mm Hg	123.4 (16.7)	123.3 (16.7)	125.6 (16.5)	<0.0001
Diastolic BP, mm Hg	73.8 (8.9)	73.8 (8.9)	73.9 (8.7)	0.52
Education				
High school or less	12 383 (19.1%)	12 114 (19.1%)	269 (23.2%)	<0.0001
College/some college	30 661 (47.4%)	30 074 (47.3%)	587 (50.5%)	
Postgraduate	21 172 (32.7%)	20 873 (32.8%)	299 (25.7%)	
Ethnicity				0.45
Not Hispanic/Latino	61 205 (94.6%)	60 111 (94.6%)	1094 (94.2%)	
Hispanic/Latino	2937 (4.5%)	2877 (4.5%)	60 (5.2%)	
Unknown/not reported	578 (0.9%)	570 (0.9%)	8 (0.7%)	
Race				0.004*
White	57 050 (88.2%)	55 994 (88.1%)	1056 (90.9%)	
Black	3581 (5.5%)	3529 (5.6%)	52 (4.5%)	
American Indian/Alaska Native	200 (0.3%)	197 (0.3%)	3 (0.3%)	
Asian	1796 (2.8%)	1776 (2.8%)	20 (1.7%)	
Native Hawaiian/other Pacific islander	32 (0.1%)	32 (0.1%)	0 (0.0%)	
More than one race	621 (1.0%)	614 (1.0%)	7 (0.6%)	
Unknown/not reported	1440 (2.2%)	1416 (2.2%)	24 (2.1%)	
Family income, $				0.01
<$20 000	8141 (12.6%)	7973 (12.5%)	168 (14.5%)	
$20 000–$49 999	25 115 (38.8%)	24 662 (38.8%)	453 (39.0%)	
$50 000–$99 999	19 129 (29.6%)	18 785 (29.6%)	344 (29.6%)	
≥$100 000	7638 (11.8%)	7533 (11.9%)	105 (9.0%)	
Smoking				0.004
Never	32 478 (50.2%)	31 938 (50.3%)	540 (46.5%)	
Former	27 302 (42.2%)	26 759 (42.1%)	543 (46.7%)	
Current	4074 (6.3%)	4013 (6.3%)	61 (5.3%)	
Family history of cardiovascular disease	41 469 (64.1%)	40 673 (64.0%)	796 (68.5%)	0.002
Treated diabetes	1348 (2.1%)	1300 (2.1%)	48 (4.1%)	<0.0001
Sleep duration				
≤5 h	4779 (7.4%)	4655 (7.3%)	124 (10.7%)	<0.0001
6 h	16 976 (26.2%)	16 643 (26.2%)	333 (28.7%)	
7 h	24 975 (38.6%)	24 576 (38.7%)	399 (34.3%)	
8 h	14 780 (22.8%)	14 528 (22.9%)	252 (21.7%)	
9 h	2552 (3.9%)	2511 (4.0%)	41 (3.5%)	
≥10 h	311 (0.5%)	303 (0.5%)	8 (0.7%)	
Acetylsalicylic acid use	12 835 (19.8%)	12 592 (19.8%)	243 (20.9%)	0.35
Nonsteroidal anti-inflammatory drug use	11 372 (17.6%)	11 098 (17.5%)	274 (23.6%)	<0.0001
Corticosteroid use	649 (1.0%)	599 (0.9%)	50 (4.3%)	<0.0001
Treated hypercholesterolemia	6835 (10.6%)	6614 (10.4%)	221 (19.0%)	<0.0001

(*Continued*)

Table 1. Continued

Characteristic	Overall (n=64 720)	PPI nonuser n=63 558 (98.2%)	PPI user n=1162 (1.8%)	*P* value
Hormone therapy use				<0.0001
Never	25 830 (39.9%)	25 457 (40.1%)	373 (32.1%)	
Former	9249 (14.3%)	9057 (14.3%)	192 (16.5%)	
Current	29 582 (45.7%)	28 985 (45.6%)	597 (51.4%)	

Data are mean±SD and frequency (%). *P* values are for χ^2 test for categorical variables and *t* test for continuous variables.
*Comparing White to non-White women. BP indicates blood pressure; and PPI, proton pump inhibitor.

fully adjusted hazard model (HR, 1.16 [95% CI, 1.06–1.27]). Adjusting for interactions between BMI*smoking, BMI*treated diabetes, and BMI*treated hypercholesterolemia did not also affect the main results (HR, 1.17 [95% CI, 1.08–1.27]).

The association between PPI use duration categories (non-user, <1 year, 1–3 years, >3 years) and hypertension is shown in Table 3. The age-adjusted model showed a significant trend for higher hypertension risk with longer PPI duration of use compared with nonusers (HRs, 1.30, 1.40, 1.57, respectively; *P* for trend <0.0001). This trend was attenuated but remained significant upon further adjustments (fully adjusted HRs, 1.13, 1.17, 1.28, respectively; *P* for trend <0.001).

Table 4 shows the results of stratified analyses. The association between PPI use and hypertension risk was stronger in women ages 50 to 59 years (HR, 1.24) versus older age groups (HR, 1.17 for 60–69, 1.12 for 70 and above); however, the difference in HRs was not significant (interaction *P*=0.23). Those in the <30 kg/m^2 BMI category had a nonsignificant higher risk (HR, 1.17) compared with those in the ≥30 kg/m^2 category (HR, 1.10, interaction *P*=0.18). Those whose measured BP at baseline was SBP<120 mm Hg and DBP <80 mm Hg had a significantly higher risk (HR, 1.47, interaction *P*=0.0001) compared with SBP=120 to 139 or DBP=80 to 89 mm Hg (HR,1.11) and SBP ≥140 or DBP ≥90 mm Hg (HR,1.03). There were no differences in hypertension risk among those with or without treated diabetes.

Table 2. Rates and Hazard Ratios of Incident Hypertension According to Baseline PPI Use

Baseline PPI use	PPI nonuser	PPI user
No., %	63 558 (98.2%)	1162 (1.8%)
Incident hypertension cases (N)	28 332	619
Crude hypertension rate (per 1000 person-years)	51	71
	Hazard ratio (95% CI)	
Model 1	Ref (1.0)	1.38 (1.27–1.49)
Model 2	Ref (1.0)	1.36 (1.26–1.48)
Model 3	Ref (1.0)	1.31 (1.21–1.42)
Model 4	Ref (1.0)	1.18 (1.09–1.28)
Fully adjusted model	Ref (1.0)	1.17 (1.08–1.27)
Propensity score adjusted	Ref (1.0)	1.17 (1.15–1.19)

Cox proportional hazard regression model 1 adjusted for age. Model 2 includes age and demographic variables (education, income, race, ethnicity). Model 3 includes age and lifestyle variables (smoking history, smoking pack years, alcohol intake, Dietary Approaches to Stop Hypertension diet score, physical activity, and sleep duration). Model 4 includes age and clinical risk factors (family history, body mass index, treated diabetes, treated hypercholesterolemia, acetylsalicylic acid use, nonsteroidal anti-inflammatory drug use, corticosteroid use, hormone therapy use). Fully adjusted model includes all variables in models 1, 2, 3, and 4. Propensity score adjustment was done using inverse probability weighting of the propensity score estimated using age, demographic, lifestyle, and clinical risk factors. PPI indicates proton pump inhibitor.

Hypertension Risk by Year-3 PPI Use

The prevalence of PPI use increased at the year-3 clinic visit from 1.8% to 4.7% (n=2234) and 95.3% (n=45 435) were nonusers. Time-varying models showed PPI users had a 29% higher age-adjusted risk of hypertension compared with nonusers (HR, 1.29 [95% CI, 1.22–1.36]; Table S2). The association was attenuated but remained significant in the fully adjusted model (HR, 1.12 [95% CI, 1.05–1.19]). When using information from the year-3 visit as the beginning of hypertension follow-up, PPI users had a 34% higher age-adjusted risk of hypertension (HR, 1.34 [95% CI, 1.25–1.43]) and the risk was attenuated but remained significant in the fully adjusted model (HR, 1.17 [95% CI, 1.09–1.25]). Using propensity score adjustment did not change the results from the fully adjusted model (HR, 1.17 [95% CI, 1.14–1.20]; Table S3).

When examining the change in PPI use between baseline and year-3 visits, the crude incident rate of hypertension (per 1000 person-years) was 75 in continued PPI users, 68 in new users, 57 in former users, and 51 in the never users. In the fully adjusted models, compared with PPI never users, the new and continued PPI users had significantly higher risk of hypertension (HR, 1.13 [95% CI, 1.04–1.22]; HR, 1.20 [95% CI, 1.05–1.37], respectively) while there was no association in the former users (HR, 0.96 [95% CI, 0.77–1.19]; Table 5).

Blood Pressure Change by PPI Use

PPI new users had significantly higher 3-year change in SBP (+3.39 mm Hg, *P*=0.049) compared with never users, whereas changes in SBP in continued and former users were not significant (Table 6). There were

Table 3. Rates and Hazard Ratios of Incident Hypertension According to Baseline PPI Dration

Baseline PPI use	Nonuser	<1 y	1–3 y	>3 y	
Overall N, %	63 558 (98.2)	500 (0.8)	517 (0.8)	145 (0.2)	
Incident hypertension cases	28 332	254	282	83	
Crude incidence rate per 1000 person-years	51	66	73	83	
	Hazard ratio (95% CI)				*P* value for trend
Model 1	Ref (1.0)	1.30 (1.15–1.47)	1.40 (1.25–1.58)	1.57 (1.26–1.95)	<0.0001
Model 2	Ref (1.0)	1.28 (1.13–1.45)	1.41 (1.25–1.58)	1.52 (1.23–1.89)	<0.0001
Model 3	Ref (1.0)	1.26 (1.11–1.42)	1.32 (1.17–1.48)	1.47 (1.18–1.84)	<0.0001
Model 4	Ref (1.0)	1.12 (0.99–1.27)	1.20 (1.06–1.35)	1.30 (1.04–1.61)	<0.0001
Fully adjusted model	Ref (1.0)	1.13 (0.99–1.28)	1.17 (1.04–1.33)	1.28 (1.03–1.61)	<0.001

PPI indicates proton pump inhibitor. Covariates for Cox proportional hazard regression models as in Table 2.

no significant 3-year changes in DBP according to PPI use (Table S4).

DISCUSSION

In a large cohort of older menopausal women enrolled from the community setting into the WHI-OS, PPI use at baseline was associated with a 17% higher risk of incident hypertension compared with nonuse over an average follow-up of 8.7 years. The association remained significant after controlling for demographic, lifestyle, and clinical risk factors. Propensity score adjustment to account for residual confounding showed similar results. PPI use duration showed a statistically significant incremental positive trend with incident hypertension ($P<0.001$), where those using >3 years had a 28% higher multivariable adjusted risk. Stratified analysis by baseline subgroups showed that risk of developing hypertension was significantly greater in those whose baseline measured BP was within normal range (SBP <120 and DBP <80 mm Hg) as compared with their counterparts with higher BPs at baseline. Women who had become new PPI users by year-3 clinic exam had a 13% higher risk of hypertension, and continued users had 20% higher risk of hypertension, whereas former users had no significant association. Moreover, PPI new users had significantly higher 3-year change in measured SBP (+3.39 mm Hg) whereas no significant change was observed in continued and former users. Overall, the present findings support the hypothesis that PPI use is associated with increased hypertension risk in older women.

The literature on PPI use and BP regulation is scarce. Hove et al. conducted a clinical trial on men with diabetes

Table 4. Association of Incident Hypertension and Baseline PPI Use (No, Yes) Stratified by Baseline Subgroups

	PPI nonuser (referent)			PPI user				
Subgroups	No.	Hypertension cases	Crude rate*	No.	Hypertension cases	Crude rate	Hazard ratio (95% CI)	*P* for interaction
Age groups, y								0.23
50–59	23 204	8891	40	350	172	61	1.24 (1.06–1.44)	
60–69	27 353	12 744	54	523	281	71	1.17 (1.04–1.32)	
≥70	13 001	6697	70	289	166	85	1.12 (0.95–1.31)	
Body mass index groups								0.18
<30 kg/m^2	50 395	21 072	46	760	381	64	1.17 (1.05–1.30)	
≥30 kg/m^2	12 423	6943	75	387	229	85	1.10 (0.96–1.26)	
Blood pressure								0.0001
SBP < 120 and DBP <80	25 553	6237	23	382	141	41	1.47 (1.24–1.75)	
SBP=120–139 or DBP=80–89	26 728	13 608	61	544	294	73	1.11 (0.98–1.25)	
SBP ≥140 or DBP ≥90	11 192	8447	135	234	183	149	1.03 (0.89–1.20)	
Treated diabetes								0.64
No	62 189	27 454	50	1114	585	69	1.17 (1.08–1.28)	
Yes	1300	846	111	48	34	127	1.14 (0.79–1.63)	

*Crude rate per 1000 person-years. All Cox proportional hazard regression models are fully adjusted for age, demographic, lifestyle, and clinical risk factors as in Table 2. DBP indicates diastolic blood pressure; PPI, proton pump inhibitor; and SBP, systolic blood pressure.

Table 5. Rates and Hazard Ratios of Incident Hypertension According to Change in PPI Use at Year 3

Baseline PPI use	PPI never user	PPI new user	PPI continued user	PPI former user
Overall N, %	45 182 (94.8%)	1720 (3.6%)	514 (1.1%)	253 (0.5%)
Incident hypertension cases	16 473	742	235	92
Crude incidence rate per 1000 person-years	51	68	75	57
	Hazard ratio (95% CI)			
Model 1	Ref (1.0)	1.31 (1.21–1.41)	1.43 (1.26–1.63)	1.09 (0.89–1.34)
Model 2	Ref (1.0)	1.30 (1.20–1.40)	1.43 (1.26–1.63)	1.08 (0.88–1.32)
Model 3	Ref (1.0)	1.27 (1.18–1.37)	1.34 (1.18–1.54)	1.05 (0.84–1.30)
Model 4	Ref (1.0)	1.17 (1.08–1.26)	1.18 (1.04–1.34)	0.99 (0.80–1.22)
Fully adjusted model	Ref (1.0)	1.13 (1.04–1.22)	1.20 (1.05–1.37)	0.96 (0.77–1.19)

Covariates for Cox proportional hazard regression models are as in Table 2. PPI indicates proton pump inhibitor.

where 20 participants were randomized to a PPI and 21 participants were given a placebo for 12 weeks.[27] Ambulatory BP was measured at baseline and at the end of the trial. They found a significant increase in daytime SBP in those given PPIs (mean±SD, baseline: 142±18, 12 weeks: 149±15 mm Hg) versus placebo (baseline: 145±16, 12 weeks: 138±16 mm Hg; *P* value for difference in change=0.01). A significant increase in daytime DBP was also observed in those given PPIs (baseline: 70±6, 12-weeks: 72±6 mm Hg) versus placebo (baseline: 74±7, 12 weeks: 71±9 mm Hg; *P* value for difference=0.02). This trial was the first to show an effect of PPIs on BP. However, it was limited by small sample size (n=41), short duration of PPI use (12 weeks), and being restricted to men with diabetes, which affected the generalizability of its findings. Another trial was conducted by Montenegro et al. on healthy men to examine the effect of PPIs on NO production and BP regulation.[11] The trial involved 15 participants who were given a PPI or placebo and then administered an oral sodium nitrite. Nitrite ingestion resulted in acute lowering of SBP in the placebo group (lowest mean-6±1.26 mm Hg). However, no significant change in SBP was observed when participants were given a PPI. Moreover, they found that PPIs greatly reduced intragastric NO formation after oral nitrites as measured directly in expelled stomach gas by chemiluminescence. This trial provided further evidence that PPIs could affect BP regulation and supported the hypothesis that this is mediated by NO production in the stomach. However, it measured only acute changes in BP and did not investigate the impact of long-term PPI use. Whether there would be subsequent changes in risk of developing hypertension was not evaluated. It should be noted that small changes in measured BP could have an appreciable impact on hypertension prevalence. A study by Fan et al. estimated that a 4/2 mm Hg increase in SBP/DBP could increase hypertension prevalence in a population from 33.4% to 41.4%.[28]

To the best of our knowledge, our study is the first to investigate the association between PPI use and incident hypertension in a prospective cohort study design. We found that PPI use is associated with increased risk of hypertension and that the association was robust to controlling relevant lifestyle and clinical factors, to the potential effect of death as a competing risk, and to time-varying PPI use and covariate information. Moreover, PPI new users had a significant increase in mean SBP measured in the clinical setting over a 3-year interval. This suggests that PPI use could have an impact on BP regulation and longer-term hypertension development. Those who reported the longest duration of PPI use (>3 years) had the highest risk of developing hypertension. This underscores the importance of improving guidance for clinicians regarding BP monitoring during PPI use and the duration for which PPIs should be used by their patients.

Postulated mechanisms by which PPIs could affect BP have centered around endothelial dysfunction and NO production.[29–31] NO is the most potent endogenous

Table 6. Mean Systolic Blood Pressure According to PPI Use at Baseline and Year 3

PPI use	PPI never user	PPI new user	PPI continued user	PPI former user
Overall N, %	45 182 (94.8%)	1720 (3.7%)	514 (1.1%)	253 (0.5%)
Crude baseline SBP, mm Hg	120.60 (0.07)	121.51 (0.37)†	123.07 (0.67)†	121.31 (0.97)
Crude year-3 SBP, mm Hg	121.75 (0.08)	123.51 (0.39)†	123.71 (0.71)†	122.17 (1.02)
Adjusted difference in SBP, mm Hg*	2.54 (0.83)	3.39 (0.90)†	2.03 (1.04)	2.38 (1.24)

*Data are least squares mean±SE from linear regression. Model was fully adjusted including age, demographic, lifestyle, and clinical variables as in Table 2.
†*P* value <0.05 after Bonferroni post hoc test using never user as reference.

vasodilator and is essential in maintaining normal BP.[7] NO is produced via 2 pathways; the first is through the NO synthase enzyme in the endothelium, the second is the nitrate–nitrite–NO pathway, which depends on the acidic environment of the stomach.[8,9] An in-vitro study found that PPIs can directly inhibit NO synthase in human endothelial cells.[32] Several ex-vivo studies found that PPIs could reduce acetyl choline-induced relaxation in blood vessels, which further supports a direct effect on the endothelium.[33–35] Another animal study investigated the impact of PPIs on the nitrate–nitrite–NO pathway.[10] They found that pretreatment with a PPI blunted the BP-lowering effect of oral sodium nitrite. This has also been shown to be true in humans in the previously discussed trial by Montenegro et al.[11] It should be noted that the impact of PPIs on endothelial dysfunction is hypothesized to require long-term exposure (months to years) whereas the impact on nitrate–nitrite–NO pathway would require only short-term exposure as PPIs could suppress gastric acid production within days.[10,11,36] Moreover, the impact of PPIs on acid production is known to be reversible upon discontinuation.[37] Our findings suggest that the impact of PPIs on hypertension risk was found in those using PPIs for prolonged periods (>1 year). The new and continued users had an increased risk of hypertension whereas the former users had no significant association. Most approved indications for PPIs require only 4 to 8 weeks of treatment. Recent guidelines have emphasized the importance of prescribing PPIs according to recommended durations.[1,6]

The strengths of our study include the large cohort of older menopausal women in whom at present both PPI use and hypertension burden are high, use of medication inventories to define PPI use instead of self-report, ability to assess change in PPI use over 2 time points, ability to assess both measured BP and clinically diagnosed hypertension, the large number of incident hypertension cases within a follow-up period in which PPIs were predominantly prescription only, and substantial covariate data on demographic, lifestyle, and clinical factors that allowed extensive adjustment for relevant confounders to evaluate robustness of observed associations. Study limitations include possibility of reverse causation where PPI users might have had undiagnosed hypertension or a condition that strongly predisposes to developing hypertension. However, the main findings did not change when we excluded women with high measured BP at baseline (SBP ≥140 or DBP ≥90 mm Hg), nor when we controlled for major clinical factors and medications. Incident hypertension ascertainment was based on self-report and there is a possibility for outcome misclassification. However, the previous finding of strong test–retest reproducibility and agreement with Centers for Medicare & Medicaid Services medical claims data[18] enhances confidence that misclassification on hypertension status during follow-up is not fully accounting for the significant positive associations. In fact, because PPI use was assessed before hypertension case ascertainment, any misclassification on outcome would likely have resulted in a weaker association biased toward the null. Residual confounding, particularly confounding by indication, remains a concern given the observational study design. However, our findings were consistent after propensity score adjustment. Oral health status was not examined, which may affect the oral microbiome and the nitrate–nitrite–NO pathway.[38] Finally, because the WHI-OS was designed to study older menopausal women, additional investigation is needed to confirm our results in younger women and men.

Conclusions

PPI use was associated with increased risk of hypertension in menopausal women, with a significant trend according to longer duration of use. PPI new users showed a significant increase in measured SBP over a 3-year interval. Given the widespread use of PPIs in older adults, clinicians should consult guidelines for the appropriate indication and duration of PPI use to avoid potential adverse events.

ARTICLE INFORMATION

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Affiliations

Department of Epidemiology and Environmental Health, University at Buffalo—SUNY, Buffalo, NY (A.I.S., J.W.-W., A.E.M., K.M.H., M.J.L.); School of Pharmacy, University of Washington, Seattle, WA (S.L.G.); Department of Family Medicine, Warren Alpert Medical School of Brown University, Pawtucket, RI (C.B.E.); College of Pharmacy, The Ohio State University, Columbus, OH (M.D.); College of Medicine, Sulaiman AlRajhi University, Bukariyah, Saudi Arabia (N.S.); University of Texas Medical Branch, Galveston, TX (C.P.M.); Arbor Research Collaborative for Health, Ann Arbor, MI (D.L.); Department of Epidemiology & Biostatistics, University of California Irvine School of Population and Public Health, Irvine, CA (S.L.); Department of Medicine, Columba University Irving Medical Center, New York, NY (D.S.); and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (S.W.).

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figures S1–S3

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