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April 27, 2018

The Honorable Claire C. Cecchi
United Stated District Court, District of New Jersey
50 Walnut Street, Courtroom MLK 5B
Newark, NJ 07101

Re: **Defendants' Letter Brief in Support of Proposed Scheduling Order**
In Re: Proton-Pump Inhibitor Products Liability Litigation (No. II)
Case No. 2:17-md-02789-CCC-MF

Dear Judge Cecchi:

Defendants respectfully submit this letter in support of our proposed scheduling order, attached as Exhibit H. In light of recent action by FDA that expressly rejected Plaintiffs' primary theory of liability, Defendants suggest that the Court adopt a schedule that frontloads discovery and motion practice on the threshold issues of general causation and preemption, deferring full generic and case-specific discovery until after the Court decides these issues. If the Court is not inclined to do so, Defendants respectfully request that, at a minimum, the Court rule on dispositive motions on both general causation and preemption before the parties engage in time-consuming, expensive, and potentially wasteful case-specific discovery.

INTRODUCTION

It has been nearly three decades since FDA first approved PPI medications as safe and effective for use in the United States. PPIs were a major advance over the prior standard of care (H2-blockers and antacids), providing far more effective acid suppression and symptom relief. Since their approval, millions of Americans have taken PPIs, and the medications have had a dramatically positive impact on both clinical outcomes and patient quality of life.

In 2016, new observational studies raised questions about a potential association between chronic kidney disease ("CKD") and use of proton pump inhibitor medications ("PPIs"). Thereafter, but before the medical and regulatory communities had an opportunity to weigh in on the reliability of those studies, Plaintiffs' attorneys commenced a sprawling litigation, taking advantage of the natural overlap between a disease that is common in the general population and the large number of people who have taken PPIs at some point in their lives.

It is already apparent that Plaintiffs may have jumped the gun, raising the specter of a large, wasteful and disruptive litigation that has no sound scientific or regulatory basis. Indeed, both the medical and regulatory communities now have had the opportunity to weigh in, finding that the available evidence does not support a causal relationship between PPI use and CKD and that no changes should be made to the warnings provided in the PPI product labels. As a result, this case is different from many pharmaceutical product liability litigations, and a different approach to the sequencing and management of discovery is needed.

First, in 2017, prominent scientific and medical organizations reviewed the very data cited by plaintiffs in their Master Complaint and have determined that, because of significant methodological limitations, the data does not provide reliable evidence of causality. This conclusion is reflected in published statements of leading organizations such as the American Gastroenterological Association ("AGA") and the National Kidney Foundation. Indeed, no reputable organization in the field has concluded that PPI medications cause CKD.

Second, beginning in 2016, FDA conducted a formal review of the kidney safety of PPI medications and the adequacy of the relevant information included in the product labeling. That review, which included detailed analysis of the studies at issue here, concluded that significant potential sources of bias existed in the studies, the "evidence for causal association [was] too weak to offset [the] severe risk of bias," and "biological explanations [for an association with CKD] seem speculative at this time." Based on these findings, by late 2017, FDA determined that no changes should be made to the warnings provided in the product labeling for PPI medications and publicly announced its conclusions.

While the litigation ship has sailed, these developments raise significant questions regarding Plaintiffs' ability to provide reliable expert evidence and data to establish general causation. Defendants also believe that there are strong bases for a preemption defense, including FDA's regulatory determination which makes clear that Defendants could not independently have made any relevant changes to the existing warnings in PPI labeling.[1]

Accordingly, and against this unique backdrop, Defendants respectfully request the Court set a schedule that requires the parties to undertake limited discovery, to conduct *Daubert* hearings, and to brief summary judgment motions on the threshold issues of general causation and preemption before engaging in time-consuming, expensive, and disruptive full discovery of Defendants and individual Plaintiffs.[2] Early resolution of these threshold issues will advance the ultimate objective of the MDL process: addressing issues common to all Plaintiffs and providing valuable information that will help the Court and parties evaluate and resolve this litigation as efficiently as possible. Moreover, PSC's recent shotgun filings of thousands of lawsuits that name every conceivable PPI product and claim a wide array of kidney injuries, as well as the PSC's request to toll thousands of additional cases to allow time to identify proper defendants and injuries, make clear that most of these cases are not ready for case-specific adjudication, and thus no prejudice will come to Plaintiffs if the Court adopts Defendants' proposed schedule.

BACKGROUND

Observational Studies: Questions about CKD Risk with PPIs. None of the hundreds of clinical trials conducted over the last three decades have reported an association between PPI use and CKD. However, starting in 2016, certain observational studies raised questions about a

[1] Defendants also believe that Plaintiffs' design defect claims are preempted under the rationale in *Yates v. Ortho–McNeil–Janssen Pharm., Inc.*, 808 F.3d 281, 298 (6th Cir. 2015).

[2] Production of Plaintiff Fact Sheets ("PFS") and proof of use and injury records should occur simultaneously with the bifurcated approach Defendants are suggesting so as to allow the parties and the Court to determine which Defendants, if any, are properly in each case and to winnow the Plaintiff pool as appropriate.

potential risk. As the Court will hear at Science Day, those studies have significant methodologic limitations, which preclude them (either individually or as a group) from providing reliable evidence of causation. Indeed, the study authors themselves emphasize the inherent limitations of their studies and acknowledge that they do not establish causality. For example, the authors of the Lazarus 2016 study (the first and most widely cited study on this topic) note numerous limitations of their analysis and expressly state that the study "does not provide evidence of causality." (*See* Ex. A at 244-45.) Likewise, the authors of a recent meta-analysis evaluating the safety of PPIs concluded that the strength of the evidence linking PPI use and CKD was "low" and that causality "cannot be established." (*See* Ex. B at 8-9.)

Medical and Scientific Organizations: Evidence Is Low Quality and Insufficient for Causality. In 2017, the AGA—the preeminent U.S. medical association of gastroenterologists—published a review of the data on PPI use and CKD. AGA found that the overall quality of the evidence was "very low" and that, while "thought-provoking," the available studies have "inherent limitations" that preclude them from supporting causality. (*See* Ex. C at 707, 709 Table 1.) Based on this review, AGA recommended *against* routine monitoring of kidney function in patients treated with PPIs. (*See id.* at 706-07.) Likewise, the National Kidney Foundation (the leading organization in the U.S. dedicated to the awareness, prevention and treatment of kidney disease) has stated that, "[while] some studies suggest there is an increased risk of chronic kidney disease," "[i]t has not been proven that PPI use causes chronic kidney disease." (*See* Ex. D at 2.) Defendants are not aware of any reputable medical or scientific organization that has concluded otherwise.

FDA: Data Insufficient to Establish Causality / No Basis for Regulatory Action. In 2016, FDA's Office of Surveillance and Epidemiology ("OSE") reviewed the data purportedly linking PPI use with CKD, focusing on two of the key studies referenced by plaintiffs (Lazarus 2016 and Xie 2016). With regard to Lazarus, FDA identified problems with potential "confounding and outcome misclassification" and concluded that the data "does not permit a confident conclusion that identifies PPIs as a cause for CKD." (*See* Ex. E at FDA-00000027, FDA-00000037, FDA-00000041.) As to Xie 2016, FDA determined that the study findings are "subject to severe risk of bias," "evidence for causal association [was] too weak to offset [the] severe risk of bias," and "biological explanations [for an association with CKD] seem speculative at this time." (*See id.* at FDA-00000004, FDA-00000015-17.)

These OSE reviews coincided with FDA opening a Tracked Safety Issue ("TSI") for PPIs and CKD. FDA opens a TSI when FDA staff identify a potential signal of a serious risk with a medication, and FDA can take any corrective action necessary, including requiring labeling changes or withdrawing the medication. (*See* Ex. F at 1-3.) In October 2017, FDA completed its review and concluded that "no action is necessary at this time based on available information." In particular, the Agency did not request any changes to the PPI labeling. (*See* Ex. G at 6.)

In sum, the scientific, medical and regulatory communities reviewed the very studies Plaintiffs rely on and concluded that they do not establish causality and do not support any relevant changes to the PPI labeling. Given this, serious questions exist about Plaintiffs' ability to put forth reliable evidence establishing general causation. Further, based on FDA's regulatory determination, Defendants believe that plaintiffs' claims are preempted by federal law.

ARGUMENT

The Court Should Address General Causation and Preemption First. The *Manual for Complex Litigation* advises that, in complex proceedings like this one, courts "should tailor case-management procedures to the needs of the particular litigation and to the resources available from the parties and the judicial system." Federal Judicial Center, *Manual for Complex Litigation (Fourth)* § 10.1, at 8 (2004). The *Manual* also explicitly advises courts to "take[] up early" the issue of general causation, *id.* § 22.634, at 411, noting that general causation is a "pivotal" issue that may "provide the foundation for a dispositive motion," *id.* § 11.422, at 54–55. Following this recommendation, numerous MDL courts—including the court which oversaw the Nexium/fracture litigation—have structured discovery to focus initially on general causation.[3]

This litigation presents the quintessential case for early consideration of general causation. Recent scientific and regulatory evaluations consistently have found no sound scientific basis on which to conclude that there is a causal link between PPIs and CKD. Given that, addressing general causation at the outset has the potential of saving significant time and resources and may "preempt[] the need for almost all of the discovery" that otherwise would be undertaken. *In re Agent Orange Prod. Liab. Litig.*, 506 F. Supp. 762, 767-68 (E.D.N.Y. 1980). While such an approach defers certain case-specific discovery, it does not alter the burden that Plaintiffs undertook when they commenced this litigation—to provide reliable expert evidence and data to establish that PPI medications are capable of causing CKD. Moreover, considering the PSC's request for tolling and tacit acknowledgment that the lion's share of their cases are not yet ripe for case-specific discovery, presumably any interruption would (at most) only impact a small percentage of the plaintiffs.

Similarly, the potential that Plaintiffs' claims are preempted—for the prescription PPIs, over-the-counter PPIs, or both—also warrants early consideration by the Court. If the Court finds that FDA would not have permitted Defendants to independently make changes to the warnings provided with—and/or the design of—PPIs, Plaintiffs' state law claims would be subject to dismissal pursuant to the U.S. Supreme Court's holding in *Wyeth v. Levine*, 555 U.S. 555 (2009). Further, much of the discovery that would be relevant to general causation also would be relevant to preemption, making it relatively straightforward for the Court and parties to sequence the discovery in a way that focuses the litigation on potentially dispositive issues. Attached as Exhibit H is a proposed schedule that would implement this frontloaded approach. Under this schedule, *Daubert* hearings would take place in the fall of 2019.

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[3] *See, e.g.*, *In re Nexium Esomeprazole*, 662 F. App'x 528, 530 (9th Cir. 2016) (memorandum disposition); *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 800 (3d Cir. 2017); *In re Mirena IUD Prod. Liab. Litig.*, No. 16-2890, 2017 WL 4785947, at *3 (2d Cir. Oct. 24, 2017) (per curiam), *petition for cert. docketed*, No. 17-1037 (Jan. 22, 2018); *In re: Incretin-Based Therapies Prods. Liab. Litig.*, MDL No. 2452, Dkt. 2401 (S.D. Cal. Mar. 21, 2018); *In re: Incretin-Based Therapies Prods. Liab. Litig.*, MDL No. 2452, Dkt. 325 (S.D. Cal. Feb. 18, 2014); *In re Bextra & Celebrex Liab. Litig.*, MDL No. 1699, Dkt. 178, at 1-4 (N.D. Cal. Mar. 16, 2007); *In re Viagra Prods. Liab. Litig.*, MDL No. 1724, Dkt. 38, at 1 (D. Minn. June 30, 2006); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, MDL No. 1407, Dkt. 340, at 1 (W.D. Wash. Mar. 22, 2002).

Frontloading general causation and preemption will save the parties from conducting potentially dozens of depositions and producing millions of pages of documents about issues that are not relevant to those potentially dispositive defenses, including Defendants' marketing of PPIs. In the alternative, if the Court does not frontload general causation and preemption, it should at a minimum consider dispositive motions on those issues immediately after Plaintiffs complete all generally applicable discovery.[4] (*See* Ex. H at ¶¶ 1(b) & n.1, 2 [allowing additional time for marketing and other discovery without delaying dispositive motions].)

The Court Should Defer the Selection of, and Discovery in, Individual Cases for Early Trials. While common discovery is taking place (whether limited to general causation and preemption or not), the Court should not require the parties to conduct case-specific discovery beyond the production of PFS's, pharmacy records, and medical records. During recent discussions with the Court regarding bundling of complaints and tolling agreements, Plaintiffs' counsel advised the Court that they will need a substantial amount of time to identify which PPIs each Plaintiff used. As a result, the contours of the docket—including which Defendants belong in which cases—will not be clear for some time. Rather than rush to select cases that may not be representative of the docket as a whole, the Court should wait until it becomes clear which Plaintiffs can establish that they: (1) used certain PPIs, including which PPIs those Plaintiffs used; and (2) suffered a kidney injury following that use, as documented in medical records. Further, the Court's rulings on the dispositive motions will put the parties in the best position to decide which cases, if any, are appropriate for additional case-specific discovery (presumably, only those where plaintiffs have established use of a PPI and a kidney injury that followed PPI use). Until the docket becomes clearer, it is impossible for the Court and the litigants to select cases that will provide meaningful information to the parties.

Defendants' proposed schedule will not unduly delay case-specific discovery. While the parties complete production of PFS's and records, conduct common discovery, and brief dispositive motions, they can meet and confer to identify a process for selecting cases for early discovery and prepare a case management order governing further discovery in those cases, if needed. Those steps will ensure that, in the event the Court denies Defendants' motions, the parties are ready to move quickly to prepare cases for trial.

CONCLUSION

Accordingly, Defendants respectfully request that the Court adopt a scheduling order that limits the initial phase of discovery to the issues of general causation and preemption, with briefing and hearings on *Daubert* and summary judgment motions to follow immediately thereafter. If the Court declines to do so, Defendants request that, at a minimum, the Court provide for briefing and hearings on these threshold issues before the parties engage in expensive, time-consuming, and potentially unnecessary case-specific discovery.

[4] In conjunction with entering a schedule for discovery that is generally applicable to Defendants, Defendants also request that the Court establish reasonable limits on the volume of discovery Plaintiffs may conduct, including the number of custodial files and depositions Plaintiffs may take. Defendants are submitting a separate brief in support of their proposed case management order regarding discovery limits.

Dated: April 27, 2018

Respectfully submitted,

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Exhibit A

Original Investigation

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

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IMPORTANCE Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide and have been linked to acute interstitial nephritis. Less is known about the association between PPI use and chronic kidney disease (CKD).

OBJECTIVE To quantify the association between PPI use and incident CKD in a population-based cohort.

DESIGN, SETTING, AND PARTICIPANTS In total, 10 482 participants in the Atherosclerosis Risk in Communities study with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m^2 were followed from a baseline visit between February 1, 1996, and January 30, 1999, to December 31, 2011. The data was analyzed from May 2015 to October 2015. The findings were replicated in an administrative cohort of 248 751 patients with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m^2 from the Geisinger Health System.

EXPOSURES Self-reported PPI use in the Atherosclerosis Risk in Communities study or an outpatient PPI prescription in the Geisinger Health System replication cohort. Histamine$_2$ (H_2) receptor antagonist use was considered a negative control and active comparator.

MAIN OUTCOMES AND MEASURES Incident CKD was defined using diagnostic codes at hospital discharge or death in the Atherosclerosis Risk in Communities Study, and by a sustained outpatient estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 in the Geisinger Health System replication cohort.

RESULTS Among 10 482 participants in the Atherosclerosis Risk in Communities study, the mean (SD) age was 63.0 (5.6) years, and 43.9% were male. Compared with nonusers, PPI users were more often of white race, obese, and taking antihypertensive medication. Proton pump inhibitor use was associated with incident CKD in unadjusted analysis (hazard ratio [HR], 1.45; 95% CI, 1.11-1.90); in analysis adjusted for demographic, socioeconomic, and clinical variables (HR, 1.50; 95% CI, 1.14-1.96); and in analysis with PPI ever use modeled as a time-varying variable (adjusted HR, 1.35; 95% CI, 1.17-1.55). The association persisted when baseline PPI users were compared directly with H_2 receptor antagonist users (adjusted HR, 1.39; 95% CI, 1.01-1.91) and with propensity score–matched nonusers (HR, 1.76; 95% CI, 1.13-2.74). In the Geisinger Health System replication cohort, PPI use was associated with CKD in all analyses, including a time-varying new-user design (adjusted HR, 1.24; 95% CI, 1.20-1.28). Twice-daily PPI dosing (adjusted HR, 1.46; 95% CI, 1.28-1.67) was associated with a higher risk than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21).

CONCLUSIONS AND RELEVANCE Proton pump inhibitor use is associated with a higher risk of incident CKD. Future research should evaluate whether limiting PPI use reduces the incidence of CKD.

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Chronic kidney disease (CKD) affects approximately 13.6% of adults in the United States,[1] is associated with a substantially increased risk of death and cardiovascular events,[2] and accounts for a disproportionately large burden on the financial resources of Medicare.[1] The increasing prevalence of CKD among communities cannot be fully explained by trends in known risk factors, such as diabetes mellitus and hypertension, suggesting that other variables may contribute to the disease process.[3,4] Medication use may be a potential factor, particularly given tendencies toward polypharmacy.[5] Identifying iatrogenic risk factors for CKD may help to promote the rational use of medications and reduce the burden of CKD worldwide.

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in the United States, and it has been estimated that between 25% and 70% of these prescriptions have no appropriate indication.[6] The duration of use frequently extends beyond recommended guidelines.[7,8] There is also a trend toward PPI use in infants and children.[9,10] Since the introduction of PPIs to the US market in 1990, several observational studies have linked PPI use to uncommon but serious adverse health outcomes, including hip fracture,[11] community-acquired pneumonia,[12] *Clostridium difficile* infection,[13] acute interstitial nephritis,[14,15] and acute kidney injury (AKI).[16-18] It is plausible that PPI use may also be a risk factor for CKD, potentially mediated by recurrent AKI,[19,20] or by hypomagnesemia, which has been associated with PPI use[21] and with incident CKD.[22] To our knowledge, no population-based studies have evaluated the association between PPI use and the risk of CKD.

The objective of this study was to quantify the association between PPI use and incident kidney disease in the general population. We hypothesized that PPI use is an independent risk factor for CKD and that the use of Histamine$_2$ (H_2) receptor antagonists, another common class of medications used to treat gastroesophageal reflux disease, is not. As a secondary outcome, we also evaluated the association between PPI use and AKI. Analyses were performed in the Atherosclerosis Risk in Communities (ARIC) study, a long-running population-based cohort, and were replicated in patients receiving care in the Geisinger Health System, an integrated health system in rural Pennsylvania.

Methods

Study Design and Setting of the ARIC Study

The ARIC study is a prospective cohort study of 15 792 adults 45 to 64 years old who were recruited as a population-based sample from 4 US communities (Forsyth, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland). Participants attended the first visit between January 12, 1987, and March 29, 1990, and attended subsequent visits at 3-year intervals until their fourth visit between February 1, 1996, and January 30, 1999. Visit 5 occurred between June 1, 2011, and August 30, 2013. The dates of our study analysis were from February 1, 1996 (ARIC study visit 4) to December 31, 2011. The ARIC study has been approved by the institutional review boards at the University of Minnesota (Minneapolis), The Johns Hopkins University (Baltimore, Maryland), Wake Forest University (Winston-Salem, North Carolina), University of North Carolina (Winston-Salem), University of Texas Health Sciences Center at Houston, and University of Mississippi Medical Center (Jackson). Participants provided written informed consent. All participants were followed up through an annual telephone survey and a review of community hospital discharge lists until December 31, 2011. Deaths were determined by a telephone survey of alternative contacts and surveillance of local newspaper obituaries, state death lists, and death certificates from the Department of Vital Statistics. Further details about the ARIC study cohort have been published previously.[23]

Participants in the ARIC Study

For the present study, we included the 11 656 participants who attended visit 4. The ratio of urinary albumin level to creatinine level, an important risk factor for CKD, was first obtained at this visit, and few participants reported PPI use before 1996. Participants who were missing data for the estimated glomerular filtration rate (eGFR) or the ratio of urinary albumin to creatinine (n = 215) or who had an eGFR of less than 60 mL/min/1.73 m^2 (n = 725) were excluded. Participants with missing data for years of education, health insurance status, cigarette smoking, body mass index (BMI), mean resting systolic blood pressure, use of antihypertensive or anticoagulant medication, or prevalent hypertension, diabetes mellitus, or cardiovascular disease (n = 234) were also excluded, resulting in a study population of 10 482 participants. The use of the full data set with multiple imputation for missing variables did not change the inference; therefore, we used the complete case analysis. The study population for the secondary outcome of AKI excluded persons with known end-stage renal disease (ESRD) or an eGFR of less than 15 mL/min/1.73 m^2 (n = 50). Therefore, it included some participants with an eGFR of less than 60 mL/min/1.73 m^2 but was otherwise similarly constructed (n = 11 145).

Measurement of Incident Kidney Disease in the ARIC Study

Incident CKD was defined by diagnostic codes that indicated CKD at hospital discharge (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]) or death (*ICD-10-CM*) or by incident ESRD, as determined through linkage with the United States Renal Data System registry.[24,25] In an earlier validation study[24] that used at least a 25% decline in the eGFR to less than 60 mL/min/1.73 m^2 at a follow-up outpatient visit as a reference standard for CKD, the sensitivity of diagnostic codes for defining CKD was 35.5%, and the specificity was 95.7%. Incident AKI was defined by hospitalization or death, with *ICD-9-CM* or *ICD-10-CM* diagnostic codes of 584.x or N17.x, respectively.[26] Participants who died before developing CKD, were lost to follow-up, or had disease-free survival to December 31, 2011, were censored.

Measurement of PPI Use and Other Covariates in the ARIC Study

The use of PPIs and H_2 receptor antagonists was measured at the baseline study visit through direct visual inspection of pill bottles for all medications used during the preceding 2 weeks. Exposure to antihypertensive, anticoagulant, aspirin, statin,

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Table 1. Baseline Characteristics of the Study Populations

Variable	Atherosclerosis Risk in Communities Study				Geisinger Health System Replication Cohort			
	PPI Users (n = 322)	H_2 Receptor Antagonist Users[a] (n = 956)	Nonusers (n = 9204)	*P* Value	PPI Users (n = 16 900)	H_2 Receptor Antagonist Users[a] (n = 6640)	Nonusers (n = 225 211)	*P* Value
Age, mean (SD), y	62.8 (5.5)	63.1 (5.5)	62.5 (5.6)	.008	50.0 (15.9)	50.3 (16.3)	49.5 (16.3)	<.001
Male sex, %	42.5	39.3	44.4	.01	43.2	42.6	43.5	.32
White race, %	86.0	84.2	77.9	<.001	94.6	96.4	95.5	<.001
Education ≥12 y, %	81.7	79.4	81.8	.18	NA	NA	NA	NA
Health insurance, %	92.2	88.9	85.6	<.001	NA	NA	NA	NA
Annual household income, %								
≥$25 000	72.0	66.4	66.2		NA	NA	NA	NA
<$25 000	23.6	29.7	29.7	.22	NA	NA	NA	NA
No response	4.3	3.9	4.2		NA	NA	NA	NA
eGFR, mean (SD), mL/min/1.73 m^2	87.8 (13.4)	86.5 (13.5)	88.9 (13.1)	<.001	94.9 (17.7)	95.2 (18.2)	96.0 (18.0)	<.001
Ratio of urinary albumin to creatinine, median (IQR), mg/g	4.0 (2.0-7.5)	3.6 (1.8-7.1)	3.7 (1.7-7.5)	.71	NA	NA	NA	NA
Cigarette smoking, %								
Current	11.5	15.5	15.2		25.7	26.1	23.9	
Former	48.4	44.2	43.2	.23	26.4	25.4	23.9	<.001
Never	40.1	40.3	41.6		47.9	48.5	52.2	
BMI, mean (SD)	29.4 (5.3)	29.4 (5.8)	28.7 (5.6)	<.001	30.8 (7.3)	30.8 (7.4)	30.2 (7.1)	<.001
Systolic blood pressure, mean (SD), mm Hg	126.5 (18.3)	128.2 (18.6)	127.0 (18.8)	.16	126.4 (15.8)	128.2 (16.7)	128.0 (17.7)	<.001
Prevalent medical condition, %								
Hypertension	54.3	50.0	44.8	<.001	33.3	34.0	30.2	<.001
Diabetes mellitus	14.9	18.0	15.6	.14	10.8	9.7	10.4	.06
Cardiovascular disease	13.7	14.1	10.8	.003	11.3	11.8	8.7	<.001
Concomitant medication use, %								
Antihypertensive	55.3	48.5	39.9	<.001	32.0	31.3	20.6	<.001
ACE-I/ARB	16.8	13.4	12.9	.12	15.5	13.4	9.6	<.001
Diuretic	16.1	12.1	9.6	<.001	13.8	12.6	8.3	<.001
Aspirin	64.9	67.6	54.9	<.001	7.8	5.9	3.9	<.001
Nonsteroidal anti-inflammatory drug	27.6	32.8	33.2	.11	13.9	14.4	9.5	<.001
Statin	20.2	13.6	10.3	<.001	13.9	11.7	6.1	<.001
Anticoagulant	1.9	2.8	1.7	.04	2.5	2.9	1.1	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; H_2, histamine$_2$; IQR, interquartile range; NA, not available; PPI, proton pump inhibitor.

[a] For the purposes of this table, participants using both a PPI and an H_2 receptor antagonist were classified as PPI users. In the Atherosclerosis Risk in Communities study, this represented 24 of the 322 PPI users. In the Geisinger Health System replication cohort, this represented 815 of the 6640 PPI users.

diuretic, and nonsteroidal anti-inflammatory medications was measured in the same way. Subsequent exposure to PPIs and H_2 receptor antagonists was obtained as part of the annual telephone follow-up, which included questions about medication use starting in September 2006. At each telephone follow-up from 2006 onward, participants were asked to assemble all medications they were taking and to "read the names of all the medications prescribed by a doctor."

Baseline plasma and urinary creatinine levels were measured by the modified kinetic Jaffé method.[24] The equation developed by the Chronic Kidney Disease Epidemiology Collaboration was used to calculate the eGFR.[27] The urinary albumin level was measured using a nephelometer (BN100; Dade Behring or IMMAGE; Beckman).[24] Three domains of socioeconomic status were measured, including self-reported highest level of education, health insurance status, and annual household income in the previous 12 months. Cigarette smoking status was defined categorically as a current, former, or never smoker at baseline, and the BMI was derived. Prevalent hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or self-reported use of antihypertensive medication within the past 2 weeks. Prevalent diabetes mellitus was defined by a fasting blood glucose concentration of at least 126 mg/dL, a random glucose concentration of at least 200 mg/dL, self-report of a physician diagnosis of diabetes mellitus, or reported use of medication for diabetes in the past 2 weeks (to convert glucose concentration to millimoles per liter, multiply by 0.0555). Preva-

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lent cardiovascular disease was defined as a composite outcome of prevalent coronary heart disease or stroke at visit 4.

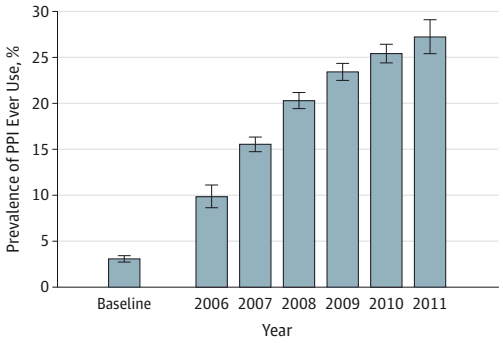
Geisinger Health System Replication Cohort

The replication cohort consisted of 248 751 patients with an outpatient eGFR of at least 60 mL/min/1.73 m^2 receiving care between February 13, 1997, and October 9, 2014, in the Geisinger Health System, a large rural health care system in central and northeastern Pennsylvania. Participants were selected at the earliest time point when they had both creatinine level and systolic blood pressure available. Incident CKD was defined as the first outpatient eGFR of less than 60 mL/min/1.73 m^2 that was sustained at all subsequent assessments of the eGFR or as the development of ESRD, which was ascertained through linkage to the United States Renal Data System registry. Incident AKI was defined as an *ICD-9-CM* code of 584.x, and death was ascertained through linkage to the National Death Index. Individuals who did not develop the outcome of interest were censored at their last follow-up or death. Medication use was determined by prescriber prescription within 90 days before baseline. The frequency of PPI use was categorized as once daily or twice daily according to the prescription and was assumed to be once daily if not specified. Comorbidities were captured by inpatient and outpatient billing codes.

Statistical Analysis

Baseline characteristics of PPI users and non-PPI users were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. The Wilcoxon rank sum test was used for continuous variables that were not normally distributed. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CIs of incident CKD associated with PPI use. The proportional hazards assumption was tested using Schoenfeld residuals. Exposure to PPIs was modeled as a binary variable at baseline and in secondary analyses as a time-varying ever-use variable, in which a participant was considered an ever user at the first instance of PPI use and at all time points thereafter. In the ARIC study, time-varying PPI use represented baseline use, with updates in 2006 and yearly thereafter; in the replication cohort, it was evaluated by assessing all health care professional prescriptions throughout the study period. In the ARIC study, adjustment was performed for demographic variables (age, sex, race, and study center), socioeconomic status (health insurance and highest level of education), clinical measurements (baseline eGFR, logarithm of the ratio of urinary albumin to creatinine, cigarette smoking, mean systolic blood pressure, and BMI), prevalent comorbidities (diabetes mellitus and cardiovascular disease), and concomitant use of medications (antihypertensive medication and anticoagulant medication). Annual household income and concomitant use of nonsteroidal anti-inflammatory drugs, aspirin, diuretics, or statin medications were considered possible confounders a priori; however, they did not affect the results of adjusted analyses and were not included in the final model. In the replication cohort, fewer comorbidities were available; therefore, analyses were adjusted for age, sex, race, baseline eGFR, cigarette smoking, BMI, systolic blood pressure, diabetes mellitus, history of cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Subgroup analyses were performed, stratified by the median age, sex, race (in the ARIC study only), diabetes mellitus, and concomitant medication use.

Figure 1. Prevalence of Proton Pump Inhibitor (PPI) Ever Use Over Time in the Atherosclerosis Risk in Communities Study



In the replication cohort, the risk of CKD was also evaluated in once-daily and twice-daily PPI users. Similar analyses were performed for the secondary outcome of AKI. Absolute risk differences were estimated as the difference between the expected 10-year risk among PPI users and the expected 10-year risk had they not used PPIs.

Five sensitivity analyses were performed. First, the study population was limited to participants using H_2 receptor antagonists or PPIs, and the risk of kidney disease associated with PPI use was assessed using H_2 receptor antagonists as the active comparator. Second, the association between PPI use and incident kidney disease was examined in a propensity score–matched cohort, in which logistic regression was used to estimate the probability of PPI use based on observable predictors of PPI use, and controls not using PPIs were selected using 1:1 nearest-neighbor matching. Third, a new-user design was used, whereby the risk associated with time-varying PPI ever use was assessed only among persons not using PPIs at baseline.[28] Given that new use was not available until 2006 in the ARIC study, this analysis was performed only in the replication cohort. Fourth, the association between H_2 receptor antagonist use and incident kidney disease was assessed as a negative control. Fifth, persons with a baseline ratio of urinary albumin to creatinine exceeding 30 mg/g (or 1+ protein on dipstick in the replication cohort) were excluded from the study population. All analyses were performed using statistical software (Stata/IC, version 13.1; StataCorp LP).

Results

Study Population

In the ARIC study, 10 482 participants were followed up for a median of 13.9 years. In the replication cohort, 248 751 participants were followed up for a median of 6.2 years. At baseline in both cohorts, PPI users were more likely than nonusers to have a higher BMI and take antihypertensive, aspirin, or statin medications

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Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease[a]

	Atherosclerosis Risk in Communities Study (n = 10 482)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

Abbreviations: CKD, chronic kidney disease; H_2, histamine$_2$; NA, not available; PPI, proton pump inhibitor.

[a] All analyses were adjusted unless otherwise specified. Adjustment variables for the Atherosclerosis Risk in Communities Study were age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, ratio of urinary albumin to creatinine, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, and anticoagulant medication use. Adjustment variables for the Geisinger Health System replication cohort were age, sex, race, baseline estimated glomerular filtration rate, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Propensity score–matched analyses were adjusted for propensity scores only, which were estimated using the same variables.

(**Table 1**). The characteristics of H_2 receptor antagonist users were similar to those of PPI users. The prevalence of ever use of PPIs increased substantially during the follow-up period (**Figure 1**).

Association Between PPI Use and Kidney Disease in the ARIC Study

In the ARIC study, there were 56 incident CKD events among the 322 baseline PPI users (14.2 per 1000 person-years), and 1382 events among 10 160 baseline nonusers (10.7 per 1000 person-years). In unadjusted analysis, participants who used PPIs at baseline had 1.45 (95% CI, 1.11-1.90; P = .006) times the risk of incident CKD relative to that of nonusers (**Table 2**). The risk was similar after adjustment for potential confounders, including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications (HR, 1.50; 95% CI, 1.14-1.96; P = .003), as was the association when PPI use was modeled as a time-varying ever-use variable (HR, 1.35; 95% CI, 1.17-1.55; P < .001). Subgroup analyses were consistent with the primary results (**Figure 2**). The 10-year estimated absolute risk of CKD among the 322 baseline PPI users was 11.8% while the expected risk had they not used PPIs was 8.5% (absolute risk difference, 3.3%).

A slightly stronger association was seen between PPI use and AKI (**Table 3**). For example, in unadjusted analysis, participants who used PPIs at baseline had 1.72 (95% CI, 1.28-2.30; P < .001) times the risk of incident AKI relative to those who did not report use. The corresponding risks were similar after adjustment for potential confounders (HR, 1.64; 95% CI, 1.22-2.21; P < .001) and when PPI use was analyzed as a time-varying ever-use variable (HR, 1.49; 95% CI, 1.25-1.77; P < .001).

Association Between PPI Use and Kidney Disease in the Replication Cohort

In the replication cohort, there were 1921 incident CKD events among 16 900 baseline PPI users (20.1 per 1000 person-years) and 28 226 events among 231 851 baseline nonusers (18.3 per 1000 person-years). Proton pump inhibitor use was significantly associated with incident CKD in unadjusted analyses (HR, 1.20; 95% CI, 1.15-1.26; P < .001), in adjusted analyses (adjusted HR, 1.17; 95% CI, 1.12-1.23; P < .001), and when estimated using a time-varying ever-use model (adjusted HR, 1.22; 95% CI, 1.19-1.25; P < .001) (Table 2). Twice-daily PPI dosing (adjusted HR, 1.46; 95% CI, 1.28-1.67; P < .001) was associated with a higher risk of CKD than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21; P < .001). The 10-year absolute risk of CKD among the 16 900 baseline PPI users was 15.6%, and the expected risk had they not used PPIs was 13.9% (absolute risk difference, 1.7%).

Similar associations were seen with incident AKI (Table 3). Proton pump inhibitor use resulted in a higher risk of incident AKI in unadjusted analysis (HR, 1.30; 95% CI, 1.21-1.40;

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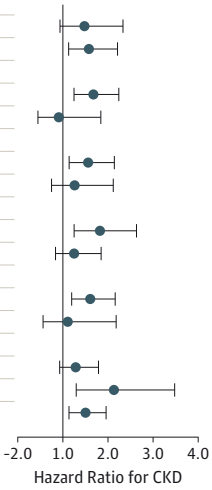
Figure 2. Association Between Proton Pump Inhibitor Use and Incident Kidney Disease Stratified By Subgroups

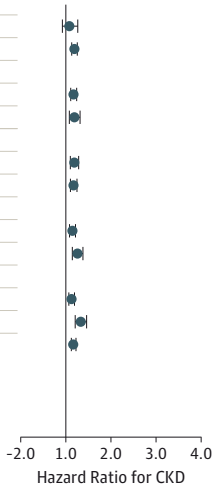
Atherosclerosis Risk in Communities Study

	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	556	5468	20	164
Old	882	5014	36	158
Race				
White	1060	8253	48	277
Black	378	2229	8	45
Diabetes mellitus				
No	982	8826	41	274
Yes	456	1656	15	48
Sex				
Male	757	4596	30	137
Female	681	5886	26	185
ACE-I/ARB use				
No	1148	9116	47	268
Yes	290	1366	9	54
Diuretics use				
No	1205	9433	38	272
Yes	233	1049	18	50
Overall	1438	10482	56	322

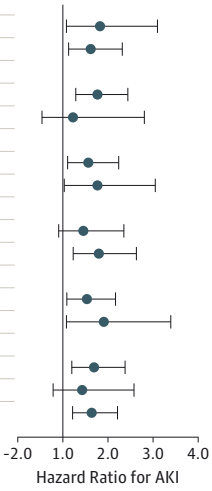


Geisinger Health System Replication Cohort

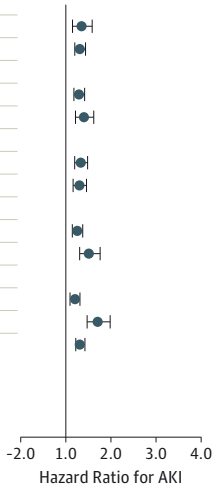
	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	2761	127542	1175	8518
Old	27386	121209	1746	8382
Diabetes mellitus				
No	22907	222829	1463	15081
Yes	7240	25922	458	1819
Sex				
Male	12808	108070	721	7304
Female	17339	140681	1200	9596
ACE-I/ARB use				
No	24694	223579	1380	14277
Yes	5453	25172	541	2623
Diuretics use				
No	25055	226879	1408	14569
Yes	5092	21872	513	2331
Overall	30147	248751	1921	16900



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	326	5617	15	174
Old	634	5528	32	184
Race				
White	1731	8768	41	309
Black	229	2377	6	49
Diabetes mellitus				
No	655	9316	33	300
Yes	305	1829	14	58
Sex				
Male	492	4891	18	151
Female	468	6254	29	207
ACE-I/ARB use				
No	734	9574	34	294
Yes	226	157	13	64
Diuretics use				
No	777	9903	36	294
Yes	183	1242	11	64
Overall	960	11145	47	358



	Overall Population		Baseline PPI Users	
	No. of Events	No. of Participants	No. of Events	No. of Participants
Age				
Young	2033	127542	168	8518
Old	8143	121209	560	8382
Diabetes mellitus				
No	7226	222829	516	15081
Yes	2950	25922	212	1819
Sex				
Male	5804	108070	384	7304
Female	4372	140681	344	9596
ACE-I/ARB use				
No	8398	223579	517	14277
Yes	1778	25172	211	2623
Diuretics use				
No	8568	226879	512	14569
Yes	1608	21872	216	2331
Overall	10176	248751	728	16900



Young refers to an age that is below the cohort median (62 years in the Atherosclerosis Risk in Communities study and 50 years in the Geisinger Health System replication cohort). ACE-I indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; and PPI, proton pump inhibitor.

P < .001), adjusted analysis (HR, 1.31; 95% CI, 1.22-1.42; P < .001), and time-varying ever-use analysis (adjusted HR, 1.54; 95% CI, 1.47-1.60; P < .001). Twice-daily PPI dosing (adjusted HR, 1.62; 95% CI, 1.32-1.98; P < .001) was associated with a higher risk of AKI than once-daily dosing (adjusted HR, 1.28; 95% CI, 1.18-1.39; P < .001).

Sensitivity Analyses

When compared directly with H_2 receptor antagonist use, PPI use was associated with incident CKD in the ARIC study (adjusted HR, 1.39; 95% CI, 1.01-1.91; P = .05) and in the replication cohort (adjusted HR, 1.29; 95% CI, 1.19-1.40; P < .001). Baseline PPI use was also associated with incident CKD in propensity score–matched analyses (HR, 1.76; 95% CI, 1.13-2.74; P = .01 in the ARIC study and HR, 1.16; 95% CI, 1.09-1.24; P < .001 in the replication cohort) and in the new-user analysis (adjusted HR, 1.24; 95% CI, 1.20-1.28; P < .001). The use of H_2 receptor antagonists was not associated with increased risk of incident CKD in either cohort (adjusted HR, 1.15; 95% CI, 0.98-1.36; P = .10 in the ARIC

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Table 3. Proton Pump Inhibitor Use and the Risk of Incident Acute Kidney Injury[a]

	Atherosclerosis Risk in Communities Study (n = 11 145)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	47	358	728	16 900
H_2 receptor antagonist users	104	1053	347	6640
Nonusers	809	9734	9101	225 211
Association Between PPI Use and Incident AKI	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.72 (1.28-2.30)	<.001	1.30 (1.21-1.40)	<.001
Baseline PPI use vs no PPI use	1.64 (1.22-2.21)	<.001	1.31 (1.22-1.42)	<.001
Time-varying PPI ever use vs never PPI use	1.49 (1.25-1.77)	<.001	1.54 (1.47-1.60)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.58 (1.05-2.40)	.03	1.30 (1.13-1.48)	<.001
Baseline PPI use vs propensity score-matched no PPI use	2.00 (1.24-3.22)	.005	1.29 (1.16-1.43)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.66 (1.57-1.75)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.03 (0.84-1.26)	.78	0.98 (0.89-1.10)	.78

Abbreviations: AKI, acute kidney injury; H_2, histamine$_2$; NA, not available; PPI, proton pump inhibitor.

[a] All analyses were adjusted unless otherwise specified. Adjustment variables for the Atherosclerosis Risk in Communities Study were age, sex, race, study center, education, health insurance status, baseline estimated glomerular filtration rate, ratio of urinary albumin to creatinine, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, and anticoagulant medication use. Adjustment variables for the Geisinger Health System replication cohort were age, sex, race, baseline estimated glomerular filtration rate, smoking status, body mass index, systolic blood pressure, diabetes mellitus, cardiovascular disease, antihypertensive medication use, anticoagulant medication use, and statin, aspirin, and nonsteroidal anti-inflammatory drug use. Propensity score–matched analyses were adjusted for propensity scores only, which were estimated using the same variables.

study and adjusted HR, 0.93; 95% CI, 0.88-0.99, $P = .03$ in the replication cohort). Similar results were obtained when persons with baseline albuminuria were excluded (adjusted HR, 1.45; 95% CI, 1.09-1.96; $P = .01$ in the ARIC study and adjusted HR, 1.19; 95% CI, 1.13-1.25; $P < .001$ in the replication cohort). Sensitivity analyses using AKI as an outcome were also consistent (Table 3).

Discussion

In a prospective community-based cohort of more than 10 000 adults, we found that baseline use of PPIs was independently associated with a 20% to 50% higher risk of incident CKD, after adjusting for several potential confounding variables, including demographics, socioeconomic status, clinical measurements, prevalent comorbidities, and concomitant use of medications. The observed association persisted when PPI exposure was modeled as a time-varying ever-use variable and was replicated in a separate administrative cohort of 248 751 individuals. The risk was specific to PPI medications because the use of H_2 receptor antagonists, which are prescribed for the same indication as PPIs, was not independently associated with CKD. Similar findings were demonstrated for the outcome of AKI and collectively suggest that PPI use is an independent risk factor for CKD and for AKI.

Previous studies[14-18] have also identified an association between PPI use and AKI, most specifically in the form of acute interstitial nephritis. Our study adds to the existing literature by describing an association between PPI use and incident CKD. We note that our study is observational and does not provide evidence of causality. However, a causal relationship between PPI use and CKD could have a considerable public health effect given the widespread extent of use. More than 15 million Americans used prescription PPIs in 2013, costing more than $10 billion.[29] Study findings suggest that up to 70% of these prescriptions are without indication[6] and that 25% of long-term PPI users could discontinue therapy without developing symptoms.[30] Indeed, there are already calls for the reduction of unnecessary use of PPIs.[31]

Observational cohort studies represent one of the best methods to study adverse effects of medications used in real-world settings. However, several limitations inherent in observational design must be considered. First, unlike a randomized clinical trial, participants who are prescribed PPIs may be at a higher risk of CKD for reasons unrelated to their PPI use. For example, PPI users in both the ARIC study and the replication cohort were more likely to be obese, have a diagnosis of hypertension, and carry a greater burden of prescribed medications. In recognition of this potential bias, we performed adjustment for multiple confounders, including BMI, hypertension, diabetes mellitus, and concomitant medication use, compared PPI users directly with H_2 receptor antagonist users, and conducted propensity score–matched analyses. Each of these sensitivity

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analyses showed a consistent association between PPI use and a higher risk of CKD.

A second limitation of our study is the potential for surveillance bias, whereby outcome assessment might have occurred more often in persons using PPIs. In the ARIC study, incident CKD was detected using hospitalization discharge codes, while outpatient creatinine levels were used in the replication cohort. However, the association between PPI use and new CKD persisted after accounting for predictors of more frequent contact with the medical system such as insurance status and comorbid illness. A third limitation is the low sensitivity of hospital discharge codes for diagnosing CKD in the ARIC study. However, the study results were replicated in the Geisinger Health System cohort, in which CKD was defined by direct laboratory measurements. Fourth, the inclusion of baseline PPI users can invoke selection bias, whereby baseline users represent a special group of PPI users who tolerate the medication without the development of CKD. In our study, there were few prevalent PPI users at baseline, which should lead to less bias.[32] In addition, the results were replicated in a new-user design in the replication cohort, in which baseline PPI users were excluded. A fifth potential limitation is that neither PPI nor H_2 receptor antagonist use was captured as directly observed therapy. In recent years, both have become available over the counter in the United States. Therefore, medication exposure in the ARIC study and the replication cohort may have been misclassified.

Notable strengths of the ARIC study include a large representative community-based sample, baseline visits occurring soon after PPIs were introduced into the United States, visual confirmation of medications used, comprehensive data pertaining to potential confounders, and close monitoring for more than 13 years of follow-up. Sensitivity analyses, including a time-varying exposure model, propensity score matching, and replication in a large second cohort, showed robust results. We also demonstrated specificity to PPI use rather than H_2 receptor antagonist use.

Conclusions

In summary, we found that PPI use is an independent risk factor for CKD and AKI, but H_2 antagonist use is not. Further research is required to investigate whether PPI use itself causes kidney damage and, if so, the underlying mechanisms of this association.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lazarus, Grams.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Lazarus, Chen, Sang, Grams.
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Exhibit B

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Original Article

The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis

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ABSTRACT

Background: Existing epidemiological studies illustrate that proton pump inhibitors (PPIs) may be related to adverse kidney outcomes. To date, no comprehensive meta-analysis has been conducted to evaluate and quantify this association.

Methods: We performed a systematic review and meta-analysis of studies to assess the association between PPI use and the risk of adverse kidney outcomes. We searched MEDLINE, Embase, SCOPUS, Web of Science, CINAHL, Cochrane Library and grey literature with no language restrictions (through 31 October 2016). Adverse kidney outcomes were acute interstitial nephritis (AIN), acute kidney injury (AKI), chronic kidney disease (CKD) and end-stage renal disease (ESRD). The risk ratios (RRs) and confidence intervals (CIs) were pooled using a random effects model. The strength of evidence (SOE) for each outcome was assessed using the Grading of Recommended Assessment, Development and Evaluation system.

Results: Of 2037 identified studies, four cohort and five case–control studies with ∼2.6 million patients were included. Of these, 534 003 (20.2%) were PPI users. Compared with non-PPI users, PPI users experienced a significantly higher risk of AKI [RR 1.44 (95% CI 1.08–1.91); P = 0.013; SOE, low] and CKD [RR 1.36 (95% CI 1.07–1.72); P = 0.012; SOE, low]. Moreover, PPIs increased the risk of AIN [RR 3.61 (95% CI 2.37–5.51); P < 0.001; SOE, insufficient] and ESRD [RR 1.42 (95% CI 1.28–1.58); P < 0.001; SOE, insufficient].

Conclusion: PPI usage was associated with adverse kidney outcomes; however, these findings were based on observational studies and low-quality evidence. Additional rigorous studies are needed for further clarification.

Keywords: acute interstitial nephritis, acute kidney injury, chronic kidney disease, meta-analysis, proton pump inhibitor

INTRODUCTION

The use of proton pump inhibitors (PPIs) has dramatically increased worldwide for common gastrointestinal diseases, such as gastroesophageal reflux disease, acid-related dyspepsia, gastroduodenal ulcers and the eradication of *Helicobacter pylori*. They are also used for long-term prophylaxis to decrease the risk of gastroduodenal lesions in patients taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants or antiplatelet therapy [1–3]. This pharmacological class has been used in both primary care and in hospital

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settings and accounts for a large portion of health care spending in several countries [4–7]. PPIs are available over-the-counter (OTC) in several countries [8, 9]. It was reported that >25 billion doses of PPIs were prescribed to patients in the USA from 2007 to 2011, amounting to US $79 billion [10]. Additionally, it is evident that >50% of PPI prescriptions are inappropriate or unnecessary, particularly for elderly patients [11–13].

Indeed, PPIs are considered safe and well-tolerated medications. The incidence of adverse events in pre-marketing trials was low and only minor and self-limiting events, including headache, abdominal pain, flatulence, diarrhoea, constipation, nausea and rashes, were reported [14, 15]. However, previous studies revealed that PPIs might elevate the risk of rare adverse events. These potential rare events are highlighted by the US Food and Drug Administration and Health Canada and include bone fractures, *Clostridium difficile* infection and hypomagnesemia [16–18]. PPIs have also been associated with community-acquired pneumonia, spontaneous bacterial peritonitis and dementia [19–21].

In addition, previous studies illustrated that PPIs may be associated with adverse kidney outcomes [22–26]. A large population-based study found a relationship between PPI use and the risk of acute interstitial nephritis (AIN) and acute kidney injury (AKI) [27]. Recently, prior studies on US cohorts were extended and demonstrated an association between long-term PPI usage and chronic kidney disease (CKD), probably mediated through AIN, recurrent AKI and hypomagnesemia [28–30]. Despite growing concern about the association between PPIs and adverse kidney outcomes, no systematic review or meta-analysis of this topic has been conducted. This study was therefore conducted to systematically review and synthesize the association between PPI use and the risk of adverse kidney outcomes. Evidence from this study can be used to promote rational prescriptions of PPIs in institutional and community settings.

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MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Method Guide for Effectiveness and Comparative Effectiveness Reviews, 2014 Edition [31] and the Meta-analysis of Observational Studies in Epidemiological Guidelines (Supplementary Data, Table S1) [32].

Search strategy

An experienced information specialist developed electronic search strategies using an iterative process and in collaboration with the search team. We searched electronic databases, including MEDLINE, Embase, SCOPUS, Web of Science, CINAHL and the Cochrane Library, from inception to 31 October 2016. The search strategy included pharmacological class or individual PPIs (e.g. proton pump inhibitors, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, dexlansoprazole) and adverse kidney outcomes (e.g. acute interstitial nephritis, acute kidney injury, chronic kidney disease, end-stage renal disease). Details of the search strategies are described in Online Appendix S1.

Grey literature from ClinicalTrial.gov, Google Scholar and jane.biosemantics.org were sought from inception to 31 October 2016 for the identification of additional studies. We also searched for the abstracts of conference proceedings from the major international nephrology and gastroenterology congresses (European Renal Association–European Dialysis and Transplant Association, American Society of Nephrology, International Society of Nephrology, American Gastroenterology Association, American College of Gastroenterology) between 2012 and 2016. Relevant studies were also sought from reference lists of included studies and prior systematic reviews.

Study selection and outcome measures

Eligible titles/abstracts and relevant full-text articles were screened independently by two investigators. A third party verified the accuracy. Any disagreement was resolved through a team discussion and/or consultation with the principal investigator (C.R.).

We included both experimental and observational studies that (Supplementary Data, Table S2) (i) evaluated the association between PPI use for any indications and the risk of adverse kidney outcomes, (ii) consisted of two or more groups in which one group represented PPI users and (iii) reported adverse kidney outcomes. We excluded studies that (i) were cross-sectional, case series/case reports, (ii) had no control group and (iii) included individuals who had a history of end-stage renal disease (ESRD) or received renal replacement therapy at the baseline. For studies with overlapping participants, the data with the longest duration, the most detailed information and/or the most relevant information were included.

The following adverse kidney outcomes were included: AIN, AKI, CKD and ESRD. Definite cases of AIN were defined as patients who presented with AIN, confirmed through pathologic results. The incidence of AKI, CKD and ESRD was defined according to the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [33, 34]. However, we defined the outcomes according to each study. If data were available, individual PPI use and dosage were investigated to explore the evidence of dose– and duration–response effects.

Data extraction

Two investigators independently extracted data using a predesigned electronic extraction form, including study characteristics, participant characteristics, intervention and predefined adverse kidney outcomes. The two investigators verified the data. Any discrepancies were resolved through a team discussion. For studies with missing data or uncertain information, the corresponding author was contacted. If the authors did not respond, the study was excluded.

Risk of bias and grading the strength of evidence (SOE)

Two investigators independently appraised the risk of bias for each included study according to the study design. However, we did not identify any clinical controlled trials. The Newcastle–Ottawa Scale (NOS) was therefore used to assess the methodological quality of included observational studies [35]. Studies were categorized as the highest quality if the summary score was >8 points. To interpret the findings, the two investigators independently assessed the SOE for each outcome using the Grading of Recommended Assessment, Development and

Evaluation (GRADE) system [36]. The SOE was ranked as insufficient, low, moderate or high. Any disagreements in the assessment of the risk of bias and grading of the SOE were resolved by a third reviewer.

Data synthesis

Only studies published in full-text were included in the data analysis to limit incomplete information [37]. However, to identify the potential influence of unpublished studies, post hoc meta-analysis was performed by adding relevant abstracts obtained from scientific meetings. For primary analysis, the risk of adverse kidney outcomes for PPI users was compared with that of non-PPI users. To maintain the consistency of result interpretations, histamine-2 receptor antagonists (H2RA) was identified as the active comparator in the secondary analysis.

When applicable, the relative risks (RRs) with the greatest degree of adjustment for potential confounding factors were identified as the common effect estimates of association across studies. The hazard ratios (HRs) were considered comparable to RRs. For studies that reported odds ratios (ORs), a corrected RR was computed using the methods described by Zhang and Yu [38]. The pooled RRs and 95% confidence intervals (CIs) were calculated using DerSimonian–Laird random effects models [39]. The number needed to harm (NNH) was calculated using event rates control from the Atherosclerosis Risk in Communities study, a prospective community-based cohort with an incidence of AKI and CKD among non-PPI users of 8.5% and 13.6%, respectively [29, 40].

Furthermore, the population attributable risks (PARs) were calculated to estimate the percentage of patients at risk of adverse kidney outcomes with PPIs. The PARs were computed with the formula $b[(r-1)/r]$, where b is the prevalence of PPI utilization and r is the pooled RRs estimated from the meta-analyses [41]. The prevalence of PPI utilization was derived from a national representative of the general population [42–44]. To approximate the number of individuals experiencing adverse kidney outcomes attributable to PPI use, we multiplied the PAR by the number of AKI and CKD cases worldwide, which was 13.3 and 497 million, respectively [45, 46].

Heterogeneity was evaluated by using the Cochran Q test, with $P < 0.10$. The I^2 index and τ^2 statistics were used to estimate the degree of inconsistency [47–49]. The heterogeneity was indicated as low ($I^2 \leq 25\%$, $\tau^2 \leq 0.04$), moderate ($I^2 > 25\%$ but $< 75\%$, $\tau^2 > 0.04$ but < 0.36) or high ($I^2 \geq 75\%$, $\tau^2 \geq 0.36$). A visually inspected funnel plot was used to investigate any evidence of publication bias. We also tested for funnel asymmetry using the Begg's and Egger's regression tests, with $P < 0.10$ [50, 51]. Additionally, the trim and fill method was employed to calibrate for publication bias [52].

Preplanned subgroup analyses were performed based on the included studies and participant characteristics. Where possible, dose– and duration–response effects were also identified. Moreover, the level of risk of bias, study characteristics and baseline study-level characteristics were pre-specified and included in a random effects univariate meta-regression to explore heterogeneity.

To address the robustness of the findings, five types of sensitivity analyses were conducted by (i) using fixed-effects models, (ii) restricting the analysis to studies with the highest quality (NOS ≥ 8 points), (iii) adjusting for key confounding factors (baseline kidney function and NSAID use), (iv) removing individual study approaches and (v) stratifying the analysis according to analytical methods.

Statistical significance for all tests was two-tailed, with $P < 0.05$. All analyses were performed using STATA software version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Search strategy

The systematic literature search details are presented in Figure 1. After screening all titles and abstracts, 110 full texts were retrieved and assessed for their eligibility against predefined inclusion/exclusion criteria. Of those, nine observational studies with 11 unique cohorts were evaluated (Table 1). The grey literature search did not provide any additional relevant abstracts and unpublished studies. Detailed definitions of all outcomes and methods in the included studies are provided (Supplementary Data, Tables S3 and S4).

Characteristics of included studies

Approximately 2.6 million participants were involved. The baseline mean age ranged from 49.9 to 66.2 years and the majority of the included studies did not provide baseline kidney function. The characteristics of the included studies and participants are summarized in Table 1 and Supplementary Data, Tables S5 and S6. The distribution of individual PPI use and comedication use at the baseline are described in Supplementary Data, Tables S7 and S8, respectively. According to the risk of bias determined by NOS, most of the included studies had high-quality summary scores ranging from 7 to 9 points (Supplementary Data, Table S9).

Adverse kidney outcomes

It was possible to pool four major adverse kidney outcomes, namely AIN, AKI, CKD and ESRD. The summary of findings and outcomes attributable to PPI utilization are illustrated in Tables 2 and 3. However, a subgroup analysis for each individual PPI and a dose– and duration–response effects assessment could not be performed due to lack of data (Supplementary Data, Table S10 and S11).

AIN

The use of PPIs was associated with a significantly increased risk of AIN compared with no PPI use [three studies [24, 26, 27], $n = 585\ 296$, pooled RR 3.61 (95% CI 2.37–5.51); $P < 0.001$; Table 2 and Supplementary Data, Figure 1A]. Because of limited data, it was impossible to perform a secondary analysis comparing PPIs to H2RA or to perform subgroup analysis.

AKI

Compared with non-PPI users, PPI users experienced a statistically higher risk of AKI [five studies [24, 25, 27, 29, 53],

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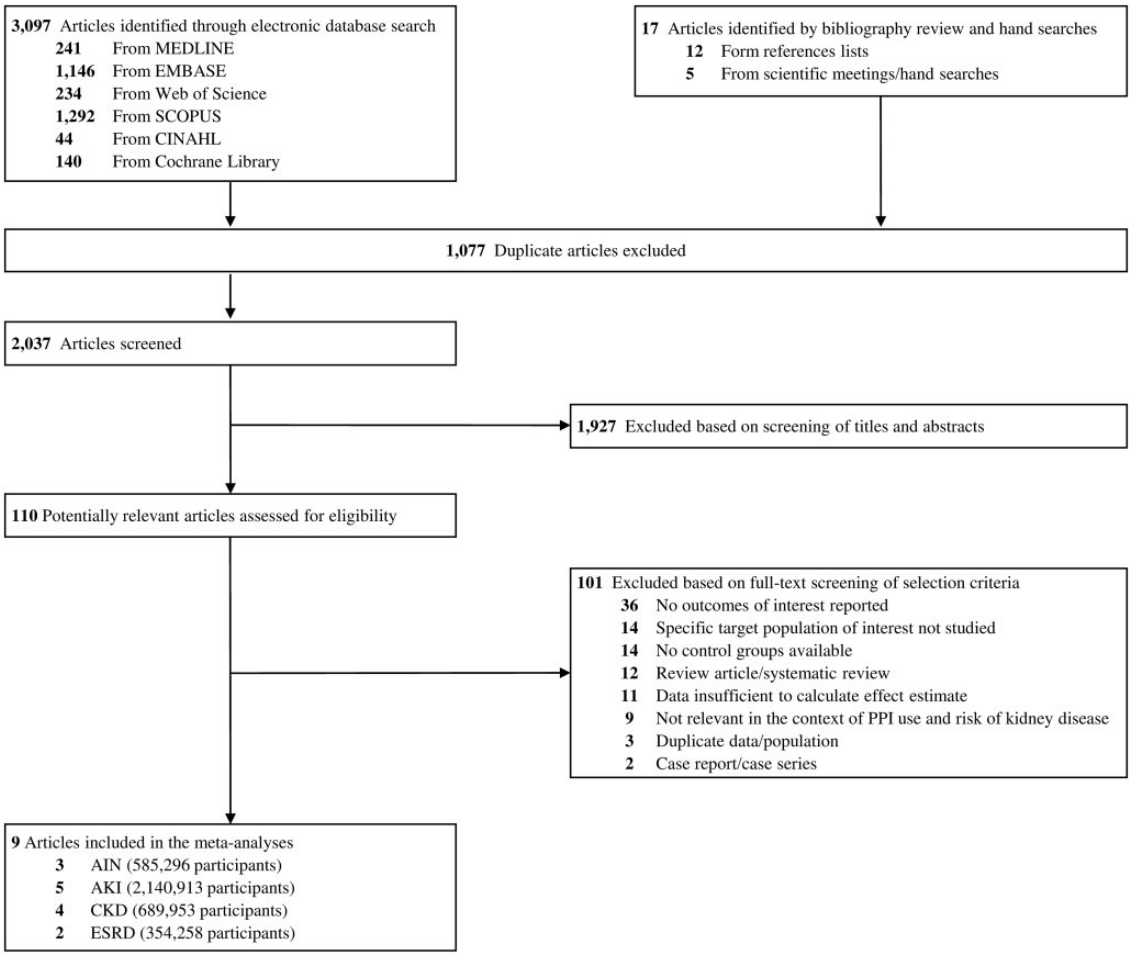

FIGURE 1: Flow chart of the literature review process. AIN, acute interstitial nephritis; AKI, acute kidney injury; CKD, chronic kidney disease; ERSD, end-stage renal disease; PPI, proton pump inhibitor.

$n = 2\ 140\ 913$, pooled RR 1.44 (95% CI 1.08–1.91); $P = 0.013$; NNH = 27 (95% CI 13–147), Table 2 and Figure 2A]. This significant and positive association existed even when H2RA was used as a comparator [pooled RR 1.32 (95% CI 1.17–1.51); $P < 0.001$; Table 2 and Supplementary Data, Figure 1B]. The PAR was found to range from 2.4 to 5.6%, suggesting that approximately 0.3–0.7 million cases with AKI worldwide were attributable to PPIs. However, the association between PPI use and AKI was insignificant in subgroup analyses where the analysis was restricted to only case–control studies or non-US study locations (Supplementary Data).

CKD

PPI users experienced a statistically higher risk of CKD compared with non-PPI users [four studies [28–30, 54], $n = 689\ 953$, pooled RR 1.36 (95% CI 1.07–1.72); $P = 0.012$; NNH 20 (95% CI 10–105); Table 2 and Figure 2B] and H2RA users [pooled RR 1.28 (95% CI 1.24–1.33); $P < 0.001$; Table 2 and Supplementary Data, Figure 1C]. The PAR was estimated to range from 2.1% to 4.9%, indicating that approximately 10.4–24.4 million cases of CKD worldwide are attributable to PPI use. Nonetheless, our subgroup analyses revealed no association between PPI use and the risk of CKD among older patients (age > 62 years), studies with large sample sizes (> 10 000 participants), case–control studies and the US study location (Supplementary Data, Table S13).

ESRD

The primary analysis demonstrated that PPI use was associated with increased risk of ESRD compared with no PPI use [two studies [30, 54], $n = 354\ 258$, pooled RR 1.42 (95% CI 1.28–1.58); $P < 0.001$; Table 2 and Supplementary Data, Figure 1D]. Owing to limited data, it was not possible to perform secondary and subgroup analyses.

Sensitivity analyses

For sensitivity analyses, we used fixed-effects models adjusted for key confounding factors (baseline kidney function and NSAID use). The stratified analysis performed according to the above analytical methods yielded main findings that were not significantly different. The summary results are provided in Supplementary Data, Tables S14, S15 and S16.

The positive association between PPI use and adverse kidney outcomes persisted even when we restricted our analysis to studies with the highest quality, except for AIN [RR 3.07 (95% CI 0.85–11.11); Supplementary Data, Table S17]. After the removal of the replication cohort studied by Lazarus *et al.* [29],

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Table 1. Characteristics of included studies in the systematic review and meta-analysis

Author, year	Study design	Country	Data source	Study period	PPI users, *n* (%)	PPI use defined as
Leonard *et al.* [24], 2012 (AIN Cohort)	Retrospective nested case–control	UK	Health care claims database	1987–2002	52 (1.5)	Baseline use: active orally administered PPI
Leonard *et al.* [24], 2012 (AKI Cohort)	Retrospective nested case–control	UK	Health care claims database	1987–2002	20 904 (1.5)	Baseline use: active orally administered PPI
Klepser *et al.* [25], 2013	Retrospective nested case–control	USA	Insurer's claims database	2002–5	317 (7.7)	Baseline use: having a PPI claim in the 90 days prior to the index date
Blank *et al.* [26], 2014[a]	Population-based, nationwide nested case–control	New Zealand	Health care claims and prescription claims database	2005–9	387 (48.9)[b]	Baseline use: dispensed at least once
Antoniou *et al.* [27], 2015	Population-based, retrospective cohort	Canada	Health care claims database	2002–11	290 592 (50.0)	Baseline use: new users of PPI
Arora *et al.* [28], 2016	Retrospective case–control	USA	Health care claims database	2001–8	22 734 (29.7)	PPI prescription filled during a quarter
Lazarus *et al.* [29], 2016 (ARIC Cohort)	Population-based, prospective cohort	USA	Prospective data collection from four US communities	1996–11	322 (3.1)	Baseline study visit through direct visual inspection of pill bottles and by a yearly telephone survey
Lazarus *et al.* [29], 2016 (GHS Replication Cohort)	Retrospective cohort	USA	Health care claims database	1997–14	16 900 (6.8)	Baseline use: PPI prescription within 90 days before the index date
Lee *et al.* [53], 2016	Retrospective cohort	USA	Joint venture research database	2002–8	3725 (24.7)	PPI users as pre-admission medication
Peng *et al.* [54], 2016	Population-based, nationwide case–control	Taiwan	Health care claims database	2006–11	4749 (62.4)	PPI users (NS)
Xie *et al.* [30], 2016[c]	Retrospective cohort	USA	Health care claims and prescription claims database	2006–13	173 321 (50.0)	Baseline use: new users of PPI

Continued

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Table 1. Continued

Author, year	Non-PPI use defined as	Age, years, mean (SD)	Female, *n* (%)	Baseline eGFR, mL/min/1.73 m^2, mean (SD)	UACR, mg/g, median	Total sample size	Follow-up time	Outcomes reported
Leonard *et al.* [24], 2012 (AIN Cohort)	Unexposed to PPI or NSAIDs	NR	1768 (51.8)	NR	NR	3415	NR	AIN
Leonard *et al.* [24], 2012 (AKI Cohort)	Unexposed to PPI or NSAIDs	NR	670 399 (49.6)	NR	NR	1 351 832	NR	AKI
Klepser *et al.* [25], 2013	Non-PPI users (NS)	51.1 (9.4)	1922 (36.4)	NR	NR	4143	NR	AKI
Blank *et al.* [26], 2014[a]	Past users (supply terminated >90 days before index date)	64.7 (13.8)	484 (61.1)	NR	NR	791	NR	AIN
Antoniou *et al.* [27], 2015	Non-PPI users: no PPI prescription	Median 74 (IQR 69–80)	329 448 (56.7)	NR	NR	581 184	Median 120 days, 188 869 PY	AIN, AKI
Arora *et al.* [28], 2016	Non-PPI (NS)	56.6 (14.8)	4682 (6.1)	NR	NR	76 462	NR	CKD
Lazarus *et al.* [29], 2016 (ARIC Cohort)	Non-PPI users and H2RA users	62.8 (5.6)	5882 (56.1)	87.75 (13.15)	3.6–4.0	10 482	Median 13.9	AKI, CKD
Lazarus *et al.* [29], 2016 (GHS Replication Cohort)	Non-PPI users and H2RA users: prescription within 90 days before index date	49.9 (16.3)	140 654 (56.5)	95.25 (17.99)	NR	248 751	Median 6.2	AKI, CKD
Lee *et al.* [53], 2016	Non-PPI users and H2RA users: pre-admission medication	66.2 (19.0)	6501 (45.6)	NR	NR	15 063	NR	AKI
Peng *et al.* [54], 2016	Non-PPI users (NS)	65.7 (13.4)	3643 (47.8)	NR	NR	7616	Mean 4.01 (SD 3.26)	ESRD
Xie *et al.* [30], 2016[c]	Non-PPI users: no PPI prescription	56.9 (12.3)	24 089 (6.9)	86.57 (15.85)	NR	346 642	5 (IQR 5–5)	CKD, ESRD

ARIC, Atherosclerosis Risk in Communities study; eGFR, estimated glomerular filtration rate; GHS, Geisinger Health System; IQR, interquartile range; NR, not reported; NS, not specified; PY, person-years; SD, standard deviation; UACR, urine albumin:creatinine ratio.

[a]Based on definite and probable cases of AIN.

[b]Defined as current users of PPIs. Dispensed supply extended into the 30-day period before the index date.

[c]Based on propensity score–matched cohort of new PPIs users and non-PPIs users.

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Table 2. Summary of findings and SOEs from studies assessing PPI use and the risk of kidney disease

Association between PPI use and kidney outcomes	Number of studies included	Number of participants	Risk ratio (95% CI)	P-value	Heterogeneity				NNH (95% CI)	SOE
					Q statistic	P-value	I^2 index	τ^2		
AIN										
PPI users vs. non-PPI users	3	585 296	3.61 (2.37–5.51)	<0.001	0.59	0.745	0.0%	<0.001	NA	Insufficient
PPI users vs. H2RA users	NA	NA	NA	NA	NA	NA	NA	NA		
AKI										
PPI users vs. non-PPI users	5	2 140 913	1.44 (1.08–1.91)	0.013	208.67	<0.001	97.6%	0.120	27 (13–147)	Low (harm: increased risk)
PPI users vs. H2RA users	1[a]	24 951	1.32 (1.17–1.51)	<0.001	0.77	0.379	0.0%	<0.001		
CKD										
PPI users vs. non-PPI users	4	689 953	1.36 (1.07–1.72)	0.012	650.38	<0.001	99.4%	0.070	20 (10–105)	Low (harm: increased risk)
PPI users vs. H2RA users	2	218 409	1.28 (1.24–1.33)	<0.001	0.27	0.873	0.0%	<0.001		
ESRD										
PPI users vs. non-PPI users	2	354 258	1.42 (1.28–1.58)	<0.001	1.39	0.238	28.1%	0.003	NA	Insufficient
PPI users vs. H2RA users	1	193 945	1.32 (1.28–1.37)	<0.001	NA	NA	NA	NA		

NA, not applicable.
[a]On the basis of the Atherosclerosis Risk in Communities study cohort and the Geisinger Health System replication cohort from Lazarus *et al.* [29].

Table 3. Adverse kidney outcomes attributable to PPI utilization in the general population

Prevalence of PPI utilization, %	Adverse kidney outcomes			
	AKI: RR 1.44 (95% CI 1.08–1.91)		CKD: RR 1.36 (95% CI 1.07–1.72)	
	PAR, % (95% CI)	AKI attributable to patients receiving PPI, in millions[a]	PAR, % (95% CI)	CKD attributable to patients receiving PPI, in millions[b]
7.7%; 1990–2014 CPRD, UK general population [42]	2.4 (0.6–3.7)	0.3	2.0 (0.5–3.2)	9.9
7.8%; 2011–2012 NHANES, a nationally representative survey of adults ≥ 20 years of age [43]	2.4 (0.6–3.7)	0.3	2.1 (0.5–3.3)	10.4
18.5%; 2010–11 NSHAP, a nationally representative survey of community-dwelling older adults 62–85 years old [44]	5.6 (1.4–8.8)	0.7	4.9 (1.2–7.7)	24.4

CPRD, Clinical Practice Research Datalink; NHANES, National Health and Nutrition Examination Survey; NSHAP, National Social Life, Health, and Aging Project; PAR, population attributable risk.
[a]On the basis of systematic review estimates of 13.3 million AKI patients worldwide [45].
[b]On the basis of systematic review estimates of 497 million CKD patients worldwide [46].

there was no association in AKI among PPI users and non-PPI users [RR 1.47 (95% CI 0.99–2.16)]. Furthermore, the association between PPI users and CKD became statistically insignificant after the study by Peng *et al.* [54] was omitted [RR 1.35 (95 % CI 0.99–1.86)]. Supplementary Data, Table S18 presents the influence of each individual study according to the 'leave one approach'.

Assessment of heterogeneity and publication bias

Two analyses with AKI and CKD demonstrated a moderate-to-high degree of heterogeneity, with τ^2 and the I^2 index exceeding 0.04% and 75%, respectively (Table 2, Figure 2A and B). However, this heterogeneity was substantially reduced when H2RA users were used as a comparator ($P > 0.01$ for the Cochran *Q* statistic; Table 2).

A univariate meta-regression was feasible for AKI and CKD. The effect estimates are shown in Supplementary Data, Table S19. Nevertheless, the heterogeneity of the included studies was not explained by any of the baseline study-level characteristics or the risk of bias for AKI and CKD outcomes. No evidence of asymmetry was observed in the results of the Begg's and Egger's regression tests, with $P > 0.01$. The main results were not substantially different after calibration for publication bias by using the trim and fill method (Supplementary Data, Table S20). The

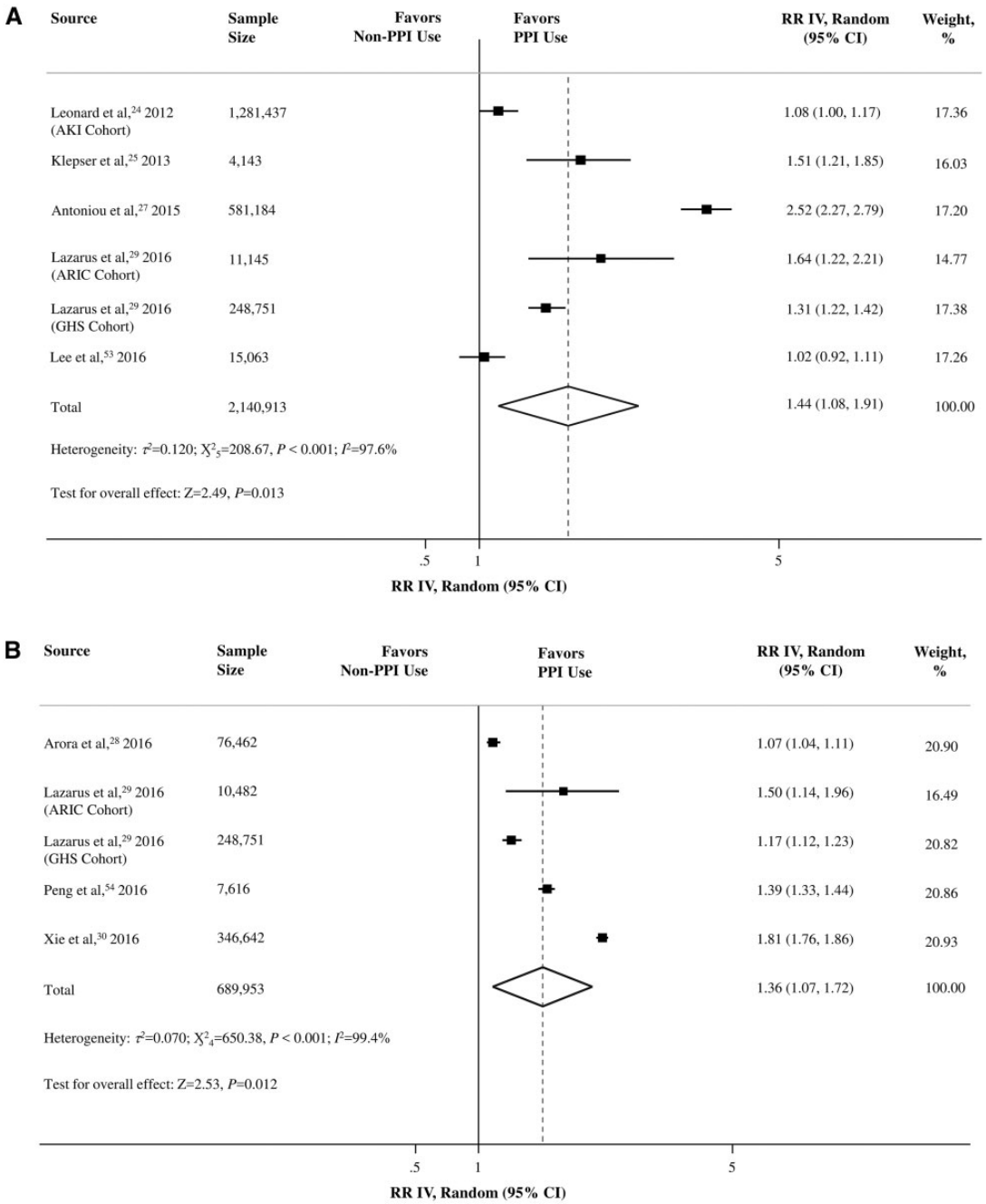

FIGURE 2: Risk ratio of kidney outcomes comparing PPI users versus non-PPI users. Forest plots showing risk ratio of (**A**) AKI and (**B**) CKD among PPI users compared with non-PPI users. AIN, acute interstitial nephritis; AKI, acute kidney injury; ARIC, Atherosclerosis Risk in Communities study; CI, confidence intervals; GHS, Geisinger Health System; IV, inverse variance; PPI, proton pump inhibitor; RR, risk ratio.

visually inspected funnel plots are shown in Supplementary Data, Figure 2.

Strength of the body of evidence

Using the GRADE system, we graded the SOE for AKI and CKD as low due to moderate study limitations, inconsistency and plausible confounding factors for the included studies. Meanwhile, AIN and ESRD were graded as insufficient because they were subject to high study limitations, were imprecise and the number of studies were limited. AIN cases could not be classified as definite due to a limited report of histologic confirmations. Details of evidence synthesis and GRADE evidence profiles are shown in Supplementary Data, Table S21.

DISCUSSION

This systematic review and meta-analysis indicated that PPI use is associated with an increased risk of adverse kidney outcomes including AIN, AKI, CKD and ESRD. Although these findings

challenge the value of PPIs in general practice, it should be noted that the strength of the body of evidence according to the GRADE system revealed low- or insufficient-quality evidence.

Our study expanded a previous systematic review [53] of case reports/case series that examined the relationship between the use of PPIs and AIN by including experimental and observational studies. Despite a comprehensive review, we did not find any clinical controlled trials. We therefore synthesized the results of the included cohort and case–control studies reporting the association between PPI use and additional adverse kidney outcomes.

To date, PPIs are some of the most common causes of AIN, particularly in elderly patients [23, 55, 56]. However, the mechanisms underlying AIN due to PPIs are not well established. Existing studies hypothesized that PPI-induced AIN is a result of a cell-mediated immune response, possibly idiosyncratic and likely characterized as dose independent [57, 58–60]. Interestingly, it has been reported that 30–70% of patients with AIN did not achieve complete kidney recovery after the discontinuation of PPIs [23, 58]. Partially recovered kidney function from PPI-induced AIN was reported in three biopsy-proven retrospective case series [23, 55, 61]. Consequently, it is speculated that undiagnosed, unrecognized and partial recovery from PPI-induced AIN could prime the kidney to develop subsequent AKI or CKD among PPI users [56].

Recently, an interconnected syndrome between AKI and CKD and progression to ESRD was recognized in large observational studies and meta-analyses [62–65]. AKI is a risk factor for CKD and CKD is a risk factor for developing AKI. Both share common risk factors and disease modifiers [62]. Although we found an association between PPI use and the risk of kidney progression, the results cannot be extrapolated to these interconnected conceptual models.

Several mechanisms are believed to explain the association between PPI use and the incidence of adverse kidney outcomes. A recent report by Yepuri *et al.* [66], for example, demonstrated that long-term PPI use may impair endothelial function and accelerate endothelial senescence, subsequently increasing oxidative stress, endothelial dysfunction and vascular senescence and contributing to the pathogenesis of the progression of kidney disease. Furthermore, PPI-induced hypomagnesemia could explain the association between PPI use and CKD, because magnesium deficiency can increase the risk of kidney progression through endothelial cell dysfunction, inflammation and oxidative stress [67–70]. In recent years, observational studies have shown that PPI use is associated with cardiovascular, neurological and kidney morbidity, which may reinforce the possibility of a mechanistic connection [21, 29, 30, 71].

Given the increasing use of PPIs worldwide, the risk of adverse kidney outcomes among PPI users could pose a substantial disease and financial burden to the health care system. Indeed, our study estimated that approximately 0.3–0.7 million AKI cases and 9.9–24.4 million CKD cases worldwide were attributable to PPI use. As more than 50–70% of PPI prescriptions are deemed inappropriate, in terms of both inappropriate initiation without indications and prolonged use without appropriate medical conditions [11–13, 72], the findings from our study support interventions or initiatives promoting appropriate PPI prescriptions, such as the Choosing Wisely PPI initiative and PPI deprescribing guidelines [1, 73, 74].

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis that reports the pooled association between PPI use and the risk of adverse kidney outcomes. This study was conducted using a rigorous and comprehensive approach without language restrictions and included a large number of participants. In addition, our sensitivity analyses, whereby H2RA users were used as an active comparator, showed consistent findings and confirmed a positive and significant association between PPI use and adverse kidney outcomes.

Several limitations of this review must be considered. First, despite a rigorous and comprehensive search, this meta-analysis is solely based on observational studies, which might be subject to selection bias and unmeasured confounders. Although several studies included sophisticated methods such propensity score analysis, confounding by indication and unmeasured confounders remain possible. In this regard, we concluded that the causality of PPI usage and adverse kidney outcomes cannot be established. Thus, caution should be employed when interpreting our findings.

Second, key baseline characteristics were not obtained across all included studies. Decreased estimated glomerular filtration rate and elevated albuminuria have been found to be associated with faster kidney disease progression [75–77]. However, only one study by Lazarus *et al.* [29] provided these data (Table 1 and Supplementary Data, Table S5). Another important limitation was that several studies allowed for concomitant medication use that might cause kidney deterioration, such as NSAIDs (range 5.4–86.7%, Supplementary Data, Table S8). This might affect the association between PPI use and adverse kidney outcomes.

Third, the included studies relied on electronic medical records and routinely collected administrative data, which might lead to information bias. Furthermore, we cannot verify the data on medication adherence over time, treatment indications and OTC prescriptions. Thus, misclassification bias should be noted.

Fourth, a moderate to high degree of inconsistency may limit our findings. We could not investigate the contribution of several studies regarding heterogeneity because of the small number of included studies. Additionally, various definitions of exposure and outcomes across studies may contribute to substantial heterogeneity between studies.

Finally, it is possible that publication bias exists. Although no evidence of asymmetry was found by the Begg's and Egger's tests, this method may be limited by the small number of included studies. However, after calibration with the trim and fill method, major findings remained unchanged.

Implications for public health and future research

Given the limited evidence, the results of this review represent the best available evidence that can inform the use of PPIs in general practice. Although the strength of the body of evidence and the magnitude of the association between the use of

PPIs and the risk of kidney outcomes are small, the clinical importance of these findings should be stated due to the increasing use of PPIs and the growing incidence of AKI and CKD worldwide [45, 78]. Accordingly, clinicians should consider the clinical risk and potential benefits when prescribing PPIs. If prescribed, routine and proactive monitoring of kidney function during PPI use should be considered, particularly among patients with a pre-existing risk of kidney disease. To promote appropriate use of PPIs and reduce unnecessary economic consequences, a patient-centred program should be implemented. Patients should also be informed about the benefits and risks of PPIs.

Our findings underscore the need for further research to understand the association between the use of PPIs and kidney outcomes, especially long-term effects. Given their potential effects on kidney function, experimental animal models are also needed, which would help in understanding the pathogenesis and clarifying potential long-term effects. In addition, collaborative pharmacoepidemiological research and proactive post-marketing safety surveillance systems are required to assess whether the association between PPI use and kidney outcomes vary according to the individual PPI, PPI indications, patient age groups and medical history. The dose– and duration–response relationship between PPI use and kidney outcome also requires further exploration.

CONCLUSION

Our findings illustrated that the use of PPIs may increase the risk of adverse kidney outcomes, particularly AKI and CKD, but the results were limited by suboptimal quality and heterogeneity of the included studies.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

S.N., K.K., C.C., C.R. and R.A. had full access to all of the data in the study. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S.N., C.R., R.A. and K.T.; acquisition, analysis or interpretation of data: all authors; drafting of the manuscript: S.N., C.R. and K.T.; critical revision of the manuscript for important intellectual content: K.N. and K.T.; statistical analysis: S.N., K.K., C.C., W.C. and C.R.; administrative, technical or material support: R.A., W.C. and K.T. and study supervision: S.N. and C.R.

The lead authors (S.N. and C.R.) affirm that the article is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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CONFLICT OF INTEREST STATEMENT

None declared.

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Exhibit C

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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEWS

The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association

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BACKGROUND & AIMS: The purpose of this review is to evaluate the risks associated with long-term use of proton pump inhibitors (PPIs), focusing on long-term use of PPIs for three common indications: gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis. **METHODS:** The recommendations outlined in this review are based on expert opinion and on relevant publications from PubMed, EMbase, and the Cochrane library (through July 2016). To identify relevant ongoing trials, we queried clinicaltrials.gov. To assess the quality of evidence, we used a modified approach based on the GRADE Working Group. The Clinical Practice Updates Committee of the American Gastroenterological Association has reviewed these recommendations. *Best Practice Advice 1*: Patients with GERD and acid-related complications (ie, erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control. *Best Practice Advice 2*: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia). *Best Practice Advice 3*: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI. *Best Practice Advice 4*: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI. *Best Practice Advice 5*: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs. *Best Practice Advice 6*: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition. *Best Practice Advice 7*: Long-term PPI users should not routinely use probiotics to prevent infection. *Best Practice Advice 8*: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Dietary Allowance (RDA). *Best Practice Advice 9*: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12. *Best Practice Advice 10*: Specific PPI formulations should not be selected based on potential risks.

Use of proton pump inhibitors (PPIs) in non-institutionalized adults in the United States doubled from 3.9% in 1999 to 7.8% in 2012.[1] During the same period the number of studies reporting on PPI-related adverse effects also doubled (Figure 1). Many PPIs are inappropriately prescribed, but this review focuses on PPIs prescribed long-term for three common conditions: gastroesophageal reflux disease (GERD),[2,3] Barrett's esophagus (BE),[4,5] and NSAID bleeding prophylaxis.[6,7] Our aim is to succinctly review the risks associated with long-term use of PPIs, and to help practitioners weigh the risks and benefits of PPIs when given for these indications.

What Are the Potential Risks Associated With Long-term Use of PPIs?

Our summary of the evidence for potential PPI-associated adverse effects is given in Table 1. Table 2 summarizes the absolute and relative risks of PPIs based on published data regarding relative risk and the background incidence of the relevant adverse effect. Throughout this review, we have assumed a class effect regarding PPIs because there is no high quality evidence that PPI formulations significantly differ in their potential adverse effects.

Kidney Disease

Case reports have linked PPIs to acute interstitial nephritis (AIN) and acute kidney injury (AKI) since 1992.[8] In 2016, two studies received widespread attention because they connected PPIs to an excess risk for chronic kidney disease (CKD) not explained solely by risk for AKI.[9,10] The first of these studies, by Lazarus et al, examined a cohort of 10,482 patients who were actively followed and a larger cohort of 249,751 patients whose data was retrieved retrospectively.[9] After adjusting for confounders, the authors found that PPIs were associated with a 50% increase in the risk for CKD in the smaller cohort and a 17% risk increase in the larger cohort. The second study, by Xie et al, compared 173,321 PPI users with 20,270 H2RA users in a VA dataset.[10] The authors included only patients who had a normal eGFR at baseline, and followed patients for up

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Best Practice Recommendations

Best Practice Advice 1: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing and for long-term symptom control.

Rationale: PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is no evidence for or against PPIs in asymptomatic patients with healed esophagitis or for PPIs beyond 12 months.

Best Practice Advice 2: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia).

Rationale: Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. However, there is no high-quality evidence on which to base this recommendation.

Best Practice Advice 3: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.

Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients.

Best Practice Advice 4: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.

Rationale: The evidence that PPIs slow progression of Barrett's is low in quality but the evidence of PPI adverse effects is also low in quality. Because there is no high quality evidence on either side of this question, this is a weak recommendation and this decision should be individualized with patients.

Best Practice Advice 5: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs.

Rationale: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs, and this benefit is likely to outweigh PPI-related risks.

Best Practice Advice 6: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

Rationale: Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed.

Best Practice Advice 7: Long-term PPI users should not routinely use probiotics to prevent infection.

Rationale: There is no evidence for or against probiotics to prevent infections in long-term users of PPIs.

Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).

Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. Many adults fall below the RDA in several vitamins or minerals and, in these adults, it is reasonable to raise intake to meet the RDA regardless of PPI use.

Best Practice Advice 9: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12.

Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit.

Best Practice Advice 10: Specific PPI formulations should not be selected based on potential risks.

Rationale: There is no convincing evidence to rank PPI formulations by risk.

to 5 years for incident CKD, defined as an eGFR of less than 60 ml/min/1.73 m^2. They found a 1.8% absolute annual excess risk for CKD associated with PPIs compared to H2RAs. Also, the PPI-CKD relationship persisted despite adjusting for AKI, implying that not all of the observed risk could be attributed to AIN. Although there was evidence that patients who used PPIs for longer durations had higher risks for CKD, patients who used PPIs for two years or more actually appeared to be protected against CKD. These studies are thought-provoking but are retrospective analyses with inherent limitations. One cannot be certain whether their observations are best explained by PPIs or by uncaptured baseline differences between PPI users and non-users (for example, in the degree of severity within important comorbidity categories such as diabetes).

Dementia

Build-up of amyloid-β (Aβ) protein predisposes to Alzheimer's disease. Microglial cells use V-type ATPases to degrade amyloid-β, and PPIs may block V-ATPases to increase isoforms of amyloid-β in mice.[11] Building on this, two recent clinical studies tested for an association between exposure to PPIs and dementia. Haenisch et al followed 3,327 non-institutionalized German adults aged 75 years or more with serial neuropsychiatric examinations. PPIs were associated with a 38% increased risk for dementia, with similar risk increases for Alzheimer's and non-Alzheimer's dementia.[12] Gomm et al extended these results by retrospectively querying an insurance database covering more than half of the German population over 75 years old.[13] They found a 44% higher risk for dementia in regular users of PPIs compared to non-users; when occasional users of PPIs were compared to non-users, there was a 16% higher risk. It is well established that patients who initiate PPIs have more comorbidities than those who do not, and this may be particularly true for older adults. In this study, adults selected for PPIs had strikingly higher baseline rates of depression, stroke, and polypharmacy. Although the study adjusted for these baseline characteristics, additional

GRADE Definitions on Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

uncaptured baseline differences between PPI users and non-users may explain the differences in rates of dementia rather than exposure to PPIs.

Bone Fracture

A link between PPIs and increased fracture risk is based on several potential mechanisms including hypochlorhydria-associated malabsorption of calcium or vitamin B12, gastrin-induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition. Numerous studies have examined this association and many but not all have reported a positive association.[14] These observational data were limited by unmeasured and/or residual confounding.[15] The results regarding the presence of a dose- or duration-based response have also been inconsistent, as have studies that investigated the effect of PPI therapy on bone mineral density (BMD) based on dual-energy X-ray absorptiometry (DXA). More recently, data regarding the effect of PPIs on volumetric BMD (vBMD) have become available. Using peripheral quantitative computer tomography (QCT), a small cross-sectional study reported that PPIs were associated with lower trabecular BMD but not cortical BMD.[16] By contrast, another cohort study reported no effect of PPI therapy on hip vBMD based on QCT.[17] Currently, there are no data to support the routine use of bone mineral density monitoring among PPI users.

Myocardial Infarction

PPIs are primarily metabolized by the cytochrome P450 isoenzyme CYP2C19. Because the anti-platelet drug clopidogrel is activated by CYP2C19, there has been concern that PPIs may decrease clopidogrel's anti-platelet effect. The COGENT study, a randomized controlled trial published in 2010, provided reassurance that PPIs do not meaningfully interact with clopidogrel.[18] COGENT randomized patients who were receiving daily aspirin to a combination pill containing omeprazole and clopidogrel versus placebo. When results from 3761 patients were analyzed, there was no difference in the cardiovascular event rate between omeprazole-clopidogrel (4.9%) compared to clopidogrel alone (5.7%). These results make it highly unlikely that there is a large increase in risk for myocardial infarction (MI) due to PPIs in patients taking clopidogrel.

Subsequently, it was postulated that PPIs might increase risk for MI based on a different mechanism, ie, that they may directly blockade vascular nitric oxide synthase to enhance vascular contractivity.[19] Shah et al tested this by mining data from patients with a low baseline risk for MI and found an excess relative risk of 9-16% for MI after a median of four years of PPI use.[20] Despite this new study, the findings of COGENT remain the most important single piece of evidence related to PPIs and MI. If PPIs do cause vasoconstriction, such an effect would likely be most obvious in patients who, like the participants in COGENT, have a high baseline risk for MI. The findings by Shah et al may be explained by residual differences between PPI users and non-users rather than by use of PPIs.

Infections

Small intestinal bacterial overgrowth. Gastric acid is bactericidal and PPIs increase bacterial counts in the

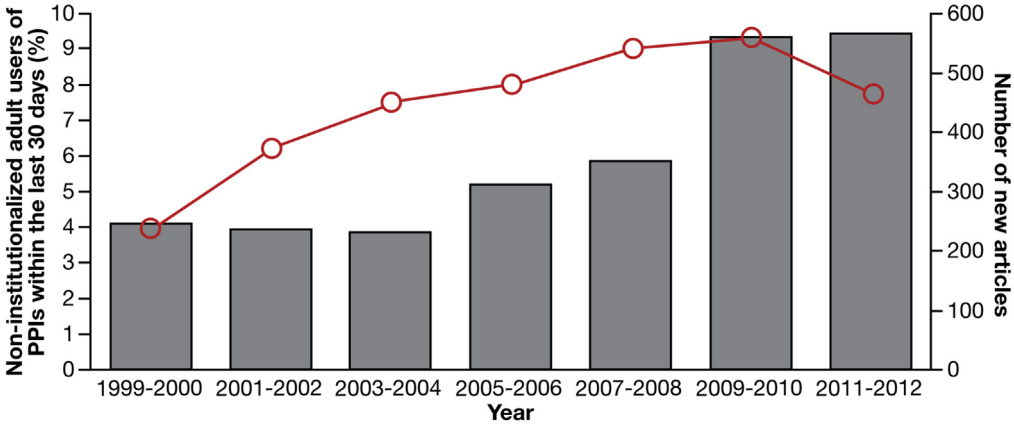

Figure 1. Use of proton pump inhibitors (PPIs) and articles reporting on their potential risks. Use of PPIs was drawn from National Health and Nutrition Examination Survey (NHANES) data from the United States (*red line*).[1] Articles reporting on PPI risks were identified by searching PubMed for relevant articles within the date ranges (*columns*).

Table 1. Summary of Evidence for Potential PPI-Associated Adverse Effects

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias towards harm • Absence of dose-response effect	Very low
Dementia	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias towards harm	Low or very low
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias towards harm • Protopathic bias	Low
Spontaneous bacterial peritonitis	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Low
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low
Micronutrient deficiencies	• Observational only	• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm	Low or very low
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

stomach and in the proximal small bowel.[21] Two studies used duodenal aspirates for the diagnosis of small intestinal bacterial overgrowth (SIBO) and a rigorous, self-controlled study design in which within-individual changes in bacterial counts were assessed before versus after PPIs.[22,23] Pereira et al found that PPIs increased the duodenal bacterial load but that participants remained asymptomatic whereas Lewis et al found both that PPIs increased bacterial counts and symptoms. In these two studies, PPIs were associated with an over 20-fold relative risk for SIBO. Overall, studies that have classified SIBO using aspirates have found an 8-fold relative risk associated with PPIs whereas studies using breath testing have found a 2-fold relative risk.[24]

***Non-typhoidal* Salmonella *and* Campylobacter.** Patients with hypochlorhydria from pernicious anemia or from gastric surgery have increased rates of *Salmonella* infections.[25] Retrospective case-control studies show an approximately 3-fold relative risk for *Salmonella* or *Campylobacter* infections after exposure to PPIs.[26] There is contradictory evidence from a retrospective study by Brophy et al which used a modified self-control study design to compare patients during the period before PPIs versus the period after PPIs.[27] Inaccurate ascertainment of PPI exposure during the period before initiation of PPIs (eg, from intermittent use) would invalidate this study's result, and all of the other studies have reached the opposite conclusion.

Spontaneous bacterial peritonitis. Alterations in gut bacteria due to hypochlorhydria may lead to changes in intestinal permeability and translocation of bacteria across the gut wall. Studies show a 2-fold relative risk for spontaneous bacterial peritonitis associated with exposure to PPIs.[28] However, accurate ascertainment of PPI exposure has unique challenges in cirrhotics who are frequently hospitalized and consequently likely to be exposed to PPIs intermittently. Prospective studies have incorporated active telephone follow up to ascertain PPI exposure yet,

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Table 2. Absolute and Relative Risks for Adverse Effects Associated With Long-term PPIs

Potential adverse effect	Relative risk	Reference for risk estimate	Reference for incidence estimate	Absolute excess risk
Chronic kidney disease[1]	10% to 20% increase	Lazarus et al[9]	Lazarus et al[9]	0.1% to 0.3% per patient/year
Dementia[2]	4% to 80% increase	Haenisch et al[12]	Haenisch et al[12]	.07% to 1.5% per patient/year
Bone Fracture[3]	30% to 4-fold increase	Yang et al[14]	Yang et al[14]	0.1% to 0.5% per patient/year
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[24]	None available	Unable to calculate
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[78]	.03% to 0.2% per patient/year
Spontaneous bacterial peritonitis[4]	50% to 3-fold increase	Xu et al[28]	Fernandez et al[79]	3% to 16% per patient/year
Clostridium difficile infection[5]	No risk to 3-fold increase	Furuya et al[31]	Lessa et al[80]	0% to .09% per patient/year
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[6]	60% to 70% increase	Lam et al[48]	Bailey et al[81]	0.3% to 0.4% per patient/year
Gastrointestinal malignancies	No association in RCTs	—	—	—

NOTE. This table provides absolute and relative risk estimates based on RCTs, meta-analyses, or large observational studies. The purpose of this table is to enable easy comparison of absolute and relative risks. Readers should not assume that we believe there is causal relationship when risk estimates are given; Table 1 provides our best summary of the evidence for potential PPI-associated adverse effects. [1]Estimates are for adults (mean age 50 years old) with a baseline eGFR >60 ml/min/1.73m^2. [2]Estimates are for non-institutionalized adults age 75 years old or more. [3]Estimates are for adults with a mean age of 77 years old. [4]Estimates are for cirrhotics with ascites and assume use of SBP prophylaxis with antibiotics. [5]Estimates are for community-acquired CDI. [6]Estimates are for non-institutionalized adults and based on vitamin B12 deficiency, defined by both a low vitamin B12 level and an elevated methylmalonic acid level.

even in these studies, it is often unclear whether or not PPI exposure actually preceded spontaneous bacterial peritonitis.

Clostridium difficile *infection*. Although PPIs have no direct effect on pH in the colon, they appear to exert a significant "downstream" effect on colonic bacteria.[29] Bacterial taxa associated with *Clostridium difficile* infection (CDI) were increased in the stool of healthy volunteers after 4-8 weeks of high-dose PPIs.[30] Observational studies show an approximately 50% relative risk for CDI associated with PPIs, although CDI remains rare enough that there is little confidence in this estimate.[31] The risk associated with PPIs is modest compared to traditional risk factors such as antibiotics,[32] but some studies suggest that PPIs may be more important within specific populations—for example, in children.[33]

Pneumonia. It has been hypothesized that, just as PPIs may have a downstream effect on the colonic microbiome, they may have an "upstream" effect on the oropharyngeal microbiome which increases risk for pneumonia.[34] In observational studies, PPIs have been associated with increased risk for community-acquired pneumonia (CAP).[35] However, this risk is borne largely by those who recently started PPIs rather than those using long-term PPIs.[36,37] This suggests either that PPIs are markers for uncaptured acute events (eg, hospitalizations) or that they are being prescribed for early symptoms of undiagnosed pneumonia (ie, protopathic bias). The OBERON study randomized 2426 ambulatory adults to a PPI versus placebo for 26 weeks for the purpose of ulcer prevention and found similar rates of pneumonia (0.9% with PPIs vs 1.9% with placebo).[38] In a post hoc, manufacturer-sponsored analysis of 24 short-term RCTs, incidence of pneumonia was similar in patients randomized to PPIs compared to placebo.[39] Randomized studies of PPIs for stress ulcer prophylaxis in the ICU have not shown an association between PPIs and ventilator-associated pneumonia.[40]

Micronutrient Deficiencies

Gastric acidity is important for the absorption of minerals (eg, calcium, iron, magnesium) ingested as salts and dietary protein-bound vitamin B12. A number of studies have investigated whether PPI-induced hypochlorhydria might result in clinically important micronutrient deficiencies.

Calcium. The existing data generally support the notion that profound acid suppression may interfere with calcium absorption.[41] However, this effect is not relevant for water-soluble calcium salts[42] or calcium contained in milk or cheese.[43] Furthermore, the malabsorption of water-insoluble calcium in the setting of achlorhydria can be completely reversed when calcium is taken with a slightly acidic meal.[42]

Iron. Few studies have specifically evaluated the potential association between PPIs and iron deficiency. In patients with Zollinger-Ellison Syndrome, six years of PPIs was not associated with decreased total body iron stores or with iron deficiency.[44] On the other hand, in patients with hereditary hemochromatosis, PPI use was associated with a

significant reduction in the absorption of non-heme iron in the short-term as well as a significant reduction in annual phlebotomy requirements in the long-term.[45]

Magnesium. Cases of profound hypomagnesemia associated with chronic PPI therapy have been reported since 2006.[46] The relative rarity of these cases in the face of highly prevalent PPI use suggests that they may represent a form of idiosyncratic reaction. Nevertheless, several observational studies have reported a modest positive association between PPI use and hypomagnesemia (pooled RR 1.43, 95% CI 1.08-1.88).[47]

Vitamin B12. Several studies have examined the association between long-term PPI use and the risk of developing vitamin B12 deficiency; most[48] but not all[49] reported a 2-4-fold increased risk of B12 deficiency associated with PPI therapy.

Gastrointestinal Malignancies

PPIs have the potential to increase risk for gastrointestinal malignancies by facilitating gastric pan-colonization by *Helicobacter pylori* and by causing hypergastrinemia. Studies in humans have not confirmed an association between PPIs and gastric cancer or gastric NETs. In a population-based study, rates of gastric cancer were elevated 5-fold in patients with GERD and similar diagnoses; in these patients, treatment with PPIs appeared to be a marker for cancer risk rather than a causative factor.[50] In a pooled analysis of four RCTs, PPIs were not associated with gastric atrophy or other pre-malignant changes.[51] In the SOPRAN and LOTUS trials, 812 adults were randomized to antireflux surgery versus PPIs and followed with serial study biopsies. After up to 12 years of follow-up, there was no difference between groups in gastric pre-malignant changes or in gastric NETs.[52] There were few events in these trials, but they mean that any absolute risk for gastric tumors related to PPIs would be very small.

Gastrin has a trophic effect on colonic epithelial cells in mice[53] and on human colorectal cancers in vitro.[54] Thorburn et al analyzed gastrin levels in banked serum from 250 patients with colorectal cancer and matched controls; median gastrin levels were similar in both groups, but an elevated gastrin was associated with a 4-fold relative increase in risk for colorectal cancer.[55] Subsequent population-based retrospective studies have explored this and have uniformly failed to confirm that PPIs increase risk for colorectal cancer. Colon cancers grow slowly, but there was no change when these results were restricted to patients with ≥7 years of PPIs.[56]

What Are the Benefits of Using PPIs?

Evidence for the benefits of PPIs for GERD, Barrett's, and NSAID bleeding prophylaxis is given in Table 3.

Gastroesophageal Reflux Disease

Gastric acid has an inflammatory effect on the distal esophagus and short-term PPIs are highly effective in treating gastroesophageal reflux disease (GERD).[57] In complicated GERD, long-term maintenance with PPIs prevents recurrence of esophagitis (80% PPIs vs 49% H2RAs)[58] and esophageal strictures (46% PPIs vs 30% H2RAs).[59] In uncomplicated GERD, there is less certainty regarding the need for daily long-term maintenance with PPIs.[60] In a trial of patients with uncomplicated GERD who responded to short-term PPIs and were subsequently randomized to "on-demand" PPIs versus placebo, 83% of patients using PPIs were symptom-free after six months compared to 56% of patients using placebo.[61] Other RCTs confirm that the majority of patients with uncomplicated GERD do well without long-term PPIs or with long-term on-demand PPIs.[62]

Barrett's esophagus

For patients with symptomatic GERD and Barrett's, PPI therapy is highly effective for symptom relief and may potentially offer a chemopreventive effect, particularly

Table 3. Summary of Evidence for the Benefit of Long-term PPIs for GERD, Barrett's Esophagus, and NSAID Bleeding Prophylaxis

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
GERD with esophagitis or stricture	• Observational • RCT	• Generalizability to patients with non-severe esophagitis • Absence of long-term data	Moderate to high
GERD without esophagitis or stricture	• Observational • RCT	• Generalizability to patients with relatively mild symptoms • Absence of long-term data • Absence of objective outcome data	Moderate
Barrett's esophagus with GERD	• Observational • RCT	• Indirect evidence extrapolated from GERD • Absence of long-term data	Moderate to high
Barrett's esophagus without GERD	• Observational	• Inconsistent results • Modest effect size	Low
NSAID bleeding prophylaxis	• Observational • RCT	• Generalizability to patients at lower baseline risk for bleeding • Absence of long-term data	High

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

since symptomatic reflux is a known risk factor for esophageal adenocarcinoma (EAC).[63] In patients with Barrett's esophagus who have no symptoms of GERD,[64] PPIs are prescribed primarily to reduce the risk of progression to EAC.[65] Epidemiologic studies generally support this practice, but there is currently no randomized data directly demonstrating that PPIs prevent progression of Barrett's to EAC.[66]

Bleeding Prophylaxis in High-Risk Patients Who Take Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal mucosal damage through multiple mechanisms including inhibition of cyclooxygenase and a reduction in prostaglandins. Acid suppression with PPIs reduces this damage and thus reduces ulcer formation and ulcer-related bleeding.[67] In RCTs, there was a 10-15% absolute risk reduction in ulcer formation[68] and in ulcer-related bleeding in high-risk patients after 6-12 months of PPIs compared to placebo.[69]

Balancing the Risks and Benefits of Long-term PPIs

Despite the long list of potential adverse effects associated with PPI therapy, the quality of evidence underlying these associations is consistently low to very low. In addition, the magnitudes of absolute risk increase for individual patients are modest, particularly at once daily dosing. We recommend that patients take long-term PPIs for complicated GERD, uncomplicated GERD with objective evidence of excess acid, Barrett's esophagus with GERD symptoms, and NSAID bleeding prophylaxis if high-risk. For patients who do not fall into these categories, the lack of solid evidence means that the risk-benefit equation is less clear.

What Measures Can Be Used to Mitigate the Potential Risks of Long-term PPI Therapy?

Mitigation of potential PPI risks could be attempted by PPI reduction or by giving risk-specific supplements. The literature regarding PPI reduction is sparse and is almost entirely limited to patients with uncomplicated GERD. Most patients with uncomplicated GERD can be reduced from twice- to once-daily PPIs.[70] In one study, a third of patients with uncomplicated GERD alleviated by PPIs were successfully transitioned to H2RAs and an additional 16% were transitioned off all acid suppression.[71] When patients with non-erosive disease cannot be transitioned off PPIs, they are usually satisfied with on-demand therapy.[62] Since PPI reduction in this scenario is so often successful, it is logical to periodically reevaluate patients on long-term PPIs to ensure that they are prescribed the lowest dose sufficient to manage their condition.

Patients with complicated GERD, on the other hand, are usually unable to successfully reduce PPIs.[72] Perhaps the most challenging category of patients are those who respond symptomatically to a daily PPI but cannot reduce below this. Because such patients face lifelong PPI therapy, we recommend that evidence be sought for an acid-related disorder (eg, by performing ambulatory esophageal pH/impedance monitoring). This testing is likely to reveal a subset of patients who have a very poor correlation between symptoms and acidic reflux events; in these patients, strenuous efforts should be made to discontinue or reduce PPIs.[73]

The literature regarding the use of supplements to ameliorate potential PPI risks is also limited. Probiotics have shown a modest benefit in preventing antibiotic-associated diarrhea but have never been tested to prevent infections in long-term users of PPIs.[74] Because the absolute rates of infections are extremely low, probiotics are unlikely to confer a benefit in this setting. Supplementation of calcium and vitamin D does not conclusively decrease risk for fracture.[75] Therefore, it is unlikely that a policy of routinely supplementing long-term users of PPIs with calcium, vitamin D, or other vitamins would be of benefit. Similarly, we cannot recommend routine BMD testing, or routine monitoring of vitamin or mineral levels in long-term users of PPIs. It should be noted that the intake of many adults falls below the RDA in calcium and other vitamins and, in these adults, it seems reasonable to raise intake to meet the RDA.[76]

In sum, the best current strategies for mitigating the potential risks of long-term PPIs are to avoid prescribing them when they are not indicated and to reduce them to their minimum dose when they are indicated.

Conclusions

Baseline differences between PPI users and non-users make it challenging to study potential PPI adverse effects retrospectively. Despite a large number of studies, the overall quality of evidence for PPI adverse effects is low to very low. When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks. When PPIs are inappropriately prescribed, modest risks become important because there is no potential benefit. There is currently insufficient evidence to recommend specific strategies for mitigating PPI adverse effects.

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Conflicts of interest
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Exhibit D

Acid Reflux and Proton Pump Inhibitors

kidney.org/atoz/content/acid-reflux-and-proton-pump-inhibitors

March 8, 2016

What is acid reflux or GERD?

The stomach makes acid to help you digest food and remove bacteria. This is a natural process. In some people, the stomach makes too much acid, which can cause discomfort. When your stomach makes too much acid, you may have symptoms like:

- Burning in your chest
- Regurgitating (bringing up) acid into your throat and mouth
- Sensing a lump in your throat when swallowing
- Burping, bloating, or a feeling of “fullness” in your stomach
- Hiccups
- Coughing
- Chest pains

These symptoms may mean you have acid reflux and heartburn, which can usually be relieved by antacids and no medical treatment. If symptoms become serious and happen more than once a week, it could mean you have gastroesophageal reflux disease (GERD). If that’s the case, your healthcare provider may suggest changes to your diet and lifestyle.

What lifestyle and diet changes can I try?

For many people, simply changing your diet and lifestyle is enough to relieve symptoms. This may include:

- Removing foods from your diet that could trigger symptoms of heartburn and/or acid reflux. To name a few:
  - Alcohol
  - Caffeine
  - Chocolate
  - Peppermint
  - Spicy Foods, black pepper
  - Acidic foods (tomatoes, tomato-based foods, citrus fruit)
  - Greasy and high fat foods (such pizza, French fries, hamburgers, deep-fried chicken)
  - Not eating 2-3 hours before bedtime
- Finding positions to sleep in that help reduce acid from reaching your throat. Elevating your head and upper body with pillows or a wedge-shaped support pillow can help.
- Quitting smoking
- Losing weight, if needed

If diet and lifestyle changes are not enough, your healthcare provider may put you on a type of medicine called proton pump inhibitors (PPIs).

What are proton pump inhibitors (PPIs)?

PPIs are a type of drug used to ease the symptoms of acid-related conditions. Some of these conditions include serious acid reflux/heartburn, GERD, peptic ulcers (a sore in the lining of the stomach), and Zollinger-Ellison syndrome, a condition in which tumors in the pancreas cause the stomach to make too much acid. PPIs work to lessen the amount of acid made in the lining of the stomach. When PPIs work, the symptoms of severe heartburn, acid reflux, and GERD bother you less. Depending on your diagnosis, your healthcare provider may give you a PPI for only a few weeks, or you may need longer treatment.

What are the types of PPIs?

There are many types of PPIs. Some need a doctor's prescription. Others can be purchased over-the-counter (OTC, sold in drugstores without a doctor's prescription). After looking at your diet and lifestyle, and depending on your overall health, your symptoms and how often you have them, your healthcare provider may recommend one of the following:

Generic Name	Brand Name
Dexlansoprazole	Dexilant
Esomeprazole	Nexium, Nexium OTC
Lansoprazole	Prevacid, Prevacid 24 hour
Omeprazole	Prilosec, Prilosec OTC
Omeprazole/Sodium Bicarbonate	Zegerid, Zegerid OTC
Pantoprazole	Protonix
Rabeprazole	AcipHex

What are the side effects of PPIs?

PPIs are considered safe and effective in most people. But depending on your overall health and how long you have to take your PPI medication, there can be different health concerns and side-effects. It is important to go over these with your healthcare provider to make sure this is the best type of care for your symptoms. As with any medication, you should consider both the benefits and risks. Here are some risks and issues that have occurred in some people:

- Increased chance of chronic kidney disease: It has not been proven that PPI use causes chronic kidney disease, but some studies suggest there is an increased risk of chronic kidney disease in individuals who have normal kidney function before using a PPI. This does not mean that everyone who uses PPIs will get chronic kidney disease, but it is important to know that there may be a risk. Studies did not include individuals who

currently have kidney disease, so it is not clear if PPI use can make kidney disease worse.

- Acute interstitial nephritis: This is a condition that causes swelling of the inside the kidney. This usually happens due to an allergic reaction, typically to medicines you may be taking, like PPIs. Swelling of the inside of your kidney can cause damage, and, if left untreated, can cause serious health problems. Using PPIs may increase the risk of developing acute interstitial nephritis. If caught early, the condition can be treated and leave no signs of damage to your kidneys.
- Increased chance of heart attack(s): Using PPIs for long periods of time (many months to years) may increase the risk of a heart attack. It is not clear why this may happen, but studies suggest that PPI use may increase this risk. Additionally, those who have had a heart attack and are on blood thinners like clopidogrel (Plavix), can have a repeat heart attack. This is because some PPIs can reduce the function of the blood thinner. It is important to talk about any history of heart disease with your healthcare provider before using PPIs.
- Nutritional deficiencies: Use of PPIs may make it hard for your body to absorb or keep certain nutrients needed for good health, like magnesium and iron.
    - Iron. Your body needs iron to make red blood cells, but PPI use may decrease your body's ability to absorb iron. This is especially important for people who have anemia (low number of red blood cells) that is caused by not enough iron, or people with kidney disease, which affects your body's ability to regulate iron.
    - Magnesium. Magnesium is needed to form healthy bones and teeth, and for normal nerve and muscle function. But PPI use can change the way your kidneys remove extra magnesium from your body, causing you to lose too much. Magnesium depletion is more common when you use both a PPI and a diuretic (a medication to remove extra water from your body). If you are taking PPIs and have magnesium depletion, ask your healthcare provider about a different class of medications known as H2 blockers (such as famotidine, ranitidine, or nizatidine)
- Increased chance of bone fracture and bone loss (osteoporosis): It is believed that PPIs can lessen the body's ability to absorb vitamin B12 or calcium, which can lead to wrist, spine, and hip fractures. This increased risk is especially true if you are on PPIs longer than a year and are age 50 or older. Also, if you are on a type of medication to reduce your chances of hip fracture (bisphosphonate medication), PPI use may interfere with this medication and increase your risk of hip fracture. If you have kidney disease and use PPIs, you should talk to your healthcare provider about the increased risk of bone fracture.
- Increased chance of dementia: In older patients, there is a concern for an increased association of PPI use and dementia (a group of symptoms that affect your memory, thinking, social abilities, and daily function). This is mainly thought to be caused by the fact that PPIs are in the blood that goes to the brain, while also interfering with B12 absorption in the body. These two effects have led some researchers to believe there is an increased association between PPI use and dementia.
- Increased chance of infection(s): Infections can be a concern when using PPIs. Since

there is a decreased production of stomach acid, which would help fight against infection, viruses and bacteria can stay in your system and infect other parts of your body. You may be at higher risk for infection if you have asthma, lung disease, decreased immunity (because of HIV/AIDS or diabetes, for example), or are older. Specifically, taking PPIs can increase the risk of the following two types of infections:

- Community-acquired pneumonia: When PPIs work to reduce the acid in your stomach and digestive tract, there may not be enough acid in the digestive tract to help with fighting against bacteria that come into your system through food. The bacteria that stays behind finds other places to 'live'. These bacteria may then cause a serious infection in your lungs called community-acquired pneumonia. This usually happens within the first few weeks or months of taking PPIs. If you have kidney disease and are on dialysis, it is important to talk to your healthcare team about the increased risk of pneumonia with PPI use.
- Increased chance of infection from Clostridium difficile(C.diff): A less acidic environment that is created by the use of PPIs can cause different types of bacteria to stay in your digestive system. Some of these bacteria can be harmless, and others can increase infections that upset your digestive tract. One bacteria of main concern is C.diff. This bacteria leads to diarrhea, fever, and other symptoms of digestive illness which, if left untreated, can cause other major health concerns.

What if I have kidney disease or kidney failure?

Before taking any antacids or PPIs, you should talk to your healthcare provider. There may be limitations on what you can take and how often you should take it, especially if you are on dialysis. Most importantly, you should not self-treat your symptoms with items bought from a drugstore or pharmacy. Any treatment should always come with the instruction of your healthcare provider.

What else should I know?

For most people, the use of PPIs is generally considered safe and effective. In fact, some experts believe the risks associated with PPIs are very small, while others are more cautious. However, many people can treat heartburn successfully with lifestyles changes alone, so experts encourage trying that first. If your healthcare provider has prescribed an antacid or PPI, be sure to follow the instructions carefully, and do not take them longer than suggested. If you have concerns about PPI use, talk to your healthcare provider.

Exhibit E

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of a Research Article

Date:	06/01/2016
Reviewer(s):	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Deputy Director:	David Shih, MD MS Division of Epidemiology I
Drug Name(s):	Proton Pump Inhibitor Class: rabeprazole (Aciphex), dexlansoprazole (Dexilant), esomeprazole (Nexium), esomeprazole magnesium (Vimovo), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), omeprazole & sodium bicarbonate (Zegerid), esomeprazole strontium
Subject:	Critique of Xie, et al., Published online April 14, 2016, Proton Pump Inhibitors and the Risk of Incident CKD and Progression to ESRD, J Am Soc Nephrol doi: 10.1681/ASN.2015121377
Application Type/Number:	NDA 20973, NDA 204736, NDA 22287, NDA 21153, NDA 22101, NDA 21957, NDA 21689, NDA 022511, NDA 021428, NDA 20406, NDA 19810, NDA 22056, NDA 20987, NDA 20988, NDA 22020, NDA 021849, NDA 21636, NDA 21706, NDA 202342
Applicant/sponsor:	Multiple
OSE RCM #:	2016-939

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EXECUTIVE SUMMARY

To guide potential regulatory actions, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to critique and interpret a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of chronic kidney disease and end-stage renal disease.

A research paper by Xie, et al., published online April 14, 2016, studied the association, in data from the Veterans Affairs (VA) healthcare system, between PPI use and subsequent occurrence of chronic kidney disease (CKD) and end-stage renal disease (ESRD). A primary analysis followed N=173,321 PPI and 20,270 H2 receptor antagonist (H2) new users (mean ages 56.8 and 55.4 years), respectively, for at least five years and used laboratory data and U.S. Renal Database System (USRDS) linkage to ascertain kidney outcomes. Xie defined (1) CKD by two estimates of glomerular filtration (eGFR) <60 mL/min/m^2, separated by ≥90 days, and (2) ESRD by USRDS match. With CKD occurring frequently (36.8 and 25.7 per 1000 person-years) and ESRD infrequently (329 and 25 cases; 0.41 and 0.26 per 1000 person-years) after PPI and H2 new use, respectively, Cox regressions estimated covariate-adjusted CKD and ESRD relative risks at HR 1.28 (95% CI 1.23-1.34) and HR 1.96 (95% CI 1.21-3.18), respectively.

Xie extended results from other observational studies to suggest ESRD, in addition to CKD, as a possible adverse outcome from PPI. However, because of validity threats from multiple sources, including confounding, selection bias, missing data, outcome misclassification, and selective reporting, however, DEPI judged the adjusted hazard ratios reported by Xie as subject to severe risk of bias because of moderate risks of bias in multiple domains.

Finding the evidence for causal association too weak to offset a severe risk of bias, DEPI could not make a recommendation for regulatory action at this time.

1. INTRODUCTION

To guide potential regulatory actions, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to critique and interpret a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of chronic kidney disease (CKD) and end-stage renal disease (ESRD).

The PPI active ingredients (drug name, year approved) include omeprazole (Prilosec, 1989), lansoprazole (Prevacid, 1995), rabeprazole (Aciphex, 1999), pantoprazole (Protonix, 2000), esomeprazole (Nexium, 2001), and dexlansoprazole (Dexilant, 2009). Labelled adult indications for PPIs, according to the December 2014 Prescribing Information for delayed-release omeprazole, include duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and maintenance of healing of erosive esophagitis.[1]

In response to a citizen petition, FDA agreed that "reasonable evidence" existed to support

[1] Highlights of Prescribing Information for PRILOSEC (omeprazole) delayed-release capsules, December 2014, Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm on January 29, 2016.

causal association between drugs in the PPI class and acute interstitial nephritis,[2] an adverse event generally regarded as a rare and reversible hypersensitivity reaction. Other concerns appearing under Warnings and Precautions in the Prescribing Information for delayed-release omeprazole include cyanocobalamin (vitamin B-12) deficiency, *Clostridium difficile*-associated diarrhea, bone fracture, and hypomagnesemia.[1]

Adding to the concern about transient kidney injury (e.g., acute interstitial nephritis), a research paper by Lazarus, et al., published online January 11, 2016, created new concern about possibly permanent kidney injury from PPI. Lazarus used data from the Atherosclerosis Risk in Communities (ARIC) study and the Geisinger Health System. In analyses subject to moderate risk of bias due to confounding and outcome misclassification, Lazarus reported statistically significant associations between PPI use at entry and subsequent CKD, with risks estimated, by hazard ratio (HR) and 95% confidence interval (CI), at HR 1.50, 95% CI 1.14-1.96 in ARIC and HR 1.17, 95% CI 1.12-1.23 in Geisinger.

A more recent research paper by Xie, et al., published online April 14, 2016, also reported association between PPI use and subsequent occurrence of chronic kidney disease (CKD) and end-stage renal disease (ESRD). DGIEP asked DEPI to analyze "the epidemiologic methods and interpretability of the [Xie] article regarding the correlation of PPI usage and CKD and ESRD to guide potential regulatory actions." Known risk factors for CKD and ESRD include black race, hypertension, diabetes, and cardiovascular disease.[3]

1.2. Regulatory History

Relevant regulatory events include:

Date	Event
September 14, 1989	First PPI (omeprazole, Prilosec, NDA 019810) approved in U.S.

This Review consulted source documents listed in the following table.

Date	Source	Document
February 29, 2016	DEPI I	Critique of Lazarus, et al., Published online January 11, 2016, Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease, JAMA Intern Med,

[2] FDA Response to Citizen Petition from Public Citizen, Retrieved from http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=4324 on January 29, 2016, Page 16.

[3] National Institute of Diabetes and Digestive and Kidney Diseases, At Risk for Kidney Disease?, Retrieved from http://www.niddk nih.gov/health-information/health-communication-programs/nkdep/learn/causes-kidney-disease/at-risk/Pages/are-you-at-risk.aspx on January 27, 2016.

Date	Source	Document
		doi:10.1001/jamainternmed.2015.7193, filed in DARRTS under multiple NDAs, including NDA 019810

2. REVIEW METHODS AND MATERIALS

DEPI used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI; Sterne, et al., 2014) to guide its risk-of-bias assessment of Xie, et al., 2016. The ACROBAT-NSRI conceives seven categories of risk to the internal validity of observational studies, (1) confounding, (2) selection, (3) measuring the intervention, (4) co-intervention, (5) missing data, (6) measuring the outcome, and (7) selective reporting.

DEPI used the 20-item scheme proposed by Elwood, 1998, to guide its assessment for causation.

3. REVIEW RESULTS

3.1 Study Overview

Xie studied the occurrence of outcomes related to the loss of kidney function in patients of the Veterans Affairs (VA) healthcare system. Primary analyses compared kidney outcomes experienced by patients who first used either a PPI or a histamine-2 (H2) receptor antagonist between October 2006 and September 2008.

3.2 Objectives: Primary and Secondary

Xie aimed to measure the association between PPI use and incident CKD or ESRD in the VA patient population.

3.3 Study Design

Xie compared PPI-exposed and H2-exposed cohorts for the occurrence of kidney outcomes.

3.4 Methods

3.4.1 Population sources and study time period

Analyses combined information in four VA-specific administrative healthcare databases. These four databases contained patient-specific information about (1) inpatient and outpatient encounters (Medical SAS Datasets), (2) inpatient and outpatient laboratory tests (VA Managerial Cost Accounting System – Laboratory Results), (3) medication prescriptions (VA Corporate Data Warehouse Production – Outpatient Pharmacy), and (4) vital status (VA Vital Status and Beneficiary Identification Records Locator Subsystem). A fifth database (United States Renal

Database System, USRDS[4]) provided information about ESRD.

Primary analyses covered drug exposures between October 2006 and September 2008 and subsequent kidney outcomes through September 2013.

3.4.2 Study subject selection

The primary analyses defined two cohorts, containing 173,321 and 20,270 PPI-exposed and H2-exposed patients, respectively. Table 1 outlines the procedures used to select these cohorts. The selection procedure started with 8,434,579 users of VA healthcare at any time between October 2006 and September 2013 (Table 1, Line 1). The PPI cohort excluded 1,246,164 patients (14.8%) who filled one or more prescriptions for PPI between October 1999 and September 2006 (Table 1, Line 2). The H2 cohort excluded 2,726,813 (32.3%), 2,515,882 (29.8%) for PPI prescription between October 1999 and September 2013 and an additional 210,931 (2.5%) for H2 prescription between October 1999 and September 2006 (Table 1, Line 2).

Application of these PPI and H2 exclusions left 7,188,415 and 5,707,766 patients, deemed PPI and H2 new-use eligible, respectively (Table 1, Line 3). As noted in Table 1, PPI prescription, but not H2 prescription, before October 2006, excluded patients from PPI new use. However, PPI or H2 prescription before October 2006 excluded patients from H2 new use. Moreover, PPI prescription during the exposure window for new use (October 2006 through September 2008; See Section 3.4.4, below) or PPI prescription during extended follow-up for chronic kidney disease outcomes (October 2008 through September 2013; See Section 3.4.5, below) excluded patients from H2 new use. Xie did not mention a procedure for restricting the new user cohorts to patients with evidence of VA healthcare contact during a "new-use clean period" (a fixed time interval before October 2006).

As shown in Table 1, Line 4, 371,496 (5.2%) of 7,188,415 PPI new-use eligible patients filled a PPI prescription between October 2006 and September 2008. By comparison, 45,514 (0.8%) of 5,707,766 H2 new-use eligible patients filled an H2 prescription between October 2006 and September 2008.

Xie required laboratory data (serum creatinine concentrations) to identify both (1) patients with normal kidney function before PPI or H2 new use and (2) patients with reduced kidney function after PPI or H2 new use. Xie excluded from analysis 159,315 (42.9%) of 371,496 PPI new users and 21,369 (47.0%) of 45,514 H2 new users without the required laboratory data before or after first use, (Table 1, Lines 5 and 6).

Finally, from the group of 212,181 PPI new users with laboratory data available (Table 1, Line 7), Xie excluded 38,860 (18.3%) with evidence of CKD (estimated glomerular filtration rate,

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[4] A national data system, funded by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), collaborates with the Centers for Medicare & Medicaid Services. This data system collects information about patients who seek Medicare coverage for kidney transplantation or kidney dialysis for ESRD (a stage of renal impairment that requires kidney transplantation or a regular course of dialysis to maintain life). See http://www.usrds.org/.

eGFR, <60 mL/min/m^2) during the 90 days before PPI new use. From the group of 24,145 H2 new users with laboratory data available (Table 1, Line 7), Xie excluded 3,875 (16.0%) with evidence of CKD during the 90 days before H2 new use. This requirement for normal kidney function at baseline left 173,321 PPI new users and 20,270 H2 new users at risk for incident CKD or ESRD (Table 1, Line 8).

Table 1: Procedure for selecting new users of proton pump inhibitors (PPI) and histamine-2 (H2) receptor blockers.[1]

	PPI cohort			H2 cohort		
Populations	Selection Criterion	N	%	Selection Criterion	N	%
1. Entire population	VA use after 10/2006	8,434,579	100.0	VA use after 10/2006	8,434,579	100.0
2. Excluded from new use	PPI between 10/1999 and 09/2006	1,246,164	14.8	PPI between 10/1999 and 09/2013 [2]	2,515,882	29.8
				H2 between 10/1999 and 09/2006 [2]	210,931	2.5
3. New-use eligible	Line 1 - Line 2	7,188,415	100.0	Line 1 - Line 2	5,707,766	100.0
4. New users	PPI between 10/2006 and 09/2008	371,496	5.2	H2 between 10/2006 and 09/2008	45,514	0.8
5. New users	Line 4	371,496	100.0	Line 4	45,514	100.0
6. Excluded for missing laboratory data	Serum creatinine results unavailable [3]	159,315	42.9	Serum creatinine results unavailable [3]	21,369	47.0
7. New users with complete data	Line 5 - Line 6	212,181	100.0	Line 5 - Line 6	24,145	100.0
8. New users at risk for CKD or ESRD	Baseline eGFR ≥60 mL/min/m^2 [4]	173,321	81.7	Baseline eGFR ≥60 mL/min/m^2 [4]	20,270	84.0

1. Counts derived from Figure 1 in Xie, et al., 2016.
2. Exclusions applied sequentially in the order shown.
3. At least one result available within 90 days before PPI or H2 new use and one result available at any time after new use.
4. Estimated glomerular filtration rate (eGFR), calculated using (1) a serum creatinine result in the 90 days before PPI or H2 new use and (2) race-, sex-, and age-specific equations from the Chronic Kidney Disease Epidemiology Collaboration (Levey, et al., 2009).

3.4.3 IRB/OMB approval, patient consent if needed.

The Institutional Review Board (IRB) for the VA Saint Louis Health Care System approved the study by Xie.

3.4.4 Exposure

A new prescription, filled between October 2006 and September 2008, for omeprazole (98.60%) or another PPI (1.40%) defined the PPI exposure group. A new prescription, filled between October 2006 and September 2008, for ranitidine (97.91%) or another H2 (2.09%) defined the H2 exposure group.

3.4.5 Outcome

Xie used outpatient laboratory data and USRDS linkage to define six outcomes, as follows,

- First post-exposure eGFR <60 mL/min/m^2.
- First of two post-exposure eGFRs <60 mL/min/m^2, ≥90 days apart.
- First post-exposure eGFR >30% below pre-exposure eGFR.
- First post-exposure creatinine ≥two-fold higher than pre-exposure creatinine.
- ESRD (date kidney replacement required, according to USRDS match).
- ESRD or first post-exposure eGFR >50% below pre-exposure eGFR.

Xie used race-, sex-, and age-specific equations from the Chronic Kidney Disease Epidemiology Collaboration to derive eGFR from laboratory data (serum creatinine concentrations; Levey, et al., 2009).

3.4.6 Analysis plan

The primary analyses used Cox proportional hazards regression to model time to kidney outcome after exposure to PPI or H2. The primary analysis simulated an intent-to-treat-style analysis, with patients placed at risk for the duration of follow-up after cohort entry.[5] Xie et al., censored at incident CKD, death, or September 30, 2013. Models adjusted for baseline differences in 21 covariates, including pre-exposure eGFR, age, race, sex, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *H. pylori* infection, Barrett esophagus, achalasia, esophageal stricture, and esophageal adenocarcinoma. To determine covariate values, Xie used information available in VA healthcare data between October 1999 and the baseline eGFR (eGFR ≥60 mL/min/m^2 in the 90 days before new use). Xie used (1) laboratory data to determine hepatitis C and HIV status and (2) ICD-9-CM and CPT codes in VA Medical SAS datasets to determine other medical comorbidities (ATTACHMENT 1).

A secondary analysis, restricted to the N=173,321 PPI new users, used Cox regression to examine associations between estimated durations of PPI use (time between first prescription and date of last use, with date of last use not defined by Xie) and kidney outcomes. These analyses started follow-up on the date of last use.

Supportive analyses used Cox regression and the new-use cohorts (1) to examine the association

[5] As noted in Section 3.4.2, the design for the H2 group excluded patients who switched to PPI after H2 new use. This provision deviates from a pure intention-to-treat design.

between PPI and acute kidney injury (AKI, simply defined, without further elaboration by Xie, as "0.3 mg/dl or 50% increase in serum creatinine within 30 days") and (2) to adjust the associations between PPIs and kidney outcomes for incident AKI.

Finally, Xie reported results from nine sensitivity analyses. Two sensitivity analyses used propensity-score matched cohort designs to compare kidney outcomes (1) between PPI and H2 new users and (2) between PPI new users and PPI nonusers. For the latter analysis, Xie selected PPI nonuser controls from the set of VA patients with (1) no PPI prescription before October 2008, (2) an eGFR ≥60 mL/min/m^2 baseline between October 2006 and September 2008, (3) at least one outpatient visit no more than 90 days after baseline, and (4) at least one eGFR measured after baseline. To estimate propensity scores, Xie used logistic regression, a PPI use vs. nonuse response, and the same 21 covariates used for adjusted Cox regressions. Xie used a standardized difference criterion <0.1 units to show covariate balance between PPI-exposed and comparison groups.

With detailed descriptions of method often lacking, the remaining seven sensitivity analyses additionally adjusted the primary new user cohort analyses for,

1. Number of eGFR measurements between October 1999 and cohort entry.
2. Non-steroidal anti-inflammatory drug (NSAID) use for ≥30 days before cohort entry.
3. NSAID use for ≥30 days after cohort entry.
4. Urinary albumin-to-creatinine ratio before cohort entry, in 26,737 of 173,321 (15.4%) PPI new users and 2,322 of 20,270 (11.5%) H2 new users with values for the urinary albumin-to-creatinine ratio.
5. Serum bicarbonate, in 156,761 of 173,321 (90.4%) PPI new users and 17,561 of 20,270 (86.6%) H2 new users with values for the urinary albumin-to-creatinine ratio.
6. Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use for ≥30 days before cohort entry.
7. ACEI or ARB use for ≥30 days after cohort entry.

3.5 Results

3.5.1 Baseline characteristics

Baseline characteristics for the PPI and H2 new-user cohorts included (1) mean (standard deviation) age 56.8 (11.8) and 55.4 (12.8) years, (2) 93.0% and 93.4% male sex, and (3) 18.5% and 18.7% black race. Four baseline comorbidities were substantially more prevalent (≥one percentage point absolute difference) among H2 than PPI new users, (1) cerebrovascular disease (22.7% vs. 15.3%), (2) peripheral artery disease (24.7% vs. 18.1%), (3) dementia (25.0% vs. 18.7%), and (4) diabetes mellitus (44.0% vs. 41.7%). Hepatitis C was substantially less prevalent among H2 than PPI new users, 5.9% vs. 8.6%. Administrative claims documented a

possible medical reason for gastric acid suppression much more frequently in PPI than H2 new users (e.g., gastroesophageal reflux disease, 50.1% vs. 18.6%).

3.5.2 Other covariates

Table 2 compares H2 and PPI new users according to six covariates used in sensitivity analyses. On average, eGFR measurement before cohort entry occurred more frequently in PPI than H2 new users. Xie observed NSAID use before cohort entry and ACEI or ARB use before and after cohort entry more frequently in PPI than H2 new users. Xie observed NSAID use after cohort entry less frequently in PPI than H2 new users. In the subset of patients with urinary albumin to creatinine ratio (UACR) measured before cohort entry, Xie found evidence of proteinuria (UACR > 20 mg/g) more frequently in PPI than H2 new users (26.7% vs. 25.3%).

Table 2: Other covariate characteristics of H2 and PPI new users.

Covariate		H2 N=20,270	PPI N=173,321
Number of eGFR measurements before cohort entry	mean (SD)	4.72 (5.73)	6.93 (7.21)
NSAIDs for ≥30 days before cohort entry	%	42.9	51.9
NSAIDs for ≥30 days after cohort entry [1]	%	31.2	25.7
Urinary albumin to creatinine ratio >20 mg/g [2]	%	25.3	26.7
ACEIs or ARBs for ≥30 days before cohort entry	%	30.0	39.8
ACEIs or ARBs for ≥30 days after cohort entry [1]	%	43.3	48.0

LEGEND: NSAID – non-steroidal anti-inflammatory drug; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker.

1. Use between cohort entry and censoring event, (1) CKD (first of two eGFRs <60 mL/min/m^2, ≥90 days apart), (2) death, or (3) end of follow-up (September 30, 2013).
2. Urinary albumin to creatinine ratio before cohort entry, in 2,322 H2 and 26,737 PPI new users.

3.5.3 Exposure to PPI or H2 during follow-up

PPI new users filled PPI prescriptions that covered a median 15 (interquartile range, IQR, 3-42) months of use. H2 new users filled H2 prescriptions that covered a median 3 (IQR, 1-9) months of use. As shown in Table 3, one-third (33.5%) and nearly one-half (46.9%) of PPI new users filled PPI prescriptions that covered more than two years (720 days) and one year (360 days) of treatment during follow-up, respectively.

Table 3: PPI new users, according to days of PPI use between date of new use (between October 2006 and September 2008) and end of follow-up (incident CKD, death, or September 30, 2013).

PPI days	N	%
≤30	23,621	13.6
31-90	29,886	17.2
91-180	18,338	10.6
181-360	20,148	11.6
961-720	23,293	13.4
>720	58,035	33.5
ALL	173,321	100.0

3.5.4 Unadjusted results

Table 4 summarizes results from unadjusted analysis. Xie observed incident CKD in 2,234 (25.7 per 1000 person-years) and 26,193 (36.8 per 1000 person-years) H2 and PPI new users, respectively. Xie observed ESRD in 25 (0.26 per 1000 person-years) and 329 (0.41 per 1000 person-years) H2 and PPI new users, respectively. Direct calculation of relative incidence (incidence rate ratio, IRR) after PPI vs. H2 new use produced results consistent with unadjusted Cox regression (hazard ratio, HR) for CKD, IRR 1.43 and HR 1.41, but not ESRD, IRR 1.56 and HR 2.17.

Table 4: Six incident kidney outcomes after H2 or PPI new use, sorted by decreasing frequency.

	H2		PPI		Risk Measure [2]				
Kidney outcome [1]	Events	Rate	Events	Rate	IRR	HR	95% CI	RD	NNH
eGFR <60	4,429	54.1	48,171	72.4	1.34	1.33	1.29-1.37	18.3	55
>30% eGFR drop	3,949	45.3	43,842	61.7	1.36	1.43	1.38-1.48	16.4	61
CKD	2,234	25.7	26,193	36.8	1.43	1.41	1.35-1.48	11.1	90
ESRD or >50% eGFR drop	947	10.2	12,952	16.8	1.64	1.65	1.54-1.76	6.6	153
2-fold S_{cr} increase	759	8.2	10,766	13.9	1.70	1.71	1.59-1.84	5.7	175
ESRD	25	0.3	329	0.4	1.56	2.17	1.35-3.48	0.1	6,780

LEGEND: Rate – incidence per 1000 person-years; IRR – incidence rate ratio; HR – hazard ratio; 95% CI – 95% confidence interval for the hazard ratio; RD – risk difference per 1000 person-years; NNH – number needed to harm (1000/RD).

1. Incident kidney outcomes: eGFR <60 – eGFR <60 mL/min/m^2; >30% eGFR drop – eGFR >30% below baseline; CKD – chronic kidney disease, defined by first of two eGFRs <60 mL/min/m^2 ≥90 days apart; ESRD or >50% eGFR drop – end-stage renal disease (USRDS match) or eGFR >50% below baseline; 2-fold S_{cr} increase – serum creatinine ≥2 times baseline; ESRD – end-stage renal disease (USRDS match).
2. All results reported by Xie, except for IRR. DEPI calculated IRR from rates reported by Xie. DEPI reproduced NNH values reported by Xie from rates reported by Xie.

3.5.5 Primary results

Table 5 shows associations between PPI exposure and six kidney outcomes, expressed as the hazard ratio (HR) and 95% confidence interval (95% CI) for PPI vs. H2 new use, before and after adjustment for 21 baseline covariates. Showing substantial change in HR estimates from covariate adjustment, Xie estimated PPI-specific risk at HR 1.28 (95% CI 1.23-1.34) and HR 1.96 (95% CI 1.21-3.18) for the CKD and ESRD outcomes, respectively.

Table 5: Hazard ratios (HR) and 95% confidence intervals (95% CI) for PPI vs. H2 new use, from Cox proportional hazards regression before and after adjustment for 21 baseline covariates.

	Unadjusted		Adjusted		
Kidney outcome [1]	HR	95 CI	HR	95 CI	Δ [2]
eGFR <60	1.33	1.29-1.37	1.22	1.18-1.26	33
CKD	1.41	1.35-1.48	1.28	1.23-1.34	32
2-fold S_{cr} increase	1.71	1.59-1.84	1.53	1.42-1.65	25
>30% eGFR drop	1.43	1.38-1.48	1.32	1.28-1.37	26
ESRD	2.17	1.35-3.48	1.96	1.21-3.18	18
ESRD or >50% eGFR drop	1.65	1.54-1.76	1.47	1.38-1.57	28

1. Defined in Table 4 footnote.

FDA-00000012

Reference ID: 4095731

2. Percent reduction, in excess relative risk, achieved by adjustment.

3.5.6 Results from secondary, supportive, and sensitivity analyses

Figure 1 shows a result from Cox regression of ESRD occurrence after last PPI exposure, as determined by prescriptions filled by patients. Relative to patients who filled PPI prescriptions covering 30 or fewer days of treatment, this covariate-adjusted analysis showed ESRD occurring more frequently after exposure to >90 days of PPI, but not after 31-90 days.

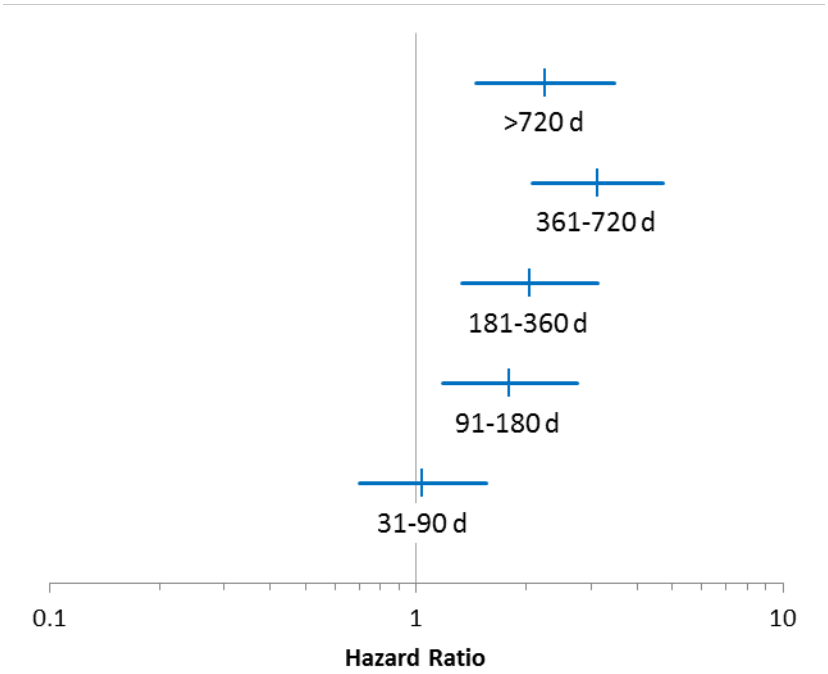

Figure 1: ESRD occurrence after last PPI exposure, according to duration of exposure, as measured by covariate-adjusted hazard ratio and 95% confidence interval, relative to ≤30 days of exposure.

An incompletely described, but supportive analysis identified a greater than two-fold PPI-associated risk of acute kidney injury (HR 2.15, 95% CI 2.00-2.32).

Table 6 shows results from Cox proportional hazards regression analyses for kidney outcomes in PPI vs. H2 new users and in PPI users vs. nonusers. When compared against primary analyses that adjusted for 21 covariates, propensity-score-matched sensitivity analyses produced the same HR estimate for the CKD outcome, but a much lower HR estimate for the ESRD outcome. Propensity-score-matched analyses with PPI-nonuse control produced higher PPI risk estimates than analyses with H2-new-use control.

Results from all sensitivity analyses were consistent with results from primary analysis (details not reproduced or discussed further in this review).

Table 6: Hazard ratios (HR) and 95% confidence intervals (95% CI) from Cox proportional hazards regression analyses of kidney outcomes in PPI vs. H2 new users and in PPI users vs. nonusers.

	PPI vs. H2 Adjusted [2]		PPI vs. H2 PS-matched [3]		PPI vs. non-PPI PS-matched [4]	
Kidney outcome [1]	HR	95 CI	HR	95 CI	HR	95 CI
eGFR <60	1.22	1.18-1.26	1.23	1.17-1.30	1.57	1.54-1.60
CKD	1.28	1.23-1.34	1.28	1.18-1.38	1.81	1.76-1.86
2-fold S_{cr} increase	1.53	1.42-1.65	1.63	1.47-1.81	1.86	1.80-1.93
>30% eGFR drop	1.32	1.28-1.37	1.32	1.25-1.39	1.67	1.64-1.70
ESRD	1.96	1.21-3.18	1.48	0.49-4.50	1.61	1.26-2.04
ESRD or >50% eGFR drop	1.47	1.38-1.57	1.59	1.45-1.74	1.83	1.77-1.89

1. Defined in Table 4 footnote.
2. PPI (N=173,321) vs. H2 (N=20,270) H2 adjusted by Cox regression for 21 baseline covariates.
3. PPI (N=20,270) vs. H2 (N=20,270), propensity-score (PS) matched.
4. N=173,321 PPI and N=173,321 non-PPI, propensity-score (PS) matched.

3.6 Strengths and Limitations

Limits to interpretation, mentioned by Xie, include (1) a non-representative study population (mostly white and older U.S. military veterans), (2) measurement errors inherent to administrative healthcare data, and (3) no information about over-the-counter medication use. Study strengths, mentioned by Xie, include (1) large sample size, (2) multiple kidney outcomes, including severe outcomes, such as ESRD, and (3) consistent results from sensitivity analysis.

3.7 Conclusions

According to Xie, the results suggested, "PPI exposure associates with increased risk of incident CKD, CKD progression, and ESRD."

4. DISCUSSION

Xie completed a cohort study of kidney outcomes after PPI exposure in VA patients with normal baseline kidney function (estimated glomerular filtration rate, eGFR, ≥60 mL/min/1.73 m^2). The primary analysis followed N=173,321 PPI and 20,270 H2 new users (mean ages 56.8 and 55.4 years), respectively, for at least five years and used laboratory data and U.S. Renal Database System (USRDS) linkage to ascertain kidney outcomes. Xie defined (1) chronic kidney disease (CKD) by two estimates of glomerular filtration (eGFR) <60 mL/min/m^2, separated by ≥90 days, and (2) end-stage renal disease (ESRD) by USRDS match. With CKD occurring frequently (36.8 and 25.7 per 1000 person-years) and ESRD infrequently (329 and 25 cases; 0.41 and 0.26 per 1000 person-years) after PPI and H2 new use, respectively, Cox regressions estimated covariate-adjusted CKD and ESRD relative risks at HR 1.28 (95% CI 1.23-1.34) and HR 1.96 (95% CI 1.21-3.18), respectively.

The following discussion of study results from Xie considers, in sequence, validity concerns, causal meaning, and implications for FDA regulatory action.

4.1 Validity

Xie deserves merit as a large study, which used objective data to ascertain kidney outcomes. Xie used statistical methods and diagnostic codes in administrative healthcare data to control for critical medical comorbidities. Sensitivity analyses addressed concerns related to possible effects from concomitant exposures to NSAIDs, ACEIs, or ARBs. Finally, Xie studied a heavily exposed patient group, with one of every third patient endorsing prescriptions sufficient for two years of treatment (Table 3).

However, a risk-of-bias assessment identified moderate threats to validity from the following five sources, confounding, selection bias, missing data, outcome misclassification, and selective reporting (ATTACHMENT 2). Because of threats from these multiple sources, DEPI judged the adjusted hazard ratios reported by Xie as subject to severe risk of bias because of moderate risks of bias in multiple domains.

Several validity threats deserve special comment. To protect against causal interpretation confounded by the medical indications for the use of a drug of concern, DEPI favors observational study designs with an active treatment control. In this context, Xie compared patients exposed to PPI, the drug of concern, to patients exposed to H2, an active drug viewed as a PPI alternative. However, data in Xie show substantial clinical non-equivalence between patients exposed to PPI or H2. For example, data in Xie show a comorbidity burden substantially greater in H2-exposed than PPI-exposed patients. The VA administrative healthcare record documented a PPI- or H2-use indication much more often in PPI-exposed than H2-exposed patients. Finally, statistical control for the measured medical comorbidities and indications produced substantial change (18-33%, depending on outcome, Table 5) in the estimates of risk from PPI vs. H2. These observations signify substantial potential for residual confounding due to factors either not considered by Xie or poorly captured in administrative healthcare databases.

Study selection required information in VA databases about eGFR, both before and after new use. Xie excluded new users frequently for this reason, with exclusions occurring more frequently in H2 than PPI new users (47.0% vs. 42.9%; Table 1). The direction and magnitude of any selection bias depends on the CKD or ESRD risk experience of the excluded patients. Suppose unobserved patients excluded for unavailable eGFR experienced higher absolute risks for CKD and ESRD. With H2 users excluded more often than PPI new users, analyses, restricted to patients not excluded, overestimate the true kidney risks from PPI relative to H2. Extreme bias could occur, if exclusion depended on both exposure and outcome, considered together.

CKD outcome information could be missing differentially between patient groups studied by Xie. Because of laboratory services differentially received from non-VA sources after PPI vs. H2 use, non-ascertainment or late ascertainment of CKD could have occurred more frequently after PPI than H2 new use. Biased outcome classification could have occurred, as well, if decisions by VA clinicians to order blood tests, including serum creatinine used for eGFR calculation, depended, directly or indirectly, on prior PPI or H2 use. Because the USRDS data source plausibly provided universal coverage, however, the ERSD results reported by Xie could

be safe from bias from missing data or outcome misclassification.

Design elements in Xie complicate interpretation of the hazard ratios reported by Cox regression. Simple cohort designs, with relative treatment outcomes modeled by Cox regression, can mimic results expected from randomized clinical trials (RCT) with outcomes analyzed according to the intention to treat. An intention-to-treat interpretation does not apply to Xie, because Xie used information, knowable only later, to exclude patients up front from the H2 new-use cohort. Critically, Xie excluded, from the H2 new-use cohort, patients who subsequently filled prescriptions for PPI. By excluding from the control group presumably high-risk patients who switched from H2 to PPI, the Xie design exaggerates outcome risk estimates, relative to true intention-to-treat analogues. Xie does not mimic the as-treated RCT either. Xie's basic analysis did not use methods designed to estimate risks specifically related to time on PPI vs. H2.

As final concerns, unmeasurable over-the-counter PPI use threatens the accuracy of the Xie risk estimates. Over-the-counter PPI use by H2 new users, for example, could cause Xie to underestimate kidney risks from PPI. As described in the DEPI February review of Lazarus, et al., 2016, reliance on an imperfect eGFR proxy for directly measured GFR could add bias due to selection and outcome misclassification.

Determining the probable direction of overall bias in the face of multiple sources of bias is difficult. Individual sources of bias may have competing effects on the direction on the association between exposure and outcome.

4.2 Causality

The Xie CKD result in VA patients, HR 1.28 (95% CI 1.23-1.34), mirrors results from two studies, by Lazarus, HR 1.50 (95% CI 1.14-1.96) in ARIC and HR 1.17 (95% CI 1.12-1.23) in Geisinger. However, the same limits to causal interpretation apply to Xie and Lazarus (ATTACHMENT 3). Neither study presents supporting evidence specific to (1) CKD pathology (e.g., kidney failure due to interstitial as opposed to glomerular injury) or (2) PPI dose.

Arguably, the larger ESRD risk (HR 1.96) estimated in Xie supports PPI causal explanation more forcefully for than the lower CKD risks estimated in Xie and Lazarus. However, producing doubt about the integrity of the Cox regression, the ESRD result from unadjusted Cox regression (HR 2.17) contradicts the ratio of incidence densities (IRR 1.56; Table 4). Moreover, the result for adjusted Cox regression appears non-robust in sensitivity analysis for ESRD (Table 6).

Case reports establish (Sierra, et al., 2007) and FDA labels recognize acute interstitial nephritis (AIN) as a possible consequence from PPI hypersensitivity. Xie cites case series that report permanent loss of kidney function occurring frequently in patients after AIN from PPI. However, biological explanations, which attribute CKD or ESRD to subclinical PPI hypersensitivity leading insidiously to interstitial nephritis and fibrosis, seem speculative at this time.

4.3 Public Health Implications

Because of widespread PPI use, small relative risk from PPI could translate into large public health impact. Critically, Xie identifies possible risks manifesting not only as laboratory test abnormalities (reductions in eGFR), but also as ESRD, an unequivocally severe clinical outcome. In analyses specific to the VA patient population and unadjusted for covariate differences, Xie bounds the absolute risks (numbers needed to harm, NNH) at one CKD and one ESRD per 90 and 6780 PPI exposures (Table 4), respectively.

One result in Xie suggests ESRD risks larger in patients with PPI >90 days than in patients with PPI ≤90 days (Figure 1). This result, combined with other evidence, could support recommendations for clinical prudence. For example, clinical prudence could demand not only limiting PPI to recommended durations for well-established indications, but also monitoring kidney function during long-term PPI.

5. CONCLUSION

Xie used observational study methods to estimate covariate-adjusted CKD and ESRD relative risks from PPI vs. H2 at HR 1.28 (95% CI 1.23-1.34) and HR 1.96 (95% CI 1.21-3.18), respectively. Xie extended results from other observational studies to suggest ESRD, in addition to CKD, as a possible adverse outcome from PPI. Because of validity threats from multiple sources, including confounding, selection bias, missing data, outcome misclassification, and selective reporting, however, DEPI judged the adjusted hazard ratios reported by Xie as subject to severe risk of bias.

6. RECOMMENDATIONS FOR DGIEP

Finding the evidence for causal association too weak to offset a severe risk of bias, DEPI cannot make a recommendation for regulatory action at this time.

7. REFERRENCES

1. Elwood, M, 1988, Critical Appraisal of Epidemiology Studies and Clinical Trials, 2nd edition, New York: Oxford University Press.
2. Lazarus, B, Y Chen, FP Wilson, Y Sang, AR Chang, J Coresh, and ME Grams, Published online January 11, 2016, Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease, JAMA Intern Med, doi:10.1001/jamainternmed.2015.7193.
3. Levey, AS, LA Stevens, CH Schmid, YL Zhang, AF Castro, 3rd, HI Feldman, JW Kusek, P Eggers, F Van Lente, T Greene, J Coresh and EPI-CKD (Chronic Kidney Disease Epidemiology Collaboration), 2009, A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med, 150:604-12.
4. Sierra, F, M Suarez, M Rey and MF Vela, 2007, Systematic Review: Proton Pump Inhibitor-Associated Acute Interstitial Nephritis, Aliment Pharmacol Ther, 26:545-53.
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http://www.riskofbias.info on June 29, 2015.

6. Xie, Y, B Bowe, T Li, H Xian, S Balasubramanian, and Z Al-Aly, Published online April 14, 2016, Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD, J Am Soc Nephrol, doi: 10.1681/ASN.2015121377.

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C Kim / (OB)

D Griebel / J Korvick / A Mulberg / B Strongin / V Moyer (OND)

ATTACHMENT 1: ICD-9-CM and CPT code sets used to define medical comorbidities.[1]

Condition	ICD-9-CM	CPT Code
Cerebrovascular Disease	433.01, 433.11, 433.21, 433.31, 433.81, 433.91	NA
Cardiovascular Disease	398.91, 402.01, 402.11, 402.91, 410, 411, 413, 414.0, 414.9, 428, 36.01, 36.02, 36.05, 36.06, 36.09-36.17, 36.19	92980- 92982, 92984- 92996, 3351, 33521- 33523, 33533- 33536
Dementia	290, 294, 331	NA
Diabetes Mellitus	250.1-250.7, 250.9	NA
Hepatitis C	070.41, 070.44, 070.51, 070.54	NA
HIV	042, V08, 488–490	NA
Hypertension	401.1, 401.9, 402.1, 402.9, 404.1, 404.9, 405.11, 405.19, 405.91, 405.99	NA
Hyperlipidemia	272.0,272.2,272.4	NA
Chronic Lung Disease	491, 492, 493, 496, 518.1,518.2	NA
Peripheral Artery Disease	440.0-440.9, 38.13-38.16, 38.18,39.22,39.24 -39.26,39.28	35450, 35452, 35454, 35456, 35458, 35459, 35470-35475, 35879, 75962, 75964, 75966, 75968, 33322, 33335, 33860, 33870, 35511, 35516,35518, 35521, 35531, 35533, 35536, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35560, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35612, 35616, 35621, 35623, 35631, 35636, 35641, 35646, 35650, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671

1. Xie, Y, B Bowe, H Xian, S Balasubramanian, and Z Al-Aly, 2016, Estimated GFR Trajectories of People Entering CKD Stage 4 and Subsequent Kidney Disease Outcomes and Mortality, Am J Kidney Dis, Article in Press, doi: 10.1053/j.ajkd.2016.02.039.

ATTACHMENT 2: Risk-of-bias assessment [1].

Domain	Risk of Bias Judgment	Support for Judgment
Bias due to confounding	MODERATE	Observational (non-randomized) study design with controls for important confounding variables (age, race, hypertension, diabetes, and cardiovascular comorbidity).
Bias in selection of participants into the study	MODERATE	PPI new use permits previous H2 use, but H2 new use prohibits previous PPI use. The H2 new user cohort excludes patients with any PPI use during follow-up. Selection for study requires results from kidney function tests. Clinical decisions to measure kidney function plausibly relate to both PPI exposure and kidney disease risk.
Bias in measurement of interventions	LOW	Exposure determined by prescriptions filled by patients. Both prescription non-adherence and over-the-counter PPI use possible.
Bias due to departures from intended intervention	LOW	Sensitivity analysis addressed co-intervention with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
Bias due to missing data	MODERATE	Follow-up via USRDS for ESRD viewed as complete. However, complete follow-up for non-ESRD endpoints presumes all medical care received from VA.
Bias in measurement of outcomes	MODERATE	Frequency of assessments for CKD endpoints plausibly related to exposure, either directly or indirectly.
Bias in selection of the reported result	MODERATE	No evidence for a statistical analysis plan completed in advance of data analysis.
Overall bias	SEVERE	Moderate risk of bias in multiple domains.

1. Sterne JAC, JPT Higgins, BC Reeves on behalf of the development group for ACROBAT-NRSI, September 2014, A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24, Retrieved from http://www riskofbias.info on June 29, 2015.

ATTACHMENT 3: Assessment for causation [1].

A. Description of evidence

1. Exposure	Prescription for proton pump inhibitor (PPI).
2. Outcome	Incident chronic kidney disease (CKD), defined by two eGFRs <60 mL/min/m^2, ≥90 days apart. Incident end-stage renal disease (ESRD), defined by linkage to the United States Renal Database System.
3. Design	Cohort
4. Study population	N=173,321 VA patients, with (1) no PPI prescription between October 1999 and September 2006, (2) PPI prescription (new use) between October 2006 and September 2008, (3) eGFR ≥60 mL/min/m^2 within 90 days before new use, and (4) at least one eGFR after new use. N=20,270 VA patients, with (1) no PPI or H2 prescription between October 1999 and September 2006, (2) H2 prescription (new use) between October 2006 and September 2008), (3) no PPI prescription between October 2009 and September 2013, (4) eGFR ≥60 mL/min/m^2 within 90 days before new use, and (4) at least one eGFR after new use.
5. Main result	Covariate-adjusted hazard ratio (HR; PPI vs. H2) and 95% confidence interval (CI): CKD HR 1.28 (95% CI 1.23-1.34) and ESRD HR 1.96 (95% CI 1.21-3.18).

B. Non-causal explanations

6. Observation bias	Risk of bias from exposure and outcome misclassification scored as low and moderate, respectively; See ATTACHMENT 2.
7. Confounding	Risk of bias due to confounding scored as moderate; See ATTACHMENT 2.
8. Chance	Excluded by lower 95% confidence limit >1.0.

C. Features consistent with causation

9. Time relationship	Study design fixes first PPI exposure as a temporal intermediate between states of normal and reduced kidney function. However, analyses do not distinguish disease risks according to (1) current vs. past exposure, (2) time since first exposure, or (3) time since last exposure.
10. Strength	1.2-fold risk (observed for CKD) generally regarded as weak support for causal inference. Stronger 2.0-fold ESRD risk observed in primary analysis, but lower 1.5-fold risk observed in propensity-score-matched sensitivity analysis.
11. Dose response	No useful information.
12. Consistency	Association also observed for acute kidney injury.
13. Specificity	No information.

D. External validity

14. Eligible population	VA patients with (1) PPI or H2 new use soon after eGFR measured ≥60 mL/min/1.73 m^2 and (2) at least one eGFR measured after new use.
15. Source population	VA patients with PPI or H2 new use and recent eGFR ≥60 mL/min/1.73 m^2.
16. Target population	Adults with normal kidney function and medical indication for PPI or H2.

E. Consistency with other evidence

17. Consistency	Results from other observational studies also show association between PPI and acute kidney injury. Xie replicates Lazarus, et al., 2016.
18. Specificity	PPI associated with many different adverse outcomes, including interstitial nephritis,

		acute kidney injury, atrophic gastritis, vitamin B12 deficiency, *Clostridium difficile*-associated diarrhea, osteoporosis-related bone fracture, hypomagnesemia, and community-acquired pneumonia.[2]
19.	Plausibility	CKD as possible result from subclinical PPI hypersensitivity leading to interstitial nephritis and fibrosis.
20.	Coherence	No information added by Xie.

1. Elwood, M, 1988, Critical Appraisal of Epidemiology Studies and Clinical Trials, 2nd edition, New York, Oxford University Press.

2. Schoenfeld, AJ, and D Grady, Published online January 11, 2016, Adverse Effects Associated with Proton Pump Inhibitors, JAMA Intern Med, 2016, doi:10.1001/jamainternmed.2015.7927.

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/s/

JACQUELINE D LEEHOFFMAN
05/09/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of a Research Article

Date:	02/29/2016
Reviewer(s):	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Deputy Director:	David Shih, MD MS Division of Epidemiology I
Drug Name(s):	Proton Pump Inhibitor Class: rabeprazole (Aciphex), dexlansoprazole (Dexilant), esomeprazole (Nexium), esomeprazole magnesium (Vimovo), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), omeprazole & sodium bicarbonate (Zegerid), esomeprazole strontium
Subject:	Critique of Lazarus, et al., Published online January 11, 2016, Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease, JAMA Intern Med, doi:10.1001/jamainternmed.2015.7193
Application Type/Number:	NDA 20973, NDA 204736, NDA 22287, NDA 21153, NDA 22101, NDA 21957, NDA 21689, NDA 022511, NDA 021428, NDA 20406, NDA 19810, NDA 22056, NDA 20987, NDA 20988, NDA 22020, NDA 021849, NDA 21636, NDA 21706, NDA 202342
Applicant/sponsor:	Multiple
OSE RCM #:	2016-166

TABLE OF CONTENTS

EXECUTIVE SUMMARY

To guide potential regulatory actions, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to critique and interpret a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of chronic kidney disease.

A research paper by Lazarus, et al.,[1] published online January 11, 2016, extends to chronic kidney disease a general concern about adverse outcomes from PPI use.

Lazarus completed two cohort studies of proton pump inhibitors (PPIs) and incident chronic kidney disease (CKD) in persons with normal kidney function (estimated glomerular filtration rate, eGFR, ≥60 mL/min/1.73 m^2). The main study followed N=10,482 Atherosclerosis Risk in Communities (ARIC) participants (median age 62 years) for median 13.9 years and determined the association between PPI use (3.1% in 2 weeks before cohort entry between 1996 and 1999) and subsequent CKD, defined by (1) Renal Data System Registry match or (2) diagnostic code algorithm applied to hospital and death records. A confirmatory study followed N=248,751 Geisinger Health System patients (median age 50 years) for median 6.2 years and determined the association between PPI use (6.8% in 90 days before cohort entry between 1997 and 2014) and subsequent CKD, defined by (1) Renal Data System Registry match or (2) first sustained outpatient eGFR <60 mL/min/1.73 m^2. Adjusting for baseline covariates, Cox proportional hazards regression analyses detected statistically significant associations between PPI use at cohort entry and subsequent CKD, with risk estimated by hazard ratio (HR) and 95% confidence interval (CI) at HR 1.50, 95% CI 1.14-1.96 (p=0.003) in ARIC and HR 1.17, 95% CI 1.12-1.23 (P<0.001) in Geisinger.

A risk-of-bias assessment identified moderate threats to study validity from confounding and outcome misclassification. Even though Lazarus used reasonably sound and acceptable observational methods and included statistical controls for main CKD risk factors (older age, black race, hypertension, diabetes, cardiovascular disease, and proteinuria), the evidence in Lazarus alone does not permit a confident conclusion that identifies PPIs as a cause for CKD. In addition, DEPI found little evidence from external sources to support causal association between PPIs and CKD.

To guide regulatory actions, DEPI recommends that DGIEP combine results from Lazarus with evidence from other sources, such as evidence about PPIs and other forms of kidney injury, including acute kidney injury.

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[1] Lazarus, B, Y Chen, FP Wilson, Y Sang, AR Chang, J Coresh, and ME Grams, Published online January 11, 2016, Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease, JAMA Intern Med, doi:10.1001/jamainternmed.2015.7193.

Reference ID: 3893803

1. INTRODUCTION

To guide potential regulatory actions, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to critique and interpret a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of chronic kidney disease.

The PPI active ingredients (drug name, year approved) include omeprazole (Prilosec, 1989), lansoprazole (Prevacid, 1995), rabeprazole (Aciphex, 1999), pantoprazole (Protonix, 2000), esomeprazole (Nexium, 2001), and dexlansoprazole (Dexilant, 2009). Labelled adult indications for PPI use, according to the December 2014 Prescribing Information for delayed-release omeprazole, include duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and maintenance of healing of erosive esophagitis.[2]

A research paper by Lazarus, et al., 2016,[1] extends to chronic kidney disease a general concern about adverse outcomes from PPI use. In response to a citizen petition, FDA agreed that "reasonable evidence" exists to support causal association between drugs in the PPI class and acute interstitial nephritis.[3] However, medicine generally regards acute interstitial nephritis as a rare and reversible hypersensitivity reaction not typically associated with long-term consequences, such as chronic kidney disease. Other concerns appearing under Warnings and Precautions in the Prescribing Information for delayed-release omeprazole include cyanocobalamin (vitamin B-12) deficiency, *Clostridium difficile* associated diarrhea, bone fracture, and hypomagnesemia.[2]

The DGIEP consult to DEPI requested a critique of "the epidemiologic methods and interpretability of the [Lazarus] article regarding the correlation of PPI usage and chronic kidney disease to guide potential regulatory actions." Known causes for chronic kidney disease include black race, hypertension, diabetes, and cardiovascular disease.[4]

1.2. Regulatory History

Relevant regulatory events include:

Date	Event
September 14, 1989	First PPI (omeprazole, Prilosec, NDA 019810) approved in U.S.

[2] Highlights of Prescribing Information for PRILOSEC (omeprazole) delayed-release capsules, December 2014, Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm on January 29, 2016.

[3] FDA Response to Citizen Petition from Public Citizen, Retrieved from http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=4324 on January 29, 2016, Page 16.

[4] National Institute of Diabetes and Digestive and Kidney Diseases, At Risk for Kidney Disease?, Retrieved from http://www.niddk nih.gov/health-information/health-communication-programs/nkdep/learn/causes-kidney-disease/at-risk/Pages/are-you-at-risk.aspx on January 27, 2016.

Reference ID: 3893803

This Review consulted source documents listed in the following table.

Date	Source	Document
April 5, 2005	CDER ODS	Mackey, AC, ODS Postmarketing Safety Review, lansoprazole (Prevacid), esomeprazole (Nexium), and interstitial nephritis
August 23, 2011	Citizen Petition	Public Citizen, Retrieved from http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0741-0001 on January 20, 2016
August 22, 2013	CDER DEPI-II	Greene, P, Proton Pump Drug Utilization, RCM # 2013-1526
October 29, 2014	CDER DPV-II	Volpe, C, Pharmacovigilance Memorandum, Dexilant (dexlansoprazole) and acute interstitial nephritis
October 29, 2014	CDER DPV-II	Volpe, C, Pharmacovigilance Review, Prilosec OTC, Prevacid 24HR, Zegerid OTC, Nexium 24HR, and Acute Interstitial Nephritis, TSI 1306, RCM# 2011-4606
October 31, 2014	CDER	FDA Response to Citizen Petition from Public Citizen, Retrieved from http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=4324 on January 29, 2016.
December 16, 2014	CDER DNDP	Memorandum, Change in Status of Trackable Safety Issue (TSI) 1306

2. REVIEW METHODS AND MATERIALS

DEPI used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI)[5] to guide its risk-of-bias assessment of Lazarus, et al., 2016.[1] The ACROBAT-NSRI conceives seven categories of risk to the internal validity of observational studies, (1) confounding, (2) selection, (3) measuring the intervention, (4) co-intervention, (5) missing data, (6) measuring the outcome, and (7) selective reporting.

[5] Sterne JAC, JPT Higgins, BC Reeves on behalf of the development group for ACROBAT-NRSI, September 2014, A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24, Retrieved from http://www riskofbias.info on June 29, 2015.

DEPI used the 20-item scheme proposed by Elwood, 1998,[6] to guide its assessment for causation.

1.1. Background

To guide potential regulatory actions, the Division of Gastroenterology and Inborn Error Products (DGIEP) asked the Division of Epidemiology I (DEPI) to critique and interpret a recently published scientific article about the use of proton pump inhibitor (PPI) medications and the subsequent occurrence of chronic kidney disease.

The PPI active ingredients (drug name, year approved) include omeprazole (Prilosec, 1989), lansoprazole (Prevacid, 1995), rabeprazole (Aciphex, 1999), pantoprazole (Protonix, 2000), esomeprazole (Nexium, 2001), and dexlansoprazole (Dexilant, 2009). Adult indications for PPI use prescribed by physician, according to the December 2014 label for omeprazole, include H. pylori infection, peptic (duodenal and gastric) ulcer disease (PUD), gastroesophageal reflux disease (GERD), gastrin-secreting tumors (Zollinger-Ellison syndrome), and erosive esophagitis.[7] With respect to long-term use, the label notes that controlled studies of omeprazole for maintenance of healing of erosive esophagitis "do not extend beyond 12 months" and "some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years." Directions for over-the-counter omeprazole instructs consumers to limit use to 14-day treatment courses, repeated no more frequently than every four months, unless directed by a doctor.[8]

Labelled warnings specifically associated with long-term omeprazole use include atrophic gastritis, acute interstitial nephritis, vitamin B deficiency, bone fracture, and hypomagnesemia. A research paper by Lazarus, et al.,[1] published online January 11, 2016, extends to chronic kidney disease a general concern about adverse outcomes from long-term PPI use. The DGIEP consult to DEPI requests a critique of "the epidemiologic methods and interpretability of the (Lazarus) article regarding the correlation of PPI usage and chronic kidney disease to guide potential regulatory actions."

3. REVIEW RESULTS

3.1 Study Overview

Lazarus reported results from two studies of proton pump inhibitors (PPI) and chronic kidney disease (CKD), a primary study completed in the Atherosclerosis Risk in Communities (ARIC) research cohort and a secondary study completed in Geisinger Health System data.

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[6] Elwood, M, 1988, Critical Appraisal of Epidemiology Studies and Clinical Trials, 2nd edition, New York: Oxford University Press.

[7] Highlights of Prescribing Information, PRILOSEC (omeprazole), December 2014, Retrieved from Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) on January 19, 2016.

[8] Prilosec OTC Product Monograph, Retrieved from http://www.prilosecotc.com/en-us/hcp/prilosec-otc-dosage on November 23, 2015.

3.2 Objectives: Primary and Secondary

Lazarus aimed to measure the association between PPI use and incident chronic kidney disease in the general population.

3.3 Study Design

Both ARIC and Geisinger used cohort designs to study PPI and CKD.

3.4 Methods

3.4.1 Population sources and study time period

ARIC, a long-running prospective cohort study, recruited 15,792 45-64 year-old adults, between January 12, 1987, and March 29, 1990, from four U.S. communities (Forsyth, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland).[9] The timeframe for the ARIC PPI-CKD analysis covered the period February 1, 1996 through December 31, 2011.

Geisinger, an integrated health system currently serving more than 3 million residents of Pennsylvania and New Jersey,[10] adopted an outpatient electronic health record (EHR) in 1995.[11] The timeframe for the Geisinger analysis covered the period February 13, 1997, through October 9, 2014.

3.4.2 Study subject selection

For the primary PPI-CKD analysis in ARIC, Lazarus selected 10,482 of 11,656 (89.9%) persons who attended, between February 1, 1996, and January 30, 1999, an ARIC study visit (ARIC study visit 4). At baseline (cohort entry), Lazarus excluded (1) N=215 (1.8%) persons with values missing for kidney health variables (estimated glomerular filtration rate, eGFR, or urinary albumin to creatinine ratio), (2) N=725 (6.2%) persons with poor kidney function (eGFR <60 mL/min/1.73 m^2), and (3) N=234 (2.0%) persons with values missing for critical confounding variables.[12] Lazarus initiated the PPI-CKD cohort analysis at ARIC study visit 4 because (1) ARIC first measured the urinary albumin to creatinine ratio at study visit 4 and (2) few ARIC participants reported PPI use before 1996.

For the PPI-CKD analysis in Geisinger, Lazarus constructed a cohort, defined by the first

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[9] Bash, LD, J Coresh, A Kottgen, RS Parekh, T Fulop, Y Wang and BC Astor, 2009, Defining Incident Chronic Kidney Disease in the Research Setting: The Aric Study, Am J Epidemiol, 170:414-24.

[10] About US – Geisinger, Retrieved from https://www.geisinger.org/pages/about-geisinger/index.html on January 20, 2016.

[11] Paulus, RA, K Davis and GD Steele, 2008, Continuous Innovation in Health Care: Implications of the Geisinger Experience, Health Aff (Millwood), 27:1235-45.

[12] Required data items included years of education, health insurance status, cigarette smoking, body mass index, systolic blood pressure, use of antihypertensive or anticoagulant medication, or prevalent hypertension, diabetes mellitus, or cardiovascular disease.

Reference ID: 3893803

Geisinger Health System outpatient encounter between February 13, 1997, and October 9, 2014, with information complete for blood creatinine concentration and systolic blood pressure. After excluding patients with poor kidney function (eGFR <60 mL/min/1.73 m^2), this cohort contained 248,751 patients.

3.4.3 IRB/OMB approval, patient consent if needed.

Six university institutional review boards (IRB) approved the parent ARIC study. Participation in ARIC required written informed consent. Lazarus did not mention the IRB status of the Geisinger study.

3.4.4 Exposure

At baseline, the ARIC PPI-CKD analysis defined PPI exposure as use during the preceding 2 weeks. To determine use, investigators visually inspected, at the baseline ARIC study visit, the pill bottles, submitted by ARIC participants, "for all medications used during the preceding 2 weeks." Starting in September 2006, ARIC used annual telephone follow-up to update prescription medication use. Specifically, at each annual telephone follow-up, ARIC participants, asked to assemble all current medications, "read the names of all the medications prescribed by a doctor."

The Geisinger PPI-CKD analysis (1) determined PPI exposure at baseline by prescription, in the EHR, recorded in the 90 days before baseline and (2) updated PPI exposure throughout the study follow-up period according to prescription information in the EHR.

In both studies, the primary comparator was PPI non-use, with cohort entry defined by baseline visit in ARIC and first date in Geisinger with non-missing values for both creatinine and systolic blood pressure.

3.4.5 Outcome

ARIC ascertained hospitalization, end-stage renal disease (ESRD), and death endpoints through annual telephone survey, community hospital surveillance, obituaries in local newspapers, state departments of vital statistics, U.S. Renal Data System Registry[13] match, and National Death Index match.[14] ARIC investigators extracted ICD-CM-9 discharge codes from hospital records and ICD-10 cause of death codes from death registry matches. ARIC defined incident CKD by (1) Renal Data System Registry match or (2) diagnostic code algorithm applied to hospital and death records (ATTACHMENT 1).

The Geisinger PPI-CKD defined incident CKD by (1) Renal Data System Registry match or (2)

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[13] A national data system, funded by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), collaborates with the Centers for Medicare & Medicaid Services. See http://www.usrds.org/.

[14] Rebholz, CM, J Coresh, SH Ballew, B McMahon, SP Whelton, E Selvin and ME Grams, 2015, Kidney Failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: Comparing Ascertainment of Treated and Untreated Kidney Failure in a Cohort Study, Am J Kidney Dis, 66:231-9.

first outpatient eGFR <60 mL/min/1.73 m^2, "sustained at all subsequent assessments of the eGFR."

3.4.6 Analysis plan

To estimate eGFR, ARIC used plasma creatinine concentrations measured by a modified kinetic Jaffé method and race-, sex-, and age-specific equations from the Chronic Kidney Disease Epidemiology Collaboration.[15]

ARIC definitions for three critical confounding variables, determined at baseline, follow,

- Prevalent hypertension – systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication in past 2 weeks.

- Prevalent diabetes mellitus – fasting blood glucose concentration ≥126mg/dL, random glucose concentration ≥200 mg/dL, self-reported physician diagnosis of diabetes mellitus, or self-reported use of antidiabetic medication in past 2 weeks.

- Prevalent cardiovascular disease – self-reported physician diagnosis of coronary heart disease or stroke.

Primary analyses used Cox proportional hazard regression to estimate hazard ratios and 95% confidence intervals, with the exposure (PPI use vs. nonuse) defined by PPI use in the 2 weeks before cohort entry (ARIC) or PPI prescription in the 90 days before cohort entry (Geisinger), the outcome defined as time to incident CKD, and follow-up censored early upon death, loss to follow-up (ARIC), or last encounter (Geisinger).

ARIC analyses adjusted for factors, measured at baseline, including demographic variables (age, sex, race, and study center), socioeconomic status (health insurance and highest level of education), clinical measurements (eGFR, logarithm of urinary albumin to creatinine ratio, cigarette smoking status, systolic blood pressure, and body mass index), prevalent comorbidities (diabetes mellitus and cardiovascular disease), and concomitant medications (antihypertensive and anticoagulant). Factors considered a priori for adjustment included annual household income and concomitant use of nonsteroidal anti-inflammatory drugs (NSAID), aspirin, diuretics, and statins. With results not shown, Lazarus asserted that excluding these additional factors from final models "did not affect the results of adjusted analyses."

Geisinger analyses adjusted for factors, measured at baseline, including demographic variables (age, sex, and race), EHR measurements (eGFR, smoking status, body mass index, and systolic blood pressure), comorbidities captured by outpatient and inpatient billing codes (diabetes mellitus and cardiovascular disease), and prescriptions for concomitant medications (antihypertensive, anticoagulant, statin, aspirin, and NSAID).

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[15] Levey, AS, LA Stevens, CH Schmid, YL Zhang, AF Castro, 3rd, HI Feldman, JW Kusek, P Eggers, F Van Lente, T Greene, J Coresh and EPI-CKD (Chronic Kidney Disease Epidemiology Collaboration), 2009, A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med, 150:604-12.

When calculating adjusted risk differences, Lazarus did not describe the method used to adjust 10-year cumulative risks for covariates.

Secondary and supportive covariate-adjusted Cox regression analyses,

1. Defined PPI use as a time-varying exposure.

2. Replaced CKD with acute kidney injury (AKI; ICD-9-CM 584.x hospitalization or ICD-10 N17x death in ARIC and medical encounter for ICD-9-CM 584.x in Geisinger).[16]

3. Subgrouped by age, sex, race, diabetes, or concomitant medications (diuretics and angiotensin-converting enzyme inhibitor; ACE-I, or angiotensin receptor blocker, ARB).

4. Compared PPI use vs. histamine 2 (H2) receptor antagonist use.

5. Compared PPI use vs. nonuse, with nonuse controls selected by 1:1 nearest neighbor propensity score match.

6. Excluded baseline PPI users (Geisinger only).

7. Excluded persons with albuminuria (albumin to creatinine ratio >30 mg/g in ARIC and 1+ protein on dipstick in Geisinger).

3.5 Results

3.5.1 Exposure prevalence

At study visit 4 (February 1, 1996, through January 30, 1999), ARIC recorded recent (within 2 weeks) PPI use (with or without H2 use) and H2 use (without PPI use) in 322 (3.1%) and 956 (9.1%) of 10,482 participants, respectively. The prevalence of PPI use increased over time, from 10% in 2006 to 27% in 2011.

At baseline medical encounters between February 13, 1997, and October 9, 2014, Geisinger recorded recent (within 90 days) PPI use (with or without H2 use) and H2 use (without PPI use) in 16,900 (6.8%) and 6640 (2.7%) of 248,751 patients, respectively.

3.5.2 Other variables

Table 1 summarizes baseline information, according to study population (ARIC or Geisinger) and exposure category (PPI use, H2 use, or nonuse). PPI vs. nonuse differences important to confounding included hypertension (ARIC: 54.3% vs. 44.8%; Geisinger 33.3% vs. 30.2%), diabetes (ARIC: 14.9% vs. 15.6%; Geisinger: 10.8% vs. 10.4%), cardiovascular disease (ARIC: 13.7% vs. 10.8%; Geisinger: 11.3% vs. 8.7%), and concomitant NSAID use (ARIC: 27.6% vs. 33.2%; Geisinger: 13.9% vs. 9.5%). PPI, H2, and nonuse categories differed substantially

[16] PPI-AKI analyses, which included persons with eGFR between 15 and 59 mL/min/1.73 m^2, selected 11,145 participants, rather than 10,482 participants, from ARIC.

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according to concomitant antihypertensive, diuretic, aspirin, and statin use (Table 1).

Table 1: Baseline characteristics of study populations for selected other variables. Copied from Table 1 in Lazarus, et al., 2016.[1]

	ARIC (N=10,482)			Geisinger (N=248,751)		
Other variable	PPI N=322	H2 N=956	Nonuse N=9204	PPI N=16,900	H2 N=6640	Nonuse N=225,211
Age, mean (SD), y	62.8 (5.5)	63.1 (5.5)	62.5 (5.6)	50.0 (15.9)	50.3 (16.3)	49.5 (16.3)
Male sex, %	42.5	39.3	44.4	43.2	42.6	43.5
White race, %	86.0	84.2	77.9	94.6	96.4	95.5
Health insurance, %	92.2	88.9	85.6	NA	NA	NA
Annual household income <$25,000	23.6	29.7	29.7	NA	NA	NA
eGFR, mean (SD), mL/min/1.73 m^2	87.8 (13.4)	86.5 (13.5)	88.9 (13.1)	94.9 (17.7)	95.2 (18.2)	96.0 (18.0)
Prevalent medical condition, %						
Hypertension	54.3	50.0	44.8	33.3	34.0	30.2
Diabetes	14.9	18.0	15.6	10.8	9.7	10.4
Cardiovascular disease	13.7	14.1	10.8	11.3	11.8	8.7
Concomitant medication use						
Antihypertensive	55.3	48.5	39.9	32.0	31.3	20.6
ACE-I/ARB	16.8	13.4	12.9	15.5	13.4	9.6
Diuretic	16.1	12.1	9.6	13.8	12.6	8.3
Aspirin	64.9	67.6	54.9	7.8	5.9	3.9
NSAID	27.6	32.8	33.2	13.9	14.4	9.5
Statin	20.2	13.6	10.3	13.9	11.7	6.1

3.5.3 Primary results

Over median 13.9 year follow-up, ARIC ascertained 56 (14.2 per 1000 person-years) and 1382 (10.7 per 1000 person-years) CKD events in baseline PPI users and PPI nonusers, respectively (unadjusted hazard ratio, HR, 1.45, 95% confidence interval, CI, 1.11-1.90; adjusted HR 1.50, 95% CI 1.14-1.96). ARIC analyses estimated 10-year CKD risk at 11.8% and 8.5% in baseline PPI users and PPI nonusers, respectively (covariate-adjusted risk difference, RD, 3.3%; number needed to treat (NNT) to cause one additional CKD case, NNT, 30; covariate-adjusted risk odds ratio, ROR, 1.44; confidence interval not reported).

Over median 6.2 year follow-up, Geisinger ascertained 1921 (20.1 per 1000 person-years) and 28,226 (18.3 per 1000 person-years) CKD events in baseline PPI users and PPI nonusers, respectively (HR 1.20, 95% CI 1.15-1.26; adjusted HR 1.17, 95% CI 1.12-1.23). Geisinger analyses estimated 10-year CKD risk at 15.6% and 13.9% in baseline PPI users and PPI nonusers, respectively (RD 1.7%; NNT 59).

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3.5.4 Results from subgroup, secondary, and sensitivity analyses

Subgroup analyses suggested CKD risk from PPIs higher in baseline diuretic users than diuretic nonusers.

With 56 CKD and 47 AKI events in baseline PPI users from ARIC and 1921 CKD and 728 AKI events in baseline PPI users from Geisinger, Table 2 shows all results from primary, secondary, and sensitivity analysis in Lazarus, et al., 2016.[1]

Table 2: Study results (covariate-adjusted hazard ratios, HR, and 95% confidence intervals, CI) extracted from Table 2, Table 3, and text in Lazarus, et al., 2016.[1]

	Chronic Kidney Disease Outcome				Acute Kidney Injury Outcome			
	ARIC		Geisinger		ARIC		Geisinger	
Comparison	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Inactive comparator analyses (PPI use vs. PPI nonuse)								
primary result	1.50	1.14-1.96	1.17	1.12-1.23	1.64	1.22-2.21	1.31	1.22-1.42
PPI twice daily	NA		1.46	1.28-1.67	NA		1.62	1.32-1.98
PPI once daily	NA		1.15	1.09-1.21	NA		1.28	1.18-1.39
PPI as time-varying effect	1.35	1.17-1.55	1.22	1.19-1.25	1.49	1.25-1.77	1.54	1.47-1.60
baseline PPI users excluded	NA		1.24	1.20-1.28	NA		1.66	1.57-1.75
propensity score matched	1.76	1.13-2.74	1.16	1.09-1.24	2.00	1.24-3.22	1.29	1.16-1.43
albuminurics excluded	1.45	1.09-1.96	1.19	1.13-1.25				
Active comparator analysis								
PPI use vs. H2 use	1.39	1.01-1.91	1.29	1.19-1.40	1.58	1.05-2.40	1.30	1.13-1.48
Negative control analysis								
H2 use vs. H2 nonuse	1.15	0.98-1.36	0.93	0.88-0.99	1.03	0.84-1.26	0.98	0.89-1.10

With results not shown, Lazarus asserted that analyses of a fuller ARIC dataset, with multiple imputations for missing variables, produced the same inferences as analyses of an ARIC dataset restricted to participants with complete data.

3.6 Strengths and Limitations

Limits to interpretation, mentioned by Lazarus, included bias from (1) uncontrolled confounding related to observational (non-randomized) study design, (2) medical surveillance for adverse outcomes more active in PPI users than nonusers, (3) poor sensitivity of hospital discharge codes for CKD (ARIC only), (4) selecting prevalent PPI users, in addition to incident (new) PPI users, and (5) PPI exposure misclassification caused by false reporting (ARIC), medication non-adherence (Geisinger), or over-the-counter PPI use.

Strengths of ARIC, mentioned by Lazarus, included (1) large sample size, (2) community-representative sampling, (3) cohort inception date before widespread PPI use, (4) statistical control for many confounding variables, (5) lengthy follow-up time, (6) sensitivity analyses testing importance of some study limitations, (7) results replicated in Geisinger, and (8) H2 exposure considered both as an active PPI comparator and a negative control.

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3.7 Conclusions

Lazarus accepted PPI use, but not H2 use, as an independent risk factor for CKD and AKI. Lazarus identified further research as required in order to identify PPI as the cause for CKD or AKI.

4. DISCUSSION

Lazarus completed two cohort studies of proton pump inhibitors (PPIs) and incident chronic kidney disease (CKD) in persons with normal kidney function (estimated glomerular filtration rate, eGFR, ≥60 mL/min/1.73 m^2). The main study followed N=10,482 Atherosclerosis Risk in Communities (ARIC) participants (median age 62 years) for median 13.9 years and determined the association between PPI use (3.1% in 2 weeks before cohort entry between 1996 and 1999) and subsequent CKD, defined by (1) Renal Data System Registry match or (2) diagnostic code algorithm applied to hospital and death records. A confirmatory study followed N=248,751 Geisinger Health System patients (median age 50 years) for median 6.2 years and determined the association between PPI use (6.8% in 90 days before cohort entry between 1997 and 2014) and subsequent CKD, defined by (1) Renal Data System Registry match or (2) first sustained outpatient eGFR <60 mL/min/1.73 m^2. Adjusting for baseline covariates, Cox proportional hazards regression analyses detected statistically significant associations between PPI use at cohort entry and subsequent CKD, with risk estimated by hazard ratio (HR) and 95% confidence interval (CI) at HR 1.50, 95% CI 1.14-1.96 (p=0.003) in ARIC and HR 1.17, 95% CI 1.12-1.23 (P<0.001) in Geisinger.

The following discussion of study results from Lazarus considers, in sequence, validity concerns, causal meaning, and implications for FDA regulatory action.

4.1 Validity

Standardized baseline assessments for kidney function and statistical control for critical confounders provided strong support for the validity of the primary result from ARIC. Additional support derived from secondary analyses completed in electronic healthcare data (Geisinger) and from sensitivity analyses that evaluated several sources of bias. One sensitivity analysis evaluated potential selection bias created by including prevalent or chronic PPI users in the main analysis.

Risk-of-bias assessment identified moderate threats to validity from confounding and outcome misclassification (ATTACHMENT 2). Lazarus used statistical methods, not randomization, to balance PPI-use and PPI-nonuse groups for baseline differences possibly related to CKD risk. Lazarus controlled for major CKD risk factors, including older age, black race, hypertension, diabetes, cardiovascular disease, and proteinuria.[4] However, a PPI exposure might signal poor health status, possibly related to the clinical indication for PPI use. Poor health could lead to other drug exposures with kidney toxicity. Drugs of concern might include, for example, nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and iodinated contrast dyes. Uncontrolled differences in the baseline health status of PPI users and nonusers could explain differences in CKD incidence observed by Lazarus.

Lazarus defined CKD by kidney function lost below eGFR 60 mL/min/1.73 m^2. However,

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ARIC analyses used a diagnostic code algorithm (ATTACHMENT 1) to detect this eGFR-defined outcome. Two validation studies, previously completed in ARIC, [17] measured the accuracy of this algorithm. The first study, with 2540 hospitalizations in Washington County ARIC, validated the algorithm against a gold standard defined by mean eGFR <60 mL/min/1.73 m^2, as determined from outpatient creatinine blood tests in the year before hospitalization. The second study, of 546 hospitalizations randomly selected across ARIC, validated the algorithm against a gold standard determined by duplicate, blind, and independent reviews, of complete hospital records, for concurrent eGFR <60 mL/min/1.73 m^2, in the absence of acute kidney injury. The first and second validation studies estimated accuracy at 35.5% sensitivity and 95.7% specificity and 36.2% sensitivity and 97.7% specificity, respectively.

Using methods shown in ATTACHMENT 4, DEPI evaluated the potential for bias related to outcome misclassification. The evaluation concerned the 3.3% covariate-adjusted 10-year risk difference (RD) and the 1.44 covariate-adjusted risk odds ratio (ROR) observed by Lazarus in ARIC. Assumption of non-differential misclassification (i.e., equal misclassification in PPI-exposed and non-exposed groups) corrected the RD to 10.6% and the ROR the 2.03. However, the CKD classification algorithm used coded information derived from hospitalization records. For this reason, the diagnostic code algorithm could detect CKD with better sensitivity in persons more prone to hospitalization. Under conditions of differential outcome misclassification, with algorithm sensitivity 28% higher (0.453 vs. 0.355) in possibly hospitalization-prone PPI-exposed persons, the 1.44 ROR observed by Lazarus in ARIC becomes an unbiased estimate of the true association between PPI use and CKD. Differential misclassification defined by algorithm sensitivity >28% higher in PPI-exposed than non-exposed person could provide a non-causal explanation for the PPI-associated CKD risk observed by Lazarus in ARIC.

Lazarus used Chronic Kidney Disease Epidemiology Collaboration race-, sex-, and age-specific equations to estimate glomerular filtration rate (GFR) from direct measurements of blood creatinine concentration.[15] Lazarus used these equations to exclude ARIC participants and Geisinger patients from cohort membership, to validate a CKD diagnostic code algorithm in ARIC, and to detect incident CKD in Geisinger. In validation studies, these equations predicted CKD (GFR <60 mL/min/m^2) with a 0.96 area under the receiver-operating characteristic curve and with 91% sensitivity and 87% specificity at an eGFR <60 mL/min/m^2 decision threshold. [15] CKD misclassifications, related to GFR estimation, add uncertainty to the primary results observed in ARIC and Geisinger. However, these CKD classification errors should not cause a systematic bias that falsely identifies PPIs as a cause for CKD, unless PPI use associates with high muscle mass, independently of age, sex, race, or other determinants of serum creatinine concentration. Factors that can elevate blood creatinine concentration independently of GFR include dietary protein, muscle mass, and certain medications (e.g., cimetidine, trimethoprim, and probenecid).[18] The H2 blocker cimetidine is a well-known and potent inhibitor of GFR-

[17] Grams, ME, CM Rebholz, B McMahon, S Whelton, SH Ballew, E Selvin, L Wruck and J Coresh, 2014, Identification of Incident CKD Stage 3 in Research Studies, Am J Kidney Dis, 64:214-21.

[18] Lerma EV. Chapter 1. Approach to the Patient with Renal Disease. In: Lerma EV, Berns JS, Nissenson AR. eds. CURRENT Diagnosis & Treatment: Nephrology & Hypertension. New York, NY: McGraw-Hill; 2009.

independent creatinine secretion by renal tubules. Therefore, cimetidine use may elevate blood creatinine and cause eGFR equations to underestimate glomerular function. Acting to remove from the at-risk cohort cimetidine users with eGFR artificially reduced below the 60 mL/min/m^2 threshold, the cimetidine effect on renal tubular function could lead to bias that produces attenuated associations, between H2 blockers and CKD, as measured by Lazarus.

4.2 Causality

With caution related to the previously mentioned effect of cimetidine on renal tubular function, CKD association specifically with PPIs, and not H2s, adds causal meaning to the primary results observed by Lazarus in ARIC and Geisinger. However, Lazarus offered only very limited or no information about CKD risks associated with PPI dose, duration of use, or time since first use. Main analyses in Lazarus examined CKD risk in relation to baseline PPI use, without regard to the duration of use in baseline users or subsequent use by baseline nonusers. This design mimics intention-to-treat (ITT) analysis in a clinical trial. To approximate risks associated with adherent PPI use (the as-treated clinical trial analog), sensitivity analyses treated PPI use as a time-varying exposure. These sensitivity analyses lowered the covariate-adjusted CKD risk estimated in ARIC from HR 1.50 (95% CI 1.14-1.96) to 1.35 (95% CI 1.17-1.65)[19] and increased the risk estimated in Geisinger from HR 1.17 (95% CI 1.12-1.23) to HR 1.22 (95% CI 1.19-1.25; Table 2). Regardless, paucity of information in Lazarus severely limited possibility for causal judgments that depend on knowledge about disease risk and time since first exposure, dose intensity, or dose duration.

Lazarus used Geisinger to confirm results in ARIC. Specifically, Lazarus observed statistically significant association between PPIs and CKD in two studies (ARIC vs. Geisinger) with different population sources (non-clinical vs. clinical), different timeframes associated with lower vs. higher baseline frequencies of PPI use, and different data sources for defining study outcomes (diagnostic codes vs. clinical laboratory data). Reproducing results in studies with different design features provides support for causal significance.

Case reports establish[20] and FDA labels recognize acute interstitial nephritis (AIN) as a rare hypersensitivity reaction to drugs in the PPI class. In a case-control study, nested in a new user cohort, identified in national healthcare data, routinely collected by New Zealand, Blank, et al., 2014,[21] (1) found 46 definite and 26 probable AIN cases, validated by medical records, (2) estimated absolute AIN risk at 6 cases per 100,000 person-years, and (3) estimated relative risk

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http://accessmedicine.mhmedical.com/content.aspx?bookid=372&Sectionid=39961135. Accessed February 09, 2016.

[19] ARIC updated PPI use annually, starting in September 2006, >7.5 years after cohort entry between February 1996 and January 1999. Absence of new PPI use information, in the long period after cohort entry, severely limits the meaningfulness of the ARIC sensitivity analysis that treats PPI use as a time-varying effect.

[20] Sierra, F, M Suarez, M Rey and MF Vela, 2007, Systematic Review: Proton Pump Inhibitor-Associated Acute Interstitial Nephritis, Aliment Pharmacol Ther, 26:545-53.

[21] Blank, ML, L Parkin, C Paul and P Herbison, 2014, A Nationwide Nested Case-Control Study Indicates an Increased Risk of Acute Interstitial Nephritis with Proton Pump Inhibitor Use, Kidney Int, 86:837-44.

Reference ID: 3893803

for definite AIN from current vs. past PPI use with matched odds ratio, 5.2, 95% CI 2.2-12.0. Blank's estimates for the relatively infrequent occurrence of AIN and strong association with PPIs compares with Lazarus's estimates for the more frequent occurrence of CKD and weak association with PPIs.

The medical literature contains results from three studies of PPIs and AKI, currently the subject of a separate review in DEPI.

- In a case-control study nested in a 2002-2005 cohort constructed with claims data from a private insurer in an unnamed Midwestern U.S. state, Klepser, et al., 2013, [22] estimated relative AKI incidence (presence vs. absence of PPI prescription in past 90 days) at covariate-adjusted OR 1.72, 95% CI 1.27-2.32.

- In a matched case-control study completed in 1987-2002 data from the U.K. General Practice Research Database, Leonard, et al., [23] estimated relative AKI incidence (current PPI-only use, without NSAIDS, vs. nonuse of PPI or NSAID) at covariate-adjusted OR 1.05, 95% CI 0.97-1.14.

- In a propensity-score matched comparison of 2002-2011 >66 year-old new PPI users and nonusers in Ontario, Canada, Antoniou, et al., 2015,[24] estimated relative AKI incidence over all follow-up time at HR 2.52, 95% CI 2.27-2.79.

Lazarus claimed no awareness of other population-based studies of PPIs and CKD. A rapid DEPI search of PubMed verified this claim (ATTACHMENT 5). The lack of other PPI-CKD studies and limitations[25] in the PPI-AKI studies available preclude causal certainty that derives from consistency of findings across studies.

4.3 Public Health Implications

Lazarus used an accepted definition for CKD, eGFR <60 mL/min/m^2, understood as sustained loss of kidney function in excess of age, sex, and race norms. CKD occurs commonly in populations, estimated in ARIC, by Cox proportional hazards regression, at 8.5% over 10 years, for participants not exposed to PPIs. Because CKD occurs commonly, a relative risk increase,

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[22] Klepser, DG, DS Collier and GL Cochran, 2013, Proton Pump Inhibitors and Acute Kidney Injury: A Nested Case-Control Study, BMC Nephrol, 14:150.

[23] Leonard, CE, CP Freeman, CW Newcomb, PP Reese, M Herlim, WB Bilker, S Hennessy and BL Strom, 2012, Proton Pump Inhibitors and Traditional Nonsteroidal Anti-Inflammatory Drugs and the Risk of Acute Interstitial Nephritis and Acute Kidney Injury, Pharmacoepidemiol Drug Saf, 21:1155-72.

[24] Antoniou, T, EM MacDonald, S Hollands, T Gomes, MM Mamdani, AX Garg, JM Paterson and DN Juurlink, 2015, Proton Pump Inhibitors and the Risk of Acute Kidney Injury in Older Patients: A Population-Based Cohort Study, CMAJ Open, 3:E166-71.

[25] Division of Epidemiology I, Review of an Observational Cohort Study of Proton Pump Inhibitors and Acute Kidney Injury, Response to OSE RCM # 2013-1923 (in preparation).

often considered small (e.g., $1.39 = \frac{11.8\%}{8.5\%}$ risk ratio in ARIC), could signify an absolute risk increase regarded as large (e.g., from 8.5% to 11.8% in ARIC, corresponding to one additional CKD case for every 30 persons exposed to PPIs.[26] With PPI use (3.1% prevalence) infrequent in ARIC at cohort entry (1996-1999), PPIs could be said to explain only 1.2% of all CKD observed in ARIC over 10 years.[27] This accounting would change in settings of very frequent PPI use.

One should not regard kidney function just below the eGFR 60 mL/min/m^2 threshold as an outcome with immediate consequence for personal health or as a good indication of public health burden from CKD. Morbidity from CKD generally occurs only at much lower eGFR. Therefore, proper understanding of the possible public health impact of permanent PPI-related kidney injury requires information about the causal effects of PPIs on kidney damage severe enough to cause symptoms, require medical treatment, or shorten life span.

5. CONCLUSION

Lazarus used sound and acceptable observational methods to study PPIs and chronic kidney disease (CKD). Because of limitations inherent to the observational method and inadequate information from other sources, however, evidence in Lazarus alone does not permit a confident conclusion that identifies PPIs as a cause for CKD.

6. RECOMMENDATIONS FOR DGIEP

To guide regulatory actions, combine results from Lazarus with evidence from other sources, such as evidence about PPIs and other forms of kidney injury, including acute kidney injury.

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[26] Because of the poor sensitivity of the diagnostic code algorithm used by ARIC, the PPI-associated true risk difference may be >10% (ATTACHMENT 4), corresponding to one additional CKD case for every 9 or 10 persons exposed.

[27] Calculated as a population attributable risk percent, $PAR\% = 100 \cdot \frac{I_p - I_u}{I_p}$, where $I_u = 0.085$

$I_p = 0.031 \cdot 0.118 + (1 - 0.031) \cdot 0.085$.

ATTACHMENT 1: Diagnostic code algorithms chronic kidney disease.[28]

Grams et al, AJKD, "Identification of Incident CKD Stage 3 in Research Studies"

TABLE S1. Diagnostic code algorithm for identifying chronic kidney disease

ICD-9-code	Description	ICD-10-code
582	Chronic glomerulonephritis	N03
583	Nephritis and nephropathy	
585, 585.x where x≥3	Chronic kidney disease	N18, N18.x where x≥3
586	Renal failure	N19
587	Renal sclerosis	N26
588	Disorders resulting from impaired renal function	N25
403	Hypertensive chronic kidney disease	I12
404	Hypertensive heart and kidney disease	I13
593.9	Unspecified disorder of the kidney and ureter	
250.4	Diabetes with renal complications	E10.2, E11.2, E13.2
V42.0	Kidney replaced by transplant	Z94.0
55.6	Transplant of kidney	
996.81	Complications of transplanted kidney	
V45.1	Renal dialysis status	Z99.2
V56	Admission for dialysis treatment or session	Z49
39.95	Hemodialysis	
54.98	Peritoneal dialysis	
	Encounter for adjustment and management of vascular access device	Z45.2

*Codes in blue are counted as incident CKD stage 3 only if a concomitant AKI code (ICD-9: 584.x, ICD-10: N17) is not present.

[28] Grams, ME, CM Rebholz, B McMahon, S Whelton, SH Ballew, E Selvin, L Wruck and J Coresh, 2014, Identification of Incident CKD Stage 3 in Research Studies, Am J Kidney Dis, 64:214-21.

ATTACHMENT 2: Risk-of-bias assessment [1, 2].

Domain	Risk of Bias Judgment	Support for Judgment
Bias due to confounding	MODERATE	Observational (non-randomized) study design with strong controls for important confounding variables (age, race, socioeconomic status, hypertension, diabetes, NSAID use, and concomitant medications representing multiple comorbidities).
Bias in selection of participants into the study	LOW	Cohorts assembled from a prospectively recruited general population source with low baseline prevalence of long-term PPI use.
Bias in measurement of interventions	LOW	PPI exposure determined by direct interview with confirmation by visual inspection of pill bottles.
Bias due to departures from intended intervention	NO INFORMATION	Though analyses control for baseline use of an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB), Lazarus provided no information about ACE-I or ARB use during follow-up.
Bias due to missing data	LOW	Multi-modality follow-up, through next of kin, hospitals, Renal Data System Registry, and National Death Index, accepted as complete.
Bias in measurement of outcomes	MODERATE	Despite poor sensitivity (35.5%), administrative codes identify loss of kidney function with good specificity (95.7%) [3].
Bias in selection of the reported result	MODERATE	No evidence for a statistical analysis plan completed in advance of data analysis.
Overall bias	MODERATE	Moderate risk of bias in more than one domain.

1. Sterne JAC, JPT Higgins, BC Reeves on behalf of the development group for ACROBAT-NRSI, September 2014, A Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24, Retrieved from http://www riskofbias.info on June 29, 2015.
2. Risk-of-bias assessed for the association in ARIC between recent initiation of PPI use and subsequent chronic kidney disease, defined as a loss in kidney function (glomerular filtration rate).
3. Under random (non-differential) misclassification, specificity is more important than sensitivity (ATTACHMENT 4). The Discussion addresses bias concerns related to non-random (differential) sensitivity error.

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ATTACHMENT 3: Assessment for causation [1].

A. Description of evidence

1.	Exposure	PPI use during preceding 2 weeks (ARIC) or PPI prescription in preceding 90 days (Geisinger).
2.	Outcome	Incident chronic kidney disease (CKD) by (1) Renal Data System Registry match or (2) diagnostic code algorithm applied to hospital and death records (ARIC) or (1) Renal Data System Registry match or (2) first sustained outpatient estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (Geisinger).
3.	Design	Cohort
4.	Study population	10,482 persons who attended an ARIC study visit between February 1, 1996, and January 30, 1999, with (1) non-missing values for eGFR and urinary albumin to creatinine ratio, (2) eGFR ≥60 mL/min/1.73 m^2, and (3) non-missing values for critical confounding variables; 248,751 patients with a Geisinger Health System outpatient encounter between February 13, 1997, and October 9, 2014, with eGFR ≥60 mL/min/1.73 m^2 and non-missing values for systolic blood pressure.
5.	Main result	Covariate adjusted hazard ratio (PPI use vs. nonuse at cohort entry), HR 1.50, 95% CI 1.14-1.96 (ARIC); HR 1.17, 95% CI 1.12-1.23 (Geisinger)

B. Non-causal explanations

6.	Observation bias	Risk of bias from exposure and outcome misclassification scored as low and moderate, respectively; See ATTACHMENT 2.
7.	Confounding	Risk of bias due to confounding scored as moderate; See ATTACHMENT 2.
8.	Chance	Excluded by p-value, 0.003 (ARIC) and <0.001 (Geisinger).

C. Features consistent with causation

9.	Time relationship	Primary analyses determined PPI use prospectively in subjects with normal kidney function; cause-effect time relationship between PPI use and CKD less firmly established in sensitivity analyses treating PPI use as a time-varying effect.
10.	Strength	1.2- to 1.5-fold risk association generally regarded as weak for purposes of causal inference
11.	Dose response	In Geisinger, HR 1.15 (95% CI 1.09-1.21) and HR 1.46 (1.28-1.67) for once and twice daily PPI dosing, respectively.
12.	Consistency	Consistent associations observed for acute kidney injury outcome (ICD-9-CM 584.x), HR 1.64 (95% CI 1.22-2.21) and HR 1.31 (95% CI 1.22-1.42) in ARIC and Geisinger, respectively.
13.	Specificity	Weaker and statistically non-significant associations observed for H2 use vs. nonuse, HR 1.15 (95% CI 0.98-1.36) and HR 0.93 (95% CI 0.88-0.99) in ARIC and Geisinger, respectively.

D. External validity

14.	Eligible population	U.S. adults with normal kidney function (eGFR ≥60 mL/min/1.73 m^2)
15.	Source population	ARIC formed as probability samples, 45-64 year-old residents of three U.S. communities and 45-64 year-old black residents of one U.S. community, with clinic participation by

		68% of enumerated eligible persons;[29] Geisinger Health System constituted as an open integrated healthcare delivery system with dominant market share in north central Pennsylvania.[11]
16.	Other populations	Subgroup analyses in Geisinger showed statistically significant association between PPI and CKD in older patients (>50 years), in men and women, and in patients with and without diabetes; results according to race not reported in Geisinger (4.5% non-white race); results according to race in ARIC not informative because of small sample size (8 PPI-exposed CKD cases in black race participants).
E. Consistency with other evidence		
17.	Consistency	Results from observational studies show associations between PPIs and acute kidney injury.
18.	Specificity	PPIs associated with many different adverse outcomes, including interstitial nephritis, acute kidney injury, atrophic gastritis, vitamin B12 deficiency, *Clostridium difficile*-associated diarrhea, osteoporosis-related bone fracture, hypomagnesemia, and community-acquired pneumonia.[30]
19.	Plausibility	Biological mechanism possibly related to PPI-associated acute interstitial nephritis.
20.	Coherence	Lazarus references evidence for increasing CKD prevalence not explained by known risk factors (diabetes mellitus and hypertension).

1. Elwood, M, 1988, Critical Appraisal of Epidemiology Studies and Clinical Trials, 2nd edition, New York, Oxford University Press.

[29] Jackson, R, LE Chambless, K Yang, T Byrne, R Watson, A Folsom, E Shahar and W Kalsbeek, 1996, Differences between Respondents and Nonrespondents in a Multicenter Community-Based Study Vary by Gender Ethnicity. The Atherosclerosis Risk in Communities (ARIC) Study Investigators, J Clin Epidemiol, 49:1441-46.

[30] Schoenfeld, AJ, and D Grady, Published online January 11, 2016, Adverse Effects Associated with Proton Pump Inhibitors, JAMA Intern Med, 2016, doi:10.1001/jamainternmed.2015.7927.

ATTACHMENT 4: DEPI evaluation for outcome misclassification bias.

Lazarus used an imperfect diagnostic code algorithm to detect chronic kidney disease (CKD), defined as kidney function lost below eGFR 60 mL/min/1.73 m^2. Grams, et al., 2014,[17] estimated the accuracy of this algorithm in ARIC at 0.355 sensitivity and 0.957 specificity. For different values of sensitivity and specificity, Supplemental Table 1 and Supplemental Figure 1, Panel A, correct the covariate-adjusted 0.033 risk difference (RD) and the 1.44 risk odds ratio (ROR), observed by Lazarus in ARIC, for non-differential misclassification errors caused by imperfections in the diagnostic code algorithm. Supplemental Figure 1, Panel B, corrects the 1.44 observed ROR for constant 0.957 specificity and 0.355 sensitivity in persons not exposed to PPI, and variable sensitivity in persons exposed to PPI.

Supplemental Table 1: 10-year risks for chronic kidney disease (CKD; eGFR <60 mL/min/m^2), corrected for non-differential misclassification.[1]

		10-year CKD risks Corrected for misclassification			
S_e	S_p	PPI	No PPI	RD	ROR
0.355	0.957	0.240	0.135	0.106	2.03
1.00	0.98	0.100	0.066	0.034	1.56
1.00	0.97	0.091	0.057	0.034	1.66
1.00	0.96	0.081	0.047	0.034	1.80
1.00	0.95	0.072	0.037	0.035	2.02
1.00	0.94	0.062	0.027	0.035	2.41
0.75	0.98	0.134	0.089	0.045	1.59
0.75	0.97	0.122	0.076	0.046	1.68
0.75	0.96	0.110	0.063	0.046	1.82
0.75	0.95	0.097	0.050	0.047	2.04
0.75	0.94	0.084	0.036	0.048	2.44
0.50	0.98	0.204	0.135	0.069	1.64
0.50	0.97	0.187	0.117	0.070	1.74
0.50	0.96	0.170	0.098	0.072	1.88
0.50	0.95	0.151	0.078	0.073	2.11
0.50	0.94	0.132	0.057	0.075	2.52
0.40	0.98	0.258	0.171	0.087	1.68
0.40	0.97	0.238	0.149	0.089	1.79
0.40	0.96	0.217	0.125	0.092	1.94
0.40	0.95	0.194	0.100	0.094	2.17
0.40	0.94	0.171	0.074	0.097	2.59
0.25	0.98	0.426	0.283	0.143	1.88
0.25	0.97	0.400	0.250	0.150	2.00
0.25	0.96	0.371	0.214	0.157	2.17
0.25	0.95	0.340	0.175	0.165	2.43
0.25	0.94	0.305	0.132	0.174	2.90

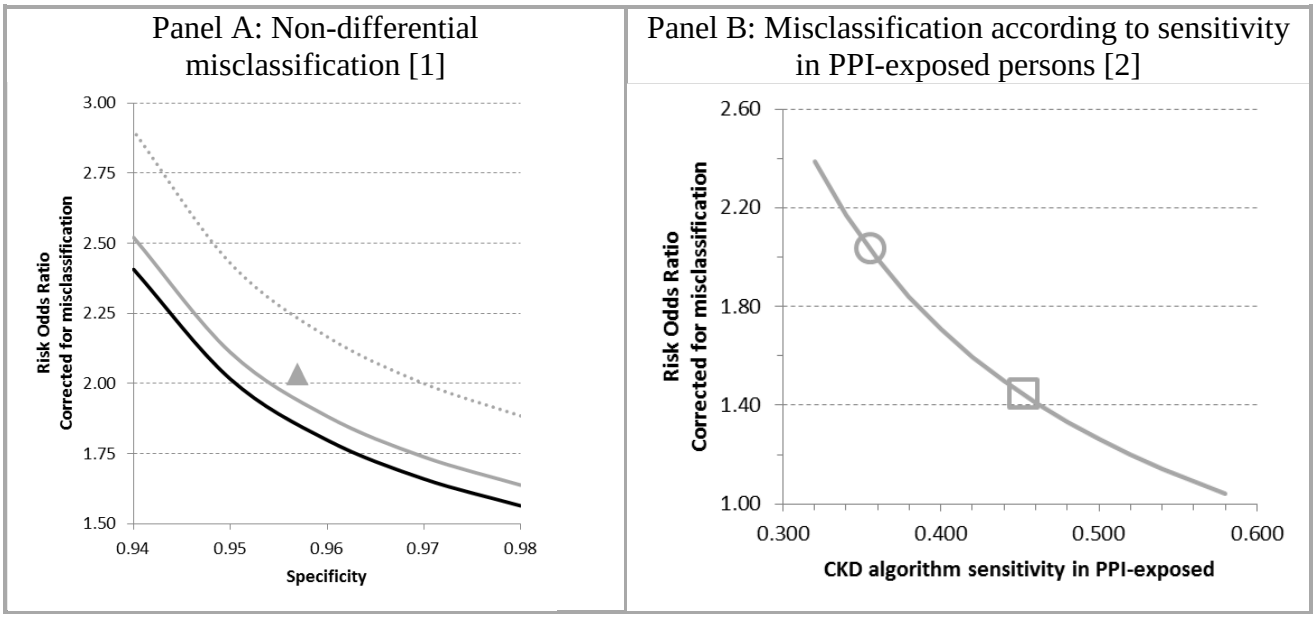
ABBREVIATIONS: S_e, sensitivity of diagnostic code algorithm for CKD; S_p, specificity of diagnostic code algorithm for CKD; PPI, exposed to proton pump inhibitors; no PPI, not exposed

Reference ID: 3893803

to proton pump inhibitors; RD, risk difference between PPI exposed and not exposed; ROR, risk odds ratio for PPI exposed vs. non-exposed

1. 10-year risk, corrected for exposure-non-differential misclassification bias, calculated by means of the following equation, derived by DEPI, $\frac{X + Sp - 1}{Se + Sp - 1}$, where X=observed covariate-adjusted risk, estimated in ARIC at 0.118 and 0.085 for persons exposed and not exposed to PPI, respectively.

Supplemental Figure 1: 10-year risks for chronic kidney disease (CKD; eGFR <60 mL/min/m^2), corrected for non-differential and differential misclassification.



1. See footnote to Supplemental Table 1 for a description of the method used to correct for non-differential misclassification. Solid black, solid gray, and dotted gray curves show corrections for CKD diagnostic code algorithm sensitivities of 1.00, 0.50, and 0.25, respectively. The triangle shows the risk odds ratio (2.03) corrected for 0.355 sensitivity and 0.957 specificity.
2. All corrections assume 0.957 specificity, regardless of PPI exposure, and 0.355 sensitivity in persons not exposed to PPI. The circle shows the risk odds ratio (2.03) corrected for 0.355 sensitivity in PPI-exposed persons. The square shows a risk odds ratio of 1.44 (the covariate-adjusted 10-year risk odds ratio observed by Lazarus in ARIC), which corresponds to 0.453 sensitivity in PPI-exposed persons.

ATTACHMENT 5: Rapid DEPI search of PubMed.

A DEPI search of PubMed, completed on January 26, 2016, using the search string shown below, identified 483 articles.

((((((((((((((((omeprazole) OR pantoprazole) OR lansoprazole) OR rabeprazole) OR esomeprazole) OR dexlansoprazole) OR dexrabeprazole)) OR proton pump inhibitors[MeSH Major Topic])) OR 2-Pyridinylmethylsulfinylbenzimidazoles))))) AND kidney diseases[MeSH Terms]) AND ("1989/01/01"[PDat] : "2016/12/31"[PDat]) AND English[lang]) OR (((((("proton pump inhibitor"[Title/Abstract] OR "proton pump inhibitors"[Title/Abstract] OR "PPI"[Title/Abstract])))) AND (("kidney"[Title/Abstract] OR "renal"[Title/Abstract]))) AND ("1989/01/01"[PDat] : "2016/12/31"[PDat]) AND English[lang]))

Subsequent title and abstract screening of these 483 PubMed articles identified only one primary research article in humans about PPIs and chronic kidney disease, Lazarus, et al., 2016,[1] the subject for this DEPI review. The PubMed search also captured the five influential articles, cited in the Discussion, including,

1. The systematic review of PPI-associated acute interstitial nephritis (AIN) by Sierra, et al., 2007.[20]

2. The New Zealand case-control study of AIN by Blank, et al., 2014.[21]

3. The U.S. managed-care-organization-nested case-control study of AKI by Klepser, et al., 2013.[22]

4. The U.K General Practice Research Database case-control studies of AIN and acute kidney injury (AKI) by Leonard, et al., 2012.[23]

5. The Ontario propensity score-matched cohort study of AKI by Antoniou, et al., 2015.[24]

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/s/

JOEL L WEISSFELD
02/29/2016

SUKHMINDER K SANDHU
02/29/2016

DAVID C SHIH
02/29/2016

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/s/

JACQUELINE D LEEHOFFMAN
06/20/2017

Exhibit F

Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)

What is FDA posting?

The following reports list potential signals of serious risks/new safety information that were identified using the FAERS database during the indicated quarter. Data from AERS was moved to FAERS for the launch of FAERS on September 10, 2012. The appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a ***potential safety issue***, but it does not mean that FDA has identified a causal relationship between the drug and the listed risk. If after further evaluation the FDA determines that the drug is associated with the risk, it may take a variety of actions, including requiring changes to the labeling of the drug, requiring development of a Risk Evaluation and Mitigation Strategy (REMS), or gathering additional data to better characterize the risk.

FDA wants to emphasize that the listing of a drug and a potential signal of a serious risk/new safety information on this Web site does not mean that FDA has determined that the drug has the risk. FDA is not suggesting that healthcare providers should not prescribe the drug or that patients taking the drug should stop taking the medication while an evaluation of the potential safety issue is being conducted. Patients who have questions about their use of the identified drug should contact their health care

provider.

FDA will complete its evaluation of each potential safety issue and may issue additional public communications as appropriate.

Why is FDA posting this information?

FDA is posting these reports in accordance with Title IX, Section 921 of the Food and Drug Administration Amendments Act of 2007 (FDAAA; **see insert**). FDA will publish a new list of potential signals of serious risks/new safety information identified each quarter.

Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355).

This section in FDAAA, among other things, directs FDA to "conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter." When a potential signal of a serious risk is identified from AERS data, it will be posted in the required report in the quarter in which it is first identified. A potential signal of a serious risk may in some cases constitute new safety information as defined in FDAAA (newly created section 505-1(b)(3) of the FDCA) which includes, among other things, information derived from adverse event reports about a serious risk associated with use of a drug that FDA has become aware of since the drug was approved or, for drugs that have REMS, since the REMS was required or last assessed. FDA will post each potential signal of a serious risk in the quarter in which it is first identified. If additional new safety information is developed concerning a potential signal that has already been posted, it will be addressed by FDA in new safety communications, but will not appear again as a new quarterly posting.

How was the list generated?

FDA staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) regularly examine the FAERS database as part of routine safety monitoring. When a potential signal of a serious risk is identified from FAERS data, it is entered as a safety issue into CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) or into CBER's Therapeutics and Blood Safety Branch's Safety Signal Tracking (SST) system. Potential signals of serious risks are normally based upon a collection of FAERS reports, although a single FAERS report could lead to further evaluation of a potential safety issue.

What information is provided?

The table in each report lists the names of products and potential safety issues that were entered into the above CDER or CBER tracking systems where the FAERS

database identified (or contributed to identification of) the potential safety issues. Additional information on each potential safety issue, such as an FDA Drug Safety Communication, is also provided.

A new report will be made available each quarter showing newly identified potential signals of serious risks/new safety information identified from the FAERS database during the previous quarter. Information from previous quarters with updates will remain available on the website until an FDA regulatory action has been taken. FDA actions may include a determination either that a) the drug is not associated with the risk and therefore no regulatory action is required, or b) the drug may be associated with the risk, and one of the following is required: a modification to the product labeling; development of a REMS; marketing suspension or withdrawal; or gathering additional data to characterize the risk. After FDA has determined that either no regulatory action is required or has taken a regulatory action for each issue on a quarterly report, no further updates will be made and the quarterly report will be archived. **Archived Reports (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm282324.htm)**

Quarterly Reports

2017

- **January - March 2017 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm565425.htm)**
- **April - June 2017 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm579459.htm)**
- **July - September 2017 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm592379.htm)**

2016

- **January - March 2016 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm509478.htm)**
- **April - June 2016 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm523358.htm)**
- **July - September 2016 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm534355.htm)**
- **October - December 2016 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm549834.htm)**

2015

- **January – March 2015 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm484290.htm)**
- **April – June 2015 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance /AdverseDrugEffects/ucm484292.htm)**
- **July – September 2015 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm484294.htm)**
- **October - December 2015 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm491645.htm)**

2014

- **January – March 2014 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm398223.htm)**
- **July - September 2014 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm456300.htm)**
- **October - December 2014 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm456326.htm)**

2013

- **July – September 2013 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm376571.htm)**
- **October – December 2013 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm391572.htm)**

2012

- **January – March 2012 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm307608.htm)**
- **April - June 2012 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance /AdverseDrugEffects/ucm324020.htm)**
- **July – September 2012 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm334542.htm)**
- **October - December 2012 (/Drugs/GuidanceComplianceRegulatoryInformation /Surveillance/AdverseDrugEffects/ucm349375.htm)**

2011

- **October - December 2011 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm295585.htm)**

2010

- **April - June 2010 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm223734.htm)**

2009

- **October – December 2009 (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm210293.htm)**

Resources for You

- **Drug Safety and Availability (/Drugs/DrugSafety/default.htm)**
- **Postmarket Drug Safety Information for Patients and Providers (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm)**
- **MedWatch: The FDA Safety Information and Adverse Event Reporting Program (/Safety/MedWatch/default.htm)**
- **Report a Serious Medical Product Problem Online (https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm)**
- **Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)**
- **DailyMed (National Library of Medicine) (http://dailymed.nlm.nih.gov/dailymed/about.cfm)**

More in FDA Adverse Event Reporting System (FAERS) (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm)

FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm)

FDA Adverse Event Reporting System (FAERS) Public Dashboard (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm)

Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm)

FDA Adverse Event Reporting System (FAERS) Electronic Submissions (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm)

Exhibit G

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS): April - June 2017

fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm579459.htm

Product Name: Trade (Active Ingredient) *or* Product Class	**Potential Signal of a Serious Risk / New Safety Information**	**Additional Information (as of September 30, 2017)**
Adrenalin® (epinephrine injection), for intramuscular and subcutaneous use	Adrenaline (epinephrine) injection and wrong drug errors	FDA published a Dear Healthcare Provider Letter (DHCP letter) on its website to communicate the change in formulation and removal of the mydriasis indication for Adrenalin®. Adrenalin® DHCP letter The carton/container labeling for Adrenalin® was updated to remove the mydriasis indication. Adrenalin® package insert labeling
• Aldara® (imiquimod) cream, 5%, for topical use only • Zyclara (imiquimod) cream, 3.75%, for topical use • Zyclara (imiquimod) cream, 2.5%, for topical use	Drug induced vitiligo-like depigmentation	FDA is evaluating the need for regulatory action.
Ameluz® (aminolevulinic acid hydrochloride) gel, 10%, for topical use	Transient global amnesia	The “Warnings and Precautions,” “Adverse Reactions,” and “Patient Counseling” sections of the labeling for Ameluz were updated to include transient amnestic episodes. Ameluz® labeling
• Campath (alemtuzumab) injection, for intravenous use • Lemtrada (alemtuzumab) injection, for intravenous use	Acute acalculous cholecystitis	FDA is evaluating the need for regulatory action.

Carafate® (sucralfate) oral suspension	Medication error: administration error	The labeling for Carafate® was updated to revise the name of the drug from “Carafate suspension” to “Carafate oral suspension.” The labeling for Carafate® was changed to include warnings of fatal complications with inappropriate intravenous administration of Carafate® oral suspension. Carafate® labeling
Coartem (artemether/lumefantrine) tablets	Hemolytic anemia	FDA is evaluating the need for regulatory action.
• Epipen® (epinephrine injection, USP), Auto-injector 0.3 mg, for intramuscular or subcutaneous use • Epipen® Jr (epinephrine injection, USP) Auto-injector 0.15 mg, for intramuscular or subcutaneous use	Device failure	FDA issued a warning letter to Meridian Medical Technologies, Inc., summarizing significant violations of current good manufacturing practice requirements for combination products. Epipen® Warning Letter

Dipeptidyl peptidase-4 inhibitors • Glyxambi (empagliflozin and linagliptin) tablets, for oral use • Janumet (sitagliptin and metformin hydrochloride) tablets, for oral use • Janumet XR (sitagliptin and metformin hydrochloride extended-release) tablets, for oral use • Januvia (sitagliptin) tablets, for oral use • Jentadueto (linagliptin and metformin hydrochloride) tablets, for oral use • Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets, for oral use • Kazano (alogliptin and metformin hydrochloride) tablets, for oral use • Kombiglyze XR (saxagliptin and metformin hydrochloride extended-release) tablets, for oral use • Nesina (alogliptin) tablets, for oral use • Onglyza (saxagliptin) tablets, for oral use • Oseni (alogliptin and pioglitazone) tablets, for oral use • Qtern (dapagliflozin and saxagliptin) tablets, for oral use • Tradjenta (linagliptin) tablets, for oral use	Rhabdomyolysis	FDA is evaluating the need for regulatory action.
Gilenya® (fingolimod) capsules, for oral use	Rebound multiple sclerosis upon discontinuation of fingolimod	FDA is evaluating the need for regulatory action.

Gleevec® (imatinib mesylate) tablets, for oral use	Decline in renal function	The “Warning and Precautions” section of the labeling for Gleevec® was updated to include renal toxicity. Gleevec® labeling
• GlucaGen (glucagon [rDNA origin] for injection), for subcutaneous, intramuscular, or intravenous use • Glucagon for injection, for subcutaneous, intramuscular, or intravenous use	Necrolytic migratory erythema	FDA is evaluating the need for regulatory action.
• Keytruda® (pembrolizumab) injection, for intravenous use • Opdivo® (nivolumab) injection, for intravenous use	Complications of allogeneic hematopoietic stem cell transplantation	FDA is evaluating the need for regulatory action.
Keytruda® (pembrolizumab) injection, for intravenous use	Stevens-Johnson syndrome and toxic epidermal necrolysis	The “Warning and Precautions” section of the labeling for Keytruda was updated to include Stevens-Johnson syndrome and toxic epidermal necrolysis. Keytruda® labeling
Pomalyst® (pomalidomide) capsules, for oral use	Ischemic colitis	FDA decided that no action is necessary at this time based on available information.

Proton Pump Inhibitors • Aciphex (rabeprazole sodium) delayed-release tablets, for oral use • Esomeprazole strontium delayed-release capsules, for oral use • Nexium (esomeprazole magnesium) delayed-release capsules, for oral use • Nexium (esomeprazole magnesium) for delayed-release oral suspension • Nexium I.V. (esomeprazole sodium) for injection, for intravenous use • Prevacid (lansoprazole), delayed-release capsules, for oral use • Prevacid Solutab (lansoprazole) delayed-release orally disintegrating tablets • Prilosec (omeprazole) delayed-release capsules • Prilosec (omeprazole) delayed-release oral suspension • Protonix (pantoprazole sodium) delayed-release tablets, for oral use • Protonix (pantoprazole sodium) for delayed-release oral suspension • Protonix IV (pantoprazole sodium) for injection, for intravenous use	Polyps of stomach and duodenum	FDA is evaluating the need for regulatory action.

Proton Pump Inhibitors • Aciphex (rabeprazole sodium) delayed-release tablets, for oral use • Esomeprazole strontium delayed-release capsules, for oral use • Nexium (esomeprazole magnesium) delayed-release capsules, for oral use • Nexium (esomeprazole magnesium) for delayed-release oral suspension • Nexium I.V. (esomeprazole sodium) for injection, for intravenous use • Prevacid (lansoprazole), delayed-release capsules, for oral use • Prevacid Solutab (lansoprazole) delayed-release orally disintegrating tablets • Prilosec (omeprazole) delayed-release capsules • Prilosec (omeprazole) delayed-release oral suspension • Protonix (pantoprazole sodium) delayed-release tablets, for oral use • Protonix (pantoprazole sodium) for delayed-release oral suspension • Protonix IV (pantoprazole sodium) for injection, for intravenous use	Chronic kidney disease/ acute kidney injury	FDA decided that no action is necessary at this time based on available information.
Repatha (evolocumab) injection, for subcutaneous use	Skin and subcutaneous tissue bacterial infections	FDA is evaluating the need for regulatory action
Taxotere (docetaxel) injection concentrate, intravenous infusion	Docetaxel and neutropenic enterocolitis	FDA is evaluating the need for regulatory action.

Uvadex® (methoxsalen) injection, solution	Embolism and thrombosis	FDA is evaluating the need for regulatory action.

Exhibit H

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: PROTON-PUMP INHIBITOR PRODUCTS LIABILITY LITIGATION (No. II)	**1:17-MD-2789 (CCC)(MF) (MDL 2789)**
	Judge Claire C. Cecchi
This Document Relates to: ALL ACTIONS	**[PROPOSED] CASE MANAGEMENT ORDER #__**

CASE MANAGEMENT ORDER NO. __
(INITIAL SCHEDULING ORDER)

This Order is intended to conserve judicial and party resources, eliminate duplicative discovery, serve the convenience of the parties and witnesses, and promote the just and efficient conduct of this litigation. The following shall apply in all cases in MDL No. 2789:

1. **General Causation and Preemption**

   a. There will be frontloaded discovery regarding general causation and preemption. Discovery is limited to general causation and preemption, unless expressly so authorized by an Order of this Court.

   b. Common fact discovery (i.e., fact discovery not specific to an individual Plaintiff) regarding general causation and preemption shall be completed by April 12, 2019.[1]

   c. On or before April 19, 2019, Plaintiffs shall designate and provide reports from their expert witnesses with respect to issues of general causation and preemption.

[1] If the Court does not frontload discovery regarding general causation and preemption, then the deadline to complete common marketing-related fact discovery would be June 12, 2019. However, to avoid delaying dispositive motions, the deadline to complete common fact discovery regarding general causation and preemption would remain April 12, 2019.

Along with their experts' reports, Plaintiffs shall identify at least two days on which their experts are available for deposition between May 28 and June 14.

d. On or before May 24, 2019, Defendants shall designate and provide reports from their expert witnesses with respect to issues of general causation and preemption. Along with their experts' reports, Plaintiffs shall identify at least two days on which their experts are available for deposition between June 17 and July 5.

e. Expert witness depositions shall conclude by July 5, 2019.

f. Schedule for dispositive and *Daubert* motions regarding general causation and preemption:

i. **Motions and Briefs**: July 31, 2019

ii. **Response in Opposition Briefs**: August 30, 2019

iii. **Reply Briefs**: September 16, 2019

iv. **Hearing and Argument**: October 15, 2019

2. Common Marketing Discovery[2]

a. Common marketing discovery shall not begin prior to November 18, 2019. To the extent any Common Marketing Discovery has begun against any Defendant, it is now stayed until November 18, 2019.

b. Common marketing discovery shall conclude by January 13, 2020.

3. Early Discovery Pool Cases

a. By November 29, 2019, the parties shall submit an agreed upon Case Management Order ("CMO") or competing proposals addressing an early discovery pool, including:

[2] The Court's rulings on dispositive motions regarding general causation and preemption may render the remainder of this schedule unnecessary.

i. Which cases will be eligible;

ii. How and when cases will be selected; and

iii. Case-specific discovery to be conducted in the early discovery pool cases.

b. Case-specific discovery in the early discovery pool cases shall begin on January 14, 2020.

c. Case-specific discovery in the early discovery pool cases shall be completed by April 3, 2020.

4. Early Trial Cases

a. Selection and Additional Fact Discovery

i. By April 17, 2020, a subset of cases from the early discovery pool shall be selected for early trial. A separate CMO shall address the early trial selection process and the scope of additional fact discovery to be conducted in the early trial cases.

ii. Additional fact discovery in the early trial cases shall be completed by May 29, 2020.

b. Expert Schedule

i. On or before June 12, 2020, Plaintiffs shall designate and provide reports by their case-specific expert witnesses for the early trial cases.

ii. The schedule for case-specific expert disclosures by Defendants and expert depositions shall be the subject of a subsequent CMO.

c. Dispositive and *Daubert* Motions

i. The briefing schedule for dipositive and *Daubert* motions in the early trial cases shall be the subject of a subsequent CMO.

ii. A hearing on any dispositive and *Daubert* motions shall take place on August 25, 2020.

d. First Early Trial

i. The first early trial shall commence on September 21, 2020.

ii. The schedule for pretrial preparation and subsequent early trials shall be the subject of a subsequent CMO.