of Hematology/Oncology, Department of Medicine (Dr Lewis), San Francisco General Hospital, San Francisco.
Correspondence: Dr Fiebig, Clinical Laboratory, San Francisco General Hospital, Bldg NH, Room 2M24, 1001 Potrero Ave, San Francisco, CA 94110 (efiebig@ucsf.edu).
Author Contributions: *Study concept and design:* Fiebig, Jones, Logan, Wang, and Lewis. *Acquisition of data:* Fiebig, Jones, Logan, Wang, and Lewis. *Analysis and interpretation of data:* Fiebig, Jones, and Lewis. *Drafting of the manuscript:* Fiebig. *Critical revision of the manuscript for important intellectual content:* Fiebig, Jones, Logan, Wang, and Lewis. *Statistical analysis:* Fiebig. *Administrative, technical, and material support:* Jones. *Study supervision:* Jones.
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Orlistat and Acute Kidney Injury: An Analysis of 953 Patients

Obesity is a significant health problem that is growing in prevalence.[1,2] Orlistat (Xenical; Roche, Basel, Switzerland), an inhibitor of pancreatic lipases that limits the intestinal absorption of dietary fat, has proven effective in augmenting weight loss.[3,4] In the United States, orlistat is available over the counter and by prescription. Single-person case reports have recently suggested that orlistat may cause oxalate-induced acute kidney injury (AKI).[5,6] The putative mechanism is similar to enteric hyperoxalaturia in which unabsorbed dietary fat binds enteric calcium and reduces its ability to bind and sequester oxalate in the gut. This results in excessive absorption of free oxalate and subsequent deposition in the renal parenchyma.[6] To explore the relationship between orlistat and AKI, we conducted a before- and after-analysis of incident orlistat users.

Methods. The province of Ontario, Canada, has a single-payer universal health insurance program that covers all residents and has emigration rates of less than 1% per year. We conducted this study using 6 of Ontario's linked health care databases. Detailed descriptions of these databases are provided in the eAppendix (http://www.archinternmed.com).

Orlistat is available in Ontario by prescription and is an insured benefit of the provincial formulary for residents older than 65 years and those who receive disability benefits or social assistance. Using the Ontario Drug Benefits database, we identified all such patients who filled their first prescription for orlistat between January 1, 2002, and March 31, 2008. For each new orlistat user, we identified AKI events occurring in the 12 months before and after the initial orlistat prescription, including acute dialysis or a hospital diagnosis of AKI recorded on the patient's discharge abstract (eAppendix). For patients with multiple AKI events, we counted only the first event before and after initiation of orlistat. We expected more AKI events in the 12 months following the initial orlistat prescription. As a test of specificity, we replicated our analysis using upper gastrointestinal tract hemorrhage as a tracer outcome, since there is no plausible reason why orlistat would be associated with this outcome. We compared the number of AKI events in the 2 observation periods using the McNemar test. All *P* values were 2-sided, and the threshold for statistical significance was .05.

Table. Baseline Characteristics of Patients at the Time of Initial Orlistat Prescription

Characteristic	Patients (n=953)
Age, mean (SD), y	58 (12)
Female sex, No. (%)	634 (66)
Comorbidities, No. (%)	
Chronic kidney disease[a]	100 (11)
Hypertension	733 (78)
Coronary artery disease including angina	439 (46)
Congestive heart failure	169 (18)
Medication use in the year prior to orlistat prescription, No. (%)	
Diabetes drugs	942 (99)
HMG-CoA reductase inhibitors	666 (70)
Angiotensin-converting enzyme inhibitors	637 (67)
Antiplatelets[b]	444 (47)
Calcium channel blockers	404 (42)
β-Blockers	319 (34)
Nonsteroidal anti-inflammatory drugs (non-ASA)	318 (33)
Thiazide diuretics	308 (32)
Angiotensin receptor blockers	300 (32)
Loop diuretics	286 (30)
Potassium-sparing diuretics	97 (10)
Warfarin	53 (6)
Renal Function Data Subset[c]	**Patients (n=27)**
Most recent serum creatinine, mg/dL, median (IQR)	1.01 (0.76-1.22)
Most recent eGFR, mL/min/1.73 m^2, median (IQR)[d]	75 (64-94)
Most recent eGFR category, No. (%)	
Normal: ≥90 mL/min/1.73 m^2	10 (37)
Normal: 60-89 mL/min/1.73 m^2	13 (48)
CKD IIIa: 45-59 mL/min/1.73 m^2	≤5[e]
CKD IIIb: 30-44 mL/min/1.73 m^2	≤5[e]
CKD IV: 15-29 mL/min/1.73 m^2	0
CKD V: <15 mL/min/1.73 m^2	0

Abbreviations: ASA, acetylsalicylic acid; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IQR, interquartile range.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 76.25.
[a] Defined using administrative data (see eAppendix for details).
[b] Does not include over-the-counter ASA.
[c] Outpatient serum creatinine concentrations from the Gamma-Dynacare database were available for only 44 patients.
[d] eGFR was calculated from serum creatinine concentrations using the modified Modification of Diet in Renal Disease equation.
[e] In accordance with privacy regulations, cell sizes less than or equal to 5 cannot be reported.

Results. During the 87-month accrual period, we identified 953 new users of orlistat. The **Table** displays their demographic and baseline data. In the 12 months preceding the initial orlistat prescription, 5 patients expe-

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rienced an AKI event, compared with 18 patients who experienced an AKI event in the 12-month period following the initial prescription ($P=.01$). As expected, we found no significant difference in the number of upper gastrointestinal tract hemorrhage events between the 2 observation periods (6 events in each period, $P=.77$).

Comment. Compared with the year before an incident orlistat prescription, we observed significantly more AKI events in the year after prescription, with 2% of newly treated patients experiencing an AKI event within a year of commencing the drug. This finding supports the association between AKI and orlistat suggested in recent case reports.[5,6] As expected, we found no association between orlistat and upper gastrointestinal tract hemorrhage.

Our study's sample size was large and the self-matched design reduced confounding. We gathered data from reliable databases (eAppendix), and we addressed an important drug safety issue. However, we did not have data to assign AKI events to oxalate nephropathy, and the assessment of AKI using administrative data invariably underestimates its incidence and prevalence. Also, physicians with knowledge of the case report literature may have been less likely to prescribe orlistat to patients who had recently experienced an AKI event. Although it is possible that factors other than orlistat contributed to the AKI events, it is unlikely that such factors occurred at a differential rate between the 2 observation periods. Despite these limitations, we conclude that in the appropriate setting, physicians should consider orlistat as a potential cause of AKI.

Matthew A. Weir, MD
Michael M. Beyea, PhD
Tara Gomes, MHSc
David N. Juurlink, MD, PhD
Muhammad Mamdani, MPH, MA, PharmD
Peter G. Blake, MB
Ron Wald, MDCM, MPH
Amit X. Garg, MD, PhD

Author Affiliations: Division of Nephrology, Department of Medicine, University of Western Ontario, London, Ontario, Canada (Drs Weir, Blake, and Garg); Kidney Clinical Research Unit, London Health Sciences Centre, London (Drs Weir, Beyea, Blake, and Garg); Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada (Drs Juurlink, Mamdani, and Garg and Ms Gomes); Leslie Dan Faculty of Pharmacy (Ms Gomes and Dr Mamdani) and Department of Health Policy, Management, and Evaluation (Drs Juurlink and Mamdani), University of Toronto, Toronto; Division of Clinical Pharmacology and Toxicology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto (Dr Juurlink); and Applied Health Research Center, Keenan Research Centre in the Li Ka Shing Knowledge Institute (Drs Mamdani and Wald) and Division of Nephrology (Dr Wald), St Michael's Hospital, Toronto.
Correspondence: Dr Weir, London Kidney Clinical Research Unit, Room ELL-101, Westminster Tower, London Health Sciences Centre, 800 Commissioners Rd E, London, ON N6A 4G5, Canada (mweir@uwo.ca).

Author Contributions: Drs Weir, Juurlink, Mamdani, and Garg and Ms Gomes had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Weir, Gomes, Juurlink, Mamdani, Blake, and Garg. *Acquisition of data:* Weir, Beyea, Gomes, and Garg. *Analysis and interpretation of data:* Weir, Gomes, Juurlink, Mamdani, Wald, and Garg. *Drafting of the manuscript:* Weir. *Critical revision of the manuscript for important intellectual content:* Weir, Beyea, Gomes, Juurlink, Mamdani, Blake, Wald, and Garg. *Statistical analysis:* Beyea, Gomes, and Garg. *Obtained funding:* Juurlink, Mamdani, and Garg. *Administrative, technical, and material support:* Weir, Mamdani, and Garg. *Study supervision:* Juurlink, Blake, Wald, and Garg.
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Online-Only Material: The eAppendix is available at http://www.archinternmed.com.
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COMMENTS AND OPINIONS

Gastroesophageal Reflux Disease Stimulation of NSAID-Associated Atrial Fibrillation

The association between atrial fibrillation (AF) and nonsteroidal anti-inflammatory drug (NSAID) use demonstrated by De Caterina et al[1] may be augmented by at least 2 common mechanisms not included among those that they proposed. Reflux esophagitis is extremely common during NSAID use and has been independently associated with AF[2]; its treatment with protein pump inhibitors (PPIs) has been associated with less frequent AF.[3,4] Prolonged, habitual, physical effort, which may increase NSAID use, may also induce a much greater frequency of AF,[5] potentially contributing to the NSAID-AF association.

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