Published in final edited form as:

J Nephrol. 2013 ; 26(2): 281–288. doi:10.5301/jn.5000104.

Trends in the incidence of intestinal perforation in US dialysis patients (1992–2005)

Ju-Yeh Yang^{1,2}, Tsung-Chun Lee³, Maria E. Montez-Rath¹, Manisha Desai⁴, and Wolfgang C. Winkelmayer¹

¹Division of Nephrology, Stanford University School of Medicine, Palo Alto, California - USA

²Division of Nephrology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City - Taiwan

³Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei - Taiwan

⁴Division of General Medical Disciplines, Stanford University School of Medicine, Palo Alto, California - USA

Abstract

Background—Little is known about the incidence of intestinal perforation in patients undergoing dialysis. Concerns exist that sevelamer hydrochloride may increase the risk of intestinal perforation. We examined long-term trends for the incidence of intestinal perforation among US dialysis patients.

Methods—We studied all dialysis patients (1992–2005) who had Medicare as primary payer. We used ICD-9 diagnosis code 569.83 to ascertain events of intestinal perforation. We studied (a) all perforations and (b) perforations that did not appear to be associated with specific causative conditions (specific diseases or iatrogenic procedures within 7 days of perforation). We used Poisson regression to model the annual number of intestinal perforations and tested for any changes in levels and temporal trends of incidence rates before versus after January 1, 1999.

Results—Overall, 1,060,132 patients contributed 2.7 million patient-years. We observed 12,355 events of intestinal perforation and 7,814 spontaneous perforations. The corresponding incidence rates were 4.6 (total) and 2.9 (spontaneous perforation) episodes per 1,000 person-years, respectively. For both outcome definitions, 30-day mortality was 42%. Unadjusted and adjusted incidence rates were not materially different over time. Formal tests for any changes in the level or slope of incidence comparing time periods before and after January 1, 1999, indicated no evidence for any changes in the incidence of intestinal perforation over time.

© 2012 Società Italiana di Nefrologia

Address for correspondence: Wolfgang C. Winkelmayer, MD, ScD, Division of Nephrology, Stanford University School of Medicine, 780 Welch Rd., Suite 106, Palo Alto, CA 94304, USA, wcw1@stanford.edu.

USRDS disclaimer statement: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government. Special thanks to the staff of the USRDS (Chronic Disease Research Group) for their kind assistance.

Financial support and conflict of interest statement: All other authors report no conflict.

Conclusions—In US dialysis patients, incidence of intestinal perforation was low, but associated with high short-term mortality. We did not detect any significant changes in the incidence of intestinal perforation before versus after approval of sevelamer hydrochloride in late 1998.

Keywords

Adverse events; Dialysis; Gastrointestinal; Health services research; Safety; Phosphate binders

Introduction

No studies have been conducted to systematically evaluate the incidence of intestinal perforation in patients undergoing dialysis. Intestinal perforation is rare in the general population, but carries a high risk of mortality (1–6). We recently observed that patients undergoing dialysis had high rates of acute nonvariceal gastrointestinal bleeding, which was up to 2 orders of magnitude higher than in the nondialysis population (7). As a result, it seemed important to define rates of another, potentially fatal gastrointestinal event, intestinal perforation, in these vulnerable patients.

Sevelamer is an anion-exchange resin which lowers serum phosphorus by binding phosphate in the digestive tract and therefore decreasing absorption. It was first approved by the US Food and Drug Administration (FDA) in October 1998 as sevelamer hydrochloride tablets (400 mg and 800 mg) to control hyperphosphatemia in patients with chronic kidney disease on dialysis. In clinical trials of sevelamer, adverse gastrointestinal events constituted the leading reasons listed for the dropping-out of participants.

Concerns have been raised that sevelamer hydrochloride may increase the risk of adverse gastrointestinal (GI) events, including abdominal bloating, diarrhea and constipation, in comparison with other calcium-based phosphate binders (8–12). Ileus, intestinal obstruction and intestinal perforation have also been reported. Madan et al reported a case of lower GI bleeding due to fecalith ulceration potentially from sevelamer (13). Nolan et al reported 80 cases of intestinal obstruction and 79 cases of intestinal perforation using the Adverse Event Reporting System (AERS) database of the FDA, following sevelamer approval (12). Due to the limitations of the AERS database, including the inability to track duplicate reports of the same episode, the manufacturer of sevelamer rejected these claims and a formal evaluation of the matter by the FDA in response to a Citizen Petition in 2006 did not lead to any major regulatory action (14).

Surprisingly, no systemic investigation of intestinal perforation following market approval of sevelamer has been published thus far. Therefore, we conducted this study to examine temporal trends of the incidence of intestinal perforation, a potential fatal adverse event, among US dialysis patients between 1992 and 2005. Specifically, we hypothesized that any meaningful risk at a population level of intestinal perforation from sevelamer would become apparent in formal time-trend analyses given its rapid and widespread adoption following its market introduction in 1998.

Subjects and methods

Study population

We studied all maintenance dialysis patients included in the US Renal Data System (USRDS) between 1992 and 2005 who had Medicare (Part A+ Part B) as primary payer. The USRDS database includes almost all patients receiving chronic dialysis in the United States, and consists of the health care claims submitted by providers to Medicare. Using this database, we obtained information on the outcome of interest, intestinal perforation, as well as the presence of several comorbidities from Medicare claims files. We obtained demographic data and selected clinical information from USRDS Standard Analysis Files.

Patients under the age of 18 years or whose kidney function recovered were excluded. We observed eligible patients until they died, underwent renal transplantation, experienced an intestinal perforation or to the end of study period (i.e., December 31, 2005).

Study outcomes

We used the International Classification of Diseases (9th revision; ICD-9) diagnosis code 569.83 to ascertain intestinal perforation events. This code is specific for intestinal perforation, and distinct from codes for peptic ulcer perforation or appendicitis with perforation. The code had been validated and widely used to study gastrointestinal perforation in other populations (15–17). In preliminary analyses of our cohort, we found that 10% of episodes were recurrent claims, 90% of which occurred within 60 days of the first episode. As a result, we decided to only study first (incident) episodes. However, we conducted sensitivity analyses that included these recurrent episodes, defined as distinct episodes if they appeared 30, 60 or 90 days after a first episode. Results were not materially different from the analyses of first episodes presented herein.

Primary analyses considered diagnosed intestinal perforations regardless of their cause. Temporal changes of certain risk factors for the incidence of intestinal perforation, however – e.g., the increasing adoption and use of invasive procedures and changes in the treatments of underlying disease – might affect the incidence of overall intestinal perforation over time. To distinguish spontaneous perforations from ones associated with specific causative conditions, we defined as spontaneous perforations those events that had no identifiable leading disease (e.g., intestinal tumors, inflammatory bowel disease or ischemic bowel disease) on the same claim or no potential iatrogenic procedures (e.g., endoscopy or colonoscopy) within 7 days before the date the perforation was reported.

We also assessed the proportion of patients who died within 30 days from the index gastrointestinal perforation event.

Statistical analysis

We tabulated the characteristics of patients who had, versus who did not have, a gastrointestinal perforation event in years 1992 and 2005, without formally testing for any differences between strata. For the purpose of estimating event incidence rates, the observation of a single patient may have been interrupted by ineligible payer histories (with

Medicare Part A and B not being the primary payer), dialysis modality switches, transplantation or calendar years. This means that a patient can have more than 1 observation per year and several observations across years, thus correlations among observations within each subject are expected. Therefore, we used Poisson regression with generalized estimating equation (GEE) methods to model the annual number of intestinal perforations (18). Since the proportions of missing data were only 0.04% for race and 1.9% for dialysis modality, we used complete data analysis. To formally test for any changes in the incidence of intestinal perforation after the launch of sevelamer in late 1998, we used intervention analysis and tested for any changes in level and/or trend (slope) prior to versus after January 1, 1999 (19, 20). A change in level would reflect an immediate effect and a change in trend would represent a gradual effect (19). To keep individual level data, we used a log link function rather than collapsing all data by year. We report unadjusted and fully adjusted results. Adjusted models included variables for age, sex, race, dialysis vintage, dialysis modality, history of renal transplantation and several comorbidities (diabetes, heart failure, coronary artery disease, chronic obstructive lung disease, cerebral vascular disease, hypertension, arrhythmia, valvular heart disease, peripheral vascular disease, chronic liver disease and malignancy).

Information on the proportion of patients who died within 30 days of the index intestinal perforation event was obtained from the death date in the USRDS patient file. All analyses were performed using the SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

This work was approved by the Institutional Review Board of Stanford University School of Medicine and conducted under a data use agreement to W.C.W. from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This manuscript was reviewed by NIDDK and approved for submission.

Results

Overall, 1,060,132 patients contributed 2.7 million patient-years to this study. We observed 12,355 events of intestinal perforation and 7,814 events of spontaneous intestinal perforation. The annual proportion of patients at risk who experienced an episode of gastrointestinal perforation was 0.4% in both 1992 and 2005. Table I compares the characteristics of cohort members in 1992 and 2005, stratified by whether they experienced a perforation event. The corresponding incidence rates were 4.6 (95% confidence interval [95% CI], 4.5–4.7) per 1,000 person-years for all intestinal perforations and 2.9 (95% CI, 2.8–3.0) per 1,000 person-years for spontaneous perforation episodes. The 30-day mortality rates after intestinal perforation were 42.3% (95% CI, 41.4%–43.2%) for all intestinal perforations and 42.4% (95% CI, 41.3%–43.5%) for spontaneous perforations.

Annual incidence rate ratios (compared with 1992) before and after adjustment for demographic and comorbid factors over time are shown in Figure 1. While estimates of association varied from year to year, almost all of the annual estimates were statistically indistinguishable from the incidence in 1992. Formal tests for any changes in the level or slope of incidence comparing time periods before and after 1999 provided no evidence for any changes in the incidence of intestinal perforation (Tab. II).

Discussion

This is the first population-based, systematic observation of intestinal perforation in US dialysis patients. We found that the overall incidence of intestinal perforation was low, at 4.6 events per 1,000 person years, while nearly half of the patients (42%) who experienced an intestinal perforation died within 30 days. The overall in-hospital mortality rates of intestinal perforation were 10%–20% in the general population (1–6). We also tested whether the incidence of intestinal perforation changed after market introduction of sevelamer hydrochloride in late 1998, a hypothesis that was motivated by safety concerns that had previously been weighed by the US FDA. We did not find any evidence supporting significant changes in the incidence comparing the pre-1999 era versus the 1999 and later period.

The drug information document for sevelamer indicates that “the safety and efficacy in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established” (Renagel® (sevelamer hydrochloride). Prescribing Information. Available at: http://www.renagel.com/docs/renagel_pi.pdf. Accessed March 6, 2012). In patients with bowel obstruction, sevelamer is contraindicated. Despite clinical concerns about the GI safety of sevelamer, however, there is no direct pathologic evidence about how sevelamer might affect the GI tract. It is possible that any adverse effect of sevelamer on GI function and structure could resemble the mechanisms hypothesized to be responsible for polystyrene sulfonate–induced GI injury. Polystyrene sulfonate is another anion-exchange resin used to treat hyperkalemia (21–23). It has been speculated that polystyrene sulfonate may cause transmural colonic infarction due to rapid electrolyte shifts (24), epithelial damage by its osmotic action (21) and ischemic lesions by vasospasm (22). Although some studies have suggested the coadministered sorbitol might be the main pathogenetic factor (21, 22), there is also a case report of polystyrene sulfonate–related ischemic colitis in which case no sorbitol was given (23).

The manufacturer of sevelamer hydrochloride introduced a closely related drug, sevelamer carbonate, in 2009 and has attempted through marketing to direct consumers to using the newer version. Whether sevelamer carbonate has similar side effects on the GI tract as sevelamer hydrochloride is not clear. After the expected expiration of key patents for sevelamer in 2013 and 2014, sevelamer hydrochloride may become available as a generic medication quickly, as indicated by past and current legal action between the current manufacturer and other companies (25).

The current study has several limitations. Most importantly, we do not have individual patient level data on sevelamer use. Among patients whose primary payer was Medicare, oral prescription drugs were usually covered by separate pharmaceutical benefits programs or Medicaid, which are data that we do not possess. Instead, we used calendar time as a proxy (instrument) for sevelamer exposure. We know that prior to FDA approval of sevelamer hydrochloride in October 1998, no patients were exposed to it other than the few participants in regulatory trials. We also know that sevelamer hydrochloride was quickly adopted in the United States, with over 900,000 filled prescriptions in 2005 (Fig. 2) (14) and an almost 50% share of the prescription phosphate binder market (26, 27). In 2007,

approximately 50% of patients in the Medicare end-stage renal disease program who had prescription drug coverage through Medicare Part D used sevelamer monotherapy, with an additional 20% of patients using various combinations of phosphate binders that may also have included sevelamer (26). These data support using calendar time as an instrument for sevelamer exposure. Thus, we applied a modified quasi-experimental approach to evaluate longitudinal effects of an intervention (19, 20). We tested both immediate and gradual effects of the introduction and subsequent widespread adoption of sevelamer, and kept individual level data for multivariate adjustments. It is evident that such widespread use would yield a detectable increase in intestinal perforation incidence in parallel with such widespread market adoption if such a risk were large. In contrast to the increasing number of prescriptions, we did not detect any signal of correspondingly increased incidences of intestinal perforation over time, indicating that such risks from sevelamer, if present, have to be relatively small. Of note, the design applied assumes absence of time-dependent confounding by unobserved characteristics, an assumption that cannot be tested. On one side, temporal changes of certain risk factors might affect the incidence of intestinal perforation; on the other side, sevelamer might play a trigger factor that interacts with risk factors for intestinal perforation to induce it (e.g., sevelamer causing GI symptoms that then lead to endoscopy, which increases the risk for intestinal perforation). In light of this concern, we not only studied all intestinal perforations, but also attempted to restrict outcomes to those that were seemingly idiopathic (e.g., without a recorded trigger such as recent endoscopy). Another potential limitation of our study is that we focused only on the outcome of intestinal perforation, the most often fatal GI adverse event. We did not study the more ominous end points of GI obstruction or ileus. The strength of our study includes a large and representative study population, which conferred adequate precision to detect even relatively small risks or changes in temporal trends.

Conclusion

In conclusion, from this first population-based, systematic observation of intestinal perforation in US dialysis patients, we found that the incidence of intestinal perforation was low, at 0.4% per year, but fatal with a 30-day mortality exceeding 42%. We did not find any significant changes in the incidence of intestinal perforation over time in general, or before versus after approval of sevelamer during a period from 1992 to 2005. Given the widespread use of sevelamer in approximately 50% of US dialysis patients in 2005, it is unlikely that sevelamer contributes meaningfully to the risk of intestinal perforation on a population level.

Acknowledgments

W.C.W. reports having served as a scientific advisor or consultant to Affymax, Amgen, Astellas, Vifor-Fresenius, GlaxoSmithKline and Sandoz. He has received unrestricted research support from Fibrogen. We most gratefully acknowledge the generous sponsorship of Far Eastern Memorial Hospital, New Taipei City, Taiwan, which supported J.-Y. Y.'s visiting scholarship at Stanford University.

References

1. Tan KK, Hong CC, Zhang J, Liu JZ, Sim R. Predictors of outcome following surgery in colonic perforation: an institution's experience over 6 years. *J Gastrointest Surg*. 2011; 15(2):277–284. [PubMed: 20824374]

2. Mueller MH, Karpitschka M, Renz B, et al. Co-morbidity and postsurgical outcome in patients with perforated sigmoid diverticulitis. *Int J Colorectal Dis.* 2011; 26(2):227–234. [PubMed: 20676663]
3. Tan KK, Hong CC, Zhang J, Liu JZ, Sim R. Surgery for perforated colorectal malignancy in an Asian population: an institution's experience over 5 years. *Int J Colorectal Dis.* 2010; 25(8):989–995. [PubMed: 20390285]
4. Tan KK, Bang SL, Sim R. Surgery for small bowel perforation in an Asian population: predictors of morbidity and mortality. *J Gastrointest Surg.* 2010; 14(3):493–499. [PubMed: 19997984]
5. Biondo S, Ramos E, Deiros M, et al. Prognostic factors for mortality in left colonic peritonitis: a new scoring system. *J Am Coll Surg.* 2000; 191(6):635–642. [PubMed: 11129812]
6. Tan KK, Zhang J, Liu JZ, Shen SF, Earnest A, Sim R. Right colonic perforation in an Asian population: predictors of morbidity and mortality. *J Gastrointest Surg.* 2009; 13(12):2252–2259. [PubMed: 19707836]
7. Yang JY, Lee TC, Montez-Rath ME, et al. Trends in acute non-variceal upper gastrointestinal bleeding in dialysis patients. *J Am Soc Nephrol.* 2012; 23(3):495–506. [PubMed: 22266666]
8. Evenepoel P, Selgas R, Caputo F, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrol Dial Transplant.* 2009; 24(1):278–285. [PubMed: 18820280]
9. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. *N Engl J Med.* 2010; 362(14):1312–1324. [PubMed: 20375408]
10. Tonelli M, Wiebe N, Culleton B, et al. Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant.* 2007; 22(10):2856–2866. [PubMed: 17906326]
11. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GF. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. *Am J Kidney Dis.* 2009; 54(4):619–637. [PubMed: 19692157]
12. Nolan CR, Qunibi WY. High incidence of intestinal obstruction and perforation during treatment with sevelamer HCl [abstract]. *J Am Soc Nephrol.* 2006; 17:358A.
13. Madan P, Bhayana S, Chandra P, Hughes JI. Lower gastrointestinal bleeding: association with Sevelamer use. *World J Gastroenterol.* 2008; 14(16):2615–2616. [PubMed: 18442219]
14. Division of Dockets Management, Food and Drug Administration. [Accessed September 5, 2011] Re: Comments of Genzyme cooperation docket no. 2006P-0186. Available at: <http://www.fda.gov/ohrms/dockets/dockets/06p0186/06p-0186-c000001-01-vol1.pdf>
15. Rabeneck L, Paszat LF, Li C. Risk factors for obstruction, perforation, or emergency admission at presentation in patients with colorectal cancer: a population-based study. *Am J Gastroenterol.* 2006; 101(5):1098–1103. [PubMed: 16573783]
16. Chang CH, Lin JW, Chen HC, Kuo CW, Shau WY, Lai MS. Non-steroidal anti-inflammatory drugs and risk of lower gastrointestinal adverse events: a nationwide study in Taiwan. *Gut.* 2011; 60(10):1372–1378. [PubMed: 21415083]
17. Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol.* 2009; 104(7):1633–1641. [PubMed: 19574968]
18. Stürmer T, Glynn RJ, Kliebsch U, Brenner H. Analytic strategies for recurrent events in epidemiologic studies: background and application to hospitalization risk in the elderly. *J Clin Epidemiol.* 2000; 53(1):57–64. [PubMed: 10693904]
19. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* 2002; 27(4):299–309. [PubMed: 12174032]
20. Fischer MA, Vogeli C, Stedman M, Ferris T, Brookhart MA, Weissman JS. Effect of electronic prescribing with formulary decision support on medication use and cost. *Arch Intern Med.* 2008; 168(22):2433–2439. [PubMed: 19064827]
21. Abraham SC, Bhagavan BS, Lee LA, Rashid A, Wu TT. Upper gastrointestinal tract injury in patients receiving Kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol.* 2001; 25(5):637–644. [PubMed: 11342776]

22. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol.* 1997; 21(1):60–69. [PubMed: 8990142]
23. Tapia C, Schneider T, Manz M. From hyperkalemia to ischemic colitis: a resinous way. *Clin Gastroenterol Hepatol.* 2009; 7(8):e46–e47. [PubMed: 19281864]
24. Parfitt JR, Driman DK. Pathological effects of drugs on the gastrointestinal tract: a review. *Hum Pathol.* 2007; 38(4):527–536. [PubMed: 17367604]
25. Genzyme Corporation. [Accessed September 5, 2011] Form 10-k filed to the United States Securities and Exchange Commission: 2010 annual report pursuant to section 13 or 15(d) of the securities exchange act of 1934. Available at: http://www.Genzyme.Com/corp/investors/xbrl/as_filed_q4_2010_form_10-q.Pdf
26. Collins AJ, Foley RN, Herzog C, et al. US Renal Data System 2010 annual data report. *Am J Kidney Dis.* 2011; 57(1 A8):e1–e526.
27. Genzyme Corporation. [Accessed September 1, 2011] 2006 annual report. Available at: http://www.genzyme.com/2006_ann_rpt/renal.asp

Fig. 1.

Relative incidence rates of intestinal perforation (1992–2005). A) All intestinal perforation; B) Spontaneous intestinal perforation. The panels depict annual incidence rate ratios (each year compared with 1992) and corresponding 95% confidence intervals. Adjusted models include: age, sex, race, dialysis vintage, dialysis modality, history of past kidney transplantation, and 11 comorbidities (diabetes, heart failure, coronary artery disease, chronic obstructive lung disease, cerebral vascular disease, hypertension, arrhythmia, valvular heart disease, peripheral vascular disease, chronic liver disease and malignancy).

Fig. 2.
Number of annual prescriptions of sevelamer in the United States. Adapted from the comments by Genzyme Corporation to the Division of Dockets Management of the US Food and Drug Administration: Annual number of prescriptions for sevelamer hydrochloride in the United States based on data from the IMS Health National Prescription Audit (14).

TABLE I
COHORT CHARACTERISTICS BY GASTROINTESTINAL PERFORATION STATUS (1992 AND 2005)

	1992			2005		
	Total	No perforation	Perforation	Total	No perforation	Perforation
Number (% of total)	176,390	175,757 (99.6)	633 (0.4)	329,124	327,964 (99.6)	1,160 (0.4)
Age, years	59.5 ± 15.7	59.5 ± 15.7	61.5 ± 14.6	62.4 ± 15.2	62.4 ± 15.3	65.8 ± 14.2
Male	91,786 (52.0)	91,484 (52.1)	302 (47.7)	178,023 (54.1)	177,448 (54.1)	575 (49.6)
Race						
White	107,223 (60.8)	106,774 (60.8)	449 (70.9)	189,085 (57.5)	188,310 (57.4)	775 (66.8)
Black	62,833 (35.6)	62,663 (35.7)	170 (26.9)	119,640 (36.4)	119,309 (36.4)	331 (28.5)
Asian	4,019 (2.3)	4,013 (2.3)	6 (0.9)	12,296 (3.7)	12,266 (3.7)	30 (2.6)
Native	2,213 (1.3)	2,205 (1.3)	8 (1.3)	4,945 (1.5)	4,926 (1.5)	19 (1.6)
Other	71 (0.0)	71 (0.0)	0 (0.0)	3,042 (0.9)	3,038 (0.9)	4 (0.3)
Missing	31 (0.0)	31 (0.0)	0 (0.0)	116 (0.0)	115 (0.0)	1 (0.1)
Dialysis modality						
Hemodialysis	146,126 (82.8)	145,672 (82.9)	454 (71.7)	300,877 (91.4)	299,887 (91.4)	990 (85.3)
Peritoneal dialysis	26,270 (14.9)	26,112 (14.9)	158 (25.0)	24,074 (7.3)	23,929 (7.3)	145 (12.5)
Missing	3,994 (2.3)	3,973 (2.3)	21 (3.3)	4,173 (1.3)	4,148 (1.3)	25 (2.2)
Dialysis vintage, years; median (IQR)	1.3 (0.1–3.5)	1.3 (0.1–3.5)	1.8 (0.2–4.3)	1.9 (0.3–4.4)	1.9 (0.3–4.4)	2.4 (0.4–5.6)
Primary kidney disease						
Glomerulonephritis	27,115 (15.4)	27,004 (15.4)	111 (17.5)	34,890 (10.6)	34,721 (10.6)	169 (14.6)
Hypertensive	56,290 (31.9)	56,075 (31.9)	215 (34.0)	96,069 (29.2)	95,699 (29.2)	370 (31.9)
Diabetes	56,904 (32.3)	56,763 (32.3)	141 (22.3)	143,494 (43.6)	143,153 (43.6)	341 (29.4)
Other	28,085 (15.9)	27,942 (15.9)	143 (22.6)	42,484 (12.9)	42,261 (12.9)	223 (19.2)
Missing	7,996 (4.5)	7,973 (4.5)	23 (3.6)	12,187 (3.7)	12,130 (3.7)	57 (4.9)
History of comorbid conditions						
Diabetes	54,800 (31.1)	54,647 (31.1)	153 (24.2)	212,010 (64.4)	211,350 (64.4)	660 (56.9)
Hypertension	63,052 (35.7)	62,810 (35.7)	242 (38.2)	305,979 (93.0)	304,896 (93.0)	1,083 (93.4)
Coronary artery disease	23,957 (13.6)	23,868 (13.6)	89 (14.1)	125,562 (38.2)	125,076 (38.1)	486 (41.9)
Cerebral vascular disease	10,476 (5.9)	10,444 (5.9)	32 (5.1)	59,287 (18.0)	59,054 (18.0)	233 (20.1)
Heart failure	42,741 (24.2)	42,569 (24.2)	172 (27.2)	184,201 (56)	183,497 (56.0)	704 (60.7)

	1992			2005		
	Total	No perforation	Perforation	Total	No perforation	Perforation
Arrhythmia	24,473 (13.9)	24,381 (13.9)	92 (14.5)	107,539 (32.7)	107,069 (32.6)	470 (40.5)
Valvular heart disease	8,856 (5.0)	8,819 (5.0)	37 (5.8)	70,621 (21.5)	70,327 (21.4)	294 (25.3)
Peripheral vascular disease	20,376 (11.6)	20,276 (11.5)	100 (15.8)	122,278 (37.2)	121,801 (37.1)	477 (41.1)
Chronic obstructive lung disease	13,734 (7.8)	13,668 (7.8)	66 (10.4)	80,803 (24.6)	80,403 (24.5)	400 (34.5)
Cancer	9,552 (5.4)	9,503 (5.4)	49 (7.7)	40,211 (12.2)	40,011 (12.2)	200 (17.2)
Chronic liver disease	17,853 (10.1)	17,790 (10.1)	63 (10.0)	81,377 (24.7)	81,072 (24.7)	305 (26.3)
History of kidney transplant	9,337 (5.3)	9,291 (5.3)	46 (7.3)	17,842 (5.4)	17,748 (5.4)	94 (8.1)

IQR = interquartile range.

TESTS FOR CHANGES IN THE INCIDENCE OF INTESTINAL PERFORATION COMPARING TIME PERIODS BEFORE AND AFTER 1999

TABLE II

	Unadjusted			Adjusted*		
	Estimate (95% CI)	p Value		Estimate (95% CI)	p Value	
All events						
Level	-0.059 (-0.130 to 0.012)	0.11		-0.050 (-0.121 to 0.022)	0.17	
Slope	-0.001 (-0.019 to 0.017)	0.89		-0.002 (-0.020 to 0.017)	0.86	
Spontaneous events						
Level	-0.075 (-0.164 to 0.015)	0.10		-0.061 (-0.150 to 0.029)	0.18	
Slope	-0.009 (-0.032 to 0.013)	0.42		-0.009 (-0.032 to 0.015)	0.46	

CI = confidence interval.

* Adjusted for age, sex, race, dialysis vintage, dialysis modality, history of renal transplantation, and comorbidities including diabetes, heart failure, coronary artery disease, chronic obstructive pulmonary disease, cerebral vascular disease, hypertension, arrhythmia, valvular heart disease, peripheral vascular disease, chronic liver disease and malignancy.