Methodological options for the evaluation of drug safety: from spontaneous reports to pharmacoepidemiology

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HABILITATIONSSCHRIFT

Methodological Options for the Evaluation of Drug Safety: From Spontaneous Reports to Pharmacoepidemiology

Zur Erreichung der

Venia Legendi der Universität Zürich

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1. Selected Publications Representing the "Kumulative Habilitationsschrift"

The following six publications have been selected as a documentation of my research activities in the field of drug safety and pharmacoepidemiology:

- **Russmann S**, Lauterburg BH, Helbling A. Kava hepatotoxicity. *Ann Intern Med* 2001;135(1):68-9. *(Case report)*
  Impact Factor (2005): 13.254

- **Russmann S**, Kaye JA, Jick SS, Jick H. Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. *Br J Clin Pharmacol* 2005;60(1):76-82.
  Impact Factor (2005): 2.777

- Jick SS, Kaye JA, **Russmann S**, Jick H. Risk of non-fatal venous thromboembolism comparing ORTHO EVRA™ with oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception* 2006; 73(3);223-228.
  Impact Factor (2005): 1.713

- Jick SS, Kaye JA, **Russmann S**, Jick H. Risk of Nonfatal Venous Thromboembolism Comparing Oral Contraceptives Containing Norgestimate or Desogestrel with Oral Contraceptives Containing Levonorgestrel. *Contraception* 2006; 73(6):566-570.
  Impact Factor (2005): 1.713

- Jick H, Kaye JA, **Russmann S**, Jick S. NSAIDs and acute myocardial infarction in patients with no major risk factors. Pharmacotherapy 2006; 26(10):1379-87.
  Impact Factor (2005): 1.920

- **Russmann S**, Lamerato L, Marfatia A, Motsko SP, Pezzullo J, Olds G, Jones JK. Risk of Impaired Renal Function After Colonoscopy: A Cohort Study in Patients Receiving Either Oral Sodium Phosphate or Polyethylene Glycol. American Journal of Gastroenterology, 2007 in press.
  Impact Factor (2005): 5.116

2. Background and Presentation of a Conceptual Framework

Spontaneous reports and "the birth of pharmacovigilance"

Although new drugs have to undergo testing in pre-clinical and clinical (Phase I to III) trials, rare adverse drug reactions are often not identified before the post-marketing phase (Phase IV) in the form of spontaneous reports. Probably the most tragic historical example is the disaster of thalidomide-induced birth defects (1, 2), and the consequent efforts to systematically collect and evaluate reports of spontaneous adverse drug reactions constituted the birth of active drug safety surveillance, or "pharmacovigilance". Until today, probably most acute severe adverse drug reactions are first made public and reach prescribing and regulatory health professionals through spontaneous reports by vigilant health care providers or patients. Such reports may subsequently be evaluated by trained health professionals based on categorized criteria of "intrinsic" evidence, i.e. temporal relationship, exclusion of other causes, improvement upon dechallenge and reoccurrence after rechallenge, as well as specific diagnostic evidence. In addition, "extrinsic" evidence, i.e. information from other comparable reports and mechanistic hypotheses based on pathophysiological and pharmacological considerations, is also taken into account. The combined evidence is then evaluated and weighted according to guidelines, resulting in a semi-quantitative case causality assessment ranging from "unlikely" over "possible and "probable" to "certain". Eventually, these adverse drug reaction reports are collected in large databases such as the one maintained by the WHO Collaborating Centre for International Drug Monitoring, which are supposed to generate „signals", i.e. identify and communicate previously unknown drug safety issues (3).

The principle limitation of such spontaneous reporting systems is the fact that neither the true drug exposure (the "denominator"), nor the true incidence of adverse drug reactions (the "numerator") within the monitored population are known, i.e. any attempts to quantify the occurrence of adverse drug reactions would have to be based on rather crude and generally unreliable assumptions (4). Further, unspecific reactions with a high „background rate" or those with a long latency time are generally not suitable for detection through spontaneous reports. In spite of these intrinsic limitations, I support the view that spontaneous reports make a significant contribution to drug safety as long as their use and interpretation is limited to non-quantitative signal generation (5).

Randomized clinical trials for the evaluation of drug safety

In contrast to spontaneous reporting systems, precise quantitative information is the principle strength of (controlled, randomized) clinical trials. Consequently there is little doubt that they constitute the gold standard for efficacy outcomes, and the mandatory systematic collection and analysis of all adverse events during clinical trials also contributes important safety information. However, also clinical trials have intrinsic limitations, and some of these are particularly relevant for drug safety: the detection of rare but serious adverse reactions would require the inclusion of several thousand or even ten-thousand patients; the setting of clinical trials is “artificial” and does therefore not reflect a drug’s safety profile in clinical practice, for instance certain subpopulations with a potentially higher risk for adverse reactions are excluded, drugs are taken in highly standardized dosage regimens and only during a short time; and furthermore long time periods for planning and conduct of clinical trials with high associated costs usually preclude the availability of required safety information for the right question at the right time (e.g. when a new safety issue is raised after marketing) in the relevant population.

Pharmacoepidemiology and Drug Safety

Epidemiological or “observational” studies are generally considered to be inferior to clinical trials as far as the level of evidence for efficacy outcomes is concerned. However, particularly in the area of drug safety they can overcome many of the mentioned intrinsic limitations of clinical trials: they can efficiently include a large number of patients considered to be representative of the population that uses a drug in clinical practice including patients at risk for adverse reactions; they reflect “real-life”-drug use and therefore also allow the study of drug utilization patterns; and they are generally easier, faster, more flexible and more economical to realize than clinical trials.

The basic formal epidemiological study designs and essential principles, i.e. (comparison) cohort studies and case-control study designs that aim to isolate exposures and outcomes of interest in the best possible way are also applied in drug safety epidemiology. Also the principle tools to control for confounding, i.e. restriction, stratification with and without pooled estimates (6), and regression modeling, have been used for a long time. However, the availability of large high quality automated databases that include the electronic information of several million patients has increased exponentially during the past five to ten years. In addition, refined and easier to use statistical methods and software allow better control of residual confounding, e.g. through conditional logistic regression or propensity score-based regression modeling (7). These changes have indeed taken the contribution of pharmacoepidemiology for the efficient evaluation of drug safety to a new dimension.

3. Discussion of the Selected Publications

Kava hepatotoxicity

Although this first selected publication is "just" a case report, it is a good example for the value and subsequent impact of a well-documented published spontaneous report when little other safety data is available (8). Almost simultaneously with two other groups (9, 10), we published the first cases of severe hepatotoxicity associated with phytotherapeutics containing Kava-lactones. Beyond the usual extensive differential diagnostic workup, we also performed a relatively specific lymphocyte transformation test, and the formal causality assessment was therefore able to link hepatotoxicity with a high probability to Kava exposure in this case. Subsequently we also followed this signal with two prospective studies (11, 12). Because Kava was sold as a non-prescription phytotherapeutic in most countries, it was less strictly regulated, and there was consequently relatively little safety information from preclinical and clinical trials available. Kava-induced hepatotoxicity is presumably very rare, and it is therefore also unlikely that this safety issue would have been detected in clinical trials. And because Kava products were sold over the counter, they were also not documented in available patient databases precluding an epidemiological study. In the light of weak evidence for efficacy, the risk-benefit assessment of regulatory authorities was eventually driven by well-documented case-reports indicating a potentially lethal adverse reaction, and Kava was subsequently withdrawn from the markets in Australia, New Zealand, most European (including Switzerland, Germany and France) and other countries world-wide.

Flucloxacillin hepatotoxicity

The second selected publication also concerns hepatotoxicity, being one of the most severe and therefore clinically relevant adverse drug reactions (13). Here however, we were able to conduct an epidemiological study and to estimate the absolute and relative incidence of hepatotoxicity associated with flucloxacillin in one of the world's largest and best-validated databases, the UK General Practice Research Database. Several important principles of drug safety epidemiology are demonstrated in this study. First, we rigorously validated all potential cases through review of original clinical records, excluded patients with identifiable other causes of liver disease, and thus achieved the best possible specificity for the diagnosis of flucloxacillin-induced liver disease. Because unspecific case criteria tend to bias the relative risk estimate to the null in epidemiological studies, this in fact also increases the sensitivity to detect differences as compared to the comparison cohort. Second, the selection

of a suitable comparison cohort exposed to a drug with little or even no hepatotoxicity helps to correct the absolute incidence for any possible residual unspecific hepatotoxicity and may also allow clinically relevant comparisons with alternative treatments. Third, we used a *time-period* incidence as opposed to an incidence *rate* and included only first-time drug exposures. This decision was based on a thorough study of all significant reports in the literature, leading to the hypothesis that the adverse reaction of interest strikes early in susceptible patients or not at all.

Venous thromboembolism associated with a new hormonal contraceptive patch

The next two publications represent good examples of the value of epidemiological safety studies for the fast and efficient evaluation of an urgent safety signal that was generated by spontaneous reports (14, 15). About a dozen reports of fatal venous thromboembolism in young women using a new contraceptive patch had raised major concern about its safety, and the US regulatory authority (FDA) urgently required additional safety data from the manufacturer. Attempts to derive quantitative risk estimates from spontaneous reports and marketing data were uninterpretable due to unknown adverse event reporting rates, and imprecise drug exposure information in the population at risk. In addition, venous thromboembolism is not a specific drug-attributable event (relatively high "background risk"), but may have other known or unknown causes, i.e. individual case causality evaluation can at the most conclude on a possible causal relationship with the drug exposure of interest. Further, a clinical trial could not be conducted under the given time pressure for a regulatory decision, and would have been unable to include a sufficient number of patients to quantify a rare drug effect anyway. The incidence under the drug of interest therefore had to be compared to the incidence during exposure to a suitable comparison drug in a comparable population in a readily available data souce.

We were able to conduct such a study in a large US insurance claims database, plus an additional study that put the comparison drug of our first study into the perspective of the ongoing discussion of the risk of venous thromboembolism in users of second vs. third generation oral contraceptives. In these two studies we found evidence for an increased risk of venous thromboembolism associated with use of the new contraceptive patch vs. no use, but not vs. an established oral contraceptive, and the contraceptive patch has consequently not been withdrawn.

Selective COX2-inhibitors and myocardial infarction

This study addresses an issue that has received considerable attention after the cyclooxygenase-2 selective (COX2) nonsteroidal anti-inflammatory drug (NSAID) rofecoxib (Vioxx®) had been associated with an increased risk of cardiovascular events and

subsequently been withdrawn from the market (16). Although this finding was first observed in a large randomized clinical trial, the results of this trial left many questions unanswered, such as an extended comparison with other NSAIDs and other populations. We therefore conducted a database study on this issue, and in order to achieve the best possible control of confounding, we used a nested case-control design where we excluded all patients with other identifiable causes and risk factors for myocardial infarction (restriction as a tool to control for confounding), matched cases and controls on age, gender, time and practice, and subsequently performed a conditional logistic regression analysis considering additional covariables including cumulative drug exposure (17). Our findings indicated that those NSAIDs with a high selectivity for COX2 (rofecoxib, celecoxib and diclofenac) were associated with a higher risk of myocardial infarction, whereas ibuprofen and naproxen were not.

Renal function after colonoscopy using different bowel cleansing preparations
The last study concerns a safety issue that was triggered by spontaneous reports of severe renal dysfunction after use of oral bowel cleansing agents containing sodium phosphate (18). For this study we were able to link the large database of the Henry Ford Health System, with the local database of affiliated gastroenterology clinics in Detroit, and subsequently conducted a cohort study comparing users of sodium phosphate vs. poylethylenglycol for bowel preparation before colonoscopy. In this study we first used restriction as a powerful and robust method to control for confounding related to a possibly preferred use of polyethylenglycol in patients with preexisting renal dysfunction: we a priori excluded patients with severe preexisting renal dysfunction from the study population. Although we needed to exclude a substantial proportion of patients, we believe that this step was necessary in order to obtain robust and interpretable results that are not heavily based on assumptions of regression models. For the further analysis we then applied a propensity score-based regression model, which is a relatively new method that conceptually attempts to mimic the randomization process in a clinical trial, and is supposed to be more robust when several covariables but only a limited number of outcomes have to be analyzed (7).

4. Future Perspectives

The presented research and related background and discussion aimed to provide examples and a conceptional framework for the application of pharmacoepidemiological methods in the evaluation of drug safety. I would like to emphasize that I do not consider pharmacoepidemiology as an alternative, but as a necessary complementary approach, and

would indeed define four principle sources for information in the evaluation of drug safety i.e. 1) pre-clinical in-vitro and animal studies, 2) clinical trials, 3) spontaneous reports, and 4) formal epidemiological drug safety studies, such as the ones that have been presented and discussed. The integration of information from all of these four principle sources and approaches is essential for a comprehensive evaluation of a drug's safety profile in a relevant context.

Today, pharmacoepidemiology makes a substantial contribution to the evaluation of drug safety, and given an increasing number and size of suitable databases on the one hand, and new regulatory requirements and recommendations on the other hand, this contribution will likely further increase its impact on drug safety for clinicians, pharmaceutical industrial or regulatory authorities in the near future (19). In particular, pharmacoepidemiology is increasingly used as a suitable method for a more proactive safety management during the early post-marketing phase of new drugs.

Although the presented studies mainly focused on the use of pharmacoepidemiology for the quantification of absolute and relative risks and the identification of risk factors, one may argue that for drugs that continue to be marketed the "safety mission is not completed" until the gained knowledge is actually transferred back to the studied populations at risk through the implementation of preventive measures in clinical practice. In this context I finally want to mention that the same electronic patient data systems that are used for the conduct of pharmacoepidemiological studies, may also be used for the subsequent development and local implementation of preventive measures (20). Indeed, at the University Hospital Zurich we currently plan to use electronic drug prescriptions and comprehensive patient information, not only for the local identification of drug safety issues, but also for the establishment of so-called electronic clinical decision support systems, which have been shown to be effective for the improvement of outcomes and reduction of costs in hospitalized patients.

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Zusammenfassung der Habilitationsschrift

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  Impact Factor (2005): 5.116

Background and Presentation of a Conceptual Framework

Three principle methods are available for the evaluation of a drug's clinical safety profile, i.e. spontaneous reports, clinical trials, and formal pharmacoepidemiological studies.

Spontaneous reports

Most acute severe adverse drug reactions are first made public and reach prescribing and regulatory health professionals through spontaneous reports by vigilant health care providers or patients. For a standardized assessment, the combined evidence from individual reports is evaluated and weighted according to guidelines, resulting in a semi-quantitative case causality assessment. Reports are subsequently collected in large databases, which are supposed to generate „signals", i.e. identify previously unknown drug safety issues. The principle limitation of such spontaneous reporting systems is the fact that neither the true drug exposure, nor the true incidence of adverse drug reactions are known, i.e. any attempts to quantify the occurrence of adverse drug reactions will provide a rather crude and generally unreliable approximation. Further, unspecific reactions with a high „background rate" or those with a long latency time are generally not suitable for detection through spontaneous reports.

Randomized clinical trials for the evaluation of drug safety

In contrast to spontaneous reporting systems, precise quantitative information is the principle strength of clinical trials. They consequently constitute the gold standard for efficacy outcomes, and the mandatory systematic collection and analysis of all adverse events during clinical trials also contributes important safety information. However, also clinical trials have intrinsic limitations, and some of these are particularly relevant for drug safety: the detection of rare but serious adverse reactions would require the inclusion of several thousand or even ten-thousand patients; the setting of clinical trials is "artificial" and does therefore not reflect a drug's safety profile in clinical practice; and furthermore long time periods for planning and conduct of clinical trials with high associated costs usually preclude the availability of required safety information for the right question at the right time in the population of interest.

Pharmacoepidemiology and Drug Safety

Epidemiological or "observational" studies are generally considered to be inferior to clinical trials as far as the level of evidence for efficacy outcomes is concerned. However, particularly in the area of drug safety they can overcome many of the mentioned intrinsic limitations of clinical trials: they can efficiently include a large number of patients considered to be representative of the population that uses a drug in clinical practice; they reflect "real-life"-drug use and therefore also allow the study of drug utilization patterns; and they are generally easier, faster, more flexible and more economical to realize than clinical trials. In

recent years, the availability of large high quality automated databases that include the electronic information of several million patients has increased exponentially. In addition, refined and easier to use statistical methods allow better control of residual confounding, and also current regulatory guidelines now demand a proactive post-marketing safety management using pharmacoepidemiological methods.

Discussion of the Selected Publications

Kava hepatotoxicity

In this publication we describe one of the first cases of severe hepatotoxicity associated with phytotherapeutics containing Kava-lactones. Although "just" a case report, it is a good example for the value and subsequent impact of a well-documented published spontaneous report when little other safety data is available. In the light of weak evidence for efficacy, the risk-benefit assessment of regulatory authorities was eventually driven by well-documented case-reports indicating a potentially lethal adverse reaction, and Kava was subsequently withdrawn from the markets in many countries world-wide including Switzerland.

Flucloxacillin hepatotoxicity

The second presented work also concerns hepatotoxicity, but in this case we were able to conduct an epidemiological study and to estimate the absolute and relative incidence of hepatotoxicity associated with flucloxacillin in one of the world's largest and best-validated databases, the UK General Practice Research Database. Several important principles of drug safety epidemiology are demonstrated in this study: the importance of thorough case review and validation, the necessary exclusion of patients with identifiable other causes of the outcome of interest, criteria for the selection of a suitable comparison cohort, and the role of "susceptible" time in the study case definition.

Venous thromboembolism associated with a new hormonal contraceptive patch

The next two publications represent good examples of the value of epidemiological safety studies, when a fast and efficient evaluation of an urgent safety signal is required. About a dozen reports of fatal venous thromboembolism in young women using a new contraceptive patch had raised major concern about its safety, and attempts to derive quantitative risk estimates from spontaneous reports and marketing data, or from clinical trials data was too unreliable due to the above mentioned intrinsic limitations of these approaches. In this situation we were able to conduct two epidemiological safety studies in a large US insurance claims database. We found evidence for an increased risk of venous thromboembolism associated with use of the new contraceptive patch vs. no use, but not vs. an established oral contraceptive.

Selective COX2-inhibitors and myocardial infarction

This study addresses an issue that has received considerable attention after the cyclooxygenase-2 selective (COX2) nonsteroidal anti-inflammatory drug (NSAID) rofecoxib (Vioxx®) had been associated with an increased risk of cardiovascular events and subsequently been withdrawn from the market. We addressed several issues that had been left unanswered and used a study design and data analysis that aimed for the best possible control of confounding. Our findings indicated that those NSAIDs with a high selectivity for COX2 were associated with a higher risk of myocardial infarction, whereas others were not, a result that is compatible with pathophysiological considerations as well as with other studies.

Renal function after colonoscopy using different bowel cleansing preparations

The last study concerns a safety issue that was triggered by spontaneous reports of severe renal dysfunction after use of oral bowel cleansing agents containing sodium phosphate. In this study we first used restriction as a powerful and robust method to control for confounding, and then applied a propensity score-based regression model, which is a relatively new method that conceptually attempts to mimic the randomization process in a clinical trial, and is supposed to be more robust when several covariables but only a limited number of outcomes have to be analyzed. Our results suggest that at least in patients with normal kidneys there is no increased risk of renal dysfunction after use of sodium phosphate compared to polyethylenglycol.

Future Perspectives

Today, pharmacoepidemiology makes a substantial contribution to the evaluation of drug safety, and given an increasing number and size of suitable databases on the one hand, and new regulatory requirements and recommendations on the other hand, this contribution will likely further increase its impact on drug safety for clinicians, pharmaceutical industry and regulatory authorities in the near future. In addition, the same electronic patient data systems that are used for the conduct of pharmacoepidemiological studies, may also be used for the subsequent development and local implementation of preventive measures. Indeed, at the University Hospital Zurich we currently plan to use electronic drug prescriptions and comprehensive patient information not only for the local identification of drug safety issues, but also for the establishment of so-called electronic clinical decision support systems, which have been shown to be effective for the improvement of outcomes and reduction of costs in hospitalized patients.

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IN RESPONSE: We appreciate the interest in our recent article on smoking and renal abnormalities in nondiabetic persons. As Drs. Mehler and Estacio point out, smoking has been found to have adverse effects on renal function not only in patients with type 1 diabetes mellitus but also in those with type 2 diabetes mellitus (1). We agree with their plea that physicians should strongly encourage cessation of smoking in patients with type 2 diabetes mellitus. Our finding that smoking is also associated with both albuminuria and renal function changes in patients without diabetes argues that smoking has renal effects independent of the diabetic setting. It adds to our knowledge about the mechanism of albuminuria. Increased urinary albumin excretion seems to be a phenomenon related not only to diabetes and hypertension but also to smoking, central obesity (Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE. A central body fat distribution is related to renal abnormalities. Unpublished data), and the use of oral contraceptives and hormone replacement therapy (2). This may partly explain why microalbuminuria may also be found in 5% to 6% of nondiabetic and nonhypertensive persons.

We thank Dr. Jay for drawing attention to the medical literature as early as 1922. At that time, it indeed was already reported that smoking could cause Bright disease, known in those days as congestion, degeneration, and damage of the kidney. Furthermore, it was described that tobacco induced a pronounced contraction of the vessels of the kidney (3). These and other historical data, as pointed out by Dr. Jay, underline the importance and difficulties of the struggle for smoking cessation. Microalbuminuria is thought to be an early marker for worsened renal and cardiovascular prognosis. Therefore, our finding that patients who stopped smoking no longer had an increased risk for microalbuminuria argues for a more aggressive and intensive approach to encourage smoking cessation in patients with microalbuminuria, both those with diabetes and those without.

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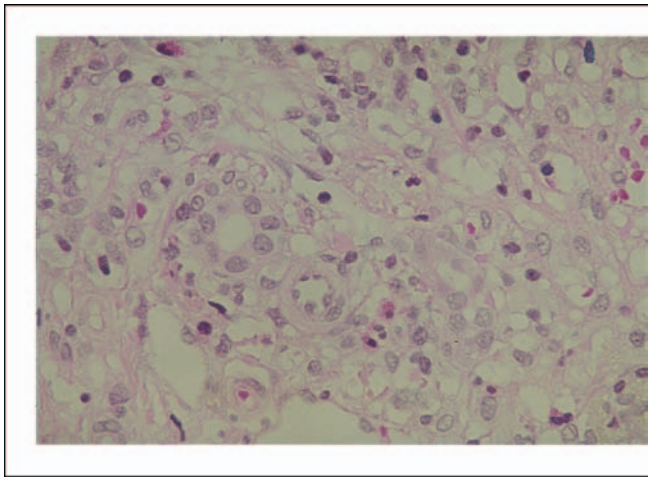
Kava Hepatotoxicity

TO THE EDITOR: Phytotherapeutic preparations for sleep and anxiety disorders that contain kava-lactones are available over the counter in many countries. A 33-year-old woman took the drug Laitan (Schwabe Pharma AG, Kuessnacht, Switzerland) (210 mg of kava-lactones daily) for 3 weeks. The patient reported intake of no other drugs except the homeopathic medication Exsepta (Tentan AG, Rothrist, Switzerland). Two months later, she restarted use of the kava preparation. After another 3 weeks, 1 day after intake of 60 g of alcohol, she developed malaise, loss of appetite, and jaundice. Levels of aminotransferases, bilirubin, and alkaline phosphatase were elevated 60-, 15- and 3-fold, respectively (aspartate aminotransferase, 40.8 μkat/L [2450 U/L]; alanine aminotransferase, 40.5 nkat/L [2430 U/L]; total bilirubin, 399 μmol/L [23 mg/dL]; alkaline phosphatase, 4.98 μkat/L [299 U/L]). Prothrombin time was normal. Tests for autoantibodies and results of viral serologic tests were negative, except for low titers of Epstein–Barr virus IgM. Liver biopsy showed infiltrated portal tracts, bridging necroses, destruction of interlobular bile ducts, and canalicular cholestasis (**Figure**). Liver enzyme levels returned to normal within 8 weeks after withdrawal of Laitan. A lymphocyte transformation test (1) performed after recovery indicated strong and concentration-dependent T-cell reactivity to Laitan (stimulation index, 13.2) but not Exsepta. Phenotyping of cytochrome P4502D6 activity with debrisoquine showed that the patient was a poor metabolizer. We also performed phenotyping in a patient who had had positive results on a rechallenge test (3) and found that she was a poor metabolizer of debrisoquine. Since the local prevalence of CYP2D6 deficiency is 9% (4), the probability that two consecutive patients are deficient is less than 0.01%.

Figure. **Liver biopsy specimen showing an inflamed portal tract.**



A mixed cellular infiltrate is dominated by lymphocytes, exhibits eosinophil granulocytes and activated macrophages, and involves an interlobular bile duct (hematoxylin–eosin stain; original magnification, × 175).

The histologic findings and the results of the lymphocyte transformation test are compatible with an immune-mediated reaction, possibly mediated through a reactive metabolite. In humans, kavalactones are metabolized through hydroxylation (2), but the involved enzymes have not been identified. The present data strongly suggest that kava preparations may be hepatotoxic and that CYP2D6 deficiency is a risk factor, as is the antianginal agent perhexiline (5).

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Medication Assistance Programs

TO THE EDITOR: Prescription medications are the most rapidly expanding component of national health care expenses. Ninety billion dollars were spent on prescription drugs in 1998, and this number is projected to increase to $171 billion by 2007, representing 8% of total national health care expenditures (1). Approximately 16% of the U.S. population does not have health insurance, and a greater percentage has health insurance that does not include a prescription medication benefit (2). Therefore, it is becoming increasingly difficult for some segments of the population to purchase the prescription drugs that they need.

Many pharmaceutical companies offer assistance by providing free or reduced-cost medications to patients who meet specific financial criteria. A wide range of medications for many indications are provided in these programs. Drugs may be provided free, or patients may be required to pay a fee or shipment charge. Medications are supplied by direct delivery to the patient or physician, or the patient may be issued a benefit card or voucher that must be presented at a pharmacy. The amount of medications given and the length of time that a patient may be enrolled vary.

Physician involvement is necessary for patient enrollment in these programs, so clinicians must be informed about them to increase patient access to medications. Information concerning medication assistance programs sponsored by pharmaceutical companies can be obtained from a variety of sources, including Pharmaceutical Research and Manufacturers of America, such publications as *Reimbursement Assistance Programs Sponsored by the Pharmaceutical Industry* and the *Directory of Prescription Drug Patient Assistance Programs*, and various Internet sites (3, 4). However, the best source of information about assistance programs and specific details concerning patient eligibility and program enrollment is the manufacturer of the medication.

Of course, these programs are not the solution to this universal problem of medication access, and it is important to note that they operate at the discretion of the pharmaceutical company and may therefore be terminated at any time. Nonetheless, it is equally important to be aware of their existence as a possible source for medications. The Appendix Table, available on the *Annals* Web site (www.annals.org), provides an extensive listing of many medications whose manufacturers offer medication assistance programs (5).

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Acute Renal Failure Related to High-Dose Celecoxib

TO THE EDITOR: A 57-year-old woman developed acute renal failure on 6 July 2000. She had been prescribed celecoxib, 200 mg/d, 10 months earlier for symptomatic osteoarthritis and had been followed with bimonthly visits thereafter. Her baseline creatinine and blood urea nitrogen (BUN) levels were normal at 88 μmol/L (1.0 mg/dL) and 3.9 mmol/L (11 mg/dL), respectively. In the last half of June 2000, her orthopedist doubled the daily celecoxib dose to 400 mg. Two weeks later, on 6 July 2000, she presented with marked dependent edema and markedly elevated blood pressure (160/110 mm Hg). Creatinine and BUN levels were elevated at 265 μmol/L (3.0 mg/dL) and 15.4 mmol/L (43 mg/dL), respectively. Celecoxib ther-

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Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: Cohort study using data from the UK General Practice Research Database

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Aims
To provide additional quantification of the risk of flucloxacillin-related liver disease and to describe time trends in flucloxacillin prescribing in the UK.

Methods
This was a cohort study using data from the UK General Practice Research Database. We identified patients with a first-time prescription for flucloxacillin or, for comparison, oxytetracycline from 1992 to 2002 and cases who developed clinically documented cholestatic liver disease of uncertain origin after first-time use of these drugs. We also determined the annual frequency of first-time use of flucloxacillin from 1991 to 2000.

Results
We identified 283 097 and 131 189 first-time users of flucloxacillin and oxytetracycline, respectively. The risk of cholestatic liver disease per 100 000 first-time users was 8.5 (95% CI 5.4, 12.6) in the 1–45 days and 1.8 (95% CI 0.6, 4.1) in the 46–90 days after starting flucloxacillin, and 0.8 (95% CI 0.02, 4.3) in the 1–45 days after starting oxytetracycline. The frequency of first-time use of flucloxacillin remained stable between 1991 and 2000.

Conclusions
Flucloxacillin is now established as an important cause of cholestatic liver disease. Warnings about the risk have not had an impact on prescribing practices in the UK, where it remains the predominantly prescribed antistaphylococcal oral antibiotic. This situation in the UK is in sharp contrast to regulatory actions and changes in prescribing habits in Australia after identification of the risk of cholestasis associated with flucloxacillin, and to the predominant use of the alternative drug dicloxacillin in the USA.

Introduction

Flucloxacillin is a penicillinase-resistant halogenated semisynthetic isoxazolyl penicillin used for the oral antibiotic treatment of soft tissue infections caused by *Staphylococcus aureus* (*S. aureus*). Initial case reports from the Netherlands and Scandinavia in the 1980s reported cholestatic liver disease of unknown origin occurring in flucloxacillin users, and subsequently numerous similar reports including several case series from Australia [1–13]. From these reports a well-defined clinical picture of flucloxacillin-associated liver disease was described, which consisted of prolonged painless

jaundice with elevation of cholestatic liver enzymes diagnosed within 2–6 weeks after prescription, and as much as 3 weeks after the drug was stopped. Although most patients eventually recovered within several months, a chronic vanishing bile duct syndrome was reported in some patients [5, 9, 10, 14], and fatal cases were also described [5, 7]. In the early 1990s two population-based epidemiological studies were performed with data from the UK General Practice Research Database (GPRD), which estimated the risk of cholestatic liver disease within 45 days after first-time use of flucloxacillin at about 7 in 100 000 patients [15, 16].

By 1994 the Australian Adverse Drug Reactions Advisory Committee had received 310 reports of liver disease in association with the use of flucloxacillin, including 17 cases with a fatal outcome [17]. After 1994 the Australian Department of Human Services and Health restricted the use of flucloxacillin to severe infections, all advertising by the manufacturer was stopped, and cephalexin and erythromycin were recommended and advertised as alternative treatments [18]. Subsequently prescription dispensings in Australia decreased by about 30% between June 1994 and December 1995 [18]. In the UK only a warning was published by the Medicines Controls Agency (MCA) in the Current Problems in Pharmacovigilance bulletin in 1992 [19], and flucloxacillin is still recommended as first-line treatment for soft-tissue infections caused by *S. aureus* [20].

The primary objective of the current study was to update the frequency estimation of cholestatic liver disease associated with the use of flucloxacillin within the population of the GPRD from 1992 to 2002. Given that in Australia a major change in the usage pattern of flucloxacillin occurred, the second objective of this study was to investigate the prescribing practices of flucloxacillin in the UK following the MCA warning letter and publications in medical journals regarding the risk of flucloxacillin-induced cholestatic liver disease.

Methods

Data resource

The General Practice Research Database (GPRD) is a population-based patient database that comprehensively records medical diagnoses, hospital referrals, prescriptions and demographic details from UK general practices. The GPRD has been described in detail and has been used extensively for pharmacoepidemiological studies. The data have been validated for completeness and quality by the Boston Collaborative Drug Surveillance Program and others [21]. Data collection for the GPRD has also been described in detail in the previous report on cholestatic liver disease associated with flucloxacillin [16]. All the information we received was identified by an anonymous patient number only.

Study population

From the GPRD we derived a study population of all subjects with a first-time prescription of flucloxacillin or oxytetracycline, recorded after 31 October 1992 (end date of previous study [15]) to the end of data collection in 2002.

Case definition

To detect cases of cholestatic liver disease of uncertain origin, we used similar criteria as in the previous studies [15, 16]. All subjects with a coded diagnosis related to cholestatic liver disease recorded within 1–45 days after a prescription for flucloxacillin were identified from the study population. The restriction to cholestatic forms of liver disease and to the interval of 1–45 days after prescription were chosen because of the characteristic clinical picture of flucloxacillin-associated liver disease described in clinical reports of liver disease associated with flucloxacillin [1–13]. For comparison we identified all subjects with a coded diagnosis related to cholestatic liver disease 1–45 days after a prescription for oxytetracycline, a drug that has not been associated with cholestatic liver disease. In addition we also looked for cases of cholestatic liver disease with an onset between 46 and 90 days after prescription of flucloxacillin in the cohort of flucloxacillin users. The comparison with the risk of cholestatic liver disease in oxytetracycline users and during the period of 46–90 days in flucloxacillin users was chosen in order to control for potential selection bias that may be related to the prescription of antibiotic treatment or other unknown factors. The computer-recorded information on all those subjects was then individually reviewed by two of the authors (SR and HJ). For those cases where computer-recorded data were consistent with the diagnosis of idiopathic cholestatic liver disease, detailed clinical records were requested from the corresponding practices, including relevant consultant letters, laboratory test results and hospitalization summaries. Subsequently cases were classified as characteristic of drug-induced cholestatic liver disease when they showed the typical clinical and laboratory features of drug-induced cholestatic liver disease, i.e. painless jaundice with predominant elevation of alkaline phosphatase and bilirubin concentrations, and when no other causes of cholestasis were identifiable. In cases where we did not receive requested patient records because patients had transferred out of the practice, we based our assessment on the available computer-recorded information, which often included laboratory

liver function tests. We excluded all subjects where a causal relationship was unlikely, i.e. if the history and/or laboratory findings were not suggestive of cholestatic liver disease, if a cause of liver disease other than the drug under study was likely, or if the onset of liver disease had occurred before exposure to the drug under study.

Prescribing practices over time

The number of first-time flucloxacillin users and the number of all subjects in the GPRD was recorded for each year between 1991 and 2000, and the frequency of first-time flucloxacillin users per 1000 subjects in the GPRD was calculated.

Data analysis

We calculated the 45 day risks of cholestatic liver disease and their 95% confidence intervals for the time periods of 1–45 days and 46–90 days after the first recorded exposure to flucloxacillin, and 1–45 days after the first recorded exposure to oxytetracycline. For the categorical covariates of male or female sex, and age below 60 years or higher, risk ratios and their 95% confidence intervals were calculated. All calculations were done with STATA statistical software, version 8.2 for MacOS X (STATA corporation, College Station, Texas, USA).

Results

We identified 283 097 patients with a first-time prescription for flucloxacillin and 131 189 patients with a first-time prescription for oxytetracycline from 1 November 1992 until end of data collection in 2002. Age and sex distributions of these two populations are shown in Table 1. After initial review of the computerized patient records, clinical records were requested for 36 subjects, of which 23 were received. After reviewing all available additional clinical information we identified 30 cases considered to be idiopathic cholestatic liver disease. Of these cases, 24 occurred in the 1–45 days after starting flucloxacillin, five occurred in the 46–90 days thereafter, and one occurred in the 1–45 days after starting oxytetracycline. The diagnostic GPRD codes and individual features of all included cases are presented in Tables 2 and 3, respectively. Six out of the 24 cases occurring 1–45 days after flucloxacillin were hospitalized. In all but two cases flucloxacillin was prescribed for soft tissue infections. The median total dose and duration of treatment in the identified cases of flucloxacillin-induced cholestatic liver disease 1–45 days after exposure were 8 g (range 5–56 g) and 7 days (range 5–28 days), respectively, and the median latency time between start of flucloxacillin treatment and diagnosis of liver disease was 25.5 days (range 14–44 days). The concomitant use of a potentially hepatotoxic drug was observed in 4 out of the 24 cases that occurred 1–45 days post flucloxacillin, and in one out of the five cases that occurred 46–90 days after flucloxacillin. In one case augmentin, in

Table 1a
Distribution of flucloxacillin users by age and sex

Age (years)	Male	Female	Total row	%
<20	30599	28973	59572	21.0
20–39	38213	46603	84816	30.0
40–59	32966	36466	69432	24.5
60–79	22696	27267	49963	17.6
>79	5814	13500	19314	6.8
Total column	130288	152809	283097	
%	46.0	54.0		

Table 1b
Distribution of oxytetracycline users by age and sex

Age (years)	Male	Female	Total row	%
<20	10414	7546	17960	13.7
20–39	19780	23279	43059	32.8
40–59	16449	21170	37619	28.7
60–79	12281	14696	26977	20.6
>79	2015	3559	5574	4.2
Total column	60939	70250	131189	
%	46.5	53.5		

Table 2
GPRD diagnostic codes of included cases

GPRD code	Diagnosis
Oxmis codes	
7852	Jaundice
576 A	Obstructive jaundice
7852 JC	Cholestatic jaundice
Read codes	
J66y600	Obstructive jaundice nos
1675.11	Jaundice – symptom
J633.00	Hepatitis unspecified
R024.00	Jaundice (not of newborn)
R024111	Jaundice

Table 3
Individual features of all included cases

	Age (years)	Sex	Latency time (days)	Treatment duration (days)	Total dose (g)	Indication	Concomitant medication and comments
a) Cases 1–45 days after first exposure to flucloxacillin							
Cases where detailed clinical records were available							
1	69	F	41	10	10	Phlebitis	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
2	61	F	24	7	7	Eczema	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
3	58	F	33	7	7	Sebaceous cyst	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
4	69	M	25	7	28	Unknown	Diagnostic work-up identified no other cause of liver disease.
5	61	M	42	14	28	Skin infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
6	35	F	25	7	14	Vaginal infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
7	87	F	26	7	7	Cellulitis	Missed diagnosis caused extensive invasive and noninvasive work-up.
8	68	F	33	14	14	Postop. wound infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
9	69	M	14	7	14	'Rash'	Augmentin 2 days after flucloxacillin
10	47	F	29	7	7	Cellulitis/ abscess	Erythromycin 7 days after flucloxacillin.
11	78	M	18	14	28	Cellulitis/ abscess	Diagnostic work-up identified no other cause of liver disease.
12	42	F	22	5	5	Rosacea	Diagnostic work-up identified no other cause of liver disease.
13	76	F	19	14	56	Postop. wound infection	History includes explicit expert diagnosis of flucloxacillin-induced liver disease.
14	62	F	32	28	28	Phlebitis	History includes explicit expert diagnosis of drug-induced liver disease. Erythromycin 12 days before flucloxacillin

three cases erythromycin, and in one case trimethoprim-sulfamethoxazole were prescribed in close temporal relationship to flucloxacillin (Table 3), and they can therefore not be ruled out as alternative causes for cholestasis in these patients.

The estimated 45-day risk per 100 000 first-time users 1–45 days after flucloxacliin (8.48, 95% CI 5.43, 12.61) was substantially higher than the risk 46–90 days after flucloxacillin (1.77, 95% CI 0.57, 4.12) and 1–45 days after oxytetracycline (0.76, 95% CI 0.02, 4.25) (Table 4).

Only 25% of all first-time flucloxacillin users were age 60 years or more, whereas 67% of patients with cholestatic liver disease after flucloxacillin exposure were within this age group. Subjects with an age of 60 years or above were 6.1 times more likely to develop cholestatic liver disease after flucloxacillin exposure than those with an age below 60 years (95% CI 2.9, 13.0). Sixteen out of the 24 cases were female (67%) compared with 54% in the study population (relative risk 1.7, 95% CI 0.7, 3.9).

The number of first-time flucloxacillin users between 1991 and 2000 remained stable at about 23 first-time users per 1000 subjects in the GPRD per year (Figure 1), and also the average number of prescriptions per user per year remained stable with a mean value of 1.23 (range of mean values for each year from 1991 to 2000 1.20–1.27).

Discussion

In the absence of a validated specific diagnostic test, the establishment of the causal relationship of an adverse event and a drug is a diagnosis of exclusion that is particularly difficult if the manifestation occurs after stopping the treatment and the recovery is prolonged, as is typical for flucloxacillin-induced cholestasis [5, 7, 10,

Table 3
Continued

	Age (years)	Sex	Latency time (days)	Treatment duration (days)	Total dose (g)	Indication	Concomitant medication and comments
Cases where only computer-recorded data were available							
15	43	F	30	7	14	Postop. wound infection	
16	83	F	21	5	5	Toe infection	
17	61	F	24	7	14	Leg abscess	
18	46	M	17	12	12	Finger wound infection	
19	15	M	21	4	8	Hand wound infection	
20	16	F	16	7	7	Chest infection	Trimethoprim/sulfamethoxazole 8 days before flucloxacillin
21	73	M	34	7	14	Pneumonia	
22	68	F	37	7	7	Phlebitis	
23	88	F	44	7	7	Cellulitis	
24	85	M	36	6	6	Skin infection	
b) Cases 46–90 days after first exposure to flucloxacillin							
Cases where detailed clinical records were available							
1	81	F	82	7	7	Cellulitis	Three prescriptions within 6 weeks. Latency time, dose and treatment duration refer only to first prescription. History includes explicit expert diagnosis of drug-induced liver disease.
Cases where only computer-recorded data were available.							
2	84	F	49	5	10	Cellulitis/ abscess	
3	88	F	75	6	6	Abscess	
4	49	F	63	5	5	"lump superficial	Erythromycin 15 days after flucloxacillin.
5	54	F	58	27	27	Phlebitis	First flucloxacillin for 7 days, then flucloxacillin plus ampicillin for 20 days. Latency time refers to first prescription.
c) Case 1–45 days after oxtetracycline							
Detailed clinical records were available							
1	47	M	26	5	5	Cough	Computer-recorded data and detailed patient records were available.

Table 4
45 day risk estimates for cholestatic liver disease after first exposure to flucloxacillin or oxytetracycline

	1–45 days post flucloxacillin	46–90 days post flucloxacillin	1–45 days post oxytetracycline
Study population	283 097	283 097	131 189
Cases	24	5	1
45 day risk with 95% CI per 100 000 users	8.48 (5.43, 12.61)	1.77 (0.57, 4.12)	0.76 (0.02, 4.25)

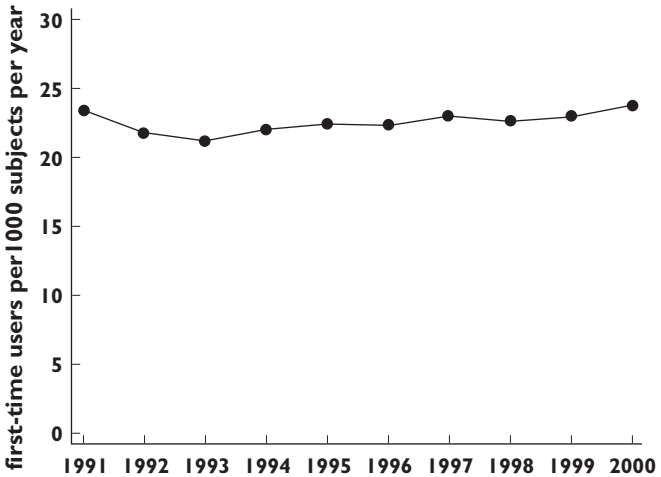

Figure 1
Flucloxacillin use in the UK from 1991 to 2000. Number of first-time flucloxacillin users per 1000 subjects in the GPRD between 1991 and 2000

16]. This may explain the long time-lag between the first marketing of flucloxacillin in the 1970s and the first reports of its idiosyncratic hepatotoxicity in the mid 1980s.

After a large number of individual case reports of flucloxacillin-associated cholestatic liver disease appeared between 1982 and 1993, the association was confirmed by two formal epidemiological studies, which provided a frequency estimation of flucloxacillin-associated cholestatic liver disease of about 7 per 100 000 first-time users [15, 16]. The current follow-up study yielded a similar risk estimate of 8.5 per 100 000 users.

This study relates only to cases of cholestatic liver disease, whereas other forms of liver disease that may be drug-induced were not studied. As in the previous studies oxytetracycline was chosen as a comparison drug because it is a frequently prescribed antibiotic and it has rarely been reported to cause cholestatic hepatitis [15, 16]. Additionally we also determined the risk of developing cholestatic liver disease of unknown origin 46–90 days after exposure to flucloxacillin, i.e. at a time when we assumed that exposure to flucloxacillin was much less likely to be the cause of liver disease. However, a latency time of more than 45 days may be possible in rare cases, and our study does not exclude the possibility that cholestatic liver disease was caused by flucloxacillin in one or more of the five patients where the diagnosis was made between 46 and 90 days after exposure.

Age over 55 years, female sex and a treatment duration longer than 14 days have previously been proposed as risk factors for flucloxacillin-induced liver disease [13, 22]. The current study estimated a six-fold higher risk of cholestatic liver disease after flucloxacillin in patients aged 60 years and older compared with younger patients. By contrast, female sex was not clearly identified as a risk factor, and only one case of cholestasis occurring 1–45 days after flucloxacillin use, and two cases occurring 46–90 days thereafter had a treatment duration of more than 14 days.

We did not detect any material changes in the frequency of first-time prescriptions of flucloxacillin in this UK population-based study between 1991 and 2000. Following the large number of publications in the early 1990s concerning the risk of flucloxacillin-induced liver injury, the UK regulatory authority only published a single warning concerning this issue in 1992 [19]. By comparison the use of flucloxacillin decreased by about 30% after 1994 in Australia, and this was presumably the result of a range of initiatives and interventions that were implemented concurrently and repeatedly over several years, including a governmental restriction of the indication for flucloxacillin use to severe infections, changing the product information, stopping of advertising and recommending cephalexin and erythromycin as alternative treatments [4, 18]. The risk of drug-induced cholestatic liver disease for these alternative drugs has been estimated to be lower, i.e. about 3.6 and 2.0 per 100000 users for erythromycin and cephalexin, respectively [23, 24]. Dicloxacillin is another halogenated isoxazolyl penicillin that is used as oral treatment for *S. aureus* infections in the United States, and that was introduced onto the Australian market in 1997 to provide another alternative to flucloxacillin [25]. It has been reported to have a similar efficacy in soft tissue infections to flucloxacillin [26, 27], but is not marketed in the UK. In previous publications it was stated that there are fewer spontaneous reports of liver disease related to dicloxacillin as compared with flucloxacillin, and that the risk may be lower [4, 22, 25]. The question of the comparative hepatotoxic risk of flucloxacillin and dicloxacillin is highly relevant to public health. However, in the current absence of formal population-based epidemiological studies investigating the risk of liver disease associated with dicloxacillin, differences in the reporting frequency of adverse reactions for flucloxacillin and dicloxacillin cannot be ruled out as the reason for the higher number of reports of liver disease after flucloxacillin use.

We noted that in the previous epidemiological study covering the period from 1985 to 1991, flucloxacillin was diagnosed by the treating physician as the cause of liver disease in only two out of 10 cases, and in one of those two only after flucloxacillin rechallenge with sub-

sequent recurrence of jaundice [16]. By contrast, in the current study that included cases from 1992 to 2002 we identified such an explicit flucloxacillin attribution in eight out of the 14 cases that occurred 1–45 days after flucloxacillin where we received detailed patient records. This finding may well reflect an increased awareness of flucloxacillin's potential hepatotoxicity amongst physicians in the UK, who nevertheless continue to use flucloxacillin as a first-line treatment for soft-tissue infections caused by *S. aureus* [20]. Though one case of cholestatic liver disease per 12 000 first-time users may be considered to be a relatively rare event, it must be taken into account, that the risk is apparently higher in older patients, that flucloxacillin-induced liver disease is a potentially irreversible and lethal disease [5, 7, 17], and that the cases identified in this study only represent a small proportion of the absolute number of cases that occur each year in the UK, where flucloxacillin is a frequently used drug with about two million prescriptions per year [19].

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Contraception 73 (2006) 223–228

Contraception

Original research article

Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 μg of ethinyl estradiol

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Abstract

Context: There is concern that a new transdermal contraceptive patch containing ethinyl estradiol (EE) and the progestin norelgestromin increases the risk for venous thromboembolism (VTE) compared to previously marketed oral contraceptives (OCs).

Objective: Quantitative information was obtained on the risk of nonfatal VTE in women using the contraceptive patch in comparison to women using OCs, norgestimate (either monophasic or triphasic) and 35 μg EE (norgestimate-35), an OC that has been marketed for over a decade.

Design, Setting and Participants: Nested case-control design based on information from PharMetrics, a US-based company that collects and organizes information on claims paid by managed care plans. The study was nested among all women aged 15 to 44, who started either the contraceptive patch or norgestimate-35 after April 1, 2002. Cases were women with current use of one of these two study drugs and a documented diagnosis of VTE in the absence of identifiable clinical risk factors (idiopathic VTE). Up to four controls were matched to each case by age and calendar time.

Main Outcome Measures: Odds ratios (ORs) comparing the risk of nonfatal VTE in new users of the two contraceptives and incidence rates of nonfatal VTE for new users of each of the study contraceptives.

Results: We identified 68 newly diagnosed, idiopathic cases of VTE in the study population. In the case-control analysis, the OR comparing the contraceptive patch to norgestimate-35 was 0.9 (95% CI 0.5–1.6). The overall incidence rate for VTE was 52.8 per 100,000 women-years (95% CI 35.8–74.9) among users of the contraceptive patch and 41.8 per 100,000 women-years among users of norgestimate-35 (95% CI 29.4–57.6), and the age-adjusted VTE incidence rate ratio (IRR) for current use of the contraceptive patch vs. norgestimate-35 was 1.1 (95% CI 0.7–1.8).

Conclusions: The risk of nonfatal VTE for the contraceptive patch is similar to the risk for OCs containing 35 μg ethinylestradiol and norgestimate.

Keywords: Contraceptive patch; Oral contraceptives; Venous thromboembolism

1. Introduction

The combination transdermal contraceptive patch has been marketed since 2002. This transdermal patch contains 0.75 mg ethinyl estradiol (EE) and 6 mg of the progestin norelgestromin (the active metabolite of norgestimate) and releases on average 20 μg of EE and 150 μg of norelgestromin into the systemic circulation per 24 h. According to a recent statement by the US Food and Drug Administration (FDA) in a press release dated November 10, 2005, "Women who use the transdermal patch are exposed to about 60 percent more total estrogen in their blood than if they were taking a typical birth control pill containing 35 μg of estrogen" [1]. A pharmacodynamic study found that the maximal blood level (peak blood level) of EE is about 60% lower with the patch than with a birth control pill containing 30 μg EE [2]. The new bold warning in the approved product labeling for the contraceptive patch states, "However, it is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using the transdermal patch compared with women using oral contraceptives (OCs) containing 35 μg of EE" [1].

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Oral contraceptives containing estrogen–progestin combinations have been associated with an increased risk of deep vein thrombosis and subsequent pulmonary embolism, collectively referred to as venous thromboembolism (VTE) [3–8]. The absolute risk of venous thrombosis has been reported to increase from a baseline risk of less than 1 per 10,000 women-years to 3 to 4 per 10,000 women-years during use of OCs. [7].

In the premarketing clinical trials of the transdermal patch, one case of idiopathic VTE and one case of VTE after surgery were diagnosed in 3330 users with a cumulative treatment duration of about 1800 years (22,176 cycles) [9]. However, the low number of users in the clinical trials limited a precise risk estimate of this uncommon adverse event and a reliable quantitative comparison with other OCs.

We conducted a study that compared the risk of nonfatal VTE in women using the transdermal patch to that of women using monophasic or triphasic norgestimate-containing OCs with 35 μg of EE (norgestimate-35), which have been marketed for over a decade.

2. Methods

2.1. Data resource

Data for this study were derived from the PharMetrics database. PharMetrics is a US-based, ongoing longitudinal database with information on about 55 million people going back as far as 1995. The database is made up of data contributed by managed care health plans throughout the United States and contains information on paid claims for pharmaceuticals, medical diagnoses and procedures as well as demographic information such as patient's year of birth, gender and enrollment details for each subject in the database. Drug prescriptions are coded using the National Drug Code provided by the US FDA. Each drug claim is entered as a separate entry and includes information on the specific entity dispensed, the date of dispensing, the quantity dispensed and the length of the supply. All diagnoses are coded using the ICD-9 coding system. Procedure codes are also included in the database coded using the CPT-4 system. All events described above are noted with the date on which the initial service was delivered. Additional codes describe other aspects of the patient's condition at the time of the hospitalization.

The methods applied in this study were similar to those previously described for the study of contraceptive safety [5,6]. The present study was designed to take into account the evaluation of a recently marketed drug and the use of a comparison drug, which has been marketed for over a decade, since no other more recently marketed OC was available. We required that all cases and controls be new users of either study drug after April 1, 2002, when the transdermal patch was first marketed. Important variables that were controlled in the design were (1) age, since users of the new drug may have a different age distribution than users of the older comparison drug; and (2) calendar time (i.e., the date of diagnosis), since the two contraceptives will have highly different usage characteristics in relation to calendar time. We also explored duration of use, which may be correlated with both drug use and the risk of VTE.

2.2. Base population

We conducted a case-control study nested in the population of users of the transdermal patch and norgestimate-35 OCs, aged 15 to 44 in the PharMetrics database. All subjects were required to have filled at least one new prescription for a study drug after April 1, 2002, the date that the transdermal patch was first marketed in the United States. Follow-up medical information was available as far forward as March 31, 2005.

As a first step, we organized the PharMetrics data files sent to us into individual patient records. This enabled us to create a comprehensive chronological record for each patient that contained information on all drugs prescribed, diagnoses and procedures, both inpatient and outpatient. To assess the eligibility of each potential case and control, the authors conducted a review of each individual patient computer record with the particular study contraceptive identity masked. Agreement on inclusion of women as cases or controls was achieved by consensus without knowledge of contraceptive exposure.

2.3. Cases

Cases were women aged 15 to 44 years old who were current users of the transdermal patch or norgestimate-35 and who had a first-time recorded claim for a clinically diagnosed deep vein thrombosis or pulmonary embolism with hospitalization, a visit to the emergency room or positive indication of VTE from diagnostic test results, and who subsequently received prolonged anticoagulation therapy. Cases were included if the diagnosis of VTE was recorded for the first time after April 1, 2002. A requirement for inclusion was that there were at least 6 months of medical history prior to the diagnosis (index date). In addition, in order to determine when subjects started using the study contraceptive, we required that there be at least 4 months of history in their claims record before the first recorded study contraceptive. The 4-month period is based on the finding that contraceptive prescriptions in the PharMetrics database are written for no longer than 3 months at a time. Thus, a window of at least 4 months provided assurance that the first identified prescription is a new prescription and not a refill of an existing prescription. The case had to be currently exposed to one of the study drugs. Exposure was determined from the prescription claims data prior to the date of diagnosis of VTE (index date). Current exposure was defined as having a recorded claim for a study contraceptive prescription whose filled use extended to within 30 days before the index date or beyond the index date. Long-term anticoagulation must have been started promptly, and no estrogen-containing contraceptive could

Table 1
Characteristics of cases and controls

Characteristic	Cases ($n=68$)		Controls ($n=266$)	
	n	%	*n*	%
Age				
15–29	27	40	104	39
30–39	26	38	103	39
40–44	15	22	59	22
Index year[a]				
2002	8	12	31	11
2003	33	49	130	50
2004	22	32	85	31
2005	5	7	20	7

[a] Year of diagnosis of the VTE event.

be initiated after the date of diagnosis, strengthening the clinical diagnosis of VTE.

Potential cases were excluded from the case group if important clinical risk factors for VTE were present in the 3 months prior to the index date [10]. These included significant lower limb injury, major surgery, severe trauma or pregnancy. Subjects with any history of cancer (other than nonmelanoma skin cancer), renal failure, chronic cardiovascular disease, or inflammatory or autoimmune conditions were also excluded.

2.4. Controls

Up to four women who did not have a diagnosis of VTE were matched to each case by year of birth and the index date of the case (calendar time). When more than four matched controls were available for a case, we used random selection to select four controls. As with cases, all controls were required to be current users of one of the study contraceptives, to have at least 6 months of enrollment in their health plan prior to the index date (the event date of their matched case), to have started their study contraceptive use after April 1, 2002, and to have at least 4 months of history in their claims record before the first recorded study drug prescription to confirm that they were new users. The exclusion criteria applied to cases were also applied to controls.

2.5. Statistical methods

We analyzed the matched case-control data using conditional logistic regression. Duration of contraceptive use prior to the index date and switching from a different hormonal contraceptive were considered as potential confounders, as well as number of physician and emergency room visits in the 6 months prior to the index date.

We analyzed the cohort data to estimate incidence rates and 95% confidence intervals. Current person-time was accumulated from the first study drug prescription to the last prescription plus 45 days. If there was a gap in the prescription fill dates of greater than 100 days, the person-time accumulation stopped at the last prescription before the gap, plus 45 days; person-time accumulation then resumed at the next record of a prescription for a study drug. We estimated incidence rate ratios (IRRs) using Poisson regression. We examined possible effect modification by including multiplicative interaction terms in the model, and we compared the fit of nested models using likelihood ratio testing [11].

Duration of contraceptive use was defined as the time interval (in months) from the first use of the study contraceptive to the index date. A subject was defined as a switcher if there was a recording for a different hormonal contraceptive product at any time in the patient's record that preceded the use of the study contraceptive.

Calculations were performed using SAS release 8.02 (SAS Institute, Cary, NC) and Stata release 8.2 (StataCorp LP, College Station, TX).

This study was exempt from review by the Boston University Medical Center Institutional Review Board.

3. Results

We identified 68 cases of VTE and 266 controls (women without VTE), matched by year of birth and index date. Among the 68 cases of idiopathic VTE, there were 31 among women currently exposed to the transdermal patch and 37 currently exposed to norgestimate-35. Fifty-seven cases were hospitalized, 38 (67%) with a diagnosis of pulmonary embolism and 11 were diagnosed as outpatients, only 4 (36%) with a diagnosis of pulmonary embolism. All 11 cases in the outpatient setting were prescribed warfarin and 9 cases also received low-molecular-weight heparin.

Characteristics of the cases and controls are listed in Table 1 and their exposure to the transdermal patch or norgestimate-35 is summarized in Table 2. The unadjusted matched odds ratio (OR) for VTE for the transdermal patch vs. norgestimate was 0.9 (95% CI 0.5–1.6) (Table 2). After adjusting for duration of exposure, the OR remained 0.9. A history of switching from another hormonal contraceptive had no effect on the OR, nor did restricting the analysis to women who were hospitalized for VTE, or adjusting for the frequency of physician's office or emergency room visits during the 6-month period before the index date.

In the study population, there were 215,769 women who satisfied all the conditions for inclusion in this study. These women contributed an estimated 147,323 women-years of current exposure to the study contraceptives (58,752 women-years for the transdermal patch and

Table 2
Odds ratio for VTE comparing users of contraceptive patch to users of norgestimate-35

Exposure	Cases		Controls		Odds ratio[a]	95% CI
	n	%	*n*	%		
Norgestimate-35	37	54	139	52	1.0	Reference
Contraceptive patch	31	46	127	48	0.9	0.5–1.6

[a] Conditional on age, index date.

88,571 women-years for the comparison contraceptive). The overall incidence rate for VTE in the study population was 52.8 per 100,000 women-years (95% CI 35.8–74.9) among users of the contraceptive patch and 41.8 per 100,000 women-years among users of norgestimate-35 (95% CI 29.4–57.6). Adjusted for age, the VTE IRR for current use of the transdermal patch vs. norgestimate-35 was 1.1 (95% CI 0.7–1.8). The data did not provide evidence for effect modification by age ($p=.10$). Regardless of which contraceptive was used, the incidence of VTE increased with increasing age. The incidence per 100,000 women-years was 26.7 (95% CI 17.6–38.9) among women aged 15–29 years, 67.2 (95% CI 43.9–98.5) among women aged 30–39 years and 197 (95% CI 110–326 per 100,000 women-years) among women aged 40–44 years ($p<.001$ for test of trend).

4. Discussion

Spontaneous reports of thrombosis in users of the transdermal patch have raised major public concern about its safety. In contrast to OCs, no gastrointestinal or hepatic first-pass metabolism occurs after transdermal application, and for postmenopausal estrogen therapy it has been suggested that this difference may result in a lower clinical risk of VTE with transdermal estradiol than oral estrogen [12,13]. So far, no formal studies have been available to investigate whether these spontaneous reports reflect a higher risk of VTE or indeed whether the transdermal contraceptive patch may have a lower risk of VTE than comparable OCs.

The findings of this study provide evidence that the risk of nonfatal VTE with subsequent long-term anticoagulation is not higher in current transdermal contraceptive patch users compared to current users of the norgestimate-35 OC (OR 0.9, 95% CI 0.5–1.6; IRR 1.1, 95% CI 0.7–1.8). In the current study, the risk of VTE in users of the transdermal patch was compared to the risk in users of norgestimate-35 because norelgestromin is the active metabolite of norgestimate, the progestin released by the transdermal patch. This methodology is the most efficient design to study risk differences in relation to the route of administration and also allows for the important comparison to a drug that has been marketed for more than a decade.

The current epidemiologic study used a case-control design, which has often been used in the past to study the safety of hormonal contraceptives [3,5,6,14,15]. A nested case-control study design is standard for drug safety studies for evaluating contraceptive safety since it insures comparability between cases and the comparison group at the time of the case event [16]. As in prior studies, age and calendar time were closely controlled, i.e., the controls were matched to cases on year of birth, and the date from which exposure was determined (the index date) was identical in cases and controls. This procedure equalizes the potential influence of age and calendar time on the relative effect of the two contraceptives. There is, however, one feature of this study that differs from prior studies. Whereas prior studies compared contraceptives that had been marketed for many years, the current study involves the comparison of an estrogen-containing contraceptive (the transdermal patch) that has been marketed for only 3 years with norgestimate-containing OCs that have been available for more than a decade. In the PharMetrics database, new use of the transdermal patch increased markedly over the first few years after April 2002, whereas that of norgestimate-35 decreased over the same time period. Among women included in this study, the proportion who started using the transdermal patch rose progressively from 23% in 2002 to 55% in 2004, whereas the proportion of norgestimate-35 users fell correspondingly. We have controlled for this difference by including only women with new use of one or the other study contraceptives after April 1, 2002, the date that the transdermal patch became available. Although it is possible that norgestimate-35 may have been used by cases or controls in the distant past, previous studies have convincingly demonstrated that only current use is relevant to the risk of VTE, and thus this possible difference in the past use of the two study drugs is unlikely to have had a material effect on the results obtained [3].

We limited the study to nonfatal outcomes because the PharMetrics database does not capture deaths that occur outside a health care facility. However, fatal cases of VTE during use of hormonal contraceptives have been reported to represent only a small proportion of all VTE cases, and failure to identify them in this study is unlikely to have materially distorted the findings [5]. We also excluded patients with chronic medical conditions such as cancer, coronary artery disease and autoimmune disease. Although these were not commonly observed in this generally healthy young population of contraceptive users, the exclusion of such patients from the study population limits concerns about selective prescribing of the study drug based on the presence of clinical risk factors.

As in any epidemiology study, there may be some misclassification of cases. Any such misclassification would be nondifferential since we identified cases and controls without knowledge of the contraceptive to which they had been exposed. Nondifferential misclassification of a dichotomous variable tends to bias results toward the null. However, since we used the same operational definition of VTE in this study as in many other studies that we have carried out where differences in risk of VTE have been found, we consider this to be a minor issue [5,6,10,14].

We could not evaluate the effect of smoking in the current study since it is not regularly recorded in the PharMetrics database. However, smoking is believed to increase primarily the risk of *arterial* cardiovascular events in users of OCs, but not the risk of VTE, and smoking has not been a material confounder in previous studies comparing the association between OCs and VTE [5,6,15,17,18]. Also, neither height nor weight was recorded

in the current study. Although body mass index (BMI) is independently associated with a modestly increased risk for VTE, BMI has not confounded the association between use of hormonal contraceptives and VTE in prior studies [3,5,6,14]. Furthermore, when we evaluated the ICD-9 diagnosis for obesity we did find that obesity was associated with an increased risk ratio for VTE (OR=2.3), but inclusion of obesity in the model with exposure did not materially change the effect of exposure, providing additional reassurance that obesity is not an important confounder in this study. Although the ICD code is not an ideal proxy for obesity, we believed that the diagnosis would most often be used in the most obese women. Obesity was associated with VTE as it has been in past studies [3,5,6,14], yet it did not confound the effect of the contraceptives we compared. This indicates that the ICD code was probably a reasonable proxy given that the information was limited. If there were a strong tendency for the patch to be preferentially prescribed to thinner women, it is possible that the OR for VTE with the patch calculated in this study is an underestimate of the true risk.

The effect of duration of use of contraceptives could not be fully explored since the study period encompassed only 3 years and a substantial proportion of contraceptive users had used them for less than 1 year. Further studies over time will allow for a more comprehensive evaluation of the effect of longer duration of use.

Samples of the transdermal patch were distributed in the first years that the drug was marketed. This would not have been true of norgestimate-35 during the study period. We cannot rule out some influence of this difference that applied to both cases and controls, but the nature of the results was such that any effect is likely to have been modest.

Over 215,000 women exposed to one of the study drugs in our study population provided information on the clinically important question of the risk of VTE in relation to the transdermal patch. Because of the prospective nature of data collection, the information on exposure was collected before the outcome had occurred, all eligible patients with the outcome were included, and the likelihood of correct diagnoses of VTE was increased by the documentation of long-term use of anticoagulants. We were able to tightly control potential confounding due to age and calendar time. The rate of VTE associated with combination contraception use in this study was higher than that found in previous studies [5,6], but this study encompassed women up to age 44, whereas the earlier studies included only women up to age 39. This difference would at least partially account for the somewhat higher rate of VTE in this study.

In summary, although higher mean circulatory levels of EE have been reported among users of the contraceptive patch compared to users of combined OCs, our results indicate that the risk of nonfatal idiopathic VTE among new users of the transdermal patch is similar to that of new users of norgestimate-35.

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Contraception

Original research article

Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel

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Abstract

Context: Previous studies have reported that users of the "third-generation" oral contraceptives (OCs) containing the progestins gestodene and desogestrel have about twice the risk for venous thromboembolism (VTE) compared to users of older OCs containing levonorgestrel. Estimates of the risk for VTE among users of norgestimate-containing OCs compared to other OCs, however, are lacking.

Objective: The purpose of this study is to obtain quantitative information on the risk of nonfatal VTE in women using OCs containing either norgestimate or desogestrel in comparison with women taking OCs containing levonorgestrel.

Design, Setting and Participants: Based on information from PharMetrics, a United States-based company that collects and records information on claims paid by managed care plans, we used a nested case-control study design to estimate relative risks of nonfatal VTE among 15- to 39-year-old current users of OCs containing norgestimate with 35 μg of ethinyl estradiol (EE), desogestrel with 30 μg of EE or levonorgestrel with 30 μg of EE, both monophasic and triphasic preparations, during the period January 2000 to March 2005. Cases were women with a well-documented VTE of uncertain origin that was diagnosed in current users of a study drug. Up to four controls were closely matched to each case by age and calendar time, and odds ratios (ORs) were calculated using conditional logistic regression comparing the risk of VTE among users of the three contraceptives. We also estimated and compared the incidence rates for all three OCs.

Results: Based on 281 newly diagnosed idiopathic cases of VTE and 1055 controls, we found that the adjusted ORs for nonfatal VTE comparing norgestimate- or desogestrel-containing OC users to users of levonorgestrel-containing OCs were 1.1 [95% confidence interval (CI), 0.8–1.6] and 1.7 (95% CI, 1.1–2.4), respectively. The incidence rates of VTE were 30.6 (95% CI, 25.5–36.5), 53.5 (95% CI, 42.9–66.0) and 27.1 (95% CI, 21.1–34.3) per 100,000 woman-years for users of norgestimate-, desogestrel- and levonorgestrel-containing OCs, respectively. The incidence rate ratios for norgestimate-containing OCs compared to levonorgestrel-containing OCs and desogestrel-containing OCs compared to levonorgestrel-containing OCs were 1.1 (95% CI, 0.8–1.5) and 2.0 (95% CI, 1.4–2.7), respectively.

Conclusions: The risk of nonfatal VTE among users of desogestrel-containing OCs is significantly elevated compared to that of levonorgestrel-containing OCs. The risk of VTE in users of norgestimate-containing OCs was closely similar to that of users of levonorgestrel-containing OCs.

Keywords: Oral contraceptives; Venous thromboembolism; Odds ratio; Incidence rate ratio

1. Introduction

Three reports published in *Lancet* in 1995 found an approximately twofold increased risk of venous thromboembolism (VTE) for oral contraceptives (OCs) containing either desogestrel or gestodene, compared to OCs containing levonorgestrel [1–3]. Norgestimate-containing OCs, which are not commonly used in the UK, are among the most commonly prescribed OCs in the Unites States. Reliable information on the effects of norgestimate-containing OCs on the risk for VTE has not been published since most of the earlier studies on the risk of VTE among users of OCs were conducted in Europe and other countries where norgestimate-containing OCs are uncommonly prescribed and information was therefore limited. The question remains whether the progestin norgestimate is more similar to the levonorgestrel-containing "second-generation" or to the desogestrel-containing "third-generation" OCs with respect to its effect on the risk of VTE [4]. Since "third-generation"

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OCs have been reported to increase the risk of VTE, and because norgestimate-containing contraceptives are widely prescribed in the United States, we conducted a study to compare the risk of nonfatal VTE in users of norgestimate-containing OCs with 35 μg of ethinyl estradiol (EE) and, separately, desogestrel-containing OCs with 30 μg of EE (a "third-generation" pill used in the United States) to the risk of nonfatal VTE in users of levonorgestrel-containing OCs with 30 μg of EE. This is the first study that we know of to evaluate the effects on VTE risk of norgestimate- and desogestrel-containing OCs in the United States.

2. Methods

2.1. Data resource

Data for this study were derived from the PharMetrics database. PharMetrics is a United States-based ongoing longitudinal database with information on about 55 million people starting as early as 1995. The database is made up of data contributed by managed care plans throughout the United States, and it contains information on paid claims for pharmaceutical agents, medical diagnoses and procedures as well as demographic information on all subjects. Demographic information such as patient's year of birth, gender and enrollment details are provided in the database. Drug prescriptions are coded using the National Drug Code provided by the U.S. Food and Drug Administration. Each drug claim is recorded as a separate entry and includes information regarding the specific entity dispensed, the date of dispensing, the quantity dispensed and the length of the supply. All diagnoses are coded using the *ICD-9* coding system. Procedures are also included in the database coded using the CPT-4 system. All events described above are noted with the date on which the initial service was delivered. Additional codes describe other aspects of the patient's condition at the time of the hospitalization.

The methods applied in this study are closely similar to those we have used extensively in the past for the study of contraceptive safety [1,5,6].

2.2. Base population

We conducted a case-control study nested in the population of 15- to 39-year-old users of all norgestimate-containing OCs with 35 μg of EE, desogestrel-containing OCs with 30 μg of EE or levonorgestrel-containing OCs with 30 μg of EE, both monophasic and triphasic formulations, in the PharMetrics database from 2000 to 2005. All subjects were required to have filled at least one prescription for a study drug. Medical information was available until as late as March 31, 2005.

2.3. Study design

As a first step, we organized the PharMetrics data for each woman into a comprehensive chronological record containing information on all drugs prescribed, diagnoses and procedures, both inpatient and outpatient for each patient. The authors conducted a review of each individual patient's computer record, with the particular study contraceptive identity masked, to assess the eligibility of each potential case and control. Agreement on inclusion of women as cases or controls was achieved by consensus without knowledge of contraceptive exposure.

2.4. Cases

Cases were women aged 15 to 39 years old, who were current users of norgestimate-, desogestrel- or levonorgestrel-containing OCs and had a first-time recorded diagnosis of deep vein thrombosis or pulmonary embolism at any time during the study period, followed by long-term anticoagulation. At least 6 months of recorded medical history was required prior to the diagnosis (index date), and each case had to be currently exposed to one of the study drugs at the index date. Current exposure was defined as having a recorded claim for a study contraceptive prescription whose filled use extended to within 30 days before the index date or beyond the index date. Potential cases were excluded from the case group if well documented; important clinical risk factors for VTE were present in the 3 months prior to the index date. These included important lower-limb injury, invasive surgery, severe trauma or pregnancy. We also excluded women with any history of cancer (excluding nonmelanoma skin cancer), renal failure or inflammatory or autoimmune conditions [1–8]. Finally, we excluded women with VTE if estrogen-containing contraceptives were prescribed after the index date, suggesting that the diagnosis of idiopathic VTE was not confirmed.

2.5. Controls

Up to four women who did not have a diagnosis of VTE were matched to each case by the year of birth and the index date of the case. As with cases, all controls were required to be current users of one of the study contraceptives and to have at least 6 months of enrollment in their health plan prior to the index date (the event date of their matched case). All of the exclusion criteria applied to cases were applied to controls.

2.6. Statistical methods

We analyzed the case-control study data using conditional logistic regression. All models were controlled for age and calendar time through matching. We also evaluated the effects of covariates by entering them individually and collectively into the regression model, including the exposure variable. History of each of the following potential risk factors was considered in the analyses: menstrual disorders, endometriosis, uterine fibroids, hypertension, hyperlipidemia, type II diabetes, cardiovascular disease (varicose veins, peripheral vascular disease, unstable angina, atherosclerosis, dysrhythmias, coagulation defects and congestive heart failure) and asthma. We also evaluated

Table 1
Characteristics of cases and controls and univariable effects

Characteristics	Cases (%), $n=281$	Controls (%), $n=1055$	OR	95% CI
Age (years)				
<20	26 (9)	103 (10)	–	–
20–29	114 (41)	426 (40)	–	–
30–39	141 (50)	526 (50)	–	–
Index year				
2000	21 (7)	81 (8)	–	–
2001	66 (23)	246 (23)	–	–
2002	66 (23)	251 (24)	–	–
2003	70 (25)	259 (25)	–	–
2004	51 (18)	190 (18)	–	–
2005	7 (2.5)	28 (2.5)	–	–
Fibroids	4 (1)	7 (<1)	2.0	0.5–7.2
Endometriosis	1 (<1)	8 (<1)	0.4	0.1–3.5
Menstrual disorders	34 (12)	74 (7)	1.8	1.1–2.7
Hypertension	9 (3)	21 (2)	1.6	0.7–3.5
Hyperlipidemia	12 (4)	24 (2)	1.9	0.9–3.9
Cardiovascular disease	5 (2)	8 (1)	2.5	0.8–7.8
Diabetes	8 (3)	6 (<1)	6.1	2.0–19.0
Asthma	13 (5)	31 (3)	1.6	0.8–3.0
Back pain	28 (10)	50 (5)	2.2	1.4–3.7
Any emergency room visits	36 (13)	31 (3)	5.2	3.1–8.7
Any physician visits	43 (15)	94 (9)	1.8	1.2–2.7
Switchers	14 (5)	70 (7)	0.8	0.6–1.2

whether or not there were physician visits in the 90 days prior to the index date and, separately, emergency room visits in the 90 days prior to the index date as indicators of subjects' general health. Duration of contraceptive use prior to the index date was considered as a potential confounder or risk modifier. Duration was defined as the time interval (in months) from the first use of the study contraceptive to which they were currently exposed to the index date. Finally, women were classified as having a recorded history of switching hormonal contraceptives if they had any claim for a hormonal contraceptive in the 6 months prior to the index date that differed from the one to which they were currently exposed on their index date.

We analyzed the cohort data to estimate incidence rates of VTE for each study drug. Current person-time was accumulated from the first study drug prescription to the last prescription plus 45 days. If there was a gap in the prescription fill dates of greater than 100 days, the person-time accumulation stopped at the last prescription before the gap, plus 45 days; person-time accumulation then resumed at the next record of a prescription for a study drug. Finally, we calculated crude incidence rate ratios (IRRs) and age-adjusted IRRs using the Mantel–Haenszel method.

Calculations were performed using SAS release 8.02 (SAS Institute, Cary, NC) and Stata release 8.2 (StataCorp LP, College Station, TX).

This study was exempt from review by the Boston University Medical Center's institutional review board.

3. Results

Approximately 1.3 million women in the PharMetrics database filled at least one prescription for a study OC during the study period. From this population, we identified 281 cases of idiopathic VTE and 1055 controls (women without VTE) matched by year of birth and index date. Characteristics of the cases and controls are listed in Table 1. The risk of VTE increased with increasing age, and cases were significantly more likely than controls to have diabetes, menstrual disorders and back pain. They were also more likely to have had recent emergency room visits or outpatient visits to a physician.

Norgestimate-containing OCs were the most widely used OC in this population. Five hundred eleven controls (48%) were currently exposed to norgestimate-containing OCs compared to 316 users (30%) of levonorgestrel-containing OCs and 228 users (22%) of desogestrel-containing OCs. Among the 281 cases of idiopathic VTE, 124 (44%) were currently exposed to norgestimate-containing OCs, 70 (25%) were exposed to levonorgestrel-containing OCs at the index date and 87 (31%) were currently exposed to desogestrel-containing OCs. The unadjusted odds ratios (ORs) for VTE controlling for the matching factors only were 1.1 [95% confidence interval (CI), 0.8–1.5], comparing norgestimate-containing OCs to levonorgestrel-containing OCs, and 1.7 (95% CI, 1.2–2.4), comparing desogestrel-containing OCs to levonorgestrel-containing OCs. When we included the covariates that were independently associated with VTE in the model, the ORs and 95% CIs did not change (Table 2).

We also evaluated the effect of duration of OC use, which was neither a confounder nor an effect modifier of the relation between the study OCs and VTE. The median durations of use for users of norgestimate-containing OCs were 7.8 months for cases and 7.3 months for controls. For users of desogestrel-containing OCs, the median durations were 8.7 and 7.6 months for cases and controls, respectively,

Table 2
Odds ratio for VTE comparing users of norgestimate- and desogestrel-containing OCs to users of levonorgestrel-containing OCs, adjusted and unadjusted ORs

Exposure	Cases (%), $n=281$	Controls (%), $n=1055$	OR[a]	95% CI	Adjusted OR[b]	95% CI
Levonorgestrel	70 (25)	316 (30)	1.0	Reference	1.0	Reference
Norgestimate	124 (44)	511 (48)	1.1	0.8–1.5	1.1	0.8–1.5
Desogestrel	87 (31)	228 (22)	1.7	1.2–2.4	1.7	1.2–2.4

[a] Conditional on age, index date.
[b] Adjusted for fibroids, endometriosis, menstrual disorders, hypertension, hyperlipidemia, CVD, diabetes, asthma, back pain, recent emergency room visits and recent physician visits.

and for users of levonorgestrel-containing OCs, the median durations were 8.5 and 8.2 months, respectively. Lastly, we evaluated the effects of switching OCs some time in the 6 months prior to the index date. Switching from another OC to the current OC was not a confounder of the OC VTE relation.

The incidence rate of VTE in norgestimate-containing OC users was 30.6 per 100,000 woman-years (95% CI, 25.5–36.5). For desogestrel-containing OC users, the incidence rate was 53.5 per 100,000 woman-years (95% CI, 42.9–66.0), and for levonorgestrel-containing OC users, the rate was 27.1 per 100,000 woman-years (95% CI, 21.1–34.3). The IRR for use of norgestimate-containing OCs compared to levonorgestrel-containing OCs was 1.1 (95% CI, 0.8–1.5). For desogestrel-containing OCs compared to levonorgestrel-containing OCs, the IRR was 2.0 (95% CI, 1.4–2.7). These IRRs were not materially changed when age was taken into account.

4. Discussion

The results of this study indicate that the risk of nonfatal VTE is similar in users of norgestimate- and levonorgestrel-containing OCs and significantly higher among current users of desogestrel-containing OCs compared to current users of the levonorgestrel-containing OCs [OR, 1.7 (95% CI, 1.1–2.4); IRR, 2.0 (95% CI, 1.4–2.7)], and these findings are consistent with the results of earlier studies [1–5]. As in prior studies, age and calendar time were closely controlled, that is, the controls were matched to cases by year of birth, and the date from which we evaluated exposure to the study drugs was identical in cases and controls.

To date, studies that evaluated the effects of different OC products in relation to VTE risk did not have enough information on women exposed to norgestimate-containing pills to be able to assess the effects of these OCs. Therefore, there has been some question as to the thrombogenic effects of these formulations compared to other OC preparations. This study provides evidence that norgestimate-containing OCs have a risk of VTE that is comparable to that of levonorgestrel-containing OCs and is lower than the risk in desogestrel-containing OCs. Also, this study was able to provide additional evidence that users of desogestrel-containing OCs have an increased risk of VTE compared to users of levonorgestrel-containing OCs [1–5]. The consistency of this result with previous findings provides reassurance that the quality of the data used in this study is satisfactory for the conduct of this type of drug safety study.

In an earlier study using the PharMetrics database, we evaluated the risk of nonfatal VTE in users of the contraceptive patch compared to users of norgestimate-containing OCs. In that study, we found no increased risk in the users of the patch (OR 0.9) [9]. However, there has been uncertainty as to whether the norgestimate-containing OC users were also at an elevated risk for VTE compared to users of levonorgestrel-containing OCs, a "second-generation" OC [4]. The present study provides evidence that the risk of VTE in users of the patch is similar to that in users of either levonorgestrel- or norgestimate-containing OCs.

We included women aged 15 to 39 years in this study (which differs from the recently published study of the contraceptive patch where we included women up to 44 years old [9]) so that the results would be comparable to those in earlier studies [1,5,6].

In this investigation, we studied the effect of OCs on the risk of nonfatal VTE. We limited the study to nonfatal outcomes because the PharMetrics database does not capture deaths that occur outside a healthcare facility, and by design, we required evidence of anticoagulation therapy after the VTE event. Fatal cases of VTE in women taking contraceptives have been reported to represent a small proportion of all cases. Failure to identify fatal VTE in this study is unlikely to have materially distorted the finding because the OR for nonfatal and fatal VTE comparing third- to second-generation OCs was similar in a previously published study [1].

The database has certain limitations that merit discussion. We were not able to obtain original clinical records to validate the VTE diagnoses in the cases. However, we were able to review all computer-recorded information for each case, and we applied strict criteria to the case definition. Cases were required to have diagnoses and procedures that were consistent with a confirmed VTE diagnosis, and they must have been treated with long-term anticoagulation therapy, a regimen that would not be prescribed to otherwise healthy young women in the absence of a thrombosis. In a prior study using a UK general practice database where we did not send for records [5], we found a result similar to that of the current study and to that of an earlier study conducted using the UK database where we did perform record validation [1].

We excluded women with a prior VTE and women with chronic medical conditions such as cancer, inflammatory disease, autoimmune disease or renal failure in order to avoid potential confounding due to preferential prescribing of one contraceptive compared to the other because of existing clinical risk factors for VTE. We also excluded women with recent surgery, major trauma, lower limb injury or pregnancy because they are known to be strong risk factors for VTE. We could not evaluate potential confounding due to smoking since it is not regularly recorded in the PharMetrics database. Also, neither height nor weight was recorded. Although we cannot rule out the possibility that these factors were confounders in these data, it should be noted that smoking was not associated with VTE when OCs containing high doses of estrogen were used [7,8,10]. More recently, a modest association between smoking and VTE has been found in some studies involving low-dose estrogen-containing contraceptives. However, it has not been a material confounder in these studies [1–3,5].

Similarly, while BMI is independently associated with a modest increased risk for VTE, it has also not confounded the association between second- or third-generation OCs and VTE in prior studies [1–3,5]. Although there is no information on BMI in these data, there is an *ICD* code for obesity that we evaluated in relation to the effect on the risk of VTE in this study. There was an increased risk of VTE among those with a diagnosis of obesity (OR, 1.7; 95% CI, 0.8–3.6), but a diagnosis of obesity did not confound the relation between the study OCs and VTE.

Over 1 million women exposed to one of the study drugs in this population provided information for this report. This study was not subject to exposure recall bias that can be a concern with interview-based case-control studies. The study was population-based with information on exposure collected prospectively before the outcome occurred. All eligible patients with the outcome were included, and diagnoses were made together with the recording of long-term use of anticoagulants. We were also able to tightly control potential confounding due to age and calendar time.

The findings of this study provide the first substantial evidence that norgestimate-containing OCs confer a risk for nonfatal VTE similar to that of the levonorgestrel-containing OCs, and they add additional evidence that OCs containing desogestrel are associated with a higher risk of VTE compared to norgestimate- and levonorgestrel-containing OCs.

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ORIGINAL RESEARCH ARTICLES

Nonsteroidal Antiinflammatory Drugs and Acute Myocardial Infarction in Patients with No Major Risk Factors

Hershel Jick, M.D., James A. Kaye, M.D., Dr.P.H., Stefan Russmann, M.D., and Susan S. Jick, D.Sc.

Study Objective. To assess the risk of long-term use of five nonsteroidal antiinflammatory drugs (NSAIDs)—rofecoxib, celecoxib, ibuprofen, naproxen, and diclofenac—in relation to acute myocardial infarction.

Design. Five separate nested case-control studies, one for each NSAID, designed to minimize important biases present in other observational studies.

Setting. University-affiliated research program.

Data Source. The United Kingdom General Practice Research Database (GPRD).

Measurements and Main Results. We identified all people in the GPRD aged 30–79 years who had a first recorded prescription for rofecoxib, celecoxib, ibuprofen, naproxen, or diclofenac after January 1, 1999. Cases of newly diagnosed, first-time acute myocardial infarction were then identified from the study population, along with matched control subjects. Relative risk estimates for acute myocardial infarction in patients with no recorded major clinical risk factors for acute myocardial infarction were determined for each NSAID according to receipt of 2–4, 5–9, 10–19, or 20 or more prescriptions compared with receipt of only 1 prescription. Results were adjusted for relevant variables possibly related to the risk for acute myocardial infarction. No material elevation of risk according to the number of prescriptions received for ibuprofen or naproxen was noted. However, a substantial increased risk similar to that found in clinical trials was noted in patients who received 10 or more prescriptions for rofecoxib, celecoxib, or diclofenac.

Conclusion. Extensive use of rofecoxib, celecoxib, and diclofenac increases the risk of acute myocardial infarction, but similar use of ibuprofen and naproxen does not.

Key Words: cyclooxygenase 2, COX-2, nonsteroidal antiinflammatory drugs, NSAIDs, acute myocardial infarction, AMI, observational study, rofecoxib, celecoxib, diclofenac.

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Three long-term randomized clinical trials have produced information about the risk of myocardial infarction and other cardiovascular events associated with use of the cyclooxygenase 2 (COX-2)–selective nonsteroidal antiinflammatory drugs (NSAIDs) rofecoxib and celecoxib.[1–3] One of these studies evaluated patients with rheumatoid arthritis who were randomly assigned to treatment with rofecoxib or the nonselective

NSAID naproxen,[1] and the other two studies evaluated patients with a history of colon polyps who were randomly assigned to treatment with a COX-2 inhibitor or placebo.[2, 3] Each of these trials found an important elevation in the risk of myocardial infarction in particular or a group of serious cardiovascular adverse events collectively among people receiving these COX-2 inhibitors compared with those receiving placebo or naproxen.

Aspirin was reported to be protective against myocardial infarction in observational studies[4, 5] published in the early 1970s, and a protective effect subsequently was demonstrated repeatedly in randomized trials.[6, 7] However, none of the nonaspirin NSAIDs available before the marketing of COX-2 inhibitors has been subjected to long-term clinical trials; therefore, judgment as to their effect on the risk of myocardial infarction must necessarily be derived from observational studies. A systematic review of more than a dozen observational studies that evaluated a large group of NSAIDs (including most recently COX-2 inhibitors) in relation to the risk of myocardial infarction was recently published.[8] The authors reported the following findings: the pooled relative risk (RR) for patients with myocardial infarction compared with control subjects for all current NSAID users combined compared with nonusers was 1.09 (95% confidence interval [CI] 1.06–1.13); no RR greater than 1.5 was found for any of the individual NSAIDs when all users were considered; and a "statistically increased risk" was found for diclofenac (RR ~1.4) and rofecoxib (RR ~1.4). The interpretation of such observational studies involves careful consideration of numerous factors that influence the risk of myocardial infarction and that may also affect the patterns of usage of NSAIDs in general and certain NSAIDs in particular.

In this study of five NSAIDs and the risk of myocardial infarction, we employed a study design not previously used in an attempt to minimize important biases that may have been present in previous observational studies. Our study was designed to reflect the major findings reported from randomized trials in that we sought to assess the relation of long-term use (> 10 mo) of rofecoxib, celecoxib, ibuprofen, naproxen, and diclofenac rather than considering only current use. In addition, unlike most previous studies (trials and observational), we assessed the risk for acute myocardial infarction in patients who had no previous recorded clinically important risk factors for myocardial infarction. The study was based on data from the United Kingdom General Practice Research Database (GPRD), a database whose completeness and validity have been repeatedly demonstrated.[9]

Methods

Base Population

We identified all people aged 30–79 years in the GPRD who had a first recorded use of rofecoxib, celecoxib, ibuprofen, naproxen, or diclofenac after January 1, 1999 (the year rofecoxib was marketed; celecoxib was first marketed in 2000). We conducted five separate nested case-control studies, one focusing on each of the five study NSAIDs. Subjects could be included in more than one study if they had a first recorded prescription for more than one study drug after January 1, 1999. The study period ended in September 2005 (although all practices contributing information to the GPRD may not have updated their information to that time).

Cases

For each of the five NSAIDs separately, we identified all people in the base population with a first-time Oxford Medical Information System code or Read code for myocardial infarction after January 1, 2001, who had at least one prescription for the NSAID of interest before their index date (the date of the first recorded diagnosis of myocardial infarction) and who had at least 2 years of history recorded in the GPRD before their index date. We limited cases to those diagnosed after January 1, 2001, to ensure that enough time had passed for study subjects to have sufficient opportunity to be exposed to any of the study drugs. To better isolate the potential effect of the NSAIDs of interest on the risk of myocardial infarction, we excluded cases with any of the following diagnoses more than 1 month before the diagnosis of myocardial infarction: ischemic heart disease (angina, previous myocardial infarction, cardiac catheterization, coronary artery angioplasty, or coronary artery bypass surgery), diabetes mellitus, treated hypertension, and cancer (other than nonmelanoma skin cancer). The computerized record of each case was reviewed by hand to ensure that each case fulfilled the eligibility criteria.

Control Selection

Each case was matched with up to four

controls who did not have a myocardial infarction by year of birth (within 2 yrs), sex, calendar time (index date), and general practice. In the naproxen study, because of the smaller base population of naproxen users, up to three controls were matched to each case. The "index date" for each control was the date of myocardial infarction in their matched case. The same exclusion and inclusion criteria applied to cases were applied to the controls, including the criteria of first use of the NSAID of interest in each study after January 1, 1999, and before the index date; presence of at least 2 years of recorded history in the GPRD before the index date; and exclusion for the same diseases listed above for the cases.

Exposure

Exposure for all study subjects was determined for the time before the index date. A subject was considered exposed if they had received two or more prescriptions for the study NSAID of interest before the index date but after January 1, 1999. Those with receipt of only one prescription of the study NSAID before their index date composed the reference group. This reference group was based on the randomized studies[1–3] that provided evidence that receipt of only one prescription does not increase the risk of myocardial infarction.

Analysis

We examined the effect of each NSAID of interest in a separate study (one in each of the five study populations of people who had at least one prescription for the NSAID of interest). We used conditional logistic regression to estimate odds ratios and 95% confidence intervals for various levels of exposure (2–4, 5–9, 10–19, and ≥ 20 prescriptions) of the primary NSAID of interest in each study compared with a single prescription as the reference level of exposure. We controlled each of the analyses for smoking (never, current, past, unknown), body mass index ([BMI] < 24 kg/m^2, 24–28 kg/m^2, > 28 kg/m^2, unknown), history of rheumatoid arthritis, history of hyperlipidemia, and use of the other study NSAIDs and aspirin before the index date. Exposure to the other study NSAIDs (i.e., those other than the NSAID of primary interest in each study) and aspirin was defined as 10 or more recorded prescriptions at any time before the index date for each drug separately (with < 10 prescriptions, including none, as the reference level).

Duration of use of the NSAID of primary interest in each study was calculated as the time from the date of the first prescription to 1 month after the date of the last prescription. (In the United Kingdom, one prescription is usually equivalent to a 30-day supply.) Cumulative dose was calculated as the sum over all prescriptions of the product of the number of pills in a prescription and the strength of the pills in that prescription. We estimated the correlation between number of prescriptions and duration of use and the correlation between number of prescriptions and cumulative dose by using a nonparametric measure (Spearman correlation coefficient).

Statistical calculations were performed by using SAS Release 9.1 software (SAS Institute Inc., Cary, NC).

Results

We identified more than 600,000 patients in the GPRD who had received a first prescription for at least one of the five study drugs some time after January 1, 1999. Characteristics of the cases and controls are given in Table 1. The mean duration of recorded history before the index date for cases and controls combined was 11.2 years in the rofecoxib study, 11.0 years in the celecoxib study, 9.1 years in the ibuprofen study, 10.2 years in the naproxen study, and 9.8 years in the diclofenac study. The duration of recorded history was similar for cases and controls within each study.

Rofecoxib

Among subjects who received one or more prescriptions for rofecoxib, we identified 112 patients with myocardial infarction and 421 matched controls who had received rofecoxib for the first time after January 1, 1999, and before their index date (Table 1). About one third of cases (and controls) were age 59 years or younger, one third were 60–69 years, and one third were 70 years or older. Nearly two thirds were male.

The RR estimate comparing cases and controls for all rofecoxib users who were prescribed at least two prescriptions (range 2–54 prescriptions) compared with those who were prescribed only one prescription was 1.5 (95% CI 1.0–2.4). The adjusted RR estimates, according to number of prescriptions received are provided in Table 2. The RR estimate for those prescribed 2–4 and 5–9 prescriptions compared with one prescription

Table 1. Characteristics of Case Patients and Control Subjects by Drug Study

	No. (%) of Patients	
	Cases	Controls
Rofecoxib	112	421
Age (yrs)		
≤ 59	32 (28.6)	124 (29.5)
60–69	38 (33.9)	141 (33.5)
≥ 70	42 (37.5)	156 (37.1)
Sex		
Female	42 (37.5)	164 (39.0)
Male	70 (62.5)	257 (61.1)
Current smoker	41 (36.6)	92 (21.9)
Rheumatoid arthritis	10 (8.9)	14 (3.3)
Celecoxib	109	423
Age (yrs)		
≤ 59	28 (25.7)	109 (25.8)
60–69	35 (32.1)	140 (33.1)
≥ 70	46 (42.2)	174 (41.1)
Sex		
Female	56 (51.4)	218 (51.4)
Male	53 (48.6)	205 (48.5)
Current smoker	51 (46.8)	86 (20.3)
Rheumatoid arthritis	12 (11.0)	23 (5.4)
Ibuprofen	303	1205
Age (yrs)		
≤ 59	135 (44.6)	538 (44.6)
60–69	93 (30.7)	373 (31.0)
≥ 70	75 (24.8)	294 (24.4)
Sex		
Female	82 (27.1)	328 (27.2)
Male	221 (72.9)	877 (72.8)
Current smoker	130 (42.9)	261 (21.7)
Rheumatoid arthritis	7 (2.3)	9 (0.8)
Naproxen	100	287
Age (yrs)		
≤ 59	57 (57.0)	168 (58.5)
60–69	25 (25.0)	74 (25.8)
≥ 70	18 (18.0)	45 (15.7)
Sex		
Female	33 (33.0)	94 (32.8)
Male	67 (67.0)	193 (67.3)
Current smoker	47 (47.0)	70 (24.4)
Rheumatoid arthritis	6 (6.0)	5 (1.7)
Diclofenac	235	929
Age (yrs)		
≤ 59	98 (41.7)	397 (42.7)
60-69	74 (31.5)	299 (32.2)
≥ 70	63 (26.8)	233 (25.1)
Sex		
Female	62 (26.4)	243 (26.2)
Male	173 (73.6)	686 (73.8)
Current smoker	94 (40.0)	234 (25.2)
Rheumatoid arthritis	12 (5.1)	11 (1.2)

were 1.5 and 1.0, respectively. For people who were prescribed 10–19 prescriptions (14 cases, 40 controls), the RR estimate was 1.7 (95% CI 0.8–3.8) and for those prescribed 20 or more prescriptions (9 cases, 16 controls) it was 3.1 (95% CI 1.1–8.9). A test for trend by exposure category provided evidence that an increasing number of prescriptions is associated with an increasing risk of myocardial infarction (p=0.07). Of note, five of the nine patients who received 20 or more prescriptions for rofecoxib received their last prescription 4 or more months before their myocardial infarction.

Duration of rofecoxib use (i.e., the time from the date of the first prescription to a date 1 month after the last prescription before the index date) correlated with the number of rofecoxib prescriptions (r=0.97, p<0.0001). For those with a single prescription, the duration of use was 1 month by definition. For those with 2–4 prescriptions, the median duration was 3.6 months (interquartile range [IQR] 2.3–6.2 mo); for 5–9 prescriptions, 9.4 months (IQR 7.2–13.3 mo); for 10–19 prescriptions, 21.1 months (IQR 14.6–27.0 mo); and for 20 or more prescriptions, 34.7 months (IQR 29.8–41.3 mo).

Cumulative dose also correlated with the number of rofecoxib prescriptions (r=0.89, p<0.0001). For those with a single prescription, the median cumulative dose was 350 mg (IQR 350–700 mg); for 2–4 prescriptions, 1400 mg (IQR 1050–2100 mg); for 5–9 prescriptions, 4550 mg (IQR 2625–5600 mg); for 10–19 prescriptions, 9638 mg (IQR 7700–14,000 mg); and for 20 or more prescriptions, 15,525 mg (IQR 12,250–24,150 mg).

A higher proportion of cases than controls had a history of rheumatoid arthritis, and cases were more likely than controls to be current smokers (Table 1). The RR for a history of rheumatoid arthritis (adjusted for the number of rofecoxib prescriptions, BMI, smoking, hyperlipidemia, and exposure to the other NSAIDs and aspirin) was 2.7 (95% CI 1.0–7.1). The RR for current smoking (adjusted for the number of rofecoxib prescriptions, BMI, hyperlipidemia, rheumatoid arthritis, and exposure to the other NSAIDs and aspirin), with never smoking as the reference, was 3.7 (95% CI 2.0–6.7).

Celecoxib

Among subjects who received one or more prescriptions for celecoxib, we identified 109 patients with myocardial infarction and 423 matched controls who had received celecoxib for the first time after January 1, 1999, and before their index date (Table 1). Case patients in the celecoxib study tended to be older than those in the rofecoxib study, and more than half were female.

Table 2. Distribution of Number of Prescriptions of Rofecoxib for Cases and Controls

No. of Prescriptions	No. of Cases (n=112)	No. of Controls (n=421)	Relative Risk Estimate[a]	95% CI
1	43	202	1.0	Reference
2–4	32	113	1.5	0.9–2.6
5–9	14	50	1.0	0.4–2.1
10–19	14	40	1.7	0.8–3.8
≥ 20	9	16	3.1	1.1–8.9

CI = confidence interval.
[a]Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidemia, and use of other NSAIDs (≥ 10 vs < 10 prescriptions, separately for celecoxib, ibuprofen, naproxen, diclofenac, and aspirin).

Table 3. Distribution of Number of Prescriptions of Celecoxib for Cases and Controls

No. of Prescriptions	No. of Cases (n=109)	No. of Controls (n=423)	Relative Risk Estimate[a]	95% CI
1	47	216	1.0	Reference
2–4	31	115	1.3	0.7–2.4
5–9	16	46	1.5	0.8–3.2
10–19	10	34	1.8	0.7–4.3
≥ 20	5	12	1.8	0.5–6.0

CI = confidence interval.
[a]Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidemia, and use of other NSAIDs (≥ 10 vs < 10 prescriptions, separately for rofecoxib, ibuprofen, naproxen, diclofenac, and aspirin).

The RR estimate comparing cases and controls for all celecoxib users combined who were prescribed at least two prescriptions (range 2–51 prescriptions) compared with those who were prescribed only one prescription was similar to that obtained with rofecoxib, 1.4 (95% CI 0.9–2.1). The RR estimates according to number of prescriptions received are shown in Table 3. A test for trend by category provided evidence for the hypothesis that the risk of myocardial infarction increases with an increasing number of celecoxib prescriptions (p=0.08).

Duration of use correlated with the number of celecoxib prescriptions (r=0.96, p<0.0001). In the highest exposure category (≥ 20 prescriptions), the median duration of use was 31.2 months (IQR 27.4–38.1 mo).

Cumulative dose also correlated with the number of celecoxib prescriptions (r=0.92, p<0.0001). In the highest exposure category, the median cumulative dose was 228,000 mg (IQR 162,000–240,000 mg).

Case patients were twice as likely to have rheumatoid arthritis compared with controls, and they were more than twice as likely to be current smokers (Table 1). The RR for a history of rheumatoid arthritis (adjusted for the number of celecoxib prescriptions, BMI, smoking, hyperlipidemia, and exposure to the other NSAIDs and aspirin) was 1.7 (95% CI 0.7–3.9). The RR for current smoking (adjusted for the number of celecoxib prescriptions, BMI, hyperlipidemia, rheumatoid arthritis, and exposure to the other NSAIDs and aspirin), with never smoking as the reference, was 6.7 (95% CI 3.5–12.6).

Ibuprofen

Among ibuprofen users who received one or more prescriptions, we identified 303 patients with myocardial infarction and 1205 controls who received ibuprofen for the first time after January 1, 1999, and before their index date (Table 1). About 45% were younger than age 59 years, 30% were age 60–69 years, and 25% were 70 years or older. Almost three quarters of the case patients were male.

The RR estimate comparing cases and controls for all ibuprofen users who were prescribed at least two prescriptions (range 2–51 prescriptions) compared with those who were prescribed only

Table 4. Distribution of Number of Prescriptions of Ibuprofen for Cases and Controls

No. of Prescriptions	No. of Cases (n=303)	No. of Controls (n=1205)	Relative Risk Estimate[a]	95% CI
1	201	845	1.0	Reference
2–4	78	279	1.2	0.8–1.6
5–9	14	49	1.2	0.6–2.3
10–19	8	23	1.0	0.4–2.4
≥ 20	2	9	0.9	0.2–4.2

CI = confidence interval.
[a]Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidemia, and use of other NSAIDs (≥ 10 vs < 10 prescriptions, separately for rofecoxib, celecoxib, naproxen, diclofenac, and aspirin).

Table 5. Distribution of Number of Prescriptions of Naproxen for Cases and Controls

No. of Prescriptions	No. of Cases (n=100)	No. of Controls (n=287)	Relative Risk Estimate[a]	95% CI
1	56	185	1.0	Reference
2–4	37	66	2.2	1.2–4.0
5–9	1	24	0.2	0.02–1.3
10–19	3	6	1.9	0.4–10.3
≥ 20	3	6	2.5	0.5–13.8

CI = confidence interval.
[a]Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidemia, and use of other NSAIDs (≥ 10 vs < 10 prescriptions, separately for rofecoxib, celecoxib, ibuprofen, diclofenac, and aspirin).

one prescription was 1.2 (95% CI 0.9–1.6). The adjusted RR estimates according to number of prescriptions received are shown in Table 4. There was no evidence of a trend by category in the relation between the risk of myocardial infarction and the number of prescriptions received (p=0.6).

Duration of use (r=0.98, p<0.0001) and cumulative dose (r=0.72, p<0.0001) both correlated with the number of prescriptions. The highest exposure category (≥ 20 prescriptions) corresponded to a median duration of use of 35.2 months (IQR 28.0–49.1 mo) and a median cumulative dose of 780,000 mg (IQR 739,200–1,200,000 mg).

The proportion of cases with rheumatoid arthritis was again higher than the proportion of controls, but these proportions were each only approximately one fifth the respective proportions of cases and controls with rheumatoid arthritis in the rofecoxib and celecoxib studies. As in the other studies, cases were much more likely than controls to be current smokers (Table 1). The RR for a history of rheumatoid arthritis (adjusted for the number of ibuprofen prescriptions, BMI, smoking, hyperlipidemia, and exposure to the other NSAIDs and aspirin) was 4.8 (95% CI 1.5–15.0). The RR for current smoking (adjusted for the number of ibuprofen prescriptions, BMI, hyperlipidemia, rheumatoid arthritis, and exposure to the other NSAIDs and aspirin), with never smoking as the reference, was 3.7 (95% CI 2.7–5.2).

Naproxen

Among subjects who received one or more prescriptions for naproxen, we identified 100 case patients and 287 controls who received naproxen for the first time after January 1, 1999, and before their index date (Table 1). More than half the cases and controls were younger than 59 years and less than one fifth were age 70 years or older. Two thirds of the case patients were male.

The RR estimate comparing cases and controls for all naproxen users who were given at least two prescriptions (range 2–78 prescriptions) compared with those who were given only one prescription was 1.4 (95% CI 0.8–2.3). The adjusted RR estimates by number of prescriptions are presented in Table 5. No evidence of a trend by category was noted in the relation between the

Table 6. Distribution of Number of Prescriptions of Diclofenac for Cases and Controls

No. of Prescriptions	No. of Cases (n=235)	No. of Controls (n=929)	Relative Risk Estimate[a]	95% CI
1	141	571	1.0	Reference
2–4	46	254	0.7	0.5–1.0
5–9	17	60	1.2	0.6–2.2
10–19	17	26	2.5	1.2–5.0
≥ 20	14	18	2.6	1.2–5.9

CI = confidence interval.
[a]Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidemia, and use of other NSAIDs (≥ 10 vs < 10 prescriptions, separately for rofecoxib, celecoxib, ibuprofen, naproxen, and aspirin).

risk of myocardial infarction and increasing numbers of naproxen prescriptions (p=0.4).

Rheumatoid arthritis was again more common among the cases than the controls, with the respective proportions intermediate between those in the COX-2 inhibitor studies and those in the ibuprofen study. As in all the other studies, the proportion of current smokers was substantially higher among cases than among controls (Table 1). The RR for a history of rheumatoid arthritis (adjusted for the number of naproxen prescriptions, BMI, smoking, hyperlipidemia, and exposure to the other NSAIDs and aspirin) was 3.3 (95% CI 0.7–15.7). The RR for current smoking (adjusted for the number of naproxen prescriptions, BMI, hyperlipidemia, rheumatoid arthritis, and exposure to the other NSAIDs and aspirin), with never smoking as the reference, was 3.9 (95% CI 2.0–7.6).

Diclofenac

Among subjects who received one or more prescriptions for diclofenac, we identified 235 case patients and 929 matched controls who received diclofenac for the first time after January 1, 1999, and before their index date (Table 1). About 40% of cases (and controls) were age 59 years or younger, one third were 60–69 years, and one quarter were 70 years or older. Nearly three quarters were male.

The RR estimate comparing cases and controls for all diclofenac users who were prescribed at least two prescriptions (range 2–63 prescriptions) compared with those who were prescribed only one prescription was 1.0 (95% CI 0.8–1.4). The adjusted RR estimates according to number of prescriptions received are provided in Table 6. The RR estimate for those prescribed 2–4 and 5–9 prescriptions compared with one prescription were 0.7 and 1.2, respectively. For people who were prescribed 10–19 prescriptions (17 cases, 26 controls), the RR estimate was 2.5 (95% CI 1.2–5.0) and for those prescribed 20 or more prescriptions (14 cases, 18 controls) it was 2.6 (95% CI 1.2–5.9). A test for trend by category provided evidence that an increasing number of prescriptions is associated with an increasing risk of myocardial infarction (p=0.02).

Duration of use correlated with the number of diclofenac prescriptions (r=0.97, p<0.0001). For those with 10–19 prescriptions, the median duration of use was 28.4 months (IQR 16.2–35.9 mo); for 20 or more prescriptions, it was 38.8 months (IQR 29.0–55.5 mo).

Cumulative dose also correlated with the number of diclofenac prescriptions (r=0.81, p<0.0001). For those with 10–19 prescriptions, the median cumulative dose was 52,500 mg (IQR 42,000–60,900 mg); and for those with 20 or more prescriptions, it was 114,800 mg (IQR 88,350–150,500 mg).

The proportions of cases and controls with a history of rheumatoid arthritis were similar to those in the naproxen study, and cases were again much more likely than controls to be current smokers (Table 1). The RR for a history of rheumatoid arthritis (adjusted for the number of diclofenac prescriptions, BMI, smoking, hyperlipidemia, and exposure to the other NSAIDs and aspirin) was 2.6 (95% CI 0.9–7.1). The RR for current smoking (adjusted for the number of diclofenac prescriptions, BMI, hyperlipidemia, rheumatoid arthritis, and exposure to the other NSAIDs and aspirin), with never smoking as the reference, was 2.3 (95% CI 1.6–3.4).

Discussion

Three randomized clinical trials have provided virtually irrefutable evidence that prolonged use

of the COX-2 inhibitors rofecoxib and celecoxib increases the risk for acute myocardial infarction specifically, and cardiovascular disorders in general, by as much as 2-fold or more.[1–3] Randomized clinical trials regularly yield the most reliable information on the safety of drugs, particularly when adverse effects are reasonably common and the trials are both large and extended in time. Trials are particularly useful in people who are at high risk for the adverse effect of interest, since observational (nonrandomized) studies often contain important biases that cannot be precisely measured and controlled and thus often affect and distort their results.[10] Randomized trials are designed to minimize such biases among the comparison groups. Large controlled trials are particularly salutary in evaluating the relation of NSAID use and the risk of myocardial infarction and other cardiovascular events.

The first reported randomized study, Vioxx Gastrointestinal Outcomes Research (VIGOR), compared patients who received rofecoxib 50 mg/day with those receiving naproxen 500 mg twice/day.[1] The risk of myocardial infarction was reported to be 0.1% (4/4029) in naproxen recipients and 0.4% (16/4047) in recipients of rofecoxib. Astonishingly, the authors (and others responsible for the publication) chose to provide only the RR for myocardial infarction of 0.2 (95% CI 0.1–0.7) for naproxen compared with rofecoxib. The authors concluded that their results were "consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection." There is no mention of the possibility that rofecoxib might increase the risk for myocardial infarction. Nor is there information on time of exposure before the date of myocardial infarction.

The Adenomatous Polyp Prevention on Vioxx (APPROVE) study compared patients who received rofecoxib 25 mg (half the dose used in the VIGOR study) with those who received placebo, with follow-up for as long as 36 months.[3] The RR comparing rofecoxib users with placebo users from the start of the trial up to 18 months was reported to be 1.18. By contrast, the RR for months 19–36 was reported to be 4.45. Had this study been designed with a follow-up period of 18 months or less, no difference between rofecoxib and placebo would have been found.

In the Adenoma Prevention with Celecoxib (APC) study, which compared two doses of celecoxib and placebo with 36 months of follow-up, the increased risk of serious cardiac events was 2.3 for patients receiving celecoxib 200 mg twice/day and 3.4 for patients receiving 400 mg twice/day compared with placebo.[2] The effect in celecoxib users appeared to start at about 10–12 months after treatment began, and the risk was higher in those who received the higher dose.

Thus, there is convincing evidence from these trials that the increased cardiovascular risk attributable to the two COX-2 preparations is highly correlated with the cumulative dose received.

Our study provides additional persuasive evidence on this issue, since the findings are compatible with those of randomized studies. As in the trials discussed above,[1–3] extensive use appears to be a critical determinant of the effect. In our study, we emphasized the extent of use for each study drug of interest rather than the currency of use. By focusing on a particular NSAID of interest in each of our separate studies, we avoided the problem with other investigations that categorized patients as having been exposed to the particular NSAID that was prescribed closest in time to the index date when they may have received more extended use of another NSAID previously (and the previously used NSAID may have had more influence on their risk for myocardial infarction). This likely explains at least in part why our results are more similar to those of the clinical trials[1–3] than are other observational studies,[8] which yielded generally null effects. The previous observational studies on NSAIDs and myocardial infarction, with a few exceptions,[11, 12] identified subjects who were currently exposed to an NSAID and compared current use of each drug with noncurrent exposure as the referent. We found an increased risk of myocardial infarction in rofecoxib users who received 20 or more prescriptions, a finding that is concordant with the results of the APPROVE study,[3] in which the increased risk for myocardial infarction among those receiving rofecoxib as compared with placebo became manifest after approximately 18 months of treatment.

An important additional new finding from our study is that prolonged use of diclofenac, a commonly used NSAID, also increases the risk for acute myocardial infarction more than 2-fold in the highest exposure categories. The public health implication of this finding is substantial since we estimate, based on the GPRD, that more than 15 million people in the United Kingdom

have been prescribed diclofenac, sometimes on a continuous basis, in the past 20 years. Approximately 11% of these have 10 or more prescriptions recorded. Note that diclofenac has the highest COX-2 selectivity among the traditional NSAIDs.[13]

A majority of studies[8] included people with important clinical risk factors for myocardial infarction (e.g., angina and diabetes). In all instances, as expected, the cases compared with controls had a substantially higher proportion of people with these prior illnesses. There is an assumption in the analysis that the severity of these illnesses (all treated as dichotomous variables) is the same in cases and controls, which is surely incorrect since the cases had a myocardial infarction and the controls did not. The net effect of these considerations is that they may distort the results to a measurable amount. Because most published studies encompass thousands of cases and controls, such biases—if present—will tend to result in small but "statistically significant" differences between cases and controls, which are sometimes inferred to be causal when, in fact, they are due to small biases relative to cases and controls.[10] In our study, we excluded cases and controls with preexisting risk factors for myocardial infarction. Failure to remove these subjects from an observational study may well bias any true drug effect that is present.

Conclusion

The extent of NSAID use appears to be the critical determinant in the relation of most marketed NSAIDs to myocardial infarction. The findings of this study are consistent with the results of the clinical trials with respect to the effect of prolonged use of rofecoxib and celecoxib and the risk of myocardial infarction. In this study, this increased risk also appeared to be present in diclofenac users but not in users of ibuprofen or naproxen.

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Risk of Impaired Renal Function After Colonoscopy: A Cohort Study in Patients Receiving Either Oral Sodium Phosphate or Polyethylene Glycol

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OBJECTIVES: We aimed to evaluate frequency, predictors, and monitoring of renal dysfunction related to the use of oral sodium phosphates for colonoscopy in clinical practice.

METHODS: Cohort study using clinical records and electronic patient information from the Henry Ford Health System, Detroit, MI. We identified patients undergoing colonoscopy using sodium phosphate or polyethylene glycol (PEG), and estimated the risk of renal impairment associated with bowel preparation and other risk factors.

RESULTS: Out of 7,897 patients, 6,833 had used sodium phosphate; 1,617 patients had renal dysfunction within 12 months prior to colonoscopy and 3,928 patients had no creatinine measurement within 12 months prior to or 6 months postcolonoscopy. Among the remaining 2,352 patients, 88 had incident renal dysfunction (glomerular filtration rate [GFR] $<$60 mL/min) after colonoscopy. The relative risk (RR) estimate for renal dysfunction comparing sodium phosphate with PEG was 1.13 (95% CI 0.58–2.23) without adjustment, and 1.14 (95% CI 0.55–2.39) after multivariate adjustment. Significant univariate risk factors were age $\geq$65 yr, African-American race, low baseline GFR, hypertension, and use of angiotensin-converting enzyme inhibitors (ACE inhbitors), angiotensin-renin blockers, or thiazide diuretics.

CONCLUSIONS: In patients without preexisting renal disease, the risk of renal impairment after colonoscopy appears to be similar between sodium phosphate and PEG users. Sodium phosphate use in patients with preexisting renal disease is not recommended, but common in clinical practice. Sodium phosphate should not be used in patients with preexisting serious renal disease, adequate hydration should be assured in all patients, and renal function should be monitored before and after colonoscopy in those at risk of renal dysfunction.

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INTRODUCTION

Reports of renal failure after colonoscopy using sodium phosphate-containing bowel cleansing preparations have raised concern about their safety (1–6). The labeling of oral sodium phosphates has therefore been repeatedly updated, and now includes a contraindication for its use in serious renal disease and congestive heart failure, and recommends its cautious use in patients with impaired renal function, heart disease, ascites, dehydration, and electrolyte disturbances, as well as in elderly patients. In addition, the need for adequate hydration is emphasized and there is a warning not to exceed the recommended dose.

These warnings are also supported by previous studies showing that oral sodium phosphates may cause intravascular volume depletion and may increase the calcium phosphate product, providing a plausible pathophysiological hypothesis for the occurrence of nephrocalcinosis and subsequent renal impairment (7). Indeed, nephrocalcinosis has been described in cases where renal histology was available, although only one reported case has a baseline histology before colonoscopy that provides additional evidence for a causal relationship (6).

In clinical trials, no cases of renal failure after use of oral sodium phosphates were reported. However, the population in these trials may not represent patients who receive sodium phosphates in clinical practice where risk factors for the development of renal complications may be more prevalent, and they included only a limited number of patients, preventing the detection of very rare adverse events. So far, no studies have evaluated the incidence and relative risk of renal

complications after use of oral sodium phosphates as compared to other preparations in clinical practice.

We conducted a formal epidemiological study in recipients of oral bowel preparation agents containing either sodium phosphate or polyethylene glycol (PEG) that aimed to evaluate the risk of incident renal complications after colonoscopy in clinical practice and its association with the used bowel preparation.

METHODS

Data Source

Information for this study was derived from the procedure database of the Gastroenterology Department at Henry Ford Health System (HFHS) Detroit campus, Detroit, MI, and the administrative databases within HFHS. The Gastroenterology database contains detailed information on colonoscopies including date, bowel cleansing preparation, and adequacy of preparation, as well as the medical record number as a unique patient identifier that allows linkage to the HFHS administrative databases and electronic medical record. The HFHS database contains information on medical care encounters, diagnoses, procedures, outpatient drug prescriptions, laboratory results, and patient demographics. Additionally, for patients enrolled in Health Alliance Plan (HAP), an HFHS owned and operated health maintenance organization, external claims for care are also available. Drug prescriptions are coded using the National Drug Code (NDC) provided by the U.S. Food and Drug Administration (FDA). All diagnoses are coded using the ICD-9 coding system; procedures are coded using the CPT4 coding system. All events are noted with the date on which the initial service was delivered. We also had access to original medical records and laboratory results of all patients enrolled in HAP.

The study was approved by the HFHS Human Rights Committee with a waiver of authorization.

Study Population

The study was based within the population of all patients who had a colonoscopy at the HFHS Detroit center's gastroenterology clinic between November 1, 1999 and October 31, 2005, who received oral bowel cleansing preparations containing either sodium phosphate (Phospho-soda®, C.B. Fleet Company, Inc., Lynchburg, VA) or PEG (COLYTE®, Schwarz Pharma, Inc., Milwaukee, WI), and were enrolled in the HAP from 12 months prior to 6 months postcolonoscopy. From this population, we excluded all patients with preexisting renal disease within 12 months prior to colonoscopy according to predefined criteria (Table 1). Subsequently, we obtained all creatinine values determined within 12 months prior to and 6 months postcolonoscopy for the remaining patients, and calculated glomerular filtration rate (GFR) estimates according to the modification of diet in renal disease (MDRD) study formula (8). We then excluded additional patients with a GFR <60 mL/min within 12 months prior to colonoscopy, and those who did not have a creatinine determination within 12 months prior to and 6 months postcolonoscopy. This selection process assured that our final study population included only patients with sufficient information for identification and differential diagnostic evaluation of renal impairment in relation to colonoscopy.

Table 1. Criteria for the Identification of Preexisting Renal Diseases

Outcome	Criteria
Undergoing dialysis	ICD-9 diagnosis: V45.1, V56–V56.8
	HFHS billing codes for dialysis
	External claims for dialysis
History of kidney transplant	ICD-9 diagnosis: V42.0
Acute renal failure	ICD-9 diagnosis: 584.5–584.9
Chronic renal failure	ICD-9 diagnosis: 585
Unspecified renal failure	ICD-9 diagnosis: 586
Functional renal impairment stage 3 or greater	GFR <60 mL/min

We also extracted additional electronic information on demographics, preexisting concomitant drug use, and comorbidities for all patients in the study population (Table 2). Drug prescriptions within 3 months prior to colonoscopy were identified as a proxy for current drug use. For the identification of comorbidities, we searched for related diagnostic codes or procedures within 12 months prior to colonoscopy. In addition to specific conditions of interest, the diagnostic coding was used to calculate the Charlson comorbidity index. Originally developed to assess survival probability based on inpatient medical record review, this methodology is also useful with administrative databases as a means of measuring underlying burden of illness (9, 10).

Definition, Identification, and Validation of Cases

From the study population, we identified all patients where the first creatinine determination within 6 months after colonoscopy corresponded to a GFR <60 mL/min and showed a decrease of at least 10 mL/min *versus* the last value before colonoscopy. The focus on the first creatinine value after colonoscopy was based on the assumption that renal damage in relation to colonoscopy would manifest soon thereafter. We also searched for patients with at least a twofold increase in creatinine, regardless of whether the GFR after colonoscopy was <60 mL/min. Two physicians, with expertise in causality assessment of suspected adverse drug reactions (Stefan Russmann and Judith K. Jones), then reviewed the original clinical records of these patients, while being blinded with regard to the bowel preparation agent used (this information is not part of the clinical records but kept in the Gastroenterology database, which was later incorporated into the main dataset for the final analysis). Patients with an identifiable, likely cause of renal impairment other than bowel preparations were subsequently excluded. The remaining patients were considered as "idiopathic" cases of renal impairment, and therefore, to have at least a possible causal

Table 2. Baseline Characteristics of the Study Population

Characteristics	Sodium Phosphate Users (N = 2,083)		Polyethylene Glycol Users (N = 269)	
Sex				
Female	1,158	(55.6%)	137	(50.9%)
Male	925	(44.4%)	132	(49.1%)
Age (yr)				
<65	1,284	(61.6%)	131	(48.7%)
≥65	799	(38.4%)	138	(51.3%)
Race				
African American	1,454	(69.8%)	183	(68.0%)
White	548	(26.3%)	82	(30.5%)
Others	81	(3.9%)	4	(1.5%)
Colonoscopy date				
Nov 1, 1999 to Oct 31, 2000	224	(10.8%)	56	(20.8%)
Nov 1, 2000 to Oct 31, 2001	285	(13.7%)	27	(10.0%)
Nov 1, 2001 to Oct 31, 2002	350	(16.8%)	34	(12.6%)
Nov 1, 2002 to Oct 31, 2003	477	(22.9%)	36	(13.4%)
Nov 1, 2003 to Oct 31, 2004	420	(20.2%)	34	(12.6%)
Nov 1, 2004 to Oct 31, 2005	327	(15.7%)	82	(30.5%)
Inpatient colonoscopy	199	(9.6%)	97	(36.1%)
GI bleeding 30 days prior to colonoscopy	241	(11.6%)	77	(28.6%)
Hospitalization 12 months prior to colonoscopy	435	(20.9%)	126	(46.8%)
Baseline GFR ≥60 and <90 mL/min	1,023	(49.1%)	119	(44.2%)
Baseline comorbidities*				
Hypertension	1,277	(61.3%)	179	(66.5%)
Diabetes mellitus	504	(24.2%)	68	(25.3%)
Congestive heart failure	74	(3.6%)	40	(14.9%)
Liver cirrhosis	34	(1.6%)	8	(3.0%)
Charlson comorbidity index				
0	1,007	(48.3%)	94	(34.9%)
1–2	876	(42.1%)	128	(47.6%)
≥3	200	(9.6%)	47	(17.5%)
Current drug therapy†				
Angiotensin-converting enzyme inhibitors	411	(19.7%)	52	(19.3%)
Angiotensin-renin blockers	87	(4.2%)	20	(7.4%)
Loop diuretics	99	(4.8%)	27	(10.0%)
Thiazide diuretics	415	(19.9%)	42	(15.6%)
Beta blockers	397	(19.1%)	75	(27.9%)
Calcium channel blockers	382	(18.3%)	50	(18.6%)
Nonsteroidal antiinflammatory drugs	449	(21.6%)	46	(17.1%)

*Diagnoses within 12 months prior to colonoscopy.
†Prescriptions within 3 months prior to colonoscopy.

relationship to colonoscopy with bowel preparation. In addition, we also searched for any diagnoses indicating renal dysfunction (Table 1) after colonoscopy in the base population, in order to assure that there were no patients with clinically diagnosed renal dysfunction, but no available creatinine value.

Data Analysis

We calculated the incidence of renal impairment during the 6-month period after colonoscopy, and estimated the unadjusted relative risk (RR) in patients receiving oral sodium phosphate *versus* PEG as the incidence ratio for these two groups. We used logistic regression in order to calculate odds ratios (OR) as an estimate of RR, and to control for the possible effects of patient demographics, drug use, and comorbidities at the time of colonoscopy. In addition, we used propensity score methodology as an alternative way to control for confounding, *i.e.*, we generated a logistic regression model that calculated a patient's propensity to receive sodium phosphate or PEG based on patient demographics, current drug use, and medical history. Subsequently, we used this propensity score as a continuous covariate in a logistic regression model that measured the association between bowel preparation and renal impairment, and also as the basis for stratification of the study population into quintiles for stratified analysis according to the Mantel-Haenszel method (11, 12).

Data were analyzed using STATA 8.2 for MacOS X (STATA Corp LP, College Station, TX) and SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

We identified a base population of 7,897 patients with continuous health plan enrollment that underwent colonoscopy and used either oral sodium phosphate or PEG for preparation. Within 12 months prior to colonoscopy, 595 out of

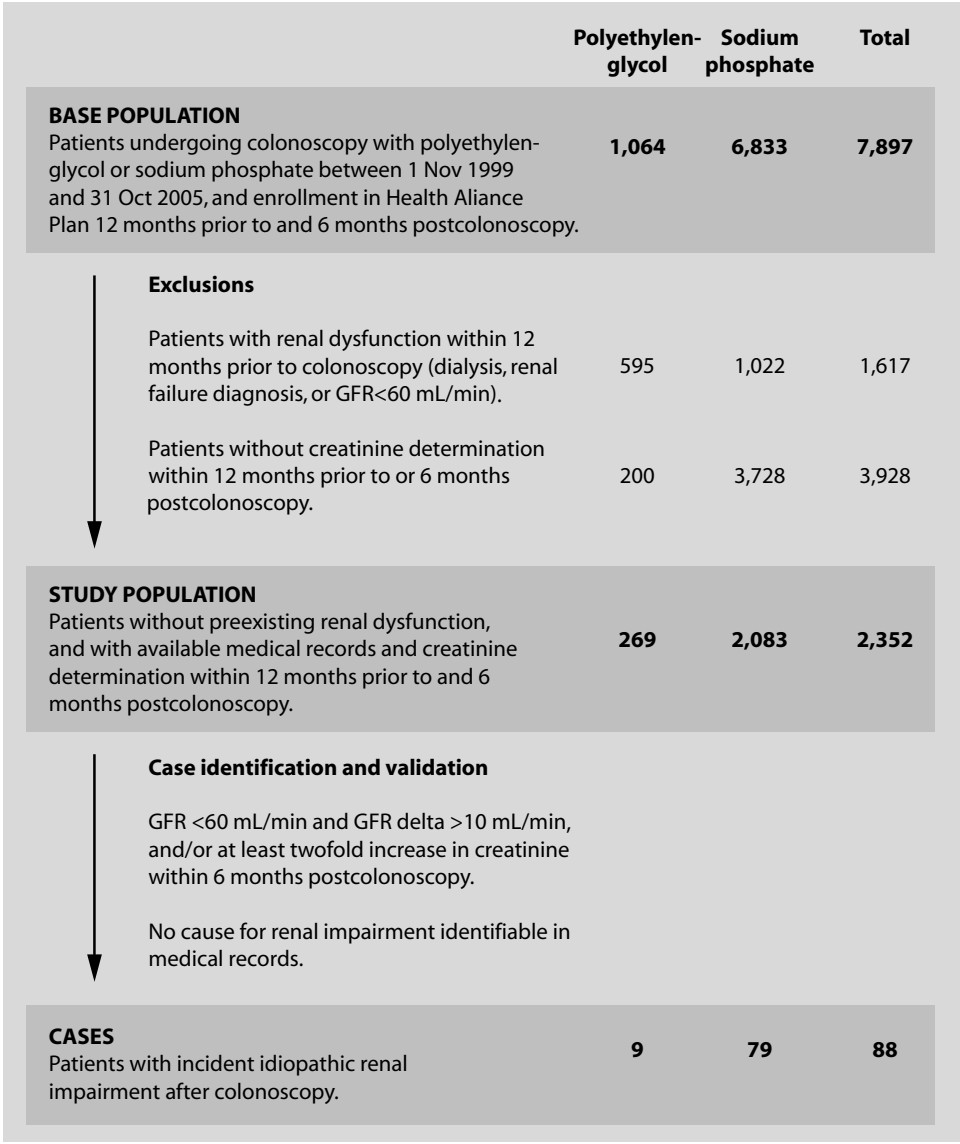

Figure 1. Identification of study population and cases.

1,064 PEG users (55.9%) and 1,022 out of 6,833 sodium phosphate users (15.0%) had renal dysfunction. Of the remaining 469 PEG and 5,811 sodium phosphate users, 43 (9.2%) and 1,025 (17.6%), respectively, had no creatinine determination within 12 months prior to colonoscopy, and 190 (40.5%) and 3,540 (60.9%), respectively, had no creatinine determination within 6 months postcolonoscopy. Two hundred (42.6%) and 3,728 (64.2%), respectively, had no creatinine determinations within 12 months prior to or 6 months postcolonoscopy, leading to a final study population of 2,352 patients (Fig. 1). Furthermore, we identified 1,621 patients in the base population who had a GFR <90 mL/min within 12 months prior to colonoscopy, but no creatinine determination within 6 months thereafter. Of those, 1,517 patients had used sodium phosphate, of which 174 even had a GFR <60 mL/min.

Demographics and baseline characteristics before colonoscopy of the study population are presented in Table 2. Compared to the patients receiving sodium phosphate, those receiving PEG were on average older and had a higher prevalence of heart failure, use of diuretics or drugs acting on the angiotensin system, and comorbidities according to the Charlson index. They were also more likely to have a colonoscopy as an inpatient procedure, and to be hospitalized for any reason during the 12 months before colonoscopy. However, in the study population, the proportion of patients with mild renal impairment before colonoscopy (GFR between 60 and 90 mL/min) was similar in PEG and sodium phosphate users (44.2 *vs* 49.1%). Table 2 also shows an increase in the use of PEG in 2005.

Within the study population, we identified 100 patients that fulfilled the study's criteria for renal impairment after

Table 3. Reasons for Exclusion of 12 Patients With Renal Dysfunction After Colonoscopy From Study Cases Because Other Likely Causes of Renal Dysfunction Were Identified During Review Blinded to Bowel Preparation

Likely Cause for Renal Dysfunction	Category
Three months after colonoscopy: Hospital admission due to syncope. Cardiac catheter with contrast medium application and diagnosis of aortic and mitral valve stenosis with pulmonary hypertension. Recovery of renal function a few days after admission.	Prerenal and/or contrast medium
Five months after colonoscopy: Pneumonia with acute decompensation of chronic heart failure. Recovery of renal function after treatment of pneumonia and heart failure.	Prerenal
One month after colonoscopy: Hospitalization for recurrent lower gastrointestinal hemorrhage. Known alcohol abuse was the possible additional cause of dehydration. Recovery of renal function after rehydration.	Prerenal
Three months after colonoscopy: Hospital admission with acute upper gastrointestinal bleeding and hypotension. Recovery of renal function after rehydration.	Prerenal
Four months after colonoscopy: Hospitalization for acute pneumonia. Recovery of renal function after treatment of pneumonia.	Prerenal
Four months after colonoscopy: Severe lower gastrointestinal hemorrhage and acute renal failure with hematuria.	Prerenal
Five months after colonoscopy: Hospital admission with 6-wk history of diarrhea. Diagnosis of acute renal failure due to hypovolemia. Recovery of renal function after rehydration.	Prerenal
Two weeks after colonoscopy: Patient found unconscious at home, and with clavicular fracture and chronic alcoholism. Recovery of renal function after rehydration.	Prerenal
Two months after colonoscopy: Recurrent (not incident) acute nephrolithiasis. Several events of nephrolithiasis before colonoscopy.	Postrenal
Two days after colonoscopy: Lower urinary tract obstruction and infection. Clots in urine. Cytology suggested malignancy. Recovery of renal function after passage of urinary catheter.	Postrenal
Three months after colonoscopy and shortly after prostatectomy: Bladder neck obstruction with urinary tract infection and irreversible acute renal failure.	Postrenal
Creatinine value of 9.5 mg/dL at discharge without indication of renal disease in medical record. "Do not correlate" comment in laboratory file.	Laboratory error

colonoscopy. Twelve patients had other identifiable causes for postcolonoscopy renal dysfunction and were therefore excluded: seven had a likely prerenal cause for decreased GFR other than isolated cardiovascular decompensation after colonoscopy, one had a likely prerenal cause plus contrast medium application, three had a likely postrenal cause other than incident nephrolithiasis, and in one a very high creatinine value was identified as a laboratory error (Table 3). The remaining 88 patients were considered as cases of incident idiopathic renal impairment after colonoscopy. Seventy-nine patients had used oral sodium phosphate, and nine had used PEG, corresponding to 3.8% and 3.3% of the exposed patients in the study population, respectively. Of those, 50 patients had a GFR decrease of at least 20 mL/min, and 13 had at least a twofold increase in creatinine after colonoscopy. Looking at the further course of GFR, 36 cases did not have additional creatinine determinations within 6 months postcolonoscopy, and in 31 patients, GFR returned to >60 mL/min. In 21 cases, GFR remained <60 mL/min, and out of those, 17 had used sodium phosphate and four had used PEG, *i.e.*, 21.5% of the 79 cases who had used sodium phosphate *versus* 44.4% of the nine cases who had used PEG.

Baseline characteristics and unadjusted RR for impaired renal function after colonoscopy in relation to these factors are presented in Table 4. As shown, age ≥65 yr, African-American race, low baseline GFR, hypertension, and the use of angiotensin converting enzyme (ACE) inhibitors, angiotensin-renin blockers, or thiazide diuretics showed a significant univariate association with renal impairment. In contrast, the use of oral sodium phosphate was not associated with renal impairment when compared with PEG.

Adjusted RR estimates are presented in Table 5. Regardless of whether conventional logistic regression or propensity score methodology was used to control confounding, adjusted RR estimates were very similar to the unadjusted RR (Table 4) and indicated a comparable risk of renal impairment after the use of sodium phosphate or PEG. Restriction of the analysis to the 50 cases with a decrease in GFR of at least 20 mL/min after colonoscopy resulted in very similar RR estimates. The data did not provide evidence for effect modification of the RR by decreased baseline GFR, age ≥65 yr, or use of ACE inhibitors, angiotensin-renin blockers, or diuretics (RR after stratification over bowel preparation agent were similar to each other and to the combined estimates). Also, adjustment for differences in the latency time from colonoscopy to creatinine determination did not alter the risk estimates.

DISCUSSION

Reports of acute renal failure after bowel preparation with sodium phosphates have raised concern about its safety (1–6). Nephrocalcinosis was found in renal biopsies in some of these patients (1, 2, 4, 6), and it has been shown that oral sodium phosphates used for bowel preparation can lead to hypovolaemia, hyperphosphataemia, and hypocalcaemia with a subsequent increase in the calcium-phosphorus solubility product (13–18). Although these findings provide a plausible mechanistic hypothesis for the development of acute and chronic renal injury associated with sodium phosphate, the public health implication of this safety signal is unclear. Because spontaneous reports allow no quantification of the risk,

Table 4. Risk of Impaired Renal Function After Colonoscopy in Relation to Selected Factors

Factors	Patients With Factor and With Impaired Renal Function* N	Risk[†a]	Patients Without Factor and With Impaired Renal Function* N	Risk[†b]	RR[‡]	(95% CI)
Sodium phosphate use	79	3.8%	9	3.3%	1.13	(0.58–2.23)
Female	55	4.2%	33	3.1%	1.36	(0.89–2.08)
Age ≥65 yr	60	6.4%	28	2.0%	3.23	(2.08–5.03)
African-American race	70	4.3%	18	2.5%	1.70	(1.02–2.83)
Inpatient colonoscopy	6	2.0%	82	4.0%	0.51	(0.22–1.15)
GI bleeding 30 days prior to colonoscopy	10	3.1%	78	3.8%	0.82	(0.43–1.57)
Hospitalization 12 months prior to colonoscopy	10	1.8%	78	4.4%	0.41	(0.21–0.79)
GFR ≥60 and <90 mL/min	74	6.5%	14	1.2%	5.60	(3.18–9.86)
Comorbidities[§]						
Hypertension	73	5.0%	15	1.7%	2.99	(1.73–5.19)
Diabetes mellitus	25	4.4%	63	3.5%	1.23	(0.78–1.94)
Congestive heart failure	7	6.1%	81	3.6%	1.70	(0.80–3.59)
Liver cirrhosis	0	0%	88	3.8%	–	–
Charlson index ≥2	20	3.5%	68	3.8%	0.90	(0.55–1.47)
Current drug therapy[¶]						
ACE inhibitors	28	6.0%	60	3.2%	1.90	(1.23–2.95)
Angiotensin-renin blockers	10	9.3%	78	3.5%	2.69	(1.43–5.05)
Loop diuretics	4	3.2%	84	3.8%	0.84	(0.31–2.26)
Thiazide diuretics	31	6.8%	57	3.0%	2.26	(1.47–3.45)
Beta blockers	17	3.6%	71	3.8%	0.95	(0.57–1.60)
Calcium channel blockers	23	5.3%	65	3.4%	1.57	(0.99–2.50)
Nonsteroidal antiinflammatories	19	3.8%	69	3.7%	1.03	(0.63–1.70)

*GFR <60 mL/min after colonoscopy and decrease from baseline before colonoscopy >10 mL/min;
[†a]Risk of impaired renal function in patients with factor; [†b]Risk of impaired renal function in patients without factor.
[‡]Unadjusted relative risk (RR) of impaired renal function after colonoscopy for presence *versus* absence of factor;
[§]Diagnoses within 12 months prior to colonoscopy;
[¶]Prescriptions within 3 months prior to colonoscopy.

and the risk of renal impairment has not been studied in a large number of patients in a clinical practice setting, it is unknown whether severe cases reported in the literature may only be the "tip of the iceberg." Further, sodium phosphates may also increase the risk of chronic subclinical renal impairment in clinical practice. On the other hand, previous clinical trials comparing sodium phosphates with PEG in patients without preexisting renal disease demonstrated sodium phosphate's equal or superior tolerability and efficacy as well as its safety (19).

Our study, therefore, aimed to clarify whether impaired renal function after colonoscopy with oral sodium phosphates or PEG is an underrecognized problem in clinical practice, and what risk factors may play a role. In addition, we wanted to evaluate whether renal function is monitored before and after colonoscopy, and whether the use of oral sodium phosphates for bowel preparation complies with the labeled restrictions in clinical practice, which can only be addressed by an observational study in a clinical practice setting.

Table 5. Absolute Numbers and Unadjusted Absolute Risk of Incident Impaired Renal Function After Colonoscopy, and Adjusted Odds Ratios Estimating the Risk of Renal Impairment Associated With Sodium Phosphate *versus* Polyethylene Glycol

	All Patients (N)	Patients With Impaired Renal Function* (N)	(%)	Adjusted Odds Ratio Using Conventional Logistic Regression[†] (95% CI)	Adjusted Odds Ratio Using Propensity Score Based Logistic Regression[‡] (95% CI)
Polyethylene glycol	269	9	3.3	1.0 (ref)	1.0 (ref)
Sodium phosphate	2,083	79	3.8	1.07 (0.51–2.23)	1.14 (0.55–2.39)

*GFR <60 mL/min after colonoscopy and decrease from baseline before colonoscopy >10 mL/min;
[†]Adjusted odds ratios (OR) and 95% confidence intervals (CI) estimated from a logistic regression model with the following covariates: age, sex, African-American race, hospitalization within 12 months prior to colonoscopy, hypertension, baseline GFR ≥60 and <90 mL/min, and current use of angiotensin-converting enzyme inhibitors, angiotensin-renin blockers, thiazide, or loop diuretics;
[‡]Propensity score predicting the likelihood of use of polyethylene glycol or sodium phosphate, conditional on all covariates listed in Table 3 (age entered as a continuous variable), as a covariate in a logistic regression model. Results when propensity score was used to stratify subjects into five approximately equal-sized strata, followed by Mantel-Haenszel analysis were almost identical (OR 1.14, 95% CI 0.56–2.30).

In the base population of all patients who underwent colonoscopy and used sodium phosphate (Phospho-soda®) or PEG (COLYTE®), we found a large number of patients with preexisting renal disease, *i.e.,* patients undergoing renal dialysis, patients with a clinical diagnosis of acute or chronic renal failure, and/or a GFR <60 mL/min. More than half of all PEG users (56%) had such renal diseases within 12 months prior to colonoscopy. This high proportion is not unexpected because use of sodium phosphate is not recommended in patients with serious renal diseases, and PEG is a possible alternative. Nevertheless, 15% of all patients using sodium phosphate also had renal diseases within the preceding 12 months. In addition, the baseline renal function was apparently not determined in 17.6% of sodium phosphate users; and in 22% of all users of sodium phosphate, the last GFR before colonoscopy was <90 mL/min, but renal function was apparently not monitored thereafter. Although at least the higher use of PEG in 2005 is likely to be related to an increased awareness that sodium phosphate is not recommended in patients with renal dysfunction, these results indicate a major discrepancy between its use in clinical practice and the manufacturer's recommendations regarding restricted use and monitoring of renal function before and after colonoscopy in patients at risk of renal dysfunction.

In the study population of patients without preexisting renal dysfunction, the unadjusted as well as the adjusted RR of renal impairment after colonoscopy were similar in users of sodium phosphate as compared to PEG users. The similarity between the unadjusted and the adjusted RR estimates using two different methods supports the robustness of our results regarding the assumptions of regression modeling and indicates that the use of sodium phosphate is safe if labeled contraindications and precautions are followed. The reason for the restriction to patients without preexisting renal disease and the focus on "idiopathic" renal impairment was that we wanted to exclude patients in which the use of oral sodium phosphate is not recommended. More importantly, particularly in an observational study, it would have been virtually impossible to differentiate whether a further decrease in renal function after colonoscopy would be most likely related to bowel preparation, or merely reflect a "natural" progression of the preexisting renal disease. Further, differences in the incidence of renal impairment between users of oral sodium phosphate and PEG would have been confounded by the preferential use of PEG in patients with preexisting renal disease, and restriction is the most powerful and robust method to control for confounding in this situation. We also excluded patients without creatinine determination after colonoscopy, because we would not have been able to evaluate the incidence of subclinical chronic kidney injury in these patients. Because we excluded patients without creatinine measurements, we note that there may have been some selection towards patients with a particular concern about renal impairment in our study population. It is therefore likely that the absolute risk of renal impairment was overestimated in our study population as compared to the base population. However, the necessary selection of patients with creatinine determinations was applied to both PEG and sodium phosphate users, and therefore does not necessarily introduce bias when comparing these two cohorts. At the same time, it is unlikely that this exclusion would have prevented the detection of clinically significant renal disease, because a clinical diagnosis would likely have been recorded and creatinine been determined in such a situation.

The current study also identified risk factors of incident moderate or severe renal dysfunction after colonoscopy. Preexisting mild renal impairment, high age, African-American race, and hypertension were univariate predictors of renal impairment after colonoscopy. Also, 42% of the patients with renal impairment after colonoscopy had a recent prescription for ACE inhibitors or angiotensin-renin blockers, as compared to 23% in noncases. Similarly, in 21 reported cases of renal failure after oral sodium phosphate use for bowel preparation, eight (38%) had used these drugs (1, 3). Use of thiazide diuretics was also associated with renal dysfunction in our study, and it is possible that drugs that affect fluid and electrolyte balance including compensatory mechanisms predispose to renal dysfunction after colonoscopy. Although these univariate risk factors may in part be causally related to each other, which prevents a reliable multivariate estimate of their independent effects, they can serve as useful indicators of an increased risk in clinical practice.

An important limitation of our study is the lack of a creatinine determination soon after colonoscopy in all patients. Transient decreases in GFR after colonoscopy may therefore not have been captured in some patients. However, time from colonoscopy to creatinine determination did not affect the RR estimate when added to the regression model, and therefore does not appear to be a significant source of bias in our study. Further, as it is in the case for all observational research, the possible effects of unknown or unmeasured confounders cannot be addressed. On the other hand, the current study also has important and unique strengths: (a) we present the first population-based data evaluating the use and renal safety of bowel preparation for colonoscopy in clinical practice, including a large number of oral sodium phosphate users; (b) all clinical information was continuously recorded, and diagnoses were confirmed by review of original patient records, which also confirmed the high quality of the HFHS patient database in general; (c) as mentioned above, although PEG is preferentially used in patients with preexisting renal disease, the exclusion of patients with preexisting severe renal dysfunction led to a similar proportion of patients with preexisting mild renal dysfunction in our comparison groups, and multivariate analysis with two different approaches provided additional control for possible indication bias.

In summary, our results indicate that, in patients with no or only mild preexisting renal dysfunction, the risk of moderate or severe renal impairment after colonoscopy is not higher after use of oral sodium phosphate *versus* PEG, and this includes an evaluation of subclinical functional renal damage based on GFR estimates. The risk of severe irreversible renal impairment after colonoscopy appears to be very low in patients without preexisting renal disease. However, renal

failure with a probable causal relationship to sodium phosphate has been well documented in a small number of patients in the literature, most of which had risk factors that were also found in our study. Therefore, our study does not argue with the causation of impaired renal function in isolated cases, and this may particularly affect patients with insufficient hydration, diuretic treatment, and other risk factors. Indeed, our results suggest that such risk factors may particularly be an underrecognized problem in clinical practice, because we found that many patients with preexisting renal disease receive sodium phosphate without appropriate monitoring. Future studies may further look at this particular population. Therefore, it must be reemphasized that sodium phosphate should not be used in patients with moderate or severe renal impairment or in patients with congestive heart failure. In the presence of risk factors of renal dysfunction, sodium phosphate should be used cautiously, and this includes elderly patients and those taking drugs that affect fluid and electrolyte balance such as ACE inhibitors, angiotensin-renin blockers, and diuretics. Adequate hydration must be assured in all patients using bowel preparation agents, and renal function should be monitored before and after colonoscopy in those at risk of renal dysfunction.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Case reports of renal failure and nephrocalcinosis after use of oral sodium phosphates have raised safety concerns.
- The labeling of oral sodium phosphates has been updated and it recommends against using them in patients at risk of renal dysfunction.

What Is New Here

- The risk of renal impairment after colonoscopy was relatively low (<4%), and similar in users of sodium phosphates and PEG with a glomerular filtration rate (GFR) >60 mL/min.
- Contraindicated use of sodium phosphates by patients with impaired renal function is not uncommon in clinical practice.
- Renal function is frequently not determined before and not monitored after colonoscopy, even in patients with preexisting renal dysfunction.

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CONFLICT OF INTEREST

Guarantor of the article: Stefan Russmann, M.D., and Judith K. Jones, M.D., Ph.D.

Specific author contributions: Stefan Russmann and Judith K. Jones had full access to all study data and take responsibility for the integrity and accuracy of the data analysis; study concept and design: Judith K. Jones, Stefan Russmann, Lois Lamerato, Aditya Marfatia, and Gregory Olds; extraction of data: Lois Lamerato; case review: Stefan Russmann and Judith K. Jones; analysis and interpretation of data: Stefan Russmann, Judith K. Jones, Lois Lamerato, Aditya Marfatia, John C. Pezzullo, and Stephen P. Motsko; drafting of the manuscript: Stefan Russmann; critical revision of the manuscript: Stefan Russmann, Judith K. Jones, Lois Lamerato, Aditya Marfatia, John C. Pezzullo, Stephen P. Motsko, and Gregory Olds; statistical expertise: John C. Pezzullo, Stefan Russmann, and Stephen P. Motsko; and supervision: Judith K. Jones.

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