Genetic Susceptibility to Nonsteroidal Anti-Inflammatory Drug–Related Gastroduodenal Bleeding: Role of Cytochrome P450 2C9 Polymorphisms

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Background & Aims: Several nonsteroidal anti-inflammatory drugs (NSAIDs) are metabolized by the cytochrome P450 2C9 (CYP2C9). Two common variants of the CYP2C9 gene (CYP2C9*2 and *3) were reported to significantly affect the activity of the CYP2C9 enzyme. The aim of this study was to evaluate the impact of CYP2C9 polymorphisms on the risk of gastroduodenal bleeding in acute NSAID users. Methods: This case-control study included 26 patients with endoscopically documented NSAID-related gastroduodenal bleeding lesions and 52 age-, sex- and NSAID use–matched controls with no lesions at endoscopy. Both cases and controls were Helicobacter pylori negative and acute users of an NSAID or cyclooxygenase-2 inhibitor that undergoes CYP2C9 metabolism (ie, celecoxib, diclofenac, ibuprofen, naproxen, or piroxicam). Two marker single nucleotide polymorphisms in the CYP2C9 gene, identifying the CYP2C9 *2 and *3 allele, were evaluated in all subjects. Results: Setting the CYP2C9*1/*1 wild type as reference, significantly higher frequencies of CYP2C9*1/*3 (34.6% vs 5.8%; P < .001; odds ratio [OR], 12.9; 95% confidence interval [CI], 2.917–57.922) and CYP2C9*1/*2 (26.9% vs 15.4%; P = .036; OR, 3.8; 95% CI, 1.090–13.190) were identified in bleeding versus control patients, whereas no differences between bleeding and controls were observed in the distribution of CYP2C9*2/*3 heterozygotes. Considering allele carriers, the presence of CYP2C9*3 allele was associated with a significant high risk of bleeding (adjusted OR, 7.3; 95% CI, 2.058–26.004). Conclusions: CYP2C9 genotyping may identify subgroups of persons who potentially are at increased risk of gastroduodenal bleeding when treated with NSAIDs metabolized by CYP2C9. Further studies that evaluate the effectiveness of a strategy using CYP2C9 genotyping in NSAID users are needed before genotyping is introduced into clinical practice.

Gastroduodenal bleeding associated with the use of nonsteroidal anti-inflammatory drugs (NSAID) is the most frequent adverse drug reaction responsible for high rates of both hospitalization and mortality in Western countries. Several risk factors for NSAID-related gastroduodenal bleeding have been identified, including old age, a history of peptic ulcer disease, high dosages of NSAIDs, concomitant use of different NSAIDs, or a NSAID plus aspirin, steroids, or warfarin. Several NSAIDs, such as diclofenac, ibuprofen, naproxen, piroxicam, and the cyclooxygenase-2 selective inhibitor celecoxib are metabolized by the cytochrome P450 2C9 (CYP2C9). The gene coding for CYP2C9 carries numerous inherited single nucleotide polymorphisms in its coding sequence. Compared with the CYP2C9*1 wild type, the two most common variants of the CYP2C9 gene are CYP2C9*2, encoding for Arg144→Cys, and CYP2C9*3, encoding for Ile359→Leu amino acid substitutions in the CYP2C9 enzyme. Both in vitro and in vivo studies performed with NSAID substrates report that the variant CYP2C9*3 allele decreases enzyme activity to a significantly higher degree than does CYP2C9*2. An estimated 6% to 10% of whites have a CYP2C9*3 variant. An increased frequency of adverse drug reactions was observed in CYP2C9*3 carriers treated with warfarin and possibly phenytoin, whereas the clinical consequences, if any, of CYP2C9 polymorphisms on NSAID-related gastroduodenal bleeding are still undefined.
The aim of this study was to evaluate the impact of CYP2C9 polymorphisms on the risk of gastroduodenal bleeding in acute NSAID users.

Materials and Methods

Patients and Controls

This was a case-control study that involved acute NSAID users. It was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice and was approved by the local ethics committee. All patients gave their written informed consent before participation in the study.

All patients consecutively admitted from January 1, 2004, to December 31, 2005, to the Geriatric Unit of the Casa Sollievo della Sofferenza Hospital (Istituto di Ricovero e Cura a Carattere Scientifico, San Giovanni Rotondo, Italy) because of acute upper gastrointestinal bleeding were screened for study inclusion. At baseline the following demographic and clinical indicators were collected by structured interview, clinical evaluation, and review of records from the patients’ general practitioners: date of birth, sex, clinical history, current pathologies, and medication history. The inclusion criteria for patients were (1) diagnosis of upper gastrointestinal tract bleeding based on the presence of symptoms (hematemesis, melena, or anemia with a loss of >3 g hemoglobin) and endoscopic stigmata of a recent hemorrhage defined according to Laine and Peterson\(^9\) as a flat pigmented spot (red, purple, brown, or black), an adherent clot, a visible vessel, or active bleeding; (2) short duration (ie, <1 month) of treatment with an NSAID that undergoes CYP2C9 metabolism (ie, celecoxib, diclofenac, ibuprofen, naproxen, or piroxicam).\(^4\) Patient exclusion criteria were as follows: (1) bleeding from esophageal varices; (2) coagulation diseases; (3) upper gastrointestinal neoplasia; (4) the presence of Helicobacter pylori infection as evaluated by gastric histology, the rapid urease test, the \(^13\)C-urea breath test, or a combination; (5) chronic use of NSAIDs; (6) acute or chronic use of aspirin; (7) concomitant use of gastroprotective drugs (ie, proton pump inhibitors), histamine 2 blockers, or misoprostol; and (8) to avoid potential competition in drug metabolism, concomitant use of other drugs extensively metabolized by CYP2C9 (ie, the oral antidiabetics tolbutamide and glipizide, the antihypertensive irbesartan and losartan, phenytion, sildenafl, terbinafine, and warfarin).\(^5\)

Control patients were selected from all patients consecutively admitted to our unit during the study period who (1) were acute (ie, <1 month) NSAID users, (2) underwent an upper gastrointestinal endoscopy without gastroduodenal lesions, and (3) fulfilled the same exclusion criteria as bleeding cases (ie, \(H\) pylori negative, no use of aspirin, gastroprotective drugs, or other drugs metabolized by CYP2C9). From this population, subjects who consecutively matched with bleeding cases for age (±3 years), sex, and NSAID use were enrolled as controls. The selection was performed as 2 controls versus 1 bleeding case.

Drug Use and Comorbidity

Drug use was evaluated at the time of endoscopy during a structured interview of patients, their relatives, or both and by retrospective data collection from patients’ files. Drug use was identified according to the Anatomical Therapeutics Chemical Classification code system.\(^10\) In this system, drugs are divided into 14 main anatomical groups, each then further divided into 2 sublevels: therapeutic and pharmacologic. During the interview, the names of specific drugs were recorded as well as the doses, the use patterns (acute, chronic, on demand), and the duration of treatment. Patients were defined as acute NSAID users if they had taken a drug of this class sporadically (on an as-needed basis) or regularly for a period >7 days and <30 days before endoscopy.\(^11\) Patients who were taking NSAIDs regularly for a period >1 month were defined as chronic users and were excluded from the study. Patients who were taking >1 NSAID concomitantly were defined as acute users if at least one of the drugs was taken acutely as defined previously.

Gastroprotective therapy was defined as treatment with a histamine 2 blocker (ranitidine at a dose of 150–300 mg/day or famotidine at a dose of 20–40 mg/day) or a proton pump inhibitor (omeprazole at a dose of 10–20 mg daily, lansoprazole at a dose of 15–30 mg daily, pantoprazole at a dose of 20–40 mg daily, rabeprazole at a dose of 10 to 20 mg daily, or esomeprazole at a dose of 20–40 mg daily) or misoprostol at a dose of 400–800 \(\mu\)g daily for >7 days before endoscopy.

Comorbidity was examined using the Cumulative Illness Rating Scale (CIRS).\(^12\) The CIRS uses 5-point ordinal scales (score 1–5) to estimate the severity of disease in each of 13 systems, including cardiac, vascular, respiratory, eye-ear-nose-throat, upper and lower gastrointestinal diseases, hepatic, renal, genitourinal, musculoskeletal, skin disorders, nervous system, endocrine-metabolic, and psychiatric or behavioral problems. On the basis of the ratings, the 2 following scores are derived: (1) the CIRS–Comorbidty Index (CIRS-CI) score, which reflects the number of concomitant diseases, and is derived from the total number of categories in which moderate or severe levels (grades, from 3 to 5) of disease are quoted (range, from 0 to 13); and (2) the CIRS–Severity Index, which reflects the overall severity of diseases and the average rating of 13 disease categories, excluding psychiatric or behavioral problems (range, from 1 to 5).

Endoscopy and \(H\) pylori Infection

Endoscopic diagnoses for esophageal, gastric, and duodenal lesions were based on the Cotton and Williams criteria.\(^13\) Bleeding of the upper gastroduodenal tract was diagnosed on the basis of symptoms (hematemesis, me-
lenta, or anemia with a loss of >3 g hemoglobin) and endoscopic stigma of a recent hemorrhage defined according to Laine and Peterson \(^9\) as a flat pigmented spot (red, purple, brown, or black), an adherent clot, a visible vessel, or active bleeding.

During endoscopy, gastric biopsies were taken from both the antrum and from the body. Two antral and two body biopsies were used for histologic analysis, and one from each site was used for the rapid urease test (CLO test; Delta West Pty Ltd, Western Australia). For histologic examination, biopsy specimens were immediately fixed in buffered neutral formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin and modified Giemsa for the detection of \(H. pylori\) and evaluated according to the Sydney classification. \(^14\) In 5 patients of the bleeding group gastric biopsies were not taken during endoscopy. In those patients the presence of \(H. pylori\) infection was evaluated by means of the \(^13\)C-urea breath test performed according to standard method. \(^15\) Patients were considered \(H. pylori\) negative if both histology and the rapid urease test were negative; patients were considered \(H. pylori\) positive if one the tests (ie, histology, rapid urease test, or the \(^13\)C-urea breath test) was positive for \(H. pylori\) infection. \(^16\)

**Genetic Analyses**

From all subjects included in the study, genomic DNA was obtained from peripheral blood leukocytes according to standard methods and processed twice in blinded fashion in different laboratories. The CYP2C9 alleles were identified according to the Human Cytochrome P450 Allele Nomenclature Committee. \(^3\) The 2 single nucleotide polymorphisms rs1799853 (C\(^{450}\)→T) identifying the CYP2C9*2 allele and rs1057910 (A\(^{1075}\)→C) identifying the CYP2C9*3 allele were detected by restriction fragment length polymorphism analysis as previously described. \(^17\) Briefly, genotyping of the CYP2C9*2 allele was performed by digestion of polymerase chain reaction (PCR) products with the AvaII endonuclease as previously described. \(^18\) The CYP2C9*3 allele was identified by PCR by using a forward primer (5’-CAGCTGAAGTCCAGGAAGAGAT-3’) and a mutated reverse primer (5’-AGGGCTGGTGGGAGAGGTCCC-3’), which inserts a site for the SmlI enzyme. PCR was performed on 25-μL volume samples, in an Applied Biosystem GeneAmp PCR System 9700 thermal cycler (Applied Biosystem, Foster City, CA). Each sample contained 0.5 μg of genomic DNA, 15 pmoles of each primer, 100 mmol/L dNTP, 10 mmol/L Tris HCl pH 8.3, 50 mmol/L KCl, 1.5 mmol/L MgCl2, and 1 U thermostable Taq polymerase. The 30 cycles consisted of steps at 95°C for 1 minute, at 60°C for 50 seconds, and at 72°C for 1.5 minutes. Then, 15-μL volumes of the amplification products were digested for 5 hours at 37°C with 2 U SmlI restriction enzyme. The fragments were fractionated by 3.0% agarose-gel electrophoresis, and visualized under UV light.

As genetic control, the analyses of 2 common polymorphisms in genes unrelated to NSAID treatment, (ie, the apolipoprotein E [APOE] and angiotensin-converting enzyme [ACE]), were performed according to methods previously described. \(^19,20\) No differences were observed between bleeding and controls in frequencies of the APOE genotypes \((P = .514; ie, 0.04 [e2/e2], 0.04 [e2/e3], 0.04 [e2/e4], 0.77 [e3/e3], 0.12 [e3/e4] vs 0.10 [e2/e3], 0.04 [e2/e4], 0.69 [e3/e3], and 0.17 [e3/e4], respectively) and the ACE genotypes \((P = .418; ie, 0.04 [I/I], 0.50 [I/D], and 0.46 [D/D] vs 0.13 [I/I], 0.44 [I/D], and 0.42 [D/D], respectively). The Hardy-Weinberg equilibrium was satisfied in both bleeding and controls for APOE \((P = .104 and P = .458, respectively) and ACE loci \((P = .357 and P = .761, respectively).

**Statistical Analysis**

The estimated minimum number of both cases and controls required for detecting a significant association among the CYP2C9 genotypes and bleeding (ie, an odds ratio >2), \(^21\) assuming a statistical significance at the 5% level and a statistical power of 80%, was 26. The analysis showed an effect size of 0.771 and a statistical power of 0.894. The Hardy-Weinberg equilibrium was confirmed by means of the R Statistical Software Package version 2.4.1 (The R Project for Statistical Computing; http://www.r-project.org/).

Hypotheses regarding differences between groups were tested using Fisher’s exact test for dichotomous variables and the Mann–Whitney U test for continuous variables. Relative allelic frequencies were calculated by the gene counting method. \(^22\) The Pearson \(χ^2\) test was used for genotype/allele/allele-carrier frequency tables. Binary logistic regression analysis was used to estimate crude odds ratios (ORs) and the 95% confidence intervals (95% CI) in testing for possible association between the genotype/allele-carrier and bleeding. In the analysis, co-morbidity (CIRS-CI) was also evaluated as confounding factor. All statistical analyses were made with the R statistical software package, version 2.4.1. Tests in which the \(P\) value was smaller than the Type I error rate of .05 were declared significant.

**Results**

During the 2-year inclusion period, 78 patients with a diagnosis of NSAID-related upper gastrointestinal bleeding were consecutively admitted to our unit and screened for inclusion in the study. Fifty-two patients were excluded because they were \(H. pylori\) positive (21 patients [group 1]) or they were chronic users of NSAIDs (14 patients [group 2]), or they were taking gastroprotective drugs (15 patients [group 3], including 7 patients who were treated chronically with NSAIDs) or other drugs extensively metabolized by CYP2C9 (9 patients
Thus, the final study population included 26 bleeding patients as cases (9 men and 17 women, mean age 74.2 ± 7.8 years, range from 60 to 85 years) with endoscopically documented gastroduodenal bleeding after recent NSAID use. For the control group, 52 age- (±3 years), sex-, and NSAID-matched subjects (18 men and 34 women, mean age 74.4 ± 10.9 years, range from 60 to 88 years) were identified from a population of 116 patients consecutively admitted to our unit who were acute users of NSAIDs and who had a negative upper gastrointestinal endoscopy. The ethnic origin of all patients and controls was from the Northern Apulia Region.

Table 1 shows clinical characteristics of patients and controls. The following CYP2C9-metabolized NSAIDs were taken by bleeding patients (cases) and controls: celecoxib (5 cases and 10 controls), diclofenac (11 cases and 22 controls), ibuprofen (3 cases and 6 controls), naproxen (2 cases and 4 controls), piroxicam (5 cases and 10 controls). Endoscopic diagnoses in 26 bleeding patients were gastric ulcer (7 patients), duodenal ulcer (8 patients) and erosive gastritis (11 patients).

Setting the CYP2C9*1/*1 wild type as the reference category, significantly higher frequencies of the CYP2C9*1/*3 (34.6% vs 5.8%, \( P \leq .001 \)) and CYP2C9*1/*2 (26.9% vs 15.4%, \( P = .036 \)) genotypes were found in bleeding versus control patients (Table 2). No significant differences between bleeding and control patients were observed regarding the distribution of the heterozygotes CYP2C9*2/*3 (3.8% vs 3.8%, \( P = .546 \)). The CYP2C9*1/*3 and CYP2C9*1/*2 genotypes were significantly associated

| Table 1. Clinical Characteristics of Patients and Controls at Baseline |
|-------------------------|-----------------|-----------------|
| Variable                | Bleeding (n = 26) | Controls (n = 52) | \( P \) value for bleeding vs control |
| Sex (M/F), n            | 9/17            | 18/34           | .801            |
| Age (y), mean ± SD      | 74.2 ± 7.8      | 74.4 ± 10.9     | .934            |
| Age (y) range           | 60–85           | 60–88           | —               |
| Previous GI tract disorders, n (%) | 2 (7.8) | 2 (3.8) | .839 |
| Concomitant drugs (n), mean ± SD | 4.7 ± 2.3 | 4.3 ± 2.3 | .471 |
| Subjects taking concomitant drugs | | | |
| Antihypertensive drugs (%) | 50.0 | 40.4 | .573 |
| Cardiac therapy, cardiac glycoside (%) | 11.5 | 5.8 | .660 |
| Psycholeptics (%) | 7.7 | 7.7 | .652 |
| Insulins and analogues (%) | 15.4 | 9.6 | .704 |
| Cumulative Illness Rating Scale | | | |
| No. of moderate-severe concomitant diseases, mean ± SD | 2.3 ± 1.0 | 2.5 ± 1.6 | .562 |
| Mean severity score, mean ± SD | 1.5 ± 0.2 | 1.5 ± 0.3 | 1.000 |
| NSAIDs taken by patients and controls | | | |
| Celecoxib, n          | 5               | 10              | —               |
| Ibuprofen, n          | 3               | 6               | —               |
| Diclofenac, n         | 11              | 22              | —               |
| Naproxen, n           | 2               | 4               | —               |
| Piroxicam, n          | 5               | 10              | —               |
| Reasons for NSAID treatment | | | |
| Osteoarthritis pain, % | 80.8 | 76.9 | .918 |
| Oncologic pain, %     | 7.7             | 15.4            | .489            |
| Neurologic pain, %    | 11.5            | 7.7             | .894            |

Gi, intestinal; NSAID, nonsteroidal anti-inflammatory drug.
Angiotensin-converting enzyme inhibitors and diuretics.
Benzodiazepines (Anatomical Therapeutics Chemical Classification code, N05BA).

Table 2. Observed Genotypes at the CYP2C9 Locus in Bleeding Patients and Controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Bleeding (a) (n = 26)</th>
<th>Controls (b) (n = 52)</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>n (%)</td>
<td>( P ) value</td>
<td>OR</td>
</tr>
<tr>
<td>CYP2C9*1/*1</td>
<td>9 (34.6)</td>
<td>39 (75.0)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CYP2C9*1/*2</td>
<td>7 (26.9)</td>
<td>8 (15.4)</td>
<td>0.036</td>
<td>3.8</td>
</tr>
<tr>
<td>CYP2C9*1/*3</td>
<td>9 (34.6)</td>
<td>3 (5.8)</td>
<td>0.001</td>
<td>12.9</td>
</tr>
<tr>
<td>CYP2C9*2/*3</td>
<td>1 (3.8)</td>
<td>2 (3.8)</td>
<td>0.546</td>
<td>2.2</td>
</tr>
</tbody>
</table>

NOTE. Adjusted analysis was performed including comorbidity (Cumulative Illness Rating Scale–Comorbidity Index) as a confounding factor. OR, odds ratio; CI confidence interval.

\( a \)Hardy-Weinberg equilibrium, \( P = .496 \).
\( b \)Hardy-Weinberg equilibrium, \( P = .276 \).
with a higher risk of NSAID-related gastroduodenal bleeding (odds ratio [OR], 12.9; 95% confidence interval [CI], 2.917–57.922 and OR, 3.8; 95% CI, 1.090–13.190, respectively), whereas the presence of the genotype CYP2C9*2/*3 was not significantly associated with a risk of bleeding (OR, 2.2; 95% CI, 0.177–26.592). No CYP2C9*2/*2 or CYP2C9*3/*3 homozygotes were found in patients or control subjects. No differences were observed when the analyses included comorbidity (CIRS-CI) as confounding factor (Table 2).

Considering the allele carriers, the presence of the CYP2C9*3 allele was associated with a significantly higher risk of bleeding (CIRS-CI adjusted OR, 7.3; 95% CI, 2.058–26.004), whereas no association between the CYP2C9*2 allele and risk of bleeding was observed in this population (CIRS-CI adjusted OR, 2.0; 95% CI, 0.634–6.317).

**Discussion**

This study provides evidence for a genetic susceptibility to NSAID-related gastroduodenal bleeding during a short-term treatment with CYP2C9-metabolized NSAIDs (ie, celecoxib, diclofenac, ibuprofen, naproxen, and piroxicam). For the study we selected only patients with endoscopically documented gastroduodenal bleeding lesions in the absence of confounding factors such as *H pylori* infection, concomitant therapies with other CYP2C9-metabolized drugs, or gastroprotective antisecretory therapies. Because in long-term NSAID users adaptation of the gastroduodenal mucosa might influence the prevalence of NSAID-related gastroduodenal lesions,24 we included only patients who were treated with a short course of NSAIDs (ie, <1 month). Age- and sex-matched controls were identified from NSAID users without endoscopically documented bleeding lesions. The Hardy-Weinberg equilibrium was also verified to exclude genetic bias. Indeed, the frequencies of 2 main genotypes in control subjects included in this study were comparable to the genotype distribution reported in the largest genotyping studies that included almost 1400 whites: 75.1% vs 65.3% for the wild-type CYP2C9*1/*1 and 15.4% vs 20.4% for the CYP2C9*1/*2.5 No homozygotes CYP2C9*2/*2 or CYP2C9*3/*3 were found in our population, in agreement with the low prevalences of 0.9% and 0.4%, respectively, reported previously in large studies.5

Our findings reported that, compared with the wild-type CYP2C9*1/*1, the CYP2C9*1/*3 and CYP2C9*1/*2 heterozygotes had a significant increased risk of NSAID-related gastroduodenal bleeding. Considering the allele carriers, our data showed that the CYP2C9*3 allele, and not the CYP2C9*2 allele, increased the risk of NSAID-related gastroduodenal bleeding compared with the wild-type CYP2C9*1. Reliability of this association was confirmed by the absence of significant differences in the distribution of genotype frequencies between bleeding cases and controls in genes unrelated to NSAIDs treatment, such as APOE and ACE polymorphisms.

This finding is in agreement with in vitro studies reporting that the Ile555→Leu amino acid substitution in the CYP2C9 enzyme (CYP2C9*3) confers a significantly greater reduction in metabolic activity than the Arg144→Cys (CYP2C9*2) amino acid substitution when diclofenac and flurbiprofen24 or piroxicam, tenoxicam, mefenamic acid, and diclofenac were used as substrates.25 Our findings are also in agreement with in vivo studies that reported a greater impairment in the pharmacokinetics of celecoxib, diclofenac, ibuprofen,28 lornoxicam,29 and piroxicam30 in persons carrying the CYP2C9*3 allele rather than carriers of the CYP2C9*2 allele. For naproxen and diclofenac, although in vitro data reported an extensive CYP2C9-dependent metabolism in human liver microsomes, about 40% to 50% and 80%, respectively, other studies suggest a minor role of CYP2C9 in the overall clearance of these NSAID,31 possibly because multiple CYP or non-CYP enzymatic systems may be involved in their metabolism32 or that unmeasured CYP2C9 alleles act as confounding factors.3

Interestingly, in our study the CYP2C9*3 allele seemed to increase the risk of NSAID-related bleeding only when the neutral wild-type CYP2C9*1, and not the functional allele CYP2C9*2, was present. This finding may be explained by a combined effect of gene variants in CYP2C9 and CYP2C8 genes. Because CYP2C9*2 is tightly linked to allele *3 in the related highly active enzyme CYP2C8, an increase in enzyme activity as a result of linkage with highly active variants of CYP2C8 could explain this phenomenon.33 Alternatively, the presence of CYP2C9 promoter variants (and variants in the 5'-flanking region of the human CYP2C9 gene),34 may explain a stronger reduction in enzyme activity in CYP2C9*1/*3 heterozygotes compared with CYP2C9*2/*3 compound heterozygotes or with CYP2C9*1/*1 wild type. As regards the CYP2C9*2/*3, however, given the great confidence interval (from 0.18 to 26.6) that could reflect an imprecise OR value rather than lack of association with bleeding, it is difficult to draw negative conclusions.

The study sample was limited to 26 cases and 52 controls. In an a priori sample-size estimation, we set the power of the study at ≥80%, and the post hoc calculated power was 89.4%. For this reason the findings of this study may be considered quite solid in suggesting an association of CYP2C9*1/*3 and CYP2C9*1/*2 with NSAID-related gastroduodenal bleeding.

The only published study that evaluated CYP2C9 polymorphisms in patients with NSAID-related gastrointestinal bleeding reported a significantly increased risk of bleeding in patients carrying the CYP2C9*2 allele, either in heterozygosis or homozygosis, and not the CYP2C9*3 allele.35 Different inclusion criteria for patients (patients were included who were not evaluated for *H pylori* infection and who were taking antisecretory drugs and NSAIDs not
metabolized by CYP2C9 such as salicylates or paracetamol) and controls (subjects who required NSAID therapy and did not undergo an endoscopy) probably account for the different results in genetic analyses.

In conclusion, the use of NSAIDs that undergo CYP2C9 metabolism should be used with caution in persons carrying the CYP2C9*1/*3 or CYP2C9*1/*2 mutations. This suggests that CYP2C9 genotyping may be useful in identifying the subgroup of persons who are at potentially greater risk of gastroduodenal bleeding when treated with NSAIDs metabolized by CYP2C9. Further studies that evaluate the effectiveness of a strategy using CYP2C9 genotyping in NSAID users are needed before genotyping is introduced into clinical practice. Because interethnic differences in the frequency of CYP2C9 variant alleles do exist, these findings cannot be extrapolated to persons other than whites.

References

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