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Cytochrome P450 2C9 Variants Influence Response to Celecoxib for Prevention of Colorectal Adenoma

Andrew T. Chan, M.D., M.P.H.[1,2], **Ann G. Zauber, Ph.D.**[3], **Meier Hsu, M.S.**[3], **Aurora Breazna, Ph.D.**[4], **David J. Hunter, M.B.B.S., Sc.D.**[2,4], **Rebecca B. Rosenstein, Ph.D.**[4], **Craig J. Eagle, M.D.**[4], **Ernest T. Hawk, MD, MPH**[5], and **Monica M. Bertagnolli, M.D.**[6]

1 *Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

2 *Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

3 *Memorial Sloan-Kettering Cancer Center, New York, NY*

4 *Pfizer, Inc., New York, NY, Department of Epidemiology, Harvard School of Public Health, Boston, MA*

5 *MD Anderson Cancer Center, Houston*

6 *Department of Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Abstract

Background & Aims—Variants in the cytochrome P450 2C9 (*CYP2C9*) gene are associated with impaired metabolism of celecoxib. We examined the influence of *CYP2C9*2 (R144C)* and *CYP2C9*3 (I359L)* variants on dose-related response or toxicity in a randomized trial of celecoxib.

Methods—We identified individuals with *CYP2C9*2* and *CYP2C9*3* genotypes (≥1 variant allele) in the Adenoma Prevention with Celecoxib trial. Following adenoma removal, patients were assigned randomly to groups given placebo or low-dose (200 mg, twice-daily) or high-dose (400 mg, twice-daily) celecoxib and underwent follow-up colonoscopies at 1 and/or 3 years.

Results—Among 1660 patients, 21% were *CYP2C9*2* and 12% were *CYP2C9*3* genotypes. Overall, celecoxib was associated with a dose-dependent reduction in adenoma, compared with placebo, with relative risks (RR) of 0.65 (0.56–0.76) for the low-dose and 0.54 (0.46–0.63) for the high-dose groups. However, the additional protective effect of the high dose, compared with the low dose, was observed only in those with *CYP2C9*3* genotypes (RR, 0.51; 0.30–0.87). The high dose, compared with low dose, was not associated with significant risk reduction among those with *CYP2C9*2* (RR, 0.83; 0.57–1.21) or wild-type (RR, 0.89; 0.72–1.11) genotypes. Compared with placebo, a higher incidence of cardiovascular events was associated with both doses among patients with wild-type genotypes, but only with the high dose among patients with variant genotypes.

Correspondence: Andrew T. Chan, MD, MPH, Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, GRJ-728A, Boston, MA 02114. Phone: 617 724 0283 Fax: 617 726 3673; Email: E-mail: achan@partners.org.

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Conclusions—The greater efficacy of high-dose celecoxib, compared with the low dose, in preventing colorectal adenoma appears confined to individuals with slow-metabolizer (*CYP2C9*3*) genotypes. Genetic variability influences susceptibility to the potential benefits and hazards of celecoxib.

Introduction

Although colorectal cancer can be effectively prevented through early detection and removal of precursor adenomatous polyps, suboptimal rates of population screening highlight the importance of investigating chemopreventative strategies.[1] Recently, two randomized, placebo-controlled, clinical trials have offered compelling evidence that the cyclooxygenase-2 (COX-2) selective inhibitor celecoxib reduces the risk of sporadic colorectal adenoma among patients with a prior history of adenoma.[2, 3] In the Adenoma Prevention with Celecoxib (APC) trial, patients who had recently undergone colonoscopic removal of an adenoma were randomly assigned to receive placebo, low-dose (200 mg twice daily) of celecoxib, or high-dose (400 mg twice daily) celecoxib and underwent follow-up colonoscopies at 1 and 3 years. The estimated cumulative incidence of the detection of one or more new adenomas by year 3 was 60.7 percent for patients receiving placebo, as compared with 43.2 percent for those receiving low-dose celecoxib (relative risk [RR], 0.67; 95% confidence interval [CI] 0.59–0.77; P<.001) and 37.5 perecent for those receiving high-dose celecoxib (RR, 0.55; 95% CI, 0.48–0.64; P<.001).[2] Unfortunately, in a separate, adjudicated safety analysis, the APC trial also revealed unexpected dose-related cardiovascular toxicity.[4]

The highly polymorphic cytochrome p450 enzyme isoform 2C9 (CYP2C9) is the principal enzyme responsible for the metabolism of several drugs, including some non-selective, non-aspirin NSAIDs, celecoxib, and warfarin.[5] A substantial body of *in vitro* and *in vivo* evidence demonstrated that the variant CYP2C9*3 allele (I359L), with an estimated prevalence among Causasians of 6%, is associated with impaired metabolism of these drugs.[5–13] The more common CYP2C9*2 (R144C) allele, with an estimated prevalence of 10% among Causasians, has also been associated with a less substantial reduction in enzyme activity in some,[5, 10, 11, 14, 15] but not all studies.[9, 12]

Because inter-individual variability in metabolism may influence both drug efficacy and safety, we examined the influence of CYP2C9 genetic variants on the effect of celecoxib in patients enrolled in the APC trial. Because the APC trial was a placebo-controlled, randomized trial examining both low-dose and high-dose celecoxib, we had a unique opportunity to examine the influence of CYP2C9 variant genotypes on celecoxib dosing and subsequent risk of both adenoma and adverse events.

Methods

Study Population

Patients were derived from the Adenoma Prevention with Celecoxib (APC) trial, (ClinicalTrials. gov NCT00005094) for which the methods and main results have been previously described in detail.[2] The flow of patients through the study is summarized in the Figure. In brief, the APC trial was a randomized, placebo-controlled trial designed to examine the effect of celecoxib on occurrence of endoscopically detected adenomas among patients who had undergone colonoscopic removal of all colorectal adenomas within 6 months of study entry and had a high risk of recurrent adenomas on the basis of a history of either multiple adenomas or removal of a single adenoma more than 5 mm in diameter. 2,035 patients were randomly assigned to placebo, 200 mg of celecoxib twice daily (low-dose), or 400 mg of celecoxib twice daily (high-dose). Randomization was stratified on the basis of the use or

nonuse of low-dose aspirin (325 mg or less every other day or 162.5 mg or less every day) and clinical site. Further details about the trial are available in the supplementary materials.

The APC trial was sponsored by the National Cancer Institute and Pfizer Inc through a clinical trials agreement. All patients provided written informed consent before enrollment and the study protocol was approved by the human subjects committee at each study site.

Outcome Ascertainment

A study investigator performed follow-up colonoscopies with endoscopic removal of polyps at one and three years after randomization. A central study pathologist examined, in a blinded fashion, all polyps removed during these colonoscopies. Adverse events were reported by investigators and classified according to criteria from the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1.

Genotyping

Among the 2,035 patients who were enrolled in the study, 1,707 patients at the baseline exam provided a blood specimen suitable for separation into components, which was subsequently stored at −70°C in a central tissue bank. All patients who provided specimens provided separate, informed consent and a genotyping study protocol was approved by the Human Subjects Committee at Partners Healthcare. All genotyping was performed, in a blinded fashion, at the Dana-Farber Harvard Cancer Center High Throughput Polymorphism Detection Core on de-identified patient samples using previously described methods (see supplementary materials for details).[16] Among the 1707 patients, genotyping was unsuccessful for the *2 allele in 15 patients, for the *3 allele in 14 patients, and for both alleles in 18 patients. These patients were subsequently excluded from the analysis. We inserted blinded quality control samples equal to 10% of the total number of samples to validate genotype identification procedures; concordance for these samples was 100%. As in our previous study,[16] we further validated our genotyping quality by examining Hardy-Weinberg equilibrium among the non-Hispanic White patients who did not develop an adenoma over follow-up. Using the χ^2 goodness-of-fit test, the genotype distribution was in Hardy-Weinberg equilibrium for the *2 allele (p=.86) and *3 allele (p=.99).

Statistical Analysis

Consistent with the primary efficacy analyses,[2] we used the detection of an adenoma during a post-randomization colonoscopy, regardless of whether the patient adhered to the treatment regimen, as the primary endpoint. We used the Mantel-Cox test, which is a life-table extension of the Mantel-Haenszel statistic, with stratification for aspirin use or nonuse, sex, and age (<65 vs. ≥65 years). The Mantel-Cox procedure also provides a summary risk ratio, which is the weighted average of the relative risk over the two intervals and across strata of aspirin use, sex, and age. Patients with no follow-up colonoscopy (n=163) were excluded from both follow-up intervals. A patient with a colonoscopy at year 3 but with no colonoscopy at year 1 was included in the analysis through year 1, with the assumption that the patient had no adenoma at year 1, and was then included in the analysis through year 3 according to the findings of the colonoscopy at year 3. The analyses at year 3 excluded patients with an adenoma at year 1 colonoscopy and patients with no adenoma at year 1 and no colonoscopy at year 3. According to methods of Kaplan-Meier, three-year cumulative incidences were calculated and patients at risk at each timepoint were those without previously detected adenomas.

Investigator-reported adverse events were analyzed according to prespecified categories to describe cardiovascular and thrombotic disorders, renal and hypertensive disorders, and gastrointestinal ulceration and hemorrhage. The analyses included all events occurring after the first dose of study medication and up to 30 days after the last dose of study medication,

including events among patients who continued study medication in the 24 month extension study. The outcome of an adverse event was based on a time-to-event analysis, and a Cox proportional hazards model adjusting for low-dose aspirin use was used to estimate the relative risk.

Among the 1660 patients successfully genotyped, 1102 had no variant *2 or *3 alleles (wild-type/wild-type), 346 had one *2 allele (wild-type/*2), 78 had one *3 allele (wild-type/*3), 17 had one *2 allele and one *3 allele (*2/*3), 11 had two *2 alleles (*2/*2), and 6 had two *3 alleles.(*3/*3) Consistent with prior studies, we defined patients with wild-type genotypes as having no *2 or *3 alleles (wild-type/wild-type), patients with CYP2C9*2 genotypes as having ≥ one *2 allele (wild-type/*2 or *2/*2), and patients with CYP2C9*3 genotypes as having ≥ one *3 allele (wild-type/*3 or *3/3).[11, 16, 17] The 17 patients with one *2 allele and one *3 allele were defined as CYP2C9*3 genotypes. The genotype groups were assessed for differences in baseline characteristics using analysis of variance for continuous variables and Chi-squared tests for categorical variables. To test whether the dose effect differed between genotype groups, we used the Cox proportional hazards model with ties handled by the exact method, which assumes that ties arise from grouping continuous, untied data. A linear contrast was constructed from coefficients of this model to assess whether the CYP2C9*2 or CYP2C9*3 genotype was different from wild-type genotype with respect to risk reduction associated with dose. The statistical significance of this contrast was obtained using the Wald method.[18, 19] We used the SAS version 9.1 (SAS institute, Cary, NC) for all analyses. All P values are two-sided.

Results

Among the 2,035 patients who were randomly assigned to treatment, 1,707 (84%) provided a suitable blood specimen for genotyping and 1660 (97%) of these patients were successfully genotyped (Figure). Overall, 1,102 (66%) had wild-type genotypes, 357 (21%) had CYP2C9*2 genotypes (≥ one *2 allele) and 201 (12%) had CYP2C9*3 genotypes (≥ one *3 allele). Baseline characteristics were largely similar according to genotype (Table 1). Variant genotypes were more frequently observed in non-Hispanic whites, consistent with other studies,[20] as well as in users of low-dose aspirin and patients with a prior history of hypertension.

We first examined the main effect of CYP2C9 genotype on adenoma risk. The estimated cumulative incidence through the year 3 colonoscopy of one or more adenomas according to genotype is provided in Table 2. Although there was some evidence of an overall association of the CYP2C9*2 genotype with adenoma risk, this appeared to be confined to the subgroup of patients who were taking low-dose aspirin (RR, 1.44; 95% CI, 1.14–1.81) and was not evident among patients who were randomly assigned to placebo (RR, 1.17; 95% CI, 0.96–1.43). The CYP2C9*3 genotype did not appear to be independently associated with adenoma risk across all subgroups.

Because genotype is associated with celecoxib metabolism, we then investigated the influence of celecoxib on risk of adenoma according to CYP2C9 genotype (Table 3). For patients of all genotypes, the estimated cumulative incidence of one or more adenomas by year 3 was 60.5% for those receiving placebo, as compared with 42.5% for those receiving low-dose (200 mg twice daily) celecoxib (RR, 0.65; 95% CI, 0.56–0.76; P<.001) and 36.9% for those receiving high-dose (400 mg twice daily) celecoxib (RR, 0.54; 95% CI, 0.46–0.63; P<.001), consistent with the primary analysis of the trial.[2] Within each subgroup defined by genotype, both low-dose and high-dose celecoxib was associated with a lower risk of adenoma compared with placebo.

To specifically examine the influence of genotype on celecoxib dose and adenoma risk, we compared the cumulative incidence of adenoma among the group receiving high-dose celecoxib with the group receiving low-dose celecoxib **(**Table 3). Among all genotypes, high-dose celecoxib was associated with a 5.6% greater reduction in 3-year cumulative incidence of adenoma compared with low-dose celecoxib (RR, 0.82; 95% CI, 0.69–0.98; P=.03). However, the effect of dose appeared to be confined to patients with CYP2C9*3 genotypes. Among individuals with CYP2C9*3 genotypes, high-dose celecoxib was associated with a 19.7% greater reduction in cumulative incidence of adenoma compared with low-dose (RR, 0.51; 95% CI, 0.30–0.87; P=.01). In contrast, compared with low-dose celecoxib, high-dose was associated with a 5% reduction in cumulative incidence of adenoma (RR, 0.83; 95% CI, 0.57–1.21, P=.33) among those with CYP2C9*2 genotypes and a 2.9% reduction in cumulative incidence of adenoma (RR, 0.89; 95% CI, 0.72–1.11; P=.31) among those with wild-type genotypes. A formal test of whether the increased risk reduction of higher dose treatment differed between the CYP2C9*3 genotype compared to wildtype genotype approached statistical significance (P=.09).

Although the number of events was limited, we conducted an exploratory analysis examining the influence of CYP2C9 genotype on investigator-reported adverse events associated with celecoxib treatment. We focused on cardiovascular and thrombotic disorders, renal and hypertensive disorders, and gastrointestinal ulceration and hemorrhage separately, consistent with the primary analysis of trial (Table 4). Among patients of any genotype, there was a dose-related increase in cardiovascular and thrombotic disorders with a RR of 1.69 (95% CI, 1.02–2.80) for high-dose compared with placebo. This substantially agreed with the primary analysis of the trial,[2] as well as a separate, prespecified analysis of adjudicated cardiovascular events that was previously reported.[4] However, the dose relationship between celecoxib and cardiovascular and thrombotic events appeared to vary somewhat according to genotype. Among those with wild-type genotypes, the cumulative incidence of cardiovascular and thrombotic events was 5.7% among those who received placebo, compared with 9.6% for low-dose celecoxib (RR, 1.62; 95% CI, 0.90–2.92) and 8.1% for high-dose (RR, 1.37; 95% CI, 0.75–2.51). However, in the subgroups with variant genotypes, the excess incidence of cardiovascular and thrombotic events appeared primarily among those assigned to high-dose celecoxib, but not low-dose. Among those with either CYP2C9*2 or CYP2C9*3 genotypes, the cumulative incidence of cardiovascular and thrombotic events was 4.0% among those who received placebo, compared with 3.1% for low-dose celecoxib (RR 0.83; 95% CI, 0.25–2.72) and 10.9% for high-dose celecoxib (RR 2.76; 95% CI, 1.08–7.06). These associations appeared consistent when examining the CYP2C9*2 and CYP2C9*3 genotypes separately (Table 4).

For all patients of any genotype, there did not appear to be a dose-related increase in either renal and hypertensive disorders or gastrointestinal ulceration and hemorrhage, consistent with the overall results of the trial.[2] When examined according to subgroups defined by genotype, there were also no consistent differences in risk. Although there appeared to be, compared with placebo, a higher risk of renal and hypertensive events associated with low-dose celecoxib (RR 2.64; 1.22–5.68) among those with CYP2C9*3 genotypes, this was not observed with the high-dose (RR 1.30; 95% CI, 0.57–2.97).

Discussion

In this large, randomized, placebo-controlled trial, celecoxib was associated with a decrease in the three-year cumulative incidence of adenoma among patients with wild-type, variant CYP2C9*2 (≥ one R144C) or CYP2C9*3 (≥ one I359L allele) genotypes of CYP2C9, the principal enzyme responsible for celecoxib metabolism from the active to inactive state. However, compared with the lower dose, the additional benefit of the higher dose was restricted to those with the CYP2C9*3 genotype. Although statistical power was limited by the small

number of events, it also appeared that among patients with variant genotypes, the increased incidence of cardiovascular and thrombotic events was primarily observed with high-dose celecoxib but not low-dose. In contrast, among patients with wild-type genotypes, both doses of celecoxib appeared associated with risk. There did not appear to be a significant independent main effect of genotype on risk of adenoma or cardiovascular events.

Our results regarding a differential effect of celecoxib on adenoma recurrence according to CYP2C9 genotype are consistent with our present understanding of the role of CYP2C9 in phase 1 drug metabolism and the functional alterations associated with variant genotypes.[5–13] The CYP2C9 enzyme metabolizes celecoxib from its active state to an inactive form; the CYP2C9*3 genotype is associated with significantly greater impairment of this metabolism than either the CYP2C9*2 or wild-type genotype. Thus, high-dose celecoxib may overwhelm a diminished capacity to inactivate drug among individuals with CYP2C9*3 genotypes. This may lead to substantially increased accumulation of active celecoxib, in turn potentiating greater anti-cancer efficacy. In contrast, the metabolic capacity of patients with wild-type or CYP2C9*2 genotypes may be sufficient to inactivate high-dose and low-dose celecoxib with equivalent efficiency. Thus, for individuals with these genotypes, high and low doses of celecoxib may yield comparable levels of bioavailability, resulting in no clinically apparent difference in therapeutic effectiveness.

To our knowledge, our study is the first to examine the relationship between CYP2C9 genetic variants and randomly assigned celecoxib use with clinical outcomes. In support of our findings, previous work demonstrated the relevance of CYP2C9 genetic variation with other drug substrates and endpoints. Several studies have shown that CYP2C9 genetic variants are associated with decreased elimination of warfarin, resulting in an increased risk of overanticoagulation and complications from bleeding.[11, 21–23] Previous case-control studies have also demonstrated that compared with wild-type, individuals with CYP2C9 variant genotypes have a lower risk of colorectal cancer associated with ibuprofen,[24] as well as an increased risk of gastroduodenal bleeding related to NSAIDs.[17]

Interestingly, although there did not appear to be an overall independent effect of CYP2C9 genotype on risk of adenoma, patients in our study with the CYP2C9*2 genotype appeared to have a somewhat higher risk of adenoma in the subgroup using low-dose aspirin. Previous studies have suggested that CYP2C9 variant genotype may be independently associated with adenoma risk through differential metabolism of carcinogens and endogenous prostanoids or induction of COX-2.[13, 16, 25–27] This finding may also be explained by an effect of the *3 variant allele in CYP2C8, which is in strong linkage with the CYP2C9 *2 allele.[28] In support of this hypothesis, we did not observe any increase risk of adenoma related to the CYP2C9*3 variant, which is not strongly linked to the *3 allele of CYP2C8. The *3 allele of CYP2C8 has been associated with impaired metabolism of arachidonic acid, which influences adenoma risk as well as vascular tone, potentially also explaining the higher prevalence of baseline hypertension among patients in this trial with CYP2C9*2 genotypes.[29]

Given the importance of the APC trial in identifying unexpected toxicity associated with celecoxib,[4] we also examined the influence of CYP2C9 genetic variation on risk of adverse events. For both renal and hypertensive events, there did not appear to be a consistent differential effect of celecoxib according to genotype. We also did not find a relationship between variant genotype and gastrointestinal bleeding associated with celecoxib. This finding contrasts with a small case-control study which did observe an association between CYP2C9 variant genotype and short-term risk of NSAID-related gastroduodenal bleeding.[17] However, most patients in this case-control study were exposed to COX-2 non-selective NSAIDs (e.g. diclofenac) which may be associated with a greater risk of bleeding than celecoxib. In fact, in

the main analysis of the APC trial, an overall association between celecoxib and gastrointestinal bleeding was not observed.[2]

Interestingly, among individuals with either CYP2C9*2 or CYP2C9*3 genotypes, the excess number of cardiovascular and thrombotic events associated with celecoxib was restricted to those randomized to high-dose treatment. Overall, these data highlight the potential that individuals with impaired metabolism may be at particularly high risk of dose-related cardiovascular toxicity. Although it is unclear why low-dose celecoxib was not strongly related to cardiovascular and thrombotic events among individuals with variant genotypes, it is important to note that other randomized trials of celecoxib also did not demonstrate an increased risk of cardiovascular events associated with low-dose (200 mg twice daily or 400 mg once daily).[3, 30–32] Nonetheless, because we had a limited number of events, our findings should be viewed as exploratory and support the importance of examining CYP2C9 genotype within ongoing clinical trials focused on adverse events associated with celecoxib.[32]

Our study had several strengths. First, celecoxib treatment was randomly assigned, dosing was strictly defined, treatment duration was long-term, and use of other NSAIDs (except low-dose aspirin) was not permitted.[2] Thus, it is unlikely that our findings are related to differential dosing, heterogeneity in treatment duration, or exposure to other CYP2C9-metabolized NSAIDs. Second, patients were randomized to two different doses of celecoxib, permitting a detailed assessment of the effect of genotype on dose. Other studies examining single doses of celecoxib or exposure irrespective of dose would be unable to uncover a specific effect of genotype on dose-related outcomes. Third, as all patients were enrolled in a randomized trial, treatment and colonoscopic surveillance for outcomes, as well as reporting of adverse events, were uniform and standardized.

Several limitations of this study deserve comment. First, we had a limited number of patients with the CYP2C9*3 genotype although our study is consistent with the prevalence of this variant in other cohorts not specifically selected according to genotype.[11, 16, 33] Second, as we have previously mentioned, we had a limited number of adverse events for analysis, especially among patients with variant genotypes. Nonetheless, our study represents the largest cohort of patients who have been randomized to long-term treatment with celecoxib for whom toxicity data are available. Third, although two copies of the I359L allele (CYP2C9*3 homozygotes) may be associated with greater impairment of drug metabolism than one copy (CYP2C9*3 heterozygotes),[9, 12, 34] we did not have enough patients with two copies of I359L alleles to analyze outcomes according to gene dosage. Fourth, we restricted our analysis of CYP2C9 variants to CYP2C9*2 and CYP2C9*3 polymorphisms, which are the most prevalent polymorphisms among non-Hispanic whites.[5, 20, 35, 36] However, because non-Hispanic Whites composed more than 90% of our study population, it is unlikely that misclassification of genotypes which are more prevalent among non-Whites would influence our results. Importantly, our results were also not materially altered when we restricted our analyses to non-Hispanic White patients (data not shown). Given potential differences in the prevalence of genetic variants as well as their associated metabolizer phenotypes in non-White populations, further studies are warranted to examine CYP2C9 variants and celecoxib use in other populations.

At baseline, there were differences in low-dose aspirin use according to genotype. Unlike many non-aspirin NSAIDs, aspirin is not primarily metabolized by CYP2C9.[37–40] Thus, it is unlikely that this association reflects genotype-specific differences in tolerance to aspirin therapy. Nonetheless, because low-dose aspirin therapy was included as a stratification variable, we were able to carefully adjust for use of low-dose aspirin in all of our multivariate models to minimize any potential confounding.

Our study has specific clinical implications. Although celecoxib effectively prevents colorectal neoplasia, the associated cardiovascular risk does not permit routine use of the drug for population-based chemoprevention. Despite this, efforts to use genetic information to personalize and optimize chemoprevention have been identified as a high priority and may be warranted for specific patients.[41] For example, high dose celecoxib at 400 mg twice daily is currently approved by the Food and Drug Administration for adjunctive treatment of patients with familial adenomatous polyposis. Celecoxib treatment also has been proposed for specific individuals who are at high risk for colorectal cancer, low risk for cardiovascular events, and unable to tolerate routine endoscopic surveillance. Finally, celecoxib treatment is continuing in studies examining its potential role in multi-agent chemoprevention or as an adjunctive treatment in patients with established cancers.[42, 43] Our data suggest that for the vast majority of individuals without CYP2C9*3 genotypes, high-dose celecoxib does not confer any additional chemopreventive benefit. Thus, consideration of celecoxib for any chemopreventive strategy should be based on the potential risks and benefits associated with low-dose.

Finally, our study provides proof-of-principle that genetic determinants can influence an individual's pharmacokinetic response to celecoxib with a significant, clinically apparent impact on outcome.[41] Because celecoxib is widely used for other indications, such as treatment of arthritis,[44] determining the influence of CYP2C9 genotype on responsiveness to therapy as well as susceptibility to toxicity within other patient populations remains critically important.

In summary, this study observed a pharmacogenetic association between CYP2C9*3 variant genotype and risk of adenoma according to celecoxib dosing within a large, randomized, placebo-controlled trial. Although the number of patients with variant genotypes was relatively small, limiting the statistical power, there was also a potential relationship between CYP2C9 variant genotypes and risk of cardiovascular and thrombotic events according to celecoxib exposure. These data support the potential importance of genetic variability in determining susceptibility to the benefits and hazards of celecoxib. Further research is needed to examine the routine use of genetic information in tailoring treatment with celecoxib across a range of doses, indications for use, and patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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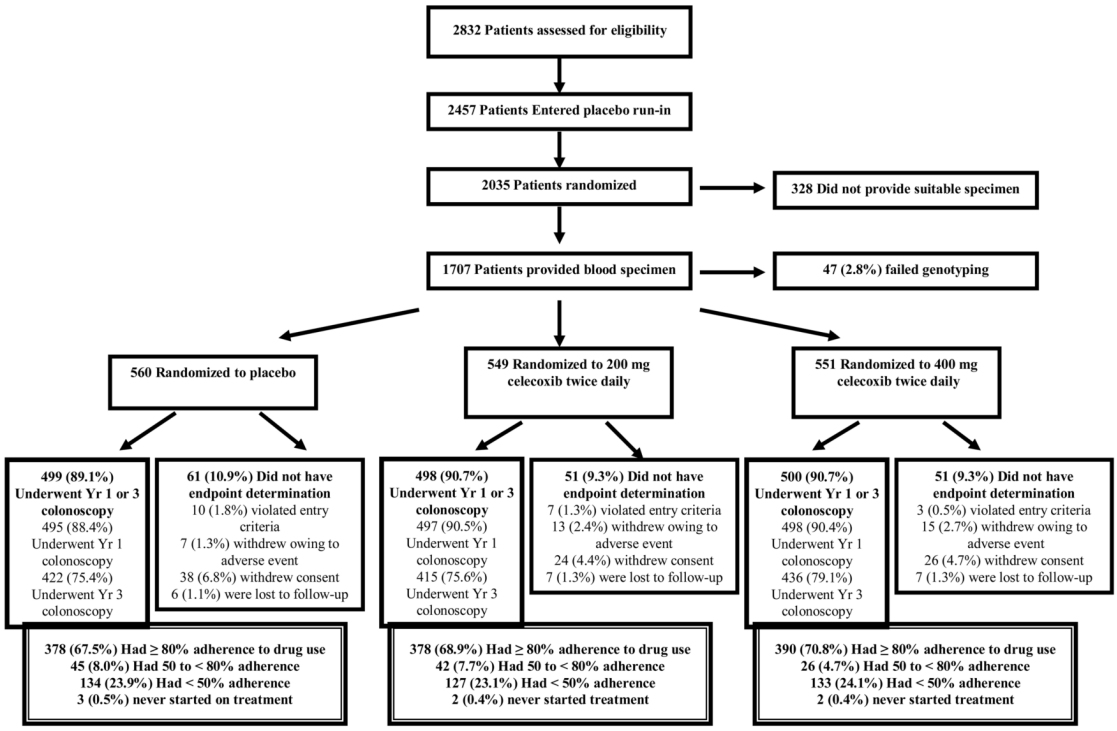

Figure. Flow of Patients Through the Study

Patients who violated study entry criteria were those for whom the presence of an adenoma on colonoscopy at baseline could not be confirmed. Patients who withdrew consent for study participation included those who withdrew from the study for medical or nonmedical reasons, those who failed to complete a post-randomization colonoscopy for nonmedical reasons, or those who did not adhere to the protocol for other reasons. Adherence to the use of study medication was calculated as the duration of use in days, divided by 1095. Percentages do not always total 100 due to rounding.

Table 1

Baseline Characteristics of the Patients According to CYP2C9 Genotype [a]

Characteristics	All (n =1660)	Wild-type (n = 1102)	CYP2C9*2 (n = 357)	CYP2C9*3 (n = 201)	*P* value[b]
Age, median y, (range)	59 (31, 88)	59 (31, 84)	59 (34, 88)	60 (38, 80)	.09
Women (%)	31.9	32.4	29.7	33.3	.57
Race or ethnic group (%)[c]					
Non-hispanic White	92.2	89.7	96.9	98.0	<.001
Non-hispanic Black	5.2	7.0	2.0	1.0	
Hispanic	1.8	2.3	1.0	0.5	
Asian/Pacific Islander/Other	0.8	1.0	0.3	0.5	
Current cigarette smoker (%)	16.6	17.4	16.3	12.4	.25
Body-mass index[d]					
Men	28.8 (0.1)	28.8 (0.2)	28.7 (0.3)	28.8 (0.4)	.99
Women	29.0 (0.3)	28.8 (0.3)	29.6 (0.7)	29.0 (0.8)	.56
Colorectal cancer in a parent (%)	21	20.3	25.2	17.9	.08
Findings at baseline colonoscopy					
No. of adenomas	2.1 (0.04)	2.1 (0.05)	2.1 (0.08)	2.1 (0.11)	.96
At least one adenoma ≥ 1cm (%)	42.6	44.1	39.2	43.8	.26
Multiple adenomas (%)	55.9	56.7	55.5	52.0	.47
Adenoma burden, cm.[e]	1.50 (0.03)	1.50 (0.04)	1.45 (0.06)	1.51 (0.09)	.81
History of cardiovascular events (%)[f]	14.2	14.0	17.1	10.5	.09
History of hypertension (%)	40.4	37.8	46.5	43.8	.01
History of diabetes (%)	9.3	9.0	8.7	12.4	.27
Use of low-dose aspirin (%)[g]	32.0	29.7	37.0	35.8	.02
Randomized to placebo (%)	33.7	34.5	33.9	29.4	--
Randomized to celecoxib, 200 mg twice daily (%)	33.1	32.7	32.5	36.3	--
Randomized to celecoxib, 400 mg twice daily (%)	33.2	32.9	33.6	34.3	--

[a] Data are expressed as mean (SD) unless otherwise indicated. Wild-type genotypes include individuals with no *2 (R144C) or *3 (I359L) alleles. CYP2C9*2 genotypes include individuals with ≥ one *2 allele. CYP2C9*3 genotypes include individuals with ≥ one *3 allele. Individuals with one *2 allele and one *3 allele were classified as having CYP2C9*3 genotypes.

[b] Test of difference between wild-type, CYP2C9*2, and CYP2C9*3 genotype groups was calculated by analysis of variance for continuous variables, χ^2 for categorical variables.

[c] Race or ethnic group was determined by the investigator using predefined categories.

[d] Body-mass index is the weight in kilograms divided by the square of the height in meters.

[e] The adenoma burden was defined as the sum of the diameter of all adenomas reported during colonoscopy at baseline.

[f] Cardiovascular events were defined as myocardial infarction, cerebrovascular disease, congestive heart failure, angina, and atherosclerotic heart disease.

[g] Low-dose aspirin was defined as 325 mg or less every other day or 162.5 mg or less every day.

Table 2

Risk of Adenoma According to CYP2C9 Genotype[a]

	Wild-type	CYP2C9*2	CYP2C9*3
All patients, No. at risk[b]	996	318	183
Cumulative incidence, 3 yrs, % ± SE	44.8 ± 1.6	52.1 ± 2.9	46.7 ± 3.8
RR (95% CI)[c]	1.0	1.16 (1.00–1.35)	1.05 (0.86–1.28)
P value[d]	--	.05	.66
By celecoxib treatment			
Patients randomized to placebo, No. at risk[b]	338	111	50
Cumulative incidence, 3 yrs, % ± SE	57.2 ± 2.8	68.4 ± 4.6	64.6 ± 7.0
RR (95% CI)[e]	1.0	1.17 (0.96–1.43)	1.06 (0.78–1.42)
P value[d]	--	.13	.72
Patients randomized to celecoxib 200 mg twice daily, No. at risk[b]	330	99	69
Cumulative incidence, 3 yrs, % ± SE	39.9 ± 2.8	46.0 ± 5.3	49.3 ± 6.2
RR (95% CI)[e]	1.0	1.20 (0.89–1.62)	1.25 (0.90–1.72)
P value[d]	--	.24	.20
Patients randomized to celecoxib 400 mg twice daily, No. at risk[b]	328	108	64
Cumulative incidence, 3 yrs, % ± SE	37.0 ± 2.8	41.0 ± 4.9	29.6 ± 5.9
RR (95% CI)[e]	1.0	1.11 (0.81–1.53)	0.79 (0.50–1.25)
P value[d]	--	.50	.72
By aspirin strata			
Patients taking aspirin,[f] *No. at risk*[b]	303	116	62
Cumulative incidence, 3 yrs, % ± SE	44.6 ± 3.0	60.4 ± 4.7	47.1 ± 6.6
RR (95% CI)[g]	1.0	1.44 (1.14–1.81)	1.15 (0.82–1.60)
P value[d]	--	.003	.43
Patients not taking aspirin,[f] *No. at risk*[b]	693	202	121
Cumulative incidence, 3 yrs, % ± SE	44.9 ± 2.0	47.4 ± 3.7	46.4 ± 4.7
RR (95% CI)[g]	1.0	1.02 (0.84–1.24)	1.00 (0.78–1.28)
P value[d]	--	.82	.99

[a] Wild-type genotypes include individuals with no *2 (R144C) or *3 (I359L) alleles. CYP2C9*2 genotypes include individuals with ≥ one *2 allele. CYP2C9*3 genotypes include individuals with ≥ one *3 allele. Individuals with one *2 allele and one *3 allele were classified as having CYP2C9*3 genotypes.

[b] No. at risk include patients who underwent a follow-up colonoscopy at year 1 and/or year 3.

[c] Relative risk calculated by the Mantel-Cox test, with stratification for celecoxib treatment, aspirin use, time, age and sex, with the wild-type genotype as the referent group.

[d] The P value is the Cochran-Mantel-Haenszel test of general association compared to the wild-type genotype.

[e] Relative risk calculated by the Mantel-Cox test, with stratification for aspirin use, time, age, and sex, with the wild-type genotype as the referent group.

[f] Patients were stratified at study entry according to the use or nonuse of low-dose aspirin (325 mg or less every other day or 162.5 mg or less every day). Patients not taking aspirin at baseline were required to abstain from taking it during the trial.

[g] Relative risk calculated by the Mantel-Cox test with stratification for celecoxib treatment, time, age, and sex, with the wild-type genotype as the referent group.

Table 3

Risk of Adenoma According to Celecoxib Dose, Stratified by CYP2C9 Genotype[a]

	Placebo	Celecoxib, 200 mg Twice Daily	Celecoxib, 400 mg Twice Daily
All patients, No. at risk.[b]	499	498	500
Cumulative incidence, 3 yrs, % ± SE	60.5 ± 2.3	42.5 ± 2.3	36.9 ± 2.2
RR (95% CI) compared with placebo[c]	1.0	0.65 (0.56–0.76)	0.54 (0.46–0.63)
P value[d]	--	<.001	<.001
RR (95% CI) compared with 200 mg[e]	--	1.0	0.82 (0.69–0.98)
P value[f]	--	--	.03
By genotype			
Patients with wild-type genotypes, No. at risk[b]	338	330	328
Cumulative incidence, 3 yrs, % ± SE	57.2 ± 2.8	39.9 ± 2.8	37.0 ± 2.8
RR (95% CI) compared with placebo[c]	1.0	0.64 (0.53- 0.77)	0.56 (0.46–0.68)
P value[d]	--	<.001	<.001
RR (95% CI) compared with 200 mg[e]	--	1.0	0.89 (0.72, 1.11)
P value[f]	--	--	0.31
*Patients with CYP2C9*2 genotypes, No. at risk*[b]	111	99	108
Cumulative incidence, 3 yrs, % ± SE	68.4 ± 4.6	46.0 ± 5.3	41.0 ± 4.9
RR (95% CI) compared with placebo[c]	1.0	0.63 (0.47–0.86)	0.54 (0.40–0.74)
P value[d]	--	.003	<.001
RR (95% CI) compared with 200 mg[e]	--	1.0	0.83 (0.57–1.21)
P value[f]	--	--	.33
*Patients with CYP2C9*3 genotypes, No. at risk*[b]	50	69	64
Cumulative incidence, 3 yrs, % ± SE	64.6 ± 7.0	49.3 ± 6.2	29.6 ± 5.9
RR (95% CI) compared with placebo[c]	1.0	0.76 (0.51–1.13)	0.41 (0.24–0.70)
P value[d]	--	0.18	<.001
RR (95% CI) compared with 200 mg[e]	--	1.0	0.51 (0.30–0.87)
P value[f]	--	--	.01

[a] Wild-type genotypes include individuals with no *2 (R144C) or *3 (I359L) alleles. CYP2C9*2 genotypes include individuals with ≥ one *2 allele. CYP2C9*3 genotypes include individuals with ≥ one *3 allele. Individuals with one *2 allele and one *3 allele were classified as having CYP2C9*3 genotypes.

[b] No. at risk include patients who underwent a follow-up colonoscopy at year 1 and/or year 3.

[c] Relative risk calculated by the Mantel-Cox test, with stratification for aspirin use, time, age and sex, with the placebo group as the referent group.

[d] The p value is the Cochran-Mantel-Haenszel test of general association compared to the placebo group.

[e] Relative risk calculated by the Mantel-Cox test, with stratification for aspirin use, time, age and sex, with the celecoxib 200 mg twice daily group as the referent group.

[f]The p value is the Cochran-Mantel-Haenszel test of general association compared to celecoxib 200 mg twice daily group.

Table 4

Incidence of Adverse Events after Randomization According to Celecoxib Dose, Stratified by CYP2C9 Genotype[a]

	Placebo	Celecoxib, 200 mg Twice Daily	Celecoxib, 400 mg Twice Daily
Cardiovascular disorders[b]			
All patients			
No. with event/No. at risk	24/557	34/547	41/549
Cumulative incidence, 3 yrs, % ± SE	5.1 ± 1.1	7.4 ± 1.3	9.0 ± 1.4
RR (95% CI)	1.0	1.41 (0.83–2.37)	1.69 (1.02–2.80)
By genotype			
Patients with wild-type genotypes			
No. with event/No. at risk	18/377	29/358	25/362
Cumulative incidence, 3 yrs, % ± SE	5.7 ± 1.4	9.6 ± 1.8	8.1 ± 1.6
RR (95% CI)	1.0	1.62 (0.90–2.92)	1.37 (0.75–2.51)
*Patients with CYP2C9*2 genotypes*			
No. with event/No. at risk	4/121	3/116	8/118
Cumulative incidence, 3 yrs, % ±	3.9 ±1.9	2.8 ± 1.6	9.4 ± 3.2
RR (95% CI)	1.0	0.81 (0.18–3.63)	2.75 (0.82–9.25)
*Patients with CYP2C9*3 genotypes*			
No. with event/No. at risk	2/59	2/73	8/69
Cumulative incidence, 3 yrs, % ± SE	4.4 ±3.0	3.4 ± 2.4	13.3 ± 4.4
RR (95% CI)	1.0	0.80 (0.11–5.67)	2.69 (0.56–12.79)
Renal and hypertensive disorders[c]			
All patients			
No. with event/No. at risk	97/557	126/547	99/549
Cumulative incidence, 3 yrs, % ± SE	19.8 ± 1.9	26.2 ± 2.1	20.8 ± 2.0
RR (95% CI)	1.0	1.37 (1.05–1.79)	1.02 (0.77–1.35)
By genotype			
Patients with wild-type genotypes			
No. with event/No. at risk	66/377	76/358	63/362
Cumulative incidence, 3 yrs, % ± SE	20.3 ± 2.3	23.6 ± 2.5	20.5 ± 2.4
RR (95% CI)	1.0	1.23 (0.88–1.71)	0.99 (0.70–1.40)
*Patients with CYP2C9*2 genotypes*			
No. with event/No. at risk	22/121	25/116	20/118
Cumulative incidence, 3 yrs, % ±SE	19.2 ± 3.9	25.0 ± 4.5	19.9 ± 4.2
RR (95% CI)	1.0	1.27 (0.71–2.25)	1.00 (0.55–1.85)
*Patients with CYP2C9*3 genotypes*			
No. with event/No. at risk	9/59	25/73	16/69
Cumulative incidence, 3 yrs, % ± SE	17.2 ± 5.6	41.0 ± 6.5	23.4 ± 5.5
RR (95% CI)	1.0	2.64 (1.22–5.68)	1.30 (0.57–2.97)

	Placebo	Celecoxib, 200 mg Twice Daily	Celecoxib, 400 mg Twice Daily
Gastrointestinal ulceration/hemorrhage[d]			
All patients			
No. with event/No. at risk	57/557	56/547	55/549
Cumulative incidence, 3 yrs, % ± SE	11.9 ± 1.6	11.8 ± 1.6	11.7 ± 1.5
RR (95% CI)	1.0	0.97 (0.67–1.41)	0.95 (0.66–1.38)
By genotype			
Patients with wild-type genotypes			
No. with event/No. at risk	41/377	35/358	38/362
Cumulative incidence, 3 yrs, % ± SE	12.9 ± 2.0	10.9 ± 1.8	12.2 ± 1.9
RR (95% CI)	1.0	0.84 (0.54–1.32)	0.92 (0.59–1.43)
*Patients with CYP2C9*2 genotypes*			
No. with event/No. at risk	10/121	16/116	9/118
Cumulative incidence, 3 yrs, % ± SE	8.5 ± 2.7	17.2 ± 4.1	9.5 ± 3.1
RR (95% CI)	1.0	1.85 (0.84, 4.07)	0.99 (0.40, 2.46)
*Patients with CYP2C9*3 genotypes*			
No. with event/No. at risk	6/59	5/73	8/69
Cumulative incidence, 3 yrs, % ± SE	13.7 ±5.3	7.9 ± 3.4	12.1 ± 4.3
RR (95% CI)	1.0	0.62 (0.19–2.02)	0.98 (0.34–2.84)

[a] Wild-type genotypes include individuals with no *2 (R144C) or *3 (I359L) alleles. CYP2C9*2 genotypes include individuals with ≥ one *2 allele. CYP2C9*3 genotypes include individuals with ≥ one *3 allele. Individuals with one *2 allele and one *3 allele were classified as having CYP2C9*3 genotypes. Adverse events include those that were reported during the time after the first dose of the study drug until 30 days after the last dose of study drug. The analysis excludes seven participants with genotype information that were randomized but never initiated treatment: three patients in the placebo group, two assigned to 200 mg of celecoxib twice daily, and two assigned to 400 mg of celecoxib twice daily. Data on adverse events include events reported among 639 patients who continued blinded treatment beyond the 36 month core phase of the study who were enrolled in the 24 month extension study.

[b] Cardiovascular events include cardiovascular death or circulatory collapse, stroke, myocardial infarction, congestive heart failure, venous thrombosis or thromboembolism, cardiovascular therapeutic procedures, vascular therapeutic procedures, cerebrovascular disease, and vascular disease. Four of the cardiovascular events occurred after 36 months. All four of these patients had wild-type genotypes: one patient was randomized to placebo with an event at 38 months; two patients were randomized to 200 mg twice daily with events at 40 and 49 months; one patient was randomized to 400 mg twice daily with an event at 44 months.

[c] Renal and hypertensive events include elevated creatinine, fluid retention or edema, hypertension, proteinuria and renal failure. Eighteen of the renal events occurred after 36 months. Eleven patients had wild-type genotypes: 4 patients were randomized to placebo with events at 36.1, 36.4, 38, and 41 months; four patients were randomized to 200 mg twice daily with events at 36.3, 36.6, 36.8, and 36.9 months; three patients were randomized to 400 mg twice daily with events at 36.2, 36.3, and 41 months. Four patients had CYP2C9*2 genotypes: two patients were randomized to placebo with events at 36.1 and 36.4 months; one patient was randomized to 200 mg twice daily with an event at 36.5 months; one patient was randomized to 400 mg twice daily with an event at 41 months. Three patients had CYP2C9*3 genotypes: one patient was randomized to placebo with an event at 36.3 months; two patients were randomized to 400 mg twice daily with events at 36.6 and 36.8 months.

[d] Gastrointestinal ulceration and hemorrhage events include anemia, gastrointestinal bleeding, gastritis/duodenitis, upper or lower gastrointestinal ulceration, and other hemorrhage. Eleven of the gastrointestinal events occurred after 36 months. Eight patients had wild-type genotypes: three were randomized to placebo with events at 36.3, 36.5, and 37.5 months; three were randomized to 200 mg twice daily with events at 37, 38, and 48 months; two were randomized to 400 mg twice daily with events at 36.7 and 42 months. Two patients had CYP2C9*2 genotypes: one patient was randomized to placebo with an event at 37 months; one patient was randomized to 200 mg twice daily with an event at 36.3 months. One patient had a CYP2C9*3 genotype and was randomized to 400 mg twice daily with an event at 36.6 months.