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Brief Communication

Risk of Cardiovascular Events in a Randomized Placebo-Controlled, Double-Blind Trial of Difluoromethylornithine plus Sulindac for the Prevention of Sporadic Colorectal Adenomas

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Abstract Nonsteroidal anti-inflammatory drugs (NSAID) have been associated with adverse cardiovascular (CV) outcomes in cancer prevention and other clinical trials. A recent meta-analysis suggested that baseline CV risk is associated with NSAID-associated adverse CV events. We evaluated the effect of baseline CV risk on adverse CV events in a phase III trial of difluoromethylornithine (DFMO) plus the NSAID sulindac versus placebo in preventing colorectal adenomas. Trial data were analyzed to determine baseline CV risk. CV toxicity outcomes were then assessed overall and excluding high CV-risk patients. Baseline CV risk scores were evenly distributed within our overall trial population of 184 placebo (low risk, 27%; moderate risk, 34%; high risk, 39%) and 191 DFMO/sulindac (low risk, 30%; moderate risk, 29%; high risk, 41%) patients. In patients with a high baseline CV risk, the number of adverse CV events was greater among DFMO/sulindac (n = 9) than among placebo (n = 3) patients. Excluding patients with a high baseline CV risk, the numbers of adverse CV events were similar in the DFMO/sulindac (n = 7) and placebo (n = 6) arms. A high CV risk score at baseline may confer an increased risk of CV events associated with treatment with DFMO/sulindac, and a low baseline score may not increase this risk. These results have implications for future NSAID-based cancer prevention clinical trials.

Since the first reports of adverse cardiovascular (CV) events associated with cyclooxygenase-2–specific nonsteroidal anti-inflammatory drug (NSAID) inhibitors in clinical cancer prevention trials (1, 2), clinical cancer prevention trials involving NSAIDs have increased their emphasis on assessing the risk-benefit profile of these agents (3). Despite evidence of the efficacy of low-dose aspirin and NSAIDs in reducing colorectal adenomas and of low-dose aspirin in reducing colorectal cancer (from heart disease prevention studies), the U.S. Preventive Services Task Force currently recommends against using aspirin or NSAIDs for colorectal cancer prevention among average-risk individuals (listed as a rating "D" recommendation; ref. 4). In April 2005, the U.S. Food and Drug Administration issued a "black box" warning of NSAID-related CV and gastrointestinal toxicity to be placed on all marketed prescription NSAIDs (5).

Our group recently showed the dramatic efficacy of a combination of the polyamine inhibitor >D, L-α-difluoromethylornithine (DFMO) and the NSAID sulindac in a randomized double-blind, placebo-controlled phase III trial for colorectal adenoma prevention (6). DFMO plus sulindac treatment produced a 70% reduction in recurrent adenomas and 91.5% reduction in advanced adenomas (versus placebo; ref. 6). There were no significant differences in adverse events, including grade 3 or greater CV toxicity (6). It is acknowledged, however, that the study was not powered to evaluate the differences in CV toxicity, and there was a greater number of grade 3+ CV events in the treatment group (n = 16) than in the placebo group (n = 9; Table 4 of the original article; ref. 6).

The Cross Trial Safety Analysis, a recent pooled analysis of CV events in six clinical trials involving nonarthritis patients using celecoxib or placebo, showed that celecoxib is indeed associated with a dose-dependent increased risk of CV events (7). This landmark study proposed three baseline CV risk categories based on clinical information obtained from routine medical assessments: low, moderate, and high risk (7).

Our previously reported clinical analysis of DFMO plus sulindac (6) did not incorporate adverse CV events in association with the baseline CV risk categories proposed by the Cross

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Trial Safety Analysis. Therefore, in light of the new data indicating the importance of baseline CV risk in NSAID-based trials, we conducted the present study of the risk of serious CV events associated with the interaction between baseline CV risk and DFMO plus sulindac in our phase III colorectal adenoma prevention trial.

Materials and Methods

Patient population

This study involves analysis of patient data from the multicenter colon adenoma prevention trial, as described elsewhere (6). Three hundred seventy-five patients were randomized to receive treatment either with DFMO plus sulindac or with placebo. Stratification was done for study site and prior low-dose aspirin usage, and the planned treatment duration was 36 mo (6). Clinical data were collected at baseline interview and recorded in the study chart. Adverse events were recorded using the coding symbols from the thesaurus of adverse reaction terms (COSTART). At the second interim analysis, the study was halted by the Data Safety and Monitoring Board because clinical efficacy end points were achieved; thus, 267 patients completed the trial. Adverse event data were available for all patients enrolled in the trial.

Baseline CV risk assessment

Additional data relevant to CV risk were identified for analysis, including age, family history of heart disease, tobacco history, diabetes, history of CV disease (including myocardial infarction, coronary artery disease, congestive heart failure, and cerebrovascular accident), hypertension, hyperlipidemia, as well as low-dose aspirin usage. Using these available data and the proposed criteria for low, moderate, and high baseline CV risk defined by Solomon et al. (7), we reclassified all trial patients into one of these three risk categories.

CV event reporting

Our composite end point for CV events in the trial included myocardial infarction, coronary artery disease, congestive heart failure, cerebrovascular accident, and chest pain. Only grade 3+ toxicities were included in the primary analysis, such that grade 3+ chest pain, for example, included only those cases hospitalized or those who had complete outpatient cardiac evaluations for chest pain.

Statistical analysis

Descriptive analyses were reported for the following clinicopathologic variables collected at baseline: age, use of low-dose aspirin, history of CV disease, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, and current or prior tobacco history. Comparisons of normally distributed continuous data (i.e., age) between the treatment group and the placebo group were done using the Student t test. Comparisons of categorical data across treatment groups were done using the χ^2 test for independence. Statistical significance level was assumed at $P < 0.05$. All analyses were conducted using SAS 9.1 statistical software (SAS, Inc.).

Results

Selected CV risk factors and the calculated baseline CV risk scores from our original sample of 184 placebo and 191 DFMO/sulindac patients are presented in Table 1. No statistically significant differences in the proportion of CV risk factors at baseline were identified across the two study arms. Computed baseline CV risk scores were evenly distributed between the placebo and DFMO/sulindac arms: 27% versus 30% low risk, 34% versus 29% moderate risk, and 39% versus 41% high risk, respectively [$P > 0.05$ (not significant) for all comparisons].

Descriptive comparisons of all patients experiencing grade 3+ CV events, including assessment of baseline CV risk, are

Table 1. Selected characteristics of all patients, including baseline cardiovascular risk factors

	Placebo (n = 184)	DFMO/sulindac (n = 191)
Age (y)		
Mean ± SD	61 ± 8.2	60 ± 8.6
Range	42-78	41-79
Age >75 y, n (%)	8 (4)	7 (4)
Use of low-dose aspirin, n (%)	69 (38)	77 (40)
History of cardiovascular disease, n (%)*	102/181 (56)	108/186 (58)
History of high blood pressure or hypertension or medication taken, n (%)*	72/181 (40)	73/186 (39)
History of hyperlipidemia or medication taken, n (%)*	55/181 (30)	54/186 (29)
History of diabetes or medication taken, n (%)*	17/181 (9)	23/186 (12)
Current or prior cigarette smoker, n (%)*,†	25/99 (25)	27/100 (27)
Risk score*,†,‡:		
Low risk score, n (%)	49/181 (27)	55/186 (30)
Moderate risk score, n (%)	61/181 (34)	54/186 (29)
High risk score, n (%)	71/181 (39)	77/186 (41)

NOTE: $P > 0.05$ (not significant) for each of the above comparisons.

*The denominator is the number of subjects for whom information was recorded in either medical history form or concomitant medication form. Missing values are not included.

†Self-reported information.

‡Risk score, derived from Solomon et al. (7): low—no known risk factors; moderate (one of the following)—age >75 y, HTN or medication taken, hyperlipidemia or medication taken, current or prior smoker, or use of low dose ASA; high—diabetes or medication taken, prior history of cardiovascular disease (coronary artery disease, myocardial infarction, congestive heart failure, cerebrovascular accident), or ≥2 risk factors from moderate category.

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Table 2. Baseline characteristics of the patients who have at least one grade ≥3 cardiovascular adverse event, defined as myocardial infarction, coronary artery disease, congestive heart failure, cerebrovascular accident, and chest pain

	Placebo (*n* = 9)	DFMO/sulindac (*n* = 16)
Age (y)		
Mean ± SD	64 ± 10	62 ± 10
Range	49-74	41-76
Age >75 y, *n* (%)	0	1 (6)
Use of low-dose aspirin, *n* (%)	2 (22)	10 (63)
History of cardiovascular disease, *n* (%)*	7 (78)	9 (56)
History of high blood pressure or hypertension or medication taken, *n* (%)*	6 (67)	5 (31)
History of hyperlipidemia or medication taken, *n* (%)*	3 (33)	6 (38)
History of diabetes or medication taken, *n* (%)*	1 (11)	4 (25)
Current or prior cigarette smoker, *n* (%)*,†	1/5 (20)	3/7 (43)
Risk score*,†,‡:		
Low risk score, *n* (%)	3 (33)	3 (19)
Moderate risk score, *n* (%)	3 (33)	4 (25)
High risk score, *n* (%)	3 (33)	9 (56)

*The denominator is the number of subjects for whom information was recorded in either medical history form or concomitant medication form. Missing values are not included.

†Self-reported information.

‡Risk score, derived from Solomon et al. (7): low—no known risk factors; moderate (one of the following)—age > 75 y, HTN or medication taken, hyperlipidemia or medication taken, current or prior smoker, or use of low dose ASA; high—diabetes or medication taken, prior history of cardiovascular disease (coronary artery disease, myocardial infarction, congestive heart failure, cerebrovascular accident), or ≥2 risk factors from moderate category.

presented in Table 2. It is apparent from these data that a disproportionately greater number of patients with high CV risk score at baseline experienced CV events in the DFMO/sulindac arm ($n = 9$) compared with placebo ($n = 3$). If all patients with high baseline CV risk are excluded from the analysis, the numbers of CV events in the placebo ($n = 6$) and treatment ($n = 7$) arms are approximately equal.

Our assessment of chest pain in this trial is not uniformly adopted by other studies, calling into question whether our aggregate CV end point is affected by inclusion of chest pain events. Thus, we have done an additional analysis to exclude these patients from the aggregate CV event definition. If grade 3+ chest pain events ($n = 8$) are excluded from the analysis and CV event is defined as coronary artery disease, myocardial infarction, congestive heart failure, or cerebrovascular accident, the effects are similar: 12 events occurred in the treatment arm (9 with high baseline CV risk, 3 with low or moderate risk), compared with 5 events in the placebo arm (3 with high baseline CV risk, 2 with low or moderate risk). Thus, only 3 patients in the treatment arm with low-moderate baseline CV risk suffered grade 3+ coronary artery disease, myocardial infarction, congestive heart failure, or cerebrovascular accident, compared with 2 low-moderate risk patients in the placebo arm.

Discussion

Our present results suggest that baseline CV risk score modifies the effect of DFMO/sulindac treatment on CV events: the risk of an adverse CV event associated with DFMO/sulindac increased with a high, but not with a low, baseline CV risk score. These findings are consistent with data from larger studies such as the Cross Trial Safety Analysis (7). With such small numbers, however, our study did not have sufficient power to perform formal tests for a statistical interaction between baseline CV risk and the intervention.

Cyclooxygenase-2 overexpression is clearly important in the progression of the adenoma-carcinoma sequence (8). Several randomized trials have now shown that cyclooxygenase-2–selective NSAIDs substantially and significantly reduce adenoma recurrence, but at the cost of a significant overall increase in CV events (2, 9). Currently, cyclooxygenase-2–selective NSAIDs cannot be recommended for prevention of colorectal adenomas or cancer. Preliminary data suggest that similar adverse CV results are associated with less selective NSAIDs including sulindac, but confirmation of this effect awaits the results of ongoing trials. Therefore, how to safely test NSAID-based regimens in relatively healthy participants with a low threshold for adverse events has been a major challenge for cancer prevention over the past several years. Our trial attempted to minimize potential adverse effects of sulindac by using a relatively low dose. The recent pooled Cross Trial Safety Analysis (7) provides new insights into the importance of assessing baseline CV risk in NSAID-based clinical trials. This importance is further underscored by the present reanalysis of CV toxicity data from our phase III colorectal adenoma prevention trial of DFMO plus sulindac, which indicates that CV toxicity seemed to be associated with baseline CV risk scores.

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We believe that future cancer prevention clinical trials involving NSAIDs should consider stratifying patients by baseline CV risk or simply exclude high-CV-risk patients from enrollment in the interest of patient safety. This latter approach is a key feature of a phase III colon cancer prevention trial of DFMO plus sulindac under development within the Southwest Oncology Group.

Disclosure of Potential Conflicts of Interest

E. Gerner and F. Meyskens are co-founders of Cancer Prevention Pharmaceuticals, LLC. The other authors disclosed no potential conflicts of interest.

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