JNCI Journal of the National Cancer Institute Advance Access published August 8, 2007

ARTICLE

Arterial Thromboembolic Events in Patients with Metastatic Carcinoma Treated with Chemotherapy and Bevacizumab

Frank A. Scappaticci, Jamey R. Skillings, Scott N. Holden, Hans-Peter Gerber, Kathy Miller, Fairooz Kabbinavar, Emily Bergsland, James Ngai, Eric Holmgren, Jiuzhou Wang, Herbert Hurwitz

Background Although combination treatment with bevacizumab (humanized monoclonal antibody against vascular endothelial growth factor) and chemotherapy improves survival of patients with various metastatic carcinomas, an increased risk of arterial thromboembolic events has been observed in some trials. We characterized this risk by performing post hoc analyses of randomized controlled trials that evaluated combination treatment with bevacizumab and chemotherapy versus chemotherapy alone. Low-dose aspirin was permitted in these trials, and its safety was also analyzed.

Methods Data were pooled from five randomized controlled trials that included a total of 1745 patients with metastatic colorectal, breast, or non–small-cell lung carcinoma. The risk of an arterial or venous thromboembolic event was assessed by simple incidence rates, rates per 100 person-years, and/or hazard ratios (HRs). The association between patient characteristics and risk of an arterial thromboembolic event was investigated primarily by Cox proportional hazards regression. The relationship between low-dose aspirin and bleeding was explored by incidence rates and rates per 100 person-years.

Results Combined treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with increased risk for an arterial thromboembolic event (HR = 2.0, 95% confidence interval [CI] = 1.05 to 3.75; $P = .031$) but not for a venous thromboembolic event (HR = 0.89, 95% CI = 0.66 to 1.20; $P = .44$). The absolute rate of developing an arterial thromboembolism was 5.5 events per 100 person-years for those receiving combination therapy and 3.1 events per 100 person-years for those receiving chemotherapy alone (ratio = 1.8, 95% CI = 0.94 to 3.33; $P = .076$). Development of an arterial thromboembolic event was associated with a prior arterial thromboembolic event ($P<.001$) or age of 65 years or older ($P = .01$). Baseline or on-study aspirin use was associated with modest increases in grade 3 and 4 bleeding events in both treatment groups, from 3.6% to 4.7% for bevacizumab-treated patients and from 1.7% to 2.2% for control subjects.

Conclusions Combination treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with an increased risk of arterial thromboembolism but not venous thromboembolism.

J Natl Cancer Inst 2007;99:1232–9

Bevacizumab (rhuMab VEGF; Genentech, Inc, South San Francisco, CA), a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF-A), improved survival when combined with chemotherapy for first-line treatment of metastatic colorectal cancer (1). Combination treatment with bevacizumab and chemotherapy also improved survival in patients with previously treated metastatic colorectal cancer (2) and previously untreated nonsquamous non–small-cell lung cancer (3) and improved progression-free survival in patients with previously untreated metastatic breast cancer (4). In the pivotal placebo-controlled phase III trial in patients with metastatic colorectal cancer (1), 3.3% (95% confidence interval [CI] = 1.8% to 5.5%) of bevacizumab-treated patients experienced an arterial thromboembolic event versus 1.0% (95% CI = 0.3% to 2.6%) in the placebo arm. Furthermore, in another combination therapy trial in patients with metastatic colorectal cancer (5), an increased incidence of arterial thromboembolism, but not of venous thromboembolism, was observed among those patients receiving bevacizumab.

Affiliations of authors: Genentech, Inc, South San Francisco, CA (FAS, JRS, SNH, HPG, JN, EH, JW); Indiana Cancer Pavilion, Indianapolis, IN (KM); Department of Medicine, University of California at Los Angeles, Los Angeles, CA (FK); University of California at San Francisco Cancer Center, San Francisco, CA (EB); Duke University Medical Center, Durham, NC (HH).

Correspondence to: Frank A. Scappaticci, MD, PhD, Genentech, Inc, BioOncology, 455 East Grand Ave, South San Francisco, CA 94080 (e-mail: anthon@gene.com).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djm086

To determine the risk of both arterial and venous thromboembolic events and to identify characteristics among patients treated with bevacizumab and chemotherapy that are associated with an increased risk of arterial thromboembolic events, we performed post hoc analyses of pooled, prospectively collected safety data from five Genentech-sponsored randomized controlled trials. These trials evaluated the combination treatment of bevacizumab and chemotherapy compared with chemotherapy alone in patients with metastatic colorectal cancer (1,5,6), breast cancer (7), or non–small-cell lung cancer (8). Because use of low-dose aspirin (≤325 mg/day) was permitted in these trials, we also analyzed the relationship between development of arterial thromboembolic events and aspirin use among patients receiving combination treatment with bevacizumab and chemotherapy and among control patients and compared the risk of bleeding events among these groups.

CONTEXT AND CAVEATS

Prior knowledge

An increased risk of arterial thromboembolic events had been observed in some clinical trials of combination treatment with bevacizumab (humanized monoclonal antibody against vascular endothelial growth factor) and chemotherapy in patients with various metastatic carcinomas.

Study design

Pooled analysis of five randomized controlled trials that included a total of 1745 patients with metastatic cancer

Contribution

Combination treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with a modest increase in the risk of arterial thromboembolism but not venous thromboembolism. The absolute rate of developing an arterial thromboembolic event was 5.5 per 100 person-years for those in the bevacizumab group and 3.1 for those in the chemotherapy-alone group. Risk factors associated with an arterial thromboembolic event were history of an arterial thromboembolic event and age 65 years or older.

Implications

The risk factors for arterial thromboembolism should be considered when making treatment decisions for individual patients.

Limitations

Raw incidence rates may have overestimated the risk of an arterial thromboembolic event because of the delayed time to progression in the bevacizumab-treated group compared with the control group. Associations between risk of an arterial thromboembolic event and different tumor or histologic types, between risk and different chemotherapeutic agents combined with bevacizumab, and between risk and different disease settings (especially, metastatic versus adjuvant settings) could not be assessed.

Patients and Methods

Studies and Patient Assignment

Trials were selected from completed Genentech-sponsored randomized studies of combination treatment with bevacizumab and chemotherapy compared with chemotherapy alone. Five randomized trials (1,5–8) met these criteria at the time of the analysis and included a total of 1745 patients (see Table 1). Patients were assigned to the group receiving combination treatment with bevacizumab and chemotherapy (i.e., the bevacizumab-treated group) or to the control group receiving chemotherapy alone (i.e., control group) on the basis of their initial treatment assignment (chemotherapy with or without bevacizumab, respectively). Patient eligibility criteria for these studies are described in detail elsewhere (1,5–8). Patients were excluded from the trials if they had uncontrolled hypertension, myocardial infarction, unstable angina, congestive heart failure with a New York Heart Association classification of class II or higher, serious cardiac arrhythmia requiring medication, grade 2 or higher peripheral vascular disease within 1 year before entry, any history of stroke, chronic daily treatment with aspirin (>325 mg/day), nonsteroidal anti-inflammatory medications at doses known to inhibit platelet function, or current full-dose anticoagulation (within 10 days before treatment). Use of aspirin was determined by concomitant medication entries. Collection of arterial thromboembolic events in these studies was not prespecified. The phase III studies included interim analyses for safety. The primary endpoints for these trials were progression-free survival and overall survival. Progression-free survival was censored 30 days after the last study assessment.

Identification of Patients with Arterial Thromboembolic Events, Venous Thromboembolic Events, and Bleeding During First-Line Therapy

Patients with an arterial thromboembolic event were identified from study databases by one of the following adverse events: angina pectoris, arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia. Patients who had a venous thromboembolic event were identified by one of the following adverse events: deep thrombophlebitis, pulmonary embolus, mesenteric venous occlusion, thrombophlebitis, retinal vein thrombosis, embolus, embolus upper extremity, thrombosis, and phlebitis. A list of patients with a bleeding event (grades 3 and 4, National Cancer Institute Common Terminology Criteria for Adverse Events, version 2) was assembled from the study databases, and patients with a bleeding event were identified by use of one of the following adverse events: ecchymosis or petechiae, epistaxis, eye hemorrhage, gastrointestinal hemorrhage, gum hemorrhage, injection site hemorrhage, hematemesis, hematuria, hemoptysis, hemorrhage, hemothorax, melena, menorrhagia, metrorrhagia, purpura, rectal hemorrhage, retroperitoneal hemorrhage, subarachnoid hemorrhage, and vaginal hemorrhage.

Risk Factors and Statistical Analyses

Baseline risk factors analyzed were the following: the use of bevacizumab, age, sex, hypertension at baseline, history of arterial thromboembolism, history of atherosclerosis, history of diabetes mellitus, history of myocardial infarction, history of stroke or transient ischemic attack, and history of venous thrombosis. The risk factor "hypertension at baseline" was defined by one of the following three criteria: hypertension (systolic blood pressure of >150 mmHg or diastolic blood pressure of >100 mmHg) present at study entry; hypertension described in the medical history section of the study

databases; or use of antihypertensive medication before study entry. The blood pressure parameters listed above are the reflected criteria specified in the protocols. The risk factor "history of atherosclerosis" was created with medical history terms associated with arterial disease (these included coronary artery disease, stroke, transient ischemic attack, cerebrovascular disease, peripheral vascular disease, arteriosclerosis, and atherosclerosis). The risk factor "history of arterial thromboembolic event" was created by excluding terms from the "history of atherosclerosis" that describe diseases or conditions that were considered asymptomatic. Use of lipid-lowering drugs was identified by concomitant medications associated with the medication class "hypolipidemics."

For each treatment group, the overall incidence of arterial thromboembolic events was determined with simple descriptive statistics, and the time-to-arterial thromboembolic event analysis was performed by the Kaplan–Meier method (9). A Cox proportional hazards regression analysis of the time to the first arterial thromboembolic event was used to calculate hazard ratios (HRs), and *P* values were calculated by the log-rank test. Because of the relatively small number of events in these analyses, steps to assess the validity of the proportional hazards assumption were not undertaken. To adjust for different durations of follow-up, arterial thromboembolic event rates per 100 person-years were computed as previously described (10). Poisson regression (11) was used to compare rates per 100 person-years as a ratio between bevacizumab-treated patients and control patients. The number of person-years of observation was defined as the sum of the times from the start of treatment to the first arterial thromboembolic event for patients with an event; for patients without an arterial thromboembolic event, the observation time was defined as the start of treatment to the last date of treatment plus 30 days. First date of treatment was defined as the date when the first bevacizumab or control treatment was administered.

The effect of each potential risk factor on the hazard of arterial thromboembolic events across the entire pooled population was evaluated. Cox proportional hazards regression was used to compute a hazard ratio (i.e., hazard with the factor relative to the hazard without the factor), its 95% confidence interval, and *P* value for each factor; those with univariate *P* values of .05 or less were analyzed by use of backward elimination in a Cox model multivariable analysis. Again, the validity of the proportional hazards assumption was not checked.

Baseline risk factors that were statistically significant in the multivariable Cox proportional hazards analysis were used to assign patients from the pooled population to subgroups. Overall incidences of arterial thromboembolic events and the rate of such an event per 100 person-years were calculated for each subgroup.

The overall incidence of bleeding events in the pooled population was tabulated by grade, bevacizumab exposure, and aspirin use. Incidences of grade 3 and 4 bleeding events were tabulated by aspirin use and bevacizumab exposure across the entire pooled population and by tumor type. To account for potential imbalances between aspirin users and nonusers (because aspirin use was not a stratification factor), odds ratios (ORs) for the incidence of a bleeding event were computed for those groups by treatment and then compared between aspirin users and nonusers by use of the Breslow–Day test (12) of homogeneity of odds ratios. Rates of grade 3 and 4 bleeding events per 100 person-years were determined by the same methods used to obtain the rates of an arterial thromboembolic event per 100 person-years.

To explore the effect of these risk factors on the survival benefits of bevacizumab therapy, we evaluated the association between risk factors and survival outcomes in the pivotal large phase III study in metastatic colorectal cancer (AVF2107g) (1). Hazard ratios with 95% confidence intervals were calculated from a Cox proportional hazards model. Again, the validity of the proportional hazards assumption was not checked. All statistical tests were two-sided and were done with SAS, version 9.1 (SAS Institute Inc, Cary, NC).

Results

Population Characteristics

The pooled population for these analyses included 1745 patients, of whom 963 were randomly assigned to receive bevacizumab and 782 were randomly assigned to control groups (Table 1). Among

Table 1. Studies in the pooled population and number of patients with an arterial thromboembolic event*

		Control group			Bevacizumab-treated group		
Study (reference)	Tumor type	Chemo. regimen	No. of patients with an event	No. of patients	Chemo. regimen	No. of patients with an event	No. of patients
AVF2107g (1)†	Colorectal	IFL	5	396	IFL or FU/LV	20	501
AVF2119g (7)‡	Breast	Cape	1	215	Cape	1	229
AVF2192g (5)§	Colorectal	FU/LV	5	104	FU/LV	10	100
AVF0780g (6)‖	Colorectal	FU/LV	1	35	FU/LV	3	67
AVF0757g (8)¶	NSCLC	Carbo/Tax	1	32	Carbo/Tax	3	66
Total			13	782		37	963

* Chemo. = chemotherapy; AVF = antivascular endothelial growth factor; IFL = irinotecan; Cape = capecitabine; FU/LV = fluorouracil and leucovorin; NSCLC = non–small-cell lung cancer; Carbo = carboplatin; Tax = paclitaxel.

† Bevacizumab at 5 mg/kg was given intravenously every 2 weeks.

‡ Bevacizumab at 15 mg/kg was given intravenously every 3 weeks.

§ Bevacizumab at 5 mg/kg was given intravenously every 2 weeks.

‖ Bevacizumab at 5 or 10 mg/kg was given intravenously every 2 weeks.

¶ Bevacizumab at 7.5 or 15 mg/kg was given intravenously every 3 weeks.

Table 2. Incidence of an arterial thromboembolic event in the pooled population by treatment, type of event, baseline risk factors, and aspirin use*

Group	Control patients (n = 782)	Bevacizumab-treated patients (n = 963)	P†
Overall			
Incidence No. (%)	13 (1.7)	37 (3.8)	
Difference in incidence (95% CI)		2.1 (0.7 to 3.7)	
Follow-up, py	419	673	
Rate per 100 py (95% CI)	3.1 (1.8 to 5.3)	5.5 (4.0 to 7.6)	
Ratio of rate per 100 py (95% CI)		1.8 (0.94 to 3.33)	.076
HR‡ (95% CI)		2.0 (1.05 to 3.75)	.031
By type of event, No. (%)			
Stroke/TIA	4 (0.5)	16 (1.7)	
MI/angina	8 (1.0)	14 (1.5)	
Other	1 (0.1)	8 (0.8)	
All	13 (1.7)	37 (3.8)§	
By baseline risk factors, % (No. of events/ No. of patients)			
Age ≥65 y‖	2.5 (7/279)	7.1 (24/339)	
History of ATE‖	3.4 (2/59)	15.7 (14/89)	
Age <65 y and no history of ATE	1.0 (5/490)	1.8 (11/602)	
Age <65 y and history of ATE	7.7 (1/13)	9.1 (2/22)	
Age ≥65 y and no history of ATE	2.6 (6/233)	4.4 (12/272)	
Age ≥65 y and history of ATE	2.2 (1/46)	17.9 (12/67)	
By baseline risk factors and aspirin use, % (No. of events/No. of patients)			
Aspirin nonusers	1.7 (12/698)	3.6 (30/827)	.027
Age <65 y and no history of ATE	1.1 (5/462)	2.0 (11/552)	.315
Age <65 y and history of ATE	0.0 (0/7)	6.7 (1/15)	>.999
Age ≥65 and no history of ATE	3.0 (6/200)	4.4 (10/225)	.459
Age ≥65 y and history of ATE	3.4 (1/29)	22.9 (8/35)	.033
Aspirin users	1.2 (1/84)	5.1 (7/136)	.159
Age <65 y and no history of ATE	0.0 (0/28)	2.0 (1/51)	>.999
Age <65 y and history of ATE	16.7 (1/6)	0.0 (0/6)	>.999
Age ≥65 y and no history of ATE	0.0 (0/34)	4.3 (2/47)	.507
Age ≥65 y and history of ATE	0.0 (0/16)	12.5 (4/32)	.286

* CI = confidence interval; py = person-years; HR = hazard ratio; TIA = transient ischemic attack; MI = myocardial infarction; ATE = arterial thromboembolic event.

† *P* value for the rate per 100 py is from Poisson regression, that for the hazard ratios is from log-rank test, and that for the percentage incidence is from Fisher's exact test. All statistical tests were two-sided.

‡ The comparison was bevacizumab therapy versus control therapy.

§ One patient in this group had both a stroke and a myocardial infarction.

‖ These groups are not mutually exclusive: the group aged 65 years or older includes patients regardless of their history of ATE and vice versa.

the 1745 patients, 1203 (69%) had colorectal cancer, 444 (25%) had breast cancer, and 98 (6%) had non–small-cell lung cancer. The cytotoxic agents administered varied with tumor type; however, 1447 (94%) of the 1745 patients received a fluoropyrimidine-based therapy (5-fluorouracil or capecitabine). In addition, 1191 (69%) of the bevacizumab-treated patients received it at a dose intensity of 2.5 mg/kg per week, and 529 (31%) received it at 5 mg/kg per week.

Overall Incidence of Arterial Thromboembolic Events and Venous Thromboembolic Events

Treatment with bevacizumab and chemotherapy, compared with treatment with chemotherapy alone, increased the overall incidence of arterial thromboembolic events from 1.7% (chemotherapy alone) to 3.8% (combination treatment), which is a difference of 2.1% (95% CI = 0.7% to 3.7%), and increased the absolute rate per 100 person-years of exposure from 3.1 to 5.5 events (ratio = 1.8, 95% CI = 0.94 to 3.33; *P* = .076) (Table 2). In Fig. 1, the risk of arterial thromboembolism is represented by study in a funnel plot. A test for heterogeneity did not detect a difference in risk among studies. In a Kaplan–Meier analysis of the time-to-arterial thromboembolic event for patients in the pooled population, bevacizumab-treated patients had a higher incidence of an arterial thromboembolic event than control patients (HR for an arterial thromboembolic event = 2.0, 95% CI = 1.05 to 3.75; *P* = .031) (Fig. 2). Among patients who developed arterial thromboembolism, the median time to the first event during first-line therapy was 2.1 months in the chemotherapy-alone group and 2.6 months in the bevacizumab-treated group.

An arterial thromboembolic event that resulted in death within 30 days of onset was documented in 0.62% (95% CI = 0.29% to 1.35%) of bevacizumab-treated patients and in 0.26% (95% CI = 0.08% to 0.9%) of control patients. Most arterial thromboembolic events were myocardial or cerebrovascular events; others included thrombi in the left ventricle, aorta, or arteries of the mesentery, pelvis, or extremities (Table 2).

The incidence of venous thromboembolism was also determined for patients in the five pooled studies. The rate of grade 3 and 4

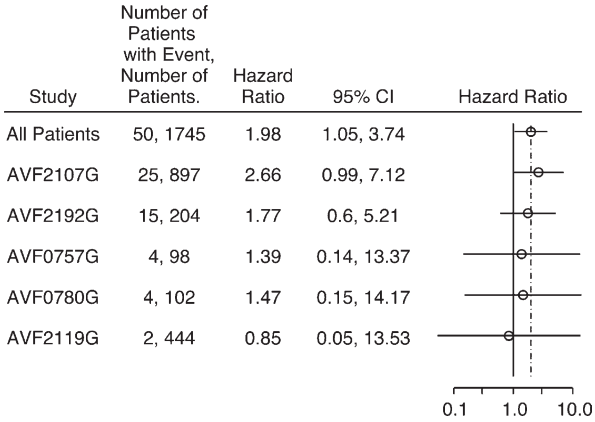

Fig. 1. Funnel plot of the risk of arterial thromboembolism by study. The test for heterogeneity of the treatment effect between studies 2107 and 2192 and the other trials combined was not statistically significant ($P_{heterogeneity}$ = .385). **Open circles** = hazard ratios; **horizontal error bars** = 95% confidence intervals.

venous thromboembolism for patients during first-line therapy was 9.97% (95% CI = 8.08% to 11.86%) among bevacizumab-treated patients and 9.85% (95% CI = 7.76% to 11.93%) among control patients.

Risk Factor Analyses

Univariate and multivariable Cox proportional hazards analyses were used to investigate the relationship between potential risk factors and the occurrence of arterial thromboembolic events across the entire population. Statistically significant baseline risk factors for the occurrence of an arterial thromboembolic event in the univariate analyses included the categorical variables exposure to bevacizumab (yes or no), age of 65 years or older (yes or no), hypertension at baseline (yes or no), history of arterial thromboembolic event (yes or no), history of atherosclerosis (yes or no), and history of myocardial infarction (yes or no). In a multivariable Cox proportional hazards analysis of these risk factors, three were statistically significant for an association with the incidence of arterial thromboembolic events: history of arterial thromboembolic event (P<.001), age of 65 years or older (P = .01), and exposure to bevacizumab (P = .04) (Table 3).

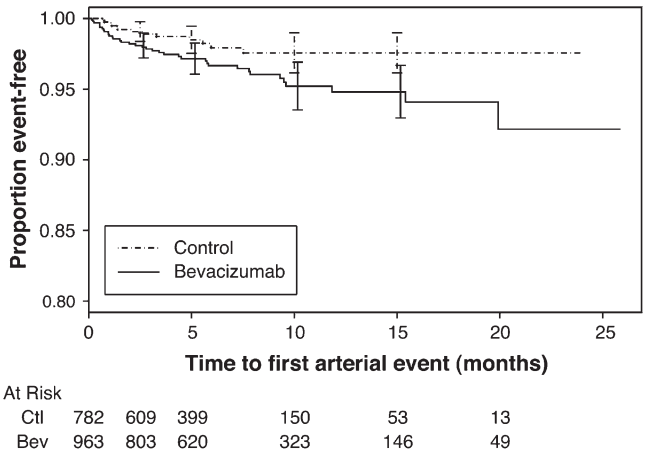

Fig. 2. Kaplan–Meier analysis of time-to-arterial thromboembolic event for patients in the pooled population. **Error bars** = 95% confidence intervals; Ctl = control; Bev = bevacizumab.

Relationship Between Incidence of Arterial Thromboembolic Events and Baseline Risk Factors

Patients in the pooled population were nonexclusively assigned to subgroups on the basis of age (younger than 65 years or 65 years or older) and history of arterial thromboembolic event (present or absent). Incidences of arterial thromboembolic events were calculated with respect to bevacizumab exposure in each subgroup (Table 2). However, many of these subgroups represented small numbers of patients, which may result in real differences remaining undetected. To further describe the risk of an arterial thromboembolic event, risk factors were analyzed as a function of rate per 100 person-years. No statistically significant differences were observed between control and bevacizumab-treated patients among any subgroup. In patients with neither baseline risk factor, the rate of arterial thromboembolic events per 100 person-years of follow-up was 1.9 in control patients and 2.6 in bevacizumab-treated patients (ratio = 1.39, 95% CI = 0.48 to 3.99; P = .544). The subgroups with the strongest trend toward an increased rate of arterial thromboembolic events per 100 person-years in the bevacizumab-treated group were patients aged 65 years or older (4.7 in control group patients versus 10.0 in bevacizumab-treated patients, ratio = 2.1, 95% CI = 0.91 to 4.89; P = .082), patients with a history of an arterial thromboembolic event (5.9 in control patients versus 24.4 in bevacizumab-treated patients, ratio = 4.18, 95% CI = 0.95 to 18.4; P = .060), and patients with both risk factors (3.6 in control patients versus 27 in bevacizumab-treated patients, ratio = 7.6, 95% CI = 0.99 to 58.7; P = .052).

Risk–Benefit Analysis

Clinical outcome data for the 813 patients with metastatic colorectal cancer in the AVF2107g trial (i.e., the intent-to-treat or efficacy population) are shown in Table 4. Clinically and statistically significant improvements in overall survival were associated with bevacizumab treatment in the overall population and in all subgroups, except for the group with both risk factors (age 65 years or older and history of an arterial thromboembolic event). Nevertheless, the point estimates of benefit in this group were consistent with the overall population (HR for progression = 0.55 and 0.54, respectively; HR for death = 0.59 and 0.66, respectively). Thus, it appears that the risks and benefits for bevacizumab treatment were consistent across all subgroups examined.

Aspirin Use and Arterial Thromboembolism

In the pooled population, aspirin use was identified in a small fraction of patients—84 (11%) of the 782 patients in the control group and 136 (14%) of the 963 patients in the bevacizumab-treated group. The prevalence of several factors that were related to an increased arterial thromboembolic event risk varied between aspirin users and nonusers in the pooled population. The risk factors, history of an arterial thromboembolic event, age 65 years or older, use of lipid-lowering drugs, history of diabetes, and history of hypertension, were observed more frequently among aspirin users than nonusers (P<.001, for all parameters). In particular, 60 (27.3%) of the 220 aspirin users had a history of arterial thromboembolic event, compared with 88 (5.6%) of the 1525 aspirin nonusers. For

Table 3. Cox proportional hazards regression analysis of potential baseline risk factors for an arterial thromboembolic event*

Risk factor	Comparison†	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*†
Bevacizumab treatment	Yes/no (728/963)	1.99 (1.05 to 3.75)	.03	1.95 (1.04 to 3.67)	.04
Age, y	≥65/<65 (618/1127)	3.00 (1.69 to 5.30)	<.001	2.17 (1.17 to 4.01)	.01
Sex	Male/female (760/985)	0.57 (0.32 to 1.01)	.05		
Hypertension at baseline	Yes/no (799/946)	1.89 (1.06 to 3.34)	.03		
History of ATE	Yes/no (148/1597)	5.18 (2.86 to 9.39)	<.001	3.65 (1.92 to 6.92)	<.001
History of atherosclerosis	Yes/no (192/1553)	4.17 (2.32 to 7.49)	<.001		
History of diabetes mellitus	Yes/no (224/1521)	1.91 (0.98 to 3.73)	.06		
History of myocardial infarction	Yes/no (110/1635)	4.90 (2.56 to 9.38)	<.001		
History of stroke or TIA	Yes/no (25/1720)	3.16 (0.77 to 13.02)	.11		
History of venous thrombosis	Yes/no (79/1666)	0.47 (0.07 to 3.41)	.46		

* HR = hazard ratio; CI = confidence interval; ATE = arterial thromboembolic event; TIA = transient ischemic attack. *P* values (two-sided) from Wald's test.

† The number in each group is shown in parentheses.

patients aged 65 years or older, 129 (58.6%) of the 220 aspirin users had a history of arterial thromboembolic event, compared with 489 (32.1%) of the 1525 aspirin nonusers.

Incidences of arterial thromboembolic events were calculated with respect to aspirin use in each risk factor subgroup (Table 2). The number of events was too small to permit a consistent assessment of 95% confidence intervals across all subgroups. Among patients who did not use aspirin in the overall population, an increased incidence of arterial thromboembolic events was associated with bevacizumab treatment (3.6%), compared with control treatment (1.7%) (OR = 2.15, 95% CI = 1.09 to 4.24, *P* = .03, Fisher's exact test). An increased incidence was also found among aspirin users in the overall population, but the difference was not statistically significant (5.1% in bevacizumab-treated patients versus 1.2% in control patients; OR = 4.50, 95% CI = 0.54 to 37.27, *P* = .16, Fisher's exact test). In the subgroup of patients with both baseline arterial thromboembolic event risk factors (age ≥65 years and history of arterial thromboembolism), an increased incidence of arterial thromboembolic events was statistically significantly associated with bevacizumab therapy in aspirin nonusers—eight (22.9%) of the 35 bevacizumab-treated patients versus one (3.4%) of the 29 control patients (OR = 8.30, 95% CI = 0.97 to 70.87, *P* = .03, Fisher's exact test)—but not in aspirin users—four (12.5%) of the 32 bevacizumab-treated patients versus zero (0%) of the 16 control patients (OR = infinity, 95% CI not calculable, *P* = .29, Fisher's exact test).

Aspirin Use and Bleeding Events

Grade 3 and 4 bleeding events occurred in 36 (3.7%) of 963 bevacizumab-treated patients in the pooled population and 14 (1.8%) of 782 control patients (Table 5). The rate of bleeding events per 100 person-years of follow-up was 5.3 among bevacizumab-treated patients and 3.3 among control patients (ratio = 1.6, 95% CI = 0.86 to 2.97; *P* = .13). In both bevacizumab-treated and control patients, aspirin use was associated with an approximately 1.3-fold increase in grade 3 and 4 bleeding events. Among groups stratified by individual tumor types or among the overall population, no statistically significant increase in risk for a bleeding event was found between aspirin users and nonusers among control and bevacizumab-treated patients.

Discussion

In a pooled analysis of five randomized controlled trials, we found a modest increase in the risk of arterial thromboembolic events among patients with metastatic cancer treated with bevacizumab, and we identified clinical characteristics that may be associated with an increase in this risk. Although the mechanism responsible

Table 4. Progression-free and overall survival for patients in the AVF2107g trial by statistically significant baseline risk factors for an arterial thromboembolic event*

Baseline risk factor(s)	No.	No. of events, HR (95% CI) PFS	No. of events, HR (95% CI) OS
All patients	813	514, 0.54 (0.45 to 0.66)	399, 0.66 (0.54 to 0.81)
Age ≥65 y†	263	157, 0.57 (0.40 to 0.83)	126, 0.63 (0.43 to 0.93)
History of ATE†	72	39, 0.70 (0.26 to 1.85)	38, 0.32 (0.12 to 0.85)
Age <65 y and no history of ATE	508	346, 0.53 (0.43 to 0.66)	247, 0.73 (0.57 to 0.94)
Age <65 y and history of ATE	17	11, 0.50 (0.08 to 3.07)	8, 0.14 (0.03 to 0.72)
Age ≥65 y and no history of ATE	208	129, 0.51 (0.34 to 0.75)	96, 0.60 (0.39 to 0.92)
Age ≥65 y and history of ATE	55	28, 0.55 (0.22 to 1.37)	30, 0.59 (0.27 to 1.28)

* HR = hazard ratio; CI = confidence interval; ATE = arterial thromboembolic event; OS = overall survival; PFS = progression-free survival. Hazard ratios represent the risk of progression or death in the bevacizumab-treated group compared with the control group. Twenty-five patients could not be classified by age and history of ATE.

† These groups are not mutually exclusive: the group aged 65 years or older includes patients regardless of their history of ATE, and vice versa.

Table 5. Grade 3 and 4 bleeding events in the pooled population by treatment and aspirin use*

Tumor type	Control patients			Bevacizumab-treated patients			P†
	Aspirin nonusers, % (No. of patients with events/No. of patients)	Aspirin users, % (No. of patients with events/No. of patients)	Total, % (No. of patients with events/No. of patients)	Aspirin nonusers, % (No. of patients with events/No. of patients)	Aspirin users, % (No. of patients with events/No. of patients)	Total, % (No. of patients with events/No. of patients)	
All patients‡	1.7 (12/690)	2.2 (2/92)	1.8 (14/782)	3.6 (29/814)	4.7 (7/149)	3.7 (36/963)	.945
CRC	2.4 (11/458)	2.6 (2/77)	2.4 (13/535)	4.4 (24/550)	3.4 (4/118)	4.2 (28/668)	.718
NSCLC	0 (0/28)	0 (0/4)	0 (0/32)	9.1 (5/55)	18.2 (2/11)	10.6 (7/66)	NA§
Breast	0.5 (1/204)	0 (0/11)	0.5 (1/215)	0 (0/209)	5.0 (1/20)	0.4 (1/229)	.217

* CRC = colorectal cancer; NSCLC = non–small-cell lung cancer; NA = not available.

† $P_{interaction}$ was calculated with the Breslow–Day homogeneity of odds ratios test. All statistical tests were two-sided.

‡ The rate per 100 person-years (95% confidence interval [CI]) was 3.33 (1.97 to 5.63) for the control group and 5.34 (3.85 to 7.40) for bevacizumab-treated group ($P = .13$ by Poisson regression). Hazard ratio (95% CI) for an event in the bevacizumab-treated group compared with the control group was 1.69 (0.91 to 3.15), log-rank $P = .09$.

§ This value was not calculable because no events were observed in the control arm.

for this increased risk is unclear, VEGF may be involved. The role of VEGF in endothelial cell maintenance and function is the subject of an ongoing investigation (13), but there is evidence implicating anti-VEGF therapy in the development of arterial thromboembolic events (14). Arteriovascular disease leading to thrombosis is promoted by inflammation (15–17). In preclinical models, angiogenesis and the increased expression of VEGF in acute disease may increase expression of proinflammatory genes; however, chronic exposure to VEGF has been associated with the decreased expression of proinflammatory genes in endothelial cells, including genes for cyclooxygenase 2, E-selectin, and tissue factor (18,19). These genes may be regulated in a biphasic manner, and it is possible that anti-VEGF therapy may disrupt a negative feedback loop that leads to potential in situ thrombus formation. In the clinical setting, agents that target the VEGF axis have been associated with arterial thromboembolic events (20,21). Although the overall increase in the risk of an arterial thromboembolic event was modest, the risk appeared to be increased more in patients who had a history of an arterial thromboembolic event and were aged 65 years or older.

To place the increased risk of an arterial thromboembolic event into the context of the survival benefit provided by bevacizumab therapy in metastatic colorectal cancer, we reanalyzed clinical efficacy results from the pivotal trial (AVF2107g) for several risk groups. Although the subgroups in the analysis were not defined prospectively, the clinical benefit associated with bevacizumab therapy was maintained for all subgroups (22). Although death from an arterial thromboembolic event was uncommon, we did not capture functional disabilities from these events, and the risk factors (i.e., history of arterial thromboembolism and age ≥65 years) identified in this study should be considered when making treatment decisions for individual patients.

The concomitant use of bevacizumab, chemotherapy, and aspirin did not appear to substantially increase the risk of serious bleeding compared with the use of aspirin and chemotherapy alone. In addition, the small number of arterial thromboembolic events and also of aspirin users in our study did not allow definitive conclusions about the prophylactic benefit of aspirin. The use of low-dose aspirin for the prophylaxis of arterial thromboembolic events in high-risk patients is supported by an extensive body of literature (23) and is a recommended standard of care (24). The increased risk of bleeding attributable to bevacizumab treatment was not substantially altered by the use of aspirin. Aspirin-based prophylaxis for an arterial thromboembolic event should be carefully considered for individual patients with metastatic adenocarcinoma who are at high risk for an arterial thromboembolic event and who have no contraindications for aspirin use.

Although the overall rate of venous thrombosis among patients in this study was approximately 10%, it is important to note that the incidence was not increased with bevacizumab use. The relative safety of concurrent administration of bevacizumab and full-dose warfarin has been reported (25). Patients who develop a venous thromboembolism while receiving bevacizumab therapy should be managed according to the standard of care.

This study has several limitations. The raw incidence rates in these analyses may overestimate the risk of an arterial thromboembolic event because of the delayed time to progression and correspondingly longer safety observation period in the bevacizumab-treated group, compared with the control group. Use of Kaplan–Meier hazard estimates and the rate of events per 100 person-years partially corrected for this difference, and results continued to indicate a modest risk of an arterial thromboembolism that was associated with bevacizumab use, compared with the control group. Whether the *P* value for the imbalance in arterial thromboembolic events is less than .05 depends on whether one summarizes the results by use of hazard ratios or rates per person-years of follow-up. However, both methods of analysis are consistent in that they suggest that there is an increase in arterial thromboembolic events in patients treated with bevacizumab. Several important clinical questions cannot be addressed by these analyses: will the risk of an arterial thromboembolic event vary 1) between different tumor types or tumors with different histologies, 2) between different chemotherapeutic agents combined with bevacizumab, or 3) between different disease settings (most notably metastatic versus adjuvant settings)? Functional disability from arterial thromboembolism was not captured in the

studies analyzed and, therefore, the impact of bevacizumab on this aspect cannot be determined. Because these studies excluded patients who had any history of stroke or a myocardial infarction within 12 months of enrollment, the risks and benefits of bevacizumab treatment among such patients have not been established. Ongoing clinical trials should clarify these issues. Nevertheless, these results provide important information for clinicians who use bevacizumab to treat patients with metastatic cancer.

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Funding

Genentech and Roche funded this study, decided to submit the manuscript for publication, and provided writing assistance. Genentech clinicians designed the study, provided administrative oversight, analyzed the data, and participated in data interpretation.

Funding to pay the Open Access publication charges for this article was provided by Genentech, Inc.

Notes

Drs Scappaticci, Skillings, Holden, and Holmgren own stock in Genentech. Dr Miller is conducting research sponsored by Pfizer, Roche, Glaxo-Smith-Kline, Bristol-Myers-Squibb, Amgen, and Entremed; she has been a consultant with Pfizer and Entremed. Dr Kabbinavar is a member of the Genentech Speakers Bureau. One of Dr Bergsland's investigator-initiated studies received bevacizumab from Genentech. Dr Wang was formerly employed by Genentech (from January 2005 to July 2006).

Present address: Seattle Genetics, Inc, Bothell, WA (H. P. Gerber).

The five clinical trials that are the subject of the pooled analyses reported in this paper were supported by Genentech, Inc.

Clinical trial registration numbers from ClinicalTrials.gov—AVF2192g: NCT00109226, AVF2107g: NCT00109070, AVF2119g: NCT00109239. There are no registration numbers for AVF0780g and AVF0757g because these studies were completed in 1999.

We acknowledge the patients who participated in these studies and their family members.

Results of the pooled analyses were presented in part at the Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, 2005.

Manuscript received October 25, 2006; revised June 12, 2007; accepted July 3, 2007.