Adverse Events Associated with Bevacizumab and Chemotherapy in Older Patients with Metastatic Colorectal Cancer

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Abstract

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Background: The safety of bevacizumab in older metastatic colorectal cancer (mCRC) patients is not well understood. The purpose of this analysis was to determine the prevalence of treatment-associated adverse events (AEs), to describe patterns of bevacizumab use in patients with preexisting comorbidities, and to determine incidence of and risk factors for serious adverse events in patients who do and do not receive bevacizumab.

Methods: Patients age ≥ 65 were identified from SEER–Medicare and categorized by mCRC diagnosis pre and post-bevacizumab approval (2001-3 vs. 2005-7). Preexisting conditions known to increase risk of bevacizumab-related AEs were identified in the year pre-diagnosis. Factors associated with bevacizumab receipt were identified using logistic regression. Incidence rates for all AEs and specific serious AEs (deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, myocardial infarction (MI), gastrointestinal (GI) hemorrhage and perforation) were determined. A competing risks regression analysis was used to determine risk factors for first AE.

Results: Of 6,821 total patients, 3,282 (48%) were diagnosed after 2005 and 622 (9%) received first-line bevacizumab. Likelihood of bevacizumab receipt was lower in patients age ≥ 75 (OR 0.41, 95% CI 0.36-0.47), non-whites (OR 0.67, 95% CI 0.55-0.81), patients with higher comorbidity index (OR 0.52, 95% CI 0.44-0.62), and patients with preexisting cerebrovascular

disease (0.49, 95% CI 0.33-0.72). Preexising gastrointestinal conditions, by contrast, were associated with an increased likelihood of bevacizumab receipt (OR 2.26, 95% CI 1.96-2.61). Overall AE incidence rate was not increased among patients receiving first-line bevacizumab compared to patients receiving first-line chemotherapy alone (141 AEs vs. 135 AEs / 100,000 person-days (PD)). Incidence rates for specific AEs (DVT/PE, stroke, MI, GI hemorrhage, and perforation) were also similar between patients who did and did not receive first-line bevacizumab. In a competing risks regression, bevacizumab receipt (2005-7) was not associated with an increased risk of first AE compared with receipt of chemotherapy alone (2001-7) when controlling for age, race, comorbidity index, gender, chemotherapy regimen, and preexisting conditions (HR 0.97, 95% CI 0.87-1.08, p=0.55).

Conclusions: In a population of older mCRC patients, bevacizumab receipt was less likely in patients who were older, non-white, and had preexisting cerebrovascular comorbidities. First-line bevacizumab receipt was not associated with increased overall AE incidence or risk of first AE compared with chemotherapy alone.

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Introduction

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), was initially approved by the Food and Drug Administration (FDA) in February, 2004 for the first-line treatment of mCRC based on a survival benefit seen in randomized clinical trials.**[1]** A number of bevacizumab-associated adverse events have been observed in randomized clinical trials, including gastrointestinal perforation, thromboembolic events, hypertension, and wound healing complications.**[1-6]** The likelihood of these adverse events is thought to be increased in patients with certain preexisting conditions, including prior thrombosis, recent hemorrhage, or uncontrolled hypertension. The relative safety of bevacizumab in older patients – particularly those with preexisting medical comorbidities -- is not well documented.

As mCRC is largely a disease of the elderly, the relative safety of bevacizumab in older patients is of great interest to clinicians. Safety data obtained in randomized clinical trials, however, may not be readily applicable to patients treated in real-world clinical settings. First, patients enrolled in randomized trials are generally more functional and younger than the broader population of patients with mCRC. For example, based on incidence estimates from the SEER database (2004-2008), the median age of colorectal cancer diagnosis is 70 years, with over 60% of diagnoses made in patients 65 years and older.**[7]** However, the median age for patients enrolled in the landmark phase III bevacizumab randomized trials in mCRC is approximately 60 years.**[1, 3-4]** Further, follow-up from randomized trials is not long enough to detect clinically significant late adverse events. In some situations, serious safety concerns may emerge many years after initial FDA approval (e.g. rofecoxib, erythropoietin-stimulating agents). Observational cohort studies

and claims databases, for example, provide an opportunity to investigate adverse events associated with newer agents in less tightly controlled clinical settings.**[8]**

Observational cohort data have suggested that arterial thromboembolic risk associated with bevacizumab may be higher in older patients.**[9-10]** In a recent analysis using SEER-Medicare data (2002-2007), bevacizumab use was associated with a small survival benefit in older patients as well as a slightly increased risk of stroke and gastrointestinal perforation.**[11]** While this analysis indeed provides some data on relative safety of bevacizumab in older patients, the patterns and adverse events associated with bevacizumab use in light of common preexisting conditions in elderly patients remains unclear.

The purpose of this analysis was therefore to determine the prevalence of treatment-associated adverse events in older mCRC patients, to describe patterns of bevacizumab use in patients with preexisting conditions known to increase risk of drug-related adverse events, and to determine the incidence of and risk factors for serious adverse events (including deep vein thrombosis and pulmonary embolus (DVT/PE), stroke, myocardial infarction, gastrointestinal hemorrhage, and gastrointestinal perforation) in patients who do and do not receive bevacizumab.

Methods

Data Source

The source of data for this study was the National Cancer Institute's merged SEER-Medicare database, which links SEER data on cancer diagnoses and survival to claims for covered medical services for Medicare enrollees.**[12-14]** The various local SEER registries represent approximately 28% of the United States population; the combined SEER-Medicare database includes claims for approximately 94% of patients age 65 and older diagnosed with cancer in one of the SEER regions.**[13]** The SEER-Medicare linkage is updated periodically, and in early 2011

was updated to include SEER cancer diagnoses through 2007 with Medicare claims through December 31, 2009.

Patient Selection

Patients were included in the study if they were diagnosed with de novo metastatic (American Joint Committee on Cancer 7th edition stage IV) adenocarcinoma of the colon, rectosigmoid colon, or rectum between March 1, 2001 (following entrance of the Greater California, Kentucky, Louisiana, and New Jersey registries into the SEER program) and December 31, 2007.**[15]** Since the SEER program only obtains stage at diagnosis, we were unable to include patients with earlier stage colorectal cancer who subsequently developed relapse or recurrence. The time period was limited to 2001-2007 in order to capture patients treated in both the pre and post bevacizumab-era. Patients were categorized based on the time period in which they were diagnosed (2001-2003 vs. 2005-2007). Patients diagnosed in 2004 were excluded from the analysis as bevacizumab usage could not be accurately captured by claims data in the immediate period following its approval and before the establishment of a J code. In order to avoid including non-elderly patients with incomplete claims data, patients were excluded from analysis if they were younger than age 65, carried a diagnosis of end stage renal disease, qualified for Medicare as a result of disability, lacked Medicare parts A and B in the 12 months before and after diagnosis, were ever diagnosed with another primary cancer, or did not have histologically confirmed disease. Because the Centers for Medicare and Medicaid Services (CMS) do not require submission of individual claims for services by Medicare HMOs, patients who were enrolled in a Medicare HMO in the 12 months before and after diagnosis were excluded.**[13]** Finally, patients for whom the diagnosis of mCRC was made by death certificate, by autopsy, or in the same month as death were excluded. Patients were followed from the time of diagnosis

until death, or until the last date of available Medicare claims (December 31, 2009). Non-cancer comorbidity was determined using the Klabunde comorbidity score, based on the presence of ICD-9-CM diagnosis codes for 13 comorbidities in the 12 months prior to diagnosis.**[16-18]**

Identification of Chemotherapy and Bevacizumab Usage

Medicare claims can be used to identify chemotherapy utilization in colorectal cancer with good sensitivity.**[19]** First-line treatment was defined as chemotherapy receipt within 3 months of diagnosis. While it is presumed that most patients will receive first-line chemotherapy within 3 months of mCRC diagnosis, a sensitivity analysis was used to determine if increasing this window to 4 and 6 months respectively would significantly change the estimated number of first-line chemotherapy recipients. In order to capture all first-line chemotherapy receipt (in addition to bevacizumab receipt), generic chemotherapy administration, diagnostic, and procedural codes as well as J codes for specific agents (5-fluorouracil, oxaliplatin, irinotecan) were identified. Capecitabine use was identified in the outpatient and hospital inpatient (MedPAR) files as well as the Durable Medical Equipment (DME) file. Patients were considered to have received bevacizumab only if its specific J code could be identified. If no chemotherapy claims were present within 3 months of diagnosis (either generic claims or specific J codes), then patients were considered not to have received first-line chemotherapy. Identification of subsequent 'lines' of therapy using SEER-Medicare claims is challenging, as the duration of therapy and the reasons for switching treatments (e.g. disease progression, toxicity) are not readily apparent from claims records. Nonetheless, subsequent bevacizumab use was identified for patients who did not initially receive bevacizumab as part of first-line therapy.

For all patients who received first-line chemotherapy (with or without bevacizumab), the 'backbone' chemotherapy regimen was determined based on claims for all chemotherapy drugs

within the first 3 months after diagnosis. For example, if a patient had a claim for both 5-FU and oxaliplatin within 3 months of diagnosis, they were considered to have received these drugs together in combination.

Definition of Adverse Events and Preexisting Conditions:

In order to make the distinction between preexisting conditions and adverse events, an index date for each patient is defined as follows: for patients who receive chemotherapy within 3 months of diagnosis, the index date will be the date of first chemotherapy receipt. For patients who do not receive chemotherapy within 3 months of diagnosis, the index date will be the date of diagnosis.

Identification of Preexisting Conditions

Conditions known to potentially increase risk of bevacizumab-related adverse events (as described in the package insert and reported in the literature) were identified in the 12 months prior to the index date using relevant ICD-9-CM codes.**[20]** The conditions of interest were broadly categorized as follows: cardiovascular, cerebrovascular, gastrointestinal, tissue integrity, and pulmonary (**Appendix 1**).

Identification of Bevacizumab-Related Adverse Events

Adverse events were identified from the time period between index date and either death or end of follow up. There was significant overlap between preexisting conditions and adverse events (**Appendix 1**). Adverse events were divided into the same five categories as preexisting conditions. In order to avoid double counting a preexisting condition as an adverse event, patients who, for example, experienced a deep vein thrombosis in the 12 months prior to the index date could not be identified as experiencing this same condition as an adverse event, even if claims for this diagnosis appeared after the index date. It is impossible to determine whether claims for deep vein thrombosis after the index date would represent a new diagnosis or simply

follow up claims from the previously identified preexisting condition. Nonetheless, a separate sensitivity analysis was performed to allow for 'double counting' a specific condition as both a preexisting condition and an adverse event.

To identify occurrence of hypertensive urgency/emergency, ICD-9-CM codes for hypertension and related hypertensive conditions were used, but with the additional restriction that claims must be either in the MedPAR file (indicating hospitalization) or on the same date as a claim indicating an ER visit. To ensure that hypertension was the essential cause of the hospitalization/ER visit and not a secondary condition, hypertension must have been cited as the primary diagnosis.

Data Analysis

Summary statistics were used to describe various characteristics of the study population, including age, race, klabunde comorbidity index, gender, and time period of diagnosis. Prevalence of total adverse events (and adverse events by category) was determined by time period of diagnosis (2001-2003 vs. 2005-2007) and by first-line chemotherapy regimen. Similarly, prevalence of preexisting conditions was determined for patients across both time periods.

In order to determine patterns of bevacizumab use in relation to preexisting conditions, multivariate logistic regression analysis was used to determine factors associated with first-line bevacizumab use in patients diagnosed in 2005-2007. Independent variables include age, race, gender, klabunde index, and preexisting condition category.

Adverse event incidence rates were determined for all treated patients stratified by time period of diagnosis and first-line treatment regimen (chemotherapy with or without bevacizumab). Person-time was determined using cumulative follow-up time (from index date until end of

follow up or death) for all patients. Incidence rates were reported as number of adverse events by person-time under observation (per 100,000 person-days). Incidence rates for all adverse events were determined initially. Subsequently, incidence rates for five common adverse events observed in our cohort and thought to be highly associated with bevacizumab usage (DVT/PE, stroke, myocardial infarction, gastrointestinal hemorrhage, and gastrointestinal perforation) were determined separately using the same process outlined above. Adverse event incidence rates were not determined for patients who did not receive first-line therapy.

A competing risks regression model was created to determine factors associated with first adverse event, taking into consideration death as a competing risk. The purpose of this analysis was to determine whether patients receiving first-line bevacizumab experienced a shorter time to their first treatment-related adverse event than patients receiving first-line chemotherapy without bevacizumab. As such, the primary comparison in the competing risk regression analysis was time to first adverse event for patients diagnosed in 2005-2007 who received first-line chemotherapy and bevacizumab versus patients diagnosed in 2001-2007 who received chemotherapy alone. The competing risks regression model was adjusted for a variety of factors that might influence risk of first adverse event (age, gender, race, comorbidity index, chemotherapy backbone, and preexisting condition). Secondary analyses specifically assessing time to first specific adverse events (DVT/PE, stroke, myocardial infarction, gastrointestinal hemorrhage, and gastrointestinal perforation) were also conducted in similar fashion by diagnosis time period and treatment cohort. In addition, time to first adverse event was compared between bevacizumab and non-bevacizumab treated patients specifically diagnosed in the 2005-2007 time period, adjusting for the same variables mentioned above (age, gender, race,

comorbidity, chemotherapy backbone, and preexisting condition) in the multivariate model and by propensity score weights.

Results

Patient and Treatment Characteristics

A total of 6,821 patients (median age 77) were identified across both time periods (2001-2003 and 2005-2007). Patients were well matched by age, gender, comorbidity score, and race between both diagnosis time periods **(Table 1)**. Similar to other SEER-Medicare mCRC analyses, approximately 62% of patients did not receive first-line chemotherapy as defined by chemotherapy claims within 3 months of diagnosis.**[11, 21]** In a sensitivity analysis adjusting the window of first-line chemotherapy, the majority of patients similarly did not receive chemotherapy at 4 and 6 months from diagnosis (55% and 51% respectively).

Table 1: Demographic and Treatment Characteristics – mCRC Cohort by Diagnosis Year

Characteristic	**Diagnosed 2001-2003 (n=3,539)**	**Diagnosed 2005-2007 (n=3,282)**	**p value***
Mean Age	77.4 (range 65-101)	77.3 (range 65-106)	0.56
< 75	1,354 (38%)	1,202 (39%)	0.39
≥ 75	2,185 (62%)	2,000 (61%)	
Gender			
Male	1,673 (47%)	1,558 (47%)	1.00
Female	1,866 (53%)	1,724 (53%)	
Race			
White	2,957 (84%)	2,708 (83%)	0.27
Non-white	582 (16%)	574 (17%)	
Klabunde score			
< 1	2,386 (74%)	2,177 (72%)	0.06
≥ 1	840 (26%)	848 (28%)	
First-line CTx**			
No 1st line CTx	2,213 (63%)	1,990 (61%)	0.09
1st line CTx alone	1,326 (37%)	670 (20%)	
1st line CTx + bev	NA	622 (19%)	
* 2-sided p values, α = 0.05 ** CTx = chemotherapy			

In 2005-2007, a total of 1,292 patients received some type of first-line chemotherapy, 48% of whom received chemotherapy in combination with bevacizumab. Chemotherapy backbones shifted over time. While 5-FU or capecitabine alone and 5-FU/Capecitabine + irinotecan were the two most common regimens received in 2001-2003, claims for 5-FU/capecitabine + oxaliplatin were seen much more commonly after 2005 **(Table 2)**. Subsequent-line bevacizumab use was seen in approximately 6% of patients diagnosed in 2001-2003.

Table 2: Chemotherapy Regimens by Diagnosis Period – Patients Receiving First-Line Treatment

Chemotherapy regimen or 'backbone'	Dx 2001-3 (chemo alone) (n=1,326)	Dx 2005-7 (chemo alone) (n=670)	Dx 2005-7 (chemo + bevacizumab) (n=622)
5-FU or capecitabine alone	701 (53%)	197 (29%)	85 (14%)
5-FU or capecitabine + oxaliplatin	13 (1%)	215 (32%)	353 (57%)
5-FU or capecitabine + irinotecan	404 (30%)	32 (5%)	85 (14%)
Irinotecan, Oxaliplatin, or both	29 (2%)	76 (11%)	69 (11%)
Unknown chemotherapy regimen	179 (13%)	150 (22%)	30 (5%)

Across both time periods, the majority of patients who did not initially receive first-line bevacizumab also did not receive bevacizumab in later lines of therapy. For example, only 9% of patients who did not receive first-line chemotherapy and 22% of patients who received first-line chemotherapy alone subsequently received bevacizumab at some point before death or end of follow up.

Preexisting Conditions and Adverse Events

Preexisting conditions affecting the cardiovascular (24%) and gastrointestinal (23%) systems were most common, whereas preexisting conditions affecting tissue integrity (1%) and

pulmonary systems (1%) were the least common (**Table 3**). Frequencies of preexisting conditions were comparable across both diagnosis time periods.

The majority of patients (57%) experienced some type of adverse event following the index date. Cardiovascular (36%) and gastrointestinal (29%) adverse events were most common in both time periods. Within each organ system category, a greater proportion of patients were affected by adverse events than by preexisting conditions **(Table 3)**. Tissue integrity adverse events were slightly more common among patients diagnosed in 2005-2007.

Table 3: Preexisting Conditions (Top) and Adverse Events (Bottom) by Diagnosis Year

Preexisting Condition	**Dx 2001-2003 (n=3,539)**	**Dx 2005-2007 (n=3,282)**	**P value***
Cardiovascular	**811 (23%)**	**794 (24%)**	**0.33**
CHF	535 (15%)	572 (17%)	
MI	127 (4%)	94 (3%)	
DVT/PE	92 (3%)	138 (4%)	
Hypertensive emergency/urgency	3 (<1%)	2 (<1%)	
Angina	292 (8%)	203 (6%)	
Cerebrovascular	**180 (5%)**	**150 (5%)**	**1.00**
Cerebrovascular infarction/stroke	66 (2%)	82 (3%)	
Transient ischemic attack	116 (3%)	84 (3%)	
CNS hemorrhage/intracranial bleed	15 (<1%)	11 (<1%)	
Gastrointestinal	**815 (23%)**	**782 (24%)**	**0.33**
Gastrointestinal hemorrhage	767 (22%)	735 (22%)	
Gastrointestinal perforation	34 (1%)	35 (1%)	
Epistaxis	29 (1%)	38 (1%)	
Tissue Integrity	**43 (1%)**	**38 (1%)**	**1.00**
Wound dehiscence	16 (<1%)	25 (1%)	
Internal organ fistula	29 (1%)	15 (<1%)	
Pulmonary	**13 (<1%)**	**22 (1%)**	**0.07**
Pneumonitis/interstitial lung disease	0 (0%)	2 (<1%)	
Hemoptysis	10 (<1%)	18 (1%)	

Adverse Event	**Dx 2001-2003 (n=3,551)**	**Dx 2005-2007 (n=3,348)**	**P value**
Cardiovascular	**1,275 (36%)**	**1211 (37%)**	**0.39**
CHF	719 (20%)	638 (19%)	

MI	203 (6%)	201 (6%)	
DVT/PE	531 (15%)	538 (16%)	
Hypertensive emergency/urgency	4 (<1%)	6 (<1%)	
Angina	220 (6%)	210 (6%)	
Cerebrovascular	**337 (10%)**	**366 (11%)**	**0.18**
Cerebrovascular infarction/stroke	136 (4%)	187 (6%)	
Transient ischemic attack	146 (4%)	116 (4%)	
CNS hemorrhage/intracranial bleed	71 (2%)	60 (2%)	
Toxic/metabolic encephalopathy	48 (1%)	95 (3%)	
Gastrointestinal	**1,000 (28%)**	**992 (30%)**	**0.07**
Gastrointestinal hemorrhage	874 (25%)	806 (25%)	
Gastrointestinal perforation	110 (3%)	150 (5%)	
Epistaxis	70 (2%)	99 (3%)	
Tissue Integrity	**159 (5%)**	**214 (7%)**	**<0.001**
Wound dehiscence	64 (2%)	112 (3%)	
Internal organ fistula	103 (3%)	110 (3%)	
Pulmonary	**69 (2%)**	**50 (2%)**	**1.00**
Pneumonitis/interstitial lung disease	0 (0%)	0 (0%)	
Hemoptysis	49 (1%)	32 (1%)	
Infusion reaction	21 (1%)	19 (1%)	
*2-sided p value, alpha level 0.05			

Factors Associated with Bevacizumab Use

Of the 3,282 patients diagnosed with mCRC in 2005-2007, 622 (19%) received first-line bevacizumab-containing therapy. Multiple logistic regression analysis was used to determine factors associated with first-line bevacizumab use in this cohort. Age ≥ 75 (OR 0.41, 95% CI 0.36-0.47), non-white race (OR 0.67, 95% CI 0.55-9.81) and higher klabunde comorbidity index (OR 0.52, 95% CI 0.44-0.62) were all associated with a decreased likelihood of bevacizumab use. The presence of preexisting tissue integrity and pulmonary conditions were not significantly associated with likelihood of bevacizumab use. Cerebrovascular preexisting conditions were associated with a decreased odds of bevacizumab use (OR 0.49, 95% CI 0.33-0.72) while gastrointestinal preexisting conditions were associated with an increased odds of bevacizumab use (OR 2.26, 95% CI 1.96-2.61) **(Table 4)**. In a separate logistic regression analysis focusing specifically on patients with a history of gastrointestinal preexisting condition in the 12 months

prior to index date, epistaxis does not predict an increased odds of bevacizumab use (OR 1.97, p=0.06) while both gastrointestinal hemorrhage (OR 3.42, p=0.004) and gastrointestinal perforation (OR 6.58, p<0.001) do.

Table 4: Factors Associated with First-Line Bevacizumab Use (2005-2007)

Independent variables	OR	95% CI	P value
Age ≥ 75	**0.41**	**0.36-0.47**	**<0.001**
Female gender	0.90	0.79-1.03	0.13
Non-white race	**0.67**	**0.55-0.81**	**<0.001**
Klabunde index ≥ 1	**0.52**	**0.44-0.62**	**<0.001**
Preexisting conditions			
Cardiovascular	**1.20**	**1.01-1.42**	**0.04**
Cerebrovascular	**0.49**	**0.33-0.72**	**<0.001**
Gastrointestinal	**2.26**	**1.96-2.61**	**<0.001**
Tissue integrity	1.54	0.92-2.60	0.10
Pulmonary	1.59	0.75-3.35	0.23
Reference: Age <75, male gender, white race, klabunde <1, no preexisting condition			

Incidence of Adverse Events

Adverse event incidence rates were determined by diagnosis year and first-line treatment category. Patients who did not receive first-line chemotherapy were not included in this analysis, since the observed adverse events in these patients could not be attributed to chemotherapy or biologic use. Patients who received first-line chemotherapy without bevacizumab in 2005-2007 had the highest adverse event incidence rate across all categories (**Table 5**). These incidence rates do not take into consideration the various factors that might influence oncologists to treat with bevacizumab versus chemotherapy alone. However, adverse event incidence rates were comparable between patients in 2001-2003 receiving first-line chemotherapy (135 events / 100,000 person-days) and patients in 2005-2007 receiving first-line chemotherapy + bevacizumab (141 events / 100,000 person-days). Incidence of specific adverse events (DVT/PT, stroke, myocardial infarction, gastrointestinal hemorrhage, gastrointestinal

perforation) were also similar between patients diagnosed in 2001-2003 receiving first-line chemotherapy and patients diagnosed in 2005-2007 receiving first-line chemotherapy + bevacizumab.

Table 5: Incidence Adverse Events by Treatment Cohort and Diagnosis Time Period

	Incidence Rate (AEs / 100,000 person-days)					
Dx Time Period and Treatment Cohort	**All AEs**	**DVT/PE**	**Stroke**	**GI hemorrhage**	**GI perforation**	**Myocardial infarction**
Dx 2001-2003						
First-line CTx alone (no bev)	135	36	5	17	2	7
Dx 2005-2007						
First-line CTx alone (no bev)	166	35	10	25	6	12
First-line CTx + bev	141	35	8	17	6	8

Time to First Adverse Event – Competing Risks Regression Analysis

In a competing risks regression model, treatment with chemotherapy and bevacizumab in 2005-2007 was not associated with a decreased time to first adverse event compared with receipt of chemotherapy alone in 2001-2007 (HR 0.97, p=0.955), taking into consideration other factors (e.g. preexisting conditions, age, race, gender) that may also predispose patients to earlier adverse events during the course of treatment. (**Table 6**) Adjusting for these same factors, bevacizumab-treated patients similarly did not experience a decreased time to specific adverse events (DVT/PE, stroke, gastrointestinal hemorrhage, gastrointestinal perforation, myocardial infarction) compared with non bevacizumab-treated patients. (**Figure 1**)

Table 6: Factors Associated with 1st Adverse Event (Any AE) in Patients Receiving First-Line Therapy – Competing Risks Regression Model

Independent variable	HR	95% CI	P value
1st line chemotherapy + bevacizumab (2005-2007)	**0.97**	**0.87-1.08**	**0.55**
Age ≥ 75	1.05	0.91-1.16	0.66
Klabunde score ≥ 1	1.04	0.93-1.17	0.45
Non-white race	1.03	0.91-1.16	0.66
Female Gender	1.02	0.94-1.11	0.67
Chemotherapy backbone regimen			
5-FU/Capecitabine + oxaliplatin	0.92	0.81-1.04	0.17
5-FU/Capecitabine + irinotecan	1.00	0.89-1.12	0.97
Irinotecan, oxaliplatin, or both	0.99	0.83-1.19	0.93
Regimen unknown	1.07	0.93-1.22	0.35
Preexisting conditions			
Cardiovascular	1.02	0.92-1.12	0.73
Cerebrovascular	1.06	0.86-1.30	0.58
Gastrointestinal	0.94	0.87-1.03	0.17
Tissue integrity	0.97	0.73-1.29	0.84
Pulmonary	0.91	0.57-1.46	0.70
Ref: 1st line chemo alone without bevacizumab (2001-2007) age <75, klabunde <1, white race, male gender, no preexisting condition, 5-FU or capecitabine alone			

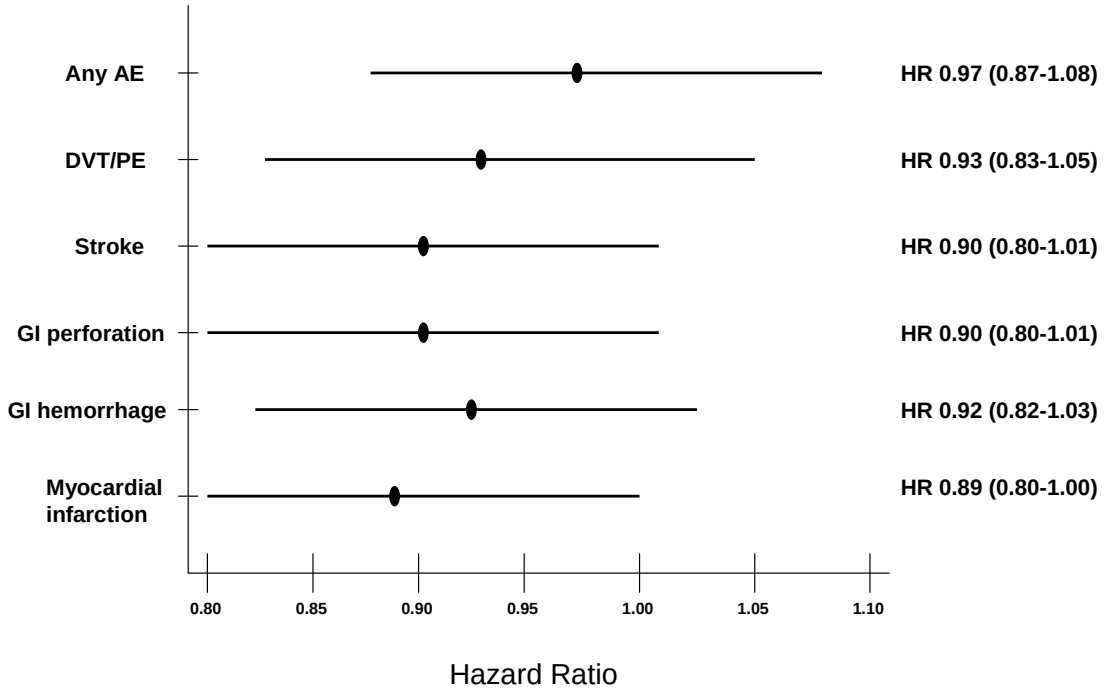

Figure 1: Time to First Adverse Event Chemo+Bev (2005-2007) vs. Chemo alone (2001-2003)

In a separate competing risks regression analysis focusing solely on patients diagnosed in 2005-2007 (post bevacizumab approval), treatment with chemotherapy and bevacizumab was also not associated with a shorter time to adverse event than treatment with chemotherapy alone during this same time period (HR 1.02, 95% CI 0.90-1.16, p=0.77).

Discussion

We investigated the safety of bevacizumab in older mCRC patients with various underlying comorbidities. Using SEER-Medicare claims data for mCRC patients age ≥ 65 diagnosed between 2001 and 2007, we determined the 1) prevalence of preexisting conditions which are thought to increase risk of bevacizumab-related adverse events, 2) factors associated with

bevacizumab utilization, and 3) risk factors for bevacizumab-related adverse events that have been reported in the package insert and clinical trials.

Our findings suggest that, when controlling for various factors that might impact the risk of adverse events, older bevacizumab-treated patients do not experience an increased risk of adverse events (including DVT/PE, stroke, myocardial infarction, gastrointestinal hemorrhage, and gastrointestinal perforation) during the course of treatment compared with non bevacizumab-treated patients. We also did not find an increased adverse event incidence rate in patients who receive chemotherapy with bevacizumab compared with patients who receive chemotherapy alone. Importantly, we found that most preexisting conditions, with the exception of cerebrovascular conditions, were not associated with a decreased utilization of bevacizumab in older patients. While we did not observe an increased incidence of stroke in bevacizumab-treated patients, prior history of stroke or cerebrovascular hemorrhage may be a significant deterrent to bevacizumab utilization for most clinicians, as cautioned in the bevacizumab product label. It is possible that clinicians are more wary of bevacizumab use in patients with cerebrovascular conditions because these patients may be more debilitated at baseline and because cerebrovascular adverse events may be particularly morbid and difficult to manage. Interestingly, preexisting gastrointestinal hemorrhage or perforation were both associated with a significantly increased odds of bevacizumab utilization. While bevacizumab use is contraindicated in the setting of an acute gastrointestinal perforation, both hemorrhage and perforations are common problems associated with an intact primary tumor in patients with metastatic colorectal cancer. It is possible that patients who survive these complications may be more robust and therefore better candidates for treatment. These findings suggest that

oncologists' decisions to prescribe bevacizumab are influenced by some, but not all, of the precautions listed in the package insert.

Unlike a recent SEER-Medicare study which demonstrated a slightly increased risk of stroke and gastrointestinal perforation in bevacizumab recipients, we did not find such a pattern when controlling for backbone chemotherapy regimen and a variety of important preexisting conditions. Our findings suggest that in well-selected older patients, bevacizumab use is not associated with a significantly increased risk of treatment-related adverse events.

In considering these findings, several limitations should be noted. First, there are many factors that influence treatment decision-making and adverse event risk (e.g. disease extent, ECOG performance status) that are not measured or available in SEER-Medicare. While previous studies have used claims indicators to estimate performance status, there are no widely used, reliable methods using SEER-Medicare claims to assess performance status at the time of diagnosis when treatment decisions are being made.**[22]** As patients with poorer ECOG performance status may, in general, be less likely to receive bevacizumab in first-line treatment and more likely to experience adverse events, our findings may have underestimated the relative risk of bevacizumab use. Though we included clinical and demographic factors which may also influence treatment choices and outcomes and can be reliably assessed using SEER-Medicare (age, race, comorbidity, gender), we were unable to control for certain important factors like ECOG performance status which influence treatment decision-making and adverse event risk.

The cohort identified in this study consisted exclusively of patients diagnosed with de novo metastatic disease. Because the SEER program only obtains stage at diagnosis, patients with earlier stage colorectal cancer who developed relapse or recurrence could were not included. Since patients with de novo and relapsed mCRC are largely treated in the same way, our findings

can be extrapolated to the broader population of mCRC patients, though it is possible that toxicity from prior adjuvant chemotherapy regimens or prior surgery in the relapsed population may influence adverse event risk.

Next, in order to capture the spectrum of potential bevacizumab-related adverse events, we looked for claims for events that have been attributed to bevacizumab in the literature and package insert. Yet many of these adverse events (e.g. hypertension, gastrointestinal hemorrhage, DVT/PE) are common among colorectal cancer patients, regardless of treatment regimen. In fact, mCRC patients who do not receive bevacizumab may be more likely to experience certain adverse events by nature of the various factors (e.g. performance status, disease extent, surgical complications) which led to the initial decision not to use bevacizumab as part of first-line therapy. We may therefore have captured general treatment or disease-related adverse events rather than bevacizumab-specific adverse events. While it is possible to control for many underlying disease characteristics in a randomized, controlled clinical trial, it is difficult to do so using claims data. As such, our findings may have overestimated the relative safety of bevacizumab compared with chemotherapy alone. Another key limitation of SEER-Medicare is that we were only able to capture adverse events associated with Medicare claims; many important toxicities which did not result in resource utilization or appropriate diagnosis coding may therefore have been missed in this analysis.

Next, our main comparison focuses on patients treated with chemotherapy + bevacizumab in the post-bevacizumab era (2005-2007) versus patients treated with chemotherapy alone in both eras (2001-2007). We chose not to focus solely on patients receiving chemotherapy alone in the pre-bevacizumab era (2001-2003) because the chemotherapy regimens used were vastly different between these two time periods. For example, only 1% of patients in 2001-2003 were identified

as receiving regimens combining 5-FU or capecitabine with oxaliplatin whereas nearly 44% of patients in 2005-2007 received this combination. Including the broader group of chemotherapy-only treated patients allowed for inclusion of modern chemotherapy regimens, which is likely to be an important factor influencing adverse event risk. In order to further mitigate the effect of chemotherapy regimen on the primary outcome (time to first adverse event), we adjusted for chemotherapy backbone in the competing risks regression model.

Another limitation of this analysis is that we chose to capture various preexisting conditions that might increase the risk of bevacizumab-related adverse events, but were limited by the database from determining whether presence of the specific preexisting condition increased the risk of an adverse event of the same type. For example, a claim for DVT/PE in the 12 months prior to diagnosis may appear in a particular patient's claims several years after the initial event. For the purposes of the primary analysis, we chose to take a conservative approach by not double counting preexisting conditions and adverse events of the same type in the same patient. However, because of our inability to distinguish claims for new adverse events versus ongoing claims for a preexisting condition, we may not have been able to assess whether bevacizumab exacerbates complications related to a specific preexisting condition. We therefore conducted a sensitivity analysis to allow for double counting preexisting conditions and adverse events of the same type. In so doing, we found that patients who received chemotherapy + bevacizumab in the post-bevacizumab era (2005-2007) did not have a decreased time to first adverse event relative to patients treated with chemotherapy alone (2001-2007) (HR 0.97, 95% CI 0.87-1.08, p=0.55), similar to the findings from our primary analysis. We did find, however, that patients with preexisting cardiovascular conditions had a decreased time to first adverse event (HR 1.13, 05% CI 1.02=1.25, p=0.02) compared to patients without this comorbidity. Nonetheless, we could not

confirm that the adverse events experienced by these patients were de novo events. A key limitation of SEER-Medicare is therefore the inability to identify new diagnoses versus ongoing claims for previous diagnoses.

Despite these limitations, our results suggest that in a large population of older patients with mCRC treated in real-world clinical settings, patients who receive bevacizumab may not experience an increased incidence or decreased time to adverse events than patients receiving chemotherapy alone. Our findings also suggest that preexisting comorbidities do not necessarily deter oncologists from using bevacizumab in selected older patients. Few previous studies have used SEER-Medicare to explore the safety of newer biologics and chemotherapeutics in older patient populations. Particularly since older patients are not adequately represented in clinical trials, it is critical that registry and claims databases be used for safety assessments when feasible. While SEER-Medicare is an excellent source of data on older patients with cancer, similar research using other large insurance claims databases that may have more detail on the nature and timing of specific adverse events would be valuable. Understanding the major safety signals for newer agents in older patients will help to facilitate more informed risk-benefit discussions between patients and oncologists.

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Appendix 1: Preexisting Conditions, Adverse Events, and ICD-9-CM Codes

Category	ICD-9-CM code
Cardiovascular	
Congestive heart failure	428.0, 428.1, 428.2 (428.20 – 428.23), 428.3 (428.30-428.33), 428.4 (428.40-428.43), 428.9
Deep vein thrombosis / pulmonary embolus	415.1, 415.13, 453.2, 453.3, 453.4 (453.40-453.42), 453.8 (453.81-453.89), 453.9
Acute Myocardial infarction	410.0-410.9, 411.0
Hypertensive urgency or emergency, hypertensive encephalopathy, complications of hypertension (blindness, retinopathy, renal failure, CHF) (accompanied by code for ER visit or hospitalization)	360.42, 362.11, 401.0, 402, 403.0, 403, 404, 405, 437
Angina	411.1, 413
Central Nervous System/Cerebrovascular	
Cerebrovascular infarction/stroke	433.01-433.91, 434.11, 434.91
Transient Ischemic Attack (TIA)	435.3, 435.9
Encephalopathy (metabolic/toxic) *	348.31, 349.82
CNS hemorrhage/intracranial bleed	430, 431, 432
Gastrointestinal	
Gastrointestinal hemorrhage	578.0, 578.1, 578.9
Gastrointestinal perforation	569.83
Epistaxis	784.7
Tissue integrity	
Wound dehiscence	998.30-998.33
Internal organ fistulas (including gastrointestinal fistula)	530.84, 537.4, 569.81, 576.4, 593.82, 596.1, 596.2, 599.1, 619.0, 619.1, 619.2, 619.8, 619.9, 576.4, 998.6, 565.1, 569.81
Pulmonary	
Pneumonitis, Interstitial lung disease	495.8, 495.9
Infusion reaction *	999.88, 999.89
Hemoptysis	786.3, 786.30, 786.39

*Adverse event only