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Research Article

Cardiovascular Events in Cancer Patients Treated with Highly or Moderately Emetogenic Chemotherapy: Results from a Population-Based Study

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Studies on cardiovascular safety in cancer patients treated with highly or moderately emetogenic chemotherapy (HEC or MEC), who may have taken the antiemetic, aprepitant, have been limited to clinical trials and postmarketing spontaneous reports. Our study explored background rates of cardiovascular disease (CVD) events among HEC- or MEC-treated cancer patients in a population-based setting to contextualize events seen in a new drug development program and to determine at a high level whether rates differed by aprepitant usage. Medical and pharmacy claims data from the 2005–2007 IMPACT National Benchmark Database were classified into emetogenic chemotherapy categories and CVD outcomes. Among 5827 HEC/MEC-treated patients, frequencies were highest for hypertension (16–21%) and composites of venous (7–12%) and arterial thromboembolic events (4–7%). Aprepitant users generally did not experience higher frequencies of events compared to nonusers. Our study serves as a useful benchmark of background CVD event rates in a population-based setting of cancer patients.

1. Background/Objective

Chemotherapy-induced nausea and vomiting (CINV) negatively impacts the quality of life in cancer patients [1] and may lead to nonadherence to or dose reductions in chemotherapy [2]. Potential cardiac effects of antiemetics warrant special attention, given an estimated 13–60% burden of cardiovascular-related diseases that increases with age, among cancer patients [3–5]. Cardiovascular disease (CVD) can be preexisting, a result or natural progression of the malignancy or an adverse event resulting from chemotherapeutic treatment, such as anthracyclines and alkylating agents [6, 7]. For example, cyclophosphamide treatment has been associated with a 7–28% incidence of heart failure, cisplatin has been associated with an 8.5% incidence of venous thromboembolism, including deep vein thrombosis and pulmonary embolism [8], and doxorubicin/daunorubicin has been associated with 0.5–3% incidence of arrhythmias [9].

Aprepitant is currently the only FDA-approved neurokinin (NK1) receptor antagonist (RA) that, when coadministered with other antiemetics, such as corticosteroids (dexamethasone) and serotonin 5-HT_3 receptor antagonists (e.g., dolasetron, granisetron, ondansetron, and palonosetron), augments the prevention of acute and, particularly, delayed CINV [10]. Although aprepitant has been shown to be generally well tolerated in clinical trials [11], isolated cases of serious adverse events, such as bradycardia [12] and hypertension [13], have been reported in two highly emetogenic chemotherapy (HEC) studies comparing aprepitant plus ondansetron and dexamethasone to the standard regimen of ondansetron and dexamethasone, alone [14, 15]. Other cardiovascular events (>0.5% and greater than standard therapy), regardless of causality, have also been reported in patients treated with the aprepitant regimen in either HEC or MEC studies, including myocardial infarction, tachycardia,

Table 1: Characteristics of 5827 patients with select* cancers and ≤4 cycles of HEC, MEC, or HEC/MEC combined, 2005–2007 IMPACT National Benchmark Database (OptumInsight, Eden Prairie, MN).

Characteristic	HEC and/or MEC ($N = 5827$)			HEC only ($N = 330$)			MEC only ($N = 5269$)			HEC/MEC combined ($N = 228$)		
	Total	No Aprep	Aprep	Total	No Aprep	Aprep	Total	No Aprep	Aprep	Total	No Aprep	Aprep
% Male	21.90	27.56	11.14	45.45	52.73	38.18	19.57	25.59	7.52	41.67	47.48	32.58
% Female	78.10	72.44	88.86	54.55	47.27	61.82	80.43	74.41	92.48	58.33	52.52	67.42
Mean age (yrs)	54.7	56.3	51.7	54.8	55.8	53.8	54.6	56.2	51.4	56.2	57.1	54.8
% Age ≥60	32.52	38.22	21.69	35.15	38.79	31.52	32.23	38.29	20.10	35.53	35.97	34.83
% Age ≥65	14.35	18.31	6.82	14.85	16.97	12.73	14.22	18.33	5.98	16.67	19.42	12.36
% Breast cancer	60.41	50.98	78.31	26.67	19.39	33.94	64.07	53.74	84.74	24.56	18.71	33.71
% Colorectal cancer	7.00	9.30	2.64	6.97	6.67	7.27	6.95	9.45	1.94	8.33	8.63	7.87
% Head and neck cancer	5.85	5.74	6.07	26.97	26.67	27.27	3.93	4.18	3.42	19.74	20.14	19.10
% Lung cancer	25.73	32.91	12.09	36.67	44.85	28.48	24.05	31.51	9.11	48.68	53.96	40.45
% Ovarian cancer	5.59	6.47	3.93	6.67	7.27	6.06	5.60	6.55	3.70	3.95	3.60	4.49
% Prior history of CVD‡	50.76	55.28	42.19	61.52	64.85	58.18	49.86	54.68	40.21	56.14	58.99	51.69

*Breast, colorectal, head and neck, lung, and ovarian cancers.
‡Prior history of CVD is defined as a diagnosis of any of the following prior to the start of HEC and/or MEC: hypertension, diabetes, coronary artery disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, deep vein thrombosis (DVT), and pulmonary embolism (PE).
Note: percentage by type of cancer may add to >100% due to patients having multiple cancer types.

deep vein thrombosis, flushing, hypertension, and hypotension [12]. However, results from clinical trials may not reflect those observed in clinical practice, and population-based studies of the cardiovascular effects of aprepitant are lacking. We aimed to quantify background rates of several CVD-related events among HEC and/or MEC-treated cancer patients for two purposes: to understand expected rates among cancer patients in order to contextualize events which may be seen in our clinical development program of a similar patient population with a similar drug and to further understand at a high level whether rates differed by the decision to treat with aprepitant, recognizing that users versus nonusers may differ with respect to disease severity, access to care, preexisting conditions, and other factors. Therefore, the objective of this study was to use a large, US healthcare claims database to assess the frequency of CVD-related events among HEC and/or MEC-treated cancer patients and to determine if the frequency was impacted by the decision to treat with aprepitant.

2. Methods

A retrospective cohort study of adult patients with select cancers, treated with HEC and/or MEC, was conducted using 2005–2007 data from the IMPACT National Benchmark Database (OptumInsight, Eden Prairie, MN), a comprehensive, deidentified healthcare claims database that is representative of the nonelderly, insurance-carrying population in the United States. At the time of our analysis, the database contained inpatient/outpatient and pharmacy claims, a subset of lab results and enrolment information on over 82 million members from 45 healthcare plans serving nine census regions from 1997 to 2007. The IMPACT database is HIPAA compliant and features encrypted member and provider IDs.

The study included several cancer types commonly treated with HEC or MEC, namely, breast, colorectal, head and neck, lung, and ovarian cancer patients (Table 4), in adults with ≤4 cycles of HEC and/or MEC as documented in one or more claims in the year 2006. We choose ≤4 cycles because two-thirds of all treated patients had up to and including 4 cycles. The study analysis period was defined as the first day of the first HEC and/or MEC cycle to 30 days past the first day of the last cycle. The start of a new cycle of chemotherapy was defined by a period of more than 7 days but less than 45 days between cycles. The start of treatment was the first HEC and/or MEC claim in 2006, with 3 months prior with no claim ("wash-in" period) to ensure that there was no CVD effect of HEC/MEC treatment in 2005 that was carried over into 2006. The end of treatment was reached after 45 days of no additional HEC and/or MEC claim following the last claim ("wash-out" period) to ensure that all CVD effects from HEC/MEC treatment in 2006 were captured. To illustrate, for patients whose first HEC or MEC claim was between January 1, 2006 and March 31, 2006, the enrolment criteria for inclusion in the study extended as far back as October 1, 2005. For patients whose last claim in 2006 was seen after December 1, 2006, enrolment into 2007 to look for further treatment and the 45 day "wash-out" period was required.

Data on aprepitant exposure and chemotherapy was obtained from the inpatient/outpatient and pharmacy claims. Chemotherapeutic agents were defined as HEC if they were associated with >90% of treated patients having emesis, and

Table 2: Cardiovascular-related events in 5827 patients with select* cancers and ≤4 cycles of HEC, MEC, or HEC/MEC combined, 2005–2007 IMPACT National Benchmark Database (OptumInsight, Eden Prairie, MN).

Cardiovascular and thromboembolic events	HEC and/or MEC ($N = 5827$)		HEC only ($N = 330$)		MEC only ($N = 5269$)		HEC plus MEC ($N = 228$)	
	n	%	*n*	%	*n*	%	*n*	%
Angina pectoris	32	0.55	3	0.91	28	0.53	1	0.44
Arterial disorder	9	0.15	2	0.61	7	0.13	0	—
Arterial occlusive disease	2	0.03	0	—	2	0.04	0	—
Arterial thromboembolic (excluding chest pain/discomfort)	254	4.36	23	6.97	220	4.18	11	4.82
Arterial thromboembolic (including chest pain/discomfort)	881	15.12	72	21.82	754	14.31	55	24.12
Cardiac arrest	25	0.43	4	1.21	19	0.36	2	0.88
Cardiac disorder	3	0.05	0	—	3	0.06	0	—
Cardio-respiratory arrest	27	0.46	4	1.21	21	0.40	2	0.88
Cardiogenic shock	1	0.02	0	—	1	0.02	0	—
Cerebral ischemia	62	1.06	8	2.42	53	1.01	1	0.44
Cerebrovascular accident	52	0.89	3	0.91	49	0.93	0	—
Chest pain or discomfort	719	12.34	62	18.79	610	11.58	47	20.61
Circulatory collapse	14	0.24	1	0.30	13	0.25	0	—
Embolism	97	1.66	8	2.42	83	1.58	6	2.63
Hypertension	966	16.58	68	20.61	854	16.21	44	19.30
Hypotension	149	2.56	11	3.33	126	2.39	12	5.26
Iliac artery embolism	2	0.03	1	0.30	1	0.02	0	—
Increased platelets	7	0.12	0	—	7	0.13	0	—
Intermittent claudication	9	0.15	2	0.61	4	0.08	3	1.32
Myocardial infarction	11	0.19	1	0.30	10	0.19	0	—
Myocardial ischemia	11	0.19	0	—	11	0.21	0	—
Peripheral embolism	38	0.65	4	1.21	30	0.57	4	1.75
Peripheral ischemia	—	—	0	—	0	—	0	—
Sudden death	—	—	0	—	0	—	0	—
Syncope	140	2.40	12	3.64	117	2.22	11	4.82
Venous thromboembolic	450	7.72	40	12.12	383	7.27	27	11.84

*Breast, colorectal, head and neck, lung, and ovarian cancers.

MEC, if associated with 30–90% of patients having emesis (Table 5). Chemotherapies were classified by a physician within our department using previously published criteria as guidance [16, 17]. Cardiovascular outcomes of interest included arterial and venous thromboembolic events, individually as well as a composite event, as well as cardiac arrest, hypertension, hypotension, increased platelets, sudden death, and syncope (Table 4). Patient characteristics included gender, age, tumor type, and prior history of cardiovascular disease. Prior CVD was defined as the presence of a claim for hypertension, diabetes, coronary artery disease, myocardial infarction, congestive heart failure, ischemic stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolism anytime before HEC or MEC initiation.

Subjects who used either HEC or MEC were categorized into 3 emetogenic chemotherapy groups: HEC-only, MEC-only, or HEC/MEC combined. All analyses, including the distribution (% or mean) of patient characteristics and the frequency of CVD outcomes of interest, were tabulated overall and stratified by aprepitant usage and emetogenic category of chemotherapy. Analyses were not further stratified by number of chemotherapy cycles, however, due to insufficient sample size. This study was purely descriptive, and therefore, no formal statistical comparison was made between aprepitant users and nonusers. Rather, the data was visually inspected for noteworthy absolute differences of ≥5% or relative differences of ≥1.5 times.

3. Results

The number of cancer patients with the cancer types of interest who had at least 3 months of continuous enrolment and pharmacy benefit, at least one HEC or MEC claim, and ≤4 cycles of chemotherapy was 5827. Among these patients, the distribution of patients by cancer type was 60.4% with breast, 25.7% with lung, 7.0% with colorectal,

Table 3: Cardiovascular-related events in 5827 patients with select* cancers and ≤4 cycles of HEC, MEC, or HEC/MEC combined, by aprepitant status, 2005–2007 IMPACT National Benchmark Database (OptumInsight, Eden Prairie, MN).

Cardiovascular and thromboembolic events	HEC and/or MEC				HEC only				MEC only				HEC/MEC combined			
	No Aprep (N = 2010)		Aprep (N = 3817)		No Aprep (N = 165)		Aprep (N = 165)		No Aprep (N = 1756)		Aprep (N = 3513)		No Aprep (N = 89)		Aprep (N = 139)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Angina pectoris	20	0.52	12	0.60	2	1.21	1	0.61	18	0.51	10	0.57	0	—	1	1.12
Arterial disorder	3	0.08	6	0.30	1	0.61	1	0.61	2	0.06	5	0.28	0	—	0	—
Arterial occlusive disease	1	0.03	1	0.05	0	—	0	—	1	0.03	1	0.06	0	—	0	—
Arterial thromboembolic (excludes chest pain/discomfort)	196	5.13	58	2.89	14	8.48	9	5.45	175	4.98	45	2.56	7	5.04	4	4.49
Arterial thromboembolic (includes chest pain/discomfort)	611	16.01	270	13.43	40	24.24	32	19.39	534	15.20	220	12.53	37	26.62	18	20.22
Cardiac arrest	22	0.58	3	0.15	2	1.21	2	1.21	18	0.51	1	0.06	2	1.44	0	—
Cardiac disorder	2	0.05	1	0.05	0	—	0	—	2	0.06	1	0.06	0	—	0	—
Cardio-respiratory arrest	24	0.63	3	0.15	2	1.21	2	1.21	20	0.57	1	0.06	2	1.44	0	—
Cardiogenic shock	1	0.03	0	—	0	—	0	—	1	0.03	0	—	0	—	0	—
Cerebral ischemia	50	1.31	12	0.60	4	2.42	4	2.42	45	1.28	8	0.46	1	0.72	0	—
Cerebrovascular accident	46	1.21	6	0.30	3	1.82	0	—	43	1.22	6	0.34	0	—	0	—
Chest pain or discomfort	488	12.78	231	11.49	36	21.82	26	15.76	420	11.96	190	10.82	32	23.02	15	16.85
Circulatory collapse	11	0.29	3	0.15	1	0.61	0	—	10	0.28	3	0.17	0	—	0	—
Embolism	77	2.02	20	1.00	5	3.03	3	1.82	68	1.94	15	0.85	4	2.88	2	2.25
Hypertension	697	18.26	269	13.38	41	24.85	27	16.36	629	17.90	225	12.81	27	19.42	17	19.10
Hypotension	117	3.07	32	1.59	7	4.24	4	2.42	104	2.96	22	1.25	6	4.32	6	6.74
Iliac artery embolism	1	0.03	1	0.05	0	—	1	0.61	1	0.03	0	—	0	—	0	—
Increased platelets	6	0.16	1	0.05	0	—	0	—	6	0.17	1	0.06	0	—	0	—
Intermittent claudication	5	0.13	4	0.20	1	0.61	1	0.61	3	0.09	1	0.06	1	0.72	2	2.25
Myocardial infarction	11	0.29	0	—	1	0.61	0	—	10	0.28	0	—	0	—	0	—
Myocardial ischemia	9	0.24	2	0.10	0	—	0	—	9	0.26	2	0.11	0	—	0	—
Peripheral embolism	25	0.65	13	0.65	2	1.21	2	1.21	21	0.60	9	0.51	2	1.44	2	2.25
Peripheral ischemia	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Sudden death	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
Syncope	96	2.52	44	2.19	4	2.42	8	4.85	86	2.45	31	1.77	6	4.32	5	5.62
Venous thromboembolic	308	8.07	142	7.06	24	14.55	16	9.70	268	7.63	115	6.55	16	11.51	11	12.36

*Breast, colorectal, head and neck, lung, and ovarian cancers.

Table 4: ICD-9 codes for selected cancers and cardiovascular-related events.

Cancer	ICD-9-CM code(s)
Breast	174.0-174.6, 174.8, 174.9, 175, 175.0, 175.9
Colorectal	153, 153.0-153.9, 154, 154.0-154.3, 154.8, 230.3-230.6
Head and neck	140.0-140.9, 141.0-141.9, 142.0-142.9, 143.0-143.9, 144.0-144.9, 145.0-145.9, 146.0-146.9, 147.0-147.9, 148.0-148.9, 149.0-149.9, 161.0-161.9
Lung	162.2-162.5, 162.8, 162.9
Ovarian	183.0
CVD-related events	**ICD-9-CM code(s)**
Arterial Thromboembolic events	
Angina pectoris	413.x
Arterial disorder	459.9
Arterial occlusive disease	362.34
Cardiac disorder	997.1
Cardio-respiratory arrest	427.5, 799.1
Cardiogenic shock	785.51
Cerebral ischemia	435, 435.8, 435.9, 437.1
Cerebrovascular accident	436, 437
Chest pain or discomfort	586.5x
Circulatory collapse	785.5, 785.50
Embolism	433, 434.x, 444.0–444.2, 444.21, 444.22, 444.81, 444.89, 444.9, 445, 445.01, 445.02, 445.81, 445.89
Iliac artery embolism	444.81
Intermittent claudication	440.21
Myocardial infarction	410.x
Myocardial ischemia	414.8
Peripheral embolism	444.x
Peripheral ischemia	414
Cardiac Arrest	427.5
Hypertension	401.x, 405.x, 401.0, 401.1, 401.9, 796.2
Hypotension	458.x
Increased platelets	238.71, 287.1
Sudden death	798, 798.2
Syncope	780.0, 780.2, 780.9
Venous thromboembolic events	
Deep vein thrombosis	451.1, 451.11, 451.19, 451.2, 451.81, 451.83, 451.84, 453.1–453.4, 453.41, 453.42, 453.8, 453.9
Phlebitis	451.x
Phlebitis superficial	451.1
Pulmonary embolism	415.1, 415.11, 415.12, 415.19
Superior vena cava occlusion	459.2, 901.2, 38.8
Thrombophlebitis	451.x4
Thrombophlebitis superficial	451.0, 451.82, 671.2x
Varicophlebitis	454.1, 454.2, 454.8
Vena cava thrombosis	453.2
Venous thrombosis	453.0, 453.4, 453.9

5.9% with head and neck, and 5.6% with ovarian cancer (Table 1). Over 90% of patients had treatment by MEC-only, followed by 5.7% with HEC-only and 3.9% with both HEC and MEC. Females comprised the majority across chemotherapy groups (55% HEC-only; 80% MEC-only; 58% HEC/MEC combination), and this gender difference was greater among those who took aprepitant compared to those who did not. The mean age (~55 years) was similar across the chemotherapy groups, as was the percentage aged 60 years or older. Those taking aprepitant, however, were 2 to 4.8 years younger, on average, and comprised fewer patients aged 60+ years compared to those who did not take aprepitant. In HEC-only patients, 32% of aprepitant users were 60+ compared to 39% of nonusers; in MEC-only patients, the percentages were 20% versus 38%, respectively; and in the HEC/MEC combination group, the percentages were 35% versus 36%, respectively. Using a more traditional cutpoint of age 65+ years, similar results were found with aprepitant users having a smaller proportion of older patients than nonusers. Over half of patients had a history of CVD *before* their chemotherapy treatment, with the HEC-only group having a higher burden (62%) compared to the MEC-only group (50%) and HEC/MEC combined group (56%). The proportion with a prior history of CVD was lower in aprepitant users compared to nonusers.

Overall, the frequencies of cardiovascular and thromboembolic-related events *following* any HEC or MEC treatment were mostly driven by the MEC-only treatment group, comprising 90% of patients (Table 2). There were no sudden deaths. The frequencies of increased platelets, arterial disorder, arterial occlusive disease, cardiac disorder, cardiogenic shock, iliac artery embolism, intermittent claudication and peripheral ischemia were low ($n \leq 10$) in this cohort.

Hypertension occurred in 16% of the MEC-only chemotherapy group and was slightly higher among the smaller HEC-only and HEC/MEC combination groups. Chest pain or discomfort occurred in 12% of the MEC-only patients, in 19% of HEC-only patients, and in 21% of combined HEC/MEC patients. All other single adverse CVD events occurred at a frequency less than 5%, including MI and cerebrovascular accident, with the exception of hypotension, which occurred in 5.3% of those treated with HEC/MEC combined. The composite measure for arterial thromboembolic events, excluding chest pain and discomfort, ranged from 4% among the MEC-only group to 7% in the HEC-only

group. The composite of venous thromboembolic events was 12% for the HEC-only and the HEC/MEC combined groups and 7% for the MEC-only group.

Stratified by the decision to include aprepitant in the antiemetic regimen (Table 3), the analysis demonstrated that in the MEC-only treated group, the composite of arterial thromboembolic events (without chest pain and discomfort), cardiac arrest, cardiorespsiratory arrest, cerebral ischemia, cerebrovascular accident, embolism, hypotension, and hypertension were more frequent ($\geq$1.5 times or $\geq$5% absolute difference) among those who did not use aprepitant compared to those who did. Though based on small numbers ($n \leq 10$), nonusers also had a higher rate of circulatory collapse (10 versus 3), increased platelet (6 versus 1), intermittent claudication (3 versus 1), and myocardial ischemia (9 versus 2). In all but two events (arterial disorder and arterial occlusive disorder) of the CVD-related categories among the MEC-only treated group, the frequency of CVD events was lower among aprepitant users versus nonusers.

For the HEC-only and the combined HEC/MEC chemotherapy groups, the numbers of individual cardiovascular-related events were generally too small ($n \leq 10$) to make reliable comparisons across aprepitant status. However, where cells sizes were larger, HEC-only-treated patients who did not use aprepitant compared to users had a higher frequency of chest pain/discomfort as a diagnosis, a composite diagnosis of arterial thromboembolic events, excluding chest pain and discomfort, hypertension, and a composite measure of venous thromboembolic events. Though rare ($n \leq 10$), additional events that were more frequent among nonusers compared to aprepitant users included angina pectoris (2 cases versus 1), embolism (5 versus 3), and hypotension (7 versus 4); in contrast, aprepitant users had a higher frequency of syncope (4 cases versus 8) than nonusers.

Among patients treated with both HEC and MEC, there was a higher frequency of chest pain and discomfort as a diagnosis and a composite diagnosis of arterial thromboembolic events, including chest pain, in nonusers of aprepitant compared to users. Users had a higher frequency of hypotension (6 cases versus 6), intermittent claudication (2 versus 1), and peripheral embolism (2 versus 2).

4. Discussion

The proportion of patients with CVD events was low ($\leq$5%) for many events across all chemotherapy groups, except for hypertension and the composite measures for arterial thromboembolic and venous thromboembolic events. This is in line with population-based data showing an annual incidence (per 1000 persons) of myocardial infarction of about 4 for men and 2 for women (Atherosclerosis Risk In Communities Surveillance data, 1987–2001), an annual incidence (per 1000 persons) of angina pectoris of 4 to over 8 among men ages 45–54 and 65+ years, respectively, and 0.9 to over 4 among women ages 45–54 and 65+ years, respectively (National Heart, Lung, and Blood Institute data, 2006), and a 33.6% prevalence of hypertension among US adults 20 years and older (National Health and Nutrition Examination Survey data, 2003–2006) [18].

CVD occurrences were slighter higher for those treated with HEC only or HEC/MEC combined than those treated with MEC-only. In addition, the HEC/MEC combined group experienced a slightly elevated frequency of hypotension compared to the HEC-only or MEC-only groups. It is noteworthy that sample sizes for the HEC-only and HEC/MEC combination groups are orders of magnitude smaller than the MEC-only group, and, thus, slightly higher percentages observed in these two groups may be due to sample variability.

Those who did not use aprepitant compared to those who did generally experienced higher frequencies of certain CVD-related events, namely, cardiac arrest, hypertension, hypotension, the composite of arterial thromboembolic events without chest pain/discomfort, and, in particular, cardio-respiratory arrest, cerebral ischemia, cerebrovascular accident, and embolism among the MEC-only treated group; arterial thromboembolic events with chest pain among the HEC/MEC combined chemotherapy groups; arterial thromboembolic events without chest pain, hypertension, and venous thromboembolic events in the HEC-only treated group. While there were some CVD-related events that occurred at a higher frequency among aprepitant users compared to nonusers, the absolute number of events was small, and most events were either similar across the two groups or higher in the nonaprepitant user group. In particular, in the MEC-only group, with its large numbers of users and nonusers, arterial disorder was higher among aprepitant users but the occurrence of all other events was either similar or lower among aprepitant users compared to nonusers. This may be explained by the fact that nonusers were more likely than users to be older and have a prior history of cardiovascular disease.

Aprepitant is a substrate and dose-dependent inhibitor and inducer of the cytochrome P4503A4 (CYP3A4) isoenzyme, and drugs metabolized by CYPA34 can have a potential drug interaction with aprepitant [19]. For example, cyclophosphamide is an anticancer agent that is metabolized to its active metabolites by CYPA34 [10] and is also associated with cardiac side effects such as acute heart failure, pericardial effusion, and arrhythmia [7]. Coadministration with aprepitant causes a decrease in plasma concentrations of the active metabolites of cyclophosphamide by 5% [20], a level which may not be clinically significant [10].

Some 5-HT_3 RA antiemetics (e.g., dolasetron, granisetron and ondansetron) have been associated with reversible, clinically insignificant changes to electrocardiographic (ECG) parameters (i.e., PR, QTS, QT, and JT intervals) [21], and their coadministration could have a diluting or enhancing effect on the occurrence of cardiovascular events.

As with all administrative databases, the claims data collected were not designed for research purposes, and, thus, are limited in scope and lack detailed clinical information available in medical records, such as ECG readings and lab data on MI-induced elevations of troponin, and so forth. A claim may represent a condition to be ruled out rather than diagnosis of the condition, itself. Discharge diagnosis for the identification of cardiovascular and thromboembolic events can have several sources of error, including variation

Table 5: Chemotherapeutic agents according to HEC or MEC status.

HEC or MEC	Chemotherapeutic agent	Strength	NDC or J-code
	Oral		
MEC (low)	Arsenic	10 MG/10 ML	60553011110
MEC (low)	Arsenic	10 MG/10 ML	63459060010
MEC (low)	Carboplatin	50 MG/0 ML	15321030
MEC (low)	Carboplatin	150 MG/10 ML	15321130
MEC (low)	Carboplatin	450 MG/40 ML	15321230
MEC (low)	Carboplatin	50 MG	15321330
MEC (low)	Carboplatin	150 MG	15321430
MEC (low)	Carboplatin	450 MG	15321530
MEC (low)	Carboplatin	10 MG/ML	591333712
MEC (low)	Carboplatin	10 MG/ML	591333889
MEC (low)	Carboplatin	10 MG/ML	703324411
MEC (low)	Carboplatin	10 MG/ML	703324611
MEC (low)	Carboplatin	10 MG/ML	703324811
MEC (low)	Carboplatin	10 MG/ML	703324911
MEC (low)	Carboplatin	50 MG	703326401
MEC (low)	Carboplatin	150 MG	703326601
MEC (low)	Carboplatin	450 MG	703326801
MEC (low)	Carboplatin	10 MG/ML	703424401
MEC (low)	Carboplatin	10 MG/ML	703424601
MEC (low)	Carboplatin	10 MG/ML	703424801
MEC (low)	Carboplatin	10 MG/ML	10019091202
MEC (low)	Carboplatin	10 MG/ML	10019091203
MEC (low)	Carboplatin	50 MG	10019091501
MEC (low)	Carboplatin	150 MG	10019091601
MEC (low)	Carboplatin	450 MG	10019091701
MEC (low)	Carboplatin	50 MG	50111096576
MEC (low)	Carboplatin	150 MG	50111096676
MEC (low)	Carboplatin	450 MG	50111096776
MEC (low)	Carboplatin	50 MG	55390015001
MEC (low)	Carboplatin	150 MG	55390015101
MEC (low)	Carboplatin	450 MG	55390015201
MEC (low)	Carboplatin	10 MG/ML	55390015301
MEC (low)	Carboplatin	10 MG/ML	55390015401
MEC (low)	Carboplatin	10 MG/ML	55390015501
MEC (low)	Carboplatin	10 MG/ML	61703033918
MEC (low)	Carboplatin	10 MG/ML	61703033922
MEC (low)	Carboplatin	10 MG/ML	61703033950
MEC (low)	Carboplatin	10 MG/ML	61703033956
MEC (low)	Carboplatin	150 MG	63323016721
MEC (low)	Carboplatin	450 MG	63323016800
MEC (low)	Carboplatin	10 MG/ML	63323016905
MEC (low)	Carboplatin	10 MG/ML	63323016915
MEC (low)	Carboplatin	10 MG/ML	63323016945
MEC (low)	Carboplatin	10 MG/ML	63323017245
MEC (low)	Cyclophosphamide	100 MG	13560693
MEC (low)	Cyclophosphamide	200 MG	13561693
MEC (low)	Cyclophosphamide	500 MG	13562693
MEC (low)	Cyclophosphamide	500 MG	15050241

Table 5: Continued.

MEC (low)	Cyclophosphamide	50 MG	15050301
HEC or MEC	Chemotherapeutic agent	Strength	NDC or J-code
MEC (low)	Cyclophosphamide	50 MG	15050302
MEC (low)	Cyclophosphamide	25 MG	15050401
MEC (low)	Cyclophosphamide	100 MG	15053941
MEC (low)	Cyclophosphamide	200 MG	15054641
MEC (low)	Cyclophosphamide	500 MG	15054741
MEC (low)	Cyclophosphamide	25 MG	54412925
MEC (low)	Cyclophosphamide	50 MG	54413025
MEC (low)	Cyclophosphamide	25 MG	54808925
MEC (low)	Cyclophosphamide	50 MG	54813025
MEC (low)	Cyclophosphamide	500 MG	10019095501
MEC (low)	Cytarabine	1 GM	9329501
MEC (low)	Cytarabine	1 GM	703519401
MEC (low)	Cytarabine	1 GM	55390013301
MEC (low)	Cytarabine	1 GM	55390080801
MEC (low)	Daunorubicin	20 MG	703503203
MEC (low)	Daunorubicin	20 MG/4ML	55390010810
MEC (low)	Daunorubicin	20 MG	55390028110
MEC (low)	Daunorubicin	2 MG/ML	56146030101
MEC (low)	Daunorubicin	2 MG/ML	61958030101
MEC (low)	Doxorubicin	20 MG	13109691
MEC (low)	Doxorubicin	20 MG	13109694
MEC (low)	Doxorubicin	20 MG/10 ML	13114691
MEC (low)	Doxorubicin	20 MG/10 ML	13114694
MEC (low)	Doxorubicin	20 MG/10 ML	13124691
MEC (low)	Doxorubicin	50 MG/20 ML	13115679
MEC (low)	Doxorubicin	50 MG/20 ML	13125679
MEC (low)	Doxorubicin	50 MG	186153101
MEC (low)	Doxorubicin	50 MG	10019092102
MEC (low)	Doxorubicin	50 MG	55390023301
MEC (low)	Doxorubicin	50 MG	55390024301
MEC (low)	Epirubicin	2 MG/ML	9509101
MEC (low)	Epirubicin	2 MG/ML	9509301
MEC (low)	Epirubicin	50 MG	61703034735
MEC (low)	Idarubicin	5 MG	13250694
MEC (low)	Idarubicin	20 MG	13252686
MEC (low)	Idarubicin	1 MG/ML	13253678
MEC (low)	Idarubicin	1 MG/ML	13255667
MEC (low)	Idarubicin	1 MG/ML	13259691
MEC (low)	Ifosfamide	1 GM	15055605
MEC (low)	Ifosfamide	1 GM	15055611
MEC (low)	Ifosfamide	1 GM	15055641
MEC (low)	Ifosfamide	3 GM	15055741
MEC (low)	Ifosfamide	5 GM/3 GM	703410048
MEC (low)	Ifosfamide	1 GM	63323014210
MEC (low)	Irinotecan	20 MG/ML	9752901
MEC (low)	Irinotecan	20 MG/ML	9752902
MEC (low)	Pentostatin	10 MG	62701080001
MEC (low)	Temozolomide	5 MG	85124801

Table 5: Continued.

MEC (low)	Temozolomide	5 MG	85124802
HEC or MEC	Chemotherapeutic agent	Strength	NDC or J-code
MEC (low)	Temozolomide	5 MG	85124803
MEC (low)	Temozolomide	20 MG	85124401
MEC (low)	Temozolomide	20 MG	85124402
MEC (low)	Temozolomide	250 MG	85125201
MEC (low)	Temozolomide	250 MG	85125202
MEC (low)	Temozolomide	100 MG	85125901
MEC (low)	Temozolomide	100 MG	85125902
MEC (low)	Temozolomide	100 MG	85136601
MEC (low)	Temozolomide	100 MG	85136602
MEC (low)	Temozolomide	250 MG	85141701
MEC (low)	Temozolomide	140 MG	85142501
MEC (low)	Temozolomide	140 MG	85142502
MEC (low)	Temozolomide	180 MG	85143001
MEC (low)	Temozolomide	180 MG	85143002
MEC (low)	Temozolomide	20 MG	85151901
MEC (low)	Temozolomide	20 MG	85151902
MEC (low)	Temozolomide	20 MG	54868414205
MEC (low)	Temozolomide	20 MG	54868414206
MEC (low)	Temozolomide	5 MG	54868534801
MEC (low)	Temozolomide	100 MG	54868535002
MEC (low)	Temozolomide	250 MG	54868535400
MEC (high)	Carmustine	100 MG	15301238
MEC (high)	Carmustine	100 MG	15301297
MEC (high)	Cisplatin	50 MG/50 ML	15322022
MEC (high)	Cisplatin	50 MG/50 ML	15322097
MEC (high)	Cisplatin	1 MG/ML	703574711
MEC (high)	Cisplatin	1 MG/ML	703574811
MEC (high)	Cisplatin	1 MG/ML	10019091001
MEC (high)	Cisplatin	1 MG/ML	10019091002
MEC (high)	Cisplatin	50 MG/50 ML	55390011250
MEC (high)	Cisplatin	50 MG/50 ML	55390041450
MEC (high)	Cisplatin	1 MG/ML	63323010351
MEC (high)	Cisplatin	1 MG/ML	63323010364
MEC (high)	Cisplatin	1 MG/ML	63323010365
MEC (high)	Cyclophosphamide	1 GM	13563670
MEC (high)	Cyclophosphamide	1 GM	15050541
MEC (high)	Cyclophosphamide	1 GM	15054812
MEC (high)	Cyclophosphamide	1 GM	15054841
MEC (high)	Cyclophosphamide	1 GM	10019095601
MEC (high)	Cytarabine	2GM	55390013401
MEC (high)	Cytarabine	2GM	55390080901
MEC (high)	Cytarabine	2000 MG/20 ML	61703031922
MEC (high)	Cytarabine	2000 MG/20 ML	61703031922
MEC (high)	Dactinomycin	0.5 MG	6329822
MEC (high)	Dactinomycin	0.5 MG	67386081155
MEC (high)	Doxorubicin	200 MG/100 ML	13116683
MEC (high)	Doxorubicin	75 MG/37.0 ML	13117687
MEC (high)	Etoposide	500 MG/20 ML	15306120

Table 5: Continued.

MEC (high)	Etoposide	1 GM/50 ML	15306220
HEC or MEC	Chemotherapeutic agent	Strength	NDC or J-code
MEC (high)	Etoposide	500 MG/20 ML	55390029201
MEC (high)	Etoposide	1000 MG/50 ML	55390029301
MEC (high)	Etoposide	500 MG/20 ML	55390049201
MEC (high)	Etoposide	1000 MG/50 ML	55390049301
MEC (high)	Melphalan	2 MG	81004535
MEC (high)	Melphalan	2 MG	173004535
MEC (high)	Melphalan	50 MG	173013093
MEC (high)	Melphalan	50 MG	173013093
MEC (high)	Melphalan	2 MG	54868433901
MEC (high)	Melphalan	2 MG	54868433902
MEC (high)	Melphalan	2 MG	59572030250
MEC (high)	Methotrexate	1 GM	55390014301
MEC (high)	Methotrexate	1000 MG/40 ML	63323012140
MEC (high)	Methotrexate	1 GM	63323012250
MEC (high)	Methotrexate	1 GM	66479013929
MEC (high)	Procarbazine	50 MG	4005301
MEC (high)	Procarbazine	50 MG	54482005301
HEC	Cisplatin	100 MG/100 ML	15322122
HEC	Cisplatin	100 MG/100 ML	55390011299
HEC	Cyclophosphamide	2GM	13564670
HEC	Cyclophosphamide	2GM	15050641
HEC	Cyclophosphamide	2GM	15054941
HEC	Cyclophosphamide	2GM	10019095701
HEC	Dacarbazine	200 MG	26815120
HEC	Dacarbazine	200 MG	703507501
HEC	Dacarbazine	200 MG	703507503
HEC	Dacarbazine	200 MG	55390009010
HEC	Dacarbazine	200 MG	61703032722
HEC	Dacarbazine	100 MG	63323012710
HEC	Dacarbazine	200 MG	63323012820
HEC	Mechlorethamine	10 MG	6775331
HEC	Mechlorethamine	10 MG	67386091151
HEC	Streptozocin	1 GM	9084401
HEC	Streptozocin	1 GM	703463601
	Injectables		
MEC (low)	Cyclophosphamide; oral	25 MG	J8530
MEC (low)	Injection, arsenic trioxide	1 MG	J9017
MEC (low)	Cyclophosphamide	100 MG	J9070
MEC (low)	Cyclophosphamide	200 MG	J9080
MEC (low)	Cyclophosphamide	500 MG	J9090
MEC (low)	Cyclophosphamide, lyopholized	100 MG	J9093
MEC (low)	Cyclophosphamide, lyopholized	200 MG	J9094
MEC (low)	Cyclophosphamide, lyopholized	500 MG	J9095
MEC (low)	Injection, epirubicin HCL	2 MG	J9178
MEC (low)	Injection, irinotecan	20 MG	J9206
MEC (low)	Injection, ifosfamide	1 GM	J9208

Table 5: Continued.

HEC or MEC	Chemotherapeutic agent	Strength	NDC or J-code
MEC (low)	Injection, idarubicin hydrochloride	5 MG	J9211
MEC (low)	Injection, mitoxantrone hydrochloride	Per 5 MG	J9293
MEC (low)	Lomustine, oral	10 MG	S0178
MEC (high)	Injection, carboplatin	50 MG	J9045
MEC (high)	Injection, carmustine	100 MG	J9050
MEC (high)	Cisplatin, powder or solution	PER 10 MG	J9060
MEC (high)	Cyclophosphamide	1.0 GM	J9091
MEC (high)	Cyclophosphamide, lyophilized	1.0 GM	J9096
MEC (high)	Injection, dactinomycin	0.5 MG	J9120
MEC (high)	Injection, melphalan hydrochloride	50 MG	J9245
MEC (high)	Pracarbazine hydrochloride, oral	50 MG	S0182
HEC	Cisplatin	50 MG	J9062
HEC	Cyclophosphamide	2.0 GM	J9092
HEC	Cyclophosphamide, lyophilized	2.0 GM	J9097
HEC	Dacarbazine	100 MG	J9130
HEC	Dacarbazine	200 MG	J9140
HEC	Injection, mechlorethamine hydrochloride (nitrogen mustard)	10 MG	J9230
HEC	Injection, streptozocin	1 GM	J9320

MEC (low): moderately emetogenic chemotherapy associated with 30–60% of patients having emesis, MEC (high): moderately emetogenic chemotherapy associated with 60–90% of patients having emesis, HEC: highly emetogenic chemotherapy associated with >90% of patients having emesis.

in coding procedures, coding errors, incomplete coding, lack of specificity in available codes, and error in clinical diagnosis [22]. Misclassification of outcomes could lead to biased results. Nevertheless, the usefulness of claims data for certain CVD events has been assessed by other investigators. For example, a validation study of claim codes from a commercial insurance claims database, similar to IMPACT, against the gold standard medical records, showed a positive predictive value of 88% for both myocardial infarction and ischemic stroke [23].

This was a high-level analysis performed to provide overall background rates in a population of cancer patients similar to those under study in our clinical development program. It was not designed to draw causal inferences in differences between users of aprepitant and nonusers. The decision whether to treat with aprepitant most likely depends on many factors, such as the ability to pay for medications, physician experience, emetogenic potential of the chemotherapeutic agent, drug-drug interactions, and whether treatment is for acute or delayed CINV [24, 25]. We did not attempt to unmask or correct for potential channeling bias, nor did we consider other possible confounding factors between the aprepitant user and nonuser groups, including drug severity and comorbidity. Our comparisons did not take into account possible confounding due to drug-drug interactions with specific cardiotoxic chemotherapeutic agents or other coadministered antiemetics. We did not account for chemotherapeutic drug dosages and did not have adequate sample size for assessing effects among individual cycles of chemotherapy. As a next step, we would have corrected for as many of these shortcomings as possible in a subsequent, more rigorous pharmacoepidemiology study had our clinical development program advanced.

Despite these limitations, this analysis provided a "real world" clinical practice baseline picture of the frequency of CVD-related events that occur during use of highly or moderately emetogenic chemotherapy, serving as a useful benchmark for safety signals identified during one of our clinical trial programs. Results should also serve for future supportive care studies. The preliminary information on experiences of the aprepitant antiemetic group compared to nonusers was helpful but should be interpreted cautiously.

Conflict of Interests

Both coauthors and all individuals named in the acknowledgments were employed by GlaxoSmithKline, Inc. throughout the conduct of the study.

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