Research Article

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

Thao T. Vo and Jeanenne J. Nelson

Worldwide Epidemiology, GlaxoSmithKline, 5 Moore Drive, Mailstop 17.2124.2A, Research Triangle Park, Durham, NC 27709-3398, USA

Correspondence should be addressed to Jeanenne J. Nelson, jeanenne.j.nelson@gsk.com

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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-HT3 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,
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 enrollment 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 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 enrollment 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, enrollment 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 = 3827) | HEC only (N = 330) | MEC only (N = 5269) | HEC plus MEC (N = 228) |
|-----------------------------------------|--------------------------|--------------------|---------------------|------------------------|
| n %                                     | 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 2.43            | 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 ischema                       | — —                     | 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 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      | Aprep    | No Aprep | Aprep            | No Aprep | Aprep |
|                                         | (N = 2010)    | (N = 3817)| (N = 165)| (N = 165)       | (N = 1756)| (N = 3513) |
| Angina pectoris                         |               |          |          |                  |          |        |
|                                         | 20            | 12       | 2        | 1.21             | 1.61     | 0.51   | 10    | 0.57  | 0     | 1     | 1.12  |
| Arterial disorder                       | 3             | 6        | 1        | 0.61             | 1.61     | 0.06   | 5     | 0.28  | 0     | —     | —     |
| Arterial occlusive disease              | 1             | 1        | 0        | —                | 0        | 1.03   | 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) |  | | | | | | | | | | | |
| Cardiac arrest                          | 22            | 0.58     | 3        | 0.15             | 2        | 1.21   | 1     | 0.61  | 18    | 0.51  | 1     | 0.06  | 2     | 1.44  | 0     | —     |
| Cardiac disorder                        | 2             | 0.05     | 1        | 0.05             | 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        | —      | 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        | —      | 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        | —      | 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, 153, 153.0-153.9, 154, 154.0-154.3, 154.8, 230.3-230.6, 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 |
| 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                                                |

Table 4: Continued.

| CVD-related events                  | ICD-9-CM code(s) |
|-------------------------------------|------------------|
| 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 aprepiant 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 aprepiant 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 aprepiant 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 ≤ 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.
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, cardiorespiratory arrest, cerebral ischemia, cerebrovascular accident, embolism, hypotension, and hypertension were more frequent (≥1.5 times or ≥5% absolute difference) among those who did not use aprepitant compared to those who did. Though based on small numbers (n ≤ 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 apreipitant 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 ≤ 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 ≤ 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, apreipitant 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 (≤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 apreipitant 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 apreipitant 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 nonapreipitant user group. In particular, in the MEC-only group, with its large numbers of users and nonusers, arterial disorder was higher among apreipitant users but the occurrence of all other events was either similar or lower among apreipitant 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 CYP3A4 can have a potential drug interaction with apreipitant [19]. For example, cyclophosphamide is an anticancer agent that is metabolized to its active metabolites by CYP3A4 [10] and is also associated with cardiac side effects such as acute heart failure, pericardial effusion, and arrhythmia [7]. Coadministration with apreipitant 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-HT3 RA antiemetics (e.g., dolasetron, granisetron and ondansetron) have been associated with reversible, clinically insignificant changes to electrocardiographic (ECG) parameters (i.e., PR, QRS, 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       |
|------------|------------------------|---------------------|---------------------|
| 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              | 50111096666         |
| 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            |
| Chemotherapeutic agent | Strength | NDC or J-code |
|------------------------|----------|---------------|
| Cyclophosphamide       | 50 MG    | 15050301      |
| Cyclophosphamide       | 25 MG    | 15050401      |
| Cyclophosphamide       | 100 MG   | 15053941      |
| Cyclophosphamide       | 200 MG   | 15054641      |
| Cyclophosphamide       | 50 MG    | 15054741      |
| Cyclophosphamide       | 25 MG    | 54808925      |
| Cyclophosphamide       | 50 MG    | 54813025      |
| Cyclophosphamide       | 500 MG   | 10019095501   |
| Cytarabine             | 1 GM     | 9329501       |
| Cytarabine             | 1 GM     | 703519401     |
| Cytarabine             | 1 GM     | 55390013301   |
| Cytarabine             | 1 GM     | 55390080801   |
| Daunorubicin           | 20 MG    | 703503203     |
| Daunorubicin           | 20 MG/4ML| 55390010810   |
| Daunorubicin           | 20 MG    | 55390028110   |
| Daunorubicin           | 2 MG/ML  | 56146030101   |
| Daunorubicin           | 2 MG/ML  | 61958030101   |
| Doxorubicin            | 20 MG    | 13109691      |
| Doxorubicin            | 20 MG    | 13109694      |
| Doxorubicin            | 20 MG/10 ML | 13114691   |
| Doxorubicin            | 20 MG/10 ML | 13114694   |
| Doxorubicin            | 20 MG/10 ML | 13124691   |
| Doxorubicin            | 50 MG/20 ML | 13115679   |
| Doxorubicin            | 50 MG/20 ML | 13125679   |
| Doxorubicin            | 50 MG    | 186153101     |
| Doxorubicin            | 50 MG    | 10019092102   |
| Doxorubicin            | 50 MG    | 55390023301   |
| Doxorubicin            | 50 MG    | 55390024301   |
| Epirubicin             | 2 MG/ML  | 9509101       |
| Epirubicin             | 2 MG/ML  | 9509301       |
| Epirubicin             | 50 MG    | 61703034735   |
| Idarubicin             | 5 MG     | 13250694      |
| Idarubicin             | 20 MG    | 13252686      |
| Idarubicin             | 1 MG/ML  | 13253678      |
| Idarubicin             | 1 MG/ML  | 13255667      |
| Idarubicin             | 1 MG/ML  | 13259691      |
| Ifosfamide             | 1 GM     | 15055605      |
| Ifosfamide             | 1 GM     | 15055611      |
| Ifosfamide             | 1 GM     | 15055641      |
| Ifosfamide             | 3 GM     | 15055741      |
| Ifosfamide             | 5 GM/3 GM| 703410048     |
| Ifosfamide             | 1 GM     | 63323014210   |
| Irinotecan             | 20 MG/ML | 9752901       |
| Irinotecan             | 20 MG/ML | 9752902       |
| Pentostatin            | 10 MG    | 62701080001   |
| Temozolomide           | 5 MG     | 85124801      |
| MEC (low) | Temozolomide | 5 MG | 85124802 |
|----------|--------------|------|----------|
| 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 | 20 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| 85151902 |
| MEC (low) | Temozolomide | 20 MG| 54868414205 |
| 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| 55390014150 |
| 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 | 2 GM| 55390013401 |
| MEC (high) | Cytarabine | 2 GM| 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.

|           | 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              | 2 MG              | 54868433901         |
| MEC (high)| Melphalan              | 2 MG              | 54868433902         |
| 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            | 6170302722          |
| 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           |

|             | Chemotherapeutic agent     | Strength      | NDC or J-code     |
|--------------|-----------------------------|---------------|-------------------|
| 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             |

**Injectables**
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         |

**HEC (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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