# Incidence and Risk of Cardiac Events in Patients With Previously Treated Multiple Myeloma Versus Matched Patients Without Multiple Myeloma: An Observational, Retrospective, Cohort Study

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## Abstract

**The present study provides a unique look at real world cardiac event rates for a large group of multiple myeloma (MM) patients treated with selected anti-MM treatments. The cardiac event risk for any cardiac event, including hypertensive or arterial events, cardiac dysrhythmias, congestive heart failure, ischemic heart disease, cardiomyopathy, and conduction disorders, was greater in MM patients with ≥ 3 previous drugs (n = 1723) compared with patients without MM (n = 8615).**

**Background:** Multiple myeloma (MM) patients have age-, disease-, and treatment-related risk factors for cardiac events. **Materials and Methods:** We analyzed the 2006 to 2011 MarketScan database to determine whether the risk of cardiac events is greater in MM patients than in non-MM patients. Included were 1723 MM patients treated with corticosteroids and ≥ 3 drugs (bortezomib, immunomodulatory derivatives, and alkylating agents or anthracyclines). The index date (ID) was the date on which the 3-drug exposure criterion was met. Also included were 8615 age- and gender-matched non-MM patients (5:1). The distribution of non-MM patients' IDs matched that of the MM patients' IDs. Baseline was 6 months before the ID. The follow-up duration was from the ID to study end (ie, 2011 or end of enrollment or prescription drug coverage). Hazard ratios (HRs) and 95% confidence intervals (CIs) were adjusted for baseline variables when the univariate analyses showed a 10% difference. **Results:** The median duration of observation was 9 months (range, 0-60 months) for MM patients and 19 months (range, 0-66 months) for non-MM patients. The risk of any cardiac event (HR, 2.2; 95% CI, 1.9-2.5), dysrhythmia (HR, 4.1; 95% CI, 3.5-4.8), congestive heart failure (HR, 2.9; 95% CI, 2.2-3.7), cardiomyopathy (HR, 2.6; 95% CI, 1.8-3.8), and conduction disorders (HR, 1.7; 95% CI, 1.2-2.5) was significantly greater for MM than for non-MM patients. The incidence of hypertensive or arterial events and ischemic heart disease was similar between the 2 groups. **Conclusion:** The present study provides the first known comparison of cardiac event risk in patients with MM versus age- and gender-matched patients without MM. The cardiac event risk was greater in MM patients with ≥ 3 previous drugs for any cardiac event, dysrhythmias, congestive heart failure, cardiomyopathy, and conduction disorders compared with patients without MM.

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## Introduction

Multiple myeloma (MM) is the second most prevalent hematologic malignancy. The estimated prevalence of MM in the United States in 2011 was 0.023% or 83,367 persons. The estimated age-standardized incidence rate in the United States and Europe has been estimated to be 4 to 6 cases of MM/100,000 men and women.[1,2] The availability of new, improved pharmacologic treatment of MM has resulted in improved survival.[3] Currently, in the United States, the median survival from diagnosis is approximately 6.1 years.[4]

Patients with MM often have cardiac comorbidities as a result of several factors, including those unrelated to the disease (eg, diabetes, lipid levels, smoking history, weight, lack of exercise, unhealthy diet, older age, history of cardiac events, underlying coronary artery disease, hypertension, or pre-existing chronic obstructive pulmonary disease[5]), disease-related factors, and treatment-related comorbidities. Age is an important risk factor, given that the median age at the diagnosis of MM is 65 years.[6-8] Additionally, the MM-related cardiac risk factors include underlying and undiagnosed cardiac amyloidosis,[9-11] hyperviscosity,[12,13] high-output failure,[14-17] arteriovenous shunting,[18] anemia,[19,20] and renal dysfunction.[21-25] Furthermore, MM treatments have known associated cardiac risks.[26] For example, anthracycline therapy can cause dysrhythmia, congestive cardiomyopathy with reduced left ventricular ejection fraction, and heart failure.[27,28] Corticosteroids carry risks for arrhythmias, hyperglycemia or diabetes mellitus, and obesity. Alkylating agents have been linked to myopericarditis, acute cardiomyopathy, thrombosis, and reduced left ventricular ejection fraction.[28] Immunomodulatory drugs can cause arrhythmias and myocardial infarction.[29] Proteasome inhibitors carry risks for arrhythmias, congestive heart failure (CHF), atrioventricular block, ischemic heart disease (IHD), and hypertension.[5,30-40] Finally, stem cell transplantation has been linked to IHD, cardiomyopathy, CHF, and rhythm disorders.[41,42] The supportive care measures used for MM patients can also be associated with cardiac toxicity, including medications that can prolong the QT interval (5-HT3 antagonists, quinolones, macrolides).

Although the cardiac risk factors are evident, the incidence or prevalence of cardiac events in MM patients is unknown. For the most part, detailed cardiac monitoring is typically used only in initial clinical trials involving patients with multiply relapsed and/or refractory MM. However, patients with severe cardiac comorbidities are often excluded from study participation, making the generalizability of the cardiac safety profile difficult.[5,43,44] Estimating the frequency of cardiac events in patients with MM would aid in understanding the magnitude of these events and would inform clinical development programs for new therapeutic agents. To the best of our knowledge, the present insurance claims analysis is the first analysis to examine the incidence, prevalence, and risk of cardiac events in previously treated real world patients with MM. We compared the risk of cardiac events in 1723 patients treated with $\geq$ 3 MM treatments with that of 8615 controls without MM.

## Materials and Methods

### Data Source

The present observational retrospective cohort study used demographic, pharmacy, and medical claims data from the Thomson Reuters MarketScan claims database. MarketScan is a Health Insurance Portability and Accountability Act–compliant, fully integrated patient-level database containing inpatient, outpatient, drug, laboratory, health risk assessment, and benefit design information from commercial and Medicare supplemental insurance. Both the commercial and the Medicare supplemental data were used in the present study. The commercial data included medical encounters from active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and their dependents insured by employer-sponsored plans (ie, non-Medicare eligible). The Medicare supplemental data included Medicare-eligible retirees with employer-sponsored Medicare supplemental plans. The analysis included data from January 1, 2006 to December 31, 2011.

The present research was conducted in compliance with the Declaration of Helsinki. Given the de-identified nature of the data used in the present study, informed consent was not required by Health Insurance Portability and Accountability Act rules.

### Subjects

The inclusion criteria for the study were age $\geq$ 18 years; $\geq$ 6 months of continuous insurance enrollment, with a follow-up period after the ID of $\geq$ 1 day; prescription drug coverage; and no gaps in coverage for $>$ 31 days. The MM cohort included all enrollees meeting the inclusion criteria with a diagnosis of MM (International Classification of Diseases, 9th revision, diagnosis code 203.0, 203.00, 203.01, or 203.02) on any type of claim at some point after 6 months of continuous coverage. The MM patients also had to have received an agent from each of the following classes of anti-MM therapy available from 2006 to 2011: proteasome inhibitor (bortezomib), $\geq$ 1 immunomodulatory derivative (lenalidomide or thalidomide), and either an alkylating agent or an anthracycline. A history of $\geq$ 3 drugs was required to reduce the possibility of misclassification bias and to reproduce a relapsed and/or refractory MM population. A non-MM cohort of patients who had met the inclusion criteria and did not have a diagnosis of MM was the comparator group. Five comparators were individually selected for each MM patient. The comparators were selected to match the MM patients by gender and age (within 5 years) as of the index date (ID).

### Study Definitions

*Index Date.* The ID for the MM patients was the date they met the criteria of exposure to selected anti-MM treatments according to the inclusion criteria or the first day after 6 months of continuous coverage (baseline period) for patients who met the drug exposure criteria during the baseline period. Patients in the non-MM cohort were assigned IDs such that the distribution of IDs matched that of the MM group.

*Baseline Period.* The baseline period for each patient was defined as the 6 months (183 days) of continuous enrollment preceding the ID.

*Follow-up Period.* The follow-up period started the day after the ID and continued until any of the following (whichever came first) had occurred: the calendar end date of the study (December 31, 2011); the end of continuous enrollment; or the end of prescription drug coverage.

### Outcomes

The present study assessed the incidence and prevalence of selected cardiac events (hypertensive or arterial events, cardiac dysrhythmias, conduction disorders, cardiomyopathy, CHF, and IHD) from inpatient and outpatient claims associated with the International Classification of Disease, 9th revision, diagnosis codes (Supplemental Tables 1 and 2; online version).

The patients' baseline characteristics were derived from the claims rendered during the baseline period. The following baseline characteristics were included: age, gender, calendar year of ID, and geographic region. The presence of comorbidities, including any of the cardiac event outcomes of interest, was also captured. In addition to the cardiac comorbidities, the prevalence of chronic kidney disease (CKD), diabetes mellitus, hypertension, hyperlipidemia, amyloidosis, Charlson comorbidity index (CCI) score,[45] and stem cell transplantation were captured.

### Statistical Analysis

Univariate comparisons of the baseline characteristics between the groups were conducted using 2-sided Student's $t$ tests (continuous variables) and $\chi^2$ tests (categorical variables). Non-normally distributed continuous variables were analyzed using nonparametric tests (Wilcoxon-Mann-Whitney rank sum test).

The incidence rates (per 1000 person-years, with 95% confidence intervals [CIs]) of any event were computed as the number of patients with $\geq 1$ event of interest divided by the person-time at risk until the first event. The analyses of incidence rates were performed after removing any prevalent cases, including from the non-MM comparators, to maintain matching between the MM and non-MM cohorts. The follow-up data were censored at either the date of the first occurrence of the cardiac event for patients with the event of interest or the date corresponding to the end of their follow-up period (disenrollment or end of study period).

For the prevalence estimates in both cohorts, the numerator included all patients with cardiac events, regardless of whether the cardiac event was recorded during baseline or the follow-up period. The incidence (risk) of cardiac events in the MM and non-MM cohorts was compared using Cox proportional hazards regression, which included the baseline covariates and the time-varying variable amyloidosis (to account for any occurrence of amyloidosis before the cardiac event of interest in the analyses). Each of the covariates was first examined on univariate analysis. The final models were adjusted for any covariates that modified the hazard ratio (HR) for MM by $\geq 10\%$.

## Results

The MarketScan database included a total of 52,840 patients with a diagnosis of MM from January 1, 2006 to December 31, 2011. Of those 52,840 patients, 20,647 (39%) did not meet the study inclusion criteria. The reasons for exclusion were no prescription drug coverage during the baseline and follow-up periods (n = 10,702; 52%); < 6 months of baseline enrollment or the absence of $\geq 1$ day of follow-up data (n = 9829; 48%); and age < 18 years (n = 116; 0.6%). Of the remaining potentially eligible 32,193 MM patients, 1723 had claims indicating exposure to the anti-MM agents delineated in the inclusion criteria to approximate a multiply relapsed and/or refractory MM population. The 1723 patients were included in the present analysis, and 8615 patients without MM were included as the matched non-MM cohort.

The matching resulted in equal median ages of the 2 cohorts (61 $\pm$ 10.9 years) and gender distribution (59.6% male) and an equal ID distribution. The median follow-up length was significantly longer in the non-MM cohort (median, 19 months; range, 0-66 months) than in the MM cohort (median, 9 months; range, 0-66 months). The patients' geographic region was also significantly different. The prevalence of diabetes was significantly greater in the MM cohort than in the non-MM cohort, as was the CCI score (median, 3; range, 0-15; vs. median, 0; range, 0-10). As expected, the prevalence of CKD was markedly greater in the MM cohort (17% vs. 1.9%; Table 1).

The prevalence of any cardiac event was 60.1% in the MM cohort and 54.5% in the non-MM cohort. The prevalence of dysrhythmias, cardiomyopathy, CHF, and conduction disorders was significantly greater in patients with MM than in those without MM. In contrast, the hypertensive or arterial events were significantly greater in patients without MM (49.4% vs. 43.1%). The prevalence of IHD was similar between the 2 cohorts (Figure 1).

The incidence rate per 1000 person-years of individual cardiac events in the MM cohort was 97.8 (95% CI, 82.6-97.7), 120.1 (95% CI, 103.5-138.6), 38.7 (95% CI, 29.9-49.3), 34.0 (95% CI, 25.9-43.9), 274.7 (95% CI, 246.6-305.1), and 364.2 (95% CI, 324.7-407.2) for IHD, CHF, cardiomyopathy, conduction disorders, cardiac dysrhythmias, and hypertensive/arterial events, respectively. The incidence rate of any of the included cardiac events was 676.9 (95% CI, 610.6-748.4). The incidence rate per 1000 person-years of individual cardiac events in the non-MM cohort was 55.9 (95% CI, 51.8-60.2), 21.2 (95% CI, 18.9-21.2), 8.1 (95% CI, 6.8-9.7), 12.5 (95% CI, 10.8-12.5), 52.3 (95% CI, 48.4-56.6), and 245.6 (95% CI, 232.5-245.6) for IHD, CHF, cardiomyopathy, conduction disorders, cardiac dysrhythmias, and hypertensive or arterial events, respectively. The incidence rate for any of the included cardiac events was 257.1 (95% CI, 241.2-273.7; Supplemental Figure 1A; online version).

When the incidence rates were compared, the unadjusted incidence rate ratios showed that the risk of any and all individual types of cardiac events was significantly greater statistically for the MM cohort than for the non-MM cohort (Supplemental Figure 1B; online version). Through multivariable analyses, the adjusted HRs also showed that the MM cohort had a statistically significant increased risk of any cardiac event (HR, 2.19; 95% CI, 1.95-2.48), including cardiac dysrhythmias (HR, 4.09; 95% CI, 3.47-4.81), CHF (HR, 2.88; 95% CI, 2.21-3.75), cardiomyopathy (HR, 2.59; 95% CI, 1.78-3.78), and conduction disorders (HR, 1.74; 95% CI, 1.21-2.51). No significant difference were found between the MM cohort and non-MM cohort in the risk of hypertensive or arterial events (HR, 1.12; 95% CI, 0.98-1.27) or IHD (HR, 1.01; 95% CI, 0.81-1.27; Figure 2).

## Discussion

Patients with MM have patient-, disease-, and treatment-related risk factors for cardiac events. Despite the awareness of cardiac risks, the present knowledge of cardiac event incidence and prevalence in MM patients is limited to that reported from clinical trials. However, participants in clinical trials represent highly selected patient

**Table 1 Baseline Characteristics**

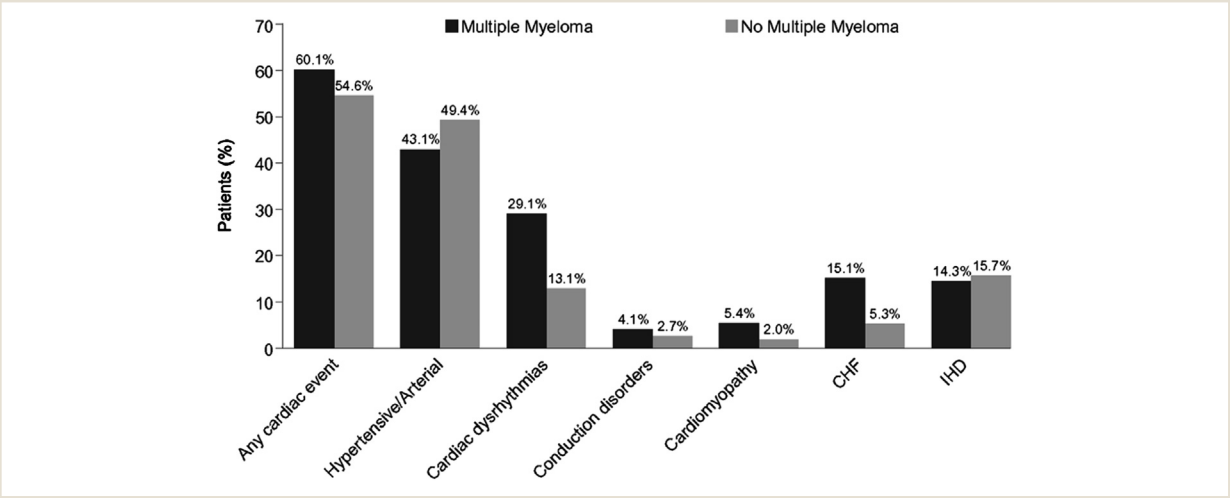
| Patient Characteristics | Patients With MM and Exposure to ≥3 Drugs[a] (n = 1723) | Matched Comparator Cohort (No MM; n = 8615) | *P* Value |
|---|---|---|---|
| Follow-up duration (mo) | | | <.001 |
| Median | 9 | 19 | |
| Range | 0-60 | 0-66 | |
| Age at ID (y) | | | .98 |
| Mean | 62.4 | 62.4 | |
| Median | 61 | 61 | |
| Range | 24-91 | 23-92 | |
| Gender | | | 1.0 |
| Male | 1027 (59.6) | 5135 (59.6) | |
| Female | 696 (40.4) | 3480 (40.4) | |
| Year of ID | | | 1.0 |
| 2006 | 88 (5.1) | 440 (5.1) | |
| 2007 | 233 (13.5) | 1165 (13.5) | |
| 2008 | 346 (20.1) | 1730 (20.1) | |
| 2009 | 390 (22.6) | 1950 (22.6) | |
| 2010 | 442 (25.7) | 2210 (25.7) | |
| 2011 | 224 (13.0) | 1120 (13.0) | |
| CV comorbidities at baseline | | | |
| Any CV event | 898 (52.1) | 3021 (35.1) | <.0001 |
| Hypertensive/arterial events | 663 (38.5) | 2485 (28.8) | <.0001 |
| Cardiac dysrhythmias | 295 (17.1) | 483 (5.6) | <.0001 |
| Conduction disorders | 37 (2.1) | 66 (0.8) | <.0001 |
| Cardiomyopathy | 59 (3.4) | 71 (0.8) | <.0001 |
| CHF | 155 (9.0) | 174 (2.0) | <.0001 |
| IHD | 180 (10.4) | 718 (8.3) | .005 |
| Hypertension | 627 (36.4) | 2361 (27.4) | <.0001 |
| Hyperlipidemia | 302 (17.5) | 1917 (22.3) | <.0001 |
| Amyloidosis | 34 (2.0) | 2 (0.02) | <.0001 |
| Other comorbidities at baseline | | | |
| Stem cell transplant | 76 (4.4) | 0 (0.0) | <.0001 |
| CKD | 293 (17.0) | 161 (1.9) | <.0001 |
| Diabetes | 288 (16.7) | 1171 (13.6) | .0007 |
| CCI | | | |
| Mean ± SD | 4.2 ± 2.5 | 0.6 ± 1.2 | <.0001 |
| Median | 3 | 0 | |
| Range | 0-15 | 0-10 | |

Data presented as n (%), unless otherwise indicated.
Abbreviations: CCI = Charlson comorbidity index; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; ID = index date; MM = multiple myeloma; SD = standard deviation.
[a]Patients with MM had exposure to the following 3 drugs or drug classes taken on or before the disease ID: bortezomib, an immunomodulatory drug, and either an alkylating agent or anthracycline.

samples and might not be representative of the broader MM population outside of clinical trials. To the best of our knowledge, the present study is the first to estimate the risk of cardiac events in a nonclinical trial population of patients with MM who had received multiple anti-MM therapies compared with age- and gender-matched patients without MM.

The prevalence of cardiac events in previously treated patients with MM and patients without MM was high at 60.1% and 54.6%, respectively. Patients with MM had a statistically significant increased risk of cardiac dysrhythmias, conduction disorders, cardiomyopathy, and CHF compared with patients without MM, with adjusted HRs ranging from 1.74 to 4.09. It is difficult to determine whether the increased cardiac risk found for MM patients resulted from MM-unrelated factors, disease-related comorbidities, or treatment-related factors; it might be a combination of each. Factors such as older age and male gender predispose MM patients to an increased cardiac risk; however, the very strength of the present study lies in the control for these variables using the matched non-MM cohort. Given that the

**Figure 1** Prevalence of Cardiac Events Among Patients With and Without Multiple Myeloma



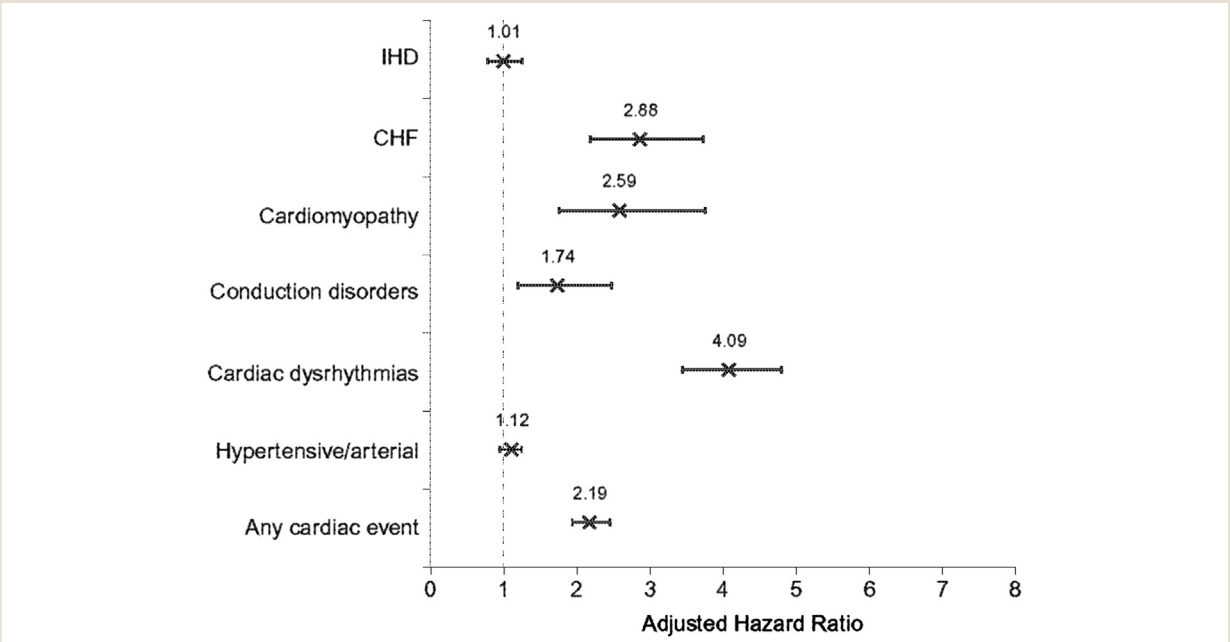

Abbreviations: CHF = congestive heart failure; IHD = ischemic heart disease.

risk of hypertensive or arterial events or IHD was not significantly increased in MM patients despite an increased prevalence of diabetes mellitus and CKD, these cardiac events might not be specifically related to the disease or treatment. Alternatively, a combination of factors might be at work in the lack of a difference in arterial events between the 2 groups. The lack of a difference might have resulted from (1) recent-onset diabetes mellitus due to corticosteroid use; (2) only recent-onset MM-related renal dysfunction in the MM cohort receiving frequent steroids; (3) hypotension in the MM cohort (eg, drug-induced, post-stem cell transplant hypotension,[46] hypotension related to amyloid autonomic dysfunction or adrenal insufficiency[47]); and (4) longer follow-up data available for the non-MM cohort. Although MM is also more frequent among blacks, and black race is a risk factor for cardiac events[48,49] the MarketScan database does not include information about race, precluding our examining the effect of race on these findings. Similarly, other cardiac risk factors, such as body mass index, physical activity, diet, and smoking status, are also not captured in the database. The disease-related effects of MM, including hyperviscosity,[12,13] high-output failure,[14-17] arteriovenous shunting,[18] and anemia,[19,20] are risk factors for cardiac events. CKD, which was significantly more prevalent among the MM patients, is also an effect of the disease[21,22,25] and a risk factor for cardiac events.[50,51] Amyloid light-chain amyloidosis, which has been estimated to occur in 10% of patients with MM, has been associated with several cardiac events, including CHF/cardiomyopathy and potentially fatal dysrhythmias or conduction disorders. It might be that the presence of unrecognized concomitant amyloid light-chain amyloidosis could also be associated with increased real world treatment-related toxicities—as such, patients often would not meet MM clinical trial eligibility criteria by outright exclusion or poor performance status.

The cardiotoxicity of anticancer drug treatments, in particular, anthracyclines, has been well documented.[26] Proteasome inhibitors have also been implicated in cardiac toxicity by a variety of preclinical mechanisms.[26-28] However, in a phase III study of 646 MM patients whose disease had progressed during or after $\geq$ 1 previous therapy (66% had received $>$ 1 previous therapy) and were receiving treatment with bortezomib and liposomal doxorubicin or bortezomib alone, the incidence of heart failure events was 3% in patients treated in both groups.[52] Similarly, the incidence of a decrease in ejection fraction (9% vs. 7%), ejection fraction $<$ 45% (3% vs. 2%), and CHF (1% vs. 1%) was similar between the 2 groups.[52] From the phase II and III registration trials of bortezomib, the incidence proportion of associated cardiotoxicity in patients with a variety of malignancies ranged from 0% to 18%.[53] A recent meta-analysis did not find evidence that bortezomib was associated with an increased risk of cardiotoxicity compared with control treatments. However, it was found that the overall incidence of all-grade cardiotoxicity with bortezomib among MM patients (4.3%; 95% CI, 2.8%-6.6%) was greater than that of patients with non-MM cancer types (2.3%; 95% CI, 0.7%-6.9%).[53] These data from clinical trials, combined with the findings of our study of real world patients, suggest that the incidence of cardiac toxicity in MM patients might be related more to nontreatment factors. More recently, in registration trials of the proteasome inhibitor carfilzomib, cardiac failure events (eg, CHF, pulmonary edema, ejection fraction decreased) were reported in 7% of patients.[54] However, in the phase III C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of **P**at**I**ents with **R**elapsed Multiple My**E**loma (ASPIRE) study comparing carfilzomib, lenalidomide, dexamethasone to lenalidomide and dexamethasone alone, the rate of grade $\geq$ 3 cardiac failure was 3.8% versus 1.8%, respectively.[55] A recently published study of 32 intensively treated and multiply relapsed MM survivors found that most patients had established cardiovascular and/or respiratory dysfunction, greater than the levels expected in the general population of a similar age.[56]

To put these rates into context, in the present study, a commercial claims database was used to assemble a large population of

**Figure 2** Adjusted Hazard Ratios (HRs) for Cardiac Events Among Patients With Multiple Myeloma (MM) Versus Patients Without MM. Factors Modifying the HR for MM by ≥ 10% Were Included in the Analyses. Each Analysis Was Limited to Patients Without the Outcome Event During Baseline. Ischemic Heart Disease (IHD) Was Adjusted for Any Other Baseline Cardiac Comorbidity, Cardiac Dysrhythmias, Charlson Comorbidity Index (CCI) Score, and Chronic Kidney Disease (CKD). Congestive Heart Failure (CHF) Was Adjusted for Baseline Anthracycline Exposure, Any Other Baseline Cardiac Comorbidity, Cardiac Dysrhythmias, CCI Score, and CKD. Cardiomyopathy and Conduction Disorders Were Adjusted for Any Other Baseline Cardiac Comorbidity, Cardiac Dysrhythmias, CHF, CCI Score, and CKD. Cardiac Dysrhythmia Events Were Adjusted for CCI Score. Hypertensive or Arterial Events Were Adjusted for Any Other Baseline Cardiac Comorbidity. HRs Adjusted for Covariates that Modified the HR for MM by ≥ 10% and Included the Following Variables for Each Outcome: Any Cardiac Event: No Covariates Identified; Hypertensive or Arterial Events: Any Cardiovascular Event During Baseline; Cardiac Dysrhythmias: CCI; Conduction Disorders: Any Cardiovascular Event During Baseline, Cardiac Dysrhythmias During Baseline, CHF During Baseline, CCI, CKD; Cardiomyopathy: Any Cardiovascular Event During Baseline, Cardiac Dysrhythmias During Baseline, CHF During Baseline, CCI, CKD; CHF: Any Cardiovascular Event During Baseline, Cardiac Dysrhythmias During Baseline, Anthracycline Exposure, CCI, CKD; IHD: Any CV Event During Baseline, Cardiac Dysrhythmias During Baseline, CCI, CKD




previously treated MM patients. The strengths of our study included the large number of MM patients and non-MM comparator patients and the age and gender matching between the 2 groups. In addition, because these data were collected prospectively for a large population, we were able to provide analyses within a period that would not be possible in a prospective study. The MarketScan database contains adjudicated claims with a high validity for diagnoses. Because we defined the MM cohort according to their having received ≥ 3 anti-MM treatments increased the likelihood that the patients were correctly classified as having MM (ie, to avoid misclassification bias that could potentially occur from using a MM ICD-9 diagnostic code for patients with monoclonal gammopathy of undetermined significance undergoing an initial diagnostic workup). We also used this definition in an attempt to reproduce the relapsed and/or refractory MM population often enrolled in clinical trials of novel MM agents. Where available, we used validated algorithms to identify the cardiac outcomes.[57-61]

The present study had some limitations. First, most of the study population obtained health insurance through their employer; thus, the MarketScan claims database better represents the demographic distribution of employed populations and underrepresents the elderly, unemployed, and disabled. As such, the age distribution of the MM patients in the study cohort was younger than that of the typical MM population. Smaller effect differences might have been observed in a study of older MM patients age-matched to patients without MM, because age-related cardiac risks might dilute the effects of MM-specific characteristics that contribute to cardiac risk. As stated, this claims database also does not collect data on other variables that are known risk factors for cardiac events. Also, patient-, disease-, and treatment-related information such as the type of MM, performance status, history of response to therapies, cancer treatment, and cardiac risks at analysis were lacking. Also, because the body mass index was not available in the MarketScan database, we were unable to control for or assess the effect of obesity on the study outcomes. The potential also exists that the non-MM cohort was different from that of a general non-MM population of older adults. However, the incidence of cardiac events in the non-MM matched cohort was similar to that found in large U.S. population-based epidemiologic studies of similarly aged patients.[62] We did not study specific anti-MM drug combinations or regimens; thus, patients not treated with these

selected anti-MM drugs might not have the same cardiac risk as the patients included in the present analysis. In the era of combination treatments, the difficulty in ascertaining which adverse events are truly attributable to treatment exposure from a single agent or are the culmination of treatment exposure across all lines of therapy is an issue that is also present in clinical trials. The contribution of steroids to cardiac events in the present study is also unknown. We did not account for the use of steroids, a risk factor for cardiac events, in either group. The MM patients had most likely all been exposed to steroids; however, steroid use in the comparator group was unknown, because we could not reliably identify steroid use from the claims. We limited our analysis to 2011 to understand the cardiac risk before the availability of novel drugs, such as carfilzomib and pomalidomide. An updated analysis that includes newer anti-MM agents that have been approved since 2012 is warranted. Finally, and importantly, in this type of observational, descriptive study, causal determinations could not be determined between treatment exposure and cardiac events.

## Conclusion

Given the median age of MM patients and the increasing overall survival in the era of novel therapeutic agents, the likelihood of cardiac comorbidities will likely continue to increase. What has been unknown is how the cardiac risk of MM patients compares to that of the general population, given the possibility of, not only the usual nondisease-related risk factors, but also disease- and treatment-related factors. Adding to the lack of understanding of cardiac safety in MM patients is the observation that although detailed cardiac monitoring is typically included in early phase clinical trials, patients with severe cardiac comorbidities are often excluded from study participation, just as are those with significant renal or hepatic dysfunction.

The current study, with its stated limitations, provides a unique look at real world cardiac event rates for a large group of MM patients treated with selected anti-MM treatments. The cardiac event risk for any cardiac event, including hypertensive or arterial events, cardiac dysrhythmias, CHF, IHD, cardiomyopathy, and conduction disorders was greater for MM patients with $\geq 3$ previous drugs than for patients without MM.

Although additional safety and pharmacokinetic studies are often performed in renal and hepatic dysfunction, detailed investigation of novel agents in patients with cardiac disease are less common. In the absence of data from real world patients with a high prevalence of concurrent cardiac disease, the attribution of adverse cardiac events to novel agents must be made with caution, especially in the absence of a control arm.

Understanding the mechanism of cardiotoxicity in those with and without baseline cardiac disease is critical to preventing, identifying, and treating cardiac dysfunction as early as possible to avoid progressive, irreversible cardiac damage and maximizing the clinical benefit of anti-MM therapy throughout the spectrum of cancer survivorship. New and more precise studies that advance the interpretation of the results are warranted.

### *Clinical Practice Points*

- Patients with MM have patient-, disease-, and treatment-related risk factors for cardiac events.
- The present knowledge of cardiac event incidence and prevalence in MM patients is limited to that reported from clinical trials.
- New drugs are evaluated in patients with relapsed or refractory MM before newly diagnosed patients; however, these are highly selected patients with no cardiac issues and might not represent the broader MM population outside of clinical trials.
- After drug approval and subsequent treatment of patients with relapsed or refractory MM in the real world, it can be difficult to discern cardiac risk from a drug versus the disease.
- Real world data are essential to understanding the background cardiac profile of a heavily treated real-world population.
- The results from the present study show that heavily treated MM patients have an increased risk of cardiac events, in particular dysrhythmias, CHF, cardiomyopathy, and conduction disorders, compared with similarly aged patients without MM.

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## Disclosure

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## Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clml.2016.11.009.

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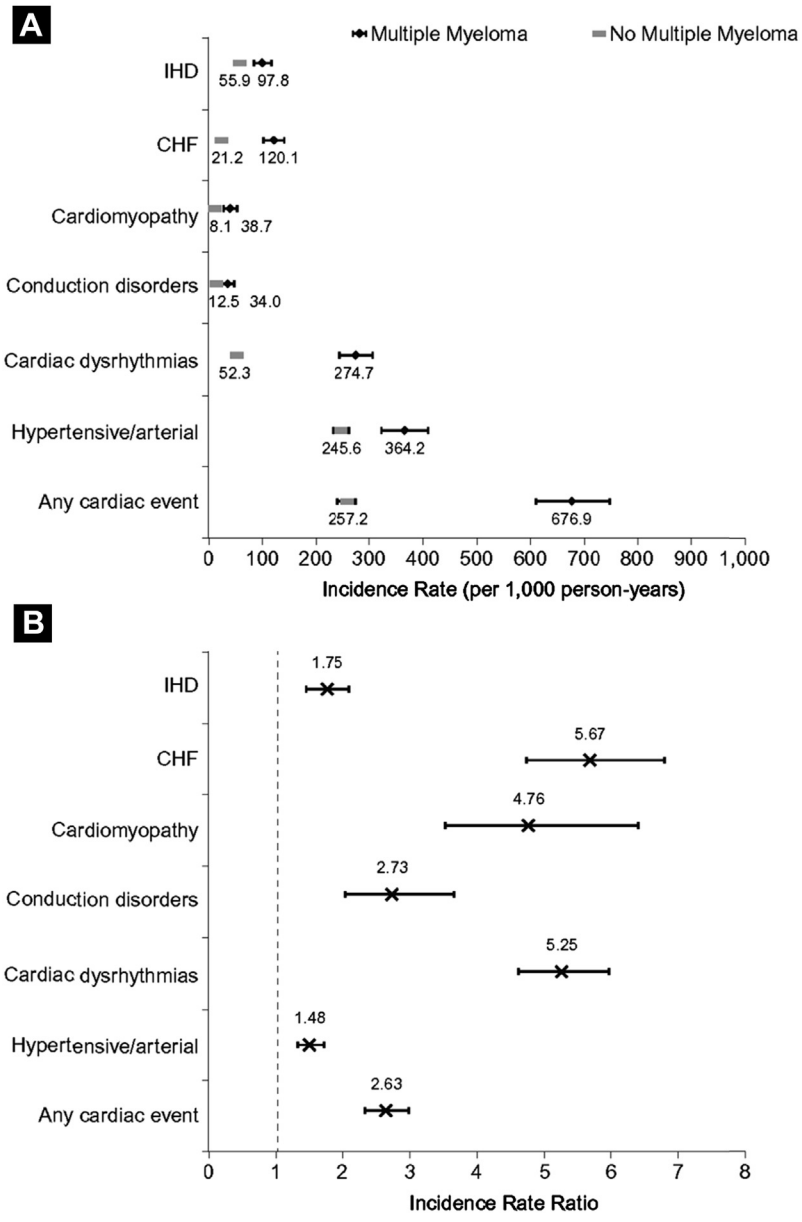
**Supplemental Figure 1** Incidence Rates and Incidence Rate Ratios of Cardiac Events Among Patients With and Without Multiple Myeloma. (A) Incidence Rates and 95% Confidence Intervals. (B) Incidence Rate Ratios and 95% Confidence Intervals




Abbreviations: CHF = congestive heart failure; IHD = ischemic heart disease.

**Supplemental Table 1** HCPS or NDC Codes Used to Classify Patients

| Chemotherapy Class | Drug Name | HCPCS or NDC Codes |
|---|---|---|
| Proteasome inhibitor | Bortezomib | J9041 or 63020004901 |
| IMiDs | Lenalidomide, thalidomide | 59572-105-xx, 59572-205-xx, 59572-210-xx, 59572-215-xx, 59572-220-xx, 59572-402-xx, 59572-405-xx, 59572-410-xx, 59572-415-xx, OR 59572-425-xx |
| An alkylating agent | Bendamustine, busulfan, carmustine, chlorambucil, cyclophosphamide, dacarbazine, ifosfamide, ifosfamide/mesna, lomustine, mechlorethamine, hydrochloride, melphalan, streptozotocin, thiotepa | J9245, J8600, J9070, J8530, J9208, 00013560693, 00013561693, 00013562693, 00013563670, 00013564670, 00015050041, 00015050141, 00015050241, 00015050301, 00015050302, 00015050303, 00015050348, 00015050401, 00015050541, 00015050641, 00015053941, 00015054641, 00015054712, 00015054741, 00015054812, 00015054841, 00015054912, 00015054941, 00054412925, 00054413025, 00054808925, 00054813025, 00641226241, 00641226341, 00641226441, 00641226541, 10019095501, 10019095550, 10019095601, 10019095616, 10019095701, 10019095711, 38779050603, 38779050604, 38779050605, 54569571200, 54569571300, 54868500500, 54868500501, 54868521800, 54868521801, 54868521802, 00015055605, 00015055611, 00015055641, 00015055711, 00015055741, 00338399101, 00338399301, 00703342711, 00703342911, 10019092501, 10019092582, 10019092602, 10019092616, 63323014210, 63323014212, 63323017420, 63323017460, 00173004535, 52609000105, 54868433900, 54868433901, 54868433902, 54868433903, 54868433904, 59572030250, 00173013093, 52609300100, 59572030101, 67457019501, or 67457021501 |
| Anthracyclines | Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone | J9000, J9001, J9178, 00013100691, 00013101679, 00013107694, 00013108691, 00013109691, 00013109694, 00013110679, 00013111683, 00013113691, 00013114691, 00013114694, 00013115679, 00013116683, 00013117687, 00013123691, 00013124691, 00013125679, 00013126683, 00013128683, 00015335122, 00015335222, 00015335322, 00069303020, 00069303120, 00069303220, 00069303320, 00069303420, 00186153013, 00186153101, 00186153231, 00186153241, 00186153261, 00186153281, 00186157512, 00469100161, 00469883020, 00469883130, 00469883250, 00702023110, 00702023206, 00702023301, 00702023510, 00702023606, 00702023701, 00703504001, 00703504303, 00703504601, 10019092001, 10019092102, 38779065206, 38779065209, 49452243701, 53905023206, 53905023606, 54868313100, 55390023110, 55390023210, 55390023301, 55390023510, 55390023610, 55390023701, 55390023801, 55390024110, 55390024210, 55390024301, 55390024510, 55390024610, 55390024701, 55390024801, 63323010161, 63323088305, 63323088310, 63323088330, 17314960001, 17314960002, 59676096001, 59676096002, 61471029512, 00009509101, 00009509301, 00591346983, 00591347057, 00703306711, 00703306911, 10139006101, 10139006125, 10518010410, 10518010411, 25021020325, 25021020351, 55390020701, 55390020801, 59762509101, 59762509301, 61703034735, 61703034859, 61703035901, 61703035902, 61703035959, 61703035991, 61703035992, 61703035993, 63323015100, 63323015105, 63323015125, 63323015175, 66758004201, or 66758004202 |

Abbreviations: HCPCS = Healthcare Common Procedure Coding System; IMiDs = immunomodulatory drugs; NDC = national drug code.

**Supplemental Table 2** ICD-9 Codes Used to Classify Patients

| Cardiac Event or Comorbidities | ICD-9 Codes |
|---|---|
| Hypertensive or arterial events | 401.xx-405.xx, 440.xx-449.xx |
| Cardiac dysrhythmias | 427.xx, 785.0 |
| Conduction disorders | 426.xx |
| Cardiomyopathy | 425.x |
| Congestive heart failure | 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.xx |
| Ischemic heart disease | 410.xx, 411.xx, 413.xx, 414.xx |
| Any cardiovascular event | Any of above events |
| Amyloidosis | 277.30, 277.39 |
| Chronic kidney disease | 585.x |
| Diabetes mellitus | 250.xx |
| Hyperlipidemia | 272.0-272.4 |
| Hypertension | 401-405 |

Abbreviation: ICD-9 = International Classification of Diseases, ninth revision.