1. ABSTRACT

- **Title**

  A retrospective analysis of pre-existing and acquired major adverse cardiovascular events (MACE) in a real-world cohort of multiple myeloma (MM) patients treated with proteasome inhibitors

- **Keywords**

  Major adverse cardiovascular events, multiple myeloma, proteasome inhibitor, carfilzomib, bortezomib

- **Rationale and Background**

  Proteasome inhibitors are an effective treatment for multiple myeloma and have formed the backbone of intial myleoma treatment since bortezomib's intial US approval in 2003. However, proteasome inhibitors may be associated with cardiovascular events. Bortezomib is a first-generation proteasome inhibitor that has been associated with cardiac failure. Carfilzomib, a potent second-generation irreversible proteasome inhibitor, has been increasingly incorporated into the treatment paradigm of MM since its US approval in 2012. Cardiovascular (CV) toxicities have emerged as a potential complication of carfilzomib during clinical trials involving patients with both newly diagnosed and advanced multiple myeloma and are reported to exceed CV toxicities associated with bortezomib. Given documented improvements in patient survival with the advent of novel therapies for multiple myeloma, there is a growing need to distinguish between pre-existing CV risk and treatment-specific CV risk. Furthermore, there is a need to study underlying proteasome inhibitor-associated CV toxicity, such that optimal preventive and early treatment strategies can be identified.

- **Research Question and Objectives**
  - Primary objective:

    Estimate the incidence of MACE in bortezomib- and carfilzomib- treated patients with MM

    Estimate the incidence of extended MACE in bortezomib- and carfilzomib-treated patients with MM

  - Secondary objective:

    Compare pre-treatment cardiovascular risk profile and overall comorbidities in bortezomib- and carfilzomib-treated patients with MM

  - Exploratory objective:

    To identify risk factors for MACE and extended MACE in MM patients: overall (e.g., proteasome inhibitor-treated), bortezomib-treated, and carfilzomib-treated

- **Study Design**

  Retrospective chart review analysis of cardiovascular outcomes of patients with MM treated with proteasome inhibitors.

- **Setting**

Patients eligible for this study received treatment for MM at one of the following institutions: Brigham & Women's Hospital, Dana Farber Cancer Institute, or Massachusetts General Hospital, Boston from 2003 through 2016.

- **Subjects and Study Size, Including Dropouts**

  Inclusion Criteria:
  - Patients with a diagnosis of MM who have received ≥ 1 prior treatments prior to treatment with carfilzomib or bortezomib
  - Treatment for at least 1 cycle with bortezomib (21-day cycle) or carfilzomib (28-day cycle)
  - Age ≥ 18 years

  A total of 416 proteasome inhibitor-treated patients were included. Final sample size of the treatment cohorts included 202 patients treated with bortezomib and 214 patients treated with carfilzomib.

- **Variables and Data Sources**
- **Exposure Assessment**
  - Dose and frequency of proteasome inhibitor use was recorded for each patient. Details of previous MM treatment regimens was recorded for all patients. Data pertaining to duration of medication usage was collected as comprehensively as was possible.

- **Outcome Assessment**
- Major cardiovascular event (MACE): Primary outcome for this study was a composite endpoint defined as any one of the following:
  - Death due to cardiovascular cause
  - Surgical or percutaneous coronary revascularization (PCI)
  - Hospital admission for arterial thrombosis or heart failure (HF). Arterial thrombosis is defined as cardiovascular thrombosis in the form of non-fatal myocardial infarction, non-hemorrhagic stroke and peripheral arterial disease.

- Extended MACE: The secondary outcome was a compositve endpoint defined as any one of the following:
  - Death due to cardiovascular cause
  - Surgical or percutaneous coronary revascularization (PCI)
  - Hospital admission for arterial thrombosis or heart failure (HF). Arterial thrombosis is defined as cardiovascular thrombosis in the form of non-fatal myocardial infarction, non-hemorrhagic stroke and peripheral arterial disease.
  - All-cause death
  - Venous thromboembolic event (VTE)
  - Addition of antihypertensive medication.

- **Covariate Assessment**
- Pre-treatment CV risk factors
- Charlson comorbidity score (Charlson et al. 1987)
- Eastern Cooperative Oncology Group (ECOG) performance status score (where available).
- CV baseline conditions: Hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, cerebrovascular disease (CVD), peripheral vascular disease (PVD), congestive heart failure, arrhythmias, smoking history, obstructive sleep apnea, and obesity (body mass index > 30 kg/m2).
- Pre-treatment use of cardiovascular medications (ANY antiplatelet agents, anticoagulants, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, or antiarrhythmic agents).
- **Results**

  The primary objective was to estimate the incidence proportion of patients who experience a MACE and extended MACE during treatment with proteasome inhibitors.

  MACE: overall, 18 (4.3%) patients experienced MACE during treatment with a proteasome inhibitor. In the bortezomib cohort, nine patients experienced MACE (4.5%) with three heart failure hospitalizations and three myocardial infarctions, one CV-related death, one non-hemorrhagic stroke, and one PCI. In the carfilzomib cohort, nine patients had a MACE (4.2%) with six heart failure hospitalizations and three myocardial infarctions.

  Extended MACE: overall, 155 (37.3%) patients experienced extended MACE during treatment with a proteasome inhibitor. Of these 155, 87 patients in the bortezomib cohort had an extended MACE (43.0%) and 68 patients in the carfilzomib cohort had an extended MACE (31.8%).

  The secondary objective was to compare pre-treatment cardiovascular risk profile and overall comorbidities by proteasome inhibitor (i.e., in bortezomib- and carfilzomib-treated patients). Significant differences between the two populations were identified as the carfilzomib cohort was more male (61% v 51%; p=0.04), older age at myeloma diagnosis (61 v 58 years; p=0.02), older age at proteasome inhibitor treatment (66 v 62 years; p=0.01), had fewer prior regimens (median 4 v 5; p=0.001), had more prior bortezomib (p<0.0001), had more hypertension (98% v 64%; p=0.002), had lower Charlson comorbidity index (3 v 4; p<0.0001), a higer proportion of two or more cardiovascular risk factors (64% v 50%; p=0.01), and had less ACE inhibitor/angiotensin receptor blocker treatment (14% v 23%; p=0.02) compared to the bortezomib cohort.

  The exploratory objective was to identify baseline risk factors that were associated with the development of MACE and extended MACE among all proteasome inhibitor-treated patients.

  MACE:Pre-treatment covariates that were associated with MACE during proteasome inhibitor treatment included age at proteasome inhibitor treatment (OR 1.05, 95% CI: 1.00-1.11), hypertension (OR 3.73, 95% CI 1.06-13.08), peripheral arterial disease (OR 7.04, 95% CI 1.78-27.88), atrial fibrillation (OR 3.44, 95% CI 1.17-10.16), and Charlson comorbidity index (OR 1.50, 95% CI 1.07-2.10).

Extended MACE:Pre-treatment covariates that were associated with extended MACE during proteasome inhibitor treatment included greater than five prior regimens (OR 1.70, 95% CI 1.07-2.69), peripheral arterial disease (OR 4.43, 95% CI 1.37-14.38), atrial fibrillation (OR 1.89, 95% CI 1.02-3.53), Charlson comorbidity index (OR 1.35, 95% CI 1.15-1.59), VTE (OR 1.94, 95% CI 1.14-3.30), aspirin/antiplatelet therapy (OR 0.61, 95% CI 0.41-0.92), and prior bortezomib treatment (OR 0.62, 95% CI 0.41-0.92).

- **Discussion**

  In this retrospective cohort study reporting MACE after initiation of a proteasome inhibitor treatment in RRMM patients, the overall incidence proportion was slightly higher than 4%. The incidence proportion of MACE and extended MACE was similar between the bortezomib and carfilzomib- treatment cohorts. Additionally, several pre-treatment risk factors associated with MACE during proteasome inhibitor treatment were identified including history of hypertension, peripheral arterial disease, and atrial fibrillation.

- **Marketing Authorization Holder(s)**

  Amgen Inc.

- **Names and Affiliations of Principal Investigators**

  [redacted]

  Assistant Professor of Medicine, Harvard Medical School,

  Cardio-Oncology Program, Brigham and Women's Hospital/Dana Farber Cancer Institute,

  [redacted]

  Assistant Professor of Medicine, Harvard Medical School,

  Cardio-Oncology Program, Brigham and Women's Hospital/Dana Farber Cancer Institute,