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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

# Proteasome Inhibitor-Related Cardiotoxicity: Mechanisms, Diagnosis, and Management

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## Abstract

**Purpose of Review** Multiple myeloma is the second most common hematologic malignancy in the USA, with over 32,000 new cases and nearly 13,000 deaths expected in 2019. The past few decades in myeloma research have yielded significant advances, leading to the expansion of novel anti-myeloma agents. This review describes the incidence and mechanisms of cardiotoxicity for the FDA-approved proteasome inhibitors in myeloma and proposes strategies to assess and manage resultant cardiovascular adverse events.

**Recent Findings** Proteasome inhibition precipitates protein aggregation and alters transcriptional activation of NF-κB targets which contributes to a pro-apoptotic signaling cascade in myeloma cells. Similar effects in cardiomyocytes and vascular smooth muscle endothelium, along with off-target downregulation of autophagy and signaling alterations of nitric oxide homeostasis, may be linked to observed cardiotoxic effects. There is preliminary evidence for cardioprotective potential for rutin, dexrazoxane, and apremilast that could have clinical applicability in the future.

**Summary** Of the proteasome inhibitors used in clinical practice, carfilzomib is the most strongly associated with cardiotoxicity. Patients with anticipated carfilzomib treatment should undergo assessment and optimization of baseline cardiovascular risk, with close monitoring during treatment. Previous clinical trials were not specifically designed to assess proteasome inhibitor-related cardiotoxicity, creating a need for future studies to identify and risk stratify vulnerable individuals and to develop potential cardioprotective strategies in attenuating cardiac injury.

**Keywords** Carfilzomib · Bortezomib · Chemotherapy-induced cardiomyopathy

## Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the USA, with over 32,000 new cases and nearly 13,000 deaths expected in 2019 [1]. The past few decades in myeloma research have yielded significant advances in the understanding and treatment of the disease, leading to the expansion of novel anti-myeloma agents to include immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) as well as advanced targeted therapies such as epigenetic modulators and humanized monoclonal antibodies. These developments have translated into improved long-term clinical response and survival, with 5-year relative survival rates increased from the 1975–1977 rate of 25% to the 2008–2014 rate of 52% [1]. Moreover, the improved efficacy and safety profile of these novel agents and the identification of high-risk patients with smoldering multiple myeloma (SMM) have influenced current trends of myeloma management to favor treatment at an earlier point in the natural history of the paraproteinemia using biochemical and radiographic biomarkers [2]. Consequently, the management of chronic treatment-related adverse effects has become a more pertinent issue as the prognostic outlook of patients with various stages of the plasma cell dyscrasia treated with advanced therapies continues to improve.

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While the use of anti-myeloma therapies has allowed for improvements in overall survival (OS), the post-treatment course of the disease is frequently complicated by cardiovascular adverse events (CVAEs) which in turn contribute to treatment-associated morbidity and mortality [3]. The concept of cardiotoxicity refers to the effect of antineoplastic intervention on accelerating the onset of cardiovascular (CV) disease. It also relates to its direct effect on the structure or function of the heart and vasculature, including systemic hypertension, myocardial dysfunction and congestive heart failure (CHF), coronary heart disease, arrhythmias, thromboembolic disease, pulmonary hypertension, valvular disease, pericardial complications, or other vascular diseases including stroke and peripheral vascular disease [4]. The exact risk conferred by anti-myeloma agents, as shown in clinical trials, may vary depending on which endpoints were used to define cardiotoxicity. For example, the imaging modality used for detection of left ventricular ejection fraction (LVEF), the degree of drop in LVEF, as well as the clinical assessment of CHF vary between studies. In addition, current data about cardiotoxicity were generated in clinical trials from which patients with severe pre-existing CV comorbidities were often excluded. Despite these uncertainties, there is mounting evidence and concern in clinical practice for cardiotoxicity mediated by newer antineoplastic agents in MM, especially with PIs, a medication class that has emerged as the backbone of combined therapy for relapsed or refractory MM (RRMM) as well as newly-diagnosed multiple myeloma (NDMM).

Currently, there are no validated protocols or established guidelines to help identify patients at high risk of CV toxicity during PI therapy or to manage associated cardiotoxicity. This review provides an overview of the clinical data leading to FDA approval of the presently available PIs along with known associated CVAEs. We present mechanistic insights into proteasome inhibition and its effects on malignant plasma cells as well as the unintended consequences of cardiomyocyte and endothelial cell impairment. We conclude by outlining current and anticipated methods of diagnosis and management of proteasome inhibitor-related cardiotoxicity.

## Baseline Cardiovascular Adverse Events (CVAEs) in Multiple Myeloma

The median age of diagnosis of MM is approximately 70 years [5]. Since the disease predominantly affects the elderly, a significant proportion of patients with MM have cardiovascular risk factors or comorbidities at the time of diagnosis. A retrospective cohort study of 32,193 patients with NDMM or RRMM in the USA demonstrated the presence of cardiac comorbidities in nearly 2/3 of patients at baseline, with most frequently observed conditions including ischemic heart disease (IHD), arrhythmia, and CHF [6]. Aspects related to the features of MM itself also serve as risk factors that can contribute to cardiovascular complications. The CRAB features of MM (elevated calcium, renal insufficiency, anemia, and bone lesions) [7] all have potential to lead to cardiovascular manifestations: severe hypercalcemia can cause life-threatening arrhythmias, renal insufficiency increases the risk of CV disease 2–4 fold [8], anemia is independently associated with increased CVD risk [9] and can lead to arrhythmias and hypertension [10], and AV shunts in the context of bone lesions can lead to heart failure. Accumulation of amyloid light-chain immunoglobulins can lead to overt clinical AL amyloidosis in up to 15% of patients with MM as well as clinically occult amyloid deposits in up to 38% of patients during the course of their disease, and may present as heart failure when there is cardiac involvement [11]. Similar to cases of senile amyloidosis in which wild type transthyretin (ATTRwt) deposits in the heart, AL amyloidosis also impairs diastolic function with heart failure with preserved ejection fraction (HFpEF), a diagnosis which may be identified with non-invasive lab (BNP, troponin) and imaging data (echocardiography or radionucleotide imaging) [12].

Given that patients with MM already have an elevated risk of CV disease at the time of diagnosis, early identification of patients at high risk for CVAEs becomes important as these patients may require more extensive and careful monitoring prior to the initiation of cardiotoxic therapies. Co-management of the underlying hematologic disorder alongside with a cardiology-based discussion is essential in individuals who are deemed to have a higher likelihood of developing clinical cardiovascular impairment during or after treatment. In the same vein, since PIs have become a centerpiece of the treatment of MM, it is important to recognize the specific cardiotoxic risks associated with the FDA-approved drugs bortezomib, carfilzomib, and ixazomib, as well as newer agents undergoing investigation including marizomib and oprozomib.

## Pre-Clinical Data and Mechanistic Underpinnings to Explain PI-Related Cardiotoxicity

Understanding the mechanisms of PI cardiotoxicity may help facilitate the development of methods for prevention or treatment of cardiotoxicity (Fig. 1). In pre-clinical studies with rats, it was found that carfilzomib accumulated in the heart and led to strong inhibition of the cardiac proteasome [14]. Cardiomyocytes are especially sensitive to proteasome inhibition, as they are non-proliferative and have elevated proteasome activity compared with other tissues [15]. In myeloma cells, proteasome inhibition results in rapid accumulation of incompatible regulatory proteins within the endoplasmic reticulum (ER). This ER stress culminates in unfolded protein response (UPR) with induction of apoptotic cascade [16]. Likewise, in cardiomyocytes, the inhibition of proteasomal-dependent protein turnover of sarcomeres can lead to

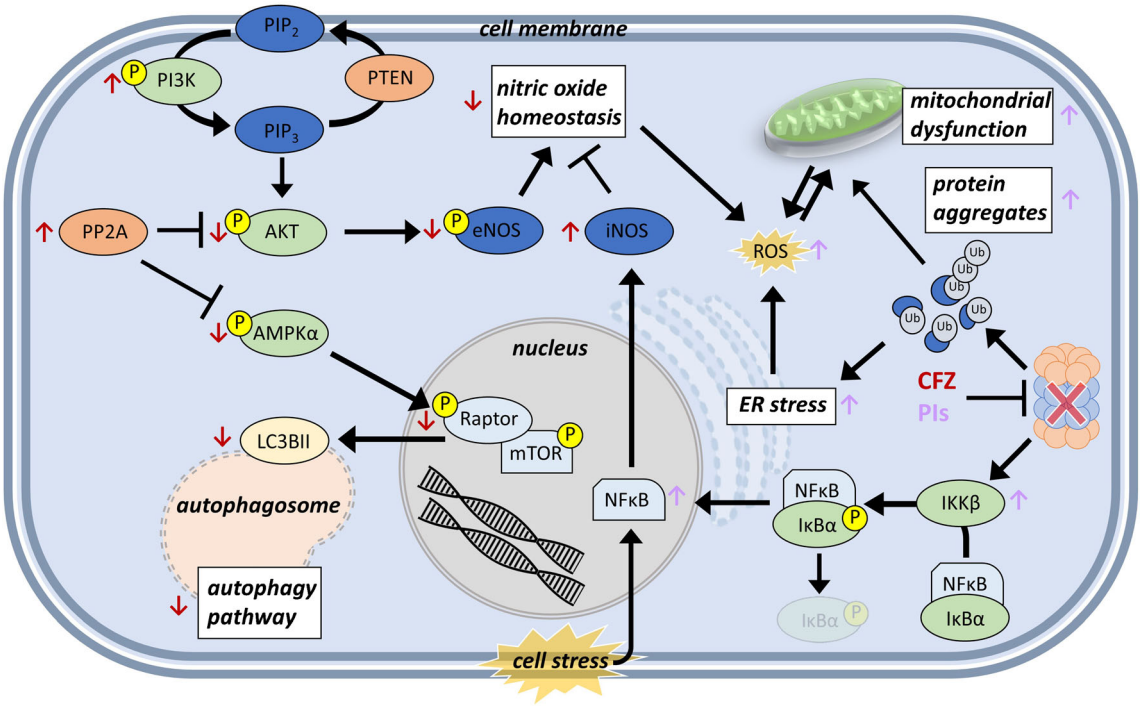


**Fig. 1** Proteasome inhibitor-related cardiotoxicity—mechanistic underpinnings [33••, 13]. The ubiquitin-proteasome system (UPS) plays a central role in non-lysosomal protein quality control, allowing eukaryotic cells to maintain normal cellular homeostasis and adapt to physiologic changes. Proteins that are destined for turnover are tagged with polyubiquitin chains by ubiquitin conjugation system and are recognized by the proteasome complex which participates in the vast majority of regulated intracellular proteolysis including both short-lived and long-lived proteins. Studies in animal models suggest that proteasome inhibition with bortezomib and MLN-273 (shown in lilac) may cause IKKβ-dependent increased phosphorylation and downregulation of IκBα which activates NF-κB, with many downstream effects. Inhibition of proteasomal-dependent protein turnover of sarcomeres can lead to the abnormal accumulation of ubiquitinated proteins that associate with one another to form sequentially higher order protein aggregates toxic to cellular function, contributing to increased mitochondrial dysfunction and sarcoplasmic/endoplasmic reticulum stress. Recent data with carfilzomib (shown in red) suggest that its cardiotoxicity may stem from off-target effects of the drug, resulting in activation of PP2A and inactivation of downstream autophagy signaling. Treatment with proteasome inhibitors, including carfilzomib, may result in uncoupled eNOS expression with increased production of reactive oxygen species which further exacerbates cardiotoxicity. Key: AMPKα AMP-activated protein kinase; CFZ carfilzomib; IKKβ inhibitor of nuclear factor kappa-B kinase subunit beta; IκBα nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha; LC3BII light chain 3B II; NFκB nuclear factor kappa-light-chain-enhancer of activated B cells; PI proteasome inhibitor; PI3K phosphoinositide 3-kinase; PIP2 phosphatidylinositol 4,5-bisphosphate; PIP3 phosphatidylinositol (3,4,5)-trisphosphate; PP2A protein phosphatase 2A; PTEN phosphatase and tensin homolog; ROS reactive oxygen species; Raptor regulatory-associated protein of mTOR; Ub ubiquitin; eNOS endothelial nitric oxide synthase; iNOS inducible nitric oxide synthase; mTOR mammalian target of rapamycin

imbalance of proteins, with abnormal accumulation of ubiquitinated proteins that associate with one another to form sequentially higher order protein aggregates toxic to cellular function [17]. These may include soluble oligomers and aggresomes that eventually create insoluble inclusion bodies, resulting in cellular injury that can ultimately lead to caspase-mediated apoptosis and cell death [18, 19]. Abnormal protein aggregates have been found in human cardiomyopathies including HCM, DCM, and desmin-related cardiomyopathies as well as heart failure [19–22].

Signaling cascades leading to maladaptive hypertrophy in cardiomyocytes may be activated with proteasome inhibitor treatment. The prominent role of transcription factor nuclear factor kappa B (NF-κB) in promoting myelomagenesis provided the initial basis for targeting the proteasome in multiple myeloma [23, 24]. Bortezomib cytotoxicity in MM may be explained by the blockade of proteasomal processing of p100 to p52, a mediator in the noncanonical NF-κB pathway [25]. However, in cell lines with primarily canonical NF-κB pathway signaling, proteasome inhibition with both bortezomib and boronic acid MLN-273 resulted in IKKβ-dependent increased phosphorylation and downregulation of IκBα which activated NF-κB via the canonical pathway [25]. This suggests that PIs may exhibit unique patterns of NF-κB activity in different cell lines. The transcriptional activation of NF-κB plays a major role in the pathophysiology of many cardiovascular diseases, in some cases leading to pathologic remodeling. For example, in the ischemia/reperfusion model following myocardial infarction, NF-κB is activated downstream of mitogen-activated protein kinase (MAPK) signal transduction cascades such as extracellular signal-regulated kinases (ERKs), c-Jun NH2-terminal kinases (JNKs), and p38

[26–28]. While this signaling may be cardioprotective in the short term by preventing apoptosis, prolonged activation of NF-κB may be detrimental and promotes heart failure through chronic inflammation leading to ER stress responses and death with accumulation of damaged or dying cardiomyocytes [29]. Other signaling cascades such as NFAT-calcineurin activation leading to congestive heart failure was seen in mouse models of desmin-related cardiomyopathy treated with relatively higher doses of bortezomib [30]. In animals, proteasome inhibition with bortezomib and MLN-273 has been shown to induce left ventricular dysfunction with enlarged cardiomyocytes demonstrating vacuolization, mitochondrial dysfunction, and fibrosis [30–32]. Finally, a recent finding describes off-target effects of carfilzomib in mice related to activation of PP2A and inactivation of downstream signaling, implicating the disruption of autophagy as a major contributor to cardiotoxicity from the drug [33••]. This finding was not reproduced with bortezomib and was unexpected when compared with previous studies with other proteasome inhibitors. This suggests that unique classes of proteasome inhibitors may have distinct mechanisms for cardiotoxicity, an issue further confounded by the utilization of different animal models.

Endothelial dysfunction in the vasculature is linked to the cardiovascular effects, particularly hypertension, which is often seen in these patients [34]. One supporting finding is that the majority of CVAEs are transient, with levels of natriuretic peptides returning back to near-baseline values [35••]. Episodes of thrombotic microangiopathy have also been reported, providing additional evidence for systemic endothelial involvement [36]. Proteasome inhibition alters signaling in vascular smooth muscle endothelium, leading to increased vasoconstriction, vascular tone, vasospasms, and decreased response to vasodilators such as nitric oxide and acetylcholine [37–39]. Nitric oxide is converted from L-arginine by isoforms of nitric oxide synthase (NOS). Since the UPS plays a significant role in endothelial NOS (eNOS) regulation, it is not surprising that inhibition of the complex would impact downstream effectors [40]. In pigs, treatment with MLN 273 resulted in uncoupled eNOS expression, which was ultimately associated with increased coronary artery oxidative stress and functional and structural changes to the heart consistent with a hypertrophic-restrictive cardiomyopathy phenotype [31, 41]. It is conceivable that other PIs may have similar effects in vivo. In addition, eNOS uncoupling in the vasculature leads to the reduction of molecular oxygen to generate reactive oxygen species (ROS) [42, 43]. In situations like diabetic cardiomyopathy, ROS-driven pathways lead to hypertrophy and fibrosis of the myocardium via NF-κB activation, leading to increased inflammation and remodeling [44]. In murine studies, the increased formation of ROS has been hypothesized to be the reason behind compounded and synergistic cardiotoxicity from anthracyclines when used with proteasome inhibition [45]. Along this vein, NO releasing agents like nitrates or phosphodiesterase inhibitors may be useful in treating carfilzomib-related adverse events. Alternatively, nitroglycerine and nifedipine may be useful to reduce vasospasms associated with endothelial dysfunction.

## Mechanism of Anti-Myeloma Efficacy and Evidence of Cardiotoxicity for Currently FDA-Approved PIs

The barrel-shaped 20S catalytic core particle of the proteasome degradation complex comprised four heptameric rings, with two internal β rings containing protease active sites comprised proteolytic subunits [46]. Subunits β1, β2, and β5 have caspase-like activity, trypsin-like activity, and chymotrypsin-like activity respectively and mediate proteolytic cleavage. Of note, immunoproteasome versions of these β subunits can be found in lymphocytes and monocytes from IFN-γ and TNF-α stimulation and are referred to as β1i, β2i, and β5i subunits. Both the 20S constitutive proteasome and the 20s immunoproteasomes are targeted by the currently FDA-approved PIs which consist of bortezomib, carfilzomib, and ixazomib as well as newer drugs in development including oprozomib and marizomib (Table 1).

### Bortezomib (BTZ, Velcade, PS-341)

Bortezomib is a PI that binds reversibly to the β5 (chymotrypsin-like) as well as β5i subunits of the immunoproteasome [47]. The efficacy of bortezomib in clinical practice was based on two large phase 2 studies: the SUMMIT and the CREST trials [48, 49]. Bortezomib received accelerated approval by the FDA in 2003 for patients with RRMM who have progressed after 3 or more prior lines of therapy. In 2005, the phase 3 APEX trial compared outcomes for patients who received bortezomib to patients who were treated with the standard of care at that time, high-dose dexamethasone [50]. The outcomes of this international trial demonstrated superior response rates, time to progression (TTP), and OS in the bortezomib group, even in the context of more than 62% of patients in the dexamethasone arm crossing over to receive bortezomib. With this new evidence, bortezomib emerged as the treatment of choice for relapsed MM as it was approved by the FDA in 2005 for RRMM after failure of 1 or more prior lines. Soon after, the FDA approved bortezomib as an upfront treatment of NDMM in 2008 with supporting data from the VISTA trial [51]. This trial became especially relevant because it brought bortezomib in VMP (bortezomib, melphalan, prednisone) combination therapy to the forefront as the standard of care for induction therapy in patients ineligible for ASCT.

Although there have been occasional case reports and series of cardiotoxicity from bortezomib leading to heart failure [52–56], ischemic heart disease [57], and complete heart block [58], the onset of cardiac symptoms has typically been

**Table 1** Current anti-myeloma proteasome inhibitors, mechanisms, and known associated cardiotoxicity

| Drug name | FDA approval year | Mechanism | Known cardiotoxicity | References |
|---|---|---|---|---|
| Bortezomib (BTZ, Velcade, PS-341) | 2003 (RRMM after ≥ 3 prior lines of therapy), 2005 (RRMM after ≥ 1 prior lines of therapy), 2008 (NDMM), 2012 (subcutaneous route), 2014 (retreatment in relapse) | Reversible binding to β5 and β5i subunits | Only in case studies: heart failure, ischemic heart disease, complete heart block | Bockorny et al. [52], Gupta et al. [53], Honton et al. [54], Voortman and Giaccone [55], Enrico et al. [56], Takamatsu et al. [57], Dasanu [58] |
| Carfilzomib (CFZ, Kyprolis, PR-171) | 2012 (RRMM after ≥ 2 prior lines of therapy including bortezomib and an IMiD) | Irreversible binding to β5 and β5i subunits | Arrhythmias (13.3%), heart failure (7.2%), ischemic heart disease (3%), cardiomyopathy (2%), pulmonary hypertension (2%) | Siegel et al. [69] |
| | 2015 (in KRd regimen, RRMM after ≥ 1 prior lines of therapy) | | Hypertension (4.3%), heart failure (3.8%), ischemic heart disease (3.3%) | Stewart et al. [70], Siegel et al. [71] (ASPIRE) |
| | 2016 (in Kd regimen, RRMM after ≥ 1 prior lines of therapy) | | Hypertension (12.2%), heart failure (4.1%), arrhythmias (2.4%), ischemic heart disease (1.8%) | Waxman et al. [75••] |
| | N/A | | Heart failure (41%), hypertension (23%), arrhythmia (7%), ischemic heart disease (6%), pulmonary hypertension (7%) | Cornell et al. [35••] (PROTECT, CFZ-based regimen most commonly with pomalidomide and dexamethasone) |
| Ixazomib (Ninlaro, MLN9708) | 2015 (in ILd regimen, RRMM after ≥ 1 prior lines of therapy) | Reversible binding to β5 and β5i subunits, inhibition of β1 and β2 subunits at high concentrations | None found in TOURMALINE-MM1 trial | Moreau et al. [79•] (TOURMALINE-MM1) |
| Oprozomib (ONX 0912, PR-047) | Not yet approved | Irreversible binding to β5 and β5i subunits | Unknown | Unknown |
| Marizomib (NPI-0052) | Not yet approved | Irreversible binding to β5 and β2 subunits | Unknown | Unknown |

associated with a higher cumulative dose of the drug while larger studies failed to demonstrate clinically significant cardiotoxicity [59]. Of note, CVAEs were not closely monitored or well reported in earlier trials, and the APEX trial was the first to monitor cardiac events, with reports of similar CVAEs in bortezomib and non-bortezomib groups (15% vs 13% of CVAEs). Both a 2014 meta-analysis of prospective phase II and III trials evaluating bortezomib in cancer patients (including MM, lymphoma, non-small-cell-lung cancer, Waldenström's macroglobulinemia, and ovarian cancer) with cardiotoxicity data and a 2013 retrospective analysis of key phase II and III trials with bortezomib in MM alone did not show significant increased cardiotoxic effects from the drug [60, 61]. The main limitation of these large studies is that some of the phase II and III trials did not adjudicate these endpoints and thus may have generated incomplete data due to lack of documentation regarding concomitant therapies or cardiovascular comorbidities.

The mechanism for bortezomib chemoresistance has been attributed to changes in expression of proteasome subunits [62, 63]. While combination therapy may be effective in resensitizing myeloma to PIs, there is both clinical and preclinical data to suggest other proteasome inhibitors with irreversible binding to proteasome subunits, including carfilzomib [64, 65], may subvert mechanisms of bortezomib resistance.

### Carfilzomib (CFZ, Kyprolis, PR-171)

Carfilzomib binds irreversibly to β5 (chymotryptic-like activity) and β5i immunoproteasome, with equivalent potency against the β5 and the LMP7 (β5i) subunits [66]. This drug was found to have greater selectivity for β5 subunits, with minimal affinity to β1 and β2 subunits when compared with bortezomib [67]. Unlike boronates, carfilzomib has little affinity for off-target enzymes including serine proteases [14], a mechanism for why carfilzomib is thought to be associated with less treatment-induced peripheral neuropathy when compared with bortezomib [68]. Carfilzomib was found to cause proteasome inhibition in excess of 80% of patients [14], and its efficacy in bortezomib-resistant lines may involve its ability to achieve prolonged and possibly more profound inhibition of the proteasome. However, although second-generation PIs like carfilzomib may exhibit favorable efficacy when compared with bortezomib, they also present a unique toxicity profile.

Carfilzomib received FDA approval in 2012 for use in RRMM for patients who have received at least two prior therapies including bortezomib and an IMiD, based on evidence demonstrating improved overall response rates compared with bortezomib in multiple multicenter phase II studies. However, several early studies of carfilzomib noted an increased risk of CVAEs. A pooled analysis of phase II studies with carfilzomib (PX-171-003-A1, PX-171-003-A0, PX-171-004, and PX-171-005) that included 526 patients showed 22% of patients from these trials developed cardiac side effects: 13.3% experienced arrhythmias (mainly atrial fibrillation), 7.2% exhibited heart failure, 2% developed treatment-associated cardiomyopathy, and 3% suffered from ischemic heart disease [69]. In addition, 42% of these patients reported dyspnea.

In 2015, carfilzomib combination regimen with lenalidomide and dexamethasone (KRd) was approved by the FDA for RRMM with 1 or more prior lines based on significantly improved PFS and improved quality of life with KRd in the international, randomized, phase III ASPIRE trial which compared KRd regimen with Rd. [70, 71••]. The ASPIRE trial reported that the KRd group had increased cases of CVAE when compared with Rd., with hypertension rates of 4.3% compared with 1.8%, heart failure rate of 3.8% compared with 1.8%, and IHD rates of 3.3% compared with 2.1%.

Finally, in 2016, the FDA approved the use of carfilzomib with low-dose dexamethasone (Kd) in patients with RRMM for which 1 or more prior lines of therapy failed. This was based on the results from phase III superiority trial, ENDEAVOR, which compared Kd with bortezomib with low-dose dexamethasone (Vd), which had been the standard of care in RRMM [72, 73••]. Notably, the ENDEAVOR trial excluded bortezomib-refractory patients as well as patients with LVEF< 40% or clinical symptoms NYHA III/IV or recent MI or symptoms of cardiac ischemia. In addition, rates of grade 2 or higher peripheral neuropathy were seen in only 6% of the Kd group when compared with 32% of the Vd group.

A pattern of increased cardiotoxicity has been demonstrated with carfilzomib. These toxicities include hypertension (HTN), arrhythmia, heart failure (HF), ischemic heart disease (IHD), cardiomyopathy, thromboembolic events, pulmonary hypertension, and rarely sudden cardiac death [69, 74]. The higher potency and irreversible inhibition by carfilzomib, along with dose-limiting neuropathy associated with bortezomib, may be the link between carfilzomib and higher incidences of CVAEs. In the ENDEAVOR study, an expected increased incidence of any-grade dyspnea, hypertension, and heart failure were detected [73••]. However, the study only reported clinically overt HF, biomarkers were not measured, and LV function changes were only sequentially measured in a subpopulation analysis of 151 patients. For those patients, serial echocardiography showed only two patients in each group had reduced LVEF. In a systemic review and meta-analysis of 24 prospective clinical trials that included 2594 patients found a large range of reported CVAEs, with all-grade CVAE ranging from 0 to 52% and high-grade CVAE ranging from 0 to 45% [75••]. Using a random effects model, the study found an all-grade overall CVAE rate of 18.1% and high-grade CVAE rate of 8.2%. The pronounced CV adverse effects were heart failure (4.1%) and hypertension (12.2%),

with lower risk of arrhythmias (2.4%) and ischemic events (1.8%). All-grade dyspnea (23.9%) and edema (24.7%) were common, although underlying causes were seldom documented. CVAEs were especially significant with higher doses (45 mg/m$^2$ or higher). The study concluded that, based on the 3 RCTs included in the study (ASPIRE, ENDEAVOR, and FOCUS), the use of carfilzomib was associated with a 2-fold increased risk of high-grade CVAE. Another study analyzing the safety profile across the RRMM clinical trials demonstrated a risk profile that was transient and manageable so that these risks were rarely associated with treatment discontinuation or dose reduction, while rates of fatal CVAEs were not elevated.

In an effort to better define risk factors and outcomes in patients who receive PI therapy, a prospective, observational study, the PROTECT trial, was conducted [35••]. Of 95 RRMM patients enrolled, 65 were initiated on carfilzomib therapy, and 30 treated on bortezomib. This was followed by baseline assessments over 6 months with cardiac biomarkers including troponin I or T, BNP, NT-proBNP, ECG, and echocardiography, with monitoring over 18 months for the development of CVAEs. The study found that a total of 64 CVAEs occurred with 55% grade 3 or greater severity. Of these events, 51% were in patients treated with carfilzomib and 17% of those were treated with bortezomib. The most common diagnoses for carfilzomib-treated patients included 41% of cases with all grades of heart failure and 21% of cases with grade 3 or 4 hypertension. The median time to first CVAE was 31 days, with 86% within the first 3 months. The study also demonstrated an association between BNP and NT-proBNP rise and increased CVAE risk, especially if natriuretic peptides were elevated during the mid-first cycle of treatment. Levels of troponin I or T, ECG, and echocardiographic parameters were not predictive of CVAEs.

The PROTECT trial reported a much higher incidence of CVAE than prior studies, possibly due to its prospective nature as well as that CVAE were captured as a primary endpoint. However, it also points to the fact that patients in clinical practice usually have higher incidence of cardiac comorbidities. The actual incidence and pathophysiology of CVAE for carfilzomib-treated patients is unclear in the real world as clinical trials often enroll healthy patients. A recently published study that retrospectively assessed 635 patients treated with carfilzomib in the general population using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database from 2000 through 2013 for incidence of cardiac adverse events, excluding pre-existing diagnoses corresponding with these cardiac adverse events of interest, found that 22% of patients developed hypertension and 14% developed heart failure [76••].

In many of the aforementioned trials, assessment for CVAEs was not always consistent and was not always verified by a cardiologist. Moreover, the data from carfilzomib trials carry certain flaws that may inaccurately predict incidence of CVAEs. For instance, carfilzomib-treated patients were seen more often which can contribute to ascertainment bias, whereas post hoc analysis, lack of blinded studies, and studies lacking placebo present additional sources of bias.

### Ixazomib (Ninlaro, MLN9708)

Ixazomib, like bortezomib, acts as on a reversible inhibitor on the β5 (chymotrypsin-like) and β5i subunits of the immunoproteasome, with additional inhibition of β1 and β2 subunits at higher concentrations [77, 78]. Ixazomib was the first orally bioavailable drug approved by the FDA in 2015 for RRMM used in combination with lenalidomide and dexamethasone for patients in which 1 or more prior lines of treatment failed. Its approval followed the TOURMALINE-MM1 trial [79•]. This randomized phase III trial compared ixazomib versus placebo in combination with lenalidomide and dexamethasone and found that PFS was significantly longer with ixazomib with limited toxic effects (nausea and vomiting were most common). With regard to CVAEs, the trial showed that HTN, HF, arrhythmia, and MI did not differ significantly between the two groups. This is possible due to the reversibility of proteasome inhibition with ixazomib, similar to that with bortezomib. However, the trial did exclude patients with clinical symptoms of arrhythmia, HTN, HF, unstable angina, or myocardial infarction within the previous 6 months. Of note, ixazomib-dexamethasone has been used safely in relapsed or refractory primary systemic AL amyloidosis where cardiac involvement is present, although in the trial, the primary endpoint of hematologic response was not met [80].

### Other Proteasome Inhibitors

Oprozomib (ONX 0912, PR-047), like carfilzomib, is an epoxyketone PI that is orally bioavailable. As a structural homolog of carfilzomib, it irreversibly binds to the β5 subunits. Phase I/II data suggest that oprozomib could have clinical activity in MM, both in RRMM [81•] and NDMM [82•]. While GI side effects were commonly reported, there is some evidence for peripheral neuropathy with relatively few cardiovascular side effects. Only some recent data has evaluated ECG data [83], which have not proved to be useful in detecting cardiotoxicity in carfilzomib trials [35••, 84]. It will be essential to test for CVAE mediated by this drug since its structure and mechanism are equivalent to that of carfilzomib.

Marizomib (NPI-0052) is a salinosporamide that acts as an irreversible PI of the β5 and β2 subunits of the proteasome. The drug has a unique efficacy and safety profile, with little cross-resistance with other PIs. There are currently several phase I trials using marizomib that demonstrate promising activity in RRMM [85, 86], with phase II trials underway. Little data regarding CVAE from this drug is available.

Overall, despite reports of cardiotoxicity from PIs, it is difficult to establish the extent to which reported cardiopulmonary events were attributable to patients' baseline comorbidities or toxicity from previous or current treatments. Studies that factor in detailed accounts of previous cardiovascular history and prior treatment along with concomitant anti-myeloma agent usage are in need.

## Discussion: Diagnosis and Treatment

Despite the lack of clear guidelines on the diagnosis and treatment of proteasome inhibitor-related cardiotoxicity, there are general recommendations regarding the management of other associated cardiovascular disorders drawn from real-world clinical experience (Table 2). Although carfilzomib has been the predominant drug for which studies have created an extensive profile for cardiotoxicity, broad guidelines for other newer PIs may be extrapolated from experience with carfilzomib.

### Early Detection

It is essential that clinicians gather a clear history from patients so that cardiovascular risk factors are optimized prior to initiation of PIs. Most reports of cardiotoxicity with carfilzomib reveal clinical events that occur early during treatment, and less common late events with no clear relationship with cumulative toxicity [70, 87, 88]. This supports early follow-up with a cardiovascular clinician after PI treatment. As carfilzomib is associated with heart failure and hypertension, it is important to optimize medications for patients with these conditions. A history of atrial fibrillation and flutter or heart failure was significantly more prevalent in patients who experienced CVAEs from PIs [89]. A case series of 12 patients with CVAEs after carfilzomib-based treatment determined that patients had a history of the specific CVAE that they exhibited, with improvement after discontinuation of the therapy [90]. Finally, in a study of 60 patients, baseline cardiovascular disease was associated with an increased incidence of cardiac events (23.5% vs 7%) [91].

While the exposure of cardiomyocytes to toxic insults may result in transient or subclinical impairments in healthy populations, patients with baseline dysfunction exacerbated from underlying cardiac disease, prior drug exposure, or even from genetic cardiomyopathies have increased sensitivity for additional hits and may exhibit fulminant CVAEs. In the preclinical rat myocyte model, bortezomib and carfilzomib potentiated cardiotoxic effects of doxorubicin [18]. Clinical evidence suggests that prior radiation to the chest, anthracycline, or doxorubicin exposure may all be indicators for higher-risk susceptibility to the CVAEs induced by carfilzomib, making these cases attributable to a "multiple hit" phenomenon [34, 74, 90, 92, 93]. This highlights the importance of a careful history of previous heart conditions along with a clear history of previous treatments in helping clinicians suspect and diagnose carfilzomib-induced cardiotoxicity at an earlier time point. In patients with higher CVAE risk, certain precautions may be considered, such as early cardiologist referral before commencement of treatment if cardiac risk factors are identified, as well as an oncologist consideration for adjustments of the rate of infusion or initiation of the drug at a lower dose with gradual up-titration [74, 90, 94, 95]. Newer agents like ixazomib or oprozomib, on the other hand, bypass this concern for infusion rates and doses while expanding availability of PI treatment.

**Table 2** Assessment and management of proteasome inhibitor-mediated cardiotoxicity

| |
|---|
| Pre-treatment optimization |
| Assess baseline cardiovascular risk (clinical, EKG, TTE, +/− stress test) |
| Identify unique cardiovascular risk factors (i.e., prior stem cell transplant, prior heavy cytotoxic treatment, prior anthracyclines, concurrent AL amyloid) |
| Control pre-existing cardiovascular risk factors |
| Utilize goal-directed medical therapy for patients with heart failure (beta-blockers, ACE inhibitors, ARBs, aldosterone antagonists, diuretics) |
| Monitoring during treatment |
| Promptly evaluate any new cardiovascular symptom |
| Consider reducing IV fluid rates/volumes in patients with risk factors for volume overload |
| Consider VTE prophylaxis in high-risk patients |
| Consider holding treatment with development of cardiotoxicity (i.e., clinical HF, ventricular dysfunction) and weighting of risks and benefits of continuing therapy |
| Post-treatment assessment |
| Work up any cardiovascular signs or symptoms emerging after therapy (first rule out PE, asthma/COPD, respiratory infection) |
| Continue clinical follow-ups tailored to pre-treatment cardiovascular disease and on-treatment morbidity |

### Monitoring for Cardiotoxicity During Proteasome Inhibitor Therapy

During treatment, certain cardiopulmonary processes known to be associated with PI administration should be watched closely. Blood pressure elevations should be treated promptly, and vitals should be obtained at initial visits to have a baseline for comparison. Typical symptoms and signs of heart failure and fluid overload should be evaluated by a cardiologist after ruling out other etiologies (i.e., pulmonary embolus, pneumonia, anemia, anxiety).

In a recent case series of carfilzomib-treated patients, treatment-emergent dyspnea and left ventricular systolic and/

or diastolic dysfunction were described in 6 patients [92]. The investigators did not find troponin to be having predictive capacity [35••]. Following BNP levels is common in other reports, including a patient on carfilzomib as a phase Ib clinical trial [96], a case series of 12 patients [90], the PROTECT study [35••], and a retrospective analysis from University of Arkansas [97], to name a few. However, it is difficult to discern whether or not elevations in BNP levels correlate with increased clinical symptoms or hospitalizations [34, 74], and RCTs will be needed to answer this question definitively. It may be helpful to obtain baseline BNP levels prior to initiating a PI and trend BNP at the discretion of the provider, especially during the mid-first cycle of therapy for carfilzomib and for the first 3 months of therapy [35••]. However, changes to chemotherapy should not be based solely on BNP levels, as patients would often have BNP elevation without associated symptoms or hospitalizations. New BNP elevations may warrant closer monitoring for changes in body weights and regular assessment for fluid overload. As previously mentioned, electrocardiographic LVH has little utility in screening for cardiotoxicity. Similarly, TTE has limited value for predicting or demonstration CVAEs, with variable findings of associated normal systolic and diastolic function as well as abnormal LV longitudinal strain [34, 74, 90, 92]. However, even though large trials like ENDEAVOR suggest that there is limited utility of serial echocardiography as a risk mitigation tool for patients receiving carfilzomib, this is difficult to extrapolate to patients with more baseline cardiac comorbidities since ENDEAVOR excluded such patients. Monitoring with echocardiography may help detect subclinical or impending pulmonary hypertension and heart failure in patients prior to therapy, and should still be standard of care, especially in the case in patients of advanced age, with prior risk factors (anthracyclines, doxorubicin, radiation therapy), risks for amyloidosis, or other cardiovascular risk factors. In the future, further assessment on LV longitudinal strain or other imaging strategies may provide more sensitive, non-invasive detection of cardiotoxicities and prove useful in ruling out alternative causes.

## Management of Cardiotoxicity

In patients scheduled for carfilzomib therapy who have risk factors for cardiotoxicity, practitioners may consider prophylactic measures, as well as typical methods to manage heart failure should it arise. Prophylactically, reduction in intravenous fluid volume to be administered with PI infusions, along with prolongation of infusion time of carfilzomib may lead to better tolerability for the therapy. Typically, patients receive 1.5 to 6 l of fluids in cycle 1 of therapy, and about 250–500 mL prior to each treatment over 6 treatments, with additional 250–500 mL if needed following administration of carfilzomib [98]. Since this fluid is mainly to reduce tumor lysis syndrome, in the setting of chronic renal failure, or to prevent and reduce fatigue, the amount of fluid may be adjusted on an individual patient basis. This is especially true in cases of chronic heart failure, stable renal function, elderly patients over age 75, and cardiac risk factors. Since patients receiving PI infusions with corticosteroid are also vulnerable to fluid overload from the fluid-retaining properties of the steroids, reduction of fluids with each cycle may be appropriate. For patients with a history of chronic heart failure, management of heart failure by a cardiologist with goal-directed medical therapy is ideal, including beta-blockers and diuretics. Addition of cardiovascular medications, particularly anti-hypertensives, may also be appropriate given the effect carfilzomib plays on the endothelium which leads to common side effects of hypertension. In patients with stable renal function, ACE inhibitors or ARBs may serve the dual purpose as heart failure medication for beneficial ventricular remodeling and anti-hypertensive.

In patients who present with overt signs of cardiotoxicity, clinicians should first rule out alternative etiologies for dyspnea, hypertension, chest pain, and heart failure. Manufacturer-based guidelines for the management of non-hematologic toxicities for patients on lenalidomide and carfilzomib endorse resuming full dose of lenalidomide with modifications on dosing of carfilzomib. These three carfilzomib modifications are listed as follows: (1) for CHF, hold dose until resolution or return to baseline, after which may result at a reduced dose or permanently discontinue. If no resolution after 4 weeks, subject to be withdrawn from all study treatment, (2) for HTN crisis (SBP sustained > 180 or DBP > 110), hold carfilzomib until resolution to baseline, then resume at 1 dose decrement; (3) LVEF reduction < 40% or < 55% if drop is greater than 20% from baseline, hold carfilzomib until LVEF returns to ≥ 40. Resume at 1 dose decrement; and (4) if held due to LVEF drop < 55%, hold carfilzomib until LVEF returns to within 15% of baseline. Resume at 1 dose decrement. [98]. Mount Sinai lists a succinct institutional guideline which recommends holding carfilzomib until toxicity resolves to grade < 2, and if decision is made to re-challenge the patients, a dose reduction may be considered [90].

Modification of dosing for carfilzomib may be useful even with the irreversibility of the drug as cases show that withdrawal or dose reduction with initiation of heart failure medications may potentially reverse cardiomyopathy, while others show resolved cardiac dysfunction while resuming these medications [90, 91, 99]. Hemodialysis has not been found to be helpful to enhance elimination since there is 97% plasma protein binding of carfilzomib [98]. Further understanding of the potential mechanisms that lead to carfilzomib-induced cardiotoxicity through pre-clinical data is useful in understanding alternative methods for preventing and treating these adverse events.

## Future Directions

Based on proposed mechanisms for cardiotoxicity, various new agents have been presented to counteract PI-related cardiotoxicity. Animal model studies have noted that three compounds named rutin, dexrazoxane, and apremilast have been shown to reverse carfilzomib-induced cardiotoxicity in rat models. Rutin, or vitamin P, is a bioflavonoid that was found in rat hearts to inhibit NF-κB, directly reducing pathologic hypertrophic remodeling and oxidative stress [100•]. In this study, rutin was able to decrease cardiac enzyme release and cause upregulation of α-MHC mRNA expression with downregulation of β-MHC and BNP mRNA expression. Overall, the vitamin was able to reverse histopathological changes in the heart induced by carfilzomib. The exact mechanisms through which rutin was able to achieve this endpoint is still unclear. Interestingly, dexrazoxane, an inhibitor of topoisomerase IIB and free radical scavenger that had previously been found to be cardioprotective in doxorubicin-induced cardiotoxicity [101], was found to perform similarly to rutin in rat cardiomyocytes [102•]. Finally, a PDE4 inhibitor called apremilast that is used in psoriasis for its anti-inflammatory effect was also found in rat models to have similar ability to reverse carfilzomib-induced cardiotoxicity [103•]. The drug additionally demonstrated reversal of the increased NF-κB, ERK, and JNK mRNA expression along with reversal of increased inflammatory markers such as TNF-α that was seen with carfilzomib treatment. Provided that this evidence is weak for cardioprotective effect of rutin, dexrazoxane, and apremilast against carfilzomib as they have only been demonstrated in rat models at one institution, these are still far from being applicable in the clinical setting.

An alternative approach to reduce cardiotoxicity involves adapting current PIs to curtail their off-target effects on the heart. For example, the findings of carfilzomib-related inactivation of autophagy proteins in mice indicate a prophylactic role for metformin for its known effects of AMPKα activation, autophagy regulation, and apoptosis inhibition [33••]. In this study, metformin treatment was able to protect mice from cardiotoxicity without interfering with proteasome inhibition. Of note, bortezomib administration did not result in similar findings when compared with carfilzomib, suggesting a unique mechanism for carfilzomib toxicity. Another method that works further upstream involves the modification of drugs for proteasome inhibition to selectively target the immunoproteasome with minimal inhibition of the constitutive proteasome. Some of the currently available immunoproteasomes include UK-101 and IPSI-001 which are specific to the β1i subunit. Of note, IPSI-001 has demonstrated effectiveness in MM cell line models and in patient samples with hematological malignancies, even in setting of bortezomib resistance with fewer toxicities towards nonmalignant cells [104]. PR-924 has similar findings, with additional findings in mouse xenograft models of MM [105]. Development of more clinically applicable selective immunoproteasome inhibitors will be possible with increased understanding of the structural differences between the constitutive and the inducible proteasomes. For example, the finding of the crystal structure of murine immunoproteasome has revealed key structural differences between the β5 and β5i catalytic subunits that explain the observed selectively of ON 0914 for the immunoproteasome [106].

Finally, the administration of current PIs may be modified with regard to route of delivery, dosing, and infusion times. For example, a phase III trial conducted by the Intergroupe Francophone du Myelome (IFM) demonstrated that neurotoxicity risk could also be reduced by subcutaneous administration [107], leading to its approval by the FDA in 2012 for subcutaneous administration. In fact, a meta-analysis for subcutaneous versus intravenous bortezomib suggested that subcutaneous route might also reduce incidence of thrombocytopenia, renal, and urinary disorders [108•]. Examples of decreasing neurotoxicity without losing efficacy have also been seen with bortezomib by using a reduced-intensity regimen and extending infusion time to a weekly schedule [107, 109–111]. Similar changes to carfilzomib may be able to reduce some of its cardiotoxic side effects, but it remains to be seen whether or not changing carfilzomib's route of administration, dosing, or interval would impact its effectiveness. Along this vein, oprozomib is an extremely appealing alternative, as it is an oral homolog of carfilzomib and thus far has not been found to have associated cardiotoxicity.

## Conclusion

The development of highly efficacious and targeted anti-myeloma therapies has led to advancements in treatment regimens with significantly improved response and survival outcomes. This quickly expanding armamentarium of potent therapies necessitates careful pre-clinical and clinical experimental design to accurately identify emerging treatment-related adverse events. Since previous studies involving PIs were not designed to specifically detect cardiotoxicity, the precise incidence of CVAEs that can be directly attributed to the drug is difficult to discern. In particular, carfilzomib, which has demonstrated the most clinically significant CVAEs, and newer agents such as ixazomib, oprozomib, and marizomib warrant increased cardiovascular scrutiny in order to determine whether these toxicities are attributable to the drug class as a whole.

Ideally, concomitant prospective tracking of CVAEs in clinical trials using PIs would be ideal, with consistent protocols of using biomarkers and cardiovascular imaging in order to identify individuals at risk for developing cardiotoxicity. Uniform cardiovascular evaluation protocols to establish patients' baseline characteristics, biochemical and immunological profile throughout

the study, and post-trial surveillance are needed to better understand the true incidence of cardiotoxicity, its risk factors, natural history, and most effective management strategies. In addition, national/international registries should be assembled to track the "real-world" and long-term effects of these agents used in the general population in order to effectively devise cardioprotective and surveillance strategies for cardiotoxicity. Such collaborations between cardiology and hematology could potentially allow for present and future cancer treatments of MM to proceed with attenuated cardiotoxicity risk with cardioprotective and imaging strategies and provide mechanistic insight into the development of heart failure that may benefit the general population as a whole.

## Compliance with Ethical Standards

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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