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STATE-OF-THE-ART REVIEW

Cardiovascular Toxicity of Proteasome Inhibitors: Underlying Mechanisms and Management Strategies

JACC: CardioOncology State-of-the-Art Review

Georgios Georgiopoulos, MD, PhD,[a,b,*] Nikolaos Makris, MD,[a,*] Ageliki Laina, MD,[a] Foteini Theodorakakou, MD,[a] Alexandros Briasoulis, MD,[a] Ioannis P. Trougakos, PhD,[c] Meletios-Athanasios Dimopoulos, MD, PhD,[a] Efstathios Kastritis, MD, PhD,[a,†] Kimon Stamatelopoulos, MD, PhD[a,†]

ABSTRACT

Proteasome inhibitors (PIs) are the backbone of combination treatments for patients with multiple myeloma and AL amyloidosis, while also indicated in Waldenström's macroglobulinemia and other malignancies. PIs act on proteasome peptidases, causing proteome instability due to accumulating aggregated, unfolded, and/or damaged polypeptides; sustained proteome instability then induces cell cycle arrest and/or apoptosis. Carfilzomib, an intravenous irreversible PI, exhibits a more severe cardiovascular toxicity profile as compared with the orally administered ixazomib or intravenous reversible PI such as bortezomib. Cardiovascular toxicity includes heart failure, hypertension, arrhythmias, and acute coronary syndromes. Because PIs are critical components of the treatment of hematological malignancies and amyloidosis, managing their cardiovascular toxicity involves identifying patients at risk, diagnosing toxicity early at the preclinical level, and offering cardioprotection if needed. Future research is required to elucidate underlying mechanisms, improve risk stratification, define the optimal management strategy, and develop new PIs with safe cardiovascular profiles. (J Am Coll Cardiol CardioOnc 2023;5:1–21) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Proteasome inhibitors (PIs) have shifted the paradigm for treating patients with plasma cell dyscrasias, improving their overall survival. Multiple myeloma (MM), the most common plasma cell dyscrasia, remains the second most common disease among hematologic malignancies.[1] By targeting the peptidases of the 20S constitutive proteasome and the 20s immunoproteasomes, PIs are considered the backbone of combination treatments for patients with newly diagnosed and relapsed or refractory MM (RRMM). PIs are used extensively in combination with immunomodulatory drugs (IMiDs), monoclonal antibodies, and chemotherapy representing a drug class with a wide spectrum of indications for several other hematological malignancies.

From the [a]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [b]School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom; and the [c]Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Greece. *Drs Georgiopoulos and Makris contributed equally to this work as first authors. †Drs Kastritis and Stamatelopoulos contributed equally to this work as senior authors.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome

AE = adverse event

AF = atrial fibrillation

ARB = angiotensin receptor blocker

ASCT = autologous stem cell transplantation

BP = blood pressure

CVAE = cardiovascular adverse event

eNOS = endothelial nitric oxide synthase

ESC = European Society of Cardiology

FMD = flow-mediated dilatation

GLS = global longitudinal strain

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IHD = ischemic heart disease

IMiD = immunomodulatory drug

Kd = carfilzomib and dexamethasone

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

MM = multiple myeloma

NO = nitric oxide

NP = natriuretic peptide

OS = overall survival

PBMC = peripheral blood mononuclear cell

PFS = progression-free survival

PH = pulmonary hypertension

PI = proteasome inhibitor

PrA = proteasome activity

PWV = pulse wave velocity

RRMM = relapse or refractory multiple myeloma

SBP = systolic blood pressure

TMA = thrombotic microangiopathy

UPP = ubiquitin proteasome pathway

Vd = bortezomib and dexamethasone

VTE = venous thromboembolism

WM = Waldenström's macroglobulinemia

Consequently, prevention, early identification, and treatment of PI-related adverse effects (AEs) are important aspects of care to maximize benefits, and optimize prognosis, of patients on PI-containing regimens. PI-based therapy is associated with cardiovascular adverse events (CVAEs), including primarily hypertension, heart failure (HF), arrhythmias, and ischemic heart disease (IHD). Its increased utilization poses a clinically relevant challenge to address the inevitably increasing CVAEs. Despite the profound need for definite recommendations in the field, inference about the cardiotoxic burden of PIs on patients with MM has been hampered by lack of sufficient data due to significant heterogeneity in the definition of cardiotoxicity endpoints, exclusion of high cardiovascular risk patients across clinical trials, and variable approaches to the detection and treatment of PI-related CVAEs. In this review, we aim to summarize available evidence on PIs pharmacology and underlying molecular-cellular mechanisms leading to PI-related cardiotoxicity. We also outline strategies for prevention, early detection, and treatment of PI-related CVAEs.

HIGHLIGHTS

- Therapeutic proteasome inhibitors (PIs) are critical components of multiple myeloma (MM) and the treatment of other malignancies.
- Carfilzomib possesses the most severe and frequent cardiovascular toxicity profile among PIs.
- Imaging and cardiac biomarkers are recommended by expert consensus groups for monitoring cardiovascular toxicity.
- Future research should focus on optimizing strategies to detect and prevent PI cardiovascular toxicity.

MECHANISMS OF ACTION AND INDICATIONS OF PIs

Proteostasis is a critical component for cellular proteome stability and thus for proper cellular function and viability.[2] In most mammalian cells, the ubiquitin proteasome pathway (UPP) is responsible for the degradation of up to 80% to 90% of intracellular proteins, and it is thus considered the major cellular proteolytic pathway.[3] Components of the UPP are the ubiquitin-conjugating enzymes and the proteasome, which comprises a complicated multisubunit molecular machine responsible for the removal of both short-lived ubiquitinated normal proteins and/or nonrepairable unfolded polypeptides.[4] Consequently, declined proteasome activity (PrA) results in gradually increasing proteome instability that can trigger stress-induced premature senescence, cell cycle arrest, and ultimately, apoptosis.[5]

Given that MM plasma cells produce excessive amounts of immunoglobulins, inducing significant proteotoxic stress, it is not surprising that these cells are highly dependent on PrA to survive and therefore particularly sensitive to PIs. Effective proteasome inhibition leads to high levels of proteotoxic and oxidative stress in MM cells and, ultimately through a multitude of downstream effects, inhibition of angiogenesis and eventually their selective death.[4] In recent years, PIs have become a primary treatment option for plasma cell dyscrasias and lymphomas.[6] All Food and Drug Administration-approved PIs (carfilzomib, bortezomib, ixazomib) target the chymotrypsin-activity of 20S unit of proteasome. Contemporary oncologic indications per therapeutic PI, as well as per disease, are summarized in the following text and are depicted in **Table 1**.

MULTIPLE MYELOMA

BORTEZOMIB. Bortezomib received full regulatory approval in 2005 for the treatment of RRMM. The combination of bortezomib with lenalidomide and dexamethasone as induction before autologous stem cell transplantation (ASCT) is the most widely used frontline therapy in Europe and the United States. Bortezomib-based induction regimens result in significant improvement in response and overall survival (OS)/progression-free survival (PFS), albeit with higher rates of peripheral neuropathy.[7]

In newly diagnosed patients with MM noneligible for transplantation, bortezomib in combination with melphalan and prednisone is indicated. Bortezomib has also been combined with IMiDs, notably with lenalidomide, for the induction treatment of patients who are not candidates for ASCT,[8] improving both their PFS and OS. In addition, bortezomib as maintenance therapy after ASCT improves depth of responses and OS/PFS.[9]

TABLE 1 Approved for Clinical Use and Experimental PIs

PI	Binding	Approval	Approved Combinations	Route of Administration	Adverse Events (Most Common)
Bortezomib	Baronate (reversible)	NDMM (transplant eligible and ineligible), RRMM, MCL AL amyloidosis	Vd or VTd VMP or Dara-VMP V+PLD, Dara-Vd, Pan-Vd Dara-CyBorD VR-CAP	Subcutaneous	PN, nausea, vomiting, constipation, cytopenias, infections
Carfilzomib	Epoxyketone (irreversible)	RRMM	Kd, KRd, Dara-Kd	Intravenous	HF, HTN, CAD, AKI, TMA (including TTP/HUS), cytopenias
Ixazomib	Baronate (reversible)	RRMM	IRd	Orally	Nausea, vomiting, and diarrhea, PN, peripheral edema, cytopenias
Oprozomib (ONX0912)	Epoxyketone (irreversible)	–	–	Orally	Nausea, vomiting, diarrhea
Marizomib (NPI-0052)	B-lactone (irreversible)	–	–	Intravenous	Fatigue, headache, nausea, vomiting, diarrhea, dizziness
Delanzomib (CEP-18770)	Baronate (reversible)	–	–	Intravenous Orally	Nausea, vomiting, anorexia, fatigue, pyrexia, thrombocytopenia, neutropenia, PN

AKI = acute kidney injury; AL = light chain amyloidosis; CAD = coronary artery disease; Dara-CyBorD = daratumumab; bortezomib, cyclophosphamide, and dexamethasone; Dara-Kd = daratumumab, carfilzomib, and dexamethasone; Dara-Vd = daratumumab, bortezomib, and dexamethasone; Dara-VMP = daratumumab, bortezomib, melphalan, and prednisone; HF = heart failure; HTN = hypertension; HUS = hemolytic uremic syndrome; IRd = ixazomib, lenalidomide, and dexamethasone; Kd = carfilzomib and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; MCL = mantle cell lymphoma; NDMM = newly diagnosed multiple myeloma; Pan-Vd = panobinostat, bortezomib, and dexamethasone; PI = proteasome inhibitor; PN = peripheral neuropathy; RRMM = relapsed/refractory multiple myeloma; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura; V+PLD = bortezomib and pegylated liposomal doxorubicin; Vd = bortezomib and dexamethasone; VMP = bortezomib, melphalan, and prednisone; VR-CAP = bortezomib, cyclophosphamide, doxorubicin, and dexamethasone; VTd = bortezomib, thalidomide, and dexamethasone; WM = Waldenstrom macroglobulinemia.

Further, bortezomib-based combinations remain a major option for patients with relapsed or refractory disease.[10]

CARFILZOMIB. Carfilzomib is a next-generation irreversible selective PI that received accelerated approval in 2012 for the treatment of RRMM.[11] As an irreversible PI carfilzomib is more potent and likely therapeutically durable than bortezomib. The randomized phase 3 study ENDEAVOR (Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients) compared the combination of bortezomib and dexamethasone (Vd) to carfilzomib and dexamethasone (Kd) in RRMM patients and showed significant improvement in the PFS and OS.[12] Also, the combination of carfilzomib with lenalidomide and dexamethasone showed significantly improved PFS and OS in RRMM.[13] Carfilzomib has also been approved in combination with daratumumab (anti-CD38 monoclonal antibody) and dexamethasone, which showed a significant improvement in the median PFS, with no new AEs in the daratumumab and dexamethasone cohort.[14] Thus, carfilzomib-based combinations became the preferred PI-based therapy for patients with RRMM, even among those resistant to bortezomib.

However, the carfilzomib-based combinations did not show any significant benefit compared with bortezomib-based combinations in newly diagnosed MM patients not eligible for ASCT.[15,16] Increased cardiac and renal toxicity of the carfilzomib combinations seems to be a major factor that may offset any benefit in terms of MM progression and OS in this patient population, especially among the elderly. Carfilzomib-based regimens have been evaluated in younger, transplant-eligible patients, with more success.

IXAZOMIB. Ixazomib is the first orally administered approved PI. It was developed to overcome the need for drug administration in the clinic and also to avoid bortezomib resistance and some of its AEs. It was approved for the treatment of patients with RRMM in combination with lenalidomide and dexamethasone.[17]

Further, in newly diagnosed non-transplant-eligible patients, the combination of ixazomib with cyclophosphamide and dexamethasone as an upfront option is in active use with a manageable toxicity profile.[18] Ixazomib is also suitable for maintenance therapy. The phase 3 TOURMALINE-MM3 trial (A Study of Oral Ixazomib Citrate [MLN9708] Maintenance Therapy in Participants With Multiple Myeloma Following Autologous Stem Cell Transplant) in post-ASCT patients showed that ixazomib reduced risk of progression or death by 28%.[19] In the phase 3 TOURMALINE-MM4 trial that included transplant-ineligible patients, ixazomib maintenance reduced by 34.1% the risk of death or progression.[20]

OTHER PLASMA CELL DYSCRASIAS AND HEMATOLOGIC MALIGNANCIES

In AL amyloidosis, a rare plasma cell dyscrasia, clonal plasma cells produce an excessive amount of toxic

TABLE 2 Advantages and Disadvantages of Clinically Available PIs

PIs	Advantages	Disadvantages and Adverse Events
Bortezomib	• Subcutaneous administration • No dose adjustment needed for patients with renal impairment • Limited marrow toxicity • Extensive clinical experience in various disease settings (even beyond myeloma) • Relatively low risk of CV events	• Peripheral neuropathy • GI symptoms (nausea, vomiting, constipation) • Transient thrombocytopenia • Infections (high risk of VZV reactivation requiring prophylaxis)
Carfilzomib	• Low risk of peripheral neuropathy • No dose adjustment needed for renal impairment (but close monitoring for renal toxicity is recommended) • More potent PI than bortezomib after head-to-head comparison in relapsed/refractory myeloma	• Moderate risk of CV events (heart failure, hypertension, coronary artery disease) • Intravenous administration (twice weekly or once weekly) • Acute renal injury • Risk of drug-induced thrombotic microangiopathy • Increased amylase levels • Transient thrombocytopenia • Infections (high risk of VZV reactivation requiring prophylaxis)
Ixazomib	• Oral administration • No dose adjustment for patients with mild or moderate renal impairment • Relatively low risk of CV events	• GI symptoms common (nausea, vomiting and diarrhea) • Reduced dose needed for severe renal impairment (limited data) • Moderate risk of peripheral neuropathy • Peripheral edema • Cytopenias (mainly thrombocytopenia) • Infections (high risk of VZV reactivation requiring prophylaxis)

CV = cardiovascular; GI = gastrointestinal; PI = proteasome inhibitor; VZV = varicella-zoster virus.

immunoglobulin free light chains that tend to misfold and form amyloid fibrils and aggresomes depositing in tissues. Proteasome inhibition blocks the degradation of misfolded protein resulting in intracellular accumulation and cell apoptosis. Bortezomib is considered the cornerstone for the treatment of AL amyloidosis. The combination of bortezomib with cyclophosphamide and dexamethasone has been established as the standard of care.[21] Recently, ANDROMEDA (A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination With Cyclophosphamide, Bortezomib and Dexamethasone [CyBorD] Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light-Chain [AL] Amyloidosis) indicated that the addition of daratumumab to bortezomib with cyclophosphamide and dexamethasone further improved response rates in previously untreated AL amyloidosis patients.[22] The overall response rate was higher in patients without advanced cardiac involvement (stage IIIb). To that end, patients with AL amyloidosis and with advanced cardiac involvement may not tolerate standard bortezomib doses, and dose modifications are usually proposed.[23]

In Waldenström's macroglobulinemia (WM), although PIs have been proven to be effective,[24] they are not approved for this disease.

Besides plasma cells dyscrasias, bortezomib has also been approved for the treatment of newly diagnosed and relapsed/refractory mantle cell lymphoma.

The advantages and disadvantages of the available PIs are summarized in Table 2.

NOVEL PIs UNDER INVESTIGATION

New PIs with increased activity or more favorable pharmacodynamics and pharmacokinetics or route of administration are under investigation. The most common AEs have not been noted to be cardiovascular. No head-to-head comparisons with approved PIs regarding cardiovascular toxicity are available. Oprozomib (ONX 0912) induced durable responses in patients with RRMM or WM as single agent, even among patients who are refractory to bortezomib or carfilzomib, in a dose-escalation phase 1b/2 study,[25] and was also evaluated in combination regimens (pomalidomide and dexamethasone) in RRMM with encouraging results.[26] Marizomib (NPI 0052) as single agent was in general well-tolerated and appears to be active for relapsed refractory MM patients.[27] Data regarding delanzomib's (CEP 18770) safety or efficacy in hematological malignancies are not yet available.

KEY POINTS.

- Bortezomib is one of the most widely used frontline therapies for transplant eligible or transplant ineligible patients with MM.
- Carfilzomib significantly prolongs PFS and OS in the relapse/refractory setting.
- Novel PIs with more favorable features are under investigation, but data regarding their efficacy are limited.

MECHANISMS OF CARDIOVASCULAR TOXICITY BY PI

PIs and especially carfilzomib may exhibit a variety of cardiovascular AEs. Understanding the underlying

pathophysiological and inherent compensatory mechanisms of PI-related cardiovascular toxicity, is crucial to develop effective strategies for early identification and management of high-risk patients, ensuring continuation of life-saving cancer therapy (**Central Illustration**). Median age at the time of diagnosis of MM is 66 years, with 54% above 65 years at diagnosis.[28] Old age is marked by reduced UPP activity and consequently increased proteome instability, and 2 conditions may predispose to cardiovascular toxicity related to PIs. First, there is higher prevalence of traditional cardiovascular risk factors in the elderly,[29] and patients with MM often present a history of exposure to other potentially cardiotoxic therapies such as anthracyclines and/or chest radiotherapy, which can further increase the likelihood of cardiotoxicity.[30] Second, aging induces proteome instability across all human cell types and is associated with decreased activity of the ubiquitin conjugation pathway, as well as with down-regulated proteasome and transcription factor NRF1/NRF2 (transcriptional regulator of antioxidant/proteostatic genes) functionality.[31-33] Consequently, AEs related to PIs would be expected to be enhanced in the elderly.

Carfilzomib with its irreversible proteasome inhibition properties is associated with an increased incidence of hypertension (9%-27%),[12,34] HF/left ventricular (LV) systolic dysfunction (4.1%-16.2%),[34,35] IHD (1.8%-17.6%),[34,35] and arrhythmias (2.4%-7%).[35,36] Bortezomib is associated with cardiovascular toxicity as well,[37-39] albeit not to the degree of carfilzomib. On the other hand, the oral PI ixazomib is generally not associated with a high risk for cardiovascular toxicity, apart from scarce evidence.[40] All 3 PIs have been related to thrombotic microangiopathy (TMA).[41-43] We present the commonest cardiac and vascular AEs according to their frequency.

KEY POINTS.

- Patients with MM are older and often carry accumulating risk factors for cardiovascular toxicity.
- Aging is a major mediator for proteasome dysfunction, increasing vulnerability to PI-related cardiovascular toxicity.
- Among currently available PIs, carfilzomib is associated with the highest potential for cardiovascular toxicity.

CARDIAC ADVERSE EVENTS

LV SYSTOLIC DYSFUNCTION—HF. Basic Mechanisms. Terminally differentiated cardiomyocytes are postmitotic cells and are thus especially sensitive to proteasome inhibition.[44] Further, the high metabolic demand of the heart, met by increased oxidative phosphorylation rates results in high production of reactive oxygen species, challenging normal proteostasis[45] (**Figure 1**). Proteasome dysfunction has been implicated in cardiovascular disease.[33] Protein aggregates have been detected in human hypertrophic, dilated, and desmin-related cardiomyopathies,[46] whereas marked proteasome dysfunction was observed in explanted failing hearts and myectomy samples from patients with hypertrophic cardiomyopathy.[47] Thus, pharmacologic proteasome inhibition may be deleterious for the heart, particularly when aging or cardiac dysfunction is present.

Heart-targeted genetic knockdown of proteasome in *Drosophila* disrupted cardiac activity and reduced health/lifespan.[48] Increased protein phosphatase 2A (PP2A) activity and disruption of autophagy through inhibition of AMPKα and its downstream autophagic targets, may substantially contribute to LV dysfunction induced by carfilzomib in mice.[49] Moderate local proteasome inhibition in cardiomyocytes was found to aggravate myocardial ischemia-reperfusion injury in mice,[50] which contradicts previous reports showing a protective effect of systemic PI on ischemia/reperfusion hearts[51] (**Table 3**).

Interestingly, under specific stressful conditions, short-term PI may exert beneficial effects mainly on LV hypertrophy by both preventing and reducing its extent in mouse models of chronic pressure overload, as well as in hypertensive Dahl salt-sensitive rats[52] (**Table 3**). Whether these beneficial effects are direct or indirect through triggered compensatory mechanisms in response to PI, merits further investigation.

Epidemiology and association with individual drugs. Carfilzomib has been linked to increased occurrence of CVAEs compared with other PIs[53] (**Table 4**). Although the mechanisms mediating these drug- and organ-specific AEs remain largely elusive, carfilzomib-induced cardiovascular toxicity is partly attributed to its property of inhibiting PrA irreversibly.[54] Another contributing factor could be the wider dose range for carfilzomib as compared with bortezomib due to its dose-dependent peripheral neuropathy.[55]

In a systematic review and meta-analysis of 24 clinical trials,[35] the incidence of cardiac AEs was 18.1%, and the incidence of HF, 4.1% for carfilzomib-treated patients. Similar findings were reported from another recent meta-analysis[56] including 5,583 patients and a network meta-analysis,[57] with carfilzomib-treated patients presenting more than 2.5-fold increase in the risk for cardiovascular toxicity compared with control subjects. Data on the

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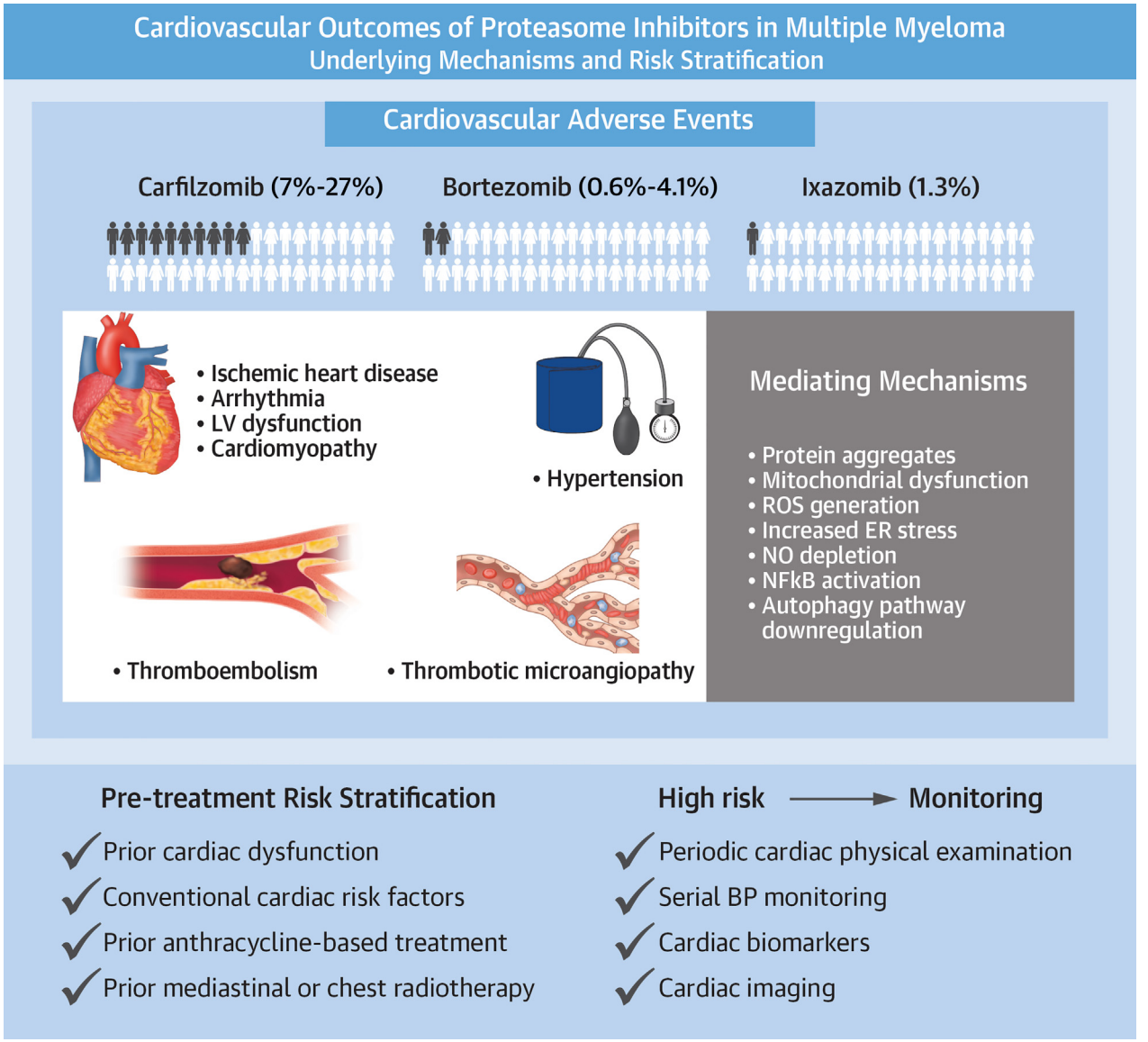
CENTRAL ILLUSTRATION **Cardiovascular Adverse Events of Proteasome Inhibitors, Mechanisms, and Risk Stratification**

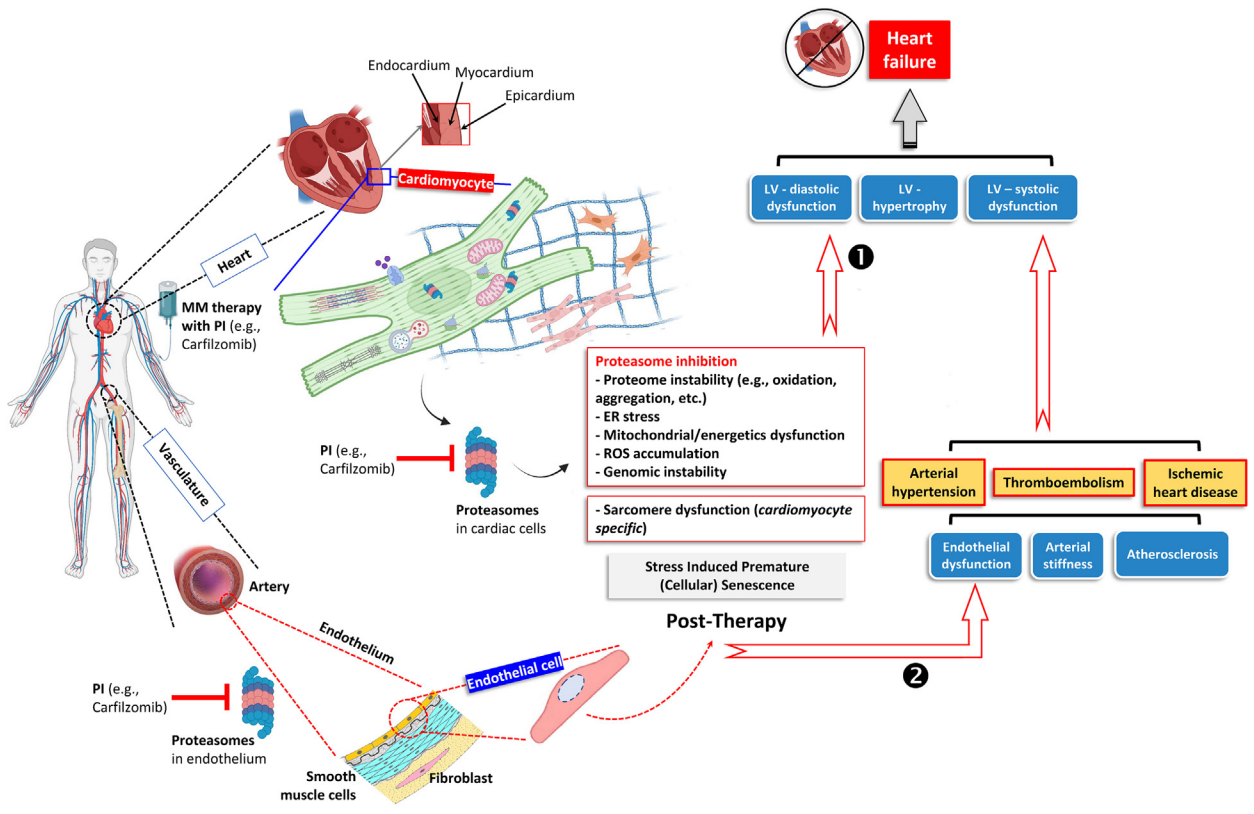


Georgiopoulos G, et al. J Am Coll Cardiol CardioOnc. 2023;5(1):1–21.

Proteasome inhibitors and especially carfilzomib may exhibit a variety of cardiovascular adverse events. Understanding the underlying pathophysiological mechanisms of proteasome inhibitor–related cardiovascular toxicity, is crucial to develop effective strategies for early identification and management of high-risk patients, ensuring continuation of life-saving cancer therapy. BP = blood pressure; ER = endoplasmic reticulum; LV = left ventricular; NFkB = nuclear factor kappa B; NO = nitric oxide; ROS = reactive oxygen species.

prevalence of HF with preserved ejection fraction (HFpEF) in patients on carfilzomib are limited. In a prospective study, patients on PIs experienced signs and symptoms of HF with normal or near-normal LV ejection fraction (LVEF).[58] A case report demonstrated a patient on carfilzomib with symptoms of HF, normal LVEF, and elevated LV end-diastolic pressures.[59] Hypertension is closely related to the pathogenesis of HFpEF[60] and is carfilzomib's most common CVAE. In a recent prospective study that examined 48 patients with MM receiving carfilzomib, we found that deteriorating left atrial function and structure and

FIGURE 1 Effects of Proteasome Inhibitors on Cardiac and Vascular Cells



The extent of damage at the cellular level is similar among different mitotic (eg, endothelial) or post-mitotic (eg, cardiomyocytes) cell types, as it relates to increasing proteome instability (eg, polypeptides oxidation, aggregation, etc.), endoplasmic reticulum (ER) stress, mitochondrial/energetics dysfunction, reactive oxygen species (ROS) accumulation, genomic instability, and stress-induced premature senescence; nonetheless, at a higher tissue/organ (ie, heart, vasculature) organization level, induced damage is likely tissue-specific. The relative enrichment of cardiac ventricles (vs atria) in cardiomyocytes, along with the noted ventricle/atria-specific differences in electrophysiological, contractile, and secretory processes of resident cardiomyocytes may explain the predisposition of the ventricle to proteasome inhibition–mediated adverse events (AEs). **Arrows** indicate sequence of events. LV = left ventricular; MM = multiple myeloma; PI = proteasome inhibitor.

decreasing segmental LV longitudinal strain preceded reductions in LVEF, which remained within normal range.[61] On the other hand, these changes were independent of arterial blood pressure (BP) alterations, endothelial function, inflammation, and cardiac injury levels, suggesting an at least partly direct effect on cardiac diastolic function by carfilzomib.[61]

Although there are limited data, some risk factors specifically predicting carfilzomib-related cardiovascular toxicity have been identified. Pooled evidence from carfilzomib studies indicate that pre-existing cardiovascular disease,[62] age >75 years, obesity, twice-a-week carfilzomib regimen,[34] concomitant use of immunomodulators,[63] carfilzomib doses >45 mg/m^2,[35] and chronic obstructive pulmonary disease[36] may increase susceptibility for cardiovascular toxicity.

Regarding bortezomib, a retrospective observational cohort study including 1,790 patients with MM[64] reported a nonsignificant increase in the risk of hospitalization for HF, after propensity score matching between patients receiving bortezomib and lenalidomide. The results did not materially change after adjustment for previous history of HF. Due to the relatively small sample size, further research should elucidate the risk of cardiotoxicity in patients with a previous history of HF receiving bortezomib. Similar findings were reported from a retrospective analysis of 3,954 patients in phase 2 and 3 trials investigating bortezomib for MM[65] and a meta-analysis that included 25 prospective phase 2 and 3 trials evaluating bortezomib in 4,330 patients with different types of solid and hematologic cancers.[66] **Table 4** depicts bortezomib trials with cardiovascular toxicity data.

TABLE 3 Experimental Studies of PI Effect on Endothelial Cells, Cardiac Cells, T Cells and Platelets

Experimental Model	PI	Dose	Duration of PI	Mechanism	Results
Endothelium					
In vitro					
Rat aortic rings[109,114]	MG132	100-250 nmol/L (low dose) 50-100 nmol/L (low dose)	48 h 72 h	Enhanced eNOS expression and activity Antioxidative enzymes upregulation	Improved ACh-induced endothelial-dependent vasorelaxation
Rat aortic rings[115]	MG132	50-100 nmol/L (low dose)	48 h	Reduced superoxide production and suppressed endothelin levels	Prevented TNFα-induced endothelial dysfunction
Rabbit aortic strips[90]	CFZ	10^{-9}–10^{-7} mol/L			Increased basal tone Impaired vasodilatory response to NTG, NFP, and ACh-induced endothelial-dependent vasorelaxation
Ex vivo					
Hypercholesterolemic pigs[88]	MLN-273	0.08 mg/kg s.c. twice weekly[a]	12 weeks	eNOS uncoupling	Reduced ACh-induced coronary endothelial-dependent vasorelaxation
In vivo					
Hypercholesterolemic pigs[127]	MLN-273	0.08 mg/kg s.c. twice weekly[a]	12 weeks	Decreased renal endothelin, NFκB, and augmented eNOS expression	Improved ACh-induced renal endothelial-dependent vasorelaxation
Heart					
In vitro					
Rat cardiomyoblastic cells[128]	BTZ	5-10 nmol/L[b]	48 h or 72 h	Increased ER stress	Cytotoxicity and reduced survival
Neonatal rat cardiomyocytes[52]	MG132	0.05 to 0.1 μmol/L (low dose)	24 h or 48 h	Down-regulation of Akt1 and erk1/2	Hypertrophic growth suppression
In vivo					
Rats[128]	BTZ	0.2 mg/kg thrice weekly	1-3 weeks	Mitochondrial dysfunction ATP depletion	Significant drop in LVEF
Mice with TAC vs sham surgery[129]	BTZ	1 mg/kg, once every 2 days		Calcineurin-NFAT pathway	Cardiac hypertrophy (sham group) LV dilation and dysfunction (TAC group)
Mice[49]	CFZ	8 mg/kg	2 doses/every 48 h for 6 days	Increased PP2A activity and inhibition of AMPKα	Decreased left ventricular function
Mouse model of CR-PSMI[50]				Suppressed activation of pro-survival kinase Akt and PKCε	Aggravates acute I/R injury
Rat models of I/R[51]	PR-39	10 nmol/kg	At the start of reperfusion	Reduced NFκB activation, ICAM-1 and VCAM-1 expression, neutrophil infiltration, myeloperoxidase activity	Reduced infarct size
Mouse model of chronic pressure overload[130]	Epoxomicin	0.5 mg/kg/day (nontoxic)	5 days		LVH prevention
Mice submitted to aortic banding[131]	Epoxomicin	0.5 mg/kg (nontoxic)		Suppressed NFkB activation	Hypertrophy suppression
Dahl salt-sensitive rats[52]	BTZ	50 μg/kg body weight (low dose)	8 weeks		Significant reduction in absolute heart weights and in the heart weight/tibia length ratio
Isoprenaline induced hypertrophic mice[132]	PS-519	1 mg/kg/day	1 week	Suppressed NFkB activation	Prevented Iso-induced LVH at 7 days
Genetically modified mouse model of HCM[131]	Epoxomicin	0.5 mg/kg/day (nontoxic)	1 week		Increased fractional area shortening
T cells					
Tonsillar T cells[133]	Lactacystin	10 μmol/L			Repressed the mitogen-induced T-cell proliferation
Mice[134]	Bortezomib	0.75 mg/kg	Twice weekly 4 days	Suppressed NFkB activation	T-cell apoptosis
Platelets					
Mice[111]	MG132	30 μmol/L			Suppressed occlusive thrombus formation in $FeCl_3$-damaged carotid arteries

[a]Max degree of 60% to 80% inhibition at 1 hour after drug administration. [b]Within the range inducing cytostatic/cytotoxic effects in human tumor cells.

ACh = acetylcholine; BTZ = bortezomib; CFZ = carfilzomib; CR-PSMI = cardiomyocyte restricted proteasome inhibition; eNOS = endothelial nitric oxide synthase; HCM = hypertrophic cardiomyopathy; I/R = ischemia/reperfusion; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NFkB = nuclear factor kappa B; NFP = nifedipine; NTG = nitroglycerin; PI = proteasome inhibition; TAC = transverse aortic constriction; TNF-a = tumor necrosis factor alpha.

In the seminal TOURMALINE study (A Phase 3 Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma)[17] that led to ixazomib's approval by the Food and Drug Administration, no significant differences in cardiovascular toxicity rates between the ixazomib and the control group were reported. Similarly, cardiovascular toxicity events were not frequent for ixazomib combinations in a recent effectiveness and safety real-world study.[67] To date, 1 case report suggested a CVAE of ixazomib on LV function.[40] Acutely decompensated HF was reported following treatment with ixazomib; LV function did not improve after ixazomib discontinuation.

Risk factors, screening, and prevention. Recent cardio-oncology guidelines from the European Society of Cardiology (ESC)[68] propose a surveillance plan for patients on PIs, whereas the rest of the management approach presented is based upon expert opinion in consensus statements and position papers or guideline recommendations for other cardiotoxic anticancer medications. Meticulous patient evaluation and appropriate risk stratification is of paramount importance before initiating a potential cardiotoxic therapy. This includes detailed physical examination and thorough history-taking, emphasizing on risk factors for cardiovascular disease and toxicity.[68-70] **Table 5** depicts our proposed approach based on the HFA-ICOS (Heart Failure Association-International Cardio-Oncology Society) risk score before treatment initiation, among other published recommendations and evidence.[68,70] LVEF is currently the only echocardiographic parameter recommended for pretreatment risk stratification with carfilzomib (**Table 5**).[70-72] Other cardiac and peripheral hemodynamic parameters may be useful in this process, but further study is needed. LV diastolic dysfunction and septal E/e′ at baseline correlated with severe carfilzomib-related AEs in MM patients.[73] Interestingly, a recently developed CVAEs risk score including LV hypertrophy, global longitudinal strain (GLS), BP variation, pulse wave velocity (PWV), and office systolic BP (SBP) provided a high (90%) negative predictive value for CVAEs in 116 MM patients treated with carfilzomib.[74] However, this model requires further validation on an independent, larger sample.

Patients on carfilzomib therapy should be monitored with echocardiographic evaluation at baseline (ESC guidelines Class I, Level of Evidence: C) and every 3 cycles (Class IIa, Level of Evidence: B for very high/high risk and Class IIb, Level of Evidence: C for low/moderate risk) for signs of cardiotoxicity[53,68,69,75,76] (**Table 5**). GLS may identify LV dysfunction in patients with cancer on chemotherapy earlier than LVEF.[77] Recently in SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes), a randomized controlled trial, a GLS-based surveillance approach was more sensitive to define eligibility for successful cardioprotective treatment therapy than LVEF changes after 1-year follow-up.[78] However, analysis of the 3-year follow-up data from this study showed no difference between LVEF- and GLS-guided cardioprotection.[79] These findings support LVEF as the most widely available valid parameter (particularly with 3-dimensional echocardiography) for monitoring of PI-related cardiotoxicity. GLS is still recommended in addition to LVEF.[68] Cardiac magnetic resonance is indicated in patients with suboptimal echocardiographic images or when tissue characterization is needed.[68,75] Of importance, the same imaging modality should be consistently used at the pre- and post-treatment evaluation.[69] In a prospective study, elevated natriuretic peptides (NPs) during the first cycle of treatment with carfilzomib were associated with 36-fold risk of CVAEs.[58] NPs should be measured at baseline (Class I, Level of Evidence: C for very high/high-risk and Class IIa, Level of Evidence: C for low/moderate-risk) and during every cycle for the first 6 cycles with carfilzomib or bortezomib (Class IIa, Level of Evidence: B)[68,80] (**Table 5**). Patients with AL cardiac amyloidosis on PIs in particular should be monitored with echocardiogram every 3 cycles (Class IIa, Level of Evidence: C), and NPs and cardiac troponin every 3 to 6 months (Class I, Level of Evidence: B).[68] The guidelines' recommendations for echocardiographic and biomarkers monitoring for patients on PIs are not based on a strong level of evidence (mostly Levels of Evidence: C and B).[68]

Cardioprotection in high-risk patients and subclinical LV systolic dysfunction. Because specific recommendations on the management of PI cardiotoxicity are limited, recommendations for traditional cardiotoxic anticancer therapy may apply[68,69] until specific evidence is available. Patients receiving PIs with either reduced LVEF at baseline or estimated high risk for cardiotoxicity should be considered for cardioprotective therapy including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and beta-blockers, preferably carvedilol or nebivolol as depicted in **Table 5**.[68,69,81] Statins should also be considered for primary prevention in patients at high or very high risk for cardiovascular toxicity.[68] Asymptomatic decline in LVEF to 40% to 49%, or deterioration by 15% in GLS, or elevation of serum

TABLE 4 Carfilzomib and Bortezomib Trials With Cardiovascular Toxicity Data

First Author, Year	Drug	Design	Sample	HF/General Cardiac Toxicity
Hájek et al, 2017[98]	Carfilzomib monotherapy vs low-dose corticosteroids and optional cyclophosphamide	Randomized phase 3 study	315 patients with RRMM	–
Durie et al, 2017[8]	Rd with or without bortezomib	Randomized, open-label, phase 3 trial	525 patients with NDMM without intention for immediate ASCT	All grade cardiac events in 51 (21.2%) vs 32 (14.2%) and grade ≥3 cardiac events in 18 (7.5%) vs 8 (3.5%) for bortezomib vs control group patients
Siegel et al, 2018[135]	KRd vs Rd	Prespecified analysis of randomized, open-label, multicenter, phase 3 study	792 patients with RRMM (ASPIRE prespecified analysis)	All grade HF in 7.1% vs 4.1% and grade ≥3 HF in 4.3% vs 2.1% for KRd group vs Rd group
Facon et al, 2019[15]	Carfilzomib or bortezomib with melphalan-prednisone	Randomized, open-label, multicenter, phase 3 study	955 transplant-ineligible patients with NDMM	All grade HF in 51 (10.8%) vs 20 (4.3%) and grade ≥3 HF in 39 (8.2%) vs 13 (2.8%) for carfilzomib vs bortezomib
Ailawadhi et al, 2020[136]	Low-dose vs high-dose carfilzomib with dexamethasone	Randomized phase 2 trial	121 patients with RRMM	–
Kumar et al, 2020[16]	Carfilzomib or bortezomib plus Rd	Multicenter, open label, phase 3, randomized, controlled trial	1087 patients with NDMM without intention for immediate ASCT	Grade ≥3 cardiac, pulmonary or renal toxicity in 84 (16%) vs 25 (5%) for carfilzomib vs bortezomib (led by the difference in dyspnea and HF)
Kastritis et al, 2020[137]	MDex vs BMDex	Investigator-initiated, multicenter, randomized, controlled, open-label clinical trial	109 patients with AL amyloidosis	All grade dyspnea in 13 (24.5%) vs 20 (35.7%) and grade ≥3 dyspnea in 1 (2%) vs 2 (3.5%) for BMDex vs MDex patients
Jackson et al, 2021[138]	KRdc or Rdc or Tdc	Multicenter, randomized, open-label, phase 3 trial	1,056 transplant-eligible, newly diagnosed patients with MM	All grade events: HF in 5 (1%), pulmonary oedema in 4 (0.8%) and grade ≥3 events: HF in 4 (0.8%), pulmonary edema in 2 (0.4%) in the KRdc group vs none in Rdc/Tdc control group
Yong et al, 2021[99]	KCd vs VCd followed by carfilzomib maintenance	Phase 2 randomized, controlled, multicenter trial	300 patients in second-line MM treatment	All grade cardiac events in 17 (8.7%) vs 8 (8.3%) for the KCd arm vs the VCd arm and grade ≥3 cardiac events only in the KCd arm, 6 (3.6%)
Gregersen et al, 2022[139]	Carfilzomib and dexamethasone maintenance	Randomized, open-label, phase 2 trial	168 patients with salvage ASCT in MM	–
Bahlis et al, 2021[140]	VenDVd vs VenDd	Phase 1 study	48 patients with RRMM	All grade dyspnea in 5 (21%) vs 7 (29%) and grade ≥3 dyspnea in none vs 1 (4%) for VenDVd vs VenDd patients

AF = atrial fibrillation; ASCT = autologous stem-cell transplantation; BMDex = oral melphalan, dexamethasone, and bortezomib; DVT = deep vein thrombosis; HF = heart failure; HTN = hypertension; IHD = ischemic heart disease; KCd = carfilzomib with cyclophosphamide and dexamethasone; KRdc = carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide; MDex = oral melphalan and dexamethasone; MI = myocardial infarction; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; Rd = lenalidomide and dexamethasone; Rdc = lenalidomide, dexamethasone, and cyclophosphamide; RRMM = relapsed/refractory multiple myeloma; Tdc = thalidomide, dexamethasone, and cyclophosphamide; VCd = bortezomib with cyclophosphamide and dexamethasone; VenDd = venetoclax plus daratumumab and dexamethasone with bortezomib; VenDVd = venetoclax plus daratumumab and dexamethasone without bortezomib; other abbreviations as in Table 1.

Continued on the next page

cardiac biomarkers during cardiotoxic medication are potential indications for initiation of cardioprotective treatment.[69] LVEF reduction is considered more clinically relevant as a potential trigger for introduction of cardioprotective therapy than biomarkers or changes in GLS. Due to lack of specific evidence, in our center, we consider cardiac troponin and NPs as ancillary markers, which, when available, may assist borderline decisions for cardioprotection combined with imaging biomarkers (**Figure 2**). Whether carfilzomib should be withheld in asymptomatic LVEF depression to 40% to 49% and what is the extent of NP increase to prompt intervention remain unclear[69,72,81] (**Table 5**).

Management of treatment complications. During carfilzomib infusion, intravenous fluids are given to reduce the risk of renal function impairment and tumor lysis syndrome.[53,82] Fluid administration should be conservative, aiming at 250 to 500 mL of intravenous normal saline for each dose of carfilzomib in cycle 1, and further hydration in subsequent cycles should be administered upon the discretion of the physician.[53,82] A starting dose for carfilzomib of 70 mg/m^2 could be reduced to 56 mg/m^2 and 45 mg/m^2 subsequently for toxicity reasons, whereas 56 mg/m^2 could be reduced to 45 mg/m^2 and 36 mg/m^2 and a starting dose of 27 mg/m^2 to 20 mg/m^2 and 15 mg/m^2, respectively.[83] For bortezomib, the respective dose

TABLE 4 Continued

IHD	Arrhythmia	Thrombosis/Vascular Toxicity	HTN
–	–	–	All grade HTN in 23 (15%) vs 9 (6%) for carfilzomib vs control group
–	All grade arrhythmias in 12 (5%) vs 12 (5.3%) and grade ≥3 arrhythmias in 4 (1.8%) vs 3 (1.2%) for bortezomib vs control group patients	All grade vascular events in 31 (12.9%) vs 22 (11.1%) and grade ≥3 vascular events in 22 (9%) vs 21(9%) for bortezomib vs control group patients	–
All grade IHD in 6.9% vs 4.6% and grade ≥3 IHD 3.8% vs 2.3% for KRd group vs Rd group	–	–	All grade HTN in 17.1% vs 8.7% and grade ≥3 HTN in 6.4% vs 2.3% for KRd group vs Rd group
All grade IHD in 14 (3%) vs 9 (1.9%) and grade ≥3 IHD in 10 (2.1%) vs 6 (1.3%) for carfilzomib vs bortezomib	–	–	–
–	–	–	All grade HTN in 16% vs 17% for low-dose vs high-dose carfilzomib and grade ≥3 HTN in 5% of total patients
–	–	–	–
–	–	–	–
All grade MI in 2 (0.4%) and grade ≥3 MI in 2 (0.4%) in the KRdc group vs none in Rdc/Tdc control group	-	All grade DVT in 36 (7.1%) vs 34 (6.6%) and grade ≥3 DVT in 6 (1.2%) vs 7 (1.4%) for KRdc group vs Rdc/Tdc control group	All grade HTN in 3 (0.6%) vs 3 (0.6%) and grade ≥3 HTN in 2 (0.4%) vs 1 (0.2%) for KRdc group vs Rdc/Tdc control group
–	–	All grade HTN in 10 (5.1%) vs 2 (2.1%) for the KCd arm vs the VCd arm and grade ≥3 HTN only in the KCd arm, 7 (3.6%)	–
–	All grade and grade ≥3 AF in 1 (1%) vs 1 (1%) for carfilzomib-dexamethasone maintenance group vs control group	All grade thrombosis in 1 (1%) and grade ≥3 thrombosis in 1 (1%) for carfilzomib-dexamethasone maintenance group vs none in control group	All grade HTN in 15 (18.3%) vs 3 (3.5%) and grade ≥3 HTN in 3 (4%) vs 1 (1%) for carfilzomib-dexamethasone maintenance group vs control group
–	–	–	All grade HTN in 2 (8%) vs 8 (33%) and grade ≥3 in none vs 4 (17%) for VenDVd vs VenDd patients

reductions are from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2.[84] In case of dyspnea or other symptoms attributable to cardiac dysfunction, carfilzomib should be withheld and the patient reassessed for adjudicated diagnosis.

Patients with symptomatic LV dysfunction should be treated according to international guidelines for the management of HF.[68,72,81] Symptomatic LV dysfunction should prompt discontinuation of carfilzomib. LVEF reduction may be reversible after carfilzomib discontinuation and appropriate cardioprotective treatment.[62] According to a published consensus paper, no specific suggestions for the continuation of treatment can be given when LV function recovers either fully or to asymptomatic LV dysfunction.[53,82] Carfilzomib may be permanently discontinued or continued with reduced dose on a case-by-case scenario by a multidisciplinary team[53,82] (**Table 5**). For patients on PIs, HFpEF diagnosis should be based on the presence of symptoms and/or signs, LVEF >50% and evidence of structural heart abnormalities (such as LV hypertrophy), or LV diastolic dysfunction, or elevated LV filling pressures, or increased NPs.[81] Management of HFpEF includes diuretics for congestion, treatment of hypertension, and lifestyle modification counselling.[81]

Emerging science. Both systolic and diastolic LV function may deteriorate after carfilzomib treatment in humans.[61,62,85,86] In a prospective study from our center with carfilzomib-treated patients, a reversible reduction of LV ejection fraction (LVEF) by ≥20% was observed in 12% of the population.[62] Another prospective study of 88 nonconsecutive patients with MM, showed that mean GLS decreased, whereas prevalence of diastolic dysfunction increased after 6 months of carfilzomib treatment.[86] Interestingly, in a cohort of 48 patients with RRMM treated with carfilzomib who were serially assessed by

TABLE 5 Proposed Prevention and Management of PI Cardiovascular Toxicity Based on Our Center's Approach

Risk Categories/Adverse Event	Risk Factors/Markers	Definition	Recommendation
Risk stratification before treatment initiation			
Very high risk[68,70]	Known cardiomyopathy, CAD, CVD, PVD	Any of very high-risk factors	Refer to unit with cardio-oncology service[68,70]; echocardiographic surveillance every 3 cycles (Class IIa, Level of Evidence: B), NP every cycle during the first 6 cycles (Class IIa, Level of Evidence: B)[68]
High risk[68,70]	DVT, PE, LVEF <50%, QTc>480 ms, age >75 y, prior anthracycline treatment	Any of high-risk factors or ≥3 medium-high risk factors or ≥2 medium-high and ≥1 medium-low or ≥1 medium-high and ≥3 medium-low	Refer to unit with cardio-oncology service[68,70]; echocardiographic surveillance every 3 cycles (Class IIa, Level of Evidence: B), NP every cycle during the first 6 cycles (Class IIa, Level of Evidence: B)[68]
Medium risk[68,70]	Medium-high factors: LVEF = 50%-54%, QTc = 450-480 ms (men), 460-480 ms (women), AF, Aflutter Medium-low factors: cTn or NPs above lab reference range, DM, hyperlipidemia, CKD, prior chest radiotherapy, smoking, BMI >30 kg/m^2	1-2 medium-high risk factors or 1 medium-high and 0-2 medium-low or 2-4 medium-low	Close cardiovascular monitoring, consider cardio-oncology referral[68,70]; echocardiographic surveillance every 3 cycles (Class IIb, Level of Evidence: C), NP every cycle during the first 6 cycles (Class IIa, Level of Evidence: B)[68]
Low risk[68,70]		0-1 medium-low factors	Cardiovascular monitoring according to local practice[68,70]; echocardiographic surveillance every 3 cycles (Class IIb, Level of Evidence: C), NP every cycle during the first 6 cycles (Class IIa, Level of Evidence: B)[68]
Cardiac amyloidosis[68]			Echocardiographic surveillance every 3 cycles (Class IIa, Level of Evidence: C), NP and cTn every 3-6 months (Class I, Level of Evidence: B)[68]
Estimated high risk for cardiotoxicity[69]	[a]LVEF <50%, prior anthracycline or anthracycline-transtuzumab combination, prior chest radiotherapy, age >75 y, hypertension, DM, or smoking	[a]No specific recommendation regarding the number of risk factors	[a]Start cardioprotective therapy[69]
Monitoring for subclinical cardiotoxicity			
Cardiac toxicity (imaging)	LVEF by echocardiography or CMR[75] Time points: baseline (Class I, Level of Evidence: C), every 3 cycles[68]	Cardiotoxicity defined as LVEF <50% and/or >10% absolute reduction from baseline[68]	[a]Start cardioprotective therapy[53,69,72]; Hold treatment?? (no evidence)
	GLS	>15% relative worsening from baseline[68]	[a]Start cardioprotective therapy[53,69]
	LV diastolic dysfunction markers or LA size and function markers	No recommendations	No recommendations
Cardiac toxicity (biomarkers)[68,80]	cTn	Elevation (no evidence on the degree)	[a]Start cardioprotective therapy[53,69]; Perform echo; Exclude ACS
	NP; time points: baseline (Class I, Level of Evidence: C for very high/high-risk and Class IIa, Level of Evidence: C for low/moderate-risk) and every cycle during the first 6 cycles[68,80]	Elevation (no evidence on the degree)	No evidence for actions following elevation
Vascular toxicity (imaging)	[a]Endothelial function by FMD, PWV	No recommendations	No recommendations
Vascular toxicity (hemodynamic)	BP monitoring by ABPM, HBPM Time points: baseline and HBPM weekly during the first 3 months and monthly thereafter[53,68,69]	>130/80 for ABPM, >135/85 for HBPM	Add/modify antihypertensive treatment (Preferable ACE inhibitor/ARB, CCB)[53,68,69,100]

Continued on the next page

echocardiography, we found that segmental LV dysfunction and deterioration of left atrial (LA) structure and function preceded global systolic and diastolic LV deterioration and right ventricular dysfunction.[61] Importantly, these initial changes in LV and LA were associated with PrA in peripheral blood mononuclear cells (PBMCs) and were independent of endothelial function, BP, and arterial stiffness changes suggesting a direct association between carfilzomib and myocardial dysfunction irrespective of other combination components or concomitant peripheral vascular toxicity. Further research to identify the optimal preventive strategy by either targeting mechanisms of direct or of indirect

TABLE 5 Continued

Risk Categories/Adverse Event	Risk Factors/Markers	Definition	Recommendation
Treatment of subclinical and clinical overt complications			
Asymptomatic LV systolic impairment or evidence of myocardial damage	LVEF and GLS by echocardiography or CMR[75]	LVEF <50%, or >10% absolute reduction or GLS relative decline >15% or Troponin elevation (no evidence on the degree)[68]	[a]Start cardioprotective therapy[53,69,72]
Heart failure[53,69,81,72]	NPs, LVEF, diastolic dysfunction	LVEF <50% and symptoms and signs of heart failure by definition of AHA or ESC guidelines (HFrEF, HFmrEF)[72,81]	[b]Treat by guideline recommendation. Add HF medication[81]; [a]Treatment should be discontinued and then reinitiated with same or reduced dose if grade returns to 1[53] (no evidence)
Grade ≥3 hypertension[53,68,69]	Office peripheral arterial BP	>160/100 mm Hg or complicated (malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Add/modify antihypertensive treatment[53,69] Treatment should be discontinued if SPB >180 mm Hg and/or DBP >110 mm Hg and resumed when SBP <160 mm Hg and DBP <100 mm Hg [53,68]
ACS	ECG, troponin	cTn elevation >99th percentile URL and Symptoms of acute myocardial ischemia or New ischemic ECG changes/ pathological q waves or Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology[141]	[b]Treatment of ACS by guidelines[91,92] No evidence on PI treatment discontinuation at post-ACS phase

Cardioprotective therapy refers to beta-blockers (BB) preferably nebivolol and carvedilol, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs). Heart failure treatment refers to BB, ACE inhibitors/ARBs and mineralocorticoid receptor antagonist (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), sodium/glucose cotransporter-2 inhibitors (SGLT2i). [a]Indicates recommendations for proteasome inhibitors (PIs) from position papers and not from guideline recommendations. [b]Indicates recommendations from guidelines for other anticancer cardiotoxic medication generalized for PIs.

ABPM = ambulatory blood pressure monitoring; ACS = acute coronary syndrome; Aflutter - atrial flutter; AHA = American Heart Association; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CKD = chronic kidney disease; CMR = cardiac magnetic resonance; cTn = cardiac troponin; CVD = cerebrovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; DVT = deep venous thrombosis; ECG = electrocardiogram; ESC = European Society of Cardiology; FMD = flow-mediated dilation; GLS = global longitudinal strain; HBPM = home blood pressure monitoring; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; LA = left atrial; LV = left ventricle; LVEF = left ventricular ejection fraction; NP = natriuretic peptide; PE = pulmonary embolism; PVD = peripheral vascular disease; PWV = pulse wave velocity; SBP = systolic blood pressure; URL = upper reference limit.

myocardial damage through peripheral vascular injury is warranted. We recently reported that in MM patients treated with Kd and daratumumab, deterioration of cardiac dysfunction after 6 months was less frequent[87] compared with those who received Kd only.

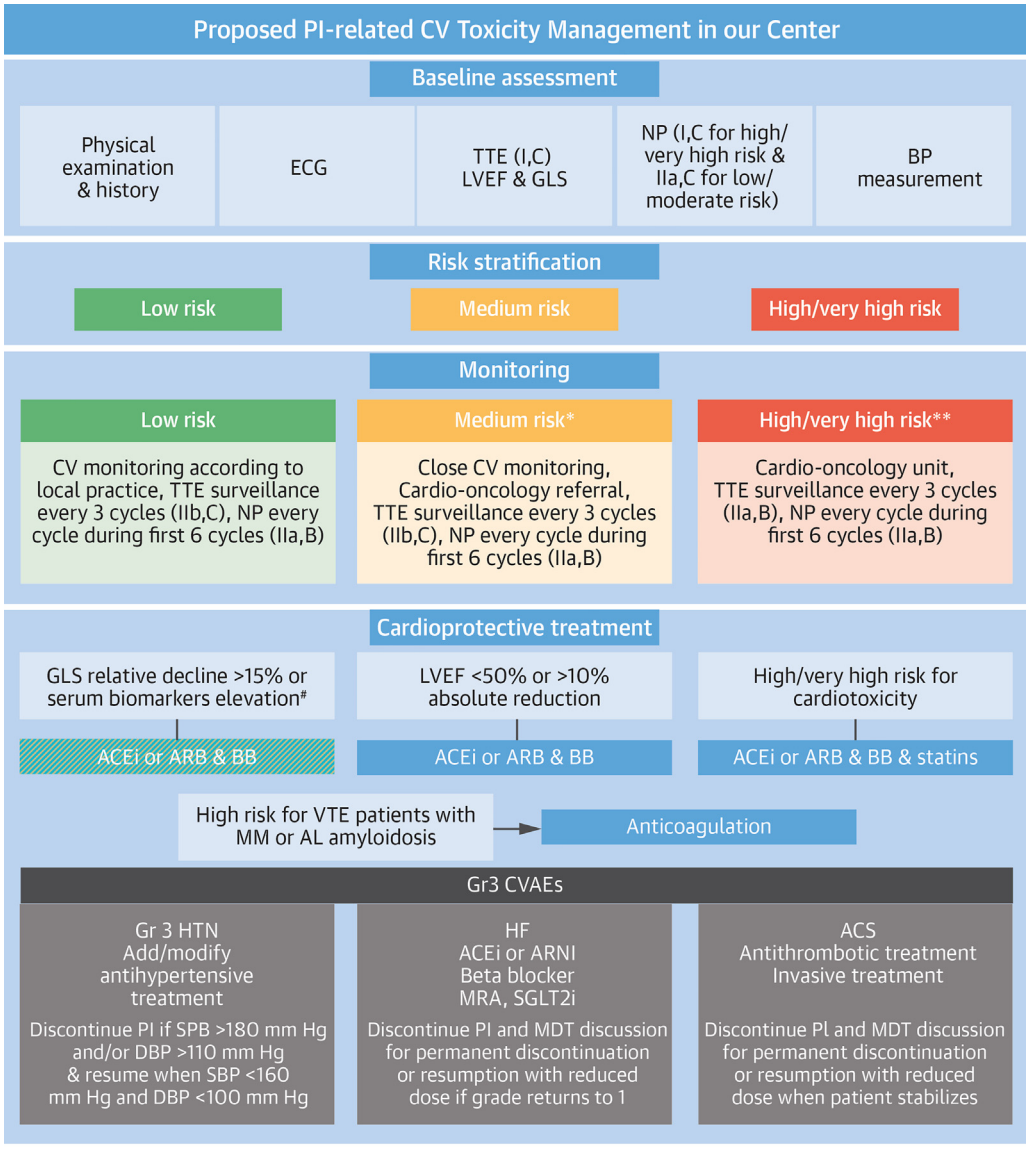
ISCHEMIC HEART DISEASE. Experimental, clinical, and autopsy studies have demonstrated that low UPP activity and increased ubiquitin conjugates are associated with unstable coronary, aortic, and carotid lesions and vascular aging.[88] Bortezomib promoted an unstable rupture-prone plaque phenotype in Apo-E-deficient mice, and chronic proteasome inhibition induced coronary artery endothelial dysfunction in hypercholesterolemic pigs treated for 3 months with MLN-273[89] (**Table 3**). Proteasome inhibition alters signaling in vascular smooth muscle endothelium, leading to increased vasoconstriction and decreased response to vasodilators such as nitric oxide (NO) and acetylcholine[90] (**Table 3**).

Carfilzomib treatment was reported to increase the risk of IHD by 45%.[34] Other studies presented an incidence of 6% and 4.6% for IHD during carfilzomib treatment.[36,56]

Management of carfilzomib-related acute coronary syndrome (ACS) should be provided according to contemporary guidelines[68,91,92] (**Table 5**). Caution is advised in MM patients with thrombocytopenia that may require adjustment in their antiplatelet treatment.[93] Grade ≥3 ACS event (myocardial infarction with troponin elevation)[94] requires withholding carfilzomib. Following stabilization of a patient with ACS no specific recommendations can be given regarding the resumption of carfilzomib. A recent consensus[53] suggests that if the event related to carfilzomib was severe (grade 3 or 4), dose reductions or definitive discontinuation may be needed. A multidisciplinary team should reconsider patient's management, including permanent discontinuation or continue with dose reduction[53,82] (**Table 5**).

ARRHYTHMIAS. The incidence of new arrhythmias was found to be 7% for patients on carfilzomib,[36] and in a systematic review and meta-analysis, arrhythmias included atrial fibrillation (AF), conduction abnormalities, and ventricular and supraventricular arrhythmias.[63] However, limited data exist on the prevalence of specific arrhythmias other than AF. Patients with MM are at very high risk for AF.[95]

FIGURE 2 Proposed Management of PI-Related CV Toxicity at Our Cardio-Oncology Center



*LVEF = 50-54%, AF/flutter, QTc= 450-480 msec (men), 460-480 msec (women), elevated troponin or NP, DM, Hyperlipidemia, CKD, prior chest radiotherapy, smoking, BMI >30 kg/m^2
**Known cardiomyopathy, CAD, CVD, PVD, DVT, PE, LVEF <50%, QTc >480 msec, age >75, prior anthracycline treatment
#Troponin and NPs elevation, when available, may assist borderline decisions for cardioprotective treatment in addition to imaging biomarkers

The proposed algorithm for the management of proteasome inhibitor (PI)-related cardiovascular (CV) toxicity consists of PI-specific recommendations from guidelines, guidelines' recommendations for cardiotoxic anticancer medications, and recommendations from consensus and position papers. Guideline recommendations for monitoring by echocardiographic and circulating biomarkers are not supported by a strong level of evidence. **Arrows** indicate recommendations. The **striped box** indicates lower strength of recommendation and decisions are made by consensus based on combined assessment of multiple biomarkers, clinical evidence, and shared decision-making with the patient. ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; BP = blood pressure; CV = cardiovascular; CVAE = cardiovascular adverse event; DBP = diastolic blood pressure; ECG = electrocardiogram; GLS = global longitudinal strain; Gr = grade; HBPM = home blood pressure monitoring; HF = heart failure; HTN = hypertension; IV = intravenous; LVEF = left ventricular ejection fraction; MDT = multidisciplinary; MRA = mineralocorticoid receptor antagonist; NP = natriuretic peptide; SBP = systolic blood pressure; SGLT2i = sodium/glucose cotransporter-2 inhibitor; TTE = transthoracic echocardiogram; VTE = venous thromboembolism.

Experimental data in mice suggest a role for proteasome in the pathogenesis of AF,[96] but further research is required to elucidate the molecular mechanisms involved in PI-related AF and other arrhythmias. Patients on PIs are at low relative risk for QTc prolongation.[68]

AF during cancer is associated with increased risk of thromboembolism,[68] and the guidelines from the ESC recommend anticoagulation for patients with a CHADS-VASc score of ≥1 for men and ≥2 for women.[68] New oral anticoagulant agents are preferred in the absence of contraindications, high bleeding risk, and drug-drug interactions.[68]

KEY POINTS.

- Risk stratification for cardiovascular toxicity is important before treatment initiation with carfilzomib.
- Patients at high or very high risk for PI-related cardiovascular toxicity benefit from a closer surveillance program and cardioprotective therapy.
- With a grade ≥3 cardiac toxicity event, carfilzomib should be held, and when the patient returns to normal or a grade 1 cardiac AE, multidisciplinary team discussion regarding the management plan is warranted.

VASCULAR AEs

ARTERIAL HYPERTENSION. Basic mechanisms. From a mechanistic point of view, experimental evidence indicates that carfilzomib-associated hypertension may be mediated by the interference of carfilzomib with reduced availability of NO and endothelial dysfunction.[97] An in vitro experimental study using rabbit hearts and aortas[90] showed that carfilzomib increased resting vasoconstricting tone, enhanced the spasmogenic results of several agents, and attenuated the antispasmogenic effect of vasodilating agents (**Table 3**). A detailed description of the endothelial mediating mechanisms of PI-related cardiovascular toxicity can be found in the "Thrombotic microangiopathy and endothelial dysfunction" section.

Epidemiology and association with individual drugs. Carfilzomib was found to increase the incidence of hypertension more than 3-fold compared with patients not treated with carfilzomib.[34,36] The ENDEAVOR study[12] examined the combination of carfilzomib with dexamethasone (Kd) vs Vd in patients with RRMM. One of the most common AEs reported was hypertension (9% in the Kd group vs 3% in the Vd group). It should be noted that patients with severe established cardiovascular disease were excluded from this study. Another study from our center showed that 6.7% of patients with MM during carfilzomib treatment had a grade ≥3 hypertension event.[62] Two recent meta-analyses of trials with carfilzomib-treated patients revealed an incidence of 4.3% and 5.3% during treatment.[35,56] In a recent trial comparing carfilzomib vs low-dose corticosteroids and cyclophosphamide in RRMM patients, carfilzomib was related to more episodes of grade ≥3 (3% vs 0%) or all-grade (15% vs 6%) hypertension compared with the control group.[98] Another clinical trial comparing the combination of either carfilzomib or bortezomib with cyclophosphamide and dexamethasone reported a 3.6% incidence of grade ≥3 hypertension in the carfilzomib group and no hypertension events in the bortezomib group[99] (**Table 4**).

Neither bortezomib[65,66] nor ixazomib[17] have been found to increase the incidence of hypertension.

Screening and prevention. Patients on PIs should be evaluated with either ambulatory or home BP measurement before treatment with carfilzomib.[53,68,69] Patients with newly diagnosed or poorly controlled hypertension should have BP controlled before carfilzomib initiation[68] (**Table 5**).

During treatment, BP monitoring is recommended at every clinical visit and via home monitoring weekly during the first 3 months and monthly thereafter, setting a target BP of <140/90 mm Hg for office measurements, and mean BP <130/80 mm Hg for ambulatory BP measurement or <135/85 mm Hg for home BP measurement[53,68,69,100] (**Table 5**). Regarding AL cardiac amyloidosis, treatment with PIs warrants the same BP surveillance schedule[68] (**Table 5**). Untreated hypertension could lead to other CVAEs.[68]

Management of treatment complications. For patients who have grade ≥3 hypertension,[94] or with SBP >180 mm Hg or diastolic BP >110 mm Hg, carfilzomib should be temporarily withheld,[53,68] and their antihypertensive medication should be adjusted according to current guidelines. ACE inhibitor/ARBs and dihydropyridine calcium channel blockers should be prioritized for the management of anticancer therapy-related hypertension[100] (**Table 5**). Beta-blockers should be considered in case ACE inhibitor/ARBs and calcium channel blockers are not tolerated.[101] If beta-blockers are indicated for other reasons (eg, HF or coronary artery disease), they should be continued.[68] Once BP is controlled <160 mm Hg for SBP and <100 mm Hg for diastolic BP, carfilzomib may be resumed.[53,68]

Emerging science. Hypertension is closely related to PWV, which is a marker of arterial stiffening.[102] We and others have found no increase in PWV in MM patients treated with PIs.[61,103] However, elevated

pretreatment PWV >9 m/s could identify patients at risk for carfilzomib-related CVAEs, suggesting that pre-existing vascular injury may predispose to cardiovascular toxicity.[104] Noninvasive measurement of aortic BP could provide incremental information and improve prediction of cardiovascular outcomes beyond peripheral BP.[105] Whether aortic BP may improve early detection and prediction of cardiovascular PI-related toxicity has not been investigated. Preliminary findings from our group indicated that aortic SBP independently predicts carfilzomib-associated hypertensive events with higher predictive value than peripheral BP.[106] We also reported that baseline impaired LV or LA strain could identify patients at increased risk for hypertension during carfilzomib treatment.[61]

THROMBOTIC MICROANGIOPATHY AND ENDOTHELIAL DYSFUNCTION. Basic mechanisms. The vascular wall is composed of both postmitotic (smooth muscle cells) and mitotic (endothelial cells, fibroblasts) cell lineages.[107,108] Therefore, PI-induced proteasome dysfunction can increase proteome instability in vascular wall cells, leading to premature senescence, cell cycle arrest, and apoptosis[33] (**Figure 1**). Accumulating evidence indicates that UPP is functionally involved in modulating endothelial nitric oxide synthase (eNOS) expression and activation in endothelial cells, in regulating endothelial-dependent contracting and vasodilating factors and in endothelial cell oxidative stress responses.[109] UPP has also been implicated in vascular inflammation, through nuclear factor kappa B (NFkB) activation and adhesion molecules activation.[110] Notably, beyond inflammation, proteasome inhibition also suppressed thrombus formation and reduced platelet aggregation in mice.[111]

The PI-related AE of TMA offers additional evidence that systemic endothelial dysfunction is involved after PI.[112] Although the exact pathophysiologic mechanisms have not been identified, microvascular damage is mediated by inhibition of vascular endothelial growth factor (VEGF).[113]

On the other hand, several reports have demonstrated protective stress responses in endothelial cells by proteasome inhibition, mainly through up-regulation of antioxidant enzyme expression and eNOS[109,110] (**Table 3**). Low-dose proteasome inhibition improved endothelial-dependent vasodilation in rat aortic rings in vitro, through up-regulation of eNOS expression and activity, and endothelin-1 down-regulation.[109,114,115] These data suggest that partial proteasome inhibition may mediate eNOS-dependent vascular protection, likely by triggering a counteracting gene expression response; alternatively, transient beneficial effects upon mild proteasome inhibition may relate to increased half-life of cytoprotective proteasome degraded proteins.

Compensatory mechanisms to proteasome inhibition-related cardiovascular toxicity. In response to transient or prolonged proteasome inhibition, cells mount counteractive (mainly genomic[48]) responses aiming to compensate for the reduced protein degradation rates and restore balanced UPP activity. Impaired proteasome function or pharmacologic proteasome inhibition results in a compensatory activation of UPP or autophagy lysosomal pathway[116] in an age-dependent manner.[49] In a cohort of MM patients receiving carfilzomib, patients with low recovery rate of PrA, exhibited worse flow-mediated dilatation (FMD), compared with those with higher proteasome recovery.[117] Along this line, expression of proteasome genes in PBMCs, expected to increase as a response to low PrA, was inversely associated with FMD attenuation.[117] Therefore, experimental and limited clinical evidence indicate the presence of compensatory cellular mechanisms in response to PI treatment that could account either for tolerance when normally functioning or for toxicity when exhausted. Recognizing and targeting such compensatory pathways could fuel future research to reverse severe toxicity.[49]

Epidemiology and association with individual drugs. TMA has been associated with all 3 PIs and manifests as anemia, thrombocytopenia, microvascular thrombosis, endothelial injury, and consequently, organ damage, mostly renal dysfunction.[41-43] TMA usually occurs during the second or third cycle of treatment, but data on exact incidence are scarce. A recent review described 27 cases of TMA following bortezomib or ixazomib treatment.[41] Median time from PI initiation to TMA was 34 days for bortezomib and 78 days for ixazomib, whereas 18 patients required hospitalization and 2 died. Acute kidney injury was the most common manifestation of TMA and led to renal replacement therapy in 10 patients. Similar findings were reported in another review of published cases associated with carfilzomib in 17 patients.[43]

For patients presenting with TMA, limited evidence suggests PI discontinuation, renal replacement therapy, plasma exchange, transfusions, empirical antibiotics, and the anti-complement component 5 (C5) antibody eculizumab.[43]

Emerging science. In agreement with previous experimental evidence, we recently reported that treatment with carfilzomib impairs endothelial function, assessed by brachial artery FMD, both acutely and in the long term.[117] FMD changes were associated

with 26 S PrA in PBMCs and its recovery.[117] Interestingly, both pre- and post-treatment FMD predicted carfilzomib-related CVAEs. Microvascular endothelial function as assessed by the reactive hyperemia index also deteriorated following carfilzomib treatment in 24 MM patients and was associated with carfilzomib-related CVAEs.[85] These findings suggest the possible utility of markers of endothelial dysfunction in the clinical evaluation of carfilzomib-related cardiovascular toxicity. Considering the limitations of FMD for clinical use, different methodologies among centers of excellence, and lack of established normal values,[118] the use of FMD as a biomarker in this setting requires further clinical validation.

VENOUS THROMBOEMBOLISM. Patients with MM are at increased risk of venous thromboembolism (VTE) due to MM factors and concomitant treatment with IMiDs.[68,119] Recent ESC guidelines recommend the use of therapeutic dose low-molecular weight heparin for patients with previous VTE and MM and prophylactic dose low-molecular weight heparin for patients with MM and risk factors for VTE, such as carfilzomib-lenalidomide combinations.[68]

PULMONARY HYPERTENSION. Case reports have suggested a relationship between treatment with carfilzomib[120] and bortezomib[121] and pulmonary hypertension (PH). The mechanisms of PI-related PH have not yet been clarified. Existing hypotheses include PI-related endothelial oxidative stress and effect on eNOS causing impaired NO availability and subsequent impaired vasodilation.[120] Symptoms could be nonspecific, including breathlessness and fatigue. Echocardiography determines the probability of PH, and right heart catheterization establishes the diagnosis. Management includes treatment discontinuation and referral to a PH center.[122]

KEY POINTS.

- Arterial hypertension is the most common PI-related cardiovascular toxicity, and BP should be closely monitored during treatment for these patients.
- Experimental and clinical data suggest that endothelial dysfunction is an important mechanism mediating PI-related cardiovascular toxicity.

An approach to the management of PI-related cardiotoxicity from our center is proposed, which is based on integrated contemporary evidence and published recommendations (**Figure 2**).

FUTURE PERSPECTIVES: GAPS IN EVIDENCE

Despite extensive clinical use of PIs and continuing research on the pathophysiology of PI-related cardiotoxicity, there are still gaps in evidence that merit investigation. Further elucidation is required on the compensatory cellular mechanisms following PI to reveal potential new therapeutic targets for cardiotoxicity prevention and management. There is no consensus whether patients with asymptomatic declines in LVEF to 40% to 49% should discontinue PI therapy and data regarding frequency, type of NP, cutoff values, and the specific subpopulations to be serially monitored are generally lacking, necessitating further research. Similarly, the optimal timing of reducing drug dosages, discontinuing or re-initiating a PI are not delineated. Given the strong etiologic link between hypertension, which is the most common CVAE of carfilzomib, and HFpEF,[60] more research on the prevalence of HFpEF as a PI-related AE in these patients is warranted. The clinical utility of markers of endothelial dysfunction and aortic hemodynamics as possible biomarkers in risk stratification and monitoring of these patients needs additional investigation. Furthermore, the possible predictive value of microRNAs,[123] precision medicine,[124,125] and genetic scores for PI-related CVAEs is promising in cardio-oncology but has not been explored for PIs. Prospective data validating the benefit of traditional cardioprotective medications (ACE inhibitors/ARBs and beta-blockers) in patients treated with carfilzomib are lacking. Finally, additional translational evidence is required on the possible cardioprotective role of metformin,[49] apremilast,[126] and daratumumab.[87]

CONCLUSIONS

PIs comprise a contemporary and effective therapy for patients with MM and other hematologic malignancies. Despite expanding indications, PIs and particularly carfilzomib, may induce CVAEs that should be carefully weighed against the benefits. PI-related CVAEs might be attributed to accelerated or triggered atherosclerotic complications, or direct injury to the myocardium and the vessels. Cardiovascular toxicity is mainly associated with carfilzomib encompassing different clinical presentations ranging from new-onset hypertension to heart failure. The role of vascular toxicity in the form of quantifiable vascular markers may represent a novel promising approach to monitor and treat cardiovascular toxicity. A 3-fold strategy based on selecting PIs with safer risk profile, early identification of susceptible patients at risk, and prompt detection of cardiovascular toxicity is advised to improve clinical outcomes in this population. As more randomized trials assessing PIs for different clinical indications are

available, the optimal management strategy of patients eligible for these treatments should be further refined with evidence-based data.

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ADDRESS FOR CORRESPONDENCE: Prof Kimon Stamatelopoulos, Vascular Laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Medical School, National and Kapodistrian University of Athens, PO Box 11528, 80 Vas. Sofias Street, Athens 11528, Greece. E-mail: kstamatel@med.uoa.gr.

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