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# Carfilzomib-induced Cardiotoxicity: An Analysis of the FDA Adverse Event Reporting System (FAERS)

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## Abstract

**Background:** Carfilzomib and other proteasome inhibitors (PIs) have revolutionized treatment of multiple myeloma (MM). PIs have proven to be highly effective, but are associated with significant cardiovascular adverse events (AEs). No prior study has compared the cardiotoxicity of carfilzomib against other PI's and all other classes of medications.

**Objectives:** The purpose of this study is to characterize the cardiotoxicity of carfilzomib with respect to other PIs and all classes of medications using the US Food and Drug Administration Adverse Events Reporting System (FAERS) database and to define the observed cardiotoxicity profile.

**Methods:** The FAERS database was queried between years 2017 and 2020 to identify AEs associated with PIs. Data extracted included concomitant medications used, type and severity of AEs and patient characteristics including age, sex, and time from medication initiation to adverse event. Cardiotoxicities assessed included acute myocardial infarction, heart failure, and supraventricular tachycardia. The reporting odds ratio (ROR) and information component assessed the strength of association between PIs and cardiotoxicity.

**Results:** Over the study period, 21,026 adverse events were reported in patients taking carfilzomib among 55,195 total adverse events in patients taking PI's were identified from 6,548,048 total events reported in the FAERS database. The most common AE associated with carfilzomib was development of heart failure (1116 adverse events); disproportionality analysis revealed a stronger association with hypertension and QT prolongation with carfilzomib than other PI's.

**Conclusions:** While they have demonstrated efficacy and revolutionized treatment of MM, carfilzomib and other PI's are associated with cardiotoxicities.

**Keywords:** Cardio-oncology, Epidemiology, Adverse events

## 1. Introduction

Carfilzomib is a second-generation proteasome inhibitor (PI), a class of medications that has revolutionized treatment of multiple myeloma (MM). It is derived from epoxomicin and irreversibly binds the 20S proteasome eventually leading to cell death in patients with MM [12]. Carfilzomib initially received fast track status from the United States Food and Drug Administration (FDA) in January 2011 before being approved in 2012 for use in refractory MM [12]. Following FDA approval, its clinical use has grown dramatically due to

demonstrated clinical efficacy, such as a recent study showing that when used in conjunction with dexamethasone, it has demonstrated proved progression-free survival in patients with relapsed or refractory multiple myeloma compared to the combination of bortezomib and dexamethasone [5].

Despite the remarkable efficacy of PIs (carfilzomib, bortezomib, and ixazomib) in treating MM, these medications also cause significant cardiovascular adverse events. Therefore, cardiotoxicity and especially cardiac failure are now considered class effects of proteasome inhibitors. However, patients

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with MM commonly have risk factors for cardiac events attributable to patient-specific characteristics, MM itself and MM treatment, demonstrated in both clinical trials and meta-analyses. Further analyses of large datasets may help identify how each of these factors contribute to cardiac event risk. To date, no administrative database studies has been performed. The purpose of this study is to characterize further the cardiotoxicity of carfilzomib with respect to other PIs and all other classes of medications and to leverage the large sample size of a US administrative database to identify previously unreported cardiotoxicities and better define the cardiac risk profile of these medications.

## 2. Methods

The US Food and Drug Administration Adverse Events Reporting System (FAERS) database was retrospectively queried from years 2017 through 2020 to identify adverse events associated with proteasome inhibitors (PIs). The FAERS is a database documenting greater than 15 million adverse event reports, medication error reports and medication quality complaints submitted to the FDA since inception in 1968; reports since 2004 are publicly available from the FDA's website. Each report includes a case identification number used to link files within the database and identify updates to prior reports. Medical information contained in the database includes concomitant medications used, type of adverse reaction, and the severity of the reaction. Routine demographic information such as age, sex, geographic region of report, type of reporter (health care professional, consumer, pharmaceutical company or unknown) and the time from medication to adverse event are included in the database. The database is a registry of all submissions to the FAERS system.

This analysis included all reports of adverse events attributed to carfilzomib, bortezomib and ixazomib. The database was queried from January 1, 2017 to December 31, 2020. These dates were selected to minimize bias: 2016 was the first full year ixazomib was available on the market and 2020 was the last year the full database was available at the time of analysis. Cardiotoxic events were identified by the listed MedDRA preferred term, and were grouped into myocardial infarction, hypertension, heart failure, arrhythmia events, pericardial effusion and QTc prolongation. Cardiotoxic events which were life-threatening, necessitating hospitalization, or led to death or disability were considered as severe. The MedDRA database is a hierarchical database which organizes medical symptoms and

### Abbreviations

FAERS	Food and Drug Administration Adverse Events Reporting System
FDA	Food and Drug Administration
IC	Information Component
MM	Multiple Myeloma
PI	Proteasome inhibitor
ROR	Reporting Odds Ratio

diseases into pertinent organ systems. MedDRA terms used to identify adverse reactions are listed in Table 4. To reduce bias from including multiple reports per patient, when multiple reports were recorded from the same patient, only the final report was included in this analysis. The database was accessed March 21, 2021. Dyspnea was not included as a cardiotoxic effect due to the potential for it to represent cardiotoxicity (for example, as a manifestation of heart failure) or non-cardiac toxicity (for example, pulmonary, renal or thyroid toxicity), consistent with other studies [21].

Patients taking a PI were identified from the database and categorized as taking carfilzomib, other PIs, carfilzomib and other PI or no PI. Characteristics of patients taking carfilzomib are presented using summary statistics. To further characterize patients and the reactions associated with carfilzomib, all patients on carfilzomib were included single cohort, regardless of concomitant use of other PI. The severity of reaction was dichotomized into serious and non-serious using FAERS-supplied criteria.

A disproportionality analysis was performed to assess cardiotoxicity risk using the reporting odds ratio (ROR) and information component (IC). The ROR measures the association between a specific exposure (medication) and odds of developing a specific outcome (cardiotoxic event) and is deemed statistically significant if its 95% confidence interval does not include 1.0. This methodology has been employed with multiple antineoplastic agents, including ibrutinib [18,23] and osimertinib [1]. The IC, described by Bate et al. and first applied to pharmacovigilance by the Uppsala Monitoring Group [2], is calculated

$$IC = \log_2 \left( \frac{n_{obs} + 0.5}{n_{expected} + 0.5} \right)$$

In this equation,  $n_{obs}$  represents the number of observed events and  $n_{expected}$  represents the number of expected events;  $IC_{025}$  representing the lower bound of a 95% credibility interval of the IC and an association is deemed statistically significant when

the  $IC_{0.25} > 0$ . The IC method for disproportionality analysis has been used by other groups to describe cardiotoxic effects of ibrutinib [18] and the class of checkpoint inhibitors [4]. Adverse events classified as cardiotoxic were acute hypertension, dyspnea, edema, heart failure, myocardial infarction, any arrhythmia, and QT prolongation. The risk of carfilzomib-associated cardiotoxicity was compared with other PIs and all other entries in the database. Time-to-adverse event data, when available, is reported as median and interquartile range (IQR). All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

### 3. Results

Over the three years evaluated, 6,548,048 adverse events were reported in the FAERS database, 55,195 of which were observed in patients taking PIs. There were 19,486 adverse events reported in patients taking carfilzomib and no other PI, 34,169 in patients taking other PI's and 1540 in patients taking carfilzomib and at least one additional PI. Characteristics of patients on these medications are described in Table 1. Among patients on carfilzomib without other PI, 2893 (14.8%) adverse events were classified as acute myocardial infarction, heart failure, arrhythmia (both supraventricular and ventricular), pericardial disease or hypertension; among patients on other PI's, 2373 (6.9%) adverse events were categorized as one of these cardiotoxic categories; among patients on a combination of carfilzomib and other PI, 221 (14.4%) adverse events were categorized as one of these cardiotoxic categories. Adverse cardiac events related to proteasome inhibitors reported in FAERS database over this interval are listed in Table 2.

Among 21,026 adverse events associated with carfilzomib use, approximately 54.1% (with sex reported) were observed in males. Approximately 45.4% of adverse events were considered serious. In 44.7% of the cases, adverse events necessitated hospitalization, were life-threatening, or led to death. Among the 3034 patients with time-to-event data available, a median of 64 (IQR 10-188) days elapsed between initiation of carfilzomib and the adverse event.

The most common cardiotoxic event associated with carfilzomib was development of heart failure (1116 adverse events), representing 5.3% of all carfilzomib-associated adverse events. Of these, 1065 (95.4%) adverse events were associated with carfilzomib and 51 (4.6%) were associated with a combination of carfilzomib and another medication. Additionally, 764 (68.5%) of these adverse events

were serious. For those patients with time-to-event data available, the median time to event was 31 (IQR 9-70) days.

Hypertension was the second most common reported cardiotoxicity associated with carfilzomib, with 694 adverse events recorded in the FAERS database. This represented 3.3% of all adverse reactions associated with carfilzomib. Of these, 663 (95.5%) were associated solely with carfilzomib and 31 (4.5%) were reported in patients taking a combination of carfilzomib and another medication. Approximately 51.4% (357) of the adverse events due to hypertension were serious. Among patients with time-to-event data available, the median time to event was 8 (IQR 1–14.5) days.

The disproportionality analysis revealed carfilzomib had a stronger association with hypertension than other PI's with a ROR of 4.6 (95% confidence interval: 4.0–5.4), QT prolongation with ROR 6.9 (95% confidence interval: 4.9–9.7) and heart failure with ROR 2.7 (95% confidence interval: 2.5–3.0), respectively. The reporting odds ratios for all PI's are listed in Table 3 and illustrated in Fig. 1a. When compared to the full database, carfilzomib was associated with higher risk of heart failure (ROR 5.6, 95% confidence interval 5.3–6.0), QT prolongation (ROR 4.9, 95% confidence interval 4.2–5.7), and pericardial effusion (ROR 3.6, 95% confidence interval 3.0–4.3). Toxicities with the highest IC were heart failure ( $IC = 2.443$ ,  $IC_{0.25} = 2.353$ ) and QT prolongation ( $IC = 2.216$ ,  $IC_{0.25} = 1.991$ ); all calculated IC and  $IC_{0.25}$  are depicted in Fig. 1b.

Dyspnea and edema were not considered as cardiotoxicities due to the potential of both cardiac and noncardiac dysfunction to cause them. Nevertheless, this analysis identified 1481 (7.0% of all carfilzomib-related adverse reactions) cases of dyspnea and 486 (2.3% of all carfilzomib-related adverse reactions) cases of edema. The association between carfilzomib and these reactions were relatively weak: disproportionality analysis revealed ROR of 1.8 (95% confidence interval 1.7–1.9) and IC 0.69 ( $IC_{0.25} = 0.61$ ) for dyspnea and ROR 1.0 (95% confidence interval 0.9–1.1) and IC -0.21 ( $IC_{0.25} = -0.35$ ) for edema.

### 4. Discussion

Analysis of FAERS database revealed that 13.5% of all adverse events associated with carfilzomib were cardiac related. When compared to all other medications in FAERS, carfilzomib was associated with higher risk of heart failure, pericardial effusion and QT prolongation (Table 2). The ROR was highest for heart failure, followed by QTc prolongation and then

Table 1. Characteristics of patients with cardiac adverse event related to proteasome inhibitor.

Characteristic	All Events n = 19486	ACS n = 362	Any Arrhythmia n = 753	Heart Failure n = 1065	Hypertension n = 663	Pericardial Effusion n = 50	Dyspnea n = 1276	Edema n = 373
Age (years)	65.53 ± 11.25	67.33 ± 8.4	65.79 ± 12.13	67.92 ± 10.67	68.55 ± 8.28	67.97 ± 8.83	65.86 ± 10.15	65.9 ± 9.75
Sex								
F	7257 (40.8%)	70 (22.5%)	202 (29.4%)	420 (44%)	278 (47%)	30 (69.8%)	541 (46.1%)	149 (43.3%)
M	10512 (59.2%)	241 (77.5%)	484 (70.6%)	535 (56%)	313 (53%)	13 (30.2%)	633 (53.9%)	195 (56.7%)
Time to AE (days)	60 (10–175)	13 (3–42)	32 (8–99)	31 (8–67)	8 (1–12)	2 (2–2)	35 (3–156)	2 (2–14)
Serious AE	8735 (44.8%)	321 (88.7%)	559 (74.2%)	732 (68.7%)	333 (50.2%)	31 (62%)	899 (70.5%)	156 (41.8%)
AE Severity								
Death	2381 (12.2%)	136 (37.6%)	256 (34%)	208 (19.5%)	55 (8.3%)	15 (30%)	211 (16.5%)	42 (11.3%)
Disabled	145 (0.7%)	0 (0%)	3 (0.4%)	4 (0.4%)	0 (0%)	0 (0%)	39 (3.1%)	8 (2.1%)
Hospitalized	5094 (26.1%)	129 (35.6%)	209 (27.8%)	390 (36.6%)	217 (32.7%)	9 (18%)	515 (40.4%)	84 (22.5%)
Life Threatening	1113 (5.7%)	56 (15.5%)	91 (12.1%)	130 (12.2%)	61 (9.2%)	7 (14%)	134 (10.5%)	22 (5.9%)
Other Serious	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonserious	10751 (55.2%)	41 (11.3%)	194 (25.8%)	333 (31.3%)	330 (49.8%)	19 (38%)	377 (29.5%)	217 (58.2%)
AE Caused by Carfilzomib	11331 (58.1%)	269 (74.3%)	559 (74.2%)	790 (74.2%)	496 (74.8%)	43 (86%)	865 (67.8%)	278 (74.5%)
Year of AE								
2017	5060 (26%)	116 (32%)	218 (29%)	331 (31.1%)	157 (23.7%)	30 (60%)	336 (26.3%)	83 (22.3%)
2018	8340 (42.8%)	85 (23.5%)	214 (28.4%)	377 (35.4%)	273 (41.2%)	10 (20%)	493 (38.6%)	172 (46.1%)
2019	2902 (14.9%)	104 (28.7%)	174 (23.1%)	218 (20.5%)	136 (20.5%)	6 (12%)	241 (18.9%)	62 (16.6%)
2020	3184 (16.3%)	57 (15.7%)	147 (19.5%)	139 (13.1%)	97 (14.6%)	4 (8%)	206 (16.1%)	56 (15%)
AE Reported by Professional	17535 (90%)	322 (89%)	681 (90.4%)	975 (91.5%)	608 (91.7%)	46 (92%)	1080 (84.6%)	343 (92%)
Region of AE								
Asia	341 (1.8%)	7 (1.9%)	18 (2.4%)	21 (2%)	21 (3.2%)	0 (0%)	32 (2.6%)	6 (1.6%)
Americas	7839 (41.2%)	91 (25.7%)	217 (29.9%)	271 (26.1%)	219 (34.5%)	16 (33.3%)	613 (50.2%)	197 (54%)
Europe	10867 (96.6%)	250 (90.6%)	493 (91.3%)	751 (94%)	405 (95.7%)	30 (88.2%)	576 (89.4%)	165 (97.1%)
Australia	320 (81.4%)	13 (44.8%)	14 (25.5%)	17 (30.4%)	10 (52.6%)	2 (33.3%)	32 (45.1%)	3 (42.9%)
Africa	3 (1.2%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)

Abbreviation: AE = Adverse Event. Notes: Values in this table are reported as n (%) or mean ± standard deviation. Values of N may vary due to data missing from the database.

pericardial effusion. In comparison to other PIs, carfilzomib was associated higher ROR for QT prolongation, followed by hypertension and then pericardial effusion. Previous work demonstrated an association between MM and cardiac events in patients undergoing treatment for MM, though prior studies have been unable to differentiate whether the association was explained by patient-characteristics, MM itself or MM treatment [11]. This work demonstrates that at least part of this association is explained by treatment agent, with carfilzomib having a higher ROR than other PIs.

Cardiotoxicity, particularly cardiac failure, was first reported as an adverse event associated with carfilzomib, but it is now considered as a class effect of the PIs following reports of cardiotoxicity resulting from bortezomib and ixazomib [10,13]. In clinical trials, there was an 18.2% rate of any cardiovascular adverse event (event rates ranged from 0% to 52%) and an 8.2% risk (events ranged from 0% to 45%) of high-grade cardiovascular adverse events [6,21]. Moreover, the addition of carfilzomib to a regimen of lenalidomide and dexamethasone was associated with an increase in

Table 2. Adverse events related to proteasome inhibitors reported in FAERS database between 2017 and 2020.

Event	All PIs	Carfilzomib	Other PIs	Carfilzomib + Other PIs	No PIs
All Adverse Events	55,195	19,486	24,169	1540	6,492,853
ACS	753 (1.4%)	362 (1.9%)	377 (1.1%)	14 (0.9%)	60,237 (0.9%)
Any Arrhythmia	1802 (3.3%)	753 (3.9%)	1006 (2.9%)	43 (2.8%)	140,888 (2.2%)
Heart Failure	1807 (3.3%)	1065 (5.5%)	691 (2%)	51 (3.3%)	63,893 (1%)
Hypertension	943 (1.7%)	663 (3.4%)	249 (0.7%)	31 (2%)	137,219 (2.1%)
Pericardial Effusion	182 (0.3%)	50 (0.3%)	50 (0.1%)	82 (5.3%)	11,434 (0.2%)
Dyspnea	3011 (5.5%)	1276 (6.5%)	1530 (4.5%)	205 (13.3%)	263191 (4.1%)
Edema	1490 (2.7%)	373 (1.9%)	1004 (2.9%)	113 (7.3%)	143086 (2.2%)

Abbreviations: ACS = Acute Coronary Syndrome, PI = Proteasome inhibitor.

Table 3. Reporting Odds Ratios and Information Criteria of selected toxicities associated with proteasome inhibitors reported in FAERS database between 2017 and 2020.

Adverse Event	Carfilzomib vs Full Database		Carfilzomib vs PIs	
	ROR (95% CI)	IC (IC_025-IC-975)	ROR (95% CI)	IC (IC_025-IC-975)
Acute Coronary Syndrome	1.94 (1.75–2.15)	0.99 (0.84–1.14)	1.63 (1.41–1.88)	0.44 (0.26–0.63)
Any Arrhythmia	1.77 (1.65–1.9)	0.83 (0.72–0.93)	1.3 (1.18–1.43)	0.24 (0.12–0.37)
Heart Failure	5.61 (5.28–5.96)	2.44 (2.35–2.53)	2.72 (2.47–2.99)	0.74 (0.63–0.85)
Hypertension	1.59 (1.47–1.71)	0.69 (0.58–0.8)	4.65 (4.02–5.38)	0.99 (0.85–1.14)
Pericardial Effusion	3.58 (3.02–4.26)	0.53 (0.13–0.92)	4.31 (3.11–5.97)	–0.36 (–0.81 - 0.09)
QT Prolongation	4.91 (4.23–5.7)	2.22 (1.99–2.44)	6.9 (4.93–9.66)	1.04 (0.75–1.34)
Dyspnea	1.79 (1.7–1.89)	0.69 (0.61–0.77)	1.62 (1.5–1.74)	0.26 (0.17–0.36)
Edema	1.05 (0.96–1.15)	–0.21 (–0.35–0.06)	0.78 (0.7–0.87)	–0.5 (–0.66–0.33)

Abbreviations: ROR = Reporting Odds Ratio, IC = Information Criterion, 95% CI = 95% confidence interval.

the rate of cardiac failure of any severity from 4.1% to 6.4%, severe cardiac failure from 1.8% to 3.8% and ischemic heart disease (3.3% versus 2.1%) [20]. Likewise, a study evaluating carfilzomib with cyclophosphamide against corticosteroid with cyclophosphamide noted an increase in the rate of cardiac failure of any severity from 1% to 5% and

severe cardiac failure from 1% to 2% [8]. Dimopolos et al. also demonstrated carfilzomib has a more dangerous cardiotoxicity profile than bortezomib, with carfilzomib demonstrating increased rates of cardiac failure (8% versus 2.8%) and ischemic heart disease (2.5% versus 2%) when compared to bortezomib and dexamethasone [5]. Bortezomib-associated cardiotoxicity has also been shown in animal models [15,17]. Multiple reports have demonstrated an array of adverse events with bortezomib [3,9] and more recently ixazomib [10], though a recent study by Richardson et al. did not support these findings [14]. Conversely, a study by Kastritis et al. showed a reversible reduction in left ventricular ejection fraction in 12% of MM patients receiving carfilzomib [5]. The present study is consistent with most of the current evidence demonstrating increased risk of cardiotoxicity with carfilzomib. Furthermore, the study revealed a higher rate of myocardial infarction and heart failure with carfilzomib when compared to other PIs.

The pathophysiology of carfilzomib-mediated cardiotoxicity is incompletely understood, despite evaluation of it and other PIs in multiple studies [15]. A metaanalysis performed by Rahman et al. found a pooled RR of 2.34 (95% CI 1.66–3.32,  $P < 0.00001$ ) of heart failure among those treated with carfilzomib vs controls in four phase III randomized controlled trials [16], while a metaanalysis performed by Shah et al. found a pooled RR of 2.03 (95% CI 1.19–3.46,  $p = 0.010$ ) of cardiotoxicity among those treated with carfilzomib compared to controls [19]. Following this, a mouse model revealed treatment with carfilzomib was associated with diminished proteasomal activity in the heart, postulated to cause reduction of left ventricular systolic function and prophylactic metformin tempered this effect [7]. In the same study, carfilzomib was also associated with enhanced protein phosphatase 2 activity and decreased downstream AMP-activated protein kinase activity. Other work has suggested proteasome inhibition leads to

Table 4. MedDRA terms used to identify cardiovascular toxicities.

Cardiac Condition	MedDRA Term
Acute Coronary Syndrome	Acute myocardial infarction
	Coronary artery disease
	Acute myocardial infarction
	Acute coronary syndrome
	Coronary artery stenosis
	Myocardial infarction
	Coronary artery occlusion
	Angina pectoris
	Angina unstable
	Myocardial ischemia
	Arteriospasm coronary
	Microvascular coronary artery disease
	Acute Heart Failure
Cardiac failure congestive	
Ejection fraction decreased	
Cardiac failure	
Cardiomyopathy	
Left ventricular failure	
Ventricular hypokinesia	
Myocarditis	
Right ventricular failure	
Cardiogenic shock	
Cardiac failure chronic	
Cardiotoxicity	
Stress cardiomyopathy	
Cytotoxic cardiomyopathy	
Cardiac failure congestive	
Supraventricular Tachycardia	Left ventricular dysfunction
	Atrial flutter
	Atrial fibrillation
	Supraventricular tachycardia
Pericardial Effusion	Supraventricular tachycardia
	Cardiac tamponade
QTc Prolongation	Pericardial effusion
	Electrocardiogram QT prolongation

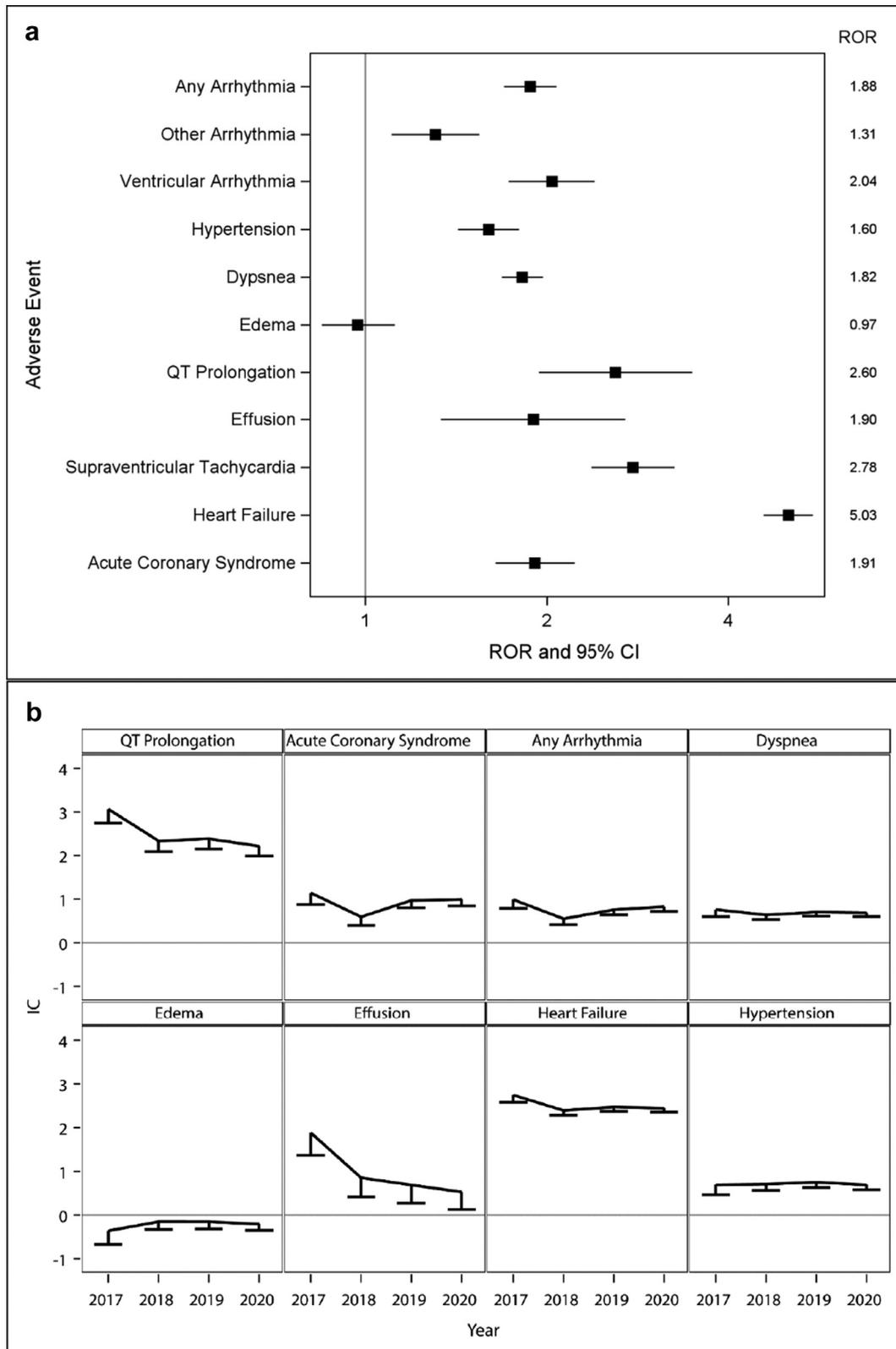


Fig. 1. (a) Forest diagram depicting reporting odds ratio (ROR) and 95% confidence intervals (95% CI) of cardiac adverse events associated with carfilzomib reported in the FAERS database. (b) Cumulative Information Criterion values for selected adverse events associated with carfilzomib from 2017 to 2020.

decreased endothelial nitric oxide synthase activity and nitric oxide levels within the heart [22]; irreversible proteasome inhibition is associated with better outcomes in MM than reversible proteasome inhibition, but irreversible inhibition of endothelial nitric oxide synthase likely produces a more pronounced decrease in nitric oxide levels than reversible inhibition. However, the mechanisms of the other adverse events, such as acute hypertension and QTc prolongation, remain unclear.

The study supports baseline cardiovascular risk assessment, with electrocardiography and echocardiography, prior to treatment with carfilzomib. Close monitoring for signs and symptoms of cardiac failure, cardiac ischemia, arrhythmias, and QTc prolongation is of utmost importance in patients receiving this medication.

#### 4.1. Limitations

Limitations of this study are primarily due to its retrospective nature of the FAERS database. Due to the nature of the database, information such as time to event and grade of toxicity is occasionally not reported. Because the database only contains adverse reactions, patients without adverse reactions are not captured, so the exact denominator of PI treated patients could not be determined. The exact rates of adverse cardiac events cannot be conclusively determined as all adverse events are not reported in FAERS.

## 5. Conclusions

Carfilzomib and PIs in general have revolutionized treatment for multiple myeloma. Unfortunately, Carfilzomib and other PIs are associated with higher risk of cardiotoxic adverse events. Awareness of this increased cardiovascular risk may lead to baseline cardiovascular risk assessment in all patients starting this therapy. Additionally, early diagnosis and management of these cardiotoxicities may potentially minimize interruptions to the treatment.

#### Authors contribution

Conception and design of Study: BB, EK Literature review: BB, EK. Acquisition of data: BB. Analysis and interpretation of data: BB. Research investigation and analysis: BB, EK, DA. Drafting of manuscript: BB, EK. Revising and editing the manuscript critically for important intellectual contents: BB, EK, DA, AV. Data preparation and presentation: BB, DA. Supervision of the research: DA, AV. Research coordination and management: BB, AV. Funding for the research: BB, EK, DA, AV.

#### Conflict of interest

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The remaining authors have nothing to disclose.

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