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ORIGINAL RESEARCH

Cardiovascular Events After Hematopoietic Stem Cell Transplant

Incidence and Risk Factors

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ABSTRACT

BACKGROUND Hematopoietic stem cell transplantation (HSCT) is associated with various cardiovascular (CV) complications.

OBJECTIVES We sought to characterize the incidence and risk factors for short-term and long-term CV events in a contemporary cohort of adult HSCT recipients.

METHODS We conducted a multicenter observational study of adult patients who underwent autologous or allogeneic HSCT between 2008 and 2019. Data on demographics, clinical characteristics, conditioning regimen, and CV outcomes were collected through chart review. CV outcomes were a composite of CV death, myocardial infarction, heart failure, atrial fibrillation/flutter, stroke, and sustained ventricular tachycardia and were classified as short-term (≤100 days post-HSCT) or long-term (>100 days post-HSCT).

RESULTS In 3,354 patients (mean age 55 years; 40.9% female; 30.1% Black) followed for a median time of 2.3 years (Q1-Q3: 1.0-5.4 years), the 100-day and 5-year cumulative incidences of CV events were 4.1% and 13.9%, respectively. Atrial fibrillation/flutter was the most common short- and long-term CV event, with a 100-day incidence of 2.6% and a 5-year incidence of 6.8% followed by heart failure (1.1% at 100 days and 5.4% at 5 years). Allogeneic recipients had a higher incidence of long-term CV events compared to autologous recipients (5-year incidence 16.4% vs 12.1%; $P = 0.002$). Baseline CV comorbidities were associated with a higher risk of long-term CV events.

CONCLUSIONS The incidence of short-term CV events in HSCT recipients is relatively low. Long-term events were more common among allogeneic recipients and those with pre-existing CV comorbidities. (J Am Coll Cardiol CardioOnc 2023;5:821-832) © 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/).

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ABBREVIATIONS AND ACRONYMS

Bu4 = busulfan 4

CARE-BMT = University of Michigan Cardiovascular Registry in Bone Marrow Transplantation

Clo = clofarabine

CV = cardiovascular

Cy = cyclophosphamide

Flu = fludarabine

GVHD = graft-versus-host disease

HSCT = hematopoietic stem cell transplant

Mel = melphalan

TBI = total body irradiation

Hematopoietic stem cell transplant (HSCT) is a potentially curative therapy for many hematologic cancers and nonmalignant bone marrow disorders.[1] As the indications for HSCT broaden, the number of HSCTs performed annually continues to steadily rise.[2] Improvements in the safety and efficacy of HSCT have expanded its use to older adults and patients with comorbidities who are at higher risk of cardiovascular (CV) disease.

Despite the significant improvement in survival afforded by HSCT, the therapy is associated with short- and long-term complications resulting in a high burden of morbidity and mortality. Patients undergoing HSCT are subject to multiorgan injury because of the toxicity of the conditioning regimens and ensuing hyperinflammatory responses, often leading to hemodynamic instability and exacerbation of underlying comorbidities. CV complications such as cardiomyopathy, arrhythmias, acute thrombosis, pulmonary hypertension, and pericardial effusions are among the potential adverse events that occur after HSCT.[3] Long-term CV complications of HSCT, such as heart failure and atherosclerotic disease, are increasingly recognized as survival improves.

The incidence of CV complications varies widely depending on the study and is related to a variety of factors such as age at transplant, comorbid conditions, prior cardiotoxic cancer treatments, type of HSCT, and the specific conditioning regimen. However, the landscape of HSCT has rapidly evolved, and contemporary data on the incidence of CV complications are lacking. Prior data on the incidence of CV events after HSCT are primarily informed by cohorts receiving HSCT between 1980 and 2005 when high doses of cardiotoxic conditioning regimens were used more frequently. Additionally, prior studies frequently excluded HSCT recipients with known CV disease. Given the shifting demographic trends, a greater prevalence of older adults with pre-existing CV diseases is frequently being considered for HSCT.

Understanding the contemporary incidence and risk factors of CV complications can assist clinicians and institutions in establishing evidence-based risk stratification management strategies to improve HSCT outcomes from the cardiac standpoint. We sought to examine the incidence and risk factors of short- and long-term CV complications in a large, multicenter cohort of adult HSCT recipients between 2008 and 2019.

METHODS

STUDY DESIGN AND POPULATION. We conducted an observational cohort study using data from the University of Michigan Cardiovascular Registry in Bone Marrow Transplantation (CARE-BMT) to examine the incidence of CV complications and their predictors in adult patients undergoing HSCT. The registry included all adult patients (≥18 years of age) who underwent an autologous or allogeneic HSCT for malignant or nonmalignant bone marrow disorders at Michigan Medicine (n = 2,435) and Rush University (n = 919) between January 2008 and December 2019 (N = 3,354). Institutional Review Board approvals and consent procedures were obtained separately at each site according to local institutional policies.

DATA COLLECTION. Electronic medical records were reviewed to collect comprehensive information on demographics (age at transplant, sex, and race), medical history, pre-existing CV risk factors (history of smoking and body mass index), underlying hematologic diagnosis, transplant type (autologous vs allogeneic), conditioning regimen, prior cardiotoxic therapies (anthracycline use and chest radiation), and outcomes including CV events and graft-versus-host disease (GVHD). If collected before HSCT, data most recent to the start of HSCT were recorded. Data were entered into REDCap (Vanderbilt University), a secure Health Insurance Portability and Accountability Act-compliant web-based application hosted at the University of Michigan, using a standardized data collection form that provided definitions for each variable collected. We relied on the documentation of the primary health care providers (history and physical examination notes, discharge summaries, and office visits) to identify diagnoses and events. Questionable diagnoses or events were reviewed by the primary investigators (S.S.H. for the University of Michigan and T.O. for Rush University) for adjudication. Quality control was performed routinely using

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both automated approaches integrated in REDCap and a manual review of previously collected data by an independent member of the team to ensure accuracy of the data.

CONDITIONING REGIMENS AND PRIOR CANCER TREATMENT. Conditioning regimen data were available in a subset of the University of Michigan cohort (n = 2,008 [82.5%]) and were obtained through a review of the electronic medical records. Conditioning regimens were classified based on intensity as myeloablative, reduced intensity, or nonmyeloablative. All conditioning regimens for autologous HSCT are myeloablative and included melphalan (Mel); carmustine, etoposide, cytarabine, and Mel; or cyclophosphamide (Cy) with total body irradiation (TBI). For allogeneic HSCT, myeloablative conditioning included Cy/TBI, busulfan and Cy, clofarabine (Clo) and busulfan 4 (Bu4), or fludarabine (Flu) and Bu4. Reduced-intensity conditioning regimens were defined as Flu and Mel (≤140 mg/m^2), Flu and busulfan 2, or Clo and busulfan 2. Lastly, nonmyeloablative conditioning included Fl and Cy and fludarabine and low-dose TBI.

The anthracycline dose was calculated using an established method, which weights the cumulative dose of each agent in terms of its cardiotoxicity relative to doxorubicin (doxorubicin = 1, daunorubicin = 0.83, epirubicin = 0.67, idarubicin = 5, and mitoxantrone = 4). A cut point of ≥250 mg/m^2 was used to classify high and low exposure groups.[4] Prior chest radiation was classified as a binary variable (yes vs no).

CV EVENTS. CV events were identified through medical record review. The primary outcome was the incidence of CV events, defined as a composite of CV death, nonfatal myocardial infarction, need for coronary revascularization, stroke, new-onset heart failure, and new diagnosis of atrial fibrillation or flutter or sustained ventricular tachycardia. Outcomes were also examined separately. We defined short- and long-term CV events based on the timing in relation to the transplant date as follows: short-term (between transplant and ≤100 days post-transplant) and long-term (>100 days post-transplant).

STATISTICAL ANALYSIS. We report pre-HSCT demographics and clinical characteristics stratified by transplant type (autologous vs allogeneic) and institution. Categoric variables are expressed as a number and percentage, whereas continuous variables are expressed as the mean ± SD or median (25th-75th quartiles) for normally and non-normally distributed continuous data, respectively. Characteristics between autologous and allogeneic recipients were compared using chi-square tests for categoric variables and 2-sample Student's *t*-tests or Mann-Whitney *U* tests for normal and non-normal continuous variables, respectively.

Cumulative incidence curves accounting for the competing risk of non-CV death were generated for short- and long-term CV events as well as individual CV events, comparing autologous and allogeneic transplant. Cumulative incidences for short- and long-term CV events were also stratified by institution, conditioning intensity, conditioning regimens, and diagnosis requiring transplant. Incidence curve comparisons were made using Gray's test.[5] For short-term CV events, follow-up times were censored at the last known follow-up if it occurred ≤100 after transplant or at 100 days. For long-term CV events, a landmark analysis was conducted conditional on survival to 100 days post-transplant with follow-up times censored at the last known follow-up.

To identify pre-HSCT risk factors for CV events, separate Fine-Gray subdistribution hazard models were generated to account for the competing risk of non-CV death adjusted for age at transplant, sex, transplant type, and institution. We also generated a multivariable model adjusted for all risk factors as well as the interaction of each risk factor with transplant type (autologous vs allogeneic). Risk factors included age at transplant, sex, transplant type, institution, race, smoking history, body mass index, hypertension, diabetes, chronic kidney disease, coronary artery disease, atrial fibrillation/flutter, heart failure, anthracycline history ≥250 mg/m^2, and left ventricular ejection fraction. In exploratory models, we assessed whether transplant type was an effect modifier by stratifying the model by transplant type and including an interaction term between transplant type and each risk factor in a multivariable model adjusted for the other risk factors. Additionally, we examined the association between the development of GVHD and CV events in our cohort. An age-adjusted Fine-Gray subdistribution hazard model was generated with the development of GVHD as a time-dependent covariate.[6] Complete case analyses were conducted excluding patients with missing data. All model results are presented as HRs and 95% CIs. All analyses were performed using R Version 4.2.3 (R Foundation for Statistical Computing).

RESULTS

CHARACTERISTICS OF STUDY COHORT. The overall cohort had a median age of 58 years (Q1-Q3: 49-65

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TABLE 1 Baseline Characteristics by Transplant Type

	Autologous (n = 2,004)	Allogeneic (n = 1,350)	*P* Value
Demographics			
Age at transplant, y	56.6 ± 12.8	52.3 ± 13.8	<0.001
Race/ethnicity			<0.001
White	1,153 (77.5)	1,187 (87.9)	—
African American	254 (12.7)	52 (3.9)	—
Hispanic	111 (5.5)	66 (4.9)	—
Asian	44 (2.2)	23 (1.7)	—
Other	42 (2.1)	22 (1.6)	—
Male	1,190 (59.4)	792 (58.7)	0.71
Clinical characteristics			
Body mass index, kg/m^2[a]	29.7 ± 6.3	28.8 ± 6.2	<0.001
Smoking history[b]			0.032
Never	1,048 (55.2)	669 (51.4)	—
Former or current	850 (42.4)	633 (46.9)	—
Hypertension	977 (48.8)	528 (39.1)	<0.001
Diabetes mellitus	276 (13.8)	168 (12.4)	0.29
Chronic kidney disease	169 (9.3)	31 (2.3)	<0.001
Coronary artery disease	186 (9.3)	170 (12.6)	0.003
Myocardial infarction	39 (22.7)	45 (27.8)	0.34
Peripheral artery disease	32 (1.6)	23 (1.7)	0.93
Aortic aneurysm	16 (0.8)	9 (0.7)	0.45
Atrial fibrillation/flutter	108 (5.4)	71 (5.3)	0.87
Heart failure	73 (3.7)	51 (3.8)	0.93
Transplant diagnosis			
Multiple myeloma	1,062 (53.3)	29 (2.2)	<0.001
Diffuse large B-cell lymphoma	295 (14.8)	32 (2.4)	<0.001
Hodgkin lymphoma	197 (9.9)	11 (0.8)	<0.001
Acute myeloid leukemia	0 (0.0)	596 (44.2)	<0.001
Acute lymphocytic leukemia	0 (0.0)	185 (13.7)	<0.001
Myelodysplastic syndrome	0 (0.0)	179 (13.3)	<0.001
Other	437 (21.8)	318 (23.6)	<0.001
Conditioning regimen[c]			
Cy/TBI	11 (1.3)	103 (10.0)	<0.001
Mel	411 (42.2)	0 (0.0)	<0.001
Flu/Bu4	0 (0.0)	619 (59.9)	<0.001
BEAM	476 (48.9)	4 (0.4)	<0.001
Flu/Bu2	0 (0.0)	97 (9.4)	<0.001
Flu/Mel	2 (0.2)	70 (6.8)	<0.001
Flu/Cy	0 (0.0)	48 (4.6)	<0.001
Clo/Bu4	0 (0.0)	58 (5.6)	<0.001
Other	73 (7.5)	35 (3.4)	<0.001
Conditioning intensity[c]			
Myeloablative	973 (100)	793 (76.6)	<0.001
Reduced intensity	0 (0.0)	194 (18.7)	<0.001
Nonmyeloablative	0 (0.0)	48 (4.6)	<0.001
Prior cancer treatment			
Anthracycline exposure	549 (27.4)	754 (55.9)	<0.001
Anthracycline dose ≥250 mg/m^2	122 (6.1)	171 (12.7)	<0.001
Chest radiation[c]	40 (3.9)	18 (1.8)	0.05

Values are mean ± SD or n (%). [a]Missing n = 288 (8.6%). [b]Missing n = 254 (7.6%). [c]Of 1,035 (allogeneic) and 973 (autologous) patients with available data.

BEAM = carmustine, etoposide, cytarabine, and melphalan; Bu2 = busulfan 2; Bu4 = busulfan 4; Clo = clofarabine; Cy = cyclophosphamide; Flu = fludarabine; Mel = melphalan; TBI = total body irradiation.

years) and included 40.9% women; 30.1% were Black. In total, 2,004 (59.7%) and 1,350 (40.2%) received an autologous and allogeneic HSCT, respectively. When comparing characteristics by institution, HSCT recipients at Rush University were more likely to be Black (20.4% vs 4.9%); more likely to have received an allogeneic transplant (71.2% vs 55.4%); and less likely to have a history of coronary artery disease (6.0% vs 12.4%), myocardial infarction (2.3% vs 2.6%), and atrial fibrillation or flutter (4.0% vs 5.8%) (Supplemental Table 1).

Overall, the most common diagnoses requiring transplant in the autologous group were multiple myeloma (53.3%) and diffuse large B-cell lymphoma (14.8%), whereas the most common diagnoses in the allogeneic group were acute myeloid leukemia (44.2%), acute lymphocytic leukemia (13.7%), and myelodysplastic syndrome (13.3%) (**Table 1**). Compared with autologous HSCT recipients, allogeneic recipients were younger (mean 52 vs 57 years); more likely to be White (87.9% vs 77.5%); and more likely to have a history of smoking (46.9% vs 42.4%), coronary artery disease (12.6% vs 9.3%), and prior anthracycline use (55.9% vs 27.4%). Conversely, autologous HSCT recipients were more likely to have a history of hypertension (48.8% vs 39.1%) and chronic kidney disease (9.3% vs 2.3%) (**Table 1**).

Among allogeneic recipients, the majority received myeloablative conditioning (76.6%) (**Table 1**). Allogeneic recipients who received reduced-intensity conditioning were older; more likely to be Black; and had a higher prevalence of hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, and myocardial infarction (Supplemental Table 2).

INCIDENCE OF OVERALL CV EVENTS BY TRANSPLANT TYPE. Overall, 133 (4.0%) and 312 (10.2%) short- and long-term CV events occurred, respectively, over a median follow-up time of 2.3 years (Q1-Q3: 1.0-5.4 years). In autologous recipients, the cumulative incidence of CV events at 1, 5, and 10 years was 5.5%, 12.1%, and 20.0%, respectively. Allogeneic recipients had higher cumulative incidences of CV events at 1, 5, and 10 years, with rates of 7.7%, 16.4%, and 21.9%, respectively (**Table 2**). There was no difference in the incidence of short-term CV events between transplant types ($P = 0.77$) (**Figure 1**). However, allogeneic recipients had a higher incidence of long-term CV events compared to autologous recipients ($P < 0.001$) (**Figure 1**). Similar incidence rates of CV events by transplant type were observed between institutions (Supplemental Figure 1).

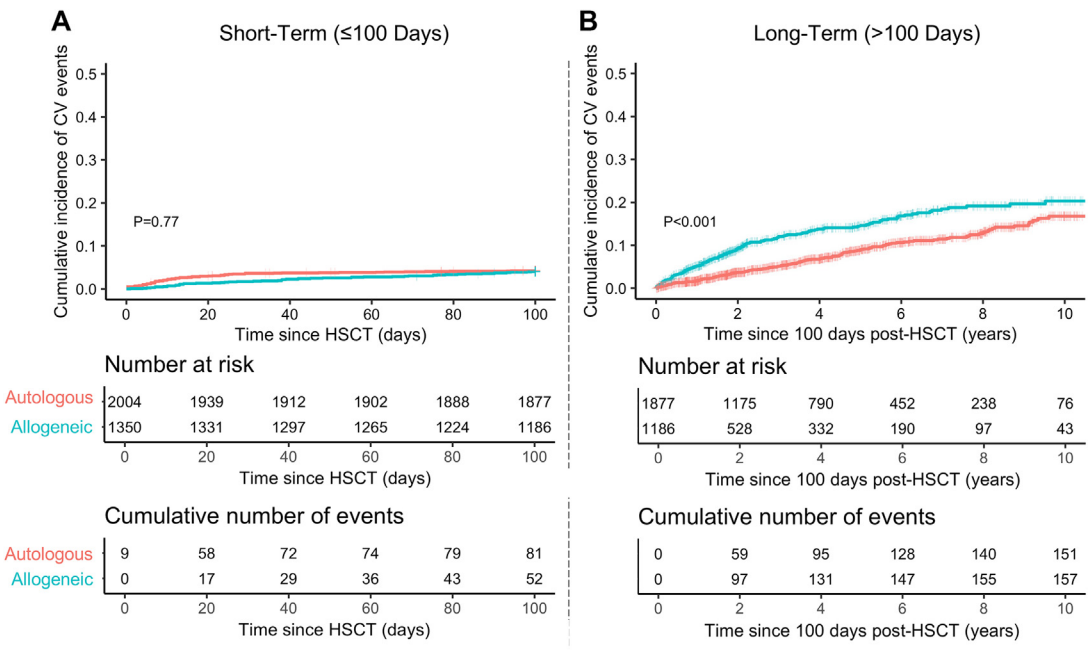
TABLE 2 Cumulative Incidence of CV Events by Transplant Type

	100 Days			1 Year			5 Years			10 Years		
	Autologous	Allogeneic	*P* Value	Autologous	Allogeneic	*P* Value	Autologous	Allogeneic	*P* Value	Autologous	Allogeneic	*P* Value
Overall	4.2	4.0	0.73	5.5	7.7	0.017	12.1	16.4	0.002	20.0	21.9	0.40
Atrial fibrillation or flutter	2.8	2.3	0.37	3.6	3.6	0.99	6.7	6.9	0.79	10.5	9.5	0.59
Heart failure	1.1	1.1	0.96	1.9	2.1	0.66	5.0	6.0	0.26	9.2	8.2	0.47
Myocardial infarction	0.2	0.6	0.09	0.3	1.6	<0.001	1.1	3.7	<0.001	2.7	6.5	0.003
Stroke	0.1	0.2	0.55	0.3	0.6	0.003	0.6	1.3	0.005	0.6	2.4	0.012
Ventricular tachycardia	0.1	0.1	0.78	0.1	0.2	0.70	0.4	0.8	0.30	0.6	1.0	0.32
CV death	0.0	0.1	0.99	0.1	0.8	0.004	0.2	1.4	0.002	0.5	2.3	0.004

CV = cardiovascular.

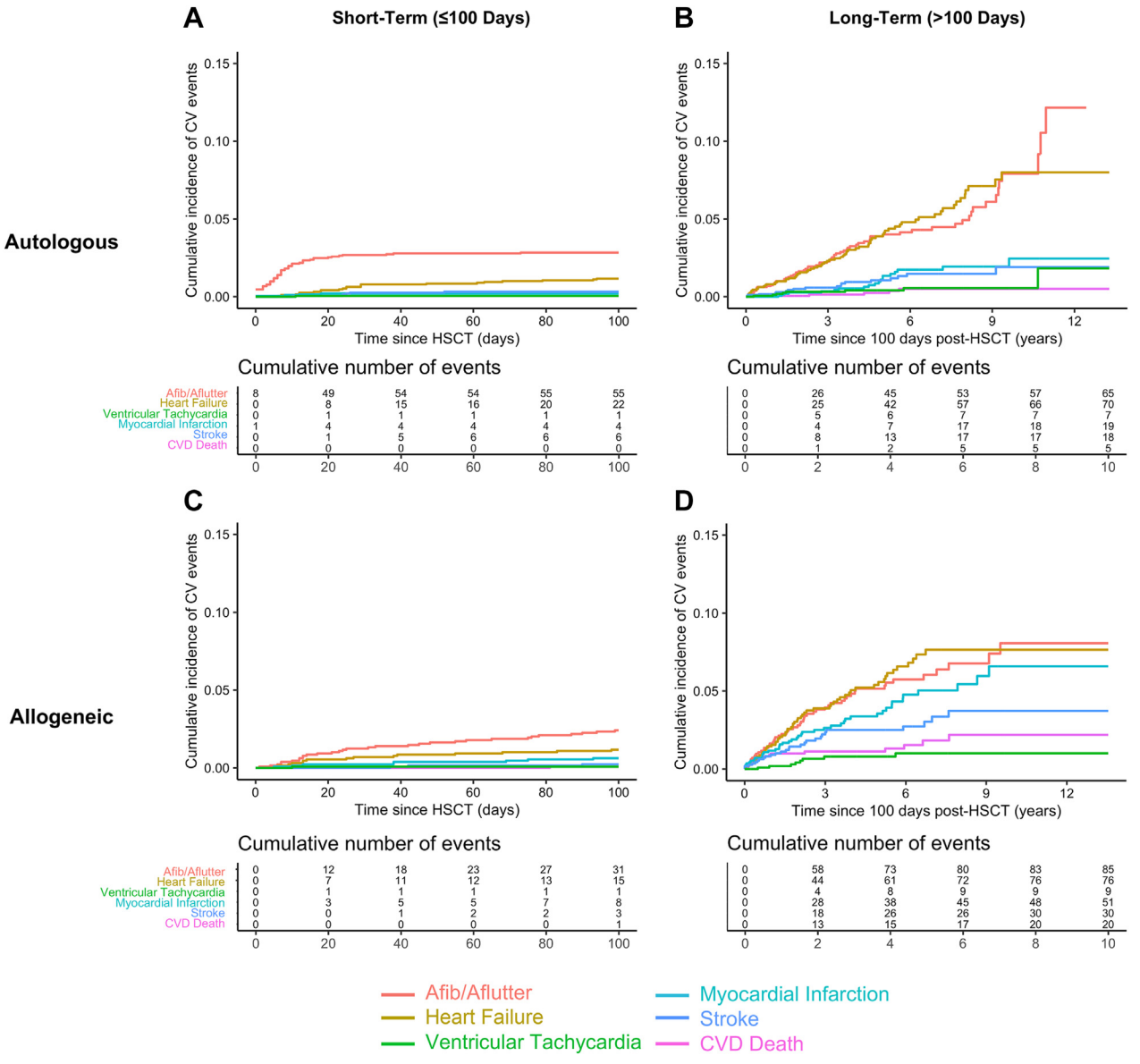
INCIDENCE OF INDIVIDUAL CV EVENTS BY TRANSPLANT TYPE. Atrial fibrillation or flutter was the most common short-term CV event in autologous and allogeneic recipients (100-day incidence = 2.8% and 2.3%, respectively) and had the highest cumulative 5-year incidence (5-year incidence = 6.7% and 6.9%, respectively) (Figure 2, Table 2). The second most common CV event was heart failure, with a 100-day incidence of 1.1% for both allogeneic and autologous recipients and a 5-year incidence of 5.0% and 6.0%, respectively. The incidence of other CV events (myocardial infarction, stroke, ventricular tachycardia, and CV death) was low. There were no differences in the rates of individual CV events between

FIGURE 1 Cumulative Incidence of CV Events by Transplant Type



Cumulative incidence curves for (A) short-term and (B) long-term cardiovascular (CV) events comparing autologous (red) and allogeneic (blue) hematopoietic stem cell transplantation (HSCT) recipients. CV events includes composite of CV death, nonfatal myocardial infarction, new-onset heart failure, and new diagnosis of atrial fibrillation or flutter or sustained ventricular tachycardia. There was no difference in the risk of short-term CV events between transplant types; however, allogeneic recipients had a higher risk of long-term CV events compared to autologous recipients.

FIGURE 2 **Cumulative Incidence of Individual CV Events by Transplant Type**



Cumulative incidence curves for (A) short-term, autologous; (B) short-term, allogeneic; (C) long-term, autologous; and (D) long-term, allogeneic cardiovascular (CV) events. Non-CV death was treated as a competing risk. CV events include CV death (pink), nonfatal myocardial infarction (light blue), new-onset heart failure (yellow), new diagnosis of atrial fibrillation/flutter (red), and sustained ventricular tachycardia (green). The most common short- and long-term CV events were atrial fibrillation (Afib)/atrial flutter (Aflutter) and heart failure. Allogeneic recipients had a higher risk of long-term myocardial infarction, ventricular tachycardia, and stroke compared to autologous recipients. CHF = congestive heart failure; CVD = cardiovascular disease; HSCT = hematopoietic stem cell transplantation.

transplant types in the short term at 100 days post-HSCT. However, in the long term, allogeneic recipients had significantly higher incidences of myocardial infarction, ventricular tachycardia, and stroke compared to autologous recipients (Table 2).

INCIDENCE OF CV EVENTS BY CONDITIONING REGIMEN. Among allogeneic recipients, the incidence rates for short-term CV events were similar between myeloablative, reduced intensity, and non-myeloablative conditioning intensities (P = 0.87)

(Supplemental Figure 2). However, in the long term, reduced intensity conditioning had a significantly higher incidence of CV events (P = 0.048) (Supplemental Figure 2). The 5-year cumulative incidence of CV events in the recipients of reduced-intensity conditioning was 21.3% compared to 16.2% in recipients of myeloablative conditioning (**Table 3**). Regarding specific conditioning regimens, the 100-day incidence CV events was highest in recipients who received Flu/Mel (7.2%) conditioning and lowest in patients who received Cy/TBI (1.8%) (Supplemental Table 3). Similarly, Flu/Mel and Clo/Blu4 had the highest 5- and 10-year cumulative incidences (10.2% and 26.0%, 10.5% and 20.3%, respectively), whereas the lowest incidence occurred in recipients who received Cy/TBI (Supplemental Table 3). The type of conditioning regimen was significantly associated with the development of myocardial infarction (P = 0.005), stroke (P = 0.004), and ventricular tachycardia (P = 0.004) (Supplemental Figure 3). Recipients who received Clo/Bu4 had the highest incidence of atrial fibrillation or flutter (5-year incidence = 12.5%). Flu/Cy was associated with the highest incidence of heart failure (5-year incidence = 15.5%). Recipients who received Flu/Mel had the highest incidence of ventricular tachycardia and cardiovascular disease death (5-year incidence = 5.7% and 4.7%, respectively) (Supplemental Table 3, Supplemental Figure 3). The recipients of Clo/Bu4 and Flu/Mel also had a higher incidence of heart failure compared to other therapies (Supplemental Table 3).

INCIDENCE OF CV EVENTS BY TRANSPLANT DIAGNOSIS. Among autologous recipients, patients diagnosed with diffuse large B-cell lymphoma had the highest incidence of short-term CV events, whereas patients diagnosed with multiple myeloma had the highest incidence of long-term CV events (Supplemental Figure 4). Allogeneic recipients diagnosed with myelodysplastic syndrome had the highest rates of both short- and long-term CV events (Supplemental Figure 4).

RISK FACTORS FOR CV EVENTS. In Fine-Gray hazard models adjusted for age, sex, transplant type, and institution, a history of chronic kidney disease was associated with a greater risk of short-term CV events, whereas a higher pretransplant body mass index was associated with a lower risk of short-term CV events (Supplemental Figure 5). In contrast, a higher pretransplant body mass index, history of hypertension, chronic kidney disease, coronary artery disease, and heart failure and a pretransplant left ventricular ejection fraction <50% were significantly associated with a greater risk of long-term CV events (Supplemental Figure 5).

TABLE 3 Incidence Rate of Cardiovascular Events by Conditioning Intensity Among Allogeneic Hematopoietic Stem Cell Transplantation Recipients

	Total (Events)	100 Days (%)	1 Year (%)	5 Years (%)
Myeloablative	793 (119)	3.9	7.0	16.2
Reduced intensity	194 (38)	3.9	8.9	21.3
Nonmyeloablative	48 (7)	4.3	8.6	15.5

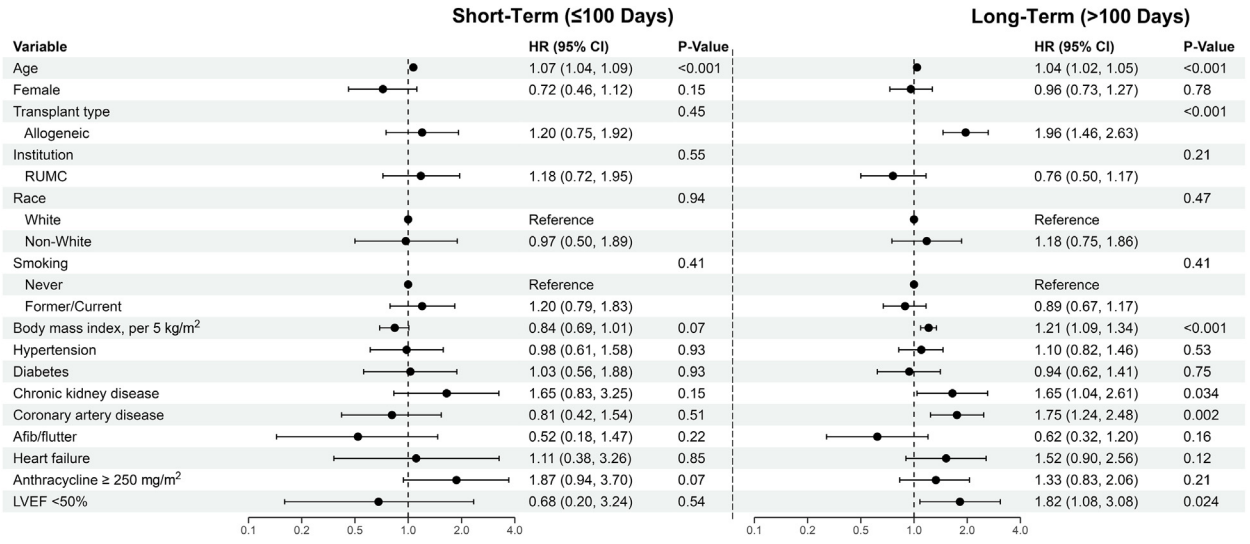
In a multivariable Fine-Gray hazard model including all risk factors, age at transplant was the only risk factor that remained significant for short-term CV events (**Figure 3**). However, older age at transplant, allogeneic recipients, a greater body mass index, lower pretransplant left ventricular ejection fraction, and a history of chronic kidney disease and coronary artery disease were all significantly associated with long-term CV events (**Figure 3**). Allogeneic recipients had a nearly 2 times greater risk of developing long-term CV events compared to autologous recipients (HR: 1.96; 95% CI: 1.46-2.63). When stratified by transplant type, similar risk factors were identified (Supplemental Figure 6). However, a history of prior anthracycline use ≥250 mg/m^2 was associated with short-term CV events in autologous but not in allogeneic recipients ($P_{interaction}$ = 0.003) (Supplemental Figure 6). Similarly, a pretransplant left ventricular ejection fraction <50% and a history of heart failure were significantly associated with a higher risk of long-term CV events in autologous recipients but not in allogeneic recipients ($P_{interaction}$ = 0.004 and 0.030, respectively) (Supplemental Figure 6). The association between transplant type and CV events did not differ significantly by race or sex ($P_{interaction}$ = 0.44 and 0.71, respectively).

Data on GVHD were available in a subset of allogeneic recipients in the University of Michigan cohort (n = 904 [83%]). Of those, 430 (48%) developed GVHD. In an age-adjusted Fine-Gray model in which GVHD was modeled as a time-dependent covariate, the onset of GVHD was significantly associated with the development of CV events (HR: 1.68; 95% CI: 1.15-2.46; P = 0.008).

DISCUSSION

We investigated the CV risks of HSCT in a large contemporary cohort of allogeneic and autologous transplant recipients. The incidence of CV events during transplant and up to 100 days post-HSCT was 4.1%. The overall 5-year cumulative incidence of CV

FIGURE 3 Pre-HSCT Multivariable Risk Model for Short- and Long-Term CV Events

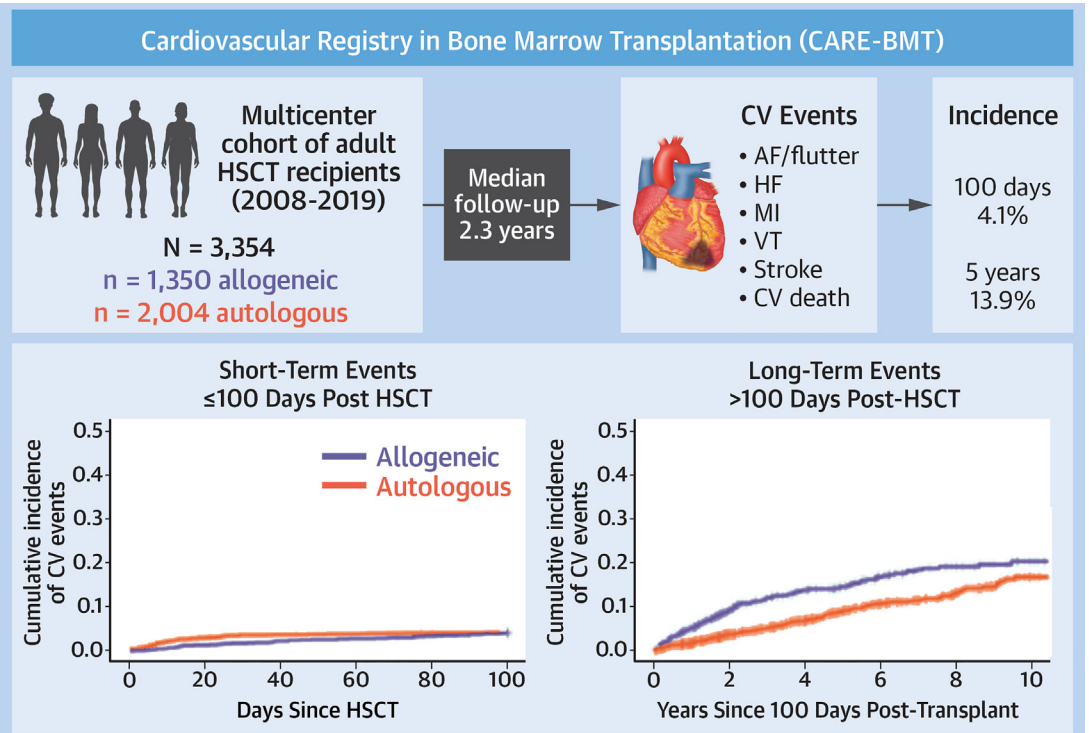


Forest plots showing HRs and 95% CIs from a multivariable Fine-Gray subdistribution hazard model for short- and long-term cardiovascular (CV) events. The multivariable model includes the following pre-transplant risk factors: age at transplant, sex, transplant type, institution, race, smoking history, body mass index, hypertension, diabetes, chronic kidney disease, coronary artery disease, atrial fibrillation/flutter, heart failure, anthracycline history ≥250 mg/m^2, and left ventricular ejection fraction (LVEF). Age, transplant type, and pre-existing CV comorbidities were associated with long-term CV risk.

events was 13.9%. The most common CV event was atrial fibrillation or flutter (6.7%-6.9%) followed by heart failure (5.0%-6.0%) (**Central Illustration**). Other severe CV events such as myocardial infarction, stroke, and CV death were uncommon. Compared to autologous recipients, allogeneic recipients had a higher incidence rate of long-term CV events (>100 days post-transplant). CV comorbidities were associated with a higher risk of long-term, but not short-term, CV events in both autologous and allogeneic recipients. Certain associations differed according to transplant type, with reduced left ventricular ejection fraction and anthracycline exposure more strongly associated with CV events in autologous HSCT recipients compared to allogeneic recipients. Overall, our study provides important contemporary data to guide the development of an evidence-based framework for the pre-HSCT CV evaluation.

Assessing CV risk is a central component of the pre-HSCT evaluation. Concerns for CV complications of HSCT emerged from the early transplant era, during which heart failure, pericarditis, and arrhythmias were reported in up to 43% of patients, attributed to the high-dose Cy included in conditioning regimens.[7,8] Prior cohort studies examining the incidence of CV complications after HSCT often included HSCT recipients between 1980 and 2005 when higher doses of cardiotoxic conditioning regimens were used more frequently. The landscape of HSCT has rapidly evolved, with improvement in patient selection, modification of conditioning regimens, and refinement of protocols for the prevention and management of complications. We report an incidence of <5% for in-hospital and peri-HSCT CV complications for both allogeneic and autologous HSCT. Our findings are congruent with a recent smaller study of 669 allogeneic recipients treated between 2009 and 2015, which reported an overall incidence of CV events of 4.5% at 100 days after transplant.[9] Atrial fibrillation or flutter was the predominant short-term CV complication, occurring in 2.8% and 2.3% of autologous and allogeneic recipients, rather than heart failure or other severe events such as myocardial infarction, stroke, or CV death, which occurred in ≤1% of patients in the first 100 days of HSCT. Prior reports have also shown that arrhythmias are the most frequent short-term CV event after HSCT with estimates ranging from 2% to 10% of adult recipients, with atrial fibrillation, atrial flutter, and supraventricular tachycardia being the most common.[9-12] These data are reassuring and

CENTRAL ILLUSTRATION **Contemporary Incidence of Cardiovascular Events After Hematopoietic Stem Cell Transplantation in the CARE-BMT Cohort**



Cumulative Incidence of CV Events by Transplant Type

	100 Days			5-Year		
	Autologous (%)	Allogeneic (%)	*P* Value	Autologous (%)	Allogeneic (%)	*P* Value
Overall	4.2	4.0	0.73	12.1	16.4	0.002
AF/flutter	2.8	2.3	0.37	6.7	6.9	0.79
HF	1.1	1.1	0.96	5.0	6.0	0.26
MI	0.2	0.6	0.09	1.1	3.7	<0.001
Stroke	0.1	0.2	0.55	0.6	1.3	0.005
VT	0.1	0.1	0.78	0.4	0.8	0.30
CV death	0.0	0.1	0.99	0.2	1.4	0.002

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The CARE-BMT (Cardiovascular Registry in Bone Marrow Transplantation) study is a contemporary, multicenter observational study of adult hematopoietic stem cell transplantation (HSCT) recipients between 2008 and 2019. The incidence of cardiovascular (CV) events during transplant and up to 100 days post-HSCT was 4.1% overall, whereas the 5-year cumulative incidence of CV events was 13.9%. There was no difference in the incidence of short-term CV by transplant type; however, allogeneic recipients had a higher incidence rate of long-term CV events. The most common CV event was atrial fibrillation (AF) or flutter followed by heart failure (HF). Other severe CV events such as myocardial infarction (MI), stroke, and CV death were uncommon. BMT = bone marrow transplant; VT = ventricular tachycardia.

indicate that contemporary protocols for HSCT are well tolerated from the CV standpoint.

Despite the greater recognition of CV events after HSCT and the changes in HSCT practices over time, long-term CV events are still high and more common years post-HSCT. Notably, we report a 10-year incidence of heart failure of 9.2% and 8.2% in autologous and allogeneic recipients, respectively, estimates comparable to what has been reported in older observational studies with 10-year estimates ranging from 5.6% to 10.8%.[13-17] Differences in estimates likely relate to differences in clinical characteristics, notably age and the prevalence of CV comorbidities. Our contemporary study population includes a greater proportion of HSCT recipients over 60 years of age (43% vs 8%-22%) and a higher prevalence of hypertension, diabetes mellitus, chronic kidney disease, and coronary artery disease compared to prior studies—all established risk factors for heart failure.[13-18] Prior studies frequently excluded HSCT recipients with a history of CV disease, contributing to these differences in patient characteristics.[13-16]

Interestingly, a low left ventricular ejection fraction was associated only with long-term CV complications, suggesting patients with low ejection fraction could tolerate HSCT. However, because of the exclusion of most patients with an ejection fraction <35% from HSCT, this finding is exploratory at best. Additionally, a greater body mass index was associated with a lower risk of short-term CV events but a higher risk of long-term CV events, likely reflecting the well-described "obesity paradox."[19] Patients undergoing HSCT with a higher body mass index may have better survival,[20-23] likely indicating less cachexia and overall better clinical status. However, in the long-term, obesity can promote chronic inflammation, leading to cardiometabolic abnormalities that are highly associated with CV disease risk. Prior anthracycline use is an established risk factor for HSCT-related complications.[24-26] We found this relationship to be heavily attenuated in this contemporary cohort, likely because of the overall lower proportion of patients with that exposure (<40%) compared to earlier studies. Similarly, the prevalence of chest radiation exposure is lower in this cohort, suggesting possible changes in treatment trends over time.

We also report differences in CV events related to transplant type and conditioning regimens. Allogeneic HSCT recipients had a higher incidence of long-term CV events compared to autologous recipients despite being younger in age on average and may be explained by the risk of GVHD. GVHD is a highly inflammatory complication of allogeneic that has been linked to vascular injury and accelerated atherogenesis.[27-30] The treatment of GVHD, which includes the use of immunosuppressants and chronic corticosteroids, contributes to a higher prevalence of post-HSCT CV risk factors such as dyslipidemia, hypertension, and insulin resistance.[31,32] Indeed, we found that the onset of GVHD in allogeneic recipients was high, with an incidence of nearly 50%, and was significantly associated with the development of CV events. Interestingly, among allogeneic recipients, those who received reduced-intensity conditioning regimens had a higher incidence of long-term CV events compared to myeloablative regimens, whereas the incidence of short-term CV events was similar. Reduced-intensity conditioning was developed as an alternative to reduce toxicities associated with conventional myeloablative conditioning.[33,34] Its use in patients perceived at higher risk of HSCT complications because of a higher burden of comorbidities and association with an increased risk of GVHD may explain this observation.[33,35]

Lastly, we found the associations between anthracycline exposure and left ventricular ejection fraction and CV events were greater in autologous compared to allogeneic HSCT recipients. Our findings are similar to a study by Armenian et al,[13] which reported a greater cardiotoxic effect of anthracycline exposure for predicting late heart failure among autologous recipients compared to allogeneic recipients, although no other studies have examined this. Although the exact mechanisms for these differences are unknown, the most likely reason is selection bias because patients perceived to be at higher risk of complications may be generally excluded from allogeneic HSCT, but others with similar profiles are likely to be accepted for autologous HSCT. Other potential explanations include the administration of high-dose chemotherapy as part of the conditioning regimen of autologous HSCT recipients, which could exacerbate pre-existing cardiomyopathy, and the potential protective effects of a "reset" of the immune system induced by allogeneic HSCT, eliminating pre-existing immune-related factors that may have contributed to the cardiomyopathy before HSCT.

STUDY STRENGTHS AND LIMITATIONS. CARE-BMT is 1 of the largest multicenter cohorts of HSCT recipients dedicated to the study of CV complications. This study provides a comprehensive assessment of contemporary incidence rates of CV complications, including examinations by transplant type, conditioning regimen, and intensity, to account for the

shifting demographics of HSCT recipients. CV events were abstracted through medical chart review by trained physicians without the reliance of billing data. The main limitation of the study is its observational nature and inability to account for confounding factors such as physician and patient decision making with regard to eligibility for transplant and their perception of risk. Accordingly, findings related to interaction analyses between transplant types such as body mass index, left ventricular ejection fraction, and condition regimens are exploratory at best. Moreover, we did not account for certain post-transplant events such as infections or immunosuppressive regimens, which may have an impact on CV events.

In conclusion, our study found that the incidence of CV events was relatively low within the first 100 days post-transplant in a contemporary cohort of adult HSCT recipients, with the most common event being atrial fibrillation or flutter. However, the incidence of long-term CV events, particularly heart failure, was higher in allogeneic recipients and in those with pre-existing CV comorbidities. These findings highlight the importance of evaluating CV risk before stem cell transplant and the need for ongoing monitoring for CV complications in the long term post-transplant, especially given the shifting demographics toward an older eligible transplant population with greater age-related comorbidities. Further research is needed to determine the best strategies for the prevention and management of these complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a contemporary cohort of HSCT recipients, the incidence of cardiovascular events is relatively low within the first 100 days post-transplant with the most common event being atrial fibrillation or flutter regardless of transplant type. However, the incidence of long-term cardiovascular events, particularly heart failure, was higher in allogeneic recipients and in those with pre-existing CV comorbidities.

TRANSLATIONAL OUTLOOK: These findings highlight the importance of evaluating cardiovascular risk before stem cell transplant and the need for ongoing monitoring for cardiovascular complications in the long-term post-transplant.

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KEY WORDS atrial fibrillation, bone marrow transplant, cardiovascular disease, heart failure, hematopoietic stem cell transplant, risk factor

APPENDIX For supplemental tables and figures, please see the online version of this paper.