Circulation

AHA SCIENTIFIC STATEMENT

Cardiovascular Management of Patients Undergoing Hematopoietic Stem Cell Transplantation: From Pretransplantation to Survivorship: A Scientific Statement From the American Heart Association

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ABSTRACT: Hematopoietic stem cell transplantation can cure various disorders but poses cardiovascular risks, especially for elderly patients and those with cardiovascular diseases. Cardiovascular evaluations are crucial in pretransplantation assessments, but guidelines are lacking. This American Heart Association scientific statement summarizes the data on transplantation-related complications and provides guidance for the cardiovascular management throughout transplantation. Hematopoietic stem cell transplantation consists of 4 phases: pretransplantation workup, conditioning therapy and infusion, immediate posttransplantation period, and long-term survivorship. Complications can occur during each phase, with long-term survivors facing increased risks for late effects such as cardiovascular disease, secondary malignancies, and endocrinopathies. In adults, arrhythmias such as atrial fibrillation and flutter are the most frequent acute cardiovascular complication. Acute heart failure has an incidence ranging from 0.4% to 2.2%. In pediatric patients, left ventricular systolic dysfunction and pericardial effusion are the most common cardiovascular complications. Factors influencing the incidence and risk of complications include pretransplantation therapies, transplantation type (autologous versus allogeneic), conditioning regimen, comorbid conditions, and patient age. The pretransplantation cardiovascular evaluation consists of 4 steps: (1) initial risk stratification, (2) exclusion of high-risk cardiovascular disease, (3) assessment of cardiac reserve, and (4) optimization of cardiovascular reserve. Clinical risk scores could be useful tools for the risk stratification of adult patients. Long-term cardiovascular management of hematopoietic stem cell transplantation survivors includes optimizing risk factors, monitoring, and maintaining a low threshold for evaluating cardiovascular causes of symptoms. Future research should prioritize refining risk stratification and creating evidence-based guidelines and strategies to optimize outcomes in this growing patient population.

Key Words: AHA Scientific Statements ■ arrhythmias, cardiac ■ atherosclerosis ■ bone marrow transplantation ■ heart failure ■ risk assessment

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for various disorders, including malignancies, bone marrow failure syndromes, and other genetic disorders.[1–3] Leukemias, aplastic anemia, lymphomas, and multiple myeloma are the most common indications for HSCT. Patients undergoing HSCT are subject to challenges to nearly all organs in that dramatic inflammatory responses lead to hemodynamic instability and exacerbate underlying comorbidities. Cardiovascular complications such as cardiomyopathy, arrhythmias, acute thrombosis, pulmonary hypertension, and pericardial effusions are potential adverse events occurring during HSCT. Long-term cardiovascular complications of HSCT such as heart failure and atherosclerotic disease are increasingly recognized as the number of survivors grows.

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Elderly patients and those with preexisting cardiovascular disease represent a growing proportion of HSCTs performed annually in the United States. They are at a greater risk of developing cardiovascular complications.[4] These concerns have led to the cardiovascular evaluation becoming a core component of the pretransplantation assessment. However, the practice varies significantly across institutions because guidelines on performing the pre-HSCT cardiovascular evaluation and managing HSCT complications are lacking.

This American Heart Association scientific statement aims to summarize the data surrounding the incidence and risk factors of HSCT-related complications and to provide guidance on the cardiovascular management of the patient undergoing HSCT, from the pre-HSCT evaluation to survivorship.

OVERVIEW OF HSCT

The process of HSCT entails eradicating recipient hematopoietic cells through chemotherapy with or without total body radiation (conditioning regimen), followed by repopulation of the bone marrow by infusion of either donor-derived cells (allogeneic HSCT) or patient-derived cells (autologous HSCT) collected before chemotherapy (Figure 1).[1] HSCT allows the delivery of high-dose cytotoxic therapies that might otherwise be fatal in conventional settings to eradicate cancer cells. Allogeneic HSCT additionally allows the replacement of abnormal or malignant host bone marrow cells, leading to subsequent donor alloreactivity and eventual development of a "graft-versus-tumor" effect that can eradicate residual cancer cells in the setting of hematologic malignancies.[2]

Phases of HSCT

The phases of HSCT can be broadly delineated as (1) the pre-HSCT workup, (2) conditioning therapy and HSCT infusion (including the inpatient stay), (3) the immediate post-HSCT period (30–100 days after infusion), and (4) long-term survivorship (>100 days after infusion). The pre-HSCT period includes the selection of the donor and collection of hematopoietic cells, evaluation for comorbidities that may affect toxicities associated with HSCT, and disease-modifying therapies (chemotherapy for malignancies, exchange transfusion for sickle cell disease) to reduce disease burden before HSCT.

Once optimized, the patient is typically admitted to a specialized HSCT inpatient unit to initiate conditioning therapy, followed by the infusion of hematopoietic cells. Specific conditioning regimens are chosen according to the recipient's underlying condition, comorbidities, and disease status and vary widely by institutional practices. Conditioning regimens are broadly classified as myeloablative (causing profound pancytopenia), nonmyeloablative (causing minimal pancytopenia), or reduced intensity (reduced doses of myeloablative regimens). Chemotherapy conditioning regimens may or may not be accompanied by total body irradiation. Symptoms occurring during conditioning include nausea and vomiting and those related to less common acute toxicities

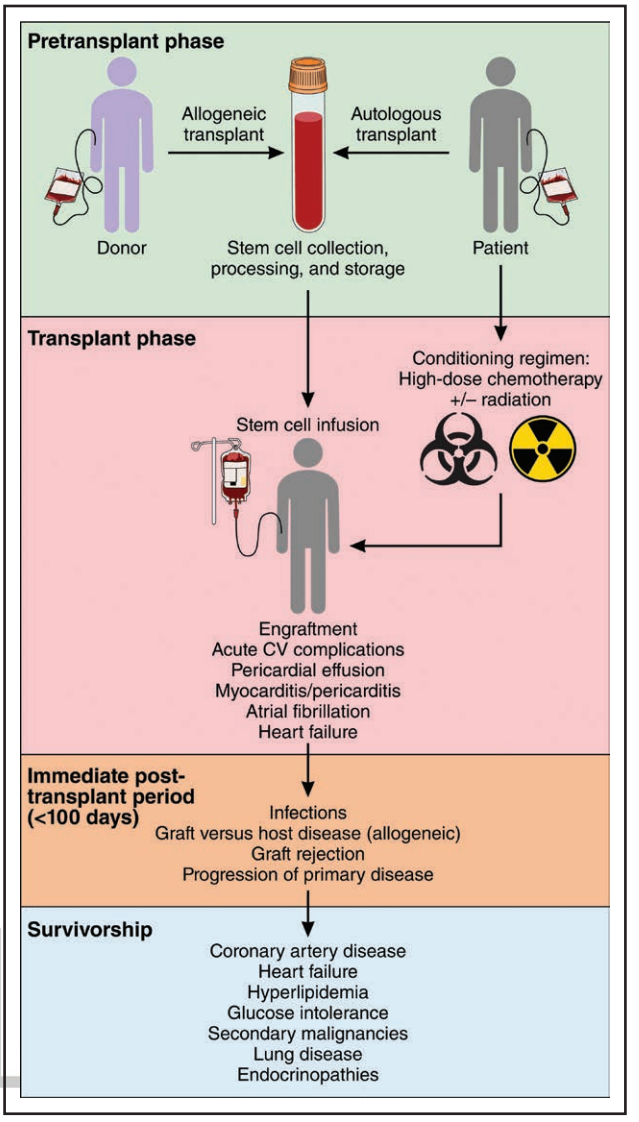

Figure 1. Phases of HSCT.
The phases of hematopoietic stem cell transplantation (HSCT) include the pretransplantation workup, transplantation, immediate posttransplantation period (30–100 days after infusion), and long-term survivorship (>100 days after infusion). The pretransplantation workup focuses on evaluating patient eligibility and comorbidities, donor selection, and harvesting of hematopoietic cells. Eligible patients then undergo conditioning therapy, followed by infusion of hematopoietic cells. Repopulation of the patient's bone marrow, or engraftment, usually occurs within 14 days after infusion. In the immediate posttransplantation phase, common complications include infections, graft rejection, and progression of primary disease and graft-vs-host disease (in allogeneic recipients) related to pancytopenia and acute inflammatory responses. Late complications during the survivorship period are often related to chemotherapy, radiation, and corticosteroid treatments. These typically manifest as cardiovascular (CV) diseases, secondary malignancies, lung disease, and endocrinopathies.

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unique to specific conditioning regimens (eg, fever from alemtuzumab and heart failure from cyclophosphamide). After conditioning, patients become pancytopenic as their bone marrow cells are destroyed and hematopoietic cells are not yet engrafted. Patients often experience mucositis, frequent blood product transfusions, and infections. Other complications that may occur in the first month after infusion include acute kidney injury, hepatic veno-occlusive disease, acute lung injury, and cardiovascular complications such as atrial fibrillation and heart failure.[1] After stem cell repopulation of the recipient's bone marrow, or engraftment, patients typically recover from acute toxicities and are discharged by postinfusion day 30.

The first 100 days are defined by close outpatient follow-up and high risk for readmission due to complications. With the maturation of hematopoietic cells during this time, allogeneic HSCT recipients are at risk for acute graft-versus-host disease (GVHD), which results from donor cells recognizing recipient antigens as foreign, causing an immune-mediated inflammatory syndrome. Much of the risk of acute toxicities of HSCT subsides after the first 100 days after infusion. In allogeneic HSCT recipients, signs of chronic GVHD may occur and require treatment.

After 100 days after HSCT, long-term survivors are at increased risk for many late effects attributable to complications of treatment with chemotherapy, radiation, and corticosteroids.[5] Common late effects include cardiovascular disease, secondary malignancies, chronic lung disease, frailty, gonadal failure, and other endocrinopathies such as metabolic syndrome and diabetes.[5–13]

Table. Incidence of Short- and Long-Term Cardiovascular Complications Related to HSCT

Complication	Short-term, %	Long-term, %
Arrhythmias		
Atrial fibrillation/flutter	2–10	5.6–10.8
Ventricular tachycardia	0.1	0.1–1.0
Heart failure	0.4–2.2	2–9.2
Pediatric-specific	<1	3
Pericarditis/myocarditis	<1–2	*
Pericardial effusion	<1–3	*
Vascular diseases		4–47
Stroke	<1	0.3–2.4
Myocardial infarction	<1	0.3–6.5
Ischemic heart disease	<1	10–15
Hypertension		15–38

HSCT indicates hematopoietic stem cell transplantation.
*No data available.

INCIDENCE OF SHORT- AND LONG-TERM CARDIOVASCULAR COMPLICATIONS IN THE ADULT AND PEDIATRIC POPULATION

Various cardiovascular complications associated with HSCT can occur during inpatient hospitalization and years after transplantation (Table). The incidence and risk of complications of HSCT are linked to several factors, including therapies received before the transplantation process, the type of transplantation (autologous versus allogeneic), the conditioning regimen, comorbid conditions, and the age of the patient.

Incidence of Acute Complications

Adult Recipients

New-onset arrhythmias are the most frequent cardiovascular complications associated with HSCT, occurring in 2% to 10% of adult recipients.[14–17] Of these, atrial fibrillation and atrial flutter are the most common, with lethal arrhythmias such as ventricular tachycardia occurring rarely.[15,17] In a large contemporary study of 3354 adult HSCT recipients between 2008 and 2019, the most common cardiovascular event within the first 100 days after HSCT was the development of atrial fibrillation or flutter, with an incident rate of 104 and 88 events per 1000 person-years in autologous HSCT and allogeneic HSCT recipients, respectively.[18] The cumulative incidence of atrial fibrillation or flutter was 2.5%. Ventricular tachycardia was rare, occurring in 0.1% of patients. Arrhythmias are associated with poor in-hospital outcomes and greater 1-year mortality.[16,19]

Studies estimate that the incidence of acute heart failure ranges from 0.4% to 2.2%.[14,20–23] Other serious cardiovascular complications such as myocardial infarction, stroke, ventricular tachycardia, or cardiovascular death are rare, occurring in 0.1% of patients in a contemporary cohort, a rate lower than previously reported (0.9%) in an older study of HSCT recipients between 1977 and 1997.[20,24] Other events such as pericardial effusion, pericarditis, and myocarditis are rare (<1%) but are associated with poorer overall survival and nonrelapse mortality.[25] Pericardial effusion and pericarditis predominantly occur early after HSCT (<100 days) and have been associated with engraftment syndrome and GVHD,[26] although the exact mechanisms in adult patients are unknown.

Pediatric Recipients

Data on pediatric patients are limited. In a single-center study of 227 pediatric HSCT recipients, 6% of patients developed left ventricular systolic dysfunction, and 27% developed a pericardial effusion of any size according to echocardiogram screenings within 100 days after HSCT.[27] Moderate to large pericardial effusions occurred in 4% to 12% of pediatric HSCT recipients.[14,27–30] Pulmonary hypertension is another potentially fatal but rare complication (<1%).[27,31]

Incidence of Long-Term Complications

Adult Recipients

Long-term HSCT survivors experience a greater incidence of cardiovascular events, including arrhythmias, ischemic heart disease, stroke, vascular disease, and rhythm disorders, compared with the general population, as well as comorbid conditions such as hypertension, hyperlipidemia, and diabetes that increase the risk of cardiovascular events.[32,33] Dyslipidemia commonly occurs after HSCT, with estimates ranging from 40% to 80%, and contributes to the risk of thromboembolic and atherosclerotic events.[34] In addition, high rates of insulin resistance after HSCT (17%–52%) place patients at higher risk of dyslipidemia.[34] Estimates of cardiovascular events after HSCT vary greatly because of differences in population risk profile, with 10-year cumulative incidence ranging from 18% to 47%.[32] Arrhythmias and heart failure are the most common long-term cardiovascular complications.[20] The 5-year incidence rates of atrial fibrillation or flutter after HSCT range between 7.1% and 10.6%.[9,36] Previously reported to range between 5.6% and 10.8%,[9,33,37–39] the 10-year incidence of heart failure appears to be consistent with contemporary data: 9.2% and 8.2% in autologous HSCT and allogeneic HSCT recipients, respectively, among patients who survived to at least 100 days after HSCT.[20]

Pediatric Recipients

In a cohort of 661 patients ≤21 years of age who received HSCT between 1995 and 2008, the 5-year incidence of cardiovascular events (including cardiomyopathy, stroke, cardiac-related death, coronary artery disease, and myocardial infarction) was 1%. Over a median follow-up of 8 years, 3% of patients experienced cardiomyopathy.[40] Cardiomyopathy secondary to iron overload is more common in the pediatric population with hematologic indications that require frequent transfusions such as β-thalassemia.[41] In a separate study of 826 adolescent and young adult HSCT recipients, the incidence of stroke, heart failure, and myocardial infarction was <1% for each.[42] Incident diabetes and dyslipidemia frequently occurred (7% and 63%, respectively), which could increase the risk of cardiovascular disease later in life.[40]

RISK FACTORS FOR CARDIOVASCULAR COMPLICATIONS

Risk factors related to cardiovascular complications of HSCT can be categorized into patient-specific factors (age, preexisting cardiovascular comorbidities), HSCT-related factors (transplantation type, conditioning regimen), and cancer-related factors (type of malignancy, prior chemotherapy, and radiation; Figure 2).

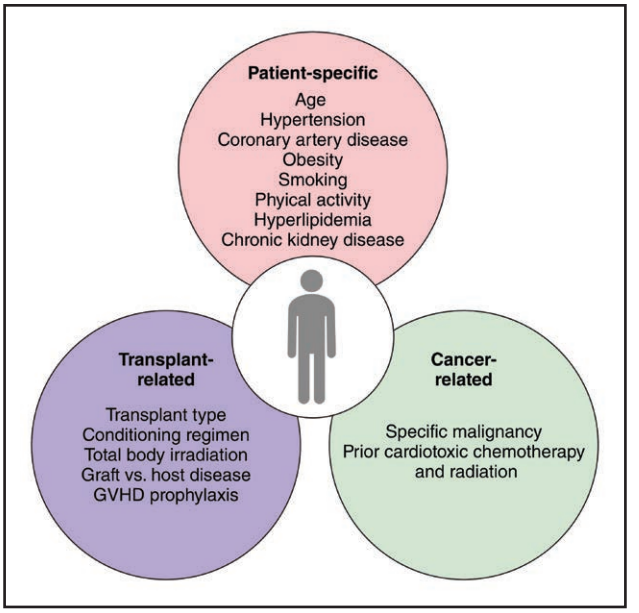


Figure 2. Risk factors for HSCT-related cardiovascular complications.
Summary of patient-specific, transplantation-related, and cancer-related risk factors for cardiovascular complications after hematopoietic stem cell transplantation (HSCT). GVHD indicates graft-vs-host disease.

Patient-Specific Factors

Comorbidities, including hypertension, chronic kidney disease, coronary artery disease, and heart failure, are important risk factors for developing short- and long-term cardiovascular complications.[20] Lifestyle factors, including obesity, smoking, and physical inactivity, have also been associated with both short- and long-term cardiovascular complications of HSCT.[9,38,43,44]

Older age at transplantation is linked to nearly all post-HSCT cardiovascular complications, including arrhythmias and heart failure.[17,38,45] The risk of heart failure in recipients >55 years of age is 4 times greater compared with recipients ≤39 years of age.[38] Age-related structural and functional changes and an increase in the prevalence of diabetes, hypertension, and obesity in older adults are likely drivers of that association.[17,38,46] One study of post-HSCT survivors found that women had a 2-fold greater risk of developing heart failure compared with men despite clinical characteristics.[38] Differences in body composition and adipose tissue distribution have been proposed as a potential explanation for sex-based differences.[47]

Preexisting cardiomyopathy, defined as reduced left ventricular ejection fraction (LVEF), has been associated with an increased risk of short- and long-term cardiovascular complications, including heart failure and atrial arrhythmias.[19,48,49] This relationship may differ according to transplantation type, with a more prominent association observed in autologous

HSCT, possibly because of this subgroup's less stringent cardiovascular exclusion criteria.[20] Some studies have suggested that survival rates and complications are similar in HSCT recipients with and those without reduced LVEF.[50,51] However, bias is highly likely because patients with reduced LVEF included in these retrospective studies were carefully selected and likely represent a subset with demonstrated cardiovascular stability. Nevertheless, these data bring into question the absolute exclusion of patients from HSCT on the basis of LVEF alone.

HSCT-Related Factors

In the early era of HSCT, during which high-dose cyclophosphamide and total body irradiation were common, conditioning regimens were the major contributors to the development of cardiovascular complications. In a contemporary cohort, fludarabine/melphalan had the highest cardiovascular event rate (100-day incidence, 7.2%; 10-year incidence, 26.0%). Fludarabine/busulfan and clofarabine/busulfan also had high 10-year incidences of cardiovascular events (20.3% and 19.3%, respectively).[20] Total body irradiation, although historically associated with metabolic syndrome and CVD,[32,52] was recently found not to be a significant contributor to the risk of cardiovascular events after HSCT.[20,53,54] Whether reduced-intensity conditioning leads to lower incidence of cardiovascular events is unclear because it is often adopted in HSCT recipients who are perceived to be at higher risk of developing cardiovascular events, including those with a higher prevalence of preexisting cardiovascular comorbidities.[19,20,55,56]

Allogeneic HSCT recipients are at higher risk of long- but not short-term cardiovascular events compared with autologous HSCT recipients.[20,54] The difference could be explained partly by the occurrence of GVHD in allogeneic HSCT recipients, which is associated with a 68% increased risk of cardiovascular events after accounting for age at transplantation and sex.[20] GVHD is a common complication of allogenic HSCT that leads to a hyperinflammatory state, promoting vascular injury and atherogenesis.[57–60] In addition, the treatment of GVHD, which includes immunosuppressants, contributes to a higher prevalence of post-HSCT cardiovascular risk factors such as dyslipidemia, hypertension, and insulin resistance.[32,61]

Cancer-Related Factors

Data on differences in cardiovascular events related to specific malignancies treated with HSCT are limited. One study examined the incidence of short- and long-term cardiovascular events of the most common transplantation diagnoses for autologous and allogeneic transplantation, which included leukemias, lymphomas, multiple myeloma, and myelodysplastic syndrome. Among autologous HSCT recipients, recipients with diffuse large B-cell lymphoma had the highest rate of short-term cardiovascular events (100-day incidence, 7.0%); however, recipients with multiple myeloma had the highest incidence of long-term cardiovascular events >5 years after HSCT (10-year incidence, 23.0%).[20] Allogeneic HSCT recipients with myelodysplastic syndrome had the highest rates of cardiovascular events at all follow-up times (100-day incidence, 2.9%; 10-year incidence, 15.0%).[20]

Several therapies for hematologic malignancies treated with HSCT are associated with cardiotoxicity. Anthracyclines, used in close to 50% of HSCT candidates, have been linked to an increased risk of heart failure and cardiovascular death in a dose-dependent manner, with cumulative doses >250 mg/m^2 identified as a cut point for heart failure risk.[19,20,24,38,62] Although anthracycline use has decreased over time, newer cancer therapies, including monoclonal antibodies,[63,64] proteosome inhibitors,[65,66] immunomodulatory agents,[67,68] and tyrosine kinase inhibitors,[69–71] all confer a small risk of cardiotoxicity independently of their role in HSCT. Otherwise, beyond anthracyclines, there are no data on synergistic cardiotoxicity between pre-HSCT cancer therapy and HSCT.

MECHANISMS OF CARDIAC COMPLICATIONS

The pathogenesis of cardiovascular disease after HSCT is multifactorial and results from multiple cardiovascular insults throughout the HSCT process, often exacerbating preexisting cardiovascular disease. Known mechanisms include direct endothelial injury related to the conditioning regimen, the acute hyperinflammatory state secondary to engraftment syndrome, and chronic inflammation in GVHD.

High-dose alkylating agents in conditioning regimens such as cyclophosphamide can cause various cardiovascular complications, including heart failure, atrial arrhythmias, pericardial effusion, and myocarditis through inflammatory and oxidative stress pathways.[72,73] Cardiotoxicities from busulfan, carmustine, and melphalan are rare.[74–77] Inflammation, oxidative stress, calcium homeostasis alterations, and programmed cell death are mechanisms involved in cardiotoxicity caused by alkylating agents.[78–81] These agents cause endothelial dysfunction, calcium overload, myocardial damage, and apoptosis activation in the myocardium.[79–81] Reduced-intensity conditioning was developed as a less toxic alternative for certain patients.[54]

Postconditioning, infusion of the hematopoietic stem cells, and engraftment can lead to cardiovascular complications, primarily by affecting hemodynamics. Dimethyl sulfoxide, a standard cryoprotective agent used

to preserve hematopoietic stem cells, has been linked to hypertension and bradycardia, which are generally manageable.[82] Contributors to the effect of dimethyl sulfoxide include its dose, cell lysis products, red blood cell content, total nuclear cell content, and acute volume expansion, as well as the recipient's age.[82]

Engraftment syndrome is an early complication of HSCT characterized by the release of proinflammatory cytokines, resulting in activated leukocytes, endothelial injury, and vascular leak.[83] This hyperinflammatory state can exacerbate preexisting cardiovascular conditions and induce acute heart failure and arrhythmias at least partially through acute hemodynamic changes.[83]

Chronic inflammation and oxidative stress due to endothelial injury are key to the development of long-term atherosclerosis after HSCT.[44,59,60] Radiation therapy, a component in the treatment of various malignancies and conditioning regimens, causes direct cellular injury, leading to an upregulation of proinflammatory markers and oxidative stress–mediated chronic inflammation.[84,85] Subsequent chronic oxidative stress and inflammation induce endothelial cell proliferation, impaired remodeling, vascular thickening, fibrosis, and thrombi formation in arteries, which can progress to premature atherosclerosis and coronary artery disease.[86]

The inflammatory state induced by GVHD promotes vascular injury and plaque instability, leading to accelerated atherosclerosis and predisposing recipients to arterial complications.[57–60] The onset of GVHD also has been associated with the development of established cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia, which are thought to stem from adverse effects of immunosuppression from steroids, calcineurin inhibitors, and other agents used to treat GVHD.[61,87] Other GVHD prophylactic therapies have reports of early cardiac toxicities after HSCT, including posttransplantation cyclophosphamide, methotrexate, and tacrolimus, although data on incidence rates are limited.[55]

Maintenance immunomodulatory therapies such as lenalidomide given after HSCT in patients with multiple myeloma can increase the risk of venous thromboembolism and stroke, although rare when these therapies are given in conjunction with anticoagulants. Lenalidomide increases platelet aggregation, cytokine production, and the activity of endothelial tissue factor, contributing to thrombosis.[88,89]

THE PRE-HSCT CARDIOVASCULAR EVALUATION

There are no published evidence-based guidelines on pre-HSCT cardiovascular screening or assessment. Current management strategies are based primarily on expert opinion. The protocols for pre-HSCT assessment vary widely, with most centers establishing institutional guidelines for determining HSCT eligibility and referring for a cardiovascular evaluation.

The approach of cardiovascular specialists differs between pediatric and adult HSCT recipients. For the pediatric patient, greater emphasis is placed on preempting late complications of therapy. In the older adult, the focus is on optimizing comorbid conditions that may compromise the ability of the patient to withstand the challenges of the immediate peritransplantation period such as sepsis, severe anemia and thrombocytopenia, significant fluid and electrolyte disturbances, and major organ dysfunction.

There are 4 steps in the pre-HSCT cardiovascular evaluation: (1) initial risk stratification, (2) exclusion of high-risk cardiovascular disease, (3) assessment of cardiac reserve, and (4) optimization of cardiovascular reserve (Figure 3).

Identifying Patients at Risk of Cardiovascular Complications

Identifying HSCT recipients at risk of cardiovascular complications is challenging because of the variability of recipient characteristics, the relatively low incidence of cardiovascular events, and different influencing factors. The CARE-BMT (Cardiovascular Registry in Bone Marrow Transplantation) risk score is an externally validated, simple-to-calculate, point-based, pre-HSCT risk score derived from a large, contemporary multicenter cohort of adult allogeneic and autologous HSCT recipients (n=2435).[90] The risk model includes the following variables: age at transplantation, transplantation type, race, history of coronary artery disease, heart failure, peripheral artery disease, creatinine, triglycerides, and prior anthracycline exposure (Figure 4).[90] Outcomes included a composite of cardiovascular death, myocardial infarction, heart failure, stroke, atrial fibrillation or flutter, and sustained ventricular tachycardia. The CARE-BMT risk score ranges from 0 to 16 points (Figure 4). The areas under the curve for predicting cardiovascular events at 100 days, 1 year, 5 years, and 10 years after HSCT were 0.66, 0.71, 0.73, and 0.76, respectively. The model performed equally well in autologous and allogeneic HSCT recipients. The final risk model identified low-risk (0–1 point; 5-year cumulative incidence, 3.8%), intermediate-risk (2–4 points; 5-year cumulative incidence, 12.7%), and high-risk (≥5 points; 5-year cumulative incidence, 31.5%) groups. The CARE-BMT risk model is currently the only risk score developed in adult HSCT recipients using pre-HSCT variables aimed at predicting cardiovascular events.[90]

Other studies have examined risk models predicting long-term cardiovascular complications in pediatric or mixed (adults and pediatric) survivors of HSCT and have limited usefulness in the pre-HSCT cardiovascular risk stratification of adult patients.[11,29,91]

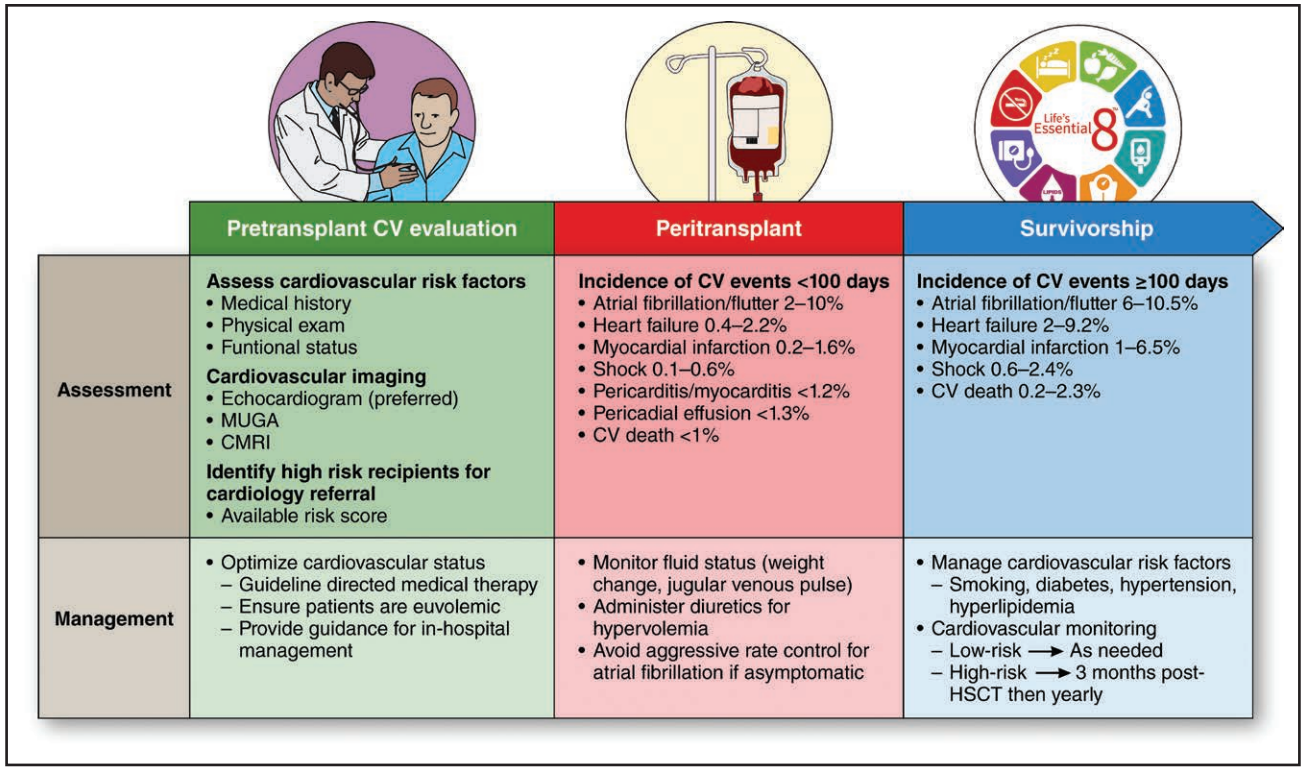


Figure 3. The HSCT cardiovascular evaluation and management.
The cardiovascular (CV) assessment is a critical component at all stages of the hematopoietic stem cell transplantation (HSCT). Before transplantation, determining a patient's risk of cardiovascular complications is essential to evaluate eligibility and safety. This preliminary cardiovascular examination includes a thorough assessment of cardiovascular risk factors and cardiovascular imaging, preferably with echocardiography. The application of risk scores such as CARE-BMT (Cardiovascular Registry in Bone Marrow Transplantation) aids in identifying patients at high risk, warranting more comprehensive evaluation. To prepare for transplantation, patients should receive guideline-directed medical therapy as required, in addition to optimizing their cardiovascular status. During the transplantation process, it is crucial to frequently monitor for acute cardiovascular complications, the most common being atrial fibrillation or flutter and heart failure. Management at this stage includes monitoring fluid balance and administering diuretics in cases of hypervolemia. The posttransplantation phase, specifically after 100 days, shifts focus toward long-term survival and monitoring for long-term cardiovascular complications. For low-risk patients, cardiovascular monitoring can be done as necessary. However, high-risk patients should undergo cardiovascular imaging, preferably an echocardiogram, 3 months after the transplantation, followed by annual checkups. CMRI indicates cardiac magnetic resonance imaging; and MUGA, multiple gated acquisition scan.

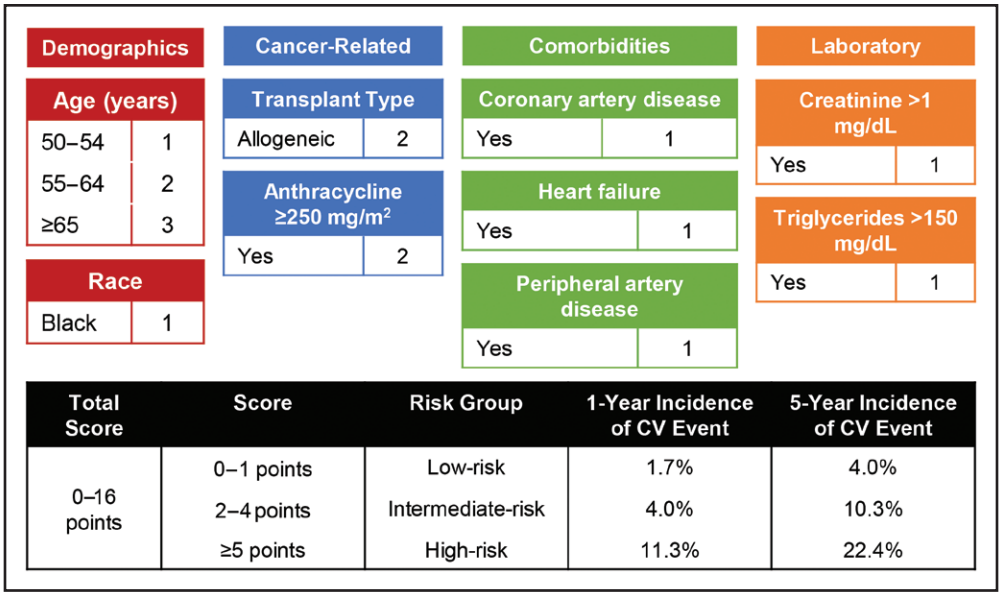
The Hematopoietic Cell Transplantation–Comorbidity Index is widely used in oncology settings to predict nonrelapse mortality and overall survival in patients being considered for HSCT on the basis of the presence of several pretransplantation comorbidities (Figure 5).[92] The Index assigns a weighted score to various comorbidities, including coronary artery disease, congestive heart failure, history of myocardial infarction, or ejection fraction <50%, with total scores ranging from 0 to 29. The C statistic for predicting nonrelapse mortality at 2 years is 0.69.[92] Although the Hematopoietic Cell Transplantation–Comorbidity Index score has clinical implications for transplantation eligibility, this score was not derived to specifically examine the risk of cardiovascular events, nor has it been associated with cardiovascular events in other studies.

Although risk scores are useful for systematic screening and referrals, they do not account for patient symptoms. Patients who exhibit signs or symptoms of potential undiagnosed cardiovascular disease should be referred for further evaluation.

Exclusion of High-Risk Cardiovascular Disease

There are no absolute cardiovascular contraindications to HSCT in the stable outpatient. However, high-risk cardiovascular conditions with poor cardiac reserve such as advanced heart failure, untreated severe valvular heart disease, and severe triple-vessel or left main obstructive coronary artery disease are associated with poor outcomes (1-year survival, 30%–50%) regardless of HSCT and preclude candidacy unless a pre-HSCT corrective intervention is possible. Thus, the most critical step in the pretransplantation assessment is to rule out the presence of high-risk cardiovascular disease through a detailed history and physical examination, along with the indicated testing.

Assessment of cardiac function is routinely performed before HSCT. Most institutional guidelines exclude



Total Score	Score	Risk Group	1-Year Incidence of CV Event	5-Year Incidence of CV Event
0–16 points	0–1 points	Low-risk	1.7%	4.0%
	2–4 points	Intermediate-risk	4.0%	10.3%
	≥5 points	High-risk	11.3%	22.4%

Figure 4. Calculating the CARE-BMT risk score for cardiovascular risk stratification.
Points are assigned for age, race, transplantation type, anthracycline dosage, comorbidities, and laboratory values, summing to a total risk score. The total score, which ranges from 0 to 16, classifies patients into low-risk (0–1 points), intermediate-risk (2–4 points), and high–risk (≥5 points) groups for the 1-year and 5-year incidence of cardiovascular (CV) events after transplantation, with corresponding percentages shown for each risk category. CARE-BMT indicates Cardiovascular Registry in Bone Marrow Transplantation. Modified with permission from Vasbinder et al.[90] © 2024, American Heart Association, Inc.

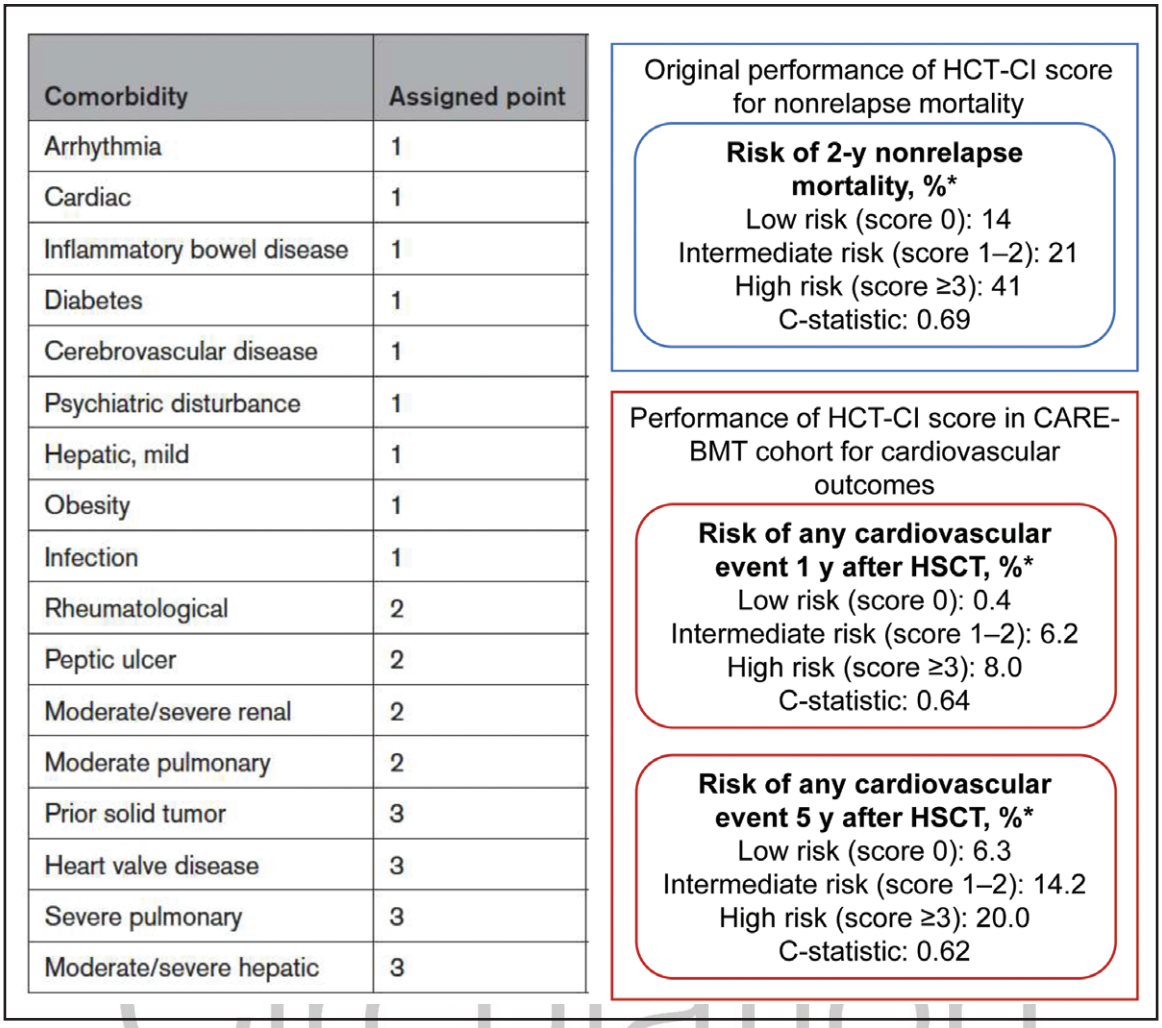
patients with an ejection fraction ≤35% from HSCT candidacy. The data surrounding that exclusion criterion are limited, and likely, a subset of patients with preexisting cardiomyopathy and optimized cardiovascular status would fare well through HSCT.[51,93,94] Echocardiography is preferred as the initial test because it allows the examination of various parameters beyond left ventricular function, including chamber sizes, valvular regurgitation or stenosis, and estimation of intracardiac pressures (diastolic function). In the unlikely situation in which echocardiography is not available or images are poor despite contrast, either cardiac magnetic resonance imaging or multiple gated acquisition scan can be used to estimate LVEF.[95] Cardiac magnetic resonance imaging has the additional benefits of providing both detailed morphological and functional data without the use of radiation; however, its limited availability and high costs make widespread use challenging. Multiple gated acquisition scan provides data limited to chamber sizes and biventricular ejection fraction, but it is more accessible.[95]

A review of previously performed computed tomography imaging studies can provide valuable information on the presence of coronary and aortic calcifications. Signs of atherosclerotic disease should prompt initiation of statin therapy in the absence of contraindications. HSCT candidates with a high pretest probability of coronary artery disease and poor exercise tolerance, with or without angina, should be evaluated for high-risk ischemia. Coronary computed tomography angiography and myocardial stress perfusion imaging are valuable for evaluating high-risk ischemic heart disease. Coronary angiography and revascularization should be limited in patients with high-risk coronary artery disease and those with angina refractory to medical therapy to avoid delaying HSCT and in anticipation of developing thrombocytopenia during HSCT.

Evaluating Cardiac Reserve

Once the probability of high-risk cardiovascular disease is deemed low, the next step in the pre-HSCT cardiovascular evaluation is the assessment and optimization of cardiovascular reserve, or the ability of the cardiovascular system to withstand stressors imparted by the HSCT process, including the cardiotoxicity of conditioning regimens, rapid volume shifts, and increased oxygen demand due to anemia and the systemic inflammatory response. Quantifying cardiovascular reserve relies on a detailed assessment of symptoms attributable to cardiovascular disease, functional status, risk factors, signs of increased intracardiac pressures on examination, and cardiovascular structure and function.

The history and physical examination aim to determine the contribution of cardiovascular disease to the patient's symptoms.[96] For example, jugular venous distention in a patient with HSCT should prompt additional workup given its high positive predictive value for heart failure. In contrast, a low jugular venous pulse is reassuring. An assessment of exercise tolerance is crucial because the absence of symptoms of heart failure in patients with poor exercise capacity is not meaningful. Poor cardiopulmonary fitness is common in patients with multimorbidity, especially those with cancer, who experience rapid muscle



Comorbidity	Assigned point
Arrhythmia	1
Cardiac	1
Inflammatory bowel disease	1
Diabetes	1
Cerebrovascular disease	1
Psychiatric disturbance	1
Hepatic, mild	1
Obesity	1
Infection	1
Rheumatological	2
Peptic ulcer	2
Moderate/severe renal	2
Moderate pulmonary	2
Prior solid tumor	3
Heart valve disease	3
Severe pulmonary	3
Moderate/severe hepatic	3

Figure 5. The HCT-CI Score and its Predictive Performance for CV Events.
The figure presents the components of Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score and its predictive performance for cardiovascular outcomes in the CARE-BMT cohort. It delineates the risk percentages for 2-year non-relapse mortality in the original HCT-CI study, and cardiovascular events at 1- and 5-year intervals post-hematopoietic stem cell transplantation (HSCT) in the CARE-BMT cohort, stratified by low, intermediate, and high-risk categories based on HCT-CI scores. Additionally, the figure includes C-statistic values to quantify the predictive accuracy of the HCT-CI score for each outcome. Note the relatively poor performance of the HCT-CI score in predicting cardiovascular outcomes.

wasting and adverse effects related to their treatment.[97] There are currently no objective criteria defining adequate or inadequate exercise capacity. The Eastern Cooperative Oncology Group and Karnofsky scores are derived from questionnaires routinely used by oncologists to assess patients' ability to perform daily activities, from which one may infer exercise tolerance.[98,99] Maximal oxygen consumption (Vo_2max) obtained with cardiopulmonary stress testing is a highly validated measure used as an outcome in several exercise studies in patients undergoing HSCT.[97] The 6-minute walk test is a simpler alternative that is well validated in certain patient populations such individuals with pulmonary hypertension, but data are lacking in patients with HSCT.[100] Specific risk thresholds have yet to be determined. Nevertheless, a lack of improvement in exercise tolerance after a 2-week daily exercise regimen suggests pathology beyond frailty that warrants investigation.[101,102] Ongoing studies are examining the clinical utility of a prerehabilitation (prehab) exercise program to improve the cardiopulmonary fitness of HSCT candidates, their HSCT outcomes, and their quality of life.[97]

Optimizing Cardiac Reserve

Every effort to optimize patients' cardiovascular status should be made before HSCT, including treating reversible disease; optimizing volume status and blood pressure; and maximal dosing of guideline-directed medical therapy.[103] Patients with adequate cardiopulmonary reserve, defined as having adequate exercise tolerance (≥4 metabolic equivalents) without experiencing cardiovascular symptoms and on optimal medication regimen, should still be considered for HSCT regardless of whether their cardiac function, as measured by LVEF, has

recovered. Excluding patients from HSCT for cardiovascular reasons should be limited to the occasional patient with severe, nontreatable disease, poor cardiopulmonary reserve, or a life expectancy of <1 year.

IN-PATIENT MANAGEMENT OF ACUTE CARDIOVASCULAR COMPLICATIONS

Providing early guidance to the hematology and oncology teams as to the management of the possible exacerbation of comorbid cardiovascular conditions such as heart failure and atrial fibrillation during transplantation is essential. Iatrogenic volume overload is common in patients with cancer.[104–108] Because large volumes of fluids are administered during HSCT, patients at risk for heart failure should undergo daily weight monitoring, with diuretics administered for 2- to 3-lb fluctuations within 24 hours to avert hypervolemia.[105] Moreover, volume shifts and systemic inflammation related to engraftment or infections can trigger supraventricular arrhythmias, most commonly atrial fibrillation. Because the circumstances during which atrial fibrillation or flutter may occur can vary significantly, individualizing the treatment approach is essential. Avoiding aggressive rate control is recommended if the patient is asymptomatic and hemodynamically stable. Hypervolemia often triggers and maintains atrial fibrillation; hence, careful assessment for hypervolemia and administration of diuretics should precede rate control initiation. Cardioversion and rhythm control strategies should be reserved for urgent scenarios (eg, hemodynamic instability) in patients receiving HSCT because they frequently experience thrombocytopenia and cannot undergo anticoagulation. The management of acute myocardial infarction during HSCT presents analogous complexities, particularly in the context of the pancytopenic phase, with respect to anticoagulation risk. In the absence of high-risk features and when symptoms have resolved, it may be judicious to defer percutaneous coronary angiography until the thrombocytopenia has abated, thereby mitigating the potential life-threatening hemorrhagic complications associated with the application of heparin and dual antiplatelet therapy. Conversely, the presence of high-risk indicators such as ST-segment elevation, ischemic cardiomyopathy, or persistent chest discomfort unresponsive to conventional medical intervention should not deter timely therapeutic measures. Strategically managing these scenarios through serial platelet transfusions in the periprocedural context, eschewing glycoprotein IIb/IIIa inhibitors, and postponing the initiation of a secondary antiplatelet agent until platelet count restoration can effectively attenuate the inherent bleeding risks in this clinical setting. Last, special consideration must be given to the risk of drug-drug interactions with concurrent cancer therapeutics related to alterations in the cytochrome P450 or P-glycoprotein metabolism.[109,110]

SURVIVORSHIP AND MANAGEMENT OF LONG-TERM CARDIOVASCULAR COMPLICATIONS

HSCT survivors experience a higher burden of cardiovascular risk factors and long-term events, including cardiomyopathy, ischemic heart disease, stroke, peripheral vascular disease, and rhythm disorders, than the general population. Guidelines on screening and preventive measures for vascular complications in long-term HSCT survivors have been published by the American Society of Blood and Bone Marrow Transplantation.[111,112] The optimization of cardiovascular risk factors and monitoring are cornerstones of the long-term cardiovascular management of HSCT survivors.[10] There are no data to guide the optimal frequency of monitoring in HSCT survivors, with existing guidelines focusing on cardiovascular monitoring of the broader adult cancer survivor population. A 3-month cardiovascular assessment after HSCT in patients with preexisting cardiovascular disease is typical in many institutions, with earlier evaluations in patients who experienced complications during HSCT. Patients are then seen every 1 to 3 years, with factors such as cardiovascular comorbidity burden dictating the frequency of monitoring.[5] A risk score such as CARE-BMT in adults and pediatric-specific risk models could potentially help identify patients who will require more frequent assessments.[29,90,91]

Given the overall higher risk of this patient population, a low threshold to evaluate for cardiovascular causes of symptoms should be maintained.[95] Routine imaging during or after HSCT is not typically recommended for low-risk, asymptomatic individuals. Individuals considered at high risk for developing cardiovascular complications may benefit from routine imaging surveillance in survivorship with echocardiography.[95] Cardiac biomarkers (cardiac troponin and BNPs [B-type natriuretic peptides]) are useful for the overall diagnosis and management of cardiovascular complications. However, there are no data supporting their systematic measurement for cardiovascular monitoring in asymptomatic patients. No guidelines prescribe exact time frames for imaging surveillance in HSCT recipients, although yearly assessment of echocardiography has been recommended for symptomatic cancer survivors.[113] The frequency of monitoring should be made considering individual patient characteristics.[5,95]

Pediatric Considerations

The International Late Effects of Childhood Cancer Guideline Harmonization Group has released updated cardiomyopathy surveillance guidelines for childhood cancer survivors, which recommend echocardiographic surveillance in asymptomatic patients every 2 years for those who received a cumulative anthracycline dose ≥250 mg/m^2 or chest radiation therapy ≥30 G or anthracycline ≥100 mg/m^2 and chest radiation ≥15 Gy.[114] Survivors who received 100 to <250 mg/m^2 anthracycline or 15 to <30 Gy radiation should undergo surveillance every 5 years.[10]

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FUTURE DIRECTIONS

As HSCT use expands to an aging population with multimorbidity, cardiovascular specialists' role in patient management grows increasingly important. Multidisciplinary collaboration among health care professionals is crucial for driving advancements in this field, ensuring optimal care for this complex patient population. Future research should prioritize refining risk stratification and creating evidence-based guidelines and strategies to optimize outcomes.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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†Significant.

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REFERENCES

1. Rotz SJ, Ryan TD, Hayek SS. Cardiovascular disease and its management in children and adults undergoing hematopoietic stem cell transplantation. *J Thromb Thrombolysis*. 2021;51:854–869. doi: 10.1007/s11239-020-02344-9
2. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813–1826. doi: 10.1056/NEJMra052638
3. Wilcox NS, Rotz SJ, Mullen M, Song EJ, Ky Hamilton B, Moslehi J, Armenian SH, Wu JC, Rhee JW, Ky B. Sex-specific cardiovascular risks of cancer and its therapies. *Circ Res*. 2022;130:632–651. doi: 10.1161/CIRCRESAHA.121.319901
4. Phelan R, Chen M, Bupp C, Bolon YT, Broglie L, Brunner-Grady J, Burns LJ, Chhabra S, Christianson D, Cusatis R, et al. Updated trends in hematopoietic cell transplantation in the United States with an additional focus on adolescent and young adult transplantation activity and outcomes. *Transplant Cell Ther*. 2022;28:409.e1–409.e10. doi: 10.1016/j.jtct.2022.04.012
5. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C, Burns LJ, Chaudhri N, Davies S, Okamoto S, et al; Center for International Blood and Marrow Transplant Research. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2012;47:337–341. doi: 10.1038/bmt.2012.5
6. Rotz SJ, Ryan TD, Hlavaty J, George SA, El-Bietar J, Dandoy CE. Cardiotoxicity and cardiomyopathy in children and young adult survivors of hematopoietic stem cell transplant. *Pediatr Blood Cancer*. 2017;64:e26600. doi: 10.1002/pbc.26600
7. Hurria A, Jones L, Muss HB. Cancer treatment as an accelerated aging process: assessment, biomarkers, and interventions. *Am Soc Clin Oncol Educ Book*. 2016;35:e516–e522. doi: 10.1200/EDBK_156160
8. McDonald AM, Chen Y, Wu J, Hageman L, Francisco L, Kung M, Wong FL, Ness E, Landier W, Battles K, et al. Total body irradiation and risk of breast cancer after blood or marrow transplantation: a blood or marrow transplantation survivor study report. *J Clin Oncol*. 2020;38:2872–2882. doi: 10.1200/JCO.20.00231
9. Armenian SH, Sun C-L, Francisco L, Steinberger J, Kurian S, Wong FL, Sharp J, Sposto R, Forman SJ, Bhatia S. Late congestive heart failure after hematopoietic cell transplantation. *J Clin Oncol*. 2008;26:5537–5543. doi: 10.1200/JCO.2008.17.7428
10. Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GM, Huang JT, Pelletier W, Perkins JL, Rivard LS, Schechter T, et al. Late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation: a Children's Oncology Group report. *Biol Blood Marrow Transplant*. 2016;22:782–795. doi: 10.1016/j.bbmt.2016.01.023
11. Armenian SH, Yang D, Teh JB, Atencio LC, Gonzales A, Wong FL, Leisenring WM, Forman SJ, Nakamura R, Chow EJ. Prediction of cardiovascular disease among hematopoietic cell transplantation survivors. *Blood Adv*. 2018;2:1756–1764. doi: 10.1182/bloodadvances.2018019117
12. Sun CL, Francisco L, Kawashima T, Leisenring W, Robison LL, Baker KS, Weisdorf DJ, Forman SJ, Bhatia S. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2010;116:3129–3139; quiz 3377. doi: 10.1182/blood-2009-06-229369
13. Sun CL, Kersey JH, Francisco L, Armenian SH, Baker KS, Weisdorf DJ, Forman SJ, Bhatia S. Burden of morbidity in 10+ year survivors of hematopoietic cell transplantation: report from the Bone Marrow Transplantation Survivor Study. *Biol Blood Marrow Transplant*. 2013;19:1073–1080. doi: 10.1016/j.bbmt.2013.04.002
14. Alblooshi R, Kanfar S, Lord B, Atenafu EG, Michelis FV, Pasic I, Gerbitz A, Al-Shaibani Z, Viswabandya A, Kim DDH, et al. Clinical prevalence and outcome of cardiovascular events in the first 100 days postallogeneic hematopoietic stem cell transplant. *Eur J Haematol*. 2021;106:32–39. doi: 10.1111/ejh.13482
15. Chiengthong K, Lertjitbanjong P, Thongprayoon C, Bathini T, Sharma K, Prasitlumkum N, Mao MA, Cheungpasitporn W, Chokesuwattanaskul R. Arrhythmias in hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Eur J Haematol*. 2019;103:564–572. doi: 10.1111/ejh.13322
16. Tonorezos ES, Stillwell EE, Calloway JJ, Glew T, Wessler JD, Rebolledo BJ, Pham A, Steingart RM, Lazarus H, Gale RP, et al. Arrhythmias in the setting of hematopoietic cell transplants. *Bone Marrow Transplant*. 2015;50:1212–1216. doi: 10.1038/bmt.2015.127
17. Singla A, Hogan WJ, Ansell SM, Buadi FK, Dingli D, Dispenzieri A, Gastineau DA, Gertz MA, Hayman SR, Inwards DJ, et al. Incidence of supraventricular arrhythmias during autologous peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19:1233–1237. doi: 10.1016/j.bbmt.2013.05.019
18. Vasbinder A, Hoeger CW, Catalan T, Anderson E, Chu C, Kotzin M, Xie J, Kaakati R, Berlin HP, Shadid H, et al. Cardiovascular events after hematopoietic stem cell transplant: incidence and risk factors. *JACC CardioOncol*. 2023;5:821–832. doi: 10.1016/j.jaccao.2023.07.007
19. Peres E, Levine JE, Khaled YA, Ibrahim RB, Braun TM, Krijanovski OI, Mineishi S, Abidi MH. Cardiac complications in patients undergoing a reduced-intensity conditioning hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45:149–152. doi: 10.1038/bmt.2009.97
20. Vasbinder A, Catalan T, Anderson E, Chu C, Kotzin M, Murphy D, Cheplowitz H, Diaz KM, Bitterman B, Pizzo I, et al. Cardiovascular risk stratification of patients undergoing hematopoietic stem cell transplantation: the CARE-BMT risk score. *J Am Heart Assoc*. 2024;13:e033599. doi: 10.1161/JAHA.123.033599
21. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977-1997. *Bone Marrow Transplant*. 2001;28:283–287. doi: 10.1038/sj.bmt.1703133
22. Gul Z, Bashir Q, Cremer M, Yusuf SW, Gunaydin H, Arora S, Slone S, Nieto Y, Sherwani N, Parmar S, et al. Short-term cardiac toxicity of autologous

hematopoietic stem cell transplant for multiple myeloma. *Leuk Lymphoma*. 2015;56:533–535. doi: 10.3109/10428194.2014.926346
23. Mo XD, Xu LP, Liu DH, Zhang XH, Chen H, Chen YH, Han W, Wang Y, Wang FR, Wang JZ, et al. Heart failure after allogeneic hematopoietic stem cell transplantation. *Int J Cardiol*. 2013;167:2502–2506. doi: 10.1016/j.ijcard.2012.06.021
24. Sakata-Yanagimoto M, Kanda Y, Nakagawa M, Asano-Mori Y, Kandabashi K, Izutsu K, Imai Y, Hangaishi A, Kurokawa M, Tsujino S, et al. Predictors for severe cardiac complications after hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2004;33:1043–1047. doi: 10.1038/sj.bmt.1704487
25. Liu Y-C, Gau J-P, Hong Y-C, Yu Y-B, Hsiao L-T, Liu J-H, Chiou T-J, Chen P-M, Tzeng C-H. Large pericardial effusion as a life-threatening complication after hematopoietic stem cell transplantation: association with chronic GVHD in late-onset adult patients. *Ann Hematol*. 2012;91:1953–1958. doi: 10.1007/s00277-012-1541-z
26. Norkin M, Ratanatharathorn V, Ayash L, Abidi MH, Al-Kadhimi Z, Lum LG, Uberti JP. Large pericardial effusion as a complication in adults undergoing SCT. *Bone Marrow Transplant*. 2011;46:1353–1356. doi: 10.1038/bmt.2010.297
27. Rotz SJ, Ryan TD, Jodele S, Jefferies JL, Lane A, Pate A, Hirsch R, Hlavaty J, Levesque AE, Taylor MD, et al. The injured heart: early cardiac effects of hematopoietic stem cell transplantation in children and young adults. *Bone Marrow Transplant*. 2017;52:1171–1179. doi: 10.1038/bmt.2017.62
28. Rotz SJ, Dandoy CE, Taylor MD, Jodele S, Jefferies JL, Lane A, El-Bietar JA, Powell AW, Davies SM, Ryan TD. Long-term systolic function in children and young adults after hematopoietic stem cell transplant. *Bone Marrow Transplant*. 2017;52:1443–1447. doi: 10.1038/bmt.2017.162
29. Chow EJ, Chen Y, Hudson MM, Feijen EAM, Kremer LC, Border WL, Green DM, Meacham LR, Mulrooney DA, Ness KK, et al. Prediction of ischemic heart disease and stroke in survivors of childhood cancer. *J Clin Oncol*. 2018;36:44–52. doi: 10.1200/JCO.2017.74.8673
30. Rhodes M, Lautz T, Kavanaugh-Mchugh A, Manes B, Calder C, Koyama T, Liske M, Parra D, Frangoul H. Pericardial effusion and cardiac tamponade in pediatric stem cell transplant recipients. *Bone Marrow Transplant*. 2005;36:139–144. doi: 10.1038/sj.bmt.1705023
31. Kawashima N, Fukasawa Y, Nishikawa E, Ohta-Ogo K, Ishibashi-Ueda H, Hamada M, Ichikawa D, Narita A, Okuno Y, Muramatsu H, et al. Echocardiography monitoring of pulmonary hypertension after pediatric hematopoietic stem cell transplantation: pediatric pulmonary arterial hypertension and pulmonary veno-occlusive disease after hematopoietic stem cell transplantation. *Transplant Cell Ther*. 2021;27:786.e1–786.e8. doi: 10.1016/j.jtct.2021.05.017
32. Armenian SH, Sun C-L, Vase T, Ness KK, Blum E, Francisco L, Venkataraman K, Samoa R, Wong FL, Forman SJ, et al. Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease. *Blood*. 2012;120:4505–4512. doi: 10.1182/blood-2012-06-437178
33. Chow EJ, Mueller BA, Baker KS, Cushing-Haugen KL, Flowers ME, Martin PJ, Friedman DL, Lee SJ. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. *Ann Intern Med*. 2011;155:21–32. doi: 10.7326/0003-4819-155-1-201107050-00004
34. Lu Y, Ma X, Pan J, Ma R, Jiang Y. Management of dyslipidemia after allogeneic hematopoietic stem cell transplantation. *Lipids Health Dis*. 2022;21:65. doi: 10.1186/s12944-022-01665-3
35. Deleted in proof
36. Chang EK, Chanson D, Teh JB, Iukuridze A, Peng K, Forman SJ, Nakamura R, Wong FL, Cai L, Armenian SH. Atrial fibrillation in patients undergoing allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2021;39:902–910. doi: 10.1200/JCO.20.02401
37. Chow EJ, Wong K, Lee SJ, Cushing-Haugen KL, Flowers ME, Friedman DL, Leisenring WM, Martin PJ, Mueller BA, Baker KS. Late cardiovascular complications after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:794–800. doi: 10.1016/j.bbmt.2014.02.012
38. Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, Venkataraman K, Wong FL, Forman SJ, Bhatia S. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood*. 2011;118:6023–6029. doi: 10.1182/blood-2011-06-358226
39. Murbraech K, Smeland KB, Holte H, Loge JH, Lund MB, Wethal T, Holte E, Rosner A, Dalen H, Kvaloy S, et al. Heart failure and asymptomatic left ventricular systolic dysfunction in lymphoma survivors treated with autologous stem-cell transplantation: a national cross-sectional study. *J Clin Oncol*. 2015;33:2683–2691. doi: 10.1200/JCO.2015.60.8125
40. Duncan CN, Brazauskas R, Huang J, Shaw BE, Majhail NS, Savani BN, Flowers MED, Battiwalla M, Beebe K, Dietz AC, et al. Late cardiovascular morbidity and mortality following pediatric allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2018;53:1278–1287. doi: 10.1038/s41409-018-0155-z
41. Majhail N, Lazarus H, Burns L. Iron overload in hematopoietic cell transplantation. *Bone Marrow Transplant*. 2008;41:997–1003.
42. Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton BK, Battiwalla M, Majhail NS, et al. Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia. *Blood Adv*. 2020;4:983–992. doi: 10.1182/bloodadvances.2019001126
43. Tichelli A, Passweg J, Wojcik D, Rovo A, Harousseau JL, Masszi T, Zander A, Bekassy A, Crawley C, Arat M, et al. Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2008;93:1203–1210. doi: 10.3324/haematol.12949
44. Armenian SH, Sun CL, Mills G, Teh JB, Francisco L, Durand JB, Wong FL, Forman SJ, Bhatia S. Predictors of late cardiovascular complications in survivors of hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2010;16:1138–1144. doi: 10.1016/j.bbmt.2010.02.021
45. Steuter JA, Villanueva ML, Loberiza FR, Armitage JO, Bociek RG, Ganti AK, Tarantolo SR, Vose JM, Easley A, Bierman PJ. Factors affecting the development of atrial fibrillation and atrial flutter (AF/AFL) following autologous hematopoietic SCT (auto-HSCT). *Bone Marrow Transplant*. 2013;48:963–965. doi: 10.1038/bmt.2012.253
46. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, Karia K, Panguluri SK. Cardiovascular risks associated with gender and aging. *J Cardiovasc Dev Dis*. 2019;6:19. doi: 10.3390/jcdd6020019
47. Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, Orav EJ, Gelber RD, Colan SD. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. 1995;332:1738–1743. doi: 10.1056/NEJM199506293322602
48. Fujimaki K, Maruta A, Yoshida M, Sakai R, Tanabe J, Koharazawa H, Kodama F, Asahina S, Minamizawa M, Matsuzaki M, et al. Severe cardiac toxicity in hematological stem cell transplantation: predictive value of reduced left ventricular ejection fraction. *Bone Marrow Transplant*. 2001;27:307–310. doi: 10.1038/sj.bmt.1702783
49. Armenian SH, Chow EJ. Cardiovascular disease in survivors of hematopoietic cell transplantation. *Cancer*. 2014;120:469–479. doi: 10.1002/cncr.28444
50. Qazilbash MH, Amjad AI, Qureshi S, Qureshi SR, Saliba RM, Khan ZU, Hosing C, Giralt SA, De Lima MJ, Popat UR, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients with low left ventricular ejection fraction. *Biol Blood Marrow Transplant*. 2009;15:1265–1270. doi: 10.1016/j.bbmt.2009.06.001
51. Tang WH, Thomas S, Kalaycio M, Sobecks R, Andresen S, Jarvis J, Rybicki L, Pohlman B, Francis GS, Bolwell BJ. Clinical outcomes of patients with impaired left ventricular ejection fraction undergoing autologous bone marrow transplantation: can we safely transplant patients with impaired ejection fraction? *Bone Marrow Transplant*. 2004;34:603–607. doi: 10.1038/sj.bmt.1704610
52. Friedman DN, Hilden P, Moskowitz CS, Suzuki M, Boulad F, Kernan NA, Wolden SL, Oeffinger KC, Sklar CA. Cardiovascular risk factors in survivors of childhood hematopoietic cell transplantation treated with total body irradiation: a longitudinal analysis. *Biol Blood Marrow Transplant*. 2017;23:475–482. doi: 10.1016/j.bbmt.2016.12.623
53. Auberle C, Lenihan D, Gao F, Cashen A. Late cardiac events after allogeneic stem cell transplant: incidence, risk factors, and impact on overall survival. *Cardiooncology*. 2023;9:1. doi: 10.1186/s40959-022-00150-1
54. Tichelli A, Bucher C, Rovo A, Stussi G, Stern M, Paulussen M, Halter J, Meyer-Monard S, Heim D, Tsakiris DA, et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood*. 2007;110:3463–3471. doi: 10.1182/blood-2006-10-054080
55. Duléry R, Mohty R, Labopin M, Sestili S, Malard F, Brissot E, Battipaglia G, Médiavilla C, Banet A, Van de Wyngaert Z, et al. Early cardiac toxicity associated with post-transplant cyclophosphamide in allogeneic stem cell transplantation. *JACC CardioOncol*. 2021;3:250–259. doi: 10.1016/j.jaccao.2021.02.011
56. Sengsayadeth S, Savani BN, Blaise D, Malard F, Nagler A, Mohty M. Reduced intensity conditioning allogeneic hematopoietic cell transplantation for adult acute myeloid leukemia in complete remission: a review from the Acute Leukemia Working Party of the EBMT. *Haematologica*. 2015;100:859–869. doi: 10.3324/haematol.2015.123331
57. Ghimire S, Weber D, Mavin E, Wang XN, Dickinson AM, Holler E. Pathophysiology of GvHD and other HSCT-related major complications. *Front Immunol*. 2017;8:79. doi: 10.3389/fimmu.2017.00079

58. Tichelli A, Gratwohl A. Vascular endothelium as "novel" target of graft-versus-host disease. *Best Pract Res Clin Haematol.* 2008;21:139–148. doi: 10.1016/j.beha.2008.02.002
59. Rovo A, Tichelli A; Late Effects Working Party of the European Group for Blood and Marrow Transplantation. Cardiovascular complications in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Semin Hematol.* 2012;49:25–34. doi: 10.1053/j.seminhematol.2011.10.001
60. Scott JM, Armenian S, Giralt S, Moslehi J, Wang T, Jones LW. Cardiovascular disease following hematopoietic stem cell transplantation: pathogenesis, detection, and the cardioprotective role of aerobic training. *Crit Rev Oncol Hematol.* 2016;98:222–234. doi: 10.1016/j.critrevonc.2015.11.007
61. Miller LW. Cardiovascular toxicities of immunosuppressive agents. *Am J Transplant.* 2002;2:807–818. doi: 10.1034/j.1600-6143.2002.20902.x
62. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med.* 2020;7:26. doi: 10.3389/fcvm.2020.00026
63. Giudice V, Vecchione C, Selleri C. Cardiotoxicity of novel targeted hematological therapies. *Life (Basel).* 2020;10:344. doi: 10.3390/life10120344
64. Corrigendum to: cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res.* 2019;115:868. doi: 10.1093/cvr/cvz082
65. Nowis D, Maczewski M, Mackiewicz U, Kujawa M, Ratajska A, Wieckowski MR, Wilczynski GM, Malinowska M, Bil J, Salwa P, et al. Cardiotoxicity of the anticancer therapeutic agent bortezomib. *Am J Pathol.* 2010;176:2658–2668. doi: 10.2353/ajpath.2010.090690
66. Xiao Y, Yin J, Wei J, Shang Z. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. *PLoS One.* 2014;9:e87671. doi: 10.1371/journal.pone.0087671
67. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, Prince HM. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia.* 2010;24:22–32. doi: 10.1038/leu.2009.236
68. Fahdi IE, Gaddam V, Saucedo JF, Kishan CV, Vyas K, Deneke MG, Razek H, Thorn B, Bissett JK, Anaissie EJ, et al. Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol.* 2004;93:1052–1055. doi: 10.1016/j.amjcard.2003.12.061
69. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood.* 2014;124:3829–3830. doi: 10.1182/blood-2014-10-604272
70. Ganatra S, Sharma A, Shah S, Chaudhry GM, Martin DT, Neilan TG, Mahmood SS, Barac A, Groarke JD, Hayek SS, et al. Ibrutinib-associated atrial fibrillation. *JACC Clin Electrophysiol.* 2018;4:1491–1500. doi: 10.1016/j.jacep.2018.06.004
71. Pineda-Gayoso R, Alomar M, Lee DH, Fradley MG. Cardiovascular toxicities of Bruton's tyrosine kinase inhibitors. *Curr Treat Options Oncol.* 2020;21:67. doi: 10.1007/s11864-020-00764-6
72. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol.* 1991;9:1215–1223. doi: 10.1200/JCO.1991.9.7.1215
73. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood.* 1986;68:1114–1118.
74. Vaickus L, Letendre L. Pericarditis induced by high-dose cytarabine therapy. *Arch Intern Med.* 1984;144:1868–1869.
75. Kanj SS, Sharara AI, Shpall EJ, Jones RB, Peters WP. Myocardial ischemia associated with high-dose carmustine infusion. *Cancer.* 1991;68:1910–1912. doi: 10.1002/1097-0142(19911101)68:9<1910::aid-cncr2820680911>3.0.co;2-e
76. Olivieri A, Corvatta L, Montanari M, Brunori M, Offidani M, Ferretti GF, Centanni M, Leoni P. Paroxysmal atrial fibrillation after high-dose melphalan in five patients autotransplanted with blood progenitor cells. *Bone Marrow Transplant.* 1998;21:1049–1053. doi: 10.1038/sj.bmt.1701217
77. Van Besien K, Devine S, Wickrema A, Jessop E, Amin K, Yassine M, Maynard V, Stock W, Peace D, Ravandi F, et al. Regimen-related toxicity after fludarabine-melphalan conditioning: a prospective study of 31 patients with hematologic malignancies. *Bone Marrow Transplant.* 2003;32:471–476. doi: 10.1038/sj.bmt.1704166
78. Ayza MA, Zewdie KA, Tesfaye BA, Wondafrash DZ, Berhe AH. The role of antioxidants in ameliorating cyclophosphamide-induced cardiotoxicity. *Oxid Med Cell Longev.* 2020;2020:4965171. doi: 10.1155/2020/4965171
79. Dhesi S, Chu MP, Blevins G, Paterson I, Larratt L, Oudit GY, Kim DH. Cyclophosphamide-induced cardiomyopathy: a case report, review, and recommendations for management. *J Investig Med High Impact Case Rep.* 2013;1:2324709613480346. doi: 10.1177/2324709613480346
80. al-Nasser IA. In vivo prevention of cyclophosphamide-induced Ca2+ dependent damage of rat heart and liver mitochondria by cyclosporin A. *Comp Biochem Physiol A Mol Integr Physiol.* 1998;121:209–214. doi: 10.1016/s1095-6433(98)10135-6
81. Asiri YA. Probucol attenuates cyclophosphamide-induced oxidative apoptosis, p53 and Bax signal expression in rat cardiac tissues. *Oxid Med Cell Longev.* 2010;3:308–316. doi: 10.4161/oxim.3.5.13107
82. Konuma T, Ooi J, Takahashi S, Tomonari A, Tsukada N, Kobayashi T, Sato A, Kato S, Kasahara S, Ebihara Y, et al. Cardiovascular toxicity of cryopreserved cord blood cell infusion. *Bone Marrow Transplant.* 2008;41:861–865. doi: 10.1038/sj.bmt.1705993
83. Spitzer TR. Engraftment syndrome: double-edged sword of hematopoietic cell transplants. *Bone Marrow Transplant.* 2015;50:469–475. doi: 10.1038/bmt.2014.296
84. Han X, Zhou Y, Liu W. Precision cardio-oncology: understanding the cardiotoxicity of cancer therapy. *NPJ Precis Oncol.* 2017;1:31. doi: 10.1038/s41698-017-0034-x
85. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. *Front Oncol.* 2015;5:39. doi: 10.3389/fonc.2015.00039
86. Cuomo JR, Sharma GK, Conger PD, Weintraub NL. Novel concepts in radiation-induced cardiovascular disease. *World J Cardiol.* 2016;8:504–519. doi: 10.4330/wjc.v8.i9.504
87. Bachier C, Eiznhamer D, Milgroom A, Lenco M, Patel N, Skaar JR. Costs and adverse events associated with ibrutinib or ruxolitinib in chronic graft-versus-host disease. *Blood.* 2020;136:14–15. doi: 10.1182/blood-2020-137756
88. Li W, Garcia D, Cornell RF, Gailani D, Laubach J, Maglio ME, Richardson PG, Moslehi J. Cardiovascular and thrombotic complications of novel multiple myeloma therapies: a review. *JAMA Oncol.* 2017;3:980–988. doi: 10.1001/jamaoncol.2016.3350
89. Chakraborty R, Bin Riaz I, Malik SU, Marneni N, Mejia Garcia A, Anwer F, Khorana AA, Rajkumar SV, Kumar S, Murad MH, et al. Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma: a systematic review and meta-analysis. *Cancer.* 2020;126:1640–1650. doi: 10.1002/cncr.32682
90. Vasbinder A, Hoeger CW, Catalan T, Anderson E, Chu C, Kotzin M, Murphy D, Cheplowitz H, Bitterman B, Pizzo I, et al. Cardiovascular risk stratification of patients undergoing hematopoietic stem cell transplantation: the CARE-BMT risk score. *J Am Heart Assoc.* 2024;13:e033599. doi: 10.1161/JAHA.123.033599
91. Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, Border WL, Feijen EAM, Green DM, Meacham LR, et al. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol.* 2015;33:394–402. doi: 10.1200/JCO.2014.56.1373
92. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106:2912–2919. doi: 10.1182/blood-2005-05-2004
93. Hertenstein B, Stefanic M, Schmeiser T, Scholz M, Göller V, Clausen M, Bunjes D, Wiesneth M, Novotny J, Kochs M. Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplant. *J Clin Oncol.* 1994;12:998–1004. doi: 10.1200/JCO.1994.12.5.998
94. Lehmann S, Isberg B, Ljungman P, Paul C. Cardiac systolic function before and after hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2000;26:187–192. doi: 10.1038/sj.bmt.1702466
95. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand JB, Ewer M, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2017;35:893–911. doi: 10.1200/JCO.2016.70.5400
96. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail.* 2018;6:543–551. doi: 10.1016/j.jchf.2018.04.005
97. Mohananey D, Sarau A, Kumar R, Lewandowski D, Abreu-Sosa SM, Nathan S, Okwuosa TM. Role of physical activity and cardiac rehabilitation in patients undergoing hematopoietic stem cell transplantation. *JACC CardioOncol.* 2021;3:17–34. doi: 10.1016/j.jaccao.2021.01.008
98. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer.* 1984;53:2002–2007. doi: 10.1002/1097-0142(19840501)53:9<2002::aid-cncr2820530933>3.0.co;2-w
99. Jang RW, Caraiscos VB, Swami N, Banerjee S, Mak E, Kaya E, Rodin G, Bryson J, Ridley JZ, Le LW, et al. Simple prognostic model for patients with advanced cancer based on performance status. *J Oncol Pract.* 2014;10:e335–e341. doi: 10.1200/JOP.2014.001457

100. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med*. 2013;34:631–636. doi: 10.1055/s-0032-1323746
101. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, Ulrich CM, Bohus M. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*. 2011;117:2604–2613. doi: 10.1182/blood-2010-09-306308
102. Santa Mina D, Dolan LB, Lipton JH, Au D, Camacho Pérez E, Franzese A, Alibhai SMH, Jones JM, Chang E. Exercise before, during, and after hospitalization for allogeneic hematological stem cell transplant: a feasibility randomized controlled trial. *J Clin Med*. 2020;9:1854. doi: 10.3390/jcm9061854
103. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2022;145:e1033, *Circulation*. 2022;146:e185, and *Circulation*. 2023;147:e674]. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
104. Ballo O, Eladly F, Koschade S, Büttner S, Stratmann JA, Brunnberg U, Kreisel EM, Frank F, Wagner S, Steffen B, et al. Fluid overload is associated with increased 90-day mortality in AML patients undergoing induction chemotherapy. *Ann Hematol*. 2021;100:2603–2611. doi: 10.1007/s00277-021-04593-x
105. Rondón G, Saliba RM, Chen J, Ledesma C, Alousi AM, Oran B, Hosing CM, Kebriaei P, Khouri IF, Shpall EJ, et al. Impact of fluid overload as new toxicity category on hematopoietic stem cell transplantation outcomes. *Biol Blood Marrow Transplant*. 2017;23:2166–2171. doi: 10.1016/j.bbmt.2017.08.021
106. Hingorani SR. Fluid: too much or too little: transplant mortality may hang in the balance. *Biol Blood Marrow Transplant*. 2017;23:2020–2022. doi: 10.1016/j.bbmt.2017.10.032
107. Rondon-Clavo C, Scordo M, Hilden P, Shah GL, Cho C, Maloy MA, Papadopoulos EB, Jakubowski AA, O'Reilly RJ, Gyurkocza B, et al. Early fluid overload is associated with an increased risk of nonrelapse mortality after ex vivo CD34-selected allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:2517–2522. doi: 10.1016/j.bbmt.2018.07.031
108. Konuma T, Oiwa-Monna M, Mizusawa M, Isobe M, Kato S, Takahashi S, Tojo A. Early fluid overload predicts higher non-relapse and overall mortality in adults after single-unit cord blood transplantation. *Bone Marrow Transplant*. 2019;54:2096–2101. doi: 10.1038/s41409-019-0634-x
109. van Leeuwen RWF, Jansman FGA, van den Bemt P, de Man F, Piran F, Vincenten I, Jager A, Rijneveld AW, Brugma JD, Mathijssen RHJ, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. *Ann Oncol*. 2015;26:992–997. doi: 10.1093/annonc/mdv029
110. Fradley MG, Beckie TM, Brown SA, Cheng RK, Dent SF, Nohria A, Patton KK, Singh JP, Olshansky B; on behalf of the American Heart Association Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and Council on Cardiovascular and Stroke Nursing. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e41–e55. doi: 10.1161/CIR.0000000000000986
111. Coghlan JG, Handler CE, Kottaridis PD. Cardiac assessment of patients for haematopoietic stem cell transplantation. *Best Pract Res Clin Haematol*. 2007;20:247–263. doi: 10.1016/j.beha.2006.09.005
112. Rizzo JD, Wingard JR, Tichelli A, Lee SJ, Van Lint MT, Burns LJ, Davies SM, Ferrara JL, Socie G. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2006;12:138–151. doi: 10.1016/j.bbmt.2005.09.012
113. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P, et al; ESMO Guidelines Committee. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31:171–190. doi: 10.1016/j.annonc.2019.10.023
114. Feijen EAM, Leisenring WM, Stratton KL, Ness KK, van der Pal HJH, van Dalen EC, Armstrong GT, Aune GJ, Green DM, Hudson MM, et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. *JAMA Oncol*. 2019;5:864–871. doi: 10.1001/jamaoncol.2018.6634