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STATE-OF-THE-ART REVIEW

Cardiovascular Disease After Hematopoietic Stem Cell Transplantation in Adults

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

The use of hematopoietic cell transplantation (HCT) has expanded in the last 4 decades to include an older and more comorbid population. These patients face an increased risk of cardiovascular disease after HCT. The risk varies depending on several factors, including the type of transplant (autologous or allogeneic). Many therapies used in HCT have the potential to be cardiotoxic. Cardiovascular complications after HCT include atrial arrhythmias, heart failure, myocardial infarction, and pericardial effusions. Before HCT, patients should undergo a comprehensive cardiovascular assessment, with ongoing surveillance tailored to their individual level of cardiovascular risk. In this review, we provide an overview of cardiotoxicity after HCT and outline our approach to risk assessment and ongoing care. (JACC CardioOncol 2024;6:475–495) © 2024 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/).

Hematopoietic cell transplantation (HCT) is a potentially curative option for a wide variety of malignant and nonmalignant conditions.[1] First described in 1957, by the end of 2019, approximately 1.5 million people had undergone HCT, with a frequency of 84,000 transplants per year globally.[2-4] The increased transplantation activity over the last 4 decades has been driven by the global adoption of HCT accompanied by modifications to transplantation regimens facilitating procedures in patients who are older and have more comorbidities with a higher baseline cardiovascular risk.[5] Advances in patient and donor selection, reduced toxicity conditioning, and improved supportive care during transplantation have increased survival and decreased nonrelapse mortality.[6,7] These changes have led to a focus on competing causes of increased morbidity and mortality in which cardiovascular disease plays a leading role.

Characterizing cardiovascular disease in the adult HCT population can be difficult; each transplantation candidate is different and requires a personalized approach to cardiovascular assessment. In this review, we cover the breadth of what is known about cardiovascular disease in this population, focusing on acute and late complications, risk prediction, surveillance, and treatment of complications.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CHIP = clonal hematopoiesis of indeterminate potential

CMR = cardiac magnetic resonance

CPET = cardiopulmonary exercise testing

ESC = European Society of Cardiology

GVHD = graft-versus-host disease

HbA_{1c} = glycosylated hemoglobin

HCT = hematopoietic cell transplantation

HF = heart failure

HLA = human leukocyte antigen

LVEF = left ventricular ejection fraction

MAC = myeloablative conditioning

RIC = reduced-intensity conditioning

RR = risk ratio

AUTOLOGOUS AND ALLOGENEIC STEM CELL TRANSPLANTS

Autologous and allogeneic HCT have a variety of indications, as detailed in **Figure 1**.[1] The overall processes in both types of transplantation are similar, but the main treatment effect and the indication for transplantation differ between transplantation types. Initially, stem cells are harvested from the patient (in autologous HCT) or donor (in allogeneic HCT). Patients then receive conditioning therapy to ablate the bone marrow to varying degrees. After conditioning, hematopoietic progenitor cells (CD34+ stem cells) are infused back into the patient to reconstitute the lymphohematopoietic system. In autologous transplantation performed for malignant diseases, the treatment effect is provided by the cytotoxic conditioning therapy, and HCT salvages the bone marrow and prevents potentially fatal myelosuppression. When autologous transplantation is used to treat autoimmune diseases, the HCT acts to reset the immune system.[8] In allogeneic transplantation, the main treatment effect is provided by the donor stem cells attacking the tumor cells (graft-versus-tumor effect) or through replacing dysfunctional bone marrow in nonmalignant diseases.

In allogeneic HCT, donors are matched through human leukocyte antigen (HLA) typing. Five loci (each with 2 alleles) are typed and compared, with matching described as a score out of 10. The loci are HLA-A, HLA-B, HLA-C, DRB1, and DQB1. Although allogeneic transplantation outcomes have been improved by the use of matched related donors, matched unrelated donors are frequently used because of the lack of siblings.[9] In some cases, mismatched related or unrelated donors are used. A mismatch of 1 allele or antigen is tolerable in unrelated donors, but sibling, parent, or children family donors can be half-matched (haploidentical). There is a greater risk of graft rejection, graft-versus-host disease (GVHD), and nonrelapse mortality as the mismatch increases. However, this has been mitigated by improvements in post-transplantation GVHD prophylaxis, such as the use of post-transplantation cyclophosphamide (**Table 1**, Supplemental Appendix).[10,11]

In contemporary practice, peripheral blood is the main source of stem cells for both types of transplantation. Before collection, cells are mobilized from the bone marrow by various methods. Granulocyte colony-stimulating factor (eg, filgrastim) is used for stem cell mobilization in autologous HCT patients and allogeneic HCT donors. C-X-C motif chemokine receptor 4 inhibitors, such as plerixafor, can be used to augment mobilization in select cases. In autologous HCT, chemotherapy (commonly cyclophosphamide) (**Table 1**) followed by granulocyte colony-stimulating factor is an alternative method for mobilization when high numbers of stem cells are required and/or tumor burden needs to be decreased further. In certain diseases, such as lymphoma, the chemotherapy used for mobilization can also be part of a disease-specific treatment regimen.

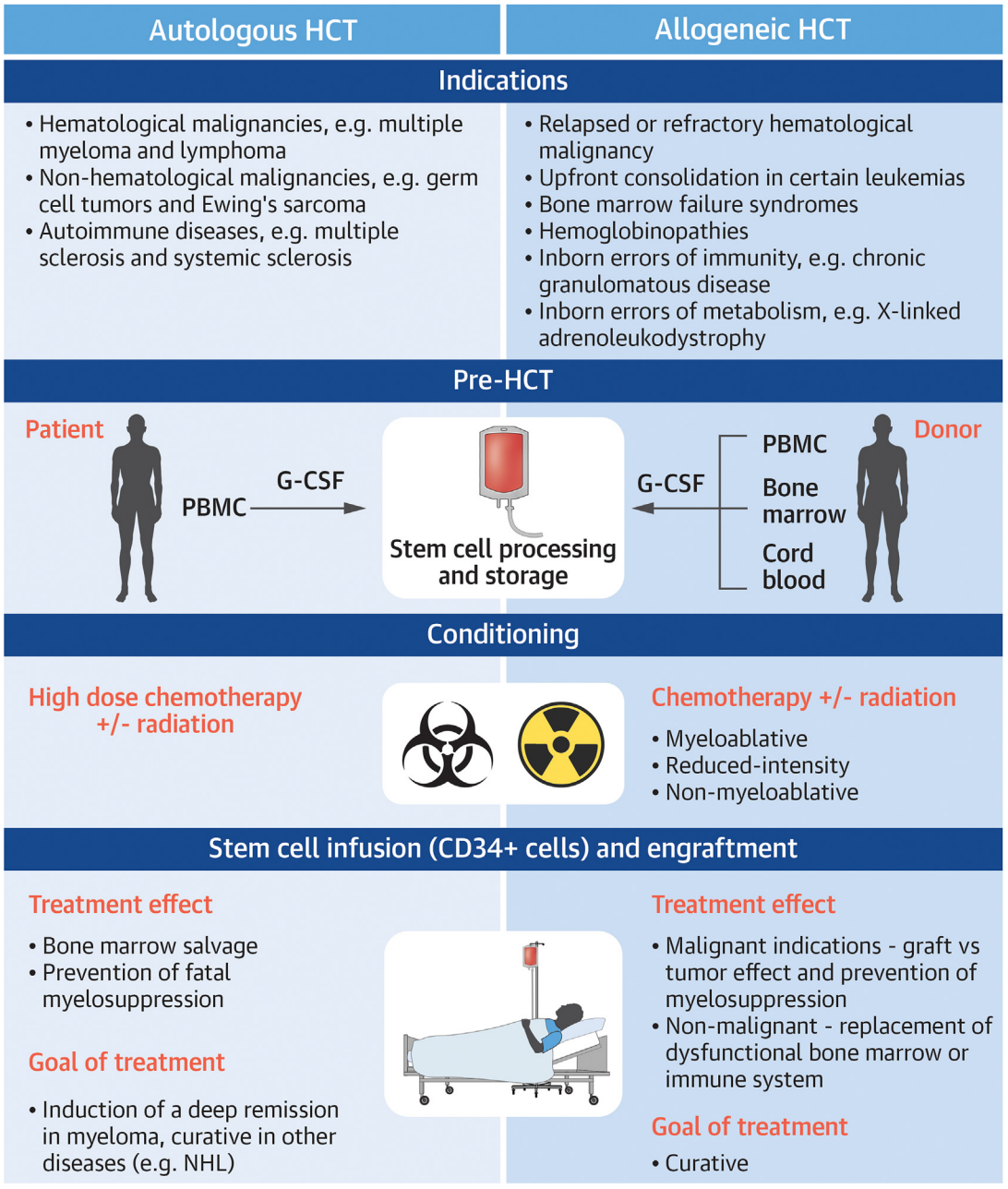
In allogeneic HCT, other sources of stem cells include bone marrow harvesting and umbilical cord blood. For allogeneic HCT in the malignant setting, peripheral blood stem cells demonstrate faster engraftment, a superior graft-versus-tumor effect, and a reduced incidence of graft failure compared with cells derived from bone marrow but at the expense of an increased risk of chronic GVHD.[12,13] Umbilical cord blood requires less stringent HLA matching but is associated with delayed engraftment and an increased risk of infections. Often, a judgment is made before allogeneic HCT regarding the optimal donor and cell source that will give the best treatment effect.

Conditioning therapy for autologous HCT is myeloablative, whereas conditioning for allogeneic HCT includes myeloablative conditioning (MAC), reduced-intensity conditioning (RIC), or nonmyeloablative conditioning.[14] MAC ablates the bone marrow using combination therapies, and RIC uses lower doses of the same agents (**Table 1**). MAC regimens are associated with a reduced risk of relapse but are more toxic and generally have a higher risk of GVHD. For older patients, the increased nonrelapse mortality induced by MAC has made RIC the preferred option.[15]

HIGHLIGHTS

- HCT is associated with adverse cardiovascular outcomes.
- Patients should have cardiovascular comorbidities optimized before HCT.
- Ongoing surveillance should be tailored to the individual's cardiovascular risk.
- Future research should focus on the validation of cardiovascular risk prediction tools, screening, and surveillance strategies.

FIGURE 1 **Indications, Procedures, and Goals of Autologous and Allogeneic HCT**



This figure details the indications for hematopoietic stem cell transplantation (HCT), as well as the pre-HCT procedures and condition regimens. Briefly, 1) stem cells are harvested, 2) patients receive conditioning tailored to their comorbidities and underlying disease, 3) stem cells are reinfused with autologous and allogeneic HCT having different primary treatment effects. The desired treatment effects and goals of treatment are also detailed. G-CSF = granulocyte-colony stimulating factor; NHL = non-Hodgkin lymphoma; PBMC = peripheral blood mononuclear cell.

TABLE 1 Common Treatments Used During HCT and Description of Associated Cardiotoxicity

Treatment (Drug Class)	Usual Dose (Regimen)	Acute and Long-Term Effects (Incidence Rates if Available)	Additional Comments
Conditioning Therapy and GVHD Prophylaxis			
Cyclophosphamide (Cy; alkylating agent/ nitrogen mustard)	120 mg/kg (Cy/TBI) 120 mg/kg (Bu/Cy) 7.2 g/m^2 (Cy/vincristine/prednisolone) 120-140 mg/kg (Flu/Cy) 50 mg/kg for 2 doses: GVHD prophylaxis after transplantation. Role before transplantation: mobilize and prime stem cells from bone marrow. Role after transplantation: expand the donor stem cell pool for haploidentical and mismatched donors and act as GVHD prophylaxis; studies using haploidentical HCST with PTCy reported noninferior survival outcomes compared with matched unrelated donors and umbilical cord blood donors.[49-51]	Cyclophosphamide before transplantation: Common effects, primarily with noncontemporary, high-dose cyclophosphamide regimens, include heart failure with LVSD (1.5%-28%), pericarditis (9%-16%), hemorrhagic myocarditis/ perimyocarditis (13%), and pericardial effusions including tamponade (11%).[45,47,48,52-56] Cyclophosphamide after transplantation: Common effects include heart failure (5.1%), LVSD (14.3%-21.9%), pericarditis (3.8%), pericardial effusion (1.7%-13.6%), arrhythmia (3.6%), and acute coronary syndrome (1.2%-1.5%).[25,26,29]	Acute-onset cardiotoxicity is typically mediated by metabolites generated from hepatic metabolism of cyclophosphamide.[53,57] Cardiotoxic effects are exerted through inflammation, oxidative stress, and alterations in calcium homeostasis, leading to endothelial dysfunction, cardiomyocyte damage, and apoptosis.[58,59] There is no proven role for pretreatment with antioxidants.[57] Potential increased risks exist in older patients, those receiving lymphoma treatment, and those with prior mediastinal or left chest radiotherapy.[52,56] Three retrospective studies with different populations and follow-up times examined the incidence of cardiomyopathy after PTCy.[25,26,29] One study of predominantly haploidentical HCT showed no increase in cardiomyopathy with PTCy compared with controls.[26] Most patients with cardiomyopathy in this study had concurrent sepsis. A second study found no difference in the incidence of cardiotoxicity (CTCAE defined) with or without PTCy in the first 100 days in matched allo-HCT.[29] A third study found an increased incidence of cardiac events with PTCy within 100 days of HCT.[25] In this study, most patients with PTCy underwent haploidentical transplants compared with the no-PTCy group, who were mainly identical sibling or matched unrelated transplantation recipients.
Conditioning Therapies			
Busulfan (alkylating agent)	12.8 mg/kg (Bu/Cy) 8-10 mg/kg (Flu/Bu/TT) 6.4 mg/kg (Bu/Flu reduced intensity conditioning). Role: conditioning before transplantation.	Rare: cardiac tamponade, endocardial fibrosis.[60]	Busulfan is combined with fludarabine in reduced-intensity conditioning regimens. Cardiotoxic mechanisms are similar between alkylating agents (see cyclophosphamide).[57-59]
Carmustine (alkylating agent/nitrogen mustard)	300 mg/m^2 (BEAM) 300-500 mg/m^2 (CVP). Role: conditioning before transplantation.	Rare: myocardial ischemia.[61,62]	Unclear mechanism of reversible myocardial ischemia.
Cytarabine (antimetabolite and nucleoside analogue)	800-1,600 mg/m^2 (used primarily as part of BEAM). Role: conditioning before transplantation.	Common: symptomatic sinus bradycardia (2.8%).[63-67] Rare: sinoatrial block, pericarditis, and cardiac tamponade.[68-72]	All the cases of bradycardia self-resolved without pacing. Cessation of chemotherapy and corticosteroid treatment improved pericarditis. Unclear mechanism for cardiotoxicity.
Etoposide (topoisomerase II inhibitor)	400-800 mg/m^2 (BEAM) 600-2,400 mg/m^2 (CVP). Role: conditioning before transplantation.	Rare: acute myocardial infarction.[73,74]	Evidence for acute myocardial infarction is derived from 3 cases in which bleomycin, etoposide, and cisplatin were used to treat testicular tumors.[73,74] It is unclear what the relative contribution of these 3 drugs is to thrombus formation or what the underlying mechanisms promoting thrombosis are.
Fludarabine (antimetabolite and nucleoside analogue)	125-150 mg/m^2 (Flu/Mel) 150-160 mg/m^2 (Flu/Bu) 150-80 mg/m^2 (Flu/Cy) 150 mg/m^2 (Flu/Bu/TT) 90-160 mg/m^2 (Flu/TBI). Role: conditioning before transplantation.	Common: heart failure with LVSD (14.3% when used in combination with melphalan).[75,76]	It is unclear if there is a synergistic risk of left ventricular failure when melphalan is administered with fludarabine. The mechanism of cardiotoxicity is unclear.
Melphalan (alkylating agent)	140 mg/m^2 (BEAM) 200 mg/m^2 (high-dose regimen) 140 mg/m^2 (Flu/Mel). Role: conditioning before transplantation. BEAM is primarily used for auto-HCT conditioning, whereas Flu/Mel is used for allo-HCT conditioning.	Common: atrial fibrillation (4.9%-8%), supraventricular tachycardia (1.6%-5.1%), and heart failure with LVSD (1.2%-14.3%).[75-81] Rare: ventricular tachycardia, sinus node arrest.[82,83]	It is unclear if there is a synergistic risk of left ventricular failure when melphalan is administered with fludarabine.[76,81] Cardiotoxic mechanisms are similar between alkylating agents (see the cyclophosphamide section).[57-59]
Thiotepa (alkylating agent)	5-10 mg/m^2 (Flu/Bu/TT). Role: conditioning before transplantation.	Common: heart failure with LVSD (5.3%).[84] Rare: ventricular arrhythmia.[85]	Ventricular arrhythmia may not be related to the use of thiotepa but to cardiac manifestations of systemic sclerosis combined with the concomitant use of cyclophosphamide in the cases in which it was reported. Cardiotoxic mechanisms are similar between alkylating agents (see the cyclophosphamide section above).[57-59]

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TABLE 1 Continued

Treatment (Drug Class)	Usual Dose (Regimen)	Acute and Long-Term Effects (Incidence Rates if Available)	Additional Comments
TBI	Up to 14.4 Gy (fractionated) was used for disease control/conditioning before transplantation. Around 2 Gy was used to prevent graft rejection. There is emerging evidence that 2 Gy TBI combined with regimens such as treosulfan had a synergistic effect and could be used as a reduced-intensity conditioning option before transplantation.[86,87] Role: conditioning before transplantation.	Common: diabetes (6.8%) and dyslipidemia, with 26.8% for low HDL and 39.2% for hypertriglyceridemia, at 5 y after HCT.[88-93]	Previous reports have linked TBI to pericarditis and left ventricular dysfunction. However, these are confounded by the concomitant use of other drugs with cardiotoxic effects such as high-dose anthracyclines and cyclophosphamide.[94-96] Insulin resistance and dyslipidemia are possibly caused by radiation-induced damage to the pancreas and liver combined with gonadal dysfunction after HCT.[88,97-99]
GVHD Prophylaxis and Treatment			
Alemtuzumab (anti-CD52 antibody causing T-cell depletion)	commonly 60-90 mg (within FCC regimen for aplastic anemia) and 30-60 mg (allo-HCT with lower dose for related sibling donor and higher dose for unrelated donor). Role: GVHD prophylaxis and treatment.	Rare: ST-segment elevation and LVSD (with unobstructed coronary arteries), myocardial infarction without ST-segment elevation, dysarrhythmias (sinus node, atrial and ventricular), and LVSD without evidence of acute coronary syndrome.[32-36]	Myocardial infarction is possibly triggered by cytokine release, but mechanism is not clear.
Calcineurin inhibitors (calcineurin inhibition prevents IL-2 transcription and upregulation of the T-cell response)	Cyclosporine 3 mg/kg/d starting dose (IV). Tacrolimus 0.03 mg/kg/d loading IV, aiming for a trough level of 5-15 ng/mL. Role: GVHD prophylaxis and treatment.	Common: hypertension (30%-60%).[100] Unknown incidence: although the incidence after solid organ transplantation was 13.4%,[101] no data were available to define the incidence after HCT.	Hypertension is mediated through renal sodium retention and systemic and renal vasoconstriction.[102] Diabetogenic effects are mediated through increased adipose and skeletal muscle insulin resistance, along with pancreatic beta cell dysfunction.[103]
Mycophenolate mofetil (inhibits de novo purine synthesis, thereby inhibiting T- and B-cell proliferation)	1 g TDS initially (oral) and then gradually weaned off. Role: GVHD prophylaxis and treatment.	No known associations.	
Stem Cell Cryopreservation			
Dimethylsulfoxide (stem cell cryopreservation solvent)	Role: stem cell cryopreservation before infusion. Used as the cryopreservative in approximately 5%-10% of samples in contemporary practice.	Rare: ventricular arrhythmias, hypertension, bradycardia, and cardiac arrest.[30,31]	Unclear mechanism; bradycardia and hypertension are the most common side effects.

Definitions used to describe the frequency of adverse events are as follows: common = ≥1% incidence, uncommon = 0.1% to <1% incidence, and rare = <0.1% incidence.

allo = allogeneic; auto = autologous; BEAM = carmustine/etoposide/cytarabine/melphalan; Bu = busulfan; CTCAE = common terminology criteria for adverse events; Cy = cyclophosphamide; CVP = cyclophosphamide/vincristine/prednisolone; FCC = fludarabine/campath/low-dose cyclophosphamide; Flu = fludarabine; GVHD = graft-versus-host disease; HCT = hematopoietic stem cell transplantation; IL-2 = interleukin 2; IV = intravenous; LVSD = left ventricular systolic dysfunction; Mel = melphalan; PTCy = post-transplantation cyclophosphamide; TBI = total body irradiation; TDS = three times a day.

Although conditioning typically involves chemotherapy alone, the exact regimen used depends on the underlying disease, disease status, and comorbidities. In autologous HCT, the goal of treatment depends on the disease being treated (**Figure 1**), but allogeneic HCT is always performed with curative intent.

KEY POINTS

- Autologous HCT uses MAC before stem cell infusion.
- In autologous HCT performed for malignant disease, the main treatment effect is provided by the conditioning therapy.
- Allogeneic HCT uses varying intensities of conditioning therapy (MAC, RIC, or nonmyeloablative conditioning), balancing the risk of toxicity with the risk of relapse.
- In allogeneic HCT performed for malignant disease, the main treatment effect is caused by the graft-versus-tumor response.
- Allogeneic transplantation recipients have different degrees of donor HLA matching, which impact the likelihood of developing GVHD.

LITERATURE REVIEW. We conducted a literature review on cardiovascular outcomes after HCT and cardiovascular risk prediction before HCT. The search strategies and full-text papers that we reviewed are included in the Supplemental Appendix. We excluded case reports, editorials, and review articles. Cardiovascular outcome definitions varied between

studies, and many papers predated the contemporary definition of chemotherapy-related cardiac dysfunction.[16-20] Our recommendations for the cardiovascular care of HCT patients were constructed from critical review of relevant societal guidelines, position statements, and their supporting literature.

Most of the data describing cardiovascular complications after HCT originated from patients who underwent the procedure between 1980 and 2005. However, there is an emerging literature base describing patients treated in later eras.[21-29] The cardiovascular risk profile has changed over time; older eras are associated with higher doses of cardiotoxic therapies, whereas contemporary practice uses lower doses of cardiotoxic therapies but in patients who are older and have more comorbidities. Where possible, we include data derived from patients who underwent HCT after 2005, and a comparison is made to previous eras where appropriate. The results of the literature searches are synthesized into a narrative review.

CARDIOTOXICITY: TREATMENT EFFECTS

Many parts of the HCT process have been implicated in cardiotoxicity, including treatment given before HCT (eg, anthracyclines and radiotherapy), constituents of the stem cell cryopreservation media (dimethylsulfoxide), conditioning therapy (including total body irradiation), and drugs used for GVHD prophylaxis such as alemtuzumab.[30-36] Often, different classes of drugs are used in combination before HCT and during conditioning, making it a challenge (and possibly incorrect) to attribute a particular adverse effect to a single treatment. Many HCT recipients receive treatment with anthracyclines before HCT, a class of drugs with a well-defined association to heart failure (HF) and cardiovascular morbidity and mortality.[37-40] Although the use of anthracyclines has declined, novel therapies used to treat hematologic cancers, such as proteosome inhibitors[41] and tyrosine kinase inhibitors,[42,43] are associated with cardiotoxicity independent of the HCT process.

In contemporary cohorts, different combinations of conditioning therapy have been associated with different risks of cardiotoxicity. In 1 study, fludarabine/melphalan was associated with the highest cumulative incidence of cardiovascular events at 100 days (7.2%) and 10 years (26%) after HCT.[28] The historical use of high-dose cyclophosphamide for transplantation conditioning has been associated with hemorrhagic myocarditis and acute HF in up to 28% of patients.[44-47] This is now uncommon because of the use of lower doses of cyclophosphamide in modern conditioning regimens.[48]

There has been an increased use of cyclophosphamide for GVHD prophylaxis after allogeneic HCT. Three studies analyzed the incidence of cardiotoxicity with post- transplantation cyclophosphamide.[25,26,29] However, only 1 study found an increased incidence of short-term cardiac events in patients treated with post-transplantation cyclophosphamide (19%) compared with controls (6%).[25] The most common cardiovascular events within 100 days after starting post-transplantation cyclophosphamide were left ventricular systolic dysfunction (incidence of 14.3%), symptomatic heart failure (incidence of 5.1%), atrial arrhythmias (incidence of 3.1%-4.8%), and pericardial effusions (incidence of 1.5%).[25,29] A summary of the therapies used in HCT and their associated adverse cardiovascular outcomes is provided in **Table 1**.

SHORT- AND LONG-TERM CARDIOVASCULAR COMPLICATIONS IN AUTOLOGOUS AND ALLOGENEIC TRANSPLANTATION

Most studies classify short-term cardiovascular complications after autologous and allogeneic HCT as events that occur within 100 days after transplantation, but there is variability between studies.[21,23,26,29,38,39,44,77,94,104-120] Although the 100-day time point has been used for both transplantation types, it originated from the historical time frame used to define acute GVHD after allogeneic HCT. Acute GVHD is now defined by disease features, not temporality.[121] Many studies classify long-term cardiovascular complications after autologous and allogeneic HCT as those occurring 1 to 2 years or more after transplantation rather than 100 days or more after transplantation.[22,24,37,51,122-134]

Cardiovascular outcome definitions vary between studies, and many papers were published before the contemporary definition of chemotherapy-related cardiac dysfunction.[16-20] We use the term HF to refer to symptomatic cardiac dysfunction occurring after HCT and asymptomatic left ventricular systolic dysfunction in which a left ventricular ejection fraction (LVEF) decline has been reported in the absence of symptoms.

With both types of transplantation, there is an increased risk of infection, relapse, and graft rejection within 100 days of HCT. Allogeneic HCT carries the additional risk of acute GVHD. Cardiovascular complications are relatively uncommon within 100 days after HCT.[28] Engraftment syndrome, occurring early after autologous and allogeneic transplantation, is associated with a proinflammatory state that can exacerbate underlying cardiovascular disease.[135]

TABLE 2 Incidence, Risk Factors, and Mechanisms of Different Cardiovascular Toxicities in Autologous and Allogeneic HCT

		Autologous HCT	Allogeneic HCT
Atrial arrhythmias (fibrillation or flutter [AF])	Short-term	• The most common complication occurring within 100 days after autologous HCT.[28,77,108,109,116,137,140] • The incidence in contemporary studies ranges from 2.8% to 8.5% (lower than older cohorts).[28,109,116] • Most cases occur in the first 3 weeks after HCT.	• The most common complication occurring within 100 days after allogeneic HCT. • The incidence ranges from 2.5% to 9%.[21,28,29,38,110,113,119,140]
	Long-term	• The 5-year cumulative incidence is 6.7%.[28] • The most common indication for autologous HCT is MM. • MM patients are at an increased risk of AF after HCT.[28,77,108,137]	• The 5-year cumulative incidence ranges from 6.9% to 10.6%.[22,24,28] • The development of AF is associated with an increased risk of death, with the HR for all-cause mortality after transplantation ranging from 10.6 to 12.8.[22,24]
	Risk factors	• Risk factors identified at the time of transplantation are melphalan use, increasing age, previous AF, hypertension, premature supraventricular complexes, conduction disease, prior mediastinal irradiation, and increased serum levels of B_2 microglobulin.[77,109,116,136] • Specific to the MM population: renal dysfunction, baseline hypertension, left atrial dilatation, previous atrial arrhythmias, left ventricular dysfunction, and excess intravenous fluid in the first 14 days after HCT.[77,108,137]	• Melphalan is particularly arrhythmogenic; the incidence of AF associated with its use ranges from 6% to 11% (**Table 1**).[77,119] • Other risk factors are prior AF, age ≥50 years, HLA-unrelated donor, dyslipidemia, and a prolonged QTc interval before HCT. • Several echocardiographic measures not in routine practice, such as left atrial ejection fraction, are associated with the development of AF.[22,24]
	Mechanisms	• Patients are at an increased risk of developing atrial arrhythmias because of infections, large fluid balance changes, electrolyte imbalances, and proinflammatory states such as during engraftment syndrome.[135] • Despite sepsis being an established risk factor for AF, this association was not investigated or adjusted for in any of these studies.[148]	
Heart failure	Short-term	• The short-term incidence of heart failure is low (≤1.1%).[28,77] • One study of 32 consecutive patients with serial echocardiography after HCT reported that 31% (n = 10) experienced a decline in their LVEF by ≥10% to ≤50% within 6 weeks after HCT.[138] Of these 10 patients, 2 developed severe pulmonary edema, with 1 fatality.	• The incidence of heart failure ranges from 1.1% to 2.3%.[21,26-29,38,105,114,140,141] • One study reported an incidence of 21.9% in 176 patients, but most of these cases occurred in the setting of ongoing sepsis.[26] • In 1 study of 136 patients, up to 17% (n = 23) experienced a decline in LV systolic function by ≥10% to <53% within 100 days after HCT, with 11 of these patients developing symptomatic heart failure and 3 requiring ventilatory support.[141] In this study, the decision to perform echocardiography was at the discretion of the treating physician.
	Long-term	• The 5-year cumulative incidence is 5%, rising to 9.2% at 10 years.[28] • The 10-year incidence is similar to rates in older patients who underwent HCT before 2009, with 1 study finding a cumulative incidence of 4.8% at 5 years, rising to 9.1% at 15 years.[37]	• The 5-year cumulative incidence is 6%, rising to 8.2% at 10 years.[28] • The long-term incidence is similar between patients who underwent HCT before 2006 and after 2008.[37,94,123,126,127] • Many patients have asymptomatic declines in LVEF in the long-term.[20,22] • The exact timing of these declines after HCT and their clinical significance remain unclear.
	Risk factors	• Risk factors included cumulative anthracycline dose, high doses of chest-directed radiation (>30 Gy), diabetes, and hypertension.[37] • Risk factors are synergistic; the odds ratio of LV systolic dysfunction with a cumulative anthracycline dose ≥250 mg/m^2 is 9.9, rising to 35.3 in the presence of coexistent hypertension or 26.8 in the presence of diabetes.[37,131]	• Risk factors include a greater number of chemotherapy cycles before transplantation (≥5), high anthracycline dose (>400 mg/m^2) before transplantation, more transplantation-related complications, higher HCT comorbidity index, increasing age, the presence of pre-existing diabetes and/or hypertension, and increasing severity of GVHD.[26,27,29,38,114]
	Mechanisms	Cyclophosphamide • High-dose cyclophosphamide (usually ≥180 mg/kg cumulative dose) causes hemorrhagic myocarditis and acute heart failure. • In several previous studies, the cardiovascular mortality was as high as 9.5%, and acute heart failure affected up to 28% of patients.[44-47] • This is rarely encountered in modern practice because contemporary transplantation regimens use lower cyclophosphamide doses (**Table 1**).[48] • Studies examining CV outcomes with the use of post-transplantation cyclophosphamide are summarized in **Table 1**.[25,26,29] Anthracyclines • High cumulative anthracycline dose caused a well-characterized cardiomyopathy.[149] • The risk of cardiotoxicity secondary to anthracyclines is modulated by coexistent risk factors, such as hypertension and diabetes, in conjunction with genetic variation in pathways involved with free radical generation and anthracycline metabolism.[37,122,127,128]	

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TABLE 2 Continued

		Autologous HCT	Allogeneic HCT
Arterial disease	Short-term	• The cumulative incidence of myocardial infarction and stroke is 0.2% and 0.1%, respectively.[28]	• The cumulative incidence of myocardial infarction and stroke is 0.6% and 0.2%, respectively.[28]
	Long-term	• The cumulative incidence of myocardial infarction and stroke at 10 years after HCT remains low at 2.7% and 0.6%, respectively.[28] • In older studies of transplant cohorts, the cumulative incidence of a combination of myocardial infarction, stroke, and peripheral artery disease was 2.3% at 15 years after HCT.[133]	• The 5-year and 10-year cumulative incidence of myocardial infarction is 3.7% and 6.5%, respectively.[28] • The 5-year cumulative incidence of percutaneous coronary intervention is 2%.[22] • The 5-year and 10-year cumulative incidence of stroke is 1.3% and 2.4%, respectively.[28] • In previous transplantation eras, the cumulative incidence of a combination of myocardial infarction, stroke, and peripheral arterial disease was 6% to 7.5% at 15 years and 22.1% at 25 years after HCT.[133,142]
	Risk factors	• Risk factors included hypertension, dyslipidemia, diabetes, obesity, and smoking.[124,127]	• Risk factors included hypertension, dyslipidemia, diabetes, obesity, and smoking.[124,127]
	Mechanisms	GVHD • The increased incidence in allogeneic HCT is driven by GVHD-associated vascular injury and atherosclerosis. This is further influenced by the metabolic changes induced by medications used to treat GVHD, such as corticosteroids and calcineurin inhibitors (Table 1).[22,126,127,133,142] • GVHD has been postulated to have a direct effect on arteries and arterioles through alloreactive cytotoxic T lymphocyte infiltration, leading to endothelial injury, increased lipid deposition and accelerated atherosclerosis.[134,143,144] Radiation • Radiation increases oxidative stress and inflammation in vascular cells, which may cause injury through loss of vascular elastic tissue and muscle fibers, fibrosis of the adventitia, or accelerated atherosclerosis.[145] • The incidence of arterial disease is as high as 15% at 10 years after HCT if the patient had chest radiation combined with diabetes, hypertension, or hyperlipidemia.[139] • Most data on radiation are from previous transplantation eras; contemporary radiotherapy techniques incorporate advances that result in a lower mean heart dose, and the risk of radiation-induced arterial disease is attenuated in contemporary transplantation regimens.[145]	
Pericardial disease	Short-term	• Rarely encountered; not enough information to estimate incidence.	• The short-term cumulative incidence ranges from 0.8% to 1.7%.[29,106]
	Long-term	• Rarely encountered; not enough information to estimate incidence.	• The 2-year cumulative incidence is 3.1% in 1 study.[106] • The incidence does not seem to increase thereafter, with another study showing the 5-year cumulative incidence of 3%.[22] • The incidence is noted to be as high as 13.6% in the first year after HCT in haploidentical transplantation.[26]
	Risk factors	• Rarely encountered; no significant risk factors.	• Risk factors include increasing age (>50 years), multiple transplant procedures, and chronic GVHD.[106]
	Mechanisms	• It is unclear but may be related to pericardial inflammation in allogeneic transplantation. • The proportion of patients who develop tamponade alongside the effusion ranges from 8% to 83%; however, in case series, the mortality rate is low because of timely intervention with pericardiocentesis.[26,106]	
Ventricular arrhythmias		• Ventricular arrhythmias are uncommon across both transplantation types. • The short-term cumulative incidence of ventricular arrhythmias after autologous HCT is 0.1%, rising to 0.6% at 10 years.[28] • After allogeneic HCT, the short-term cumulative incidence is 1.0%, the 5-year cumulative incidence is 0.8% to 1%, and the 10-year cumulative incidence is 1%.[22,28] • The mechanisms causing ventricular arrhythmias in the HCT population are unclear.	
Heart conduction disorders		• Historically, there is an increased incidence of late conduction system disease across both types of HCT. • This is thought to be related to previous exposure to high-dose chest radiation, and it has declined in contemporary cohorts as the mean heart dose has reduced.[150]	

AF = atrial fibrillation; HLA = human leukocyte antigen; LV = left ventricular; LVEF = left ventricular ejection fraction; MM = multiple myeloma; QTc = corrected QT interval; other abbreviations as in Table 1.

Patients often require intravenous fluid or blood products to support them through HCT, and large shifts in fluid balance can trigger cardiovascular complications such as arrhythmias and symptomatic heart failure. In the long-term, there is a higher incidence of adverse cardiovascular outcomes in HCT patients compared with the general population, particularly in allogeneic transplantation recipients.[28,126]

The HCT population is a highly selected cohort because patients with pre-existing cardiovascular disease are less likely to be offered HCT, lowering the rate of cardiovascular adverse events. The most common adverse cardiac outcomes for each transplantation and associated risk factors are discussed later and are summarized in **Table 2**. The results of the literature search are provided in the Supplemental Appendix.

AUTOLOGOUS HCT. Atrial fibrillation (AF) is the most common short-term cardiovascular event after autologous HCT, occurring in 2.8% to 8.5% of transplantations.[28,109,116] Most cases occur within 3 weeks after HCT, but it is also not uncommon in the long-term, with a 5-year cumulative incidence of 6.7%.[27]

Risk factors for developing AF include conditioning with melphalan, increasing age, previous AF, and hypertension at the time of HCT.[77,109,116,136] Multiple myeloma is the most common indication for autologous HCT, and patients undergoing transplantation for multiple myeloma have an increased risk of developing AF or flutter, with the incidence ranging from 10% to 27% in the short-term.[108,137] Risk factors for AF specific to the multiple myeloma population included baseline renal dysfunction, hypertension, previous AF, left atrial dilatation, left ventricular dysfunction, and excess intravenous fluid administration in the first 14 days after HCT.[77,108,137]

The cumulative incidence of HF within 100 days of autologous HCT is up to 1.1%, rising over time to 9.2% at 10 years after HCT.[28,77] Risk factors for developing HF include a high cumulative anthracycline dose before HCT, diabetes, and hypertension.[37] When LVEF is measured routinely after autologous HCT, short-term declines in LVEF appear to be relatively common. One study showed 10 of 32 patients had an LVEF decline of 10% or more to less than 50% up to 6 weeks after autologous HCT.[138] Two patients developed pulmonary edema (1 fatal), and 2 developed AF.

Arterial disease is uncommon after autologous HCT. The cumulative incidence of myocardial infarction within 100 days of HCT is 0.2%, rising to 2.7% at 10 years.[28] The cumulative incidence of stroke is lower, at 0.1% within 100 days of HCT, rising to 0.6% at 10 years.[28] Ventricular arrhythmias are uncommon after autologous HCT, with a 10-year cumulative incidence of 0.6%.[28] Pericardial disease is rarely encountered after autologous HCT.

Autologous transplantation recipients have an elevated risk of developing hypertension, diabetes, and dyslipidemia compared with matched controls. In 1 study of patients who survived 1 year or more after transplantation, the 10-year cumulative incidence of developing 2 or more cardiovascular risk factors was 26%.[139]

ALLOGENEIC HCT. AF is the most common cardiovascular complication after allogeneic HCT. The short-term incidence is 2.5% to 9%,[21,29,38,110,113,119,140] rising to 6.9% to 10.6% at 5 years after HCT.[22,24,28] Risk factors for the development of AF after allogeneic HCT include conditioning with melphalan, increasing age, prior AF, and the use of HLA-unrelated donors.[77,119]

HF is uncommon in the short-term after allogeneic HCT, affecting 1.1% to 2.3% of patients.[21,26-29,38,105,114,140,141] The cumulative incidence increases over time, reaching 8.2% at 10 years after HCT.[28] Risk factors for the development of HF include a high cumulative dose of anthracycline, increasing age, GVHD, pre-existing hypertension, and diabetes.[26,27,29,38,114] Similar to autologous HCT, when LVEF is measured routinely after allogeneic HCT, declines in LVEF are common. In 1 study, 23 of 136 patients had a decline in LVEF of 10% or more to less than 53% within 100 days after allogeneic HCT, and 11 developed symptomatic HF.[27] In the long-term, another study of allogeneic HCT recipients found that 44% had declines in their LVEF, and 28% were symptomatic.[20] Declines in LVEF also occur with the use of post-transplantation cyclophosphamide. One study with a median follow-up of 243 days found that 21.9% of patients developed a fall in LVEF of 10% or more to less than 53%; however, the majority of these patients (94%) also had sepsis.[26] More research is needed to determine which patients with early declines in LVEF will develop clinically significant HF.

Arterial disease within 100 days after allogeneic HCT is uncommon.[28] Although the cumulative incidence of stroke remains low at 2.4% up to 10 years after HCT, the risk of myocardial infarction increases with a 10-year cumulative incidence of 6.5%.[28] The incidence of long-term arterial events after allogeneic HCT is comparable across transplantation eras.[133,142] Certain risk factors for arterial disease are common in the allogeneic HCT population, including hypertension, dyslipidemia, diabetes, obesity, and smoking.[124,127]

GVHD after allogeneic HCT has been postulated to cause accelerated atherosclerosis by alloreactive cytotoxic T lymphocytes infiltrating arterial walls, leading to increased lipid deposition.[134,143,144] Despite this, GVHD has not been shown to be independently associated with arterial events after adjustment for other important variables such as age and cardiovascular comorbidities.[126,127,133,142] However, GVHD is associated with an increased risk of developing a cardiac event after allogeneic HCT (HR = 1.68), and acute GVHD is associated with an increased risk of cardiovascular death (HR = 4.0).[28,127] Chest-directed radiation is associated with vascular injury and an increased risk of coronary artery disease in older transplantation cohorts (OR: 5.2).[124,125,145] In contemporary practice, the risk of arterial disease secondary to radiotherapy has been attenuated by advances in treatment that result in a reduced mean heart dose.[28,145]

Although pericardial effusions occur after allogeneic HCT, they are uncommon in adults. The short-term incidence ranged from 0.8% to 1.7%, rising to 3.0% to 3.1% within 5 years after HCT.[22,29,106]

However, 1 study of haploidentical HCT recipients receiving post-transplantation cyclophosphamide found that 13.6% had a pericardial effusion within the first year after transplantation.[26] The mortality associated with tamponade in this population is low because most patients have timely intervention.[26,106] Risk factors include increasing age, chronic GVHD, and multiple transplantation procedures.[106] Although ventricular tachycardia and conduction system disorders occur, they are uncommon in both the short- and long-term (**Table 2**).

In patients who survive 1 year or more after allogeneic HCT, the 10-year cumulative incidence of developing 2 or more cardiovascular risk factors (hypertension, diabetes, and/or dyslipidemia) can be as high as 40%.[139] In patients on immunosuppression after allogeneic HCT, the incidence of dyslipidemia can be as high as 80%.[146,147] Stage II to IV GVHD has been associated with an increased risk of developing cardiovascular risk factors (hypertension risk ratio [RR]: 9.1, diabetes RR: 5.8, and dyslipidemia RR: 3.2), partly because of the effect of medications used to treat GVHD (**Table 1**).[139] Total body irradiation has been associated with increased rates of diabetes and dyslipidemia, possibly through radiation-induced pancreatic or hepatic dysfunction, combined with gonadal dysfunction after HCT.[88,90-93,97-99,139]

CARDIOVASCULAR AND ALL-CAUSE MORTALITY. Cardiovascular death remains low in both the short-term and long-term, with a 5-year cumulative incidence of 0.2% for autologous transplantation and 1.4% for allogeneic transplantation.[28,126] The leading cause of mortality in both types of transplantation is the relapse of the primary disease.[37,122,124,132,140] In long-term survivorship cohort studies, late mortality after both allogeneic and autologous transplantation has improved. However, life expectancy decreased compared with the general population, and recent reports of improvements in life expectancy were not because of a reduction in death from cardiovascular disease.[6,7]

INDIRECT CAUSES OF CARDIOVASCULAR DISEASE SECONDARY TO AUTOLOGOUS AND ALLOGENEIC HCT. Both autologous and allogeneic HCT are associated with toxicity in other organs and tissues, which may contribute to cardiovascular disease. This includes thrombotic microangiopathy causing systemic and pulmonary hypertension and pericardial effusions, hepatic veno-occlusive disease leading to fluid overload and HF, and sepsis leading to arrhythmias and depression of myocardial contractility.[151-154]

Damage to other organs can also have a long-term impact on the risk of cardiovascular disease. Hypertension can be aggravated by renal disease accrued during the course of the transplantation, and cardiometabolic derangements occur secondary to gonadal dysfunction, thyroid disease, and liver cirrhosis.[155] Depression and anxiety are also prevalent before, during, and after autologous and allogeneic HCT, impacting patient lifestyle choices, engagement with treatment, and physical conditioning.[156,157]

KEY POINTS

- Atrial arrhythmias are the most common short-term complication in autologous and allogeneic HCT.
- After autologous HCT, the main long-term complications are HF and atrial arrhythmias.
- After allogeneic HCT, the main long-term complications are atrial arrhythmias, HF, and myocardial infarction.
- Autologous and allogeneic HCT recipients have an elevated risk of hypertension, dyslipidemia, and diabetes after transplantation.

CLONAL HEMATOPOIESIS OF INDETERMINANT POTENTIAL

Recently, clonal hematopoiesis of indeterminate potential (CHIP) has emerged as an age-dependent risk factor for both cardiovascular disease (predominantly coronary artery disease) and cancer.[158,159] CHIP refers to the clonal expansion of stem and progenitor cells caused by a somatic variant endowing the cells with a survival and proliferation advantage. Numerous genes are implicated in CHIP, and the mechanisms linking different variants to coronary artery disease vary between genes.[158,160]

CHIP-related sequence variants are prevalent in autologous HCT recipients, occurring in 29.9% of patients treated for lymphoma and 21.6% to 22.8% of patients treated for myeloma.[161-163] The presence of CHIP in patients who undergo autologous HCT for lymphoma and multiple myeloma indicate a worse overall survival rate compared with controls, with an increased incidence of cardiovascular disease.[161-163] In 1 study of patients with multiple myeloma treated with autologous HCT who had 1 CHIP-related sequence variant, the 5-year incidence of cardiovascular disease was noted to be 21.1% compared with 8.4% in controls.[163] Donors are not routinely screened for CHIP-related sequence variants, and there is no evidence to suggest an increased incidence of

cardiovascular disease after allogeneic transplantation from donors with these variants.[164]

KEY POINTS

- Patients who require autologous HCT for lymphoma or myeloma and have CHIP-related sequence variants may be at an increased risk of cardiovascular disease.
- More research is required to understand the associations between CHIP-related sequence variants and cardiovascular disease after transplantation.

CARDIOVASCULAR ASSESSMENT AND RISK PREDICTION

The goal of baseline cardiovascular assessment is to identify patients at highest risk of cardiovascular disease, optimize their risk factors, and facilitate the safe delivery of the HCT (**Central Illustration**). Baseline assessment includes clinical examination and a comprehensive history. There should be a focus on cardiovascular risk factors and underlying cardiovascular disease, with measurement of body mass index, blood pressure, lipids, and glycosylated hemoglobin (HbA_{1c}). Healthy lifestyle modification should be advised, including smoking cessation. Because of a lack of evidence in HCT cohorts, the management of hypertension, dyslipidemia, and diabetes should follow general guidelines.

A baseline 12-lead electrocardiogram should be performed to identify arrhythmias, and the Fridericia formula should be used to calculate the corrected QT interval.[19] Three small studies found that increased QT dispersion before HCT was associated with HF after transplantation, but this effect may have been transient and related to cyclophosphamide cardiotoxicity.[111,165,166]

The role of cardiac biomarker assessment before transplantation is unclear. Several small studies suggest that serial measurement of natriuretic peptides or troponin T early after HCT may be useful for detecting cardiotoxicity.[105,167,168] Patients who undergo HCT are susceptible to hemodynamic changes through alterations in fluid balance secondary to the infusion of large volumes of intravenous fluid and blood products, and most have recently completed induction chemotherapy or were undergoing consolidation therapy. These factors impair the baseline interpretation of natriuretic peptides (N-terminal pro-B-type natriuretic peptide or B-type natriuretic peptide) and cardiac troponin levels. Because of this, baseline assessment of natriuretic peptides and cardiac troponin is not recommended in asymptomatic patients.[169,170]

IMAGING IN THE ADULT POPULATION. Cardiac imaging should be used to determine left ventricular systolic function and identify structural heart disease before transplantation.[19] Most centers use echocardiography because of wide availability and lesser costs.[171] When feasible, 3-dimensional LVEF measurement with echocardiography is preferred over 2-dimensional LVEF measurement because of reduced variability and better correlation with cardiac magnetic resonance (CMR).[172,173]

Speckle tracking techniques such as global longitudinal strain have a role in identifying subclinical myocardial damage,[174] and there is evidence to support the use of global longitudinal strain in light-chain cardiac amyloidosis as a prognostic marker for patients who undergo HCT. More data are required to define its use after HCT performed for other diseases.[175]

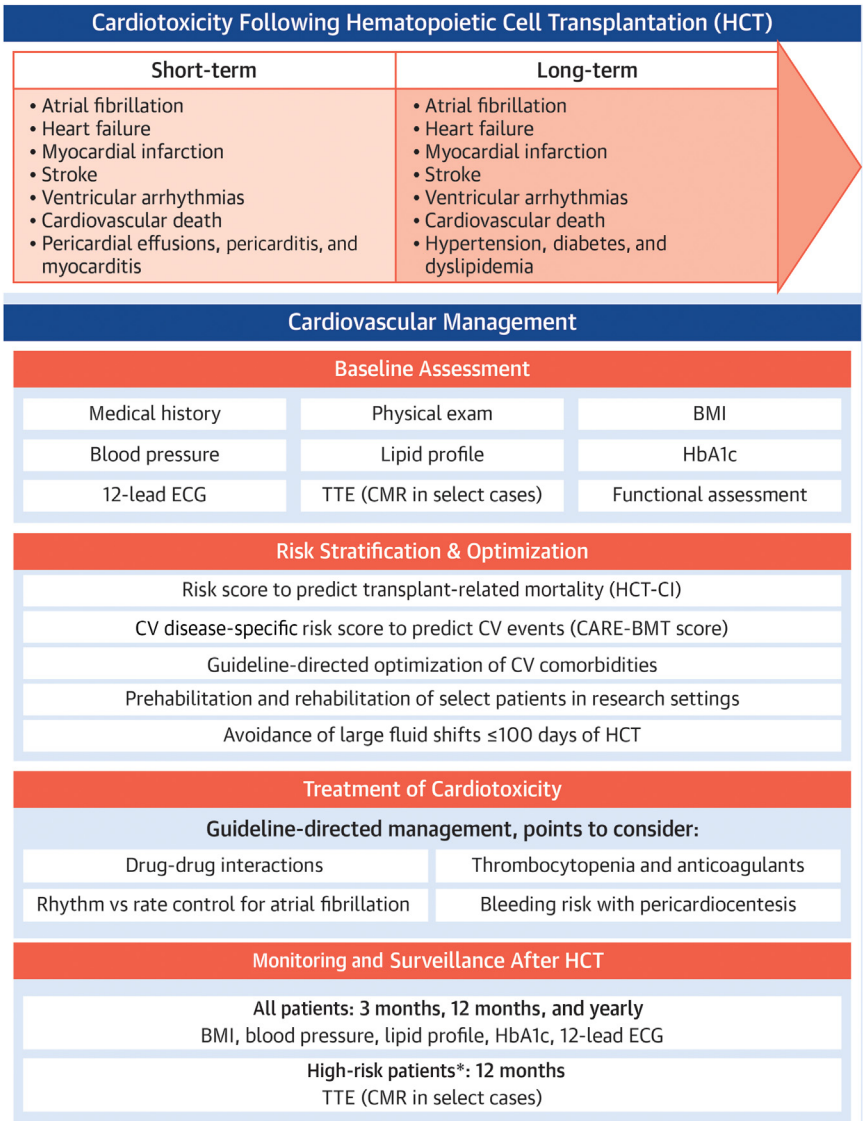
In select cases in which echocardiography is nondiagnostic, CMR should be used over nuclear techniques to minimize radiation dose and provide an assessment of cardiac structure and function. There is no evidence to suggest that routine stress testing or cardiac computed tomography should be used before HCT in the absence of ischemic symptoms.

REDUCED LVEF, CARDIOVASCULAR DISEASE RISK, AND MORTALITY. Studies investigating the association between a reduced LVEF before HCT and both adverse cardiovascular outcomes and transplantation-related mortality have mixed results (Supplemental Appendix).[16,18,21,38,52,115,117,129,132,176-179] Many of these studies included mixed allogeneic and autologous HCT populations.[18,117,129,176,177,179]

Several studies have shown an increased incidence of short-term adverse cardiovascular outcomes (including arrhythmia, HF, and myocardial infarction) and mortality in those with a reduced baseline LVEF.[16,21,38,176] Other studies have shown no increase in short-term cardiotoxicity or mortality in those with a reduced LVEF.[18,52,117,132,177,178] In the long-term, 2 studies have shown no increase in the incidence of HF[129] or mortality[115] with reduced LVEF before HCT.

All of the studies were retrospective and have a high likelihood of selection bias; patients were carefully selected and must have been clinically stable despite an impaired LVEF. In practice, patients are excluded from HCT if they have an impaired LVEF, although the cutoff varies across centers, ranging from 50% or less to 35% or less.[171] It is possible that some patients may have been excluded from HCT based on measurement

CENTRAL ILLUSTRATION **Short- and Long-Term Cardiotoxicity and Proposed Recommendations for the Assessment, Treatment, and Monitoring of Cardiovascular Complications**



Gent DG, et al. JACC CardioOncol. 2024;6(4):475–495.

The short- and long-term cardiovascular (CV) complications are briefly noted here, with Table 2 providing additional detail including incidence rates. Various potential strategies are recommended for baseline assessment, risk stratification, and optimization, as well as monitoring and surveillance, although this should be tailored to the individual patient. Additional research is needed to define the optimal strategies for surveillance, risk assessment, and risk mitigation. *High risk = pre-existing CV disease, multiple poorly controlled CV risk factors, graft-versus-host disease, high doses of chest-directed radiotherapy, doxorubicin ≥250 mg/m^2, the use of alkylating agents, or total body irradiation during transplant conditioning. BMI = body mass index; CARE-BMT = Cardiovascular Registry in Bone Marrow Transplantation; CMR = cardiac magnetic resonance; ECG = electrocardiogram; HbA1c = glycated hemoglobin; ECG = electrocardiogram; HCT = hematopoietic stem cell transplantation; HCT-CI = hematopoietic stem cell transplant comorbidity index; TTE = trans-thoracic echocardiogram; CMR = cardiac magnetic resonance.

error because of the imprecision inherent to 2-dimensional LVEF assessment with echocardiography.[172,180] Some centers use RIC if the ejection fraction is impaired; however, only 2 studies evaluating outcomes in patients with an LVEF below 50% used RIC in patients with a reduced LVEF.[18,117] In 1 of these studies, 81.6% received RIC, and there was a significantly lower 1-year overall survival in patients with an

LVEF <43%.[18] There is also evidence to suggest that impaired cardiac reserve measured through changes in LVEF with exercise had a stronger association with short-term mortality than resting LVEF.[179]

The discrepancy in the study outcomes suggests that some patients with a reduced LVEF may have been able to safely undergo HCT. However, because of the lack of data, the decision to perform HCT with an LVEF of 50% or less and/or the use of RIC is based on expert consensus of hematologists and cardiologists at individual transplant centers.

CARDIOPULMONARY EXERCISE TESTING. Cardiopulmonary exercise testing (CPET) represents an integrative approach to the assessment of cardiorespiratory fitness and cardiac reserve. CPET allows dynamic, noninvasive assessment of the hematopoietic, pulmonary, cardiovascular, skeletal muscle, and neural systems. Patients may have baseline impairments beyond left ventricular dysfunction that have a systemic impact on their ability to tolerate the physiological demands of HCT, including anemia, infections, large fluid volume shifts, and insults secondary to the conditioning regimen.[181]

Three small pilot studies have shown that CPET in the HCT population is feasible (completion rates of 91%-95%) and safe.[182-184] Patients with impaired maximal respiratory oxygen uptake are at higher risk of mortality and an increased length of hospital stay within the first 100 days after HCT.[184] CPET may have a role before HCT in identifying patients who would benefit from prehabilitation and/or rehabilitation to improve cardiac reserve[185] and after HCT in the ongoing assessment of patients with exertional cardiovascular symptoms within 12 months after HCT by unmasking impairments in cardiorespiratory fitness.[186,187] Future work should determine if CPET is better than resting LVEF measurement at predicting adverse cardiovascular outcomes and transplantation-related mortality.

RISK STRATIFICATION SCORES. Before transplantation, the most widely used risk stratification tool to predict nonrelapse mortality and overall survival is the hematopoietic cell transplantation comorbidity index.[171,188] The hematopoietic cell transplantation comorbidity index covers various organ systems and has categories for arrhythmia, HF, coronary artery disease, and valve disease. The score is not validated for the assessment of cardiovascular-specific risk, and the discriminatory performance of the score is modest for the prediction of nonrelapse mortality and overall survival.[188]

Cardiovascular risk prediction scores have also been proposed to detect acute and long-term cardiotoxicity (Supplemental Appendix).[29,125,189] Recently, Vasbinder et al[40] developed the Cardiovascular Registry in Bone Marrow Transplantation (CARE-BMT) score for cardiovascular risk stratification in adult autologous and allogeneic transplantation recipients. The model includes 8 variables available at the time of transplantation and was used to predict a composite of cardiovascular death, myocardial infarction, HF, stroke, AF, or flutter and sustained ventricular tachycardia at 100 days, 5 years, and 10 years after HCT. The model performed well in the validation cohort across both types of transplantation. Two genome-wide association studies identified single-nucleotide variations that were associated with an increased risk of both early (<1 year)[128] and late (≥1 year)[122] cardiomyopathy. However, external validation is needed to incorporate these into clinical risk prediction models.

KEY POINTS

- Baseline cardiovascular risk assessment should include a comprehensive history and examination, body mass index assessment, blood pressure measurement, lipid profile, and HbA_{1c}.
- Twelve-lead electrocardiography and transthoracic echocardiography (or CMR) should be performed before HCT in all patients.
- The decision to perform HCT in patients with an LVEF of 50% or less is based on expert consensus within individual transplant centers.
- More research is needed to determine the utility of CPET before and after HCT.
- Cardiovascular-specific risk scores have been developed but require validation and are not in routine clinical use.

CARDIOVASCULAR CARE OF HCT RECIPIENTS

THE ROLE OF PREHABILITATION AND REHABILITATION IN HCT. Patients who undergo HCT physically decondition because of the intensity of the treatment, potential complications, and prolonged bed rest (typically 4 weeks or more). There is limited evidence for any role of pharmacologic cardioprotection. The OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) trial showed a modest benefit of enalapril and carvedilol administered before chemotherapy, preventing a decline in LVEF of −3.1% at 6 months after chemotherapy. However, this endpoint was driven by patients who received chemotherapy for acute leukemia, not those who

TABLE 3 Management of Cardiovascular Toxicities Secondary to HCT

	Management
Atrial fibrillation or flutter	• Patients at risk should be identified before HCT (Table 2). • The initial approach is the same as in other contexts; efforts should be made to identify and treat potentially reversible causes, such as anemia, infection, and/or electrolyte imbalances. Rate or rhythm control • There is no strong evidence to recommend rate control over rhythm control for atrial fibrillation or flutter that develops after HCT. • In the short-term after HCT, the likelihood of rhythm control failing increases because of changes in electrolytes and volume status secondary to IV fluids and blood products; infections from immunosuppression; and proinflammatory states induced by engraftment syndrome, GVHD, and graft failure. • If rate control is chosen, then beta blockers are preferred over nondihydropyridine calcium channel blockers as first-line agents to avoid the risk of drug-drug interactions. • Aggressive rate control in the context of ongoing inflammation should be avoided in the absence of symptoms attributable to the arrhythmia. • Indications for rhythm control include unacceptable hypotension with rate-controlling medication and symptomatic heart failure, similar to other situations. • The management of atrial fibrillation in the long-term should follow general guidelines.[195,196] Anticoagulation • There is no prospective randomized evidence to recommend either direct-acting oral anticoagulant drugs or low molecular weight heparin in the HCT cohort. • Anticoagulant decisions are made on a case-by-case basis, considering other organ involvement (especially renal or hepatic dysfunction) and drug-drug interactions.[19,186] • Unless the patient has a clear indication for anticoagulation with a VKA, such as moderate to severe mitral stenosis or a mechanical heart valve, then VKA is not preferred because of potentially labile INRs in the period after transplantation. • Anticoagulation should be avoided if there is active or recent major bleeding and/or the platelet count is <25,000/μL.
Heart failure	Acute heart failure (within 100 days after HCT) • Within 100 days after HCT, patients rarely develop acute heart failure secondary to the conditioning regimen and treatment before HCT. • Left ventricular systolic dysfunction can occur secondary to sepsis, and it may be difficult to differentiate this from cardiotoxicity secondary to transplant conditioning and treatment before HCT. • Because of a lack of evidence regarding the treatment of acute heart failure after HCT, management should follow general heart failure guidelines.[197,198] Late onset heart failure • The treatment of late onset LV dysfunction after HCT in adults should follow general heart failure guidance because of the lack of prospective data specific to the HCT cohort.[197,198] • Previous studies have focused on the effect of neurohormonal blockade and statin therapy in different cancer cohorts to prevent the onset of LV dysfunction rather than the treatment of established LV dysfunction.[186,199,200] • In patients with a good prognosis (≥1 year), cardiac resynchronization therapy should be considered in the presence of standard indications. • There is limited evidence to guide advanced heart failure interventions for late onset heart failure after HCT, and treatment should be determined on a case-by-case basis.
Vascular arterial disease	• Patients at risk of arterial disease should be risk stratified and given primary prevention treatment (eg, lifestyle advice and statin therapy) as per general population guidance. • Given the increased incidence of arterial disease, particularly after allogeneic HCT, patients should have their CV risk factors assessed on a yearly basis (blood pressure, BMI, lipids, and HbA_{1c}). • In the absence of clinical signs or symptoms of ischemia, there is no indication to perform functional imaging and/or computed tomography angiography to screen for disease. • Physicians should be aware of drug-drug interactions, such as those between CYP 450 inhibitors like verapamil or diltiazem and calcineurin inhibitors. • Patients with symptoms consistent with arterial disease should be managed according to general guidance. • If invasive procedures that carry a risk of bleeding are indicated, such as percutaneous coronary intervention requiring long-term antiplatelet therapy, physicians should manage thrombocytopenia and strategies to reduce the risk of bleeding, such as deferring intervention until the platelet count has increased (if it is not a time-critical procedure) and using dual antiplatelet therapy for the shortest period possible (1-3 months) before switching to single antiplatelet therapy.[19]
Pericardial effusion and pericarditis	• Unless the effusion is causing signs and symptoms of cardiac tamponade (eg, sinus tachycardia, distended internal jugular vein, hypotension, or pulsus paradoxus), the patient should be observed clinically with a repeat scan to ensure the effusion has resolved. • The optimal time interval for repeat scanning is unclear, but general guidance suggests repeating the echocardiogram 7-14 days after the index echocardiogram in small to medium effusions (>4 to ≤20 mm), with a repeat scan in 4 to 6 weeks if the effusion is resolving.[19] • If pericardiocentesis is required, then modifications to standard practice should be used to account for potential complications, such as thrombocytopenia and hepatomegaly, as described by Jacob et al.[201] • Pericardial effusions are unlikely to reoccur in this cohort, but if they do, the optimal repeat interventions should be decided on a case-by-case basis. • Pericarditis is uncommon, but when it occurs, it should be treated as per standard guidelines (eg, colchicine with or without corticosteroids if appropriate).

BMI = body mass index; CYP = cytochrome; HbA_{1c} = glycosylated hemoglobin; INR = international normalized ratio; VKA = vitamin K antagonist; other abbreviations as in Tables 1 and 2.

underwent autologous HCT for a variety of indications.[190]

HCT recipients already have an increased risk of cardiovascular disease and mortality, and there has been interest in the role of physical exercise before (prehabilitation) and after (rehabilitation) HCT to attenuate this risk. Contemporary data surrounding exercise interventions have been summarized in reviews by Mohananey et al[185] and Scott et al.[191] Overall, exercise interventions improve aerobic capacity and muscle strength while increasing quality of life and reducing fatigue in HCT survivors.

Sarcopenia is common after HCT and is associated with reduced progression-free and overall survival.[192,193] Several studies have reported reduced loss of lean body mass with exercise interventions.[185] Classic cardiac rehabilitation (eg, following percutaneous coronary intervention or coronary artery bypass grafting) typically incorporates psychosocial assessment, lifestyle modification, and nutritional assessment. These components are highly relevant to the HCT population and should be incorporated into prehabilitation and rehabilitation programs.

The HCT cohort provides unique challenges regarding exercise prescription. These include defining the safe level and intensity of exercise for patients with bone lesions in myeloma and secondary metastasis from other malignancies, identifying the optimal location for exercise in patients at risk of neutropenia, defining the optimal duration and timing of exercise, and determining the best mix of aerobic and resistance training. More research is needed to generate exercise programs tailored to individual patients and their underlying disease, with supporting evidence that these programs improve quality of life and reduce cardiovascular disease and mortality in HCT survivors.

MANAGEMENT OF TOXICITIES. The management strategy for cardiovascular disease occurring in the HCT population is outlined in **Table 3**. The acute management of cardiovascular complications is also discussed in a recent American Heart Association scientific statement.[194]

MONITORING DURING THE FIRST 12 MONTHS AND LONG-TERM SURVEILLANCE. Given the increased incidence of cardiovascular complications across different patient cohorts, long-term surveillance is required for those deemed to be at high risk of complications. Recommendations for surveillance include the International Late Effects of Childhood Cancer Guideline Harmonization Group for childhood, adolescent, and young adult patients; the European Society of Cardiology (ESC) cardio-oncology guidelines; and individual position and scientific statements for the adult population.[19,194,202,203]

Guidelines from the ESC and the American Society of Clinical Oncology recommend different surveillance strategies based on cardiovascular disease risk.[19,204] High-risk patients include those with allogeneic HCT, pre-existing cardiovascular disease, multiple poorly controlled cardiovascular risk factors, GVHD, previous cancer treatment including high doses of chest-directed radiotherapy, doxorubicin-equivalent dosages at 250 mg/m^2 or higher, and the use of alkylating agents or total body Irradiation during transplant conditioning. According to these expert consensus statements, all patients are recommended to have a physical examination, 12-lead electrocardiography, and a review of cardiovascular risk factors (including body mass index, blood pressure, lipids, and HbA_{1c}) 3 and 12 months after HCT and then yearly thereafter. Those at high risk (ie, those with 1 or more of the high-risk features) are recommended to have a repeat transthoracic echocardiogram 12 months after HCT.[204] An additional echocardiogram at 3 months after HCT can be considered in high-risk patients as per ESC guidance.[19]

CONCLUSIONS

The HCT population is at risk of a variety of cardiovascular complications. The risk varies between patients and is influenced by several factors including comorbidities, age, type of transplantation, and treatment before transplantation. Adult patients are susceptible to a variety of cardiovascular diseases, and it can be challenging to identify those at increased risk. The evidence for risk stratification based on LVEF measurement before HCT and biomarkers is weak, and many of the treatment recommendations for cardiovascular complications are extrapolated from general population guidance. Long-term follow-up is based on surveillance for cardiomyopathy and modification of cardiovascular risk factors. More prospective studies in the HCT population are needed to inform risk prediction and the short- and long-term management of cardiovascular complications.

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KEY WORDS cardio-oncology, cardiotoxicity, hematopoietic cell transplantation, hematopoietic stem cell transplantation, survivorship

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

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