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Late Cardiovascular Morbidity and Mortality Following Pediatric Allogeneic Hematopoietic Cell Transplantation

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Abstract

We analyzed late cardiovascular outcomes of 661 patients who survived at least two years from hematopoietic cell transplantation for childhood hematologic malignancy between 1995 and 2008.

Center for International Blood and Marrow Transplant Research data was supplemented with

surveys focused on cardiotoxicity and potential risk factors. The median duration of follow-up was

97 months (range 24–230). 4.2% of survivors experienced at least one of the primary outcomes

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including coronary artery disease (0.2%), cerebrovascular accident (0.6%), cardiomyopathy (3%), and cardiac-related death (0.5%). Patients who received anthracycline chemotherapy (HR 4.67, $p=0.036$) or cranial or chest radiation (HR 5.58, $p<0.0001$; HR 2.18, $p=0.0087$) were at increased risk for developing one of the primary outcomes. Dyslipidemia was diagnosed in 18% of survivors. Pre-transplant anthracycline (HR 1.74, $p<0.0001$) and chest radiation (HR 1.34, $p=0.0371$) were risk factors for dyslipidemia. Overweight/obese body mass status was present in 63% of patients at baseline, 65% at 2 years, and 52% at most recent evaluation. Diabetes was diagnosed in 7% of subjects. In conclusion, severe cardiovascular complications were infrequently reported. The incidence of risk factors including obesity and dyslipidemia were significant and will likely increase the risk of cardiovascular disease over time in transplant survivors.

Introduction

Survivors of allogeneic hematopoietic cell transplantation (HCT) are at risk for cardiovascular (CV) late effects including early cardiac death.¹⁻³ Contributing to this risk are genetic predisposition, pretransplant therapeutic exposures, the transplant conditioning regimen, graft-versus-host disease (GVHD) and associated-therapies, post-transplant complications, and life style factors.⁴⁻⁸ The majority of the literature regarding late CV complications of childhood leukemia therapy comes from the study of non-transplant survivors.^{7, 9-11} Far less is known about these late effects following HCT in childhood.

This multicenter study sought to establish the incidence of severe CV related adverse outcomes in a cohort of long-term survivors of childhood transplantation. We examined the incidence of risk factors associated with CV disease and how they, along with patient and treatment related factors, influenced the development of CV adverse outcomes.

Materials and Methods

Study Population

The study population included patients aged 21 years or less at the time of transplant who survived, relapse-free at least two years following first allogeneic HCT for hematologic malignancy between January 1, 1995 and December 31, 2008. Transplants were performed at twelve Pediatric Blood and Marrow Transplantation Consortium (PBMTTC) centers. All patients received a myeloablative conditioning regimen based on the definition published by Bacigalupo, et al.¹² All stem cell sources and donor types were included except syngeneic twins. Patients who developed one of the primary CV outcomes of interest within the first two years following transplant were excluded from the analysis to distinguish acute toxicity from late effects.

Data Collection

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR) database and from pre- and post-HCT supplemental forms. The CIBMTR has a research database with information on more than 425,000 patients. Computerized checks for discrepancies, physicians' review of submitted data and center

audits ensure data quality. Data are collected before transplant, 100 days and six months after transplant, annually until 6 years, and every other year thereafter, or until death.

Data regarding patient demographics, disease, survival, relapse, graft type, and the presence of GVHD is collected for all patients participating in the CIBMTR repository. A subset of participants are selected for research level data collection including all patients in this study. Centers report the presence of clinically significant organ impairment including the presence of CV and related late effects.

Data not available in the CIBMTR database were collected on forms focused on pre- and post-transplant exposures. Data obtained from the pre-transplant form included the use of anthracycline chemotherapy in isotoxic doxorubicin equivalents, the use of cranial and/or chest radiation, history of medication treated hypertension, lipid abnormalities, clinically significant cardiomyopathy, coronary artery disease (CAD)/MI, stroke/cerebrovascular accident (CVA), the presence of diabetes treated with medications, and the presence of cardiac structural defect(s). Data from the post-transplant form included the prescription of medications used to treat hypertension, diabetes, or lipid abnormalities; dyslipidemia; the development of new cardiomyopathy, CAD/MI, stroke/CVA; and height and weight at 2 years post-transplant and at most recent follow-up.

Primary Cardiovascular Outcomes—The primary aim of this study was to establish the cumulative incidence of CV outcomes (CAD/MI, stroke/CVA, cardiomyopathy, and cardiac-related death) in patients who survived disease-free a minimum of two years following allogeneic transplant. CAD/MI or stroke/CVA were recorded if any of the diagnoses were reported by a physician two years or longer after transplant. Clinically significant cardiomyopathy was defined as the presence of decreased ejection or shortening fraction that was determined to be clinically significant by the attending transplant physician and required ongoing treatment or follow-up. There was no specific ejection or shortening fraction required for the diagnosis of cardiomyopathy. It was not determined if the diagnosis was based on routine clinical screening or clinical symptom. Cardiac-related death was reported if the primary cause of death reported was cardiovascular in nature. All reports of cardiac-related deaths were reviewed by two study physicians.

Cardiovascular Risk Factors

We examined the incidence of risk factors associated with CV disease including obesity based on body mass index (BMI), diabetes, hypertension, and dyslipidemia. We additionally investigated patient (age, diagnosis, gender, and race) and treatment related factors (pre-HCT therapy, conditioning regimen, and GVHD) and their effect on CV outcomes.

The BMI was calculated prior to the start of transplant conditioning, 2 years post-HCT, and at most recent follow-up. Normative BMI values are not defined for children less than 2 years old and patients in this age group were excluded from the baseline assessment. BMI status was classified as underweight, normal weight, obese, and overweight based on Centers for Disease Control and Prevention (CDC) definitions.^{13, 14} For survivors aged 2 to 20 years, BMI was characterized by calculating an age and sex specific percentile according to the 2000 CDC Growth Charts.¹⁵ In this age group BMI status below 5th percentile was

classified as underweight, 5%–84.9% normal weight, 85%–94.9% overweight, and 95% and above as obese. For patients older than 20 years a BMI less than 18.5 was classified as underweight, 18.5–24.9 as normal weight, 25–29.9 as overweight, and 30 and greater as obese.

Dyslipidemia was defined as a triglyceride level >150 mg/dl, high-density lipoprotein (HDL) cholesterol level <40 mg/dl, and/or low-density lipoprotein (LDL) cholesterol level >130 mg/dl. A subject was classified as having diabetes if the diagnosis was documented in the patient's medical record and he/she received insulin or oral hypoglycemic medication two years or later after transplant. Hypertension was defined as having elevated blood pressure that was treated with medication.

Statistical Analysis

Descriptive statistics were used to summarize patient demographic, disease, HCT-related variables, dyslipidemia, and BMI status. The cumulative incidence function was used to estimate the probability of experiencing a primary CV outcome. No adjustments were made for age at follow-up. Univariate models were developed to assess risk factors for the primary CV outcomes, dyslipidemia, and obesity. Death and relapse were treated as competing risks. Multivariable regression models were not developed due to sample size limitations. All tests were two-sided and 5% level of significance was used throughout. The same data points were not routinely collected over the entire length of the study at all centers and clinical standards of care evolved over time resulting in missing data. When data were missing, patients were excluded from those analyses affected by the missing data, but included in all other analyses. Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Study Population and Transplant Characteristics

The final study population included 661 patients. The selection schema is provided in Figure 1. Patient and transplant characteristics are presented in Table 1. The median age at transplantation was 9 years (range <1–21 years). The median duration of follow-up was 8 years (range 2–19 years) from transplantation. The CIBMTR completeness index of follow-up, the ratio of observed versus expected data follow-up, was 96% at 5 years and 86% at 10 years, meaning that forms were complete for 96% of patients at 5 years following transplant. Pre-transplant treatment and CV characteristics are provided in Table 2.

Primary Cardiac Outcomes

There were 30 diagnoses of one of the primary cardiac outcomes in 28 patients including cardiomyopathy (3%), stroke/CVA (0.6%), cardiac-related death (0.5%), and CAD/MI (0.2%) (Table 3). The cumulative incidence of the primary outcomes was 1% (95% confidence interval, CI, 1–2%) at 5-years and 3% (95% CI 2–4%) at 7-years post-transplant. Pre-transplant anthracycline chemotherapy (HR 4.67, $p=0.0361$), cranial radiation (HR 5.58, $p<0.0001$), and chest radiation (HR 2.86, $p=0.0087$) were associated with the development of one or more of the primary outcomes. Patients who received both chest and cranial radiation were at greatest risk for developing one of the primary outcomes compared

to those who received neither treatment (HR 12.97, $p < 0.001$). The doses of anthracycline or radiation were not significantly predictive of the development of one of the primary outcomes Age at transplant, sex, underlying disease, race, donor type, graft source, conditioning regimen, the use of TBI, the diagnosis of GVHD, the diagnosis of dyslipidemia, and BMI were not predictive of the development of one of the primary cardiovascular outcomes. There were 39 patients who had pre-transplant cardiac structural defect, coronary artery disease/myocardial infarction, and/or cardiomyopathy. Of those 39 patients, only 1 (2.5%) developed the primary outcome following transplant.

Dyslipidemia, Diabetes, and Hypertension

The cumulative incidence of dyslipidemia diagnosed at any time after transplant was 56% (95% CI 52–60) and 63% (95% CI 59–67) at 2 years and 5 years post-HCT. The details of cholesterol and triglyceride abnormalities are provided in Table 3. In single predictor, univariable analysis patients who received pre-transplant anthracycline chemotherapy (HR 1.74, $p < 0.001$) or chest radiation (1.34, $p = 0.0371$) were more likely to be diagnosed with dyslipidemia than those who did not receive those therapies. The risk of dyslipidemia increased 1% for every 10 mg/m² increase in the cumulative dose of anthracycline received ($p = 0.0313$). Increased doses of radiation were not significantly associated with risk of dyslipidemia. Chronic GVHD was a risk factor for the development of dyslipidemia (HR=1.45, $p = 0.0277$). Age, sex, underlying diagnosis, race, donor type, graft source, conditioning regimen, the use of TBI, and BMI were not predictive of the development of dyslipidemia. Pre-transplant triglyceride, HDL, and LDL levels were not available for 42%, 77%, and 77% of patients. Therefore, a potential association between pre- and post-transplant dyslipidemia could not be assessed.

Diabetes requiring medication was diagnosed in 7% of patients at any time following transplant. Half of the patients received anti-hypertensive medications at some point after HCT inclusive of the first two years after transplant with 9% still taking them at most recent follow-up.

Body Mass Index

The BMI status of the population at baseline, two years after transplant, and at most recent evaluation are presented in Table 4. There were more patients with obese status than any other category at each time point assessed. Age, pre-transplant therapy, sex, race, diagnosis, donor source, graft source, conditioning regimen, the use of TBI, presence of GVHD, and baseline BMI were not associated with obesity at 2 years from transplant.

Graft-versus-Host Disease and Survival

Grade II–IV acute GVHD was diagnosed in 45% of the population at any time post-HCT and chronic GVHD in 45% of patients; 11% diagnosed greater than 2 years from transplant. The overall and progression-free survival at 7 years of patients who were alive, disease-free at least 2 years post-transplant were 94% and 89%, respectively. The causes of death in the entire study population were GVHD (22 patients, 42%), relapse of primary disease (14 patients, 27%), subsequent malignancy (7 patients, 13%), infection (3 patients, 6%), and other/unknown (6 patients, 12%). There were three cardiac-related deaths including 2

cardiac deaths in patients with chronic GVHD and one patient who died of anoxic brain injury following cardio-pulmonary arrest. The patients who died of cardiac related causes included a 14 year old female patient who received an unrelated donor peripheral blood stem cell transplant for AML, a 14 year old male patient who received a matched sibling bone marrow transplant for AML, and a 7 year old boy who received an unrelated donor, bone marrow transplant. The ages provided were those at transplantation. There were two other deaths in the patients who had one of the primary CV outcomes, one of relapse of the primary disease and the other of a subsequent malignancy.

Discussion

In this multicenter study, we investigated the long-term CV outcomes of 661 patients transplanted for hematologic malignancy during childhood. The largest previously published multicenter studies of late CV toxicity from groups in the United States and the European Group for Blood and Marrow Transplantation included less than 200 per report making this the largest report of these issues following HCT in childhood to date.^{16, 17}

We report a cumulative incidence of cardiomyopathy, stroke/CVA, CAD/MI, and cardiac-related death of 1% at 5 years and 3% at 7 years post-transplantation. This suggests that the incidence of CV late effects will increase as the cohort ages, consistent with data from survivors of non-transplant childhood leukemia therapy and adult HCT.^{1, 7, 18–20} Stroke/CVA, CAD/MI, and cardiac-related death each occurred in less than 1% of survivors. The low incidence of these events may be explained by the duration of follow-up and the age of the patients at the time of reporting. Studies of survivors of adult transplantation have shown the development of CV outcomes at a younger than expected age and that greater toxicity is seen with longer duration of follow-up.^{3, 18, 21–23} Given the median age of 18.5 years at last follow-up, the survivors in this cohort are young for the development of CV late effects. We hypothesize that the incidence of CV toxicity will increase as the cohort ages and future study will be needed.

Cardiomyopathy was diagnosed in 3% of patients making it the most common of the primary late effects assessed. This may be explained by the number of patients who received anthracycline chemotherapy and/or radiation therapy prior to transplantation. Anthracycline chemotherapy use is a well-established, dose-dependent risk factor for cardiomyopathy in cancer survivors that is worsened by radiation exposure.¹⁰ The median cumulative dose of anthracycline received by patients in this cohort, 112 mg/m², is below that associated with greatest risk of cardiotoxicity.^{10, 11, 24, 25} However, there was a wide range of cumulative dose received with the highest reported dose of 634 mg/m² and increasing doses of anthracycline were predictive of the development of one of primary outcomes. Based on the small number of events we were unable to determine the additive impact of transplant-specific factors on the development of cardiomyopathy in patients who received anthracycline chemotherapy.

We found that cranial radiation was associated with increased risk of developing one of the primary outcomes. The pathophysiologic mechanism underlying this risk is unclear. A potential explanation relates radiation-mediated hypothalamic-pituitary dysfunction leading

to growth hormone deficiency and decreased synthesis of insulin-like growth factor-1 (IGF-1).²⁶ Deficiency of growth hormone and/or IGF-1 have been linked to myocardial hypokinesis, altered cardiac growth, and abnormal response to exercise.^{26–29} A single center study compared the cardiac structure and function of 13 survivors of childhood cancer therapy who received cranial radiation therapy without systemic chemotherapy to their healthy siblings.²⁶ They found that the childhood cancer survivors who received cranial radiation therapy had lower IGF-1 levels, smaller cardiac volumes and decreased left ventricular systolic and diastolic function compared to their siblings. A separate study of childhood cancer survivors reported that treatment with cranial radiation and anthracycline chemotherapy were associated with decreases in left ventricular mass and dimension greater than those who received anthracycline chemotherapy without radiation.³⁰

We did not identify associations of transplant specific factors with the development of one of the primary cardiovascular outcomes. The only transplant-related factor associated with any study outcome was that of chronic GVHD with dyslipidemia. This result may have been confounded by the use of medications used to treat GVHD that can cause lipid abnormalities such as corticosteroid and sirolimus. The lack of association of TBI with the development of one of the primary CV outcomes, dyslipidemia, or obesity was unexpected and differs from prior reports that identified it as an independent risk factor for late CV toxicity.^{31, 32} A potential explanation is that survivors who received non-TBI based conditioning may have had additional factors that increased their risk for CV outcomes making it difficult to distinguish the impact of TBI. Another potential explanation is that the conditioning agents used instead of TBI may have late deleterious cardiovascular effects similar to those seen following radiation therapy.

Cholesterol abnormalities and dyslipidemia are risk factors for childhood CV illness that influence the development of disease in adulthood.³³ Data from the 2011–2014 National Health and Nutrition Examination Surveys (NHANES) showed that 21% of children aged 6–19 years had at least one abnormal cholesterol measure with low HDL and high non-HDL reported in 13.4% and 8.4% of those tested.³⁴ The prevalence increased with BMI status and older age.³⁴ We report low HDL and high LDL cholesterol measures in 15% and 10% of patients tested, comparable to those described in the NHANES of otherwise healthy children.³⁵ The American Academy of Pediatrics (AAP) and expert panel recommendations advise universal lipid screening of all 9–11 year old children with additional screening of younger children and adolescents based on individual CV risk factors and family history.^{36, 37} Due to the large amount of missing cholesterol data we are unable provide data derived screening guidelines for transplant survivors. However, we suggest that at minimum patients should have the routine surveillance recommended by expert panel and the AAP.^{34, 36, 37, 35} Furthermore, we advocate for heightened surveillance in survivors with additional risk factors including history of GVHD, obesity and older age. The large number of patients with missing lipid measurements in our study suggests that regular monitoring may not be performed at all transplant centers. If dyslipidemia screening is not routinely performed by the HCT center, then survivors should be counselled to have testing completed by another medical professional.

Childhood obesity is a significant problem in the general population and pediatric cancer survivors. The negative impact of childhood obesity on factors associated with CV health is well-documented and may influence the development of hypertension, cholesterol abnormalities, diabetes, and insulin insensitivity in adulthood.^{38, 39} Reports of obese and overweight/obese status in the general population of 2–19 year old children are 16.9% and 31.7%.⁴⁰ There is a range of obesity estimates in adult survivors of childhood non-transplant leukemia therapy with reported rates of 16–43%.^{41–45} This study found rates of overweight/obese BMI status of 63% and 52% of those with available data at baseline and most recent follow-up respectively, exceeding those reported in the general population and survivors of non-HCT childhood cancer therapy. However, 35% of patients had missing BMI data at baseline and it is possible that this affected the reported rates of overweight/obese status. The high rate of obese/overweight BMI status at baseline may have been in part due to recent pretransplant leukemia directed therapies, including corticosteroid. These results support routine assessment for and counseling about optimal weight and body mass in transplant survivors. Interventions to effectively decrease the risk of obesity are needed.

There are limitations to this study. There was lack of uniformity in clinical practice between centers and standards of care changed during the 13-year study window resulting in missing data that may have affected the reported outcomes with a bias likely in the direction of underreporting. Precise start dates for medications were not reliably recorded in the medical record, which made it impossible to determine the date of diagnosis for conditions such as diabetes that relied on medication use. In these cases, we were unable to discern acute toxicity from true late effect. Patients with diabetes/hyperglycemia and/or hypertension treated with nonpharmaceutical, lifestyle modification were not reported as having either late effect. It is possible that this lead to an underestimation of the true incidence of these long-term toxicities. Additionally, we were unable to assess potential predictive factors, such as genetics and lifestyle behaviors due to the retrospective nature of the study and we were unable to perform multivariate analysis due to the small number of primary events. We were unable to investigate the incidence or impact of body composition alteration, such as sarcopenic obesity, on CV health as these data were not routinely collected by the participating centers. Finally, while the patients in this cohort are representative of those transplanted for hematologic malignancy, the results cannot be extrapolated to those transplanted for other indications. Future study of the CV late effects in survivors of transplant for non-malignant conditions is needed.

In summary, this is the largest study of CV late effects in survivors of childhood allogeneic HCT to date. We have shown that while the primary outcomes of interest were infrequently reported, related late effects and CV risk factors are common in survivors of HCT for childhood hematologic malignancy. The cumulative incidence of these events is expected to increase as the cohort ages. Prospective, long-term studies are needed to further elucidate the roles of genetics, lifestyle, and the transplant process in the development of cardiotoxicity, along with testing interventions to decrease the high incidence of cardiac risk factors described in this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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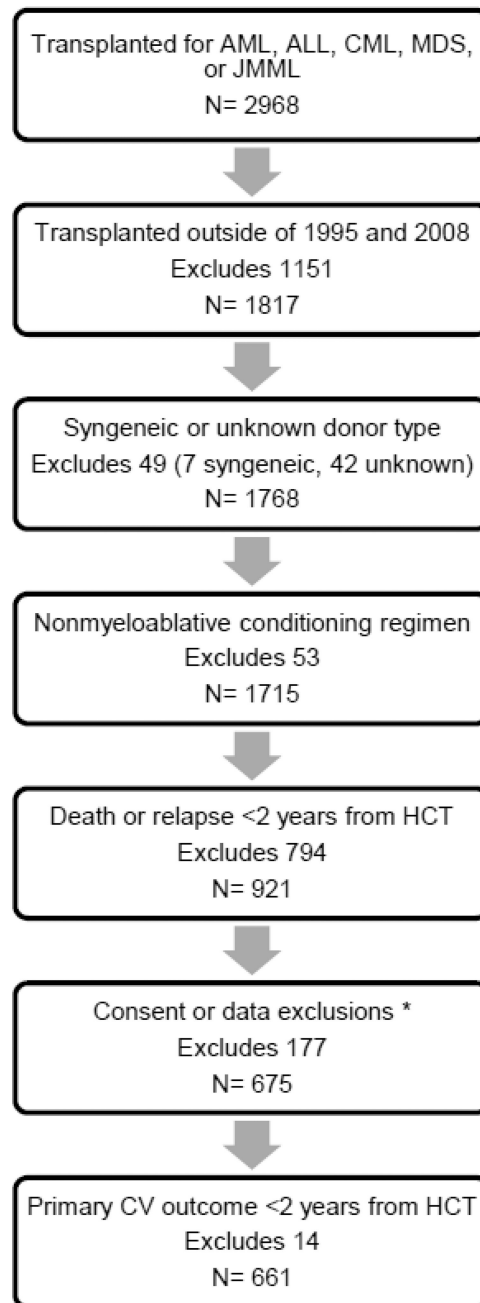


Figure 1.
Study population schema

* Includes subjects who did not consent to CIBMTR research; had missing research data or information about diagnosis or outcome at 2 years; subjects who had a second transplant in the 2 years after first HCT; data no longer required by CIBMTR, and study forms incomplete by study closing date.

Table 1

Characteristics of the study population

Variable	N (%)
Year of transplant	
1995–1999	161 (24)
2000–2004	229 (35)
2005–2008	271 (41)
Age at HCT, years (N=661)	
Median, range	8.8 (0.3–20.9)
0–4	173 (26)
5–9	200 (30)
10–14	164 (25)
15–21	124 (19)
Age at end of study follow-up, years	
Median, range	18.5 (3.0–38.0)
0–9	73 (11)
10–19	326 (49)
20–29	236 (36)
30–38	26 (4%)
Male/Female	367 (56)/294 (44)
Race	
Caucasian	509 (82) *
African American	46 (7) *
Hispanic	40 (6) *
Asian	25 (4) *
Other	5 (1) *
Unknown	36 (5)
Underlying disease	
ALL	326 (49)
AML	203 (31)
MDS	65 (10)
CML	55 (8)
JMML	12 (2)
Donor	
Matched, related donor	236 (36)
Matched, unrelated donor	169 (25)
Mismatched, unrelated donor	236 (36)
Unknown matching, unrelated donor	20 (3)

Variable	N (%)
Graft type	
Bone marrow	381 (58)
Peripheral blood stem cells	87 (13)
Umbilical cord blood	193 (29)
Conditioning regimen	
CY/TBI	453 (83) *
BU/CY	91 (17) *
CY/other (not TBI or BU)	3 (<1) *
Other	114 (17)
GVHD prophylaxis	
CSA + MTX + other	292 (46) *
CSA + other (not MTX or MMF)	134 (22) *
FK506 + MTX +/- other	69 (11) *
T-cell depletion + other	58 (9) *
CSA + MMF + other	53 (8) *
Other	23 (4) *
Unknown	32 (5)
Corticosteroid in GVHD prophylaxis regimen	
Yes	204 (32) *
No	432 (68) *
Missing	25 (4)

CY= cyclophosphamide, BU = busulfan, TBI= total body irradiation, CSA= cyclosporine, MTX= methotrexate

* Percentage reported based on number of subjects with available data, patients with unknown data excluded.

Table 2

Pretransplant treatment and CV characteristics

Variable	N (%) [*]
PreHCT anthracycline	
Yes	482 (73)
No	175 (27)
Unknown	4 (<1)
Median anthracycline dose, mg/m ² (range)	112 (7-634)
PreHCT cranial radiation	
Yes	118 (19)
No	504 (81)
Unknown	39 (6)
Median cranial radiation dose, cGy (range)	1200 (12-5040)
PreHCT chest radiation	
Yes	86 (14)
No	540 (86)
Unknown	35 (5)
Median chest radiation dose, cGy (range)	700 (10-5040)
Hypertension	
Yes	25 (4)
No	576 (96)
Unknown	60 (9)
Diabetes or hyperglycemia	
Yes	14 (2)
No	604 (98)
Unknown	43 (7)
Triglycerides >150 mg/dl	
Yes	91 (24)
No	292 (76)
Missing	278 (42)
HDL cholesterol <40 mg/dl	
Yes	4 (3)
No	151 (97)
Missing	506 (77)
LDL cholesterol >130 mg/dl	
Yes	3 (2)
No	151 (98)
Missing	507 (77)

Variable	N (%) [*]
Cardiomyopathy	
Yes	10 (2)
No	629 (98)
Not assessed	22 (3)
Cardiac structural defect at diagnosis	
Yes	29 (4)
No	628 (96)
Missing	4 (<1)
CAD/myocardial infarction	
Yes	1 (<1)
No	632 (99)
Missing	28 (4)

HDL= high-density lipoprotein, LDL= low-density lipoprotein, CAD= coronary artery disease

* Percentages reported for the categories “unknown” and “missing” reflect the entire population, n=661. The percentages reported for all other variables are based on the available data and excludes the number of subjects with missing data.

Table 3

Cardiovascular and metabolic events.

Variable	N (%) ^δ
CAD/MI	1 (0.2)
Stroke/CVA	4 (0.6)
Cardiomyopathy	22 (3)
Cardiac-related death	3 (0.5)
Multiple events [*]	
Cardiomyopathy + cardiac-related death	1 (0.2)
Cardiomyopathy + stroke/CVA	1 (0.2)
Dyslipidemia ^φ	
Yes	98 (18)
No	453 (82)
Unknown	110 (17)
Triglyceride >150 mg/dl	
Yes	72 (14)
No	425 (86)
Unknown	164 (25)
HDL cholesterol <40 mg/dl	
Yes	98 (30)
No	231 (70)
Unknown	332 (50)
LDL cholesterol >130 mg/dl	
Yes	63 (20)
No	253 (80)
Unknown	345 (52)
Diabetes or hyperglycemia	
Yes	47 (8)
No	560 (92)
Unknown	54 (8)

CAD= coronary artery disease; MI= myocardial infarction; CVA= cerebrovascular accident

^{*} The individual events included in the category multiple events were counted separately in the rows above (e.g. 22 total patients had cardiomyopathy; 20 had only cardiomyopathy, 2 had cardiomyopathy and another event)

^φ Dyslipidemia defined as a triglyceride level >150 mg/dl, HDL cholesterol level <40 mg/dl, and/or LDL cholesterol level >130 mg/dl.

^δ Percentages reported for the category "unknown" reflect the entire population, n=661. The percentages reported for all other variables are based on the available data and excludes the number of subjects with missing/unknown data.

Table 4

BMI status at baseline, 2 years post-transplant, and most recent follow-up

	Baseline, N (%) ^{φ*}	Two Years, N (%) ^φ	Most Recent Follow-up, N (%) ^φ
Underweight	10 (3)	15 (3)	54 (9)
Normal weight	133 (34)	159 (32)	242 (39)
Overweight	31 (8)	51 (10)	75 (12)
Obese	215 (55)	276 (55)	251 (40)
Missing Data	213 (35)	160 (24)	39 (6)

* 59 subjects (9%) were excluded from the baseline assessment due to age less than 2 years.

^φ Percentages reported for the category "Missing Data" reflect the entire population. The percentages reported for all other variables are based on the available data and excludes the number of subjects with missing data.