

## Heart and Vascular Health after Transplant

### Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023



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## Disclosures

- Medtronic – Grant support
- Abbott – Consulting
- AstraZeneca – Consulting
- AbbVie – Consulting
- Johnson and Johnson – Consulting
- Myovant/Pfizer – Consulting



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## Road Map for This Session...

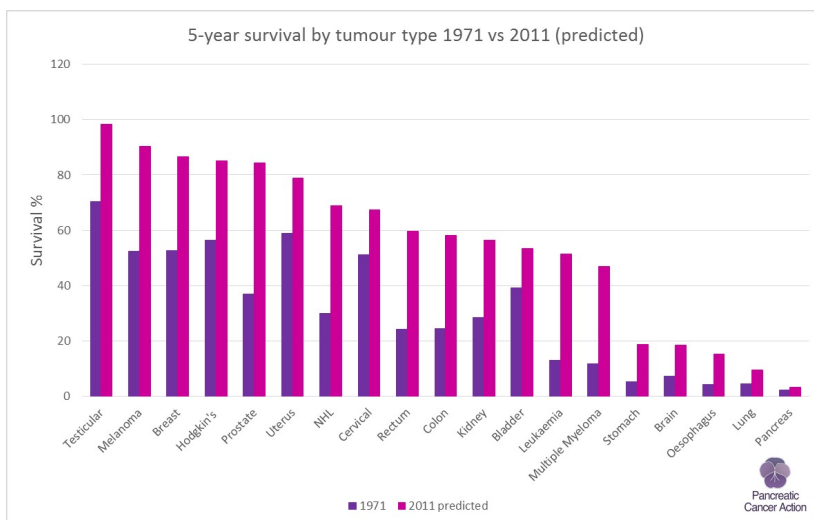
- Review short- and long-term cardiovascular toxicities post stem cell transplantation
- Highlight cardiovascular risk mitigation strategies for stem cell transplant survivors



## Scope of the Problem

- 1 of 3 adults have Cardiovascular (CV) disease (82 million)
- 12 million cancer patients; 14 million cancer survivors
- Approximately 30% of patients receiving cancer therapy will have cardiovascular complications
- Some complications may not become apparent for 10-20 years after completion of treatments

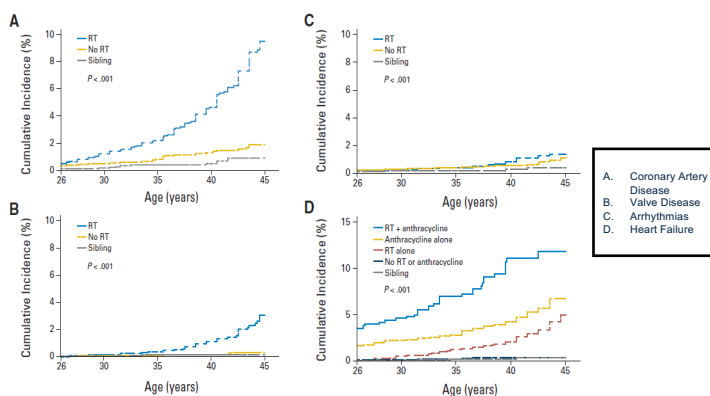
## Trends in 5 Year Cancer Survival



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## CV Disease: Common after Cancer Treatment

- Cardiovascular disease is significantly higher among adult survivors of a pediatric cancer compared to their siblings
- The most commonly encountered cardiovascular complications are heart failure and coronary artery disease
- This is significantly increased in individuals who received chest radiation and/or anthracycline-based chemotherapy



Armstrong et al. JCO 2013;31:3673-3680

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## Cardiovascular Complications after Stem Cell Transplant – Not Common But Serious



- CV disease accounts for <10% of all post transplant-related complications
- ...but when a CV complication occurs, it can be associated with high mortality rate and decreased quality of life for long term survivors
- At 25 years post transplant, 22% of survivors will experience a cardiovascular event
- Therefore it is essential to reduce CV risk in transplant survivors

Ohmoto et al. Bone Marrow Transplant. 2021; 56: 2637-2643.  
Trichelli et al. Blood. 2007; 110: 3463-3471.

## CV Events Post SCT are Associated with:

- Exposure to anthracyclines
- Exposure to radiotherapy (especially chest)
- Exposure to targeted therapy and/or immunotherapy
- Exposure to high-dose cyclophosphamide
- Graft-versus-host disease
- Baseline CV disease and risk factors



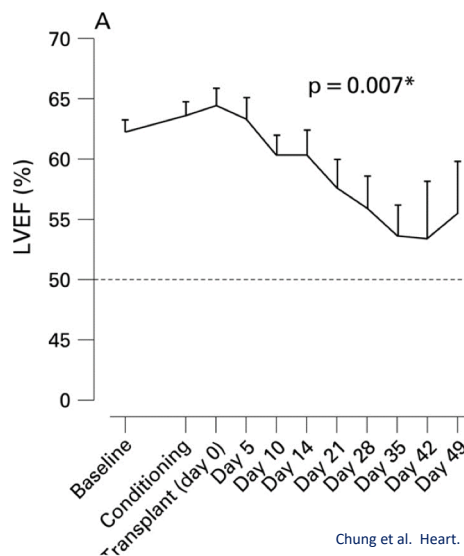
## Early Cardiotoxicity from SCT: First 100 Days

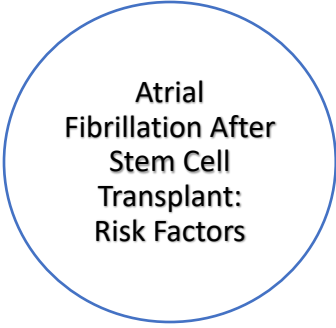
- Heart Failure
- Arrhythmias
- Pericarditis



## Early Cardiotoxicity: Heart Failure (HF) and LV Dysfunction

- Incidence of asymptomatic decrease in heart function (ejection fraction) may occur in up to 33% of patients
- The incidence of symptomatic HF is <5%
- Overall, acute, major cardiotoxic events are uncommon
- **The risk is increased in patients with prior anthracycline treatment**





**Atrial  
Fibrillation After  
Stem Cell  
Transplant:  
Risk Factors**

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Older Age

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Premature atrial complexes or atrio-ventricular conduction delay on pre transplant ECG

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Pre-existing cardiovascular disease

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Elevated creatinine

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Left atrial enlargement

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Melphalan pre-conditioning chemotherapy

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Prior exposure to anthracyclines or mediastinal radiation



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## Pericarditis

**Pericarditis is inflammation of the lining around the heart**

**Incidence in patients post SCT is 3.2%**

**Patients with pericarditis were more likely to have received total body irradiation (odds ratio [OR], 4.57;  $P = .003$ )**

**Colchicine was an effective intervention, with  $\geq 90$  days of treatment associated with reduced recurrence.**



Freyer, Fradley et al. Transplant Cell Ther. 2021;  
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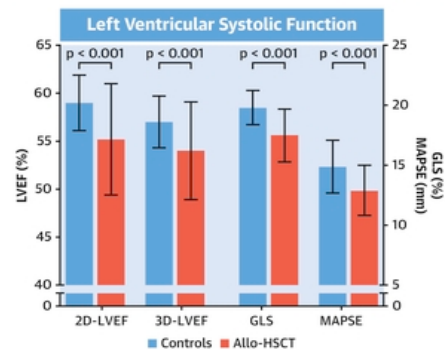
## Late Cardiotoxicity: >100 days post transplant

- Heart Failure
- Arterial Events (heart attacks, strokes)
- Valvular disease
- Autonomic Dysfunction (fast resting heart rate, positional dizziness, fainting)

## Late Heart Failure

- Found in 44.2%, of whom 28.3% were symptomatic.
- Associated with:
  - Age
  - total dose of anthracycline
  - GVHD
  - number of co-morbidities at the time of transplant
- Shortness of breath is the most common presenting symptom
- Risk persists for decades

**CENTRAL ILLUSTRATION: Left Ventricular Systolic Function in Long-Term Survivors Treated as Children, Adolescents, and Young Adults With Allo-HSCT**



Massey, R.J. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):460-71.

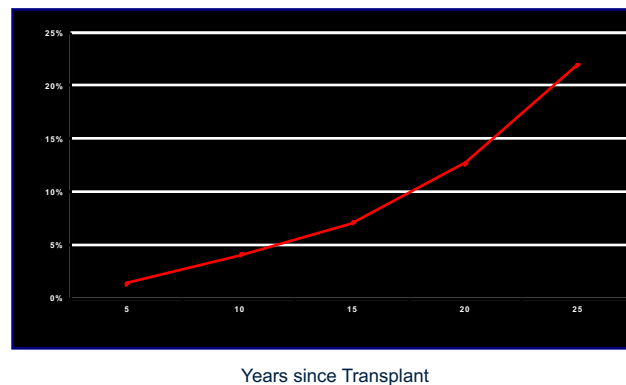
## Late Arterial Events – Heart Attacks and Strokes

- Risk increases with increasing age at transplant
- Risk increases >4x in patients with existing or *de novo* cardiovascular risk factors (17% vs. 4%)
- Risk higher with allogeneic vs. autologous-HSCT



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### Cumulative Incidence of An Arterial Event

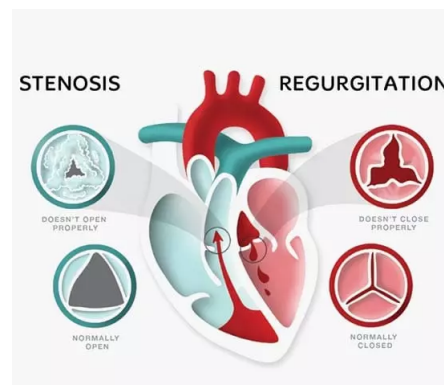


Tichelli, A. Blood 110:3463, 2007

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## Valve Disease and Radiation

- Most often associated with mantle/mediastinal radiation
- May also be associated with anthracycline exposure
- Aortic and mitral valves most commonly affected
- Presents 10+ years post treatments
- Common symptoms include shortness of breath, dizziness or fainting, swelling, chest discomfort, fatigue



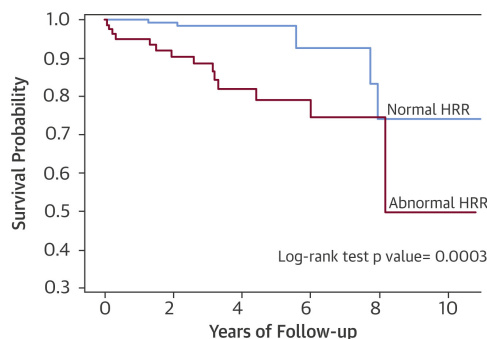
Cutter et al. J Natl Cancer Inst. 2015 Apr; 107(4): djv008  
www.herheart.org

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## Radiation Induced Autonomic Dysfunction

- Autonomic dysfunction is a condition where the nerves that control vital functions like heart rate, blood pressure, and digestion are damaged
- In cancer patients and survivors, this is most commonly due to radiation but can also be related to chemotherapy
- It can cause symptoms like dizziness, palpitations/elevated heart rate, fatigue, weakness, and cognitive impairment
- May have an association with increased long-term mortality



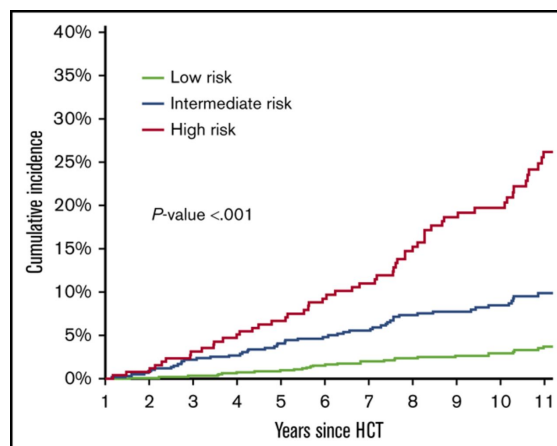
Patients at risk (n)	0	2	4	6	8	10
Normal HRR	179	123	57	16	7	7
Abnormal HRR	84	53	31	18	3	3

Groarke et al. J Am Coll Cardiol. 2015; 65(6):573-83.

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## Risk factors for cardiovascular disease among hematopoietic cell transplantation survivors

- Age at index date (<30, 30-<50, ≥50 years)
- Anthracycline dose ( $\leq 250$ ,  $>250$  mg/m<sup>2</sup>)
- Hypertension
- Diabetes
- Smoking
- Chest radiotherapy

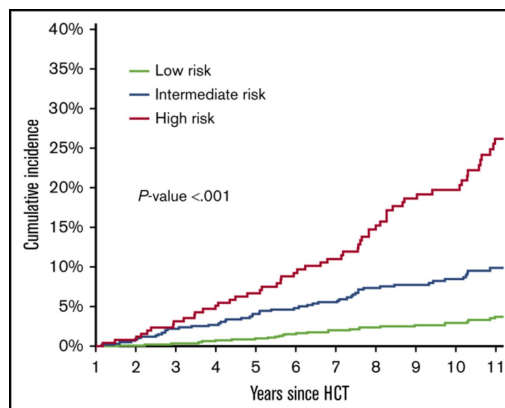


Armenian et al. Blood Adv. 2018; 2: 1756-1764

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## Prediction of cardiovascular disease among hematopoietic cell transplantation survivors

- Low risk group ( $\leq 3$  risk factors)
  - 10-year cumulative incidence of CVD = 3.7%,
- Intermediate risk group (4-5 risk factors)
  - 10-year cumulative incidence of CVD = 9.9%
- High-risk group ( $\geq 6$  risk factors)
  - 10-year cumulative incidence of CVD = 26.2%



## What Can I do To Reduce My Risk of Heart Disease after SCT?



## Prevent Cardiovascular Disease: Learn your ABCs

**A**

### Assess Risk and Aspirin

- Assess each patient's risk of ASCVD risk individually
- Aspirin 81 mg daily for select high-risk patients\*

**B**

### Blood Pressure

- Goal blood pressure <130/80 mmHg

**C**

### Cholesterol, Coronary Artery Disease Screening and Cigarettes

- Assess patient ASCVD risk and risk enhancers to determine if statin therapy is recommended\*
- Smoking cessation counseling, therapy

**D**

### Diet and Diabetes

- Frequent blood glucose monitoring and metformin for diabetes if possible
- Diet rich in fruits, vegetables, nuts, whole grains, and fish and low in saturated and trans fat

**E**

### Exercise and Echocardiogram

- At least 150 minutes per week of moderate intensity physical activity or 75 minutes per week of vigorous exercise

## Aspirin

- The role of aspirin in primary prevention is controversial especially in women
- May consider aspirin in certain high risk cancer populations:
  - Prior radiation to the chest or carotid vascular beds

## Blood Pressure

- Prevalence of hypertension in SCT survivors is estimated at ~18%
- In cancer survivors, hypertension significantly increased the risk for:
  - Coronary artery disease (RR, 6.1)
  - Heart failure (RR, 19.4)
  - Valvular disease (RR, 13.6)
  - Arrhythmia (RR, 6.0; all P values < .01)
- Maintain blood pressure at <130/80mmHg



Armstrong et al. J Clin Oncol 2013;31:3673-80  
Alizadehasl et al. Curr Res Transl Med. 2023.

## Coronary Artery Disease – Screening

Expert consensus documents recommend for high-risk patients:

- Functional, non-invasive stress testing in asymptomatic individuals 5-10 years after exposure to radiation
- Reassessment every 5 years

### Cardiac stress test

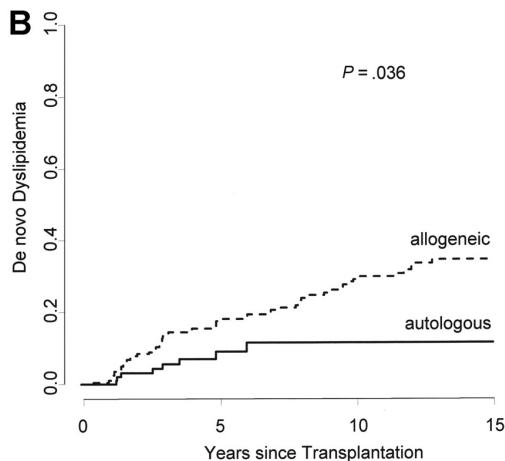
1. Vitals taken at rest
2. Begin walking on treadmill
3. Vitals taken every 3 minutes as intensity increases
4. Exercise until reaching or near maximum heart rate
5. Gradually cool down

Lancellotti et al. J Am Soc Echocardiogr. 2013; 26: 1013-32



## Cholesterol Control

- Lipid abnormalities commonly occur prior to the initiation of cancer treatment due to shared risk factors of CV disease and cancer
- SCT survivors often experience significant metabolic abnormalities including hyperlipidemia even if pre-transplant lipids were normal
- The incidence increases with the duration of post-transplant survival
- Requires aggressive monitoring and treatment to secondary prevention levels



Abou-Mourad YR. Bone Marrow Transplant 45: 295, 2010

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## Moderate Intensity Statin Recommendations

- Established clinical atherosclerotic cardiovascular disease (ASCVD)
- Primary elevations of low-density lipoprotein-cholesterol (LDL-C)  $\geq 190$  mg/dL
- Age 40 to 75 with diabetes, and LDL-C 70 to 189 mg/dL,
- Age 40 to 75 with LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher
- 10-year ASCVD Risk Calculated from the Pooled Cohort Equation
  - Age ; Gender; Race; Total Cholesterol; HDL Cholesterol; Systolic Blood Pressure; Hypertension Treatment; Diabetes; Smoking



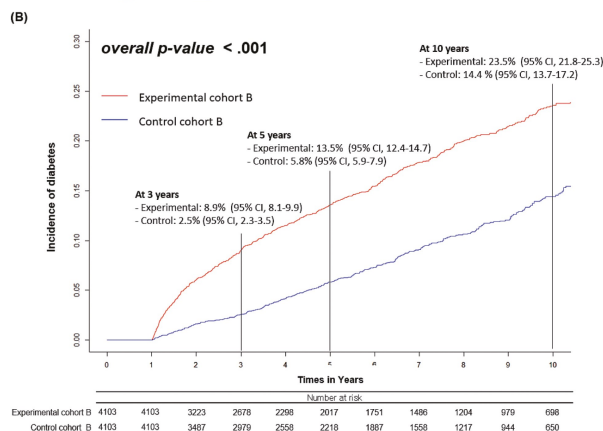
2013 Prevention Guidelines Tools  
**CV RISK CALCULATOR**

Arnett et al. J Am Coll Cardiol. 2019; 74: e177-e232

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## Diabetes and Diet

- STC survivors have increased rates of de novo diabetes and obesity compared to the general population
- Obesity increases the risk of recurrence and reduces the likelihood of disease-free and overall survival among those diagnosed with cancer
- Higher intake of vegetables/fruits and whole grains has been shown to be associated reduced mortality and less cancer recurrence



Ha et al. *J Clin Endocrinol Metab.* 2022; 107: 943-952

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## Exercise

- At least 20 prospective studies have shown that physically active cancer survivors have a lower risk of cancer recurrences and improved survival compared with those who are inactive
- Exercise has been shown to improve:
  - cardiovascular fitness,
  - muscle strength,
  - body composition,
  - fatigue, anxiety, depression
  - overall quality of life



## Echocardiogram

- Screening with an LVEF assessment should be considered at 6 months, 12 months for all patients
- High risk patients should get screening echos every 2 years and medium risk patients every 5 years
- Screening should focus on those at high risk for developing cardiotoxicity
  - High-dose anthracycline
  - High-dose radiotherapy
  - Lower-dose anthracyclines in combination with radiation
  - Lower-dose anthracyclines along with multiple cardiovascular risk factors



Armenian et al. J Clin Oncol. 2017; 35: 893-911.  
Curigliano et al. Ann Oncol 2012;23 Suppl 7:vii155-66

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## Summary

- Most patients with CV disease can safely undergo SCT
- Unique CV toxicities (arrhythmias, pericarditis, heart failure, arterial events, valve disease) can occur early and late after transplant and are related to both the transplant itself and the treatments received leading up to it.
- Focus on risk factor modification and seek out cardio-oncology evaluation to ensure optimal cardiovascular health.
- Seek out evaluation from a cardio-oncologist if you are a transplant survivor with risk factors for the development of CV complications



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# QUESTIONS?



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