Supplemental Material

Data S1.

Supplemental Methods

Definition of Cardiac Event

Childhood cancer survivor (CCS) had potentially heart failure if “yes” was answered to one of the following questions of the DCOG-LATER (Dutch Childhood Oncology Group - Long term Effects after Childhood Cancer) questionnaire: “Do you have now or did you ever have one of the following conditions, if yes please estimate at what age it started and if you use medications at this moment: heart attack, chest pain, valvular disease, inflammation of the sac around your heart (pericarditis), weak heart muscle (cardiomyopathy), heart failure, arrhythmias/ palpitations, other heart disease?”; “Did you ever have one of the following surgeries: replacement of the heart valve, other surgery to the heart (including stenting), did you ever have a pacemaker or ICD?”.

When using the GP (general practitioner) DCOG-LATER questionnaire, we considered CCS to have potentially heart failure when “yes” was answered to one of the following questions: ”Did the CCS develop one of the following conditions since the diagnosis of the primary childhood cancer: arrhythmia, valvular disease, cardiac conduction disorders, angina, ischemia or infarction, heart failure, pericarditis or other cardiovascular disorder?, If “yes”, information on diagnosis year and treatment institute were established with the following question: ”in what year was it diagnosed and what and where was the treatment?”. In order to validate the self-reported heart failure data, we extracted heart failure information from the medical records for all CCS with potentially heart failure. We used an extraction-flowchart method especially developed for consistent and valid grading (see Figure S2).[1] This method consists of an extraction form and a set of flowcharts for specific cardiac conditions which allows grading of the heart failure according to the CTCAEv3.0 and v4.0.1

We defined grading of heart failure as follows: grade 3 (severe), grade 4 (life-threatening or disabling) or grade 5 (fatal).[1] We considered the date on which a symptomatic heart failure was first confirmed by diagnostic testing as the cardiac incidence date. We included heart failures occurring after the 5-year survival date and heart failures that started within 5 years after primary childhood cancer diagnosis

and were still on-going after 5-year survival: the incidence date is then set on 5 years + 1 day.

Data S2.

Supplemental Results

CE origins

Around 17% of the CCS reported potential heart failure (n=484) in the DCOG-LATER questionnaire. We were able to validate almost all of them (n=474; 97.9%) and we graded by extracting relevant data on the potential heart failure from their DCOG-LATER hospital medical chart, from their GP or other hospital records. However, 10 (2.1%) CCS did not give permission to request information from their GP or other hospital and we were unable to extract sufficient information from their medical notes at the DCOG-LATER hospital. Nevertheless, we were able to establish the nature and grade of the potential CE for these CCS, by the information they provided on the DCOG-LATER questionnaire. Of the 484 CCS who reported a cardiac event (CE) in the DCOG-LATER questionnaire, 58 (11.8%) CCS had a symptomatic heart failure and were therefore included in the study as a cardiac case. Six percent (n=46) of the GPs reported a potential CE in the GP DCOG-LATER questionnaire. All of them could be validated and graded by extracting relevant data from their medical chart. Of the GPs who reported a potential CE in the GP DCOG-LATER questionnaire, we found that 6 (13.0%) CCS had a symptomatic heart failure and were therefore included in the study as a cardiac case. From the DCOG-LATER outpatient clinics we found 7.9% (n=161) CCS who had a potential CE. All of the potential CEs could be validated and graded by extracting relevant data about the potential CE from their cardiology medical chart. In 52 (32.3%) CCS the heart failure was symptomatic and these patients were therefore included in the study as a cardiac case. In order to assess completeness of reporting, we randomly collected 20 CCS who did not report a potential CE and validated this by extracting data from their medical records, none of the CCS had a CE.

Table S1. Cumulative incidence of heart failure (≥ grade 3) over time since diagnosis (follow-up) in childhood cancer survivors according to the nonparametric estimator of cause-specific cumulative incidence, with death from any cause as competing risk.

Treatment groups	*follow-up 10 yr*	*95% CI*	*follow-up 20 yr*	*95% CI*	*follow-up 30 yr*	*95% CI*	*follow-up 40 yr*	*95% CI*
Overall	0.4%	0.2-0.5	1.3%	1.0-1.7	3.0%	2.3-3.6	4.4%	3.4-5.5
Cardiotoxic treatment yes/no								
No cardiotoxic treatment*	0.0%	0.0-0.0	0.0%	0.0-0.0	0.1%	0.0-0.3	0.3%	0.0-0.7
Cardiotoxic treatment†	0.7%	0.41-1.0	2.6%	2.0-3.3	6.3%	4.9-7.7	10.6%	7.4-13.9
Types of cardiotoxic treatment								
Cardotoxic CT only	0.8%	0.4-1.1	2.8%	2.1-3.6	6.4%	4.7-8.1	10.5%	6.6-14.4
Chest RT only	0.5%	0.0-1.4	0.5%	0.0-1.5	1.2%	0.00-3.0	3.0%	0.0-5.9
Cardiotox CT and chest RT	0.5%	0.0-1.1	2.5%	0.8-4.2	9.6%	5.13-14.12	27.8%	5.1-50.6
Types of cardiotoxic chemotherapy								
Mitoxantrone (+/-anthracyclines)	1.5%	0.1-3.5	11.4%	3.6-19.1	16.9%	4.1-29.7	16.9%	4.1-29.7
1-100 mg/m2 anthracycline‡	0.2%	0.1-0.7	0.7%	0.0-1.7	1.2%	0.0-2.7	1.2%	0.0-2.7
100-250 mg/m2 anthracycline‡	0.5%	0.1-0.8	1.4%	0.7-2.2	4.0%	1.8-6.2	37.3%	0.0-87.5
>250 mg/m2 anthracycline‡	1.2%	0.4-2.0	5.2%	3.4-7.1	13.0%	9.4-16.6	24.3%	15.3-33.3
Period of treatment								
1970-1979	0.2%	0.0-0.5	0.5%	0.0-0.9	1.4%	0.6-2.2	2.9%	1.7-4.2
1980-1989	0.4%	0.1-0.7	1.6%	1.0-2.2	3.9%	2.8-4.9	xx	xx
1990-2001	0.4%	0.2-0.6	1.5%	0.9-2.0	xx	xx	xx	xx

* No cardiotoxic treatment defined as treated without anthracyclines, mitoxantrone and radiotherapy involving the heart

† Cardiotoxic treatment defined as treated with anthracyclines, mitoxantrone and/ or radiotherapy involving the heart

‡ Without mitoxantrone

Table S2. Cumulative incidence of heart failure (≥ grade 3) at attained age in childhood cancer survivors according to the nonparametric estimator of the cause-specific cumulative incidence, with death from any other cause as competing risk.

Treatment groups	*10 years of age*	*95% CI*	*20 years of age*	*95% CI*	*30 years of age*	*95% CI*	*40 years of age*	*95% CI*	*50 years of age*	*95% CI*
Overall	0.2%	0.0-0.4	0.8%	0.5-1.1	2.0%	1.6-2.5	3.7%	2.9-4.4	5.3%	3.7-6.9
Cardiotoxic treatment yes/no										
No cardiotoxic treatment†	0.0%	0.0-0.0	0.0%	0.0-0.0	0.1%	0.0-0.1	0.3%	0.0-0.6	0.3%	0.06-0.6
Cardiotoxic treatment◊	0.5%	0.0-0.9	1.7%	1.1-2.3	4.0%	3.1-4.9	7.3%	5.6-8.9	11.6%	7.4-15.8
Types of cardiotoxic treatment										
Cardotoxic CT only	0.3%	0.0-0.6	1.5%	0.9-2.1	3.9%	2.9-4.9	6.4%	4.7-8.2	11.6%	7.1-16.1
Chest RT only	0.0%	0.0-0.0	0.0%	0.0-0.0	0.5%	0.0-1.5	2.6%	0.0-5.1	2.6%	0.0-5.1
Cardiotox CT and chest RT	2.9%	0.0-7.4	4.7%	0.0-9.3	7.4%	2.5-12.2	14.6%	7.4-21.7	33.2%	2.8-63.7
Types of cardiotoxic chemotherapy										
Mitoxantrone (+/anthracyclines)	0.0%	0.0-0.0	0.3%	0.2-0.7	0.6%	0.0-1.4	1.2%	0.0-2.7	1.2%	0.0-2.7
1-100 mg/m2 anthracycline*	0.3%	0.0-0.6	0.8%	0.3-1.4	2.3%	1.3-3.4	4.5%	1.9-7.0	18.3%	0.0-43.3
100-250 mg/m2 anthracycline*	0.4%	0.0-1.1	3.0%	1.5-4.6	7.0%	4.8-9.2	13.0%	9.3-16.7	19.2%	12.7-25.8
>250 mg/m2 anthracycline*	0.0%	0.0-0.0	4.1%	0.6-7.7	12.9%	5.5-20.3	12.9%	5.5-20.3	12.9%	5.5-20.3

† No cardiotoxic treatment defined as treated without anthracyclines, mitox
heart

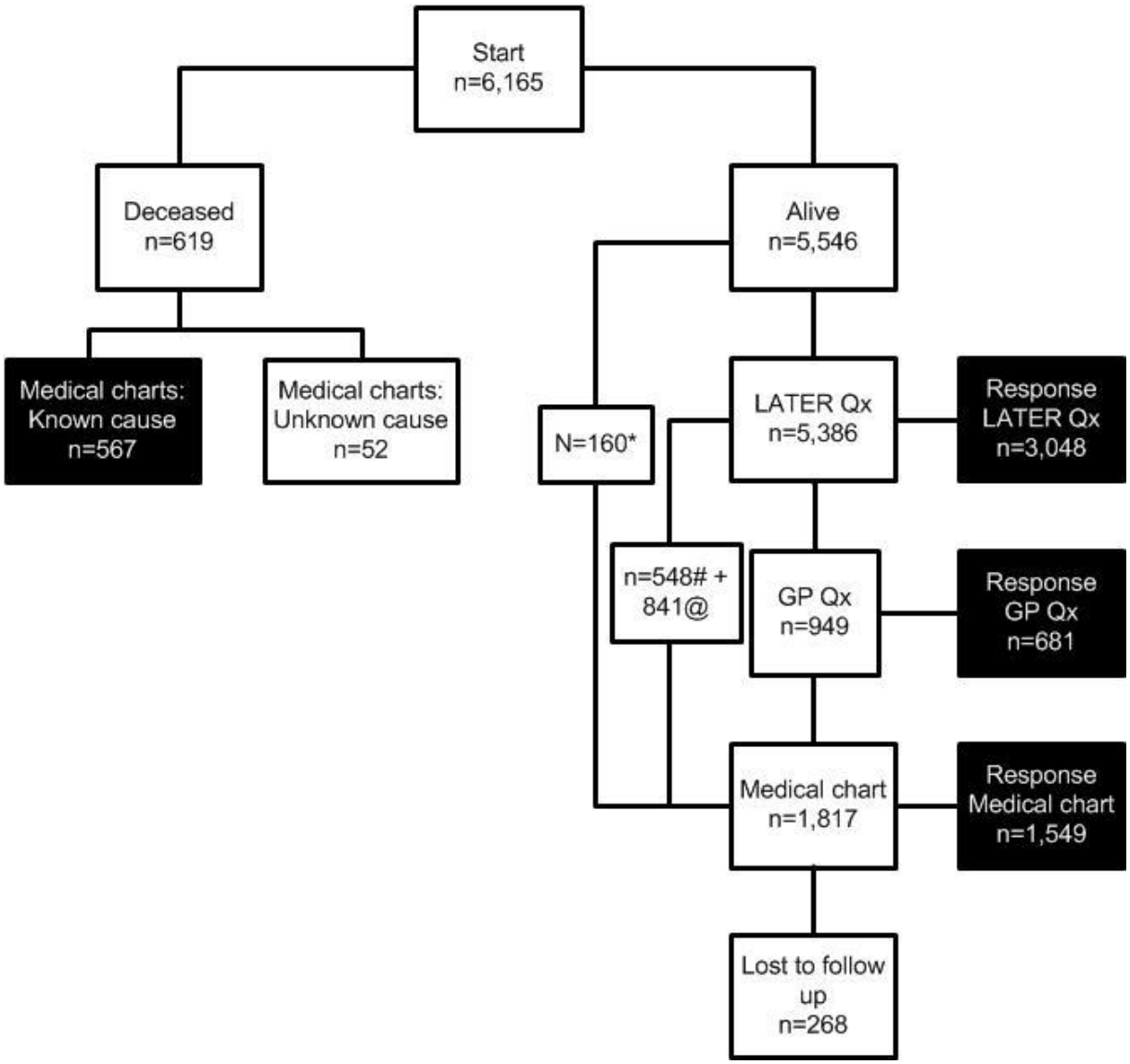
◊ Cardiotoxic treatment defined as treated with anthracyclines, mitoxantror
heart

* Without mitoxantrone

CT= chemotherapy (anthracyclines and mitoxantrone)

Chest RT =radiotherapy involving the heart

Figure S1. Flowchart of the cardiac data collection.



Qx= Questionnaire, LATER= Long term Effects after Childhood Cancer

* CCS were who living abroad, were in active cancer treatment or could not be traced at the time of follow-up

CCS who did not participate in the LATER questionnaire, and did not give permission for GP questionnaire

@ CCS who were seen within the last 2 years of follow-up in the LATER outpatient clinic

Figure S2. Flowchart heart failure[1]

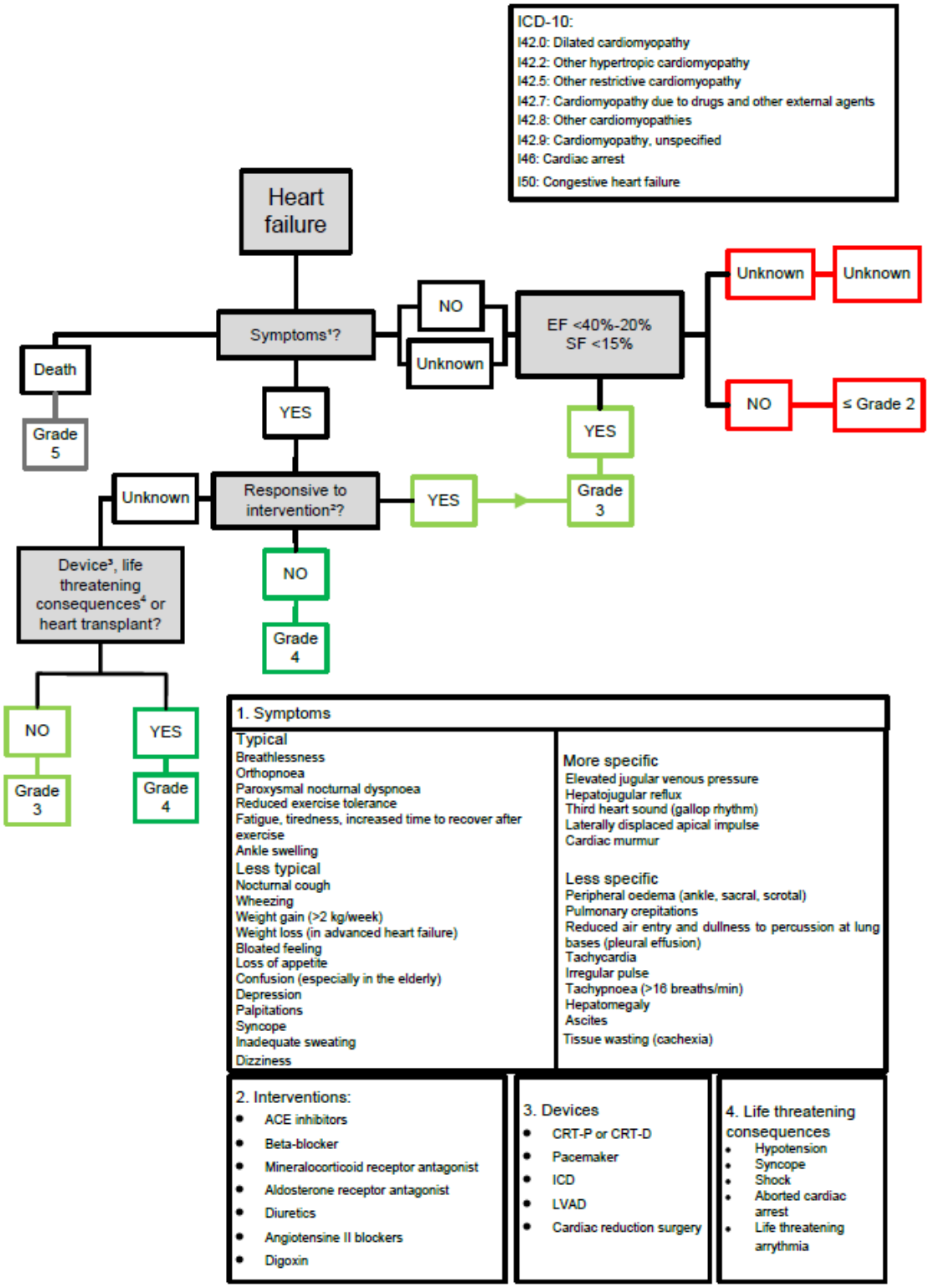


Figure S3. Cumulative incidence of heart failure at time since childhood cancer diagnosis for four mutually exclusive treatment groups.

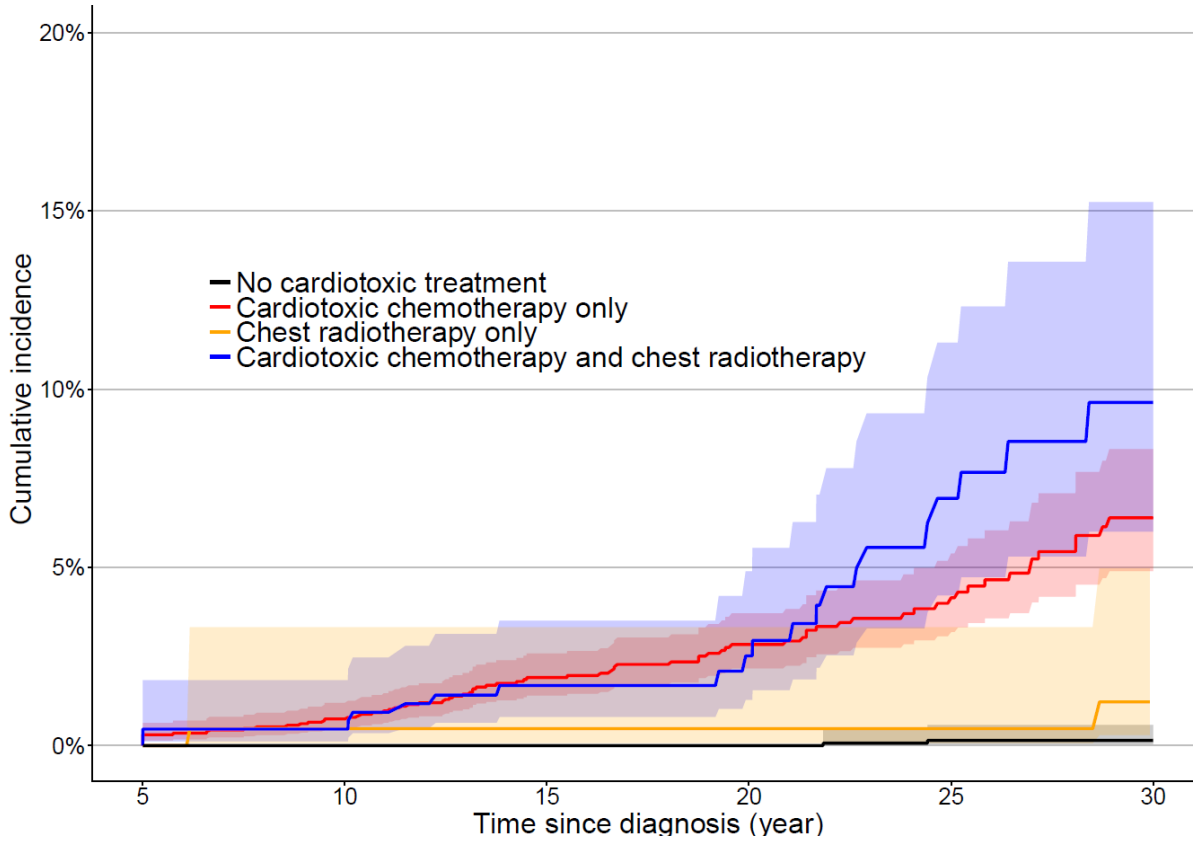
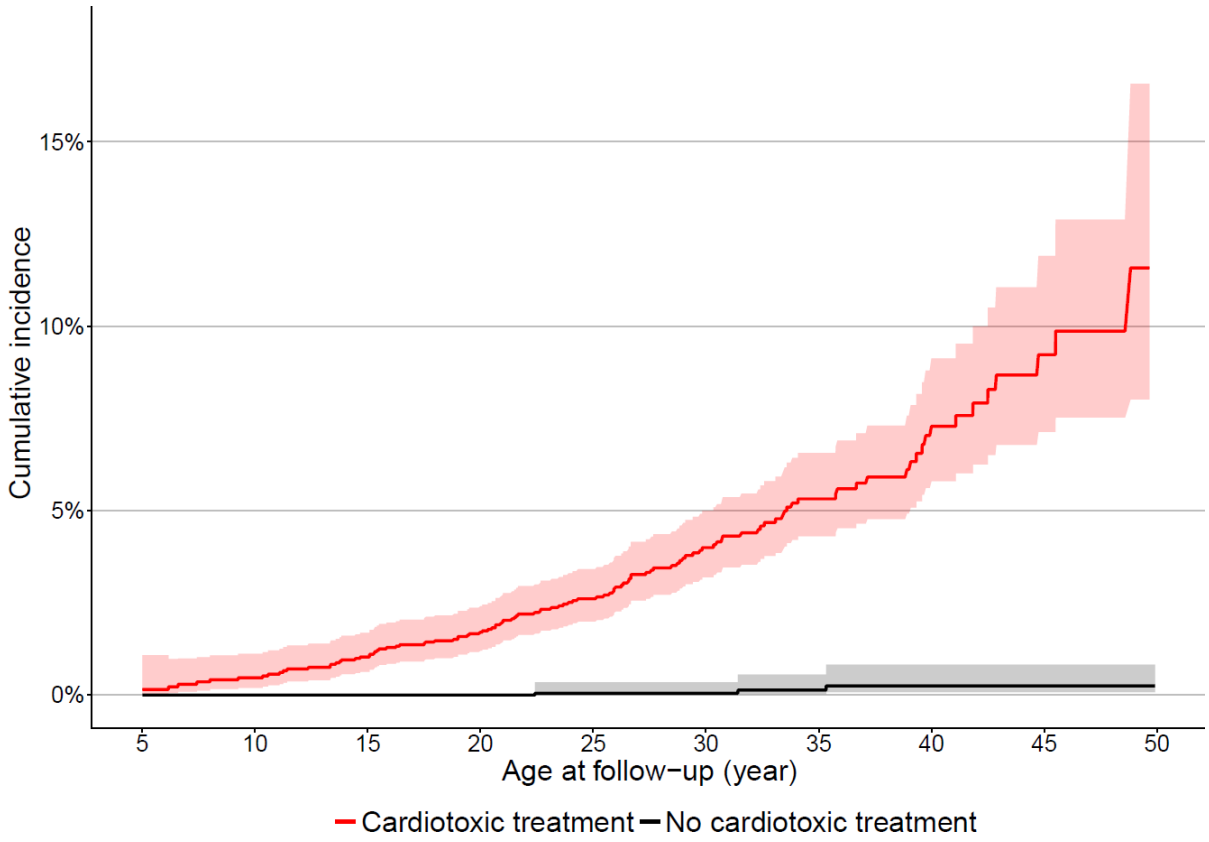


Figure S4. Cumulative incidence of heart failure at attained age for cardiotoxic treatment and no cardiotoxic treatment.



Supplemental Reference:

1. Feijen EAM, van der Pal HJ, van Dalen EC, Mulder RL, Bardi E, Kuehni C, Tissing WJ, Kremer LC. A new method to facilitate valid and consistent grading cardiac events in childhood cancer survivors using medical records. *PloS one.* 2014;9:e100432.