Is screening for abnormal ECG patterns justified in long-term follow-up of childhood cancer survivors treated with anthracyclines?

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Abstract

Background: ECG and echocardiography are noninvasive screening tools to detect subclinical cardiotoxicity in childhood cancer survivors (CCSs). Our aims were as follows: (1) assess the prevalence of abnormal ECG patterns, (2) determine the agreement between abnormal ECG patterns and echocardiographic abnormalities; and (3) determine whether ECG screening for subclinical cardiotoxicity in CCSs is justified.

Procedure: We retrospectively studied ECG and echocardiography in asymptomatic CCSs more than 5 years after anthracycline treatment. Exclusion criteria were abnormal ECG and/or echocardiogram at the start of therapy, incomplete follow-up data, clinical heart failure, cardiac medication, and congenital heart disease. ECG abnormalities were classified using the Minnesota Code. Level of agreement between ECG and echocardiography was calculated with Cohen kappa.

Results: We included 340 survivors with a mean follow-up of 14.5 years (range 5–32). ECG was abnormal in 73 survivors (21.5%), with ventricular conduction disorders, sinus bradycardia, and high-amplitude R waves being most common. Prolonged QTc (>0.45 msec) was found in two survivors, both with a cumulative anthracycline dose of 300 mg/m² or higher. Echocardiography showed abnormalities in 44 survivors (12.9%), mostly mild valvular abnormalities. The level of agreement between ECG and echocardiography was low (kappa 0.09). Male survivors more often had an abnormal ECG (corrected odds ratio: 3.00, 95% confidence interval: 1.68–5.37).

Conclusions: Abnormal ECG patterns were present in 21% of asymptomatic long-term CCSs. Lack of agreement between abnormal ECG patterns and echocardiographic abnormalities may suggest that ECG is valuable in long-term follow-up of CCSs. However, it is not clear whether these abnormal ECG patterns will be clinically relevant.

KEYWORDS
anthracycline-induced cardiotoxicity, childhood cancer, echocardiography, electrocardiography, late-onset cardiotoxicity, QTc interval

1 | INTRODUCTION

Survival of children with cancer has improved over the last decades to almost 80%,1–3 resulting in a growing number of childhood cancer survivors (CCSs). These survivors are at a risk of (life-threatening) late effects of their cancer treatment, including secondary malignant
neoplasms, metabolic syndrome, hypertension, and cardiovascular diseases.\textsuperscript{4,5} Several studies reported a significant increase in mortality risk due to cardiac causes compared with the general population.\textsuperscript{6–8} CCSs are more likely than their siblings to experience congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities. The cumulative incidence of these adverse cardiac outcomes continues to increase up to 30 years after diagnosis.\textsuperscript{9} Anthracyclines and radiotherapy are the main causes of cardiotoxicity in CCSs.

Anthracycline-induced clinical heart failure is reported in 1–5\% of survivors and subclinical heart failure in up to 65\%.\textsuperscript{10–12} While echocardiography is the most common test for screening and monitoring of late-onset (subclinical) cardiotoxicity, there is an ongoing discussion about the additional value of electrocardiography (ECG). In the recently published international recommendations for cardiomyopathy surveillance, screening for conduction abnormalities (where ECG is essential) was mentioned as a topic that will be addressed by future evidence-based international guideline development.\textsuperscript{13} In the Dutch and American guidelines, evidence of ECG abnormalities during long-term follow-up is limited to conduction disorders.\textsuperscript{14,15} Previous literature reported a higher incidence of prolonged QT dispersion intervals or prolonged QTc.\textsuperscript{16,17} Conduction abnormalities and specifically QT prolongation are a major risk factor for sudden cardiac events and death.

Supportive data show that ECG screening identifies healthy young people (age \textless 35 years) and athletes who are harboring potentially serious cardiac diseases.\textsuperscript{18} In Italy, screening young athletes with an ECG has been suggested to be effective in decreasing the annual rate of sudden cardiac death (SCD).\textsuperscript{19} There is an ongoing debate on the feasibility and interpretation of large-scale ECG screening in young adults,\textsuperscript{16,20} since the majority of SCDs in the young affect the general population and not only athletes.\textsuperscript{21}

The American Heart Association (AHA) recently published a scientific statement on the topic of screening with ECG for detection of cardiovascular disease in the general young population (12–25 years of age). Their recommendation is to consider screening with ECG in selected groups (in order to find cardiovascular abnormalities) combined with comprehensive history taking and physical examination.\textsuperscript{22} Long-term CCSs treated with anthracyclines could be classified as such a selected group.

In this study, we aim to assess the prevalence of abnormal ECG patterns and determine the agreement between abnormal ECG patterns and echocardiographic abnormalities in asymptomatic long-term CCSs. In addition, we investigate whether ECG screening for subclinical cardiotoxicity in this population is justified.

2 \hspace{1em} METHODS

2.1 \hspace{1em} Study population

Participants were CCSs enrolled in the Late Effects Clinic of the Radboud University Medical Center in the Netherlands, from May 2006 through May 2010 with the aim to provide comprehensive long-term follow-up care. Eligibility for inclusion in the current analysis was diagnosis of pediatric cancer at age 18 years or less and evaluation 5 years or more after anthracycline treatment. Survivors were evaluated according to the national guidelines for follow-up of CCSs ranging from once every 2–5 years depending on cumulative anthracycline dosage and/or mediastinal irradiation.\textsuperscript{14} Exclusion criteria were abnormal ECG and/or echocardiogram at the start of therapy, incomplete data (ECG and/or echocardiographic) at follow-up, clinical heart failure, cardiac medication, and congenital heart disease. Clinical parameters such as age (at diagnosis and at follow-up), body mass index (BMI), diagnosis, previous cancer treatment, follow-up duration/years after anthracycline treatment, and irradiation to the heart region (including mediastinal, thoracic, spinal, left or whole upper abdominal, or total body irradiation [TBI]) were obtained by medical record review. We calculated the cumulative anthracycline dose as the sum of the doxorubicin and daunorubicin doses. Survivors underwent a complete physical examination, a clinical history was obtained, and a 12-lead ECG and echocardiography were performed. Clinical heart failure was defined by the New York Heart Association classification (NYHA).\textsuperscript{23}

2.2 \hspace{1em} ECG and echocardiography

A resting 12-lead ECG (Philips PageWriter Touch) was performed and evaluated by two independent cardiologists (LK and LB), who were unaware of the medical history. Disagreement between the cardiologists was resolved by consensus reached by subsequent joined evaluation of the electrocardiographic findings. The following ECG parameters were noted: heart rate, PQ-, QRS-, and QT-intervals, voltage parameters (total QRS voltage in limb leads), repolarization changes, arrhythmias, and other abnormalities. QTc interval was calculated using Bazett formula.\textsuperscript{24} A QTc interval of more than 450 msec was defined as prolonged according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI).\textsuperscript{25} Abnormal electrocardiograms were coded according to the Minnesota Code, see Supplementary Table S1.\textsuperscript{26} If more than one abnormality according to the Minnesota Code was applicable to the ECG, the major abnormality code was used. Abnormal ECG patterns that could not be defined by the Minnesota Code were coded as “other.” These other abnormal ECG patterns were coded independently by two experienced cardiologists.

The prevalence of abnormal ECG patterns in our group of long-term survivors was compared with the prevalence of abnormal ECG patterns in the general population, derived from the literature.\textsuperscript{18,20} Transthoracic echocardiography at rest was performed by experienced echocardiographic technicians and supervised by a cardiologist who was unaware of the treatment details. Images were obtained with a 3.0- and 5.0-MHz transducer using a commercially available system, the Vivid 7 echographic scanner (GE, Vingmed Ultrasound, Horten, Norway).

Measurements of the left ventricular cardiac dimensions, left ventricular mass, and systolic and diastolic left ventricular function were assessed according to recommendations for chamber quantification by the American Society of Echocardiography’s Guidelines and Standard Committee and the Chamber Quantification Writing Group.\textsuperscript{27} An M-mode echocardiogram was performed in the parasternal...
long- and short-axis views to measure the left ventricular internal dimensions at end-systole and end-diastole (LVIDd, LVIDs) and the posterior and septal wall thickness at end-diastole (LVPWd, IVSd, respectively). Measurements of left ventricular dimensions and left ventricular mass (LVM) were indexed by body surface area (BSA). The left ventricular systolic function was indicated using fractional shortening (FS), ejection fraction (EF), rate-corrected velocity of circumferential fiber shortening (VCFc), and end-systolic wall stress (ESWS). FS (%) was obtained using the following formula: \( \frac{(LVIDd - LVIDs)}{LVIDd} x 100 \). EF was calculated with the modified Simpson’s rule, while ESWS was calculated with the modified formula of Rowland.26 The VCFc was assessed using the formula by Colan et al.29 Left ventricular diastolic function was estimated using the ratio of peak early (E) to late atrial (A) mitral Doppler flow velocities (E/A ratio).30 LVM was calculated with the formula of Devereux and Reichek.31 Left ventricular diameter was measured in concordance with the guidelines of the ACC/AHA and classified as increased when LVIDd and/or LVIDs was above 2 standard deviations of the normal values. In addition to the above, all echocardiographic studies were assessed for valvular abnormalities (stenosis and/or insufficiency), hypo/dyskinesia of a myocardial wall, and contractile myocardial function. Valvular disease was evaluated according to the ACC/AHA guidelines.32 As mild tricuspid and pulmonic regurgitation are common in the general population, these were considered as being physiological.

In case of normal cardiac evaluation, follow-up was advised according to the national guidelines for follow-up of CCSs.14 In case of abnormalities on either ECG or echocardiogram, a survivor-tailored advice was formulated depending on the severity of the abnormality.

2.3 | Statistical analysis

Characteristics of the study population, such as age (at diagnosis and at follow-up), BMI, follow-up duration, and cumulative anthracycline dose were summarized using mean and standard deviation or median and range after checking for normal distributions. The level of agreement between any abnormal ECG pattern and any echocardiographic abnormality was calculated by Cohen kappa. Comparisons were made between the group with normal ECGs and the group with abnormal ECG patterns in relation to gender, follow-up duration, age at diagnosis, anthracycline dosage (defined as cumulative anthracycline dose <300 and ≥300 mg/m²), and irradiation to the heart. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in logistic regression models. In the multivariable model, all variables were corrected for each other to obtain independent associations with abnormal ECG patterns for each variable. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0.

3 | RESULTS

3.1 | Study characteristics

During the study period, 414 long-term CCSs visited our Late Effects Clinic. None were using anti-arrhythmic drugs. Survivors were excluded from this study because of clinical heart failure and/or use of cardiac medication (n = 19), no past anthracycline exposure (n = 36), or incomplete data at follow-up (either echocardiography or ECG or both) (n = 19) (Fig. 1). Table 1 shows the characteristics of the remaining 340 survivors. All were younger than 44 years of age, while 65% (221 of 340 survivors) were aged 24 years or less. None of the survivors included in our study had symptoms suggestive of cardiac disease and/or rhythm abnormalities during their visit. CCSs excluded in our study population did not use any medication affecting cardiac rhythm or QTc.

3.2 | ECG and echocardiography

Abnormal ECG patterns were found in 73 survivors (21.5%) (Table 2). Ventricular conduction disorders patterns, high amplitude R waves, and sinus bradycardia were the most common patterns found.

A prolonged QTc was found in two survivors; both of whom had a normal QTc at diagnosis.

Echocardiographic parameters are shown in Table 3. Only one survivor with a cumulative anthracycline dose of 300 mg/m² had an abnormal FS of 24% and an EF of 48% at 13.5 years of follow-up. Forty-four (12.9%) survivors had an abnormal echocardiography, with mitral insufficiency and increased left ventricular dimension (LVIDd and/or LVIDs) being the most common (Table 3). These abnormalities were not seen in their previous echocardiograms. No survivor had more than one abnormal echo finding.

The level of agreement between abnormal ECG patterns and echocardiographic abnormalities was low, with a kappa of 0.09.
### Table 1: Characteristics of 340 long-term survivors of childhood cancer

| Characteristic                                         | Number (%)     |
|--------------------------------------------------------|----------------|
| Male gender, number (%)                                | 185 (54%)      |
| Age at diagnosis, years (mean ± SD)                    | 6.9 ± 4.7      |
| Age at follow-up, years (mean ± SD)                    | 21.4 ± 8.4     |
| Follow-up duration, years (mean ± SD)                  | 14.5 ± 7.4     |
| BMI                                                     | 22.0 ± 4.9     |
| Diagnosis                                              |                |
| ALL                                                     | 117            |
| AML                                                     | 23             |
| CNS tumor, other                                       | 2              |
| Ependymoma                                             | 1              |
| Ewing sarcoma                                          | 13             |
| Germ cell tumor                                        | 1              |
| Ganglieneuroma                                          | 1              |
| Hepatoblastoma                                         | 6              |
| Hodgkin disease                                        | 38             |
| LCH                                                     | 1              |
| Neuroblastoma                                          | 18             |
| NHL                                                     | 64             |
| Pancreatic cystadenofibroma                             | 1              |
| Rhabdomyosarcoma                                       | 11             |
| Renal tumor, not Wilms tumor                           | 2              |
| Nasopharyngeal carcinoma                               | 1              |
| Non-rhabdo soft-tissue sarcoma                         | 2              |
| Osteosarcoma                                           | 11             |
| Wilms tumour                                           | 27             |
| CAD (median and range) (mg/m²)                          | 180 (30–600)   |
| CAD <120 mg/m², n (%)                                  | 47 (14)        |
| CAD 120–300 mg/m², n (%)                               | 201 (59)       |
| CAD >300 mg/m², n (%)                                  | 92 (27)        |
| Mediastinal irradiation, n (%)                          | 49 (14)        |

**ALL**, acute lymphoblastic leukemia; **AML**, acute myeloid leukemia; **CAD**, cumulative anthracycline dose; **CNS**, central nervous system; **LCH**, Langerhans cell histiocytosis; **NHL**, Non-Hodgkin lymphoma; **SD**, standard deviation.

### Table 2: ECG abnormalities in 340 long-term survivors of childhood cancer

| ECG abnormality                                      | Number, of total (%) |
|-------------------------------------------------------|----------------------|
| QRS axis deviation (MC 2)                             | 73/340 (21.5%)       |
| Left-axis deviation (MC 2-1)                          | 1                    |
| High-amplitude R waves (MC 3)                         | 14                   |
| Left high-amplitude R waves (MC 3-1)                  | 1                    |
| T-wave items (MC 5)                                   | 1                    |
| AV conduction defect (MC 6)                           | 4                    |
| First-degree AV block (MC 6-3)                        | 29                   |
| Ventricular conduction disorders (MC 7)               | 1                    |
| LBBB (MC 7-1-1)                                       | 1                    |
| RBBB (MC 7-2-1)                                       | 1                    |
| IRBBB (MC 7-3)                                        | 24                   |
| LAH (MC 7-7)                                          | 3                    |
| Arrhythmias (MC 8)                                    | 15                   |
| Sinus bradycardia (-60/min)                           | 6                    |
| Sinus bradycardia (-50/min, MC 8-8)                   | 9                    |
| Other                                                 | 9                    |
| Aspecific repolarization abnormality                   | 3                    |
| Aspecific IVCAs                                        | 4                    |
| Prolonged QTc                                          | 2                    |

Major ECG abnormalities include codes MC 3-1, MC 7-1-1, and MC 7-2-1. Minor ECG abnormalities include codes MC 2-1, MC 5, MC 6-3, MC 7-3, MC 7-7, MC 7-8, other and prolonged QTc. AV, atrioventricular; IVCA, intraventricular conduction abnormalities; LAH, left anterior hemiblock; LBBB, left bundle branch block; MC, Minnesota Code; RBBB, right bundle branch block.

### 3.3 | Comparison between survivors with a normal ECG (n = 237) and survivors with an abnormal ECG pattern (n = 73)

All variables were analyzed with univariable and multivariable logistic regression and the results are shown in Table 4. No differences were found in age at diagnosis and follow-up duration between the groups, with all ORs for these continuous variables centered around the null value of 1. When comparing the survivors in the anthracycline dosage groups, a cumulative anthracycline dose less than 300 versus 300 mg/m² or higher, no difference was seen in the number of abnormal ECG patterns (corrected OR: 0.86, 95%CI: 0.63–1.18). Entering the cumulative anthracycline dose as a continuous variable in the multivariable model did not change the results. The two survivors with abnormal QTc received a cumulative anthracycline dose of 600 and 360 mg/m², respectively; neither received radiotherapy. With a corrected OR of 0.60 (95%CI: 0.27–1.37), radiotherapy was not found to be a risk factor for abnormal ECG patterns either. The only strong association with ECG patterns was found for gender, with males having an abnormal ECG pattern three times more often than females (corrected OR: 3.00, 95%CI: 1.68–5.37).

### 4 | DISCUSSION

Screening for conduction abnormalities was recently recommended as one of the topics of future research in CCSs. This study demonstrates that 21.5% of young asymptomatic CCSs have abnormal ECG patterns, mostly defined by the Minnesota Code. Landier et al. reported a low percentage of abnormal ECGs (<1%) in a large cohort of CCSs. They concluded that ECG was a screening tool with negligible yield, but they defined an abnormal ECG solely as a prolonged QTc (>450 msec for males and >460 msec for females). Our prevalence of prolonged QTc in the total population of CCSs is in concordance with these findings (prevalence 2/340 = 0.05%). However, in our study, we included other abnormalities as well and studied the ECG more extensively. This resulted in the detection of other potential ECG abnormalities (mostly defined by the Minnesota Code) with a
In our study population, we found ECG abnormalities that were coded as "other" and could not be coded according to the Minnesota Code. Although the role of monitoring of these "other" ECG abnormalities in cancer survivors is not yet clear, we are of the opinion that these abnormalities may need further follow-up. These "other" ECG abnormalities were seen in 12% of the population with abnormal ECG patterns and in only 2.6% of the whole study population.

IRBBB is commonly found among healthy athletes and is perceived as a benign finding. The same is true for heart rates between 50 and 60 beats/min without conduction abnormalities. A study by Liao et al. showed an increased likelihood of development of a CRBBB when having an IRBBB. CRBBB, in contrast to IRBBB, has been associated with a higher risk of cardiovascular death.

High-amplitude R waves could be a result of physical training. Conversely, a population study in Belgium showed a relative risk of 2.8 for cardiovascular disease in adults aged 25–79 years with left ventricle hypertrophy on ECG (assessed by high-amplitude R waves with the Minnesota Code). It is not clear yet whether the abnormal ECG patterns found in our population are a sign of cardiac damage.

Studies on ECG abnormalities in the general pediatric and adolescent population are scarce. Comparison of our data with the published reference studies was difficult due to different age groups, different definitions of an abnormal ECG, and different selection criteria. Marek et al. conducted a large study in 32,561 healthy young adults aged 14–19 years and found abnormal ECG findings in only 2.5%. Part of these ECG abnormalities were also found in our study, for example, left-axis deviation, prolonged QTc, first-degree AV block, and sinus bradycardia. The prevalence of these ECG abnormalities in our group of CCSs under 19 years of age did not differ from those measured by Marek et al. in the healthy young population.

QTc prolongation is a risk factor for arrhythmias and can lead to life-threatening torsades de pointes (TdP). Previous studies showed that cancer survivors previously exposed to anthracyclines, in combination with electrolyte disturbances (hypokalemia, hypocalcaemia, hypomagnesemia), or the use of QTc prolonging drugs are at a risk of developing TdP. Other studies also demonstrated prolonged QTc as a late effect of the anthracycline treatment.

Symptomatic cardiac events may occur in CCSs. A study by van der Pal et al. demonstrated 50 cardiac events in a group of 1,362 survivors. Of these 50 cardiac events, nine were reported as cardiac

### Table 3: Echocardiographic parameters and abnormalities in 340 long-term survivors of childhood cancer

| Echocardiographic parameters                  | Mean ± SD (range) |
|----------------------------------------------|-------------------|
| Left ventricular dimensions                  |                   |
| IVSd/BSA (cm²)                               | 0.36 ± 0.08       |
| LVPWd/BSA (cm²)                              | 0.40 ± 0.09       |
| LVIDd/BSA (cm²)                              | 2.99 ± 0.55       |
| LVIDs/BSA (cm²)                              | 1.93 ± 0.40       |
| Left ventricular systolic function           |                   |
| FS (%)                                       | 35 ± 4.4 (24-53)  |
| EF (%)                                       | 64 ± 5.6 (48-82)  |
| VCFc (circ/sec)                              | 1.18 ± 0.16       |
| ESWS (g/m²)                                  | 58.8 ± 16.7       |
| Left ventricular diastolic function          |                   |
| E/A ratio                                    | 1.85 ± 0.58       |
| Left ventricular mass/BSA (g/m²)             | 57.9 ± 15.0       |
| Echocardiographic abnormalities              | Number            |
| Total                                        | 44 (12.9%)        |
| Valvular abnormalities                       |                   |
| Aortic stenosis                              | 1                 |
| Aortic regurgitation                         | 5                 |
| Mitral stenosis                              | 0                 |
| Mitral insufficiency                         | 11                |
| Mitral valve prolapse                        | 2                 |
| Left ventricular dysfunction                 |                   |
| Septal motion abnormalities                  | 7                 |
| Increased left ventricular dimension         | 8                 |
| Others                                       | 10                |

E/A ratio, early/late ventricular filling; FS, shortening fraction; BSA: Body surface area; E/A ratio: early/late ventricular filling; EF: ejection fraction; FS: shortening fraction; ESWS: end systolic wall stress; IVSd: intraventricular septum during diastole; LVIDd: left ventricular internal dimension during diastole, LVIDs: left ventricular internal dimension during systole, LVPWd: diameter left ventricular posterior wall during diastole.

Prevalence of 21.5%. In this group of ECG abnormalities, ventricular conduction disorders (29/73 = 40%), mainly incomplete right bundle branch block (IRBBB), sinus bradycardia (under 60 beats/min, 15/73 = 21%), and high amplitude R waves (14/73 = 19%), mainly of LV origin, were most common.

### Table 4: ORs for an abnormal ECG calculated by multivariable logistic regression for dichotomous and continuous variables in 340 long-term survivors of childhood cancer

|                     | Normal ECG | Abnormal ECG | OR (95%CI)      | Corrected OR (95%CI) |
|---------------------|------------|--------------|-----------------|----------------------|
| Male gender*        | 131/267    | 54/73        | 2.95 (1.66–5.25)| 3.00 (1.68–5.37)     |
| CAD (≥300 vs. <300 mg/m²)* | 76/267 | 16/73        | 0.84 (0.62–1.14)| 0.86 (0.63–1.18)     |
| Mediastinal radiation* | 40/267 | 9/73         | 0.80 (0.37–1.73)| 0.60 (0.27–1.37)     |
| Age at diagnosis**  |            |              | 1.02 (0.96–1.07)| 1.02 (0.96–1.08)     |
| Follow-up duration**|            |              | 0.98 (0.95–1.02)| 0.99 (0.95–1.02)     |

CAD, cumulative anthracycline dose; CI, confidence interval; OR, odds ratio.
* Dichotomous variables.
** Continuous variables (in years).
arrhythmia. Cardiac arrhythmia was defined in the Common Criteria for Adverse Events (CTCAE version 3.0) and includes clinical cardiac arrhythmia (grade 3) or life-threatening arrhythmia (grade 4). Grades 1 and 2 (subclinical rhythm disturbances) may be present in asymptomatic CCSs of which our group of survivors is an example. The high prevalence of subclinical cardiotoxicity may imply that grade 1 and 2 arrhythmias occur more often than the overt cardiac events reported by van der Pal et al. Actual occurrence of arrhythmias was not assessed in this study and should be done by using more than just ECG, for example, an event recorder or Holter monitoring. The relevance and progression to overt clinical symptoms should be further evaluated in a prospective manner.

In the present study, we found low agreement between abnormal ECG patterns and echocardiographic abnormalities. Landau et al. also showed a poor correlation between ECG and echocardiographic abnormalities. The fact that a normal echocardiogram does not rule out an abnormal ECG, and vice versa, is not surprising. Echocardiography is the most widely used bedside modality to diagnose subclinical anthracycline-induced cardiotoxicity, but it is a poor tool for arrhythmias and conduction abnormalities. The number of CCSs with abnormalities on ECG or echocardiography was too low to detect correlations between specific subgroups, for example, “high-amplitude R waves” (MC 3-1) with the echocardiographic abnormality “increased LV dimension” (LVIDd and/or LVIDs). The ECG abnormalities were not associated with the cumulative anthracycline dose, duration of follow-up, and age at diagnosis, as described earlier by Postma et al.

We did find male gender to be a risk factor for abnormal ECG patterns. Previous literature showed female gender as a risk factor for anthracycline-induced cardiotoxicity using echocardiography. In our study, we focused on abnormal ECG patterns. The prevalence of ECG abnormalities is also higher in men in the general population, indicating that this finding might be independent of anthracycline exposure. In a recent study by Mulrooney et al., male gender was reported as a risk factor for cardiomyopathy (defined as an EF <50%).

An analysis with coronary heart disease and conduction abnormalities could not be done because of their low prevalence of conduction abnormalities (4.4%). In our study, however, we included all ECG abnormalities (21.5% of survivors).

Although one in five survivors had an abnormal ECG, it is still unclear whether these abnormal ECG patterns are clinically relevant. The ECG findings in our study are heterogeneous and not necessarily indicative of subclinical cardiomyopathy.

In the present Dutch guideline and the COG guideline for long-term follow-up of CCSs, screening with ECG is recommended only at baseline and when clinically indicated. This study contributes to the knowledge that abnormal ECG patterns are common in asymptomatic CCSs, although it remains difficult to indicate the long-term clinical implications of our findings. However, the latter was not the aim of our present study.

We agree with others that more research is needed to indicate if, and which, abnormal ECG patterns will lead to (clinical) cardiac disease in the future. A prospective follow-up study of long-term CCSs with abnormal ECG patterns should be conducted to identify those of clinical relevance. Only then can one answer the question whether screening with ECG in long-term follow-up of CCSs is justified.

One of the limitations of the present study was its retrospective nature.

We had no data on whether survivors who did not visit the Late Effects Clinic upon invitation had clinical symptoms of cardiotoxicity. In addition, data on other possible risk factors for an abnormal ECG (such as smoking, hypercholesterolemia, and diabetes mellitus) were not available for our population. These data have now been incorporated in new national studies.

We conclude that abnormal ECG patterns were present in 21.5% of asymptomatic long-term CCSs visiting the Late Effects Clinic. The lack of agreement between abnormal ECG patterns and echocardiographic abnormalities may justify using both tests during follow-up. However, it is not clear whether the abnormal ECG patterns will be clinically relevant in the future. Our findings support the need for prospective studies on the relevance of ECG screening in the long-term follow-up of asymptomatic CCSs. In the meantime, we advise to perform an ECG at the first visit during LATER follow-up of CCSs as proposed in the current guidelines. We also advise to perform ECG following the initial ECG when there are symptoms suggestive of cardiotoxicity or conduction abnormalities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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