Childhood cancer survivors: cardiac disease & social outcomes
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A new method to facilitate valid and consistent grading cardiac events in childhood cancer survivors using medical records


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Abstract

Background

Cardiac events (CEs) are among the most serious late effects following childhood cancer treatment. To establish accurate risk estimates for the occurrence of CEs it is essential that they are graded in a valid and consistent manner, especially for international studies. We therefore developed a data-extraction form and a set of flowcharts to grade CEs and tested the validity and consistency of this approach in a series of patients.

Methods

The Common Terminology Criteria for Adverse Events version 3.0 and 4.0 were used to define the CEs. Forty patients were randomly selected from a cohort of 72 subjects with known CEs that had been graded by a physician for an earlier study. To establish whether the new method was valid for appropriate grading, a non-physician graded the CEs by using the new method. To evaluate consistency of the grading, the same charts were graded again by two other non-physicians, one with receiving brief introduction and one with receiving extensive training on the new method. We calculated weighted Kappa statistics to quantify inter-observer agreement.

Results

The inter-observer agreement was 0.92 (95% CI 0.80-1.00) for validity, and 0.88 (0.79-0.98) and 0.99 (0.96-1.00) for consistency with the outcome assessors who had the brief introduction and the extensive training, respectively.

Conclusions

The newly developed standardized method to grade CEs using data from medical records has shown excellent validity and consistency. The study showed that the method can be correctly applied by researchers without a medical background, provided that they receive adequate training.
**Introduction**

Due to the improvement in treatment protocols and new treatment modalities survival from childhood cancer is currently around 80%.\(^1\) Inherent to this improvement in childhood cancer survival is the growing population of childhood cancer survivors (CCS). However, around 75% of survivors will have at least one late adverse effect (e.g. endocrine, neurologic or psychosocial late adverse effects) induced by the cancer treatment.\(^2\) Knowledge of the incidence and risk factors for specific late adverse effects is essential, as it contributes to optimal follow-up care for survivors and recommendations for less toxic treatments for future childhood cancer patients. Frequent late effects within CCS are cardiac events (CE), such as heart failure, ischemia, pericarditis, valvular disease and arrhythmia, all of which cause long-term morbidity and early mortality.\(^3,4\) After a median follow-up time of more than thirteen years, the cumulative incidence of symptomatic heart failure is 1.7-2%, ischemia 0.44-0.7%, pericarditis 0.14-1.3%, valvular disease 0.44-1.6% and arrhythmia 0.66%.\(^3,5\)

A major limitation in current studies of CEs is the lack of uniform outcome definitions for the events in question. Definitions vary between research groups; even those within the same country. In addition, the CEs are often graded by several physicians (from different specialities), based on expert opinion, and without a clear grading protocol.\(^3,5-8\) For example, in a previous study of van der Pal et al.\(^3\) two authors (both physicians) graded CEs using the Criteria for Adverse Events (CTCAE) version 3.0 (heart failure, ischemia, pericarditis, valvular disease and arrhythmia grade 3-5) consulting a cardiologist when uncertain.\(^3\) On the other hand, Mulrooney et al.\(^5\) used self-reported CEs. Survivors were asked if they had ever been told by a doctor or other healthcare professional, that they have, or have had, a CE (i.e. heart failure, myocardial infarction, valvular abnormalities or pericardial disease). Within this study the severity of the CEs could not be established. Therefore, the lack of uniform outcome definitions for CEs makes it impossible to compare the results of existing studies and to summarize the evidence, thus making it difficult to make recommendations for clinical practice. Furthermore, Atkinson et al.\(^9\) showed that agreement between different clinicians when reporting adverse events is “moderate” at
best, even when clear outcome definitions (i.e. the CTCAE) are used. This study shows that even uniform outcome definitions for CEs are not sufficient and that there is a need for a clear grading protocol.

At this moment a large pan-European study is being conducted; PanCareSurfUp (PanCare Childhood and Adolescent Cancer Survivor care and Follow-up studies (PCSF)). One of the main objectives of PCSF is to identify CCS who have developed a symptomatic CE. Seven different European countries (the United Kingdom, France, Italy, Switzerland, Slovenia, Hungary and the Netherlands) will contribute cardiac data to this study and the incidence and absolute risk of cardiac disease among 5-year CCS will be determined. Furthermore, a nested case-control study will be undertaken to investigate the nature of the dose-response relationship between cumulative dose of specific anti-cancer drugs, cumulative dose of irradiation, and the risk of a CE. Outcome assessors will have different specialties, i.e. physicians and non-physicians (e.g. data managers or research nurses). To adequately analyse the data from the different countries the CEs need to be graded and validated in a uniform manner across Europe.

The aim of this study was to test the validity and consistency of a newly developed data-extraction form in combination with a flowchart to grade CEs in a group of CCS with a known CE.

Methods

Study population

We included CCS with a previously defined symptomatic CE from the cohort described in van der Pal et al. 2012.³ This cohort consisted of 1362 5-year CCS who were diagnosed with childhood cancer in the Emma’s Children Hospital/ Academic Medical Center between January 1966 and January 1996. Seventy-two survivors were suspected of a symptomatic CE during follow-up. After careful review forty-two patients were coded as a symptomatic CE (CTCAEv3.0 grade ≥3) and 30 patients were coded as an asymptomatic CE (CTCAEv3.0 grade ≤2). Our outpatient clinic for follow-up after treatment for childhood cancer was reviewed by the Institutional Review Board of the Academical Medical Center in Amsterdam and the study was deemed as patient care and was therefore exempt from the
The new method: data-extraction form/flowchart method for CEs

We developed a standardized data-extraction form (see SI 1), a set of flowcharts (one for each CE, i.e. heart failure, ischemia, pericarditis, valvular disease and arrhythmia; see SI 1), a manual with background information and a training presentation. The method is developed to distinguish between a CE of grade ≤2 and grade 3, 4 and 5. Grade ≤2 is predominantly asymptomatic. The method consists of two steps; 1) extraction of all relevant information from the available medical records, questionnaire (patient or physician) or interview using the standardized data extraction form and 2) assignment of a grade to the CEs using the appropriate flowchart. In Figure 1 the flowchart of heart failure is shown as an example. Each flowchart is constructed in the same manner; a step diagram and clarifying text blocks. We used a combination of the CTCAE v3.0 and CTCAE v4.0 for the definitions of CEs (see Table 1). Besides the data-extraction form and flowcharts we wrote a manual, including background information on the different CEs, and an extensive explanation on the use of the method (see Supporting information S1, Table S1, Figure S1-S5). Finally outcome assessors attended a presentation (see Presentation S1) to explain the method in more detail with the use of examples.
<table>
<thead>
<tr>
<th>Table 1. Definitions of cardiac events (using CTCAEv3.0 and CTCAEv4.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3</strong></td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Ischemia</td>
</tr>
<tr>
<td>Pericarditis</td>
</tr>
<tr>
<td>Valvular disease</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

as reported in the Criteria for Adverse Events (CTCAE) v4.0
CHF= congestive heart failure, EF= ejection fraction, SF= shortening fraction, ICD= implantable cardioverter defibrillator, CRT= cardiac resynchronisation therapy, Note: If a CE doesn’t comply with any of these criteria, it should be graded as grade ≤2.
Validity and consistency of the data-extraction form/flowchart method for CEs

In Figure 2 the methodology for testing the validity and consistency is schematically shown. The validity of our new method was tested by comparing the CE grading outcome of the physician of the forty randomly selected patients from the seventy-two CCS from a previous study, with the new grading outcome using the data-extraction form/flowchart method as graded by a non-physician. This non-physician had been involved in the development of the new method, but could be considered as a non-physician who had received an extensive training.

The consistency of the new method was tested by comparing the grading of the non-physician involved in the development of the new method with the grading of two other non-physicians, of whom one who had received a brief introduction to the method, based on the text below the flowcharts, and a second had received extensive training on the new method by means of the full manual and a presentation with an example case-study. In the first consistency test we compared the grading of the non-physician involved in the development of the method with the grading of the non-physician who received solely a brief introduction. In the second consistency test we compared the grading of the non-physician involved in the development of the method with the grading of the non-physician who received an extensive training. In this way we were able to test the robustness of the new method as well as the additional value of the extensive training. The first consistency test shows if the method on its own is sufficient for consistent grading of cardiac events. By comparing the results of the first consistency test with those of the second consistency test we can determine the additional value of the extensive training. The non-physicians were blinded for the results of the physician and the other non-physicians.

Data extraction

The necessary information was taken from medical charts. The medical charts were readily available since they were already collected for the study of van de Pal et al. To properly grade the CE information was needed on symptoms, diagnostic tests, medication and surgery. The goal was to get complete data on all those subjects for each CE.
**Statistical analysis**

To determine the agreement between the different outcome assessors we calculated a weighted Kappa.\textsuperscript{12,13} The weighted Kappa is used when there are several ordered grades and is calculated with the following formula:

\[
\frac{\text{probability of observed matches} - \text{probability of expected matches}}{1 - \text{probability of expected matches}}.
\]

The disagreements are weighted according to their squared distance from perfect agreement. \textit{R} was used to calculate the weighted Kappa and 95% confidence intervals.\textsuperscript{14} Values of Kappa between 0.40 and 0.59 are considered to reflect a fair agreement, between 0.60 and 0.74 to reflect a good agreement and 0.75 or more to reflect an excellent agreement.\textsuperscript{15}

**Results**

**Study population**

The median age of the forty persons (18 females), was 9.9 years (range 0.6-17.2) at the time of cancer diagnosis and 31.1 years (range 13.5-46.4) at the time of follow-up, with a median follow-up time of 21.6 years (range 5.1-36.1) since diagnosis. Fifteen subjects (37.5%) had received anthracyclines alone, ten subjects (25%) radiotherapy involving the heart region and eleven subjects (27.5%) anthracyclines and radiotherapy involving the heart region. Four subjects (10%) had not received any known cardiotoxic treatment.

Nineteen subjects (47.5%) had been diagnosed with heart failure (grade ≤2 n=6, grade 3 n=8, grade 4 n=2, grade 5 n=3) as first occurring CE, three subjects (7.5%) with ischemia (grade 3 n=2, grade 4 n=1), one subject (2.5%) with pericarditis (grade 4 n=1), fourteen subjects (35%) with valvular disease (grade ≤2 n=11, grade 3 n=2, grade 4 n=1) and three subject (7.5%) with arrhythmia (grade ≤2 n=1, grade 3 n=2).
Figure 1. Flowchart heart failure.

1a. The first question is “Symptoms?”, “number 1” refers to block 1 under the step diagram, in this block symptoms of heart failure are shown, so the user knows which symptoms could occur; When the answer is “NO”

1b. Is the “EF <40%-20% or the FS <15%” → YES grade 3 heart failure
    → NO grade ≤2 heart failure

When the answer is “YES” → Go to question “Responsive to intervention?”

2. Question “Responsive to intervention?”, block 2 in which common interventions for heart failure are shown;
When the answer is “NO” → grade 4 heart failure
When the answer is “YES” → grade 3 heart failure
When it is “UNKNOWN” → go to question “ Device3, life threatening consequences4 or heart transplant?”
3. Question “Device\(^3\), life threatening consequences\(^4\) or heart transplant?”, block 3 under the step diagram, in this block devices used as treatment for heart failure are shown. In block 4 the life threatening consequences associated with heart failure are stated;
   - When the answer is “NO” \(\Rightarrow\) grade 3 heart failure
   - When the answer is “YES” \(\Rightarrow\) grade 4 heart failure

Ref. [10, 11].

ICD-10= International classification of disease version 10
EF= ejection fraction
SF= shortening fraction
CRT-P or D= cardiac resynchronisation therapy pacemaker or defibrillator
ICD= implantable cardioverse defibrillator
LVAD= left ventricular assistance device

**Validity and consistency of the data-extraction form/flowchart method for CEs**

The results of the validity test are shown in Table 2. The inter-observer agreement for the comparison between the grading of the main non-physician and the grading of the physician in the previous study\(^3\) was 0.92 (0.80-1.00). Three CEs were graded differently: two of them were graded as grade 3 by the non-physician and as grade ≤2 in the previous study.\(^3\) The third CE was graded differently due to incomplete medical records.

The results of the two consistency assessments are presented in Table 3 and 4. The inter-observer agreement for the comparison between the non-physician involved in the development of the new method and the results of a non-physician who only received a brief introduction of the method was 0.88 (0.79-0.98). Eight CEs were graded differently (Table 2b), but always in an adjacent severity category.

The inter-observer agreement for the comparison between the non-physician involved in the development of the new method and the results of a non-physician who received extensive training on the new method by means of the above mentioned manual and presentation was 0.99 (0.96-1.00). Only one CE was graded differently (Table 2c).
**Figure 2.** Methodology of testing the validity and consistency of the data-extraction form/flowchart method for CEs
Table 2. Result for validity (physician (P) vs non-physician (NP))

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade ≤2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>NP</td>
<td>Grade ≤2</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>2*</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Grade unknown n=1 not included

Kappa = 0.92 (0.80-1.00)

Table 3. Result first consistency assessment (non-physician (NP) vs non-physician (brief introduction) (NPB))

<table>
<thead>
<tr>
<th></th>
<th>NP</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade ≤2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>NPB</td>
<td>Grade ≤2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Kappa = 0.88 (0.79-0.98)

Table 4. Result second consistency assessment (non-physician (NP) vs non-physician (extensive training) (NPE))

<table>
<thead>
<tr>
<th></th>
<th>NP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade ≤2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>NPE</td>
<td>Grade ≤2</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Kappa = 0.99 (0.96-1.00)
Discussion

This study demonstrates that our new standardised method for grading CEs in CCS using a data-extraction form and a set of flowcharts is valid and consistent. The random selection of the known cases resulted in a variation of CEs including different diagnoses and different levels of severity; therefore all five flowcharts were tested in this current study. With this method non-physicians can score CEs in an accurate manner. However, the best results from non-physicians were achieved when extensive training was given. Not all relevant data was extracted by the non-physician who received only a brief introduction of the method, resulting in a lower inter-observer agreement. The non-physician who received only a brief introduction of the method also had a limited knowledge of CEs. None of the previous studies focussing on CEs after cancer treatment had used a standardised method for the definition of the outcomes as described in this paper. The extraction form describes very specifically the information that is essential in order to grade the CE. This information can often be extracted from test results or letters, which are easy to interpret. Therefore, a strength of our method is that the invested time for retrieving necessary information for grading the CEs is minimal.

A limitation of this current study is that although the data-extraction/flowchart method may be used with several types of data (e.g. questionnaire, interviews or information from doctors), the current study only validated the method through the use of medical charts. With this study we wanted to confirm in principle that the data-extraction form/flowchart method is a valid and consistent method of grading a CE. The completeness in medical charts, compared to other sources of data, can be considered a benefit for this purpose. The external validity of the results of this study has not yet been tested in other institutes.

PanCareSurFup is a large pan-European study, of which one of the main objectives is to collect symptomatic CEs. Based on our findings, we believe that the data-extraction form/flowchart method can be safely used to consistently grade the CEs, across the different European countries. The current method is developed for CEs, but the CTCAE is available for adverse events of different organ systems. A similar method could be
developed for different other organs systems, which could then be applied in collaborative research.
We conclude that our newly developed method is a valid and consistent way to grade CEs. This method can be used by assessors with different medical background, provided that they receive proper instruction about the method, for which the manual and the training presentation are available.

Acknowledgements
The authors thank the other non-physicians (NPE and NPB); I. Lange en B.G.K. Niemeijer (Emma Children’s Hospital/ Academic Medical Center Amsterdam, the Netherlands) for assistance in grading the CEs. The authors also thank M. Brown for editing the article. Finally the authors thank the PanCare Childhood and Adolescent Cancer Survivor care and Follow-up studies Consortium.

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Appendix

Manual
Use of method

What
The following data is necessary for grading.
1. A specific description of the different symptoms of cardiac events, including (life threatening) symptoms
2. Information on additional diagnostic results (echocardiography, laboratory test, coronary angiography, blood etc.)
3. Information about cardiac medication and response to the medication
4. Information about non-surgical treatment (Implantable cardioverter-defibrillator, Cardiac resynchronization therapy etc.)
5. Information about possible cardiac surgery
For the purpose of extracting this information, a data collection form is developed (see Table S1).

How
The extra information for the first step of validation of the cases will be collected from one or more of the following:
• questionnaire/telephone to health care professional
• questionnaire/telephone to patient or their family, friends or social carer
• “late effects” clinic visit
• hospital discharge letter
• other
If the data is collected from a questionnaire, visit or letter, this should information should be validated with the medical chart or treating physician
**Table S1. Data-extraction form**

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>ID nr</td>
<td></td>
</tr>
<tr>
<td>Month of birth</td>
<td></td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
</tr>
<tr>
<td>Month of incidence</td>
<td></td>
</tr>
<tr>
<td>Year of incidence</td>
<td></td>
</tr>
<tr>
<td>Month of follow-up</td>
<td></td>
</tr>
<tr>
<td>Year of follow-up</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of ascertainment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire health care professional</td>
<td></td>
</tr>
<tr>
<td>Questionnaire to survivor or their family, friends or social carer</td>
<td></td>
</tr>
<tr>
<td>(Outpatient) Clinic visit</td>
<td></td>
</tr>
<tr>
<td>Medical records</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac event</th>
<th>Description of cardiac event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>date ______</td>
</tr>
<tr>
<td>Ischemia</td>
<td>date ______</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>date ______</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>date ______</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>date ______</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms (yes/no)</th>
<th>Additional diagnostic results (yes/ no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening symptoms (yes/no)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication (yes/ no)</th>
<th>Cardiac surgery + data (yes/ no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Dose</td>
</tr>
<tr>
<td>Responsive to medication (yes/ no)</td>
<td></td>
</tr>
</tbody>
</table>

Outcome flowchart: ____________________________

Method of validation: Medical records/ Treating physician/ other: _____________
Explanation data-extraction form:

- **Name**: Name of the person who is validating.
- **Date**: Date of validation
- **ID nr**: PanCareSurFup number which is given to the patient in WP1.
- **Month of birth**: The month in which the patient is born.
- **Year of birth**: The year in which the patient is born.
- **Month of incidence**: The month in which the first primary tumour is diagnosed.
- **Year of incidence**: The year in which the first primary tumour is diagnosed.
- **Month of follow-up**: The month until there is follow-up for the patient, concerning cardiac disease (last contact moment).
- **Year of follow-up**: The year until there is follow-up for the patient, concerning cardiac disease (last contact moment).
- **Method of ascertainment**: How was the (extra) information collected?
- **Cardiac event**: Which cardiac event, and on what date. For every cardiac event there should be a separate form.
- **Cardiac event nr.**: Fill in the number of the cardiac event, first event is the earliest event.
- **Description of the cardiac event**: The cardiac event should be elaborated on, e.g. if it is valvular disease, which valve and whether it is reguration or stenosis. It should also be stated if the patient is responsive to the given treatment.
- **Other condition**: Fill in if the patient ever had/has any other conditions (yes/ no). If the patient ever had/has other severe conditions this should be described in the square, also congenital heart defects can be stated here.
- **Symptoms**: Fill in if the patient ever had/has any symptoms (yes/ no). In the square it should state which symptoms.
- **Life threatening symptoms**: Fill in if the patient ever had/has any life threatening symptoms (yes/ no). In the square it should state the life threatening symptoms like hemodynamic comprise, life threatening arrhythmias, survived cardiac arrest etc.
- **Additional diagnostic results**: Fill in if the patient ever had any diagnostic tests (yes/ no). Every echo/ ecg/ blood or other test which is conducted in order to diagnose the cardiac disease.
- **Medication**: Fill in if the patient ever used/uses any medication (yes/ no). Which medication (generic name) is used for the cardiac disease, what is the dose and since when (– until when) does the patient take this medication.
- **Responsive to medication**: Is the patient responsive to the medication, did the patient deteriorate after medication (yes/ no)?
- **Cardiac surgery + date**: Did the patient had any cardiac surgery (yes/ no). Which type of cardiac surgery did the patient had for the cardiac disease and on what date. Types of surgery that should be included e.g.:
  - Medical device: Pacemaker, ICD, CRT-P, CRT-D, LVAD
  - Heart transplantation/ cardiac reduction surgery
  - Angiography/ Stenting/ Angioplasty/ CABG
  - Valvular surgery
  - Pericardectomy
  - Ablation
  - Antiarrhythmic surgery (e.g. Maze)
  - Cardioversion
- **Validation**: Which method was used to validate the information about this cardiac event? If it is other please elaborate.
Grading
The CTCAEv3.0 is used to grade the cardiac events, only grade 3, 4 and 5 are included. The flowcharts in Figure S1-S5 can be used to grade the cardiac events. For heart failure and ischemia we included life threatening consequences (grade 4), from CTCAEv4.0, this to make grading more simple/consistent.

Heart failure

Definition
Heart failure is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function (Table S2-4).

Grading
If it is not known if there were any symptoms present/related to the cardiac event, but an echocardiography was performed, and EF <40% or SF <15%, this cardiac event should be grade 3. If there is no echocardiography performed or there are no results, this cardiac event should not be included.

If the survivor is responsive to the given treatment? If so this cardiac event should be grade 3, if the survivor is not responsive to treatment, this cardiac event should be grade 4.

If it is not known, whether the survivor is responsive to the given treatment but there is evidence of a heart transplant or medical device this cardiac event should be grade 4, if not this cardiac event should be grade 3.
Table S2. Definition of heart failure

Heart failure is a clinical syndrome in which patients have the following features:

**Symptoms typical of heart failure** (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)

AND

**Signs typical of heart failure** (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly)

AND

**Objective evidence of a structural or functional abnormality of the heart at rest** (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Table S3. Common clinical manifestation of heart failure

<table>
<thead>
<tr>
<th>Dominant clinical feature</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral oedema/congestion</td>
<td>Breathlessness Tiredness, Fatigue Anorexia</td>
<td>Peripheral oedema Raised jugular venous pressure Pulmonary edema Hepatomegaly, ascites Fluid overload (congestion) Cachexia</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Severe breathlessness at rest</td>
<td>Crackles or rales over lungs, effusion tachycardia, tachypnoea</td>
</tr>
<tr>
<td>Cardiogenic shock (low output syndrome)</td>
<td>Confusion Weakness Cold</td>
<td>Poor peripheral perfusion SBP &lt;90 mmHg Anuria or oliguria</td>
</tr>
<tr>
<td>High blood pressure (hypertensive heart failure)</td>
<td>Breathlessness</td>
<td>Usually raised blood pressure, left ventricular hypertrophy and preserved ejection fraction</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>Breathlessness Fatigue</td>
<td>Evidence of right ventricular dysfunction Raised jugular venous pressure, peripheral edema, hepatomegaly, gut congestion</td>
</tr>
</tbody>
</table>
Table S4. New York Heart Association functional classification based on severity of symptoms and physical activity

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitations of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitations of physical activity. Comfortable at rest, but ordinary physical activity result in undue breathlessness, fatigue or palpitations</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitations of physical activity. Comfortable at rest, but less than ordinary physical activity result in undue breathlessness, fatigue or palpitations</td>
</tr>
<tr>
<td>Class IV</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

Ischemia\textsuperscript{3, 4}

Definition

The clinical presentations of coronary artery disease (CAD) include silent ischaemia, stable angina pectoris, unstable angina, myocardial infarction (MI), heart failure, and sudden death. In this study only unstable angina and myocardial infarction are included. The main symptom of CAD is the chest pain.

Grading

If it is not known whether the event was symptomatic or if the symptoms were related to the cardiac event, or if the event was symptomatic, but testing was not consistent with ischemia or whether it was unknown, this cardiac event should not be included (≤grade 2/unknown).

If testing was consistent with ischemia, but was not a myocardial infarction or if the event had not any life threatening consequences this cardiac event should be grade 3, if the event was a myocardial infarction or if the event had any life threatening consequences this cardiac event should be grade 4.
Ischemia

Symptoms?¹

- NO
  - ≤ Grade 2
  - NO
  - Unknown

- YES
  - ≤ Grade 2

Testing consistent
with ischemia²

- Unknown
  - Unknown
  - NO
  - ≤ Grade 2

- YES

Myocardial infarction³ or life threatening
consequences⁴

- Unknown
  - NO
  - Grade 3

- Grade 3

1. Symptoms:
   - Chest, upper extremity, jaw or epigastric
   - Discomfort with exertion or at rest
   - Dyspnoea
   - Diaphoresis
   - Nausea
   - Syncope

2. Testing consistent with ischemia
   - ECG changes
   - Angiography
   - Echocardiography
   - Radionuclide imaging
   - MRI
   - CT

   Intervention (If this is the only information
   you have):
   - Angioplasty
   - Stent
   - Coronary artery bypass graft (CABG)

3. Myocardial
   infarction:
   - Elevated biomarkers:
     - Myoglobin
     - Creatine kinase
     - Troponin I
     - Troponin T

4. Life threatening
   consequences:
   - Hypotension
   - Syncope
   - Shock
   - Aborted cardiac arrest
   - Life threatening
   arrhythmia

Death

ICD-10:
- I20: Angina pectoris
- I21: Acute myocardial infarction
- I22: Subsequent myocardial infarction
- I24.0 Coronary thrombosis not resulting in myocardial infarction
- I24.8 Other forms of acute ischaemic heart disease
- I24.9 Acute ischaemic heart disease, unspecified
- I25.0 Atherosclerotic cardiovascular disease, so described
- I25.1 Atherosclerotic heart disease
- I25.2 Old myocardial infarction
- I25.6 Silent Myocardial ischaemia
- I25.8 Other forms of chronic ischaemic heart disease
- I25.9 Chronic ischaemic heart disease, unspecified
- I46: Cardiac arrest

Figure S1. Flowchart Ischemia
Pericarditis\textsuperscript{5, 6}

Grading
Pericarditis with only symptoms (e.g. chest pain), without physiological consequences like pericardial constriction/effusion is a grade 2 event, and should not be included.

If the survivor also has physiological consequences like pericardial constriction and pericardial effusion and no life threatening consequences or it is unknown whether there were life threatening consequences, this cardiac event should be grade 3.

If there were life threatening consequences, this cardiac event should be grade 4.

\textbf{Figure S2.} Flowchart Pericarditis

\begin{itemize}
\item ICD-10:
  \begin{itemize}
  \item I30.0: Acute non-specific idiopathic pericarditis
  \item I30.8: Other forms of acute pericarditis
  \item I30.9: Acute pericarditis, unspecified
  \item I31: Other diseases of pericardium
  \item I46: Cardiac arrest
  \end{itemize}
\end{itemize}
**Valvular disease** 

*Grading*

Only events with symptoms of severe regurgitation or stenosis and controlled with interventions should be grade 3. If it is unknown whether the survivor had symptoms of severe regurgitation or stenosis or if the symptoms were related to the cardiac event, but is controlled with an intervention, this cardiac event should be grade 3. If the valvular disease is not controlled with intervention or if it is unknown but the survivor needs a valve replacement or valvuloplasty or has life threatening symptoms this cardiac event should be grade 4. If it is known that the survivor had symptoms, but it is unknown whether the valvular disease was controlled with interventions and it is unknown whether the survivor had a valve replacement or valvuloplasty or had life threatening symptoms this cardiac event should be grade 3.

**Arrhythmia** 

*Grading*

Arrhythmia events are a grade 3 event, if they are controlled with medicine, surgery or a device (including cardioversion). If not, this cardiac event should not be included (≤grade 2). To clarify; symptomatic events, but without medication, surgery or a device should be a grade 2 event, thus not an inclusion. If there were any life threatening consequences of the arrhythmia, this cardiac event should be grade 4.
Valvular disease

Symptoms¹?

- Syncope
- Angina pectoris
- Dizziness
- Exertional shortness of breath

Controlled with interventions²?

- ACE inhibitors
- Calcium channel blockers
- Beta-blockers
- Enalapril
- Diuretics
- Digoxin

Life threatening³?

- Hemodynamic compris

ICD-10:
- I34: Nonrheumatic mitral valve disorders
- I35: Nonrheumatic aortic valve disorders
- I36: Nonrheumatic tricuspid valve disorders
- I37: Pulmonary valve disorders
- I46: Cardiac arrest

Figure S3. Flowchart Valvular disease.
Arrhythmia

1. Symptoms:
   • Palpitations
   • Dizziness/lightheadedness
   • Presyncope
   • Dyspnea
   • Chest pain

2. Medicine
   • Beta-blockers
   • Digoxin
   • Calcium channel blockers
   • Amiodarone
   • Sotalol
   • Flecainide
   • propafenone
   • Electrolytes
   • Anti thrombins/anti platelets
   • N-3 Fatty acid and lipids

Device/surgery:
   • ICD
   • Pacemaker
   • CRT-P/CRT-D
   • Ablation
   • Antiarrythmic surgery
   • Cardioversion

3. Life threatening consequences:
   • Congestive HF
   • Hypotension
   • Syncope
   • Shock
   • Aborted cardiac arrest

ICD-10:
I44: Atrioventricular and left bundle-branch block
I45: Other conduction disorders
I46: Cardiac arrest
I47: Paroxysmal tachycardia
I48: Atrial fibrillation and flutter
I49: Other cardiac arrhythmias

Figure S4. Flowchart Arrhythmia
References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P et al. (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC and endorsed by the ESICM. Eur Heart J 29:2388-442.

2. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M et al. (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology Developed in collaboration with the Heart Failure Association (HFA) of the ESC.. Eur Heart J doi:10.1093/eurheartj/ehs104.


