


# Too often and too early: the risk of cardiac ischaemia in adult survivors of childhood cancer

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Childhood cancer survivors (CCS) are at increased risk of chronic health conditions such as recurrent cancers, second cancers and cardiovascular disease to mention the most common ones.<sup>1</sup> Already at the age of 30, the more severe chronic health conditions have occurred with an estimated cumulative incidence of 42.4%,<sup>1</sup> which accumulate up to 53.6% at 50 years.<sup>2</sup> The cardiovascular burden of disease comprises mainly heart failure, valvular disease and pericardial disease, while for coronary artery disease, the incidence of myocardial infarction (compared with all the competing other events) seems to be low at 1.3% at 30 years after diagnosis. However, this incidence increases to 5.3% by the age of 45 and has a continuously raised HR of 5 compared with age matched siblings.<sup>3,4</sup> These figures raise the issue for continuous cardiovascular surveillance of CCS up until older age and also for the need for risk models and prevention programmes.

In the study of Feijen *et al*<sup>5</sup> in this issue of the journal, we see the cardiac ischaemia perspective of the European adult who survived cancer in childhood or early adulthood (<20 years), the majority of whom are between 20 and 49 years of age. Some of the patients were followed up into their 60s and 70s, which may seem unprecedented. The result is new for elderly CCS: there is a cumulative incidence of severe cardiac ischaemic events of 5.4% at the age of 60 years, which is probably still underestimated (see below). The results confirm previous studies that there is an increasing cumulative incidence of severe cardiac ischaemic events with age, at 20 years 0.02%, at 30 years 0.16%, at 40 years 0.71 %, at 50 years 2.46% and at 60 years 5.4% with the second possible take home message that there is still the possibility of prevention as their type of

coronary artery disease is also slowly progressive.

The main impact of the study is made by the number of pooled data of 36205 CCS, provided by a consortium of European investigators from seven countries in the PanCareSurFup study, funded by a European grant.<sup>5</sup> Each of the eight cohorts that comprised this study had a somewhat different method of gathering the data, but the general picture is that of questionnaires sent to the participants, followed by a validated assignment of reported cardiac ischaemia events from medical records in 3 grades of severity. Grade 3 events are symptomatic episodes, in which concurrent imaging methods or interventions established the cause, grade 4 events are nonfatal acute myocardial infarctions and grade 5 events death by ischaemic heart disease, while events of lower severity (reporting of hypertension or arrhythmia) are discarded. The paper studies the cardiac ischaemia events from the patient's perspective: the confrontation with their first event that is of some importance and the age at which these events occur with a cumulative incidence. A restriction is that only symptomatic events were used for this study; asymptomatic events cannot be timed well and may only be given as prevalences.

There is an interesting result of the study by Feijen *et al*<sup>5</sup> in the distribution of the 302 *first* cardiac ischaemic events: 43 events were grade 3, the majority of 169 events were grade 4 (myocardial infarctions) and a not insignificant grade 5

event of death by ischaemic heart disease occurred in 90 patients as a first event. The low incidence of grade 3 events may be somewhat surprising, when the incidence of coronary events is regarded as the accumulation of coronary artery disease burden, so from less severe to more severe events. What is known about it in the general population? The Framingham study data of 1985 with patients between 35 and 84 years, initially free of clinical coronary heart disease and after a follow-up of 26 years, roughly demonstrate a *first* event distribution of stable and unstable angina events in 46%, myocardial infarction events in 49% and 9% sudden death.<sup>6</sup> In a prospective cohort study from London between 1996 and 1998 with patients between 25 and 74 years of age, a *first* event distribution was seen of stable and unstable angina in 57%, myocardial infarction in 29% and sudden cardiac death in 13%.<sup>7</sup> So, in the general population, a more or less comparable incidence is observed of grade 3 and 4 *first* events and, although still impressive as a first event, significantly less sudden death. In both of the studies from the general population, there was a male preponderance of events. If similar first event rates would occur in CCS as in the general population, with a myocardial infarction being the common first event that is recognised as grade 4, we may be missing a fourfold or more of expected grade 3 cardiac events in the present data reported in the study of Feijen *et al*. Explanations are underreporting and a lack of validation possibility of angina complaints that may have been reported in the questionnaires. Since we are interested in coronary problems, their possible prevention at an early age, and especially since there may be distribution differences between men and women of these events, the solution is not to discard grade 3 events. The proper solution would be to further improve the

**Table 1** incidences of severe cardiac ischaemic events

Study population	Comparison	Cumul incidence in CCS	Risk estimate
CCSS n=14358, 5-year CCS, grade 3–5 events <sup>3,4</sup>	Siblings n=3899	1.3% at 30 years after diagnosis 5.3% at age 45 years	HR 5.0 (2.3–10.4)
ALICCS n=32308, limited to 5-year CCS <sup>8</sup>	General population n=211489	1.7% at age 35 years* 5.5% at age 45 years* 13.6% at age 55 years*	RR 3.5 (2.0–6.2)
PanCareSurFup n=36205, 5-year CCS <sup>5</sup>	NA	0.2% at age 30 years† 0.7% at age 40 years† 2.5% at age 50 years† 5.4% at age 60 years†	NA

\*Data from figure 1, limited to myocardial infarctions in every age group.

†Data are grade 3–5 severe cardiac ischaemic events. CCS, childhood cancer survivors.

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validation of such events. The 90 patients with grade 5 events from the current study still comprise more patients than expected from these distributions, giving rise to a suggestion that either the myocardial infarctions in this CCS population may also have been underestimated, or that sudden death may not always have had an ischaemic or cardiac reason. From the Framingham study, we know that one in three myocardial infarctions are undetected.<sup>6</sup>

For the overall impression of the current coronary artery disease problems in CCS, there are two study cohorts with which to compare the incidence and risk of hospitalisation for myocardial infarctions/severe ischaemic events (see table 1): the Adult Life After Childhood Cancer in Scandinavia (ALiCCS) study from the Scandinavian Nordic countries<sup>8</sup> and the Childhood Cancer Survivor Study (CCSS) study from the USA.<sup>3,4</sup> Overall, the results are similar with increasing risk with age, an approximate fivefold increased risk of events in CCS at any age. The results are also reminiscent of a previously observed threshold risk for those of >35 years old.<sup>2</sup> This does not withstand the finding that 15% of the events in the current study already occurred in those <30 years old and that the cumulative incidence risk curves in these studies indicate that CCS have similar incidences of severe cardiac ischaemic events as patients in the general population who are 10–15 years older.

Competing risks in the population of CCS are widespread (death by recurring malignancy as the most threatening, but also death by heart failure) and may become another reason for underestimating the real risk. In the present study, competing risk summed up to a total mortality rate of 15%, but the analysis of cumulative incidence was done with a Gogol-like introduction of dead persons into the analysis with each of them having a weight in the analysis appropriate for the time spent prior to their death.<sup>5</sup>

One shortcoming of the present study is that event rates were not compared with event rates occurring in the general population or in siblings. The authors

compared patients who received cardiotoxic treatments to patients who were not treated or were treated with surgery only (14.6% of patients). For 60 year olds, the cumulative incidences of symptomatic cardiac ischaemic events in the present study were 6.2% for patients treated with cardiotoxic treatments and 3.2% for patients who were not. The association of events with risk factors such as radiotherapy, male sex and a previous diagnosis of Hodgkin disease is necessary for at least two reasons: to identify persons at high risk, but also to identify those at low risk for this specific event, who are still in the majority. The risk factors mentioned in the present study are corroborated by other reports,<sup>4</sup> but are still incomplete because of the lack of addition of common cardiovascular risk factors (hypertension, smoking, hypercholesterolemia, diabetes mellitus, obesity). A planned nested case-control study including these risk factors will possibly add to further risk stratification.<sup>5</sup> Of interest is that CCS carry the risk of cardiotoxic treatments on the development of atherosclerosis and inflammation and have an increased presence of common cardiovascular risk factors, where risk factors potentiate risk instead of add risk.<sup>4</sup> The study of risk for the specific outcome of cardiac ischaemic events in models would open the possibility to prevent cardiovascular events with lifestyle interventions at an early age (hypertension as the most prominent risk factor) and also to better identify the CCS at low risk for this type of outcome.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; internally peer reviewed.



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**To cite** Kok WE. *Heart* 2021;**107**:6–7.

Published Online First 6 October 2020



► <http://dx.doi.org/10.1136/heartjnl-2020-316655>

*Heart* 2021;**107**:6–7.

doi:10.1136/heartjnl-2020-317812

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