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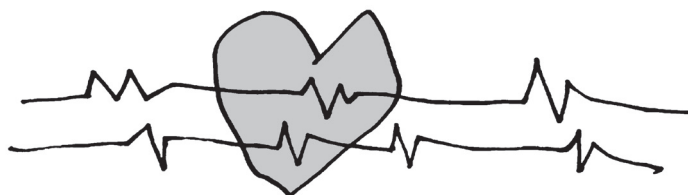
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Chapter 8

The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors

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Summary

Background

The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG LATER), developed a guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors (CCS). In this paper we present the methods, available evidence and final recommendations of our guideline.

Materials and methods

A multidisciplinary working group specified clinical questions that should be answered to get to recommendations for the guideline. We performed short or extensive evidence summaries and determined methodological quality of studies and levels of evidence in order to answer all clinical questions. When evidence was lacking for CCS, we carefully extrapolated evidence from other populations. Final recommendations were based on evidence and consensus.

Results

There was high level evidence for the increased risk of cardiac dysfunction in CCS and its main risk factors. Evidence was lacking regarding the prognosis, diagnosis and treatment of cardiac dysfunction in CCS. We recommended echocardiographic screening for asymptomatic cardiac dysfunction in CCS treated with cardiotoxic treatments and counseling about potential advantages and disadvantages of our screening recommendations.

Conclusion

The DCOG LATER guideline recommends risk-based screening for asymptomatic cardiac dysfunction in CCS, but it should be noted that recommendations are not completely supported by evidence in CCS.

Background

Since the survival of childhood cancer approaches 75%, there is a large and growing group of young people that is confronted with health problems caused by childhood cancer treatment.^{1,2} Because of the high risk of health problems there is consensus that childhood cancer survivors (CCS) require long-term follow-up care focused on these late effects of cancer treatment.³⁻⁵ The Late Effects of Childhood Cancer task force of The Dutch Childhood Oncology Group (DCOG LATER) has developed a guideline to ensure optimal and uniform follow-up care for all CCS in the Netherlands, covering all potential late health problems in CCS.

One of the late effects of childhood cancer treatments that frequently causes morbidity and mortality in this population is cancer treatment-induced cardiac disease.⁶⁻⁸ Especially anthracycline- and/or radiotherapy-induced cardiac dysfunction are common, and frequently present in an asymptomatic stage, before progressing to symptomatic heart failure.⁹⁻¹³

In this paper we report on the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction in 5 year CCS. We focused on the screening and treatment options for asymptomatic, cancer-treatment induced cardiac dysfunction, with the ultimate goal to prevent subsequent symptomatic heart failure in CCS. We present the methods of guideline development, the available evidence for the guideline and the final recommendations of the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction.

Methods

For the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction, we formed a working group, including a pediatric oncologist, medical oncologists, a pediatric cardiologist, an adult cardiologist, a general pediatrician, and epidemiologists. We had meetings from 2007 until 2010 to discuss the available evidence and to draft a proposal for recommendations. All steps were subsequently discussed within a wider group of the DCOG LATER task force, which coordinated all organ-based guidelines that were part of the overall DCOG LATER guideline for follow-up of CCS.

To identify relevant evidence and get to final recommendations for the guideline for follow-up of asymptomatic cardiac dysfunction, the working group first formulated clinical questions that were relevant to our guideline. We thereby focused on clinical questions regarding early detection and potential treatment of asymptomatic cardiac dysfunction. We categorized the clinical questions into four topics: (1) *Incidence / Prevalence or Etiology / Risk factors*, (2) *Prognosis*, (3) *Diagnosis* and (4) *Therapy*.

Two clinical questions were selected for an extensive evidence summary because of relevancy and lack of knowledge within the wider DCOG LATER collaboration: (1) "What is

the predictive value of a reduced left ventricular ejection fraction (EF) or left ventricular fractional shortening (FS) of the heart (asymptomatic cardiac dysfunction) on the occurrence of future clinical heart failure or death?" (topic Diagnosis), and (2) "What is the effectiveness of medical interventions (ACE-inhibitors, beta-blockers) in patients with asymptomatic left ventricular dysfunction in general on the occurrence of heart failure and mortality?" (topic Therapy). For these two questions, we performed systematic literature searches to identify relevant studies. To answer the other clinical questions formulated by the working group, we made short evidence summaries. These were based on information reported in other guidelines for follow-up of CCS,¹⁴⁻¹⁶ two textbooks on late effects of childhood cancer treatment,^{17, 18} relevant systematic reviews from a study on systematic reviews in pediatric oncology,¹⁹ studies suggested by working group members or studies identified by performing simple MEDLINE searches. We included studies that investigated cancer-treatment induced cardiac abnormalities that the authors of the study defined as cardiotoxicity, cardiac dysfunction, left ventricular dysfunction or heart failure. In line with studies in the pediatric oncology field, we used the terms asymptomatic cardiac dysfunction throughout the guideline to indicate abnormal function of the heart as found during a diagnostic procedure in a patient without symptoms; and clinical heart failure as an abnormal function of the heart in a patient with accompanying symptoms and signs. A report on the search strategy for the two extensive evidence summaries, as well as a summary of the included studies for all clinical questions is provided in the appendix. We determined methodological quality of individual studies and level of evidence of all clinical questions based on the manual of the Dutch Evidence Based Guideline Development platform (EBRO platform),²⁰ which was adjusted for the purpose of the DCOG LATER overall guideline (Table 1).

Within our working group the clinical relevance of evidence and lack of evidence was discussed. When evidence was lacking for CCS, we carefully extrapolated evidence from other populations. Other considerations of the working group in addition to the available evidence were summarized. We categorized our recommendations as follows: (1) *Who do we need to screen?*; (2) *What is the time interval for screening and for how long should we screen?*; (3) *What is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction?* (4) *What should be done when abnormalities are identified?* The final recommendations were based on evidence, additional considerations of the working group and consensus about the estimate of the expected individual risk, the availability of a test with adequate predictive and diagnostic value to detect relevant outcomes and the availability of adequate therapy when abnormalities are detected. The working group continuously monitored evidence and updated recommendations when necessary up to April 2011.

The final recommendations of the DCOG LATER guidelines were presented to relevant professional organizations and the national organization of parents of children with cancer. Recently, the DCOG LATER task force determined indicators based on several consensus meetings. The task force has aimed to update the guideline periodically (every 3 – 5 years).

Table 1 Assessment of methodological quality and level of evidence. Based on the Dutch Evidence Based Guideline Development ²⁰ and adjusted for the purpose of the DCOG LATER overall guideline

Methodological quality	Intervention research	Diagnostic research	Etiologic and prognostic research
A1	Systematic review of good quality, summarizing at least two independent studies of A2 level		
A2	Double-blind, randomized controlled trial of good quality and with an appropriate size	Comparative study with a reference test (golden standard) of good quality and with an appropriate size	Cohort or case-control study of good quality and with an appropriate size
B	Comparative study, but not with characteristics as mentioned for A2	Comparative study, but not with characteristics as mentioned for A2	Cohort or case-control study, but not with characteristics as mentioned for A2
C	Non-comparative intervention study	Study without a reference test	Cross-sectional research
D	Consensus of experts, based on evidence in other populations, case reports and / or clinical experience		

Level of evidence	Evidence is based on
Level 1	Research at level A1 or at least 2 independent studies at level A2, that support each other's conclusions and do not show conflicting evidence
Level 2	Research at level A2 or at least 2 independent studies at level B, that support each other's conclusions and do not show conflicting evidence
Level 3	Research at level B or at least 2 independent studies at level C, that support each other's conclusions and do not show conflicting evidence
Level 4	Research at level C or 2 or more independent studies at higher level, that do not support each other's conclusions and show conflicting evidence
Consensus	There is no evidence, but consensus only (level D) to support the conclusion
Not identified	There is research (at any level), that has not identified data to support the conclusion
No evidence	There is no evidence and no consensus to support the conclusion

Results

Available evidence

The answers to our clinical questions, the associated levels of evidence and references for the topics: (1) *Incidence / Prevalence or Etiology / Risk factors*, (2) *Prognosis*, (3) *Diagnosis* and (4) *Therapy* are presented in Table 2.

Additional considerations of the working group

1. Who do we need to screen?

Although it has been shown that treatment with a higher cumulative anthracycline dose is associated with higher risks of cardiac dysfunction, a cut-off dose suitable for screening

Table 2 The available evidence

Who do we need to screen?		Level of evidence reference
Incidence / Prevalence	What is the risk of cardiac disease after treatment with anthracyclines for childhood cancer?	
	Increased risk for	
	Symptomatic cardiac dysfunction	Level 1 ^{10, 12, 25, 27}
	Asymptomatic cardiac dysfunction	Level 1 ^{9, 13, 25}
	What is the risk of cardiac disease after cardiac irradiation for childhood cancer?	
	Increased risk for	
	Symptomatic cardiac dysfunction	Level 1 ^{8, 11, 25}
	Asymptomatic cardiac dysfunction	Level 2 ^{13, 54}
	What is the risk of cardiac disease after treatment with mitoxantrone for childhood cancer?	
	Increased risk for	
	Symptomatic cardiac dysfunction	Level 2 ²⁶
	Asymptomatic cardiac dysfunction	Level 2 ²⁶
What is the risk of cardiac disease after treatment with ifosfamide or cyclophosphamide for childhood cancer?		
Increased risk for		
Symptomatic cardiac dysfunction	No evidence	
Asymptomatic cardiac dysfunction	Not identified ¹³	
Etiology / Risk factors	What are the most important risk factors for cardiac disease in childhood cancer survivors?	
	Increased risk for	
	CCS treated with higher doses of anthracyclines (symptomatic cardiac dysfunction)	Level 1 ^{10-12, 25, 27}
	CCS treated with higher doses of anthracyclines (asymptomatic cardiac dysfunction)	Level 1 ^{9, 13, 21-25}
	CCS treated with higher doses of cardiac radiotherapy (symptomatic cardiac dysfunction)	Level 1 ^{11, 25, 27, 28}
	CCS treated with higher doses of cardiac radiotherapy (asymptomatic cardiac dysfunction)	Not identified ^{25, 54}
	CCS treated with higher doses of mitoxantrone (symptomatic and asymptomatic cardiac dysfunction)	Not identified ²⁶
	Female CCS (symptomatic cardiac dysfunction)	Level 1 ^{11, 25, 27}
	Female CCS (asymptomatic cardiac dysfunction)	Level 4 ^{13, 23}
	CCS treated at a younger age (symptomatic cardiac dysfunction)	Level 2 ¹¹
	CCS treated at a younger age (asymptomatic cardiac dysfunction)	Level 2 ¹³
	Pregnant CCS (symptomatic cardiac dysfunction)	Not identified ²⁹
	Pregnant CCS (asymptomatic cardiac dysfunction)	Level 3 ³⁰

is difficult to determine.^{9, 13, 21-25} Cardiac dysfunction and clinical heart failure do occur after low anthracycline doses.^{12, 24, 25} For mitoxantrone, the working group agreed that an increased risk of cardiac dysfunction is likely, but thus far no high quality studies have been performed to determine the risk after different cumulative doses.²⁶ Similarly, higher doses of cardiac irradiation are related to a higher risk of cardiac disease, but again no clear cut-

Table 2 The available evidence (*continued*)

What is the time interval for screening and for how long should we screen?		Level of evidence reference
Prognosis	What is the risk for deterioration of cardiac disease in childhood cancer survivors?	
	Increased risk for deterioration of:	
	Anthracycline-induced cardiac dysfunction	Level 1 ^{21, 24, 33, 34}
	Radiotherapy-induced cardiac dysfunction	No evidence
	What is the deterioration rate of cardiac disease in childhood cancer survivors?	
	Deterioration rate of:	
	Anthracycline-induced cardiac function	No evidence
	Radiotherapy-induced cardiac dysfunction	No evidence
	Is there a well-defined risk period for deterioration?	
Risk period for deterioration:		
Anthracycline-induced cardiac function	No evidence	
Radiotherapy-induced cardiac dysfunction	No evidence	
What is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction?		Level of evidence reference
Diagnosis	What is the prognostic value of abnormal echocardiographic parameters^a in childhood cancer survivors with asymptomatic cardiac disease?	
	Prognostic for	
	Symptomatic anthracycline-induced cardiac dysfunction	No evidence
	Symptomatic cardiac dysfunction after cardiac radiotherapy	No evidence
	What is the prognostic value of abnormal radionuclide angiographic parameters^a in childhood cancer survivors with asymptomatic cardiac disease?	
	Prognostic for	
	Symptomatic anthracycline-induced cardiac dysfunction	No evidence
	Symptomatic cardiac dysfunction after cardiac radiotherapy	No evidence
	What is the diagnostic value of abnormal biomarkers^a in childhood cancer survivors with asymptomatic cardiac disease compared to echocardiography?	
	Good diagnostic value for	
	Symptomatic/asymptomatic anthracycline-induced cardiac dysfunction	Not identified ⁴⁷
	Symptomatic/asymptomatic cardiac dysfunction after cardiac radiotherapy	No evidence
What is the prognostic value of other abnormal diagnostic tests (ECG, MRI)^a in childhood cancer survivors with asymptomatic cardiac disease?		
Prognostic for		
Symptomatic anthracycline-induced cardiac dysfunction	No evidence	
Symptomatic cardiac dysfunction after cardiac radiotherapy	No evidence	
What is the prognostic value of abnormal echocardiographic parameters (EF/FS) in the general population with asymptomatic cardiac disease? (Supplementary table 1) ^p		
Prognostic for		
Development of clinical heart failure and death (EF, FS)	Level 1 ³⁵⁻⁴³	

off value for a safe cumulative dose can be defined, especially for asymptomatic cardiac dysfunction.^{8, 11, 25, 27, 28} Other risk factors for cardiac dysfunction (like age at treatment, gender, pregnancy) were difficult to summarize, because available studies analyzed differ-

Table 2 The available evidence (*continued*)

What should be done when abnormalities are found?		Level of evidence reference
Therapy	What is the effect of ACE-inhibitors in childhood cancer survivors with asymptomatic anthracycline-induced cardiac dysfunction?	
	Effective on	
	Left ventricular end systolic wall stress	Level 2 ⁵⁰
	Increased risk for	
	Dizziness and hypotension	Level 2 ⁵⁰
	No identified effect on	
	Development of clinical heart failure and death	Level 2 ⁵⁰
	Other echocardiographic parameters of cardiac function (ejection fraction, fractional shortening)	Level 2 ⁵⁰
	Other parameters of cardiac function (maximal cardiac index on exercise testing)	Level 2 ⁵⁰
	What is the effect of other cardiovascular medication^a in childhood cancer survivors with asymptomatic cardiac dysfunction?	
	Effective on	
	Deterioration of cardiac dysfunction, development of clinical heart failure and death	No evidence
What is the effect of ACE-inhibitors in the general population with asymptomatic cardiac dysfunction? (Supplementary table 1)^b		
Effective on		
Death (all causes of asymptomatic cardiac dysfunction, including IHD)	Level 1 ^{35, 37, 38, 42}	
Development of clinical heart failure (all causes of asymptomatic cardiac dysfunction, including IHD)	Level 1 ^{35, 38, 42}	
What is the effect of beta-blockers in the general population with asymptomatic cardiac dysfunction? (Supplementary table 1)^b		
Effective on		
Death (asymptomatic cardiac dysfunction caused by IHD)	Level 2 ⁵⁵⁻⁵⁷	
Development of clinical heart failure (asymptomatic cardiac dysfunction caused by IHD)	Level 2 ⁵⁵⁻⁵⁷	

^a As studied in included studies

^b Clinical questions in purple indicate questions on evidence in the general (adult) population
 Abbreviations: DCOG LATER: The Late Effects of Childhood Cancer task force of The Dutch Childhood Oncology Group; CCS: childhood cancer survivors; ECG: electrocardiogram; MRI: magnetic resonance imaging; EF: ejection fraction; FS: fractional shortening; ACE: angiotensin-converting enzyme; IHD: ischemic heart disease

ent risk factors using different methods or there was conflicting or lack of evidence.⁸⁻¹⁰ We therefore focused on results of multivariate analyses in high-quality studies,^{11, 13, 23, 25, 27, 29} or when no high quality studies were available on the only available studies.³⁰ Based on available evidence and consensus, we recommended screening for asymptomatic cardiac dysfunction in all CCS treated with potentially cardiotoxic cancer treatment (anthracyclines, cardiac radiotherapy and mitoxantrone). We defined cardiac radiotherapy as any radiotherapy field that includes (part of) the heart (mediastinal, thoracic, spinal, left or

whole upper abdominal or total body irradiation). We recommended more frequent follow-up for survivors treated with high doses of anthracyclines (cut-off 300 mg/m²), high doses of cardiac radiotherapy (cut-off 30 Gray) or a combination of the two (any dose). We felt that there is not enough evidence and consensus to further adjust these recommendations for age at treatment and/or gender of the survivor. Because of the potentially severe consequences of missing cardiac dysfunction during pregnancy,^{31, 32} we decided to recommend extra screening for female survivors in the third trimester of pregnancy, even though strong evidence for this recommendation is lacking.^{29, 30}

2. What is the time interval for screening and for how long should we screen?

There is evidence for deterioration of asymptomatic anthracycline-induced cardiac dysfunction,^{21, 24, 33, 34} but an appropriate interval and period for screening is difficult to define. Based on studies in (adult) patients with asymptomatic cardiac dysfunction due to causes other than treatment for childhood cancer,³⁵⁻⁴³ we assumed that CCS with asymptomatic cardiac dysfunction similarly are at increased risk to develop clinical heart failure and (cardiac) death (see topic Diagnosis). We considered it unlikely that this risk of deterioration decreases with longer follow-up. We agreed that frequency of screening is a balance between the risk of missing (progressive) cardiac dysfunction and the burden of regular visits to a clinic. Based on consensus we recommended follow-up once every five years or once every two/three years for the lower and higher risk groups respectively. We further recommended lifelong follow-up until more evidence is available regarding very long-term risks of cardiac dysfunction.

3. What is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction?

Within the working group there was consensus that echocardiography is a fairly accurate, non-invasive diagnostic tool to detect cardiac dysfunction. Based on the evidence in adults with cardiac dysfunction due to causes other than treatment for childhood cancer (Supplementary table 1, appendix),³⁵⁻⁴³ we concluded that in CCS a decreased EF and/or FS is probably predictive for the occurrence of future clinical events. However, the exact cut-off point for abnormal cardiac function that is predictive for future clinical events is difficult to determine from included studies. We therefore recommended to consult a cardiologist when cardiac function is borderline abnormal (FS 25%-29%, EF 45%-49%) and referral to a cardiologist when cardiac function is clearly abnormal (FS<25%, EF<45%).

Studies in adults have shown that asymptomatic diastolic dysfunction can be predictive for the development of clinical heart failure.⁴⁴ However, only a few studies in CCS have suggested an increased risk of treatment-induced diastolic dysfunction and no study has evaluated the prognostic value of it.^{33, 45} Also the clinical implications of other asymptomatic

echocardiographic parameters in CCS, like tissue Doppler echocardiography are unclear. We therefore did not include these abnormalities in our recommendations.

It is possible that on a routine echocardiogram other abnormalities than a decreased FS/EF, or incidental findings like anatomical variations are identified. We therefore added this possibility to our recommendations. Radionuclide angiography is an alternative to determine cardiac function when echocardiography is not suitable.⁴⁶ We found no evidence for a high prognostic value of other abnormal diagnostic tests (ECG, MRI) in CCS with asymptomatic cardiac disease.

Three systematic reviews evaluated the potential of biomarkers (mainly B-type natriuretic peptide and N-terminal pro BNP) to detect cardiac dysfunction or clinical heart failure in the adult general population and in CCS.⁴⁷⁻⁴⁹ These studies concluded that these biomarkers are not suitable for screening asymptomatic patients in the general population and that there is not enough evidence on their use in CCS. We therefore decided that at this point in time there is no place for screening of asymptomatic cardiac dysfunction by biomarker assessment.

4. What should be done when abnormalities are identified?

One randomized controlled trial (RCT) of ACE-inhibitors in CCS with anthracycline-induced asymptomatic cardiac dysfunction showed no positive effects on clinical endpoints, only a small effect on one subclinical outcome and side-effects like dizziness.⁵⁰ Because of the small sample size of this RCT and based on the effects of ACE-inhibitors in other populations with asymptomatic cardiac dysfunction,^{35, 37, 38, 42} we felt that it is reasonable to hypothesize a positive and potentially clinical effect of ACE-inhibitors in CCS. However, the working group agreed that any potential benefit should be weighed against the potential side-effects individually. Since further research is essential, we recommended providing ACE-inhibitor treatment in a research setting, or when this is not possible, to at least carefully monitor the effects of treatment for future studies.

5. Additional considerations.

Because of lack of evidence regarding several important topics within the field of cancer-treatment induced cardiac dysfunction, we additionally recommended that CCS should be counseled regarding this lack of evidence and the potential advantages and disadvantages of screening for asymptomatic cardiac dysfunction after childhood cancer treatment. After careful counseling, the individual survivor and the health care professional together should decide on the optimal follow-up of the survivor.

Final recommendations for screening and follow-up

Based on the available evidence and the stated considerations, we formulated recommendations for screening and follow-up for cardiac dysfunction in CCS. These are summarized in Table 3.

Table 3 DCOG LATER recommendations for cardiac follow-up for childhood cancer survivors

Who do we need to screen?	
Childhood cancer survivors, treated with:	
Anthracyclines (doxorubicin, epirubicin, daunorubicin)	
Cardiac radiotherapy (irradiation of the mediastinum, thorax, spine, left or whole upper abdomen or total body irradiation)	
Mitoxantrone	
What is the diagnostic test we have to use to detect asymptomatic cardiac dysfunction?	
Main test and parameters	
Echocardiography: left ventricular systolic function (FS and/or EF)	
Alternative test and parameters	
RNA: left ventricular systolic function (EF)	
What is the time interval for screening?	
Echocardiography	
Anthracyclines <300 mg/m ²	Once every 5 years
Anthracyclines ≥300 mg/m ²	Once every 2/3 years
Anthracyclines and cardiac radiotherapy (regardless of received doses)	Once every 2/3 years
Cardiac radiotherapy <30 Gy	Once every 5 years
Cardiac radiotherapy ≥30 Gy	Once every 2/3 years
Mitoxantrone ≥40 mg/m ²	Once every 5 years
Pregnant survivors treated with any cardiotoxic treatment	Once in the third trimester of pregnancy
RNA	
In case echocardiography is not feasible (adipositas) : <i>Schedule like echocardiography</i>	
What should be done when abnormalities are found?	
Echocardiography	
FS ≥ 30%, EF ≥ 50%, no other abnormalities: <i>No action</i>	
FS ≥ 30%, EF ≥ 50%, but other abnormalities: <i>Consultation cardiologist</i>	
FS 25%-29%, EF 45%-49%: <i>Consultation / referral to cardiologist (consider ACE-inhibitor treatment, preferably in research setting, or with careful monitoring of the effects of treatment)</i>	
FS < 25%, EF < 45%: <i>Referral to cardiologist (consider treatment with ACE-inhibitor, preferably in research setting, or with careful monitoring of the effects of treatment)</i>	
Other considerations	
Counseling	
All survivors at risk of cardiac dysfunction	
<i>Individual estimated risk of cardiac dysfunction</i>	
<i>Individual counseling about potential advantages and disadvantages of screening</i>	

Abbreviations: DCOG LATER: The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group; FS: fractional shortening; EF: ejection fraction; Gy: Gray; RNA: radionuclide angiography; ACE: angiotensin-converting enzyme

Guideline implementation and quality indicator

The implementation of the DCOG LATER guidelines has been an ongoing process. The final recommendations of the DCOG LATER guidelines were presented to relevant professional organizations and the national organization of parents of children with cancer, who agreed on them. A website with patient information has been launched and a booklet comprising the recommendations of all organ-based guidelines was published.⁵¹ Also, all Dutch pediatric cancer centers now have an outpatient clinic for late effects after childhood cancer treatment. In 2010, DCOG LATER members defined indicators that can be used to evaluate guideline adherence in the outpatient clinics. The indicator for cardiac screening is the percentage of CCS treated with a cumulative anthracycline dose of ≥ 300 mg/m² that has received an echocardiogram during a three year period. In the nearby future all outpatient clinics will be evaluated.

Discussion

In this article we described the development of the DCOG LATER guideline on asymptomatic cardiac dysfunction after cancer therapy in CCS, the available evidence and our final recommendations for screening. Based on evidence summaries and consensus, we recommended regular medical follow-up of CCS treated with potential cardiotoxic therapies and additional screening for asymptomatic dysfunction with referral to a cardiologist in case of abnormalities.

The DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction is based on a comprehensive summary of evidence in CCS and when necessary, careful extrapolation of evidence from other populations. Ideally, we would have performed a systematic review for all clinical questions included in the guideline. However, because of the time-consuming process of a systematic review, this was not possible within the available time. Although we did not perform extensive evidence searches for all clinical questions, we tried to be transparent in the choices we made regarding extensive or less extensive evidence searches. All studies were methodologically judged and the levels of evidence of conclusions of clinical questions were systematically summarized.

There is extensive evidence to support the increased risk of cardiac dysfunction in CCS treated with anthracyclines and/or cardiac radiotherapy. An important finding was that few studies have evaluated the prognosis and diagnostic and therapeutic options for CCS with asymptomatic cardiac dysfunction. Also, studies evaluating benefits, risks and costs of screening of this population are lacking. Although there is lack of evidence with regard to prognostic, diagnostic and therapeutic questions in CCS treated with potentially cardiotoxic therapies, there was consensus across the working group to recommend regular risk-based screening by echocardiography, mainly based on evidence from other populations.

However, the number needed to screen or treat was impossible to define with the available evidence. The working group additionally recommended that CCS should be counseled regarding the potential advantages and disadvantages of screening for cardiac dysfunction after childhood cancer treatment. A potential advantage is that early treatment of asymptomatic cardiac dysfunction might decrease the risk of deterioration to clinical heart failure. Potential disadvantages of screening are false positive results, uncertainty about the course and outcome of an abnormality, potential impediments in purchasing an insurance/mortgage, and side effects of the treatment. The survivor and health care professional should discuss all possibilities and together decide on the optimal follow-up of the survivor.

It should be noted that our guideline is focused on asymptomatic cardiac dysfunction. It does not cover other cardiac late effects, such as valvular disease, ischemic heart disease or arrhythmias. Cardiovascular risk factors, such as hypertension, hypercholesterolemia and endocrine abnormalities, have been covered by other guidelines within the overall DCOG LATER guideline.⁵¹ Furthermore, our recommendations are suited for the Dutch situation. In the Netherlands, distances to the nearest late effects outpatient clinic are relatively small and all inhabitants of the country have health insurance and access to medical care. Also, all Dutch pediatric cancer centers had already started initiatives to provide care and follow-up for CCS. Therefore, implementation of a follow-up guideline for CCS was feasible. This may not be true in other countries. However, regardless of the medical system, the levels of evidence are universal and recommendations could therefore easily be adjusted to other health care systems.

Other collaborative groups have published guidelines with recommendations for the surveillance of CCS.¹⁴⁻¹⁶ There are similarities between these guidelines and ours, for example in including survivors treated with anthracyclines and/or cardiac radiotherapy and in using echocardiography as the main screening tool. But there are also marked differences, for example in the exact definitions of risk groups, the associated frequency of screening and the use of additional tests. In addition, two other guidelines do not clearly describe the exact process of summarizing evidence and getting to recommendations.^{15, 16} The Childhood Oncology Group summarized levels of consensus, while we summarized methodological quality and the level of evidence.^{14, 52} International collaboration in guideline development for CCS and possible harmonization of the recommendations will be the focus of future international research.

The lack of evidence that we described signifies that future studies should focus on the prognosis, diagnosis and therapeutic options of cardiac dysfunction in CCS as well as on advantages and disadvantages of screening of asymptomatic survivors, including cost-effectiveness analyses. Especially studies evaluating the effect of screening practices and medical interventions for cardiac dysfunction need well-set-up designs. These studies should preferably be RCTs, but we recognize that performing a RCT in clinics where screening or medical treatment is already recommended is not always feasible. For these

situations alternative study designs, adjusting for the potential selection bias that is related to non-randomized studies, are essential.⁵³

In conclusion, we summarized the method of guideline development, available evidence and final recommendations of the DCOG LATER guideline for follow-up of asymptomatic cardiac dysfunction. We recommend risk-based follow-up primarily based on echocardiography in five year CCS. Each individual CCS should be counseled on potential advantages and disadvantages of our screening recommendations.

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Appendix

Used evidence for the clinical questions and evidence summaries

1. Incidence / Prevalence and Etiology / Risk factors

Regarding the incidence / prevalence and etiology / risk factors of cardiac dysfunction we formulated 5 clinically relevant questions (Table 2). Evidence for the short evidence summaries for these clinical questions was based on 4 systematic reviews,^{8-10, 26} 13 observational studies^{11-13, 21-25, 27-30, 54} and 2 case-reports^{31, 32} that we identified with a limited literature search (as described in the methods section).

2. Prognosis

With regard to the prognosis of asymptomatic cardiac dysfunction we formulated three clinically relevant questions (Table 2).

Evidence for the short evidence summaries for these clinical questions was based on 4 observational studies^{21, 24, 33, 34} that we identified with a limited literature search (as described in the methods section).

3. Diagnosis

With regard to the diagnosis of asymptomatic cardiac dysfunction we formulated 5 clinically relevant questions (Table 2). These questions included one question for which an extensive evidence summary was done: *"What is the predictive value of a reduced left ventricular ejection fraction or left ventricular fractional shortening of the heart (asymptomatic cardiac dysfunction) on the occurrence of future clinical heart failure or death?"*. For the other four clinical questions a short evidence summary was performed. We identified 1 systematic review⁴⁷ in childhood cancer survivors (CCS) with a limited literature search (as described in the methods section).

For the extensive evidence summary question, 9 studies were included.³⁵⁻⁴³ The complete search strategy and results are listed in Supplementary table 1 in this appendix. We included studies from landmark papers, guidelines and a Medline search for systematic reviews if they were a guideline, systematic review or randomized controlled trial (RCT) discussing/studying cardiac dysfunction, asymptomatic heart failure, reduced left ventricular (LV) function or decreased fractional shortening (FS) or ejection fraction (EF) and included a clinical outcome measure such as mortality or clinical heart failure. We had knowledge of 2 landmark studies,^{58, 59} including 1 systematic review.⁵⁹ From this systematic review, we extracted 5 relevant studies.^{35, 38, 39, 41, 42} We found five relevant guidelines,⁶⁰⁻⁶⁴ from which we additionally included 3 relevant studies,^{37, 40, 65} including 1 review⁶⁵ that referred to 1 relevant study.³⁶ Our Medline search for systematic reviews resulted in 138 abstracts, of which 22 reviews were explored in full text. From these, no additional systematic reviews

were included. Two more guidelines were found and explored, yielding no additional relevant studies.^{66, 67} Supplementary table 2 in this appendix shows the methodological quality of all included studies for this clinical question.

4. Therapy

With regard to the treatment of asymptomatic cardiac dysfunction we formulated 3 clinically relevant questions (Table 2). For one question (divided into two questions in the tables) an extensive evidence search was performed: *“What is the effectiveness of medical interventions (ACE-inhibitors and beta-blockers) in patients with asymptomatic left ventricular dysfunction in general on the occurrence of heart failure and mortality?”*. For the two other clinical questions for which a short evidence summary was performed, we could include 1 RCT in CCS that was identified with a limited literature search (as described in the methods section).⁵⁰

For the extensive summaries 7 studies were included.^{35, 37, 38, 42, 55-57} The complete search strategy and results are listed in Supplementary table 1. We included studies from guidelines, a Medline search for RCTs and a Medline search for systematic reviews if they were a guideline, RCT or systematic review discussing/studying ACE-inhibitor or beta-blocker treatment in patients with heart failure of any etiology of which at least 40% was asymptomatic or in New York Heart Association (NYHA) stage I or II, and included a clinical outcome such as mortality or (hospitalization for) clinical heart failure. We found 4 relevant guidelines^{60-62, 64} referring to 7 relevant studies.^{35, 37, 38, 42, 55-57} Our search for systematic reviews resulted in 321 abstracts, of which 84 were explored in full text. Of these none were eligible. The search for RCTs resulted in 76 abstracts, of which 45 studies were explored in full text. Of these no additional studies were included. Supplementary table 2 shows the methodological quality of all relevant studies for these clinical questions.

Supplementary table 1. Literature searches for the extensive evidence summaries

Search for studies for clinical question: <i>"What is the predictive value of a reduced left ventricular ejection fraction or left ventricular fractional shortening of the heart (asymptomatic cardiac dysfunction) on the occurrence of future clinical heart failure or death?"</i>		
Step	Description	Results
1	Assessment of two landmark papers and their references	<ul style="list-style-type: none"> • 1 observational study ⁵⁸ • 1 systematic review ⁵⁹, referring to 5 relevant studies ^{35, 38, 39, 41, 42}
2	Guideline search: Dutch guideline on heart failure; Additional search for international guidelines at www.guideline.gov : "heart failure" (November 2007)	<ul style="list-style-type: none"> • 1 Dutch guideline ⁶⁴ • 4 international guidelines ⁶⁰⁻⁶³
3	Assessment of relevant studies from included guidelines	<ul style="list-style-type: none"> • 1 systematic review ⁶⁵, referring to 1 relevant study ³⁶ • 2 additional relevant studies ^{37, 40}
4	Medline search for systematic reviews: #1 Cardiac dysfunction OR heart failure heart OR heart diseases OR heart disease OR disease, heart OR diseases, heart OR cardiac diseases OR cardiac disease OR diseases, cardiac OR disease, cardiac OR cardiotoxicity OR cardiomyopathy OR cardiomyopathy, congestive OR heart failure OR heart failure, congestive OR ventricular dysfunction OR ventricular dysfunction, left OR ventricular dysfunction, right #2 Fractional Shortening OR Ejection Fraction: ('stroke volume' [MeSH Terms] OR (shortening [All Fields] AND fraction [All Fields]) OR (fractional [All Fields] AND shortening [All Fields]) OR (ejection [All Fields] AND fraction [All Fields]) #3 (#1 AND #2) AND systematic[SB] #4 Limits: Publication Date from 2005 to Feb 2009, English	<ul style="list-style-type: none"> • Search: 138 titles • Included for full text assessment: 22 titles • Inclusion: 2 guidelines ^{66, 67}, yielding no additional relevant studies
Search for studies for clinical question: <i>"What is the effectiveness of interventions (ACE-inhibitors and beta-blockers) in patients with asymptomatic left ventricular dysfunction in general on the occurrence of heart failure and mortality?"</i>		
Step	Description	Results
1	Guideline search: Dutch guideline heart failure; Additional search for international guidelines at www.guideline.gov : "heart failure" (November 2007)	<ul style="list-style-type: none"> • 1 Dutch guideline ⁶⁴ • 3 international guidelines ⁶⁰⁻⁶²
3	Assessment of relevant studies from included guidelines	<ul style="list-style-type: none"> • 7 relevant studies ^{35, 37, 38, 42, 55-57}

2	<p>Medline search RCTs:</p> <p>#1 Ace-inhibitor: ('angiotensin-converting enzyme inhibitors' [TIAB] NOT Medline [SB]) OR 'angiotensin-converting enzyme inhibitors' [MeSH Terms] OR 'angiotensin-converting enzyme inhibitors' [Pharmacological Action] OR ace inhibitor [tw] OR ACE-inhibitors [tw] OR angiotensin converting enzyme inhibitor [tw] OR Lisinopril [tw] OR Enalapril [tw] OR Captopril [tw] OR Benazepril [tw] OR cilazapril [tw] OR enalaprilat [tw] OR fosinopril [tw] OR perindopril [tw] OR quinapril [tw] OR quinaprilat [tw] OR ramipril [tw] ORtrandolapril [tw] OR zofenopril [tw]</p> <p>#2 Bètablokker: ('adrenergic beta-antagonists' [TIAB] NOT Medline [SB]) OR 'adrenergic beta-antagonists' [MeSH Terms] OR 'adrenergic beta-antagonists' [Pharmacological Action] OR beta blocker [tw] OR bètablokker [tw] OR adrenergic beta-antagonists [tw] OR beta-antagonists [tw] OR adrenergic beta antagonists [tw] OR beta antagonists [tw] OR acebutolol [tw] OR atenolol [tw] OR betaxolol [tw] OR bisoprolol [tw] OR carvedilol [tw] OR celiprolol [tw] OR esmolol [tw] OR labetalol [tw] OR metoprolol OROS [tw] OR nebivolol [tw] OR oxprenolol [tw] OR pindolol [tw] OR propanolol [tw] OR ('sotalol' [MeSH Terms] OR sotalol [tw])</p> <p>#3 Heart failure/cardiac dysfunction heart OR heart diseases OR heart disease OR disease, heart OR diseases, heart OR cardiac diseases OR cardiac disease OR diseases, cardiac OR disease, cardiac OR cardiotoxicity OR cardiomyopathy OR cardiomyopathy, congestive OR heart failure OR heart failure, congestive OR ventricular dysfunction OR ventricular dysfunction, left OR ventricular dysfunction, right</p> <p>#4 ((#1 OR #2) AND #3) AND (randomised controlled trial [Publication Type] OR (randomised [Title/Abstract] AND controlled [Title/Abstract] AND trial [Title/Abstract]))</p> <p>#5 Limits: Publication Date from 2005/01/01 to 2009/02/01, Humans, Meta-analysis, Randomised Controlled Trial, English, Core clinical journals</p>	<ul style="list-style-type: none"> • Search: 76 titles • Included for full text assessment: 45 titles • Studies on asymptomatic heart failure (≥40% of study population): 0
3	<p>Medline search for systematic reviews:</p> <p>#1 Ace-inhibitor ('angiotensin-converting enzyme inhibitors' [TIAB] NOT Medline [SB]) OR 'angiotensin-converting enzyme inhibitors' [MeSH Terms] OR 'angiotensin-converting enzyme inhibitors' [Pharmacological Action] OR ace inhibitor [tw] OR ACE-inhibitors [tw] OR angiotensin converting enzyme inhibitor [tw] OR Lisinopril [tw] OR Enalapril [tw] OR Captopril [tw] OR Benazepril [tw] OR cilazapril [tw] OR enalaprilat [tw] OR fosinopril [tw] OR perindopril [tw] OR quinapril [tw] OR quinaprilat [tw] OR ramipril [tw] ORtrandolapril [tw] OR zofenopril [tw]</p> <p>#2 Bètablokker ('adrenergic beta-antagonists' [TIAB] NOT Medline [SB]) OR 'adrenergic beta-antagonists' [MeSH Terms] OR 'adrenergic beta-antagonists' [Pharmacological Action] OR beta blocker [tw] OR bètablokker [tw] OR adrenergic beta-antagonists [tw] OR beta-antagonists [tw] OR adrenergic beta antagonists [tw] OR beta antagonists [tw] OR acebutolol [tw] OR atenolol [tw] OR betaxolol [tw] OR bisoprolol [tw] OR carvedilol [tw] OR celiprolol [tw] OR esmolol [tw] OR labetalol [tw] OR metoprolol OROS [tw] OR nebivolol [tw] OR oxprenolol [tw] OR pindolol [tw] OR propanolol [tw] OR ('sotalol' [MeSH Terms] OR sotalol [tw])</p> <p>#3 Heart failure/cardiac dysfunction heart OR heart diseases OR heart disease OR disease, heart OR diseases, heart OR cardiac diseases OR cardiac disease OR diseases, cardiac OR disease, cardiac OR cardiotoxicity OR cardiomyopathy OR cardiomyopathy, congestive OR heart failure OR heart failure, congestive OR ventricular dysfunction OR ventricular dysfunction, left OR ventricular dysfunction, right</p> <p>#4 ((#1 OR #2) AND #3) AND systematic [SB]</p> <p>#5 Limits: 2005 – Feb 2009, English</p>	<ul style="list-style-type: none"> • Search: 321 titles • Included for full text assessment: 84 titles • Studies on asymptomatic heart failure (≥40% of study population): 0

Abbreviations: ACE: angiotensin-converting enzyme; RCT: randomized controlled trial; MeSH: Medical Subject Headings; SB: subset; TIAB: title/abstract words; tw: text words

Supplementary table 1. Included studies for the clinical questions for which an extensive evidence summary was performed

What is the predictive value of a reduced left ventricular ejection fraction or left ventricular fractional shortening of the heart (asymptomatic cardiac dysfunction) on the occurrence of future clinical heart failure or death?					
Topic Reference	Study design Follow-up	Participants Comparison	Main outcomes	Additional remarks	Quality of the study
Ejection Fraction					
SOLVD prevention 1992 ³⁵	Placebo arm from an RCT Mean: 37.4 (range: 14.6 – 62) months	2117 patients with asymptomatic LV dysfunction, randomized to placebo LVEF<35% (echocardiogram)	All-cause mortality: 15.8% Development of clinical heart failure: 30.2% All-cause mortality or development of clinical heart failure: 38.6%	Of all patients in the trial (including treatment arm), 67% was in NYHA I, 10% had an idiopathic etiology, most ischemic heart disease	A2
SAVE 1992 ⁴²	Placebo arm from an RCT Mean: 42 months	No comparison group 1116 patients, 3 – 16 days after a MI, LVEF<40% and no overt CHF, randomized to placebo	All-cause mortality: 25% Development of clinical heart failure: 16%	Cardiac function was determined by RNA	A2
McDonagh 2001 ⁴¹	Prospective cohort study 4 years	No comparison group 1653 of 2000 at random selected participants of a large survey (aged 25 – 74); 1467 had a reliable echocardiogram.	All-cause mortality: - No LVSD: 4.1% - LVSD: 21% * symptomatic LVSD: 20% * asymptomatic LVSD: 25% LVEF≤40%: 9.8% LVEF > 40%: 3.4%	LV systolic dysfunction was defined as LVEF≤30% Of patients with LVSD, 49% was asymptomatic	A2
TRACE 1995 ³⁸	Placebo arm from an RCT 24 – 50 months	Comparison of all-cause mortality between participants with LVSD and without LVSD 873 patients with an MI in the previous week and EF ≤35% (= wall motion index ≤35%), randomized to placebo	Mortality: LVEF<25%: 68% LVEF 25 – 30%: 54% LVEF>30%: 29%	41% NYHA I	A2
No comparison group					

Diagnosis

Wang 2003 ⁵⁸	Prospective cohort study 12 year, continuous surveillance on cardiovascular events	4257 men and women aged 40-95 year from the Framingham Heart Study ⁶⁸ , without a history of congestive heart failure and a reliable echocardiogram	Congestive heart failure: LVEF<50%: 5.9 per 100 person-years (95% CI 3.9 – 7.8) LVEF>50%: 0.7 per 100 person-years (95% CI 0.6 – 0.8) Mortality: LVEF<50%: 8.1 per 100 person-years (95% CI 5.9 – 10.3) LVEF>50%: 2.1 per 100 person-years (95% CI 1.9 – 2.3)	Mild ALVD: LVEF≤50% (n=129) Of patients with ALVD, 49% had a previous MI	A2
CARE study 2003 ⁴⁰	Prospective cohort study Median 5 year	3860 stable patients with a history of an MI, LVEF>25% and no clinical heart failure	Multivariate model Clinical heart failure: LVEF, decrease of 1%: HR 1.04 (1.03 – 1.05) CHF and mortality: LVEF, decrease of 1%: HR 1.03 (1.02 – 1.04)	A2	
Gianuzzi 1996 ³⁶	Prospective cohort study 29 +/- 11 months (range 6 to 58 months)	508 consecutively selected patients from the heart failure ward	All-cause mortality: LVEF ≤ 25%: RR 1.85 (1.6 – 2.9)	73% asymptomatic LV dysfunction 94% ischemic heart disease Patients were treated with cardiovascular medication	A2
Jong 2003 ³⁷	Cohort study, follow-up >10 year after RCT Median: 11.2 years (IQR: 10.3 – 12.1) after randomization	2117 patients with EF<35%, who participated in the SOLVD prevention trial and were originally randomized to a placebo (no treatment during mean 3.2 years).	All-cause mortality: EF≤28%: 73.6% EF>28%: 57%	A2	

Fractional Shortening		A2	
Lauer 1992 ³⁹	Prospective cohort study Mean: 4.15 years	1493 men from the Framingham Heart Study ⁶⁸ without known cardiovascular disease and a reliable echocardiogram	All-cause mortality and cardiac events: (multivariate linear regression analysis) a decrease of FS with 4% was associated with an RR of 1.42 (95% CI 1.12 – 1.81) FS≤30%: RR 2.63 (95% CI 1.20 – 5.76)
What is the effectiveness of interventions (ACE-inhibitors and beta-blockers) in patients with asymptomatic left ventricular dysfunction in general on the occurrence of heart failure and mortality?			
Topic	Reference	Study design	Participants
		Interventions	Main outcomes
			Additional remarks
			Quality of the study
ACE-inhibitors			
SOLVD prevention 1992 ³⁵	Double-blind, placebo-controlled RCT Mean: 37.4 (range: 14.6 – 62) months	4228 asymptomatic patients with EF <35%, and no medication for heart failure Enalapril: N=2111 Placebo: N=2117	All-cause mortality: Enalapril: 313 (14.8%) Placebo: 334 (15.8%) Risk reduction: 8% (95% CI -8% to +21%) Clinical heart failure or all-cause mortality: Enalapril: 630 (29.8%) Placebo: 818 (38.6%) Risk reduction: 29% (95% CI 21% to 36%)
			Flather 2000 ⁶⁹ : 74% of all SOLVD-A2 patients (including another RCT with symptomatic patients) had a previous MI. Exner 1999 ⁵⁶ : one third of the SOLVD prevention trial was in NYHA II EF was determined by echocardiography
Therapy			

SAVE 1992 ⁴²	Double-blind, placebo-controlled RCT	2231 asymptomatic patients with EF ≤40%, 3 – 16 days after MI	<p>All-cause mortality: Captopril: 20% versus placebo 25% (RR 19%, 3 – 32%, P=0.014)</p> <p>Development of clinical heart failure: Captopril: 11% versus placebo 16%, RR 37% (20-50%, P<0.001)</p>	EF was determined by RNA	A2
Jong 2003 ³⁷	Cohort study after RCT 11.2 years (QR: 10.3 – 12.1) since randomization	3581 patients of the SOLVD prevention trial (asymptomatic patients with EF <35%), treated previously with enalapril or placebo during a mean of 37.4 months, who survived the time of the trial	<p>All-cause mortality: Enalapril: 1074 (50.9%) Placebo: 1195 (56.4%) HR: 0.86 (95% CI 0.77 – 0.93)</p> <p>Increased life expectancy (median): 9.2 months (95% CI 0 – 19.2 months)</p>	Patients with a lower EF had more benefit of treatment EF was determined by echocardiography	A2
TRACE 1995 ³⁸	Double-blind, placebo-controlled RCT	1749 patients with an MI in the previous week and EF ≤35%	<p>All-cause mortality: Trandopril versus placebo: RR 0.78 (0.67 – 0.91)</p> <p>Clinical heart failure: Trandopril versus placebo: RR 0.71 (0.56 – 0.89)</p>	41% of patients was in NYHA I EF was determined by echocardiography	A2
Beta-blockers					
CAPRICORN 2001 ⁵⁵	Double-blind, placebo-controlled RCT	1959 patients with MI 3-21 days before randomization, EF ≤ 40% or wall-motion score index ≤ 1.3 and at least 24 hours on a stable dose of ACE-inhibitor treatment.	<p>All-cause mortality: Carvedilol: 116 (12%) Placebo: 141 (15%) HR: 0.77 (0.60 – 0.98)</p> <p>Hospitalization for heart failure: Carvedilol: 118 (12%) Placebo: 138 (14%) HR 0.86 (0.67 – 1.09)</p>	Eligible patients had LV dysfunction with or without heart failure, but patients with severe heart failure were excluded. EF was determined by echocardiography, RNA or ventriculography	A2

B	B	B	B	B	B	B
Exner 1999 ⁵⁶	Retrospective analysis of RCT	Mean follow-up 35 months	4228 patients participating in the SOLVD prevention trial ³⁵	Patients that used a beta-blocker at the start of the trial, in addition to study medication: N=1015 (24%)	Patients that did not use a beta-blocker at the start of the trial, in addition to study medication: N=3213 (76%)	<p>All-cause mortality: Using a beta-blocker: IR 4.3/100 person-years No beta-blocker: IR 5.6/100 person-years</p> <p>Multivariate model, using a beta-blocker in addition to ACE-inhibitor allocation: * All-cause mortality: RR 0.70 (0.52 – 0.95) * All-cause mortality or hospitalization for clinical heart failure: RR 0.64 (0.49 – 0.83)</p> <p>Cardiovascular mortality: Captopril: 13.1% No captopril: 22.1% (RR 0.58, 0.43 – 0.79) Severe heart failure: Captopril: 16.5% No captopril: 22.6% (RR 0.68, 0.55 – 0.83)</p> <p>Multivariate model (including captopril use): * Cardiovascular mortality: RR 0.70 (0.56 – 0.88) * Severe heart failure: RR 0.79 (0.64 – 0.9)</p>
Vantrimpont 1997 ⁵⁷	Retrospective analysis of RCT	Mean clinical follow-up of surviving patients: 42 months (+/-10 months)	2231 patients participating in the SAVE trial ⁴²	Patients that used captopril (a beta-blocker) at the start of the trial, in addition to study medication: N=789 (35%)	Patients that did not use captopril at the start of the trial, in addition to study medication: N=1442 (65%)	<p>Cardiovascular mortality: Captopril: 13.1% No captopril: 22.1% (RR 0.58, 0.43 – 0.79) Severe heart failure: Captopril: 16.5% No captopril: 22.6% (RR 0.68, 0.55 – 0.83)</p> <p>Multivariate model (including captopril use): * Cardiovascular mortality: RR 0.70 (0.56 – 0.88) * Severe heart failure: RR 0.79 (0.64 – 0.9)</p>

Abbreviations: SOLVD: studies of left ventricular dysfunction; RCT: randomized controlled trial; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SAVE: survival and ventricular enlargement; MI: myocardial infarction; RNA: radionuclide angiography; LVSD: left ventricular systolic dysfunction; TRACE:trandolapril cardiac enlargement; 95% CI: 95% confidence interval; ALVD: asymptomatic left ventricular dysfunction; CARE: cholesterol and recurrent events; IQR: interquartile range; FS: fractional shortening; RR: relative risk; ACE: angiotensin-converting enzyme; P: P-value; N: number; HR: hazard ratio; IR: incidence rate.