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1 Incidence and risk factors for capecitabine-induced cardiotoxicity: a retrospective study of 452
2 consecutive patients with metastatic breast cancer

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24 **ABSTRACT**

25 **Objectives:** Case-reports of capecitabine cardiotoxicity resemble those seen with intravenous 5-
26 fluorouracil with chest pain as the predominant manifestation, but few studies of capecitabine
27 cardiotoxicity are available. We aimed to determine the incidence of symptomatic cardiotoxicity
28 from capecitabine in breast cancer patients and to identify risk factors.

29 **Methods:** We reviewed medical records of consecutive women with breast cancer treated with
30 capecitabine (1000 mg/m² twice daily) from 2002 to 2012 at one institution.

31 **Results:** Twenty-two of 452 patients (4.9%) (95%CI: 2.9%-6.9%) had symptoms of cardiotoxicity
32 (chest pain: n = 13, dyspnea: n = 9, palpitations: n = 2). Eleven patients had changes on ECG (atrial
33 fibrillation: n = 5, ST deviations: n = 3, T-wave abnormalities: n = 2, and QTc prolongation: n = 1).
34 Two patients (0.4%) sustained acute myocardial infarction. One patient (0.2%) developed cardiac
35 arrest with lethal outcome. Four of six patients (66%) retreated with capecitabine had recurrent
36 symptoms at retreatment. Cardiac comorbidity (p = 0.001), hypercholesterolemia (p = 0.005) and
37 current smoking (p = 0.023) were risk factors for cardiotoxicity in univariate analyses and remained
38 significant when adjusted for age. Patients with cardiac co-morbidity were 5.5 times (95% CI: 2.0-
39 14.8) more likely to develop cardiotoxicity. In the subgroup of patients with apparently no cardiac
40 co-morbidity the incidence of cardiotoxicity was lower (3.7 %) and hypercholesterolemia (p =
41 0.035) and current smoking (p = 0.020) were risk factors of cardiotoxicity.

42 **Conclusion:** The incidence of cardiotoxicity from capecitabine resembles that of intravenous 5-
43 fluorouracil (≈5 %). Cardiac co-morbidity, hypercholesterolemia and current smoking were
44 associated with development of cardiotoxicity.

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4 46 **Strengths and limitations of this study**
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- 7 • Our study is a large single center study including all patients with breast cancer treated with
8 capecitabine over a 10-year period.
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11 • The primary end-point, cardiotoxicity, is mainly diagnosed on the basis of subjective symptoms
12 (chest pain, dyspnea, palpitations) which may cause information bias.
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15 • In spite of a relatively large sample size, the number of events is low which limit the power of
16 the logistic regression analyses used to analyse for risk factors.
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19 • Our study is a retrospective clinical study. The patients' history records are incomplete with
20 respect to information on risk factors for cardiovascular disease (hypertension,
21 hypercholesterolemia, diabetes and smoking) and baseline electrocardiograms.
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56 INTRODUCTION

57 Capecitabine is an oral pro-drug of 5-fluorouracil (5-FU) that is converted to 5-FU in a three-stage
58 process involving several enzymes.¹ The last step is catalyzed by thymidine phosphorylase.¹ Many
59 tissues throughout the body express thymidine phosphorylase, but some human carcinomas express
60 this enzyme in higher concentrations than surrounding normal tissues.¹ This, in theory should
61 increase the concentration of 5-FU at the tumour site and decrease the concentration of 5-FU in
62 healthy tissues resulting in less side effects.¹

63 Capecitabine is licensed for adjuvant treatment in patients with colon cancer stage III and for the
64 treatment of metastatic colorectal cancer, metastatic breast cancer and advanced gastric cancer
65 (combination therapy). The main side effects from capecitabine are hand-and-foot syndrome,
66 diarrhea, stomatitis, fatigue, anorexia, nausea and vomiting, abdominal pain, myelosuppression,
67 hyperbilirubinemia and cardiotoxicity.²⁻⁵

68 Case reports of cardiotoxicity after administration of capecitabine are similar to those seen with
69 intravenous 5-FU treatment with chest pain as the predominant manifestatio.⁶⁻¹⁴ Other less frequent
70 clinical manifestations are arrhythmias, myocardial infarction, heart failure, cardiogenic shock and
71 sudden death.¹⁵ Cardiotoxicity from 5-FU occurs with an incidence of 0.55% to 19.9%.¹⁵ There are
72 few studies of capecitabine cardiotoxicity with incidences ranging from 3% to 35%.¹⁶⁻²⁰

73 Patients with breast cancer may have increased risk for cardiotoxicity from capecitabine compared
74 to other cancer patients because of treatment with other carditotoxic therapies such as radiotherapy
75 of the chest, trastuzumab and anthracyclines. We aimed to study the pattern and incidence of
76 cardiotoxicity in women with metastatic breast cancer treated with capecitabine and to identify
77 potential risk factors for capecitabine-induced cardiotoxicity.

79 MATERIAL AND METHODS

80 Selection of patients

81 We included patients with metastatic breast cancer consecutively treated with capecitabine from
82 first of January 2002 to 31. December 2012. Inclusion criteria were female, metastatic breast cancer
83 and capecitabine treatment (+/- trastuzumab). The chemotherapy regimen was capecitabine 2000
84 mg/m² divided in two daily doses for 14 days followed by one week off.

85 Data collection

86 Approval from the Danish Data Protection Agency was obtained. We collected data from medical
87 records on age, height, weight, body surface area, capecitabine dose, cardiotoxicity, cardiac
88 comorbidity (previous acute myocardial infarction, ischemic heart disease, arrhythmias, heart
89 failure or reduced ejection fraction), hypertension, smoking status, hypercholesterolemia, diabetes,
90 electrocardiogram (ECG) (before treatment start and if symptoms), hemoglobin levels, creatinine
91 levels and previous treatment with anthracyclines, trastuzumab, breast- and thoracic radiotherapy.
92 Renal function (estimated glomerular filtrationrate, eGFR) was estimated by the Chronic Kidney
93 Disease Epidemiology Collaboration equation for Caucasian women incorporating age and plasma
94 creatinine concentrations. All the collected data were prospectively defined.

95 End point: cardiotoxicity

96 Cardiotoxicity was defined as significant symptoms of likely cardiac origin or changes on ECG that
97 started during treatment with capecitabine and was not present before treatment start. Medical
98 records were reviewed by one of the authors. Cases with suspected cardiotoxicity were further
99 reviewed by one cardiologist (MVN) who made the final decision to classify the case as
100 cardiotoxicity or not. All patients were followed to cessation of capecitabine. Endpoints were
101 evaluated unblinded and the investigators had access to patients' medical record.

102 Statistics

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4 103 Mann-Whitney U test was used to compare differences in age between patients with cardiotoxicity
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6 104 and patients without cardiotoxicity. Fisher's exact test and chi squared test were used to analyze
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8 105 differences in numeric variables between the two groups. Chi squared test for trend were used to
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10 106 analyze differences for ordinal variables. Possible risk factors for cardiotoxicity were tested using
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12 107 univariate binomial logistic regression and adjusted for age with multivariate binomial logistic
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14 108 regression. In order to test the robustness of the data and due to missing data, sensitivity analyses
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16 109 were performed for variables that tended to be significant or were significant in univariate analyses.
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18 110 Sensitivity analyses were performed both with multiple imputation and as worst- and best case
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20 111 scenarios for one variable at a time. Due to the low number of events (=22), the potential risk of
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22 112 over fitting of the statistical models and the risk of collinearity among the covariates, we only
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24 113 adjusted for age in the multivariate logistic regression analyses. C statistics were performed for
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26 114 variables that were significant in univariate logistic regression analyses. P-values below 0.05 were
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28 115 regarded significant. IBM SPSS software version 21 was used for all analysis.
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35 117 **RESULTS**

36 118 **Study population**

37 119 A total of 452 consecutive women with metastatic breast cancer were eligible for analysis (Figure
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39 120 1). Patient characteristics are listed in table 1. Median age was 63 years, 333 patients initially (74%)
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41 121 received 100% dose, while 84 patients (19%) were treated with 75% dose and 26 patients (6%)
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43 122 were treated with 50% dose, respectively. Totally, 242 patients (54%) had previously received
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45 123 treatment with anthracyclines, 54 patients (12%) were treated previously or concurrent with
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47 124 trastuzumab, while 132 patients (29%) had a history of left-sided breast irradiation. Radiotherapy
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49 125 was given approximately 3 months after the primary diagnosis of breast cancer and mean time from
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51 126 diagnosis to start of capecitabine was 4 years (0.9-58 years). Forty-two patients (9.3%) had cardiac
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127 comorbidities prior to initiation of treatment. Of these 6 (1%) had a history of ischemic heart
 128 disease while 37 (8%) had other types of cardiac disease including atrial fibrillation (n = 13),
 129 supraventricular tachyarrhythmia (n = 3), pericardial exudates (n = 3), epirubicin-induced
 130 cardiomyopathy (n = 3), atrio-ventricular blocks (n = 1), aortic valve disease (n = 1) and reduced
 131 left ventricular ejection fraction of unknown cause (n = 4).

132 Table 1: Patient characteristics

Characteristic	All patients (n = 452)	Patients with Cardiotoxicity (n = 22)	Patients without Cardiotoxicity (n = 430)	P-value ^b
	No. (%)	No. (%)	No. (%)	
Age (n = 452)				
Median	63	63	63	0.742
Range	28 – 88	36 – 82	28 – 88	
Capecitabine dose (n = 443)				
50%	26 (6)	1 (5)	25 (6)	0.636
75%	84 (19)	6 (27)	78 (18)	
100%	333 (74)	15 (68)	318 (74)	
IHD (incl. previous ACS) (n = 436)	6 (1)	0	6 (1)	1.000
Other cardiac diseases (n = 436)	37 (8)	7 (32)	30 (7)	0.000
ECG at treatment start ^d (n =				

161)				
Normal	132 (29)	9 (41)	123 (29)	0.454
Abnormal	29 (6)	3 (14)	26 (6)	
Hypertension (n = 442)	126 (28)	9 (41)	117 (27)	0.186
Hypercholesterolemia (n = 390)	53 (12)	7 (32)	46 (11)	0.002
Diabetes mellitus (n = 435)	21 (5)	1 (5)	20 (5)	1.000
Smoking status (n = 371)				
Current smoker	105 (23)	9 (41)	96 (22)	0.264
Former smoker	66 (15)	4 (18)	62 (14)	
Never smoked	200 (44)	5 (23)	195 (45)	
BMI (n = 382)				
Underweight (BMI <18.5)	21 (5)	3 (14)	18 (4)	0.337
Normal (BMI 18.5-24.9)	208 (46)	8 (36)	200 (47)	
Overweight (BMI 25.0-29.9)	109 (24)	9 (41)	100 (23)	
Obese (BMI > 29.9)	44 (10)	0	44 (10)	
Number of risk factors for IHD ^c (n = 452)				
0	131 (29)	3 (14)	128 (30)	0.005
1	182 (40)	8 (36)	174 (41)	
2	90 (20)	5 (23)	85 (20)	
3	32 (7)	3 (14)	29 (7)	

4	17 (4)	3 (14)	14 (3)	
5	0	0	0	
Previous treatment with anthracyclines (n = 444)	242 (54)	9 (41)	233 (54)	0.189
Previous or concurrent treatment with trastuzumab (n = 403)	54 (12)	3 (14)	51 (12)	0.752
Previous breast irradiation (n = 431)	275 (61)	8 (36)	267 (62)	0.052
Left side	132 (29)	5 (23)	127 (30)	0.218
Right side	115 (25)	1 (5)	114 (27)	
Bilateral	25 (6)	2 (9)	23 (5)	
Side unknown	3 (1)	0	3 (1)	
Previous thoracic irradiation (n = 407)	96 (21)	4 (18)	92 (21)	1.000
Anemia ^a (n = 437)	126 (28)	3 (14)	123 (29)	0.164
eGFR (n = 429)				
Low (< 60 mL/min/1.73m ²)	71 (17)	6 (27)	65 (15)	0.105
Normal (≥ 60 mL/min/1.73m ²)	358 (79)	13 (59)	345 (80)	

133 ^adefined according to the World Health Organization: Hgb < 7.4 mmol/L for non-pregnant females.

134 ^bP-value for the statistical tests of differences between patients with cardiotoxicity and patients

135 without cardiotoxicity.

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4 136 ^cRisk factors for IHD includes: hypertension, hypercholesterolemia, diabetes mellitus, smoking, and
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6 137 BMI.

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8 138 ^dAll patients do routinely have ECG taken before treatment start and all ECGs are routinely seen by
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10 139 doctors, but not all ECGs were available in the medical records.

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12 140 ACS = acute coronary syndrome; BMI = body mass index; ECG = electrocardiogram; eGFR =
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14 141 estimated glomerular filtration rate; IHD = ischemic heart disease.

15 16 17 18 142 **Cardiotoxicity**

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20 143 Twenty-two cases of cardiotoxicity (4.9%) (95% Confidence interval (CI): 2.91%-6.89%) were
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22 144 identified from medical records (Supplementary table). The most common complaints were chest
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24 145 pain (13 patients) followed by dyspnea (9 patients) and palpitations (2 patients) (Figure 2). Eleven
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26 146 of these 22 patients (50%) had changes on ECG. Five patients had atrial fibrillation (1 paroxysmal
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28 147 and 4 new onset), while three patients had ST deviations and two patients developed negative or
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30 148 fluctuating T-waves. Of the 13 patients with chest pain two (0.4%) had elevated troponins and were
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32 149 classified as acute myocardial infarctions. One patient (0.2%) with dyspnea and progressing
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34 150 chestpain developed cardiac arrest with lethal outcome.

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38 151 First occurrence of cardiotoxicity was in first cycle for 11 patients (50%), second cycle for four
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40 152 patients (18%), third cycle for 3 patients (14%) and fourth cycle for 1 patient (4.5%), while three
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42 153 patients (14%) had late occurrence of cardiotoxicity (8th, 9th and 12th cycle).

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44 154 Cardiac therapy was initiated in 10 of the 22 patients with cardiotoxicity (Supplementary table),
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46 155 while 6 were retreated with capecitabine. Three patients were retreated at the same dose intensity
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48 156 without initiation of cardiac therapy, two were retreated at the same dose intensity, but received
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50 157 cardiac therapy with verapamil, and one patient were treated at reduced dose. The three patients
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52 158 treated with full dose and no initiation of cardiac therapy all had recurrent symptoms at retreatment,
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54 159 while one patient treated with verapamil had recurrent symptoms. The other two patients, one
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4 160 treated with verapamil and one treated at reduced dose intensity, did not have symptoms at
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6 161 retreatment.

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8 162 Seven events of cardiotoxicity occurred in the sub-group of patients with cardiac co-morbidity (n =
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10 163 42) (16.7 %), while 15 patients in the sub-group of patients with apparently no cardiac co-morbidity
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12 164 (n = 410) developed cardiotoxicity (3.7 %).

165 **Risk factors for cardiotoxicity**

166 In univariate logistic regression analyses cardiac comorbidity (p = 0.001), hypercholesterolemia (p
167 = 0.005) and current smoking (p = 0.023) were risk factors for cardiotoxicity (Table 2) and they
168 remained significant after adjustment for age with multivariate logistic regression. Patients with
169 cardiac co-morbidity were 5.5 times (95% CI: 2.0-14.8) more likely to develop cardiotoxicity than
170 patients without cardiac co-morbidity. In the subgroup of patients with apparently no cardiac co-
171 morbidity hypercholesterolemia (p = 0.035) and current smoking (p = 0.020) were significant risk
172 factors in univariate analyses and remained significant after adjustment for age (Table 2).

173 Sensitivity analyses were performed for variables significant in the univariate analyses. In the entire
174 study group, hypercholesterolemia, cardiac co-morbidity and current smoking remained significant
175 risk factors after multiple imputation of missing values (p = 0.008, p = 0.001 and p = 0.023,
176 respectively) and after imputation with worst- and best-case scenarios (hypercholesterolemia p =
177 0.005 (best-case), p = 0.032 (worst-case); cardiac co-morbidity p = 0.007 (worst-case), p = 0.001
178 (best-case); current smoking p = 0.045 (worst-case), p = 0.032 (best-case)). In the subgroup of
179 patients with apparently no cardiac co-morbidity current smoking remained significant after both
180 multiple imputation analyses (p = 0.021) and worst- and best-case analyses (p = 0.025 and p =
181 0.042, respectively), while hypercholesterolemia was unaffected by multiple imputation (p = 0.043)
182 but susceptible to worst- and best-case analyses. The p-value for the univariate regression analysis
183 was significant (p = 0.035) when cases with missing data were imputed with best case scenario

184 (none having hypercholesterolemia), but became insignificant ($p = 0.132$) in worst case scenario (all
 185 having hypercholesterolemia).

186 Table 2: Univariate and bivariate logistic regression models of risk factors for cardiotoxicity. Bold
 187 P-values indicate a significant difference ($P < 0.05$).

Variable	Beta coefficient (95%-CI)	Odds ratio (95%-CI)	P-value	Beta coefficient (95%-CI)	Odds ratio (95%-CI)	P-value
	Univariate			Bivariate: Adjusted for age		
All patients (N = 452) (events = 22)						
Age ^a	0.01 (-0.03-0.04)	1.01 (0.97-1.05)	0.789	-	-	-
Hypercholesterolemia ^{a,b}	1.42 (0.43-2.40)	4.12 (1.54-11.00)	0.005	1.42 (0.38-2.46)	4.14 (1.46-11.75)	0.008
Hypertension ^b	0.58 (-0.29-1.46)	1.79 (0.75-4.31)	0.192	0.60 (-0.33-1.52)	1.82 (0.72-4.57)	0.206
Diabetes ^b	-0.07 (-2.12-1.99)	0.94 (0.12-7.32)	0.949	-0.11 (-2.17-1.96)	0.90 (0.11-7.13)	0.921
Smoking ^b						
Current smoker	1.30 (0.17-2.42)	3.66 (1.19-11.21)	0.023	1.30 (0.18-2.42)	3.66 (1.19-11.22)	0.023
Former smoker	0.92 (-0.42-2.27)	2.52 (0.66-9.66)	0.179	0.92 (-0.43-2.27)	2.51 (0.65-9.67)	0.181

BMI ^a	-0.05 (-0.16- 0.06)	0.95 (0.85- 1.06)	0.38 0	-0.05 (-0.16- 0.07)	0.96 (0.85- 1.07)	0.41 3
Previous irradiation of left breast ^b	-0.14 (-1.05- 0.78)	0.87 (0.35- 2.18)	0.76 3	-0.13 (-1.05- 0.80)	0.88 (0.35- 2.22)	0.78 5
“Cardiac co- morbidity” ^b	1.63 (0.67- 2.59)	5.12 (1.96- 13.39)	0.00 1	1.70 (0.70- 2.69)	5.47 (2.02- 14.80)	0.00 1
Anemia ^b	-0.86 (-2.12- 0.39)	0.42 (0.12- 1.47)	0.17 6	-0.86 (-2.12- 0.39)	0.42 (0.12- 1.47)	0.17 6
eGFR ^a	-0.01 (-0.03- 0.02)	0.99 (0.97- 1.02)	0.48 7	-0.01 (-0.03- 0.02)	0.99 (0.97- 1.02)	0.63 8
Previous anthracyclines ^b	-0.58 (-1.43- 0.29)	0.56 (0.24- 1.34)	0.19 4	-0.73 (-1.77- 0.31)	0.48 (0.17- 1.36)	0.17 1
Previous or concurrent trastuzumab ^b	0.08 (-1.17- 1.34)	1.08 (0.31- 3.80)	0.90 3	0.11 (-1.17- 1.41)	1.12 (0.31- 4.09)	0.86 4
Dose of capecitabine ^a	-0.01 (-0.03- 0.02)	1.00 (0.97- 1.02)	0.66 6	-0.01 (-0.03- 0.02)	1.00 (0.97- 1.02)	0.68 2
Previous thoracic irradiation ^b	0.08 (-1.08- 1.24)	1.08 (0.34- 3.44)	0.89 2	0.12 (-1.05- 1.28)	1.12 (0.35- 3.60)	0.84 7
Patients with no history of heart disease (n = 399) (events = 15)						
Age ^a	0.001 (-0.04- -)	1.00 (0.96- -)	0.94 -	-	-	-

	0.05)	1.05)	9			
Hypercholesterolemi a ^b	1.32 (0.01- 2.55)	3.75 (1.10- 12.81)	0.03 5	1.34 (0.04- 2.63)	3.81 (1.04- 13.94)	0.04 3
Hypertension ^b	0.05 (-1.11- 1.22)	1.05 (0.33- 3.38)	0.92 9	0.04 (-1.17- 1.25)	1.04 (0.31- 3.51)	0.94 7
Diabetes ^b	0.48 (-1.61- 2.57)	1.62 (0.20- 13.10)	0.65 1	0.48 (-1.63- 2.58)	1.61 (0.20- 13.26)	0.65 8
Smoking ^b						
Current smoker	1.64 (0.26- 3.01)	5.13 (1.30- 20.33)	0.02 0	1.63 (0.25- 3.00)	5.09 (1.28- 20.18)	0.02 1
Former smoker	0.18 (-2.10- 2.46)	1.20 (0.12- 11.76)	0.87 6	0.19 (-2.10- 2.47)	1.21 (0.12- 11.85)	0.87 2
BMI ^a	-0.04 (-0.18- 0.09)	0.96 (0.84- 1.09)	0.53 0	-0.04 (-0.17- 0.10)	0.96 (0.84- 1.10)	0.57 8
Previous irradiation of left breast ^b	-0.41 (-1.56- 0.76)	0.67 (0.21- 2.13)	0.49 5	-0.41 (-1.56- 0.77)	0.67 (0.21- 2.15)	0.49 7
Anemia ^b	-1.62 (-3.51- 0.43)	0.20 (0.03- 1.54)	0.12 1	-1.62 (-3.51- 0.43)	0.20 (0.03- 1.54)	0.12 1
eGFR ^a	0.00 (-0.03- 0.03)	1.00 (0.97- 1.03)	0.87 6	0.01 (-0.03- 0.05)	1.01 (0.97- 1.05)	0.66 8
Previous anthracyclines ^b	0.67 (-0.39- 1.72)	1.96 (0.68- 5.60)	0.21 2	0.92 (-0.33- 2.18)	2.52 (0.72- 8.86)	0.15 0

Previous or concurrent trastuzumab ^b	0.42 (-0.87-1.72)	1.53 (0.42-5.60)	0.52 5	0.48 (-0.87-1.83)	1.62 (0.42-6.26)	0.48 4
Dose of capecitabine ^a	-0.01 (-0.04-0.02)	0.99 (0.96-1.02)	0.57 3	-0.01 (-0.04-0.02)	0.99 (0.96-1.02)	0.57 9
Previous thoracic irradiation ^b	0.35 (-1.02-1.72)	1.42 (0.36-5.59)	0.62 1	0.40 (-0.99-1.79)	1.48 (0.37-5.96)	0.57 7

188 ^ascale variable. ^bcategorical variable. 95%-CI = 95% confidence interval; BMI = body mass index;

189 "Cardiac co-morbidity" = all types of heart disease; eGFR = estimated glomerular filtration rate.

190 C Statistics: Predictors of cardiotoxicity

191 The ability of the variables, cardiac co-morbidity, hypercholesterolemia and current smoking, to
 192 discriminate between patients that will develop cardiotoxicity and those who will not was tested
 193 with c-statistics. In unselected patients the presence of cardiac co-morbidity was a poor predictor of
 194 cardiotoxicity (c = 0,617 (95%CI 0.483-0.754), p = 0.061), as was the presence of
 195 hypercholesterolemia (c = 0.662 (95%CI 0.478-0.766), p = 0.072) and smoking status (c = 0.651
 196 (95%CI 0.523-0.779), p = 0.031). In the subgroup of patients with apparently no cardiac co-
 197 morbidity the presence of hypercholesterolemia (c = 0.601 (95%CI 0.427-0.775), p = 0.216) and
 198 smoking status (c = 0.691 (95%CI 0.526-0.857), p = 0.031) were poor factors to discriminate
 199 between patients who will develop cardiotoxicity and those who will not.

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201 DISCUSSION

202 Incidence of cardiotoxicity

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4 203 We observed an incidence of cardiotoxicity from capecitabine at $\approx 5\%$ in women with metastatic
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6 204 breast cancer which is similar to incidences reported in previous studies of both men and women
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8 205 treated with capecitabine,¹⁸⁻²⁰ although some studies have reported lower¹⁶ or higher incidences.¹⁷
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10 206 The difference in incidences in-between studies may be due to different risk profiles in the study
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12 207 populations. Moreover, prospective studies with regular cardiac assessments may detect more
13
14 208 cardiotoxicity since they may identify asymptomatic patients and patients with mild symptoms.
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16 209 The incidence of cardiotoxicity in our study and other studies of capecitabine cardiotoxicity is
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18 210 within the range of incidences of cardiotoxicity in studies with 5-FU^{15, 17, 20-22} and a large study
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20 211 found similar incidences for the two treatments.²⁰ However, a prospective study with 644 patients
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22 212 reported similar incidences of cardiotoxicity for capecitabine and continuous 5-FU infusion
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24 213 schedules, but a lower incidence for short (bolus) 5-FU infusion schedules.¹⁸
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29 214 **Pattern of cardiotoxicity**

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31 215 The most common event of cardiotoxicity was chest pain, which was the main symptom in 59% of
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33 216 the 22 cases. Most of the patients with chest pain had normal ECG and normal coronary enzymes
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35 217 and severe events, such as acute myocardial infarction and cardiac arrest with lethal outcome, was
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37 218 rare. This pattern is in concordance with other studies¹⁵ and the sudden onset of chest pain and the
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39 219 rare occurrence of life-threatening complications correspond well to the theory of fluoropyrimidine
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41 220 induced vasospastic angina. Furthermore, the angiographically normal arteries reported in several
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43 221 case reports^{6-8, 11} and the presence of silent ischemic episodes on Holter recordings²³ supports this
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45 222 theory.
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50 223 **Retreatment of patients with cardiotoxicity**

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52 224 Retreatment with capecitabine after occurrence of cardiotoxicity was attempted in 6 of 22 patients
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54 225 with little success. Four patients had recurrent cardiac symptoms, suggesting that retreatment should
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4 226 be done with great precaution. However, a retrospective study of 668 patients¹⁶ and a prospective
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6 227 study of 644 patients¹⁸ treated with 5-FU or capecitabine reported a benefit from dose-reduction and
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8 228 initiation of anti-angina therapy that prevented symptoms at retreatment in 9 of 12 patients and 12
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10 229 of 15 patients, respectively. Their findings suggest that retreatment at reduced dose and with
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12 230 appropriate anti-angina therapy are feasible, however close cardiac monitoring is crucial.
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14 231 Furthermore, nitroglycerin was effective to abolish symptoms of cardiotoxicity.¹⁶ In contrast, a
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16 232 small and non-randomized study could not demonstrate an prophylactic effect of calcium channel
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18 233 blockers on occurrence of cardiotoxicity.²⁴ Larger studies with systematic, predefined strategies for
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20 234 dose reduction and initiation of anti-angina therapy are needed.
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25 235 **Risk factors for cardiotoxicity**

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27 236 Patients with cardiac comorbidity were at increased risk of cardiotoxicity, which is in accordance
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29 237 with four previous studies of 5-FU or capecitabine cardiotoxicity,^{17, 21, 23, 25} while four other studies
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31 238 found no increased risk for patients with pre-existing heart disease.^{19, 26-28} While heart disease may
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33 239 be a risk marker for cardiotoxicity, it is not a prerequisite for cardiotoxicity to occur. The patient
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35 240 who sustained cardiac arrest and died in our study had no cardiac co-morbidities and no risk factors
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37 241 for ischemic heart disease. Likewise, severe cardiotoxicity has been reported for several patients
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39 242 without cardiac co-morbidity.^{11, 29-32} Also, we found that a history of heart disease was a poor
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41 243 predictor of cardiotoxicity.
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45 244 In the present study hypercholesterolemia and current smoking were risk factors for cardiotoxicity
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47 245 both in the entire study group and in the subgroup of patients with no apparent cardiac co-
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49 246 morbidity. Similarly, a larger prospective study of 644 patients without cardiac co-morbidities
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51 247 reported that smoking was associated with ECG changes in bivariate analyses.¹⁸ However, they
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53 248 found no association between ECG changes and hyperlipidaemia.¹⁸ While Kosmas et al.¹⁸
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55 249 prospectively measured cholesterol and triglyceride levels in blood; our study is based on medical
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4 250 recordings. Thus incomplete data with risk of information bias is a limitation of the present study.

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6 251 Both studies have a low number of events limiting the statistical power and multiple testing

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8 252 increases the risk of false positive results.

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10 253 Previous treatment with potentially cardiotoxic therapy with anthracyclines or previous or current

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12 254 treatment with trastuzumab did not increase the risk of cardiotoxicity. However, two of three

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14 255 patients with epirubicin-induced cardiomyopathy developed cardiotoxicity during treatment with

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16 256 capecitabine suggesting that the degree of pre-existing heart damage may be relevant. Patients with

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18 257 previous left-sided breast irradiation were not at increased risk of cardiotoxicity in our study.

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20 258 Similarly, a large prospective study of 5-FU cardiotoxicity found that previous breast irradiation

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22 259 was not a risk factor.²¹ The lack of association between other cardiotoxic therapies and

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24 260 capecitabine-induced cardiotoxicity suggests that the mechanisms behind these cardiotoxicities are

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26 261 different. Moreover, radiation-induced cardiovascular disease may be a late event.³³ In our study the

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28 262 mean time from chest irradiation to capecitabine start was 4 years.

29 30 31 32 33 263 **Methodological considerations**

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35 264 The predominant manifestation of cardiotoxicity from fluoropyrimidines is chest pain followed by

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37 265 other subjective symptoms. Only approximately 50% of the patients have objective signs (mostly

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39 266 ECG changes) of cardiotoxicity. Thus, the event (cardiotoxicity) is based mainly on subjective

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41 267 symptoms and is therefore affected by the patient's own perception and reaction to the symptoms

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43 268 and the physician's assessment of the patient's symptoms. Both patients and physicians may pay

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45 269 more attention to cardiac symptoms if the patient has heart disease before treatment start. These

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47 270 factors may explain some of the difference in incidence in-between studies. Research in new and

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49 271 sensitive cardiac biomarkers like e.g. copeptin to detect myocardial ischemia is needed.³⁴

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51 272 In spite of a relatively large sample size, the number of events is low (22 events) which cause

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53 273 statistical difficulties. Due to the limited number of events, the statistical power is low and the risk

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4 274 of type II statistical errors increases. With respect to the logistic regression analyses, the low
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6 275 number of events limits the number of covariates allowed in the model. The low number of events
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8 276 and multiple testing (increasing the risk of false positive results) are weaknesses of most studies
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10 277 analysing risk factors and it makes the conclusions that can be drawn from these studies less valid.
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12 278 Like most other large studies on this subject our study is retrospective which may results in
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14 279 incomplete data. Missing data affects power and if not missing at random, they may cause bias. We
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16 280 dealt with the missing data by sensitivity analyses with worst and best case scenarios and with
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18 281 multiple imputation. The sensitivity analyses showed that missing data had little influence on our
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20 282 study results.
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24 283 A major limitation is that baseline ECGs was only preserved for 36% of the patients. Among the 11
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26 284 patients with ECG changes during capecitabine treatment, 2 had missing baseline ECGs.
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29 **Conclusion**

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31 286 The incidence of cardiotoxicity from capecitabine of $\approx 5\%$ is close to that of 5-FU with incidences
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33 287 of 1%-5% in larger studies. Our study results suggest that cardiac co-morbidity and current smoking
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35 288 are risk factors for cardiotoxicity. Whether smoking cessation can prevent some cases of
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37 289 cardiotoxicity deserves further investigations. All the identified risk factors were poor predictors of
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39 290 cardiotoxicity and initial optimal cardiac treatment, information about the risk and follow-up if
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41 291 symptoms present are the options today.
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48 293 Contributors:

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50 294 AP: Data collection, data processing, statistics, writing of the paper and incorporation of input from
51
52 295 the other authors. NS and KV: Conception and design of the study, data collection and review of the
53
54 296 manuscript. MVN: Review of cases with suspected cardiotoxicity and review of the manuscript.
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4 297 FOL: Conception and design of the study and review of the manuscript. MS: Interpretation of study
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6 298 results and statistics and review of the manuscript. DN: Conception and design of the study, data
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8 299 collection, data interpretation, input to the manuscript and review of the manuscript.
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10
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14
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18
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29 307 Competing interests: None declared.
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32 308 Ethics: Approval from the Danish Data Protection Agency was obtained.
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35 309 Data sharing statement: No additional data are available.
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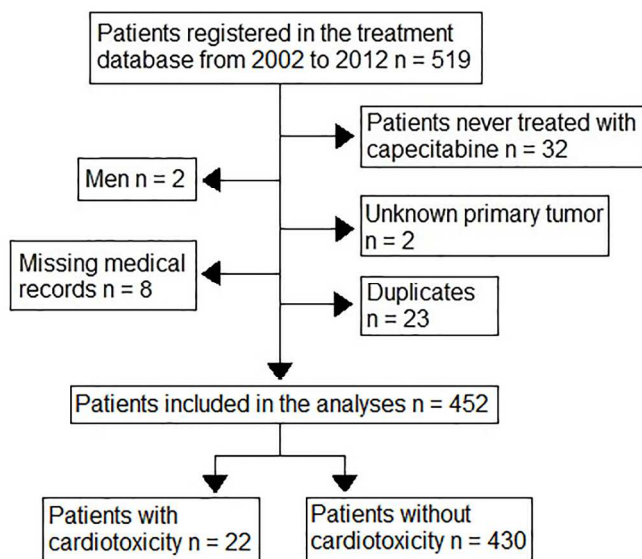


Figure 1: Flow diagram

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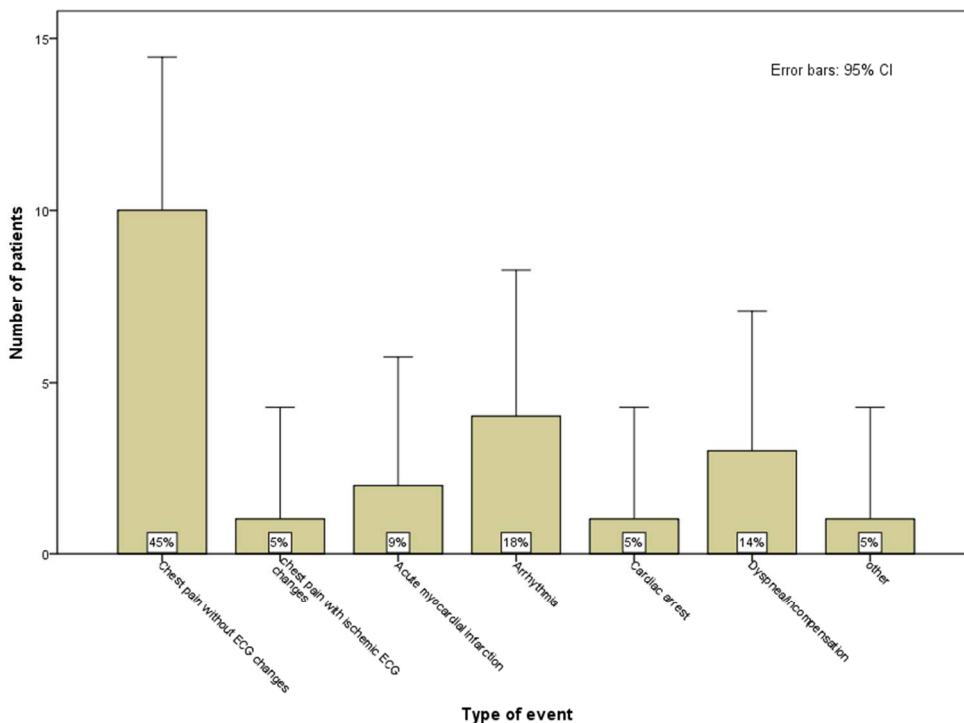


Figure 2: The distribution of the different manifestations of cardiotoxicity

Explaining text: Proportion of patients with chest pain without ECG changes (n = 10), chest pain with ECG changes but not acute myocardial infarction (n = 1), acute myocardial infarction (n = 2), arrhythmia (n = 4), cardiac arrest (n = 1), dyspnea/incompensation (n = 3) and other (n = 1, with QT prolongation and right bundle branch block). Patients with more than one of the manifestations (n = 2) are classified according to their primary complaint. The percentages showed on each bar reflect the distribution of symptoms among the 22 patients with cardiotoxicity.

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Supplementary table: Details about patients with cardiotoxicity and initiated therapy

Case	Location of metastases	Pre-existing cardiovascular disease	Cycle of onset	Dose intensity at onset	Type of event	Description	ECG changes	Raised cardiac biomarkers?	Cardiac therapy	Subsequent treatment with capecitabine, dose	Symptoms at retreatment
1	Liver, lung, abdomen	No	1	100%	Chest pain	Oppressive chest pain	-	-	No	Yes, 100%	Yes, oppressive chest pain
2	Right lung, pleura, mediastinal lymph nodes, adrenal glands, abdominal carcinosis, columna and pelvis	Atrial fibrillation, NYHA 3, moderate pulmonary hypertension, LVEF = 53% after 1. cycle, hypertension	2	75%	Incompensation, dyspnea	Dyspnea and peripheral edema	ST-depressions in V5-V6	-	-	No	-
3	Liver	No	1	100%	Chest pain	Exertional chest pain radiating to the neck	No changes from pretreatment ECG (inverted T-waves in V1-V2)	-	-	No	-
4	Liver, bone Th3 + Th7, lymph nodes in left axilla	No	2	75%	Cardiac arrest	Chest pain and progressing dyspnea, cardiac arrest, death	Asystole	-	Adrenalin and amiodaron	-	-
5	Mediastinal lymph nodes,	Hypertension, hyperlipidem	1	75%	QTc prolongation, right	Asymptomatic	QTc prolongation, right	-	-	No	-

	thyroid gland, bone Th1 + Th5	ia			bundle branch block		bundle branch block				
6	Neck, sternal and left axillary lymph nodes	No	1	100%	Chest pain	Intermittent, retrosternal, oppressive chest pain radiating to both arms, LVEF 60% at echocardiography	Normal	No	No	No	-
7	Mediastinal lymph nodes	No	4	75%	Chest pain	Chest pain, dyspnea and malaise	Normal	No	No	No	-
8	Pleura, bone	No	1	100%	Chest pain	Compressive chest pain	No changes, ST-depression in V2-V4	-	Metoprolol and Isosorbidm ononitrate	No	-
9	Pleura	No	1	100%	Arrhythmia	Dyspnea	Atrial fibrillation/atrial flutter, 170 bpm.	-	Adenosine, metoprolol and amiodaron	No	-
10	Liver, lung, bone	No	2	75%	Chest pain, Arrhythmia	Chest pain and palpitations	Atrial fibrillation, 119 bpm	-	Verapamil	Yes, 75%	Palpitations, dyspnea, atrial fibrillation
11	Liver, lungs, neck and right supraclavicular lymph nodes	SVT, previous pulmonary embolism, hyperlipidemia	1	100%	AMI	Oppressive chest pain radiating to right side, dyspnea. Effect of nitroglycerin iv. Normal coronary angiography and normal	Initially ST-elevation in V1-V3, AVF and V6. Negative T-waves in	Marginal raised TnI (52 ng/l) and raised CK-MB (4.4 µg/l)	Nitroglycerin iv, Acetylsalicylic Acid and Magnesium Hydroxide, clopidogrel,	No	-

						echocardiography	lead II-III		fondaparinux		
12	Lungs, mediastinal lymph nodes	Hypertension, diabetes, hyperlipidemia	3	50%	Dyspnea	Dyspnea and light chest pain	Normal	No	No	Yes, 50%	No
13	Bone	Epirubicin-induced cardiomyopathy	9	100%	Chest pain, arrhythmia	Compressive chest pain	Atrial fibrillation and non-sustained VT	-	-	No	-
14	Bone, skin, liver and left axillary lymph nodes	Hypertension, NYHA 2-3 Echo: LVEF 50-55%, mitral valve insufficiency, discrete pulmonary, hypertension	3	75%	Incompensatio, dyspnea	Progressing dyspnea, NYHA 3, peripheral edema, cardiomegaly Echo: LVEF unchanged, moderate to severe pulmonary hypertension, tricuspid insufficiency	Bundle branch block	-	Furosemide and potassium-chloride	No	-
15	Neck and infraclavicular lymph nodes	Atrial fibrillation, COPD	3	100%	Arrhythmia, pulmonary congestion	Dyspnea, dizziness, malaise X-ray: pulmonary congestion and pericardial exudate	Atrial fibrillation 117 bpm	-	Digoxin, Centyl Mite with potassium-chloride	No	-
16	Brain	No	8	100%	Chest pain	Oppressive chest pain radiating to the neck	Normal	-	-	Yes, 100%	Recurrent episodes with chestpain

17	Mediastinal lymph nodes	No	2	100%	Chest pain	Oppressive chestpain radiating to neck and arm, dyspnea	Sinus rhythm, supraventricular extra systoles, no ST-deviations	No	Verapamil	Yes, 75%	No
18	Sternum and sacroiliac bone	Hyperlipidemia	1	100%	Chest pain	Compressive chest pain radiating to the back and both arms. Echo: normal	Normal	-	No	No	-
19	CNS, liver, right axillary lymph nodes	Hypertension, hyperlipidemia	12	75%	AMI	Chest pain radiating to head, neck and jaw. LVEF = 40 %.	Normal	Raised troponins (400 ng/l), CK-MB unknown	Acetylsalicylic Acid with magnesium hydroxide (magnyl), clopidogrel, fondaparinux, metoprolol, ACE-inhibitor, Statin	No	-
20	Pelvis bone, right axillary lymph nodes	Hypertension, hyperlipidemia	1	100%	Chest pain	Oppressive chest pain Echo: normal	-	-	-	No	-
21	Lung, bone	Epirubicin-induced cardiomyopathy, LVEF = 34-40%	1	100%	Arrhythmia	Dizziness and palpitations.	Telemetry: Atrial flutter 150 bpm, neg. T-waves in I and AVL	-	Metoprolol, ACE-inhibitor	No	-

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22	Pelvic and columnar bone	Atrial fibrillation, hypertension, hyperlipidemia	1	100%	Chest pain	Chest pain	Fluctuating negative T-waves in lead II, III, aVF and V1-V5	-	No	Yes, 100%	Episodes with pain located to jaw and chest
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COPD = chronic obstructive pulmonary disease, bpm = beats per minute, NYHA = New York Heart association functional classification, LVEF = left ventricular function, TnI = cardiac troponin I, SVT = supraventricular tachycardia, LMWH = low molecule weight heparin, CK-MB = creatine kinase MB, CNS = central nerve system

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6 + Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and risk factors for capecitabine-induced symptomatic cardiotoxicity: a retrospective study of 452 consecutive patients with metastatic breast cancer

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1 Incidence and risk factors for capecitabine-induced symptomatic cardiotoxicity: a retrospective
2 study of 452 consecutive patients with metastatic breast cancer

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21 e-mail: anne.polk@hotmail.com

22 Keywords: capecitabine, cardiotoxicity, risk factors, chest pain, breast cancer

23 Word count: 3840 incl. tables and statements but excl. references

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4 24 **ABSTRACT**

5
6 25 **Objectives:** Case-reports of capecitabine cardiotoxicity resemble those seen with intravenous 5-
7
8 26 fluorouracil with chest pain as the predominant manifestation, but few studies of capecitabine
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10 27 cardiotoxicity are available. We aimed to determine the incidence of symptomatic cardiotoxicity
11
12 28 from capecitabine in breast cancer patients and to identify risk factors.

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15 29 **Methods:** We reviewed medical records of consecutive women with breast cancer treated with
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17 30 capecitabine (1000 mg/m² twice daily) from 2002 to 2012 at one institution.

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21 31 **Results:** Twenty-two of 452 patients (4.9%) (95%CI: 2.9%-6.9%) had symptoms of cardiotoxicity
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23 32 (chest pain: n = 13, dyspnea: n = 9, palpitations: n = 2). Eleven patients had changes on ECG (atrial
24
25 33 fibrillation: n = 5, ST deviations: n = 3, T-wave abnormalities: n = 2, and QTc prolongation: n = 1).
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27 34 Two patients (0.4%) sustained acute myocardial infarction. One patient (0.2%) developed cardiac
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29 35 arrest with lethal outcome. Four of six patients (66%) retreated with capecitabine had recurrent
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31 36 symptoms at retreatment. Cardiac comorbidity (p = 0.001), hypercholesterolemia (p = 0.005) and
32
33 37 current smoking (p = 0.023) were risk factors for cardiotoxicity in univariate analyses and remained
34
35 38 significant when adjusted for age. Patients with cardiac co-morbidity were 5.5 times (95% CI: 2.0-
36
37 39 14.8) more likely to develop cardiotoxicity. In the subgroup of patients with apparently no cardiac
38
39 40 co-morbidity the incidence of cardiotoxicity was lower (3.7 %) and hypercholesterolemia (p =
40
41 41 0.035) and current smoking (p = 0.020) were risk factors of cardiotoxicity.

42
43 42 **Conclusion:** The incidence of cardiotoxicity from capecitabine resembles that of intravenous 5-
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45 43 fluorouracil (≈5 %). Cardiac co-morbidity, hypercholesterolemia and current smoking were
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47 44 associated with development of cardiotoxicity.

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4 46 **Strengths and limitations of this study**
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- 7 • Our study is a large single center study including all patients with breast cancer treated with
8 capecitabine over a 10-year period.
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11 • The primary end-point, cardiotoxicity, is mainly diagnosed on the basis of subjective symptoms
12 (chest pain, dyspnea, palpitations) which may cause information bias.
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15 • In spite of a relatively large sample size, the number of events is low which limit the power of
16 the logistic regression analyses used to analyse for risk factors.
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19 • Our study is a retrospective clinical study. The patients' history records are incomplete with
20 respect to information on risk factors for cardiovascular disease (hypertension,
21 hypercholesterolemia, diabetes and smoking) and baseline electrocardiograms.
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56 INTRODUCTION

57 Capecitabine is an oral pro-drug of 5-fluorouracil (5-FU) that is converted to 5-FU in a three-stage
58 process involving several enzymes.¹ The last step is catalyzed by thymidine phosphorylase.¹ Many
59 tissues throughout the body express thymidine phosphorylase, but some human carcinomas express
60 this enzyme in higher concentrations than surrounding normal tissues.¹ This, in theory should
61 increase the concentration of 5-FU at the tumour site and decrease the concentration of 5-FU in
62 healthy tissues resulting in less side effects.¹

63 Capecitabine is licensed for adjuvant treatment in patients with colon cancer stage III and for the
64 treatment of metastatic colorectal cancer, metastatic breast cancer and advanced gastric cancer
65 (combination therapy). The main side effects from capecitabine are hand-and-foot syndrome,
66 diarrhea, stomatitis, fatigue, anorexia, nausea and vomiting, abdominal pain, myelosuppression,
67 hyperbilirubinemia and cardiotoxicity.²⁻⁵

68 Case reports of cardiotoxicity after administration of capecitabine are similar to those seen with
69 intravenous 5-FU treatment with chest pain as the predominant manifestatio.⁶⁻¹⁴ Other less frequent
70 clinical manifestations are arrhythmias, myocardial infarction, heart failure, cardiogenic shock and
71 sudden death.¹⁵⁻¹⁹ Cardiotoxicity from 5-FU occurs with an incidence of 0.55% to 19.9%.¹⁵ There
72 are few studies of capecitabine cardiotoxicity with incidences ranging from 3% to 35%.²⁰⁻²⁴

73 We aimed to study the pattern and incidence of symptomatic cardiotoxicity in women with
74 metastatic breast cancer treated with capecitabine and to identify potential risk factors for
75 capecitabine-induced cardiotoxicity.

76

77 MATERIAL AND METHODS

78 Selection of patients

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4 79 We included patients with metastatic breast cancer consecutively treated with capecitabine from
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6 80 first of January 2002 to 31. December 2012. Inclusion criteria were female, metastatic breast cancer
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8 81 and capecitabine treatment (+/- trastuzumab). The chemotherapy regimen was capecitabine 2000
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10 82 mg/m² divided in two daily doses for 14 days followed by one week off.

13 14 83 **Data collection**

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16 84 Approval from the Danish Data Protection Agency was obtained. We collected data from medical
17
18 85 records on age, height, weight, body surface area, capecitabine dose, cardiotoxicity, cardiac
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20 86 comorbidity (a history of previous acute myocardial infarction, ischemic heart disease, arrhythmias,
21
22 87 heart failure or reduced ejection fraction), risk factors for ischemic heart disease (a history of
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24 88 hypertension or intake of antihypertensive drugs, smoking status, a history of hypercholesterolemia
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26 89 or intake of lipid lowering drugs, a history of diabetes or intake of antidiabetics), electrocardiogram
27
28 90 (ECG) (before treatment start and if symptoms), hemoglobin levels, creatinine levels and previous
29
30 91 treatment with anthracyclines, trastuzumab, breast- and thoracic radiotherapy. Renal function
31
32 92 (estimated glomerular filtrationrate, eGFR) was estimated by the Chronic Kidney Disease
33
34 93 Epidemiology Collaboration equation for Caucasian women incorporating age and plasma
35
36 94 creatinine concentrations. All the collected data were prospectively selected.

37 38 39 40 41 95 **Registration of symptoms and identification of cases with cardiotoxicity**

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43 96 Before start of chemotherapy and before each cycle adverse events were scored according to
44
45 97 NCI/CTCAE V. 3.0. ECGs were performed before first cycle of capecitabine and at clinical
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47 98 suspicion of cardiotoxicity. Medical records were reviewed by one of the authors. Cardiotoxicity
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49 99 was defined as significant symptoms of likely cardiac origin (chest pain or acute myocardial
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51 100 infarction (confirmed with elevation in troponins over the cut-off point), palpitations, dyspnea of
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53 101 likely cardiac origin and incompensation) and/or changes on ECG that started during treatment with
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4 102 capecitabine and was not present before treatment start. Cases with suspected cardiotoxicity were
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6 103 further reviewed by one cardiologist (MVN) who made the final decision to classify the case as
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8 104 cardiotoxicity or not. All patients were followed to cessation of capecitabine. Endpoints were
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10 105 evaluated unblinded and the investigators had access to patients' medical record.
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106 **Statistics**

107 Mann-Whitney U test was used to compare differences in age between patients with cardiotoxicity
108 and patients without cardiotoxicity. Fisher's exact test and chi squared test were used to analyze
109 differences in numeric variables between the two groups. Chi squared test for trend were used to
110 analyze differences for ordinal variables. Possible risk factors for cardiotoxicity were tested using
111 univariate binomial logistic regression and adjusted for age with multivariate binomial logistic
112 regression. In order to test the robustness of the data and due to missing data, sensitivity analyses
113 were performed for variables that tended to be significant or were significant in univariate analyses.
114 Sensitivity analyses were performed both with multiple imputation and as worst- and best case
115 scenarios for one variable at a time. Due to the low number of events (=22), the potential risk of
116 over fitting of the statistical models and the risk of collinearity among the covariates, we only
117 adjusted for age in the multivariate logistic regression analyses. C statistics were performed for
118 variables that were significant in univariate logistic regression analyses. P-values below 0.05 were
119 regarded significant. IBM SPSS software version 21 was used for all analysis.
120

121 **RESULTS**

122 **Study population**

123 A total of 452 consecutive women with metastatic breast cancer were eligible for analysis (Figure
124 1). Patient characteristics are listed in table 1. Median age was 63 years, 333 patients initially (74%)
125 received 100% dose, while 84 patients (19%) were treated with 75% dose and 26 patients (6%)

126 were treated with 50% dose, respectively. Totally, 242 patients (54%) had previously received
 127 treatment with anthracyclines, 54 patients (12%) were treated previously or concurrent with
 128 trastuzumab, while 132 patients (29%) had a history of left-sided breast irradiation. Radiotherapy
 129 was given approximately 3 months after the primary diagnosis of breast cancer and mean time from
 130 diagnosis to start of capecitabine was 4 years (0.9-58 years). Forty-two patients (9.3%) had cardiac
 131 comorbidities prior to initiation of treatment. Of these 6 (1%) had a history of ischemic heart
 132 disease while 37 (8%) had other types of cardiac disease including atrial fibrillation (n = 13),
 133 supraventricular tachyarrhythmia (n = 3), pericardial exudatives (n = 3), epirubicin-induced
 134 cardiomyopathy (n = 3), atrio-ventricular blocks (n = 1), aortic valve disease (n = 1) and reduced
 135 left ventricular ejection fraction of unknown cause (n = 4).

136 Table 1: Patient characteristics

Characteristic	All patients (n = 452)	Patients with Cardiotoxicity (n = 22)	Patients without Cardiotoxicity (n = 430)	P-value ^b
	No. (%)	No. (%)	No. (%)	
Age (n = 452)				
Median	63	63	63	0.742
Range	28 – 88	36 – 82	28 – 88	
Capecitabine dose (n = 443)				
50%	26 (6)	1 (5)	25 (6)	0.636
75%	84 (19)	6 (27)	78 (18)	
100%	333 (74)	15 (68)	318 (74)	

IHD (incl. previous ACS) (n = 436)	6 (1)	0	6 (1)	1.000
Other cardiac diseases (n = 436)	37 (8)	7 (32)	30 (7)	0.000
ECG at treatment start ^d (n = 161)				
Normal	132 (29)	9 (41)	123 (29)	0.454
Abnormal	29 (6)	3 (14)	26 (6)	
Hypertension (n = 442)	126 (28)	9 (41)	117 (27)	0.186
Hypercholesterolemia (n = 390)	53 (12)	7 (32)	46 (11)	0.002
Diabetes mellitus (n = 435)	21 (5)	1 (5)	20 (5)	1.000
Smoking status (n = 371)				
Current smoker	105 (23)	9 (41)	96 (22)	0.264
Former smoker	66 (15)	4 (18)	62 (14)	
Never smoked	200 (44)	5 (23)	195 (45)	
BMI (n = 382)				
Underweight (BMI <18.5)	21 (5)	3 (14)	18 (4)	0.337
Normal (BMI 18.5-24.9)	208 (46)	8 (36)	200 (47)	
Overweight (BMI 25.0-29.9)	109 (24)	9 (41)	100 (23)	
Obese (BMI > 29.9)	44 (10)	0	44 (10)	
Number of risk factors for				

IHD ^c (n = 452)				
0	131 (29)	3 (14)	128 (30)	0.005
1	182 (40)	8 (36)	174 (41)	
2	90 (20)	5 (23)	85 (20)	
3	32 (7)	3 (14)	29 (7)	
4	17 (4)	3 (14)	14 (3)	
5	0	0	0	
Previous treatment with anthracyclines (n = 444)	242 (54)	9 (41)	233 (54)	0.189
Previous or concurrent treatment with trastuzumab (n = 403)	54 (12)	3 (14)	51 (12)	0.752
Previous breast irradiation (n = 431)	275 (61)	8 (36)	267 (62)	0.052
Left side	132 (29)	5 (23)	127 (30)	0.218
Right side	115 (25)	1 (5)	114 (27)	
Bilateral	25 (6)	2 (9)	23 (5)	
Side unknown	3 (1)	0	3 (1)	
Previous thoracic irradiation (n = 407)	96 (21)	4 (18)	92 (21)	1.000
Anemia ^a (n = 437)	126 (28)	3 (14)	123 (29)	0.164
eGFR (n = 429)				
Low (< 60 mL/min/1.73m ²)	71 (17)	6 (27)	65 (15)	0.105

Normal (≥ 60 mL/min/1.73m ²)	358 (79)	13 (59)	345 (80)	
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137 ^adefined according to the World Health Organization: Hgb < 7.4 mmol/L for non-pregnant females.

138 ^bP-value for the statistical tests of differences between patients with cardiotoxicity and patients
139 without cardiotoxicity.

140 ^cRisk factors for IHD includes: hypertension, hypercholesterolemia, diabetes mellitus, smoking, and
141 BMI.

142 ^dAll patients do routinely have ECG taken before treatment start and all ECGs are routinely seen by
143 doctors, but not all ECGs were available in the medical records.

144 ACS = acute coronary syndrome; BMI = body mass index; ECG = electrocardiogram; eGFR =
145 estimated glomerular filtration rate; IHD = ischemic heart disease.

146 **Cardiotoxicity**

147 Twenty-two cases of symptomatic cardiotoxicity (4.9%) (95% Confidence interval (CI): 2.91%-
148 6.89%) were identified from medical records (Supplementary table). The most common complaints
149 were chest pain (13 patients) followed by dyspnea (9 patients) and palpitations (2 patients) (Figure
150 2). Eleven of these 22 patients (50%) had changes on ECG. Five patients had atrial fibrillation (1
151 paroxysmal and 4 new onset), while three patients had ST deviations and two patients developed
152 negative or fluctuating T-waves. Of the 13 patients with chest pain two (0.4%) had elevated
153 troponins and were classified as acute myocardial infarctions. One patient (0.2%) with dyspnea and
154 progressing chestpain developed cardiac arrest with lethal outcome.

155 First occurrence of cardiotoxicity was in first cycle for 11 patients (50%), second cycle for four
156 patients (18%), third cycle for 3 patients (14%) and fourth cycle for 1 patient (4.5%), while three
157 patients (14%) had late occurrence of cardiotoxicity (8th, 9th and 12th cycle).

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4 158 Cardiac therapy was initiated in 10 of the 22 patients with cardiotoxicity (Supplementary table),
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6 159 while 6 were retreated with capecitabine. Three patients were retreated at the same dose intensity
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8 160 without initiation of cardiac therapy, two were retreated at the same dose intensity, but received
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10 161 cardiac therapy with verapamil, and one patient were treated at reduced dose. The three patients
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12 162 treated with full dose and no initiation of cardiac therapy all had recurrent symptoms at retreatment,
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14 163 while one patient treated with verapamil had recurrent symptoms. The other two patients, one
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16 164 treated with verapamil and one treated at reduced dose intensity, did not have symptoms at
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18 165 retreatment.
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21 166 Seven events of cardiotoxicity occurred in the sub-group of patients with cardiac co-morbidity (n =
22
23 167 42) (16.7 %), while 15 patients in the sub-group of patients with apparently no cardiac co-morbidity
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25 168 (n = 410) developed cardiotoxicity (3.7 %).
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28 29 169 **Risk factors for symptomatic cardiotoxicity**

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31 170 In univariate logistic regression analyses cardiac comorbidity (p = 0.001), hypercholesterolemia (p
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33 171 = 0.005) and current smoking (p = 0.023) were risk factors for cardiotoxicity (Table 2) and they
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35 172 remained significant after adjustment for age with multivariate logistic regression. Patients with
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37 173 cardiac co-morbidity were 5.5 times (95% CI: 2.0-14.8) more likely to develop cardiotoxicity than
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39 174 patients without cardiac co-morbidity. In the subgroup of patients with apparently no cardiac co-
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41 175 morbidity hypercholesterolemia (p = 0.035) and current smoking (p = 0.020) were significant risk
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43 176 factors in univariate analyses and remained significant after adjustment for age (Table 2).
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47 177 Sensitivity analyses were performed for variables significant in the univariate analyses. In the entire
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49 178 study group, hypercholesterolemia, cardiac co-morbidity and current smoking remained significant
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51 179 risk factors after multiple imputation of missing values (p = 0.008, p = 0.001 and p = 0.023,
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53 180 respectively) and after imputation with worst- and best-case scenarios (hypercholesterolemia p =
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55 181 0.005 (best-case), p = 0.032 (worst-case); cardiac co-morbidity p = 0.007 (worst-case), p = 0.001
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(best-case); current smoking $p = 0.045$ (worst-case), $p = 0.032$ (best-case)). In the subgroup of patients with apparently no cardiac co-morbidity current smoking remained significant after both multiple imputation analyses ($p = 0.021$) and worst- and best-case analyses ($p = 0.025$ and $p = 0.042$, respectively), while hypercholesterolemia was unaffected by multiple imputation ($p = 0.043$) but susceptible to worst- and best-case analyses. The p-value for the univariate regression analysis was significant ($p = 0.035$) when cases with missing data were imputed with best case scenario (none having hypercholesterolemia), but became insignificant ($p = 0.132$) in worst case scenario (all having hypercholesterolemia).

Table 2: Univariate and bivariate logistic regression models of risk factors for symptomatic cardiotoxicity. Bold P-values indicate a significant difference ($P < 0.05$).

Variable	Beta coefficient (95%-CI)	Odds ratio (95%-CI)	P-value	Beta coefficient (95%-CI)	Odds ratio (95%-CI)	P-value
	Univariate			Bivariate: Adjusted for age		
All patients (N = 452) (events = 22)						
Age ^a	0.01 (-0.03-0.04)	1.01 (0.97-1.05)	0.789	-	-	-
Hypercholesterolemia ^{a,b}	1.42 (0.43-2.40)	4.12 (1.54-11.00)	0.005	1.42 (0.38-2.46)	4.14 (1.46-11.75)	0.008
Hypertension ^b	0.58 (-0.29-1.46)	1.79 (0.75-4.31)	0.192	0.60 (-0.33-1.52)	1.82 (0.72-4.57)	0.206
Diabetes ^b	-0.07 (-2.12-	0.94 (0.12-	0.94	-0.11 (-2.17-	0.90 (0.11-	0.92

	1.99)	7.32)	9	1.96)	7.13)	1
Smoking ^b						
Current smoker	1.30 (0.17-	3.66 (1.19-	0.02	1.30 (0.18-	3.66 (1.19-	0.02
Former smoker	2.42)	11.21)	3	2.42)	11.22)	3
	0.92 (-0.42-	2.52 (0.66-	0.17	0.92 (-0.43-	2.51 (0.65-	0.18
	2.27)	9.66)	9	2.27)	9.67)	1
BMI ^a	-0.05 (-0.16-	0.95 (0.85-	0.38	-0.05 (-0.16-	0.96 (0.85-	0.41
	0.06)	1.06)	0	0.07)	1.07)	3
Previous irradiation of left breast ^b	-0.14 (-1.05-	0.87 (0.35-	0.76	-0.13 (-1.05-	0.88 (0.35-	0.78
	0.78)	2.18)	3	0.80)	2.22)	5
“Cardiac co- morbidity” ^b	1.63 (0.67-	5.12 (1.96-	0.00	1.70 (0.70-	5.47 (2.02-	0.00
	2.59)	13.39)	1	2.69)	14.80)	1
Anemia ^b	-0.86 (-2.12-	0.42 (0.12-	0.17	-0.86 (-2.12-	0.42 (0.12-	0.17
	0.39)	1.47)	6	0.39)	1.47)	6
eGFR ^a	-0.01 (-0.03-	0.99 (0.97-	0.48	-0.01 (-0.03-	0.99 (0.97-	0.63
	0.02)	1.02)	7	0.02)	1.02)	8
Previous anthracyclines ^b	-0.58 (-1.43-	0.56 (0.24-	0.19	-0.73 (-1.77-	0.48 (0.17-	0.17
	0.29)	1.34)	4	0.31)	1.36)	1
Previous or concurrent trastuzumab ^b	0.08 (-1.17-	1.08 (0.31-	0.90	0.11 (-1.17-	1.12 (0.31-	0.86
	1.34)	3.80)	3	1.41)	4.09)	4
Dose of capecitabine ^a	-0.01 (-0.03-	1.00 (0.97-	0.66	-0.01 (-0.03-	1.00 (0.97-	0.68
	0.02)	1.02)	6	0.02)	1.02)	2
Previous thoracic	0.08 (-1.08-	1.08 (0.34-	0.89	0.12 (-1.05-	1.12 (0.35-	0.84

irradiation ^b	1.24)	3.44)	2	1.28)	3.60)	7
Patients with no history of heart disease (n = 399) (events = 15)						
Age ^a	0.001 (-0.04-0.05)	1.00 (0.96-1.05)	0.94 9	-	-	-
Hypercholesterolemia ^b	1.32 (0.01-2.55)	3.75 (1.10-12.81)	0.03 5	1.34 (0.04-2.63)	3.81 (1.04-13.94)	0.04 3
Hypertension ^b	0.05 (-1.11-1.22)	1.05 (0.33-3.38)	0.92 9	0.04 (-1.17-1.25)	1.04 (0.31-3.51)	0.94 7
Diabetes ^b	0.48 (-1.61-2.57)	1.62 (0.20-13.10)	0.65 1	0.48 (-1.63-2.58)	1.61 (0.20-13.26)	0.65 8
Smoking ^b						
Current smoker	1.64 (0.26-3.01)	5.13 (1.30-20.33)	0.02 0	1.63 (0.25-3.00)	5.09 (1.28-20.18)	0.02 1
Former smoker	0.18 (-2.10-2.46)	1.20 (0.12-11.76)	0.87 6	0.19 (-2.10-2.47)	1.21 (0.12-11.85)	0.87 2
BMI ^a	-0.04 (-0.18-0.09)	0.96 (0.84-1.09)	0.53 0	-0.04 (-0.17-0.10)	0.96 (0.84-1.10)	0.57 8
Previous irradiation of left breast ^b	-0.41 (-1.56-0.76)	0.67 (0.21-2.13)	0.49 5	-0.41 (-1.56-0.77)	0.67 (0.21-2.15)	0.49 7

Anemia ^b	-1.62 (-3.51- 0.43)	0.20 (0.03- 1.54)	0.12 1	-1.62 (-3.51- 0.43)	0.20 (0.03- 1.54)	0.12 1
eGFR ^a	0.00 (-0.03- 0.03)	1.00 (0.97- 1.03)	0.87 6	0.01 (-0.03- 0.05)	1.01 (0.97- 1.05)	0.66 8
Previous anthracyclines ^b	0.67 (-0.39- 1.72)	1.96 (0.68- 5.60)	0.21 2	0.92 (-0.33- 2.18)	2.52 (0.72- 8.86)	0.15 0
Previous or concurrent trastuzumab ^b	0.42 (-0.87- 1.72)	1.53 (0.42- 5.60)	0.52 5	0.48 (-0.87- 1.83)	1.62 (0.42- 6.26)	0.48 4
Dose of capecitabine ^a	-0.01 (-0.04- 0.02)	0.99 (0.96- 1.02)	0.57 3	-0.01 (-0.04- 0.02)	0.99 (0.96- 1.02)	0.57 9
Previous thoracic irradiation ^b	0.35 (-1.02- 1.72)	1.42 (0.36- 5.59)	0.62 1	0.40 (-0.99- 1.79)	1.48 (0.37- 5.96)	0.57 7

192 ^ascale variable. ^bcategorical variable. 95%-CI = 95% confidence interval; BMI = body mass index;

193 "Cardiac co-morbidity" = all types of heart disease; eGFR = estimated glomerular filtration rate.

194 C Statistics: Predictors of symptomatic cardiotoxicity

195 The ability of the variables, cardiac co-morbidity, hypercholesterolemia and current smoking, to
 196 discriminate between patients that will develop symptomatic cardiotoxicity and those who will not
 197 was tested with c-statistics. In unselected patients the presence of cardiac co-morbidity was a poor
 198 predictor of symptomatic cardiotoxicity ($c = 0,617$ (95%CI 0.483-0.754), $p = 0.061$), as was the
 199 presence of hypercholesterolemia ($c = 0.662$ (95%CI 0.478-0.766), $p = 0.072$) and smoking status
 200 ($c = 0.651$ (95%CI 0.523-0.779), $p = 0.031$). In the subgroup of patients with apparently no cardiac
 201 co-morbidity the presence of hypercholesterolemia ($c = 0.601$ (95%CI 0.427-0.775), $p = 0.216$) and

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4 202 smoking status ($c = 0.691$ (95%CI 0.526-0.857), $p = 0.031$) were poor factors to discriminate
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6 203 between patients who will develop cardiotoxicity and those who will not.
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11 12 205 **DISCUSSION**

13 14 15 206 **Incidence of symptomatic cardiotoxicity**

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17 207 We observed an incidence of symptomatic cardiotoxicity from capecitabine at $\approx 5\%$ in women with
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19 208 metastatic breast cancer which is similar to incidences reported in previous studies of both men and
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21 209 women treated with capecitabine,²²⁻²⁴ although some studies have reported lower²⁰ or higher
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23 210 incidences.²¹ The difference in incidences in-between studies may be due to different risk profiles in
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25 211 the study populations. Moreover, prospective studies with regular cardiac assessments may detect
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27 212 more cardiotoxicity since they may identify asymptomatic patients and patients with mild
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29 213 symptoms.

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33 214 The incidence of symptomatic cardiotoxicity in our study and other studies of capecitabine
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35 215 cardiotoxicity is within the range of incidences of symptomatic cardiotoxicity in studies with 5-
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37 216 FU^{15, 21, 24-26} and a large study found similar incidences for the two treatments.²⁴ However, a
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39 217 prospective study with 644 patients reported similar incidences of cardiotoxicity for capecitabine
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41 218 and continuous 5-FU infusion schedules, but a lower incidence for short (bolus) 5-FU infusion
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43 219 schedules.²²

44 45 46 47 220 **Pattern of symptomatic cardiotoxicity**

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49 221 The most common event of symptomatic cardiotoxicity was chest pain, which was the main
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51 222 symptom in 59% of the 22 cases. Most of the patients with chest pain had normal ECG and normal
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53 223 coronary enzymes and severe events, such as acute myocardial infarction and cardiac arrest with
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55 224 lethal outcome, was rare. This pattern is in concordance with other studies¹⁵ and the sudden onset of
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4 225 chest pain and the rare occurrence of life-threatening complications correspond well to the theory of
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6 226 fluoropyrimidine induced vasospastic angina. Furthermore, the angiographically normal arteries
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8 227 reported in several case reports^{6-8, 11} and the presence of silent ischemic episodes on Holter
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10 228 recordings²⁷ supports this theory.

14 229 **Retreatment of patients with symptomatic cardiotoxicity**

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16 230 Retreatment with capecitabine after occurrence of cardiotoxicity was attempted in 6 of 22 patients
17
18 231 with little success. Four patients had recurrent cardiac symptoms, suggesting that retreatment should
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20 232 be done with great precaution. However, a retrospective study of 668 patients²⁰ and a prospective
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22 233 study of 644 patients²² treated with 5-FU or capecitabine reported a benefit from dose-reduction and
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24 234 initiation of anti-angina therapy that prevented symptoms at retreatment in 9 of 12 patients and 12
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26 235 of 15 patients, respectively. Their findings suggest that retreatment at reduced dose and with
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28 236 appropriate anti-angina therapy are feasible, however close cardiac monitoring is crucial.
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30 237 Furthermore, nitro-glycerine was effective to abolish symptoms of cardiotoxicity.²⁰ In contrast, a
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32 238 small and non-randomized study could not demonstrate an prophylactic effect of calcium channel
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34 239 blockers on occurrence of cardiotoxicity.²⁸ Larger studies with systematic, predefined strategies for
35
36 240 dose reduction and initiation of anti-angina therapy are needed.

41 241 **Risk factors for symptomatic cardiotoxicity**

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43 242 Patients with cardiac comorbidity were at increased risk of symptomatic cardiotoxicity, which is in
44
45 243 accordance with four previous studies of 5-FU or capecitabine cardiotoxicity,^{21, 25, 27, 29} while other
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47 244 studies found no increased risk for patients with pre-existing heart disease.^{23, 30-33} While heart
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49 245 disease may be a risk marker for cardiotoxicity, it is not a prerequisite for cardiotoxicity to occur.
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51 246 The patient who sustained cardiac arrest and died in our study had no cardiac co-morbidities and no
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53 247 risk factors for ischemic heart disease. Likewise, severe cardiotoxicity has been reported for several
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4 248 patients without cardiac co-morbidity.^{11, 34-37} Also, we found that a history of heart disease was a
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6 249 poor predictor of cardiotoxicity.
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9 250 In the present study hypercholesterolemia and current smoking were risk factors for symptomatic
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11 251 cardiotoxicity both in the entire study group and in the subgroup of patients with no apparent
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13 252 cardiac co-morbidity. Similarly, a larger prospective study of 644 patients without cardiac co-
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15 253 morbidities reported that smoking was associated with ECG changes in bivariate analyses.²²
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17 254 However, they found no association between ECG changes and hyperlipidaemia.²² While Kosmas
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19 255 et al.²² prospectively measured cholesterol and triglyceride levels in blood; our study is based on
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21 256 medical recordings. Thus incomplete data with risk of information bias is a limitation of the present
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23 257 study. Both studies have a low number of events limiting the statistical power and multiple testing
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25 258 increases the risk of false positive results.
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28 259 Previous treatment with potentially cardiotoxic therapy with anthracyclines or previous or current
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30 260 treatment with trastuzumab did not increase the risk of symptomatic cardiotoxicity. However, two
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32 261 of three patients with epirubicin-induced cardiomyopathy developed symptomatic cardiotoxicity
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34 262 during treatment with capecitabine suggesting that the degree of pre-existing heart damage may be
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36 263 relevant. Patients with previous left-sided breast irradiation were not at increased risk of
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38 264 cardiotoxicity in our study. Similarly, a large prospective study of 5-FU cardiotoxicity found that
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40 265 previous breast irradiation was not a risk factor.²⁵ The lack of association between other cardiotoxic
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42 266 therapies and capecitabine-induced cardiotoxicity suggests that the mechanisms behind these
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44 267 cardiotoxicities are different. Moreover, radiation-induced cardiovascular disease may be a late
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46 268 event.³⁸ In our study the mean time from chest irradiation to capecitabine start was 4 years.
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51 269 **Methodological considerations**

52 270 The predominant manifestation of symptomatic cardiotoxicity from fluoropyrimidines is chest pain
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54 271 followed by other subjective symptoms and ECG changes or other objective signs of cardiotoxicity
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4 272 are not always present. In our study, only approximately 50% of the patients had objective signs
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6 273 (mostly ECG changes) of cardiotoxicity. Thus, the event (cardiotoxicity) was based mainly on
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8 274 subjective symptoms and is therefore affected by the patient's own perception and reaction to the
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10 275 symptoms and the physician's assessment of the patient's symptoms. Both patients and physicians
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12 276 may pay more attention to cardiac symptoms if the patient has heart disease before treatment start.
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14 277 These factors may explain some of the difference in incidence in-between studies. Research in new
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16 278 and sensitive cardiac biomarkers like e.g. copeptin to detect myocardial ischemia is needed.³⁹
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18 279 In spite of a relatively large sample size, the number of events is low (22 events) leading to wide
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20 280 confidence intervals, low statistical power and increased risk of type II statistical errors. With
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22 281 respect to the logistic regression analyses, the low number of events limits the number of covariates
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24 282 allowed in the model. The low number of events and multiple testing (increasing the risk of false
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26 283 positive results) are weaknesses of most studies analysing risk factors and it makes the conclusions
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28 284 that can be drawn from these studies less valid.
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30 285 Like most other large studies on this subject our study is retrospective which may results in
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32 286 underestimation of the incidence of cardiotoxicity due to incomplete data and overlooking patients
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34 287 with mild symptoms and asymptomatic patients . Missing data affects power and if not missing at
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36 288 random, they may cause bias. We dealt with the missing data by sensitivity analyses with worst and
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38 289 best case scenarios and with multiple imputation. The sensitivity analyses showed that missing data
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40 290 had little influence on our study results.
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42 291 A major limitation is that baseline ECGs was only preserved for 36% of the patients. Among the 11
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44 292 patients with ECG changes during capecitabine treatment, 2 had missing baseline ECGs.
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51 **Conclusion**

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53 294 The incidence of symptomatic cardiotoxicity from capecitabine of $\approx 5\%$ is close to that of 5-FU
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55 295 with incidences of 1%-5% in larger studies. Our study results suggest that cardiac co-morbidity and
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4 296 current smoking are risk factors for symptomatic cardiotoxicity. Whether smoking cessation can
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6 297 prevent some cases of symptomatic cardiotoxicity deserves further investigations. All the identified
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8 298 risk factors were poor predictors of symptomatic cardiotoxicity and initial optimal cardiac
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10 299 treatment, information about the risk and follow-up if symptoms present are the options today.
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16 301 Contributors:

17
18 302 AP: Data collection, data processing, statistics, writing of the paper and incorporation of input from
19
20 303 the other authors. NS and KV: Conception and design of the study, data collection and review of the
21
22 304 manuscript. MVN: Review of cases with suspected cardiotoxicity and review of the manuscript.
23
24 305 FOL: Conception and design of the study and review of the manuscript. MS: Interpretation of study
25
26 306 results and statistics and review of the manuscript. DN: Conception and design of the study, data
27
28 307 collection, data interpretation, input to the manuscript and review of the manuscript.
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37
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52 316 Ethics: Approval from the Danish Data Protection Agency was obtained.
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55 317 Data sharing statement: No additional data are available.
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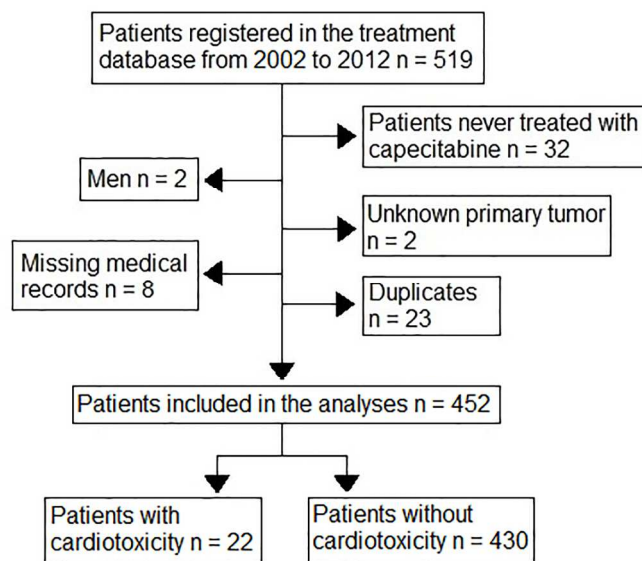


Figure 1: Flow diagram

179x135mm (300 x 300 DPI)

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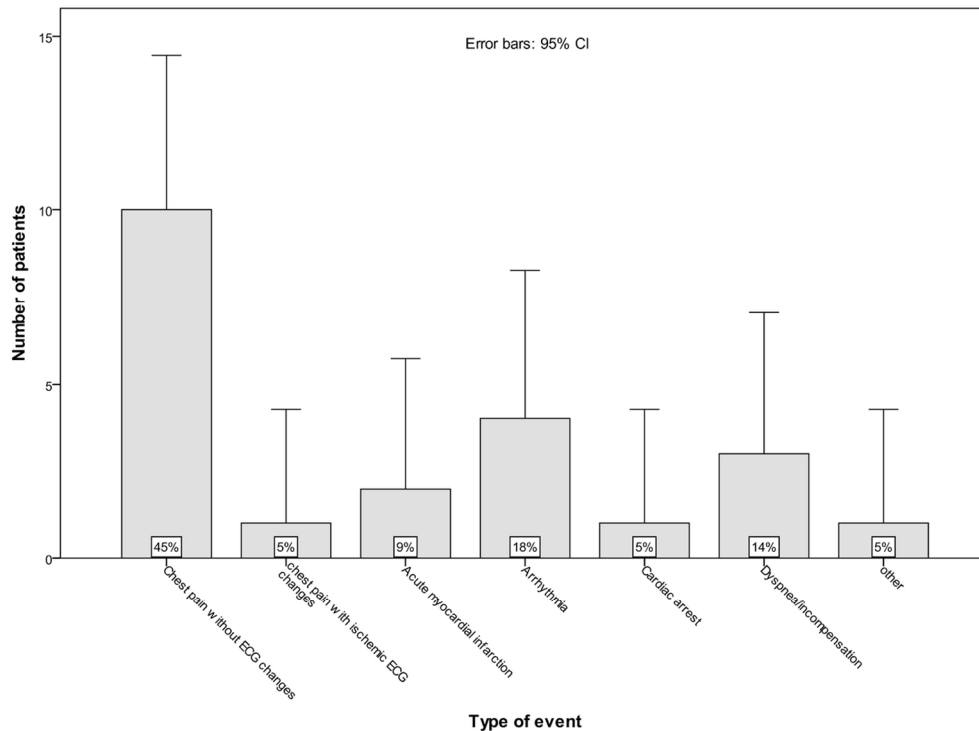


Figure 2: The distribution of the different manifestations of cardiotoxicity.

The percentages showed on each bar reflect the distribution of symptoms among the 22 patients with cardiotoxicity. Proportion of patients with chest pain without ECG changes ($n = 10$), chest pain with ECG changes but not acute myocardial infarction ($n = 1$), acute myocardial infarction ($n = 2$), arrhythmia ($n = 4$), cardiac arrest ($n = 1$), dyspnea/incompensation ($n = 3$) and other ($n = 1$, with QT prolongation and right bundle branch block). Patients with more than one of the manifestations ($n = 2$) are classified according to their primary complaint.

119x94mm (300 x 300 DPI)

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Supplementary table: Details about patients with cardiotoxicity and initiated therapy

Case	Location of metastases	Pre-existing cardiovascular disease	Cycle of onset	Dose intensity at onset	Type of event	Description	ECG changes	Raised cardiac biomarkers?	Cardiac therapy	Subsequent treatment with capecitabine, dose	Symptoms at retreatment
1	Liver, lung, abdomen	No	1	100%	Chest pain	Oppressive chest pain	-	-	No	Yes, 100%	Yes, oppressive chest pain
2	Right lung, pleura, mediastinal lymph nodes, adrenal glands, abdominal carcinosis, columna and pelvis	Atrial fibrillation, NYHA 3, moderate pulmonary hypertension, LVEF = 53% after 1. cycle, hypertension	2	75%	Incompensation, dyspnea	Dyspnea and peripheral edema	ST-depressions in V5-V6	-	-	No	-
3	Liver	No	1	100%	Chest pain	Exertional chest pain radiating to the neck	No changes from pretreatment ECG (inverted T-waves in V1-V2)	-	-	No	-
4	Liver, bone Th3 + Th7, lymph nodes in left axilla	No	2	75%	Cardiac arrest	Chest pain and progressing dyspnea, cardiac arrest, death	Asystole	-	Adrenalin and amiodaron	-	-
5	Mediastinal lymph nodes,	Hypertension, hyperlipidem	1	75%	QTc prolongation, right	Asymptomatic	QTc prolongation, right	-	-	No	-

	thyroid gland, bone Th1 + Th5	ia			bundle branch block		bundle branch block				
6	Neck, sternal and left axillary lymph nodes	No	1	100%	Chest pain	Intermittent, retrosternal, oppressive chest pain radiating to both arms, LVEF 60% at echocardiography	Normal	No	No	No	-
7	Mediastinal lymph nodes	No	4	75%	Chest pain	Chest pain, dyspnea and malaise	Normal	No	No	No	-
8	Pleura, bone	No	1	100%	Chest pain	Compressive chest pain	No changes, ST-depression in V2-V4	-	Metoprolol and Isosorbidm ononitrate	No	-
9	Pleura	No	1	100%	Arrhythmia	Dyspnea	Atrial fibrillation/atrial flutter, 170 bpm.	-	Adenosine, metoprolol and amiodaron	No	-
10	Liver, lung, bone	No	2	75%	Chest pain, Arrhythmia	Chest pain and palpitations	Atrial fibrillation, 119 bpm	-	Verapamil	Yes, 75%	Palpitations, dyspnea, atrial fibrillation
11	Liver, lungs, neck and right supraclavicular lymph nodes	SVT, previous pulmonary embolism, hyperlipidemia	1	100%	AMI	Oppressive chest pain radiating to right side, dyspnea. Effect of nitroglycerin iv. Normal coronary angiography and normal	Initially ST-elevation in V1-V3, AVF and V6. Negative T-waves in	Marginal raised TnI (52 ng/l) and raised CK-MB (4.4 µg/l)	Nitroglycerin iv, Acetylsalicylic Acid and Magnesium Hydroxide, clopidogrel,	No	-

						echocardiography	lead II-III		fondaparinu x		
12	Lungs, mediastinal lymph nodes	Hypertension, diabetes, hyperlipidemia	3	50%	Dyspnea	Dyspnea and light chest pain	Normal	No	No	Yes, 50%	No
13	Bone	Epirubicin-induced cardiomyopathy	9	100%	Chest pain, arrhythmia	Compressive chest pain	Atrial fibrillation and non-sustained VT	-	-	No	-
14	Bone, skin, liver and left axillary lymph nodes	Hypertension, NYHA 2-3 Echo: LVEF 50-55%, mitral valve insufficiency, discrete pulmonary, hypertension	3	75%	Incompensatio, dyspnea	Progressing dyspnea, NYHA 3, peripheral edema, cardiomegaly Echo: LVEF unchanged, moderate to severe pulmonary hypertension, tricuspid insufficiency	Bundle branch block	-	Furosemide and potassium-chloride	No	-
15	Neck and infraclavicular lymph nodes	Atrial fibrillation, COPD	3	100%	Arrhythmia, pulmonary congestion	Dyspnea, dizziness, malaise X-ray: pulmonary congestion and pericardial exudate	Atrial fibrillation 117 bpm	-	Digoxin, Centyl Mite with potassium-chloride	No	-
16	Brain	No	8	100%	Chest pain	Oppressive chest pain radiating to the neck	Normal	-	-	Yes, 100%	Recurrent episodes with chestpain

17	Mediastinal lymph nodes	No	2	100%	Chest pain	Oppressive chestpain radiating to neck and arm, dyspnea	Sinus rhythm, supraventricular extrasystoles, no ST-deviations	No	Verapamil	Yes, 75%	No
18	Sternum and sacroiliac bone	Hyperlipidemia	1	100%	Chest pain	Compressive chest pain radiating to the back and both arms. Echo: normal	Normal	-	No	No	-
19	CNS, liver, right axillary lymph nodes	Hypertension, hyperlipidemia	12	75%	AMI	Chest pain radiating to head, neck and jaw. LVEF = 40 %.	Normal	Raised troponins (400 ng/l), CK-MB unknown	Acetylsalicylic Acid with magnesium hydroxide (magnyl), clopidogrel, fondaparinux, metoprolol, ACE-inhibitor, Statin	No	-
20	Pelvis bone, right axillary lymph nodes	Hypertension, hyperlipidemia	1	100%	Chest pain	Oppressive chest pain Echo: normal	-	-	-	No	-
21	Lung, bone	Epirubicin-induced cardiomyopathy, LVEF = 34-40%	1	100%	Arrhythmia	Dizziness and palpitations.	Telemetry: Atrial flutter 150 bpm, neg. T-waves in I and AVL	-	Metoprolol, ACE-inhibitor	No	-

22	Pelvic and columnar bone	Atrial fibrillation, hypertension, hyperlipidemia	1	100%	Chest pain	Chest pain	Fluctuating negative T-waves in lead II, III, aVF and V1-V5	-	No	Yes, 100%	Episodes with pain located to jaw and chest
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COPD = chronic obstructive pulmonary disease, bpm = beats per minute, NYHA = New York Heart association functional classification, LVEF = left ventricular function, TnI = cardiac troponin I, SVT = supraventricular tachycardia, LMWH = low molecule weight heparin, CK-MB = creatine kinase MB, CNS = central nerve system

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6 + Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(b) Report category boundaries when continuous variables were categorized	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.