CHAPTER 4

Outcome after ST-elevation myocardial infarction in cancer patients treated with primary percutaneous coronary intervention

Am J Cardiol 2013 doi:10.1016/j.amjcard.2013.08.019

M.A. Velders,
H. Boden,
S.H. Hofma,
S. Osanto,
B.L. van der Hoeven,
A.A.C.M. Heestermans,
S.C. Cannegieter,
J.W. Jukema,
V.A.W.M. Umans,
M.J. Schalij,
A.J. van Boven.

Abstract

The simultaneous occurrence of cancer and coronary heart disease is increasing in the Western world. Nevertheless, the influence of cancer on ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) has not been investigated extensively. This multicenter registry included STEMI patients treated with primary PCI from 2006 to 2009. Patients were stratified according to history of cancer and primary focus lay on all-cause and cardiac mortality during 1-year follow-up. Adjusted effect sizes were calculated using Cox proportional hazard models. In total, 208 patients had a history of cancer (diagnosed ≤6 months ago in 20.7%, 6 months-3 years ago in 21.7% and >3 years ago in 57.6%) and 3215 patients had no history of cancer. Chemotherapy had been administered previously to 23% of patients with cancer. Patients with cancer were older, more frequently women, and more commonly known with previous MI or anemia. Reperfusion rates were similar after PCI. Patients with cancer showed greater all-cause (17.4% vs. 6.5% in other patients) and cardiac mortality at 1-year (10.7% vs. 5.4% in other patients), due to high early cardiac death (23.8%) in recently diagnosed cancer patients. After adjustment, a recent cancer diagnosis predicted cardiac mortality at 7-days (HR 3.34, 95% CI 1.57-7.08). The adverse prognosis was partly explained by anemia and occurrence of cardiogenic shock, whereas outcome was independent of cancer treatment. In conclusion, patients with cancer showed greater mortality after STEMI. A cancer diagnosis in the 6 months prior to primary PCI was strongly associated with early cardiac mortality.

Introduction

Coronary heart disease (CHD) and cancer are the most common causes of death in the Western world, together responsible for 3.5 million deaths in Europe every year.[1] Simultaneous occurrence of CHD and cancer is increasingly frequent because of high incidences and improving life expectancies for these patients. Moreover, frequently applied treatment methods for cancer have known cardiovascular side effects, which may predispose these patients to cardiac disease. Chemotherapeutic regimens like anthracyclines and antimetabolites have cardiotoxic properties potentially leading to irreversible cardiomyopathy or cardiac ischemia.[2] External radiation to the thorax is associated with cardiac sequelae including accelerated coronary artery disease, valvular disease, constrictive pericarditis and/or restrictive cardiomyopathy.[3] In addition, cancer is commonly associated with a hypercoagulable state,[4] increasing the risk for venous and possibly arterial thrombosis.[5,6] Regardless of the numerous factors influencing development and prognosis of CHD in patients with cancer, there is little to no data covering the influence of cancer on outcome after myocardial infarction.

The aim of the present multicenter study was to investigate the influence of cancer and cancer treatment on outcome after ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Methods

The current Dutch registry prospectively included STEMI patients treated in 3 tertiary centers in the Netherlands. The design of this registry has been described previously.[7] In short, all consecutive patients undergoing primary PCI for STEMI between January 2006 and December 2009 were included. Patients without return of spontaneous circulation after out-of-hospital cardiac arrest were excluded, as well as patients permanently living outside the Netherlands to allow follow-up through municipality records. Approval from local ethics committees was not required.

Protocols included field triage faxed to the operator on call and in-ambulance treatment with aspirin, heparin and loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered up-front in one center and during procedure in the other centers. Patients treated in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized prehospital, in-hospital and outpatient clinical framework for STEMI care.[8] These patients were intensively monitored at the outpatient clinic for 1 year, after which they were referred to the general practitioner or regional cardiology clinic. In the other centers, local residents were managed at the outpatient clinics and patients referred from regional hospitals were referred back for further management by regional cardiologists.

STEMI was defined as symptoms of angina lasting >30 minutes along with typical electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block) and a typical rise and fall of cardiac biomarkers. Patients with a history of non-melanoma skin cancer were included in the group without cancer. The cancer population was further subdivided according to time elapsed between diagnosis of cancer and primary PCI (diagnosed >3 years ago, 6 months to 3 years ago or ≤6 months ago). First moment of diagnosis was used, unless the patient had recently been diagnosed with progression of disease. For example, cancer diagnosed 5 years ago but identified to have metastasized in the 6 months prior to PCI was considered to be diagnosed in the last 6 months. However, metastasized disease identified 5 years ago was considered to be diagnosed more than 3 years ago.

Socioeconomic status was based on the average socioeconomic class of the patient's residential address using income, access to employment and educational level. These scores are measured yearly by the 'Netherlands Institute for Social Research', an independent government agency.[9] Vital status was obtained using municipality records. Hospital records and general practitioners provided causes of death. Deaths were considered cardiac unless a clear non-cardiac cause could be identified.

Stratification was done according to history of cancer and subsequently according to time of diagnosis. Continuous variables are presented as mean with standard deviation or median with interquartile range and were compared using Student's t-test or non-parametrical tests where appropriate. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare cumulative incidences of the endpoint between groups. To evaluate cancer as a predictor of mortality, multivariable Cox proportional hazard models were used. Univariable predictors of mortality were incorporated in the multivariable models using a forward stepwise approach with a cut-off p-value of <0.10. Second, a confounder model was created in order to investigate the theoretical causal pathway between cancer and mortality. The model included age, gender, socioeconomic status and smoking status. Confounders were chosen according to their relation with both the occurrence of cancer and mortality. Subsequently, explanatory factors were added to the confounder model. Only those factors that could possibly be a consequence of the presence of cancer were added (previous MI, out-of-hospital cardiac arrest, anemia on admission, cardiogenic shock during PCI, TIMI flow after procedure, stent placement, treatment with abciximab, enzymatic infarct size, cancer treatment). Analyses were performed using SPSS version 21 (IBM, Armonk, New York).

Results

During the inclusion period, 208 patients (6.0%) treated for STEMI had a history of cancer (hereafter referred to as patients with cancer) and 3215 patients (92.3%) had no known history of cancer. Cancer history was uncertain in 60 patients (1.7%). Baseline characteristics are shown in Table 1.

Patients with cancer were on average older, more often women and more frequently suffered from hypertension compared to patients without a history of cancer. Patients with cancer were less frequently smokers but more commonly had a previous myocardial infarction. Furthermore, previous peripheral vascular disease, cerebrovascular disease, renal insufficiency and anemia were more common in patients with a history of cancer. Also, the time interval between diagnosis and balloon inflation was significantly longer in patients with a history of cancer compared to patients without a history of cancer.

Table 1. Baseline characteristics

	History of cancer		p-Value
Variable	**Yes** (N=208)	**No** (N=3215)	
Age (years ± standard deviation)	69.6 ± 11.0	62.8 ± 12.4	<0.001
Male gender	141 (67.8)	2427 (75.5)	0.013
Diabetes mellitus, non-insulin dependent	17 (8.3)	275 (8.6)	0.871
Diabetes mellitus, insulin-dependent	6 (2.9)	86 (2.7)	0.843
Hypertension*	88 (42.7)	1135 (35.4)	0.034
Hypercholesterolemia†	46 (22.4)	738 (23.1)	0.839
Current smoker	61 (31.0)	1487 (46.8)	<0.001
Previous myocardial infarction	35 (17.0)	335 (10.4)	0.003
Previous percutaneous coronary intervention	21 (10.2)	267 (8.3)	0.345
Previous coronary artery bypass grafting	5 (2.4)	79 (2.5)	0.970
Prior peripheral vascular disease	18 (8.8)	146 (4.5)	0.006
Prior cerebrovascular disease	24 (11.7)	191 (5.9)	0.001
Prior renal insufficiency‡	17 (8.3)	109 (3.4)	<0.001
Anemia on admission §	53 (11.8)	152 (5.2)	<0.001
Out of hospital cardiac arrest	18 (8.7)	203 (6.3)	0.183
Cardiogenic shock during PCI ‖	18 (8.7)	196 (6.1)	0.140
Creatine phosphokinase peak (median U/l, IQR)	1360 (686-2790)	1365 (616/2611)	0.894
Symptom-to-balloon time (median minutes, IQR)	186 (136-259)	180 (130-284)	0.708
Diagnosis-to-balloon time (median minutes, IQR)	86 (68-107)	79 (65-99)	0.024
Door-to-balloon time (median minutes, IQR)	52 (37-77)	46 (33-67)	0.077

Values are expressed as counts (percentages). * Blood pressure ≥140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment; ‡ eGFR<60 ml/min/1.73m^2; § Admission hemoglobin <12 g/dl (<7.4 mmol/l) for women and <13 g/dl (<8.1 mmol/l) for men. ‖ defined as systolic blood pressure lower than 90 mmHg with signs of tissue hypoperfusion requiring treatment in form of inotropic agents or assistant devices.

Table 2. Procedural characteristics

	History of cancer		p-Value
Variable	**Yes** (N=208)	**No** (N=3215)	
Coronary culprit vessel			0.826
Left anterior descending	91 (43.8)	1291 (40.2)	
Left circumflex	32 (15.4)	509 (15.8)	
Right	79 (38.0)	1337 (41.6)	
Left main	3 (1.4)	40 (1.2)	
Bypass graft	3 (1.4)	36 (1.1)	
Number of vessels narrowed >50%			0.293
1	87 (41.8)	1522 (47.4)	
2	71 (34.1)	1005 (31.3)	
3	50 (24.0)	685 (21.3)	
Stenting	192 (92.3)	3082 (95.9)	0.014
Drug-eluting stents	124 (60.8)	2263 (70.8)	0.002
Bare-metal stents	67 (32.8)	812 (25.4)	0.019
Intra-aortic balloon pump use	14 (6.7)	124 (3.9)	0.041
TIMI flow pre-procedure			0.058
Grade 0	132 (63.5)	2198 (68.5)	
Grade 1	26 (12.5)	356 (11.1)	
Grade 2	35 (16.8)	358 (11.1)	
Grade 3	15 (7.2)	299 (9.3)	
TIMI flow post-procedure ≤2	21 (10.1)	270 (8.4)	0.384
Abciximab treatment	137 (67.2)	2397 (75.1)	0.012
Discharge medication			
Aspirine / Coumadin derivative	187 (98.4)	3097 (99.3)	0.202
Clopidogrel	186 (97.9)	3058 (98.0)	0.885
Beta-blocker	160 (84.2)	2812 (90.5)	0.005
Ace-inhibitor / Angiotensin II antagonist	139 (73.2)	2220 (71.5)	0.622
Statin	171 (90.0)	2897 (93.2)	0.095

Values are expressed as counts (percentages). TIMI = Thrombolysis in myocardial infarction. Other abbreviations as in table 1.

During PCI, cancer patients were less likely to receive coronary stents (Table 2). In case of stenting, the percentage of patients receiving bare-metal stents was higher in patients with a history of cancer although the majority of patients received drug-eluting stents. Additionally, patients with cancer were more frequently treated with intra-aortic balloon pumps. Finally, patients with cancer were less likely to receive abciximab treatment compared to patients without a history of cancer and were less frequently discharged on beta-blocker therapy.

Table 3. Cancer characteristics

Variable	Diagnosis >3 years ago			Diagnosis 6 months < 3 years ago			Diagnosis ≤6 months ago			
Cancer location	n (%)	*Chemo*	**Radiation**	n (%)	*Chemo*	**Radiation**	n (%)	*Chemo*	**Radiation**	**Total**
Oral cavity	3 (1.5)	*0/3*	**0/3**	3 (1.5)	*0/3*	**1/3**	-	-		6 (3.0)
Larynx	7 (3.4)	*0/7*	**5/7**	2 (1.0)	*0/2*	**2/2**	1 (0.5)	*0/1*	**0/1**	10 (4.9)
Lung	3 (1.5)	*1/3*	**1/3***	3 (1.5)	*2/3*	**1/3***	4 (2.0)	*1/4*	**2/4***	10 (4.9)
Breast	25 (12.3)	*4/25*	**12/25***	5 (2.5)	*2/5*	**4/5***	3 (1.5)	*1/3*	**1/3***	33 (16.3)
Esophagus	1 (0.5)	*1/1*	**1/1**	2 (1.0)	*0/2*	**0/2**	2 (1.0)	*2/2*	**0/2**	5 (2.5)
Stomach	1 (0.5)	*0/1*	**0/1**	-	-		1 (0.5)	*0/1*	**0/1**	2 (1.0)
Pancreas	-	-		-	-		2 (1.0)	*0/2*	**0/2**	2 (1.0)
Colorectal	17 (8.4)	*2/17*	**0/17**	4 (2.0)	*0/4*	**1/4**	8 (3.9)	*1/8*	**1/8**	29 (14.3)
Kidney	7 (3.4)	*0/7*	**0/7**	1 (0.5)	*0/1*	**0/1**	1 (0.5)	*0/1*	**0/1**	9 (4.4)
Bladder	12 (5.9)	*3/12*	**0/12**	6 (3.0)	*0/6*	**0/6**	7 (3.4)	*3/7*	**0/7**	25 (12.3)
Prostate	6 (3.0)	*0/6*	**1/6**	14 (6.9)	*8/14*	**7/14**	10 (4.9)	*5/10*	**1/10**	30 (14.8)
Testis	5 (2.5)	*1 /5*	**2/5**	-	-		-	-		5 (2.5)
Ovary	1 (0.5)	*0/1*	**0/1**	1 (0.5)	*0/1*	**0/1**	-	-		2 (1.0)
Uterus / cervical	5 (2.5)	*0/5*	**1/5**	-	-		-	-		5 (2.5)
Skin (melanoma)	8 (3.9)	*0/8*	**0/8**	1 (0.5)	*0/1*	**0/1**	-	-		9 (4.4)
Lymphoma	11 (5.4)	*7/11*	**7/11**	2 (1.0)	*1/2*	**2/2**	1 (0.5)	*1/1*	**1/1**	14 (6.9)
Other†	5 (2.5)	*1/5*	**0/5**	-	-		-	-		5 (2.5)
Primary tumor unknown	-	-		-	-		2 (1.0)	*0/2*	**0/2**	2 (1.0)
Total	117 (57.6)	*20/117*	**30/117**	44 (21.7)	*13/44*	**18/44**	42 (20.7)	*14/42*	**6/42**	203 (100)

Note: hormone treatment was counted as chemotherapy.
*: Left sided chest radiation was performed in 9 breast cancer patients (6 with diagnosis >3 years ago , 3 with diagnosis 6 months – 3 year ago and 1 with diagnosis ≤6 months ago) and in 0 lung cancer patients.
†: leukemia (N=1), sarcoma (N=1), carcinoid (N=1) and mandibular neoplasm (N=2).

The characteristics of cancer history are shown in table 3. Exact moment of diagnosis was unknown in 5 patients. One year survival status was available in 99.8% of patients. Patients with cancer showed significantly greater all-cause mortality compared to patients without a history of cancer (in-hospital 9.1% vs. 3.4%, p<0.001; 7-day 9.7% vs. 3.1%, p<0.001; 1-year 17.4% vs. 6.5%, p<0.001, Figure 1A). Moreover, cardiac mortality was greater in patients with cancer compared to patients without a history of cancer (in-hospital 8.7% vs. 3.4%, p<0.001; 7-day 9.2% vs. 3.1%, p<0.001; 1-year 10.7% vs. 5.4%, p=0.002, Figure 1B). Stratification on moment of diagnosis showed that patients with cancer diagnosed ≤6 months ago suffered the highest rates of all-cause (in-hospital 19.0%, 7-day 23.8%, 1-year 50.0%, Figure 1C) and cardiac mortality (in-hospital 19.0%, 7-day 23.8%, 1-year 28.9%, Figure 1D).

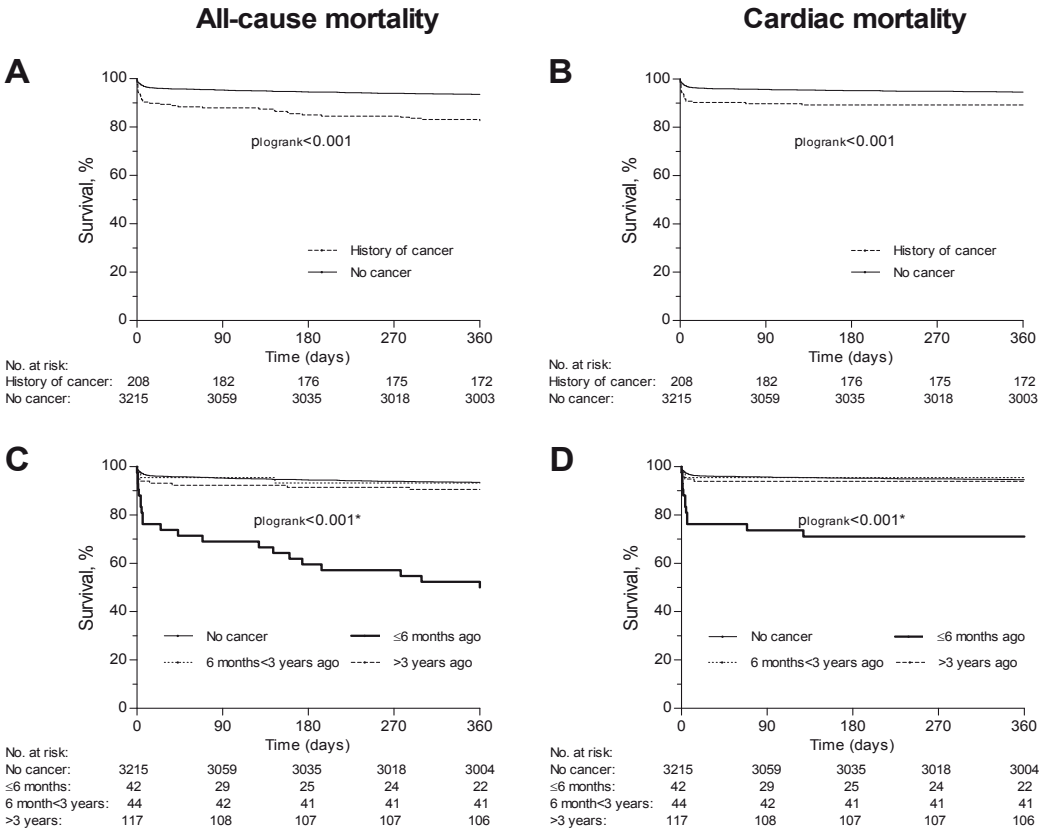

Figure 1: (A) Freedom from 1-year all-cause mortality according to history of cancer. **(B):** Freedom from 1-year cardiac mortality according to history of cancer. (**C):** Freedom from 1-year all-cause mortality according to moment of cancer diagnosis. **(D):** Freedom from 1-year cardiac mortality according to moment of cancer diagnosis.
*plogrank<0.001 for comparison between cancer diagnosis ≤6 months ago and other groups for both all-cause and cardiac mortality. Other comparisons were non-significant.

Table 4. Cancer and cardiac mortality after STEMI

Variable	Cardiac mortality, 7-day				Cardiac mortality, 1-year			
	Cum. Inc.	Crude HR 95% CI	Adjusted HR* 95% CI	p-Value	Cum. Inc.	Crude HR, 95% CI	Adjusted HR† 95% CI	p-Value
No cancer	3.1	Reference	Reference	-	5.4	Reference	Reference	-
Any cancer	9.2	3.06 (1.87-5.00)	2.15 (1.26-3.68)	0.005	10.7	2.09 (1.34-3.25)	1.14 (0.69-1.87)	0.611
Diagnosis								
>3 years ago	5.2	1.70 (0.75-3.88)	1.29 (0.52-3.21)	0.589	6.0	1.15 (0.54-2.44)	0.71 (0.29-1.75)	0.459
6 months < 3 years ago	4.5	1.48 (0.37-5.99)	1.83 (0.44-7.61)	0.406	4.5	0.85 (0.21-3.44)	0.83 (0.20-3.38)	0.795
≤ 6 months ago	23.8	8.27 (4.32-15.85)	3.34 (1.57-7.08)	0.002	28.9	6.31 (3.51-11.33)	1.80 (0.91-3.54)	0.090

Cum. incidence = cumulative incidence of events based on Kaplan-Meier curve.
*Adjusted for age, gender, history of diabetes mellitus, history of peripheral vascular disease, previous myocardial infarction, anemia, out-of-hospital cardiac arrest, cardiogenic shock during PCI, stenting, thrombolysis-in-myocardial infarction flow <3 after procedure and enzymatic infarct size.
†Adjusted for age, history of diabetes mellitus, history of peripheral vascular disease, culprit lesion, out-of-hospital cardiac arrest, cardiogenic shock during PCI, stenting, thrombolysis-in-myocardial infarction flow <3 after procedure, enzymatic infarct size.

Table 5. Factors associated with the effect of cancer on 7-day cardiac mortality

Variable	Crude HR, 95% CI	Adjusted HR, 95% CI
Confounder model (age, gender, socioeconomic status, smoking)	8.27 (4.32-15.85)	5.49 (2.54-11.88)
Confounder model + anemia	-	3.40 (1.52-7.57)
Confounder model + anemia, cardiogenic shock	-	2.71 (1.21-6.09)
Confounder model + anemia, cardiogenic shock, previous chemotherapy	-	3.44 (1.43-8.26)

Abbreviations as in table 4.

Table 4 lists the association of cancer with cardiac mortality during follow-up. After multivariable adjustment, any history of cancer was found to predict cardiac mortality at 7-days. Stratification on moment of diagnosis showed that this was driven by patients with a cancer diagnosis in the last 6 months, which strongly predicted early cardiac mortality. The explanatory analyses (table 5) showed that anemia at admission explained a major part of the effect size of recent cancer on cardiac mortality. The rate of admission anemia was already high in the total cancer population (11.8% compared to 5.2% in the population without cancer), but in patients with recent cancer diagnosis the rate of anemia was even higher at 65.9%.

The other major contributing factor was cardiogenic shock during PCI, which occurred in 16.7% of these patients.

Individual corrections for the following variables were performed (the values of the variables are mentioned in parentheses, comparing patients with a recent cancer diagnosis to patients without a history of cancer): previous MI (19% vs. 10.4%), out-of-hospital cardiac arrest (9.5% vs. 6.3%), TIMI flow (TIMI 3 achieved in 92.7% vs. 91.6%), stenting (90.5% vs. 95.9%), treatment with abciximab (48.8% vs. 75.1%) or enzymatic infarct size (median 1342 U/l (IQR 689 to 2854) vs. 1360 U/l (IQR 686 to 2790)) did not provide any additional reduction in the effect size. Finally, previous treatment with chemotherapy was added to the confounder models, which had been administered in one third of patients with a recent cancer diagnosis. However, no association between chemotherapy and cardiac mortality was observed. Previous thoracic radiation was not added to the explanatory models because none of the patients that had received thoracic radiation suffered cardiac death.

Discussion

The present multicenter study evaluated the influence of cancer on the prognosis of STEMI patients. Most notably, a cancer diagnosis in the 6 months prior to primary PCI was a strong predictor of early cardiac mortality. The adverse effect of cancer on prognosis after STEMI was partly explained by a high prevalence of anemia and the occurrence of cardiogenic shock, whereas outcome was independent of cancer treatment.

In the present population, patients with cancer were on average older and more often female. Previous myocardial infarctions were more frequent compared to patients without cancer because of higher average age, but also likely influenced by a greater risk of cardiac events.[5] In contrast, patients with cancer were less likely to smoke. As expected, cancer patients showed higher all-cause mortality compared to patients without a history of cancer. Strikingly, also cardiac mortality was more common in cancer patients, due to high mortality in patients with a recent cancer diagnosis. A large part of the effect on mortality could be explained by anemia, which was very common after a recent cancer diagnosis. Factors contributing to cancer-related anemia include impaired erythropoiesis, hemolysis, chemotherapy, nutritional deficiencies and interaction between tumor and immune system.[10] Anemia is known to predict cardiovascular death and heart failure in STEMI patients, due to the increased myocardial oxygen demand associated with the increased stroke volume and tachycardia required to maintain adequate systemic oxygen delivery.[11] Additionally, presence of cardiogenic shock explained part of the adverse outcome. The higher rate of previous infarctions in patients with cancer most likely contributed to the increased rate of cardiogenic shock. Also, patients with cancer were less likely to receive coronary stenting during primary PCI. Whether

this reflects a more conservative approach or was intended to shorten the need for dual antiplatelet therapy is unclear. The higher rate of implanted bare-metal stents supports the latter theory. Moreover, the higher rate of intra-aortic balloon pump implantation suggests that in general they were not withheld from aggressive treatment. As final TIMI flow was similar to patients without cancer, failed reperfusion did not appear to contribute to the development of cardiogenic shock. Furthermore, correction for stenting, abciximab treatment, TIMI flow and infarct size did not change the effect of recently diagnosed cancer on cardiac death, suggesting that the higher mortality rate was unrelated to the procedure and infarct size.

Contrary to expectations, no association between adverse outcome and chemotherapy or radiation was observed, and therefore a cancer-specific effect on prognosis after STEMI was suspected. The observed cancer types in these patients support this, as they have all been associated with risk of CHD.[5] Cancer is commonly associated with a hypercoagulable state due to reduced fibrinolysis and expression of procoagulant factors by tumors.[4,12] The most characterized factors are cancer procoagulant and tissue factor. Tissue factor has been related to increased myocardial ischemia-reperfusion injury in animal studies as well as mortality and reinfarction in patients with acute myocardial infarction.[13-16] Moreover, cancer is a known predictor of stent thrombosis.[17]

Recently diagnosed patients with cancer represent a challenge for the operator performing primary PCI. Antithrombotic treatment and vascular access increase the risk of bleeding which may worsen the anemia present in many of these patients, increasing the risk of heart failure. At the same time, antithrombotic treatment is essential to avoid ischemic complications associated with hypercoagulability. Another complicating factor is the frequent need for surgical procedures, potentially causing cessation of antiplatelet therapy and increased risk of stent thrombosis.[18] It might be preferable to use balloon angioplasty without stents to limit the duration of dual antiplatelet therapy. If stents need to be used, those with fast endothelialization rates, i.e. bare-metal or everolimus-eluting stents, should likely be preferred to minimize the risk of stent thrombosis.[19] Also, coronary artery bypass grafting may have advantages over stenting. However, these suggestions remain speculative without definitive randomized data.

To our knowledge, this multicenter registry was the first cohort to systematically investigate the association between cancer and prognosis after STEMI. The wide range of patients included across 3 regions in the Netherlands supports the generalizability of the findings. However, the observational design limits conclusions of causality, and findings should be considered hypothesis-generating. Additional research is needed to fully clarify the mechanism behind the adverse prognosis. Furthermore, the number of cancer patients was relatively small and the enzymatic correction for infarct size may have underestimated the actual infarct size. Also, it was not possible to measure whether all individual cancer patients received the same treatment as patients without cancer. However, there were no signs of lim-

itations in the care applied to the cancer population. Finally, follow-up data on re-infarction and stent thrombosis after PCI may have provided more insight into the mechanisms of death but were not available.

Acknowledgements

The Department of Cardiology of Leiden University Medical Center received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, Lantheus medical imaging, St. Jude Medical, Edwards Life sciences & GE Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Scarborough P, Rayner M (2012). European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis.
2. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231-2247.
3. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, Mabuchi K, Marks LB, Mettler FA, Pierce LJ, Trott KR, Yeh ET, Shore RE. Radiation-related heart disease: current knowledge and future prospects. Int J Radiat Oncol Biol Phys 2010;76:656-665.
4. De Cicco M. The prothrombotic state in cancer: pathogenic mechanisms. Crit Rev Oncol Hematol 2004;50:187-196.
5. Zöller B, Ji J, Sundquist J, Sundquist K. Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden. Eur J Cancer 2012;48:121-128.
6. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. Lancet Oncol 2005;6:401-410.
7. Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, Umans VA, Jukema JW, Hofma SH, Schalij MJ. Influence of Gender on Ischemic Times and Outcomes After ST-Elevation Myocardial Infarction. Am J Cardiol 2013;111:312-318.
8. Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, Viergever EP, van Rees C, Padmos I, Sedney MI, van Exel HJ, Verwey HF, Atsma DE, van der Velde ET, Jukema JW, van der Wall EE, Schalij MJ. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007;153:14.e1-e11.
9. Status scores. The Netherlands Institute for Social Research. 2012. www.scp.nl/english/.
10. Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, Krzakowski M, Ludwig H, Pecorelli S, Schmoll H, Schneider M, Schrijvers D, Shasha D, Van Belle S. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology 2005;68 Suppl 1:3-11.
11. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of Hemoglobin Levels With Clinical Outcomes in Acute Coronary Syndromes. Circulation 2005;111:2042-2049.
12. Gouin-Thibault I, Achkar A, Samama MM. The thrombophilic state in cancer patients. Acta Haematol 2001;106:33-42.
13. Seljeflot I, Hurlen M, Hole T, Arnesen H. Soluble tissue factor as predictor of future events in patients with acute myocardial infarction. Thromb Res 2003;111:369-372.
14. Steppich BA, Braun SL, Stein A, Demetz G, Groha P, Schömig A, von Beckerath N, Kastrati A, Ott I. Plasma TF activity predicts cardiovascular mortality in patients with acute myocardial infarction. Thromb J 2009;7:11.
15. Campo G, Valgimigli M, Ferraresi P, Malagutti P, Baroni M, Arcozzi C, Gemmati D, Percoco G, Parrinello G, Ferrari R, Bernardi F. Tissue factor and coagulation factor VII levels during acute myocardial infarction: association with genotype and adverse events. Arterioscler Thromb Vasc Biol 2006;26:2800-2806.
16. Chong AJ, Pohlman TH, Hampton CR, Shimamoto A, Mackman N, Verrier ED. Tissue factor and thrombin mediate myocardial ischemia-reperfusion injury. Ann Thorac Surg 2003;75:S649-S655.

17. Van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol 2009;53:1399-1409.

18. Abualsaud AO, Eisenberg MJ. Perioperative management of patients with drug-eluting stents. JACC Cardiovasc Interv 2010;3:131-142.

19. Joner M, Nakazawa G, Finn AV, Quee SC, Coleman L, Acampado E, Wilson PS, Skorija K, Cheng Q, Xu X, Gold HK, Kolodgie FD, Virmani R. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333-342.