Gender differences in the assessment and treatment of myocardial infarction

BACKGROUND Previous studies have shown that there are gender-related differences in the assessment and treatment of myocardial infarction, despite international guidelines that prescribe identical treatment for women and men. We investigated whether these differences occurred in Norway.

MATERIAL AND METHOD All patients admitted to Norwegian hospitals with myocardial infarction from 1 January 2013 to 31 December 2014 and registered in the Norwegian Myocardial Infarction Registry were included. Data from the registry were used to analyse differences in the assessment, treatment, complications and survival of women and men in different age groups.

RESULTS A total of 26 447 myocardial infarctions were registered in the Norwegian Myocardial Infarction Registry in the period 2013–2014. Fewer women than men were assessed by means of coronary angiography. Percutaneous coronary intervention (PCI) was used to virtually the same extent for both genders if coronary stenosis was found. Women were recommended secondary prophylactic medication to a lesser extent than men. There were no major differences between men and women in the incidence of complications in the course following myocardial infarction or in survival.

INTERPRETATION Fewer women than men suffering acute myocardial infarction were assessed by means of coronary angiography, and women were recommended secondary prophylactic medication less often than men. The reason for the gender differences is not known, but comorbidity and a potentially greater risk of adverse reactions in women may be contributory factors. The different views of doctors providing treatment may also play a part.

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Each year, some 13 000 Norwegians are admitted to Norwegian hospitals with acute myocardial infarction (1). Several studies have shown that women may have less clear symptoms and clinical findings, wait longer for treatment, less frequently undergo invasive assessment and receive less secondary prophylactic medication on discharge than men (2–13). Both short-term and long-term survival after myocardial infarction have improved considerably over the last few decades for women and men alike, but some studies have revealed lower survival for women, particularly in cases of ST-elevation myocardial infarction (STEMI) (14–21). Gender differences have also been found in Norway with respect to therapy for patients with myocardial infarction (22, 23). European guidelines for treatment of myocardial infarction recommend that no be made between the assessment and treatment of women and men (24–26).

We have used data from the Norwegian Myocardial Infarction Registry to investigate whether there are still differences in the assessment, treatment, complications and survival of women and men with STEMI and non-ST-elevation myocardial infarction (nSTEMI) admitted to Norwegian hospitals in the period 2013–2014.

Material and method

All patients with the diagnosis myocardial infarction admitted to Norwegian hospitals from 1 January 2013 to 31 December 2014 and registered in the Norwegian Myocardial Infarction Registry were included in this study. Only patients with Norwegian national identity numbers were included. Primary admissions and transfers were registered separately at each hospital, but linked together at national level into a single myocardial infarction course.

Registration of all patients admitted to Norwegian hospitals with acute myocardial infarction is required by law; see section 2–1 of the Norwegian Cardiovascular Disease Registry Regulations (27). According to section 8 of the Health Register Act, registration is not conditional on the patient's consent (28). The register contains information on gender, age, known risk factors, previous illnesses and medicines, symptoms and clinical findings on admission and on in-hospital assessment, therapy and complications, and drugs prescribed on discharge. The dates of symptom onset, arrival at the first hospital and invasive treatment were also recorded. The time of invasive treatment was fixed as the time of balloon dilation or direct insertion of a stent into a coronary artery.

MAIN POINTS

Fewer women than men suffered myocardial infarction in Norway in 2013–2014.

The average age for myocardial infarction was higher for women than for men.

Fewer women than men with myocardial infarction were assessed by means of coronary angiography.

Fewer women than men were prescribed secondary prophylactic medication after myocardial infarction

Table 1 Characteristics of patients with myocardial infarction admitted to Norwegian hospitals in 2013–2014

	STEMI n = 6 386					NSTEMI n = 17 558				
	Women n = 1 862		Men n = 4 524			Women n = 6 741		Men n = 10 817		
	Number	(%)	Number	(%)	P-value	Number	(%)	Number	(%)	P-value
Diabetes mellitus										
< 50 years	15	(15)	44	(8)	0.06	29	(15)	81	(12)	0.37
50–59 years	38	(18)	111	(10)	< 0.001	90	(19)	289	(18)	0.01
60–69 years	48	(12)	159	(12)	0.36	222	(22)	547	(21)	0.64
70–79 years	65	(14)	127	(14)	0.54	316	(21)	644	(25)	0.04
≥ 80 years	114	(17)	102	(16)	0.73	689	(19)	725	(22)	0.01
Hypertension										
< 50 years	21	(21)	71	(13)	0.16	46	(24)	146	(22)	0.84
50–59 years	74	(34)	260	(23)	0.002	176	(37)	516	(31)	0.10
60–69 years	157	(38)	469	(35)	0.16	464	(46)	1 190	(45)	0.86
70–79 years	218	(48)	379	(43)	0.39	831	(56)	1 433	(55)	0.44
≥ 80 years	365	(54)	285	(43)	< 0.001	2 191	(61)	1 737	(54)	< 0.001
Smoking[1]										
< 50 years	78	(76)	396	(74)	0.18	134	(70)	469	(71)	0.67
50–59 years	180	(83)	807	(73)	0.01	344	(73)	1 161	(71)	0.23
60–69 years	309	(75)	949	(71)	0.07	695	(68)	1 886	(71)	0.18
70–79 years	253	(56)	528	(60)	0.06	830	(56)	1 704	(65)	< 0.001
≥ 80 years	186	(27)	350	(53)	< 0.001	1 050	(29)	1 783	(55)	< 0.001
Statin-treated dyslipidaemia										
< 50 years	14	(14)	65	(12)	0.91	30	(16)	170	(26)	0.01
50–59 years	39	(18)	199	(18)	1.00	146	(31)	573	(35)	0.07
60–69 years	81	(20)	350	(26)	0.02	397	(39)	1 206	(45)	0.002
70–79 years	115	(25)	249	(28)	0.09	646	(44)	1 370	(53)	< 0.001
≥ 80 years	150	(22)	189	(29)	0.01	1 264	(35)	1 466	(45)	< 0.001

[1] Former or current smoker. Smoking status was not recorded for 3 080 (12.9 %)

For the other variables the percentage was unknown < 1.2 %.

The registration and quality assurance of information in the Norwegian Myocardial Infarction Registry have been described previously (1). The time of death entered in the register is taken from the National Population Registry.

For the diagnosis acute myocardial infarction, the Norwegian Myocardial Infarction Registry adheres to the third universal definition of myocardial infarction (29). The diagnosis is based on the rise and/or fall in troponin value and one of the following additional criteria: ischaemic symptoms, new ST elevation, ST depression, T-wave inversion or left bundle branch block, development of pathological Q waves, imaging of new myocardial damage or identification of an intracoronary thrombus by angiography or autopsy (29).

Myocardial infarction with symptom onset ≤ 28 days before hospitalisation was registered as acute myocardial infarction in accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Troponin was

Table 2 Time course for myocardial infarction in patients admitted to Norwegian hospitals in 2013–2014

	STEMI					NSTEMI				
	Women		Men			Women		Men		
	Hours (median)	(lower, upper quartile)	Hours (median)	(lower, upper quartile)	P-value	Hours (median)	(lower, upper quartile)	Hours (median)	(lower, upper quartile)	P-value
Time from symptom onset to admission to first hospital[1]										
< 50 years	2.3	(1.5, 2.3)	2.0	(1.3, 3.8)	0.48	3.0	(1.8, 7.8)	3.3	(1.9, 7.0)	0.28
50–59 years	2.4	(1.7, 4.3)	2.0	(1.4, 3.7)	0.25	3.3	(1.9, 8.0)	3.5	(2.0, 7.0)	0.84
60–69 years	2.3	(1.5, 3.5)	2.0	(1.5, 4.0)	0.49	4.0	(2.1, 7.8)	3.5	(2.0, 7.5)	0.10
70–79 years	3.0	(1.9, 5.2)	2.0	(1.5, 4.7)	0.002	3.8	(2.0, 6.9)	3.7	(2.0, 7.4)	0.81
≥ 80 years	3.4	(1.8, 6.4)	3.0	(1.7, 5.6)	0.13	3.8	(2.0, 7.8)	3.7	(2.0, 7.0)	0.68
Time from admission to first hospital to coronary angiography[2]										
< 50 years	1.0	(0.4–3.9)	0.7	(0.4–1.8)	0.07	37	(17.0–62.5)	34	(17.2–61.0)	0.62
50–59 years	0.8	(0.4–2.7)	0.7	(0.4–1.9)	0.09	41	(16.8–69.0)	41	(18.6–65.2)	0.49
60–69 years	0.7	(0.4–2.1)	0.7	(0.4–2.3)	0.87	49	(25.4–81.9)	45	(22.8–72.4)	< 0.001
70–79 years	0.9	(0.6–5.4)	0.8	(0.6–3.3)	0.36	51	(26.5–93.8)	53	(26.0–89.2)	0.87
≥ 80 years	1.1	(0.5–2.4)	0.7	(0.4–2.7)	0.18	71	(35.7–119.1)	58	(26.9–108.2)	< 0.001

[1] Registration of the time course from symptom onset to admission was lacking for 660 (11.7 %) STEMI and 4 590 (32.5 %) nSTEMI patients

[2] Registration of the time course from admission to the first hospital to coronary angiography was lacking for 60 (1.2 %) STEMI and 474 (5.9 %) nSTEMI patients

the preferred biochemical marker of myocardial infarction. The reference limits (99th percentile) for troponin I depend on the manufacturer. A diagnostic limit of ≥ 30 ng/l for troponin T was used in Norway up to May 2013. Since 1 June 2013, the international limit of troponin T > 14 ng/l for diagnosing myocardial infarction has also been recommended in Norway (30).

All myocardial infarctions were classified as being one of types 1–5, where type 1 was defined as a spontaneous myocardial infarction attributable to ischaemia due to plaque fissure, erosion or rupture, or by dissection with intraluminal thrombus. Type 2 infarction was defined as secondary to ischaemia due to imbalance between the myocardium's oxgen requirement and supply, type 3 infarction as cardiac death assumed to be attributable to ischaemia, type 4 infarction as related to invasive coronary procedure or stent thrombosis and type 5 infarction as related to coronary surgery.

Since European guidelines do not distinguish clearly between the different types of cardiac infarction when it comes to therapy, we have chosen to present the results for all types together. Myocardial infarctions were also classified as ST-elevation infarctions (STEMI) or non-ST-elevation infarctions (nSTEMI) on the basis of changes in admission ECG: STEMI with new ST-segment elevation or newly developed left bundle branch block, nSTEMI with normal ECG, ST depression, T-wave inversion or other ST-T changes.

Continuous variables are presented as average ± SD (standard deviation) or median (lower, upper quartile), differences between groups were analysed using a T test or non-parametric tests. Category data are presented as numbers and percentages, differences between groups were analysed using the chi-squared test. Survival is presented in the form of Kaplan-Meier curves. All patients were followed until death or until 30 June 2015. Differences in survival between women and men in different age groups were analysed using Cox's regression analysis and are presented as unadjusted hazard ratio (HR) with a 95 % confidence interval (CI). In all analyses, a p-value of < 0.05 is regarded as statistically significant. The data were analysed using the statistics programs SPSS version 21 and STATA version 14.

The legal basis for the compilation and publication of data from the register is section 3–1 of the Cardiovascular Regulations, and does not require the approval of a regional ethics committee.

Results

Clinical characteristics

In the period 2013–2014, 26 447 cases of myocardial infarction suffered by 24 820 different patients were recorded in the Norwegian Myocardial Infarction Registry. This corresponds to 83 % in 2013 and 88 % in 2014 of all myocardial infarctions recorded in the Norwegian Patient Registry. Type 1 myocardial infarction accounted for 81 % (n = 21 500). A total of 6 539 (25 %) of all myocardial infarctions recorded were classified as STEMI and 19 014 (72 %) as nSTEMI. A total of 894 myocardial infarctions (3 %) could not be classified.

The percentage of women was 29 % for STEMI and 39 % for nSTEMI. The gender distribution for type 1 myocardial infarction was not significantly different from the gender distribution for all types of myocardial infarction combined. The average age for incurring myocardial infarction was 77.2 years (± 13 years) for women and 69.4 years (± 14 years) for men. For both STEMI and non-STEMI, affected women were older than affected men.

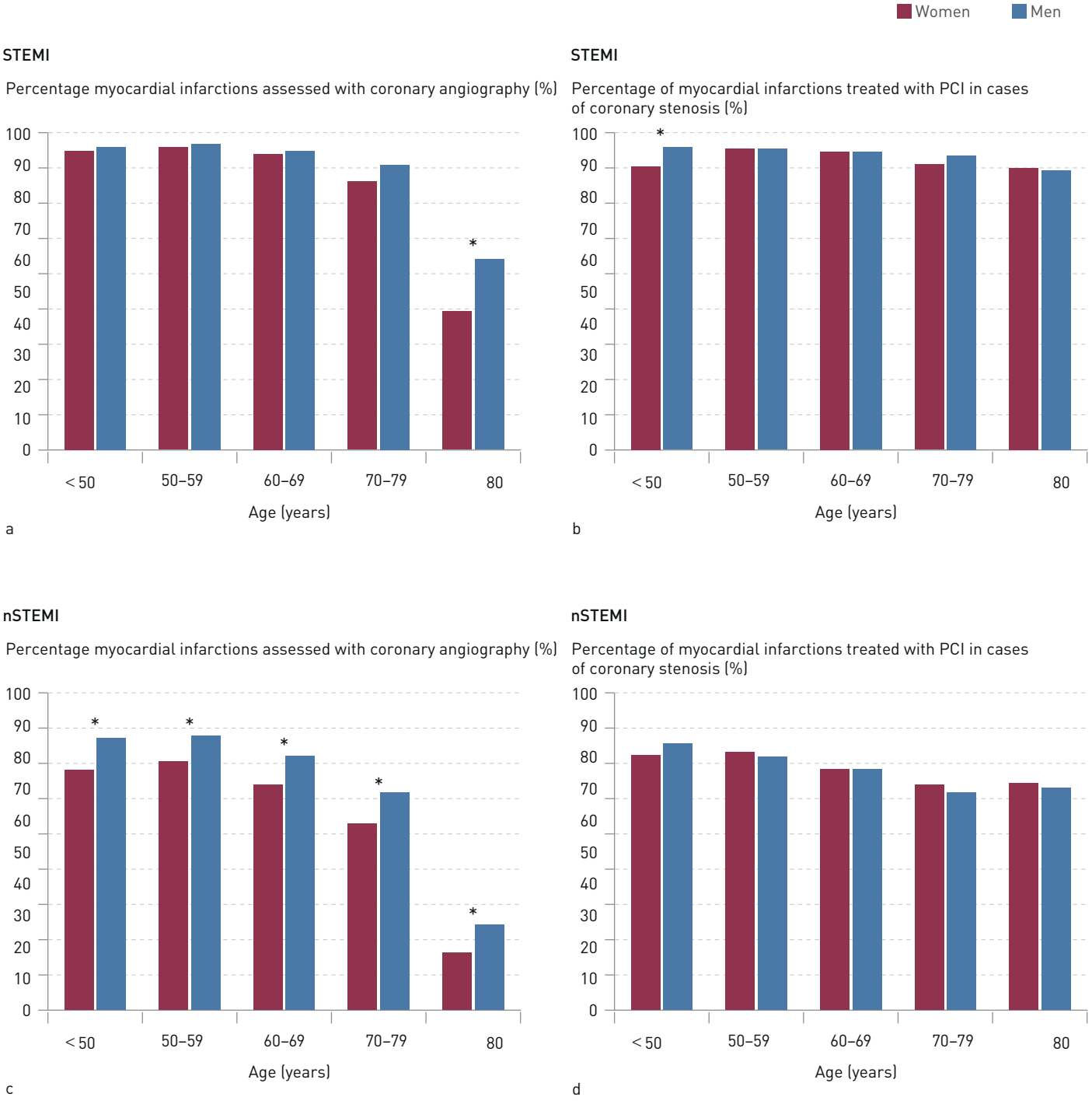

Figure 1 *Percentage of myocardial infarctions assessed using coronary angiography (a, c) and percentage using percutaneous coronary intervention (PCI) (b, d) in cases of coronary stenosis in patients admitted to Norwegian hospitals in 2013–2014*

The clinical characteristics of women and men in the various age groups are shown in Table 1. Smoking was more common among the oldest men than among the women of the same age. There were few gender differences with respect to diabetes mellitus and hypertension, but women in the age group 50–59 had a higher incidence of diabetes mellitus than men in the same age group, and fewer women than men aged over 60 were using statins at the time of admission.

There was little gender difference in the time delay from symptom onset until admission to hospital, but in many cases of myocardial infarction the time course was not registered (Table 2).

Treatment

Coronary angiography was carried out for 5 517 (84 %) of the STEMIs and 10 345 (54 %) of the non-STEMIs. Fewer women

Table 3 Medication on discharge for patients with myocardial infarction admitted to Norwegian hospitals in 2013–2014

	STEMI n = 5 932					NSTEMI n = 17 757				
	Women, n = 1 650		Men, n = 4 282			Women, n = 6 812		Men, n = 10 945		
	Number	(%)	Number	(%)	P-value	Number	(%)	Number	(%)	P-value
Platelet inhibitors (at least one)										
< 50 years	95	(96.9)	517	(98.5)	0.29	179	(90.9)	653	(96.5)	0.001
50–59 years	207	(99.0)	1083	(98.9)	0.83	458	(94.8)	1 656	(97.9)	< 0.001
60–69 years	400	(98.3)	1280	(98.7)	0.64	993	(96.2)	2 659	(97.4)	0.08
70–79 years	389	(95.8)	796	(98.6)	0.001	1 423	(92.9)	2 518	(94.9)	0.002
≥ 80 years	491	(92.6)	522	(93.5)	0.56	2 980	(83.5)	2 758	(86.3)	0.004
Two different platelet inhibitors										
< 50 years	86	(87.8)	498	(94.9)	0.02	159	(80.7)	593	(87.6)	0.04
50–59 years	200	(95.7)	1 035	(94.5)	0.69	399	(82.6)	1 435	(84.8)	0.35
60–69 years	374	(91.9)	1 207	(93.1)	0.19	805	(78.0)	2 241	(82.1)	0.02
70–79 years	353	(86.9)	723	(89.6)	0.14	1 066	(69.6)	1 970	(74.3)	< 0.001
≥ 80 years	372	(70.2)	424	(76.0)	0.03	1 620	(45.4)	1 725	(54.0)	< 0.001
Statins										
< 50 years	87	(88.8)	494	(94.1)	0.12	158	(80.2)	623	(92.0)	< 0.001
50–59 years	190	(90.9)	1 034	(94.4)	0.14	418	(86.5)	1 571	(92.8)	< 0.001
60–69 years	381	(93.6)	1 232	(95.0)	0.50	893	(86.5)	2 516	(92.2)	< 0.001
70–79 years	359	(88.4)	748	(92.7)	0.01	1 272	(83.1)	2 334	(88.0)	< 0.001
≥ 80 years	351	(66.2)	437	(78.3)	< 0.001	2 012	(56.4)	2 193	(68.7)	< 0.001
Beta-blocker										
< 50 years	76	(77.6)	422	(80.4)	0.72	120	(60.9)	483	(71.3)	0.01
50–59 years	166	(79.4)	902	(82.4)	0.28	342	(70.8)	1 298	(76.7)	0.02
60–69 years	311	(76.4)	1 067	(82.3)	0.03	740	(71.7)	2 167	(79.4)	< 0.001
70–79 years	322	(79.3)	662	(82.0)	0.21	1 196	(78.1)	2 126	(80.2)	0.28
≥ 80 years	401	(75.7)	429	(76.9)	0.54	2 690	(75.4)	2 442	(76.5)	0.52
ACE/AII receptor inhibitors										
< 50 years	48	(49.0)	290	(55.2)	0.46	64	(32.5)	258	(38.1)	0.15
50–59 years	133	(63.6)	637	(58.2)	0.29	193	(40.0)	749	(44.3)	0.16
60–69 years	239	(58.7)	837	(64.5)	0.08	486	(47.1)	1 458	(53.4)	0.002
70–79 years	240	(59.1)	507	(62.8)	0.19	825	(53.9)	1 585	(59.8)	< 0.001
≥ 80 years	292	(55.1)	311	(55.7)	0.60	1 769	(49.6)	1 535	(48.1)	0.42

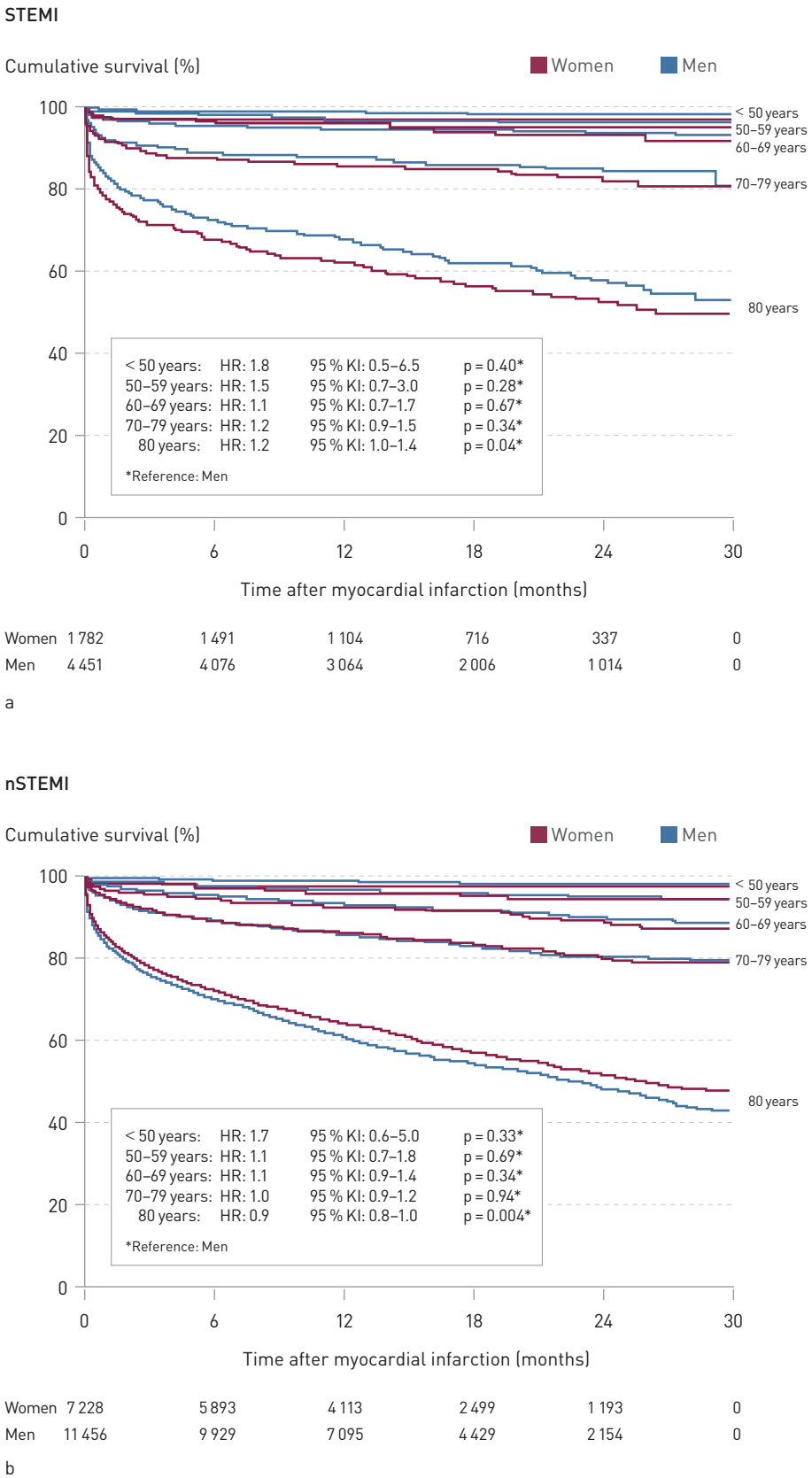

Figure 2 *a, b Cumulative survival following myocardial infarction in patients admitted to Norwegian hospitals in 2013–2014*

than men with non-STEMI underwent angiography (Fig. 1). There was still a gender difference when infarction types 2–5 were excluded from the analysis, and also after adjustment for age within each age group (data not shown).

There was no gender difference for STEMI in patients under the age of 80. For both STEMI and non-STEMI, fewer women than men were found by coronary angiography to have significant coronary stenosis, but the difference was numerically much larger for non-STEMI. For patients found to have significant coronary stenosis, there was no gender difference in the percentage who had percutaneous coronary intervention (PCI), with the exception of a somewhat lower percentage of women aged < 50 with STEMI. There was no difference for most age groups in the time delay from hospitalisation to revascularisation (Table 2).

The use of secondary prophylactics such as platelet inhibitors (acetylsalicylic acid and adenosine diphosphate receptor inhibitors (ADP receptor inhibitors)), betablockers, renin-angiotensin system inhibitors (angiotensin convertase inhibitors (ACE inhibitors))/angiotensin II receptor inhibitors (AII receptor inhibitors)) and statins in patients discharged alive is presented in Table 3. Fewer women than men with non-STEMI were discharged with secondary prophylactics, particularly statins. Similar findings were obtained when type 1 myocardial infarction was analysed separately (Table 4). There were no gender differences in the use of anticoagulants on discharge (data not shown).

Complications

Heart failure was the most frequent complication of myocardial infarction and was most common in the oldest patients (Table 5). Somewhat more men than women experienced ventricular fibrillation/tachycardia the first two days after the infarction. Apart from this, there were limited gender differences in the incidence of complications after myocardial infarction.

Survival

Cumulative survival after STEMI and non-STEMI in women and men in various age groups is presented in Figure 2. The median follow-up time was 443 days (lower quartile 244, upper quartile 662). There were no significant differences in survival between women and men aged < 80.

Women aged ≥ 80 had higher survival than men for non-STEMI (unadjusted HR 0.9, 95 % CI 0.8–1.0, p = 0.004; age-adjusted HR 0.8, 95 % CI 0.8–0.9, p < 0.001). For STEMI there was also a gender difference in survival in the age group ≥ 80, but

after age-adjustment there was no longer a difference (age-adjusted HR 1.0, 95 % CI 0.9–1.2, p = 0.79).

Discussion

This study of gender differences in the assessment, treatment, complications and survival of patients with myocardial infarction treated at all Norwegian hospitals in the period 2013–2014 shows that coronary angiography was carried out on fewer women than men, but when coronary stenosis was found, PCI was performed to virtually the same extent on both genders. In non-STEMI cases in particular, women were discharged from hospital with fewer secondary prophylactic drugs than men. There were few differences between men and women in the incidence of complications or in survival.

The international guidelines for treatment of myocardial infarction (24–26) recommend early coronary angiography for all patients with myocardial infarction. Nonetheless, this study shows that many patients, particularly those with non-STEMI, were not offered this assessment, and consequently did not have the option of PCI. This applied to more women than men. These national data from 2013 and 2014 reflect the findings described from Ullevål Hospital in the period 2006–2007 (22) and of Melberg et al. in 2005 (23). Similar gender discrepancies have also been published recently in a country-wide French registry study (12).

The value of invasive assessment and treatment is not as well documented for women as for men (31, 32), and this may have a bearing on the choice of treatment strategy. Greater comorbidity in women may also help to explain some of the gender differences. We did not investigate in this study whether there were differences at hospital level – different local therapy traditions may also have been of significance. It has previously been shown that more patients with myocardial infarction were invasively assessed if they were admitted to a hospital where there was the option of coronary angiography (23).

The differences cannot be explained by dissimilarities in symptoms and clinical findings in connection with suspected myocardial infarction in women and men, as only patients with the diagnosis myocardial infarction were registered in the Norwegian Myocardial Infarction Registry and hence included in this study. We find reason to stress that the guidelines of the European Society of Cardiology, which it is recommended be used in Norway, do not distinguish between women and men in their recommendations for invasive assessment and treatment of myocardial infarction (24–26).

Secondary prophylactic drugs such as acetylsalicylic acid, ADP receptor inhibitors and statins are important for preventing reinfarction and further atherosclerosis development and are recommended for all patients after myocardial infarction (24–26). The reason that some patients, particularly women with non-STEMI, still did not receive these drugs on discharge from hospital is not clear. Less use of dual platelet inhibition may be due to a lower percentage of PCI in women, but the guidelines recommend dual platelet inhibition whether PCI is carried out or not. Higher comorbidity in women, and consequently a greater risk of complications and drug side effects, may also have been of significance, particularly in connection with the oldest patients.

Most earlier studies do not show any difference in survival among women compared with men in different age groups after myocardial infarction, but some studies have shown lower survival after myocardial infarction in women, particularly in STEMI cases (15–21, 33, 34). A high level of invasive assessment and treatment, also for women with STEMI, may have contributed to our not finding similar gender differences in this study.

There are some limitations associated with the Norwegian Myocardial Infarction Registry and this data analysis. Only myocardial infarction that led to hospitalisation was registered. We did not have an overview of cases of myocardial infarction that did not lead to hospitalisation, or of patients who died due to myocardial infarction outside hospital. A few hospitals did not deliver complete data for the whole period. All hospitals were requested to ensure that all cases were registered via special patient administration systems, but the Norwegian Myocardial Infarction Registry was not able to check this at local level. However, the coverage compared with the Norwegian Patient Register is good. Data on the same patient from more than one hospital were linked up in the register. This led to a certain degree of uncertainty, particularly in cases of different registration of the same variable.

This country-wide study, based on reporting to the Norwegian Myocardial Infarction Registry of myocardial infarctions in Norway in 2013–2014, shows that there were few differences in invasive treatment, complications and survival between women and men with myocardial infarction, but that women were less often assessed with coronary angiography than men, and less often recommended secondary prophylactic medication.

The Norwegian Myocardial Infarction Registry wishes to contribute to improving the treatment of myocardial infarction in Norway. By identifying differences between Norwegian practice and accepted treatment recommendations, it is our hope to contribute to equal and good treatment of all patients with myocardial infarction.

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