Optimization of care for ST-elevation myocardial infarction

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CHAPTER 5

Prognosis of elderly patients suffering ST-elevation myocardial infarction during 2001-2011: a report from the SCAAR registry

Submitted

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Abstract

Background: Elderly patients constitute a growing part of the population presenting with ST-elevation myocardial infarction (STEMI). The use of primary percutaneous coronary intervention (PCI) in this high-risk population remains poorly investigated.

Methods: Using the SCAAR registry, we identified consecutive elderly STEMI patients (aged≥80 years) undergoing primary PCI during a 10-year period. Temporal trends in care and 1-year prognosis were investigated and long term outcome was compared to a control group of PCI treated patients aged 70-79 years. Relative survival was calculated by dividing the observed survival rate with the expected survival rate of the general population. Adjusted endpoints were calculated using Cox regression.

Results: In total, 4876 elderly STEMI patients were included. During the study period, average age and presence of comorbidity increased, as well as the use of antithrombotic therapy. Procedural success remained constant. One-year mortality was exclusively reduced between the most recent versus the earliest cohort, while the risk of re-infarction, heart failure, stroke and bleeding remained similar. The risk of death was higher for elderly patients early after PCI, after which the prognosis was slightly better compared to the general population. Long term risk of adverse events increased markedly with age.

Conclusions: The prognosis of patients over 80 years of age treated with PCI for STEMI was relatively unchanged during the study period, despite changes in patient characteristics and treatment. Advanced age increased the risk of adverse events, but survivors of the early phase after primary PCI had a slightly improved prognosis compared to the general population.

Introduction

The average age of patients presenting with an acute coronary syndrome is rising as a consequence of the aging populations in the Western world.[1-2] The increasing burden of elderly patients on health care resources stresses the need for research focused specifically on this part of the population. Nevertheless, elderly patients are underrepresented in clinical trials.[3] It is known that elderly patients presenting with ST-elevation myocardial infarction (STEMI) are less likely to receive revascularization compared to younger patients and that average delay to treatment is longer when referred for revascularization.[4-5] Over the recent years, the use of primary percutaneous coronary intervention (PCI) and other evidence-based treatments in elderly patients have been increasing and improvements in outcome have been reported.[6-8] However, most studies focused exclusively on survival and little is known about the long term results of primary PCI in these patients.

In the present population-based cohort study we sought to investigate temporal changes in presentation, treatment and prognosis of octogenarians and nonagenarians treated with PCI for STEMI over a 10 year period.

Methods

Objectives and endpoints

Our objective was to investigate temporal trends in patient and treatment characteristics, as well as changes in 1-year all-cause mortality, re-infarction, heart failure admissions, stroke and bleeding over a 10 year period in patients over 80 years of age. Long term outcome rates of the elderly population (stratified according to ages 80-89 and >90 years) were compared to a control group of patients aged 70-79 years. Additionally, survival of the elderly population was compared to the general population and driving factors of safety endpoints, i.e. stroke and bleeding, were investigated.

Patient selection

All consecutive patients over 80 years of age undergoing primary PCI for STEMI in Sweden between January 1st 2001 and December 31st 2010 were identified through the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Analyses were based on first recorded invasive coronary procedure during the inclusion period to avoid duplicate entries. In addition, a control group of patients aged 70-79 years was identified using identical criteria. Primary PCI was defined as any use of a guidewire for more than diagnostic purposes in patients with STEMI or a new left bundle branch block and suspicion of ongoing ischemia. Patients without a Swedish personal identification number were excluded.

SCAAR is a Swedish nationwide registry for angiography and PCI and is a part of the SWEDEHEART registry, which also enrolls patients hospitalized in coronary care units and those undergoing cardiac surgery in the country.[9] Data in SCAAR are collected prospectively and are audited and monitored as previously described.[10] Vital status and date of death were obtained from the Swedish National Population Register until December 31st 2010. Information on previous medical history and patient follow-up were obtained from the National Inpatient Register, which holds information on discharge diagnoses of all hospitalizations in Sweden according to ICD (International Classification of Diseases) code.[11] In-hospital major bleeding was obtained from SCAAR and was defined as any bleeding associated with a hemoglobin drop of ≥5 g/dl or intracranial bleeding.

Merging of SCAAR with the national databases was performed by the Epidemiologic Center of the Swedish National Board of Health and Welfare using Swedish personal identification numbers. The merging was approved by the ethics committee of Uppsala University and the study complied with the Declaration of Helsinki. The SCAAR registry is sponsored by the Swedish Health Authorities and is independent of commercial funding.

Statistical analyses

Elderly patients were divided into cohorts according to year of PCI; 2001-2004, 2005-2006, 2007-2008 and 2009-2010. Patient grouping was based on comparability of group size and a median follow-up of 1 year. The years 2001 to 2004 were grouped together due to the relatively smaller numbers of patients treated in those years. Categorical variables are presented as frequency values and proportions. Continuous variables are presented as mean ± standard deviation or median and interquartile range where appropriate. Cox proportional hazards analyses were used to adjust for confounders. The log minus log test was evaluated to test the proportional hazard assumption. The multivariable models that corrected for patient characteristics incorporated the following variables: age, gender, diabetes mellitus, hypertension, hyperlipidemia, smoking, prior myocardial infarction, prior coronary artery bypass grafting, peripheral vascular disease, previous kidney failure, previous stroke, cancer in the last 3 years, number of vessel disease and hospital of PCI. Subsequently, multivariable correction was performed for treatment characteristics, adding the following variables to the patient characteristics model: stenting technique and type, aspirin use before/during PCI, P2Y12 receptor inhibitor use before/during PCI, glycoprotein IIb/IIIa inhibitor use before/during PCI and thrombolysis prior to PCI. Effect sizes were reported as hazard ratios (HR) with 95% confidence interval (CI).

Long term cumulative incidences of outcome were compared using Kaplan Meier curves and log rank tests. To investigate an excess of mortality in the elderly STEMI population after primary PCI, interval specific relative survival rates were calculated using intervals 0-0.05, 0.05-0.2, 0.2-0.5, 0.5-1, 1-2, 2-3 and 3-4 years. Relative

survival was measured as the absolute survival rate of the elderly STEMI population divided by the expected survival rate in the year of intervention from the general population with identical gender and age. Age, gender and intervention year mortality estimates of the general population were obtained from life tables of Statistics Sweden. Finally, forward stepwise Cox proportional hazard models were performed to identify factors associated with stroke and bleeding at 1-year, with a p-value for inclusion of <0.05. Calculations were performed using SPSS version 20 (IBM corporation, Armonk, NY, USA). STATA 12 (Statacorp LP, College Station, TX, USA) was used for the relative survival analysis.

Table 1. Baseline characteristics

	2001-2004 (N=814)	**2005-2006** (N=1222)	**2007-2008** (N=1427)	**2009-2010** (N=1413)	**p for trend**
Age, mean years ± SD	83.1 ± 2.7	83.7 ± 3.1	84.0 ± 3.2	84.0 ± 3.3	<0.001
Age ≥90 years	23 (2.8)	61 (5.0)	92 (6.4)	98 (6.9)	<0.001
Male gender	449 (55.2)	641 (52.5)	720 (50.5)	716 (50.7)	0.130
Diabetes mellitus	114 (14.3)	170 (13.9)	187 (13.1)	205 (14.5)	0.813
Hypertension	291 (36.1)	514 (42.1)	628 (44.0)	746 (52.8)	<0.001
Hyperlipidemia	91 (11.7)	138 (11.3)	192 (13.5)	243 (17.2)	<0.001
Current smoker	53 (6.6)	76 (6.2)	94 (6.6)	102 (7.2)	0.775
History of					
Myocardial infarction	189 (23.4)	222 (18.2)	190 (13.3)	189 (13.4)	<0.001
Coronary artery bypass grafting	17 (2.1)	28 (2.3)	37 (2.6)	41 (2.9)	0.010
Peripheral vascular disease	38 (4.7)	51 (4.2)	53 (3.7)	60 (4.2)	0.737
Stroke	99 (12.2)	182 (14.9)	184 (12.9)	180 (12.7)	0.241
Kidney failure	9 (1.1)	17 (1.4)	29 (2.0)	42 (3.0)	0.006
Cancer in the last 3 years	31 (3.8)	45 (3.7)	47 (3.3)	70 (5.0)	0.131
Onset symptoms to PCI, median min (IQR)	317 (169-865)	255 (163-485)	230 (148-451)	235 (145-450)	0.003
First ECG to PCI, median min (IQR)	82 (37-173)	84 (50-148)	77 (49-131)	78 (50-120)	0.074
Follow-up duration, median years (IQR)	7.1 (6.4-8.2)	4.9 (4.4-5.4)	2.9 (2.5-3.4)	1.0 (0.5-1.5)	-

Results

During the study period, 5471 patients over 80 years of age underwent primary PCI for STEMI. After exclusion of duplicate procedures, a total of 4876 patients remained. Baseline characteristics are shown in Table 1. Within this group, the average age increased gradually over time and so did the proportion of patients of very advanced age. The ratio of male to female patients was the same during the study period. Hypertension, hyperlipidemia, prior coronary artery bypass grafting and a

history of kidney failure were more common over time, while the percentage of patients with prior myocardial infarctions declined. A reduction in time from symptom onset to PCI was observed between the earliest and the later cohorts. Additionally, presence of cardiogenic shock decreased over time.

Procedural characteristics showed a pronounced increase in the use of the radial approach during PCI (Table 2). The total rate of stenting was stable over time, although stent type varied. Procedural success was similar over the years and was over 90% for all cohorts. The use of antithrombotic therapy increased while glycoprotein IIb/IIIa inhibitor treatment was common in the earlier years but gradually decreased and bivalirudin use increased.

Table 2. Angiographic and procedural characteristics

	2001-2004 (N=814)	**2005-2006** (N=1222)	**2007-2008** (N=1427)	**2009-2010** (N=1413)	**p for trend**
Vascular access					<0.001
Femoral access	610 (94.3)	1056 (86.4)	1103 (77.3)	820 (58.1)	
Radial access	37 (5.7)	163 (13.3)	320 (22.4)	588 (41.6)	
Angiographic findings					<0.001
Single vessel disease	274 (37.4)	393 (32.8)	533 (37.4)	512 (36.3)	
Dual vessel disease	192 (26.2)	346 (28.9)	403 (28.2)	405 (28.7)	
Triple vessel disease	185 (25.2)	341 (28.4)	369 (25.9)	343 (24.3)	
Left main disease	80 (10.9)	109 (9.1)	104 (7.3)	114 (8.1)	
Treatment technique					<0.001
Balloon angioplasty	80 (9.9)	116 (9.5)	175 (12.3)	169 (12.0)	
Bare-metal stenting	650 (80.0)	816 (66.7)	1175 (82.5)	1106 (78.4)	
Drug-eluting stenting	82 (10.1)	290 (23.8)	74 (5.2)	135 (9.6)	
Stent length, mean mm ± SD	17.1 ± 6.1	18.0 ± 6.2	17.6 ± 5.8	17.8 ± 5.8	0.003
Stent diameter, mean mm ± SD	3.1 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	0.041
Procedural success	725 (92.6)	1110 (91.0)	1303 (91.5)	1287 (91.4)	0.651
Medication					
Any anti-thrombotic treatment before PCI	505 (62.7)	1054 (87.5)	1227 (86.2)	1235 (87.7)	<0.001
Aspirin before PCI	482 (59.4)	1015 (83.2)	1152 (80.9)	1167 (82.9)	<0.001
P2Y12 inhibitor before PCI	192 (23.8)	636 (52.3)	956 (67.1)	1030 (73.2)	<0.001
GPIIb/IIIa inhibitor before PCI	42 (5.2)	113 (9.3)	108 (7.6)	42 (3.0)	<0.001
GPIIb/IIIa inhibitor during PCI	400 (49.3)	657 (53.8)	570 (40.0)	334 (23.7)	<0.001
Bivalirudin during PCI	-	166 (15.7)	485 (34.1)	779 (55.3)	<0.001
Thrombolysis before PCI	95 (11.8)	43 (3.6)	17 (1.2)	17 (1.2)	<0.001

In the beginning of the study period, slightly more than 10% of patients received thrombolysis prior to PCI, compared to marginal numbers of patients in later years.

Temporal trends in outcome

Stratification of outcome according to year of treatment in general showed similar rates of 1-year mortality (Table 3). The only statistically significant difference

Table 3. Trends in 1-year clinical outcome over time

	2001-2004 (N=814)	2005-2006 (N=1222)	2007-2008 (N=1427)	2009-2010 (N=1413)
Mortality				
Any event	213 (26.4)	308 (25.2)	346 (24.3)	302 (23.1)
Age-adjusted, HR (95% CI)	1.25 (1.04-1.49)	1.12 (0.96-1.32)	1.05 (0.90-1.22)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.12 (0.93-1.36)	1.11 (0.95-1.31)	1.09 (0.93-1.27)	″
Treatment-adjusted, HR (95% CI)†	1.00 (0.81-1.23)	1.12 (0.94-1.33)	1.06 (0.90-1.24)	″
Myocardial infarction				
Any event	102 (15.4)	149 (14.8)	182 (15.1)	145 (13.4)
Age-adjusted, HR (95% CI)	1.13 (0.87-1.45)	1.06 (0.85-1.34)	1.09 (0.88-1.36)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.12 (0.85-1.47)	1.04 (0.83-1.32)	1.12 (0.90-1.40)	″
Treatment-adjusted, HR (95% CI)†	1.08 (0.81-1.45)	1.12 (0.88-1.44)	1.14 (0.91-1.42)	″
Heart failure admission				
Any event	141 (21.6)	203 (20.3)	255 (21.2)	190 (18.2)
Age-adjusted, HR (95% CI)	1.20 (0.97-1.50)	1.11 (0.91-1.36)	1.17 (0.97-1.41)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.14 (0.90-1.45)	1.12 (0.91-1.37)	1.20 (0.99-1.45)	″
Treatment-adjusted, HR (95% CI)†	1.15 (0.89-1.47)	1.15 (0.93-1.42)	1.21 (1.00-1.47)	″
Stroke				
Any event	27 (4.2)	50 (5.1)	65 (5.5)	40 (4.5)
Age-adjusted, HR (95% CI)	1.02 (0.62-1.66)	1.21 (0.79-1.83)	1.30 (0.88-1.93)	Reference
Comorbidity-adjusted, HR (95% CI)*	1.17 (0.70-1.96)	1.27 (0.83-1.94)	1.38 (0.93-2.06)	″
Treatment-adjusted, HR (95% CI)†	1.18 (0.69-2.03)	1.35 (0.86-2.11)	1.40 (0.94-2.10)	″
Bleeding, post-discharge				
Any event	30 (4.7)	58 (5.9)	59 (5.0)	51 (5.2)
Age-adjusted, HR (95% CI)	0.91 (0.58-1.43)	1.14 (0.78-1.65)	0.96 (0.66-1.40)	Reference
Comorbidity-adjusted, HR (95% CI)*	0.95 (0.59-1.53)	1.16 (0.79-1.70)	0.98 (0.67-1.44)	″
Treatment-adjusted, HR (95% CI)†	0.88 (0.53-1.46)	1.18 (0.78-1.78)	1.01 (0.69-1.48)	″

* Adjusted for: Age, gender, DM, hypertension, hyperlipidemia, smoking, prior MI, prior CABG, peripheral vascular disease, previous kidney failure, previous stroke, cancer, number of vessel disease, hospital.

† Adjusted for characteristics under * and stenting technique and type, aspirin before/under PCI, P2Y12 before/under PCI, GPI before/under PCI, thrombolysis.

in mortality was observed between the earliest and the most recent cohorts, which was eliminated after correction for comorbidity and treatment factors. Re-infarction and heart failure admissions did not change over time. Additionally, post-discharge stroke and bleeding rates remained stable. In-hospital major bleeding was rare (1.5% in 2001-2004, 0.7% in 2005-2006, 0.1% in 2007-2008 and 0.1% in 2009-2010) and adjusted in-hospital bleeding rates were not calculated due to the low number of events.

Long term results

Long term outcome was stratified according to age: 4593 patients were aged 80-89 years (mean 83.3 ± 2.6 years) and 274 patients were older than 90 years (mean 91.3 ± 1.7 years). The control group consisted of 8169 PCI treated patients aged 70-79 years (mean 74.4 ± 2.8 years). An approximate doubling of mortality risk per decade increase in age was observed (Figure 1). Mortality early after PCI explained a major part of the differences between the age groups, although curves continued to diverge during follow-up.

Relative survival analyses showed a lower survival of elderly STEMI patients compared to the general population in the first few months after PCI (Figure 2). After this early period, survival was slightly higher compared to the general population up to 3-years.

Compared to patients aged 70-79 years, the risks of a new myocardial infarction or heart failure were higher for patients over 80 years of age during follow-up (Figure 3A and 3B). Moreover, stroke rates were higher in patients over 80 years compared to those aged 70-79 years, with an early peak in stroke in the population above 90 years (Figure 4A). During the first year after PCI, stroke rates were 2.8%, 4.8% and 6.9% for patients aged 70-79 years, 80-89 years and more than 90 years, respectively. In the patients aged 80 years and above, a previous history of stroke was the sole predictor of another stroke during the first year of follow-up (HR 2.38, 95% CI 1.69-3.35).

Bleeding was more common in patients over 80 years of age (Figure 4B). During the first year after PCI, bleeding rates were 3.9%, 5.3% and 4.6% for patients aged 70-79 years, 80-89 years and more than 90 years, respectively. Multivariable analyses showed that male gender (HR 1.70, 95% CI 1.27-2.29); a history of peripheral vascular disease (HR 2.11, 95% CI 1.22-3.64) and cancer in the last 3 years (HR 1.99, 95% CI 1.17-3.38) were associated with bleeding during the first year of follow-up in patients aged 80 years or higher.

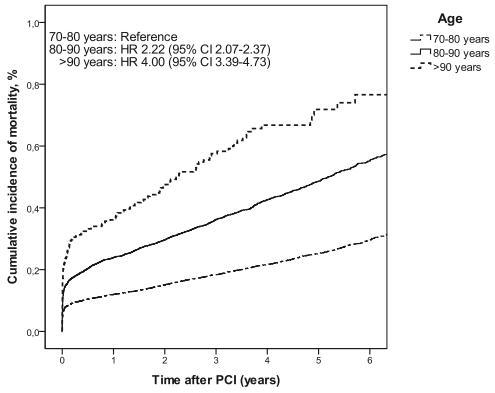

Figure 1. Long term mortality during follow-up.

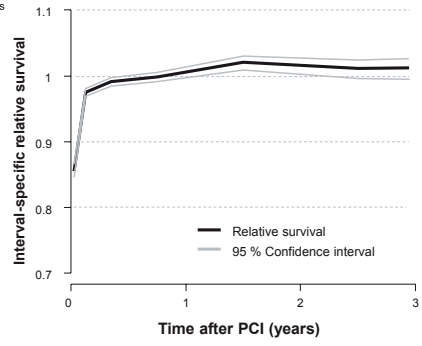

Figure 2. Relative survival of the elderly STEMI population (≥80 years) compared to the general population during 3-year follow-up.

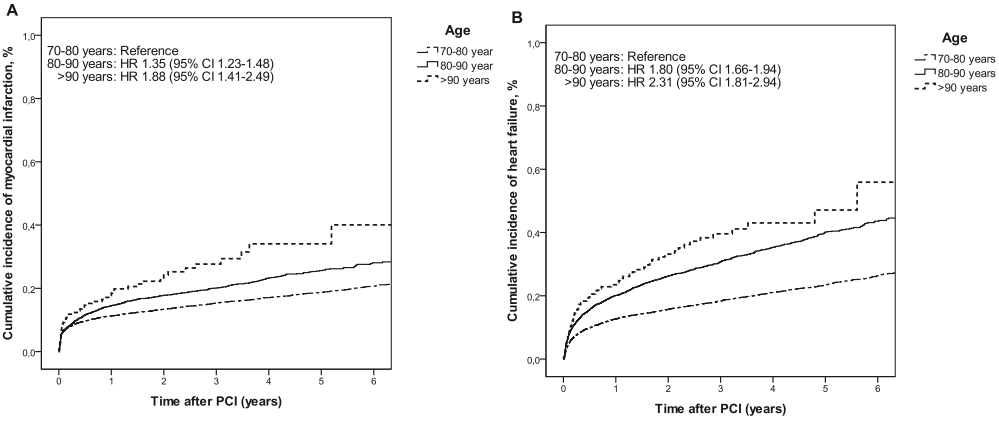

Figure 3: (A) Myocardial infarction and (**B**) heart failure during long term follow-up.

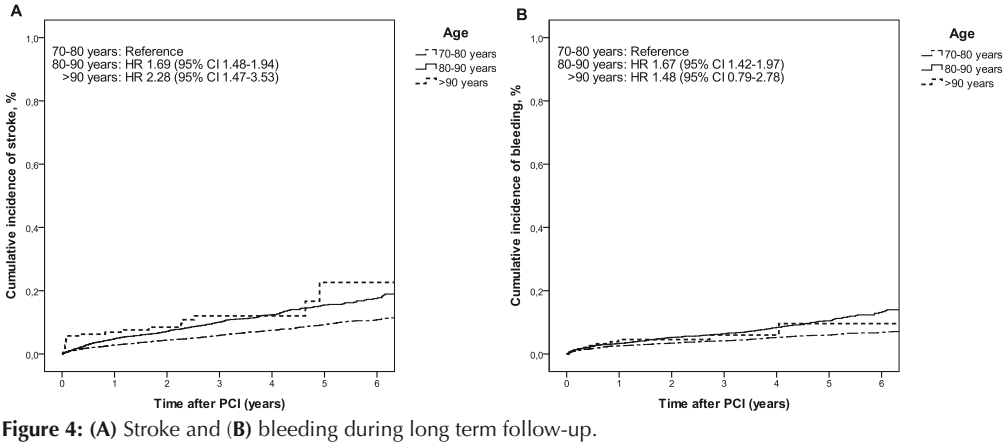

Figure 4: (A) Stroke and (**B**) bleeding during long term follow-up.

Discussion

Our main findings were that patients with STEMI over the age of 80 years treated with primary PCI during the 10-year inclusion period of the present population-based cohort study generally showed a similar prognosis over time, despite changes in patient and treatment characteristics. Importantly, elderly STEMI patients showed a similar and even slightly improved long term survival after the early phase from PCI compared to the general population. Nonetheless, the long term risk of adverse events increased with age, stressing the importance of appropriate risk stratification in older patients.

Elderly patients constitute a growing part of the population presenting with STEMI and the use of invasive and antithrombotic therapy is increasing in these patients.[2,6] However, the impact of these developments on the prognosis remains unclear. In the present study, the average age in the group of patients over 80 years of age rose gradually over time and the proportion of nonagenarians more than doubled. The increase in age was associated with higher comorbidity, although a sharp decline in prior myocardial infarctions was seen. The 1-year prognosis of elderly patients suffering an STEMI was relatively unchanged, with the exception of a significant difference in mortality between the earliest and the most recent cohorts. Thus, the temporal improvements in mortality were smaller than other reports.[4,6,8] However, the survival benefit reported in these previous studies was largely driven by the increased appliance of PCI, whereas the population in our study consisted exclusively of invasively treated patients.

During the study period, the occurrence of cardiogenic shock was observed to decrease, which may have been related to both decreases in prior myocardial infarctions and improving symptom to PCI times. The overall use of antithrombotic medication during and after PCI increased, and adjunctive treatment shifted gradually from glycoprotein IIb/IIIa inhibitor use to bivalirudin. The shift toward bivalirudin, increased radial access and decreased use of thrombolysis could probably explain the decrease in in-hospital major bleedings.[12,13] Interestingly, the rates of radial approach were markedly higher compared to other reports, suggesting a high level of comfort with radial access among Swedish operators.[14] Bleeding and stroke rates after discharge did not change over times. Whether this indicates a relatively similar dual antiplatelet strategy over the years is unclear, as data on dual antiplatelet therapy compliance were not available.

During long term follow-up, a strong association between advanced age and the occurrence of adverse events was observed. However, the relative survival analysis indicated that long term prognosis was comparable and even slightly improved in patients over 80 years of age compared to the expected survival rate of the general population (based on age, gender and year of birth), although survival was reduced in the first few months after primary PCI. Survival rates in our investigation were similar to a recent Danish study, but our study showed a slightly higher mortality of

nonagenarians.[15] The higher rates of a new myocardial infarction and heart failure in old patients are generally explained by more extensive coronary artery disease and comorbidity with age.[16,17]

Stroke rates diverged early after PCI and remained increased in patients over 80 years of age compared to patients 70-79 years of age during long term follow-up. The early peak in stroke in nonagenarians suggested a possible procedure related association. Patients with a previous stroke were found to be at risk a new stroke, an observation that may help to tailor therapy in these patients.[18] Bleeding during long term follow-up was doubled in patients aged 80-89 years compared to those aged 70-79 years. Reassuringly, bleedings were rare in patients during the first year after PCI. Risk factors of bleeding in elderly patients with STEMI during the first year after PCI included a history of peripheral vascular disease, potentially explained by the increased use of anticoagulants in these patients, and concomitant cancer.[19] The etiology of bleeding in cancer patients is multifactorial, including abnormalities in platelet number and function due to cancer treatment, need for invasive procedures and use of anticoagulants for prevention of deep venous thromboembolism.[20] Male gender also predicted bleeding events, which contrasts with the commonly reported observation that women have a higher risk of bleeding after PCI.[21] The higher bleeding risk possibly reflected a generally worse state of health of male patients in the elderly population.[22]

Limitations

The current study was observational and thus shares the limitations of all observational analyses. Nevertheless, registry studies remain important to study clinical outcomes and practices in populations underrepresented in clinical trials. The current study only included elderly patients treated with PCI, which limits the generalizability of our results to invasively treated patients. Additionally, in-hospital bleeding was not based on ICD codes. Although in-hospital registration may have varied during the observation period, registration rates generally improved over time and therefore the higher rates of bleeding in the earlier cohorts are unlikely to be influenced by this. Furthermore, 1-year follow-up was not available for patients treated in 2010, potentially influencing the comparison between the cohorts. However, a sensitivity analysis showed similar findings after exclusion of patients treated in the year 2010.

Conclusions

In this large population-based study of elderly patients with STEMI, we found a generally unchanged prognosis over a 10-year time period, despite changes in patient characteristics and medical treatment. Although higher age was associated with increased risk of adverse events, elderly patients surviving the early phase after primary PCI showed a similar and even slightly improved relative survival compared

the general population, supporting the use of primary PCI in these high-risk patients.

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