Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction

PhD dissertation

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Preface

This PhD thesis is the outcome of the research that I conducted during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, and the Department of Internal Medicine, Herning Hospital.

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2. Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, Jensen LO, Thayssen P, Ravkilde J, Tilsted HH, Mehnert F, Johnsen SP. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. Accepted in EuroIntervention, June 2012.

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Contents

1. Introduction

1.1. Epidemiology of acute myocardial infarction

Ischemic heart disease continues to be a significant health problem worldwide. According to the World Health Organization, ischemic heart disease is the leading cause of death globally, with an estimated 7.2 million deaths in 2004, corresponding to 12.2% of all deaths[1]. More than 7 million people each year have an acute myocardial infarction (MI), which is classified into two categories: ST-elevation MI (STEMI) and non–ST-elevation MI (NSTEMI)[2]. In Denmark, approximately 10,000 people had an MI in 2005, of whom 6300 were men and 3700 were women[3]. Among men, approximately 23% die before hospital admission, and among men admitted to the hospital, 24% die within 1 year. The corresponding numbers for women are 27% and 31%, respectively[4].

1.2. Definition of acute myocardial infarction

The term "myocardial infarction" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI[5]:

A. Detection of rise and/or fall of troponins with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block)
- Development of pathological Q waves

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

B. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, new left bundle branch block, or evidence of fresh thrombus by coronary angiography or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of troponins in the blood.

C. For percutaneous coronary intervention (PCI), increases in biomarkers greater than 3×99th percentile upper reference limit. A subtype is related to a stent thrombosis.

D. For coronary artery bypass grafting, biomarker increases greater than 5×99th percentile upper reference limit plus either new Q waves or new left bundle branch block, or documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium.

E. Pathological findings of an acute MI.

Based on ECG findings, acute MI is divided into STEMI and NSTEMI. This division has important implications because of different treatment strategies.

A. STEMI:

New ST elevation at the J-point in two contiguous leads with the following cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads

B. NSTEMI (ST depression and T-wave changes): New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

1.3. Treatment of ST-elevation myocardial infarction

The treatment of STEMI consists of rapid revascularization of the infarct-related coronary artery either by thrombolysis or by primary PCI (PPCI), antiplatelet and antithrombotic therapies to reduce the risk of recurrent ischemic events, treatments aimed at reducing the effect of myocardial necrosis, and secondary medical prevention to prevent future events.

1.3.1. Revascularization

The first treatment used for revascularization—that is, restoring the epicardial and microvascular blood flow to the myocardium—was pharmacological thrombolysis. Several randomised controlled trials (RCTs) conducted during the 1980s have shown this treatment to improve outcome after STEMI compared to no revascularization[6;7]. Thrombolysis is still widely used in most countries.

PPCI can be defined as balloon angioplasty used as the primary revascularization strategy for STEMI without previous or concomitant thrombolysis. During the 1990s, numerous studies compared immediate PPCI to thrombolysis. These studies showed that PPCI results in lower rates of death, non-fatal reinfarction, and stroke compared to thrombolysis[8-19]. These results were found in low-risk patients[10], high-risk patients[15], and elderly patients[17] and persisted up to 5 years[18]. A few studies found no difference in outcome between the two treatment modalities[20;21].

However, most STEMI patients are admitted to hospitals without angioplasty facilities where immediate PPCI is not an option. The prognosis after PPCI depends on the time from symptom onset to first balloon inflation and on the time from hospital arrival to first balloon

inflation (door-to-balloon time), with a longer duration of time associated with poor outcome[22-25]. Thus, the beneficial effect of PPCI compared to thrombolysis might be attenuated if STEMI patients are admitted to hospitals without on-site angioplasty facilities and transportation to an invasive-treatment hospital is necessary. A number of studies have compared transfer to an invasive-treatment hospital for PPCI to on-site thrombolysis. All of these studies found transfer to be feasible and safe, and they also reported better outcome after transfer for PPCI compared to thrombolysis[26-31]. These results also seem to apply to high-risk patients[29] and are sustained during long-term follow-up[32;33].

One of these studies was the Danish trial in Acute Myocardial Infarction-2 (DANAMI-2)[26]. In this trial, 1572 patients with STEMI were randomised to be treated with PPCI or thrombolysis. A total of 443 patients were enrolled at an invasive-treatment hospital, and 1129 patients were enrolled at referral hospitals with no on-site angioplasty facilities. Of these 1129 patients, the 567 patients assigned to PPCI had to be transferred for it. The primary study endpoint was a composite of death, reinfarction, and stroke at 30 days. Among the patients randomised at referral hospitals, the endpoint was reached in 8.5% in the PPCI group compared to 14.2% in the thrombolysis group (P=0.002). The corresponding numbers for patients enrolled at the invasive-treatment hospitals were 6.7% and 12.3% (P=0.05). Both for patients randomised at referral hospitals and invasive-treatment hospitals, the rate of reinfarction drove the difference in the composite endpoint, whereas no differences were found in the rate of death and stroke. Of the patients transferred for PPCI, 96% were transferred within 2 hours.

The benefit of PPCI over thrombolysis depends on the length of the delay caused by PPCI. It has been suggested that the benefit is lost with a PPCI-related delay between 60 minutes and 114 minutes[34;35]. Thus, current European and U.S. guidelines recommend PPCI as the preferred treatment for STEMI if time from first medical contact to balloon inflation is 2 hours or less[36] and 90 minutes or less[37], respectively.

In the beginning of the PPCI era, balloon angioplasty without stenting was performed. Angioplasty with stenting improves the prognosis, mainly because of lower rates of target vessel/lesion revascularization (TVR/TLR) and reinfarction[38]. First, bare metal stents (BMS) were used, but after the invention of drug-eluting stents (DES), these latter stents have been used with increasing frequency. Several studies comparing BMS to DES in STEMI patients have found that DES was associated with a better prognosis[39;40]. Again, the better prognosis was explained by lower rates of TVR and TLR, but no difference in mortality was found. However, restenosis has been associated with an increased risk of MI and death[41].

1.3.2. Antiplatelet and antithrombotic treatment

Antithrombotic treatment, including antiplatelet drugs, is an essential adjunctive medical therapy to PPCI. Since the early thrombolysis studies[42], aspirin has been an important part of STEMI treatment that reduces mortality and the rate of reinfarction. It remains one of the cornerstones in the treatment of acute MI (AMI)[43]. Clopidogrel is also recommended for STEMI treatment. STEMI patients treated with thrombolysis who received clopidogrel had higher rates of vessel patency compared to patients not receiving clopidogrel, but they did not have lower mortality[44;45]. However, other studies found that adding clopidogrel to aspirin was associated with significantly lower mortality, irrespective of revascularization

status[46;47]. Finally, in patients treated with PPCI, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors are associated with a reduction in death, reinfarction, and revascularization rates[48-52]. Unfractionated heparin is the antithrombotic therapy most commonly used as an adjunctive to PPCI, although limited data support its use[53]. In recent years, new antithrombotic treatments, such as prasugrel, ticagrelor and bivalirudin, have been introduced, and they appear to be superior to the drugs mentioned above [54-57].

1.3.3. Secondary medical prevention

According to current guidelines, STEMI patients treated with PPCI should receive aspirin lifelong and clopidogrel for 12 months[37]. Dual antiplatelet therapy reduces mortality and major cardiovascular events[43;58]. Significant evidence supports the use of statin therapy as secondary prevention after MI. These drugs provide a significant reduction in mortality and in recurrent ischemic events[59]. Long-term treatment with β-blockers is also recommended because of evidence of a mortality benefit from their use[60;61]. Finally, current guidelines recommend that angiotensin converting enzyme (ACE) inhibitors be prescribed at discharge for all patients without contraindications[62].

1.4. Translating randomised controlled trials to everyday clinical settings

PPCI is the preferred treatment for STEMI based on findings from RCTs. After the DANAMI-2 trial, PPCI has been implemented as the standard treatment for STEMI patients in Denmark, and consequently, Danish STEMI patients are almost exclusively treated with PPCI. However, translating RCT results into everyday clinical settings might be problematic. The external validity of an RCT is impaired if participants are not

representative of the target population for the treatment or if the treatment is not comparable to what is offered in everyday clinical settings.

The first issue is common because of strict inclusion and exclusion criteria that result in selected patient populations[63-70]. Traditionally, women and the elderly have been excluded or underrepresented in RCTs that include patients with acute coronary syndrome. Lee et al.[64] found that in RCTs of acute coronary syndromes published from 1991–2000, women made up only 25% of the study population, and patients older than 75 years only 9%, although 43% of patients with MI in the United States are women and 37% are 75 years or older. Similarly, Björklund et al.[67] found that of the STEMI patients admitted to Swedish hospitals participating in the ASSENT-2 trial and treated with thrombolysis, only 26% were included in the trial. The patients excluded from the trial were older and had a more adverse baseline risk profile than the selected patients.

The DANAMI-2 trial also involved a selected patient population. Of the 4278 patients screened for participation, only 1572 were included in the study. The rest were excluded because they did not meet the inclusion criteria, refused to participate, had contraindications to thrombolysis or angiography, and various other reasons[71].

The latter phenomenon of treatment not being representative of everyday practice occurs when patients participating in RCTs receive a different level of treatment compared to non-participants. For example, the time used for inter-hospital transfer has been reported to be longer in real-world settings compared to RCTs. Nallamothu et al.[72] found the median door-to-balloon time to be 180 minutes in real-world patients transferred for PPCI compared to

the 90–120 minutes achieved in RCTs comparing transfer for PPCI to thrombolysis. Only 4.2% of the real-world STEMI patients were treated within the 90 minutes recommended in the current U.S. guidelines. Likewise, Bahit et al.[69] found that patients included in trials comparing different thrombolytics were more likely to receive guideline-recommended medical treatment at discharge compared to patients treated with thrombolysis who were not included in a trial.

Such differences in care may translate into differences in outcomes; this disparity has been observed among STEMI patients treated with thrombolysis in whom the prognosis was better for RCT patients compared to those not included in a trial, even after adjustment for differences in baseline patient characteristics[63;67;69]. Thus, extrapolating results from RCTs to real-life settings might be problematic. It is not clear whether it has been possible to achieve outcomes after PPCI in real-world settings that are comparable to trial results.

This thesis focuses on the outcomes in women, older patients, and patients with low socioeconomic status (SES) treated with PPCI in everyday clinical practice after implementing PPCI as the standard treatment for STEMI in Denmark.

1.5. Sex-related differences in outcome after ST-elevation myocardial infarction

PubMed was searched to identify articles on sex-related differences in treatment and outcome after STEMI and PPCI-treated STEMI using the following search strategy: "Myocardial Infarction"[Mesh] AND "Sex Distribution"[Mesh] OR Sex Factors"[Mesh] AND "Treatment Outcome"[Mesh] AND "Angioplasty, Balloon, Coronary"[Mesh]. The search was limited to include only English-language studies in humans. Additional studies

were found by searching the reference lists from the identified publications. Table 1 shows the relevant studies on sex-related differences in treatment and outcome in STEMI patients and PPCI-treated STEMI patients.

Table 1. Studies on differences in treatment for and outcome after ST-elevation myocardial infarction related to sex					
Author, year, country	N	Study design	Study population	Outcome	Results
Sex-related differences present					
Benamer et al., 2011, France[73]	16,760	Cohort	STEMI. PPCI	In-hospital mortality	Women 9.8%, men 4.3%, P<0.0001 Female sex independent predictor of mortality, Adj. OR 1.38 (1.16–1.63)
Lawesson et al., 2010, Sweden[74]	2132	Cohort	STEMI. PPCI or TT	In-hospital, 1 year, and long-term (1–10 years) mortality	Acute reperfusion: women 78.1%, men 80.5%, P=0.28 PPCI: women 41.4%, men 41.5%, P=0.98 TT: women 44.6%, men 48.4%, P=0.19 In-hospital: Adj. OR 2.85 (1.31–6.19) 1-year: Adj. OR 2.00 (1.03–3.89) Long-term: Adj. OR 0.93 (0.60–1.45)
Berger et al., 2009, USA[75]	136,247	Cohort	STEMI or NSTEMI	30-day mortality	STEMI: women 12.3%, men 5.8%, NSTEMI: women 6.4%, men 4.3%

					STEMI: OR 2.29 (2.18–2.40) NSTEMI: OR 1.50 (1.28–1.75) STEMI: Adj. OR 1.15 (1.06–1.24) NSTEMI: Adj. OR 0.55 (0.43–0.70) Subgroup with angiographic data STEMI: women 4.8%, men 2.3% NSTEMI: women 3.5%, men 2.7% STEMI: OR 2.16 (1.83–2.56) NSTEMI: OR 1.28 (0.94–1.74) STEMI: Adj. OR 1.23 (0.96–1.57) NSTEMI: Adj. OR 0.76 (0.53–1.10)
Champney et al., 2009, USA[76]	361,429	Cohort	STEMI or NSTEMI	In-hospital mortality	STEMI, 50–59 years: Adj. OR 1.22 (1.08–1.38) STEMI, 80–89 years: Adj. OR 1.03 (0.98–1.08)
Pathak et al., 2008, USA[77]	58,308	Cohort	STEMI	PPCI	Men vs. women OR=1.2 (1.1–1.4)

Jneid et al., 2008, USA[78]	78,254	Cohort	STEMI or NSTEMI	Clinical performance measures, invasive procedures, in-hospital death	Aspirin within 24 h: Adj. OR 0.86 (0.81–0.90) β-blockers within 24 h: Adj. OR 0.90 (0.86–0.93) Reperfusion therapy: Adj. OR 0.75 (0.70–0.80) Door-to-needle time <30 min: Adj. OR 0.78 (0.65–0.72) Door-to-balloon time <30 min: Adj. OR 0.87 (0.79–0.95) PPCI: Adj. OR 0.83 (0.78–0.87) In-hospital death (overall): Adj. OR 1.04 (0.99–1.10) In-hospital death (STEMI): Adj. OR 1.12 (1.02–1.23)
Berger et al., 2006, USA[79]	9015	Cohort	STEMI. PPCI	In-hospital mortality	Overall: women 6.7%, men 3.4%, P<0.001 <75 years: women 4.8%, men 2.6%, P<0.001 >75 years: women 11.8%, men 9.7%, P=0.20 Overall: Adj. OR 1.25 (0.98–1.58) <75 years: Adj. OR 1.37 (1.01–1.98) >75 years: Adj. OR 1.00 (0.68–1.49)
Lansky et al.,	2082	Subgroup	STEMI.	In-hospital, 30 days and	In-hospital: women 6.4%, men 3.2%, P=0.002

2005, USA[80]		analysis in RCT	PPCI	1 year MACE (death, reinfarction, TVR, or stroke)	30 days: women 9.5%, men 4.4%, P<0.001 1 year: women 23.9%, men 15.4%, P<0.001 Female sex predictor of 1 year MACE: Adj. OR 1.64 (1.24–2.17)
Vakili et al., 2001, USA[81]	1044	Cohort	STEMI. PPCI	In-hospital mortality	Adj. OR 2.33 (1.2–4.6)
Barron et al., 1998, USA[82]	84,663	Cohort	STEMI. TT or no reperfusion	Reperfusion therapy In-hospital mortality	Reperfusion therapy: Adj. OR 0.88 (0.83–0.92) In-hospital mortality: Adj. OR 1.5 (1.3–1.7)
No sex-related differences after adjustment					
Eitel et al., 2011, Germany[83]	335	Cohort	STEMI. PPCI	Myocardial salvage, in-hospital, 30-day, and 6-month mortality	Myocardial salvage: Female sex not an independent predictor (P=0.63) In-hospital mortality: Crude HR 2.81 (1.09–7.30) Adj. HR 1.93 (0.72–5.30) 30-day mortality: Crude HR 6.21 (1.00–4.86)

					Adj. HR 1.29 (0.52–3.22) 6-month mortality: Crude HR 1.61 (0.76–3.45)
Jackson et al., 2011, USA[84]	8771	Cohort	STEMI. PPCI	In-hospital mortality	Women 6.0%, men 3.5% OR 1.79 (1.45–2.22) Adj. OR 1.30 (0.98–1.72)
Sadowski et al., 2011, Poland[85]	26,035	Cohort	STEMI	PPCI, in-hospital & 1-year mortality	PPCI: women 47.8%, men 57.4%, P<0.0001 Mortality: In-hospital: women 11.9%, men 6.9%, P<0.0001 Adj. OR 1.13 (1.01–1.26) 1-year: women 22.0%, men 14.1%, P<0.0001 Adj. OR 1.02 (0.96–1.09)
De Luca et al., 2010, Europe & USA[86]	1662	Meta-analysis	STEMI. PPCI	1-year mortality	Women 6.4%, men 3.6%, P=0.016 Adj. HR 1.01 (0.56–1.83)
Zimmerman et al., 2009,	566	Cohort	STEMI. PPCI	30-day mortality	Women 8.4%, men 5.6%, P=0.31 Adj. OR 0.93 (0.44–1.95)

Germany[87]					
Koeth et al., 2009, Germany[88]	3857	Cohort	STEMI complicated by cardiogenic shock. PPCI or TT	In-hospital mortality	Death: women 67.7%, men 57.5%, P<0.0001 Death: Adj. OR 1.16 (0.98–1.38) Early reperfusion: women 49.9%, men 62.7%, P<0.0001 Early reperfusion: Adj. OR 0.92 (0.77–1.09)
Motovska et al., 2008, Czech Republic[89]	1050	Subgroup analysis in RCT	STEMI. PPCI or TT	30-day mortality	TT: women 15%, men 9%, P=0.043 PPCI: women 8.2%, men 6.2%, P=0.41 TT: Adj. OR 1.19 (0.54–2.63) PPCI: Adj. OR 0.74 (0.26–2.05)
Suessenbacher et al., 2008, Austria[90]	1087	Cohort	STEMI. PPCI	In-hospital mortality	Women: 13.7%, men: 7.2%, P=0.001 Sex not independent predictor of death OR 1.25 (0.75–2.09)
Cohen et al., 2005, Multicenter[91]	2741	Cohort	STEMI. TT or no reperfusion	30-day MACE (death, reinfarction, angina)	Reperfusion: women 38.2%, men 47.3%, N.S. Mortality: women 17.8, men 13.3, N.S. Sex not independent predictor of not receiving

					reperfusion or mortality
De Luca et al., 2004, The Netherlands[92]	1548	Cohort	STEMI. PPCI	1-year mortality	Women 6.0%, men 2.3%, RR 2.58 (1.52–4.4) Adj. RR 1.54 (0.97–1.2.43)
Antoniucci et al., 2001, Italy[93]	1019	Cohort	STEMI. PPCI	6-month death & MACE (death, reinfarction, TLR)	Death: women 12%, men 7%, P=0.028 MACE: women 31%, men 24%, P=0.043 Death: Adj. OR 1.05 (0.65–1.72) MACE: Adj. OR 1.05 (0.79–1.41)
Azar et al., 2000, USA[94]	182	Cohort	STEMI. PPCI	Death & MACE (AMI, TVR, death) after 30 days and total follow-up (7±4 months)	Death (30 days): women 10%, men 0.9%, P<0.05 MACE (30 days): women 15%, men 4.4%, P<0.05 Death (total): women 15%, men 4.4%, P<0.05 MACE (total): women 40%, men 15%, P<0.01 Sex not independent predictor of mortality/MACE
Hochman et al., 1999, USA[95]	12,142	Subgroup analysis in RCT	STEMI or NSTEMI	30-day composite endpoint of death and reinfarction	STEMI: Adj. OR 1.27 (0.98–1.63) NSTEMI: Adj. OR 0.93 (0.72–1.21) CAG: women 53.0%, men 59.3%, P<0.001
Stone et al.,	395	Subgroup	STEMI.	In-hospital mortality	Overall: women 9.3%, men 2.8%, P=0.005

1995, USA[96]		analysis in RCT	PPCI or TT		Thrombolysis: women 14.0%, men 3.5%, P=0.006 PPCI: women 4.0, men 2.1%, P=0.46 Sex not independent predictor of mortality, P=0.25
No sex-related differences					
Sjauw et al., 2010, The Netherlands[97]	3277	Cohort	STEMI. PPCI	30-days, 1- & 3-year mortality	30-days: crude HR 0.87 (0.67–1.12) Adj. HR 1.09 (0.77–1.53) 1-year: crude HR 0.85 (0.68–1.06) Adj. HR 1.03 (0.76–1.34) 3-years: crude HR 0.87 (0.71–1.10) Adj. HR 1.10 (0.76–1.49)
Adj.=adjusted; AMI=acute myocardial infarction; CAG=coronary arteriography; HR=hazard ratio; MACE=major adverse cardiac events; NSTEMI=non–ST-elevation myocardial infarction; OR=odds ratio; PPCI=primary percutaneous coronary intervention; RCT=randomised controlled trial; STEMI=ST-elevation myocardial infarction; TLR=target lesion revascularization; TT=thrombolytic therapy; TVR=target vessel revascularization.					

To date, reports on sex-related differences in outcome after STEMI have been inconsistent, with some studies reporting a worse prognosis in women compared to men and other studies finding no differences. No studies appear to have identified a worse outcome in men compared to women. In a U.S. study involving 78,254 AMI patients, of whom 25,353 had STEMI, Jneid et al.[78] found that even after adjustment for differences in baseline characteristics and treatments, women with STEMI had a higher risk of in-hospital mortality compared to men (adjusted odds ratio (OR) 1.12 (1.02–1.23)). In a more recent study of 16,760 patients exclusively treated with PPCI, Benamer et al.[73] found similar results.

Some of the studies have reported the sex-related differences to be age dependent. Berger et al.[79] conducted a cohort study of 9015 consecutive STEMI patients treated with PPCI in New York state. In-hospital mortality was twofold higher in women than in men (6.7% versus 3.4%). After adjustment for differences in baseline characteristics, no difference in mortality between sexes was found. However, in patients <75 years of age, women still had an increased risk of in-hospital mortality (adjusted OR 1.37 (1.01–1.98)), whereas there was no significant difference in mortality between men and women ≥75 years of age.

Jackson et al.[84] also found female sex to be associated with higher unadjusted in-hospital mortality (6.02% versus 3.45%, OR 1.79 (1.45–2.22)). However, in propensity-matched analysis, female sex was not associated with a higher mortality. These results were based on 8771 STEMI patients treated with PPCI.

It appears that only a single study has found no differences at all in outcome between men and women. Sjauw et al.[97] evaluated short- and long-term outcomes as well as delivered quality of care in 3277 unselected STEMI patients treated with PPCI. They found

no statistically significant crude differences in outcome between men and women (30-day hazard ratio (HR) 0.87 (0.67–1.12), 1-year HR 0.85 (0.68–1.06), and 3-year HR 0.87 (0.71–1.10)) despite more adverse clinical characteristics in women. Adjustment for these differences changed the result only modestly (30-day adj. HR 1.09 (0.77–1.53), 1-year adj. HR 1.03 (0.76–1.34), and 3-year adj. HR 1.10 (0.76–1.49)).

Almost all previous studies have found a worse outcome among women compared to men in the crude analyses. One reason could be that the women were older with a higher level of comorbidity than men[73;78;79;84;97]. Furthermore, more women than men presented with heart failure and cardiogenic shock[79;84]. The differences in outcome have also been explained by differences in the treatment between men and women. Jneid et al.[78] found that women were less likely to receive early medical treatment and invasive procedures compared to men. In the STEMI subpopulation, women were less likely to receive reperfusion therapy compared to men, and of the women treated, fewer had door-to-needle times <30 minutes and door-to-balloon times <90 minutes. Pathak et al.[77] reported similar results. In a study of 58,308 STEMI patients, they found that men were more likely to be treated with PPCI compared to women (OR 1.2 (1.1–1.4)). Benamer et al.[73] reported that compared to men, the success rate of PCI was significantly lower in women. Finally, in a STEMI population of 84,663 patients, Barron et al.[82] found that women were less likely to be treated with reperfusion therapy compared to men (OR 0.88 (0.83–0.92)).

Limitations of existing literature.

Most of the existing studies are based on selected populations, lack long-term follow-up, or include only limited details about patient and treatment characteristics. Very few of the

studies include information on secondary medical prevention during follow-up. Thus, it is difficult to draw more firm conclusions, and the effectiveness and safety of PPCI in women remains insufficiently described.

1.6. Age-related differences in outcome after ST-elevation myocardial infarction

The following search strategy was used to identify articles on age-related differences in treatment for and outcome after PPCI: “Myocardial Infarction”[Mesh] AND “Treatment Outcome”[Mesh] AND “Angioplasty, Balloon, Coronary”[Mesh] AND “Aged, 80 and over”[Mesh]. The search was limited to include only English-language studies in humans. Additional studies were found by searching the reference lists from the identified publications. Table 2 shows the relevant studies on age-related differences in treatment and outcome in STEMI patients and PPCI-treated STEMI patients.

Table 2. Studies on differences in treatment for and outcome after ST-elevation myocardial infarction related to age					
Author, year, country	N	Study design	Study population	Outcome	Results
Age-related differences present					
Gharacholou et al., 2011, USA[98]	5745	Subgroup analysis in RCT	STEMI. PPCI	30-day & 90-day mortality	30-day: <65y 1.8%, 65–74y 4.0%, ≥75y 10.0% 90-day: <65y 2.1%, 65–74y 4.4%, ≥75y 12.5% Age independent predictor of 90-day mortality 65–74y vs. <65y, Adj. OR 2.04 (1.46–2.86) ≥75y vs. <65y, Adj. OR 5.64 (4.20–7.56)
Gottlieb et al., 2010, Israel[99]	1026	Cohort	STEMI. PPCI, TT, or no reperfusion	Reperfusion, 7-day, 30-day, & 1-year mortality	Reperfusion: <65y 64%, 65–74y 63%, >75 46%, P<0.0001 7-day: <65y 1.7%, 65–74y 4.8%, >75y 11.1%, P<0.0001. Adj. RR (>75y vs. <65y) 4.7 (2.0–11.3) 30-day: <65y 2.7%, 65–74y 7.4%, >75y 17.3%, P<0.0001. Adj. RR (>75y vs. <65y) 2.5 (1.3–5.1) 1-year: <65y 4.3%, 65–74y 10.5%, >75y 27.9%,

					P<0.0001. Adj. RR (>75y vs. <65y) 2.7 (1.6–4.8)
Ergelen et al., 2010, Turkey[100]	2424	Cohort	STEMI. PPCI	In-hospital & intermediate-term (median 21–22 months) mortality	In-hospital: young 1.2%, old 5.4%, P<0.001 Intermediate: young 1.3%, old 5.0%, P=0.001 Age predictor of intermediate mortality, Adj. OR=1.07 (1.03–1.10)
Zimmermann et al., 2009, Germany[101]	504	Cohort	STEMI, PPCI	30-day & 1-year mortality	30-day: <75 6.4%, ≥75 13.0%, P<0.001 30-day: age predictor of death, Adj. OR 1.05 (1.01–1.09) 1-year: <75 9.9%, ≥75 24.3%, P<0.001 1-year: age predictor of death, Adj. OR 1.04 (1.00–1.08)
Forman et al., 2009, USA[102]	11,160	Pooled analysis of 5 RCTs and 2 registries	STEMI, PPCI	Mortality	RCTs: age predictor of 5 year mortality Adj. OR 1.06 (1.04–1.08) Registries: age predictor of 2-year mortality Adj. OR 1.16 (1.09–1.23)
Pathak et al., 2008, USA[74]	58,308	Cohort	STEMI	PPCI	OR=0.6 (0.5–0.7)

Guagliumi et al., 2004, multi centre[103]	2082	Subgroup analysis in RCT	STEMI. PPCI	1-year mortality	1-year: <55y 1.6%, 55–65y 2.1%, 65–75y 7.1%, >75 11.1%, P<0.0001. Adj. OR 1.06 (1.04–1.09)
Cohen et al., 2003, USA[104]	4620	Cohort	STEMI. PPCI	In-hospital & 1-year mortality	In-hospital: <65y 0.6%, 65–79y 2.2%, ≥80 4.6% In-hospital: <65 vs. 65–74 Adj. RR 2.91 (1.48–5.72) In-hospital: <65 vs. ≥80 Adj. RR 3.64 (1.48–8.94) 1-year: <65y 2.1%, 65–79y 4.9%, ≥80 11.0% 1-year: <65 vs. 65–74 Adj. RR 1.87 (1.27–2.75) 1-year: <65 vs. ≥80 Adj. RR 3.02 (1.78–5.13)
Eagle et al., 2002, multi centre[105]	1763	Cohort	STEMI	Reperfusion	≥75 vs. <75, OR 2.63 (2.04–3.38) Adj. OR 2.37 (1.82–3.08)
DeGeare et al., 2000, USA[106]	3032	Pooled analysis of 3 RCTs	STEMI. PPCI	In-hospital mortality	<75 1.8%, ≥75 10.2%, P=0.001 Age independent predictor of death
Barron et al., 1998, USA[82]	84,663	Cohort	STEMI. TT or no	Reperfusion therapy In-hospital mortality	Reperfusion, <65y vs. >75y OR 0.40 (0.36–0.43) Age >65y independent predictor of mortality

			reperfusion		
White et al., 1996, multi centre[107]	41,021	RCT	TT with streptokinase or TPA	30-day mortality	<65y 3.0%, 65–74y 9.5%, 75–85y 19.6%, >85y 30.3% Age predictor of death after adjustment, P<0.00001 Angioplasty: <65y 24.8%, 65–74y 19.8%, 75–85y 13.1%, >85y 9.2%
No age-related differences after adjustment					
Wenaweser et al., 2007, Switzerland[108]	319	Cohort	STEMI. PPCI	6-month MACE (death, cardiac rehospitalisation, TVR)	<75 20%, ≥75 23%, NS
Sakai et al., 2006, Japan[109]	1087	Cohort	STEMI, PPCI	30-day mortality	<75 4.0%, ≥75 8.1%, P=0.0057 Age not predictor of death, Adj. OR 1.79 (0.91–3.5)
Adj.=adjusted; MACE=major adverse cardiac events; NS=non-significant; OR=odds ratio; PPCI=primary percutaneous coronary intervention; RCT=randomised controlled trial; RR=relative risk; STEMI=ST-elevation myocardial infarction; TPA=tissue plasminogen activator; TT=thrombolytic therapy; TVR=target vessel revascularization.					

Studies on differences in outcome after PPCI in older compared to younger patients almost unanimously report worse outcome in older patients. In a pooled analysis of three RCTs including 3032 STEMI patients eligible for PPCI, DeGeare et al.[106] found that in-hospital mortality was 10.2% in patients ≥75 years of age compared to 1.8% in patients <75 years of age (P=0.001). In multivariable analysis, age was one of the strongest independent predictors of death. Gharacholou et al.[98] recently reported similar results in a subgroup analysis from the APEX-AMI Trial that included 5745 STEMI patients expected to undergo PPCI. The 90-day mortality was 2.3%, 4.8%, and 13.1% in patients ages <65 years, 65–74 years, and ≥75, respectively. After multivariable adjustment, age was the strongest independent predictor of death (HR 2.07 (1.84–2.33) per 10 years of increase).

Only a few small studies have reported results partly in contrast to those mentioned above. In a study including 1087 consecutive STEMI patients treated with PPCI, Sakai et al.[109] found that the crude 30-day mortality was significantly higher in older patients compared to younger participants (8.1% versus 4.0%, P=0.0057). However, in multivariable analysis, age was not found to be an independent predictor of mortality.

There are several possible reasons for the worse prognosis found in older compared to younger patients. DeGeare et al.[106], mentioned above, found that older patients had more comorbidities than younger patients but were treated with PCI with the same frequency. Compared to younger patients, older patients had a lower PPCI success rate and more post-AMI complications. Similarly, in the study by Gharacholou et al.[98], the older patients had a higher baseline risk of adverse outcomes than young patients; they were less likely to be treated with antiplatelet therapies and antithrombotic therapies during admission; and they had a lower PPCI success rate. There were no differences in discharge medications. Finally,

Sakai et al.[109] found that overt cardiogenic shock on arrival was more prevalent in older patients compared to younger patients.

Limitations of existing literature.

Most important, none of the existing studies take into account the higher mortality of elderly people in general, both among patients and in the general population. Furthermore, most of the existing studies lack long-term follow up, are based on selected populations, or include only limited details about patient and treatment characteristics. None of the studies include information on secondary medical prevention during follow-up. Thus, the effectiveness and safety of PPCI in elderly patients are insufficiently described

1.7. Differences in outcome after acute myocardial infarction related to socioeconomic status

Only a very few articles address differences in outcome after STEMI related to SES. Thus, the following search strategy was used to identify articles on SES-related differences in treatment for and outcome after AMI in general: "Patient Education as Topic"[Mesh] OR "Employment"[Mesh] OR "Socioeconomic Factors"[Mesh] OR "Social Class"[Mesh] AND "Myocardial Infarction"[Mesh] AND "Treatment Outcome"[Mesh] AND "Angioplasty, Balloon, Coronary"[Mesh]. The search was limited to include only English-language studies in humans. Additional studies were found by searching the reference lists from the identified publications. Table 3 shows the relevant studies on SES-related differences in treatment and outcome in patients with AMI.

Table 3. Studies on differences in treatment for and outcome after acute myocardial infarction related to socioeconomic status						
Author, year, country	N	Study design	Measure of SES	Study population	Outcome	Results
SES-related differences present						
Mehta et al., 2011, USA[110]	11,326	Post-hoc analysis of RCT	Years of education: 1: <8 years 2: 8–12 years 3: 12–16 years 4: >16 years	STEMI. TT	In-hospital, 30-day, and 1-year mortality	In-hospital: 1=11%, 2=3.5%, 3=2.3%, 4=1.5%, P<0.0001 30-day: 1=12.0%, 2=4.2%, 3=2.6%, 4=2.0%, P<0.0001 1-year: 1=17.5%, 4=3.5%, P<0.0001 1-year: Adj. HR 0.96 (0.94–0.98) per year of increase in education
Gerber et al., 2010, Israel[111]	1179	Cohort	Neighbourhood SES	AMI	13-year survival	Low 61%, middle 74%, high 82% Low vs. high: Adj. HR 1.47 (1.05–2.06) Middle vs. high: Adj. HR 1.19 (0.86–1.63)
Rosvall et al., 2008,	46,407	Cohort	Income	AMI, surviving 28 days	Revascularization within 1 month, 5-year mortality	Revascularization: women, low income 1.2%, high income 2.1%, P<0.001

Sweden[112]						Revascularization: Men, low income 1.3%, high income 3.4%, P<0.001 Mortality: women, low vs. high income, Adj. HR 2.24 (1.69–2.97) Mortality: men, low vs. high income, Adj. HR 1.99 (1.79–2.21)
Beard et al., 2008, Australia[113]	129,045	Cohort	Area-level socioeconomic disadvantage	AMI	CAG, PCI, mortality	High SES reference CAG: high vs. low, Adj. RR 0.72 (0.61–0.86) PCI: high vs. low, Adj. RR 0.68 (0.54–0.87) Mortality: high vs. low, Adj. RR 1.36 (1.23–1.51)
Gerber et al., 2008, USA[114]	705	Cohort	Neighbourhood's median household income. Self-	AMI	Mortality	Low vs. high: Income: crude HR 2.10 (1.42–3.12) Adj. HR 1.62 (1.08–2.45) Education: crude HR 2.21 (1.47–3.32)

			reported education			Adj. HR 1.01 (0.65–1.56)
Chang et al., 2007, Canada[115]	5622	Cohort	Neighbourhood median household income	AMI	1-year mortality, revascularization	Revascularization: low income 36%, high income 48%, P<0.001, Adj. OR 1.06 (1.04–1.09) Mortality: low income 19.1%, high income 9.1%, P<0.001, Adj. OR 0.94 (0.91–0.98)
Casale et al., 2007, USA[116]	16,985	Cohort	Income, insurance status	STEMI	PPCI performed	Insurance: Medicaid vs. commercial, Adj. HR 0.81 (0.74–0.90), P<0.0001 Income: low-income vs. non-low-income Adj. HR 0.87 (0.80–0.95), P<0.001
Rasmussen et al., 2006, Denmark[117]	21,391	Cohort	Education, income	AMI	30-day & long-term mortality	Low vs. high income: Age 30–64 years 30-day: Adj. RR 1.54 (1.36–1.79) Long-term: Adj. RR 1.65 (1.45–1.85) Age 65–74 years

						30-day: Adj. RR 1.27 (1.15–1.41) Long-term: Adj. RR 1.38 (1.27–1.50) Short vs. long education Age 30–64 years 30-day: Adj. RR 1.24 (1.03–1.50) Long-term: Adj. RR 1.33 (1.11–1.59) Age 65–74 years 30-days: Adj. RR 1.09 (0.94–1.28) Long-term: Adj. RR 1.07 (0.94–1.22)
Rao et al., 2004, USA[118]	132,130	Cohort	Income: low, middle, and high	AMI	Aspirin during admission, reperfusion at admission, 30-day & 1-year mortality	Aspirin: low 77.1%, middle 78.1%, high 79.1%, P<0.01 Reperfusion: low 15.6%, middle 18.1%, high 18.5, P<0.01 30-day mortality: high vs. middle, Adj. RR 0.89 (0.85–0.94) Low vs. middle, Adj. RR 1.09 (1.04–1.13) 1-year mortality:

						High vs. middle, Adj. RR 0.92 (0.88–0.97) Low vs. middle, Adj. RR 1.05 (1.00–1.10)
Philbin et al., 2000, USA[119]	28,698	Cohort	Income	AMI	CAG, PCI, CABG	Low income reference CAG: low vs. high, Adj. OR 1.22 (1.10–1.35) PCI: low vs. high, Adj. OR 1.74 (1.48–2.05) CABG: low vs. high, Adj. OR 1.48 (1.23–1.78)
Rathore et al., 2000, USA[120]	169,079	Cohort	Poverty defined by ZIP code of residence	AMI	2 admission therapies (aspirin & reperfusion) 2 discharge therapies (aspirin & β-blockers)	Admission aspirin: poor 77.8%, non-poor 81.2, P=0.001. Adj. RR 0.97 (0.96–0.98) Reperfusion: poor 60.0%, non-poor 64.1, P=0.001. Adj. RR 0.92 (0.89–0.95) Discharge aspirin: poor 69.0%, non-poor 70.2%, P=0.001. Adj. RR 0.97 (0.97–1.00) Discharge β-blocker: poor 48.1%, non-poor 56.3%, P=0.001. Adj. RR 0.93 (0.91–

						0.96)
Salomaa et al., 2000, Finland[121]	6485	Cohort	Income	AMI	28-day & 1-year mortality	Low vs. high income 28-day Men: Adj. RR 3.18 (2.82–3.58) Women: Adj. RR 2.17 (1.76–2.68) 1-year Men: Adj. RR 3.18 (2.84–3.55) Women: Adj. RR 2.34 (1.88–2.92)
Alter et al., 1999, Canada[122]	51,591	Cohort	Neighbourhood income	AMI	CAG, 1-year mortality	CAG: Adj. HR 1.17 (1.12–1.22) for each $10,000 increase 1-year mortality: Adj. HR 0.90 (0.86–0.94) for each $10,000 increase
No SES-related differences after adjustment						
Bernheim et al., 2007, USA[123]	2142	Cohort	Self-reported income	AMI	Quality of care, 1-year mortality	Low income vs. high income Reperfusion: 56.4% vs. 83.5%, P<0.001 Discharge aspirin: 90.7% vs. 96.9% P<0.001

						Mortality: Crude HR 2.80 (1.37–5.72) Adj. HR 1.07 (0.48–2.35)
Pilote et al., 2007, Canada[124]	145,882	Cohort	SES according to postal area	AMI	Cardiac drug use, invasive procedures, and mortality	Low vs. high SES β-blockers: low 62%, high 63% Statins: low 30%, high 31% CAG: low 27%, high 28% PCI: low 9%, high 9% 30-day mortality: low 13%, high 15% 1-year mortality: low 21%, high 24%
Alter et al., 2006, Canada[125]	3407	Cohort	Self-reported income	AMI	2-year mortality	High-income vs. low-income: Crude HR 0.45 (0.35–0.57) Adj. HR 0.77 (0.54–1.10)
Rao et al., 2003, USA[126]	10,498	Subgroup analysis in RCT	Self-reported income	AMI, UAP	30-day & 6-month mortality	Low vs. high income 30-day: Adj. HR 1.3 (0.8–2.1) 6-month: Adj. HR 1.4 (0.9–2.1)
Adj.=adjusted; AMI=acute myocardial infarction; CABG=coronary artery bypass graft surgery; CAG=coronary arteriography; HR=hazard ratio;						

PCI=percutaneous coronary intervention; PPCI=primary percutaneous coronary intervention; RCT=randomised controlled trial; RR=relative risk;

SES=socioeconomic status; STEMI=ST-elevation myocardial infarction; TT=thrombolytic therapy; UAP=unstable angina pectoris.

Mehta et al.[110] recently published a post-hoc analysis of data from the GUSTO III trial examining the association of SES, as ascertained by years of education, with short- and long-term outcomes in 11,326 patients with STEMI treated with thrombolysis. They found that the low-SES patients had a significantly higher mortality in-hospital, after 30 days, and after 1 year. After 1 year, 17.5% and 3.5% of the low-SES and high-SES patients, respectively, had died ($P<0.0001$). Even after adjustment for differences in baseline variables, low SES remained an independent predictor of 1-year mortality (HR 0.96 (0.94–0.98) per year of increase in education). No other SES-based studies appear to have focused on STEMI patients. Most other studies on SES-related differences in outcome after AMI in general find low SES to be related with worse outcome and less frequent use of medical treatments and invasive treatments.

One of the few exceptions is a study by Rao et al.[126]. The purpose of that study was to determine the association between household income and the medical and invasive treatment of acute ischemic heart disease; to determine the association between household income and occurrence of death or recurrent MI; and to explore the relationship among income, processes of care, and outcomes. After multivariable adjustment, there were no differences in care processes, and only a trend towards worse outcome among low-income patients.

Again, there are several possible explanations for the observed differences. Metha et al.[109] found that low-SES patients had a longer duration of time from symptom onset to treatment and a higher Killip class on admission compared to high-SES patients. Furthermore, low-SES patients were less likely to be treated with aspirin and β-blockers both during admission and after discharge but more likely to be treated with an ACE inhibitor.

Compared to high-SES patients, the low-SES patients were more likely to have a coronary angiography performed but less likely to be treated with PCI or coronary artery bypass graft. In another study of 16,985 STEMI patients, Casale et al.[116] found low SES to be an independent predictor of not receiving PPCI (adjusted OR 0.87 (0.80–0.94)).

Limitations of existing literature.

The majority of studies on this topic neither give detailed individual-level data on SES nor have long-term follow-up. They include only limited details about patient and treatment characteristics, making it difficult to identify the mechanisms driving the possible SES-related differences in clinical outcome, and no studies include information about medical treatment beyond 90 days after hospital discharge. Furthermore, only a few studies have been performed in countries with tax-financed healthcare for all residents, which—in theory—should guarantee equal access to treatment independent of SES.

2. Aims

The aims of the thesis were defined as follows:

2.1. Study 1

To compare patient characteristics, treatment, and outcome after PPCI between real-world patients treated after widespread implementation of PPCI and those in the DANAMI-2 population to assess whether it has been possible to achieve trial results in real-world settings.

2.2. Study 2

To compare patient characteristics, treatment, and outcome after PPCI according to sex and age in unselected real-world patients; and

To indirectly assess effectiveness and safety of PPCI by comparing the survival of PPCI-treated STEMI patients with survival in the general population across sex and age groups.

2.3. Study 3

To compare patient characteristics, treatment, and outcome after PPCI according to SES in unselected real-world patients.

3. Materials and methods

3.1. Data sources

3.1.1. The Western Denmark Heart Registry

The Western Denmark Heart Registry (WDHR) collects detailed data related to patients and procedures for all interventions carried out in the three coronary intervention centres in Western Denmark (Odense University Hospital, Aarhus University Hospital, Skejby, and Aarhus University Hospital, Aalborg). Since January 1999, reporting to the registry has been mandatory. Data quality is ensured by automatic validation rules at data entry combined with systematic validation procedures and random spot-checks of data after entry[127]. All three studies used data from this registry.

3.1.2. Medical records

Study 1 used data from the medical records of all Danish patients treated with PPCI at Aarhus University Hospital, Skejby, between April 2004 and December 2006.

3.1.3. DANAMI-2 database

The DANAMI-2 trial was conducted from December 1997 to October 2001, and all data were stored in a database. We had free access to all data regarding patients treated with PPCI in the DANAMI-2 trial. These data were used in study 1.

3.1.4. The Civil Registration System

All three studies used data from the Danish Civil Registration System, which has kept records of sex, date of birth, and changes in vital status since 1968[128]. The records carry a

unique 10-digit civil registration number assigned to every Danish citizen at birth and used in all Danish registers, enabling unambiguous record linkage among them.

3.1.5. The Danish National Causes of Death Registry

Study 3 used data from the Danish National Causes of Death Registry, which was established in 1943[129]. When a Danish citizen dies, the medical doctor in charge of the treatment must report the cause of death using the International Classification of Diseases (ICD) codes. Version 10 (ICD-10) is currently used.

3.1.6. The Danish National Patient Registry

The Danish National Patient Registry, established in 1977, collects data for all non-psychiatric hospitalizations, including dates of admission and discharge, and up to 20 discharge diagnoses assigned by the treating physician[130]. Diagnoses have been coded according to ICD-10 since 1993. Before 1993, they were coded according to the 8th revision (ICD-8). All three studies used data from this register.

3.1.7. The Integrated Database for Labour Market Research

Studies 2 and 3 used data from the Integrated Database for Labour Market Research (IDA), established in 1990 and administered by Statistics Denmark. This database contains variables describing all Danish citizens by data on their family and household, education, employment, and income. The database is updated annually, and the data are supplied by tax authorities, educational institutions, and employment services[131].

3.1.8. The Danish Medicines Agency's Register of Medicinal Product Statistics

All three studies used data from the Danish Medicines Agency's Register of Medicinal Product Statistics, a national prescription registry that contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark since 1995. The information includes type of drug according to the Anatomic Therapeutic Chemical classification system and date dispensed.

3.1.9. The Danish Transfusion Database

The Danish Transfusion Database is a national clinical registry monitoring the use of all blood components administered in Denmark. It contains information about the date of transfusion as well as the types and number of blood components administered to the patients. The database was established in 1997. These data were used in studies 2 and 3.

3.1.10. The Laboratory Information Systems

The Laboratory Information Systems in the Central Denmark and North Denmark Regions were initiated in 1990 in Central Denmark and in 1992 in North Denmark and were complete from 1996 in Central Denmark and 1997 in North Denmark. Data are collected prospectively. The data include the test name, result, measuring unit, and the ordering and analysis dates. Data were used in studies 2 and 3.

3.2. Study design

All studies were cohort studies, and the cohorts consisted of STEMI patients treated with PPCI. In study 2, a cohort consisting of general population controls was also included.

All patients treated with PPCI at Aarhus University Hospital, Skejby, between April 2004 and December 2006, were included in study 1. Furthermore, of the 790 patients randomly assigned to PPCI in the DANAMI-2 trial, balloon inflation was performed in 686 patients[26]. The DANAMI-2 population in study 1 consisted of these 686 patients.

Study 2 included all patients treated with PPCI at one of the three coronary intervention centres of Western Denmark (Odense University Hospital, Aarhus University Hospital, Skejby, and Aarhus University Hospital, Aalborg) from 2002 to 2008. Furthermore, each patient was matched by sex, year of birth, and level of comorbidity with up to 10 individuals from the general population who were alive on the date of the associated patient's PPCI. These controls were sampled using the Danish Civil Registration system.

Study 3 included all patients treated with PPCI at one of the three coronary intervention centres of Western Denmark from 2002 to 2008.

3.3. Exposures

3.3.1. Study 1

Patients treated with PPCI in everyday clinical practice were compared to an RCT population.

3.3.2. Study 2

Patients treated with PPCI were compared according to sex and age.

3.3.3. Study 3

Patients treated with PPCI were compared according to SES.

From the IDA database, we obtained information on employment status the year prior to hospital admission for each patient (employed or unemployed). Unemployed status indicated that the patient was either unemployed, received a pension or an early retirement benefit, or was otherwise economically inactive.

We also retrieved personal income information for each patient and cohabiting partner, including imputed rent for owner-occupied dwellings, interests received, pension withdrawals, unemployment benefits, and the like. This broad definition of income was used in an attempt to reflect the wealth of each patient because it has been suggested that wealth is a more sensitive indicator of SES than income[132]. We calculated the patient and cohabiting partner's combined average income in the five years before admission. All patients were divided into tertiles of increasing income. The high-income group comprised the one third of the patients with the highest income; the low-income group comprised the rest of the patients.

Information on the highest completed educational level as registered the year prior to admission was obtained from the Student Registry of Statistics Denmark. Patients were divided into two groups: long (short-, medium-, and long-term higher education) and short (vocational education, upper or lower secondary school, and primary school).

3.4. Outcome

3.4.1. Composite endpoint

In studies 1 and 2, the primary endpoint was a composite of death, reinfarction, and stroke after 30 days, 1 year, and 2 years.

3.4.2. Major adverse cardiac events

In study 3, the primary endpoint was major adverse cardiac events (MACE), defined as cardiac death, recurrent MI, and TVR after 30 days, 1 year, and maximum follow-up.

3.4.3. All-cause mortality

Data on all-cause mortality were ascertained from The Danish Civil Registration System.

3.4.4. Cardiac death

Cause of death was retrieved from the Danish National Causes of Death Registry. The following ICD-10 codes defined cardiac death: I0, I1, I20-25, I27, I3, I4, I50, I51, R96, and R99.

3.4.5. Reinfarction/recurrent myocardial infarction

Reinfarction/recurrent MI was defined as hospitalization for MI occurring >28 days after the index PCI[14]. Data on MI were obtained from the Danish National Patient Registry using ICD-10 code I21.

3.4.6. Stroke

Stroke was defined as hospitalization with stroke during follow-up using ICD-10 codes I61 and I63-64. These data were obtained from the Danish National Patient Registry.

3.4.7. Target vessel revascularization

Data on TVR was obtained from the WDHR. TVR was defined as a new PCI on the index vessel during follow-up.

3.5. Covariates

In all three studies, a number of variables were included in the analysis because of their potential association with the exposures and outcomes investigated. We included information on some or all of the following variables: sex, age, comorbidity, hypertension, hypercholesterolemia, diabetes, smoking status, previous MI, SES, biochemical data, duration of symptoms, Killip class on admission, sited culprit lesion, Thrombolysis In Myocardial Infarction (TIMI) flow before and after PPCI, number of treated lesions, type of stent implanted, stent length, procedure time, in-lab complications, successful procedure, blood transfusions, antithrombotic and antiplatelet treatment during PPCI, and the use of aspirin, clopidogrel, β-blockers, statins, ACE inhibitors, diuretics, and nitro-glycerine during follow-up.

Data on comorbidity at the time of PPCI were obtained from the Danish National Patient Registry. Based on the last 10 years of hospitalization history of each patient, we computed the Charlson Comorbidity Index score. The index applies a weight of 1, 2, 3, or 6 points to each of 19 major disease categories, according to their impact on patient survival. The Charlson Comorbidity Index has been validated for the prediction of mortality for patients with a wide range of conditions[133] and for use with hospital discharge registry data[134]. We defined three levels of comorbidity: a score of 0 ("low"); a score of 1–2 ("moderate comorbidity"); and a score of >2 ("high comorbidity").

3.6. Statistical analysis

All analyses were performed using STATA (StataCorp, College Station, Texas, USA). We used version 10.0 in study 1 and version 11.0 in studies 2 and 3. All tests of significance

were two tailed with P<0.05 considered significant. In all three studies, we compared baseline characteristics using Student's *t*-tests for continuous variables and the χ^2-test for categorical variables.

3.6.1. Study 1

We used Cox proportional hazards regression to compute crude and adjusted HRs and 95% confidence intervals (CIs) for the endpoints. The patients were censored at the time of death, MI, or stroke or followed up for 2 years. The DANAMI-2 population served as the reference in all analyses. We included covariates in the multivariable analyses using the "change-in-estimate" method[135] and retained only covariables that changed the HR for an outcome by more than 10%. The final models included sex, age, duration of symptoms, smoking status, type of stent (DES/BMS), peri-procedural use of GPIIb/IIIa inhibitors, and use of aspirin, clopidogrel, statins, and β-blockers after 1 year.

3.6.2. Study 2

We used Cox proportional hazards regression to compute crude and adjusted HRs and 95% CIs for the endpoints. The patients were censored at the time of death, MI, or stroke or followed up for 2 years. The patients were divided into three age groups (<65 years, 65–80 years, and >80 years). The male patients and the youngest age group served as the reference in all analyses. We included sex, age, comorbidity, and duration of symptoms in the adjusted analysis. To optimize the precision of the risk estimate, we used the change-in-estimate method[135] and additionally included covariates that changed the HR for an outcome by more than 10%. As a result, we also adjusted for differences in estimated Glomerular filtration rate (eGFR) and grade of anaemia in the final multivariable model.

The hazards were not proportional throughout the follow-up period when comparing patients and general population controls; therefore, we estimated the HRs within the periods during which the proportionality assumption held in these analyses (i.e., 0–90 days and >90 days–2 years); and we used a Cox model with delayed entry and age as the time-scale. The general population controls served as the reference.

3.6.3. Study 3

We used Cox proportional hazards regression to compute crude and adjusted HRs and 95% CIs for the endpoints in each stratum of income, education, and employment status, using "high income", "long education", and "employed" as reference. The patients were censored at the time of death, recurrent MI, or TVR or followed for up to 8.8 years. Mean follow-up time was 3.7 years. First, we adjusted the crude HRs for patient characteristics. To examine the interrelations among the three different indicators of SES, we mutually adjusted for the socioeconomic factors (e.g., models examining the effects of income on mortality were adjusted for education and employment). Second, we additionally adjusted for the admission findings and procedure-related data. Finally, we additionally adjusted for secondary medical prevention during follow-up.

3.6.4. Multiple imputation

The percentages of patients with complete data for all of the variables were 42%, 33%, and 33% in studies 1, 2, and 3, respectively. Data were missing for a varying proportion of the patients for the variables listed above. For most of the variables, only a minor proportion of the patients had missing data (0.0%–15%); however, in studies 2 and 3, information about the laboratory data, smoking status, and history of hypertension, diabetes, and

hypercholesterolemia were missing in 23% to 40% of the patients. We used multiple imputation to impute missing values for all variables because exclusion of all patients with missing data would have reduced the sample size substantially and because complete case analyses commonly produce biased estimates[136]. In addition to all measured variables, we included the event indicator and the Nelson–Aalen estimator of the cumulative hazard to the survival time in the imputation model[137]. Analyses were carried out on five imputed datasets and the results combined using Rubin's Rules[138]. We imputed missing values for hypertension, hypercholesterolemia, diabetes, smoking status, previous MI, biochemical data, duration of symptoms, Killip class on admission, sited culprit lesion, TIMI flow before and after PPCI, number of treated lesions, type of stent implanted, stent length, procedure time, in-lab complications, successful procedure, and antithrombotic and antiplatelet treatment during PPCI.

3.7. Permissions

Our studies were approved by the Danish Data Protection Agency (journal number 2008-41-1835). Permission to use data from medical records was given by the Danish National Board of Health (journal number 7-604-04-2/26/EHE).

4. Results

The main results of the three studies are summarized below.

4.1. Study 1

We identified 1320 patients treated with PPCI at Aarhus University Hospital and 686 patients treated with PPCI in the DANAMI-2 study. Of the 1320 real-world patients, 636 (48.2%) fulfilled the DANAMI-2 inclusion criteria, 642 (48.6%) did not, and for 42 patients (3.2%), information was insufficient to determine whether they fulfilled the criteria.

Compared to the DANAMI-2 patients, the real-world patients were older and had a higher level of comorbidity. A higher proportion of the real-world population used cardiovascular medications after 1 year, except for aspirin.

Table 4 presents the clinical outcomes for the two populations. In a comparison between the entire real-world population and the DANAMI-2 population, the cumulative risks of the composite endpoint after 1 and 2 years were 17.8% and 22.0%, respectively, in the real-world population compared with 13.6% and 17.3% in the DANAMI-2 population. These differences remained after adjustment. The difference was primarily the result of higher mortality and a higher incidence of stroke in the real-world population after both 1 and 2 years. Incidence of reinfarction and TVR did not differ.

Table 5 presents the endpoints for the real-world population eligible according to DANAMI-2 criteria and the DANAMI-2 population. There was no difference in the composite endpoint, but all-cause mortality was significantly lower in the real-world population after 30 days, with a cumulative risk of 2.7% compared to 5.2% in the

DANAMI-2 population. However, after adjustment, this subgroup and the DANAMI-2 population did not differ.

Table 4. Crude and adjusted hazard ratios of clinical outcomes in the real-world population versus the DANAMI-2 population

Endpoints	Real-world, all (N=1320), N (%)	DANAMI-2 (N=686), N (%)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Combined				
• 30 days	93 (7)	40 (5.8)	1.2 (0.8–1.8)	2.1 (1.1–3.9)*
• 1 year	235 (17.8)	93 (13.6)	1.3 (1.1–1.7)*	1.8 (1.3–2.6)*
• 2 years	291 (22.0)	119 (17.3)	1.3 (1.1–1.6)*	1.7 (1.2–2.3)*
Death				
• 30 days	72 (5.5)	36 (5.2)	1.0 (0.7–1.5)	1.9 (0.9–3.8)
• 1 year	119 (9.0)	55 (8.0)	1.1 (0.8–1.5)	2.0 (1.2–3.3)*
• 2 years	154 (11.7)	65 (9.5)	1.2 (0.9–1.7)	2.2 (1.4–3.5)*
Reinfarction				
• 1 year	97 (7.3)	41 (6.0)	1.3 (0.9–1.8)	1.0 (0.6–1.6)
• 2 years	118 (8.9)	58 (8.5)	1.1 (0.8–1.5)	0.9 (0.6–1.4)
Stroke				
• 30 days	15 (1.1)	5 (0.7)	1.6 (0.6–4.3)	2.1 (0.5–9.9)
• 1 year	33 (2.5)	8 (1.2)	2.2 (1.0–4.7)	3.6 (1.2–10.6)*
• 2 years	44 (3.3)	13 (1.9)	1.8 (1.0–3.3)	2.4 (1.0–5.8)*
TVR				
• 30 days	52 (3.9)	21 (3.1)	1.3 (0.8–2.1)	1.4 (0.7–2.8)
• 1 year	132 (10.0)	55 (8.0)	1.3 (0.9–1.7)	1.3 (0.9–2.0)
• 2 years	152 (11.5)	70 (10.2)	1.1 (0.9–1.5)	1.2 (0.8–1.8)

CI=confidence interval; HR=hazard ratio; TVR=target vessel revascularization. *P<0.05.

‡ Adjusted for sex, age, duration of symptoms, smoking status, type of stent (drug-eluting stent/bare metal stent), peri-procedural use of glycoprotein IIb/IIIa inhibitors, and use of aspirin, clopidogrel, statins, and β-blockers after 1 year.

Table 5. Crude and adjusted hazard ratios of clinical outcomes in the real-world population eligible for participation in DANAMI-2 versus the DANAMI-2 population

Endpoints	Real-world, eligible (N=636), N (%)	DANAMI-2 (N=686), N (%)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Combined				
• 30 days	24 (3.8)	40 (5.8)	0.6 (0.4–1.1)	0.9 (0.4–2.0)
• 1 year	90 (14.1)	93 (13.6)	1.0 (0.8–1.4)	1.1 (0.7–1.7)
• 2 years	114 (17.9)	119 (17.3)	1.0 (0.8–1.3)	1.1 (0.7–1.7)
Death				
• 30 days	17 (2.7)	36 (5.2)	0.5 (0.3–0.9)*	0.8 (0.3–1.9)
• 1 year	34 (5.3)	55 (8.0)	0.7 (0.4–1.0)	0.9 (0.5–1.6)
• 2 years	49 (7.7)	65 (9.5)	0.8 (0.5–1.2)	1.0 (0.6–1.8)
Reinfarction				
• 1 year	53 (8.3)	41 (6.0)	1.4 (0.9–2.1)	1.2 (0.7–2.2)
• 2 years	60 (9.4)	58 (8.5)	1.1 (0.8–1.6)	1.0 (0.6–1.8)
Stroke				
• 30 days	4 (0.6)	5 (0.7)	0.9 (0.2–3.2)	0.8 (0.1–6.6)
• 1 year	6 (0.9)	8 (1.2)	0.8 (0.3–2.3)	0.9 (0.2–4.7)
• 2 years	10 (1.6)	13 (1.9)	0.8 (0.4–1.9)	0.7 (0.2–2.5)
TVR				
• 30 days	21 (3.3)	21 (3.1)	0.9 (0.5–1.7)	1.3 (0.5–3.0)
• 1 year	57 (9.0)	55 (8.0)	1.1 (0.8–1.6)	1.2 (0.7–2.1)
• 2 years	64 (10.1)	70 (10.2)	1.0 (0.7–1.4)	1.0 (0.6–1.7)

CI=confidence interval; HR=hazard ratio; TVR=target vessel revascularization. *P<0.05.

‡ Adjusted for sex, age, duration of symptoms, smoking status, type of stent (drug-eluting stent)/bare metal stent), peri-procedural use of glycoprotein IIb/IIIa inhibitors, and use of aspirin, clopidogrel, statins, and β-blockers after 1 year.

4.2. Study 2

We identified 7385 patients treated with PPCI and 42,965 general population controls. Compared to men overall, women were older and had more comorbidities, a longer duration of symptoms, and a higher Killip class on admission. Fewer women than men had a stent implanted, and more women than men had in-lab complications. When comparing medical treatments that occurred during PPCI and 1 and 2 years afterwards, men and women did not differ substantially.

Table 6 presents the composite endpoint after 30 days, 1 year, and 2 years stratified by sex and age. Without stratifying by age, women had a higher cumulative risk of the composite endpoint and a higher mortality than men. However, after adjustment for possible confounding factors, only the difference in the cumulative risk of the composite endpoint after 1 year remained statistically significant. Among patients ages 65–80 years, women had a higher cumulative risk of the composite endpoint than men after 1 and 2 years. After adjustment, men and women in this age group did not differ. Men and women in the other age groups also did not differ, either in the crude or adjusted estimates.

Table 6. Crude and adjusted hazard ratios of the composite endpoint after 30 days, 1 year, and 2 years in women versus men stratified by age

Age	Sex	Patients with endpoint, n/N (%)	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
30 days				
Composite endpoint				
All	Male	311/5405 (5.8)	1.00	1.00
	Female	180/1980 (9.1)	1.58 (1.31–1.90)*	1.16 (0.95–1.41)
≤65	Male	91/3127 (2.9)	1.00	1.00
	Female	23/773 (3.0)	0.99 (0.63–1.56)	0.90 (0.56–1.44)
65–80	Male	141/1798 (7.8)	1.00	1.00
	Female	76/792 (9.6)	1.20 (0.91–1.59)	1.13 (0.83–1.53)
≥80	Male	79/480 (16.5)	1.00	1.00
	Female	81/415 (19.5)	1.21 (0.89–1.65)	1.23 (0.88–1.72)
1 year				
Composite endpoint				
All	Male	574/5405 (10.6)	1.00	1.00
	Female	317/1980 (16.0)	1.55 (1.35–1.78)*	1.18 (1.02–1.37)*
≤65	Male	181/3127 (5.8)	1.00	1.00
	Female	52/773 (6.7)	1.17 (0.86–1.59)	1.13 (0.82–1.56)
65–80	Male	248/1798 (13.8)	1.00	1.00
	Female	134/792 (16.9)	1.23 (1.00–1.52)*	1.16 (0.92–1.46)
≥80	Male	145/480 (30.2)	1.00	1.00
	Female	131/415 (31.6)	1.07 (0.84–1.35)	1.13 (0.87–1.46)
2 years				
Composite endpoint				
All	Male	755/5405 (14.0)	1.00	1.00
	Female	396/1980 (20.0)	1.49 (1.32–1.68)*	1.14 (0.99–1.30)
≤65	Male	247/3127 (7.9)	1.00	1.00

	Female	68/773 (8.8)	1.12 (0.86–1.46)	1.08 (0.82–1.42)
65–80	Male	320/1798 (17.8)	1.00	1.00
	Female	177/792 (22.4)	1.28 (1.06–1.54)*	1.21 (0.99–1.47)
≥80	Male	188/480 (39.2)	1.00	1.00
	Female	151/415 (36.4)	0.95 (0.77–1.17)	1.00 (0.80–1.27)

CI=confidence interval; HR=hazard ratio.

* P<0.05; †adjusted for age, comorbidity, duration of symptoms, estimated glomerular filtration rate, and grade of anaemia.

Table 7 and Figure 1 present mortality rates and cumulative event curves of the PPCI patients and sex-, age-, and comorbidity-matched controls from the general population stratified by sex and age. For both sexes, the 90-day mortality rate was significantly higher among patients than controls in all age groups. The mortality rates were highest among women and older patients compared to men and younger patients. The adjusted mortality rate ratios during the first 90 days were higher for women compared to men except for the older age group, although the differences were not statistically significant. For both men and women, the adjusted mortality rate ratios were highest in younger patients and lowest in older patients. After 90 days, there were no differences in the mortality rates compared with the general population, except for a higher mortality rate among the youngest women.

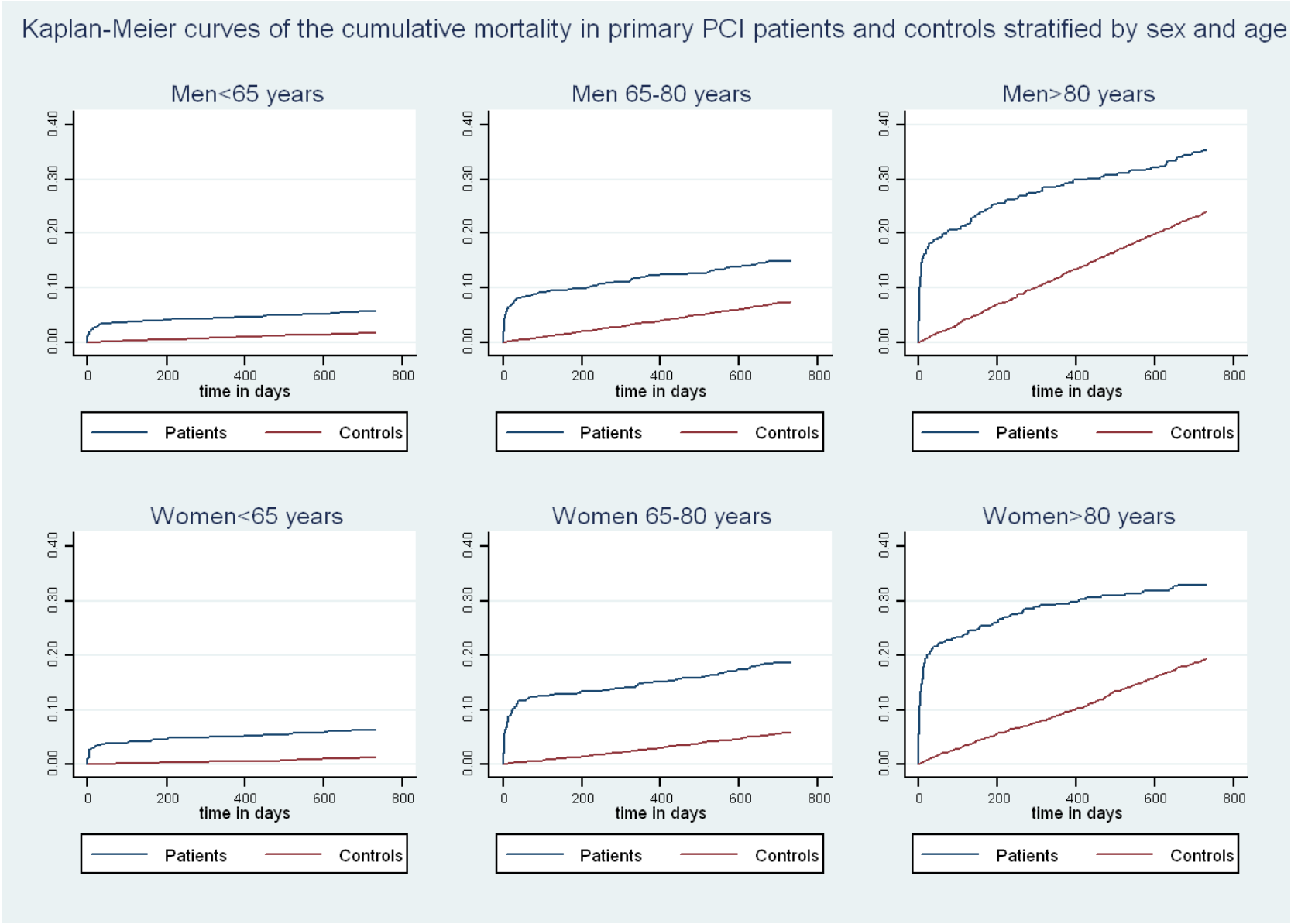
Table 7. Mortality rates and mortality rate ratios of primary percutaneous coronary intervention patients vs. age-, sex-, and comorbidity-matched controls from the general population

	0–90 days				90 days–2 years			
Sex	Mortality rates* PPCI vs. general population	PPCI, No. deaths/N	General population, No. deaths/N	Adjusted mortality rate ratios† (95% CI)	Mortality rates* PPCI vs. general population	PPCI, No. deaths/N	General population, No. deaths/N	Adjusted mortality rate ratios† (95% CI)
Female								
• All ages	435,4 vs. 20.4	194/1980	54/10822	18.2 (13.3–24.9)	37.1 vs. 22.5	124/1786	456/10768	1.19 (0.96–1.48)
• <65 years	152.1 vs. 0.8	28/773	1/5065	153.5 (20.5–1149)	13.8 vs. 3.5	19/745	35/5064	2.21 (1.15–4.25)
• 65–80 years	424.3 vs. 13.5	76/792	13/3942	29.9 (16.4–54.5)	41.5 vs. 20.8	56/716	151/3929	1.36 (0.96–1.92)
• >80 years	1092.4 vs. 90.8	90/415	40/1815	10.8 (7.3–16.0)	80.7 vs. 79.9	49/325	270/1775	0.86 (0.62–1.19)
Male								
• All ages	267.7 vs. 14.4	337/5405	113/32143	14.0 (11.2–17.5)	24.0 vs. 16.9	226/5068	1009/32030	1.06 (0.91–1.23)
• <65 years	127.0 vs. 5.9	95/3127	31/21399	16.2 (10.6–24.5)	9.2 vs. 5.4	54/3032	215/21368	1.17 (0.83–1.64)
• 65–80 years	367.2 vs. 18.2	151/1798	39/8789	16.1 (11.2–23.0)	32.2 vs. 25.4	97/1647	423/8750	0.99 (0.79–1.25)
• >80 years	915.8 vs. 90.5	91/480	43/1955	9.7 (6.6–14.2)	104.1 vs. 105.3	75/389	371/1912	0.98 (0.76–1.26)

CI=confidence interval; PPCI=primary percutaneous coronary intervention.

* per 1000 person years; † Mortality rate ratio adjusted for Charlson Comorbidity Index score.

Figure 1


Kaplan-Meier curves of the cumulative mortality in primary PCI patients and controls stratified by sex and age
Men<65 years
Men 65-80 years
Men>80 years
Women<65 years
Women 65-80 years
Women>80 years
0.00
0.10
0.20
0.30
0.40
0
200
400
600
800
time in days
Patients
Controls

4.3. Study 3

We identified 7385 patients treated with PPCI. In a comparison of low-SES to high-SES patients, female sex, older age, a longer duration of symptoms, and a high level of comorbidity were in general more prevalent. Low-SES patients had more in-lab complications, fewer successful procedures, and fewer stent implantations compared to high-SES patients. Of the stents implanted, fewer were DES in low-SES compared to high-SES patients.

Table 8 presents the clinical outcomes after 30 days, 1 year, and maximum follow-up according to income, education, and employment status. Compared to high-income patients, low-income patients had a higher cumulative risk of MACE after 30 days, 1 year, and maximum follow-up because of a higher incidence of cardiac death and recurrent MI. After adjustment for patient characteristics, the differences in MACE were substantially attenuated and no longer statistically significant. Further adjustment for admission findings, procedure-related data, and secondary medical prevention during follow-up had a very modest effect on the associations.

With education as the indicator of SES, no statistically significant differences were observed in the crude HRs of MACE between the two groups.

Unemployed patients had a higher cumulative incidence of MACE after 30 days, 1 year, and maximum follow-up, primarily explained by higher cardiac mortality. After adjustment for patient characteristics, none of the differences were statistically significant. There were no significant changes after further adjustment for admission findings, procedure-related data, and medical treatment during follow-up.

All-cause mortality was significantly higher among the low-SES patients at all points in time when income or employment status was used as the indicator of SES. After adjustment for patient characteristics, the differences were much attenuated but persisted after maximum follow-up. Using employment status as the indicator of SES, the differences also persisted after 30 days and 1 year. Again, further adjustment had a very modest effect on the associations. When education was used as the indicator of SES, no differences in all-cause mortality were observed.

Table 8. Crude and adjusted hazard ratios (HRs) at 30 days, 1 year, and maximum follow-up according to socioeconomic status

	Unadjusted HR (95% CI)	Adjusted 1* HR (95% CI)	Adjusted 2† HR (95% CI)	Adjusted 3‡ HR (95% CI)
30-days MACE				
Income				
High	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not high	1.87 (1.53–2.29)	1.09 (0.85–1.39)	0.98 (0.74–1.31)	0.97 (0.73–1.29)
Education				
Long	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not long	1.02 (0.75–1.39)	0.84 (0.65–1.09)	0.76 (0.57–1.00)	0.74 (0.55–0.98)
Employment status				
Employed	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not employed	2.55 (2.07–3.13)	1.10 (0.82–1.47)	0.97 (0.70–1.34)	0.95 (0.68–1.31)
1-year MACE				
Income				
High	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not high	1.61 (1.39–1.87)	1.13 (0.94–1.36)	1.09 (0.89–1.33)	1.07 (0.88–1.31)
Education				
Long	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not long	1.00 (0.80–1.26)	0.85 (0.70–1.03)	0.83 (0.67–1.02)	0.83 (0.68–1.03)
Employment status				
Employed	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not employed	1.93 (1.67–2.23)	1.09 (0.89–1.34)	1.07 (0.85–1.33)	1.03 (0.82–1.28)
MACE at maximum follow-up				
Income				

High	1.00 (reference)	1.00	1.00	1.00
Not high	1.56 (1.39–1.77)	1.16 (1.00–1.35)	1.13 (0.96–1.33)	1.11 (0.94–1.30)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.21 (0.91–1.38)	0.93 (0.77–1.11)	0.90 (0.57–1.09)	0.91 (0.76–1.09)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	1.78 (1.58–2.00)	1.14 (0.97–1.35)	1.13 (0.94–1.35)	1.10 (0.92–1.32)

CI=confidence interval; MACE=major adverse cardiac events; TVR=target vessel revascularization; MI=myocardial infarction.

* Adjusted for patient characteristics.

† Adjusted for patient characteristics, admission findings, and procedure-related data.

‡ Adjusted for patient characteristics, admission findings, procedure-related data, and medical treatment during follow-up.

5. Discussion

5.1. Methodological considerations

5.1.1. Selection bias

Selection bias occurs when the association between exposure and outcome differs for those who participate and those who do not participate in a study[139]. This bias could impede the external validity of the study and may occur both when identifying the patients to be included in the study and during the follow-up period. All studies in this thesis used the WDHR and other population-based registries that enabled valid identification of the study population independent of the study hypothesis. All three studies were therefore in principle based on all patients treated with PPCI in Western Denmark. However, selection bias might be present if the risk of sudden cardiac death before hospital admission is associated with study exposure. Previous studies indicate that sudden cardiac death is associated with male sex, old age[140;141], and low SES[142]. In the DANAMI-2 population in study 1, selection bias was probably present because they were included in an RCT with several inclusion criteria and exclusion criteria. As mentioned earlier, only 1572 patients out of 4278 STEMI patients screened for participation in the study were included.

Loss to follow-up may also be a potentially important source of selection bias. Selection bias occurs when the loss to follow-up is related both to the risk of exposure and the outcome. However, all studies in this thesis were based on nationwide population-based registries (the Danish Civil Registration System and the Danish National Patient Registry) with data of high validity and virtually complete follow-up.

5.1.2. Information bias

Information bias may occur when there is systematic error in the information collected about or from study participants (measurement of exposure, outcome, or confounding factors). Such information is often referred to as being misclassified if the measured variable is categorical[139]. Misclassification can either be non-differential, with the measurement error evenly distributed between the groups compared, or differential, with an uneven distribution of the error among the groups compared. Differential misclassification leads to systematic error resulting in an over- or underestimation of the true association. Non-differential misclassification of a dichotomous exposure will most likely bias the association towards null.

All studies in this thesis were based on data recorded prospectively. Thus, any misclassification would most likely be non-differential. In addition, the validity of the diagnoses included in the studies was high, with misclassification occurring in approximately 20% of cases[143;144], and any misclassification is unlikely to depend on the exposure. In all three studies, one of the outcomes was death. Information bias from errors in this outcome is unlikely because deaths were recorded completely by the Danish Civil Registration System independent of the exposure.

The socioeconomic information used in study 3 is likely to have been recorded without error. However, the data were updated only once per year and thus might not reflect the SES on the date of the PPCI. It is also possible that the SES deteriorated after PPCI. For example, those who were employed at the time of PPCI were in fact disability pensioners during the majority of the follow-up period. Both scenarios could introduce a misclassification of SES into our data.

In study 3, data on cardiac death relied on data from death certificates, which has been found to have a low reproducibility[145]. This limitation weakens the conclusions regarding cardiac death.

5.1.3. Confounding

A confounding factor must be associated both with the exposure and with the outcome, without being an intermediate step in the pathway between exposure and outcome. Thus, a confounder must have an effect and must be imbalanced between the exposure groups to be compared[139]. There are several methods to account for confounders in observational studies. We used stratification, restriction, matching, and adjustment in multivariable regression analyses[139]. In the studies included in this thesis, we were able to adjust for a range of potential confounding factors including patient characteristics, admission findings, and procedure-related data and secondary medical prevention during follow-up. Nevertheless, the estimates could be affected by residual or unmeasured confounding.

Residual confounding results from misclassification or use of crude categories for some of the included covariates, e.g., comorbidity using the Charlson Comorbidity Index. High comorbidity was defined as a Charlson Comorbidity Index score >2, which covers a wide range of comorbidity levels.

The estimates may also have been affected by unknown confounding factors as well as unmeasured confounding factors, such as patient compliance, diet, exercise, and other lifestyle habits for which information was not available.

5.1.4. Statistical precision

The 95% CI widths reflected the precision in all studies. The large population-based studies resulted in a high statistical precision in all main analyses. However, the statistical precision of the associations in some of the secondary analyses was lower because of the relatively low number of endpoints (e.g., stroke), and some caution is required when interpreting the findings from these analyses as they were more sensitive to chance.

5.2. Comparison with the existing literature

5.2.1. Study 1

To our knowledge, no previous study has directly compared characteristics, treatment, and outcome between unselected PPCI patients and patients enrolled in an RCT. However, similar studies have been made in patients treated with thrombolysis. In accordance with our findings, these studies found that patients not included in RCTs have a higher baseline risk and worse outcome than included patients and that these differences were most distinct in real-world patients ineligible for the RCTs[63;67;69;146].

In contrast to our results, these studies also found that patients enrolled in RCTs were more likely to be treated with guideline-recommended medications than patients not enrolled[69;146]. Bahit et al.[69] found that even patients who were eligible in the TIMI 9 trial but not enrolled had a more adverse baseline risk profile and worse outcome than the trial patients. The difference persisted after adjustment for differences in patient characteristics. In our study, the eligible patients also had a higher baseline risk, but their clinical outcomes were comparable with those of the DANAMI-2 patients. One reason for this difference might be the better

medical treatment in the real-world patients, which can be explained by improvement in the use of guideline-recommended medications over time[147].

Another possible explanation is the introduction of DES in the period between the DANAMI-2 trial and our study. Several RCTs have demonstrated that incidences of TVR and reinfarction are lower among patients using DES compared to BMS[148-150], whereas no difference in mortality emerged. In partial contrast to these results, we found no differences in the incidences of TVR and reinfarction between the DANAMI-2 population exclusively treated with BMS and the real-world population, of whom 54% received treatment with a DES.

Finally, only two of the five participating invasive-treatment hospitals offered PPCI as a 24-hour routine treatment at the time the DANAMI-2 trial began, and transportation of patients with STEMI from local hospitals to the invasive centres was not routine[26]. Thus, some of the DANAMI-2 patients were treated during a learning phase, which may have unfavourably affected clinical outcomes in the trial compared to the more current real-world population.

5.2.2. Study 2

Women in the present study had a higher baseline risk than men, which is in accordance with previous STEMI studies[84;90;151]. We found no differences in adjusted outcomes between men and women, which is also consistent with other studies[84;90;92]. However, only a few studies have previously focused specifically on PPCI-treated STEMI patients[84;90;92], and these studies have been relatively small and limited by a maximum follow-up period of 1 year.

In contrast to our results, other groups have found a worse prognosis among women compared to men, even after adjustments[76;78;80]. Again, only a few of the reports focused on PPCI-treated STEMI patients[80], and the patient populations have in general been relatively

small, with short follow-up periods and limited information available on patient and treatment characteristics, in particular information on medical treatments used during follow-up. Thus, it is not clear whether the reported differences are related to sex or caused by differences in medical treatments used during follow-up; several studies of MI have reported that men more often than women receive guideline-recommended medical treatments at discharge[78;151]. In our population, we found no major differences in the use of heparin, aspirin, and clopidogrel during the PPCI procedure or in the use of guideline-recommended medical treatments after 1 year and 2 years. Women used diuretics and nitro-glycerine more often than men. Some previous studies found an interaction between sex and age, with a worse prognosis among women compared to men in younger age groups and no differences between men and women in older age groups[76]; however, we could not confirm such an interaction.

To our knowledge, no previous work has compared the mortality of a PPCI-treated STEMI population with the mortality of the corresponding general population. Launbjerg et al.[152] found annual mortality to be twice as high in patients with MI compared to the corresponding general population for up to 10 years. In contrast, we found only the overall mortality to be higher in our STEMI population compared to the general population during the first 90 days. The adjusted mortality rate ratios were higher in younger patients compared to older patients for both men and women. Thus, even in the acute phase, there is no excess relative mortality among older patients compared to younger patients. After 90 days, we found no difference in mortality between the two populations, except for a higher mortality rate ratio in the youngest women. This difference was caused by very few deaths due to the low mortality rate in the general population controls. This indicates that men and women of all ages benefit from PPCI to the same degree.

5.2.3. Study 3

Our study is in accordance with and extends the findings of a number of other reports that have observed that SES-related differences in clinical outcome can be either partially[110;112;113;118;122] or completely[124;125] ascribed to differences in baseline patient characteristics.

However, the possibility of making direct comparisons with and between the existing studies is to some extent limited. SES is a multi-dimensional concept in which the different dimensions (e.g., income, education, and employment status) are closely related. With a few exceptions, the existing studies have focused on only a single dimension/measure of SES and have consequently been unable to explore the independent roles of the different dimensions.

Furthermore, very few reports have included data regarding individual-level SES measures[110;117;125]. Various area-based measures of SES have been used—for example, median household income, the proportion of university-educated participants, and employment rates—as well as composite indexes formed by combining these variables. However, use of area-based measures to estimate an individual's SES results in considerable misclassification, and individual-level measures are therefore preferred[153].

The finding that employment status and income, rather than education level, were predictors of clinical outcome in our study is also partly in accordance with the results of previous studies. Aside from different area-based SES indexes, income has so far been the most frequently used measure of SES. Most reports focusing on income have observed that differences in clinical outcome persist after adjustment for differences in patient characteristics[112;118;122], although this finding has not been confirmed by all studies[125].

Additionally, among publications using educational level as the measure of SES, some have reported differences in outcome that persisted after adjustment for patient characteristics[110] while other groups have observed that differences could be explained by differences in baseline characteristics[114]. One study that used both income and education level as measures of SES found that income was associated with poor outcomes in all patients, while education level was associated only with outcome in patients younger than 65 years of age[117]. To our knowledge, no recent studies have examined the role of employment status in relation to outcome after STEMI.

Several reports on MI have stated that high-SES patients are more likely to receive guideline-recommended medications at discharge than are low-SES patients[118;120;154]. Other studies have observed that low-income patients were less likely to receive secondary medical prevention after 3 months[155] and that discontinuation of evidence-based medication was associated with not graduating from high school[156]. The latter publication also reported that medication therapy discontinuation was associated with higher mortality. To our knowledge, none of the studies regarding SES-related differences in clinical outcome after STEMI have included information about secondary medical prevention. Therefore, it is unclear whether the reported SES-related differences in clinical outcome could be mediated by differences in the secondary medical prevention employed during follow-up. We observed no substantial SES-related differences in the use of guideline-recommended medications during the PPCI procedure or after 1 and 2 years. Therefore, differences in acute treatment or long-term secondary medical prevention appeared not to explain the poor outcomes in low-SES patients.

6. Conclusions

6.1. Study 1

Real-world patients had a more adverse baseline prognostic profile and a poorer clinical outcome compared with the DANAMI-2 patients. However, the clinical outcome in the real-world patients eligible in the DANAMI-2 trial was comparable to that for the DANAMI-2 patients following invasive and medical treatment.

6.2. Study 2

Clinical outcome after PPCI was comparable in men and women after controlling for differences in baseline risk profiles. After 90 days post-PPCI, the mortality rates of PPCI-treated patients were comparable to the mortality of the general population independent of sex and age.

6.3. Study 3

Even in a universal, tax-financed healthcare system, low-SES STEMI patients treated with PPCI face a worse prognosis than high-SES patients. The poor outcome appears to be primarily explained by differences in baseline patient characteristics rather than by differences in acute treatment or long-term secondary medical prophylaxis. Employment status and income, but not education level, were associated with clinical outcomes.

7. Perspectives

The external validity of RCTs might be impaired because of strict inclusion and exclusion criteria, possibly leaving future patients with similar characteristics susceptible to unintended harm from an inappropriate generalization of trial results. Thus, it is crucial for the development of medical science that the results from well-conducted RCTs be verified in everyday clinical practice.

The Danish registries, including the Danish heart registries and other registries and databases within the field of public health, offer a tremendous opportunity for conducting such studies. However, although we could control for a wide range of factors that may affect clinical outcome after PPCI, we could not, because of the observational study design, exclude the possibility that confounding factors still influenced the results, including factors for which information was unavailable (e.g., lifestyle habits and patient compliance). Thus, future RCTs must target minimizing the exclusion of patient populations when such patients will likely form a group to which the results are generalized.

This minimization could be achieved by using pragmatic RCTs that retain the rigour of randomisation (thus eliminating selection bias) but that are conducted in routine clinical settings, thus imposing fewer restrictions on patient populations and practice settings than traditional RCTs. In fact, a key aim for pragmatic RCTs is to reflect the heterogeneity of patients encountered in clinical practice and to keep exclusion criteria to a minimum. These features result in a high external validity.

We have concluded that, because of differences in patient characteristics, women and patients with low SES have worse outcomes after PPCI compared to men and high-SES patients, respectively. Despite an increase in sex- and SES-directed studies in recent years, major gaps

remain in our understanding of differences in presentation, prognosis, and response to treatment related to these variables. Future studies should focus on understanding the behavioural, social, biological, and physiological mediators that link sex and SES with outcomes after PPCI. Furthermore, efforts should be made to include measures of SES in all future cardiovascular disease research, which could help facilitate understanding of the complex link between SES and outcome.

8. Summary

The efficacy of primary percutaneous coronary intervention (PPCI) has been documented in a number of randomised controlled trials (RCT) comparing PPCI to thrombolysis. However, translating RCT results into real-world settings is a challenge because the external validity of the trials may be impaired if the participants and/or the offered care are not representative of routine clinical practices. Traditionally, women, older patients, and patients with low socioeconomic status (SES) are underrepresented in RCTs addressing acute coronary syndromes.

The aims of this thesis were to compare patient characteristics, treatment, and outcome after PPCI between real-world patients and those in an RCT population (study 1), and to compare patient characteristics, treatment, and outcome after PPCI according to sex, age, and SES in real-world patients (studies 2, and 3).

In study 1, we included 1320 real-world patients treated with PPCI and 686 patients treated with PPCI in the DANAMI-2 trial. Compared with the DANAMI-2 population, real-world patients had a higher baseline risk of adverse outcome and a higher cumulative risk of the composite endpoint of mortality, reinfarction, and stroke after 2 years (adjusted hazard ratio (HR)=1.7 (1.2–2.3)). The results for the real-world patients eligible according to the DANAMI-2 criteria were comparable to the results from the DANAMI-2 trial.

Study 2 included 7385 patients treated with PPCI and 42,965 matched general population controls. Women had a more adverse baseline risk profile than men. The cumulative risks of the composite endpoint after 2 years was 20.0% for women compared to 14.0% for men (adjusted HR=1.14 (0.99–1.30)). When comparing patients and controls after 90 days, the mortality among

the PPCI patients was comparable to the mortality in the matched general population independent of sex and age.

We included the 7385 patients treated with PPCI in study 3. They were divided into high- and low-SES groups according to income, education, and employment status. Overall, low-SES patients had a more adverse baseline risk profile than high-SES patients. Compared to high-SES patients, low-SES patients had a higher cumulative risk of major adverse cardiac events (MACE) when using income and employment status as the indicator of SES. After adjustment for patient characteristics, the differences were substantially attenuated (maximum follow-up HR=1.16 (1.00–1.35) and HR=1.14 (0.97–1.35)). With education as the indicator of SES, no differences were seen in the crude HRs of the composite endpoint between the two groups.

In conclusion, our studies indicate that it has been possible to achieve trial results in real-world settings; and that women, older patients, and low-SES patients have the same prognosis as their counterparts after adjustment for differences in baseline characteristics.

9. Dansk resume

Effekten af primær perkutan coronar intervention (PPCI) er dokumenteret i flere randomiserede kontrollerede undersøgelser (RCT), som har sammenlignet PPCI med trombolyse. Det kan imidlertid være problematisk at overføre resultater fra RCT til den kliniske hverdag, hvis studiernes eksterne validitet er for dårlig. Dette er tilfældet, hvis studiepopulationen ikke afspejler den population, som behandlingen er beregnet på. Kvinder, ældre og patienter med lav socioøkonomisk status (SES) er traditionelt underrepræsenterede i RCT vedrørende akut koronar syndrom.

Formålene med denne afhandling var at sammenligne patientkarakteristika, behandling og prognose efter PPCI mellem uselekterede patienter og patienter inkluderet i en RCT (studie 1), og at sammenligne patientkarakteristika, behandling og prognose efter PPCI i daglig klinisk praksis i forhold til køn, alder og SES (studie 2 og 3).

1320 uselekterede patienter behandlet med PPCI og 686 patienter behandlet med PPCI i DANAMI-2 undersøgelsen blev inkluderet i studie 1. De uselekterede patienter havde sammenlignet med DANAMI-2 populationen en mere ufordelagtig risikoprofil og en højere kumulativ risiko for det samlede endepunkt bestående af død, reinfarkt og apopleksi efter 2 år (justeret HR=1,7 (1,2-2,3)). Resultaterne blandt de uselekterede patienter som opfyldte inklusionskriterierne til DANAMI-2 undersøgelsen var sammenlignelige med de resultater man opnåede i DANAMI-2 undersøgelsen.

Studie 2 inkluderede 7385 patienter behandlet med PPCI og 42965 matchede kontrolpersoner fra baggrundsbefolkningen. Kvinder behandlede med PPCI havde en dårligere risikoprofil end tilsvarende mænd. Den kumulative risiko af det samlede endepunkt efter 2 år var 20,0% for kvinder og 14.0% for mænd (justeret HR=1.14 (0.99–1.30)). 90 dage efter PPCI var dødeligheden i

patientpopulationen sammenlignelig med dødeligheden i den matchede baggrundsbefolkning, uafhængig af køn og alder.

Vi inkluderede de 7385 patienter behandlet med PPCI i studie 3. De blev delt i grupper med høj og lav SES i forhold til indkomst, uddannelse og beskæftigelsesstatus. Patienter med lav SES havde en ringere risikoprofil end patienter med høj SES. Patienter med lav SES havde en højere kumulativ risiko for major adverse cardiac events (MACE) sammenlignet med patienter med høj SES, når man brugte indkomst og beskæftigelsesstatus som mål for SES. Efter justering for forskelle i patientkarakteristika blev forskellene væsentlig mindre (maksimum follow-up HR=1.16 (1.00–1.35) og HR=1.14 (0.97–1.35)). Der blev ikke fundet forskelle i rå eller justerede estimater med uddannelse som mål for SES.

Sammenfattende viser vores studier, at det har været muligt at opnå resultater i den daglige klinik der kan sammenlignes med resultater opnået i RCT, og at kvinder, ældre og patienter med lav SES har den samme prognose som deres modsætninger, når man tager højde for forskelle i patientkarakteristika.

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11. Appendices

STUDY 1

Comparison of Primary Percutaneous Coronary Intervention in Real-World Populations Versus Clinical Trial Populations

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The efficacy of primary percutaneous coronary intervention (PPCI) has been documented in several randomized-controlled trials. We sought to examine the clinical outcome after PPCI of real-world patients eligible and ineligible for inclusion in a randomized trial (DANAMI-2) and to compare it to the outcome of the DANAMI-2 population. We did a population-based follow-up study comparing 1,320 consecutive real-world patients treated with PPCI from 2004 to 2006 to 686 patients treated with PPCI in the DANAMI-2 trial. By reviewing medical records we determined whether the real-world patients were eligible in the DANAMI-2 trial. The real-world population had a more adverse baseline risk profile. Cumulative incidences of the composite end point of all-cause mortality, reinfarction, and stroke after 1 year and 2 years were 17.8% and 22.0%, respectively, in the real-world population compared to 13.6% and 17.3% in the DANAMI-2 population. After adjustment for differences in baseline characteristics and treatment, differences persisted after 1 year (adjusted hazard ratio 1.8, 95% confidence interval 1.3 to 2.6) and 2 years (adjusted hazard ratio 1.7, 95% confidence interval 1.2 to 2.3). Results for the real-world patients eligible according to DANAMI-2 criteria were comparable to the results from the DANAMI-2 trial. In conclusion, real-world patients had a more adverse baseline prognostic profile and a poorer clinical outcome compared to the DANAMI-2 patients. However, clinical outcome in the real-world patients eligible in the DANAMI-2 trial was comparable to that for the DANAMI-2 patients after invasive and medical treatment. **© 2010 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2010;105:1684–1691)**

To our knowledge, a direct comparison of unselected patients treated with primary percutaneous coronary intervention (PPCI) versus those enrolled in a trial has not been performed. We therefore conducted a follow-up study comparing characteristics, treatment, and outcome after PPCI between real-world patients treated after widespread implementation of PPCI and those in the Danish Multicenter Randomized Study on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) population to assess whether it is possible to achieve trial results in real-world settings.

Methods

We completed a population-based historical follow-up study in the central Denmark region (approximately 1.2 million). The National Health Service provides tax-supported health care for all inhabitants, allowing free access to general practitioners and hospitals. All acute medical conditions, including ST-elevation myocardial infarction, are exclusively treated at public hospitals in Denmark. Each Danish citizen receives a unique identification number at birth that encodes gender and date of birth and allows accurate linkage among public registries.

The Western Denmark Heart Registry (WDHR) collects detailed patient- and procedure-related data for all interventions carried out in western Denmark since 1999. We identified all PPCIs performed at Aarhus University Hospital (Skejby, Denmark), which serves the central Denmark region, from April 2004 to December 2006 (n = 1,371; Figure 1). Medical records were reviewed. We determined whether patients fulfilled criteria for eligibility in the DANAMI-2 trial or met 1 of the exclusion criteria. The first author reviewed all records. If it was uncertain whether the electrocardiogram fulfilled the inclusion criteria, a consultant in cardiology (TN) reviewed them, and an agreement was reached. Based on data from the patient records, the real-world population was divided into subgroups according to whether they fulfilled the criteria for eligibility in the DANAMI-2 trial. Patients ineligible for the DANAMI-2 trial were further divided into high-risk and low-risk subgroups.

The DANAMI-2 trial was conducted from December 1997 to October 2001. Patients were enrolled from 24 referral hospitals without angioplasty facilities and 5 invasive-treatment hospitals with such facilities. Of 4,278 screened patients, 1,572 (37%) were included in the study and randomly assigned to fibrinolysis at the referral hospital or PPCI at an invasive-treatment hospital. The primary end

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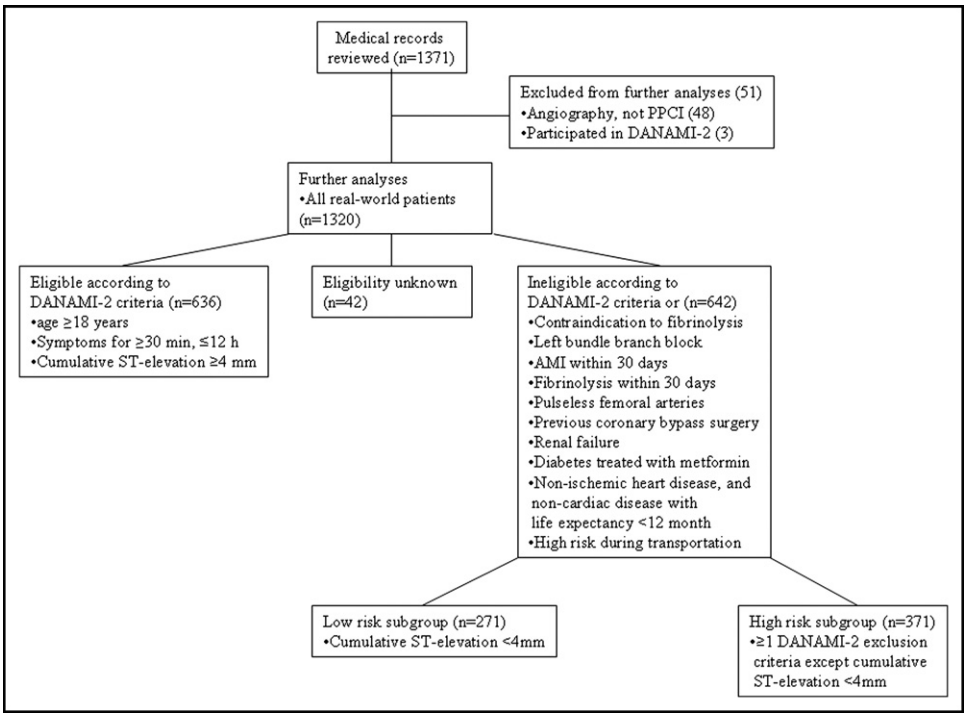

Figure 1. Flow diagram of identification of real-world patient groups. AMI = acute myocardial infarction.

Table 1
Baseline characteristics of patients in four real-world groups versus the DANAMI-2 population

Variable	Real World, All (n = 1,320)	Real World, Eligible (n = 636)	Real-World, Not Eligible, High Risk (n = 371)	Real-World, Not Eligible, Low Risk (n = 271)	DANAMI-2 (n = 686)
Age (mean)	65.2 (64.5–65.9)†	65.0 (64.0–66.0)*	65.9 (64.7–67.1)†	64.2 (62.7–65.8)	63.1 (62.2–64.0)
Male gender (%)	978/1,320 (74.1%)	471/636 (74.1%)	281/371 (75.7)	200/271 (73.8%)	508/686 (74.0%)
Co-morbidity					
None	784/1,320 (59.4%)†	403/636 (63.4%)	197/371 (53.1%)‡	161/271 (59.4%)*	463/686 (67.5%)
Low	396/1,320 (30.0%)	171/636 (26.9%)	122/371 (32.9%)*	88/271 (32.5%)	185/686 (27.0%)
High	140/1,320 (10.6%)†	62/636 (9.7%)*	52/371 (14.0%)‡	22/271 (8.1%)	38/686 (5.5%)
Previous myocardial infarction	164/1,320 (12.4%)*	62/636 (9.7%)	48/371 (12.9%)	46/271 (17.0%)†	63/686 (9.2%)
Previous heart failure	55/1,320 (4.2%)*	24/636 (3.8%)	20/371 (5.4%)*	9/271 (3.3%)	15/686 (2.2%)
Previous cerebrovascular disease	113/1,320 (8.6%)*	43/636 (6.7%)	45/371 (12.1%)†	20/271 (7.4%)	38/686 (5.5%)
Previous peripheral vascular disease	85/1,320 (6.4%)	34/636 (5.3%)	30/371 (8.1%)*	20/271 (7.4%)	31/686 (4.5%)
Diabetes mellitus	118/1,310 (9.0%)	42/633 (6.6%)	55/366 (15.0%)‡	15/269 (5.6%)	49/686 (7.1%)
Moderate/severe renal disease	30/1,320 (2.3%)	9/636 (1.4%)	14/371 (3.8%)*	6/271 (2.2%)	8/686 (1.2%)
Any tumor	101/1,320 (7.7%)*	58/636 (9.1%)*	27/371 (7.3%)	14/271 (5.2%)	33/686 (4.8%)
Coronary heart disease in family	455/1,200 (37.9%)	230/597 (38.5%)	101/308 (32.8%)	112/260 (43.1%)	250/664 (37.7%)
Smoker					
Never	287/1,197 (24.0%)*	143/602 (23.8%)	77/301 (25.6%)*	54/258 (20.9%)	133/677 (19.7%)
Previous	270/1,197 (22.6%)	126/602 (20.9%)	78/301 (25.9%)	61/258 (23.6%)	146/677 (21.6%)
Active	640/1,197 (53.5%)*	333/602 (55.3%)	146/301 (48.5%)*	143/258 (55.4%)	398/677 (58.8%)
Hypertension	370/1,225 (30.2%)‡	164/607 (27.0%)‡	107/317 (33.8%)‡	84/263 (31.9%)†	137/682 (20.1%)
Duration of symptoms (hours)	4.4 (4.2–4.6)‡	3.5 (3.4–3.7)*	7.5 (6.7–8.4)‡	4.1 (3.9–4.4)	3.8 (3.7–4.0)
Patient delay	1.4 (1.3–1.5)‡	1.2 (1.0–1.3)‡	2.1 (1.7–2.7)‡	1.3 (1.2–1.5)‡	0.8 (0.7–0.9)
Admission delay	1.4 (1.3–1.4)‡	1.1 (1.1–1.2)‡	2.0 (1.8–2.2)‡	1.3 (1.2–1.4)‡	0.7 (0.7–0.8)

Data are presented as means (95% confidence intervals or percentages).
* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.00001$.

point was a composite end point of death, reinfarction, and stroke at 30 days. Of the 790 patients randomly assigned to PPCI, balloon inflation was performed in 686 patients (87%).[1] The DANAMI-2 population in our study consisted of these 686 patients.

The National Patient Registry, established in 1977, collects data for all nonpsychiatric hospitalizations at Danish hospitals, including dates of admission and discharge and up to 20 discharge diagnoses assigned by the treating physician and coded according to the *International Classifica-*

Table 2
Procedural and medical therapy characteristics of patients in four real-world groups versus the DANAMI-2 population

Variable	Real World, All (n = 1,320)	Real World, Eligible (n = 636)	Real World, Not Eligible, High Risk (n = 371)	Real World, Not Eligible, Low Risk (n = 271)	DANAMI-2 (n = 686)
Door-to-balloon time	0.67 (0.65–0.69)	0.61 (0.59–0.64)	0.72 (0.67–0.78)*	0.74 (0.69–0.80)*	0.65 (0.61–0.68)
Number of narrowed coronary arteries					
0	26/1,242 (2.1%)*	13/604 (2.2%)*	8/351 (2.3%)*	5/251 (2.0%)*	2/686 (0.3%)
1	627/1,242 (50.5%)*	322/604 (53.3%)	161/351 (45.9%)†	123/251 (49.0%)*	397/686 (57.9%)
2	343/1,242 (27.6%)	163/604 (27.0%)	101/351 (28.8%)	70/251 (27.9%)	184/686 (26.8%)
3	246/1,242 (19.8%)*	106/604 (17.5%)	81/351 (23.1%)*	53/251 (21.1%)*	103/686 (15.0%)
Sited culprit lesion					
Left main coronary artery	15/1,283 (1.2%)	5/617 (0.8%)	8/359 (2.2%)*	2/265 (0.8%)	4/686 (0.6%)
Left anterior descending coronary artery	597/1,283 (46.5%)	344/617 (55.8%)*	170/359 (47.4%)	58/265 (21.9%)‡	333/686 (48.5%)
Left circumflex coronary artery	212/1,283 (16.5%)*	82/617 (13.3%)	63/359 (17.5%)*	61/265 (23.0%)†	86/686 (12.5%)
Right coronary artery t	459/1,283 (35.8%)	186/617 (30.1%)*	118/359 (32.9%)	144/265 (54.3%)‡	263/686 (38.3%)
Stent implantation	1,210/1,320 (91.7%)	583/636 (91.7%)	340/371 (91.6%)	246/271 (90.8%)	638/686 (93.0%)
Number of stents					
0	110/1,320 (8.3%)	53/636 (8.3%)	31/371 (8.4%)	25/271 (9.2%)	48/686 (7.0%)
1	922/1,320 (69.8%)	451/636 (70.9%)	253/371 (68.2%)	187/271 (69.0%)	496/686 (72.4%)
2	218/1,320 (16.5%)	104/636 (16.4%)	62/371 (16.7%)	45/271 (16.6%)	121/686 (17.6%)
3	53/1,320 (4.0%)	24/636 (3.8%)	16/371 (4.3%)	11/271 (4.1%)	18/686 (2.6%)
≥4	17/1,320 (1.3%)	4/636 (0.6%)	9/371 (2.4%)*	3/271 (1.1%)	3/686 (0.4%)
Drug-eluting stents	633/1,170 (54.1%)‡	278/566 (49.1%)‡	201/328 (61.3%)‡	131/236 (55.5%)‡	0
Bare metal stents	537/1,170 (45.9%)‡	288/566 (50.9%)‡	127/328 (38.7%)‡	105/236 (44.5%)‡	636/636 (100%)
Glycoprotein IIb/IIIa during primary percutaneous coronary intervention	1,065/1,317 (80.9%)‡	539/635 (84.9%)‡	263/369 (71.3%)‡	227/271 (83.8%)‡	302/686 (44.0%)
Clopidogrel 1 year	1,166/1,303 (89.5%)‡	587/629 (93.3%)‡	301/366 (82.2%)‡	241/266 (90.6%)‡	178/392 (45.4%)
Statin 1 year	1,134/1,303 (87.0%)‡	561/628 (89.3%)‡	301/367 (82.0%)‡	237/266 (89.1%)‡	424/619 (68.5%)
β blocker 1 year	1,111/1,301 (85.4%)	552/627 (88.0%)*	290/366 (79.2%)	231/266 (86.8%)	509/619 (82.2%)
Nitroglycerin 1 year	558/1,258 (44.4%)‡	261/599 (43.6%)‡	152/359 (42.3%)‡	128/258 (49.6%)‡	65/619 (10.5%)
Aspirin 1 year	1,184/1,304 (90.8%)‡	584/627 (93.1%)*	318/368 (86.4%)‡	243/267 (91.0%)†	598/619 (96.6%)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist	776/1,280 (60.6%)‡	377/612 (61.6%)‡	240/363 (66.1%)‡	130/263 (49.4%)*	232/619 (37.5%)

Data are presented as means (95% confidence intervals or percentages).
* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.00001$.

tion of Diseases, 10th Revision, since 1993. In the 2 patient groups data on previous health status was obtained from the registry. Based on the complete hospitalization history of each patient, we computed the Charlson Comorbidity Index score. The Charlson Comorbidity Index has been validated for the prediction of mortality for patients with a wide range of conditions[2] and has been adapted and validated for use with hospital discharge registry data.[3] We defined 3 levels of co-morbidity: 0 co-morbidity ("none") for patients with no recorded underlying diseases included in the Charlson Comorbidity Index; a score of 1 to 2 ("low co-morbidity"); and a score >2 ("high co-morbidity").

We obtained data on use of cardiovascular drugs by real-world patients from population-based prescription databases. These databases contain information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in the central Denmark region. Information includes type of drug according to the anatomic therapeutic chemical classification system and date dispensed. We identified all prescriptions for antiplatelet drugs, nitroglycerin, statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and selective and nonselective β blockers filled within 90 days, 1 year and 2 years after hospital discharge. All drugs are available only by prescription, except for aspirin. However, aspirin is also available by prescription, and patients with chronic diseases and pensioners are reimbursed for it. Data on use of cardiovascular drugs in the DANAMI-2 population were obtained from the DANAMI-2 database except for data on clopidogrel, which were obtained from prescription databases.

Data on location of the culprit lesion, number of diseased vessels, and type and number of stents used were obtained from the WDHR and the DANAMI-2 database.

The primary end point was a composite end point of all-cause mortality, reinfarction, and stroke at 30 days and at 1 year and 2 years. Secondary end points were all-cause mortality, reinfarction, stroke, and target vessel revascularization (TVR) at 30 days and at 1 year and 2 years. Admission with

Table 3
Crude and adjusted hazard ratios of clinical outcomes in the real-world population versus the DANAMI-2 population

End Points	Real World, All (n = 1,320)	DANAMI-2 (n = 686)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Combined				
30 days	93 (7%)	40 (5.8%)	1.2 (0.8–1.8)	2.1 (1.1–3.9)*
1 year	235 (17.8%)	93 (13.6%)	1.3 (1.1–1.7)*	1.8 (1.3–2.6)*
2 years	291 (22.0%)	119 (17.3%)	1.3 (1.1–1.6)*	1.7 (1.2–2.3)*
Death				
30 days	72 (5.5%)	36 (5.2%)	1.0 (0.7–1.5)	1.9 (0.9–3.8)
1 year	119 (9.0%)	55 (8.0%)	1.1 (0.8–1.5)	2.0 (1.2–3.3)*
2 years	154 (11.7%)	65 (9.5%)	1.2 (0.9–1.7)	2.2 (1.4–3.5)*
Reinfarction				
1 year	97 (7.3%)	41 (6.0%)	1.3 (0.9–1.8)	1.0 (0.6–1.6)
2 years	118 (8.9%)	58 (8.5%)	1.1 (0.8–1.5)	0.9 (0.6–1.4)
Stroke				
30 days	15 (1.1%)	5 (0.7%)	1.6 (0.6–4.3)	2.1 (0.5–9.9)
1 year	33 (2.5%)	8 (1.2%)	2.2 (1.0–4.7)	3.6 (1.2–10.6)*
2 years	44 (3.3%)	13 (1.9%)	1.8 (1.0–3.3)	2.4 (1.0–5.8)*
Target vessel revascularization				
30 days	52 (3.9%)	21 (3.1%)	1.3 (0.8–2.1)	1.4 (0.7–2.8)
1 year	132 (10.0%)	55 (8.0%)	1.3 (0.9–1.7)	1.3 (0.9–2.0)
2 years	152 (11.5%)	70 (10.2%)	1.1 (0.9–1.5)	1.2 (0.8–1.8)

* $p < 0.05$.
‡ Adjusted for gender, age, duration of symptoms, smoking status, type of stent (drug-eluting stent/bare metal stent), periprocedural use of glycoprotein IIb/IIIa inhibitor, and use of aspirin, clopidogrel, statins, and β blockers after 1 year.
CI = confidence interval; HR = hazard ratio.

Table 4
Crude and adjusted hazard ratios of clinical outcomes in the real-world population eligible for participation in DANAMI-2 versus the DANAMI-2 population

End Points	Real World, Eligible (n = 636)	DANAMI-2 (n = 686)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Combined				
30 days	24 (3.8%)	40 (5.8%)	0.6 (0.4–1.1)	0.9 (0.4–2.0)
1 year	90 (14.1%)	93 (13.6%)	1.0 (0.8–1.4)	1.1 (0.7–1.7)
2 years	114 (17.9%)	119 (17.3%)	1.0 (0.8–1.3)	1.1 (0.7–1.7)
Death				
30 days	17 (2.7%)	36 (5.2%)	0.5 (0.3–0.9)*	0.8 (0.3–1.9)
1 year	34 (5.3%)	55 (8.0%)	0.7 (0.4–1.0)	0.9 (0.5–1.6)
2 years	49 (7.7%)	65 (9.5%)	0.8 (0.5–1.2)	1.0 (0.6–1.8)
Reinfarction				
1 year	53 (8.3%)	41 (6.0%)	1.4 (0.9–2.1)	1.2 (0.7–2.2)
2 years	60 (9.4%)	58 (8.5%)	1.1 (0.8–1.6)	1.0 (0.6–1.8)
Stroke				
30 days	4 (0.6%)	5 (0.7%)	0.9 (0.2–3.2)	0.8 (0.1–6.6)
1 year	6 (0.9%)	8 (1.2%)	0.8 (0.3–2.3)	0.9 (0.2–4.7)
2 years	10 (1.6%)	13 (1.9%)	0.8 (0.4–1.9)	0.7 (0.2–2.5)
Target vessel revascularization				
30 days	21 (3.3%)	21 (3.1%)	0.9 (0.5–1.7)	1.3 (0.5–3.0)
1 year	57 (9.0%)	55 (8.0%)	1.1 (0.8–1.6)	1.2 (0.7–2.1)
2 years	64 (10.1%)	70 (10.2%)	1.0 (0.7–1.4)	1.0 (0.6–1.7)

* $p < 0.05$.
‡ Adjusted for gender, age, duration of symptoms, smoking status, type of stent (drug-eluting stent/bare metal stent), periprocedural use of glycoprotein IIb/IIIa inhibitor, and use of aspirin, clopidogrel, statins, and β blockers after 1 year.
Abbreviations as in Table 3.

myocardial infarction within 28 days of the index infarction was not regarded as a new event according to the World Health Organization MONICA definition.[4] TVR was defined as a repeated PCI on the index vessel or coronary artery bypass grafting.

Data on reinfarction and stroke were obtained from the National Patient Registry, and deaths were ascertained from the Danish Civil Registration System, which has kept records on changes in vital status of the entire Danish population since 1968. Data on TVR were obtained from the WDHR and the DANAMI-2 database.

Patients were censored at the time of death or followed up for 2 years. We compared baseline characteristics of the

Table 5
Crude and adjusted hazard ratios of clinical outcomes in high-risk and low-risk real-world populations not eligible for participation in DANAMI-2 versus the DANAMI-2 population

End Points	High Risk/Low Risk (n = 371/271)	DANAMI-2 (n = 686)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Combined				
30 days				
DANAMI-2 (reference)		40 (5.8%)	1.0	1.0
High risk	55 (14.8%)		2.6 (1.8–4.0)†	2.3 (1.1–4.6)*
Low risk	11 (4.1%)		0.7 (0.4–1.3)	0.4 (0.2–1.2)
1 year				
DANAMI-2 (reference)		93 (13.6%)	1.0	1.0
High risk	99 (26.7%)		2.1 (1.6–2.8)†	2.3 (1.5–3.5)†
Low risk	36 (13.3%)		1.0 (0.7–1.4)	0.7 (0.4–1.3)
2 years				
DANAMI-2 (reference)		119 (17.3%)	1.0	1.0
High risk	116 (31.3%)		2.0 (1.5–2.6)†	2.3 (1.6–3.4)†
Low risk	49 (18.1%)		1.0 (0.7–1.4)	0.9 (0.5–1.5)
Death				
30 days				
DANAMI-2 (reference)		36 (5.2%)	1.0	1.0
High risk	46 (12.4%)		2.4 (1.6–3.8)†	2.1 (1.0–4.4)*
Low risk	6 (2.2%)		0.7 (0.4–1.2)	0.2 (0.0–0.8)*
1 year				
DANAMI-2 (reference)		55 (8.0%)	1.0	1.0
High risk	65 (17.5%)		2.3 (1.6–3.3)†	2.6 (1.5–4.5)*
Low risk	19 (7.0%)		0.6 (0.3–1.1)	0.4 (0.2–0.9)*
2 years				
DANAMI-2 (reference)		65 (9.5%)	1.0	1.0
High risk	79 (21.3%)		79 (21.3%)	3.1 (1.8–5.1)†
Low risk	14 (5.2%)		0.4 (0.2–1.0)*	0.5 (0.2–1.1)
Reinfarction				
1 year				
DANAMI-2 (reference)		41 (6.0%)	1.0	1.0
High risk	23 (6.2%)		1.1 (0.7–1.9)	0.7 (0.3–1.6)
Low risk	19 (7.0%)		1.1 (0.7–1.8)	1.0 (0.5–2.1)
2 years				
DANAMI-2 (reference)		58 (8.5%)	1.0	1.0
High risk	29 (7.8%)		1.0 (0.7–1.6)	0.9 (0.5–1.8)
Low risk	26 (9.6%)		1.1 (0.7–2.0)	1.1 (0.5–2.1)
Stroke				
30 days				
DANAMI-2 (reference)		5 (0.7%)	1.0	1.0
High risk	8 (2.2%)		3.1 (1.0–9.5)*	3.2 (0.4–28.1)
Low risk	3 (1.1%)		2.1 (0.9–4.7)	2.5 (0.3–22.1)
1 year				
DANAMI-2 (reference)		8 (1.2%)	1.0	1.0
High risk	15 (4.0%)		3.7 (1.6–8.8)†	5.9 (1.7–20.4)*
Low risk	9 (3.3%)		2.8 (1.1–7.2)*	4.5 (1.0–19.9)*
2 years				
DANAMI-2 (reference)		13 (1.9%)	1.0	1.0
High risk	19 (5.1%)		3.0 (1.5–6.0)†	3.9 (1.4–10.6)*
Low risk	11 (4.1%)		1.5 (0.4–6.2)	2.5 (0.8–8.3)
Target vessel revascularization				
30 days				
DANAMI-2 (reference)		21 (3.1%)	1.0	1.0
High risk	18 (4.9%)		1.7 (0.9–3.1)	1.6 (0.6–3.8)
Low risk	13 (4.8%)		1.3 (0.9–2.0)	1.1 (0.4–3.2)
1 year				
DANAMI-2 (reference)		55 (8.0%)	1.0	1.0
High risk	39 (10.5%)		1.4 (1.0–2.2)	1.5 (0.9–2.7)
Low risk	31 (11.4%)		1.4 (0.9–2.2)	1.2 (0.6–2.2)

Table 5
(*continued*)

End Points	High Risk/Low Risk (n = 371/271)	DANAMI-2 (n = 686)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
2 years				
DANAMI-2 (reference)		70 (10.2%)	1.0	1.0
High risk	45 (12.1%)		1.3 (0.9–1.9)	1.6 (1.0–2.7)
Low risk	37 (13.7%)		1.5 (0.8–3.1)	1.1 (0.6–2.1)

* $p < 0.05$; † $p < 0.001$.
‡ Adjusted for gender, age, duration of symptoms, smoking status, type of stent (drug-eluting stent/bare metal stent), periprocedural use of glycoprotein IIb/IIIa inhibitor, and use of aspirin, clopidogrel, statins, and β blockers after 1 year.
Abbreviations as in Table 3.

real-world population to the DANAMI-2 population using Student's *t* test for continuous variables and chi-square test for categorical variables. We used Cox proportional hazards regression to compute crude and adjusted hazard ratios and 95% confidence intervals for the end points. The DANAMI-2 population served as the reference in all analyses. We included covariates in multivariable analyses using the "change-in-estimate" method[5] and retained only covariables that changed the hazard ratio for an outcome by >10%. The final models included gender, age, duration of symptoms, smoking status, type of stent (drug-eluting/bare metal), periprocedural use of glycoprotein IIb/IIIa inhibitor, and use of aspirin, clopidogrel, statins, and β blockers after 1 year. All tests of significance were 2-tailed with a p value <0.05 considered statistically significant.

The number of patients with no missing data was 1,164. Of the 30 covariates listed in Tables 1 and 2, data were missing in 18, ranging from 1% to 9%, except for clopidogrel in which 15.5% were missing. To account for missing values of these covariates, a multiple imputation strategy was applied. All variables in Tables 1 and 2 and the combined end point were included in the imputation model.[6] Factors known to influence the occurrence of missing data were also included (i.e., real-world patient/DANAMI-2 patient).[7] We also included the logarithm of the survival time, as recommended by van Buuren et al.[7] Imputation and subsequent analyses were conducted using the ice and micombine procedures in STATA 10.0 (STATA Corp., College Station, Texas). Analyses were carried out on 5 imputed datasets and the results combined appropriately using the rules of Rubin.[8]

We analyzed data using STATA 10.0. Our study was approved by the Danish Data Protection Agency (journal number 2008-41-1835).

Results

Of the total study population of 2,006 patients, follow-up data were missing for 1 patient from the real-world population. Of the 1,320 real-world patients, 636 (48.2%) fulfilled the DANAMI-2 inclusion criteria, 642 (48.6%) did not, and in 42 patients (3.2%), there was insufficient information to determine whether they fulfilled the criteria. Contraindications for fibrinolysis were present in 32 patients; 229 patients had a prehospital delay >12 hours; 48 patients had left bundle branch block; 465 did not fulfill the electrocardiographic criteria; and in 208 patients, another exclusion criterion was present. Patients ineligible according to DANAMI-2 criteria consisted of 371 high-risk patients (28.1%) and 271 low-risk patients (20.5%).

Tables 1 and 2 present patient, procedural, and medical treatment characteristics of real-world and DANAMI-2 patients. Compared to DANAMI-2 patients, real-world patients were older and had a higher prevalence of previous myocardial infarction, congestive heart failure, cerebrovascular disease, tumors, and hypertension. In contrast, there were fewer smokers in real-world patients. Time from symptom onset to revascularization was longer in real-world patients, and more patients had a nonpathological angiogram or 3-vessel disease. The left circumflex artery was more often the culprit lesion in the real-world group. There were no differences in the number of stents used, but a larger proportion of real-world patients had a drug-eluting stent implanted. A larger proportion of the real-world population used cardiovascular medications after 1 year, except for aspirin.

In contrast, real-world patients eligible according to DANAMI-2 criteria did not differ from the DANAMI-2 population regarding prevalence of previous myocardial infarction, congestive heart failure, cerebrovascular disease, 1- and 3-vessel disease, culprit lesion in the left circumflex artery, and smoking status. In addition, these patients had a shorter time from symptom onset to revascularization, their culprit lesion was more often located in the left anterior descending artery, and a larger proportion used β blockers compared to the DANAMI-2 population.

In the high-risk subgroup of patients ineligible according to DANAMI-2 criteria, prevalences of peripheral vascular disease, diabetes, and renal insufficiency were higher than in the DANAMI-2 group. The culprit lesion was more often located in the left main artery or left circumflex artery, and a larger proportion of patients had ≥4 stents implanted.

The low-risk subgroup of patients ineligible according to DANAMI-2 criteria had a higher prevalence of previous myocardial infarction, and the culprit lesion was more often located in the right coronary artery or left circumflex artery.

Table 3 presents clinical outcomes for the populations. In a comparison between the entire real-world population and the DANAMI-2 population, cumulative risks of the composite end point after 1 year and 2 years were 17.8% and 22.0%, respectively, in the real-world population compared to 13.6% and 17.3% in the DANAMI-2 population. These differences remained after adjustment. The difference was

primarily the result of higher mortality and a higher incidence of stroke in the real-world population after 1 year and 2 years. There was no difference in the incidence of reinfarction and TVR.

Table 4 presents end points for the real-world population eligible according to DANAMI-2 criteria and the DANAMI-2 population. There was no difference in the composite end point, but all-cause mortality was significantly lower in the real-world population after 30 days, with a cumulative risk of 2.7% compared to 5.2% in the DANAMI-2 population. However, after adjustment, this subgroup and the DANAMI-2 population did not differ.

Table 5 presents end points for the high-risk and low-risk subgroups of the real-world population ineligible according to DANAMI-2 criteria and the DANAMI-2 population. The high-risk subgroup had a higher cumulative incidence of the composite end point throughout the follow-up period, which remained after adjustment for covariates. This difference was explained by a higher mortality and a higher incidence of stroke in the real-world group after 30 days and at 1 year and 2 years. Incidence of reinfarction and TVR did not differ between groups.

The low-risk subgroup had a risk of the composite end point similar to that of the DANAMI-2 population. However, the low-risk group had lower mortality after 30 days and 1 year and a higher risk of stroke after 1 year. Groups did not differ in the incidence of reinfarction and TVR.

Discussion

The main findings of this population-based follow-up study are that real-world patients in general had a more adverse prognostic profile compared to the DANAMI-2 population. The outcome after PPCI in the overall real-world population was also worse compared to the DANAMI-2 population. Differences remained after adjustment for differences in patient characteristics and treatment. However, clinical outcomes in real-world patients fulfilling the criteria for inclusion in DANAMI-2 were comparable to those in the DANAMI-2 trial.

To our knowledge, no previous study has directly compared characteristics, treatment, and outcome between unselected PPCI patients and patients enrolled in a randomized-controlled trial (RCT), although there have been published several studies on PPCI in real-world settings.[9,10] However, similar studies have been performed in patients treated with fibrinolysis. In accordance with our findings, these studies found that patients not included in RCTs had a higher baseline risk and worse outcome than included patients and that these differences were most distinct in real-world patients ineligible for RCTs.[11–14] In contrast to our results, they also found that patients ineligible for RCTs were less likely to be treated with guideline-recommended medications.[11,12] Bahit et al[11] found that even patients who were eligible in the Thrombolysis In Myocardial Infarction (TIMI) 9 trial but not enrolled had a more adverse baseline risk profile and worse outcome than trial patients. The difference persisted after adjustment for differences in patient characteristics. In our study, eligible patients also had a higher baseline risk, but their clinical outcomes were comparable to those of the DANAMI-2 patients. One reason for this difference might be the better medical treatment in real-world patients, which can be explained by improvement in the use of guideline-recommended medications over time that other studies have identified.[15] In addition, guidelines have been changed since the initiation of DANAMI-2. In the 1996 US guidelines for management of myocardial infarction, thienopyridines such as clopidogrel are not mentioned as a conjunctive antithrombotic to reperfusion therapy.[16] In contrast, the 2004 guidelines recommend treatment with thienopyridines for up to 12 months after stent implantation.[17] Recommendations regarding treatment with β blockers, angiotensin-converting enzyme inhibitors, and statins have also changed.[16,17]

Another possible explanation is the introduction of drug-eluting stents in the period between the DANAMI-2 trial and our study. Several RCTs have demonstrated that incidences of TVR and reinfarction are lower in patients using drug-eluting stents compared to bare metal stents,[18–20] whereas no difference in mortality emerged. In partial contrast to these results, we found no differences in incidences of TVR and reinfarction between the DANAMI-2 population exclusively treated with bare metal stents and the real-world population, of whom 54% received treatment with a drug-eluting stent.

Only 2 of the 5 participating invasive-treatment hospitals offered PPCI as a 24-hour routine treatment at the time the DANAMI-2 trial began, and transportation of patients with ST-elevation myocardial infarction from local hospitals to the invasive centers was not routine.[1] Thus, some DANAMI-2 patients were treated during a learning phase, which may have unfavorably affected clinical outcomes in the trial compared to the more current real-world population.

Main strengths of our study are its prospective, population-based design and the possibility of unambiguous individual-level linkage between public data sources, thus providing detailed information on patient characteristics and treatment and allowing virtually complete follow-up.

Limitations include use of hospital discharge diagnoses, which may not always be accurate. However, the predictive value of a myocardial infarction discharge diagnosis in Denmark is reported to be high, with misclassification occurring in 10% to 20% of cases.[21,22] We have no reason to suspect differences in the quality of the data from the National Patient Registry between patient populations.

Real-world patients were treated in a single high-volume hospital with a high specialization with PPCI, which has been shown to be associated with a better prognosis compared to hospitals with low volume or with a lower level of specialization with PPCI.[23,24] Whether our results are applicable to such hospitals is unclear.

Although we controlled for a wide range of factors possibly affecting clinical outcome, because of the observational study design, we cannot exclude the possibility that confounding factors still influenced the results, factors for which information was not available, including lifestyle habits and patient compliance.

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STUDY 2

Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention

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ABSTRACT

Aims: To compare the outcome after primary percutaneous coronary intervention (PPCI) according to sex and age, including comparison of sex- and age-specific mortality of PPCI patients with that of the general population.

Methods and results: This population-based follow-up study included 7385 STEMI-patients treated with PPCI and 42965 matched general population controls. The primary outcome was the composite endpoint of mortality, reinfarction, and stroke at 30 days, 1 year, and 2 years. Women were older and had a more adverse baseline risk-profile than men. The risks of the composite endpoint after 30 days, 1 year, and 2 years were 9.1%, 16.0%, and 20.0%, respectively, for women compared to 5.8%, 10.6%, and 14.0% for men (adjusted hazard ratio (HR) (30 days)=1.16 (0.95-1.41), adjusted HR (1 year)=1.18 (1.02-1.37), and adjusted HR (2 years)=1.14 (0.99-1.30)). The risk of an adverse outcome increased similarly among women and men with increasing age. When comparing patients and controls, we found a higher mortality among patients up to 90 days after PPCI. However, after 90 days, the mortality among the PPCI patients was comparable to the mortality in the general population in all sex- and age-groups.

Conclusion: Clinical outcome after PPCI was comparable in men and women after controlling for possible confounding. After 90 days post-PPCI, the mortality of treated patients was comparable to the mortality of the general population, independent of sex and age.

Keywords: STEMI, primary angioplasty, epidemiology, sex, age

Introduction

The efficacy of primary percutaneous coronary intervention (PPCI) is documented in a number of randomized controlled trials (RCT) comparing PPCI to thrombolysis in patients with ST-elevation myocardial infarction (STEMI)[1]. However, women and elderly patients are underrepresented in published trials on acute coronary syndromes which impairs the possibilities of translating RCT results into real-world settings[2,3]. In addition, female and elderly patients eligible for PPCI are less likely to receive the treatment compared to their counterparts[4, 5]. The existing data are conflicting. Some studies report a worse outcome in women compared to men even after adjustment for differences in baseline characteristics[4]; whereas, no differences are found in other studies[6, 7]. Other studies find the sex-related differences to be age-dependent, suggesting younger women have a particularly adverse prognosis compared to men[8]. Most studies evaluating age-related differences in outcome after PPCI find elderly patients face a worse prognosis than young patients[9]. However, none of these studies take into account the higher mortality of elderly people in general. Most of the existing studies lack long-term follow up, are based on selected populations, or include limited details about patient and treatment characteristics making it difficult to draw more firm conclusions. Thus, the effectiveness and safety of PPCI in women and elderly patients are insufficiently described.

We, therefore, conducted a follow-up study comparing the patient and treatment characteristics, as well as short- and long-term outcome, after PPCI according to sex and age in unselected real-world patients. Further, to indirectly measure effectiveness and safety, we compared the survival of PPCI treated STEMI patients with survival in the general population across sex- and age-groups, which, to our knowledge, has not been done before.

Methods

We completed a population-based historical follow-up study in Western Denmark with approximately 3.3 million inhabitants (56% of the Danish population). The National Health Service provides tax-supported healthcare, guaranteeing unfettered access to medical care. All acute medical conditions are exclusively treated at public hospitals in Denmark. The Danish Civil Registration System keeps records of sex, date of birth, and vital status. The records carry a 10-digit civil registration number assigned to every Danish citizen and used in all Danish registers, enabling unambiguous record linkage between them.

Identification of patients

The Western Denmark Heart Registry (WDHR) collects detailed data related to patients and procedures for all interventions carried out in the 3 coronary intervention centres of Western Denmark (Odense University Hospital, Aarhus University Hospital [Skejby], and Aarhus University Hospital [Aalborg]). Reporting to the registry is mandatory and data quality is ensured by automatic validation rules at data entry combined with systematic validation procedures and random spot-checks of data after entry[10]. We identified all Danish STEMI-patients from 2002-2008 who underwent PPCI within 12 hours of symptom onset (N=7385). Each patient was matched by sex, year of birth, and level of comorbidity with up to 10 individuals from the general population who were alive on the date of the associated patient's PPCI. These controls were sampled using the Danish Civil Registration system. The total number of controls was 42965. The median number of controls was 5 and 520 patients did not have a control.

Patient characteristics and treatment

We obtained data regarding hypertension, a family history of coronary heart disease, smoking, Killip class, duration of symptoms, and all procedure-related data from the WDHR. Duration of

symptoms was defined as time from symptom onset to guiding-catheter insertion during PPCI because time of balloon inflation was only available in a minority of patients and only a few minutes elapse from guiding-catheter insertion to first intervention. Whether the procedure was successful was assessed by the treating physician. In lab complications included contrast reactions, coronary artery perforation, tamponade, acute CABG/PCI, and arrhythmias.

The Danish National Patient Registry collects data for all hospitalizations at Danish hospitals, including dates of admission and discharge and discharge diagnoses assigned by the treating physician and coded according to the International Classification of Diseases, 10th revision since 1993. Based on the last 10 years of hospitalization history for each patient and control, we computed the Charlson Comorbidity Index score[11] which has been adapted for use with hospital discharge registry data[12]. We defined three levels of comorbidity: a score of 0 ("low"); a score of 1–2 ("moderate comorbidity"); and a score >2 ("high comorbidity").

The Integrated Database for Labour Market Research at Statistics Denmark contains information about the Danish population and their affiliation with the labour market. Information about marital status and other socioeconomic factors were ascertained here.

The Danish Transfusion Database is a national registry monitoring the use of all blood components. We obtained information regarding the types and number of blood components administered from the day of admission to 7 days post-admission.

We obtained data regarding the use of cardiovascular drugs from The Danish Medicines Agency's Register of Medicinal Product Statistics, a national prescription registry that contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark. The Information includes type of drug (according to the Anatomic Therapeutic Chemical classification system) and the date dispensed. We identified all prescriptions for aspirin, clopidogrel, nitroglycerin, statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II

receptor antagonists, and selective and nonselective β-blockers filled from hospital discharge until the end of follow up. All the drugs were available only by prescription, except for aspirin. However, aspirin is available by prescription, and patients with chronic diseases and pensioners are reimbursed for it.

For a subset of the patients (N=4856), data from the Laboratory Information Systems in Central- and North Denmark Regions were obtained, including data regarding haemoglobin, total cholesterol, troponin-T, creatine kinase-myocardial band, and blood glucose levels. The highest value measured over 7 days, starting from the time of admission, was obtained except for haemoglobin where the lowest value was obtained. We calculated the estimated glomerular filtration rate (eGFR) using the four-component MDRD equation incorporating age, race, sex, and serum creatinine level[13]. Race was not included because Denmark has a primarily Caucasian population and race data were unavailable. Based on haemoglobin values, we classified anaemia as no anaemia (>8.4 mmol/L), borderline (≤ 8.4 mmol/L to >7.8 mmol/L), mild (≤ 7.8 mmol/L to >6.5 mmol/L), moderate (≤ 6.5 mmol/L to > 5.3 mmol/L), and severe (≤ 5.3 mmol/L) anaemia for men and the same categories for women with all intervals starting and ending 1 mmol/l below the corresponding intervals for men.

Clinical outcomes

The primary endpoint was a composite endpoint of all-cause mortality, reinfarction (ICD-10 I21), and stroke (ICD-10 I61, I63-64) at 30 days, 1 year, and 2 years. We defined a reinfarction as hospitalization for myocardial infarction occurring >28 days after the index PCI[14]. Thus, the composite endpoint at 30 days consists of death and stroke on day 0-30 and reinfarction on day 28-30. Data on reinfarction and stroke were obtained from the National Patient Registry (data available

until the end of 2009), and deaths were ascertained from The Danish Civil Registration System (data available until the end of 2010).

Statistical analyses

The patients were censored at the time of death or followed up for 2 years. We compared baseline characteristics using Student's *t*-test for continuous variables and the χ^2-test for categorical variables. We used Cox proportional hazards regression to compute crude and adjusted hazard ratios (HR) and 95% confidence intervals for the endpoints. The patients were divided in three age groups (<65 years, 65-80 years, and >80 years). The male patients and the youngest age group served as the reference in all analyses and all tests of significance were two tailed with $p<0.05$ considered statistically significant. The hazards were not proportional throughout the follow-up period when comparing patients and general population controls; therefore, we estimated the HRs within the periods during which the proportionality assumption held in these analyses (i.e., 0-90 days and >90 days-2 years); and we used a Cox model with delayed entry using age as the time-scale. The general population controls served as the reference. We also did the analyses using conditional Cox regression to see if survival bias was present. This did not change the estimates.

The number of patients with complete data for all variables was 2408 (33%). For most of the variables, only a minor proportion of the patients were missing data (0.0%-13%); however, 23% to 40% of patients were missing data for the laboratory data, smoking status, family history of ischemic heart disease, history of hypertension, and hypercholesterolemia. We used multiple imputation to impute missing values for all variables. Besides all measured variables, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model[15]. Analyses were conducted on five imputed datasets and the results combined using Rubin's Rules[16].

Sex, age, comorbidity, and duration of symptoms were forced into all of the multivariable analyses. To optimize the precision of the risk estimate, we used the change-in-estimate method when selecting additional covariates to be included.[17] Using this method, covariates were selected based on a relative change of more than 10% in the estimated exposure effect. eGFR and grade of anaemia were in this way identified as possible confounding factors and consequently also included in the final multivariable model. When comparing patients and general population controls, we adjusted for comorbidity as a continuous variable to reduce residual confounding.

We analyzed data using STATA version 11.0 (StataCorp, College Station, Texas, USA). Our study was approved by the Danish Data Protection Agency (journal number 2008-41-1835).

Results

Patient and treatment characteristics

Compared to men overall, women were older, had more comorbidities, a longer duration of symptoms, and a higher Killip class. More women had a family history of coronary heart disease; whereas, fewer women were smokers or previous smokers and had previous myocardial infarctions. Compared to men, women had shorter mean stent lengths and procedure times, fewer women had a stent implanted, women had a higher incidence of in lab complications, and more women received red blood cell and platelet transfusions. Women had lower troponin-T and eGFR levels and a lower prevalence of anaemia than men; whereas, total cholesterol and blood glucose levels were higher compared with men. When comparing medical treatments that occurred during PPCI and 1 and 2 years afterwards, there were no differences between men and women except that diuretics and nitroglycerin were used more frequently among women and fewer women received a glycoprotein IIb/IIIa inhibitor during PPCI. Compared to men, women were less likely to be married and had a lower income. After stratifying by age, the same differences were present in the young and middle

age groups except that no differences in comorbidity, procedure times, and levels of troponin-T and total cholesterol were found. In the old age group, the only differences were a more frequent use of diuretics after 1 and 2 years, a lower prevalence of anaemia, and previous and active smokers among women than men (see supplementary material online, Table S1 and Table S2).

Clinical outcome among PPCI patients

Table 1 presents the composite endpoint and cumulative mortality after 30 days, 1 year, and 2 years stratified by sex and age. Without stratifying by age, women had a higher cumulative risk of the composite endpoint and a higher mortality than men. However, after adjustment for possible confounding factors (sex, age, comorbidity, duration of symptoms, eGFR and grade of anaemia), only the difference in the cumulative risk of the composite endpoint after 1 year remained statistically significant. Among patients aged 65-80 years, women had a higher cumulative risk of the composite endpoint than men after 1 and 2 years. After adjustment, there were no differences between men and women in this age group. There were no differences between men and women in the other age groups in the crude or adjusted estimates.

No differences were found in the cumulative risk of reinfarction or stroke, except that women had a higher cumulative risk of stroke after 30 days compared to men. However, this finding was based on very few outcomes (see supplementary material online, Table S3).

Comparison with the general population

Table 2 and Figure 1 present mortality rates and cumulative mortality curves of the PPCI patients and sex, age and comorbidity matched general population controls stratified by sex and age. For both sexes the 90 days mortality rate was significantly higher among patients than controls in all age groups. The mortality rates were highest among women and older patients compared to men

and younger patients. The adjusted mortality rate ratios during the first 90 days were higher for women compared to men except for the old age group; although, the differences were not statistically significant. For both men and women, the adjusted mortality rate ratios were highest in younger patients and lowest in older patients. After 90 days, there were no differences in the mortality rates compared with the general population, except for a higher mortality rate among the youngest women. (For demographic information on patients and controls, see supplementary material online, Table S4)

Discussion

The present study shows that women presenting with STEMI and treated with PPCI had adjusted short- and long-term outcomes similar to men. Women were older and overall had a more adverse baseline risk profile than men, which explained their higher risk in some of the crude and non-stratified analyses. There were no substantial differences in the medical treatments received during the PPCI procedure or after discharge.

We found a higher mortality among patients up to 90 days after admission for STEMI when comparing mortality between patients and general population controls. This difference was present in both men and women of all ages, but the mortality rates were highest among women and older patients compared to men and younger patients. The adjusted mortality rates ratios during the first 90 days were highest in younger patients and lowest in older patients. After 90 days the mortality among the PPCI patients dropped to a level comparable with the mortality in the background population.

Women in the present study had a higher baseline risk than men and we no differences in adjusted outcomes between men and women, which is consistent with previous STEMI studies[5-7, 18].

However, only few studies have previously focused on PPCI treated STEMI patients[6, 7, 18], and these studies have included relatively few patients with a maximum follow-up period of 1 year.

In contrast to our results, other studies found a worse prognosis among women compared to men, even after adjustments[4, 8, 19]. Few of these studies focused on PPCI treated STEMI patients[19]. Furthermore, the patient populations have in general been relatively small, with short follow-up periods and limited information available on patient and treatment characteristics, especially information on medical treatments used during follow-up. Thus, it is not clear whether the reported differences are related to sex or caused by differences in medical treatments used during follow-up, since several studies of myocardial infarction have reported that men more often than women receive guideline recommended medical treatments at discharge[4, 5]. In our study population, we found no differences in the use of heparin, aspirin, and clopidogrel during the PPCI procedure or in the use of guideline recommended medical treatments after 1 and 2 years. Women used diuretics and nitroglycerin more often than men. Some previous studies found an interaction between sex and age, with a worse prognosis among women compared to men in younger age groups and no differences between men and women in older age groups[8]. We could not confirm the existence of such an interaction.

To our knowledge, no previous study has compared the mortality of a PPCI-treated STEMI population with the mortality of the corresponding background population. Launbjerg et al.[20] found the annual mortality to be twice as high in patients with myocardial infarction compared to the corresponding background population for up to 10 years. In contrast, we only found the overall mortality to be higher in our STEMI population compared to the background population during the first 90 days. The adjusted mortality rate ratios were highest in younger patients compared to older patients for both men and women. Thus, even in the acute phase, there is no excess relative mortality among older patients compared to younger patients. After 90 days we found no difference

in mortality between the 2 populations, except for a higher mortality in the youngest women. This difference was caused by very few deaths due to the low mortality in the general population controls. This indicates that men and women of all ages benefit from PPCI to the same degree.

Study strengths and limitations

The main strengths of our study are the large number of patients, the long follow-up period, the prospective, population-based design, and the possibility of unambiguous individual-level linkage between public data sources, which provided detailed information on patient characteristics, treatments, and use of medications and allowed complete follow-up, minimizing the risk of selection bias. The Danish Civil Registration System and the Danish National Patient Registry made it possible to identify matched controls from the background population, which is unique.

Some previous study populations come from databases based on RCTs[19]. This may cause problems with the external validity of these studies because of the strict inclusion and exclusion criteria in the RCTs and the potential exclusion of more women than men, as more women than men present with shock or hypotension[6-8] which are characteristics that often lead to exclusion from trials. Thrombolysis is still widely used in most countries. It is unclear what factors are used to determine whether thrombolysis or PPCI is used. If these factors are different between men and women, as some studies indicate[4], it may cause bias. Our study was carried out in Denmark, where PPCI is the standard treatment of STEMI. Thus, STEMI patients are almost exclusively treated with PPCI, optimizing the external validity and minimizing the risk of bias, since the WDHR contains data on all procedures without any inclusion or exclusion criteria. This also means that our study-population is different from most other registry study populations and a direct comparison of patient characteristics might be problematic. However, it might explain why our study population has a better baseline risk-profile compared to other registry studies[6-8]. This is the case for both women

and men of all ages, and thus we have no reason to believe that it had any substantial influence on the relative risk estimates.

We used hospital discharge diagnoses, which may not always be accurate. However, the validity of the diagnoses included in this study were high (e.g., misclassification occurring approximately 20% of cases)[21, 22]. We controlled for a wide range of factors possibly affecting outcome; yet, due to the observational study design, we cannot exclude the possibility that confounding factors still influenced the results, factors for which information was not available, including lifestyle habits and patient compliance.

Conclusion

Clinical outcome after PPCI was comparable in men and women after controlling for differences in baseline risk-profiles. After 90 days post-PPCI, the mortality rates of PPCI treated patients were comparable to the mortality of the general population independent of sex and age.

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LEGENDS

Figure legends:

Figure 1. Kaplan-Meier curves of the cumulative mortality in primary PCI patients and controls stratified by sex and age. PPCI = primary percutaneous coronary intervention.

Table 1. Crude and adjusted hazard ratios of clinical outcomes after 30 days, 1 year and 2 years in women versus men stratified by age

Age	Sex	Patients with endpoint, n/N (%)	Unadjusted HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
			30 days			
			Combined endpoint			
All	Male	311/5405 (5.8)	1.00		1.00	
	Female	180/1980 (9.1)	1.58 (1.31-1.90)	<0.0001	1.16 (0.95-1.41)	NS
≤65	Male	91/3127 (2.9)	1.00		1.00	
	Female	23/773 (3.0)	0.99 (0.63-1.56)	NS	0.90 (0.56-1.44)	NS
65-80	Male	141/1798 (7.8)	1.00		1.00	
	Female	76/792 (9.6)	1.20 (0.91-1.59)	NS	1.13 (0.83-1.53)	NS
≥80	Male	79/480 (16.5)	1.00		1.00	
	Female	81/415 (19.5)	1.21 (0.89-1.65)	NS	1.23 (0.88-1.72)	NS
			Mortality			
All	Male	295/5405 (5.5)	1.00		1.00	
	Female	168/1980 (8.5)	1.58 (1.31-1.91)	<0.0001	1.15 (0.94-1.42)	NS
≤65	Male	86/3127 (2.8)	1.00		1.00	
	Female	23/773 (3.0)	1.08 (0.68-1.72)	NS	0.98 (0.61-1.58)	NS
65-80	Male	134/1798 (7.5)	1.00		1.00	
	Female	64/792 (8.1)	1.09 (0.81-1.46)	NS	1.02 (0.74-1.41)	NS
≥80	Male	75/480 (15.6)	1.00		1.00	
	Female	81/415 (19.5)	1.28 (0.93-1.75)	NS	1.30 (0.93-1.83)	NS

		1 year				
		Combined endpoint				
All	Male	574/5405 (10.6)	1.00		1.00	
	Female	317/1980 (16.0)	1.55 (1.35-1.78)	<0.0001	1.18 (1.02-1.37)	0.03
≤65	Male	181/3127 (5.8)	1.00		1.00	
	Female	52/773 (6.7)	1.17 (0.86-1.59)	NS	1.13 (0.82-1.56)	NS
65-80	Male	248/1798 (13.8)	1.00		1.00	
	Female	134/792 (16.9)	1.23 (1.00-1.52)	0.05	1.16 (0.92-1.46)	NS
≥80	Male	145/480 (30.2)	1.00		1.00	
	Female	131/415 (31.6)	1.07 (0.84-1.35)	NS	1.13 (0.87-1.46)	NS
		Mortality				
all	Male	444/5405 (8.2)	1.00		1.00	
	Female	256/1980 (12.9)	1.61 (1.38-1.88)	<0.0001	1.17 (0.98-1.38)	NS
≤65	Male	117/3127 (3.7)	1.00		1.00	
	Female	37/773 (4.8)	1.28 (0.89-1.86)	NS	1.20 (0.82-1.79)	NS
65-80	Male	197/1798 (11.0)	1.00		1.00	
	Female	99/792 (12.5)	1.15 (0.90-1.46)	NS	1.07 (0.82-1.39)	NS
≥80	Male	130/480 (27.1)	1.00		1.00	
	Female	120/415 (28.9)	1.09 (0.85-1.40)	NS	1.15 (0.88-1.51)	NS
		2 years				
		Combined endpoint				
All	Male	755/5405 (14.0)	1.00		1.00	
	Female	396/1980 (20.0)	1.49 (1.32-1.68)	<0.0001	1.14 (0.99-1.30)	NS
≤65	Male	247/3127 (7.9)	1.00		1.00	

	Female	68/773 (8.8)	1.12 (0.86-1.46)	NS	1.08 (0.82-1.42)	NS
65-80	Male	320/1798 (17.8)	1.00		1.00	
	Female	177/792 (22.4)	1.28 (1.06-1.54)	0.009	1.21 (0.99-1.47)	NS
≥80	Male	188/480 (39.2)	1.00		1.00	
	Female	151/415 (36.4)	0.95 (0.77-1.17)	NS	1.00 (0.80-1.27)	NS
			Mortality			
All	Male	563/5405 (10.4)	1.00		1.00	
	Female	318/1980 (16.1)	1.59 (1.39-1.83)	<0.0001	1.15 (0.99-1.35)	NS
≤65	Male	149/3127 (4.8)	1.00		1.00	
	Female	47/773 (6.1)	1.28 (0.92-1.78)	NS	1.21 (0.86-1.71)	NS
65-80	Male	248/1798 (13.8)	1.00		1.00	
	Female	132/792 (16.7)	1.22 (0.99-1.51)	NS	1.16 (0.92-1.45)	NS
≥80	Male	166/480 (34.6)	1.00		1.00	
	Female	139/415 (33.5)	0.99 (0.79-1.24)	NS	1.06 (0.83-1.36)	NS

CI: confidence interval; HR: hazard ratio; NS: non-significant.

*adjusted for age, comorbidity, duration of symptoms, estimated glomerular filtration rate, and grade of anemia

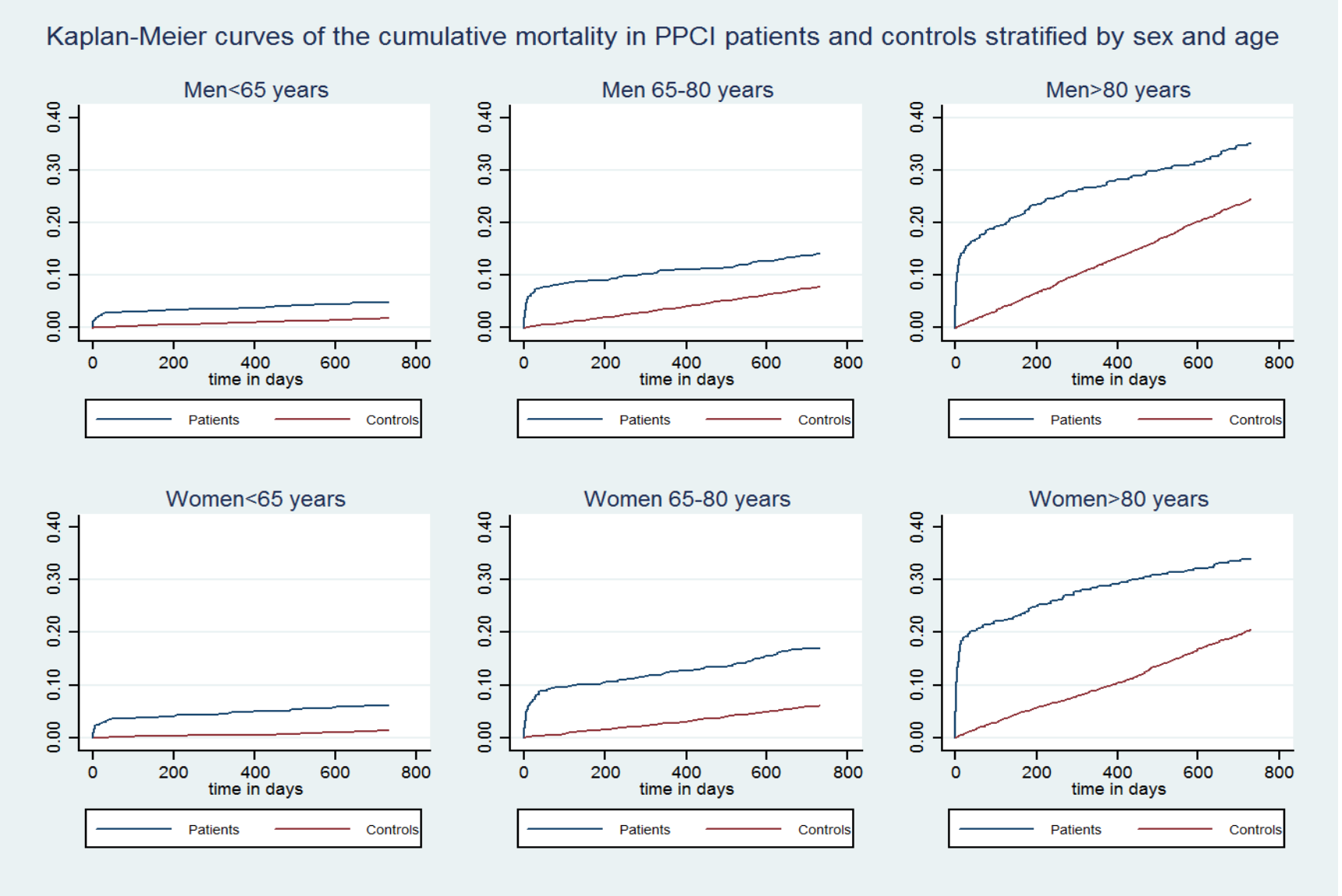
Table 2. Mortality rates and mortality rate ratios of primary percutaneous coronary intervention patients vs. age sex and comorbidity matched controls from the general population.

Sex	0-90 days				90 days-2 years			
	Mortality rates* PPCI vs. general population	PPCI, No. deaths/N	General population, No deaths/N	Adjusted mortality rate ratios† (95% CI)	Mortality rates* PPCI vs. general population	PPCI, No. deaths/N	General population, No deaths/N	Adjusted mortality rate ratios† (95% CI)
Female								
• All ages	435,4 vs. 20.4	194/1980	54/10822	18.2 (13.3-24.9)	37.1 vs. 22.5	124/1786	456/10768	1.19 (0.96-1.48)
• <65 years	152.1 vs. 0.8	28/773	1/5065	153.5 (20.5-1149)	13.8 vs. 3.5	19/745	35/5064	2.21 (1.15-4.25)
• 65-80 years	424.3 vs. 13.5	76/792	13/3942	29.9 (16.4-54.5)	41.5 vs. 20.8	56/716	151/3929	1.36 (0.96-1.92)
• >80 years	1092.4 vs. 90.8	90/415	40/1815	10.8 (7.3-16.0)	80.7 vs. 79.9	49/325	270/1775	0.86 (0.62-1.19)
Male								
• All ages	267.7 vs. 14.4	337/5405	113/32143	14.0 (11.2-17.5)	24.0 vs. 16.9	226/5068	1009/32030	1.06 (0.91-1.23)
• <65 years	127.0 vs. 5.9	95/3127	31/21399	16.2 (10.6-24.5)	9.2 vs. 5.4	54/3032	215/21368	1.17 (0.83-1.64)
• 65-80 years	367.2 vs. 18.2	151/1798	39/8789	16.1 (11.2-23.0)	32.2 vs. 25.4	97/1647	423/8750	0.99 (0.79-1.25)
• >80 years	915.8 vs. 90.5	91/480	43/1955	9.7 (6.6-14.2)	104.1 vs. 105.3	75/389	371/1912	0.98 (0.76-1.26)

CI: confidence interval; PPCI: primary percutaneous coronary intervention.

*per 1000 person years; †Mortality rate ratio adjusted for Charlson comorbidity score index.

Figure 1


Kaplan-Meier curves of the cumulative mortality in PPCI patients and controls stratified by sex and age
Men<65 years
Men 65-80 years
Men>80 years
Women<65 years
Women 65-80 years
Women>80 years
0.00
0.10
0.20
0.30
0.40
0
200
400
600
800
time in days
Patients
Controls

STUDY 3

Dimensions of socioeconomic status and clinical outcome after primary percutaneous coronary intervention

Jakobsen et al. Socioeconomic status and outcome after primary PCI

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ABSTRACT

Background: The association between low socioeconomic status (SES) and high mortality from coronary heart disease is well-known. However, the role of SES in relation to the clinical outcome after primary percutaneous coronary intervention (PPCI) remains poorly understood.

Methods and Results: We studied 7385 patients treated with PPCI. Participants were divided into high-SES and low-SES groups according to income, education, and employment status. The primary outcome was major adverse cardiac events (MACE: cardiac death, recurrent myocardial infarction, and target vessel revascularization) at 30 days, 1 year, and maximum follow-up. Low-SES patients had more adverse baseline risk profiles than high-SES patients. The cumulative risk of MACE after maximum follow-up was higher among low-income patients and unemployed patients compared with their counterparts (income: HR 1.56, 95% CI 1.39-1.77; employment status: HR 1.78, 95% CI 1.58–2.0)). After adjustment for patient characteristics, these differences were substantially attenuated (income: HR 1.16, 95% CI 1.00–1.35; employment status: HR 1.14, 95% CI 0.97–1.35). Further adjustment for admission findings, procedure-related data, and medical treatment during follow-up did not significantly affect the associations. With education as the SES indicator, no between-group differences were observed in the risk of the composite endpoint.

Conclusions: Even in a tax-financed health care system, low-SES patients treated with PPCI face a worse prognosis than high-SES patients. The poor outcome appears to be largely explained by differences in baseline patient characteristics. Employment status and income (but not education level) were associated with clinical outcomes.

Keywords: STEMI, primary PCI, socioeconomic status, outcome

There is a well-known association between low socioeconomic status (SES) and high incidence of and mortality from coronary heart disease.[1, 2] One possible explanation is the inverse relationship between SES and the prevalence of almost all well-established cardiovascular risk factors[3]. Furthermore, existing literature suggests that SES-related differences may exist in quality of care, with low-SES patients receiving fewer relevant diagnostic examinations and less care than patients with high SES (e.g., coronary arteriography, coronary intervention, and evidence-based medical treatment).[2, 4-6]

Primary percutaneous coronary intervention (PPCI) is the recommended treatment for ST-elevation myocardial infarction (STEMI). The efficacy of PPCI has been documented in a number of randomised controlled trials comparing PPCI to thrombolysis.[7, 8] There also appear to be SES-related differences in care among STEMI patients; a number of studies have observed that low-SES patients eligible for PPCI are less likely to receive the treatment than their high-SES counterparts.[2, 4, 5] However, the exact role of SES in relation to post-STEMI outcomes remains poorly understood. Most studies on this topic neither provide detailed individual-level data about SES nor explore different dimensions of SES.[2, 4, 6, 9] They also include only limited details about patient and treatment characteristics,[2, 9] making it difficult to clarify the mechanisms driving the possibly SES-related differences in clinical outcomes. Furthermore, no studies include follow-up information about medical treatment beyond 90 days after hospital discharge, although differences in long-term adherence to secondary medical prophylaxis may potentially be an important factor underlying SES-related differences in clinical outcomes.[1, 5, 6, 10]

We therefore conducted a follow-up study of PPCI-treated patients from Denmark, a country that provides tax-financed health care to all residents and considers PPCI as the standard treatment for STEMI, which should theoretically guarantee equal access to treatment independent of

individual SES. We compared patient and treatment characteristics, as well as short- and long-term outcomes after PPCI according to SES in unselected real-world patients.

Methods

We completed a population-based, historical follow-up study in the Western part of Denmark with approximately 3.3 million inhabitants (56% of the Danish population). The Danish National Health Service provides tax-financed healthcare, guaranteeing unfettered access to medical care. All acute medical conditions are treated exclusively at public hospitals. The Danish Civil Registration System keeps records of sex, date of birth, and changes in vital status. The records carry each patient's unique civil registration number, which is used for all Danish registries, thereby enabling unambiguous record linkage among registries.

Identification of patients

PPCI has been implemented as the standard treatment for STEMI in Denmark since the DANAMI-2 trial,[8] and Danish STEMI patients are almost exclusively treated with PPCI. The Western Denmark Heart Registry (WDHR) collects detailed data related to patients and procedures for all interventions conducted in the three coronary intervention centres in west Denmark: Odense University Hospital, Aarhus University Hospital (Skejby), and Aarhus University Hospital (Aalborg). Reporting to the registry is mandatory and data quality is ensured by automatic validation rules at data entry, combined with systematic validation procedures and random spot-checks of data after entry.[11] We identified all Danish STEMI-patients from 2002-2008 who underwent PPCI within 12 hours of symptom onset (n=7385).

Socioeconomic status

The Integrated Database for Labour Market Research (IDA) collects individual-level socioeconomic data on Danish citizens. From the IDA database, we obtained information about employment status the year prior to hospital admission for each patient (employed or unemployed). Unemployed status indicates that the patient was unemployed, received a pension or an early retirement benefit, or was otherwise economically inactive.

We also retrieved personal income information for each patient and cohabiting partner, including imputed rent for owner-occupied dwellings, interests received, pension withdrawals, unemployment benefits, and the like. This broad definition of income was used in an attempt to reflect the wealth of each patient because it has been suggested that wealth is a more sensitive indicator of SES than income.[12] We calculated the combined average income of each patient and their cohabiting partner in the five years before admission. All patients were divided into tertiles of increasing income. The one-third of patients with the highest income was defined as the high-income group; the remaining two-thirds of patients were defined as the low-income group.

Information regarding the highest completed level of education as registered the year prior to admission was obtained from the Student Registry of Statistics Denmark. Patients were divided into two groups: Long (short-, medium-, and long-term higher education) and short (vocational education, upper or lower secondary school, and primary school).

We also conducted the analyses with three categories in each measure of SES (income: high, medium, and low; education: higher education, vocational/secondary school, and primary school; employment status: employed, unemployed, and pensioner). For all three measures of SES, no differences were present between the two groups with lowest SES.

Patient and treatment characteristics

We obtained data about hypertension, smoking status, Killip class on admission, duration of symptoms, and all procedure-related data from the WDHR.

The Danish National Patient Registry collects data for all hospitalizations at Danish hospitals, including dates of admission and discharge and discharge diagnoses coded according to the International Classification of Diseases (10th revised edition since 1993) (ICD-10). Based on the last 10 years of each patient's hospitalization history, we computed the Charlson Comorbidity Index score which has been validated for the prediction of mortality for patients with a wide range of conditions[13] and has been validated for use with hospital discharge registry data.[14] We defined three levels of comorbidity: a score of 0 ("low"); a score of 1–2 ("moderate comorbidity"); and a score of >2 ("high comorbidity").

The Danish Transfusion Database is a national registry monitoring the use of all blood components. We obtained information regarding the types and number of blood components administered to the patients from the day of admission to 7 days post-admission.

We obtained data regarding the use of cardiovascular drugs from the Danish Medicines Agency's Register of Medicinal Product Statistics, a national prescription registry that contains information on all redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark. The information includes type of drug (according to the Anatomic Therapeutic Chemical classification system) and date dispensed. We identified all prescriptions for aspirin, clopidogrel, nitroglycerin, statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, and selective and nonselective β-blockers filled until two years after hospital discharge. All the drugs were available only by prescription, except for aspirin. However, aspirin is available by prescription, and patients with chronic diseases and pensioners are reimbursed for it.

For a subset of patients (n=4856), data from the Laboratory Information Systems in the Central Denmark and North Denmark Regions were obtained, including data regarding

haemoglobin, serum creatinine level, total cholesterol, troponin-T, and the creatinkinase-myocardial band. For all laboratory values, the highest value measured over 7 days, starting from the time of admission, was obtained except for haemoglobin where the lowest value was obtained. We calculated the estimated glomerular filtration rate (eGFR) using the four-component MDRD equation incorporating age, race, sex, and serum creatinine level.[15] Race was not included because race data was unavailable. Based on haemoglobin values, we classified anaemia into categories for men and women as follows: no anaemia (men, > 8.4 mmol/L; women, >7.4 mmol/L); borderline (men, 7.9–8.4 mmol/L; women, 6.9–7.4 mmol/L); mild (men, 6.6–7.8 mmol/L; women, 5.6–6.8 mmol/L), moderate (men, 5.4–6.5 mmol/L; women, 4.4–5.5 mmol/L), and severe (men, ≤ 5.3 mmol/L; women, ≤ 4.3 mmol/L).

Clinical outcomes

The primary endpoint of this study was major adverse cardiac events (MACE, defined as cardiac death, recurrent myocardial infarction (MI), and target vessel revascularization (TVR)) at 30 days, 1 year, and maximum follow-up.

Data on recurrent MI was obtained from The National Patient Registry (information was available until the end of 2009). We defined a recurrent MI as hospitalization for MI occurring >28 days after the index PCI.[16] Therefore, MACE at 30 days consists of cardiac death and TVR on days 0–30 and recurrent MI on days 28–30.

Deaths were ascertained from the Danish Civil Registration System (information was available until the end of 2010). Data on TVR was obtained from the WDHR. TVR was defined as a new PCI on the index vessel.

Cause of death was retrieved from the Cause of Death Registry. When a Danish citizen dies, the cause of death is reported using ICD-10 diagnosis codes. The following codes defined cardiac

death: I0, I1, I20-25, I27, I3, I4, I50, I51, R96, and R99 (information was available until the end of 2009).

Statistical analyses

The patients were censored at the time of death or followed for up to 8.8 years. Mean follow-up time was 3.7 years. We compared baseline characteristics using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. We used Cox proportional-hazards regression to compute crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the endpoints in each stratum of income, education, and employment status, using "high income", "long education", and "employed" as reference. All tests of significance were two-tailed, with $p < 0.05$ considered statistically significant.

First, we adjusted the crude HRs for patient characteristics. To examine the interrelations between the three different indicators of SES, we mutually adjusted for socioeconomic factors (e.g., models examining the effects of income on mortality were adjusted for education and employment). Next, we added adjustments for the admission findings and procedure-related data. Finally, we added an adjustment for medical treatment during follow-up. All variables listed in Data Supplement Table I were included as covariates in the multivariable models. The analyses were repeated in strata of men and women to examine whether sex affected the associations. Because it might be difficult to use employment status, income, and education as a reflection of SES when the patients in question are above retirement age, we repeated the analyses twice while first restricting it to patients younger than 65 years and then additionally restricting to patients younger than 60 years of age. The analyses were also repeated without mutual adjustment for socioeconomic factors.

The number of patients with complete data for all measured variables was 2983 (33%). For most variables, only 0.0–11% of patients had missing data. However, 23% to 40% of patients had

missing data regarding laboratory data; smoking status; and history of hypertension, diabetes, and hypercholesterolemia. We used multiple imputation to impute missing values for all variables. In addition to all measured variables, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to survival time in the imputation model.[17] Analyses were conducted on five imputed datasets, and the results were combined using Rubin's Rules.[18] To examine the robustness of our analyses, we also conducted complete case analyses restricted to patients with available information about all variables.

We analysed data using STATA version 11.0 (StataCorp, College Station, Texas, USA). Our study was approved by the Danish Data Protection Agency (journal number 2008-41-1835).

Results

Patient and treatment characteristics

Table 1 presents the patient characteristics, admission findings and data related to the PPCI procedure, and medical treatment during follow-up according to SES as indicated by income, education, and employment status. In general, female sex, older age, diabetes, impaired renal function, anaemia, longer duration of symptoms, and high level of comorbidity were more prevalent among low-SES patients than high-SES patients. Low-SES patients were less likely to be treated with GPIIb/IIIa inhibitors during PPCI; they had a lower TIMI Grade flow after PPCI, more in-lab complications, less successful procedures, and fewer stent implantations. Of the stents implanted, fewer were drug-eluting stents compared with high-SES patients. Low-SES patients were less likely to be treated with statins than high-SES patients, but more likely to be treated with diuretics, ACE-inhibitors, and nitroglycerin during follow-up. The low-SES patients were more likely to live alone.

Low-income patients and unemployed patients had a higher prevalence of hypertension; had lower total cholesterol levels, had a higher Killip class on admission; and received more blood

transfusions than their counterparts. The left main coronary artery was also more likely to be identified as the culprit lesion among low-income patients and unemployed patients, while fewer of these patients were active smokers compared with high-income and employed patients, respectively. When education was employed as the indicator of SES, these differences were not present; in contrast, the least educated patients were more likely to be active smokers than their counterparts. (For the full table, see online-only Data Supplement Table I).

Clinical outcomes

Overall, 550 patients (7.4%), 962 patients (13.0%), and 1357 patients (18.4%) experienced a MACE within 30 days, 1 year, and maximum follow-up, respectively.

Table 2 presents clinical endpoints after 30 days, 1 year, and maximum follow-up according to income, education, and employment status. Compared with high-income patients, low-income patients had a higher cumulative risk of MACE after 30 days, 1 year, and maximum follow-up because of a higher incidence of cardiac death and recurrent MI (online-only Data Supplement Table II). After adjustment for patient characteristics, the differences in MACE were substantially attenuated and no longer statistically significant. Further adjustment for admission findings, procedure-related data, and medical treatment during follow-up had very modest effects on the associations.

With education as the indicator of SES, no statistically significant differences were observed in the crude or adjusted HRs of MACE between the two groups.

Unemployed patients had a higher cumulative incidence of MACE after 30 days, 1 year, and maximum follow-up, primarily explained by higher cardiac mortality and a greater incidence of recurrent MI. After adjustment for patient characteristics, none of the differences were statistically

significant. There were no significant changes after further adjustment for admission findings, procedure-related data, and medical treatment during follow-up.

Compared with their counterparts, all-cause mortality was significantly higher among the low-income patients and unemployed patients at all points in time. After adjustment for patient characteristics, the differences were much attenuated but persisted after maximum follow-up. Using employment status as the indicator of SES, the differences also persisted after 30 days and 1 year. Again, further adjustment had a very modest effect on the associations. When education was used as the indicator of SES, no differences in all-cause mortality were observed.

No substantial differences were observed when the analyses were stratified according to sex, the population was restricted to patients younger than 60 or 65 years of age, or without mutually adjusting for socioeconomic factors. Finally, no substantial differences were observed when the findings from the analyses based on the entire study population were compared with the complete case analyses (data not shown).

Discussion

The main findings of our study were that low-SES patients presenting with STEMI and treated with PPCI were older and had a worse baseline risk profile than high-SES patients. These differences could almost entirely explain the poorer crude short- and long-term outcomes in low-SES patients compared with high-SES patients. Differences in admission findings, procedure-related data, and the use of long-term secondary medical prevention only had minor effects.

Our study is in accordance with and extends the findings from a number of other studies, which have observed that SES-related differences in clinical outcome can be either partially[1, 2, 6, 19] or completely[10, 20] ascribed to differences in baseline patient characteristics. However, the possibility of making direct comparisons with and between previously published studies is

somewhat limited. SES is a multi-dimensional concept in which the different dimensions (e.g., income, education, and employment status) are closely related. With few exceptions, previously published studies have focused on only a single measure of SES, and have consequently been unable to explore the independent roles of the different dimensions of SES. Furthermore, very few studies have included data regarding individual-level SES measures.[1, 20, 21] Various area-based measures of SES have been used—for example, median household income, the proportion of university-educated subjects, and employment rates, as well as composite indexes formed by combining these variables. However, use of area-based measures to estimate an individual's SES results in considerable misclassification, and individual-level measures are therefore preferred.[22] The finding that employment status and income, rather than education level, were predictors of clinical outcome in our study is also partly in accordance with the results of previous studies. Aside from different area-based SES indexes, income has so far been the most frequently used measure of SES. Most studies focusing on income have observed that differences in clinical outcome persist after adjustment for differences in patient characteristics,[2, 6, 19] although this finding has not been confirmed by all studies.[20] Additionally, among studies using education level as the measure of SES, some studies observed differences in outcome that persisted after adjustment for patient characteristics,[1] while others observed that differences could be explained by differences in baseline characteristics.[23] One study that used both income and education level as measures of SES observed that income was associated with poor outcomes in all patients, while education level was only associated with outcome in patients younger than 65 years of age.[21] It is possible that "healthy choices" are inculcated early in the Danish school system experience which might explain why we found no association between educational level and outcome. To our knowledge, no recent studies have examined the role of employment status in relation to outcomes after STEMI.

Several studies of MI have reported that high-SES patients are more likely to receive guideline-recommended medications at discharge than are low-SES patients.[5, 6] Other studies have observed that low-income patients were less likely to receive secondary medical prevention after 3 months,[24] and that discontinuation of evidence-based medication was associated with not graduating from high school.[25] The latter study also reported that medication therapy discontinuation was associated with higher mortality. To our knowledge, none of the studies regarding SES-related differences in clinical outcomes after STEMI have included information about secondary medical prevention. Therefore, it is unclear whether the reported SES-related differences in clinical outcome could be mediated by differences in the secondary medical prevention employed during follow-up. We observed no substantial SES-related differences in the use of guideline-recommended medications during the PPCI procedure or after 1 year or 2 years. Thus, in the setting of a universal, tax-financed, health care system the poor outcomes in low-SES patients appeared not to be explained by differences in acute treatment or long-term secondary medical prevention.

The fact that the poor outcome related to low SES was primarily explained by differences in baseline characteristics, including higher comorbidity, highlights the need for primary prevention strategies. These strategies should be aimed at low-SES groups.

Study strengths and limitations

The main strengths of this study are the large number of patients; the long follow-up period; the prospective, population-based design; and the unambiguous individual-level linkage between public data sources. The latter provided detailed information regarding patient characteristics, SES, treatment and use of medications, and allowed complete follow-up, minimizing the risk of selection bias.

Thrombolysis is still widely used in most countries. The mechanisms that determine whether to use thrombolysis or PPCI are unclear. If these mechanisms differ among groups with different SESs, as some studies indicate,[2, 4, 5] bias may result. The present study was conducted in Denmark, where STEMI patients are almost exclusively treated with PPCI. This clinical situation optimizes external validity and minimizes the risk of bias in this study because the WDHR contains data regarding all procedures without any inclusion or exclusion criteria. However, selection bias might be present if the risk of sudden cardiac death before hospital admission is associated with SES. Previous studies indicate that sudden cardiac death is associated with low SES.[26] If this is the case, the SES-associated differences in outcomes that we report may be a conservative estimate of the true difference in outcomes.

The limitations of this study include the use of hospital discharge diagnoses, which may not always be accurate. However, the validity of the majority of the diagnoses included in this study is high.[27] Furthermore, any misclassification is unlikely to depend on SES. Moreover, although we controlled for a wide range of factors that may affect clinical outcome, we cannot, due to the observational study design, exclude the possibility that confounding factors still influenced the results, including factors for which information was unavailable (e.g., lifestyle habits and patient compliance). Race is often closely intertwined with SES[5, 6, 20] and thus might bias the results since race data was unavailable. However, our results are not likely to be substantially biased by race because the population of Denmark is primarily Caucasian.

Our results might not apply to countries without tax-financed health care where SES-related differences in care may also contribute to the SES-related differences in clinical outcome. Our findings may therefore be a conservative estimate of the SES-related differences in clinical outcome that could be found in such countries.

Conclusions

Even in a universal, tax-financed, health care system, low-SES STEMI patients treated with PPCI face a worse prognosis than high-SES patients. The poor outcome appears to be primarily explained by differences in baseline patient characteristics, rather than differences in acute treatment or long-term secondary medical prophylaxis. Employment status and income, but not education level, were associated with clinical outcomes.

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Disclosures

None.

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Table 1. Patient characteristics, admission findings and procedure related data, and medical treatment during follow-up according to socioeconomic status.

Variable	Income		Education		Employment status	
	High (n=2508)	Low (n=4877)	Long (n=1013)	Short (n=6372)	Employed (n=2826)	Unemployed (n=4559)
Patient characteristics						
Male sex	82.1%	68.6%*	82.0%	71.8%*	84.4%	66.2%*
Age						
• <65	82.1%	37.7%*	65.5%	50.5%*	93.3%	27.7%*
• 65-80	14.8%	45.5%*	30.0%	35.9%*	6.4%	52.9%*
• >80	3.1%	16.8%*	4.5%	13.3%*	0.3%	19.4%*
Comorbidity						
• Low	75.8%	61.0%*	75.2%	64.6%*	79.9%	57.5%*
• Medium	21.3%	29.9%*	21.5%	27.8%*	18.0%	32.5%*
• High	2.9%	9.1%*	3.3%	7.6%*	2.1%	10.0%*
Diabetes	7.5%	10.5%*	6.1%	10.1%*	6.4%	11.4%*
Previous myocardial infarction	13.3%	17.1%*	13.2%	17.2%*	12.0%	18.2%*
Smoking status						
• Never	19.3%	22.3%*	25.4%	20.6%*	16.3%	24.5%*
• Previous	21.7%	25.7%*	27.0%	23.8%	18.2%	28.2%*
• Active	59.0%	52.0%*	47.6%	55.6%*	65.5%	47.3%*

Admission findings & procedure related data

Duration of symptoms (hours)	3.3 (3.3-3.4)	3.6 (3.5-3.6)*	3.4 (3.2–3.5)	3.5 (3.5–3.6)*	3.3 (3.2–3.4)	3.6 (3.5-3.7)*
Killip class on admission						
• I	93.1%	89.3%*	91.3%	90.5%	93.8%	88.6%*
• II	3.3%	5.7%*	4.6%	4.9%	3.0%	6.0%*
• III	1.8%	2.4%	1.9%	2.2%	1.6%	2.6%*
• IV	1.8%	2.6%*	2.2%	2.4%	1.6%	2.8%*
Stent implantation	94.4%	92.1%*	94.4%	92.7%*	95.4%	91.3%*
Stent type						
• BMS	50.0%	56.1%*	48.6%	54.9%*	48.6%	57.5%*
• DES	50.0%	43.9%*	51.4%	45.1%*	51.4%	42.5%*
TIMI Grade flow after PCI						
• 0	1.7%	2.7%*	1.0%	2.6%*	1.6%	2.9%*
• 1	0.7%	1.4%*	0.8%	1.3%	0.8%	1.4%*
• 2	4.8%	5.7%	5.6%	5.3%	4.2%	6.1%*
• 3	92.7%	90.2%*	92.6%	90.8%*	93.4%	89.6%*
In-lab complication	2.3%	3.3%*	2.5%	3.0%	2.2%	3.4%*
Successful procedure	97.0%	95.2%*	97.5%	95.5%*	97.6%	94.7%*
Red blood cell transfusion	1.6%	3.5%*	2.5%	2.9%	1.7%	3.6%*

Heparin during PCI	98.2%	98.4%	98.0%	98.4%	98.2%	98.4%
GPIIb/IIIa during PCI	73.9%	67.5%*	74.2%	69.0%*	75.2%	66.2%*
Aspirin during PCI	96.9%	96.3%	95.9%	96.6%	96.7%	96.4%
Clopidogrel during PCI	84.4%	83.0%	84.5%	83.3%	84.3%	83.0%
Medical treatment during follow-up						
Aspirin						
• 1 year	91.8%	90.8%	89.4%	91.4%	92.5%	90.2%
• 2 years	89.4%	88.9%	87.3%	89.4%	89.6%	88.7%
Clopidogrel						
• 1 year	67.1%	66.2%	67.4%	66.3%	66.6%	66.4%
• 2 years	8.7%	10.1%	10.5%	9.4%	8.1%	10.6%*
β-blocker						
• 1 year	82.1%	81.1%	79.5%	81.8%	82.7%	80.6%
• 2 years	76.6%	77.7%	74.7%	77.7%	77.4%	77.3%
Statin						
• 1 year	91.9%	86.2%*	90.4%	87.9%*	91.1%	86.2%*
• 2 years	89.6%	84.8%*	87.6%	86.4%	88.8%	85.0%*
ACE-inhibitor						
• 1 year	54.6%	56.9%	53.8%	56.4%	54.5%	57.1%*
• 2 years	52.7%	55.9%*	54.4%	54.8%	52.1%	56.6%*
Diuretics						
• 1 year	22.3%	38.9%*	25.5%	34.2%*	20.1%	42.0%*
• 2 years	23.6%	38.5%*	25.4%	34.3%*	20.9%	41.6%*

Nitroglycerin						
• 1 year	14.0%	21.3%*	15.1%	19.3%*	13.2%	22.5%*
• 2 years	14.3%	21.3%*	15.4%	19.2%*	13.3%	22.5%*

Data are presented as mean values with 95% confidence intervals, or as a percentage. ACE indicates angiotensin converting enzyme; BMS, bare metal stent; DES, drug-eluting stent; GPIIb/IIIa, glycoprotein IIb/IIIa inhibitors; PCI, percutaneous coronary intervention.

*$p < 0.05$

Table 2. Crude and adjusted hazard ratios (HRs) of clinical endpoints at 30 days, 1 year, and maximum follow-up, according to socioeconomic status.

	Unadjusted	**Adjusted 1***	**Adjusted 2†**	**Adjusted 3‡**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
30-days MACE				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	1.87 (1.53–2.29)	1.09 (0.85–1.39)	0.98 (0.74–1.31)	0.97 (0.73–1.29)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.02 (0.75–1.39)	0.84 (0.65–1.09)	0.76 (0.57–1.00)	0.74 (0.55–0.98)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	2.55 (2.07–3.13)	1.10 (0.82–1.47)	0.97 (0.70–1.34)	0.95 (0.68–1.31)
1-year MACE				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	1.61 (1.39–1.87)	1.13 (0.94–1.36)	1.09 (0.89–1.33)	1.07 (0.88–1.31)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.00 (0.80–1.26)	0.85 (0.70–1.03)	0.83 (0.67–1.02)	0.83 (0.68–1.03)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	1.93 (1.67–2.23)	1.09 (0.89–1.34)	1.07 (0.85–1.33)	1.03 (0.82–1.28)

MACE at maximum follow-up				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	1.56 (1.39–1.77)	1.16 (1.00–1.35)	1.13 (0.96–1.33)	1.11 (0.94–1.30)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.21 (0.91–1.38)	0.93 (0.77–1.11)	0.90 (0.57–1.09)	0.91 (0.76–1.09)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	1.78 (1.58–2.00)	1.14 (0.97–1.35)	1.13 (0.94–1.35)	1.10 (0.92–1.32)
30-day cardiac mortality				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	2.83 (2.16–3.71)	1.23 (0.89–1.70)	1.06 (0.72–1.55)	1.08 (0.74–1.59)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.16 (0.74–1.82)	0.87 (0.63–1.21)	0.79 (0.55–1.13)	0.73 (0.50–1.08)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	4.58 (3.40–6.18)	1.33 (0.90–1.97)	1.09 (0.70–1.72)	1.06 (0.68–1.67)
1-year cardiac mortality				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	3.11 (2.42–4.01)	1.29 (0.96–1.74)	1.11 (0.78–1.57)	1.11 (0.79–1.57)

Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.25 (0.79–1.98)	0.92 (0.67–1.25)	0.85 (0.60–1.20)	0.83 (0.58–1.18)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	5.07 (3.83–6.69)	1.40 (0.98–2.01)	1.24 (0.82–1.86)	1.19 (0.79–1.79)
Cardiac mortality at maximum follow-up				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	3.10 (2.48–3.87)	1.26 (0.97–1.65)	1.11 (0.83–1.50)	1.10 (0.82–1.48)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.35 (0.91–2.00)	0.92 (0.69–1.23)	0.84 (0.59–1.18)	0.82 (0.59–1.16)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	5.16 (4.03–6.61)	1.50 (1.09–2.06)	1.32 (0.93–1.89)	1.31 (0.91–1.86)
30-day all-cause mortality				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	2.65 (2.08–3.39)	1.16 (0.86–1.55)	0.99 (0.70–1.40)	1.00 (0.71–1.42)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.16 (0.78–1.74)	0.87 (0.65–1.17)	0.80 (0.58–1.12)	0.75 (0.53–1.06)
Employment status				

Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	4.47 (3.40–5.87)	1.54 (1.08–2.20)	1.31 (0.87–1.97)	1.27 (0.84–1.91)
1-year all-cause mortality				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	3.01 (2.44–3.69)	1.20 (0.94–1.53)	1.07 (0.81–1.43)	1.04 (0.79–1.38)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.24 (0.82–1.87)	0.90 (0.69–1.17)	0.86 (0.64–1.16)	0.86 (0.64–1.16)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	5.16 (4.09–6.51)	1.53 (1.13–2.06)	1.37 (0.98–1.91)	1.32 (0.94–1.84)
All-cause mortality at maximum follow-up				
Income				
High	1.00 (reference)	1.00	1.00	1.00
Not high	3.06 (2.67–3.51)	1.23 (1.04–1.45)	1.19 (0.99–1.43)	1.14 (0.95–1.37)
Education				
Long	1.00 (reference)	1.00	1.00	1.00
Not long	1.38 (0.99–1.84)	0.93 (0.77–1.11)	0.86 (0.69–1.08)	0.87 (0.71–1.08)
Employment status				
Employed	1.00 (reference)	1.00	1.00	1.00
Not employed	5.33 (4.57–6.22)	1.52 (1.25–1.86)	1.42 (1.14–1.75)	1.48 (1.19–1.84)

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiac events (cardiac death, recurrent myocardial infarction and target vessel revascularization).

*Adjusted for patient characteristics and mutual adjustment for socioeconomic factors (see Data Supplement Table I)

† Adjusted as in * and also for admission findings and procedure-related data (see Data Supplement Table I)

‡ Adjusted as in † and also for medical treatment during follow-up (see Data Supplement Table I)

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