Association between reduced left ventricular ejection fraction following non-ST-segment elevation myocardial infarction and long-term mortality in patients of advanced age

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ABSTRACT

Objectives: We sought to investigate the association between LVEF and clinical outcomes after NSTEMI, and the benefit of guideline-recommended pharmacotherapy in elderly patients.

Background: New-onset reduction in LVEF is common after NSTEMI in patients of advanced age. There is little information about outcomes in relation to LVEF, and the benefit of guideline-recommended pharmacotherapy in elderly patients.

Materials and methods: The SWEDEHEART registry was used to identify all patients in Sweden >80 years with NSTEMI from 2011 to 2014. A normal LVEF was defined as >50%; mildly reduced, 40%–49%; moderately reduced, 30%–39%; and severely reduced, <30%. Cox regression was used to calculate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between a reduced LVEF compared with a normal LVEF and all-cause mortality. Similarly, the presence versus absence of treatment with guideline-recommended medications at discharge and mortality was evaluated.

Results: 6287 patients were included where 59%, 20%, 13%, and 6% had a normal, mildly reduced, moderately reduced, and severely reduced LVEF, respectively. During a median follow-up of 2.4 years, 2211 (35%) patients died. All three categories of impaired LVEF were associated with higher mortality: mildly reduced (1.44, 1.25–1.65), moderately reduced (1.93, 1.67–2.23), and severely reduced (3.24, 2.74–3.85). Patients who were treated with beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, or statins at discharge had lower mortality.

Conclusions: New-onset reduction of the LVEF is common in advanced-age patients with NSTEMI and is associated with higher mortality. Treatment with guideline-recommended medications is associated with a better prognosis.

1. Introduction

Mortality due to acute myocardial infarction has decreased in the last few decades, but both morbidity and mortality remain high in patients with heart failure [1,2]. Ischemic heart disease is the leading cause of systolic heart failure, also termed heart failure with reduced ejection fraction, for which guideline-directed therapy is of great importance to improve the prognosis. In contrast, heart failure with preserved ejection fraction is frequently encountered in the aging population, for which recommendations regarding practice of care are missing [3,4]. A history of either myocardial infarction or chronic ischemic heart disease is a well-known important precipitating factor for the development and/or aggravation of heart failure. After non-ST-segment elevation myocardial infarction (NSTEMI), patients of advanced age are more vulnerable to the development of acute heart failure than are younger patients because their ongoing ischemic burden is often underestimated [5–7]. Because of the high prevalence of comorbidities and concerns about complications, these patients are often treated

conservatively, and revascularization is withheld [8]. The prognosis of ischemic heart failure is worse than the prognosis of other etiologies of heart failure [9]. The European Society of Cardiology/American College of Cardiology/American Heart Association guidelines recommend appropriate revascularization as well as initiation of medical management with beta-adrenergic blockers (BBs), angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists (ACEIs/ARBs), and statins, which are the main line of therapy to reduce mortality and rehospitalization following NSTEMI [8]. Angiotensin receptor-neprilysin inhibitors were recently found to be superior to ACEIs alone in patients with heart failure with reduced ejection fraction [10]. Despite improvements in medical therapy and the increased availability of device therapies, management of heart failure remains a challenge for clinicians. However, patients of advanced age are underrepresented or often excluded from participation in randomized controlled trials; thus, clinical data in this patient population are scarce. In the present study, we investigated the association between new-onset of reduced left ventricular ejection fraction (LVEF) and long-term mortality after NSTEMI and examined how often guideline-recommended medications are used after NSTEMI in patients >80 years of age with a reduced LVEF.

2. Materials and methods

2.1. Study population

Data were collected from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) [11] registry as previously described [6]. SWEDEHEART is a nationwide registry on cardiac care and includes virtually all myocardial infarctions, cardiac revascularizations, and cardiac surgeries in Sweden. All information used in the present study, including comorbidities and medication at discharge, was collected from the SWEDEHEART registry. All 17,935 patients aged >80 years with NSTEMI from 2011 to 2014 in Sweden were eligible for inclusion in the study. We excluded patients with a history of heart failure (n = 4636), other serious diseases such as cancer or dementia that may have led to the withholding of recommended treatment (n = 2795), all patients with type 3 to 5 myocardial infarction (n = 410), and lack of information on the LVEF during the index hospitalization (n = 3807). The final study population comprised 6287 patients with information about LVEF during the index hospitalization for NSTEMI. The patients' baseline characteristics were assessed on the day of admission. Baseline medications were those that patients were using before admission, and medications used after discharge were those with which patients were discharged. This study was approved by the local ethics committee and adhered to the Declaration of Helsinki.

2.2. Definition of acute heart failure

Patients were categorized according to their LVEF as evaluated by echocardiography during the index hospitalization: mildly reduced, 40% to 49%; moderately reduced, 30% to 39%; and severely reduced, <30%. A normal LVEF was defined as >50%. Echocardiography using a standard protocol is normally performed by dedicated physicians (so-called clinical physiologists or cardiologists) assigned to work at cardiac care units in Sweden.

2.3. Exposure and outcome

Patients with a reduced LVEF during the index hospitalization for NSTEMI were considered exposed, while patients with a normal LVEF were used as referents. The primary outcome was all-cause mortality. Patients were followed from the admission date until death or 10 March 2016, which was the last date on which information about all-cause mortality was available, whichever came first.

2.4. Statistical analysis

For descriptive statistics, numerical variables are summarized as mean and standard deviation, and categorical variables are summarized as frequency and percentage. The age-adjusted overall survival rate according to the LVEF was assessed using the Kaplan–Meier method. Cox regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between a reduced versus normal LVEF and the outcome all-cause mortality after adjustment for age, sex, diabetes, hypertension, history of myocardial infarction and heart failure, stroke, and chronic kidney disease. The association between cardiovascular medications at discharge (i.e., BBs, ACEIs/ARBs, mineralocorticoid receptor antagonists [MRAs], *CCB*, loop diuretics [LDs], and statins) and the LVEF was also assessed. In addition, patients with and without treatment with cardiovascular drugs at discharge were compared. Furthermore, the patients were stratified to

whether they were treated with percutaneous coronary intervention (PCI) during hospitalization, and the association between the LVEF and all-cause mortality was evaluated in each subgroup. One model estimated the crude HR with 95% CI for all-cause mortality at 30 days, 1 year, and end of follow-up; a second model was adjusted for age; and a third model was adjusted for age, sex, diabetes, LVEF, previous stroke, previous myocardial infarction, and estimated glomerular filtration rate.

In all analyses, P-values of <0.05 were considered statistically significant. The collected data were analyzed with STATA version 13.1 software (Stata Corporation, College Station, TX).

3. Results

3.1. Study population

In total 6287 patients were included in the present study. Their mean age was 85 years, and men and women were equally distributed. In total, 63% of patients had a history of hypertension, 23% had diabetes, 31% had prior myocardial infarction, and 12% had prior stroke. According to the echocardiographic examinations performed during hospitalization, a reduced LVEF was present in 40% of patients, and 47% had an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 (Table 1). The patients with a lower LVEF were more often men, had a higher heart rate, and more often had diabetes and chronic kidney disease; however, they were less likely to have a history of cardiac revascularization. In addition, during hospitalization, patients with an LVEF of <40% were less likely to undergo PCI than patients with an LVEF of ≥40%.

At admission, 53% of patients were treated with aspirin, 50% with BBs, 44% with ACEIs or A2-blockers, and 34% with statins (Table 1). There were small differences in the use of medication at admission among patients with different LVEFs post-MI.

3.2. LVEF

During the index hospitalization, 40% of patients had a reduced LVEF (mildly reduced in 20%, moderately reduced in 14%, and severely reduced in 6%) (Table 1).

3.3. Mortality in relation to LVEF

During a median follow-up of 2.4 years, 2211 patients died (Table 2). The incidence rate of death during follow-up was 11, 16, 23, and 44 deaths per 100 person-years among patients with a normal, mildly reduced, moderately reduced, and severely reduced LVEF, respectively. After adjustment for confounders, patients with a reduced versus normal LVEF had higher mortality in all three categories of reduced LVEF: mildly reduced (HR, 1.44; 95% CI, 1.25–1.65), moderately reduced (HR, 1.93; 95% CI, 1.67–2.23), and severely reduced LVEF (HR, 3.24; 95% CI, 2.74–3.85). The cumulative age-adjusted mortality during follow-up is described in Fig. 1.

A total of 1042 deaths occurred during 1 year of follow-up. The association between LVEF and death at 1 year was similar to the association found at the end of follow-up (Table 2).

A total of 306 deaths occurred within 30 days of admission (Table 2). The incidence rate of death during 30 days of follow-up was 28, 48, 117, and 304 deaths per person-year, in each category of LVEF. The absolute risks of death within 30 days among patients with a normal, mildly reduced, moderately reduced, and severely reduced LVEF were 2.3%, 3.9%, 9.3%, and 23.0%, respectively. The adjusted relative risks were more than three-fold higher among patients with a moderately reduced LVEF (HR, 3.59; 95% CI, 2.47–5.21) and more than six-fold higher among patients with a severely reduced LVEF (HR, 6.71; 95% CI, 4.63–9.73).

The study population was stratified into those who underwent PCI (n = 3760; 59%) and those who were treated conservatively

Table 1
Baseline characteristics of 6287 patients above 80 years of age with non-ST segment elevation myocardial infarction in relation to left ventricular ejection fraction.

Variables[a]	All patients	Left ventricular ejection fraction				P-value
		≥50%	40–49%	30–39%	<30%	
Number of patients, n (%)	6287 (100)	3738 (60)	1284 (20)	862 (14)	403 (6)	
Age, years	84.6 (3.7)	84.4 (3.5)	84.7 (3.7)	85.0 (3.8)	85.5 (4.1)	<0.001
Male sex, n (%)	3158 (50)	1783 (48)	671 (52)	476 (55)	228 (57)	<0.001
BMI	25.9 (10)	26.1 (12)	25.7 (4.0)	25.5 (4.3)	24.7 (4.2)	0.043
Heart rate, bpm	85.4 (24)	82.8 (23)	85.6 (23)	91.3 (24)	96.4 (26)	<0.001
Systolic blood pressure, mm Hg	152.8 (30)	156.4 (30)	151.4 (28)	145.7 (29)	138.5 (28)	<0.001
Hemoglobin, g/dl	131.1 (16)	131.5 (16)	130.8 (17)	130.2 (17)	129.7 (17)	0.033
HbA1C mmol/l	44.6 (12)	44.8 (12)	44.8 (13)	44.1 (10)	44.1 (11)	0.955
Hs Troponin T, n (%)	4257 (68)	2494 (67)	901 (70)	602 (70)	260 (65)	0.052
Troponin T, n (%)	448 (7)	276 (7)	82 (6)	60 (7)	30 (8)	0.644
Troponin I, n (%)	1535 (25)	935 (25)	297 (23)	193 (23)	110 (27)	0.115
CKMB, n (%)	6 (0.1)	3 (0.1)	2 (0.2)	1 (0.1)	0 (0)	0.803
Serum LDL, mmol/l	2.83 (1.1)	2.9 (1.1)	2.8 (1.1)	2.7 (1.1)	2.7 (1.1)	<0.001
Diabetes, n (%)	1426 (23)	790 (21)	303 (24)	222 (26)	111 (28)	0.001
Previous MI, n (%)	1920 (31)	1113 (30)	405 (32)	275 (32)	127 (32)	0.450
Previous stroke, n (%)	733 (12)	427 (11)	145 (11)	113 (13)	48 (12)	0.539
Previous PCI, n (%)	983 (16)	609 (16)	200 (16)	129 (15)	45 (11)	0.171
Hypertension, n (%)	3938 (63)	2431 (65)	764 (60)	516 (60)	227 (56)	<0.001
Treatment received during hospitalization						
PCI	2578 (41)	1624 (43)	534 (42)	308 (36)	112 (28)	<0.001
No PCI	3709 (59)	2114 (57)	750 (58)	554 (64)	291 (72)	
Estimated glomerular filtration rate, ml/min/1.73 m^2						
≥60	3185 (53)	1937 (55)	674 (55)	411 (50)	163 (43)	<0.001
30–59	2390 (40)	1382 (39)	479 (39)	356 (43)	173 (45)	
<30	380 (6.4)	201 (5.7)	71 (5.8)	62 (7.5)	46 (12.0)	
Medication at admission						
Aspirin, n (%)	3328 (53)	1973 (53)	670 (53)	473 (55)	212 (53)	0.667
P2Y12i, n (%)	589 (9.4)	358 (9.6)	109 (8.5)	80 (9.3)	42 (11)	0.610
OAC, n (%)	587 (9.4)	310 (8.3)	141 (11)	95 (11)	41 (10)	0.006
ACEi, n (%)	1646 (26)	958 (26)	332 (26)	241 (28)	115 (29)	0.329
A2-blockers, n (%)	1133 (18)	709 (19)	232 (18)	144 (17)	48 (12)	0.004
Betablockers, n (%)	3107 (50)	1863 (50)	642 (50)	411 (48)	191 (48)	0.615
CCB, n (%)	1747 (28)	1113 (30)	322 (25)	214 (25)	98 (24)	0.001
Insulin, n (%)	625 (10)	334 (8.9)	141 (11)	100 (12)	50 (12)	0.010
Oral antidiabetics, n (%)	686 (11)	392 (11)	141 (11)	102 (12)	51 (13)	0.416
Diuretics, n (%)	2163 (35)	1276 (34)	441 (35)	291 (34)	155 (39)	0.360
MRA/aldosterone blockers, n (%)	167 (3.4)	90 (3.1)	38 (3.9)	23 (3.5)	16 (5.1)	0.226
Statins, n (%)	2144 (34)	1297 (35)	433 (34)	285 (33)	129 (32)	0.644
Digitalis, n (%)	174 (2.8)	100 (2.7)	30 (2.4)	35 (4.1)	9 (2.2)	0.078
Nitrates, n (%)	1376 (22)	828 (22)	258 (20)	193 (23)	97 (24)	0.297
Any anticoagulant, n (%)	4962 (79)	2986 (80)	1022 (78)	658 (76)	296 (74)	0.003

Abbreviations: Bmp, beat per minute; BMI, body mass index; CK-MB, creatine kinase-muscle/brain; PCI, percutaneous coronary intervention; ACEi, angiotensin-converting enzyme inhibitor; A2-blocker, angiotensin receptor blocker; CCB, calcium channel blocker.

[a] Variables are summarized using mean and standard deviation unless otherwise stated.

Table 2
Risks of early and late mortality in patients above 80 years of age with non-ST Segment elevation myocardial infarction, in relation to left ventricular ejection fraction.

	Left ventricular ejection fraction			
	≥50%,	40–49%	30–39%,	<30%
Number of patients, n (%)	3738 (60)	1284 (20)	862 (14)	403 (6.4)
	HR, (95% CI)	HR, (95% CI)	HR, (95% CI)	HR, (95% CI)
30-day mortality				
Number of deaths (%)	85(2.3)	50 (3.9)	80 (9.3)	91 (23)
Crude	1.0	1.71 (1.20–2.44)	4.18 (3.07–5.69)	10.68 (7.90–14.43)
Age-adjusted	1.0	1.67 (1.18–2.38)	4.01 (2.95–5.46)	9.78 (7.21–13.25)
Multivariable adjustment[a]	1.0	1.41 (0.91–2.18)	3.59 (2.47–5.21)	6.71 (4.63–9.73)
1-year mortality				
Number of deaths (%)	392 (11)	231 (18)	229 (27)	190 (47)
Crude	1.0	1.78 (1.51–2.09)	2.83 (2.40–3.33)	5.96 (5.00–7.10)
Age-adjusted	1.0	1.73 (1.47–2.03)	2.69 (2.29–3.17)	5.42 (4.55–6.47)
Multivariable adjustment[a]	1.0	1.78 (1.46–2.16)	2.59 (2.13–3.16)	4.97 (4.01–6.15)
Mortality at end of follow-up				
Number of deaths (%)	1031 (28)	489 (38)	419 (49)	272 (67)
Crude	1.0	1.52 (1.37–1.69)	2.16 (1.92–2.41)	3.91 (3.41–4.47)
Age-adjusted	1.0	1.48 (1.33–1.65)	2.05 (1.83–2.30)	3.60 (3.15–4.13)
Multivariable adjustment[a]	1.0	1.44 (1.25–1.65)	1.93 (1.67–2.23)	3.24 (2.74–3.85)

CI: Confidence interval, HR: hazard ratio.

[a] Adjusted by age, sex, diabetes, hypertension, previous myocardial infarction, previous stroke and eGFR, medicines at discharge (Aspirin, P2Y12i, ACEi, A2-blockers, betablockers, diuretics, aldosterone blockers, statins).
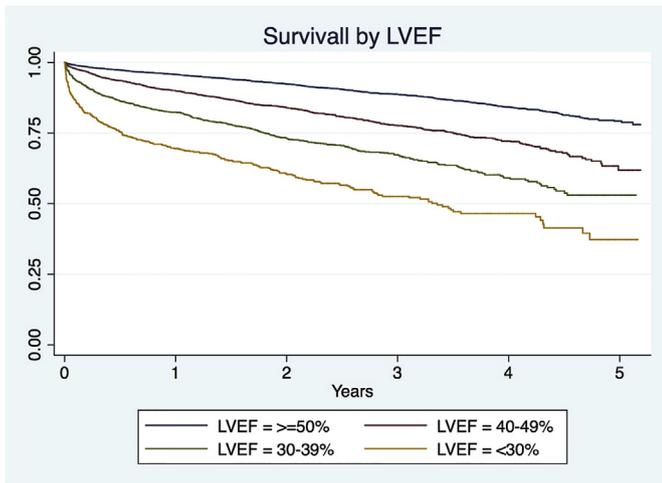
Fig. 1. Age-adjusted cumulative survival in relation to LVEF.

3.4. Medication at discharge

In total, 85% of patients were prescribed BBs, 53% ACEIs, 20% A2-blockers, 25% CCB, 43% LDs, 7.3% MRAs, and 78% statins at discharge (Table 4). With increasing impairment of LVEF, patients were less likely to receive all medication except for oral anticoagulants, ACEIs, insulin, digitalis, and LDs. The largest difference was found for LDs; 26% of patients among those with an LVEF of >50% and 66% of patients among those with an LVEF of <30% were taking LDs.

Treatment with statins, aspirin, and P2Y12i was associated with a lower mortality in both patients with normal and reduced LVEF (Table 5, supplement). Treatment with *CCB*, ACEi, and ARBs was associated with lower mortality only in patients with reduced LVEF. Treatment with LDs was associated with higher mortality in all categories of LVEF (Table 5, supplement). Treatment with MRAs was not associated with mortality. Fig. 2A−F, depicts the cumulative age-adjusted survival in patients with and without treatment with betablockers, ARBs, ACEi, statins, LDs, and MRAs.

4. Discussion

In this study, we determined the prevalence and prognostic implications of a reduced LVEF after NSTEMI in patients aged >80 years. We found that 40% of patients in this age group had previously unknown impairment of the LVEF when investigated

(n = 2604; 41%) during the index hospitalization (Table 3). An association was found between a reduced LVEF and higher mortality both in patients who were treated with PCI and those who were not, although the association seemed to be stronger among patients who underwent PCI during hospitalization.

Table 3
Risks of early and late mortality in patients above 80 years of age with non-ST segment elevation myocardial infarction, in relation to left ventricular ejection fraction, stratified by treatment with or without PCI.

	Left ventricular ejection fraction			
	≥50%	40−49%	30−39%	<30%
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Patients treated with PCI during hospitalization **n = 3760**				
30-day mortality				
Number of deaths (%)	14 (0.9)	9 (1.7)	12 (3.9)	19 (17)
Crude	1.0	1.96 (0.85−4.53)	4.62 (2.14−9.98)	17.21 (8.31−36.66)
Age-adjusted	1.0	1.96 (0.85−4.53)	4.40 (2.03−9.53)	16.27 (7.83−33.77)
Multivariable adjustment[a]	1.0	2.17 (0.78−6.03)	3.69 (1.28−10.64)	13.62 (5.08−36.51)
1-year mortality				
Number of deaths (%)	85 (5.2)	46 (8.6)	40 (13)	42 (38)
Crude	1.0	1.67 (1.17−2.39)	2.62 (1.80−3.82)	8.45 (5.76−12.39)
Age-adjusted	1.0	1.67 (1.17−2.39)	2.54 (1.74−3.69)	8.20 (5.59−12-03)
Multivariable adjustment[a]	1.0	1.95 (1.28−2.97)	2.27 (1.41−3.65)	8.89 (5.59−14.13)
Mortality at end of follow-up				
Number of deaths (%)	284 (18)	135 (25)	91 (30)	56 (50)
Crude	1.0	1.52 (1.24−1.87)	1.90 (1.50−2-41)	4.53 (3.37−6.10)
Age-adjusted	1.0	1.51 (1.23−1.86)	1.83 (1.45−2.32)	4.34 (3.22−5.85)
Multivariable adjustment[a]	1.0	1.52 (1.17−1.97)	1.59 (1.18−2.14)	4.63 (3.25−6.58)
Patients without PCI during hospitalization **n = 2604**				
30-day mortality				
Number of deaths (%)	71 (3.4)	41 (5.5)	68 (12)	72 (25)
Crude	1.0	1.63 (1.10−2.40)	3.77 (2.69−5.27)	8.32 (5.97−11.59)
Age-adjusted	1.0	1.60 (1.08−2.36)	3.70 (2.64−5.18)	8.00 (5.73−11-16)
Multivariable adjustment[a]	1.0	1.33 (0.82−2.16)	3.57 (2.39−5.33)	6.03 (4.01−9.08)
1-year mortality				
Number of deaths (%)	307 (15)	185(25)	189 (34)	148 (51)
Crude	1.0	1.79 (1.49−2.15)	2.70 (2.25−3.24)	4.78 (3.93−5.83)
Age-adjusted	1.0	1.73 (1.44−2.08)	2.63 (2.19−3.16)	4.53 (3.71−5.52)
Multivariable adjustment[a]	1.0	1.75 (1.41−2.19)	2.64 (2.11−3.29)	4.31 (3.67−5.51)
Mortality at end of follow-up				
Number of deaths (%)	747 (35)	354 (47)	328 (60)	216 (74)
Crude	1.0	1.52 (1.34−1.73)	2.15 (1.89−2.45)	3.34 (2.86−3.88)
Age-adjusted	1.0	1.48 (1.30−1.68)	2.08 (1.83−2.37)	3.19 (2.74−3.72)
Multivariable adjustment[a]	1.0	1.43 (1.21−1.68)	2.04 (1.73−2.41)	2.96 (2.43−3.60)

CI: Confidence interval, HR: hazard ratio.

[a] Adjusted for age, sex, diabetes, hypertension, previous myocardial infarction, previous stroke and eGFR, prescribed medication at discharge (Aspirin, P2Y12i, ACEi, A2-blockers, betablockers, diuretics, aldosterone blockers, statins).

Table 4
Medication prescribed at discharge for 6287 patients above 80 years of age in relation to left ventricular ejection fraction assessed during hospitalization for non-ST segment elevation myocardial infarction.

Medication at discharge	All patients	Left ventricular ejection fraction				P-value
		≥50%	40−49%	30−39%	<30%	
Aspirin, n (%)	5501 (88)	3347 (90)	1111 (87)	733 (85)	310 (77)	<0.001
P2Y12i, n (%)	4707 (75)	2905 (78)	971 (76)	591 (69)	240 (60)	<0.001
OAC, n (%)	920 (15)	478 (13)	213 (17)	163 (19)	66 (17)	<0.001
ACEi, n (%)	3307 (53)	1820 (49)	717 (56)	538 (62)	232 (58)	<0.001
A2-blockers, n (%)	1232 (20)	778 (21)	252 (20)	153 (18)	49 (12)	<0.001
Betablockers, n (%)	5362 (85)	3175 (85)	1125 (88)	743 (86)	319 (80)	<0.001
CCB, n (%)	1582 (25)	1151 (31)	274 (21)	123 (14)	34 (8.5)	<0.001
Insulin, n (%)	637 (10)	345 (9.2)	147 (12)	93 (11)	52 (13)	0.021
Oral antidiabetics, n (%)	642 (10)	379 (10)	130 (10)	96 (11)	37 (9.2)	0.735
Diuretics n (%)	2703 (43)	1350 (36)	569 (46)	491 (57)	266 (66)	<0.001
MRA/aldosterone blockers, n (%)	354 (7.3)	139 (4.8)	73 (7.5)	94 (14)	48 (15)	<0.001
Statins, n (%)	4882 (78)	2996 (80)	1008 (79)	630 (73)	248 (62)	<0.001
Digitalis, n (%)	201 (3.2)	98 (2.6)	45 (3.5)	36 (4.2)	22 (5.5)	0.003
Nitrates, n (%)	1834 (29)	1214 (30)	373 (29)	234 (27)	103 (26)	0.151

Abbreviations: OAC, oral anticoagulant; ACEi, angiotensin-converting enzyme inhibitor; A2-blockers, angiotensin receptor blocker; CCB, calcium channel blocker. MRA; mineralocorticoid receptor antagonist/aldosterone blockers.

with echocardiography during hospitalization for NSTEMI. There was a strong and graded association between a reduced LVEF and mortality at 30 days, 1 year, and at the end of follow-up. In addition, patients with a reduced LVEF were less likely to receive treatment at discharge with BBs, ACEIs/ARBs, and statins despite the fact that being treated with any of these medications was associated with lower mortality during follow-up.

According to current guidelines, age should not be considered a reason to withhold treatment with PCI during NSTEMI [12−14]. Interestingly, only 41% of patients in our cohort underwent PCI, and revascularization was withheld in 59% despite the fact that they had no life-threatening disease, severe dementia, or any other reason to withhold active treatment. No robust data from randomized controlled trials are available to guide clinicians in the decision of whether to initiate BBs or ACEIs/ARBs in patients with new-onset acute heart failure with a reduced LVEF. Previous heart failure studies involved outpatients who were hemodynamically stable and did not have myocardial infarction. As a result, there is a lack of information and knowledge regarding how to implement guideline-directed therapy in patients of advanced age with new-onset impairment of the LVEF following NSTEMI. In fact, whether to initiate a guideline-recommended therapy is currently decided at the discretion of the attending physician. Interestingly, we found that the use of BBs, ACEIs/ARBs, MRAs, and statins was more than doubled at discharge compared with admission. However, patients with a reduced LVEF were less likely to receive guideline-recommended treatment than patients with a normal LVEF. This may partly explain the higher mortality found in patients with an impaired LVEF. Furthermore, the reason for the higher mortality among patients treated with LDs at discharge may have been related to confounding-by-indication, meaning that patients treated with LDs may have had more severe heart failure and kidney dysfunction.

In numerous studies, statins have been found to reduce mortality in patients with coronary artery disease, and guidelines recommend initiation of a maximum tolerable dose following myocardial infarction [15,16]. However, statin use in patients with heart failure with a reduced LVEF has not been shown to reduce mortality [17−19]. Our observations in this study population suggest that statins are prescribed at discharge to a high proportion of advanced-age patients in Sweden following myocardial infarction. In addition, we found that statin therapy was associated with a lower mortality both in patients with normal and reduced LVEF.

5. Strengths and limitations

The main strength of this study is that we were able to include all patients of advanced age who underwent care for NSTEMI at a cardiac care unit in Sweden from 2011 to 2014. This led to a study population that was rather large, which in turn led to many events and high precision in our estimates. In addition, during the study period contemporary invasive techniques and treatments were used routinely. The validity of the variables included in the SWE-DEHEART registry has previously been found to have a high validity [20].

The main limitation is that we did not have information on the LVEF before admission to the hospital. However, we did have information about the history of heart failure. We excluded all patients with a history of heart failure, and although this may not have eliminated all misclassification of exposure, we believe that the vast majority of our study population had a normal LVEF at admission to the hospital for NSTEMI. There may have been selection bias because the coverage of the SWEDEHEART registry is not complete, meaning that all patients with NSTEMI will not be cared for at a unit which report to the registry. This may be especially true for elderly, frail patients who probably are more likely to be cared for in a general internal medicine ward, than younger patients with NSTEMI. However, the coverage for NSTEMI nationwide in Sweden is thought to be 85−90% in the SWEDEHEART registry. As in every observational study, residual confounding may have been present. In addition, we had no information about what doses of medications were prescribed or if the prescriptions changed during follow-up. Furthermore, we had no information about if patients filled their prescriptions. However, since we did find associations between being treated versus not being treated with almost all medication we believe that most patients in fact did use their prescribed medications.

6. Conclusions

In conclusion, our data suggest that new-onset impairment of the LVEF is frequently observed during hospitalization for NSTEMI in patients of advanced age. In addition, a reduced LVEF is associated with a higher mortality and this association becomes stronger as LVEF decrease. Treatment with guideline-recommended medication as statins, ACEi, ARBs, and platelet-inhibitors is associated with a lower mortality in elderly patients with a reduced LVEF. Both revascularization with PCI and treatment with drugs aimed at heart

failure therapy should be considered in patients of advanced age complicated by a reduced LVEF following NSTEMI.

7. Clinical perspectives

Prognosis of ischemic heart failure is poor and remains a challenge for clinicians. In fact, whether to initiate a guideline-recommended therapy is currently decided at the discretion of the attending physician. As patients of advanced age are under-represented or often excluded from participation in randomized controlled trials; thus, clinical data in this patient population are scarce. New-onset reduction of LVEF is frequent in advanced-age patients with NSTEMI and is associated with higher mortality. Here, treatment with guideline-recommended medications should be initiated and encouraged in clinical practice to treat elderly to reduce mortality due to reduced LVEF.

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Disclosures

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References

[1] J. Chen, A.F. Hsieh, K. Dharmarajan, F.A. Masoudi, H.M. Krumholz, National trends in heart failure hospitalization after acute myocardial infarction for Medicare beneficiaries: 1998–2010, Circulation 128 (2013) 2577–2584.

[2] J.J. McMurray, M.A. Pfeffer, Heart failure, Lancet 365 (2005) 1877–1889.

[3] R.S. Bhatia, J.V. Tu, D.S. Lee, P.C. Austin, J. Fang, A. Haouzi, Y. Gong, P.P. Liu, Outcome of heart failure with preserved ejection fraction in a population-based study, N. Engl. J. Med. 355 (2006) 260–269.

[4] S.D. Solomon, M. Zile, B. Pieske, A. Voors, , et al.Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators, The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial, Lancet 380 (2012) 1387–1395.

[5] K.P. Alexander, K. Newby, C.P. Cannon, P.W. Armstrong, et al., Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology, Circulation 115 (2007) 2549–2569.

[6] P. Reinius, L. Mellbin, M.J. Holzmann, A.J. Siddiqui, Percutaneous coronary intervention (PCI) has better prognosis than conservative treatment in patients over 80 years old suffering from non ST-elevation myocardial infarction (NSTEMI), Int. J. Cardiol. 15 (267) (2018) 57–61.

[7] A. Torabi, J.G. Cleland, A.S. Rigby, N. Sherwi, Development and course of heart failure after a myocardial infarction in younger and older people, J. Geriatr. Cardiol. 11 (2014) 1–12.

[8] J. Chen, K. Dharmarajan, Y. Wang, H.M. Krumholz, National trends in heart failure hospital stay rates, 2001 to 2009, J. Am. Coll. Cardiol. 61 (2013) 1078–1088.

[9] M.C. Bahit, R.D. Lopes, R.M. Clare, L.K. Newby, et al., Heart failure complicating non-ST-segment elevation acute coronary syndrome: timing, predictors, and clinical outcomes, J Am Coll Cardiol HF 1 (3) (2013) 223–229.

[10] J.J. McMurray, M. Packer, A.S. Desai, J. Gong, M.P. Lefkowitz, , et al.PARADIGM-HF Investigators and Committees, Angiotensin-neprilysin inhibition versus enalapril in heart failure, N. Engl. J. Med. 371 (2014) 993–1004.

[11] Nationella kvalitetsregisters täckningsgrad-beskrivning, beräkning och bedömning: http://www.vardanalys.se/Global/Rapporter. September 9, 2017.

[12] M. Haim, A. Battler, S. Behar, P.M. Fioretti, V. Boyko, M.L. Simoons, D. Hasdai, Acute coronary syndromes complicated by symptomatic and asymptomatic heart failure: does current treatment comply with guidelines? Am. Heart J. 147 (2004) 859–864.

[13] D.D. McManus, M. Chinali, J.S. Saczynski, J.M. Gore, J. Yarzebski, F.A. Spencer, D. Lessard, R.J. Goldberg, 30-year trends in heart failure in patients hospitalized with acute myocardial infarction, Am. J. Cardiol. 107 (3) (2011) 353–359.

[14] C. Berry, R.N. Doughty, C. Granger, L. Køber, et al., The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC), Eur. Heart J. 33 (2012) 1750–1757.

[15] K.K. Ray, C.P. Cannon, C.H. McCabe, R. Cairns, A.M. Tonkin, F.M. Sacks, G. Jackson, E. Braunwald, Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial, J. Am. Coll. Cardiol. 46 (2005) 1405–1410.

[16] C. Baigent, A. Keech, P.M. Kearney, L. Blackwell, G. Buck, C. Pollicino, A. Kirby, T. Sourjina, R. Peto, R. Collins, R. Simes, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (2005) 1267–1278.

[17] D. Preiss, R.T. Campbell, H.M. Murray, et al., The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials, Eur. Heart J. 36 (2015) 1536–1546.

[18] J. Kjekshus, E. Apetrei, V. Barrios, M. Böhm, , et al.for the CORONA Group, Rosuvastatin in older patients with systolic heart failure, N. Engl. J. Med. 357 (2007) 2248–2261.

[19] L. Tavazzi, A.P. Maggioni, R. Marchioli, S. Barlera, , et al.GISSI-HF Investigators, Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial, Lancet 372 (2008) 1231–1239.

[20] T. Jernberg, M.F. Attebring, K. Hambraeus, T. Ivert, S. James, A. Jeppsson, B. Lagerqvist, B. Lindahl, U. Stenestrand, L. Wallentin, The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART), Heart 96 (2010) 1617–1621.