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ORIGINAL RESEARCH ARTICLE

Optimal Medical Therapy Prescription in Patients with Acute Coronary Syndrome in the Netherlands: A Multicenter Pilot Registry

Niels P. G. Hoedemaker[1] · Robbert J. de Winter[1] · Arnoud van't Hof[2] · Evelien Kolkman[3,4] · Peter Damman[5]

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Abstract

Background Unlike neighboring countries, the Netherlands does not have a national acute coronary syndrome (ACS) registry to evaluate quality of care.

Objective We conducted a pilot registry in two hospitals to assess the prescription of guideline-recommended therapies in Dutch patients with ACS.

Methods We included all consecutive patients with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) ($n = 1309$) admitted to two Dutch percutaneous coronary intervention centers between March 2015 and February 2016. We collected follow-up medication use and reasons for discontinuation at discharge and 1, 6, and 12 months post-discharge. We assessed the use of optimal medical therapy (OMT), defined as the combined prescription of aspirin, P2Y12 inhibitors, statins, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.

Results OMT prescription was 43.2% at discharge, 60.1% at 1 month, and 28.7% at 12 months. At 1 month, OMT prescription was significantly lower in patients with NSTEMI (51.8 vs. 65.7% for STEMI; $p < 0.001$). OMT prescription was lower in women (6 months: 55.4 vs. 62.0%, $p = 0.036$) and in elderly patients.

Conclusion In this pilot study that aimed to extend a national Dutch ACS registry to patients with STEMI and NSTEMI, OMT prescription was comparable to that in other local registries, was lower in women and patients with NSTEMI, and decreased with increasing age.

1 Introduction

During the last two decades, the development of invasive and medical therapies has improved outcomes in both patients with ST-segment elevation myocardial infarction (STEMI) and those with non-ST-segment elevation myocardial infarction (NSTEMI) [1, 2].

Guideline-recommended therapies in patients with acute coronary syndrome (ACS) include invasive treatments such as coronary angiography with subsequent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and optimal medical therapy (OMT) [3, 4]. OMT consists of aspirin, P2Y12 inhibitor, statin, β-blocker, and an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB). β-blockers and ACEi/ARBs have a class IA recommendation in patients with ACS with a reduced left ventricular ejection fraction (LVEF ≤ 40%) [3, 4]. Dual therapy with a P2Y12 inhibitor and a coumarin or novel oral anticoagulant (NOAC) as a replacement for aspirin is also considered OMT. Additionally, prescription of a proton pump inhibitor (PPI) is recommended in patients with ACS aged ≥ 65 years receiving dual antiplatelet therapy (DAPT) and NOACs [5].

National registries in Denmark, Sweden, and the UK have contributed to improve adherence to the abovementioned guideline-recommended therapies, which has been linked to an overall benefit for patients with ACS [6–8].

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✉ Niels P. G. Hoedemaker
n.p.g.hoedemaker@olvg.nl

1 Heart Center, Department of Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

2 Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands

3 Diagram B.V, Zwolle, The Netherlands

4 Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands

5 Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands

KeyPoints

Guideline-recommended optimal medical therapy (OMT) for secondary prevention after acute coronary syndrome (ACS) consists of aspirin, P2Y12 inhibitors, statins, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.

Most European countries have a national ACS registry, which has contributed to improving adherence to OMT; however, the Netherlands does not have a national ACS registry.

In this multicenter pilot registry of two Dutch hospitals, OMT use was significantly lower among patients with non-ST-elevation myocardial infarction, women, and elderly patients.

Similar findings were observed in other registry studies, so further efforts to improve OMT use should focus on these subgroups.

However, the Netherlands does not have a national ACS registry. A report by the National Cardiovascular Database Registry (NCDR) demonstrated the feasibility of a Dutch ACS registry but only enrolled patients with STEMI over a 4-week period [9]. The current study is a pilot study from two Dutch PCI centers that aimed to expand the NCDR registry by including both patients with STEMI and those with NSTEMI over a full year of enrollment. We assessed the prescription of guideline-recommended medical therapies and reasons for drug discontinuation after ACS.

2 Methods

2.1 Study Setting and Design

This study combines ACS registries from two PCI centers in the Netherlands: the Academic Medical Centre (AMC) in Amsterdam and Isala Hospital Zwolle. Both centers recorded their own separate prospective observational registries, based on the variable set of the NCDR, the predecessors of the current Netherlands Heart Registry (NHR). The NHR was established in 2017, 1 year after the enrollment of this study was completed. Representatives from both centers agreed to combine the two registries with the aim to assess medication prescription.

2.2 Patients

We enrolled all consecutive patients with STEMI or NSTEMI admitted to our hospitals from 1 March 2015 until 29 February 2016. Patients were diagnosed if they had ischemic symptoms lasting > 20 min and elevated cardiac biomarkers and/or new ST-segment elevation in two contiguous leads, left bundle branch block, ST-T or T-wave changes, or Q-waves on a 12-lead electrocardiogram. Only patients with type 1 myocardial infarction (MI) according to the Third Universal Definition of MI were included [10]. Any discrepancies on the assessment of MI type were discussed until consensus was reached.

2.3 Treatment

The preferred treatment strategy in patients with STEMI was primary PCI. In patients with NSTEMI, the timing and performance of angiography and revascularization were in accordance with the European guidelines [3, 4]. Patients undergoing angiography were pretreated with aspirin, heparin, and a P2Y12 inhibitor (ticagrelor 180 mg or clopidogrel 600 mg loading dose). CABG was performed if indicated. Prescription of guideline-recommended therapies and referral to cardiac rehabilitation was in accordance with the 2012 STEMI and 2015 NSTE-ACS guidelines from the European Society of Cardiology (ESC) and was encouraged in all patients [3, 4].

2.4 Data Collection and Follow-Up

Data were prospectively recorded in a dedicated case report form using an anonymized patient identification number. Variables included demographics, risk factors, medical history, procedural characteristics, LVEF measured by echocardiography, and medication prescription at discharge and 1, 6, and 12 months post-discharge. We collected follow-up data on medication prescription and (at one center) discontinuation from hospital records and/or via telephone interviews with a trained research physician at 1, 6, and 12 months. We obtained vital status from the Dutch national population registry. The two datasets were collected and merged for analysis at the AMC in Amsterdam. This study was conducted with a waiver from the medical ethical committee of the AMC in Amsterdam. According to Dutch law applicable at the time of the study period, written informed consent for the conduct of this registry study was not required.

2.5 Definitions and Outcomes

The main outcome of this study was OMT at discharge and during follow-up. OMT was defined as a combination of aspirin, P2Y12 inhibitor, statin, β-blocker, and ACEi/ARB. Prescription of dual therapy (P2Y12 inhibitor with a NOAC) with a statin, β-blocker, and ACEi/ARB was also regarded as OMT. We assessed OMT prescription stratified by ACS type (STEMI vs. NSTEMI), sex, and age. We also evaluated

OMT, β-blocker, and ACEi/ARB prescription in patients with a preserved (> 40%) or reduced (≤ 40%) LVEF. Furthermore, we evaluated prescriptions among patients with a class IA indication for ACEi/ARBs and in patients with STEMI (LVEF ≤ 40%, hypertension, diabetes mellitus, anterior MI) or NSTEMI (LVEF ≤ 40%, hypertension, diabetes mellitus) [3, 4]. We assessed the duration of DAPT prescription follow-up and switching between novel P2Y12 inhibitors (ticagrelor or prasugrel) and clopidogrel. Finally, we evaluated PPI prescriptions among patients receiving DAPT or a NOAC and aged ≥ 65 years [5].

2.6 Statistical Analysis

Continuous variables are presented as mean and standard deviation or as median and interquartile range (IQR) for normal and skewed distributions, respectively. All categorical variables are presented as absolute frequencies and percentages. Differences between groups were evaluated using the unpaired *t* test or Mann–Whitney test (nonparametric) for continuous variables and the χ^2 test for categorical variables. The linear-by-linear association test was used to evaluate differences between age groups. We identified variables associated with OMT prescription at discharge and 12-month follow-up based on differences in baseline characteristics and variables of interest according to guideline recommendations. We calculated odds ratios (ORs) and adjusted ORs based on univariate and multivariate logistic regression models, respectively. All variables identified (age ≥65 years, female sex, hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease [creatinine clearance ≤ 50 ml/min], previous MI, previous CABG, previous stroke, STEMI, PCI performance, and CABG performance) were used in the multivariate model. A p value of < 0.05 (two-sided) was considered statistically significant. All analyses were performed using SPSS version 25.0.

3 Results

Between March 2015 and February 2016, a total of 1309 patients with ACS were included in the registry: 528 (40.3%) from the Amsterdam registry and 781 (59.7%) from the Zwolle registry.

3.1 Baseline and Procedural Characteristics

Table 1 displays the baseline and procedural characteristics. The mean age was 64.9 years, and 28.6% of the patients were women (Table 1). Hypertension was present in 45.6%, and 17.2% had diabetes mellitus. Approximately two-thirds of patients were admitted with STEMI (64.6%) and one-third with NSTEMI (35.4%). The majority of patients underwent coronary angiography (94.9%), and 81.8% of the patients were treated with PCI. PCI performance was significantly higher among patients with STEMI than those with NSTEMI (90.7 vs. 62.8%; $p < 0.001$). CABG was performed in 7.3% of patients.

3.2 Mortality Outcome

Vital status from the Dutch national population registry at 1 year was obtained for 1300 patients (99.3%). Nine patients were not registered as inhabitants of the Netherlands so their vital status could not be obtained. In-hospital mortality was 3.7%, 30-day mortality 4.5%, and 1-year mortality 7.4%.

3.3 Medication at Discharge and During Follow-Up

A flow chart of patients recruited and lost to medication follow-up is provided in the Electronic Supplementary Material (ESM; Tables 4 and 5). Prescription of medication categories is displayed in Table 2. Prescription at discharge was highest for aspirin (88.8%), statins (86.6%), and P2Y12 inhibitors (84.8%). Prescription rates increased at 1 month but decreased at 6 and 12 months. Combined prescription of medication is presented in Table 3. OMT prescription at discharge was 43.2%, increased to 60.1% at 1 month, and was 50.8% and 28.7% at 6 and 12 months, respectively. Patients not receiving OMT at discharge had a significantly shorter admission length than did those receiving OMT (1.0 days [IQR 0.0–5.0] vs. 3.0 [IQR 1.0–5.0]; $p < 0.001$). OMT prescription at discharge and 1 and 6 months was higher among patients with a reduced ejection fraction, but this was not statistically significant (Fig. 1a).

3.4 Antiplatelet Therapy

Ticagrelor was the most prescribed P2Y12 inhibitor, with 58.9% of patients receiving it at discharge, whereas 25.3% of the patients received clopidogrel and < 1% received prasugrel. At discharge, 79.9% of patients received DAPT and 4.0% received dual therapy (NOAC and P2Y12 inhibitor). This decreased to 43.0% DAPT and 7.0% dual therapy at 12 months. Complete 12-month follow-up on DAPT prescription was available in 715 patients (54.6%). In total, 52 patients (7.3%) stopped using DAPT between discharge and 1 month, 12.9% stopped between 1 and 6 months, and 33.0% stopped between 6 and 12 months. Approximately half of the patients (46.9%) received DAPT for at least 12 months. From discharge until 1 month, 28 patients (3.6%) switched from a novel P2Y12 inhibitor to clopidogrel, and 14 patients (1.8%) switched to a novel P2Y12 inhibitor. Between 1 and 6 months, 36 patients (4.5%) switched to clopidogrel, and nine patients (1.1%) switched to a novel P2Y12 inhibitor. Between 6 and 12 months, 23 patients (2.4%) switched

Table 1 Baseline characteristics

Characteristics	Overall (n = 1309)
Demographics	
Age, years	64.9 ± 12.7
Women	374/1309 (28.6)
Risk factors	
Hypertension	578/1268 (45.6)
Diabetes mellitus	218/1270 (17.2)
Smoking status	
Current	435/1238 (35.1)
Past smoker	170/1238 (13.7)
Never smoked	461/1238 (37.2)
Unknown	172/1238 (13.9)
Hypercholesterolemia	338/1255 (26.9)
Family history of CVD	420/1156 (36.3)
Medical history	
COPD	87/1054 (8.3)
Chronic kidney disease	105/1093 (9.6)
Previous MI	108/1093 (8.3)
Previous PCI	131/1309 (10.0)
Previous CABG	51/1309 (3.9)
Previous stroke	63/1063 (5.9)
Clinical presentation	
STEMI	845/1309 (64.6)
NSTEMI	464/1309 (35.4)
Killip class > 2	60/436 (13.8)
Cardiogenic shock	58/1309 (4.4)
OHCA	74/1309 (5.7)
Invasive treatment during admission	
Coronary angiography	1242/1309 (94.9)
PCI	978/1195 (81.8)
Stent type	
DES	784/853 (91.9)
BMS	14/853 (1.6)
BVS	55/853 (6.4)
CABG	87/1195 (7.3)
LVEF during admission	
Preserved (> 40%)	320/430 (74.4)
Reduced (≤ 40%)	110/430 (25.6)
Length of stay, days	2.0 (1.0–5.0)

Data are presented as mean ± standard deviation, *N* (%), or median (interquartile range) unless otherwise indicated

BMS bare metal stent, *BVS* bioresorbable scaffold, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *DES* drug-eluting stent, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *OHCA* out-of-hospital cardiac arrest, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

from a novel P2Y12 inhibitor to clopidogrel, and three patients (0.3%) switched from clopidogrel to a novel P2Y12 inhibitor.

3.5 β-Blockers, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin-Receptor Blockers According to Ejection Fraction

β-blocker prescription at discharge was similar for patients with preserved or reduced LVEF (82.4 vs. 81.1%; p = 0.763). At 1, 6, and 12 months, β-blocker rates were higher among patients with reduced LVEF. ACEi/ARB prescription was markedly higher among patients with reduced LVEF. At discharge, 63.7% of the patients with STEMI with a class IA indication for ACEi/ARBs were treated according to ESC guidelines. This rate increased to 86.7%, 83.8%, and 81.9% at 1-, 6-, and 12-month follow-up, respectively. Among patients with NSTEMI with a class IA indication for ACEi/ARBs, 72.4% were prescribed one of these drugs in accordance with the guidelines. This later increased to 79.3% at 1 month, 75.5% at 6 months, and 74.7% at 12 months. Co-prescription of a β-blocker and an ACEi/ARB in patients with reduced LVEF was 62.1% at discharge, 77.5% at 1 month, 71.8% at 6 months, and 70.0% at 12 months. Additional results on combined prescriptions according to LVEF are presented in Tables 2 and 3 in the ESM.

3.6 Proton Pump Inhibitors

Among patients receiving DAPT, PPI prescription was 73.7% and approximately 85% during follow-up (1 month, 86.4%; 6 months, 84.5%; and 12 months, 86.2%). PPI prescription was even higher for patients receiving NOACs: 84.1% at discharge and 91.4%, 89.0%, and 91.6% at 1, 6, and 12 months, respectively. A PPI was prescribed in 79.3% of patients aged ≥ 65 years at discharge and in 93.2%, 90.5%, and 89.5% at 1, 6, and 12-month follow-up.

3.7 STEMI vs. NSTEMI

OMT at discharge was no different between patients with STEMI or NSTEMI (43.9 vs. 41.9%; p = 0.524; Fig. 1b). OMT prescription was significantly higher among patients with STEMI at 1 and 6 months (65.7 vs. 51.8%, p < 0.001 and 54.2 vs. 46.0%, p = 0.017, respectively). This difference was mainly because of higher rates of P2Y12 inhibitors and ACEi/ARBs among patients with STEMI (Tables 4 and 5 in the ESM). There were no differences in OMT at 12 months (28.5 vs. 29.0%, p = 0.891).

Table 2 Medication at discharge 1, 6, and 12 months after acute coronary syndrome

Timepoint	Medication	Overall ($n = 1309$)	LVEF > 40% ($n = 320$)	LVEF ≤ 40% ($n = 110$)	p value
Discharge	Aspirin	986/1110 (88.8)			
	P2Y12 inhibitor	941/1110 (84.8)			
	Statin	958/1110 (86.3)			
	β-blocker	860/1110 (77.5)	253/307 (82.4)	77/95 (81.1)	0.763
	ACE inhibitor/ARB	676/1110 (60.9)	187/307 (60.9)	64/95 (67.4)	0.256
	NOAC	164/1110 (14.8)			
	PPI	806/1110 (72.6)			
1 month	Aspirin	870/961 (90.5)			
	P2Y12 inhibitor	843/961 (87.7)			
	Statin	897/960 (93.4)			
	β-blocker	850/959 (88.6)	240/270 (88.9)	74/80 (92.5)	0.350
	ACE inhibitor/ARB	750/957 (78.4)	194/270 (71.9)	66/80 (82.5)	0.056
	NOAC	191/961 (19.9)			
	PPI	804/934 (86.1)			
6 months	Aspirin	765/893 (85.7)			
	P2Y12 inhibitor	726/893 (81.3)			
	Statin	799/892 (89.6)			
	β-blocker	738/890 (82.9)	216/266 (81.2)	66/71 (93.0)	0.017
	ACE inhibitor/ARB	668/890 (75.1)	193/266 (72.6)	56/71 (78.9)	0.282
	OAC	172/892 (19.3)			
	PPI	745/889 (83.8)			
12 months	Aspirin	729/877 (83.1)			
	P2Y12 inhibitor	452/876 (51.6)			
	Statin	768/878 (87.5)			
	β-blocker	675/876 (77.1)	209/264 (79.2)	60/70 (85.7)	0.219
	ACE inhibitor/ARB	637/875 (72.8)	180/264 (68.2)	58/70 (82.9)	0.016
	OAC	155/877 (17.7)			
	PPI	714/875 (81.6)			

Data are presented as *N* (%) unless otherwise indicated

ACE angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker, *LVEF* left ventricular ejection fraction, *NOAC* novel oral anticoagulation, *PPI* proton pump inhibitor

3.8 Sex Differences

Women had lower OMT prescription rates at discharge (45.9 vs. 36.6%; $p = 0.005$) and during follow-up, but this was only significantly different at 6 months (62.0 vs. 55.4%; $p = 0.036$; Fig. 1c). The differences can be explained by lower rates of P2Y12 inhibitor and statin prescriptions among women (Tables 6 and 7 in the ESM).

3.9 Age

In general, OMT prescription decreased with age, both at discharge and during follow-up (Fig. 2). This decreasing trend was significant at 1-month follow-up ($p = 0.001$). Figure 3 displays prescription rates for individual OMT medications according to age. The use of aspirin, P2Y12 inhibitors, and statins decreased with age, whereas NOAC and PPI prescriptions increased with age (Tables 8 and 9 in the ESM).

3.10 Predictors of Optimal Medical Therapy (OMT)

We performed univariate and multivariate logistic regression to identify predictors of OMT prescription at discharge and 12-month follow-up (Table 10 in the ESM). Univariate predictors of OMT prescription at discharge were female sex and undergoing PCI or CABG. After multivariate adjustment, female sex (OR 0.64; $p = 0.007$) and undergoing CABG (OR 0.35; $p = 0.003$) remained associated with OMT prescription at discharge. Univariate predictors of OMT prescription at 12 months were female sex, previous stroke, and undergoing CABG. However, after multivariate adjustment, only undergoing CABG remained independently associated with OMT prescription at discharge (OR 0.25; p = 0.007).

Table 3 Medication combinations at discharge and 1, 6, and 12 month after acute coronary syndrome

Timepoint	Medication	Overall ($n = 1309$)	LVEF > 40% ($n = 320$)	LVEF ≤ 40% ($n = 110$)	p value
Discharge	DAPT or dual therapy	929/1110 (83.7)			
	DAPT	885/1110 (79.7)			
	Dual therapy	44/1110 (4.0)			
	DAPT or dual therapy and statin	842/1110 (75.9)			
	DAPT and statin	807/1110 (72.7)			
	Dual therapy and statin	35/1110 (3.2)			
	OMT	479/1110 (43.2)	145/307 (47.2)	53/95 (55.8)	0.145
	OMT with aspirin	458/1110 (41.3)	138/307 (45.0)	48/95 (50.5)	0.341
	OMT with NOAC	21/1110 (1.9)	7/307 (2.3)	5/95 (5.3)	0.135
1 month	DAPT or dual therapy	837/961 (87.1)			
	DAPT	782/961 (81.4)			
	Dual therapy	55/961 (5.7)			
	DAPT or dual therapy and statin	790/960 (82.3)			
	DAPT and statin	741/960 (77.2)			
	Dual therapy and statin	49/960 (5.1)			
	OMT	575/956 (60.1)	159/270 (58.9)	50/80 (62.5)	0.563
	OMT with aspirin	540/956 (56.5)	150/270 (55.6)	44/50 (55.0)	0.930
	OMT with NOAC	35/956 (3.7)	9/270 (3.3)	6/80 (7.5)	0.106
6 months	DAPT or dual therapy	717/892 (80.4)			
	DAPT	637/893 (71.3)			
	Dual therapy	80/892 (9.0)			
	DAPT or dual therapy and statin	651/891 (73.1)			
	DAPT and statin	580/892 (65.0)			
	Dual therapy and statin	71/891 (8.0)			
	OMT	452/889 (50.8)	137/266 (51.5)	41/71 (57.7)	0.349
	OMT with aspirin	394/889 (44.3)	113/266 (42.5)	33/71 (46.5)	0.546
	OMT with NOAC	58/889 (6.5)	24/266 (9.0)	8/71 (11.3)	0.566
12 months	DAPT or dual therapy	438/876 (50.0)			
	DAPT	377/876 (43.0)			
	Dual therapy	61/876 (7.0)			
	DAPT or dual therapy and statin	391/876 (44.6)			
	DAPT and statin	336/876 (38.4)			
	Dual therapy and statin	55/876 (6.3)			
	OMT	251/874 (28.7)	84/264 (31.8)	24/70 (34.3)	0.695
	OMT with aspirin	209/874 (23.9)	65/264 (24.6)	20/70 (28.6)	0.500
	OMT with NOAC	42/874 (4.8)	19/264 (7.2)	4/70 (5.7)	0.663

DAPT dual antiplatelet therapy, *LVEF* left ventricular ejection fraction, *NOAC* novel oral anticoagulation, *OMT* optimal medical therapy

With regard to this result, we identified that P2Y12 inhibitor use (37 vs. 89.5% at discharge and 25.4 vs. 54.1%) was significantly lower among patients who underwent CABG.

4 Discussion

In this study, we report adherence to guidelines in OMT prescriptions in consecutive patients with ACS from two PCI centers in the Netherlands. Our results can be summarized as follows. First, 43.2%, of patients were discharged with OMT, which increased to 60.1% at 1 month and decreased to 28.7% at 12 months. Second, OMT prescription was numerically higher among patients with reduced LVEF, but this difference was not statistically significant. Third, OMT prescription was lower in patients with NSTEMI (at 1 and 6 months) and in women. Fourth, there was a decreasing trend in OMT prescription with increasing age. Finally, discontinuation was highest for P2Y12 inhibitors (as per guidelines) and ACEi/ARBs.

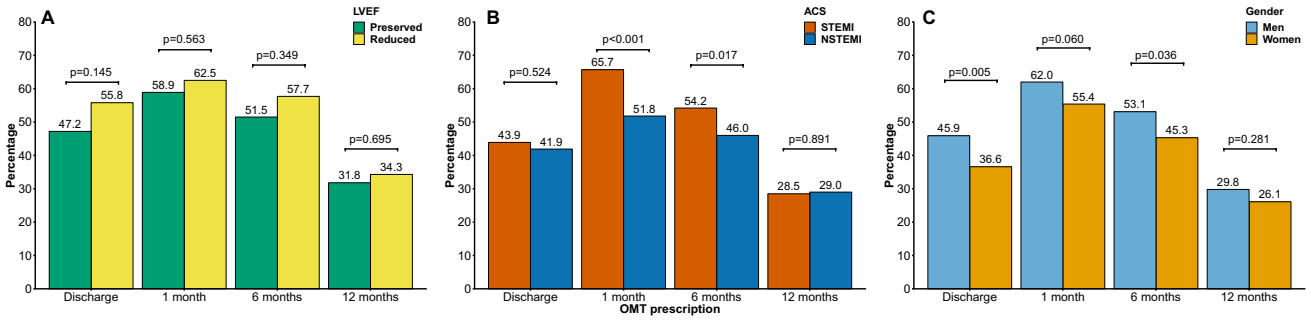

Fig. 1 Optimal medical therapy prescription at discharge, 1, 6, and 12 months in different subgroups. **a** optimal medical therapy (OMT) in patients with acute coronary syndrome (ACS) with a preserved versus a reduced left ventricular ejection fraction (LVEF). **b** OMT prescription in patients with ACS with ST-elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). **c** displays differences in OMT prescription between men and women

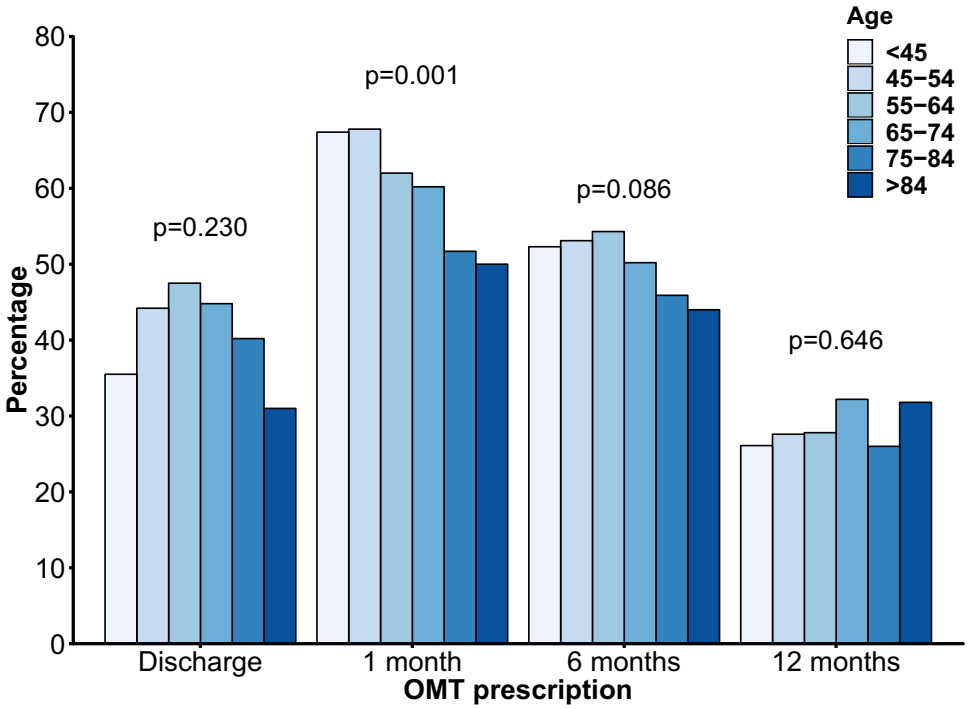

Fig. 2 Optimal medical therapy prescription at discharge, 1, 6, and 12 months stratified by age. *OMT* optimal medical therapy

4.1 Context and Interpretation

The discharge OMT prescription rate in our study (43.2%) corresponds with that in a single-center registry study with > 9000 patients with ACS from one of the participating centers in this current study (43.7%) [11]. Additionally, a similar pattern of increased OMT at 1 month and decreased OMT at 12 months was observed, but OMT at 1 month (60.1%) in the current study was higher than the 46.6% in the single-center study. This study was conducted in two PCI centers where early discharge and transfer back to the referring regional non-PCI centers is common. This could explain why the median length of stay for patients without OMT at discharge was 2 days shorter than those with OMT and account for the observed increase in OMT during the first month of follow-up. Another study that used claims data from Dutch health insurance companies observed guideline-recommended OMT prescription rates of 49% during the first 12 months after ACS [12]. However, that study only

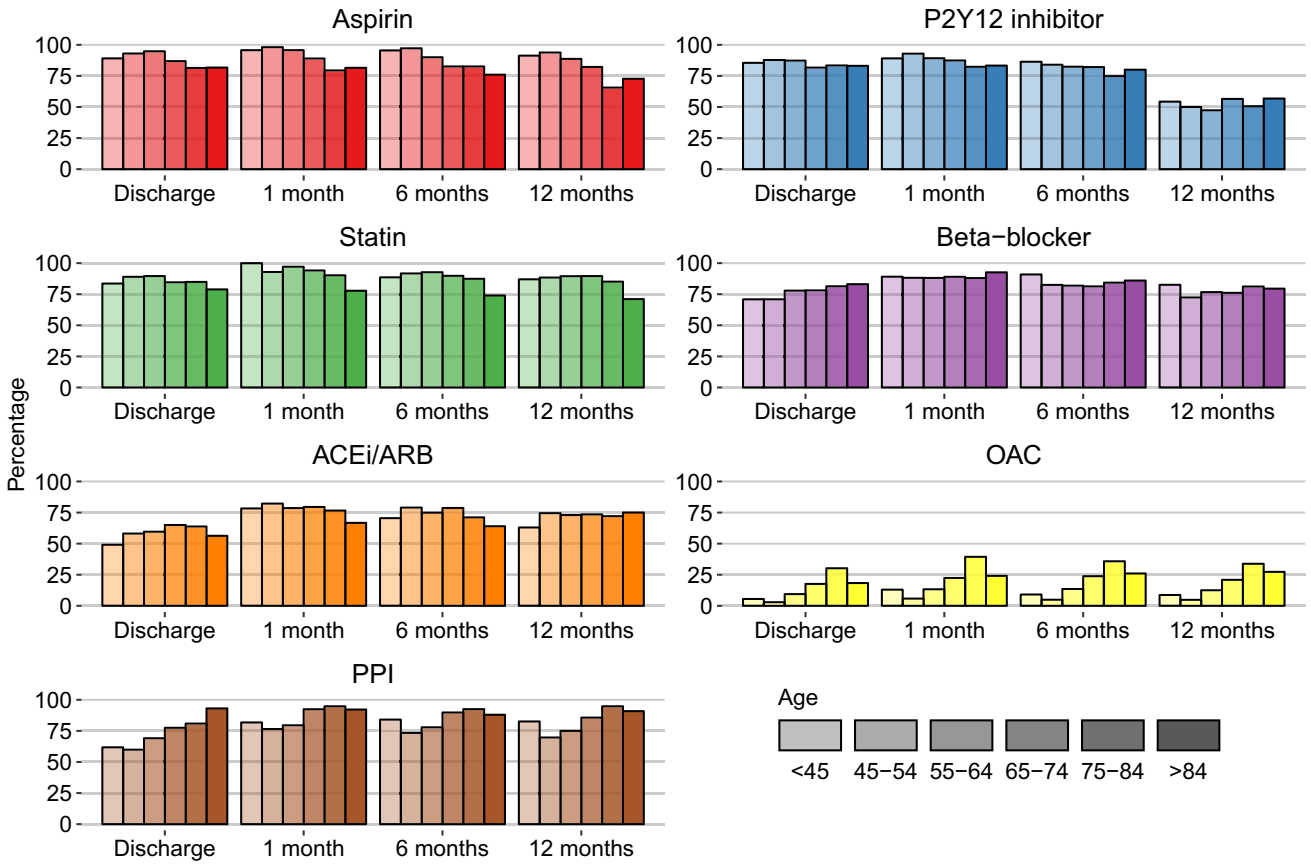

Fig. 3 Optimal medical therapy prescription at discharge, 1, 6, and 12 months stratified by age. *ACEi/ARB* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *OAC* oral anticoagulants, *OMT* optimal medical therapy, *PPI* proton pump inhibitors

counted fulfilled pharmacy prescriptions, which could explain the lower percentage of OMT use.

4.2 Antiplatelet Therapy

We observed DAPT durations of at least 12 months in approximately 50% of patients, with 33% stopping DAPT between 6 and 12 months. This indicates that a substantial group of patients terminated DAPT before 6 months. There may be several explanations for this. A shorter DAPT duration is recommended for patients with high bleeding risk [3, 4]. Moreover, patients with an indication for NOACs (≤ 20% in our study) may use triple therapy with DAPT for only 1–6 months and thereafter continue on dual therapy alone [5]. Recently, the AUGUSTUS and RE-DUAL PCI trials demonstrated that a NOAC in addition to a P2Y12 inhibitor could be an additional treatment option in patients with ACS with atrial fibrillation who underwent PCI [13, 14]. Furthermore, approximately 5% of patients switched from prasugrel or ticagrelor to clopidogrel. The TROPICAL-ACS and TOPIC studies demonstrated that switching from a novel P2Y12 inhibitor to clopidogrel was safe for ischemic endpoints and reduced bleeding [15, 16]. However, the GLOBAL LEADERS trial failed to show a benefit from ticagrelor monotherapy in patients with ACS [17]. The majority of patients with an indication for a PPI (i.e., DAPT, NOAC, age ≥ 65 years) were treated in accordance with ESC recommendations [5].

Remarkably, CABG during hospitalization was an independent negative predictor of OMT prescription at discharge and 12 months. This was most likely because of a significantly lower rate of P2Y12 inhibitor use among patients who underwent CABG. A recent Swiss study observed similar results, and these may be explained by clinicians' reluctance to reinitiate DAPT after cardiac surgery [18].

4.3 OMT in Left Ventricular Ejection Fraction ≤ 40%

We observed numerically higher rates of OMT in patients with a reduced LVEF compared with those with preserved LVEF, a finding that was in accordance with ESC guidelines. At 6 and 12 months, β-blocker prescriptions decreased in patients with preserved LVEF. National registry studies have challenged the usefulness of long-term β-blocker treatment in patients with ACS with preserved LVEF

in the PCI era [19, 20]. Five ongoing randomized trials (AβYSS, NCT03498066; BETAMI, NCT03646357; DANBLOCK, NCT03778554; REBOOT-CNIC, NCT03596385; REDUCE-SWEDEHEART, NCT03278509) are studying the effect of β-blocker withdrawal on hard clinical endpoints in patients with ACS. Our study showed that discharge ACEi/ARB prescriptions in patients with a class IA indication were 63.7% in patients with STEMI and 72.1% in those with NSTEMI, which later increased to 86.7 and 79.3% at 1 month, respectively. Room for improvement of ACEi/ARB treatment during the first month may still exist since most of their benefit is observed during the first week [21].

4.4 Subgroups

While OMT prescription at discharge did not differ between STEMI and NSTEMI, it was lower in patients with NSTEMI at 1 and 6 months. In particular, antiplatelet and statin therapy rates were lower in patients with NSTEMI. Patients with NSTEMI more often had a higher risk profile that included diabetes mellitus and previous cardiovascular events, indicating a risk–treatment paradox that has been previously reported in patients with NSTEMI [22, 23].

Additionally, OMT prescription was lower among women, which was also observed in other studies [24, 25]. Our results showed this difference was caused by lower P2Y12 inhibitor and statin use in women. In the PLATO trial, female sex was independently associated with major bleeding [26]. This could explain the difference in P2Y12 inhibitor use at discharge and 1 month. It has been reported that women stopped a statin more often than men because of side effects associated with statins, but women also received less information related to their cardiovascular risk profile and so may have been unaware of the importance of statin therapy [27].

Likewise, the decreasing trend in OMT prescription that was observed in the elderly could also be explained by a decrease in antiplatelet therapy and statins. Age is an important risk factor, and short-term DAPT may be more beneficial in elderly patients [28]. Although the benefits of statin therapy in elderly patients are clear, the treatment–benefit ratio of statins should be evaluated according to patients' life expectancy [29]. Nevertheless, in the current aging ACS population, it remains important to know that OMT prescription is associated with a survival benefit in all ages [30].

4.5 Discontinuation

We assessed drug discontinuation in one of the participating centers that recorded reasons for withdrawal and found discontinuation was highest for P2Y12 inhibitors and ACEi/ARBs. As expected, P2Y12 inhibitors were mostly stopped because DAPT, triple, or dual therapy treatment ended as per guidelines. The incidence of bleeding and dyspnea as a reason for discontinuation of P2Y12 inhibitors corresponds with results from another Dutch registry [31]. ACEi/ARBs were stopped in 27% and 20%, respectively. Although not all reasons for withdrawal were known, the rate of ACEi discontinuation because of cough (3.3%) was comparable with that in other reports (4.2–5.1%) [32, 33]. Statin-related myalgia or myopathy was the most reported side effect (4.5%). The discontinuation rate in our study was lower than in randomized and observational studies, ranging from 8.8 to 12.0% [34–36]. However, statin users in these studies had both primary and secondary prevention indications. Possibly, muscle-related statin discontinuation is lower in secondary than in primary prevention because patients who have experienced a cardiovascular event are more willing to persist with (less intensive) statins, despite muscle symptoms.

4.6 Limitations

Several limitations of this study should be addressed. First, this was an observational study in two PCI centers and may not reflect practice elsewhere. Second, the limited sample size and missing data for several baseline characteristics prevented us from analyzing a relation between OMT and outcome. We were only able to obtain mortality data through the Dutch national population registry and were unable to report other important clinical outcomes such as cause of death, recurrent MI, or revascularization. Third, during follow-up, the number of patients with known medication decreased, which could be a potential cause of bias. Fourth, the date of P2Y12 inhibitor cessation was not available, and we only collected DAPT prescription data at 1, 6, and 12 months post-discharge. Therefore, we could not calculate the exact DAPT duration and were unable to determine the number of patients who completed almost 12 months of DAPT (i.e., 335–364 days). Finally, we did not account for multiple testing.

5 Conclusions

In this pilot study that aimed to extend the national Dutch ACS registry to patients with STEMI and NSTEMI, OMT prescription was comparable to other local registries and was lower in women and patients with NSTEMI and decreased with age.

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Declarations

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Conflict of interest P. Damman has received an unrestricted research grant from AstraZeneca Netherlands B.V. Niels PG Hoedemaker, Robbert J de Winter, Arnoud van 't Hof, and Evelien Kolkman have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval This study was conducted with a waiver from the medical ethical committee of the Academic Medical Center in Amsterdam. According to Dutch law applicable at the time of the study period, written informed consent for the conduction of this registry study was not required.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

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