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Time trends in adherence to guideline recommendations for anticoagulation therapy in patients with atrial fibrillation and myocardial infarction

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ABSTRACT

Background Poor adherence to guideline recommendations for anticoagulation in patients with acute myocardial infarction (MI) and atrial fibrillation (AF) is previously reported. The aim of the present cohort study was to assess time trends in prescription of anticoagulation therapy in a nationwide registry-based cohort of patients with acute MI and AF.

Methods All patients, registered in the Norwegian Myocardial Infarction Registry (NORMI) between 2013 and 2019 with ECG-verified AF at hospitalisation, were included in the cohort study. The primary outcome was the prescription rate of anticoagulation therapy at hospital discharge and follow-up through 2019.

Results AF was observed in 8565 (10.9% of 78369) patients registered in the NORMI from 2013 through 2019. The congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex (female) score was ≥2 in 7845 (92%) of the hospitalised patients with AF, and in 7174 (96%) of 7440 patients discharged alive. Only 3704 (47.2%) of these patients were treated with anticoagulation prior to the MI. The prescription rate of anticoagulation therapy at discharge was 55% in 2013, increasing to 78% in 2019 (annual per cent change 6.0 (95% CI 0.7 to 11.6)). Patients prescribed anticoagulation therapy had reduced risk of all types of stroke or death at follow-up compared with patients without prescription of anticoagulation therapy (multivariate-adjusted HR 0.8, 95% CI 0.7 to 0.8, p<0.001).

Conclusions The prescription rate of anticoagulation therapy in patients with MI and AF increased during the study period, but many patients were still undertreated with respect to stroke prevention.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] The incidence of AF is increasing, and one in three middle-aged persons may develop AF during their lifetime.[2] AF is associated with increased morbidity and mortality and remains one of the major causes of stroke.[3][4] The European Society of Cardiology (ESC) guidelines strongly recommend treatment with anticoagulation therapy in patients with AF with an increased risk of stroke.[4] However, several studies have previously demonstrated low physician adherence to this recommendation.[5–7] In patients with AF and myocardial infarction (MI), the prescription of anticoagulation has been particularly challenging, since these patients also need antiplatelet treatment.[7] However, the ESC guidelines underscore the importance of treatment with anticoagulation also in these patients.[4]

The aim of the present cohort study was to investigate time trends in adherence to the ESC guideline for prescription of anticoagulation therapy in patients with AF discharged from hospitals in Norway after MI in the period from 2013 to 2019.

METHODS

The Norwegian Myocardial Infarction Registry

The Norwegian Myocardial Infarction Registry (NORMI), a part of the Norwegian Cardiovascular Disease Registry, is a national

Key questions

What is already known about this subject?
► Poor adherence to guideline recommendations for anticoagulation therapy in patients with acute myocardial infarction (MI) and atrial fibrillation (AF) is previously reported.

What does this study add?
► The prescription rate of anticoagulation therapy in Norway in patients with MI and AF increased during the period 2013–2019, but many patients were still undertreated with respect to stroke prevention.

How might this impact on clinical practice?
► Knowledge of current clinical practice may improve adherence to guideline recommendations and consequently improved treatment of patients with MI and AF.
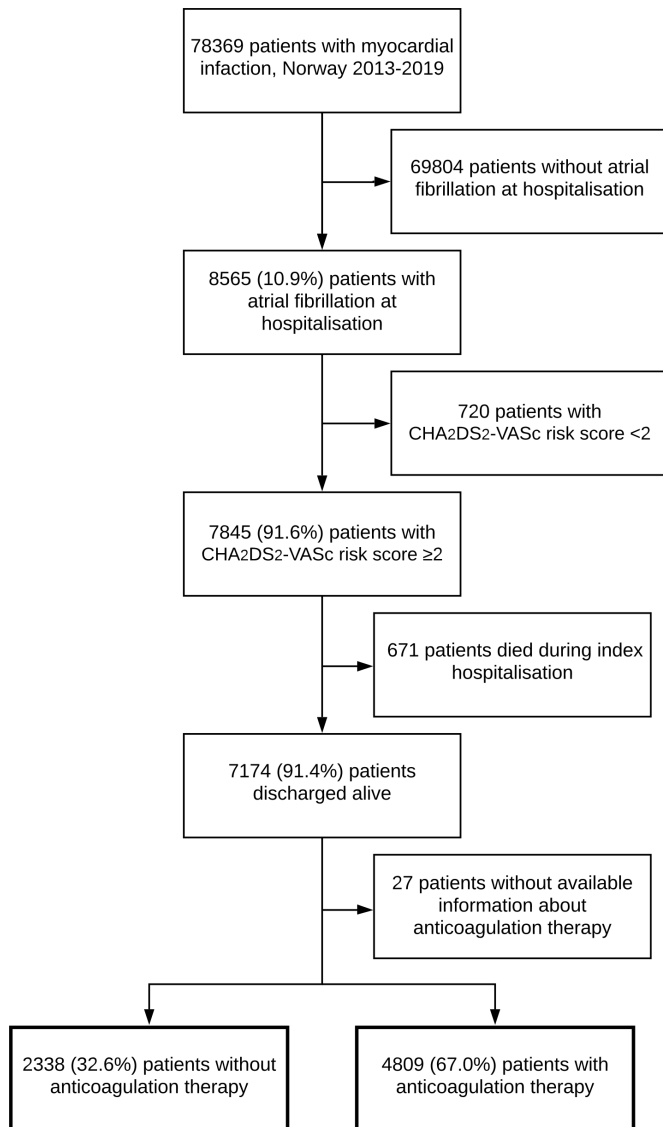
Figure 1 Patients admitted to hospitals in Norway with myocardial infarction from 2013 to 2019. CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex (female).

quality register. Registration into NORMI is mandatory without requiring patient's consent. For definition of MI, the NORMI adhered to the Third and Fourth Universal Definition of Myocardial Infarction during the study period.[8 9] NORMI contains information on gender, age, cardiovascular risk factors, previous diseases and medication, symptoms and clinical findings, ECG (rhythm and ischemic changes), in-hospital therapy and complications including death as well as drugs prescribed at hospital discharge. The registration and quality of the information in the register have been described previously.[10 11]

The Norwegian Cardiovascular Disease Registry contains information on stroke (all types) and all-cause death after hospital discharge.

Study population
All patients admitted to hospitals in Norway with acute MI between 1 January 2013 and 31 December 2019 and registered in the NORMI were considered for inclusion in this cohort study. In patients with more than one MI during the inclusion (study) period, only data from the first MI (index MI) were used. The diagnosis of AF was based at ECG findings at hospital admission.

Outcomes and follow-up
The primary outcome was the prescription rate of anticoagulation therapy at hospital discharge in patients with the combination of MI and AF and an indication for anticoagulation. The secondary outcome was a composite of all-cause mortality or non-fatal stroke (all types) during follow-up. Follow-up data were available until 31 December 2019.

Stroke risk and indication for anticoagulation therapy
The stroke risk in patients with AF was estimated based on the ESC recommended congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex (female) (CHA_2DS_2-VASc) risk score tool.[4 12] The CHA_2DS_2-VASc scores were calculated from information at hospitalisation (with addition of 1 point on discharge due to acute MI). A CHA_2DS_2-VASc risk score of ≥2 was considered as an indication for anticoagulation therapy.[4]

Patient and public involvement
This study used existing data from Norwegian national health registries. Registration into these registries is mandatory (the Norwegian Cardiovascular Disease Registry Regulation and the Norwegian Health Register Act), and consent by the patient was not required.

Statistics
Continuous variables are presented as the mean±SD or median (25th percentile, 75th percentile), and differences between groups were analysed using independent samples t tests. Categorical variables are presented as numbers and percentages, and differences between groups were analysed by the χ^2 test. Time trends were analysed (log-linear model) using the Joinpoint Regression Program (V.4.0; SEER software, National Cancer Institute, USA) and are presented as the expected annual per cent changes (APC) with a 95% CI. Kaplan-Meier curves for event-free survival after hospital admission for the first MI in the study period were estimated and Cox regression analyses were used to calculate HRs with 95% CIs for the combined endpoint all-cause mortality or non-fatal stroke. Non-fatal stroke competing risk analysis with all cause death as competing event was based on Fine and Gray's proportional subhazards model. The following covariates were included in the multivariable analyses: gender, age, smoking, previous stroke, previous MI, history of heart failure, diabetes, antihypertensive treatment, renal failure (estimated glomerular

Table 1 Clinical characteristics at hospital discharge in patients with myocardial infarction, atrial fibrillation and CHA_2DS_2-VASc risk score ≥2, Norway 2013–2019, n=7174

	All patients		No anticoagulation therapy		Anticoagulation therapy		
	n=7174		n=2338 (32.6%)		n=4809 (67.0%)		
	n	%	n	%	n	%	P*
Female	2896	40.4	946	40.5	1940	40.3	0.94
Mean age (year (SD))	80 (10)		80 (11)		80 (9)		0.13
Age <50 years	43	0.6	19	0.8	22	0.5	<0.001
Age 50–59 years	178	2.5	72	3.1	104	2.2	0.02
Age 60–69 years	848	11.7	302	12.9	533	11.1	0.02
Age 70–79 years	2110	29.4	599	25.6	1504	31.3	<0.001
Age≥80 years	4005	55.8	1446	57.8	2646	55.0	0.04
Previous coronary heart disease							
Myocardial infarction	2238	31.2	709	30.3	1524	31.7	0.24
Percutaneous coronary intervention	1440	20.1	440	18.8	996	20.7	0.07
Coronary artery bypass grafting	1079	15.0	286	12.3	789	16.4	<0.001
Previous stroke (all types)	1070	14.9	329	14.1	735	15.3	0.17
Smoking	2724	38.0	839	35.9	1879	39.1	0.01
Previous antihypertensive treatment	4353	10.7	1359	58.3	2976	61.9	0.003
Previous diabetes mellitus diagnosis	1756	24.5	544	23.3	1205	25.1	0.1
Previous heart failure diagnosis	1439	20.1	392	16.8	1039	21.6	<0.001
Renal failure (eGFR <60 mL/min)	3666	51.1	1290	52.1	2435	50.6	0.20
Type 1 myocardial infarction	4810	67.1	1668	71.3	3125	65.0	<0.001
Type 2 myocardial infarction	2274	31.7	648	27.7	1616	33.6	<0.001
ST-elevation myocardial infarction	957	13.3	372	15.9	580	12.1	<0.001
Coronary angiography	3198	44.6	990	42.3	2199	45.7	0.01
Percutaneous coronary intervention	1998	27.9	655	28.0	1336	27.8	0.96
Mean CHA_2DS_2-VASc risk score at discharge (SD)	4.4 (1.4)		4.3 (1.4)		4.5 (1.4)		<0.001

P*=comparison of anticoagulated and non-anticoagulated patients.
CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex (female); eGFR, estimated glomerular filtration rate.

filtration rate (eGFR) <60 mL/min) and out-of-hospital cardiac arrest (prior to hospitalisation for index MI). The proportional hazard assumptions were checked with the proportional-hazards assumption test based on Schoenfeld residuals and log-log plot of survival. A p value of <0.05 was regarded as statistically significant. The data were analysed using STATA, V.17 (StataCorp LLC, College Station, Texas).

RESULTS

From 1 January 2013, through 31 December 2019, 78 369 patients with MI were registered in the NORMI (figure 1). AF was identified in ECG at hospitalisation in 8565 (10.9%) patients. The yearly proportion of patients with MI with AF was stable throughout the study period. The prevalence of AF increased with age (<50 years, 1.6%; 50–59 years, 2.5%; 60–69 years, 5.5%; 70–79 years, 12.0% and ≥80 years, 20.9%). A total of 7845 (92%) patients with

AF had CHA_2DS_2-VASc risk score ≥2 at hospitalisation. Of 7440 patients with AF discharged alive, 7174 (96%) had CHA_2DS_2-VASc risk score ≥2.

Clinical characteristics at hospital discharge after MI in patients with AF and CHA_2DS_2-VASc risk score ≥2 are described in table 1.

Anticoagulation therapy

Among the 7845 patients with AF and CHA_2DS_2-VASc risk score ≥2 at hospitalisation, 3704 (47.2%) patients used anticoagulation therapy prior to the MI. Among the 7174 patients with AF and CHA_2DS_2-VASc risk score ≥2 discharged alive from hospital after MI, 4809 (67.0%) patients were prescribed anticoagulation therapy. Patients with a previous diagnosis of hypertension or heart failure were more likely to be discharged with anticoagulation therapy compared with patients discharged without anticoagulation therapy, but we found no
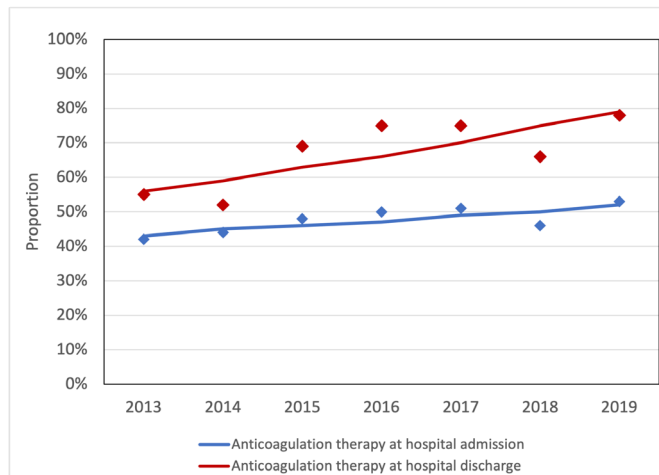
Figure 2 Proportion of patients with atrial fibrillation prescribed anticoagulation therapy prior to and after hospitalisation for acute myocardial infarction, Norway 2013–2019.

differences regarding gender, diabetes and previous stroke (table 1).

The use of anticoagulation therapy increased during the study period with an APC of 3.1 (95% CI 0.1 to 0.6) and 6.0 (95% CI 0.7 to 11.6) pre and post-MI, respectively (figure 2). In 2013, 55% of the patients with AF and CHA_2DS_2-VASc risk score ≥2 discharged alive from hospital after MI were prescribed anticoagulation therapy, and in 2019, the proportion has increased to 78%.

The prescription of different anticoagulation drugs at hospital discharge during the study period is presented in figure 3. Warfarin was the preferred anticoagulation therapy in the beginning of the study period, while most patients were prescribed a non-vitamin K oral anticoagulant (NOAC) at the end of the period.

Single antiplatelet therapy and dual antiplatelet therapy in combination with anticoagulation therapy were prescribed to 3323 (46.3%) and 1753 (24.4%) of the
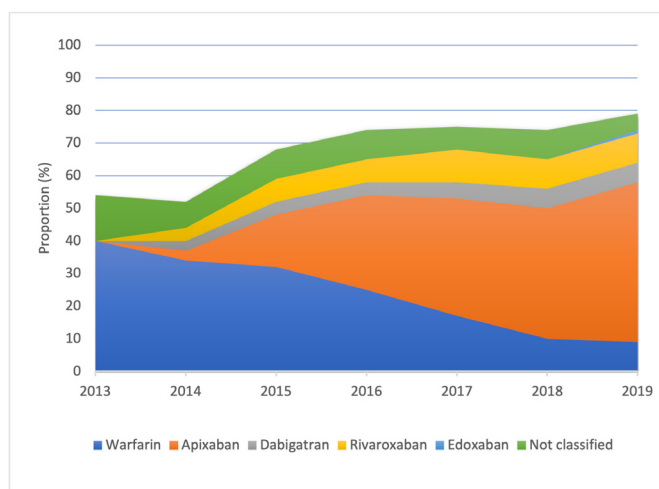

Figure 3 Prescription of different anticoagulation drugs after hospitalisation for acute myocardial infarction in patients with atrial fibrillation, Norway 2013–2019.

7174 patients discharged alive with MI, AF and CHA_2DS_2-VASc risk score ≥2, respectively.

Event-free survival
Patients were followed up for a median duration of 639 days (25th, 75th percentile 183, 1339).

A total of 1343 (57.4%) patients with AF and CHA_2DS_2-VASc risk score ≥2 discharged alive from hospital after MI without anticoagulation therapy died or suffered a stroke during follow-up, while 2167 (45.1%) patients discharged with anticoagulation therapy died and/or suffered a stroke (table 2). Patients prescribed anticoagulation therapy had a reduced risk of all types of stroke or death (multivariate-adjusted HR 0.8, 95% CI 0.7 to 0.8, p<0.001) compared with patients without a prescription of anticoagulation therapy (figure 4). Subdistribution HR for non-fatal stroke (all type) with all cause death as competing event was 0.8 (95% CI 0.6 to 1.1, p=0.116) for patients with versus patients without a prescription of anticoagulation therapy.

DISCUSSION
In this nationwide study of patients with acute MI admitted to hospitals in Norway from 2013 to 2019, the prevalence of ECG-verified AF at hospitalisation was 10.9%. Of 47.2% of the patients with AF and CHA_2DS_2-VASc risk score ≥2 used anticoagulation therapy prior to the MI, and 67.0% of the patients with CHA_2DS_2-VASc risk score ≥2 discharged alive were prescribed anticoagulation therapy. The prescription rate of anticoagulation therapy increased with 6.0% per year during the study period, from 55% in 2013 to 78% in 2019. Patients without prescription of anticoagulation therapy at hospital discharge had increased risk of stroke (all types) or all-cause death compared with patients with anticoagulation therapy.

More than half of the patients with AF at hospitalisation in this study were not treated with anticoagulation therapy prior to the MI. AF confers a fivefold increased risk of stroke on average, and 20%–30% of all strokes are attributed to this arrhythmia.[4] Anticoagulation therapy effectively reduces the risk of stroke, but low prescription rates of anticoagulation therapy have repeatedly been reported.[4–7 13 14] Up to one-third of AF cases are undiagnosed due to the asymptomatic and intermittent nature of AF.[4 15] The ESC guideline recommends screening for AF in patients at increased risk of stroke and AF screening is cost-effective in the high-risk population.[4 16] However, there is currently limited long-term continuous ECG recording equipment available that is suitable, affordable and sufficiently easy to use for screening purposes.[17] New and more effective diagnostic tools to identify AF will probably be more generally available in the future.[18]

Acute MI confers an excess risk of thromboembolic complications in patients with AF.[19] The ESC guidelines recommend anticoagulation therapy in most patients with AF and MI (ie, patients with CHA_2DS_2-VASc risk

Table 2 Long-term outcomes* in patients with myocardial infarction, atrial fibrillation and CHA$_2$DS$_2$-VASc risk score ≥2, Norway 2013–2019, n=7174

	No anticoagulation therapy	Anticoagulation therapy	Unadjusted HR (95% CI, p)	Multivariate-adjusted HR* (95% CI, p)
	n=2338	n=4809		
	n (%)	n (%)		
All type stroke or all-cause death	1343 (57.4)	2167 (45.1)	0.9 (0.8 to 0.9, <0.001)	0.8 (0.7 to 0.8, <0.001)
All-cause death	1316 (56.3)	2104 (43.8)	0.9 (0.8 to 0.9, <0.001)	0.8 (0.7 to 0.8, <0.001)

*Age, gender, smoking, previous stroke and myocardial infarction, history of diabetes and heart failure, antihypertensive treatment, renal failure (eGFR <60 mL/min) and out-of-hospital cardiac arrest.
†Median follow-up time 639 days (25th, 75th percentile: 182, 1339).
CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex (female).

score ≥2).[4 20 21] Although the proportion of patients prescribed anticoagulation therapy increased significantly during the study period, many patients were discharged from hospital without such treatment. The combination of antiplatelet drugs with anticoagulation therapy results in twofold to threefold increase in risk of bleeding complications, and the choice of antithrombotic treatment requires careful consideration of stroke risk, the risk of a new MI and the risk of bleeding.[22 23] Many patients with MI and AF are old, have additional comorbidities and consequently increased risk of death and stroke due to other reasons as well as increased bleeding risk, probably explaining the reduced utilisation of guideline-recommended therapy.

Several studies have described increased risk of stroke and death after MI in patients with AF compared with MI in patients without AF.[24] Warfarin effectively reduces the risk of stroke and mortality in patients with AF, but its use

is limited by the narrow therapeutic interval.[25 26] NOACs are associated with a similar, or even larger, reduction in risk of stroke as warfarin, and also lower risk of major bleeding.[27] Despite NOAC is recommended in the guidelines, as many as 9% of the patients discharged with anticoagulation therapy were prescribed warfarin in 2019. The observed shift in treatment from warfarin to NOACs in this study is probably part of the explanation for the increased use of anticoagulation therapy. Improved outcome in patients prescribed anticoagulation therapy compared with patients without anticoagulation therapy in this study highlights the importance of adherence to international guidelines in treatment of patients with MI and AF.

The main strengths of this study are the large and unselected population comprising nearly all patients hospitalised with MI in Norway from 2013 to 2019, and a nearly complete follow-up. However, there are several

Multivariate adjusted HR 0.8, 95% CI 0.7-0.8, p<0.001*

*Reference: No anticoagulation therapy

Number at risk																		
No anticoagulation therapy	2338	(578)	1683	(200)	1397	(114)	1219	(116)	1020	(66)	891	(75)	744	(54)	646	(52)	527	(33)	406
Anticoagulation therapy	4809	(811)	3673	(336)	3012	(220)	2585	(211)	2052	(147)	1688	(143)	1302	(79)	1036	(79)	738	(63)	485
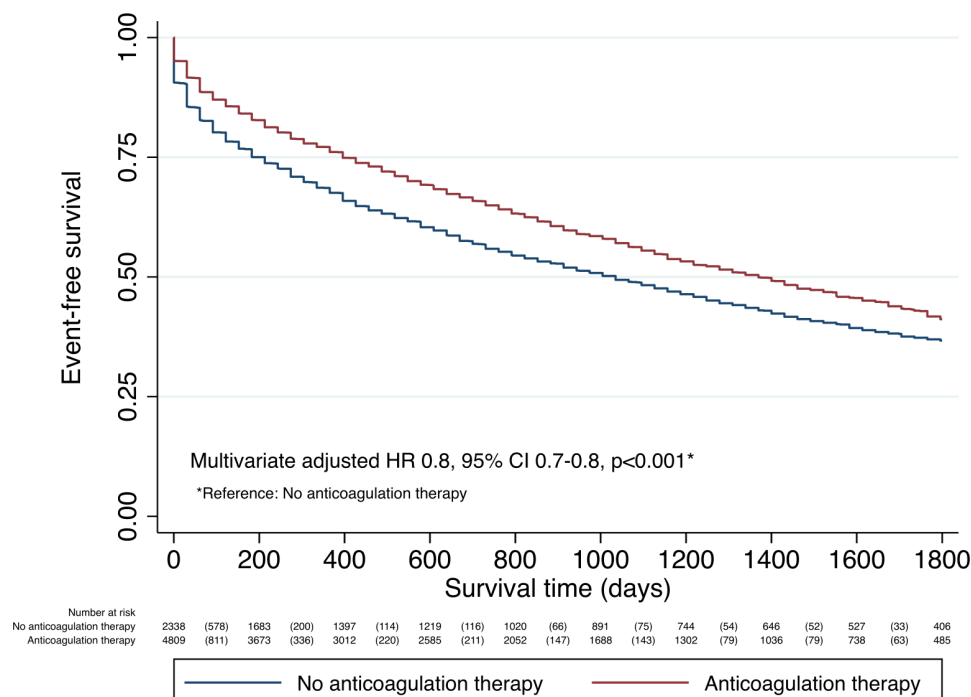
Figure 4 Event-free survival in patients with myocardial infarction and atrial fibrillation, Norway 2013–2019.

important limitations associated with the study design and the NORMI. This study was an observational study, making it impossible to demonstrate causal associations between treatment and outcomes. Only MIs that led to hospitalisation were registered in the NORMI. A few hospitals did not deliver complete data for the whole period, but the coverage compared with the Norwegian Patient Register was >90%.[10] The NORMI did not have complete coverage for all variables. We only obtained deidentified data from the NORMI and the Norwegian Cardiovascular Disease Registry and could not verify the information through medical records at the individual patient level. The NORMI does not have all the necessary variables to calculate the risk of bleeding and frailty.[28 29] Furthermore, drug dosages and drug compliance of anti-coagulation therapy after discharge from hospitals were not available. Consequently, we have only been able to adjust for a limited number of covariates. Unmeasured confounders still exist. The findings of the study must be interpreted with caution and generalisation of the results should be avoided.

In conclusion, the prescription rate of anticoagulation therapy in patients with MI and AF with an indication for anticoagulation therapy increased during the study period. However, still many patients with MI and AF did not receive guidelines recommended treatment with anticoagulation therapy and had a higher risk of stroke or death during follow-up. This study highlights an area with potential for improvement in the treatment of acute MI.

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