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Pharmacy-dispensed drugs for secondary prevention after myocardial infarction

ORIGINALARTIKKEL

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BACKGROUND

Secondary prophylactic drugs are important for avoiding further cardiovascular events after myocardial infarction. We have examined whether patients collect these drugs from pharmacies and whether there are differences in survival between those who collect versus do not collect the drugs.

MATERIAL AND METHOD

All patients <80 years registered in the Norwegian Myocardial Infarction Registry in 2013–16 were included in the study. The Norwegian Prescription Database was used to determine whether patients collected their prescriptions from pharmacies.

RESULTS

During the study period, 32 328 patients under the age of 80 were registered in the Norwegian Myocardial Infarction Registry, of whom 96 % were discharged alive. The proportion of patients who were prescribed acetylsalicylic acid was 95 %, two antiplatelet agents, 83 %; a statin, 90 %; beta-blockers, 76 %; and ACE inhibitors/AII receptor blockers, 55 %. The proportions of patients who collected each of these drugs from a pharmacy within six months were 94 %, 90 %, 96 %, 95 % and 94 %, respectively. The combined incidence of death, stroke and myocardial infarction during the follow-up period (median 944 days) was higher among patients who did not collect all of their prescribed drugs (adjusted HR 1.7; 95 % CI 1.6–1.8). Among patients who died, the median time to death was 509 days for those who collected all of their prescribed drugs versus 126 days for those who did not (p <0.001).

INTERPRETATION

Most patients do collect prescribed drugs from a pharmacy after myocardial infarction. A shorter time to death among patients who do not collect the drugs may suggest a high degree of general morbidity in this group.

Each year, approximately 13 000 Norwegians are hospitalised with acute myocardial infarction (1). Patients with established coronary artery disease are at increased risk of further cardiovascular events and premature mortality (2). Patients with a history of myocardial infarction are advised to modify their lifestyle and to take prophylactic drugs to prevent further events (3–6).

Many patients do not achieve the recommended treatment targets for secondary prophylaxis (7–10). We recently published data from the Norwegian Myocardial Infarction Registry showing that patients with established coronary artery disease achieved on average only three of six treatment targets for secondary prophylaxis (smoking cessation, blood pressure <140/90 mm Hg, LDL cholesterol <1.8 mmol/l, body mass index <25 kg/m^2 and regular use of acetylsalicylic acid and a statin), and less than 2 % achieved all treatment targets (11). Patients who achieved few treatment targets had poorer long-term prognoses than those who achieved more.

Several studies have also shown that patients do not always use prophylactic drugs after myocardial infarction as prescribed (12–14). Failure to comply with recommendations for medication use given upon discharge from hospital following myocardial infarction can have an impact both on achievement of treatment targets for secondary prevention and on survival (13, 14).

Using data from the Norwegian Myocardial Infarction Registry and the Norwegian Prescription Database, we have examined the extent to which patients under the age of 80 admitted to Norwegian hospitals with myocardial infarction in the period 2013–16 were prescribed drugs for secondary prevention, whether they collected those drugs from pharmacies after discharge from hospital, and whether those who collected the drugs showed better survival outcomes than those who did not.

Material and method

All patients <80 years with a diagnosis of acute myocardial infarction admitted to Norwegian hospitals between 1 January 2013 and 31 December 2016 and registered in the Norwegian Myocardial Infarction Registry were included in the study. It is a statutory

requirement for all patients admitted to Norwegian hospitals with acute myocardial infarction to be registered in the Norwegian Myocardial Infarction Registry. Registration does not require patient consent. The registry contains information on sex, age, known risk factors, medical history and previous medication use, symptoms and clinical findings on arrival and on assessment, treatment, complications while in hospital, and medications upon discharge. The registration and quality assurance of information in the Norwegian Myocardial Infarction Registry has been described previously (1, 15, 16). The diagnosis of myocardial infarction was based on a rise and/or fall in troponin plus one of the following additional criteria: ischaemic symptoms, new ST-segment elevation/ST-segment depression/T-wave inversion/left bundle-branch block, development of pathological Q-waves, visual identification of new myocardial damage using echocardiography or MRI, or detection of an intracoronary thrombus by angiography or autopsy (17). For patients who experienced multiple myocardial infarctions in the period 2013–16, data from the first myocardial infarction were used.

Information on drugs dispensed by pharmacies in the first six months after myocardial infarction was obtained from the Norwegian Prescription Database. This database contains information on all medicines dispensed on prescription from all Norwegian pharmacies. For medicines dispensed on 'blue prescriptions', three months' supply can generally be collected at a time. We chose to include drugs dispensed by pharmacies in the first six months after myocardial infarction in order to capture new dispensing of drugs in the study period to patients who had already been using them *before* their myocardial infarction. The Norwegian Prescription Database lacks information on individual drug dispensing in hospitals and care institutions. We therefore excluded patients ≥80 years of age from the study.

Time of death is updated in the Norwegian Myocardial Infarction Registry by linking to the National Population Register. Information on stroke after discharge from the index hospital stay was obtained from the Norwegian Cardiovascular Disease Registry. All research data were supplied in de-identified format by the Norwegian Institute of Public Health.

Continuous variables are presented as median (interquartile range), and differences were analysed using non-parametric tests. Categorical data are presented as numbers. Percentages and differences between groups were analysed using chi-squared tests. Survival in the absence of a new non-fatal myocardial infarction or non-fatal stroke is shown using Kaplan-Meier curves. Follow-up data were available for myocardial infarction and stroke up to and including 31 December 2016 and for survival up to and including 31 December 2017. Differences in the incidence of new cardiovascular events and death were analysed by Cox regression analysis and are presented as hazard ratios (HR) with 95 % confidence intervals (CI). We adjusted for variables that have been shown to affect survival and that were available for analysis: age (continuous variable), sex, previous treatment for hypertension, renal failure, heart failure, diabetes, smoking, stroke during hospital stay, and findings on coronary angiography.

For all analyses, p-values <0.05 were considered statistically significant. Data were analysed using STATA statistical software, version 15.

The study has been approved by the Regional Committee for Medical and Health Research Ethics South East Norway (REK 2016/170).

Results

In the period 2013–16, a total of 47 204 patients were registered in the Norwegian Myocardial Infarction Registry, of whom 32 328 (68 %) were <80 years of age. The median age was 65 years (interquartile range 57–72), 23 437 (72 %) were men, and 9 934 (31 %) had ST-segment elevation on ECG. A total of 31 105 (96 %) patients were discharged from hospital alive. Clinical characteristics upon admission, the results of invasive testing, and inpatient treatment are shown for these patients in Table 1.

Table 1

Clinical characteristics upon admission, results of invasive testing, and inpatient treatment for patients <80 years with myocardial infarction discharged alive from hospitals in Norway in 2013–16 (N = 31 105). Number (%) unless otherwise specified

	Women (n = 8 524)	Men (n = 22 581)	P-value
Median age (interquartile range)	68 (60–74)	64 (55–71)	< 0.001
ST-segment elevation myocardial infarction	2 118 (25)	7 264 (32)	< 0.001
Previous illnesses/risk factors			
Myocardial infarction	1 314 (15)	4 941 (22)	< 0.001
Diabetes mellitus	1 641 (19)	4 085 (18)	0.016
Statin-treated dyslipidaemia	2 864 (34)	7 786 (34)	0.157
Smoking[1]	5 736 (67)	16 136 (71)	< 0.001
Treatment for hypertension	4 065 (48)	9 456 (42)	< 0.001
Coronary angiography	6 529 (77)	19 674 (87)	< 0.001
Percutaneous coronary intervention (PCI)	4 291 (50)	15 450 (68)	< 0.001

[1]Former or current smoker

Upon discharge from hospital, acetylsalicylic acid was prescribed for 29 447 (95 %) patients, two different antiplatelet agents for 25 960 (83 %), a statin for 27 985 (90 %), beta-blockers for 23 579 (76 %), and renin-angiotensin system inhibitors (ACE inhibitors/AII receptor blockers) for 16 982 (55 %). Women were less likely than men to be prescribed secondary prophylactic drugs (Table 2).

Table 2

Secondary prophylactic drugs prescribed to patients <80 years discharged alive following treatment for myocardial infarction in Norway 2013–16 (N = 31 105). Number of patients for whom each drug was prescribed upon discharge from hospital, and number who collected these drugs from a pharmacy within six months of discharge. Number (%).

	Women (n = 8 524)		Men (n = 22 581)		P-value	
	Prescribed	Collected from pharmacy[1]	Prescribed	Collected from pharmacy[1]	Prescribed	Collected
Acetylsalicyclic acid	7 851 (92)	7 222 (92)	21 596 (96)	20 448 (95)	< 0.001	< 0.001
Two different antiplatelet agents	6 699 (79)	5 834 (87)	19 261 (85)	17 571 (91)	< 0.001	< 0.001
Statin	7 294 (86)	6 845 (94)	20 691 (92)	19 880 (96)	< 0.001	< 0.001
Beta-blockers	6 163 (72)	5 815 (94)	17 416 (77)	16 661 (96)	< 0.001	< 0.001
Angiotensin convertase inhibitors/angiotensin II receptor blockers	4 371 (51)	4 081 (93)	12 611 (56)	11 954 (95)	< 0.001	< 0.001

[1]Percentages are of the total number of patients who were prescribed that drug

The numbers and percentages of patients who collected their prescribed drugs from a pharmacy within the first six months after discharge from hospital are shown in Table 2. Of the 30 717 post-myocardial infarction patients registered as having been prescribed one or more secondary prophylactic drugs upon discharge from hospital, 4 422 (14 %) did not

collect one or more of those drugs from a pharmacy within the first six months. The patients who did not collect their prescribed drugs from a pharmacy were older than those who collected them (median age 69 years vs. 64 years, p <0.001), were more likely to have had a previous myocardial infarction (30 % vs. 19 %, p <0.001), more likely to have diabetes (25 % vs. 17 %, p <0.001) and hypertension (52 % vs. 42 %, p <0.001), and less likely to have ST-segment elevation myocardial infarction (16 % vs. 33 %, p <0.001). Of the 29 847 patients who were prescribed secondary prophylactic drugs upon discharge from hospital and who were alive six months after a myocardial infarction, 3 833 (13 %) did not collect one or more of their prescribed drugs from a pharmacy within the first six months after discharge.

Fewer women than men collected their prescribed prophylactic drugs from a pharmacy after myocardial infarction (Table 2). Among those who did not collect the drugs, the women were older than the men (median age 70 years vs. 68 years, p <0.001).

Even when patients were not prescribed drugs upon discharge from hospital, 418 (1 %) collected acetylsalicylic acid from a pharmacy in the course of the first six months after myocardial infarction, 893 (3 %) collected two different antiplatelet agents, 1 239 (4 %) collected a statin, 1 912 (6 %) collected beta-blockers and 2 650 (9 %) collected ACE inhibitors/AII receptor blockers.

A total of 3 425 (11 %) patients who were prescribed one or more prophylactic drugs upon discharge died in the course of the study period (median follow-up time 1 004 days (interquartile range 639–1 400)), 614 (2 %) patients experienced a non-fatal stroke, and 2 282 (7 %) patients experienced a new non-fatal myocardial infarction (median follow-up time 944 days (interquartile range 548–1 339)).

The combined incidence of death, non-fatal stroke and non-fatal myocardial infarction was significantly higher in the patients who did not collect their prescribed drugs from a pharmacy following myocardial infarction than in those who collected all prescribed drugs (adjusted HR 1.7 (95 % CI 1.6–1.8)) (Table 3, Figure 1). The patients who did not collect their prescribed drugs and who died during the study period were older than the remainder of the study population (median age 73 years vs. 65 years, p <0.001). Among patients who died after discharge, the median time to death was longer in those who collected all their prescribed drugs from a pharmacy than in those who did not collect one or more (median 509 days (interquartile range 225–889) vs. 126 days (interquartile range 37–535), p <0.001). No sex differences in time to death, stroke or new myocardial infarction were found in either the group that collected their prescribed drugs or the group that did not collect the drugs (data not shown).

Table 3

Survival in patients <80 years who were prescribed one or more prophylactic drugs upon discharge from hospital following treatment for myocardial infarction in Norway 2013–16 (n = 30 717) stratified by whether or not they collected all prescribed drugs.

	Collected n = 26 295 n (%)	Did not collect n = 4 422 n (%)	Unadjusted hazard ratio (95 % CI)	Adjusted[3] hazard ratio (95 % CI)
Composite endpoint (death, non-fatal stroke and non-fatal myocardial infarction)[1]	4 134 (16)	1 539 (35)	2.6 (2.4–2.7)	1.7 (1.6–1.8)
Death[2]	2 236 (9)	1 189 (27)	3.6 (3.4–3.9)	2.1 (2.0–2.3)
Non-fatal stroke	462 (2)	152 (3)	2.2 (1.8–2.7)	1.6 (1.3–1.9)
Non-fatal myocardial infarction	1 893(7)	389 (9)	1.4 (1.3–1.6)	1.1 (1.0–1.3)

[1]Median follow-up time for composite endpoint: 944 days (interquartile range 548–1 339)

[2]Median follow-up time for endpoint 'death': 1 004 days (interquartile range 639–1 400)

[3]Adjusted for age, sex, previous treatment for hypertension, renal failure, heart failure, diabetes, smoking, stroke during hospital stay, and findings on coronary angiography

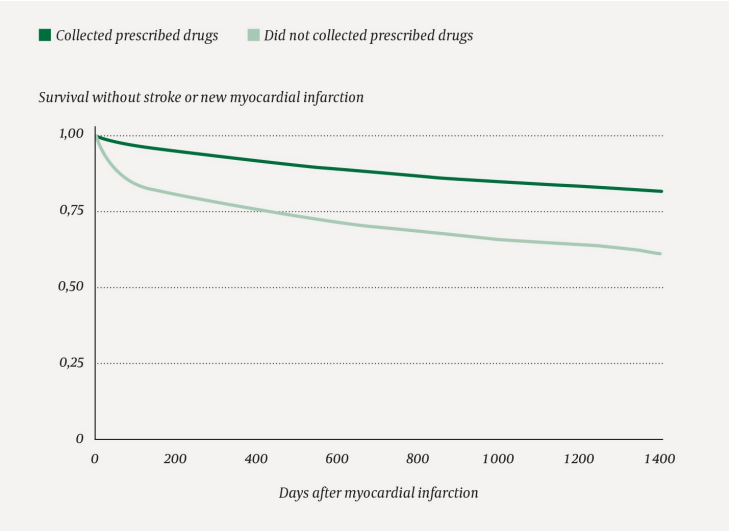

Figure 1 *Survival without new myocardial infarction or stroke in myocardial infarction patients under 80 years of age (n = 30 717) who collected (n = 26 295) or did not collect (n = 4 422) one or more prescribed prophylactic drugs from a pharmacy after discharge from a hospital in Norway 2013–16.*

Discussion

This study of all registered myocardial infarction patients under 80 years of age in Norway in the period 2013–16 shows that not all patients were prescribed the recommended secondary prophylactic drugs upon discharge from hospital. For example, 17 % of patients were discharged without two different antiplatelet agents and 10 % without a statin. Thirteen per cent of patients failed to collect one or more of their prescribed drugs from a pharmacy within six months. Fewer women than men were prescribed the drugs, and women were also less likely to collect them. Patients who did not collect the drugs had poorer survival outcomes than those who did.

Lifestyle interventions and secondary prophylactic drugs such as antiplatelet agents and statins reduce the risk of subsequent cardiovascular events and are recommended for all patients after myocardial infarction (3–5). Nevertheless, major international studies show that the majority of patients with coronary artery disease do not achieve the recommended treatment targets for secondary prevention (smoking cessation, blood pressure <140/90 mm Hg, LDL cholesterol <1.8 mmol/l, body mass index <25 kg/m^2 as well as regular use of acetylsalicylic acid and a statin) (9). Similar findings have recently been reported in Norway (11, 18). Possible explanations may be inadequate prescribing of drugs recommended after myocardial infarction, lack of compliance with the recommendations, inefficacy of therapeutic interventions (lifestyle interventions and drugs), and inadequate follow-up by the health care system following discharge from hospital. In common with previous studies from the Norwegian Myocardial Infarction Registry, the current study shows that not all patients were prescribed secondary prophylactic drugs on discharge (1, 12, 19). The reasons for this are unclear, but multiple comorbidities and an increased risk of adverse effects may have been contributing factors, particularly in the oldest patients.

Several previous studies have shown poor patient compliance with recommended secondary prophylactic drug therapy after myocardial infarction (13). In this study, however, the vast majority of patients collected their prescribed prophylactic drugs from pharmacies. However, we lack information on the extent to which they actually used them.

For reasons that are unclear, women were less likely than men to collect their prescribed prophylactic drugs. Many factors affect adherence to pharmaceutical treatment (20). That the women were older than the men, with consequently greater general morbidity and increased likelihood of being in residential care, might have played a part. An inverse correlation between educational level and incidence of myocardial infarction has been shown previously in Norway, especially in women (21). Education may also have influenced the extent to which recommendations regarding drug treatment were followed, but it was not possible to assess this in the current study.

Although survival after myocardial infarction is good and is improving in Europe and Norway, many patients with coronary artery disease still experience further cardiovascular events (1, 2, 11, 22). We have recently shown poorer event-free survival in patients with previous coronary artery disease compared to patients with no such history, along with low levels of achievement of treatment targets for secondary prophylaxis (11). Our current study showed poorer event-free survival in patients <80 years of age who did not collect secondary prophylactic drugs from pharmacies after myocardial infarction. However, this finding must be interpreted with great caution. The median time to death among patients who did not collect secondary prophylactic drugs from a pharmacy was only about four months, which may indicate high levels of general morbidity in this group and a large number of patients requiring residential care. Medication use may therefore also have been greater than indicated by the Norwegian Prescription Database.

In spite of the high levels of drug collection from pharmacies, we believe it is worth emphasising the importance of follow-up of patients after myocardial infarction. European studies have shown that fewer than half of patients take part in organised follow-up programmes for secondary prevention after myocardial infarction (9). There are no clear Norwegian recommendations on how such follow-up should be organised, and in our experience practices vary across hospitals. Unfortunately, neither the treatment received nor the treatment goals achieved after discharge from hospital are recorded in the Norwegian Myocardial Infarction Registry. Compliance with recommended medication use, dose adjustments and other changes in medication use – as well as lifestyle interventions – are important for increasing the number of treatment goals for secondary prophylaxis achieved and for reducing the number of new cardiovascular events.

This study includes a large number of patients and almost 100 % follow-up, but it also has several weaknesses. It is an observational study, and any causal relationship between failure to collect drugs from pharmacies and new cardiovascular events must be interpreted with great caution. A few hospitals did not provide complete data to the Norwegian Myocardial Infarction Registry for the entire period. However, the registry had more than 90 % coverage for the period, and a high degree of completeness and accuracy (1, 15, 16). As we did not have an overview of patients who received medications from care institutions, total medication use may have been underestimated. In addition, some patients were already using the drugs in question prior to their myocardial infarction, and may therefore have had no need to collect new drugs in the first six months after discharge. It was not possible to adjust for this. Finally, this study reported the dispensing of prophylactic drugs from pharmacies, and not the actual use of those drugs.

In summary, this study from the Norwegian Myocardial Infarction Registry and the Norwegian Prescription Database shows that most patients who have experienced myocardial infarction do collect the secondary prophylactic drugs prescribed for them from pharmacies.

MAIN POINTS

In 2013–2016, most patients <80 years of age with myocardial infarction were prescribed drugs recommended for secondary prevention upon discharge from hospital, but 17 % of

patients were discharged without two different antiplatelet agents and 10 % without a statin.

Fewer women than men were prescribed drugs for secondary prevention, and women were less likely to collect the drugs from pharmacies.

Fourteen per cent of patients failed to collect one or more drugs prescribed for secondary prevention from a pharmacy within six months of discharge.

Post-myocardial infarction patients who did not collect drugs prescribed for secondary prevention from pharmacies had poorer survival than patients who collected the drugs.

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