Measuring quality of care in the treatment of acute coronary syndrome

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Chapter 6

Age and Gender Differences in Medical Adherence after Myocardial Infarction: Women do not receive optimal treatment: The Netherlands Claims Database.

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ABSTRACT

BACKGROUND: Following myocardial infarction, medication is, besides lifestyle interventions, the cornerstone treatment to improve survival and minimize the occurrence of new cardiovascular events. Still, data on nationwide medication adherence are scarce. This study assesses medical adherence during one year following myocardial infarction, stratifying per type of infarct, age and gender.

METHODS: In the Netherlands, all inhabitants are by law obliged to have health insurance and all claims data are centrally registered. In 2012 and 2013, all national diagnose-codings of ST-Elevation myocardial infarction (STEMI) and Non-ST-Elevation myocardial infarction (NSTEMI) were acquired. Furthermore, information on retrieved medication was extracted from the Dutch Pharmacy Information System. Twelve months after discharge, the retrieved medication at the pharmacy of each pharmacological therapy (aspirin-species, P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor, vitamin-K antagonists or novel oral anticoagulant) were analysed.

RESULTS: In total, 59,534 patients (67 ± 13 years, 39,545 (66%) male, 57% NSTEMI) were included of whom 52,672 (88%) patients were analysed for one-year medical adherence. STEMI patients more often achieved optimal medical adherence than NSTEMI patients (60% vs. 40%, $p \leq 0.001$). In both STEMI and NSTEMI, use of all five indicated drugs was higher in male patients compared to female (STEMI male 61% vs. female 57%, $p \leq 0.001$; NSTEMI male 43% vs. female 37%, $p \leq 0.001$. With increasing age, a gradual decrease was observed in the use of aspirin, P2Y12-inhibitors and statins.

CONCLUSION: Age and gender differences existed in medical adherence after myocardial infarction. Medical adherence was lower in women, young patients and elderly patients, specifically in NSTEMI patients.

INTRODUCTION

Cardiovascular disease, mostly due to coronary artery disease, is the most frequent cause of death worldwide with 17.5 million cases in 2012.[1] Following acute myocardial infarction, optimal medical therapy is, besides lifestyle interventions, the cornerstone treatment to increase survival, improve cardiac function and minimize the occurrence of new cardiovascular events.[2, 3] The European Society of Cardiology (ESC) and American Heart Association /American College of Cardiology guidelines recommend to prescribe the 'Golden Five', which is a combination of two types of platelet inhibitors (aspirin-specie and a P2Y12-inhibitor), a statin, a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II (AT2) inhibitor. Specifically, beta-blocker and ACE/AT2-inhibitor use is indicated for patients with LV dysfunction (Class I, level A) and recommended if not contra-indicated in the remaining group (Class IIa, level A).[4-6] With the increasing incidence of acute myocardial infarction and the improved prognosis, the group of patients needing lifelong medication continues to expand.[7] In 2016, the EUROASPIRE investigators reported an adherence rate of cardio-protective medication in surviving patients among 24 European countries ranging from 75% - 94% after 6 months.[8] Data was retrieved by reviewing medical records and patient interviews. However, until now, no complete data are available on nationwide medication adherence during prolonged follow-up.

In the Netherlands, it is mandatory for all inhabitants to have health insurance. All claims data are registered in the central claims database of the insurance companies in the Netherlands.[9] This database contains diagnose codings and demographic parameters of all patients. Additionally, all medication claims data are registered in Dutch Pharmacy Information System. This national database serves as a unique opportunity to assess medication adherence following acute myocardial infarction, stratified by diagnose, age and gender.

METHODS

In the Netherlands, all reimbursements of hospitalised patients are coded by diagnosis and treatment according to a national financial coding system. Hospital claims are send to the patient's insurance company and subsequently collected in the central database of the insurance companies in The Netherlands, the Dutch Hospital Care Information System. Furthermore, information on prescriptions which are retrieved by the patient and claimed by the pharmacist, can be extracted from the Dutch Pharmacy Information System. These two databases can link on an individual patient level by the data manager of the national insurance companies (Vektis B.V., Zeist, The Netherlands).

Patients

All patients with a diagnose code for a ST-segment Elevation Myocardial Infarction (STEMI) (code 0320.11.204) or a non-ST-segment Elevation Myocardial Infarction (NSTEMI) (code 0320.11.205) in 2012 and 2013 were selected. The following characteristics were retrieved: age, gender, treatment by percutaneous coronary intervention during initial hospitalisation, and mortality during 12 months after first diagnose registration. Mortality data are retrieved from the Hospital Care Information System in which deregistration from the insurance company with given reason 'dead' is recorded. For the analysis on medical adherence during long-term follow-up, patients who died during twelve months follow-up were excluded, since these patients could not have used medication during the entire period. The remaining patients were considered the study population.

Medication

Twelve months after discharge of the initial event, the fulfilled prescriptions of each pharmacological therapy (aspirin (acetylsalicylic acid and carbasalate calcium), P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor, vitamin-K antagonists (VKA) or Novel Oral Anticoagulant (NOAC)) were collected. Medicine usage was defined by using the then prevailing Anatomical Therapeutic Chemical (ATC)-code and the Defined Daily Dose (DDD). DDD is composed by the World Health Organisation Collaborating Centre for Drug Statistics Methodology and is the assumed average maintenance dose per day for a drug used for its main indication in adults. For each pharmacological therapy the minimum number of used tablets per day above a dosage threshold was used. The DDD-definition per medication is validated in previous studies and in this cohort.[10-12] The use of national claims data was validated by comparing national claims data of four representative hospitals to local data, which is obtained by local patient records review. The overall accuracy was above 95%.[12]

An aspirin included the ATC-codes B01AC06 (acetylsalicylic acid) or B01AC08 (carbasalate calcium), P2Y12-inhibitor by ATC-codes B01AC04 (clopidogrel), B01AC22 (prasugrel) and B01AC24 (ticagrelor), statins by ATC-codes C10AAxx (all HMG CoA reductase inhibitors), beta-blocker by ATC-codes C07xxxx (all beta-blocking agents and combinations), ACE/AT2-inhibitors by ATC-codes C09A, C09B and C09C (including combinations), Vitamin-K-antagonists by ATC-codes B01AA04 (phenprocoumon) and B01AA07 (acenocoumarol), and Novel Oral Anticoagulants by ATC-codes B01AE07 (dabigatran etexilate), B01AF01 (rivaroxaban) and B01AF02 (apixaban).

Optimal medical adherence was defined by the usage of aspirin, P2Y12-inhibitor, statin, beta-blocker, ACE/AT2-inhibitor. Additionally, replacement of aspirin with a VKA or NOAC was also considered optimal medical adherence, according to the current international

guidelines.[4, 5] Furthermore, the use of at least three or four out of five medications was analysed.

Statistical analyses

Data will be presented as absolute numbers and as a proportion of the total population, including numerator and denominator. Comparisons were done by chi-square test. A p-value below 0.05 was considered significantly different. Data was analysed using SAS® Version 9.3 (SAS Institute, Cary NC).

Ethical considerations

Informed consent was not acquired because personal identifiable data was encrypted and anonymised. For the use of anonymised national data, permission of the national insurance companies was provided. The Leiden University Medical Center gave permission and a declaration of "medical-ethical permittance not necessary" at the start of the study (reference number P15.265).

RESULTS

Patients

In 2012 and 2013, a total of 59,534 patients were diagnosed with an acute myocardial infarction in the Netherlands. Patients had a mean age of 67 ± 13 years and 66% was male. The majority was diagnosed with a NSTEMI (57%, mean age of 69 ± 13 years, 64% male), 43% with a STEMI (64% male mean age of 64 ± 13 years, 70% male). After one year, 6,862 (12%) patients died (2,986 STEMI; 3,876 NSTEMI) which resulted in a follow-up population of 52,672 patients. Of these patients, 2,061 patients were diagnosed with both STEMI and NSTEMI during the study period, resulting in a total follow-up population of 23,655 STEMI and 31,078 NSTEMI admissions in 52,672 unique patients during 2012 and 2013.

Table 1: Baseline characteristics.

	Total	STEMI	NSTEMI
Total number of patients	**N = 59,534**	**N = 25,630**	**N = 33,904**
Age (yrs.)	67 ± 13	64 ± 13	69 ± 13
Male gender	39,545 (66%)	17,879 (70%)	21,666 (64%)
Treated with percutaneous coronary intervention	31,638 (53%)	20,016 (78%)	11,622 (34%)

STEMI = ST-segment Elevation Myocardial Infarction; NSTEMI = Non-ST-segment Elevation Myocardial Infarction.

Percutaneous coronary intervention

Of all AMI-patients, 31,638 were treated with a PCI (57% of all male, 46% of all female patients, $p \leq 0.001$). In STEMI-patients, 14,308 (80%) male patients received more often a PCI compared to 5,708 (74%) of the female patients ($p \leq 0.001$). Also in NSTEMI-patient, women were less often treated with PCI (male 38% vs female 28%, $p \leq 0.001$).

Medical adherence

Of all STEMI-patients, 20,355 (86%) used an aspirin, 20,297 (86%) a P2Y12-inhibitor, 21,193 (90%) a statin, 19,975 (84%) a beta-blocker, 18,435 (78%) an ACE/AT2-inhibitor during the year following STEMI. 14,167 (60%) patients received optimal medical adherence (use of all five recommended medications or replacement of aspirin with VKA of NOAC). As is shown in **Table 2**, NSTEMI patients were significantly less often treated with the combination of recommended medication, resulting in only 12,500 (40%) patients being treated optimally.

Table 2: Medical adherence in STEMI and NSTEMI patients, during one year after acute myocardial infarction.

	AMI	STEMI	NSTEMI	p-value
	N = 52,672*	N = 23,655	N = 31,078	
Aspirin	42,717 (81%)	20,355 (86%)	21,789 (70%)	≤ 0.001
P2Y12-inhibitor	39,990 (76%)	20,297 (86%)	20,134 (65%)	≤ 0.001
Statin	44,548 (85%)	21,193 (90%)	22,858 (74%)	≤ 0.001
Beta-blocker	43,189 (82%)	19,975 (84%)	22,079 (71%)	≤ 0.001
ACE-inhibitor/AT2-inhibitor	38,795 (74%)	18,435 (78%)	19,584 (63%)	≤ 0.001
Vitamin K antagonist	8,669 (16%)	3,122 (13%)	4,594 (15%)	≤ 0.001
Novel oral anticoagulant	184 (0%)	44 (0%)	95 (0%)	0.006
Optimal medical adherence	25,615 (49%)	14,167 (60%)	12,500 (40%)	≤ 0.001
With aspirin	22,311 (42%)	12,534 (53%)	10,815 (35%)	≤ 0.001
With VKA or NOAC	3,304 (6%)	1,633 (7%)	1,685 (5%)	≤ 0.001
At least 4 out of 5	38,795 (74%)	19,527 (83%)	19,609 (63%)	≤ 0.001
At least 3 out of 5	46,885 (89%)	22,130 (94%)	24,082 (77%)	≤ 0.001

ACE-inhibitor = angiotensin-converting-enzyme-inhibitor, AT2-inhibitor = angiotensin-2-inhibitor, VKA = vitamin-K antagonist, NOAC = novel oral anticoagulant. Optimal medical adherence is defined as the use of a combination of aspirin (or replaced by VKA or NOAC), P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor.
* Unique patients when combining STEMI and NSTEMI patients.

Differences in gender

In general, medical adherence was higher in male STEMI and NSTEMI patients (**Table 3**). As shown in **Figure 1 & 2 & Table 3**, differences between male and female patients were less evident in STEMI patients than in NSTEMI patients. Following STEMI, female patients

were less often treated with aspirin (84% vs. 87%, p ≤ 0.001), statins (86% vs. 91%, p ≤ 0.001) and ACE/AT2-inhibitor (75% vs. 79%, p ≤ 0.001). Optimal medical adherence was achieved in 57% of all female patients compared to 61% in male patients (p ≤ 0.001) (**Figure 1**). Following NSTEMI, 37% of female patients and 43% of male patients was treated optimally (p ≤ 0.001) (**Figure 1**). Differences between female and male patients

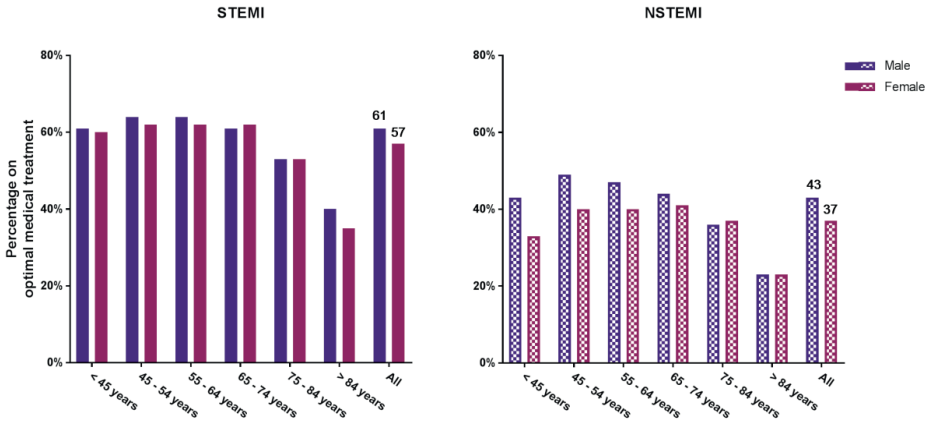

Figure 1: Optimal medical adherence

Table 3: Medical adherence in female and male patients, during one year after acute myocardial infarction.

	Male Gender	Female Gender	p-value
	N = 35,456	N = 17,216	
Aspirin	29,423 (83%)	13,294 (77%)	≤ 0.001
P2Y12-inhibitor	27,566 (78%)	12,424 (72%)	≤ 0.001
Statin	30,958 (87%)	13,590 (79%)	≤ 0.001
Beta-blocker	29,179 (82%)	14,010 (81%)	0.010
ACE-inhibitor/AT2-inhibitor	26,559 (75%)	12,236 (71%)	≤ 0.001
Vitamin K antagonist	5,597 (16%)	3,072 (18%)	≤ 0.001
Novel oral anticoagulant	115 0 (0%)	69 (0%)	0.163
Optimal medical adherence	17,988 (51%)	7,627 (44%)	≤ 0.001
With aspirin	15,728 (44%)	6,583 (38%)	≤ 0.001
With VKA or NOAC	2,260 (6%)	1,044 (6%)	0.169
At least 4 out of 5	27,077 (76%)	11,718 (68%)	≤ 0.001
At least 3 out of 5	32,261 (91%)	14,624 (85%)	≤ 0.001

ACE-inhibitor = angiotensin-converting-enzyme-inhibitor, AT2-inhibitor = angiotensin-2-inhibitor, VKA = vitamin-K antagonist, NOAC = novel oral anticoagulant.
Optimal medical adherence is defined as the use of a combination of aspirin (or replaced by VKA or NOAC), P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor.

were most outspoken in the use of aspirin (73% vs. 80%, $p \leq 0.001$), P2Y12-inhibitors (65% vs. 71%, $p \leq 0.001$) and statins (75% vs. 84%, $p \leq 0.001$).

Differences in age

As is shown in **Figure 1**, optimal medical adherence decreases with higher age. In STEMI patients, 37% of the patients older than 84 years achieved medical adherence, compared to 60% in all STEMI patients ($p \leq 0.001$). In NSTEMI patients, 23% of patients older than 84 years of age are treated optimally, compared to 41% of all NSTEMI patients ($p \leq 0.001$).

As is shown in **Figure 2 and 3**, in both STEMI and NSTEMI patients, for all five recommended drugs, optimal adherence was observed in the middle aged categories (45 – 74 years). In STEMI patients, with increasing age, a gradual decrease is observed in the use of aspirin, P2Y12-inhibitors and statins. These results can be noted in NSTEMI patients as well although, in contrast, the use of beta-blockers increased with higher age.

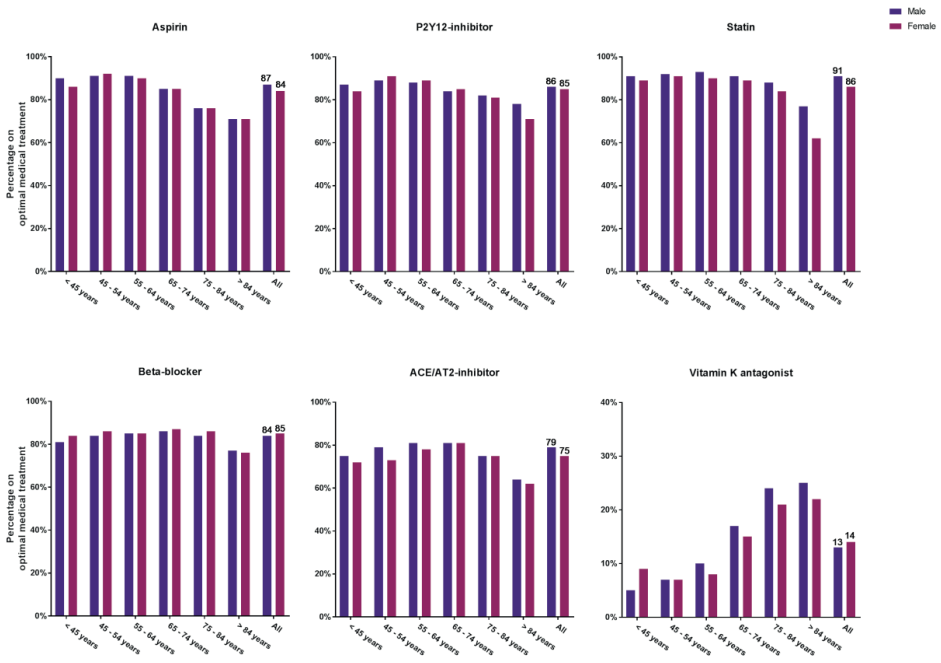

Figure 2: Medical adherence during one year after STEMI.

Specific subgroups

In patients younger than 45 years, medication after STEMI is similar to middle aged patients. However, following NSTEMI, patients are less often treated with beta-blockers

or ACE/AT2-inhibitors. Additionally, younger female patients receive treatment less often when compared to their peers or to middle aged patients. Furthermore, elderly female patients are least often treated with statins.

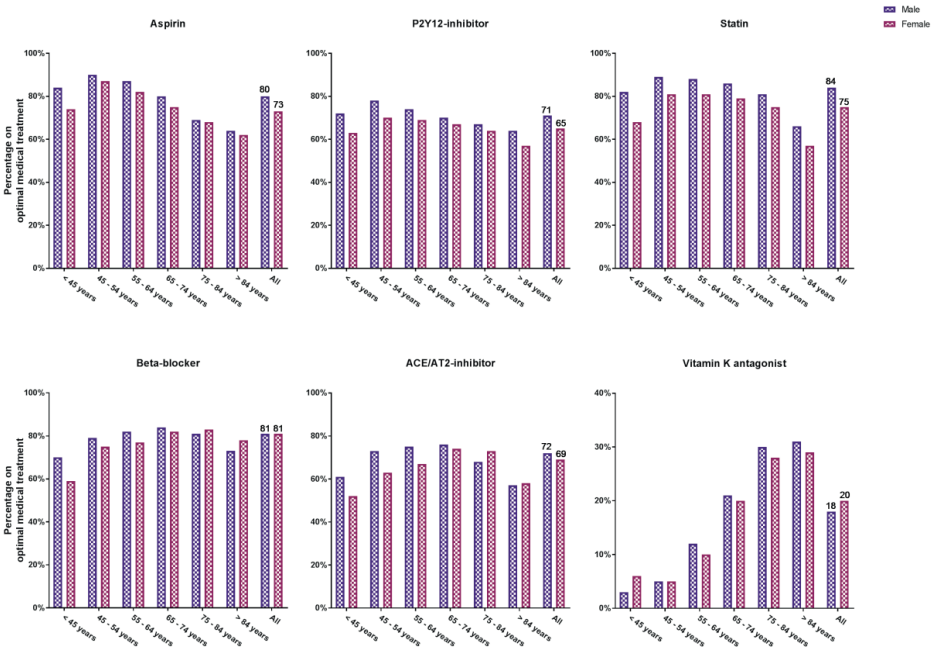

Figure 3: Medical adherence during one year after NSTEMI.

DISCUSSION

In the current study on medical adherence after acute myocardial infarction in the Netherlands, the findings can be summarized as follows: (i) 60% of STEMI patients and 40% of NSTEMI patients achieved optimal medical adherence; (ii) Medical adherence is lower in female patients and the elderly, especially following NSTEMI; (iii) important differences in medical adherence exist per age group, particularly in female patients.

STEMI versus NSTEMI patients

Despite pathophysiological differences between STEMI and NSTEMI, the ESC guidelines for medical adherence are nearly identical.[4, 5] Double platelet inhibition is recommended for one year (or shorter in case of VKA or NOAC usage) and aspirin and statin usage is recommended life-long.[4, 5]

Furthermore, beta-blocker and ACE/AT2-inhibitor use is indicated for patients with LV dysfunction (Class I, level A) and recommended if not contra-indicated in the remaining group (Class II, level A).[4-6] When comparing this study with previous large registries, an additional improvement in medication adherence over time can be observed, suggesting an increased focus on adequate medication prescription after AMI.[8, 13, 14] Additionally, the current study shows a higher medical adherence in STEMI patients, also observed in a study by Somma et al. in a voluntary registry at discharge in 72,352 patients.[15] A potential cause for these differences can be that STEMI patients more often receive treatment by percutaneous coronary intervention and are more often treated in tertiary care facilities with more focus on guideline-based medicine than smaller centers without possibilities for intervention.[15] However, the lower medical adherence in NSTEMI-patients could also be explained by a high percentage of female patients in which a conservative treatment is considered. This may relate to the risk-treatment paradox, which describes a treatment selection bias in which low-risk individuals are more likely to receive therapy than those patients at higher risk for poor outcomes.[16] We elaborate more on the gender effect in the next section. Furthermore, whether receiving a PCI may affect the medical adherence, should be further studied.

Additionally, the use of medication has not been studied in patients with a type 2 acute coronary syndrome (secondary to non-cardiac causes, such as anemia, fever or tachycardia), who could be registered as a NSTEMI as well.[4, 5, 17] When comparing the current results with previous studies such as the EUROASPIRE IV Study (2015), and the study of Koopman et al. (2013), an additional improvement in medication adherence over time can be observed, suggesting an increased focus on adequate medication prescription after an acute myocardial infarction.[8, 14] To our knowledge, no previous studies were conducted, comparing medical adherence during longer follow-up in STEMI and NSTEMI on a national scale.

Gender differences

It is remarkable that the current study demonstrates that women are receiving less optimal medical therapy in all age groups and all drug categories (with exception of NOAC or VKA this was however prescribed in a small number of patients). Although this was observed in both STEMI and NSTEMI patients. It is particularly worse in the NSTEMI group. The clinical relevance of gender differences varies by age, type of infarction and type of medication. For example, small differences are observed in the use of beta-blockers, larger differences are observed in the use of statins. Previous studies have shown that the symptom pattern is more atypical in women, making it more difficult to diagnose cardiac pathology.[18, 19] Additionally, women are still considered at lower risk of acute myocardial infarction, which makes physicians less aware of the risk of new cardiovascular events, causing lower

medical adherence. Smolina et al. confirmed these gender differences and showed that treatment was less often initiated in women.[20] However, once acute myocardial infarction has occurred, young women are at high risk of complications.[26] Although trials enrolled few women, benefits concerning safety and outcome have been observed regardless of gender.[19] Data from this study stress the need for appropriate secondary prevention after acute myocardial infarction, especially in women and may be considered a wakeup call.

Age differences

Medication adherence in NSTEMI patients seems lowest in young patients and the elderly, especially in female patients. These important differences in medical adherence per age group, particularly in female patients, have been confirmed before.[13, 14, 20-25] In the youngest patients (aged < 45 years) due to more atypical symptoms, a greater difficulty in certainty of diagnosis does exist.[4, 18] Besides, elderly patients are least often treated, especially with statins. This could be due to the fact that older patients have increased prevalence of comorbid conditions and a higher risk for developing side-effects like bleeding, bradycardia and hypotension,[26-28] which could results in a less favourable risk/benefit ratio with increasing age.[29] Additionally, discontinuation of medication or well-considered conservative treatment in elderly patients could be treatment of choice by physician or patient.[30, 31] Finally, the physician's perception of lack of benefit from medical treatment could play a role. Treatment-benefits in elderly are scarcely tested in clinical trials. On the other hand, the potential beneficial effect of medical treatment is highest in the population with the highest risk of cardiovascular events: the elderly.[23, 25] A cohort study in the of United Kingdom's Myocardial Ischaemia National Audit Project (MINAP) showed that potential survival gain by higher medical adherence after myocardial infarction is greatest in young patients but can be observed at all ages.[25]

Strengths and limitations

This study evaluates nationwide pharmacy-epidemiological data in all myocardial infarction patients in the Netherlands in 2012 and 2013. Although these claims data provide less detailed individual patient information, there are no missing data and no loss to follow-up of patients, since all health care costs are registered, regardless of the hospital where care has been provided. Furthermore a previous validation of claims data study showed good reliability.[32] However, some limitations have to be addressed. First, the data show retrieval from the pharmacy but do not differentiate if these drugs have actually been used by the patient. It is however reasonable to assume that patients who still after one year of follow-up do ask for drug delivery actually take the prescribed medication. Furthermore, detailed information about why patients are non-adherent is not evaluated. For example, contra-indications or intolerance to certain drugs could be an appropriate reason for discontinuation.

CONCLUSION

Age and gender differences exist in medical adherence after myocardial infarction. Medical adherence is lower in women, young patients and elderly patients, specifically in NSTEMI patients.

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