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PRESCRIPTION OF EVIDENCE-BASED MEDICINE DRUGS BY GENERAL PRACTITIONERS TO PATIENTS AFTER MYOCARDIAL INFARCTION: OUTCOMES FROM THE CZECH REPUBLIC

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Abstract: Ischemic heart disease is the most frequent cause of both serious morbidity and mortality of adult population in developed countries. The main aim of the study was to carry out the analysis of general practitioners (GP) prescription of evidence-based therapy in patients after myocardial infarction (MI). Data were retrospectively collected in 2011, by a single application with the help of software that GPs use in their surgeries. All patients of a particular GP who had MI in their history and who were at the time of data collection treated only by GPs (not by the specialists of internal medicine or cardiology) were always included. Four hundred ninety one patients were included in the study. The average age was 70.7 (± 11.6) and 69.2% of the involved patients were men. Seventy nine percent of patients used β-blockers, 80% antiplatelet drugs, 77% statins and 79% used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs). Forty four percent of patients used drugs from all four groups. The significant prescription decrease was proved in all four groups in dependence on patients' age ($p < 0.05$). Although the evidence-based medicine usage in patients after MI in the Czech Republic is comparable to other countries, it is not optimal. More intensive involvement of pharmacists in the care of patients after MI would further improve the situation.

Keywords: myocardial infarction; general practitioners; secondary prevention; evidence-based medicine

Worldwide, coronary artery disease (CAD) continues to represent a major cause of morbidity as 12.8% of all deaths are accounted for it. In Europe, every sixth man and every seventh woman will die of myocardial infarction (MI) (1). In the Czech Republic (CR), the statistical data are as follows: in 2010 the overall mortality of adult population due to cardiovascular disease (CVD) represented 50.2% of all known causes of death. Cardiovascular mortality in women was higher (55.9%) than in men (44.6%) (2). In the same year and country, 23.6% of inhabitants died of CAD. Despite the fact that statistical data from the CR indicate a worse situation compared to those in western European countries, over the last decades a permanent decline in the standardized overall cardiovascular mortality and, in particular, a significant decline in the standardized CAD mortality have been observed. When we focus on central European countries, Germany, Austria, Slovenia and Poland show lower mortality for CAD than the CR. On the other hand, in Slovakia and Romania CAD mortality is more than one third higher (2, 3).

A patient after MI faces a high cardiovascular risk. Unfavorable prognosis of these patients may be changed by a proper secondary prevention which is the most potent when a combination of life style modifications and pharmacotherapy are applied (1, 4, 5). In the CR, the secondary prevention is carried out by GPs who collaborate with cardiologists or internal medicine specialists in patients with unfavorable prognosis and a very high mortality risk.

According to the evidence-based medicine (EBM) long-term pharmacological treatment in patients after MI should include antiplatelet therapy, statin mediated hypolipidemic treatment, β-

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blockers and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) for ACEIs intolerance. Treatment with acetylsalicylic acid (ASA) at a daily dose of 75 to 100 mg decreases patient mortality (including recurrence of infarction) by approximately 25%. Clopidogrel (75 mg/day) should function as a substitution, if true ASA allergy is presented. In some cases a dual antiplatelet therapy and an oral anticoagulant are recommended (1, 5).

β-Blockers reduce mortality and recurrence of infarction comparably to ASA (by 20–25%) and should be initiated in all patients (if not contraindicated) after MI regardless of their cardiovascular risk. ACEIs prevent myocardial remodelling and thus participate in prevention of chronic cardiac failure due to coronary emergency. The total reduction of mortality is approximately 20–25%. Current recommendations suggest ACEIs/ARBs to be used in the secondary prevention in all patients without contraindications irrespective of their ejection fraction (1, 6).

Furthermore, statins are recommended in all patients in secondary prevention of MI (if not contraindicated) irrespective of cholesterol concentration because they lower both cardiovascular as well as total mortality (approximately by 30%) (1, 5).

Despite the conclusive evidence of benefit of above mentioned drugs in the secondary prevention of MI, their use in clinical practice is still insufficient (1). That is why it is important to constantly observe and assess clinical practice in order to adopt appropriate measures and further increase the rates of usage of EBM therapy after MI. We could presume that with appropriate treatment, mortality of patients after MI would further decrease (7).

The main aim of the study was to carry out an analysis of GP prescription of evidence-based therapy in patients after MI and to determine the proportion of patients using individual evidence-based drugs and their combinations. In addition, possible differences in prescription of evidence-based drugs and their combinations dependent on gender and age of patients were investigated.

EXPERIMENTAL

A retrospective cross-sectional study was conducted during the year 2011. Eighteen GPs who were at that time also consultants in a professional company (Society of General Practice of Czech Medical Association of J. E. Purkyně) in the area of rational pharmacotherapy and education for other members of this company took part in this study. The Society unites about 4,200 GPs (more than 80% of all GPs in the Czech Republic).

Using the electronic medical records of GPs all patients being positive for MI (International Classification of Diseases, ICD-9: 410.xx; ICD-10: I21, I22) and treated for MI only by GP (not by the specialists of internal medicine or cardiology) at the time of data collection were included in the study.

From each medical record patient gender, age, year of MI, and drug anamnesis were collected. We focused on the prescription of β-blockers, statins, ACEIs or ARBs, antiplatelet agents (EBM drugs

Table 1. Characteristic of the study group.

Patients	Characteristic	Mean ± SD (range)
Total (491)	Age (years)	70.7 ± 11.6 (35–96)
	Years after MI	8.0 ± 6.6 (0–33)
	Total number of prescribed drugs	6.4 ± 3.3 (2–26)
Men (340)	Age (years)	68.8 ± 11.5 (35–96)
	Years after MI	7.9 ± 6.6 (0–33)
	Total number of prescribed drugs	6.2 ± 3.3 (2–26)
Women (151)	Age (years)	75.1 ± 10.7 (43–96)
	Years after MI	8.2 ± 6.4 (0–26)
	Total number of prescribed drugs	6.9 ± 3.4 (2–22)

SD – standard deviation; MI – myocardial infarction (the first episode)

Table 2. Proportions of patients after MI treated with EBM therapy.

Patients	β-Blockers (%)	ACEIs (%)	ARBs (%)	ACEIs or ARBs (%)	Statins (%)	Antiplatelet agents – monotherapy (%)	Antiplatelet agents – dual therapy (%)	Anticoagulants* – only (%)	Combination of antiplatelet** and anticoagulant therapy (%)
Total (491)	79.0	63.3	16.7	79.0	77.2	71.9	7.1	9.8	1.2
Male (340)	79.1	67.7	12.0	79.5	78.3	70.9	8.8	10.2	1.5
Female (151)	78.8	53.6	27.2	77.5	74.2	73,5	3.3	8,6	0.7

MI – myocardial infarction; EBM – evidence-based medicine; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; * other anticoagulant except for warfarin did not occur in any patient; **acetylsalicylic acid only

after MI) and combinations of all of these drugs. Current medication (at the time when the data were collected) was decisive for us.

Statistical analysis

All statistical analysis of data was carried out in PASW® 18.0 software (version 18.0, IBM Corporation, Armonk, NY, U. S., 2009). A p-value < 0.05 was considered significant. For baseline characteristics, data are presented as percentages for binary variables and as the means ± standard deviations and ranges for metric variables. Actual age of patients and the number of years after MI were compared by means of non-parametric Mann-Whitney test. Dependence of a binary value (typically prescription – non-prescription of a drug from the particular evidence-based group) on factors, covariate or their combination was statistically evaluated by means of Generalized Linear Models (GLM+), variant binary distribution – logistic link function. In the special case of binary independent variable, the odds-ratio result was equivalent to analysis of four-square table. In another special case of continuous metric independent variable (especially age), the numerical results were equivalent to a common logistic regression. Another variant of GLM+ – Poisson Distribution, logarithmic link function, was used for analysis models with the number of evidence-based drugs prescribed as a dependent variable.

RESULTS

All addressed GPs participated in the study and the total cohort of patients after MI comprised 491 patients (i.e., 27.3 patients/GP). The basic characteristic of the study group divided according to gender of patients is shown in Table 1. Men and women differed significantly in the mean age ($p < 0.001$).

The oldest episode of MI was recorded in the year 1978 and the most actual in 2011.

Drugs from each of four EBM groups were prescribed to 77.2–80.2% of all patients. Proportions of patients treated with EBM therapy according to gender of patients are shown in Table 2. Men and women differed significantly in the prescription rate of ACEIs (ARBs respectively) only ($p = 0.002$).

Prescription of individual EBM drugs did not differ in any case significantly in dependence on gender (β-blockers $p = 0.142$; ACEIs/ARBs $p = 0.880$; statins $p = 0.158$; antiplatelet agents $p = 0.085$). Each of all four drug groups was significantly less prescribed to older patients (β-blockers $p < 0.001$, ACEIs/ARBs $p = 0.007$, statins $p < 0.001$; antiplatelet agents $p = 0.023$). When genders were

analyzed separately, the decrease of prescription probability with the age of patients was significant for men only in ACEIs/ARBs (men p = 0.001; women p = 0.352) and antiplatelet agents (men p = 0.009; women p = 0.864).

Probability of prescription of β-blockers decreased by 4.5% (95% CI = 2.3–6.7), of ACEIs/ARBs by 2.8% (95% CI = 0.7–4.8), of statins by 4.3% (95% CI = 2.3–6.5) and of antiplatelet agents by 2.4% (95% CI = 0.3–4.4) with each year of age.

Furthermore, patients were classified according to the number of EBM drugs prescribed. All four groups of drugs (β-blockers + ACEIs/ARBs + statins + antiplatelet drugs) were given to 44.4% of patients. Numbers of EBM therapies prescribed are shown in Figure 1.

The number of prescribed evidence-based drugs did not significantly differ in dependence of gender. Neither the chance of prescription of all four groups of EBM drugs after MI was different between men and women. However, there was a significant difference according to the age of patients (p = 0.002). Mean number of EBM drugs decreased by 0.7% (95% CI = 0.2–1.1) with each year of age.

DISCUSSION AND CONCLUSION

This study is unique because it assessed the treatment of patients in secondary prevention of MI treated by GPs only (not by specialists in internal medicine or cardiology). Every patient in the Czech Republic is registered with one GP. According to the standard of ischemic heart disease therapy (6), the secondary prevention in patients after IM is carried out by GPs who collaborate with cardiology specialists or internal medicine specialists in highly risk patients with unfavorable prognosis. One of the reasons for implementation of this precaution is economics because therapy led by GPs is less expensive for health care payer.

The patients' treatment in the study could have been set during the hospitalization in hospital but at the time of data collection was led only by GPs who are therefore fully responsible for treatment.

We found out that the EBM drugs after MI are underused. Approximately every fifth patient does not use β-blocker, ACEI/ARB, statin and it is impossible to predict that this fact was only connected with contraindication of particular drugs. In the case of antiplatelet drugs, the prescription of these drugs after MI is higher. All four recommended groups of drugs were prescribed only to 44.4% of patients. Nevertheless, the results of presented study are comparable to those obtained in other international studies, despite that there are some differences in their design. Tight comparisons between studies are limited by the variation of population selection, measurements of consumption of medications and the year(s) studied. Table 3 shows the approximate comparison of selected parameters from similar studies.

It is important to note that displayed studies derived the data from various national databases, used usually even more sources for better reliability and involved larger numbers of patients than our study did. Further, they observed medication of patients with the diagnosis of MI approximately 3–6

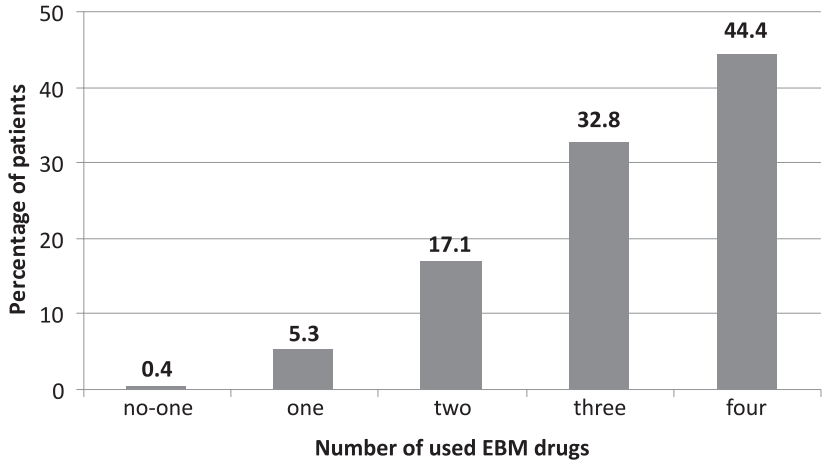

Figure 1. Number of EBM drugs (β-blockers, statins, ACEIs/ARBs, antiplatelet drugs) prescribed after MI (100% = 491 patients). ACEIs – angiotensin-converting enzyme inhibitors, ARBs – angiotensin receptor blockers

months after they were discharged or admitted to the hospital (8–12). The design of our study did not allow us to differentiate patients immediately after their release from hospital from those in long-term secondary prevention of MI. But patients in the long-term secondary prevention prevailed (patients were in average 8.0 ± 6.6 years after MI).

The time frame of other studies is comparable to our work as the evidence for the use of all four drug groups indicated in the secondary prevention of MI was clear at the time when they were conducted. The EBM drug therapy after MI had a definitive breakthrough at the end of the 1990s. Works that observed the trends of prescription of EBM drugs in patients after MI through the years indicated rising prevalence of their use, which is in accordance with the progressive dissemination of the evidence (12, 14).

Nevertheless, it is questionable whether all physicians were aware of this information, as guidelines, usually written by cardiology experts, are applied initially in academic institutions and the education of GPs comes as the final step. This fact could explain higher proportions of patients using recommended drugs, especially statins, antiplatelet agents and combination therapy in French study of Tuppin et al. (8), where higher rates of outpatient cardiologist appointments and hospitalization of patients in university hospitals were found. American study of Lee et al. (11) and Canadian work of Austin et al. (10) similarly indicated that the use of EBM drugs was associated with physician and hospital characteristics and suggested that it therein could be caused by the temporality of the availability of the evidence. As the regional consultants of the Society of General Practice of Czech Medical Association of J. E. Purkyně were approached in our study, we could expect that the results are influenced by greater awareness of evidence-based procedures and willingness to keep them than in other GPs. However, all of them are regularly provided with updated guidelines and other important information. As we do not know any further characteristics (i.e., years of practice) of GPs involved in the study we are not able to yield any conclusion regarding that.

Another reason for higher proportions of patients using recommended drugs in French study of Tuppin et al. (8) could be derived from lower mean age of patients involved (64.8 years). In our study (the mean age of patients was 70.7 ± 11.6 years), we found continuous decline in the prescription of EBM drugs and their combination for older patients, especially in the group of statins and β-blockers (of 4.3 and 4.5%, respectively, for 1 year of age). For Norwegian study of Reikvam et al. (13) the results for patients over the age of 70 years only are stated in Table 3 and it is likely to be the reason for lower numbers of prescribed EBM drugs after MI in comparison with our work. In the same study (13), the proportions of those drugs prescribed to patients under 70 years were higher (β-blockers 89%; ACEIs 29%; statins 82%). Also other studies confirmed that the age is a negative individual predictive factor of prescription of EBM drugs after MI. Australian work of Vermeer et al. (7) suggested patients over 65 years of age were less likely to receive β-blockers, ACEIs and dual antiplatelet therapy. The study of Schoenenberger et al. (15) yielded similar results for β-blockers and ASA in patients over 60 years and the work of Lee et al. (11) for β-blockers, statins (patients over 65 years) and ACEIs/ARBs (patients over 80 years). In the case of ACEIs/ARBs and antiplatelet drugs, we recorded lower but still significant decrease of their prescription in dependence on the patient age. However, this dependence was only significant in men. Since there were twice more men than women in our study, the overall results could be influenced by this fact. The reason why the chance of prescription of ACEIs/ARBs and antiplatelet drugs decreased only in men could be the aim of further research.

Some authors suggested that the decline of the prescription of EBM drugs with the age of patients could be assigned to the rising number of comorbidities with age (15), which could further prevent the prescription of some drugs because of contraindications or increased risk of adverse events. However, older patients would have greater treatment benefits from EBM drugs, because they are at a higher risk of mortality. For example, data from the PROSPER study (16) concerning use of pravastatin in patients aged 70–82 years or from the CURE study (17) bringing evidence for clopidogrel in patients over 65 years further affirm this claim. Valid data about the use of EBM therapies in older patients (especially over 80 years of age) are lacking, which may further enhance distrust of prescription of preventive drugs.

As we did not observe other diagnoses and possible contraindications or adverse drug events for that a particular EBM therapy was not prescribed or was withdrawn, we are not able to further analyze this problem. However, the importance of possible contraindications should not be overestimated. If theoretical assumptions are kept, then for instance ACEIs should not be indicated in patients with angioedema, oversensitivity to the particular drug or

Table 3. Comparison of selected parameters with chosen international studies.

Place and year of study implementation	Czech (2011)	France (8) (2006)	Austria (9) (2004)	Canada (10) (2003–2005)	USA (11) (2003)	Norway (12) (1999/2000)
Number of patients	491	11671	4105	290767	1135	767
Age [years]	70.7	64.8	68.8	77.0	63.8	> 70
BBs [%]	79.0	82.4	74	78.1	63.9	74
ACEIs/ARBs [%]	79.0	79.5	67	78.4	51.8	38*
Statins [%]	77.2	85.4	67	79.2	62.6	35
Antiplatelet agents [%]	88.5	92.0	–	–	–	70**
BBs+ACEIs/ARBs + statins [%]	51.9	–	41	–	29.9	–
BBs+ACEIs/ARBs + statins + antiplatelet agents [%]	44.4	62.1	–	–	–	–

BBs– β-blockers; ACEIs – angiotensin-converting enzyme inhibitors; ARBs – angiotensin receptor blockers; *ACEIs only; **aspirin/anticoagulants

pregnancy (total contraindications) (18). The occurrence of these conditions is not, nevertheless, so frequent (19). Conversely, in case of relative contraindications (i.e., hyperkalemia, severe damage to the kidneys) it is not possible to strictly rule out the prescription of ACEI. It depends on the particular case of an individual patient. The similar situation is in statins, too. In the case of β-blockers and antiplatelet agents, there would be a higher impact of possible contraindications on their prescription and, as it was mentioned above, especially these groups are therein less often prescribed to older patients (7, 11, 15). In patients with contraindication of β-blockers (chronic obstructive pulmonary disease), verapamil is a reasonable option for those without heart failure and with caution for those with impaired left ventricular function (1). It was used only by 3.0% of patients in our study so it does not explain another 18% of patients receiving neither β-blocker nor verapamil. It would be noted that some comorbidities may contrary contribute to a higher prescription rate of some drugs (i.e., ACEIs/ARBs in diabetics) (9).

Significant differences in the use of EBM drugs after MI in relation to gender were not found. Conversely, other papers reported such differences in the case of statins that were more likely prescribed to men (7, 11) and even of statins, β-blockers and ACEIs/ARBs together in the same direction (11). From Table 2 it is obvious that women were less often prescribed ACEIs and more often prescribed ARBs than men ($p = 0.002$). One of the possible explanations can be the fact that cough, as an adverse effect, appears more often in women (20).

The results of our study could be overestimated in dependence on a degree of compliance of patients to the prescribed therapy because we observed only whether a particular drug was prescribed, not if the prescription was filled and the medication really used. This fact probably led to significant differences in the results of Lee et al. (11) and our results as it is stated in Table 3. In the American study, authors obtained the data from the database of pharmacy claims for EBM drugs after MI not the data exactly from prescribed physicians, which would yield higher numbers. For example, Eagle et al. reported that the discontinuation of the evidence-based therapy after 6 months after discharge for acute coronary syndromes ranged between 8–20%. Further analyses of medical and social reasons of non-compliance are necessary and could significantly contribute to the improvement of therapy of patients after MI.

Approximately one fourth of analyzed patients used two or fewer EBM drugs. We can suggest precautions that could contribute to higher rationality of GP prescription. We suppose that among complicated patients, who GP should consult with specialists, should be involved patients after MI if GP hesitates over the prescription of one of the four EMB drugs. Health care payers (health insurance companies) have to play their control role in order to contribute to pharmacotherapy optimization either by targeted analysis of drug consumption or by delegating the control function to pharmacists. Pharmacists can participate in the system both by screening the drug problems in providing consulting service in pharmacies and by developing the cooperation with GPs at drug information centres.

The main limits of our study are the following: the participation of only a specific group of GPs from our country; no information about socio-demographic characteristics of GPs; low number of studied patients; cross-sectional design of the study does not allow us differentiate patients in the long-term secondary prevention of MI from those early after an event; no information about other diagnoses and possible contraindications for not receiving a particular drug and a lack of doses of prescribed evidence-based drugs.

In conclusion, the results of our study show that the use of EBM drugs in patients after MI in the Czech Republic is comparable to other countries although it is suboptimal. In our analysis, we found out a relationship between age and prescription of all of four EBM drugs for secondary prevention of MI. β-Blockers, ACEIs/ARBs, statins and antiplatelet agents were less likely prescribed to older patients. There were not significant differences in the prescription of them in dependence on gender. Despite the fact that the results in the Czech Republic are similar to those abroad, there are still a large percentage of patients who are not treated adequately. It is important to further improve the quality of care of patients in the secondary prevention of MI.

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