Statin Prescription by Croatian Family Doctors – Lack of Systematic Proactive Approach to Cardiovascular Disease Prevention

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ABSTRACT

The aim of this study was to investigate statin prescription by family doctors (GP) in primary (PP) and secondary (SP) prevention of cardiovascular diseases (CVDs). Patients’ socio-demographic data, total cholesterol (TC) and LDL-cholesterol (LDL-C) thresholds for statin prescription, indications, data on GP and practices were registered. Statins were prescribed in 11.2% enlisted patients (64.11% PP, 35.88% SP), mostly aged 70+. In PP, thresholds were TC 6.2 ± 1.09 mmol/L, LDL-C 3.6 mmol/L, in SP 5.4 ± 1.26 mmol/L, 2.7 mmol/L, respectively. Most frequently prescribed statin in PP was 10 mg atorvastatin (49.28%), in SP it was 20 mg simvastatin (48.36%). Participating GPs were women, aged 39 ± 5.49, working for 13 ± 6 years, the average number of enlisted patients per GP 1562 ± 299. There was statistically significant difference in statin prescription in PP (χ² = 752.9; p < 0.001) and SP (χ² = 64; p < 0.001). Statin prescription in PP is due to pharmaceutical marketing and lack of independent continuing medical education. The fact that statins are most frequently prescribed in patients aged 70+ (35.28% in PP, 49.35% SP) reveals lack of preventive proactive CVDs approach in younger age groups, which is concerning.

Key words: statin prescription patterns, cardiovascular diseases, general practitioner

Introduction

Cardiovascular diseases (CVDs) are responsible for 53.6% of all deaths registered annually in Croatia, and therefore represent the leading cause of death¹. One of the key risk factors in developing atherosclerosis is hypercholesterolemia, which makes its control and treatment crucial for the primary (PP) and secondary prevention (SP) of CVDs. Statins are efficient in treating hyperlipidemia and reducing the risk of adverse cardiovascular (CV) events both in PP and SP². The inhibition of HMG-CoA reductase (crucial in biosynthesis of the endogenous cholesterol) decreases concentration of total cholesterol (20%), LDL-cholesterol (28%) and triglycerides (13%), while HDL-cholesterol level increases (5%)³. By preventing LDL-cholesterol oxidation, and its macrophage accumulation⁴, as well as inhibiting smooth muscle cell proliferation⁵, these drugs exhibit an anti-atherogenic effect. The landmark study demonstrating the importance of statin use in secondary CHD prevention is the Scandinavian Simvastatin Survival Study (4S), carried out in 4444 CHD patients for 5.4 years. Statin use resulted in a 35%-decrease in LDL-cholesterol, a 10%-decrease in triglyceride concentrations, and an 8%-rise in HDL-cholesterol concentrations, leading to 42%-decrease in mortality caused by CHD, and a 30%-decrease in all-cause mortality. These results were even more favourable for diabetics: 43%-decrease in CVD caused mortality, and 46% in all-cause mortality 6%. Similar results were shown in SP after myocardial infarction (CARE and
LIPID studies) with pravastatin. The effects of statins in reducing both CVD and all-cause mortality are significant in primary CHD prevention, as demonstrated in the WOSCOPS study with pravastatin and the AFCAPS/TexCAPS study with lovastatin.

The Heart Protection Study (HPS) demonstrated benefits of simvastatin in SP for population with increased risk of developing the disease, as well as benefits in those aged 65+. The EUROASPIRE study, carried out in 9 European countries, showed that in period 1991-1995, hypolipemics were administered to only 32% of the discharged CHD patients, mostly in inadequately low doses. The study was pursued in 15 European countries under the name EUROASPIRE 2 (1999–2000). It showed increased percentage of CHD patients receiving hypolipemics up to 43%, but the cholesterol level was unsatisfactory after 1.4 years >5 mmol/L. According to Reiner, only 8.83% of Croatian patients indicated for statin use are prescribed statins and are usually subgrouped, so they do not lower total cholesterol concentration and CVD risk level. Prospective meta-analysis of the data pooled from 14 randomised statin studies, including 90,056 persons in total, demonstrated decrease in the incidence of coronary events, strokes and need for revascularisation in referent five-year period by one-fifth per mmol/L of LDL-cholesterol concentration, independently of the initial lipid status and other subjects’ features. The same study revealed the increase in therapeutic benefits over the years of permanent statin use.

European statin prescription trends, observed in 1997–2003 period, showed significant increase in 13 European countries, Ireland and Norway taking the lead. Based on Croatian Institute for Health Insurance (CIHI) data for year 2003, simvastatin occupied the sixteenth position on top 20 list of most commonly prescribed drugs in the Republic of Croatia. According to Croatian Agency for Medical Products and Medical Devices data for year 2004, simvastatin held the first, and atorvastatin the eleventh position on the list of the most frequently sold drugs based on financial indicators, while on the list of the ten most often used prescription drugs, simvastatin held the sixth position, and atorvastatin was not among the top ten. The data issued by the same Agency for year 2005, demonstrated that simvastatin kept the leading position on the most frequently sold drugs list based on financial indicators, while atorvastatin appeared at the fifth position. In the list of the most frequently used prescription drugs per 1000 insured people simvastatin occupied the fifth, and atorvastatin the tenth position.

According to the CIHI guidelines, the statins may be prescribed to PP patients whose total serum cholesterol levels, after 3-month-lasting hypolipemic diet, are still >7 mmol/L, based on the results of two independent measurements carried out in a 3-month interval, and the statin therapy can be initiated with PP patients under the age of 70. According to the same guidelines, in SP these drugs are to be prescribed to the patients who suffered myocardial infarction, ischemic stroke (CVI), transectomy ischemic attack (TIA) or have carotid artery plaque documented by ultrasound, or with peripheral artery occlusive disease, coronary disease documented by coronography or ergometry, as well as to diabetics having a total serum cholesterol level >5 mmol/L.

Management of patients at CV risk, or those with already diagnosed CV diseases, represents major segment in everyday work of a GP. It includes both non-pharmacological intervention targeted at potential patient (counselling on lifestyle changes in terms of an appropriate diet, physical activity, and smoking cessation), and pharmacological intervention when indicated (treating arterial hypertension, diabetes and hyperlipidemia). Statin prescription practices by GP have rarely been the subject of investigation and consideration of domestic authors. Our study aims at answering he question: In what manner, and to whom, does a GP prescribe statins in primary and secondary CV prevention? We decided to investigate the following:

- What patterns of statin prescription do GPs exercise in primary and secondary CV prevention; are there any differences in statin prescription between PP and SP and if so, what is the nature of these differences? (main goal)
- Do GPs follow statin prescription guidelines recommended by professional societies and those required by CIHI? (secondary goal)

Subjects and Methods

**The sample**

Study sample was constituted of 7 GPs just having started their residency in family medicine, providing healthcare services for the average of 1 600 insured patients and have electronic medical records. They performed AUDIT analysis of their statin prescription in primary and secondary prevention (four of practices are in Zagreb and one in Sunja, Murter and Umag, Croatia). They registered sociodemographic data (age and age groups (<40, 40–49, 50–59, 60–69, ≥70 years), gender), total and LDL-cholesterol levels at which statins were initially prescribed, type and dose of prescribed statin, as well as the reason for prescribing it (PP - healthy - asymptomatic individuals at risk for CVD i.e. «pre-event» preventive action, or SP-individuals with established CVD or diabetes, i.e. «re-event» prevention). Indications for SP were noted (documented coronary heart disease, transitory ischemic attack, stroke, diabetes, peripheral artery occlusive disease). Data on the participating GP (age, gender, years of service, residency) and their practices (number of enrolled patients, age groups, average number of daily visits per GP) were collected, too.

**Statistics**

Data analysis was performed using descriptive statistical methods. The $\chi^2$-test was used to determine statistically significant differences in statin prescription in primary and secondary prevention as well as the significance of different dosing of prescribed statins in PP or
SP Student t-test and Mann-Whitney U-test were used to determine differences between total and LDL-cholesterol threshold concentrations for statin prescription in PP compared to SP. Results were interpreted according to 95%-significance level (p<0.05). Data were processed by using Statistica 6.0 software package, StatSoft Inc, 1984–2001, Tulsa, USA.

Results

Out of 10 939 beneficiaries of 7 GP’s practices, 1282 (11.72%) were prescribed statins. In the age group 40+ (N=7 139), statins were administered to 1281 (17.80%) patients. Within primary prevention 822 (64.11%) subjects received statins, out of which 71.17% were women and 28.83% men. The average age of examinees was 62.9±12.45 years. Statins were most frequently prescribed to patients aged 70+ and almost equally frequent to patients aged 50–59, and 60–69, but rarely in patients aged 40–49 or under (Table 1). The most frequently prescribed statin in primary prevention was atorvastatin (49.28%), followed by simvastatin (45.19%). The most commonly prescribed statin dose was 10 mg (54.38%), then 20 mg (45.19%), while 40 mg (3.68%) and 80 mg (1.58%) doses were only seldom prescribed. The average total cholesterol level at which statin was initially prescribed was 6.2±1.09 mmol/L, median LDL-C 3.6 (0.4–6.4) mmol/L. In secondary prevention statins were received by 460 (35.88%) subjects, out of which 61.74% were women and 38.26% men. The average age of examinees was 68.3±9.57 years. Statins were most frequently prescribed in 70+ age group, followed by 60–69 and 50–59 to 40–49 or under (Table 1). The most frequently prescribed statin was simvastatin (48.36%), followed by atorvastatin (46.62%). The most frequent dose prescribed in secondary prevention was 20 mg (55.89%), 10 mg (33.70%), 40 mg (7.30%) and 80 mg statin a day (3.08%). There was no statistically significant difference in type of prescribed statin in primary and secondary prevention ($\chi^2=1.15$, p=0.765). However, $\chi^2$-test demonstrated significant difference ($\chi^2=38.3$; p<0.001) between statin doses prescribed in primary and secondary prevention; 40 and 80 mg statin doses were more frequently prescribed in the latter.

The average total cholesterol level threshold at which statin was prescribed in secondary prevention was 5.4±1.26 mmol/L, median LDL-C of 2.7 (0.4–5.6) mmol/L.

Student t-test revealed significant difference (t=10.88; p<0.001) between total cholesterol levels as indications for statin treatment in PP and SP (the latter being statistically significantly lower). The same goes for LDL-C concentrations, as revealed by Mann-Whitney U-test (Z=4.64; p<0.001).

Out of 1 281 statin receiving examinees, 236 (18.42%) were diabetics, which equals to 34.20% of all diabetics registered in GP’s practices (690), 72 were patients with TIA/CVI (5.62%), and 244 (19.05%) were coronary heart disease patients.

All 7 participating GPs were women who hadn’t completed their residency yet, aged 39±5.49 years, in service for 13±6 years (median 10 years; range 4–20 years). The average number of enrolled patients per GP was 1.56±2.99 (median 1.473; 1.279–1.960), average number of daily visits 46±10.88 (median 45; 27–60). There was a significant difference among them: two of them together prescribed significantly more statins than all the others ($\chi^2=668.0$; p<0.001), both in primary ($\chi^2=752.9$; p<0.001) and secondary CVD prevention ($\chi^2=64$; p<0.001).

Discussion

Our study showed interesting ratio of statin prescription in PP (64.11%) compared with SP (35.88%). The fact that in primary CVD prevention statins are most frequently prescribed in population aged 70+ raises concerns. Age groups 40–69 are unfairly neglected in PP of cardiovascular diseases. GPs have no proactive approach to identification and treatment of risk factors in those age groups, thus reducing the total risk of developing CVD. Since 70+ population seeks medical attention most often, it is not surprising that this population segment is most often treated as well. In year 2001, Croatian Ministry of Health and Social Welfare launched the National Plan and Programme for Prevention of Cardiovascular Diseases. There is also Plan and Programme for Healthcare Measures covered by the Basic Health Insurance. However, these programmes have never been implemented, so the GPs are neither bound by any obligations, nor encouraged to pursue with the systematic, active identification and management of CV risk factors in the CVD primary prevention.

Even more so, do GPs, as the parties contracting with the CIHI, economize on statin prescriptions? The CIHI contract obliges them to allocate only limited financial means for drug prescription purposes; in case of breaching their contract obligations, the CIHI is entitled to fine them. Out of total financial means CIHI allocated to GPs in 2005, for covering prescription drugs aimed at CV pre-

| TABLE 1 |
| DISTRIBUTION OF STATIN PRESCRIPTION IN PRIMARY AND SECONDARY CARDIOVASCULAR (CV) PREVENTION |
| Patients | Type of CV Prevention N (%) | Primary | Secondary |
| Gender | | | |
| Men | 237 (28.83) | 176 (38.26) |
| Women | 585 (71.17) | 284 (61.74) |
| Total | 822 (100.00) | 460 (100.00) |
| Age | | | |
| <40 | 23 (2.80) | 3 (0.65) |
| 40–49 | 97 (11.80) | 16 (3.48) |
| 50–59 | 207 (25.18) | 67 (14.57) |
| 60–69 | 205 (24.94) | 147 (31.96) |
| ≥70 | 290 (35.28) | 227 (49.35) |
| Total | 822 (100.00) | 460 (100.00) |
vention, 62.5% was spent on antihypertensive drugs, 22.6% on statins, and 14.4% on oral antidiabetics. Is such statin prescription satisfactory? Should all diabetics having total cholesterol level >4.5 mmol/L be prescribed statins, or should it be restricted to those with documented coronary heart disease – the answer to this question is still pending. However, most diabetics, in order to reach the target TC levels of <4.5 mmol/L and LDL-C levels of <2.5 mmol/L, require statin prescription. In the Republic of Croatia the statin prescription should be increased, but it depends on financial resources of a particular country. For instance, in 2002, European Union member states spent 15–18% of their healthcare budget on drugs. Out of total 2003 budget allocated for drugs, Croatia spent 30% on drugs for prevention and treatment of CV diseases, while Sweden spent 69%, Finland 52% and Great Britain 49%.

The initial treatment of hyperlipidemia in primary and secondary prevention is exceptionally non-pharmacological one. Only in case when three-month-lasting hypolipemic diet fails to yield satisfactory results, pharmacotherapy, using statins as the first-choice drugs, is applied. It is hard to change patterns of deep-rooted patients' behaviour, since there is no perception of anticipated risk in asymptomatic patients. Patient and GP create a joint motivational plan and set the goals to be accomplished in the specific time frame, the patient thus being an active partner in caring for his/her own health. Lifelong compliance with new patterns of behaviour, and continuous treatment with prescribed drugs, should turn into a permanent lifestyle of a risky patient. However, long-term compliance with general measures is not easy, only 10% of people succeed in it. Some insurance companies established in Great Britain, South Africa and USA, go so far as to cut down health insurance premiums to those leading a healthy life and respond to screening uptake.

Significant variations in primary and secondary statin prescription among the participating GPs cannot be explained either by differences in their individual characteristics (age, gender, years of service) or by differences in their practices (degree of computerisation, the number of beneficiaries they care for, number of daily visits), since they are marginal. The differences in morbidity of population enlisted per GP are also negligible. Possible explanation may lie within the fact that none of the 7 GPs included in the study have completed their residency yet.

Statin prescription is one of the important quality care indicators in family medicine. It is expected to improve after residency completion. Our study should conﬁrm or refute this presumption. Since the effect of simvastatin is best documented, we expected this statin to be the most frequently prescribed in both primary and secondary prevention. According to the current state of knowledge, all statins are similarly effective in long-term CVD prevention, exhibiting the so-called »class effect«, which was investigated in both primary and secondary prevention. Mutual pharmacokinetic differences are only minimal; therefore, bearing in mind their similar efﬁciency, a cheaper drug should be prescribed. The results of our investigation demonstrated that atorvastatin was the most frequently prescribed statin in the primary prevention. This could be explained by impact of aggressive pharmaceutical marketing. Biased medical education sponsored by pharmaceutical companies reﬂects in GPs' prescribing patterns, since there is no independent extra-institutional education.

Our research showed that a 10 mg statin daily dose was most frequently prescribed in PP, while in SP it was a 20 mg dose. According to the GOALLS study, the majority of patients in secondary prevention treatment require 20 mg simvastatin to reach target total cholesterol level, which is in accordance with our results, while 14% of the patients need an 80 mg simvastatin dose. In our study, 80 mg daily dose was administered to only 3.8% of the patients. The randomised, controlled IDEAL study demonstrated that higher statin doses are equally safe, as it is shown in the 4S study, too. It demonstrated that relative risk reduction attained by simvastatin in diabetics almost doubled (55%) compared with non-diabetics (32%). Nevertheless, in our study the number of statin-receiving diabetics was fairly low. The total number of diabetics registered in our 7 GPs' practices is conforming to the estimated data on diabetes prevalence in adult Croatian population, which is 9.5%. In his/her everyday practice, a GP carries out an opportunistic screening of persons at risk of developing diabetes, although the Programme for Cardiovascular Disease Prevention in Family Medicine from 2003 recommends each and every person aged over 40 to have blood glucose test once in 2 years, and repeat it every 5 years if the baseline findings are within normal levels. Again, there is no possible way of implementing this programme into everyday practice. The significant obstacle for implementing preventive activities, both in majority of European countries and in Croatia, is an excessive daily workload of FD and the lack of time for such activities. Instead of a systematic proactive approach to primary prevention in population with CVD risk factors, prevention activities are non-systematic, individual, non-integral and sporadic. Preventive, proactive approach is increasingly more often replaced by a reactive, curative approach (aimed at sheer »fire extinguishing«), less beneficial for the patient, and more expensive for the entire healthcare system.
GPs participating in our study did not follow CIHI guidelines for prescribing statins in primary prevention. They prescribed them at lower average total cholesterol levels, while in secondary prevention statin prescription met the prescribing guidelines regarding both indications and required total cholesterol threshold levels. However, the question remains whether CIHI regulations are exclusively powered by administrative and financial motives, or based on the recommendations and guidelines of professional societies. Croatian Society of Cardiology and Croatian Society of Hypertension adopted ESC-ESH guidelines, which adjust statin treatment to the total ab-
time, treatment is strongly and clearly recommended by

The total CVD risk is crucial for the CV risk assessment, since it is always higher than the simple sum of individual factors because of their mutual interactions. For example total CVD risk can be high due to patient’s age, gender, smoking status, and systolic blood pressure, despite TC concentration <7mmol/L. By rigid compliance with CIHI guidelines in PP is strict, a GP is not allowed to prescribe statin to such a patient, while at the same time, treatment is strongly and clearly recommended by

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PROPISIVANJE STATINA OD STRANE OBITELJSKIH LIJEČNIKA U HRVATSKOJ – IZOSTANAK SUSTAVNOG PROAKTIVNOG PRISTUPA PREVENCIJI KARDIOVASKULARNIH BOLESTI

S A Ţ E T A K

Cilj je bio istražiti propisivanje statina od strane obiteljskih liječnika (LOM) u primarnoj (PP) i sekundarnoj (SP) prevenciji kardiovaskularnih bolesti. Zabilježeni su socio-demografski podatci o bolesnicima, koncentracija ukupnog i LDL-kolesterola koje su bile indikacija za za propisivanj statina, kao i podatci o liječnicima. Statini su propisani u 11,2% svih bolesnika u skrbi (64,11% PP, 35,88% SP), najčešće životne dobi 70+. U primarnoj prevenciji indikacija za propisivanje bila je koncentracija ukupnog kolesterol 6,2±1,09 mmol/L, LDL-kolesterol 3,6 mmol/L, a u SP 5,4±1,26; 2,7 mmol/L. Najpropisivaniji statin u PP bio je atorvastatin u dozi 10 mg (49,28%), a u SP simvastatin (48,36%) u dozi 20 mg. Sve LOM bsu žene, dobi 39±5,49 godina, radnog staža 13±6 godina, s prosječnim brojem pacijenata u skrbi 1562±299. Statistički značajna razlika među njima utvrđena je u preskripciji statina u PP (χ²=752,9; p<0,001) i SP (χ²=64, p>0,001). Preskripcija statina u PP rezultat je utjecaja farmaceutskih tvrtki i nedostatka od njih neovisne kontinuirane edukacije LOM. Najčešće propisivanje statina u dobi 70+ (35,28% in PP, 49,35% SP) ukazuje na nedostatak proaktivnog pristupa u prevenciji KV bolesti mladim dobnim skupinama.