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The impact of reimbursement criteria on the appropriateness of 'statin' prescribing

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ABSTRACT

Background In Belgium, regulations restrict the reimbursement of statins to patients with total serum cholesterol above 250 mg/dl (6.41 mmol/l) after a three-month lipid-lowering diet We investigated the possible impact of these regulations on characteristics of Belgian patients receiving a lipid-lowering drug.

Design From 1998 to 2000, standard questionnaires on coronary risk factors and treatments with lipid-lowering drugs were completed by 301 GPs sampled at random in the 11 Belgian Provinces. Questionnaires had to be completed for 18 consecutive patients 35 years old or more attending GPs' practices, irrespective of the underlying motive for attendance.

Results Of the 5511 patients included in the study, 1519 (28%) had established coronary disease or diabetes mellitus, or ≥ 2 non-cholesterol coronary risk factors. Most (70%) of these patients were not treated with a lipid-lowering drug. Only 22% of patients with established coronary disease, 10% of patients with diabetes mellitus and 9% of patients with ≥ 2 coronary risk factors were treated with a statin. Fifty-nine percent of fibrate users and 50% of statin users had a pre-treatment cholesterol level above 250 mg/dl, but had no or only one non-cholesterol coronary risk factor.

Conclusions In Belgium, the majority of patients at higher risk of coronary event do not benefit from lipid-lowering drugs, particularly the statins. In contrast, one of two statin users and three of five fibrate users should probably not receive the drug prescribed. Regulation based on blood cholesterol level encourages the overlooking of other risk factors relevant for selecting patients having the greatest chance to benefit from statin treatment.

Keywords : statin ; fibrate ; regulations ; cholesterol ; coronary heart disease

Introduction

The 'statins' (i.e. the 3-hydroxy-3-methylgIutaryl Coenzyme A reductase inhibitors) are powerful cholesterol reducers, and randomized trials have demonstrated the ability of simvastatin, pravastatin and lovastatin to reduce all cause mortality, the mortality and incidence of coronary diseases [1], as well as the incidence and mortality from cerebrovascular diseases [2,3]. The impact of statins on coronary and all cause mortality increases with increasing number of coronary risk factors, particularly when there is evidence of established coronary disease or type II diabetes mellitus.

The introduction in 1989 of simvastatin in the Belgian pharmacopoeia and authorization for its reimbursement led to a substantial increase in expenses for the Belgian Health Insurance Institute (the Belgian governmental institution that regulates public expenditure for health and social care). In order to contain drug expenses, the Belgian Health Insurance Institute imposed a set of criteria that patients had to meet for being reimbursed for a treatment with lipid-lowering drugs, especially the statins.

Criteria for reimbursement of lipid-lowering drugs were likely to exert a profound influence on prescribing patterns of physicians, mainly the general practitioners (GPs), who are taking care of most common lipid disorders. Although several studies already documented that substantial proportions of patients at high coronary risk do not receive an appropriate lipid-lowering treatment [4,5], no study investigated whether the existence of reimbursement criteria would affect the appropriateness of their prescribing. The objective of the study (called the 'CHD Monitor') was to investigate the manner in which lipid-lowering drags were prescribed to patients attending GP practices in Belgium, and examining how prescribing patterns changed with variations in reimbursement criteria.

Reimbursement criteria for statin use in Belgium

From 1990 until 1996, reimbursement criteria for statins changed six times. Overall, during that 7-year period, two types of patients were eligible for reimbursement for their statin treatment: the first type had to have a total blood cholesterol ≥ 300 mg/dl (7.69 mmol/l) and clinically established hereditary lipid disorders. The second type had to have a total blood cholesterol above 250 mg/dl (6.41 mmol/l) after a compulsory 3-month diet followed by a 3-month treatment with a fibrate, and (i) a history of coronary disease, or (ii) two or more of the following five coronary risk factors: uncontrolled high blood pressure (systolic > 140 mmHg or diastolic > 90 mmHg), high density lipoprotein cholesterol (HDL) below 35 mg/dl (0.90 mmol/l), diabetes mellitus, father with coronary disease before 45 years of age, mother with coronary disease before 55 years of age. Neither smoking nor obesity were part of reimbursement criteria, for the reason that these factors were considered to be modifiable.

The publication of statin trials [6-8] made obsolete the rule of compulsory treatment with fibrates, a class of lipid-lowering drugs without demonstrated efficacy on all cause mortality [9,10]. Also, for most physicians, the list of selected coronary risk factors was not satisfactory. In July 1996, all reimbursement criteria for statins were dropped, but total blood cholesterol still had to be above 250 mg/dl (6.41 mmol/l) after a 3-month lipid-lowering diet.

Evolution of statin use in Belgium from 1989 until 2000

Simvastatin was introduced in Belgium in 1989, pravastatin in 1994 and atorvastatin in 1996. Few patients took other statins (e.g. fluvastatin and cerivastatin) marketed in Belgium.

Figure 1 shows estimates of numbers of patients taking a statin in Belgium (derived from data on drug prescription provided by International Medical Services, Brussels, Belgium). The number of patients taking a statin remained stable up to 1996, around 60,000 statin users. Of note is the absence of impact of the 4S study [6] on the number of patients receiving a statin. In 1996, after revision of reimbursement criteria, a seven-fold increase in the number of patients taking a statin occurred, reaching 425,961 patients by mid 2000.

Methods

From September 1998 to February 2000, we performed a survey of the management of lipid disorders in a sample of GPs. GPs participated on a voluntary basis.

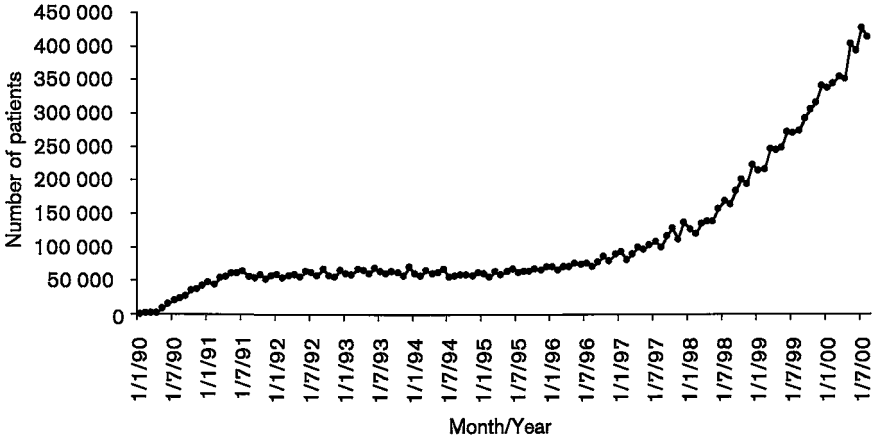
From administrative records including the 20,851 GPs registered in Belgium in the year 1998, we selected at random a sample of GPs who qualified since 1965 that was representative of GP distribution in the 11 Belgian Provinces (Brussels was considered as a Province). In case of refusal to participate or of absence, another GP was selected at random in the same province, and then contacted.

In order to collect data on adult patients representative of GP practices, each GP was instructed to select at any time during a normal working week 18 consecutive adult patients, 35 year old or more, regardless of motive for attending the practice.

For each patient in the sample, the GP used a structured questionnaire for collecting standardized information on coronary risk factors, history of cardiovascular diseases, current cardiovascular status, and treatment taken for cardiovascular disease, according to definitions of the Belgian Lipid Club in 1997 [11]. Since 1993, the Belgian Lipid Club edits and regularly updates guidelines on the management of lipid disorders largely disseminated among health care providers. These guidelines closely follow therapeutic consensus reached in Europe and in the USA [12-14].

The most recent total blood cholesterol level (measured in the last 12 months) was recorded. In case of unknown recent cholesterol level, the GP was invited to prescribe, but not undertake, a blood test. When patients took a lipid-lowering drug, the total blood cholesterol level before treatment initiation was demanded.

Fig. 1 *Estimated time-trend in numbers of patients taking a statin in Belgium.*



Classification of patients

A patient was labelled as a 'CHD patient' if he or she had a history of angina pectoris (stable and unstable), myocardial infarction, sudden cardiac arrest, arrhythmia due to coronary ischaemia, or a history of intervention on coronary arteries (CABG or PTCA).

Non-cholesterol risk factors used for patient classification were the criteria required before 1996 to obtain a reimbursement of statins. When control of hypertension was reported by GPs as 'unknown', the patient was considered as having uncontrolled hypertension. Current smoking status and obesity (body mass index ≥ 30 kg/ m^2) were added, as these two factors were taken into account by the Belgian Lipid Club [11]. Hence, risk factors used for classifying patients without coronary disease were close to those used by European recommendations for assessing the coronary risk in primary prevention [12], with addition of the body mass index.

Classification of patients distinguished between (i) patients with established coronary disease, (ii) patients with diabetes mellitus, and (iii) patients with two or more of the remaining six coronary risk factors. Diabetic patients were considered as a separate category as there is mounting evidence that statin use in diabetic patients results in sharp decrease in cardiovascular mortality [15,16]. Also, since their last revision, guidelines emphasize the distinction between diabetic and non-diabetic patients for the evaluation of coronary risk in primary prevention [12,13].

Patients with more than one coronary risk factor were further categorized according to their blood total cholesterol reported in the study, with (i) the lower limit of 251 mg/dl (6.44 mmol/l) set as minimal level for obtaining a reimbursement for statin treatment in Belgium, and (ii) the lower limit of 191 mg/dl (4.90 mmol/l) recommended by European guidelines for initiating pharmacological control of high blood cholesterol [12].

To compare difference in proportions between groups of patients, relative risks were computed with their 95% confidence interval (95% CI). The Chi-square test was used for testing the statistical difference between two proportions. All statistical tests were two sided.

Table 1 *Characteristics of patients in sample*

Factor	Men (% of total)	Women (% of total)	Total (% of total)
Total number	2463	3048	5511
Mean age	59.2	59.8	59.6
35-54	944 (38)	1158 (38)	2102 (38)
55-74	1175 (48)	1363 (45)	2538 (46)
≥ 75	344 (14)	527 (17)	871 (16)
Distribution by region:			
Flanders	1281 (52)	1545 (51)	2826 (51)
Brussels	251 (10)	330 (11)	581 (11)
Wallonia	931 (38)	1173 (38)	2104 (38)
Patients with:			
Established coronary disease	508 (21)	335 (11)	843 (15)
Diabetes mellitus	219 (9)	280 (9)	499 (9)
Treated with insulin	33 (1)	53 (2)	86 (2)
Hypertension	703 (28)	996 (33)	1699 (31)
Controlled*	494 (20)	716 (23)	1210 (22)
Uncontrolled*	66 (2)	97 (3)	163 (3)
Control unknown*	143 (6)	183 (6)	326 (6)
HDL <35mg/dl†	133 (5)	97 (3)	230 (4)
Father with coronary disease < 45 years	92 (4)	89 (3)	181 (3)
Mother with coronary disease < 55 years	33 (1)	58 (2)	91 (2)
Current smoker	531 (22)	368 (12)	899 (16)
Body mass index ≥ 30	398 (16)	607 (20)	1005 (18)
Patients with total blood cholesterol:			
> 250 mg/dl†	465 (19)	670 (22)	1135 (21)
≥ 190 and ≤ 250 mg/dl‡	1489 (60)	1837 (60)	3326 (60)
Unknown	421 (17)	451 (15)	872 (16)
Patient with past CABG or PTCA‡	215 (9)	79 (3)	294 (5)
Patient currently taking:			
Statin	245 (10)	262 (9)	507 (9)
Fibrate	180 (4)	316 (10)	496 (9)

*As reported by GPs.
†250 mg/dl is 6.41 mmol/l; 190 mg/dl is 4.87 mmol/l; 35 mg/dl is 0.90 mmol/l.
‡CABG: coronary artery bypass graft; PTCA: Percutaneous transluminal coronary angioplasty.

Results

A total of 2331 GPs were randomly selected and contacted, out of whom 301 (13%) had a practice and agreed to participate in the study (154 GPs from Flanders, 32 GPs from Brussels and 115 GPs from Wallonia).

Information was collected on 5511 patients. Characteristics of patients are displayed in Table 1. The distribution of patients by region was similar to the population distribution by region. The larger number of women reflected the fact that women are more likely to attend medical practice.

At the moment of the study, 1003 patients were taking either a statin (507 patients, i.e. 9%), or a fibrate (496 patients, i.e. 9%). Before treatment initiation, 86% of statin users had a total blood cholesterol above 250 mg/dl (6.41 mmol/dl). The remaining 14% had a pre-treatment total blood cholesterol below 251 mg/dl (6.44 mmol/l), with a mean of 238 mg/dl (6.10 mmol/l). The latter users were patients paying for the statins without being reimbursed.

Table 2 shows that 1519 (28%) of 5511 patients had established coronary disease or diabetes mellitus, or ≥ 2 non-cholesterol coronary risk factors. Most (70%) of these patients were not treated with a lipid-lowering drug. Only 22% of patients with established coronary disease, 10% of patients with diabetes mellitus and 9% of patients with ≥ 2 coronary risk factors were treated with a statin. When the study was conducted, 344 (23%) of the 1519 patients had a total blood cholesterol above 250 mg/dl (6.41 mmol/ l), and thus met the reimbursement criteria for receiving a statin. However, only 25% of patients with both high blood cholesterol and established

coronary disease were treated with a statin. These proportions were of 11% for patients with diabetes mellitus, and 15% of patients with ≥ 2 coronary risk factors.

According to European guidelines [12], lipid-lowering drug therapy should be initiated in high risk patients with total blood cholesterol above 190 mg/dl (4.87 mmol/l). Table 2 indicates that most patients with established coronary disease, diabetes mellitus or ≥ 2 coronary risk factors and with total blood cholesterol above 190 mg/dl (4.87 mmol/l) did not receive a lipid-lowering drug.

The remaining 3992 patients (72% of the total) had no or only one coronary risk factor, and had no established coronary disease or diabetes mellitus. Two hundred and ninety-four (7%) of them took a fibrate, and 254 (6%) took a statin. Given that the entire sample comprised 496 patients taking a fibrate and 507 patients taking a statin, it can be computed that 59% of fibrate users and 50% of statin users had a pre-treatment cholesterol level above 250 mg/dl (6.41 mmol/l) but had no or only one non-cholesterol coronary risk factor.

When focusing on statin treatment, patients with established coronary disease had 3.8 (95% CI: 3.2-4.5, $P < 0.0001$) more chance to receive a statin treatment than patients without coronary disease, diabetes mellitus or less than two coronary risk factors. In comparison, patients with diabetes mellitus had only 1.7 (95% CI: 1.2-2.4, $P = 0.0012$) more chance to receive a statin treatment.

There was no difference in risk factors between men and women taking statins (data not shown). Fibrates were more likely to be taken by women with no or only one coronary risk factor.

Table 3 shows the year during which statin treatment was initiated. The type of patients who received a statin changed over time: when the 4S study was published in 1994 ([6]; the first randomized trial that demonstrated the ability of a statin (the simvastatin) to decrease all cause mortality among coronary patients), the majority of new statin users were coronary patients. In July 1996 the conditions for statin reimbursement were abolished, except the total blood cholesterol level of 250 mg/dl (6.41 mmol/l). Just after, the number of new statin users soared, but the majority of them were patients with no or only one coronary risk factor.

Table 2 *Taking of lipid-lowering drug by patients with established coronary disease or at high risk for coronary disease*

Patient risk profiles	Total No.	Taking a fibrate		Taking a statin		No lipid-lowering drug	
		No.	(%)	No.	(%)	No.	(%)
All patients	**5511**	**496**	**(9)**	**507**	**(9)**	**4508**	**(82)**
Patients with established coronary disease or diabetes mellitus or with ≥ 2 coronary risk factors	**1519**	**202**	**(13)**	**253**	**(17)**	**1064**	**(70)**
Patients with established coronary disease	*843*	*124*	*(15)*	*789*	*(22)*	*530*	*(63)*
WithTC > 250 mg/dl[*]	190	27	(14)	47	(25)	116	(61)
With TC > 190 mg/dl and ≤ 250 mg/dl	458	72	(16)	97	(21)	289	(63)
With unknown TC	47	4	(8)	2	(4)	41	(88)
Patients with diabetes mellitus, and without established coronary disease	360	47	(13)	37	(10)	276	(77)
With TC > 250 mg/dl	83	13	(16)	9	(11)	61	(73)
With TC > 190 mg/dl and ≤ 250 mg/dl	187	27	(14)	18	(10)	142	(76)
With unknown TC	22	2	(9)	1	(5)	19	(86)
Patients with ≥ 2 coronary risk factors[†], and without coronary disease nor diabetes mellitus	316	31	(10)	27	(9)	258	(82)
With TC > 250 mg/dl	71	8	(11)	11	(15)	52	(73)
With TC > 190 mg/dl and ≤ 250m g/dl	160	18	(11)	12	(8)	130	(81)
With unknown TC	38	0	(0)	0	(0)	38	(100)
Patients without coronary disease and without diabetes mellitus, having one or no coronary risk factor[†]	**3992**	**294**	**(7)**	**254**	**(6)**	**3444**	**(86)**
Patients without coronary disease with one coronary risk factor other than diabetes mellitus	1359	92	(7)	92	(7)	1175	(86)
Patient without coronary disease and without coronary risk factor	2633	202	(8)	162	(6)	2269	(86)

[*]TC: total blood cholesterol; 250 mg/dl is 6.41 mmol/l; 190 mg/dl is 4.87 mmol/l.
[†]Non-cholesterol risk factors including: uncontrolled high blood pressure (systolic >140 mmHg or diastolic > 90 mmHg), high density lipoprotein cholesterol (HDL) below 35 mg/dl (0.90 mmol/l), diabetes mellitus, father with coronary disease before 45 years old, mother with coronary disease before 55 years old, current smoking status and obesity (i.e. body mass index ≥ 30kg/m^2). When control of hypertension was reported by GPs as 'unknown', the patients was considered as having uncontrolled hypertension.

Table 3 Year of statin treatment initiation and coronary risk factors

Year	Pts starting a statin treatment[*]	Pts with established coronary disease		Pts with ≥ 2 coronary risk factors[†]		Pts with no or 1 coronary risk factor	
	No.	No.	(%)	No.	(%)	No.	(%)
1990-93	55	21	(38)	14	(25)	20	(37)[¶]
1994[‡]-95	44	30	(68)	8	(18)	6	(14)[¶]
1996[§]	28	13	(46)	3	(11)	12	(43)
1997-99	347	108	(31)	45	(12)	194	(57)[¶]
Total	474	172	(36)	70	(15)	232	(49)

[*]Year of statin initiation was unknown for 33 patients taking a statin at the moment of the study.
[†]Patients without established coronary disease and with ≥ 2 non-cholesterol factors including diabetes, uncontrolled hypertension, HDL-cholesterol < 35 mg/dl (0.90 mmol/l), current smoker, obesity, father with coronary disease before 45 years old, and mother with coronary disease before 55 years old.
[‡]Year of publication of 4S study.
[§]In July 1996, the Belgian Health Insurance Association abandons non-cholesterol coronary factors as criteria for reimbursement of statins.
[¶]χ^2 test between years 1990-93 and 1994-95: $P = 0.01$; between years 1994-95 and years 1997-99: $P < 0.0001$.

Discussion

Our study shows that in Belgium, lipid-lowering drugs were mainly taken by patients with low absolute coronary risk, while the majority of patients at higher coronary risk did not receive such treatment, particularly the statins.

Irrespective of the blood cholesterol level, the efficacy and cost-effectiveness of statin use is optimal in patients accumulating non-cholesterol risk factors for coronary disease [17]. In that respect, lipid-lowering drug use by patients with no or with only one non-cholesterol risk factor could be qualified as overuse. Hence, overall, one of two statin users, and two of five fibrate users should probably not receive a lipid-lowering drug. In contrast, when total blood cholesterol was above 190 mg/dl (4.87 mmol/l), more than two-thirds of patients with established coronary disease, diabetes mellitus, or two or more other non-cholesterol coronary risk factors did not take a lipid-lowering drug. It is thus possible that about half of the 200 million Euros spent by the Belgian Health Insurance in 2000 for reimbursing statins had a low health impact.

In Belgium, most common lipid disorders are managed by GPs, and this study reflects pharmacological management of lipid disorders by Belgian GPs. GPs participated to the study on a voluntary basis. Refusal of GPs to participate was probably not linked to particular prescribing patterns or to a selection of the type of patients included in the study sample. It is thus unlikely that results would have been much different if the participation rate had been higher. Our calculations of overuse rates are conservative. If we had considered diabetes mellitus as a common coronary risk factor, statin overuse derived from Table 2 would have only been slightly modified from 254 to 265 patients.

The study provides an illustration of the distortion that reimbursement criteria based on blood cholesterol level produce in prescribing patterns and how it tends to make prescribing less rational. The treatment with a lipid-lowering drug of coronary patients in this study was 37%, as compared with 63% in the Euroaspire II study conducted in nine European countries in 1999-2000 [4]. The restrictive reimbursement criteria that prevailed in Belgium from 1990 until 1996 maintained the number of statin users at a low level. The positive side of that policy was that most statin users were at high coronary risk. The negative side was substantial, however, as many patients at high coronary risk were maintained for years under fibrate treatments of doubtful efficacy [9,10,18,19], or left without lipid-lowering treatment, simply because their total blood cholesterol was not above 250 mg/dl (6.41 mmol/l).

The threshold of 250 mg/dl (6.41 mmol/l) kept as the unique criteria for allowing statin reimbursement in 1996 led physicians and marketing strategies of pharmaceutical companies to focus on cholesterol levels, while neglecting the importance of non-cholesterol coronary risk factors and overlooking the most cost-effective ways to use these drugs. As a result, in 2000, management of lipid disorders in Belgian coronary patients was below European average, while lipid-lowering drugs were largely overused in patients at low coronary risk. Nevertheless, the number of patients with total cholesterol above 250 mg/dl (6.41 mmol/l) and high risk profile, not treated by a statin, shows that reimbursement rules are not the sole factor responsible for misuse of lipid-lowering drugs. The reluctance to add a drug to often polymedicated patients and the administrative burden of the procedure to obtain reimbursement for lipid-lowering drugs certainly played a role. The latter factors are indirectly related to reimbursement criteria, but they may also influence the prescribing habits of the physicians.

The present policy of reimbursing statins is economically not tenable as it has been estimated that about 2.2 million Belgian people (almost one-fifth of the population) have a total blood cholesterol above 250 mg/dl (6.41 mmol/l) [20]. In 1999, about 450,000 Belgian patients took a lipid-lowering drug. We have serious doubts that the Belgian Health Insurance would afford reimbursing statins for even half of people with total blood cholesterol above 250 mg/dl (6.41 mmol/l). It would be wiser to adopt a reimbursement policy more in line with European recommendations for pharmacological treatment of lipid disorders, for example, 190 mg/dl (4.87 mmol/l) of total blood cholesterol as lower limit for initiating statin treatment but targeting patients with established coronary disease, diabetes mellitus and patients cumulating other coronary risk factors. Also, for obtaining a better match with guidelines, practice-based interventions should accompany the dissemination of recommendations for lipid-lowering drug prescription.

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