Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries – findings from the EUROASPIRE IV survey

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Introduction

It is well known that dyslipidaemia is one of the most important causal risk factors for coronary heart disease (CHD) (1,2). Although the use of lipid-lowering drugs in primary prevention is less cost-effective, at least to some extent in subjects at low total cardiovascular (CV) risk, there are absolutely no doubts concerning the imperative use of lipid lowering drugs, more precisely statins, for secondary prevention, i.e. in patients with established CHD. Randomized controlled trials have clearly proven that LDL-cholesterol (LDL-C) lowering with statins can reduce the risk of recurrent cardiovascular events in these patients (3). It has also been shown that further lowering of LDL-C beyond the levels that can be achieved with less potent statins or at a lower dose of a given statin, is associated with more CHD prevention (3,4).

Therefore the US guidelines recommend to use high-intensity statin therapy in coronary patients in order to achieve a lowering of LDL-C by at least 50% (5). European guidelines recommend a LDL-C goal of < 1.8 mmol/L (<70 mg/dL) or at least 50% reduction of LDL-C in patients with documented CHD (2,6).

The objectives of this study based upon the hospital arm of the EUROASPIRE IV survey were to examine how lipid lowering drugs were prescribed in CHD patients at discharge from hospitals throughout Europe and how the intake of these drugs was reported by the patients when they were seen for a standardized interview 1.35 years (0.95-1.93) (median +/- interquartile range) later.

Materials and methods

The design, methodology and main results of the EUROASPIRE IV survey have been described elsewhere (7). EUROASPIRE IV was a cross-sectional survey conducted at 79 centres in 24 European countries during May 2012 to April 2013 using standardised methods and the same equipment in every centre**.** In a defined geographical area in each of these countries, consecutive male or female patients aged 18-80 years were identified from hospital admission and discharge lists or diagnostic registers by the following diagnoses of first or recurrent CHD occurring at a time 6-36 months preceding the interview: (i) coronary artery bypass grafting (CABG), (ii) percutaneous coronary intervention (PCI), (iii) acute myocardial infarction (AMI), and (iv) acute myocardial ischemia (ischemia).

Data collection

Data collection was conducted by trained research staff that reviewed patient medical records, interviewed and examined the patients at the hospital using standardized methods and instruments at least six months after the hospitalization for the acute event or procedure that included them in the survey. Personal and demographic details and drug use were recorded and risk factors monitored. Information on advised and adopted lifestyle changes since the hospital stay was obtained from questionnaires.

At the time of interview venous (fasting) blood was drawn for serum total and high-density lipoprotein cholesterol (HDL-C), triglycerides, and glycated haemoglobin (HbA1c) while LDL-C was calculated according to Friedewald's formula. The central laboratory was the Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland, which is

accredited by the Finnish Accreditation Service and fulfils the requirements of the standard SFS-EN ISO/IEC 17025:2005. Venous blood samples were taken in a sitting position with light stasis into a tube containing clot activator (Venosafe, Terumo Europe, Leuven, Belgium) for lipid assays and into a potassium EDTA tube (Venosafe) for HbA1c assay. Serum was separated by centrifuging at 2000 g for 10 min at room temperature. After that serum was aliquoted into two bar-code-labelled tubes and stored together with whole EDTA blood tubes locally at a minimum of -70 °C and then transported frozen to the central laboratory where all measurements were performed on a clinical chemistry analyzer (Architect c8000; Abbott Laboratories, Abbott Park, Illinois, USA). Total and HDL-C and triglycerides were analysed in serum, and HbA1c in whole blood with the following methods: enzymatic method for total cholesterol, a homogenous method for direct measurement of HDL-C, an enzymatic glycerol phosphate oxidase method for triglycerides, and an immunoturbidimetric method for HbA1c. Non-HDL-cholesterol was calculated.

The laboratory takes part in Lipid Standardization Program organized by CDC, Atlanta, Georgia, USA and External Quality Assessment Schemes organized by Labquality, Helsinki, Finland. During the course of the study, comprising two months in 2013, the coefficient of variation (mean±SD) and systematic error (bias) (mean±SD) were 1.3%±0.2 and 1.7%±1.1 for total cholesterol, 1.6%±0.5 and – 1.5%±1.6 for HDL-C, 2.3%±0.1 and – 1.2%±2,6 for triglycerides, and 1.9%±0.1 and 1.4%±0.2 for HbA1c, respectively.

Height and weight were measured in light indoor clothes without shoes (SECA scales 701 and measuring stick model 220). Obesity was defined as a body mass index $\geq$ 30 kg/m2.

Waist circumference was measured using a metal tape applied horizontally at the point midway in the mid-axillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing. Central obesity was defined as a waist circumference of $\geq$ 88 cm for women and $\geq$ 102 cm for men.

Blood pressure was measured twice on the right upper arm in a sitting position using an automatic digital sphygmomanometers (Omron M6) and the mean was used for all analyses.

Breath carbon monoxide was measured in ppm using a smokelyser (Bedfont Scientific, Model Micro +). Smoking at the time of interview was defined as self-reported smoking, and/or a breath carbon monoxide exceeding 10 ppm. Persistent smoking was defined as smoking at interview among patients reporting to be smokers in the month prior to the index event.

Habitual physical activity was assessed by the International Physical Activity Questionnaire (IPAQ). High physical activity was defined as proposed in http://www.ipaq.ki.se/scoring.pdf

For this substudy all the patients who participated at the interview were considered (n=7998) but 1180 were excluded because of missing LDL-C values, mainly due to the non-fasting state at interview; 83 and 87 were excluded because the type or dose of the statin was missing at discharge from hospital and/or at the time of the interview respectively. Therefore the results from this analysis are based on data of 6648 patients.

Based on data collected at discharge from hospital and during the interview the patients were at both occasions divided in three groups:

- on a high-intensity statin therapy
- on a moderate or low intensity statin therapy
- not on statins

Drug regimens that are known to lower LDL-C on average by approximately > 50% were considered as high-intensity statin therapy (patients taking >=40 mg atorvastatin/day, >=20 mg rosuvastatin/day, >= 40 mg simvastatin + 10 mg ezetimibe/day, >=20 mg atorvastatin + 10 mg ezetimibe/day, >= 80 mg fluvastatin+ 10 mg ezetimibe/day).

All the other drug regimens were considered as low or moderate intensity statin treatment.

Data management

Data management was undertaken at the ESC Euro Heart Survey department, European Heart House, Nice, France. All the data were collected electronically using a unique identification number for a country, a centre and an individual. The data was submitted from all centers via Internet to the data management centre where checks for completeness, internal consistency and accuracy were run. All data were stored under the provisions of the National Data Protection Regulations.

Statistical analyses

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Results

From a total of 6648 CHD patients 9.6% were not on a statin therapy at the time of discharge from the hospital; this increased to 14% at interview. 37.6% of the patients were prescribed a high-intensity statin therapy at discharge which decreased to 32.7% at the time of the interview. Table 1 presents the results regarding lipid lowering drug therapies at discharge from hospital and at interview by centers, gender and recruiting event.

The distribution of the three statin treatment groups was not very different between genders; the small differences suggest that less women were on a statin treatment and that less women were on high-intensity statin therapy both at discharge ($p=0.0016$) and at interview as compared to men ($p=0.0056$).

When subdivided according to the recruiting event it seems that more patients hospitalized because of an acute ischaemic event were not on a statin treatment at the time of the interview while less patients who entered the survey after a CABG were on a high-intensity statin, both at discharge and at interview (both $p<0.0001$).

The largest differences in distribution according to three statin treatment groups were observed between the centers. At discharge from hospital there were significant differences: in some centers (in Spain, Latvia and Cyprus) less than 5% of the patients were not discharged with a statin therapy as compared to more than 20% in the centers from Bosnia-Herzegovina and the Netherlands. High-intensity statin therapy was prescribed at discharge in <10% of the patients in the centers from Germany, Bosnia-Herzegovina and the Netherlands in contrast to > 50% in Croatia, France, Ireland, Latvia, Romania Slovenia, Spain and the United Kingdom.

Table 1. Statin use at discharge and at interview

Centre	N	Statin class at discharge			Statin class at interview		
		No %(N)	Low/mod %(N)	High %(N)	No %(N)	Low/Mod %(N)	High %(N)
Belgium	317	10.7(34)	64.0(203)	25.2 (80)	6.0 (19)	62.5 (198)	31.5 (100)
Bosnia Herzegovina	82	22.0(18)	72.0 (59)	6.1 (5)	19.5 (16)	72.0 (59)	8.5 (7)
Bulgaria	101	10.9(11)	77.2 (78)	11.9 (12)	24.8 (25)	67.3 (68)	7.9 (8)
Croatia	373	8.0 (30)	18.5 (69)	73.5 (274)	19.8 (74)	29.0 (108)	51.2 (191)
Cyprus	64	1.6 (1)	90.6 (58)	7.8 (5)	3.1 (2)	85.9 (55)	10.9 (7)
Czech Republic	454	10.8(49)	47.6(216)	41.6 (189)	7.3 (33)	54.8 (249)	37.9 (172)
Finland	438	13.5(59)	69.9(306)	16.7 (73)	18.3 (80)	57.3 (251)	24.4 (107)
France	332	6.9 (23)	36.1(120)	56.9 (189)	4.5 (15)	47.3 (157)	48.2 (160)
Germany	490	11.2(55)	84.9(416)	3.9 (19)	16.7 (82)	76.1 (373)	7.1 (35)
Greece	44	13.6 (6)	52.3 (23)	34.1 (15)	4.5 (2)	63.6 (28)	31.8 (14)
Ireland	189	5.3 (10)	19.6 (37)	75.1 (142)	6.9 (13)	18.0 (34)	75.1 (142)
Latvia	263	4.2 (11)	14.1 (37)	81.7 (215)	6.5 (17)	25.5 (67)	68.1 (179)
Lithuania	423	16.8(71)	73.3(310)	9.9 (42)	27.0(114)	60.8 (257)	12.3 (52)
Netherlands	194	23.2(45)	70.1(136)	6.7 (13)	9.8 (19)	73.2 (142)	17.0 (33)
Poland	349	5.2 (18)	47.0(164)	47.9 (167)	18.3 (64)	46.7 (163)	35.0 (122)
Romania	486	5.6 (27)	31.7(154)	62.8 (305)	12.1 (59)	40.1 (195)	47.7 (232)
Russian Federation	347	7.5 (26)	52.2(181)	40.3 (140)	27.7 (96)	49.0 (170)	23.3 (81)

Serbia	368	8.7 (32)	75.5(278)	15.8 (58)	7.3 (27)	85.6 (315)	7.1 (26)
Slovenia	215	5.1 (11)	29.8 (64)	65.1 (140)	10.2 (22)	33.5 (72)	56.3 (121)
Spain	162	3.7 (6)	6.2 (10)	90.1 (146)	7.4 (12)	12.3 (20)	80.2 (130)
Sweden	323	7.1 (23)	77.7(251)	15.2 (49)	9.3 (30)	64.7 (209)	26.0 (84)
Turkey	199	10.6(21)	45.2 (90)	44.2 (88)	18.6 (37)	52.8 (105)	28.6 (57)
Ukraine	229	11.8(27)	75.1(172)	13.1 (30)	20.5 (47)	73.4 (168)	6.1 (14)
United Kingdom	206	12.6(26)	35.9 (74)	51.5 (106)	13.1 (27)	37.4 (77)	49.5 (102)
Gender							
Men	5029	8.9(450)	52.7(2649)	38.4(1930)	13.3(671)	53.2 (2674)	33.5(1684)
Women	1619	11.7 (190)	52.9 (857)	35.3 (572)	16.1(261)	53.5 (866)	30.4 (492)
Recruiting event							
CABG	816	12.9 (105)	61.3 (500)	25.9 (211)	11.2 (91)	61.9 (505)	27.0 (220)
PTCA	3693	8.5 (314)	53.3 (1967)	38.2 (1412)	12.9(477)	53.8 (1985)	33.3 (1231)
AMI	1451	9.6 (140)	44.3 (643)	46.0 (668)	15.0(218)	47.3 (686)	37.7 (547)
ISCHAEMIA	688	11.8 (81)	57.6 (396)	30.7 (211)	21.2(146)	52.9 (364)	25.9 (178)
All	**6648**	**9.6 (640)**	**52.7 (3506)**	**37.6 (2502)**	**14.0(932)**	**53.2 (3540)**	**32.7 (2176)**

The distribution according to the three statin treatment groups changed also differently between centers between the time of the hospital discharge and the interview. In some centers (Spain, Poland, Russian federation, Croatia, Ukraine) the proportions of patients not on a statin doubled and this was independent of the proportion at hospital discharge (Table 1).

In only 6 out of the 24 countries the number of patients on a high-intensity statin therapy had increased substantially between the discharge from hospital and interview (Belgium, Finland, Germany, Lithuania, the Netherlands and Sweden).

Among the patients who were not on a statin treatment at discharge, such a therapy was initiated in 63.0% (403/640). However, statin therapy was discontinued in 11.6% (695/6008) of all the patients who were on a statin therapy at discharge. Table 2 presents the distribution of the three statin treatment groups at discharge and at interview.

Table 2: Changes in statin use from discharge to interview (N).

	Statin class at discharge			
Statin class at interview	No	Low/Mod	High	**Total**
No	237	458	237	932
Low/Mod	298	2641	601	3540
High	105	407	1664	2176
Total	640	3506	2502	6648

Among patients who were not treated with a statin or were on a low/moderate dose of a statin at discharge from hospital a switch to a high-intensity statin therapy was made in 12.3% (512/4146). However, among those on a high-intensity statin therapy at discharge the dosage was reduced or the therapy completely stopped in 33.5% (838/2502).

Women represented 24.4% of the total CHD patient population but 33.8% of all the patients who were not on a statin at discharge and at the interview were women (80/237).
68.4% of the total study population was aged 60 years or more.

In those not treated with statins at discharge and at interview (n=237) and in those on a low/moderate intensity statin therapy at discharge but no statin therapy at interview (n=458) the proportion of those aged >=60 years was 75%.

15.6% of CHD patients reported smoking at interview or had a CO in breath > 10 ppm. That proportion was slightly lower (10.7%) in those who had switched from “no statin” at discharge to a low/moderate dose statin therapy at interview but it was higher (20.0%) in those who moved from “no statin” into “high-intensity statin” group. It was also higher in patients who switched from high-intensity treatment to “no statin” therapy at the interview (21.9%).

37.1% of the whole study population was obese: the prevalence of obesity was higher (42.9%) in those who had moved from the “no statin” into the high-intensity statin group and in those who had changed from high-intensity to “no statin” at the time of the interview (46.0%).

One in five patients had insufficient physical exercise; this proportion was comparable in all statin treatment groups.

Self-reported diabetes was prevalent in 25.7% of the patients. It was slightly higher in those who were initiated a low/moderate dose treatment after discharge (31.3%) and in those in whom the dosage was increased from low/moderate to high-intensity treatment (30.0%).

Table 3 presents prevalences of smoking, obesity, low physical activity and diabetes at the time of the interview according to the different statin therapy status at discharge and at the time of the interview.

Table 3. Prevalence of smoking, obesity, low physical activity and diabetes

Statin class					
Discharge	Interview	**% Smoking[1]**	**% Obesity[2]**	**% Low PA[3]**	**% Diabetes[4]**
No	No	15.2% (36/237)	34.2% (81/237)	20.9% (33/158)	23.6% (56/237)
No	Low/Mod	10.7% (32/298)	38.5% (114/296)	22.5% (53/236)	31.3% (93/297)
No	High	20.0% (21/105)	42.9% (45/105)	25.3% (20/79)	25.7% (27/105)
Low/mod	No	17.7% (81/458)	38.1% (174/457)	21.4% (73/341)	21.4% (97/454)
Low/Mod	Low/Mod	15.1% (400/2641)	35.0% (921/2635)	18.6% (375/2019)	25.2% (662/2631)
Low/Mod	High	15.2% (62/407)	38.1% (154/404)	21.3% (68/320)	30.0% (121/404)
High	No	21.9% (52/237)	46.0% (109/237)	22.2% (39/176)	27.0% (64/237)
High	Low/Mod	15.3% (92/601)	37.7% (226/600)	19.4% (91/468)	25.5% (153/599)
High	High	15.6% (259/1664)	38.5% (638/1659)	17.9% (236/1322)	25.8% (426/1653)
All	**All**	**15.6% (1035/6648)**	**37.1% (2462/6630)**	**19.3% (988/5119)**	**25.7% (1699/6617)**

[1]Self-reported smoking or CO in breath > 10 ppm; [2]Body Mass Index ≥ 30 kg/m²;[3]Low score according to IPAQ questionnaire; [4]Self-reported diabetes

The therapeutic control of LDL-C was clearly related to the lipid lowering drug regimen as shown in Table 4.

Table 4 : Therapeutic control of LDL-C at the time of the interview according to the the different statin treatment groups .

Statin Class at interview	LDL-C < 2.5 mmol/L % (N)	LDL-C < 1.8 mmol/L % (N)
No statin	28.3 (264/932)	9.0 (84/932)
Low/moderate intensity	59.4 (2102/3540)	17.5 (618/3540)
High-intensity	67.9 (1478/2176)	26.6 (578/2176)
TOTAL	57.8 (3844/6648)	19.3 (1280/6648)

Target values of LDL-C < 2.5 mmol/L or < 1.8 mmol/L at the time of the interview were achieved by 57.8% and 19.3% of the patients respectively. Among those who were not on statin treatment at that time these LDL-C target levels were achieved by only 28.3% and 9.0% respectively. Nevertheless, among patients on a high-intensity statin therapy these target levels were achieved by 67.9 and 26.6% respectively. More men than women and more older patients than younger achieved LDL-C < 1.8 mmol/L at interview (Figures 1 and 2).

Figure 1 : Proportions of men and women who achieved LDL-C < 1.8 mmol/L at the time of the interview

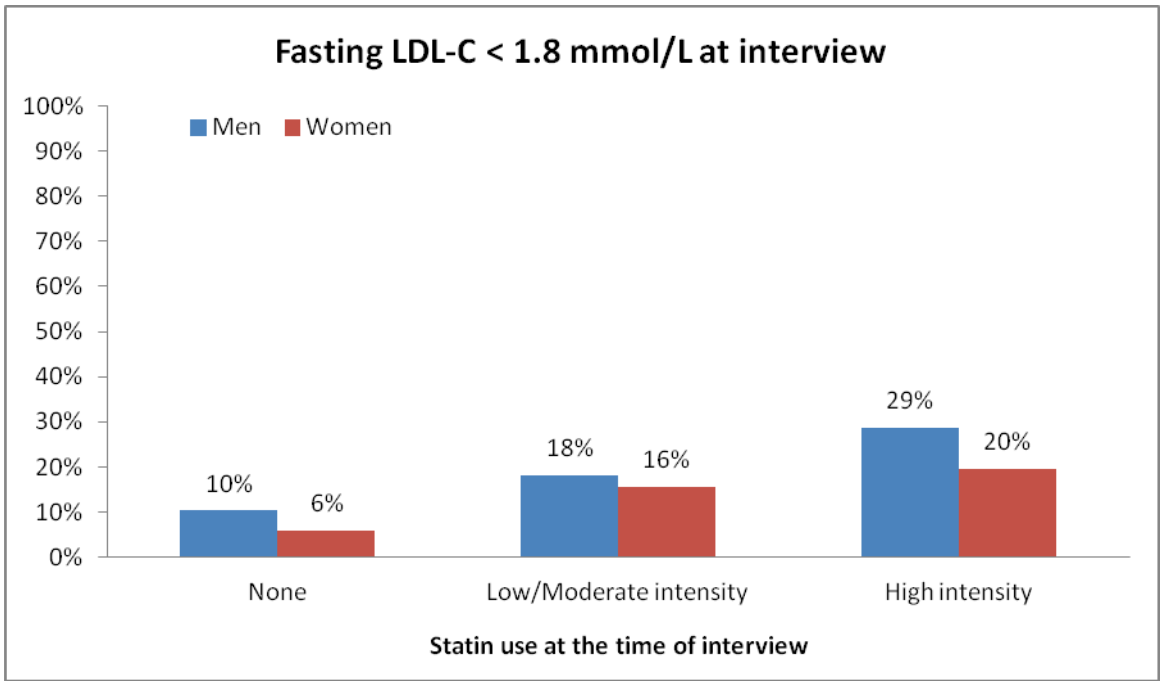
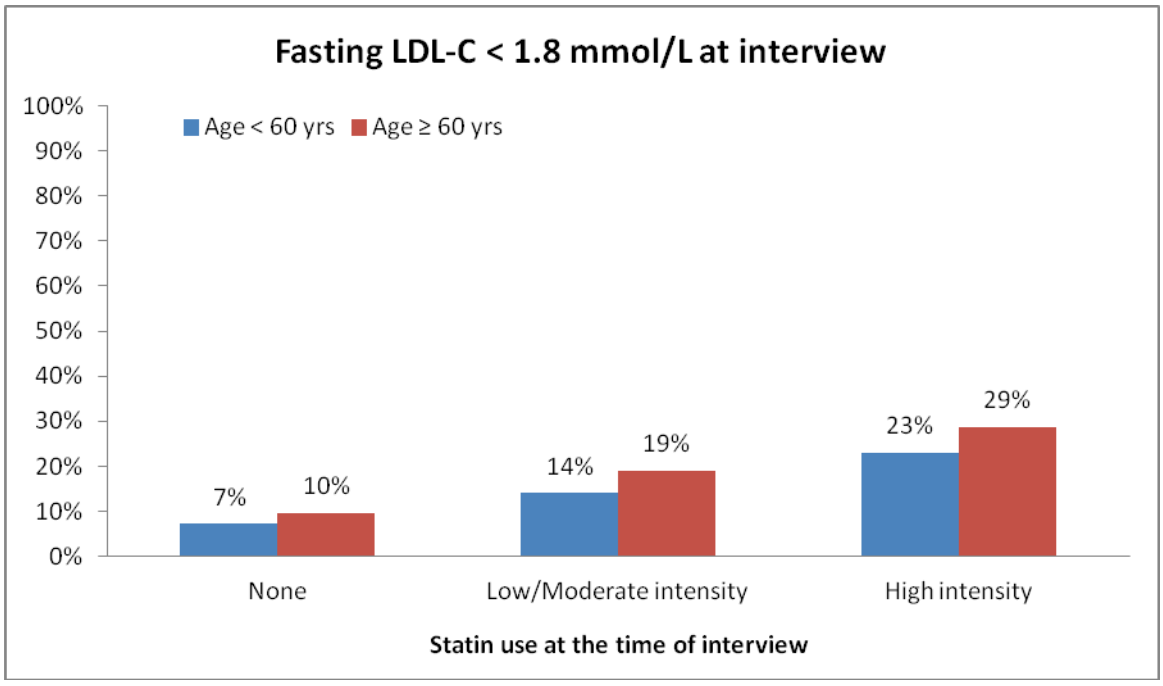


Figure 2 : Proportions of patients with a fasting LDL-C < 1.8 mmol/L by age groups



All patients were also classified in four groups according to the actions which were taken regarding statin use between the discharge from the hospital and the interview (see Table 5):

- 1. No statin therapy at discharge but statin treatment at interview (Initiated).

- 2. Statin therapy at discharge but no statin treatment at interview (Discontinued).

- 3. No or low/moderate intensity statin therapy at discharge but high-intensity statin treatment at interview (Changes to high).

- 4. High-intensity statin therapy at discharge but low/moderate intensity statin or no treatment at all at interview (Returned to low).

Women were less represented in group 1 and more in group 4. In the older age group more patients had their statin dosage reduced or had stopped statins. Time between discharge and interview had no effect on the actions taken. More CABG patients were prescribed statin treatment between the discharge and the interview if discharged without statin treatment but in those discharged on a high-intensity statin, the statin dosage was more often reduced. In patients with an acute ischaemic event and in patients who continued smoking less statin treatment was initiated if discharged without any statin therapy and more discontinuation of therapy occurred. More actions concerning statin treatment of all kinds had been taken in the patients who were found to be obese or sedentary at the time of interview. Patients with diabetes were more represented in group 1.

As expected the proportions of patients who have achieved LDL-C < 1.8 mmol/L at interview were greater in those in whom statin treatment was initiated between discharge and interview but to whom statins were not prescribed at discharge and in those in whom therapy was switched to a high-intensity statin treatment (Table 5).

Table 5. Action taken regarding statin use

	Action taken regarding statin use			
	% Initiated[1]	% Discontinued[2]	% Changed to high[3]	% Returned to low[4]
Gender				
Men	68.3% (233/341)	10.7% (380/3548)	13.0% (306/2358)	31.4% (480/1531)
Women	61.2% (79/129)	12.6% (134/1067)	11.5% (89/775)	38.7% (163/421)
Age				
< 60 years	66.4% (85/128)	9.8% (143/1456)	14.5% (126/866)	30.6% (220/718)
≥ 60 years	66.4% (227/342)	11.7% (371/3159)	11.9% (269/2267)	34.3% (423/1234)
Time discharged				

< 1 year	66.6% (225/338)	11.6% (368/3172)	13.1% (291/2213)	33.4% (433/1297)
≥ 1 year	65.9% (87/132)	10.1% (146/1443)	11.3% (104/920)	32.1% (210/655)
Recruiting diagnosis				
CABG	82.4% (56/68)	9.2% (50/541)	13.2% (60/453)	38.5% (60/156)
PTCA	68.9% (175/254)	10.6% (283/2661)	12.1% (215/1781)	32.7% (371/1134)
AMI	63.1% (65/103)	11.9% (117/981)	14.2% (81/569)	31.3% (161/515)
ISCHAEMIA	35.6% (16/45)	14.8% (64/432)	11.8% (39/330)	34.7% (51/147)
Smoking				
No	67.3% (272/404)	10.7% (421/3937)	12.3% (331/2682)	32.7% (543/1659)
Yes	60.6% (40/66)	13.7% (93/678)	14.2% (64/451)	34.1% (100/293)
Obesity				
No	64.9% (192/296)	10.5% (305/2897)	11.6% (233/2014)	31.6% (372/1179)
Yes	69.0% (120/174)	12.2% (209/1718)	14.5% (162/1119)	35.1% (271/773)
Low physical activity				
No	65.8% (241/366)	10.8% (403/3742)	12.2% (307/2519)	32.3% (514/1589)
Yes	68.3% (71/104)	12.7% (111/873)	14.3% (88/614)	35.5% (129/363)

Diabetes				
No	64.5% (223/346)	11.5% (394/3434)	12.1% (283/2332)	32.8% (475/1448)
Yes	71.8% (89/124)	10.2% (120/1181)	14.0% (112/801)	33.3% (168/504)
LDL-C < 1.8 mmol/L				
No	8.0% (19/237)	20.8%(1103/5313)	14.9%(541/3634)	27.5%(457/1664)
Yes	23.1% (93/403)	9.4% (65/695)	23.6% (121/512)	19.2%(161/838)

1 : No statin at discharge: % statin at interview

2 : Statin at discharge: % no statin at interview

3 : No or low/moderate intensity statin at discharge: % high intensity statin at interview

4 : High intensity statin at discharge: % low/moderate intensity statin or no statin at interview

Table 6. Lipid levels at goal: LDL-C vs. Non-HDL-cholesterol

	LDL-C		
Non-HDL-C	< 1.8 mmol/L	≥ 1.8 mmol/L	**Total**

< 2.6 mmol/L	1124	850	1974
≥ 2.6 mmol/L	156	4518	4674
Total	1280	5368	6648

Among 1280 patients who achieved the LDL-C target, 156 (12,2%) were not at goal for non-HDL-C. If only non-HDL-C had been used as a target, then 850 out of the 1974 patients (43.0 %) who were at goal for non-HDL-C would not achieve LDL-C target value. Among all patients in EUROASPIRE IV 1124/6648 (16.9%) were at goal for both LDL-C and non-HDL-C.

A similar analysis was made for the 1699 patients with self reported diabetes and these results are presented in table 7.

Table 7. Lipid levels at goal: LDL-C vs Non-HDL-cholesterol in patients with diabetes

	LDL-C		
Non-HDL-C	< 1.8 mmol/L	≥ 1.8 mmol/L	**Total**
< 2.6 mmol/L	411	176	587
≥ 2.6 mmol/L	74	1038	1112

Total	485	1214	1699

Among the 485 CHD patients with diabetes who achieved LDL-C target, only 74 (15.3%) were not at goal for non-HDL-C. If only non-HDL-C had been used as a target 176 out of the 587 (30.0 %) CHD patients with diabetes who were at goal for non-HDL-C would not be at goal for LDL-C. Among all CHD patients with self-reported diabetes in EUROASPIRE IV 411/1699 (24.0%) were at goal for both LDL-C and non-HDL-C.

Discussion

The results of the EUROASPIRE IV survey concerning lipid lowering therapy in CHD patients show that despite the clear evidence of the benefits of lipid-lowering treatment with statins in secondary prevention, many coronary patients with dyslipidaemia are still inadequately treated and a significant number of patients on lipid-lowering therapy is still not reaching the LDL-C treatment goals. According to these results every tenth patient in European centers has been discharged from the hospital after a coronary event without any statin treatment and only one third of CHD patients were prescribed a high-intensity statin therapy at discharge. This happens in spite of the recommendations of both European and US guidelines (2,5). On average this is much better than some recently published results for certain European countries (not included in this survey) indicating that more than one third of patients do not receive a statin prescription at hospital discharge after an MI (8).

It is also worrying that 6-36 months after a CHD event the number of patients without any statin therapy increased by about 50% and that the number of patients on high-intensity statin treatment decreased significantly. The reasons why the physicians often prescribe low-intensity statin treatment instead of high-intensity therapy when needed are different and complex but quite often it is the fear of adverse effects of statins (9,10) Even more feared are the patients who are frequently confused with the information from the media suggesting that

statins have many serious adverse effects so they stop taking the statins after some time or do not adhere to the prescribed dose (9,11,12). Although high levels of adherence are undoubtedly associated with reductions in adverse clinical CHD outcomes, including all-cause mortality and fatal and nonfatal cardiovascular events (the most consistent benefits being at adherence levels 80% or greater) while poor statin adherence is associated with increased risk of adverse CHD outcomes, taken in general non-adherence to statin therapy is a big problem (13,14). It is well known that adherence to statin therapy declines with time and according to a study on patients with established CHD falls to 71% after six months of treatment, and declines to only 45% after three years (15). Our results are much better than these but they were obtained several years later than the mentioned study. However, it is also well known that patients with established CHD have better adherence to statins than those without proven CHD (16). Statin resistance and/or intolerance might be another reason, at least for some patients, why did the number of patients without statin treatment in our survey increase and the number of those on high-intensity treatment decrease between the CHD event and interview (17)

Gender issue should be particularly addressed. Although only every fourth patient with CHD in EUROASPIRE IV survey was a women, the fact that much less women were on statin treatment and that less women were on high-intensity statin therapy both at discharge and at interview as compared to men deserves special attention and concern. It reflects the phenomenon registered in some other studies as well. For example, it has been shown that women, particularly younger women and women with ST-segment elevation AMI, are less likely to be prescribed evidence-based treatment at discharge including statins than their male counterparts (18). This gap between men and women did narrow over time during the last 15 years in most parts of the world, including those outside Europe, but it still exists (19).

According to the results of this study CHD patients older than 60 years get much less prescribed statin therapy than the younger patients. The dose of a statin is also more often reduced in these patients and they also stop taking statins after a CHD event more often. This is similar to the data on primary prevention of CHD indicating that older people often do not receive proper primary prevention treatment in general and that low use of statins in primary prevention when they are concerned, is more rule than the exception (20,21). Nevertheless, a substantial increase in prevalence and incidence of prescribing statins in the older subjects with the greatest relative increase in those older than 80 years can be seen in the last decade across all CV risk categories, at least in most developed countries (22).

Significant differences in distribution according to three statin treatment groups which were observed between the centers from different countries are very difficult to interpret. One might suppose that they reflect different socioeconomic situations and different reimbursement policies. Financial constraints might be responsible for this, especially in low- and middle-income European countries. This could maybe explain, for instance, why more than 20% patients were discharged after a CHD event without a statin and why a high-intensity statin therapy was prescribed at discharge in only <10% of the patients in the centers from Bosnia-Herzegovina. However, if this is true, it is hard to understand why a similar percentage was seen in the centers from the Netherlands or why high-intensity statin therapy was prescribed at discharge in only <10% of the CHD patients in the centers from Germany, which are both high-income countries.

On the other hand, variation between centres within a certain country was even larger than the between-country variation indicating that the local policy plays a prominent role so that the differences between countries in the use of statins (as well as their changes) should be interpreted with great caution. So the proportions of patients discharged without a statin in some countries with multiple centres differed up to 7 fold. The proportions of patients not using a statin at the time of interview differred between centres in a single county even more – up to 22 fold.

It is also of great concern that in only every fourth European country the number of CHD patients on a high-intensity statin therapy had increased between the discharge from hospital and interview - almost all of them being high-income countries. This cannot be explained only by economic reasons. Financial constrains could be a possible explanation for lower-income countries as it has been shown that higher copayments act as a disincentive for persistent and adherent use of statin therapy, but this might also not be the only explanation even for these countries (23,24).

It is worrying that only every eighth CHD patient who was not treated with a statin or was on a low/moderate dose of a statin at discharge from hospital switched afterwards to a high-intensity statin therapy. Even more disturbing is that in one third of patients on a high-intensity statin therapy at discharge the dosage was later reduced or the therapy completely stopped. We believe that this might reflect the lack of their physicians' knowledge or adherence to the guidelines (11,12,25).

The therapeutic control of LDL-C in EUROASPIRE IV survey was clearly related to the intensity of LDL-C lowering drug regimen. A substantial number of CHD patients on lipid-lowering drugs who did not achieve the LDL-C target levels is of concern indicating that statins are still either not used as effectively as they should be or that there is poor patient compliance, or both. The same phenomenon was also seen in EUROASPIRE III (26). One of the possible reasons might be that despite the fact that the majority of cardiologists and primary care physicians support the concept of preventive cardiology and treatment of LDL-C to the target values, this still does not always reflect in their current practice, the knowledge of graduated medical students on dyslipidemia and its treatment is not satisfactory and the general public perceptions, knowledge and awareness of CVD risk factors including dyslipidaemia are insufficient (11,12,27). Obviously, there are still challenges and many barriers to implement the CVD prevention guidelines, even when dyslipidaemia treatment is concerned (28).

In the ECS/EAS guidelines it is recommended to use non-HDL-C as a secondary target particularly in patients with diabetes or obesity, because in these patients atherogenic particles other than LDL may also be important and non-HDL-C measures account for all atherogenic lipoproteins (2,6). Therefore, non-HDL-C is believed to provide in these patients maybe even a better estimate of CVD risk than LDL-C. In CHD patients the goal for non-HDL-C is set at < 2.6 mmol/L (~100 mg/dL). It has been shown that patients who achieved LDL-C target levels without reaching target non-HDL-C levels had a 32% increased risk of CHD events compared with those who achieved dual target levels for LDL-C and non-HDL-C (29). A possible explanation might be that non-HDL-C is a better predictor of plaque inflammation, and therefore its vulnerability, than LDL-C (30,31). In our survey only 12.2% CHD patients who achieved LDL-C target level were not at goal for non-HDL-C and only 25.3% CHD patients with diabetes who achieved LDL-C target were not at goal for non-HDL-C.

But on the contrary, if only the non-HDL-C target would have been used, much more patients would not have been at goal for LDL-C. Therefore it is recommended to continue to use LDL-C as a primary target and to look at non-HDL-C in patients who are at goal for LDL-C, particularly those with diabetes or obesity. The results presented here indicate that statins are the treatment of choice for a vast majority of these patients if applied properly and in adequate intensity. However, as every fourth CHD patient with diabetes who achieved LDL-C target value still has a residual CVD risk, this has to be taken into consideration and other additional therapeutic options for these patients should be considered. In this context it is interesting that

very few CHD patients, including those with diabetes, were prescribed fibrates together with a statin although it is well known that many of these patients have atherogenic dyslipidaemia which is characterised not only by increased LDL-C but primarily by increased levels of triglycerides and decreased HDL-C (32,33,34,35,36). In these patients even more attention should be directed towards other modifiable CV risk factors and combination of lipid lowering drugs might be considered to get LDL-C even lower resulting in more prevention as shown in the IMPROVE-IT trial (37). It could be hypothesized that although today most of the patients with dyslipidemia are treated with statins as monotherapy, this might change in the near future (38). The pattern could follow what happened with antihypertensive treatment which was also several decades ago based upon monotherapy. However, today combinations of two, three or even four drugs lowering the blood pressure by influencing different blood-pressure-lowering mechanisms are widely used to achieve the treatment goals as defined by the guidelines. In the meantime, the results of outcome trials with other lipid lowering drugs combinations are eagerly awaited.

Abstract

Objective. Since dyslipidaemia is one of the most important risk factors for coronary heart disease (CHD), lowering of LDL-cholesterol (LDL-C) causes significant reduction in morbidity and mortality, particularly in patients with established CHD. The aim of this survey was to assess how statins were prescribed in CHD patients at discharge after a coronary event from hospitals throughout Europe and how the intake of these drugs was reported by the patients when they were seen more than one year later in relationship with their achieved LDL-C levels.

Methods. 6648 CHD patients' data from centres in 24 European countries were gathered using standardized methods. Lipid measurements were performed in one central laboratory. Patients were divided in three groups: high-intensity statin therapy, moderate or low intensity statin therapy and no statin therapy at all.

Results. 90.4% CHD patients were on statin therapy at the time of discharge from the hospital which decreased to 86% one year later. Only 37.6% of these patients were prescribed a high-intensity statin at discharge which even decreased to 32.7% later. In only 6 countries

(all of them high-income countries) the number of patients on a high-intensity statin therapy increased substantially after the hospital discharge. It is worrying that statin therapy was discontinued in 11.6% of the patients who were on a statin therapy at discharge and that only 19.3% of all CHD patients achieved target values of LDL-C < 1.8 mmol/L one year after the event.

Conclusions. Too many CHD patients with dyslipidaemia are still inadequately treated and most of these patients on statin therapy are not achieving the treatment targets. Therapeutic control of LDL-C is clearly related to the intensity of lipid lowering drug regimen after the CHD event indicating that a considerable potential still exists throughout Europe to reduce CHD mortality and morbidity rates through more efficient LDL-C lowering.

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