ORIGINAL ARTICLE

Lipid-lowering drugs as primary prevention in general practice: Do patients reach guideline goals and continue treatment? ADDITION Denmark

LISE GRAVERSEN¹, BO CHRISTENSEN¹, KNUT BORCH-JOHNSEN^{2,3},
TORSTEN LAURITZEN¹ & ANNELLI SANDBAEK¹

¹Department of Public Health, Section for General Practice, University of Aarhus, ²Steno Diabetes Centre, Gentofte, Denmark, and ³Institute of Public Health, Research Centre for Quality in Health Care, University of Southern Denmark, Odense, Denmark

Abstract

Objective. To describe lipid-lowering treatment in a primary care setting and how well target levels are reached. Furthermore, the aim is to describe long-term adherence to treatment. **Design.** Population-based cross-sectional study with follow-up. **Setting.** A total of 139 general practices from three of five Danish regions, taking part in the ADDITION study from 2001 to 2006. **Subjects.** The study population comprises 1468 patients who started lipid-lowering drugs and were followed for a minimum of one year after starting treatment. Median time of follow-up after starting drug therapy was 936 days (range: 366–2068). **Results.** Of 1468 patients starting treatment, a total of 781 (53%) reached the treatment goal of total cholesterol <5.0 and low-density lipoprotein <3 mmol/l within one year after drug therapy start. The percentage increased throughout the study period from 27% of patients initiating treatment in 2001 to 66% of patients initiating treatment in 2005. Age over 50, repeated cholesterol measurements within three months after treatment start, larger initial dose, and calendar year of treatment start were associated with reaching the goal within the first year, and most recent total cholesterol measurement before start of treatment >7 mmol/L was associated with not reaching the goal in the first year. Among patients followed for a minimum of three years after drug therapy started ($n = 536$), adherence was 77%, 72%, 75% in the first, second, and third year respectively. **Conclusion.** Initial doses and the percentage reaching their goal increased substantially throughout the study period. Adherence to lipid-lowering treatment is relatively high in a primary care setting. However, current practice shows room for improvement if treatment recommendations are to be met.

Key Words: Adherence, cardiovascular risk factors, dyslipidemia, family practice, prevention

Introduction

Clinical and epidemiological studies clearly establish the link between dyslipidemia and cardiovascular disease (CVD) [1]. All relevant Danish medical associations have reached consensus on lipid-lowering drugs to prevent cardiovascular disease, and based on these the Danish College of General Practitioners (DSAM) published guidelines setting clear treatment targets for cholesterol levels [2,3]. According to the 1998 guideline based on the Framingham risk charts adjusted to the Danish population, drug therapy is to be initiated as primary prevention in asymptomatic patients when the compiled individual risk of CVD within 10 years exceeds 20%.

Despite the evidence for lipid-lowering drug treatment, not all patients reach target levels [4–7], not all continue treatment in the long run [8–11], and optimal lipid-lowering drug therapy is delayed due to small starting doses [5] and delays in dose augmentation [12]. Poor adherence to lipid-lowering treatment is known to affect the clinical outcome [11,13].

The patient's sex [14,15], age [10,11,15,16], and educational level [9] have been suggested to influence the patient's ability to reach target levels and adherence to lipid-lowering drug treatment. To reach target and adhere to treatment have also been associated with comorbidity [5,14,17]. However, we do not know whether this reflects better acceptance of treatment

Management of dyslipidemia in general practice is progressing towards better adherence to guidelines.

- The initial doses prescribed and the percentage reaching the guideline goal within one year after treatment initiation increased considerably from 2001 to 2005.
- Well above 70% were adherent to treatment over a three-year period.
- However, current practice shows room for improvement if treatment recommendations are to be met.

among patients who are already medicated, preferential treatment of patients with comorbidities, or treatment maintenance owing to frequent visits to the GP. The evidence on the influence of polypharmacy is conflicting [14,16,18].

Given the evidence indicating suboptimal prevention of CVD, it is vital that awareness of primary prevention procedures for managing lipid-lowering treatment is optimized.

Aim

The aim of the present study was to describe lipid-lowering treatment in a primary care setting and how well targets levels are reached. Furthermore, we aimed to describe long-term adherence to treatment.

Material and methods

Design

The study population was extracted from the ADDITION study, an ongoing international study aiming to evaluate screening procedures for type 2 diabetes and evidence of effect in general practice among patients between 40 and 69 years of age [19]. The screening procedure is presented elsewhere [20].

We identified patients who completed screening for diabetes, but were cleared for diabetes and had no history of CVD. Patients without available laboratory data, with a diagnosis of CVD before treatment start (registry or self-reported), or with a history of liver disease (registry) were excluded, since active liver disease is a contraindication for the most common lipid-lowering drugs, statins.

The study population consisted of 1468 patients who received no lipid-lowering drugs at the time of screening, but started lipid-lowering drugs during follow-up. Patients starting lipid-lowering drugs were identified in the Danish Prescription Database if at

least one prescription of lipid-lowering drugs was dispensed in the follow-up period. Patients were included independently of their risk of CVD at baseline. A total of 113 of those were given a CVD diagnosis between treatment start and study end (these were not excluded). Patients started drug therapy between 2001 and 2005, and were followed until the end of 2006. Optimizing treatment by adjusting dose and drug choice can be time-consuming, but nevertheless can be expected to be finalized within a year. In order to avoid categorizing patients on their way to reaching their goal as not having reached that goal due to a too short a follow-up time, we excluded patients followed for less than one year after initiating treatment. Median time of follow-up after starting drug therapy was 936 days (range: 366–2068).

Description of data and sources

Baseline data were obtained from questionnaires completed by patients or obtained from case record forms completed by general practitioners (GPs) at screening [21].

The Danish National Hospital Registry provided data on ICD-10 codes to identify patients with CVD prior to initiating lipid-lowering treatment (ICD-10: I20–25, I60–64, I672, I69–70, I74) and liver diseases (ICD10: K70–77, C22). Prescription data were obtained from the Danish Prescription Database. Data on blood tests were obtained from the regional laboratory databases. Statistics Denmark provided demographic data on deceased and relocated patients, so that their blood tests were not registered in this study. Statistics Denmark connected all data using the unique civil registry number assigned to all Danish citizens. Patient baseline characteristics at the time of screening are shown in Table I. Median time from screening to drug therapy start was 638 days (range: 1–1705).

Treatment goal

According to the guideline available at the time of the study, drug therapy was required in patients with $\geq 20\%$ risk of CVD within 10 years. Target levels were defined as total cholesterol < 5 mmol/L and LDL < 3 mmol/L [2]. Among the patients without LDL measurements ($n = 237$), reaching a total cholesterol < 5 mmol/L was considered as reaching the goal.

Determinants for reaching treatment goal

Sex and educational level were recorded when entering the ADDITION study (baseline) and age at the time of treatment start was extrapolated from baseline. Use

Table I. Baseline characteristics obtained when patients entered the ADDITION study.

	Men (n = 695)		Women (n = 773)	
	n	%	n	%
Age				
<50 years	97	14	45	6
≥50 years	598	86	728	94
Systolic blood pressure*				
<140 mmHg	257	38	287	38
140–159 mmHg	282	41	304	40
160–179 mmHg	100	15	122	16
≥180 mmHg	41	6	45	6
Total cholesterol				
<6 mmol/L	154	22	112	14
6–7 mmol/L	230	33	242	31
7–8 mmol/L	184	26	221	29
≥8 mmol/L	127	18	198	25
Smoking status				
Non-smoking	430	65	519	70
Smoking	228	35	224	30
Body mass index				
<30 kg/m ²	464	67	560	72
≥30 kg/m ²	231	33	213	28
Waist circumference**				
Normal	171	25	174	23
Large	524	75	599	77
Impaired fasting glucose and/or impaired glucose tolerance				
No	573	82	633	82
Yes	122	18	140	18
Educational level				
No vocational education	94	15	239	34
1–3 years vocational education	332	52	301	42
>3 years vocational education	209	33	172	24
Ethnicity				
Danish	604	87	657	85
Other	90	13	113	15
Cohabiting				
Single	104	16	199	27
Cohabiting	553	84	550	73
CVD in close family				
Yes	195	31	247	35
No	442	69	469	66
Ten-year risk of any CVD (SCORE)***				
<20%	92	15	564	82
≥20%	523	85	126	18

Notes: Percentages are presented by column.

*Antihypertensive treatment prior to screening was equally distributed among the systolic blood pressure groups (35–45% were in treatment).

**Waist circumference was considered large when >80 cm for women and >94 cm for men.

***<20% risk of cardiovascular disease (CVD) within 10 years was considered low risk and ≥20% high risk according to the 1998 guideline, the existing guideline at the time of screening.

of heart/circulation drugs and polypharmacy were used as proxies for comorbidity. These were assessed by prescription patterns three months prior to reaching the treatment goal. To obtain a comparable time

interval in the group not reaching the goal, we used the median time to treatment goal in the group reaching goal within one year. Polypharmacy was assessed as the number of different prescriptions dispensed and categorized: 0–1, 2–4, and >5 [22]. Heart/circulation drug therapy was assessed as any drug with the ATC classification (Anatomical Therapeutic Chemical Classification System): “CO”. We used repeated cholesterol measurements within three months after starting drug therapy as a proxy for close follow-up. To analyse the development in guideline adherence, we used the initial dose and starting year grouped according to the calendar year for the first prescription of lipid-lowering drugs filled.

Adherence

No consensual standard for what constitutes adequate adherence was available, but in this study we focused on adherence in terms of continuing treatment over years. We calculated adherence based on total number of tablets dispensed per year. If the patient dispensed drugs for less than 80% of the days in a year, the patient was assessed as non-adherent [6,9,17].

Statistics

Data are presented as percentages. Multiple logistic regressions were used to determine factors associated with reaching goal. Stata version 10 was used for all analyses.

Ethics

The Scientific Ethics Committee and the Danish Data Protection Agency have approved the ADDITION study.

Results

Of 1468 patients, 959 (65%) reached the treatment goal within follow-up; 781 (53%) reached the goal within one year after drug therapy start. The percentage increased throughout the study period from 27% of patients initiating treatment in 2001 to 66% of patients initiating treatment in 2005. All 781 had total cholesterol measurements; 544 (70%) had an LDL measurement. In the group reaching the goal, the median time from drug-therapy start until treatment goal was reached was 97 days (range 1–1526, 25% above 259). Twenty-eight patients reached the treatment goal according to our definition before treatment start. Parameters possibly associated with reaching goal are shown in Table II. Age over 50,

Table II. Patient characteristics and their association with reaching treatment goal.

	Do not reach goal (<i>n</i> = 657)		Reach goal (<i>n</i> = 781)		OR crude	95% CI	OR adjusted	95% CI
	<i>n</i>	%	<i>n</i>	%				
Sex								
Men	301	43	394	57	1		1	
Women	386	50	387	50	0.77	0.62–0.94	0.82	0.64–1.04
Age								
≤ 50	75	58	67	42	1		1	
> 50	612	46	714	54	1.63	1.09–2.44	1.62*	1.03–2.56
Educational level								
No vocational education	148	44	185	56	1		1	
1–3 years vocational education	289	46	344	54	0.97	0.76–1.24	0.91	0.69–1.20
> 3 years vocational education	194	51	187	49	0.79	0.60–1.03	0.75	0.55–1.03
Most recent total cholesterol before treatment start								
<6 mmol/L	62	28	162	72	1		1	
6–7 mmol/L	148	34	287	66	0.74	0.52–1.06	1.23	0.90–1.67
7–8 mmol/L	222	52	209	48	0.36*	0.25–0.51	0.57*	0.42–0.77
≥8 mmol/L	255	67	123	33	0.18*	0.13–0.27	0.22*	0.14–0.33
Heart/circulation drugs before treatment start								
No	302	50	308	50	1		1	
Yes	385	45	473	55	1.51*	1.23–1.86	0.75	0.52–1.09
Polypharmacy before treatment start								
0–1	379	48	405	52	1		1	
2–4	282	45	338	55	1.12	0.91–1.39	1.37	0.94–1.98
>5	26	41	38	59	1.37	0.81–2.30	1.32	0.70–2.49
Cholesterol measurements within 3 months after treatment start								
No	376	59	261	41	1		1	
Yes	311	37	520	63	2.41*	1.95–2.98	3.3*	2.59–4.21
Initial dose								
10 mg Simvastatin	156	65	83	35	1		1	
20 mg Simvastatin	253	43	337	57	2.50*	1.83–3.42	2.47*	1.75–3.48
40 mg Simvastatin	162	37	277	63	1.79*	1.52–2.11	1.73*	1.44–2.08
Other	116	58	84	42	1.11	0.97–1.26	1.30*	1.12–1.51
Start year								
2001	19	73	7	27	0.19	0.08–0.46	0.25*	0.10–0.65
2002	115	66	58	34	0.26	0.18–0.38	0.35*	0.23–0.55
2003	191	53	167	47	0.45	0.34–0.60	0.56*	0.41–0.78
2004	202	46	241	54	0.62	0.47–0.81	0.65*	0.49–0.87
2005	160	34	308	66	1		1	

Notes: Percentages are presented by row. *Statistically significant results.

cholesterol measurements within three months after treatment start, larger initial dose, and calendar year of treatment start were associated with reaching goal, and most recent cholesterol before treatment start >7 mmol/L was associated with not reaching the goal when looking at the population reaching the goal within the first year. Parameters associated with reaching the goal were similar when looking at the population initiating treatment in 2005 exclusively.

Updated information on smoking status and the total risk of CVD were not available at the time of treatment, but smoking status and the total risk of CVD at the time of screening were not associated with reaching the goal. Of 1468 patients, 1268 (86%) started Simvastatin, 139 (9%) started Atorvastatin, 26 (2%) started Pravastatin, and 35 (3%) started others. Among patients starting Simvastatin, a starting

dose of 10 mg decreased from 73% in 2001 to 10% in 2005 and a starting dose of 40 mg increased from 10% in 2001 to 44% in 2005 (Figure 1). A total of 24% had their dose increased during the study period. The median time from drug therapy start to when dose was increased was 300 days (range 56–1008, 25% above 599 days).

In the population followed for minimum three years (*n* = 536), adherence was stable: 77% (CI 95%: 74–81) in the first year, 72% (CI 95%: 68–76) in the second year, and 75% (CI 95%: 71–78) in the third year.

Discussion

Our main findings show that 53% reach goal within one year after treatment start; this percentage rose from 27% in 2001 to 66% in 2005. The initial dose

Figure 1. Initial dose of Simvastatin according to year of first prescription.

also rose substantially during this period and well over 70% were adherent over a three-year period.

The strengths of this study were that data on prescriptions and blood tests came from complete databases [23,24], that the study reflects the usual care and is therefore unbiased by the trial set-up, and that a broad range of clinics participated (139 clinics from three of five Danish regions). Moreover, the participants were included in connection with screening for diabetes, whereby we avoided selection bias that would arise if GPs included patients with a propensity to accept and adhere to lipid-lowering treatment.

Unfortunately, we had no data to assess whether medication was discontinued for clinically appropriate reasons apart from a diagnosis of active liver disease. McGinnis *et al.* reported that 30% of “discontinuers” had reasons for stopping treatment that were documented in their medical records; 19% of those were due to adverse effects [11]. Reports on adverse drug events and blood tests for creatine kinase and alanin-aminotransferase (indicators of adverse drug effects) could have improved our understanding of non-adherence.

Primary prevention is controversial due to the possible morbid attachment and the relatively high number needed to treat. In Denmark, treatment is recommended only for patients at high risk of CVD to confine these problems. Patients in this study were however, at different risk of CVD at baseline (see Table I). A large proportion (82% for women and 15% for men) were at low risk of CVD at baseline according to the guideline, but nevertheless a medical doctor has found indications for starting treatment. Total risk could have increased from baseline to treatment start; nevertheless we have reason to believe that some patients started treatment in spite of a low risk of CVD. Unfortunately, we could not stratify on level of risk as no exact information on total CVD risk at the time of treatment start was available. The difference in level of risk at the time

of screening between men and women was striking and unlikely to be fully explained by changes in risk factors between the time of screening and treatment start. Pearson *et al.* also report women to be over-represented among patients at lower risk of CVD being dispensed lipid-lowering treatment [7].

Only 24% had their dose increased and the increase was substantially delayed in this study. Other studies have shown that optimal lipid-lowering drug therapy is delayed due to small starting doses [5], that most patients remain on the initial dose [4], and that dose increase is delayed [11]. Erhardt *et al.* showed that more than one-third of physicians believed that patients became concerned about the severity of their condition if their dose was increased [4]. Fortunately, we saw increasing initial doses over time in the study period.

The lack of a consensual standard for what constitutes adherence is a major obstacle when comparing our results with other studies. Studies that used a similar method for calculating adherence found rates from 39% to 74% in the first year declining to 22–55% in the third year [9,25,26]. Even though they are not entirely comparable, this indicates that adherence is relatively high in this study.

This study provided no reasons for the suboptimal treatment. Research suggests that GPs accept higher levels of risk factors than guidelines recommend [27] and Erhardt *et al.* showed that although only 47% of patients reached and maintained the goal, 61% of physicians believed that a sufficient number of patients achieved their goals [4]. Moreover, the communication between GP and patient could be insufficient. Mann *et al.* showed that only 12% of the patients were aware they would be taking the lipid-lowering drug for the rest of their lives [10].

Initial doses and the proportion reaching the goal increased during the study period, indicating an increasing adherence to guidelines. This supports a progressive adoption of clinical guidelines in clinical practice and a development towards recommendations for more aggressive preventive treatment. However, current practice shows room for improvement if treatment recommendations are to be met.

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Conflicts of interest

Bo Christensen has received lecture fees from the medical industry when lecturing on prevention of cardiovascular disease. Apart from this the authors declare no conflict of interest associated with this manuscript.

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