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Whom are we treating with lipid-lowering drugs? Are we following the guidelines?

Evidence from a population-based study – the Tromsø Study 2001

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Abstract

Objective: The beneficial effect of lipid-lowering drugs (LLDs) is well documented. Despite increasing sales of LLDs, little is known about what characterizes LLD users. Our objective was to describe LLD users in a general population according to socio-demographic factors, cardiovascular risk factors and coronary heart disease (CHD), and to study the achievement of cholesterol treatment goals according to national guidelines.

Methods: The Tromsø Study is a population-based study of chronic diseases, risk factors and drug use in the municipality Tromsø in north Norway. The fifth survey was conducted in 2001 and included 7973 men and women (attendance rate 78.1%). Self-reported use of LLDs and/or proprietary LLDs was included as LLD use in the analysis.

Results: LLD use was reported in 9.6% of all women and 14.0% of all men, of whom 36.5% achieved the nationally recommended lipid goal. Among individuals with CHD, 49.9% of all women and 55.4% of all men were LLD users. The individuals with a risk condition (hypertension and/or diabetes) and total cholesterol level above the target of 5.0 mmol/l, and healthy individuals with total cholesterol level ≥ 8.0 mmol/l, constituted 47.2% of the study population without CHD. In this group which is eligible for primary prevention, 8.0% of the women and 7.4% of the men reported LLD use.

Conclusions: Only half of all subjects with CHD were taking an LLD. The large discrepancy between national recommendations and actual LLD use in primary prevention should be addressed in future revisions of the guidelines.

Key words: lipid-lowering drugs, guidelines, population-based study.

Introduction

A benefit of reducing the level of total cholesterol in primary and secondary prevention of coronary heart disease (CHD) has been documented through well-designed clinical trials [1–5]. The benefit is reflected in current national guidelines, which aim to achieve levels of total cholesterol ≤ 5.0 mmol/l and LDL-cholesterol ≤ 3.0 mmol/l [6]. In addition to a healthy diet, lipid-lowering drugs (LLDs) are recommended for secondary prevention in subjects with CHD, and primary prevention among subjects with a high absolute risk of CHD. By defining both the population eligible for LLD treatment and cholesterol goals, guidelines may serve as a tool to maximize health benefit and resource utilization.

The total cholesterol levels in the Norwegian population are known to be high, yet a steady decrease in mean total cholesterol level has been observed since the 1970s [7]. Concurrently, repeated screenings of the Tromsø population (the Tromsø Study) reveal a decrease in mean total cholesterol level, e.g. from 6.8 mmol/l to 6.4 mmol/l in 60- to 64-year-old subjects in 1994 and 2001, respectively (Professor Egil Arnesen, personal communication, Institute of Community Medicine, University of Tromsø).

From 1994 onwards, there has been a considerable increase in sales of LLDs in all Scandinavian countries, and in Norway in particular (Figure 1) [8, 9]. The statins constituted 99.5% of total LLD sales in 2002. In the municipality of Tromsø, north Norway, LLD sales are higher than the average in Norway. In 2002, the LLD sales in Tromsø corresponded to 277 defined daily doses (DDD)/1000 inhabitants per day in the adult population aged over 50 years, compared with 266 DDD/1000 inhabitants per day in Norway [8].

Most studies evaluating LLD use are based on prescriptions [10, 11], sales statistics [12] or case records which allow linkage of data on LLD use to documented heart disease status [13–16]. However, only a few population studies have been performed [17–20]. Information is limited

about the characteristics of LLD users in the general population, and management of LLD in primary prevention in particular. We used data from the Tromsø Study to provide a cross-sectional description of LLD use in a general population according to socio-demographic factors, cardiovascular risk factors and established CHD, and to study whether the nationally recommended cholesterol goals were achieved in the LLD users.

Subjects and methods

The Tromsø Study is a repeated population-based study in the municipality of Tromsø, situated at 69°N (current population 63 000). About half of the inhabitants are employed in tertiary services (public and private sector) [21]. Fisheries and commerce represent other important sources of income. The fifth Tromsø study was conducted in 2001 by the Institute of Community Medicine, University of Tromsø, in collaboration with the Norwegian Institute of Health (previously the National Health Screening Service), and was primarily designed to explore drug use, risk factors and chronic diseases in individuals. In 1994, all inhabitants aged 55–74 years and 5–10% of samples in other age groups were invited to an extensive examination (attendance rate 77.0%). Of these, all subjects still residing in Tromsø in 2001 were invited to the fifth survey (n = 7413). In addition, all inhabitants aged 30, 40, 45, 60 and 75 years in 2001 were invited, making up a total of 10 421 invited people. The attendance rate was 78.1%. The present cross-sectional analysis includes 7973 of the attendants: 3434 (43.1%) men and 4539 (56.9%) women. Individuals who had stroke as the only self-reported cardiovascular disease (n = 170) were excluded because of the inability to classify according to stroke subtype [22]. The mean age was 59.5 years, and 60.5% of the participants were aged over 60 years.

The screening consisted of self-administered questionnaires, clinical measurements and laboratory tests, similar to previous screenings [23]. The questionnaire included questions on socio-demographic factors (years of education), previous myocardial infarction (MI) (yes/no),

prevalent angina pectoris (yes/no), current diabetes (yes/no) and cigarette smoking (yes/previously/no). This was enclosed in the letter of invitation and collected at the following visit, where height, weight, blood pressure and blood samples were collected. The body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in metres, and categorized in weight classes according to the WHO classification [24]. Trained personnel recorded the blood pressure with an automatic device (Dinamap Vital Signs Monitor, Tampa, FL). Non-fasting total cholesterol and triglyceride levels were analysed using standard enzymatic methods at the Department of Clinical Chemistry, University Hospital of North Norway.

As only non-fasting blood samples were available, which influence the triglyceride concentration, and thereby the estimation of LDL-cholesterol concentration from Friedewald's formula [25], we defined the lipid treatment goal as a total cholesterol level ≤ 5.0 mmol/l.

Diabetes was defined by self-report of having diabetes or use of an anti-diabetic drug (ATC group A10). Similarly, angina pectoris was defined by self-report of angina pectoris or use of nitrates (ATC group C01D). Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [26] or a self-report of current antihypertensive treatment.

In line with the National Cholesterol Guidelines [6], the population was stratified into three subgroups according to risk of cardiovascular disease:

1. Established CHD: subjects with angina and/or myocardial infarction
2. Risk condition: subjects with diabetes and/or hypertension
3. Presumed healthy: subjects reporting no established CHD or risk condition

This produced two groups for the study:

1. Eligible primary prevention group: subjects with risk condition and total cholesterol ≥ 5.0 mmol/l, and presumed healthy subjects with total cholesterol ≥ 8.0 mmol/l
2. Eligible secondary prevention group: subjects with established CHD.

The proprietary names of medicines used regularly during the 4 weeks preceding the study were reported on the questionnaire and registered on the fifth level of the Anatomical Therapeutic Chemical (ATC) system, version 2000 [8]. In addition the questionnaire included a predefined question with answering categories (yes/previously/no) on the use of LLDs, antihypertensive drugs and blood sugar-lowering drugs. Subjects reporting either a proprietary name of LLD (ATC group C10) and/or current LLD use were included as LLD user in the analysis. The answers 'previously' (*n* = 105) and 'missing' (*n* = 262), together with no proprietary name of a LLD reported, were categorized as 'no' in the LLD use categories. Analysis of LLD use, excluding those with missing data on LLD use, did not change the results significantly.

Statistical analysis

Logistic regression analysis was used to calculate age-adjusted odds ratios (ORs) and their 95% confidence intervals (95%CIs) for LLD use in relation to socio-demographic factors, cardiovascular risk factors and CHD. Multivariable logistic regression was used to identify predictors of LLD use in general. We chose to analyse the predictors of use separately for primary (no CHD) and secondary (CHD present) prevention with adjustment for age, length of education, BMI, smoking status, hypertension and diabetes. The SAS software package SAS Institute Inc., version 8 was used.

Ethics

Approval was granted by the Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics in Northern Norway. Participants gave written, signed, informed consent.

Results

In the total study population, 14.0% of the men and 9.6% of the women reported LLD use (Table 1). A total of 648 (19.0%) men and 711 (15.8%) women had total cholesterol levels at or below the recommended 5.0 mmol/l. Among these, the percentages of LLD users were 33.5% and 16.6% in men and women, respectively (Table 1). LLD use decreased with increasing total cholesterol level. Among all LLD users, 36.9% had achieved the nationally recommended lipid goal of total cholesterol ≤ 5mmol/l – 45.6% of the male and 27.4% of the female LLD users, respectively.

A total of 16.6% and 8.0% of all men and women reported CHD, respectively (Table 1). About half of the remaining men and women had a risk condition (diabetes and/or hypertension), with no gender differences. In the CHD subgroup, only 55.4% of the men and 49.9% of the women were LLD users. Only 40.0% of the men and 22.6% of the women with CHD had total cholesterol levels below the recommended 5.0 mmol/l. Interestingly, a few subjects in this secondary prevention group – 2.7% men and 7.2% women – had total cholesterol > 8.0 mmol/L. A minority of these were LLD users (Table 1).

Among subjects reporting a previous MI , users of LLDs reported their MI to be somewhat closer in time compared with the non-users: 8.6 compared with 11.2 mean years ($p = 0.0007$). No such difference was found among those reporting angina pectoris (data not shown).

In the risk condition subgroup, LLD use decreased with increasing cholesterol level. Only 12.5% of the men and 7.3% of the women had total cholesterol levels below the recommended 5.0 mmol/l (Table 1). Among subjects with total cholesterol levels > 8.0 mmol/l, only 8.0% of the men and 5.9% of the women were LLD users (Table 1).

In the presumed healthy subgroup, 3.6% of the men and 6.2% of the women had cholesterol > 8.0 mmol/l. In this treatment-eligible group, the proportion of LLD users was very low (Table 1).

Altogether, the percentage of subjects eligible for the primary prevention group constituted 47.2% of the study population without CHD. LLD use was low in this group: 7.4% in men and 8.0% in women, respectively

Table 2 presents predictors for LLD use among all participants, stratified by gender. LLD use was positively associated with age, self-reported CHD and the presence of major cardiovascular risk factors apart from smoking. By contrast, LLD use was significantly higher among ex-smoking men compared with never smokers (OR = 1.52, 95%CI = 1.18–1.99), and was negatively associated with length of education in both genders (Table 2).

In Table 3 we analysed the predictors for LLD use in the primary and secondary prevention subgroups. The multivariable analysis in people with no CHD showed that hypertension, diabetes, increasing BMI, decreasing level of education and older age were predictors of LLD use among women (Table 3). Hypertension and diabetes were the only significant predictors among men. Among those with CHD, younger age was the significant predictor of LLD use in both genders (Table 3).

Discussion

It is widely accepted that LLDs should be used in secondary prevention of cardiovascular diseases. The fact that only 50% of the subjects with CHD were taking an LLD and, further, that only one in three achieved the recommended lipid target are matters for concern. Our findings correspond to a comparatively low treatment rate among patients with CHD observed in general practice in Norway in 1997 [13]. In view of the threefold increase in sales of LLDs in Norway since then, the low LLD use in this treatment-eligible group was not expected [8]. However, LLD users reported having had an MI more recently than non-users, and the low treatment rate could be explained partly by factors such as failure to prescribe LLDs to symptom-free individuals who had an MI many years before, and problems with long-term adherence to treatment, which is common in clinical practice [27]. To ensure appropriate cholesterol management in accordance with guidelines in this treatment-eligible group, the presumed high level of attention given to cardiovascular disease as a result of repeated screenings of the Tromsø population, and subsequent feedback to health practitioners, is evidently not sufficient.

This study identifies a large discrepancy between guidelines for LLDs in primary prevention and clinical practice. As much as 47.2% of our study population without CHD had elevated levels of total cholesterol. Only a minority of these were on LLD therapy. If the guidelines were to be followed, this would imply a more aggressive primary prevention strategy, including LLD use in cases where total cholesterol targets are not achieved by dietary intervention alone.

Only a third of all LLD users achieved the guideline-defined total cholesterol target. This phenomenon has been documented in other studies [14, 15, 28, 29], and may be caused by an inadequate upward adjustment of dose after initiation of LLD treatment [28]. In a study from

primary care, a higher mean pre-treatment total cholesterol level was observed in unselected subjects in primary care compared with those included in randomized controlled trials [29] – a mean pre-treatment total cholesterol level of 7.12 mmol/l was seen among simvastatin users compared with 6.75 mmol/l in subjects included in the landmark Scandinavian Simvastatin Survival (4S) Study [1]. However, target lipid goals defined by the guidelines might be achieved with a higher dose of an LLD, and subsequently a greater percentage reduction in total cholesterol levels compared with clinical trials [30, 31]. The study by Hippisley-Cox et al. in primary care found that, despite not achieving the total cholesterol target level, the percentage lowering of total cholesterol levels by LLDs corresponded to that in randomized controlled trials, indicating probable benefits [29]. The issue of whether the total cholesterol level reduction should be a steering tool for practitioners for reaching a fixed cholesterol value should be a matter for revised national guidelines.

A limitation of this cross-sectional study is that it is gives no information about lipid values before the initiation of LLD use. We do not know the pre-treatment level or the absolute cholesterol reduction for those under treatment. Also, a limitation is that the socio-demographic, morbidity and drug use variables are based on self-reports. The formulation of questions on morbidity and drug use in the questionnaire used in this study has, however, been used in other surveys performed by the Norwegian Institute of Health. Validation of questionnaire information from these comparable surveys has shown agreement with medical records for prevalent diabetes (96%), MI (81%), current drugs for hypertension (97%), insulin (95%) and oral anti-diabetics (100%) [32, 33]. These results are in agreement with other studies that show accurate recall of medical and drug use history for well-defined chronic conditions, including angina pectoris [34, 35]. No validation has been performed in this study with regard to self-report of LLD use. However, 85% of those reporting current LLD use also reported a proprietary LLD in another part of the questionnaire, which consolidates the information on

LLD use. Previous validation studies have shown high reliability (86–87%) for the self-reported use of cardiovascular drugs as a classification of treatment status of subjects in population-based studies [36, 37].

The strength of this study is the population-based setting, and we have information on both users and non-users of LLD. The study describes LLD use in presumably healthy individuals, who are not registered in either pharmacy or medical records. Another strength is the inclusion of clinical measurements such as total cholesterol level, blood pressure, weight and height.

Ongoing LLD treatment of only half of all the subjects with CHD should be a matter of concern. Strategies leading to improved LLD treatment among individuals with CHD have been identified and include initiation of statin therapy in hospital [38, 39], ongoing reminders during visits to the doctor in primary health care, and community pharmacist intervention programmes on cholesterol risk management [40]. Furthermore, our study demonstrates a wide gap between clinical practice and guidelines for intervention in cases of hypercholesterolaemia. Actual adherence to current guidelines in an elderly population such as this one, with relatively high levels of total cholesterol, would imply a heavy load on the health-care system. To what extent the health-care system should prioritize LLD therapy for primary prevention should therefore be a matter for discussion in future revisions of national guidelines.

In conclusion, this study identifies a gap between guidelines for the management of cholesterol and clinical practice. Among people without CHD, 47% had a serum cholesterol levels above the recommended level, and only a minority of these were on LLD therapy. Only half of those reporting CHD were on LLDs. Only a third of all LLD users had achieved nationally recommended lipid goals. All these findings are a matter for concern.

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Figures

Figure 1. Sales of lipid-lowering drugs (ATC C10) in the Scandinavian countries 1995–2002 [8, 9].

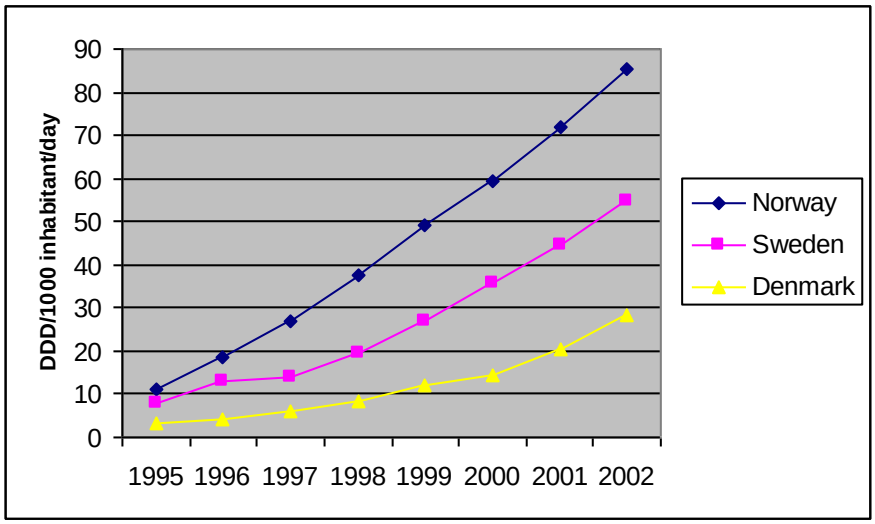

Table 1. The proportion of LLD users according to risk groups, gender and serum cholesterol – the Tromsø Study 2001

Serum	Total population				Established CHD				Risk conditions*				None			
cholesterol	Men		Women		Men		Women		Men		Women		Men		Women	
mmol/L	n	(% LLD)	n	(% LLD)	n	(% LLD)	n	(% LLD)	n	(% LLD)	n	(% LLD)	n	(% LLD)	n	(% LLD)
≤ 5 .0	648	(33.5)	711	(16.6)	209	(83.3)	81	(90.1)	180	(19.4)	141	(22.7)	255	(2.8)	466	(1.5)
5.1 - 5.9	1104	(13.3)	1193	(12.7)	167	(54.5)	97	(60.8)	467	(9.9)	434	(14.1)	465	(2.2)	626	(3.8)
6.0 - 6.9	1023	(7.2)	1366	(7.8)	134	(27.6)	95	(34.7)	456	(5.5)	650	(8.8)	423	(2.4)	582	(2.4)
7.0 - 7.9	473	(5.5)	856	(4.1)	40	(17.5)	60	(15.0)	250	(7.2)	472	(4.0)	178	(0.6)	291	(2.1)
≥ 8.0	162	(8.1)	388	(5.2)	15	(26.7)	26	(19.2)	88	(8.0)	222	(5.9)	56	(3.6)	129	(1.6)
Total	3408	(14.0)	4514	(9.6)	565	(55.4)	359	(49.9)	1441	(9.1)	1919	(9.5)	1377	(2.2)	2094	(2.5)

CHD, coronary heart disease; LLD, lipid-lowering drug.
*Risk conditions: hypertension and/or diabetes.
Numbers may vary as a result of missing values.

Table 2. The proportion of LLD users and the risk (OR and 95%CI) of being an LLD user according to socio-demographic factors, cardiovascular risk factors and established CHD – the Tromsø Study 2001

	Women					Men				
Factor	*n*	(% LLD)	OR	95%CI	*p*	*n*	(% LLD)	OR	95%CI	*p*
Age (years)										
< 50	1184	(0.8)	0.09	(0.04–0.18)		898	(2.0)	0.09	(0.05–0.15)	
50–59	712	7.8)	1	(ref.)		356	(19.1)	1	(ref.)	
60–69	1423	(13.4)	1.81	(1.33–2.48)		1215	(17.6)	0.92	(0.68–1.24)	
70+	1219	(14.5)	2.00	(1.46–2.75)	**	965	(19.0)	0.97	(0.71–1.31)	**
Total	4539	(9.6)				3434	(14.0)			
Education (years)										
≤ 9	2110	(13.9)	1	(ref.)		1403	(18.5)	1	(ref.)	
10–12	1015	(7.5)	0.76	(058–0.99)		937	(12.8)	0.86	(0.67–1.09)	
> 12	1203	(3.6)	0.49	(0.44–0.70)	**	952	(8.4)	0.68	(0.51–0.90)	**
Smoking										
Yes	1263	(8.2)	1.08	(0.84–1.40)		969	(10.6)	1.00	(0.74–1.36)	
Previously	1272	(10.2)	1.12	(0.88–1.42)		1555	(18.7)	1.52	(1.18–1.99)	*
Never	1968	(9.9)	1	(ref.)		886	(9.7)	1	(ref.)	
BMI (kg/m^2)[a]										
≤ 18.0	64	(7.8)	0.87	(0.34–2.23)		11	(9.1)	0.58	(0.07–4.59)	
18.1–24.9	1794	(6.4)	1	(ref.)		1058	(9.6)	1	(ref.)	
25.0–29.9	1716	(9.4)	1.21	(0.94–1.56)		1709	(15.0)	1.65	(1.29–2.10)	
≥ 30.0	936	(15.8)	2.05	(1.58–2.66)	**	627	(18.5)	2.23	(1.67–2.97)	**
Hypertension[b]										
No	2282	(4.3)	1	(ref.)		1676	(7.4)	1	(ref.)	
Yes	2250	(14.8)	2.31	(1.79–2.99)	*	1848	(19.7)	2.13	(1.69–2.70)	*
Diabetes[c]										
No	4270	(8.6)	1	(ref.)		3286	(12.9)	1	(ref.)	
Yes	175	(33.1)	3.69	(2.62–5.19)	*	169	(38.5)	3.43	(2.47–4.80)	*
Angina pectoris[d]										
No	4089	(6.6)	1	(ref.)		2987	(8.3)	1	(ref.)	
Yes	304	(47.4)	8.56	(6.54–11.20)	*	399	(54.9)	11.55	(9.06–14.72)	*
Myocardial infarction										
No	4250	(7.6)	1	(ref.)		3047	(8.7)	1	(ref.)	
Yes	144	(61.1)	12.26	(8.52–17.63)	*	352	(59.1)	12.01	(9.31–15.49)	*

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; LLD, lipid-lowering drug; OR, odds ratio; all variables adjusted for age except age groups.
Numbers may vary as a result of missing values
*$p < 0.05$.
**p trend < 0.05.
[a]WHO classification.
[b]Hypertension: systolic BP ≥ 140 and/or diastolic BP ≥90 mmHg or reporting to be on treatment for hypertension.
[c]Diabetes: self-reported diabetes and/or self-reported use of an anti-diabetic drug (ATC group A10).
[d]Angina pectoris: self-reported angina pectoris or self-reported use of nitrate (ATC group C01D).

Table 3. Multivariably adjusted odds ratios (ORs) and their 95% confidence intervals for LLD use in subjects with and without CHD – the Tromsø study 2001

	No CHD (primary prevention)				CHD (secondary prevention)			
	Women (n = 3839)		Men (n = 2721)		Women (n = 330)		Men (n = 508)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age (10 years)	1.23	(1.06–1.43)*	1.03	(0.88–1.21)	0.54	(0.38–0.78)*	0.51	(0.38–0.67)*
Education (years)[a]	0.76	(0.62–0.92)*	0.92	(0.76–1.12)	0.94	(0.74–1.18)	1.08	(0.89–1.31)
BMI[a]	1.26	(1.10–1.43)*	1.09	(0.93–1.29)	1.07	(0.85–1.34)	1.05	(0.86–1.29)
Smoking								
Never	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Previously	1.17	(0.84–1.61)	1.17	(0.76–1.79)	0.99	(0.59–1.66)	0.91	(0.54–1.54)
Yes	1.06	(0.73–1.54)	0.93	(0.57–1.52)	0.86	(0.47–1.59)	0.73	(0.39–1.38)
Prevalent co-morbidity								
Hypertension	2.16	(1.52–3.07)*	3.19	(2.07–4.92)*	1.42	(0.83–2.43)	1.51	(1.00–2.28)
Diabetes	3.69	(2.27–5.97)*	6.04	(3.69–9.87)*	1.24	(0.62–2.45)	0.86	(0.48–1.55)

*$p < 0.05$.

BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; LLD, lipid-lowering drug; OR, odds ratio.

[a]Unit equals one standard deviation.