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Contemporary lipid clinic and achievements in low-density lipoprotein-cholesterol reductions in very high-risk patients

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ABSTRACT

INTRODUCTION: Numerous studies have shown that lowering of low-density lipoprotein-cholesterol (LDL-C) reduces the risk of cardiovascular disease (CVD). To optimise treatment, some patients are referred to a lipid clinic. The reduction in LDL-C achieved in a lipid clinic in contemporary practice is, however, not well described. The aim of the present study was to assess the LDL-C lowering effect among very high-risk patients with or without statin-associated muscle symptoms (SAMS) after treatment at a specialised lipid clinic endorsing European guidelines.

METHODS: Medical records from 653 patients referred to our Lipid Clinic from 1 January 2013 to 1 May 2017 were examined retrospectively. Very high-risk patients were defined as either having CVD or diabetes mellitus Type 2 who were active smokers and/or had hypertension. The reduction in LDL-C and the number of patients reaching the LDL-C treatment target were investigated by comparing baseline data with the most recent values recorded.

RESULTS: We identified 208 patients at a very high-risk for CVD. They obtained an LDL-C reduction of 23% corresponding to a reduction in LDL-C of 0.7 mmol/l ($p < 0.001$). The percentage of patients reaching their LDL-C goal increased from 13% to 32%. In patients who had experienced SAMS, LDL-C was reduced by 26% corresponding to a reduction in LDL-C of 0.9 mmol/l ($p < 0.001$), and the percentage of patients reaching their LDL-C goal increased from 8% to 23%.

CONCLUSIONS: Very high-risk patients with or without SAMS obtained a clinically meaningful reduction in LDL-C of approximately 25% owing to their Lipid Clinic treatment.

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Cardiovascular disease (CVD) remains a leading cause of morbidity and death worldwide [1]. CVD is mainly caused by atherosclerosis with the most common clinical manifestations being ischaemic heart disease (IHD), ischaemic stroke and peripheral artery disease (PAD). The principal driver of atherosclerosis is subendothelial retention of apolipoprotein-B-containing lipoproteins, especially low-density lipoprotein cholesterol (LDL-C). Patients with established CVD, diabetes mellitus (DM) and chronic kidney disease are known to be at a high or very high-risk of future CVD events [2-4]. The risk of CVD in these subjects may be increased by up to five fold compared with low-risk patients [5]. In both primary and secondary prevention of CVD, it is therefore crucial to lower LDL-C to reduce the risk of CVD [2, 6-12]. In some patients, it can be challenging to reach the individual

LDL-C goal due to statin intolerance, including statin-associated muscle symptoms (SAMS), or an inadequate response to treatment [7]. In Denmark, patients who are difficult to treat can be referred to a lipid clinic for specialised evaluation, but the effectiveness of this approach remains unknown. The reduction in LDL-C achieved in a lipid clinic in contemporary practice is, however, not well described. We hypothesised that a lipid clinic is an effective clinical unit, and the aim of the study was to assess the LDL-C lowering effect among very high-risk patients with or without SAMS after treatment at a lipid clinic endorsing European Guidelines.

METHODS

Study design

Medical records from 653 patients referred to the Lipid Clinic at Viborg Regional Hospital, Denmark, from 1 January 2013 to 1 May 2017 were examined. The patients were referred to the Lipid Clinic from general practitioners or hospital physicians. Causes for referrals were hypercholesterolaemia, dyslipidaemia, statin intolerance, hypertriglyceridaemia or general evaluation of lipid status.

Patient evaluation

LDL-C level was measured prior to the first and latest visit. The highest registered LDL-C level was also noted. For each patient, the type of lipid-lowering therapy (LLT) at the first and latest visit was noted. For some patients, the latest visit was the final visit, whereas other patients had further planned visits in the Lipid Clinic. Thus, the study was cross-sectional and the latter group of patients was not in maximal tolerated LLT. It was noted if a patient experienced SAMS defined as the patient's experience of myalgia with or without creatinine kinase elevation associated with statin treatment. SAMS was noted only if myalgia occurred repeatedly with statin treatment and disappeared when treatment was discontinued [13]. Cardiovascular risk was determined by the presence of DM and/or CVD, as registered based on The International Classification of Disease codes for DM and CVD in the patients' medical records. In few cases of diagnostic doubt, data were controlled in The National Health Records. CVD was defined as patients who had IHD, stroke and PAD.

The first visit in the clinic consisted of 30 minutes of conversation with a lipid nurse about any family history of CVD and optimisation of lifestyle factors including exercise, healthy diet education, reduction of alcohol consumption and smoking cessation, if relevant. The same day, the patient was examined by a doctor who educated the patient about their disease and adjusted his or her LLT. The typical follow-up regime included visits 1.5, 4.5, 9.5 and 21.5 months after the first visit. Additional visits were planned as necessary. In patients treated with a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor, the follow-up regime included visits one, four, seven and 13 months after the first visit. Hereafter, the patients visited the clinic every six months. At the follow-up visits, the lifestyle interventions and effects of LLT as well as potential side effects were evaluated. If necessary, adjustments were made to the treatment. Each patient was followed until the optimal tolerated treatment was achieved or until the patient did not want to try another treatment regimen. Thus, the observation time varied for each patient. Patients with only one visit in the clinic were excluded from this study.
The study was approved by the Danish Data Protection Agency (Ref:1-16-02-696-16) and the Danish Patient Safety Authority.

Definition of very high-risk

Patients at very high risk of CVD were defined according to the European Society of Cardiology (ESC) guidelines of 2016 as patients who had established CVD or had DM Type 2 in combination with another high-risk factor such as active smoking and/or hypertension [14].

Outcome

The primary outcome was reduction of LDL-C in the very high-risk patients with or without SAMS. The secondary outcome was the proportion of patients who achieved their LDL-C goal of < 1.8 mmol/l. The LDL-C goals were in line with the national cardiovascular guidelines in 2018, which were based on endorsed ESC guidelines [14].

Statistical analysis

Patient groups were tested for normality with the D'Agostino-Pearson omnibus K2 normality test. To compare the before and after results, a Wilcoxon matched-pairs signed-rank test was used. When comparing two non-related subgroups, a Mann Whitney test was used. Statistical analyses were made.

Trial registration: not relevant.

RESULTS

All patients

Data from 653 patients were collected of whom 57 were excluded due to missing data. Thus, the study included 596 patients, among whom 282 were males and 314 females. Baseline characteristics are shown in **Table 1**. There were 148, 39 and 21 patients diagnosed with IHD, stroke and PAD, respectively. Three patients had DM Type 1 and 74 patients had DM Type 2.

The reduction in LDL-C for all patients was 19.4%, corresponding to a reduction in LDL-C of 0.7 mmol/l ($p < 0.001$). The absolute reduction in LDL-C was equally improved in male and female patients. Approximately 30% of the patients had experienced SAMS at some point. The percentage of patients in LLT increased from 53% to 80%. Triglyceride (TG) and high-density lipoprotein (HDL) levels were unchanged between the first and latest visit.

TABLE 1 Baseline characteristics of the study population.

	Male (N_m = 282)	Female (N_f = 314)	All (N_{tot} = 596)
Age, mean ± SD, yrs	51.5 ± 13.3	55.4 ± 14.9	53.4 ± 14.3
Current smoker, n	57	56	113
Hypertension, n	96	112	208
Concentration of low-density lipoprotein-cholesterol			
Median (IQR), mmol/l:			
1st visit	3.5 (2.5-4.6)	3.8 (2.7-4.7)	3.6 (2.6-4.7)
Latest visit	2.4 (1.8-3.4)	2.8 (2.1-3.8)	2.6 (1.9-3.6)
Highest	5.1 (4.3-5.9)	5.3 (4.6-6.1)	5.2 (4.4-6.0)
Relative reduction, %	20	18.4	19.4
Total relative reduction, %	45.1	45.3	46.2
Absolute reduction, (IQR), mmol/l:			
Median	0.7 (0.1-1.7)***	0.7 (0.0-1.8)***	0.7 (0.0-1.7)***
Total, median	2.3 (1.2-3.4)	2.4 (1.2-3.4)	2.4 (1.2-3.4)
Statin-associated muscle symptoms, n (%)	87 (30.8)	92 (29.3)	179 (30.0)
Lipid-lowering therapy, n (%)			
1st visit	158 (56.0)	155 (49.4)	313 (52.5)
Latest visit	234 (82.3)	242 (77.1)	476 (79.9)

IQR = interquartile range; SD = standard deviation.
***) p < 0.001.

Very high-risk patients

A total of 208 patients were identified as being at a very high risk of CVD. In these patients, LDL-C was reduced by 22.6%, corresponding to a reduction in LDL-C of 0.7 mmol/l (p < 0.001), **Table 2**. At the latest visit, 32.2% reached their LDL-C goal and the percentage of patients in LLT increased from 70.2% to 88.5%. Compared with their highest LDL-C ever measured, they achieved a 49% reduction at the latest visit. The very high-risk patients in LLT compared with those without LLT at the first visit experienced a LDL-C reduction of 0.6 (0.1-1.5) mmol/l and 1.1 (0.1-2.1) mmol/l, corresponding to a relative reduction of 21.2% and 26.2% (p < 0.001), respectively. The reduction in LDL-C was significantly higher in the latter group. The TG and HDL levels were unchanged between the first and latest visit.

TABLE 2 Achieved reductions of concentration of low-density lipoprotein-cholesterol in patients at very-high risk for cardiovascular disease (N = 208).

Concentration of low-density lipoprotein-cholesterol	
Median (IQR), mmol/l:	
1st visit	3.1 (2.2-4.1)
Latest visit	2.2 (1.6-3.0)
Highest	4.9 (3.9-5.8)
Concentration goal reached, n (%):	
1st visit	27 (13.0)
Latest visit	67 (32.2)
Relative reduction, %	22.6
Total relative reduction, %	49
Absolute reduction, (IQR), mmol/l:	
Median	0.7 (0.1-1.6)***
Total, median	2.4 (1.5-3.6)
Lipid-lowering therapy, n (%)	
1st visit	146 (70.2)
Latest visit	184 (88.5)

IQR = interquartile range.
***) $p < 0.001$.

Very high-risk subgroups with or without statin-associated muscle symptoms

Among the very high-risk patients, 90 had experienced SAMS. They had a reduction in LDL-C of 0.9 mmol/l, which was the same as the subgroup without SAMS ($p = 0.17$). The reduction in LDL-C was significant in both subgroups ($p < 0.001$), **Table 3**. At the latest visit, the LDL-C level was significantly lower in the subgroup without SAMS than in the subgroup with SAMS ($p = 0.002$). Patients reaching their LDL-C goal increased to 23.3% and 42.4% in the subgroups with and without SAMS, respectively. Compared with their highest LDL-C ever measured, a reduction of about 50% was achieved in both subgroups. The percentage of patients in LLT increased from 51.1% to 84.4% and from 84.7% to 91.5% in the subgroups with and without SAMS, respectively. In the subgroup with SAMS, 41.1% were treated with statins at the first visit, increasing to 65.6% at the latest visit. Among the remaining patients, 12.2% and 6.7% were in monotherapy with either a PCSK9 inhibitor or ezetimibe, respectively. In the subgroup without SAMS, 88.1% were in statin treatment at their latest visit. In patients without SAMS, the TG and HDL levels were unchanged between the first and latest visit. In patients with SAMS, the HDL level was unchanged, but a significant increase in the median TG level from 1.6 (1.8-2.6) mmol/l to 2.0 (1.2-2.8) mmol/l was observed between the first and latest visit ($p = 0.049$).

TABLE 3 Achieved reductions of concentration of low-density lipoprotein-cholesterol in patients at very high-risk, with and without statin-associated muscle symptoms.

	+ SAMS (N = 90)	– SAMS (N = 118)
Concentration of low-density lipoprotein-cholesterol		
Median (IQR), mmol/l:		
1st visit	3.5 (2.6-4.3)	2.7 (2.1-3.8)
Latest visit	2.5 (1.8-3.2)	2.0 (1.4-2.8)
Highest	5.0 (4.1-5.8)	4.8 (3.8-5.7)
Concentration goal reached, n (%):		
1st visit	7 (7,8)	20 (16.9)
Latest visit	17 (23.3)	50 (42.4)
Relative reduction, %	25.7	18.5
Total relative reduction, %	48	56.3
Absolute reduction, (IQR), mmol/l:		
Median	0.9 (0.2-1.8)***	0.5 (0.1-1.5)***
Total, median	2.4 (1.5-3.4)	2.7 (1.5-3.7)
Lipid-lowering therapy, n (%)		
1st visit	46 (51.1)	100 (84.7)
Latest visit	76 (84.4)	108 (91.5)

IQR = interquartile range; SAMS = statin-associated muscle symptoms.
***) $p < 0.001$.

DISCUSSION

Our study emphasises the importance of a lipid clinic in managing patients with uncontrolled LDL-C. Improved lipid profiles were observed both in patients with and without SAMS. The patients in our study were a highly selected group of patients whom their own general practitioner or hospital physicians had found it difficult to treat and achieve individual LDL-C goals in line with guidelines. The LDL-C reduction in the very high-risk patients was 22.6%. However, compared with the highest LDL-C ever measured, LDL-C was reduced by 49% at the latest visit to the Lipid Clinic. This is close to what can be obtained by treatment with high-intensity statins and reflects both patients who have started LLT, changed from low- to high-intensity statin, are up-titrated in statin dose or have had ezetimibe or a PCSK9 inhibitor added [15, 16]. A meta-analysis made by the Cholesterol Treatment Trialists estimated a 22% annual risk reduction for major vascular events and CVD death by each 1.0 mmol/l reduction in LDL-C [2]. Thus, as the very high-risk patients in our study achieved an LDL-C reduction of 0.7 mmol/l, this is expected to lower their CVD risk by approximately 15%. In total, including their highest LDL-C recorded, these patients had their LDL-C reduced by about 2.4 mmol/l, corresponding to a 50% lower risk of

CVD.

The optimised treatment regimes organised in the Lipid Clinic increased the percentage of very high-risk patients who reached their LDL-C goal from 13% to 32.2%, and LDL-C was lowered by 0.7 mmol/l. This was achieved mainly by optimised medication as described above, but also by educating the patients by raising their understanding of their disease (hyperlipidaemia and atherosclerosis), leading to better compliance and an optimised lifestyle.

Despite the optimised treatment and lifestyle education, a large percentage of the patients in our study did not reach their LDL-C goal. The data are cross-sectional, and many patients are therefore still in the process of optimising their treatment. This may explain why many of the patients had not reached their LDL-C goal at the latest visit. We wondered if patients who experienced SAMS would have a lower reduction in LDL-C, hence not reaching their treatment goal. Comparing the very high-risk patients with and without SAMS, we found that the percentage of patients in LLT almost matched each other at the latest visit; however, patients who had experienced SAMS consumed fewer statins. At the latest visit, patients without SAMS had a significantly lower LDL-C and more had reached their LDL-C goal than among patients with SAMS. Thus, our results indicate that patients who have experienced SAMS are more challenging to treat and that SAMS may be a contributing factor to the low percentage of patients reaching their LDL-C goal. However, through the specialised treatment and education in a lipid clinic, they can obtain reductions in LDL-C similar to results observed in patients without SAMS.

The majority of the patients in our study were treated before the spring of 2017, and the use of PCSK9 inhibitors was therefore not a treatment option. From the spring of 2017 and onwards, the Lipid Clinic had the option to use PCSK9 inhibitors in highly selected very high-risk patients who had an inadequate treatment response – or who had intolerance to statin/ezetimibe. Only 22 of the 596 included patients were started on a PCSK9 inhibitor. However, several of our patients not reaching their LDL-goal are probably now candidates for treatment with PCSK9 inhibitors in pursuance of current guidelines. Future treatment, including reimbursement rules for PCSK9 inhibitors, will be influenced by the 2019 ESC/European Atherosclerosis Society treatment guidelines [17]. These guidelines have just been endorsed by the Danish Cardiologic Society and implemented in the national Danish cardiovascular guidelines 2020.

Limitations

The performance of the Lipid Clinic in reducing LDL-C found in this study is a clear underestimate. First, some patients ended their course of treatment in the Lipid Clinic before the most efficient treatment was found. Second, we know that many of the patients are still being followed in the clinic and their LDL-C level at the latest visit was therefore measured while they were in the process of optimising their treatment. The full effect of the Lipid Clinic is therefore expected not yet to have been obtained in these patents. From the existing data, it was not possible to see how many patients are still being followed in the clinic. Third, the use of PCSK9 inhibitors was only possible in the last few months of the data collection period. Thus, several candidates for PCSK9 inhibitor treatment may have had their final visit in the Lipid Clinic before it was possible for them to initiate such treatment.

Our data did not allow for evaluation of treatment effects over time.

In 2020, new guidelines have been published, and the treatment targets have been adjusted. The percentage of patients reaching their treatment target in our study is therefore not directly comparable to the new guidelines.

CONCLUSIONS

Very high-risk patients with or without SAMS who were treated in the Lipid Clinic had a reduction in LDL-C of

approximately 25%. This is an underestimate of the true efficiency of the Lipid Clinic, since not all patients were evaluated at their final visit and some were still being up-titrated in terms of treatment intensity. Thus, our hypothesis that the Lipid Clinic is an effective clinical unit for treating complex lipid patients, including those with SAMS is confirmed. This study demonstrates that a lipid clinic in contemporary practice can provide meaningful and important reductions in LDL-C levels among very high-risk patients who are difficult to treat by non-specialists.

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