

# LDL GOAL ACHIEVEMENT IN CHRONIC CORONARY HEART DISEASE PATIENTS: A COMPARISON BETWEEN USUAL CARE AND A STRUCTURED FOLLOW-UP PROGRAMME IN 766 CONSECUTIVE PATIENTS IN CARDIOLOGY PRACTICE

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## *Background*

The LDL cholesterol (LDL-C) goal achievement in patients with coronary heart disease (CHD), as recommended by Guidelines, is generally low.

## *Objective*

We sought to compare the outcomes of two different strategies in chronic CHD patients remitted from general practitioners to an out-of-hospital cardiology practice, one conventional follow-up (CFU) and one structured follow-up (SFU).

## *Methods*

All 302 consecutive patients with angiographically documented CHD seen during one year were reviewed and lipid levels after one cardiologist consultation were collected retrospectively the following year (CFU). During the two succeeding years, all 464 patients with this diagnosis were followed prospectively in the cardiology practice in a simple, structured manner until LDL-C  $\leq 2.0$  mmol/L was reached, using more potent statins and with the addition of ezetimibe if baseline LDL-C was  $\geq 2.5$  mmol/L or if a potent statin did not reduce the LDL-C level to  $\leq 2.0$  mmol/L (SFU).

## *Results*

At baseline, only 1/3 of all patients had LDL-C  $\leq 2$  mmol/L. After CFU this increased to 59%, while following the SFU programme 90% reached this goal. The mean LDL-C levels decreased from 2.4 to 2.2 mmol/L after CFU and from 2.5 to 1.8 mmol/L in the SFU group, all differences significant at  $p < 0.001$ .

## *Conclusion*

A simple structured follow-up programme in out-of-hospital cardiology practice can bring 90 % of these patients to a LDL-C level of 2.0 mmol/L or lower, which was the goal at the time of start of this programme, with the use of more potent statins and the addition of ezetimibe when needed.

At the time of the start of the present study, the 2007 European Society of Cardiology/ European Atherosclerosis Society (ESC/ EAS) guidelines on cardiovascular disease prevention [1] stated that patients with documented coronary heart disease (CHD) should have total cholesterol <4.5 mmol/L and LDL cholesterol (LDL-C) <2.5 mmol/L, or < 4.0 and <2.0 «if feasible». In the EURO-ASPIRE I, II and III studies, the percentage of CHD patients with total cholesterol above 4.5 mmol/L decreased from 95 % in the first period to 77% and then to 46 % in the last period during 2006-2007 [2]. In the fourth EUROASPIRE study [3], data were collected during May 2012 to April 2013. Only one fifth of the CHD patients reached a LDL-C level of 1.8 mmol/L or less. Accordingly, still most of the patients do not reach the recommended LDL-C levels.

The reasons for these discrepancies have been attributed to unsatisfactory effect of lipid lowering drugs, to side effects of drugs and to poor patient compliance. We hypothesized that the most important factor was underutilisation of effective drugs, and that side effects could be dealt with. We therefore firstly sought to assess the baseline prevalence of lipid level goal achievement in chronic CHD patients in the community, thereafter to assess the change after one consultation by a cardiologist (conventional follow-up «CFU») and finally to assess the impact of a simple structured follow-up programme in out-of hospital cardiology practice (structured follow-up «SFU»).

## Methods

Gardermoen Heart Centre (GHC) is a single-doctor cardiology practice outside hospital and part of the public regional health service. The area that is served has approximately 90.000 inhabitants. Only patients remitted from general practitioners (GPs) are accepted for cardiology investigation. Patients are remitted for symptoms, for «follow-up» or for administrative reasons, such as the need for a cardiac examination for a driving license. All patients are given one or more diagnoses in the electronic patient journal system (EPJ, WinMed2+). For patients with documented CHD the ICD-10 number I 25.1 (atherosclerotic heart

disease) is applied. A prerequisite for this diagnosis is the availability of a hospital file reporting findings from a coronary angiography with obstructive disease.

### Conventional follow-up (CFU), retrospective study

During the first part of the year 2011, all patients with the I 25.1 diagnosis from the preceding year (2010) were identified by the search system in the EPJ. The files from these patients were retrospectively reviewed regarding demographic data, cardiac history, the use of cardiac drugs and lipid levels at the time of the index consultation. The patients had been given relevant prescriptions for lipid lowering drugs, and advice regarding guideline LDL-C levels had been given to the remitting GPs in the report from the cardiologist. However, as no quality control study was planned at this time, this information was not given in a structured manner. This approach was named «conventional follow-up», CFU.

In order to assess the impact of this CFU, the offices of the remitting GPs were contacted by the secretaries of GHC during the year 2011, up to one year after the index consultation, and the results of LDL-C and total cholesterol levels determined by the GP as part of the follow-up after the cardiology consultation were requested. In case no follow-up lipid levels were available, as in patients without further contact with their primary physician, patients declining follow-up, or contact with their primary physician without lipid analyses (n=20), a total of 26%, the baseline LDL levels were used as follow-up results. In patients, already at LDL goal at baseline (36%), the baseline LDL was also applied as follow-up value,

### Structured follow-up (SFU), prospective study

All patients with an ICD-10 diagnosis of I 25.1 seen at GHC during the two succeeding years, 2011-2012 (excluding revisits of patients seen during 2010) were prospectively followed in the cardiology practice with the aim of achieving an LDL-C level of 2.0 mmol/L or lower. For patients with an additional indication for clinical revisit the follow-up was based on office visits, or else

the follow-up was based on telephone or mail contact.

The following scheme was applied as first intervention:

- In patients with a baseline LDL-C of 2.0 mmol/L or less (n=146) no actions were taken and the patients continued ongoing lipid lowering medication.
- In patients without statin treatment (n=46) and LDL-C >2.0 mmol/L (no patient without statin had LDL-C ≤2 mmol/L) atorvastatin 40 mg OD was started.
- In patients on a statin, but LDL-C >2.5 mmol/L (n=150), ezetimibe 10 mg OD was added. If the patient was on a low dose or on treatment with a little potent statin, change of statin medication or increase of dosage were also considered.
- In patients on statin treatment with baseline LDL-C 2.5 mmol/L or less but above 2.0 (n=122) a clinical judgement was made whether a change in statin medication or an increase of dosage would be expected to decrease the LDL-C level to 2.0, otherwise ezetimibe was added
- If this first intervention did not bring the LDL-C level to the target level, the following measures were applied:
- Atorvastatin was increased to 80 mg OD when needed. If atorvastatin 80 mg OD in combination with ezetimibe were insufficient to reach LDL-C ≤2.0, atorvastatin was exchanged with rosuvastatin 40 mg OD.
- In the case of symptomatic side effects or liver or muscle enzymes more than three times the upper reference limit, statin medication was changed or statin dose was reduced with the addition of ezetimibe.
- When LDL-C reached 2.0 mmol/L or lower no further changes in lipid lowering drugs or dosages were performed.
- If rosuvastatin 40 mg OD plus ezetimibe did not bring the LDL-C to 2.0 mmol/L or lower, failure of reaching the LDL-C goal was accepted and no further action was taken

All reported results are on tolerated drugs. If LDL-C was lowered to 2.0 mmol/L or less but the drug(s) were not tolerated, the last LDL-C level on tolerated drug(s) is reported. The tolerance for unpleasantness is different in different patients. All patients were specifically asked for the more commonly expected subjective side effects and drug changes performed if the patients did not accept the symptoms. An interval of four weeks between each drug and dosage change was aimed at.

Dietary advice, weight control measures and advice regarding exercise and smoking habits were given to the patients in both groups at the baseline/index consultation in a similar fashion. Even if the SFU were followed up by the cardiologists' office and the patients in the CFU were not, most of the follow-up was based on telephone or mail contact, and no lifestyle interventions were applied during these contacts.

The study was presented to the Regional Committee of Ethics which had no objections to the protocol. As this was regarded by the Committee as «quality control» of own practice, no formal assessment from the Committee was needed according to the response letter from the Chairman of the Regional Committee of Ethics.

## Statistics

Independent samples t-tests, paired samples t-tests, Mc Nemar tests and Chi-Square tests were applied as appropriate.

## Results

The CFU (2010) and SFU (2011 and 2012) cohorts were similar for demographics and clinical data, as depicted in Table 1. The high number of males may in part be explained by the large proportion of patients remitted for assessment of ability to drive vehicles heavier than 3.5 tons, a more common occupational and recreational task in males.

On average 28 (SD 21) months had elapsed since the previous consultation with a relevant specialist or hospital department, cardiology, cardio-thoracic or vascular surgeon, «vascular» neurologist or cardiac rehabilitation.

The lipid levels at baseline were similar in both cohorts (Table 2). No more

	2010	2011-12
	CFU	SFU
	n=302	n=464
Mean age, years (SD)	65 (10)	65 (10)
Mean BMI (SD)	29 (4)	29 (5)
Male gender	84%	85%
CABG	38%	34%
Diabetes Mellitus	15%	20%
Current smoker	15%	14%
On beta-blocker	72%	66%
Remitted for symptoms	44%	44%

**Table 1.** Selected baseline patient characteristics in the two groups with mean values (SD) or percentages: CFU, conventional follow-up cohort; SFU, structured follow-up. There were no significant differences between the two cohorts for any of these variables.

than one third (36 and 32% respectively) of these patients with previously documented CHD had LDL-C levels as recommended by the guidelines at that time. The changes after CFU were modest, but statistically highly significant with an average drop of 0.2 mmol/L and a further 23% of the subjects reached the recommended LDL-C level. In contrast, in the SFU group, the changes were much larger. The mean LDL-C level decreased from 2.5 to 1.8 mmol/L, and the percentage of patients who reached the recommended LDL-C level increased from 32% to 90% (Table 2). The mean levels of total cholesterol at baseline, at follow-up in the two groups, and the proportion of subjects who reached the recommended cholesterol levels closely paralleled those of LDL-C.

The mean time to goal achievement or acceptance of failure was 3.0 (SD 2.4) months in the SFU group. Only in the SFU group reliable information regarding the use of lipid-lowering drugs was available as these patients were followed closely at GHC as part of the protocol for the research project. Compared with baseline, the use of simvastatin decreased, the use of atorvastatin increased, as did the use of rosuvastatin, while the use of ezetimibe increased from 11% to 52% at the end of the follow-up period (Table 3). Only 46 patients or 10% of the 464 patients in the SFU group failed to reach the LDL-C goal. The reasons for this were inadequate effect of drugs in 13 patients, muscle pain or CK elevation in six patients, gastro-intestinal symptoms or increased hepatic enzymes in six patients, other side effects in four patients and 17 patients were unwilling to participate, non-compliant or lost to follow-up.

## Discussion

The present study demonstrates in accordance with several previous studies that no more than one third of chronic CHD patients in the community have acceptable LDL-C levels according to guidelines at the time of the launch of this project. After one single specialist consultation, this number increased to nearly 60%, while our simple structured follow-up programme within specialist practice was able to bring as many as 90% to the desired level, after a mean period of time of three months, by changing to more potent statins and/or adding ezetimibe.

	CFU n=302			SFU n=464		
	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference
LDL-C	2.4±0.9	2.2±0.8	0.2±0.6	2.5±0.9	1.8±1.2	0.7±0.8
Chol	4.3±0.9	4.0±1.0	0.3±0.7	4.3±1.0	3.4±1.2	0.7±0.9
LDL-C ≤2	36%	59%	23%	32%	90%	58%
Chol ≤4	45%	63%	18%	48%	88%	40%

**Table 2.** Mean (SD) values for LDL cholesterol (LDL-C) and total cholesterol (Chol) in mmol/L, and percentage of patients at lipid level goal in the conventional follow-up (CFU) and structured follow-up (SFU) cohorts at baseline and at follow-up, and the differences between baseline and follow-up. Within- and between group differences for all variables were significant at  $p < 0.001$ .

SFU n=464	Baseline			Follow-up		
			Mean dose			Mean dose
Simvastatin	216	47%	38 mg	84	18%	36 mg
Atorvastatin	185	40%	53 mg	319	69%	58 mg
Rosuvastatin	5	1%	26 mg	50	11%	36 mg
Other statin	12	3%		2	0.4%	
No statin	46	10%		9	2%	
Ezetimibe	49	11%	10 mg	239	52%	10 mg

**Table 3.** Numbers and percentages of patients on different lipid lowering drugs and dosages (mg/day) in the structured follow-up (SFU) cohort, at baseline and at follow-up. The differences in percentages of patients on each drug between baseline and follow-up were all significant at  $p < 0.001$  (except «other statin», low numbers,  $p = 0.012$ ) while there were no significant changes in any of the dosages used.

### Study design

The comparison between the CFU and the SFU groups were not randomised, but the study compared patients in out-of-hospital practice in two succeeding periods of time. It would have been difficult to assess the results in the CFU group within the context of a RCT, as the study intervention itself (patients giving their informed consent to participate) would be expected to influence the awareness of lipid level goal achievement. The baseline data in both groups were recorded in the cardiology practice, retrospectively in the CFU group and prospectively in the SFU group. The follow-up data in the SFU group were also recorded prospectively in the cardiology practice. The follow-up data in the CFU group, however, were collected retrospectively from the GPs offices. Only the lipid level data were considered to be of sufficient quality to be included in the study, while the time of the analyses and the follow-up drugs prescribed were not. Even in these times of electronic prescriptions, the list of drugs for patients is to a large degree incorrect and the data on drugs and dosages would be expected to be of low quality. Thus, for scientific reasons we deliberately chose not to request these data from the GPs offices. The two groups were also comparable regarding baseline clinical and demographic variables. Accordingly, even if the two groups were not randomised, the «real life» characteristics of the design make the comparison of interest.

### LDL-C lowering drugs

LDL-C reduction by statin treatment reduces cardiovascular events in a linear fashion [4] and more intensive statin treatment further decreases the LDL-C levels and gives a corresponding decrease in cardiovascular events, with each 1.0 mmol/L LDL-C reduction giving a 22% reduction in the annual rate of major vascular events [5].

As there are large individual variations in the response to statin drugs and dosages, an individual approach seems attractive. The need for lipid lowering drugs in addition to statins may also vary between individuals. Increasing dosages of one statin has on average a small effect on the lowering of LDL-C, a doubling of the statin dosage can be expected to reduce the LDL-C level by 6% only [6]. In the present study, we therefore chose to add on ezetimibe if LDL-C was  $\geq 2.5$  mmol/L on statin treatment. The combination of a statin and ezetimibe reduces the LDL-C levels by approximately 50% compared with placebo [7], while ezetimibe added on top of a statin gives a further LDL-C decrease from 39% to 56% compared with statin alone [8]. In the IMPROVE-IT study [9], post-MI patients were randomized to 40 mg simvastatin and ezetimibe, or simvastatin alone. After a mean follow-up time of six years, the mean LDL-C levels were 1.4 and 1.8 mmol/L respectively and the corresponding event rates 32.7% and 34.7%, a significant 2 percentage point difference. These findings support the view that also non-statin LDL-C lowering improves patient outcome.

A comparison between statin up-titration (doubling of the dosage) and addition of ezetimibe in patients on a statin but with an LDL-C level of more than 3.1 mmol/L demonstrated no differences in the resulting LDL-C levels but more than twice as many adverse effects in the statin up-titrating group [10]. A meta-analysis has

demonstrated that in patients who failed to reach the LDL-C goal, adding on ezetimibe will decrease LDL-C by 24% and increase the number of patients reaching the LDL-C goal by 3.4 times [11]. Accordingly, lipid lowering, also with the non-statin ezetimibe, seems to be associated with a reduced risk of future cardiovascular events and the addition of ezetimibe compares favourably to increasing statin dosages regarding side effects.

There were no changes in available lipid lowering drugs during these periods of time. Ezetimibe was marketed in Norway in 2003 and was available for prescription for GPs from 2007, with full reimbursement as decided by The Norwegian Medicines Agency. Generic atorvastatin was available from 2008.

The 2007 Guidelines [1] stated that «selective cholesterol absorption inhibitors can be used in combination with statins in patients not reaching treatment goals with statins». Accordingly, both potent statins and ezetimibe were available for prescription, also for GPs, during these periods of time, and ezetimibe was also recommended by the guidelines at that time.

In the SFU group in the present study, the high percentage of patients reaching the treatment goal was achieved by changing to more potent statins, and not by increasing dosages, as could be expected. Furthermore, about half of patients needed the addition of ezetimibe. This is both in accordance with guidelines and a recent statement from the European Atherosclerosis Society, recommending adding ezetimibe as first choice non-statin lipid-lowering drug if LDL remains above target despite maximally tolerated statin [12].

### Reasons for failure to reach treatment goals

In the USAGE survey [13] the primary reason for discontinuation of statins was side effects, in 62%. The most common side effect was muscle pain [14]. A Danish study [15] has demonstrated that negative statin-related news stories both increased statin discontinuation as well as risks for myocardial infarction and death from cardiovascular disease. Financial problems may play

a role in some health systems. In the MI FREE trial [16] full coverage of medication expenses for post-MI patients increased the adherence to preventive medications including statins.

In a systematic review from 2006 [17], there was a non-significant tendency to lower incidence of myalgia in statin-treated patients, but a borderline significant excess of CK elevation. In a recent cohort study [18], most patients who stopped taking statins and were rechallenged were still taking a statin 12 months after the statin-related event. In the PRIMO study, an observational study without a control group [19], 10.5% of the patients reported any muscular complaint, and 15% and 18% of those who used atorvastatin or simvastatin respectively. Accordingly, there is little documentation for side effects of drugs that might explain low adherence. Still, in clinical practice, muscle pain perceived related to statin use is common. There may be differences between patients included in RCTs and those in clinical practices possibly because of rigorous inclusion criteria in RCTs [20, 21].

In the present study, however, by following the study scheme for drug treatment, we were able to overcome the problem with muscle side effects so that only 6/464 patients or 1.3% failed to reach the treatment goal for this reason. Other side effects were also rare affecting 10/464 patients or 2.2%.

### Organisation of care

Based on our current data we strongly believe that the reason for the general low goal achievement in chronic CHD patients is underuse of effective drugs and not lack of effect or side effects. Under the present national health system, lipid lowering drugs are available to a small cost for the patients, so expenses cannot explain the low baseline goal achievement. The problem with muscle pain, perceived or real, can be overcome by using the present scheme, lowering statin dosage, changing to another statin and/or adding ezetimibe. In our study, using only potent statins and ezetimibe, only 13/464 or 2.8% were non-responders, in spite of no use of secondary drugs like fibrates, bile acid sequestrants or niacin derivatives,

the latter being no longer available for prescription.

The most recent guidelines [22] have moved the recommended LDL-C level down to 1.8 mmol/L. In the present study, no further actions were taken when LDL-C reached 2.0 mmol/L, so it is not possible to infer what proportion of patients could have reached 1.8 mmol/L.

These guidelines state that «cardiologists working out-of-hospital have an essential role in CVD prevention, acting as consultants to general practitioners». Based on the present data, the cardiologist might even be given a more central role in this respect, as LDL-C goal achievement in patients under the care of GPs and seen once by a cardiologist is reached in less than 60% of the patients, while under the present programme a number of 90% was reached. In the present population, the average time since the patients had seen any relevant specialist was 28 months. Perhaps any patient with chronic CHD should see a cardiologist every 2-3 years.

### Importance of adherence to therapy

A metaanalysis [23] has found that good adherence to prescribed statins was associated with lower all-cause mortality compared with non-adherence, with a relative risk of 0.55 (0.46-0.67). That study calculated that a proportion as high as nine % of all CVD events could be attributed to poor adherence to cardiovascular medications, concluding with «developing cost-effective measures to increase adherence should be considered a priority». We have no exact measure of the patient adherence to the prescribed drugs, but as only 13/464 patients failed to reach the treatment goal because of unsatisfactory drug effect, one might assume that the adherence was quite high.

### Abandon LDL-C levels as treatment goal?

The 2013 AHA/ACC guidelines have rejected specific LDL-C levels as treatment goals, arguing that there is no evidence from randomised, controlled studies to support the use of specific LDL-C goals [24]. In individuals with clinical atherosclerotic

cardiovascular disease, one of four targeted groups, high-intensity statin therapy (rosuvastatin 20-40 mg or atorvastatin 80 mg) is recommended to achieve at least a 50 % reduction in LDL-C levels if tolerated. While generic atorvastatin is available, making this affordable, rosuvastatin is still expensive. Furthermore, as much as 80 mg of atorvastatin might not be tolerated in a substantial part of the patients. It is not always possible to know the baseline LDL-C level, without stopping the drug for some time, in patients already on some treatment. Making scientific comparisons are also easier when specific goals are applied. The IMPROVE-IT study has also been published [9] after the presentation of these guidelines, demonstrating the additional effect of ezetimibe, making the addition of this drug a proven treatment in patients intolerant to high dose statins or with unsatisfactory lipid lowering effect of maximally tolerated statin dosages. Accordingly, there are still advantages with LDL-C level based guidelines. It has also been demonstrated that the application of the ACC/AHA guidelines may be associated with undertreatment of high risk patients [25].

### Conclusions

The present study demonstrates, like numerous previous studies, that in CHD patients, LDL-C goal achievement in general practice is low. By using a simple, structured follow-up programme in out-of hospital cardiology practice it is possible to get 90% of these patients to the LDL-C goal of 2.0 mmol/L or less, which was the level recommended at the start of this programme. The effect was achieved by changing to more potent statins and with the addition of ezetimibe in about half of the patients. This programme can be recommended in the follow-up of high risk patients like these chronic CHD patients, and could also be useful in the follow-up for other high risk patient groups. The potential influence of cardiologist in out of-hospital practice may be greater than previously assumed.

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### Authorship:

MH has conceived and designed the research, acquired the data, drafted the manuscript and given final approval of the version to be submitted.

TRP has participated in the analysis and interpretation of data, in the preparation of the article, revising it critically for important intellectual content and given final approval of the version to be submitted.

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