

openheart Use of lipid-lowering therapy after ischaemic stroke and expected benefit from intensification of treatment

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ABSTRACT

Objectives Elevated low-density lipoprotein cholesterol (LDL-C) increases the risk of recurrent cardiovascular disease (CVD) events. We examined use of lipid-lowering therapy (LLT) following ischaemic stroke, and estimated benefits from guideline-based up-titration of LLT.

Methods The Norwegian COgnitive Impairment After STroke (Nor-COAST) study, a multicentre prospective cohort study, collected data on LLT use, dose intensity and LDL-C levels for 462 home-dwelling patients with ischaemic stroke. We used the Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health (SMART-REACH) model to estimate the expected benefit of up-titrating LLT.

Results At discharge, 92% received LLT (97% statin monotherapy). Patients with prestroke dementia and cardioembolic stroke aetiology were less likely to receive LLT. Older patients (coefficient -3 mg atorvastatin per 10 years, 95% CI -6 to -0.5) and women (coefficient -5.1 mg atorvastatin, 95% CI -9.2 to -0.9) received lower doses, while individuals with higher baseline LDL-C, ischaemic heart disease and large artery stroke aetiology received higher dose intensity. At 3 months, 45% reached LDL-C ≤ 1.8 mmol/L, and we estimated that 81% could potentially reach the target with statin and ezetimibe, resulting in median 5 (IQR 0–12) months of CVD-free life gain and median 2% 10-year absolute risk reduction (IQR 0–4) with large interindividual variation.

Conclusion Potential for optimisation of conventional LLT use exists in patients with ischaemic stroke. Awareness of groups at risk of undertreatment and objective estimates of the individual patient's benefit of intensification can help personalise treatment decisions and reduce residual cholesterol risk.

Trial registration number NCT02650531.

INTRODUCTION

The incidence of fatal and non-fatal cardiovascular disease (CVD) events has decreased over the last decades.^{1,2} In Norway, mortality from stroke has decreased by nearly 40% in the last 10 years, and mortality from myocardial infarction has decreased by approximately 50%.¹ A large proportion of Norwegian stroke patients suffer minor strokes and

Key questions

What is already known about this subject?

- Target achievement for low-density lipoprotein cholesterol (LDL-C) is suboptimal in patients with established cardiovascular disease.
- Achieved LDL-C levels is largely dependent on dose intensity of lipid-lowering drugs prescribed, baseline LDL-C levels and patients' adherence to therapy.

What does this study add?

- We explore clinical factors influencing physician's prescription patterns after ischaemic stroke, where age, sex, ischaemic stroke subtype, coexisting coronary artery disease and baseline LDL-C were related to dose intensity.
- We estimated that 81% could potentially reach an LDL-C ≤ 1.8 mmol/L with statin plus ezetimibe leading to median 5 months cardiovascular disease-free life-gain.
- Estimated benefit from intensification of therapy varies between individuals.

How might this impact on clinical practice?

- Awareness of patient groups at risk of undertreatment, like women, and awareness of an individual patient's vascular risk and the benefits of intensifying treatment might help avoid undertreatment and overtreatment.
- The Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health (SMART-REACH) model can be used to objectively estimate expected benefit.

are independent and home-dwelling after 3 months.³ Thus, a growing number of patients are living with established CVD and need optimal secondary prevention and follow-up to prevent recurrent events.

Patients with ischaemic stroke are at high risk of recurrent CVD events.⁴ In Norway, one of four strokes is recurrent, despite more than 90% of patients being prescribed guideline-recommended medications at discharge.³ Drugs lowering low-density lipoprotein cholesterol (LDL-C) are one of the



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strategies to reduce the risk of recurrence.^{5–8} Although the optimal LDL-C target remains unclear,⁶ recent studies indicate that lower treatment targets are more beneficial.⁸ There has been an increase in both statin use and dose over time,^{9,10} but gaps still exist between guideline-recommendations^{2,6,11,12} and current practice with suboptimal target achievement for LDL-C.^{6,9,13–15} This gap could be associated with both patient-related factors, such as poor drug adherence and perceived adverse effects,^{12,13} and physician-related factors like choice of drug type and dose intensity.^{12,13} Awareness of an individual patient's CVD risk, perceived risk of adverse effects and the expected harm-benefit ratio may also influence how lipid-lowering therapy (LLT) is prescribed and used.^{2,6,12,15,16}

Little is known about the current use of LLT among patients with recent ischaemic stroke, especially the dose intensity of LLT. Moreover, a considerable interindividual variation in risk of recurrent events, competing risks and remaining life expectancy exist,⁴ with corresponding variation in the net benefit from more intensive LLT.^{4,17} Objective estimates of an individual patient's benefit might assist in making well-balanced decisions on whether to intensify treatment or not. Our study therefore aimed to address two sets of questions. First, how do current prescription patterns and achieved LDL-C reduction differ in subgroups of patients who had stroke? Next, what is the expected treatment benefit when theoretically up-titrating LLT according to guidelines?

METHODS

Study population

Home-dwelling patients from the multicentre, prospective Nor-COAST (Norwegian COgnitive Impairment After STroke) cohort study were included (n=729), online supplemental figure S1. Patients admitted with ischaemic stroke at five Norwegian stroke units were consecutively included between May 2015 and March 2017.¹⁸ Patients were assessed with self-report questionnaires, clinical examinations and blood sampling after 3 and 18 months (online supplemental methods). We excluded patients who died within the first 3 months (n=29), nursing home patients (n=36) and patients lacking medication information (n=3). Patients between 45 and 80 years (n=462) were included as we used a risk prediction model derived and validated in this age range.^{4,17}

Use of LLT

LLT was identified using the following Anatomical Therapeutic Chemical classification system codes: C10AA, C10AX and C10B. We used the Defined Daily Doses (DDDs)¹⁹ to convert to atorvastatin equivalent doses by the following formula: (Dose of statin/DDD for that statin)×DDD for atorvastatin=atorvastatin equivalent dose. High-intensity statins (HIS) was defined as ≥40mg atorvastatin, ≥20mg rosuvastatin or 80mg simvastatin per day.⁶ We measured medication adherence by the 4-item

Morisky Medication Adherence Scale (MMAS-4), where a score of 4 points was defined as high adherence.²⁰

LDL-C control and expected LDL-C with up-titration of LLT

LDL-C ≤1.8mmol/L was defined as target attainment^{2,11} and 3-month levels were used as the basis for theoretical intensification. Guidelines recommend statins at maximally tolerated dose (*step 1*) and use of ezetimibe (*step 2*) in patients unable to achieve the target with statin monotherapy or statin intolerance.^{2,6,11} The potent and expensive proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are mainly considered for patients still not reaching targets (*step 3*).^{6,11}

We included patients receiving LLT at discharge in these analyses. We used mean % reduction in LDL-C derived from randomised clinical trials as previously presented and validated²¹ (online supplemental methods, online supplemental table S1). First, all patients with LDL-C >1.8mmol/L not using HIS was up-titrated to HIS, assuming a 50.2% mean reduction in LDL-C (the effect of atorvastatin 80mg).²¹ If the expected LDL-C then was >1.8mmol/L, ezetimibe was added, assuming a mean 22.7% reduction in LDL-C.²¹ We also estimated the effect of adding ezetimibe without increased statin doses, assuming patients already used maximally tolerated statin.

Estimated benefit from up-titration of LLT

We estimated individual benefit in terms of gain in months free of recurrent stroke, myocardial infarction or cardiovascular mortality¹⁷ and 10-year absolute risk reduction (ARR), by using the externally validated SMART-REACH (Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health) model.¹⁷ The model is a competing risk-adjusted lifetime model previously validated in Nor-COAST,⁴ which uses the following predictors: sex, smoking, diabetes mellitus, systolic blood pressure, total cholesterol, creatinine, number of locations of CVD (coronary, cerebral and/or peripheral arterial disease), atrial fibrillation and heart failure (online supplemental methods and online supplemental table S2).

We first calculated the life expectancy without recurrent cardiovascular events based on 3-month levels of predictors in the model, defined as the median estimated survival without a recurrent event.¹⁷ We next estimated potential treatment benefit defined as the difference in CVD-free life expectancy with and without up-titration of LLT. CVD-free life expectancy with achieved LDL-C level after up-titration was calculated by incorporating an HR of 0.78 for major cardiovascular events per 1.0mmol/L reduction in LDL-C⁵ in the SMART-REACH model. The individuals' 10-year ARR was defined as the difference between current 10-year CVD risk and the 10-year risk with achieved LDL-C levels after up-titration.

Statistical analysis

Logistic and linear regression was used with LLT prescription (yes/no) and atorvastatin equivalent dose (mg/day) as dependent variables, respectively, to identify predictors of LLT use and intensity. Potential predictors were selected a priori based on previous studies^{9 10 22} and clinical reasoning, leading to inclusion of the following covariates, first one at a time, and next, adjusted for age and sex: age, sex, LDL-C, prestroke LLT, frailty by the 5-item Fried criteria¹³ as a continuous variable from 0 (robustness) to 5 (frail), the Global Deterioration Scale as continuous variable from 1 (normal) to 7 (severe dementia). A history of ischaemic heart disease was included as a categorical variable (yes/no). Stroke subtype was divided into five categories according to the Trial of Org 10172 in Acute Stroke Treatment classification: large artery disease, cardioembolic stroke, small vessel disease, undetermined strokes and other aetiology (grouped with 'undetermined'). We report coefficients or odds ratios (OR) with 95% confidence intervals (CI). Two-sided p values <0.05 were regarded as statistically significant. However, due to multiple comparisons, p values between 0.01 and 0.05 should be interpreted with caution. We imputed missing data for LDL-C and covariates to predict CVD risk by means of single imputation using predictive mean matching (online supplemental table S2 shows extent of missing data). Data analysis was performed using Stata V.16 or R V.4.0.2.

Patient and public involvement

The Nor-COAST study included two user representatives from the national unions for patients with stroke and dementia. The user representatives have been actively participating in the planning and performance of the study. They have been invited to Nor-COAST meetings and separate meetings have been held two to three times per year. They become consecutively informed about the study progress and are invited to share their views on endpoints, ethics, and dissemination of the results to the users.

RESULTS

Baseline characteristics and LLT at discharge

Mean age was 69.0 years (SD 8.1), 38% were female, 24% were smoking and 35% (n=161) were already using LLT at admission (table 1). At discharge, 92% (n=427) were prescribed LLT, of whom 422 received statins, either alone (n=414) or in combination with ezetimibe (n=8), whereas five patients were receiving ezetimibe alone. Mean statin dose was 41 mg (SD 21) atorvastatin equivalent dose and 64% (n=276) received HIS. Type and doses of LLT are shown in online supplemental table S3.

Unadjusted and adjusted associations between patient characteristics and prescription of LLT (yes/no) at discharge are shown in online supplemental table S4. Patient characteristics associated with dose intensity at discharge are shown in table 2.

Achieved LDL-C levels and LLT at follow-up

For patients prescribed LLT at discharge (n=427), mean LDL-C decreased from 3.1 (SD 1.1) to 2.1 (SD 0.7) mmol/L 3 months poststroke. For LLT naïve patients the corresponding decrease was from 3.5 (SD 1.0) to 2.0 (SD 0.7) mmol/L. In total, 45% (n=193) achieved the LDL-C target of ≤ 1.8 mmol/L and 33% of these had reached the target by receiving non-HIS, 62% by HIS, 1% by ezetimibe monotherapy, 2% by statin plus ezetimibe and 2% without LLT (discontinued). In total, 14 patients had discontinued statins between discharge and 3 months. In total, 58% (n=249) had LDL-C ≤ 2.0 mmol/L, 11% (n=45) ≤ 1.4 mmol/L and 2% (n=10) ≤ 1.0 mmol/L and 78% reported high medication adherence at 3 months.

Lipid profiles according to subgroups of patients are shown in online supplemental table S5, where women, younger patients and patients with no prestroke LLT had higher LDL-C at admission. LLT for patients not reaching the target by subgroups of patients is shown in online supplemental table S6. Target attainment in different subgroups of LLT regimens is shown in online supplemental figure S2. Table 3 shows characteristics in categories defined by quartiles of relative LDL-C reduction. Patients with the largest reduction were younger, had higher LDL-C at index stay, 82% were prescribed HIS and 86% reported optimal adherence. Among patients with the smallest LDL-C reduction, 78% had prestroke LLT.

In total, 73% of the 352 patients with available medication lists at 18 months reported high medication adherence and 11% (n=38) had discontinued statins (10% of men and 13% of women, $p=0.337$, 9% with HIS and 14% with non-HIS, $p=0.229$), of whom four had switched to ezetimibe monotherapy. Treatment patterns for those still persistent to statins are shown in online supplemental figure S3. Of patients with no LLT at discharge or 3 months (n=26), six patients started between 3 and 18 months.

Expected LDL-C levels when theoretically up-titrating LLT

Figure 1 shows LDL-C distribution after theoretically up-titrating LLT according to guidelines, proportions achieving the guideline target for each step and proportions using different LLT. Of the n=234 patients not at target at 3 months, n=87 were receiving non-HIS and could undergo up-titration to HIS (step 1), online supplemental figure S4. Up-titration in these subjects would result in an additional n=43 achieving an LDL-C level ≤ 1.8 mmol/L (overall cohort with LDL-C ≤ 1.8 mmol/L; 55% (n=236) at this stage). Of the remaining 45% (n=191) not at the LDL-C target, six patients were already receiving concomitant ezetimibe. Ezetimibe could be added to the remaining 44% (n=185) receiving HIS who were not at the target (step 2). After this step, an additional 26% would have reached the target (total at target, 81% (n=347)). After intensification, mean LDL-C was 1.7 mmol/L (SD 0.4). Mean LDL-C for those not reaching the target after intensification (n=80)

Table 1 Clinical characteristics at index stay by lipid-lowering therapy use at discharge

	Prescribed lipid-lowering therapy (n=427)			Not prescribed lipid-lowering therapy (n=35)	Total population (n=462)
	Non-high intensity statin (n=146)	High-intensity statin* (n=276)	Any† (n=427)		
Demographics					
Age (years)	70.4 (8.0)	68.0 (8.0)	68.8 (8.1)	70.7 (8.2)	69.0 (8.1)
Sex, female	57 (39)	105 (38)	163 (38)	14 (40)	177 (38)
Education	12.3 (3.8)	12.6 (3.7)	12.6 (3.7)	11.5 (3.4)	12.5 (3.7)
Home care services	7 (5)	5 (3)	15 (4)	5 (14)	20 (4)
Cardiovascular characteristics					
Atrial fibrillation	38 (26)	46 (17)	84 (20)	16 (46)	100 (22)
Diabetes mellitus	32 (22)	50 (18)	84 (20)	6 (17)	90 (20)
History of hypertension	84 (58)	146 (53)	233 (55)	17 (49)	250 (54)
Prestroke lipid-lowering therapy	69 (47)	89 (32)	160 (37)	1 (3)	161 (35)
Previous cerebrovascular disease	41 (28)	52 (19)	97 (23)	10 (29)	107 (23)
Ischaemic heart disease	30 (21)	46 (17)	77 (18)	2 (6)	79 (17)
Peripheral artery disease	15 (10)	19 (7)	34 (8)	0 (0)	34 (7)
Heart failure	2 (1)	6 (2)	8 (2)	3 (9)	11 (2)
Glomerular filtration rate (mL/min/1.73 m ²)	79 (15)	78 (16)	79 (16)	77 (21)	79 (16)
Body mass index (kg/m ²)	26.2 (4.2)	27.0 (4.3)	26.7 (4.2)	26.0 (3.7)	26.7 (4.2)
Current smoker	34 (23)	101 (37)	100 (24)	9 (26)	109 (24)
Physically active	36 (25)	77 (28)	115 (27)	8 (23)	123 (27)
Lipid levels at index stay					
Total cholesterol (mmol/L)	4.6 (1.2)	5.1 (1.3)	5.0 (1.3)	4.7 (1.4)	5.0 (1.3)
LDL cholesterol (mmol/L)	2.8 (0.9)	3.3 (1.1)	3.1 (1.1)	3.0 (1.3)	3.1 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.6)	1.4 (0.6)	1.4 (0.6)	1.3 (0.4)	1.4 (0.5)
Stroke characteristics and other comorbidities					
NIHSS discharge	1.4 (1.8)	1.7 (2.4)	1.6 (2.2)	2.0 (3.9)	1.7 (2.4)
Stroke subtype (n=447)					
Large artery disease	10 (7)	38 (14)	48 (12)	1 (3)	49 (11)
Cardioembolic	34 (24)	54 (20)	88 (21)	15 (43)	103 (23)
Small vessel disease	35 (25)	62 (24)	99 (24)	5 (14)	104 (23)
Other cause	5 (4)	6 (2)	11 (3)	1 (3)	12 (3)
Undetermined or multiple causes	59 (41)	104 (39)	166 (40)	13 (37)	179 (40)
Charlson comorbidity index	3.8 (1.7)	4.3 (1.9)	3.6 (1.8)	4.1 (1.9)	3.6 (1.8)
Frail	14 (10)	16 (6)	30 (7)	2 (6)	32 (7)
Cognitive impairment	3 (2)	4 (2)	7 (2)	6 (17)	13 (3)
Independent functional status at discharge‡	102 (70)	196 (71)	303 (71)	21 (60)	324 (70)
Other secondary preventive drugs at discharge					
Antithrombotic drugs	144 (99)	275 (100)	424 (99)	34 (97)	458 (99)
Antihypertensive drugs	113 (77)	205 (74)	321 (75)	25 (71)	346 (75)
Total number of medications	5.3 (2.6)	5.2 (2.4)	5.2 (2.5)	4.0 (3.0)	5.1 (2.6)

Values are n (%) or mean (SD) (n observations). Detailed definitions in online supplemental methods.

*Defined as ≥ 40 mg atorvastatin, ≥ 20 mg rosuvastatin or 80 mg simvastatin per day.

†5 patients received ezetimibe monotherapy.

‡Defined as ≤ 2 on Modified Rankin Scale.

HDL, high density lipoprotein; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

Table 2 Linear regression with statin dose intensity (mg) as dependent variable, for participants prescribed statin monotherapy at discharge (n=414)

	Unadjusted analysis			Age- and sex-adjusted analysis	
	n	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Age, years	414	-0.30 (-0.55 to -0.05)	0.019	-0.26 (-0.51 to -0.01)	0.039
Sex, female	414	-5.1 (-9.2 to -0.9)	0.017	-4.5 (-8.6 to -0.3)	0.036
LDL-C† (mmol/L)	414	2.7 (0.9 to 4.5)	0.004	2.8 (0.9 to 4.6)	0.003
Prestroke use of LLT	414	-2.4 (-6.6 to 1.8)	0.268	-1.8 (-6.1 to 2.4)	0.402
Frailty‡	414	0.2 (-2.0 to 2.3)	0.889	1.3 (-0.9 to 3.5)	0.249
Cognitive impairment§	408	0.2 (-3.0 to 3.4)	0.918	0.8 (-2.4 to 4.0)	0.626
Ischaemic heart disease	414	6.1 (0.8 to 11.4)	0.024	6.7 (1.3 to 12.1)	0.016
Index stroke aetiology¶	399				
Large artery disease		Reference category		Reference category	
Cardioembolic stroke		-11.8 (-19.4 to -4.2)	0.002	-11.6 (-19.1 to -4.1)	0.003
Small vessel disease		-11.3 (-18.8 to -3.8)	0.003	-11.3 (-18.8 to -3.9)	0.003
Undetermined or multiple causes		-9.2 (-16.2 to -2.3)	0.010	-9.4 (-16.3 to -2.4)	0.008

*Atorvastatin equivalent dose.

†Measured at first day after admission.

‡Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail.

§Prestroke, measured by Global Deterioration Scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia.

¶Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.

LDL-C, low-density lipoprotein cholesterol.

was 2.2 mmol/L (SD 0.4). Assuming all patients were already using maximally tolerated statin dose and only ezetimibe could be added, 75% (n=319) could potentially reach the target.

Expected benefit when theoretically up-titrating LLT

For all patients prescribed LLT (n=427), the median 10-year CVD risk was 42% (IQR 31%–54%) and lifetime risk was 70% (IQR 64%–76%). Median CVD-free life expectancy was 80.2 years (IQR 76.2–83.2). Overall median estimated lifetime benefit when up-titrating LLT was 5 months (IQR 0–12). Median CVD-free life gain was <6 months for 52% (n=220), 6–12 months for 27% (n=115) and >12 months for 22% (n=92). Estimated median 10-year ARR was 2% (IQR 0%–4%).

For patients with LDL-C above 1.8 mmol/L (n=234), the median estimated lifetime benefit by up-titrating was 11 months (IQR 7–17), with 39% having >12 months of estimated CVD-free life gain (figure 2). Characteristics for patients stratified by tertiles of months of gain in CVD-free life are shown in online supplemental table S7. Estimated 10-year ARR for these patients was median 4% (IQR 3%–5%), and the median 10-year risk level could be reduced from 40% (IQR 31%–52%) to 35% (IQR 27%–46%). Further up-titration to the LDL-C target 1.4 mmol/L would lead to median 17 months (IQR 11–25) of estimated lifetime benefit (online supplemental figure S5). Two illustrative patient examples are shown in figure 3.

DISCUSSION

In this observational study of patients ≤80 years, we showed high LLT prescription rates, and although LDL-C levels in many cases were not far from target, less than half of patients reached the target. Age, sex, stroke aetiology and baseline LDL-C were related to LLT intensity prescribed. Younger patients, women and patients receiving HIS had larger % LDL-C reduction. We estimated that 81% could potentially reach the target with well-established low-cost drugs leading to median of 11 months CVD-free life-gain for patients with elevated LDL-C, but with large inter-individual variation.

The prescription rates and mean statin doses were higher in Nor-COAST than in other studies.^{9 14 15 22–24} In total, 63% of those not reaching the target reported using HIS, illustrating that highest tolerated statin dose monotherapy may for many patients not yield target attainment.^{12 14} However, a previous study has noted that LDL-C levels down to mean 1.4 mmol/L is possible with optimal adherence and optimised dose of statin plus ezetimibe.²⁵ The Nor-COAST study was conducted between 2015 and 2018 and most physicians were presumably treating towards a target of LDL-C <2.0 mmol/L.²⁶ However, most patients with dose adjustments had their dose reduced in line with other studies,²⁷ few used alternative LLT and 11% discontinued statins within 18 months.

As in other studies,^{9 10 22 27} female sex and advanced age were associated with lower dose intensity. Other studies have shown that females less often receive evidence-based CVD drugs, more often experience adverse effects

Table 3 Characteristics in categories defined by quartiles of % LDL-cholesterol reduction from index stay to the 3-month visit for patients prescribed LLT at discharge (n=427)

	≤Q1 <8% reduction (n=107)	Q1–Q2 9%–35% reduction (n=107)	Q2–Q3 36%–51% reduction (n=107)	Q3 >51% reduction (n=106)
Median % reduction (IQR)	–6 (–28 to 0)	23 (16 to 29)	44 (39 to 48)	57 (54 to 61)
Age, mean (SD)	70.3 (8.1)	69.3 (7.8)	68.9 (8.3)	66.9 (7.9)
Sex, female	28 (26)	42 (39)	44 (41)	49 (46)
Body mass index (kg/m ²), mean (SD)	26.7 (4.1)	26.6 (4.8)	26.5 (4.1)	27.0 (3.9)
Current smoker at admission	26 (24)	22 (21)	23 (22)	29 (27)
Hypertension	81 (76)	66 (62)	44 (41)	42 (40)
Prestroke use of LLT	83 (78)	51 (48)	18 (17)	8 (8)
Diabetes mellitus	28 (26)	20 (19)	19 (18)	17 (16)
History of ischaemic heart disease	41 (28)	19 (18)	13 (12)	4 (4)
Prior stroke	45 (42)	29 (27)	11 (10)	12 (11)
Charlson comorbidity index	4.3 (1.8)	3.8 (2.0)	3.2 (1.4)	3.1 (1.8)
Frail	7 (7)	9 (8)	6 (6)	8 (8)
Cognitive impairment	4 (4)	3 (3)	0 (0)	0 (0)
Stroke subtype (n=412)				
Large artery disease	10 (9)	14 (14)	13 (12)	11 (11)
Cardioembolic stroke	33 (31)	24 (24)	18 (17)	13 (13)
Small vessel disease	19 (18)	24 (24)	27 (26)	29 (29)
Other	3 (3)	3 (3)	5 (5)	0 (0)
Undetermined	40 (38)	36 (35)	43 (41)	47 (47)
LDL-C at index stay, mean (SD)	2.1 (0.8)	2.8 (0.8)	3.5 (0.9)	4.0 (0.9)
LDL-C at 3 months, mean (SD)	2.4 (0.8)	2.1 (0.6)	2.0 (0.5)	1.7 (0.4)
10-year CVD risk (%),* median (IQR)	50 (38–63)	43 (33–54)	40 (30–52)	37 (29–49)
Discontinued statin between 0 and 3 months	7 (7)	6 (6)	1 (1)	0 (0)
Optimal medication adherence† (n=351)	70/87 (81)	67/87 (77)	69/90 (77)	75/87 (86)
Non-high intensity statin	50 (47)	37 (35)	37 (35)	19 (18)
High-intensity statin	50 (47)	64 (60)	69 (64)	87 (82)
At target at 3 months	29 (27)	41 (38)	47 (44)	76 (72)

Values are n/N (%) if other not specified. Detailed definitions of variables in online supplemental methods.

*Estimated by the Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health (SMART-REACH) model.

†Corresponding to 4 points on Morisky Medication Adherence Scale 4.

CVD, cardiovascular disease; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

and have lower awareness of their CVD risk.² Current prescription patterns in the elderly might be explained by heterogeneity in underlying health status,^{2 6 16} as well as age and polypharmacy being risk factors for adverse effects and interactions.⁶ Although emerging evidence supports similar relative CVD risk reductions regardless of age,² previous guidelines recommendations have been less concise. The ARR with intensified LLT can be substantial, while actual increase in life-expectancy in elderly might be limited due to risk of both CVD events and competing risks (figure 3).^{2 6 16}

Cardioembolic stroke was associated with no LLT prescription, while large artery disease aetiology and coexisting coronary disease was associated with higher

dose intensity. Evidence has historically been more robust for these patients,^{7 8 14 15} and previous studies have reported that coronary patients receive LLT and HIS more often than patients with peripheral and cerebrovascular disease.^{14 15} However, the large overlap between ischaemic stroke subtypes, different CVD entities and the high prevalence of atherosclerosis regardless of stroke aetiology illustrate the need for optimal lipid control in all subtypes.²⁸ Furthermore, consistent relative treatment effects across multiple subgroups of patients have been demonstrated in landmark meta-analyses^{5 6} and observational studies show reduced risk of CVD events and mortality with statins also in cardioembolic stroke.²⁹ Though, some of these patients

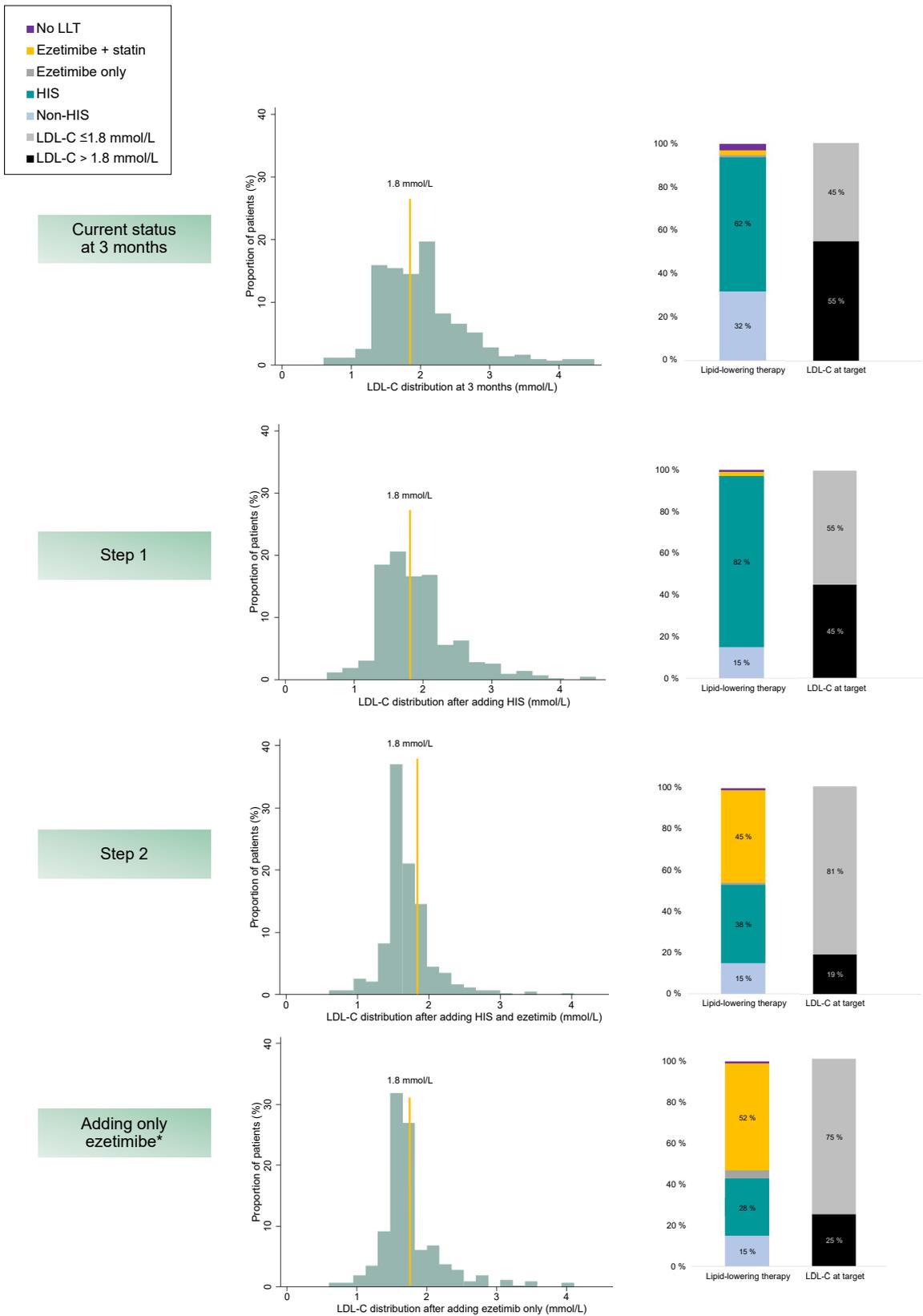


Figure 1 Distribution of LDL-C, proportions at target ≤ 1.8 mmol/L and LLT in use at 3 months and after hypothetically up-titrating LLT according to guideline-recommendations. First (step 1) by adding/up-titrating to high intensity statin, and next (step 2) by adding ezetimibe. *Assuming already on maximally tolerated statin dose. Proportions are n of the total population (n=427). Patients with no LLT, are patients who have discontinued prescribed LLT between discharge and 3 months. LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; HIS, high-intensity statin.

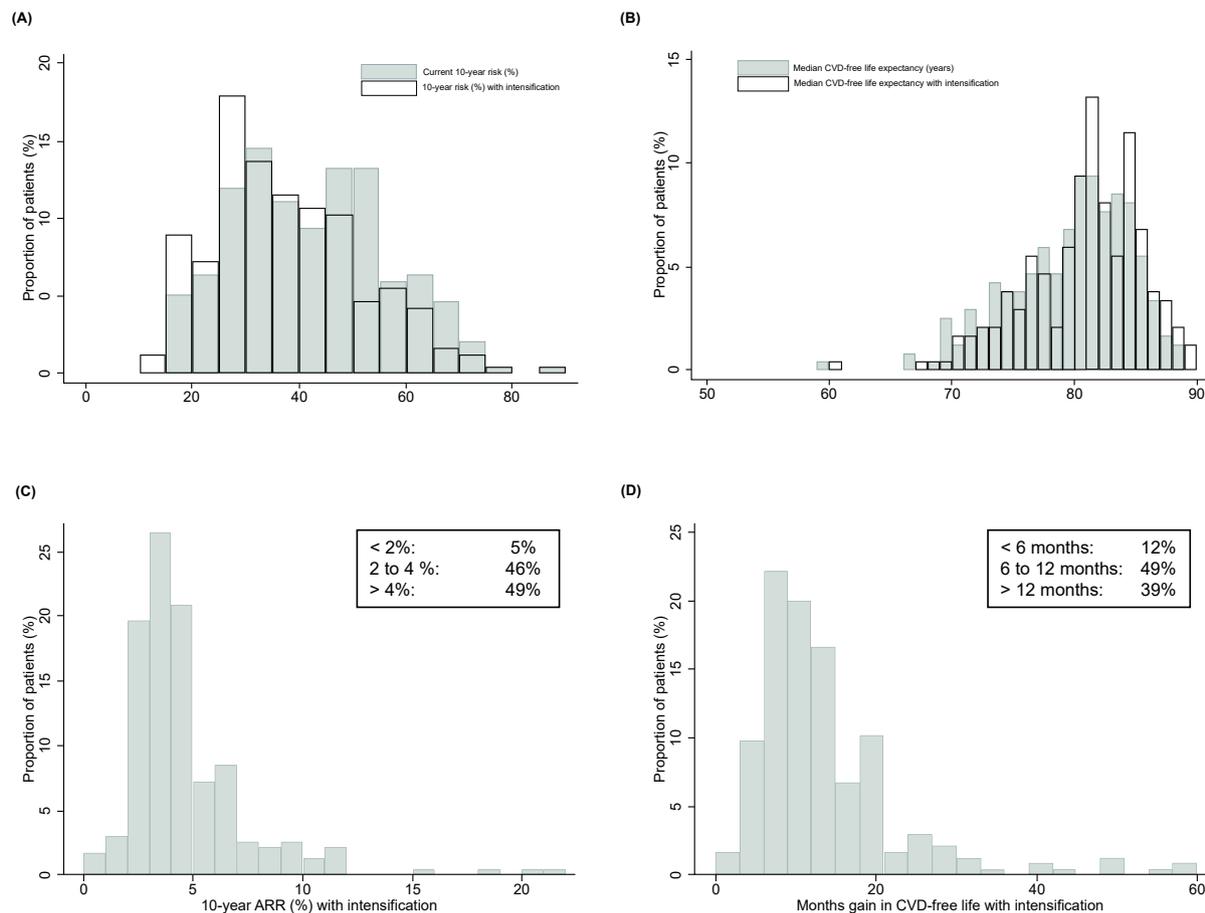


Figure 2 Estimated prognostic impact of intensification of lipid-lowering therapy according to the guideline-recommendations for patients with LDL-C above 1.8 mmol/L at 3 months (n=234). The top row shows (A) the distribution of the estimated 10-year CVD before and after intensification and (B) estimated median life-expectancy free from CVD events before and after intensification. The bottom row shows (C) distribution of estimated 10-year ARRs with intensification and (D) distribution in gain in months free from CVD events with intensification. ARR, absolute risk reduction; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

might not have atherosclerosis and treating lipids less intensively might better harmonise with the individual patients' expected benefit.

Concordance with guidelines might not be the ultimate marker of successful treatment for all.³⁰ However, not achieving targets might well be influenced by lack of familiarity with guidelines, physicians' and patients' preferences and uncertainty of clinical benefit of LLT which might lead to misinterpretations about the benefit-harm tradeoffs.^{12 14–16 27} Statin intolerance and narrow reimbursement criteria for PCSK9-inhibitors might also be important reasons.¹⁵ Moreover, levels are often not far from targets; the physicians might then take a more pragmatic approach. Comparable to a large simulation study,²¹ 81% was expected to reach LDL-C \leq 1.8 mmol/L with safe, effective low-cost drugs. Though, the efficiency is likely to be lower in real-life settings (online supplemental table S8) and PCSK9 inhibitors would be required especially if aiming for more stringent targets.^{6 12 21} However, the estimated individual benefit of a more intensive approach varies, depending on baseline CVD risk, level of LDL-C, remaining life-expectancy and

competing risks.^{2 6 17} Benefit on group level was largest in younger patients with relatively high LDL-C levels, however, younger age also means longer treatment duration and thereby higher costs to achieve those benefits (figure 3). Amount of benefit considered meaningful is also highly subjective and conditional on adverse effects, costs and patient preferences.³¹ Furthermore, only estimating further up-titration for patients with LDL-C above 1.8 mmol/L underestimated the actual potential benefit, since CVD risk is linearly related to LDL-C reduction^{5 6} (online supplemental figure S5).

Strengths and limitations

The strengths of this study include prospective consecutively inclusion and assessing LLT intensity three time-points,^{6 11} whereas previous studies are hampered by retrospective design^{9 23} with data collected a long period after an event^{9 23 27} or solely at discharge.^{10 22} Although proportions with frailty and dementia were low, including clinical information about these features and ischaemic stroke aetiology is a strength that previous studies lack or have based on registry data and diagnostic codes

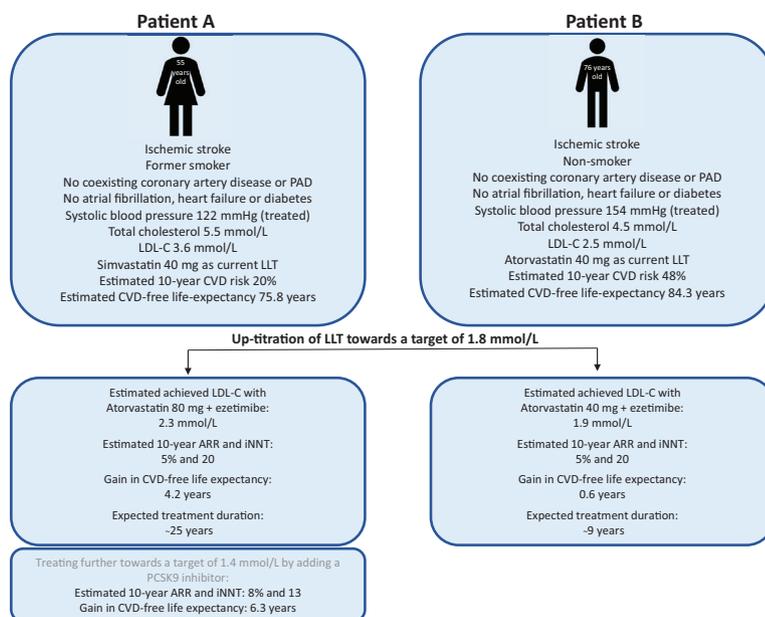


Figure 3 Two patient examples. The benefit of intensification of current lipid-lowering therapy estimated by the SMART-REACH model for a patient aged 55 years (A) versus 76 years (B) and expected treatment duration. ARR, absolute risk reduction; CVD, cardiovascular disease; iNNT, individual number-needed-to-treat (1 divided by ARR); LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

only.^{9 10} Using a lifetime risk prediction model adjusted for competing risk avoids overestimating treatment benefit in older individuals and underestimation of benefit in younger individuals.¹⁷ The Nor-COAST participants have characteristics comparable to patients in the Norwegian Stroke Registry³² and generalisation at least to Norwegian stroke patients and comparable populations is plausible.

Several limitations merit considerations. Information regarding drug-related adverse effects or patient preferences was not available. Information bias due to obtaining LLT use by interview and self-reported medication adherence might overestimate the actual LLT use. MMAS-4 is a general tool, not specific to LLT, and patients may consider their overall adherence as good although adherence to LLT is suboptimal. Other methods of measuring adherence to LLT like use of pharmacy registry data could have given other results. Self-reported use might also lead to a conservative estimate of the expected LDL-C levels achieved with intensified LLT. We did not account for interindividual variations in percentage LDL-C reduction achieved with the same drug dose.^{6 12} Whereas most variables only had limited missingness, there was considerable missing for LDL-C at 3 months (24%). Our cohort does not represent a randomized controlled trial setting from which the LDL-C reductions and hazard ratio were retrieved, and these results only give an indication of the impact of conventional LLT.^{2 30}

In conclusion, almost all patients who had stroke received LLT, but below 50% reached the LDL-C target. We show potential for reducing residual cholesterol

risk with safe, effective well-established low-cost LLT. Awareness of patient groups at risk of undertreatment, like women, and awareness of the individual patient's benefit of intensifying treatment might help avoid undertreatment and overtreatment. The SMART-REACH model can be used to objectively estimate expected benefit. When benefits are known, these can be balanced against potential costs and perceived side-effects, to assist physicians and patients in well-informed treatment decisions.

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