SUPPLEMENTARY MATERIAL

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Supplementary methods

Data collection and definitions used in Nor-COAST

Information about medications in use was obtained by clinical interview at the index stay, 3 and 18 months. If medication information was missing, we contacted general practitioners and home care services or used the electronic summary care record for safer healthcare in Norway. Patients unable to attend the outpatient clinic appointment were assessed by telephone interview or by proxy information.

Atrial fibrillation was defined by self-report or documented on electrocardiogram or telemetry during admission. Prestroke diabetes mellitus was defined as self-reported diabetes or HbA1c ≥ 48 mmol/mol at index stay or prescribed antidiabetic drugs at admission. Hypertension was defined as self-reported hypertension or use of antihypertensive drugs. Prestroke use of lipid-lowering therapy was defined as use of ATC classes: C10AA, C10B, C10AC or C10AX. Prevalence of previous cerebrovascular disease and coronary heart disease was retrieved from hospital medical records. Estimated glomerular filtration rate was based on the CKD-EPI equation (1). Physically active was defined as self-reported adherence to physical activity guidelines defined as minimum 75 min per week of high-intensity exercise or minimum 150 min per week of moderate intensity exercise. Stroke severity was measured according to National Institutes of Health Stroke Scale (NIHSS). Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification by experienced stroke physicians (2). Frailty was measured by a modified version of the Fried frailty criteria (3), giving a score from 0 (robustness) to 5 (frail) based on reduced grip strength, slow gait speed, self-reported fatigue, low physical activity and unintentional weight loss. Cognitive impairment was defined as score ≥ 3 on Global Deterioration Scale (4), a global measure of cognitive function and ability to perform daily life activities. Trained study nurses used all available information from interviews with caregivers during hospital stay to give a score from 1 (normal cognitive function) to 7 (severe dementia). Independent functional status was defined as Modified Rankin Scale ≤2.

Estimation of achievable LDL-C levels when up-titrating LLT according to guideline recommendations

We used the mean percentage change in LDL-C reduction with statins and ezetimibe as presented and validated by Cannon et al. (5) (as shown in **Supplementary table S1**) to estimate potentially achievable LDL-C levels when up-titrating therapy for those not already at the target at 3 months. When information of drug and dose was missing at 3 months (6%), we used the drug and dose prescribed at discharge (6). For patients already using a high-intensity statin (HIS), achieved LDL-C levels at 3 months were used when calculating the effect of adding ezetimibe. For patients using non-high intensity statins, we calculated additional LDL-C reduction (based on LDL-C levels achieved at 3 months) by switching from non-high intensity statin to HIS, for example for switching from atorvastatin 10 mg (associated with 35.5% LDL-C reduction) to atorvastatin 80 mg (associated with 50.2% LDL-C reduction), the assumed additional LDL-C reduction was 23% (1-(1-0.502)/(1-0.355)) (5). After up-titrating all to a high-intensity statin, we assumed a mean 22.7% reduction in LDL-C when adding ezetimibe (5, 7).

Assessment of cardiovascular risk and benefit of LDL-C lowering by the SMART-REACH model

The SMART-REACH model is a Fine and Gray model consisting of two complementary competing-risk-adjusted cause specific hazard functions; one for vascular events, and one for non-vascular mortality, where age is used as the underlying time function (8). The model uses the following predictors: age, sex, current smoking, diabetes mellitus, systolic BP, history of heart failure, history of atrial fibrillation, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and number of locations of vascular disease (cerebrovascular, coronary and peripheral artery disease). Since the model is intended for use in patients with stable cardiovascular disease, clinical measurements at the 3-month visit were used in the analysis. Detailed definition of the variables in the model have been previously published when validating the model in Nor-COAST (9). Missing data for the relevant variables and mean levels at 3 months are shown in **Supplementary Table S2.**

The SMART-REACH model was used to estimate life expectancy (years) without a recurrent cardiovascular event for individual patients and 10-year risk of CVD events by calculating the cumulative cause-specific event-risk truncated at 10 years after age at baseline (8, 10). To estimate the benefit of the guideline-recommended intensification of LLT, the cardiovascular risk was estimated twice with the SMART-REACH model for each individual. First, we estimated the risk with the 3-month LDL-C levels, and next we estimated the risk with the achieved LDL-C levels after intensification. The difference between estimated 10-year risk and healthy life-expectancy with 3-month LDL-C levels and estimated risk after intensification corresponds to the individuals' absolute benefit.

The effect of LLT on CVD events depends on the estimated reduction in LDL-C compared to baseline. A hazard ratio of **0.78 was assumed per 1.0 mmol/L reduction in LDL-C** (11). The individuals' expected relative risk reduction was calculated by $0.78^{\text{LDL-C reduction in mmol/L}}$. LDL-C reduction in mmol/L was defined as the 3-month LDL-C level minus achieved LDL-C level after intensification.

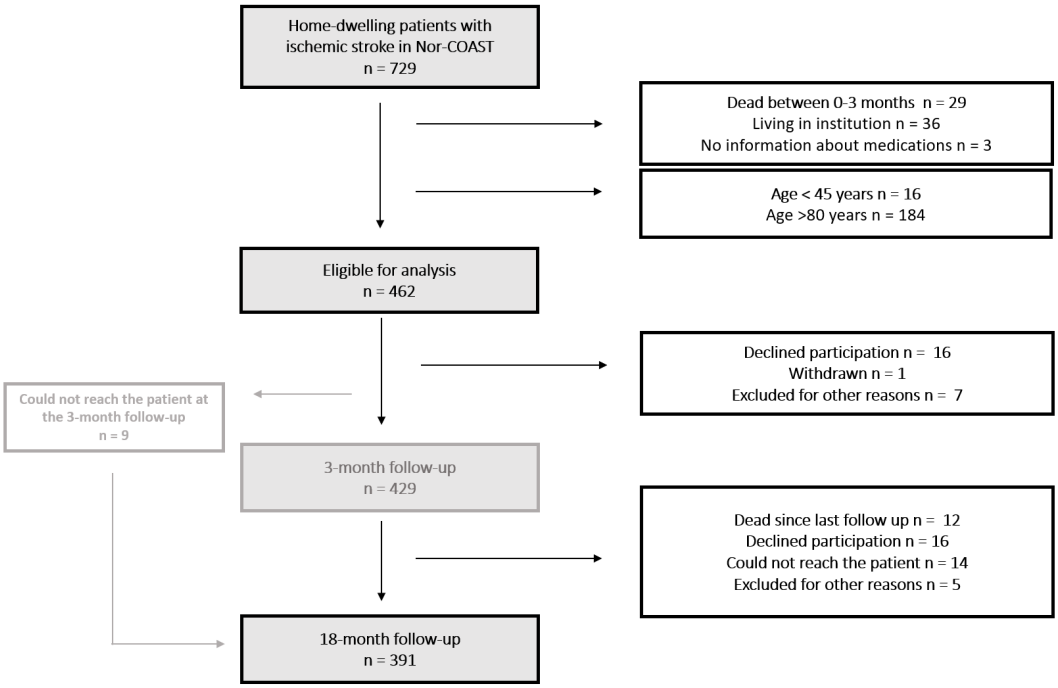


Figure S1. Flowchart of inclusion and exclusion of participants in current analysis

Table S1. Mean and standard deviation (SD) percentage change in LDL-C reduction with statins and ezetimibe, as presented and validated by Cannon et al. (5)

Drug	Dose, mg	Mean (reference)	SD (reference)
Atorvastatin	10	35.5% (12)	10.6% (5, 13)
	20	41.4% (12)	13.5% (5, 13)
	40	46.2% (12)	12.5% (5, 13)
	80	50.2% (12)	13.8% (5, 13)
Fluvastatin	20	17.0% (13)	8.0% (13)
	40	23.0% (13)	10.0% (13)
	80	26.0% (13)	9.0% (13)
Lovastatin	10	21.0% (14)	10.1% (5)
	20	24.0% (15)	11.0% (15)
	40	30.0% (15)	11.0% (15)
	60	34.5% (5)	11.7% (5)
Pravastatin	10	20.0% (13)	11.0% (13)
	20	24.0% (13)	11.0% (13)
	40	30.0% (13)	13.0% (13)
	80	33.0% (14)	11.2% (5)
Rosuvastatin	5	38.8% (12)	13.2% (5)
	10	44.1% (12)	12.5% (5, 13)
	20	49.5% (12)	13.3% (5, 13)
	40	54.7% (12)	12.9% (5, 13)
Simvastatin	5	23.0% (14)	11.0% (5, 13)
	10	27.4% (12)	13.7% (5, 13)
	20	33.0% (12)	10.4% (5, 13)
	40	38.9% (12)	14.0% (5, 13)
	80	45.0% (12)	11.7% (5, 13)
Ezetimibe	10	22.7% (7)	16.5% (16)

Table S2. Levels of cardiovascular risk factors at 3 months for variables included in the SMART-REACH model (8) and n (%) missing for the relevant variables at 3 months (N=462)

	Mean (SD) or n (%)	n (%) missing at 3 months
Age, years	69.0 (8.1)	0 (0%)
Sex, female	177 (38%)	0 (0%)
Current smoking[b]	54 (12%)	65 (14%)
Diabetes mellitus	90 (20%)	0 (0%)
Congestive heart failure	11 (2%)	0 (0%)
Atrial fibrillation	100 (22%)	0 (0%)
Systolic blood pressure (mmHg)	140 (19)	69 (15%)
Creatinine (µmol/L)	82 (22)	116 (25%)
Total cholesterol (mmol/L)	4.0 (0.9)	110 (24%)
LDL cholesterol (mmol/L)	2.1 (0.7)	112 (24%)
Cerebrovascular disease	462 (100%)	0 (0%)
History of ischemic heart disease	79 (17%)	0 (0%)
History of peripheral artery disease	34 (7%)	0 (0%)

Abbreviations: LDL, low-density lipoprotein

Table S3. Types and daily doses of statins and ezetimibe for patients using lipid lowering drugs at discharge and 18 months (n)		
	Discharge* (n = 427)	**18 months** (n = 321)**
Simvastatin n (%)	**80 (19%)**	**56 (17%)**
10 mg	3	4
20 mg	18	11
40 mg	56	33
80 mg	3	6
Unknown dose	0	2
Pravastatin n (%)	**6 (1%)**	**6 (2%)**
10 mg	1	**0**
20 mg	4	3
40 mg	0	2
80 mg	1	1
Atorvastatin n (%)	**328 (77%)**	**245 (76%)**
10 mg	5	17
20 mg	52	55
40 mg	191	121
60 mg	0	2
80 mg	80	48
Unknown dose	0	2
Rosuvastatin n (%)	**3 (1%)**	**4 (1%)**
5 mg	2	2
10 mg	0	1
20 mg	1	1
40 mg	0	0
Fluvastatin n (%)	**5 (1%)**	**3 1%)**
20 mg	2	0
40 mg	1	2
80 mg	2	1
Ezetimibe 10 mg monotherapy n (%)	**5 (1%)**	**7 (2%)**
Ezetimibe 10 mg in addition to statin n (%)	**8 (2%)**	**13 (4%)**

*In total, 412 were prescribed statins at discharge, while 10 patients received statins between 0-3 months, which was defined as statins at discharge. In addition, 5 patients received ezetimibe monotherapy. **Type and dose regardless of prescription at discharge or not. No patients used PCSK9-inhibitors.

Table S4. Logistic regression with prescription of lipid-lowering therapy at discharge as dependent variable (n= 462)

		Unadjusted analysis		Age- and sex adjusted analysis	
	n	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, years	462	0.97 (0.92 to 1.02)	0.185	0.97 (0.92 to 1.01)	0.191
Sex, female	462	0.93 (0.46 to 1.88)	0.831	1.00 (0.50 to 2.10)	0.989
LDL-C[a] (mmol/L)	462	1.13 (0.83 to 1.55)	0.439	1.09 (0.79 to 1.51)	0.584
Prestroke LLT	462	20.4 (2.76 to 150.30)	0.003	23.6 (3.18 to 175.39)	0.002
Frailty[b]	462	0.77 (0.56 to 1.07)	0.123	0.80 (0.57 to 1.13)	0.205
Cognitive impairment[c] prestroke	456	0.59 (0.43 to 0.80)	0.001	0.60 (0.44 to 0.83)	0.002
History of ischemic heart disease	462	3.63 (0.85 to 15.5)	0.081	4.30 (0.99 to 18.7)	0.051
Index stroke etiology[d]	447				
Cardio embolic stroke		Reference category		Reference category	
Large artery disease		8.18 (1.04 to 63.8)	0.045	8.09 (1.03 to 63.27)	0.046
Small vessel disease		3.38 (1.17 to 9.66)	0.023	3.24 (1.13 to 9.30)	0.029
Undetermined or multiple causes		2.16 (1.00 to 4.66)	0.051	2.06 (0.95 to 4.48)	0.068

[a]Measured at first day after admission [b]Measured by modified Fried Frailty criteria with 0 as reference corresponding to robust, and 5 to frail. [c]Measured by Global deterioration scale with 1 as reference corresponding to normal cognitive function and 7 to severe dementia. [d]Classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. There were no patients with large artery disease as stroke etiology not receiving lipid-lowering therapy at discharge. Abbreviations: OR, odds ratio; LDL-C, Low-density lipoprotein cholesterol.

Table S5. Lipid profile according to subgroups of stroke patients at index stay and 3 months follow-up (n=427)

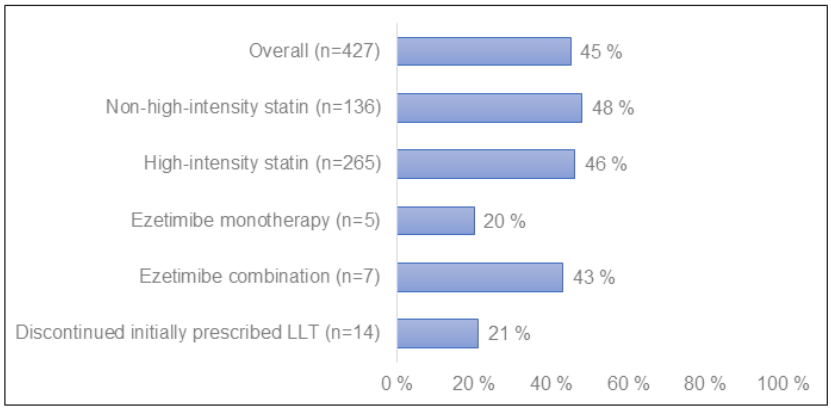
	Index stay				3-month follow-up				
	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Total-C (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	LDL-C ≤1.8 mmol/L	Mean distance from target[c]
All (n=427)	5.0 (1.3)	3.1 (1.1)	1.4 (0.6)	53 (12%)	4.0 (0.8)	2.1 (0.7)	1.5 (0.5)	193 (45%)	0.7 (0.6)
Men (n=264)	4.7 (1.2)	3.0 (1.1)	1.3 (0.5)	39 (15%)	3.8 (0.8)	2.1 (0.7)	1.4 (0.5)	115 (44%)	0.7 (0.6)
Women (n=163)	5.3 (1.3)	3.3 (1.1)	1.6 (0.6)	14 (9%)	4.2 (0.8)	2.1 (0.6)	1.7 (0.5)	78 (48%)	0.7 (0.6)
Age groups									
45 – 59 years (n=61)	5.2 (1.2)	3.3 (1.0)	1.4 (0.5)	6 (10%)	3.9 (0.8)	2.1 (0.7)	1.5 (0.5)	25 (41%)	0.8 (0.6)
60 – 69 years (n=135)	5.2 (1.3)	3.4 (1.2)	1.4 (0.5)	9 (7%)	3.9 (0.8)	2.1 (0.7)	1.4 (0.6)	60 (44%)	0.7 (0.6)
70 – 80 years (n=231)	4.7 (1.2)	2.9 (1.0)	1.5 (0.6)	38 (17%)	4.0 (0.8)	2.0 (0.6)	1.6 (0.5)	108 (47%)	0.7 (0.6)
No prestroke LLT (n=267)	5.4 (1.1)	3.5 (1.0)	1.5 (0.5)	9 (3%)	3.9 (0.8)	2.0 (0.7)	1.6 (0.5)	122 (46%)	0.7 (0.6)
Prestroke LLT (n=160)[a]	4.2 (1.1)	2.4 (1.0)	1.4 (0.6)	44 (28%)	4.0 (0.8)	2.1 (0.7)	1.4 (0.5)	71 (44%)	0.7 (0.8)
Stroke subtype									
Large artery disease (n=48)	5.0 (1.2)	3.1 (1.1)	1.4 (0.7)	5 (10%)	3.8 (0.8)	2.0 (0.6)	1.5 (0.4)	25 (52%)	0.6 (0.4)
Cardioembolic stroke (n=88)	4.7 (1.2)	2.9 (1.1)	1.4 (0.4)	15 (17%)	4.0 (0.8)	2.2 (0.8)	1.4 (0.4)	37 (42%)	0.8 (0.7)
Small vessel disease (n=99)	5.1 (1.3)	3.2 (1.2)	1.6 (0.6)	12 (12%)	4.0 (0.8)	2.0 (0.7)	1.6 (0.7)	48 (49%)	0.7 (0.6)
Undetermined or other (n=177)	5.1 (1.2)	3.2 (1.1)	1.4 (0.5)	19 (11%)	4.0 (0.80)	2.1 (0.6)	1.5 (0.5)	77 (44%)	0.6 (0.6)

Values are mean (SD) or n (%). [a]39% of men were using LLT at admission and 34% of women. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]Mean (SD) distance (mmol/L) from the LDL-C target 1.8 mmol/L for patients not at target. Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Table S6. Lipid-lowering therapy (LLT) at 3 months for patients prescribed LLT at discharge not reaching the target (n=234) by subgroups of stroke patients

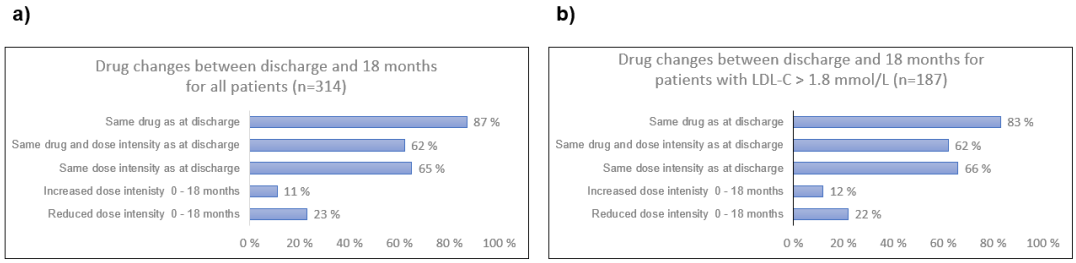
	Discontinued LLT[a]	Non-HIS	HIS	Ezetimibe monotherapy	Ezetimibe + statin[c]
All	11 (5%)	71 (30%)	144 (61%)	4 (2%)	4 (2%)
Men (n=149)	8 (5%)	46 (31%)	87 (58%)	4 (3%)	4 (3%)
Women (n=85)	3 (4%)	25 (29%)	57 (67%)	0 (0%)	0 (0%)
Age groups (years)					
<60 (n=36)	2 (6%)	9 (25%)	25 (69%)	0 (0%)	0 (0%)
60 – 69 (n=75)	4 (5%)	19 (25%)	50 (67%)	1 (1%)	1 (1%)
70 – 80 (n=123)	5 (4%)	43 (35%)	60 (56%)	3 (3%)	3 (2%)
Stroke subtype[b]					
Large artery disease (n=23)	0 (0%)	4 (17%)	17 (74%)	0 (0%)	2 (9%)
Cardioembolic stroke (n=51)	3 (6%)	19 (37%)	29 (57%)	0 (0%)	0 (0%)
Small vessel disease (n=51)	7 (8%)	22 (43%)	24 (47%)	1 (2%)	0 (0%)
Undetermined or other (n=100)	4 (4%)	25 (25%)	66 (66%)	3 (3%)	2 (2%)

[a]Discontinued LLT between discharge and 3 months. [b]According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. [c]3 out of 4 received high-intensity statin. Abbreviations: LLT, lipid-lowering therapy; HIS, high-intensity statin; LDL-c, low-density lipoprotein cholesterol



Supplementary figure S2. Proportions at LDL-C target at 3 months in subgroups of lipid-lowering therapy regimen.

Abbreviations: LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol



Supplementary Figure S3. Statin drug type and dose intensity at 18 months follow-up compared to discharge

For a) all patients with information on medications in use and persistent to statins at 18 months (n=314) and b) patients still not reaching the LDL-C target ≤1.8 mmol/L at 18 months (n=187). A total of 352 patients prescribed statins at discharge had medication lists at 18 months follow-up (18% missing).

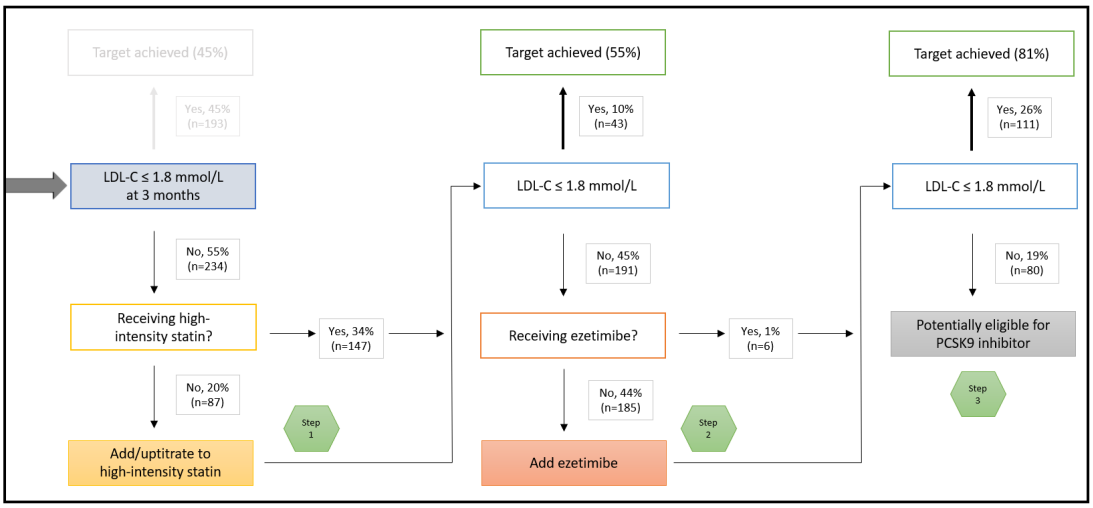


Figure S4. Estimation of effect of up-titration of lipid lowering treatment according to guideline recommendations and proportion of patients reaching LDL-C ≤1.8 mmol/L

With Step 1; Adding / up-titrating to high intensity statin, Step 2; Adding ezetimibe. Proportions are n of the total population (n=427). Abbreviations: LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Table S7. Characteristics for patients according to tertiles (T1 to T3) of months gain in CVD-free life by up-titrating lipid-lowering therapies according to the stepwise guideline-recommendation for patients with LDL-C above the guideline recommended target 1.8 mmol/L (n=234)

	T1 (n=79)	T2 (n=79)	T3 (n=76)
Median CVD-free life months (IQR)	**6.0 (4.8 to 7.2)**	**10.8 (9.6 to 12)**	**18.6 (16.8 to 25.8)**
Age, y	73.1 (5.6)	69.1 (6.8)	63.2 (9.5)
Sex, female	19 (24%)	36 (46%)	30 (39%)
Diabetes mellitus	26 (33%)	12 (15%)	7 (9%)
≥ 2 vascular areas[a] involved	31 (39%)	13 (16%)	8 (11%)
Current smoker at 3 months	12 (15%)	6 (8%)	7 (9%)
Systolic blood pressure (mmHg)[b]	141 (22)	142 (15)	141 (18)
Total Cholesterol [b], mmol/L	4.0 (0.5)	4.3 (0.6)	4.8 (0.8)
HDL Cholesterol [b], mmol/L	1.5 (0.7)	1.5 (0.4)	1.4 (0.4)
LDL Cholesterol [b], mmol/L	2.1 (0.3)	2.4 (0.4)	2.9 (0.7)
Estimated GFR (ml/min/1.73 m²) [b, c]	70 (16)	78 (16)	85 (16)
High sensitive CRP (mg/L) [b]	3.3 (7.3)	3.1 (4.1)	3.7 (8.0)
Frail[d]	2 (3%)	6 (8%)	2 (3%)
Prestroke dementia[e]	4 (5%)	1 (1%)	0 (0%)
Ischemic stroke subtype			
Large artery disease	9 / 75 (12%)	10 / 75 (13%)	4 / 75 (5%)
Cardioembolic stroke	18 / 75 (24%)	16 / 75 (21%)	17 / 75 (23%)
Small vessel disease	20 / 75 (27%)	10 / 75 (13%)	21 / 75 (28%)
Other, undetermined or unknown	28 / 75 (37%)	39 / 75 (52%)	33 / 75 (44%)

Values are n / N (%) or mean (standard deviation) if other not specified. [a]Number of vascular areas were one if only stroke, two if combined with either coronary artery disease or peripheral artery disease, and three if all three areas were affected. [b]Measured at 3 months follow-up. [c]CKD-EPI equation. [d]Frailty measured by 5-item Fried frailty criteria. [e]Cognitive impairment defined as score ≥ 3 on Global Deterioration Scale. Abbreviations: CVD, Cardiovascular disease; IQR, Interquartile range; LDL, Low density lipoprotein; HDL, High density lipoprotein; GFR, Glomerular Filtration Rate; CRP, C-reactive protein.

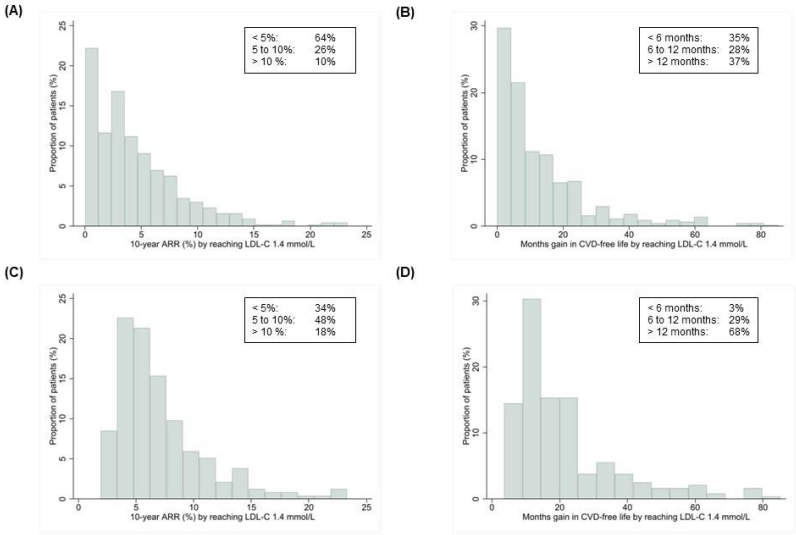


Figure S5. Estimated prognostic impact of reaching an LDL-C level of 1.4 mmol/L

The top row shows (A) distribution of estimated 10-year ARRs (B) distribution in gain in months free from CVD events for all patients prescribed LLT (n=427) when reacing LDL-C 1.4 mmol/L. The bottom row shows (C) distribution of estimated 10-year ARRs and (D) distribution in gain in months free from CVD events for patients with LDL-C above 1.8 mmol/L at 3 months (n=234) when reaching LDL-C 1.4 mmol/L. Abbreviations: LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; ARR, absolute risk reduction.

Table S8. Sensitivity analysis using other effect estimates for % LDL-C reduction when intensifying LLT

	% estimated at target at 3 months with HIS only	Mean LDL-C (mmol/L) (SD) obtained after adding HIS	% estimated at target when adding ezetimibe	Mean LDL-C (mmol/L) (SD) obtained after adding HIS and ezetimib
Main analysis	55%	1.9 (0.6)	81%	1.7 (0.4)
Using LDL-C values at index stay	58%	1.9 (0.7)	84%	1.7 (0.4)
Using % reduction obtained by Rosuvastatin 40 mg[c]	58%	1.9 (0.6)	82%	1.7 (0.4)
Using mean % reduction obtained in Nor-COAST[a]	49%	2.0 (0.6)	68%	1.8 (0.5)
Using % reduction obtained in SWEDEHEART (17)[b]	48%	2.0 (0.6)	66%	1.8 (0.5)

[a]Mean % reduction for patients prescribed HIS at discharge not at LLT prestroke (n=181) was 42.5% (SD 26), for ezetimibe naïve (n=5) the mean % reduction was 16.2%. [b]Mean % reduction in LDL-C obtained with high-intensity statin in SWEDEHEART was 39.7% (SD 15.7) (17), when adding ezetimibe 14.7% (SD 21.3). [c]Rosuvastatin 40 mg is assumed to reduce LDL-C by 54.7% and ezetimibe 22.7%. Abbreviations: HIS, high-intensity statin; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

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