

SUPPLEMENTARY DATA

Supplementary Table 1

Coding of lipid-lowering therapy into usual dose / intensive therapy

Lipid-lowering intensity	therapy	Category theoretical reduction	based on LDL-c	Lipid-lowering medication in this category
Usual dose		1 (1- <30%)		pravastatin 10-40 mg, fluvastatin 20-40 mg, monotherapy with ezetimib or bile acid sequestrants
		2 (30 - <40%)		simvastatin 10-20 mg, atorvastatin 10 mg
Intensive		3 (40 - <45%)		simvastatin 40 mg, atorvastatin 20 mg, rosuvastatin 5 mg, combination of simvastatin 10 mg and ezetimib 10 mg
		4 (\geq 45%)		simvastatin 80 mg, atorvastatin 40-80 mg, rosuvastatin 10-40 mg, combination of simvastatin >10 mg and ezetimib

SUPPLEMENTARY DATA

Supplementary Table 2

Patient Characteristics according to plasma LDL-c levels

N (%)	<2.0 mmol/l	2.0-2.5 mmol/l	>2.5 mmol/l
Men, n (%)	376 (76)	268 (74)	615 (64)
Age (years)	60 ± 10	61 ± 10	60 ± 10
Smoking current, n (%)	106 (22)	74 (20)	269 (45)
Pack-years	15 IQR(0-34)	12 IQR(0-32)	13 IQR(0-30)
Current alcohol use, n (%)	290 (59)	184 (51)	341 (36)
Alcohol units per week, n (%)			
<1	53 (11%)	46 (13%)	108 (11%)
1-10	192 (39%)	140 (39%)	327 (34%)
11-20	88 (18%)	58 (16%)	142 (15%)
21-30	27 (6%)	20 (6%)	53 (6%)
31-40	9 (2%)	7 (2%)	13 (1%)
>40	8 (2%)	8 (2%)	14 (2%)
Duration of diabetes (years)	4 IQR(1-10)	4 IQR(1-10)	3 IQR(0-9)
BMI (kg/m²)	29 ± 5	29 ± 5	29 ± 5
Systolic blood pressure, mmHg	144 ± 19	143 ± 19	147 ± 22
Diastolic blood pressure, mm Hg	82 ± 11	81 ± 11	84 ± 12
<u>Laboratory measurements</u>			
Glucose, mmol/L	8.6 ± 3.0	8.5 ± 2.5	8.9 ± 3.0
HbA1c, %	7.0 ± 1.2	7.0 ± 1.2	7.2 ± 1.4
HbA1c, mmol/mol	53.0 ± 13.1	53.0 ± 13.1	55.2 ± 15.3
eGFR, ml/min/1.73 m²	78.5 ± 22.4	77.2 ± 20.1	76.4 ± 20.6
Micro-albuminuria, n (%)	108 (22)	92 (25)	227 (24)
Total Cholesterol, mmol/L	3.8 ± 1.3	4.2 ± 0.5	5.6 ± 1.0
LDL-c, mmol/L	1.5 ± 0.4	2.3 ± 0.2	3.5 ± 0.8
HDL-c, mmol/l	1.1 ± 0.4	1.1 ± 0.3	1.2 ± 0.3
non-HDL-c, mmol/L	2.7 ± 1.3	3.1 ± 0.5	4.4 ± 1.1
Triglycerides, mmol/L	1.7 IQR(1.0-2.9)	1.6 IQR(1.1-2.3)	1.7 (IQR 1.3-2.4)
<u>Medication</u>			
Glucose lowering medication, n (%)	347 (71)	247 (68)	589 (62)
Insulin, n (%)	125 (25)	86 (24)	217 (23)
Usual dose lipid-lowering therapy, n (%)	119 (24)	140 (39)	269 (28)
Intensive lipid-lowering therapy, n (%)	287 (58)	127 (35)	166 (17)
<u>Type of vascular disease</u>			
Coronary artery disease, n(%)	271 (55)	190 (52)	337 (65)
Cerebrovascular disease, n(%)	98 (20)	60 (17)	187 (20)
Peripheral artery disease, n(%)	57 (12)	42 (12)	162 (17)
Abdominal Aortic Aneurysm, n(%)	27 (6)	15 (4)	45 (5)

Baseline characteristics based on lipid lowering therapy

* BMI = body mass index, eGFR = estimated Glomerular Filtration Rate by the Modification of Diet in Renal Disease (MDRD) equation, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol

** Continuous variables are depicted as mean ± SD and count variables as n(%) and not normally distributed variables as median IQR

SUPPLEMENTARY DATA

Supplementary Table 3

Causes of mortality according to plasma LDL-c levels

<u>Causes of mortality</u>	<u>LDL-c <2.0 mmol/l</u>	<u>LDL-c 2.0-2.5 mmol/l</u>	<u>LDL-c >2.5 mmol/l</u>
Total death	68 (14%)	62 (17%)	255 (27%)
Vascular	39 (8%)	26 (7%)	149 (16%)
Malignancy	16 (3%)	21 (6%)	59 (6%)
Infection	4 (1%)	3 (1%)	16 (2%)
Unnatural causes	2 (0%)	0 (0%)	2 (0%)
Other non-vascular	3 (1%)	3 (1%)	14 (1%)
No classification	4 (1%)	9 (2%)	15 (2%)

SUPPLEMENTARY DATA

Supplementary Table 4

Relation between HDL-c and cardiovascular events and mortality according to intensity of lipid-lowering therapy

	No lipid lowering therapy (n= 702)	Usual dose therapy (n=528)	Intensive therapy (n=580)	Interaction Intensive vs Usual dose
<u>Myocardial infarction</u>				
n	49	42	24	
Model I	0.91 (0.82-1.00)	0.86 (0.75-0.98)	1.05 (0.92-1.19)	
Model II	0.90 (0.80-1.02)	0.86 (0.75-0.99)	1.15 (0.99-1.35)	
Model III	0.91 (0.81-1.02)	0.85 (0.74-0.99)	1.17 (1.00-1.37)	p=0.07
<u>Ischemic Stroke</u>				
n	35	15	21	
Model I	0.85 (0.74-0.96)	0.97 (0.81-1.17)	1.01 (0.87-1.16)	
Model II	0.86 (0.74-0.99)	0.98 (0.81-1.19)	0.95 (0.79-1.13)	
Model III	0.85 (0.74-0.99)	1.00 (0.84-1.20)	0.94 (0.78-1.13)	p=0.94
<u>Vascular mortality</u>				
n	108	63	43	
Model I	0.96 (0.90-1.02)	0.96 (0.87-1.05)	1.02 (0.92-1.13)	
Model II	0.98 (0.91-1.05)	0.97 (0.88-1.07)	1.03 (0.91-1.16)	
Model III	0.98 (0.92-1.05)	0.98 (0.88-1.08)	1.03 (0.91-1.16)	p=0.59
<u>Composite of major vascular events</u>				
n	158	98	79	
Model I	0.95 (0.90-1.00)	0.93 (0.87-1.01)	1.01 (0.93-1.09)	
Model II	0.96 (0.90-1.02)	0.95 (0.87-1.03)	1.02 (0.93-1.11)	
Model III	0.97 (0.91-1.02)	0.95 (0.87-1.03)	1.02 (0.93-1.12)	p=0.23
<u>All-cause mortality</u>				
n	217	105	63	
Model I	0.96 (0.91-1.00)	0.98 (0.92-1.06)	1.04 (0.95-1.13)	
Model II	0.97 (0.92-1.02)	0.98 (0.91-1.06)	1.07 (0.97-1.18)	
Model III	0.97 (0.93-1.02)	0.99 (0.92-1.07)	1.07 (0.97-1.19)	p=0.55

Hazard ratio (95% confidence interval) per 0.1 mmol/l increase in HDL-c, stratified according to lipid lowering therapy

Model 1: age + sex

Model 2: Model 1 + BMI, smoking, pack-years, alcohol, LDL-c, TG, systolic blood pressure

Model 3: Model 2 + eGFR, glucose, HbA1c