ONLINE SUPPLEMENTARY

Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease

Appendix 1. List of all potential covariates assessed at baseline

- Age at study entry (baseline)
- Gender (male or female)
- LDL cholesterol (baseline)
- Body mass index (BMI)
- Systolic blood pressure (single most recent value at baseline)
- Diastolic blood pressure (single most recent value at baseline)
- Alcohol misuse
- Smoking status (non-smoker; ex-smoker; smoker; unknown)
- Atrial fibrillation
- Chronic kidney disease
- Diabetes (using a Read codes diagnosis of diabetes and HBA1C reference ranges documented in the clinical record: non-diabetic; poorly-controlled diabetic; well-controlled diabetic; diabetic – control status unknown)
- History of dyslipidaemia
- Family history of CVD
- Family history of hyperlipidaemia
- Treated hypertension (diagnosis of hypertension and a treatment with at least one antihypertensive medication within 12 months prior to entry date)
- Hypothyroidism
- Liver disease
- Migraine
- Nephrotic syndrome
- Rheumatoid arthritis
- Severe mental illness
- Systemic lupus erythematosus
- Medication count (at baseline – within 12 months prior to entry date)
- Prescription of other lipid lowering medications (Including fibrates, bile sequestrants, nicotinic acid at baseline – within 12 months prior to entry date)
- Prescription of corticosteroids at baseline – within 12 months prior to entry date)
- Prescription of antipsychotics at baseline – within 12 months prior to entry date)
- Potency of initial prescribed statin (low; medium, high)
- Change in statin potency
- Time (year) of statin therapy initiation
- HDL cholesterol (baseline)
- Number of LDL-C measurements recorded within exposure period (24 months after statin therapy initiation).

Appendix 2. Characteristics of eligible patients being treated with statins and incident cardiovascular disease within 24 months of initiating statin therapy (n=23,947)

Characteristics		Total number (%)	Optimal statin responders, n (%)	Sub-optimal statin responders, n (%)
		23,947 (100)	**11,800 (49.3)**	**12,147 (50.7)**
Follow-up time (days)	Median (IQR)	133 (40 – 340)	135 (41 – 337)	130 (38 – 342)
Females	No. (%)	8,968 (37.5)	4,437 (37.6)	4,531 (37.3)
Age (years)	Mean (SD)	66.5 (11.0)	66.9 (10.9)	66.2 (11.0)
Baseline LDL cholesterol (mmol/L)	Mean (SD)	3.7 (1.2)	4.1 (1.0)	3.3 (1.1)
Post-treatment LDL cholesterol within 24 months (mmol/L)	Mean (SD)	2.3 (0.9)	1.9 (0.6)	2.7 (1.0)
Body mass index (kg/m2)	Mean (SD)	28.2 (5.2)	28.1 (5.0)	28.4 (5.3)
Alcohol misuse	No. (%)	180 (0.8)	67 (0.6)	113 (0.9)
Smoking				
Non-smoker	No. (%)	344 (1.4)	154 (1.3)	190 (1.6)
Ex-smoker		378 (1.6)	152 (1.3)	226 (1.9)
Smoker		344 (1.4)	146 (1.2)	198 (1.6)
Unknown status		22,816 (95.5)	11,339 (96.2)	11,477 (94.9)
Atrial fibrillation	No. (%)	1,023 (4.3)	510 (4.3)	513 (4.2)
Chronic kidney disease	No. (%)	635 (2.7)	301 (2.6)	334 (2.8)
Dyslipidaemias	No. (%)	1,657 (6.9)	767 (6.5)	890 (7.3)
Potency of initial statin prescribed				
Low	No. (%)	6,306 (26.4)	2,577 (21.8)	3,729 (30.7)
Medium		15,425 (64.4)	8,166 (69.2)	7,259 (59.8)
High		2,205 (9.2)	1,057 (9.0)	1,148 (9.5)

Appendix 3. Characteristics of eligible patients being treated with statins and free from cardiovascular disease at baseline. Patients are stratified by year of initiation of statin therapy

	2000 or earlier	2001 – 2005	2006 – 2010	2011 - 2016	p-value
	4,201 (2.54)	**66,944 (40.47)**	**67,751 (40.96)**	**26,515 (16.03)**	
Follow-up time (years), median (IQR)	7.7 (3.4-13.9)	8.8 (4.7-11.4)	6.4 (4.3-8.2)	3.0 (1.90–4.0)	0.0001
Females	2,072 (49.3)	34,371 (51.3)	31,785 (46.9)	12,142 (45.8)	<0.0001
Age (years), Mean (SD)	62.4 (10.1)	64.2 (11.6)	61.5 (11.7)	60.1 (12.0)	0.0001
Baseline LDL cholesterol (mmol/L), Mean (SD)	4.7 (1.1)	4.1 (1.1)	4.1 (1.1)	4.0 (1.2)	0.0001
Body mass index (kg/m2), Mean (SD)	28.2 (4.7)	28.9 (5.5)	29.2 (5.8)	29.5 (6.0)	<0.0001
Alcohol misuse	10 (0.2)	249 (0.4)	503 (0.7)	469 (1.8)	<0.0001
Smoking					<0.0001
Non-smoker	32 (0.8)	1,068 (1.6)	1,026 (1.5)	435 (1.6)	
Ex-smoker	21 (0.5)	758 (1.1)	741 (1.1)	318 (1.2)	
Smoker	23 (0.6)	719 (1.1)	882 (1.3)	379 (1.4)	
Unknown status	4,125 (98.2)	64,399 (96.2)	65,102 (96.1)	25,383 (95.7)	
Index of Multiple Deprivation (patients)					<0.0001
1	601 (23.8)	8,979 (24.0)	9,417 (23.1)	2,948 (19.6)	
2	575 (22.8)	8,362 (22.3)	9,012 (22.2)	3,193 (21.2)	
3	516 (20.5)	7,622 (20.3)	8,057 (19.8)	3,029 (20.1)	
4	454 (18.0)	6,929 (18.5)	7,678 (18.9)	3,125 (20.7)	
5	375 (14.9)	5,601 (14.9)	6,529 (16.0)	2,786 (18.5)	
Atrial fibrillation	103 (2.5)	2,224 (3.3)	1,836 (2.7)	686 (2.6)	<0.0001
Chronic kidney disease	12 (0.3)	357 (0.5)	3,114 (4.6)	986 (3.7)	<0.0001
Diabetes					<0.0001
Non diabetic	3,739 (89.0)	54,662 (81.7)	57,663 (85.1)	21,920 (82.7)	
Poorly-controlled diabetic	106 (2.5)	3,586 (5.4)	3,649 (5.4)	1,905 (7.2)	
Well- controlled diabetic	70 (1.7)	1,528 (2.3)	1,304 (1.9)	351 (1.3)	
Diabetic - control status unknown	286 (6.8)	7,168 (10.7)	5,135 (7.6)	2,339 (8.8)	
Dyslipidaemias	776 (18.5)	5,579 (8.3)	5,063 (7.5)	2,027 (7.6)	<0.0001
Potency of initial statin prescribed					<0.0001
Low	2,679 (63.8)	21,391 (32.0)	12,693 (18.7)	2,580 (9.7)	
Medium	1,449 (34.5)	42,042 (62.8)	53,078 (78.3)	20,695 (78.1)	
High	73 (1.7)	3,511 (5.2)	1,982 (2.9)	3,240 (12.2)	

Appendix 4. Effect estimates for association between sub-optimal LDL-C response at 24 months to initiated statin therapy and the risk of incident cardiovascular events using different statistical approaches. Patients with post-treatment LDL-C after 3 months of statin initiation (n=149,781).

	Group	Number of CVD events	Rate of CVD events (per 1,000 person-years)	Crude/unadjusted models		Adjusted models	
				Cox regression	Competing-risks survival regression	Cox regression	Competing-risks survival regression
				HR (95% CI)	sHR (95% CI)	HR (95% CI)	sHR (95% CI)
Overall CVD-related event *	Optimal	9821	19.9	1	1	1	1
	Sub-optimal	11387	22.7	1.16 (1.13 – 1.19)	1.12 (1.09 – 1.15)	1.21 (1.17 – 1.24)	1.18 (1.15 – 1.21) ‡
Coronary artery disease †	Optimal	5557	11.3	1	1	1	1
	Sub-optimal	6739	13.4	1.21 (1.17 – 1.25)	1.16 (1.12 – 1.21)	1.28 (1.24 – 1.33)	1.22 (1.18 – 1.26) §
Stroke/TIA *	Optimal	2174	4.4	1	1	1	1
	Sub-optimal	2317	4.6	1.08 (1.01 – 1.14)	1.02 (0.96 – 1.08)	1.16 (1.09 – 1.23)	1.11 (1.04 – 1.18) ‖
Peripheral vascular disease *	Optimal	1345	2.7	1	1	1	1
	Sub-optimal	1523	3.0	1.13 (1.05 – 1.21)	1.08 (1.00 – 1.16)	1.15 (1.06 – 1.24)	1.10 (1.02 – 1.19) #
CVD-related death *	Optimal	745	1.5	1	1	1	1
	Sub-optimal	808	1.6	1.09 (0.98 – 1.20)	1.04 (0.94 – 1.15)	1.25 (1.12 – 1.38)	1.20 (1.08 – 1.33) **

Cox regression provides hazard ratio whereas competing-risks survival regression (Fine-Gray Model) provides sub-hazard ratio

* Age and baseline LDL-cholesterol level were adjusted for in the multivariable models (both Cox and competing-risks) for overall CVD-related events, stroke/TIA, PVD, and CVD-related deaths.

† Age was adjusted for in the multivariable model (both Cox and competing-risks) for coronary artery disease.

‡ Competing risks for overall CVD-related event were non-CVD-related death and transfer out of practice.

§ Competing risks for coronary artery disease model were death, transfer out of practice, stroke/TIA and PVD.

|| Competing risks for stroke/TIA model were death, transfer out of practice, coronary artery disease and PVD.

Competing risks for PVD model were death, transfer out of practice, coronary artery disease, and stroke/TIA.

** Competing risks for CVD-related death were non-CVD-related death, transfer out of practice, coronary artery disease, stroke/TIA and PVD.

LDL-C - Low-density lipoprotein cholesterol; CPRD - Clinical Practice Research Datalink; HES - Hospital Episodes Statistics; ONS - Office of National Statistics; CVD - Cardiovascular disease; PVD – Peripheral vascular disease; TIA - transient ischaemic attack; HR - hazard ratio; CI - confidence interval; sHR - sub-hazard ratio.

Appendix 5. Association between LDL-C reduction within 24 months of statin therapy initiation and risk of cardiovascular disease. Patients with reduction in LDL-C within 24 months of initiating statin therapy (n=146,355)

	Optimal response (n=80,493) Odds Ratio (95% CI)	**Sub-optimal response (n=65,862)** Odds Ratio (95% CI)
Overall CVD event	0.87 (0.84 – 0.90)*	0.94 (0.91 – 0.98)*
Coronary artery disease	0.91 (0.88 – 0.95)*	0.96 (0.92 – 1.01)
Stroke/TIA	0.82 (0.77 – 0.87)*	0.87 (0.80 – 0.95)*
Peripheral vascular disease	0.87 (0.80 – 0.94)*	1.03 (0.94 – 1.14)
CVD-related death	0.88 (0.79 – 0.98)*	0.90 (079 – 1.03)

* Statistically significant association; LDL-C - Low-density lipoprotein cholesterol; CI – confidence interval; CVD – cardiovascular disease; TIA – transient ischaemic attack