Online Supplemental Material

Content

Supplemental Methods

Laboratory measurements

Lipid traits, including blood levels of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured in fasting participants using standardized assays. LDL-C was calculated using the Friedewald formula in individuals with triglyceride levels < 400 mg/dL.[1] CRP levels were determined using a nephelometer (Dade Behring BN100) and BNP levels were measured with a high-sensitivity immunoradiometric assay (Shionogi, Japan). The inter-assay coefficients of variation were 2.2% (CRP) and 12.2% (BNP), respectively.[2]

Ultrasound of the carotid artery

Images were obtained at three sites (at the carotid bulb, at the proximal internal carotid artery [ICA] and at the distal common carotid artery [CCA]) on both, the left and the right carotid arteries. Mid- and far-wall measurements were obtained at each site by a single reader and used to calculate intima media thickness (IMT), as described in detail elsewhere.[3] The reproducibility of the carotid IMT measurement was good, as previously reported, with intraclass correlation coefficients ranging from 0.74 (mean ICA IMT) to 0.90 (maximum CCA IMT).[4]

Adjudication of incident CVD events

Framingham participants are under regular surveillance for new-onset CVD events. All relevant information regarding incident events is reviewed by a panel of three physicians who adjudicate CVD events using standardized criteria. CVD was defined as myocardial infarction (fatal and nonfatal), angina, coronary insufficiency (acute coronary syndrome), peripheral vascular disease (intermittent claudication), cerebrovascular events (stroke or transient ischemic attack), and heart failure, consistent with prior publications.[5]

Supplemental Tables

Supplemental Table 1. Baseline characteristics of the subclinical disease sample (n=2917), stratified by LDL group

LDL (in mg/dL) group	Total subclinical disease sample	LDL<100 mg/dl No treatment (n=528)	100≤LDL<130 mg/dl No treatment (n=899)	LDL<130 mg/dl On treatment (n=167)	LDL≥130 mg/dl No treatment (n=1192)	LDL≥130 mg/dl On treatment (n=131)
Clinical and biochemical features						
Age, years; mean ± SD	58.4 ± 9.6	56.3 ± 9.7	57.9 ± 9.8	63.7 ± 8.6	58.5 ± 9.3	62.9 ± 7.4
Women, n (%)	1613 (55.3)	337 (63.8)	485 (53.9)	73 (43.7)	644 (54.0)	74 (56.5)
LDL cholesterol, mg/dL; mean ± SD	127.9 ± 33.3	83.6 ± 13.0	115.8 ± 8.4	104.3 ± 18.9	156.7 ± 22.3	157.2 ± 23.7
HDL cholesterol, mg/dL; mean ± SD	52.0 ± 16.0	58.1 ± 19.9	52.2 ± 15.9	44.9 ± 13.3	50.7 ± 13.9	47.5 ± 11.6
Total cholesterol, mg/dL; mean ± SD	205.8 ± 37.0	163.1 ± 22.7	192.6 ± 18.4	182.3 ± 26.2	234.4 ± 26.9	237.9 ± 30.5
Lipid-lowering treatment, n (%)	298 (10.2)	0 (0.0)	0 (0.0)	167 (100.0)	0 (0.0)	131 (100.0)
Statin treatment, n (%)	221 (7.6)	0 (0.0)	0 (0.0)	137 (82.0)	0 (0.0)	84 (64.1)
Systolic BP, mmHg; mean ± SD	127.8 ± 18.7	123.0 ± 18.0	126.7 ± 18.4	137.0 ± 19.6	128.7 ± 18.3	133.5 ± 18.0
Diastolic BP, mmHg; mean ± SD	75.6 ± 9.4	73.5 ± 9.5	75.2 ± 9.1	76.3 ± 9.2	76.4 ± 9.5	77.7 ± 9.3
BP-Treatment, n (%)	708 (24.3)	83 (15.7)	222 (24.7)	97 (58.1)	251 (21.1)	55 (42.0)
Body mass index, kg/m²; mean ± SD	27.8 ± 5.2	26.6 ± 5.2	27.8 ± 5.4	29.4 ± 4.9	28.1 ± 5.1	28.6 ± 4.3
Smoking, n (%)	426 (14.6)	71 (13.5)	122 (13.6)	14 (8.4)	197 (16.5)	22 (16.8)
Diabetes, n (%)	220 (7.5)	32 (6.1)	64 (7.1)	37 (22.2)	67 (5.6)	20 (15.3)

BNP, pg/mL, median (Q1, Q3)*	7.8 (4.0, 16.9)	8.8 (4.0, 19.6)	8.2 (4.0, 18.7)	10.2 (4.0, 22.5)	6.8 (4.0, 14.6)	8.9 (4.0, 16.6)
CRP, mg/L, median (Q1, Q3)†	2.0 (0.9, 4.5)	1.8 (0.7, 4.9)	1.8 (0.8, 3.9)	2.4 (1.0, 4.9)	2.1 (1.0, 4.6)	2.8 (1.2, 4.8)
Carotid US abnormalities, n (%)	793 (27.2)	99 (18.8)	205 (22.8)	84 (50.3)	350 (29.4)	55 (42.0)

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; SD, standard deviation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; US, ultrasound

"Carotid ultrasound abnormality" was defined as i) increased (≥ 80% sex-specific percentile) carotid IMT (intima-media thickness), a combined standardized measure including information from the internal and common carotid artery OR ii) an extreme increase of the common carotid IMT ≥1 mm OR iii) significant (≥25%) narrowing of the common or internal carotid arteries, consistent with prior publications.[3, 5]

*Sample size with available BNP levels, n=2902

†Sample size with available CRP levels, n=2818

Supplemental Table 2. Detailed information regarding individuals on lipid-lowering treatment (LLT)

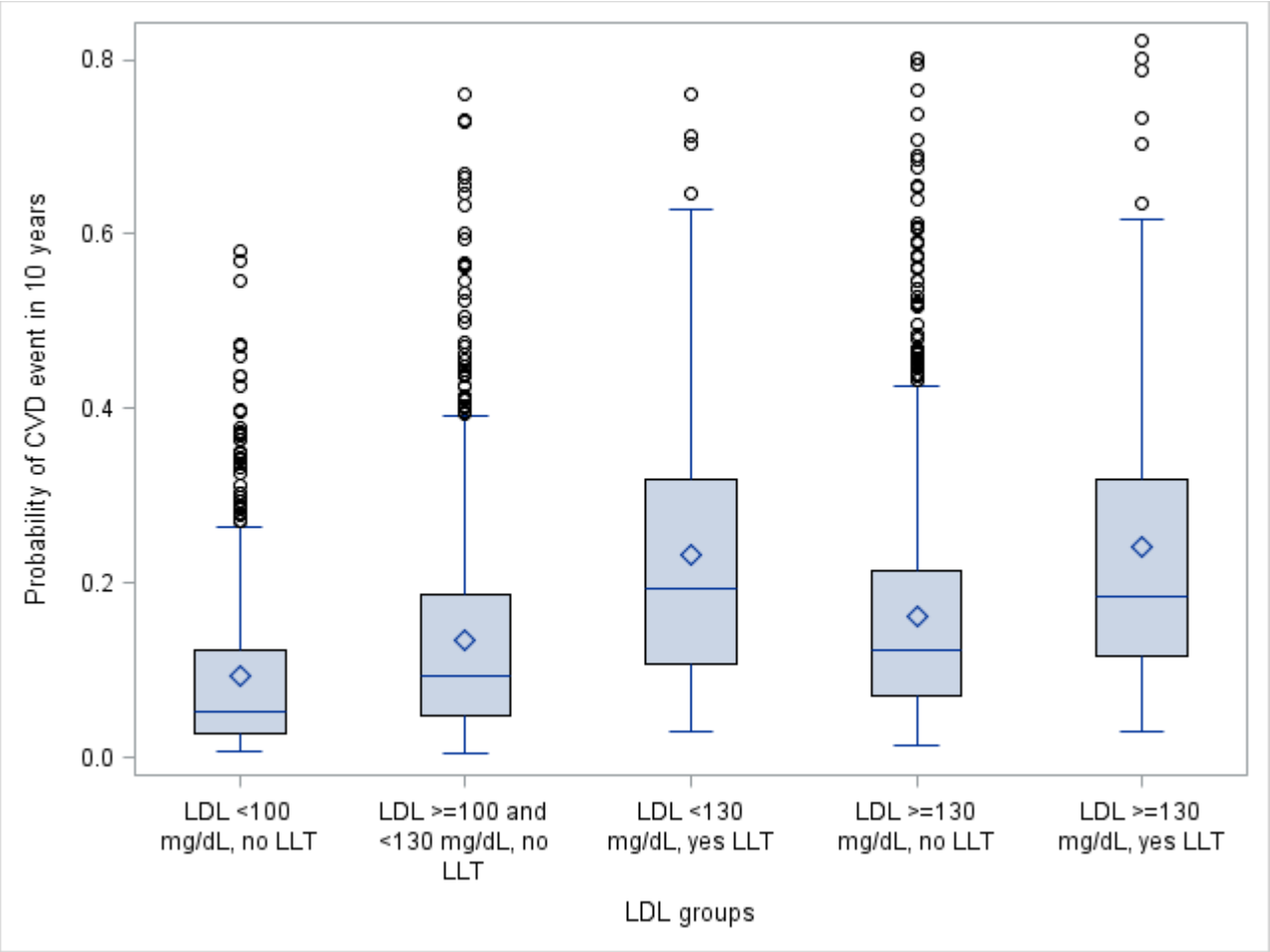
	Overall sample (N = 3012)				
LDL (in mg/dL) group	**Group 1: LDL<100 No treatment (N=546)**	**Group 2: 100≤LDL<130 No treatment (N=931)**	**Group 3: LDL<130 On treatment (N=170)**	**Group 4: LDL≥130 No treatment (N=1233)**	**Group 5: LDL≥130 On treatment (N=132)**
Average LDL levels across exams 1 to 6, mg/dL; mean ± SD	93.1 ± 16.7	116.7 ± 15.7	138.8 ± 21.7	143.6 ± 21.9	168.5 ± 23.9
Individuals on lipid-lowering treatment (LLT) at exam 6, n (%)	0	0	170 (100.0)	0	132 (100.0)
Individuals on statins at exam 6, n (%)	0	0	140 (82.4)	0	84 (63.6)
Individuals on LLT, but not on statins at exam 6, n (%)	0	0	30 (17.6)	0	48 (36.4)
Average duration of LLT (statin+non-statin), years ± SD			4.6 ± 3.6		5.1 ± 3.5
Average LDL levels across all those exams **BEFORE** lipid-lowering treatment was initiated, mg/dL, mean ± SD			150.4 ± 27.5		175.4 ± 30.6

LLT indicates lipid-lowering treatment (statins + non-statins).

The duration of lipid-lowering treatment (LLT) was estimated by taking as start date of LLT the middle of the time period between the last exam without LLT and the first exam where LLT was noted.

Supplemental Figure

Supplemental Figure 1. 10-year probability of a CVD event according to LDL group[6] (baseline risk)



The horizontal line in the box indicates the median; the diamond reflects the mean.

Supplemental References

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