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Changes in HDL cholesterol and cardiovascular outcomes after lipid modification therapy

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Abstract

Background—Lipid modification therapy (LMT) produces cardiovascular benefits principally through reductions in low density lipoprotein cholesterol (LDL-C). While recent evidence, using data from 454 participants in the Framingham Offspring Study (FOS), has suggested that increases in high density lipoprotein cholesterol (HDL-C) are also associated with a reduction in cardiovascular outcomes, independently of changes in LDL-C, replication of this finding is important. We therefore present further results using data from the EPIC Norfolk (UK) and Rotterdam (Netherlands) prospective cohort studies.

Methods—A total of 1,148 participants, 446 from the EPIC-Norfolk and 702 from the Rotterdam study were assessed for lipids before and after starting LMT. Subsequent risk of cardiovascular events, ascertained through linkage with mortality records and hospital databases, was investigated using Cox Proportional hazards regression. Random effects meta-analysis was used to combine results across studies.

Results—Based on combined data from the EPIC-Norfolk and Rotterdam studies there was some evidence that change in HDL-C resulting from LMT was associated with reduced cardiovascular risk (hazard ratio per pooled SD (= 0.34 mmol/l) increase = 0.74, 95% CI 0.56-0.99, adjusted for age, sex, and baseline HDL-C). However, this association was attenuated and was not (statistically) significant with further adjustments for non-HDL-C and for cigarette

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⁸KKR, NWJW both contributed equally to this manuscript.

Competing interests KKR has received honoraria for advisory boards, consultancy, or lectures (modest) from Pfizer, Astra Zeneca, Merck, Schering Plough and Roche.

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smoking history, prevalent diabetes, SBP, BMI, use of antihypertensive medication, previous MI, prevalent angina, previous stroke (0.92, 0.70-1.20).

Conclusions—Following adjustment for conventional non-lipid CVD risk factors, this study provides no evidence to support a significant benefit from increasing HDL-C independent of the effect of lowering non-HDL-C.

Keywords

Lipids; Lipoproteins; HDL; Atherosclerosis; Myocardial infarction

INTRODUCTION

Observational data have shown consistent positive relationships between atherogenic lipid fractions such as low density lipoprotein cholesterol (LDL-C) and risk of cardiovascular disease (CVD) and in contrast inverse relationships exist with high density lipoprotein cholesterol (HDL-C).[1] Trials of lipid modification therapy (LMT) have supported a causal relationship between LDL-C and CVD as they have shown that LMT reduces cardiovascular events across a spectrum of risk [2] and from multiple interventions.[2-9] It is postulated from meta-regression data that the relative benefits of some interventions like cholesterol exchange resins and fibrates are predictable and related to the degree of LDL-C reduction and consequently more modest than for instance statins. [10, 11] Some interventions such as fibrates and nicotinic acid which have a complex array of effects including reducing LDL-C and triglyceride as well as raising HDL-C, have also shown cardiovascular benefit in specific populations [4-7] but to what extent components other than LDL-C (or non-HDL cholesterol) altered by LMT contribute to CVD risk remains inconclusive.

The principal benefit of LMT is believed to be related to the magnitude of LDL-C reduction, with the most powerful agents, the statins, showing the most consistent benefit at a population level. [2] However, LMT also results in variable changes in levels of HDL-C and triglycerides (TG) and the extent to which changes in HDL-C are related to cardiovascular events after adjustment for LDL-C remain unclear. This is particularly important as randomized controlled trials of the HDL-C raising agent torcetrapib resulted in an increase in all cause mortality and while it is now believed that these effects were related to drug toxicity, the evidence base for HDL-C raising remains far from conclusive. [12] While ongoing outcome trials of different HDL-C raising agents are awaited, a recent analysis of observational data from the Framingham Offspring Study (FOS), suggests that HDL-C differences resulting from LMT may be relevant to cardiovascular benefit even after adjusting for changes in LDL-C. [13] Replication of such findings is important in other populations as single studies may provide chance associations and by combining available data in an updated meta-analysis both power and precision can be improved. We carried out such additional analyses by studying the relationship between changes in HDL-C and CVD outcomes in two further prospective cohort studies, the EPIC Norfolk (UK) [14] and Rotterdam (Netherlands) [15] studies.

METHODS

Participants and measures

EPIC-Norfolk is a general population study of residents of Norfolk, United Kingdom, (then) aged between 40 and 74 years and recruited between 1993 and 1997 by use of general practice registers. [14] The study was approved by the Norwich District Health Authority Ethics Committee and all participants gave signed informed consent. The Rotterdam study is a general population study of residents of the well-defined Ommoord district in the city of

Rotterdam (Netherlands), aged 55 years and over, recruited in 1990 and again in 1999 using the municipal register [15, 16]. The Rotterdam study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of the Netherlands Ministry of Health, Welfare and Sports. For the initial 1990 cohort, measures are available from baseline and up to 3 follow-up assessments. For the 1999 cohort, measures are available from a baseline and one further follow-up assessment.

For both the EPIC-Norfolk and Rotterdam studies individuals were selected for inclusion in the current study if they were on lipid modifying therapy (LMT) at a second assessment but not at a first. These participants are known to have started LMT at some point between the two assessments, though the exact date of initial treatment is unknown. Change in HDL and non-HDL cholesterol following commencement of LMT was estimated as the difference between lipid measurements at the second and first health assessments. Incident CVD endpoints were ascertained from the date of the second assessment until the most recent available follow-up.

EPIC-Norfolk

A total of 446 EPIC-Norfolk participants who had attended the first two health checks and who had lipid data available were on LMT at the second but not the first health check (and had not been admitted to hospital with MI or stroke before the second health check) were eligible for and were included in this study. Of these 242 were men and 204 were women, with mean age 62.5 (range 42 to 78). The median time between the two health checks was 44 months (range 26-76). Non-fasting serum total and high density lipoprotein (HDL-C) cholesterol levels were measured at both health checks (mmol/l) using an RA 1000 Technicon analyzer (Bayer Diagnostics, Basingstoke, United Kingdom). Low density lipoprotein (LDL-C) cholesterol was determined using the Friedewald formula. Details of medication use (including LMT and antihypertensives) were obtained at each health check from self-report questionnaire. Assessment of systolic blood pressure (mm/Hg) was based on the mean of two readings taken by trained nurses and body mass index was determined according to the Quetelet index (kg/m^2). At baseline, details of previous physician-confirmed medical conditions, including angina, myocardial infarction, stroke and diabetes, were noted, along with current and lifetime cigarette smoking behaviour. All deaths to 31st March 2008 were recorded through linkage with data from the UK Office for National Statistics. Data on all hospital admissions to 31st March 2008, throughout England and Wales were obtained through linkage with the National Health Services health district database. Mortality and morbidity outcomes were classified initially according to International Classification of Diseases, 9th revision (ICD-9), and subsequently according to the 10th revision (ICD-10). For this report, CVD events included mortality from CVD (ICD-9 codes 401–448; ICD-10 codes I10–I79), hospital admission due to MI (ICD-9 codes 410; ICD-10 I21-I22), and hospital admission due to stroke (ICD 9 codes 430 to 438; ICD 10 as codes I60 to I69).

Rotterdam

A total of 702 (of 10,944) Rotterdam participants who had attended two health checks, who had lipid data available, and were on LMT at the second but not at the first health check (and had not been admitted to hospital with MI or stroke before the second health check) were eligible for and were included in this study. Of these, 300 were men and 402 were women, with mean age 63.5 (range 55 to 86). The median time between the two health checks was 75 months (range 19-167). Baseline and follow-up assessments included details of medical history, current and lifetime cigarette smoking behaviour, medication use (including LMT and antihypertensives), body mass index (kg/m^2), and systolic blood pressure (mm/Hg), based on the mean of two readings taken by trained nurses with a random-zero

sphygmomanometer after a 5-minutes rest. Non-fasting serum total and high density lipoprotein (HDL-C) cholesterol were measured (mmol/l) using an automated enzymatic procedure. As LDL-C and TG were not measured for all participants during all examination rounds in the Rotterdam study, a measure of non-HDL-C was calculated as total minus HDL-C. Morbidity and mortality were assessed by information from general practitioners, by discharge reports from medical specialists, and from the municipal health authorities in Rotterdam. Cardiovascular events were independently coded by two research physicians and reviewed by a medical expert in cardiovascular disease. As above, CVD events included mortality from CVD (ICD-10 codes I10-I79), hospital admission due to MI (ICD-10 I21-I22), and hospital admission due to stroke (ICD-10 codes: I60-I69).

Statistical analysis

The association between change in HDL-C resulting from LMT (HDL) and incident cardiovascular endpoints in the EPIC-Norfolk and Rotterdam studies was investigated through Cox proportional hazards regression. Results are presented as hazard ratios per (study-specific) SD increase in HDL, stratified by age (in 10-year bands) and sex, and with progressive additional adjustments for; A. Baseline HDL-C, B. Baseline non-HDL-C, and non-HDL, and C. Cigarette smoking history, prevalent diabetes, SBP, BMI, use of antihypertensive medication, previous MI, prevalent angina, previous stroke. Results for non-HDL are presented per (study-specific) SD decrease. HDL-C, HDL, non-HDL-C, non-HDL, SBP, and BMI were all included as continuous variables. Cigarette smoking was included as a categorical variable (current, former and never smokers). Adjusted analyses were performed on a complete case basis. Pooled estimates of effect from both studies, for HDL-C and in non-HDL-C and CVD risk, were obtained through random effects meta-analysis, and presented for a 1 SD increase in HDL and a 1 SD decrease in non-HDL (where the SDs were calculated as the weighted mean of the SDs from both studies).

RESULTS

Table 1 shows descriptive data for the EPIC-Norfolk and Rotterdam studies. Of the 446 participants in the EPIC-Norfolk study 60 died from CVD or were admitted to hospital due to MI or stroke (39 in men and 21 in women) during median 8.4 years of follow-up (range 15 days to 10.1 years). Of these 27 were deaths from CVD, 20 were fatal or non-fatal strokes, and 38 were CHD deaths or non-fatal MIs. HDL-C was modestly increased at the second compared to the first health check (mean difference = 0.13 mmol/l, 95% CI 0.10–0.16, $p < 0.0001$), LDL-C (mean difference = –1.96 mmol/l, 95% CI –2.07– –1.85, $p < 0.0001$) and non-HDL-C (mean difference = –2.11 mmol/l, 95% CI –2.22– –1.99, $p < 0.0001$) was substantially reduced. Similarly, of the 702 participants in the Rotterdam study 46 died from CVD or were admitted to hospital due to MI or stroke 28 in men and 18 in women) during median 2.7 years of follow-up (range 82 days to 9.0 years). Of these 26 were deaths from CVD, 17 were fatal or non-fatal strokes, and 17 were CHD deaths or non-fatal MIs. HDL-C was modestly increased at the second compared to the first health check (mean difference = 0.08 mmol/l, 95% CI 0.05–0.11, $p < 0.0001$), and non-HDL-C (mean difference = –2.00 mmol/l, 95% CI –2.10– –1.90, $p < 0.0001$) was substantially reduced.

Table 2 shows the association between changes in lipids resulting from LMT and incident CVD endpoints in the EPIC-Norfolk and Rotterdam studies. Based on data from the EPIC-Norfolk study, there was some evidence that increases in HDL-C resulting from LMT were associated with a reduced risk of CVD. However, this association was attenuated and no longer (statistically) significant following progressive adjustment for baseline non-HDL-C and non-HDL-C, and for the range of CVD risk factors included. While individuals from the Rotterdam study whose HDL-C increased after LMT experienced fewer CVD endpoints

over follow-up, these associations were not (statistically) significant and no differences were observed after adjustment for baseline non-HDL-C and non-HDL-C, and for the range of CVD risk factors included.

Figure 1 shows pooled estimates of the hazard ratios for change in HDL-C using data from the EPIC-Norfolk and Rotterdam studies. A 1 SD (= 0.34 mmol/l based on the weighted mean of the SD from both studies) increase in HDL-C resulting from LMT was associated with a 26% reduced risk of CVD with adjustment for age, sex and baseline HDL-C (hazard ratio 0.74, 95% CI 0.56-0.99, with no evidence of between study heterogeneity, $I^2 = 24.6\%$, $p = 0.25$). However, with further adjustment for non-HDL-C and non-HDL-C this association was attenuated and was not (statistically) significant (0.81, 0.62-1.06, $I^2 = 0\%$, $p = 0.40$), and was further attenuated with adjustment for all risk factors considered (0.92, 0.70-1.20, $I^2 = 0\%$, $p = 0.43$, $I^2 = 0\%$, $p = 0.43$). Similarly, Figure 2 shows pooled estimates of association for change in non-HDL-C, and shows that there was a 34% reduced risk of CVD for a 1 SD (= 1.31 mmol/l based on the weighted mean of the SD from both studies) decrease in non-HDL-C, following adjustment for age, sex, baseline HDL-C, HDL and baseline non-HDL-C (0.66, 0.50-0.88, $I^2 = 0\%$, $p = 0.50$). This effect remained (and was statistically significant) following adjustment for all risk factors considered (0.68, 0.50-0.92, $I^2 = 0\%$, $p = 0.36$).

Discussion

Previous findings based on data from 454 participants in FOS of whom 79 experienced a CVD event, reported an association between change in HDL-C subsequent to starting on LMT, independent of changes in LDL-C and a range of other CVD risk factors [13]. Based on new data from a combined sample of 1148 EPIC-Norfolk and Rotterdam study participants and 106 CVD endpoints, our findings give limited support for this association, suggesting that this is of smaller magnitude than previously observed and that it is not independent of changes in non-HDL-C and of conventional non-lipid CVD risk factors.

Epidemiological studies have demonstrated a continuous inverse relationship between HDL-C and risk of CVD. [1] A recent study showed that low HDL-C after statin therapy was associated with an increased risk of cardiac events in patients who underwent percutaneous coronary intervention [17]. However, attempts to convincingly prove that raising HDL-C is beneficial have been thwarted to some extent by use of treatments which are not well tolerated (such as nicotinic acid) [18] or study design [19, 20], or the relative weak potency of the agents used [19] resulting in inadequate power. [21] Newer and more potent agents have been limited by significant drug toxicity [12] leading to some to reconsider the whole concept of HDL-C raising.

Whilst concerns have been raised about raising HDL-C and the risk of non-CV deaths, the analysis of Burillo et al suggested that after exclusion of Torcetrapib outcome data in the Illuminate trial there was no association between HDL-C increase and non-CVD risk [22]. Torcetrapib had a number of off target effects related to drug interaction on the renin angiotensin system and as no association was found between increasing HDL-C levels per se and adverse outcomes in that trial, this suggests it was the drug/ and or mechanism rather than HDL-C increase.

We sought to replicate the earlier observation that changes in HDL-C associated with LMT are associated with a lower risk of CV events independent of changes in LDL-C (or non-HDL-C). [13] The present study demonstrates directionally consistent findings in the EPIC-Norfolk and Rotterdam cohorts. However, these are more modest and are attenuated after adjustment in particular for non-lipid related factors.

In a combined population from EPIC Norfolk and Rotterdam including about 100 new incident cases, we observed that a 1SD rise in HDL-C of 0.34 mmol/l with LMT was associated with a 26% lower risk of CVD consistent with the observations in the FOS. This relationship was considerably attenuated after adjustment for other cardiovascular risk factors to a non-significant and more modest 8% relative risk reduction. The magnitude of attenuation after adjusting for non-HDL observed here is not surprising given the inverse association between HDL-C and apo B containing lipoproteins in particular VLDL. We did not adjust for TG levels (as this was not available in the Rotterdam study) and given the observation that TG is no longer associated with CVD after adjustment for non-HDL-C and HDL-C [1] we do not believe that this altered our findings. The further attenuation after adjustment for traditional risk factors is not surprising given the inverse relationship between BMI and smoking and HDL-C [23, 24] and the effect of lifestyle modification such as weight loss and smoking cessation on HDL-C levels.

In contrast the RR per 1SD lowering of non-HDL-C was approximately similar in both EPIC Norfolk and Rotterdam cohorts and overall was associated with a 32% lower risk of CVD (per SD decrease of 1.31 mmol/l) even after adjustment for traditional risk factors and change in HDL-C. The magnitude of the risk reduction is comparable to the 23% risk reduction observed per mmol/L observed in the 90 person Cholesterol Treatment Trialists Initiative given that non-HDL-C also encompasses other atherogenic lipoproteins such as VLDL and IDL, which adds confidence in the methods used both in the present study and in the earlier FOS.

Previous analysis of FOS data included 454 participants of whom 79 experienced a CVD event defined as development of angina pectoris, coronary insufficiency, myocardial infarction, coronary death, transient ischemic attack, and fatal or nonfatal thrombotic stroke. [13] These results showed that a 5mg/dL increase in HDL was associated with a 20% reduced of CVD after adjusting for age, sex and baseline HDL-C (hazards ratio 0.80, 95% CI 0.69-0.94) and a 21% reduced risk after adjustment for a range of CVD risk factors (0.79, 95% CI 0.67-0.93) [13]. Based on a (random effects) meta-analysis combining data from FOS with new data from the EPIC-Norfolk and Rotterdam studies, there was some support for an association adjusted only for age, sex and baseline HDL-C (pooled estimate of hazards ratio per 5mg/dl (where 38.67 mg/dL = 1 mmol/l) = 0.86, 95% CI 0.79 – 0.95). However, this association was attenuated and was not (statistically significant) after adjustment for the full range of CVD risk factors considered (hazards ratio 0.91, 95% CI 0.79 – 1.04).

This combined meta-analysis of FOS, EPIC Norfolk and Rotterdam standardised per 5mg/dl increment in HDL-C suggests that the earlier observation of strong independent associations between HDL-C and CHD likely reflect chance and that the true association is more modest, as the present study approximately doubles the number of cases, while being at least directionally consistent with FOS. Another potential discrepancy between the findings in EPIC Norfolk and Rotterdam and the FOS study is that FOS adjusted for LDL-C rather than non-HDL-C, given the strong inverse association between HDL and VLDL and IDL, it is likely that further attenuation in risk would have been observed in that study. Overall we found that the combined data suggested a more modest 9% RR reduction rather than a 21% reduction previously observed in FOS, consistent with larger studies with increased power regressing towards more conservative point estimates than those observed in a single study.

It should be noted that while the combined meta-analysis of FOS and the present studies (EPIC Norfolk and Rotterdam) adjusted for LDL-C and non-HDL-C respectively which may limit the interpretation, the combined data are broadly consistent with the assertion that changes in atherogenic lipids predict future risk of CVD. Meta-analysis of associations for

LDL-C from the analysis of FOS [13] with new data on associations for non-HDL-C from the EPIC-Norfolk and Rotterdam studies showed that per 10mg/dl lowering of atherogenic lipid there was a 8% lower risk of CVD (pooled estimate of hazards ratio = 0.92, 95% CI = 0.88 – 0.96 after adjusting for age, sex, baseline LDL-C/non-HDL C and for the range of other CVD risk factors considered) with no evidence of significant heterogeneity across studies.

While the present analyses have focused on HDL-C, there is emerging evidence that HDL function rather than HDL-C although partly correlated may be critical to atherosclerosis [25]. The present data do not exclude the possibility that strategies which improve HDL function and cholesterol efflux will not improve CVD risk.

A note of caution is also required when interpreting our data. While we have attempted via multivariable adjustment to control for confounders we cannot exclude the possibility of residual confounding as a possible explanation. Finally while the majority of treatments were statins we do have combined all LMT together and cannot exclude the possibility of differential effects in different LMT classes.

In conclusion the present findings give limited support to the possibility of beneficial effects of HDL-C raising in ongoing clinical trials. While we found some evidence of association between changes in HDL-C and reduced risk of CVD, our findings suggest that these effects are not independent of non-LDL-C lowering or of changes in conventional non-lipid CVD risk factors and that they are more modest than those previously described.

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Figure 1. Association between change in HDL-C (HDL-C, per pooled SD = 0.34 mmol/l increase) resulting from LMT and incident CVD: study-specific and pooled hazard ratios (95% confidence intervals) from the EPIC-Norfolk and Rotterdam studies. Adjusted for

A. Age, sex, baseline HDL-C and HDL.

B. Age, sex, baseline HDL-C, HDL, baseline non-HDL-C and non-HDL

C. Age, sex, baseline HDL-C, HDL, baseline non-HDL-C and non-HDL, cigarette smoking history, prevalent diabetes, SBP, BMI, use of antihypertensive medication, previous MI, prevalent angina, previous stroke.

Figure 2. Association between change in non-HDL-C (non-HDL-C, per pooled SD = 1.31mmol/l decrease) resulting from LMT and incident CVD: study-specific and pooled hazard ratios (95% confidence intervals) from the EPIC-Norfolk and Rotterdam studies. Adjusted for
 B. Age, sex, baseline HDL-C, HDL, baseline non-HDL-C and non-HDL
 C. Age, sex, baseline HDL-C, HDL, baseline non-HDL-C and non-HDL, cigarette smoking history, prevalent diabetes, SBP, BMI, use of antihypertensive medication, previous MI, prevalent angina, previous stroke.

Table 1
Descriptive data from the EPIC-Norfolk and Rotterdam studies

	EPIC-Norfolk	Rotterdam
Contributing participants	446	702
Median follow-up (years)	8.4	2.7
Age (mean, SD)	62.5 (7.3)	63.5 (5.6)
Sex (% Female)	45.7	57.3
HDL-C at first assessment (mean (SD) mmol/l)	1.31 (0.36)	1.30 (0.43)
HDL-C at second assessment (mean (SD) mmol/l)	1.44 (0.42)	1.39 (0.36)
HDL (mean (SD) mmol/l)	0.13 (0.29)	0.08 (0.36)
Total cholesterol at first assessment (mean (SD) mmol/l)	7.43 (1.31)	7.04 (1.39)
Total cholesterol at second assessment (mean (SD) mmol/l)	5.45 (1.06)	5.13 (1.01)
Total-cholesterol (mean (SD) mmol/l)	-1.98 (1.21)	-1.91 (1.33)
Non-HDL-C at first assessment (mean (SD) mmol/l)	6.13 (1.30)	5.71 (1.40)
Non-HDL-C at second assessment (mean (SD) mmol/l)	4.02 (1.06)	3.75 (0.99)
non-HDL (mean (SD) mmol/l)	-2.11 (1.25)	-2.00 (1.34)
SBP at first assessment (mean (SD) mg/Hg)	141 (17.7)	140 (21.0)
BMI at first assessment (mean (SD) kg/m ²)	26.8 (3.6)	27 (3.4)
Cigarette smoking (% current)	9.0	20.7
Prevalent diabetes (%)	7.0	6.6
Previous MI (%)	16.4	11.1
Prevalent angina (%)	25.6	
Previous stroke (%)	2.2	1.9
Use of antihypertensive medication (%)	39.5	36.8

Table 2
Associations between changes in HDL-C (HDL-C) and non-HDL-C (non-HDL-C)
resulting from LMT, baseline HDL-C, and baseline non-HDL-C, and incident CVD in the
EPIC-Norfolk and Rotterdam studies.

	HR (95% CI)		
	A	B	C
EPIC-Norfolk (60 CVD endpoints)			
HDL-C (per SD increase)	0.68 (0.51 – 0.92)	0.76 (0.56 – 1.04)	0.85 (0.62 – 1.17)
non-HDL-C (per SD decrease)		0.63 (0.45 – 0.89)	0.62 (0.43 – 0.89)
Baseline HDL-C (per SD increase)	0.81 (0.59 – 1.11)	0.83 (0.60 – 1.14)	0.81 (0.58 – 1.14)
Baseline non-HDL-C (per SD increase)		1.07 (0.74 – 1.54)	1.06 (0.72 – 1.56)
Rotterdam (46 CVD endpoints)			
HDL-C (per SD increase)	0.86 (0.58 – 1.28)	0.91 (0.60 – 1.39)	1.03 (0.67 – 1.58)
non-HDL-C (per SD decrease)		0.74 (0.47 – 1.18)	0.81 (0.50 – 1.31)
Baseline HDL-C (per SD increase)	0.47 (0.12 – 1.85)	0.54 (0.14 – 2.13)	0.65 (0.21 – 2.03)
Baseline non-HDL-C (per SD increase)		1.04 (0.97 – 1.13)	1.05 (0.97 – 1.15)

A. Adjusted for age, sex, baseline HDL-C and HDL.

B. Adjusted for age, sex, baseline HDL-C, HDL, baseline non-HDL-C and non-HDL.

C. Adjusted for age, sex, baseline HDL-C, HDL, baseline non-HDL-C, non-HDL, cigarette smoking history, prevalent diabetes, SBP, BMI, use of antihypertensive medication, previous MI, prevalent angina, previous stroke.