

Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes

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Abstract

Aims/hypothesis The apolipoprotein B (ApoB):apolipoprotein A (ApoA)-I ratio may be a better indicator of cardiovascular disease (CVD) risk in people with type 2 diabetes than traditional lipid risk markers (LDL-cholesterol, HDL-

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cholesterol and triacylglycerol), but whether the ApoB:ApoA-I ratio should be used to indicate lipid-lowering therapy is still debated.

Methods The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomised 9,795 patients with type 2 diabetes to fenofibrate (200 mg daily) or placebo and followed them up for a median of 5 years. We compared ApoB, ApoA-I, ApoAII and the ApoB:ApoA-I ratio with traditional lipid variables as predictors of CVD risk. We estimated the HR of the effect of 1 SD difference in baseline concentrations of lipids, apolipoproteins and respective ratios on the risk of CVD events and also used receiver operating characteristic curve analysis.

Results In the placebo group, the variables best predicting CVD events were non-HDL-cholesterol:HDL-cholesterol, total cholesterol:HDL-cholesterol (HR 1.21, $p < 0.001$ for both), ApoB:ApoA-I (HR 1.20, $p < 0.001$), LDL-cholesterol:HDL-cholesterol (HR 1.17, $p < 0.001$), HDL-cholesterol (HR 0.84, $p < 0.001$) and ApoA-I (HR 0.85, $p < 0.001$). In the fenofibrate group, the first four predictors were very similar (but ApoB:ApoA-I was fourth), followed by non-HDL-cholesterol and ApoB. Lipid ratios and ApoB:ApoA-I performed better than any single lipid or apolipoprotein in predicting CVD risk.

Conclusions/interpretation In patients with type 2 diabetes in the FIELD study, traditional lipid ratios were as strong as the ApoB:ApoA-I ratio in predicting CVD risk. The data provide little evidence for replacement of traditional lipids and their ratios with measures of ApoB, ApoA-I and their ratio.

Keywords Cardiovascular risk · Diagnostic tests · Lipids · Lipoproteins · Non-HDL-cholesterol · Type 2 diabetes

Abbreviations

ApoA Apolipoprotein A
ApoB Apolipoprotein B
CARDS Collaborative Atorvastatin Diabetes Study

CVD	Cardiovascular disease
ERFC	Emerging Risk Factors Collaboration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
ROC	Receiver operating characteristic
TRL	Triacylglycerol-rich lipoproteins

Introduction

Atherosclerotic cardiovascular disease (CVD) results from the interplay of genetic and environmental factors. The new epidemic of type 2 diabetes and the dyslipidaemia associated with it is fuelling an alarming wave of premature CVD. Diabetic dyslipidaemia is a cluster of lipid and apolipoprotein abnormalities, which include elevated triacylglycerol-rich lipoproteins (TRLs), an excess of small dense LDL particles (independent of the concentration of LDL-cholesterol) and reduced concentrations of both HDL-cholesterol and the major HDL apolipoprotein, apolipoprotein A (ApoA)-I [1, 2].

There is evidence that the number of TRL and LDL particles (as distinct from concentrations of the triacylglycerol and cholesterol transported by them) is a major determinant of cardiovascular risk [3–6]. As TRL and LDL particles contain a single molecule of apolipoprotein B (ApoB), the concentration of ApoB in plasma provides a measure of the concentration of all potentially atherogenic lipoproteins and thus may be a better indicator of cardiovascular risk than the simple measurement of LDL-cholesterol [7–10]. This may be particularly important for people with type 2 diabetes, who tend to have increased concentrations of atherogenic TRL and small LDL particles, such that the LDL-cholesterol concentration no longer reflects the particle concentration of LDL [1, 11].

Another measure of the concentration of all potentially atherogenic lipoproteins is the level of non-HDL-cholesterol, as determined by subtracting the concentration of cholesterol in HDL from that in total plasma [12]. There is growing evidence that the concentration of non-HDL-cholesterol is superior to LDL-cholesterol as a predictor of future cardiovascular events [13–16]. As a consequence, non-HDL-cholesterol has been introduced into many guidelines as a secondary target for therapy in people with elevated serum triacylglycerols, even if they have achieved recommended LDL goals [17–21]. The question of whether non-HDL-cholesterol has the same predictive power as ApoB is a debated issue [7, 12, 15, 22, 23]. One recent study suggested that concentrations of non-HDL-cholesterol and ApoB are virtually identical in terms of their ability to predict cardiovascular events [24].

The other common lipid abnormality in people with type 2 diabetes is a low level of potentially protective HDL particles, whether measured as HDL-cholesterol or as ApoA-I [1, 2]. People with type 2 diabetes have a double problem: (1) a high particle concentration of atherogenic lipoproteins (TRL and LDL); and (2) a low concentration of HDL particles [25]. Measurements that may capture this combined problem include ratios of total to HDL-cholesterol, non-HDL-cholesterol to HDL-cholesterol, LDL-cholesterol to HDL-cholesterol and ApoB to ApoA-I [16, 17, 19, 26–29]. The ApoB:ApoA-I ratio was superior to traditional lipid and apolipoprotein levels as a predictor of CVD in large case-control studies (the Interheart study and the Apolipoprotein-Related Mortality Risk study) [30, 31] and in people treated with statins [32]. These analyses have fuelled recommendations that routine assessment of ApoB and ApoA-I should replace measurements of the standard lipids, particularly in people with diabetes [33–35]. It is uncertain, however, whether the ApoB:ApoA-I ratio is superior to lipid ratios such as total cholesterol:HDL-cholesterol, non-HDL-cholesterol:HDL-cholesterol or LDL-cholesterol:HDL-cholesterol. The Emerging Risk Factors Collaboration (ERFC) group analysed 68 studies including more than 300,000 people and found comparable HRs for the non-HDL-cholesterol:HDL-cholesterol and ApoB:ApoA-I ratios [36]. The Collaborative Atorvastatin Diabetes Study (CARDS) investigators reported that the ApoB:ApoA-I ratio was only marginally superior to that of LDL-cholesterol:HDL-cholesterol in predicting cardiovascular events in people with type 2 diabetes [37].

In this study we evaluated the performance of a range of lipid and apolipoprotein concentrations, including ApoA-II, as well as relevant ratios (expanding the ERFC data), in predicting cardiovascular risk in 9,795 patients with type 2 diabetes from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (International Standard Randomised Controlled Trial registration no. ISRCT64783481) [38].

Methods

Participants The FIELD participants have been described in detail elsewhere [38]. Briefly, type 2 diabetic patients aged 50 to 75 years were eligible if they had an initial plasma total cholesterol concentration of 3.0 to 6.5 mmol/l and a total cholesterol:HDL-cholesterol ratio of 4.0 or higher, or a plasma triacylglycerol concentration of 1.0 to 5.0 mmol/l, without requiring lipid-modifying treatment at study entry. Significant renal impairment (plasma creatinine >130 µmol/l), chronic liver disease, symptomatic gallbladder disease or a cardiovascular event within 3 months of recruitment were exclusion criteria.

All patients provided written informed consent and the study protocol was approved by local and national ethics committees in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Procedures We randomly assigned 9,795 patients to micronised fenofibrate 200 mg once daily (Laboratoires Fournier, Dijon, France) or matching placebo. Patients were followed up at 4- to 6-month intervals for a median of 5 years while receiving routine care from their usual healthcare professionals. Total cholesterol, HDL-cholesterol, triacylglycerol, ApoB, ApoA-I and ApoA-II were measured at baseline and at study end (Fig. 1). All blood samples were analysed in one of two central laboratories in Adelaide, Australia or Helsinki, Finland. The laboratories participated in national quality assurance schemes for all analytes and were aligned for lipid and HbA_{1c} analyses through the Canadian External Quality Assurance Laboratory in Vancouver. Methods used to measure lipids were accredited by the Centers for Disease Control Lipid Standardization Program.

The pre-specified outcome for subgroup studies and the outcome used in this secondary study was total cardiovascular events, a term comprising coronary heart disease death, cardiovascular death, non-fatal myocardial infarction, stroke and coronary or carotid revascularisation. All events were adjudicated by an outcomes assessment committee blinded to treatment allocation.

Statistical analysis All analyses were performed on an intention-to-treat basis. Variables of interest were total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerol, ApoB, ApoA-I and the following Apo and lipid ratios: total cholesterol:HDL-cholesterol, LDL-cholesterol:HDL-cholesterol, non-HDL-cholesterol:HDL-cholesterol and ApoB:ApoA-I. The effect of one SD increment in these variables on total cardiovascular events was assessed

by HRs and 95% CIs in univariate Cox proportional hazards analyses. Adjusted multivariate analyses followed; these included the variable or ratio of interest adjusted for treatment, age, sex, prior myocardial infarction, prior coronary artery bypass graft surgery, smoking status, insulin use, HbA_{1c}, creatinine and country of residence. The strengths of association among the variables were ranked by the two statistics. The proportional hazards assumptions were met in all models. The *p* value is a measure of strength of the association between the treatment and the lipid variable based on the likelihood-ratio test. The *p* value for interaction was based on the Wald test of the interaction term from an adjusted model with the lipid variable or ratio of interest, treatment and the corresponding interaction term.

In addition, the relationships between quartiles of baseline lipid variable or ratios and HRs for cardiovascular risk were assessed by Cox proportional hazards analysis using the first quartile as the reference level.

The degree of predictability of cardiovascular risk for the lipids and ratios of interest was compared by receiver operating characteristic (ROC) curve analysis. This logistic regression model had the individual cardiovascular endpoint (binary data) as the dependent variable and the lipid or apolipoprotein variables or ratios of interest (continuous) as the predictor variable. Each patient was classified as a case or control, and various cut-off points were applied to the predicted probability obtained from the logistic regression. The true positive rate (sensitivity) and false positive rate (specificity) were calculated on the basis of observed versus expected values. The AUC was calculated by integrating the area between the ROC curve and the diagonal line (where sensitivity is equal to 1-specificity) based on the trapezoidal rule [39]. These AUC curves were produced for all patients and then for each treatment group.

All statistical analyses used a two-sided significance of 0.05 and were performed with SAS (version 9.2; SAS Institute, Cary, NC, USA).

Results

The baseline characteristics of the study cohort are given in Table 1. The placebo and fenofibrate groups were well matched for clinical history, medication and baseline concentrations and ratios of lipids and apolipoproteins. At study close (Table 2), the concentrations of HDL-cholesterol, ApoA-I and ApoA-II were all significantly higher in the fenofibrate than in the placebo group, the change being most marked for ApoA-II (27.2%). The concentrations of LDL-cholesterol and ApoB, and the total cholesterol:HDL-cholesterol, LDL-cholesterol:HDL-cholesterol, non-HDL-cholesterol:HDL-cholesterol and ApoB:

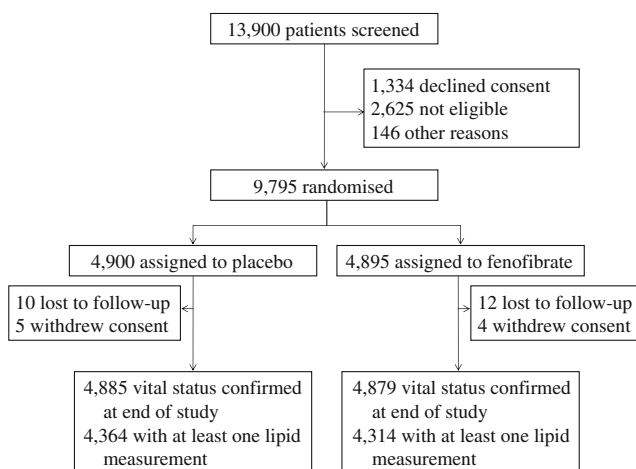


Fig. 1 Enrolment and progress of patients in the FIELD trial

Table 1 Baseline characteristics and medication per group

Characteristic	Placebo	Fenofibrate
<i>n</i>	4,900	4,895
General characteristics		
Men (%)	63	63
Age at visit 1 (years)	62 (7)	62 (7)
Duration of diabetes (years)	5 (2–10)	5 (2–10)
Clinical history		
Previous CVD (%)	22	22
History of hypertension (%)	56	57
Current or ex-smoker (%)	60	60
Laboratory data: lipids and lipoproteins		
Atherogenic		
Triacylglycerol (mmol/l)	1.73 (1.34–2.30)	1.74 (1.35–2.34)
Total cholesterol (mmol/l)	5.03 (0.71)	5.04 (0.69)
LDL-cholesterol (mmol/l)	3.07 (0.66)	3.07 (0.64)
ApoB (g/l)	0.97 (0.17)	0.97 (0.17)
Non-HDL-cholesterol (mmol/l)	3.94 (0.69)	3.95 (0.68)
Anti-atherogenic		
HDL-cholesterol (mmol/l)	1.10 (0.26)	1.10 (0.26)
ApoA-I (g/l)	1.29 (0.21)	1.29 (0.21)
ApoA-II (g/l)	0.35 (0.07)	0.35 (0.07)
Ratios		
Total cholesterol:HDL-cholesterol	4.80 (1.10)	4.81 (1.10)
Non-HDL-cholesterol:HDL-cholesterol	3.78 (1.10)	3.80 (1.09)
LDL-cholesterol:HDL-cholesterol	2.92 (0.84)	2.93 (0.82)
ApoB:ApoA-I	0.77 (0.18)	0.77 (0.18)
Other laboratory data		
HbA _{1c}	6.9 (6.1–7.8)	6.9 (6.1–7.8)
Plasma creatinine (μmol/l)	77 (16)	78 (16)
Homocysteine (μmol/l)	9.6 (8.0–11.4)	9.5 (7.9–11.6)
Microalbuminuria (%)	25	26

Unless otherwise indicated, values are mean (SD) or median (interquartile range)

ApoA-I ratios were all significantly lower in the fenofibrate group than the placebo group. These differences were even greater when patients commencing statin therapy during follow-up were excluded (Electronic supplementary material Table 1).

Relationship between baseline levels and cardiovascular outcomes The HRs for a one SD increment of each of the lipid and apolipoprotein concentrations and their ratios in the placebo and fenofibrate groups (adjusted for major risk variables of interest) are shown in Table 3. Of the lipid and apolipoprotein concentrations, significant effects were observed for HDL-cholesterol, ApoA-I, ApoB and non-HDL-cholesterol in both study groups. Baseline levels of ApoA-II weakly predicted cardiovascular events in the fenofibrate group, but not separately in the placebo group; there was no significance difference across the two treatment groups ($p=0.59$ for interaction). Similarly, total cholesterol and LDL-cholesterol were separately predictive

in the fenofibrate group, but not in the placebo group. Again, the interaction tests were not significant ($p=0.28$ and $p=0.14$, respectively).

All lipid ratios and the ApoB:ApoA-I ratio were significantly associated with cardiovascular outcomes in both groups (Table 3). The likelihood ratio statistics (χ^2) were of approximately the same magnitude for non-HDL-cholesterol:HDL-cholesterol, total cholesterol:HDL-cholesterol, LDL-cholesterol:HDL-cholesterol and ApoB:ApoA-I ratios. In terms of their ability to predict cardiovascular events, these lipid and ApoB:ApoA-I ratios performed better overall than any of the individual lipid or apolipoprotein concentrations in both groups. There was no indication that ApoB:ApoA-I ratio was superior to any of the lipid ratios.

The predictive performance of different variables for cardiovascular outcomes in the two groups was also evaluated using ROC curve analysis (Fig. 2). As judged by the area under the ROC curve, performance was equal for concentrations of HDL-cholesterol and ApoA-I, which

Table 2 Lipids and lipoproteins at study close and percentage changes from baseline

Variable	Fenofibrate group			Placebo group			Difference	
	Relative change (%) ^a	95% CI	<i>p</i> value ^b	Relative change (%) ^a	95% CI	<i>p</i> value ^b	In relative change (%)	<i>p</i> value
Triacylglycerol (mmol/l)	-25.8	-26.7, -24.9	<0.001	-4.7	-5.8, -3.6	<0.001	-21.1	<0.001
Total cholesterol (mmol/l)	-16.8	-17.2, -16.33	<0.001	-10.4	-11.0, -9.9	<0.001	-6.4	<0.001
LDL-cholesterol (mmol/l)	-22.2	-22.8, -21.5	<0.001	-17.7	-18.5, -16.9	<0.001	-4.5	<0.001
ApoB (g/l)	-17.7	-18.3, -17.1	<0.001	-10.9	-11.6, -10.2	<0.001	-6.9	<0.001
Non-HDL-cholesterol (mmol/l)	-22.8	-23.3, -22.2	<0.001	-14.3	-14.9, -13.6	<0.001	-8.5	<0.001
HDL-cholesterol (mmol/l)	1.9	1.3, 2.5	<0.001	1.4	0.9, 1.9	<0.001	0.6	0.14
ApoA-I (g/l)	1.6	1.1, 2.2	<0.001	0.0	-0.4, 0.5	0.89	1.6	<0.001
ApoA-II (g/l)	25.9	25.0, 26.8	<0.001	-1.3	-1.9, -0.7	<0.001	27.2	<0.001
Total cholesterol:HDL-cholesterol	-18.5	-19.1, -18.0	<0.001	-11.8	-12.5, -11.2	<0.001	-6.7	<0.001
LDL-cholesterol:HDL-cholesterol	-23.8	-24.5, -23.0	<0.001	-18.9	-19.8, -18.0	<0.001	-4.9	<0.001
Non-HDL-cholesterol:HDL-cholesterol	-24.3	-25.0, -23.5	<0.001	-15.4	-16.2, -14.6	<0.001	-8.9	<0.001
ApoB:ApoA-I	-19.0	-19.7, -18.3	<0.001	-10.9	-11.7, -10.1	<0.001	-8.1	<0.001

^a Relative changes between baseline and close-out were calculated for each variable using geometric means based on log-transformation of data; analyses were based on 4,289–4,367 patients in the placebo group and 4,244–4,314 patients in the fenofibrate group

^b For comparison of baseline and close data in each treatment arm (paired data)

were superior to total cholesterol and ApoB in both groups. The performance of total cholesterol:HDL-cholesterol, non-HDL-cholesterol:HDL-cholesterol, LDL-cholesterol:HDL-cholesterol and ApoB:ApoA-I ratios was also similar in

the two groups. Analyses were repeated for each treatment group separately, with similar results (data not shown).

The prediction of cardiovascular outcomes by lipid and ratio quartiles is shown in Table 4. The HR for cardiovascular

Table 3 Hazard ratios and χ^2 (likelihood ratio test) for total CVD events for one SD increment in lipid or lipid ratio variables at baseline

Variable ^{a,b}	Placebo group ^c				Fenofibrate group			
	HR	95% CI	χ^2	<i>p</i> value	HR	95% CI	χ^2	<i>p</i> value
Non-HDL-cholesterol:HDL-cholesterol	1.21	1.12–1.31	24.0	<0.001	1.28	1.18–1.39	36.2	<0.001
Total cholesterol:HDL-cholesterol	1.21	1.12–1.31	23.7	<0.001	1.28	1.18–1.39	35.8	<0.001
ApoB:ApoA-I	1.20	1.12–1.30	23.1	<0.001	1.25	1.16–1.36	31.2	<0.001
LDL-cholesterol:HDL-cholesterol	1.17	1.09–1.27	16.8	<0.001	1.29	1.19–1.40	36.2	<0.001
HDL-cholesterol	0.84	0.76–0.91	15.9	<0.001	0.83	0.76–0.92	14.3	<0.001
ApoA-I	0.85	0.78–0.93	14.0	<0.001	0.87	0.79–0.95	9.2	0.002
ApoB	1.14	1.05–1.23	11.1	0.001	1.22	1.12–1.32	22.3	<0.001
Non-HDL-cholesterol	1.13	1.04–1.22	8.9	0.003	1.23	1.13–1.33	23.8	<0.001
Triacylglycerol ^d	1.07	1.00–1.15	3.2	0.07	1.06	0.98–1.15	1.8	0.18
Total cholesterol	1.06	0.98–1.15	2.4	0.12	1.16	1.07–1.26	12.3	<0.001
LDL-cholesterol	1.05	0.98–1.14	1.8	0.18	1.16	1.07–1.26	12.9	<0.001
ApoA-II	0.96	0.88–1.04	1.1	0.29	0.91	0.83–1.00	4.3	0.04

^a There were no significant interactions between HR and treatment group

^b Adjusted for sex, age, prior myocardial infarction, prior coronary artery bypass grafting, smoking, creatinine concentration, insulin use, HbA_{1c} and country of residence

^c Values by χ^2 rank in placebo group

^d Additionally adjusted for HDL-cholesterol

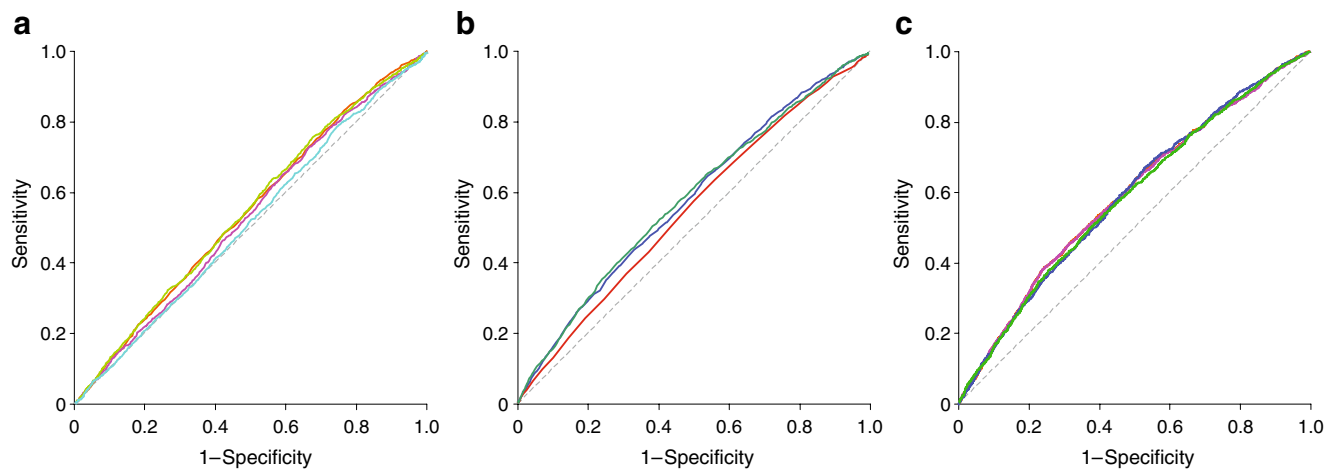


Fig. 2 Receiver operating characteristic curves with AUCs and 95% CIs for **(a)** atherogenic and **(b)** protective lipids and lipoproteins, and **(c)** lipid and lipoprotein ratios. **a** Green line, non-HDL-cholesterol (0.547 [0.531–0.564]); orange line, ApoB (0.545 [0.528–0.561]); pink line, LDL-cholesterol (0.530 [0.513–0.546]); blue line, total cholesterol (0.516 [0.500–0.533]); **(b)** green line, HDL-cholesterol (0.580

[0.564–0.597]); blue line, ApoA-I (0.578 [0.562–0.595]); red line, ApoA-II (0.551 [0.534–0.567]); **(c)** green line, LDL-cholesterol:HDL-cholesterol (0.585 [0.568–0.601]); blue line, ApoB:ApoA-I (0.589 [0.572–0.605]); orange line, total cholesterol:HDL-cholesterol (0.592 [0.575–0.608]); pink line, non-HDL-cholesterol:HDL-cholesterol (0.592 [0.575–0.608])

events in the top compared with the bottom quartile was 0.50 for HDL-cholesterol, 0.50 for ApoA-I, 0.61 for ApoA-II and 1.51 for ApoB. The HRs for HDL-cholesterol, ApoA-I and ApoA-II were attenuated in the adjusted model (including treatment effect), whereas the HR for ApoB, if anything, improved in the adjusted model. The HR for triacylglycerol was also attenuated in the adjusted model, which included HDL-cholesterol. The HRs for the unadjusted models were 2.34 for the total cholesterol:HDL-cholesterol ratio, 2.30 for the non-HDL-cholesterol:HDL-cholesterol ratio, 2.16 for the ApoB:ApoA-I ratio and 2.07 for the LDL-cholesterol:HDL-cholesterol ratio. All remained significant in the adjusted model ($p < 0.001$ for all).

Discussion

Analysis of data from 9,795 diabetes patients in the FIELD study confirms previous observations that ratios that take into account concentrations of atherogenic and anti-atherogenic lipoproteins are superior to measurements of concentrations of either atherogenic or anti-atherogenic fractions alone, in terms of their ability to predict cardiovascular events over a follow-up period of 5 years. These ratios include total cholesterol:HDL-cholesterol, non-HDL-cholesterol:HDL-cholesterol, LDL-cholesterol:HDL-cholesterol and ApoB:ApoA-I. However, in contrast to some previous reports [22, 26–31] but in confirmation of others [24, 36, 40–42], the ApoB:ApoA-I ratio performed no better as a predictor than any of the three lipid ratios. These observations were apparent in the placebo and fenofibrate groups as assessed by computing HRs from

Cox proportional hazards models and by ROC curve analysis for different variables.

Diabetic dyslipidaemia is characterised by a high concentration of potentially atherogenic TRLs and small, dense LDL particles in combination with a low concentration of potentially anti-atherogenic HDL particles. Notably, in the FIELD and the Action to Control Cardiovascular Risk in Diabetes studies the event rates were higher in participants with marked dyslipidaemia (triacylglycerol > 2.3 mmol/l and low HDL-cholesterol) than in those without [43, 44], although in FIELD the groups were not heterogeneous. Consequently, ratios that take account of the levels of atherogenic and anti-atherogenic lipoproteins have been recommended as an effective way to estimate cardiovascular risk in people with type 2 diabetes. In the CARDS study (2,350 participants with type 2 diabetes), the ratios at baseline of ApoB:ApoA-I and LDL-cholesterol:HDL-cholesterol were superior to measurements of either lipid fraction or apolipoprotein alone in terms of predicting cardiovascular events in people with diabetes [37]. The authors of that report concluded (as do we from this analysis of the FIELD study) that, in clinical practice, the measurement of the ApoB:ApoA-I ratio has little to offer over the ratio of LDL-cholesterol:HDL-cholesterol. In the current analysis of diabetic patients in the FIELD study, we also found that the HR for the ApoB:ApoA-I ratio was virtually identical to that for the total cholesterol:HDL-cholesterol and non-HDL-cholesterol:HDL-cholesterol ratios, but little better than that for the LDL-cholesterol:HDL-cholesterol ratio. This observation is fully consistent with results from the ERFC study reporting comparable HRs for non-HDL-cholesterol:HDL-cholesterol, total cholesterol:

Table 4 Effect of lipid ratios and baseline levels on cardiovascular events, by quartiles

Variables in ranges	CVD event rate	Unadjusted		Adjusted ^a	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Lipid and lipoprotein					
Triacylglycerol (mmol/l) ^b					
<1.34	2.9	1		1	
1.34–1.73	3.0	1.02 (0.86–1.20)	0.84	1.02 (0.91–1.26)	0.81
1.74–2.33	3.5	1.19 (1.01–1.39)	0.03	1.15 (0.98–1.36)	0.08
>2.33	3.8	1.32 (1.13–1.53)	<0.001	1.17 (0.99–1.39)	0.06
Total cholesterol (mmol/l)					
<4.56	2.8	1		1	
4.56–5.03	3.6	1.29 (1.10–1.51)	0.002	1.33 (1.14–1.56)	<0.001
5.04–5.54	3.5	1.26 (1.07–1.47)	0.005	1.37 (1.17–1.61)	<0.001
>5.54	3.4	1.21 (1.03–1.42)	0.02	1.41 (1.19–1.66)	<0.001
LDL-cholesterol (mmol/l)					
<2.63	2.7	1		1	
2.63–3.08	3.5	1.30 (1.10–1.52)	<0.002	1.28 (1.09–1.51)	0.002
3.09–3.52	3.6	1.35 (1.15–1.59)	<0.001	1.34 (1.14–1.57)	<0.001
>3.52	3.4	1.27 (1.08–1.50)	0.003	1.31 (1.11–1.54)	0.002
Non-HDL-cholesterol (mmol/l)					
<3.47	2.5	1		1	
3.47–3.93	3.5	1.42 (1.21–1.68)	<0.001	1.39 (1.17–1.63)	<0.001
3.94–4.40	3.4	1.38 (1.17–1.63)	<0.001	1.42 (1.20–1.68)	<0.001
>4.40	3.9	1.59 (1.35–1.87)	<0.001	1.65 (1.40–1.95)	<0.001
ApoB (g/l)					
<0.86	2.6	1		1	
0.86–0.97	3.6	1.34 (1.14–1.57)	<0.001	1.35 (1.15–1.59)	<0.001
0.98–1.09	3.3	1.38 (1.17–1.62)	<0.001	1.41 (1.19–1.66)	<0.001
>1.09	3.8	1.51 (1.28–1.77)	<0.001	1.59 (1.35–1.87)	<0.001
HDL-cholesterol (mmol/l)					
<0.92	4.5	1		1	
0.92–1.06	3.5	0.70 (0.61–0.81)	<0.001	0.76 (0.66–0.88)	<0.001
1.07–1.24	2.8	0.59 (0.51–0.68)	<0.001	0.70 (0.60–0.82)	<0.001
>1.24	2.4	0.50 (0.43–0.59)	<0.001	0.66 (0.56–0.79)	<0.001
ApoA-I (g/l)					
<1.15	4.3	1		1	
1.15–1.27	3.6	0.76 (0.66–0.87)	<0.001	0.84 (0.73–0.97)	0.02
1.28–1.41	3.1	0.73 (0.63–0.85)	<0.001	0.88 (0.76–1.03)	0.11
>1.41	2.2	0.50 (0.43–0.59)	<0.001	0.69 (0.58–0.83)	<0.001
ApoA-II (g/l)					
<0.30	3.2	1		1	
0.30–0.34	4.4	0.87 (0.75–1.00)	0.06	0.93 (0.81–1.08)	0.37
0.35–0.39	3.3	0.77 (0.66–0.90)	0.001	0.89 (0.76–1.05)	0.16
>0.39	2.3	0.61 (0.52–0.73)	<0.001	0.78 (0.65–0.93)	0.006
Lipid and lipoprotein ratios					
Total cholesterol:HDL-cholesterol					
<4.04	2.2	1		1	
4.04–4.71	2.9	1.34 (1.12–1.59)	0.001	1.27 (1.07–1.52)	0.008
4.72–5.49	3.1	1.43 (1.20–1.70)	<0.001	1.30 (1.09–1.55)	0.004
>5.49	4.9	2.34 (1.99–2.74)	<0.001	1.98 (1.67–2.34)	<0.001

Table 4 (continued)

Variables in ranges	CVD event rate	Unadjusted		Adjusted ^a	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Non-HDL:HDL					
<3.03	2.2	1		1	
3.03–3.71	2.9	1.31 (1.10–1.56)	0.003	1.23 (1.03–1.47)	0.02
3.72–4.48	3.2	1.48 (1.24–1.75)	<0.001	1.35 (1.13–1.61)	<0.001
>4.48	4.9	2.30 (1.96–2.70)	<0.001	1.95 (1.65–2.31)	<0.001
LDL-cholesterol:HDL-cholesterol					
<2.36	2.3	1		1	
2.36–2.88	2.9	1.27 (1.07–1.51)	0.007	1.22 (1.02–1.45)	0.03
2.89–3.44	3.3	1.44 (1.22–1.71)	<0.001	1.28 (1.07–1.52)	0.006
>3.44	4.6	2.07 (1.77–2.43)	<0.001	1.77 (1.50–2.09)	<0.001
ApoB:ApoA-I					
<0.65	2.2	1		1	
0.65–0.76	3.0	1.35 (1.13–1.61)	<0.001	1.26 (1.06–1.51)	0.01
0.77–0.88	3.6	1.66 (1.40–1.96)	<0.001	1.45 (1.22–1.72)	<0.001
>0.88	4.5	2.16 (1.84–2.55)	<0.001	1.83 (1.55–2.17)	<0.001

^a Adjusted for treatment group, sex, age, prior myocardial infarction, prior coronary artery bypass grafting, smoking, creatinine concentration, insulin use, HbA_{1c} and country of residence

^b Additionally adjusted for HDL-cholesterol

HDL-cholesterol and ApoB:ApoA-I ratios in non-diabetic and diabetic participants [36]. Collectively, these results provide little support for replacing measurement of non-HDL-cholesterol and HDL-cholesterol and their ratio by measurement of the ApoB:ApoA-I ratio in people with diabetes.

Baseline values of HDL-cholesterol, ApoA-I and ApoB all individually significantly predicted cardiovascular outcome in the placebo and fenofibrate groups. Surprisingly, in contrast to the baseline level of ApoB, the baseline concentration of LDL-cholesterol was a significant predictor only in the fenofibrate group. The failure of LDL-cholesterol to predict outcomes in the placebo group may reflect the fact that when LDL particle size is small (as in type 2 diabetes), the concentration of LDL-cholesterol (in contrast to ApoB) is a poor indication of LDL particle concentration or total concentration of atherogenic lipoproteins. Since fenofibrate will probably have reduced the concentration of TRLs and also increased LDL particle size, the baseline LDL concentration in the fenofibrate group may have remained more reflective of the atherogenic lipoprotein particle concentration over the course of the study than would have been the case in the placebo group.

In this analysis of people with type 2 diabetes, the baseline concentration of ApoA-II (as a single variable) predicted future cardiovascular events in the fenofibrate group. However, the HR for ApoA-II in the placebo group, while similar to that in the fenofibrate group, did not reach

statistical significance, although there was no evidence of heterogeneity by treatment of the effect.

The observation that treatment with fenofibrate increased the concentration of ApoA-II by nearly 30% raises the possibility that a proportion of the reduction in cardiovascular events in the treated group may have been the consequence of the increase in ApoA-II. A robust increase in ApoA-II concentration in people treated with fenofibrate has been reported in several studies in addition to FIELD [45–47]. To the best of our knowledge, this analysis of the FIELD study is the first to suggest that ApoA-II may have protective properties in people with diabetes. This finding extends that reported by Birjmohun et al., who found that higher levels of ApoA-II were associated with a lower risk of future coronary artery disease in the European Prospective Investigation of Cancer–Norfolk cohort [48]. It should, however, be emphasised that our study provides no clues to potential mechanisms underlying this association.

A strength of the present study is that our cohort consisted of 9,795 people with diabetes. It used ApoB and ApoB:ApoA-I ratios as CVD risk markers, which has been most strongly advocated for people who have diabetes and the atherogenic triad, with elevation of ApoB [11, 22, 33]. It should be noted that our samples were collected from fasting patients. This may partly mask any predictive power of non-fasting triacylglycerol levels, which perform better than fasting values as risk predictors [36, 49, 50]. However,

both non-HDL-cholesterol and ApoB would be expected to capture the additional risk of non-fasting triacylglycerol.

In conclusion, our analysis of 9,795 people with type 2 diabetes in the FIELD study cohort showed that baseline lipid and apolipoprotein ratios performed better than any single lipid or apolipoprotein in predicting CVD risk. Our findings also confirmed that HRs for traditional lipid ratios were as strong as those for the ApoB:ApoA-I ratio in this cohort of type 2 diabetic patients. Thus, these analyses provide little support for replacing traditional lipids and their ratios with measures of ApoB and ApoA-I, and their ratio, either as risk prediction tools or as a potential means to monitor the effects of lipid management. This information is important for clinical practice, as measurements of lipid ratios can be calculated from traditional lipid measures familiar to most clinicians.

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Duality of interest M.-R. Taskinen has received honoraria from Merck Sharpe & Dohme, Novartis, Sanofi-Aventis and Kowa, and has been an advisory board member for Merck Sharpe & Dohme and Merck/Schering-Plough. P. Barter has received research support from Pfizer and Merck Sharpe & Dohme, and honoraria from Abbott, Bristol Myers Squibb, Roche, Sanofi-Aventis, Astra Zeneca, Pfizer and Merck Sharpe & Dohme, and has been on advisory boards of Astra Zeneca, Roche, Pfizer and Merck Sharpe & Dohme. C. Ehnholm has received honoraria from the pharmaceutical industry. D. Sullivan has received honoraria from and been an advisory board member for Solvay Pharmaceuticals, AstraZeneca, Merck Sharpe & Dohme, Pfizer and Schering Plough. R. J. Simes has received an honorarium from Solvay. A. C. Keech has received honoraria from the pharmaceutical industry, has been on several pharmaceutical advisory boards and has acted as an expert witness for Medicines Australia. All other authors declare that there is no duality of interest associated with this manuscript.

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