Prediction of Cardiovascular Events in Patients with Ankylosing Spondylitis and Psoriatic Arthritis: Role of Lipoproteins in a High-risk Population

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ABSTRACT. ***Objective.*** To evaluate lipids and apolipoproteins as predictors of cardiovascular mortality and morbidity (CVD) in patients with spondyloarthritis (SpA).

Methods. In the pooled cohort of participants in the IDEAL, TNT, and CARDS trials, 50 had ankylosing spondylitis (AS), 36 had psoriatic arthritis (PsA), and 21,641 did not have AS or PsA (non-SpA). We compared lipid levels at baseline between AS or PsA and non-SpA, and hazard ratios (HR) for CVD were calculated in a Cox proportional hazard model.

Results. Atherogenic lipids were lower in samples from AS, but not in PsA, compared to non-SpA. The HR for 1 SD increase in baseline lipids for future CVD was for total cholesterol 1.39 (95% CI 0.82, 2.36) in AS, 1.01 (95% CI 0.44, 2.31) in PsA, and 1.10 (95% CI 1.07, 1.14) in non-SpA. Both high-density lipoprotein (HDL) and apolipoprotein (ApoA-1) were significantly associated with CVD in AS (HR 3.67, 95% CI 1.47, 9.06, and HR 1.89, 95% CI 1.02, 3.54, respectively), in contrast to PsA (HDL: HR 1.03, 95% CI 0.49, 2.15; ApoA-1: HR 0.79, 95% CI 0.34, 1.89) and non-SpA (HDL: HR 0.86, 95% CI 0.84, 0.89; ApoA-1: HR 0.88, 95% CI 0.85, 0.91).

Conclusion. HDL and ApoA-1 were surprisingly associated with increased risk of future CVD in patients with AS, whereas these lipids were protective in non-SpA. (J Rheumatol First Release June 1 2012; doi:10.3899/jrheum.111307)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS LIPIDS
RISK FACTOR CARDIOVASCULAR DISEASE

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The trials were sponsored by Pfizer and the work was based on a research fellowship grant from the South Eastern Regional Health Authority of Norway. A.G. Semb has received speaker honoraria and/or consulting fees from Merck/Schering-Plough, Abbott, BMS, Wyeth/Pfizer, and Roche. T.K. Kvien has received speaker and/or consulting honoraria and/or research grants from Abbott, BMS, Merck/Schering-Plough, Wyeth/Pfizer, Roche, and UCB. T.R. Pedersen has received speaker honoraria and/or consulting fees from Pfizer, Merck/Schering-Plough, and AstraZeneca. J. LaRosa is a consultant for Pfizer. J. Betteridge has received speaker honoraria and consulting fees from AstraZeneca. I. Holme has received speaker honoraria and/or consulting fees from Pfizer, Merck/Schering-Plough, AstraZeneca, and Roche.

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Accepted for publication April 19, 2012.

The cardiovascular (CV) burden of patients with spondyloarthritis (SpA), psoriatic arthritis (PsA)[1], and ankylosing spondylitis (AS)[2,3,4] is increased compared to the general population. The causes underlying this increased CV risk in patients with SpA are not entirely understood. These patients have a high prevalence of traditional risk factors, but there seems to be an additional disease-related risk for increased CV morbidity and mortality (CV disease; CVD)[1,5,6]. Lipids are well-characterized risk factors for CVD in the general population[7]. We recently presented data showing that total cholesterol had a weaker association with future myocardial infarction (MI) and ischemic stroke in patients with rheumatoid arthritis (RA) than in non-RA individuals[8]. The associations between lipid levels and risk of CV disease in RA have been suggested to be inversely related compared to the general population, where lower lipid levels appear to be associated with increased risk of CVD[9]. The relation of lipids to CVD in SpA is not well described.

We examined the relation of lipids and lipoprotein components to future CVD in patients with AS and PsA compared to those without SpA.

MATERIALS AND METHODS

To obtain data for patients with AS and PsA who were followed over time

and had a CV endpoint, we used a pooled analysis of 2 CV secondary prevention trials, the Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL)[10] and the Treating to New Targets (TNT)[11] studies, and also a primary CV prevention study in patients with diabetes, the Collaboration Atorvastatin Diabetes Study (CARDS)[12]. The remaining patients in the IDEAL, TNT, and CARDS trials served as controls. The protocol and outcome measures of the TNT, IDEAL, and CARDS trials have been published[10,11,12]. In brief, the IDEAL trial (n = 8,888) compared the effect of high-dose atorvastatin (80 mg) and conventional-dose simvastatin (20–40 mg) on CV endpoints in patients who have had an MI, with a median followup time of 4.8 years. The TNT study (n = 10,001) included patients with clinical coronary heart disease, assigned them to either 10 or 80 mg atorvastatin daily, and compared the effect of high- and low-dose atorvastatin on a CV endpoint. Median followup was 4.9 years. The aim of the CARDS trial (n = 2,838) was to assess atorvastatin 10 mg versus placebo prospectively in primary prevention of CVD in patients with type 2 diabetes. The median followup was 3.9 years.

These studies were approved by local or multicenter research ethical committees. All patients gave their informed written consent. The Declaration of Helsinki and the Guidelines on Good Clinical Practice were followed in all 3 studies.

Clinical data. All lipid and lipoprotein levels were measured from fasting blood samples, along with liver enzymes and other laboratory variables.

Comorbidity diagnoses were listed under medical history when the patients entered 1 of the 3 studies. Patients with AS were identified according to ICD-10: M45, ICD-9: 720.*, or ICD-8: 712.4. Patients with PsA were identified according to ICD-10: L40.5 first, followed by a more specific star code from M07.0-M07.3 or M09.0; and ICD-9: 696.0 or Arthropathia psoriatica first, followed by 713.3* as star code or ICD-8: 696.0.

For this exploratory analysis we used a combined CVD endpoint including hospitalization for angina pectoris, nonfatal and fatal MI, interventions (percutaneous coronary intervention or surgery, coronary artery bypass graft operation), stroke, and transient ischemic attack, to maximize the statistical power.

Statistics. The data from IDEAL, TNT, and CARDS trials were pooled. The distribution of AS/PsA and non-AS/PsA subjects within each study was summarized by treatment.

Demographic data were compared between AS or PsA and non-SpA by 1-way analysis of covariance (ANCOVA; continuous variables) and logistic regression analysis (categorical variables) adjusted for study.

Baseline lipids were compared between AS or PsA and non-SpA by ANCOVA, with adjustments for age, sex, and study. Lipid levels are presented as least-square means ± standard error of the mean. The comparison of baseline lipids and apolipoproteins between patients with and those without CVD was based on a similar ANCOVA model. Since patients with SpA more often used prerandomization statin therapy, the influence of prerandomization statin use on atherogenic lipids including total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio, and apolipoprotein B (ApoB), was tested in 4 different ANCOVA models: (1) unadjusted; (2) adjusting for age and sex; (3) adjusting for age, sex, and treatment; and (4) adjusting for age, sex, treatment, and prerandomization use of statin.

Hazard ratios (HR) with 95% CI were calculated based on a 1 (SD) increase of each lipid or apolipoprotein measure at baseline in a Cox proportional hazard model stratified by study, including baseline lipid level as the only predictor adjusted for age, sex, and treatment, with time to first occurrence of combined CVD as the endpoint. When calculating the interaction terms, the p value was based on the likelihood test of the AS or PsA versus non-SpA by baseline lipid from a Cox proportional hazard analysis model stratified by study, including 3 disease groups (2 dummy variable AS, PsA vs non-SpA) and baseline lipid (continuous variable) as the major predictors plus the corresponding interaction terms in the model, adjusted for age, sex, and treatment.

RESULTS

Of the 21,727 patients participating in the IDEAL, TNT, and CARDS trials, a total of 86 patients had SpA. Of these, 50 patients had an AS diagnosis and 36 had a PsA diagnosis.

AS/PsA subjects in TNT, IDEAL, and CARDS cohorts. The distributions of AS/PsA with respect to study and treatment groups are shown in Table 1. More subjects had AS/PsA in the high-dose groups in IDEAL and CARDS, but not in TNT. For non-AS/PsA subjects the distribution was similar in both treatments for all studies.

Demographic data. Baseline patient characteristics (Table 2) were similar across the patients with AS, PsA, and non-SpA, except that there were as expected more men with AS compared to PsA and non-SpA. Further, those with PsA had higher diastolic blood pressure and body weight, and those with AS used less aspirin compared to the PsA and non-SpA groups.

Baseline lipids and lipoprotein components. Patients with AS had significantly lower total cholesterol and low-density lipoprotein cholesterol (LDL-C) and a lower ApoB compared to non-SpA (Table 3), whereas the atherogenic lipids and apolipoprotein levels in patients with PsA did not differ from non-SpA. The results from the ANCOVA model (in which use of prerandomization statins was added in the covariates) and comparison with other models (unadjusted, adjusted for age and sex, adjusted for age, sex and treatment) suggested that the atherogenic level for each lipid in the SpA group remained lower than in those without SpA (statistically insignificant; Appendix). These results further suggest that use of prerandomization statins was not a significant confounder for lower atherogenic lipids in patients with SpA compared to others. Further, the levels of antiatherogenic lipid HDL-C and ApoA-1 were not different among AS, PsA, and non-SpA, although the total cholesterol/HDL-C and LDL-C/HDL-C ratios were lower in AS compared to non-SpA.

Thirteen out of 50 patients with AS had a CV endpoint and 37 did not (Table 4). Of the 36 patients with PsA, 8 experienced a CV endpoint. Levels of total cholesterol and LDL-C were elevated in patients experiencing compared to those not experiencing a CV endpoint in AS and non-SpA. Patients with AS who experienced CVD had significantly higher HDL-C and ApoA-1 compared to those who did not experience CVD. This observation was in contrast to patients without SpA, where patients with CVD as expected had lower levels of the antiatherogenic HDL-C and ApoA-1 compared to those not experiencing CVD.

Baseline lipids and lipoproteins as predictors of CVD. In patients with AS, the HR of the atherogenic lipids for CVD were higher than in non-SpA, although the CI was wider and the HR did not achieve statistical significance (Table 5). This was probably due to small numbers compared to the non-SpA group. However, the interaction term was non-

Table 1. Frequency distribution of AS/PsA and non-SpA patients participating in the IDEAL[10], TNT[11], and CARDS[12] studies by treatment groups and by study.

Study	Treatment Arm 1, n/N (%)	AS/PsA Treatment Arm 2, n/N (%)	Total, n/N (%)
TNT (n = 10,001)	Atorvastatin 80 mg	Atorvastatin 10 mg	
AS	3/4995 (0.06)	4/5006 (0.08)	7/10,001 (0.07)
PSA	2/4995 (0.04)	7/5006 (0.14)	9/10,001 (0.09)
Total	5/4995 (0.10)	11/5006 (0.22)	16/10,001 (0.16)
IDEAL (n = 8888)	Atorvastatin 80 mg	Simvastatin 40 mg	
AS	28/4439 (0.63)	11/4449 (0.25)	39/8888 (0.44)
PSA	16/4439 (0.36)	10/4449 (0.22)	26/8888 (0.29)
Total	44/4439 (0.99)	21/4449 (0.47)	65/8888 (0.73)
CARDS (n = 2838)	Atorvastatin 10 mg	Placebo	
AS	3/1428 (0.21)	1/1410 (0.07)	4/2838 (0.14)
PSA	1/1428 (0.07)	0	1/2838 (0.04)
Total	4/1428 (0.28)	1/1410 (0.07)	5/2838 (0.18)
	Treatment Arm 1, n/N (%)	Non-AS/PsA Treatment Arm 2, n/N (%)	Total, n/N (%)
TNT (n = 10,001)	Atorvastatin 80 mg	Atorvastatin 10 mg	
	4990/4995	4995/5006	9985/10,001
	(99.90)	(99.78)	(99.84)
IDEAL (n = 8888)	Atorvastatin 80 mg	Simvastatin 40 mg	
	4395/4439	4428/4449	8823/8888
	(99.01)	(99.53)	(99.27)
CARDS (n = 2838)	Atorvastatin 10 mg	Placebo	
	1424/1428	1409/1410	2833/2838
	(99.72)	(99.93)	(99.82)

IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; CARDS: Collaboration Atorvastatin Diabetes Study; AS: ankylosing spondylitis; PsA: psoriatic arthritis; non-SpA: non-spondyloarthritis.

significant, which indicates that there was no true difference between the HR of the atherogenic lipids as predictors of CVD in AS and in non-SpA.

The antiatherogenic HDL-C and ApoA-1 were significantly predictive of future CVD in patients with AS. This observation was supported by a significant interaction term ($p < 0.0001$ for HDL-C and $p < 0.0003$ for ApoA-1), indicating that the HR for future CVD by HDL-C and ApoA-1 for AS was different from that for non-SpA. In the latter group, higher HDL-C and ApoA-1 were significantly protective of CVD (Table 5). There were no such clear patterns in the patients with PsA.

DISCUSSION

The striking relationship between HDL-C and ApoA-1 and future CVD in patients with AS in this analysis casts light on the complexity of the conventional and disease-related risk factors for CVD in inflammatory joint diseases. Hypothetically, low levels of atherogenic lipids, previously related to inflammation in RA[13], may not be the important factor in the increased CV risk in people with RA and related diseases. A major factor may be the incapacity of HDL-C and/or ApoA-1 to be protective against CVD. Several studies have shown that the property of HDL-C in RA and AS is altered into a less antiatherogenic particle, with a lower antioxidative and antiinflammatory capacity[14,15,16], and that this downregulation of HDL-C function is restored after immune modulation with either methotrexate[17] or tumor necrosis factor (TNF) blockers[16,18] and with atorvastatin[19]. The positive effect of TNF blockade on HDL in AS has also been described[16], but less is known about this in PsA.

Population-based studies show that low concentrations of HDL-C (< 39.77 mg/dl or 1.03 mmol/l) are a risk factor for CVD[20], and increasing HDL-C with 1.16 mg/dl (0.03 mmol/l) yearly can reduce CV risk by 2%–3%[21]. The relationship is different with higher levels of HDL-C, especially above 69.50 mg/dl (1.8 mmol/l)[22], where HDL-C is not cardioprotective. This level-dependent difference for HDL-C was further confirmed by the ILLUSTRATE trial[23]. The HDL-C levels in the patients with AS and PsA in this analysis were much lower (42.47 mg/dl; 1.1 mmol/l) than those in the ILLUSTRATE trial. Further analysis of a potential regressive relationship between HDL-C and CVD was not possible in our analysis because of the low number of

Table 2. Baseline patient characteristics (mean ± SD) for continuous variable, counts (%) for categorical variables in patients with AS, PsA, and non-SpA participating in the IDEAL, TNT, and CARDS studies.

Characteristics	AS, n = 50	p	PsA, n = 36	p	Non-SpA, n = 21,641
Age, yrs	60.3 (8.6)	0.28	59.8 (8.3)	0.23	61.4 (9.0)
Female	5 (10.0)	0.08	9 (25.0)	0.41	4498 (20.8)
Blood pressure, mm Hg					
Systolic	134.5 (19.8)	0.41	137.9 (16.5)	0.43	134.9 (18.6)
Diastolic	79.3 (7.4)	0.51	83.8 (10.4)	0.01	79.6 (9.8)
Cardiovascular history					
Cerebrovascular disease	3 (6.0)	0.89	2 (5.6)	0.80	1172 (5.4)
Peripheral vascular disease	3 (6.0)	0.79	4 (11.1)	0.21	1631 (7.5)
Angina pectoris (TNT and CARDS only)	6/11 (54.6)	0.78	8/10 (80.0)	0.57	8137/12,818 (63.5)
Arrhythmia (TNT and CARDS only)	3/11 (27.3)	0.13	2/10 (20.0)	0.78	1864/12,818 (14.5)
Atrial fibrillation (IDEAL only)	1/39 (2.6)	0.27	4/26 (15.4)	0.14	65,463/8823 (7.5)
Congestive heart failure (IDEAL and TNT only)	1/46 (2.2)	0.27	0/35 (0.0)	0.95	1317/18,808 (7.0)
Risk factors					
Body mass index, kg/m^2	26.99 (3.85)	0.32	29.49 (5.81)	0.008	28.05 (4.19)
Current smoker	13 (26.0)	0.27	8 (22.2)	0.61	3786 (17.5)
Former smoker	31 (62.0)	0.55	23 (63.9)	0.56	12,682 (58.6)
Never smoker	6 (12.0)	0.08	5 (13.9)	0.25	5168 (23.9)
Hypertension	24 (48.0)	0.20	21 (58.3)	0.02	10,547 (48.7)
Diabetes	12 (24.0)	0.32	4 (11.1)	0.46	5392 (24.9)
Prerandomization statin therapy	34 (68.0)	0.95	27 (75.0)	0.50	12,860 (59.4)
Concomitant therapy					
Aspirin	31 (62.0)	0.02	27 (75.0)	0.51	16,056 (74.2)
Beta-blocker	35 (70.0)	0.66	25 (69.4)	0.84	12,431 (57.4)
Calcium antagonist	12 (24.0)	0.54	12 (33.3)	0.08	4984 (23.0)
ACE inhibitors or angiotensin II blockers	14 (28.0)	0.25	10 (27.8)	0.37	7590 (35.1)

P values are comparisons between AS or PsA and non-SpA. IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; CARDS: Collaboration Atorvastatin Diabetes Study; AS: ankylosing spondylitis; PsA: psoriatic arthritis; Non-SpA: non-spondyloarthritis; ACE: angiotensin-converting enzyme.

patients with AS and PsA, but is warranted in future studies.

The pathophysiology that takes part in the increased risk for CVD in AS and PsA is complicated. Our findings indicate that the atherogenic lipids and ApoB are not as strongly predictive of future CVD as they are in non-SpA. To our knowledge this has not been documented previously. The linear relationship between increasing atherogenic lipids and CVD in the general population is well described[7,24]. Patients with AS who experienced CVD had significantly higher atherogenic lipids at baseline compared to those who did not experience CVD. As expected, this was also the pattern in non-SpA, but not in patients with PsA.

A pattern of dyslipidemia similar to that in RA, with low total cholesterol, LDL-C, and HDL-C, has been reported in PsA, which was normalized with reduction of disease[25]. In addition, patients with active PsA disease had even lower lipids and lipoprotein compared to controls in another study[26]. Unfortunately, these data were not related to CVD in these reports. Further, van Halm and colleagues reported that increased disease activity and inflammatory indicators such as erythrocyte sedimentation rate and C-reactive protein in patients with AS was related to a decrease in lipids[5]. The reduction was nearly 2-fold higher in HDL-C compared to total cholesterol. To our knowledge, no such data relating to CVD are available for patients with AS.

Patients with SpA have an increased risk of CVD, in particular patients with AS and PsA[6]. The prevalence of various traditional CV risk factors is somewhat different between patients with AS and those with PsA. In particular, it has been found that obesity is more prevalent in PsA[27], consistent with the elevated body mass index in patients with PsA compared to patients with AS in our study. In contrast to patients with PsA, reported to have higher lipid levels compared to persons without PsA[1], there are conflicting data on lipid levels in patients with AS[6]. AS and PsA are both classified under the umbrella term spondyloarthritis, but they have different clinical characteristics. Thus, we analyzed AS and PsA separately.

Table 3. Baseline lipids and apolipoproteins in patients with AS, PsA, and non-SpA participating in the IDEAL, TNT, and CARDS studies, stratified by study and adjusted for age and sex.

Variable	AS, n = 50	PsA, n = 36	Non-SpA, n = 21,641
Total cholesterol, mg/dl			
Mean ± SD	183.6 ± 33.2	190.1 ± 31.0	187.8 ± 34.4
LS means ± SE	182.8 ± 4.5	190.4 ± 5.3	192.5 ± 0.3
p	0.03	0.70	
LDL-C, mg/dl			
Mean ± SD	109.5 ± 27.7	114.5 ± 26.8	109.8 ± 29.4
LS means ± SE	104.0 ± 3.8	110.9 ± 4.5	112.1 ± 0.2
p	0.03	0.79	
HDL-C, mg/dl			
Mean ± SD	46.3 ± 10.4	46.7 ± 11.1	47.7 ± 11.9
LS means ± SE	49.4 ± 1.6	49.0 ± 1.9	49.0 ± 0.1
p	0.83	1.00	
Total cholesterol/HDL-C ratio			
Mean ± SD	4.1 ± 1.1	4.2 ± 1.0	4.1 ± 1.2
LS means ± SE	3.8 ± 0.2	4.0 ± 0.2	4.1 ± 0.01
p	0.05	0.50	
LDL-C/HDL-C ratio			
Mean ± SD	2.5 ± 0.8	2.5 ± 0.8	2.4 ± 0.9
LS means ± SE	2.2 ± 0.1	2.3 ± 0.1	2.4 ± 0.01
p	0.05	0.58	
Triglycerides, mg/dl			
Mean ± SD	141.1 ± 64.3	147.0 ± 66.6	152.7 ± 78.0
LS means ± SE	146.1 ± 10.9	151.3 ± 12.8	157.0 ± 0.6
p	0.32	0.66	
ApoB, mg/dl			
Mean ± SD	110.9 ± 29.0	117.8 ± 26.0	115.0 ± 26.2
LS means ± SE	108.4 ± 3.7	115.5 ± 4.3	115.3 ± 0.2
p	0.06	0.97	
ApoA-1, mg/dl			
Mean ± SD	136.7 ± 20.4	142.4 ± 20.3	144.2 ± 24.8
LS means ± SE	143.2 ± 3.3	146.1 ± 3.9	145.7 ± 0.2
p	0.46	0.91	
ApoB/ApoA-1			
Mean ± SD	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
LS means ± SE	0.8 ± 0.03	0.8 ± 0.04	0.8 ± 0.002
p	0.13	0.70	

Crude data are given as mean ± SD, adjusted data as least-square means ± standard error of the means: LS means ± SEM. P values are comparisons between AS or PsA with non-SpA. IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; AS: ankylosing spondylitis; PsA: psoriatic arthritis; Non-SpA: non-spondyloarthritis; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; APO: apolipoprotein.

Several limitations to our study should be considered when interpreting the results. First, there is a potential for different associations between lipid levels and outcome in the 3 populations of the IDEAL, TNT, and CARDS studies. However, such heterogeneity was difficult to test for in our population with a limited number of events. Further, the IDEAL, TNT, and CARDS trials were not designed to analyze CVD outcome in patients with AS and PsA. The low number of patients with AS and PsA in the TNT and CARDS trials in particular point in the direction that patients with SpA may have been highly selected when included into the trials and did not have high-activity inflammatory joint disease. The IDEAL trial had fewer selection criteria for inclusion into the study than the TNT and CARDS trials, which is reflected in that the participants in the IDEAL represent ~65% of all patients with CV events screened in comparison to < 30% in the TNT, and this may be a source of selection bias and a reason for the lower prevalence of SpA in the TNT compared to IDEAL. A similar selection bias is also possible in CARDS. The selection bias when excluding seriously ill patients with SpA, upon recruitment of patients into the different studies, was not present in the non-SpA participants, i.e., the remaining patients who served as controls in our analyses. Another

Table 4. Comparison of baseline lipids and apolipoproteins between patients with and without CVD of the subgroups of AS, PsA and non-SpA participating in the IDEAL, TNT and CARDS studies, adjusted for age, sex, and study.

	AS, n = 50			PsA, n = 36			Non-SpA, n = 21,641		
Baseline Lipids	n	Mean ± SD	LS Means ± SE	n	Mean ± SD	LS Means ± SE	n	Mean ± SD	LS Means ± SE
Total cholesterol, mg/dl									
No CVD	37	178.8 ± 34.4	179.2 ± 10.0	28	189.8 ± 30.6	191.4 ± 11.3	16,849	187.8 ± 34.0	195.2 ± 0.3
CVD	13	197.2 ± 26.1	200.6 ± 12.2	8	191.1 ± 34.4	188.9 ± 15.3	4792	187.7 ± 35.6	198.4 ± 0.5
			p = 0.08			p = 0.84			p < 0.0001
LDL-C, mg/dl									
No CVD	37	106.4 ± 28.3	94.8 ± 8.2	28	115.2 ± 28.7	113.5 ± 10.0	16,849	109.5 ± 28.9	112.3 ± 0.3
CVD	13	118.2 ± 25.1	112.0 ± 10.0	8	111.9 ± 20.2	109.8 ± 13.6	4792	110.9 ± 30.9	115.6 ± 0.4
			p = 0.09			p = 0.75			p < 0.0001
HDL-C, mg/dl									
No CVD	37	43.7 ± 9.0	47.0 ± 2.7	28	46.2 ± 10.7	46.8 ± 3.8	16,849	48.2 ± 12.0	51.4 ± 0.1
CVD	13	53.7 + 11.1	56.9 ± 3.3	8	48.3 ± 12.9	47.2 ± 5.1	4792	46.0 ± 11.5	49.9 ± 0.2
			p = 0.004			p = 0.92			p < 0.0001
Total cholesterol/LDL-C									
No CVD	37	4.3 ± 1.2	4.03 ± 0.3	28	4.2 ± 1.0	4.2 ± 0.4	16,849	4.1 ± 1.2	4.0 ± 0.01
CVD	13	3.8 ± 0.7	3.6 ± 0.4	8	4.1 ± 1.1	4.1 ± 0.5	4792	4.3 ± 1.3	4.2 ± 0.02
			p = 0.26			p = 0.81			p < 0.0001
LDL-C/HDL-C ratio									
No CVD	37	2.54 ± 0.9	2.17 ± 0.2	28	2.6 ± 0.8	2.5 ± 0.3	16,849	2.4 ± 0.9	2.3 ± 0.01
CVD	13	2.28 ± 0.7	2.01 ± 0.3	8	2.4 ± 0.6	2.4 ± 0.4	4792	2.5 ± 0.9	2.5 ± 0.01
			p = 0.58			p = 0.70			p < 0.0001
Triglyceride, mg/dl									
No CVD	37	145.8 ± 71.7	188.9 ± 18.1	28	143.9 ± 59.9	156.7 ± 24.5	16,849	151.7 ± 77.8	157.8 ± 0.7
CVD	13	127.7 ± 34.5	161.3 ± 21.9	8	157.8 ± 90.2	161.1 ± 33.1	4792	156.1 ± 78.7	165.5 ± 1.3
			p = 0.21			p = 0.87			p < 0.0001
ApoB, mg/dl									
No CVD	37	107.4 ± 30.4	111.2 ± 8.9	28	116.1 ± 25.9	109.6 ± 9.9	16,849	114.3 ± 25.8	115.4 ± 0.3
CVD	13	121.5 ± 22.0	126.5 ± 11.6	8	123.6 ± 27.2	114.1 ± 13.4	4792	117.7 ± 27.6	119.4 ± 0.4
			p = 0.18			p = 0.69			p < 0.0001
ApoA-1, mg/dl									
No CVD	37	131.9 ± 17.1	136.3 ± 5.7	28	142.0 ± 20.6	148.3 ± 6.3	16,849	144.9 ± 24.9	151.3 ± 0.2
CVD	13	151.5 ± 23.2	152.2 ± 7.4	8	143.6 ± 20.6	145.1 ± 8.5	4792	141.7 ± 24.0	148.5 ± 0.4
			p = 0.03			p = 0.65			p < 0.0001
ApoB/ApoA-1 ratio									
No CVD	37	0.8 ± 0.2	0.8 ± 0.1	28	0.8 ± 0.2	0.8 ± 0.1	16,849	0.8 ± 0.2	0.79 ± 0.002
CVD	13	0.8 ± 0.2	0.8 ± 0.1	8	0.9 ± 0.2	0.8 ± 0.1	4792	0.9 ± 0.3	0.83 ± 0.004
			p = 0.82			p = 0.62			p < 0.0001

P values are based on the comparison between patients with and those without CVD. Least-square means (LS Means), standard error (SE) of LS Means. CVD: cardiovascular morbidity and mortality; IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; CARDS: Collaboration Atorvastatin Diabetes Study; AS: ankylosing spondylitis; PsA: psoriatic arthritis; Non-SpA: non-spondyloarthritis; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; APO: apolipoprotein.

limitation of the study is that none of the comorbidity diagnoses was validated. They were recorded by the physician who included the patient into the study and listed under medical history. Hence, there might be inaccuracies in retrieving the diagnosis by code. Unfortunately we did not have information on disease severity, length of disease, inflammatory status, or use of immunomodulating medications by the patients with AS and PsA. These medications may affect the risk for CVD.

However, the results regarding the association of HDL-C and ApoA-1 with increased risk of future CVD in patients with AS were robust, as they were derived from 2 different analytical strategies (Tables 4 and 5). As expected, these lipids were protective concerning CVD in non-SpA subjects. Results in PsA subjects were not conclusive. Our unexpected finding of HDL-C and ApoA-1 as risk factors for CVD in AS require replication in future studies.

ACKNOWLEDGMENT

We are grateful to the steering committees of the IDEAL, TNT, and CARDS trials for providing their databases and making this analysis possible.

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Table 5. HR (95% CI) of CVD for 1 SD increase in baseline lipid/apolipoprotein in subgroups of AS, PsA, and non-SpA participating in the IDEAL, TNT, and CARDS studies (all analyses were stratified by study and adjusted for age, sex, and treatment).

Baseline Lipid/ Apolipoprotein	AS, n = 50 HR (95% CI)	p	PsA, n = 36 HR (95% CI)	p	Non-SpA, n = 21,641 HR (95% CI)	p	Interaction AS vs Non-SpA, p	PsA vs Non-SpA, p
Total cholesterol, mg/dl	1.39 (0.82, 2.36)	0.22	1.01 (0.44, 2.31)	0.98	1.10 (1.07, 1.14)	< 0.0001	0.21	0.88
LDL-C, mg/dl	1.37 (0.78, 2.41)	0.28	0.94 (0.42, 2.14)	0.89	1.13 (1.09, 1.16)	< 0.0001	0.49	0.76
HDL-C, mg/dl	3.67 (1.49, 9.06)	0.005	1.03 (0.49, 2.15)	0.94	0.86 (0.84, 0.89)	< 0.0001	< 0.0001	0.33
Total cholesterol/HDL-C	0.64 (0.30, 1.39)	0.26	0.99 (0.46, 2.14)	0.98	1.17 (1.14, 1.20)	< 0.0001	0.06	0.55
LDL-C/HDL-C	0.77 (0.39, 1.51)	0.45	0.92 (0.41, 2.06)	0.84	1.16 (1.13, 1.19)	< 0.0001	0.10	0.44
Triglycerides, mg/dl	0.53 (0.21, 1.34)	0.18	1.11 (0.52, 2.34)	0.79	1.10 (1.07, 1.13)	< 0.0001	0.30	0.80
ApoB, mg/dl	1.19 (0.69, 2.05)	0.54	1.27 (0.62, 2.57)	0.52	1.14 (1.11, 1.18)	< 0.0001	0.50	0.71
ApoA-1, mg/dl	1.89 (1.02, 3.54)	0.05	0.79 (0.34, 1.89)	0.60	0.88 (0.85, 0.91)	< 0.0001	0.0003	0.65
ApoB/ApoA-1	0.92 (0.53, 1.61)	0.77	1.34 (0.65, 2.74)	0.42	1.18 (1.16, 1.22)	< 0.0001	0.45	0.91

CVD: cardiovascular morbidity and mortality; IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; CARDS: Collaboration Atorvastatin Diabetes Study; AS: ankylosing spondylitis; PsA: psoriatic arthritis; Non-SpA: non-spondyloarthritis; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; APO: apolipoprotein.

APPPENDIX. Baseline atherogenic lipids in AS, PsA, and non-SpA patients participating in the IDEAL, TNT, and CARDS studies.

Lipids	Model 0: Unadjusted AS/PsA, n = 86	Model 0: Unadjusted Non-SpA, n = 21,641	Model 1: Stratified by Study Adjusting for Age and Sex AS/PsA, n = 86	Model 1: Stratified by Study Adjusting for Age and Sex Non-SpA, n = 21,641	Model 2: Stratified by Study Adjusting for Age, Sex, and Treatment AS/PsA, n = 36	Model 2: Stratified by Study Adjusting for Age, Sex, and Treatment Non-SpA, n = 21,641	Model 3: Stratified by Study Adjusting for Age, Sex, Treatment, and Prerandomization Use of Statins AS/PsA, n = 36	Model 3: Stratified by Study Adjusting for Age, Sex, Treatment, and Prerandomization Use of Statins Non-SpA, n = 21,641
Total cholesterol, mg/dl								
LS Means ± SE	186.3 ± 3.7	187.8 ± 0.2	186.0 ± 3.4	192.5 ± 0.3	186.0 ± 3.4	192.5 ± 0.3	184.1 ± 3.3	190.3 ± 0.3
p	0.68		0.06		0.06		0.07	
LDL-C, mg/dl								
LS Means ± SE	111.6 ± 3.2	109.8 ± 0.2	106.9 ± 2.9	112.1 ± 0.2	106.9 ± 2.9	112.1 ± 0.2	105.0 ± 2.8	109.9 ± 0.2
p	0.58		0.07		0.07		0.08	
Total cholesterol/HDL-C ratio								
LS Means ± SE	4.2 ± 0.1	4.1 ± 0.01	3.9 ± 0.1	4.1 ± 0.01	3.9 ± 0.1	4.1 ± 0.01	3.8 ± 0.1	4.1 ± 0.01
p	0.82		0.06		0.05		0.06	
ApoB, mg/dl								
LS Means ± SE	113.8 ± 2.8	115.0 ± 0.2	111.4 ± 2.8	115.3 ± 0.2	111.4 ± 2.8	115.3 ± 0.2	109.9 ± 2.8	113.7 ± 0.2
p	0.67		0.16		0.16		0.18	

CVD: cardiovascular morbidity and mortality; IDEAL: Incremental Decrease in End points through Aggressive Lipid lowering; TNT: Treating to New Targets; CARDS: Collaboration Atorvastatin Diabetes Study; AS: ankylosing spondylitis; PsA: psoriatic arthritis; Non-SpA: non-spondyloarthritis; LS: least-square; SE: standard error; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; APO: apolipoprotein.

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