

# Assessment of Coronary Risk Based on Cumulative Exposure to Lipids in Systemic Lupus Erythematosus

Mandana Nikpour, Dafna D. Gladman, Dominique Ibanez, Paula J. Harvey, and Murray B. Urowitz

**ABSTRACT. Objective.** To quantify the independent role of each of low-density lipoprotein cholesterol (LDL-C), total cholesterol:high-density lipoprotein cholesterol ratio (TC:HDL-C), triglyceride (TG) level, and HDL-C as a marker of coronary risk in systemic lupus erythematosus (SLE).

**Methods.** Patients with lipid measurements taken before a coronary event (or last clinic visit) were included. Mean and time-adjusted mean (TAM) levels were calculated for each lipid variable in each patient. Time-dependent proportional hazards regression models were used to quantify the risk of coronary event [myocardial infarction (MI) or angina], after adjustment for age.

**Results.** Among 384 patients, over a mean (SD) followup of 3.81 (2.58) years, there were 21 “first” coronary events (6 MI, 15 angina). Mean and TAM LDL-C (HR 1.83, 95% CI 1.19–2.81,  $p = 0.006$ ), TC:HDL ratio (HR 1.43, 95% CI 1.02–2.00,  $p = 0.04$ ), and TG (HR 2.11, 95% CI 1.32–3.39,  $p = 0.0019$ ) were predictive of coronary event at subsequent visits. In contingency table analysis, TAM LDL-C cutpoint of 2.0 mmol/l had a sensitivity and negative predictive value for coronary event of 85.7% (95% CI 63.7–97.0) and 93.9% (95% CI 83.1–98.7), respectively. However, at this cutpoint the specificity was only 12.7% (95% CI 9.4–16.5).

**Conclusion.** This study links LDL-C, TC:HDL-C ratio, and TG to coronary risk in patients with SLE and quantifies the magnitude of this risk. SLE-specific risk assessment levels for lipids may be selected to optimize positive or negative predictive values. (J Rheumatol First Release Oct 15 2013; doi:10.3899/jrheum.121273)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS  
LIPIDS

LIPOPROTEINS

CORONARY ARTERY DISEASE  
RISK FACTORS

Systemic lupus erythematosus (SLE) is associated with a substantially increased risk of coronary artery disease<sup>1</sup>. This is because of an interplay between disease-related factors such as disease activity and treatment, and traditional risk

factors such as hypertension (HTN) and hyperlipidemia. In the general population, the most commonly used lipid markers of coronary risk are low-density lipoprotein cholesterol (LDL-C), total cholesterol:high-density lipoprotein cholesterol ratio (TC:HDL-C), and triglyceride (TG) level<sup>2,3</sup>. HDL-C is negatively correlated with coronary risk<sup>2,3</sup>. To date, the demonstration of an association between these lipid markers and coronary risk in SLE has been hindered by the relatively small absolute number of coronary events and the approach of using single-point-in-time (often “baseline”) measurements of these variables, as per the Framingham model. Consequently, lipid levels for coronary risk assessment, specifically in patients with SLE, are unknown.

We have previously demonstrated that traditional risk factors such as total cholesterol and blood pressure take a dynamic course over time in SLE<sup>4</sup>, varying because of changes in disease activity and treatment, and that conventional Cox hazards models are less informative than time-dependent models for identifying and quantifying the role of dynamic coronary risk factors in SLE, because they provide only a snapshot view at a single timepoint<sup>5</sup>. We have also shown that by capturing cumulative exposure, summary measures of total serum cholesterol (TC) and blood pressure (BP) are better able to estimate coronary risk

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in patients with SLE than single-point measurements<sup>5</sup>. These summary measures include mean and time-adjusted mean (TAM) of serial measurements during followup of patients.

We sought to determine the independent contribution of each of LDL-C, TC:HDL-C ratio, TG, and HDL-C to coronary risk in SLE and to quantify the hazard of coronary event associated with cumulative exposure to each of these lipid risk factors. In addition, we sought to determine lupus-specific risk assessment levels for each of these lipids.

## MATERIALS AND METHODS

*Setting and patients.* Patients in the University of Toronto SLE cohort who had 1 or more sets of fasting TC, LDL-C, HDL-C, and TG measurement/s, and were prospectively followed to the time of a coronary event or last clinic visit, were included in our study. Patients with coronary events predated the first lipid measurement were excluded.

*Lipid measurements.* Each measurement of lipids was tied to a clinic visit. Study start was defined as the first clinic visit wherein LDL-C, HDL-C, and TG measurements were taken. TC was measured in plasma using a commercial assay (Boehringer Mannheim kit 236691) and recorded in mmol/l. Lipoproteins, also reported in mmol/l, were separated from plasma into subfractions by ultracentrifuging. In patients with TG level < 4.5 mmol/l, LDL-C concentration was estimated from the Friedewald formula, where LDL-C is equal to total cholesterol minus very LDL-C and HDL-C<sup>6</sup>. In patients with TG level  $\geq$  4.5 mmol/l, LDL-C level was determined using a more direct method, where HDL-C and LDL-C were separated from each other by manganese chloride/heparin precipitation of LDL-C from the Svedberg flotation < 12 subfraction of ultracentrifuged plasma. TG level was measured fasting in plasma using a commercial assay (Boehringer Mannheim kit 236691) at every visit and recorded in mmol/l.

*Calculation of summary measures.* For each of the lipid variables TC, LDL-C, HDL-C, and TG, summary measures, that is, arithmetic mean and time-adjusted mean (TAM) were calculated, as described<sup>5</sup>, using all available measurements from study startup to each sequential visit, including the visit before the “outcome visit”. Briefly, the arithmetic mean is the sum of all individual measurements, divided by the total number of measurements. The TAM is the area under a curve of lipid level plotted against time, divided by the total length of time from first to last measurement. Thus, the TAM takes into consideration the time interval between lipid measurements and may be a more accurate estimate of “exposure” to a certain lipid level in a context where the time interval between lipid measurements might be irregular.

*Outcome variables and outcome visits.* The outcome (dependent) variables were coronary events: angina, myocardial infarction (MI), and sudden cardiac death. MI was defined as any one of definite electrocardiographic (ECG) abnormalities, or typical symptoms with probable ECG abnormalities and abnormal enzymes ( $\geq$  2 times upper limit of normal), or typical symptoms and abnormal enzymes. Angina pectoris was defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration, relieved by rest or vasodilators. In our study, all patients with angina had the diagnosis confirmed by a cardiologist and supported by one or more cardiac investigations (exercise stress testing, myocardial perfusion scintigraphy, or coronary angiography) that showed the presence of reversible myocardial ischemia or coronary artery disease. Sudden cardiac death was defined as death with undetermined cause, but presumed cardiac.

The visit closest to the actual event date was designated the event visit. The outcome visit was defined as either the event visit or the last recorded clinic visit (as of August 2008) for those who remained event-free. For patients who had more than 1 coronary event, only the first recorded event was used in analysis.

*Other independent variables.* Other covariates included individually in the proportional hazards models were sex, age, disease duration, disease activity score [Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)], organ manifestations as per SLEDAI-2K, and other classic cardiovascular risk factors (HTN, diabetes, and smoking), and medications including corticosteroids, antimalarials, immunosuppressives, and lipid-lowering agents. HTN was defined as diastolic BP > 90 or systolic BP > 140 mmHg, or treatment with antihypertensive medication. Hypercholesterolemia was defined as total cholesterol > 5.2 mmol/l or lipid-lowering therapy.

Importantly, in time-dependent models, covariates were measured in the same visit as lipids, i.e., they were “contemporaneous” with lipid measurements. Medication use was defined categorically as present or absent, irrespective of dose and duration.

*Univariate comparisons.* Univariate comparisons of demographic, disease, and treatment-related variables and traditional cardiac risk factors in patients who had coronary events and those who remained event-free were performed using t tests for continuous variables and chi-squared tests for categorical variables. In case of non-normally distributed data, Mann-Whitney U tests were used for continuous and ranked ordinal variables. Two-sided p values  $\leq$  0.05 were considered significant. Dot plots were used to depict mean LDL-C, mean HDL-C, mean TC:HDL-C ratio, and mean TG levels in patients with and without coronary artery disease (CAD).

*Time-dependent covariate models.* After ensuring proportionality of hazard for each of LDL-C, HDL-C, TC:HDL-C ratio, and TG, 3 time-dependent models were run. In the first model, for each patient, we used the most recent measurement of the lipid prior to each and every visit. In the remaining 2 models, summary measures (mean and TAM) were used in a time-dependent manner (i.e., updated from visit to visit, up to and including the visit before the outcome visit). For 42 patients who had only 1 set of lipid measurements, lipid levels were only included in the first model. For these patients, the visit subsequent to the single lipid measurement was the outcome visit.

In time-dependent proportional hazards regression analysis, we first determined univariate hazard ratios (HR) for each of the following covariates: age, sex, disease duration, SLEDAI-2K score, smoking, HTN, diabetes, corticosteroid, medications (antimalarial, immunosuppressive, and lipid-lowering). Each was updated from visit to visit (with the exception of sex, which was fixed). Among these covariates, only age was significantly associated with CAD. Therefore in each multivariable regression model, we ultimately had only 2 independent variables: age and lipid level. This is in keeping with 1 independent variable for every 10 outcomes. Results are reported as HR with accompanying 95% CI and p values for each of the lipid predictor variables and other covariates. Two-sided p values ( $p$ )  $\leq$  0.05 were considered to be significant.

*Test properties of various lipid cutpoints.* Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) analyses (with precision estimates) for CAD events were performed using contingency tables, for various lipid cutpoints.

## RESULTS

Characteristics of the study participants are presented in Table 1. In total, 384 patients, mostly female (89.8%), were included in the analysis. Mean (SD) age and disease duration at study entry were 41.6 (13.7) and 12.2 (9.6) years, respectively. Across all visits, the median SLEDAI-2K was 4 (minimum 0, maximum 51). Over a followup of 3.81 (2.58) years, 21 “first” coronary events (6 MI, 15 angina) were observed. There were no coronary events among the 42 patients who had only 1 set of lipid measurements prior to their last clinic visit. The number of lipid measurements

**Table 1.** Patient characteristics. All data are from the study start, defined as the first clinic visit wherein LDL-C, HDL-C, and TG measurements were taken, unless otherwise indicated.

Variable	N (%), Mean (SD), or Median (min, max)
No. patients	384
Female	345 (89.8)
Menopausal <sup>b</sup>	132 (38.3% of female)
Race	
White	246 (65.3)
Black	46 (12.2)
Asian	43 (11.4)
Other	42 (11.1)
Coronary events	
MI	6
Angina	15
Sudden cardiac death	0
Total	21
Age, yrs, mean (SD)	
At diagnosis	29.3 (12.7)
Study start	41.6 (13.7)
Disease duration, yrs, mean (SD)	12.2 (9.6)
SLEDAI-2K <sup>e</sup> median, min, max	4 (0, 51)
SLICC-DI <sup>f</sup> median, min, max	1 (0, 3)
Corticosteroids	246 (64.1)
Antimalarials <sup>g</sup>	238 (62.0)
Immunosuppressives <sup>h</sup>	167 (43.5)
Hypertension <sup>i</sup>	167 (43.5)
Elevated blood pressure <sup>l</sup>	49 (21.9)
Hypercholesterolemia <sup>k</sup>	160 (41.7)
Elevated cholesterol <sup>m</sup>	133 (34.6)
Diabetes <sup>n</sup>	23 (6.0)
Smoker <sup>o</sup>	46 (12.1)
Antihypertensive use <sup>p</sup>	156 (93.4% of hypertensive)
Lipid-lowering medications <sup>q</sup>	49 (30.6% of hypercholesterolemic)

<sup>b</sup> Minimum of 12 months amenorrhea, irrespective of cause. <sup>e</sup> Range 0 to 105, with higher scores indicating more active disease. <sup>f</sup> Range 0 to 46, with higher scores indicating greater disease-related damage. <sup>g</sup> Include chloroquine and hydroxychloroquine. <sup>h</sup> Include methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide. <sup>i</sup> Diastolic blood pressure (BP) > 90 or systolic BP > 140 mm Hg, or treatment with antihypertensive medication. <sup>l</sup> Diastolic BP > 90 or systolic BP > 140 mm Hg. <sup>k</sup> Cholesterol  $\geq$  5.2 mmol/l or lipid-lowering therapy. <sup>m</sup> Cholesterol  $\geq$  5.2 mmol/l. <sup>n</sup> Fasting plasma glucose > 7.0 mmol/l or diabetes therapy. <sup>o</sup> Smoking an average of  $\geq$  1 cigarette/s per day over the past month. <sup>p</sup> All classes including diuretics,  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-type II receptor blockers. <sup>q</sup> HMG Co-A reductase inhibitors (statins). MI: myocardial infarction; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC-DI: Systemic Lupus International Collaborating Clinics Damage Index.

per patient was 3.9 (2.5), comprising a total of 1492 individual measurements of each of LDL-C, TC:HDL-C ratio, TG, and HDL-C level. Because each set of lipid measurements corresponded to a visit, this was equal to the total number of visits included in the study. The time between measurements was 12.3 (7.1) months. The time from study start to visit before event (or last) visit was 2.95

(2.60) years, and the time from study start to event (or last) visit was 3.81 (2.58) years. Therefore the time between last measurement and event (or last) visit was 0.86 (0.5) years.

In univariate analysis (Table 2), patients with CAD were more likely to be hypertensive at the study start (81.0% vs 41.3%,  $p = 0.0004$ ) and during followup (90.5% vs 58.4%,  $p = 0.004$ ) and to have hypercholesterolemia at the study start (85.7% vs 39.1%,  $p < 0.0001$ ) and during followup (100.0% vs 62.3%,  $p = 0.0004$ ). Patients with CAD had higher median SLEDAI-2K scores throughout the study (10 vs 4,  $p < 0.0001$ ), but there were no significant differences in organ involvement (including nephritis) during followup in the 2 groups.

In univariate comparisons (Table 2), patients with CAD had higher LDL-C at the study start [3.51 (1.61) vs 2.75 (1.08) mmol/l,  $p = 0.04$ ] and higher mean [3.29 (1.24) vs 2.60 (0.85) mmol/l,  $p = 0.02$ ] and TAM [3.29 (1.21) vs 2.60 (0.85) mmol/l,  $p = 0.02$ ] LDL-C calculated for all visits from study start to the visit before the outcome visit. Patients with CAD also had higher TG at the study start [2.10 (1.44) vs 1.41 (0.74) mmol/l,  $p = 0.04$ ] and higher mean [1.97 (1.09) vs 1.33 (0.66) mmol/l,  $p = 0.02$ ] and TAM [1.95 (1.07) vs 1.33 (0.67) mmol/l,  $p = 0.02$ ] TG calculated for all visits from study start to the visit before the outcome visit.

Figure 1 depicts, in the form of a dot plot, mean LDL-C levels in patients with and without CAD. In time-dependent covariate proportional hazards regression models for coronary events using various measures of LDL-C, most recent LDL-C level did not reach statistical significance for prediction of coronary event. However, mean and TAM LDL-C were predictive of coronary event. In these models, the only other significant covariate was age (HR 1.08, 95% CI 1.04–1.12,  $p = 0.0001$ ). In models that included only lipid measures and age (Table 3), mean LDL-C (HR 1.81, 95% CI 1.18–2.77,  $p = 0.0065$ ) and TAM LDL-C (HR 1.83, 95% CI 1.19–2.81,  $p = 0.006$ ) were predictive of coronary event.

Although patients without CAD were more likely to have low HDL-C (< 2.0 mmol/l) in univariate analysis (Table 2), in time-dependent covariate proportional hazards regression models, none of the measures of HDL-C were significantly predictive of coronary event (Table 3).

Mean TC:HDL-C (HR 1.42, 95% CI 1.01–2.00,  $p = 0.04$ ) and TAM TC:HDL-C (HR 1.43, 95% CI 1.02–2.00,  $p = 0.04$ ) were significantly predictive of coronary event when adjusted for age (Table 3).

When adjusted for age at each lipid measurement, each of most recent TG (HR 1.94, 95% CI 1.26–2.99,  $p = 0.003$ ), mean TG (HR 2.21, 95% CI 1.39–3.54,  $p = 0.0009$ ), and TAM TG (HR 2.11, 95% CI 1.32–3.39,  $p = 0.0019$ ) were also predictive of coronary event.

Sensitivity, specificity, PPV and NPV for CAD events, and accompanying 95% CI and  $p$  values for various LDL-C,

Table 2. Univariate comparisons of patients with and without coronary events used in lipid models.

Variable	CAD, n = 21 N (%) or Mean (SD)	No CAD, n = 363 N (%) or Mean (SD)	p
Female	19 (90.5%)	326 (89.8%)	1.00
Menopause <sup>b</sup> at study start <sup>a</sup>	9 (47.4%)	100 (30.7%)	0.13
Race			
White	19 (90.5%)	227 (63.8)	0.01
Black	0	46 (12.9%)	
Asian	0	43 (12.1%)	
Other	2 (9.5%)	40 (11.2%)	
Age, yrs, mean (SD)			
At diagnosis	38.7 (14.5)	28.8 (12.4)	0.0005
At first visit	42.8 (13.3)	33.1 (12.1)	0.0004
At study start <sup>a</sup>	52.1 (12.7)	40.9 (13.5)	0.0003
Disease duration, yrs, mean (SD)			
At first visit	4.1 (6.7)	4.3 (6.1)	0.92 <sup>∞</sup>
At study start <sup>a</sup>	13.4 (9.4)	12.2 (9.7)	0.56 <sup>∞</sup>
SLEDAI-2K <sup>e</sup> , throughout study* median (min, max)	10 (0, 51)	4 (0, 51)	< 0.0001 <sup>∞</sup>
Corticosteroids			
At study start <sup>a</sup>	16 (76.2%)	230 (63.4%)	0.23
Ever during followup	17 (81.0%)	257 (70.8%)	0.32
Antimalarials <sup>f</sup>			
At study start <sup>a</sup>	13 (61.9%)	225 (62.0%)	0.99
Ever during followup	14 (66.7%)	270 (74.4%)	0.43
Immunosuppressives <sup>g</sup>			
At study start <sup>a</sup>	12 (57.1%)	155 (42.7%)	0.19
Ever during followup	14 (66.7%)	205 (56.5%)	0.36
Hypertension <sup>h</sup>			
At study start <sup>a</sup>	17 (81.0%)	150 (41.3%)	0.0004
Ever during followup	19 (90.5%)	212 (58.4%)	0.004
Hypercholesterolemia <sup>e</sup>			
At study start <sup>a</sup>	18 (85.7%)	142 (39.1%)	< 0.0001
Ever during followup	21 (100%)	226 (62.3%)	0.0004
Diabetes mellitus <sup>h</sup>			
At study start <sup>a</sup>	2 (9.5%)	29 (8.0%)	0.68
Ever during followup	2 (9.5%)	33 (9.1%)	1.00
Smoker <sup>h</sup>			
At study start <sup>a</sup>	2 (9.5%)	44 (12.2%)	1.00
Ever during followup	2 (9.5%)	55 (15.2%)	0.75
Antihypertensives <sup>o</sup>			
Ever up to study start <sup>a</sup>	19 (90.5%)	165 (45.6%)	< 0.0001
Ever during followup	18/19 (94.7%)	192/212 (90.6%)	1.00
Lipid-lowering medications <sup>∞</sup>			
Ever up to study start <sup>a</sup>	7 (43.8%)	51 (15.4%)	0.009
Ever during followup	16/21 (76.2%)	96/226 (42.5%)	0.003
LDL-C at study start <sup>a</sup>	3.51 (1.61)	2.75 (1.08)	0.04
Mean of all LDL-C	3.29 (1.24)	2.60 (0.85)	0.02
Mean LDL-C > 2.0 mmol/l	18 (85.7%)	317 (87.3%)	0.83
Mean LDL-C > 2.5 mmol/l	14 (66.7%)	169 (46.6%)	0.07
Mean LDL-C > 3.2 mmol/l	12 (57.1%)	119 (32.8%)	0.02
TAM of all LDL-C	3.29 (1.21)	2.60 (0.85)	0.02
HDL-C at study start <sup>a</sup>	1.73 (0.64)	1.57 (0.49)	0.16
Mean of all HDL-C	1.68 (0.51)	1.62 (0.47)	0.56
Mean HDL-C < 1 mmol/l	2 (9.5%)	39 (10.7%)	0.86
Mean HDL-C < 2 mmol/l	14 (66.7%)	332 (91.5%)	< 0.0001
TAM of all HDL-C	1.67 (0.49)	1.62 (0.47)	0.65
TC:HDL-C at study start <sup>a</sup>	4.22 (2.41)	3.36 (1.13)	0.12
Mean of all TC:HDL-C	3.87 (1.69)	3.19 (0.95)	0.09
Mean TC:HDL-C > 4	9 (42.9%)	104 (28.7%)	0.17
Mean TC:HDL-C > 4.5	7 (33.3%)	57 (15.7%)	0.035
Mean TC:HDL-C > 5	5 (23.8%)	40 (11.0%)	0.076
TAM of all TC:HDL-C	3.87 (1.67)	3.18 (0.97)	0.08

Table 2. Continued

Variable	CAD, n = 21 N (%) or Mean (SD)	No CAD, n = 363 N (%) or Mean (SD)	p
TG at study start <sup>a</sup>	2.10 (1.44)	1.41 (0.74)	0.04 <sup>∞</sup>
Mean of all TG	1.97 (1.09)	1.33 (0.66)	0.02
Mean TG > 1.7 mmol/l	10 (47.6%)	138 (38.0%)	0.38
Mean TG > 2.0 mmol/l	8 (38.1%)	98 (27.0%)	0.27
TAM of all TG	1.95 (1.07)	1.33 (0.67)	0.02

<sup>a</sup> Study start was the first clinic visit wherein LDL-C, HDL-C, and TG measurements were taken. \* All serial measurements in all patients. <sup>b</sup> Minimum of 12 months amenorrhea, irrespective of cause. <sup>c</sup> Range 0 to 105, with higher scores indicating more active disease. <sup>d</sup> Chloroquine and hydroxychloroquine. <sup>e</sup> Methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide. <sup>f</sup> Diastolic blood pressure (BP) > 90 or systolic BP > 140 mm Hg or treatment with antihypertensive medication. <sup>g</sup> Cholesterol  $\geq$  5.2 mmol/l or lipid-lowering therapy. <sup>h</sup> Fasting plasma glucose > 7.0 mmol/l or diabetes therapy. <sup>i</sup> An average of  $\geq$  1 cigarette/s per day over the past month. <sup>j</sup> All classes of antihypertensives including diuretics,  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-type II receptor blockers. <sup>k</sup> HMG Co-A reductase inhibitors (statins). <sup>l</sup> Nonparametric Mann-Whitney (Wilcoxon rank sum) test used. CAD: coronary artery disease; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC:HDL-C: total cholesterol high-density lipoprotein cholesterol ratio; TG: triglyceride; TAM: time-adjusted mean.

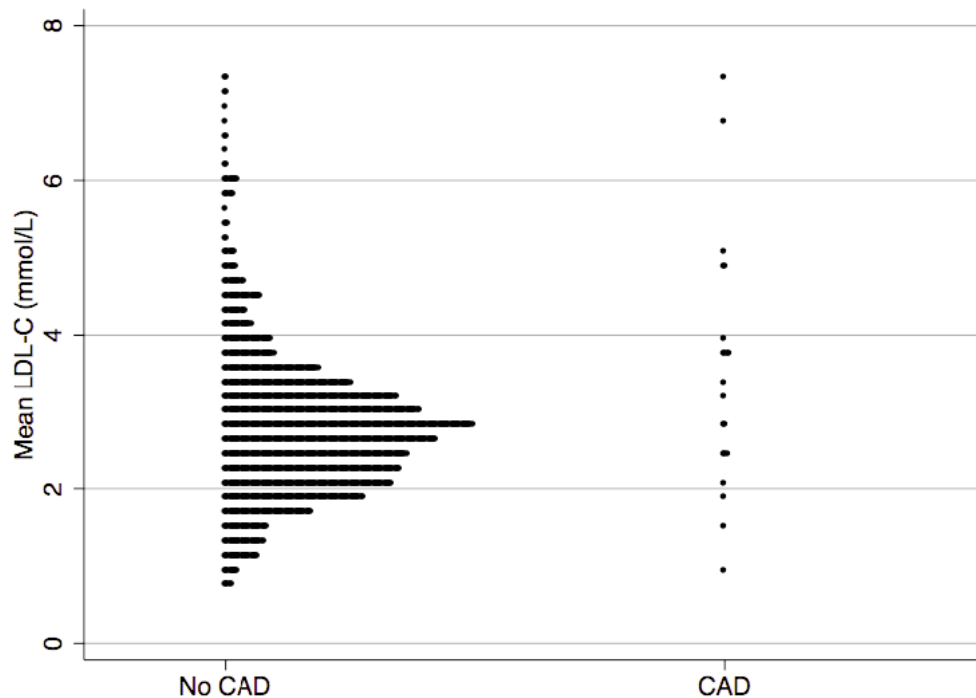


Figure 1. Dot plot of mean low-density lipoprotein cholesterol (LDL-C) up to each visit in patients with no coronary artery disease (CAD) and those with CAD.

TG, and TC:HDL-C ratio cutpoints are presented in Tables 4 and 5. A TAM LDL-C cutpoint of 2.0 mmol/l had a sensitivity and NPV for coronary event of 85.7% (95% CI 63.7–97.0) and 93.9% (95% CI 83.1–98.7), respectively. However, at this cutpoint the specificity was only 12.7% (95% CI 9.4–16.5).

The TAM TC:HDL-C ratio cutpoint of 5.0 had a specificity and NPV for CAD of 89.0% (95% CI 85.3–92.0) and

95.3% (95% CI 92.5–97.3), respectively. Mean TG cutpoint of 2.0 had NPV for CAD of 95.3% (95% CI 92.1–97.5).

## DISCUSSION

In our study, we linked 3 major lipoprotein markers of CAD risk in the general population with CAD risk in patients with SLE. From a methodological perspective, we have demonstrated that summary measures of cumulative exposure to

Table 3. Time-dependent proportional hazards regression models for coronary events including only lipid measures and age.

	Most Recent Lipid Measurement <sup>#</sup>		Mean of All Lipid Measurements <sup>#</sup>		Time-adjusted Mean of All Lipid Measurements <sup>#</sup>	
	HR* (95% CI)	p	HR* (95% CI)	p	HR* (95% CI)	p
<b>LDL-C Models</b>						
LDL-C	1.20 (0.76, 1.92)	0.43	1.81 (1.18, 2.77)	0.0065	1.83 (1.19, 2.81)	0.006
Age, yrs	1.07 (1.03, 1.10)	0.0006	1.06 (1.03, 1.10)	0.0007	1.06 (1.03, 1.10)	0.0007
<b>HDL-C Models</b>						
HDL-C	1.29 (0.60, 2.78)	0.52	1.59 (0.64, 3.94)	0.32	1.46 (0.58, 3.62)	0.42
Age, yrs	1.07 (1.03, 1.11)	0.0004	1.07 (1.03, 1.11)	0.0004	1.07 (1.03, 1.11)	0.0004
<b>TC:HDL-C Ratio Models</b>						
TC:HDL-C	1.17 (0.81, 1.68)	0.41	1.42 (1.01, 2.00)	0.04	1.43 (1.02, 2.00)	0.04
Age, yrs	1.06 (1.03, 1.10)	0.0007	1.06 (1.02, 1.10)	0.001	1.06 (1.02, 1.10)	0.001
<b>TG Models</b>						
TG	1.94 (1.26, 2.99)	0.003	2.21 (1.39, 3.54)	0.0009	2.11 (1.32, 3.39)	0.0019
Age, yrs	1.06 (1.02, 1.10)	0.0008	1.06 (1.02, 1.10)	0.0013	1.06 (1.02, 1.10)	0.0013

<sup>#</sup> The “most recent lipid measurement model” included the 42 patients with only 1 lipid measurement, whereas the other 2 models did not include these patients. \* HR: hazard ratio for each 1 year increase in age, or 1 mmol/l increase in LDL-C, HDL-C, or TG, or 1 unit increase in TC:HDL-C ratio. LDL-C: low-density lipoprotein cholesterol (mmol/l); HDL-C: high-density lipoprotein cholesterol (mmol/l); TC:HDL-C: total cholesterol:HDL-C ratio; TG: triglycerides.

Table 4. Test properties for the prediction of coronary event at a particular visit, based on LDL-C and TG cutpoint up to the prior visit. Positive predictive values (PPV) relate to lipid levels greater than specified cutpoints. Negative predictive values (NPV) related to levels less than specified cutpoints. Patients (n = 42) who had only 1 lipid measurement were excluded from these analyses.

Cutpoint (mmol/l)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<b>Mean LDL-C up to prior visit</b>				
2.0	85.7% (63.7, 97.0)	12.7% (9.4, 16.5)	5.4% (3.2, 8.4)	93.9% (83.1, 98.7)
2.5	66.7% (43.0, 85.4)	53.4% (48.1, 58.7)	7.7% (4.2, 12.5)	96.5% (93.0, 98.6)
3.2	57.1% (34.0, 78.2)	67.2% (62.1, 72.0)	9.2% (4.8, 15.5)	96.4% (93.4, 98.4)
<b>TAM LDL-C up to prior visit</b>				
2.0	85.7% (63.7, 97.0)	12.1% (8.9, 15.9)	5.3% (3.2, 8.3)	93.6% (82.5, 98.7)
2.5	66.7% (43.0, 85.4)	35.8% (30.9, 41.0)	5.7% (3.1, 9.3)	94.9% (89.8, 97.9)
3.2	57.1% (34.0, 78.2)	67.5% (62.4, 72.3)	9.2% (4.9, 15.6)	96.5% (93.4, 98.4)
<b>Mean TG up to prior visit</b>				
1.7	47.6% (25.7, 70.2)	62.0% (56.8, 67.0)	6.8% (3.3, 12.1)	95.3% (91.8, 97.7)
2.0	38.1% (18.1, 61.6)	73.0% (68.1, 77.5)	7.5% (3.3, 14.3)	95.3% (92.1, 97.5)
<b>TAM TG up to prior visit</b>				
1.7	47.6% (25.7, 70.2)	62.3% (57.1, 67.3)	6.8% (3.3, 12.2)	95.4% (91.9, 97.7)
2.0	38.1% (18.1, 61.6)	71.9% (67.0, 76.5)	7.3% (3.2, 13.8)	95.3% (92.0, 97.5)

LDL-C: low-density lipoprotein cholesterol; TAM: time-adjusted mean; TG: triglyceride.

lipid risk factors such as mean and TAM values are better able to quantify CAD risk in SLE than are single-point measurements.

In univariate analyses, patients with CAD were more likely to have hypercholesterolemia and HTN than those who remained event-free. In regression models, in addition to lipids, only age was statistically significant, with an HR of 1.08 (95% CI 1.04–1.13,  $p < 0.0001$ ) that was consistent across the models. The relatively small sample size of our study may have limited the ability to demonstrate other associations of CAD in SLE such as menopause, male sex,

disease activity score (at each visit and cumulatively over time), and corticosteroid use<sup>7,8,9</sup>.

Each mmol/l increase in mean and TAM LDL-C was associated with a 1.8-fold increase in risk of coronary event, highlighting the important role of LDL-C as an independent risk factor for coronary risk in SLE, as is the case in the general population and in other diseases such as diabetes, which are associated with increased coronary risk.

The hazard associated with each mmol/l increase in mean or TAM TG level was greater than for other lipids. A similar association between TG level and CAD was found by

Table 5. Test properties for the prediction of coronary event at a particular visit, based on TC:HDL-C cutpoint up to the prior visit. Positive predictive values (PPV) relate to lipid levels greater than specified cutpoints. Negative predictive values (NPV) related to levels less than specified cutpoints. Patients (n = 42) who had only 1 lipid measurement were excluded from these analyses.

Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Mean TC:HDL-C up to prior visit				
4.0	42.9% (21.8, 66.0)	71.4% (66.4, 76.0)	8.0% (3.7, 14.6)	95.6% (92.4, 97.7)
4.5	33.3% (14.6, 57.0)	84.3% (80.1, 87.9)	10.9% (4.5, 21.3)	95.6% (92.8, 97.6)
5.0	23.8% (8.2, 47.2)	89.0% (85.3, 92.0)	11.1% (3.7, 24.1)	95.3% (92.5, 97.3)
TAM TC:HDL-C up to prior visit				
4.0	42.9% (21.8, 66.0)	71.6% (66.7, 76.2)	8.0% (3.7, 14.7)	95.6% (92.4, 97.7)
4.5	33.3% (14.6, 57.0)	83.8% (79.5, 87.4)	10.6% (4.3, 20.6)	95.6% (92.7, 97.6)
5.0	23.8% (8.2, 47.2)	89.0% (85.3, 92.0)	11.1% (3.7, 24.1)	95.3% (92.5, 97.3)

HDL-C: high-density lipoprotein cholesterol; TAM: time-adjusted mean; TC:HDL-C: total cholesterol:HDL-C ratio.

Svenungsson, *et al*<sup>10</sup>. Although we found only a weak correlation between SLEDA1-2K and TG at each visit (correlation coefficient 0.15,  $p < 0.0001$ ), other studies have shown that in SLE, TG levels rise with increase in disease activity<sup>11</sup>. Further, higher TG in SLE could be associated with the presence of antibodies against lipoprotein lipase<sup>12</sup> and tumor necrosis factor, mechanisms through which TG may have a proatherogenic effect<sup>7</sup>.

The magnitude of CAD risk associated with each unit rise in LDL-C in SLE is similar to that for patients with diabetes mellitus, and in diabetes, TG level is also a risk factor for CAD<sup>2</sup>. This contrasts with the general population, wherein TG level is generally not considered an “independent” risk factor for CAD<sup>13</sup>.

In clinical practice, TG levels are often neglected and overshadowed by LDL-C and TC:HDL ratio, which tend to be the primary targets of lipid-lowering therapy in patients with SLE. However, although statins, which are first-line therapy for the treatment of elevated LDL-C, may also reduce accompanying elevated TG level, the achievement of target TG level may require significant weight loss or the addition of a second agent such as a fibrate<sup>2</sup>.

In the general population, HDL-C is a negative risk factor and is protective against CAD<sup>14,15,16</sup>. In coronary risk prediction algorithms such as the Framingham/Adult Treatment Panel (ATP) III model, low HDL-C ( $< 1.29$  mmol/l, in particular  $< 1.03$  mmol/l) is a risk factor for CAD<sup>15</sup>. However, in our study, HDL-C was not significantly protective against coronary events among patients with SLE. Some HDL-C, for example proinflammatory HDL-C, is in fact proatherogenic, and a total HDL-C level fails to distinguish between cardioprotective and atherogenic HDL-C<sup>17</sup>. While disease activity may reduce the total level of HDL-C in SLE, it may also lead to a proportionate rise in the proinflammatory component of HDL. Indeed, patients with SLE have been shown to have high levels of proinflammatory HDL-C, and proinflammatory HDL-C is

an independent risk factor for subclinical atherosclerosis in SLE<sup>11,18,19</sup>. Overall, our findings indicate that in patients with SLE, TC:HDL-C ratio is a preferred marker of coronary risk compared with HDL-C alone.

Several factors are taken into consideration when selecting an optimal lipid cutpoint for assessment of coronary risk. These include the overall frequency (prevalence) and severity of the outcome (in this case, coronary events), and the availability, cost, and tolerability of effective therapies. The 2004 modifications of the third US National Cholesterol Education Program (NCEP)-ATP III report recommend that the LDL-C goal be  $< 2.58$  mmol/l<sup>3</sup> for patients at highest baseline coronary risk such as those with known CAD or a CAD risk equivalent such as non-coronary forms of atherosclerotic disease or diabetes mellitus. The same guidelines recommend LDL-C  $< 3.36$  mmol/l among those at moderately high coronary risk (those with 2 or more risk factors such as smoking, HTN, and family history of premature coronary heart disease). More recent guidelines recommend even lower LDL-C targets below 1.8 mmol/l in those at highest baseline coronary risk. In our study, a TAM LDL-C cutpoint of 2.0 mmol/l had a high sensitivity and NPV ( $> 90\%$ ) for CAD event. While at cutpoints of 2.5 and 3.2 mmol/l, the sensitivity of mean and TAM LDL-C for CAD dropped, and the NPV remained high ( $> 95\%$ ). The practicality of lowering LDL-C to  $< 2.5$  mmol/l in patients with SLE is uncertain<sup>3</sup>. Further, at present there is little evidence to support lipid-lowering therapy as a means of cardiovascular risk reduction in SLE. In a study by Petri, *et al*, treatment with atorvastatin was not associated with reduction in carotid intima-media thickness in patients with SLE treated over 2 years<sup>20</sup>. In contrast, in a study by Plazak, *et al*, the progression of subclinical atherosclerosis, as assessed by coronary calcium scoring, was restrained in patients with SLE randomized to receive atorvastatin for 1 year, compared with placebo<sup>21</sup>. However, the relatively short study duration and use of surrogate

endpoints for CAD limit the interpretation of these findings.

The Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias recommends that target TC:HDL-C ratio be  $< 4^{22}$  in those with the highest baseline risk of CAD, that is, those with known CAD or CAD risk equivalent. This group recommends a target TC:HDL-C of  $< 5$  in those with 2 or more risk factors. In keeping with these recommendations, in our study, mean TC:HDL-C ratio  $< 5.0$  had a relatively high NPV for CAD event of 95.3%. The NPV for mean TC:HDL-C ratio  $< 4.0$  was 95.6%. According to the third report of the NCEP-ATP III, normal TG levels are  $< 1.7$  mmol/l, with values between 1.7 and 2.2 mmol/l representing borderline high levels<sup>2</sup>. In our study, the properties of TG cutpoints of 1.7 and 2.0 mmol/l for CAD prediction were similar, with a mean TG cutpoint of 1.7 mmol/l having greater sensitivity and a mean TG cutpoint of 2.0 mmol/l having greater specificity (73.0; 95% CI 66.7–76.2) for CAD. Both cutpoints had a high NPV of  $> 95\%$ .

In our study, PPV and NPV were calculated based on a prevalence of CAD of 5.4% (21 events in 384 patients). The reported prevalence of CAD in SLE is 5–10%<sup>1</sup> and variations in this frequency are expected to alter PPV and NPV, while sensitivity and specificity for various lipid cutpoints will remain unchanged.

As is the case in other patient groups, when evaluating overall cardiac risk in patients with SLE, lipids are considered in conjunction with other risk factors such as HTN and smoking. Indeed, the PPV for each lipid measure is relatively low, indicating that lipids alone do not fully account for CAD risk in SLE. Clinical prediction tools that incorporate a number of different risk factors are needed, akin to the Framingham risk prediction algorithm. However, to date in SLE, the role of traditional risk factors such as lipids and blood pressure has not been fully quantified, and many novel SLE-related risk factors remain unidentified. Identification and quantification of these risk factors is critical to the future development of a clinical prediction tool for coronary risk in SLE.

Our study links 3 major lipid markers used in the general population (LDL-C, TC:HDL-C ratio, and TG) to coronary risk in patients with SLE. In addition, the magnitude of risk associated with each of mean and TAM levels for each of these lipids has been quantified using time-dependent proportional hazards regression models that take into account all serial measurements available over time. Further, to our knowledge this is the first study to evaluate risk assessment levels for these lipids using an incremental cutpoint analysis with adjustments made for age. We have shown that a mean LDL-C cutpoint of at least 2.5 and possibly lower (i.e., 2.0 mmol/l) identifies patients with SLE at high CAD risk. Similarly, a mean TC:HDL-C cutpoint of 5 and mean TG of 2.0 mmol/l (or even lower, i.e., 1.7 mmol/l) also identified patients with SLE at high CAD risk. These risk assessment levels are comparable to those recom-

mended for patients with highest baseline coronary risk such as those with diabetes mellitus. Further studies are needed to confirm these findings in other SLE cohorts and to determine whether lipid-lowering therapy reduces CAD risk.

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