Serum lipoprotein dysfunction is a major determinant and independent clinical marker of coronary atherosclerosis and high cardiovascular risk in patients with rheumatoid arthritis

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Background and objective

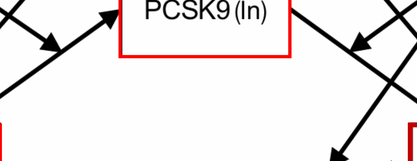
Autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), are associated with particularly high cardiovascular risk (CVR). The complexity of proatherogenic mechanisms makes the definition of single patient CVR very difficult, thus contributing to non-optimal prevention and treatment.

AUTOIMMUNE RHEUMATIC DISEASES

- Acute phase proteins
- Cytokines
- ROS
- Autoantibodies
- PCSK9

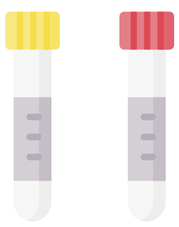
Enzymes	TG	LDL	HDL
↓ LCAT ↓ lipoprotein lipases	↑ levels	variable LDL-C ↑ small dense LDL ↑ Lp(a) and oxLDL	↓ HDL-C and ↓ apoAI ↓ PON1 ↑ SAA

Increased cell cholesterol content (due to ↑CLC ↓ CEC) and proinflammatory activation



Plaque progression *Acute events*

Patients, materials and methods



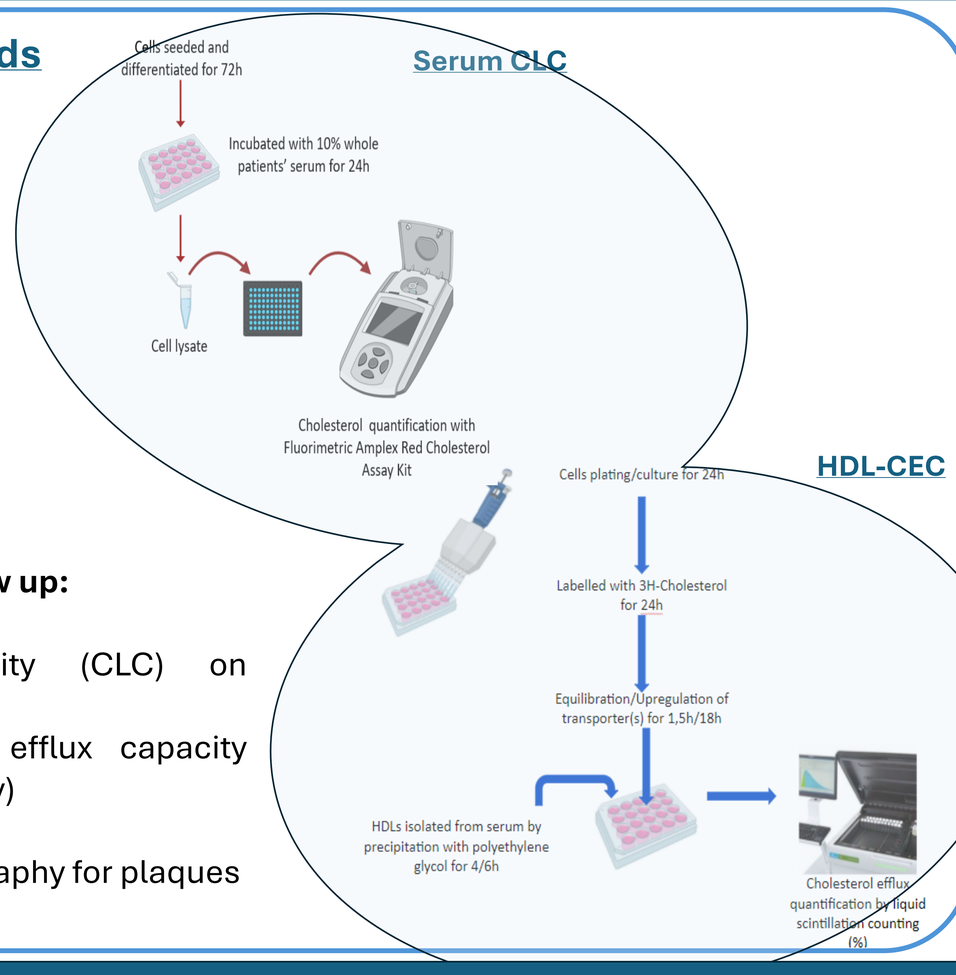
-141 patients with RA from the PROTECT- RA cohort;

-99 follow up for incidence of cardiovascular events

over 6.0±2.4 years.

Measurements at baseline and at follow up:

-Serum cholesterol loading capacity (CLC) on macrophages model;
-ABCG1 or ABCA1 HDL cholesterol efflux capacity (ABCG1-CEC or ABCA1-CEC, respectively)
-laboratory parameters
-coronary computed tomography angiography for plaques



Results

CLC and CVR in RA

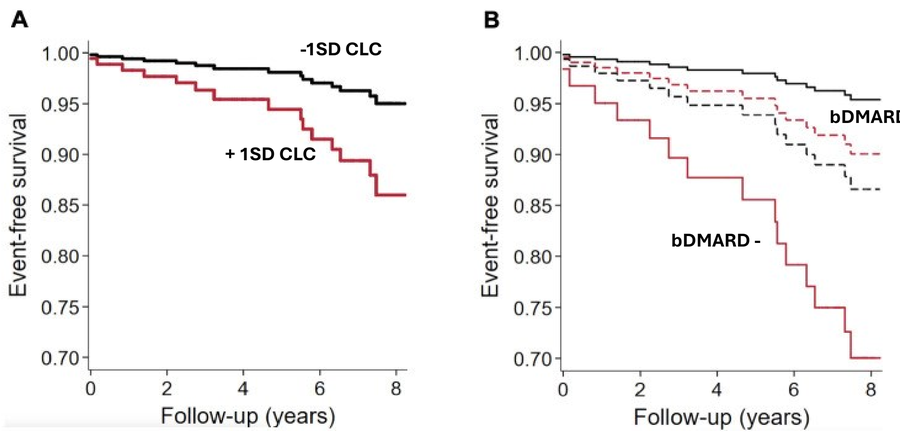


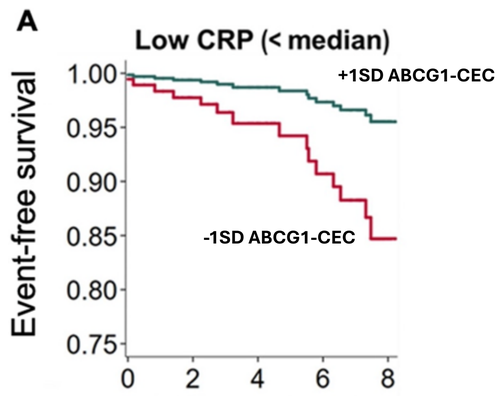
Figure 1

Red boxes: CLC mediators; Blue boxes: CLC moderators

Figure 2

Baseline CLC associated with incident cardiovascular event risk in RA patients after adjusting for Atherosclerotic Cardiovascular Disease (ASCVD) risk score (HR 1.76, [95%CI 1.16-2.67] per 1 SD higher CLC, p=0.008) (**Figure 1A**), and to high risk coronary plaque burden in biologic disease modifying drugs (bDMARD) nonusers (p<0.001) (**Figure 1B**). Major determinants of serum CLC were oxidized LDL (measured as oxidized phospholipids on apoB100), anti-oxidized LDL IgG and proprotein convertase subtilisin/kexin type 9 (PCSK9) (**Figure 2**).

ABCG1-CEC and CVR in RA



B

Baseline plaque outcomes	Adjusted RR or OR (95% CI) per 1 SD higher ABCG1	p
No. plaques total	0.91 (0.73-1.13)	0.379
No. noncalcified plaques	0.96 (0.78-1.18)	0.699
No. partially calcified plaques	0.71 (0.53-0.94)	0.018
No. calcified plaques	1.07 (0.71-1.63)	0.739
No. low attenuation plaques	0.63 (0.43-0.91)	0.013
Exteensive plaque (≥5 segments)	0.50 (0.28-0.88)	0.017

0.1 0.5 1.0 2.5

Figure 3

In patients with low C-reactive protein (CRP) (≤ median), baseline ABCG1-CEC associated inversely with CVR (HR 0.47 per 1 SD higher ABCG1-CEC, p=0.05) (**Figure 3A**). It also negatively associated with extensive coronary atherosclerosis (HR 0.50, p= 0.017), high-risk plaque burden (HR 0.063, p=0.013) (**Figure 3B**) and when both baseline and time-averaged CRP was low, also with plaque progression in time (p-for-interaction =0.001 and 0.021 respectively).

Per-patient plaque outcome/ Moderator	Adjusted Rate Ratio (95% CI) per 1 SD higher ABCA1-CEC	P value
No. new calcified plaques		
Time-averaged CRP		
<7 mg/L	0.47 (0.27-0.81)	0.007
>7 mg/L	1.02 (0.52-2.01)	0.954
No. new plaques total		
Baseline bDMARD		
No	2.65 (1.49-4.7)	0.001
Yes	0.65 (0.43-0.99)	0.044

Figure 4

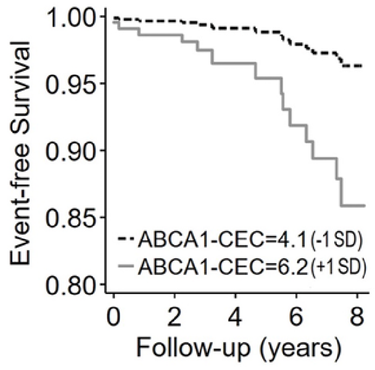


Figure 5

ABCA1-CEC and CVR in RA

ABCA1-CEC associated with fewer calcified plaques at baseline (IRR 0.52 [95% CI 0.32–0.83], p =0.007 per 1 SD higher ABCA1-CEC) in patients with low CRP. In bDMARD nonusers ABCA1-CEC associated with increased plaque progression (HR 2.65 per 1 SD higher ABCA1-CEC, p=0.001) (**Figure 4**).

In the context of inflammation and impaired pre-β HDL maturation typical of RA, higher ABCA1-CEC may reflect a proatherogenic state (**Figure 5**).

Conclusions: we demonstrated that CLC and CEC strongly, and independently from known risk factors, correlate with coronary atherosclerosis and with the risk of cardiovascular events in patients with RA. Lipoprotein function evaluated as CLC, ABCG1-CEC and ABCA1-CEC, especially considered together with the other factors (inflammation, autoantibodies, PCSK9, drugs) may help classifying CVR in AR patients and applying optimal individual strategies for prevention and treatment.

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