

Incident CHD, residual risk and traditional cardiovascular risk factors in the community: role of lipid-inflammatory axis

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Background: Coronary heart disease (CHD) can occur even in individuals who are considered to have a low overall risk estimated by traditional cardiovascular risk factors (CVRFs). In previous investigations we reported on the crucial role of the lipid-inflammatory axis in this context, demonstrating that increased concentrations of various proinflammatory biomarkers such as high-sensitive C-reactive protein (hsCRP), lipoprotein (a) (Lp(a)) or triglycerides (TGs) were strongly associated with incident CHD among individuals without or having only one of four major CVRFs (hypertension, diabetes, hypercholesterolemia, smoking) at baseline. However, whether the combination of these biomarkers would provide additional information for incident CHD prediction in this specific group of individuals from the general population remains unknown.

Methods: Overall, 63,025 CHD-free individuals from eight European prospective population-based cohorts were included. The cohort was stratified according to CVRF burden at baseline in 0/1 CVRF and ≥ 2 CVRFs. Biomarkers were assessed dichotomously above and below established cut-offs: $<VS \geq 2$. Results: During a median follow-up of 9.65 years, 3,157 participants developed a CHD event. The results of joint-effect analyses are presented in the Table. Compared to subjects with ≥ 2 CVRFs at baseline, those with low baseline risk showed a numerically stronger association between combinations of two biomarkers and incident CHD (pinter across CVRF categories ranging from 0.076 to 0.21).

However, even higher CHD risk was observed in models, incorporating all three biomarkers. Among subjects with low CV risk at baseline (0/1 CVRF), multivariable adjusted sub-distribution hazard ratios (sHRs) with 95% confidence interval (CI) for incident CHD were 1.0 (reference group) among participants with biomarker levels below established cutoffs, 1.51 (1.30-1.76) in those with one elevated biomarker, 1.98 (1.64-2.39) for two and 3.03 (1.94-4.74) for all three biomarkers being above established cutoffs. Interestingly, among those with higher baseline risk (i.e. with 2 or more CVRFs), the observed association between combined biomarkers and outcome was numerically lower (pinter 0.062 between 0/1 vs ≥ 2 CVRFs), probably due to more intensive preventive measures in this group. The corresponding sHRs (95% CI) were 1.24 (1.09-1.41) for one, 1.51 (1.32-1.73) for two and 2.08 (1.62-2.67) for three biomarkers above established cutoffs, respectively.

Conclusion: The combination of three elevated cardiometabolic biomarkers (hsCRP, Lp(a) and TG), determined together at a single time point might significantly improve CHD risk prediction particularly in low risk subjects from the general population. $<VS \geq 2$

	0-1 CVRF				≥ 2 CVRFs			
	Nevents/Ntotal	Events/1000py	sHR (95% CI)	p-value	Nevents/Ntotal	Events/1000py	sHR (95% CI)	p-value
Entire Cohort	34,779/918	2.4 (2.2, 2.5)	-		20,898/1,754	7.9 (7.6, 8.3)	-	
CRP<2 mg/L and Lp(a)<90 th pctl.	22,882/507	1.9 (1.7, 2.1)	1.0 ^{REF}		10,484/752	6.5 (6.0, 7.0)	1.0 ^{REF}	
CRP ≥ 2 mg/L and Lp(a)<90 th pctl.	8,752/302	3.4 (3.0, 3.8)	1.44 (1.25-1.66) p<0.001		7,968/774	9.7 (9.0, 10.4)	1.22 (1.10-1.35) p<0.001	
CRP<2 mg/L and Lp(a) $\geq 90^{\text{th}}$ pctl.	2,219/68	2.6 (2.1, 3.3)	1.44 (1.12-1.85) p=0.0043		1,389/107	7.0 (5.8, 8.5)	1.23 (1.00-1.50) p=0.046	
CRP ≥ 2 mg/L and Lp(a) $\geq 90^{\text{th}}$ pctl.	926/41	4.5 (3.3, 6.0)	2.17 (1.59-2.97) p<0.001		1,057/121	11.4 (9.5, 13.6)	1.61 (1.33-1.96) p<0.001	
							P_{inter} 0.14	
Entire Cohort	33,202/910	2.4 (2.3, 2.6)	-		20,364/1,739	8.0 (7.7, 8.4)	-	
TG<1.70 mmol/L and CRP<2 mg/L	19,115/326	1.5 (1.3, 1.6)	1.0 ^{REF}		7,283/422	5.4 (4.9, 5.9)	1.0 ^{REF}	
TG ≥ 1.70 mmol/L and CRP<2 mg/L	4,737/246	4.1 (3.6, 4.6)	1.56 (1.32-1.85) p<0.001		4,252/429	8.6 (7.8, 9.4)	1.26 (1.10-1.44) p=0.001	
TG<1.70 mmol/L and CRP ≥ 2 mg/L	6,698/179	2.7 (2.3, 3.1)	1.57 (1.31-1.89) p<0.001		4,609/330	7.7 (6.9, 8.6)	1.22 (1.05-1.41) p=0.0081	
TG ≥ 1.70 mmol/L and CRP ≥ 2 mg/L	2,652/159	5.3 (4.5, 6.2)	1.90 (1.57-2.31) p<0.001		4,220/558	12.2 (11.2, 13.2)	1.53 (1.34-1.75) p<0.001	
							P_{inter} 0.076	
Entire Cohort	33,202/910	2.4 (2.3, 2.6)	-		20,364/1,739	8.0 (7.7, 8.4)	-	
TG<1.70 mmol/L and Lp(a)<90 th pctl.	23,390/447	1.7 (1.6, 1.9)	1.0 ^{REF}		10,402/653	6.2 (5.7, 6.6)	1.0 ^{REF}	
TG ≥ 1.70 mmol/L and Lp(a)<90 th pctl.	6,804/355	4.3 (3.8, 4.7)	1.41 (1.22-1.62) p<0.001		7,595/860	10.1 (9.4, 10.8)	1.26 (1.14-1.40) p<0.001	
TG<1.70 mmol/L and Lp(a) $\geq 90^{\text{th}}$ pctl.	2,423/58	2.2 (1.7, 2.8)	1.33 (1.01-1.74) p=0.040		1,490/99	6.7 (5.4, 8.0)	1.22 (0.99-1.51) p=0.065	
TG ≥ 1.70 mmol/L and Lp(a) $\geq 90^{\text{th}}$ pctl.	585/50	6.7 (5.0, 8.7)	2.37 (1.78-3.17) p<0.001		877/127	12.4 (10.3, 14.7)	1.69 (1.40-2.05) p<0.001	
							P_{inter} 0.21	

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). P_{inter} = P for interaction across CVRF categories. 90th percentile of Lp(a) is 43.16 mg/dL (cohort-specific). Models adjusted for examination age, fasting status, male sex, systolic blood pressure, diabetes mellitus, BMI, and daily smoking. py = person-years.