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Can Apolipoproteins apoB and apoB/apoA1 Ratio Predict Future Cardiovascular Risk Post Acute Coronary Syndrome? A Retrospective Cohort Study

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Abstract

Background: Whether apolipoproteins B100 (ApoB) and ApoB/ApoA1 biomarkers can predict future cardiovascular events in patients with acute coronary syndrome (ACS) is unknown. We evaluated the association between these biomarkers and development of major adverse cardiovascular events within 12 months in patients with ACS.

Methods: We used data from a prospective cohort study of 1149 patients (32% women) aged 55 years or less, hospitalized for ACS (January 2009-April 2013). Baseline ApoB and ApoA1 levels were measured within the first 4 days of hospitalization for ACS. Patients were followed for 12 months for the composite of death, recurrent ACS, need for recurrent revascularization, or re-hospitalization for cardiac causes.

Results: After ACS, most patients had elevated ApoB levels (46% 0.8-1.1 g/L and 31% with >1.1 g/L). Patients with the lowest ApoB levels (<0.8 g/L) were more likely to be women, have a history of previous myocardial infarction, diabetes and to be prescribed statins compared with those with higher ApoB levels. There was no significant association with ApoB level and the risk of composite cardiovascular outcome after adjustment for age, sex, statin use, GRACE score, ACS severity and day of measurement (Hazard Ratio (HR) 0.79, 95% CI: 0.41-1.55). Increasing ApoB/ApoA1 ratio was also not associated with risk of developing composite cardiovascular events compared with lower ratios (HR 0.92 95% CI 0.45-1.87).

Conclusion: ApoB level and ApoB/ApoA1 ratio do not predict future cardiovascular events post-ACS when measured in the first 4 days in patients aged less than 55 years.

Keywords: ApoB; Residual risk; Secondary prevention; Sex differences; Menopause

Introduction

Prognosis after acute coronary syndrome (ACS) remains variable. Despite optimal strategies including statin therapies targeted to decrease low-density lipoprotein cholesterol (LDL-C), as high as 20% of patients develop secondary cardiovascular events or death [1]. Putative biological markers may play a role in risk stratification in the acute setting, distinguishing patients who develop complications from those who remain clinically stable.

Apolipoproteins including B100 (ApoB) and A1 (ApoB/ApoA1 ratio) are constituents of atherogenic lipoprotein particles, and contribute to the retention of these particles, most notably LDL-C, in the vascular sub-endothelium. Elevated ApoB levels are associated with higher atherosclerotic plaque burden [2,3] and increased ApoB/ApoA1 ratio is attributed to 49% of ACS events globally. Recently, evidence emerged that ApoB is a significant predictor for future cardiovascular events despite adequate LDL-C levels in patients with stable coronary disease [4-6]. However, this has not been evaluated in acute post-ACS populations.

Apolipoprotein biomarkers are promising as putative predictors for future cardiovascular events in ACS based on evidence in non-acute, stable coronary artery disease populations. They may be additionally attractive compared with LDL-C, as apolipoprotein levels remain stable in non-fasting states. However, the ACS setting is pro-inflammatory and ApoB levels have been shown to fall in other inflammatory conditions [7]. Additionally, it is uncertain whether the prognostic utility of apolipoproteins would be similar between peri- and post-menopausal women. Estrogen prevents ApoB misfolding into electronegative LDL-C and reduces autoantibodies directed towards oxidized ApoB, two proposed mechanisms for the atherogenicity of

ApoB in post-menopausal women [7,8]. However, whether these findings can be translated in clinical settings remains unclear.

In this study, we determine the association between ApoB levels, ApoB/ApoA1 ratios and 12-month risk of major cardiovascular events in men and women aged 55 years or less with ACS. We also evaluate this relationship according to menopausal status and explore the correlation between apolipoprotiens and an inflammatory marker post-ACS.

Methods

Study participants

Subjects were participants of the GENESIS PRAXY (GENdEr and Sex DetermInantS of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary SYndrome) a prospective observational cohort study [9] (January 2009 to April 2013). Patients with ages between 18-55 years admitted with ACS to metropolitan tertiary care and community hospital coronary care, intensive care or general cardiology units were enrolled in 24 sites in Canada, one in the US, and one in Switzerland.

Diagnosis of ACS was determined by the treating physician based on symptoms in keeping with acute myocardial ischemia within 24 hours of presentation to the hospital and one or more of: 1) ECG changes in two or more contiguous leads: transient ST segment elevations of ≥ 1 mm, ST segment depressions of ≥ 1 mm, new T wave inversions of ≥ 1 mm, pseudo-normalization of previously inverted T waves, new Q-waves (1/3 the height of the R wave or ≥ 0.04 seconds), new R wave >S wave in lead V1 (posterior MI), or new left bundle branch block; 2) increase in cardiac enzymes: positive troponin I, positive troponin T, CK-MB or total CPK >2x upper limit of the hospital's normal range.

Data collection

Biomarkers

Baseline lipid profile (LDL-C, HDL-C, total cholesterol, triglycerides, ApoB and ApoA1) and high-sensitivity C-reactive protein (hs-CRP) were collected either within 24 h of admission to the emergency department or at any moment preceding patient discharge from the hospital after the first ACS event (within 4 days of admission). Each patient had a one-time measurement for each biomarker. ApoB levels were categorized into 3 groups (<0.8 g/L, 0.8-1.1 g/L and >1.1 g/L) reflecting existing secondary prevention evidence [10-12].

Demographic and clinical characteristics

Age, ethnicity (white *vs.* other) and menopausal status in women (pre- or peri-menopausal *vs.* post-menopausal) were established on self-report. The presence of dyslipidemia, diabetes mellitus, and hypertension were based on self-report, medical chart review and prescriptions for diabetes, lipid-lowering or antihypertensive medications. The use of hormonal therapy (HT) as well as previously diagnosed medical conditions such as past cardiac history and previous percutaneous coronary interventions (PCI)/coronary artery bypass grafts (CABG) were also obtained based on self-report and chart review of medical records. Admission diagnosis, reperfusion status (none, thrombolysis, PCI, CABG), peak troponin levels and left ventricular ejection fraction were acquired through medical record review [13].

ACS severity and coronary anatomy

ACS severity was assessed by: 1) type (ST-elevation myocardial infarction (STEMI) *vs.* non-ST-elevation myocardial infarction (NSTEMI) or unstable angina), 2) peak troponin levels (tertiles above normal) acquired on admission, and 3) presence and extent of coronary artery stenosis based on medical record. The Global Registry of Acute Coronary Events (GRACE) score, a validated score used to predict in-hospital and long-term mortality or re-infarction in STEMI and NSTEMI patients was calculated using clinical data from chart review. Coronary angiography data were available in 90% of patients.

Primary endpoint

The primary endpoint over the 12-month period following the index ACS was a composite of any of: all-cause mortality, cardiovascular mortality, recurrent ACS, revascularization post-discharge, hospitalization for heart failure and hospitalization for stroke. These endpoints were based on medical chart review. Cardiovascular mortality was defined as any mortality directly caused by 1) an arrhythmia, 2) coronary artery disease, 3) congestive heart failure, or 4) any other vascular event. Any mortality not listed in one of those categories was classified as non-cardiovascular.

Statistical analysis

Baseline characteristics were compared by ApoB category using chi-square and Student's t-tests for categorical and continuous variables, respectively. To evaluate the independent association of ApoB level and separately, ApoB/ApoA1 ratios treated as continuous variables, with our primary endpoint, we estimated risk adjusted Cox Proportional Hazards models adjusted for sex, age and day of apolipoprotein measurement. As apolipoprotein level distribution approximated normality, no transformations were applied. Separate Cox models were constructed that additionally adjusted for ACS type, statin use and GRACE score. Spearman correlation coefficients were calculated between hs-CRP level and the lipid biomarkers (ApoB, ApoB/ApoA1 and LDL-C) for each day following ACS. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Ethics

This study was carried out in compliance with the Helsinki declaration and approved at McGill University.

Results

Patient characteristics

The mean age of women and men was 48 years old, and almost half of women enrolled in the study were post-menopausal (Table 1). Apoliprotein, LDL-C and hs-CRP were measured within 4 days of index ACS event in all patients with 42.4% measured on day 1, 24.2% measured on day 2 and 15.1% on day 3. Of the study cohort, 75% had elevated ApoB levels (≥ 0.8 g/L). Patients in the lowest ApoB category were more likely women, to smoke, and less likely to present with STEMI. However, they were more likely to have a previous history of myocardial infarction, previous PCI, and have hypertension and diabetes compared with those in higher ApoB categories. There was no

difference in mean ApoA1 level, hs-CRP, prevalence of triple vessel disease and GRACE score across the ApoB level categories.

Characteristics	ApoB <0.8 g/L (n=267)	ApoB 0.8-1.1 g/L (n=523)	ApoB >1.1 g/L (n=359)	p value
Age (years)	47.9	48.4	47.8	0.13
Women (%)	105 (39.3)	153 (29.3)	111 (30.9)	0.01
Post-menopausal (%)	40 (38.1)	74 (48.1)	62 (55.9)	0.03
Ethnicity (%)	_	_	_	0.91
Caucasian	223 (83.5)	432 (82.6)	300 (83.6)	_
Other	44 (16.5)	91 (17.4)	59 (16.4)	_
Admission diagnosis (%)				
STEMI	134 (50.2)	314 (60.0)	216 (60.2)	0.02
NSTEMI	90 (33.7)	167 (31.9)	123 (34.3)	0.75
Unstable Angina	39 (14.6)	33 (6.3)	13 (3.6)	<0.01
Medical history (%)				
Previous MI	64 (24.0)	68 (13.0)	40 (11.1)	<0.01
Previous PCI	59 (22.1)	63 (12.1)	35 (9.8)	<0.01
Previous CABG	12 (4.5)	13 (2.5)	11 (3.1)	0.31
Hypertension	145 (54.3)	254 (48.6)	159 (44.3)	0.05
Dyslipidemia	139 (52.1)	260 (49.7)	229 (63.8)	<0.01
Diabetes	63 (23.6)	78 (14.9)	56 (15.6)	0.01
Current smoking	80 (30.0)	211 (40.3)	149 (41.5)	<0.01
Renal disease	15 (5.6)	19 (3.6)	17 (4.7)	0.41
Previous CHF	6 (2.3)	8 (1.5)	6 (1.7)	0.76
Triple vessel disease (%)*	17 (11.6)	34 (15.7)	30 (16.5)	0.42
Left main disease (%)	10 (3.8)	10 (1.9)	14 (3.9)	0.16
Mean LVEF (%)	51.3	50.7	51.2	0.57
GRACE score (SD)	71.9 (17.5)	71.4 (16.9)	69.8 (16.6)	0.16
Lipid-lowering treatment (%)				
Statins	100 (37.5)	107 (20.5)	54 (15.0)	<0.01
Fibrates	4 (1.5)	10 (1.9)	5 (1.4)	0.82
2 or more agents	3 (1.1)	5 (1.0)	2 (0.6)	0.72
Hormonal therapy (%)	2 (0.8)	3 (0.6)	6 (1.7)	0.24
Total cholesterol mmol/L (SD)	3.31 (0.63)	4.48 (0.62)	5.85 (1.04)	<0.01
LDL mmol/L (SD)	1.70 (0.49)	2.67 (0.55)	3.92 (1.05)	<0.01
HDL mmol/L (SD)	0.96 (0.34)	0.94 (0.28)	0.96 (0.25)	0.26
TC/HDL ratio (mean)	3.76 (1.07)	5.14 (1.41)	6.40 (1.72)	<0.01
Triglycerides mmol/L (SD)	1.51 (0.96)	2.07 (1.26)	2.25 (1.16)	0.05
ApoA1 g/L (SD)	1.17 (0.27)	1.18 (0.23)	1.19 (0.21)	0.49
hs-CRP mg/dL (SD)	2.67 (54.0)	2.46 (40.1)	2.50 (37.0)	0.88

Table 1: Patient characteristics according to baseline ApoB level.

Use of statins prior to admission ranged from 15 to 37.5% across the ApoB categories in patients with ACS. Patients with higher ApoB levels were less like to have been prescribed statin therapy. Patients with lower ApoB levels (<0.8 g/L) had lower total cholesterol, LDL-C levels, total cholesterol/HDL-C ratios and triglycerides. Less than 2% of the study cohort was prescribed a non-statin lipid-lowering medication (e.g. fibrates).

Outcomes

There was no significant association between ApoB level and risk of developing the composite cardiovascular endpoint at 12 months after adjusting for age, sex, and day of measurement (adjusted HR 0.75, 95% CI: 0.39-1.45) (Table 2). When additionally adjusting for statin use, GRACE score and type of ACS, and baseline LDL-C, the primary outcome still failed to meet statistical significance (HR 0.79, 95% CI 0.41-1.55). Increased ApoB/ApoA1 ratio was also not significantly associated with development of cardiovascular events compared with lower ratios (adjusted HR 0.90, 95% CI 0.44-1.82).

Model Covariates	ApoB Hazard ratio (95% CI)	LDL-C Hazard ratio (95% CI)	ApoB/ApoA1 Hazard ratio (95% CI)
Age/Sex/Day of measurement	0.75 (0.39-1.45)	0.85 (0.68-1.05)	0.90 (0.44-1.82)
Age/Sex/Day of measurement/ LDL-C	0.57 (0.21-1.56)	--	0.98 (0.44-2.15)
Age/Sex/Statin use/ACS type/ GRACE score/Day of measurement	0.79 (0.41-1.55)	0.89 (0.71-1.10)	0.92 (0.45-1.87)
Age/Day of measurement/ menopausal status in women only	0.29 (0.09-0.94)	0.65 (0.44-0.96)	0.39 (0.11-1.32)

*Composite cardiovascular endpoint = time to any of the following (whichever is first): recurrent ACS, death, need for recurrent revascularization, re-hospitalization for cardiac cause. Abbreviations: CV: Cardiovascular; ApoB: Apolipoprotein B; LDL-C: Low-Density Lipoprotein; ApoA1: Apolipoprotein A1; ACS: Acute Coronary Syndrome; GRACE: Global Registry of Acute Coronary Events

Table 2: Multivariate models of Apo B, LDL-C and ApoB/ApoA1 and composite cardiovascular endpoint at 12 months.

Sex differences

Higher ApoB levels were associated with a lower hazard ratio (HR) for our primary outcome in menopausal women (adjusted HR 0.29, 95% CI 0.09-0.94) (Table 2). However, statistical significance was not met with ApoB/ApoA1 ratio (adjusted HR 0.39, 95% CI 0.11-1.32).

Levels of biomarkers according to day of measurement from ACS

Table 3 shows the mean and median levels of the biomarkers ApoB, ApoB/ApoA1 and LDL-C and hs-CRP in the first 4 days after ACS. All correlation coefficients between the lipid biomarkers and hs-CRP level were low (<0.34) for each day measured. Although mean and median hs-CRP and LDL-C fluctuated in the first 4 days after ACS event, levels of ApoB, ApoB/ApoA1 were generally stable.

Marker	Day 0		Day 1		Day 2		Day 3		Day 4	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
ApoB	0.93(0.24)	0.93	1.04(0.28)	1.02	1.03(0.26)	1.01	0.99(0.28)	0.96	0.91(0.29)	0.89
ApoB/ApoA1	0.80(0.33)	0.8	0.87(0.26)	0.9	0.87(0.26)	0.8	0.87(0.30)	0.8	0.86(0.36)	0.8
LDL-C	2.27(0.93)	2.13	3.11(1.10)	3.05	2.86(0.95)	2.83	2.75(1.13)	2.6	2.26(1.01)	2.09
hs-CRP	19.4(39.60)	7.1	19.6(32.60)	7.55	26.69(39.8)	12.4	32.3(53.31)	11.5	30.47(53.06)	10.4
Abbreviations: ApoB: Apolipoprotein B; ApoA1: Apolipoprotein A1; LDL-C: Low-Density Lipoprotein cholesterol; hs-CRP: high sensitivity C-Reactive Protein; ACS: Acute Coronary Syndrome										

Table 3: ApoB, ApoB/ApoA1 ratio, LDL-C level and hs-CRP according to day of measurement post ACS.

Discussion

In this study cohort of young patients, we found that most patients had elevated ApoB levels after ACS. However, there was no association between ApoB level or ApoB/ApoA1 ratio and the risk of developing cardiovascular events at 12 months.

This finding contrasts with recent post-hoc analyses of large randomized studies in secondary prevention of patients with stable CAD. ApoB levels >1.1 g/L were associated with substantial residual risk for cardiovascular disease, even with adequate LDL-C levels [10,11]. Our study shows that higher ApoB levels did not predict residual cardiovascular risk. This may be explained by multiple factors. We were also studying patients that were immediately post-ACS, while most prognostic studies analyzed patients with stable CAD or a remote history of prior MI/unstable angina [14-16]. This discordance in findings between the acute setting and stable CAD setting raise suspicion that apolipoproteins may be at least partly a negative phase reactant [17]. However, our analyses of apolipoprotein levels for each day following ACS suggest otherwise, as these were generally stable in the first 4 days following ACS. Moreover, ApoB/ApoA1 ratios, measured within 24 hours after ACS in the INTERHEART study were an important etiologic risk factor for ACS. Our study was not conducted in a population where statins were used in all patients and the adherence to those medications might have been variable in our study, leading to variable effects in our population at 12 months.

LDL-C was studied extensively in a variety of clinical contexts and its role as a therapeutic target is established [14,15]. However, residual risk persists in clinical trials despite aggressive lipid-lowering therapy. ApoB, as a single measure, does not provide additional risk prediction for future cardiovascular events over LDL-C in our study. Surprisingly, there was a non-significant trend with higher ApoB levels being associated with lower future cardiovascular risk.

Explanations for these findings are unclear. First, our population with the lowest ApoB levels was already more likely to be on a statin and therefore to have lower total cholesterol and LDL-C levels. Consequently, they may have been less likely to benefit from more aggressive lipid-lowering therapy. Second, our negative findings may reflect that our study sample had generally low GRACE scores across all ApoB strata and had few residual cardiovascular events 12 months post ACS suggesting that apolipoproteins may not yield sufficient incremental value for risk stratification in lower risk ACS populations.

In women, studies with hormonal therapy (HT) in post-menopausal women demonstrated the potential benefits of estrogen in decreasing ApoB and its risk for atherogenicity [7,16,17]. Further, ApoB were associated with increases in Coronary Artery Calcium (CAC) scores in women [18] and CAC scores in women have been associated with increases in cardiovascular events [19]. Our study was inconclusive in finding an enhanced role for ApoB in predicting future cardiovascular events in women. However, we focused mainly on women who were menopausal or peri-menopausal. Not surprisingly, with recent evidence that HT increases the risk of a thromboembolic event, HT rates were low in our study (0.5-1.0%) [20].

This study has several strengths. We focused on a cohort of young patients who were diagnosed with an ACS at enrolment. The GENESIS- PRAXY database allowed us to study a greater number of women than what is normally seen in contemporary studies with additional clinical detail such as use of HT. We are one of the first studies evaluating a sex-difference in ApoB levels and its power as a predictive tool in a post-ACS setting. Our study differed from other studies with ApoB for primary and secondary prevention in that the ApoB levels were measured soon after the inciting coronary event (at enrolment). Patients were also required to have an ACS (STEMI, NSTEMI or UA) and were not required to be on statin prior to enrolment.

This study also has several limitations. There may be residual confounding and we did not measure sequential ApoB levels after index ACS event. Although over 1000 patients were enrolled, our sample size was likely too small to detect smaller associations between ApoB level or ApoB/ApoA1 ratio and cardiovascular risk.

Conclusion

Our findings indicate that ApoB levels drawn after an ACS event do not predict residual cardiovascular risk in secondary prevention in a low risk young ACS population. Sex-differences in predicting risk were not identified except for lower cardiovascular events in menopausal women with higher ApoB levels post-ACS. Future studies

should be directed at the role of ApoB in secondary cardiovascular risk stratification in higher risk ACS cohorts.

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Competing Interests

There are no potential competing interests involving the work under consideration for publication for any of the co-authors.

Authors' Contributions

OD analyzed and interpreted the data from the database and drafted the manuscript; KR participated in the design of the study; SSD, ME and LP created the GENESIS-PRAXY database and participated in the acquisition of data; NK performed the statistical analysis, contributed to the design of the study and helped interpreting the data. All authors read and approved the final manuscript.

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