Apolipoprotein Levels in Patients with Acute Coronary Syndrome (LIPAS): A Pilot Study

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Abstract

Introduction: Lowering levels of low-density lipoprotein cholesterol (LDL-C) are proven to reduce cardiovascular risk. However, some individuals experience acute coronary events despite normal LDL-C levels. Recent studies have focused on modifiable lipoprotein targets, such as apolipoprotein B (apo-B) and apolipoprotein A-1 (apo A-1) and lipoprotein (a), as targets for therapy. Apo-B is the primary apolipoprotein of LDL-C representing total number of atherogenic particles. Apolipoprotein A-1 is the major component of HDL complex. This study will determine the prevalence of elevated apo-B and low apo A-1 among adult Filipinos with acute coronary syndrome (ACS).

Methods: This is a cross-sectional study involving 95 patients with ACS admitted in a tertiary hospital from November 2015 to May 2016. Levels of apo-B, apoA-1, lipoprotein (a), total cholesterol, triglyceride, LDL-C, and high-density lipoprotein cholesterol (HDL-C) were measured within 24 hours upon admission.

Results: Forty-eight (48%) percent of patients was diagnosed with Non ST-Elevation-ACS, 39% with ST-Elevation myocardial infarction (STEMI) and 13% with unstable angina.Thirty-two (32%) percent were on low- to high-intensity statin treatment. The mean LDL-C, non-HDL-C, and HDL-C levels were 109 mg/dL, 135 mg/dL, and 36.89 mg/dL, respectively. The prevalence of elevated apo-B (mean=103.79 mg/dL; target:<80 mg/dL) was 82%, while that of low apo A-1 (mean=119 mg/dL; target: >120 mg/dL for males, >140 mg/dL for females) was 63%. Lipoprotein (a) levels are high (mean = 48.51 nmol/L; normal:<35 nmol/L) in 42% of patients. Among those on statin therapy, the mean LDL-C was 85 mg/dl, but the mean apo B and lipoprotein (a) levels were elevated at 87.57 mg/dL and 41 nmol/L, respectively.

Conclusion: Elevated levels of apo B and lipoprotein (a) and low level of apo A-1 are highly prevalent in patients with ACS. Apo-B and lipoprotein (a) levels are likewise elevated among patients with normal LDL levels.

Keywords: lipas, acute coronary syndrome, apolipoprotein

Introduction

Acute coronary syndrome (ACS) remains a health burden among adult Filipinos. According to the latest local health statistics, diseases of the heart, including ACS, are still the leading cause of mortality.[1]

Among the risk factors for cardiovascular diseases, high lipoprotein cholesterol levels, especially low-density lipoprotein cholesterol (LDL-C), are well studied and lowering these particles are proven to reduce cardiovascular risk.[2] The latter has been incorporated in the guidelines as treatment target for the management of ACS.[3] Individuals who have cardiovascular disease and are on lipid-lowering treatment, however, still experience residual cardiovascular risk.[2, 4] Thus, new studies have been made to seek other modifiable lipid/lipoprotein targets.

Apolipoprotein B (apo-B) elevations in the serum are currently being considered as one of the targets in the treatment of cardiovascular diseases.[2] It may be a better marker of atherogenic risk than LDL-C because it measures the total number of all atherogenic particles including LDL-C, very low-density lipoprotein, intermediate-density lipoprotein, remnant lipoproteins and lipoprotein(a).[2]

Several studies have proven that high levels of apo B increase the risk of cardiovascular diseases. Epidemiological studies, such as the INTERHEART[5], ISIS[6] and AMORIS[7] studies, showed a positive relationship between apolipoproteins and cardiovascular risk. This evidence was also supported by several clinical trials which include AFCAPS/TexCAPS[8], CARDS[9] and IDEAL[10]. All of these studies advocate the determination of apo-B levels as a tool to inform both population- and patient-based assessments and decision making in cardiovascular prevention.[2]

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Apolipoprotein A-1 (apo A-1) has been found to be more strongly associated with risk reduction for myocardial infarction (MI) compared to high-density lipoprotein (HDL), and has a graded, inverse effect on coronary risk.[2] Apo A-1 remains a strong inverse predictor of subsequent cardiovascular (CV) events, possibly because its concentration is not affected by statins.[2]

Four Philippine studies on apolipoproteins have been done: two dealt with the genetics of apolipoprotein E (apo E) and its relation to Alzheimer's disease[11-12]; while the other two were case reports on familial apo A-1 deficiency and hyperhomocysteinemia, both of which measured apoplipoprotein levels.[13] A local epidemiologic study on apolipoproteins and cardiovascular risk, however, is not available.

The aim of this study was to determine the lipoprotein levels, including apoA-1 and apo-B, and their prevalence, among adult in-patients who were diagnosed with acute coronary syndrome. In general, the researchers aimed to determine the prevalence of elevated apo-B and low apoA-1 among adult in-patients with acute coronary syndrome. More specifically, to determine the clinical and demographic characteristics of in-patients diagnosed with acute coronary syndrome; and to determine the baseline lipid profile and apolipoprotein levels in ACS patients.

Methods

The study followed a cross-sectional design. The population included all adult (>18 years old) patients admitted at the pay and charity wards diagnosed with ACS, either unstable angina (UA), non ST-Elevation myocardial infarction (NSTEMI), or ST-Elevation myocardial infarction (STEMI). On the other hand, it excluded patients with: (1) cardiogenic shock; (2) significant chronic medical illness such as liver, untreated hyperthyroidism or hypothyroidism, renal disease or malignant disease, or who were pregnant; and (3) failure to provide informed consent.

Demographic and medical information was obtained through a predetermined data collection form. Baseline clinical profiles included age, sex, weight, height, body mass index (BMI), smoking history, systolic and diastolic blood pressure, diabetes, previous history of coronary artery disease (CAD), and family history of early cardiovascular disease. Smoking history was classified as current smoker and never smoked. A current smoker was defined as a person who smoked cigarettes regularly at least one cigarette once a day and never smoked was defined as a person who never smoked a cigarette in his life. Patients were diagnosed as hypertensive if told by a physician that they have hypertension, or taking anti-hypertensive medications, or if either SBP>140mmHg or diastolic BP>90 was documented on two separate occasions. Diabetes was diagnosed based on WHO criteria FBS>126 and/or if they have RBS>200 and have symptoms, and are treated on oral hypoglycemic and/ or insulin. Family history of early cardiovascular disease was determined by the presence of stroke, MI, or peripheral artery disease, in at least one of the parents, siblings or children before the age of 55 in males and 65 in females. Body mass index was calculated as weight (kg)/height^2 (m^2).

Computing sample size for this study was not possible because there was no existing prevalence data for apo-B or apoA-1 in literature. This was a pilot study and we utilized complete enumeration sampling.

Subject recruitment for blood extraction was on admission or at the emergency room (ER) upon recognition of the attending doctor that satisfied the criteria of an acute coronary syndrome. Written informed consent from each patient was obtained. Participants were allowed to withdraw anytime during the data collection.

To standardize, peripheral venous blood was drawn from all the subjects within 24 hours, after a fasting period of 10-12 hours, by the investigator or co-investigator. This 24-hour limit was crucial as this is the optimal period for assessing lipid profile in patients with myocardial infarction.[14-16] The blood samples were then submitted to the Medical Research Laboratory of the Philippine General Hospital, an ISO 9001:2008 certified laboratory for standard quality. The blood samples were centrifuged to separate the plasma, and stored in suitable collection containers. The samples were placed in multiple aliquots and stored at -80°C until analysis. Blood levels for serum cholesterol, serum triglycerides, serum LDL-C, serum high-density lipoprotein cholesterol (HDL-C), apo A-1, apo-B and lipoprotein (a) were determined enzymatically using the Cobas Integra 400 automatic analyzer by Roche Diagnostics. Non–HDL-C was calculated by subtracting HDL-C from total cholesterol.

Acute coronary syndrome (ACS) is defined as chest pain (angina) present or its equivalent (like burning sensation, pressure or tightness, shortness of breath or easy fatigability) that lasts for several minutes or longer sometimes associated with diaphoresis, accompanied by electrocardiogram (ECG) changes from the baseline, composed of three disease entities:

STEMI – the above symptoms plus elevated levels of troponin (>3x normal) and ST segment elevation on two contiguous leads in ECG

NSTEMI – above symptoms without ST elevation, either ST depression, T wave inversion or non-specific ST-T wave changes and an elevated levels of troponin

UA – above symptoms without ST elevation, either ST depression, T wave inversion or non-specific ST-T wave changes and without elevated troponin levels

Data analysis utilized frequency tables and descriptive analyses including mean, standard deviation (SD), median, lower and upper quartiles, range, and proportion, were calculated for the examined variables.

The protocol was reviewed and approved by the University of the Philippines Manila Research Ethics Board (UPMREB). All patient information was anonymized and kept confidential. The source of funding came from PLAS-Pfizer Research Grant and there was no conflict of interest with regards to the investigator and patient management.

Results

Table I shows the baseline characteristics of patients diagnosed with ACS enrolled in this study with lipid profiles taken within 24 hours of admission. The mean age is 59 years. Majority are males (64%). The mean BMI is 23.41 kg/m^2, classified as overweight based on adult Asian population. Majority of the cases are non-ST-segment elevation acute coronary syndrome (NSTE-ACS, 48%), followed by STEMI (39%) and UA (13%). The most common risk factor in the population enrolled is smoking (68%), followed by hypertension (65%), alcoholic drinker (32%), diabetes mellitus (26%), dyslipidemia (16%), and previous MI (18%). Majority of the population are taking angiotension receptor blockers (ARB's) (34%).

Table II shows the mean apolipoprotein and lipid profiles of the study cohort. The mean total cholesterol and HDL-C levels of the sample population, regardless of ACS classification, are low at 172.55±47.26 mg/dL and 36.89±9.45 mg/dL, respectively. On the other hand, the total LDL-C and non-HDL-C are elevated in all groups of ACS at 109.37 ±39.13 mg/dL and 134.69±45.94 mg/dL, respectively.

The mean apo-B is elevated (mean=103.79 mg/dL; target: <80 mg/dL) while the mean apo A-1 is low (mean =119 mg/dL; target: >120 mg/dL for males, >140 mg/dL for females) in all ACS groups. The mean lipoprotein (a) is elevated (mean=48.51 nmol/L; normal: <35 nmol/L).

Thirty one (31%) percent of the population (N=30) is on statin medication upon admission, and most of them are on low-to-moderate intensity statin therapy. Table III shows the lipid profile of the population on statin intake. The mean LDL-C level is 85 mg/dl and mean non-HDL-Clevel is 109 mg/dl. The mean HDL-C is low (36 mg/dl). The mean total triglyceride is 127 mg/dl and mean total cholesterol is147 mg/dl. The mean apo-B and lipoprotein (a) levels are elevated at 87.57 mg/dL and 41 nmol/L, respectively.

Table IV shows the prevalence of abnormal apolipoprotein and cholesterol levels. The most prevalent lipid disorder is an elevated apo-B level at 82%, followed by low HDL-C at 77%, and then a low apo A-1 at 63%.

Table I. Population baseline characteristics

Characteristics (N=95)	Mean ± SD / No. (%)
Age, yrs	58.87 ± 10.02
BMI, kg/m^2	23.41 ± 3.14
Waist circumference	
Female	31.88 ± 3.92
Male	33.44 ± 2.74
Sex	
Female	34 (36%)
Male	61 (64%)
Diagnosis	
NSTE-ACS	46 (48%)
STEMI	37 (39%)
UA	12 (13%)
Risk Factors	
Hypertension	62 (65%)
Diabetes mellitus	25 (26%)
Dyslipidemia	15 (16%)
Smoking	
current	31 (33%)
former	33 (35%)
Alcohol intake	31 (33%)
Current	30 (32%)
Previous	58 (61%)
Previous MI	17 (18%)
Family history of premature CAD	25 (26%
Medications	
Beta blocker	24 (25%)
Angiotension converting enzyme (ACE) inhibitor	11 (11.5%)
Calcium channel blockers (CCB)	8 (8%)
Angiotension receptor blockers (ARBS)	32 (34%)
Acetylsalicylic acid (ASA)	18 (19%)
Statins	
High intensity	9 (9%)
Moderate intensity	17 (18%)
Low intensity	4 (4%)
None	65 (68%)
Metformin	15 (16%)
Insulin	3 (3%)
Diuretic	1 (1%)

Table II. Apolipoprotein and lipid profile levels among patients with acute coronary syndrome

Variables	Mean ± SD
Basic lipid profile	
Total cholesterol, mg/dL	172.55 ± 47.26
Total triglyceride, mg/dL	129.75 ± 83.30
HDL, mg/dL	36.89 ± 9.45
LDL, mg/dL	109.37 ± 39.13
Non-HDL, mg/dL	134.69 ± 45.94
Apolipoprotein	
Apo lipoprotein A-1, mg/dL	119.78 ± 20.81
Apolipoprotein B, mg/dL	103.79 ± 28.75
Lp (a), nmol/L	48.51 ± 51.02

Table III. Lipid profile of patients with statin intake (n=30)

Profile	SD
Total cholesterol (mg/dL)	146.50 ± 45.48
Total triglyceride (mg/dL)	127.39 ± 87.06
HDL-C (mg/dL)	36.77 ± 10.11
LDL-C (mg/dL)	85.28 ± 35.40
Non-HDL-C(mg/dL)	109.73 ± 45.57
Apo A-1 (mg/dL)	119.12 ± 18.82
Apo B(mg/dL)	87.57 ± 29.86
Lipoprotein (a) (nmol/L)	41.01 ± 37.37

Table IV. Overall prevalence of apolipoprotein levels in patients with acute coronary syndrome

	Apolipoprotein	Prevalence (%)
Elevated Apo B	82%	73%-89%
Low Apo A1	63%	53%-72%
Elevated Lipoprotein (a)	42%	32%-52%
Elevated LDL	60%	50%-69%
Low HDL	77%	67%-84%
Elevated Non HDL	42%	32%-52%

An elevated LDL-C is found in only 60%. Lipoprotein (a) is elevated in 42% of the cohort.

Discussion

This is the first study of its kind among Filipino patients in general, and in an ACS cohort, in particular. We have shown that patients not only have high LDL-C and low HDL-C at baseline, but also have elevated apo-B and low apo A-1 levels. Furthermore, we have documented that the prevalence of these apolipoprotein abnormalities is high, at 82% and 63%, respectively.

The typical profile of a Filipino ACS patient appears to be consistent across cohort studies. The patient is a middle-aged male, smoker, has hypertension, and is neither too overweight nor obese. This profile reflects that of another ACS cohort of Ramos et al.[17] A quarter of our cohort is diabetic, and less than a fifth has dyslipidemia or history of previous myocardial infarction. Only a third of them, however, are on medications for a comorbid condition.

The baseline lipid profile of our cohort shows elevated LDL-C and Non-HDL-C levels, and a low HDL-C level, all of which are consistent with the latest NNHES 2013 data.[18] The NNHES 2013 did not measure apolipoprotein values, however.

Several studies estimated that apolipoproteins are better predictors of cardiovascular heart disease than LDL-C, particularly with apo-B and apo A-1. The large prospective observational AMORIS[7] study has demonstrated the association of coronary risk and mortality with elevated apo-B, and that this association is stronger than that for LDL-C, with risk ratios of 1.51 and 1.42, respectively. The INTERHEART[5] study also showed a similar stronger association for apo-B, with a relative risk of 1.32 compared to 1.28 for LDL-C. Further, apo-B was not only the strongest risk factor in predicting MI but also the most prevalent risk factor independent of age, sex and ethnicity.[5] It was observed that apo-B and lipoprotein (a) have good diagnostic utility in assessing cardiovascular risk and treatment of patients in the presence of normal LDL-C and/or low HDL-C levels.[2] LDL-C may underestimate the cardiovascular risk in these patients.[2] The ISIS[6] study also showed a similar comparative risk relationship for apo-B with clinical events, specifically nonfatal MI, with a relative risk of 2.66 versus 2.21 for LDL-C and 2.10 for non-HDL-C. A large 2011 meta-analysis[19], comprising 233,455 subjects, that looked into the predictive power of these particles for cardiovascular risk, corroborated these findings. With 22,950 total events, Sniderman et al. (2011)[19] showed that apo-B was the most potent marker for cardiovascular risk (relative risk ratio (RRR) 1.43), followed by non-HDL-C (RRR 1.34), then by LDL-C (RRR 1.25), and the estimates appeared to be robust. They concluded that apo-B is superior and more accurate than LDL-C or non-HDL-C as a clinical predictor.[19]

As mentioned, apo A-1 has a graded, inverse effect on coronary risk, and is a strong inverse predictor of subsequent CV events.[2] The high prevalence of low apo A-1 in our select cohort further supports this association.

A post-hoc subgroup analysis was done on those 30 patients who had prior or are on statin therapy. Majority (84%) of these patients were on moderate-to-high intensity statin treatment. The mean LDL-C (85 mg/dl) and mean non-HDL-C(109 mg/dl) levels of this subgroup were acceptable for high-risk patients (target: <100 mg/dL for LDL-C). Likewise, the mean total triglyceride (127 mg/dl) and total cholesterol levels (147 mg/dl) were apparently normal. The mean HDL-C was still low (36 mg/dl), again concordant with NNHES

2013.[18] Interestingly, we found that despite acceptable or apparently normal levels of LDL cholesterol with statin therapy, the apolipoprotein levels remained abnormal. As discussed, apo-B elevations are known to provide a sound measure of residual cardiovascular risk on treatment.[2] This notable finding may indicate residual risk for these patients, consistent with previous cohorts.[5-7]

An elevated apo-B is the most prevalent lipid particle abnormality in our cohort, followed by a low HDL-C, low apo A-1, elevated LDL-C, and elevated non-HDL-C levels (Table IV). This suggests to us that apo-B may be able to catch more high risk patients – 22% more than an elevated LDL-C, and 40% more than if elevated non-HDL-C was used instead. Sniderman et al. (2011)[19] went further than just estimate the value of apo-B for risk assessment. They illustrated that targeting non-HDL-C rather than LDL-C, as a treatment strategy, would prevent 300,000 incident coronary events over 10 years; while targeting apo-B rather than non-HDL-C potentially reduced the incident cases of coronary event by an additional 500,000 patients.[19] This incremental value that apo-B provides may perhaps form the basis of its inclusion in the recent 2016 ESC/EAS Guidelines, with Class IIa-B recommendation, as a treatment target, especially when the LDL-C level is apparently normal.[20] Statins are the most effective single class of medication that has been demonstrated to lower apo-B.[2]

In this light, the value of routinely measuring apo-B or apo A-1 in all patients becomes something to be considered. Some groups have already advocated for its routine measurement in the general population, especially with apo-B.[19] In this study, we have only shown that abnormal apo-B and apo A-1 levels are highly prevalent in our Filipino ACS patients. We have not directly demonstrated whether routine measurement would translate to reduction of coronary events. We believe that routine measurement, at this time, may not be necessary. We may, however, measure apo-B levels in ACS patients, or in a select intermediate-risk group who have apparently normal LDL-C, to identify more high risk individuals as this will have treatment implications.

Limitations and recommendations

Our study is a cross-sectional study in our center, which employed a non-random design of complete enumeration, making it prone to selection bias. These characteristics would limit the generalizability of the findings. Our population is also small, and we were not able to compute for a minimum sample size for adequate power, for the reason already described. This study, however, is a pilot study, and we mitigated most of these limitations by ensuring that we were able to assess and properly adjudicate all the ACS patients for inclusion or exclusion during the time period of the study. There is no reason for us to believe that the results for our particular cohort are overestimations.

This study has provided baseline apolipoprotein measurements and prevalence of ACS patients in our setting. This study can be improved further by increasing the number of subjects. It would also be interesting to come up with a study that measures baseline apolipoprotein levels among healthy Filipinos that can serve as reference normal values. In addition, exploring the incremental value of apolipoproteins for the Filipino, by relating them with outcome data (e.g., hospital or short-term mortality) through a prospective observational study or randomized trial, is in order.

Conclusion

Elevated levels of apo-B and lipoprotein (a) and low levels of apo A-1 are highly prevalent in patients with ACS. Apo-B and lipoprotein (a) levels are likewise elevated among patients with acceptable or near-normal LDL levels.

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