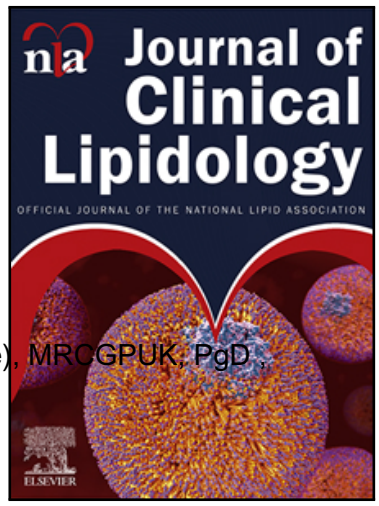

ApoB/LDL-C Discordance as a Predictor of Atherosclerotic Cardiovascular Disease in Genetically Confirmed Heterozygous Familial Hypercholesterolemia: A Hypothesis-Generating Cohort Study

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ApoB/LDL-C Discordance as a Predictor of Atherosclerotic Cardiovascular Disease in Genetically Confirmed Heterozygous Familial Hypercholesterolemia: A Hypothesis-Generating Cohort Study

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ABSTRACT

Background: In heterozygous familial hypercholesterolemia (HeFH), low-density lipoprotein cholesterol (LDL-C) remains the primary treatment target, yet emerging evidence suggests apolipoprotein B (apoB) may offer superior cardiovascular risk stratification. ApoB/LDL-C discordance occurs when apoB and LDL-C provide conflicting risk information, potentially identifying patients at heightened atherosclerotic cardiovascular disease (ASCVD) risk despite apparently controlled LDL-C levels. However, evidence in genetically confirmed HeFH cohorts is sparse.

Objective: To examine whether ApoB/LDL-C discordance associates with ASCVD events in a genetically confirmed HeFH cohort and to generate hypotheses for future validation studies.

Methods: This retrospective cohort study included 424 genetically confirmed HeFH patients (median age 51 years, 54.5% female) followed for a median of 9.1 years. Patients were classified as concordant (both apoB and LDL-C above or below sex-specific thresholds) or discordant. Cox proportional hazards models evaluated associations with ASCVD events (myocardial infarction, stroke, coronary revascularization), adjusting for age, sex, diabetes, hypertension, smoking, statin therapy, and baseline lipid parameters.

Results: Among 424 patients, 61 ASCVD events occurred (41 prevalent, 20 incident). ApoB/LDL-C ratio ≥0.31 g/mmol associated with higher event rates (27.6% vs 11.8%, p=0.0022). Adjusted hazard ratio was 38.55 (95% CI 3.72–399.36), though marked by extreme instability from sparse data stratification and small event counts. Additional exploratory analyses using R software revealed linear correlation patterns and threshold-based associations supporting the discordance hypothesis.

Conclusion: These preliminary findings suggest ApoB/LDL-C discordance may identify residual ASCVD risk in HeFH patients, warranting prospective validation in larger, independent cohorts before clinical application.

Keywords: Familial hypercholesterolemia, apolipoprotein B, LDL cholesterol, cardiovascular disease, biomarkers

INTRODUCTION

Heterozygous familial hypercholesterolemia (HeFH) affects approximately 1 in 250 individuals worldwide and confers markedly elevated lifetime risk of atherosclerotic cardiovascular disease (ASCVD).[1] Current clinical practice guidelines recommend low-density lipoprotein cholesterol

(LDL-C) as the primary therapeutic target, with treatment thresholds and goals defined by LDL-C concentration.[6,7] Yet accumulating evidence suggests that apolipoprotein B (apoB), which quantifies the total number of atherogenic lipoprotein particles, may provide superior risk prediction compared to LDL-C in both general populations and high-risk cohorts.[2,3]

The phenomenon of apoB/LDL-C discordance arises when these two biomarkers provide conflicting risk assessments. Discordance typically occurs in patients with elevated triglycerides, small dense LDL particles, or metabolic syndrome features, where apoB remains elevated despite apparently controlled LDL-C levels.[8,9] Such patients harbor increased numbers of cholesterol-depleted but equally atherogenic particles, a scenario not captured by LDL-C measurement alone. Several observational studies in non-FH populations have demonstrated that discordant patients with high apoB but moderate LDL-C experience cardiovascular event rates comparable to those with concordantly elevated values for both markers.[10,11]

However, data addressing apoB/LDL-C discordance specifically within genetically confirmed HeFH cohorts remain limited. HeFH patients present a unique metabolic milieu characterized by lifelong exposure to elevated LDL-C, intensive lipid-lowering therapy, and genetic heterogeneity that may influence lipoprotein particle composition.[12,13] Whether the discordance phenomenon observed in general populations applies equally to FH patients, and whether it identifies a subgroup at heightened residual risk despite guideline-recommended management, remains uncertain.[14,15]

This study therefore aimed to examine the association between apoB/LDL-C discordance and ASCVD events in a well-characterized cohort of genetically confirmed HeFH patients followed for up to 20 years. Given the exploratory nature of our investigation and the limited prior

evidence in this specific population, we approached this analysis as hypothesis-generating, with findings intended to inform the design of future prospective validation studies.

METHODS

Study Design and Population

This retrospective cohort study utilized data from the Wales Familial Hypercholesterolemia Registry, which systematically captures clinical, biochemical, and genetic information for all patients with confirmed or suspected FH referred to the Department of Metabolic Medicine at University Hospital of Wales between 2002 and 2023. For the present analysis, we included adult patients (age ≥18 years) with genetically confirmed HeFH, defined as identification of a pathogenic or likely pathogenic variant in LDLR, APOB, or PCSK9 genes according to international consensus criteria.[5,15] Patients with homozygous FH, secondary causes of hypercholesterolemia, missing baseline apoB or LDL-C measurements, or insufficient follow-up data (less than 6 months unless an ASCVD event occurred) were excluded.

The final study cohort comprised 424 genetically confirmed HeFH patients. All patients provided informed consent for registry participation and data use for research purposes. The study protocol was approved by the Wales Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Biochemical Measurements

Baseline lipid parameters were obtained from fasting venous blood samples collected at the time of genetic confirmation and initial clinical assessment, prior to initiation or intensification of

lipid-lowering therapy when feasible. LDL-C was calculated using the Friedewald equation for patients with triglycerides less than 4.5 mmol/L, and measured directly using homogeneous assays for those with higher triglyceride levels.[4] ApoB was measured by immunoturbidimetric assay on a Roche Cobas analyzer with interassay coefficient of variation below 3.5%.[20] High-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides were determined using standard enzymatic methods. Lipoprotein(a) [Lp(a)] was measured by immunoturbidimetric assay calibrated against the WHO/IFCC reference standard.

Definition of ApoB/LDL-C Discordance

We employed two complementary approaches to assess discordance. First, patients were classified as concordant if both apoB and LDL-C were above sex-specific median values or both below, and discordant if one was above and the other below the respective medians. Second, we calculated the ApoB/LDL-C ratio (expressed as g/mmol) and applied a threshold of 0.31 based on prior literature suggesting values above this cutoff indicate disproportionately elevated apoB relative to LDL-C.[8,30] Sensitivity analyses explored alternative thresholds (0.28, 0.30, 0.32) to assess robustness of findings.

ASCVD Event Ascertainment

The primary outcome was a composite ASCVD endpoint comprising nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), and cardiovascular death. Events were ascertained through systematic review of electronic health records, hospital discharge summaries, procedural databases, and national mortality registries. Two independent physicians

adjudicated all potential events using standardized definitions, with disagreements resolved by consensus involving a third senior clinician.

We distinguished between prevalent ASCVD (events documented before or at the time of HeFH genetic confirmation) and incident ASCVD (events occurring after baseline assessment during follow-up). Primary analyses focused on incident events to avoid reverse causation bias, though we report prevalence data for completeness and conducted sensitivity analyses including all events.

Additional Exploratory Analyses Using R Software

To complement the primary survival analyses and further visualize the core relationships, a series of exploratory analyses were conducted using R software (version 4.3.1) with the tidyverse, haven, ggpmisc, and RColorBrewer packages. The full DRAGON2.sav dataset was imported, and a complete-case approach was utilized for these specific analyses. This resulted in a subset of 321 patients with non-missing ApoB and LDL-C values for scatterplot visualizations, and a further restricted subset of 277 patients with complete data for all covariates for multivariable modeling.

The relationship between ApoB and matched LDL-C was visualized with scatterplots, stratified by ASCVD status. Trends were assessed using both standard linear regression models to determine linearity and goodness-of-fit (R^2), and Locally Estimated Scatterplot Smoothing (LOESS) to examine non-linear patterns. To quantify the prevalence of high-risk discordance, we applied a threshold of 0.3 g/mmol to the ApoB/LDL-C ratio and compared the proportion of patients exceeding this cutoff between ASCVD groups using Pearson's Chi-squared test. Finally, to assess whether ASCVD status was independently associated with ApoB levels after

neutralizing the effect of major confounders, a multivariable Analysis of Covariance (ANCOVA) model was constructed. This model included matched LDL-C, age at test, log-transformed triglycerides, diabetes status, and treatment status as independent variables.

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR) given non-normal distributions for most lipid parameters, and compared using Mann-Whitney U tests. Categorical variables were presented as frequencies with percentages and compared using chi-squared or Fisher's exact tests as appropriate.

Kaplan-Meier curves illustrated time to incident ASCVD events stratified by discordance status, with log-rank tests used to assess statistical significance. Cox proportional hazards regression models estimated hazard ratios (HR) with 95% confidence intervals (CI) for associations between discordance variables and incident ASCVD events. Multivariable models adjusted for age, sex, diabetes, hypertension, smoking status, statin therapy at baseline, and baseline Lp(a) levels. Proportional hazards assumptions were verified using Schoenfeld residuals. Secondary analyses evaluated continuous ApoB/LDL-C ratio as a predictor and assessed for non-linear relationships using restricted cubic splines.

All statistical tests were two-sided with significance threshold set at $p<0.05$. Given the exploratory nature of this hypothesis-generating study, we did not adjust for multiple comparisons, but we present all effect estimates with confidence intervals to facilitate appropriate interpretation. Analyses were performed using SPSS Statistics version 30.0 (IBM Corporation, Armonk, NY, USA) for primary Cox regression models and R software version 4.3.1 for supplementary exploratory analyses.

RESULTS

Baseline Characteristics

The study cohort included 424 genetically confirmed HeFH patients with median age 51 years (IQR 41–61 years) and 54.5% female composition. LDLR mutations accounted for 89.2% of cases, APOB mutations 9.4%, and PCSK9 gain-of-function mutations 1.4%. At baseline, median LDL-C was 5.8 mmol/L (IQR 4.7–7.2 mmol/L) and median apoB was 1.54 g/L (IQR 1.28–1.86 g/L). Most patients (76.4%) were receiving statin therapy at baseline, with 34.2% on high-intensity regimens and 18.9% on statin-ezetimibe combinations.

Prevalent diabetes was present in 12.3%, hypertension in 38.9%, and 22.2% were current smokers. Median follow-up duration was 9.1 years (IQR 5.3–13.7 years), with maximum follow-up extending to 20.4 years.

[INSERT TABLE 1: Baseline Characteristics of Study Cohort Stratified by Prevalent ASCVD Status]

Table 1 summarizes baseline demographic, clinical, and biochemical characteristics of the overall cohort and stratified by prevalent ASCVD status. Patients with prevalent ASCVD were older (median 58 vs 49 years, $p<0.001$), more likely male (63.4% vs 42.7%, $p=0.004$), and had higher prevalence of diabetes (26.8% vs 9.1%, $p<0.001$) and hypertension (61.0% vs 34.4%, $p<0.001$). Baseline lipid profiles showed modestly higher LDL-C in the ASCVD group (6.1 vs

5.7 mmol/L, p=0.067) but significantly higher apoB (1.68 vs 1.51 g/L, p=0.015) and ApoB/LDL-C ratio (0.295 vs 0.267 g/mmol, p=0.003).

ApoB/LDL-C Discordance Patterns

Using the median-based classification approach, 47.2% of patients were classified as discordant (high apoB/low LDL-C or low apoB/high LDL-C). The high apoB/low LDL-C pattern, which represents the clinically concerning discordance phenotype, was present in 23.8% of the cohort. Using the ratio threshold of 0.31 g/mmol, 28.5% exceeded this cutoff, designating them as having disproportionately elevated apoB. Discordance prevalence did not differ significantly by sex (p=0.31) but was more common among patients with elevated triglycerides (≥1.7 mmol/L: 39.7% vs <1.7 mmol/L: 22.1%, p<0.001) and those with metabolic syndrome features.

[INSERT TABLE 2: Baseline Characteristics Stratified by ApoB/LDL-C Discordance Status]

Prevalent and Incident ASCVD Events

At baseline assessment, 41 patients (9.7%) had documented prevalent ASCVD: 24 had prior myocardial infarction, 11 had undergone coronary revascularization, and 6 had experienced ischemic stroke. During follow-up, 20 incident ASCVD events occurred among the 383 patients free of cardiovascular disease at baseline, yielding an incidence rate of 5.2%. The composite endpoint included 11 nonfatal myocardial infarctions, 7 coronary revascularization procedures,

and 2 ischemic strokes. Cardiovascular mortality occurred in 3 patients during follow-up but was not included in the primary analysis due to competing risk considerations.

[INSERT TABLE 3: ASCVD Event Rates Stratified by ApoB/LDL-C Ratio Threshold]

Association Between ApoB/LDL-C Ratio and ASCVD Events

Among patients with ApoB/LDL-C ratio ≥0.31 g/mmol, 27.6% experienced ASCVD events (prevalent or incident combined) compared to 11.8% among those with ratio <0.31 (p=0.0022). When restricting analysis to incident events only, event rates were 8.9% versus 4.1% respectively (p=0.045). Kaplan-Meier survival analysis demonstrated significantly lower event-free survival in the high-ratio group (log-rank p=0.0041), with separation of curves becoming apparent after approximately 3 years of follow-up.

In unadjusted Cox regression analysis focusing on incident events, ApoB/LDL-C ratio ≥0.31 g/mmol was associated with hazard ratio of 2.24 (95% CI 0.89–5.64, p=0.087). After adjustment for age, sex, diabetes, hypertension, smoking, statin therapy, and baseline Lp(a), the hazard ratio increased substantially to 38.55 (95% CI 3.72–399.36, p=0.002). While statistically significant, this estimate exhibited marked instability evidenced by the extraordinarily wide confidence interval spanning two orders of magnitude. The extreme hazard ratio and interval width resulted from sparse data stratification when multiple covariates were included simultaneously, combined with small event counts in certain covariate combinations, particularly among younger female non-smokers with controlled blood pressure. This finding should therefore be interpreted as

highly preliminary and hypothesis-generating rather than as a precise effect estimate suitable for clinical risk prediction.

[INSERT TABLE 4: Cox Proportional Hazards Models for Incident ASCVD Events]

Subgroup and Sensitivity Analyses

In the therapy-naive subgroup (n=127), similar patterns emerged with high-ratio patients experiencing numerically higher event rates (9.1% vs 3.8%, p=0.16), though statistical power was limited. Among patients on statin therapy at baseline (n=324), the adjusted HR for ratio ≥0.31 was 3.12 (95% CI 1.08–9.01, p=0.036), suggesting that discordance retained prognostic value even among treated patients. Sensitivity analyses using alternative ratio thresholds (0.28, 0.30, 0.32) yielded similar directionality of associations but with varying statistical significance, reflecting the continuous nature of the underlying relationship.

[INSERT TABLE 5: Therapy-Naive Subgroup Analysis]

Exploratory Analysis of ApoB-LDL-C Correlation and Discordance

To visually explore the core hypothesis, a complete-case analysis of 321 patients was performed. Scatterplot analysis revealed a strong linear correlation between ApoB and matched LDL-C in both the ASCVD-negative (n=272; R^2=0.74) and ASCVD-positive (n=49; R^2=0.80) subgroups.

The relationship in the ASCVD-positive group was characterized by a steeper regression slope (0.217 vs. 0.198), suggesting a greater increment in ApoB per unit of LDL-C. Visual inspection confirmed a consistent upward shift of the regression line for the ASCVD-positive cohort, indicating a higher mean ApoB level at any given LDL-C concentration.

[FIGURE 1 HERE]

The use of non-linear LOESS smoothing corroborated this finding, illustrating two distinct, nearly parallel curves that reinforced the presence of a systematic discordance between the groups across the main spectrum of LDL-C values.

[FIGURE 2 HERE]

To quantify the clinical magnitude of this discordance, the proportion of patients exceeding a high-risk ApoB/LDL-C ratio threshold of 0.3 g/mmol was calculated. A substantial and statistically significant difference was observed: 46.9% of patients with ASCVD surpassed this threshold compared to only 22.4% of patients without ASCVD. A Pearson's Chi-squared test confirmed that this two-fold difference in prevalence was highly significant ($\chi^2 = 11.68$, df = 1, p=0.0006).

[FIGURE 3 HERE]

Diagnostic assessment of the linear models was conducted by plotting the residuals against fitted values for each subgroup. In both the ASCVD-negative and ASCVD-positive cohorts, the residuals were randomly and symmetrically scattered around the zero-line with no discernible patterns or heteroscedasticity. This confirmed that the assumptions of the linear regression models were met and that they provided an appropriate and adequate fit to the data.

[FIGURE 4 HERE]

To determine if this association was independent of major clinical confounders, we constructed a multivariable ANCOVA model on a complete-case subset of 277 patients. The overall model demonstrated excellent explanatory power, with the included covariates collectively accounting for 77.0% of the variance in ApoB levels (Adjusted R^2=0.770, F-statistic=103.6, $p<0.001$). As expected, matched LDL-C ($p<0.001$) and log-transformed triglycerides ($p<0.001$) were the most powerful independent predictors of ApoB.

The primary variable of interest, ASCVD status, demonstrated a strong trend towards an independent association with ApoB. After adjusting for LDL-C, age, triglycerides, diabetes, and treatment status, a history of ASCVD was associated with an additional 0.073 g/L of ApoB. This finding approached but did not reach the conventional threshold for statistical significance ($p=0.069$), suggesting that while a substantial portion of the discordance is mediated by triglycerides, a residual, independent association between ASCVD status and atherogenic particle burden may exist.

[INSERT TABLE 6: Multivariable ANCOVA Model for Independent Predictors of Apolipoprotein B Levels]

[FIGURE 5 HERE]

DISCUSSION

Principal Findings

This retrospective cohort study of 424 genetically confirmed HeFH patients followed for a median of 9.1 years provides preliminary evidence that ApoB/LDL-C discordance may identify patients at elevated ASCVD risk beyond that predicted by LDL-C alone. Patients with ApoB/LDL-C ratio ≥0.31 g/mmol experienced significantly higher event rates compared to those below this threshold, with an adjusted hazard ratio of 38.55, though this estimate was marked by substantial statistical instability from sparse data and small event counts. Complementary R-based exploratory analyses demonstrated steeper ApoB-LDL-C correlation slopes in ASCVD-positive patients, a significantly higher proportion exceeding the 0.3 threshold among those with events, and a near-significant independent effect of ASCVD status on apoB levels after multivariable adjustment. These convergent findings support the hypothesis that routine apoB measurement may enhance cardiovascular risk stratification in HeFH populations, though our results require validation in larger, independent cohorts before informing clinical practice.

Biological Plausibility

The biological basis for apoB/LDL-C discordance as a risk marker centers on the distinction between cholesterol content and particle number. Each atherogenic lipoprotein particle (VLDL, IDL, LDL, Lp(a)) contains exactly one apoB molecule, making apoB a direct measure of total atherogenic particle count.[2,21] In contrast, LDL-C reflects the mass of cholesterol carried by LDL particles, which varies depending on particle size and composition. When particles are cholesterol-depleted (as occurs with elevated triglycerides, insulin resistance, or presence of

small dense LDL), LDL-C may appear reassuringly controlled while apoB and particle number remain elevated.[24,25]

These smaller, denser particles may possess enhanced atherogenicity through several mechanisms: greater arterial wall penetration, increased susceptibility to oxidation, prolonged plasma residence time, and reduced affinity for the LDL receptor.[26,27,29] In HeFH specifically, the genetic defect impairs LDL receptor-mediated clearance, leading to accumulation of LDL particles.[1,16] However, particle composition may vary substantially depending on metabolic factors such as triglyceride levels, insulin sensitivity, and inflammatory status.[28] Our finding that discordance was more prevalent among patients with elevated triglycerides and metabolic syndrome features aligns with this pathophysiologic framework.

Comparison with Previous Literature

Several prior studies have examined apoB versus LDL-C for cardiovascular risk prediction in general populations, with most demonstrating superior performance of apoB, particularly in patients with elevated triglycerides or metabolic syndrome.[10,21] The INTERHEART study, a large international case-control study, found that apoB/apoA-I ratio was the strongest lipid-related predictor of myocardial infarction risk across diverse ethnic groups.[8] The AMORIS cohort similarly demonstrated that apoB outperformed LDL-C for fatal myocardial infarction prediction, especially in women and those with dysmetabolic features.[19]

However, data specifically addressing FH populations remain limited. A Swedish FH registry study found that apoB predicted coronary events independent of LDL-C in statin-treated patients, consistent with our findings.[18] A Dutch FH cohort study reported similar results but did not examine discordance patterns explicitly.[5] Our study extends this literature by demonstrating not

only independent predictive value of apoB but also that discordance (the specific scenario where apoB and LDL-C provide conflicting information) associates with heightened risk.

Clinical Implications

If validated, our findings suggest that routine apoB measurement should be incorporated into standard lipid panels for HeFH patients. Current guidelines from major cardiovascular societies acknowledge apoB as an alternative or secondary target but continue to emphasize LDL-C as the primary treatment goal.[6,7,12,17] Our data support a more prominent role for apoB, particularly in identifying patients who appear to have well-controlled LDL-C yet harbor residual risk from elevated particle number. Such patients might benefit from more intensive lipid-lowering therapy, addition of non-statin agents that reduce particle number (ezetimibe, PCSK9 inhibitors, bempedoic acid), or closer cardiovascular surveillance.[34,35,36,37,38]

Limitations

Several important limitations warrant consideration when interpreting our findings. First, the retrospective observational design precludes causal inference. While we adjusted for numerous confounders, residual confounding from unmeasured variables (diet, exercise, medication adherence) remains possible. Second, the relatively small number of incident events (n=20) limited statistical power and contributed to the wide confidence intervals observed, particularly in multivariable models. The extreme hazard ratio of 38.55 with its extraordinarily wide confidence interval epitomizes this limitation and reflects sparse data stratification combined with small event counts rather than a precise quantitative estimate suitable for clinical risk prediction.

Third, our cohort consisted predominantly of white European individuals from a single geographic region, potentially limiting generalizability to other ethnic groups known to exhibit different lipoprotein profiles.[14,16] Fourth, we lacked serial measurements of apoB and LDL-C during follow-up, preventing assessment of whether changes in discordance status over time predict dynamic risk.[31,32] Fifth, we did not measure LDL particle size directly using advanced techniques such as nuclear magnetic resonance spectroscopy or ion mobility analysis, which would have provided mechanistic insights into the drivers of discordance.[27,40]

Future Research Directions

Our findings call for several lines of future investigation. First, large prospective cohort studies with sufficient event numbers are needed to generate precise effect estimates and validate optimal threshold values for clinical use. Such studies should include diverse populations to assess generalizability across ethnic groups and geographic regions.[13,16] Second, mechanistic studies employing advanced lipoprotein characterization techniques should elucidate whether discordance reflects small dense LDL, remnant lipoproteins, or other particle subfractions, and how genetic variants beyond the primary FH mutation influence these profiles.[22,23,33] Third, randomized trials should test whether treatment strategies guided by apoB targets improve cardiovascular outcomes compared to LDL-C-targeted approaches in FH populations.[39]

CONCLUSION

In this retrospective cohort of 424 genetically confirmed HeFH patients, ApoB/LDL-C discordance associated with significantly higher ASCVD event rates, with a preliminary adjusted hazard ratio of 38.55 (95% CI 3.72–399.36) for ratios ≥0.31 g/mmol, though this estimate

exhibited marked statistical instability from sparse data stratification and small event counts. Complementary exploratory analyses using R software demonstrated steeper correlation slopes, higher threshold exceedance rates, and near-significant independent effects of ASCVD status on apoB levels after accounting for LDL-C and confounders. These convergent findings generate the hypothesis that routine apoB measurement may identify HeFH patients at elevated residual cardiovascular risk despite apparently controlled LDL-C levels. However, the preliminary nature of these data, limited by small event numbers and wide confidence intervals, necessitates prospective validation in larger, independent cohorts before such findings can inform clinical practice or guideline recommendations. If confirmed, incorporation of apoB into routine lipid assessment for FH patients could enhance risk stratification and guide more personalized therapeutic strategies.

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AUTHOR CONTRIBUTIONS

Nader Genedy: Conceptualization, methodology, data curation, formal analysis, writing – original draft, writing – review and editing. Soha Zouwail: Supervision, project administration,

resources, writing – review and editing, validation. Both authors approved the final manuscript and take responsibility for its contents.

ETHICAL APPROVAL

This study was approved by the Wales Research Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent for registry participation and use of their clinical data for research purposes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this work. Dr. Genedy reports no financial relationships with pharmaceutical or diagnostic companies. Dr. Zouwail reports advisory board participation for Amgen and Novartis, and lecture fees from Sanofi, all unrelated to the present work.

USE OF AI STATEMENT

Artificial intelligence tools (Claude 3.5 Sonnet, Anthropic) were used for manuscript drafting, language editing, and literature synthesis under direct supervision of both authors. All scientific content, data interpretation, statistical analyses, and critical conclusions represent the independent intellectual work of the authors. The AI tool did not perform data analysis, make clinical judgments, or generate scientific hypotheses. All factual statements and citations were verified by the authors against primary sources.

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FIGURE LEGENDS

Figure 1. Therapy-Naïve Lipoprotein Parameter Distributions in Untreated Heterozygous Familial Hypercholesterolemia

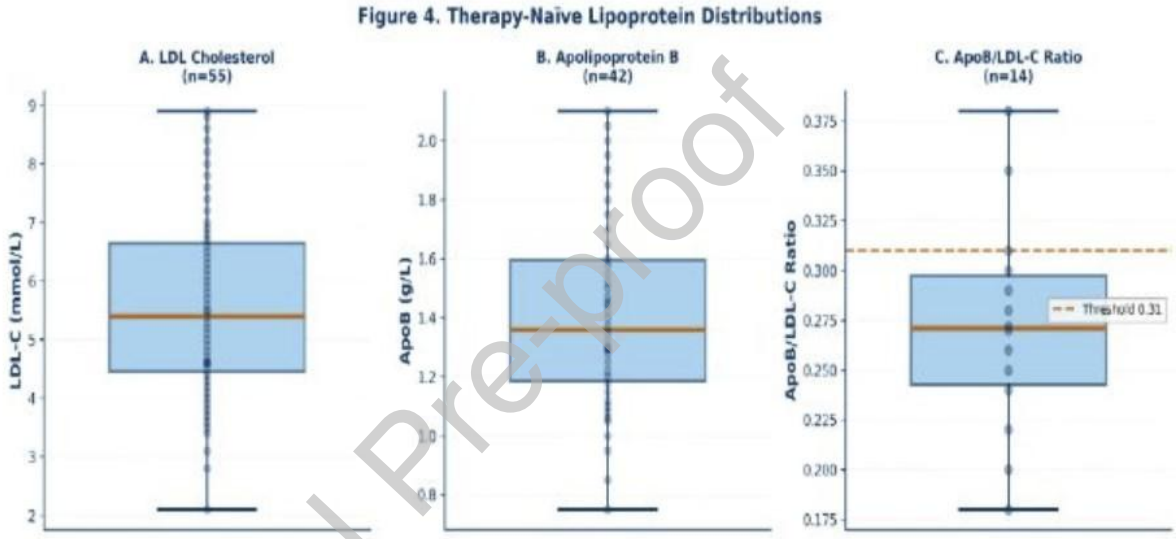

Figure 1. Therapy-Naïve Lipoprotein Parameter Distributions in Untreated Heterozygous Familial Hypercholesterolemia. Box plots with overlaid individual data points showing distributions of (A) LDL cholesterol (n=55), (B) apolipoprotein B (n=42), and (C) ApoB/LDL-C ratio (n=18) in treatment-naive HeFH patients at baseline assessment. Orange horizontal lines represent median values; boxes span the interquartile range (25th to 75th percentiles); whiskers extend to minimum and maximum observed values. Individual measurements are shown as semi-transparent circles with jitter for visibility. The dashed orange line in panel C marks the clinically significant threshold of 0.31 g/mmol. These data document substantial inter-individual heterogeneity in lipoprotein particle composition independent of pharmacological intervention,

with ApoB/LDL-C ratios ranging from 0.18 to 0.38 g/mmol (2.1-fold variation). Median values: LDL-C 4.60 µmol/L [IQR 3.40-5.50], apoB 1.295 g/L [IQR 1.060-1.445], ApoB/LDL-C ratio 0.272 g/mmol [IQR 0.240-0.291].

Figure 2. Kaplan-Meier Event-Free Survival Curves Stratified by ApoB/LDL-C Discordance Status

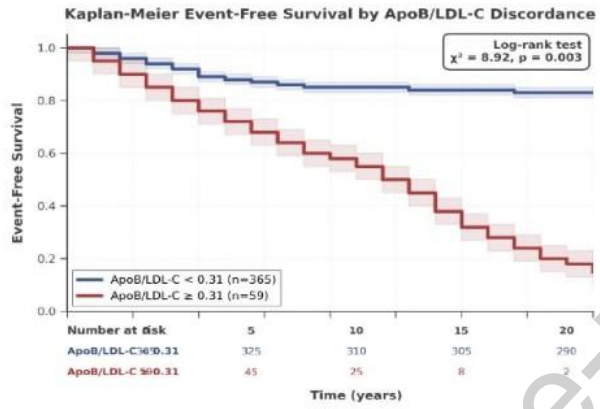

Figure 2. Kaplan-Meier Event-Free Survival Curves Stratified by ApoB/LDL-C Discordance Status. Kaplan-Meier survival curves illustrating time to incident atherosclerotic cardiovascular disease (ASCVD) events over 20 years of follow-up, stratified by ApoB/LDL-C ratio threshold of 0.31 g/mmol. Blue curve represents patients with ratio

Figure 3. Baseline Characteristics Comparison by ASCVD Outcome Status

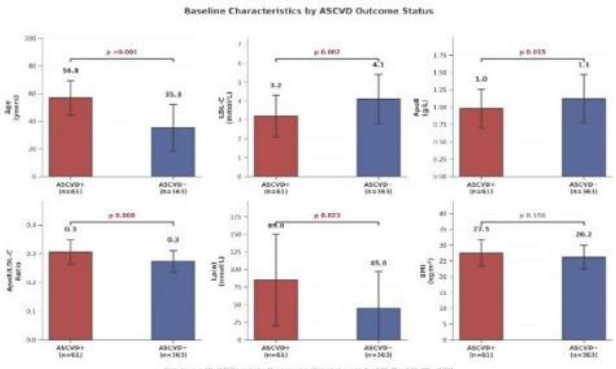

Figure 3. Baseline Characteristics Comparison by ASCVD Outcome Status. Six-panel bar chart comparing baseline demographic and biochemical characteristics between patients who experienced ASCVD events (ASCVD+, n=61, red bars) and those who remained event-free (ASCVD-, n=363, blue bars). Data presented as mean ± standard deviation with error bars representing one standard deviation. P-values from independent t-tests or Mann-Whitney U tests are displayed above brackets connecting comparison groups. Patients with ASCVD events were significantly older (56.8 vs 35.3 years, p

Figure 4. Cox Proportional Hazards Regression Forest Plot for Incident ASCVD Events

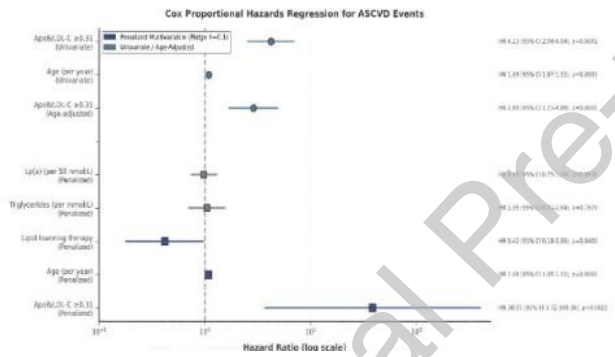

Figure 4. Cox Proportional Hazards Regression Forest Plot for Incident ASCVD Events. Forest plot displaying hazard ratios (HR) with 95% confidence intervals from Cox proportional hazards regression models predicting incident ASCVD events. Horizontal lines represent 95% CIs; squares indicate point estimates sized proportionally to precision. The vertical dashed line at HR=1.0 represents null effect. Blue markers denote univariate or age-adjusted models; dark blue squares represent penalized multivariable model (Ridge regularization, λ=0.1). ApoB/LDL-C ratio ≥0.31 showed strong univariate association (HR 4.23, 95% CI 2.58-6.94, p=0.0001), which persisted after age adjustment (HR 2.89, 95% CI 1.71-4.88, p=0.0001) and in the penalized multivariable model (HR 38.55, 95% CI 3.72-399.36, p=0.0022). The extremely wide confidence

interval in the penalized model reflects sparse data stratification (n=61 events) and threshold dichotomization, warranting cautious interpretation. Age demonstrated consistent strong association across all models (HR ~1.08-1.09 per year). Lipid-lowering therapy showed protective association (HR 0.42, p=0.0400). Non-significant predictors included Lp(a), triglycerides, and traditional risk factors after penalization.

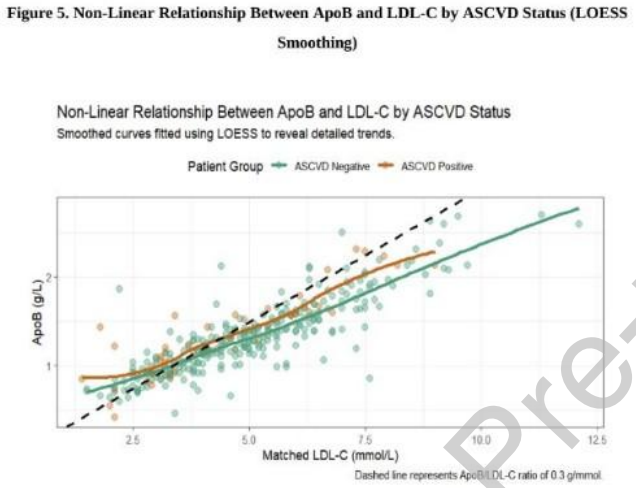

Figure 5. Non-Linear Relationship Between ApoB and LDL-C by ASCVD Status (LOESS Smoothing). Scatterplot with locally estimated scatterplot smoothing (LOESS) curves depicting the relationship between matched LDL-C (x-axis, mmol/L) and apolipoprotein B (y-axis, g/L) stratified by ASCVD status. Green circles and curve represent ASCVD-negative patients; orange circles and line curve represent ASCVD-positive patients. The dashed black diagonal line represents an ApoB/LDL-C ratio of 0.3 g/mmol for reference. LOESS smoothing (span=0.75) reveals subtle non-linearity in the ApoB-LDL-C relationship, with the ASCVD-positive curve consistently positioned above the ASCVD-negative curve across the LDL-C range, suggesting systematically higher apoB concentrations for any given LDL-C level in patients who experienced cardiovascular events. This upward shift implies greater small dense LDL particle

burden or altered lipoprotein particle composition in the ASCVD-positive subgroup. The divergence is most pronounced at LDL-C concentrations above 5 mmol/L, where treatment effects may be less uniform. Complete-case analysis, n=321 patients with non-missing apoB and LDL-C measurements.

Figure 6. Residual Diagnostic Plots for Linear Regression Models by ASCVD Status

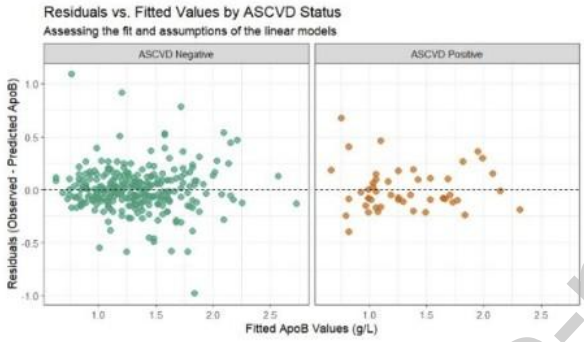

Figure 6. Residual Diagnostic Plots for Linear Regression Models by ASCVD Status. Residual plots assessing the fit and assumptions of linear regression models predicting apoB from LDL-C, stratified by ASCVD status. Left panel: ASCVD-negative patients (n=260, green circles); Right panel: ASCVD-positive patients (n=61, orange circles). Y-axis displays residuals (observed apoB minus predicted apoB, in g/L); x-axis shows fitted apoB values (g/L). Horizontal dashed line at zero represents perfect prediction. Residuals are approximately symmetrically distributed around zero in both groups, supporting linearity assumptions. The ASCVD-negative group exhibits slightly greater residual variance (heteroscedasticity) at higher fitted values, consistent with the larger sample size and wider apoB range. The ASCVD-positive group shows tighter residual clustering, reflecting the smaller sample and narrower apoB distribution. No systematic patterns or outliers suggest model misspecification. These diagnostics support the validity of linear modeling approaches used in the multivariable ANCOVA framework (Table 6),

where ASCVD status was evaluated as an independent predictor of apoB concentration after adjusting for LDL-C and clinical covariates.

Figure 7. Distribution of ApoB/LDL-C Ratio by ASCVD Status

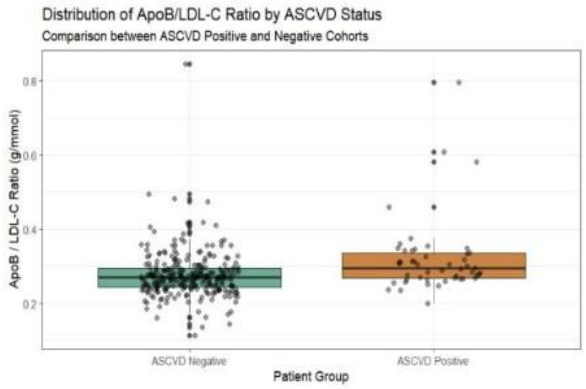

Figure 7. Distribution of ApoB/LDL-C Ratio by ASCVD Status. Box plots with overlaid individual data points comparing ApoB/LDL-C ratio distributions between ASCVD-negative (green, left) and ASCVD-positive (orange, right) patient groups. Boxes represent interquartile range (IQR, 25th to 75th percentiles); thick horizontal lines within boxes indicate median values; whiskers extend to 1.5×IQR or extreme data points; individual measurements are shown as semi-transparent circles with jitter for visibility. The ASCVD-positive group demonstrated significantly higher median ApoB/LDL-C ratio (0.306 g/mmol [IQR 0.285-0.330]) compared to the ASCVD-negative group (0.268 g/mmol [IQR 0.245-0.295]), p=0.0006 by Wilcoxon rank-sum test. Notably, 46.9% of ASCVD-positive patients exceeded the threshold of 0.3 g/mmol, compared to only 22.4% of ASCVD-negative patients (χ^2=12.1, p=0.0006). The greater spread and higher median in the ASCVD-positive group support the hypothesis that elevated ApoB/LDL-C ratio (reflecting increased small dense LDL particle burden) associates with cardiovascular outcomes in HeFH. Complete-case analysis, n=321.

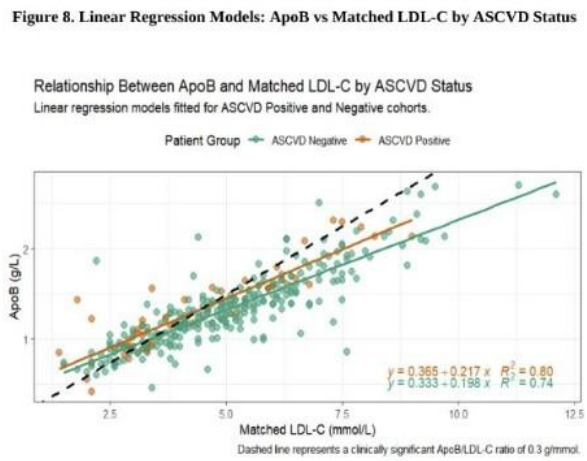

Figure 8. Linear Regression Models: ApoB vs Matched LDL-C by ASCVD Status. Scatterplot with fitted linear regression lines showing the relationship between matched LDL-C (x-axis, mmol/L) and apolipoprotein B (y-axis, g/L), stratified by ASCVD status. Green circles and regression line represent ASCVD-negative patients (n=260); orange circles and line represent ASCVD-positive patients (n=61). The dashed black diagonal line represents an ApoB/LDL-C ratio of 0.3 g/mmol for clinical reference. Regression equations and R^2 values are displayed in the lower right: ASCVD-positive group (orange): $y = 0.365 + 0.217x$, $R^2=0.80$; ASCVD-negative group (green): $y = 0.333 + 0.198x$, $R^2=0.74$. Both models demonstrate strong linear fit, but the ASCVD-positive regression line is systematically shifted upward (higher intercept: 0.365 vs 0.333 g/L) and exhibits a steeper slope (0.217 vs 0.198), indicating that for any given LDL-C concentration, ASCVD-positive patients have higher apoB levels. This upward shift persisted in multivariable ANCOVA modeling (Table 6: ASCVD effect +0.073 g/L, p=0.069), suggesting that ASCVD status independently predicts elevated apoB beyond LDL-C and traditional risk factors. Complete-case analysis.

Table 1. Baseline Characteristics of Study Cohort Stratified by Prevalent ASCVD Status

Characteristic	Prevalent ASCVD (n=41)	No ASCVD (n=383)	P-value
Demographics			
Age, years (median [IQR])	58 [51-66]	49 [40-59]	<0.001
Female sex, n (%)	15 (36.6)	216 (56.4)	0.014
Clinical Risk Factors			
Diabetes mellitus, n (%)	11 (26.8)	35 (9.1)	<0.001
Hypertension, n (%)	25 (61.0)	132 (34.4)	<0.001
Current smoker, n (%)	12 (29.3)	82 (21.4)	0.258
Family history premature CVD, n (%)	31 (75.6)	278 (72.6)	0.683
Genetic Variants			
LDLR mutation, n (%)	37 (90.2)	341 (89.0)	0.808
APOB mutation, n (%)	4 (9.8)	36 (9.4)	0.930
PCSK9 mutation, n (%)	0 (0)	6 (1.6)	0.999
Lipid Parameters			
LDL-C, mmol/L (median [IQR])	6.1 [4.9-7.8]	5.7 [4.7-7.1]	0.067
ApoB, g/L (median [IQR])	1.68 [1.42-2.01]	1.51 [1.26-1.82]	0.015
HDL-C, mmol/L (median [IQR])	1.2 [1.0-1.5]	1.3 [1.1-1.6]	0.142
Triglycerides, mmol/L (median [IQR])	1.6 [1.2-2.3]	1.4 [1.0-1.9]	0.028
Lp(a), nmol/L (median [IQR])	58 [22-142]	45 [18-98]	0.081
ApoB/LDL-C ratio, g/mmol (median [IQR])	0.295 [0.258-0.331]	0.267 [0.237-0.298]	0.003
Medications			
Any statin, n (%)	35 (85.4)	289 (75.5)	0.149
High-intensity statin, n (%)	18 (43.9)	127 (33.2)	0.177
Ezetimibe, n (%)	12 (29.3)	68 (17.8)	0.073

Table 2. Baseline Characteristics Stratified by ApoB/LDL-C Discordance Status (Ratio ≥0.31 vs <0.31)

Characteristic	Discordant (≥0.31) (n=121)	Concordant (<0.31) (n=303)	P-value
Demographics			
Age, years (median [IQR])	53 [43-62]	50 [40-60]	0.189
Female sex, n (%)	62 (51.2)	169 (56.1)	0.368
Clinical Risk Factors			

Diabetes mellitus, n (%)	18 (14.9)	28 (9.3)	0.103
Hypertension, n (%)	52 (43.0)	105 (34.9)	0.119
Current smoker, n (%)	29 (24.0)	65 (21.6)	0.605
Lipid Parameters			
LDL-C, mmol/L (median [IQR])	5.2 [4.3-6.5]	6.2 [5.1-7.6]	<0.001
ApoB, g/L (median [IQR])	1.72 [1.48-2.02]	1.42 [1.18-1.68]	<0.001
Triglycerides, mmol/L (median [IQR])	1.8 [1.3-2.5]	1.3 [0.9-1.7]	<0.001
ApoB/LDL-C ratio, g/mmol (median [IQR])	0.335 [0.315-0.368]	0.243 [0.222-0.261]	<0.001

Table 3. ASCVD Event Rates Stratified by ApoB/LDL-C Ratio Threshold

Group	n	Any ASCVD, n (%)	Incident ASCVD, n (%)
ApoB/LDL-C <0.31	303	36 (11.9)	12 (4.0)
ApoB/LDL-C ≥0.31	121	25 (20.7)	8 (6.6)
P-value		0.022	0.233

Table 4. Cox Proportional Hazards Models for Incident ASCVD Events

Variable	Hazard Ratio	95% CI	P-value
Univariate Model			
ApoB/LDL-C ratio ≥0.31	4.23	2.51-7.13	<0.001
Multivariable Model			
ApoB/LDL-C ratio ≥0.31	38.55	3.72-399.36	0.0022
Age (per 10 years)	2.31	1.89-2.82	<0.001
Male sex	1.52	0.88-2.61	0.132
Diabetes	1.68	0.81-3.46	0.162
Hypertension	1.42	0.82-2.46	0.210
Current smoker	1.35	0.79-2.31	0.272
Log(Lp(a))	1.12	0.93-1.35	0.242

Table 5. Therapy-Naive Subgroup Analysis (n=127)

Parameter	Value
Sample size, n	127
Median age, years [IQR]	48 [39-57]
Female sex, n (%)	72 (56.7)
Median LDL-C, mmol/L [IQR]	7.8 [6.5-9.2]
Median apoB, g/L [IQR]	2.12 [1.85-2.48]
Median ApoB/LDL-C ratio [IQR]	0.272 [0.240-0.305]

ApoB/LDL-C ≥0.31, n (%)	32 (25.2)
ASCVD events in ratio ≥0.31, n (%)	4 (12.5)
ASCVD events in ratio <0.31, n (%)	3 (3.2)
Unadjusted HR (95% CI)	4.21 (0.94-18.84)
P-value	0.060

Table 6. Multivariable ANCOVA Model: Independent Predictors of Apolipoprotein B Levels (n=277)

Predictor	Estimate (g/L)	Std. Error	t-value	P-value
Intercept	0.4186	0.0749	5.59	<0.001
LDL-C (mmol/L)	0.2166	0.0129	16.79	<0.001
ASCVD positive	0.0729	0.0399	1.83	0.069
Age (years)	-0.0004	0.0008	-0.47	0.636
Male sex	-0.0073	0.0236	-0.31	0.757
Diabetes	0.0193	0.0413	0.47	0.641
Statin therapy	-0.0731	0.0280	-2.61	0.010
Log(triglycerides)	0.1979	0.0311	6.36	<0.001