Original Article

# Association between the ratio of high-density lipoprotein cholesterol to apolipoprotein A-I and in-stent neoatherosclerosis: an optical coherence tomography study

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**Background:** In-stent neoatherosclerosis (ISNA) is an important cause of in-stent restenosis (ISR) with drug-eluting stent (DES) implants. High-density lipoprotein cholesterol (HDL-C) is associated with ISNA. However, few studies have focused on the functionalities of HDL-C composition, and till date, optical coherence tomography (OCT) has not been used to analyze the relationship between ISNA incidence and HDL-C-to-apolipoprotein A-I ratio (HAR) in patients with DES implants and ISR (DES-ISR). This study aimed to clarify the association between HAR and ISNA.

**Methods:** This single-center, retrospective study included patients admitted to the Affiliated Hospital of Zunyi Medical University. A total of 216 patients with 220 ISR lesions who underwent OCT for the culprit stent were included between July 2018 and November 2022. Based on HAR at admission, 33rd and 66th percentiles were identified as the cut-off points, and all eligible patients were divided into three groups: Tertile 1 (HAR ≤0.836; n=71), Tertile 2 (0.836< HAR <0.932; n=73), and Tertile 3 (HAR ≥0.932; n=72). Baseline characteristics and angiographic and OCT features were compared between the different groups. In addition, univariate and multivariate logistic regression models were used to assess the association of HAR with ISNA and in-stent thin-cap fibroatheroma (TCFA).

**Results:** Angiographic characteristics and quantitative OCT assessment values did not differ significantly among the groups. The incidences of ISNA (62.0% *vs.* 52.1% *vs.* 37.5%, P=0.01) and in-stent TCFA (35.2% *vs.* 27.4% *vs.* 15.3%, P=0.02) were significantly lower in the third tertile of the HAR group than in the first or second tertiles. The multifactor logistic regression model revealed that the highest tertile group had a reduced risk of ISNA [hazard ratio (HR) =0.185, 95% confidence interval (CI): 0.081–0.421; P<0.001] and TCFA (HR =0.197, 95% CI: 0.075–0.517; P<0.001) compared with the lowest tertile group.

**Conclusions:** OCT revealed high HAR levels to be negatively correlated with the incidences of ISNA and TCFA in patients with ISR. HAR is a better indicator of ISNA and plaque fragility than HDL-C itself, thus providing a marker and pathway for better prevention of ISNA.

**Keywords:** Neoatherosclerosis; in-stent restenosis (ISR); optical coherence tomography (OCT); high-density lipoprotein cholesterol to apolipoprotein A-I ratio (HAR)

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## Introduction

Despite the recent widespread use of drug-eluting stents (DES) and advancements in cardiovascular secondary prevention drugs, in-stent restenosis (ISR) remains a problem after percutaneous coronary intervention (PCI) (1,2). Current clinical evidence suggests that in-stent neoatherosclerosis (ISNA), a form of accelerated atherosclerosis within the stented segment, is a significant cause of late ISR (3-5). Till date, the mechanisms underlying ISNA are not yet fully understood given their complexity. Numerous studies have revealed lipoproteins as risk factors of neoatherosclerosis, ultimately contributing to the development of ISR (6,7). Improved lipid composition inhibits *de novo* atherosclerosis and ISNA progression.

The protein composition of high-density lipoprotein cholesterol (HDL-C) is 70% apolipoprotein A-I (apoA-I) and 30% apolipoprotein A-II (8). Variations in the composition of HDL-C particles can lead to differences in their metabolism and function (9). Therefore, HDL-C composition may be a more accurate reflection of its physiological role in atherosclerosis. Recently, the HDL-C-to-apoA-I ratio (HAR) has been shown to correlate with atherosclerosis, which can reflect the progression of coronary atherosclerosis and severity of coronary artery stenosis (10).

Optical coherence tomography (OCT) is a high-resolution intravascular imaging technique that allows detailed visualization of coronary artery wall structures (11). It enables the precise observation of ISR features, identification of lipid-containing neointima within the stent, and accurate measurement of the neointima and fibrous cap thickness (12). Various studies have focused on the significant association of HDL-C with *de novo* atherosclerosis and ISR (13,14). However, few studies have focused on the functionalities of HDL-C composition, and till date, OCT has not been used to analyze the relationship between ISNA incidence and HAR in patients with DES implants and ISR (DES-ISR). Therefore, we aimed to analyze the relationship between HAR and ISNA using OCT in patients with DES-ISR. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-328/rc).

### Highlight box

**Key findings**

- The high-density lipoprotein cholesterol (HDL-C)-to-apolipoprotein A-I ratio (HAR) is an independent risk factor for in-stent neoatherosclerosis (ISNA).

**What is known and what is new?**

- The HAR has been shown to correlate with atherosclerosis, which can reflect the progression of coronary atherosclerosis and severity of coronary artery stenosis.
- Analyze the relationship between HAR and ISNA using optical coherence tomography in patients with drug eluting stent-in-stent restenosis (ISR).

**What is the implication, and what should change now?**

- Focus on ratio of high-density lipoprotein cholesterol to apolipoprotein A-I in stent implanted patients, for better prevention of ISNA.

## Methods

### *Study design and patient characteristics*

This retrospective analysis was performed at the Affiliated Hospital of Zunyi Medical University and involved patients who were hospitalized at this institution. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (No. KLL-2021-323). Written informed consent was obtained from the participants of this study. Between July 2018 and November 2022, 580 consecutive patients with DES-ISR were evaluated for enrollment in this study. Patients who did not undergo OCT were excluded, which left 240 patients. Of the 240 patients, 7 were excluded because of missing baseline clinical data, 8 were excluded because of poor-quality OCT images, and 9 were excluded because of unavailability of routine blood test or lipid test results. Finally, 216 patients with 220 DES-ISR lesions were included in this study (*Figure 1*). The baseline characteristics of patients who were excluded without OCT guidance and patients with OCT guidance for exclusion without baseline are presented in the Table S1. ISR was defined as a stenosis of >50% within the stent or within 5 mm of either end of the stent. Based on HAR at admission, 33$^{rd}$ and 66$^{th}$ percentiles were identified as the cut-off points, and all eligible patients were divided into three groups: Tertile 1 (HAR ≤0.836; n=71), Tertile 2 (0.836< HAR <0.932; n=73), and Tertile 3 (HAR ≥0.932; n=72).

### *Data collection and angiographic characteristics*

Baseline clinical characteristics of the patients—such as age, sex, medical history, smoking habits, and medication

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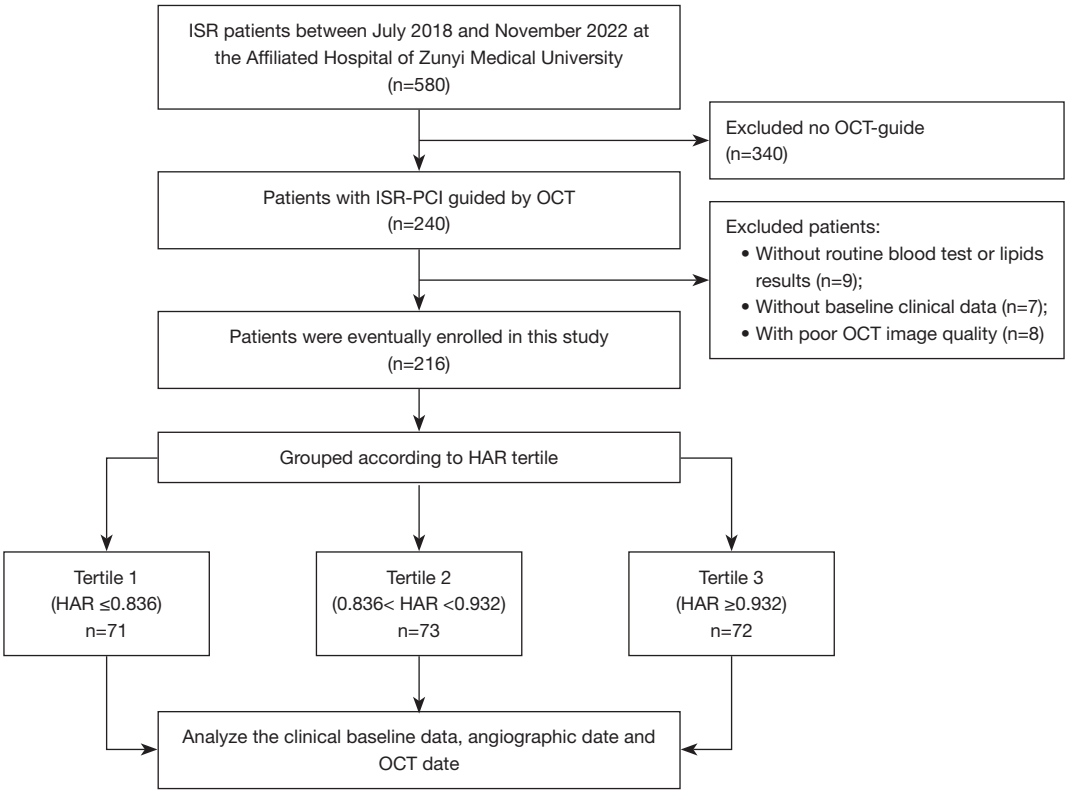


**Figure 1** Study flow chart of enrollment. According to their HAR tertile level, the patients were divided into three groups [Tertile 1 (HAR ≤0.836), n=71; Tertile 2 (0.836< HAR <0.932), n=73; and Tertile 3 (HAR ≥0.932), n=72]. ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; HAR, high-density lipoprotein cholesterol to apolipoprotein A-I ratio.

usage—were extracted from the hospital's electronic medical record systems. This was a retrospective study and that samples to assess HAR were collected as part of routine clinical practice. Blood samples of 2 mL were collected after an overnight fast of 8 h on the second day of admission. Blood tests included routine blood indicators (white blood cells, hemoglobin, platelets), blood biochemistry indicators [alanine aminotransferase, aspartate aminotransferase, total bilirubin and direct bilirubin, estimated glomerular filtration rate (eGFR)], lipids indicators [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), HDL-C, apoA-I, and apolipoprotein B], and N-terminal pro-B-type natriuretic peptide (NT-proBNP), which were measured using standard hospital laboratory techniques.

HAR was calculated by dividing the absolute value of HDL-C by the absolute value of apoA-I. Hypertension was defined as a systolic blood pressure exceeding 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg, or by the use of antihypertensive medications. Smoking was considered based on whether the patient was a current smoker or had quit smoking in the last 6 months. Diabetes was diagnosed through a combination of factors, including a previous diagnosis of diabetes, use of diabetes medications, a fasting blood glucose level exceeding 7 mmol/L, and/or a random blood glucose level greater than 11.1 mmol/L. The diagnosis of chronic cardiac insufficiency is based on body or pulmonary circulation stasis with objective evidence of elevated BNP or structural changes in the cardiac structure.

All patients underwent coronary angiography at the catheterization laboratory of the Department of Cardiology, the Affiliated Hospital of Zunyi Medical University on the second day of admission. Coronary angiography was performed by an interventional cardiologist in line with the current Chinese guidelines. Coronary angiography was conducted by inserting a catheter through either the radial or femoral artery. Following the injection of intracoronary nitrates, multiple corresponding angiographic views were captured for each patient. There were no adverse events occurred. Images were collected and analyzed with

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confidence by two independent interventional cardiologists using Syngo AX software (Siemens Medical Solutions, AX, Berlin, Germany). ISR was categorized based on Mehran's classification (15) into four types: type I, focal (≤10 mm); type II, diffuse in-stent (>10 mm, limited to the stent); type III, proliferative (>10 mm, extending beyond the stent edge); and type IV, which represents complete occlusion.

### *OCT acquisition and assessment*

OCT is an intravascular imaging technique that uses near-infrared light. This study used a frequency domain OCT system (ILUMIEN OPTIS Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA) to obtain OCT images after coronary angiography. The OCT catheter was advanced over a guidewire into the distal ISR lesion, where contrast was injected to clear the blood from the target vessel. The pullback was performed at a rate of 18 mm/s, while the rotation speed was set at 100 frames/s. OCT images were analyzed by two experienced reviewers who kept the patients' clinical information confidential and invited a third independent investigator to obtain a unanimous conclusion in case of disagreement between the two reviewers. The cardiovascular image analysis specialists all have more than 15 years of experience.

### *OCT analyses*

We used an OCT analysis software (LightLab Imaging Inc., Westford, MA, USA) to quantitatively and qualitatively analyze the entire stent segment at 1-mm intervals. The main indicators for analysis included the structural characteristics of the plaque and various lumen area features of ISR. The measurements taken were: minimum lumen area, minimum lumen diameter, minimum stent area, minimum stent diameter, neointimal hyperplasia (NIH) area, and NIH percentage, calculated as [(stent area – lumen area) ×100%]/stent area. Distal and proximal reference areas refer to areas of the greatest lumen within 5 mm distally and proximally to the stenosis within the same segment, respectively, and the midpoints of the strut were connected to measure the stent area. If the stent strut could not be observed, it was clarified by comparing adjacent slices.

For qualitative analysis, the presence of any targeted feature on the OCT vessel cross-section was considered a positive feature for that lesion. ISNA was defined by the presence of at least one of the components of a mature atherosclerotic plaque such as lipid-laden tissue or calcification within the stent (16). There are three types of OCT-guided restenosis histology (17): (I) homogeneous, characterized by uniform high-signal bands without backscatter patterns; (II) heterogeneous, characterized by mixed-signal bands with diverse backscatter patterns; and (III) layered, characterized by superficial high-signal bands and deeper low-signal bands surrounding the stent beam. Lipid plaques were characterized as regions of low signal intensity with diffuse edges (18). Thin-cap fibroatheroma (TCFA) was identified as lipid-rich neointima featuring lipid arcs greater than 180° and a fibrous cap thickness of 65 μm or less (19). Calcific plaques are clearly delineated areas exhibiting a significant signal difference and low backscatter (20). Spotty calcium was characterized as a lesion measuring less than 4 mm in length, with a calcification arc of less than 90° (21). Fibrous plaques display regions of high signal intensity that are uniformly distributed and exhibit low attenuation (22). Neointimal macrophage imaging is characterized by signal intensity that surpasses the background speckle noise, enhanced by the presence of distinct or clustered areas of convergence (23). *Figure 2* displays representative OCT images illustrating different vascular morphologies.

### *Statistical analyses*

Results for categorical variables are expressed as frequencies with percentages. For categorical variables, the Chi-squared test or Fisher's exact test was performed to detect differences. Results for continuous variables are expressed as means with standard deviations (normal distribution) and medians with interquartile ranges (skewed distribution). For continuous variables with a normal distribution, one-way analysis of variance was applied to compare differences in HAR quartiles, and the Kruskal-Wallis *H*-test was used to detect differences in continuous parameters with skewed distributions. Multivariate logistic regression models with hazard ratios (HRs) and 95% confidence intervals (CIs) were applied to investigate the relationship among HAR, ISNA, and TCFA. Based on baseline characteristics and clinical significance, Model 1 was adjusted for none. Model 2 was adjusted for age and sex. Model 3 was adjusted for sex, age, hypertension, diabetes, and smoking. Finally, Model 4 was further adjusted for NT-proBNP, eGFR, TG and LDL-C levels on the basis of model 3. Statistical analyses were performed using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA), and a two-sided significance test was used, with a P value of <0.05 indicating statistical significance.

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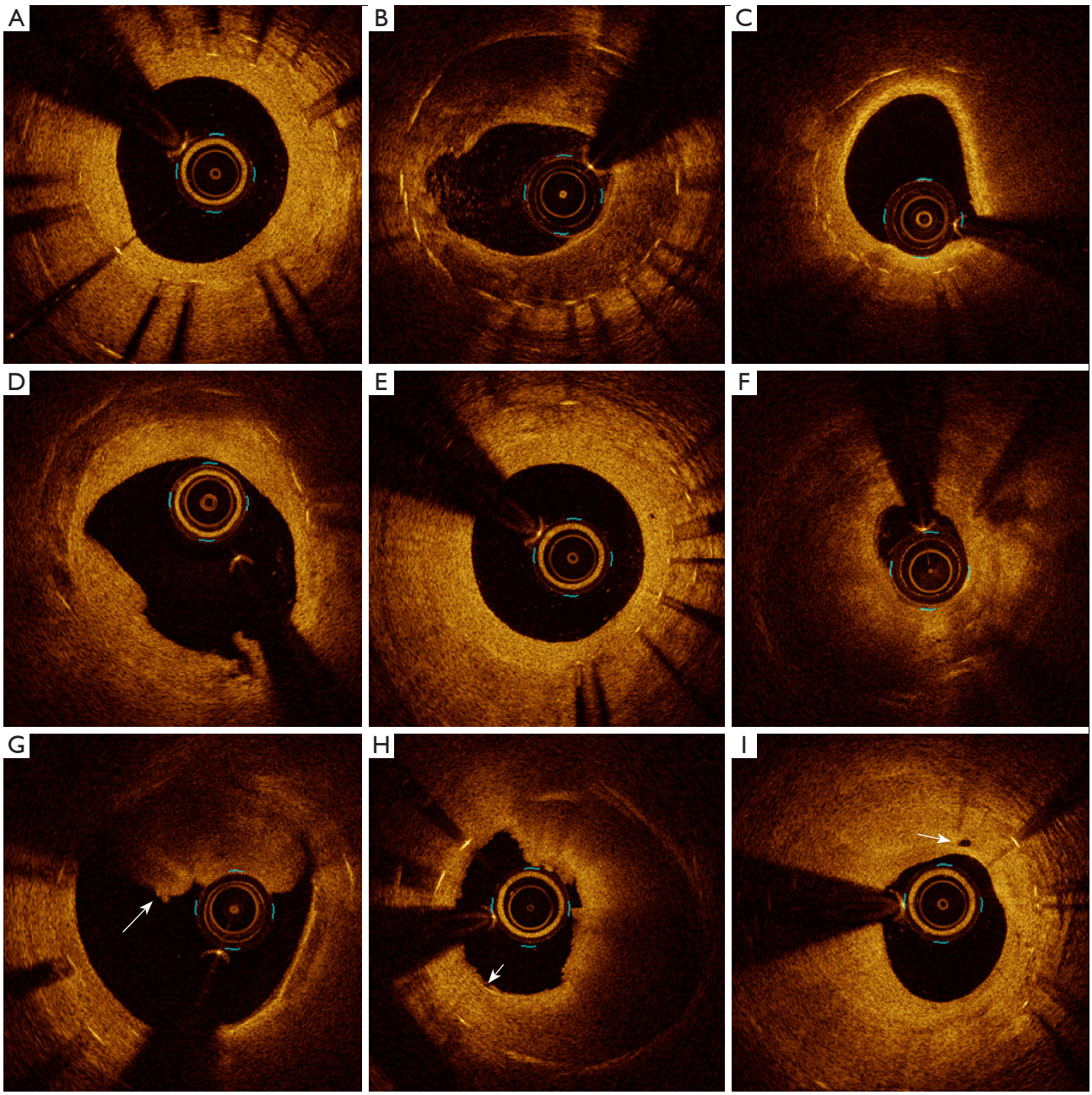


**Figure 2** Typical OCT images of different ISR vascular morphologies. (A) Homogenous. (B) Heterogeneous. (C) Layered. (D) Calcified plaque. (E) Fibrous plaque. (F) TCFA. (G) Thrombosis (arrow). (H) Macrophages (arrow). (I) Microvessels (arrow). (D,F) are types of ISNA. OCT, optical coherence tomography; ISR, in-stent restenosis; TCFA, thin-cap fibroatheroma; ISNA, in-stent neoatherosclerosis.

## Results

### *Clinical characteristics*

Baseline characteristics of included patients are shown in *Table 1*. A total of 216 patients with ISR and 220 ISR target lesions were enrolled in this study. The mean age of patients was 63.3 years, and patients included 173 men and 43 women. There were no significant differences between these patients in terms of sociodemographics, past medical history, clinical presentation and medicine use. The

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**Table 1** Baseline characteristics

| Variable | Tertile 1 (n=71) (HAR ≤0.836) | Tertile 2 (n=73) (0.836< HAR <0.932) | Tertile 3 (n=72) (HAR ≥0.932) | P |
|---|---|---|---|---|
| Age, years | 62.30±10.44 | 63.25±11.04 | 64.58±9.91 | 0.60 |
| Male | 60 (84.5) | 56 (76.7) | 57 (79.2) | 0.48 |
| Current smoker | 27 (38.0) | 30 (41.1) | 32 (44.4) | 0.73 |
| Hypertension | 49 (69.0) | 47 (64.4) | 36 (50.0) | 0.051 |
| Diabetes mellitus | 20 (28.2) | 16 (21.9) | 19 (26.4) | 0.67 |
| Chronic cardiac insufficiency | 1 (1.4) | 2 (2.7) | 6 (8.3) | 0.08 |
| Clinical presentation | | | | 0.19 |
| STEMI | 11 (15.5) | 10 (13.7) | 8 (11.1) | |
| NSTEMI | 4 (5.6) | 5 (6.8) | 3 (4.2) | |
| UA | 9 (12.7) | 1 (1.4) | 9 (12.5) | |
| Stable AP | 47 (66.2) | 57 (78.1) | 52 (72.2) | |
| Laboratory findings | | | | |
| White blood cells, $\times10^9$/L | 6.92 [5.70–8.80] | 7.42 [6.05–9.06] | 6.80 [5.13–7.69] | 0.12 |
| Hemoglobin, g/L | 142.68±15.93 | 141.34±18.19 | 136.14±19.92 | 0.06 |
| Platelet, $\times10^9$/L | 199.00 [147.00–236.00] | 206.00 [162.50–246.50] | 198.00 [150.00–239.75] | 0.46 |
| ALT, U/L | 28.00 [20.00–38.00] | 25.00 [19.00–36.00] | 24.00 [17.00–36.00] | 0.32 |
| AST, U/L | 31.00 [26.00–40.00] | 28.00 [22.00–40.00] | 28.50 [21.00–38.00] | 0.42 |
| Total bilirubin, μmol/L | 13.50 [9.40–17.24] | 12.10 [9.60–16.20] | 12.65 [8.68–17.15] | 0.67 |
| Direct bilirubin, μmol/L | 2.90 [2.10–4.00] | 2.90 [2.10–4.15] | 2.55 [2.00–3.90] | 0.70 |
| NT-proBNP, pg/mL | 260.10 [109.00–616.00] | 134.20 [60.33–663.95] | 299.50 [115.00–1,135.25] | 0.03 |
| eGFR, mL/min/1.73 $m^2$ | 83.90 [59.51–104.18] | 71.55 [60.42–95.44] | 82.79 [63.43–96.99] | 0.42 |
| Triglycerides, mmol/L | 1.92 [1.35–3.22] | 1.56 [1.13–2.45] | 1.30 [1.02–1.85] | 0.001 |
| Total cholesterol, mmol/L | 3.69 [2.97–4.27] | 3.88 [3.46–4.70] | 4.25 [3.32–5.56] | 0.001 |
| HDL-C, mmol/L | 0.89 [0.81–1.05] | 1.09 [0.97–1.24] | 1.19 [1.07–1.42] | <0.001 |
| LDL-C, mmol/L | 2.07 [1.72–2.44] | 2.34 [2.00–2.88] | 2.40 [1.75–3.33] | 0.01 |
| apoA-I, mmol/L | 1.17 [1.06–1.35] | 1.23 [1.12–1.38] | 1.16 [1.05–1.30] | 0.08 |
| apoB, mmol/L | 0.64 [0.57–0.78] | 0.70 [0.60–0.82] | 0.82 [0.60–1.04] | 0.007 |
| Medicine use | | | | |
| Aspirin | 67 (94.4) | 71 (97.3) | 66 (91.7) | 0.33 |
| Clopidogrel | 63 (88.7) | 67 (91.8) | 65 (90.3) | 0.82 |
| Statin | 60 (84.5) | 65 (89.0) | 66 (91.7) | 0.40 |

Data are presented as mean ± standard deviation, median [interquartile range], or n (%). STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST Segment Elevation Myocardial Infarction; UA, unstable angina pectoris; Stable AP, stable angina pectoris; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; HAR, high-density lipoprotein cholesterol to apolipoprotein A-I ratio.

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main baseline differences between the three groups were concentrated in NT-proBNP and lipid-related tests. Levels of NT-proBNP, TC, HDL-C, LDL-C, and apoB gradually increased with HAR. TG levels gradually decreased with increasing HAR.

### *Angiographic findings*

Angiographic characteristics of patients are shown in Table S2. Of the 220 target lesions, the mean time from stent implantation was 3 years, with 63.4% of stents implanted in the left anterior descending artery, 8.3% in the left circumflex artery, and 27.3% in the right coronary artery. P values for the pattern of ISR between the three groups were not statistically significant.

### *OCT analysis of ISR lesions*

Differences in the tissue pattern distribution of ISR among the three groups, as measured by OCT, are summarized in *Table 2*. Quantitative OCT assessment values did not differ significantly among the three groups. Qualitative OCT assessment between the three groups was as follows: the incidence of ISNA (62.0% *vs.* 52.1% *vs.* 37.5%, P=0.01) and in-stent TCFA (35.2% *vs.* 27.4% *vs.* 15.3%, P=0.02) was significantly higher in the first tertile of the HAR group than in the second or third tertiles (*Figure 3A*). As shown in *Figure 3B,3C*, the HAR was also significantly lower in the ISNA and TCFA groups than in the non-ISNA and non-TCFA groups, respectively [0.92 (0.83, 0.99) *vs.* 0.86 (0.80, 0.93), 0.90 (0.81, 0.98) *vs.* 0.84 (0.80, 0.92), respectively, both P<0.001]. In addition, patients in the first tertile of the HAR group had a higher incidence of lipid plaques (62.0% *vs.* 53.4% *vs.* 40.3%, P=0.03) and heterogeneous restenotic tissue structures (59.2% *vs.* 46.6% *vs.* 33.3%, P=0.02) than patients in the second and third tertiles; calcified plaques, thrombus, macrophages, and microvessels did not differ significantly among the three groups.

### *Independent predictors of ISNA*

To clarify whether HAR was an independent predictor of ISNA and TCFA, data from the three groups were subjected to logistic regression analysis. As shown in *Table 3*, after full adjustment for all covariates, the multivariate logistic regression model revealed that the highest tertile group had a reduced risk of ISNA [hazard ratio (HR) =0.185, 95% confidence interval (CI): 0.081–0.421; P<0.001] and TCFA (HR =0.197, 95% CI: 0.075–0.517; P<0.001) compared with the lowest tertile group.

## Discussion

To our knowledge, this was the first study to retrospectively assess the association among HAR, OCT-determined ISNA, and plaque vulnerability in ISR patients after DES implantation. We observed that (I) higher HAR values were associated with a lower incidence of ISNA compared with HDL-C; (II) patients with higher HAR values have less in-stent TCFA than those with lower HAR values; (III) lower HAR value (<0.836) is an independent risk factor of ISNA, when other clinical risk factors were calibrated.

Stent implantation is an important treatment option for coronary artery disease (24). However, ISR remains a major cause of late stent failure (25). Growing clinical and pathological evidence suggests that ISNA plays an important role in the mechanism of late ISR while contributing to adverse cardiovascular events (26). A previous study has reported that, during in-stent atherosclerosis, macrophages phagocytose large amounts of lipids to form foamy macrophages (27). As foamy macrophages continue to accumulate, the necrotic core expands, resulting in the development of TCFA and, ultimately, in plaque rupture, inducing adverse cardiovascular events (28). Therefore, the early identification of ISNA is important to prevent ISR and reduce adverse cardiovascular events, and a simple and readily available indicator of the degree of atherosclerosis is required.

HDL-C helps lower cholesterol levels by transporting cholesterol from tissues to the liver for metabolism (29). It is well known that plasma HDL-C levels are inversely correlated to atherosclerosis risk (9). By analyzing plaque characteristics in ACS patients undergoing OCT, HDL-C was found to be negatively correlated with fibrous cap thickness of the culprit lesion (30). Meanwhile, increase of HDL-C levels increase fibrous cap thickness, which increases plaque stabilization in patients with ACS (31). Therefore, increasing HDL-C levels may improve atherosclerosis and consequently reduce the incidence of cardiovascular events. However, a recent study has shown that drugs that inhibit cholesteryl ester transfer protein significantly increase HDL-C levels, but have been shown to fail to reduce cardiovascular events in clinical trials (32). Simultaneously, dysfunctional HDL-C has been isolated from the plasma of patients with diabetes and exhibits elevated pro-inflammatory capacity and impaired

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**Table 2** ISR characteristics evaluated by optical coherence tomography

| Variable | Tertile 1 (n=71) (HAR ≤0.836) | Tertile 2 (n=73) (0.836< HAR <0.932) | Tertile 3 (n=72) (HAR ≥0.932) | P |
|---|---|---|---|---|
| Quantitative assessment | | | | |
| Distal reference lumen area, $mm^2$ | 4.72 [3.56–5.95] | 5.10 [3.57–6.22] | 5.04 [3.43–6.29] | 0.88 |
| Distal reference lumen diameter, mm | 2.44 [2.10–2.69] | 2.43 [2.13–2.72] | 2.49 [2.11–2.77] | 0.91 |
| Proximal reference lumen area, $mm^2$ | 8.23 [6.36–9.42] | 8.24 [6.80–9.57] | 7.92 [6.76–9.42] | 0.80 |
| Proximal reference lumen diameter, mm | 3.24 [2.86–3.46] | 3.24 [2.94–3.48] | 3.18 [2.94–3.47] | 0.91 |
| Minimum lumen area, $mm^2$ | 1.73 [1.26–2.36] | 1.68 [1.38–2.31] | 1.77 [1.3–2.17] | 0.72 |
| Minimum lumen diameter, mm | 1.41 [1.25–1.69] | 1.44 [1.28–1.70] | 1.42 [1.25–1.65] | 0.64 |
| Minimum stent area, $mm^2$ | 6.60 [5.14–8.50] | 6.53 [4.74–7.96] | 6.54 [5.36–7.68] | 0.93 |
| Minimum stent diameter, mm | 2.75 [2.40–3.06] | 2.76 [2.38–3.13] | 2.74 [2.54–3.00] | 0.99 |
| Maximal NIH, % | 72.72 [65.82–81.04] | 73.35 [64.80–79.02] | 73.98 [67.50–79.57] | 0.84 |
| Qualitative assessment | | | | |
| Neoatherosclerosis | 44 (62.0) | 38 (52.1) | 27 (37.5) | 0.01 |
| Restenotic tissue structure | | | | 0.02 |
| Homogeneous | 22 (31.0) | 31 (42.5) | 41 (56.9) | |
| Heterogeneous | 42 (59.2) | 34 (46.6) | 24 (33.3) | |
| Layered | 7 (9.9) | 8 (11.0) | 7 (9.7) | |
| Lipid plaque | 44 (62.0) | 39 (53.4) | 29 (40.3) | 0.03 |
| TCFA | 25 (35.2) | 20 (27.4) | 11 (15.3) | 0.02 |
| Calcific plaque | 8 (11.3) | 5 (6.8) | 3 (4.2) | 0.26 |
| Spotty calcification | 6 (8.5) | 5 (6.8) | 3 (4.2) | 0.57 |
| Fibrous plaque | 25 (35.2) | 33 (45.2) | 46 (63.9) | 0.002 |
| Thrombus | 35 (49.3) | 28 (38.4) | 25 (34.7) | 0.18 |
| Neointimal macrophages | 22 (31.0) | 16 (21.9) | 11 (15.2) | 0.51 |
| Microvessels | 38 (53.5) | 38 (52.1) | 41 (56.9) | 0.83 |

Data are presented as median [interquartile range] or n (%). ISR, in-stent restenosis; NIH, neointimal hyperplasia; TCFA, thin-cap fibroatheroma; HAR, high-density lipoprotein cholesterol to apolipoprotein A-I ratio.

antioxidant activity (33,34). Therefore, it is important to assess the functional roles of HDL-C.

It is known that 70% of HDL-C is composed of apoA-I, which plays an important role in the regulation of HDL-C function (8). The relative rate of HDL-apoA-I exchange (HAE) is an important measure for assessing HDL-C functionality and is not related to HDL-C or apoA-I in itself (35). A study has confirmed that HAE decreases in patients with atherosclerosis. For example, HAE is negatively associated with atherosclerosis and cardiovascular events (36). Meanwhile, HAE decreased in patients with type 1 diabetes and metabolic syndrome (37). In summary, the inclusion of apoA-I in the assessment of HDL-C function is important for the evaluation of atherosclerosis.

Currently, several studies have demonstrated that HAR is a simple and easily accessible index for HDL-C functional assessment and can also be used as a biomarker of atherosclerotic disease (38,39). In a cross-sectional study of 263,340 patients, the association between the risk of cardiovascular death and HAR was analyzed. Interestingly, there was no significant association between HDL-C levels and the risk of death; however, the risk of cardiovascular

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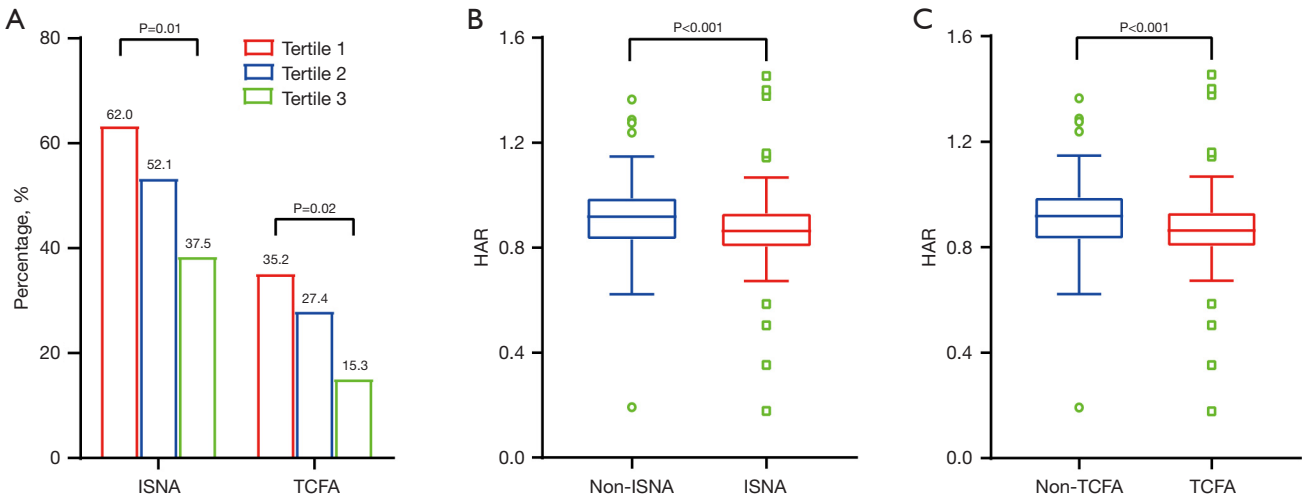


**Figure 3** Relationship between HAR with ISNA and TCFA. (A) The impact of HAR on the incidence of ISNA and TCFA. (B) Comparison of HAR levels between the non-ISNA and ISNA groups. (C) Comparison of HAR levels between the non-TCFA and TCFA groups. Significant differences are determined by the Rank-sum test. ISNA, in-stent neoatherosclerosis; TCFA, thin-cap fibroatheroma. HAR, high-density lipoprotein cholesterol to apolipoprotein A-I ratio.

**Table 3** Univariate and multivariate logistic regression models between HAR with ISNA and TCFA incidence

| Model | Tertile 1 (HAR ≤0.836) | Tertile 2 (0.836< HAR <0.932) | | Tertile 3 (HAR ≥0.932) | | P |
|---|---|---|---|---|---|---|
| | HR | HR (95% CI) | P | HR (95% CI) | P | |
| ISNA | | | | | | |
| Model 1 | 1.00 | 0.686 (0.355–1.325) | 0.26 | 0.373 (0.191–0.730) | 0.004 | 0.01 |
| Model 2 | 1.00 | 0.654 (0.333–1.283) | 0.21 | 0.341 (0.171–0.680) | 0.002 | 0.009 |
| Model 3 | 1.00 | 0.625 (0.315–1.239) | 0.17 | 0.289 (0.140–0.596) | 0.001 | 0.003 |
| Model 4 | 1.00 | 0.565 (0.275–1.162) | 0.12 | 0.185 (0.081–0.421) | <0.001 | <0.001 |
| TCFA | | | | | | |
| Model 1 | 1.00 | 0.688 (0.343–1.381) | 0.29 | 0.314 (0.141–0.700) | 0.005 | 0.01 |
| Model 2 | 1.00 | 0.693 (0.338–1.421) | 0.31 | 0.313 (0.138–0.708) | 0.005 | 0.02 |
| Model 3 | 1.00 | 0.673 (0.326–1.391) | 0.28 | 0.310 (0.134–0.717) | 0.006 | 0.02 |
| Model 4 | 1.00 | 0.508 (0.233–1.105) | 0.08 | 0.197 (0.075–0.517) | <0.001 | 0.004 |

Model 1 was adjusted for none. Model 2 was adjusted for age and gender. Model 3 was further adjusted for hypertension, diabetes mellitus, smoking on the basis of model 2. Model 4 was further adjusted for NT-proBNP, eGFR, TG and LDL-C on the basis of model 3. HAR, high-density lipoprotein cholesterol to apolipoprotein A-I ratio; ISNA, in-stent neoatherosclerosis; TCFA, thin-cap fibroatheroma; HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

death and all-cause mortality significantly increased in the high HAR group (40). Another study confirmed that HAR is positively associated with coronary stenosis severity in patients with diabetes (10). In addition, elevated HAR were significant predictors of in-hospital mortality in patients with acute coronary syndrome (41). However, some studies came to the opposite conclusion. A retrospective analysis of 2,566 patients with coronary artery disease treated with statins who were assessed for atherosclerotic progression by intravascular ultrasound showed that increased

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HAR was associated with less progression of coronary atherosclerosis (42). HAR levels were lower in patients with coronary artery disease, suggesting that lower HAR is associated with cardiovascular risk. In another prediction study on myocardial injury in 2,529 Chinese patients with coronary artery disease treated with PCI, a U-shaped association between HAR and post-PCI myocardial injury was observed, but the exact mechanism involved was unclear (43).

There is a lack of studies comparing the relationship between varying HAR levels and ISR characteristics by OCT. Our study revealed that HAR is negatively associated with the incidence of ISNA and plaque vulnerability in patients with ISR. Interestingly, both univariate and multivariate logistic regression analyses showed that HDL-C was not an independent risk factor of ISNA and TCFA. Our results illustrated that the functional status of HDL-C is far more important than HDL-C levels. The mechanism of the link between HAR and ISNA may be related to cholesterol transport. Cholesterol metabolism and transport play an important role in the development of ISNA. We suggest that reduced HAR level may reflect damage HDL-C's ability to transport additional excess cholesterol from peripheral tissues and atherosclerotic plaques to the liver. The abnormal cholesterol transport metabolism ultimately promotes the progression of ISNA plaques and leads to the development of TCFA. In conclusion, HAR can be used as a novel marker of ISNA progression after PCI.

The role of HAR needs to be validated through further experiments on ISNA incidence and plaque vulnerability. Our current study provides a new approach to explore the pathogenesis of ISNA and predict its progression, which may help in the early diagnosis of ISNA and pave the way for ISNA prevention and treatment strategies.

### *Limitations*

Our study has several limitations, and the conclusions should be interpreted with caution. First, the study is a single-center study with a small sample size, which limits the generalizability of the findings. Second, only patients with ISR who underwent OCT were included, so there may be selection bias in patients included in this study. Third, the functional status of HDL-C was not actually measured by experimental methods in this study. Finally, this cross-sectional study collected only HAR values at the time of outcome and did not assess the impact of dynamic changes in HAR values on the endpoint.

## Conclusions

In conclusion, our study showed that the incidence of ISNA and TCFA was negatively associated with HAR in patients with ISR. These results confirmed that HAR is a better indicator of ISNA and plaque fragility than HDL-C itself, thus providing a marker and pathway for better prevention of ISNA.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-328/rc

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (No. KLL-2021-323). Written informed consent was obtained from the participants of this study.

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