

Atherosclerotic Coronary Artery Disease in Patients With Cardiometabolic Syndrome

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Abstract

Major risk factors for cardiovascular disease (CVD) include aging, gender, smoking, family history and cardiometabolic syndrome. The relative residual risks for CVD after statin treatment for primary and secondary prevention have been reported by several large-scale randomized clinical trials. Statin treatment appears to prevent one-third of the onset and progression of CVD, but not the remaining two-thirds. There are three major problems regarding the residual risk of CVD: 1) Insufficient reduction of low-density lipoprotein cholesterol levels; 2) Low levels of high-density lipoprotein cholesterol and elevated triglyceride; and 3) Insufficient control of other risk factors (high blood pressure, obesity, metabolic syndrome, type 2 diabetes, etc.). Thus, a multifaceted preventive approach should be needed to prevent CVD after statin treatment.

Keywords: Cardiovascular disease; Cardiometabolic syndrome; Residual risks; Statin; Primary and secondary prevention

Introduction

Cardiometabolic syndrome is defined as metabolic dysfunction caused by a combination of insulin resistance, impaired glucose tolerance, dyslipidemia (DL), hypertension (HTN) and adiposity. Cardiometabolic syndrome is one of the risk factors for cardiovascular disease (CVD), along with aging, gender and family history. According to several large-scale randomized clinical trials, statin treatment for the primary and secondary prevention of CVD prevents one-third of the onset and progression of CVD, but not the remaining two-thirds [1]. The Treating to New Targets (TNT) Study indicated that the residual risk of CVD in statin-treated secondary prevention patients included both lipid-related and nonlipid factors, such as

increased body mass index, smoking, HTN, and diabetes mellitus (DM) [2]. The relative residual risk of CVD is still a major problem after statin treatment. There are three major problems regarding the residual risk of CVD: 1) Insufficient reduction of low-density lipoprotein cholesterol (LDL-C) levels; 2) Low levels of high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG); and 3) Insufficient control of other risk factors (high blood pressure, obesity, metabolic syndrome, type 2 diabetes, etc.) (Table 1). Recently, we examined three Registries at Fukuoka University (FU) in Japan and identified risk factors for the primary and secondary prevention of atherosclerotic coronary artery disease (CAD): the Quantitative Coronary Angiography (FU-QCA) Registry [3-10], the Coronary Computed Tomography Angiography (FU-CCTA) Registry [11-21], and the Coronary Intravascular Ultrasound (FU-IVUS) Registry [22-27] (Table 2). Here, we review the problems that persist regarding the onset and progression of CVD independent of statin treatment based mainly on our data from these three Registries.

Intensive Lipid-Lowering Therapy

According to the Fourier study, evolocumab, which is a pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, dramatically reduced LDL-C levels (to 30 mg/dL) compared to placebo (to 90 mg/dL) [28]. Evolocumab also significantly suppressed the primary endpoint (CVD events, including CV death, myocardial infarction, stroke, hospitalization for unstable angina and coronary revascularization) compared to placebo. In addition, in patients with a previous acute coronary syndrome who were receiving high-intensity statin therapy (Odyssey Outcomes study), the risk of recurrent ischemic cardiovascular events was lower among patients who received alirocumab (PCSK9 inhibitor) than among those who received placebo [29]. Thus, more intensive reduction of LDL-C after statin treatment is needed to prevent CVD.

FU-QCA Registry

The FU-QCA Registry [3-10] included data on 2,832 patients who underwent percutaneous coronary intervention (PCI): 1,158 of these patients allowed us to conduct a long-term (5 years) follow-up study [9]. QCA was quantified before and after PCI. The endpoint was major adverse cardiac events (major

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Table 1. Residual Risks of Cardiovascular Disease

Insufficient reduction of serum LDL-C levels
Low levels of serum HDL-C and elevated serum TG levels
Insufficient control of other risk factors (high blood pressure, obesity, metabolic syndrome, type 2 diabetes, etc.)

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

Table 2. Summary of Three FU Registries in Japan

Registry name	Chief researcher
FU-QCA Registry: In female patients, HDL-C < 40 mg/dL and LDL-C ≥ 100 mg/dL were more strongly related to MACEs after adjusting for various factors including statin treatment. On the other hand, the combination was not related to MACEs in male patients.	Dr. Ike
FU-CCTA Registry: The number of significantly stenosed coronary vessels significantly increased as the number of metabolic factors increased. Lower levels of HDL-C may be most useful for predicting CAD independent of statin treatment.	Dr. Shiga
FU-IVUS Registry: TG levels may be more important indicators of residual risk after statin treatment in women than in men.	Dr. Iwata

FU: Fukuoka University; QCA: Quantitative Coronary Angiography; LDL-C: low-density lipoprotein cholesterol; MACEs: major adverse cardiac events; CCTA: Coronary Computed Tomography Angiography; HDL-C: high-density lipoprotein cholesterol; CAD: coronary artery disease; IVUS: Coronary Intravascular Ultrasound; TG: triglyceride.

adverse cardiac events (MACEs): all-cause death, myocardial infarction, and target lesion revascularization). Lipid profile and medications were also evaluated. QCA was performed,

and data on the minimum lumen diameter, reference diameters, % diameter stenosis, and lesion length were obtained. Both men and women were divided into four groups according

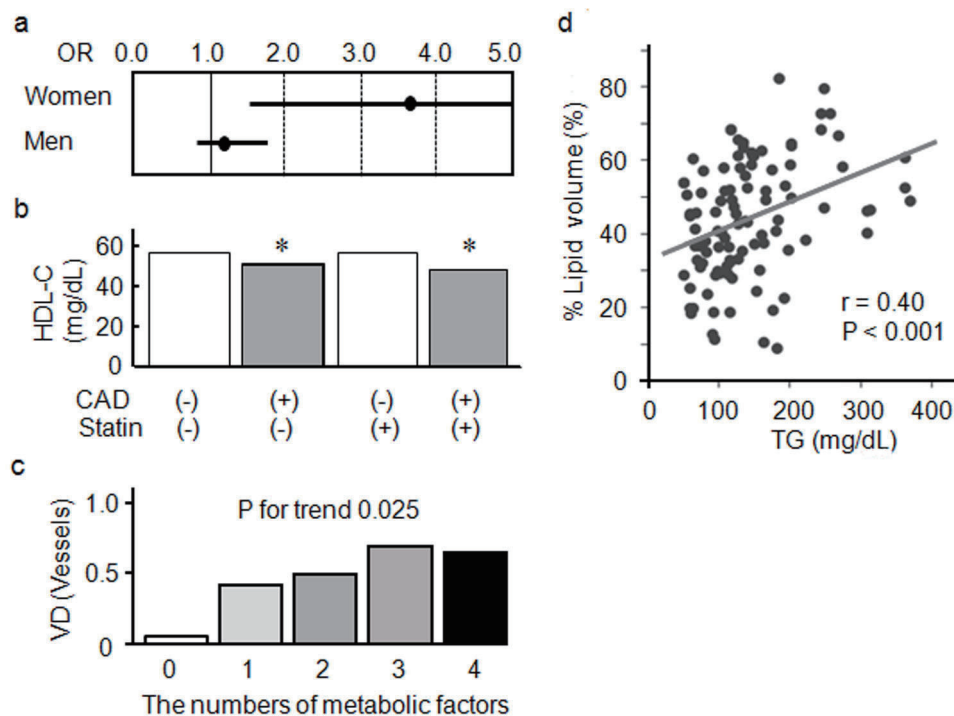


Figure 1. (a) Relationship between combination of HDL-C < 40 mg/dL and LDL-C ≥ 100 mg/dL and major adverse cardiac events after percutaneous coronary intervention. (b) Serum levels of HDL-C in patients with and without CAD in statin (-) and statin (+) groups. *P < 0.05 versus CAD (-). (c) Association between the numbers of significant VD in coronary artery disease. (d) Association between serum levels of TG and % lipid volume in women. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CAD: coronary artery disease; OR: odds ratio; VD: stenosed vessels; TG: triglyceride.

to the levels of HDL-C 40 mg/dL and LDL-C 100 mg/dL. In female patients, HDL-C < 40 mg/dL and LDL-C \geq 100 mg/dL were more strongly related to MACEs after adjusting for various factors including statin treatment (odds ratio (OR): 3.66, coefficient interval (CI): 1.62 - 8.11, $P < 0.001$) (Fig. 1a and Table 2). On the other hand, the combination of LDL-C with HDL-C was not related to MACEs in male patients (OR: 1.19, CI: 0.82 - 1.72, $P = 0.36$).

FU-CCTA Registry

About 1,000 patients who were clinically suspected to have CAD and who underwent CCTA were included in the FU-CCTA Registry [11-21]. The number of significantly stenosed coronary vessels (VD, $\geq 50\%$ coronary stenosis is diagnosed as CAD), and the Gensini score was quantified using CCTA. Lipid profile, adiponectin, pentraxin-3 and high-sensitivity C-reactive protein in blood were also measured. We evaluated coronary arteries using images showing volume-rendering, multi-planar reformation and cross-sectional views by CCTA. Shiga et al reported that serum levels of HDL-C in patients with CAD with and without statin therapy were significantly lower than those in patients without CAD with and without statin therapy (Fig. 1b) [14]. On the other hand, there were no differences in serum levels of LDL-C between patients with and without CAD. According to the results of a comparison of parameters with regard to the presence of CAD, the presence of CAD was independently associated with both age (OR: 1.05, CI: 1.02 - 1.09, $P = 0.003$) and HDL-C (OR: 0.98, CI: 0.96 - 0.99, $P = 0.04$) in patients without statin treatment and with HDL-C (OR: 0.94, CI: 0.91 - 0.98, $P = 0.0007$) in patients with statin treatment. Thus, HDL-C levels are most closely associated with the presence of CAD even after statin treatment. In particular, we need to perform CCTA in suspected CAD patients with lower HDL-C levels under statin treatment (Table 2).

Mitsutake et al analyzed the association between the number of metabolic factors or plasma levels of adiponectin and the number of stenosed vessels in CAD [11]. Metabolic factors were defined as: 1) Visceral fat area ≥ 100 cm²; 2) Serum fasting glucose ≥ 110 mg/dL; 3) Blood pressure $\geq 135/85$ mm Hg; 4) Serum TG ≥ 150 mg/dL; and 5) Serum HDL-C < 40 mg/dL. In five groups classified according to the number of metabolic factors present, plasma adiponectin significantly decreased, whereas the number of stenosed vessels significantly increased as the number of metabolic factors increased (Fig. 1c and Table 2). According to a comparison of parameters based on the number of stenosed vessels by a multivariate logistic regression analysis [11], lower levels of HDL-C in addition to higher levels of LDL-C may be useful for predicting the severity of CAD independent of medications including statin treatment and other metabolic factors such as adiponectin and visceral fat area (Table 2).

FU-IVUS Registry

The FU-IVUS Registry [22-27] included about 400 CAD pa-

tients who underwent PCI using integrated backscatter (IB)-IVUS, and who were already receiving statin treatment. Lipid profiles including fasting serum TG levels were also measured. Gray-scale and IB-IVUS examinations were performed for a 10-mm non-culprit segment of a coronary artery and the images were converted to plaque vulnerability. In both women and men, TG levels were not associated with coronary atheroma volume [26]. Interestingly, TG levels were significantly associated with lipid volume in women, but not in men, after statin treatment (Fig. 1d). Based on a multivariate stepwise regression analysis, TG ($P < 0.001$), DM ($P = 0.04$) and HTN ($P = 0.04$) were independently associated with the percentage of lipid volume in the non-culprit segment of a coronary artery in women. On the other hand, only DM showed a similar association in men ($P = 0.002$). In summary, serum TG levels were associated with lipid-rich coronary plaque in women, but not in men. The TG level may be a more important indicator of residual risk after statin treatment in women than in men (Table 2). There are gender differences in the associated factors.

Conclusions

Major residual risks for CVD include: 1) Insufficient reduction of LDL-C levels; 2) Low levels of HDL-C and elevated TG levels; and 3) Insufficient control of other risk factors. Although an increased number of metabolic factors are associated with more severe CAD, and lower HDL-C induces the onset and progression of CAD, there may be gender differences. A multifaceted preventive approach should be needed to prevent CVD after statin treatment.

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Financial Disclosure

None to declare.

Conflict of Interest

None.

Author Contributions

SM contributed to the conception and design of the work; YS, A Ike and A Iwata contributed to the acquisition, analysis, and interpretation of data for the work; YS, A Ike and A Iwata drafted the manuscript; SM critically revised the manuscript.

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