



Research Letter | Cardiology

Association of Triglyceride Deposit Cardiomyovasculopathy With Drug-Eluting Stent Restenosis Among Patients With Diabetes

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Introduction

Type 2 diabetes remains an independent risk factor for vascular failure even in the setting of advanced medical treatment approaches and technologies for vascular disease, such as percutaneous coronary intervention. Triglyceride deposit cardiomyovasculopathy (TGCV) is a rare cardiovascular disorder caused by defective hydrolysis of intracellular triglycerides and newly encoded as an orphan disease in Europe in 2019 (Orphanet ORPHAcode No. 565612).^{1,2} Orphan diseases are rare diseases that affect only a small number of individuals. TGCV is characterized by diffuse narrowing of the coronary arteries due to atherosclerosis with triglyceride deposits within the endothelial and smooth muscle cells.^{1,2} It is well known that diabetes leads to cellular TG deposition³, and our previous postmortem study revealed that some patients with diabetes who had died of cardiovascular diseases exhibited the TGCV phenotype.⁴ Therefore, we investigated the extent to which a TGCV comorbidity is associated with outcomes after percutaneous coronary intervention in patients with diabetes.

+ Supplemental content

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Methods

This retrospective single-center cohort study included data from the cardiac catheter database at Aichi Medical University Hospital between May 1, 2010, and March 31, 2018. Among 526 consecutive patients with diabetes implanted with second-generation drug-eluting stents (DESs), which are a type of medical device used in percutaneous coronary intervention, data from 81 patients were allocated to either the TGCV group or the control group for subsequent comparative analyses (eFigure and eTable in the [Supplement](#)). The primary end point was a binary in-stent restenosis (ISR) assessed using quantitative coronary angiography. The secondary end points were an in-stent late loss, a parameter used to quantify the degree of neointimal hyperplasia after coronary stenting, a target lesion revascularization, and an evaluation of angiographic ISR morphology. Follow-up coronary angiography was usually performed 8 to 12 months after percutaneous coronary intervention (eMethods in the [Supplement](#)). The study protocol was approved by the ethics committee of Aichi Medical University, and written informed consent was obtained from all patients and their families. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Continuous variables were analyzed using *t* tests and the Mann-Whitney *U* test; categorical data were analyzed using Fisher exact test. In-stent late loss between the 2 groups was compared using analysis of covariance. Univariate and multivariate logistic regression analyses were performed to study the influence of TGCV on outcomes. Statistical significance was set at a 2-tailed *P* value <.05. SPSS Statistics software, version 25.0 (IBM Corp), was used for statistical analyses.

Results

This cohort study included a total of 81 patients: 7 and 74 patients with and without TGCV, each of them having 15 and 111 lesions, respectively. Overall, the mean (SD) age was 66 (11) years; 63 were men (77.8%) and 18 were women (22.2%). Demographics include Asian race/ethnicity: 7 (100%) in

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Table. Patients Characteristics, Lesion Characteristics, and QCA and Restenosis Data^a

Variables	TGCV	Control	P value
Patients characteristics			
No. of patients	7	74	
Men	5 (71)	58 (78)	.65
Age, mean (SD), y	66.3 (12.8)	65.6 (10.6)	.88
Race/ethnicity, Asian	7 (100)	74 (100)	>.99
BMI, mean (SD), kg/m ²	22.9 (3.9)	24.2 (4.0)	.41
BMIPP wash-out, mean (SD), %	2.8 (6.0)	25.9 (10.5)	<.001
Hypertension	6 (86)	40 (54)	.13
Dyslipidemia	6 (86)	49 (66)	.42
Current smoker	2 (29)	25 (34)	>.99
Prior MI	3 (43)	9 (12)	.06
Hemodialysis	2 (29)	5 (7)	.11
Duration of diabetes, median (IQR), y	7 (1-11)	9 (1-13)	.84
HbA _{1c} , mean (SD), %			
Baseline	7.3 (1.8)	7.2 (1.4)	.92
1-y follow-up	6.9 (0.8)	6.9 (1.1)	.98
Insulin	3 (43)	9 (12)	.06
Statin use	6 (86)	71 (96)	.31
DAPT	7 (100)	73 (99)	>.99
P2Y12 inhibitor use	7 (100)	71 (96)	>.99
Lesion characteristics			
No. of lesions	15	111	
Target vessel			
RCA	6 (40)	30 (27)	
LAD	6 (40)	56 (51)	.59
LCX	3 (20)	25 (23)	
ACC/AHA type B2/C	9 (60)	96 (87)	.02
Bifurcation lesion	8 (53)	47 (42)	.58
DES type ^b			
XIENCE	8 (53)	76 (69)	
SYNERGY	0 (0)	14 (13)	
Resolute	1 (7)	9 (8)	.008
Endeavor	5 (33)	4 (4)	
Nobori	1 (7)	4 (4)	
Ultimaster	0 (0)	4 (4)	
Stent			
Diameter, mean (SD), mm	2.88 (0.36)	3.05 (0.42)	.14
Length, median (IQR), mm	18.0 (15.0-23.0)	23.0 (16.0-30.0)	.07
QCA data, mean (SD)			
Lesion length, mm	20.1 (12.8)	20.0 (9.6)	.99
Reference diameter, mm	2.63 (0.62)	2.76 (0.60)	.44
Pre			
MLD, mm	0.76 (0.48)	0.92 (0.46)	.24
%DS, %	69.8 (17.4)	72.9 (19.0)	.58
Post			
MLD, mm	2.61 (0.54)	2.61 (0.46)	.99
%DS, %	3.9 (7.7)	8.2 (10.4)	.12
Follow-up			
MLD, mm	1.41 (0.87)	2.28 (0.68)	<.001
%DS, median (IQR), %	31.0 (10.0-82.0)	13.0 (8.0-21.0)	.02
Duration to follow-up CAG, median (IQR), mo	10.1 (6.6-13.2)	9.1 (7.0-11.0)	.39

(continued)

Table. Patients Characteristics, Lesion Characteristics, and QCA and Restenosis Data^a (continued)

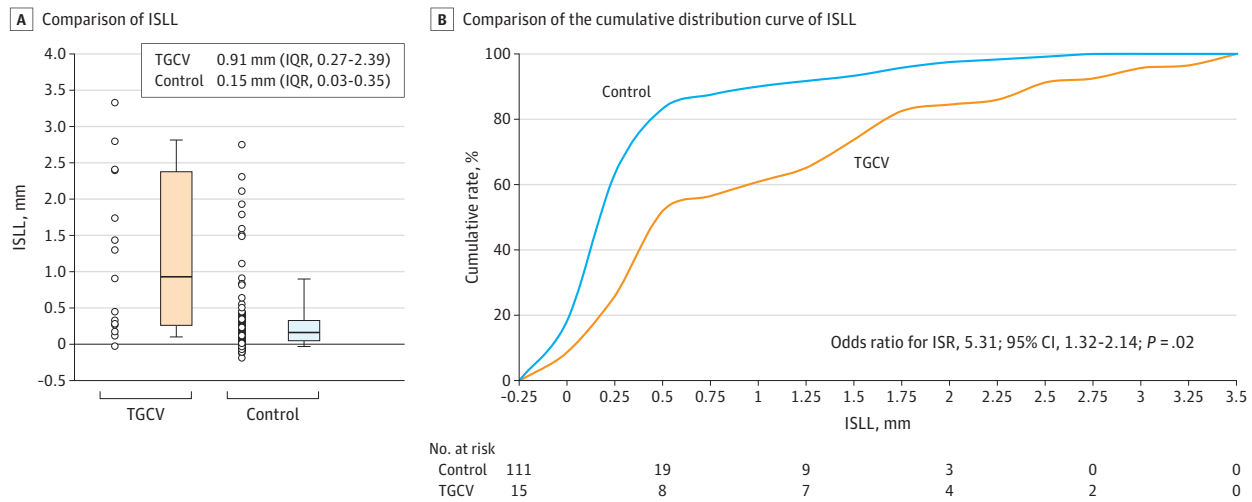
Variables	TGCV	Control	P value
Vascular failure			
ISR	7 (47)	10 (9)	<.001
TLR	5 (33)	7 (6)	.006
Restenosis morphology			
Diffuse or occlusive type	7 (100)	2 (20)	.003

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; BMI, body mass index; BMIPP, ¹²³I-β-methyl iodophenyl-pentadecanoic acid; CAG, coronary angiography; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DS, diameter stenosis; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range; ISR, in-stent restenosis; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; MLD, minimal lumen diameter; QCA, quantitative coronary angiography; RCA, right coronary artery; TGCV, triglyceride deposit cardiomyovascularopathy; TLR, target lesion revascularization.

^a Values are written as No. (%) unless otherwise specified.

^b Manufacturers of the DESs are as follows: XIENCE (Abbott Vascular), SYNERGY (Boston Scientific), Resolute (Medtronic), Endeavor (Medtronic), Nobori (Terumo Corporation), Ultimaster (Terumo Corporation).

Figure. Comparison of ISLL and the Cumulative Distribution Curve of ISLL Between the TGCV and Control Groups



A. ISLL, a parameter determined by caliper measurements using the known diameter of the angiographic catheter as a reference, was significantly higher in the TGCV group than in the control group. B. The cumulative distribution of ISLL revealed a greater value of ISLL in the TGCV group than in the control group. P value was calculated using ANCOVA with the following variables: American College of Cardiology/American Heart Association

classification type B2/C, DES type, and TGCV diagnosis. ANCOVA indicates analysis of covariance; DES, drug-eluting stent; ISLL, in-stent late loss; IQR, interquartile range; ISR, in-stent restenosis; TGCV, triglyceride deposit cardiomyovascularopathy. P < .0001 vs control.

the TGCV group vs 74 (100%) in the control group (P > .99). (Table). In-stent late loss was greater in the TGCV group than in the control group (0.91 mm [interquartile range, 0.27-2.39 mm] vs 0.15 mm [interquartile range, 0.03-0.35 mm]; P < .001) (Figure), with a higher incidence of binary ISR and target lesion revascularization in the former than in the latter group (46.7% vs 9.0% [P < .001] and 33.3% vs 6.3% [P = .006], respectively). Multivariate analysis showed that TGCV was significantly and independently associated with ISR after DES implantation (odds ratio, 5.31; 95% CI, 1.32-21.4; P = .02). Diffuse or occlusive restenosis patterns were more frequent in the TGCV group than in the control group (100.0% vs 20.0%; P = .003).

Discussion

To our knowledge, this is the first study to assess the association of TGCV with 1-year outcomes after second-generation DES implantation. Study results suggest that a higher in-stent late loss at the

1-year follow-up, with a subsequently increased rate of ISR, was observed in the TGCV group than in the control group. Furthermore, TGCV was found to be independently associated with ISR even after adjustment for confounding factors. Diffuse or occlusive restenosis morphology was more frequently observed in the TGCV group than in the control group. The plausible mechanisms for the clinical deficiency of DESs in the setting of TGCV may be associated with an increased amount of inflammatory cytokines and growth factors that are expressed in TGCV mouse models.⁵ Furthermore, mammalian target of rapamycin inhibitors used in DESs might locally affect lipolysis in triglyceride-harboring smooth muscle cells and other vascular cells within the target lesion in TGCV.⁶ This study has several limitations, including potential bias due to the retrospective nature of the analysis and a small number of patients with TGCV resulting in the multivariate analysis being potentially overadjusted.

In conclusion, comorbidity of TGCV with diabetes was associated with an increased incidence of vascular failure. These findings warrant future prospective clinical studies with larger cohorts.

ARTICLE INFORMATION

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Author Contributions: Drs Nakano and Amano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Nakano, Suzuki, Hirano, Ando, Takashima, Takahashi.

Drafting of the manuscript: Nakano, Hirano, Takashima, Amano.

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Statistical analysis: Nakano, Takahashi.

Obtained funding: Nakano, Hirano.

Administrative, technical, or material support: Suzuki, Hirano, Takashima, Amano.

Supervision: Hirano, Ando, Amano.

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Additional Information: Dr Hirano is the principle investigator for the Japan Triglyceride Deposit Cardiomyovascularopathy study group.

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SUPPLEMENT.

eMethods. Supplemental Methodological Descriptions

eFigure. Patient Flow and Informed Consent

eTable. The Diagnostic Criteria for TGCV

eReferences