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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Genetic Backgrounds Associated With Stent Thrombosis

A Pilot Study From a Percutaneous Coronary Intervention Registry

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ABSTRACT

BACKGROUND Stent thrombosis (ST) is a rare, yet devastating, complication following percutaneous coronary intervention (PCI), with poorly understood pathophysiologic characteristics and genetic backgrounds.

OBJECTIVES The authors performed a genome-wide association study to identify the common genetic loci associated with early stent thrombosis (EST) and late/very late ST (LST/VLST) in a contemporary Japanese multicenter PCI registry.

METHODS Among 8,642 PCI patients included in the registry, 42 who experienced stent thrombosis [EST (n = 15) and LST/VLST (n = 27)] were included (mean age, 67.6 ± 10.8 years; and 88.1% men). We conducted a genome-wide association study using the BioBank Japan patient population as the control (control #1: acute coronary syndrome [n = 29,542] and control #2: effort angina [n = 8,900]) to identify significant single nucleotide polymorphisms (SNPs) and evaluate the performance of polygenic risk scores (PRSs) for predicting these conditions.

RESULTS We compared patients with EST with controls #1 and #2 and identified SNPs (rs565401593 and rs561634568) in *NSD1*, and patients with LST/VLST with controls #1 and #2 and identified SNPs (rs532623294 and rs199546342) in *GRIN2A*. PRS for LST/VLST showed high predictive performance (area under the curve 0.83 [95% CI: 0.76-0.89] and 0.83 [95% CI: 0.77-0.89]), whereas PRS for EST showed modest predictive performance (area under the curve 0.71 [95% CI: 0.58-0.85] and 0.72 [95% CI: 0.58-0.85]).

CONCLUSIONS We identified different genetic predispositions between EST and LST/VLST and demonstrated that the incorporation of PRS may aid in risk prediction of this highly fatal event. (JACC Adv 2023;2:100172)
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AUC = area under the curve

CYP2C19 = cytochrome P4502C19

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EA = effort angina

EST = early stent thrombosis

GRIN2A = glutamate ionotropic receptor NMDA type subunit 2A

GWAS = genome-wide association study

KiCS = Keio interhospital cardiovascular Studies

LST = late stent thrombosis

NCBI = National Center for Biotechnology Information

NSD1 = nuclear receptor binding SET domain Protein 1

PCI = percutaneous coronary intervention

PRS = polygenic risk score(s)

SNP = single nucleotide polymorphism

ST = stent thrombosis

VLST = very late stent thrombosis

Stent thrombosis (ST) remains a major concern despite considerably improved outcomes in the field of percutaneous coronary intervention (PCI) for patients with coronary artery disease. ST has become a relatively rare complication owing to the introduction of a newer generation of drug-eluting stents (DES) and novel P2Y12 inhibitors (eg, prasugrel or ticagrelor), occurring in 0.5% to 4% of patients according to recent reports.[1,2] Nevertheless, ST remains a severe complication, with a high mortality rate (40%) and high recurrence rate.[3-5]

Mechanisms and risk factors associated with ST have been investigated, and strong genetic predisposition has been suggested as a risk factor. For example, cytochrome P4502C19 (*CYP2C19*) loss-of-function alleles (*2, *3, *17 alleles), *ABCB1*, and *ITGB3 PLA2*, all of which are involved in clopidogrel metabolism and platelet function, are representative variants associated with ST.[6,7] However, genome-wide analysis to detect common genetic variants associated with ST has not been conducted. Considering that several common genetic variants are identified to be associated with coronary artery disease or myocardial infarction,[8-13] a comprehensive genome-wide analysis to detect common genetic variants associated with ST is warranted.

Additionally, several recent studies have shown that risk factors may vary between early and late ST.[14-16] In early stent thrombosis (EST), procedural factors, such as stent under-expansion, presence of residual coronary dissection, uncovered strut, and malapposition, play an important role,[1] whereas the mechanism of late stent thrombosis (LST)/very late stent thrombosis (VLST) is associated with abnormal vascular response such as a hypersensitivity reaction and neoatherosclerosis, suggesting the involvement of genetic predisposition beyond the clinical and procedural factors.[5,14,16] Given the possible different mechanisms and risk factors between EST and LST/VLST, it is reasonable to assess individual genetic factors associated with ST in each clinical presentation.

Here, we performed a genome-wide association study (GWAS) comparing individuals with EST or LST/VLST and those with acute coronary syndrome (ACS) or effort angina (EA) to identify unique genetic determinants associated with EST and LST/VLST in Japanese patients with coronary artery disease.

METHODS

STUDY POPULATION. Patients with ST were identified from the Keio interhospital Cardiovascular Studies (KiCS) PCI registry, which is a prospective 15-center registry designed to collect clinical variables and outcome data on consecutive patients who undergo PCI, with dedicated clinical research coordinators assigned to each site. The complete list of the investigators and coordinators is provided in the Supplemental Appendix. Approximately 200 variables were collected from each patient. The clinical variables and in-hospital outcomes of patients from the KiCS PCI registry were defined in accordance with the National Cardiovascular Data Registry version 4.1.[17] The present analysis was conducted according to the principles of the Declaration of Helsinki and was approved by each participating hospital's ethics review board.

ADJUDICATION OF STENT THROMBOSIS. For the present study, definite ST was defined on the basis of the Academic Research Consortium definition.[18] As an initial step, patients who underwent PCI for definite ST were screened by 2 authors (M.S. and S.K.). After confirming the diagnosis from abstracted medical records, 132 patients with definite ST were identified, among whom 42 patients were alive, followed at their outpatient clinics at the hospitals that performed the index PCI procedure, and provided written consent for the genetic data analysis.

ST was further categorized according to the time of occurrence of ST: EST (occurring within 30 days from the index procedure), LST (occurring between 31 and 365 days), and VLST (occurring after >1 year).[18] As the VLST group had a minimal number of patients, the LST and VLST groups were combined in our study.

CLINICAL VARIABLE DEFINITION. Chronic total occlusion was indicated if the segment with 100% preprocedure stenosis was presumed to be totally occluded for at least 3 months before the procedure. Type C lesions were defined as diffuse (length >2 cm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.[19] Procedural complications included the following events during the hospitalization: postprocedural myocardial infarction, cardiogenic shock, heart failure, stroke, cardiac tamponade, new requirement for dialysis, cerebral bleeding, coronary dissection, and coronary perforation. Coronary dissection was defined as the appearance of contrast materials outside the expected luminal dimensions of

TABLE 1 Baseline Demographics and Procedural Characteristics in Patients With EST Compared With Patients With LST/VLST

	Total (N = 42)	EST (n = 15)	LST/VLST (n = 27)	*P* Value
Baseline demographics				
Days from stent implantations to the onset of stent thrombosis, d	550 (9 to 2,497)	6 (5 to 9.5)	1979 (760 to 3,330)	<0.001
Age, y	67.6 ± 10.8	66.9 ± 11.0	68.0 ± 10.9	0.732
Female, %	5 (11.9)	3 (20.0)	2 (7.4)	0.478
Body mass index, kg/m^2	24.9 ± 4.9	25.6 ± 4.8	24.7 ± 5.0	0.642
Prior myocardial infarction, %	21 (60.0)	5 (62.5)	16 (59.3)	1.000
Prior PCI, %	33 (94.3)	7 (87.5)	26 (96.3)	0.410
Prior coronary artery bypass grafting, %	3 (8.6)	1 (12.5)	2 (7.4)	0.553
Prior heart failure, %	4 (11.4)	0 (0.0)	4 (14.8)	0.279
Atrial fibrillation, %	3 (10.3)	0 (0.0)	3 (13.0)	0.637
Diabetes mellitus, %	11 (26.2)	1 (6.7)	10 (37.0)	0.387
Creatinine, mg/dL	1.57 ± 2.54	1.83 ± 3.49	1.43 ± 1.89	0.637
Hemoglobin, g/dL	12.0 ± 1.9	11.8 ± 2.2	12.2 ± 1.8	0.543
Hemodialysis, %	1 (2.4)	0 (0.0)	1 (3.7)	1.000
Stroke, %	2 (5.7)	0 (0.0)	2 (7.4)	1.000
Peripheral artery disease, %	1 (2.9)	0 (0.0)	1 (3.7)	0.99
Hypertension, %	25 (71.4)	4 (50.0)	21 (77.8)	0.389
Current smoker, %	13 (37.1)	3 (37.5)	10 (37.0)	1.000
Dyslipidemia, %	24 (68.6)	6 (75.0)	18 (66.7)	1.000
Malignancy, %	1 (3.0)	0 (0.0)	1 (3.8)	0.637
Acute coronary syndrome, %	25 (59.5)	10 (66.7)	15 (65.2)	1.000
Ejection fraction, %	54.3 (11.9)	56.5 (10.5)	53.1 (12.6)	0.375
Lesion data				
ST vessel, %				0.712
Left anterior descending	23 (54.8)	7 (46.7)	16 (59.3)	
Left circumflex coronary	4 (9.5)	2 (13.3)	2 (7.4)	
Right coronary artery	15 (35.7)	6 (40.0)	9 (33.3)	
Type of stents				0.164
Bare metal stent	7 (16.7)	2 (13.3)	5 (18.5)	
Fist-generation DES	7 (16.7)	1 (6.7)	6 (22.2)	
Newer-generation DES	24 (57.1)	12 (80.0)	12 (44.4)	
Unknown	4 (9.5)	0 (0.0)	4 (14.8)	
Stent diameter, mm	3 (2.5 to 3.5)	3 (2.5 to 3.0)	3 (2.5 to 3.5)	0.712
Stent length, mm	19.5 (18.0 to 24.5)	22.0 (18.0 to 27.0)	19.0 (18.0 to 23.0)	0.398
IVUS use, %	29 (69.0)	14 (93.3)	15 (55.6)	0.017
OCT use, %	1 (2.4)	0 (0.0)	1 (3.7)	0.016
Rotablater use, %	2 (4.8)	2 (13.3)	0 (0.0)	0.116
Lesion type				
Type C, %	14 (33.3)	9 (69.2)	5 (26.3)	0.029
Chronic total occlusion, %	2 (4.8)	2 (14.3)	0 (0.0)	0.144
Complications at the index PCI	3 (7.1)	2 (13.3)	1 (3.7)	0.287
Coronary dissection, %	1	1	0	
Post-PCI myocardial infarction, %	1	1	0	
Cerebral bleeding, %	1	0	1	
Major bleeding, %	2	2	0	
Malapposition, %	4 (9.5)	2 (13.3)	2 (7.4)	0.608
Clinical presentation at the time of ST				0.348
STEMI	27 (64.2)	12 (80.0)	15 (55.6)	
NSTEMI/UA	10 (23.8)	2 (13.3)	8 (29.6)	
Effort angina	5 (11.9)	1 (6.7)	4 (14.8)	

Continued on the next page

TABLE 1 Continued

	Total (N = 42)	EST (n = 15)	LST/VLST (n = 27)	*P* Value
Adherence				<0.001
DAPT at the time of ST	22 (52.4)	15 (100.0)	7 (25.9)	
Guideline-recommended DAPT de-escalation	7 (16.7)	0 (0.0)	7 (25.9)	
Discontinuation of APT due to major bleeding	1 (2.4)	0 (0.0)	1 (3.7)	
Discontinuation of APT due to surgery	1 (2.4)	0 (0.0)	1 (3.7)	
Discontinuation of APT due to other reasons	2 (4.8)	0 (0.0)	2 (7.4)	
Discontinuation of APT due to unknown reasons	9 (21.4)	0 (0.0)	9 (33.3)	
Living alone, %	6 (14.3)	3 (20.0)	3 (11.1)	0.543
Dementia, %	1 (2.4)	1 (0.7)	0 (0.0)	0.183

Values are median (IQR), mean ± SD, or n (%).

APT = antiplatelet therapy; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EST = early stent thrombosis; IVUS = intravascular ultrasound; LST = late stent thrombosis; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; VLST = very late stent thrombosis.

the target coronary vessel that caused flow limitations (TIMI flow grade 0-2) of the distal vessels.[20]

CONTROL ARM. All control participants for the genetic analysis were collected from the BioBank Japan (https://biobankjp.org/english/index.html), one of the largest non-European biobanks that collaboratively collects DNA and serum samples from 12 medical institutions in Japan, consisting of approximately 200,000 individuals.[21,22]

The BioBank Japan obtained informed consent from all participants and approved an application for access to and use of the data by the Sample and Data Access Committee (approval number: P0102). Ethical approval for the analysis was obtained from the Institutional Review Board of Tsukuba International Clinical Pharmacology Clinic, Japan (approval number: 0020). The control arm consisted of patients with ACS (control #1; n = 29,542) and those with EA (control #2; n = 8,900). The definitions of these diagnoses were described in the design paper of BioBank Japan; briefly, these were based on the diagnoses of attending physicians at cooperating hospitals.[21]

GENOTYPING AND QUALITY CONTROL OF SAMPLES. All genetic tests were performed with informed consent from the patients after genetic counseling. After obtaining written informed consent, genomic DNA was isolated from the peripheral white blood cells of each patient. Samples in the case group were genotyped using the Infinium Asian Screening Array-24 v1.0 BeadChip (Illumina Inc, GRCh 37), whereas the control group was genotyped using the Illumina Infinium OmniExpressExome-8 v1.0, Illumina Infinium OmniExpressExome-8 v1.2, and Illumina HumanOmniExpress-12 v1.0. (Illumina Inc).[23] This genotyping array was generated in accordance with the East Asian reference panel that includes whole-genome sequencing, allowing efficient genotyping in East Asian populations.[13,24]

All samples met the manufacturer's quality control criteria (sample call rate ≥97%) and were not in close genetic relationship (PI_HAT calculated by PLINK37 >0.1875). Single nucleotide polymorphisms (SNPs) used to evaluate the quality control of samples fulfilled the following criteria: 1) call rate ≥95%; 2) *P* value obtained by the goodness-of fit test for Hardy-Weinberg equilibrium $\geq 1.0 \times 10^{-3}$; and 3) minor allele frequency ≥0.01.

SNP GENOTYPE IMPUTATION. Haplotype phasing was conducted using EAGLE v2.4.1 (alkesgroup.broadinstitute.org/Eagle/) as a pre-phasing for the genotype imputation after SNP filtering. Next, we used Minimac3 software40 for genotype imputation.[25] As an imputation reference, we used the reference haplotypes of 1000 Genomes Project Phase 3 version 5 genotype (n = 2,504), which were recently constructed and validated for imputation accuracy.[26] Finally, after the imputation, we excluded variants with an imputation quality of Rsq <0.3 and minor allele frequency <0.01.

STATISTICAL ANALYSIS. GWAS and regional plotting. A genome-wide association test for the initial screening of potential candidate SNP markers of ST was applied to the imputed SNPs. We performed GWAS using multivariable logistic regression with the Efficient and Parallelizable Association Container Toolbox (EPACTS). Age, sex, body mass index, creatinine, hemoglobin, and top 10 principal components were used as covariates.[27] Population structure can occasionally cause confounding in GWAS, and it is addressed by including principal components as covariates. As for our analysis, we used the top 10 principal components to adjust for population stratification as

recommended by previous studies.[28-30] SNPs with $P < 5.0 \times 10^{-8}$ were used in the subsequent analyses as candidate SNPs. A value of $P < 1.0 \times 10^{-6}$ was considered "suggestive significance threshold," to avoid losing potential candidates with an estimated P of no less than GWAS significance (5.0×10^{-8}), considering the sample size of this study. The Manhattan plots and QQ-plots were drawn using R 3.6.3, whereas regional plots were drawn using LocusZoom Version 1.4. Meta-analysis was performed using the inverse-variance method.[31,32]

Gene-wise analysis. We evaluated gene-level associations and calculated the polygenic score for each gene region using the SNP-set (Sequence) Kernal Association Test (SKAT)-O.[33-35] Statistical significance was set at 2.5×10^{-6} for the SKAT-O test.

Polygenic risk score (PRS) calculation. We used PRSice (https://choishingwan.github.io/PRSice/) to calculate PRS. Briefly, trait-specific weights (beta's for continuous traits and the log of the odds ratios [ORs] for binary traits) were obtained from GWAS. In the target sample, PRS was calculated for each individual based on the weighted sum of the number of risk alleles that the individual carries multiplied by the trait-specific weights. All SNPs of the candidate genes (registered in RefGene database [http://varianttools.sourceforge.net/Annotation/RefGene]) were used for the calculation of PRS. The performance of PRS was examined by measuring the area under the curve (AUC) to assess discrimination.

Evaluation of candidate SNPs and gene features. We searched NCBI dbSNP (https://www.ncbi.nlm.nih.gov/snp/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) databases to evaluate the contribution of the candidate SNPs to ST. Gene features were identified using the NCBI Gene (https://www.ncbi.nlm.nih.gov/gene) database.

RESULTS

STUDY POPULATION (PATIENTS WITH ST EXTRACTED FROM KiCS PCI). In the present analysis, 42 patients with ST [EST (n = 15, 35.7%) and LST/VLST (n = 27, 64.3%)] who consented for the genetic data analysis among those in the KiCS PCI registry were studied. The mean ± standard deviation in age was 67.6 ± 10.8 years, and 88.1% were men. Table 1 lists the baseline demographics and procedural characteristics in patients with EST compared with those in patients with LST/VLST.

There were no significant differences between the EST and LST/VLST groups in terms of baseline patient demographics. Angiographically, patients with EST had higher complex lesions (eg, type C lesions, 69.2% vs 26.3%, $P = 0.029$) and procedure-related complications after PCI (13.3% vs 3.7%, $P = 0.287$) than patients with LST/VLST. The status of antiplatelet therapy at the time of ST is also shown in Table 1. All patients with EST were receiving dual antiplatelet therapy (DAPT) at the time of ST.

In comparison, patients with LST/VLST presented higher use of first-generation DES than patients with EST. Among 27 patients with LST/VLST, 7 received DAPT (all patients were receiving aspirin plus clopidogrel), 7 received guideline-recommended single antiplatelet therapy, whereas the remaining 13 had discontinued antiplatelet therapy at the time of ST (1 patient due to major bleeding, 1 due to surgery, and 2 due to other relevant clinical reasons [for the remaining 9 patients, the reason for discontinuation of antiplatelet therapy was unclear]).

TABLE 2 Clinical Characteristics of Control Group Participants With Acute Coronary Syndrome and Effort Angina

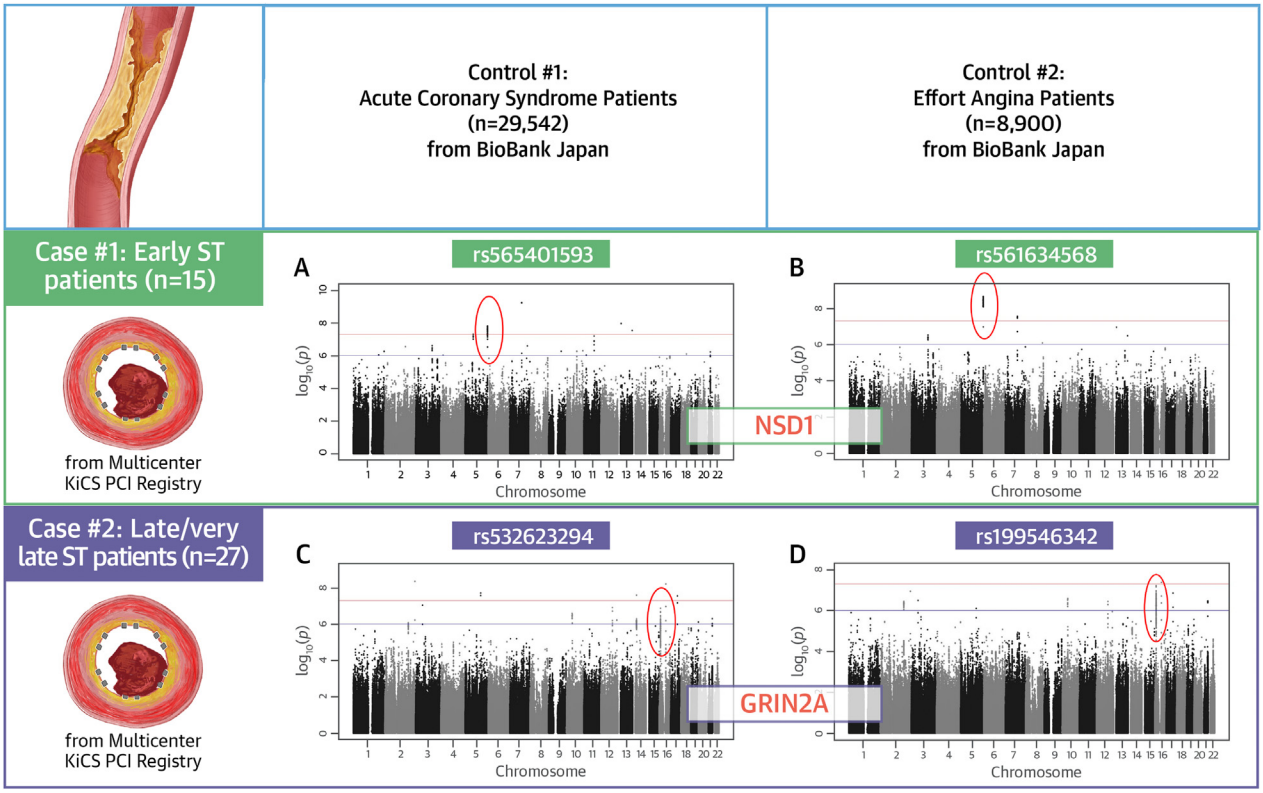
	ACS (n = 29,542)	EA (n = 8,900)
Female, %	7,794 (26.4)	2,427 (27.3)
Age, y	67.8 ± 10.1	68.9 ± 9.5
Body mass index, kg/m^2	23.8 ± 3.3	23.9 ± 3.3
Creatinine, mg/dL	0.88 ± 0.23	0.88 ± 0.23
eGFR, mL/min/1.73 m^2	67.5 ± 14.9	66.6 ± 14.4
Hemoglobin, g/dL	13.6 ± 1.7	13.6 ± 1.7
Ejection fraction, %	60.7 ± 13.2	63.0 ± 12.2
Systolic blood pressure, mm Hg	141 ± 18.0	143 ± 18.0
Diastolic blood pressure, mm Hg	82 ± 11.3	82 ± 11.4
HbA1c (NGSP), %	5.5 ± 0.6	5.5 ± 0.6
Sodium, mEq/L	141 ± 2.6	141 ± 2.7
Potassium, mEq/L	4.27 ± 0.42	4.27 ± 0.41
HDL-C, mg/dL	50.4 ± 13.8	50.5 ± 13.5
LDL-C, mg/dL	130 ± 39.3	131 ± 39.2
Albumin, g/dL	4.2 ± 0.41	4.2 ± 0.40
CK, U/L	105 ± 56.1	105 ± 54.8
CRP, mg/dL	0.25 ± 0.27	0.24 ± 0.26
WBC, μL	6,264 ± 1,738	6,110 ± 1,633
Platelet, 10^4/μL	21.7 ± 6.2	21.1 ± 5.9

Values are n (%) or mean ± SD.

ACS = acute coronary syndrome; CK = creatine kinase; CRP = c-reactive protein; EA = effort angina; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NGSP = National Glycohemoglobin Standardization Program; WBC = white blood cell.

STUDY POPULATION (CONTROL PATIENTS EXTRACTED FROM BioBank JAPAN). Table 2 lists the clinical characteristics of the control group participants with ACS (n = 29,542) and EA (n = 8,900) that were extracted from the BioBank Japan database. The mean in age was 67.8 ± 10.1 years and 68.9 ± 9.5 years, and 73.6% and 72.7% were men in the ACS and EA groups, respectively. Overall,

CENTRAL ILLUSTRATION **Genome-Wide Association Study Investigating Genetic Backgrounds of Stent Thrombosis**



Shoji S, et al. JACC Adv. 2023;2(1):100172.

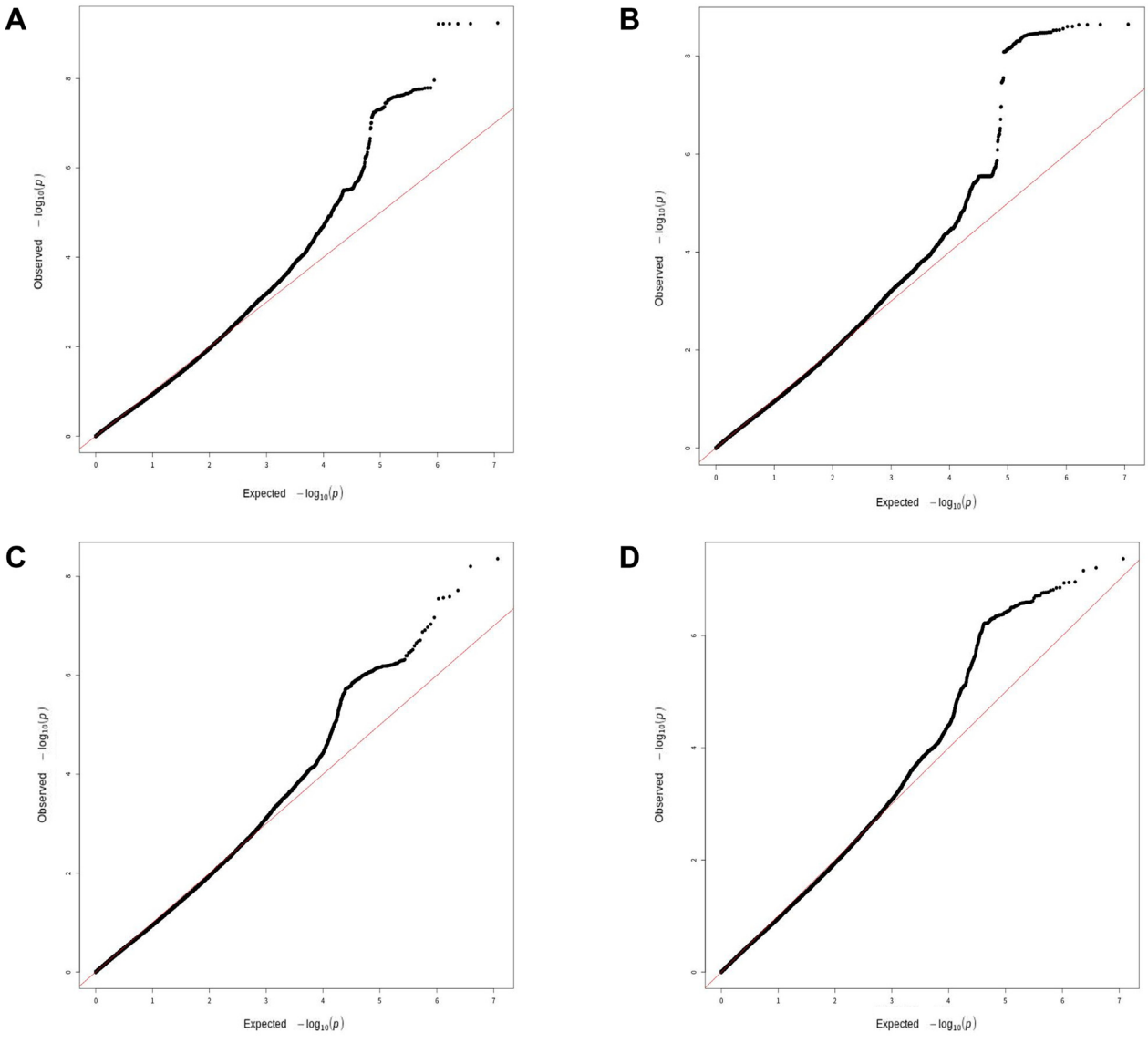
In a genome-wide association study (GWAS), we compared patients with early stent thrombosis (EST) (n = 15 from the KiCS PCI registry) with controls #1 **(A)** and #2 **(B)**, and identified significant single nucleotide polymorphisms (SNPs) [rs565401593 and rs561634568] in *NSD1*, and compared patients with late/very late stent thrombosis (LST/VLST) (n = 27 from the KiCS PCI registry) with controls #1 **(C)** and #2 **(D)**, and identified significant SNPs [rs532623294 and rs199546342] in *GRIN2A*. Control #1: acute coronary syndrome (n = 29,542), Control #2: effort angina (n = 8,900) from BioBank Japan. The x-axis represents chromosomal positions and the y-axis represents $\log_{10} P$ values. The **red horizontal lines** indicate a statistically significant level at $P < 5.0 \times 10^{-8}$ and the **blue horizontal lines** indicate a suggestive significance threshold considered as $P < 1.0 \times 10^{-6}$. KiCS = Keio interhospital cardiovascular Studies; PCI = percutaneous coronary intervention.

creatinine, hemoglobin, and ejection fractions in each group were 0.88 ± 0.23 and 0.88 ± 0.23, 13.6 ± 1.7 and 13.6 ± 1.7, and 60.7 ± 13.2 and 63.0 ± 12.2 in patients with ACS and EA, respectively.

GENOME-WIDE ASSOCIATION STUDY. The results of the GWAS are summarized in **Central Illustration** (Manhattan plot) and **Table 3**. QQ-plots of the genome-wide association are shown in **Figure 1**. The GWAS comparing patients with EST with controls #1 and #2 revealed significant SNPs (rs565401593 [Chr5:176613030_AT/A: OR 194.5, 95% CI: 31.2-1,210, $P = 1.61 \times 10^{-8}$] and rs561634568 [Chr5:176672977_T/A OR 210.0, 95% CI: 36.4-1,211, $P = 2.23 \times 10^{-9}$]) in *NSD1* (**Central Illustration A and B**, **Figures 2A and 2B**). All SNPs that reached genome-wide significance are summarized as potential candidates in Supplemental Tables 1 and 2. In a gene-wise analysis, *NSD1* variants were significantly associated with the occurrence of EST when patients with EST were compared with control #1 ($P = 1.58 \times 10^{-14}$) and control #2 ($P = 1.44 \times 10^{-21}$).

The GWAS comparing patients with LST/VLST with controls #1 and #2 revealed significant SNPs (rs532623294 [Chr16:9991046_A/T: OR 46.0, 95% CI 11.1-191.0, $P = 1.33 \times 10^{-7}$] and rs199546342 [Chr16: 9995088 CTT/C: OR 61.6, 95% CI 13.8-274.0, $P = 6.13 \times 10^{-8}$]) in *GRIN2A* (**Central Illustration C and D**, **Figures 2C and 2D**). All SNPs that reached genome-wide significance are summarized as potential candidates in Supplemental Tables 3 and 4. In a gene-wise analysis, *GRIN2A* variants were

FIGURE 1 Quantile-Quantile Plot of the Genome-wide Association



(A) Comparison between the patients with early stent thrombosis (EST) and those with acute coronary syndrome (ACS). **(B)** Comparison between the patients with EST and those with effort angina (EA). **(C)** Comparison between the patients with late ST/very late ST (LST/VLST) and those with ACS. **(D)** Comparison between the patients with LST/VLST and those with EA.

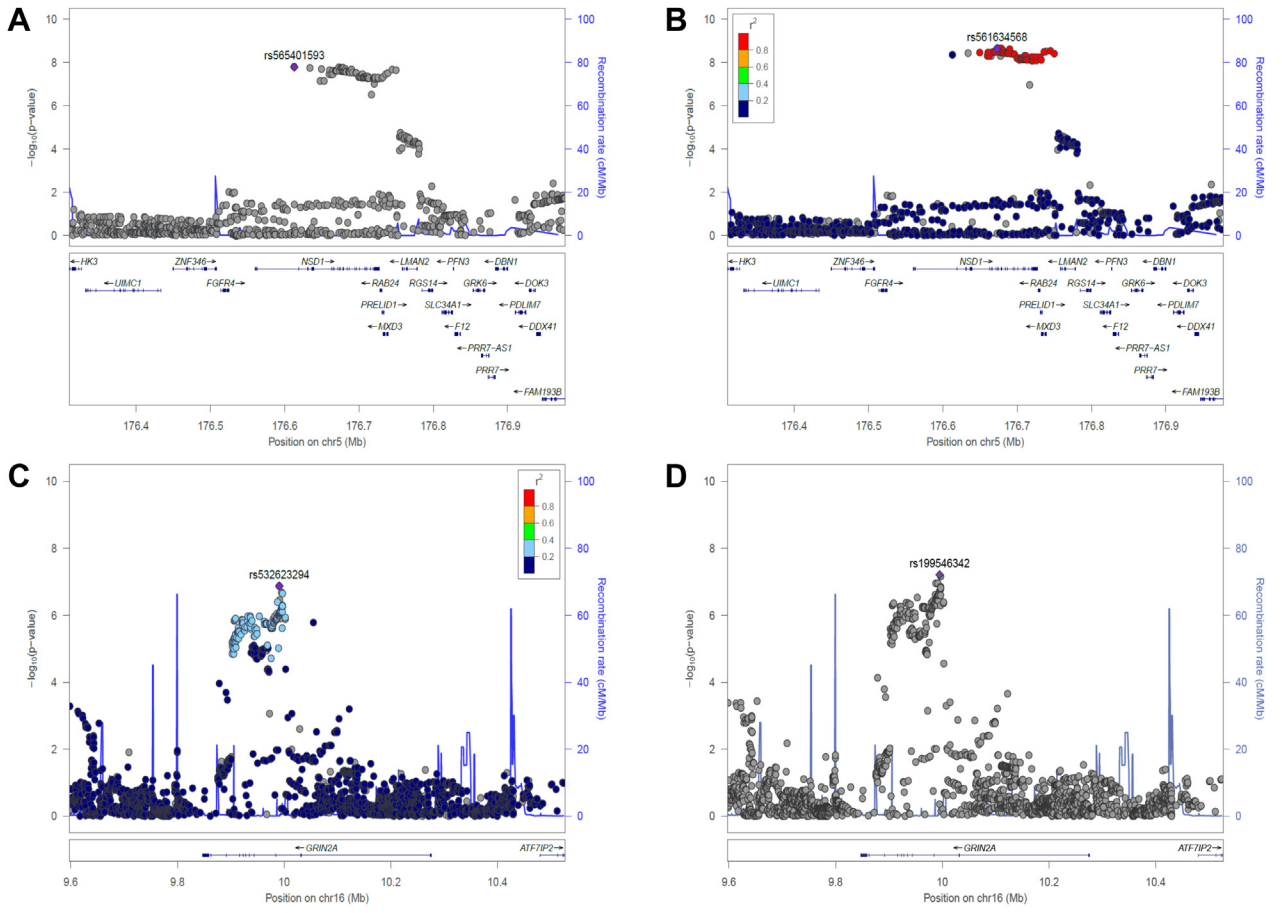
significantly associated with the occurrence of LST/VLST when patients with LST/VLST were compared with control #1 ($P = 7.04 \times 10^{-5}$) and control #2 ($P = 5.33 \times 10^{-6}$).

Finally, PRS for LST/VLST showed higher predictive performance (AUC 0.83 [95% CI: 0.76-0.89] and 0.83 [95% CI: 0.77-0.89]) (Figures 3C and 3D), whereas PRS for EST showed modest predictive performance (AUC 0.71 [95% CI: 0.58-0.85] and 0.72 [95% CI: 0.58-0.85]) (Figures 3A and 3B).

DISCUSSION

ST is a rare, but severe, complication that can occur after implanting stents during PCI. There are multifactorial factors associated with the occurrence of ST, ranging from lesion severity, stent type (especially first-generation DES), procedural technique (malapposition or procedural complication), patient characteristics (diabetes, obesity, chronic kidney disease, and stroke), adherence to antiplatelet

FIGURE 2 Regional Plots of the Lead Single Nucleotide Polymorphisms

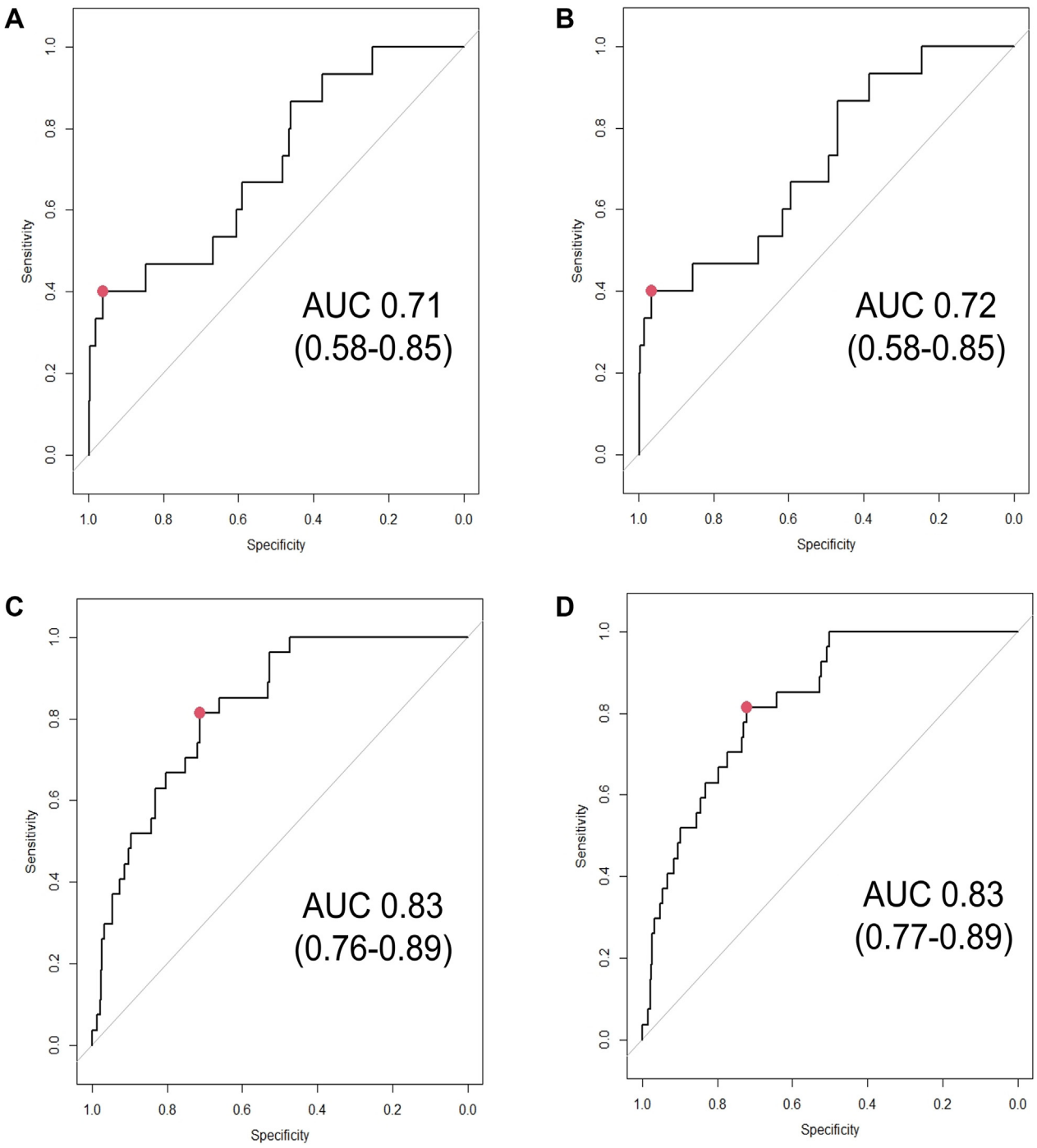


Association signals around the novel sentinel variants [**(A)** rs565401593, **(B)** rs561634568, **(C)** rs532623294, and **(D)** rs199546342] in regional plots after comparing **(A)** Patients with early stent thrombosis (EST) and those with acute coronary syndrome (ACS); **(B)** Patients with EST and those with effort angina (EA); **(C)** Patients with late ST/very late ST (LST/VLST) and those with ACS; **(D)** Patients with LST/VLST and those with EA. The x-axis represents chromosomal positions around the novel sentinel variant, and the y-axis represents $\log_{10}$ *P* values. The strongest signal in this locus is shown in **purple**. The dot color for a variant represents the degree of linkage disequilibrium (R2) estimates between each variant and the novel sentinel variant. GRIN2A = glutamate ionotropic receptor NMDA type subunit 2A; NSD1 = nuclear receptor binding SET domain protein 1.

therapy, and genetic factors. Additionally, considering the possible different mechanisms and risk factors between EST and LST/VLST, it is reasonable to assess individual clinical and genetic factors associated with ST in each clinical presentation. Therefore, we conducted comprehensive analyses to detect unique factors associated with EST and LST/VLST. The main findings of our study are as follows: 1) clinically, patients with EST had higher complex lesions and procedure-related complications than patients with LST/VLST; 2) patients with LST/VLST presented higher use of first-generation DES and lower adherence to antiplatelet therapy than patients with EST; 3) *NSD1* for EST and *GRIN2A* for LST/VLST were identified as susceptibility markers; and 4) PRS (especially for LST/VLST) could provide novel risk stratification information. Our findings suggest that the involvement of clinical factors and genetic predisposition between early and LST/VLST may vary.

Previous studies on genetic factors associated with ST have been primarily focused on mutations involved in antiplatelet metabolic pathways and high on-treatment platelet reactivity.[36,37] Renowned genetic variants include *CYP2C19* loss-of-function alleles (*2, *3, *17 alleles), *ABCB1*, and *ITGB3 PLA2*, all of which are involved in the conversion of clopidogrel to its active metabolite.[6,7] Prasugrel is metabolized to its active metabolite primarily by CYP3A5 and CYP2B6, and to a less extent by CYP2C9 and CYP2C19.[38]

FIGURE 3 **Receiver Operator Characteristic Curves for Polygenic Risk Scores for Patients With Stent Thrombosis**



(A) Comparison between patients with early stent thrombosis (EST) and those with acute coronary syndrome (ACS). **(B)** Comparison between the patients with EST and those with effort angina (EA). **(C)** Comparison between the patients with late ST/very late ST (LST/VLST) and those with ACS. **(D)** Comparison between the patients with LST/VLST and those with EA. Area under the curve (AUC) with 95% CI are shown.

TABLE 3 Summary of New Loci Identified in This Genome-Wide Association Study

GWAS	Chr.	Position (GRCh37)	REF	ALT	Gene	Lead SNP	MAF	OR	95% Lower CI	95% Upper CI	*P* Value
EST vs ACS	5	176,613,030	AT	A	Deletion: NSD1	rs565401593	0.013629	194.5132	31.2481	1210.8075	1.61E-08
EST vs EA	5	176,672,977	T	A	Intron: NSD1	rs561634568	0.011982	209.9984	36.3963	1211.6423	2.23E-09
LST/VLST vs ACS	16	9,991,046	A	T	Intron: GRIN2A	rs532623294	0.022413	46.0027	11.0895	190.8342	1.33E-07
LST/VLST vs EA	16	9,995,088	CTT	C	Deletion: GRIN2A	rs199546342	0.013761	61.6147	13.8638	273.8331	6.13E-08

ACS = acute coronary syndrome; ALT = alternative allele; Chr = chromosome; EA = effort angina; EST = early stent thrombosis; GWAS = genome-wide association study; GRCh 37 = Genome Reference Consortium Human Build 37; LST/VLST = late/very late stent thrombosis; MAF = minor-allele frequency; OR = odds ratio; REF = reference allele; SNP = single nucleotide polymorphism.

Although both clopidogrel and prasugrel are prodrugs, clopidogrel is bioactivated primarily by CYP2C19 and is therefore less effective in patients with decreased or no function variant alleles in *CYP2C19*. Among patients with ACS, the POPular Genetics (Patient Outcome after Primary PCI) trial has demonstrated noninferiority of the genotype-based antiplatelet selection strategy over standard care with respect to thrombotic events and lower incidence of bleeding, suggesting the utility of genotype-guided P2Y12 inhibitor selection strategy to prevent ischemic events including ST.[39] In contrast, our study is unique in terms of identifying common genetic variants not involved in the antiplatelet metabolic pathways, and provides further evidence and insights into a possible genetic mechanism of EST and LST/VLST to further understand the causes of ST.

To the best of our knowledge, this study is the first to show that polymorphisms located within *NSD1* were associated with EST, whereas polymorphisms located within *GRIN2A* were associated with LST/VLST. *NSD1* knockout in a mouse model increased the levels of H3K27me3 and reduced those of H3K36me2, thereby inhibiting Wnt10b expression. These results suggest that inactivation of the Wnt/β-catenin signaling pathway inhibits the proliferation, migration, and invasion of human cells.[40,41] Accordingly, *NSD1* variants could affect DNA methylation, resulting in abnormal proliferation of endothelial cells and platelet aggregation. Flow disturbance, especially the occurrence of non-streamlined flow along the malapposed stent struts, is highly relevant to acute thrombogenicity.[14,42,43] Taken together, patients with genetic factors, who are more prone to abnormal cell proliferation and platelet aggregation, may be prone to ST, superimposed by abnormalities in blood flow by stent under-expansion, residual coronary dissection, or malapposition.[15] *GRIN2A* is a member of the glutamate-gated ion channel protein family that forms N-methyl-D-aspartate receptor (NMDAR) subunits[44] that create ion channels in the cell membrane that allow the influx or efflux of cations, such as Ca^{2+}, which are important for synaptic transmissions, cellular migration, and survival. *GRIN2A* mutations increased NMDR-mediated Ca^{2+} responses and enhanced cell proliferation and invasiveness, thereby contributing to the oncogenic effects in melanomas.[45] Previous studies on the mechanisms of ST using intravascular ultrasound and optical coherence tomography have demonstrated that advanced neoatherosclerosis with neointimal rupture could be critical risk factors for ST in both DES and bare metal stent.[14,46-49] Accordingly, the proliferation and invasion functions of *GRIN2A* may cause neointimal proliferation and neoatherosclerosis in stents, possibly leading to thrombus formation. Further analysis is required to corroborate our findings and clarify the association of our newly identified genetic variants and incidence of ST in other cohorts with different ethnicities.

Prior studies have shown that different factors contributed to the occurrence of ST according to the timing after stent implantation. For the EST events, technical aspects, such as incomplete stent expansion, serves as a strong contributing factor. A measured stent area of <4.5 mm^2 with optical coherence tomography or <5.5 mm^2 with intravascular ultrasonography reflects incomplete stent expansion and is associated with ST, showing a larger effect on early events (EST).[50,51] Similarly, during the late phase, clinical and procedure-related factors were attributed to the incidence of ST; for example, a history of malignancy is strongly associated with the occurrence of LST.[1] Stent strut malapposition, especially "late acquired malapposition" caused by positive remodeling of stent-implanted vessels, has been reported as a leading mechanism underlying LST.[52] In addition to clinical factors, regarding the incidence of LST, genetic factors may play a crucial role; in the DESERT (International Drug-Eluting Stent Event Registry of Thrombosis) registry, African-American ethnicity has been shown to correlate with LST.[53] Our study has expanded these prior works and shown that different genetic variants are associated

with the occurrence of ST depending on the time of occurrence of ST after PCI, and demonstrated that the influence of genetic variants might be more prominent for LST/VLST than for EST. These findings could be the basis of future genetic research in the field of ST.

STUDY LIMITATIONS. First, owing to the necessity of informed consent for the genetic analysis, patients who died of ST and could not consent for the study were not included, which might have caused selection bias. Furthermore, despite the multicenter collaborative patient recruitment strategy over 8 years with a clear diagnostic criterion, the stringent enrollment process led to a relatively small number of cases, which could have led to underestimation of the differences in the effect size in loci related to ST. A larger sample will be required in the future. Nevertheless, it is of clinical importance that the genomic associations were obtained in our study. The precise mechanisms of the relationship between the genetic variants and the occurrence of ST remain unknown, but there are potential explanations for this: 1) number of participants in the control arm was relatively large; 2) the participants included in case and controls are homogeneous (Japanese); 3) patients with ST in our study were accurately adjudicated by the KiCS PCI event committee; and 4) genetic variants that were newly identified in our analysis could be more influential in terms of the incidence of ST than the CYP2C19-related genes. The HOST-EXAM trial showed that clopidogrel monotherapy is superior to aspirin monotherapy as chronic maintenance therapy among patients who had successfully completed the required duration of DAPT therapy post-DES PCI.[54] Moreover, the trial was conducted in South Korea, where CYP2C19 loss-of-function genetic variants are common, yet high efficacy of clopidogrel was observed. This finding suggests that the effect of CYP2C19 loss-of-function genetic variants on ST occurrence is relatively small, whereas other genetic variants such as those identified in our study might play a more important role among the Asian population. Second, noncoding variants can regulate one or more genes across long genomic distances, and the same allele or multiple alleles within a haplotype might have context-specific functions or function in different cell types.[55] There is a possibility for pleiotropic regulation of multiple genes and multiple cell types at the *NSD1*/*GRIN2A* locus; hence, evaluation of multiple variants, candidate genes, and cell types is critical to assess causality and determine how those variants might converge on phenotypes that contribute to the occurrence of EST or LST/VLST. Third, we could not identify patients with ST in the control arm due to the lack of information about ST in the BioBank Japan. However, given the extremely low incidence of ST, almost all patients in the control arm could be approximated as patients receiving a stent but remained free of ST. Fourth, the performance of PRS should be ideally evaluated using different validation cohorts. However, this was challenging in this study, as ST, although associated with high mortality, is encountered rather infrequently. Thus, we used all samples in one-stage GWAS to maximize the statistical power. Finally, as this was a pilot study involving a GWAS, further in vivo and in vitro research such as whole-genome sequencing are needed to understand the causal relationship between these promising common genetic variants and the occurrence of ST. However, considering the limited treatment strategies and poor clinical outcomes of ST, our findings may have a potential clinical application via gene-guided risk stratification of patients undergoing PCI.

CONCLUSIONS

Patients with EST had higher complex lesions and procedure-related complications than patients with LST/VLST, whereas patients with LST/VLST presented higher use of first-generation DES and lower adherence to antiplatelet therapy than those with EST. Furthermore, we identified new genetic susceptibility markers in EST and LST/VLST using GWAS. The PRS, especially for LST/VLST, could provide novel risk stratification information. Differences in clinical and genetic factors, which are dependent on the time of occurrence of ST, suggest possible differences in the mechanism of ST based on the time of ST occurrence, which further encourages well-designed future studies on the clinical and genetic factors associated with the occurrence of ST.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Genome-wide association study of demonstrated that polymorphisms located within *NSD1* were associated with EST, whereas polymorphisms located within *GRIN2A* were associated with LST/VLST. Furthermore, PRS for LST/VLST showed higher predictive performance than those for EST.

TRANSLATIONAL OUTLOOK: Our study identified different genetic predispositions between EST and LST/VLST and provided evidence that PRS may aid in the risk prediction of ST.

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KEY WORDS **early stent thrombosis, genome-wide association study, late stent thrombosis, percutaneous coronary intervention, polygenic risk score, single nucleotide polymorphism**

APPENDIX **For a list of the JCD-KiCS study site investigators and clinical coordinators as well as supplemental tables, please see the online version of this paper.**