

# Angina Severity at the Time of Revascularization in Patients With Diabetes Mellitus and Its Association With Long-term Outcomes: A Multicenter Cohort Study.

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## Original investigation

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# Abstract

**Background:** While angina severity is pertinent in determining the management strategy for patients with stable ischemic heart disease (SIHD), its contributing factors and prognostic effect remain unclear, particularly in patients with diabetes mellitus (DM).

**Methods:** From a multicenter percutaneous coronary intervention (PCI) registry, 1,911 consecutive SIHD patients without previous revascularization or heart failure between 2008 and 2015 were analyzed. Angina severity was assessed by the Canadian Cardiovascular Society (CCS) functional classification at the time of PCI. We assessed the contributing factors of CCS III/IV angina. Further, the association between CCS III/IV angina and subsequent occurrence of major adverse cardiac and cerebrovascular events (MACCE: all-cause death, acute coronary syndrome, heart failure, and stroke) within 2 years were analyzed in patients with DM and without DM.

**Results:** A total of 771 SIHD patients (40.3% of all SIHD patients) had DM at the time of revascularization. In the total cohort, 52.4% had CCS I/II, and 13.0% had CCS III/IV angina, with less prevalence of CCS III/IV angina in patients with DM than in those without DM (11.3% vs. 14.2%,  $P < 0.001$ ). In patients with DM, the prevalence of unprotected left main coronary trunk lesions and proximal left anterior descending lesion increased with angina severity. The presence of severe angina at the time of PCI was associated with MACCE in patients with DM (adjusted hazard ratio 1.93; [95% CI 1.01, 3.71];  $P = 0.047$ ), while no significant difference in those without DM (adjusted hazard ratio 0.82; [95% CI 0.42, 1.59];  $P = 0.55$ ).

**Conclusions:** In SIHD patients with DM that underwent PCI, severe angina at the time of revascularization was associated with complex coronary anatomies and long-term outcomes. These findings underscore the importance of evaluating angina-related health status while considering revascularization in SIHD patients with DM.

## Background

The prevalence of diabetes mellitus (DM) is increasing globally and has become a leading cause of death in developed countries.[1] Furthermore, approximately 40% of patients with stable ischemic heart disease (SIHD) who undergo revascularization have DM.[2] Despite comprehensive cardiovascular risk reduction strategies in patients with SIHD, the number of patients with concomitant DM has recently increased, with the incidence of major adverse cardiac and cerebrovascular events (MACCE) being higher in these patients than in those without DM,[3, 4] even with successful percutaneous coronary intervention (PCI).[5] These findings suggest that further risk stratification is required to improve the care and outcomes of SIHD patients with DM.

Measurement of patients' symptom severity is increasingly becoming a pertinent component of tailoring the management strategy for SIHD and has been reported to have potential prognostic utility.[6] However, little is known with regard to its distribution at the point of revascularization or its association with post-revascularization outcomes in the contemporary era. This is partly due to the exclusion of patients with severe or unacceptable level of angina from clinical trials. In fact, of the participants in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, only 21.1% had Canadian Cardiovascular Society (CCS) class III angina and patients with class IV were excluded.[7] Similarly, in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, 95.6% of the patients had CCS class II angina or less despite the fact that most participants had moderate to severe inducible myocardial ischemia.[8] Hence, observational studies with less-stringent inclusion criteria may provide a more realistic assessment of the distribution and severity of angina in the community, especially for severe angina, such as CCS III or IV.

This study aimed to describe 1) the association of the incidence of MACCE with DM status, 2) distribution of and contributing factors for severe angina stratified by DM status, and 3) association of angina severity with the incidence of major adverse cardiac events in SIHD patients stratified by the presence of DM. Angina severity at the point of

revascularization is almost universally available, and its association with long-term prognoses would be directly applicable for risk stratification in daily practice and future studies.

## Methods

### Study design

The Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies (JCD-KiCS), a large, ongoing, prospective, multicenter PCI registry developed in collaboration with the National Cardiovascular Data Registry (NCDR) CathPCI Registry, was designed to collect clinical data from 15 institutes in Japan of consecutive patients undergoing PCI.[9–11] All PCI procedures were performed under the direction of the intervention team of each participating hospital. All patients who consented to participate in this study were followed up by dedicated clinical research coordinators specifically trained in the present PCI registry. They were instructed to register data from consecutive hospital visits using an electronic data-capturing software system equipped with a data query engine and validations to maintain data quality. Data entered were checked for completeness and internal consistency and its quality was assured through automatic system validation and assessment of data completeness. All participants provided verbal or written consent for data collection. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of each participating hospital.

### Participants

A total of 3,463 consecutive SIHD patients who successfully underwent PCI and were discharged between July 2008 and December 2015 were enrolled. We excluded patients with prior revascularization ( $n = 1,268$ ), with heart failure at admission ( $n = 202$ ), and with missing values for CCS ( $n = 82$ ) (Fig. 1).

### Definition of Variables

Angina severity assessed by the CCS is recommended in international clinical practice guidelines as part of a formal structured assessment of a patient's disease-specific health status. [12] The CCS angina classification system is a symptom severity scale from the physician's perspective used to grade symptoms associated with physical activity on 5 levels: class 0 indicates no angina even with strenuous exertion; class I indicates angina only with strenuous exertion; class II indicates angina with walking > 200 yards on a flat surfaces, climbing stairs rapidly, or in cold or emotional situations; class III indicates angina with walking 100–200 yards on flat surfaces; and class IV indicates angina at rest or with any physical activity.[13] We defined angina severity as no angina (CCS 0), mild angina (CCS I or II), and severe angina (CCS III or IV). In our cohort, each patient's CCS class was evaluated at admission by an attending cardiologist. We were able to query the attending cardiologists to confirm the CCS classification as needed. Since the JCD-KiCS was developed in collaboration with the NCDR Cath PCI registry, the majority of clinical variables and in-hospital outcomes were defined in accordance with its data dictionary (version 4.1).[11] DM was defined as a history of DM or prescriptions for glucose-lowering medications. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of < 60 mL/min/1.73 m<sup>2</sup>, which is compatible with the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes classification Stage 3 or higher.[14] Acute coronary syndrome (ACS) was defined as ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTEMI-ACS). STEMI was diagnosed by the treating physician at each participating hospital according to the clinical presentation, presence of ST-segment elevation, Q waves and/or a new left bundle branch block on electrocardiogram, and elevated cardiac biomarkers exceeding the upper limit of normal value and consistent with or suggestive of ischemia. NSTEMI-ACS was also diagnosed by the treating physicians at each participating hospital according to the clinical presentation, cardiac biomarkers, and absence of ST-segment elevation.[15, 16] A multivessel lesion was defined as coronary artery disease involving  $\geq 2$  coronary arteries.

## Outcomes

The primary outcome was defined as the composite of all-cause death, new-onset ACS, non-fatal ischemic stroke, and new-onset heart failure within 2 years. The secondary outcome was defined as the composite of cardiovascular death, new-onset ACS, and new-onset heart failure within 2 years. To ensure the accuracy of the endpoints, the JCD-KiCS was supported by an events committee that included board-certified cardiologists (M.S. and S.K.). Initially, all endpoints were reviewed by a trained clinical research coordinator under the supervision of the project coordinator (I.U.) and categorized based on the need for adjudication or not. One committee member reviewed the abstracted record; a second or third adjudicator was called if there was a disagreement between the project coordinator and the first adjudicator.

## Statistical analysis

Baseline characteristics were summarized by the presence of DM. Continuous variables were summarized as medians with interquartile ranges and compared by Mann-Whitney U tests; categorical variables were summarized as frequencies and compared by chi-square or Fisher's exact test, as appropriate. We stratified angina severity according to the presence of DM and compared the proportion of high-risk coronary anatomies such as unprotected left main coronary trunks (LMTs), proximal left anterior descending arteries (pLADs), or multivessel lesions in each category of angina severity. Multivariable logistic regression analyses, which were adjusted for age, sex, body mass index (BMI), hypertension, CKD, prescriptions for both dual antiplatelet drugs and statins, unprotected LMT lesions, pLAD lesions, and multivessel lesions, were performed for the presence of severe angina in the total cohort, patients with DM, and those without DM. An interaction P value was calculated to determine whether the association of severe angina at the time of PCI with coronary anatomy was dependent on DM status. We used the Kaplan-Meier method to estimate the incidence of long-term outcomes with 95% confidence intervals (CIs) stratified by DM status and compared them using the log-rank test. We performed multivariable Cox proportional hazard analyses to evaluate the association of DM with the incidence of MACCE and adjusted for age, sex, BMI, CKD, prescriptions for both dual antiplatelet drugs and statins at discharge, unprotected LMT lesions, pLAD lesions, and multivessel lesions, which were selected based on clinical significance. Then, we stratified patients by DM status and calculated the incidence rate of the long-term outcomes using the Kaplan-Meier method for each category of angina severity, which were then compared using the log-rank test. We performed multivariable Cox proportional hazard analysis to evaluate the association of angina severity (with no angina as a reference) with the incidence of MACCE adjusted for age, sex, BMI, CKD, prescriptions for both dual antiplatelet drugs and statins at discharge, unprotected LMT lesions, pLAD lesions, and multivessel lesions in patients with or without DM. Two-sided P values of < 0.05 were considered statistically significant. All statistical analyses were performed using R statistical software (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria).[17]

## Results

A total of 1,911 patients with SIHD without prior revascularization or heart failure at admission were analyzed, of which 771 patients (40.3%) had DM (Fig. 1). The distribution of CCS class 0, I or II, and III or IV at baseline was 40.1% and 48.6%, 11.3% and 30.9%, and 54.9% and 14.2% in patients with DM and those without DM, respectively ( $P < 0.001$ ). Patients with DM were more likely to be male and to have comorbidities, such as hypertension, dyslipidemia, and CKD, and multivessel disease (Table 1).

Table 1  
Baseline characteristics according to DM status

Characteristic	Patients with DM, N = 771	Patients without DM, N = 1,140	P value
Age (years)	69 (62, 75)	70 (63, 76)	0.058
Female (%)	144 (18.7%)	276 (24.3%)	0.004
BMI (kg/m <sup>2</sup> )	24.3 (22.3, 26.7)	23.9 (22.1, 26.0)	0.004
Hypertension (%)	641 (83.2%)	845 (74.5%)	< 0.001
Dyslipidemia (%)	538 (69.9%)	714 (63.0%)	0.002
CKD (%)	331 (44.3%)	396 (35.9%)	< 0.001
HFrEF (%)	19 (2.5%)	23 (2.0%)	0.5
PAD (%)	106 (13.7%)	136 (12.0%)	0.3
Past history of MI (%)	54 (7.0%)	66 (5.8%)	0.3
Past history of HF (%)	50 (6.5%)	41 (3.6%)	0.004
Number of antianginal drugs (%)			0.3
0	681 (88.3%)	981 (86.1%)	
1	69 (8.9%)	123 (10.8%)	
more than 1	21 (2.7%)	36 (3.2%)	
Anginal severity (%)			< 0.001
CCS 0	309 (40.1%)	352 (30.9%)	
CCS I	133 (17.3%)	200 (17.5%)	
CCS II	242 (31.4%)	426 (37.4%)	
CCS III or IV	87 (11.3%)	162 (14.2%)	
Unprotected LMT lesion (%)	48 (6.2%)	60 (5.3%)	0.4
Proximal LAD lesion (%)	286 (37.1%)	413 (36.2%)	0.7
Number of diseased vessels (%)			< 0.001
1	353 (45.8%)	651 (57.1%)	
2	271 (35.1%)	357 (31.3%)	
3	147 (19.1%)	132 (11.6%)	
Optimal medical therapy (%)	536 (69.6%)	838 (73.7%)	0.051
Aspirin at discharge (%)	754 (98.4%)	1,118 (98.6%)	0.8
P2Y12 inhibitors at discharge (%)	736 (95.5%)	1,087 (95.4%)	> 0.9
Statin at discharge (%)	561 (73.2%)	883 (77.9%)	0.019
Beta blockers at discharge (%)	405 (52.8%)	572 (50.4%)	0.3
RAASi at discharge (%)	453 (59.1%)	535 (47.1%)	< 0.001

Data presented as median [interquartile range (IQR)] or n (%). CKD was defined as estimated glomerular filtration rate of less than 60 ml/min/1.73 m<sup>2</sup>. HFrEF was defined as ejection fraction of less than 40%. Optimal medical therapy was defined as dual antiplatelet therapy and statins at discharge. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; PAD, peripheral artery disease; MI, myocardial infarction; HF, heart failure; CCS, Canadian Cardiovascular Society functional classification; LMT, left main coronary trunk; LAD, left anterior descending; RAASi, renin-angiotensin-aldosterone system inhibitors

The prevalence of unprotected LMT lesions increased with angina severity regardless of DM status. Similarly, the prevalence of pLAD lesions increased with angina severity in those with DM, whereas no association was observed in those without DM. By contrast, the prevalence of multivessel disease was not associated with angina severity regardless of DM status (Fig. 2). In patients with DM, multivariable logistic regression analyses revealed that pLAD lesions were associated with severe angina (adjusted odds ratio [aOR] 1.68 [95% CI 1.06, 2.66];  $P=0.028$ ). In those without DM, female sex (aOR 1.59 [95% CI 1.08, 2.33];  $P=0.018$ ), absence of hypertension (aOR 0.65 [95% CI 0.45, 0.96];  $P=0.030$  for hypertension), and presence of CKD (aOR 1.57 [95% CI 1.09, 2.26];  $P=0.015$ ) were associated with severe angina. The interaction analysis demonstrated that the association of high-risk coronary anatomies with severe angina did not depend on the patient's DM status (interaction  $P$  value  $>0.05$  for all high-risk coronary anatomies, Fig. 3).

The median follow-up duration was 1,028 (interquartile range [IQR], 847-1,223) days, and the follow-up compliance rate was 91.7%. The incidence rates of the primary outcome at 2 years did not differ by DM status (8.2% and 10% in patients without and with DM, respectively;  $P=0.16$  [log-rank test]); however, patients with SIHD and DM had higher rates of the secondary outcome components than did those without DM (3.3% and 5.6% in patients without and with DM, respectively;  $P=0.014$  [log-rank test]) (Fig. 4). Multivariable Cox regression models revealed that DM was not associated with the primary or secondary outcome (adjusted hazard ratio [aHR] 1.08 [95% CI 0.79, 1.48];  $P=0.63$  and aHR 1.52 [95% CI 0.96, 2.42];  $P=0.075$ , for the primary and secondary outcomes, respectively).

Among patients with DM, severe angina was associated with a higher incidence of the primary outcome after 2 years (9.1%, 9.3%, and 17% for CCS classes 0, I or II, III or IV, respectively;  $P=0.049$  [log-rank test]), whereas no association was observed with the secondary outcome (4.9%, 5.7%, and 8.2% for CCS classes 0, I or II, III or IV, respectively;  $P=0.49$  [log-rank test]). By contrast, angina severity was not associated with the incidence of the primary or secondary outcome in those without DM (9.9%, 7.5%, and 7.4%;  $P=0.38$  and 3.2%, 3.6%, and 2.5%;  $P=0.79$  in CCS classes 0, I or II, III or IV for the primary and secondary outcomes, respectively) (Fig. 5). Multivariable Cox regression models revealed that severe angina was associated with the incidence of the primary outcome (aHR 1.93 [95% CI 1.01, 3.71];  $P=0.047$ ), whereas angina severity was not associated with the incidence of the secondary outcome (aHR 1.71 [95% CI 0.68, 4.32];  $P=0.26$ ) in patients with DM. In those without DM, the presence of severe angina was not associated with either the primary or secondary outcome (Table 2).

Table 2  
Association of baseline angina severity with long-term outcome according to DM status

Characteristic	Primary outcome						Secondary outcome					
	Patients with DM			Patients without DM			Patients with DM			Patients without DM		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Anginal severity												
CCS 0	–	–		–	–		–	–		–	–	
CCS I or II	0.96	0.57, 1.61	0.88	0.95	0.60, 1.49	0.81	1.05	0.52, 2.11	0.89	1.59	0.74, 3.42	0.23
CCS III or IV	1.93	1.01, 3.71	0.047	0.82	0.42, 1.59	0.55	1.71	0.68, 4.32	0.26	0.99	0.31, 3.22	0.99
Age (years)	1.03	1.00, 1.06	0.075	1.04	1.02, 1.07	0.002	1.01	0.97, 1.04	0.76	1.01	0.97, 1.05	0.52
Female	1	0.57, 1.74	0.99	0.73	0.44, 1.21	0.22	0.97	0.45, 2.08	0.94	1.24	0.54, 2.82	0.61
BMI (kg/m <sup>2</sup> )	0.96	0.89, 1.02	0.2	0.95	0.88, 1.02	0.13	0.92	0.83, 1.01	0.091	0.92	0.83, 1.03	0.15
CKD	2.35	1.41, 3.92	0.001	1.45	0.95, 2.22	0.083	2.4	1.21, 4.77	0.013	2.1	1.04, 4.24	0.039
Optimal medical therapy	0.57	0.36, 0.90	0.017	0.58	0.38, 0.90	0.014	0.84	0.44, 1.63	0.61	0.47	0.24, 0.94	0.032
Unprotected LMT lesion	2.3	1.20, 4.42	0.013	2.46	1.32, 4.58	0.004	2.68	1.13, 6.36	0.026	1.88	0.56, 6.28	0.31
Proximal LAD lesion	1.01	0.62, 1.63	0.98	1.24	0.81, 1.88	0.32	0.79	0.41, 1.55	0.5	0.48	0.22, 1.08	0.075
Multivessel lesion	1.2	0.75, 1.93	0.45	1.35	0.89, 2.04	0.16	1.07	0.57, 2.01	0.84	2.07	1.05, 4.09	0.037

The primary outcome was a composite of all-cause death, new-onset acute coronary syndrome, and non-fatal ischemic stroke within 2-year and the secondary outcome was a composite of cardiovascular death, new-onset acute coronary syndrome, and heart failure within 2-year. CKD was defined as estimated glomerular filtration rate of less than 60 ml/min/1.73 m<sup>2</sup>. Optimal medical therapy was defined as dual antiplatelet therapy and statins at discharge. Abbreviations: CCS, Canadian Cardiovascular Society functional classification; BMI, body mass index; CKD, chronic kidney disease; LMT, left main coronary trunk; LAD, left anterior descending; HR, hazard ratio; CI, confidence interval

## Discussion

In a large-scale, contemporary multicenter PCI registry, we observed that 1) the incidence of MACCE did not differ among patients with SIHD and DM from those without DM; 2) patients with SIHD and DM who had CCS III or IV angina had a high prevalence of high-risk coronary anatomies, such as unprotected LMT and pLAD lesions; and 3) the presence of CCS III or IV angina was associated with the incidence of MACCE in patients with DM.

While several randomized controlled trials (RCTs) and observational studies countries have reported that patients with SIHD and DM have a high incidence of MACCE in Western population,[8, 18–20] observational studies have indicated that

the DM-associated risk of MACCE was attenuated for patients with SIHD who underwent revascularization in Japan that consistent with our results.[21, 22] This discrepancy might be explained by the fact that Japanese patients with DM have a lower degree of hyperinsulinemia and insulin resistance than Western patients with DM. Our analysis indicated that Japanese patients with SIHD and DM could differ from their Western counterparts and may need risk stratification tools that are specific for Japanese patients with SIHD and DM.

Previous studies on the association of angina severity with long-term prognoses have provided mixed results, especially in those with DM.[19, 23–25] A meta-analysis of pivotal RCTs that included 5,034 patients with SIHD and DM revealed that CCS III or IV angina had higher incidences of MACCE, but the association was attenuated after adjusting for baseline characteristics.[26] Moreover, the large-size outpatient-based CLARIFY registry (Prospective observational Longitudinal Registry of patients with stable coronary artery disease) has revealed that the presence of angina solely was not associated with the incidence of subsequent myocardial infarction or all-cause death.[19] However, RCTs in this meta-analysis excluded patients who had unprotected LMT lesions or persistent severe angina.[7, 27, 28] Further, the CLARIFY registry excludes patients with planned revascularization, such as in cases of severe angina or high-risk coronary anatomies.[19, 29] The JCD-KiCS enrolled all consecutive patients who underwent PCI without any exclusion criteria. Therefore, our cohort may include a more comprehensive list of patients including those with SIHD and high-risk coronary anatomies and of the degree of patients with angina that would reflect a real-world setting. It is noteworthy that such a high prevalence of unprotected LMT lesions in patients with SIHD and concomitant DM with CCS III or IV angina was observed in our analysis and in previous studies.[30, 31] Patients with SIHD and DM who have severe angina with limited functional capacity would be reasonable candidates to undergo evaluation of their coronary anatomy before deciding on conservative management because such high-risk lesions remain a primary indication for revascularization even after pivotal RCTs, such as the COURAGE and ISCHEMIA trials.[7, 8] Further, our findings indicated that the contributing factors and prognostic implications of CCS III or IV differed by DM status. A possible explanation might be ischemic burden and cardiac autonomic neuropathies. Myocardial ischemia, which was recognized as angina, is transmitted by sympathetic nerve fibers that would be affected by neuropathies.[32] Therefore, the magnitude of angina would be influenced by both ischemic burden and cardiac autonomic neuropathies such as DM. The occurrence of CCS III or IV angina in patients with SIHD and DM with an impaired perception of angina would imply a greater ischemic burden and less myocardial reserve for hypoxemia than in those without DM.

In risk models that have evaluated the incidence of MACCE in patients with SIHD,[33, 34] pertinent variables were patients' baseline characteristics and coronary lesion complexity requiring costly and invasive procedures.[35, 36] Our study revealed that patients' functional status at the time of revascularization was an independent predictor of their long-term prognosis even after adjusting for clinical characteristics and high-risk coronary anatomies in patients with SIHD and DM. As it is easy to obtain from patients, the degree of angina and functional status could help determine the specific types and intensity of interventions, particularly when considering coronary revascularization.

This study is best understood in the context of several limitations. First, our registry did not include patients who were treated medically or with coronary artery bypass grafting (CABG), which led to selection biases. Especially, since CABG is the preferred line of treatment for revascularization in patients with SIHD and DM with multivessel disease, excluding patients who had CABG would alter the results. Second, SIHD patients with CCS 0 (silent ischemia) might have a high-risk clinical profile because they would have indications of PCI other than symptoms alleviation. However, such selection bias is likely to attenuate rather than strengthen the prognostic implication of angina severity; therefore, our results would be robust. Third, we did not enroll patients with non-obstructive coronary artery disease. Given that patients with non-obstructive coronary artery disease had better prognoses than did those with established coronary artery disease,[37] our results do not apply to such a population. Fourth, we assessed angina severity using the CCS that is known to have limited reproducibility and sensitivity to important clinical changes. Recently, patient reported outcomes such as the Seattle Angina Questionnaire were recommended for use in clinical trials and daily practice.<sup>7</sup> Further studies that evaluate

the prognostic implication for angina severity assessed by the Seattle Angina Questionnaire are warranted. Lastly, we did not measure the residual angina after PCI in patients, which is known to have a risk for future MACCE.<sup>5</sup> However, the main purpose of this analysis was to examine the clinical implications of angina severity at the point of PCI rather than to assess the treatment effects of PCI.

## Conclusions

ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass grafting; CCS: the Canadian Cardiovascular Society functional classification; CI: confidence interval; CKD: chronic kidney disease; CLARIFY: prospective observational longitudinal registry of patients with stable coronary artery disease registry; COURAGE: the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial; DM: diabetes mellitus; GFR: glomerular filtration rate; HR: hazard ratio; IQR: interquartile range; ISCHEMIA: the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial; JCD-KiCS: Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies; LAD: left anterior descending arteries; LMT: left main coronary trunks; MACCE: major adverse cardiac and cerebrovascular events; NCDR: National Cardiovascular Data Registry; NSTEMI-ACS: non-ST elevation acute coronary syndrome; OR: odds ratio; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; SIHD: stable ischemic heart disease; STEMI: ST elevation myocardial infarction.

## Abbreviations

ACS

acute coronary syndrome; BMI:body mass index; CABG:coronary artery bypass grafting; CCS:the Canadian Cardiovascular Society functional classification; CI:confidence interval; CKD:chronic kidney disease; CLARIFY:prospective observational longitudinal registry of patients with stable coronary artery disease registry; COURAGE:the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial; DM:diabetes mellitus; GFR:glomerular filtration rate; HR:hazard ratio; IQR:interquartile range; ISCHEMIA:the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial; JCD-KiCS:Japan Cardiovascular Database-Keio interhospital Cardiovascular Studies; LAD:left anterior descending arteries; LMT:left main coronary trunks; MACCE:major adverse cardiac and cerebrovascular events; NCDR:National Cardiovascular Data Registry; NSTEMI-ACS:non-ST elevation acute coronary syndrome; OR:odds ratio; PCI:percutaneous coronary intervention; RCT:randomized controlled trial; SIHD:stable ischemic heart disease; STEMI:ST elevation myocardial infarction.

## Declarations

## Ethics approval and consent to participate

The Ethics Committee of Keio University and each institutions approved this study.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

S.K. received a grant from Daiichi Sankyo during the conduct of the study; and grants from Novartis and personal fees from Bristol-Myers Squibb outside the submitted work. No other conflicts of interest relevant to this article exist.

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## Authors' contributions

**Nozomi Niimi:** Conceptualization, Formal analysis, Methodology, Writing—original draft **Satoshi Shoji:** Methodology, Writing—review and editing, Supervision **Mitsuaki Sawano:** Methodology, Data curation, Writing—review and editing, Supervision **Nobuhiro Ikemura:** Methodology, Writing—review and editing **Yasuyuki Shiraishi:** Methodology, Writing—review and editing, Supervision **Taku Inohara:** Methodology, Writing—review and editing, Supervision **Ikuko Ueda:** Project administration, Data curation **Keiichi Fukuda:** Funding acquisition, Writing—review and editing, Supervision **Shun Kohsaka:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Data curation, Writing—review and editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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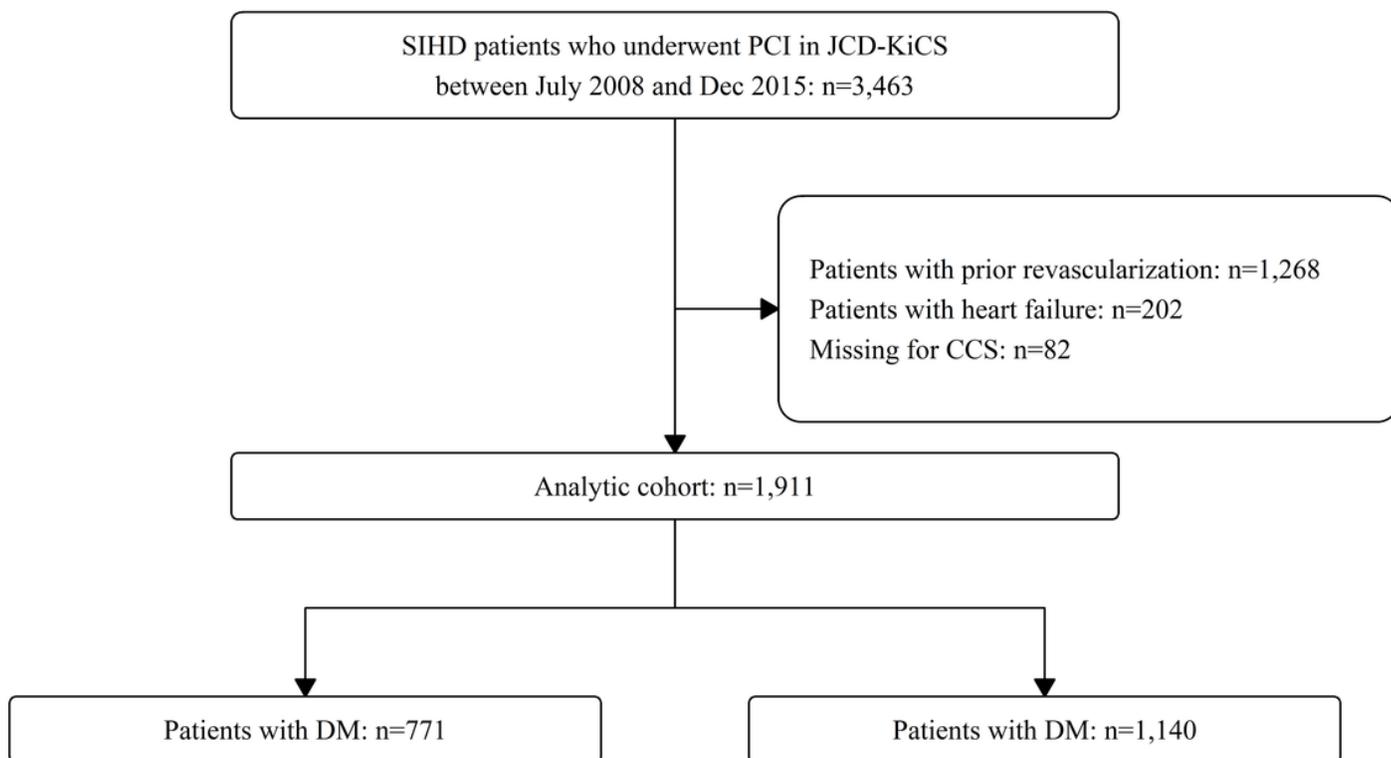
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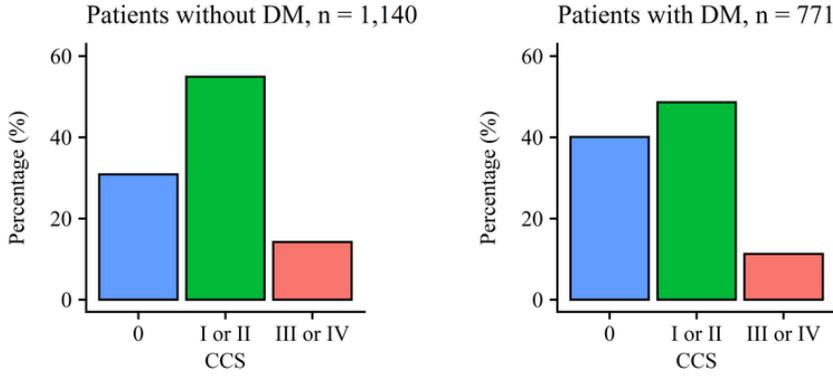
## Figures



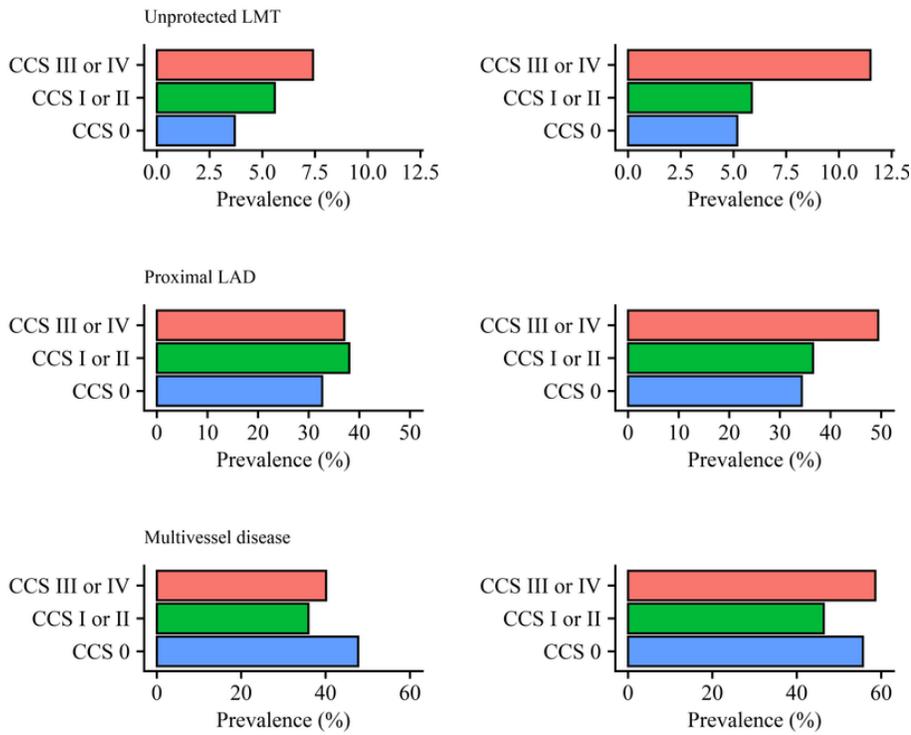
**Figure 1**

Study flow chart. Abbreviations: SIHD, stable ischemic heart disease; PCI, percutaneous coronary intervention; JCD-KiCS, The Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies; CCS, Canadian Cardiovascular Society functional classification; DM, diabetes mellitus.

**The distribution of angina severity according to DM status**



**The prevalence of high-risk coronary anatomies according to DM status and angina severity**

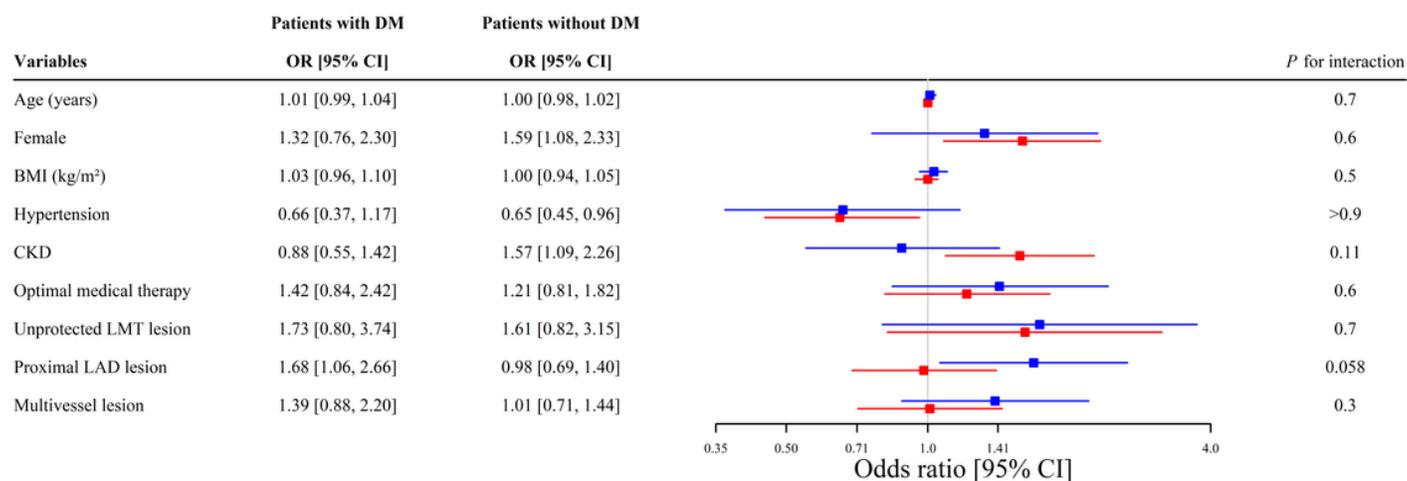


**Figure 2**

Distribution of angina and its association with the prevalence of high-risk lesions stratified by DM status. Abbreviations: CCS, Canadian Cardiovascular Society functional classification; LMT, left main coronary trunk; DM, diabetes mellitus.

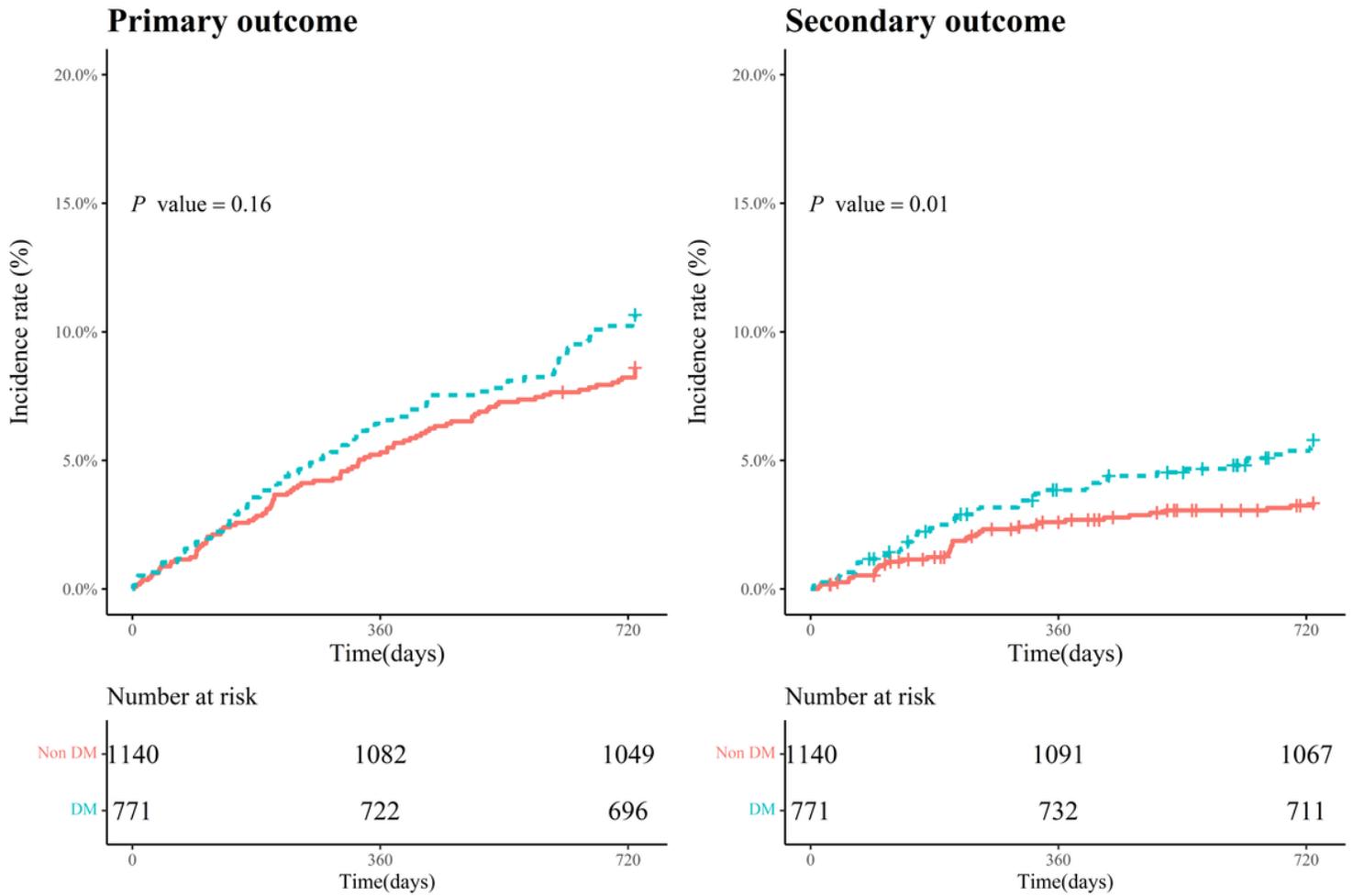
## Multivariable logistic model for CCS III or IV

■ Patients with DM ■ Patients without DM



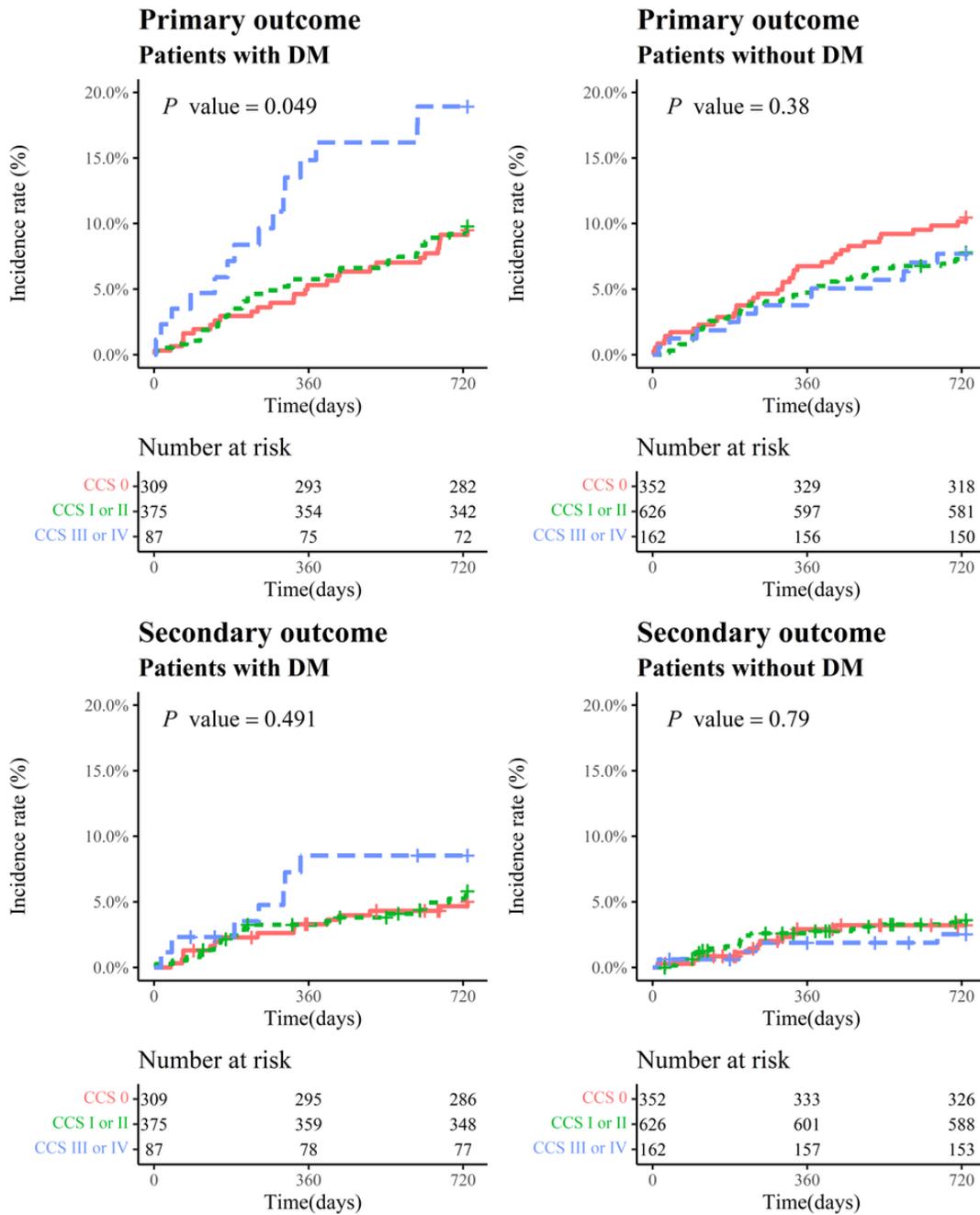
**Figure 3**

Forest plot of adjusted odds ratio for CCS III or IV angina stratified by DM status. CKD was defined as estimated glomerular filtration rate of less than 60 ml/min/1.73 m<sup>2</sup>. Optimal medical therapy was defined as dual antiplatelet therapy and statins at discharge. Abbreviations: CCS, Canadian Cardiovascular Society functional classification; BMI, body mass index; CKD, chronic kidney disease; LMT, left main coronary trunk; LAD, left anterior descending; DM, diabetes mellitus; OR, odds ratio; CI confidence interval



**Figure 4**

The association between long-term outcomes and DM status. The primary outcome was defined as a composite of all-cause death, new-onset acute coronary syndrome, non-fatal ischemic stroke, and new-onset heart failure within 2 years. The secondary outcome was defined as a composite of cardiovascular death, new-onset acute coronary syndrome, and new-onset heart failure within 2 years. Abbreviation: DM, diabetes mellitus.



**Figure 5**

Association of long-term outcomes with angina severity in SIHD patients with and without DM. The primary outcome was defined as a composite of all-cause death, new-onset acute coronary syndrome, non-fatal ischemic stroke, and new-onset heart failure within 2 years. The secondary outcome was defined as a composite of cardiovascular death, new-onset acute coronary syndrome, and new-onset heart failure within 2 years. Abbreviations: CCS, Canadian Cardiovascular Society functional classification; DM, diabetes mellitus.