Glycemic Control and Coronary Stent Failure in Patients With Type 2 Diabetes Mellitus

Irene Santos-Pardo, MD,[a] Mikael Andersson Franko, PHD,[b] Bo Lagerqvist, MD, PHD,[c] Viveca Ritsinger, MD, PHD,[d,e] Björn Eliasson, MD, PHD,[f] Nils Witt, MD, PHD,[a] Anna Norhammar, MD, PHD,[d,g] Thomas Nyström, MD, PHD[h]

ABSTRACT

BACKGROUND The impact of glycemic control in the risk of stent failure in subjects with type 2 diabetes (T2D) is currently unknown.

OBJECTIVES This study sought to study whether poor glycemic control is associated with a higher risk of stent failure in subjects with T2D.

METHODS This observational study included all patients in Sweden with T2D who underwent implantation of second-generation drug-eluting stents (DES) during 2010 to 2020. The exposure variable was the updated mean of glycated hemoglobin (HbA_{1c}). Individuals were stratified by glycemic control, with HbA_{1c} 6.1% to 7.0% (43-53 mmol/mol) as the reference group. The primary endpoint was the occurrence of stent failure (in-stent restenosis and stent thrombosis). The main result was analyzed in a complete cases model. Sensitivity analyses were performed for missing data and a model with death as a competing risk.

RESULTS The study population consisted of 52,457 individuals (70,453 DES). The number of complete cases was 24,411 (29,029 DES). The median follow-up was 6.4 years. The fully adjusted HR was 1.10 (95% CI: 0.80-1.52) for HbA_{1c} of ≤5.5% (≤37 mmol/mol), 1.02 (95% CI: 0.85-1.23) for HbA_{1c} of 5.6% to 6.0% (38-42 mmol/mol), 1.25 (95% CI: 1.11-1.41) for HbA_{1c} of 7.1% to 8.0% (54-64 mmol/mol), 1.30 (95% CI: 1.13-1.51) for HbA_{1c} of 8.1% to 9.0% (65-75 mmol/mol), 1.46 (95% CI: 1.21-1.76) for HbA_{1c} of 9.1% to 10.0% (76-86 mmol/mol), and 1.33 (95% CI: 1.06-1.66) for HbA_{1c} of ≥10.1% (≥87 mmol/mol). Sensitivity analyses did not change the main result.

CONCLUSIONS We found a significant association between poor glycemic control and a higher risk of stent failure driven by in-stent restenosis. (J Am Coll Cardiol 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

Individuals with diabetes have a 2-fold higher risk of developing coronary artery disease (CAD)[1] and an increased mortality rate following the onset of clinically manifest CAD compared with individuals without diabetes.[1,2] Target lesion revascularization (TLR) following revascularization with percutaneous coronary intervention (PCI) also seems to be more common in people with diabetes, even with the use of second-generation drug-eluting stents (DES).[3] Few studies have addressed the impact of glycemic

control on the prognosis of patients with type 2 diabetes (T2D) undergoing revascularization with PCI, showing inconclusive and/or contradictory results for the risk of major adverse cardiovascular events (MACE).[4-15] Most of these studies included a limited number of participants,[12] had differing timepoints for determining the exposure variable, and used different follow-up periods.[4-15]

To date, outcomes of TLR and target vessel revascularization (TVR) have not been fully investigated; one study was done during the era of bare-metal stents and first-generation DES,[4] whereas another has included newer generations of DES.[11] Recent studies have shown a linear association[10,12,14,15] as well as a J-shaped association[12,14] between poor glycemic control and risk of TLR. Large observational studies on the role of glycemic control and stent failure, that is, stent thrombosis (ST) or instent restenosis (ISR), are lacking.

This register-based, observational study aimed to assess whether glycemic control, measured as updated mean glycated hemoglobin (HbA$_{1c}$), is associated with the risk of stent failure following PCI with a second-generation DES in individuals with T2D.

METHODS

STUDY DESIGN. This was a retrospective, observational, nationwide, and population-based cohort study where patients and events were registered prospectively.

STUDY POPULATION. We included all patients older than 18 years with a diagnosis of T2D referred for a PCI with implantation of at least 1 DES in de novo coronary stenosis in Sweden during the period from January 1, 2010, to December 31, 2020. T2D diagnosis was defined using the current diagnosis guidelines.[16] PCIs on bypass grafts were excluded. **Figure 1** describes the main inclusion and exclusion criteria that led to the study population selection.

A database was constructed by merging the data from the Swedish National Patient Registry, Swedish Cause of Death Registry, Swedish Prescribed Drug Register, National Diabetes Register, Swedish Coronary Angiography and Angioplasty Registry, Swedish Cardiologic Intensive Care Unit Registry, and Statistics Sweden Business Registry.
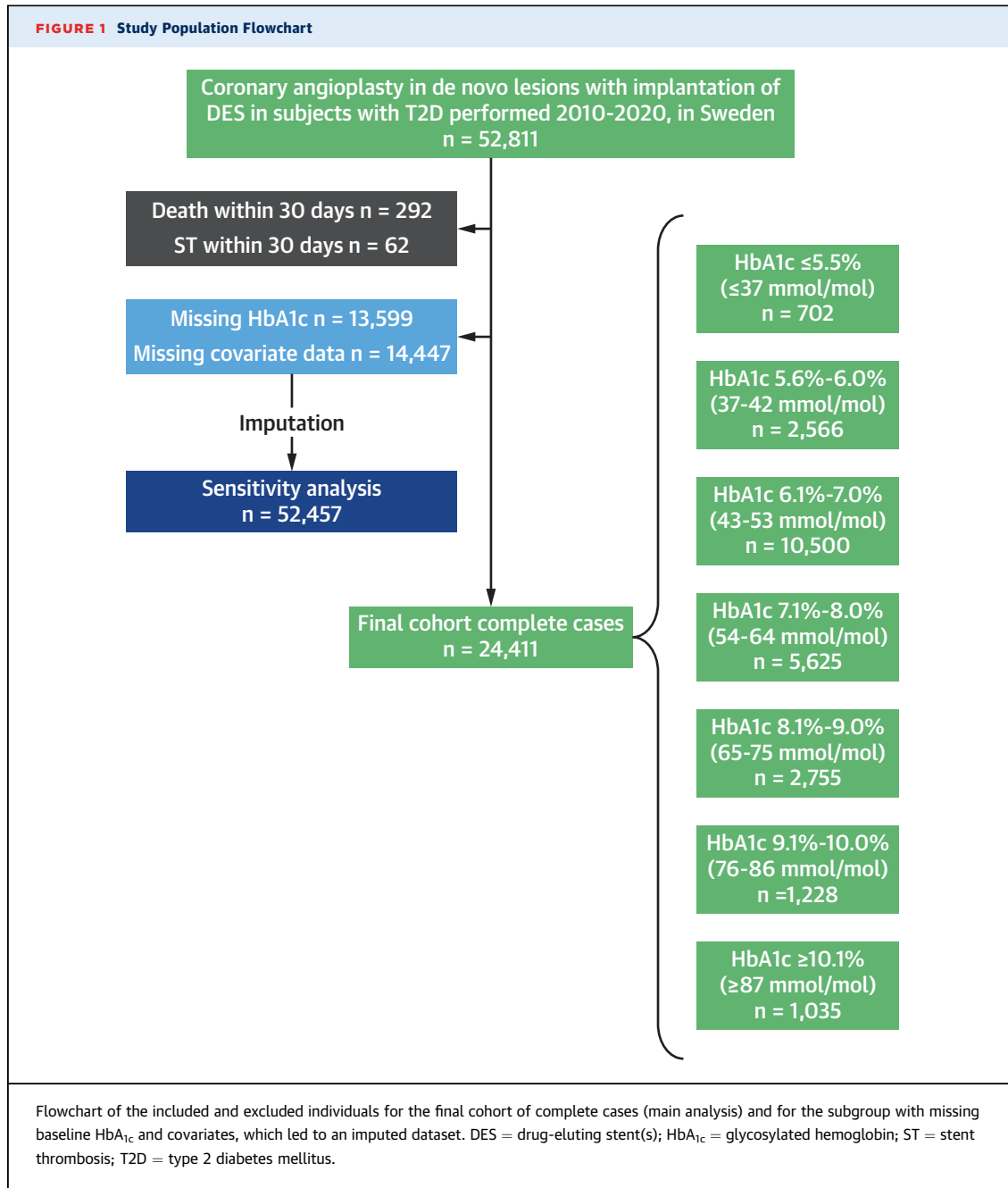
Anatomical Therapeutic Chemical Classification System codes were used to define the baseline medical therapy. An individual was considered treated with a specific medication if a prescription was retrieved from a pharmacy in Sweden within 6 months before or 3 months after the index PCI procedure.

The Swedish Ethical Review Authority approved the study, which complied with the Declaration of Helsinki. All patients were informed of their inclusion in the aforementioned registries and had the possibility to opt out.

EXPOSURE VARIABLE (HbA$_{1c}$). The exposure variable representing glycemic control is HbA$_{1c}$, and its values were retrieved from the National Diabetes Register. Because previous studies have demonstrated a J-shaped effect of glycemic control on MACE,[12,14] finding those with extremely low and high levels of HbA$_{1c}$ to have a higher risk of cardiovascular events, we chose to perform the analysis in a stratified manner and used the category of HbA$_{1c}$ of 6.1% to 7.0% (43-53 mmol/mol) as the reference to better understand the impact of different levels of glycemic control. The categorization of HbA$_{1c}$ was deemed clinically pragmatic in relation to the glycemic target recommendations found in the current diabetes management guidelines.[17] Based on their baseline HbA$_{1c}$, that is, within 1 year before and up to 6 months post-PCI, categories were defined as follows: HbA$_{1c}$ of ≤5.5 (37 mmol/mol), 5.6% to 6.0% (38-42 mmol/mol), 6.1% to 7.0% (43-53 mmol/mol), 7.1% to 8.0% (54-64 mmol/mol), 8.1% to 9.0% (65-75 mmol/mol), 9.1% to 10.0% (76-86 mmol/mol), and ≥10.1% (≥87 mmol/mol). Analyses of HbA$_{1c}$ were carried out at local laboratories with the high-performance liquid chromatography Mono S (Cytiva) method, with quality assurance done nationwide through regular calibration. We converted all HbA$_{1c}$ values to standard values based on the National Glycohemoglobin Standardization Program.[18]

ENDPOINTS. The primary endpoint was the occurrence of ISR or ST in a second-generation DES implanted during the study period. Those who died within 30 days post-PCI were excluded. Those with ST occurring within the first 30 days post-PCI were excluded as well because we deemed those STs to likely be of a purely thrombotic origin. ST was defined as definite ST in accordance with the Academic Research Consortium 2 definition.[19] ISR was defined as a reported stenosis of >50% of the luminal diameter or as a significant reduction in fractional flow reserve (ie, ≤0.80), instantaneous wave-free ratio (ie, ≤0.89), or resting full-cycle ratio (ie, ≤0.8), respectively, in a previously stented segment in the coronary vessel. Secondary endpoints were the separate components of the primary endpoint, myocardial infarction (MI), and all-cause death. Information on mortality was extracted from the

FIGURE 1 Study Population Flowchart

Flowchart of the included and excluded individuals for the final cohort of complete cases (main analysis) and for the subgroup with missing baseline HbA1c and covariates, which led to an imputed dataset. DES = drug-eluting stent(s); HbA1c = glycosylated hemoglobin; ST = stent thrombosis; T2D = type 2 diabetes mellitus.

Swedish Cause of Death Registry and included all relevant codes (I.00-I.99) in the International Classifications of Diseases-9th and -10th Revisions.

STATISTICS. Based on their distributions, continuous data are summarized as mean ± SD or as median (25th to 75th percentiles). Categorical data are presented as absolute count and percentage. Descriptive statistics of baseline characteristics are presented both aggregated and separately for each category of HbA1c values, including missing HbA1c values at baseline as a category. Survival from stent implantation to either ISR or ST was modeled with Cox regression. The proportional hazard assumption was assessed by visual inspection of the plots of the logarithm of the negative logarithm of the estimated survival density function vs the logarithm of the survival time. This assumption was further evaluated with a 2-sided score test of the scaled Schoenfeld test over time, obtaining a P value of 0.065. This assumption was considered not violated. Death,

emigration, and the end of the study period were treated as censoring events. The exposure variable was analyzed as an updated mean, meaning that HbA_{1c} levels are updated in time so that the most recent registered value was chosen. The individual risk at any time was calculated as the weighted sum of the accumulated time in each category multiplied with the corresponding category-specific coefficient. Several factors were considered to be potential effect modifiers and were adjusted for in the fully adjusted Cox models: age, sex, body mass index, level of education achieved, smoking habit, diabetes duration, estimated glomerular filtration rate, previous coronary artery bypass grafting, previous MI, previous stroke, hypertension, dyslipidemia, peripheral artery disease, malignancy, treatment with glucose-lowering medications within 6 months of the PCI, year when PCI was performed, hospital where PCI was performed, multivessel disease, complex stenosis B2 and/or C (based on the American College of Cardiology/American Heart Association classification),[20] PCI that involved a bifurcation lesion, total stent length, stent diameter and number of stents implanted, acute coronary syndrome as indication for PCI, complete revascularization, whether the patient had received acetylsalicylic acid and/or $P2Y_{12}$ inhibitors before the performance of the angioplasty, concomitant treatment with oral anticoagulants, and the administration of glycoprotein IIb/IIIa inhibitors during the procedure. The Cox model considered these covariates in a time-updated fashion in the same way the exposure variable (ie, HbA_{1c}) was handled. Information on the prescribed antiplatelet therapy following the angioplasty was extracted from the Prescribed Drug Register.

The main result is presented based on a complete cases model, excluding cases with missing data for HbA_{1c} or any of the covariates. The magnitude of missing data for each covariate can be found in Supplemental Table 1. Additional models were performed to test for the robustness of the analysis: a model using "missing HbA_{1c}" as a category, a model with imputed missing HbA_{1c} and covariate data, and a model with death as a competing risk for the primary endpoint, based on the imputed database (whole cohort). Multiple imputation was based on additive regression and predictive mean matching. Each value was imputed 10 times, after a run-in sequence of 5 iterations, to account for imputation error, and then pooled. Competing risks analysis was performed with the Fine-Gray regression model.

We also performed a Cox regression model grouping HbA_{1c} as ≤7.0% (≤53 mmol/mol) and >7.1% (>54 mmol/mol) for the primary endpoint and the

secondary endpoints of all-cause death and MI for the complete case analysis. An additional age-stratified analysis (<65 years and ≥65 years) was performed for the primary endpoint.

To explore the possible influence of insulin treatment as an interaction factor in our analysis, we performed an analysis stratified by insulin use and an additional one using insulin treatment and HbA_{1c} level as an interaction term.

Expanded, age-adjusted Kaplan-Meier survival curves were constructed to illustrate time to event and the absolute event rate between HbA_{1c} categories. The survival curves were expanded using the Simon-Makuch method. A cumulative hazards curve for the primary endpoint was also built. A 2-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using R software, version 4.3.0 (R Core Team).

RESULTS

The complete cases cohort, from which the main result is derived, comprised 24,411 individuals in whom 29,029 DES were implanted. The baseline clinical characteristics for the complete cases cohort are presented in Table 1. Median age of the cohort was 68 years, and 74% of the subjects were male. Patients with baseline HbA_{1c} above 7.1% (54 mmol/mol) were more frequently current smokers and had overweight and a previous history of dyslipidemia, MI, stroke, renal failure, and coronary artery bypass grafting surgery compared with those with HbA_{1c} within the reference range of 6.1% to 7.0% (43-53 mmol/mol). Baseline procedural characteristics are shown in Table 2. The indication for PCI did not vary significantly across different HbA_{1c} categories. Individuals with glycemic control above the HbA_{1c} reference more often had multivessel disease and were slightly less frequently completely revascularized during the index PCI procedure (Table 2). The left anterior descending artery was the most commonly stented vessel (38.6%).

The whole cohort consisted of 52,457 individuals in whom 70,453 DES were implanted during the study period. The clinical and procedural characteristics for the whole cohort are found in Supplemental Tables 2 and 3. A visual distribution of baseline HbA_{1c} data is found in Supplemental Figure 1. The **Central Illustration** summarizes the methods and main results of the study.

PRIMARY ENDPOINT. During a median follow-up time of 6.4 years (Q1-Q3: 3.8-9.1 years), there were a total of 1,873 events of stent failure in the complete cases cohort. The expanded age-adjusted Kaplan-Meier

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TABLE 1 Baseline Clinical Characteristics

	All Subjects in the Complete Case Model (N = 24,411)	HbA1c Category						
		≤5.5% (≤37 mmol/mol) (n = 702)	5.6%-6.0% (38-42 mmol/mol) (n = 2,566)	6.1%-7.0% (43-53 mmol/mol) (n = 10,500)	7.1%-8.0% (54-64 mmol/mol) (n = 5,625)	8.1%-9.0% (65-75 mmol/mol) (n = 2,755)	9.1%-10.0 (76-86 mmol/mol) (n = 1,228)	≥10.1% (≥87 mmol/mol) (n = 1,035)
Follow-up time, y	6.4 (3.8-9.1)	6.2 (3.8-8.9)	6.2 (3.7-8.6)	6.4 (3.9-9.1)	6.4 (3.9-9.2)	6.5 (3.7-9.3)	6.4 (3.6-9.1)	6.2 (3.5-8.9)
Number of HbA1c measurements per year	1.7 (1.0-2.8)	1.4 (0.9-2.2)	1.4 (0.9-2.2)	1.6 (1.0-2.6)	1.8 (1.1-3.0)	2.0 (1.1-3.4)	2.1 (1.2-3.5)	2.0 (1.2-3.7)
Male	18,041 (73.9)	566 (80.6)	1,959 (76.3)	7,766 (74.0)	4,130 (73.4)	2,004 (72.7)	853 (69.5)	763 (73.7)
Age, y	15,513 (63.5)	70 (63-76)	70 (63-76)	70 (64-77)	70 (63-77)	69 (62-76)	67 (60-75)	64 (57-71)
Age ≥65 y	15,513 (63.5)	294 (73.0)	1,073 (73.6)	5,169 (76.3)	3,364 (74.4)	1,668 (69.5)	634 (61.6)	384 (50.0)
T2D duration, y	8 (3-15)	5 (1-10)	3 (0-8)	6 (2-12)	10 (5-17)	13 (7-19)	13 (7-19)	12 (7-18)
Hypertension	13,723 (56.2)	374 (53.3)	1,294 (50.4)	5,529 (52.7)	3,371 (59.9)	1,782 (64.7)	780 (63.5)	593 (57.3)
Systolic blood pressure, mm Hg	136 (126-146)	138 (126-145)	135 (125-145)	135 (126-146)	136 (128-145)	138 (126-149)	140 (128-150)	135 (125-150)
Diastolic blood pressure, mm Hg	78 (70-80)	78 (70-82)	78 (70-80)	76 (70-80)	77 (70-80)	78 (70-80)	78 (70-82)	80 (70-85)
Dyslipidemia	13,261 (54.3)	291 (41.4)	935 (36.4)	4,893 (46.6)	3,573 (63.5)	2,005 (72.8)	895 (72.9)	669 (64.6)
Previous MI	5,769 (23.6)	148 (21.1)	534 (20.8)	2,367 (22.5)	1427 (25.4)	724 (26.3)	327 (26.6)	242 (23.4)
Previous CABG	3,225 (13.2)	69 (9.8)	273 (10.6)	1,294 (12.3)	853 (15.2)	422 (15.3)	170 (13.8)	144 (13.9)
Previous stroke	1,526 (6.3)	44 (6.3)	118 (4.6)	565 (5.4)	398 (7.1)	236 (8.6)	98 (8.0)	67 (6.5)
Previous PAD	924 (3.8)	20 (2.8)	78 (3.0)	369 (3.5)	230 (4.1)	130 (4.7)	50 (4.1)	47 (4.5)
Previous cancer	3,607 (14.8)	118 (16.8)	375 (14.6)	1,575 (15.0)	898 (16.0)	397 (14.4)	149 (12.1)	95 (9.2)
Current smoker	4,980 (20.4)	135 (19.2)	537 (20.9)	2,129 (20.3)	1,061 (18.9)	531 (19.3)	287 (23.4)	305 (29.5)
Previous smoker	10,391 (42.6)	324 (46.2)	1,142 (44.5)	4,492 (42.8)	2,384 (42.4)	1,172 (42.5)	502 (40.9)	385 (37.2)
BMI, kg/m²	28.9 (26.1-32.1)	28.3 (25.4-31.1)	28.3 (25.8-31.2)	28.4 (25.9-31.7)	29.0 (26.3-32.2)	29.4 (26.7-33.0)	30.3 (27.0-33.6)	30.4 (27.4-33.4)
BMI ≥30 kg/m²	9,327 (38.2)	235 (35.6)	857 (35.0)	3,649 (34.8)	2,205 (39.2)	1,247 (45.3)	630 (51.3)	526 (50.8)
eGFR, mL/min/1.73 m²	80 (63-92)	80 (66-93)	82 (66-92)	80 (64-91)	79 (61-92)	79 (59-93)	82 (61-96)	86 (64-98)
eGFR ≥90 mL/min/1.73 m²	6,635 (27.2)	183 (31.1)	687 (31.6)	2,607 (28.6)	1,517 (29.2)	811 (30.9)	440 (37.7)	390 (42.1)
eGFR 60-89 mL/min/1.73 m²	10,420 (42.7)	291 (49.4)	1,107 (51.0)	4,696 (51.5)	2,423 (46.7)	1,119 (42.7)	446 (38.2)	338 (36.5)
eGFR 45-59 mL/min/1.73 m²	2,860 (11.7)	63 (10.7)	258 (11.9)	1151 (12.6)	731 (14.1)	390 (8.3)	151 (12.9)	116 (12.5)
eGFR 30-44 mL/min/1.73 m²	1,358 (5.6)	34 (5.8)	79 (3.6)	504 (5.5)	361 (7.0)	218 (8.3)	93 (8.0)	64 (6.9)
eGFR 15-29 mL/min/1.73 m²	374 (1.5)	6 (1.0)	29 (1.3)	123 (1.3)	114 (2.2)	61 (2.3)	29 (2.5)	12 (1.3)
eGFR <15 mL/min/1.73 m²	150 (0.6)	12 (2.0)	11 (0.5)	43 (0.5)	46 (0.9)	23 (0.9)	9 (0.8)	6 (0.6)
HDL cholesterol, mmol/L	1.1 (0.9-1.3)	1.1 (0.9-1.4)	1.1 (1.0-1.4)	1.1 (1.0-1.3)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.0 (0.9-1.3)	1.0 (0.9-1.2)
LDL cholesterol, mmol/L	2.6 (2.0-3.4)	2.5 (1.9-3.3)	2.6 (1.9-3.3)	2.7 (2.1-3.4)	2.6 (2.0-3.3)	2.6 (2.0-3.4)	2.7 (2.0-3.5)	2.8 (2.1-3.7)
Triglyceride, mmol/L	1.8 (1.3-2.5)	1.5 (1.1-2.0)	1.5 (1.1-2.1)	1.6 (1.2-2.3)	1.8 (1.3-2.5)	1.9 (1.4-2.7)	2.0 (1.5-2.9)	2.3 (1.6-3.4)
Beta-blockers	20,200 (82.7)	581 (82.8)	2,123 (82.7)	8,669 (82.6)	4,628 (82.3)	2,303 (83.6)	1,034 (84.2)	862 (83.3)
Calcium inhibitors	361 (1.5)	11 (1.6)	31 (1.2)	149 (1.4)	87 (1.5)	49 (1.8)	24 (2.0)	10 (1.0)
ACE inhibitors	12,595 (51.6)	358 (51.0)	1,387 (54.1)	5,463 (52.0)	2,868 (51.0)	1,340 (48.6)	603 (49.1)	576 (55.7)
ARB	2,685 (11.0)	76 (10.8)	241 (9.4)	1,049 (10.0)	652 (11.6)	341 (12.4)	180 (14.7)	146 (14.1)
ASA preprocedure	22,937 (94.0)	653 (93.0)	2,402 (93.6)	9,875 (94.0)	5,315 (94.5)	2,569 (93.2)	1,149 (93.6)	968 (93.5)
P2Y12 inhibitor preprocedure	20,354 (83.4)	577 (82.2)	2,114 (82.4)	8,765 (83.5)	4,737 (84.2)	2,287 (83.0)	1,005 (81.8)	860 (83.1)
Oral anticoagulant	1,393 (5.7)	26 (3.8)	120 (4.7)	573 (5.5)	343 (6.1)	183 (6.6)	92 (7.5)	56 (5.4)
Oral lipid-lowering medications	21,619 (88.6)	607 (86.5)	2,265 (88.3)	9,318 (88.7)	4,954 (88.1)	2,433 (88.3)	1,083 (88.2)	906 (87.5)
PCSK-9 inhibitors	31 (0.1)	1 (0.1)	2 (0.1)	14 (0.1)	8 (0.1)	5 (0.2)	1 (0.1)	0 (0.0)
Glucose-lowering medications	15,112 (61.9)	261 (37.2)	877 (34.2)	5,449 (51.9)	4,297 (76.4)	2,378 (86.3)	1,057 (86.1)	793 (76.6)
Diet	9,299 (38.1)	441 (62.8)	1,689 (65.8)	5,051 (48.1)	1,328 (23.6)	377 (13.7)	171 (13.9)	242 (23.4)
Metformin	10,346 (42.4)	187 (26.6)	679 (26.5)	3,976 (37.9)	2,944 (52.3)	1,445 (52.5)	628 (51.1)	487 (47.1)
SGLT2 inhibitors	469 (1.9)	5 (0.7)	16 (0.6)	119 (1.1)	138 (2.5)	109 (4.0)	48 (3.9)	34 (3.3)
GLP-1R agonists	637 (2.6)	2 (0.3)	16 (0.6)	127 (1.2)	179 (3.2)	147 (5.3)	103 (8.4)	63 (6.1)
DPP4 inhibitors	1,408 (5.8)	9 (1.3)	41 (1.6)	394 (3.8)	458 (8.1)	281 (10.2)	126 (10.3)	99 (9.6)

TABLE 1 Continued								
	All Subjects in the Complete Case Model (N = 24,411)	**HbA$_{1c}$ Category**						
		≤5.5% (≤37 mmol/mol) (n = 702)	**5.6%-6.0% (38-42 mmol/mol) (n = 2,566)**	**6.1%-7.0% (43-53 mmol/mol) (n = 10,500)**	**7.1%-8.0% (54-64 mmol/mol) (n = 5,625)**	**8.1%-9.0% (65-75 mmol/mol) (n = 2,755)**	**9.1%-10.0 (76-86 mmol/mol) (n = 1,228)**	**≥10.1% (≥87 mmol/mol) (n = 1,035)**
Sulfonylurea	2,456 (10.1)	37 (5.3)	68 (2.7)	766 (7.3)	836 (14.9)	454 (16.5)	173 (14.1)	122 (11.8)
Insulin	6,739 (27.6)	59 (8.4)	154 (6.0)	1,444 (13.8)	2,079 (37.0)	1,615 (58.6)	776 (63.2)	612 (59.1)
Primary education	9,591 (39.3)	234 (33.3)	957 (37.3)	4,085 (38.9)	2,276 (40.5)	1,109 (40.3)	509 (41.4)	421 (40.7)
Secondary education	10,722 (43.9)	323 (46.0)	1,147 (44.7)	4,542 (43.3)	2,456 (43.7)	1,245 (45.2)	528 (43.0)	481 (46.5)
University	4,098 (16.8)	145 (20.7)	462 (18.0)	1,873 (17.8)	893 (15.9)	401 (14.6)	191 (15.6)	133 (12.9)

Values are median (Q1-Q3) or n (%). Baseline clinical characteristics for the complete cases cohort for each HbA$_{1c}$ category.

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass grafting; DDP4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, based on serum creatinine levels; GLP-1R = glucagon peptide-1 receptor; HbA$_{1c}$ = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PAD = peripheral artery disease; PCSK-9 = proprotein convertase subtilisin/kexin type 9; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

survival curves for the primary endpoint are shown in **Figure 2**. The cumulative hazard curves can be found in Supplemental Figure 2. The absolute event number, event ratio, and estimated HR per HbA$_{1c}$ category (crude, adjusted for sex and age, and fully adjusted) are presented in **Table 3**. The fully adjusted HR (95% CI) for each HbA$_{1c}$ category was as follows: 1.10 (0.80-1.52) for HbA$_{1c}$ of ≤5.5% (≤37 mmol/mol), 1.02 (0.85-1.23) for HbA$_{1c}$ of 5.6% to 6.0% (38-42 mmol/mol), 1.25 (1.11-1.41) for HbA$_{1c}$ of 7.1% to 8.0% (54-64 mmol/mol), 1.30 (1.13-1.51) for HbA$_{1c}$ of 8.1% to 9.0% (65-75 mmol/mol), 1.46 (1.21-1.76) for HbA$_{1c}$ of 9.1% to 10.0% (76-86 mmol/mol), and 1.31 (1.06-1.66) for HbA$_{1c}$ of ≥10.1% (≥87 mmol/mol).

The estimated HR for HbA$_{1c}$ of >7.1% (>54 mmol/mol) was 1.28 (95% CI: 1.16-1.42) for the fully adjusted model compared to HbA$_{1c}$ of ≤7.0% (53 mmol/mol). The absolute event numbers, event ratios, and estimated HRs can be found in Supplemental Table 4.

The relative risk for the primary endpoint in the groups with poor glycemic control was found to be higher for subjects younger than 65 years compared to those 65 years or older. The proportion of subjects younger than 65 years in the complete case analysis was 36.5%. The absolute event numbers, event ratios, and the estimated HR for each HbA$_{1c}$ category for these 2 age groups can be found in Supplemental Table 5.

The relative risks in the model stratified by insulin treatment were not significantly different for those treated or not with insulin (Supplemental Table 6). The interaction analysis between insulin and HbA$_{1c}$ levels was statistically nonsignificant (P = 0.90).

SENSITIVITY ANALYSIS. HR comparison plots between the complete cases model (presented as the main result) and the 3 models used as a sensitivity analysis are shown in **Figure 3**. The estimated HR from these additional models did not significantly differ from the main result (complete cases model) except for the highest glycemic control category, that is, HbA$_{1c}$ of ≥10.1% (≥87 mmol/mol), in the death as competing risk model. The crude death rates for each HbA$_{1c}$ category are shown in Supplemental Table 7. The observed number of events, event rates, and HR estimates for the 3 additional sensitivity analysis models are shown in Supplemental Table 8.

SECONDARY ENDPOINTS. There were 1,159 cases of ISR and 771 cases of ST during the study period. The highest risk of ISR was observed for the group with HbA$_{1c}$ of 9.1% to 10.0% (76-86 mmol/mol) with a fully adjusted HR of 1.55 (95% CI: 1.23-1.96). The highest risk of ST events was seen in the group with HbA$_{1c}$ of 7.1% to 8.0% (54-64 mmol/mol) with an HR of 1.32 (95% CI: 1.10-1.59). The absolute event numbers, event ratios, and the estimated HRs for each HbA$_{1c}$ category for ISR and ST are presented in **Table 3** for the complete cases model.

There were a total of 7,952 deaths in the complete cases cohort. The highest relative risk of all-cause death was observed in the category for HbA$_{1c}$ of ≥10.1% (≥87 mmol/mol) with an HR of 1.65 (95% CI: 1.49-1.84). The estimated HR for poor glycemic control (ie, HbA$_{1c}$ of >7.1% [>54 mmol/mol]) was 1.21 (95% CI: 1.16-1.28). The absolute event numbers, event ratios, and the estimated HRs for each HbA$_{1c}$ category for all-cause death are presented in the Supplemental Tables 4 and 9, respectively.

A total of 788 cases of MI were registered, and no significant differences among HbA$_{1c}$ categories were observed. The estimated HR for poor glycemic control (ie, HbA$_{1c}$ of >7.1% [>54 mmol/mol]) was 1.16 (95% CI: 0.99-1.36). The absolute event numbers, event ratios, and estimated HRs for each HbA$_{1c}$ category for all-cause death and MI are presented in Supplemental Tables 4 and 10, respectively.

TABLE 2 Baseline Procedural Characteristics

	All Subjects in the Complete Case Model (N = 24,411)	HbA₁c Category						
		≤5.5% (≤37 mmol/mol) (n = 702)	5.5%-6.0% (38-42 mmol/mol) (n = 2,566)	6.1%-7.0% (43-53 mmol/mol) (n = 10,500)	7.1%-8.0% (54-64 mmol/mol) (n = 5,625)	8.1%-9.0% (65-75 mmol/mol) (n = 2,755)	9.1%-10.0 (76-86 mmol/mol) (n = 1,228)	≥10.1% (≥87 mmol/mol) (n = 1,035)
Indication for PCI								
Stable angina	5,131 (21.0)	126 (17.9)	518 (20.2)	2,118 (20.2)	1,296 (23.0)	642 (23.3)	246 (20.0)	185 (17.9)
NSTEMI/UA	12,329 (50.5)	345 (49.1)	1,248 (48.6)	5,345 (50.9)	2,854 (50.7)	1,397 (50.7)	632 (51.5)	508 (49.1)
STEMI	5,800 (23.8)	190 (27.1)	679 (26.5)	2,556 (24.3)	1,221 (21.7)	580 (21.1)	284 (23.1)	290 (28.0)
Other	1,151 (4.7)	41 (5.8)	121 (4.7)	481 (4.6)	254 (4.5)	136 (4.9)	66 (5.4)	52 (5.0)
Killip class								
I	16,762 (68.7)	509 (72.5)	1,803 (70.3)	7,345 (70.0)	3,801 (67.6)	1,776 (64.5)	829 (67.5)	699 (67.5)
II	530 (2.2)	10 (1.4)	57 (2.2)	203 (1.9)	136 (2.4)	70 (2.5)	30 (2.4)	24 (2.3)
III	152 (0.6)	2 (0.3)	11 (0.4)	57 (0.5)	33 (0.6)	19 (0.7)	17 (1.4)	13 (1.3)
IV	107 (0.4)	5 (0.7)	10 (0.4)	49 (0.5)	20 (0.4)	13 (0.5)	4 (0.3)	6 (0.6)
Access site								
Femoral	6,368 (26.1)	194 (27.6)	645 (25.1)	2,682 (25.5)	1,518 (27.0)	755 (27.4)	295 (24.0)	279 (27.0)
Radial	17,490 (71.6)	502 (71.5)	1872 (73.0)	7,571 (72.1)	3,977 (70.7)	1,932 (70.1)	902 (73.5)	734 (70.9)
Other	64 (0.3)	0 (0.0)	7 (0.3)	29 (0.3)	11 (0.2)	8 (0.3)	6 (0.5)	3 (0.3)
Vessel disease								
1-vessel disease	10,422 (42.7)	323 (46.0)	1,195 (46.6)	4,663 (44.9)	2,325 (41.8)	1,038 (38.2)	469 (38.7)	409 (39.9)
2-vessel disease	6,581 (27.0)	206 (29.3)	673 (26.2)	2,776 (26.8)	1,512 (27.2)	760 (28.0)	338 (27.9)	316 (30.8)
3-vessel disease	4,160 (17.0)	93 (13.2)	354 (13.8)	1,648 (15.9)	1,069 (19.2)	548 (20.2)	250 (20.6)	198 (19.3)
Left main disease	1,430 (5.9)	33 (4.7)	137 (5.3)	607 (5.9)	357 (6.4)	181 (6.7)	72 (5.9)	43 (4.2)
Stented coronary vessel during index procedure								
Left main	710 (2.9)	22 (3.1)	65 (2.5)	312 (3.0)	157 (2.8)	85 (3.1)	43 (3.5)	26 (2.5)
LAD	9,023 (37.0)	246 (35.0)	998 (38.9)	3,908 (37.2)	2,064 (36.7)	974 (35.4)	444 (36.2)	389 (37.6)
Diagonal branches	1,107 (4.5)	26 (3.7)	125 (4.9)	487 (4.6)	236 (4.2)	134 (4.9)	64 (5.2)	35 (3.4)
LCX	5,629 (23.1)	177 (25.2)	544 (21.2)	2,408 (22.9)	1,281 (22.8)	685 (24.9)	275 (22.4)	259 (25.0)
RCA	7,011 (28.7)	208 (29.6)	724 (28.2)	2,987 (28.4)	1,688 (30.0)	765 (27.8)	349 (28.4)	290 (28.0)
Stenosis class B2 or C	14,179 (58.1)	418 (59.5)	1529 (59.6)	5,979 (56.9)	3,254 (57.8)	1,643 (59.6)	742 (60.4)	641 (61.9)
Bifurcation PCI	1,873 (7.7)	52 (7.4)	190 (7.4)	815 (7.8)	427 (7.6)	232 (8.4)	87 (7.1)	70 (6.8)
CTO PCI	4,374 (17.9)	117 (16.7)	365 (14.2)	1,734 (16.5)	1,124 (20.0)	553 (20.1)	268 (21.8)	213 (20.6)
Number of DES	1.68 (1.02)	1.67 (1.00)	1.70 (0.99)	1.66 (1.00)	1.70 (1.04)	1.72 (1.07)	1.71 (1.03)	1.75 (1.04)
Stent length, mm	26 (18-41)	26 (17-38)	26 (17-38)	24 (18-40)	26 (18-42)	26 (18-43)	27 (18-44)	28 (18-46)
Stent diameter, mm	3.04 (0.51)	3.03 (0.51)	3.06 (0.52)	3.05 (0.51)	3.03 (0.51)	3.00 (0.51)	3.01 (0.53)	3.04 (0.50)
Smallest stent diameter, mm	2.93 (0.55)	2.94 (0.56)	2.93 (0.56)	2.94 (0.54)	2.93 (0.54)	2.89 (0.54)	2.90 (0.57)	2.92 (0.55)
Glycoprotein IIb/IIIa during index procedure	1,172 (4.8)	41 (5.8)	140 (5.5)	528 (5.0)	228 (4.1)	119 (4.3)	51 (4.2)	65 (6.3)
ASA postprocedure	21,688 (88.8)	613 (87.3)	2,299 (89.6)	9,357 (89.1)	4,983 (88.6)	2,442 (88.6)	1,088 (88.6)	906 (87.5)
P2Y₁₂ inhibitor postprocedure	21,776 (89.2)	629 (89.6)	2,293 (89.4)	9,364 (89.2)	5,018 (89.2)	2,480 (90.0)	1,092 (88.9)	900 (87.0)
DOAC postprocedure	887 (3.6)	24 (3.4)	82 (3.2)	368 (3.5)	222 (3.9)	114 (4.1)	55 (4.5)	22 (2.1)
Warfarin postprocedure	2,390 (9.8)	50 (7.1)	201 (7.8)	1,006 (9.6)	567 (10.1)	319 (11.6)	148 (12.1)	99 (9.6)
Complication during index procedure	307 (1.3)	5 (0.7)	48 (1.9)	126 (1.2)	67 (1.2)	33 (1.2)	17 (1.4)	11 (1.1)
Complete revascularization during index procedure	13,586 (55.7)	417 (59.4)	1,523 (59.4)	6,029 (57.4)	3,024 (53.8)	1,407 (51.1)	621 (50.6)	565 (54.6)
Contrast media, mL	130 (90-180)	125 (91-175)	130 (91-185)	130 (90-180)	130 (90-180)	130 (90-180)	125 (90-180)	135 (95-183)
X-ray exposure dose, mGy	4,460 (2,250-8,060)	4,390 (2,380-7,370)	4,360 (2,150-7,760)	4,340 (2,230-7,900)	4,540 (2,320-8,240)	4,600 (2,430-8,330)	4,550 (2,200-8,100)	5,030 (2,260-8,890)
X-ray exposure time, min	10.5 (6.3-17.3)	10.7 (6.5-17.2)	10.3 (6.5-16.8)	10.4 (6.3-17.1)	10.5 (6.2-17.5)	10.9 (6.4-17.4)	10.6 (6.1-17.5)	10.6 (6.3-17.4)

Values are n (%) or median (Q1-Q3). Baseline procedural characteristics for the complete cases cohort and for each HbA₁c category.

ASA = acetylsalicylic acid; CTO = chronical total occlusion; DES = drug-eluting stent(s); DOAC = direct oral anticoagulant; HbA₁c = glycosylated hemoglobin; LAD = left anterior descendent artery; LCX = left circumflex artery; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

CENTRAL ILLUSTRATION Methods and Main Results of the Study
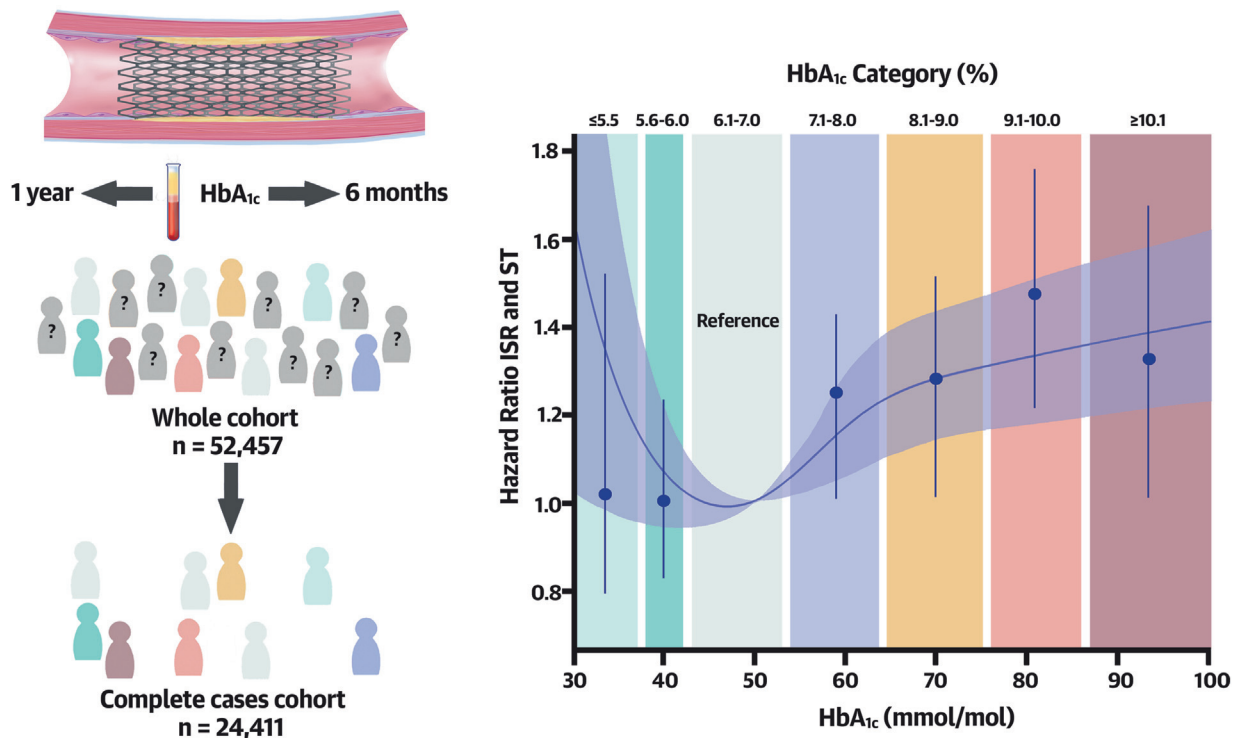
Santos-Pardo I, et al. J Am Coll Cardiol. 2024;■(■):■-■.

The initial cohort consisted of 52,457 subjects with previous diagnosis of T2D in whom at least 1 DES was implanted in de novo coronary lesions during the study period. Baseline HbA$_{1c}$ level was defined as the closest HbA$_{1c}$ value to PCI within 1 year before and up to 6 months after the procedure. Subjects with missing data for baseline HbA$_{1c}$ or any of the covariates were excluded from the complete cases cohort. The diagram shows the estimated HR with 95% CI for each HbA$_{1c}$ category and, superimposed on those, the estimated HR (dark blue line) and corresponding 95% CI (transparent blue area) when HbA$_{1c}$ is handled as a continuous variable modeled with natural cubic splines with 3 knots: HbA$_{1c}$ of 47, 55, and 66 mmol/mol. HbA$_{1c}$ levels are truncated at 30 and 100 mmol/mol. DES = drug-eluting stent; HbA$_{1c}$ = glycosylated hemoglobin; PCI = percutaneous coronary intervention; T2D = type 2 diabetes.
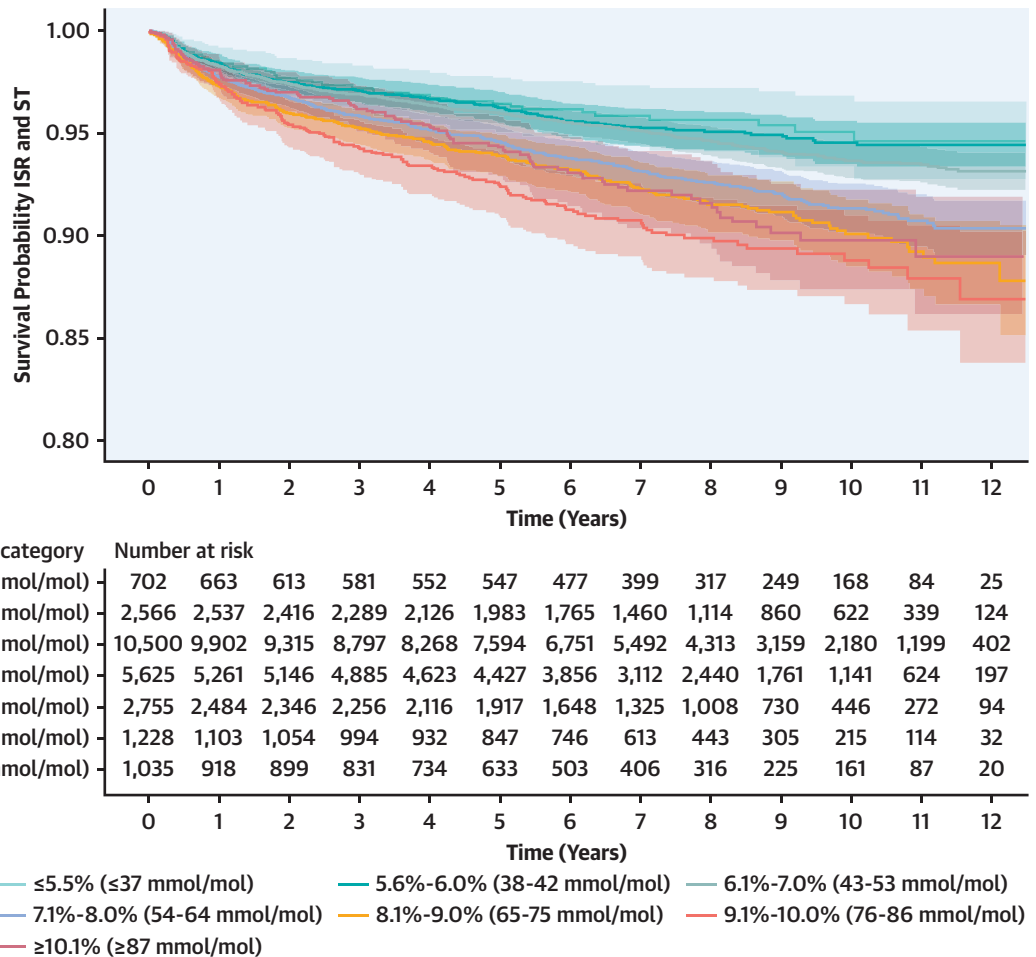
DISCUSSION

The main finding in this long-term follow-up study including 52,457 patients with a DES implanted was that the risk of stent failure increased gradually alongside poor glycemic control, independent of several clinical and procedural characteristics as well as previously identified risk factors. In patients with poor glycemic control, the risk of stent failure was 1.3-fold increased compared with patients with an HbA$_{1c}$ level of <7% (53 mmol/mol). The increased stent failure risk was driven mainly by ISR.

In a recent observational study including 13,543 patients (81% with diabetes), an increased risk of TVR with a J-shaped association was reported, that is, increased risk in the lowest and highest HbA$_{1c}$ categories, respectively.[12] We did observe such a trend for the groups with the lowest HbA$_{1c}$ levels when

exploring glycemic control as a continuous variable, but we failed to find any statistically significant association with a higher relative risk for the primary endpoint in those subgroups. Notable differences between the studies may have had an impact on this divergence; for example, HbA$_{1c}$ was handled as a preprocedure exploring factor and not as an updated mean; the follow-up time was shorter; and the endpoint differed to some extent, that is, TVR may only partially represent ISR and ST.[12]

Other recent—though small—observational studies have also demonstrated an association between poor glycemic control and increased risk of stent failure in patients with diabetes.[11,14] In a single-center PCI study in Japan including 1,568 subjects (32% with diabetes), patients with diabetes were at a higher risk of clinically driven late TLR following the implantation of a newer-generation DES. Notably, worse

FIGURE 2 Expanded, Age-Adjusted Kaplan-Meier Curves for the Primary Endpoint

HbA$_{1c}$ category	Number at risk												
	0	1	2	3	4	5	6	7	8	9	10	11	12
≤5.5% (≤37 mmol/mol)	702	663	613	581	552	547	477	399	317	249	168	84	25
5.6%-6.0% (38-42 mmol/mol)	2,566	2,537	2,416	2,289	2,126	1,983	1,765	1,460	1,114	860	622	339	124
6.1%-7.0% (43-53 mmol/mol)	10,500	9,902	9,315	8,797	8,268	7,594	6,751	5,492	4,313	3,159	2,180	1,199	402
7.1%-8.0% (54-64 mmol/mol)	5,625	5,261	5,146	4,885	4,623	4,427	3,856	3,112	2,440	1,761	1,141	624	197
8.1%-9.0% (65-75 mmol/mol)	2,755	2,484	2,346	2,256	2,116	1,917	1,648	1,325	1,008	730	446	272	94
9.1%-10.0% (76-86 mmol/mol)	1,228	1,103	1,054	994	932	847	746	613	443	305	215	114	32
≥10.1% (≥87 mmol/mol)	1,035	918	899	831	734	633	503	406	316	225	161	87	20

Expanded, age-adjusted Kaplan-Meier curves for each category of HbA$_{1c}$ for the primary endpoint, that is, in-stent restenosis and stent thrombosis. ISR = in-stent restenosis; other abbreviations as in **Figure 1**.

glycemic control at baseline and at 1 year of follow-up increased the risk of stent failure.[11] By contrast, improvements in glycemic control were not associated with a lower incidence of late TLR. Therefore, the investigators suggested the importance of glucose control, with HbA$_{1c}$ of <7.0% (<53 mmol/mol) being achieved during the early phase after PCI.[11] Because we used updated mean HbA$_{1c}$, that is, patients could change categories during a median of more than 6 years of follow-up, the time-dependent effect of HbA$_{1c}$ was taken into account.[21] This would indicate that the exposure time of glycemia is of importance for stent failure.

Chronic hyperglycemia is an important modifiable risk factor for long-term complications. Long-standing hyperglycemia affects several organs, including the heart and the coronary vessels, and diabetes is a major cause of accelerated atherogenesis leading to atherothrombosis.[22] Diabetes-related prothrombotic and proinflammatory states in connection with hyperglycemia, dyslipidemia, and hypertension can accelerate the atherosclerotic process after a stent implantation.[23] In the current study, the regression model was adjusted for most of the factors that may have an impact on stent failure after testing for statistical relevance, suggesting that achievement of good glycemic control is of substantial importance for avoiding stent failure.

In our full model, we accounted for age; however, there may be differences in the association between glycemic control and complications among older individuals with T2D.[24] Upon stratifying the cohort by

TABLE 3 Event Rates and Relative Risks of Stent Failure in Relation to HbA$_{1c}$ Levels

HbA$_{1c}$ Category	Subjects, n	Events, n	Event Rate, Events/1,000 Person-Years	Crude Model		Adjusted for Sex and Age		Full Model	
				HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Primary endpoint: in-stent restenosis and stent thrombosis									
≤5.5% (≤37 mmol/mol)	702	41	8.7 (6.0-11.3)	1.00 (0.73-1.37)	0.98	0.98 (0.71-1.34)	0.88	1.10 (0.80-1.52)	0.56
5.6%-6.0% (38-42 mmol/mol)	2,566	139	8.2 (6.8-9.5)	0.95 (0.7-1.14)	0.63	0.94 (0.78-1.13)	0.49	1.02 (0.85-1.23)	0.81
6.1%-7.0% (43-53 mmol/mol)	10,500	611	8.9 (8.2-9.6)	Reference	—	Reference	—	Reference	—
7.1%-8.0% (54-64 mmol/mol)	5,625	542	12.9 (11.8-14.0)	1.40 (1.25-1.57)	<0.001	1.40 (1.25-1.58)	<0.001	1.25 (1.11-1.41)	<0.001
8.1%-9.0% (65-75 mmol/mol)	2,755	294	14.8 (13.1-16.5)	1.57 (1.36-1.80)	<0.001	1.57 (1.36-1.80)	<0.001	1.30 (1.13-1.51)	<0.001
9.1%-10.0% (76-86 mmol/mol)	1,228	150	17.2 (14.4-19.9)	1.78 (1.49-2.13)	<0.001	1.75 (1.46-2.09)	<0.001	1.46 (1.21-1.76)	<0.001
≥10.1% (≥87 mmol/mol)	1,035	96	15.6 (12.4-18.7)	1.64 (1.32-2.04)	<0.001	1.57 (1.27-1.95)	<0.001	1.33 (1.06-1.66)	0.012
In-stent restenosis									
≤5.5% (≤37 mmol/mol)	702	29	6.1 (3.9-8.4)	1.20 (0.82-1.75)	0.35	1.18 (0.81-1.72)	0.39	1.35 (0.92-1.98)	0.13
5.6%-6.0% (38-42 mmol/mol)	2,566	85	5.0 (3.9-6.1)	0.98 (0.7-1.25)	0.90	0.98 (0.77-1.24)	0.85	1.10 (0.86-1.40)	0.44
6.1%-7.0% (43-53 mmol/mol)	10,500	360	5.2 (4.7-5.8)	Reference	—	Reference	—	Reference	—
7.1%-8.0% (54-64 mmol/mol)	5,625	326	7.8 (6.9-8.6)	1.42 (1.23-1.66)	<0.001	1.43 (1.23-1.66)	<0.001	1.24 (1.06-1.45)	0.007
8.1%-9.0% (65-75 mmol/mol)	2,755	199	10.0 (8.7-11.4)	1.79 (1.5 -2.13)	<0.001	1.79 (1.50-2.13)	<0.001	1.44 (1.20-1.73)	<0.001
9.1%-10.0% (76-86 mmol/mol)	1,228	97	11.1 (8.9-13.3)	1.94 (1.55-2.43)	<0.001	1.90 (1.52-2.38)	<0.001	1.55 (1.23-1.96)	<0.001
≥10.1% (≥87 mmol/mol)	1,035	63	10.2 (7.7-12.7)	1.82 (1.39-2.38)	<0.001	1.75 (1.34-2.29)	<0.001	1.45 (1.10-1.92)	0.008
Stent thrombosis									
≤5.5% (≤37 mmol/mol)	702	15	3.2 (1.6-4.8)	0.85 (0.50-1.43)	0.54	0.82 (0.49-1.39)	0.47	0.91 (0.54-1.54)	0.73
5.6%-6.0 % (38-42 mmol/mol)	2,566	59	3.5 (2.6-4.4)	0.93 (0.70-1.24)	0.64	0.92 (0.69-1.22)	0.57	0.97 (0.73-1.29)	0.84
6.1%-7.0% (43-53 mmol/mol)	10,500	262	3.8 (3.4-4.3)	Reference	—	Reference	—	Reference	—
7.1%-8.0% (54-64 mmol/mol)	5,625	234	5.6 (4.9-6.3)	1.41 (1.18-1.68)	<0.001	1.42 (1.19-1.70)	<0.001	1.32 (1.10-1.59)	0.003
8.1%-9.0% (65-75 mmol/mol)	2,755	107	5.4 (4.4-6.4)	1.33 (1.07-1.67)	0.012	1.34 (1.07-1.68)	0.011	1.17 (0.92-1.48)	0.20
9.1%-10.0% (76-86 mmol/mol)	1,228	54	6.2 (4.5-7.8)	1.51 (1.12-2.02)	0.006	1.47 (1.09-1.97)	0.010	1.27 (0.94-1.73)	0.12
≥10.1% (≥87 mmol/mol)	1,035	40	6.5 (4.5-8.5)	1.60 (1.15-2.23)	0.006	1.52 (1.09-2.12)	0.014	1.31 (0.93-1.84)	0.12

Events, event rates, and HRs (crude, adjusted for sex and age, and fully adjusted) for the primary endpoint (ie, in-stent restenosis or stent thrombosis) and for its separate components for each HbA$_{1c}$ category. The group 6.1% to 7.0% (43-53 mmol/mol) is set as the reference group in the Cox regression.
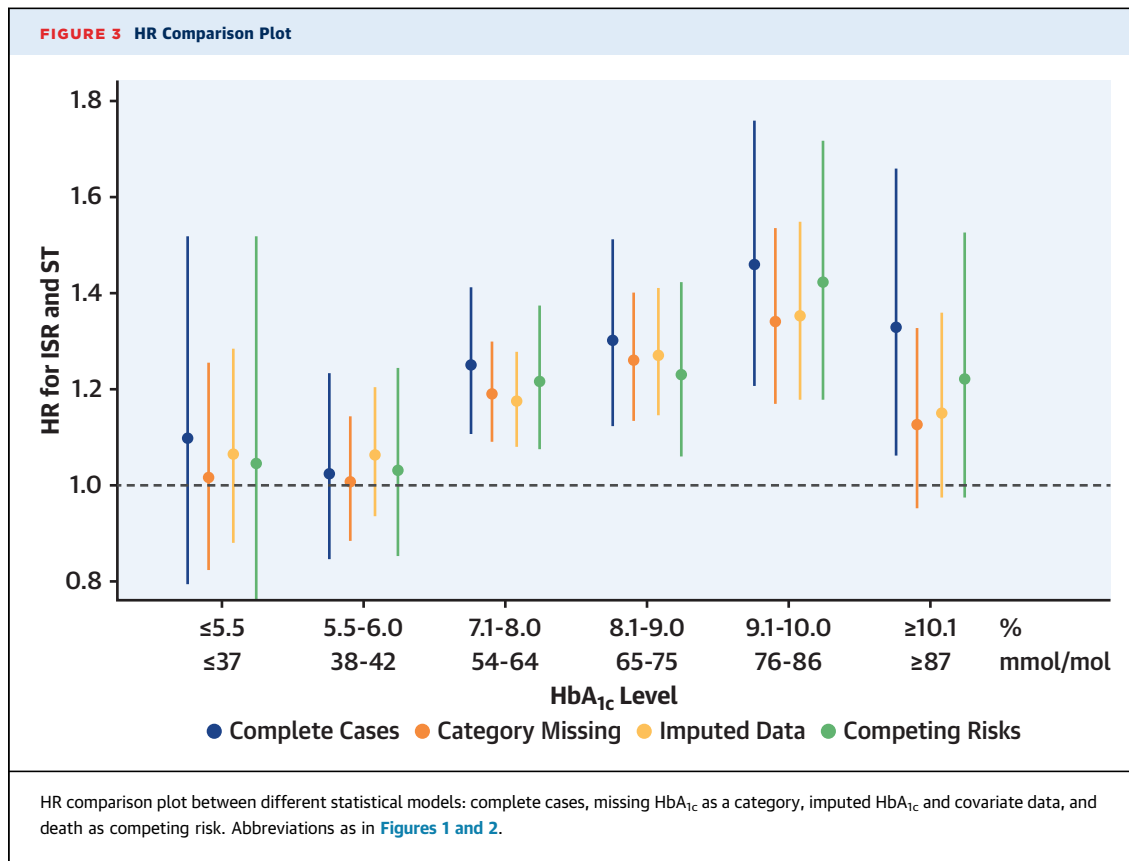
HbA$_{1c}$ = glycosylated hemoglobin.

age (<65 years and ≥65 years), we found that although the association between glycemic control and stent failure weakened for the older group, it still followed similar patterns observed in those younger than 65 years. Additionally, we noted a higher rate of events among the younger group in individuals with poor glycemic control. Because the model was adjusted for duration, the observed variation between age groups cannot be solely explained by this factor. We maintain that glycemic control following a coronary angioplasty is crucial; however, our findings may also align with the American Diabetes Association guidelines, suggesting slightly less stringent glycemic control in older individuals.[25]

No effect modification was detected for insulin treatment on the risk for stent failure in our study. This contrasts with previous studies finding insulin treatment as a predictor for MACE[26] and even stent failure outcomes.[27] Whether insulin could have a deleterious effect on atherosclerosis and neo-atherosclerosis or whether it merely represents a proxy for a more advanced diabetic cardiometabolic state is currently unclear.

In our study, we observed a significant J-shaped association between glycemic control and the risk of death. The shape of the association was mirrored for the secondary endpoint MI, but it did not reach statistical significance. These findings highlight the strong link between vascular complications and mortality with glycemic exposure, which may not always follow a linear relationship.[28] The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial found that the risk of macrovascular events and death were clearly lower only at HbA$_{1c}$ levels below 7.0% (53 mmol/mol).[29] In our study, using the same threshold, we observed a significantly higher relative risk of death among patients with HbA$_{1c}$ levels above 7.1% (54 mmol/mol), with a borderline significant association for MI. These findings corroborate those from previous studies,[29] underscoring the critical role of glycemic control in reducing cardiovascular adverse outcomes.

Finally, poor glycemic control also confers a higher risk of non-TVR, indicating that glycemic control is relevant not only with regard to the stented vessels

FIGURE 3 HR Comparison Plot

HR comparison plot between different statistical models: complete cases, missing HbA1c as a category, imputed HbA1c and covariate data, and death as competing risk. Abbreviations as in **Figures 1 and 2**.

but also in the progression of atherosclerosis in the native coronary arteries.[10]

STUDY STRENGTHS. To the best of our knowledge, this nationwide study including all patients in whom a contemporary DES was implanted in de novo lesions, in Sweden in 2010 to 2020, is the largest study addressing the association between glycemic control and specific stent failure outcomes. All patients enrolled received newer-generation DES, reflecting the risk of stent failure in a more contemporary setting than the previously published studies.[4-9] We believe that the time-updated approach for the exposure variable and all covariates confers a better understanding of the effect of overall glycemic control after the index procedure, given the fluctuating nature of glycemic control and confounders over time. This is of relevance, considering that ISR tends to occur later in newer-generation DES as compared with bare metal stents.[30] Finally, the strict complete cases analysis showed consistent results with those of the sensitivity analysis, conferring robustness to the main results.

STUDY LIMITATIONS. This is a retrospective observational study with the bias and limitations inherent to that study design. However, given the nature of the

exposure variable and the length of the follow-up, the current research question could not easily have been answered with superior study designs such as a randomized controlled clinical trial. A major limitation of this study is that the occurrence of the main outcome, that is, stent failure, was noted through a clinically driven angiography or incidentally found when a coronary angiography was performed for some other cause but not systematically searched for. It has been previously estimated that up to 50% of ISRs may be clinically silent.[23,31] Thus, we may have underestimated the strength of the association as well as the absolute rate of the outcome.

HbA1c has been endorsed in European[32] and U.S.[16] guidelines for the management of diabetes as a glycemic marker for the diagnosis and follow-up of patients with diabetes. However, several factors can theoretically affect the value of HbA1c, such as age, ethnicity, several hemoglobin variants, hemodialysis, HIV therapy, pregnancy, and anemia caused by chronic disease.[16,32] In the present study, some of these limitations on the exposure variable were not considered.

Insulin resistance has also been associated with a higher risk of ISR in subjects with—and

without—diabetes.[33,34] Subjects with insulin resistance may be overrepresented in some HbA_{1c} categories.[35] Insulin resistance per se was not accounted for in this study, and the impact of the potential interplay between these 2 key features of T2D on stent failure outcomes is currently unknown.

Finally, the generalizability of the results of this study is limited to the study population included, which consisted mainly of older men with T2D. Information on ethnicity was not available for this cohort. The percentage and characteristics of patients with T2D and multivessel disease referred to bypass surgery instead of PCI were not reliably validated and therefore have been considered unknown. The possible selection bias that this missing information implies must be considered.

CONCLUSIONS

Stent failure is a prognostically meaningful event leading to repeat revascularization, which may increase the risk of MACE. We found a significant association between poor glycemic control and risk of stent failure in subjects with T2D and CAD who were treated with implantation of a contemporary DES. These results emphasize the importance of glycemic control in patients with T2DM following coronary stenting.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr Irene Santos-Pardo, Department of Cardiology, Södersjukhuset, Sjukhusbacken 10, 11883 Stockholm, Sweden. E-mail: irene.santos-pardo@regionstockholm.se.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with type 2 diabetes mellitus, poor glycemic control is associated with a higher risk of stent failure following coronary angioplasty, driven mainly by in-stent restenosis.

TRANSLATIONAL OUTLOOK: Future studies should seek to identify the biological mechanisms linking glycemic control to in-stent restenosis in patients with type 2 diabetes after percutaneous coronary revascularization and determine whether specific approaches to achieving glycemic control are more efficacious than others with regard to preserving stent patency.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.