

Impact of diabetes on clinical outcomes of patients with hostile vascular access undergoing TAVI: insights from the HOSTILE registry

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Abstract

Background

Diabetes mellitus (DM) is associated with peripheral artery disease (PAD) and may increase the risk of vascular complications (VC) in patients with hostile femoral access undergoing TAVI.

Aims

To evaluate the association between DM, VC and clinical outcomes in this population.

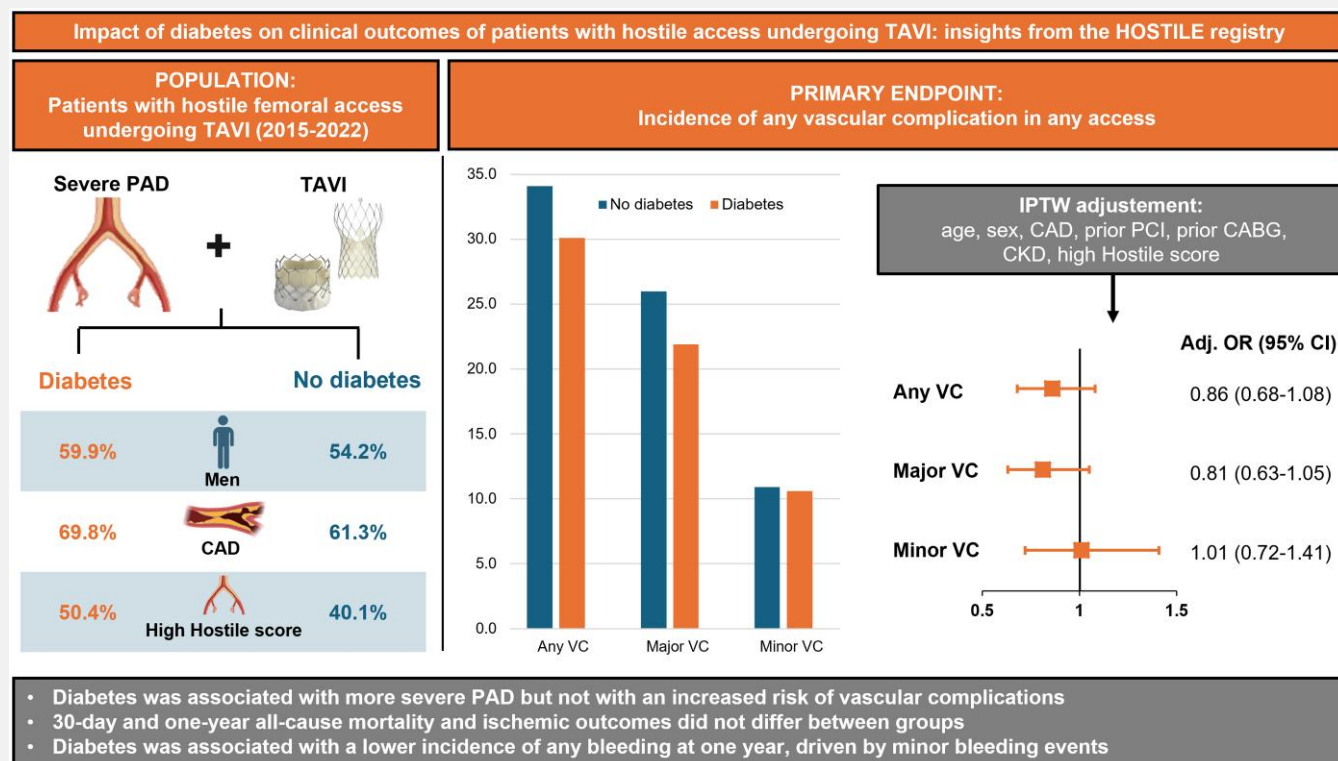
Methods and results

The HOSTILE registry is an international study including consecutive patients undergoing TAVI with hostile femoral access, defined as severe bilateral iliofemoral PAD requiring percutaneous transluminal angioplasty or alternative access. Outcomes of patients with and without diabetes were compared and stratified by access strategy. Inverse probability of treatment weighting (IPTW) was used to adjust for baseline differences. The primary endpoint was VC of any vascular access. Secondary endpoints included major and minor VC and 30-day and one-year clinical outcomes. Among 1707 patients, 559 (32.7%) had diabetes. Diabetic patients had a higher burden of comorbidities and more severe PAD, represented by higher Hostile scores. Despite this, rates of VC were similar between diabetic and non-diabetic patients (IPTW-adjusted odds ratio 0.86, 95% confidence interval 0.68–1.08, $P = .184$), consistently across access strategies. 30-day and one-year all-cause mortality and ischemic outcomes did not differ between groups. DM was associated with a lower incidence of any bleeding at one year, driven by minor bleeding events.

Conclusion

In patients with hostile femoral anatomy undergoing TAVI, diabetes was associated with more severe PAD but not with an increased risk of VC, mortality, or ischemic events. These findings support the feasibility and safety of contemporary TAVI strategies in diabetic patients with complex peripheral anatomy.

Graphical Abstract



Study population and primary endpoint. Abbreviations: CABG: coronary artery bypass graft, CAD: coronary artery disease, CI: confidence interval, CKD: chronic kidney disease, IPTW: inverse probability of treatment weighting, OR: odds ratio, PCI: percutaneous coronary intervention, TAVI: transcatheter aortic valve implantation, VC: vascular complications.

Keywords

Diabetes • Transcatheter • Aortic • Hostile • Access

Introduction

Diabetes mellitus (DM) represents a major and rising global health burden, with its impact on morbidity and mortality largely driven by diffuse vascular involvement.¹ Accelerated atherosclerosis in diabetic patients results from multiple mechanisms, including chronic inflammation, persistent hyperglycemia, endothelial dysfunction, and impaired collateral vessel formation.^{2,3} As a consequence, peripheral artery disease (PAD) is not only two- to four-fold more prevalent in patients with DM compared with those without, but is also more diffuse, rapidly progressive, and less responsive to endovascular treatment.^{4–6}

DM is also associated with an increased risk of developing severe aortic stenosis, in a dose-dependent relationship with fasting glucose levels.^{7–9} Accordingly, patients with DM referred for transcatheter aortic valve implantation (TAVI) frequently present with concomitant severe PAD, which may impair transfemoral access and necessitate percutaneous treatment of femoral arteries or the use of alternative access routes.¹⁰ Although transfemoral TAVI is consistently associated with better outcomes compared with alternative access strategies, PAD and the need for endovascular treatment are linked to a substantial risk of vascular complications.^{10–13}

The coexistence of DM and hostile femoral anatomy may complicate lesion crossing, balloon angioplasty, stent deployment, and vascular closure. This may increase the risk of access-site vascular complications (VC) as compared with nondiabetic patients. These events occur in 2–16% of TAVI procedures and are strongly associated with adverse outcomes, including a doubling of one-year mortality in cases of major VC.^{14–16} However, the specific impact of DM on vascular complications and clinical outcomes in this high-risk setting has not been adequately investigated.

This analysis from the Hostile registry aims to evaluate the impact of DM on VC and clinical outcomes in patients with hostile femoral access undergoing TAVI, treated either with femoral percutaneous transluminal angioplasty (PTA) or via alternative access strategies.

Methods

Study design and objective

The design of the Hostile registry has been previously described.¹⁷ Briefly, this international, multicenter study retrospectively (January 2015 to June 2021) and prospectively (June 2021 to February 2022) collected data on consecutive patients undergoing TAVI with hostile femoral access. Hostile femoral access was defined as severe bilateral iliofemoral PAD requiring pre-procedural PTA (including angioplasty, stenting, or intravascular lithotripsy [IVL]) to enable transfemoral TAVI, or mandating the use of alternative (non-femoral) access routes. A total of 1707 consecutive patients were included. The primary analyses compared outcomes across three access categories: transfemoral (TFA); transthoracic (TTA, including transapical and transaortic); and transalternative (TAA, including transaxillary, transcarotid, transbrachiocephalic, and transcaval). PAD severity was additionally assessed using the Hostile score, a numerical tool derived from anatomical and morphological variables across predefined iliofemoral segments. A Hostile score >8.5 indicated high iliofemoral PAD burden. The anatomical variables included in the Hostile score are listed in [Supplementary Table S1](#).

For the present analysis, clinical outcomes of patients with or without DM were compared after stratification according to main access route.

Study endpoints

The primary endpoint was the rate of VC in any access (main or secondary). Secondary endpoints included the rates of major or minor VC in main, secondary, or any access, and the 30-day and one-year rates of all-cause mortality, cardiovascular (CV) death, myocardial infarction (MI), stroke, any bleeding and major bleeding. All endpoints were defined according to the Valve Academic Research Consortium (VARC)-3 definition.¹⁸

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation or median (interquartile range) and were compared using Student's *t*-test or the Mann-Whitney *U* according to the normality of data distribution, verified using the Shapiro-Wilk test. Categorical variables are reported as number (percentage) and were compared using the chi-square test without Yates' correction for continuity or the Fisher exact test, as appropriate.

To account for confounding bias between diabetic and nondiabetic patients, a propensity score (PS) methodology with IPTW was applied as the primary analysis.¹⁹ PS were estimated with multivariable logistic regression, including variables with a difference in their distribution between the two treatment groups or deemed to be clinically relevant. The following variables were included in the model used to estimate the PS: age, sex, coronary artery disease (CAD), prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), chronic kidney disease (CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m²) and a high Hostile score (>8.5 points). Stabilized weights were computed from PS by means of IPTW. The weight for diabetic patients was the inverse of the respective PS, whereas the weight for nondiabetic patients was the inverse of 1–PS. Stabilized weights showed a median of 1.59 and a right-skewed distribution, as expected. The weights overlap was visually confirmed. Extreme weights were infrequent, with 99% of weights below 5.1, suggesting no need for weight truncation. Post-IPTW adjustment, the balance of covariates between the treatment groups was assessed by means of standardized mean differences (SMD), and variables were considered balanced if the SMD was $\leq 10\%$.¹⁹ The SMD before and after covariate balancing with the IPTW method are illustrated in [Supplementary Figure S1](#).

The impact of DM on VC was tested by means of logistic regression and expressed as odds ratio (OR) with 95% confidence interval (CI). For the other endpoints, unadjusted survival curves were constructed with the use of Kaplan–Meier estimates, and groups were compared according to Cox proportional hazards model. The proportionality assumption for the Cox models was verified using the Schoenfeld residuals method. Hazard ratios (HRs) and 95% CI are reported. Both models were weighted using IPTW, and adjusted ORs and HRs are reported.

As an additional exploratory analysis, we compared baseline characteristics between patients with and without VC in the diabetic and nondiabetic subgroups.

A two-sided *P*-value <.05 was considered statistically significant. Statistical analyses were performed using Stata version 19.0 (StataCorp, College Station, TX, USA).

Results

Among 1707 patients with hostile femoral anatomy undergoing TAVI, 559 (32.7%) had DM. Median follow-up was 14.7 (4.4–31.8) months for the whole population and did not differ between diabetic (14.9 [4.5–32.2] months) and nondiabetic patients (14.3 [4.1–30.6] months).

Baseline clinical characteristics and distribution of peripheral disease

Several differences in baseline characteristics were found between the two cohorts ([Table 1](#)). Diabetic patients were younger (80 vs 82 years, *P* < .001), more frequently male (60% vs 54%, *P* = .025), and exhibited a higher burden of comorbidities, including hypertension, CAD (70% vs 61%, *P* < .001) and CKD. Similarly, a history of PCI, CABG or stroke was more common in this group. Despite these differences, the STS score was similar between groups (4.8 [3.3–7.0] in diabetic patients vs 4.6 [3.0–6.8] in nondiabetic patients, *P* = .075).

DM was associated with more advanced peripheral artery disease ([Table 2](#)). A high Hostile score was reported in 50% of diabetic patients, vs 40% in nondiabetic ones (*P* < .001). Diabetic patients also showed a narrower minimal lumen diameter (3.2 [2.0–4.4] mm vs 3.4 [2.7–4.3] mm) with tighter stenoses. However, the anatomical distribution of disease, lesion length, calcification, tortuosity, and the treatment strategy (including the use of adjunctive techniques such as IVL) were similar between groups.

Table 1 Baseline features according to diabetic status

	Overall	No diabetes	Diabetes	P-value
N patients (%)	1707 (100.0%)	1148 (67.3%)	559 (32.7%)	
Age (years), median (IQR)	81.0 (76.9, 85.0)	82.0 (78.0, 85.4)	80.0 (75.0, 84.0)	<.001
Age ≥81 years, n (%)	910 (53.3%)	656 (57.1%)	254 (45.4%)	<.001
Male sex, n (%)	957 (56.1%)	622 (54.2%)	335 (59.9%)	.025
BMI (kg/m ²), median (IQR)	25.0 (23.0, 28.0)	25.0 (23.0, 27.5)	27.0 (24.0, 30.0)	<.001
Hypertension, n (%)	1501 (88.1%)	983 (85.9%)	518 (92.8%)	<.001
CAD, n (%)	1078 (64.1%)	694 (61.3%)	384 (69.8%)	<.001
Three-vessel disease, n (%)	238 (17.4%)	147 (15.7%)	91 (21.4%)	.009
Left main disease, n (%)	128 (10.2%)	79 (9.2%)	49 (12.6%)	.061
Prior stroke, n (%)	178 (10.4%)	107 (9.3%)	71 (12.7%)	.032
Prior PCI, n (%)	723 (42.4%)	452 (39.4%)	271 (48.5%)	<.001
Prior MI, n (%)	417 (24.4%)	265 (23.1%)	152 (27.2%)	.065
Prior CABG, n (%)	344 (20.2%)	213 (18.6%)	131 (23.4%)	.019
Atrial fibrillation, n (%)	609 (35.7%)	407 (35.5%)	202 (36.1%)	.80
LVEF ≤40%, n (%)	281 (16.5%)	167 (14.5%)	114 (20.4%)	.002
eGFR calculated (mL/min), median (IQR)	54.0 (39.3, 72.0)	55.8 (39.7, 73.7)	50.9 (38.7, 68.3)	.002
CKD, n (%)	1000 (58.6%)	637 (55.5%)	363 (64.9%)	<.001
EuroSCORE II (%), median (IQR)	5.2 (3.2, 8.9)	5.3 (3.2, 9.0)	5.0 (3.2, 8.4)	.50
STS score (%), median (IQR)	4.7 (3.1, 6.9)	4.6 (3.0, 6.8)	4.8 (3.3, 7.0)	.075
NYHA class >2, n (%)	1195 (70.0%)	777 (67.7%)	418 (74.8%)	.003
Haemoglobin (g/dL), median (IQR)	11.7 (10.3, 12.9)	11.8 (10.3, 13.0)	11.5 (10.3, 12.9)	.31
Mean aortic valve gradient pre-TAVI (mmHg), median (IQR)	42.0 (32.0, 50.0)	42.0 (33.0, 51.0)	41.0 (30.0, 48.0)	.002
AR pre-TAVI ≥moderate, n (%)	429 (25.1%)	321 (28.0%)	108 (19.3%)	<.001

Significant P-values are reported in bold.

AR, aortic regurgitation; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

Procedural characteristics and intraprocedural outcomes

Table 3 reports procedural characteristics, which were similar in the two cohorts. Overall, 30% of patients underwent TAVI through a TFA, 38% through a TTA and 32% through a TAA. Surgical closure was used in 59% of cases. Valve types were similar in the two groups, with SAPIEN valves (Edwards Lifesciences, USA) used in almost half of the cases.

VARC-3-defined procedural success was achieved in 93.6% of diabetic patients and 92.3% nondiabetic ones ($P = .36$) (Supplementary Table S2). Post-procedural valve hemodynamics were similar between the two groups, and no significant differences were observed in the rates of acute kidney injury, residual paravalvular leak, and length of hospital stay. Diabetic patients require fewer in-hospital transfusions (20.6% vs 25.4%, $P = .027$).

Vascular complications

VC at any access occurred in 30.1% of diabetic patients and 34.1% of nondiabetic ones (unadjusted OR 0.83 [95% CI: 0.67–1.04], $P = .101$) (Figure 1 and Supplementary Tables S3 and Table S4). The overall rates of major and minor VC were 21.9% and 10.6% for diabetic patients

and 26.0% and 10.9% for nondiabetic ones, respectively (unadjusted OR: 0.80 [0.63–1.01], $P = .066$ for major VC and 0.97 [0.70–1.34], $P = .834$ for minor VC). Similar rates of VC were found when considering only the main or the secondary access, and after stratifying the population according to access site or access strategy (surgical vs percutaneous) (Supplementary Table S5).

The IPTW-adjusted analyses yielded consistent results, with similar rates of overall, major and minor VC in the two cohorts (adjusted OR for VC of any access: 0.86 [0.68–1.08], $P = .184$), before and after stratifying for access strategy (Figure 2).

Baseline characteristics of patients with and without VC according to diabetic status are reported in Supplementary Tables S6–S8. In both groups, patients with VC had a lower BMI and a higher STS score, while PAD characteristics were mostly similar in the two cohorts. Patients with VC less frequently underwent surgical access closure, especially those with a TAA access. Among diabetic patients, those with VC more frequently had femoral secondary access as compared with those without VC.

30-days and one-year outcomes

At 30 days, all-cause mortality, cardiovascular death, myocardial infarction, and stroke rates were similar between diabetic and

Table 2 Peripheral vascular disease characteristics and treatment according to diabetic status

	Overall	No diabetes	Diabetes	P-value
N patients (%)	1707 (100.0%)	1148 (67.3%)	559 (32.7%)	
Hostile score, median (IQR)	8.5 (6.5, 9.5)	8.0 (6.5, 9.5)	9.0 (7.0, 10.0)	<.001
High Hostile score (> 8.5), n (%)	741 (43.5%)	459 (40.1%)	282 (50.4%)	<.001
N of iliofemoral lesions, median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	.86
N of diseased segments, median (IQR)	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	.34
N of lesions treated, median (IQR)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	.52
N of patients with at least one lesion involving the aortic bifurcation, n (%)	557 (54.0%)	368 (52.1%)	189 (58.2%)	.068
N of patients with at least one lesion with severe calcification (≥180° arch), n (%)	758 (44.4%)	506 (44.1%)	252 (45.1%)	.70
N of patients with at least one lesion with severe tortuosity (≥90°), n (%)	238 (23.2%)	174 (24.8%)	64 (19.7%)	.072
Minimal lumen diameter (mm), median (IQR)	3.4 (2.5, 4.3)	3.4 (2.7, 4.3)	3.2 (2.0, 4.4)	.033
Most severe stenosis (%), median (IQR)	61.5 (50.3, 71.0)	60.0 (50.0, 69.7)	64.0 (53.6, 75.0)	<.001
Max lesion length (mm), median (IQR)	58.2 (32.0, 100.0)	58.1 (30.0, 97.0)	59.2 (35.0, 107.0)	.28
PTA performed, n (%) ^a	518/518 (100.0%)	343/343 (100.0%)	175/175 (100.0%)	—
PTA-only, n (%)	335/518 (64.7%)	222/343 (64.7%)	113/175 (64.6%)	.97
IVL, n (%)	183/518 (35.3%)	121/343 (35.3%)	62/175 (35.4%)	.97
PTA balloon max diameter (mm), median (IQR)	8.0 (7.0, 8.0)	8.0 (6.5, 8.0)	8.0 (7.0, 8.0)	.40

Significant P-values are reported in bold.

^aThe % refers to a denominator of 518 patients, who underwent a TF access.

IVL, intravascular lithotripsy; IQR, interquartile range; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; TF, transfemoral.

nondiabetic patients (Table 4). Bleeding events were less frequent among diabetic patients (Kaplan-Meier estimates: 19.2% vs 24.5%, HR 0.77 [0.62–0.97], $P = .024$), but this trend did not reach statistical significance after IPTW adjustment (HR 0.81 [0.65–1.01], $P = .063$). No significant difference was found in major bleeding before and after adjustment.

At one year, no differences were observed in all-cause mortality, cardiovascular death, myocardial infarction, or stroke (Table 4 and Figure 3). Conversely, diabetes was independently associated with a lower risk of any bleeding at one year (HR 0.76 [0.61–0.95], $P = .017$ before IPTW and HR 0.79 [0.63–0.99], $P = .038$ after IPTW), while major bleeding was numerically lower but not statistically different (HR 0.79 [0.61–1.01], $P = 0.058$ before IPTW and HR 0.80 [0.62–1.03], $P = .086$ after IPTW).

Discussion

This analysis from the Hostile registry is the first to explore the impact of DM on clinical outcomes in patients with hostile access undergoing TAVI. The main findings are as follows (Graphical Abstract):

- (1) Diabetic patients had a higher burden of comorbidities and a higher Hostile score;
- (2) Despite this, DM was not associated with an increased risk of VC across access strategies;
- (3) Short- and mid-term mortality and ischemic outcomes were comparable between diabetic and nondiabetic patients, while overall bleeding events were less frequent among those with DM.

Peripheral artery disease is a well-established determinant of adverse outcomes after TAVI.¹⁰ A large report has shown that the need for peripheral intervention during TAVI is associated with worse clinical outcomes, including mortality, although to a lesser extent than alternative-access TAVI.¹¹ Including only patients with severe PAD, the original Hostile registry confirmed these results beyond the evident inclusion bias of previous studies.¹⁷ Additionally, a clinically useful PAD evaluation score was introduced, which can effectively predict VC in patients undergoing TAVI.²⁰

The prevalence of DM was similar in these observational studies and comparable to that found in randomized trials, but its specific impact on vascular and clinical outcomes was not previously investigated.²¹ DM is a known predictor of PAD, and diabetic patients tend to have more diffuse and aggressive disease.^{4,6} This was partially confirmed in the present analysis, as diabetic patients showed a higher Hostile score and tighter lesions, but had a similar distribution of the disease in terms of length, localisation, and calcification. Hence, they received comparable peripheral treatment.

The impact of DM on VC in patients undergoing TAVI has been poorly explored. One multicenter study found that diabetic patients had a trend towards a higher rate of VC as compared with nondiabetic ones ($P = .074$), with a significantly higher rate of arteriovenous fistula ($P = .013$).²² This could be linked to impaired wound healing and microvascular disease.²³ In contrast, our study found similar rates of VC between the two cohorts, with numerically lower absolute rates among diabetic patients despite the higher Hostile scores. Therefore, DM was not associated with an increased VC risk, and this was consistent regardless of the access route used. It should be acknowledged that, in the context of severe PAD, the additional impact of DM on VC

Table 3 Procedural features according to diabetic status

	Overall	No diabetes	Diabetes	P-value
N patients (%)	1707 (100.0%)	1148 (67.3%)	559 (32.7%)	
Procedural year ≤2018, n (%)	802 (47.0%)	538 (46.9%)	264 (47.2%)	.89
Anaesthesia, n (%)				.46
General anesthesia	1068 (65.6%)	714 (65.4%)	354 (66.0%)	
Conscious sedation	316 (19.4%)	220 (20.1%)	96 (17.9%)	
Local anesthesia	244 (15.0%)	158 (14.5%)	86 (16.0%)	
Surgical cutdown, n (%)	1032 (63.5%)	698 (64.0%)	334 (62.5%)	.56
Transfemoral	57 (11.0%)	38 (11.1%)	19 (10.9%)	.94
Transthoracic	582 (100.0%)	394 (100.0%)	206 (100.0%)	—
Transalternative	393/75.0%)	369 (75.4%)	127 (74.3%)	.79
Echo-guided puncture, n (%)	313 (20.4%)	210 (20.3%)	103 (20.6%)	.89
TAVI main access route, n (%)				.80
<i>Transfemoral</i>	518 (30.3%)	343 (29.8%)	175 (31.3%)	
Right femoral	318 (18.6%)	207 (18.0%)	111 (19.9%)	
Left femoral	200 (11.7%)	136 (11.8%)	64 (11.4%)	
<i>Transthoracic</i>	642 (37.6%)	436 (38.0%)	206 (36.9%)	
Transapical	582 (34.1%)	391 (34.1%)	191 (34.2%)	
Transaortic	60 (3.5%)	45 (3.9%)	15 (2.7%)	
<i>Transalternative</i>	547 (32.1%)	369 (32.1%)	178 (31.9%)	
Transcarotid	18 (1.1%)	12 (1.0%)	6 (1.1%)	
Transaxillary	503 (29.5%)	341 (29.7%)	162 (29.0%)	
Transbrachiocephalic	10 (0.6%)	5 (0.4%)	5 (0.9%)	
Transcaval	16 (0.9%)	11 (1.0%)	5 (0.9%)	
Secondary access used for TAVI, n (%)				.37
Femoral	786 (63.1%)	530 (61.8%)	256 (66.0%)	
Radial	437 (35.1%)	311 (36.3%)	126 (32.5%)	
Other	22 (1.8%)	7 (0.8%)	2 (0.5%)	
Valve type, n (%)				.28
Evolut/Corevalve	564 (33.3%)	378 (33.2%)	186 (33.6%)	
SAPIEN	814 (48.1%)	558 (48.9%)	256 (46.2%)	
ACURATE neo/neo2	107 (6.3%)	62 (5.4%)	45 (8.1%)	
Portico/Navitor	95 (5.6%)	66 (5.8%)	29 (5.2%)	
Other	114 (6.7%)	76 (6.7%)	38 (6.9%)	
Access closure, n (%)				.76
ProGlide	463 (30.1%)	308 (30.0%)	155 (30.2%)	
AngioSeal	24 (1.6%)	19 (1.9%)	5 (1.0%)	
Manta	72 (4.7%)	46 (4.5%)	26 (5.1%)	
Combination of devices	85 (5.5%)	55 (5.4%)	30 (5.8%)	
Covered stent	4 (0.3%)	2 (0.2%)	2 (0.4%)	
Surgery	891 (57.9%)	595 (58.0%)	296 (57.6%)	
Total contrast volume (mL), median (IQR)	100.0 (60.0, 153.0)	100.0 (60.0, 156.5)	99.0 (60.0, 150.0)	.23
Fluoroscopy time (min), median (IQR)	14.0 (6.0, 26.0)	15.0 (6.0, 27.0)	13.0 (5.0, 25.0)	.039

Significant P-values are reported in bold.

IQR, interquartile range; TAA, transalternative access; TAVI, transcatheter aortic valve implantation; TFA, transfemoral access; TTA, transthoracic access.

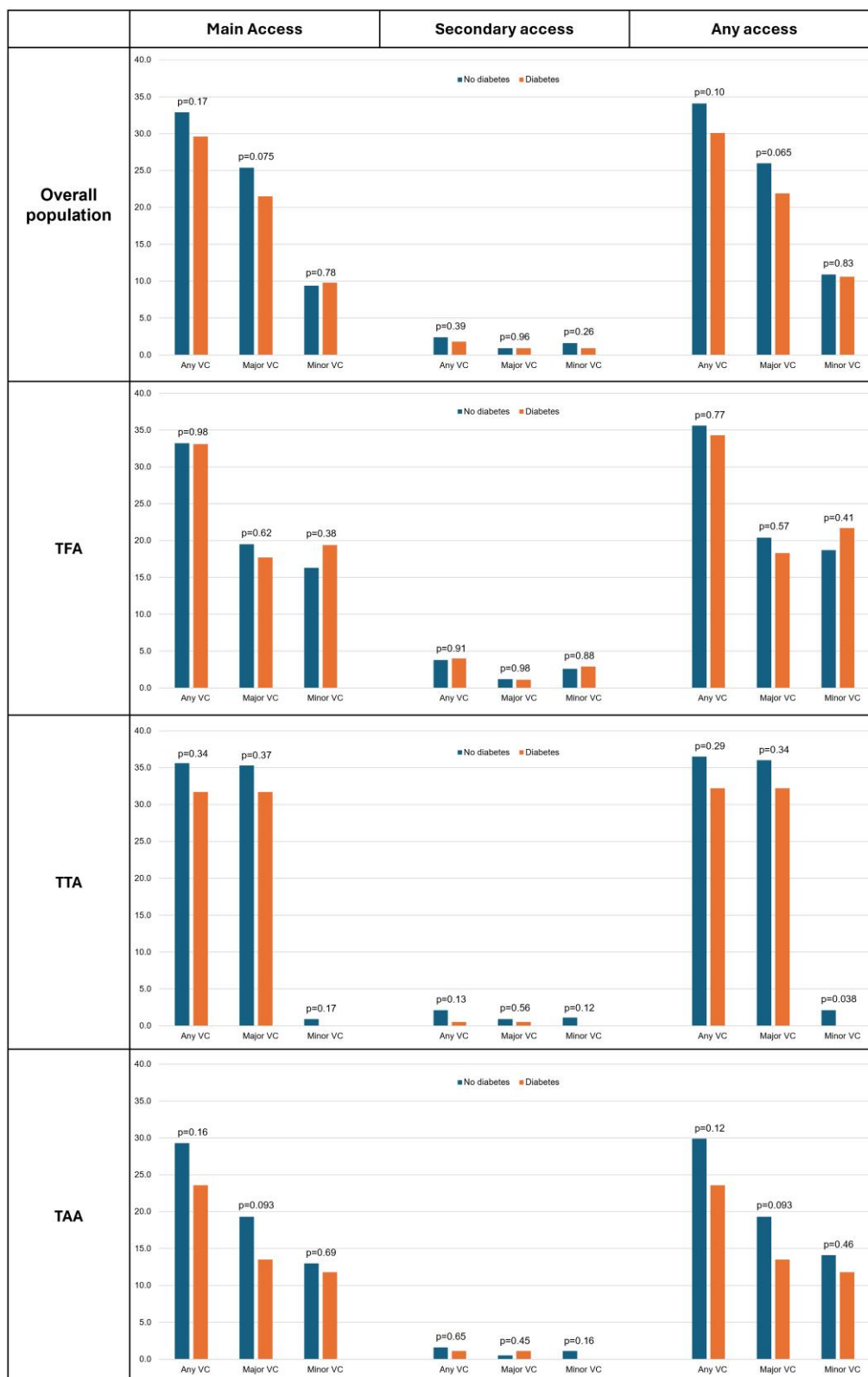


Figure 1 Rates of vascular complication (any, major and minor) according to diabetic status in the overall population and after stratifying by access route. Results are reported for main access, secondary access and any access. TAA, transalternative access; TAVI, transcatheter aortic valve implantation; TFA, transfemoral access; TTA, transthoracic access; VC, vascular complications

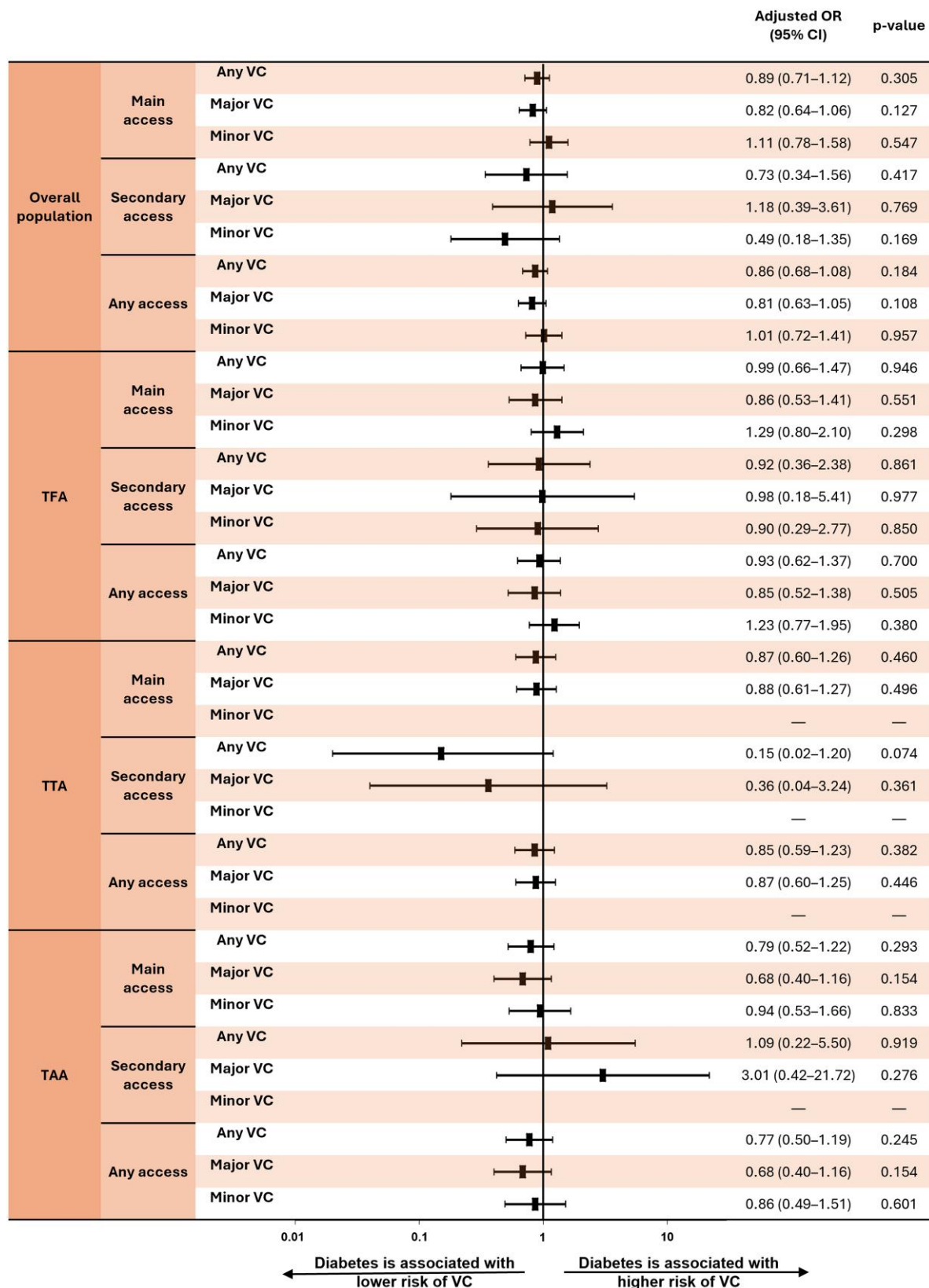


Figure 2 IPTW-adjusted odds ratio for impact of diabetes on vascular complications (any, major and minor) in the overall population and after stratifying by access route. CI, confidence interval; IPTW, inverse probability of treatment weighting; OR, odds ratio; TAA, transarterial access; TFA, transfemoral access; TTA, transthoracic access; VC, vascular complications

Table 4 Thirty-day and one-year clinical outcomes, before and after IPTW-adjustment

	No diabetes (N = 1148)	Diabetes (N = 559)				
	N of events (KM incidence)	N of events (KM incidence)	HR	P-value	Adjusted HR	P-value
30 days						
All-cause mortality	57 (5.1%)	27 (5.0%)	0.97 (0.61–1.54)	0.907	0.87 (0.54–1.40)	0.572
Cardiac death	51 (4.9%)	21 (3.9%)	0.84 (0.51–1.40)	0.510	0.77 (0.45–1.32)	0.344
Myocardial infarction	7 (0.6%)	5 (0.9%)	1.46 (0.46–4.61)	0.514	1.41 (0.44–4.53)	0.560
Stroke	28 (2.5%)	20 (3.7%)	1.47 (0.83–2.61)	0.188	1.45 (0.78–2.67)	0.239
Bleeding	278 (24.5%)	106 (19.2%)	0.77 (0.62–0.97)	0.024	0.81 (0.65–1.01)	0.063
Major bleeding	214 (18.9%)	84 (15.2%)	0.80 (0.62–1.03)	0.084	0.83 (0.64–1.07)	0.144
One year						
All-cause mortality	157 (15.4%)	72 (14.7%)	0.95 (0.72–1.25)	0.699	0.88 (0.66–1.18)	0.387
CV death	114 (11.2%)	54 (11.1%)	0.98 (0.71–1.35)	0.888	0.90 (0.64–1.26)	0.541
Myocardial infarction	13 (1.2%)	8 (1.7%)	1.35 (0.55–3.31)	0.506	1.02 (0.41–2.51)	0.968
Stroke	33 (3.1%)	23 (4.5%)	1.43 (0.84–2.44)	0.186	1.35 (0.76–2.40)	0.301
Bleeding	291 (25.9%)	110 (20.1%)	0.76 (0.61–0.95)	0.017	0.79 (0.63–0.99)	0.038
Major bleeding	223 (19.9%)	86 (15.7%)	0.79 (0.61–1.01)	0.058	0.80 (0.62–1.03)	0.086

Significant P-values are reported in bold.

IQR, interquartile range; TAA, transalternative access; TAVI, transcatheter aortic valve implantation; TFA, transfemoral access; TTA, transthoracic access.

may be difficult to detect because of a ceiling effect. Nonetheless, given the large sample size of this real-world registry, the absence of even a directional trend is reassuring, and these findings can be considered in support of the safety of contemporary TAVI strategies in diabetic patients with hostile anatomy. Given that the treatment strategies were similar in the two groups, our results do not suggest that there is a need to provide more aggressive endovascular treatment in the diabetic population in this context, as compared to non-diabetic patients. However, reduction of VC should remain an aim of the interventional community, especially in patients with severe PAD, in whom VC can be up to four times higher than in the general population undergoing TAVI.²⁴ Although the incidence of VC has declined over time, its prognostic impact remains substantial and, with the expansion of TAVI to patients with increasingly complex anatomy, will likely be relevant in the near future.^{16,25} Our exploratory analyses suggested that VC may be affected by other factors, including BMI and the choice of the secondary access. Future studies should focus on the impact of other modifiable predictors on the rates of VC in patients with hostile femoral access.

Notably, DM did not adversely affect mortality or ischemic outcomes in the present study, in contrast with some prior reports.^{24,26} An unexpected finding was the lower incidence of bleeding events among diabetic patients at one year, which remained significant after IPTW adjustment. The effect of DM on bleeding after TAVI remains debated, as a large study reported lower rates of bleeding in diabetic vs nondiabetic patients,²⁷ but this was not confirmed by a later meta-analysis.²⁶ However, in our study, major bleeding rates were not significantly different, indicating that this difference was driven by minor bleeding events, and should be considered hypothesis-generating

only. Although minor bleeding has a limited impact on hard clinical endpoints,²⁸ future prospective studies should further explore the interplay between diabetic status, bleeding patterns, and subsequent outcomes.

Finally, medical therapy is expected to play a central role in reducing VC in diabetic patients with PAD. Novel antidiabetic agents have demonstrated beneficial effects on plaque stabilisation and cardiovascular outcomes, including in patients undergoing TAVI.^{29,30} Whether these therapies may additionally influence peripheral plaque progression or stabilisation warrants dedicated prospective investigation.

Limitations

This study has several limitations. First, its observational design precludes causal inference, despite the use of robust statistical adjustment with IPTW. Consequently, these findings should be interpreted as hypothesis-generating. Second, all procedural steps were decided by the treating physician, and this, alongside the high experience of the centres involved, may limit the generalisability of the study results. Third, since information on disease duration, glycemic control, or specific antidiabetic therapies was lacking, diabetes was treated as a binary variable, and further mechanistic insights could not be inferred. Fourth, detailed information on the causes of non-cardiac deaths, VC and bleeding sub-classifications, or PAD-related outcomes such as acute limb ischemia or major amputations due to vascular causes, was not captured in this study. Fifth, differences among treated groups could emerge at a longer follow-up. Finally, this registry spans a long inclusion period, during which devices, techniques, and periprocedural management evolved.

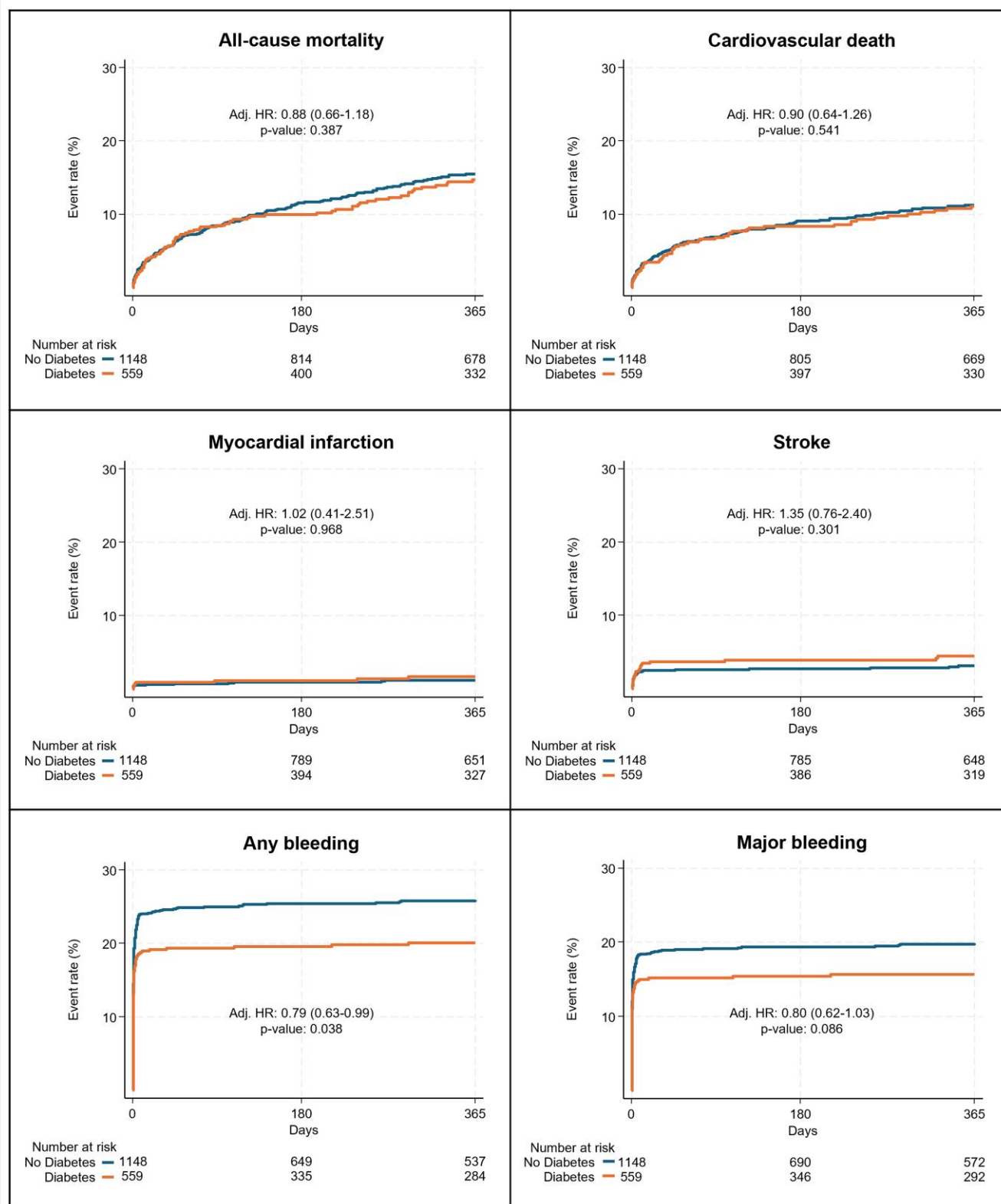


Figure 3 Kaplan-Meier curves of one-year clinical outcomes according to diabetic status. Abbreviations: Adj. HR: adjusted Hazard Ratio

Conclusions

In patients with hostile femoral anatomy undergoing TAVI, DM was associated with more severe PAD but not with an increased risk of VC, mortality, or ischemic events. An exploratory signal towards a lower incidence of bleeding was reported. These findings should be validated in larger prospective studies to better understand the complex interplay between DM, PAD, VC, and bleeding events.

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Author contributions

Francesco Tartaglia: Conceptualisation, Methodology, Writing—Original draft preparation; Tullio Palmerini: Conceptualisation, Methodology, Supervision, Writing—Reviewing and Editing; Francesco Saia: Data collection, Writing—Reviewing and Editing; Antonio Giulio Bruno: Data collection, Writing—Reviewing and Editing; Won-Keun Kim: Data collection, Writing—Reviewing and Editing; Alessandro Iadanza: Data collection, Writing—Reviewing and Editing; Ole De Backer: Data collection, Writing—Reviewing and Editing; Francesco Burzotta: Data collection, Writing—Reviewing and Editing; Nicolas M. Van Mieghem: Data collection, Writing—Reviewing and Editing; Thomas Pilgrim: Data collection, Writing—Reviewing and Editing; Italo Porto: Data collection, Writing—Reviewing and Editing; Tiziana Claudia Aranzulla: Data collection, Writing—Reviewing and Editing; Max M. Meertens: Data collection, Writing—Reviewing and Editing; Michael Joner: Data collection, Writing—Reviewing and Editing; Francesco Meucci: Data collection, Writing—Reviewing and Editing; Stefan Toggweiler: Data collection, Writing—Reviewing and Editing; Luca Testa: Data collection, Writing—Reviewing and Editing; Sergio Berti: Data collection, Writing—Reviewing and Editing; Matteo Montorfano: Data collection, Writing—Reviewing and Editing; Daniel Braun: Data collection, Writing—Reviewing and Editing; Fausto Castriota: Data collection, Writing—Reviewing and Editing; Marco De Carlo: Data collection, Writing—Reviewing and Editing; Marco Barbanti: Data collection, Writing—Reviewing and Editing; Mohamed Abdel-Wahab: Data collection, Writing—Reviewing and Editing; Georg Nickenig: Data collection, Writing—Reviewing and Editing; Tommaso Piva: Data collection, Writing—Reviewing and Editing; Pier Pasquale Leone: Data collection, Writing—Reviewing and Editing; Azeem Latib: Data collection, Writing—Reviewing and Editing; Giuseppe Tarantini: Data collection, Writing—Reviewing and Editing; Ran Kornowski: Data collection, Writing—Reviewing and Editing; Pablo Codner: Data collection, Writing—Reviewing and Editing; Antonio L. Bartorelli: Data collection, Writing—Reviewing and Editing; Gregg W. Stone: Data collection, Writing—Reviewing and Editing; Giulio Stefanini: Conceptualisation, Methodology, Supervision, Writing—Reviewing and Editing.

Francesco Tartaglia (Conceptualisation, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing [lead]), Tullio Palmerini (Conceptualisation, Supervision, Writing—review & editing [supporting]), Francesco Saia (Data curation [supporting]), Antonio Giulio Bruno (Data curation [supporting]), Won-Keun Kim (Data curation [supporting]), Alessandro Iadanza (Data curation, Writing—review & editing [supporting]), Ole De Backer (Data curation, Writing—review & editing [supporting]), Francesco Burzotta (Data curation, Writing—review & editing [supporting]), Nicolas Van Mieghem (Data curation, Writing—review & editing [supporting]), Thomas Pilgrim (Data curation, Writing—review & editing [supporting]), Italo Porto (Data curation, Writing—review & editing [supporting]), Tiziana Claudia Aranzulla (Data curation, Writing—review & editing [supporting]), Max Meertens (Data curation, Writing—review & editing [supporting]), Michael Joner (Data curation,

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Supplementary data

Supplementary data are available at [European Heart Journal – Valvular and Structural Heart Disease](https://www.ahajournals.org/doi/10.1177/2164286517700000) online.

Declarations

Data Availability

No data were generated or analysed for this manuscript.

Disclosure of Interest

Dr Tullio Palmerini has received speaker fees from Edwards Lifesciences and Medtronic. Dr Francesco Saia has received consulting and lecture fees from Abbott, Edwards Lifesciences, and Medtronic. Dr Won-Keun Kim has received personal fees from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Meril Life Sciences, and Shockwave Medical. Dr Francesco Burzotta has received speaker fees from Abiomed, Abbott, Medtronic, and Terumo. Dr Nicolas M. Van Mieghem has received research grant support from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, Edwards Lifesciences, Abiomed, PulseCath BV, and Daiichi Sankyo. Dr Thomas Pilgrim reports research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Swiss Polar Institute, the Bangerter-Rhyner Foundation, the Mach-Gaensslen Foundation, and the Monsol Foundation. Research, travel, or educational grants to the institution without personal remuneration from Biotronik, Boston Scientific, Edwards Lifesciences, and ATSens; speaker fees and consultancy fees to the institution from Biotronik, Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, Biosensors, and Highlife. Dr Stefan Toggweiler has served as a proctor/consultant for Medtronic, Edwards Lifesciences, Biosensors, Boston Scientific, and Abbott Vascular; has served as a consultant for Medira, AtHeart Medical, Veosource, Shockwave, Teleflex, and Polares Medical; has received institutional research grants from Biosensors, Boston Scientific, and Fumedica; and holds equity in Hi-D Imaging. Dr Luca Testa has received consulting fees from and served as a proctor for Abbott, Boston Scientific, Medtronic, and Merrill. Dr Sergio Berti has served as a proctor for Edwards Lifesciences, Abbott, and Boston Scientific. Dr Matteo Montorfano has received consultant fees from Abbott, Boston

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Ethical Approval was not required.

Pre-registered Clinical Trial Number

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