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Impact of diabetes mellitus on short term vascular complications after TAVR: Results from the BRAVO-3 randomized trial☆

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ABSTRACT

Aims: The impact of diabetes mellitus (DM) on clinical outcomes after transcatheter aortic valve replacement (TAVR) remains unclear. The aim of this study was to investigate the impact of DM on short-term clinical outcomes after TAVR in a large randomized trial population.

Methods and results: BRAVO-3 trial randomized 802 patients undergoing *trans*-femoral TAVR to procedural anticoagulation with bivalirudin or unfractionated heparin. The study population was divided according to the presence of DM, and further stratified according to the use of insulin. Net adverse cardiovascular outcomes (NACE – death, myocardial infarction (MI), stroke or major bleeding by Bleeding Academic Research Consortium (BARC) type 3b or above) was the primary outcome in-hospital and at 30-days.

Of the total 802 randomized patients, 239 (30%) had DM at baseline, with 87 (36%) being treated with insulin. At 30-days, DM patients experienced numerically higher rates of net adverse cardiovascular events (16.3% vs. 14.4%, $p = 0.48$) and acute kidney injury (19.7% vs. 15.1%, $p = 0.11$), while non-DM (NDM) patients had numerically higher rates of cerebrovascular accidents (3.6% vs. 1.7%, $p = 0.22$). After multivariable adjustment, DM patients had higher odds of vascular complications at 30-days (OR 1.57, $p = 0.03$) and life-threatening bleeding both in-hospital (OR 1.50, $p = 0.046$) and at 30-days (OR 1.50, $p = 0.03$) with the excess overall risk primarily attributed to the higher rates observed among non-insulin dependent DM patients.

Conclusions: Patients with DM had higher adjusted odds of vascular and bleeding complications up to 30-days post-TAVR. Overall, there was no significant association between DM and early mortality following TAVR.

Abbreviations: AKI, Acute Kidney Injury; AS, Aortic Stenosis; BRAVO-3, Bivalirudin Versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement trial; DM, Diabetes Mellitus; IDDM, Insulin Dependent Diabetes Mellitus; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; NIDDM, Non-Insulin Dependent Diabetes Mellitus; TAVR, Transcatheter Aortic Valvular Replacement.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and the discussed interpretation.

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1. Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as the standard of care for patients with severe symptomatic aortic stenosis (AS) who are deemed to be at high or prohibitive risk for surgical valve replacement [1–3]. Thanks to ongoing iterative technical improvements, rates of complications, such as bleeding and vascular adverse events after TAVR have steadily decreased [4,5]. Nonetheless, due to large-bore access and comorbidities associated with the advanced age in the population of severe AS patients undergoing TAVR periprocedural complications remain an important concern and several clinical and procedural factors have been associated with adverse events after TAVR, allowing for risk stratification and enhanced prediction of the post-procedural course [6].

Diabetes mellitus (DM) has been recognized as a risk factor for early development as well as rapid progression of AS [7,8]. Moreover, prior studies have demonstrated an increased morbidity and mortality amongst patients with DM following surgical aortic valve replacement [9]. However, it remains unclear whether similar risks exist in patients with DM following TAVR, since previous reports have yielded conflicting results [9–11].

The Bivalirudin Versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement (BRAVO-3) trial randomized patients undergoing *trans*-femoral TAVR to bivalirudin or unfractionated heparin (UFH) for peri-procedural anticoagulation [12]. We aimed to investigate the impact of DM and the role of insulin therapy on short term clinical outcomes after *trans*-femoral TAVR in the large randomized BRAVO-3 TAVR population.

2. Methods

The design and rationale of the BRAVO-3 trial (NCT01651780) has previously been described [13]. Briefly, 802 patients were enrolled between May 2012 and October 2015, across 31 centers in Europe and North America, and randomized to receive either Bivalirudin or Unfractionated Heparin during *trans*-femoral TAVR. The study was approved independently by each medical center's ethics committee and clinical events were adjudicated by an independent, centralized clinical events committee at The Icahn School of Medicine at Mount Sinai, New York, USA. The main results have been previously published [12].

2.1. Study population

High-surgical risk patients with severe AS, scheduled to undergo TAVR via *trans*-femoral approach, were prospectively enrolled in the BRAVO-3 study. Inclusion criteria included patients with severe AS who were ≥18 years of age, at high surgical risk as defined by the European System for Cardiac Operative Risk Evaluation score (EuroSCORE) of ≥18, or by the heart team, and scheduled for TAVR via *trans*-femoral approach. The key exclusion criteria were: planned surgical cut down for femoral access, common femoral artery minimal luminal diameter <6.5 mm, presence of a previous mechanical or mitral bioprosthetic valve, left ventricular ejection fraction <15%, severe aortic or mitral regurgitation, concomitant percutaneous coronary intervention (PCI), recent bleeding or neurological event, and dialysis dependence.

2.2. Clinical definitions and endpoints

Net adverse cardiovascular outcomes (NACE), comprising of all-cause mortality, myocardial infarction (MI), stroke or major bleeding as defined by the BARC ≥3b (Bleeding Academic Research Consortium) criteria, was the primary outcome measured in-hospital and at 30-days post-TAVR. Other clinical outcomes evaluated were: individual components of NACE, cardiac death, acute kidney injury (AKI) and, bleeding and vascular complications as defined by the VARC-2 (Valve Academic Research Consortium-2) criteria [14]. VARC-2 criteria defines bleeding complications as life threatening or disabling (= BARC 3b, 3c and 5), major (= BARC 3a not meeting criteria for life-threatening or disabling) and minor (= BARC 2 or 3a not meeting criteria for life-threatening, disabling or major), and defines vascular complications by segregating them into major, minor and percutaneous closure device complications. The presence or absence of DM and requirement of insulin therapy was determined by the treating physicians at each study center prior to TAVR implantation.

2.3. Statistical analysis

For our analysis, categorical data are presented as frequencies with percentages and compared using the chi square test. Continuous variables are presented as means ± standard deviation (SD), and compared using Student's *t*-test for variables with a normal distribution and Mann-Whitney *U* test for those without a normal distribution. Fischer's exact testing was used for evaluating crude event rates in the population.

The independent associations between 30-day outcomes and DM were assessed with a multivariable logistic regression model and are presented as adjusted odds ratios with 95% confidence intervals (CIs). Pre-specified variables were chosen on the basis of proven clinical relevance in the published literature. An assessment for collinearity was conducted and redundant variables were removed. Ultimately, the following baselines variables were selected for adjustment in our model for all clinical outcomes: age, sex, weight, chronic kidney disease (CKD), left ventricular ejection fraction (LVEF) < 50%, coronary artery

Table 1
Baseline characteristics.

VARIABLES	NDM (n=563, 70%)	DM (n=239, 30%)	p value
Age, (years) Mean ± SD	83.1 ± 6.2	80.4 ± 6.9	<0.0001
Male	271 (48.1%)	140 (58.6%)	0.007
Body Weight (kg)	71.1 ± 15.0	81.2 ± 18.0	<0.0001
Logistic EuroSCORE (%) Mean ± SD	17.0 ± 10.1	17.3 ± 10.9	0.72
CKD			
GFR 30–59 ml/min	270 (48.0%)	128 (53.6%)	0.33
GFR <30 ml/min	30 (5.3%)	10 (4.2%)	
PAD	69 (12.3%)	50 (20.9%)	0.002
Prior CVA/TIA	55 (9.8%)	28 (11.8%)	0.40
COPD	110 (19.5%)	45 (18.8%)	0.82
CAD	262 (46.5%)	143 (60.1%)	0.0005
Prior MI	80 (14.3%)	36 (15.4%)	0.69
Prior AF	207 (36.9%)	90 (37.7%)	0.84
Prior VT	10 (1.8%)	10 (4.3%)	0.047
Previous CABG	68 (12.1%)	49 (20.5%)	0.002
Previous BAV	36 (6.4%)	24 (10.1%)	0.07
LVEF (%) Mean ± SD	54.0 ± 12.7	52.8 ± 13.3	0.22
Hemoglobin, (g/dl) Mean ± SD	12.6 ± 1.7	12.6 ± 1.7	0.82
Platelet count, (10^3/L) Mean ± SD	217.3 ± 73.0	216.5 ± 71.3	0.89
Prior Maintenance Therapy			
Aspirin	375 (66.6%)	173 (72.4%)	0.13
P2Y12 Inhibitor	161 (28.6%)	89 (37.2%)	0.02
Aspirin plus P2Y12 inhibitor	139 (24.7%)	75 (31.4%)	0.055
Diabetes Mellitus Therapy			
Diet Controlled	N/A	24 (10.0%)	N/A
Oral medication	N/A	83 (34.7%)	N/A
Insulin	N/A	87 (36.4%)	N/A
Non-Insulin Injectable	N/A	37 (15.5%)	N/A
Other	N/A	8 (3.4%)	N/A

AF – atrial fibrillation; BAV – balloon aortic valvuloplasty; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; DM –diabetes mellitus; EuroSCORE – European System for Cardiac Operative Risk Evaluation score; LVEF – left ventricular ejection fraction; MI – myocardial infarction; N/A – not applicable; NDM – no diabetes mellitus; PAD – peripheral arterial disease; SD – standard deviation; TAVR – transcatheter aortic valve replacement; TIA – transient ischemic attack; VT – ventricular tachycardia.

Table 2
Procedural characteristics.

VARIABLES	NDM (n=563, 70%)	DM (n=239, 30%)	p-value
Procedural success	547 (97.2%)	234 (97.9%)	0.54
Balloon – Expanding Valve	336 (59.7%)	164 (68.6%)	0.02
Duration of procedure (min) Mean ± SD	40.72 ± 26.0	38.98 ± 24.6	0.39
Sheath size of valve system			
>18	64 (11.4%)	40 (16.7%)	0.13
18	301 (53.5%)	132 (51.5%)	
<18	183 (32.5%)	72 (30.1%)	
Valvuloplasty performed	442 (78.9%)	196 (83.1%)	0.18
Additional TAVR device used	23 (4.1%)	5 (2.1%)	0.16
Embolic protection device used	6 (1.1%)	5 (2.1%)	0.25
Successful deployment of access site closure	512 (90.9%)	214 (89.5%)	0.41
Post-dilation	143 (25.4%)	56 (23.4%)	0.59
Temporary Pacemaker	535 (95.0%)	223 (93.3%)	0.20
Prior loading with clopidogrel	203 (36.1%)	91 (38.1%)	0.62
Post-procedural medications			
Aspirin	485 (86.1%)	206 (86.2%)	0.83
P2Y12 inhibitor	412 (73.2%)	183 (76.6%)	0.40
Aspirin plus P2Y12 inhibitor	366 (65.0%)	160 (66.9%)	0.80
Coumadin	98 (17.4%)	44 (18.4%)	0.73
Dabigatran	10 (1.8%)	1 (0.4%)	0.13
Rivaroxaban	16 (2.8%)	8 (3.3%)	0.70

DM –diabetes mellitus; NDM – no diabetes mellitus; SD – standard deviation; TAVR – transcatheter aortic valve replacement.

disease (CAD), prior MI, prior coronary artery bypass grafting (CABG), peripheral arterial disease (PAD), valve type, and country. We also conducted a sensitivity analysis to study the influence of insulin therapy on 30-day clinical outcomes. The DM population was stratified into insulin dependent DM (IDDM) and non-insulin dependent DM (NIDDM). These subgroups entered a multivariate logistic regression model with the remaining non-DM (NDM) subjects as the reference group. The pre-specified variables mentioned above were also used in this model for adjustment for all clinical outcomes. No adjustment for multiple testing was performed. A p-value of <0.05 was considered statistically significant. All analyses were performed using Stata version 15.1 (StatCorp, College Station, Texas).

3. Results

3.1. Baseline and procedural characteristics

Table 1 describes the baseline demographic and clinical characteristics of the study population according to DM status. Of the 802 patients randomized in the BRAVO-3 trial, 239 (30%) had a prior diagnosis of DM. These patients were younger and more likely to be male, have a prior diagnosis of PAD, CAD and to have undergone a previous CABG procedure. These patients were also more likely to be on prior maintenance therapy with P2Y12 inhibitors, either as single therapy or in combination with aspirin. The majority of these patients were treated with either insulin therapy (36.4%) or oral hypoglycemic drugs (34.7%) at baseline.

Procedural characteristics are detailed in Table 2. Overall, rates of procedural success, access site closure device success, sheath size, post-procedural dilation and temporary pacemaker placement were similar between DM vs. NDM patient groups. However, patients with DM were more likely to receive a balloon-expandable valve in comparison with a self-expanding valve.

Table 3
In-hospital and 30-day clinical outcomes.

OUTCOMES	NDM (n=563, 70%)	DM (n=239, 30%)	Odds Ratio (95% CI)	p-value	Adj OR (95% CI)	p-value
NACE						
In-hospital	57 (10.1)	28 (11.7)	1.18 (0.73–1.90)	0.50	1.21 [0.72–2.03]	0.48
30-days	81 (14.4)	39 (16.3)	1.16 (0.76–1.76)	0.48	1.23 [0.79–1.93]	0.36
Death						
In-hospital	11 (2.0)	3 (1.3)	0.64 (0.18–2.31)	0.49	–	–
30-days	27 (4.8)	11 (4.6)	0.96 (0.47–1.96)	0.91	–	–
C-death						
In-hospital	10 (1.8)	3 (1.3)	0.70 (0.19–2.58)	0.60	–	–
30-days	24 (4.3)	10 (4.2)	0.98 (0.46–2.08)	0.96	–	–
MI						
In-hospital	2 (0.4)	3 (1.3)	3.57 (0.59–21.48)	0.17	–	–
30-days	4 (0.7)	4 (1.7)	2.38 (0.59–9.59)	0.22	–	–
CVA						
In-hospital	13 (2.3)	2 (0.8)	0.36 (0.08–1.59)	0.18	–	–
30-days	20 (3.6)	4 (1.7)	0.46 (0.16–1.37)	0.16	–	–
AKI						
In-hospital	39 (6.9)	27 (11.3)	1.71 (1.02–2.87)	0.04	–	–
30-days	85 (15.1)	47 (19.7)	1.38 (0.93–2.04)	0.11	–	–
VASC COMP						
In-hospital	96 (17.1)	48 (20.1)	1.22 (0.83–1.80)	0.31	1.39 (0.91–2.12)	0.13
30-days	99 (17.6)	54 (22.6)	1.37 (0.94–1.99)	0.10	1.57 (1.04–2.36)	0.03
MAJOR VASC						
In-hospital	47 (8.4)	24 (10.0)	1.23 (0.73–2.05)	0.44	–	–
30-days	48 (8.5)	27 (11.3)	1.37 (0.83–2.45)	0.22	–	–
MINOR VASC						
In-hospital	49 (8.7)	24 (10.0)	1.17 (0.70–1.96)	0.55	–	–
30-days	52 (9.8)	28 (11.7)	1.30 (0.80–2.12)	0.29	–	–
LIFE BLEED						
In-hospital	106 (18.8)	56 (23.4)	1.32 (0.91–1.90)	0.14	1.50 (1.01–2.23)	0.046
30-days	128 (22.7)	68 (28.5)	1.35 (0.96–1.90)	0.09	1.50 (1.03–2.17)	0.03

Adj OR – adjusted odds ratio; AKI – acute kidney injury; BARC – bleeding academic research consortium criteria; C-death – cardiovascular death; CVA – cerebrovascular accident; DM – diabetes mellitus; LIFE BLEED – life threatening bleeding (VARC-2 criteria); MAJOR VASC – major vascular complications (VARC -2 criteria); MI – myocardial infarction; MINOR VASC – minor vascular complications (VARC-2 criteria); NACE – net adverse cardiovascular events (all-cause death, myocardial infarction, stroke or major bleeding by BARC ≥3b); NDM – no diabetes mellitus; VASC COMP – all vascular complications (VARC-2 criteria).
Multivariate model covariates: age, sex, weight, CKD, LVEF <50, coronary artery disease (CAD), prior MI, prior CABG, peripheral arterial disease (PAD), valve type, and country.

Table 4
Outcomes according to the presence of DM and insulin-dependence status.

OUTCOMES	NIDDM vs. NDM		IDDM vs. NDM		IDDM vs. NIDDM
	OR[a] (95% CI)	p-value	OR[a] (95% CI)	p-value	p-value
NACE					
In-hospital	1.08 [0.58–1.98]	0.82	1.48 [0.72–3.05]	0.29	0.45
30-days	1.13 [0.67–1.91]	0.64	1.44 [0.76–2.73]	0.26	0.52
VASC COMP					
In-hospital	1.53 (0.95–2.46)	0.08	1.16 (0.61–2.18)	0.65	0.44
30-days	1.71 (1.08–2.73)	0.02	1.31 (0.71–2.41)	0.39	0.43
LIFE BLEED					
In-hospital	1.65 (1.05–2.58)	0.03	1.24 (0.68–2.26)	0.48	0.40
30-days	1.68 (1.10–2.56)	0.02	1.20 (0.69–2.10)	0.53	0.29

Multivariate model covariates: age, sex, weight, CKD, LVEF <50, coronary artery disease (CAD), prior MI, prior CABG, peripheral arterial disease (PAD), valve type, and country.
[a] Adjusted odds ratio; IDDM – insulin-dependent diabetes mellitus; LIFE BLEED – life threatening bleeding (VARC-2 criteria); NACE – net adverse cardiovascular events (all-cause death, myocardial infarction, stroke or major bleeding by BARC ≥3b); NDM – no diabetes mellitus; NIDDM – non-insulin dependent diabetes mellitus; VASC COMP – all vascular complications (VARC-2 criteria).

3.2. Clinical outcomes

Overall, DM patients had higher crude rates of NACE (16.3% vs. 14.4%, p = 0.48) and AKI (19.7% vs. 15.1%, p = 0.11) at 30-days, while the NDM patient subgroup had higher crude rates of cerebrovascular accidents (CVA) (3.6% vs. 1.7%, p = 0.16) and in-hospital mortality (2.0% vs. 1.3%, p = 0.49), although these differences were not statistically significant, except for higher rates of in-hospital AKI in DM patients (11.3% vs. 6.9%, p = 0.04)] [Table 3].

After multivariate logistic regression, DM patients were at 50% higher odds of developing a life-threatening bleed, both in-hospital (OR 1.50 [1.01–2.23], p = 0.046) and at 30-days (OR 1.50 [1.03–2.17], p = 0.03). These patients were also at over 50% higher odds of developing 30-day vascular complications (OR 1.57 [1.04–2.36], p = 0.03) compared to NDM patients [Table 4].

3.3. Sensitivity analysis for subgroups

We stratified DM patients according to prescribed insulin treatment. Baseline and procedural characteristics for NDM, insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM) patients are shown in Table Supplementary 1 and Supplementary 2. Compared to NDM, IDDM patients were more likely to have unsuccessful vascular closure and less often require temporary pacemaker placement.

Unadjusted comparisons between NDM, IDDM and NIDDM patient groups are presented in Table Supplementary 3. IDDM subgroup had almost 80% greater odds of developing AKI at 30 days when compared with NDM patients. NIDDM patients had numerically higher rates of vascular complications and life-threatening bleeding at 30 days in comparison to both NDM and IDDM patient subgroups.

In the sensitivity analysis adjusted for baseline differences between the three patient subgroups, NIDDM patients, when compared with NDM patients, were at 65% and 68% higher odds of developing life-threatening bleeding both in-hospital (OR 1.65 [1.05–2.58], p = 0.03) and at 30-days (OR 1.68 [1.10–2.56], p = 0.02), respectively [Table 4]. Similarly, NIDDM patients also had greater than 70% higher odds of developing vascular complications at 30-days post-TAVR (OR 1.71 [1.08–2.73], p = 0.02). Within the DM patients, there were no differences for 30-day outcomes between IDDM and NIDDM subgroups. There were also no differences between the three subgroups for 30-day all-cause mortality, NACE, MI, CVA, and AKI. There were no interactions of study drugs and DM regarding death, bleeding, vascular complications or ischemic events.

4. Discussion

The key findings of this subgroup analysis from the BRAVO-3 randomized trial are as follows: i) DM patients are more likely to develop life-threatening bleeds both in-hospital prior to discharge and at 30 days post-TAVR; ii) DM patients have a higher likelihood of developing vascular complications at 30-days post-TAVR – findings that were driven predominantly by higher adverse events rates in the NIDDM subgroup of patients; and lastly, iii) Insulin-treated DM patients had comparable short-term outcomes to NIDDM patients following transfemoral TAVR.

Although the detrimental impact of DM on the prognosis of all cardiovascular disease states and interventional procedures has been conclusively established, its influence on TAVR outcomes remains debatable. While it has been shown that DM patients with severe AS benefit more from TAVR procedures vs. surgical aortic valve replacement (SAVR) [9,15], the evidence regarding the impact of DM on clinical outcomes following TAVR has been inconclusive.

In the current study comprising of patients with severe AS undergoing *trans*-femoral TAVR, we analyzed a high proportion of DM patients, comparable with reported rates of DM in other studies [11,16–22]. As expected, DM patients had higher rates of baseline DM-associated comorbidities such as PAD and CAD. We also observed significantly lower rates of successful deployment of the access closure device in IDDM patients. Despite this, we did not observe higher risk of access-related vascular complications in this subgroup.

Importantly, in our study, we did not observe any impact of DM on either in-hospital or 30-day mortality which is consistent with some of the existing literature [18,19,23–28]. Additional observations include the study by Abramowitz et al. [21] that showed no difference in outcomes for the overall population, but reported IDDM to be an independent risk factor for mortality following TAVR. In contrast, Saia et al. [29] and Tamburino et al. [30] have reported in their studies that DM, which was an independent predictor for 30-day mortality, was not significantly associated with 1-year mortality. On the other hand, Ludman et al. [10] report in their analysis that while not for 30-days, DM was an independent predictor for long-term mortality, similar to the increased mortality for mid-term follow-up in the IDDM subgroup as reported by Conrotto et al. [22]. In another analysis stratified by gender, Conrotto et al. [31] observed that IDDM is an independent predictor for mortality at 30-days in men only. With regards to in-hospital mortality, Mendez-Bailon et al. [16] reported lower rates for DM patients undergoing both TAVR and SAVR procedures. Studies with longer periods of follow-up have reported DM patients to be at increased [11,17,32–36], as well as not increased risk of mortality [18,25,37].

Interestingly, we also observed in our study that insulin therapy does not increase the odds of short-term adverse outcomes in comparison to NIDDM subgroup. This is in contrast to previous studies that

have shown insulin therapy to be an independent risk factor for all-cause mortality in these patients [22].

4.1. Vascular and bleeding complications

There is wide variance in the reported rates of major vascular complications after TAVR, ranging from 2 to 17% [5,38–45]. While some studies have reported DM to be an independent risk factor for vascular complications [40–42], others have not [38,43,44]. In addition, many of the existing reports are further limited by small sample sizes and reliance on retrospective registry data [9–11]. Our present analysis indicates an increased risk for all vascular complications in DM patients up to 30-days post-TAVR, an observation primarily driven by the higher rates in the NIDDM subgroup.

Our analysis demonstrated a significant association between DM and life-threatening bleeding events both in-hospital as well as out to 30 days. Interestingly, it was the NIDDM, rather than the IDDM patient subgroup, that was responsible for the higher risk for life-threatening bleeding post-TAVR. The association between DM and an excess risk of bleeding post TAVR remains controversial. Similar to our results, Kochman et al. [46] demonstrated that DM is an independent predictor of serious bleeding events, which included life-threatening, disabling as well as major bleeding. Moreover, an analysis by Pilgrim et al. [47] also showed that DM is an independent predictor of life-threatening peri-procedural bleeds. On the other hand, some studies have found no association between DM and post TAVR bleeding [48–50]. Of note, in our study IDDM patients had lower rates of successful deployment of access site closure, which may be related to potentially higher rates of arterial calcification in this group; however, this did not translate to higher rates of vascular or bleeding complications.

Another interesting finding in our analysis was the higher rate of post-dilation that was performed in the NIDDM patient subgroup in comparison to the IDDM patient subgroup, despite the higher aortic valve calcium content that can be expected in the latter subgroup [8].

4.2. Limitations

There are some limitations in this study. First, our study was a post-hoc analysis of the BRAVO-3 randomized trial and therefore has intrinsic limitations of non-randomized comparisons such as allocation bias, different distribution of clinical risk factors and the possibility of confounding variables. Secondly, BRAVO-3 was a trial comparing anticoagulation therapy in TAVR procedures and as such, was not powered to detect differences in the outcomes of the DM population. Therefore, the results of this study are only hypothesis generating. Thirdly, despite the fact that we detected significantly higher odds of developing vascular complications and life-threatening bleeds in the DM patients, we cannot completely rule out the potential contribution of unmeasured factors that may have influenced these results. Finally, since the follow-up of this cohort was limited to 30 days, our conclusions are restricted to that timeframe.

5. Conclusions

In conclusion, we showed that DM patients are at higher odds of developing vascular complications at 30-days post-TAVR, as well as developing life-threatening bleeding both in hospital and at 30-days post-TAVR. These results are mainly driven by the higher odds in the non-insulin dependent DM patients. Insulin-dependent DM patients did not appear to have worse short-term outcomes in comparison with NIDDM patients. Further studies specifically examining DM patients undergoing TAVR with long-term follow-up are required to arrive at conclusive decisions.

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Declaration of Competing Interest

Dr. Deliargyris is Chief Medical Officer and full time employee of PLx Pharma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.063.

Supplementary Table 1
Baseline Characteristics According to the Presence of DM and Insulin-Dependence Status

VARIABLES	NDM (n=563, 70%)	NIDDM (n=152, 19%)	IDDM (n=87, 11%)	p value
Age, (years) Mean ± SD	83.1 ± 6.2	80.4 ± 7.4	80.3 ± 6.0	<0.0001
Male	271 (48.1%)	83 (54.6%)	57 (65.5%)	0.007
Body Weight (kg)	71.1 ± 15.0	78.1 ± 17.1	85.3 ± 18.9	<0.0001
Logistic EuroSCORE (%) Mean ± SD	17.0 ± 10.1	16.4 ± 10.2	18.8 ± 12.0	0.19
CKD	300 (53.3%)	84 (55.3%)	54 (62.1%)	0.31
PAD	69 (12.3%)	28 (18.4%)	22 (25.3%)	0.003
Prior CVA/TIA	55 (9.8%)	22 (14.6%)	6 (6.9%)	0.12
COPD	110 (19.5%)	21 (13.8%)	24 (27.6%)	0.03

Supplementary Table 1 (*continued*)

VARIABLES	NDM (n=563, 70%)	NIDDM (n=152, 19%)	IDDM (n=87, 11%)	p value
CAD	262 (46.5%)	86 (57.0%)	57 (65.5%)	0.001
Prior MI	80 (14.3%)	19 (12.9%)	17 (19.5%)	0.35
Prior AF	230 (40.9%)	58 (38.2%)	44 (50.6%)	0.22
Prior VT	10 (1.9%)	5 (3.4%)	5 (6.0%)	0.07
Previous CABG	68 (12.1%)	31 (20.4%)	18 (20.7%)	0.008
Previous BAV	36 (6.4%)	13 (8.6%)	11 (12.6%)	0.10
LVEF (%) Mean ± SD	54.02 ± 12.7	53.27 ± 13.0	51.95 ± 13.7	0.35
Hemoglobin, (g/dl) Mean ± SD	12.6 ± 1.7	12.6 ± 1.7	12.5 ± 1.8	0.87
Platelet count, (10^9/L) Mean ± SD	217.3 ± 73.0	217.5 ± 71.3	214.9 ± 71.6	0.56
Prior Maintenance Therapy				
Aspirin	375 (66.6%)	105 (69.1%)	68 (78.2%)	0.11
P2Y12 Inhibitor	161 (28.6%)	53 (34.9%)	36 (41.4%)	0.04
Aspirin plus P2Y12 inhibitor	139 (24.7%)	42 (27.6%)	33 (37.9%)	0.04

AF – atrial fibrillation; BAV – balloon aortic valvuloplasty; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; DM –diabetes mellitus; EuroSCORE – European System for Cardiac Operative Risk Evaluation score; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NDM – no diabetes mellitus; PAD – peripheral arterial disease; SD – standard deviation; TAVR – transcatheter aortic valve replacement; TIA – transient ischemic attack; VT – ventricular tachycardia.

Supplementary Table 2
Procedural Characteristics According to the Presence of DM and Insulin-Dependence Status

VARIABLES	NDM (n=563, 70%)	NIDDM (n=152, 19%)	IDDM (n=87, 11%)	p value
Procedural success	547 (97.2%)	150 (98.7%)	84 (96.6%)	0.51
Balloon – Expanding Valve	336 (59.7%)	109 (71.7%)	55 (63.2%)	0.04
Duration of procedure (min) Mean ± SD	40.72 ± 26.03	41.06 ± 26.23	35.30 ± 20.93	0.18
Sheath size of valve system				
>18	64 (11.4%)	30 (19.7%)	10 (11.5%)	0.04
18	301 (53.5%)	70 (46.1%)	53 (60.9%)	
<18	183 (32.5%)	50 (32.9%)	22 (25.3%)	
Valvuloplasty performed	442 (78.9%)	125 (82.8%)	71 (83.5%)	0.41
Additional TAVR device used	23 (4.1%)	3 (2.0%)	2 (2.3%)	0.37
Embolic protection device used	6 (1.1%)	3 (2.0%)	2 (2.3%)	0.51
Successful deployment of access site closure	512 (90.9%)	141 (92.8%)	73 (83.9%)	0.08
Post-dilation	143 (25.4%)	42 (27.6%)	14 (16.1%)	0.13
Temporary Pacemaker	535 (95.0%)	144 (94.7%)	79 (90.8%)	0.08
Prior loading with clopidogrel	203 (36.1%)	56 (36.8%)	35 (40.2%)	0.13
Post-procedural medications				
Aspirin	485 (86.1%)	131 (86.2%)	75 (86.2%)	0.98
P2Y12 inhibitor	412 (73.2%)	115 (75.7%)	68 (78.2%)	0.64
Aspirin plus P2Y12 inhibitor	366 (65.0%)	101 (66.4%)	59 (67.8%)	0.93
Coumadin	98 (17.4%)	24 (15.8%)	20 (23.0%)	0.35
Dabigatran	10 (1.8%)	1 (0.7%)	0 (0.0%)	0.29
Rivaroxaban	16 (2.8%)	7 (4.6%)	1 (1.1%)	0.30

IDDM – insulin dependent diabetes mellitus; NDM – no diabetes mellitus; NIDDM – non-insulin dependent diabetes mellitus; SD – standard deviation; TAVR – transcatheter aortic valve replacement.

Supplementary Table 3
Univariate Analysis According to the Presence of DM and Insulin-Dependence Status

OUTCOMES	NDM (n=563, 87%)	NIDDM (n=152, 19%)	IDDM (n=87, 11%)	NIDDM vs. NDM	IDDM vs. NDM	p_{trend}
				OR (95% CI)	OR (95% CI)	
NACE						
In-hospital	57 (10.1)	16 (10.5)	12 (13.8)	1.04 (0.58–1.88)	1.42 (0.73–2.77)	0.36
30-days	81 (14.4)	23 (15.1)	16 (18.4)	1.06 (0.63–1.75)	1.34 (0.74–2.42)	0.36
Death						
In-hospital	11 (2.0)	3 (2.0)	0 (0.0)	1.01 (0.28–3.67)	–	0.30
30-days	27 (4.8)	8 (5.3)	3 (3.5)	1.10 (0.49–2.48)	0.71 (0.21–2.34)	0.72
C-death						
In-hospital	10 (1.8)	3 (2.0)	0 (0.0)	1.11 (0.30–4.10)	–	0.36
30-days	24 (4.3)	7 (4.6)	3 (3.5)	1.08 (0.46–2.57)	0.80 (0.24–2.72)	0.83
MI						
In-hospital	2 (0.4)	6 (2.0)	0 (0.0)	5.65 (0.94–34.11)	–	0.53
30-days	4 (0.7)	3 (2.0)	1 (1.2)	2.81 (0.62–12.71)	1.63 (0.18–14.71)	0.37
CVA						
In-hospital	13 (2.3)	0 (0.0)	2 (2.3)	–	1.00 (0.22–1.49)	0.43
30-days	20 (3.6)	1 (0.7)	3 (3.5)	0.18 (0.02–1.35)	0.970 (0.28–3.33)	0.40
AKI						
In-hospital	39 (6.9)	16 (10.5)	11 (12.6)	1.58 (0.86–2.91)	1.94 (0.96–3.96)	0.04
30-days	85 (15.1)	26 (17.1)	21 (24.1)	1.16 (0.72–1.88)	1.79 (1.04–3.08)	0.045
VASC COMP						
In-hospital	96 (17.1)	32 (21.1)	16 (18.4)	1.30 (0.83–2.03)	1.10 (0.61–1.97)	0.46

(*continued on next page*)

Supplementary Table 3 (*continued*)

OUTCOMES	NDM (n=563, 87%)	NIDDM (n=152, 19%)	IDDM (n=87, 11%)	NIDDM vs. NDM	IDDM vs. NDM	p_{trend}
				OR (95% CI)	OR (95% CI)	
30-days	99 (17.6)	36 (23.7)	18 (20.7)	1.45 (0.94–2.24)	1.22 (0.70–2.15)	0.19
MAJOR VASC						
In-hospital	47 (8.4)	15 (9.9)	9 (10.3)	1.20 (0.65–2.21)	1.27 (0.60–2.69)	0.45
30-days	48 (8.5)	17 (11.2)	10 (11.5)	1.35 (0.75–2.42)	1.39 (0.68–2.87)	0.25
MINOR VASC						
In-hospital	49 (8.7)	17 (11.2)	7 (8.1)	1.32 (0.74–2.37)	0.92 (0.40–2.10)	0.81
30-days	52 (9.8)	20 (16.2)	8 (9.2)	1.49 (0.86–2.58)	0.995 (0.46–2.17)	0.55
LIFE BLEED						
In-hospital	106 (18.8)	38 (25.0)	18 (20.7)	1.44 (0.94–2.20)	1.12 (0.64–1.97)	0.45
30-days	128 (22.7)	46 (30.3)	22 (25.3)	1.47 (0.99–2.20)	1.15 (0.68–1.94)	0.41

AKI – acute kidney injury; BARC – bleeding academic research consortium criteria; C-death – cardiovascular death; CVA – cerebrovascular accident; DM – diabetes mellitus; IDDM – insulin-dependent diabetes mellitus; LIFE BLEED – life threatening bleeding (VARC-2 criteria); MAJOR VASC – major vascular complications (VARC -2 criteria); MI – myocardial infarction; MINOR VASC – minor vascular complications (VARC-2 criteria); NACE – net adverse cardiovascular events (all-cause death, myocardial infarction, stroke or major bleeding by BARC ≥3b); NDM – no diabetes mellitus; NIDDM – non-insulin dependent diabetes mellitus; OR – unadjusted odds ratio; VASC COMP – all vascular complications (VARC-2 criteria).

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