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Assessment of the impact of diabetes mellitus on clinical outcomes after transcatheter aortic valve implantation

Avaliação do impacto do diabetes melito nos desfechos clínicos após implante transcaterter valvar aórtico

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ABSTRACT – Background: Diabetes mellitus is associated with increased mortality in patients undergoing surgical valve replacement. However, data on the impact of diabetes mellitus on the outcomes of patients undergoing transcatheter aortic valve implantation (TAVI) are scarce and contradictory. The objective of this study was to investigate the impact of diabetes on clinical outcomes in the short and medium term in patients with severe aortic stenosis undergoing TAVI. **Methods:** This was a prospective single-center observational study which included patients with aortic stenosis undergoing TAVI, between November 2008 and September 2018. **Results:** A total of 132 patients were included, of which 49 (37%) had diabetes mellitus and, of these, 10 (20%) were insulin dependent. Patients with diabetes mellitus were younger (77 years vs. 81 years; $p < 0.001$) and had a more frequent history of coronary artery disease (63% vs. 41%; $p = 0.01$) and a lower prevalence of chronic renal failure (44% vs. 63%; $p = 0.02$). The presence of diabetes mellitus did not correlate with an increase in 30-day mortality in the clinical follow-up. There was also no difference between the groups in mortality rate due to cardiovascular causes ($p = 0.35$), success of the procedure (96% vs. 93%; $p = 0.47$), vascular complications (6% vs. 9%; $p = 0.85$), life-threatening bleeding (4% vs. 10%; $p = 0.19$), and length of hospital stay (8 vs. 7 days; $p = 0.40$). However, diabetic patients treated with insulin showed increased mortality when compared to non-diabetics, and when compared to patients with non-insulin dependent diabetes mellitus. **Conclusion:** The presence of diabetes mellitus did not influence outcome rates after TAVI, but patients with diabetes mellitus treated with insulin had a higher mortality rate in the medium-term follow-up.

Keywords: Transcatheter aortic valve replacement; Aortic valve stenosis; Diabetes mellitus

RESUMO – Introdução: O diabetes melito está correlacionado ao aumento da mortalidade em pacientes submetidos à troca valvar cirúrgica. Entretanto, os dados do impacto do diabetes melito nos desfechos dos pacientes submetidos ao implante transcaterter valvar aórtico (TAVI) ainda são escassos e contraditórios. O objetivo do presente estudo foi verificar o impacto do diabetes melito nos desfechos clínicos a curto e médio prazo em pacientes com estenose aórtica severa submetidos ao TAVI. **Métodos:** Estudo clínico observacional, prospectivo e unicêntrico, que incluiu pacientes com estenose aórtica submetidos ao TAVI, entre novembro de 2008 e setembro de 2018. **Resultados:** Foram incluídos 132 pacientes, sendo que 49 (37%) eram portadores de diabetes melito e, destes, 10 (20%) eram dependentes de insulina. Os pacientes com diabetes melito eram mais jovens (77 anos vs. 81 anos; $p < 0,001$) e tinham mais frequentemente história prévia de doença arterial coronariana (63% vs. 41%; $p = 0,01$) e menor prevalência de insuficiência renal crônica (44% vs. 63%; $p = 0,02$). A presença de diabetes melito não se correlacionou ao aumento de mortalidade aos 30 dias e no seguimento clínico. Também não houve diferença entre os grupos na taxa de mortalidade por causas cardíacas ($p = 0,35$), sucesso do procedimento (96% vs. 93%; $p = 0,47$), complicações vasculares (6% vs. 9%; $p = 0,85$), sangramento com risco de vida (4% vs. 10%; $p = 0,19$) ou tempo de internação (8 dias vs. 7 dias; $p = 0,40$). Porém, os pacientes com diabetes melito tratados com insulina apresentaram aumento de mortalidade quando comparados àqueles não diabéticos e também aos pacientes com diabetes melito não insulino-dependentes. **Conclusão:** A presença de diabetes melito não influenciou na taxa de desfechos após TAVI, porém os pacientes com diabetes melito tratados com insulina apresentaram maior taxa de mortalidade no seguimento a médio prazo.

Descritores: Substituição da valva aórtica transcaterter; Estenose da valva aórtica; Diabetes mellitus

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BACKGROUND

Diabetes mellitus (DM) is a disease that affects approximately 26% of adults aged over 65 years, and is even more prevalent in patients with cardiovascular disease.¹ The presence of DM is also closely associated with increased risk of aortic valve calcification, the main factor involved in the pathophysiology of degenerative valve stenosis.²

The association of DM and cardiovascular disease leads to worse clinical outcomes, and DM is associated with increased mortality in patients undergoing surgical replacement of the aortic valve. The outcomes are even less favorable in the subgroup of diabetic patients treated with insulin.³ Transcatheter aortic valve implantation (TAVI) has become an attractive option for the treatment of aortic stenosis, with more favorable results in diabetic patients when compared to open surgery.⁴ However, evidence of the influence of diabetes on outcomes of patients undergoing TAVI is scarce and contradictory.⁵⁻⁸

The objective of this study was to investigate the impact of diabetes on clinical outcomes in the short and medium term in patients with severe aortic stenosis undergoing TAVI.

METHODS

This was a clinical, observational study that prospectively included patients with severe aortic stenosis who underwent TAVI during the period from November 2008 to September 2018, at *Hospital A Beneficência Portuguesa de São Paulo*. The study was approved by the Research Ethics Committee of the organization, and all patients provided an informed consent (CAAE 0104.1.360.000-11).

The indications were evaluated by a Heart Team, composed of cardiac surgeons, interventional cardiologists and clinical cardiologists. The Society of Thoracic Surgeons (STS) score was used to estimate the risk of surgical mortality in this group of patients. Computed tomography angiography was the imaging method of choice for obtaining the information necessary to choose the prosthesis to be used and the procedure strategy.

Procedure technique

All patients received 1.5g cefuroxime as antibiotic prophylaxis before the intervention, followed by two other administrations of the same dosage, every 8 hours. On the day before the procedure, patients received 100mg acetylsalicylic acid (ASA), and this daily dosage was maintained indefinitely, with 75mg clopidogrel for 6 months, excepting contraindications. In patients under oral anticoagulant therapy, clopidogrel was maintained or added only in patients with coronary artery disease, and ASA was not administered. The procedures were performed in the Cath Lab with sedation or general anesthesia, and echocardiographic monitoring. A temporary transvenous pacemaker was used to aid in the balloon valvuloplasty and/or prosthesis placement, by inducing tachycardia or just preventing bradyarrhythmias. The choice of pre- and/or post-dilatation of the valve was at the

operator's discretion. After TAVI, patients were transferred to the intensive care unit.

Outcomes and definitions

All study outcomes followed the criteria established by the Valve Academic Research Consortium Consensus on Event Definition (VARC).⁹ The primary endpoint was to assess the overall mortality rate at follow-up. Secondary endpoints included cardiovascular mortality at 30 days and final follow-up, total 30-day mortality, procedural success, length of hospital stay, stroke or transient ischemic attack (TIA) rate, vascular complications, bleeding complications, and onset of renal failure, with stages 2 or 3 in Acute Kidney Injury Network (AKIN) classification.

The procedural success was defined by absence of death in the procedure and the correct positioning of a single prosthesis, with final mean gradient <20mmHg, jet velocity <3 m/s, and absence of moderate or severe regurgitation.

Data collection during follow-up

Follow-up clinical data and information from complementary tests were collected at medical visits or by telephone contact.

Statistical analysis

Categorical variables were expressed as absolute frequencies and percentages, and continuous variables were expressed as mean and standard deviation, or median and interquartile range. Categorical variables were compared using the Chi-square test, and continuous variables were compared by Student's *t* test or the Wilcoxon Rank Sum test, when appropriate. The difference between the groups for in-hospital and 30-day outcomes was tested using logistic regression.

The accumulated event curves were estimated by the Kaplan-Meier method and compared by the log-rank test. The Cox regression model for multivariate analysis included sex and age, as well as variables that reached statistical significance in the univariate analysis ($p < 0.1$), and was used to adjust for differences in baseline clinical characteristics between groups. The proportional hazard hypothesis was tested using Schoenfeld residual analysis. Statistical analysis was performed using Stata Statistical Software: Release 14 (StataCorp LP, USA).

RESULTS

A total of 132 patients were included, of which 49 (37%) had diabetes mellitus and, of these, 10 (20%) were insulin dependent. The median follow-up time was 377 days (interquartile range: 128-1,101 days). Patients with diabetes mellitus were younger (77 years vs. 81 years; $p < 0.001$) and had a more frequent history of coronary artery disease (63% vs. 41%; $p = 0.01$), previous myocardial infarction (29% vs. 10%; $p = 0.005$), dyslipidemia (84% vs. 61%; $p = 0.007$), in addition to a lower prevalence of chronic renal failure (44% vs. 63%; $p = 0.02$) than non-DM patients. There was no

difference between the groups regarding STS score (4.8% vs. 4.5%; $p=0.67$), and ejection fraction (63.8% vs. 65.7%; $p=0.35$) (Table 1). There was also no difference between the groups regarding the characteristics of the procedure and medications used, except for the size of the prosthesis placed, which was smaller in the non-DM group ($p<0.01$) (Table 2). Kaplan-Meier curves demonstrated that the presence of DM did not correlate with an increased incidence of all-cause mortality at follow-up ($p=0.24$), which was the primary endpoint of the study (Figure 1). There was also no difference between the groups in mortality rate due to cardiovascular causes ($p=0.78$) (Figure 2).

The presence of DM also did not correlate with an increase in total mortality rate (6% vs. 14%; $p=0.16$), and cardiovascular mortality rate (6% vs. 7%; $p=0.80$) at 30 days, stroke or TIA (2% vs. 2%; $p=0.89$), vascular complications (6% vs. 9%; $p=0.48$), life-threatening bleeding (4% vs. 10%; $p=0.19$), and length of hospital stay (8 vs. 7 days; $p=0.67$) (Table 3).

Even after adjusting for clinical variables (Table 4), DM was not a predictor of total (Table 5) or cardiovascular (Table 6) mortality. However, the analysis of the insulin-dependent diabetic patients group showed an increase in

total mortality compared to non-insulin dependent diabetic patients ($p<0.001$) and non-diabetic patients ($p=0.03$) (Figure 3). Even after adjusting for clinical variables, insulin-dependent diabetes mellitus remained a predictor of total mortality, resulting in a 6.7-fold increase in risk, when compared to non-insulin-dependent diabetes mellitus (RR: 6.7; 95%CI 1.98-22.7; $p=0.002$), and a 3.1-fold increase compared to non-diabetic group (RR: 3.15; 95%CI 1.30-

Table 1. Clinical characteristics of patients

Characteristics	Diabetes mellitus (n=49)	Non diabetes mellitus (n=83)	p-value
Age	77.0±6.9	81.3±6.7	<0.01
Female	21 (43)	44 (53)	0.26
Dyspnea			0.96
Class I and II	14 (29)	24 (29)	
Class III and IV	35 (71)	59 (71)	
Angina	15 (31)	26 (31)	0.93
Syncope	11 (22)	19 (23)	0.95
Coronary artery disease	31 (63)	34 (41)	0.01
Prior infarction	14 (29)	8 (10)	<0.01
Prior stroke	8 (16)	10 (12)	0.50
Carotid artery disease	8 (16)	11 (13)	0.67
COPD	10 (20)	13 (16)	0.5
Dyslipidemia	41 (84)	51 (61)	<0.01
Hypertension	45 (92)	72 (87)	0.37
PAD	15 (31)	19 (23)	0.33
Chronic renal failure	21 (44)	52 (63)	0.04
Prior pacemaker implantation	12 (24)	2 (2)	<0.01
Prior CABG	11 (22)	13 (16)	0.33
Prior aortic valve replacement	0 (0)	5 (6)	0.08
Prior PCI	36 (73)	62 (75)	0.88
STS score	4.8 (2.7-8.9)	4.5 (2.7-7.8)	0.67
Ejection fraction, %	63.8±13.0	65.7 ± 9.6	0.35
Mean gradient, mmHg	44.6±15.5	46.6±18.5	0.54

Results expressed as mean ± standard deviation, n (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons.

Table 2. Characteristics of the procedure and medications

Characteristics	Diabetes mellitus (n=49)	Non diabetes mellitus (n=83)	p-value
Type of prosthesis			0.41
CoreValve®	16 (33)	20 (24)	
Evolut R	4 (8)	12 (14)	
Sapien 3	11 (22)	19 (22)	
Sapien XT®	18 (37)	32 (39)	
Pre-dilation	13 (27)	33 (41)	0.20
Post-dilation	9 (18)	19 (23)	0.45
Valve size			<0.01
23	7 (17)	20 (47)	
26	17 (41)	15 (35)	
29	14 (34)	8 (19)	
31	3 (7)	0 (0)	
General anesthesia	35 (71)	56 (67)	0.89
Transesophageal echocardiography	30 (61)	52 (63)	0.87
Femoral access	48 (98)	82 (99)	0.22
Acetylsalicylic acid	41 (87)	67 (88)	0.88
Clopidogrel	42 (89)	65 (86)	0.54
Coumarin derivatives	5 (11)	4 (5)	0.25

Results expressed as n (%) or mean ± standard deviation.

Figure 1. Kaplan-Meier curve for the primary endpoint of total mortality stratified by the presence of diabetes mellitus at 3-year follow-up. DM: diabetes mellitus.

7.63; $p=0.011$). Non-insulin-dependent diabetes mellitus showed no negative impact on mortality, with similar or even better outcomes than those of non-diabetic patients (general mortality RR: 0.04; 95%CI 0.18-0.91; $p=0.03$) and adjusted general mortality (RR: 0.52; 95%CI 0.22-1.23; $p=0.14$).

Figure 2. Kaplan-Meier curve for the secondary endpoint of cardiovascular mortality stratified by the presence of diabetes mellitus at 3-year follow-up. DM: diabetes mellitus.

Table 3. Results of the procedure

	Total (n=132)	Diabetes mellitus (n=49)	Non diabetes mellitus (n=83)	OR	95%CI	p-value
30-day mortality	12 (9)	3 (6)	12 (14)	0.38	0.10-1.44	0.16
30-day cardiovascular mortality	9 (7)	3 (6)	6 (7)	0.83	0.20-3.5	0.80
Procedural success	124 (94)	47 (96)	77 (93)	1.83	0.35-9.44	0.47
Stroke/TIA	3 (2)	1 (2)	2 (2)	0.84	0.74-9.55	0.89
Vascular complication	11 (8)	3 (6)	8 (9)	0.61	0.15-2.42	0.48
Major vascular complication	5 (4)	1 (2)	4 (5)	0.41	0.04-3.79	0.43
Bleeding complication	23 (17)	5 (10)	18 (21)	0.41	0.14-1.18	0.10
Life-threatening bleeding	11 (8)	2 (4)	9 (10)	0.35	0.07-1.69	0.19
AKI	31 (23)	11 (22)	20 (24)	0.90	0.38-2.07	0.80
AKI AKIN 2 or 3	13 (10)	1 (2)	12 (14)	0.12	0.01-0.98	0.04
Length of hospital stay, days	7 (4-11)	8 (5-11)	7 (4-12)	-	-	0.67

Results expressed as mean n (%) or median and interquartile range. TIA: transient ischemic attack; AKI: acute kidney injury; AKIN: Acute Kidney Injury Network.

Table 4. Univariate analysis for total mortality

	RR	95%CI	p-value
Age	1.08	1.02-1.12	<0.01
Female	1.44	0.80-2.58	0.22
Hypertension	1.17	0.46-2.98	0.74
COPD	0.53	0.32-1.80	0.76
Chronic renal failure	1.60	0.83-3.07	0.16
Prior stroke	2.03	0.89-4.66	0.09
Prior CABG	0.75	0.32-1.70	0.49
Prior PCI	0.62	0.22-1.74	0.36
Prior aortic valve replacement	0.70	0.95-5.10	0.72
PAD	1.15	0.58-2.30	0.68
Ejection fraction, %	0.98	0.96-1.01	0.28
Prior pacemaker implantation	0.62	0.22-1.74	0.36
STS score	1.03	1.01-1.07	0.01

COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; PAD: peripheral artery disease; STS: Society of Thoracic Surgeons.

Table 5. Univariate analysis for total mortality

	RR	95%CI	p-value
Diabetes mellitus	0.81	0.58-2.01	0.80
Female	1.08	0.58-2.01	0.80
Age	1.06	1.01-1.11	0.03
Prior stroke	1.86	0.76-4.56	0.17
STS score	1.03	0.99-1.06	0.11

STS: Society of Thoracic Surgeons.

Table 6. Univariate analysis for cardiovascular mortality

	RR	95%CI	p-value
Diabetes mellitus	1.27	0.44-3.63	0.65
Female	1.35	0.49-3.76	0.56
Age	1.05	0.97-1.14	0.20
Prior stroke	0.59	0.77-4.51	0.61
STS score	1.02	0.96-1.07	0.48

STS: Society of Thoracic Surgeons.

Figure 3. Kaplan-Meier curve for the primary endpoint of total mortality stratified by the presence of diabetes mellitus and use of insulin at 3-year follow-up. DM: diabetes mellitus.

DISCUSSION

The main findings of this study were that DM does not seem to influence short- and medium-term outcomes in patients undergoing TAVI, with no impact on total or cardiovascular mortality. However, when comparing insulin-dependent diabetic patients to non-insulin-dependent diabetics or non-diabetic patients, there was an increase in medium-term mortality in this group of patients.

DM has great impact on mortality and morbidity in the general population, especially in patients with cardiovascular disease. It is considered a risk factor for unfavorable outcomes in the STS risk model,¹⁰ and the negative impact of diabetes mellitus has been well described in patients undergoing surgical aortic valve replacement.³

When high risk diabetic patients were randomized to TAVI or surgical replacement of the aortic valve in the PARTNER cohort A trial, a 9% mortality reduction at one year was observed in the TAVI group compared to the surgical group.⁴ However, there is conflicting evidence regarding the outcomes of DM patients referred to TAVI.

Similarly to what was found in previous studies, about one-third of patients included in our real-world registry were diabetic, but only 20% of them were treated with insulin — a percentage lower than that found in the literature, which is reported to be about 30 to 50%.^{7,11,12}

Tamburino et al.¹³ reported that DM was an independent mortality predictor at 30 days (RR: 2.66; 95%CI 1.26-5.65; $p=0.01$), and in the Iberian-American TAVI Registry,⁸ the presence of DM correlated with an increase in mortality at follow-up (RR: 1.59; 95%CI 1.09-2.31; $p=0.016$), both in the multivariate analysis. Nonetheless, in both studies, only the CoreValve® prosthesis was used, and the number of patients included was higher, which may explain the difference compared to the findings of our study. In addition, there was no report of the proportion of patients using insulin, and it was not possible to evaluate whether the type of DM treatment had influence on the results. On the other hand, several studies have shown similar outcomes in 30-day and follow-up mortality among diabetic and non-diabetic patients, even when subdivided according to the type of DM treatment.^{5,12}

In our study, we found an increase in medium-term mortality for all causes in the subgroup of patients with insulin-dependent diabetes mellitus, and not in patients with non-insulin-dependent diabetes mellitus. This is in agreement with the findings of the studies of Conrotto et al.¹¹ and Abramowitz et al.,⁶ which demonstrated a similar association. A meta-analysis including 38,686 patients of 64 trials comparing TAVI results among DM patients and non-DM patients assessed as primary endpoint the 1-year total mortality. An increase in the primary endpoint was observed in DM patients (OR: 1.14; 95%CI 1.04-1.26; $p<0.01$), and also a higher incidence of acute kidney failure after the procedure. However, in this study, there was no analysis that differentiated the type of DM treatment.⁷

In our study, as in a PARTNER 1A substudy,⁴ one-year mortality was significantly higher in non-DM patients, as compared to patients with non-insulin-dependent diabetes mellitus. After multivariate analysis, this difference was no longer significant in our study, and in the PARTNER 1A substudy this analysis was not performed. These findings corroborate the hypothesis that it is not the presence of DM that correlates with worse outcomes in patients undergoing TAVI, but the presence of insulin-dependent diabetes mellitus.

CONCLUSION

The presence of diabetes mellitus does not influence immediate and late outcome rates in patients undergoing transcatheter aortic valve implantation. Nevertheless, insulin-treated diabetes mellitus is associated with an increased medium-term mortality at follow-up.

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: Dutra GA, Mangione FM and Mangione JA; data collection: Dutra GA, Mangione FM, Mauro MF, Cristóvão SA, Soares BA and Mangione JA; data interpretation: Mangione FM; writing of the text: Dutra GA, Mangione FM and Mangione JA; approval of the final version to be published: Dutra GA, Mangione FM, Mauro MF, Cristóvão SA, Soares BA and Mangione JA.

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