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## **The Importance of the Heart Team Evaluation Before Transcatheter Aortic Valve Replacement: Results from the BRAVO-3 Trial**

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1002/ccd.28717](https://doi.org/10.1002/ccd.28717)

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**Short Title:** Heart Team Evaluation Before TAVR

**Financial disclosures:** Dr. Dangas has received grants (to the institution) from The Medicines Company (modest level) and his spouse is a consultant and advisory board member for Abbott Vascular. Dr. Mehran has received grants (to the institution) from The Medicines Company (modest level) and is a consultant and advisory board member for Abbott Vascular. Dr. Anthopoulos and Dr. Deliargyris were employees of The Medicines Company at the time of the original BRAVO-3 trial. None of the other authors have any disclosures relevant to this particular project.

**Keywords:** TAVR, Heart Team, Logistic EuroSCORE

**Word Count:** Abstract—250, Manuscript—3,456

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## Abstract

Background/Objectives: Clinicians use validated scores to risk-stratify patients undergoing TAVR. However, evaluation by the Heart Team often deems patients to be at higher risk than their formal scores suggest. We sought to assess clinical outcomes of TAVR patients defined as high-risk by the Heart Team's assessment versus the patient's logistic EuroSCORE (LES).

Methods: The BRAVO-3 trial randomized patients at high risk ( $LES \geq 18$ , or deemed inoperable by the Heart Team) to TAVR with periprocedural anticoagulation with unfractionated heparin versus bivalirudin. Endpoints included net adverse cardiac events (NACE: the composite of all-cause mortality, MI, stroke or bleeding), major adverse cardiovascular events (MACE: death, MI or stroke), the individual components of MACE, major vascular complications,  $BARC \geq 3b$  bleeding and VARC life-threatening bleeding at 30 days. We compared patients deemed high-risk based on  $LES \geq 18$  vs. high-risk by the Heart Team despite lower LES.

Results: A total of 467/800 (58.4%) patients were deemed high-risk by the Heart Team despite  $LES < 18$ . After multivariable analysis, there were no differences in the odds of endpoints between groups (NACE,  $OR_{LES \geq 18}$ : 1.32, 95% CI 0.86-2.02,  $p=0.21$ ; MACE,  $OR_{LES \geq 18}$ : 1.27, 95% CI 0.72-2.25,  $p=0.41$ ; major vascular complications,  $OR_{LES \geq 18}$ : 0.97, 95% CI 0.65-1.44,  $p=0.88$ ;  $BARC \geq 3b$ ,  $OR_{LES \geq 18}$ : 1.38, 95% CI 0.82-2.33,  $p=0.23$ ; and VARC life-threatening bleeding,  $OR_{LES \geq 18}$ : 0.99, 95% CI 0.69-1.41,  $p=0.95$ ).

Conclusion: Patients undergoing TAVR and labeled high-risk by LES  $\geq 18$  or Heart Team assessment despite LES  $< 18$  have comparable short-term outcomes. Assignment of high-risk status to over 50% of patients is attributable to Heart Team's clinical assessment.

## **Abbreviations**

TAVR: Transcatheter Aortic Valve Replacement

SAVR: Surgical Aortic Valve Replacement

LVEF: Left Ventricular Ejection Fraction

PCI: Percutaneous Coronary Intervention

GFR: Glomerular Filtration Rate

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

PVD: Peripheral Vascular Disease

CAD: Coronary Artery Disease

CABG: Coronary Artery Bypass Graft

## Introduction

The ability to carefully risk-stratify patients prior to transcatheter aortic valve replacement (TAVR) is invaluable during the selection of patients who will undergo the procedure. Given the procedure's rapidly rising popularity, the appropriate risk stratification of TAVR patients is becoming evermore important.<sup>1-7</sup> When confronted with this task, multidisciplinary Heart Teams will routinely calculate one or many validated risk scores to objectively risk-stratify patients.<sup>8</sup> The European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE) is one of the more commonly employed risk scores used to risk-stratify patients prior to TAVR despite being developed based on data from cardiac surgery patients predominantly undergoing coronary artery bypass graft surgery.<sup>9,10</sup> While the logistic EuroSCORE (LES) has been shown to overestimate operative mortality risk in patients undergoing TAVR,<sup>11</sup> there are also scenarios where a low LES misaligns with the Heart Team's overall clinical evaluation of a patient who is otherwise deemed higher risk than his/her LES would suggest due to clinical risk factors that formal risk scores fail to capture.<sup>3</sup> This low precision can largely be explained by the LES's lack of TAVR-specific variables.

In light of these discrepancies, it is important to unravel the clinical utility in risk-stratifying a patient as high-risk despite having a low risk LES score. Indeed, the BRAVO (Effect of Bivalirudin on Aortic Valve Intervention Outcomes)-3 randomized trial demonstrated that a majority of patients who underwent transfemoral-TAVR (TF-TAVR) were deemed high surgical risk or inoperable by the Heart Team as opposed to a LES  $\geq 18$ .<sup>12</sup> Consequently, the goal of the

present BRAVO-3 subgroup analysis was to compare the short-term clinical outcomes of high-risk patients as defined by their high LES scores or Heart Team assessment despite lower LES scores undergoing TF-TAVR.

## **Materials and Methods**

BRAVO-3 was an open-label, randomized, controlled trial comparing bivalirudin with unfractionated heparin (UFH) in 802 high-risk or inoperable patients undergoing TAVR in 31 European and North American sites. The results have been reported previously.<sup>12,13</sup> The local ethics committee at each site approved the study.

### *Study Population*

Patients with severe aortic stenosis (AS) who were  $\geq 18$  years of age, at high surgical risk defined as a European System for Cardiac Operative Risk Evaluation score (logistic EuroSCORE) of  $\geq 18$ , or deemed inoperable by the Heart Team, and scheduled for TAVR via transfemoral approach were eligible for enrollment. The key exclusion criteria were planned surgical cut down for access; common femoral artery minimal luminal diameter  $< 6.5$  mm; presence of a previous mechanical or mitral bioprosthetic valve; left ventricular ejection fraction (LVEF)  $< 15\%$ ; severe aortic or mitral regurgitation; concomitant PCI; recent bleeding or neurological event; and dialysis dependence.

### *Study Medications*



In patients with estimated glomerular filtration rate (GFR)  $\geq 60$  ml/min, bivalirudin was given as an initial bolus of 0.75 mg/kg, followed by a continuous infusion of 1.75 mg/kg/hr that was stopped after successful TAVR. Patients with GFR  $< 60$  ml/min received a lower adjusted infusion rate. UFH administration was recommended to be titrated to a target activated clotting time of  $>250$  sec; at the operator's discretion protamine was given at the end of the procedure for reversal of UFH action. Patients underwent TAVR according to the standard procedure at each site, including selection of a commercially available TAVR valve and periprocedural use of antithrombotic medications. The protocol recommended use of low dose aspirin 75–100 mg/day for at least 1 year and clopidogrel 75 mg/day for a period defined by local practice post-TAVR.

#### *Study Endpoints*

For the present analysis, we investigated all outcomes available in the original BRAVO-3 Trial at 48 hours or before discharge and at 30 days. These included net adverse cardiac events (NACE; defined as the composite of all-cause mortality, MI, stroke or bleeding), major adverse cardiovascular events (MACE; defined as death, MI or stroke), the individual components of MACE, major vascular complications, BARC  $\geq 3b$  bleeding and VARC life-threatening bleeding.

#### *Statistical Analysis*

We compared patients deemed high-risk due to LES  $\geq 18$  and patients deemed high-risk by the Heart Team despite otherwise lower LES. Baseline clinical, demographic and procedural characteristics of the study groups were reported as mean  $\pm$ SD for continuous variables and as

proportions for categorical variables. Continuous variables were compared using the Student's *t* test. Categorical variables were compared with the  $\chi^2$  test. The logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was calculated using a logistic-regression equation, with higher scores indicating greater surgical risk.<sup>12</sup> We performed multivariable logistic regression analysis to identify independent predictors of 48-hour and 30-day events with resultant adjusted odds ratios and 95% confidence intervals for each variable. In our multivariable models, we included the following predictors: LES  $\geq 18$ , sex, age (per year), diabetes mellitus, chronic kidney disease (CKD), COPD, left ventricular ejection fraction, atrial fibrillation and country. Statistical analyses were performed using STATA version 14.0 (College station, TX). P-values  $< 0.05$  were considered significant.

## Results

### *Baseline Clinical & Procedural Characteristics*

Overall, 800 of the 802 patients that were randomized in the BRAVO-3 study were included in the present study. Of these 800 patients, a majority (58.4%) was deemed high-risk or inoperable and therefore eligible for TAVR according to Heart Team assessment despite LES  $< 18$  and 333 (41.6%) were deemed high-risk or inoperable and therefore eligible for TAVR according to LES  $\geq 18$  (Table 1). Figures 1A and 1B show the distribution of the LES between the group which was deemed high risk by a LES  $\geq 18$  and the group which was deemed high risk by Heart Team assessment (LES  $< 18$ ). Baseline clinical and procedural characteristics are reported in Table 1. There were several differences between groups. Patients subjectively deemed as high-risk by the

Heart Team were younger than their objectively high-risk counterparts. Those eligible for TAVR according to Heart Team assessment despite LES <18 had a higher baseline LVEF. Additionally, patients eligible for TAVR according to Heart Team assessment despite LES <18 were less likely to require periprocedural general anesthesia, but were more likely to undergo balloon post-dilation following TAVR.

### *Outcomes*

The crude event rates for all outcomes are reported in Table 2. There were no significant differences in the adjusted event rates between the Heart Team group vs. the LES group (Table 3) at 48 hours or before discharge, or at 30 days.

## **Discussion**

The main findings of this subgroup analysis of the BRAVO-3 open-label, randomized controlled trial are (1) a majority of patients undergoing TAVR were deemed high-risk by Heart Team assessment rather than LES; and (2) patients deemed high-risk by the Heart Team despite otherwise lower LES appear to have similar short-term outcomes compared to those patients deemed high-risk by LES  $\geq 18$ . Our findings suggest that clinical assessment by a multidisciplinary Heart Team remains a highly valued tool in the preoperative evaluation and risk stratification of TAVR patients given its ability to account for clinical risk factors left out of formal risk score calculators.

### *Efficacy of Logistic EuroSCORE*

The Logistic EuroSCORE has been used in landmark trials of TAVR as a means of predicting 30-day morbidity and mortality. Although the LES is primarily a *surgical* risk score intended to evaluate risk of surgical outcomes, landmark TAVR trials have demonstrated its correlation with 30-day mortality also in patients undergoing TAVR across gradations of preoperative risk (Supplemental Table). While our results point to similar short-term outcomes between those deemed high-risk based on a LES  $\geq 18$  versus those deemed high-risk based upon Heart Team appraisal, previous work has demonstrated that the LES considerably over-estimates operative mortality in TAVR as well as SAVR populations when compared to other validated surgical risk scores.<sup>14</sup> In a recent meta-analysis of contemporary risk scores for TAVR by Wang et al. the investigators found a pooled odds ratio of 0.31 (95% CI 0.25-0.38) between the observed and predicted risk for the LES. This was substantially different from that of other surgical risk scores including the EuroSCORE II (OR 1.26, 95% CI 1.06–1.51) and STS Score (OR 0.95, 95% CI 0.72–1.27).<sup>8</sup> Although these initial findings would suggest that the EuroSCORE II and STS Score may be superior to the LES, Wang et al. further showed that these surgical risk scores only weakly discriminated operative mortality after TAVR with a pooled c-statistic of 0.62, limiting our ability to apply these scores to TAVR patients. Efforts to address this issue by designing TAVR-specific risk models,<sup>15-19</sup> while promising, have not been shown to be superior to their surgical counterparts in external validation studies.<sup>20,21</sup>

*The Heart Team*

Since the FDA approved TAVR for the management of severe AS in patients deemed inoperable, TAVR programs have experienced significant improvements in volume and outcomes, which can be attributed to both continuous refinements to the patient selection process and clinical trials demonstrating the procedure's efficacy in lower-risk patients. The multidisciplinary Heart Team approach in TAVR has also been hailed as a cornerstone of the procedure's growing success.<sup>23</sup> As it stands, the goal of the Heart Team is to provide a multidisciplinary, patient-centered approach to the initial evaluation of the individual with severe AS in order to select the optimal management strategy as well as assess the risk of adverse outcomes following the chosen intervention.<sup>24</sup> The 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease provides a Class I, Level C recommendation for the presence of a heart valve team during the choice of intervention.<sup>7</sup> In this regard, there is a low level of evidence guiding how to appropriately select high risk patients for TAVR vs. SAVR. Here, we present data demonstrating that the "Heart Team" approach is appropriate in selecting the optimal treatment strategy for these complex patients.

In the present study, a majority (58.4%) of the patients were deemed high-risk by the Heart Team despite being younger and less likely to have COPD, peripheral vascular disease, coronary artery disease, prior CABG, atrial fibrillation and poor renal function than their objectively high-risk counterparts. These results are in line with international and specialty guidelines and indicate that the overall clinical assessment of a patient's risk should involve a multidisciplinary Heart Team

approach that accounts for other patient characteristics that contemporary surgical risk scores fail to capture.<sup>7,22</sup> One characteristic that has been left out of surgical risk scores, but can generally be gauged clinically by a Heart Team, is a patient's functional assessment or measure of frailty. Multiple studies have shown frailty measures to be associated with improved risk stratification in patients undergoing TAVR.<sup>26-35</sup> In this context, Schoenenberger, et al. evaluated whether a frailty index (based on assessment of cognition, mobility, nutrition, and activities of daily living with either) in combination with conventional surgical risk scores improves 1-year mortality prediction in patients undergoing TAVR.<sup>36</sup> The investigators found that a combination of the frailty index with *either* the LES or STS score improved mortality prediction at 1 year underscoring the importance of a comprehensive evaluation, including both an assessment by the Heart Team and risk score calculation, of patients being considered for TAVR. The observed additive value may largely be a result of the fact that these risk scores tend to be predictors of mortality while Heart Teams base their assessments on risk of morbidity and mortality. Our findings suggest that the clinical gestalt of an experienced multidisciplinary Heart Team appears to capture an important cohort of high-risk TAVR candidates otherwise missed by leading risk stratification systems.

Recently, two trials in low-risk patients showed TAVR to be at least non-inferior to SAVR even in a low-risk cohort.<sup>37,38</sup> In addition, another recent study demonstrated an inverse relationship between center volume and 30-day mortality following TAVR with centers in the lowest quartile of TAVR procedures having worse outcomes,<sup>39</sup> highlighting the notion that the Heart Team's

assessment of patients can differ greatly between a highly experienced TAVR center and a less experienced TAVR center. Beyond clinical trial data, details of anatomy, clinical characteristics, and patient values may further influence the favored choice in each case, and a Heart Team evaluation of each patient with severe aortic stenosis is likely to benefit the individual patient. Taken together, these clinical nuances support efforts for new, validated and reliable TAVR-specific risk scores in patients to enhance the Heart Team's evaluation.

### *Limitations*

Our findings should be considered in light of the following limitations. First, this was a retrospective, subgroup analysis of the BRAVO-3 trial and is therefore underpowered to evaluate outcomes as stratified by LES. Second, the present study only analyzed one validated risk score and, consequently, these results are not generalizable to studies using other risk scores. Third, we do not know if the similar outcomes noted in our study are related to the TAVR approach or to the fact that the Heart Team is able to capture additional comorbidities associated with a poor outcome not otherwise captured by the LES. Fourth, BRAVO-3 only included patients deemed high-risk for surgery and these results may not be applicable to low-to-intermediate risk patients. Finally, we only report results up to 30 days, but we acknowledge that the LES has been shown to be a better predictor of late outcomes following TAVR.<sup>36</sup>

### *Conclusion*

In this subgroup analysis of the BRAVO-3 trial, we found no differences in short-term clinical outcomes of patients identified as high-risk due to  $LES \geq 18$  compared to patients deemed high-risk by Heart Team assessment despite their lower  $LES (<18)$ . These findings suggest that the Heart Team approach improves risk stratification of patients deemed lower risk according to  $LES$  by incorporating frailty and other high-risk patient characteristics in the clinical decision-making surrounding TAVR. Therefore, the Heart Team approach should remain an integral component in the management of patients with symptomatic, severe aortic stenosis, and not be disregarded in favor of sophisticated risk scores.



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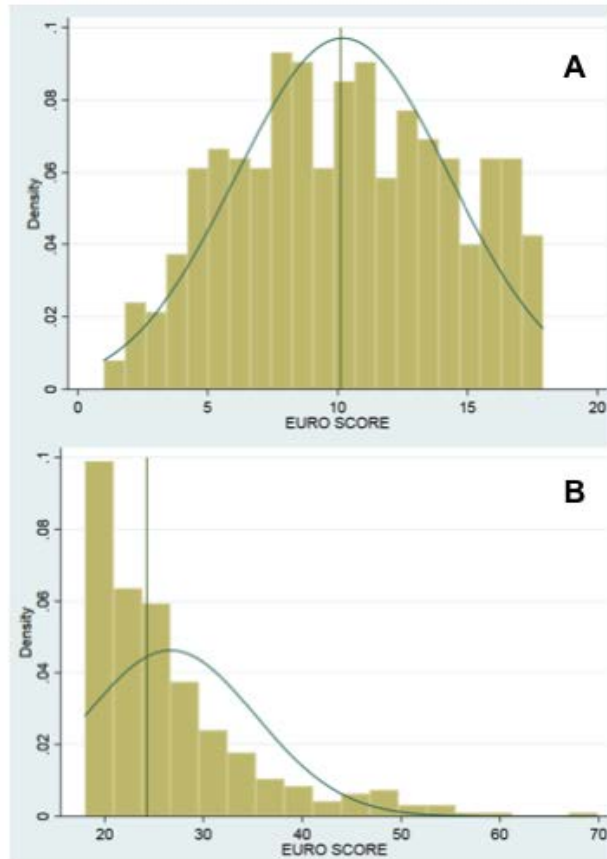
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### Figure Legends

**Figure 1.** Distribution of Logistic EuroSCORE in Patients with Logistic EuroSCORE <18 (A) and Logistic EuroSCORE  $\geq$ 18 (B). **1A:** Mean: 10.2, standard deviation: 4.1, median: 10.1. **1B:** Mean: 26.7, standard deviation: 8.6, median: 24.3.



**Table 1:** Patient baseline clinical and procedural characteristics

	<b>TAVR Eligibility According to Heart Team Assessment Despite LES &lt;18 (N= 467)</b>	<b>TAVR Eligibility According to LES ≥18 (N = 333)</b>	<b>P-Value</b>
Logistic EuroSCORE	10.2 ± 4.1	26.7 ± 8.6	--
Age (years)	81.3 ± 6.8	83.7 ± 5.8	<0.001
Female Gender	226 (48.4)	163 (49.0)	0.88
LV Ejection Fraction (%)	56.0 ± 11.6	50.3 ± 13.7	<0.001
COPD	75 (16.1)	80 (24.0)	0.005
Diabetes Mellitus	133 (28.5)	106 (31.8)	0.31
Peripheral Vascular Disease	46 (9.9)	73 (21.9)	<0.001
Coronary Artery Disease	221 (47.4)	183 (55.0)	0.04
Prior Myocardial Infarction	61 (13.2)	55 (16.7)	0.18
Prior Bypass Surgery	43 (9.2)	74 (22.2)	<0.001
Prior Stroke/TIA	43 (9.2)	40 (12.0)	0.43
Atrial Fibrillation	170 (36.4)	162 (48.7)	0.002
GFR <30ml/min	19 (4.1)	21 (6.3)	<0.001
GFR 30-59ml/min	209 (44.8)	188 (56.5)	<0.001
General Anesthesia	157 (34.0)	151 (46.2)	0.002
Balloon Expandable Valve	303 (66.0)	196 (60.9)	0.14
Self-Expandable Valve	156 (34.0)	126 (39.1)	0.14
Balloon post-dilation	132 (28.3)	66 (19.8%)	0.006
Successful Vascular Closure	422 (91.5)	303 (92.7)	0.08

LES: Logistic EuroSCORE, LV: Left Ventricular, COPD: Chronic Obstructive Pulmonary Disease, TIA: Transient Ischemic Attack, GFR: Glomerular Filtration Rate, TAVR: Transcatheter Aortic Valve Replacement



**Table 2.** Rate of Efficacy Endpoints

	<b>TAVR Eligibility According to Heart Team Assessment Despite LES &lt;18 N = 467</b>	<b>TAVR Eligibility According to LES ≥18 N = 333</b>	<b>P-value</b>
<i>48 hours or at discharge</i>			
NACE	42 (8.99%)	43 (12.91%)	0.08
MACE	14 (3.00%)	19 (5.71%)	0.06
Death	7 (1.50%)	7 (2.10%)	0.52
MI	1 (0.21%)	4 (1.20%)	0.08
Stroke	7 (1.50%)	8 (2.40%)	0.35
Major vascular complications	36 (7.71%)	35 (10.51%)	0.19
BARC ≥3b	32 (6.85%)	31 (9.31%)	0.20
VARC life-threatening bleeding	91 (19.49%)	71 (21.32%)	0.52
<i>30 days</i>			
NACE	63 (13.49%)	61 (18.32%)	0.06
MACE	31 (6.64%)	34 (10.21%)	0.07
Death	22 (4.71%)	18 (5.41%)	0.66
MI	4 (0.86%)	5 (1.50%)	0.39
Stroke	11 (2.36%)	14 (4.20%)	0.13
Major vascular complications	39 (8.35%)	36 (10.81%)	0.24
BARC ≥3b	41 (8.78%)	37 (11.11%)	0.27
VARC life-threatening bleeding	119 (25.48%)	87 (26.13%)	0.84

LES: Logistic EuroSCORE, NACE: Net Adverse Cardiovascular Events, MACE: Major Adverse Cardiovascular Events, BARC: Bleeding Academic Research Consortium, VARC: Valve Academic Research Consortium

**Table 3.** Adjusted odds of efficacy endpoints, TAVR Eligibility  
According to LES  $\geq 18$  vs. According to Heart Team Assessment Despite LES  $< 18$

	<b>OR</b>	<b>95% CI</b>	<b>P-value</b>
<b>48 hours or at discharge</b>			
NACE	1.48	0.89 - 2.45	0.13
MACE	1.79	0.79 - 4.05	0.16
Death	1.28	0.38 - 4.36	0.69
MI	9.93	0.49 - 201.35	0.14
Stroke	1.23	0.38 - 3.96	0.73
Major vascular complications	1.07	0.72 - 1.60	0.73
BARC $\geq 3b$	1.38	0.78 - 2.44	0.26
VARC life-threatening bleeding	1.03	0.70 - 1.51	0.89
<b>30 days</b>			
NACE	1.32	0.86 - 2.02	0.21
MACE	1.27	0.72 - 2.25	0.41
Death	0.91	0.43 - 1.92	0.80
MI	1.49	0.33 - 6.68	0.61
Stroke	1.41	0.57 - 3.47	0.45
Major vascular complications	0.97	0.65 - 1.44	0.88
BARC $\geq 3b$	1.38	0.82 - 2.33	0.23
VARC life-threatening bleeding	0.99	0.69 - 1.41	0.95

LES: Logistic EuroSCORE, OR: Odds Ratio, CI: Confidence Interval, NACE: Net Adverse Cardiovascular Events, MACE: Major Adverse Cardiovascular Events, BARC: Bleeding Academic Research Consortium. VARC: Valve Academic Research Consortium. *OR's adjusted for age, sex, diabetes mellitus, CKD, COPD, LVEF, atrial fibrillation and country.*

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**Title:**

The importance of the Heart Team evaluation before transcatheter aortic valve replacement: Results from the BRAVO-3 trial

**Date:**

2020-12

**Citation:**

Camaj, A., Claessen, B. E., Mehran, R., Yudi, M. B., Power, D., Baber, U., Hengstenberg, C., Lefevre, T., Van Belle, E., Giustino, G., Guedeney, P., Sorrentino, S., Kupatt, C., Webb, J. G., Hildick-Smith, D., Hink, H. U., Deliargyris, E. N., Anthopoulos, P., Sharma, S. K. ,... Dangas, G. D. (2020). The importance of the Heart Team evaluation before transcatheter aortic valve replacement: Results from the BRAVO-3 trial. *CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS*, 96 (7), pp.E688-E694. <https://doi.org/10.1002/ccd.28717>.

**Persistent Link:**

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