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► **To cite this version:**

Laurent Faroux, Thibault Lhermusier, Flavien Vincent, Luis Nombela-Franco, Didier Tchétché, et al. ST-Segment Elevation Myocardial Infarction Following Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*, 2021, 77 (17), pp.2187-2199. 10.1016/j.jacc.2021.03.014 . hal-03213608

HAL Id: hal-03213608

<https://hal.science/hal-03213608v1>

Submitted on 30 Apr 2021

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ST-Segment Elevation Myocardial Infarction Following Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Among patients with acute coronary syndrome following transcatheter aortic valve replacement (TAVR), those presenting with ST-segment elevation myocardial infarction (STEMI) are at highest risk.

OBJECTIVES The goal of this study was to determine the clinical characteristics, management, and outcomes of STEMI after TAVR.

METHODS This was a multicenter study including 118 patients presenting with STEMI at a median of 255 days (interquartile range: 9 to 680 days) after TAVR. Procedural features of STEMI after TAVR managed with primary percutaneous coronary intervention (PCI) were compared with all-comer STEMI: 439 non-TAVR patients who had primary PCI within the 2 weeks before and after each post-TAVR STEMI case in 5 participating centers from different countries.

RESULTS Median door-to-balloon time was higher in TAVR patients (40 min [interquartile range: 25 to 57 min] vs. 30 min [interquartile range: 25 to 35 min]; $p = 0.003$). Procedural time, fluoroscopy time, dose-area product, and contrast volume were also higher in TAVR patients ($p < 0.01$ for all). PCI failure occurred more frequently in patients with previous TAVR (16.5% vs. 3.9%; $p < 0.001$), including 5 patients in whom the culprit lesion was not revascularized owing to coronary ostia cannulation failure. In-hospital and late (median of 7 months [interquartile range: 1 to 21 months]) mortality rates were 25.4% and 42.4%, respectively (20.6% and 38.2% in primary PCI patients), and estimated glomerular filtration rate < 60 ml/min (hazard ratio [HR]: 3.02; 95% confidence interval [CI]: 1.42 to 6.43; $p = 0.004$), Killip class ≥ 2 (HR: 2.74; 95% CI: 1.37 to 5.49; $p = 0.004$), and PCI failure (HR: 3.23; 95% CI: 1.42 to 7.31; $p = 0.005$) determined an increased risk.

CONCLUSIONS STEMI after TAVR was associated with very high in-hospital and mid-term mortality. Longer door-to-balloon times and a higher PCI failure rate were observed in TAVR patients, partially due to coronary access issues specific to the TAVR population, and this was associated with poorer outcomes. (J Am Coll Cardiol 2021;77:2187-99)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CAD = coronary artery disease

MACCE = major adverse cardiovascular or cerebrovascular event

PCI = percutaneous coronary intervention

RCA = right coronary artery

STEMI = ST-segment elevation myocardial infarction

TAVR = transcatheter aortic valve replacement

About 50% of transcatheter aortic valve replacement (TAVR) recipients exhibit some degree of coronary artery disease (CAD), with one-half of them having multivessel disease (1). Acute coronary syndrome (ACS) events after TAVR exhibit some features different from those occurring in the non-TAVR population, including a much lower proportion of ST-segment elevation myocardial infarction (STEMI) (1% to 8% of all post-TAVR ACS) (2–4) and an increased risk of death and major adverse cardiovascular and cerebrovascular event (MACCE) in STEMI patients (compared with other ACS types) (3,4). The advanced age of TAVR recipients (5) along with the high incidence of non-STEMI patients (type 2) after TAVR (2,3) likely explain the shift in STEMI proportion between non-TAVR and TAVR patients. Also, the poor prognosis of post-TAVR STEMI could be related to patients' characteristics (high comorbidity burden) along with the involvement of pathophysiologic mechanisms other than atherothrombosis (impaired coronary flow, leaflet thrombosis, coronary embolism, late valve migration) (1). In addition, the potential interaction between the transcatheter heart valve and the coronary ostia (1,6,7) may be associated with a significant delay or even preclude primary percutaneous coronary intervention (PCI), which would likely have a major negative impact on patients' prognosis. However, to date

no study has specifically evaluated this high-risk population and most aspects of post-TAVR STEMI remain unknown. Therefore, the present study sought to determine the clinical characteristics, management, and outcomes of STEMI after TAVR.

METHODS

This was a multicenter international study including 118 patients presenting with STEMI after TAVR from 38 centers (out of 42,252 TAVR recipients, cumulative incidence of 0.3%). Mechanical coronary obstruction leading to STEMI during the TAVR procedure was not included in this analysis. CAD was defined as prior PCI, coronary artery bypass grafting (CABG), or myocardial infarction, or presence of coronary stenosis $\geq 50\%$. All patients but 1 underwent coronary angiography before TAVR, with CAD ruled out by preprocedural electrocardiography (ECG)-gated cardiac computed tomography in the remaining patient. Pre-TAVR PCI was performed if judged necessary by the local heart team. Chronic total occlusions and lesions that were either very distal or located in small vessels (< 2 mm) were generally medically managed (8). When all significant lesions in vessels of > 2 mm in diameter had been successfully treated with either CABG or PCI, revascularization was considered complete. TAVR indication, valve type, and approach were determined by the heart team of each center.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate.

Post-TAVR clinical outcomes were defined according to Valve Academic Research Consortium 2 criteria (9). Data were collected in accordance with the ethics committee of each participating center, and all patients provided signed informed consent for the procedures.

In accordance with the Fourth Universal Definition of Myocardial Infarction (10), clinical symptoms and ECG changes compatible with myocardial ischemia were taken into consideration for the diagnosis of STEMI. STEMI management was tailored by clinical judgment of the treating physician. Definite coronary embolism corresponded to the combination of angiographic evidence of coronary embolism (filling defect or abrupt occlusion in an artery without significant atherosclerosis) in addition to a probable embolic source (recent TAVR procedure, infective endocarditis, valve thrombosis, clot in the left atrial appendage), whereas possible coronary embolism corresponded to a STEMI without angiographic lesion at the time of coronary angiography associated with a probable embolic source (11). PCI failure was defined as a final diameter stenosis >30% or a post-dilation Thrombosis in Myocardial Infarction flow grade 0 or 1. Post-STEMI clinical outcomes were recorded and included all-cause death, MI, and stroke. MACCEs were defined as death, MI, or stroke. A total of 22 patients included in this study had already been included in a previous global post-TAVR ACS study not focusing on the specific characteristics of STEMI patients (3).

PRIMARY PCI COHORT SUBANALYSIS. The procedural characteristics of patients with post-TAVR STEMI who had primary PCI (n = 102) were compared with a group of all-comer (non-TAVR) primary PCI patients (control cohort). For this purpose, data from all STEMI patients (without prior TAVR) managed with primary PCI within the 15 days before and after each post-TAVR STEMI case in 5 high-volume centers from different countries (1 center per country) were also included. A total of 439 patients were included in this control cohort.

STATISTICAL ANALYSIS. Categorical variables were expressed as n (%) and continuous variables as mean ± SD or median (interquartile range [IQR]). Categorical variables were compared by means of chi-square test or Fisher exact test, as appropriate. Numeric variables were compared with the use of Student's *t*-test or Mann-Whitney nonparametric *U* test according to their distribution (assessed by the Kolmogorov-Smirnov test). Survival curves for time-to-event rates were performed by means of Kaplan-Meier estimates. The factors associated with mortality after post-TAVR STEMI in the primary PCI cohort were

TABLE 1 Baseline, TAVR Procedural Characteristics, and In-Hospital Outcomes (N = 118)

Baseline variables	
Age, yrs	80.3 ± 7.7
Female	59 (50.0)
BMI, kg/m ²	28.1 ± 5.5
Diabetes mellitus	41 (34.7)
Hypertension	100 (84.7)
Dyslipidemia	68 (57.6)
Current smoking	14 (11.9)
Atrial fibrillation	34 (28.8)
COPD	17 (14.4)
eGFR, ml/min	56.5 ± 24.9
Previous CAD	82 (69.5)
Previous MI	34 (28.8)
Previous CABG	15 (12.7)
Previous PAD	24 (20.3)
LVEF, %	54.6 ± 13.0
AV gradient, mm Hg	42.1 ± 14.7
AV area, cm ²	0.7 ± 0.2
Logistic EuroSCORE, %	15.9 ± 11.7
STS-PROM, %	5.6 ± 4.1
Pre-TAVR coronary angiography	
Coronary artery disease, vessels:	
0	41 (34.7)
1	27 (22.9)
2	25 (21.2)
3	25 (21.2)
PCI	46 (39.0)
Complete revascularization	70 (59.3)
Procedural characteristics	
Transfemoral approach	103 (87.3)
Prosthesis type	
Balloon-expandable	
Sapien/Sapien XT	25 (21.2)
Sapien 3	27 (22.9)
Inovare	1 (0.8)
Self-expanding	
CoreValve	34 (28.8)
Evolut R/Pro	24 (20.3)
Portico	1 (0.8)
Acurate neo	4 (3.4)
Centera	1 (0.8)
Mechanically expandable	
Lotus	1 (0.8)
Valve-in-valve	8 (6.8)
Antithrombotic medication at discharge:	
None	2 (1.7)
SAPT	20 (17.0)
DAPT	71 (60.1)
OAC	5 (4.2)
OAC + antiplatelet	20 (17.0)

Values are mean ± SD or n (%).

AV = aortic valve; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OAC = oral anticoagulant; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SAPT = single-antiplatelet therapy; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement.

determined with the use of a univariable Cox regression model. The proportional hazard assumption was tested by plotting log-minus-log survival. Variables with $p \leq 0.10$ on univariable analysis were entered into a multivariable Cox regression with stepwise selection (backward elimination). Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina) and Prism version 8.1.2 (GraphPad Software, San Diego, California).

RESULTS

STUDY POPULATION. The baseline and TAVR characteristics of the study population are presented in [Table 1](#). The mean age of the patients was 80.3 ± 7.7 years, with 50.0% men and an overall mean Society of Thoracic Surgeons Predicted Risk of Mortality of $5.6 \pm 4.1\%$. A total of 82 patients (69.5%) had prior CAD, and 15 patients (12.7%) had undergone CABG. Pre-TAVR coronary angiography did not find any significant lesion in 41 patients (34.7%), and multivessel disease was present in 50 patients (42.4%). Pre-TAVR PCI was performed in 46 patients (39.0%), and complete revascularization was achieved in 70 patients (59.3%). Most TAVR procedures (87.3%) were performed through a transfemoral approach, and self-expanding, balloon-expandable, and mechanically-expandable valves were implanted in 54.2%, 44.9%, and 0.8% of patients, respectively. A total of 8 valve-in-valve procedures were included (CoreValve/Evolut system: 6 cases; SAPIEN XT/3: 2 cases). Overall, the rates of stroke, major vascular complications, and life-threatening bleeding after TAVR were, respectively, 5.1%, 9.3%, and 4.2%. At discharge, 60.1% of patients were on dual antiplatelet therapy, 21.2% on oral anticoagulant, and 17.0% on single-antiplatelet therapy, and 1.7% did not receive any antithrombotic medication.

CLINICAL CHARACTERISTICS OF STEMI AFTER TAVR. The median delay between TAVR and STEMI was 255 days (IQR: 9 to 680 days) after TAVR. A total of 41 STEMIs (34.7%) occurred during the month following the TAVR procedure. Clinical characteristics of the post-TAVR STEMIs are summarized in [Table 2](#). ECG findings revealed an anterior, inferior, and lateral STEMI in 35.6%, 32.2%, and 5.9% of cases, respectively. The median time from symptom onset to hospital arrival was 130 min (IQR: 60 to 260 min). A total of 55 patients (46.6%) presented with signs of congestive heart failure at admission, including 21 patients (17.8%) in cardiogenic shock. Initial presentation was cardiac arrest in 13 patients (11.0%). Clopidogrel was used as P2Y₁₂-inhibitor in most cases

TABLE 2 Clinical Characteristics, Management, and In-Hospital Outcomes of STEMI After TAVR (N = 118)

Clinical characteristics	
Time from symptom onset to hospital arrival, min	130 (60-260)
ECG findings	
Anterior	42 (35.6)
Inferior	38 (32.2)
Lateral	7 (5.9)
LBBB	11 (9.3)
Other	20 (16.9)
Killip class	
1	63 (53.4)
2	27 (22.9)
3	7 (5.9)
4	21 (17.8)
Cardiac arrest at admission	13 (11.0)
LVEF, %	44.7 ± 13.9
Antithrombotic medication before STEMI	
None	2 (1.7)
SAPT	53 (44.9)
DAPT	36 (30.5)
OAC	10 (8.5)
OAC + antiplatelet	17 (14.4)
Management	
STEMI management	
Pre-hospital thrombolysis	1 (0.9)
Primary PCI	102 (86.4)
Noninvasive strategy	15 (12.7)
P2Y ₁₂ inhibitor	
Clopidogrel	66 (55.9)
Prasugrel	12 (10.1)
Ticagrelor	20 (17.0)
None	20 (17.0)
Anticoagulant	
Unfractionated heparin	91 (77.1)
Enoxaparin	3 (2.5)
Bivalirudin	4 (3.4)
None	20 (17.0)
GPIIb/IIIa inhibitor	8 (6.8)
Coronary angiogram	103 (87.3)
Circulatory assist device	
IAPB	0 (0.0)
ECMO	2 (1.7)
In-hospital outcomes	
Death	30 (25.4)
Stroke	8 (6.8)
Atrial fibrillation	7 (5.9)
Acute kidney injury	15 (12.7)
Antithrombotic medication at discharge	
None	1 (1.1)
SAPT	3 (3.4)
DAPT	55 (62.5)
OAC	1 (1.1)
OAC + antiplatelet	28 (31.8)

Values are median (interquartile range), n (%), or mean ± SD.

ECG = electrocardiography; ECMO = extracorporeal membrane oxygenation; GP = glycoprotein; IABP = intra-aortic balloon pump; LBBB = left bundle branch block; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in [Table 1](#).

TABLE 3 Characteristics of Patients Presenting STEMI After TAVR Who Did Not Undergo Coronary Angiography (N = 15)

Patient	Age, yrs	Sex	Device	Time Since TAVR, days	Reason Why No CA Was Performed	In-Hospital Death
#1	71	Female	Sapient XT	569	Sudden death with resuscitation failure	Yes
#2	84	Female	Sapient XT	1,391	Advanced age, late presentation	No
#3	70	Female	Sapient 3	12	Sudden death with resuscitation failure	Yes
#4	88	Male	CoreValve	680	Frail patient	No
#5	78	Female	CoreValve	256	Late presentation	No
#6	55	Male	Sapient XT	3	Transient STEMI and no significant coronary lesion on pre-TAVR coronary angiography	No
#7	86	Female	CoreValve	847	Advanced age, known severe CAD unsuitable for PCI, cardiogenic shock and complete AVB at presentation	Yes
#8	81	Female	Sapient 3	254	Hospitalized for hip fracture; while waiting for surgery, STEMI that quickly led to death	Yes
#9	80	Male	Sapient	9	Late presentation, hospitalized in a non-PCI-capable center, known severe CAD unsuitable for PCI	Yes
#10	82	Female	CoreValve	125	Late presentation	Yes
#11	79	Female	Evolut	0	Takotsubo suspicion	No
#12	82	Male	Sapient XT	1,783	Late presentation and acute kidney injury	No
#13	85	Female	CoreValve	334	Extreme frailty and pulmonary infection	Yes
#14	85	Female	CoreValve	655	Sudden death with resuscitation failure	Yes
#15	75	Female	Evolut	1,291	Sudden death with resuscitation failure	Yes

AVB = atrioventricular block; CA = coronary angiography; other abbreviations as in Tables 1 and 2.

(55.9%), and glycoprotein IIb/IIIa inhibitors were used in 8 patients (6.8%). A total of 102 patients (86.4%) were managed with primary PCI, 1 patient (0.9%) received pre-hospital thrombolysis, and 15 patients (12.7%) were managed medically. Rates of in-hospital mortality, stroke, and acute kidney injury were 25.4%, 6.8%, and 12.7%, respectively. At discharge, most patients received dual antiplatelet therapy (62.5%) or a combination of oral anticoagulant and antiplatelet (31.8%). In-hospital mortality was 20.6% in the subpopulation of patients managed with primary PCI, and 5.9% and 13.7% of patients complicated with stroke and acute kidney injury, respectively. Individual data from the 15 patients presenting with STEMI after TAVR who did not undergo coronary angiography are presented in Table 3. Among them, 9 patients (60.0%) died in hospital. Four patients presented cardiac arrest with resuscitation failure, 2 patients had a late presentation of STEMI, 1 patient was deemed to be extremely frail, 1 patient with advanced age and known CAD unsuitable for PCI presented with STEMI complicated with cardiogenic shock and complete atrioventricular block, and 1 patient was hospitalized for hip fracture and presented with STEMI with very rapid deterioration and death. The 6 remaining STEMIs following TAVR did not undergo coronary angiography owing to advanced age, frailty, late presentation, takotsubo suspicion, and transient STEMI without

significant coronary lesion on pre-TAVR coronary angiography.

PROCEDURAL FEATURES OF STEMI PATIENTS MANAGED WITH PRIMARY PCI.

Comparison of baseline variables and clinical characteristics of post-TAVR STEMI versus STEMI without prior TAVR are presented in Table 4. Compared with the control cohort, TAVR patients were older (80.7 ± 7.6 years vs. 64.1 ± 12.7 years; $p < 0.001$) and exhibited a much higher burden of comorbidities, with higher rates of diabetes mellitus (31.4% vs. 16.6%; $p < 0.001$), hypertension (83.3% vs. 50.8%; $p < 0.001$), prior CAD (69.6% vs. 12.5%; $p < 0.001$), and prior CABG (13.7% vs. 1.1%; $p < 0.001$). Table 5 presents the comparison of procedural characteristics of patients with and without prior TAVR. The proportion of coronary angiography performed through a femoral access was much higher in patients with prior TAVR (47.1% vs. 9.6%; $p < 0.001$). A switch from radial to femoral access occurred in 9 patients (8.8%) with post-TAVR STEMI. Median time from symptom onset to hospital arrival was longer in non-TAVR patients (180 min [IQR: 120 to 386 min] vs. 130 min [IQR: 60 to 260 min]; $p = 0.015$), but door-to-balloon time was 33% higher in TAVR patients (40 min [IQR: 25 to 57 min] vs. 30 min [IQR: 25 to 35 min]; $p = 0.003$), and 20.8% versus 8.6% of patients had a door-to-balloon time ≥ 60 min ($p = 0.005$). Similar results were obtained when excluding patients with prior CABG

TABLE 4 Comparison of Baseline Variables, Clinical Characteristics, and Management of STEMI After TAVR Versus STEMI Without Prior TAVR Managed With Primary PCI

	Post-TAVR STEMI (Primary PCI Cohort) (n = 102)	STEMI Without Prior TAVR (n = 439)	p Value
Baseline variables			
Age, yrs	80.7 ± 7.6	64.1 ± 12.7	<0.001
Female	47 (46.1)	105 (23.9)	<0.001
BMI, kg/m ²	27.6 ± 5.1	25.2 ± 4.9	<0.001
Diabetes mellitus	32 (31.4)	73 (16.6)	<0.001
Hypertension	85 (83.3)	223 (50.8)	<0.001
Dyslipidemia	60 (58.8)	169 (38.5)	<0.001
Current smoking	14 (13.7)	178 (40.5)	<0.001
Atrial fibrillation	26 (25.5)	24 (5.5)	<0.001
COPD	15 (14.7)	20 (4.6)	<0.001
eGFR, ml/min	58.3 ± 25.2	81.7 ± 24.9	<0.001
Previous CAD	71 (69.6)	55 (12.5)	<0.001
Previous MI	29 (28.4)	44 (10.0)	<0.001
Previous CABG	14 (13.7)	5 (1.1)	<0.001
Previous PAD	23 (22.5)	20 (4.6)	<0.001
Clinical characteristics			
ECG findings			<0.001
Anterior	38 (37.3)	165 (37.6)	
Inferior	35 (34.3)	227 (51.7)	
Lateral	5 (4.9)	30 (6.8)	
LBBB	8 (7.8)	3 (0.7)	
Other	16 (15.7)	14 (3.2)	
Killip class			<0.001
1	57 (55.9)	352 (80.2)	
2	23 (22.5)	43 (9.8)	
3	7 (6.9)	9 (2.0)	
4	15 (14.7)	35 (8.0)	
Cardiac arrest at admission	10 (9.8)	26 (5.9)	0.157
LVEF, %	44.7 ± 14.1	48.3 ± 11.8	0.038
Antithrombotic medication before STEMI			<0.001
None	2 (2.0)	340 (77.5)	
SAPT	48 (47.1)	74 (16.9)	
DAPT	31 (30.4)	4 (0.9)	
OAC	8 (7.8)	17 (3.9)	
OAC + antiplatelet	13 (12.7)	4 (0.9)	
STEMI management			
P2Y ₁₂ inhibitor			<0.001
Clopidogrel	59 (57.8)	181 (41.2)	
Prasugrel	12 (11.8)	33 (7.5)	
Ticagrelor	20 (19.6)	217 (49.4)	
None	11 (10.8)	8 (1.8)	
Anticoagulant			<0.001
Unfractionated heparin	84 (82.4)	413 (94.1)	
Enoxaparin	2 (2.0)	20 (4.6)	
Bivalirudin	2 (2.0)	5 (1.1)	
None	14 (13.7)	1 (0.2)	
GPIIb/IIIa inhibitor	8 (7.8)	67 (15.3)	0.051
Circulatory assist device	2 (2.0)	17 (3.9)	0.345

Values are mean ± SD or n (%).

Abbreviations as in Tables 1 and 2.

(p = 0.034). Similarly, procedural time (p < 0.001), fluoroscopy time (p < 0.001), dose-area product (p = 0.003), and contrast volume (p = 0.008) were higher in patients with prior TAVR (Figure 1). There were no significant differences in treatment delays and procedural performance indexes between valve types but the presence of a self-expanding transcatheter heart valve (vs. balloon-expandable) was associated with a higher fluoroscopy time (20 min [IQR: 12 to 27 min] vs. 16 min [IQR: 9 to 21 min]; p = 0.014). Nonselective injections were more frequent in patients with prior TAVR for both left and right coronary arteries (p < 0.001 for all), and ≥2 catheters were used more frequently to cannulate the right coronary artery (RCA) in patients with prior TAVR (p = 0.015). The proportions of multivessel disease (p = 0.856), bifurcation (p = 0.280), ostial lesion (p = 0.128), and calcification (p = 0.092) did not significantly differ between patients with and without prior TAVR. A nonatherothrombotic mechanism was more frequently involved in patients with prior TAVR (17.6% vs. 4.3%; p < 0.001). Definite and possible coronary embolism were considered to be the mechanism of post-TAVR STEMI in 9 (8.8%) and 5 (4.9%) patients, respectively. The coronary embolism was related to the TAVR procedure in 12 patients (the same day of the TAVR procedure in 10 patients, the day after TAVR procedure in 1 patient, and 8 days after TAVR in 1 patient) and to an infective endocarditis at the level of the TAVR bioprosthesis in 2 patients. A late valve migration causing a partial compression of the left sinus of Valsalva and the left main artery by the transcatheter heart valve occurred in 1 patient (2.4%) 70 days after TAVR (Evolut R system), and it was managed with off-pump CABG (left internal mammary artery to left anterior descending and right internal mammary artery to obtuse marginal). Finally, no case of STEMI related to a significant stenosis left untreated before TAVR was reported, but 2 cases of post-TAVR stent thrombosis occurred, and 1 case of stress cardiomyopathy was identified.

PCI failure occurred more frequently in patients with prior TAVR (16.5% vs. 3.9%; p < 0.001). Furthermore, the use of ≥2 guide catheters, nonselective injection with the guide catheter, and the use of a guide catheter extension were more frequent in TAVR patients (p < 0.05 for all). Individual data from the 14 TAVR patients presenting PCI failure are presented. Four patients presenting inferior STEMI related to an acute RCA

occlusion were not revascularized owing to failure to cannulate the RCA despite the use of multiple catheters (CoreValve/Evolut R system: n = 3; Sapien XT: 1 patient). One additional patient with an Evolut R valve system presenting with a left main stenosis was also not revascularized owing to failure to cannulate the left coronary artery. Failure to cross the lesion with the guidewire (not directly related to the transcatheter heart valve) occurred in 4 patients, including 1 patient with coronary embolism related to the TAVR procedure. No reflow occurred in 3 patients, and 1 case of coronary perforation with cardiac tamponade was recorded. Finally, 1 patient died during the procedure before PCI completion.

LATE CLINICAL OUTCOMES. Late outcomes of the whole cohort of patients with post-TAVR STEMI are presented in Table 5. A total of 50 patients (42.4%) died at a median follow-up of 7 months (IQR: 1 to 21 months) after STEMI. Overall, the rates of death, stroke, MI, and MACCE after the STEMI were 34.1 per 100 person-years (PY), 6.0 per 100 PY, 4.9 per 100 PY, and 46.9 per 100 PY, respectively (Figure 2). Late outcomes of the subpopulation with post-TAVR STEMI managed with primary PCI are presented in Table 6. Overall, the rates of death, stroke, MI, and MACCE after the STEMI were 28.1 per 100 PY, 4.8 per 100 PY, 4.4 per 100 PY, and 38.5 per 100 PY, respectively. The factors associated with an increased mortality risk after a post-TAVR STEMI in the primary PCI cohort are presented in Table 6. By multivariable analysis, estimated glomerular filtration rate <60 ml/min (hazard ratio [HR]: 3.02; 95% confidence interval [CI]: 1.42 to 6.43; p = 0.004), Killip class ≥ 2 (HR: 2.74; 95% CI: 1.37 to 5.49; p = 0.004), and PCI failure (HR: 3.23; 95% CI: 1.42 to 7.31; p = 0.005) determined a higher risk of death. Comparison of clinical outcomes in post-TAVR STEMI versus STEMI without prior TAVR are presented in Table 7.

Both in-hospital and late outcomes were poorer in patients with post-TAVR STEMI, with an increased incidence of death (p < 0.001), stroke (p = 0.008), and MACCE (p < 0.001).

DISCUSSION

This study is the first to determine the clinical, procedural characteristics, and outcomes of STEMI following TAVR, and the main findings can be summarized as follows: 1) about one-third of STEMI events after TAVR occurred within the few months following the procedure, and a nonatherothrombotic mechanism (coronary embolism, late prosthesis migration) was involved in ~15% of cases; 2) about 85% of patients were managed with primary PCI; 3) in

primary PCI patients, prior TAVR was associated with a longer door-to-balloon time and a much higher PCI failure rate, partially due to coronary access issues specific to the TAVR population; and 4) in-hospital and late outcomes following post-TAVR STEMI were poor (in-hospital and 1-year mortality rates up to 25% and 33%, respectively), with PCI failure determining an increased risk (Central Illustration).

BASELINE AND STEMI CLINICAL CHARACTERISTICS. Our study population consisted of intermediate- to high-risk patients who presented with STEMI after TAVR. Unlike patients included in previous TAVR registries (1), patients with post-TAVR STEMI exhibited higher rates of prior CAD (70% vs. ~50%) and PCI in the pre-TAVR work-up (39% vs. ~25%) (1). In fact, a history of CAD and PCI before TAVR had already been identified as independent predictors of ACS after TAVR (2,4). Also, the characteristics of the study population were very different from those reported in general STEMI registries (12,13), with a mean age of ~80 years and 50% being women. Furthermore, the rates of hypertension, diabetes mellitus, prior MI, and prior CABG (all common among TAVR patients) were higher than those reported in patients with STEMI without prior TAVR (12-14). This resulted in a much higher comorbidity burden in patients with post-TAVR STEMI managed with primary PCI compared with historical STEMI series and a non-TAVR control cohort.

Of note, patients presenting STEMI after TAVR were frequently in an unstable clinical condition at admission, with 47%, 18%, and 11% of the study population presenting congestive signs, cardiogenic shock, and cardiac arrest, respectively. This finding contrasts with features of all-comers with STEMI (12-14) and is likely related to the advanced age and multiple comorbidities of TAVR recipients. Whereas <5% of all-comers with STEMI have a left bundle branch block at the initial ECG (14,15), this feature was present in 8% of our study population, and a paced rhythm was present in 3% of patients. Conduction disturbances, which remain the most frequent complication of TAVR (16), may hinder the diagnosis of STEMI, leading to significant treatment delays. Prasugrel and ticagrelor are currently recommended over clopidogrel for P2Y₁₂-inhibitor loading in patients with STEMI undergoing primary PCI (17,18). In contrast, most patients in the present study were treated with clopidogrel. The potential increased bleeding risk in TAVR patients, the significant proportion of patients receiving long-term oral anticoagulant (~20%), and the prasugrel contraindication beyond 75 years of age likely explain this discrepancy.

ANGIOGRAPHIC CHARACTERISTICS OF STEMI AFTER TAVR. Coronary angiography and PCI are usually

TABLE 5 Comparison of Procedural Characteristics of STEMI After TAVR (Primary PCI Cohort) Versus STEMI Without Prior TAVR

	Post-TAVR STEMI (Primary PCI Cohort) (n = 102)	STEMI Without Prior TAVR (n = 439)	p Value
Time from symptom onset to hospital arrival, min	130 (60-260)	180 (120-386)	0.015
Time from door to balloon, min	40 (25-57)	30 (25-35)	0.003
Arterial access			<0.001
Radial	54 (52.9)	397 (90.4)	
Femoral	48 (47.1)	42 (9.6)	
Left coronary artery			
≥2 catheters used	6 (5.9)	18 (4.1)	0.431
Nonselective injection	23 (22.5)	5 (1.1)	<0.001
Right coronary artery			
≥2 catheters used	11 (10.8)	20 (4.6)	0.015
Nonselective injection	25 (24.5)	14 (3.2)	<0.001
Procedural time, min	46 (37-69)	36 (25-49)	<0.001
Fluoroscopy time, min	18.3 (10.1-24.5)	10.1 (6.4-16.0)	<0.001
Dose-area product, cGy × cm ²	7,609 (3,600-13,500)	4,637 (2,741-7,781)	0.003
Contrast volume, ml	170 (120-130)	146 (110-185)	0.008
Bleeding complication	7 (6.9)	36 (8.2)	0.653
Angiogram findings			
Number vessels disease			0.856
0	3 (2.9)	10 (2.3)	
1	59 (57.8)	245 (55.8)	
2	27 (26.5)	114 (26.0)	
3	13 (12.8)	70 (15.9)	
Culprit lesion			<0.001
LM	9 (8.8)	6 (1.4)	
LAD	38 (37.3)	176 (40.1)	
LCx	12 (11.8)	57 (13.0)	
RCA	32 (31.4)	187 (42.6)	
RIMA	1 (1.0)	0 (0.0)	
SVG	4 (3.9)	3 (0.7)	
None	6 (5.9)	10 (2.3)	
Atherothrombotic mechanism	84 (82.4)	420 (95.7)	<0.001
Other mechanisms			-
Stent thrombosis	2 (2.0)	3 (0.7)	
In-stent restenosis	0 (0.0)	2 (0.5)	
SCAD	0 (0.0)	2 (0.5)	
Coronary spasm	0 (0.0)	1 (0.2)	
Definite embolism	9 (8.8)	1 (0.2)	
Possible embolism	5 (4.9)	0 (0.0)	
Late valve migration	1 (1.0)	0 (0.0)	
Stress cardiomyopathy	1 (1.0)	10 (2.3)	
TIMI flow grade			0.016
0	56 (54.9)	298 (67.9)	
1	11 (10.8)	24 (5.5)	
2	19 (18.6)	46 (10.5)	
3	16 (15.7)	71 (16.2)	
% stenosis	94.2 ± 11.6	96.8 ± 7.0	0.039
Bifurcation	14 (13.7)	80 (18.2)	0.280
Ostial lesion	20 (19.6)	60 (13.7)	0.128
Calcifications	19 (18.6)	54 (12.3)	0.092
Thrombus	79 (77.5)	360 (82.0)	0.290
CA without PCI attempted	17 (16.7)	25 (5.7)	<0.001

Continued on the next page

performed in 99% and 90% of patients with STEMI, respectively (12). In the present study, the proportion of patients who did not undergo coronary angiography and PCI was notably high (13% and 27%, respectively), and these findings were in line with previous studies regarding post-TAVR ACS (3,4). The decision not to perform coronary angiography was based on resuscitation failure, critical medical situations with altered general condition or high comorbidity burden, and late presentation. In fact, coronary angiography and PCI are less likely to be performed as the patients' age increase (5), and elderly patients are commonly under-represented in STEMI registries (12-14). Thus, the advanced age along with the high comorbidity burden of current TAVR recipients would likely explain the high rate of medical management versus an invasive strategy. Future studies further evaluating the low rate of invasive procedures in this population are warranted.

A coronary embolism was considered to be responsible for the STEMI in a significant proportion (14%) of cases, and one-half of them were not revascularized (revascularization not attempted or PCI failed). The absence of strong criteria for a definite diagnosis of coronary embolism (11) and the higher likelihood of a STEMI event within the few months following TAVR raise the question of a possible underestimation of the real frequency of such mechanism in post-TAVR STEMI. Further studies with systematic intracoronary imaging and anatomopathologic examination of the thrombus are required to better determine the incidence of coronary embolism in STEMI following TAVR. One case of late valve migration compressing the left main artery requiring CABG was identified in the present study. Delayed coronary occlusion is a rare complication of TAVR (incidence of 0.22%), occurs more commonly after valve-in-valve procedures (particularly with self-expanding transcatheter valves), and is associated with a high in-hospital mortality (19). Late valve migration may also have been involved in some patients with early post-TAVR STEMI who died before undergoing coronary angiography.

PROCEDURAL CHARACTERISTICS OF STEMI AFTER TAVR. Treatment delays are a simple index of quality of care in STEMI, and their reduction has been associated with a significant decrease in myocardial damage and improved outcomes (17,20). In the present study, the median time from symptom onset to hospital arrival was shorter in patients with prior TAVR, likely explained by a greater tendency of TAVR patients to go to the hospital (high comorbidity

burden). On the other hand, the mean door-to-balloon time was 33% higher in patients with prior TAVR. Furthermore, higher rates of unselective injection, need of ≥ 2 catheters to cannulate the coronary ostia, and guide catheter extension use were also observed among patients presenting with STEMI after TAVR. All of these aspects are indirect evidence of increased complexity when an emergency PCI has to be performed in a STEMI patient with prior TAVR. This likely contributed to delayed PCI times and negatively affected the clinical outcomes of STEMI after TAVR. In addition, the decision to perform a primary PCI may have been delayed in some cases on the basis of high comorbidity burden and atypical clinical presentation.

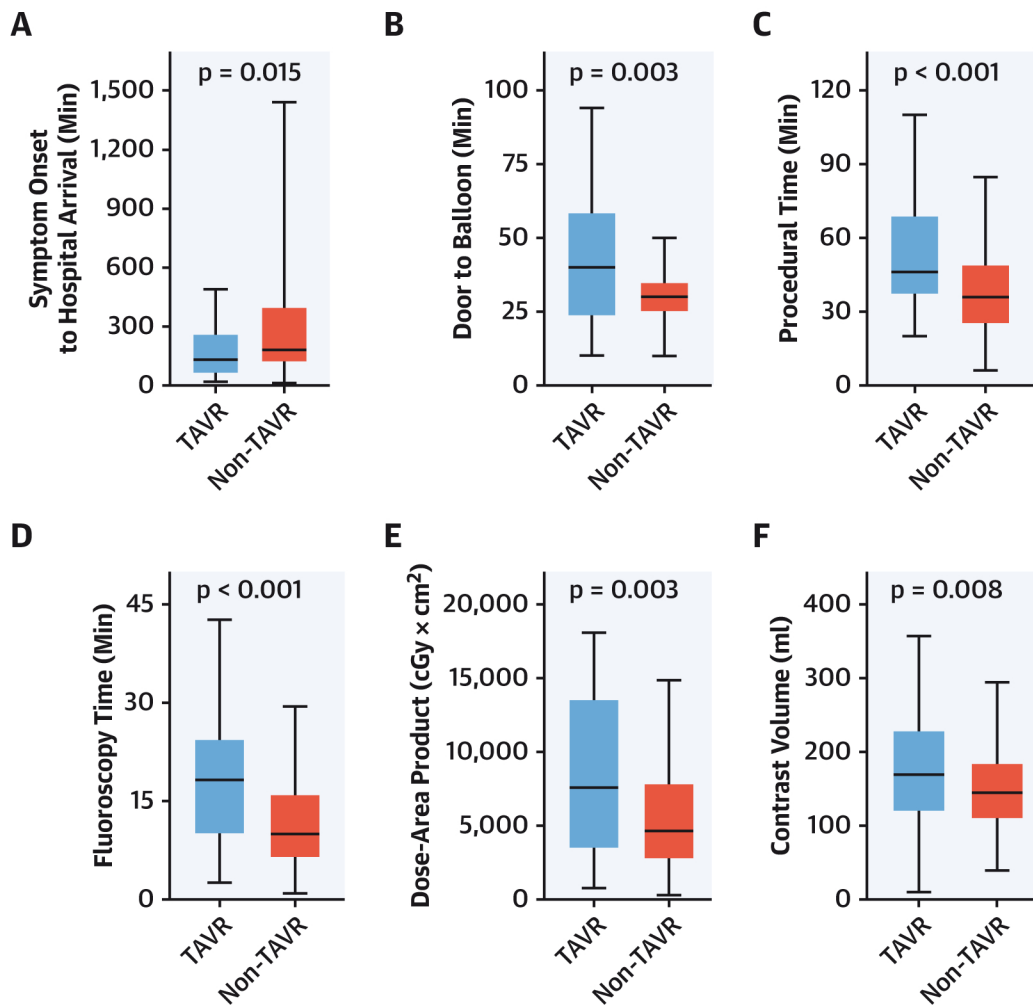
The rate of PCI failure was much higher in patients with prior TAVR (~15%) compared with the control (non-TAVR) cohort (4%) and was also markedly higher than the 6% rate usually reported in all-comer primary PCI patients (13). The reason for PCI failure was directly related to the transcatheter prosthesis in one-half of the patients, mainly owing to coronary access issues. Of note, lesion complexity was similar between patients with and without prior TAVR (as evidenced by the similar proportion of multivessel disease, bifurcation, ostial location, and calcifications). This finding further supports the hypothesis that the increased revascularization time and the higher proportion of failed PCI in TAVR patients were not related to lesion complexity discrepancies, but rather to an extrinsic factor (coronary access difficulties resulting from interaction between the transcatheter heart valve and the coronary ostia in this instance). Femoral access has been proposed to facilitate PCI after TAVR (21). In the present study, this approach was selected in one-half of the cases, and a widespread use of femoral access could contribute to reduce door-to-balloon time and PCI failure rate in patients presenting with STEMI after TAVR. Furthermore, a better understanding of the potential difficulties of coronary cannulation caused by the presence of a transcatheter heart valve, as well as techniques for enhancing coronary access, could improve PCI efficiency and outcomes of patients with post-TAVR STEMI. The fact that many patients with post-TAVR STEMI may be directed to and treated in centers with no TAVR experience further highlights the importance of establishing clear recommendations and standardized practices in this setting.

In this study, PCI failure related to coronary cannulation failure occurred in 5 patients. CoreValve/Evolut devices represented 49% of all implanted transcatheter heart valves, but 80% of PCI failures

TABLE 5 Continued			
	Post-TAVR STEMI (Primary PCI Cohort) (n = 102)	STEMI Without Prior TAVR (n = 439)	p Value
Reason for PCI not attempted			
Emergency CABG	1 (1.0)	5 (1.1)	
MINOCA	6 (5.9)	10 (2.3)	
SCAD	0 (0.0)	1 (0.2)	
Coronary spasm	0 (0.0)	1 (0.2)	
High thrombotic burden with TIMI flow grade 3	2 (2.0)	3 (0.7)	
Distal lesion	4 (3.9)	0 (0.0)	
Absolute contraindication to antiplatelet therapy	1 (1.0)	0 (0.0)	
Delayed PCI*	1 (1.0)	1 (0.2)	
Evolved STEMI (>12 h)†	2 (2.0)	2 (0.5)	
Cardiac arrest with pulseless activity	0 (0.0)	2 (0.5)	
PCI characteristics			
≥ 2 left guide catheters used	4 (7.7)	5 (2.2)	0.042
≥ 2 right guide catheters used	6 (20.0)	13 (7.1)	0.022
Nonselective injection	18 (21.2)	10 (2.4)	<0.001
Guide catheter extension	9 (10.6)	15 (3.6)	0.006
Thrombectomy	17 (20.0)	136 (32.9)	0.019
Pre-dilatation	58 (68.2)	255 (61.6)	0.249
Cutting balloon	1 (1.2)	1 (0.2)	0.214
Rotational atherectomy	1 (1.2)	1 (0.2)	0.214
Number of stents implanted	0.9 \pm 0.8	1.4 \pm 0.8	<0.001
Stented length, mm	24.4 \pm 12.2	31.7 \pm 18.7	<0.001
Stent diameter, mm	3.2 \pm 0.5	3.2 \pm 0.5	0.906
Device used			<0.001
DES	50 (58.8)	322 (77.8)	
BMS	8 (9.4)	73 (17.6)	
DEB	3 (3.5)	1 (0.2)	
POBA	10 (11.8)	10 (2.4)	
None	14 (16.5)	8 (1.9)	
Post-dilatation TIMI flow grade			<0.001
0	11 (13.0)	7 (1.7)	
1	3 (3.5)	6 (1.5)	
2	3 (3.5)	25 (6.0)	
3	68 (80.0)	376 (90.8)	
PCI failure	14 (16.5)	16 (3.9)	<0.001
Reason for PCI failure			
Failure to cannulate coronary ostium	5 (5.9)	0 (0.0)	
Failure to cross lesion	4 (4.7)	2 (0.5)	
No-reflow	3 (3.5)	12 (2.9)	
Coronary perforation	1 (1.2)	2 (0.5)	
Procedural death	1 (1.2)	0 (0.0)	
Complete revascularization	51 (60.0)	297 (71.7)	0.032
Culprit lesion revascularization only	74 (87.1)	385 (93.0)	0.068
Values are median (interquartile range), n (%), or mean \pm SD. *Cases where PCI was postponed due to coronary angiogram findings. †STEMI with chest pain evolving for more than 12 h with deep Q-wave. BMS = bare-metal stent; DEB = drug-eluting balloon; DES = drug-eluting stent; LAD = left anterior descending; LCx = left circumflex; LM = left main; MINOCA = myocardial infarction with nonobstructive coronary arteries; POBA = plain old balloon angioplasty; RCA = right coronary artery; RIMA = right internal mammary artery; SCAD = spontaneous coronary artery dissection; SVG = saphenous vein graft; TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in Tables 1 and 2.			

involved these devices. Similarly, the culprit lesion was located in the RCA in 31% of cases, but 80% of failed cannulations were related to RCA. This finding, combined with the high rate of unselective injection,

FIGURE 1 Comparison of Median Time From Symptom Onset to Hospital Arrival, Time From Door to Balloon, Procedural Time, Fluoroscopy Time, Dose-Area Product, and Contrast Volume Between Patients With and Without TAVR



(A) Time from symptom onset to hospital arrival; (B) time from door to balloon; (C) procedural time; (D) fluoroscopy time; (E) dose-area product; (F) contrast volume. The boxes represent the median with interquartile ranges, and the whiskers represent the upper and lower limits excluding the extreme values (Tukey style). TAVR = transcatheter aortic valve replacement.

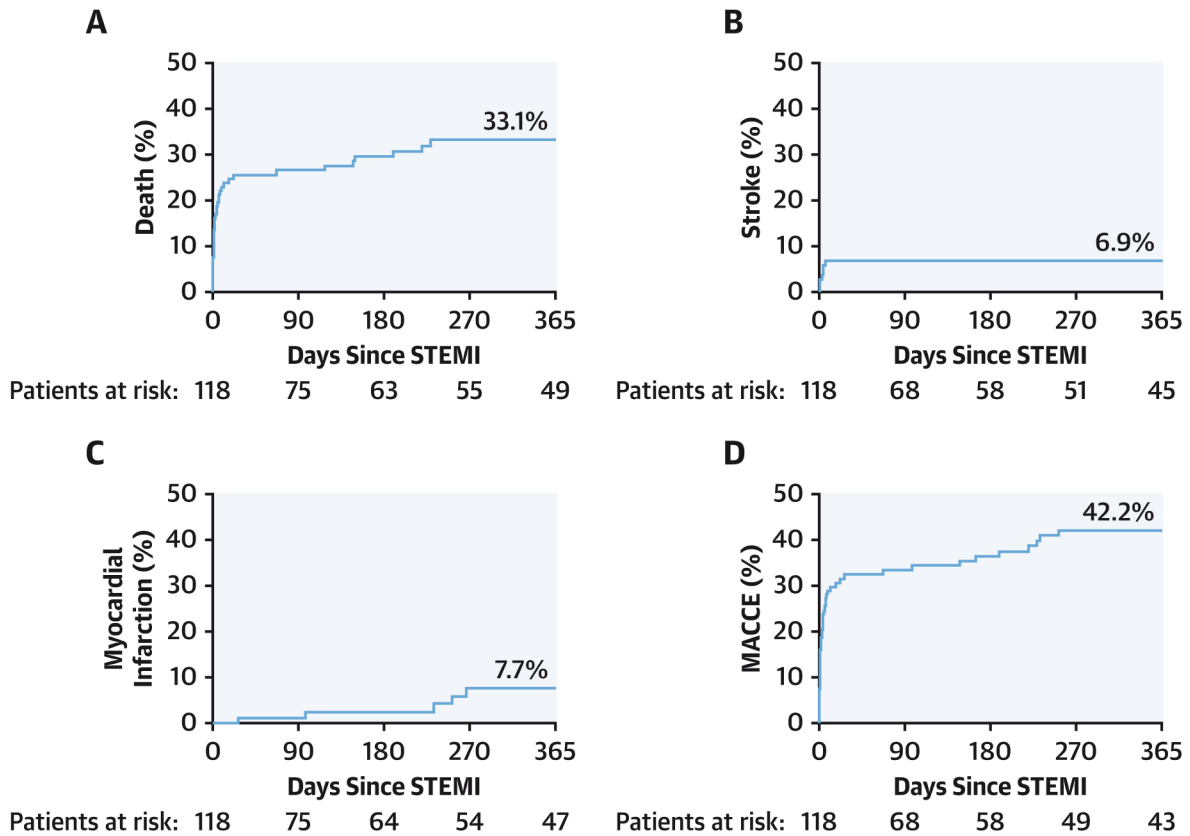
the frequent need for ≥ 2 guide catheters to adequately cannulate the RCA, and the longer fluoroscopy time in patients with self-expanding devices further suggests increased coronary access difficulties through this type of self-expanding valve systems, especially for the RCA cannulation (6,22,23). However, this should be interpreted with caution given the small number of events. Finally, the relatively high rate of conduction disturbances after TAVR (16), along with their negative clinical impact (24), has led some operators to minimize implantation depth (25). Implantation depth is also a strong determinant of coronary access issues after TAVR (23), and the optimal implantation position should

take into account both the risk of conduction disturbances and coronary access after TAVR, particularly in low-risk TAVR recipients with longer life expectancy.

CLINICAL OUTCOMES OF STEMI AFTER TAVR.

Compared with data from STEMI registries (12-14), patients presenting with STEMI after TAVR exhibited a much higher rate of adverse events and a very high in-hospital and late mortality. Also, these outcomes were worse than those observed in elderly patients presenting with ACS (5). This discrepancy may be explained by several factors. First, the long door-to-balloon times along with very high rates of PCI failure: PCI failure was strongly associated with post-

FIGURE 2 Kaplan-Meier Curves for Clinical Events After STEMI Following TAVR (Whole Cohort)



(A) All-cause death; (B) stroke; (C) myocardial infarction; (D) major adverse cardiovascular event (MACCE). STEMI = ST-segment elevation myocardial infarction; TAVR = transcatheter aortic valve replacement.

STEMI mortality, and a trend toward an increased risk of death among patients with longer door-to-balloon times was also observed. Second, the clinical characteristics of current TAVR recipients (elderly patients with high comorbidity burden) and the left ventricle changes associated with aortic stenosis also may have contributed to the poorer outcomes compared with all-comers with ACS/STEMI. The high proportion of post-TAVR STEMI patients in an unstable clinical condition, combined with the negative impact of Killip class ≥ 2 , supports the latter hypothesis. Finally, alternative pathophysiologic mechanisms, such as coronary embolism and late valve migration (causing delayed coronary occlusion), could have complicated revascularization or led to rapid death in some cases. In the present study, no significant impact of nonatherothrombotic mechanism on outcomes was observed, but a larger sample size would be necessary to demonstrate a potential association between the pathophysiologic mechanism and clinical outcomes.

STUDY LIMITATIONS. This study was performed in intermediate- to high-risk patients, and the findings may not apply to lower-risk populations with TAVR. Coronary embolism was found to be responsible for STEMI in a significant proportion of patients, but this entity suffers from a lack of consensual definition, and no adjudication committee was available in this study. The control cohort was obtained from a selected group of centers. However, the results of primary PCI in all-comer (non-TAVR) patients were obtained during the same period of time as in post-TAVR STEMI patients and were similar to those reported in other contemporary STEMI studies (12,13), suggesting an appropriate representability of this control group.

CONCLUSIONS

STEMI following TAVR is a rare event but associated with dismal in-hospital and midterm clinical outcomes. Longer door-to-balloon times and a higher PCI failure rate were observed in TAVR patients, partially

TABLE 6 Factors Associated With Death After a STEMI Following TAVR (Primary PCI Cohort)

	Univariable model		Multivariable model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (per 1-yr increase)	1.00 (0.96-1.04)	0.948	-	-
Female	1.01 (0.52-1.96)	0.980	-	-
Diabetes mellitus	1.39 (0.72-2.70)	0.329	-	-
Hypertension	1.03 (0.43-2.47)	0.948	-	-
eGFR <60 ml/min	2.88 (1.35-6.11)	0.006	3.02 (1.42-6.43)	0.004
COPD	0.98 (0.42-2.27)	0.964	-	-
Atrial fibrillation	0.85 (0.40-1.80)	0.674	-	-
Prior CAD	1.05 (0.51-2.16)	0.904	-	-
Prior PAD	1.99 (0.99-4.01)	0.053	-	-
Self-expanding THV (vs. balloon- or mechanically expandable)	0.98 (0.51-1.85)	0.937	-	-
Anterior STEMI (vs. other localization)	1.42 (0.75-2.72)	0.285	-	-
Killip class ≥ 2	2.56 (1.29-5.07)	0.007	2.74 (1.37-5.49)	0.004
Nonatherothrombotic mechanism	0.66 (0.26-1.71)	0.393	-	-
Time from door to balloon >60 min	2.10 (0.81-5.44)	0.125	-	-
PCI failure	2.70 (1.22-5.99)	0.015	3.23 (1.42-7.31)	0.005

THV = transcatheter heart valve; other abbreviations as in Tables 1 and 2.

due to coronary access issues specific to the TAVR population, and PCI failure was strongly associated with an increased mortality risk. These results highlight the urgent need for a better understanding of coronary cannulation difficulties and the techniques for enhancing coronary access and improving PCI success rates and clinical outcomes in this population. Also, further studies are required to better determine the role of nonatherothrombotic mechanisms (coronary embolism, late valve migration) among patients with STEMI after TAVR.

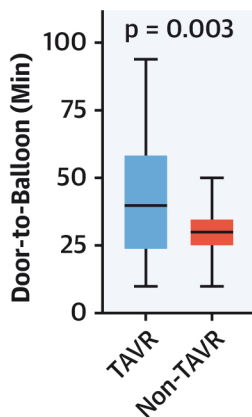
FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Faroux has received fellowship support from Institut Servier and the Association Régionale de Cardiologie de Champagne-Ardenne (ARCCA); and has received research grants from Biotronik, Edwards Lifesciences, and Medtronic. Dr. Abdel-Wahab has served as a consultant for Boston Scientific and Medtronic. Dr. Windecker has received research and educational grants from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi-Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed. Dr. Auffret has received lecture fees from Edwards Lifesciences and Medtronic. Dr. Trillo-Nouche has served as a proctor for Boston Scientific and Medtronic. Dr. Toggweiler has served as a consultant and proctor for Abbott, Boston Scientific, Biosensors, and Medtronic. Dr. Tarantini has received lecture fees from Boston Scientific, Edwards Lifesciences, Gada, and Medtronic. Dr. Saia has served as a member of advisory

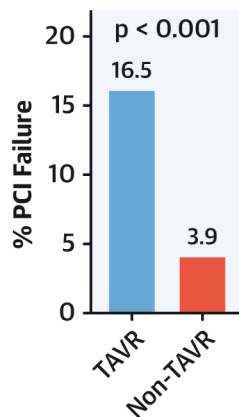
CENTRAL ILLUSTRATION ST-Segment Elevation Myocardial Infarction Following Transcatheter Aortic Valve Replacement

STEMI Following TAVR

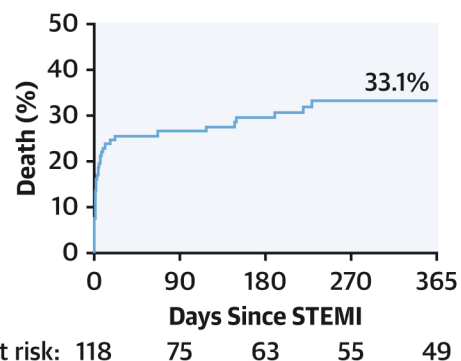
- 33% longer door-to-balloon time



- 4-fold higher PCI failure rate



- Poor clinical outcomes



Faroux, L. et al. *J Am Coll Cardiol.* 2021;77(17):2187-99.

(Left panel) Time from door to balloon (TAVR and non-TAVR primary PCI patients); (Mid panel) PCI failure rate (TAVR and non-TAVR primary PCI patients); (Right panel) Time-to-event curve for all-cause death (STEMI post-TAVR patients, whole cohort). PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TAVR = transcatheter aortic valve replacement.

boards for Abbott, Edwards Lifesciences, and Medtronic. Dr. Durand has served as a consultant for Edwards Lifesciences. Dr. Asmarats has served as a proctor for Abbott. Dr. Nejari has served as a proctor for Abbott and Boston Scientific. Dr. Muntané-Carol was supported by a grant from the Fundación Alfonso Martín Escudero (Madrid, Spain). Dr. Mangieri has received an institutional grant from Boston Scientific. Dr. Rodés-Cabau has received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific; and holds the Research Chair “Fondation Famille Jacques Larivière” for the Development of Structural Heart Disease Interventions. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: STEMI events occur usually within the few months post-TAVR, and nonatherothrombotic mechanisms are involved in ~15% of cases. Longer door-to-balloon times and a higher PCI failure rate may be partially attributed to coronary access challenges specific to the TAVR setting, and PCI failure is associated with an increased risk of mortality.

TRANSLATIONAL OUTLOOK: Further studies are needed to develop better techniques for coronary access and improve clinical outcomes in this population.

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KEY WORDS acute coronary syndrome, mortality, percutaneous coronary intervention, ST-segment elevation myocardial infarction, transcatheter aortic valve replacement