EuroIntervention 2023;19-online publish-ahead-of-print July 2023

Comparison of different percutaneous revascularisation timing strategies in patients undergoing transcatheter aortic valve implantation

Tobias Rheude[1], MD; Giuliano Costa[2], MD; Flavio Luciano Ribichini[3], MD; Thomas Pilgrim[4], MD; Ignacio J. Amat-Santos[5], MD; Ole De Backer[6], MD; Won-Keun Kim[7], MD; Henrique Barbosa Ribeiro[8], MD; Francesco Saia[9], MD; Matjaz Bunc[10], MD; Didier Tchétché[11], MD; Philippe Garot[12], MD; Darren Mylotte[13], MD; Francesco Burzotta[14], MD; Yusuke Watanabe[15], MD; Francesco Bedogni[16], MD; Tullio Tesorio[17], MD; Marco Tocci[18], MD; Anna Franzone[19], MD; Roberto Valvo[20], MD; Mikko Savontaus[21], MD; Hendrik Wienemann[22], MD; Italo Porto[23], MD; Caterina Gandolfo[24], MD; Alessandro Iadanza[25], MD; Alessandro S. Bortone[26], MD, PhD; Markus Mach[27], MD; Azeem Latib[28], MD; Luigi Biasco[29], MD; Maurizio Taramasso[30], MD; Marco Zimarino[31], MD; Daijiro Tomii[4], MD; Philippe Nuyens[6], MD; Lars Sondergaard[32], MD, PhD; Sergio F. Camara[8], MD; Tullio Palmerini[9], MD; Mateusz Orzalkiewicz[9], MD; Klemen Steblovnik[10], MD; Bastien Degrelle[11], MD; Alexandre Gautier[12], MD; Paolo Alberto Del Sole[3], MD; Andrea Mainardi[3], MD; Michele Pighi[3], MD; Mattia Lunardi[3,13], MD, MSc; Hideyuki Kawashima[15], MD; Enrico Criscione[16], MD; Vincenzo Cesario[33], MD; Fausto Biancari[17], MD; Federico Zanin[17], MD; Giovanni Esposito[19], MD; Matti Adam[22], MD; Eberhard Grube[22], MD, PhD; Stephan Baldus[22], MD; Vincenzo De Marzo[23], MD; Elisa Piredda[23], MD; Stefano Cannata[24], MD; Fortunato Iacovelli[26], MD, PhD; Martin Andreas[27], MD, PhD; Valentina Frittitta[20], MD; Elena Dipietro[20], MD; Claudia Reddavid[20], MD; Orazio Strazzieri[20], MD; Silvia Motta[20], MD; Domenico Angellotti[19], MD; Carmelo Sgroi[2], MD; Erion Xhepa[1], MD; Faraj Kargoli[28], MD; Corrado Tamburino[2], MD, PhD; Michael Joner[1*], MD; Marco Barbanti[2,34], MD

The authors' affiliations can be found in the Appendix paragraph.

GUEST EDITOR: Alec Vahanian, MD, PhD; *UFR Medecine, Université de Paris, Paris, France*

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00186

KEYWORDS

- aortic stenosis
- coronary artery disease
- TAVI

Abstract

Background: The optimal timing to perform percutaneous coronary interventions (PCI) in transcatheter aortic valve implantation (TAVI) patients remains unknown.

Aims: We sought to compare different PCI timing strategies in TAVI patients.

Methods: The REVASC-TAVI registry is an international registry including patients undergoing TAVI with significant, stable coronary artery disease (CAD) at preprocedural workup. In this analysis, patients scheduled to undergo PCI before, after or concomitantly with TAVI were included. The main endpoints were all-cause death and a composite of all-cause death, stroke, myocardial infarction (MI) or rehospitalisation for congestive heart failure (CHF) at 2 years. Outcomes were adjusted using the inverse probability treatment weighting (IPTW) method.

Results: A total of 1,603 patients were included. PCI was performed before, after or concomitantly with TAVI in 65.6% (n=1,052), 9.8% (n=157) or 24.6% (n=394), respectively. At 2 years, all-cause death was significantly lower in patients undergoing PCI after TAVI as compared with PCI before or concomitantly with TAVI (6.8% vs 20.1% vs 20.6%; p<0.001). Likewise, the composite endpoint was significantly lower in patients undergoing PCI after TAVI as compared with PCI before or concomitantly with TAVI (17.4% vs 30.4% vs 30.0%; p=0.003). Results were confirmed at landmark analyses considering events from 0 to 30 days and from 31 to 720 days.

Conclusions: In patients with severe aortic stenosis and stable coronary artery disease scheduled for TAVI, performance of PCI after TAVI seems to be associated with improved 2-year clinical outcomes compared with other revascularisation timing strategies. These results need to be confirmed in randomised clinical trials.

**Corresponding author: Department of Cardiovascular Diseases, German Heart Center Munich, Technical University Munich, Lazarettstraße 36, 80636 Munich, Germany. E-mail: joner@dhm.mhn.de*

SUBMITTED ON 06/03/2023 - REVISION RECEIVED ON 1st 21/04/2023 / 2nd 13/05/2023 - ACCEPTED ON 02/06/2023

DOI: 10.4244/EIJ-D-23-00186

Abbreviations

AS	aortic stenosis
CAD	coronary artery disease
CHF	congestive heart failure
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
IVUS	intravascular ultrasound
LAD	left anterior descending artery
LM	left main
MI	myocardial infarction
MLA	minimal lumen area
OCT	optical coherence tomography
PCI	percutaneous coronary interventions
TAVI	transcatheter aortic valve implantation
THV	transcatheter heart valve
VARC	Valve Academic Research Consortium

Introduction

Coronary artery disease (CAD) frequently coexists with severe aortic stenosis (AS) due to overlapping risk factors[1]. As both disease conditions may cause similar symptoms, assessment and management of these coexisting pathologies can be challenging. Current international guidelines recommend percutaneous coronary intervention (PCI) of coronary artery lesions with >70% stenosis in proximal segments (or >50% in case of left main disease) in patients scheduled for transcatheter aortic valve implantation (TAVI) based on angiographic assessment (class IIa recommendation, Level of Evidence C)[2].

As available evidence mainly comes from non-randomised, observational studies with inherent limitations, the optimal diagnosis and treatment of CAD in patients scheduled for TAVI are yet to be defined[3]. Assessment of CAD severity in the setting of AS, the extent of revascularisation and the optimal timing of both procedures remain a matter of debate[4-6]. Historically, percutaneous revascularisation prior to TAVI represented standard clinical practice due to concerns regarding ischaemic and haemodynamic complications during rapid ventricular pacing. Currently, the chronology of interventions is subject to individualised decision-making based on clinical and anatomical variables with potential (dis) advantages for each timing strategy[2].

Despite the high clinical relevance, available data are scarce, and their general applicability is limited by small sample sizes, the exclusive use of balloon-expandable valves (BEV) and limitation of PCI procedures to selected subgroups[7-9]. Randomised trials investigating the role of physiological assessment of CAD and revascularisation timing strategies in patients with severe AS undergoing TAVI are ongoing.

Against the background of the mentioned limitations of the previous single-centre studies, we sought to compare different PCI timing strategies in patients scheduled for TAVI in this large, international, multicentre Management of myocardial REVASCularization in patients undergoing Transcatheter Aortic Valve Implantation with coronary artery disease (REVASC-TAVI) registry with regard to adverse clinical outcomes, including all-cause death, myocardial infarction (MI), stroke and rehospitalisation for congestive heart failure (CHF) at 2 years after TAVI.

Methods

PATIENT POPULATION AND PROCEDURES

Among 2,402 patients enrolled in the REVASC-TAVI registry between January 2015 and September 2021 from 30 centres in Europe, North and South America and Japan, a total of 1,603 TAVI patients were scheduled to undergo either staged (before or after) or concomitant PCI. The REVASC-TAVI registry is an investigator-initiated registry designed to collect data of patients with severe AS scheduled for TAVI and significant coronary artery lesions, diagnosed during pre-TAVI angiography, as described previously[10]. All patients were discussed by a multidisciplinary Heart Team and found eligible for TAVI. TAVI and PCI procedures were performed according to local standards. The chronology of both procedures as well as valve type selection was at the operator's discretion. Data collection and analysis was approved by local ethics committees of the participating centres and complied with the Declaration of Helsinki. All patients provided written informed consent.

DEFINITIONS

Significant CAD was defined according to international guidelines on myocardial revascularisation[11,12]. In detail, revascularisation was indicated in the presence of an angiographic stenosis ≥70% (or ≥50% in case of protected left main [LM] or bypass graft) as determined by visual estimation, or functionally significant stenosis (instantaneous wave-free ratio [iFR] value ≤0.89 or fractional flow reserve [FFR] value ≤ 0.80) in at least 1 major coronary artery with a diameter of at least 2.5 mm, detected in a coronary angiography performed during pre-TAVI workup, or LM minimal lumen area (MLA) <6 mm^2 at intravascular ultrasound (IVUS) assessment. PCI before TAVI was defined as an elective PCI procedure performed in a different session prior to TAVI. Of note, PCI for acute coronary syndromes was excluded by definition. PCI after TAVI was defined as an elective PCI procedure performed after TAVI in a staged procedure. Concomitant PCI was defined as an elective PCI procedure performed within a single session, either before or after transcatheter heart valve (THV) implantation. The management of CAD, including indication for PCI, use of functional invasive or non-invasive tests to assess myocardial ischaemia, use of intravascular imaging, PCI strategy and duration of antithrombotic therapy, was at the operator's discretion at each centre and according to current international guidelines.

DEFINITION OF ENDPOINTS AND FOLLOW-UP

All centres contributed anonymised individual patient-level data using a dedicated electronic case report form. Baseline characteristics, angiographic characteristics and procedural details of PCI

and TAVI procedures as well as follow-up data were collected by local co-investigators at each institution. Data were then collected in a joint database for statistical analysis. All inconsistencies were resolved directly by communicating with the responsible local investigators.

All clinical endpoints, procedural data for TAVI and in-hospital complications were site-reported and categorised according to Valve Academic Research Consortium (VARC)-2 criteria, which were applicable when the registry data were collected[13]. Major endpoints of interest were all-cause death as well as a composite of all-cause death, stroke, MI or rehospitalisation for CHF at 2 years.

STATISTICAL ANALYSIS

For the purpose of the analysis, the entire patient population was divided into 3 groups, based on the timing of the PCI procedure relative to the initial diagnostic coronary angiogram (PCI before TAVI, PCI after TAVI or concomitant PCI with TAVI). Continuous variables are presented as means with standard deviation or medians with interquartile range (IQR) and were compared using the Student's t-test or Mann-Whitney U test for paired samples, as appropriate. Categorical variables are summarised as frequencies and proportions and were compared using the chi-square, Fisher's exact or McNemar tests for paired samples, as appropriate. To account for the non-randomised study design and to reduce the imbalance in baseline characteristics and the effect of a potential selection bias, an inverse probability treatment weighting (IPTW) analysis was performed, adjusted for variables selected based on their p-value in univariate analysis and on their potential influence on outcome. The selected variables were age, sex, Society of Thoracic Surgeons (STS) score, Canadian Cardiovascular Society (CCS) class, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, New York Heart Association (NYHA) Class, atrial fibrillation, estimated glomerular filtration rate, prior pacemaker, prior stroke, prior coronary artery bypass graft, prior MI, left ventricular ejection fraction, mean transvalvular gradient, multivessel CAD, LM or proximal left anterior descending (LAD) artery CAD **(Supplementary Figure 1)**.

Time-to-event curves for the main outcome variables were estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using an IPTW-adjusted Cox proportional hazards model. Additionally, a sensitivity analysis was performed after excluding cases with in-hospital mortality related to TAVI. Likewise, time-to-event curves were estimated using the Kaplan-Meier method with IPTW adjustment. A landmark analysis was performed for all-cause death and the composite endpoint from 0 to 30 days and from 31 to 720 days, respectively. All tests were 2-sided, and a p-value <0.05 was considered the threshold for statistical significance. All statistical analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

A total of 1,617 TAVI patients from the REVASC-TAVI registry underwent PCI. After excluding 14 patients with no available data about PCI timing (n=7) or those who had undergone unplanned PCI due to acute coronary ostia occlusion during TAVI (n=7), a total of 1,603 patients were included in the present analysis. PCI was planned and performed either before TAVI (65.6%; n=1,052), after TAVI (9.8%, n=157) or concomitantly with TAVI (24.6%, n=394), respectively **(Central illustration)**. PCI was performed within a median time interval of 35 days (13-63 days) before TAVI and 40 days (20-57 days) after TAVI. Baseline characteristics after IPTW analysis of the overall cohort and the 3 PCI timing groups are depicted in **Table 1**. The standardised mean difference of included variables **(Supplementary Figure 1)** indicates excellent adjustment for baseline variables.

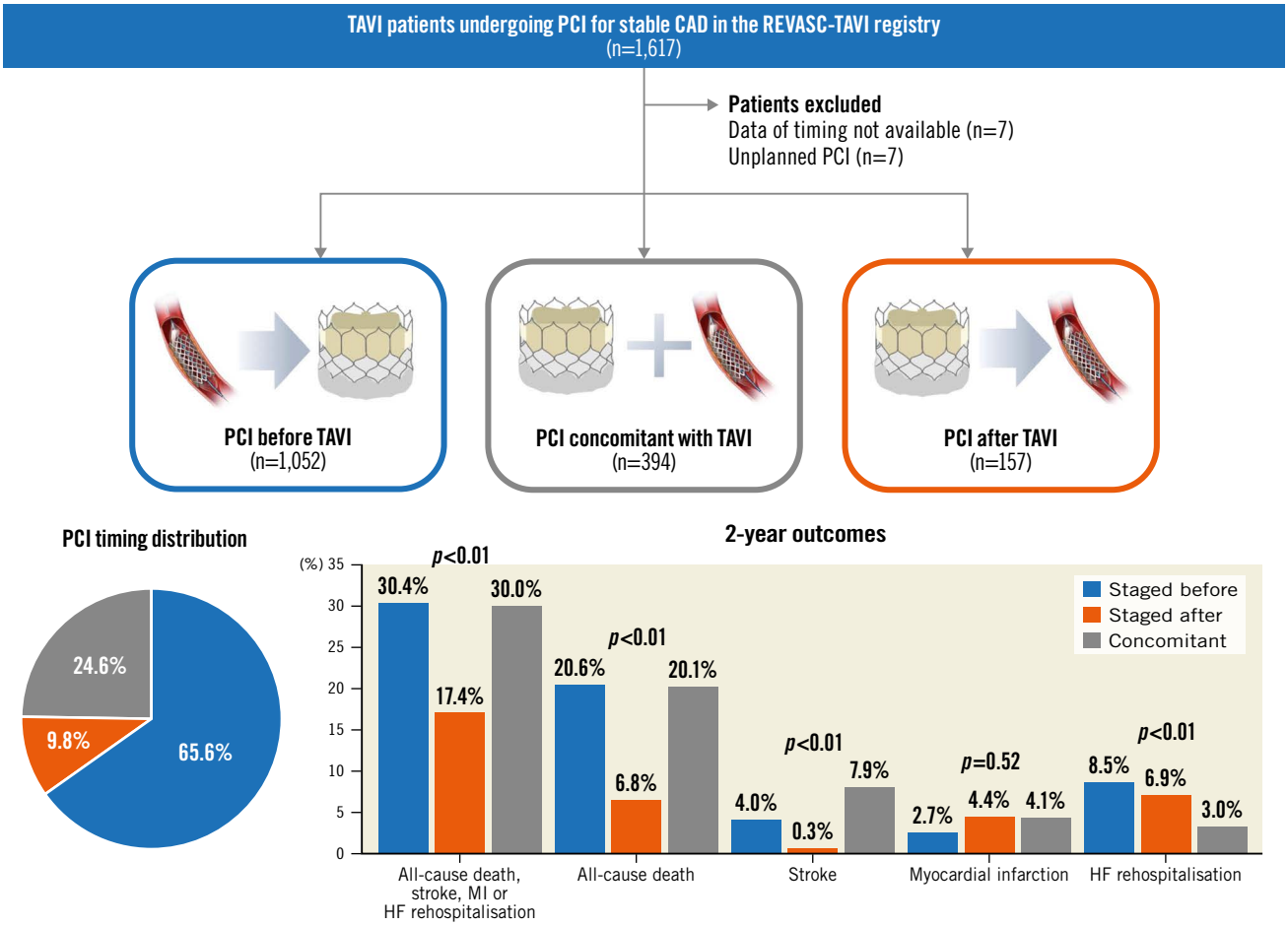
CORONARY ARTERY DISEASE CHARACTERISTICS

Angiographic characteristics of CAD found at pre-TAVI coronary angiography are depicted in **Table 2**. There were no differences with regard to the number of diseased vessels (p=0.136), multivessel CAD (p=0.484), CAD involving proximal segments (p=0.392), or LM or proximal segments (0.868) between the 3 groups. In contrast, bifurcation lesions were more frequent in patients undergoing PCI after TAVI compared to those treated before or concomitantly with TAVI (44.0% vs 32.0% vs 21.8%; p<0.001).

PROCEDURAL PCI CHARACTERISTICS

A total of 2,014 lesions were included and were treated either before TAVI (n=1,357), after TAVI (n=225) or concomitantly with TAVI (n=432) **(Table 3)**. Among the concomitant TAVI and PCI group, PCI was performed before and after THV deployment in 296/432 (68.5%) and 136/432 (31.5%) lesions, respectively. Assessment of coronary lesion severity using iFR/FFR or IVUS/optical coherence tomography was infrequent, in 9.5% and 7% of the overall cohort, respectively, with no relevant differences across the groups. Target vessel stenosis >90% or chronic total occlusions were more frequent in lesions treated before TAVI compared to those treated after or concomitantly with TAVI (p=0.021). LM or proximal LAD stenoses were more frequently treated before TAVI or concomitantly with TAVI as compared to after TAVI (11.3% vs 13.7% vs 7.1%; p=0.043 and 23.7% vs 25.2% vs 15.6%; p=0.014). In contrast, left circumflex stenoses were more frequently treated after TAVI as compared to before or concomitantly with TAVI (21.8% vs 17.5% vs 12.7%; p=0.009). Access routes differed significantly, with higher rates of the radial approach in PCI procedures performed before TAVI as compared to those performed after or concomitantly with TAVI (p<0.001). Overall, lesion preparation using rotational or orbital atherectomy was low, with 4.5% and 0.4% of the overall cohort, respectively, without differences across the groups. However, haemodynamic support differed significantly, with significantly higher rates in the concomitant PCI group (p<0.001).

CENTRAL ILLUSTRATION Outcomes of patients undergoing transcatheter aortic valve implantation and percutaneous coronary intervention for stable coronary artery disease from the international, multicentre REVASC-TAVI registry.



CAD: coronary artery disease; HF: heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation

PROCEDURAL TAVI CHARACTERISTICS AND IN-HOSPITAL OUTCOMES

Procedural characteristics and in-hospital outcomes are detailed in **Table 4**. The majority of TAVI procedures were performed with local anaesthesia and via transfemoral access, without significant differences across treatment groups (p=0.247 and p=0.325, respectively). The balloon-expandable SAPIEN 3/Ultra (Edwards Lifesciences) and the self-expanding Evolut R/PRO (Medtronic) platforms were most frequently implanted, with higher utilisation of BEV in patients undergoing PCI after TAVI or concomitantly with TAVI (p<0.001). Contrast volume differed significantly and was highest with concomitant PCI as compared to PCI before or after TAVI (230 ml vs 110 ml vs 140 ml; p<0.001), resulting from two interventions in one procedure in this group.

In-hospital all-cause mortality differed significantly and was higher with concomitant PCI or PCI before TAVI as compared to PCI after TAVI (3.7% vs 2.2% vs 0.0%; p=0.005). Likewise, disabling strokes were higher with PCI before TAVI or concomitant PCI with TAVI as compared to PCI after TAVI (1.3% vs 1.0% vs 0.0%; p=0.082). Major vascular complications and major bleeding differed significantly and were lower with PCI before TAVI as compared to PCI after TAVI or concomitant PCI with TAVI (3.5% vs 6.5% vs 8.3%; p=0.077 and 3.4% vs 6.8% vs 9.9%; p=0.025). The rates of acute kidney injury also differed significantly, with the highest rates in patients treated concomitantly with TAVI as compared to those treated before or after TAVI (p=0.011).

CLINICAL FOLLOW-UP

The median follow-up after TAVI was 393 days. No deaths were reported among patients scheduled to undergo PCI after TAVI within the median time frame of 40 days. The incidence of all-cause death at 2 years differed significantly and was lower in patients undergoing PCI after TAVI as compared to patients treated before or concomitantly with TAVI (6.8% vs 20.6% vs

Table 1. Baseline characteristics after inverse probability treatment weighting analysis.

	Overall cohort	PCI before TAVI (n=1,052)	PCI after TAVI (n=157)	Concomitant PCI (n=394)	SMD
Age, years	82.0 [78.3, 85.1]	82.2 [78.5, 85.3]	82.0 [79.0, 85.2]	82.0 [78.0, 85.0]	0.083
Female	41.1	40.9	42.3	39.9	0.024
STS score	5.0 [3.2, 5.1]	5.0 [3.2, 5.0]	5.0 [3.3, 5.1]	5.0 [3.0, 5.1]	0.070
NYHA Class III/IV	62.8	62.2	61.9	64.7	0.028
CCS class >1	31.1	31.1	28.9	33.5	0.045
Hypertension	85.6	84.8	85.9	86.6	0.017
Diabetes mellitus	32.2	31.5	33.6	31.9	0.021
Previous surgical aortic valve replacement	2.2	1.8	2.3	2.8	0.064
Previous coronary artery bypass grafting	7.7	8.5	5.8	8.8	0.029
Previous myocardial infarction	18.3	19.8	17.0	17.5	0.029
Previous stroke	8.5	8.8	10.6	5.6	0.050
Chronic obstructive pulmonary disease	15.1	14.6	15.3	15.6	0.010
eGFR, ml/min	55.1 [44.0, 63.0]	55.1 [45.0, 64.1]	55.1 [42.8, 62.2]	55.1 [44.6, 63.1]	0.078
Previous pacemaker	7.4	8.1	4.7	9.2	0.045
Atrial fibrillation	25.8	27.5	21.7	28.0	0.063
Mean transaortic gradient, mmHg	44.0 [36.0, 50.0]	44.0 [36.0, 50.0]	43.2 [35.0, 49.0]	43.0 [37.0, 51.0]	0.069
Aortic valve area, cm^2	0.7 [0.6, 0.8]	0.7 [0.6, 0.8]	0.7 [0.6, 0.8]	0.7 [0.6, 0.8]	0.048
Left ventricular ejection fraction, %	58.0 [48.0, 62.0]	58.0 [48.0, 63.0]	59.5 [48.0, 60.0]	56.0 [50.0, 62.0]	0.022
Bicuspid valve	4.0	4.6	4.7	2.4	0.099
Aspirin	74.7	81.5	71.4	69.4	0.190
Clopidogrel	48.9	73.5	34.7	32.7	0.595
Ticagrelor	0.7	1.3	0.3	0.4	0.080
Prasugrel	1.0	1.9	0.7	0.1	0.124
Vitamin K antagonist	7.4	6.9	4.5	11.6	0.175
NOAC	14.2	15.4	14.0	12.8	0.049
DAPT	39.8	56.4	29.4	26.9	0.674
DAT	7.6	8.2	7.0	7.4	0.357
TAT	5.4	8.1	3.9	3.3	0.394

Data are median [interquartile range] or %. CCS: Canadian Cardiovascular Society; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; eGFR: estimated glomerular filtration rate; NOAC: novel oral anticoagulant; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SMD: standardised mean difference; STS: Society of Thoracic Surgeons; TAT: triple antithrombotic therapy. TAVI: transcatheter aortic valve implantation

20.1%; p<0.001; PCI before vs after TAVI: hazard ratio [HR] 3.21 [1.47-7.00]; p=0.003; concomitant PCI vs PCI after TAVI: HR 3.23 [1.42-7.39]; p=0.005) **(Figure 1, Central illustration)**. Likewise, occurrence of the composite endpoint differed significantly and was lower in patients undergoing PCI after TAVI as compared to patients treated before or concomitantly with TAVI (17.4% vs 30.4% vs 30.0%; p=0.003; PCI before vs after TAVI: HR 2.0 [1.16-3.45]; p=0.013; concomitant PCI vs PCI after TAVI: HR 2.03 [1.09-3.79]; p=0.026 **(Figure 2, Central illustration)**.

A sensitivity analysis confirmed these results after excluding cases with in-hospital death related to TAVI. The incidence of all-cause death at 2 years differed significantly and was lower in patients undergoing PCI after TAVI as compared to patients treated before or concomitantly with TAVI (7.6% vs 18.6% vs 17.1%; p<0.01) **(Supplementary Figure 2)**. Likewise, occurrence of the composite endpoint differed significantly and was lower in patients undergoing PCI after TAVI as compared to patients treated before or concomitantly with TAVI (18.7% vs 28.6% vs 27.5%; p=0.05) **(Supplementary Figure 3)**.

A landmark analysis demonstrated that from 0 to 30 days and from 31 to 720 days, the rate of all-cause death differed significantly and was lower in patients undergoing PCI after TAVI as compared to

Table 2. Angiographic characteristics after inverse probability treatment weighting analysis.

	PCI before TAVI (n=1,052)	PCI after TAVI (n=157)	Concomitant PCI (n=394)	*p*-value
Diseased vessels				
1 vessel	55.1	56.3	60.3	0.136
2 vessels	26.9	22.4	27.7	
3 vessels	18.0	21.3	11.9	
Coronary segment involved				
LM	13.1	15.5	14.7	0.688
LAD	64.4	71.8	59.7	0.042
Proximal LAD	32.0	31.8	29.9	0.830
Mid-LAD	39.5	48.4	34.7	0.021
Distal LAD	7.9	4.9	5.1	0.286
Diagonal	13.4	24.0	9.1	<0.001
LCx	37.5	40.0	29.7	0.094
Proximal LCx	17.5	16.8	13.3	0.431
Mid-LCx	10.9	21.0	8.9	<0.001
Distal LCx/PDA	4.9	5.6	1.5	0.063
Obtuse marginal	13.2	7.9	13.0	0.182
RCA	47.7	40.4	46.5	0.246
Proximal RCA	28.5	25.0	30.2	0.470
Mid-RCA	20.9	20.6	19.9	0.941
Distal RCA/PL/PDA	12.2	11.3	8.0	0.310
Bypass graft	3.9	0.4	3.8	0.006
Calcific disease	25.4	17.5	21.0	0.142
Bifurcation lesions	32.0	44.0	21.8	<0.001
Multivessel CAD	44.9	43.7	39.7	0.484
Proximal CAD	64.6	59.8	65.8	0.392
LM/proximal LAD CAD	38.0	36.4	38.3	0.868

Data are presented as %. CAD: coronary artery disease; LAD: left anterior descending; LCx: left circumflex artery; LM: left main; PCI: percutaneous coronary intervention; PDA: posterior descending artery; PL: posterolateral; RCA: right coronary artery; TAVI: transcatheter aortic valve implantation

patients treated before or concomitantly with TAVI (0-30 days: 0% vs 2.5% vs 3.6%; p<0.001; 31-720 days: 6.8% vs 18.6% vs 17.1%; p=0.002) **(Figure 1)**. Likewise, the composite endpoint rate differed significantly and was lower in patients undergoing PCI after TAVI as compared to patients treated before or concomitantly with TAVI (0-30 days: 0.8% vs 4.4% vs 6.0%; p=0.002; 31-720 days: 16.8% vs 27.2% vs 25.5%; p=0.045) **(Figure 2)**.

Discussion

The current study aimed to investigate the clinical outcomes of different PCI timing strategies in patients undergoing TAVI from a large international multicentre registry. With regard to this objective, the most salient findings can be described as follows:

(i) In this international, multicentre study using balloon-expandable and self-expanding THV platforms, two-thirds of all patients scheduled for PCI underwent revascularisation before TAVI.

(ii) Performance of concomitant PCI and TAVI was associated with the highest rates of acute kidney injury, likely due to a significantly higher use of contrast medium. Moreover, in-hospital mortality was highest in this group.

(iii) Major vascular complications and major bleeds differed across treatment groups, with the lowest rates in patients undergoing PCI before TAVI.

(iv) Although the 3 study groups had similar CAD complexity and extension, PCI after TAVI was associated with significantly lower rates of all-cause death as well as the composite of all-cause death, stroke, MI or unplanned rehospitalisation for CHF at 2 years as compared with any other PCI timing strategy.

Although CAD frequently coexists with severe AS, there remain many unanswered questions regarding the optimal management of these 2 pathologies, including assessment of CAD severity, extent of myocardial revascularisation and timing of PCI and TAVI procedures[3,14]. Current guidelines give a class IIa recommendation for PCI in lesions with >70% diameter stenosis in proximal segments (Level of Evidence C) and suggest performing both procedures combined or staged according to the clinical situation and pattern of CAD[2]. Overall, data from randomised clinical trials are scarce. The ACTIVATION trial investigated the role of PCI in patients undergoing TAVI and demonstrated similar rates of death and rehospitalisation at 1 year for PCI and no PCI prior to TAVI in patients with severe aortic stenosis and minimal angina[6]. In addition, a previous analysis from the REVASC-TAVI registry demonstrated that complete myocardial revascularisation was similar to a strategy of incomplete revascularisation in reducing the risk of all-cause death, as well as the risk of a combination of death, stroke, MI, and rehospitalisation for heart failure at 2 years, regardless of the clinical and anatomical situations in TAVI patients with significant stable CAD[10]. With regard to the timing of procedures, TAVI candidates have historically undergone staged PCI prior to TAVI in a separate session, which is also reflected by this international all-comers study, with almost two-thirds of patients undergoing staged PCI before TAVI. This approach is justified by the concern that untreated significant coronary lesions might cause ischaemic and haemodynamic complications during valve implantation, although this concern remains theoretical and does not reflect clinical reality. Moreover, concerns regarding the feasibility of coronary access after TAVI, especially with long stent-frame prostheses were raised[15,16]. Of note, the THV type differed significantly in this analysis, with a more frequent use of balloon-expandable THV platforms in patients undergoing staged PCI after TAVI, which are most likely to maintain direct access to coronary ostia. In this regard, dedicated implantation techniques for self-expanding THVs have been proposed in recent years to facilitate optimal commissural alignment and simplify coronary access after TAVI[17-19].

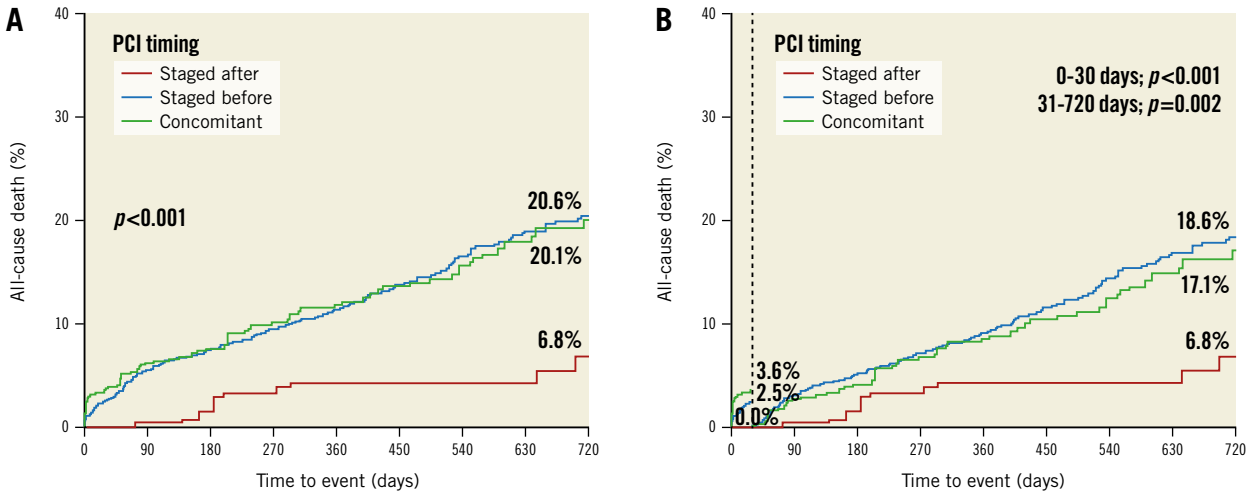


Figure 1. *All-cause death according to PCI timing strategy in patients undergoing TAVI. A) Time-to-event curves for all-cause death using the Kaplan-Meier method with inverse probability treatment weighting (IPTW) adjustment and B) landmark analysis for all-cause death from 0-30 days (vertical dotted line) and 31-720 days. PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation*

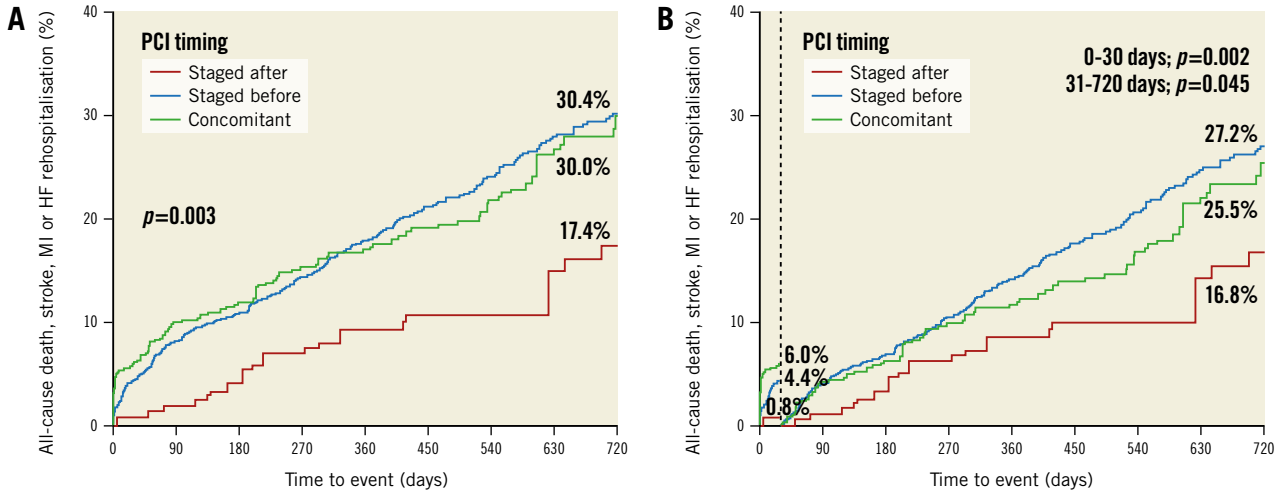


Figure 2. *Composite endpoint according to PCI timing strategy in patients undergoing TAVI. A) Time-to-event curves for the combined endpoint using the Kaplan-Meier method with inverse probability treatment weighting (IPTW) adjustment and B) landmark analysis for the combined endpoint from 0-30 days (vertical dotted line) and 31-720 days. HF: heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation*

The performance of PCI before TAVI with the subsequent need for dual antiplatelet therapy was shown to increase bleeding risk in the randomised POPular-TAVI and ACTIVATION trials[6,20]. In our cohort, we observed contrary results, with lower rates of major vascular complications and major bleedings in patients undergoing staged PCI before TAVI, which indicates that bleeding complications are multifactorial in this elderly patient population[21]. This might, to some extent, be attributed to a significantly higher radial approach rate in patients undergoing PCI prior to TAVI in this analysis and indicates that guideline recommendations favouring transradial access should generally be considered in this patient population.

There are certain clinical and anatomical conditions, including filiform subtotal coronary artery lesions, that require timely treatment and exclude the possibility of performing PCI after TAVI. However, in most cases, performance of PCI staged after TAVI seems beneficial in various matters. First, successful treatment of AS eliminates left ventricular pressure overload and microvascular dysfunction and permits adequate physiological assessment of coronary lesion severity and identification of patients deriving benefit from revascularisation[6,22,23]. Second, (intermittent) haemodynamic compromise during PCI procedures due to AS may cause renal or cerebral ischaemia, and indeed, previous observational studies demonstrated a higher stroke risk when performing PCI before TAVI[7]. We also observed a higher disabling stroke rate in patients undergoing PCI before TAVI or concomitantly with TAVI at 2 years **(Central illustration)**. Finally, we observed significantly lower all-cause death rates as well as a combination of all-cause

Table 3. Procedural PCI characteristics.

	Overall cohort (n=2,014)	PCI before TAVI (n=1,357)	PCI after TAVI (n=225)	Concomitant PCI (n=432)	*p*-value
Target vessel stenosis					
>70%	1,587 (81.3)	1,035 (79.6)	193 (87.7)	359 (83.5)	0.021
>90%	306 (15.7)	222 (17.1)	23 (10.5)	61 (14.2)	
CTO	49 (2.5)	39 (3.0)	4 (1.8)	6 (1.4)	
Target vessel					
LM	229 (11.4)	154 (11.3)	16 (7.1)	59 (13.7)	0.043
LAD	912 (45.3)	610 (45.0)	99 (44.0)	203 (47.0)	0.698
Prox LAD	465 (23.1)	321 (23.7)	35 (15.6)	109 (25.2)	0.014
Mid-LAD	560 (27.8)	366 (27.0)	74 (32.9)	120 (27.8)	0.186
Distal LAD	77 (3.8)	58 (4.3)	9 (4.0)	10 (2.3)	0.179
Diagonal	107 (5.3)	79 (5.8)	14 (6.2)	14 (3.2)	0.093
LCx	341 (17.0)	238 (17.5)	49 (21.8)	55 (12.7)	0.009
Prox LCx	198 (9.8)	131 (9.7)	32 (14.2)	35 (8.1)	0.041
Mid-LCx	133 (6.6)	93 (6.9)	16 (7.1)	24 (5.6)	0.606
Distal LCx	48 (2.4)	38 (2.8)	7 (3.1)	3 (0.7)	0.033
Obtuse marginal	127 (6.3)	90 (6.6)	10 (4.4)	27 (6.2)	0.457
RCA	585 (29.0)	405 (29.8)	56 (24.9)	124 (28.7)	0.312
Prox RCA	358 (17.8)	241 (17.8)	35 (15.6)	82 (19.0)	0.796
Mid-RCA	246 (12.2)	172 (12.7)	17 (7.6)	57 (13.2)	0.074
Distal RCA	123 (6.1)	99 (7.3)	13 (5.8)	11 (2.5)	0.009
Bypass graft	41 (2.0)	33 (2.4)	1 (0.4)	7 (1.6)	0.117
Access route					
Right radial	938 (48.8)	827 (64.3)	74 (34.4)	37 (8.7)	<0.001
Left radial	75 (3.9)	55 (4.3)	6 (2.8)	14 (3.3)	
Femoral	910 (47.3)	404 (31.4)	135 (62.8)	371 (87.7)	
Use of iFR/FFR	159 (9.5)	116 (9.7)	6 (6.2)	37 (9.5)	0.536
Use of IVUS/OCT	117 (7.0)	82 (6.9)	8 (7.8)	27 (6.9)	0.937
Use of atherectomy					
Rotational atherectomy	87 (4.5)	54 (4.1)	14 (6.5)	19 (4.4)	0.445
Orbital atherectomy	7 (0.4)	6 (0.5)	0 (0)	1 (0.2)	
Haemodynamic support	22 (1.1)	8 (0.6)	0 (0)	14 (3.3)	<0.001
Device type					
DES	1,529 (88.5)	998 (87.0)	192 (93.2)	339 (90.6)	0.011
BMS	7 (0.4)	3 (0.3)	0 (0)	4 (1.1)	
POBA	23 (1.3)	15 (1.3)	4 (1.9)	4 (1.1)	
BVS	33 (1.9)	23 (2.0)	2 (1.0)	8 (2.1)	
Number of stents	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	0.483
Total stent length, mm	23.0 [16.0, 34.0]	23.0 [16.0, 35.0]	24.5 [18.0, 37.3]	20.0 [15.0, 30.0]	0.005
Stent diameter, mm	3.00 [2.75, 3.50]	3.00 [2.75, 3.50]	3.00 [2.50, 3.50]	3.00 [3.00, 3.50]	<0.001
Use of guiding extension	74 (4.6)	64 (5.6)	5 (5.2)	5 (1.3)	0.002
Procedural success	1,924 (97.4)	1,291 (97.1)	215 (98.2)	418 (97.9)	0.526
Crossing difficulty	49 (2.6)	39 (3.1)	1 (0.5)	9 (2.1)	0.066

Data are presented as n (%) or median [interquartile range]. BMS: bare metal stent; BVS: bioresorbable vascular scaffold; CTO: chronic total occlusion; DES: drug-eluting stent; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; LAD: left anterior descending; LCx: left circumflex artery; LM: left main; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; RCA: right coronary artery; TAVI: transcatheter aortic valve implantation

death, myocardial infarction, stroke and rehospitalisation for HF in patients undergoing PCI after TAVI, which was confirmed in the landmark analysis considering events before and after 30 days. This favourable clinical course in patients treated in a separate session after TAVI underlines the prognostic importance of an individualised revascularisation timing strategy, as well as accurate THV type selection to preserve coronary access after TAVI. So far, available evidence from previous studies has been inconsistent, with similar event rates among different timing strategies, including bleeding events, vascular complications and acute kidney injury as well as all-cause mortality at 2 years in 1 study[9] and favourable (adverse event-free) survival at 2 years in another study[7]. As the

Table 4. Procedural TAVI characteristics and in-hospital outcomes after inverse probability treatment weighting (IPTW) analysis.

		PCI before TAVI (n=1,052)	PCI after TAVI (n=157)	Concomitant PCI (n=394)	*p*-value
Procedural characteristics					
Anaesthesia	N/A	2.0	2.1	4.9	0.247
	Local	87.5	85.4	84.2	
	General	10.6	12.5	10.9	
Access route	Transfemoral	94.6	92.8	94.8	0.325
	Transapical	1.4	4.1	1.3	
	Transsubclavian	2.8	3.1	2.9	
	Direct aortic	1.0	0	0.7	
	Transcarotid	0.1	0	0.3	
	Transcaval	0.1	0	0	
THV type	S3/S3 Ultra	34.3	59.4	46.1	<0.001
	SXT	0.9	0	0.2	
	Evolut R/PRO	33.8	19.7	30.7	
	CoreValve	3.3	0.9	4.8	
	Portico	8.2	3.9	5.6	
	Lotus	1.3	0.7	1.5	
	ACURATE neo/neo2	15.0	14.9	9.7	
	Allegra	0.4	0	1.0	
	Other	2.6	0.6	0.3	
Need for second valve		1.4	0.5	0.7	0.249
Post-dilatation		24.9	10.8	17.0	0.006
Contrast volume, ml		110 [80, 155]	140 [100, 187]	230 [150, 300]	<0.001
In-hospital outcomes					
All-cause death		2.2	0.0	3.7	0.005
Disabling stroke		1.3	0.0	1.0	0.082
Non-disabling stroke		1.2	2.0	1.6	0.810
Myocardial infarction		0.9	0.0	0.3	0.055
Permanent pacemaker implantation		12.4	10.8	10.6	0.738
Life-threatening bleeding		2.2	0.6	2.0	0.233
Major bleeding		3.4	6.8	9.9	0.025
Minor bleeding		6.7	10.1	10.5	0.262
Major vascular complications		3.5	6.5	8.3	0.077
Minor vascular complications		8.5	13.4	11.1	0.226
Acute kidney injury	RIFLE 1	5.4	4.1	8.6	0.011
	RIFLE 2/3	2.6	0	5.1	
Length of stay, days		5.0 [2.0, 7.0]	5.0 [3.0, 7.0]	4.0 [2.0, 7.0]	0.722

Data are presented as % or median [IQR]. N/A: not applicable; PCI: percutaneous coronary intervention; RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve

generalisability of these studies is limited by a rather small patient population, this analysis of the REVASC-TAVI registry supports performing PCI after TAVI in most cases after a thorough clinical evaluation, as suggested by current guidelines[2]. In this regard, results from the ongoing TAVI-PCI Trial currently randomising patients to either PCI before or after TAVI using a balloon-expandable THV (ClinicalTrials.gov: NCT04310046) are eagerly awaited. Performance of PCI in the same session, also suggested by current guidelines, seems unfavourable, despite several potential logistic advantages, as rates of acute kidney injury and in-hospital mortality are significantly higher with this approach compared to any other revascularisation timing approach.

Limitations

This observational, multicentre study exhibits the inherent limitations of a retrospective, non-randomised study design. In particular, the timing of both procedures was at the discretion of the treating physician without consistent selection criteria and may have been influenced by anatomical factors, comorbidities or clinical conditions not captured in this analysis. Although angiographic characteristics were well balanced across treatment groups after IPTW adjustment, further information provided by the SYNTAX score is not available. Moreover, the number of patients differed significantly across treatment groups; the PCI after TAVI group had the fewest patients. Therefore, a selection

bias cannot be excluded, limiting the generalisability of the results. As TAVI represented the target intervention in this registry, a greater level of granularity in complications during PCI procedures, beyond the reported key endpoints, is not available in this registry. Moreover, patients treated with staged PCI before TAVI who died before undergoing TAVI, or vice versa, were not captured in this registry. In addition, THV types differed significantly across the treatment groups, with a more frequent use of balloon-expandable THV platforms as compared with self-expanding valves in patients undergoing PCI after TAVI, also limiting the generalisability of the results. Furthermore, although clinical events were categorised according to standardised definitions, events were not adjudicated by an independent event adjudication committee. The results of this analysis are limited to patients with chronic coronary syndrome and cannot be extrapolated to those with acute coronary syndromes.

Conclusions

In patients with severe AS and stable CAD scheduled for TAVI, performance of PCI after TAVI seems to be associated with improved 2-year clinical outcomes compared with other revascularisation timing strategies. Further randomised trials with different available THV platforms are warranted to confirm these results.

Impact on daily practice

Significant coronary artery disease is common in patients undergoing TAVI. The optimal timing to perform PCI in TAVI patients with chronic coronary syndrome remains unknown. These registry data demonstrate that in patients with severe aortic stenosis and stable CAD scheduled for TAVI, performance of PCI after TAVI seems to be associated with improved 2-year clinical outcomes compared with other revascularisation timing strategies. Results from randomised clinical trials with different THV platforms are warranted to confirm these results.

Appendix. Authors' affiliations

1. Department of Cardiovascular Diseases, German Heart Center Munich, Technical University Munich, Munich, Germany; 2. Division of Cardiology, A.O.U. Policlinico "G. Rodolico-San Marco", Catania, Italy; 3. Division of Cardiology, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; 4. Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; 5. CIBERCV, Division of Cardiology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; 6. The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 7. Kerckhoff Heart Center, Bad Nauheim, Germany; 8. Heart Institute of Sao Paulo (InCor), University of Sao Paulo, Sao Paulo, Brazil; 9. Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy and Cardiac Thoracic and Vascular Department, Università degli Studi di Bologna, Bologna, Italy; 10. University Medical Centre Ljubljana, Ljubljana, Slovenia; 11. Clinique Pasteur, Toulouse, France; 12. Institute Cardiovasculaire Paris Sud (ICPS), Hôpital Jacques Cartier, Ramsay Santé, Massy, France; 13. Galway University Hospital, Galway, Ireland; 14. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 15. Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan; 16. Division of Cardiology, IRCSS Policlinico San Donato, San Donato Milanese, Milano, Italy; 17. Clinica Montevergine, GVM Care & Research, Mercogliano, Italy; 18. Division of Cardiology, Policlinico Umberto I, Roma, Italy; 19. Division of Cardiology, AOU Federico II, Università di Napoli, Napoli, Italy; 20. University of Catania, Catania, Italy; 21. Heart Center, Turku University Hospital, Turku, Finland; 22. Faculty of Medicine and University Hospital Cologne, Clinic III for Internal Medicine, University of Cologne, Cologne, Germany; 23. Cardiothoracic and Vascular Department, San Martino Policlinico Hospital, Genova, Italy; 24. Interventional Cardiology Unit, IRCCS Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT), Palermo, Italy; 25. UOSA Cardiologia Interventistica, Azienda ospedaliera-universitaria Senese, Policlinico Le Scotte, Siena, Italy; 26. Division of University Cardiology, Cardiothoracic Department, Policlinico University Hospital, Bari, Italy; 27. Wien University Hospital, Vienna, Austria; 28. Montefiore Medical Center, New York, NY, USA; 29. Azienda Sanitaria Locale di Ciriè, Chivasso e Ivrea, ASL TO4, Ivrea, Italy; 30. HerzZentrum Hirslanden Zürich, Zürich, Switzerland; 31. Department of Cardiology, SS. Annunziata Hospital Chieti, ASL 2 Abruzzo, Chieti, Italy and Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy; 32. Abbott Structural Heart, Santa Clara, CA, USA. 33. Sant'Andrea Hospital, Sapienza University, Rome, Italy; 34. Università degli Studi di Enna "Kore", Enna, Italy.

Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; UFR Medecine, Université de Paris, Paris, France.

Conflict of interest statement

T. Rheude received speaker fees from AstraZeneca and SIS Medical. F.L. Ribichini is a proctor for Edwards Lifesciences and Medtronic. T. Pilgrim received research grants to the institution from Biotronik, Boston Scientific, and Edwards Lifesciences; speakers/consultancy fees from Medtronic, Boston Scientific, Biotronik, Abbott, and HighLife SAS. O. De Backer received institutional research grants and/or consulting fees from Abbott and Boston Scientific. W-K. Kim received personal fees from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Meril Life Sciences, and Shockwave Medical. I.J. Amat-Santos is a proctor for Medtronic, Boston Scientific, and Meril Life Sciences. P. Garot received speaker/consultant fees from Abbott, Biosensors, Boston Scientific,

Edwards Lifesciences, GE HealthCare, and Terumo. He serves as a medical director and is a shareholder of CERC (Cardiovascular European Research Center), a CRO based in Massy, France. M. Savontaus is a consultant for Medtronic and Boston Scientific. C. Gandolfo is a proctor for Edwards Lifesciences. L. Sondergaard is Chief Medical Officer and Divisional VP for Medical Affairs at Abbott Structural Heart; and has received consultant fees and/or institutional research grants from Abbott, Boston Scientific, Medtronic, and SMT. M. Taramasso reports consultant or consultancy fees from Abbott Vascular, Edwards Lifesciences, Medtronic, Boston Scientific, Shenqi Medical, MEDIRA, ReCross, Hi-D Imaging, VentraMed, CoreMedic, Simulands, and CardioValve. M. Adam reports personal fees/speaker honoraria from Abbott, Boston Scientific, Edwards Lifesciences, JenaValve, and Medtronic. S. Baldus reports lecture fees from JenaValve and lecture and speaker fees from Edwards Lifesciences. M. Andreas is a proctor/consultant/speaker for Edwards Lifesciences, Abbott, Medtronic, Boston, Zoll, and AbbVie; and received institutional research grants from Edwards Lifesciences, Abbott, Medtronic, and LSI. C. Tamburino is a consultant for Medtronic. M. Joner reports institutional grant support from Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, and Infraredx; consulting fees from Biotronik, TRiCares, Veryan, and Shockwave; speaker fees from Abbott, AstraZeneca, Biotronik, Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, ReCor Medical, and Shockwave; participation on a steering committee at Biotronik and Edwards Lifesciences; and travel support from Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, and SIS Medical. M. Barbanti is a consultant for Boston Scientific, Edwards Lifesciences, and Medtronic. The other authors have no conflicts of interest to declare. The Guest Editor is a member of the Data and Safety Monitoring Board for a study by Venus MedTech and receives speaker honoraria (modest) from Edwards Lifesciences.

References

1. Rapp AH, Hillis LD, Lange RA, Cigarroa JE. Prevalence of coronary artery disease in patients with aortic stenosis with and without angina pectoris. *Am J Cardiol.* 2001;87:1216-7;A7.

2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, Bonis D, Paulis D, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Rafael J, Tribouilloy C, Wojakowski W. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *EuroIntervention.* 2022;17:e1126-96.

3.Tarantini G, Tang G, Nai Fovino L, Blackman D, Van Mieghem NM, Kim WK, Karam N, Carrilho-Ferreira P, Fournier S, Pręgowski J, Fraccaro C, Vincent F, Campante Teles R, Mylotte D, Wong I, Bieliauskas G, Czerny M, Bonaros N, Parolari A, Dudek D, Tchétché D, Eltchaninoff H, de Backer O, Stefanini G, Sondergaard L. Management of coronary artery disease in patients undergoing transcatheter aortic valve implantation. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions in collaboration with the ESC Working Group on Cardiovascular Surgery. *EuroIntervention.* 2023;19:37-52.

4. Vendrik J, Ahmad Y, Eftekhari A, Howard JP, Wijntjens GWM, Stegehuis VE, Cook C, Terkelsen CJ, Christiansen EH, Koch KT, Piek JJ, Sen S, Baan J Jr. Long-Term Effects of Transcatheter Aortic Valve Implantation on Coronary Hemodynamics in Patients With Concomitant Coronary Artery Disease and Severe Aortic Stenosis. *J Am Heart Assoc.* 2020;9:e015133.

5. Ahmad Y, Vendrik J, Eftekhari A, Howard JP, Cook C, Rajkumar C, Malik I, Mikhail G, Ruparelia N, Hadjiloizou N, Nijjer S, Al-Lamee R, Petraco R, Warisawa T, Wijntjens GWM, Koch KT, van de Hoef T, de Waard G, Echavarria-Pinto M, Frame A, Sutaria N, Kanaganayagam G, Ariff B, Anderson J, Chukwuemeka A, Fertleman M, Koul S, Iglesias JF, Francis D, Mayet J, Serruys P, Davies J, Escaned J, van Royen N, Götberg M, Juhl Terkelsen C, Høj Christiansen E, Piek JJ, Baan J Jr, Sen S. Determining the Predominant Lesion in Patients With Severe Aortic Stenosis and Coronary Stenoses: A Multicenter Study Using Intracoronary Pressure and Flow. *Circ Cardiovasc Interv.* 2019;12:e008263.

6. Patterson T, Clayton T, Dodd M, Khawaja Z, Morice MC, Wilson K, Kim W-K, Meneveau N, Hambrecht R, Byrne J, Carrié D, Fraser D, Roberts DH, Doshi SN, Zaman A, Banning AP, Eltchaninoff H, Le Breton H, Smith D, Cox I, Frank D, Gershlick A, de Belder M, Thomas M, Hildick-Smith D, Prendergast B, Redwood S, ACTIVATION Trial Investigators. ACTIVATION (PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION): A Randomized Clinical Trial. *JACC Cardiovasc Interv.* 2021;14:1965-74.

7. Lunardi M, Venturi G, Del Sole PA, Ruzzarin A, Mainardi A, Pighi M, Pesarini G, Scarsini R, Tavella D, Gottin L, Ribichini FL. Optimal timing for percutaneous coronary intervention in patients undergoing transcatheter aortic valve implantation. *Int J Cardiol.* 2022;365:114-22.

8. Kumar A, Sammour Y, Reginauld S, Sato K, Agrawal N, Lee JM, Meenakshisundaram C, Ramanan T, Kamioka N, Sawant AC, Mohananey D, Gleason PT, Devireddy C, Krishnaswamy A, Mavromatis K, Grubb K, Svensson LG, Tuzcu EM, Block PC, Iyer V, Babaliaros V, Kapadia S, Samady H. Adverse clinical outcomes in patients undergoing both PCI and TAVR: Analysis from a pooled multicenter registry. *Catheter Cardiovasc Interv.* 2021;97:529-39.

9. Ochiai T, Yoon SH, Flint N, Sharma R, Chakravarty T, Kaewkes D, Patel V, Nakamura M, Cheng W, Makkar R. Timing and Outcomes of Percutaneous Coronary Intervention in Patients Who Underwent Transcatheter Aortic Valve Implantation. *Am J Cardiol.* 2020;125:1361-8.

10. Costa G, Pilgrim T, Amat Santos IJ, De Backer O, Kim WK, Barbosa Ribeiro H, Saia F, Bunc M, Tchetche D, Garot P, Ribichini FL, Mylotte D, Burzotta F, Watanabe Y, De Marco F, Tesorio T, Rheude T, Tocci M, Franzone A, Valvo R, Savontaus M, Wienemann H, Porto I, Gandolfo C, Iadanza A, Bortone AS, Mach M, Latib A, Biasco L, Taramasso M, Zimarino M, Tomii D, Nuyens P, Sondergaard L, Camara SF, Palmerini T, Orzalkiewicz M, Steblovnik K, Degrelle B, Gautier A, Del Sole PA, Mainardi A, Pighi M, Lunardi M, Kawashima H, Criscione E, Cesario V, Biancari F, Zanin F, Joner M, Esposito G, Adam M, Grube E, Baldus S, De Marzo V, Piredda E, Cannata S, Iacovelli F, Andreas M, Frittitta V, Dipietro E, Reddavid C, Strazzieri O, Motta S, Angellotti D, Sgroi C, Kargoli F, Tamburino C, Barbanti M; REVASC-TAVI Registry. Management of Myocardial Revascularization in Patients With Stable Coronary Artery Disease Undergoing Transcatheter Aortic Valve Implantation. *Circ Cardiovasc Interv.* 2022;15:e012417.

11. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87-165.

12.Writing Committee Members; Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, Fremes SE, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS Jr, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:197-215.

13. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB; Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg.* 2012;42:S45-60.

14. Rheude T, Pellegrini C, Joner M. Go with the flow: physiological assessment of coronary artery stenosis severity in patients with severe aortic stenosis. *Rev Esp Cardiol (Engl Ed).* 2022;75:456-7.

15. Kim WK, Pellegrini C, Ludwig S, Möllmann H, Leuschner F, Makkar R, Leick J, Amat-Santos IJ, Dörr O, Breitbart P, Jimenez Diaz VA, Dabrowski M, Rudolph T, Avanzas P, Kaur J, Toggweiler S, Kerber S, Ranosch P, Regazzoli D, Frank D, Landes U, Webb J, Barbanti M, Purita P, Pilgrim T, Liska B, Tabata N, Rheude T, Seiffert M, Eckel C, Allali A, Valvo R, Yoon SH, Werner N, Nef H, Choi YH, Hamm CW, Sinning JM. Feasibility of Coronary Access in Patients With Acute Coronary Syndrome and Previous TAVR. *JACC Cardiovasc Interv.* 2021;14:1578-90.

16. Barbanti M, Costa G, Picci A, Criscione E, Reddavid C, Valvo R, Todaro D, Deste W, Condorelli A, Scalia M, Licciardello A, Politi G, De Luca G, Strazzieri O, Motta S, Garretto V, Veroux P, Giaquinta A, Giuffrida A, Sgroi C, Leon MB, Webb JG, Tamburino C. Coronary Cannulation After Transcatheter Aortic Valve Replacement: The RE-ACCESS Study. *JACC Cardiovasc Interv.* 2020;13:2542-55.

17. Bieliauskas G, Wong I, Bajoras V, Wang X, Kofoed KF, De Backer O, Søndergaard L. Patient-Specific Implantation Technique to Obtain Neo-Commissural

Alignment With Self-Expanding Transcatheter Aortic Valves. *JACC Cardiovasc Interv.* 2021;14:2097-108.

18. Tang GHL, Zaid S, Fuchs A, Yamabe T, Yazdchi F, Gupta E, Ahmad H, Kofoed KF, Goldberg JB, Undemir C, Kaple RK, Shah PB, Kaneko T, Lansman SL, Khera S, Kovacic JC, Dangas GD, Lerakis S, Sharma SK, Kini A, Adams DH, Khalique OK, Hahn RT, Søndergaard L, George I, Kodali SK, De Backer O, Leon MB, Bapat VN. Alignment of Transcatheter Aortic-Valve Neo-Commissures (ALIGN TAVR): Impact on Final Valve Orientation and Coronary Artery Overlap. *JACC Cardiovasc Interv.* 2020;13:1030-42.

19. Tarantini G, Nai Fovino L, Scotti A, Massussi M, Cardaioli F, Rodinò G, Benedetti A, Boiago M, Matsuda Y, Continisio S, Montonati C, Cacciavillani L, Pavei A, Masiero G, Napodano M, Fraccaro C, Fabris T, Iliceto S. Coronary Access After Transcatheter Aortic Valve Replacement With Commissural Alignment: The ALIGN-ACCESS Study. *Circ Cardiovasc Interv.* 2022;15:e011045.

20. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. *N Engl J Med.* 2020;383:1447-57.

21. Garot P, Neylon A, Morice MC, Tamburino C, Bleiziffer S, Thiele H, Scholtz S, Schramm R, Cockburn J, Cunnington M, Wolf A, Barbanti M, Tchetché D, Pagnotta P, Gilard M, Bedogni F, Van Belle E, Vasa-Nicotera M, Chieffo A, Bogaerts K, Hengstenberg C, Capodanno D. Bleeding risk differences after TAVR according to the ARC-HBR criteria: insights from SCOPE 2. *EuroIntervention.* 2022;18:503-13.

22. Pesarini G, Scarsini R, Zivelonghi C, Piccoli A, Gambaro A, Gottin L, Rossi A, Ferrero V, Vassanelli C, Ribichini F. Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation: Influence of Pressure Overload on the Evaluation of Lesions Severity. *Circ Cardiovasc Interv.* 2016;9:e004088.

23. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, Gottin L, Zanetti C, Faggian G, Ribichini F. Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention.* 2018;13:1512-9.

Supplementary data

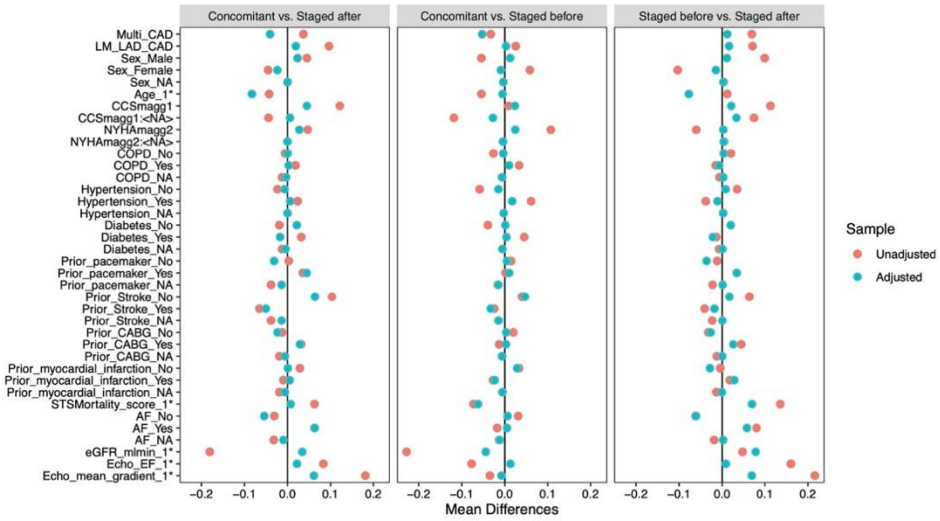
Supplementary Figure 1. Love plot for mean differences of adjusted and unadjusted cohort.

Supplementary Figure 2. All-cause death according to PCI timing strategy in patients undergoing TAVI.

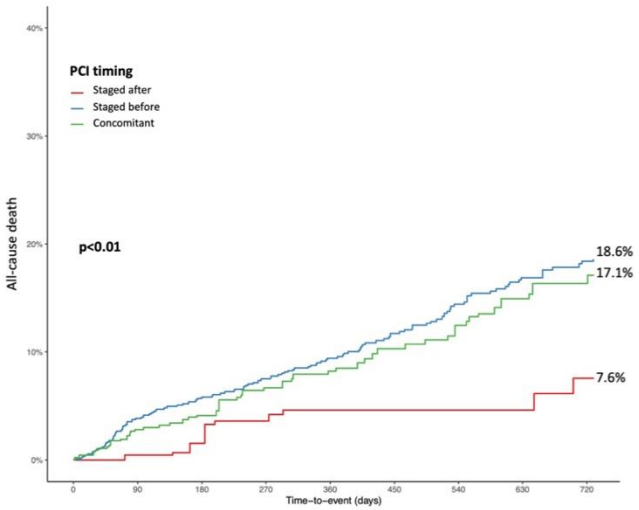
Supplementary Figure 3. Composite endpoint according to PCI timing strategy in patients undergoing TAVI.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00186

Supplementary data

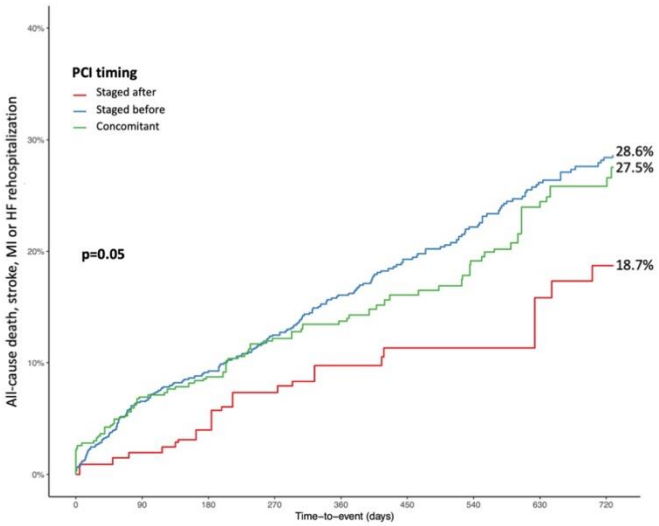


Supplementary Figure 1. Love plot for mean differences of adjusted and unadjusted cohort.



Supplementary Figure 2. All-cause death according to PCI timing strategy in patients undergoing TAVI.

Time-to-event curves for all-cause death using the Kaplan-Meier method with inverse probability treatment weighting (IPTW) adjustment. Patients with in-hospital death related to TAVI were excluded from this analysis.



Supplementary Figure 3. Composite endpoint according to PCI timing strategy in patients undergoing TAVI.
Time-to-event curves for the combined endpoint using the Kaplan-Meier method with inverse probability treatment weighting (IPTW) adjustment. Patients with in-hospital death related to TAVI were excluded from this analysis