PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION (ACTIVATION): A randomized clinical trial

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Abstract

Objectives: To determine if PCI prior to TAVR in patients with significant CAD would produce non-inferior clinical results when compared with no PCI (control arm).

Background: Percutaneous coronary intervention (PCI) in patients undergoing transcatheter aortic valve replacement (TAVR) is not without risk and there are no randomized data to inform clinical practice.

Methods: Patients with severe symptomatic AS and significant CAD with CCS class ≤2 angina were randomly assigned to receive PCI or no PCI prior to TAVR. The primary endpoint was a composite of all-cause death or rehospitalization at 1 year. Non-inferiority testing (pre-specified margin of 7.5%) was performed in the intention-to-treat population.

Results: At 17 centres, 235 patients underwent randomization. At 1 year, the primary composite endpoint occurred in 48(41.5%) of the PCI arm and 47(44.0%) of the no-PCI arm. The requirement for non-inferiority was not met (difference -2.5%, upper 95% one-sided confidence limit (CL) 8.5%; one-sided non-inferiority test p=0.067). On analysis of the as-treated population, the difference was -3.7% (upper 95% one-sided confidence limit 7.5%, p=0.050). Mortality was 16(13.4%) in the PCI arm and 14(12.1%) in the no PCI arm. At 1 year, there was no evidence of a difference in the rates of stroke, myocardial infarction or acute kidney injury, with higher rates of any bleed in the PCI arm (p=0.021).

Conclusions: Observed rates of death and rehospitalization at 1 year were similar between PCI and no PCI prior to TAVR, however the non-inferiority margin was not met and PCI resulted in a higher incidence of bleeding.

Clinical Trial registration: ACTIVATION ISRCTN 75836930 https://doi.org/10.1186/ISRCTN75836930

Condensed Abstract

The ACTIVATION Trial randomly assigned patients with severe symptomatic AS and significant CAD with CCS class ≤2 angina to receive PCI or no PCI prior to TAVR. The primary endpoint was a composite of all-cause death or rehospitalization at 1 year. Non-inferiority testing (pre-specified margin of 7.5%) was performed in the intention-to-treat population. We found that prior to TAVR, among patients with severe AS, significant CAD and minimal angina, **o**bserved rates of death and rehospitalization at 1 year were similar between PCI and no PCI prior to TAVR, however the non-inferiority margin was not met and PCI resulted in a higher incidence of bleeding.

Abbreviations List

AS	Aortic Stenosis
TAVR	Transcatheter aortic valve replacement
SAVR	Surgical aortic valve replacement
CAD	Coronary artery disease
PCI	Percutaneous coronary intervention
MACCE	Major adverse cardiovascular and cerebrovascular events
AKI	Acute kidney injury
VARC	Valve academic research consortium

Introduction

Untreated, severe symptomatic aortic stenosis (AS) is associated with high mortality. Clinical outcomes of transcatheter aortic valve replacement (TAVR) are now known to be at least equivalent (if not superior) to surgical aortic valve replacement (sAVR) regardless of risk score.[1] Demand for TAVR is predicted to increase exponentially with an ageing population.[2] Coronary artery disease (CAD) has been shown to co-exist in up two thirds of cases, most likely attributable to overlapping risk factors.[3] The presence of CAD is an independent predictor of outcome and concomitant revascularization is recommended in patients with significant CAD undergoing sAVR.[4] However, there is currently insufficient evidence regarding the role of percutaneous coronary intervention (PCI) in patients undergoing TAVR to inform guideline recommendations and clinical practice. PCI in the presence of severe AS is not without risk. [4] The aim of the percutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION trial (ACTIVATION; ISRCTN 75836930) was to determine if PCI prior to TAVR in patients with significant CAD would produce non-inferior clinical results when compared with no PCI (control arm).[5]

Methods

Trial design and oversight

The ACTIVATION trial is an investigator-led prospective, randomized, open-labelled, non-inferiority clinical trial in which PCI prior to TAVR was compared with no PCI prior to TAVR in patients with co-existing significant CAD. This trial was conducted in 17 centers in the United Kingdom, France and Germany. All aspects of trial conduct were coordinated and managed by Cardiovascular European Research Center (CERC) clinical trials unit. A complete list of trial investigators, participating sites, members of the trial steering committee (TSC), data safety monitoring board (DSMB) members and clinical events committee

members is provided in the Supplemental Material. The TSC oversaw the running of the trial. The full and final trial protocol designed by the authors and approved by TSC is available online; the original design has been previously published.[5] Ethical approval was granted to King's College London, St Thomas Hospital by the United Kingdom National Research Ethics Committee (London Dulwich) (reference number 11/LO/1596) in 2011. Prior to enrollment, all patients underwent Heart Team discussion, from which participants were identified and eligibility was reviewed by the local site investigator.

Patients

All patients provided written informed consent. Adult patients were eligible for inclusion if they fulfilled the following criteria: severe aortic stenosis deemed suitable for TAVR following heart team discussion and at least one stenosis of greater than or equal to 70% in a major epicardial artery deemed suitable for PCI (or ≥50% if protected left main stem or vein graft). Exclusion criteria included one or more of the following: acute coronary syndrome within 30 days of enrollment, Canadian Cardiac Society Angina Class III or more, unprotected left main stem disease or clinical features that would prohibit dual antiplatelet treatment. Full inclusion and exclusion criteria are provided in the trial protocol. Angiographic lesion severity assessment was determined by the operator.

Randomization and Procedures

Patients deemed to be eligible following review by the local site investigator were randomly assigned to undergo either PCI (test) or no PCI (control) prior to TAVR on a 1:1 basis. Randomization was performed using an electronic system (CliniGrid EDC, Paris, France), based on the permuted block method using randomly varying block sizes and stratified according to site. The trial sequence was generated by an independent statistician. Patients,

investigators and outcome assessors were unblinded to treatment assignment. Patients randomized to receive PCI were recommended the following dual antiplatelet therapy: loading dose of Aspirin 300mg orally and either Clopidogrel 600mg, Prasugrel 60mg or Ticagrelor 180mg if a minimum of one-week maintenance dose of dual antiplatelet therapy had not been administered. Vessels intervened on, PCI strategy, access site and duration of antiplatelet therapy were left to the discretion of the operating Interventional Cardiologist. PCI was performed using Boston Scientific bare metal or drug eluting stents. The choice of CE-marked TAVR device for implantation was not pre-specified and left to the discretion of the implanting center.

Study Endpoints

The primary endpoint of the study was a composite of all-cause mortality and rehospitalization from any cause at 1 year from the TAVR procedure. If TAVR was not undertaken, then this was 1 year from the PCI procedure or 1 year from randomization if no randomized PCI was undertaken. The main hypothesis was non-inferiority of PCI when compared with no PCI in patients prior to TAVR. To test for noninferiority, we determined whether the upper boundary of the 95% one-sided confidence limit (CL) for the absolute difference in the rate of the primary end point between the PCI group and the no PCI group was less than the prespecified non-inferiority margin of 7.5% at 1 year follow up post-TAVR. Key secondary endpoints included assessment of mortality, bleeding events and major adverse cardiovascular or cerebrovascular events (MACCE), defined as death, myocardial infarction, stroke or acute kidney injury (AKI), from randomization to 1 year. All key adverse events were adjudicated by a CEC whose members were aware of the treatment assignments because of the need to assess the relationship of events to PCI and/or TAVR. Clinical endpoint definitions provided for adjudication were updated in accordance with changing

guideline recommendations from the Valve Academic Research Consortium (VARC to VARC2 criteria, details of which are provided in the Supplemental material).[6]

Statistical Analysis

The statistical analysis plan (SAP) and the latest study protocol including amendments are provided online, with key outcomes reported in this manuscript. The sample size determination is provided in the study protocol. In brief, observational data demonstrate a 1 year mortality of 20.0% in patients undergoing PCI prior to TAVR and up to 35.7% in patients with co-existing untreated CAD awaiting TAVR.[7] Based on an assumed re-hospitalization rate over 1 year of 15% in each treatment group, and mortality rates of 20% in the PCI group and 30% in the no-PCI group, 310 patients would provide almost 90% power to demonstrate non-inferiority based on an absolute non-inferiority margin of 7.5% and losses to follow-up of 5% per year. The non-inferiority margin was chosen based on expert opinion and preceding studies (PARTNER Cohort A).[8]

For the primary analysis, cumulative event rates at 1 year post-TAVR were calculated using Kaplan-Meier estimates and the Greenwood standard errors. To test for non-inferiority, we determined whether the upper boundary of the 95% one-sided CL for the difference in the rate of the primary end point between the PCI group and no PCI group was less than the prespecified absolute non-inferiority margin of 7.5%. Further, a one-sided non-inferiority test was undertaken against the non-inferiority margin of 7.5%.

The primary analysis was also repeated on the as-treated population defined as those patients undergoing the TAVR procedure and analysed according to whether they received a PCI or no PCI. Treatment groups were also compared with a Kaplan-Meier (KM) curve, a hazard

ratio (HR) and 95% confidence interval (CI) from a Cox regression model together with a log rank test. In order to recognise the hierarchical nature of the primary endpoint, the combination of the all-cause mortality and time to first rehospitalization was also analyzed using the unmatched Win Ratio approach.

MACCE rates and bleeding were analyzed from randomization to 30 days and 1 year following the TAVR, with the TAVR date defined as above, for those not undergoing the procedure, and compared using HRs and 95% CIs. Bleeding rates are presented as any bleed and major bleeding only as well as a descriptive analysis showing a hierarchical analysis for bleeding at 30 days and 1 year. Bleeding events between groups were compared with KM curves. Statistical analyses were performed using Stata 16.1 (Stata Corp LLC, College Station, TX) and R version 3.3.2 (r-project.org) and carried out by an independent statistician; the primary analysis was verified by a second independent statistician. The study funders had no role in trial design, conception, data collection, analysis, interpretation or writing of this manuscript.

Results

Patients

A total of 235 participants were recruited between December 4, 2012 and January 11, 2019 from 17 centers in the UK, France and Germany. The TSC identified a marked reduction in recruitment rates in the 2 years prior to final patient enrollment. Based on this trajectory it was determined that a substantial amount of time would be required to complete recruitment, and that early discontinuation of the trial was appropriate. Overall recruitment rate (eFigure 1) and site-specific recruitment (eTable 2) are provided in the Supplemental Material. Participant flow is provided in the trial flow diagram (Figure 1). Of the 235 participants

recruited, 119 patients were randomly assigned to undergo PCI and 116 were randomly assigned to no PCI. All patients were included to the point at which consent was withdrawn or no longer in follow-up.

Patient baseline characteristics are provided in Table 1. Characteristics of both cohorts were similar between the groups, although there was a higher incidence of prior myocardial infarction and peripheral vascular disease in the cohort randomized to no PCI. Anti-thrombotic therapies are detailed below; all other medications are detailed in eTable 5.

Angiographic and procedural details including post TAVR hemodynamics are provided in Table 2. The randomized PCI was performed as intended in 116 (97.5%) of those randomized to PCI. The distribution of coronary disease was similar between the groups as was the distribution of lesion complexity. Significant angiographic stenosis in the left anterior descending artery was seen most frequently, identified in 73 (61.3%) of those randomised to PCI and 69 (60.5%) of those randomized to no PCI. In those randomised to PCI, PCI was indicated for single vessel coronary disease in 85 patients (71.4%) with a mean angiographic stenosis of 80±15%. The median number of lesions treated was 1 (IQR 0-2) and the median number of stents implanted was 1 (IQR 0 to 4). Mean treated lesion length was 17.4(±6.6)mm. A total of 21 (18.1%) patients received bare metal stent implantation, accounting for 39 out of 194 (20.1%) lesions treated in the PCI arm. No target vessel failure or revascularisation was recorded within the follow up period. Prior coronary artery bypass graft surgery with degenerative friable vein graft intervention accounted for just under over one fifth (21%) of lesions treated. PCI procedural complications occurred in 3 patients (2.5%) (Table 2). The TAVR procedure was performed in 110 (92.4%) of patients randomized to the PCI arm and 107 (92.2%) of those randomized to no PCI. Median time from randomization to TAVR was 41 days (PCI) and 27 days (no PCI). Reasons for not performing PCI procedure in those randomized to the PCI arm or TAVR procedure in either group are

provided in eTable 6. PCI procedural complications are provided in Table 2 and TAVR procedural complications are provided in eTable 7.

Primary Endpoint

Follow-up information was available for 94.2% of the expected follow-up time for analysis of the primary endpoint. The primary endpoint comprised a composite of all-cause mortality and rehospitalization at 1 year post TAVR and occurred in 48 (41.5%) of the PCI arm and in 47 (44.0%) of the no PCI arm. The requirement for non-inferiority was not met, with a difference of -2.5% and the 95% one-sided CL reaching 8.5% (one-sided non-inferiority test p=0.067) (Figure 2A and eTable 8 in the supplemental material).

Follow-up from randomization to 1 year post TAVR was on average 17 days longer in the PCI arm due to the additional time to TAVR in this group as a result of the PCI. On comparing the two groups from randomization to 1 year post TAVR, the estimated HR was 0.89 (95% CI 0.60 to 1.33) (Figure 2B). With regard to individual components of the primary endpoint the observed mortality at 1 year was 16 (13.4%) in the PCI arm and 14 (12.1%) in the no PCI arm with a HR of 1.00 (95% CI 0.49 to 2.06) (eFigure 10). The observed percentage of patients at 1 year post TAVR with rehospitalization was 41 (34.5%) in the PCI arm and 39 (33.6%) in the no PCI arm with a HR of 0.91 (95% CI 0.59 to 1.42) (eFigure 11). Results of an analysis performed with the use of the hierarchical Win Ratio method (where a higher win ratio indicates a better outcome) were consistent with those of the primary analysis with a win ratio (PCI vs no PCI) of 1.07 (95% CI 0.71 to 1.60; p=0.76). The primary analysis was also repeated for the as-treated population. Eighteen patients did not undergo a TAVR (nine in each group) and were excluded. An additional patient randomized to the PCI arm did not undergo PCI and was considered in the no PCI arm. Thus, there were 109

individuals in the PCI arm and 108 in the no PCI arm. Results were similar to the intention-to-treat population although the difference and upper CL was shifted in favour of PCI with 44 (40.5%) experiencing a primary event in the PCI arm versus 46 (44.1%) in the no PCI arm, a difference of -3.7% (95% one-sided CL 7.5%, one-sided non-inferiority test p=0.050) (see eTable 9 in the supplemental material).

Secondary Endpoints

Key secondary endpoints are provided in Table 3 and analysed from randomization to either 30 days or 1 year post TAVR. The HRs reflect the longer follow-up to 30 days and 1 year post TAVR in the PCI arm. Almost all events excluding bleeds (except one myocardial infarction and one episode of AKI both in the PCI arm) occurred post-TAVR. At 1 year, MACCE rate in the PCI arm was 35 (29.4%) compared to 27 (23.3%) in the non-PCI arm (HR 1.22, 95% CI 0.74-2.02). Individual components are provided in Table 3. The incidence of any bleed from randomization to 30-days post TAVR date was higher at 49 (41.2%) in the PCI arm compared to 31 (26.7%) in the no-PCI arm (HR 1.46, 95% CI 0.93 to 2.29). Eight (16.3%) of these bleeding events occurred in relation to the TAVR procedure in the PCI arm compared to 4 (12.9%) in the no-PCI arm. The incidence of any bleed from randomization to 1 year post TAVR date was higher at 53 (44.5%) in the PCI arm compared to 33 (28.4%) in the no-PCI arm (HR 1.66, 95% CI 1.07 to 2.56). The incidence of major bleeding from randomization to 1 year post TAVR date was 31 (26.1%) in the PCI arm compared with 21 (18.1%) in the no-PCI arm (HR 1.44, 95% CI 0.83 to 2.51). Time to event curves for any bleed are provided from TAVR date to 12 months post (eFigure 14) and from randomisation to 12 months (eFigure 15). Bleeding defined according to BARC criteria including hierarchical descriptions are provided in eTables 12,13.

Anti-Thrombotic Therapy

The list of patient medications according to randomization arm at baseline, 30 days and 1 year post-TAVR are provided in eTables 5, 16 and 17. At the time of randomization, there was a higher incidence of coumarin administration in the PCI arm 31 (26.1%) compared to no PCI 18 (15.9%) despite randomization however this evened out between groups at the point of discharge following TAVR (22, 18.5% PCI versus 20, 17.2% no PCI) and 30-day follow up post TAVR (33, 27.7% PCI versus 28, 24.1% no PCI) when the majority of bleeding events had occurred. At the time of randomization, 31 patients in the PCI arm and 18 patients in the were taking coumarin a15 (12.6%) patients in the PCI arm and 8 (6.9%) patients in the no PCI arm were on dual antiplatelet therapy (DAPT); 4 (3.4%) patients in the PCI arm and 5 (4.3%) patients in the no PCI arm were taking single antiplatelet and coumarin; 2 (1.7%) patients in the PCI arm and 2 (1.7%) patients in the no PCI arm were on triple therapy (dual antiplatelets and coumarin). At discharge following TAVR, 73 (62.9%) patients in the PCI arm and 36 (31.0%) patients in the no PCI arm were on DAPT; 12 (10.1%) patients in the PCI arm and 13 (11.2%) patients in the no PCI arm were taking single antiplatelet and coumarin; 9 (7.6%) patients in the PCI arm and 3 (2.6%) patients in the no PCI arm were on triple therapy. At 30 day post TAVR follow up, 59 (49.6%) patients in the PCI arm and 28 (24.1%) patients in the no PCI arm were on DAPT; 23 (19.3%) patients in the PCI arm and 20 (17.2%) patients in the no PCI arm were taking single antiplatelet and coumarin; 8 (6.7%) patients in the PCI arm and 2 (1.7%) patients in the no PCI arm were on triple therapy. At 12 month post TAVR follow up, 11 (9.2%) patients in the PCI arm and 5 (4.3%) patients in the no PCI arm were on DAPT; 16 (13.4%) patients in the PCI arm and 5 (4.3%) patients in the no PCI arm were taking single antiplatelet and coumarin; 1 (0.8%) patient in the PCI arm and 2 (1.7%) patients in the no PCI arm were on triple therapy. All other outcomes are provided in eTables 18 and 19 in the Supplemental Material

Discussion

The ACTIVATION trial is the first randomized trial of PCI versus no PCI prior to TAVR in patients with severe aortic stenosis and significant coronary disease. The trial was terminated early with a total of 235 participants due to a marked reduction in recruitment rate. The main findings of the ACTIVATION trial are as follows. First, there was no evidence of a difference in the primary endpoint of death or re-hospitalization at 1 year between patients who did or did not undergo PCI prior to TAVR, however the requirement for non-inferiority was not met, with the one-sided 95% CL reaching 8.5%, higher than the prespecified upper limit of 7.5%. On analysis of the as-treated population, the difference was -3.7% with the one-sided 95% CL at exactly 7.5% (p=0.050). Second, analysis of key secondary endpoints demonstrated no evidence for differences in MACCE at 30 days or 1 year. Third, more bleeding events were demonstrated in the arm randomized to receive PCI, with the majority occurring within 30 days of the TAVR procedure driven by increased dual antiplatelet use in the PCI arm.

The aim of the ACTIVATION trial was to determine if pre-TAVR PCI could be demonstrated to be non-inferior with respect to the primary endpoint of death or rehospitalisation at one year and whether or not this was at the expense of secondary endpoints of MACCE, AKI and bleeding at 30 days and 1 year post-TAVR. The original sample size calculation of 310 patients provided 90% power with 5% loss to follow up per year. The trial was terminated early due to a reduction in recruitment, driven by the rapidly evolving landscape of TAVR; in the final two years of recruitment, there was an increased tendency for patients to directly undergo TAVR following CT assessment (without the additional step of invasive coronary angiography) and also patients expressed a preference for reduced elective hospital visits. Despite a reduction in recruitment and a final sample size

of 235 patients, the higher than expected primary event rate (driven by rehospitalizations) suggested no difference between pre-TAVR PCI and no PCI in the as-treated population. This does not however reflect an overall benefit of either strategy and pre-TAVR PCI is not without risk in the elderly population and there was no sign at all that PCI was associated with reduced mortality despite allowing for a 10% absolute reduction. Due to the shared pathophysiology of aortic stenosis and coronary artery disease in the elderly population, coronary disease is often complex and heavily calcified and may require adjunctive calcium modification therapies and risk hemodynamic instability. There was a range of lesion complexity in this cohort ranging from single vessel, short lesions to 2 or 3 vessel angioplasty, vein graft intervention and long lesions. This trial demonstrated no difference in death or rehospitalisation, but numerically higher incidence of acute kidney injury and major bleeding in the PCI arm at 30 days post TAVR. If more patients had been enrolled into the trial, there is the possibility that we would have seen further bleeding events in the PCI arm thus increasing the difference between groups. Although the majority of bleeding events occurred at 30 day follow up with higher rates in the PCI, this only reached statistical significance at one-year post TAVR. On review of the anti-thrombotic therapy, this appears to be predominantly driven by the increased use of dual antiplatelet therapy in the PCI, whereas the distribution of triple therapy or single antiplatelet with coumarin was similar between groups. In practical terms, there was a 40% reduction in bleeding events in the no-PCI arm relative to the PCI. This finding is of particular importance as we know major bleeding and access site complications increase are associated with poor outcomes post TAVR. These findings should therefore be factored into Heart Team decision making when contemplating pre-TAVR PCI in this patient cohort. Overall this data would support deferred PCI, however, if later (post-TAVR) coronary access is deemed necessary then additional thought should be given to valve choice and ease of coronary access. At the time of

randomization a higher proportion of patients in the PCI arm were receiving coumarin, but at discharge and at 30-days post TAVR follow up, there was no difference between groups.

This patient cohort exhibited mean coronary stenosis severity of 85±15%, the median number of coronary lesions was 1 with just under two thirds of lesions in the left anterior descending coronary artery disease in both cohorts. Previous clinical studies have shown an increased risk of mortality in the presence of complex CAD with possible benefit from PCI in this cohort by reducing hemodynamic instability during TAVR and protection against impaired contractility post TAVR.[9] However, in our study there was no demonstrable difference in outcomes at one year in patients who underwent PCI compared to no PCI prior to TAVR. This could in part be due to the difference in patient groups, prior meta-analyses have examined multivessel disease with high syntax scores whereas the ACTIVATION trial cohort predominantly exhibited single vessel coronary disease. Up to one fifth of patients in the PCI arm received bare metal stents with the potential for suboptimal long term results, however however there was no suggestion of target vessel failure and the shorter duration of dual antiplatelet therapy may have been beneficial. Physiological evaluation of the significance of coronary artery lesions was not mandated in this study because of the complex interplay between aortic stenosis, epicardial coronary lesions, microvascular disease and autoregulatory processes that can make borderline or non-concordant results from hyperemic or resting intracoronary indices difficult to interpret. Physiological evaluation of coronary lesions in the presence of aortic stenosis is likely to play a role in decision making in the future if future studies can correlate this with long term outcomes.

The ACTIVATION trial population experienced minimal angina, had a mean age of 84 and reflected the intermediate to high risk TAVR population, with co-existing peripheral vascular disease, renal impairment and atrial fibrillation at baseline requiring coumarin administration

in just over one fifth of patients. Median time to TAVR from randomisation was 45 days in the PCI arm and 30 days from randomisation in the no PCI arm, suggesting patients underwent TAVR approximately 2 weeks post PCI and would have been on dual antiplatelet therapy at the time (+/-coumarin). Overall there was no suggestion of a difference between the treatment strategies with increased bleeding risk in the PCI arm. These findings should be taken into consideration by the Heart Team when deciding the best approach to coronary artery disease pre-TAVR, the duration of dual antiplatelet regime and timing of PCI in relation to TAVR. Whether or not the ACTIVATION trial results are transferable to the younger and/or low risk population is yet to be determined, longer term follow up may identify late events that may in part address this issue.

Limitations

The most important limitation of this trial is the lower than planned sample size, with 235 patients recruited compared to the intended 310 (including 5% losses). Thus, despite the lower observed event rate in the PCI arm (-2.5%), the criterion for non-inferiority was not met with the one-sided 95% CL of 8.5% compared to the pre-set margin of 7.5%. Furthermore, the current results reflect one-year outcomes, in patients with a mean age of 83 years, and definitive conclusions regarding the advantages or disadvantages of PCI in this cohort will depend on longer term follow-up. There are also other limitations, including the absence of a detailed screening log for these data and absence of blinding. These could have led to both bias in patient selection and in adjudication of non-definitive outcomes. Additionally, this trial did not include patients with significant left main stem coronary disease or those with significant (CCS class 3 or more) angina and the findings are therefore not transferable to this cohort. Assessment of coronary disease was based on angiographic lesion severity without physiological assessment.

Conclusions

In conclusion, prior to TAVR, among patients with severe AS, significant CAD and minimal angina, observed rates of death and rehospitalization at 1 year were similar between PCI and no PCI prior to TAVR, however the non-inferiority margin was not met and PCI resulted in a higher incidence of bleeding.

Clinical Perspectives

What Is known?

There is currently insufficient evidence regarding the role of percutaneous coronary intervention (PCI) in patients undergoing TAVR to inform guideline recommendations and clinical practice.

What is new?

Prior to TAVR, among patients with severe AS, significant CAD and minimal angina, observed rates of death and rehospitalization at 1 year were similar between PCI and no PCI prior to TAVR, however the non-inferiority margin was not met and PCI resulted in a higher incidence of bleeding.

What is next?

Longer term follow up is required to determine if there is a long-term mortality benefit of PCI prior to TAVR.

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Figure Legends

Figure 1. Trial Flow Diagram

Withdrawals up to 1 year following randomization. These are presented graphically in eFigure 3 in the Supplemental Material. Withdrawals up to 1 year post TAVR are provided in eTable 4.

Figure 2. Time to event curves for the primary composite endpoint

Kaplan-Meier estimates of the rate of the primary composite endpoint of death and rehospitalization in patients who underwent PCI prior to TAVR compared to no PCI. Presented as (A) cumulative risk of death/re-hospitalization from date of TAVR procedure to 1 year post-TAVR, and (B) cumulative risk of death/re-hospitalization from date of randomization to 1 year post-TAVR. The hazard ratio of 0.92 is due to longer follow up in the PCI arm.

Tables

Characteristic*	PCI (n=119)	No PCI (n=116)
Demographics		
Age (years)	83.6 (±5.0)	84.3 (±5.0)
Gender (male)	69 (58.0)	75 (64.7)
Height (cm)	166 (±8)	166 (±10)
Weight (kg)	78.4 (±15.4)	73.2 (±15.6)
BMI (kg/m^2)	28.7 (±6.1)	26.6 (±5.0)
Clinical Assessment		
Dyspnea	98 (82.4)	94 (82.5)
Syncope	14 (11.8)	13 (11.4)
NYHA Class		
I	4 (3.4)	4 (3.6)
II	41 (35.3)	43 (38.4)
III	67 (57.8)	60 (53.6)
IV	4 (3.4)	5 (4.5)
Angina grade (CCS class)		
0	81 (68.1)	79 (69.3)
1	14 (11.8)	18 (15.8)

2	23 (19.3)	16 (14.0)
3	1 (0.8)	1 (0.9)
4	0 (0.0)	0 (0.0)
EuroSCORE %	11.3 (1.4-63.8)	13.9 (1.2-77.4)
STS Score* % Missing	4.44 (1.34-26.90) 21	4.41 (1.08-36.53) 22
Creatinine (mg/L) (0.5-1.0)	10.7 (5.1-24.0)	10.9 (.2-51.7)
eGFR (mL/min)* (<60) Missing	57.0 (0.0-138.7) 0	59.0 (8.0-134.9) 5
Hemoglobin g/dL (12.0-15.5)	12.6 (8.4-15.8)	12.6 (8.9-16.8)
Platelets 10^9/L (150-450)	212 (80-507)	207 (104-576)
Risk factors and medical history		
Diabetes	35 (29.4)	27 (23.3)
Smoker	6 (5.0)	3 (2.6)
Hyperlipidemia	42 (35.3)	40 (34.5)
Hypertension	94 (79.0)	90 (77.6)
Hypercholesterolemia	40 (33.6)	34 (29.3)
Pulmonary hypertension**	13 (10.9)	11 (9.5)
Renal failure eGFR<30mL/min	17 (14.3)	22 (19.0)

Heart failure presentation	26 (21.8)	31 (27.2)
Prior myocardial infarction	14 (11.8)	26 (22.8)
Hospitalization for aortic stenosis	34 (28.6)	25 (21.9)
Prior PCI	28 (23.5)	24 (21.1)
Prior CABG	8 (6.7)	11 (9.6)
Peripheral vascular disease	15 (12.6)	24 (21.1)

Table 1. Baseline characteristics of the patient cohorts

Values are displayed as mean (±SD), median (IQR) or counts (%). Abbreviations: BMI body mass index, NYHA New York heart association functional class, CCS Canadian Cardiac Society angina class, STS Society of Thoracic Surgeons score, PCI percutaneous coronary intervention, CABG coronary artery bypass graft surgery, SD standard deviation, IQR inter-quartile range.

* All variables had fewer than 5 missing values except for STS Score (n=43) and eGFR (n=5)

**Primary or secondary pulmonary hypertension with PA systolic pressures greater than two thirds of systemic pressure.

	PCI (n=119)	**No PCI (n=116)**
Coronary Artery Disease		
Left anterior descending >70%	73 (61.3)	69 (60.5)
Circumflex >70%	42 (35.3)	38 (33.3)
Right coronary artery >70%	47 (39.5)	59 (51.8)

Left main stem >70%	3 (2.5)	6 (5.3)
Vein graft >70%		
0	90 (75.6)	93 (80.2)
1	17 (14.3)	14 (12.1)
2	8 (6.7)	6 (5.2)
3	3 (2.5)	3 (2.6)
4	0 (0.0)	0 (0.0)
5	1 (0.8)	0 (0.0)
Number of vessels intended for PCI		
0	2 (1.7)	-
1	85 (71.4)	-
2	29 (24.4)	-
3	2 (1.7)	-
4	1 (0.8)	-
PCI undertaken	116 (97.5)	-
Number of patients	116 (97.5)	
Number of lesions	194	
Lesion length (mm)	17.4(±6.6)	
Median number treated lesions	1 (0-2)	
Median number of stents	1 (0-4)	
Bare metal stent implantation		
Number of patients	21 (17.6)	
Number of stents/lesions	39/194 (20)	
PCI procedural complication	3 (2.5)	

Coronary perforation and tamponade	1 (0.8)	
Target vessel dissection	1 (0.8)	
Technical failure	1 (0.8)	
Post PCI TIMI 3 flow	163/167 lesions (98)	
Pre-PCI stenosis (%)	80.3 (±15.2)	
Post-PCI stenosis (%)	2.2 (±7.2)	
TAVR undertaken	110 (92.4)	107 (92.2)
Transfemoral TAVR access site	98 (89.0)	86 (80.4)
Valve size (mm)	26 (23-29)	26 (20-29)
Valve type		
Edwards Sapien	103 (93.6)	95 (88.8)
Other**	6 (5.5)	11 (10.3)
No valve deployed	1 (0.9)	1 (0.9)
TAVR procedural complication*	17 (14.3)	11 (9.5)
Mean prosthetic valve gradient (mmHg)	11.1(±4.6)	12.5(±6.7)
Moderate or greater para-valvular leak	4 (3.4)	1 (0.9)

Table 2. Angiographic and Procedural Characteristics

The findings of coronary +/- graft angiography, PCI details (if relevant), procedural complications and valve type. Abbreviations: TIMI Thrombolysis In Myocardial Infarction flow, PCI percutaneous coronary intervention, SD standard deviation. * TAVR-related complications are provided in eTable 7. **Other valves used 1) in PCI arm: Medtronic Corevalve, Lotus - Boston Scientific , Medtronic Core Valve Evolut, Corevalve Evolut R 2)

no PCI arm: Medtronic Corevalve, Sapien XT, Corevalve Evolut R, Lotus, Symetis, Corevalve Evolut Pro.

	PCI (n=119)	**No PCI (n=116)**	**Hazard Ratio (95% CI)**
MACCE at 30 days			
MACCE rate	10 (8.4)	10 (8.6)	1.17 (0.60-2.26), P=0.65
Death	3 (2.5)	6 (5.2)	0.45 (0.11-1.82), P=0.25
Cardiac death	1	5	
Non-cardiac death	2	1	
MI	5 (4.2)	2 (1.7)	2.14 (0.41-11.10), P=0.35
Peri-procedural	3	1	
Spontaneous	2	1	
Stroke	5 (4.2)	4 (3.4)	0.82 (0.21-3.11), P=0.77
Ischemic	4	4	
Hemorrhagic	0	0	
Rehospitalization at 30 days			
Rehospitalization	11 (9.2)	12 (10.3)	0.56 (0.24-1.31), P=0.17
Acute kidney injury at 30 days			

AKI	12 (10.1)	5 (4.3)	1.91 (0.67-5.46), P=0.22
Bleeding at 30 days			
Any Bleed	49 (41.2)	31 (26.7)	1.46 (0.93-2.29), P=0.098
During TAVR procedure	8 (6.7)	4 (3.4)	
Major Bleed	31 (26.1)	21 (18.1)	1.23 (0.68-2.22), P=0.49
During TAVR procedure	7 (5.8)	2 (1.7)	
MACCE at 1 year			
MACCE rate	23 (19.3)	22 (19.0)	1.22 (0.74-2.02), P=0.43
Death	16 (13.4)	14 (12.1)	1.00 (0.49-2.06), P=0.99
Cardiac death	7	11	
Non-cardiac death	9	3	
MI	8 (6.7)*	4 (3.4)	1.86 (0.56-6.17), P=0.30
Peri-procedural	3	1	
Spontaneous	5	3	
Stroke	7 (5.9)*	8 (6.9)	0.73 (0.26-2.03), P=0.55

Ischemic	4	8	
Hemorrhagic	2	0	
Unknown	1	0	
Rehospitalization at 1 year			
Rehospitalization	41 (34.5)	39 (33.6)	0.91 (0.59-1.42), P=0.69
Acute kidney injury at 1 year			
AKI	12 (10.1)	5 (4.3)	2.29 (0.81-6.51), P=0.11
Bleeding events at 1 year			
Any Bleed	53 (44.5%)	33 (28.4%)	1.66 (1.07-2.56), P=0.021
Major Bleed	31 (26.1%)	21 (18.1%)	1.44 (0.83-2.51), P=0.19

1
2
3
4
5
6

	PCI (n=119)	**No PCI (n=116)**	**Hazard Ratio (95% CI)**
MACCE at 30 days			
MACCE rate	10 (8.4)	10 (8.6)	1.17 (0.60-2.26), P=0.65

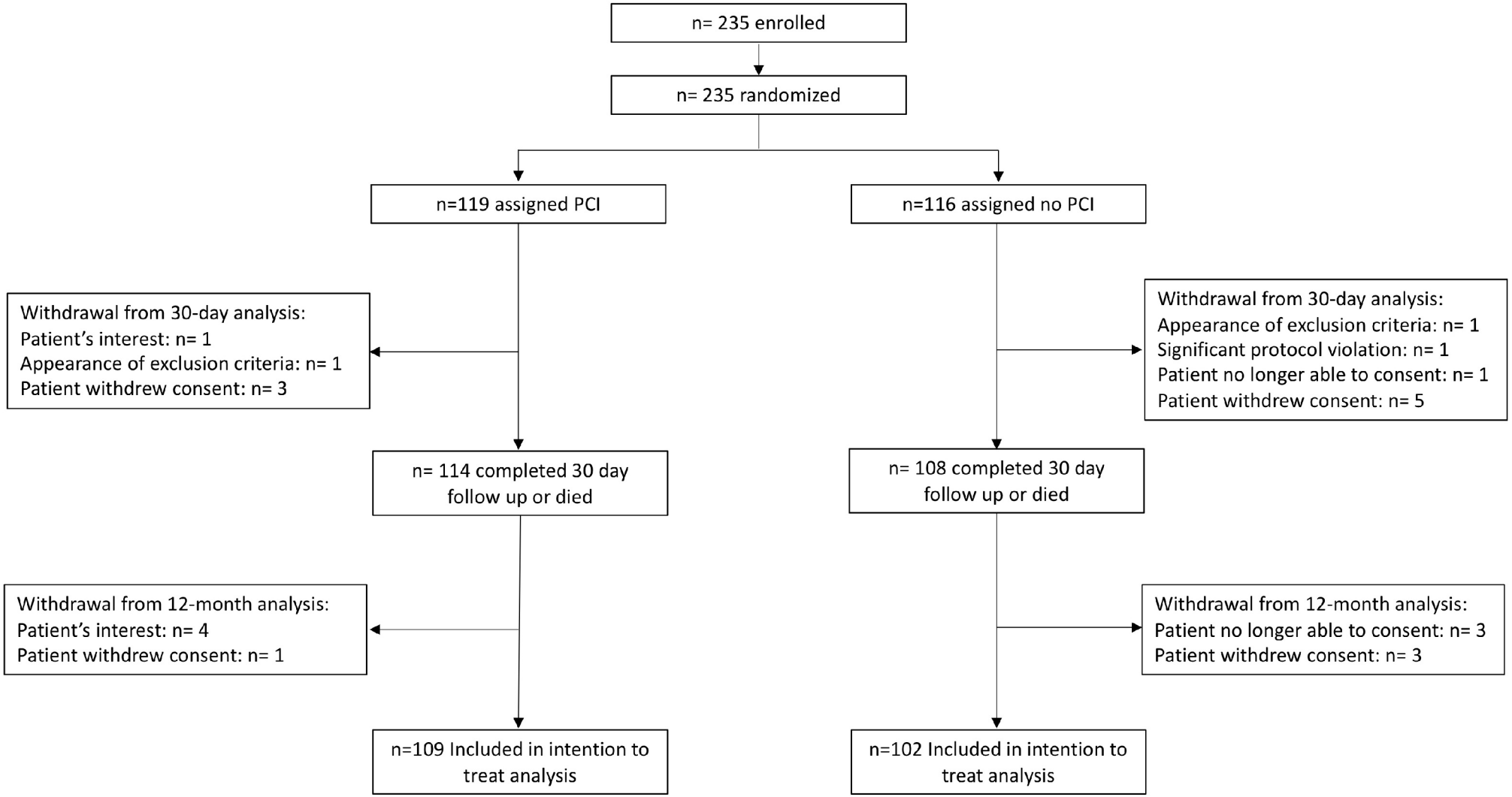
Death	3 (2.5)	6 (5.2)	0.45 (0.11-1.82), P=0.25
Cardiac death	1	5	
Non-cardiac death	2	1	
MI	5 (4.2)	2 (1.7)	2.14 (0.41-11.10), P=0.35
Peri-procedural	3	1	
Spontaneous	2	1	
Stroke	5 (4.2)	4 (3.4)	0.82 (0.21-3.11), P=0.77
Ischemic	4	4	
Hemorrhagic	0	0	
Rehospitalization at 30 days			
Rehospitalization	11 (9.2)	12 (10.3)	0.56 (0.24-1.31), P=0.17
Acute kidney injury at 30 days			
AKI	12 (10.1)	5 (4.3)	1.91 (0.67-5.46), P=0.22
Bleeding at 30 days			
Any Bleed	49 (41.2)	31 (26.7)	1.46 (0.93-2.29), P=0.098
During TAVR procedure	8 (6.7)	4 (3.4)	
Major Bleed	31 (26.1)	21 (18.1)	1.23 (0.68-2.22), P=0.49

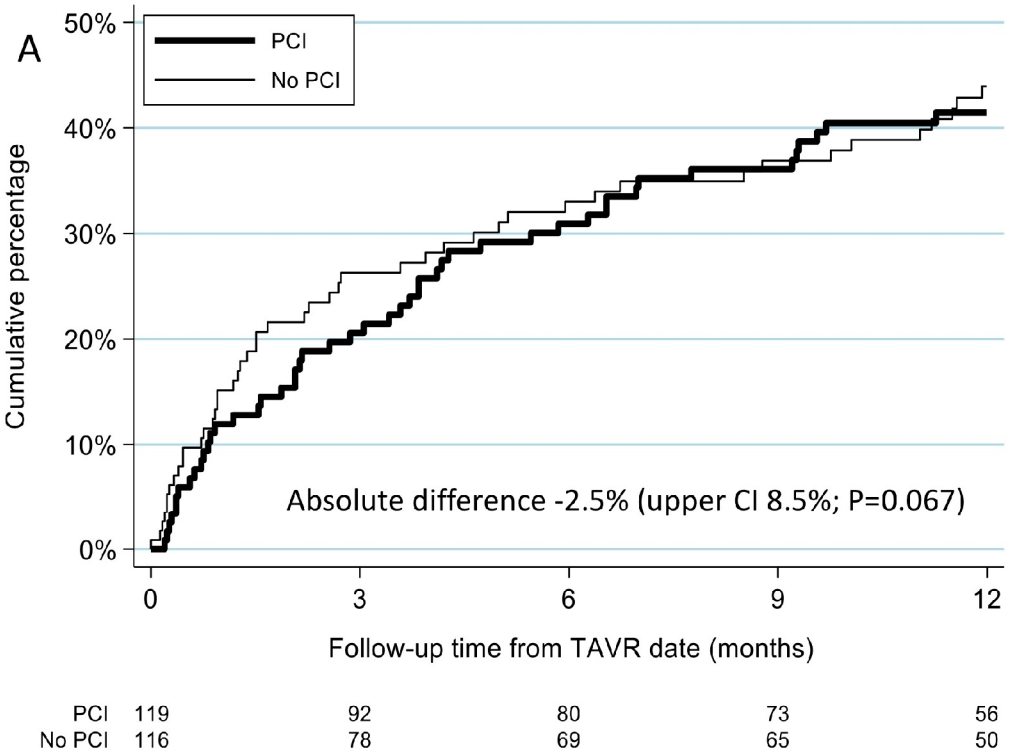
During TAVR procedure	7 (5.8)	2 (1.7)	
MACCE at 1 year			
MACCE rate	23 (19.3)	22 (19.0)	1.22 (0.74-2.02), P=0.43
Death	16 (13.4)	14 (12.1)	1.00 (0.49-2.06), P=0.99
Cardiac death	7	11	
Non-cardiac death	9	3	
MI	8 (6.7)*	4 (3.4)	1.86 (0.56-6.17), P=0.30
Peri-procedural	3	1	
Spontaneous	5	3	
Stroke	7 (5.9)*	8 (6.9)	0.73 (0.26-2.03), P=0.55
Ischemic	4	8	
Hemorrhagic	2	0	
Unknown	1	0	
Rehospitalization at 1 year			
Rehospitalization	41 (34.5)	39 (33.6)	0.91 (0.59-1.42), P=0.69
Acute kidney injury at 1 year			
AKI	12	5 (4.3)	2.29 (0.81-6.51), P=0.11

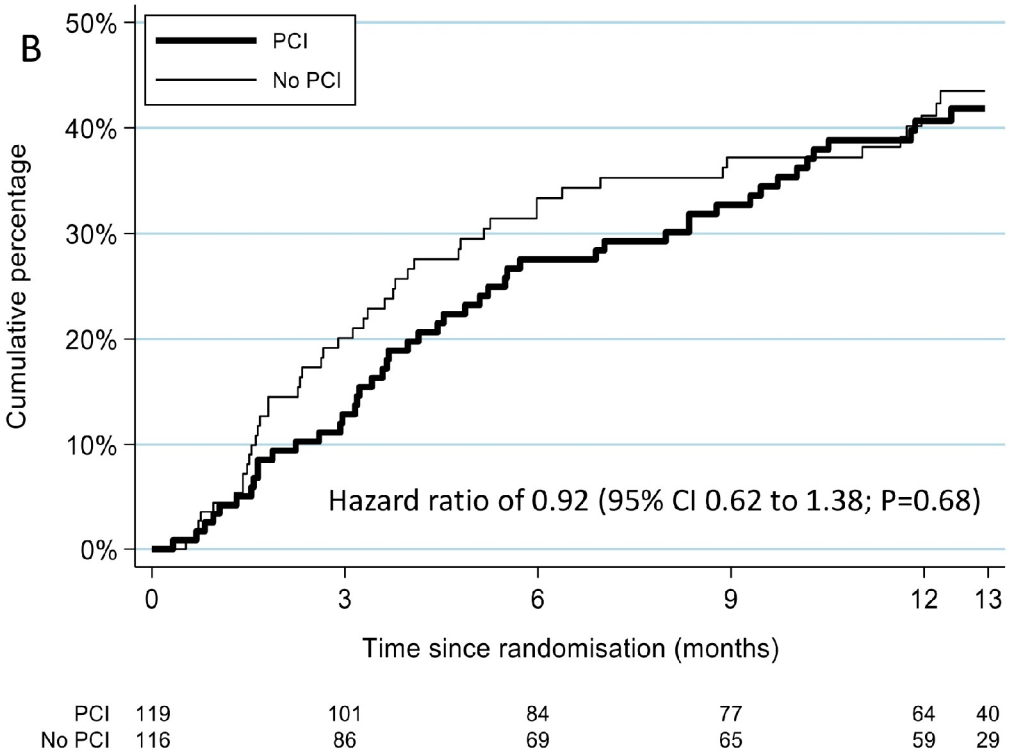
	(10.1)		
Bleeding events at 1 year			
Any Bleed	53 (44.5%)	33 (28.4%)	1.66 (1.07-2.56), P=0.021
Major Bleed	31 (26.1%)	21 (18.1%)	1.44 (0.83-2.51), P=0.19

Table 3. Key secondary endpoints with MACCE and bleeding events from randomization to 30 days and 1 year post TAVR

Data are presented as counts (%). Abbreviations: MACCE major adverse cardiovascular and cerebrovascular events, MI myocardial infarction, AKI acute kidney injury, CI confidence interval.


n= 235 enrolled
n= 235 randomized
n=119 assigned PCI
n=116 assigned no PCI
Withdrawal from 30-day analysis:
Patient's interest: n= 1
Appearance of exclusion criteria: n= 1
Patient withdrew consent: n= 3
Withdrawal from 30-day analysis:
Appearance of exclusion criteria: n= 1
Significant protocol violation: n= 1
Patient no longer able to consent: n= 1
Patient withdrew consent: n= 5
n= 114 completed 30 day follow up or died
n= 108 completed 30 day follow up or died
Withdrawal from 12-month analysis:
Patient's interest: n= 4
Patient withdrew consent: n= 1
Withdrawal from 12-month analysis:
Patient no longer able to consent: n= 3
Patient withdrew consent: n= 3
n=109 Included in intention to treat analysis
n=102 Included in intention to treat analysis


A
PCI
No PCI
Cumulative percentage
50%
40%
30%
20%
10%
0%
Absolute difference -2.5% (upper CI 8.5%; P=0.067)
0
3
6
9
12
Follow-up time from TAVR date (months)
PCI 119 92 80 73 56
No PCI 116 78 69 65 50


B
PCI
No PCI
Cumulative percentage
50%
40%
30%
20%
10%
0%
Hazard ratio of 0.92 (95% CI 0.62 to 1.38; P=0.68)
0
3
6
9
12
13
Time since randomisation (months)
PCI 119 101 84 77 64 40
No PCI 116 86 69 65 59 29