

Assessing the impact of age on outcomes following percutaneous coronary intervention in patients undergoing transcatheter aortic valve replacement—a substudy in NOTION-3

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Abstract

Background

Findings from the recent NOTION-3 trial suggest that percutaneous coronary intervention (PCI) improves outcomes in patients with severe aortic stenosis and concomitant coronary artery disease undergoing transcatheter aortic valve implantation (TAVI). Whether the benefit of PCI is consistent across age groups is uncertain.

Aims

To investigate the impact of age on outcomes from NOTION-3.

Methods

A secondary analysis of 455 patients in the NOTION-3 trial, a randomized trial comparing PCI with conservative treatment in patients with aortic stenosis and coronary artery disease undergoing TAVI. Patients were stratified into four age groups based on the quartile distribution of age (<78, 78–81, 82–84, and ≥85 years) and followed for a median of 2 years (IQR: 1–4 years). The primary outcome was major adverse cardiac events defined as a composite of all-cause death, myocardial infarction, or urgent revascularization.

Results

The risk difference for the primary endpoint comparing PCI and conservative treatment was most pronounced in patients aged 78–81 years [17% vs 42%; hazard ratio (HR): 0.36, 95% confidence interval (CI): 0.17–0.77, $P = .008$]. For the age

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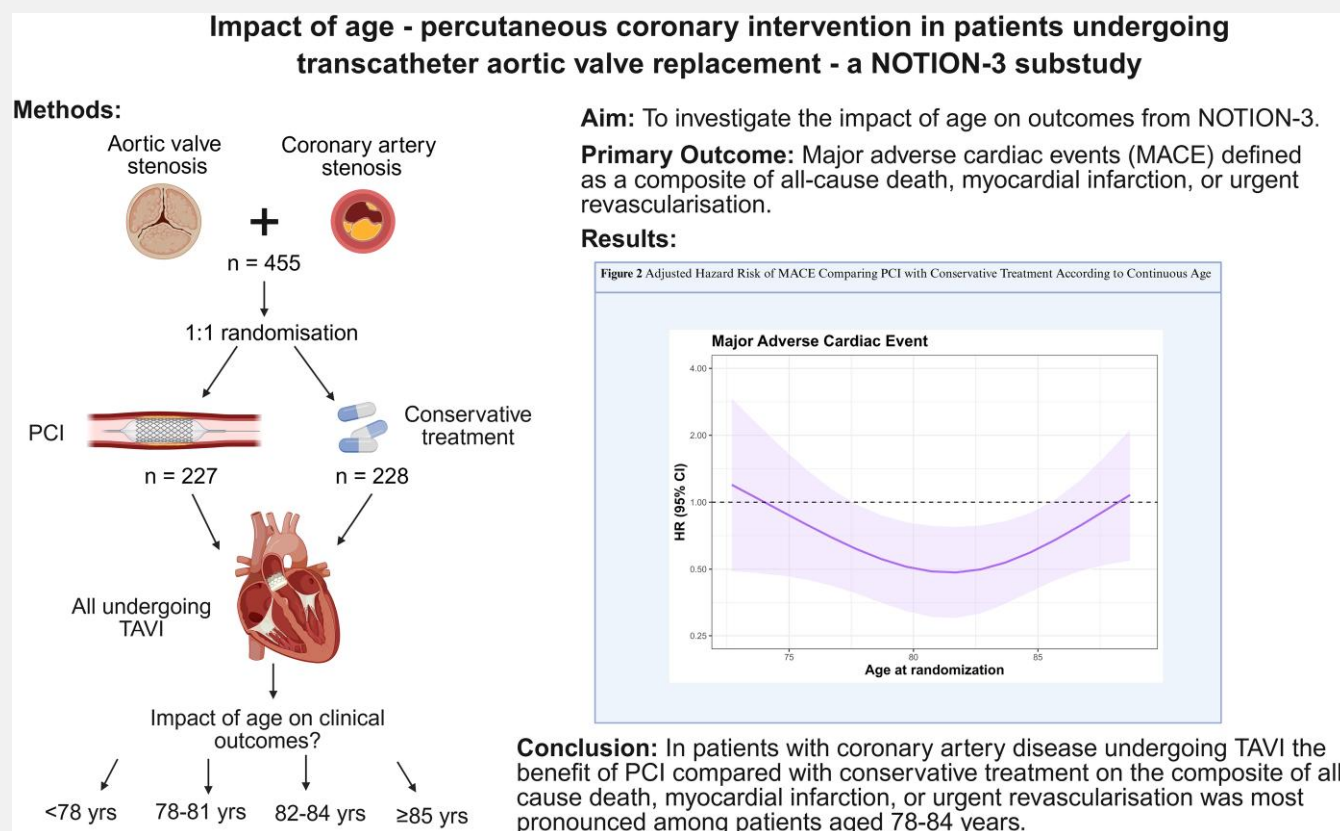
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groups <78, 82–84 and ≥85 years this risk difference between treatment groups was (HR: 1.08, 95% CI: 0.48–2.40), (HR: 0.69, 95% CI: 0.35–1.35), and (HR: 0.90, 95% CI: 0.50–1.62), respectively.

Conclusion

In patients with coronary artery disease undergoing TAVI the benefit of PCI compared with conservative treatment on the composite of all-cause death, myocardial infarction, or urgent revascularization was most pronounced among patients aged 78–84 years.

Graphical abstract



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Keywords

PCI • TAVI • Elderly • Octogenarians • Aortic stenosis • Coronary artery disease

Introduction

Aortic stenosis is the most prevalent valvular heart disease, with an increasing incidence due to ageing populations.^{1–3} Over the past two decades, the treatment of severe aortic stenosis has been transformed.⁴ Transcatheter aortic valve implantation (TAVI) has emerged as a minimally invasive alternative to surgical aortic valve replacement (SAVR) and TAVI is now the recommended treatment for patients over 70 years of age.⁵ A significant proportion of patients with aortic stenosis undergoing TAVI—approximately 40%–75%—also present with concomitant coronary artery disease⁶ and the combination is associated with a higher risk of clinical events.¹ While untreated severe aortic stenosis is associated with increased morbidity and mortality,⁷ stable coronary artery disease might just be a benign bystander.^{8,9} However, the new recommendation from ESC/EACTS revised in August 2025 is that percutaneous coronary intervention (PCI) should be considered

in patients planned for TAVI with a high-grade (≥90%) coronary artery stenosis in vessels ≥2.5 mm.

Supporting that recommendation, findings from the recent NOTION-3 trial suggest that PCI improves outcomes in patients with severe aortic stenosis and concomitant coronary artery disease undergoing TAVI.¹⁰ However, in line with observations from other studies, PCI was related to an increased risk of bleeding.^{9,10} While the main trial results indicated a benefit of PCI, these benefits may not be consistent across all patient groups, particularly in the oldest trial subjects who are often frail, with higher procedural and bleeding risks, and shorter life expectancy.^{11–14} Understanding how age impacts the outcomes of PCI combined with TAVI is critical to optimize treatment strategies for this heterogeneous patient population. Therefore, this study aims to investigate whether the clinical benefits of PCI in addition to TAVI are affected by age.

Methods

Study design and trial population

The present study is a secondary analysis including patients from the NOTION-3 trial, an international, open-label, randomized superiority trial, investigating the effect of PCI in patients with stable coronary artery disease and severe aortic stenosis who were planned for TAVI, which has previously been described in detail elsewhere.^{10,15}

In brief, between September 2017 and October 2022, patients with severe symptomatic aortic stenosis and at least one significant stenosis with a diameter stenosis of at least 90% or a fractional flow reserve of 0.80 or less in a coronary-artery of at least 2.5 mm in diameter were enrolled. All patients were planned for TAVI and were randomized in a 1:1 ratio to either undergo PCI or receive conservative treatment. Patients assigned to conservative treatment received standard clinical care after TAVI and medical treatment according to current guidelines for chronic coronary artery disease. Exclusion criteria were a life expectancy of less than 1 year, acute coronary syndrome within 14 days before the heart team made the decision of TAVI, renal failure (estimated glomerular filtration rate; <20 mL/minute/1.73 m² body-surface area) and left main coronary artery stenosis.

The NOTION-3 trial was registered with ClinicalTrials.gov, number NCT03058627.

Ethics

All participants gave informed written consent. The study design was approved by a regional ethics committee and complied with the Second Declaration of Helsinki.

Age groups

For this substudy patients were categorized into four age groups based on the quartile distribution of age at randomization (<78, 78–81, 82–84, and ≥85 years).

Follow-up and outcome

Follow-up data were collected from the NOTION-3 database. Participants were followed for all clinical events from inclusion until death or end of follow-up when the last enrolled patient was followed for more than 1 year after TAVI.

The primary outcome for this analysis was major adverse cardiac event (MACE), defined as a composite of death from any cause, myocardial infarction, or urgent revascularization. Urgent revascularization was defined as any revascularization performed during an unplanned hospital admission for acute coronary syndrome.

The secondary outcomes for this analysis included individual components of the primary endpoint; death from any cause; stroke; spontaneous or periprocedural myocardial infarction; death from cardiovascular causes; acute kidney failure; any revascularization; and bleeding, assessed according to the Valve Academic Research Consortium-2 definitions.¹⁶

Statistical analysis

Differences in baseline characteristics were examined using Student's *t*-test, Mann–Whitney *U* test, or the chi-squared test as appropriate. Unadjusted hazard ratios (HR), 95% confidence intervals (CI) and *P*-values for the primary, secondary and safety endpoints were calculated using Cox regression comparing PCI and conservative treatment in all four age groups. In the case of zero events in one or more of the groups HRs and *P*-values were not reported. Adjusted HRs, 95% CIs and *P*-values for the primary, secondary and safety endpoints were calculated using Cox regression comparing the four age groups with the youngest age group (<78 years) as reference group. The adjusted covariates had been selected based on significant differences (*P*-value < .05) in baseline and angiographic characteristics between age groups and included body mass index, history of percutaneous coronary intervention, treatment for hypercholesterolaemia, diabetes mellitus, chronic obstructive pulmonary disease, balloon-expandable heart valve and lesion with diameter stenosis ≥90%. Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores were not included in the adjusted analysis as age is included in the calculation of the score. For all models, the proportional hazards assumption was tested using

Schoenfeld residuals. The Kaplan–Meier method was used to estimate cumulative event rates over time for the primary endpoint. A restricted cubic spline curve was used to assess the impact of age on the primary endpoint on a continuous scale, including all patients between the 5th and 95th percentile of the age spectrum (72.7–89 years). The curve was derived from the adjusted Cox proportional hazard model. A *P*-value < .05 was considered statistically significant.

Statistical analyses were performed using R software version 4.4.1 or newer.

Results

Population

Of the 455 patients included in the NOTION-3 trial 103 (23%) patients were <78 years, 120 (26%) were 78–81 years, 106 (23%) were 82–84 years, and 126 (28%) were ≥85 years. [Supplementary Figure S1](#) shows the distribution of age at randomization. At baseline patients <78 years were more likely to have chronic obstructive pulmonary disease, higher body mass index, and prior PCI compared with the older groups. Patients <78 and 78–81 years also had higher rates of diabetes and were more often treated for hypercholesterolaemia. Patients ≥85 years had the highest STS-PROM scores, while patients 82–84 and 78–81 years had comparable scores and the patients <78 years had the lowest STS-PROM scores ([Table 1](#)).

Angiographic and procedural findings

The median Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score and number of physiologically significant lesions per patient were comparable between age groups ([Table 2](#)). Comparing treatment groups within each age group the patients <78 years had significantly more lesions with diameter stenosis ≥90% in the PCI group compared with the conservative treatment group (66% vs 46%, *P* = .042), whereas the occurrence of diameter stenosis ≥90% was well-balanced between PCI and conservative treatment in the other age groups ([Supplementary Table S5](#)). The timing of PCI relative to TAVI was comparable between the age groups. Likewise, complete revascularization was achieved at similar rates between groups. The patients aged 78–81 years had significantly fewer balloon-expandable heart valves compared with the three other age groups ([Table 2](#)).

Clinical outcomes according to age

The median follow-up was 2 years [interquartile range (IQR): 1–4 years], with 100% follow-up rate. When adjusting for significant differences in baseline characteristics and angiographic findings the hazard risk of MACE was higher for patients aged ≥85 compared to those aged <78 years (HR: 1.70, 95% CI: 1.00–2.87, *P* = .048) ([Table 3](#)). The adjusted hazard risk of MACE was 1.58 (95% CI: 0.93–2.69, *P* = .089) and 1.59 (95% CI: 0.93–2.73, *P* = .089) for patients aged 78–81 years and 82–84 years, respectively, compared to patients aged <78 years. The adjusted hazard risk of myocardial infarction was 2.98 (95% CI: 1.08–8.24, *P* = .036) and 3.24 (95% CI: 1.16–9.01, *P* = .025) for patients aged 78–81 years and 82–84 years, respectively, compared to patients aged <78 years ([Table 3](#)).

Impact of age on outcomes following PCI vs conservative treatment

When dividing the patients into four age groups (<78, 78–81, 82–84, and ≥85) it was observed that the difference in the primary endpoint comparing PCI and conservative treatment was most pronounced in patients aged 78–81 years ([Table 4](#)). Among patients 78–81 years, the primary endpoint occurred in 17% of those treated with PCI and

Table 1 Characteristics of the patients at baseline.^a

Characteristic	Q1 < 78 years (N = 103)	Q2 78–81 years (N = 120)	Q3 82–84 years (N = 106)	Q4 ≥ 85 years (N = 126)	P-value ^b
Median age (IQR)—yr	76 (73, 77)	79 (79, 81)	83 (82, 84)	87 (86, 88)	<.001*
Female sex—no. (%)	31 (30)	38 (32)	37 (35)	42 (33)	.89
Median body-mass index (IQR) ^c	28 (25, 32)	27 (24, 29)	26 (24, 29)	26 (23, 28)	<.001*
Median STS-PROM score (IQR)—% ^d	2 (2, 4)	3 (2, 4)	3 (2, 4)	3 (3, 5)	<.001*
New York Heart Association class—no. (%)					.84
I	8 (8)	13 (11)	12 (11)	11 (9)	
II	43 (42)	54 (45)	54 (51)	60 (48)	
III	50 (49)	50 (42)	38 (36)	54 (43)	
IV	2 (2)	3 (3)	2 (2)	1 (1)	
Median creatinine level (IQR)—μmol/liter	87 (74, 104)	91 (72, 109)	91 (74, 109)	86 (74, 109)	.69
Median aortic-valve area (IQR)- cm ²	0.70 (0.60, 0.83)	0.70 (0.60, 0.80)	0.70 (0.53, 0.80)	0.70 (0.51, 0.80)	.14
Median peak aortic-valve gradient (IQR)—mm Hg	77 (66, 90)	74 (63, 86)	75 (65, 93)	75 (66, 87)	.77
Median left ventricular ejection fraction (IQR)—%	60 (50, 60)	60 (48, 60)	60 (50, 60)	55 (50, 60)	.42
Medical history—no. (%)					
History of PCI	24 (23)	13 (11)	15 (14)	13 (10)	.022*
History of myocardial infarction	9 (9)	11 (9)	8 (8)	10 (8)	.97
History of CABG	7 (7)	6 (5)	1 (1)	3 (2)	.09
Treatment of hypercholesterolaemia	83 (81)	96 (80)	71 (67)	77 (61)	.001*
Diabetes mellitus	32 (31)	41 (34)	26 (25)	21 (17)	.011*
Treatment of hypertension	77 (75)	86 (72)	76 (72)	87 (69)	.82
Current or former smoking	61 (59)	67 (56)	57 (54)	61 (48)	.41
History of stroke or transient ischaemic attack	28 (27)	25 (21)	20 (19)	22 (17)	.30
Previous malignant disease	24 (23)	20 (17)	22 (21)	24 (19)	.65
Chronic obstructive pulmonary disease	38 (37)	29 (24)	19 (18)	27 (21)	.009*
Atrial fibrillation	30 (29)	42 (35)	35 (33)	48 (38)	.55
Peripheral artery disease	13 (13)	15 (13)	10 (9)	7 (6)	.22
Treatment with aspirin	58 (56)	62 (52)	66 (62)	68 (54)	.42
Treatment with oral anticoagulants	27 (26)	45 (38)	33 (31)	48 (38)	.19

CABG, coronary-artery bypass graft; IQR, interquartile range; PCI, percutaneous coronary intervention; Q1–Q4, 1st–4th Quartile; STS-PROM, the Society of Thoracic Surgeons Predicted Risk of Mortality.

^aPercentages may not total 100 because of rounding.

^bWilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

^cThe body mass index is calculated as the weight in kilograms divided by the square of the height in metres.

^dThe Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score ranges from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure (low risk is defined as a score ≤2%, intermediate risk >2 to 4%, and high risk as score of >4%).

*a P-value < .05 was considered statistically significant

42% of those receiving conservative treatment (HR: 0.36, 95% CI: 0.17–0.77, $P = .008$). For the youngest patients aged <78 years, the primary endpoint occurred in 23% in the PCI group and 24% in the conservative treatment group (HR: 1.08, 95% CI: 0.48–2.40, $P = .86$). For patients aged 82–84 years, the primary endpoint occurred in 27% in the PCI group and 40% in the conservative treatment group (HR: 0.69, 95% CI: 0.35–1.35, $P = .28$). And for the oldest patients aged ≥85 years, the primary endpoint occurred in 37% in the PCI group and 34% in the conservative treatment group (HR: 0.90, 95% CI: 0.50–1.62, $P = .73$) (Table 4). The cumulative incidence of the primary endpoint,

MACE, is shown in Figure 1A, 1B, 1C and 1D comparing PCI and conservative treatment for patients aged <78, 78–81, 82–84, and ≥85 years, respectively.

PCI was associated with a significantly lower risk of urgent revascularization and any revascularization in patients aged 78–81 years compared with conservative treatment (2% vs 18%, HR: 0.09, 95% CI: 0.01–0.73, $P = .024$) and (2% vs 25%, HR: 0.06, 95% CI: 0.01–0.48, $P = .008$), respectively. Similarly, there was a significantly reduced risk of any revascularization in the PCI group among patients aged 82–84 years (4% vs 26%, HR: 0.13, 95% CI: 0.03–0.56, $P = .007$) but the lower

Table 2 Angiographic findings and characteristics of the PCI and TAVI procedures.^a

Variable	Q1 < 78 years (N = 103)	Q2 78–81 years (N = 120)	Q3 82–84 years (N = 106)	Q4 ≥ 85 years (N = 126)	P-value ^b
Angiographic findings					
Median no. of physiologically significant lesions per patient (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–2)	.26
No. of patients with a lesion with fractional flow reserve ≤0.80—no./total no. (%)	60/103 (58)	80/120 (67)	55/106 (52)	68/126 (54)	.11
No. of patients with a lesion with diameter stenosis ≥90%—no./total no. (%)	58/103 (56)	66/120 (55)	62/106 (58)	85/126 (67)	.19
Median largest diameter stenosis (IQR)—%	90 (70–90)	90 (70–90)	90 (78–90)	90 (80–91)	.07
Median SYNTAX score (IQR) ^c	9 (6–14)	10 (6–15)	9 (6–12)	9 (6–14)	.49
Randomization					.54
PCI no. (%)	53 (51)	53 (44)	56 (53)	65 (52)	
Conservative treatment no. (%)	50 (49)	67 (56)	50 (47)	61 (48)	
PCI procedure					
Median no. of days from randomization to PCI (IQR)	9 (1–28)	13 (1–26)	11 (1–25)	7 (0–26)	.52
Timing of PCI—no./total no. (%) ^d					.61
After	3/53 (6)	6/53 (12)	5/56 (9)	6/52 (10)	
Before	42/53 (81)	37/53 (73)	37/56 (66)	48/52 (76)	
Concomitant with TAVI	7/53 (13)	8/53 (16)	14/56 (25)	9/52 (14)	
Complete revascularization achieved—no./total no. (%) ^d	45/53 (90)	43/53 (86)	52/56 (93)	55/52 (86)	.60
TAVI procedure					
Median no. of days from randomization to TAVI (IQR)	31 (6–57)	24 (7–60)	26 (1–61)	33 (3–63)	.78
Balloon-expandable heart valve—no. (%)	42 (41)	37 (31)	52 (49)	54 (43)	.04

IQR, interquartile range; PCI, percutaneous coronary intervention; Q1–Q4, 1st–4th Quartile; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TAVI, transcatheter aortic-valve implantation.

^aPercentages may not total 100 because of rounding.

^bWilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

^cThe Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score and higher scores indicating more complex coronary anatomy.

^dPercentages are calculated from the number of patients who were randomized to PCI. Complete revascularization was considered to be achieved if all stenoses in vessels with a diameter of more than 2.5 mm were revascularized.

risk for urgent revascularization was not significant in this age group (4% vs 10%, HR: 0.36, 95% CI: 0.07–1.84, $P = .22$). Among patients 78–81 years, PCI was also associated with a reduced risk of the combined endpoint of cardiovascular death or myocardial infarction (8% vs 30%, HR: 0.23, 95% CI: 0.08–0.68, $P = .008$) compared with conservative treatment.

Any bleeding event, including minor, major, life-threatening, or disabling bleeding, occurred numerically more frequent in the PCI group among patients <78 years compared with conservative treatment (28% vs 14%, HR: 2.43, 95% CI: 0.99–5.96, $P = .053$). Similarly, there was a numerically higher risk for any bleeding event among patients 78–81 years in the PCI group compared with conservative treatment (26% vs 13%, HR: 2.12, 95% CI: 0.92–4.91, $P = .08$). However, for patients aged 82–84 and ≥85 years the risk for any bleeding event was similar between PCI and conservative treatment group (29% vs 28%, HR: 1.03, 95% CI: 0.50–2.11, $P = .94$) and (29% vs 25%, HR: 1.17, 95% CI: 0.59–2.30, $P = .66$), respectively (Table 4).

Age as continuous variable

Figure 2, a cubic spline plot, illustrates the risk of the primary endpoint MACE according to continuous age comparing the two treatment strategies. The U-shape indicates that the patients in the middle of the age spectrum experienced the greatest risk reduction for MACE from PCI while no risk reduction for the primary endpoint was observed among the youngest and the oldest patients in the trial (Figure 2).

Discussion

The study reveals an ambivalent relationship between age and benefit from PCI in TAVI patients with coronary artery disease. The main finding of this trial was that the effect of PCI on reducing the risk of MACE was most pronounced in patients aged 78–84 years while the patients aged <78 and those ≥85 years seemed to derive less or no benefit of PCI in combination with TAVI.

Table 3 Adjusted relative hazard risks comparing age groups

Variable	Q1 < 78 years (N = 103)	Q2 78–81 years (N = 120)	Q3 82–84 years (N = 106)	Q4 ≥ 85 years (N = 126)
Events (%)				
HR (95% CI) ^a				
Primary endpoint: MACE ^b	24 (23%)	37 (31%) 1.58 (0.93–2.69)	35 (33%) 1.59 (0.93–2.73)	45 (36%) 1.70 (1.00–2.87)
Secondary endpoints				
Death from any cause	24 (23%)	27 (22%) 1.09 (0.61–1.92)	23 (22%) 0.93 (0.52–1.69)	41 (33%) 1.49 (0.87–2.55)
Myocardial infarction ^c	5 (5%)	16 (13%) 2.98 (1.08–8.24)	16 (15%) 3.24 (1.16–9.01)	11 (9%) 1.71 (0.58–5.08)
Urgent revascularization ^d	2 (2%)	13 (11%) 7.16 (1.58–32.5)	7 (7%) 3.83 (0.78–18.8)	8 (6%) 3.69 (0.76–18.0)
Death from cardiovascular causes ^e	10 (10%)	13 (11%) 1.40 (0.59–3.30)	14 (13%) 1.54 (0.66–3.58)	13 (10%) 1.24 (0.52–2.97)
Any revascularization	10 (10%)	18 (15%) 2.01 (0.90–4.47)	15 (14%) 1.63 (0.71–3.73)	11 (9%) 0.92 (0.37–2.31)
Stroke	9 (9%)	19 (16%) 2.18 (0.96–4.96)	15 (14%) 1.76 (0.75–4.17)	15 (12%) 1.67 (0.70–3.99)
Death from cardiovascular causes ^e or Myocardial infarction	10 (10%)	24 (20%) 2.50 (1.17–5.31)	26 (25%) 2.94 (1.39–6.23)	20 (16%) 1.85 (0.84–4.08)
Safety endpoints				
Any bleeding event ^f	22 (21%)	23 (19%) 0.96 (0.53–1.74)	30 (28%) 1.47 (0.83–2.59)	34 (27%) 1.30 (0.74–2.29)
Life-threatening or disabling	11 (11%)	7 (6%) 0.64 (0.24–1.69)	13 (12%) 1.35 (0.58–3.14)	12 (10%) 1.00 (0.41–2.44)
Major	2 (2%)	9 (8%) 4.41 (0.93–21.0)	7 (7%) 3.47 (0.70–17.1)	12 (10%) 5.04 (1.08–23.5)
Minor	11 (11%)	8 (7%) 0.63 (0.25–1.60)	13 (12%) 1.26 (0.55–2.87)	14 (11%) 0.97 (0.42–2.21)
Life-threatening, disabling, or major bleeding	13 (13%)	15 (12%) 1.10 (0.52–2.37)	19 (18%) 1.55 (0.75–3.23)	22 (17%) 1.49 (0.72–3.10)
Acute kidney failure	11 (11%)	14 (12%) 1.38 (0.59–3.21)	4 (4%) 0.41 (0.12–1.36)	9 (7%) 0.81 (0.31–2.10)

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; Q1–Q4, 1st–4th Quartile.

^aCox regression model. Adjusted for body mass index, history of percutaneous coronary intervention, treatment for hypercholesterolaemia, diabetes mellitus, chronic obstructive pulmonary disease, balloon-expandable heart valve and lesion with diameter stenosis ≥90%.

^bThe primary endpoint was a major adverse cardiac event (MACE), defined as a composite of death from any cause, myocardial infarction, or urgent revascularization.

^cMyocardial infarction included any spontaneous or periprocedural infarction that occurred less than 72 h after TAVI and less than 48 h after PCI.

^dUrgent revascularization included any revascularization that was performed during an unplanned hospital admission with acute coronary syndrome.

^eDeath from cardiovascular causes included death due to proximate cardiac cause (e.g. myocardial infarction, tamponade, or heart failure), death caused by a noncoronary vascular condition (e.g. neurologic condition, pulmonary embolism, or an aortic or other vascular condition), all procedure-related deaths, all valve-related deaths, sudden death, and death of unknown cause.

^fA patient may have had more than one bleeding event and thus may have events recorded in multiple categories. Bleeding was recorded according to the Valve Academic Research Consortium-2 criteria.¹⁶

Clinical outcomes across the age spectrum

While the age group 78–81 years showed a significant reduction of MACE with PCI, the patients aged 82–84 years also had a marked numerical reduction of MACE between the two treatment groups, 27% and 40% in the PCI group and conservative treatment group, respectively. The analysis of age as a continuous variable in the cubic spline

model supported this observation thus suggesting that PCI is beneficial for TAVI patients 78–84 years. We can only speculate on the reason behind the counterintuitive finding of a less beneficial outcome for the younger patients (<78 years). One explanation could be a high comorbidity burden in this group. Patients <75 years refused for surgical aortic valve replacement likely represent a selected group with more

Table 4 Unadjusted relative hazard risks of PCI vs conservative treatment

Variable	Q1 < 78 years (N = 103)	Q2 78–81 years (N = 120)	Q3 82–84 years (N = 106)	Q4 ≥ 85 years (N = 126)
Events % (PCI/Conservative)				
HR (95% CI)^a				
Primary endpoint: MACE ^b	(23/24) 1.08 (0.48–2.40)	(17/42) 0.36 (0.17–0.77)	(27/40) 0.69 (0.35–1.35)	(37/34) 0.90 (0.50–1.62)
Secondary endpoints				
Death from any cause	(23/24) 1.08 (0.48–2.41)	(17/27) 0.66 (0.30–1.47)	(16/28) 0.61 (0.26–1.41)	(35/30) 1.01 (0.54–1.88)
Myocardial infarction ^c	(6/4) 1.54 (0.26–9.25)	(8/18) 0.39 (0.13–1.21)	(11/20) 0.54 (0.20–1.50)	(6/11) 0.49 (0.14–1.67)
Urgent revascularization ^d	(0/4) -	(2/18) 0.09 (0.01–0.73)	(4/10) 0.36 (0.07–1.84)	(3/10) 0.29 (0.06–1.44)
Death from cardiovascular causes ^e	(9/10) 1.09 (0.31–3.76)	(6/15) 0.39 (0.11–1.41)	(11/16) 0.73 (0.25–2.09)	(9/11) 0.66 (0.22–1.98)
Any revascularization	(0/20) -	(2/25) 0.06 (0.01–0.48)	(4/26) 0.13 (0.03–0.56)	(5/13) 0.33 (0.09–1.23)
Stroke	(8/10) 0.81 (0.22–3.04)	(11/19) 0.56 (0.21–1.46)	(11/18) 0.60 (0.21–1.70)	(11/13) 0.73 (0.26–2.01)
Death from cardiovascular causes ^e or Myocardial infarction	(9/10) 1.08 (0.31–3.73)	(8/30) 0.23 (0.08–0.68)	(21/28) 0.79 (0.37–1.72)	(12/20) 0.53 (0.22–1.31)
Safety endpoints				
Any bleeding event ^f	(28/14) 2.43 (0.99–5.96)	(26/13) 2.12 (0.92–4.91)	(29/28) 1.03 (0.50–2.11)	(29/25) 1.17 (0.59–2.30)
Life-threatening or disabling	(11/10) 1.27 (0.39–4.18)	(8/4) 1.70 (0.38–7.60)	(13/12) 1.03 (0.35–3.08)	(12/7) 1.86 (0.56–6.19)
Major	(2/2) 1.05 (0.07–16.76)	(8/7) 1.00 (0.27–3.72)	(7/6) 1.29 (0.29–5.78)	(6/13) 0.43 (0.13–1.43)
Minor	(19/2) 10.77 (1.38–84.22)	(11/3) 3.98 (0.80–19.71)	(9/16) 0.54 (0.18–1.67)	(14/8) 1.59 (0.53–4.77)
Life-threatening, disabling, or major bleeding	(13/12) 1.24 (0.42–3.69)	(15/10) 1.47 (0.53–4.07)	(20/16) 1.27 (0.51–3.16)	(17/18) 0.90 (0.39–2.08)
Acute kidney failure	(6/16) 0.41 (0.11–1.56)	(8/15) 0.48 (0.15–1.53)	(2/6) 0.31 (0.03–2.94)	(6/8) 0.62 (0.17–2.32)

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; Q1–Q4, 1st–4th Quartile.

^aCox regression model.^bThe primary endpoint was a major adverse cardiac event (MACE), defined as a composite of death from any cause, myocardial infarction, or urgent revascularization.^cMyocardial infarction included any spontaneous or periprocedural infarction that occurred less than 72 h after TAVI and less than 48 h after PCI.^dUrgent revascularization included any revascularization that was performed during an unplanned hospital admission with acute coronary syndrome.^eDeath from cardiovascular causes included death due to proximate cardiac cause (e.g. myocardial infarction, tamponade, or heart failure), death caused by a noncoronary vascular condition (e.g. neurologic condition, pulmonary embolism, or an aortic or other vascular condition), all procedure-related deaths, all valve-related deaths, sudden death, and death of unknown cause.^fA patient may have had more than one bleeding event and thus may have events recorded in multiple categories. Bleeding was recorded according to the Valve Academic Research Consortium-2 criteria.¹⁶

severe comorbidity, which may explain the observed trend of a less benefit from PCI. The European guidelines that were in force during the period the NOTION-3 trial recruited patients, recommend SAVR for patients <75 years with a low surgical risk and TAVI for those >75 years or at high surgical risk.¹ This has recently and after publication of NOTION-3 been changed to 70 years.⁵ In this study patients <78 years were at baseline more likely to have chronic obstructive

pulmonary disease, higher body mass index, and prior PCI compared with the older groups. But when comparing surgical risk through the STS-PROM score the patients <78 years had the lowest STS-PROM scores compared with the three older age groups indicating low surgical risk in the youngest patients. Another explanation could be that the coronary artery disease in the youngest patients (<78 years) might be more mild and/or stable and therefore lead to fewer adverse events

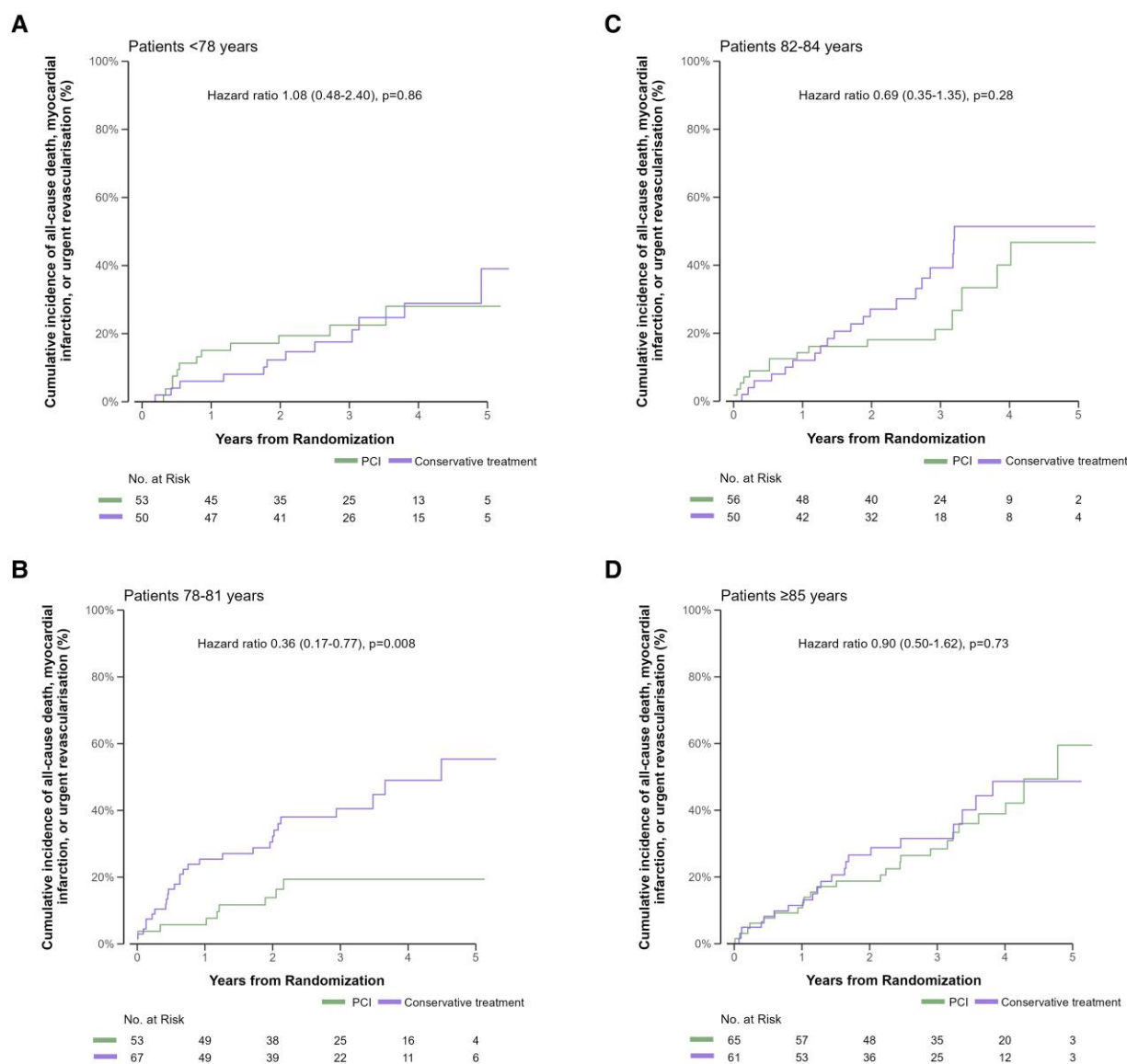


Figure 1 Cumulative incidence of MACE. Kaplan–Meier curves show cumulative incidence of MACE in (A) patients <78 years, (B) patients 78–81 years, (C) patients 82–84 years and (D) patients ≥85. HR and P-values are calculated from Cox proportional hazards model. CI denotes confidence interval, HR hazard ratio, and MACE major adverse cardiac events and is defined as a composite of death from any cause, myocardial infarction, or urgent revascularization. Created in BioRender. Nygaard, K. (<https://BioRender.com/tnpn4b1>) is licensed under CC BY 4.0.

and therefore fewer adverse events to prevent with PCI. Myocardial infarction and urgent revascularization were the main drivers behind the risk reduction in the primary endpoint MACE in the patients 78–81 years, which seemed to benefit the most from PCI. Looking at the crude numbers it is seen that the youngest patients (<78 years) experienced fewer adverse clinical events in general compared to the three older age groups (≥78 years). This was the case for both treatment groups. It is also striking that the occurrence of diameter stenosis ≥90% was well-balanced between PCI and conservative treatment in the three age groups with patients ≥78 years whereas patients <78 years had an uneven distribution of high-grade (≥90%) stenosis with 66% of patients in the PCI group having a lesion with diameter stenosis ≥90% and only 46% in the conservative treatment group. This imbalance in high-grade lesions between the two treatment groups indicating

milder coronary artery disease in the conservative treated group could be the reason behind the observed fewer adverse clinical events in the youngest subgroup (<78 years). But even when adjusting for the number of lesions ≥90% the patients 78–81 had a higher risk of both myocardial infarction and urgent revascularization compared with the patients <78 years. The lower risk for adverse clinical events in the youngest patients (<78 years) adjusted for lesion severity indicates that the explanation behind the observed less beneficial outcome comparing PCI with conservative treatment can not only be found in the imbalance in high-grade lesions between the two treatment groups. Maybe a median follow-up time of 2 years is simply too short to reveal a difference between the two treatment strategies in the youngest patients.

For patients ≥85 years, we found no difference in the risk of MACE between the two treatment groups. Patients over 85 years have already

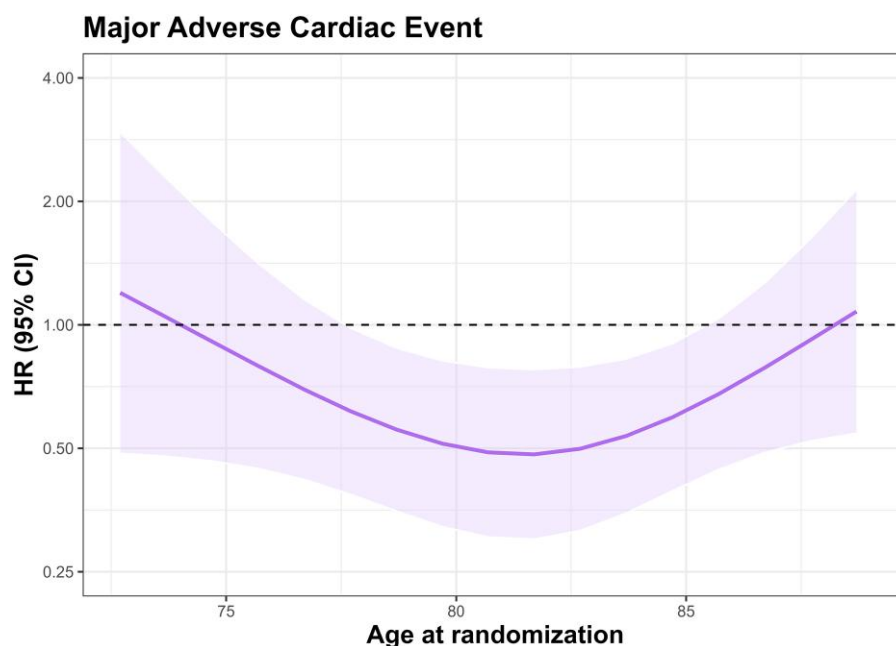


Figure 2 Adjusted hazard risk of MACE comparing PCI with conservative treatment according to continuous age. The risk differences between PCI and conservative treatment according to age. The curve was derived from the adjusted Cox proportional hazard model. Adjusted for body mass index, history of percutaneous coronary intervention, treatment for hypercholesterolaemia, diabetes mellitus, chronic obstructive pulmonary disease, balloon-expandable heart valve and lesion with diameter stenosis $\geq 90\%$. CI denotes confidence interval, HR hazard ratio, and MACE major adverse cardiac events and is defined as a composite of death from any cause, myocardial infarction, or urgent revascularization and PCI denotes percutaneous coronary intervention. Created in BioRender. Nygaard, K. (<https://BioRender.com/6xywrs1>) is licensed under CC BY 4.0.

outlived the median life expectancy in the Nordic countries¹⁷ and this reduced long-term impact of PCI may be explained by the shorter life expectancy and high mortality in this population, which is supported by the high overall mortality rate among patients ≥ 85 years in this trial (33%). The results suggest that PCI is effective in preventing the need for urgent revascularization in all age groups compared with conservative treatment when looking at the crude numbers. The interesting question is whether this prevention of subsequent urgent revascularization can prevent myocardial infarction and death. Looking at the 10-year follow-up for the FAME 2 trial, the benefit from PCI when treating stable coronary artery disease seems to be found primarily in the prevention of urgent revascularization.¹⁸ In this present trial, for the patients in the age group 78–81 years, treatment with PCI is not only associated with a lower risk of subsequent urgent revascularization compared with conservative treatment but it is also associated with a lower risk of the combined endpoint death from cardiovascular causes or myocardial infarction and the primary endpoint death from any cause, myocardial infarction, or urgent revascularization. These results suggest that for some patients an early invasive approach is lifesaving. The results presented in this trial should be interpreted carefully since the division of the patients into four age groups has markedly reduced the statistical power. But these findings highlight the need for larger trials or pooled analyses to better identify patients who benefit from an early invasive approach.

Safety of PCI across the age spectrum

There is a general reluctance to perform invasive procedures on elective indications for coronary artery disease in elderly patients.¹⁹ Indeed, elderly patients are more likely to have age-related comorbidities and have higher incidences of procedural complications than younger

patients.^{12,13,20} Despite this, several previous studies have reported reasonably low incidences of complications and beneficial clinical outcomes following PCI compared with conservative strategies for treating coronary artery disease in elderly patients.^{19,21,22} In this study, we found that bleeding occurred more frequently in the two age groups with patients ≥ 82 years than the two with patients <82 years. However, when adjusting for significant differences in baseline characteristics there was no difference in bleeding risk between age groups. In the two younger age groups with patients <82 years, PCI was associated with a higher prevalence of any bleeding compared with conservative treatment. Granulating bleeding events into life-threatening or disabling, major and minor bleedings show that the higher risk of bleeding among patients <82 years treated with PCI was mainly in minor bleedings. In contrast, among patients ≥ 82 years there was no difference in the risk of any bleeding when comparing PCI with conservative treatment. Advanced age is associated with structural changes in the vessel wall, alterations at the molecular level in the haemostatic system and functional decline of organs all resulting in a general higher risk of both haemorrhagic and thrombotic events.¹² Despite this general higher risk of bleeding with increasing age, data from this study indicate that when comparing PCI with conservative treatment an invasive treatment strategy was not associated with an increased risk of bleeding for patients ≥ 82 years. In fact, treatment with PCI only increased the risk of bleeding for patients <82 years. These findings support previous data indicating that PCI is a safe option for elderly patients^{19,21,22} even for those with aortic stenosis.

Clinical importance

The findings from this study reveal an ambivalent relationship between age and benefit from an invasive strategy in TAVI patients with coronary

artery disease. Analysing age as a continuous variable and as four age groups suggest a potential age-specific effect. Patients aged 78–84 seem to derive the greatest benefit of PCI in combination with TAVI, while those <78 and those ≥85 years seem to derive less or no benefit. Although chronological age is commonly used alongside other factors to estimate life expectancy and risk of complications, it may not fully capture the multifactorial nature of ageing. Findings from this study suggest that age is a complicated variable to incorporate into the medical judgment on how we should approach coronary artery disease in TAVI patients. However, advanced age is associated with reduced life expectancy, which remains a key consideration in treatment decisions. The decision to perform PCI should always be based on an individualized assessment, integrating life expectancy, risk factors, comorbidities, complexity and severity of the coronary artery disease, bleeding risk, and overall health status.

Limitations

Our study has several limitations. First, the risk of type I errors is inherently increased in a secondary analysis. Second, the study is underpowered to perform a formal interaction analysis which would have provided insightful knowledge. Third, when dividing the patients into four age groups the statistical power is markedly reduced. Therefore, the risk of type II errors must be considered and the results for any of these four age groups comparing the clinical outcomes following PCI vs conservative treatment should be interpreted carefully. Fourth, although the patient population represents a relatively contemporary cohort, with the enrolment of patients from 2017 through 2022, some clinical guidelines have changed over time such as the recommended antithrombotic treatment regimen and the age cut-off for TAVI.^{1,5} Fifth, the median follow-up time of 2 years may not be sufficient to reveal the long-term impact of the two different treatment strategies. Especially in the youngest subgroup <78 years who in general experienced fewer clinical events in both treatment groups. Sixth, this study predominantly includes patients with single-vessel coronary artery disease all with non-left-main coronary artery disease, and results may differ with multi-vessel or left main involvement.

Conclusions

Our findings suggest that in patients with coronary artery disease undergoing TAVI the benefit of PCI compared with conservative treatment on the composite of all-cause death, myocardial infarction, or urgent revascularization was most pronounced among patients aged 78–84 years while no risk reduction for the primary endpoint was observed among the patients aged <78 and those ≥85 years. However, further confirmatory data from larger clinical studies is needed to confirm these results.

Impact on daily practice

Our findings suggest that the discussion on invasive vs conservative treatment for coronary artery disease in patients with severe aortic stenosis planned for TAVI should focus less on chronological age and more on life expectancy, angiographic characteristics, clinical status and comorbidities.

Author contributions

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Supplementary data

Supplementary data are available at *European Heart Journal – Valvular and Structural Heart Disease* online.

Declarations

Data Availability

The data underlying this article cannot be shared publicly due the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Disclosure of Interest

Lønborg reports receiving an unrestricted grant from Boston Scientific and a research grant from Hjertereforeningen. J. Lønborg also reports receiving honoraria for lectures and presentations and support for travel from Boston Scientific. In addition, J. Lønborg serves as the Head of the Danish Society of Cardiovascular group for Interventional Cardiology. S. Koul reports receiving speaking fees from Chiesi pharma and Amarin pharma. S. Koul also reports serving in the advisory board in Novo Nordisk and Amarin pharma. L. Sondergaard reports serving as Chief Medical Officer at Abbott Structural Heart. E. Christensen reports receiving institutional grants from Abbott and Meril. In addition, E. Christensen reports receiving honoraria for lectures from Abbott. O. Kajander reports receiving consulting fees from Boston Scientific and Cardirad Oy. O. Kajander also reports receiving support for travel from Abbott Vascular. R. Linder reports receiving honoraria for lectures from Boston Scientific and Edwards. R. Sørensen reports receiving support for travel from Abbott and serving as a member of Data Safety and Monitoring Board in the Artimes trial. O. De Backer reports receiving consulting fees and speakers fee from

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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