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ORIGINAL RESEARCH

STRUCTURAL

Percutaneous Coronary Intervention in Frail Patients Undergoing Transcatheter Aortic Valve Replacement

A NOTION-3 Substudy

Hanna Ratcovich, MD, PhD,[a] Lene Holmvang, MD, DMSc,[a] Golnaz Sadjadieh, MD, PhD,[a] Reza Jabbari, MD, PhD,[a] Charlotte Glinge, MD, PhD,[a] Muhammad Sabbah, MD, PhD,[a] Karsten Tange Veien, MD,[b] Matti Niemela, MD,[c] Phillip Freeman, MD, PhD,[d] Rickard Linder, MD, PhD,[e,f] Rikke Sørensen, MD, PhD,[a] Dan Ioanes, MD,[g] Christian Juhl Terkelsen, MD, PhD, DMSc,[h,i] Julia Ellert-Gregersen, MD, PhD,[b] Evald Christiansen, MD, PhD,[h] Ashkan Eftekhari, MD, PhD,[d] Jarkko Piuhola, MD, PhD,[c] Olli Kajander, MD, PhD,[j,k] Sasha Koul, MD, PhD,[l] Mikko Savontaus, MD,[m] Pasi Karjalainen, MD, PhD,[n] Andreas Rück, MD, PhD,[e,f] Oskar Angerås, MD, PhD,[g,o] Gintautas Bieliauskas, MD,[a] Troels Højsgaard Jørgensen, MD, PhD,[a] Lars Søndergaard, DMSc,[p] Ole De Backer, MD, PhD,[a,q] Thomas Engstrøm, MD, PhD, DMSc,[a] Jacob Lønborg, MD, PhD, DMSc[a]

ABSTRACT

BACKGROUND Frailty is an important predictor of outcomes in patients with coronary artery disease (CAD) and following transcatheter aortic valve replacement (TAVR). The NOTION-3 (Third Nordic Aortic Valve Intervention) trial demonstrated that performing percutaneous coronary intervention (PCI) in addition to TAVR reduced the risk for major adverse cardiac events (MACE). Whether this benefit applies to frail patients remains uncertain.

OBJECTIVES The aim of this study was to evaluate efficacy and safety of PCI in frail TAVR patients with CAD.

METHODS NOTION-3 was an international, open-label, randomized superiority trial enrolling patients with CAD and severe aortic stenosis undergoing TAVR. Patients were randomized 1:1 to PCI or conservative treatment. Frailty was assessed post hoc using a calculated frailty score derived from baseline data on symptom-related limitations, daily function, and quality of life. Primary endpoint was a composite of all-cause mortality, myocardial infarction (MI), and urgent coronary revascularization. Safety endpoints included bleeding and acute kidney injury.

RESULTS Frailty data were available for 407 patients (90%), of whom 130 (32%) were frail. During median follow-up of 2 years (Q1-Q3: 1-4 years), PCI reduced MACE in nonfrail patients (15% vs 33%; HR: 0.42; 95% CI: 0.25-0.69; $P < 0.001$), as well as death of any cause ($P = 0.019$), MI ($P = 0.004$), and urgent revascularization ($P = 0.005$). No differences were observed in frail patients. In contrast, frail patients undergoing PCI had more bleeding events (HR: 2.51; 95% CI: 1.23-5.11; $P = 0.011$).

CONCLUSIONS In nonfrail patients with CAD undergoing TAVR, PCI lowered the risk for MACE, all-cause mortality, and MI compared to conservative treatment. In frail patients, PCI increased bleeding without clinical benefit. These findings require confirmation in larger prospective studies. (JACC Cardiovasc Interv. 2026;19:828–839)

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Frailty is a multidimensional clinical syndrome commonly observed in older adults, characterized by slowness, weakness, exhaustion, weight loss, malnutrition, poor endurance, and physical inactivity. It reflects a diminished physiological reserve and a reduced capacity to withstand stressors.[1] Frailty is highly prevalent among elderly patients with cardiovascular disease and is associated with an increased risk for major adverse cardiac events (MACE) and bleeding complications.[2-4]

In patients with severe aortic stenosis undergoing transcatheter aortic valve replacement (TAVR), frailty status has emerged as a powerful predictor of both early and late adverse outcomes following the procedure.[5-7] Furthermore, frailty is often accompanied by a higher comorbidity burden and has a greater prevalence in women.[8]

Coronary artery disease (CAD) is prevalent in more than 50% of patients undergoing TAVR.[9] The NOTION-3 (Third Nordic Aortic Valve Intervention) trial demonstrated that percutaneous coronary intervention (PCI) performed prior to or in conjunction with TAVR is associated with a lower risk for adverse events, including all-cause mortality, myocardial infarction (MI), and need for repeat revascularization at 2-year follow-up, compared with conservative treatment alone.[10] However, frailty is prevalent in patients undergoing TAVR, and these individuals may face greater challenges during recovery and could potentially benefit from less invasive therapeutic approaches. Also, frail patients are often underrepresented in clinical trials, leaving a gap in evidence regarding the risk-benefit profile of PCI in this high-risk subgroup.[11] Thus, the optimal management strategy for frail patients remains uncertain.

The aim of this NOTION-3 substudy was to evaluate the efficacy and safety of PCI performed in relation to TAVR specifically in frail patients with concomitant CAD.

METHODS

This is a substudy from the NOTION-3 trial, an international, open-label, randomized superiority trial enrolling patients with at least 1 significant coronary artery stenosis and symptomatic severe aortic stenosis undergoing TAVR. The trial protocol has been published.[12] Briefly, eligible patients selected for TAVR by the local heart team who had at least 1 significant stenosis were randomized 1:1 to PCI or conservative medical treatment after providing informed consent. Significant CAD was defined as fractional flow reserve ≤0.80 or ≥90% diameter stenosis by visual assessment.

Exclusion criteria included life expectancy <1 year, severe renal failure (estimated glomerular filtration rate <20 mL/min/1.73 m^2 body surface area), acute coronary syndrome within 14 days before TAVR, and significant left main coronary artery stenosis.

In patients randomized to PCI, complete revascularization was intended of all PCI-eligible lesions in coronary arteries ≥2.5 mm in diameter that met the fractional flow reserve or angiographic criteria. Incomplete revascularization was permitted only for ineligible lesions, and treatment of chronic total occlusions was at the operator's discretion. Post-PCI, patients received lifelong aspirin at a dose of 75 mg once daily as well as clopidogrel at a dose of 75 mg once daily for 6 months, and those on oral anti-

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFS = Clinical Frailty Scale

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TAVR = transcatheter aortic valve replacement

VARC-2 = Valve Academic Research Consortium-2

From the [a]Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [b]Department of Cardiology, Odense University Hospital, Odense, Denmark; [c]Research Unit of Biomedicine and Internal Medicine, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; [d]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; [e]Department of Medicine, Karolinska Institute, Stockholm, Sweden; [f]Division of Cardiovascular Medicine, Department of Clinical Sciences, Karolinska Institute, Danderyd University Hospital, Stockholm, Sweden; [g]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; [h]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [i]The Danish Heart Foundation, Copenhagen, Denmark; [j]Heart Hospital, Tampere University Hospital, Wellbeing Services County of Pirkanmaa, Tampere, Finland; [k]The Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [l]Department of Cardiology, Clinical Sciences, Lund University, Skane University Hospital, Lund, Sweden; [m]Heart Center, Turku University Hospital, Turku, Finland; [n]Heart and Lung Center, Helsinki University Hospital and Helsinki University, Helsinki, Finland; [o]Department of Molecular and Clinical Medicine, Institute of Medicine, Gothenburg University, Gothenburg, Sweden; [p]Abbott Cardiovascular, Santa Clara, California, USA; and the [q]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

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

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coagulation received aspirin for 1 month and clopidogrel for 6 months, later shortened to 7 days of aspirin when the AUGUSTUS trial was published, according to updated guidelines.[13]

For patients assigned to the conservative treatment group, lifelong aspirin was administrated at a dose of 75 mg once daily, as well as clopidogrel at a dose of 75 mg once daily for 3 months, according to routine treatment after TAVR. However, after the publication of the POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial in 2020,[14] patients were treated with aspirin alone. For patients on anticoagulation therapy, clopidogrel was given once daily for 3 months, but this was changed to anticoagulation alone after the presentation of the POPular-TAVI trial.[15]

FRAILTY ASSESSMENT. Frailty status was evaluated as a post hoc analysis of variables collected at baseline at the time of randomization. A calculated frailty score inspired by the levels of the Clinical Frailty Scale (CFS)[16] was performed by creating a sum of variables collected from baseline data that were related to frailty. The sum was obtained by patient-reported outcomes on quality of life from the EQ-5D-5L questionnaire covering variables such as difficulties with daily activities, level of limitation due to pain, and level of help with personal care. Also, symptom-related limitations due to dyspnea from the NYHA functional classification, angina from the Canadian Cardiovascular Society angina score, as well as from the Seattle Angina Questionnaire were included. Each of the mentioned variables was translated into points, where no limitations or no symptoms were graded as 0 or 1, and severe symptoms or impairment was given the highest points (4 or 5 depending on the number of levels in each category). A sum of 9 was the lowest score, and 48 was the highest possible score (Supplemental Table 1, Supplemental Figure 1). Patients with missing values for any of the variables were excluded from this study.

The derived calculated frailty scores were used to divide patients into tertiles. Patients in the 2 lowest tertiles were defined as nonfrail and those in the highest tertile as frail (Supplemental Table 2).

A total of 131 patients included from the top recruiting center had data available for the calculated frailty score as well as frailty assessed using the CFS as part of their clinical work-up before TAVR. This frailty assessment was used to support the distribution of frailty on the basis of the calculated frailty score. A CFS score ≥5 was defined as frail, according to precious publications.[7,17]

ENDPOINTS. The primary endpoint was MACE, defined as a composite of all-cause mortality, MI, or urgent coronary revascularization (any revascularization due to acute coronary syndrome) and was assessed until the last patient had completed 1-year follow-up after TAVR.

In the present substudy, secondary and safety endpoints included the individual components of the primary endpoint, death of cardiovascular causes, stroke, bleeding according to the Valve Academic Research Consortium-2 (VARC-2) definitions[18] (Supplemental Table 3), and acute kidney failure. Bleeding events were reported by research nurses and validated by the clinical events committee.

STATISTICAL ANALYSIS. Variables and endpoints were analyzed across frailty strata and treatment arms. Categorical data are presented as number (percentage) and were compared using the chi-square test. For continuous data, normally distributed data are presented as means and non-normally distributed data as median (Q1-Q3) and were compared using Student's *t*-test and the Wilcoxon rank sum test, respectively. *P* values ≤0.05 were considered to indicate statistical significance.

A restricted cubic spline curve was used to assess the impact of calculated frailty score on the primary endpoint on a continuous scale. The curve was derived from the unadjusted Cox proportional hazards model. Post hoc power and interaction analyses for crude event rates at 24 months were performed to ensure power for the frailty assessment tool.

To explore the association between treatment arms and primary, secondary, and safety endpoints, Cox regression was used to calculate the unadjusted HRs and *P* values. Cox regression models adjusted for death of any cause were used when associations between PCI treatment and severe or life-threatening bleeding and any revascularization in frail patients were further investigated. The proportional hazards assumptions were tested on the basis of scaled Schoenfeld residuals.

For secondary endpoints except for death of any cause, the competing risk for death of any cause was accounted for using the Fine and Gray model. Conservative treatment was used as reference, and patients were censored at the time of an event.

The cumulated incidences of primary endpoint, death of any cause, and bleeding (severe or life-threatening bleeding according to the VARC-2) were evaluated using Kaplan-Meier methodology.

TABLE 1 Baseline Demographics in Patients Stratified in Tertiles According to Calculated Frailty Score

	Tertile 1 (n = 152)	Tertile 2 (n = 125)	Tertile 3 (n = 130)	*P* Value
Age, y	82 (78-85)	81 (77-84)	81 (78-85)	0.332
Female	35 (23.0)	44 (35.2)	52 (40.0)	0.007
BMI, kg/m^2	26 (23.7-28.5)	26.6 (24.2-29.8)	27 (24.2-29.8)	0.075
STS score	2.5 (1.8-3.8)	2.8 (1.8-3.7)	3.3 (2.2-4.8)	0.001
NYHA functional class				<0.001
I	25 (16.4)	6 (4.8)	5 (3.8)	
II	83 (54.6)	71 (56.8)	45 (34.6)	
III	40 (26.3)	47 (37.6)	79 (60.8)	
IV	4 (2.6)	1 (0.8)	1 (0.8)	
CCS class				<0.001
0	82 (53.9)	52 (41.6)	46 (35.4)	
1	36 (23.7)	31 (24.8)	30 (23.1)	
2	29 (19.1)	37 (29.6)	33 (25.4)	
3	5 (3.3)	5 (4.0)	18 (13.8)	
4	0 (0.0)	0 (0.0)	3 (2.3)	
Creatinine, μmol/L	87 (74.0-107.2)	86 (76-108)	90.5 (72.2-108.0)	0.942
Median peak aortic valve gradient, mmHg	30 (23-35)	30.1 (25-37)	32 (26.3-36.0)	0.284
Median LVEF, %	60 (50-60)	58 (50-60)	60 (50-60)	0.437
Previous PCI	22 (14.5)	19 (15.2)	17 (13.1)	0.885
Previous MI	15 (9.9)	11 (8.9)	9 (6.9)	0.675
Previous CABG	4 (2.6)	6 (4.8)	5 (3.8)	0.631
Hypertension	108 (71.1)	89 (71.2)	94 (72.3)	0.969
Hypercholesterolemia	107 (70.4)	94 (75.2)	93 (71.5)	0.658
Previous TIA/stroke	32 (21.1)	17 (13.6)	36 (27.7)	0.022
Diabetes	33 (21.7)	36 (28.8)	37 (28.5)	0.306
Smoking				0.198
Never	74 (48.7)	56 (44.8)	58 (44.6)	
Ex-smoker	71 (46.7)	55 (44.0)	56 (43.1)	
Active	7 (4.6)	14 (11.2)	16 (12.3)	
Malignant disease	24 (15.8)	24 (19.2)	30 (23.1)	0.301
COPD	30 (19.7)	33 (26.4)	39 (30.0)	0.129
Previous AF	42 (27.6)	40 (32.0)	56 (43.1)	0.021
Previous PAD	12 (7.9)	15 (12.0)	13 (10.0)	0.519

Values are median (Q1-Q3) or n (%).

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

Treatment groups were compared within frailty strata using log-rank tests. All statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing).

The NOTION-3 trial was approved by the central committees of health research and national or local ethics committees of the participating sites. The principles of Declaration of Helsinki were followed.[10]

RESULTS

During the study period (September 2017 through October 2022), a total of 455 patients were enrolled at 12 hospitals. Of these, 407 patients (90%) had available data for frailty evaluation and constitute the study population for this substudy. A total of 130 patients (32%) were classified as frail (defined as the highest tertile of calculated frailty score), and 277 patients (68%) were classified as nonfrail (defined as the 2 lowest tertiles of calculated frailty score).

The median age of this study population was 82 years (Q1-Q3: 78-85 years), and 131 patients (32%) were women. There were no differences between frailty tertiles regarding age, the majorities of baseline demographics and comorbidities. However, there were more women in the higher tertiles (tertile 1, 23%; tertile 2, 35%; tertile 3, 40%; $P = 0.007$) and higher prevalences of previous transient ischemic attack or stroke (tertile 1, 21%; tertile 2, 14%; tertile 3, 28%; $P = 0.022$) and previous atrial fibrillation (tertile

TABLE 2 Angiographic Findings in Patients Stratified in Tertiles According to Calculated Frailty Score

	Tertile 1 (n = 152)	Tertile 2 (n = 125)	Tertile 3 (n = 130)	*P* Value
Median number of physiologically significant lesions per patient	1 (1-2)	1 (1-2)	1 (1-2)	0.509
Number of lesions with fractional flow reserve ≤ 0.80				0.078
0	0	63 (41.4)	61 (48.8)	
1	76 (50.0)	46 (36.8)	60 (46.2)	
2	13 (8.6)	17 (13.6)	14 (10.8)	
3	0 (0.0)	1 (0.8)	4 (3.1)	
Number of lesions with diameter stenosis ≥ 90%				0.741
0	58 (38.2)	45 (36.0)	59 (45.4)	
1	75 (49.3)	65 (52.0)	53 (40.8)	
2	14 (9.2)	13 (10.4)	13 (10.0)	
3	3 (2.0)	2 (1.6)	4 (3.1)	
4	1 (0.7)	0 (0.0)	1 (0.8)	
6	1 (0.7)	0 (0.0)	0 (0.0)	
Median largest diameter stenosis, %	90 (75-90)	90 (80-90)	90 (70-90)	0.722
Median SYNTAX I score	9 (5.8-14.0)	9 (6-13)	10 (7-14)	0.341
Access-site CAG				0.361
Radial	53 (70.7)	37 (60.7)	46 (73.0)	
Femoral	21 (28.0)	24 (39.3)	17 (27.0)	
PCI procedure				
Median number of days from randomization to PCI	7 (0-18)	17 (1-46)	9 (0.8-25.0)	0.019
Timing of PCI				0.006
Before TAVR	52 (68.4)	41 (67.2)	55 (85.9)	
Concomitant with TAVR	12 (15.8)	15 (24.6)	9 (14.1)	
After TAVR	12 (15.8)	5 (8.2)	0 (0.0)	
Result after first PCI				0.395
Complete revascularization	65 (89.0)	57 (91.9)	55 (85.9)	
Failed attempt, no further PCI planned	2 (2.7)	1 (1.6)	1 (1.6)	
Incomplete revascularization, no further PCI planned	4 (5.5)	4 (6.5)	8 (12.5)	
Incomplete revascularization, further PCI planned (staged)	2 (2.7)	0 (0.0)	0 (0.0)	
SYNTAX score after PCI	36.9 (9.9)	36.9 (8.4)	38.7 (8.9)	0.204
TAVR procedure				
Median number of days from randomization to TAVR	22 (1-53)	41 (2-60)	28.5 (7.0-73.2)	0.080
Balloon-expandable heart valve	71 (46.7)	56 (44.8)	39 (30.0)	0.010

PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; TAVR = transcatheter aortic valve replacement.

1, 28%; tertile 2, 32%; tertile 3, 41%; $P = 0.021$). Furthermore, Society of Thoracic Surgeons risk score, NYHA functional class, and Canadian Cardiovascular Society class increased with increasing frailty tertiles, reflecting that dyspnea and chest pain during physical activity was a part of the frailty evaluation (Table 1).

In terms of angiographic findings there were no differences between the groups. Similarly, for procedural characteristics, with few exceptions, patients in the middle frailty tertile had a greater number of days from randomization to PCI (tertile 1, 7 days [Q1-Q3: 0-18 days]; tertile 2, 17 days [Q1-Q3: 1-46 days]; and tertile 3, 9 days [Q1-Q3: 1-25 days]; $P = 0.019$), whereas patients in the highest frailty tertile more often underwent PCI before TAVR (tertile 1, 68%; tertile 2, 67%; tertile 3, 86%; $P = 0.006$), and less often received balloon-expandable heart valves (tertile 1, 47%; tertile 2, 45%; tertile 3, 30%; $P = 0.010$) (Table 2).

Nonfrail and frail patients were similar in their allocated randomization groups in terms of both baseline demographics and angiographic findings, except for a higher prevalence of hypertension in nonfrail patients randomized to conservative treatment and the number of lesions with fractional flow reserve ≤0.80 in nonfrail patients (Supplemental Tables 4 and 5).

The prediction of the calculated frailty score for primary endpoint is displayed in Supplemental Figure 2. Power and interaction analyses showed that in nonfrail patients (tertiles 1 and 2), PCI in addition to TAVR substantially reduced MACE at 24 months (absolute risk reduction ≈ 12%, number needed to treat ≈ 8) without increasing bleeding. In frail patients (tertile 3), the reduction in MACE was

TABLE 3 Primary and Secondary Outcomes in Nonfrail and Frail Patients in Both Randomization Groups

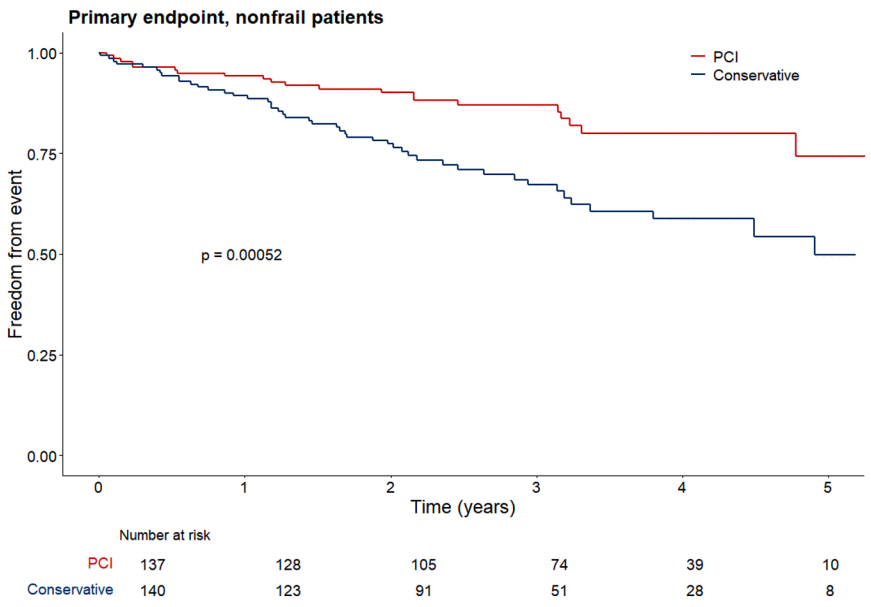
	Nonfrail				Frail			
	Conservative (n = 140)	PCI (n = 137)	HR (95% CI)[a]	*P* Value	Conservative (n = 63)	PCI (n = 67)	HR (95% CI)[a]	*P* Value
Primary end point: MACE	46 (33)	21 (15)	0.42 (0.25-0.69)	<0.001	29 (46)	32 (48)	1.00 (0.60-1.65)	0.993
Secondary end point								
Death of any cause	33 (24)	17 (12)	0.50 (0.28-0.89)	0.019	24 (38)	29 (43)	1.15 (0.67-1.99)	0.603
Myocardial infarction	20 (14)	5 (4)	0.24 (0.09-0.63)	0.004	10 (16)	9 (13)	0.83 (0.34-2.05)	0.691
Urgent revascularization	16 (11)	2 (2)	0.12 (0.03-0.52)	0.005	8 (13)	2 (3)	0.23 (0.05-1.07)	0.061
Death of cardiovascular causes	13 (9)	8 (6)	0.61 (0.25-1.46)	0.264	14 (22)	10 (15)	0.66 (0.30-1.52)	0.345
Any revascularization	29 (21)	2 (2)	0.06 (0.02-0.26)	<0.001	16 (25)	2 (3)	0.11 (0.02-0.47)	0.003
Stroke	19 (14)	13 (10)	0.65 (0.32-1.32)	0.236	13 (21)	7 (10)	0.51 (0.20-1.31)	0.161
Safety end points								
Any bleeding event[b]	30 (21)	32 (23)	1.07 (0.65-1.76)	0.802	11 (18)	25 (37)	2.51 (1.23-5.11)	0.011
Life-threatening or disabling bleeding[b]	14 (10)	9 (7)	0.62 (0.26-1.43)	0.259	3 (5)	11 (16)	3.82 (1.07-13.7)	0.040
Major bleeding[b]	11 (8)	6 (4)	0.53 (0.19-1.43)	0.208	4 (6)	7 (10)	1.68 (0.49-5.75)	0.41
Combined major and life threating bleeding[b]	23 (16)	14 (10)	0.58 (0.30-1.31)	0.11	7 (11)	18 (27)	2.75 (1.15-6.60)	0.024
Minor bleeding[b]	10 (7)	18 (13)	1.85 (0.86-4.02)	0.118	4 (6)	9 (13)	2.18 (0.67-7.08)	0.196
Acute kidney failure	17 (12)	7 (5)	0.39 (0.16-0.95)	0.037	6 (10)	3 (5)	0.46 (0.12-1.89)	0.279

[a]PCI treatment as reference. [b]Bleeding events were defined according to the Valve Academic Research Consortium 2 criteria.
MACE = major adverse cardiac event(s); PCI = percutaneous coronary intervention.

modest (absolute risk reduction ≈ 4%, number needed to treat ≈ 28) and accompanied by a possible increase in bleeding (absolute risk increase ≈ 14%, number needed to harm ≈ 7) (Supplemental Tables 6 and 7).

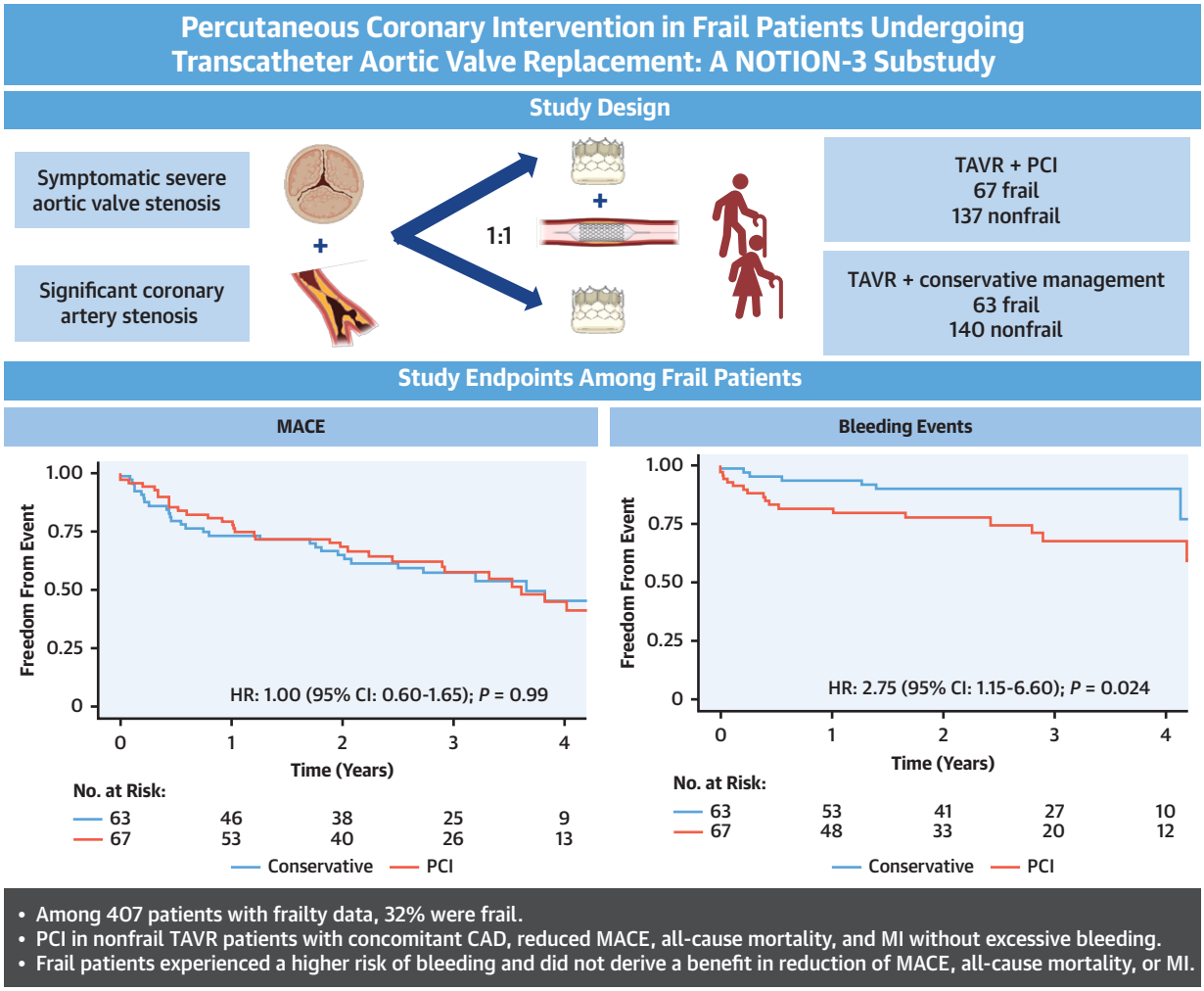
Over a median follow-up period of 2 years (Q1-Q3: 1-4 years), nonfrail patients randomized to PCI experienced a significantly lower incidence of MACE (15%) compared with those randomized to conservative treatment (33%) (HR: 0.42; 95% CI: 0.25-0.69;

FIGURE 1 Cumulative Freedom From the Primary Endpoint Among Nonfrail Patients



Kaplan-Meier curve showing the cumulative freedom from primary endpoint in nonfrail patients randomized to percutaneous coronary intervention (PCI) or conservative treatment. The primary endpoint was major adverse cardiac events (defined as a composite of death of any cause, myocardial infarction, or urgent revascularization).

CENTRAL ILLUSTRATION Study Overview and Findings



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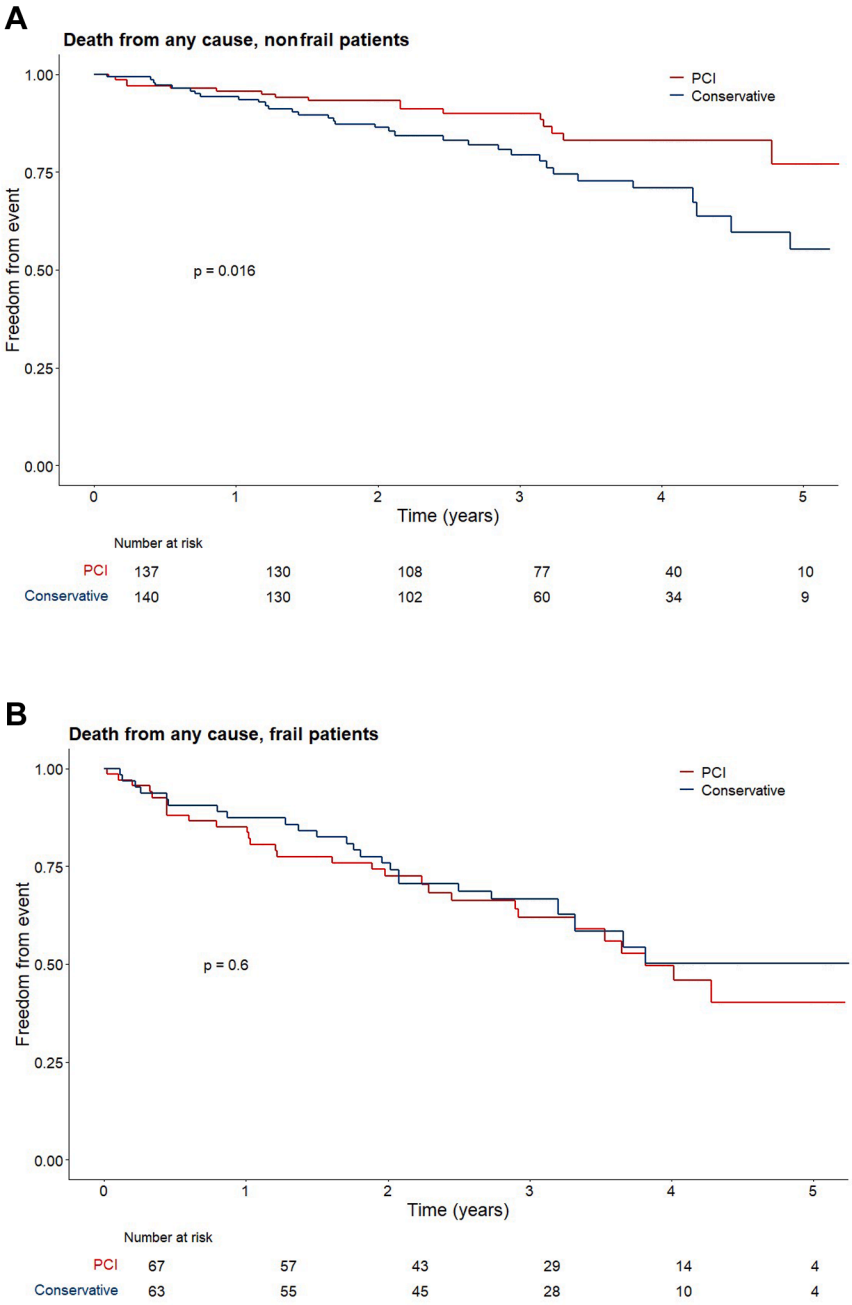
CAD = coronary artery disease; MACE = major adverse cardiac event(s); MI = myocardial infarction; NOTION-3 = Third Nordic Aortic Valve Intervention; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement.

$P < 0.001$) (Table 3). Similarly, PCI was associated with lower rate of death of any cause (HR: 0.50; 95% CI: 0.28-0.89; $P = 0.019$), fewer MIs (HR: 0.24; 95% CI: 0.09-0.63; $P = 0.004$), less urgent revascularization (HR: 0.12; 95% CI: 0.03-0.52; $P = 0.005$), and a lower incidence of any revascularization (HR: 0.06; 95% CI: 0.02-0.26; $P < 0.001$) in nonfrail patients compared with conservative treatment (Table 3). In contrary, among frail patients, PCI treatment was associated only with a lower incidence of any revascularization (HR: 0.11; 95% CI: 0.02-0.47; $P = 0.003$) (Table 3). The association was sustained after adjusting for the competing risk for death of any cause (HR: 0.10; 95% CI: 0.02-0.45; $P = 0.003$). In Kaplan-Meier analysis, there was a higher cumulated freedom from MACE in nonfrail patients allocated to the PCI treatment group compared with conservative treatment ($P < 0.001$) (Figure 1) but not in frail patients ($P = 0.99$) (Central Illustration). Similarly, there was higher cumulated freedom from death of any cause among nonfrail patients randomized to PCI compared with conservative treatment ($P = 0.016$) but not in frail patients ($P = 0.60$) (Figures 2A and 2B).

In terms of safety endpoints, there was a higher incidence of any VARC-2 bleeding event among frail patients randomized to PCI treatment (37%)

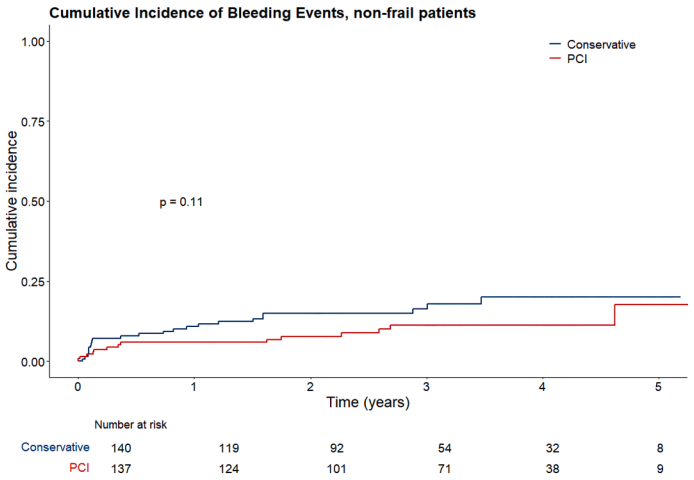
FIGURE 2 **Cumulative Freedom From Death of Any Cause in Nonfrail and Frail Patients**



Kaplan-Meier curve showing the cumulative freedom from death of any cause in nonfrail (A) and frail (B) patients randomized to percutaneous coronary intervention (PCI) or conservative treatment.

compared with conservative treatment (18%) (HR: 2.51; 95% CI: 1.23-5.11; $P = 0.011$), as well as for severe and life-threatening VARC-2 bleedings alone (27% with PCI vs 11% with conservative treatment) (HR: 2.75; 95% CI: 1.15-6.60; $P = 0.024$) (Table 3). The association of PCI treatment and severe or life-threatening VARC-2 bleeding events in frail patients was sustained when adjusted for the competing risk

FIGURE 3 Cumulative Incidence of Severe Bleeding Events in Nonfrail Patients



Kaplan-Meier curve showing the cumulative incidence of severe bleeding events in nonfrail patients randomized to percutaneous coronary intervention (PCI) or conservative treatment. Bleeding events were defined as major or life-threatening bleeding according to the Valve Academic Research Consortium 2 criteria.

for death of any cause (HR: 2.65; 95% CI: 1.10-6.36; $P = 0.029$). An interaction analysis showed significant interactions for combined major and life-threatening bleeding ($P = 0.005$), MACE ($P = 0.016$), and death of any cause ($P = 0.039$) (Supplemental Table 8). There were no differences in discharge treatment with anticoagulant or antithrombotic medications except for less aspirin among frail patients randomized to conservative treatment (48% in frail patients vs 69% in nonfrail patients; $P = 0.006$) (Supplemental Table 9).

The cumulate incidence of severe bleeding complications was higher in frail patients undergoing PCI compared with conservative treatment when adjusted for the competing risk for death of any cause ($P = 0.018$) (**Central Illustration**), whereas no such differences were seen among nonfrail patients (**Table 3**, **Figure 3**).

DISCUSSION

This is the first study to investigate the impact of frailty in patients undergoing TAVR and randomized to either PCI or conservative medical treatment for CAD. In this substudy of the NOTION-3 trial, 32% of patients were classified as frail on the basis of a calculated frailty score. Previous studies examining the prevalence of frailty in TAVR populations have reported both lower and higher rates, depending on the frailty assessment tools used.[7,19,20]

Among nonfrail patients, PCI was associated with a lower risk for MACE at a median follow-up of 2 years compared with conservative treatment, a benefit not observed among frail patients. In the main NOTION-3 trial, reductions in urgent revascularization and MI primarily drove the difference in MACE, with no significant effect on death of any cause.[10] The ACTIVATION (Percutaneous Coronary Intervention Prior to Transcatheter Aortic Valve Implantation) trial similarly reported no differences in mortality or rehospitalization at 1 year. Although frailty was not assessed in ACTIVATION, differences may reflect a more frail patient population, as it was conducted during a time when TAVR was more commonly performed in higher risk, frailer individuals.[21] In this substudy, nonfrail patients treated with PCI had lower rates of all primary endpoint components without increasing bleeding, whereas frail patients only had reduced risk for revascularization, at the cost of more bleeding events. Frail patients more often underwent PCI before TAVR and were therefore treated with dual antiplatelet therapy before the TAVR procedure. However, the number of days from randomization to PCI was highest in the middle calculated frailty score tertile of patients, who were not included in the frailty group. The interaction analyses revealed statistically significant interactions for bleeding endpoints as well as for MACE and mortality, supporting that frailty status modifies the effect of PCI and risk for bleeding. These findings require confirmation in larger prospective studies but could potentially help select patients undergoing TAVR with CAD to PCI or conservative management.

FRAILTY AND OUTCOMES. In line with findings in the present study, frailty has previously been independently linked to increasing risk for bleeding in patients undergoing PCI[22] as well as in those undergoing TAVR.[23] Several previously published studies have demonstrated the negative impact of frailty on morbidity and mortality in patients undergoing TAVR,[5,6] as well as in patients with cardiovascular disease.[24] In populations with acute coronary syndrome, frailty has been consistently associated with increased mortality, even after adjustment for age, comorbidities, and sex.[4,25,26] Furthermore, frailty has been proposed as a stronger predictor of mortality than chronological age.[4] However, most existing studies on frailty have focused on patients with acute coronary syndrome and data on patients with chronic CAD are limited. Among the few available studies,

one small study investigated 99 patients using the Canadian Study of Health and Aging frailty scale reported a higher incidence of MACE in frail compared with nonfrail patients.[27] However, the decision to perform PCI was left to the treating physician, and the number of revascularization procedures in the groups was not reported.

REVASCULARIZATION IN FRAIL PATIENTS. Recent guidelines for acute and chronic coronary syndromes emphasize the role of frailty in guiding treatment decisions, though no specific frailty assessment tool is recommended.[28,29] Our findings support incorporating frailty into more personalized and preference-based care and underscore the need for clearer guidance on managing frail patients with ischemic heart disease.

Our trial shows that regardless of frailty status, revascularization in relation to TAVR effectively reduces the future need for revascularization. This is consistent with prior observations in elderly patients with non-ST-segment elevation MI.[30,31] In contrast, other studies have reported no differences in outcomes such as days alive and out of the hospital postdischarge,[32] or rates of recurrent MI and rehospitalization,[33] between invasive and conservative strategies. Differences in study design, including premature study termination, sample size, and varying frailty definitions, may account for these discrepancies.

In our population of patients undergoing TAVR with coexisting CAD, PCI was associated with reductions in MI and all-cause death in nonfrail patients but not among frail patients. The mechanisms underlying this differential effect are likely multifactorial. Although our study cannot explain why nonfrail patients benefited from PCI in terms of death of any cause, the findings strengthen the indication for PCI in nonfrail patients with CAD and planned TAVR. In contrast, among frail patients, PCI reduced the need for subsequent revascularization but did not affect the incidence of MI or mortality rates. Given the strong association between frailty and bleeding risk, treatment decisions in these patients should be guided by multidisciplinary evaluation, incorporating frailty assessment, ischemic symptom burden, and patient preferences.

STUDY LIMITATIONS. This study is a substudy of the NOTION-3 trial, so no formal sample size or statistical power calculation was performed. Treatment-frailty interaction tests were statistically significant, but given the wide CIs and low post hoc power, these findings should be viewed as hypothesis generating. However, the numbers of frail and nonfrail patients were similar across treatment arms, and the groups were comparable in terms of baseline demographics, supporting the internal validity of the comparisons made.

Second, frailty status was determined post hoc using baseline data. Previous studies have demonstrated substantial agreement when retrospectively assessing CFS scores from medical records.[34,35] Although validated, heterogeneity in frailty assessment tools limits cross-study comparability. Our calculated frailty score required multiple criteria, reducing potential overestimation. A standardized frailty measure such as the CFS was not prospectively collected in the NOTION-3 trial. However, data from one recruiting center showed lower frailty prevalence (CFS scores of 5-9), likely reflecting definitional differences. Our calculated frailty score incorporated angina, dyspnea, and quality-of-life measures, factors not captured by the CFS. Previous studies investigating frailty use different frailty assessment tools and report both similar, higher and lower incidences, supporting the generalizability of our findings.[19]

Our results emphasize the heterogeneity within older patients undergoing TAVR and suggest that frailty assessment provides valuable additional information that may inform treatment decisions. However, these findings require confirmation in larger prospective studies and future trials should consider incorporating frailty assessment as a part of patient selection and randomization.

CONCLUSIONS

PCI in nonfrail TAVR patients with concomitant CAD reduced MACE, all-cause mortality, and MI, without excessive bleeding risk. In contrast, frail patients experienced a higher risk for bleeding and did not derive a benefit in reduction of MACE, all-cause mortality, or MI. Our findings should be viewed as hypothesis generating and require confirmation in larger prospective studies.

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ADDRESS FOR CORRESPONDENCE: Dr Hanna Ratcovich, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. E-mail: hanna.louise.ratcovich.01@regionh.dk.

PERSPECTIVES

WHAT IS KNOWN? The NOTION-3 trial demonstrated that PCI in patients with significant CAD undergoing TAVR improved outcome in terms of MACE.

WHAT IS NEW? In this substudy, we found that in frail patients undergoing TAVR, PCI did not improve outcomes and increased the risk for bleeding.

WHAT IS NEXT? Our findings emphasize frailty assessment as part of the treatment strategy in patients with CAD undergoing TAVR but require confirmation in larger randomized trials.

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KEY WORDS aging, coronary artery disease, frailty, PCI, transcatheter aortic valve replacement

APPENDIX For the supplemental figures, tables, and a video of the interactive Central Illustration, please see the online version of this paper.

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