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CLINICAL RESEARCH
Clinical trials

Physiology vs angiography-guided percutaneous coronary intervention in transcatheter aortic valve implantation: the FAITAVI trial

Flavio L. Ribichini [1,*], Roberto Scarsini [1], Gabriele Pesarini[1], Tommaso Fabris[2], Marco Barbierato[3], Gianpiero D'Amico[3], Chiara Zanchettin[2,3], Dario Gregori[2], Giulia Lorenzoni[2], Tommaso Piva[4], Elisa Nicolini[4], Caterina Gandolfo [5], Ketty La Spina [5], Massimo Fineschi[6], Francesco Gallo[3], Bernardo Baccani[6], Anna Sonia Petronio[7], Marco De Carlo[7], Sergio Berti[8], Andrea Drago[9], Francesco Saia[10], Rocco Sclafani[11], Giovanni Esposito [12], Fabrizio D'Ascenzo [13], Giuseppe Tarantini[2], and for the FAITAVI Trial investigators

[1]Division of Cardiology, Department of Medicine, University of Verona, Piazzale Aristide Stefani, 1, Verona 37126, Italy; [2]Department of Cardiac, Thoracic and Vascular Science, University of Padua, Padua, Italy; [3]Division of Cardiology, Ospedale dell'Angelo, Mestre, Venice, Italy; [4]Division of Cardiology, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy; [5]Division of Cardiology, ISMETT di Palermo, Palermo, Italy; [6]Division of Cardiology, Azienda Ospedaliera Universitaria Senese, Siena, Italy; [7]Division of Cardiology, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [8]Division of Cardiology, Ospedale del Cuore—Fondazione Monasterio, Massa, Italy; [9]Division of Cardiology, Ospedale San Bortolo di Vicenza, Vicenza, Italy; [10]Division of Cardiology, Policlinico S. Orsola-Malpighi, Bologna, Italy; [11]Division of Cardiology, Azienda Ospedaliera di Perugia—Ospedale S. Maria della Misericordia, Perugia, Italy; [12]Division of Cardiology, Policlinico Universitario Federico II di Napoli, Naples, Italy; and [13]Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza, Hospital University of Turin, Turin, Italy

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Abstract

Background and Aims The optimal approach to coronary revascularization in patients undergoing transcatheter aortic valve implantation (TAVI) remains debated. Fractional flow reserve (FFR) may improve the identification of ischaemia-producing lesions compared to angiographic assessment alone, but data in the TAVI population are lacking.

Methods In this multicentric, open-label, randomized, superiority trial with blind adjudication of adverse events, patients with aortic stenosis and intermediate coronary lesions undergoing TAVI were randomized 1:1 to FFR-guided or angiography-guided percutaneous coronary intervention (PCI). The trial was registered at ClinicalTrials.gov (NCT03360591). All randomized patients were included in the primary analysis according to the intention-to-treat principle. The primary endpoint was a major adverse cardiac and cerebrovascular event (MACCE) at 12 months of follow-up, defined as a composite of all-cause death, myocardial infarction, ischaemia-driven target vessel revascularization, disabling stroke, or major bleeding.

Results A total of 320 patients were enrolled across 15 Italian centres. The median age of the patients was 86 years [interquartile range (IQR) 83–90], and the median STS score was 3% (IQR 2–5). The median SYNTAX score was 7 (IQR 5–11). FFR-guided PCI was associated with a significantly lower rate of MACCE at 12 months compared with angiography-guided PCI (8.5% vs 16.0%; hazard ratio .52; 95% confidence interval .27–.99; $P = .047$). The difference in the primary endpoint was primarily driven by a reduction in all-cause mortality (hazard ratio .31; 95% confidence interval .10–.96). Other components of the composite were numerically lower but not statistically significant.

* Corresponding author. Tel: +39 045 8122039, Fax: +39 045 8122823, Email: flavio.ribichini@univr.it

Conclusions In patients undergoing TAVI with intermediate coronary lesions, FFR-guided PCI was associated with a reduced risk of MACCE at 12 months. These findings support a physiology-based revascularization strategy in this frail, elderly population.

Structured Graphical Abstract

Key Question

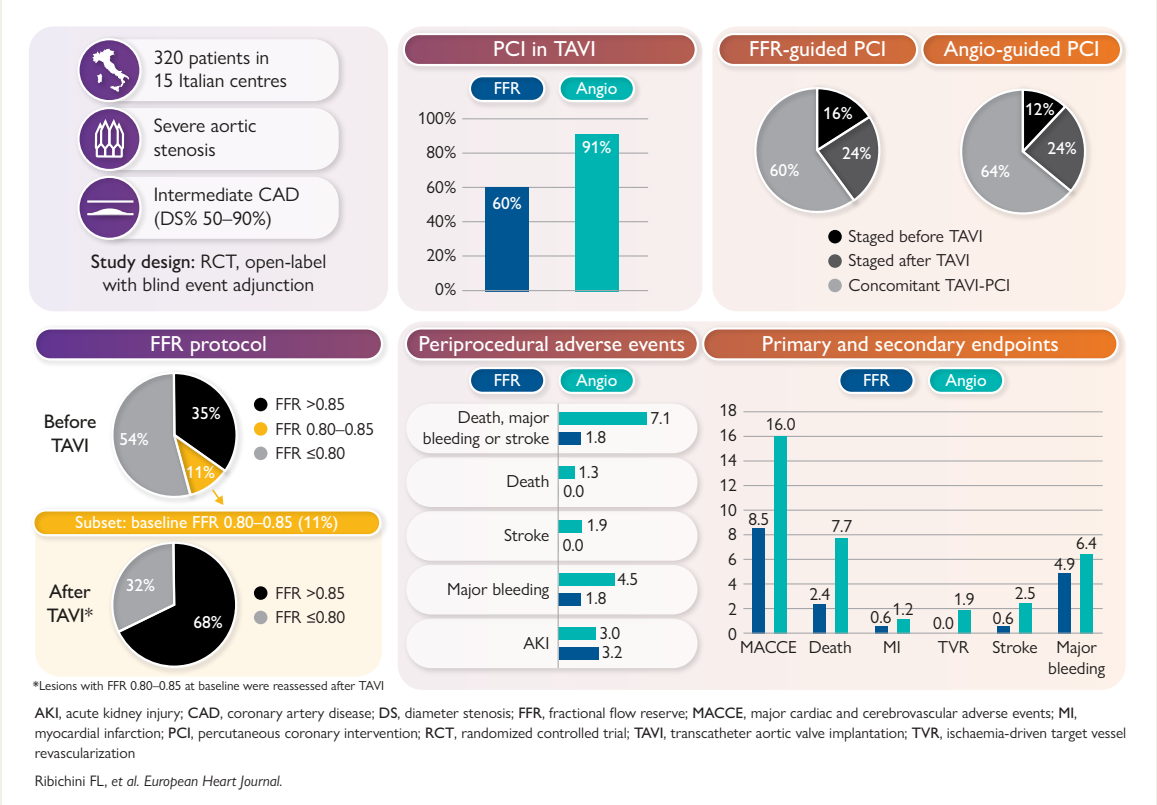
In patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) and intermediate coronary lesions, does a fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) strategy improve clinical outcomes compared with angiography-guided PCI?

Key Finding

In this trial, FFR-guided PCI was significantly associated to a reduction of 12-month major adverse cardiovascular and cerebrovascular events, including mortality, myocardial infarction, target vessel revascularization, stroke and major bleeding, compared with angiography-guided PCI. This was mainly driven by a reduction in all-cause mortality, without excess procedural or bleeding complications.

Take Home Message

FFR-guided PCI provides a safer, more selective revascularization approach in elderly TAVI patients with intermediate coronary lesions compared with angiography-guided PCI, reducing MACCE at 12 months of follow-up.



*Lesions with FFR 0.80–0.85 at baseline were reassessed after TAVI

AKI, acute kidney injury; CAD, coronary artery disease; DS, diameter stenosis; FFR, fractional flow reserve; MACCE, major cardiac and cerebrovascular adverse events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; TAVI, transcatheter aortic valve implantation; TVR, ischaemia-driven target vessel revascularization

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Study design and main results of the FAITAVI randomized controlled trial in 320 patients with severe aortic stenosis and intermediate coronary artery disease undergoing TAVI, comparing an FFR-guided PCI strategy with an angiography-guided PCI strategy. FFR-guided PCI was associated with a significantly lower 12-month incidence of major adverse cardiac and cerebrovascular events without excess periprocedural complications, acute kidney injury or major bleeding compared with angiography-guided PCI.

Keywords Transcatheter aortic valve implantation • Coronary artery disease • Percutaneous coronary intervention • Fractional flow reserve

Introduction

Coronary artery disease (CAD) is present in 40%–75% of patients undergoing transcatheter aortic valve implantation (TAVI), yet the optimal management of coexisting CAD remains unclear.[1–4] While myocardial revascularization is routinely performed at the time of surgical aortic valve replacement (SAVR), the role of percutaneous coronary intervention (PCI) during TAVI is still debated.[4]

Recent trials comparing PCI with conservative management in the TAVI population have yielded conflicting results. The 'PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION' (ACTIVATION) trial was inconclusive,[5] whereas the Third Nordic Aortic Valve Intervention (NOTION-3) trial suggested benefit from PCI of severe lesions.[6] The Transcatheter Valve and Vessels (TCW) trial further supported the feasibility of combining TAVI with PCI over SAVR with coronary artery bypass grafting (CABG).[7]

Fractional flow reserve (FFR) is superior to angiography in identifying ischaemia-producing lesions[8] and is endorsed by current revascularization guidelines.[9] Although concerns have been raised regarding the reliability of FFR in the setting of severe aortic stenosis due to altered coronary physiology, several non-randomized studies have suggested that FFR measurements remain valid and clinically useful in this population.[10–13]The Functional Assessment in TAVI (FAITAVI) trial was designed to assess whether an FFR-guided PCI strategy improves clinical outcomes compared with an angiography-guided approach in patients with severe aortic stenosis (AS) and intermediate coronary lesions undergoing TAVI.[14]

Methods

Trial design and participants

The FAITAVI study (NCT03360591) is an investigator-initiated, multicentre, prospective, open-label, randomized trial with blind adjudication of adverse events, designed to assess the superiority of FFR-guided PCI over angiography-guided PCI in patients with severe AS and concomitant CAD undergoing TAVI.

The study protocol was approved by the Ethics Committee of all participating centres, co-ordinated by the University of Verona, and conducted according to the Helsinki Declaration. The trial protocol, statistical plan, and the list of the investigators have been previously published.[14] The trial was supported by unrestricted grants from Edwards Lifesciences Corporation and Philips. Both companies were not involved in the conduct of the trial or in the writing or editing of the manuscript or the approval of the manuscript for submission. Written informed consent was obtained from all patients. An independent data and safety monitoring committee monitored the safety and well-being of the participating subjects and ensured the study's scientific integrity. An independent contract research organization was responsible for site monitoring, data collection, and statistical analysis.

FAITAVI eligibility criteria include patients with severe symptomatic AS with an indication for TAVI as posed by the local Heart Team, and at least one intermediate coronary stenosis with a diameter stenosis between 50% and 90% as per visual assessment in a major coronary artery (with a reference diameter >2.5 mm).

Patients with severe renal failure, left ventricular ejection fraction <35%, recent acute coronary syndrome, life expectancy of <1 year, and requiring valve-in-valve implantation were excluded. A complete list of the inclusion and exclusion criteria is provided in the Supplementary data online, *Appendix*.

Randomization and masking

After verification of eligibility, study participants were randomly assigned (1:1) to FFR-guided PCI or angiography-guided PCI. Randomization was performed using an unblocked, competitive allocation procedure, which does not enforce balance at each step but was chosen to ensure unpredictability of assignments. Consequently, a slight imbalance in the final allocation (164 vs 156) was observed. Masking of patients and medical staff enrolling patients or performing follow-up was not implemented. Delegated medical staff or investigators enrolled the patients, and delegated medical staff conducted the web-based randomization during the index procedure after the patient was found eligible according to both clinical and angiographic criteria.

Procedures

Patients randomized to the FFR-guided PCI strategy underwent physiology assessment of all coronary lesions with a diameter stenosis between 50% and 90% using a standard intracoronary pressure-guidewire (Verrata or Omniwire, Philips, Amsterdam, NL).

The intracoronary physiological assessment obtained before valve implantation determined the PCI strategy as follows: (i) lesions showing abnormal FFR measurements (≤.80) were treated with PCI; (ii) lesions with FFR >.85 were deferred as deemed non-ischaemia-provoking; and (iii) lesions showing borderline FFR measurements (FFR .81–.85) before TAVI were re-assessed after TAVI with the pressure guidewire. In these cases, the decision of treating or deferring treatment was based on the FFR value obtained after TAVI. In fact, previous observational studies reported an increase in the hyperaemic flow, with consequent variations of borderline FFR measurements, because of the pressure overload relief induced by TAVI.[11]

Patients allocated to the angiography-guided PCI group underwent PCI of all coronary stenoses ≥50% in vessels ≥2.5 mm. The objective of the angiography-guided PCI strategy was to obtain complete angiographic revascularization of major epicardial coronary arteries. For both trial arms, PCI could be performed before TAVI (preventive revascularization), during the same TAVI procedure (before or after valve implantation), or after TAVI if it was performed within 1 month ± 5 days of valve implantation. The SAPIEN 3 and SAPIEN 3 ULTRA (Edwards Lifesciences, Irvine, CA) transcatheter heart valves implanted through the transfemoral approach were used as per local standards of care. The use of second-generation drug-eluting stents was recommended.

Medical therapy

Patients continued their established cardio-active therapy and received appropriate intraprocedural anticoagulation according to standard hospital practice. Before the publication of the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation (POPular) trial,[15] all patients received a loading dose of clopidogrel and aspirin the day before TAVI. Afterwards, dual antiplatelet therapy (DAPT) with clopidogrel was given only to patients treated with coronary stenting. In patients with an indication for oral anticoagulation (OAC), DAPT was withdrawn after 3 months of triple therapy, followed by single antiplatelet therapy associated with OAC for 12 months and OAC monotherapy thereafter.

Follow-up

Follow-up visits at 1, 6, and 12 months documented primary and secondary endpoints, hospitalizations due to heart failure or myocardial ischaemia, and medication adherence.

Endpoints

The primary endpoint was a major adverse cardiac and cerebrovascular event (MACCE), defined as a composite of death from any cause, periprocedural or spontaneous myocardial infarction, ischaemia-driven target vessel revascularization (TVR), stroke (intended as disabling), or major bleeding [classified as Valve Academic Research Consortium-2 (VARC-2) ≥3[16]] within 12 months of the index procedure. This composite endpoint was selected to capture the overall clinical impact of both revascularization strategies on a broad range of ischemic and bleeding outcomes. We included all-cause death rather than cardiovascular death to ensure complete and unbiased event capture, given the challenges in reliably adjudicating cause of death in this elderly population.[17] Stroke and major bleeding were included as they may be influenced by the extent and timing of coronary intervention, as well as by the need for DAPT, which may differ between the two strategies. The key safety endpoint was a composite of death within 30 days of the index procedure, stroke, life-threatening bleeding, acute kidney injury (AKI), coronary artery obstruction requiring intervention, major vascular

complication, or valve-related dysfunction requiring repeat procedure (aortic balloon valvuloplasty, TAVI-in-TAVI, SAVR).

Exploratory safety endpoints were major periprocedural (within 24 h) adverse events, including the composite of periprocedural death, stroke, and major bleeding.

The list of the secondary endpoints and their definitions is available in the Supplementary data online, *Appendix*. All the endpoints were reported by the investigators, and they were analysed and adjudicated by the clinical events committee (CEC), based on the original source documents.

Statistical analysis

We estimated that the primary endpoint would occur in ∼20% of FFR-guided PCI patients and 32% of angiography-guided PCI patients at 12 months of follow-up.

These event rate estimates (20% in the FFR-guided arm and 32% in the angiography-guided arm) were derived from prior literature in comparable populations and formed the basis of the sample size calculation. In particular, 1-year MACCE rates of up to 30% have been reported in TAVI patients with complex CAD,[18] and FFR-guided PCI has consistently shown a ∼30% relative risk reduction for ischemic events compared to angiography-guided PCI in stable CAD populations.[8] These assumptions were further adjusted to reflect the high bleeding risk in the elderly TAVI population and the anticipated benefits of lesion deferral in the FFR group.

Based on these assumptions, we determined that the enrolment of 320 patients would provide the trial with 80% power to demonstrate the superiority of FFR-guided PCI strategy over angiography-guided PCI at an α level of 5%. Details on the sample size calculation are reported in the Supplementary data online, *Appendix*.

Endpoints, including safety, were analysed as per intention-to-treat. Patients lost to follow-up or event-free at study end were censored. Baseline characteristics were compared between groups to confirm effective randomization. Hazard comparisons utilized a Cox regression model with 95% confidence intervals (CIs), assessing proportionality via visual inspection of Schoenfeld residuals. The widths of CIs have not been adjusted for multiplicity, so the CIs should not be used for hypothesis testing.

The Kaplan–Meier estimator was used to create time-to-event plots for the primary and secondary endpoints.

Analysis of the primary endpoint was also conducted in prespecified subgroups defined according to age, sex, diabetes status, diameter of stenosis, left ventricular ejection fraction, the Society of Thoracic Surgeons–Procedural Risk of Mortality (STS-PROM) score, and the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score. Cox regression provided hazard ratios (HR) with 95% CIs, and statistical significance was set at $P < .05$. Analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funders have no role in the study design; data collection, management, analysis and interpretation; writing of the report; and the decision to submit the results.

Results

From November 2017 through June 2023, a total of 320 patients were enrolled at 15 Italian hospitals and were included in the primary analysis. A total of 164 patients were assigned to FFR-guided PCI and 156 to angiography-guided PCI. The study cohort had a median age of 86 years [interquartile range (IQR) 83–89], with 42% being female. Diabetes was present in 35% of patients, and 12% had a history of myocardial infarction. All patients had severe symptomatic AS, with the majority classified as New York Heart Association class III or IV (55%). The median STS score was 3 (IQR 2–5), and the median SYNTAX score was 7 (IQR 5–11). Baseline clinical and angiographic characteristics were well balanced between the study groups (*Table 1*).

TAVI was performed in 318 (99%) patients with balloon expandable valves (SAPIEN 3/SAPIEN 3 ULTRA). PCI was performed in 141 (91%) patients in the angiography-guided PCI group and in 99 (60%) patients in the FFR-guided PCI group. The median number of coronary vessels treated with PCI was 1 (1–1) in the angiography-guided PCI group vs 1 (0–1) in the FFR-guided PCI group (*Table 2*). Fifteen (9%) patients assigned to the angiography-guided PCI group did not undergo PCI. This subgroup was characterized by a significantly lower rate of TAVI device success (80.0% vs 95.6%, $P = .015$) and a greater prevalence of lesions in non-LAD vessels ($P = .0005$) (see Supplementary data online, *Tables S1* and *S2*).

Angiographic complete revascularization was achieved in 117 (75%) patients in the angiography-guided PCI group.

In the FFR-guided PCI group, a total of 195 coronary vessels were assessed using a pressure-wire. At baseline, FFR was abnormal (≤.80) in 105 vessels (54%), clearly normal (>.85) in 68 vessels (35%), and borderline (.80–.85) in 22 vessels (11%). Amongst the 22 lesions with borderline FFR at baseline, 7 (32%) became functionally significant (≤.80) following TAVI. Clinical and angiographic data of the subgroup with borderline FFR are presented in Supplementary data online, *Tables S3* and *S4*. Lesions that crossed the FFR threshold after TAVI tended to be located in the left main or LAD (6 out of 7) compared with lesions that remained stable after TAVI (see Supplementary data online, *Figure S1*). Functional complete revascularization was achieved in 162 of 164 patients (99%) in the FFR-guided PCI group. PCI was performed in two patients (1%) despite an FFR >.80.

Twelve-month follow-up data were complete for 311/320 (97%) patients. At 12-month follow-up, a MACCE occurred in 14 (8.5%) patients in the FFR-guided PCI group as compared with 25 (16.0%) in the angiography-guided PCI group (HR .52; 95% CI .27–.99; $P = .047$) (*Table 3* and *Figure 1A*). Kaplan–Meier estimates for the primary endpoint and its individual components are shown in *Figure 1* and in Supplementary data online, *Figures S2–S5*. Subgroup analysis showed that the effect of the strategy of FFR-guided PCI on the primary endpoint was consistent across prespecified subgroups (*Figure 2*).

Secondary endpoints are summarized in *Table 3*. At 12 months, death for any cause occurred in four (2%) patients in the FFR-guided PCI group as compared with 12 (8%) patients in the angiography-guided PCI group (HR .31, 95% CI .10–.96) (*Figure 1B*). Death from cardiovascular causes occurred in no patients in the FFR-guided PCI group and in three (2%) patients in the angiography-guided PCI group (see Supplementary data online, *Figure S6*). Similarly, ischaemia-driven TVR occurred in no patients in the FFR-guided PCI group, and it occurred in three (2%) patients in the angiography-guided PCI group. No significant difference was observed in the other secondary endpoints between the study arms (*Table 3*). Mechanism of target vessel failure is reported in the Supplementary data online, *Table S5*.

The key safety endpoint occurred in 20 (12.2%) patients in the FFR-guided PCI group as compared with 27 (15.4%) in the angiography-guided PCI group (HR .66; 95% CI .35–1.23). The composite of periprocedural death, stroke, or major bleeding occurred significantly less frequently in the FFR-guided group compared to the angiography-guided group (1.8% vs 7.1%, $P = .022$), as detailed in Supplementary data online, *Table S6*. Moreover, a consistent trend towards increased early risk was observed at 30-day follow-up in the angiography-guided arm across several endpoints, including MACCE (4.9% vs 8.3%, $P = .212$; Supplementary data online, *Figure S7* and Supplementary data online, *Table S5*). The incidence of AKI was similar between the study arms

Table 1 Baseline characteristics of the study cohort[a]

Characteristic	FFR-guided PCI ($n = 164$)	Angiography-guided PCI ($n = 156$)
Age, years, median (IQR)	87 (83–90)	86 (82–89)
Female sex, *n* (%)	67 (41)	68 (44)
Body mass index, kg/m^2, median (IQR)	26 (24–28)	26 (24–29)
STS-PROM score[b], %, median (IQR)	3 (2–4)	4 (2–5)
New York Heart Association class, *n* (%)		
I	6 (4)	9 (6)
II	69 (43)	56 (37)
III	80 (50)	82 (54)
IV	4 (2)	6 (4)
Symptomatic for angina, *n* (%)	26 (16)	25 (16)
Creatinine level, mg/dL, median (IQR)	1.0 (.8–1.2)	1.0 (.9–1.2)
Estimated glomerular filtration rate[c], mL/min/1.73 m^2, median (IQR)	65 (51–79)	61 (45–73)
Left ventricular ejection fraction, %, median (IQR)	58 (53–64)	59 (55–64)
Aortic valve area, cm^2, median (IQR)	.7 (.6–.9)	.7 (.6–.9)
Aortic valve gradient[b], mmHg, median (IQR)	46 (40–53)	43 (38–52)
Peak aortic valve gradient, mmHg, median (IQR)	74 (65–83)	71 (61–81)
Medical history, *n* (%)		
History of percutaneous coronary intervention	23 (14)	26 (17)
History of myocardial infarction	21 (13)	17 (11)
History of coronary-artery bypass graft	3 (2)	2 (1)
Diabetes mellitus	55 (34)	59 (38)
Chronic kidney disease	43 (26)	46 (29)
Hypertension	151 (92)	131 (84)
Treatment of hypercholesterolaemia[b]	98 (60)	115 (75)
Chronic obstructive pulmonary disease	21 (13)	26 (17)
Atrial fibrillation	47 (29)	44 (28)
Peripheral artery disease	41 (25)	41 (26)

CABG, coronary-artery bypass graft; IQR, interquartile range; PCI, percutaneous coronary intervention; STS-PROMS, Society of Thoracic Surgeons-Procedural Risk of Mortality Score.
[a]Percentages may not total 100 because of rounding.
[b]Numerically relevant differences are highlighted to aid interpretability. These were defined as an absolute difference ≥10% for categorical variables or a standardized difference >.25 for continuous variables. These indicators are provided for descriptive purposes only and were not derived from formal statistical testing, in accordance with CONSORT 2010 recommendations.
[c]Estimated based on the Cockcroft–Gault equation.

(3.0% vs 3.2%; odds ratio .95; 95% CI .26–3.48). Coronary revascularization was deferred in 75 (38%) coronary lesions, in 65 (40%) patients based on the FFR assessment. Patients in whom PCI was deferred in the FFR-guided PCI arm showed a similar risk of a MACCE at 12 months compared with patients who underwent PCI in the FFR-guided group (6 [9%] vs 8 [8%]), with no excess risk of adverse events compared with patients in the angiography-guided PCI arm (HR .49; 95% CI .23–1.37) (see Supplementary Supplementary data online, *Appendix*). Similarly, no significant differences in clinical outcomes were observed in patients with borderline FFR at baseline (see Supplementary data online, *Table S4*).

Discussion

This is the first study to directly compare FFR-guided PCI with angiography-guided PCI in patients with severe symptomatic AS undergoing TAVI. FFR-guided PCI significantly reduced the incidence of MACCE compared to angiography-guided PCI (*Structured Graphical Abstract*). Physiologic guidance allowed for a more targeted revascularization, which may have contributed to the favourable clinical outcomes observed across a variety of patient subgroups by reducing over-treatment.

The clinical challenge of managing a bystander coronary lesion identified during the diagnostic evaluation for valve intervention is

Table 2 Angiographic and characteristics of the percutaneous coronary intervention and transcatheter aortic valve implantation procedures

Variable	FFR-guided PCI (*n* = 164)	Angiography-guided PCI (*n* = 156)
SYNTAX score[a], median (IQR)	7 (5–11)	7 (5–11)
Largest diameter stenosis, %, median (IQR)	55 (46–63)	56 (48–63)
Lesions with diameter stenosis >50%[b], *n* (%)		
1	100 (61)	92 (59)
2	45 (27)	45 (29)
3	12 (7)	12 (8)
4	7 (4)	5 (3)
>4	2 (1)	0 (0)
Fractional flow reserve before transcatheter aortic valve implantation, median (IQR)	.80 (.74–.87)	–
Fractional flow reserve after transcatheter aortic valve implantation, median (IQR)	.83 (.78–.91)	–
Lesions with fractional flow reserve ≤.80 at baseline, *n* (%)	83 (54)	–
Lesions with fractional flow reserve >.85 at baseline, *n* (%)	68 (35)	–
Lesions with fractional flow reserve .80–.85 at baseline, *n* (%)	22 (11)	–
Vessel with stenosis >50%[c], *n* (%)		
Left main	6 (3)	1 (1)
Left anterior descending artery	111 (48)	106 (48)
Circumflex artery	53 (23)	57 (26)
Right coronary artery	60 (26)	56 (25)
Percutaneous coronary intervention procedure[d]		
Percutaneous coronary intervention performed[e], *n* (%)	99 (60)	141 (91)
Timing of percutaneous coronary intervention, *n* (%)		
Before transcatheter aortic valve implantation	16 (16)	17 (12)
Concomitant with transcatheter aortic valve implantation before valve implantation	41 (42)	56 (40)
Concomitant with transcatheter aortic valve implantation after valve implantation	18 (18)	34 (24)
After transcatheter aortic valve implantation	24 (24)	34 (24)
Multivessel percutaneous coronary intervention, *n* (%)	22 (15)	28 (20)
Number of treated coronary vessels, *n* (%)		
1	76 (46)	114 (73)
2	21 (13)	25 (16)
3	2 (1)	3 (2)
No. of stents, median (IQR)	1 (1–2)	1 (1–1)
Stent diameter, mm, median (IQR)	3.0 (2.7–3.5)	3.0 (2.7–3.5)
Stent length, mm, median (IQR)	22 (18–28)	22 (18–28)
Percutaneous coronary intervention-related complications, *n* (%)		
Coronary dissection	1 (.7)	1 (.7)
Coronary perforation	1 (.7)	0 (0)
Coronary occlusion	1 (.7)	1 (.7)
Vascular access complication (VARC 2)	6 (4)	3 (2)

Continued

Table 2 *Continued*

Variable	FFR-guided PCI ($n = 164$)	Angiography-guided PCI ($n = 156$)
Ventricular arrhythmias	1 (.7)	1 (.7)
Transcatheter aortic valve implantation procedure, *n* (%)		
Femoral vascular approach		
Percutaneous	158 (96)	151 (97)
Surgical	6 (4)	5 (3)
General anaesthesia	17 (10)	13 (8)
Valve pre-dilatation	30 (19)	22 (14)
Valve post-dilatation	16 (10)	15 (10)
Valve type		
SAPIEN 3	76 (48)	72 (47)
SAPIEN 3 ULTRA	86 (52)	82 (53)
Valve size		
23 mm	55 (33)	63 (41)
26 mm	77 (47)	67 (43)
29 mm	32 (20)	24 (16)
Device success (VARC2)	152 (93)	143 (92)
Transcatheter aortic valve implantation-related complications, *n* (%)		
Vascular access complication (VARC 2)	13 (8)	9 (6)
Coronary occlusion	0 (0)	0 (0)
Cardiac tamponade	0 (0)	3 (2)
Aortic annulus rupture	0 (0)	2 (1)
Conversion to open surgery	2 (1)	1 (.6)

[a]SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX).
[b]Percentages may not total 100 because of rounding.
[c]Calculated on a total number of 452 evaluated vessels.
[d]x patients in the angiography-guided strategy did not undergo PCI.
[e]Numerically relevant differences are highlighted to aid interpretability. These were defined as an absolute difference ≥10% for categorical variables or a standardized difference >.25 for continuous variables. These indicators are provided for descriptive purposes only and were not derived from formal statistical testing, in accordance with CONSORT 2010 recommendations.

particularly pertinent, given that CAD is present in over 50% of patients undergoing TAVI.

Recently, the NOTION-3 study demonstrated that PCI of severe coronary stenoses (>90% or FFR ≤80) was associated with a lower risk of adverse events compared to conservative management, with a median follow-up of 2 years post-TAVI.[6] However, at subgroup analysis, no benefit of PCI was observed in patients with coronary lesions <90%, a population specifically targeted in our study. The FAITAVI trial differs from NOTION-3 in several key aspects.

First, the FAITAVI trial focused on intermediate coronary lesions, which represent the vast majority of bystander lesions found during the workup for TAVI and that rise the therapeutic dilemma, while angiographically severe lesions (diameter stenosis >90%) were excluded. Second, the FAITAVI included lesions with a negative FFR (>.80), which were excluded in NOTION-3. Notably, FFR may underestimate the hemodynamic significance of coronary lesions in the presence of severe AS, as the FFR value can decrease across the cut-off point in ∼10% of lesions due to improved hyperaemic coronary flow after TAVI.[11] The FAITAVI trial accounted for this by reassessing post-TAVI FFR for all borderline FFR values (.81–.85).

Third, while the NOTION-3 compared outcomes between patients undergoing revascularization and those managed conservatively, the FAITAVI trial compared FFR-guided PCI with angiography-guided PCI. Lastly, the FAITAVI trial included patients with lesions in the left main coronary artery, which were excluded in the NOTION-3.

Based on the well-established benefit of FFR-guided management in patients with CAD,[8] on the benign prognosis of stable coronary lesions,[19] and on preliminary studies that investigated the diagnostic accuracy and variability of FFR in patients with severe AS before and after TAVI,[12] we hypothesized that managing coronary lesions according to their functional significance would be beneficial in the decision-making process of TAVI candidates with concomitant stable CAD. As expected, the risk of a MACCE was significantly lower in patients allocated to the FFR-guided PCI strategy. Our findings are consistent with

Table 3 Primary and secondary endpoints at 1 year

Endpoint[a]	FFR-guided PCI ($n = 164$)	Angiography-guided PCI ($n = 156$)	Hazard ratio (95% CI)[b]	*P* value
Primary endpoint: MACCE[c]	14 (8.5)	25 (16.0)	.52 (.27–.99)	.047
Secondary endpoints				
Death from any cause	4 (2.4)	12 (7.7)	.31 (.10–.96)	
Death from cardiovascular causes	0 (0)	3 (1.9)		
Myocardial infarction	1 (.6)	2 (1.2)	.47 (.04–5.23)	
Ischaemia driven revascularization	0 (0)	3 (1.9)		
Stroke	1 (.6)	4 (2.5)	.24 (.03–2.11)	
Death from any cause or myocardial infarction	5 (3.0)	12 (7.7)	.39 (.14–1.10)	
Death from cardiovascular causes, myocardial infarction or revascularization	1 (.6)	5 (3.2)	.19 (.02–1.61)	
Death from cardiovascular causes or myocardial infarction	1 (.6)	4 (2.5)	.24 (.03–2.12)	
Safety endpoints				
Major bleeding	8 (4.9)	10 (6.4)	.75 (.30–1.91)	
Acute kidney failure	5 (3.0)	5 (3.2)	.95 (.26–3.48)[d]	
Periprocedural myocardial infarction	1 (.6)	2 (1.2)	.47 (.02–4.98)[d]	
Vascular complications	13 (7.9)	9 (5.7)	1.41 (.59–3.50)[d]	

[a]Endpoints are expressed as no. (%).
[b]The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.
[c]The primary endpoint was an MACCE, defined as a composite of death from any cause, myocardial infarction, ischaemia-driven revascularization, disabling stroke, and major bleeding.
[d]Odd ratio (95% CI).

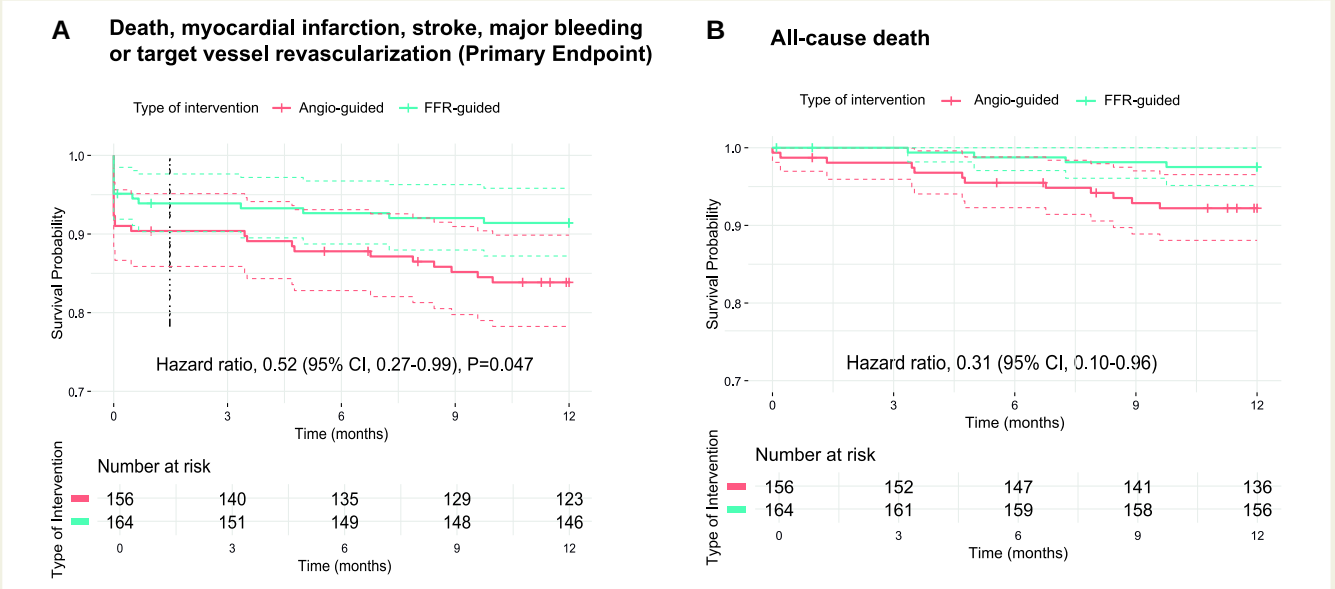

Figure 1 Kaplan–Meier plot and estimate for the primary endpoint and all-cause mortality. Panel *A* shows a Kaplan–Meier plot and estimate for the primary endpoint, defined as a composite of all-cause death, myocardial infarction, ischaemia-driven revascularization, disabling stroke, and major bleeding. Panel *B* shows a Kaplan–Meier plot and estimate for all-cause death. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

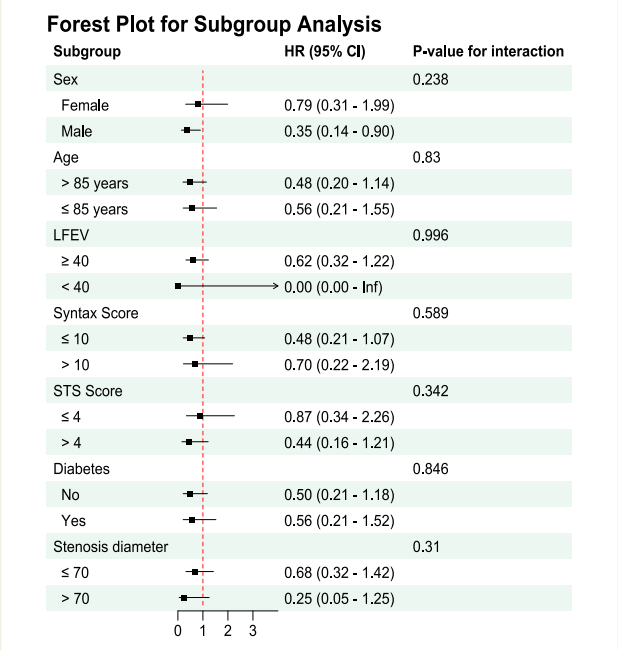

Figure 2 Subgroup analysis of the primary endpoint. Forest plot for the primary endpoint in prespecified subgroups. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects

previous research, highlighting the potential advantages of FFR-guided PCI[6–8] and extending them to complex patients undergoing TAVI.

It remains uncertain whether the reduction in endpoints is due to fewer events from lesions that were treated or from those that were deferred. One hypothesis is that in patients with AS, lesions deferred based on a negative FFR might carry an increased risk of ischemic events during follow-up, as FFR may underestimate the ischemic potential of a coronary lesion due to impaired coronary flow and microvascular dysfunction.[13,20,21] However, re-assessing FFR after valve implantation reduces such risk. In the FAITAVI trial, although post-TAVI reclassification of FFR was infrequent, lesions located in the left main and LAD demonstrated a higher likelihood of crossing the ischemic threshold following valve implantation. This observation supports the potential utility of post-TAVI physiological reassessment in anatomically high-risk territories. Furthermore, no significant differences in adverse events were observed between treated and deferred patients in the FFR-guided group, nor in patients with borderline FFR at baseline.

The event-free survival benefit observed in the FFR-guided group may be partly attributable to a reduction in early procedural complications. In our analysis, the composite endpoint of periprocedural death, stroke, or major bleeding occurred significantly less frequently in the FFR-guided group. Although differences in individual components did not reach statistical significance, the overall clustering of early adverse events in the angiography-guided arm suggests that a more selective, physiology-based revascularization strategy may reduce procedural burden and help mitigate risk in frail, elderly patients undergoing TAVI.

In the present trial, the primary endpoint was primarily driven by all-cause mortality, which may reflect the advanced age of the study population and the impact of external factors such as the COVID-19 pandemic. Although a nearly five-fold reduction in cardiovascular death, stroke, myocardial infarction, and TVR was observed in the FFR-guided group, these differences did not reach statistical significance. Notably, the components that contributed most to the positive results of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, such as ischaemia-driven revascularization, were less prominent in our study population.[8] Conversely, in the FAITAVI, the top three components of the composite endpoint contributing to the higher MACCE rate in the angiography-guided group were all-cause mortality, major bleeding, and stroke. These findings suggest that the benefit of physiology-guided PCI in this elderly and high-risk population may be driven not only by ischemic risk reduction but also by the avoidance of bleeding and cerebrovascular complications linked to more extensive revascularization and intensified antithrombotic therapy. Therefore, since causality between mortality and revascularization strategy cannot be definitively established, the lower rate of all-cause mortality in the FFR-guided arm should be interpreted with caution, particularly given the low event counts and limited power for secondary outcomes.

The FAITAVI trial has limitations. The median age of the study population was very high (86 years), which exceeds the average life expectancy in Italy and most Western countries. This reflects both the inclusion criteria and the clinical practice at the time of trial initiation, as FAITAVI began in 2017, when TAVI was primarily offered to older and higher-risk patients. In recent years, however, the indication for TAVI has expanded to younger and lower-risk populations. As a result, the FAITAVI cohort may be less representative of contemporary TAVI candidates with longer life expectancy. This demographic factor may have influenced the all-cause mortality rates observed in both arms, potentially diluting the effect of the PCI strategy on clinical outcomes. Further studies in younger, lower-risk patients and longer follow-up are warranted to confirm these results.

The estimated 1-year event rates of 32% and 20% in the angiography- and FFR-guided groups, respectively, were based on data from observational and randomized studies available evidence at the time of the protocol preparation.[13,16] The observed event rate was lower than initially estimated, and this discrepancy may reflect improvements in procedural techniques, device and operators' performance, and peri-procedural management over the course of the trial. Nevertheless, a nearly 50% actual difference of events between the two study groups confirmed the original assumption.

However, although the trial met its primary endpoint, the reduced event rates and slightly smaller effect size imply that the study may have been underpowered, especially to detect differences in secondary or individual clinical outcomes.

Complete revascularization was achieved in only 75% of the cases in the angiography-guided PCI arm compared with 99% in the FFR-guided PCI. Additionally, PCI was not performed in 9% of patients in the angiography-guided group, despite the presence of visually significant stenoses. An exploratory *post hoc* analysis of patients in the angiography-guided group who did not undergo PCI revealed two predominant patterns: lower rates of procedural success following TAVI and a higher prevalence of non-LAD target lesions, particularly involving the circumflex artery. These findings suggest that, in this frail and elderly population, operators were more likely to defer revascularization when the valve intervention was suboptimal or when the clinical course was complicated early by bleeding or other adverse events. Lesion location may have further influenced this choice, with revascularization preferentially performed on LAD lesions, whose prognostic relevance is well-established, while deferral was more common for circumflex disease. While these decisions may be clinically intuitive, they underscore the subjectivity inherent in angiography-guided strategies. In contrast, the

FFR-guided approach provides a physiology-based, lesion-specific roadmap that supports more standardized and objective revascularization decisions, even in complex or uncertain clinical scenarios.

Lastly, all TAVI procedures were performed with balloon-expandable valve with an intra-annular design that facilitates post-TAVI coronary access. The feasibility and efficacy of the trial FFR-guided strategy must also be confirmed with other trans-catheter valve structures.

Conclusions

In this randomized trial, FFR-guided PCI was superior to angiography-guided PCI in reducing MACCE at 12 months amongst patients with intermediate CAD undergoing TAVI. While the primary endpoint was mainly driven by all-cause mortality, the consistent trends observed across secondary endpoints and patient subgroups support the potential clinical benefit of a physiology-guided strategy. These findings warrant confirmation in future studies involving a broader, contemporary TAVI population.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

F. Ribichini has received honoraria from and is proctor for Edwards Lifesciences and Medtronic. R. Scarsini has received lecture fees from Abbott, Philips and B-Braun, institutional research grants from Abbott and in-kind support from Medis. G. Tarantini has received lecture fees from Medtronic, Edwards Lifesciences, Abbott, and Boston Scientific.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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The study was funded by unrestricted grants from Edwards Lifesciences Corporation and Philips, which had no role in study design, conduct, data analysis, or manuscript preparation.

Ethical Approval

The study protocol was approved by the Ethical Committee of all participating centres, co-ordinated by the University of Verona, and conducted according to the Helsinki declarations.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT03360591. The trial was registered at ClinicalTrials.gov

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