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ORIGINAL PAPER

Outcomes after TAVI in patients with atrial fibrillation and a history of recent PCI: Results from the ENVISAGE-TAVI AF trial

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Abstract

Background Patients with atrial fibrillation (AF) and a recent (≤90 days) percutaneous coronary intervention (PCI) undergoing transcatheter aortic valve implantation (TAVI) are at high bleeding risk due to the addition of oral antiplatelet (OAP) agents on top of oral anticoagulants. Data on outcomes of these patients are needed to optimize antithrombotic treatment.

Methods This analysis compared annualized clinical event rates in patients with and without a recent PCI enrolled in ENVISAGE-TAVI AF, a prospective, randomized, open-label, adjudicator-masked trial comparing edoxaban and vitamin K antagonists in AF patients after TAVI. The primary efficacy and safety outcomes were net adverse clinical events (NACE) and major bleeding.

Results Overall, 132 (94.3%) patients with a recent PCI ($n=140$) received OAP after TAVI, compared with 692 (55.9%) patients without a recent PCI ($n=1237$). Among patients with a recent PCI on OAP agents, use of dual antiplatelet therapy decreased to 5.5%, and use of single antiplatelet therapy (SAPT) increased to 78.0% over 3 months post-randomization. Conversely, use of SAPT predominated at all time points in patients without a recent PCI history. There were no significant differences in the incidence of NACE or other outcomes assessed, except for major bleeding events, which were more frequent in patients with vs without a recent PCI history (hazard ratio [95% confidence interval]: 2.17 [1.27, 3.73]; $P=0.005$).

Conclusions Patients with AF undergoing TAVI with a recent PCI have a similar risk of ischemic events and mortality, but an increased risk of major bleeding compared with patients without a recent PCI.

Keywords Atrial fibrillation · Percutaneous coronary intervention · Antiplatelet therapy · Edoxaban · Transcatheter aortic valve replacement

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Background

A high proportion (~50%) of patients undergoing transcatheter aortic valve implantation (TAVI) have a history of coronary artery disease, and 14% to 34% had a previous percutaneous coronary intervention (PCI) [1–3]. There is no evidence supporting routine PCI in patients undergoing TAVI that present with significant coronary stenosis [4], but current guidelines recommend PCI for > 70% stenosis located in proximal segments [5]. Furthermore, there are no specific recommendations related to the timing of TAVI after PCI or the use of antiplatelet therapy in patients undergoing TAVI following recent PCI [5], but physicians may delay TAVI in patients with recent PCI [4].

Patients with atrial fibrillation (AF) and recent PCI need oral antiplatelet (OAP) therapy to prevent stent thrombosis on top of treatment with an oral anticoagulant (OAC) [5–8]. Furthermore, patients with recent PCI and coronary stent implantation undergoing TAVI may have an underlying higher risk of bleeding caused by previous major bleeding, comorbidities, adherence problems, lifestyle, or occupation [5, 8]. There is a lack of data on the use of non–vitamin K antagonist oral anticoagulant (NOAC) and clinical outcomes in patients with AF undergoing TAVI with a recent PCI; furthermore, the optimal antithrombotic therapy for these patients is not well understood. In this subanalysis from the ENVISAGE-TAVI AF trial, we assessed clinical outcomes in patients with or without a recent history of PCI.

Methods

Study design

The ENVISAGE-TAVI AF trial (NCT02943785) was a multinational, multicenter, prospective, randomized, open-label, adjudicator-masked trial in which patients with prevalent or incident AF were randomized to receive edoxaban or vitamin K antagonist (VKA) between 12 h and 7 days after a successful TAVI procedure [9]. The detailed design of the trial has previously been published [9]. The trial was conducted in accordance with the International Council for Harmonisation and the Declaration of Helsinki. The ethics committees and corresponding health authorities for each site approved the protocol. All patients provided written informed consent before enrollment.

Study population

Patients 18 years or older with an indication for OAC due to prior or new-onset AF were eligible for enrollment. Key exclusion criteria included coexisting conditions that conferred a high risk of bleeding, unresolved serious periprocedural complications, and any contraindication per local label to edoxaban and VKA. Enrollment commenced in April 2017 and was completed in January 2020.

This prespecified subanalysis of ENVISAGE-TAVI AF included all randomized patients who received ≥ 1 dose of the assigned study drug. Data were collected for the duration of the treatment period and for up to 3 days after interruption or discontinuation of the study drug. Randomized patients were divided into 2 groups according to the presence or absence of a recent history of PCI. A recent PCI is defined as a procedure occurring within 90 days before TAVI and the day of randomization [8, 10–12]. Patients who underwent TAVI with PCI either prior to or during the study period could receive single antiplatelet therapy (SAPT) indefinitely. Dual antiplatelet therapy (DAPT) was only permitted after stenting for up to 3 months after PCI.

Study endpoints

The primary efficacy outcome was the incidence of net adverse clinical events (NACE), defined as the composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding (per the International Society on Thrombosis and Haemostasis [ISTH]: clinically overt bleeding associated with a reduced hemoglobin level, blood transfusion, symptomatic bleeding at a critical site, or death) [13]. The primary safety outcome was the incidence of major bleeding per ISTH criteria. Secondary outcomes included major gastrointestinal (GI) bleeding, intracranial hemorrhage, ischemic stroke, cardiovascular death, all-cause death, and clinically relevant nonmajor bleeding per ISTH criteria [9, 13].

Statistical analysis

Baseline characteristics and clinical event rates were stratified by patients with and without a recent history of PCI. Statistical comparisons for baseline characteristics of patients with vs without a recent history of PCI were made using analysis of variance for numerical parameters and Fisher's exact test for categorical parameters. Outcomes were reported as annualized event rates. Comparisons between patient groups and between treatment arms were reported as hazard ratios (HRs) with two-sided 95% confidence intervals (CIs) calculated using Cox proportional hazard regression models. Hazard ratios and *P*-values were only reported for outcomes with > 5 events in both groups. Interaction *P*-values were reported for outcomes with > 5 events in all subgroups.

Results

Patient disposition and PCI history

Of the 1426 patients randomized in the ENVISAGE-TAVI AF trial, 1377 were included in this analysis (Fig. 1); 140 (9.8%) had a recent PCI, of which 62 (44.3%) were performed within 30 days before TAVI. The temporal distribution of PCI is shown in Fig. 2. Detailed PCI characteristics for patients who received a PCI within 30 days of TAVI can be found in Table S1. In the 61 patients with available data, the left anterior descending coronary artery was the most frequently treated ($n = 32$), followed by the right coronary artery ($n = 23$). Most patients ($n = 51$) received at least one drug-eluting stent.

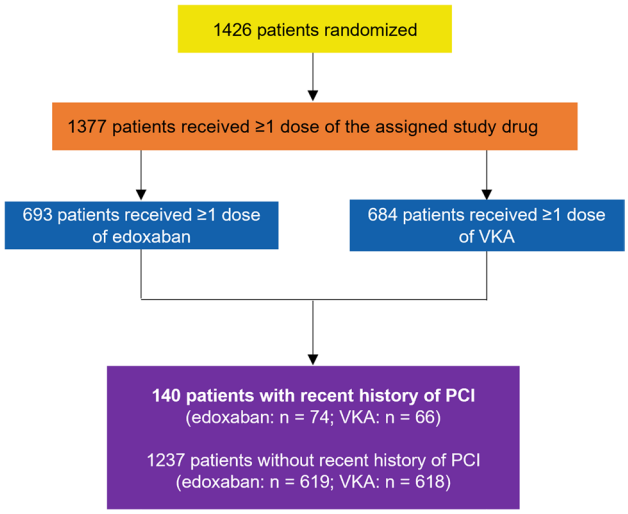

Fig. 1 Patient disposition. *PCI* percutaneous coronary intervention; *VKA* vitamin K antagonist

Patient baseline characteristics

Patients with vs without a recent PCI were more likely to have hypercholesterolemia ($P = 0.006$), prior myocardial infarction ($P = 0.004$), diabetes mellitus ($P = 0.005$), peripheral artery disease ($P = 0.0004$), and a history of stroke or transient ischemic attack ($P = 0.001$; Table 1). Baseline bleeding (HAS-BLED; hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol usage) and stroke (CHA_2DS_2-VASc; congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) risks were higher ($P < 0.0001$ for both) in patients with vs without a recent history of PCI. The use of a VKA pre-TAVI was more common than the use of a NOAC in patients without a PCI history ($P < 0.0001$ and $P = 0.02$). Additional baseline characteristics were similar between patients with a recent PCI history in the edoxaban and VKA arms (Table S2).

Use of oral anticoagulant and antiplatelet therapies over time

Most patients with a recent history of PCI (132 [94.3%]) received OAP therapy after TAVI (Fig. 3). After 90 days post-randomization, use of OAP decreased and continued to decline, with the majority receiving OAC without concomitant OAP at 1 year post-randomization. The use of OAP was less frequent in patients without a recent history of PCI, with 692 (55.9%) patients on OAP therapy after TAVI. This rate decreased to approximately 20% of patients around 90 days post-randomization. During the remainder of the observation period, approximately 15% of patients received concomitant OAP.

The use of SAPT and DAPT over time is shown in Fig. S1. DAPT was frequently prescribed in patients with

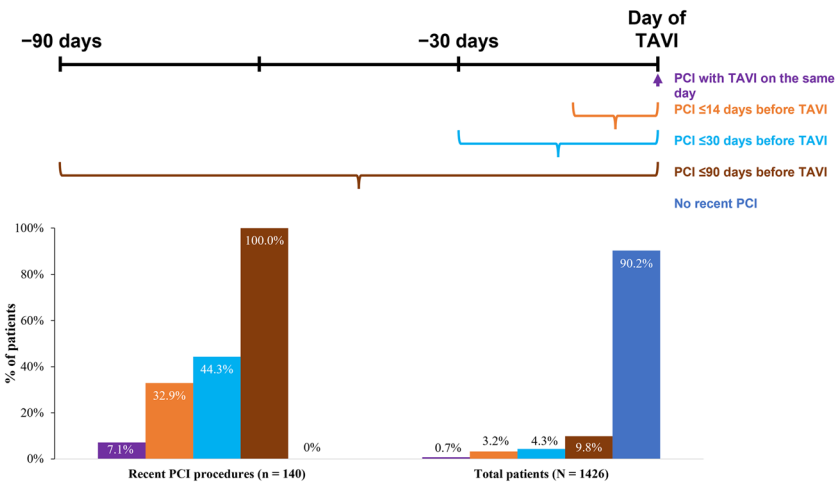

Fig. 2 Temporal distribution of PCI. *PCI* percutaneous coronary intervention; *TAVI* transcatheter aortic valve implantation

Table 1 Demographics and baseline characteristics in patients with or without recent PCI

Parameter	With recent PCI ($n=140$)	Without recent PCI ($n=1237$)	*P*-value
Age at enrollment, mean (SD)	82.1 (5.6)	82.0 (5.4)	0.8
< 65 years	2 (1.4)	8 (0.6)	
65– < 75 years	8 (5.7)	98 (7.9)	
≥ 75 years	130 (92.9)	1131 (91.4)	
Sex, male	75 (53.6)	644 (52.1)	0.8
Weight, kg, mean (SD)	75.4 (18.0)	75.3 (17.6)	0.9
Body mass index, kg/m^2, mean (SD)	27.5 (5.3)	27.7 (5.6)	0.6
Race*			
White	110 (78.6)	1036 (83.8)	0.1
Other	30 (21.4)	201 (16.2)	
Type of AF‡			
Paroxysmal	70 (50.0)	499 (40.3)	**0.03**
Persistent	18 (12.9)	140 (11.3)	
Long-standing persistent	7 (5.0)	103 (8.3)	
Permanent	44 (31.4)	474 (38.3)	
With atrial flutter	1 (0.7)	17 (1.4)	
Stroke/TIA	38 (27.1)	195 (15.8)	**0.001**
Hypertension	129 (92.1)	1129 (91.3)	0.9
Coronary artery disease	101 (72.1)	640 (51.7)	**< 0.0001**
Hypercholesterolemia	112 (80.0)	852 (68.9)	**0.006**
Diabetes mellitus	67 (47.9)	439 (35.5)	**0.005**
Hospitalization for bleeding	6 (4.3)	54 (4.4)	1
Valvular heart disease	140 (100)	1237 (100)	
Non-CNS systemic thromboembolic event	10 (7.1)	60 (4.9)	0.2
Peripheral artery disease	30 (21.4)	127 (10.3)	**0.0004**
Carotid artery disease	14 (10.0)	82 (6.6)	0.2
COPD	14 (10.0)	185 (15.0)	0.1
Myocardial infarction	31 (22.1)	160 (12.9)	**0.004**
Prior major bleeding or predisposition to bleeding	12 (8.6)	107 (8.6)	1
CABG	15 (10.7)	109 (8.8)	0.4
PCI performed within 30 days before TAVI	62 (44.3)	0	**< 0.0001**
Ejection fraction, mean (SD)	54.9 (12.1)	55.6 (11.3)	0.5
CrCl, mL/min, mean (SD)†	56.8 (22.4)	58.4 (24.3)	0.4
CrCl ≤ 50	59 (42.1)	511 (41.3)	0.9
OAP prior to randomization	114 (81.4)	508 (41.1)	**< 0.0001**
HAS-BLED score, mean (SD)	1.9 (0.9)	1.5 (0.7)	**< 0.0001**
CHA_2DS_2-VASc score, mean (SD)	5.0 (1.6)	4.4 (1.3)	**< 0.0001**
Gastrointestinal disorder	55 (39.3)	443 (35.8)	0.5
Previous PPI use	57 (40.7)	543 (43.9)	0.5
Pre-TAVI use of VKA	37 (26.4)	596 (48.2)	**< 0.0001**
Pre-TAVI use of NOAC	51 (36.4)	333 (26.9)	**0.02**
No pre-TAVI use of VKA or NOAC	52 (37.1)	308 (24.9)	**0.003**
Labile INR	7 (5.0)	101 (8.2)	0.2
Indication for dose adjustment§	71 (50.7)	566 (45.8)	0.3
STS score, mean (SD)	6.0 (4.2)	4.8 (3.8)	**0.0005**
EuroSCORE I, mean (SD)	12.8 (9.6)	12.9 (9.9)	0.9
EuroSCORE II, mean (SD)	4.6 (3.6)	4.6 (5.7)	0.9
Edoxaban arm	74 (52.9)	619 (50.0)	0.5
VKA arm	66 (47.1)	618 (50.0)	0.5
Intracranial hemorrhage	2 (1.4)	15 (1.2)	0.7

Table 1 (continued)

Parameter	With recent PCI ($n=140$)	Without recent PCI ($n=1237$)	*P*-value
Cigarette use (current or former)	54 (38.6)	391 (31.6)	0.1
Abnormal renal function	4 (2.9)	22 (1.8)	0.3
Abnormal liver function	0	3 (0.2)	1
Major bleed, anemia	12 (8.6)	107 (8.6)	1
Chronic drug usage**	52 (37.1)	175 (14.1)	**< 0.0001**
Excessive alcohol use	2 (1.4)	26 (2.1)	1
Hemoglobin, g/L, mean (SD)	113.3 (99.3)	115.9 (75.0)	0.7
Platelets, 10^9/L, mean (SD)	170.9 (58.1)	157.2 (54.8)	**0.006**

Data presented as n (%) unless otherwise noted

Bold value indicate$P< 0.05$

*Race was reported by the investigator from information obtained from patient history. "Other" includes patients of another race and those who chose not to report race. †Cockcroft–Gault formula. ‡Persistent defined as irregular rhythm occurring from 8 to 364 days; long-standing persistent for > 1 year. §Indications for adjustment of the edoxaban dose included CrCl ≤ 50 mL/min, bodyweight of ≤ 60 kg (not used as an indication in US patients), and concomitant therapy with a P-glycoprotein inhibitor (not used as an indication in US patients). **Chronic drug usage is one component of the HAS-BLED score, including antiplatelet agents, NSAIDs

AF atrial fibrillation; *CABG* coronary artery bypass graft surgery; *CHA_2DS_2-VASc* congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65 to 74 years, sex category; *CNS* central nervous system; *COPD* chronic obstructive pulmonary disease; *CrCl* creatinine clearance; *HAS-BLED* hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage; *INR* international normalized ratio; *NOAC* non–vitamin K antagonist oral anticoagulant; *NSAID* nonsteroidal anti-inflammatory drug; *OAP* oral antiplatelet; *PCI* percutaneous coronary intervention; *PPI* proton pump inhibitor; *SD* standard deviation; *STS* Society of Thoracic Surgeons; *TAVI* transcatheter aortic valve implantation; *TIA* transient ischemic attack; *VKA* vitamin K antagonist

recent PCI. Among patients with a recent history of PCI receiving OAP, the percentage of patients on SAPT (53.6%) increased over the first 3 months post-randomization, while the percentage on DAPT (37.1%) decreased. At 3 months, 78.0% of patients with a recent history of PCI received SAPT, and 5.5% received DAPT. Beyond 3 months, the use of any OAP in this subgroup was primarily SAPT.

Recent PCI and clinical outcomes

Patients with a recent PCI had a numerically higher annualized incidence of NACE than those without a recent history of PCI (22.94%/yr vs 14.28%/yr; HR [95% CI]: 1.55 [0.98, 2.45]; $P=0.06$; Fig. 4). This finding was attributable to patients with a recent PCI having a significantly higher annualized incidence of major bleeding events (15.39%/yr vs 7.40%/yr; HR [95% CI]: 2.17 [1.27, 3.73]; $P=0.005$) and numerically more frequent major GI bleeding (8.12%/yr vs 3.75%/yr; HR [95% CI]: 1.71 [0.90, 3.24]; $P=0.1$) and intracranial hemorrhage events (3.02%/yr vs 1.81%/yr) compared with those without a recent history of PCI. Differences between patients with and without a recent history of PCI in the time to first NACE and first major bleeding event were evident around 90 and 45 days post-randomization, respectively (Fig. S2). The risk of ischemic stroke was similar in patients with and without a recent PCI (2.40%/yr vs 2.32%/yr). Annualized incidences of cardiovascular death were 2.40%/yr vs 3.31%/yr and all-cause death were 4.80%/yr vs 5.61%/yr (HR [95% CI]: 0.65 [0.26, 1.63]; $P=0.4$) in patients with vs those without a recent PCI (Fig. 4, Fig. S2).

Regardless of a recent history of PCI, the incidences of NACE and major bleeding were similar between patients receiving edoxaban vs those receiving VKA (Fig. 5). In patients without a recent PCI, the incidence of major GI bleeding was significantly higher for patients receiving edoxaban compared with those receiving VKA (5.36%/yr vs 2.00%/yr; HR [95% CI]: 2.75 [1.54, 4.94]; $P=0.001$). For patients with a recent PCI, of the first 24 major bleeding events, 12 were GI (Table S3), but the annualized event rate of major GI bleeding was similar between treatment arms (7.66%/yr vs 8.70%/yr; HR [95% CI]: 0.87 [0.30, 2.56]; $P=0.8$). There was no significant interaction between the patient group and the treatment group for any of the outcomes.

Discussion

In this subanalysis of patients from the ENVISAGE-TAVI AF trial with a recent history of PCI after undergoing TAVI, the incidence of NACE and the risk of major

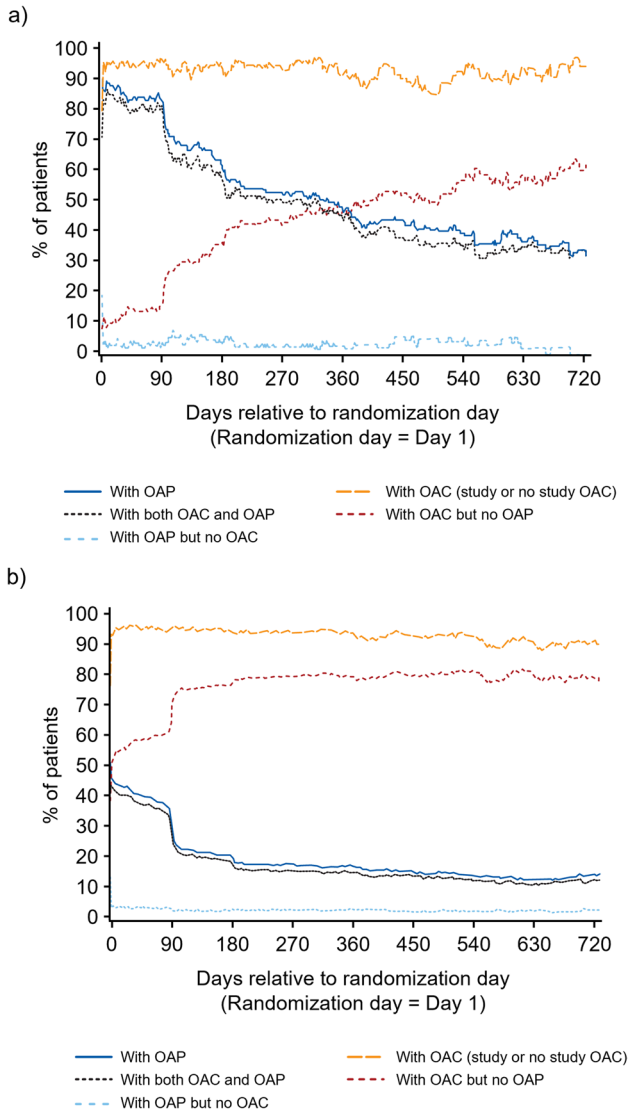

Fig. 3 Use of OAP over time in patients with (**a**) and without (**b**) recent PCI history. *OAC* oral anticoagulation; *OAP* oral antiplatelet; *PCI* percutaneous coronary intervention

bleeding and major GI bleeding were similar in patients receiving edoxaban and VKA. This finding was not shown with any other NOAC, confirming that edoxaban is a worthy alternative to VKA in this special population.

In this study, 9.8% of patients with AF undergoing TAVI had a recent PCI. In comparison, this is lower than in a study that found approximately 18% of patients with AF undergoing TAVI had a recent PCI [14]. Furthermore, these results were also lower in patients with aortic stenosis undergoing TAVI, in which 14% to 34% have a history of PCI [2, 3]. This relatively low prevalence of a previous PCI in the ENVISAGE-TAVI AF trial is likely attributable to the focus on patients who had undergone a recent PCI (≤ 90 days), whereas the previous studies had a 1- to 2-year follow-up period [2, 3, 8, 14].

Another study finding was that patients with a recent history of PCI had a higher atherosclerotic risk profile (higher prevalence of previous cardiovascular ischemic events and risk factors) and higher HAS-BLED and CHA_2DS_2-VASc risk scores than those without a recent PCI, as may be expected since PCI is performed in patients with lesions with high stenoses and/or patients with angina. This clinical profile carried neither a higher risk of stroke nor all-cause or cardiovascular death, but bleeding events occurred more frequently in this subgroup. Previous research in anticoagulated patients with AF showed both the HAS-BLED and CHA_2DS_2-VASc risk scores were moderate predictors of stroke, major bleeding, and mortality events [15]. These 2 scores performed similarly in the prediction of major bleeding events, suggesting that patients with an increased risk of stroke also have an increased bleeding risk [15, 16]. However, these previous analyses were not specific to patients with AF undergoing TAVI in contrast to the current study.

Data from previous studies involving patients with AF undergoing TAVI show that simplifying antithrombotic treatment offers a better safety profile (i.e., reduced bleeding complications) without increasing the risk of thromboembolic events [17, 18]. Thus, the consensus is to use OAC alone in patients with AF undergoing TAVI unless there is an established indication for antiplatelet therapy [8]. The presence of a recent PCI in patients with AF undergoing TAVI has a clear implication for antithrombotic therapy. Still, the need for coadministration of antiplatelet drugs and OAC increases the risk of bleeding events. Previous studies in patients with a recent PCI have investigated DAPT de-escalation strategies and demonstrated a reduction in bleeding events without an increase in ischemic events [19, 20]. The study results presented here showed that patients with a recent history of PCI received OAP approximately twice as frequently as patients without a recent PCI and had an increased rate of major bleeding. Further research exploring de-escalation of OAP in patients with AF undergoing TAVI with a recent PCI may be warranted.

Some practical implications of our findings may be related to the procedural aspects of PCI in patients with AF undergoing TAVI. First, if the clinical situation allows, it may be convenient to delay TAVI in patients having undergone PCI until antithrombotic treatment can be simplified. Although there are no specific recommendations about timing in patients with AF needing TAVI after a recent PCI [5], it is not uncommon for physicians to delay TAVI in these patients [4]. In the ACTIVATION study, patients were randomly assigned to receive PCI prior to TAVI. The median time from randomization to TAVI was 41 days in the PCI group and 27 days in the no-PCI group [4]. Second, the use of drug-eluting balloons instead of coronary stents may reduce the need for antiplatelet therapy and may be an

Outcome	Event rate, %/yr (no. of patients/Total no.) Recent PCI history	No recent PCI history	Hazard ratio (95% CI)	*P*-value
NACE	22.94 (35/140)	14.28 (220/1237)	1.55 (0.98, 2.45)	0.06
Ischaemic stroke	2.40 (4/140)	2.32 (37/1237)		
Intracranial haemorrhage	3.02 (5/140)	1.81 (29/1237)		
CV death	2.40 (4/140)	3.31 (53/1237)		
All-cause death	4.80 (8/140)	5.61 (90/1237)	0.65 (0.26, 1.63)	0.4
Major bleeding	15.39 (24/140)	7.40 (115/1237)	2.17 (1.27, 3.73)	**0.005**
Major GI bleeding	8.12 (13/140)	3.75 (59/1237)	1.71 (0.90, 3.24)	0.1
Fatal major bleeding	2.40 (4/140)	0.81 (13/1237)		

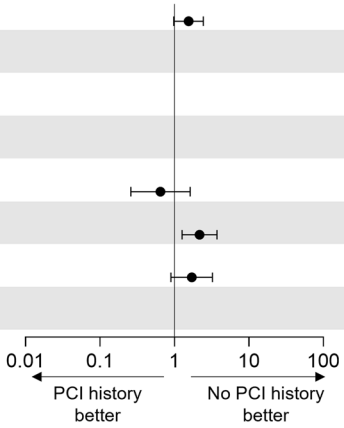

Fig. 4 Primary efficacy and primary safety outcomes in patients with and without a recent PCI history. Outcomes are reported for the on-treatment population (ie, patients on study medication or within 3 days of previous study medication). Hazard ratios and *P*-values were only reported for outcomes with > 5 events in both groups. Bold values indicate a $P<0.05$ *CI* confidence interval; *PCI* percutaneous coronary intervention

Outcome	Event rate, %/yr (no. of patients/Total no.) Edoxaban	Vitamin K antagonist	Hazard ratio (95% CI)	*P*-value	*P*-value interaction
Net adverse clinical events					0.8
PCI Yes	24.48 (21/74)	20.97 (14/66)	1.23 (0.62, 2.43)	0.6	
PCI No	14.94 (120/619)	13.57 (100/618)	1.09 (0.84, 1.43)	0.5	
Ischemic stroke					
PCI Yes	2.09 (2/74)	2.84 (2/66)			
PCI No	2.03 (17/619)	2.65 (20/618)			
Intracranial hemorrhage					
PCI Yes	2.10 (2/74)	4.26 (3/66)			
PCI No	1.43 (12/619)	2.25 (17/618)			
Cardiovascular death					
PCI Yes	3.13 (3/74)	1.41 (1/66)			
PCI No	3.44 (29/619)	3.16 (24/618)			
All-cause death					
PCI Yes	7.30 (7/74)	1.41 (1/66)			
PCI No	5.34 (45/619)	5.92 (45/618)			
Major bleeding					0.7
PCI Yes	16.21 (14/74)	14.38 (10/66)	1.17 (0.53, 2.60)	0.7	
PCI No	8.75 (71/619)	5.93 (44/618)	1.43 (0.98, 2.08)	0.07	
Major gastrointestinal bleeding					0.07
PCI Yes	7.66 (7/74)	8.70 (6/66)	0.87 (0.30, 2.56)	0.8	
PCI No	5.36 (44/619)	2.00 (15/618)	2.75 (1.54, 4.94)	**0.001**	

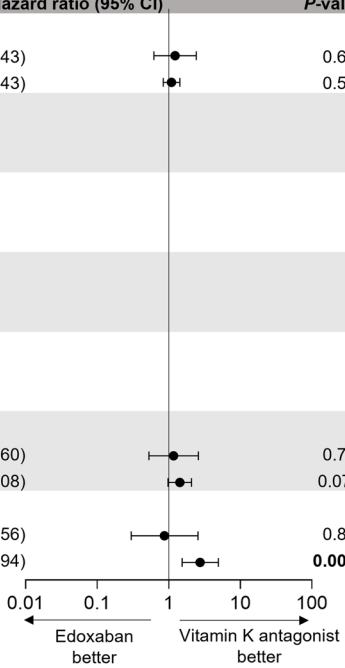

Fig. 5 Clinical outcomes in patients with and without recent PCI receiving edoxaban or VKA. Outcomes are reported for the on-treatment population (ie, patients on study medication or within 3 days of previous study medication). Hazard ratios and *P*-values were only reported for outcomes with > 5 events in both treatment groups. Interaction *P*-values were provided for outcomes with > 5 events in all subgroups. Bold values indicate a $P<0.05$ *CI* confidence interval; *PCI* percutaneous coronary intervention

option for patients at high bleeding risk, including those undergoing TAVI [21, 22]. Third, drug-eluting stents with proven efficacy and safety under short-term (1 month) DAPT may provide clinical benefits in patients with AF after TAVI [23]. Clinicians may consider simplifying and shortening antiplatelet therapy according to ischemic and bleeding risk in these patients.

The ENVISAGE-TAVI AF trial demonstrated that edoxaban was noninferior to VKA in patients with AF undergoing TAVI with regards to the primary efficacy endpoint of

NACE [9]. However, more patients on edoxaban vs VKA had increased major bleeding and major GI bleeding events [9]. Here, in patients with a recent PCI, the incidences of NACE, major bleeding, and major GI bleeding were similar between treatment arms, in this population at high risk of ischemic events and cardiovascular mortality. In patients without a recent history of PCI, there was no difference between treatment arms in the incidence of NACE. However, the incidence of major GI bleeding was higher for edoxaban vs VKA, and subsequently, the frequency of major bleeding events was numerically higher for edoxaban vs VKA. Notably, this trend was not observed in patients with a recent history of PCI. This could suggest that edoxaban may not increase the risk of major bleeding relative to VKA in instances where use of OAP is appropriately indicated.

In the ENTRUST-AF PCI (Edoxaban-based vs Vitamin K Antagonist-based Antithrombotic Regimen After Successful Coronary Stenting in Patients with Atrial Fibrillation) trial, 1506 patients with AF having undergone a successful PCI were randomized to either edoxaban plus a P2Y12 inhibitor for 12 months or to a VKA in combination with a P2Y12 inhibitor and aspirin for 1–12 months [24]. The patients in ENTRUST were younger with a lower cardiovascular risk compared to patients in the ENVISAGE-TAVI AF study. The main efficacy outcome (combination of cardiovascular death, stroke, systemic embolic events, myocardial infarction, and definitive stent thrombosis) was similar in both groups of patients in ENTRUST. The annualized rate of major bleeding was lower in patients allocated to edoxaban (20.7%) vs VKA (25.6%), although superiority was not met ($P = 0.001$ for noninferiority, $P = 0.1154$ for superiority). The present subanalysis from the ENVISAGE-TAVI AF trial extends the finding that edoxaban is noninferior to VKA in patients with AF with recent PCI to the complex group of patients with AF who have undergone TAVI.

Limitations

There are several limitations to this subanalysis, including the small number of patients with a recent history of PCI. Additionally, details on PCI procedures were only available for 61 out of 140 patients. Although information on the number of stents implanted was not specifically collected, the numbers of index lesion stents add up to 61, which is also the total number of PCI procedures for which any details are available, suggesting it is unlikely that more than one stent was used for PCI of the index lesion. There were no specific recommendations included in the ENVISAGE-TAVI AF trial regarding the PCI indication and the timing from PCI to TAVI. Notably, patients undergoing TAVI who also had concomitant coronary artery disease or recently underwent PCI were eligible for enrollment in the trial, reflecting the real-world population of patients undergoing TAVI. Additionally, when the ENVISAGE-TAVI AF trial was performed, data from randomized trials providing insight into simpler antithrombotic regimens after TAVI were not available. The rate of bleeding events in patients with AF undergoing TAVI treated with the simpler antithrombotic regimens currently recommended may be lower than what was observed in the trial. It is important to note that the results of this study are only applicable to patients undergoing TAVI who are receiving OAC due to AF, not to the general population of patients undergoing TAVI. Furthermore, the study may not have enrolled patients with clinical events, such as intracranial hemorrhage occurring shortly after PCI. This possibility may have introduced selection bias through the exclusion of patients with a recent history of PCI who experienced a bleeding or ischemic event after PCI. However, this potential limitation would have impacted the edoxaban and VKA arms equally. Larger studies adequately powered to statistically compare outcomes with edoxaban to VKA in patients with and without a recent history of PCI are needed to confirm the results presented here.

Conclusions

Among patients with prior and new-onset AF undergoing TAVI, those with vs without a recent history of PCI had a similar risk of ischemic events and cardiovascular mortality and a significantly higher risk of major bleeding events. Additionally, patients with a recent PCI who were treated with edoxaban had similar incidences of NACE, major bleeding, and major GI bleeding events compared with those treated with VKA. These results indicate that edoxaban is an alternative to VKA in this very high-risk patient population.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics statements The ENVISAGE-TAVI AF protocol was approved by the ethics committees and corresponding health authorities for all sites. All patients provided written informed consent before enrollment.

Competing interests **RM** received payments for personal fees from Abbott Vascular, AMGEN, Biosensors, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Ferrer, Medtronic, Philips, and Terumo; **LNF** is a proctor for Abbott Medical and received personal fees from Abbott Medical, Boston Scientific, and Edwards Lifesciences; **NVM** received grants or contracts from Abbott, Abiomed, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Medtronic, PulseCath BV, and Siemens; **CH** is a clinical proctor for Edwards Lifesciences and Boston Scientific; received research grants to institution from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic; and reports payment for speaker bureaus and support for attending meetings from Daiichi Sankyo and advisory board participation for Daiichi Sankyo; **MV** received grants and personal fees from Terumo and has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Bayer, CoreFlow, Idorsia Pharmaceuticals LTD, Universität Basel, Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, Biotronik, Boston Scientific, Medtronic, Vesalio, Novartis, Chiesi, and PhaseBio; **PO** has nothing to disclose; **HM** received personal fees from Daiichi Sankyo, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Edwards Lifesciences, Boston Scientific, Abbott Medical, and AstraZeneca and support for attending meetings from Daiichi Sankyo, Pfizer, Edwards Lifesciences, Boston Scientific, Abbott Medical, and AstraZeneca; **GD** received research grants to institution and support for attending meetings from Bayer and Daiichi Sankyo and consulting fees from Daiichi Sankyo; and **JS, RS, JJ,** and **MU** are employees of Daiichi Sankyo.

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