SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Statistical Analysis

Continuous variables are expressed as means (standard deviation, SD) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. We assessed the effect of the US guidance implementation on procedural outcomes and vascular and bleeding complications using logistic regression models and calculated the odds ratio (OR) for the US-guided group relative to the Fluo-guided group as the treatment effect size. In order to reduce the effects of potential confounding factors in the between-group comparisons, we used propensity-score methods[11,12]. As the main analysis, propensity score was used to assemble well-balanced groups based on 15 variables (female sex, NYHA class, diabetes mellitus, preoperative creatinine >2mg/dL, preoperative anticoagulant treatment, hypertension, peripheral artery disease (PAD), THV type, sheath to femoral artery ratio (SFAR)>1,05, history of atrial fibrillation, ongoing clopidogrel treatment, STS score, age, BMI, preoperative left ventricular ejection fraction (LVEF)) (propensity score-matched cohort) and a generalized linear mixed model (binomial distribution, logit function) was used for binary outcomes and a linear mixed model for continuous outcomes with the matched blocks as random effect.

In sensitivity analysis, we estimated the effect of the US guidance implementation on outcomes by using inverse probability of treatment weighting (IPTW) using propensity score. Treatment effects were estimated using weighted logistic (binary outcomes) or linear regression models (quantitative outcomes) with use of stabilized inverse propensity score as weight.

We also compared the survival during the follow-up between the US and Fluo guidance implementation using Cox's regression models. Using Fluo-guided patients as reference group, hazard ratio (HRs) were derived from these Cox regression models as treatment effect size measures, with their 95% confidence intervals (CIs). To account the matched design, we used the robust sandwich variance estimation to estimate the matched HRs. We assess the proportional hazard assumption using Schoenfeld residuals plots[14]. The comparison of survival during the first year between Life-threatening or bleeding complications were realized using the same methods. The propensity score was estimated using a non-parsimonious multivariable logistic regression model, with the treatment group as the dependent variable and all of the characteristics listed in Table 1 as covariates. Patients from the US-guided group were matched 1:1 to patients in the Fluo-guided group according to propensity score using the greedy nearest neighbor matching algorithm with a caliper width of 0.2 SD of logit of propensity score[12,13]. To evaluate bias reduction using the propensity score matching method, absolute standardized differences (ASD) were calculated[12]. Because of missing baseline data, (Table S1), we estimated the treatment effect size in propensity score-matched- and -adjusted cohorts after handling missing covariate values by multiple imputation using a regression switching approach (chained equations with m=10). Imputation procedure was performed under the missing at random assumption[31] using all variables listed in Table 1 (including treatment group) with a predictive mean matching method for continuous variables and multinomial or binary logistic regression model for categorical variables. In each imputed dataset, we calculated the propensity score and assembled a matched cohort to provide both adjusted and matched effect sizes. We therefore combined effect sizes from each imputed dataset using Rubin's rules[32]. Finally, the procedural outcomes and vascular and bleeding complications were described with 95% confidence intervals in patients implanted with THV of 3rd generation. Statistical testing

was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

Endpoints

All endpoints were defined according to VARC-2 (22).

Major VC were defined by the presence of any of the following: 1) any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation or new apical aneurysm; 2) access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to either death, life-threatening or major bleeding, visceral ischemia or neurological impairment; 3) distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage; 4) the use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment; 5) any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram; 6) surgery for access site-related nerve injury; 7) permanent access site-related nerve injury

Minor VC were defined by the presence of any of the following: 1) access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematoms, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment; 2) distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage; 3) any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication; 4) vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft).

Percutaneous closure device failure was defined by a failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

Table S1. Vascular, bleeding and peri-procedural complications according to Fluo-guided or US-guided vascular access: unadjusted analysis.

	Fluo-guided-2nd gen. group (n=119)	US-guided-2nd gen. group (n=119)	**Unadjusted** OR (95%CI)[1]	p
Vascular complications				
Overall VC (major or minor)	42 (35.3)	18 (15.1)	0.33 (0.27 to 0.40)	<.001
Major VC	23 (19.3)	7 (5.9)	0.26 (0.11 to 0.64)	0.003
Major VC related to vascular access	18 (15.1)	5 (4.2)	0.25 (0.09 to 0.69)	0.007
Major or minor VC related to vascular access	40 (33.6)	16 (13.5)	0.31 (0.16 to 0.59)	<.001
Minor VC	19 (16.0)	11 (9.2)	0.54 (0.24 to 1.18)	0.12
Bleeding complications				
Overall bleeding	51 (42.9)	21 (17.7)	0.29 (0.16 to 0.52)	<.001
Life-threatening or major bleeding	28 (23.5)	7 (5.9)	0.20 (0.09 to 0.49)	<.001
Transfusion	27 (22.7)	13 (10.9)	0.42 (0.20 to 0.86)	0.017
Procedural outcomes				
Mean fluoroscopic time (seconds)	1767 (631)	1230 (410)	-537 (-674 to -401)	<.001
Mean DAP	106 (75.8)	77.9 (50.9)	-28.4 (-45.0 to -11.7)	<.001
Mean Kerma	829 (590)	575 (364)	-254 (-381 to -127)	<.001
Median volume of contrast (mL)	150 (120 to 180)	133 (115 to 170)	-0.07 (-0.20 to 0.06)*	0.27
Acute kidney injury	21 (17.7)	18 (15.1)	0.83 (0.42 to 1.66)	0.60
Percutaneous closure device success	104 (87.4)	117 (98.3)	8.44 (1.89 to 37.77)	0.005

Table S2. Baseline and procedural characteristics of the 3rd generation group.

Baseline characteristics (n=308)	
Age (years)	82.5 (6.5)
Female	175 (56.8)
BMI (kg/m^2)	28.2 (21.8)
NYHA class III or IV	132 (43)
STS-PROM (%)	5.8 (3.5)
Ongoing clopidogrel therapy	94 (30.7)
Preoperative anticoagulant therapy	101 (32.8)
Comorbidities	
Diabetes mellitus	89 (28.9)
Hypertension	237 (76.9)
Coronary artery disease	198 (64.3)
Prior Stroke/TIA	54 (17.5)
COPD	61 (20.0)
Peripheral artery disease	55 (17.9)
Prior atrial fibrillation	116 (37.7)
Creatinine >2mg/dL	16 (5.2)
Echocardiographic parameters	
LVEF (%)	60 (50 to 62)
AVA (cm^2)	0.7 (0.6 to 0.8)
Mean aortic gradient (mmHg)	43 (35 to 43)
Procedural characteristics	
Main access sheath size	14 (14 to 16)
Secondary access sheath size	7 (7 to 7)
Valve type	
Sapien 3	247 (80.2)
Corevalve	2 (0.7)
Evolut R	58 (18.8)
Lotus	1 (0.3)
Valve size	
23	95 (30.8)
26	144 (46.8)
29	64 (20.8)
31	3 (0.9)
34	2 (0.7)
Sheath to femoral artery ratio > 1,05	9 (6.3)

AVA: aortic valve area; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS-PROM: Society of Thoracic Surgeons score; TIA: transient ischemic attack.

Table S3. Procedural outcomes of patients of the 3rd generation group.

	(n=308)	CI 95%
Vascular complications		
Overall VC (major or minor)	32 (10.39)	(7.22 to 14.35)
Major VC	10 (3.25)	(1.57 to 5.89)
Major VC related to vascular access	5 (1.62)	(0.53 to 3.75)
Major or minor VC related to vascular access	28 (9.09)	(6.13 to 12.87)
Minor VC	22 (7.14)	(4.53 to 10.61)
Bleeding complications		
Overall bleeding	35 (11.36)	(8.04 to 15.45)
Life-threatening or major bleeding	11 (3.57)	(1.80 to 6.30)
Transfusion	44 (14.33)	(10.58 to 18.72)
Procedural outcomes		
Paravalvular regurgitation ≥ moderate	25 (8.12)	(5.32 to 11.75)
Percutaneous closure device success	306 (99,3)	

VC: vascular complications

Figure S1. Propensity score distribution in the Fluo-guided and in the US-guided group.

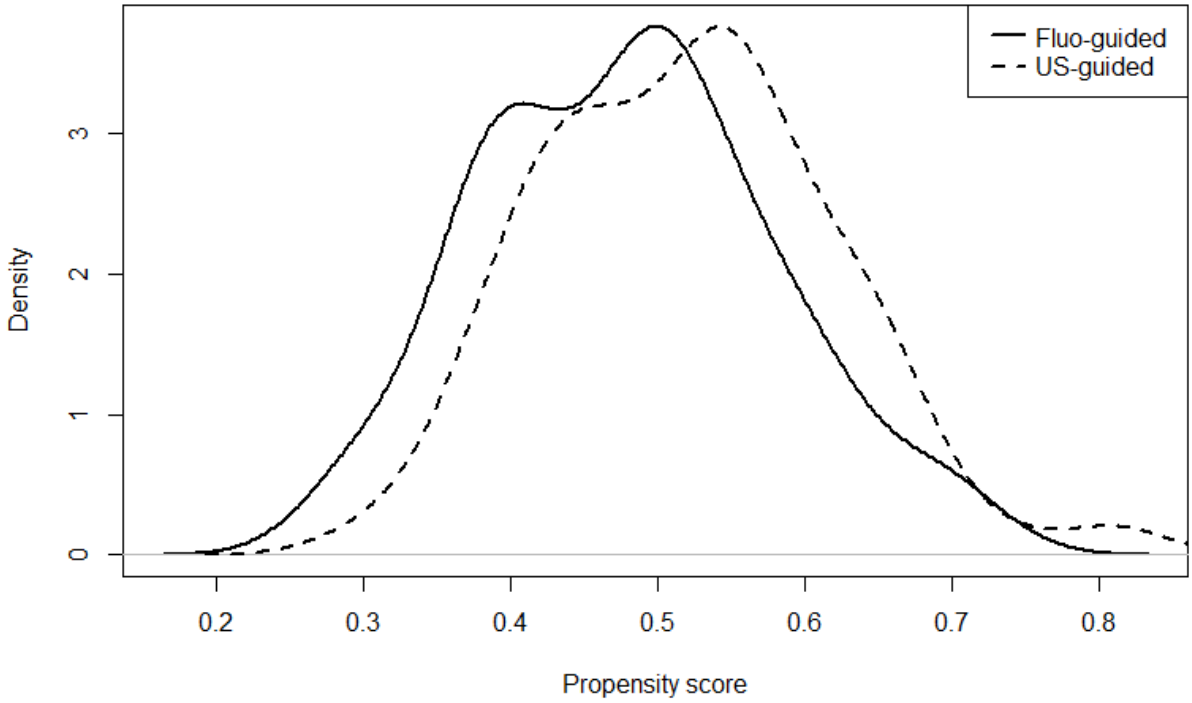
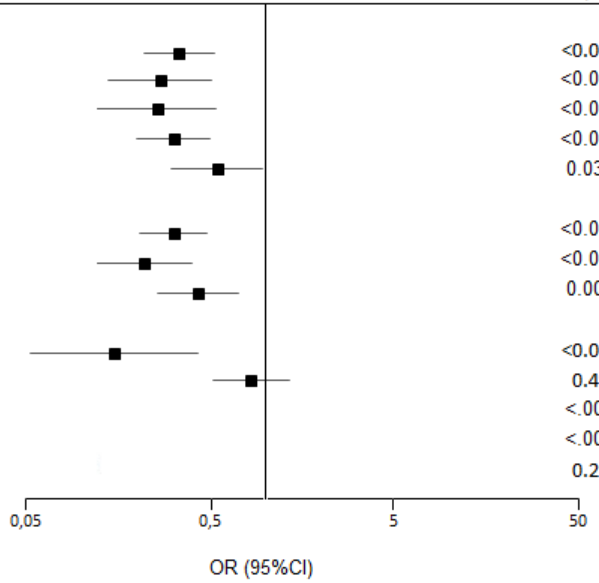


Figure S2. Vascular, bleeding and peri-procedural complications according to Fluo-guided or US-guided vascular access: IPTW adjusted Cohorts.

Outcomes	Fluo-guided 2nd gen.group (n=119)	US-guided 2nd gen.group (n=119)	IPTW OR(95%CI)	p
Vasular complications				
Overall vascular complications (major or minor)	42 (35.3)	18 (15.1)	0.34 (0.22 to 0.53)	<0.001
Major vascular complications	23 (19.3)	7 (5.9)	0.27 (0.14 to 0.51)	<0.001
Major vascular complications related to vascular access	18 (15.1)	5 (4.2)	0.26 (0.12 to 0.54)	<0.001
Major or minor vascular complications related to vascular access	40 (33.6)	16 (13.4)	0.32 (0.20 to 0.50)	<0.001
Minor vascular complications	19 (16.0)	11 (9.2)	0.55 (0.31 to 0.97)	0.039
Bleeding complications				
Overall bleeding	51 (42.9)	21 (17.6)	0.32 (0.21 to 0.48)	<0.001
Life-threatening or major bleeding	28 (23.5)	5.97 (5.9)	0.22 (0.12 to 0.40)	<0.001
Transfusion of RBC ≥ 1 unit	27 (22.7)	13 (10.9)	0.43 (0.26 to 0.72)	0.001
Procedural outcomes				
Percutaneous closure device failure	15 (12.6)	2 (1.7)	0.14 (0.41 to 0.05)	<0.001
Acute kidney injury	21 (17.6)	18 (15.1)	0.84 (0.52 to 1.36)	0.49
Mean fluoroscopic time (seconds) (SD)	1767 (631)	1230 (410)	-535 (-670 to -399)	<.001
Mean Air Kerma (mGy) (SD)	829 (590)	575 (364)	-277 (-435 to -120)	<.001
Median volume of contrast (mL) IQR)	150 (120 to 180)	133 (115 to 170)	-0.07 (-0.020 to 0.06) *	0.29



IPTW: inverse probability of treatment weighting; DAP: dose area product (Gy·cm^2); Kerma: kinetic energy released per unit mass (mGy); VC: vascular complication; SD: standard deviation.
OR indicates odds ratio expect for continuous variables where the mean difference between 2 groups are reported. * Calculated after log transformation