Treatment Adherence and Adverse Events After Combined TAVR + LAAO or TAVR + Oral Anticoagulation in Patients with Atrial Fibrillation

WATCH-TAVR OAC Compliance Substudy

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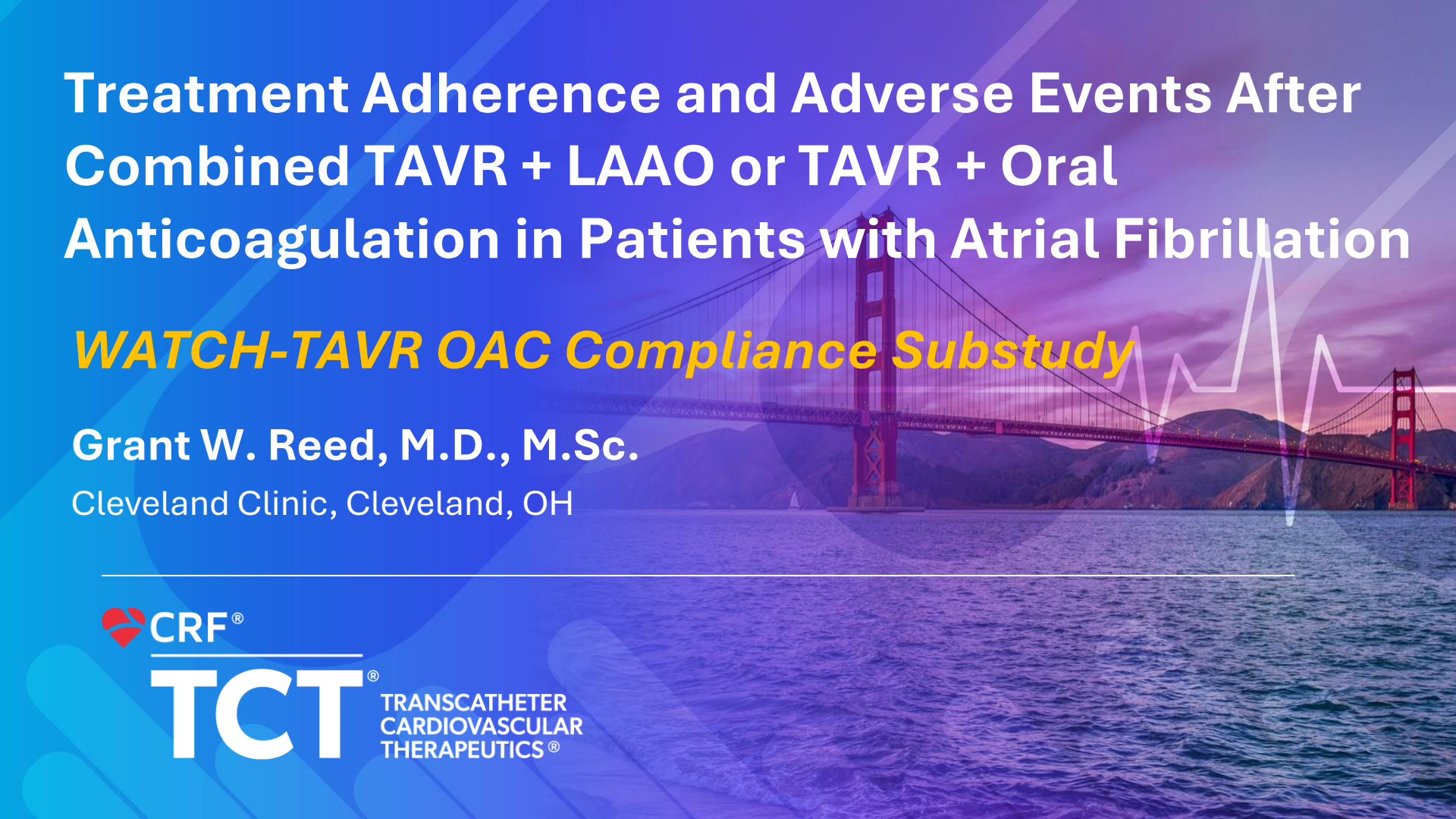

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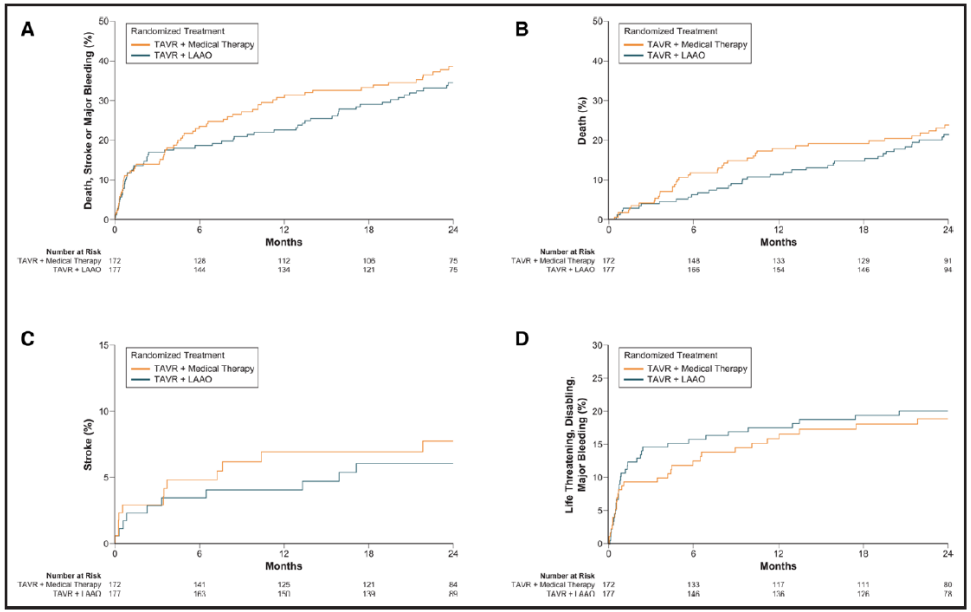
Combined LAAO + TAVR May Fill an Important Need

- Atrial fibrillation (AF) is prevalent in 15-40% of patients undergoing transcatheter aortic valve replacement (TAVR).
- TAVR patients are often at elevated risk of stroke/TIA and bleeding from oral anticoagulation (OAC).
  - Many have an indication for left atrial appendage occlusion (LAAO).
- **WATCH-TAVR** (*WATCHMAN for Patients with AF Undergoing TAVR*) Trial randomized 349 patients with severe aortic stenosis (AS) and AF to combined TAVR + LAAO with WATCHMAN 2.5 vs TAVR + OAC alone (standard of care).

Kapadia SR, et al. *Circulation*. 2024;149:734–743.

WATCH-TAVR Trial: Key Results

No difference in stroke, death, or major bleeding with TAVR + LAAO vs TAVR + OAC alone



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WATCH-TAVR Trial: Key Results

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	TAVR + LAAO (N=177)		TAVR + medical therapy (N=172)		TAVR + LAAO vs TAVR + medical therapy, HR (95% CI)*
	Events per 100 patient-years, n	Event rate, n (%)	Events per 100 patient-years, n	Event rate, n (%)	
Primary end point†	22.7	60 (33.9)	27.3	64 (37.2)	0.86 (0.60–1.22)
Secondary end points					
All-cause mortality	12.0	37 (20.9)	14.2	39 (22.7)	0.86 (0.55–1.34)
Stroke	3.4	10 (5.7)	4.6	12 (7.0)	0.76 (0.33–1.77)
Major or life-threatening bleeding	12.9	35 (19.8)	12.3	30 (17.4)	1.10 (0.67–1.79)
Cardiovascular death	6.5	20 (11.3)	8.00	22 (12.8)	0.82 (0.45–1.51)
Ischemic stroke	3.4	10 (5.7)	4.2	11 (6.4)	0.83 (0.35–1.96)
Hemorrhagic stroke	0.0	0 (0.0)	0.4	1 (0.6)	–
Arterial or venous thrombosis or embolism	5.5	16 (9.0)	1.1	3 (1.7)	5.03 (1.47–17.26)
Rehospitalization‡	6.4	18 (10.2)	8.9	22 (12.8)	0.76 (0.41–1.42)

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Possible Explanations for Lack of Impact on Bleeding

- **Differences in anti-thrombotic strategies in treatment arms**
  - TAVR + LAAO were required to be on Warfarin (goal INR 2-3) for 45-days, then aspirin + clopidogrel for 6-months
    - Only 28% were already on Warfarin, 34% were not on OAC at all
  - TAVR + OAC were allowed to continue pre-TAVR OAC, including DOAC
- **Low compliance with OAC after the procedure**
- **Bleeding risk may differ in the early vs late time frame after TAVR + LAAO:**
  - Numerically higher bleeding in first 6-months (HR 1.35, 95% CI 0.76-2.39)
  - Less bleeding between 6-months and 2-years (HR 0.63, 95% CI 0.25-1.57)

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Study Aims

1. Evaluate the association between all-cause mortality + major bleeding with adherence to OAC during follow-up
2. Compare event rates in with TAVR + LAAO vs TAVR + OAC alone within first 6-months vs 6-24 months post-procedure in patients not adherent to OAC

Study Methodology

- Major substudy of WATCH-TAVR
- RCT of 349 patients randomized to TAVR + LAAO (n=177) vs TAVR + OAC (n=172)
- **As-treated population** of patients who received TAVR + LAAO vs TAVR + OAC but were non-compliant with OAC
- Non-compliance defined as not on any OAC at any visit for the first 12-months post TAVR

Study Methodology

- **Primary endpoint**
  - Composite all-cause death + major bleeding at 24-months
- **Secondary endpoints**
  - All-cause death
  - Cardiovascular (CV) death)
  - Major bleeding
  - Stroke (ischemic or hemorrhagic)
- **Anti-thrombotic Strategies**
  - TAVR + LAAO: Warfarin (goal INR 2-3) for 45 days, then DAPT (aspirin 81 mg + clopidogrel 75 mg daily) for a total of 6 months, then SAPT
  - TAVR + OAC alone: Any OAC (DOAC or Warfarin) with or without SAPT

Results

- 162/177 (**91.5%**) randomized to TAVR + LAAO received WATCHMAN
- 86/187 (**46.0%)** randomized to TAVR + OAC were non-adherent to OAC
- Baseline characteristics remained well randomized between groups, with no differences in 21 variables

Baseline Characteristics

Characteristic	TAVR + No OAC (N=86)	TAVR + LAAO (N=162)	P-Value
Age (years)	82.2 ± 6.4	80.5 ± 8.0	**0.224**
Female	37 (43.0)	60 (37.0)	**0.358**
BMI, kg/m²	30.4 ± 6.3	32.0 ± 9.0	**0.415**
Type of AF/Flutter			**0.896**
Paroxysmal	40 (46.5)	77 (47.5)	
Other / Unknown	46 (53.5)	67 (52.5)	
History of CHF	71 (82.6)	131 (80.9)	**0.946**
LV dysfunction	21 (24.4)	37 (22.8)	**0.204**
Hypertension	79 (91.9)	148 (91.4)	**0.892**
Diabetes mellitus	34 (40.7)	69 (42.6)	**0.861**

Characteristic	TAVR + No OAC (N=86)	TAVR + LAAO (N=162)	P-Value
Prior stroke or TIA	10 (11.6)	11 (6.8)	**0.178**
Vascular disease (including MI)	30 (34.9)	55 (34.0)	**0.949**
Uncontrolled hypertension	46 (53.5)	75 (46.3)	**0.398**
Abnormal renal fxn	33 (38.4)	46 (28.4)	**0.108**
Abnormal liver fxn	1 (1.2)	4 (2.5)	**0.846**
Prior major bleeding	35 (40.7)	67 (41.4)	**1.000**
Labile INR	7 (8.1)	12 (7.4)	**0.935**
Excessive alcohol use	7 (8.1)	24 (14.8)	**0.235**
Antiplatelet agent use	35 (40.7)	65 (40.1)	**0.930**
NSAID use	25 (29.1)	39 (24.1)	**0.637**

Primary Endpoint – Death + Major Bleeding

- Significantly less Death + Major Bleeding with TAVR + LAAO
- Consistent results over entire 24-months, and in landmark analysis stratified 0 to 6-months and 6 to 24-months

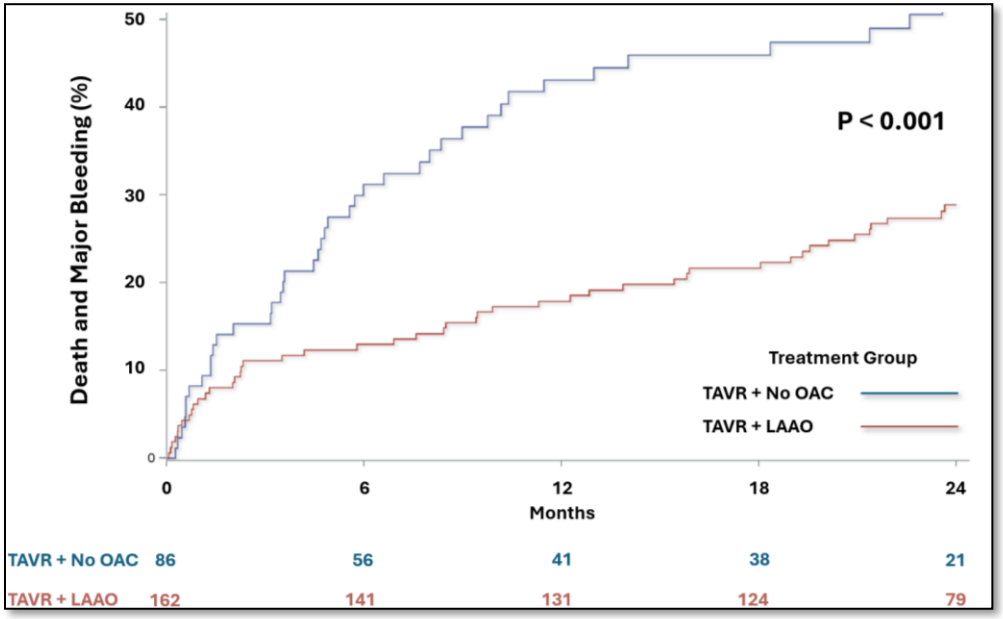
	TAVR + No OAC	TAVR + LAAO	P-Value
24-month Death + Major Bleeding			
n/N (%)	41/86 (47.7)	46/162 (28.4)	**<0.001**
Events/100 Patient Years	43.6	17.6	
HR (95% CI)	**0.45 (0.29-0.69)**		

Primary Endpoint – Death + Major Bleeding

- Significantly less Death + Major Bleeding with TAVR + LAAO
- Consistent results over entire 24-months, and in landmark analysis stratified 0 to 6-months and 6 to 24-months

	TAVR + No OAC	TAVR + LAAO	P-Value
0 to 6-month Death + Major Bleeding			
n/N (%)	25/86 (29.1)	21/162 (13.0)	**0.002**
Events/100 Patient Years	73.4	29.1	
HR (95% CI)	**0.41 (0.23-0.74)**		
6 to 24-month Death + Major Bleeding			
n/N (%)	18/66 (27.3)	28/151 (18.5)	**0.023**
Events/100 Patient Years	18.8	10.2	
HR (95% CI)	**0.51 (0.28-0.92)**		

Primary Endpoint – Death + Major Bleeding



Less composite Death + Major Bleeding with TAVR + LAAO
HR 0.449, 95% CI 0.294-0.685, P<0.001

Secondary Endpoints – Landmark Analysis

- TAVR + LAAO - first 6-months:
  - Less all-cause mortality
    - HR 0.26 (0.13-0.55), P<0.001
  - Less CV mortality
    - HR 0.35 (0.14-0.87), P=0.018

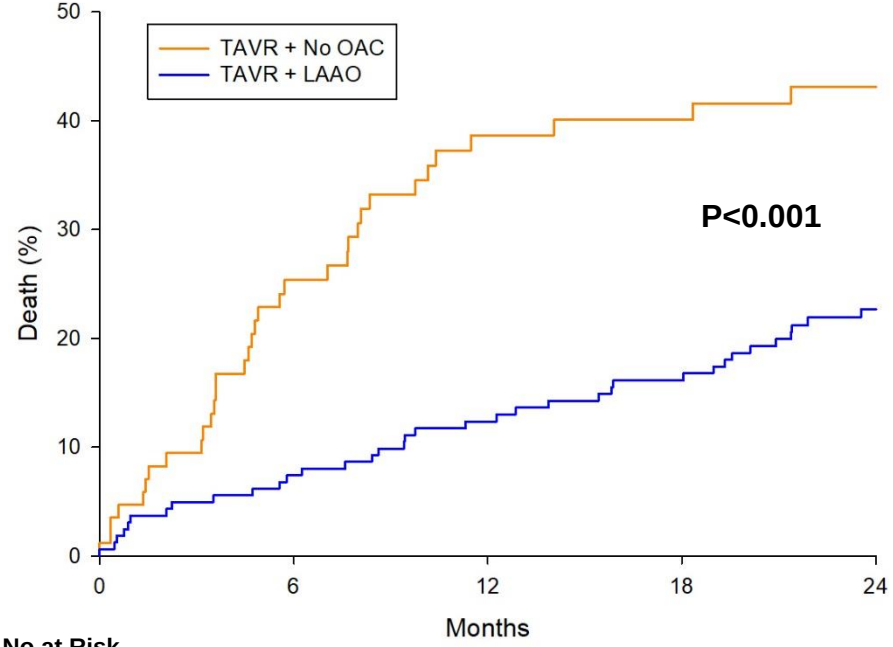
	TAVR + No OAC	TAVR + LAAO	P-Value
6-month Events			
Death			
n/N (%)	20/86 (23.3)	11/162 (6.7)	**<0.001**
Events/100 PY	54.8	14.3	
HR (95% CI)	**0.26 (0.13-0.55)**		
CV Death			
n/N (%)	11/86 (12.8)	8/162 (4.9)	**0.018**
Events/100 PY	30.1	10.4	
HR (95% CI)	**0.35 (0.14-0.83)**		
Major Bleeding			
n/N (%)	7/86 (8.1)	14/162 (8.6)	0.959
Events/100 PY	20.6	19.4	
HR (95% CI)	1.02 (0.41-2.54)		
Stroke			
n/N (%)	4/86 (4.7)	6/162 (3.7)	0.662
Events/100 PY	11.3	8.0	
HR (95% CI)	0.76 (0.21-2.68)		

Secondary Endpoints – Landmark Analysis

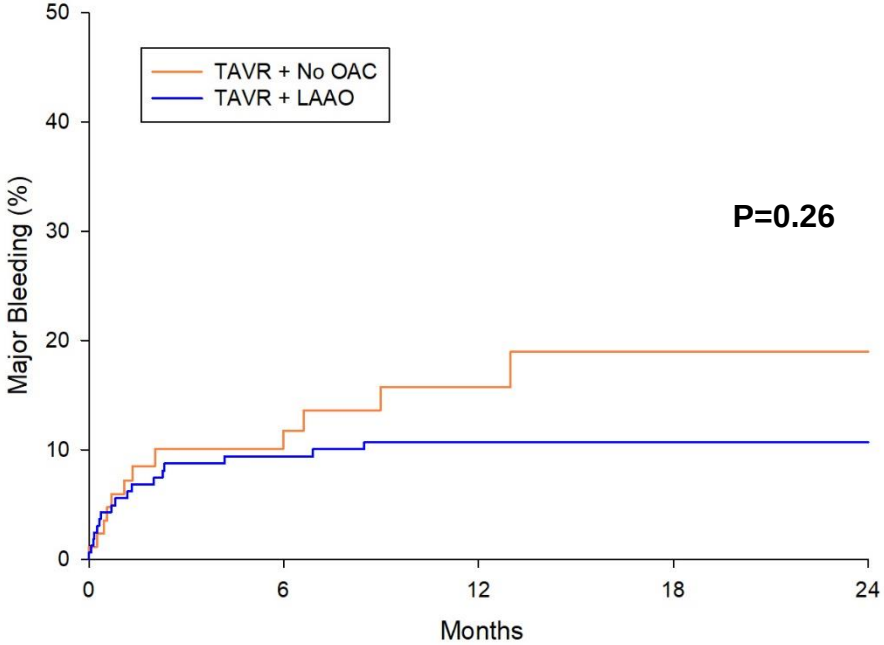
- TAVR + LAAO - first 6-months:
  - Less all-cause mortality
    - HR 0.26 (0.13-0.55), P<0.001
  - Less CV mortality
    - HR 0.35 (0.14-0.87), P=0.018
- TAVR + LAAO – 6 to 24-months:
  - Less CV mortality
    - HR 0.37 (0.16-0.89), P=0.018
  - Less Major bleeding
    - HR 0.27 (0.07-1.00), P=0.042
- No difference in stroke at any time

	TAVR + No OAC	TAVR + LAAO	P-Value
6 to 24-month Events			
Death			
n/N (%)	14/66 (21.2)	25/151 (16.6)	0.124
Events/100 PY	14.0	9.0	
HR (95% CI)	0.60 (0.31-1.15)		
CV Death			
n/N (%)	10/66 (15.2)	11/151 (7.3)	**0.018**
Events/100 PY	10.0	3.9	
HR (95% CI)	**0.37 (0.16-0.89)**		
Major Bleeding			
n/N (%)	5/66 (7.6)	5/151 (2.7)	**0.042**
Events/100 PY	5.2	1.5	
HR (95% CI)	**0.28 (0.07-1.00)**		
Stroke			
n/N (%)	2/66 (3.0)	4/151 (2.7)	0.693
Events/100 PY	2.0	1.5	
HR (95% CI)	0.71 (0.13-3.9)		

Secondary Endpoints – Cumulative Events



No at Risk				
TAVR + LAAO				
162	152	142	135	89
TAVR + No OAC				
86	63	47	45	29



TAVR + LAAO				
162	142	132	125	81
TAVR + No OAC				
86	57	42	39	21

Implications

- Results support key findings of WATCH-TAVR
- OAC discontinuation is a major risk factor for mortality within 2-years post TAVR
- Patients unable to tolerate OAC pre-TAVR or requiring OAC discontinuation post-TAVR should be recognized as a high-risk group
- Results favored TAVR + LAAO despite utilization of the older WATCHMAN 2.5 device, and requirement for Warfarin only in the TAVR + LAAO group
- Results were driven by less all-cause and CV mortality with TAVR + LAAO
- Less bleeding 6-months to 24-months with TAVR+ LAAO, after Warfarin was discontinued (at 45-days)
- No difference in stroke at any time point out to 24-months

Limitations

- Bleeding events were likely impacted by different anti-thrombotic regimens between groups.
- Impact of LAAO on CVA prevention is more likely to emerge with longer-term follow-up.
- Post-hoc analysis – possibility for selection bias.
  - However, randomization was fully preserved.
  - There remained no difference in baseline characteristics – yet a clear difference in clinical outcomes.
- Competing risks of death, bleeding, and stroke.

Conclusions

- In patients with AF and AS, non-adherence to OAC post-TAVR is associated with greater risk of composite all-cause mortality and major bleeding at 2-years compared to patients who receive combined TAVR + LAAO.
- Combined TAVR + LAAO may provide significant benefit in patients at elevated risk of OAC discontinuation post-TAVR.
- Outcomes of combined TAVR + LAAO are expected to improve with contemporary devices (WATCHMAN FLX Pro) and anti-thrombotic strategies (DOAC vs DAPT vs early SAPT post-procedure).

Thank You

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