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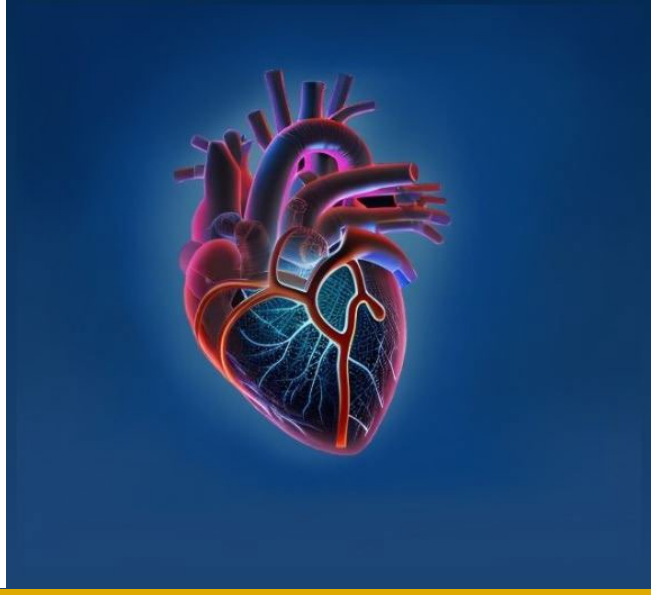
2024 Northern California Structural Heart Summit



Contemporary Post-Deployment Pharmacologic Strategies (NOAC Vs APT)

Arash Aryana, MD, PhD, FACC, FHRS
Medical Director, Cardiovascular Service Line
Medical Director, Cardiac Electrophysiology Laboratory
Mercy General Hospital and Dignity Health Heart & Vascular Institute
Clinical Professor of Cardiology, Creighton University School of Medicine

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- **Abbott**
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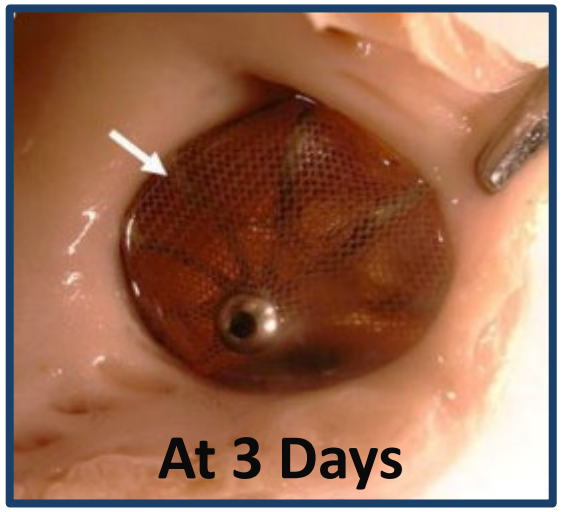
Endothelialization of LAAC Devices In Animal Models Appear Complete by 90 Days Post-Implant

- The healing process of LAAC remains incompletely understood

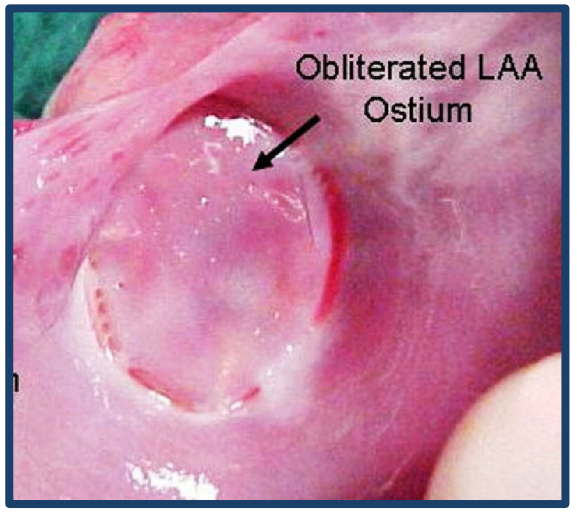
A thin layer of fibrin covering the device membrane



An organized neoendocardial surface with an extension of ingrowth into LA

A fibrous tissue pannus covering the fabric membrane with a monolayer of endothelial-like cells

LAA ostium completely obliterated by an LAAO device



Schwartz RS, et al. *JACC Cardiovasc Interv* 2010; 3:870-7.

Antithrombotic Regimen Following LAAC At Discharge

Antithrombotic regimen	U.S. NCDR Registry Data	European Registry Data
Warfarin	50.4%	
Warfarin + ASA	36.9%	16%
Warfarin only	13.5%	---
DOAC	33.1%	
DOAC + ASA	20.8%	11%
DOAC only	12.3%	---
DAPT	5.0%	60%
Other	11.4%	
SAPT	---	7%
No antithrombotic regimen	---	6%

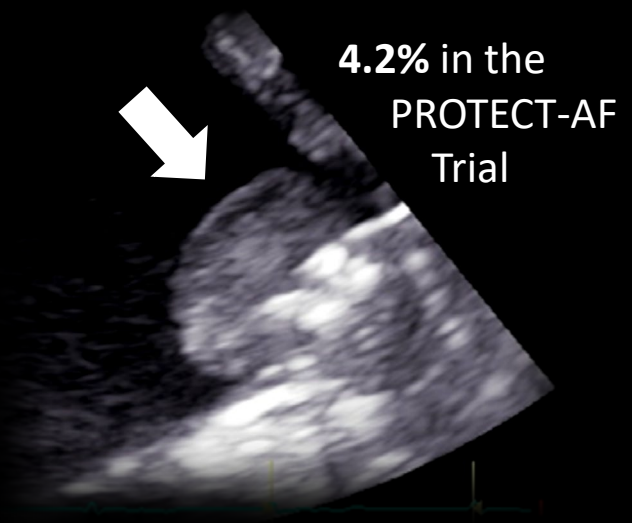
Freeman JV, et al. *J Am Coll Cardiol* 2022; 79:1785-1798.
Boersma LV, et al. *Heart Rhythm* 2017; 14:1302-1308.

OAC Post-LAAC

- PROTECT-AF and PREVAIL were designed in the era before availability of DOACs

Warfarin Discontinuation	PROTECT-AF Trial	PREVAIL Trial
At 45 days	86.8%	92.2%
At 6 months	92.2%	98.3%
At 1 year	93.2%	99.3%

Device-related thrombus (DRT)



- DRT occurred more commonly at 6- and 12-month TEE vs 45 days

Holmes DR, et al. *Lancet* 2009; 374(9689):534-42.
Holmes DR, et al. *J Am Coll Cardiol 2014; 64:1-12.*

Risk Factors for DRT

- Left ventricular systolic dysfunction
- Non-paroxysmal AF
- Prior ischemic events
- Large left atrial appendage size
- Deep device implantation (>10 mm from the pulmonary ridge)
- Iatrogenic pericardial effusion
- Hypercoagulable state
- Renal insufficiency

Mesnier J, et al. *Circ Cardiovasc Interv* 2023; 16:e012812.

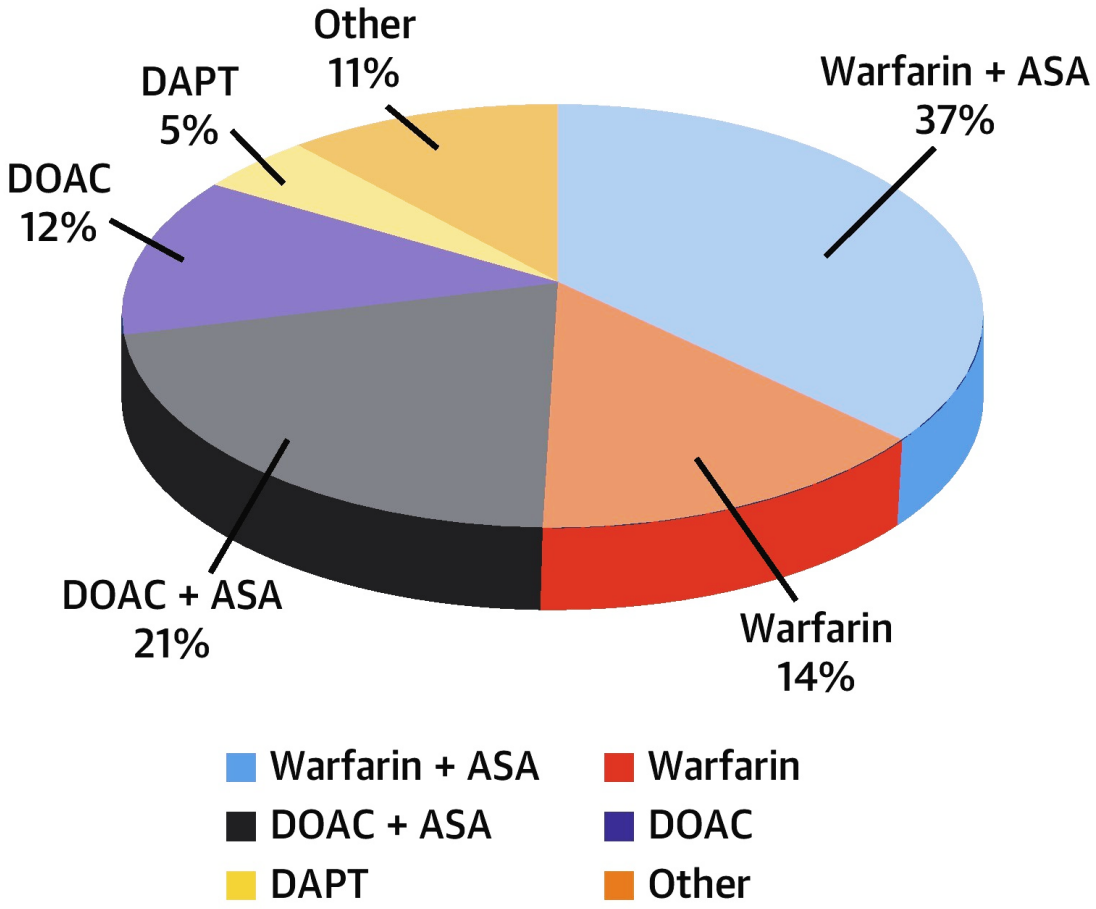
VKA + ASA Associated with Higher Rates of Adverse Events Versus VKA or DOAC Alone

Freeman JV, et al. J Am Coll Cardiol 2022; 79:1785-1798.

Most Common Discharge Antithrombotic Strategies

- ***Only 12.2% received FDA-approved postimplant regimen***

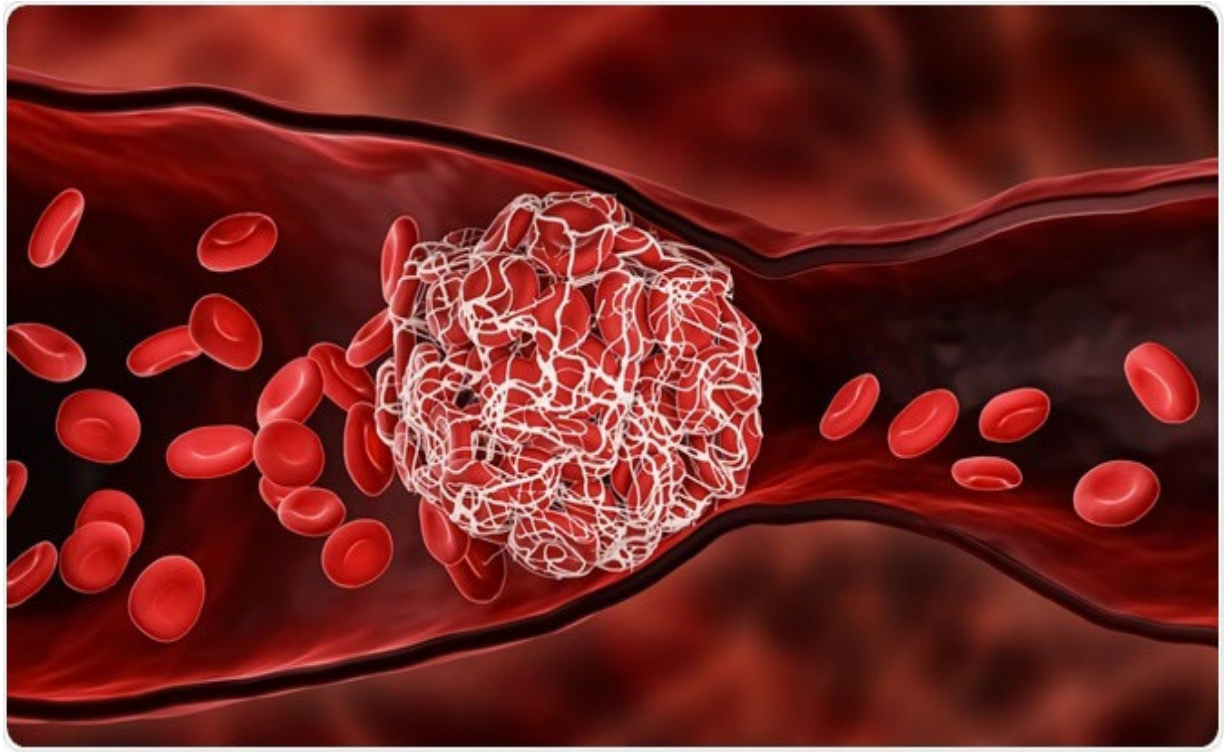
N=31,994 Patients



Use of VKA (Warfarin): Antiquated?

- Given the high bleeding risk associated with VKA early after LAAC, along with unreliable pharmacokinetics and routine lab testing, use of VKA has declined in current practice in favor of DOAC

- PINNACLE FLX trial – Replaced VKA with DOAC



Kar S, et al. *Circulation* 2021; 143:1754-1762.

Safety of DAPT Post-LAAC

- Large experience with DAPT after LAAC
- Some concerns remain about its safety and efficacy
- DAPT mostly used to reduce hemorrhagic risk after LAAC, but a potential benefit remains unclear
- Several studies have shown higher rates of bleeding with DAPT vs VKA and DOACs[1,2,3]
- Some DOACs (*e.g.,* apixaban) demonstrate a safety profile similar to SAPT[4]

1. Connolly S, et al. Lancet 2006; 367:1903–1912.
2. Ruff CT, et al. *Lancet* 2014; 383:955–962.
3. Van Rein N, et al. *Circulation* 2019; 139:775–786.
4. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139–1151.

DAPT Versus DOAC Post-LAAC

Clinical Trial	DRT	Major Bleeding
Global Prospective Amulet Registry (n=1,088)		
DAPT	70.6% } *	8.4% } *
DOAC	29.4%	4.1%

*Significant P-value

Hildick-Smith D, et al. *Eur Heart J* 2020; 41:2894–2901.
Søndergaard et al. *JACC Cardiovasc Interv* 2019; 12:1055–1063.

Device-related Thrombus, Major Bleeding and Ischemic Events Post-LAAC: Observational Studies

		DRT		
Study	**Follow-up**	DAPT	DOAC	VKA
Studies that only used DAPT as discharge medication				
ASAP trial[45]	14 months	0.7%		
Urena et al.[46]	20 months	0.0%		
APC registry[47]	13 months	4.4%		
Pracon et al.[17]	12 months	7.1%		
Studies that reported specific outcomes according to discharge medication				
Faroux et al.[48]	3 months	2.6%	0.0%	
ADRIFT trial[10]	3 months	6.1%	0.0%	
EWOLUTION registry[6]	3 months	3.1%	1.3%	0.8%
Søndergaard et al.[38]	6 months	3.1%		1.4%
Freeman et al.[5]	45 days for DRT 6 months	3.3%¶	1.8%¶	1.8%¶
AMULET registry[7]	12 months	1.6%	2.5%	

Mesnier J, et al. *Circ Cardiovasc Interv* 2023; 16:e012812.

Insights from the EWOLUTION Prospective Registry

Cox Proportional Hazards Model: Bleeding within 92 Days of LAAC

	Bleed within 92 days of implant procedure		Univariate Cox proportional hazards results[1]			Multivariate Cox proportional hazards results[2]		
Characteristic	No	Yes	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value*
Post-implant medication status								
NOAC	11.2% (105/941)	5.0% (2/40)	2.348	(0.5665, 9.7304)	0.2394	1.0		
Warfarin	15.5% (146/941)	17.5% (7/40)	0.883	(0.3906, 1.9958)	0.7647	2.439	(0.5067, 11.739)	0.2662
None	6.4% (60/941)	10.0% (4/40)	0.598	(0.2129, 1.6804)	0.3295	3.980	(0.7172, 22.086)	0.1142
Single APT	6.9% (65/941)	12.5% (5/40)	0.530	(0.2075, 1.3518)	0.1837	4.378	(0.8368, 22.903)	0.0803
DAPT	60.0% (565/941)	55.0% (22/40)	1.220	(0.6543, 2.2743)	0.5318	2.321	(0.5322, 10.118)	0.2625
Eligible for OAT	26.6% (250/941)	32.5% (13/40)	0.764	(0.3944, 1.4813)	0.4260	0.692	(0.3431, 1.3963)	0.3041

Cox Proportional Hazards Model: DRT within 92 Days of LAAC

	Thrombus on the device within 92 days of implant procedure		Univariate Cox proportional hazards results[1]			Multivariate Cox proportional hazards results[2]		
Characteristic	No	Yes	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value*
Post-implant medication status								
NOAC	16.1% (123/765)	5.0% (1/20)	2.053	(0.2748, 15.331)	0.4834	1.0		
None	6.7% (51/765)	5.0% (1/20)	1.256	(0.1682, 9.3838)	0.8240	1.795	(0.1102, 29.263)	0.6811
Single APT	6.7% (51/765)	10.0% (2/20)	0.646	(0.1499, 2.7850)	0.5580	3.265	(0.2913, 36.594)	0.3373
Warfarin	9.8% (75/765)	5.0% (1/20)	3.607	(0.4828, 26.940)	0.2112	0.617	(0.0386, 9.8577)	0.7324
DAPT	60.8% (465/765)	75.0% (15/20)	0.530	(0.1927, 1.4585)	0.2190	2.795	(0.3556, 21.976)	0.3285
Eligible for OAT	27.6% (211/765)	30.0% (6/20)	0.902	(0.3466, 2.3473)	0.8327	0.663	(0.2466, 1.7826)	0.4154

Overall Outcomes

Major bleed: 2.6%
Stroke: 0.4%
DRT: 2.6%

DRT

- DAPT: 3.1%
- DOAC: 1.3%

Bleeding Events

- DAPT: 3.8%
- DOAC: 1.9%

Bergmann MW, et al. *EuroIntervention* 2017; 13:877-884.

Insights from Other Trials and Experiences

Clinical Trial	DRT	Major Bleeding	SAEs	Early Death
Faroux et al. (n=592)				
DOAC	0%	3.2%	5.3%	1.1%
DAPT	2.6%	7.4%	11.1%	3.7%
PINNACLE FLX Trial (n=400)				
DOAC	0			
DAPT	2			
SAPT	5			

Faroux L, et al. *Int J Cardiol* 2021; 333:77-82.
Kar S, et al. *Circulation* 2021; 143:1754-1762.

Outcomes from Other Single-Center Studies Using DOAC

Mesnier J, et al. *Circ Cardiovasc Interv* 2023; 16:e012812.

	Follow-up	No. of patients	DRT	Major bleeding	Ischemic stroke
Bösche et al[24]	45 d	45	0.0%	0.0%	0.0%
Barakat et al[25]	45 d	37	0.0%	0.0%	0.0%
ADRIFT trial[10]	3 mo	34 (rixaroxaban 15 mg)	0.0%	11.4%	0.0%
		37 (rixaroxaban 10 mg)	0.0%	24.3%	2.7%
Enomoto et al[26]	2–4 mo	214	0.9%	0.5%	0.0%
EWOLUTION registry[6]	3 mo	109	1.3%	1.9%	0.0%
Faroux et al[27]	3 mo	115	0.9%	2.6%	0.9%
Cepas-Guillén et al[28]	3 mo	40 (low-dose apixaban)	0.0%	0.0%	0.0%
Cohen et al[29]	6 mo	47	0.0%	8.5%	0.0%
Freeman et al[5]	6 mo	6649 (DOAC+aspirin)	1.73%	2.83%	0.33%
		3948 (DOAC)	1.82%	1.71%	0.20%
Della Rocca et al[30]	1 y	198 (low dose, long term)	0.0%	0.5%	0.0%
PINNACLE FLX trial[22]	1 y	400 (DOAC+aspirin followed by DAPT)	1.75%	7.75%	2.6%

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Ongoing Studies on Antithrombotic Therapy After LAAC

Name	Device	No. of patients	Design and antithrombotic regimen	Primary end points	Estimated completion date
ASPIRIN-LAAO (NCT3821883)	Any device	1120	Double-blind randomized trial at 6 mo after LAAC: long-term aspirin, discontinuation of aspirin	At 24 mo: stroke, systematic embolism, major bleeding, cardiovascular death	End of 2024
ANDES (NCT03568890)	Any device	350	Open-label randomized between: DAPT for 8 wk, DOAC for 8 wk	Device-related thrombosis at 8 wk after LAAC	End of 2022
APPENDAGE (NCT04796714)	Any device	60	Open-label randomized between: DAPT for 3 mo, SAPT with aspirin (160 mg) for 3 mo	Apparition of new ischemic lesions at 3 mo on cerebral magnetic resonances	November 2022
FADE-DRT (NCT04502017)	WATCHMAN FLX	360	Open-labeled randomized between 3 arms: OAC for 6 wk then DAPT until 6 mo, OAC for 6 wk, then DAPT or half-dose OAC in clopidogrel nonresponder, half-dose DOAC	At 1-y efficacy: composite of stroke, systemic embolism, and device-related thrombosis, safety, major bleedings	December 2023

5–10% Patients Receive SAPT or NO OAC after LAAC

Antithrombotic Therapy	EWOLUTION Registry (n=1,005)[1]		Amulet Registry (n=1,005)[2]	
	% Patients	DRT	% Patients	DRT
SAPT	7.0%	3.8%	23.0%	2.2%
No therapy	6.5%	2.3%	2.0%	0%

Antithrombotic Therapy	Darmon et al. (n=152)[3]				Korsholm et al. (n=110)[4]		
	Stroke	DRT	Major bleed	Death	Stroke	DRT	Major bleed
DAPT	4.2%	0%	3.1%	9.1%			
No therapy	0%	0%	0%	18.8%			
SAPT					2.3%	1.9%	3.8%

Antithrombotic Therapy	RELEXAO Registry (n=469)[5]		
	% Patients	DRT	P-value
OAC	33.1%	4.5%	0.02*
No therapy	7.5%	15.4%	

1. Bergmann MW, et al. *EuroIntervention* 2017; 13:877-884.
2. Landmesser U, et al. *EuroIntervention* 2018; 14:e590-e597.
3. Darmon A, et al. *J Invasive Cardiol* 2020; 32:385-391.
4. Korsholm K, et al. *EuroIntervention* 2017; 12:2075-2082.
5. Fauchier L, et al. *J Am Coll Cardiol* 2018; 71:1528-1536.

Long-Term Antithrombotic Treatment After LAAC

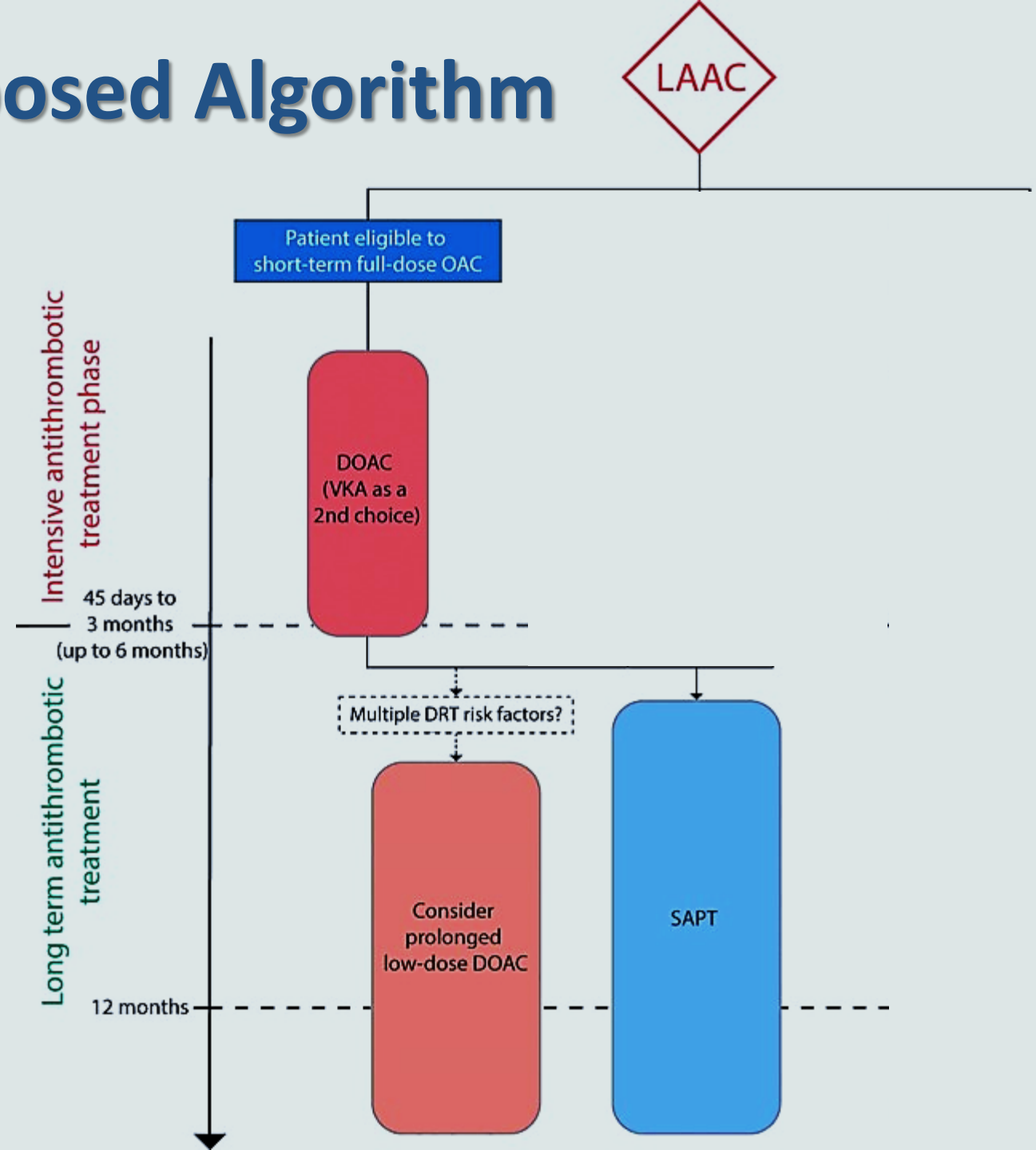
- Long-term antithrombotic strategy after LAAC remains understudied
- 1/3 of DRT occurs 6 months after LAAC; long-term SAPT associated with ↑ bleeding

Antithrombotic Therapy	Mesnier et al. (n=1,082)[2] : Hazard ratio		
	Ischemic Stroke	Death	Major Bleeding
No therapy	0.39 (95% C.I. = 0.04 to 3.79)	1.06 (95% C.I. = 0.65 – 1.71)	1.48 (95% CI 0.56 to 3.88)
P-value	0.42	0.82	0.43

- These data support the safety of shorter periods of antithrombotic therapy after LAAC in high bleeding risk patients based on clinician judgment

Mesnier J, et al. *Am J Cardiol* 2022; 171:91-98.
Mesnier J, et al. *Circ Cardiovasc Interv* 2023; 16:e012812.

A Proposed Algorithm



Circ Cardiovasc Interv 2023; 16:e012812.

Recommended Treatment and Duration for DRT

Treatment Options (Ref. #)	Duration	Comments
VKA (25,35)	8–12 weeks	Aim for INR of 2–3 For patients already on warfarin, target INR of 2.5–3.5 Consider combination with ASA*
NOAC (36–38)	8–12 weeks	Full-dose direct OAC, limited experience Apixaban, rivaroxaban (avoid dabigatran) Consider combination with ASA*
LMWH (25,35)	2–4 weeks	Consider in cases of large thrombi IVH is an alternative to LMWH in renal failure Consider combination with ASA*
Surgical excision (41)		Consider if therapy failure, recurrent embolization, or very large thrombi

Saw J, et al. *JACC Cardiovasc Interv* 2019; 12:1067-1076.

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Conclusions

- Type and duration of antithrombotic thrombotic treatment following LAAC remains unclear with a wide variations in regimens used in published studies

- While mechanistic studies suggest OAC as the most appropriate regimen early after the procedure, controversial data exist with respect to preventing DRT and ischemic events, especially with the use of newer LAAC devices with lower DRT rates

- Therefore, a tailored approach considering bleeding, DRT and ischemic risks would be the most appropriate

THANK YOU!