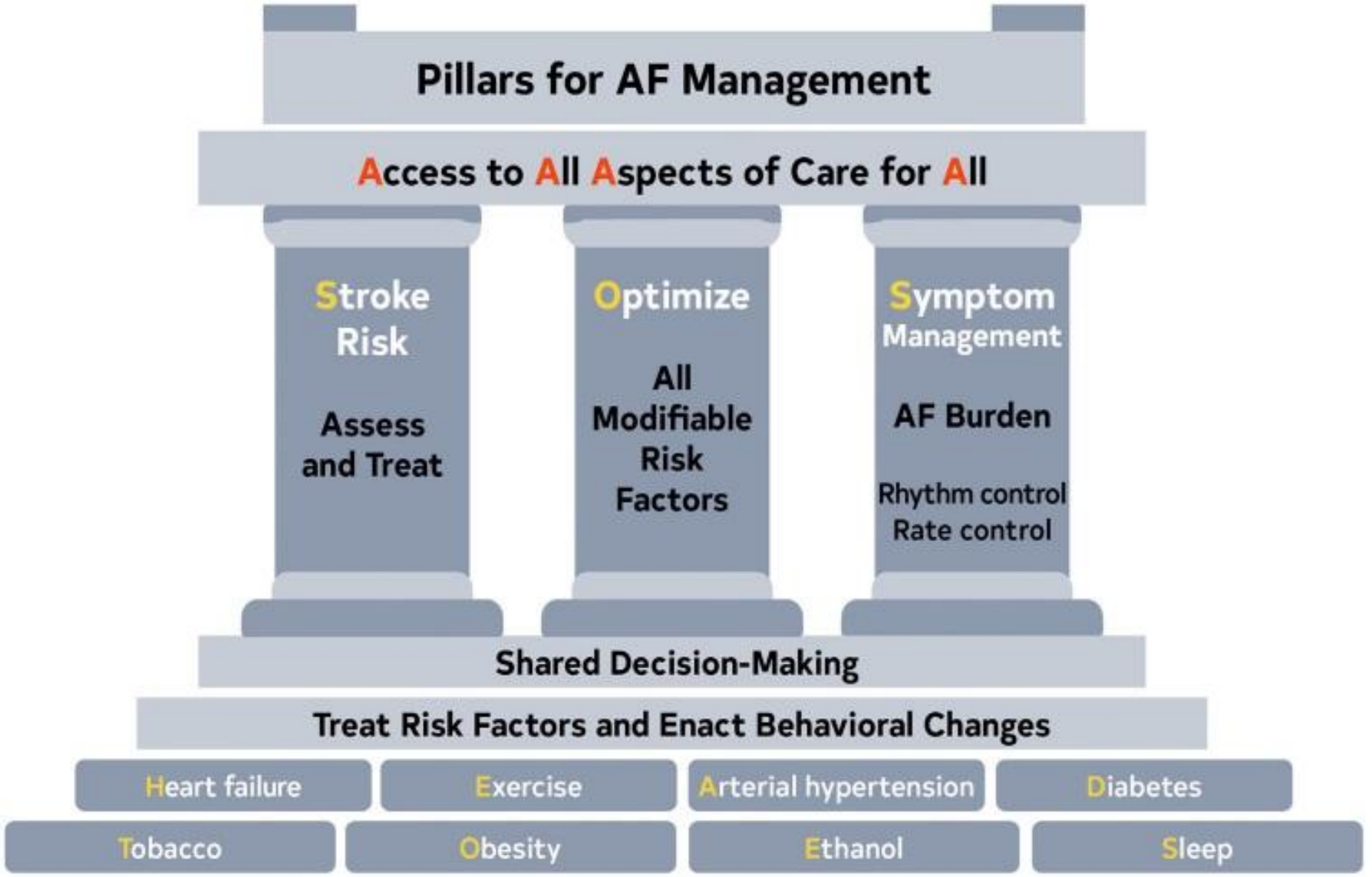
Kdy a čím zahájit antikoagulační léčbu fibrilace síní

Luděk Haman

I. interní kardioangiologická klinika FN HK

FIGURE 5 Pillars for AF Management



2023 ACC/AHA/ACCP/HRS AF guide, Circulation 11.2023

TABLE 4 Definitions

Term	Definition
AF	A supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction Electrocardiographic characteristics include (1) irregular R-R intervals (when atrioventricular conduction is present), (2) absence of distinct P waves, and (3) irregular atrial activity also known as fibrillatory waves. AF can be documented by, for example, 12-lead ECG, rhythm strips, wearables, intracardiac electrograms, but will always require visual confirmation that the diagnosis is accurate.
Clinical AF	With the increasing availability of wearable devices and other continuous monitoring technologies, the distinction between clinical and subclinical AF has become increasingly blurred, thus the writing committee felt the term clinical AF has become less useful. Yet, the term was kept because most of the evidence from randomized trials that have led to guideline recommendations for the treatment of AF refer to "clinical AF." These trials required electrocardiographic documentation of the arrhythmia for inclusion and most patients presented for clinical evaluation and/or therapy of the arrhythmia.
Subclinical AF	Subclinical AF refers to this arrhythmia identified in individuals who do not have symptoms attributable to AF and in whom there are no previous ECGs documenting AF This includes AF identified by implanted devices (pacemakers, defibrillators, or implantable loop recorders) or wearable monitors
Atrial high-rate episodes	These are defined as atrial events exceeding the programmed detection rate limit set by the device. These are recorded by implanted devices but require visual inspection to confirm AF and exclude other atrial arrhythmias, artifact or oversensing.
AF burden	AF burden encompasses both frequency and duration and refers to the amount of AF that an individual has. AF burden has been defined differently across studies. For the purpose of this guideline, AF burden will be defined as the durations of an an episode or as a percentage of AF duration during the monitoring period depending on how it was defined in the individual studies.
First detected AF	The first documentation of AF, regardless of previous symptoms
Paroxysmal AF	AF that is intermittent and terminates within ≤7 d of onset
Persistent AF	AF that is continuous and sustains for >7 d and requires intervention. Of note, patients with persistent AF who, with therapy, become paroxysmal should still be defined as persistent as this reflects their original pattern and is more useful to predict outcomes and define substrate.
Long-standing persistent AF	AF that is continuous for >12 mo in duration
Permanent AF	A term that is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm Acceptance of AF represents a therapeutic decision and does not represent an inherent pathophysiological attribute of AF

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FIGURE 4 **AF Stages: Evolution of Atrial Arrhythmia Progression**

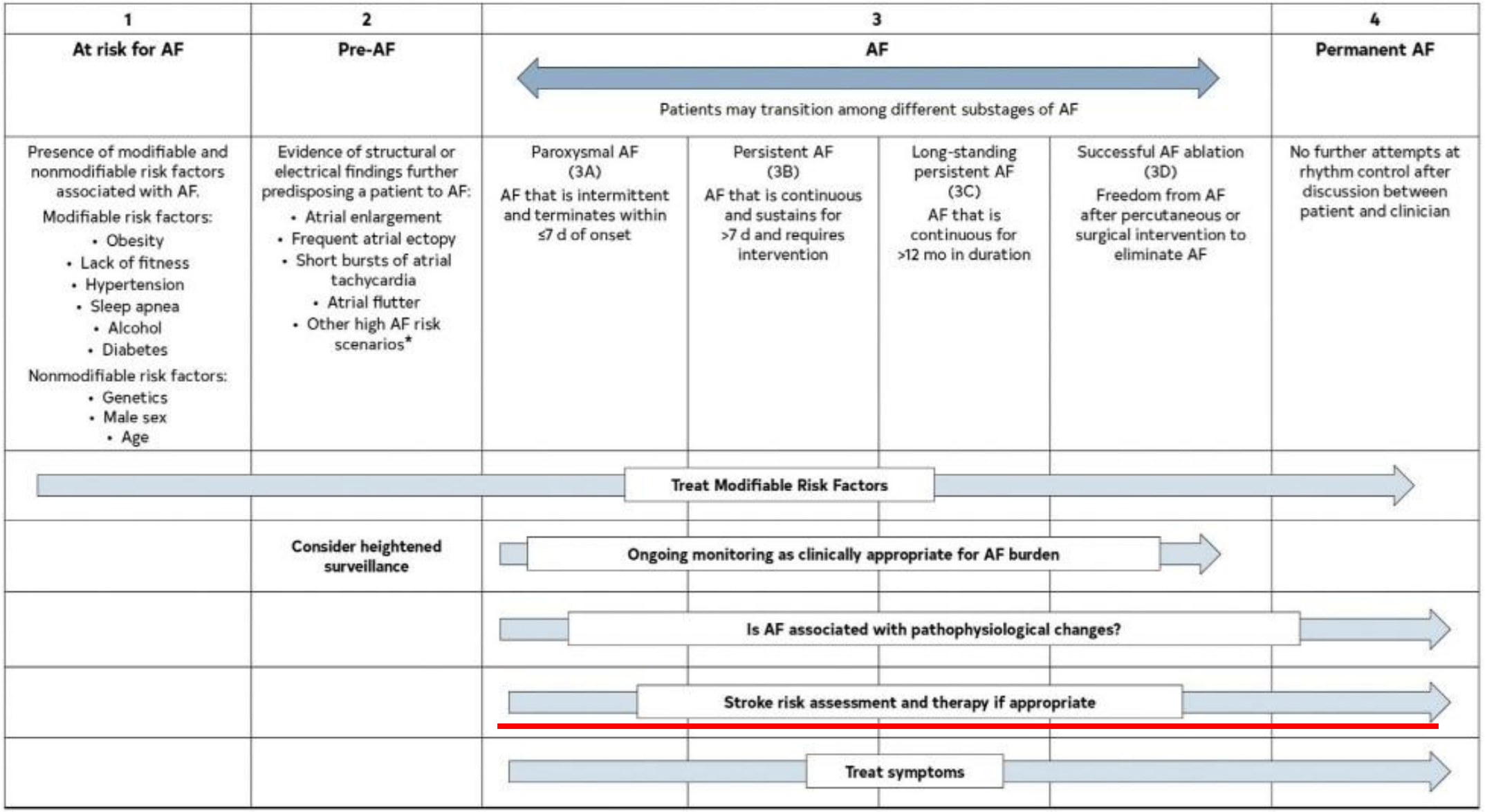

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TABLE 10 Risk Factor Definitions for CHA_2DS_2-VASc Score as in the Original Article[2]

C	Heart Failure	The presence of signs and symptoms of either right (elevated central venous pressure, hepatomegaly, dependent edema) or left ventricular failure (exertional dyspnea, cough, fatigue, orthopnea, paroxysmal nocturnal dyspnea, cardiac enlargement, rales, gallop rhythm, pulmonary venous congestion) or both, confirmed by noninvasive or invasive measurements demonstrating objective evidence of cardiac dysfunction
H	Hypertension	A resting blood pressure >140 mm Hg systolic and/or >90 mm Hg diastolic on at least 2 occasions or current antihypertensive pharmacological treatment
A_2	Age, additional risk/point	Age ≥75 y
D	Diabetes	Fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL) or treatment with hypoglycemic agent and/or insulin
S_2	Thromboembolism	Either an ischemic stroke, transient ischemic attack, peripheral embolism, or pulmonary embolism
V	Vascular Disease	Coronary artery disease (prior myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass surgery) or peripheral vascular disease (the presence of any of the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic vascular surgery, arterial and venous thrombosis)
A	Age standard risk/ weight	Age 65–74 y
Sc	Sex Category	Female sex

TABLE 8 Three Validated Risk Models for Stroke

Risk Factor	CHA_2DS_2-VASc[2]	ATRIA[1]	GARFIELD[3]
Age ≥85 y		6	0.98
Age ≥75 y	2	5	0.59
Age 65-74 y	1	3	0.20
Female sex	1	1	
Hypertension	1		0.16
Renal disease		1	0.35
Diabetes	1	1	0.21
Current smoking			0.48
Congestive heart failure	1	1	0.23
Previous stroke or TIA	2	2-8*	0.80
Vascular disease	1		0.20
Dementia			0.51
Previous bleeding			0.30
Proteinuria		1	
Low risk score	0	0-5	0-0.89
Intermediate risk score	1	6	0.90-1.59
High risk score	≥2	7-15	≥1.60
C-index (11)	0.63	0.66	-
C-index (13)	0.67	-	0.71

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TABLE 9 Some Best Known Published Clinical Scores With Potential Advantages

Year of Publication, Score Name	Score Components	Potential Advantages	No. of Validation Studies[19]	Hyperlink to Online Score Calculator, if Available
2001 $CHADS_2$[25]	CHF, hypertension, age (≥65 y is 1 point, ≥75 y is 2 points), diabetes, stroke/TIA (2 points)	$CHADS_2$ was superior to existing risk classification schemes AFI scheme: C-statistic, 0.68 (0.65-0.71) SPAF-III scheme: C-statistic, 0.74 (0.71-0.76) $CHADS_2$ score: C-statistic, 0.82 (0.80-0.84)	46	https://www.mdcalc.com/calc/40/chads2-score-atrial-fibrillation-stroke-risk
2010 CHA_2DS_2-VASc[2]	CHF, hypertension, age ≥75 y, diabetes, stroke or TIA, vascular disease, age 65-74 y, female sex	Most commonly used and studied, superior to $CHADS_2$ score. C-statistic, 0.606 (0.513-0.699) for CHA_2DS_2-VASc score vs 0.561 (0.450-0.672) for $CHADS_2$ score Improved compared with original $CHADS_2$ score	82	https://www.mdcalc.com/calc/801/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk#next-steps
2013 ATRIA[1]	Age (65-74 y is 3 points, 75-84 y is 5 points, ≥85 y is 6 points), hypertension, diabetes, CHF, proteinuria, GFR <45 mL/min/1.73 m^2, sex	Includes more age categories, renal function, and proteinuria More patients were classified as low or high risk but not as well tested in general.	11	https://www.mdcalc.com/calc/1842/atria-stroke-risk-score
2017 GARFIELD-AF[3]	Web-based, uses routinely collected clinical data, and includes a total of 16 questions	Web-based tool for predicting stroke and mortality, includes the effect of the different anticoagulants, bleeding risk and mortality to facilitate shared decision-making on the potential benefits/risks of anticoagulation	4	https://af.garfieldregistry.org/garfield-af-risk-calculator
2016 $MCHA_2DS_2$-VASc[26]	Expanded lower threshold for age to 50 y (1 point for age 50-74 y)	Validated in Asian cohort Can further identify Asian AF patients who may derive benefits from stroke prevention. In 1 study, $MCHA_2DS_2$-VASc was superior to CHA_2DS_2-VASc C-statistics = 0.708 (0.703-0.712) vs 0.689 (0.684-0.694)	1	

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation: anemia, renal disease, elderly (age ≥75 y), any previous bleeding, hypertension; $CHADS_2$, congestive heart failure, hypertension, age >75 y, diabetes, stroke/transient ischemia attack/thromboembolism; CHA_2DS_2 -VASc, indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; CHF, congestive heart failure; GARFIELD-AF, Global Anticoagulant Registry in the Field-Atrial Fibrillation; GFR, glomerular filtration rate; SPAF-III, stroke prevention atrial fibrillation, and TIA, transient ischemic attack.

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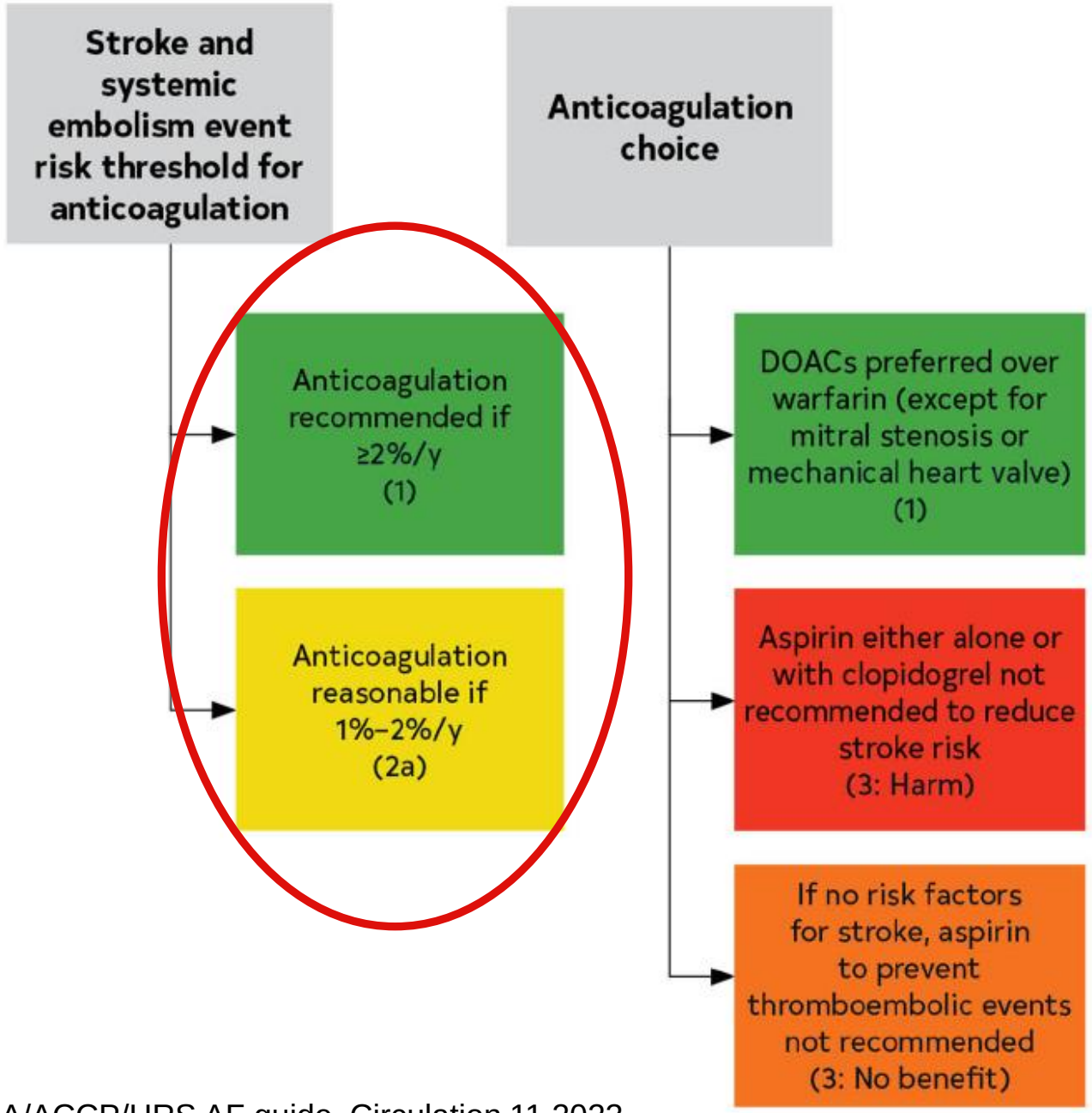
FIGURE 10 Antithrombotic Options in Patients With AF



CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)[b]
0	0.2%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

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Anticoagulation reasonable if 1%–2%/y (2a)

TABLE 11 Additional Risk Factors That Increase Risk of Stroke Not Included in CHA_2DS_2-VASc

Higher AF burden/Long duration
Persistent/permanent AF versus paroxysmal
Obesity (BMI, ≥30 kg/m^2)
HCM
Poorly controlled hypertension
eGFR (<45 mL/h)
Proteinuria (>150 mg/24 h or equivalent)
Enlarged LA volume (≥73 mL) or diameter (≥4.7 cm)

AF indicates atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; and LA, left atrium.

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„Subklinická“ FS a AHRE

Recommendations for Oral Anticoagulation for Device-Detected Atrial High-Rate Episodes Among Patients Without a Previous Diagnosis of AF
Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	RECOMMENDATIONS
2a	B-NR	1. For patients with a device-detected atrial high-rate episode (AHRE) lasting ≥24 hours[1] and with a CHA_2DS_2-VASc score ≥2 or equivalent stroke risk,[2] it is reasonable to initiate oral anticoagulation[3] within a SDM framework that considers episode duration and individual patient risk.
2b	B-NR	2. For patients with a device-detected AHRE lasting between 5 minutes and 24 hours and with a CHA_2DS_2-VASc score ≥3 or equivalent stroke risk,[2] it may be reasonable to initiate anticoagulation within a SDM framework that considers episode duration and individual patient risk.
3: No Benefit	B-NR	3. Patients with a device-detected AHRE lasting <5 minutes and without another indication for oral anticoagulation should not receive oral anticoagulation.[4,5]

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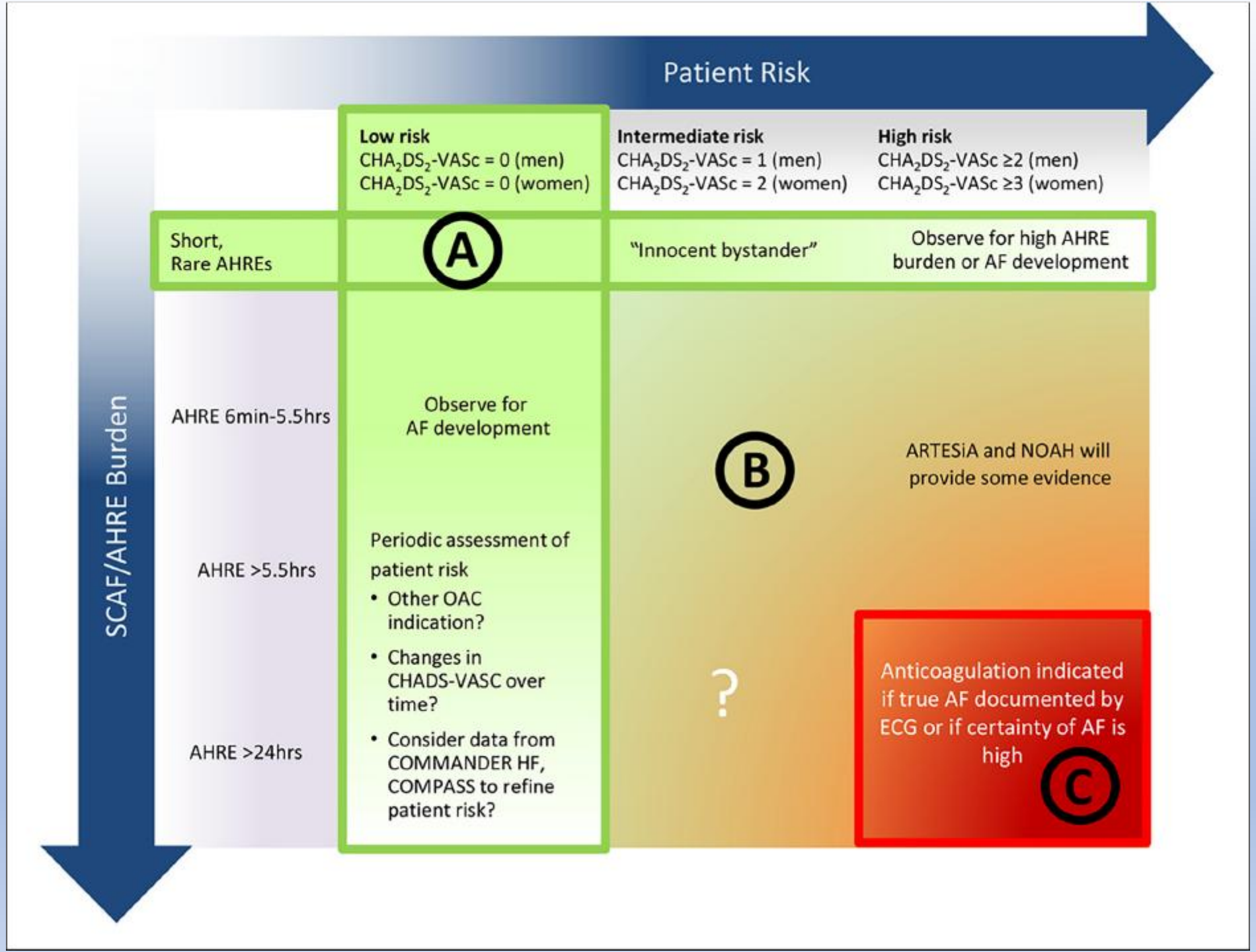
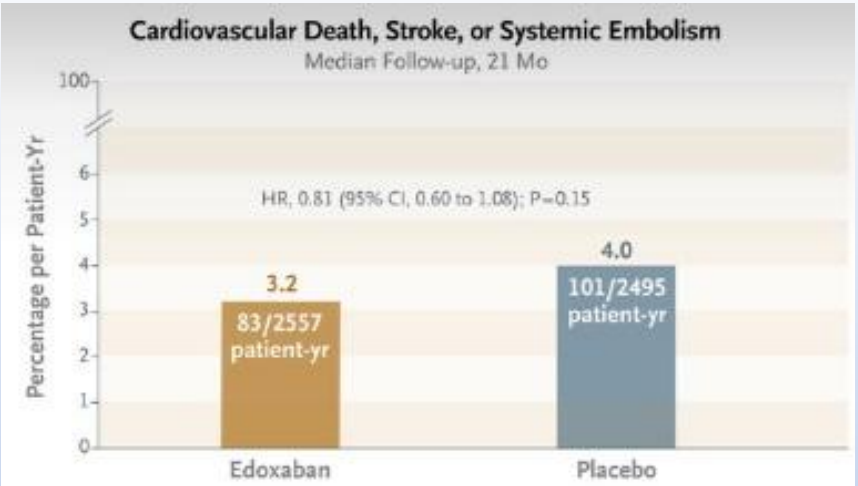
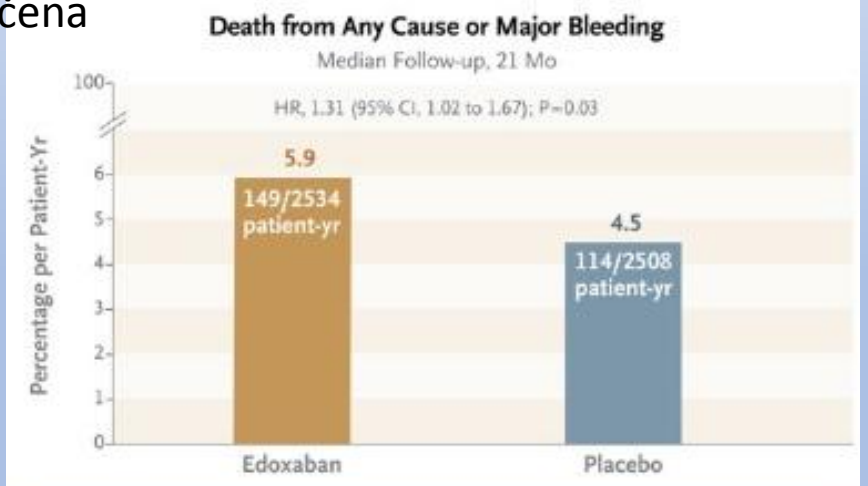

Patient Risk
SCAF/AHRE Burden
Low risk
CHA2DS2-VASc = 0 (men)
CHA2DS2-VASc = 0 (women)
Intermediate risk
CHA2DS2-VASc = 1 (men)
CHA2DS2-VASc = 2 (women)
High risk
CHA2DS2-VASc ≥2 (men)
CHA2DS2-VASc ≥3 (women)
Short,
Rare AHREs
A
"Innocent bystander"
Observe for high AHRE burden or AF development
AHRE 6min-5.5hrs
Observe for AF development
B
ARTESiA and NOAH will provide some evidence
AHRE >5.5hrs
Periodic assessment of patient risk
• Other OAC indication?
• Changes in CHADS-VASC over time?
?
Anticoagulation indicated if true AF documented by ECG or if certainty of AF is high
C
AHRE >24hrs
• Consider data from COMMANDER HF, COMPASS to refine patient risk?

AHRE nad 6min
CHADSVASc 4
Předčasně ukončena
Stroke 1%

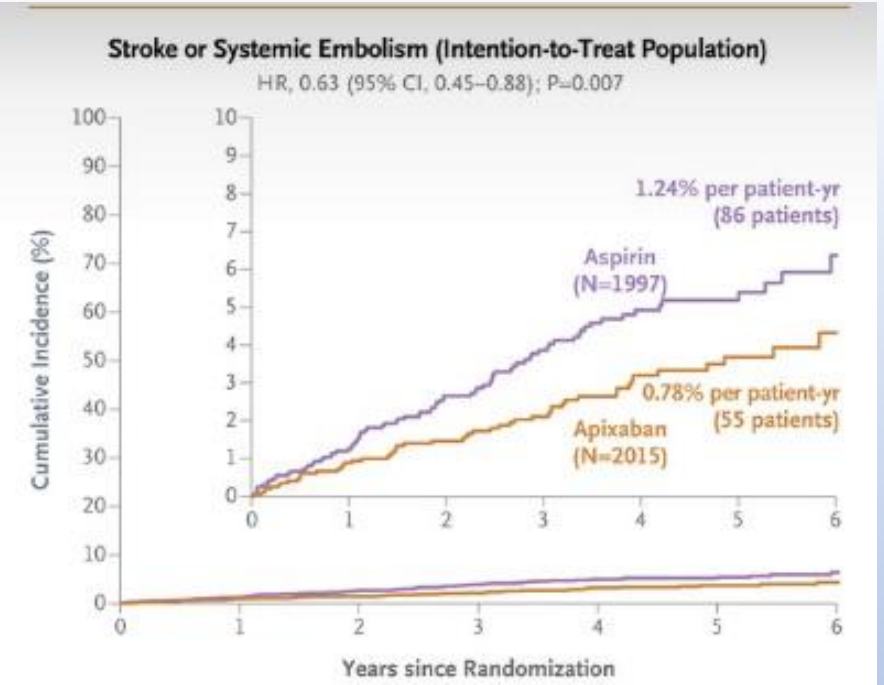


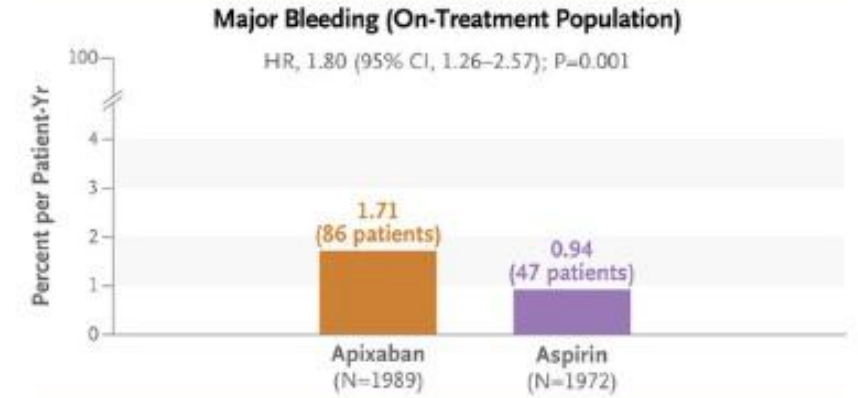


CONCLUSIONS

Among patients with AHREs but without atrial fibrillation, the incidence of a composite of cardiovascular death, stroke, or systemic embolism with edoxaban was not significantly different from that with placebo, but treatment with edoxaban led to a higher incidence of a composite of death or major bleeding.

NOAH, NEJM 8.2023





CONCLUSIONS

Among patients with subclinical atrial fibrillation, apixaban lowered the risk of stroke or systemic embolism but increased the risk of major bleeding.

Sub FS 6M-24H
CHADSVASc 3,9
Stroke ±1%
Fatální krvácení
5x api, 8x asp

ARTESIA, NEJM 11.2023

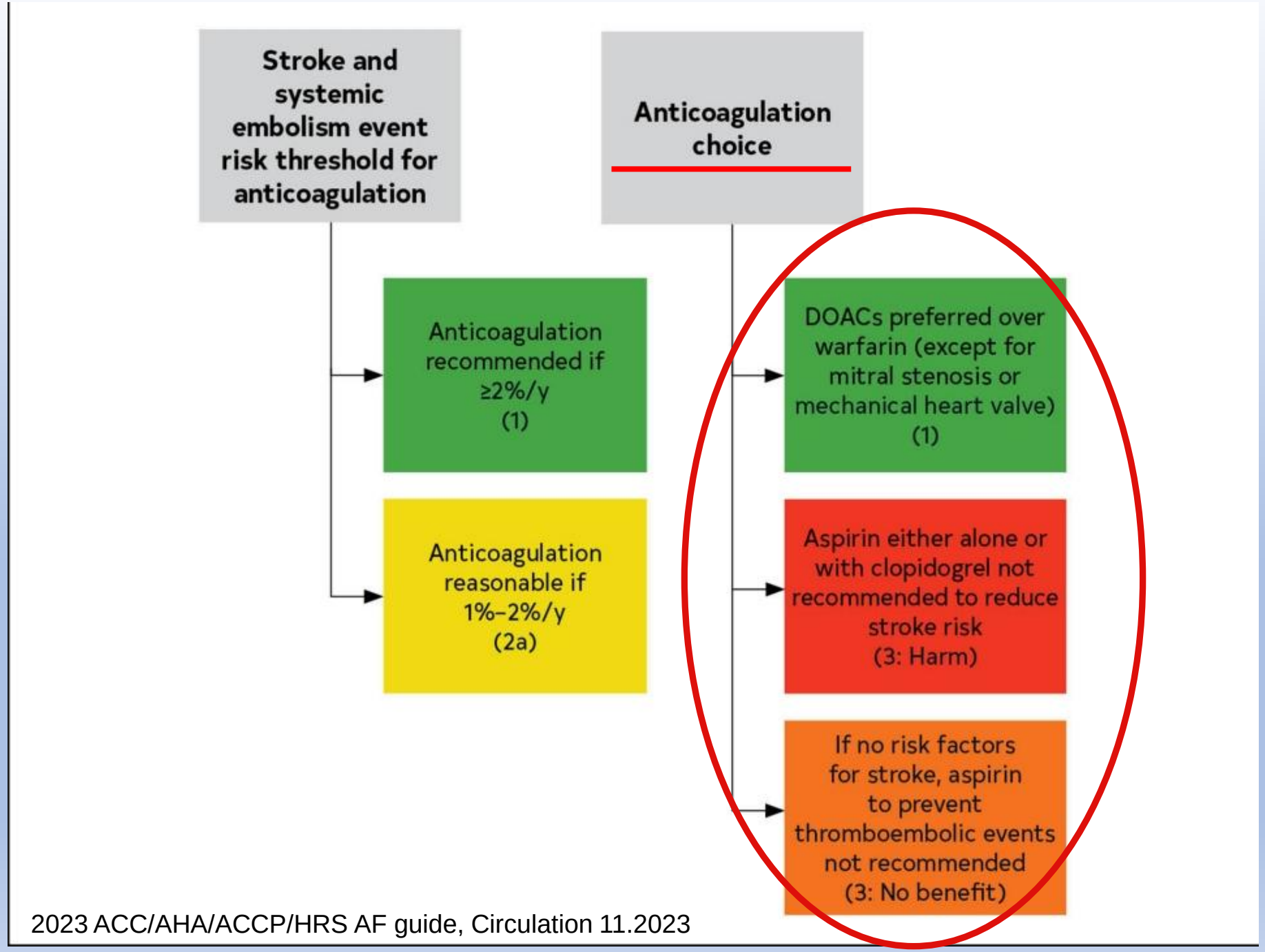


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FIGURE 1 Where DOACs Are Preferred and Where They Fared Worse

Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.

	AF*	VTE	Mechanical Heart Valves	Rheumatic AF	Thrombotic APS	ESUS	TAVR‡	LVAD
Apixaban	✓ Apixaban vs Warfarin [6]	✓† Apixaban vs Warfarin [9,14]	✗ Apixaban vs **Warfarin** [42]	?	✗ Apixaban vs **Warfarin** [39]	✗ Apixaban vs Aspirin [49,50]	✗ Apixaban vs Vitamin K Antagonist or antiplatelet [46]	?
Rivaroxaban	✓ Rivaroxaban vs Warfarin [5]	✓† Rivaroxaban vs Warfarin, Aspirin [10,13,15]	?	✗ Rivaroxaban vs **Vitamin K Antagonist** [40]	✗ Rivaroxaban vs **Warfarin** [36-38]	✗ Rivaroxaban vs **Aspirin** [47]	✗ Rivaroxaban vs **Aspirin, Clopidogrel** [44]	?

✓ DOACs had demonstrable safety and efficacy compared with standard treatment

✗ DOACs lacked safety and/or efficacy compared with standard treatment§

DOACs did not show a net benefit compared with standard treatment

? No trial performed; unknown evidence

FIGURE 1 Where DOACs Are Preferred and Where They Fared Worse

	AF*	VTE	Mechanical Heart Valves	Rheumatic AF	Thrombotic APS	ESUS	TAVR‡	LVAD
Edoxaban	✓ 7 Edoxaban vs Warfarin	✓ 12 Edoxaban vs Warfarin	?	?	?	?	‡ 43,45 Edoxaban vs Aspirin and Clopidogrel, Vitamin K Antagonist	?
Dabigatran	✓ 4 Dabigatran vs Warfarin	✓ † 11,16 Dabigatran vs Warfarin	✗ 41 Dabigatran vs **Warfarin**	?	?	✗ 48 Dabigatran vs **Aspirin**	?	✗ 92 Dabigatran vs **Phenpro-coumon and Aspirin**

✓ DOACs had demonstrable safety and efficacy compared with standard treatment

✗ DOACs lacked safety and/or efficacy compared with standard treatment§

DOACs did not show a net benefit compared with standard treatment

? No trial performed; unknown evidence

FIGURE 2 Indications for Which the Tradeoffs of Using DOACs Are Uncertain

Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.

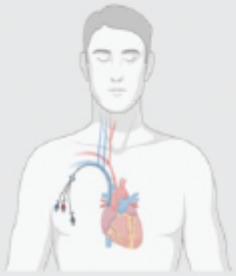
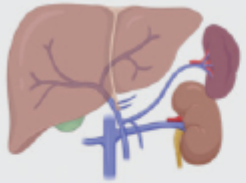
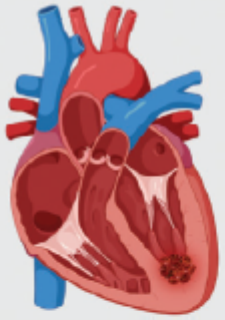
	Study	Study Design	Topline Study Results	Key Knowledge Gaps
 Catheter-Associated DVT	Brandt et al[52] 2022	Subgroup analysis of **AVERT** RCT[103]	Apixaban 2.5 mg twice daily, when compared with placebo, was associated with lower rates of VTE (HR: 0.26; 95% CI: 0.14-0.47) and no difference in major bleeding (HR: 0.69; 95% CI: 0.20-2.35).	Limited evidence, RCTs urgently needed. Pivotal VTE trials should present breakdown of results according to presence of CVCs.
	TRIM-Line[104] 2021	Pilot RCT	Thromboprophylaxis with rivaroxaban 10 mg daily, when compared with placebo, resulted in no significant different rate of VTE in patients with cancer and central venous catheters (HR: 0.66; 95% CI: 0.11-3.90). One major bleeding in rivaroxaban arm.	
	TRIM-Line Ongoing	RCT	Ongoing trial, planning to enroll 1,828 patients, is comparing rivaroxaban 10 mg daily with placebo for primary thromboprophylaxis in cancer patients with central venous catheters (CVCs).	
 Cerebral Venous Sinus Thrombosis	**RE-SPECT CVT**[54] 2022	RCT	Dabigatran 150 mg twice daily, when compared with warfarin with an INR of 2 to 3, resulted in no recurrent VTE in both groups, with 1 major bleeding event recorded in the dabigatran arm and 2 in the warfarin arm at 25 weeks.	Small sample size and low event rates. Other DOACs need to be studied.

FIGURE 2 Indications for Which the Tradeoffs of Using DOACs Are Uncertain

 Splanchnic Vein Thrombosis	**RIPORT**[106] 2022	RCT	Rivaroxaban 15 mg daily, when compared with placebo, resulted in a significantly lower rate of recurrent VTE (0 per 100 person-years vs 19.71 per 100 person-years; 95% CI: 7.49-31.92) in patients with noncirrhotic chronic portal vein thrombosis.	Small sample size. Need to study rates of recurrent VTE. Further RCTs needed.
 Left Ventricular Thrombus	Zhang et al[96] 2022	RCT	For *prevention* of LV thrombus following anterior MI, combination of rivaroxaban 2.5 mg twice daily and DAPT, when compared with DAPT alone, was associated with lower rates of LVT formation at 30 days (HR: 0.08; 95% CI: 0.01-0.62).	More RCTs with larger sample sizes are needed and other agents tested.
	Sayed et al[101] 2021	Meta-analysis	For *treatment* of LV thrombus post-MI, a pooled analysis of 3 small trials suggested no difference in stroke (OR: 0.14; 95% CI: 0.01-1.27) or LVT resolution (OR: 1.17; 95% CI: 0.37-3.45) between DOACs and warfarin, but major bleeding was lower in DOACs (OR: 0.16; 95% CI: 0.02-0.82).	Trials were underpowered. Further RCTs are needed, including for LV thrombus other than post-MI.
	REWARF-STEMI Ongoing	RCT	Ongoing trial, aiming to enroll 50 patients, is comparing rivaroxaban 15 mg daily vs warfarin in patients with LV thrombus follow acute ST-segment elevation myocardial infarction.	

Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.

Patient with atrial fibrillation
and chronic kidney disease

Determine stroke risk (CHA_2DS_2-VASc Score)
Consider oral anticoagulation if score is ≥ 1 in males / ≥ 2 in females

Determine bleeding risk (HAS-BLED Score)

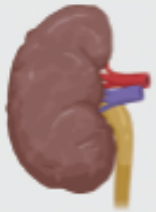
Estimate creatinine clearance (CrCl) to determine appropriate oral anticoagulant (OAC)

OAC options:	CrCl < 15 ml/min or ESRD on RRT	CrCl 15–29 ml/min	CrCl 30–49 ml/min	CrCl ≥ 50 ml/min
Vitamin K antagonist	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%
Apixaban	5 mg, b.i.d.*	2.5 mg, b.i.d.	5 mg, b.i.d.†	5 mg, b.i.d.†
Dabigatran	✖	75 mg, b.i.d.‡	150 or 110 mg, b.i.d.§	150 mg, b.i.d.‖
Edoxaban	✖	30 mg, o.d.	30 mg, o.d.	60 mg, o.d.¶
Rivaroxaban	✖	15 mg, o.d.	15 mg, o.d.	20 mg, o.d.

Address bleeding risk factors, frequent follow up, and closely monitor renal function in NOAC users

Lau, Y.C. et al. J Am Coll Cardiol. 2016;68(13):1452-64.

FIGURE 2 Indications for Which the Tradeoffs of Using DOACs Are Uncertain

	Study	Study Design	Topline Study Results	Key Knowledge Gaps
 End-Stage Renal Disease and AF*	VALKYRIE[56] 2021	RCT	Rivaroxaban 10 mg daily, when compared with VKAs with an INR of 2 to 3, was associated with lower rates of cardiovascular events (HR: 0.41; 95% CI: 0.25-0.68) and major bleeding (HR: 0.39; 95% CI: 0.17-0.90) at 18 months.	RCTs either had small sample sizes or failed to reach predefined non-inferiority criteria. RCTs with larger sample sizes are needed.
	RENAL-AF[55] 2022	RCT	Apixaban 5 mg twice daily, when compared with warfarin with an INR of 2 to 3, showed no difference in the rate of a composite of major bleeding and CRNMB at 1 year (HR: 1.20; 95% CI: 0.63-2.30). One-year rates of stroke or systematic embolism were 3.0% vs 3.3% in the apixaban and warfarin groups.	
	AXADIA-AFNET 8[57] 2023	RCT	Apixaban 2.5 mg twice daily, when compared with phenprocoumon with an INR 2 to 3, demonstrated no difference in the rate of a composite of major bleeding, CRNMB and all-cause death (HR: 0.93; 95% CI: 0.53-1.65).	

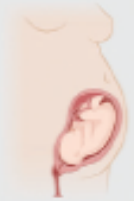
Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.

FS a ESRD/RRT pts

- SAFE-D – 150 pts, api vs warf vs 0, 2019-2022

- DANWARD – 718 pts, warf vs 0, 2019-2026
- SACK – 1500 pts, api vs 0, 2023-2028

FIGURE 2 Indications for Which the Tradeoffs of Using DOACs Are Uncertain

 Pregnancy	Bapat et al[60,61,63] 2014, 2015, and 2016	Ex vivo human models	During pregnancy, apixaban, dabigatran, and rivaroxaban are transferred across the placenta.	Until further data suggest otherwise, DOACs should be avoided in pregnancy.
	Beyer-Westendorf et al[62] 2020	Retrospective cohort	Among 336 reported DOAC-exposed pregnancies with known outcomes, 21 fetal abnormalities were reported, of which 12 were major birth defects (4.0%; 95% CI: 2.0%-6.0%). Miscarriage rate was 22.0% (95% CI: 17.7%-26.8%).	
 Breastfeeding	Ayuk et al[112] 2020 Zhao et al[113] 2020	Single-arm trial	Milk: plasma ratio is low for dabigatran and rivaroxaban (0.1 and 0.2, respectively) while the milk: plasma ratio is greater than acceptable for apixaban (2.61).	Clinical evidence for safety is lacking. Encourage careful protocols for breastfeeding women receiving rivaroxaban or dabigatran.

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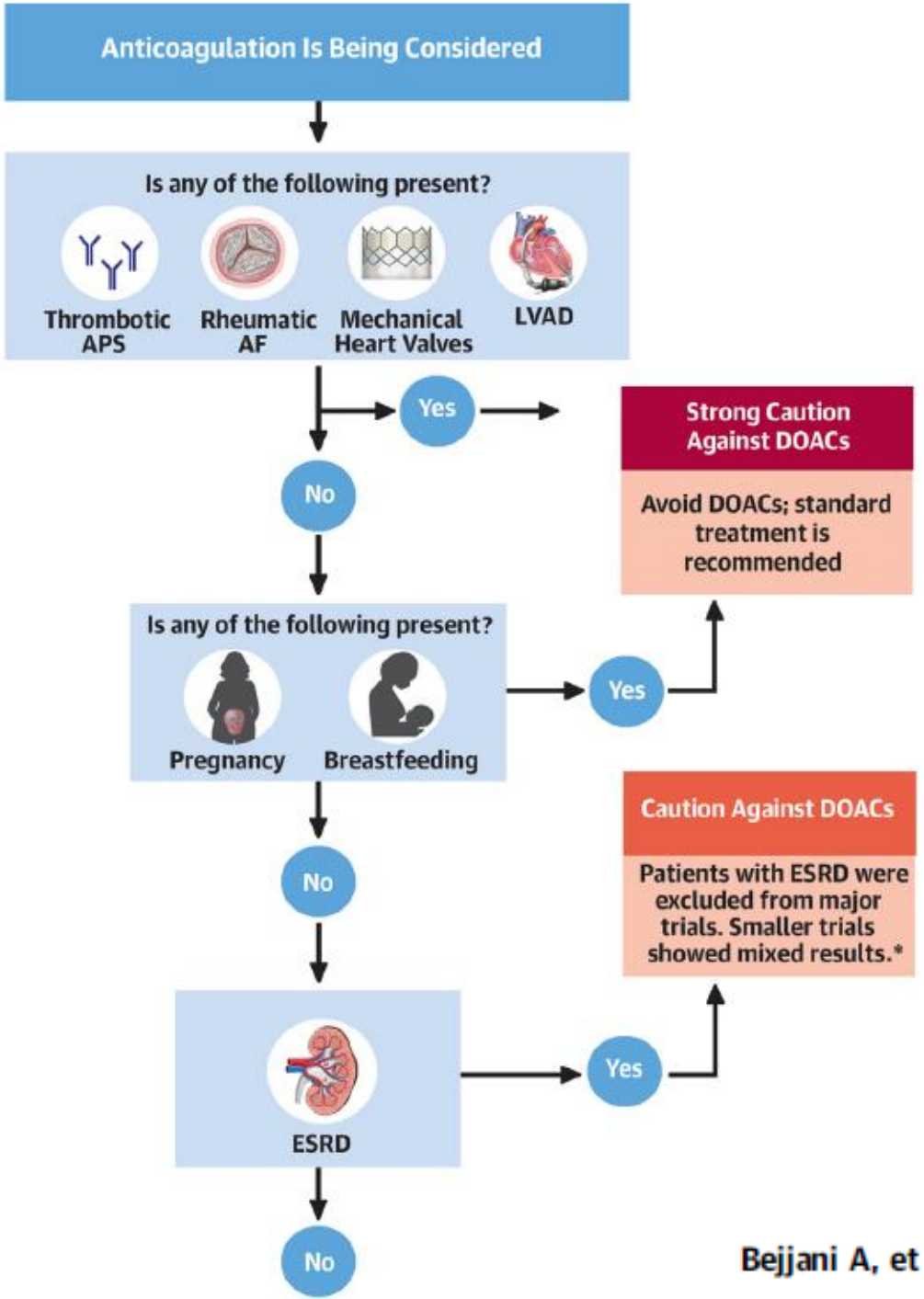
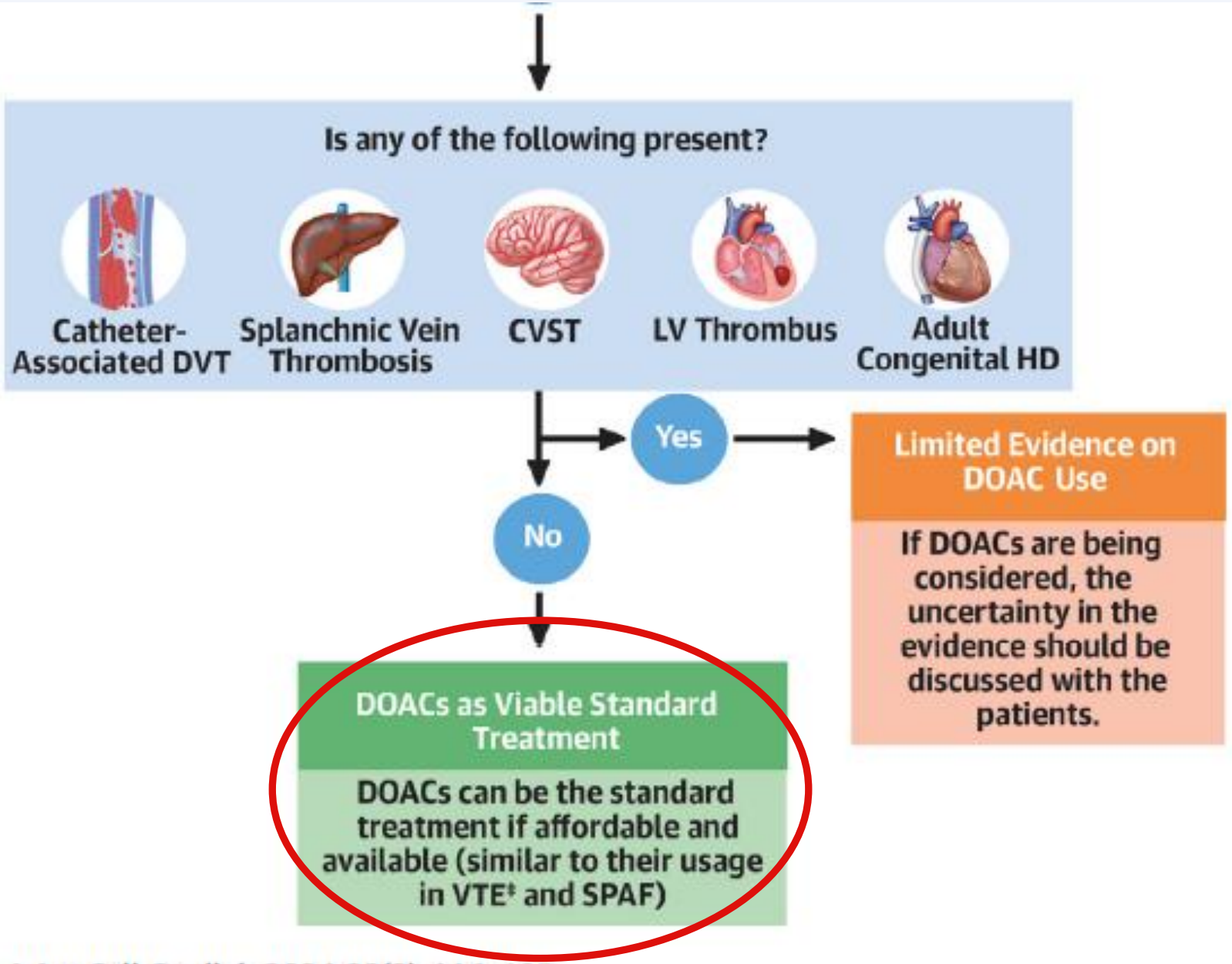


Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.



Bejjani A, et al. J Am Coll Cardiol. 2024;83(3):444-465.

Závěr

- **DOAC jsou u „klinické“ FS antikoagulans 1. volby**
- **Pozor na kontraindikace a lékové interakce** (menší četnost než u warfarinu), pravidelné sledování (zvl. renální fce)
- **Antikoagulace u AHRE a „subklinické“ FS - ?**
- **Antikoagulace u ESRD - ? (LAAO)**
- **Výběr DOAC individuální**

„Účinné a bezpečné antikoagulans je asi mýtus“