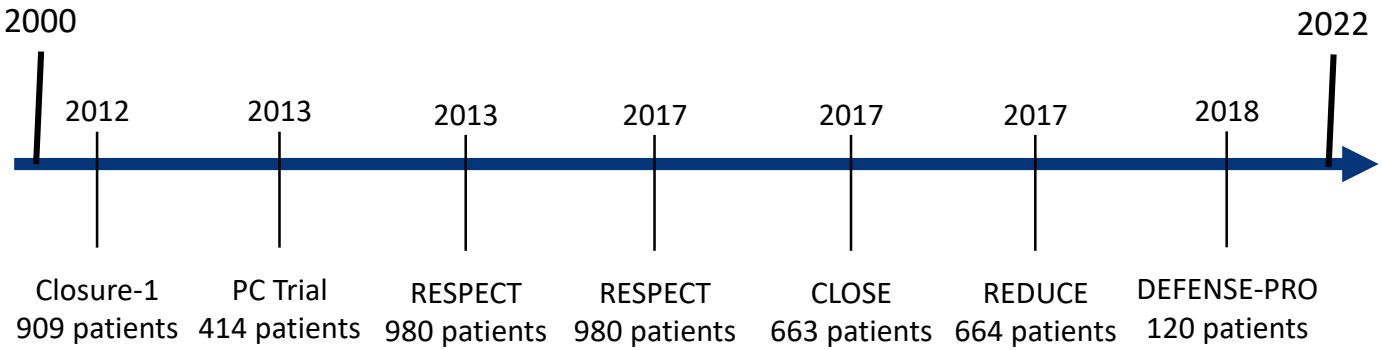
Symposium annuel
Centre cérébrovasculaire – CHUV

Fermeture du FOP et de l'auricule

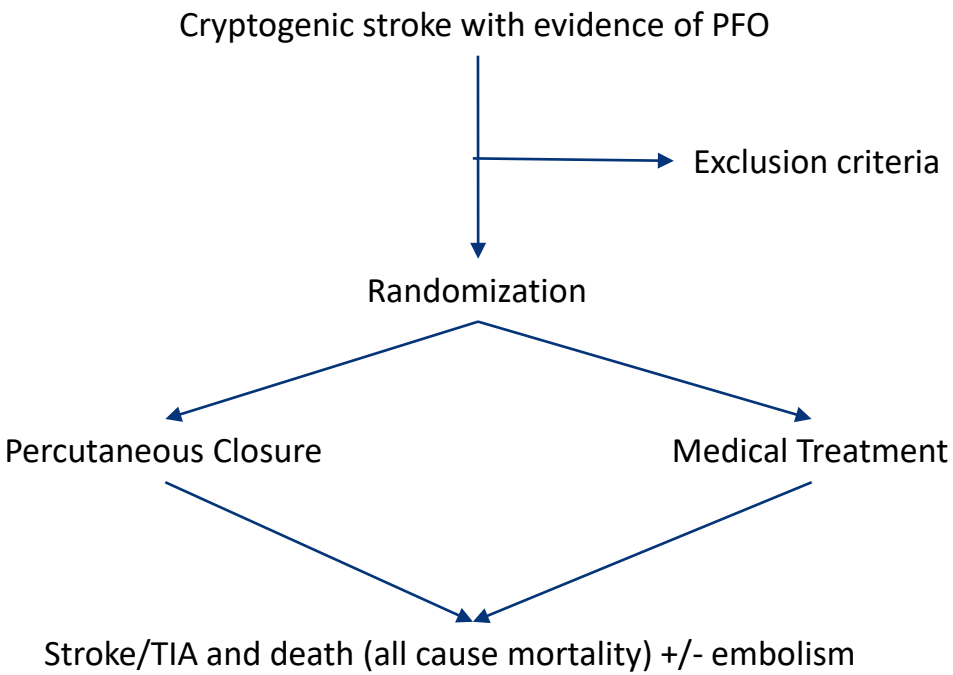
Olivier Muller
Service de cardiologie CHUV

PFO closure

RCTs PFO closure

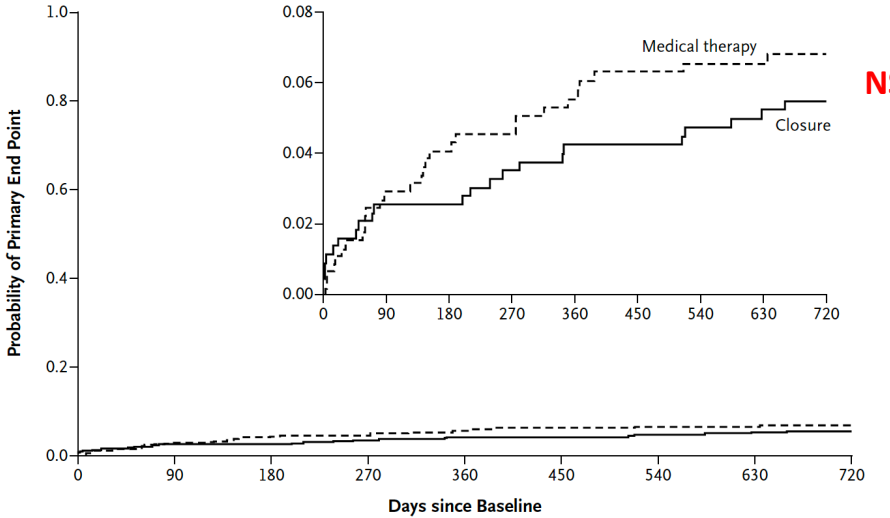


Study design initial trials



Closure-1

Closure not superior to medical therapy



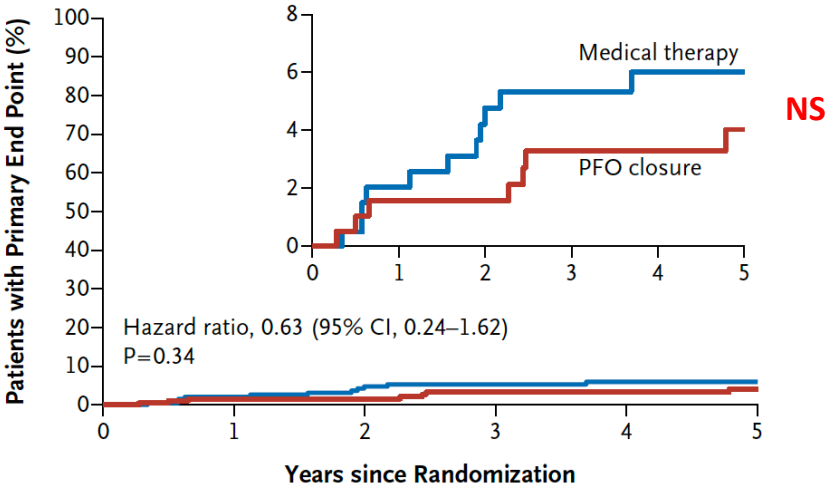
NS

No. at Risk

Closure	447	411	406	399	392	389	384	380	254
Medical therapy	462	421	405	388	378	365	359	356	242

PC trial

Closure not superior to medical therapy



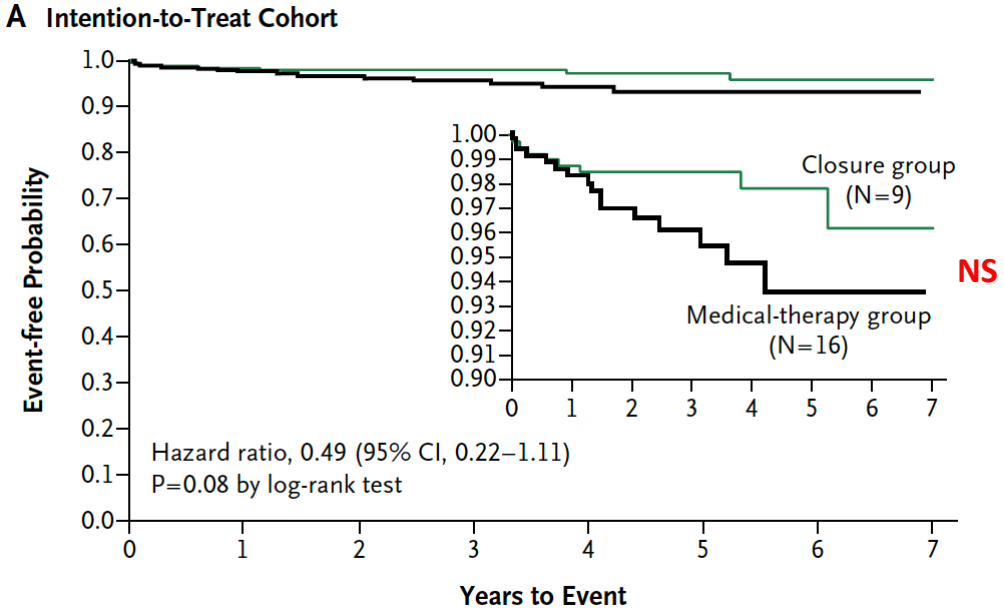
NS

No. at Risk

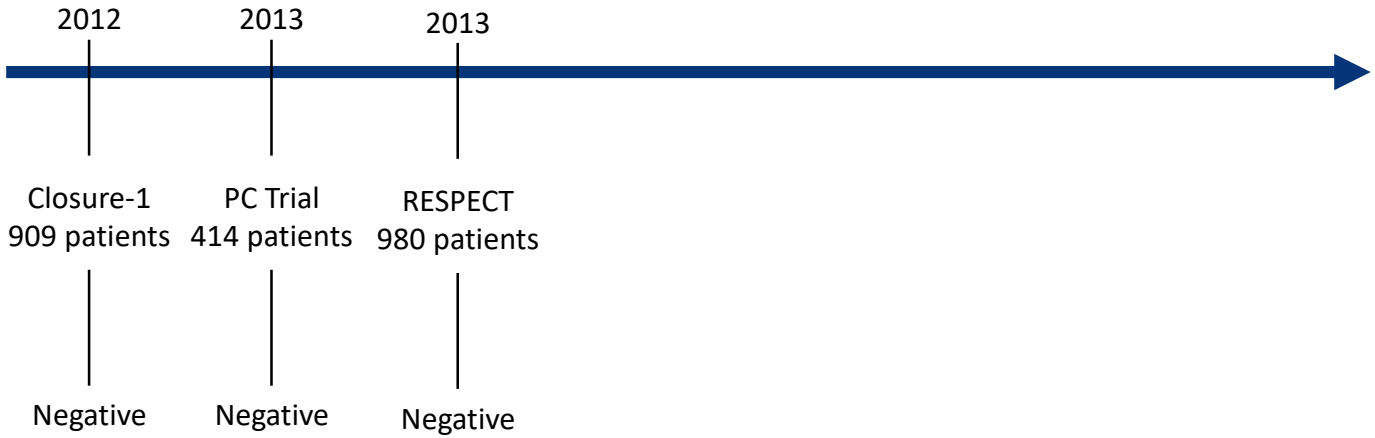
Medical therapy	210	185	170	159	131	90
PFO closure	204	186	181	163	142	110

RESPECT trial (FU 2.6 y)

Closure not superior to medical therapy



RCTs PFO closure

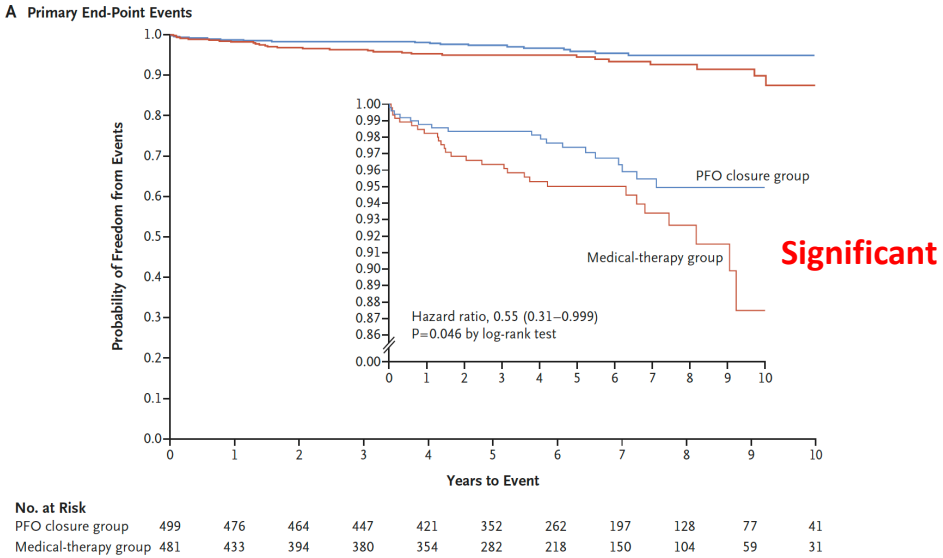


Closure-1, PC and RESPECT

- High crossover between groups
- Failure to randomise those patients whose strokes were likely to have been caused by PFO
- Inconsistent use of anticoagulants in the medical therapy group
- STARFlex occluder concerns (residual defects and left-sided thrombus formation)

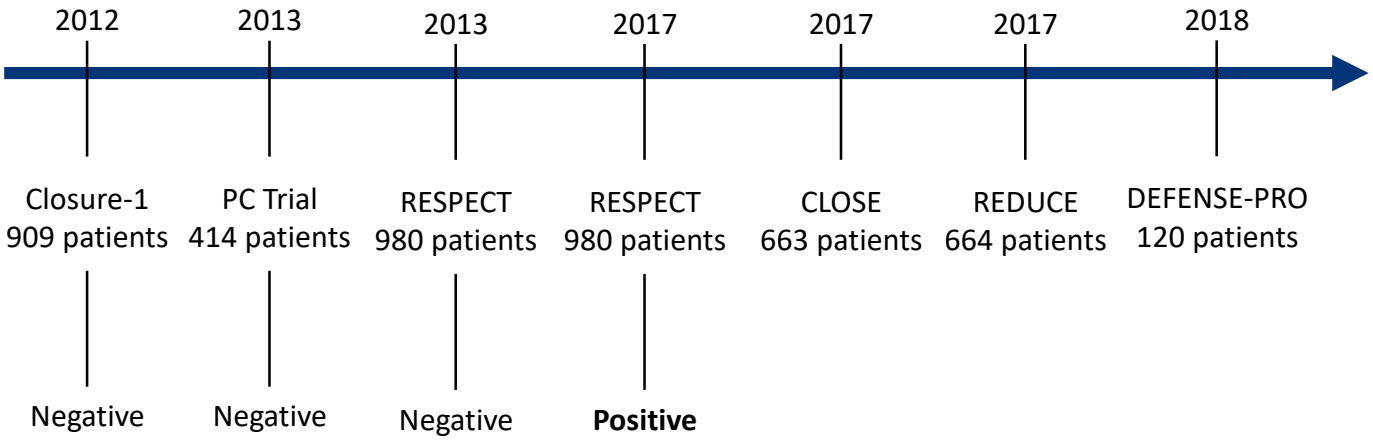
RESPECT trial extended FU (5.9 y)

Reduction in ischaemic stroke NNT = 45

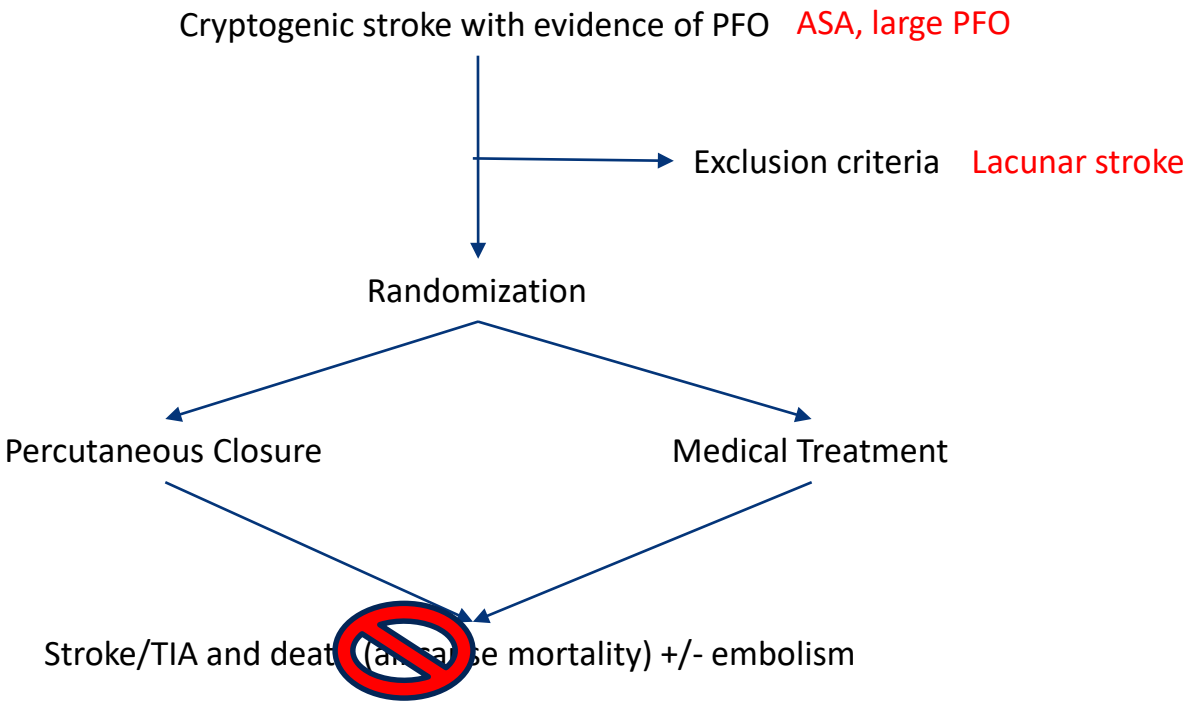


Significant

RCTs PFO closure

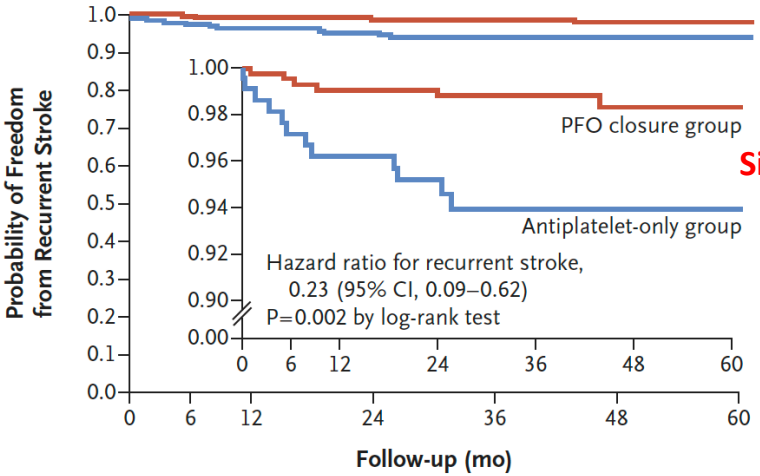


Study design : recent trials



REDUCE trial

Reduction in ischaemic stroke NNT = 25

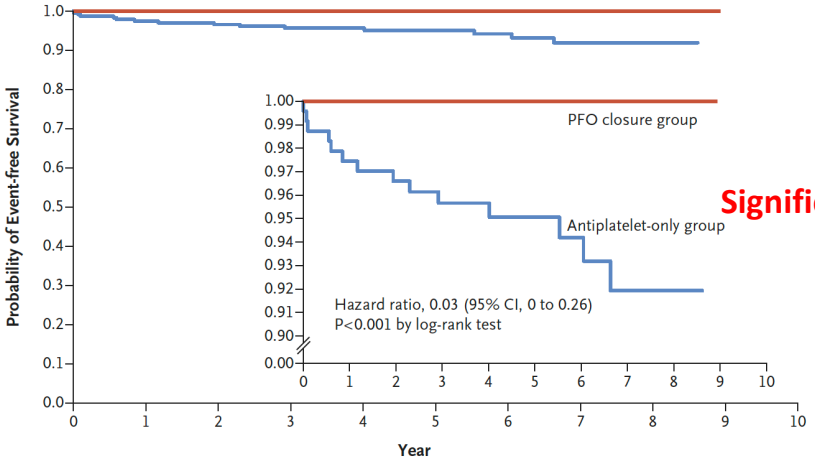


Significant

No. at Risk							
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

CLOSE trial

Reduction in ischaemic stroke NNT = 17

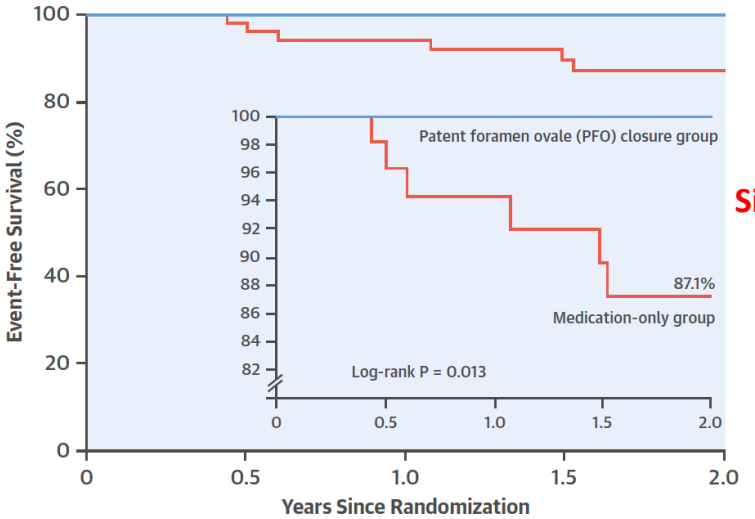


Significant

No. at Risk											
PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

Defense Pro Trial

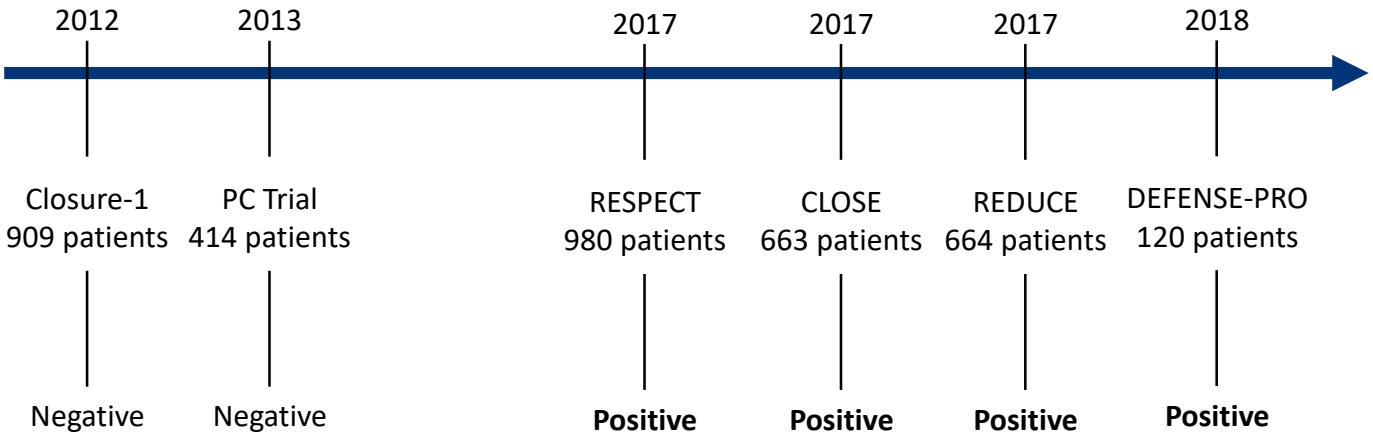
Reduction in stroke, vascular death and major bleeding NNT=8



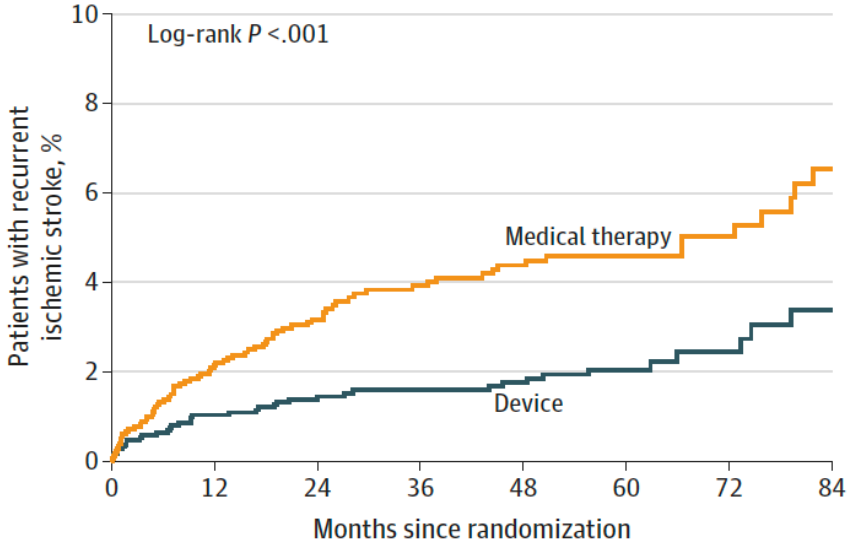
Significant

No. at Risk					
PFO closure	60	52	46	42	40
Medication-only	60	52	45	38	37

RCTs PFO closure



Pooled Individual Patient Data



No. at risk								
Device	1889	1771	1338	1245	1155	854	365	262
Medical therapy	1851	1668	1194	1094	971	699	390	253

Kent, JAMA, 2021

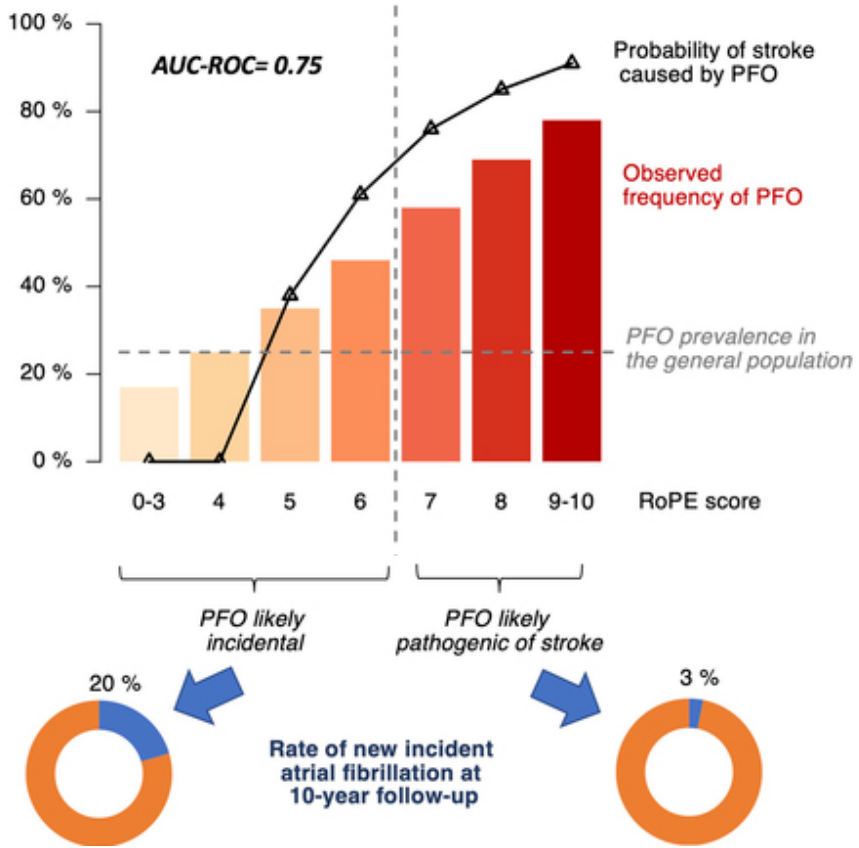
RoPE score (Risk of Paradoxical Embolism)

Table 4 RoPE score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Kent, Neurology, 2013

Validation of RoPE score



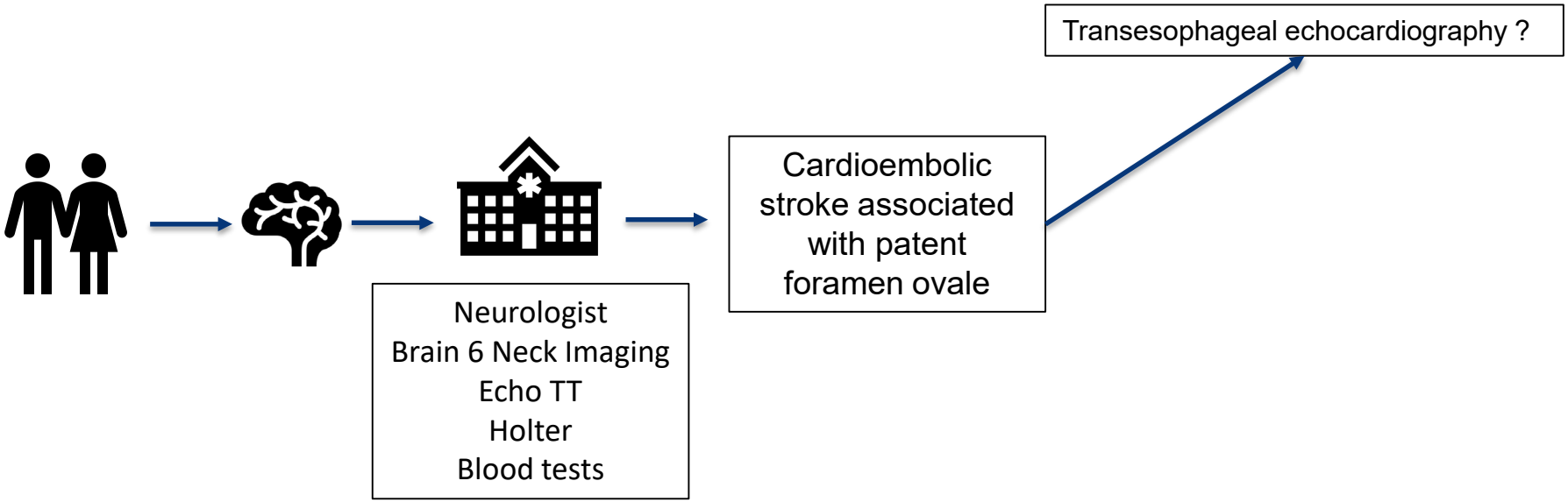
Strambo, Stroke, 2021

PASCAL (PFO-Associated Stroke Causal Likelihood)

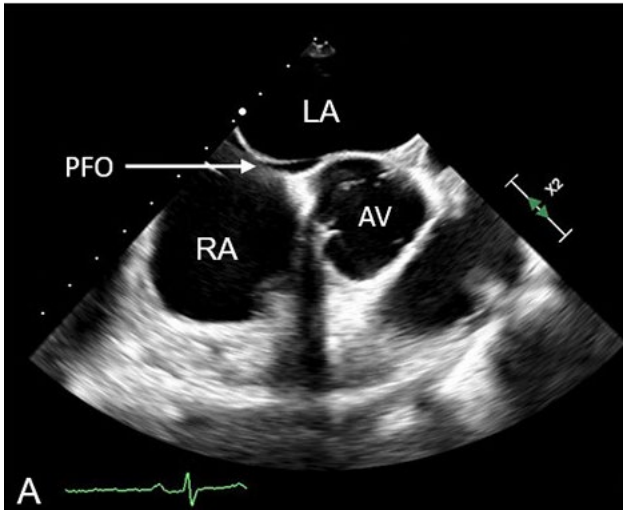
Risk source	Features	RoPE Score	
		Low[b] < 7	High[b] ≥ 7
Very high	A PFO and a straddling thrombus	Definite	Definite
High	(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO	Probable	Highly probable
Medium	Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO	Possible	Probable
Low	A small-shunt PFO without an atrial septal aneurysm	Unlikely	Possible

Elgendy, JAMA Neurol 2020

Points still unclear

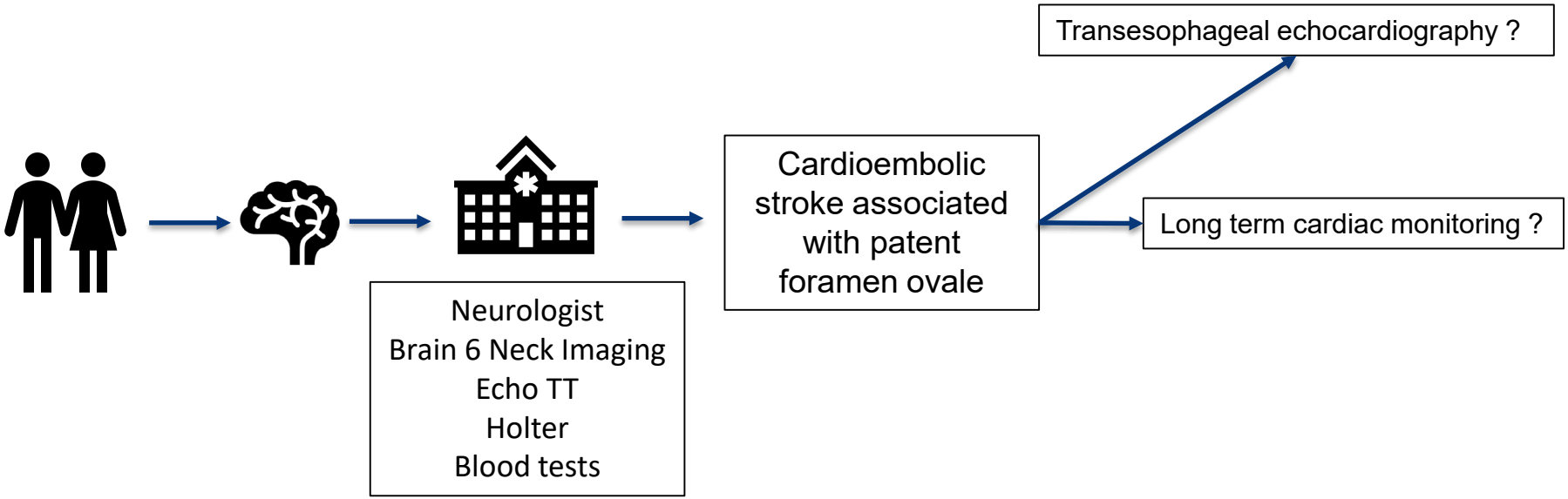


Transesophageal echocardiography



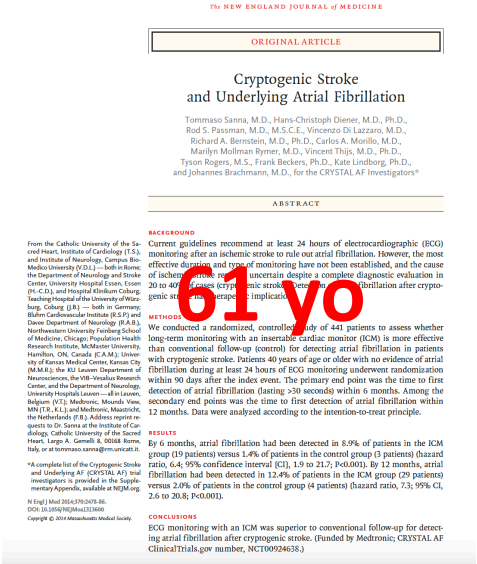
- Atrial septal defect
- Atrial myxoma, Fibroelastoma
- Aortic arch atheroma,
- Small aortic or mitral valvular vegetations

Points still unclear



Afib detection

CRYSTA – AF (6 M)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*

ABSTRACT

BACKGROUND

Current guidelines recommend at least 24 hours of electrocardiographic (ECG) monitoring after an ischemic stroke to rule out atrial fibrillation. However, the most effective duration and type of monitoring have not been established, and the cause of ischemic stroke [illegible] uncertain despite a complete diagnostic evaluation in 20 to 40 [illegible] cases (cryptogenic stroke). Detection of atrial fibrillation after cryptogenic stroke has therapeutic implications.

61 yo

METHODS

We conducted a randomized, controlled study of 441 patients to assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients with cryptogenic stroke. Patients 40 years of age or older with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring underwent randomization within 90 days after the index event. The primary end point was the time to first detection of atrial fibrillation (lasting ≥30 seconds) within 6 months. Among the secondary end points was the time to first detection of atrial fibrillation within 12 months. Data were analyzed according to the intention-to-treat principle.

RESULTS

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; P<0.001). By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; P<0.001).

CONCLUSIONS

ECG monitoring with an ICM was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke. (Funded by Medtronic; CRYSTAL AF ClinicalTrials.gov number, NCT00924638.)

From the Catholic University of the Sacred Heart, Institute of Cardiology (T.S.), and Institute of Neurology, Campus Bio-Medico University (V.D.L.) — both in Rome; the Department of Neurology and Stroke Center, University Hospital Essen, Essen (H.-C.D.), and Hospital Klinikum Coburg, Teaching Hospital of the University of Würzburg, Coburg (J.B.) — both in Germany; Bluhm Cardiovascular Institute (R.S.P.) and Davee Department of Neurology (R.A.B.), Northwestern University Feinberg School of Medicine, Chicago; Population Health Research Institute, McMaster University, Hamilton, ON, Canada (C.A.M.); University of Kansas Medical Center, Kansas City (M.M.R.); the KU Leuven Department of Neurosciences, the VIB–Vesalius Research Center, and the Department of Neurology, University Hospitals Leuven — all in Leuven, Belgium (V.T.); Medtronic, Mounds View, MN (T.R., K.L.); and Medtronic, Maastricht, the Netherlands (F.B.). Address reprint requests to Dr. Sanna at the Institute of Cardiology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy, or at tommaso.sanna@rm.unicatt.it.

*A complete list of the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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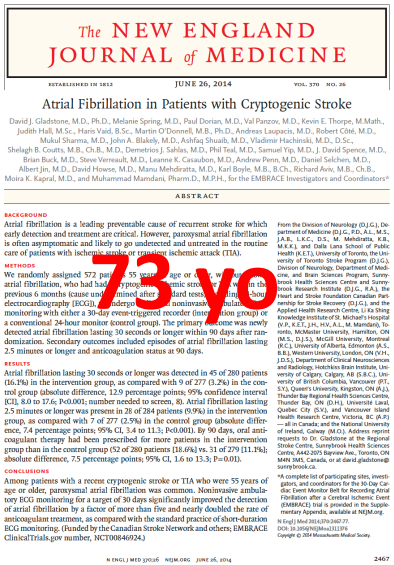
6 X Afib Detection

EMBRACE (30 D)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 26, 2014 VOL. 370 NO. 26

Atrial Fibrillation in Patients with Cryptogenic Stroke

David J. Gladstone, M.D., Ph.D., Melanie Spring, M.D., Paul Dorian, M.D., Val Panzov, M.D., Kevin E. Thorpe, M.Math., Judith Hall, M.Sc., Haris Vaid, B.Sc., Martin O'Donnell, M.B., Ph.D., Andreas Laupacis, M.D., Robert Côté, M.D., Mukul Sharma, M.D., John A. Blakely, M.D., Ashfaq Shuaib, M.D., Vladimir Hachinski, M.D., D.Sc., Shelagh B. Coutts, M.B., Ch.B., M.D., Demetrios J. Sahlas, M.D., Phil Teal, M.D., Samuel Yip, M.D., J. David Spence, M.D., Brian Buck, M.D., Steve Verreault, M.D., Leanne K. Casaubon, M.D., Andrew Penn, M.D., Daniel Selchen, M.D., Albert Jin, M.D., David Howse, M.D., Manu Mehdiratta, M.D., Karl Boyle, M.B., B.Ch., Richard Aviv, M.B., Ch.B., Moira K. Kapral, M.D., and Muhammad Mamdani, Pharm.D., M.P.H., for the EMBRACE Investigators and Coordinators*

ABSTRACT

BACKGROUND

Atrial fibrillation is a leading preventable cause of recurrent stroke for which early detection and treatment are critical. However, paroxysmal atrial fibrillation is often asymptomatic and likely to go undetected and untreated in the routine care of patients with ischemic stroke or transient ischemic attack (TIA).

73 yo

METHODS

We randomly assigned 572 patients, 55 years of age or older, who had cryptogenic stroke or TIA and no known atrial fibrillation, who had had cryptogenic ischemic stroke or TIA within the previous 6 months (cause undetermined after standard resting 12-lead electrocardiography [ECG]), to undergo 30 days of noninvasive ambulatory cardiac monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hour monitor (control group). The primary outcome was newly detected atrial fibrillation lasting 30 seconds or longer within 90 days after randomization. Secondary outcomes included episodes of atrial fibrillation lasting 2.5 minutes or longer and anticoagulation status at 90 days.

RESULTS

Atrial fibrillation lasting 30 seconds or longer was detected in 45 of 280 patients (16.1%) in the intervention group, as compared with 9 of 277 (3.2%) in the control group (absolute difference, 12.9 percentage points; 95% confidence interval [CI], 8.0 to 17.6; P<0.001; number needed to screen, 8). Atrial fibrillation lasting 2.5 minutes or longer was present in 28 of 284 patients (9.9%) in the intervention group, as compared with 7 of 277 (2.5%) in the control group (absolute difference, 7.4 percentage points; 95% CI, 3.4 to 11.3; P<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group than in the control group (52 of 280 patients [18.6%] vs. 31 of 279 [11.1%]; absolute difference, 7.5 percentage points; 95% CI, 1.6 to 13.3; P=0.01).

CONCLUSIONS

Among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older, paroxysmal atrial fibrillation was common. Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring. (Funded by the Canadian Stroke Network and others; EMBRACE ClinicalTrials.gov number, NCT00846924.)

From the Division of Neurology (D.J.G.), Department of Medicine (D.J.G., P.D., A.L., M.S., J.A.B., S.K.C., D.S., M. Mehdiratta, K.B., M.K.K.), and Dalla Lana School of Public Health (K.E.T.), University of Toronto, the University of Toronto Stroke Program (D.J.G.), Division of Neurology, Department of Medicine, and Brain Sciences Program, Sunnybrook Health Sciences Centre and Sunnybrook Research Institute (D.J.G., R.A.), the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (D.J.G.), and the Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital (V.P., K.E.T., J.H., H.V., A.L., M. Mamdani), Toronto, McMaster University, Hamilton, ON (M.S., D.J.S.), McGill University, Montreal (R.C.), University of Alberta, Edmonton (A.S., B.B.), Western University, London, ON (V.H., J.D.S.), Department of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB (S.B.C.), University of British Columbia, Vancouver (P.T., S.Y.), Queen's University, Kingston, ON (A.J.), Thunder Bay Regional Health Sciences Centre, Thunder Bay, ON (D.H.), Université Laval, Québec City, (S.V.), and Vancouver Island Health Research Centre, Victoria, BC (A.P.) — all in Canada; and the National University of Ireland, Galway (M.O.). Address reprint requests to Dr. Gladstone at the Regional Stroke Centre, Sunnybrook Health Sciences Centre, A442-2075 Bayview Ave., Toronto, ON M4N 3M5, Canada, or at david.gladstone@sunnybrook.ca.

*A complete list of participating sites, investigators, and coordinators for the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trial is provided in the Supplementary Appendix, available at NEJM.org.

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N ENGL J MED 370;26 NEJM.ORG JUNE 26, 2014 2467

5 X Afib Detection

Conclusions: Benefit – risk of PFO closure

The Benefit

Annualized incidence of stroke

- Medical therapy 1.09%
- Device closure was 0.47%

- 60%

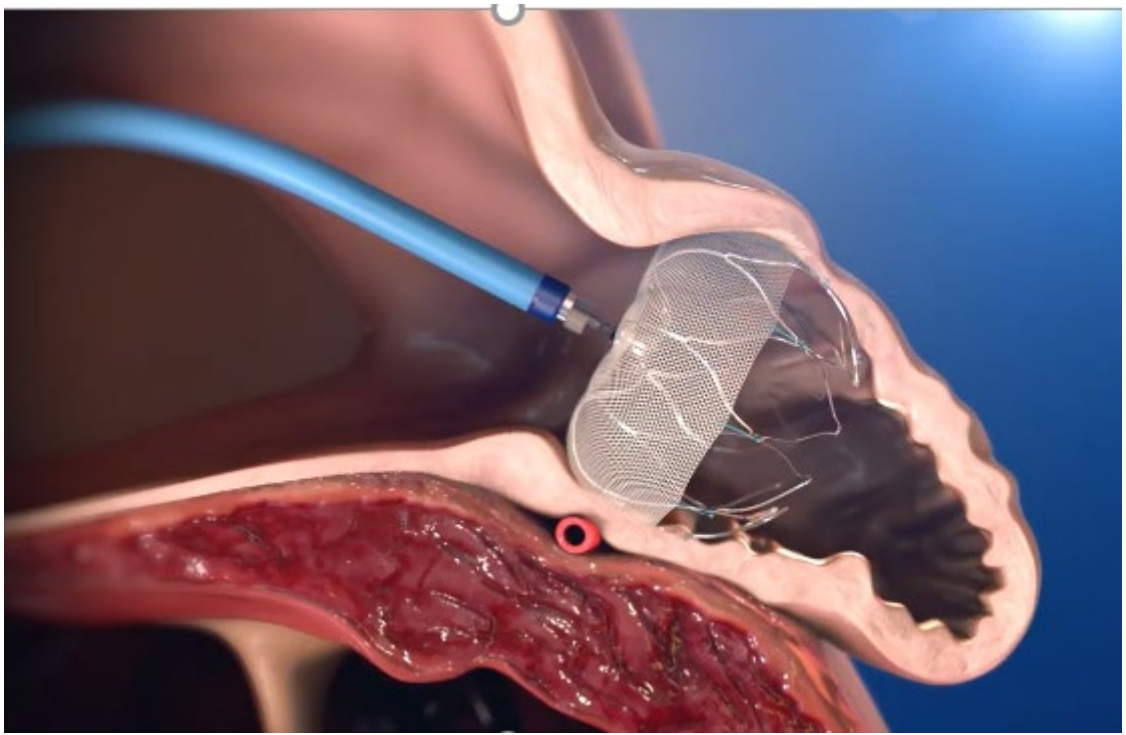
The Risk

Incidence of atrial fibrillation
FU 57 months
(> 45 days)

- Medical therapy 0.8%
- Device closure was 2.4%

X 3

LAA Closure



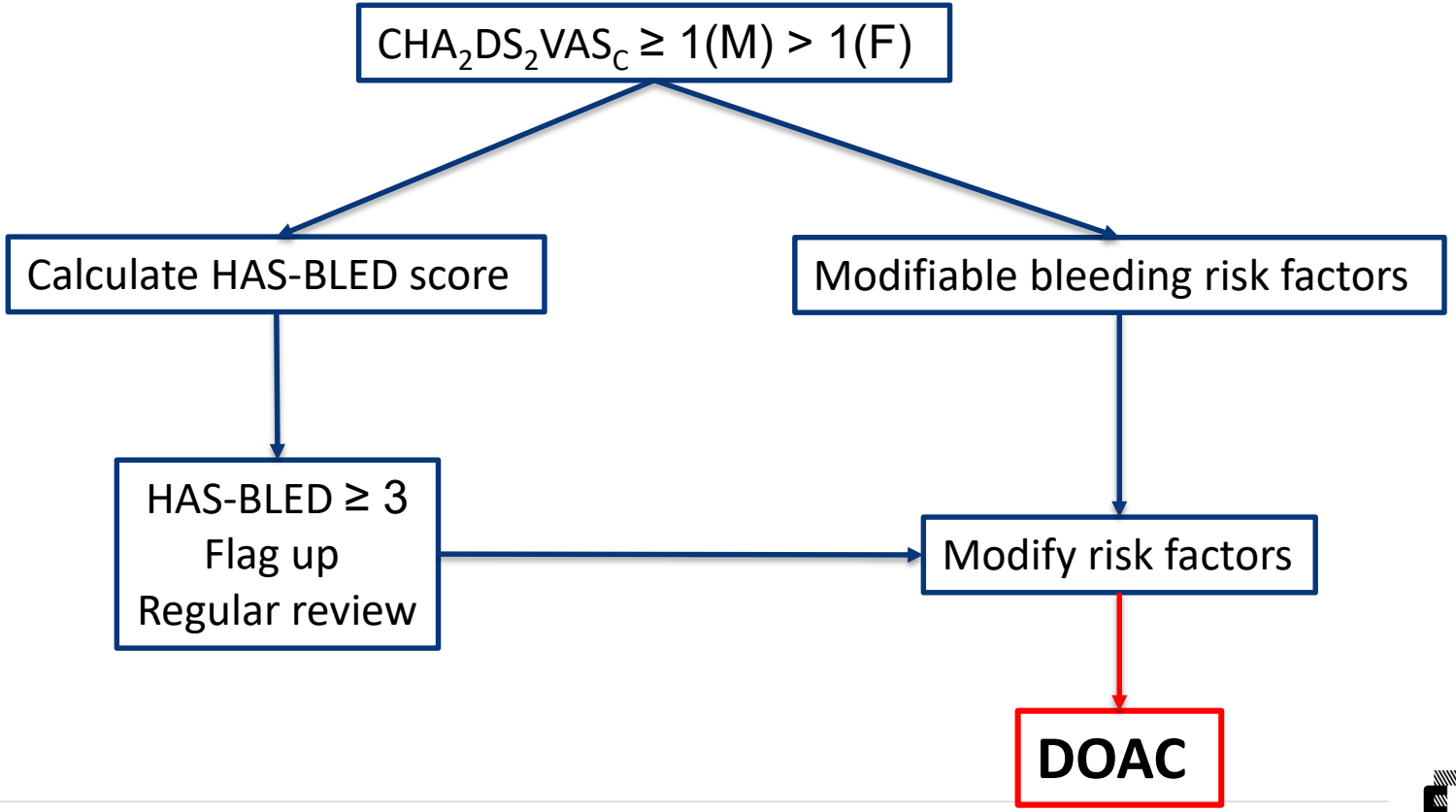
ESC guidelines

Recommendations for occlusion or exclusion of the LAA		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).[448,449,481,482]	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.[459,483]	IIb	C

Rational of LAA closure

- Studies have reported that the LAA is the source of thrombus in about *90% of nonvalvular AF* and *57% of valvular AF*
  - Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.
  - Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. J Am Coll Cardiol 1995;25:1354–61.

Atrial Fibrillation: OAC



Bleeding Score: HAS-BLED

Table 10 **Clinical risk factors in the HAS-BLED score**[395]

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR**[b] TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

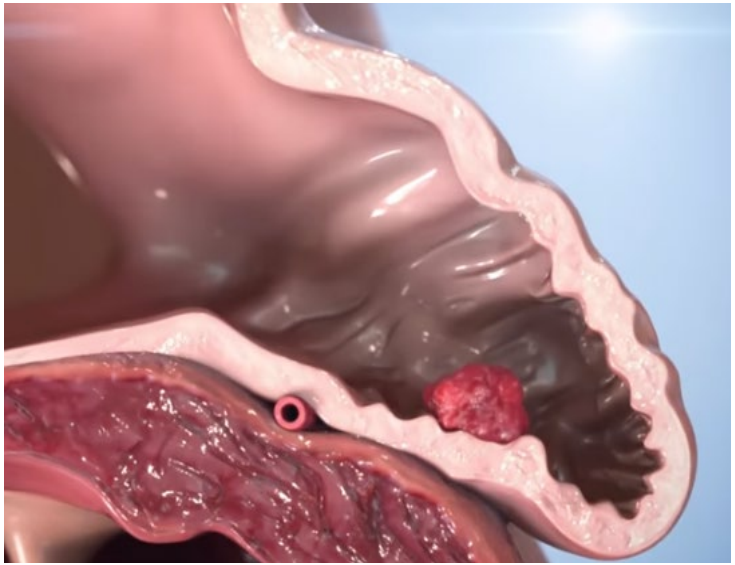
Bleeding risk

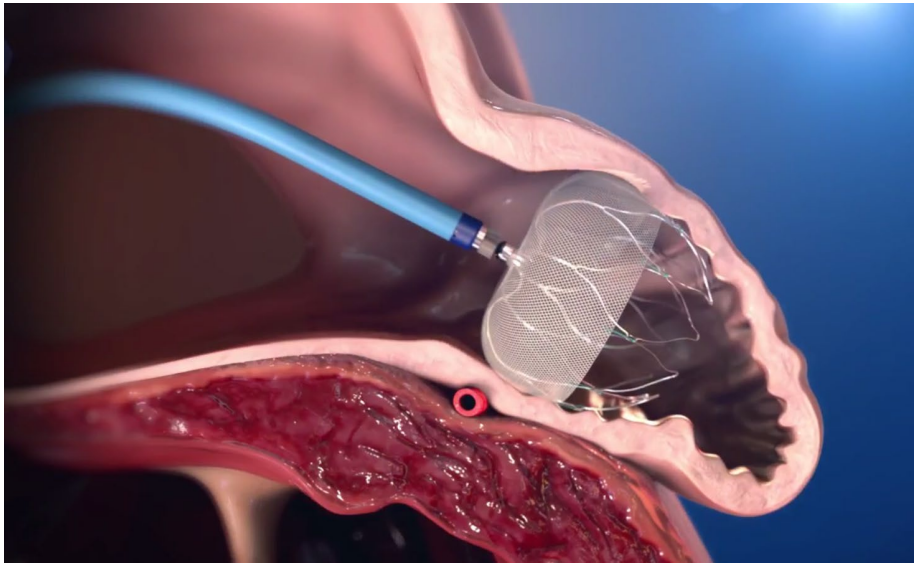
Table 9 **Risk factors for bleeding with OAC and antiplatelet therapy**

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years	Extreme frailty ± excessive risk of falls[a]	Hypertension/elevated SBP	GDF-15
Previous major bleeding	Anaemia	Concomitant antiplatelet/NSAID	Cystatin C/CKD-EPI
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intake	cTnT-hs
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OAC	von Willebrand factor (+ other coagulation markers)
Malignancy	VKA management strategy[b]	Hazardous hobbies/occupations	
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with heparin	
Previous stroke, small-vessel disease, etc.		INR control (target 2.0 - 3.0), target TTR >70%[c]	
Diabetes mellitus		Appropriate choice of OAC and correct dosing[d]	
Cognitive impairment/dementia			

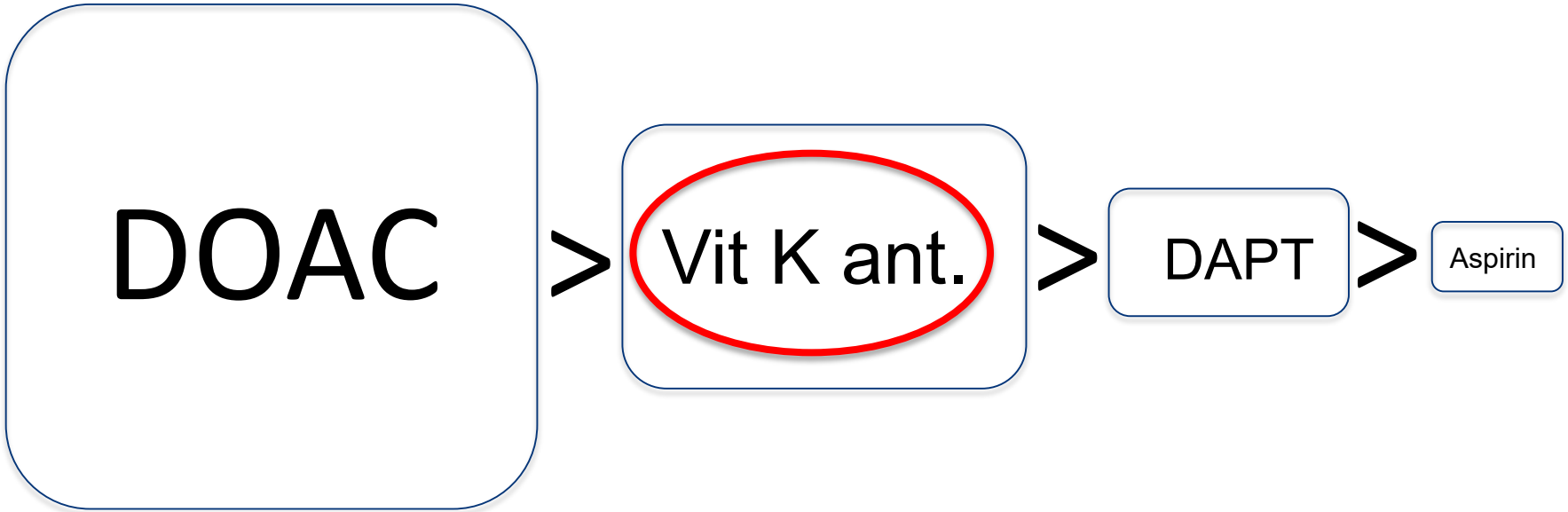
A high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients.

What is the indication for the left atrial appendage (LAAC) closure ?





Anticoagulation in Atrial Firbrillation

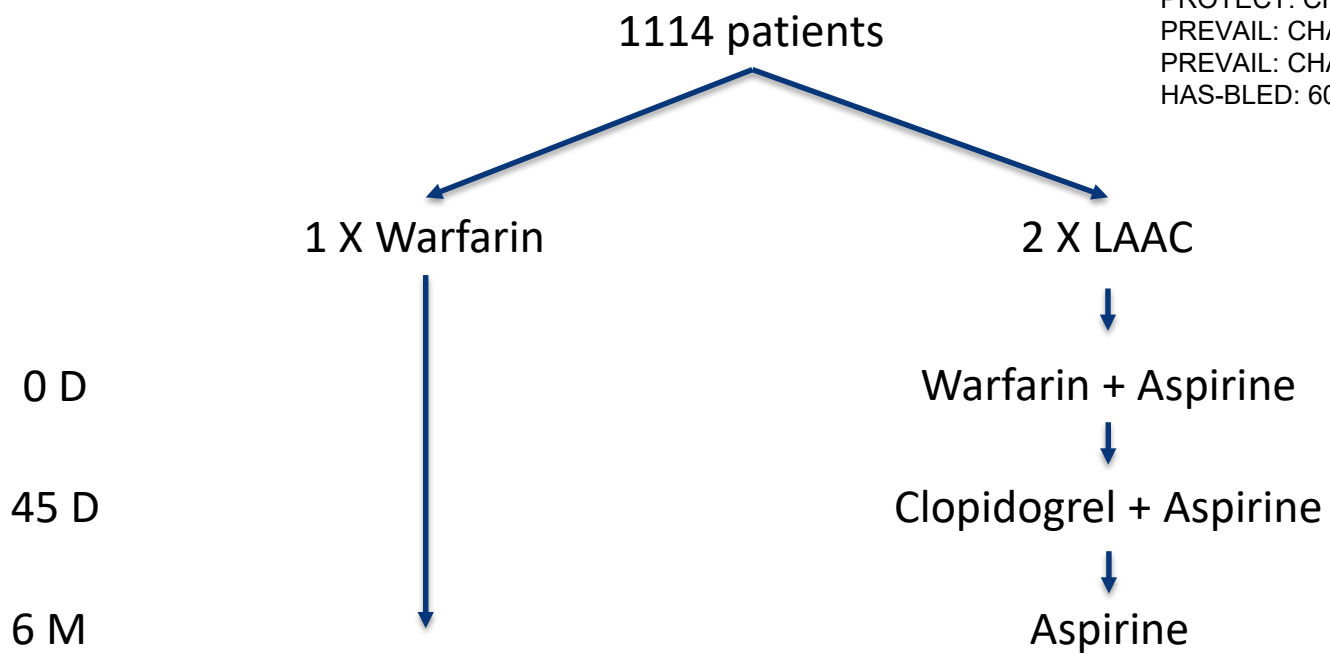


Apixaban (ARISTOTLE)
Edoxaban (ENGAGE AF TIMI 48)
Rivaroxaban (ROCKET-AF)
Dabigatran (RE-LY)

Aspirine + clopidogrel (ACTIVE W + A)

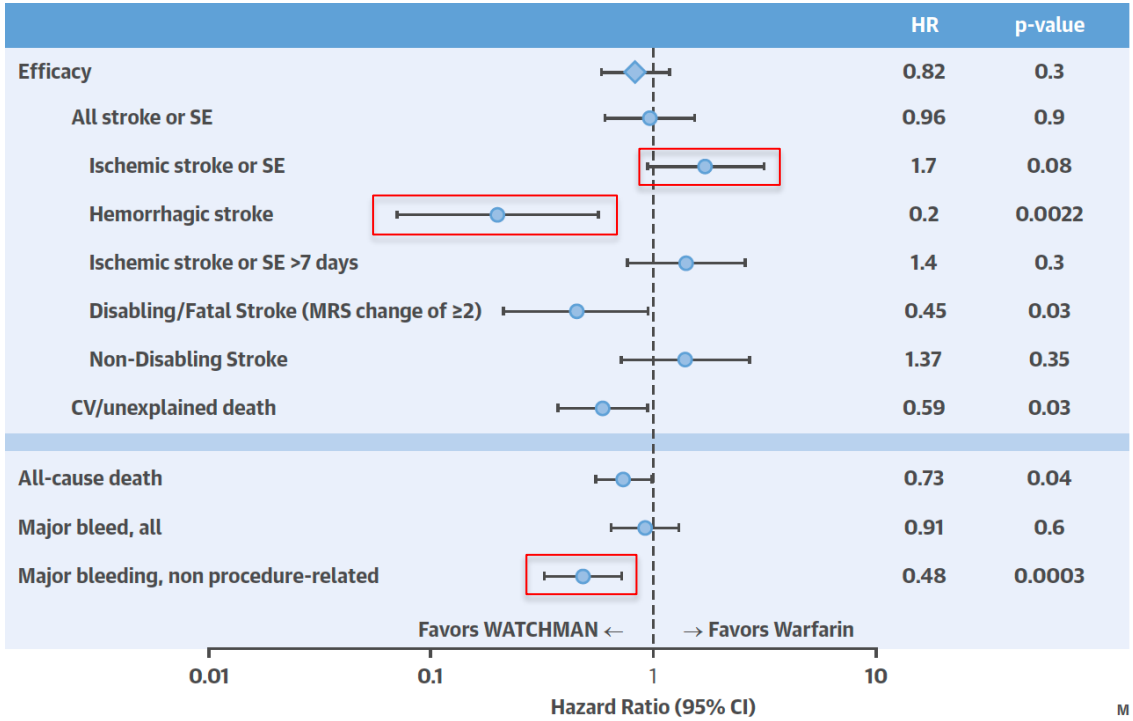
PROTECT AF + PREVAIL

PROTECT: CHADS2 ≧ 1
PREVAIL: CHADS2 ≧ 1 + 1 risk factor
PREVAIL: CHADS2 ≧ 2
HAS-BLED: 60-70% 1-2



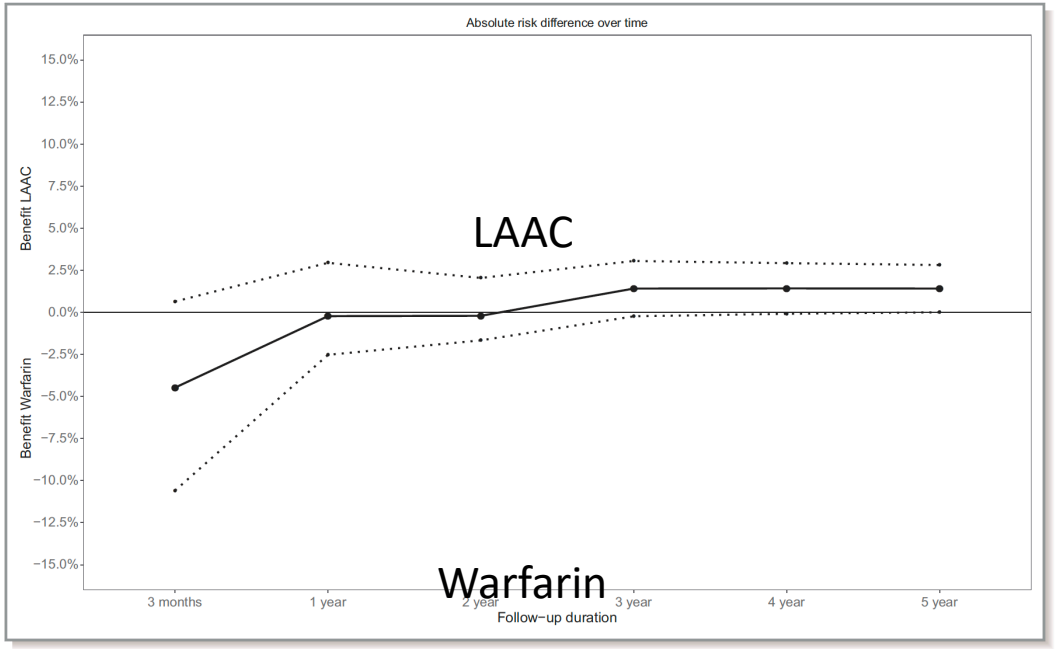
PROTECT AF and PREVAIL

5 years follow-up



J Am Coll Cardiol. 2017 Dec 19;70(24):2964-

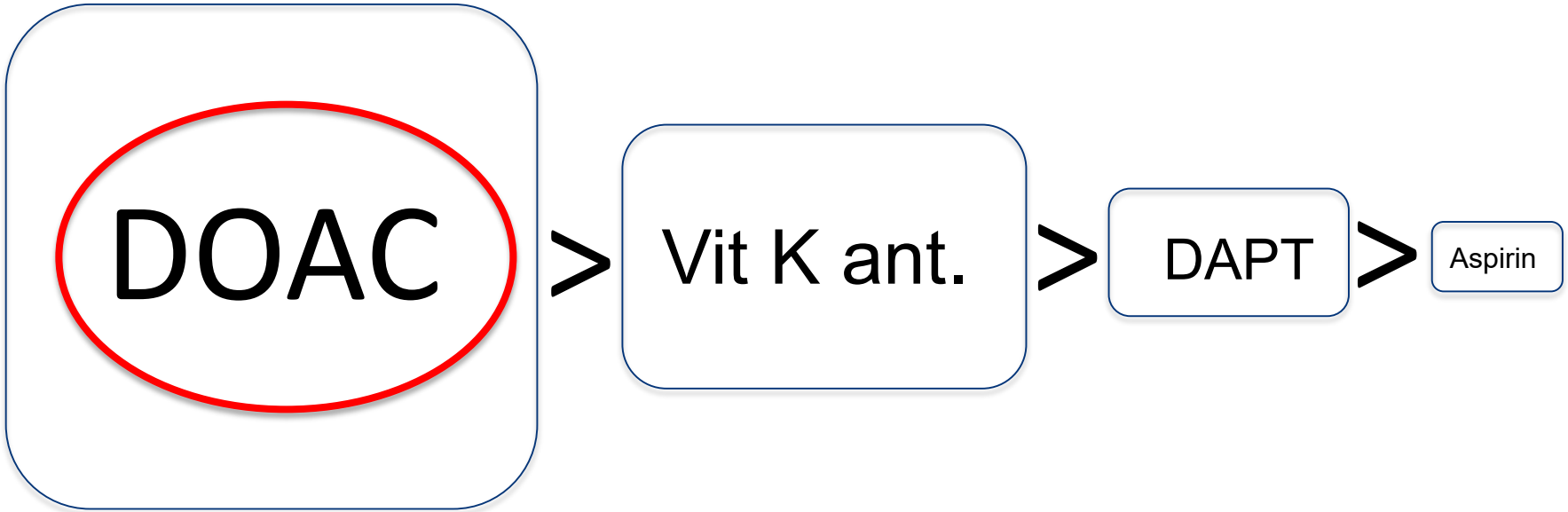
Net Clinical Benefit



Outcomes

- All death events irrespective of cause
- Ischemic stroke
- Intracranial hemorrhage
- Major extracranial bleeding and the
- major procedural complication
- Pericardial effusion

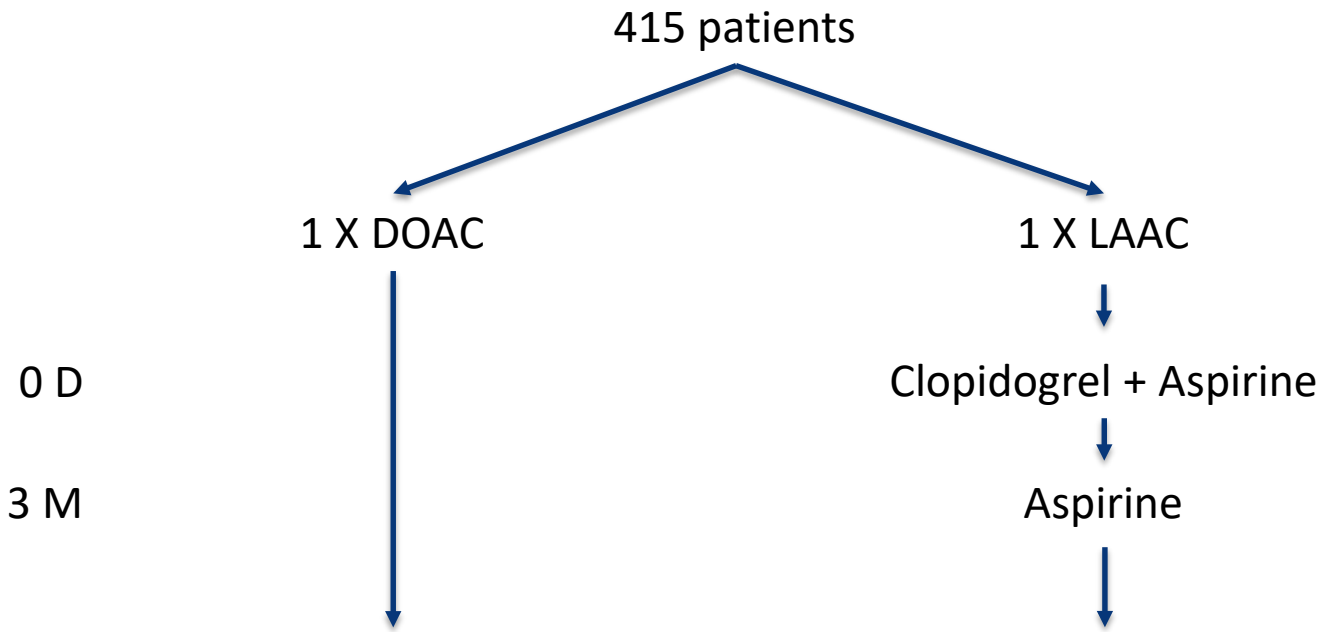
Anticoagulation in Atrial Firbrillation



Apixaban (ARISTOTLE)
Edoxaban (ENGAGE AF TIMI 48)
Rivaroxaban (ROCKET-AF)
Dabigatran (RE-LY)

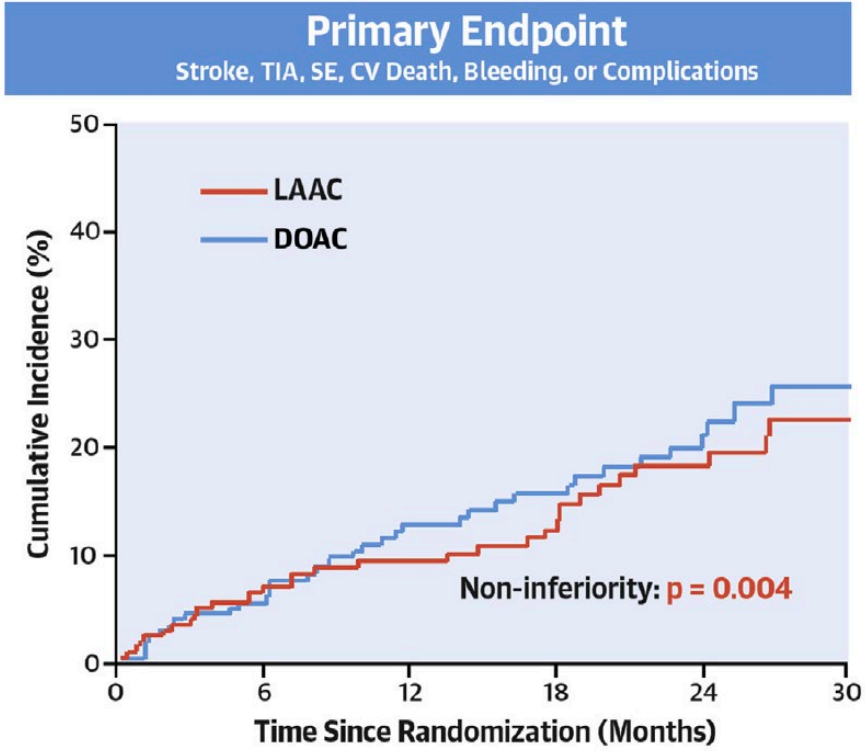
Aspirine + clopidogrel (ACTIVE W + A)

PRAGUE - 17


415 patients
1 X DOAC
1 X LAAC
0 D
3 M
Clopidogrel + Aspirine
Aspirine

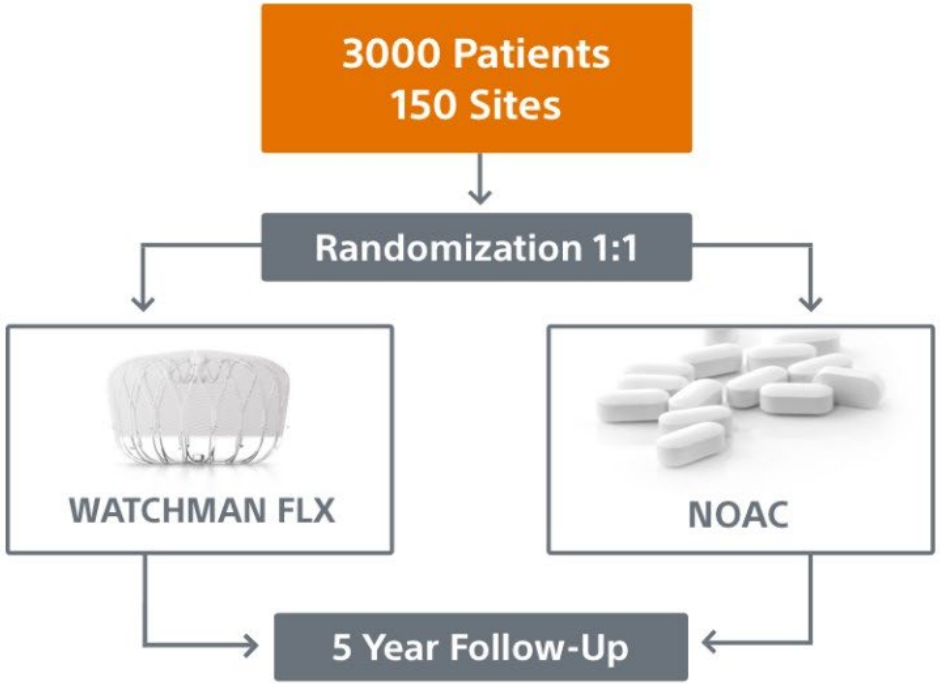
PRAGUE-17 results

- 402 High-Risk AF Pts ➡ Randomized
  - CHA_2DS_2-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Follow-up: 20.8 ± 10.8 mo (695 pt-year)



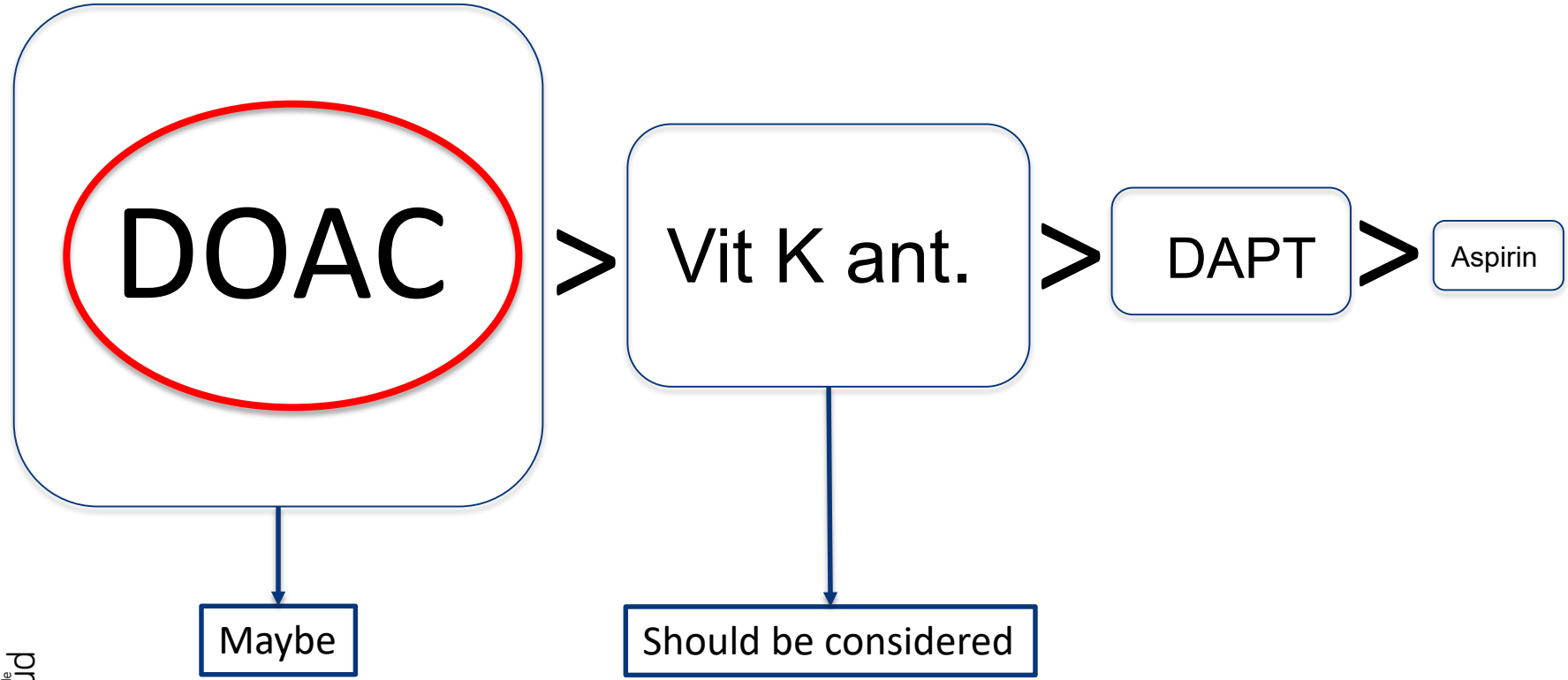
Osmancik, P. et al. J Am Coll Cardiol. 2020;75(25):3122-35.

CHAMPION-AF Clinical Trial

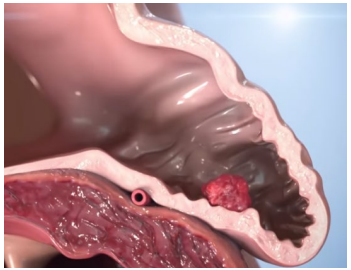


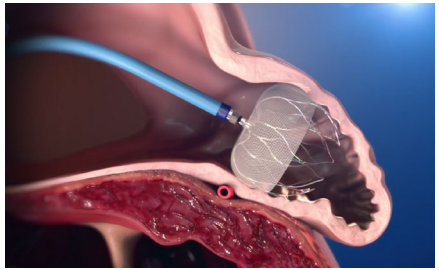
2025

Anticoagulation in Atrial Firbrillation



Absolute contraindications to oral anticoagulants





- Severe thrombocytopenia <50 platelets/lL,
- Recent high-risk bleeding event
  - Intracranial haemorrhage (ICH)
  - GI bleeding such angiodysplasia
- Iterative DAPT
- Renal failure with contraindication to DOAC