8TH REGIONAL TEACHING COURSE IN SUB-SAHARAN AFRICA

MAPUTO, MOZAMBIQUE
NOVEMBER 10 – 12, 2016

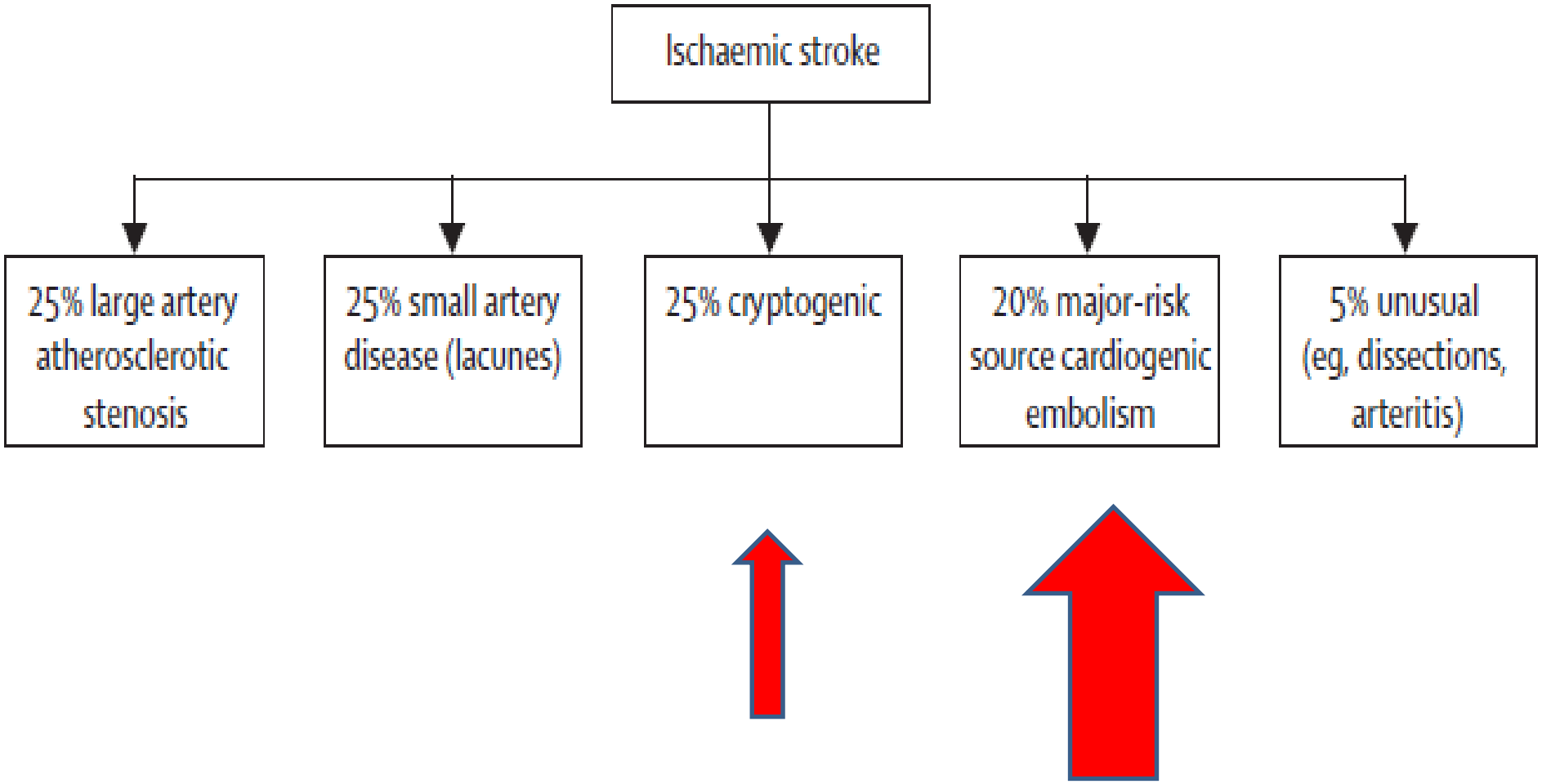
8Th Regional Teaching Course In Sub Saharan Africa

Cardiogenic stroke

A. Damasceno, MD, Ph.D., FESC
MOZAMBIQUE

Summary

- Embolic strokes
  - Origin
  - Clinical caracterization
- Specific situations
  - Atrial fibrillation
    - Primary prevention
    - Secondary prevention
  - Heart failure
- Other issues
  - PFO
  - LAA

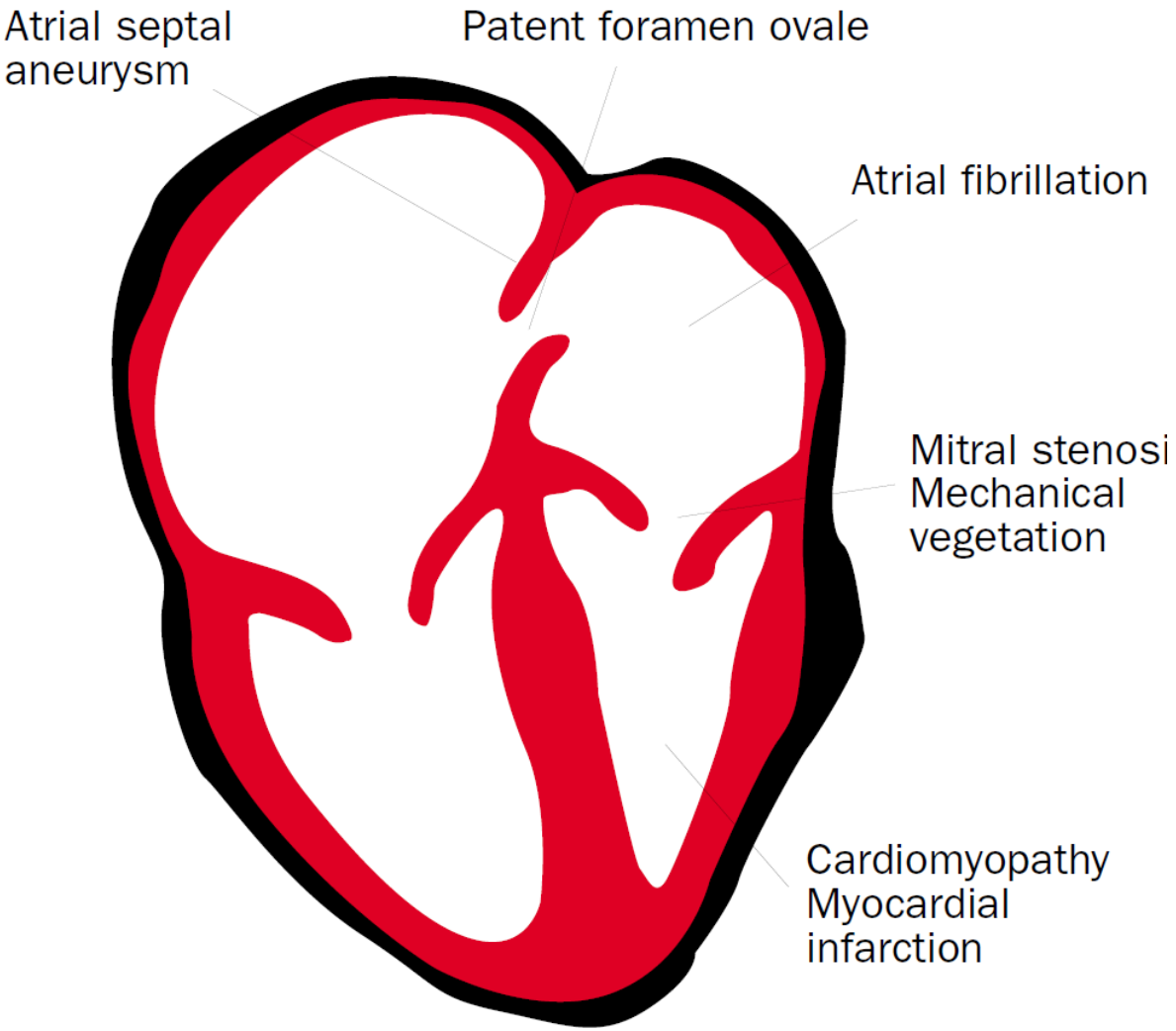


Robert G Hart et al, Lancet Neurol **2014; 13: 429–38**

Cardioembolic stroke: an update

José M Ferro

THE LANCET Neurology Vol 2 March 2003



Cardioembolic sources and embolic risk

Ferro J, THE LANCET Neurology Vol 2 March 2003

High risk	Low/uncertain risk
Atrial	
Atrial fibrillation	Patent foramen ovale
Sustained atrial flutter	Atrial septal aneurysm
Sick sinus syndrome	Atrial auto-contrast
Left atrial thrombus	
Left atrial appendage thrombus	
Left atrial myxoma	
Valvular	
Mitral stenosis	Mitral annulus calcification
Prosthetic valve	Mitral-valve prolapse
Infective endocarditis	Calcified aortic stenosis
Non-infective endocarditis	Fibroelastoma
	Giant Lambl's excrescences
Ventricular	
Left ventricular thrombus	Akinetic/dyskinetic ventricular wall segment
Left ventricular myxoma	Subaortic hypertrophic cardiomyopathy
Recent anterior myocardial infarct	Congestive heart failure
Dilated cardiomyopathy	

Ferro J, THE LANCET Neurology Vol 2 March 2003

Features suggestive of cardioembolic stroke

- Decreased consciousness at onset
- Rapid regression of symptoms (the spectacular shrinking syndrome)
- Sudden onset to maximal deficit (<5 min)
- Simultaneous or sequential strokes in different arterial territories (especially if bi-hemispheric or involving combined anterior and posterior, bilateral, or multi level posterior circulation)
- Haemorrhagic transformation of an ischaemic infarct
- Early recanalization of an occluded intracranial vessel

Ferro J, THE LANCET Neurology Vol 2 March 2003

Specific Situations

Atrial Fibrillation

- Primary prevention
- When shall we introduce anticoagulants after a TIA or an Ischaemic stroke
- Secondary Prevention

Atrial Fibrillation – Primary Prevention

- Atrial Fibrillation, even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke resulting from embolism of stasis-induced thrombi forming in the left atrial appendage (LAA).
- Embolism of appendage thrombi associated with AF accounts for ≈10% of all ischemic strokes and an even higher fraction in the very elderly in the United States.
- The absolute stroke rate averages≈3.5%/y for 70-year-old individuals with AF, but the risk varies 20-fold among patients, depending on age and other clinical features.
- AF is also an independent predictor of increased mortality.
- Paroxysmal AF increases stroke risk similar to sustained AF.

Meschia et al *Stroke* December 2014

Once the diagnosis of AF is established, the next step is to estimate an individual's risks:

- For cardioembolic stroke
- For haemorrhagic complications of antithrombotic therapy.

Meschia et al *Stroke* December 2014

Stroke Risk Stratification Schemes for Patients With AF

CHA2DS2-VASc

Scoring system
- Congestive heart failure–1 point
- Hypertension–1 point
- Age 65–74 y–1 point
  - ≥75 y–2 points
- Diabetes mellitus–1 point
- Stroke/TIA–2 points
- Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque)–1 point
- Female sex–1 point
- Risk scores range: 0–9 points

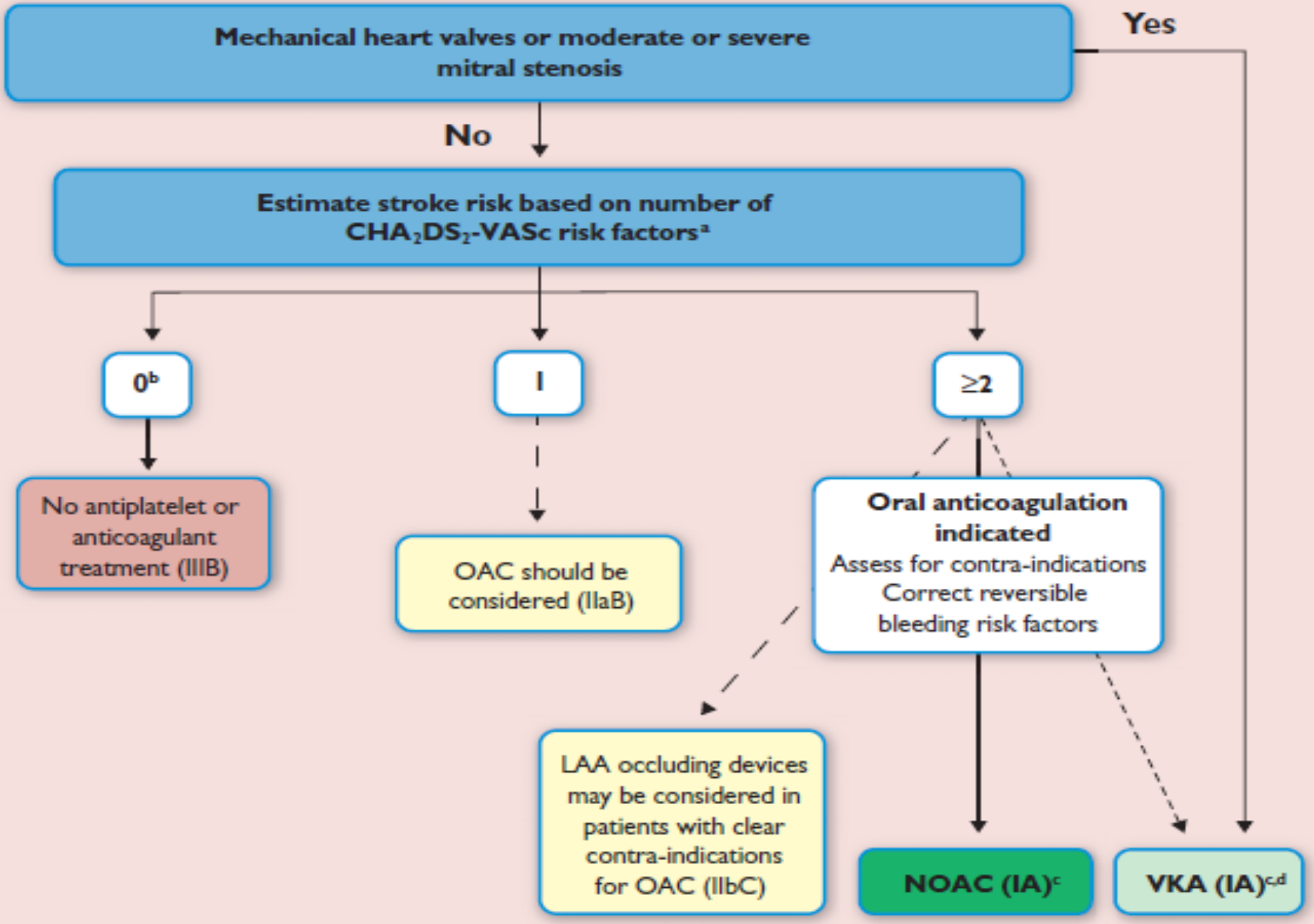
Levels of risk for thromboembolic stroke
- Low risk=0 points
- Moderate risk=1 point
- High risk ≥2 points

HAS-BLED

- Hypertension–1 point
- Abnormal renal function–1 point
- Abnormal liver function–1 point
- Prior stroke–1 point
- Prior major bleeding or bleeding predisposition–1 point
- INR in therapeutic range <60% of time–1 point
- Age >65 y–1 point
- Use of antiplatelet or nonsteroidal drugs–1 point
- Excessive alcohol use–1 point
- Risk scores range: 0–9 points
- Score >2 associated with clinically relevant and major bleeding.[382]

Meschia et al, Guidelines for the Primary Prevention of Stroke, *Stroke* December 2014

Stroke prevention in atrial fibrillation.



European Heart Journal (2016) 37, 2893–2962

What to Choose

- Vit K anticoagulants
- NOAC
- Aspirin

?

Guidelines for the Primary Prevention of Stroke

Adjusted-dose warfarin has generally been the treatment of choice for patients at high risk for cardioembolic stroke and acceptably low risk of hemorrhagic complications, particularly intracranial haemorrhage. Treatment with adjusted-dose warfarin (target INR, 2 to 3) robustly protects against stroke (RR reduction, 64%; 95% CI, 49–74)

Paroxysmal AF increases stroke risk similar to sustained AF.

Meschia et al *Stroke* December 2014

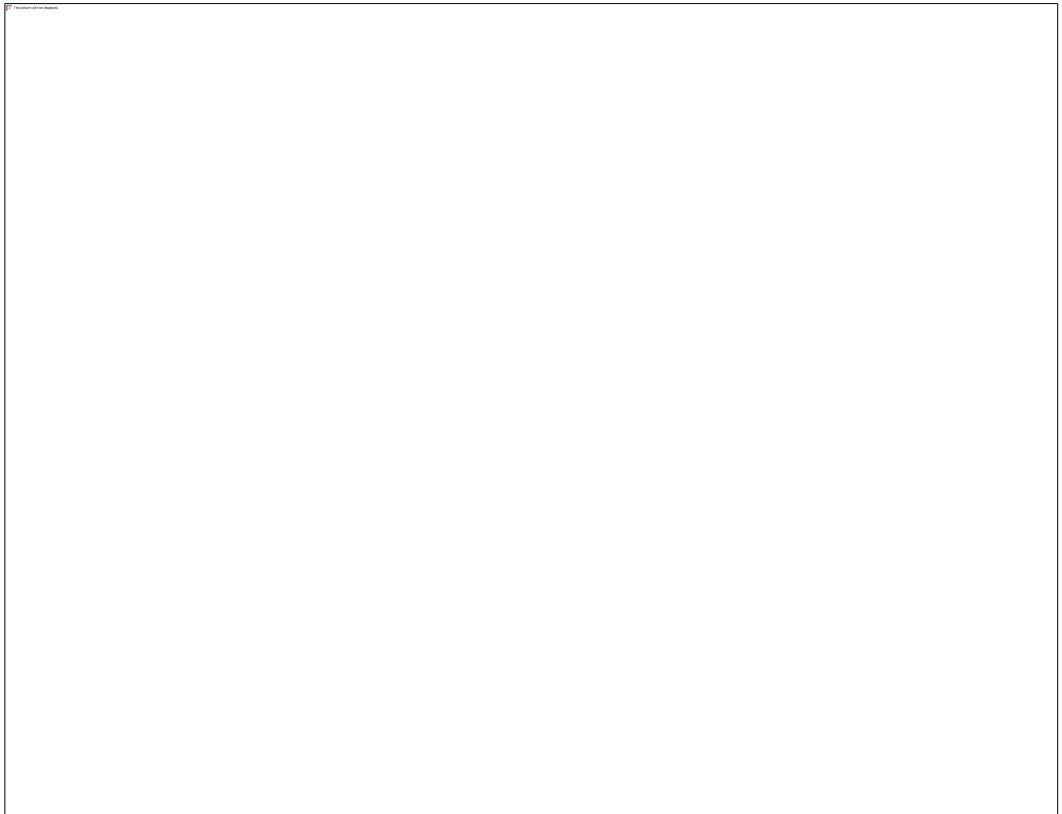
- The bleeding risk on aspirin is not different to the bleeding risk on VKA or NOAC therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients.

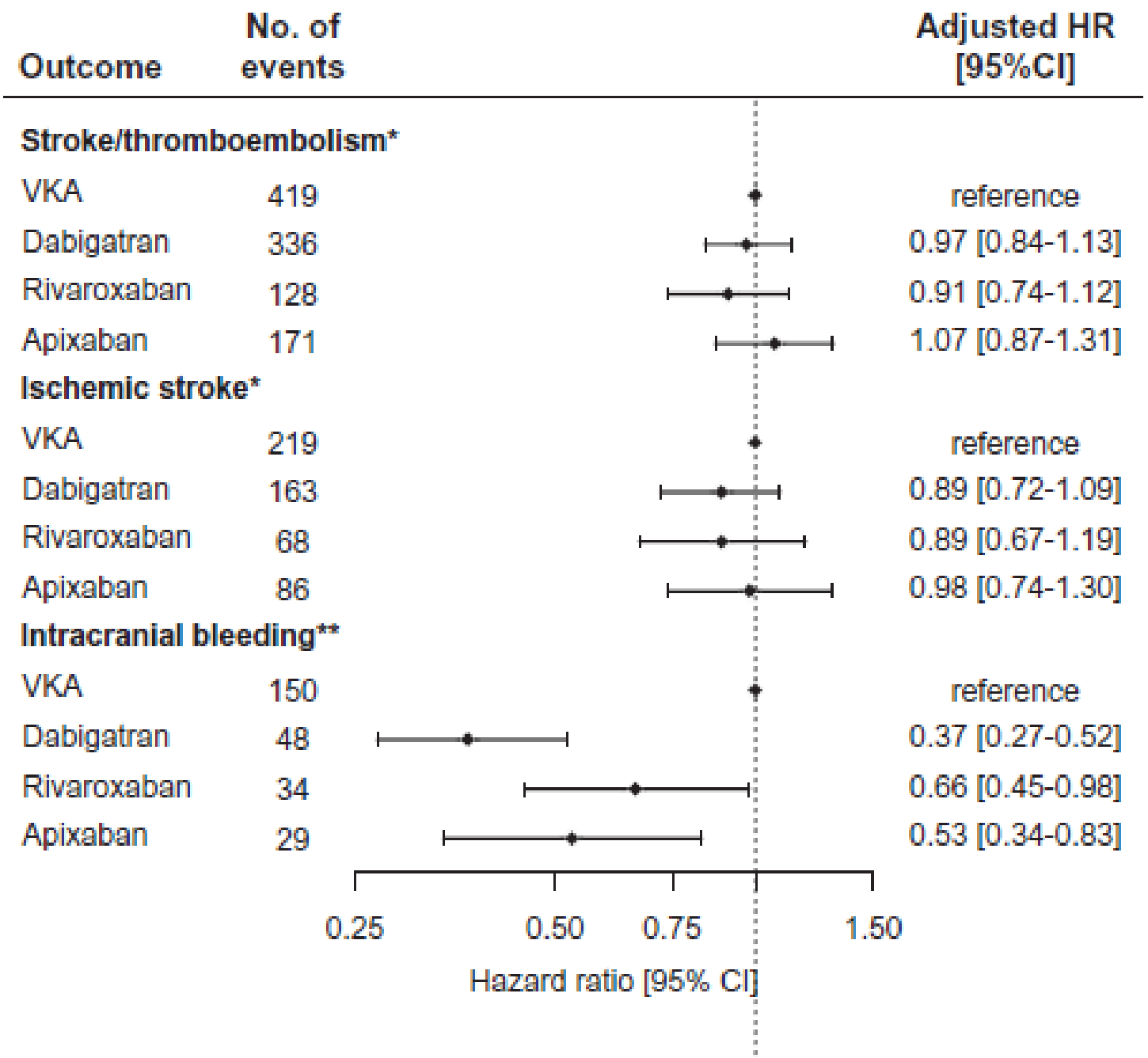
- Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (95% CI, 22–52)

European Heart Journal (2016) **00**, 1–9
doi:10.1093/eurheartj/ehw496

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

Laila Staerk[1]*, Emil Loldrup Fosbøl[2,3], Gregory Y.H. Lip[4], Morten Lamberts[1,2], Anders Nissen Bonde[1], Christian Torp-Pedersen[5], Brice Ozenne[6], Thomas Alexander Gerds[6], Gunnar Hilmar Gislason[1,3,7,8], and Jonas Bjerring Olesen[1,9]




Outcome
No. of events
Adjusted HR [95%CI]
Stroke/thromboembolism*
VKA 419 reference
Dabigatran 336 0.97 [0.84-1.13]
Rivaroxaban 128 0.91 [0.74-1.12]
Apixaban 171 1.07 [0.87-1.31]
Ischemic stroke*
VKA 219 reference
Dabigatran 163 0.89 [0.72-1.09]
Rivaroxaban 68 0.89 [0.67-1.19]
Apixaban 86 0.98 [0.74-1.30]
Intracranial bleeding**
VKA 150 reference
Dabigatran 48 0.37 [0.27-0.52]
Rivaroxaban 34 0.66 [0.45-0.98]
Apixaban 29 0.53 [0.34-0.83]
0.25
0.50
0.75
1.50
Hazard ratio [95% CI]

Conclusions

Among anticoagulant-naıve patients with AF, treatment with dabigatran, rivaroxaban, and apixaban was not associated with significant lower risk of stroke/TE, but only treatment with dabigatran and apixaban was associated with significant lower risk of intracranial bleeding, compared with VKA.

Patient with an acute TIA or Ischaemic Stroke

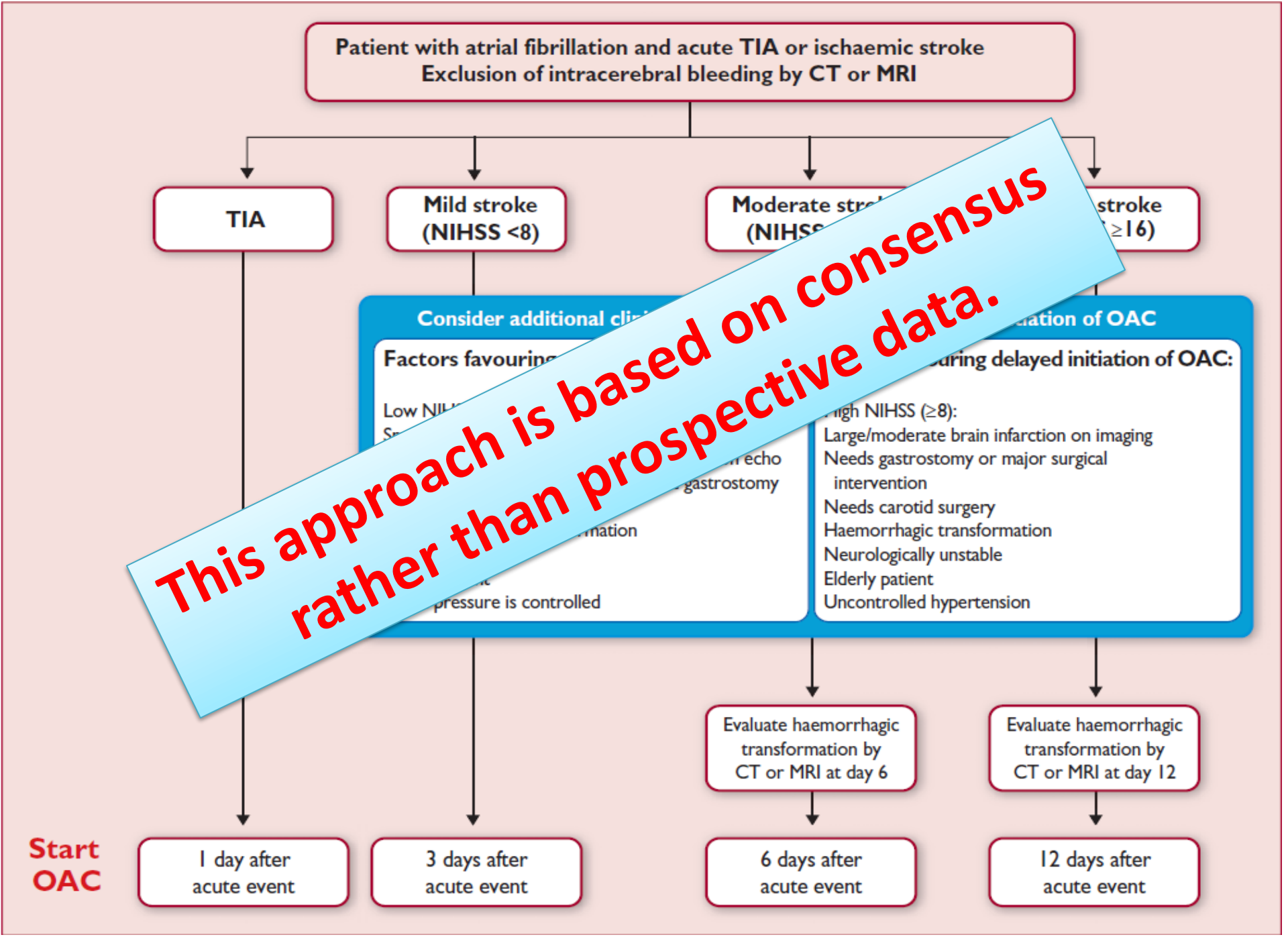
When shall we Initiate anticoagulation after transient ischaemic attack or ischaemic stroke?

- Embolism of cardiac origin accounts for about one fifth of ischaemic strokes.
- Strokes due to cardioembolism are generally severe and prone to early recurrence. The risk of long term recurrence and mortality are also high after a cardioembolic stroke.
- About 20–40% of all patients with stroke, experience haemorrhagic transformation within the first week of symptom onset.
- Haemorrhagic transformation happens in up to 71% of cardioembolic strokes. As many as 95% of haemorrhagic infarcts are caused by cardioembolism.

Ferro J, THE LANCET Neurology Vol 2 March 2003

- The traditional recommendation is to start anticoagulation early in mild cardioembolic strokes and to begin heparin therapy in severe cases with a major cardioembolic source, after the exclusion of haemorrhagic transformation with a repeated CT 3–5 days after onset.
- The time to start anticoagulation for secondary prevention is unclear. It is our practice to start it immediately in transient ischaemic attacks and minor strokes with a high-risk source of cardioembolism and nonhaemorrhagic infarcts and to delay it for 5–15 days in disabling strokes and large or haemorrhagic infarcts.

Ferro J, THE LANCET Neurology Vol 2 March 2003



This approach is based on consensus rather than prospective data.

European Heart Journal (2016) 37, 2893–2962

Atrial Fibrillation – Secondary Prevention

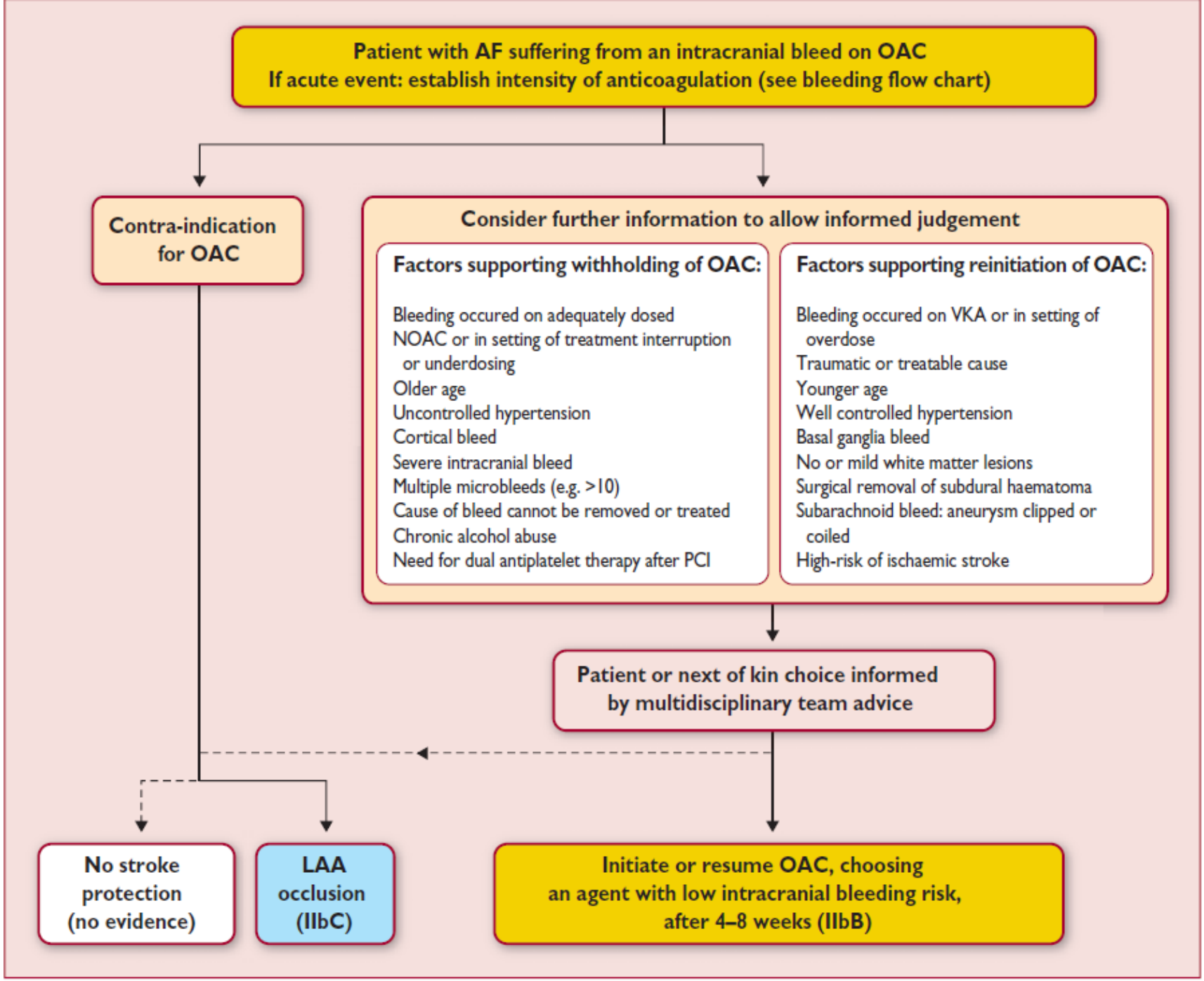
Secondary stroke prevention

- The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic stroke or TIA, emphasizing the need for OAC in these patients.
- The highest risk of recurrent stroke is in the early phase after a first stroke or TIA

Atrial Fibrillation – Secondary Prevention

Initiation of anticoagulation after intracranial haemorrhage

- The available evidence indicates that anticoagulation in patients with AF can be reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor has been treated, and that such treatment leads to fewer recurrent (ischaemic) strokes and lower mortality.
- If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low bleeding risk.



European Heart Journal (2016) 37, 2893–2962

What to do in Patients with heart failure

as primary prevention?

European Journal of Heart Failure (2012) **14**, 681–695
doi:10.1093/eurjhf/hfs073

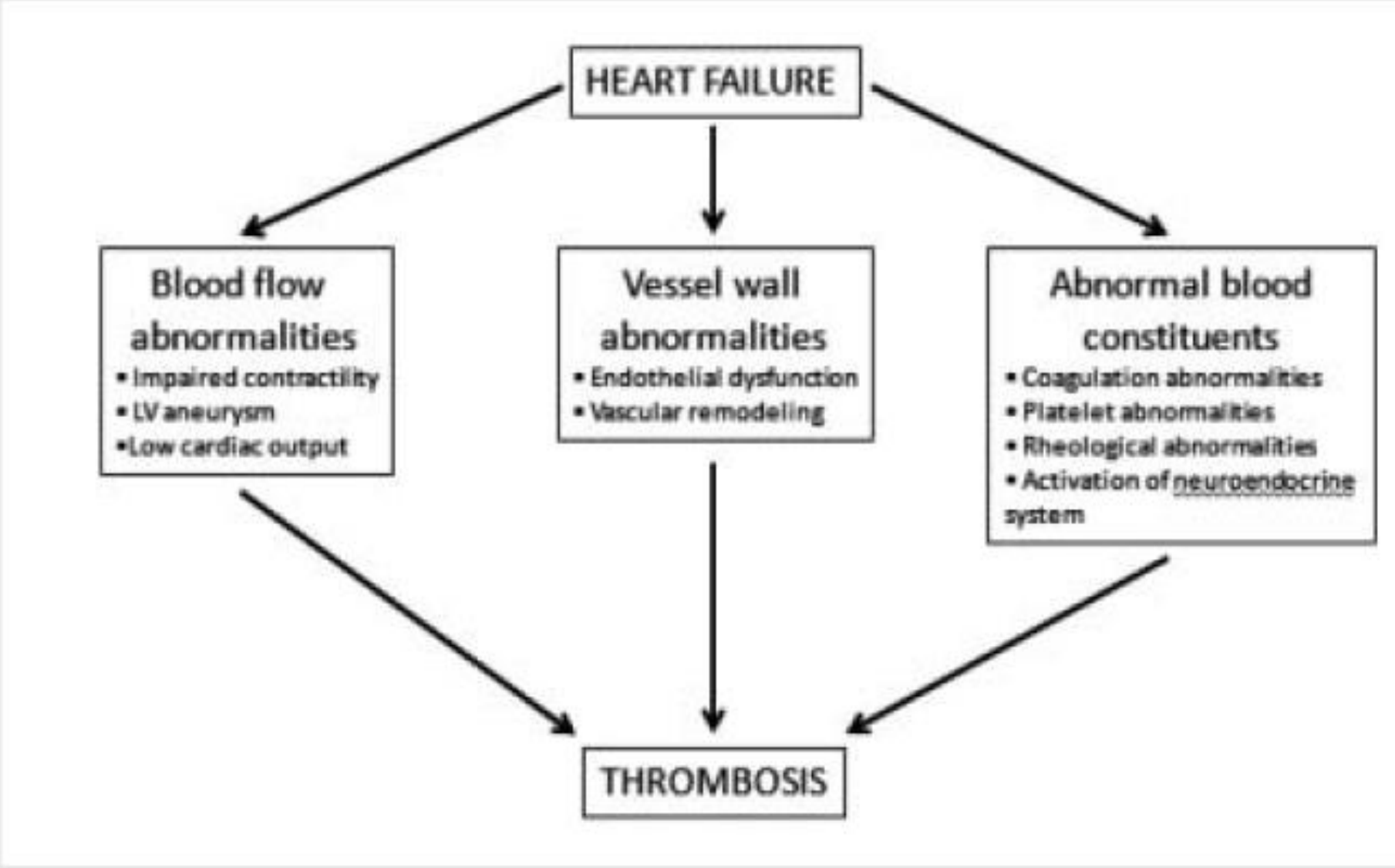
REVIEW

Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A Joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

Gregory Y.H. Lip[1]*, Piotr Ponikowski[2], Felicita Andreotti[3], Stefan D. Anker[4], Gerasimos Filippatos[5], Shunichi Homma[6], Joao Morais[7], Patrick Pullicino[8], Lars H. Rasmussen[9], Francisco Marin[10], and Deirdre A. Lane[1]

Pathophysiology of thrombosis in heart failure

Heart Failure and Sinus Rythm



Until more evidence becomes available, clinical decisions to treat patients with HF in sinus rhythm with anticoagulants must be made on a patient-by-patient basis, balancing the individual benefits against the risks of treatment, especially amongst high risk patients

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Primary Prevention

- **Other than in patients with AF (both HFrEF and HFpEF), there is no evidence that an oral anticoagulant reduces mortality/morbidity compared with placebo or aspirin.**
- **Studies testing the nonvitamin K antagonist oral anticoagulants (NOACs) in patients with HFrEF are currently ongoing.**
- **Patients with HFrEF receiving oral anticoagulation because of concurrent AF or risk of venous thromboembolism should continue anticoagulation.**
- **Similarly, there is no evidence on the benefits of antiplatelet drugs (including acetylsalicylic acid) in patients with HF without accompanying CAD, whereas there is a substantial risk of gastrointestinal bleeding, particularly in elderly subjects, related with this treatment.**

- **NOACs are preferred for patients with HFwith non-valvular AF, as NOACs compared with vitamin K antagonists seem to be at least similarly effective and even safer (less intracranial haemorrhage) in patients with HF than in subjects without HF, although concerns exist about their safety in older patients with HF and poor renal function.**

- **A left atrial occlusion device could be considered in a patient with AF as an alternative to an oral anticoagulant who is at high-risk both of thromboembolism and of bleeding in order to avoid the risk of haemorrhage due to anticoagulation risk**

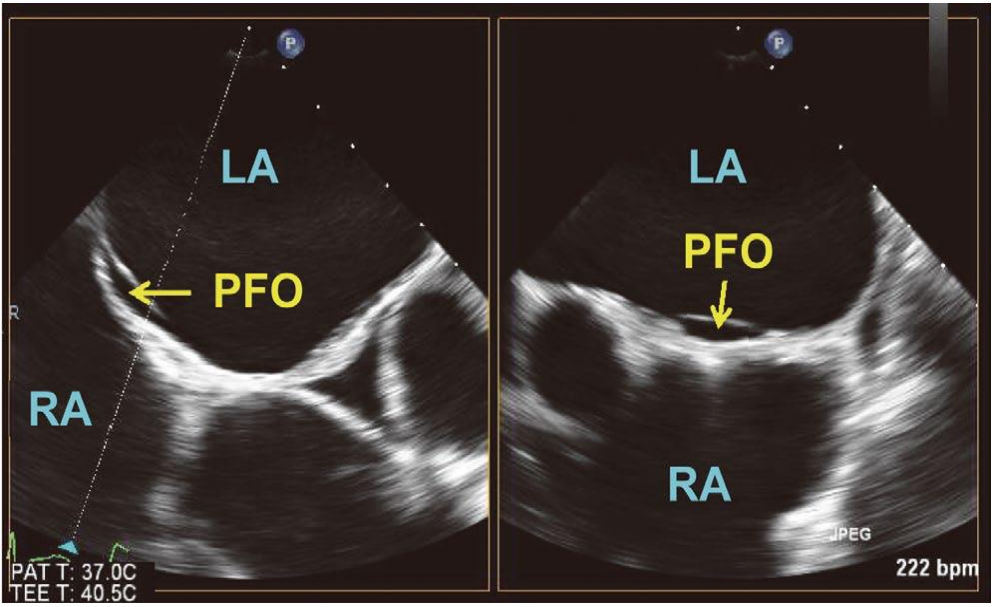
- Patient values and preferences are important determinants when balancing the risk of thrombo-embolism against bleeding.
- All antithrombotic drugs carry an intrinsic risk of bleeding complications and, at this point, there is still uncertain benefit for their use in HF patients in sinus rhythm. Discussions regarding treatment options need to actively involve the patient, with consideration of their preferences when making antithrombotic treatment decisions.
- Clinical trials are needed to see if the new oral anticoagulants that may offer a different risk–benefit profile compared with warfarin could offer the reduction in ischaemic stroke with less risk of major bleeding.
- Anticoagulation may potentially be considered by some clinicians in the following HF patient groups:
    - HFrEF with previous thrombo-embolism
    - newly diagnosed intracardiac thrombus
    - right heart failure with pulmonary hypertension

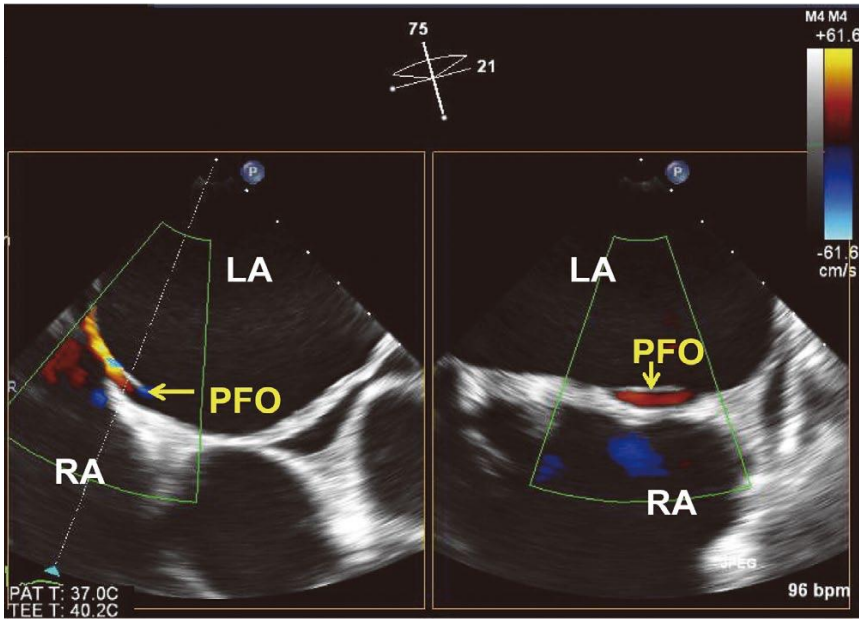
but evidence is limited and more research is needed to ascertain the long-term risk–benefit ratio.

Patent Foramen Ovale

- Patent foramen ovale is present in a third of all patients with stroke, and is normally between 2–8 mm in diameter, is found in up to 40% of patients with ischaemic stroke who are younger than 55 years of age.

Ferro J, THE LANCET Neurology Vol 2 March 2003





PFO as visualized on biplane transesophageal echocardiography

Sun YP, Circ J **2016; 80: 1665–1673**

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

Patent Foramen Ovale and Stroke

Yee-Ping Sun, MD; Shunichi Homma, MD

- A patent foramen ovale is common and found in nearly 25% of healthy individuals.
- The presence of PFO has been found to be higher in patients with cryptogenic stroke
- Patients with cryptogenic stroke and PFO are generally treated with antiplatelet therapy in the absence of another condition for which anticoagulation is necessary.
- Based on the findings of 3 large randomized clinical trials, current consensus guidelines do not recommend percutaneous closure, though this is an area of controversy.

***Sun YP, Circ J* 2016; 80: 1665–1673**

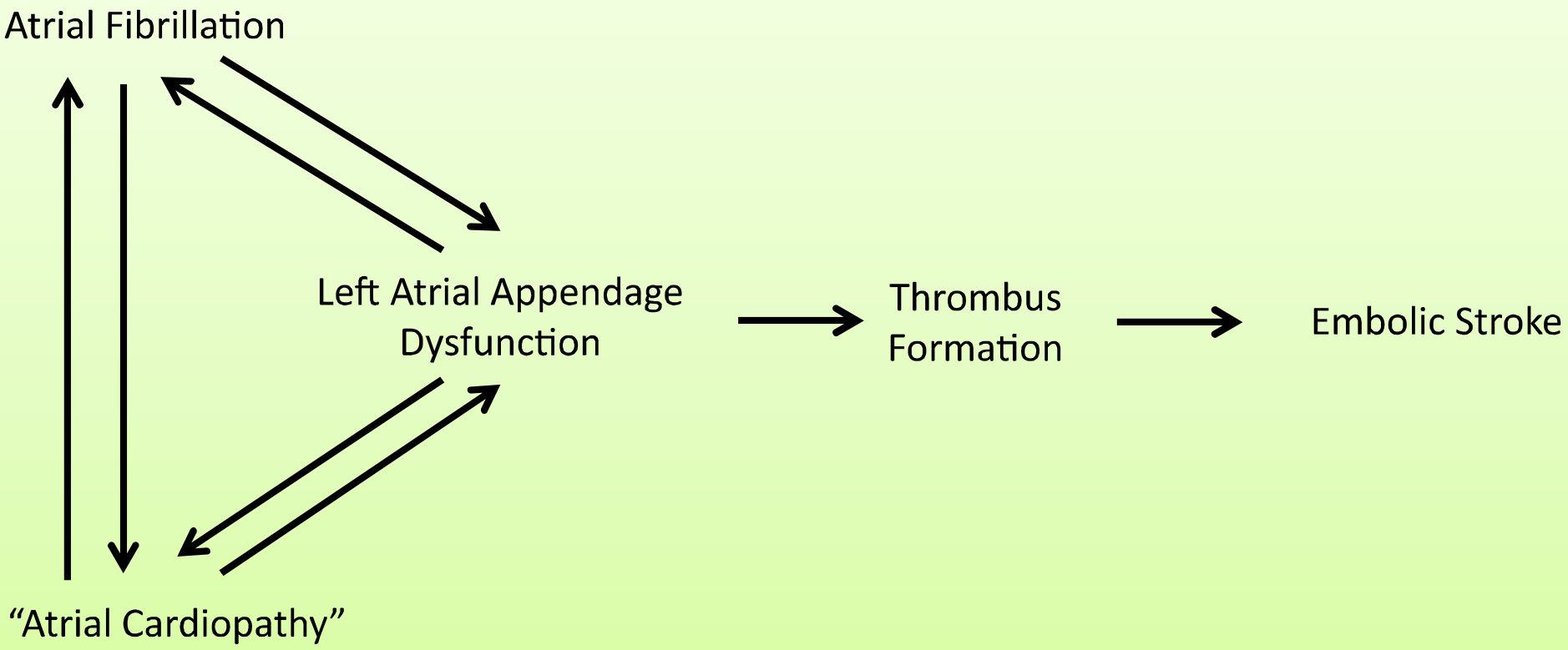
Left Atrial Appendage Function and Stroke Risk

Shadi Yaghi, MD; Christopher Song, MD; William A. Gray, MD; Karen L. Furie, MD, MPH; Mitchell S.V. Elkind, MD, MS; Hooman Kamel, MD

Yaghi et al *Stroke*. 2015;46:3554-3559

- About 30% to 40% of ischemic stroke is of unknown cause.
- Recently, biomarkers of atrial dysfunction, or atrial cardiopathy, have been associated with embolic stroke risk even in the absence of atrial fibrillation (AF), suggesting that the presence of AF is not required for left atrial thromboembolism to occur.
- Most left atrial thrombi occur in the left atrial appendage (LAA), but there is limited use of LAA dysfunction parameters, such as LAA low velocity and morphology, to predict ischemic stroke risk.

Yaghi et al *Stroke*. 2015;46:3554-3559



Atrial cardiopathy: evidence of markers of atrial dysfunction such as elevated N-terminal proBNP, evidence of p-wave dispersion on ECG, increased left atrial size, and paroxysmal supraventricular tachycardia.

- N-terminal pro-brain natriuretic peptide has been shown to be a marker of atrial dysfunction, risk of incident AF, and cardiac embolism. ECG signs related to the left atrium, such as paroxysmal supraventricular tachycardia and P-wave terminal force in lead V1 (PTFV1), have been associated with the risk of incident stroke, particularly of nonlacunar sub- types even in the absence of AF.

Yaghi et al *Stroke*. 2015;46:3554-3559

Recommendations	Class[a]	Level[b]	Ref[c]
After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.	I	B	461, 462
LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).	IIb	B	449, 453, 454
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.	IIb	B	463
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.	IIb	B	468

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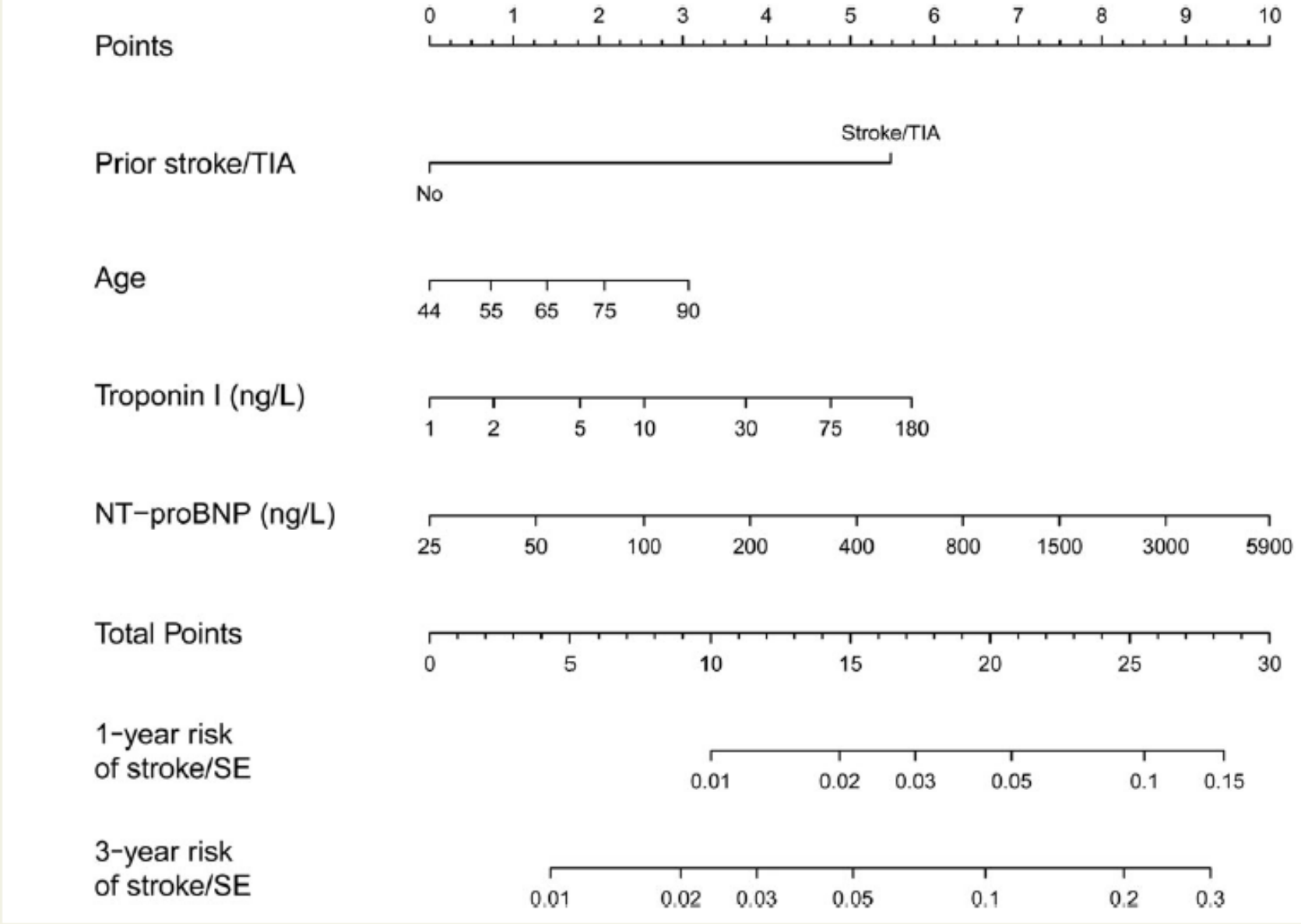
- Many questions remain about LAA closure, including whether it is as effective if compared with non-vitamin K antagonist oral anticoagulant drugs that have a lower risk of intracranial hemorrhage.
- However, the Watchman trials are nevertheless consistent with a protective effect against thromboembolism, which again supports the role of the LAA as the origin of thrombus formation in left atrial disease.

- Given the substantial benefit of anticoagulant therapy in patients with atrial disease in the form of AF, such therapy may ultimately prove beneficial for patients without AF but compelling evidence of LAA dysfunction.
- Future research is needed to identify optimal methods to assess patients for LAA dysfunction and to test the benefit of anticoagulant therapy in stroke prevention in these patients.

European Heart Journal (2016) **37**, 1582–1590
doi:10.1093/eurheartj/ehw054

The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation

Z. Hijazi et al. European Heart Journal (2016) 37, 1582–1590



Z. Hijazi et al. European Heart Journal (2016) 37, 1582–1590

Take Home Messages

- Cardioembolic stroke is frequent and preventable.
- AF should be actively diagnosed and risk stratification should be done to start anticoagulation soon for primary prevention of Stroke
- We must be careful when starting anticoagulation after a TIA or a embolic stroke
- The NOACs are still very expensive and there benefit is not what we were expecting
- Prevention in heart failure and PFO or LAA are still areas that need further data for decision