Non-Embolic and Embolic Mechanisms of Stroke

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UNIVERSITY OF LIVERPOOL

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Liverpool Centre for Cardiovascular Science

AALBORG UNIVERSITY

NIHR | National Institute for Health Research

Declaration of Interests

- Guideline membership/reviewing: ESC Guidelines on Atrial Fibrillation, 2010 and Focused Update, 2012; ESC Guidelines on Heart Failure, 2012; American College of Chest Physicians Antithrombotic Therapy Guidelines for Atrial Fibrillation, 2012; NICE Guidelines on Atrial Fibrillation, 2006 and 2014; NICE Quality Standards on Atrial Fibrillation 2015; ESC Cardio-oncology Task Force, 2015; ESC Working Group on Thrombosis position documents (2011-). Chairman, Scientific Documents Committee, European Heart Rhythm Association (EHRA). Chairman, 2018 CHEST guidelines from American College of Chest Physicians

- Steering Committees/trials: Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc.

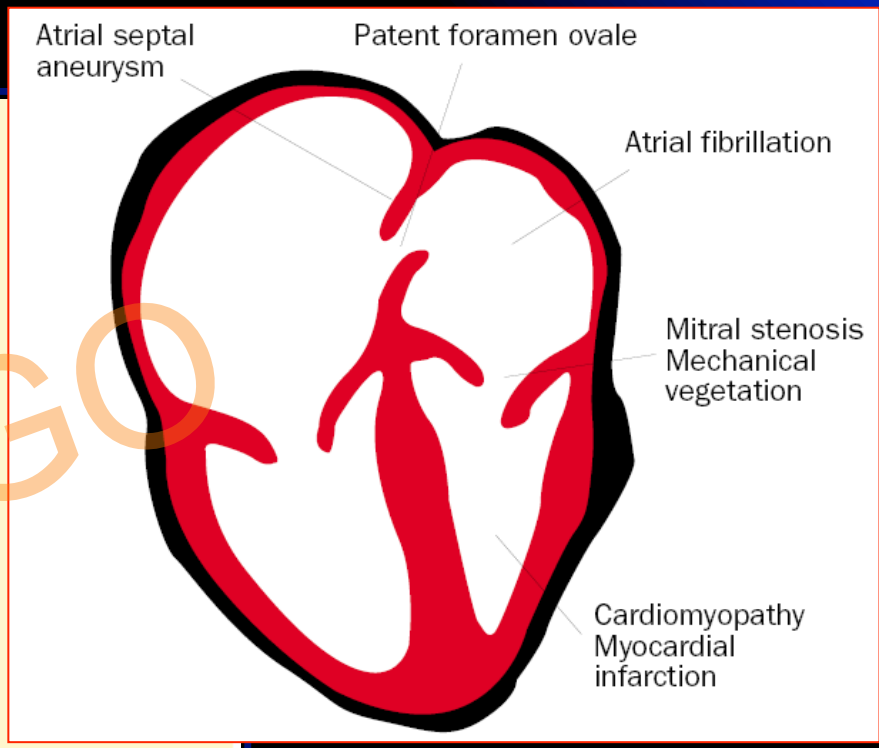
- Editorial Roles: Editor-in-Chief (clinical), Thrombosis & Haemostasis; Associate Editor, Europace; Guest Editor, Circulation, American Heart Journal.

- **Consultant/Advisor/Speaker:**
  - Consultant for Bayer/Janssen, BMS/Pfizer, Verseon, Boehringer Ingelheim, and Daiichi-Sankyo.
  - Speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo

Cardioembolic sources and embolic risk

*Ferro Lancet Neurology 2003; **2:** 177–88; Kelly et al South Med J 2003;96: 343*

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	



left ventricular
contrast, and aortic

Transthoracic Echocardiography in Acute Ischemic Stroke Patients

de Abreu et al. Stroke. 2005;36:1565-1566

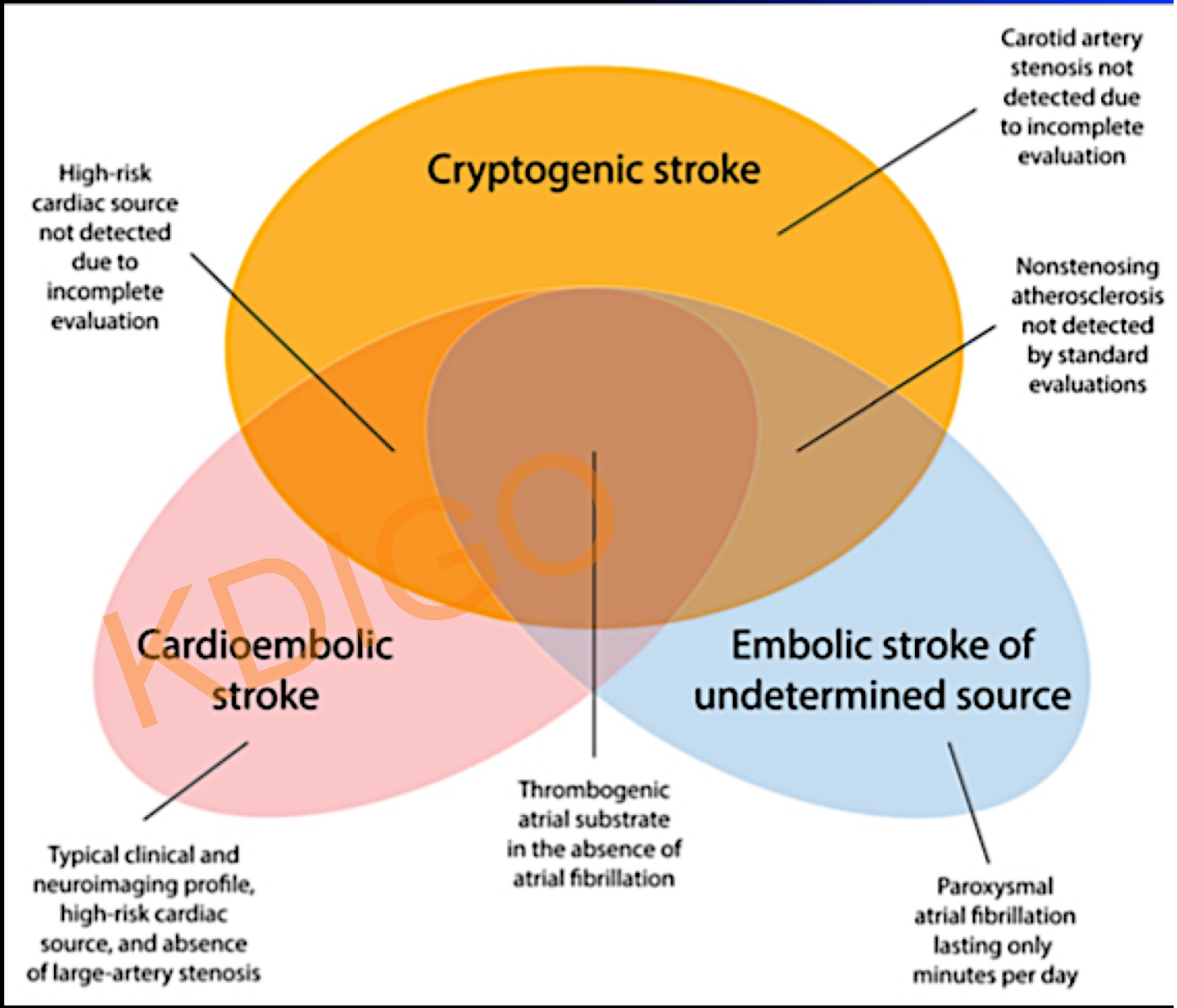
Findings	No. (%)
No findings suggesting need of anticoagulation	273 (62.8)
Dilated cardiopathy	83 (19.1)
Anterior wall dyskinesis	27 (6.2)
Left ventricle ejection fraction <35%	16 (3.7)
Mitral valve stenosis with left atria >55 mm	9 (2.1)
Intracardiac masses	2 (0.5)
Valve prosthesis	1 (0.2)
Mitral valve stenosis with left atria >55 mm+dilated cardiopathy	7 (1.6)
Dilated cardiopathy+anterior wall dyskinesis	9 (2.1)
Dilated cardiopathy+left ventricle ejection fraction <35%	8 (1.8)
Total	435 (100.1)

Overlap among cryptogenic stroke, ESUS, and cardio-embolic stroke.

Kamel and Healey
Circ Res.
2017;120:514-526

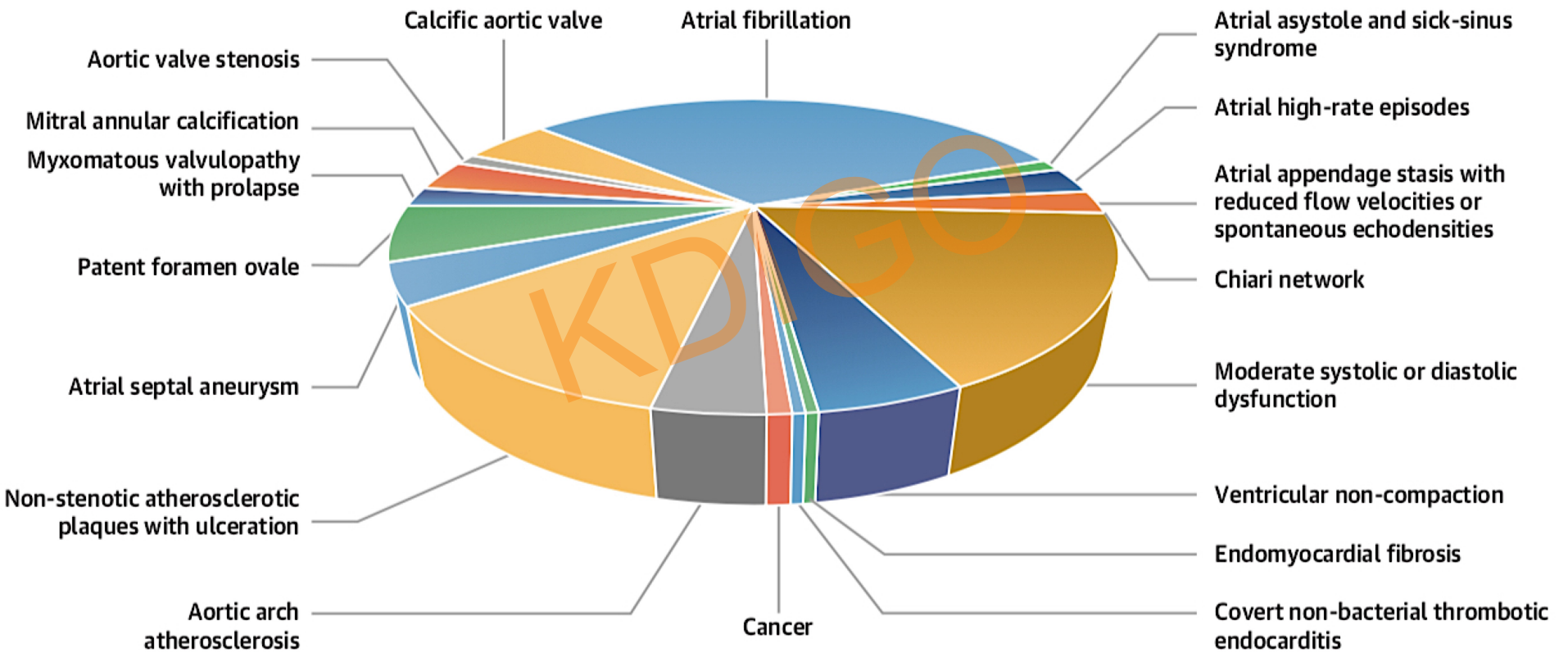
… an imperfect but substantial overlap.

Cryptogenic stroke can be used to refer to a stroke with incomplete evaluation: if cryptogenic stroke is stringently defined, it essentially equals ESUS.



Distribution of Potential Etiologies of ESUS in the Athens Stroke Registry

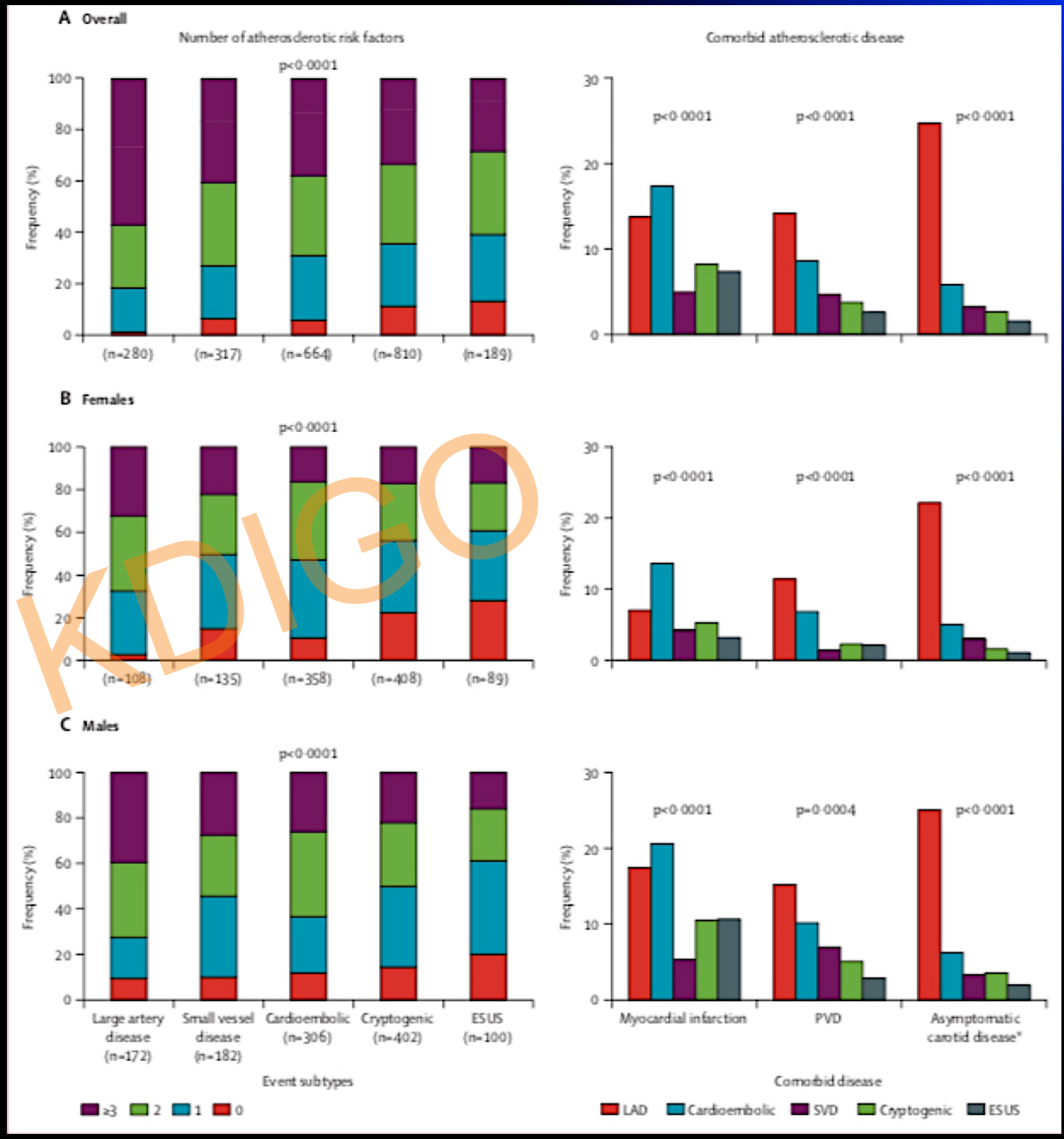
Ntaios et al Stroke 2015;46:176–81.



Number of atherosclerotic risk factors and frequency of comorbid atherosclerotic disease in different stroke/TIA subtypes: OXVASC

Li et al Lancet 2015

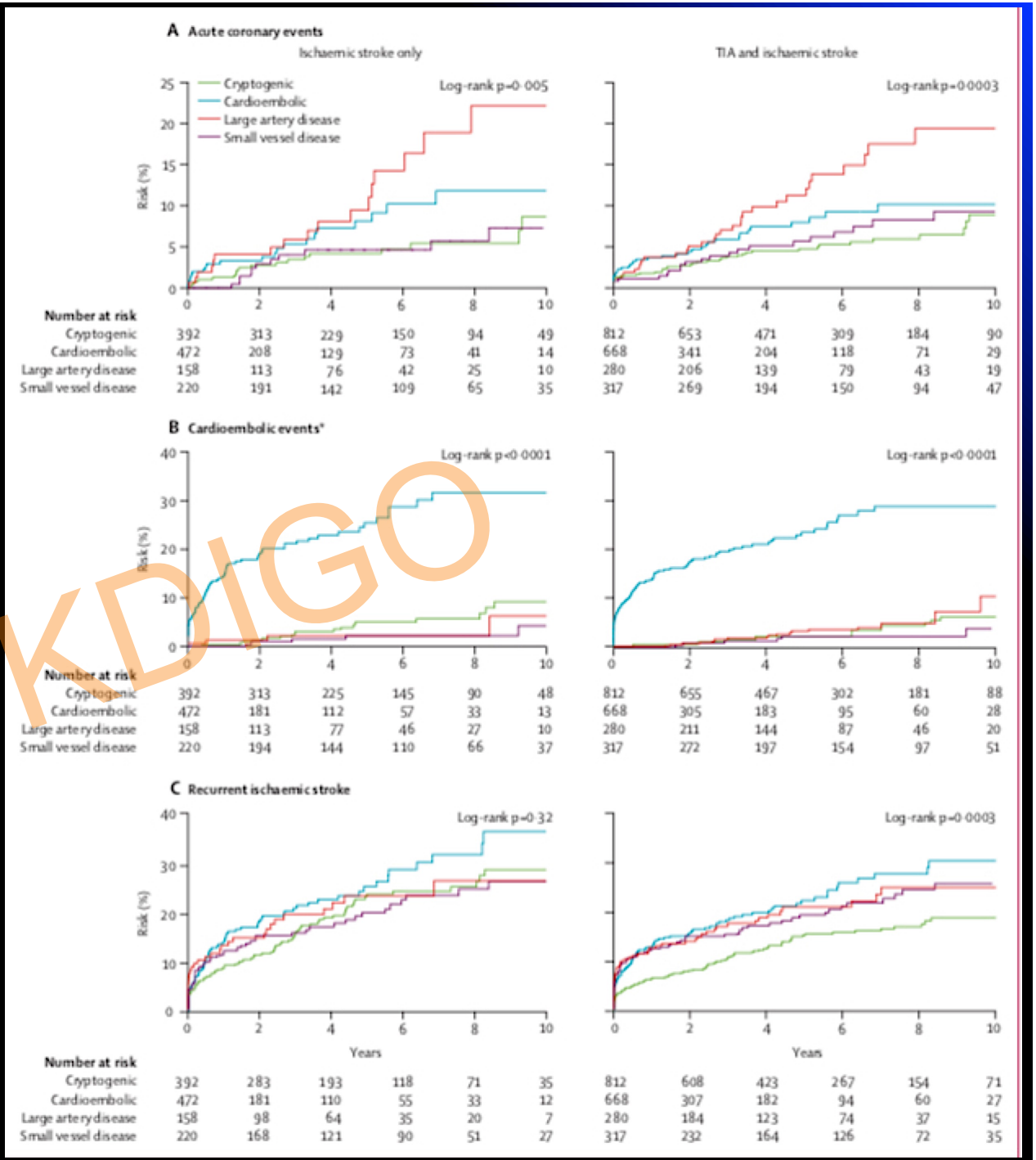
Cryptogenic group had fewer risk factors overall than the large artery disease (p<0·0001), small vessel disease (p=0·001), and cardioembolic (p=0·008) groups



10-year absolute risks of acute coronary events, cardioembolic events, and recurrent ischaemic stroke: OXVASC

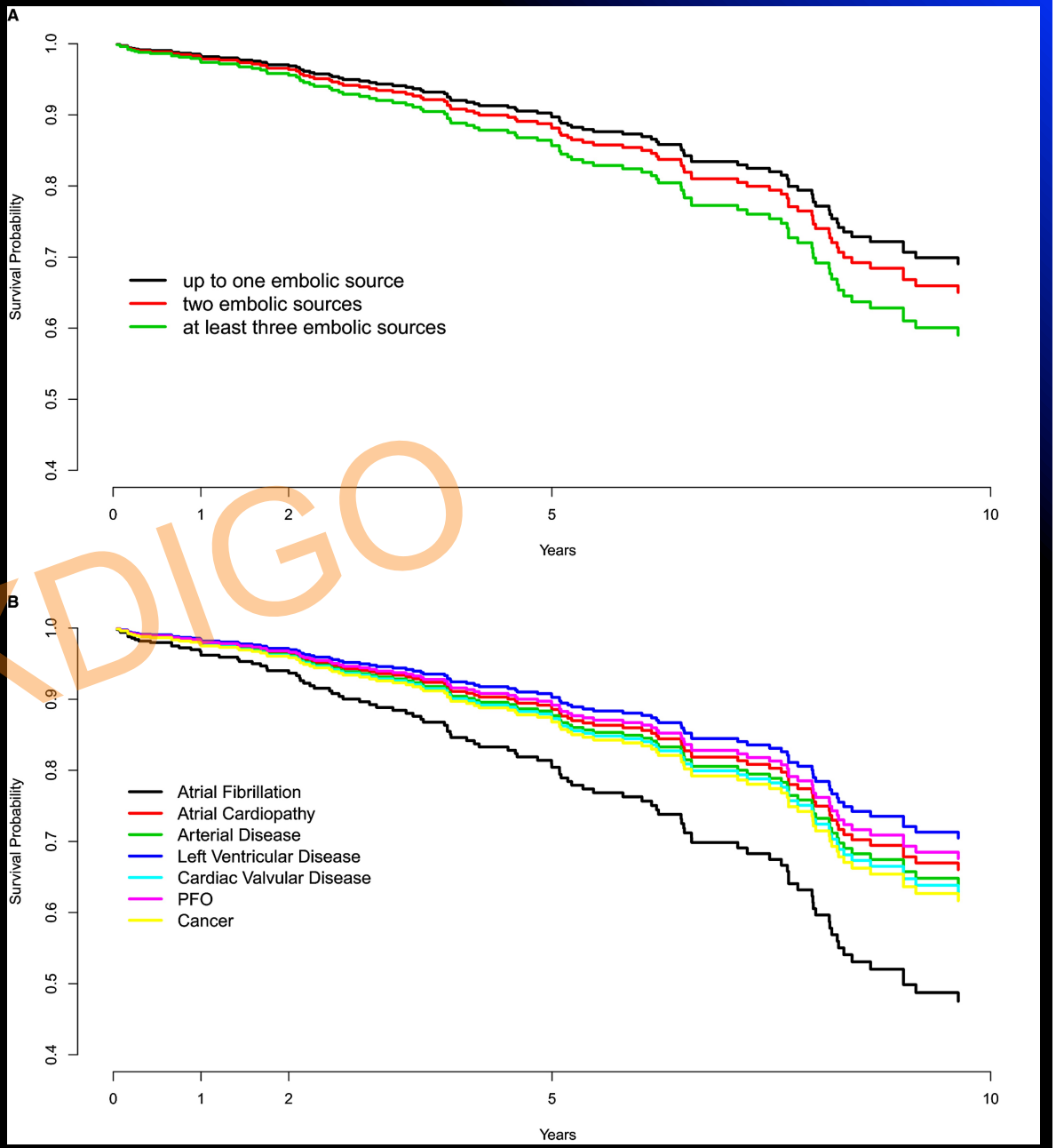
Li et al Lancet 2015

Patients with cryptogenic events had a lower risk of acute coronary events than large artery disease events (aHR 0·40, 95% CI 0·24–0·66; p=0·0003) and a similar risk to non-large artery disease events (0·76, 0·49–1·18; p=0·22)



Prevalence and Overlap of Potential Embolic Sources in Patients With Embolic Stroke of Undetermined Source

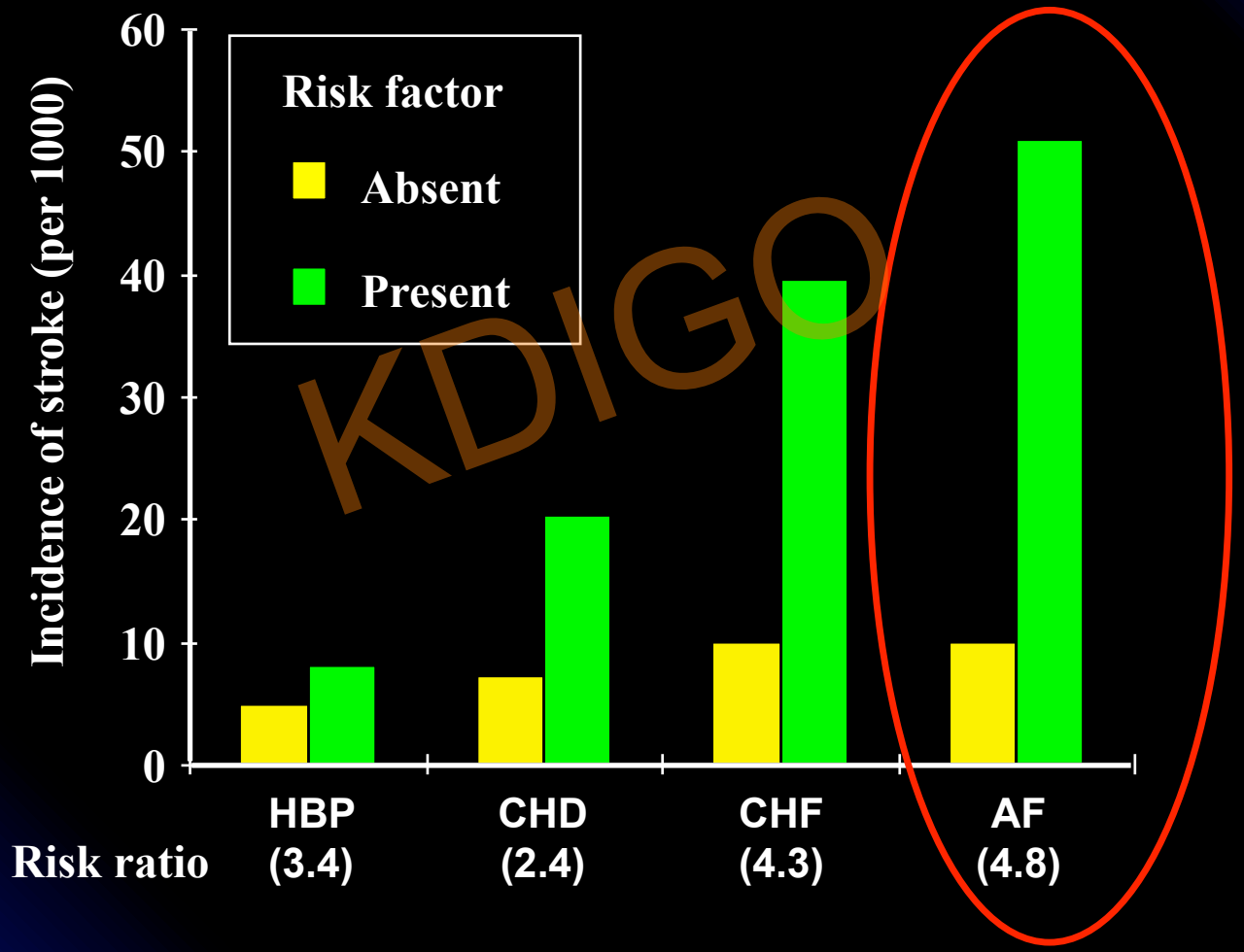
Ntaios et al
J Am Heart Assoc 2019;8:e012858.



Ten-year survival estimates of stroke recurrence in patients with embolic stroke of undetermined source, according to each potential embolic source (PES; top) and the number of PES per patient (bottom).

2-Year Age-Adjusted Incidence of Stroke per 1000

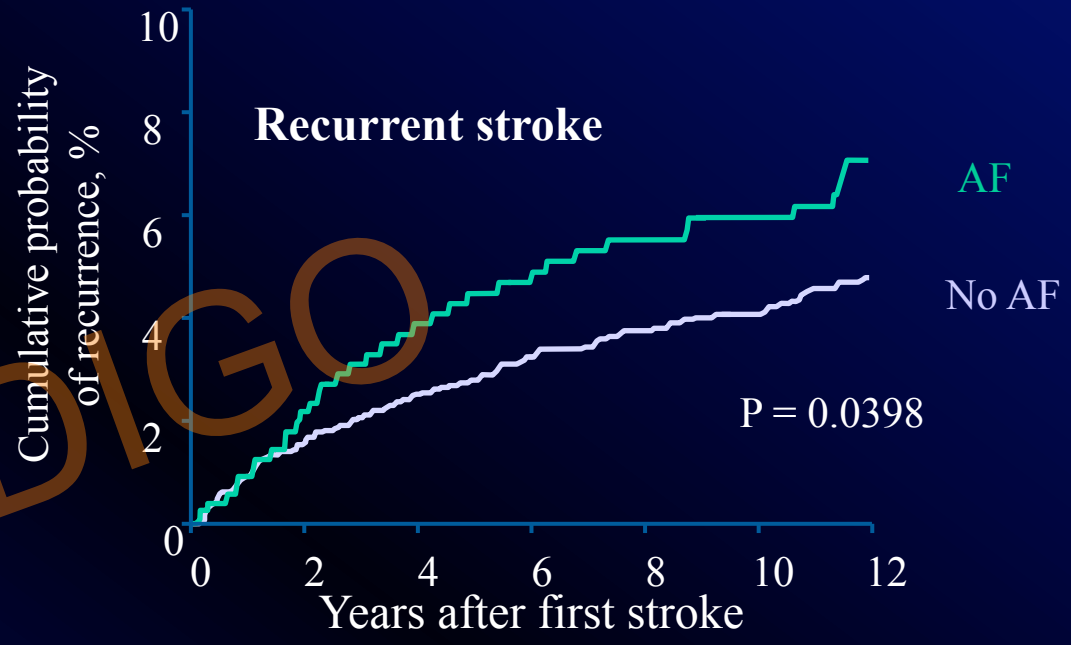
Wolf et al. Stroke 1991;22:983

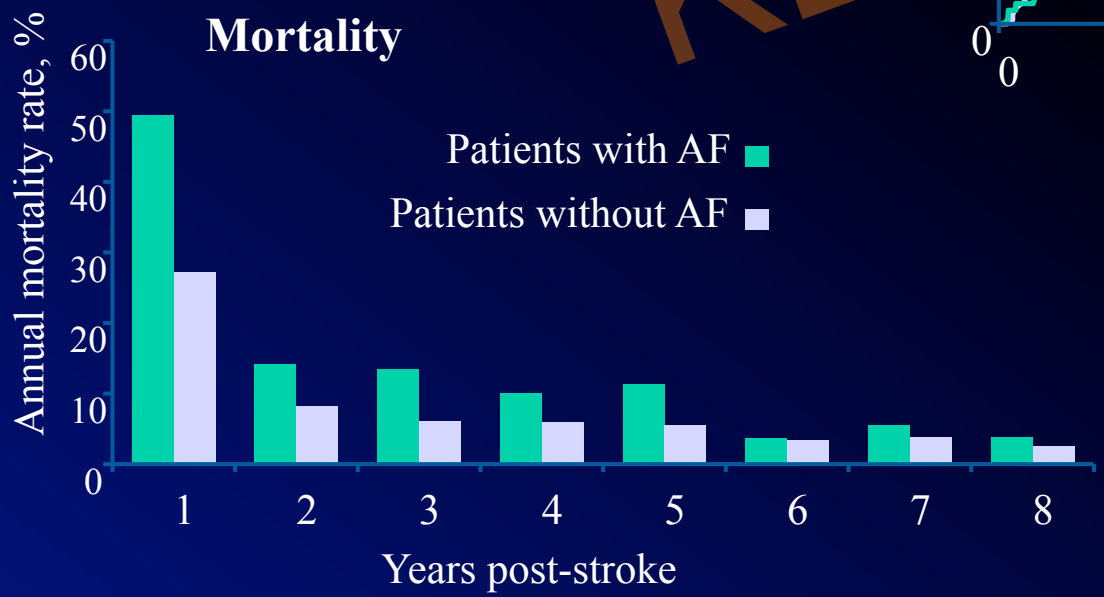


Contribution of AF to Incidence and Outcome of Ischemic Stroke Population-Based L'Aquila Study

Marini et al Stroke 2005;36(6):1115-9.

Kaplan–Meier estimates of the likelihood of recurrent stroke in patients with and without AF





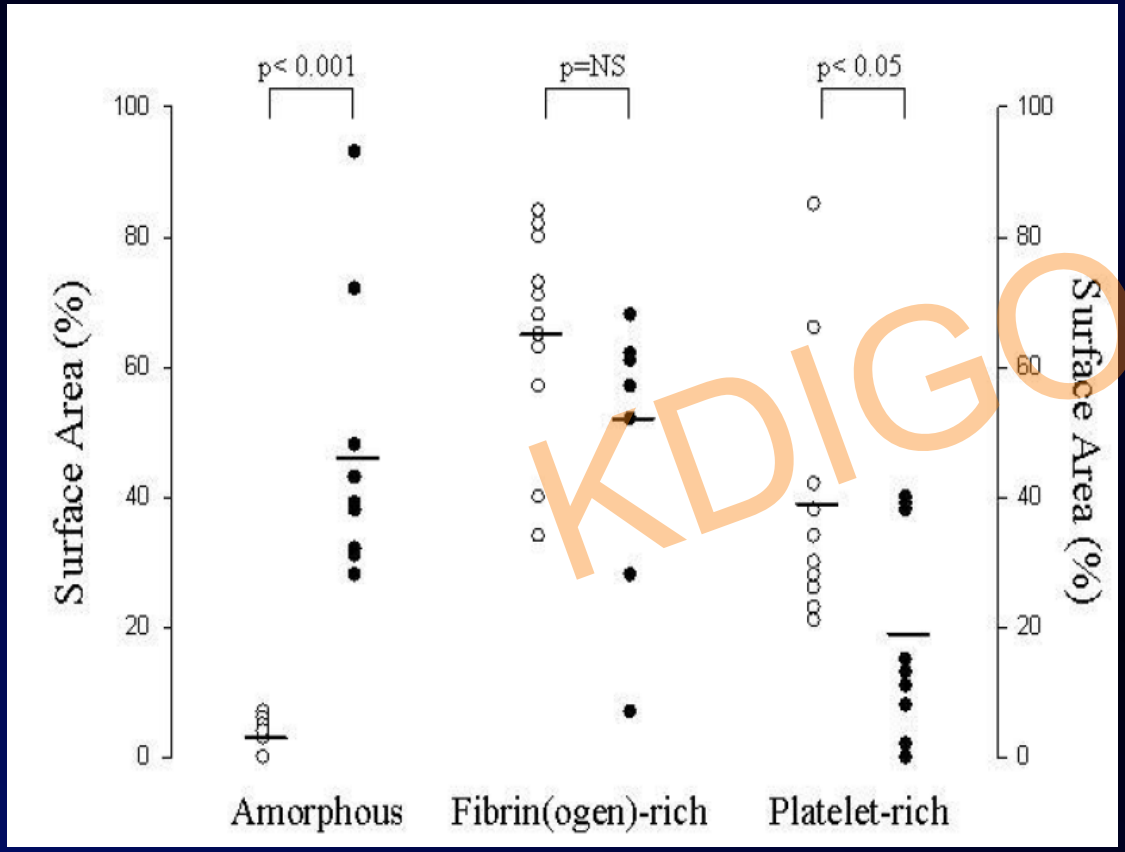
Annual Mortality Rates in Patients With and Without AF:

At 1 year, AF 49.5% vs no AF, 27.5%

Increased mortality even up to 8 years

Atrial fibrillation and thrombosis: immunohistochemical differences between *in situ* and embolized thrombi

Wysokinski et al J Thromb Haemost. 2004;2(9):1637-44.



Thrombi from 22 patients with AF :

In atrial thrombi [black circles], fibrin-rich regions predominated (P<0.0001).

The platelet content of embolized thrombi [white circles] was nearly twice that of AF atrial thrombi (P=0.02).

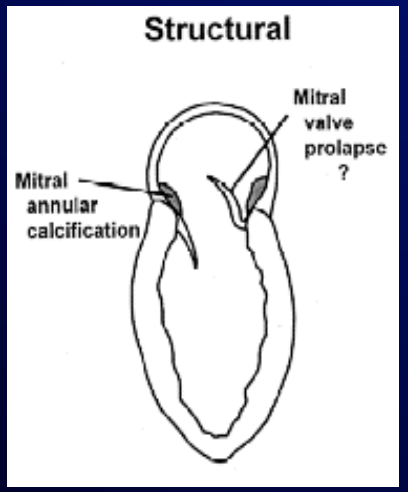
'Atrial thrombi in situ contain primarily fibrin and amorphous debris whereas embolized thrombi are comprised primarily of fibrin and platelets.'

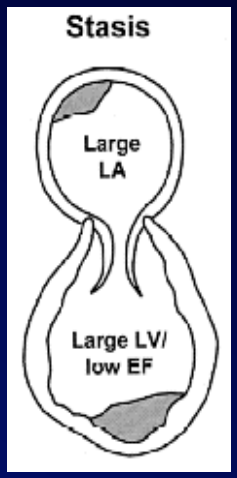
As fibrin is the major component of atrial thrombi (mean 68% in 22 thrombi) in AF ……. pathophysiologic basis for why anticoagulation reduces thromboembolism in AF.

Virchow's triad and AF……

Lip Lancet 1995; 346: 1313-14

abnormalities of vessel wall
(endothelial dysfunction or damage)

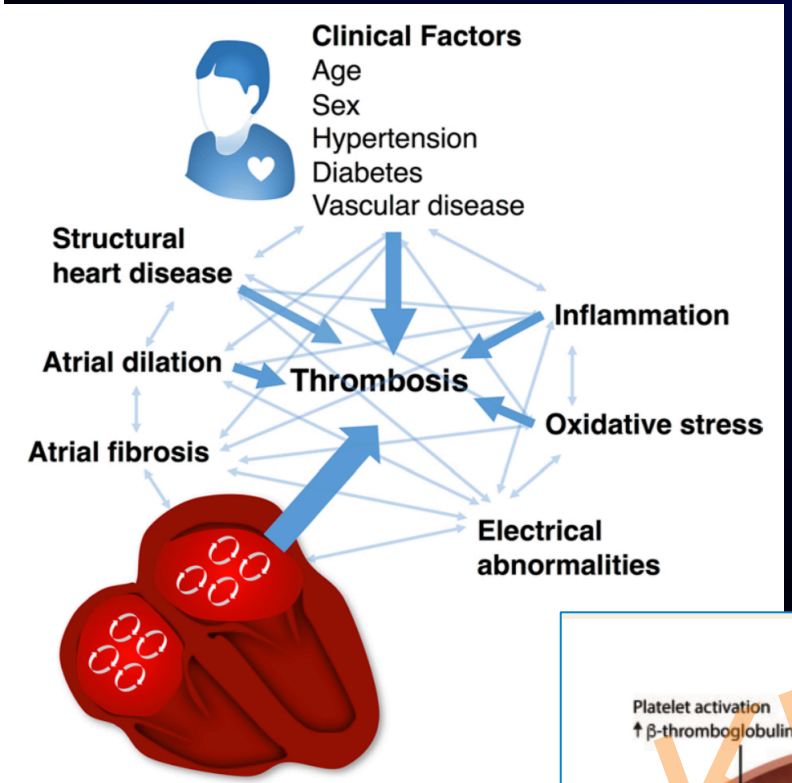




abnormalities of blood flow
(rheology, viscosity and flow reserve)

abnormalities of blood constituents
(abnormal haemostatic factors, platelet activation and fibrinolysis)

…….AF confers a prothrombotic or hypercoagulable state.



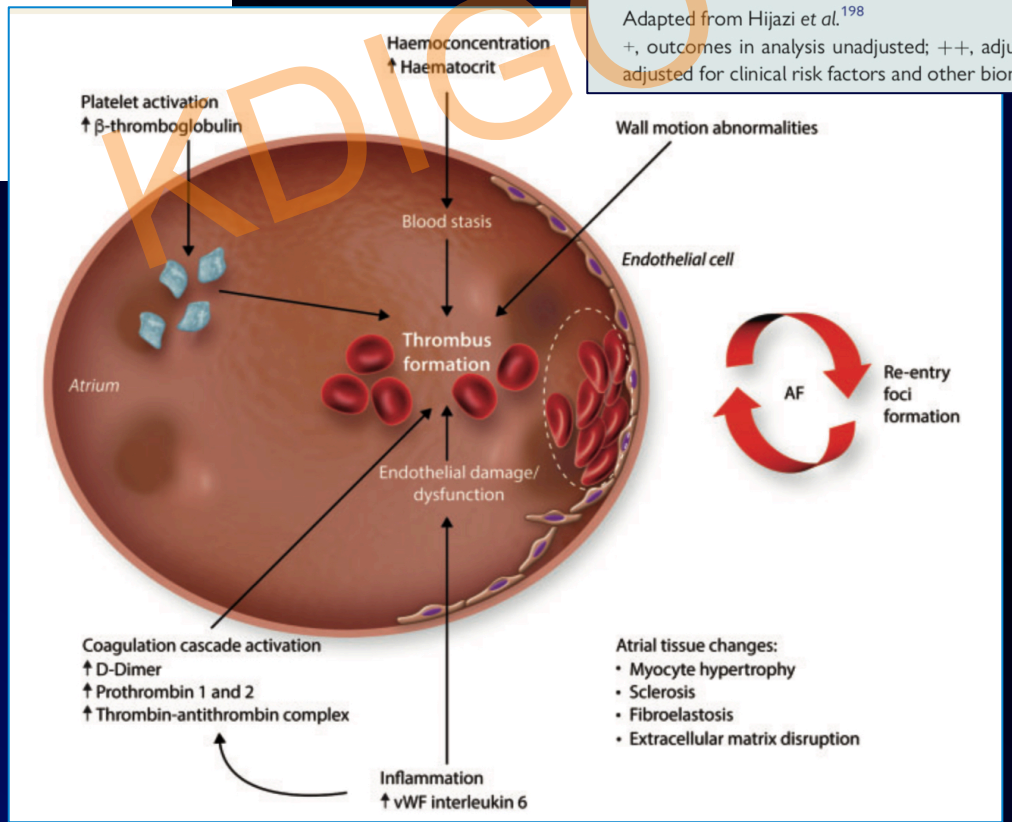
Thomas and Lip. Circ Res. 2017; 120:133-149

Biomarker	Stroke/systemic embolism	Mortality	Major bleeding
Cardiac biomarkers			
Troponin	+++	+++	+++
NT-proBNP	+++	+++	+
Renal dysfunction	+/++	++	++
Inflammation biomarkers			
CRP	+	+++	+
IL-6	++	+++	++
GDF-15	++	+++	+++
Galectin-3	+	+++	+
Endothelial function			
vWF	+	++	++
Coagulation			
D-dimer	++	++	++

Adapted from Hijazi *et al.*[198]
+, outcomes in analysis unadjusted; ++, adjusted for clinical risk factors; +++, adjusted for clinical risk factors and other biomarkers.

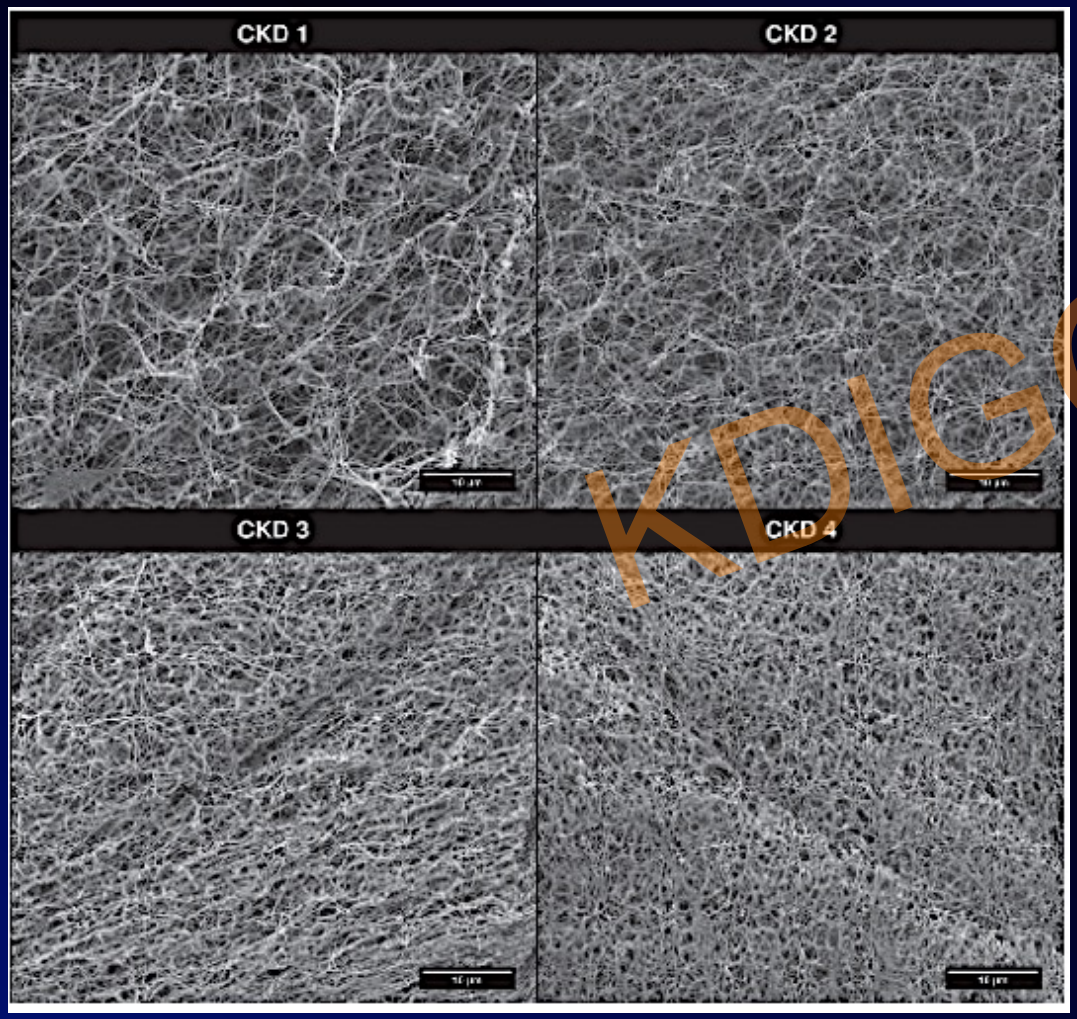
The prothrombotic state in AF

Khan and Lip Cardiovasc Res 2019; 115, 31–45



Altered fibrin clot structure in AF and worsening renal function.

Lau ... Lip. Thromb Haemost. 2016 ;116(3):408-9.



SEM of fibrin clots in worsening CKD (5,000x magnification).

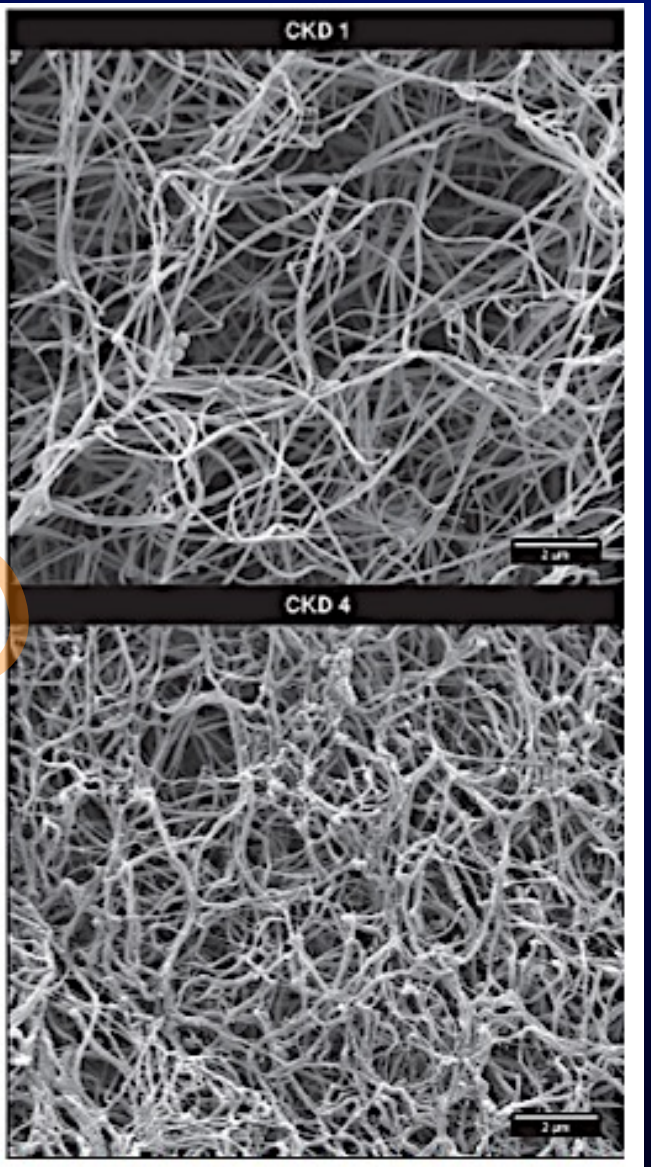


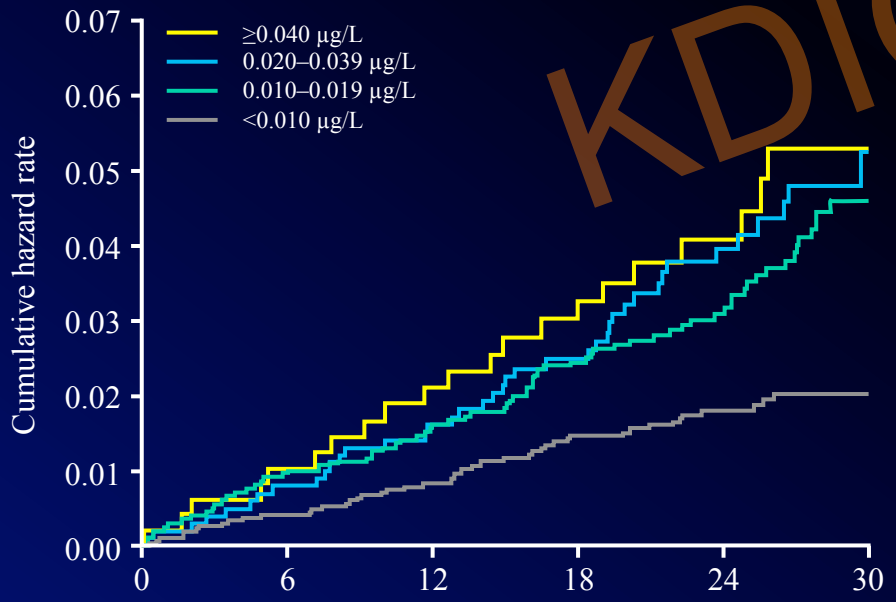
Figure 2: SEM of fibrin clots, CKD 1 vs CKD 4 (20,000x magnification). Fibrin clot in CKD 1 (Top) and Fibrin clot in CKD 4 (Bottom) at 20000x magnification, demonstrating increased fibre diameter with worst renal function.

Biomarkers in atrial fibrillation: a clinical review

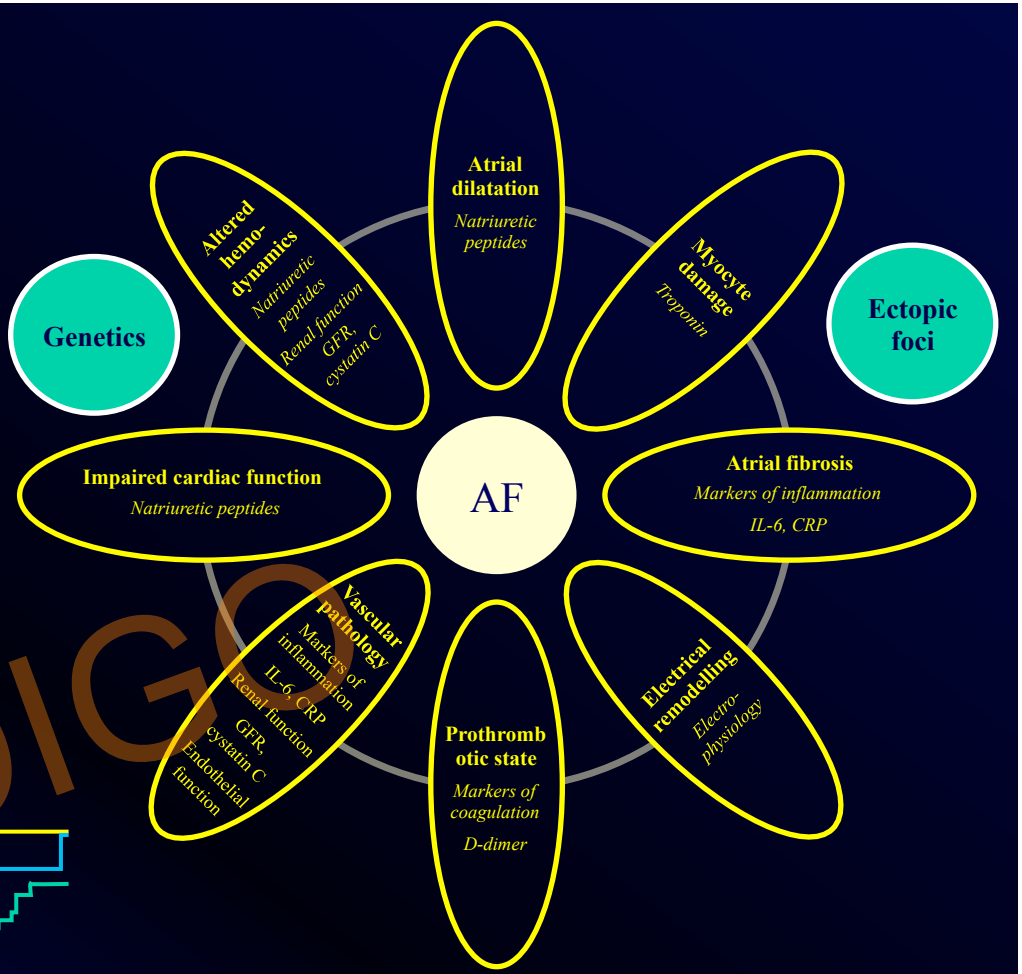
Hijazi et al Eur Heart J 2013

Various biomarkers have been used to aid risk stratification in AF ..

- D-dimer, vWf, BNP, CRP, troponin, etc



Numbers at Risk						
<0.010 µg/L	2663	2639	2598	2382	1715	701
0.010–0.019 µg/L	2006	1969	1925	1711	1269	543
0.020–0.039 µg/L	1023	989	958	835	593	212
≥0.040 µg/L	497	476	459	411	286	117



Cumulative hazard rates for stroke or systemic embolism, according to Troponin I levels at randomization in *an anticoagulated cohort* from RE-LY trial

Hijazi et al Circulation 2012;125:1605-16.

The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

Ziad Hijazi, Jonas Oldgren, Johan Lindbäck, John H Alexander, Stuart J Connolly, John W Eikelboom, Michael D Ezekowitz, Claes Held, Elaine M Hylek, Renato D Lopes, Agneta Siegbahn, Salim Yusuf, Christopher B Granger, Lars Wallentin, on behalf of the ARISTOTLE and RE-LY Investigators

Lancet. 2016 Jun 4;387(10035): 2302-2311.

Figure. Heatmap of biomarkers associated with all-cause mortality (FDR-q <0.05) are also associated with other concomitant fatal and non-fatal cardiovascular outcomes, including atherosclerotic CVD, heart failure, and CVD death. ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; FDR, false discovery rate; HF, heart failure; HR, hazard ratio.

Protein Biomarkers of CVD and Mortality in the Community

Ho et al
JAHA
2018;7:e008108

JACC: HEART FAILURE
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ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2017.07.013

CLINICAL RESEARCH

Utility of Growth Differentiation Factor-15, A Marker of Oxidative Stress and Inflammation, in Chronic Heart Failure

Insights From the HF-ACTION Study

Abhinav Sharma, MD,[a] Susanna R. Stevens, MS,[a] Joseph Lucas, PhD,[a] Mona Fiuzat, PhD,[a] Kirkwood F. Adams, MD,[b] David J. Whellan, MD,[c] Mark P. Donahue, MD, MHS,[d] Dalane W. Kitzman, MD,[e] Ileana L. Piña, MD,[f] Faiez Zannad, MD, PhD,[g] William E. Kraus, MD,[d] Christopher M. O'Connor, MD,[h] G. Michael Felker, MD, MHS[a]

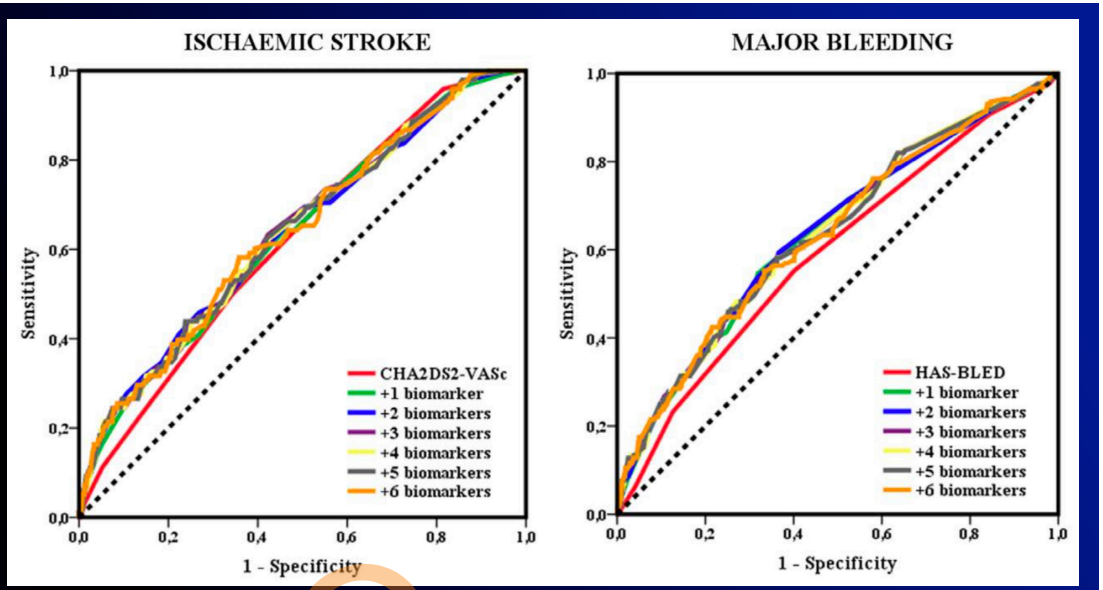
JCI insight
RESEARCH ARTICLE
JCI Insight. 2017;2(9):e91455

GDF15 is elevated in mice following retinal ganglion cell death and in glaucoma patients

Norimitsu Ban,[1] Carla J. Siegfried,[1] Jonathan B. Lin,[1] Ying-Bo Shui,[1] Julia Sein,[1] Wolfgang Pita-Thomas,[2] Abdoulaye Sene,[1] Andrea Santeford,[1] Mae Gordon,[1] Rachel Lamb,[1] Zhenyu Dong,[1] Shannon C. Kelly,[3] Valeria Cavalli,[2] Jun Yoshino,[3] and Rajendra S. Apte[1,3,4]

Refining Stroke and Bleeding Prediction in AF by Adding Consecutive Biomarkers to Clinical Risk Scores

Rivera-Caravaca .. Lip, Roldan.
Stroke 2019
DOI:10.1161/STROKEAHA.118.024305



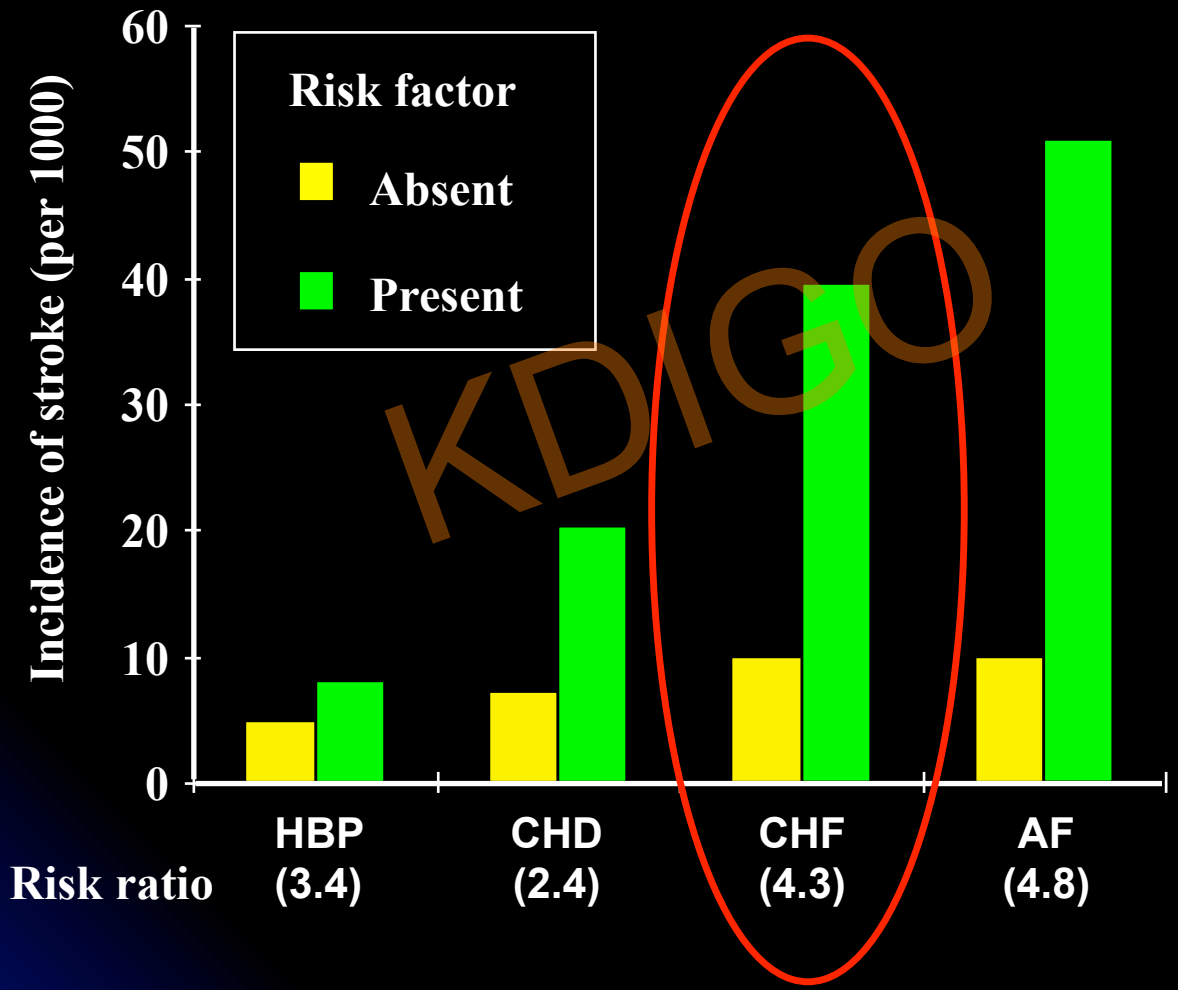
	C Index	95% CI	*Z* Score*	*P* Value*	IDI, %	95% CI	*P* Value	NRI, %	95% CI	*P* Value
Ischemic stroke										
CHA_2DS_2-VASc	0.621	0.589–0.652	…	…	…	…	…	…	…	…
+1 biomarker	0.634	0.602–0.655	0.721	0.471	1.70	0.00/4.40	0.060	−2.80	−13.20/19.00	0.667
+2 biomarkers	0.638	0.606–0.669	0.915	0.360	2.30	0.10/5.30	0.020	−5.60	−16.10/13.70	0.587
+3 biomarkers	0.641	0.610–0.672	1.153	0.249	2.70	0.70/5.30	<0.001	−4.50	−16.60/16.10	0.766
+4 biomarkers	0.639	0.607–0.670	1.024	0.306	2.70	0.60/5.50	0.020	−4.50	−14.10/15.30	0.826
+5 biomarkers	0.639	0.608–0.670	1.012	0.312	2.60	0.01/6.20	0.040	−3.30	−17.40/17.60	0.766
+6 biomarkers	0.639	0.608–0.670	1.022	0.307	2.60	0.30/6.20	0.020	−0.70	−10.90/16.70	0.999
Major bleeding										
HAS-BLED	0.600	0.561–0.625	…	…	…	…	…	…	…	
+1 biomarkers	0.636	0.605–0.667	2.158	0.031	4.00	0.90/7.80	<0.001	22.60	3.80/32.60	<0.001
+2 biomarkers	0.639	0.607–0.669	2.275	0.023	4.90	1.00/8.80	0.030	20.10	0.20/32.90	0.040
+3 biomarkers	0.639	0.607–0.669	2.249	0.025	5.20	1.90/8.90	<0.001	19.20	1.40/32.50	0.020
+4 biomarkers	0.638	0.606–0.669	2.188	0.029	5.00	1.60/8.70	<0.001	19.40	3.00/33.70	0.020
+5 biomarkers	0.635	0.604–0.666	2.003	0.045	5.00	1.90/8.80	<0.001	19.60	4.80/32.70	<0.001
+6 biomarkers	0.635	0.604–0.666	2.023	0.043	5.30	1.90/9.20	0.020	20.30	0.40/34.20	0.020

By adding consecutive biomarkers, the predictive ability of CHA_2DS_2-VASc for ischemic stroke was not increased, whereas the predictive ability of HAS-BLED for major bleeding was only slightly enhanced.

The net benefit and clinical usefulness of the biomarker-based models were marginal in comparison to the original scores based on clinical factors.

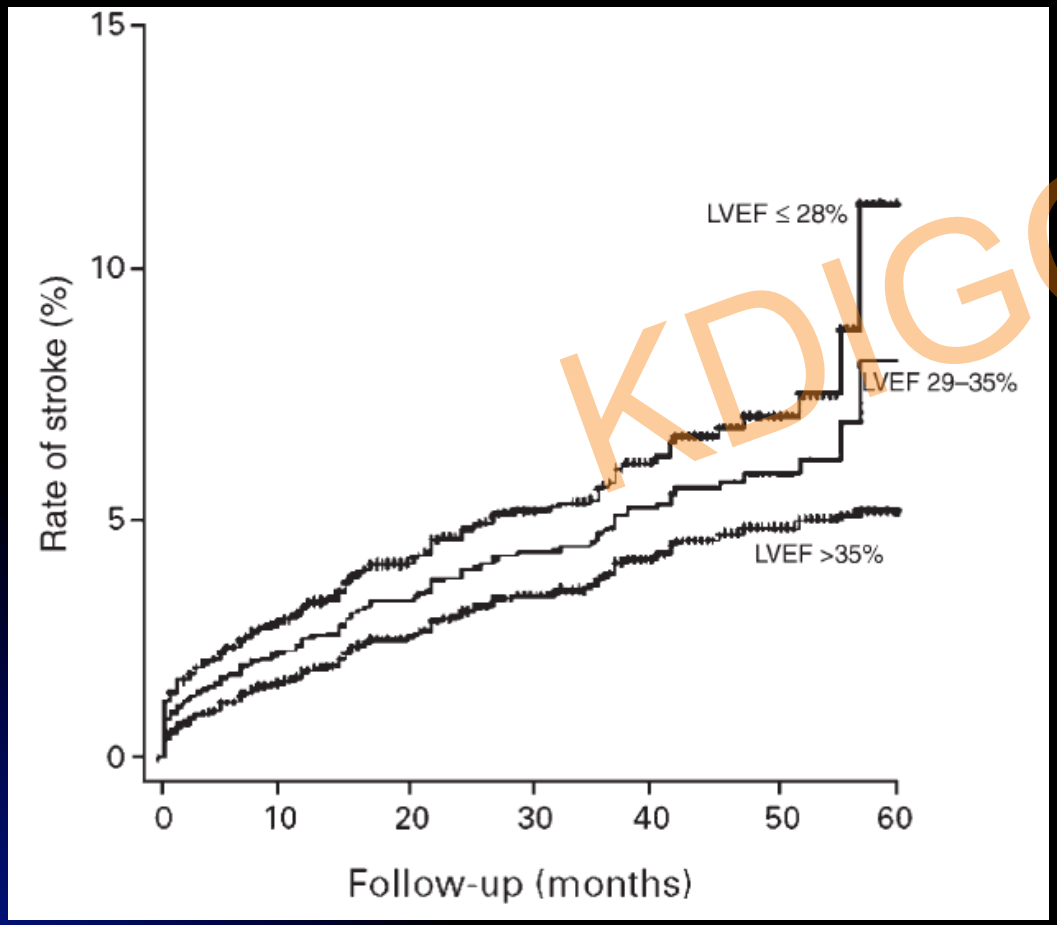
2-Year Age-Adjusted Incidence of Stroke per 1000

Wolf et al. Stroke 1991;22:983



Kaplan–Meier estimate of the cumulative stroke rate among patients in the SAVE trial

Loh et al N Engl J Med 1997;336:251–257.



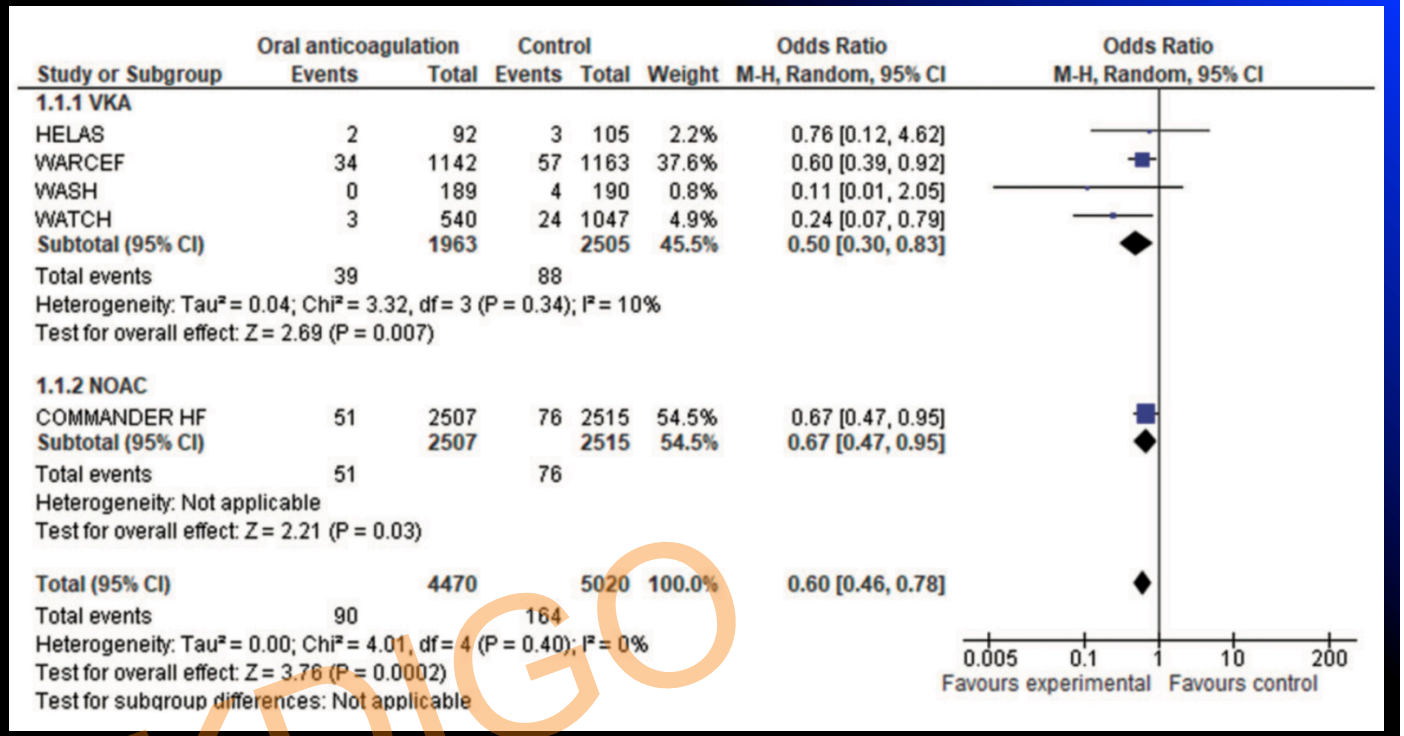
Over 5 years, the rate of stroke was 1.5%/year. *LV function, older age, and non-use of aspirin and/or anticoagulants were independent risk factors for thromboembolism.*

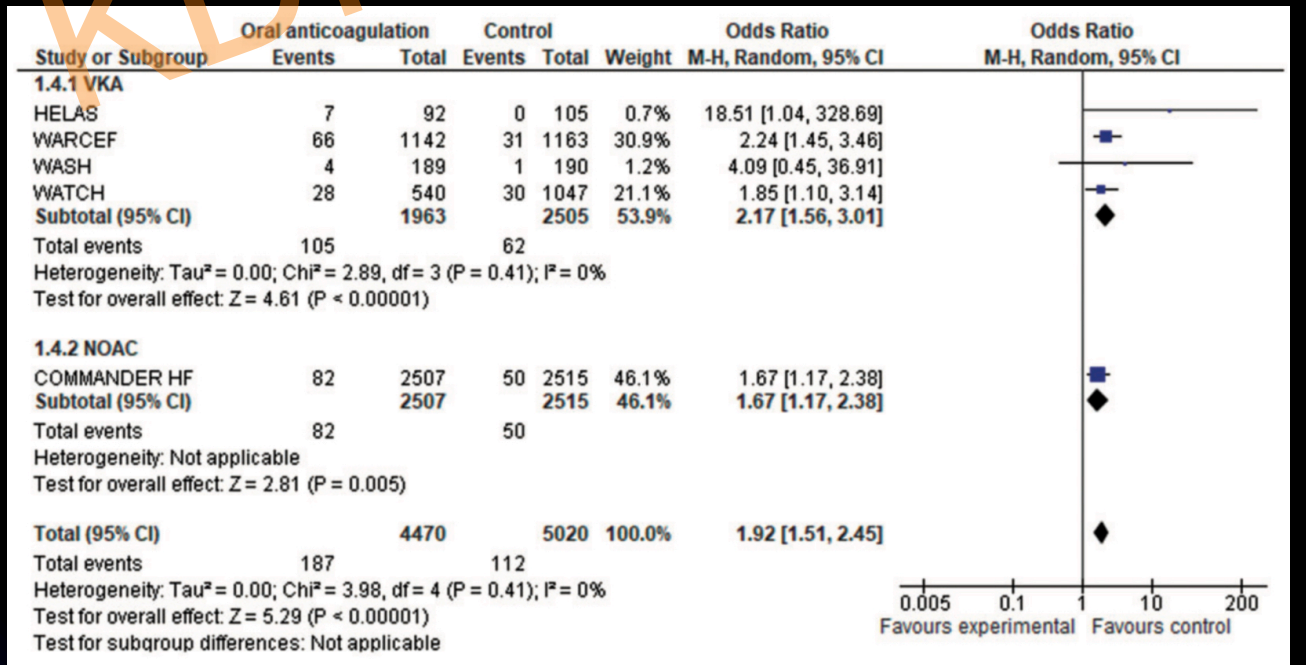
For each 5% decrease in EF, there was an 18% increase in stroke rate.

Patients with EF ≤28% had a 5-year cumulative stroke risk of 8.1% [vs 4.1% for those with EF >35%]

OAC versus antiplatelet or placebo in patients with heart failure and sinus rhythm: Systematic review and meta-analysis

Ntaios .. Lip
Int J Stroke. 2019 Dec; 14(9):856-861

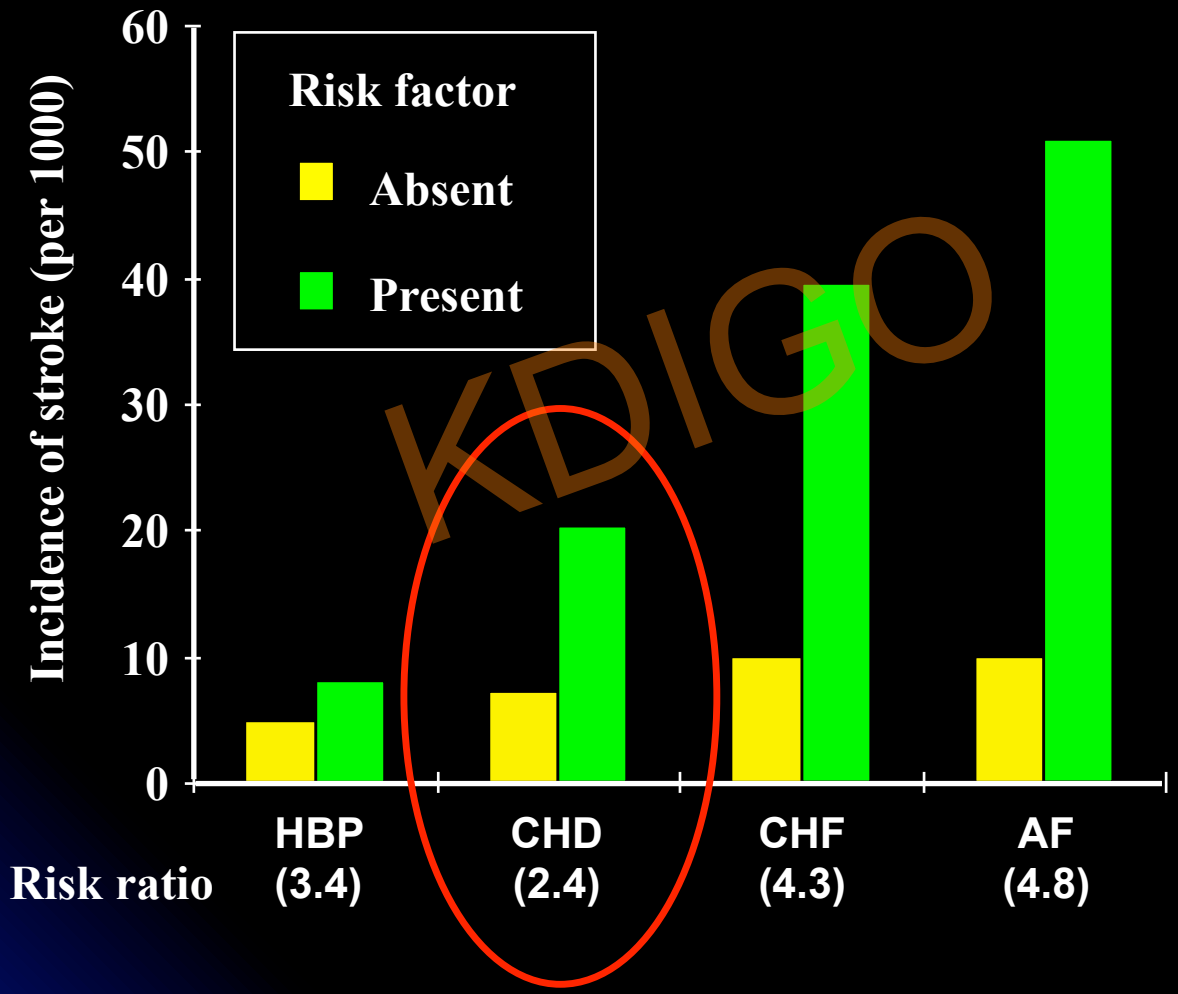




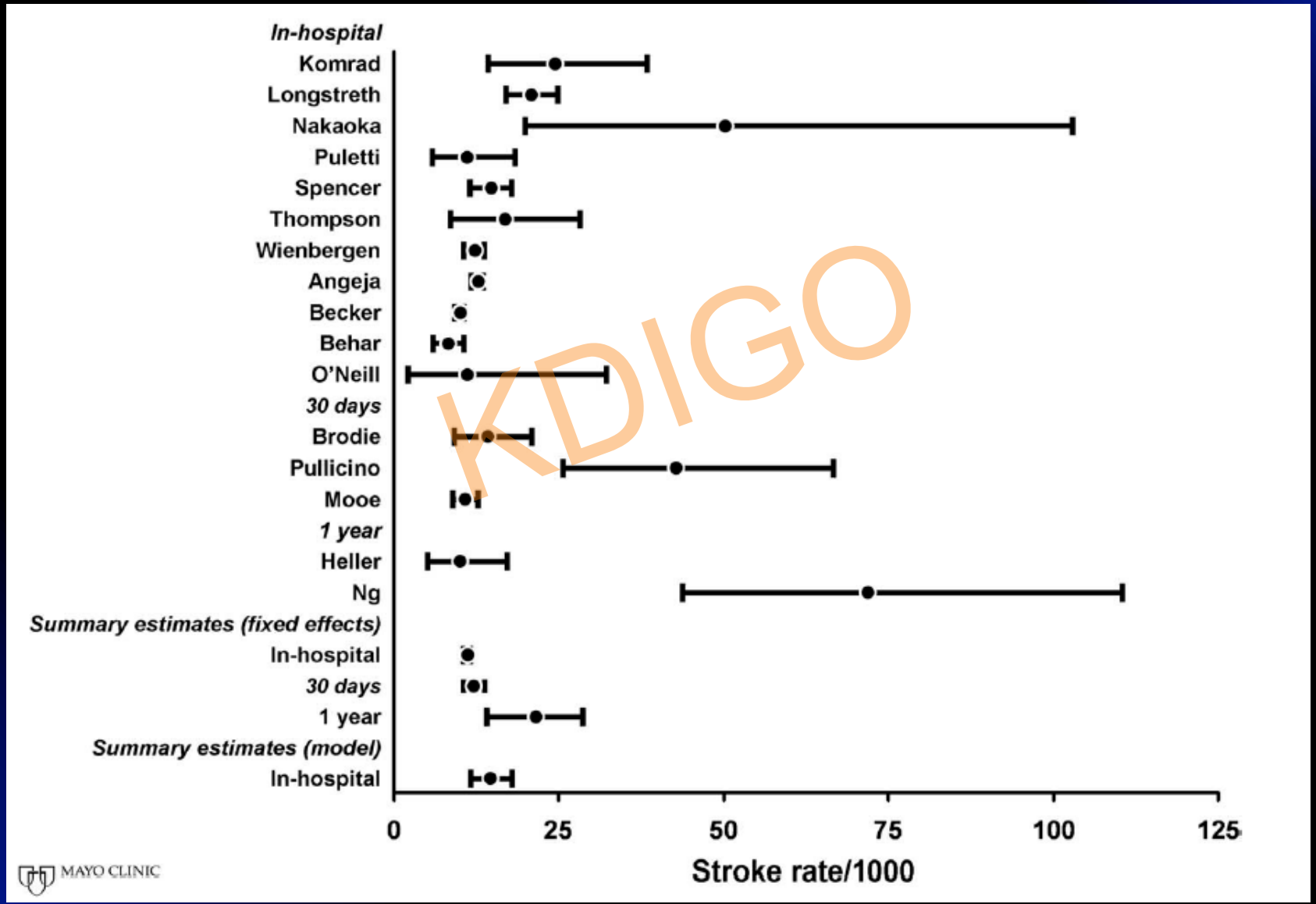
OAC vs antiplatelet or placebo for stroke (top) and major bleeding (botton)

2-Year Age-Adjusted Incidence of Stroke per 1000

Wolf et al. Stroke 1991;22:983



Stroke after Myocardial Infarction: A Meta-Analysis *Witt et al Am J Med 2006; 119, 354.e1-354.e9*



The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) *N Engl J Med 2006;354*

Clopidogrel 75mg and Aspirin (75=162mg)
vs Aspirin Alone for the Prevention of Atherothrombotic Events

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Myocardial infarction (nonfatal)	147 (1.9)	159 (2.0)	0.92 (0.74–1.16)	0.48
Ischemic stroke (nonfatal)	132 (1.7)	160 (2.1)	0.82 (0.66–1.04)	0.10
Stroke (nonfatal)	149 (1.9)	185 (2.4)	0.80 (0.65–0.997)	0.05
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.10)	<0.001

	Months					
No. at Risk						
Clopidogrel	7802	7653	7510	7363	5299	2770
Placebo	7801	7644	7482	7316	5212	2753

CI, 0.77 to 0.998; P = 0.046).

Diagnostic Evaluation of Ischemic Stroke to Determine Stroke Mechanism

Yaghi et al Circ Res. 2017;120:527-540

Diagnostic Test	Suggested Algorithm
Brain imaging	Brain MRI in patients with cryptogenic stroke
	Brain CT when stroke mechanism is known
Vascular imaging	Intracranial and extracranial vascular imaging on all patients with ischemic stroke
	MRA with fat-suppressed images when clinical suspicion for cervical artery dissection
Cardiac imaging	TTE on all patients with ischemic stroke to look for evidence of cardiac disease (evidence of prior myocardial infarction warranting ischemic cardiac evaluation or systolic heart failure)
	TEE with bubble study on patients <50 y old to look for cardiac shunts/cardiac tumors if TEE was nonrevealing
Cardiac monitoring	Thirty-day noninvasive cardiac monitoring on patients with cryptogenic stroke and ≥40 y
	Implantable cardiac monitor if 30-day monitor does not reveal AF or flutter
Hypercoagulable testing	Serum hypercoagulable workup in patients with no or minimal risk factors
Screening for malignancy	Age appropriate screening
	CT chest/abdomen/pelvis when systemic symptoms suggestive of cancer are present such as unexplained weight loss or unexplained fever

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

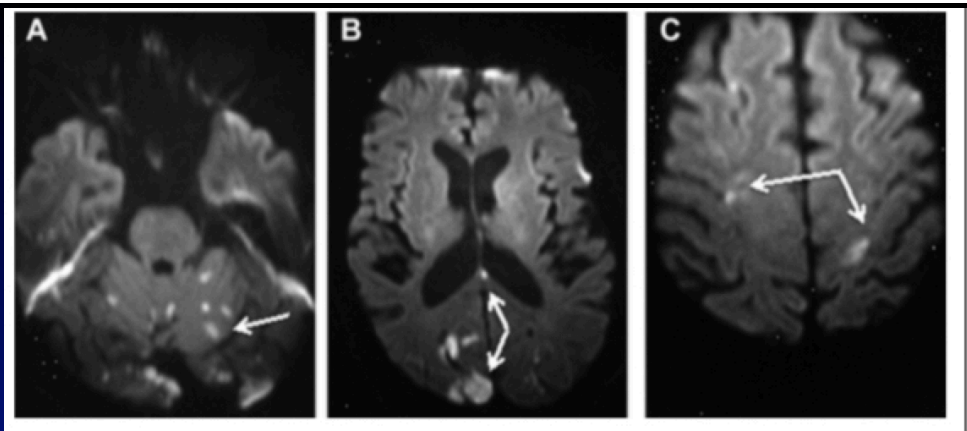
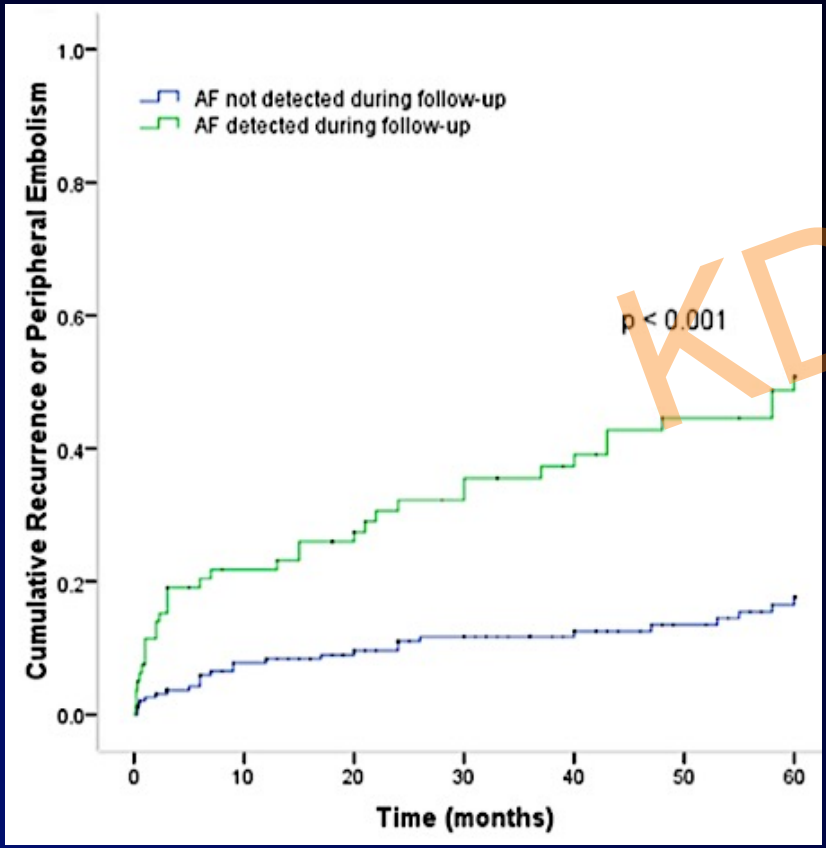


Figure 1. A and **B**, Multiple small infarcts in the posterior circulation in a patient with proximal basilar artery stenosis. **C**, Small infarcts in multiple vascular territories suggestive of a cardioaortic source.

Embolic Stroke of Undetermined Source and Detection of AF on Follow-Up: How Much Causality Is There

Ntaios … Lip et al J Stroke Cerebrovasc Dis 2016 http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.015



Cumulative probability of recurrent stroke or peripheral embolism in the AF and non-AF ESUS patients.

- Among 275 ESUS patients, AF was detected during follow-up in 80 (29.1%).
- NIHSS score was similar between the two groups (5 [2-13] versus 5 [2-14], *P* = .998).
- More recurrent strokes or peripheral embolisms occurred in the AF group compared with the non-AF group (42.5% versus 13.3%, *P* = .001).

Diagnosis of AF after stroke and transient ischaemic attack: a systematic review and meta-analysis

Sposato et al Lancet Neurology 2015; 14: 377-87

4 sequential phases of screening:	cardiac monitoring methods	%dx with poststroke AF
Phase 1 (emergency room) -	admission electrocardiogram (ECG)	7·7% (95% CI 5·0–10·8)
Phase 2 (in hospital)	serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter monitoring	5·1% (3·8–6·5)
Phase 3 (first ambulatory period)	ambulatory Holter;	10·7% (5·6–17·2)
Phase 4 (second ambulatory period)	mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording	16·9% (13·0–21·2)

Overall AF detection yield after all phases of sequential cardiac monitoring was 23·7% (95% CI 17·2–31·0).

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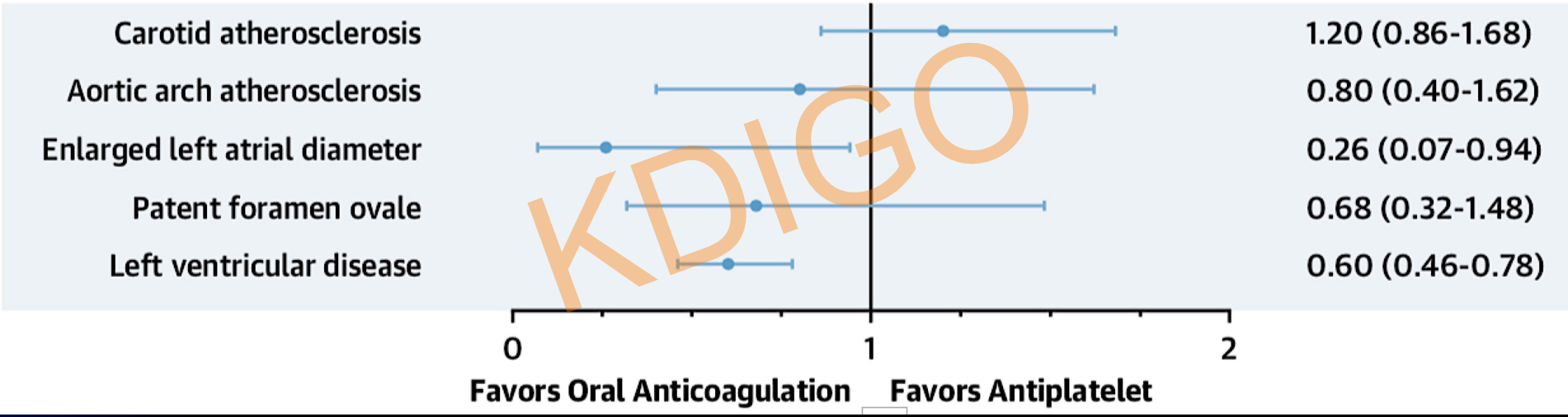
	Diagnostic Tests	Therapeutic Implications
Cardiac causes		
Paroxysmal occult AF	Noninvasive cardiac monitoring, and if no AF or flutter detected, then implantable cardiac monitoring	Anticoagulation therapy
Atrial cardiopathy	Serum NT-proBNP, echocardiography, ECG	Treatment with antiplatelet vs anticoagulation is unknown, but empirical treatment with anticoagulation may be reasonable
Atrial septal defect	Echocardiography (TEE superior to TTE)	Venous imaging if atrial septal defect detected
Atherosclerotic causes		
Aortic arch disease	Echocardiography (TEE superior to TTE)	Antiplatelet and statin therapy
Substenotic atherosclerosis	Vessel wall imaging, plaque MRI	Antiplatelet and statin therapy
Other causes		
Cancer	CT chest, abdomen, and pelvis	Antiplatelet vs. anticoagulation treatment of underlying cancer
Hypercoagulable state	Hypercoagulable work-up, including antiphospholipid antibodies	Anticoagulation therapy based on findings
Arterial dissection	MRA with fat-suppressed images	Antiplatelet therapy

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

Comparison Between Oral Anticoagulation and Antiplatelet Rx in Patients With ESUS/Cryptogenic Stroke and Underlying Potential Embolic Source

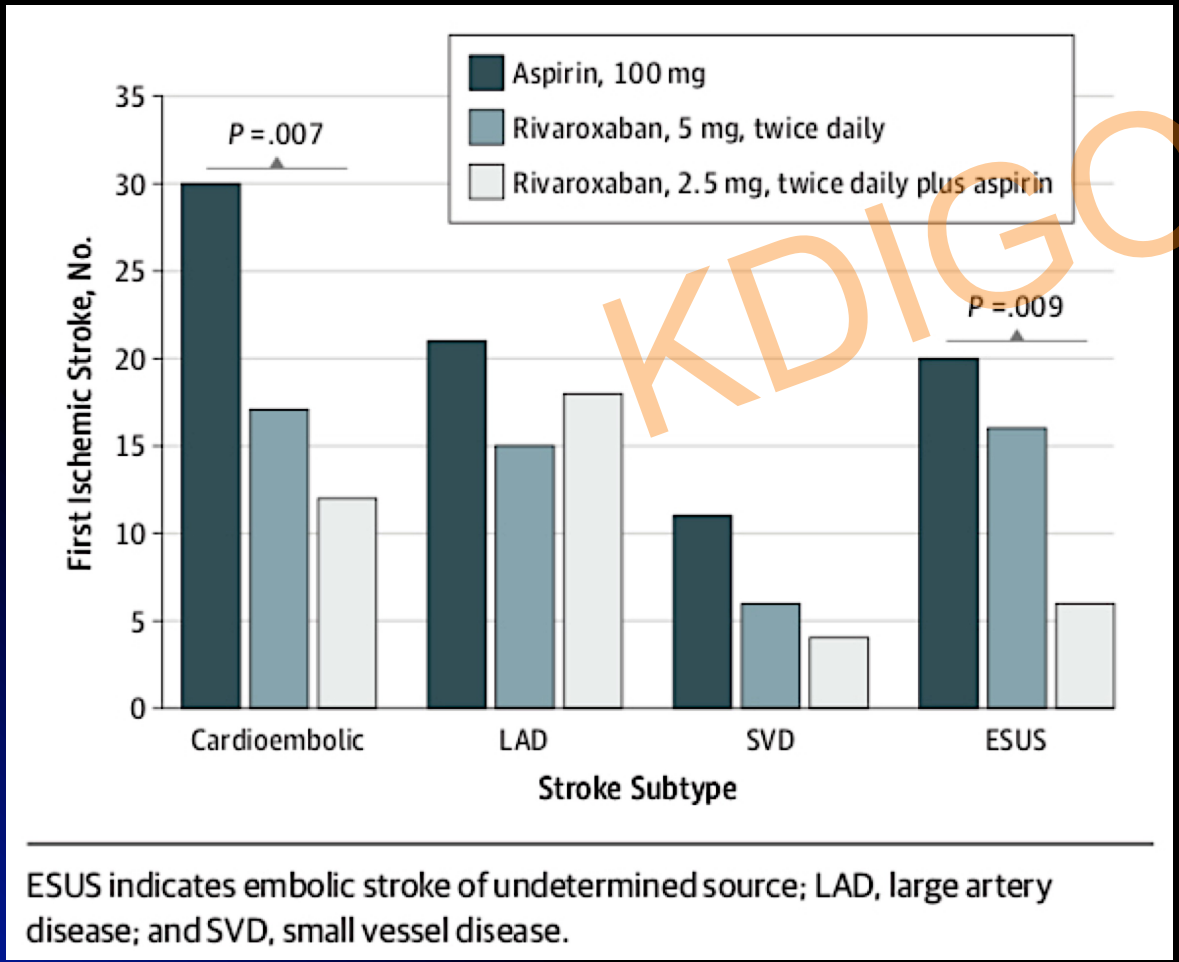
Ntaios. J Am Coll Cardiol 2020;75:333–40



HRs and 95%CIs are obtained from exploratory subgroup analyses of the NAVIGATE ESUS trial

Treatment Effect on Stroke Subtypes According to TOAST (Trial of Org 10172 in Acute Stroke Treatment) Criteria Among Participants With Ischemic or Unknown Stroke : COMPASS

Pereira et al JAMA Neurol. doi:10.1001/jamaneurol.2019.2984



ESUS indicates embolic stroke of undetermined source; LAD, large artery disease; and SVD, small vessel disease.

Significantly fewer cardioembolic strokes (hazard ratio [HR], 0.40 [95% CI, 0.20-0.78]; P = .005) and embolic strokes of undetermined source (HR, 0.30 [95% CI, 0.12-0.74]; P = .006) in the combination therapy group compared with the aspirin-only group.

For patients with systemic atherosclerosis,low-dose rivaroxaban plus aspirin was associated with large, significant reductions in cardioembolic strokes and embolic strokes of undetermined source.

Non-Embolic and Embolic Mechanisms of Stroke

- Cardioembolic stroke accounts for roughly 15% of all strokes.
- The risk profile for a potential cardiogenic source of embolism needs to be stratified.
- Common causes are AF, heart failure, CAD, hypertension…
- Evidence to guide long term medical management is …..
  - *strong* in some areas eg. atrial fibrillation.
  - *limited* in some areas – large trials of longer duration are needed.