Atrial Fibrillation 2017 - 2018

Quality of Life and Preventing Stroke

The 14 Clinical Challenges

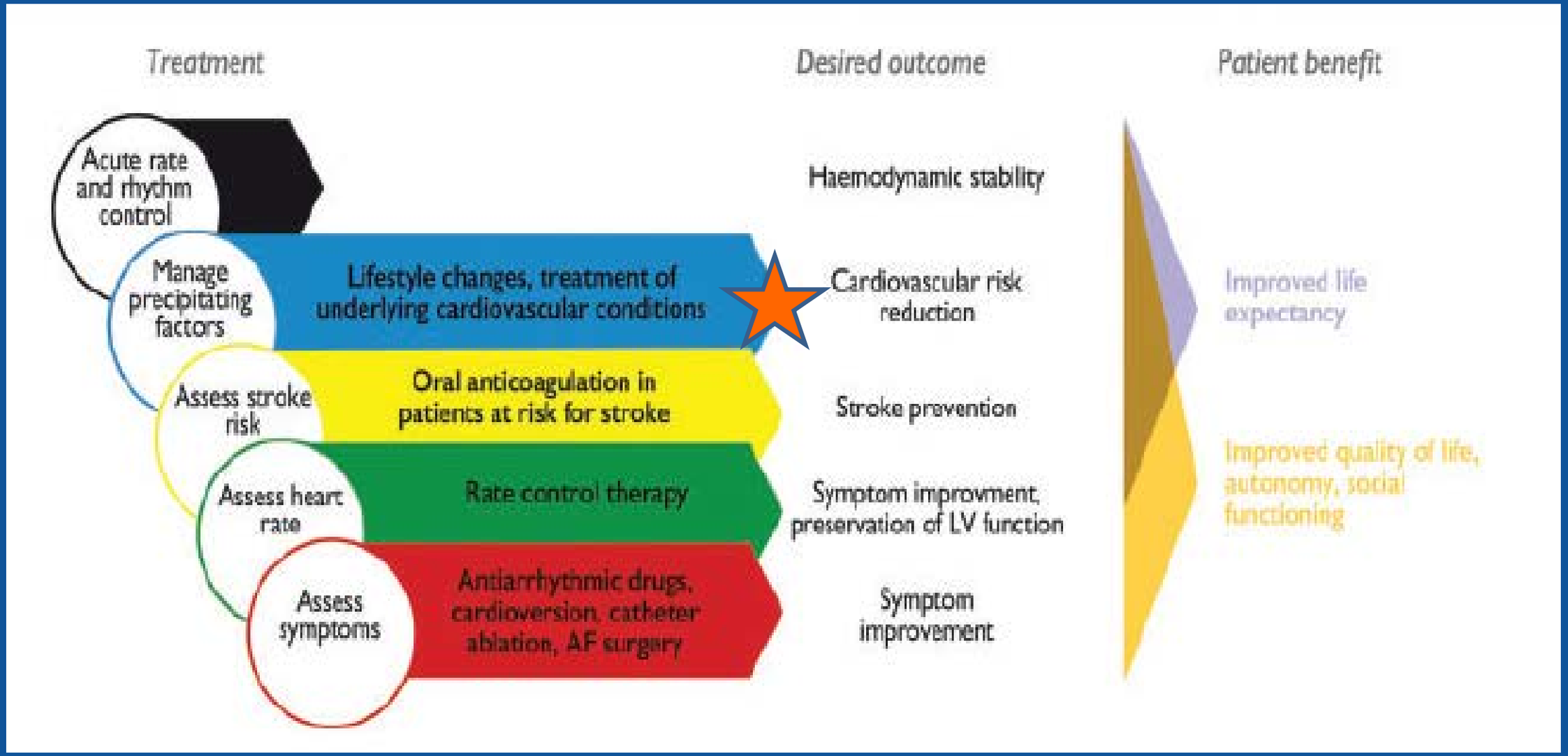
ACC New York, Dec 9, 2017

No Disclosures

AF - CLINICAL CHALLENGES (14) – 2017 - 2018

1. Presentation:	Simplified	vs Prioritized	(2)
2. Etiology:	Myocardial	vs Electrical	(2)
3. AC Rx:	When / Bridge	vs TE-NSR / SCI	(2)
4. AF / Stent:	Triple Rx	vs Double Rx	(2)
5. Warf. / NOACs:	Efficacy	vs Safety	(2)
6. Not Indicated ?	AC	vs LAA Closure	(2)
7. Screening	Screening	vs No Screening	(2)

1,2). Acute & Chronic Management Of AF



1. **D Kotecha et. al. . EHJ. 2016;37:2851 –** *ANSD – RF - <AF Death*
2. **EHJ 2016; 37:2893 -** *Simple*

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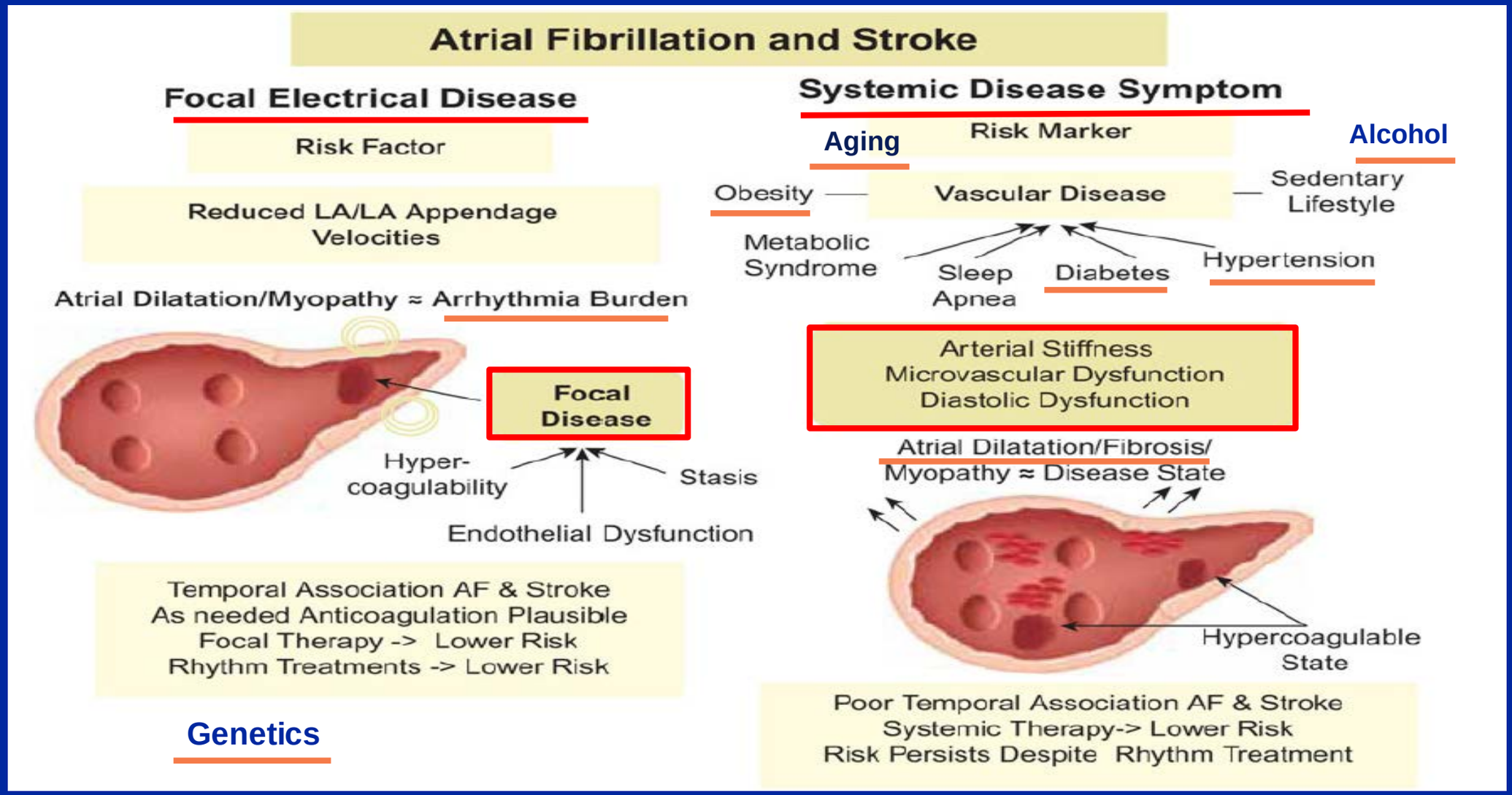
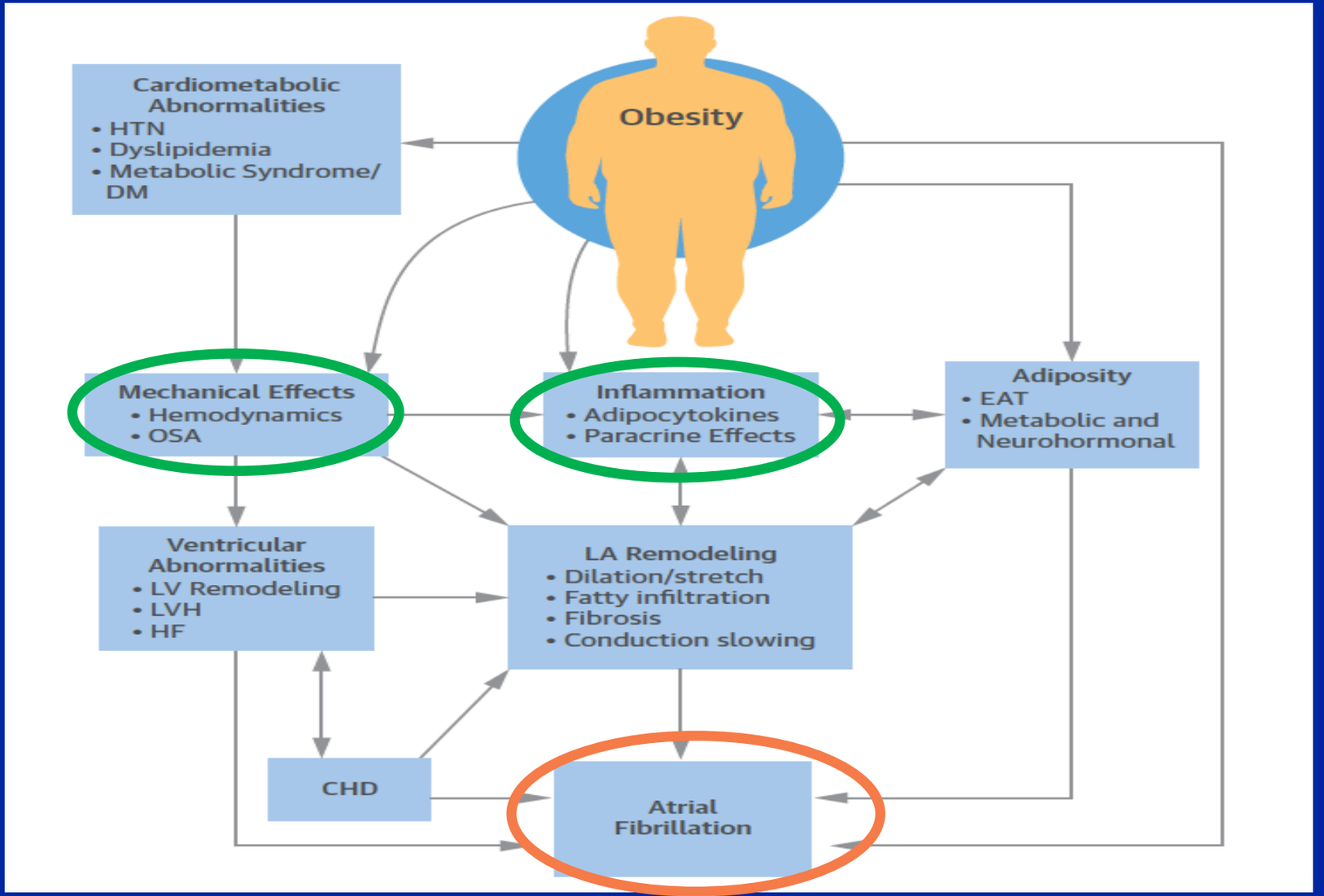
6. Not Indicated ?	AC vs LAA Closure	(2)
7. Screening	Screening vs No Screening	(2)

1). Gross Mechanisms of AF



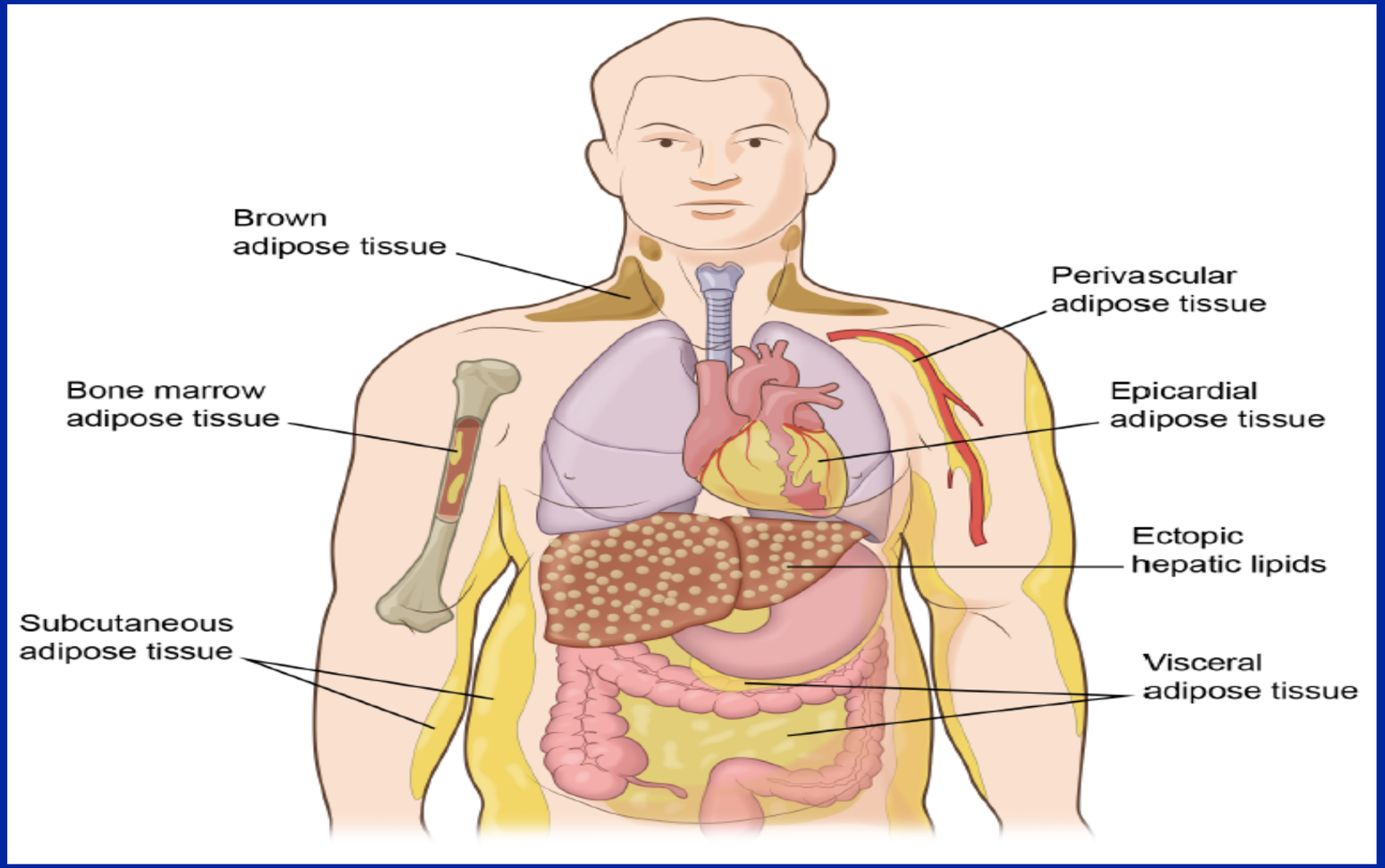
TJ Bunch et. al. Eur Heart J. 2016;37:2890
BW Calenda, V Fuster, V Reddy et. al. Nat Rev Cardiol 2016;13:549

Obesity and AF



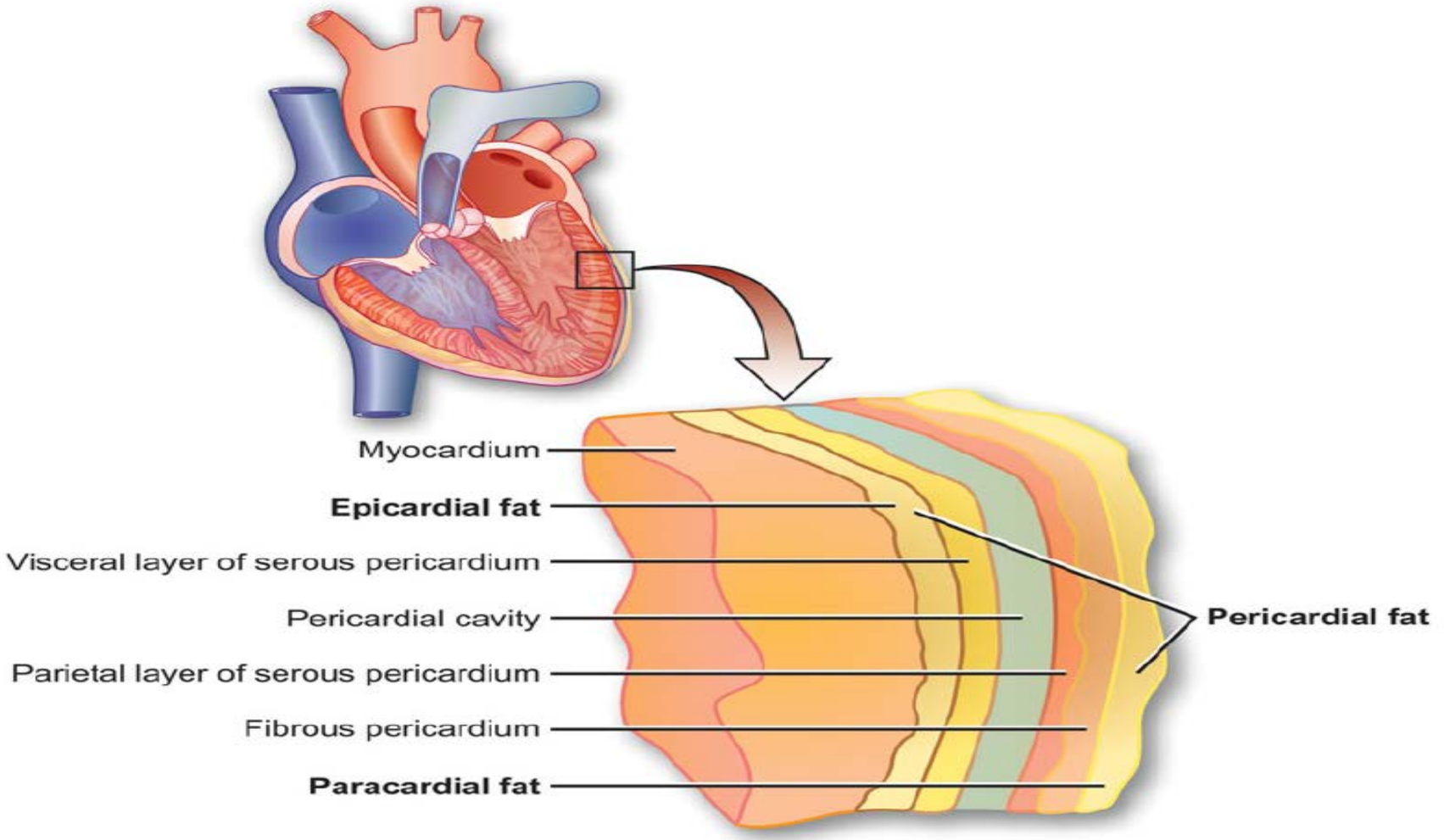
CJ Lavie et. al. J Am Coll Cardiol 2017;70:2022

Adipose Tissue Depots Occur Throughout The Body



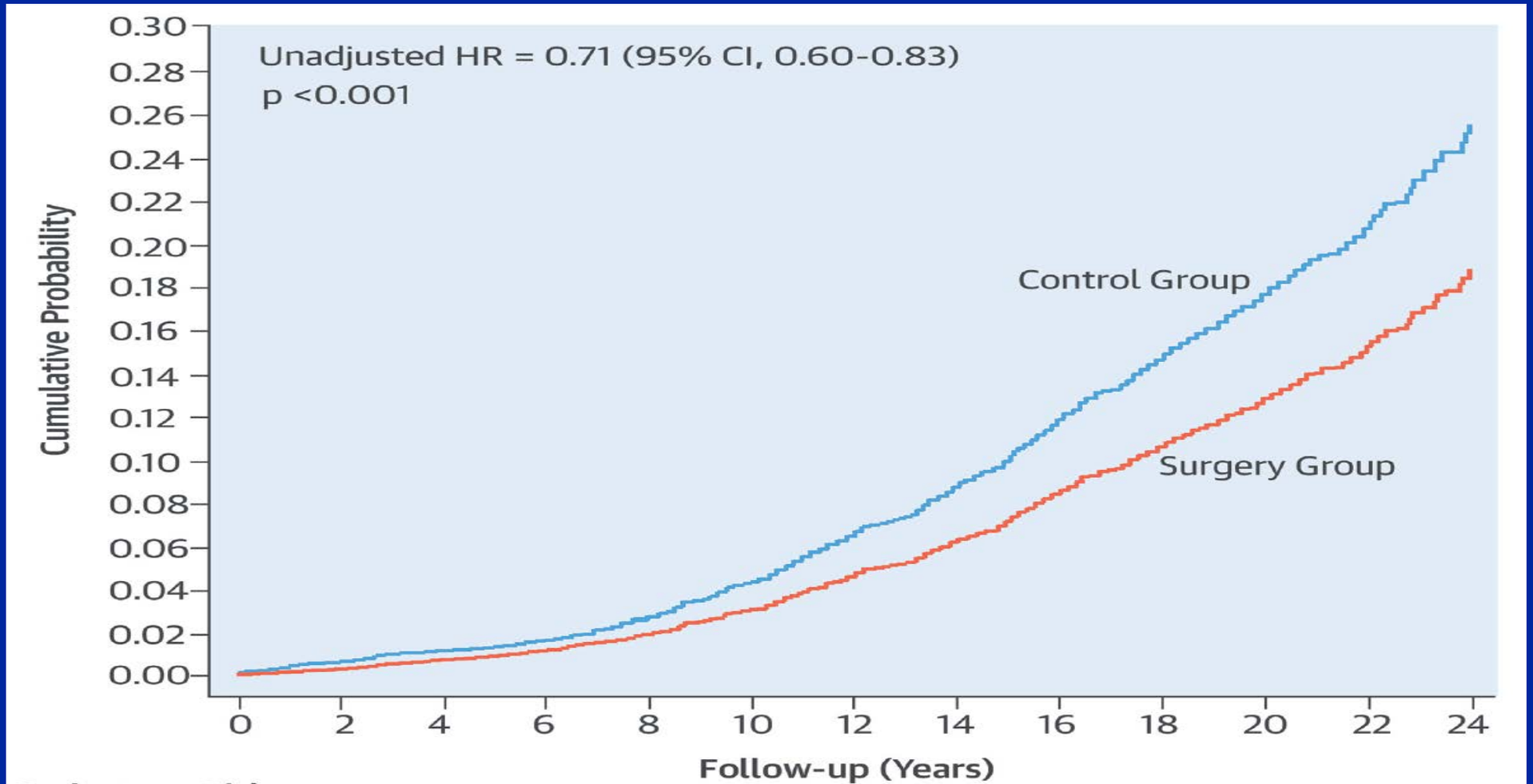
JJ Fuster et. al. Circ Res. 2016;118:1786

Definition of Epicardial Fat And Related Adipose Tissues



CX Wong et. al. Eur Heart J. 2017;38:1294

Bariatric Surgery and the Risk of AF

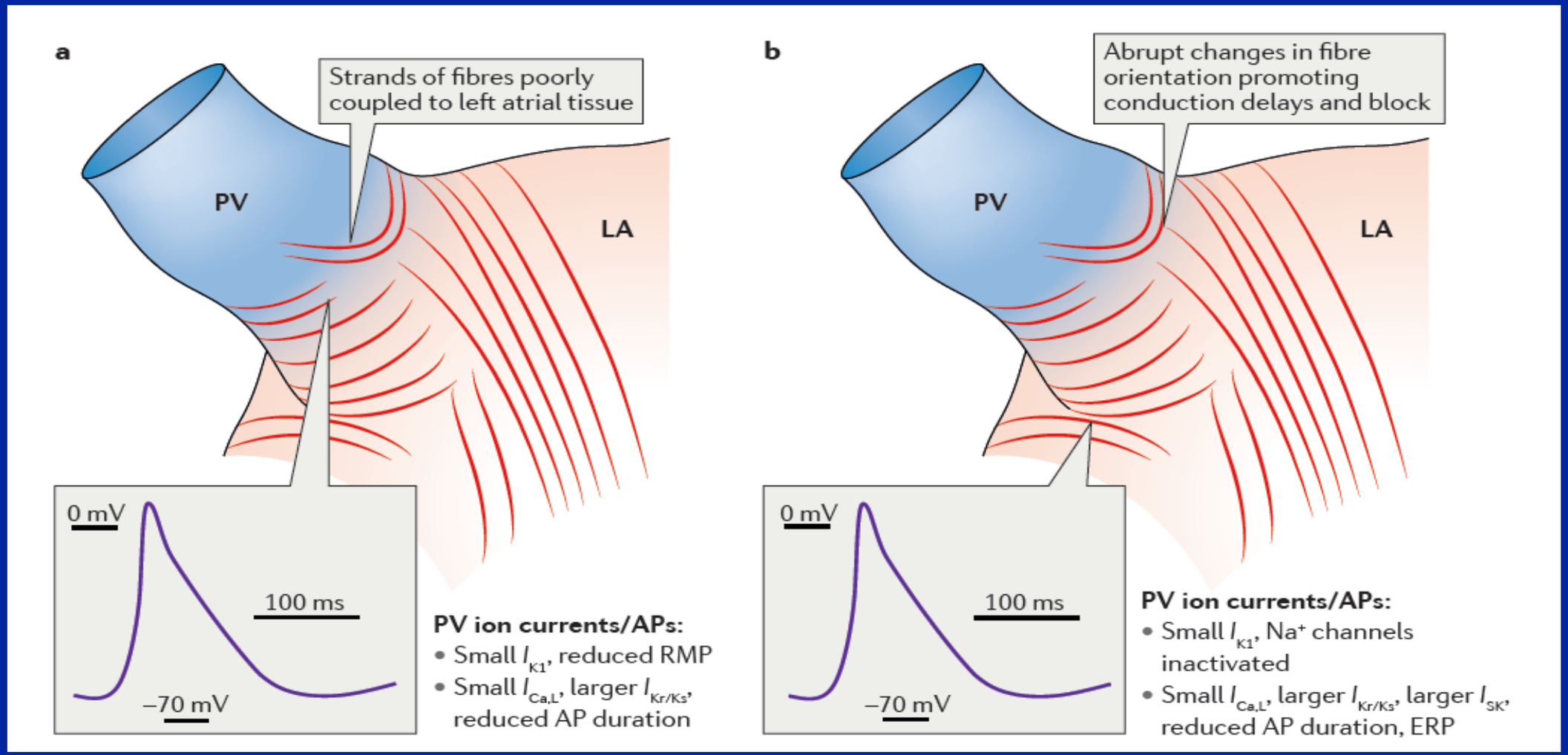


Patients at Risk

Control	2,021	1,979	1,840	1,574	570	114
Surgery	2,000	1,955	1,853	1,615	617	134

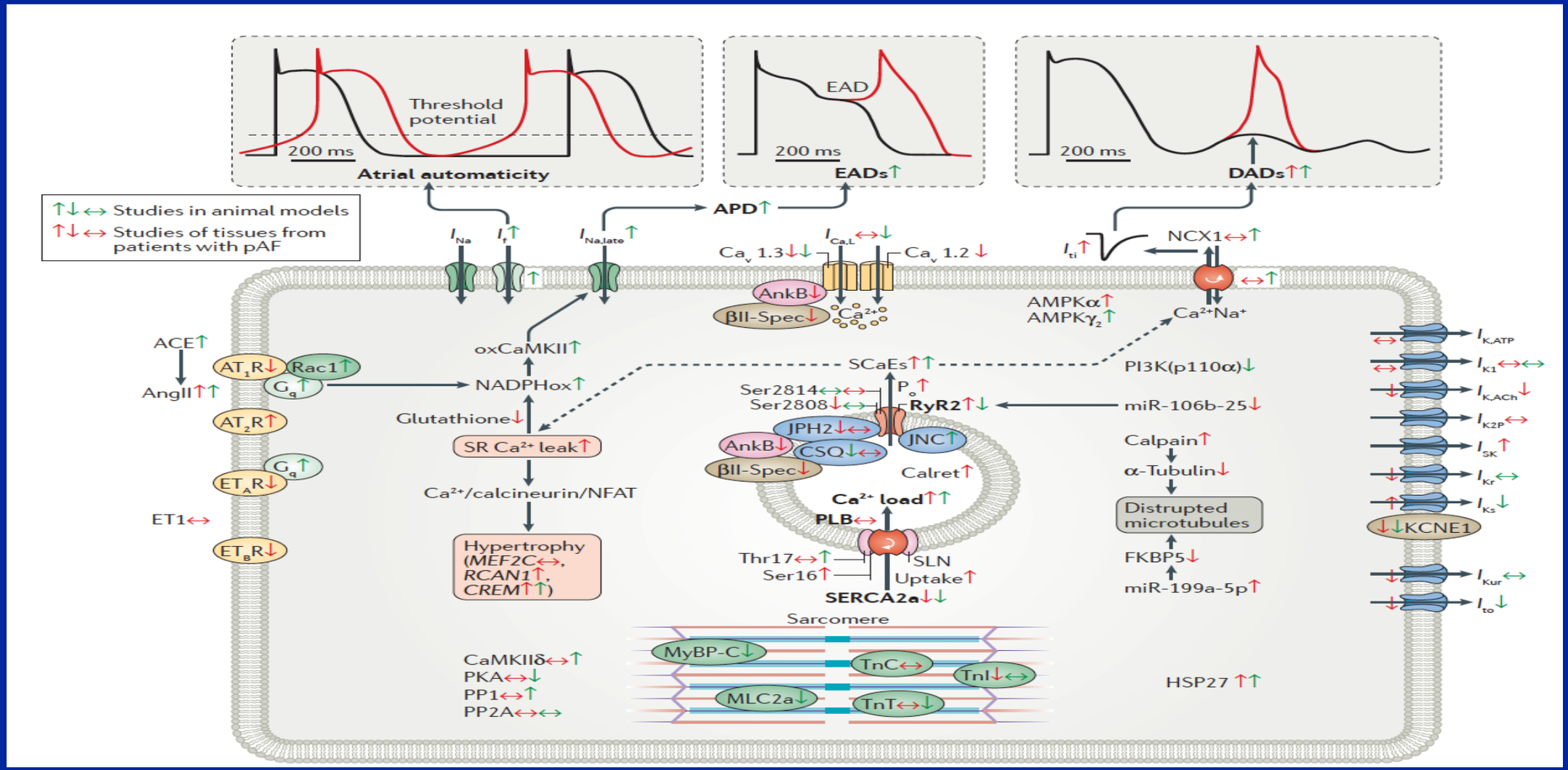
S Jamaly et. al. J Am Coll Cardiol 2016;68:2497

2) Mechanisms of AF Initiation At The Pulmonary Veins



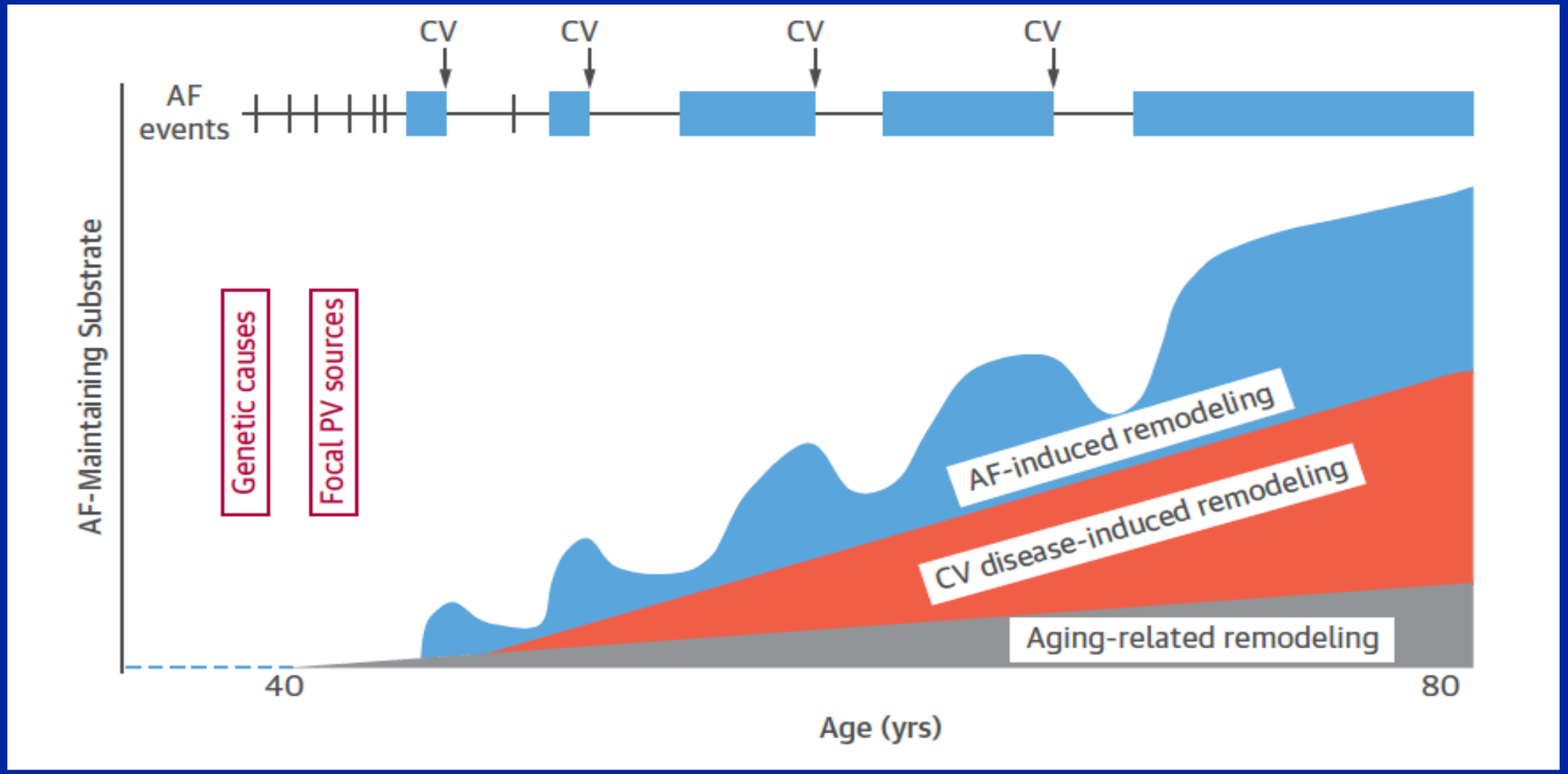
S Nattel et. al. Nat Rev Cardiol. 2016; 13: 575.

2) Molecular Mechanisms of Focal Ectopic Firing In Paroxysmal AF



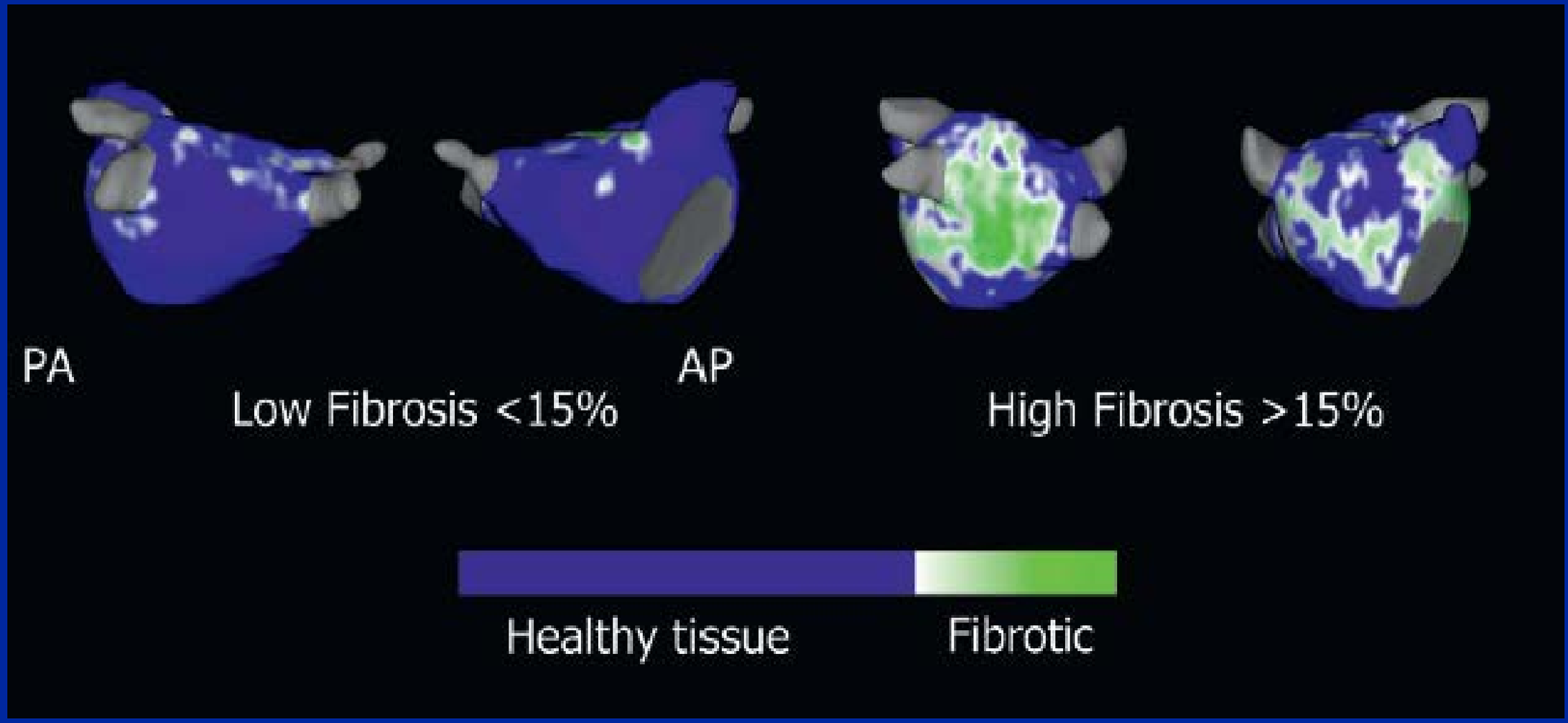
S Nattel et. al. Nat Rev Cardiol. 2016; 13: 575. – *Also Re-entry*

Natural History of AF



JB Guichard et. al. J Am Coll Cardiol 2017;70:756

LA Tissue Fibrosis on 3D LGE CMR Scans



JB King, N Marrouche et. al. J Am Coll Cardiol 2017;70:1311

Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation
The DECAAF Study

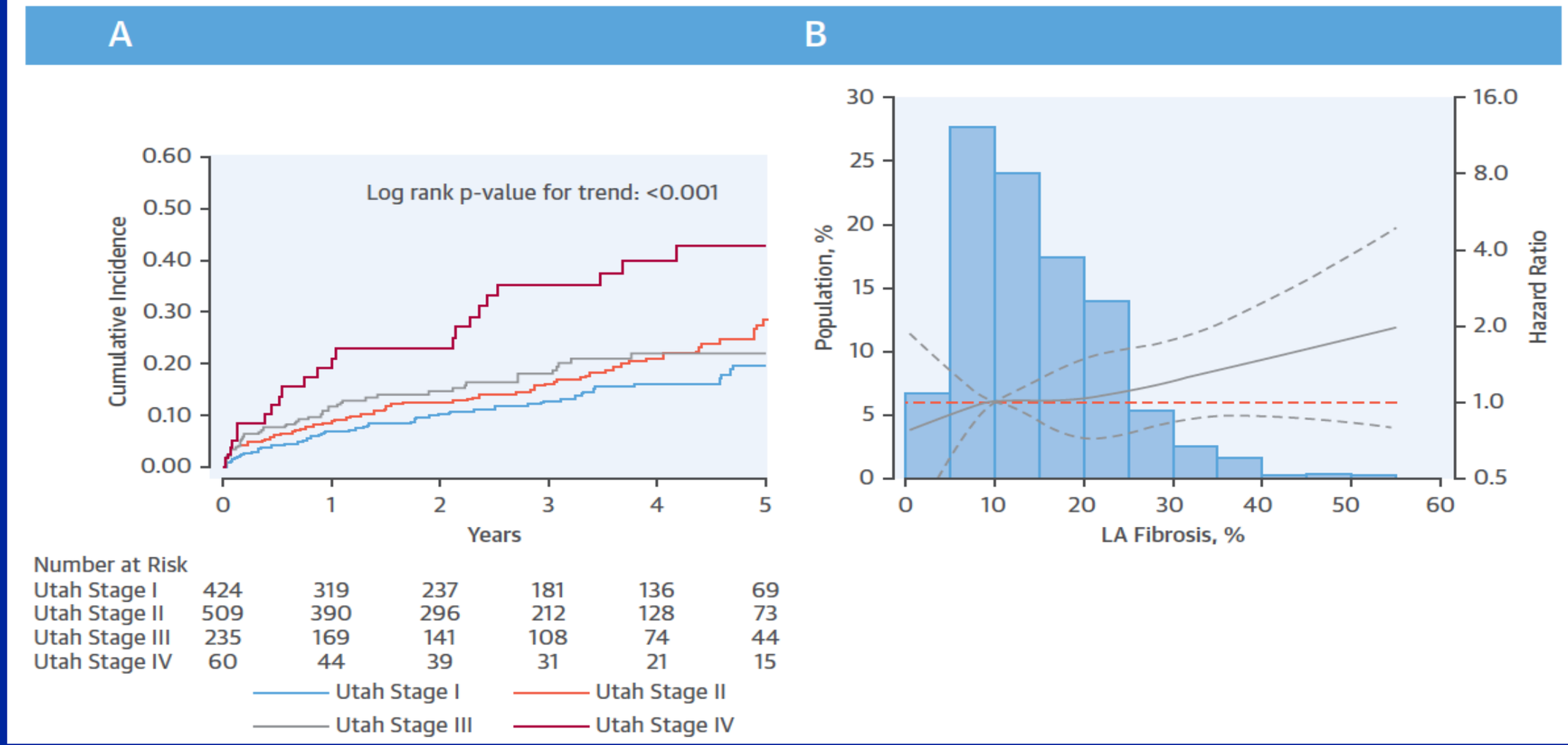
Nassir F. Marrouche, MD; David Wilber, MD; Gerhard Hindricks, MD; Pierre Jais, MD; Nazem Akoum, MD; Francis Marchlinski, MD; Eugene Kholmovski, PhD; Nathan Burgon, BSc; Nan Hu, PhD; Lluis Mont, MD; Thomas Deneke, MD; Mattias Duytschaever, MD; Thomas Neumann, MD; Moussa Mansour, MD; Christian Mahnkopf, MD; Bengt Herweg, MD; Emile Daoud, MD; Erik Wissner, MD; Paul Bansmann, MD; Johannes Brachmann, MD

Fibrosis of the LA Wall, Blinded To The Treating Physicians:

Stage 1 (<10%),
Stage 2 (≥10%-<20%),
Stage 3 (≥20%-<30%),
Stage 4 (≥30%).

JAMA. 2014;311(5):498

Risk of MACCE Utah Stage of LAG Enhancement Severity



JB King, N Marrouche et. al. J Am Coll Cardiol 2017;70:1311

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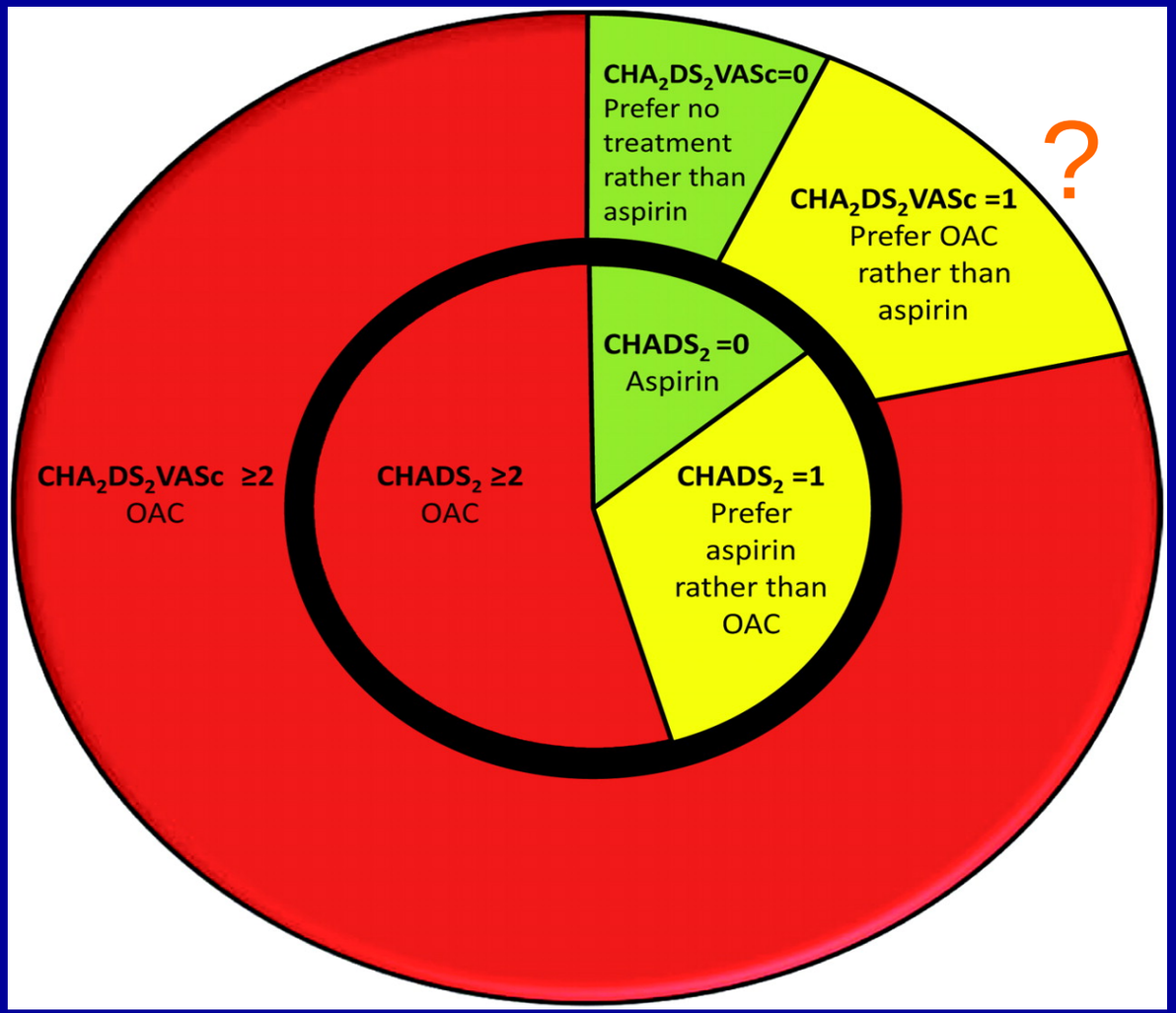
7. Screening	Screening	vs	No Screening	(2)

1a). AC When ?- The Prevention Of Stroke .



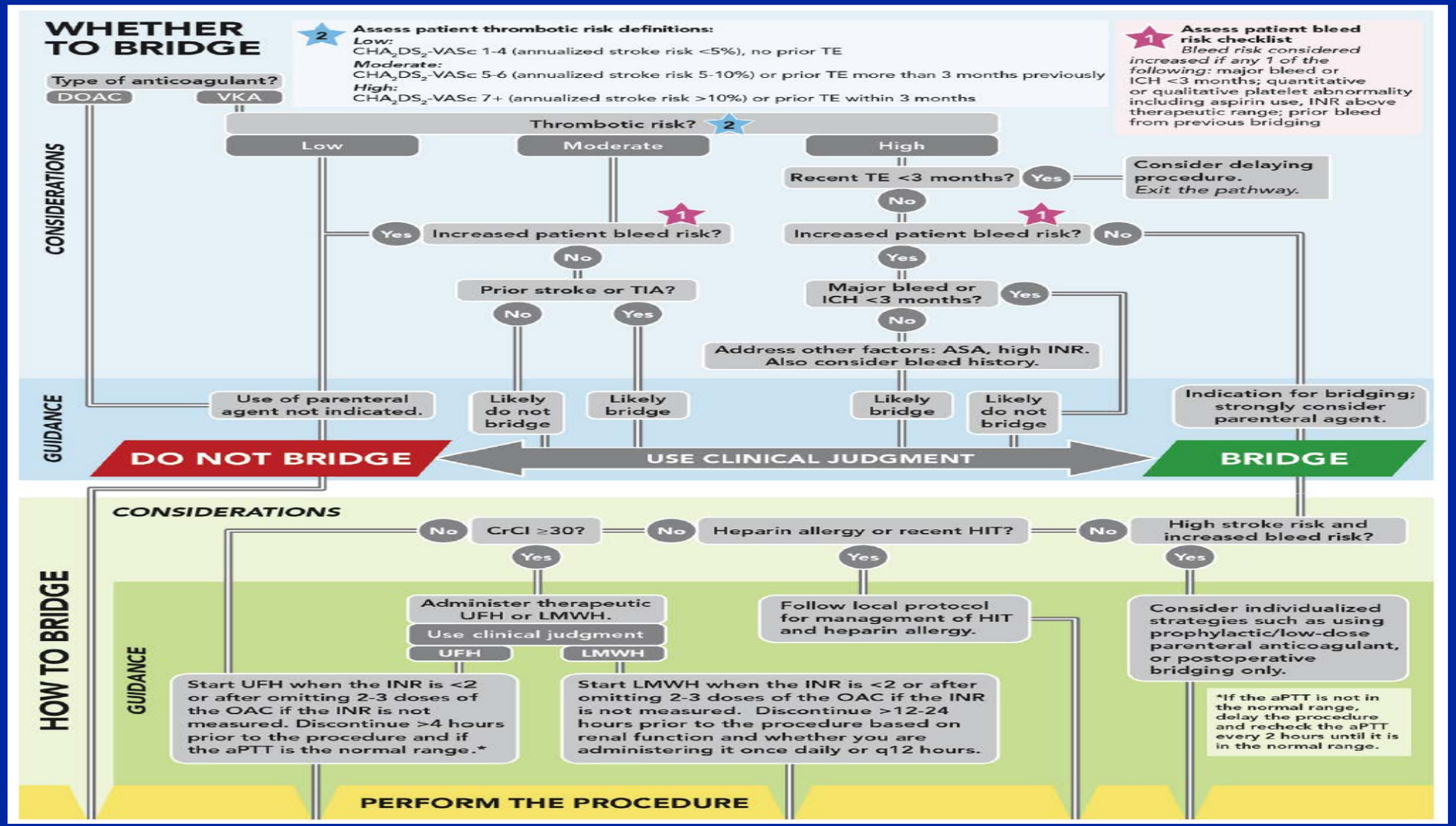
V Fuster, JS Chinitz, Circ. 2012 ; 125: 2285

***Swedish AF Cohort Register** (L Friberg, GYH Lip et al) Circ. 2012; 125: 2298*

CHA_2DS_2VASc: ESC Guidelines (P Kirchhof, AJ Camm et al) 2013 - ACC / AHA / HRS 2014

A/C Prevention - Emboli >>> Bleeding, Thrombosis > Bleeding

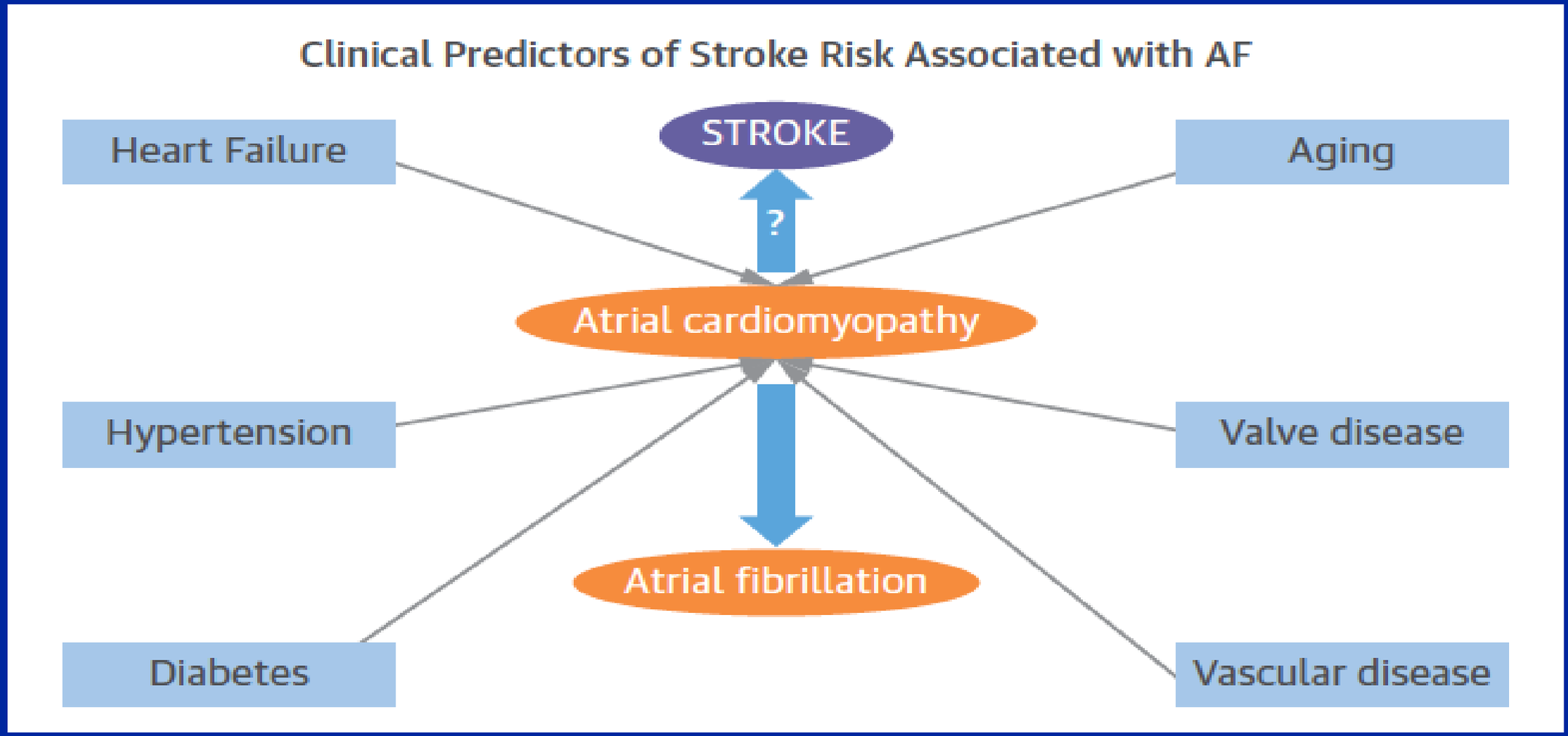
1b). To Bridge & How to Bridge for DOACs/VKAs



JU Doherty, JL Januzzi et. al. J Am Coll Cardiol 2017;69:872

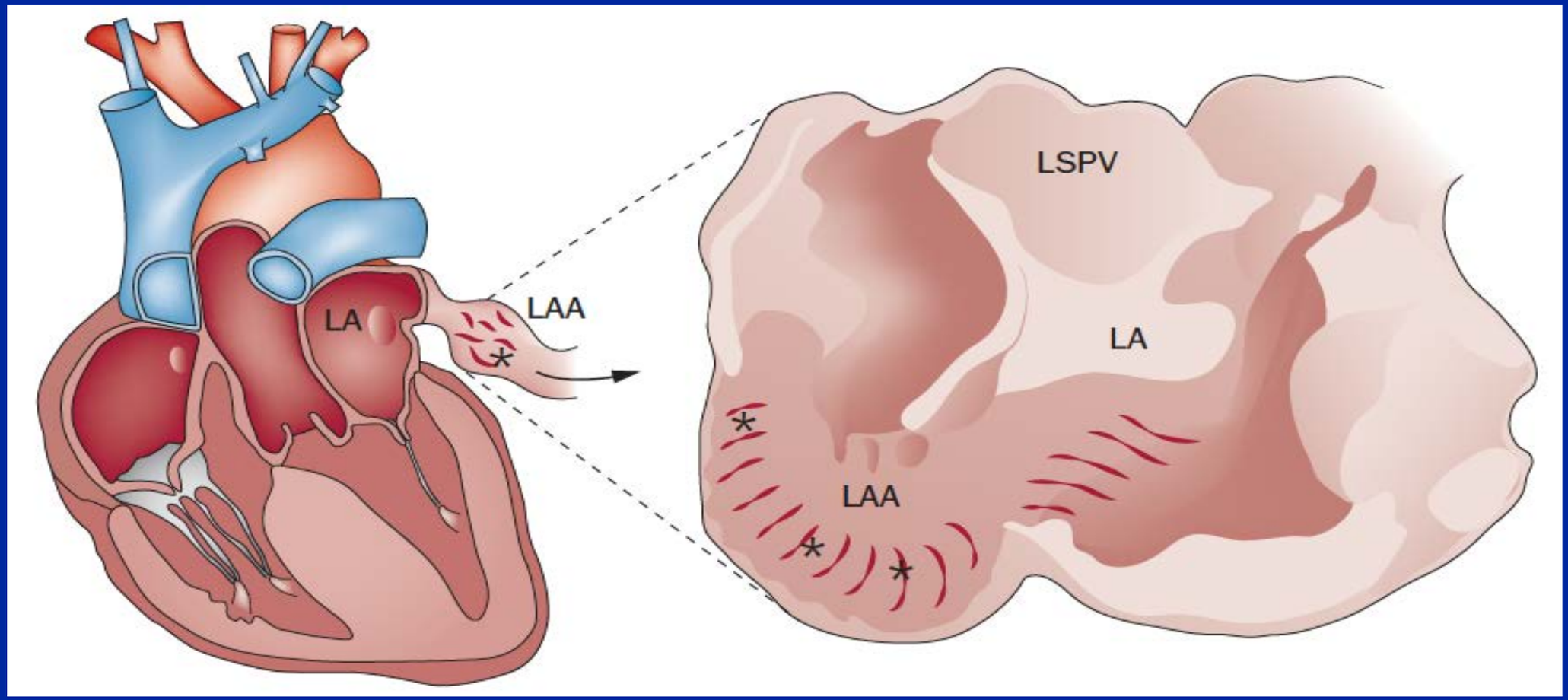
ORBIT=AF (BA Steinberg et al.), Circulation 2015; 131:488 – Exeptions Only

2a) Predictors of Stroke Risk Incorporated in the CHA_2DS_2-VASc Schemes - Atrial Cardiomyopathy



JB Guichard et. al. J Am Coll Cardiol 2017;70:756

LAA Structure / Function – Stroke in NSR
Cardiac Imaging For Assessment



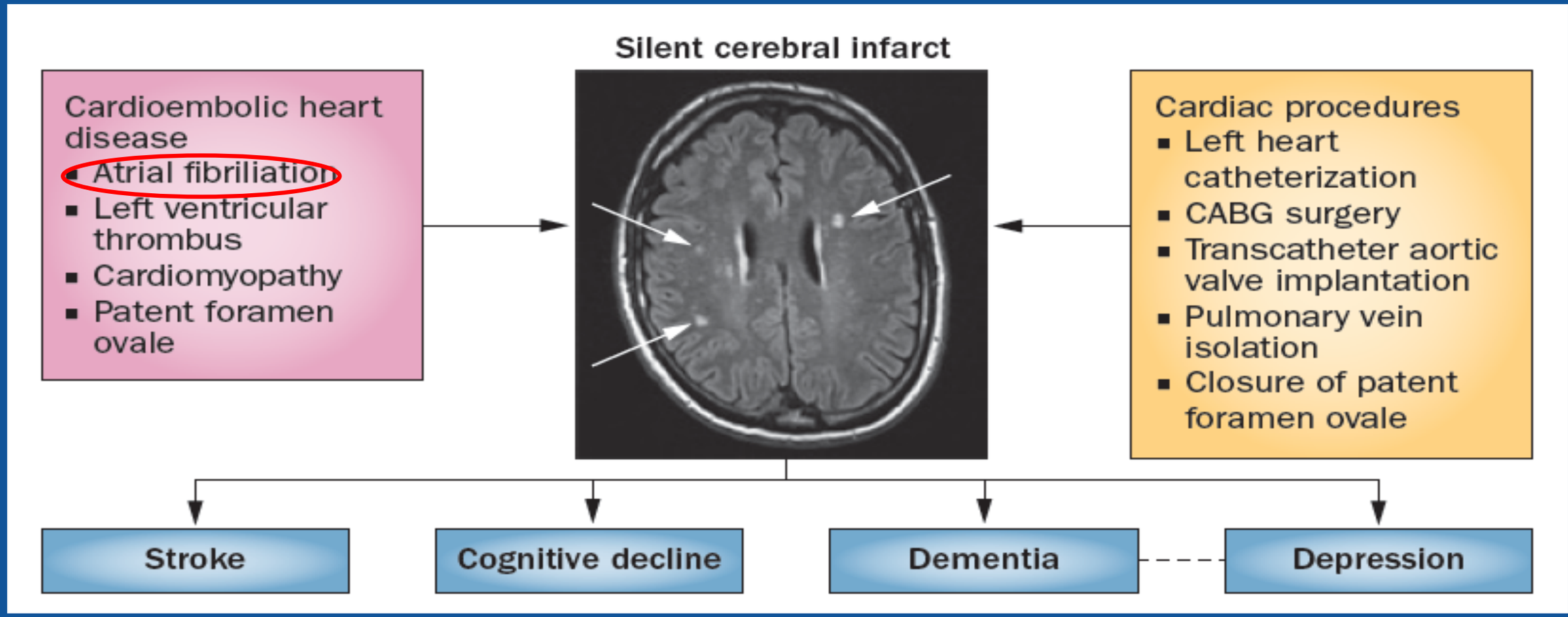
J Romero et. al. Nat Rev Cardiol. 2014;11:470

ENGAGE AF (DK Gupta et al.) EHJ 2014; 35:1457 – LA Function / NSR ?

ASSERT (M Brambatti, et al.) Circ. 2014; 129:2094- LV Function / NSR ?

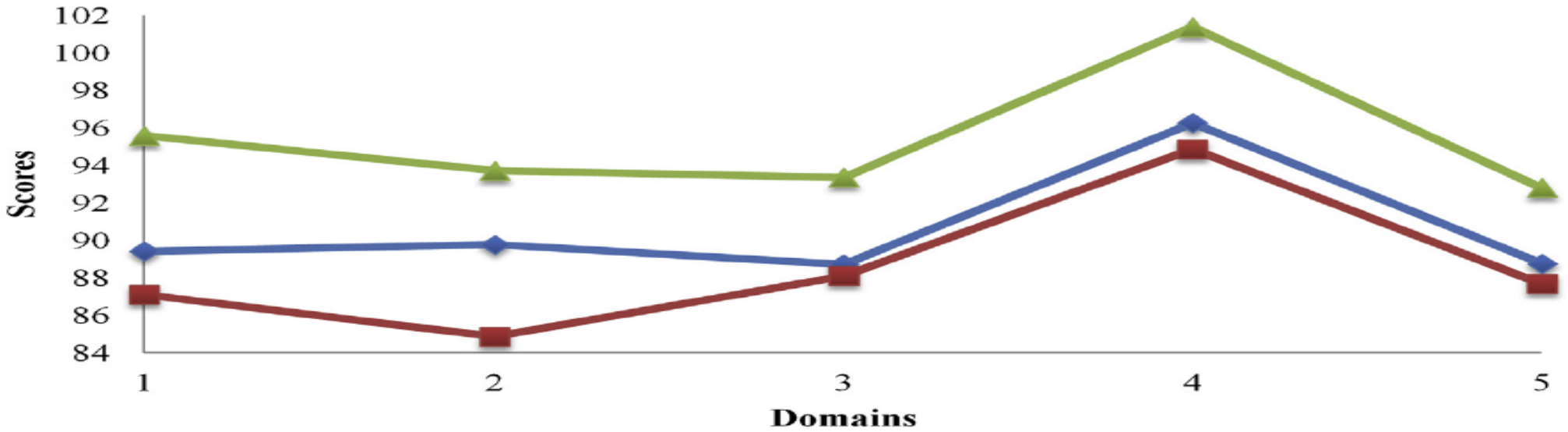
IMPACT (DT Martin et al.) EHJ; 2015; 36:1660- LV Function / NSR ?

2b). Silent Cerebral Infarcts (SCI)
Cardiac Disease And Procedures



ME Hassell et. al. Nat. Rev. Cardiol. 2013;10:696
F Gaita et. al. J Am Coll Cardiol 2013;62:1990 (Italy)
S Kalantarian et. al. Ann Intern Med. 2014;161:650 – *15 Studies, SCI*

Silent Cerebral Ischemia in AF
Correlation With Cognitive Function



	Controls (N = 90)	PRX AF (N = 90)	PER AF (N = 90)	p PRX / controls	p PER / controls	p PRX/ PER
Domains	92.4 ± 15.4	86.2 ± 13.8	82.9 ± 11.5	< 0.01	< 0.01	0.08
1-Immediate Memory	95.6 ± 17.5	89.9 ± 14.7	87.1 ± 16.9	0.02	< 0.01	0.24
2-Visuo-spatial abilities	93.8 ± 16.7	89.9 ± 18.2	84.8 ± 14.8	0.14	< 0.01	0.04
3-Language	92.9 ± 11.4	88.8 ± 9.1	88.1 ± 8.7	< 0.01	< 0.01	0.59
4-Attention	101.4 ± 21.2	96.6 ± 16.6	94.9 ± 15.6	0.09	0.02	0.47
5-Delayed memory	93.5 ± 11.7	88.7 ± 14.7	87.7 ± 14	0.02	< 0.01	0.64

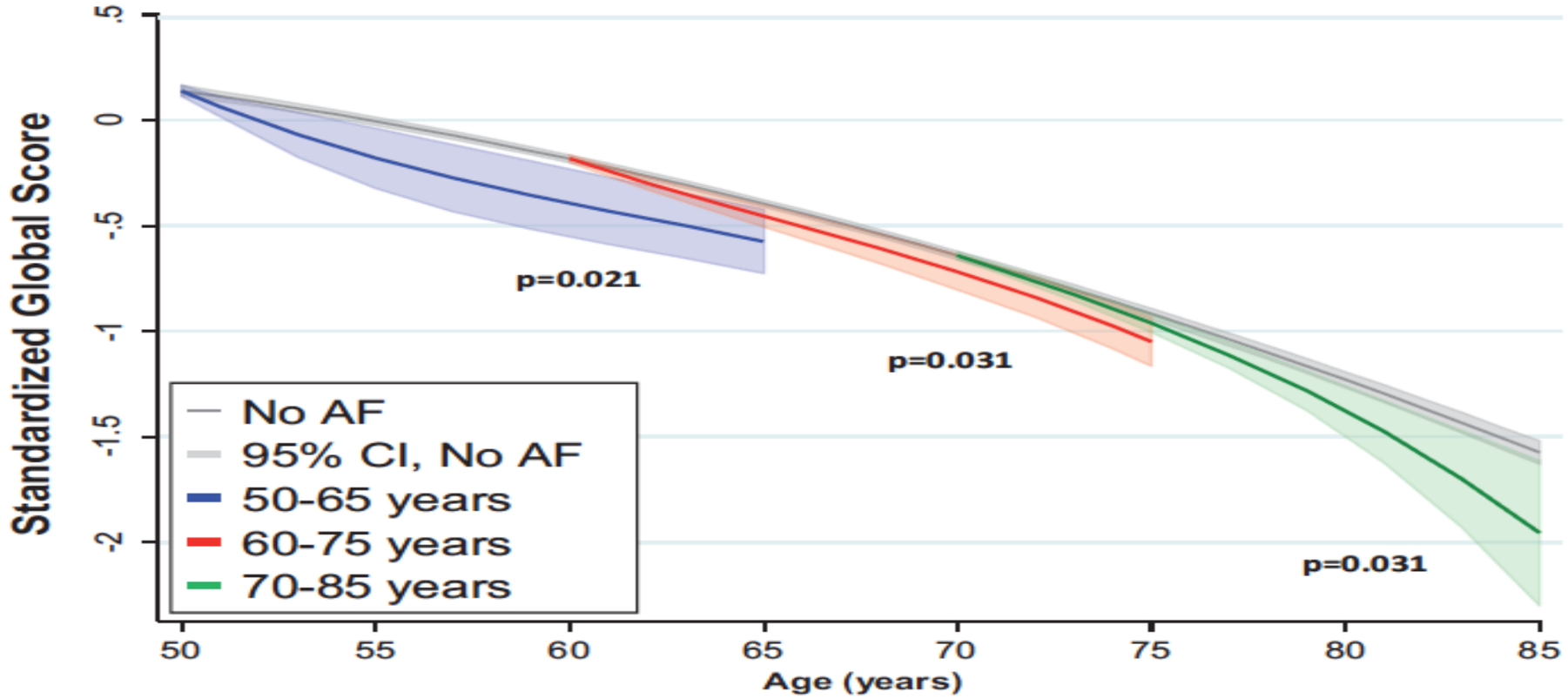
F Gaita et. al. J Am Coll Cardiol 2013;62:1990 (Italy)
S Kalantarian et. al. Ann Intern Med. 2014;161:650 *– 15 Studies, SCI*

Atrial Fibrillation as a Risk Factor for Cognitive Decline and Dementia

Data are drawn from the Whitehall II study, *N*=10,308 at study recruitment in 1985. A battery of cognitive tests was administered four time (1997-2013) to 7428 participants -414 cases of AF-, aged 45-69 years in 1997. Compared with AF-free participants, those with longer exposure to AF (5, 10, or 15 years) experienced faster cognitive decline after adjustment for sociodemographic, behavioural, and chronic diseases (*P* for trend=0.01). Stroke did not explain it. In adults aged 45-85 years AF is associated with accelerated cognitive decline and higher risk of dementia

A Singh-Manoux et al., European Heart Journal 2017; 38:2612

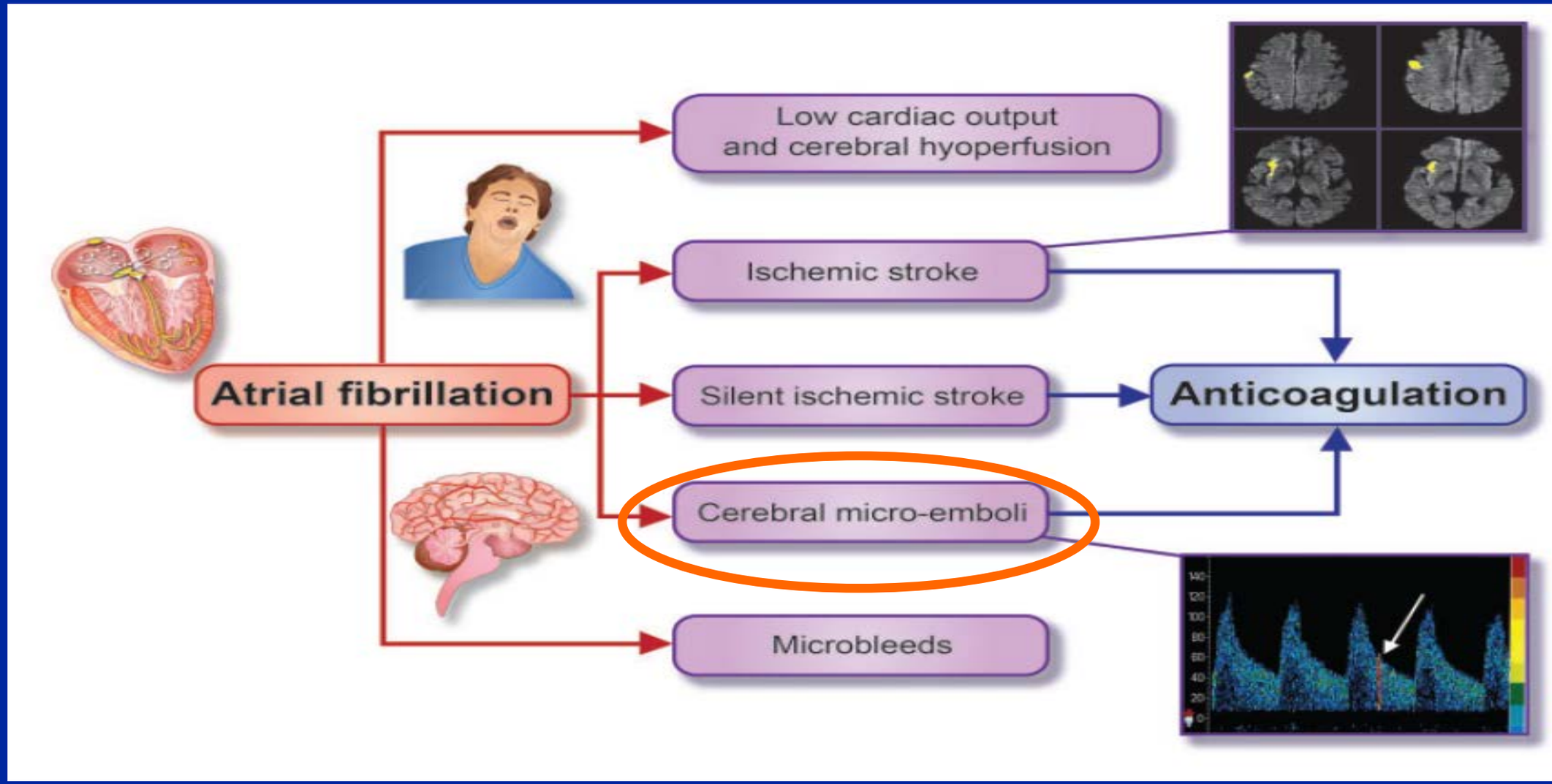
Decline In The Global Cognitive Score Function of AF



N observations	<=55 years	55-60 years	60-65 years	65-70 years	70-75 years	75-80 years	80-85 years
No AF	4084	4257	5467	4197	2443	1123	165
AF	17	58	127	162	181	134	36

A Singh-Manoux et. al. Eur Heart J. 2017;38:2612

Mechanisms Of AF Leading To Cognitive Decline Or Dementia



HC Diener et. al. Eur Heart J. 2017;38:2619

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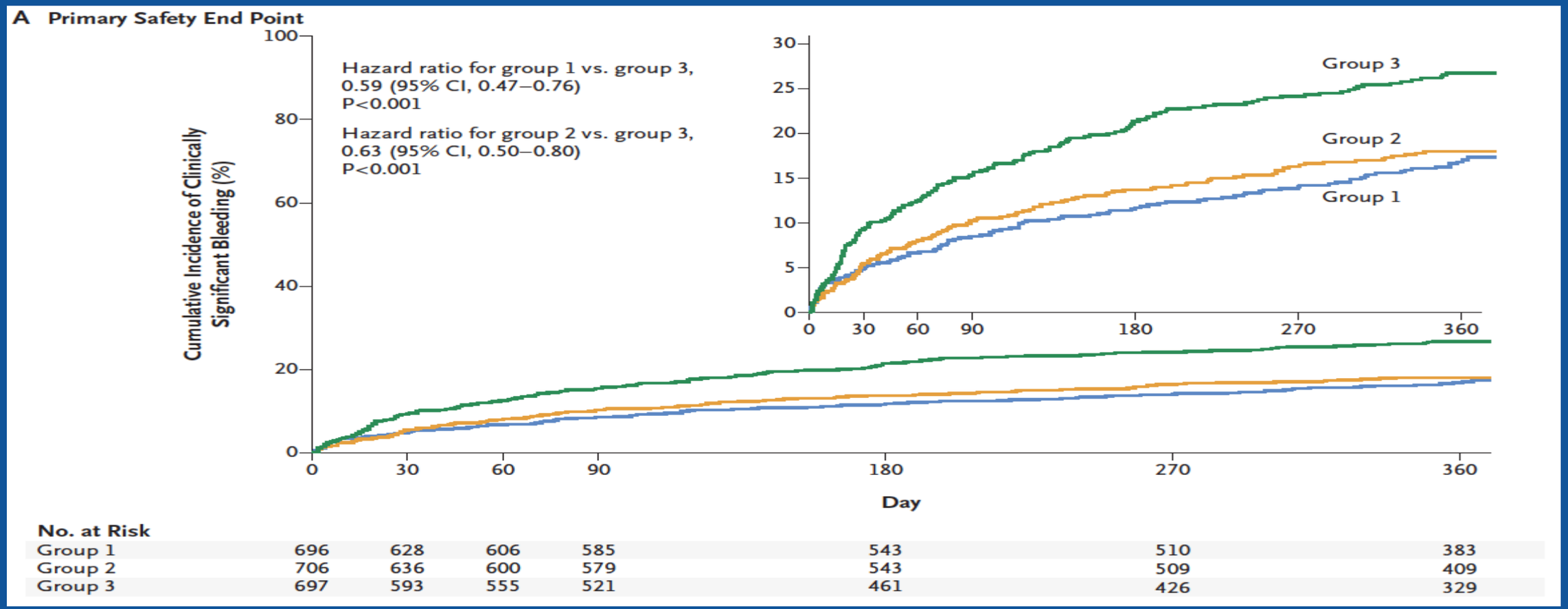
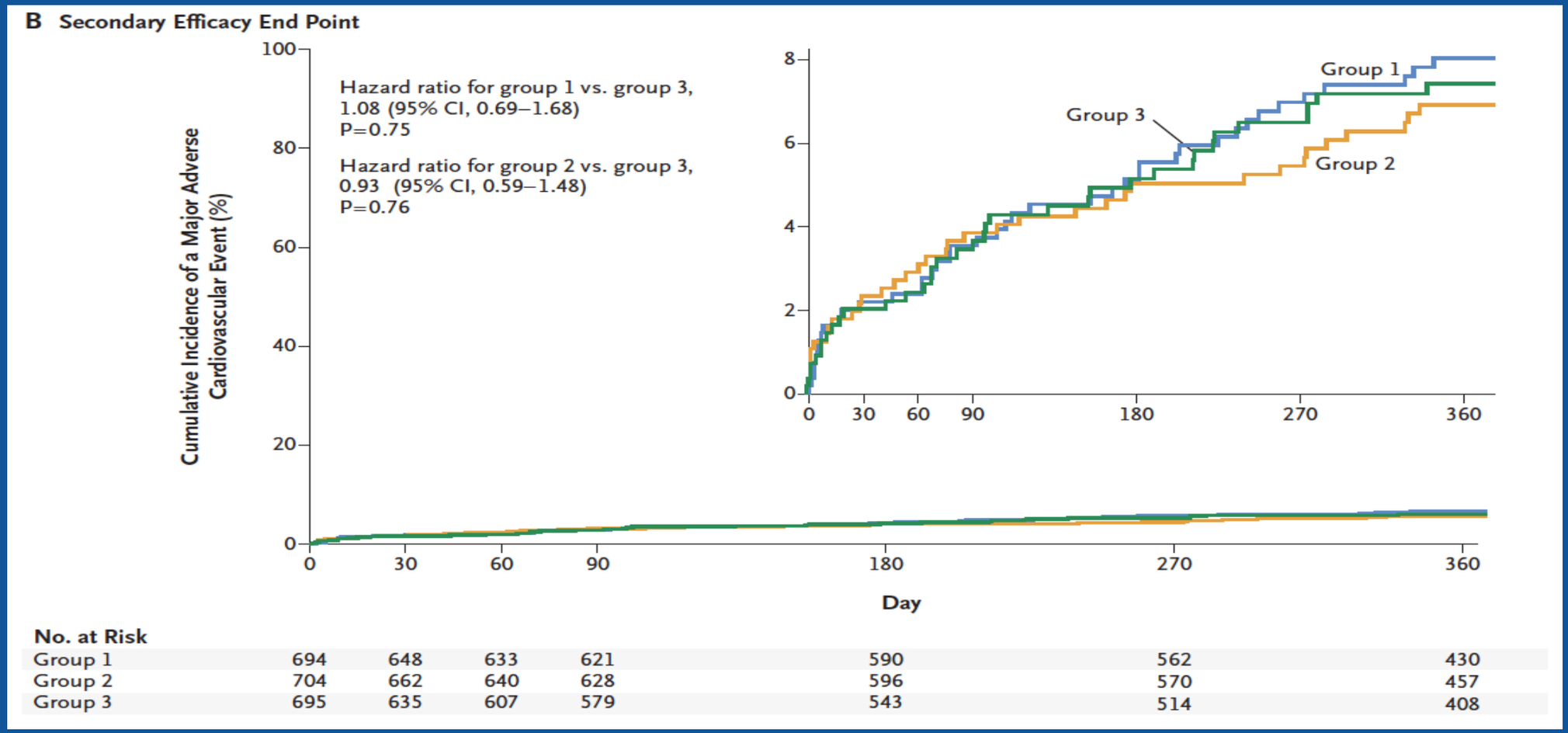
1,2). Preventing Bleeding in Pts with AF-PCI



Group 3 - D-adjusted vitamin K antagonist plus DAPT for 1, 6, or 12 months.
Group 2 - VLD rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, 12 Mo
Group 1 - LD rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 Mo

PIONEER AF-PCI (CM Gibson et. al.) NEJM 2016;375:2423

1,2) CV Events in Pts with AF-PCI



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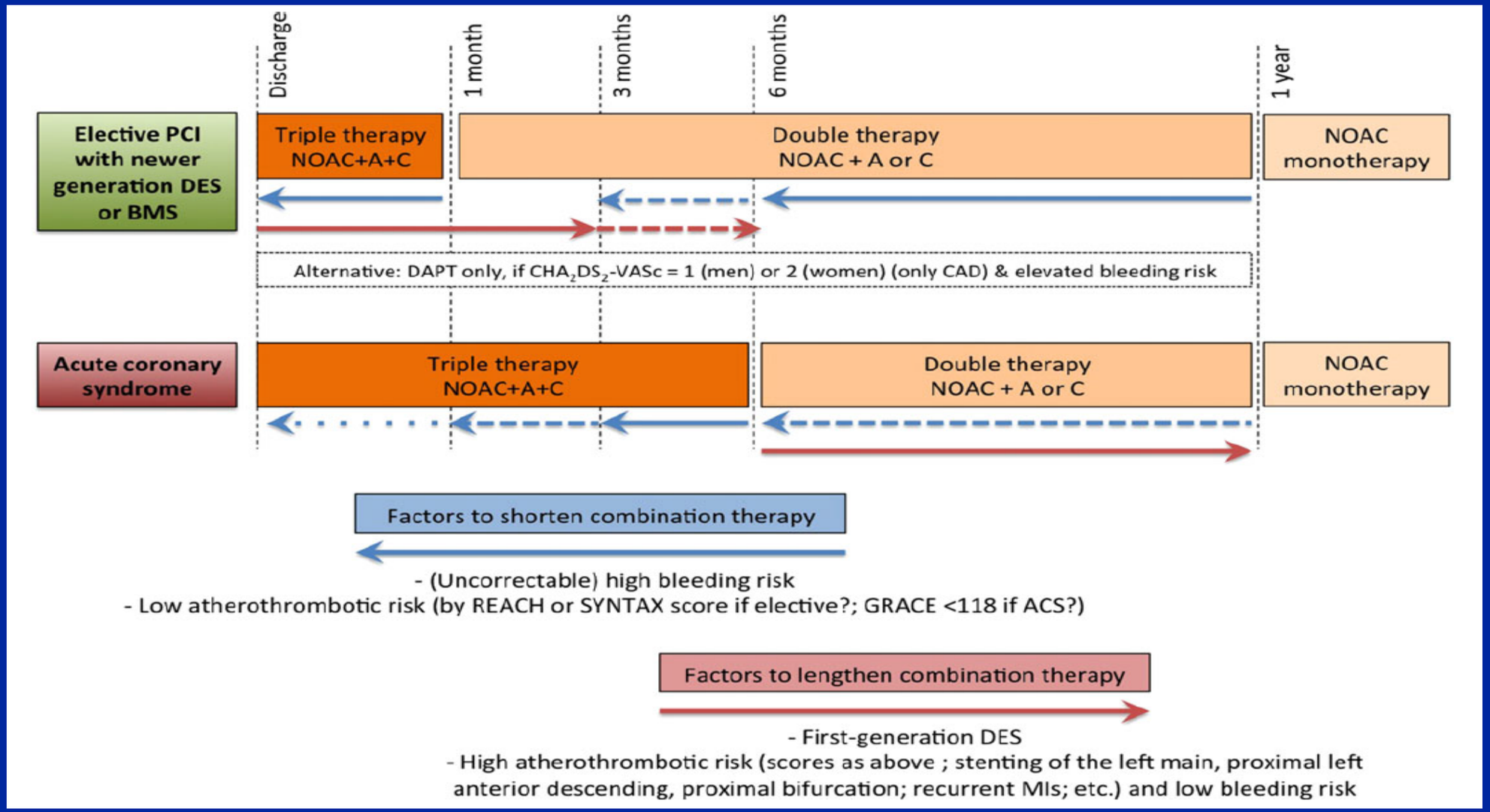
PIONEER AF-PCI (CM Gibson et. al.) NEJM 2016;375:2423

Long-term Treatment Of Patients On NOAC Therapy After Revascularization – Elective or ACS



H Heidbuchel et. al. Eur Heart J. 2017;38:2137

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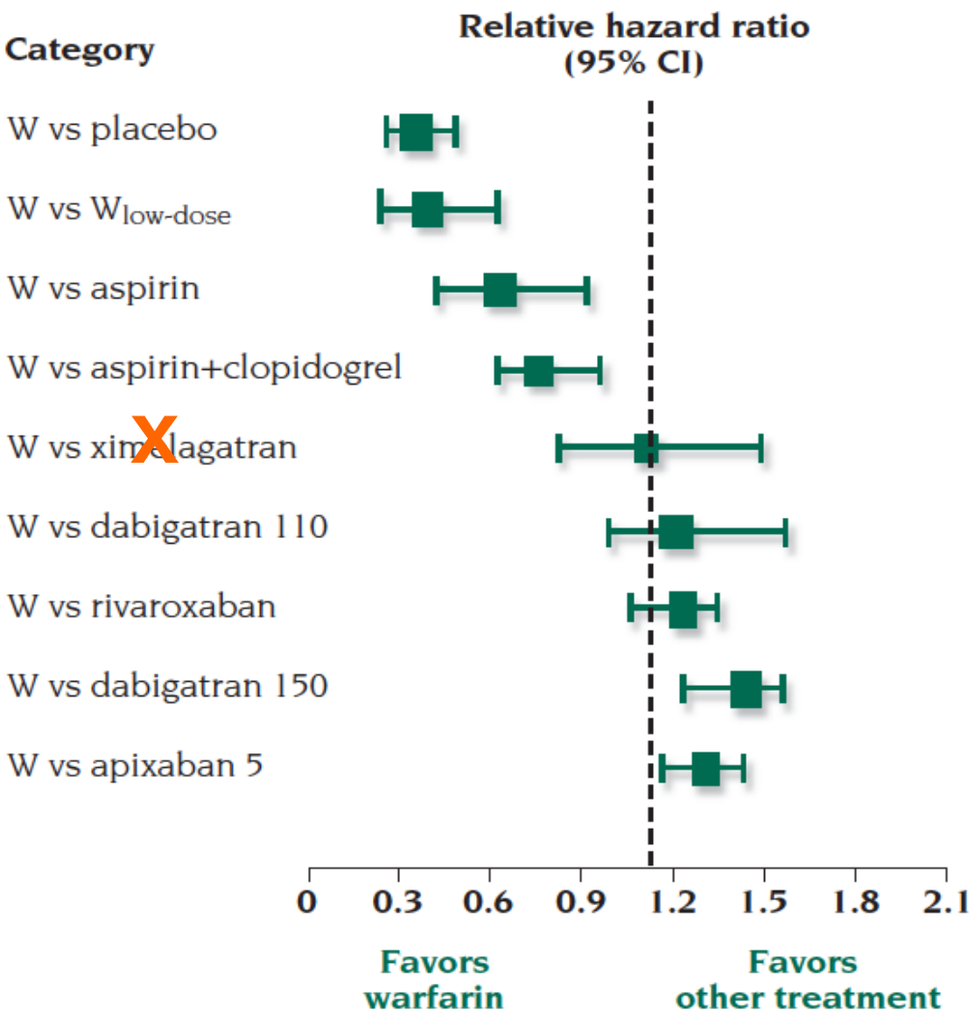
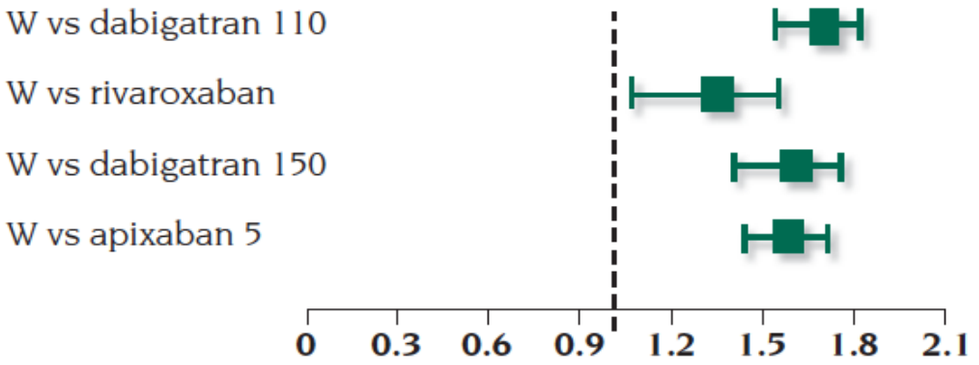
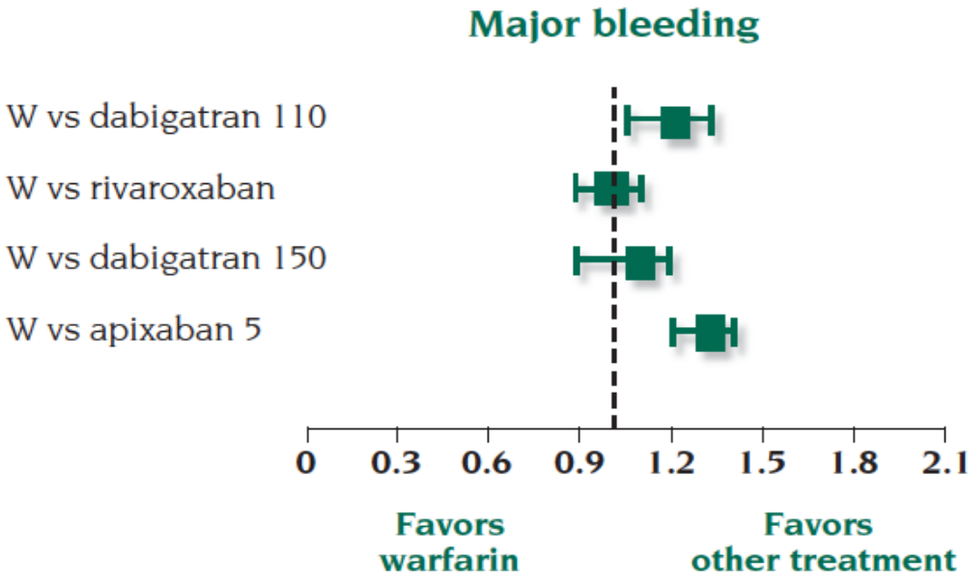
1,2). New Oral Anticoagulants - Efficacy & Safety







Dialogues in Cardiovascular Medicine 2012;17:189

1a). VHD Patients on Edoxaban or Warfarin in the ENGAGE AF-TIMI 48 Trial

VHD was defined as history or baseline echo evidence of at least moderate aortic/mitral regurgitation, aortic stenosis, or prior valve surgery -bioprosthesis replacement, valve repair, valvuloplasty. Patients with moderate to severe mitral stenosis or mechanical heart valves were excluded from the trial. Comparisons were made of rates of stroke/systemic embolic event (SSEE) & major bleeding. VHD increased the risk of death, major adverse CV events, and major bleeding but did not affect the relative efficacy or safety of higher-dose edoxaban versus warfarin in AF.

R De Caterina et al., J Am Coll Cardiol 2017; 69:1372

CT January et. al. J. Am. Coll. Card. 2014; 64: e1 – No Dabigatran in Mechanical HV

2a). Characteristics of Warfarin & NOAC Agents

	Warfarin	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Renal clearance of parent drug	<1%	27%	36%	80%	50%
Lowest CrCl drug can be prescribed per FDA label, ml/min	Can be used on dialysis	<15*	15	15	15
HR (95% CI) of stroke referent to warfarin, CrCl <50 ml/min	Reference	0.79 (0.55-1.14)	0.88 (0.65-1.19)	0.56 (0.37-0.85)	0.87 (0.65-1.18)†
HR (95% CI) of major bleeding referent to warfarin, CrCl <50 ml/min	Reference	0.50 (0.38-0.66)	0.98 (0.84-1.14)	1.01 (0.79-1.30)	0.76 (0.58-0.98)†

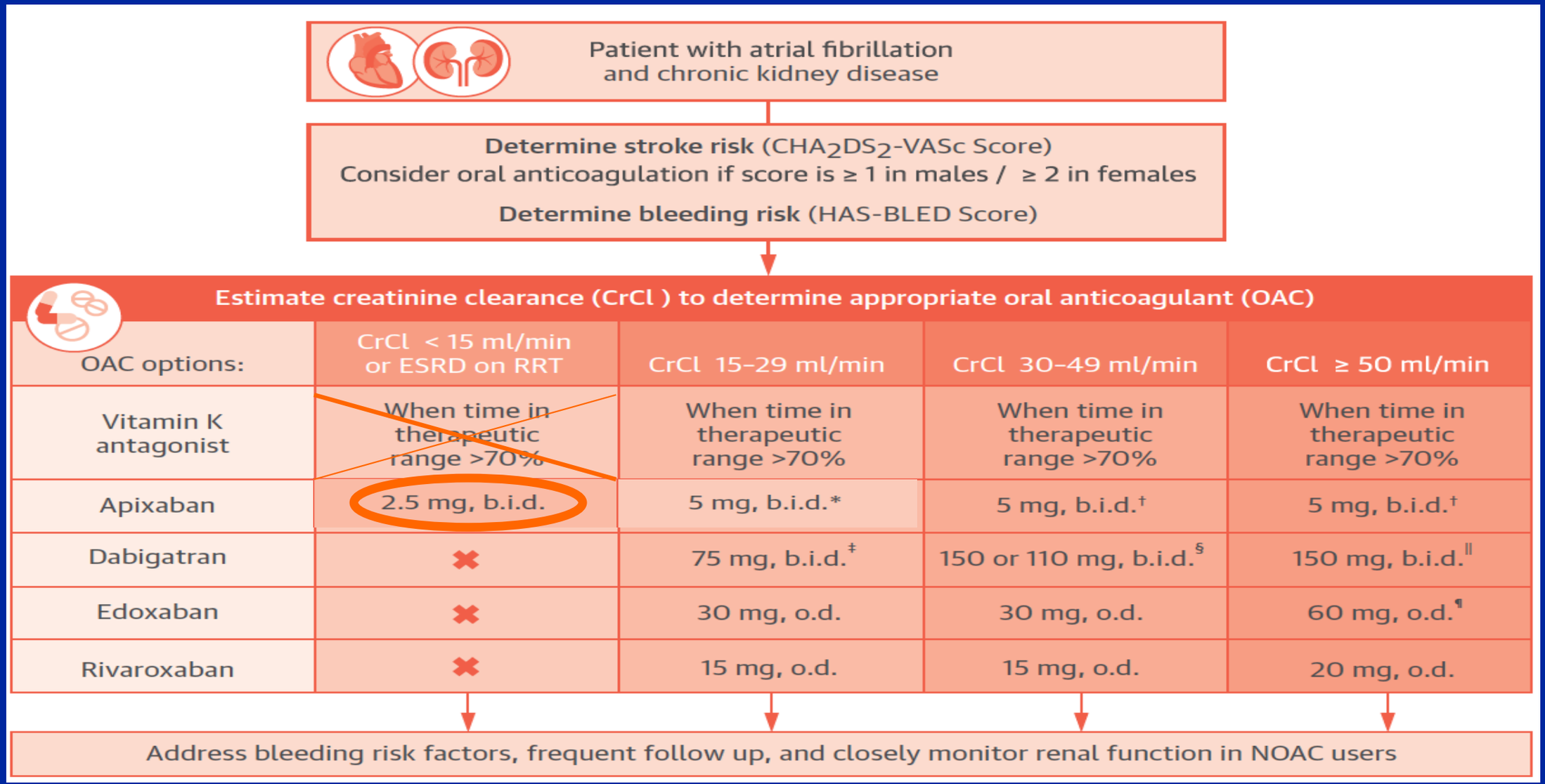
KE Chan et. al. J Am Coll Cardiol 2016;67:2888

Doses Of The Different NOACs In The 4 Large Trials In AF Patients

NOAC	Dose
Dabigatran (RELY)	150 mg twice daily 110 mg twice daily
Rivaroxaban (ROCKAT-AF)	20 mg once daily, protocol-mandated dose reduction to15 mg
Apixaban (ARISTOTLE)	5 mg twice daily, protocol-mandated dose reduction to 2.5 mg
Edoxaban (ENGAGE-AF)	60 mg once daily, protocol-mandated dose reduction to 30 mg 30 mg once daily, protocol-mandated dose reduction to15 mg

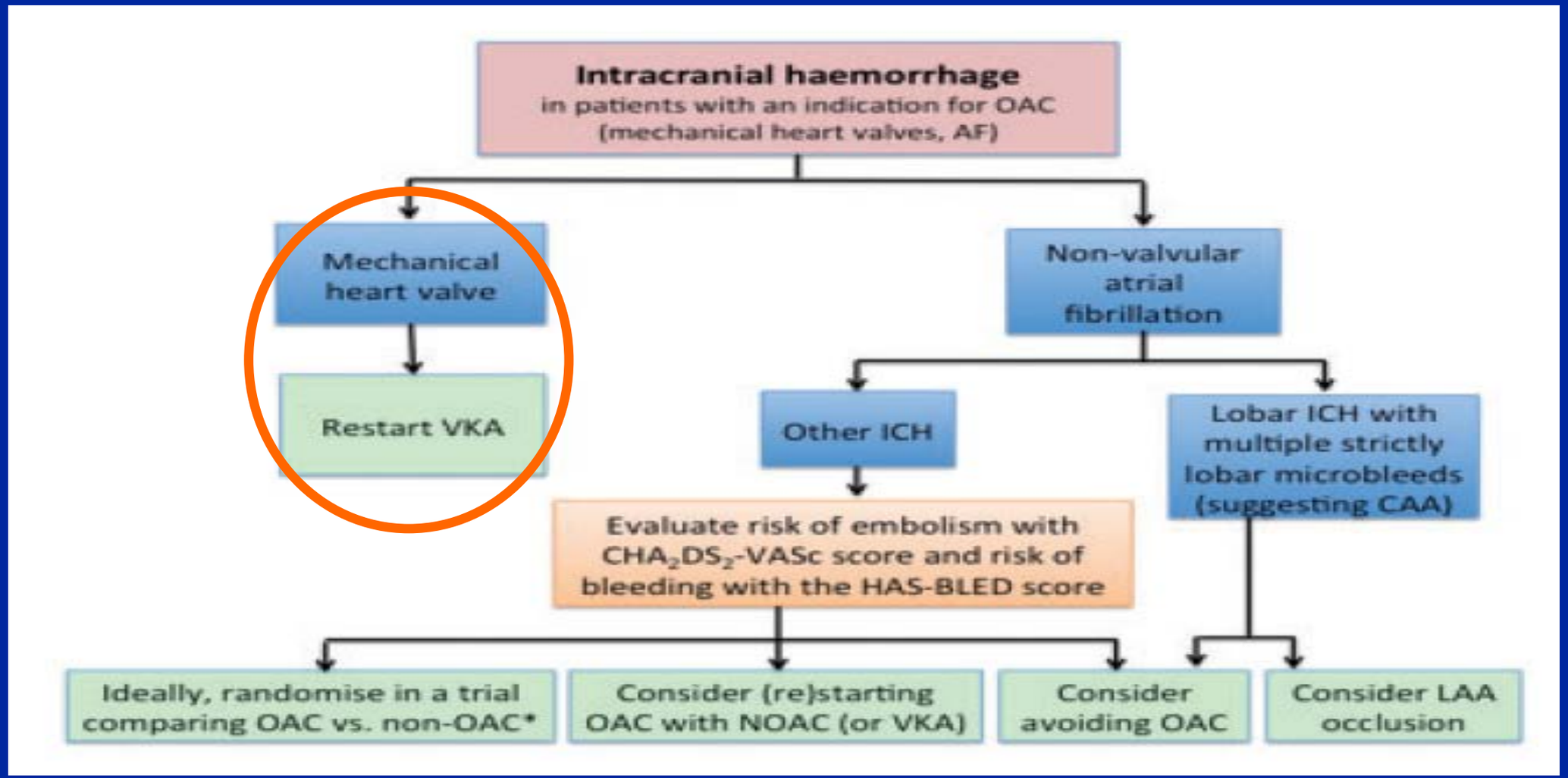
HC Diener et. al. Eur Heart J. 2017;38:860

Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and Chronic Kidney Disease



YC Lau et. al. J Am Coll Cardiol 2016;68:1452 - HIT.....(?)

2b). Initiation Or Re-initiation of Oral A/C After Intracranial Haemorrhage



***ESC Working Group on Thrombosis** (S Halvorsen et. al.) Eur Heart J. 2017;38:1455*

*H-C Diener et al. Eur Heart J 2017; 38: 860 – **Bleeding GI Tract: In 1 Week NOAC or AC***

2c). Idarucizumab & Other Reversal Agents

When available, idarucizumab is likely to be the treatment of choice for patients who present with diabigatran-induced uncontrolled or life-threatening bleeding or for those who require urgent surgery or invasive procedures. Other reversal agents are in development to reverse other NOACs. These include andexanet alfa, a recombinant truncated form of enzymatically inactive factor Xa, which binds and reverses the anticoagulant action of the factor Xa inhibitors, and PER977 (ciraparantag), a synthetic small molecule that is reported to bind to all of the NOACs.

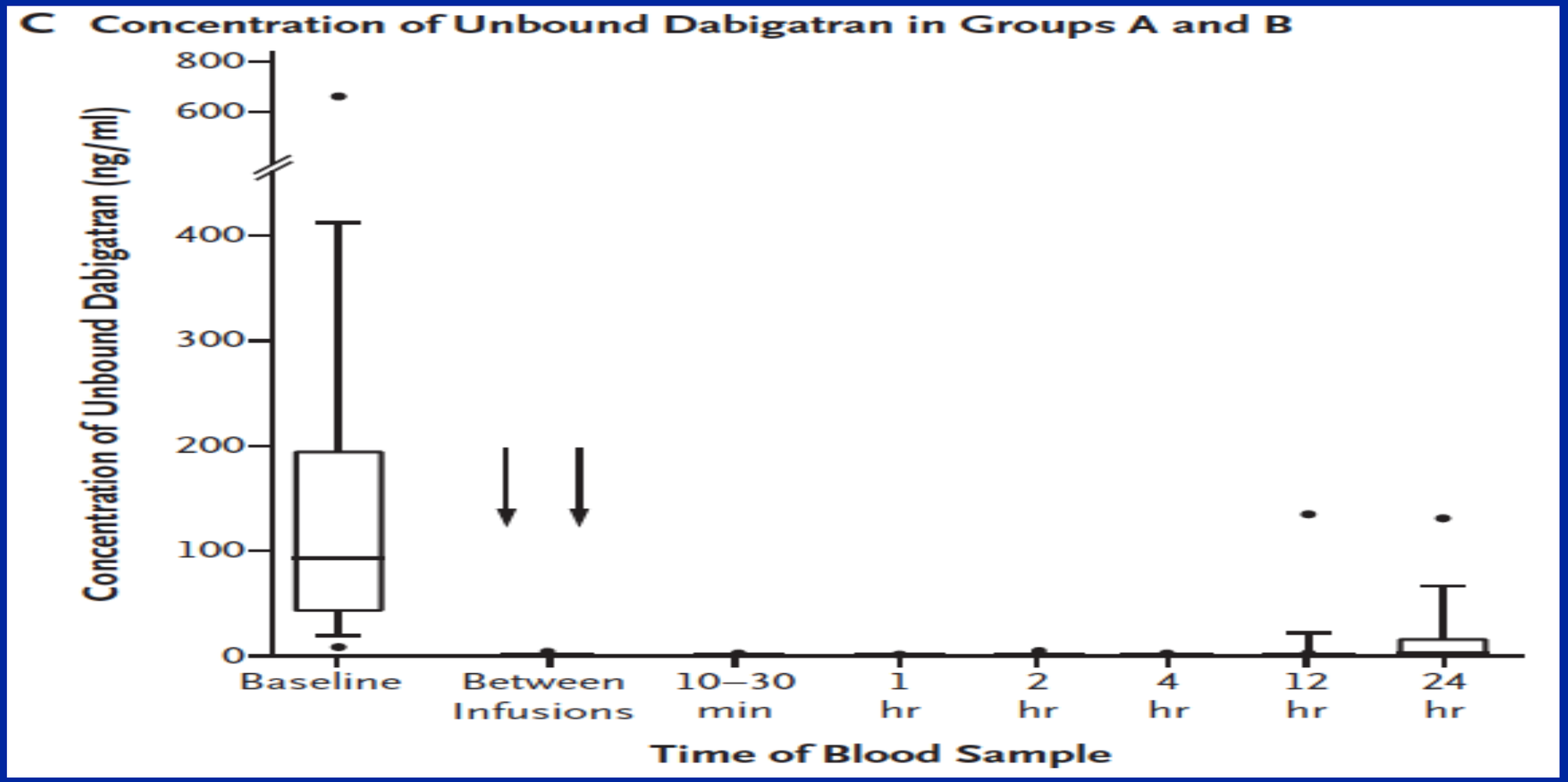
JW Eikelboon et al., Circ 2015; 132:2412 – ESC Rome, 2016 Sept

Idarucizumab for Dabigatran Reversal Full Cohort Analysis

We performed a multicenter, prospective, open-label study to determine whether 5 g of intravenous idarucizumab would be able to reverse the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding (group A) or were about to undergo an urgent procedure (group B). A total of 503 patients were enrolled: 301 in group A, and 202 in group B. The median maximum percentage reversal of dabigatran was 100%. In emergency situations, idarucizumab rapidly, durably, and safely reversed the AC effect of dabigatran.

CV Pollack et al., N Engl J Med 2017; 377:431

Key Measurements Before And After The Administration of Idarucizumab



CV Pollack et. al. N Engl J Med 2017;377:431

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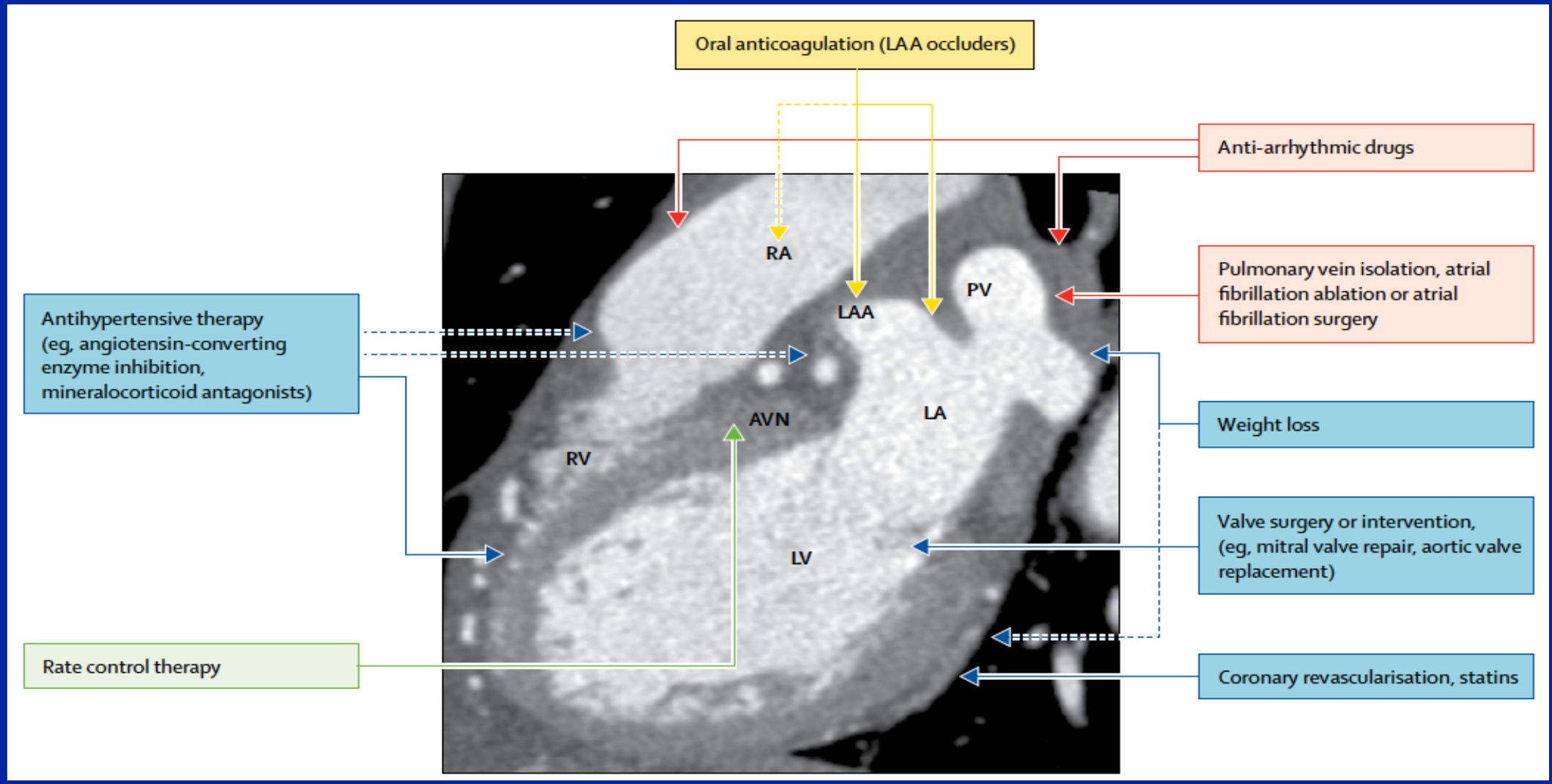
Main Cardiac Targets of The Different Domains Of AF Management



P Kirchhof. Lancet 2017;390:1873

Temperature-Controlled Radiofrequency Ablation for Pulmonary Vein Isolation in Patients With Atrial Fibrillation

Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation

BELIEF Trial

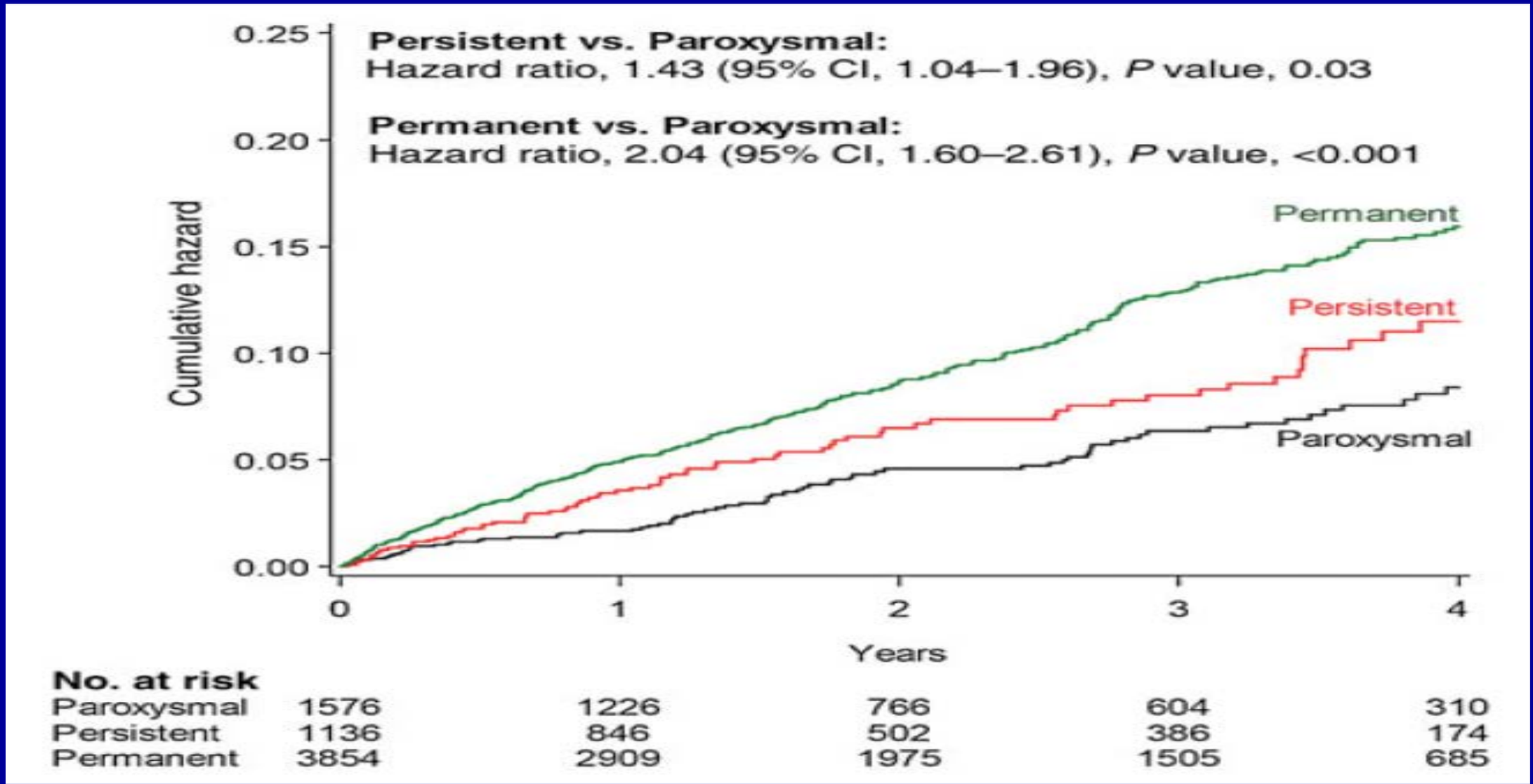
Clinical Benefit of Ablating Localized Sources for Human Atrial Fibrillation

The Indiana University FIRM Registry

Complexity and Distribution of Drivers in Relation to Duration of Persistent Atrial Fibrillation

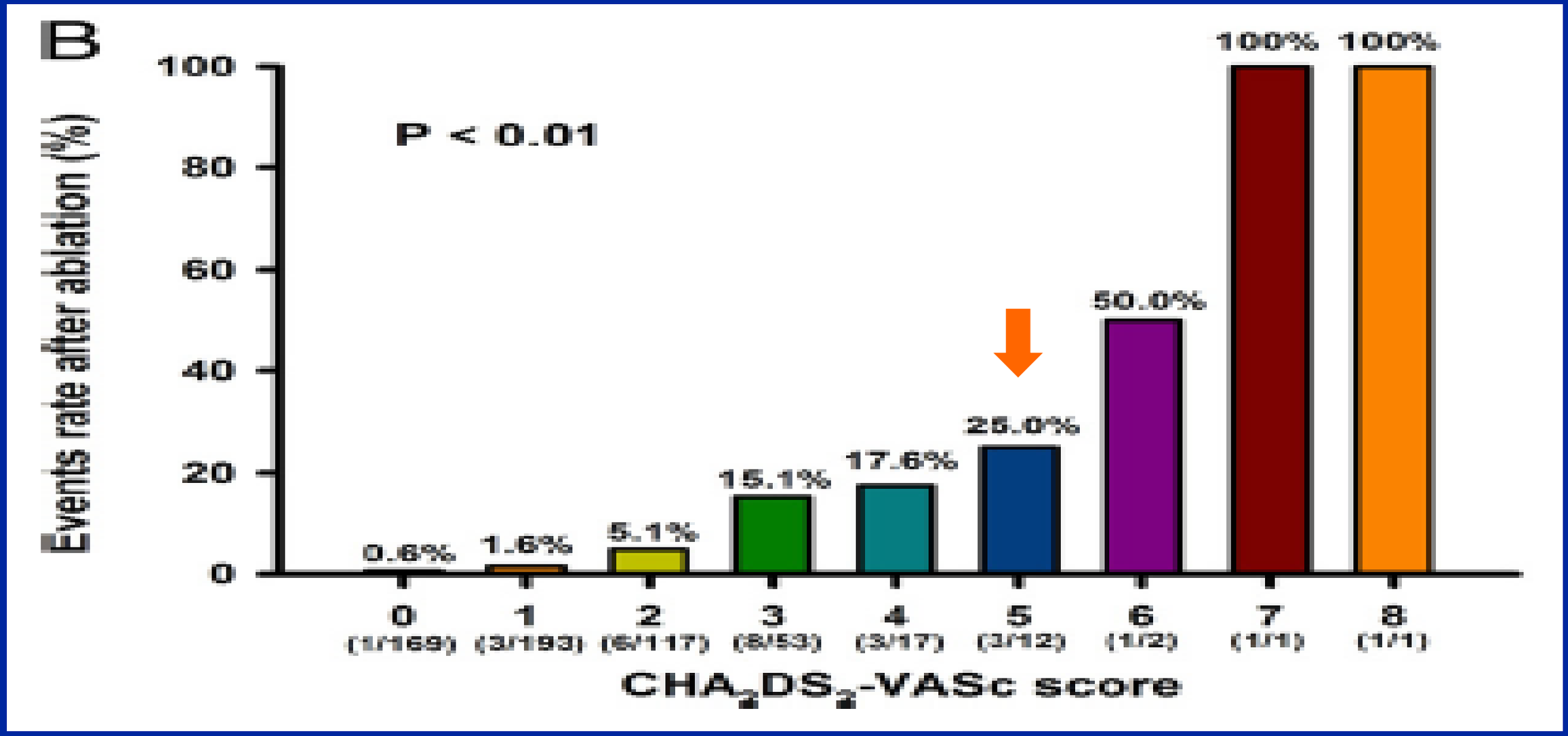
J Am Coll Cardiol 2017;70:542, J Am Coll Cardiol 2016;68:1929, J Am Coll Cardiol 2017;69:1247, J Am Coll Cardiol 2017;69:1257

1a). Cumulative Hazard Rates Of Embolic Events According To The Pattern Of AF Occurrence



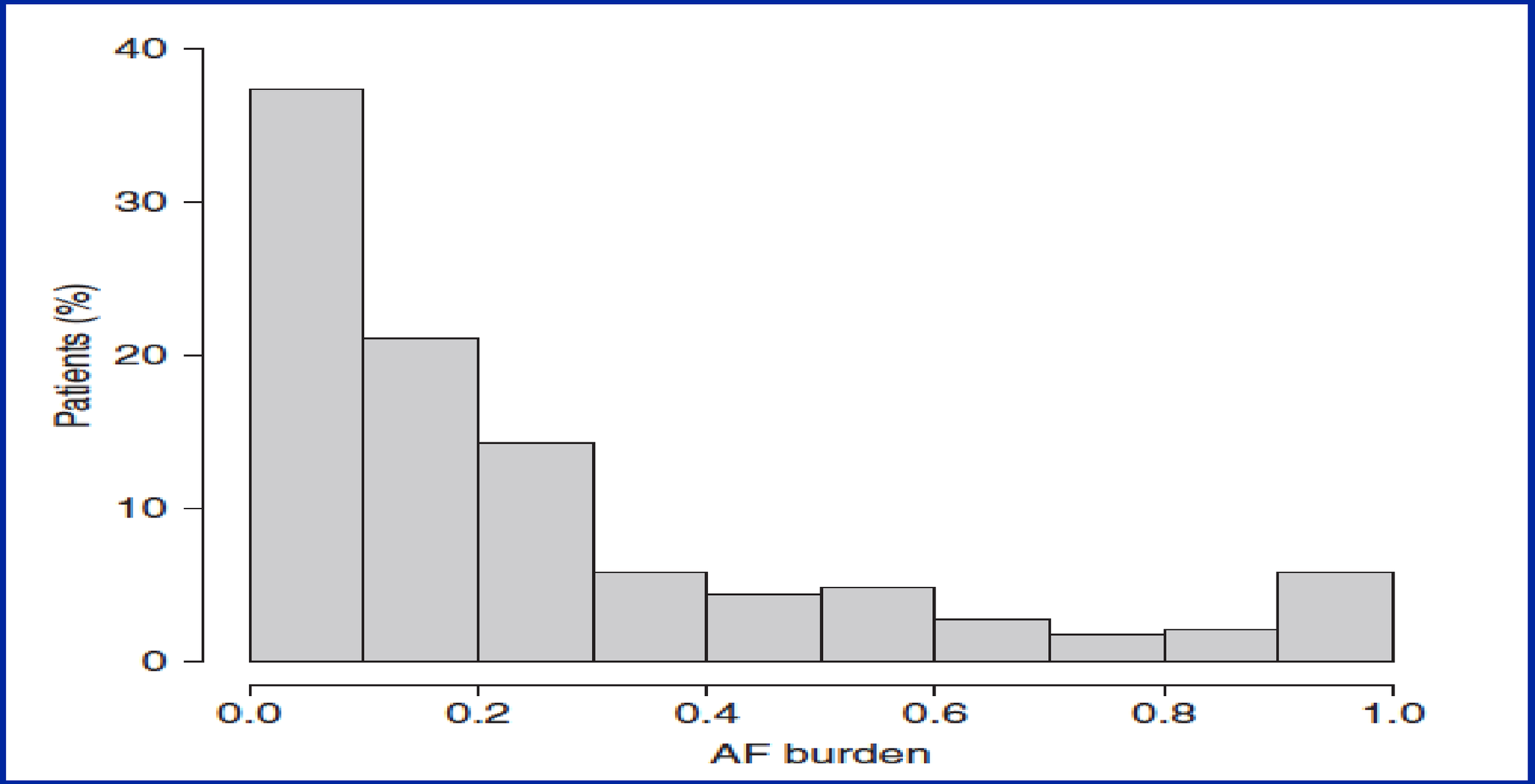
T Vanassche, SJ Connolly et. al. Eur Heart J. 2015;36:281

1b). CHA_2DS_2-VASc (Recurrent AF) in Predicting Clinical Outcomes in AF After Catheter Ablation



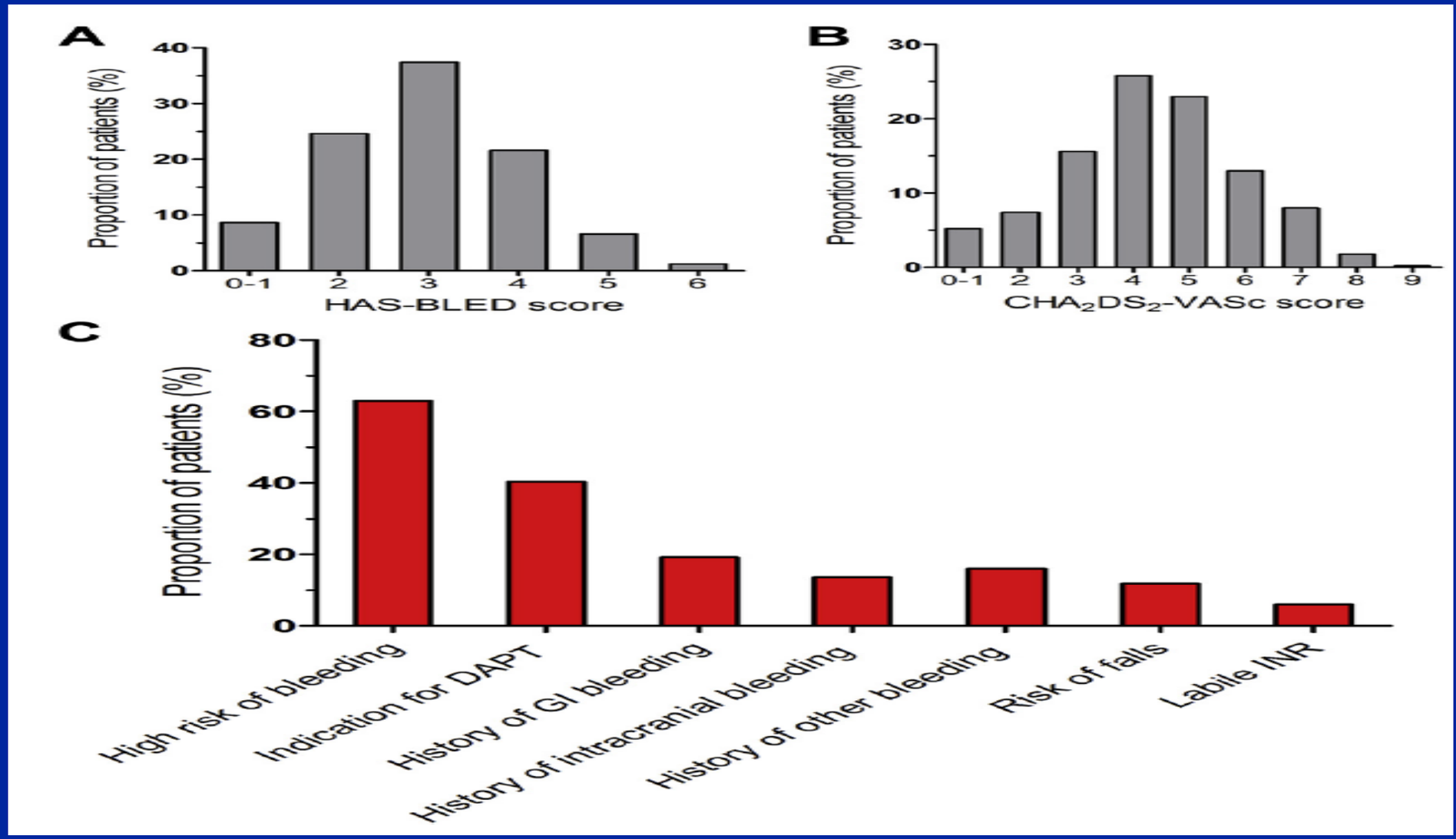
T-F Chao et al., JACC 2011; 58:2380 (Japan) – 565 Pts

1c). AF Burden - After Catheter Ablation
Several Strategies (Linq Recorder etc)



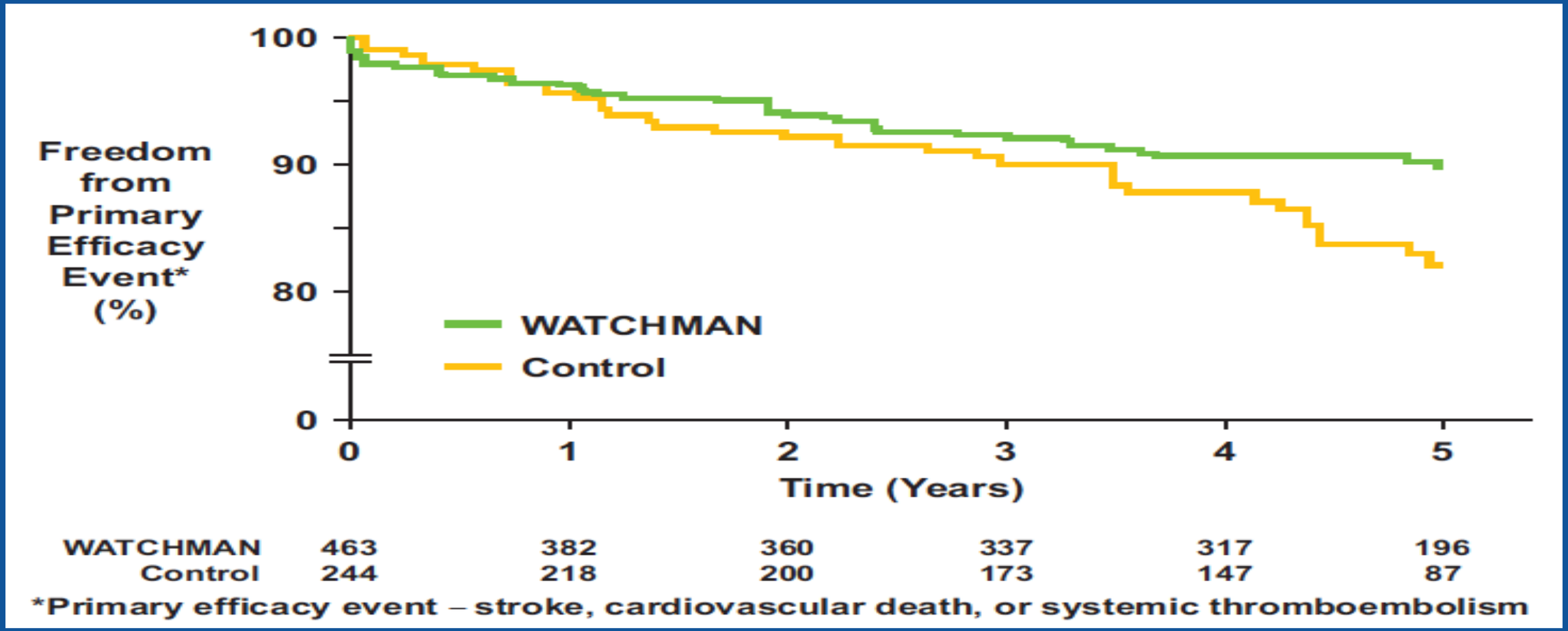
El Charitos et. al. Circulation. 2012;126:806 (Luebeck, Germ.)

2a) Bleeding Risk, Ischemic Stroke Risk, Indications for Left Atrial Appendage Closure



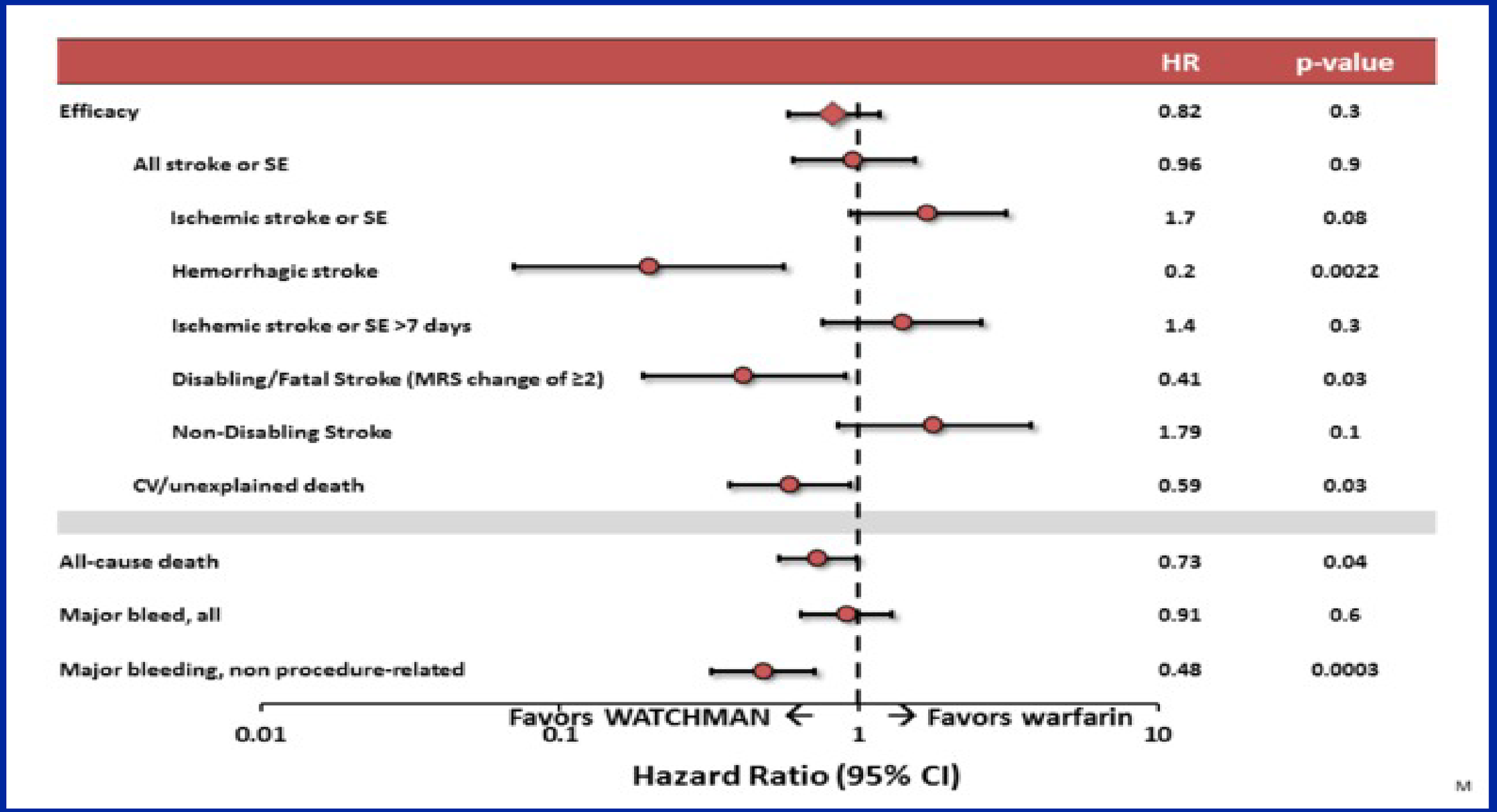
KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374

2b). Primary Efficacy Outcome of Watchman LAA Closure For Embolic Protection In AF PROTECT AF Over 60 Months



PROTECT AF - VY Reddy et. al. JAMA. **2014**;312(19):1988
- RP Whitlock et. al. Circulation. **2015**;131:756

2c). Stroke Prevention in AF With LAA Closure

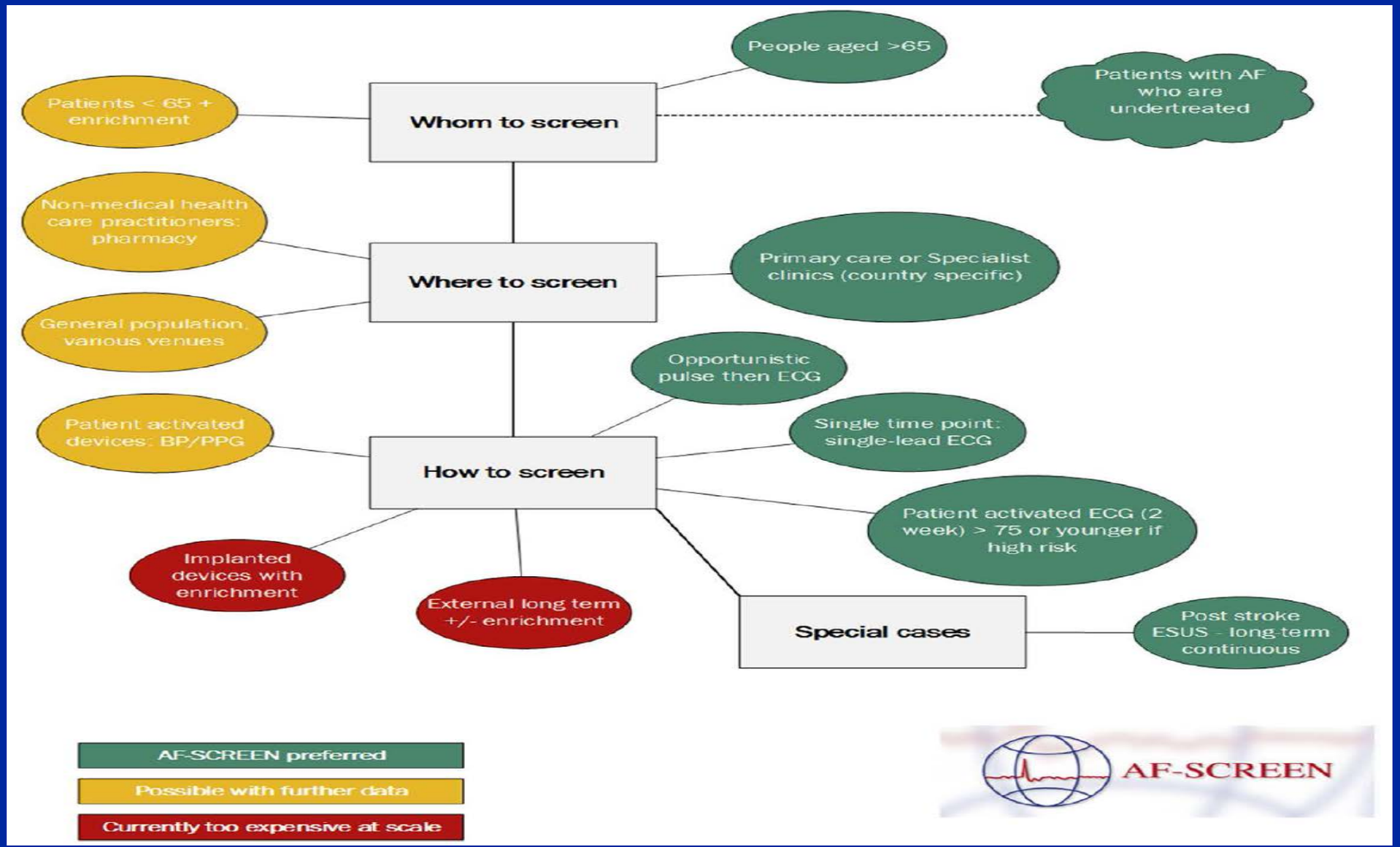


PREVAIL and PROTECT AF (VY Reddy et. al.) J Am Coll Cardiol 2017;70:2964

AF - CLINICAL CHALLENGES (14) – 2017 - 2018

1. Presentation:	Simplified	vs Prioritized	(2)
2. Etiology:	Myocardial	vs Electrical	(2)
3. AC Rx:	When / Bridge	vs TE-NSR / SCI	(2)
4. AF / Stent:	Triple Rx	vs Double Rx	(2)
5. Warf. / NOACs:	Efficacy	vs Safety	(2)
6. Not Indicated ?	AC	vs LAA Closure	(2)
7. Screening	Screening	vs No Screening	(2)

Screening for Atrial Fibrillation



B Freedman et. al. Circulation. 2017;135:1851

AF - CLINICAL CHALLENGES (14) – 2017 - 2018

1. Presentation:	Simplified	vs Prioritized	(2)
2. Etiology:	Myocardial	vs Electrical	(2)
3. AC Rx:	When / Bridge	vs TE-NSR / SCI	(2)
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7. Screening	Screening	vs No Screening	(2)

Atrial Fibrillation 2017 - 2018

Quality of Life and Preventing Stroke

The 14 Clinical Challenges

ACC New York, Dec 9, 2017

No Disclosures