Atrial Fibrillation 2016
Quality of Life and Preventing Stroke

The 14 Clinical Challenges

New York, Dec10, 2016

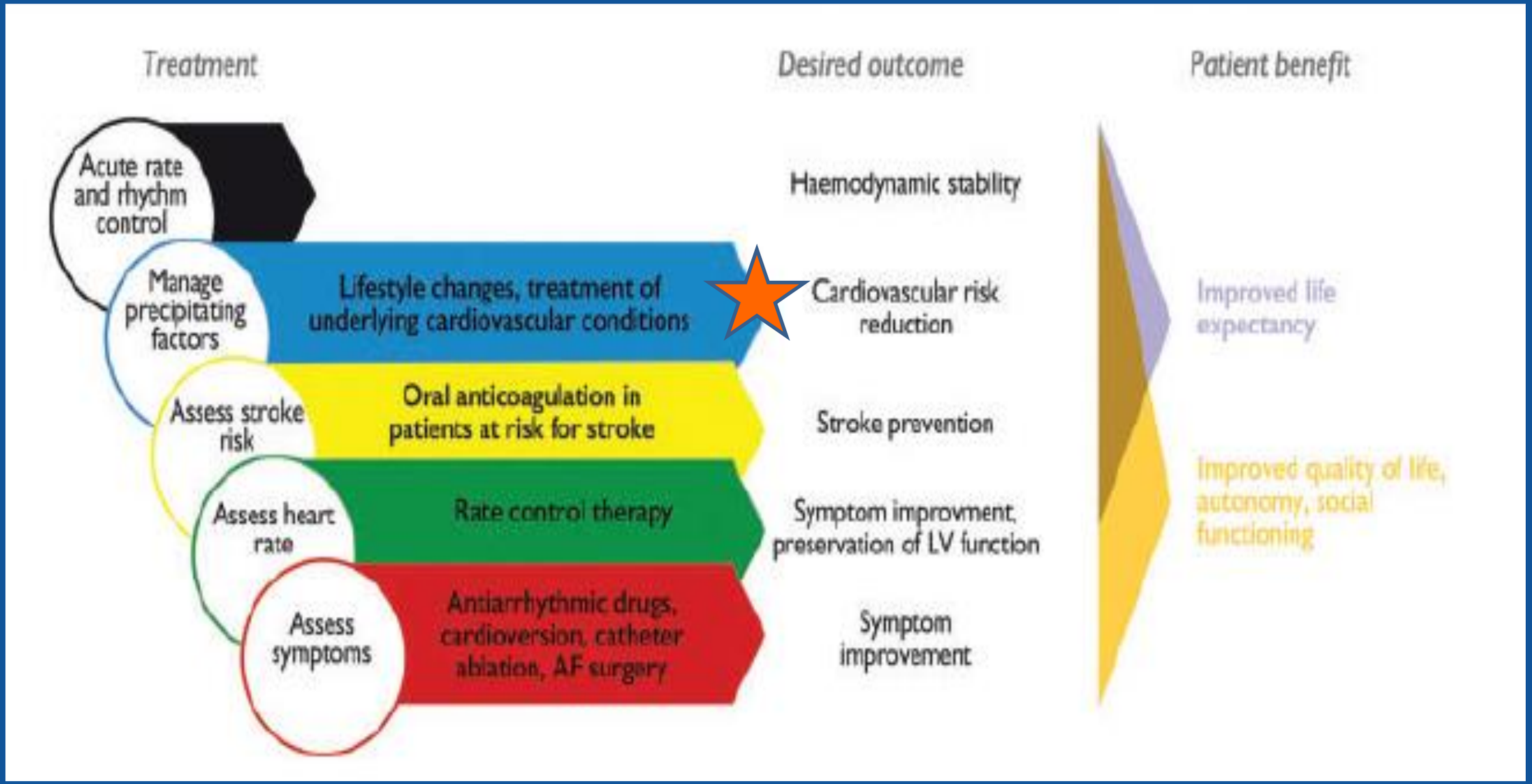
No Disclosures

AF - CLINICAL CHALLENGES (14) - 2016

1.	Presentation:	Complexity vs Symplicity (ESC)		(2)
2.	Etiology:	General vs Specific		(2)
3.	AC Rx:	When / Bridge / NSAID vs	SCI / NSR	(2)
4.	Aging:	TE & Bleeding vs	Warfarin	(2)
5.	AF / Stent:	Triple Rx vs	Double Rx	(2)
6.	Warf. / NOACs:	Efficacy vs	Safety	(2)
7.	Ablat. Yes / No	AC vs	LAA Closure	(2)

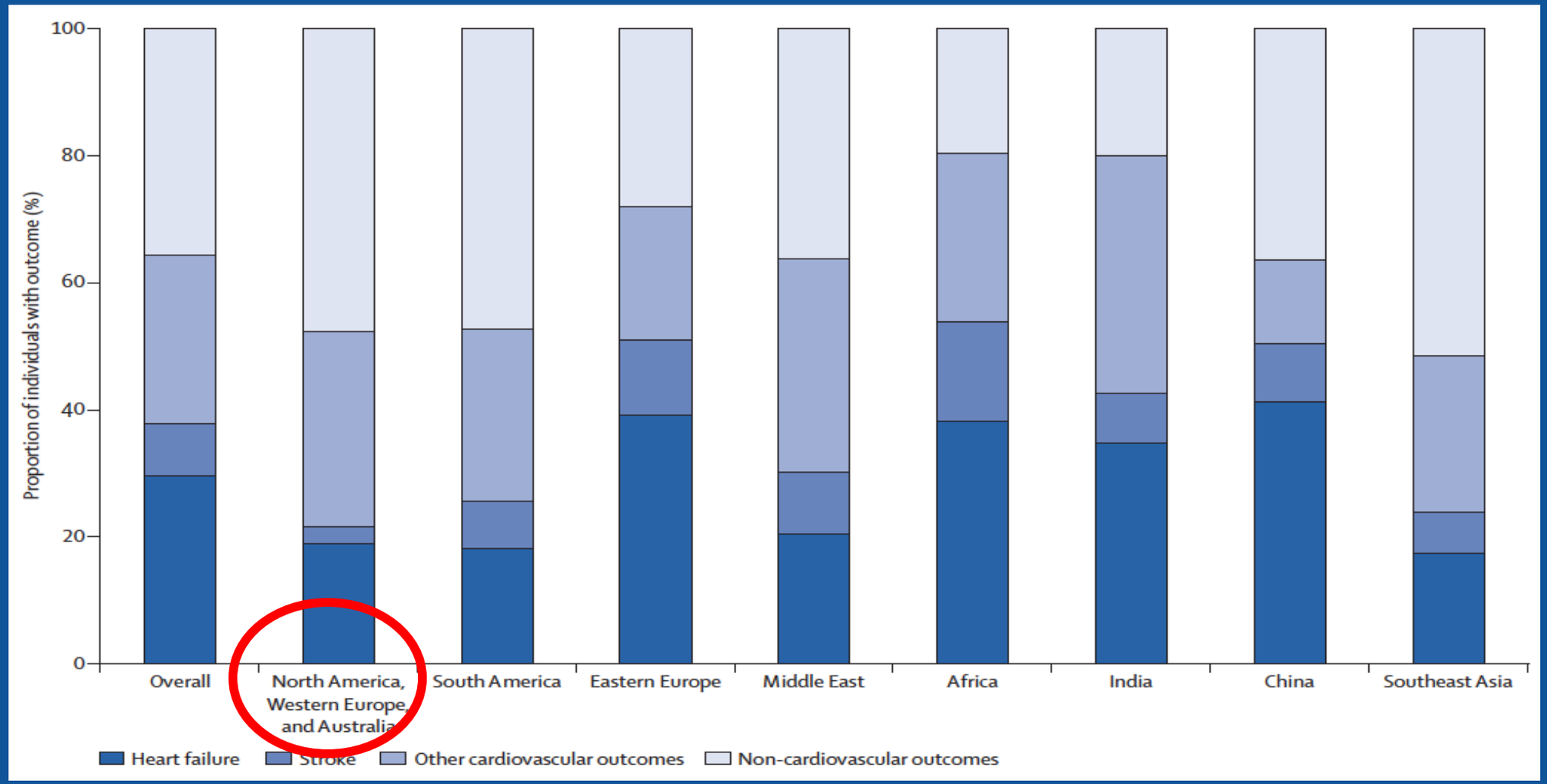
ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471

1a). Acute & Chronic Management Of AF



D Kotecha et. al. . Eur Heart J. 2016;37:2851

Death And Stroke In Patients In 47 Countries 1 Yr After Presenting With AF: A Cohort Study



RE-LY AF (JS Healey et. al.) Lancet 2016; 388: 1161.

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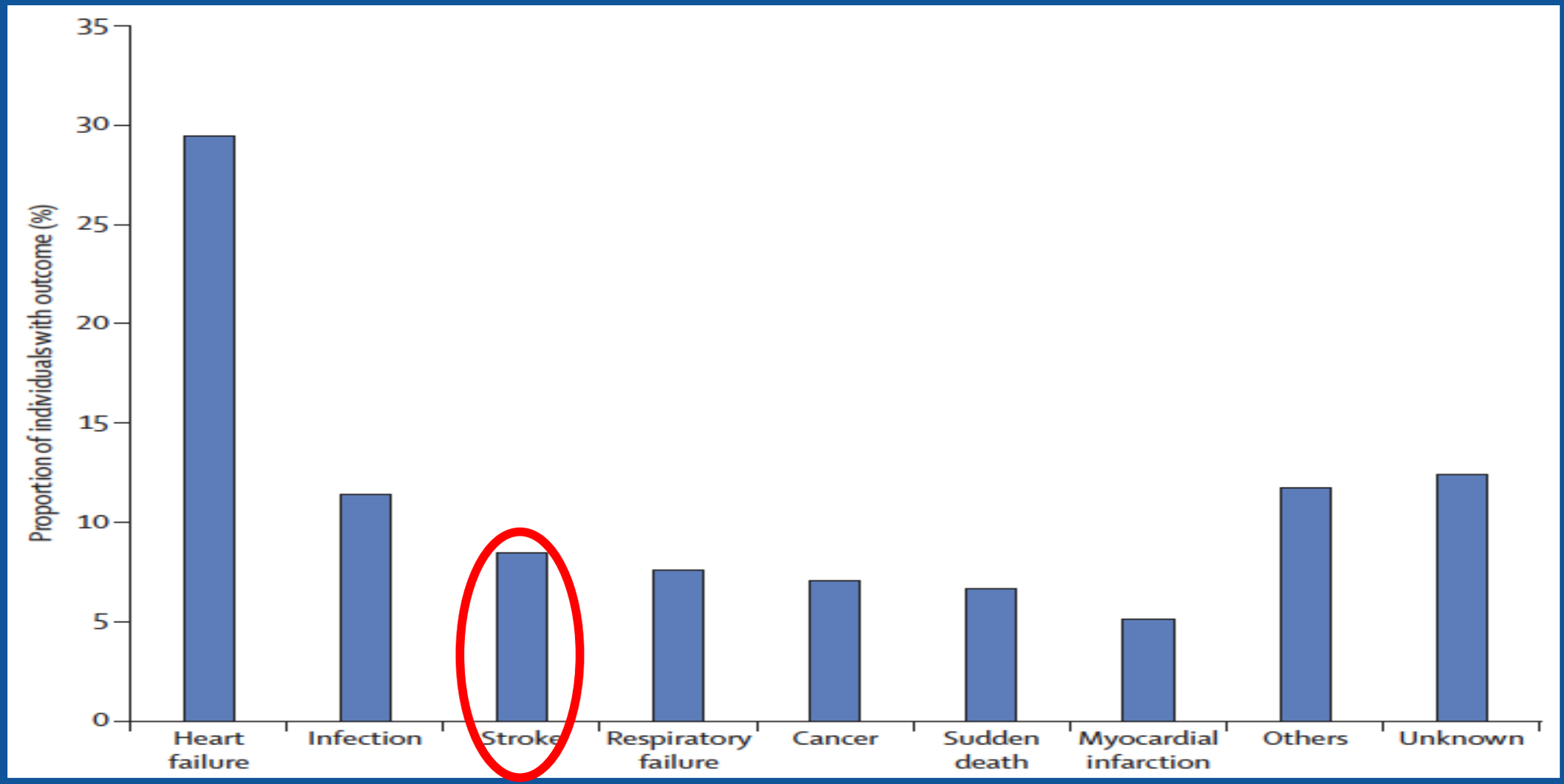
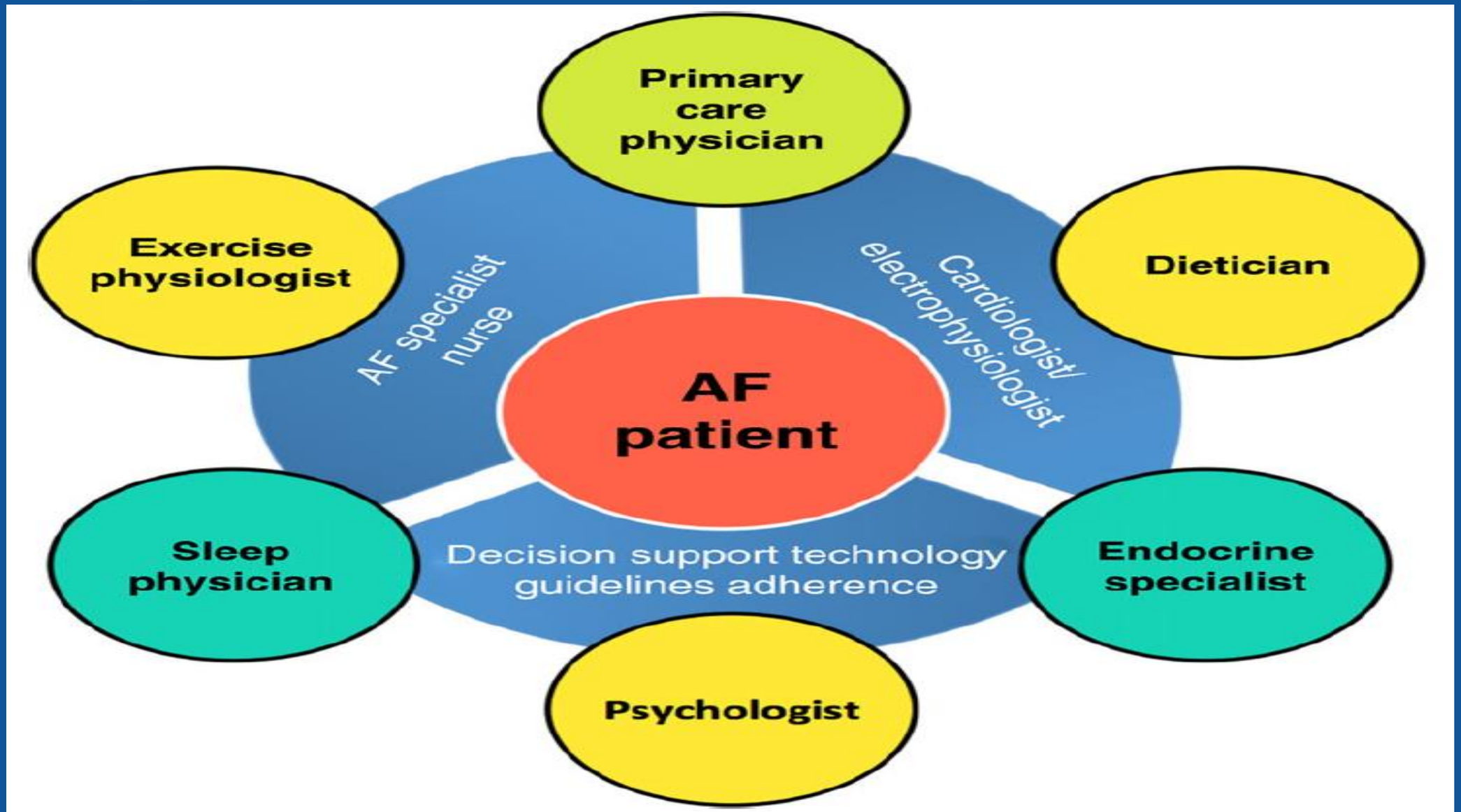


RE-LY AF (JS Healey et. al.) Lancet 2016; 388: 1161.

1b). Integrated Care For AF ?



DH Lau et. al. Eur Heart J. 2016;37:1573

2a). Five Commandments' of 2016 ESC Guidelines for the Management of Atrial Fibrillation

1. ECG screening and monitoring whenever AF might be suspected.

2. Physician-patient relationship are critical in decision making.

3. CHADS-VASc score. With a score ≥ 2 in male and ≥ 3 in female patients, AC is clearly recommended, while in a score of 1 in males and 2 in females, AC should be considered.

4. Bleeding risks should be minimized, hypertension controlled, antiplatelet or NSAID therapy should be of short duration, alcohol use moderated, and anaemia treated and normalized.

5. Use perioperative oral beta-blockers for the prevention of postoperative AF, and restore SR by CV in postoperative AF.

EHJ 2016; 37:2893

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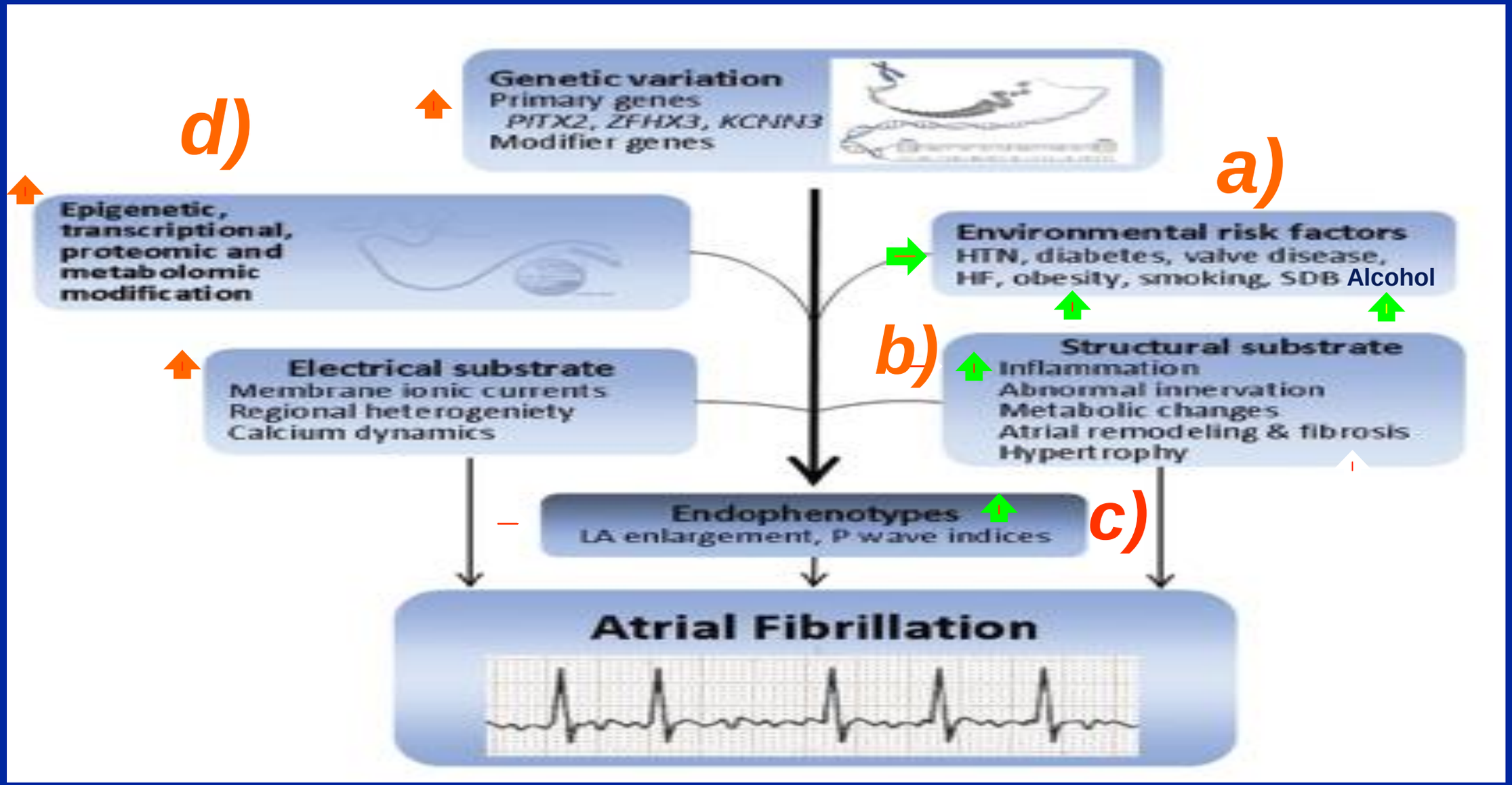
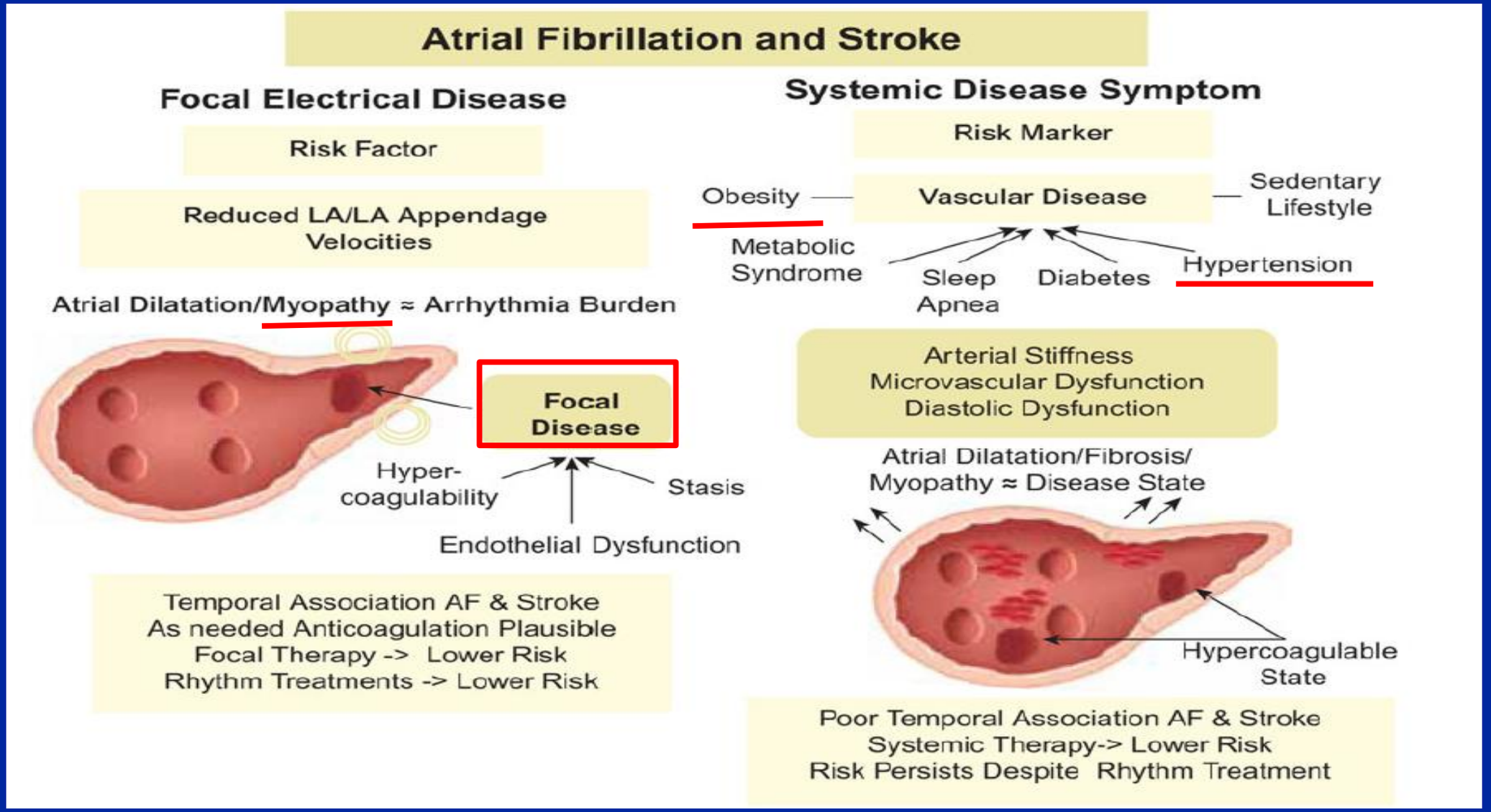
ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471

1). General Etiologies of AF – Think !!!!



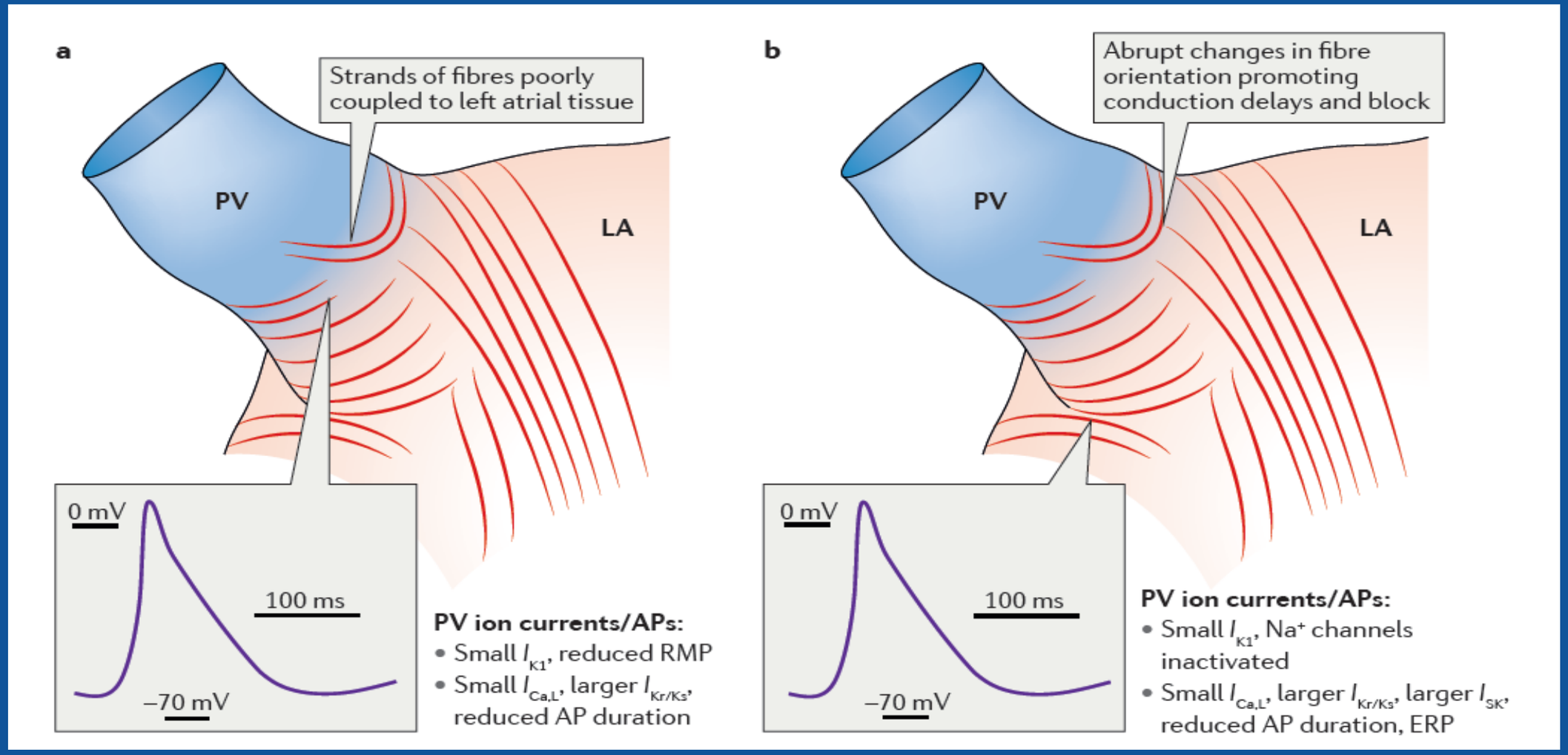
JW Magnani et. al. Circulation 2011;124:1982 - Framingham

2a). Gross Mechanisms of AF



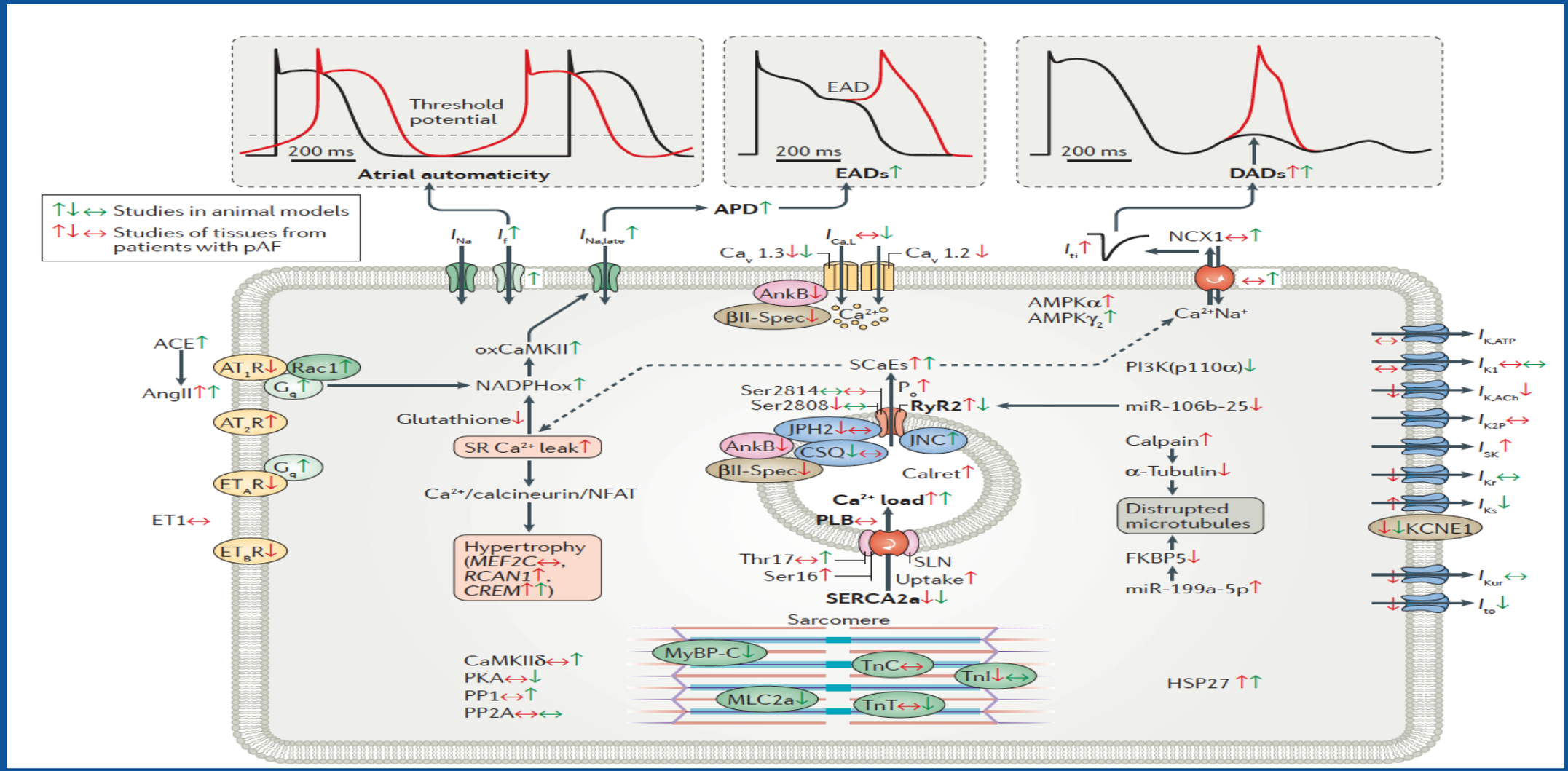
TJ Bunch et. al. Eur Heart J. 2016;37:2890

2b). Mechanisms of AF Initiation At The Pulmonary Veins



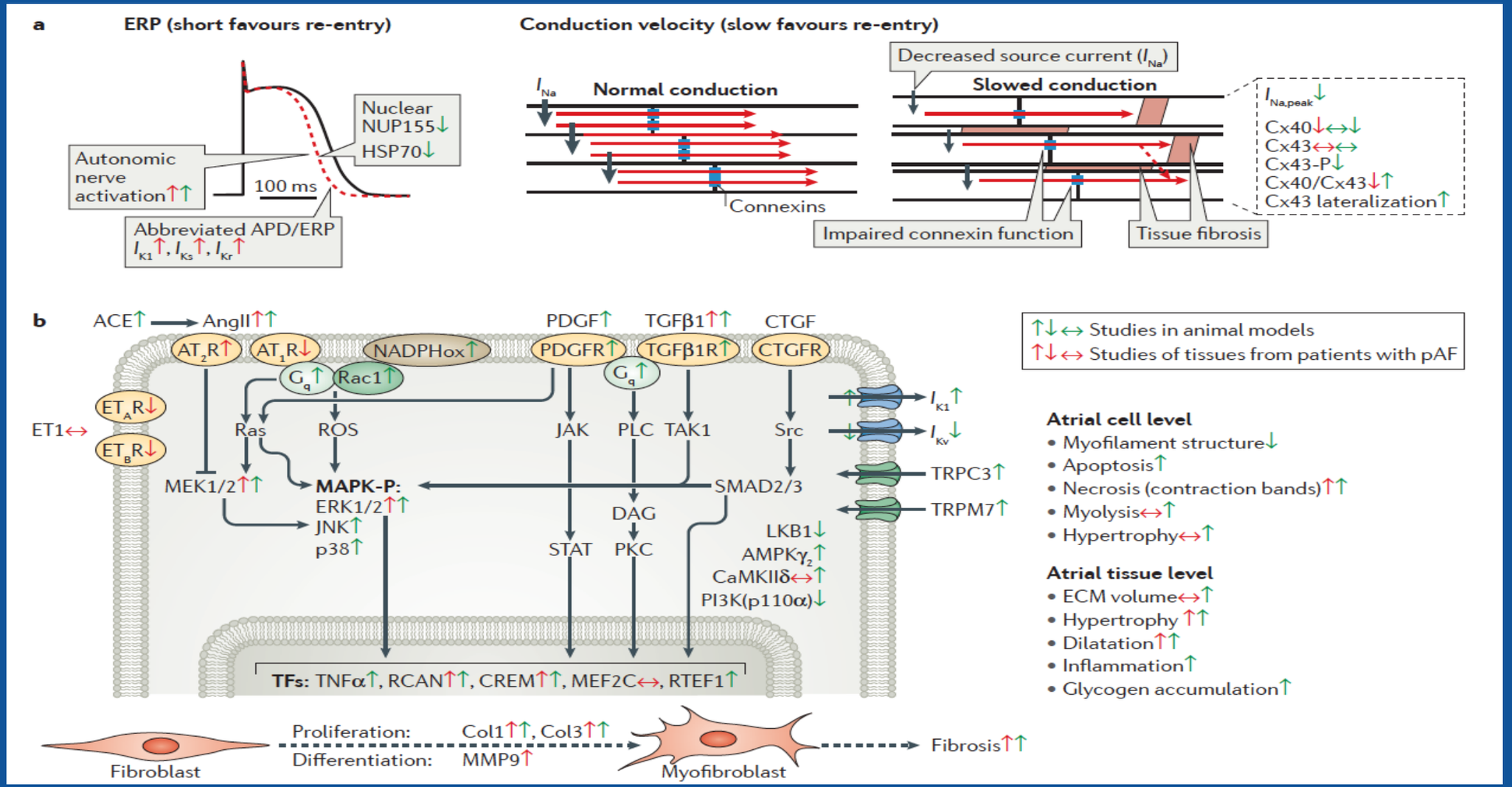
S Nattel et. al. Nat Rev Cardiol. 2016; 13: 575.

2c). Molecular Mechanisms of Focal Ectopic Firing In Paroxysmal AF



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

Molecular Mechanisms of Re-entry In Paroxysmal AF



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

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ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471

1a) Stroke Risk Stratification In AF

Components of CHA_2DS_2-VASc

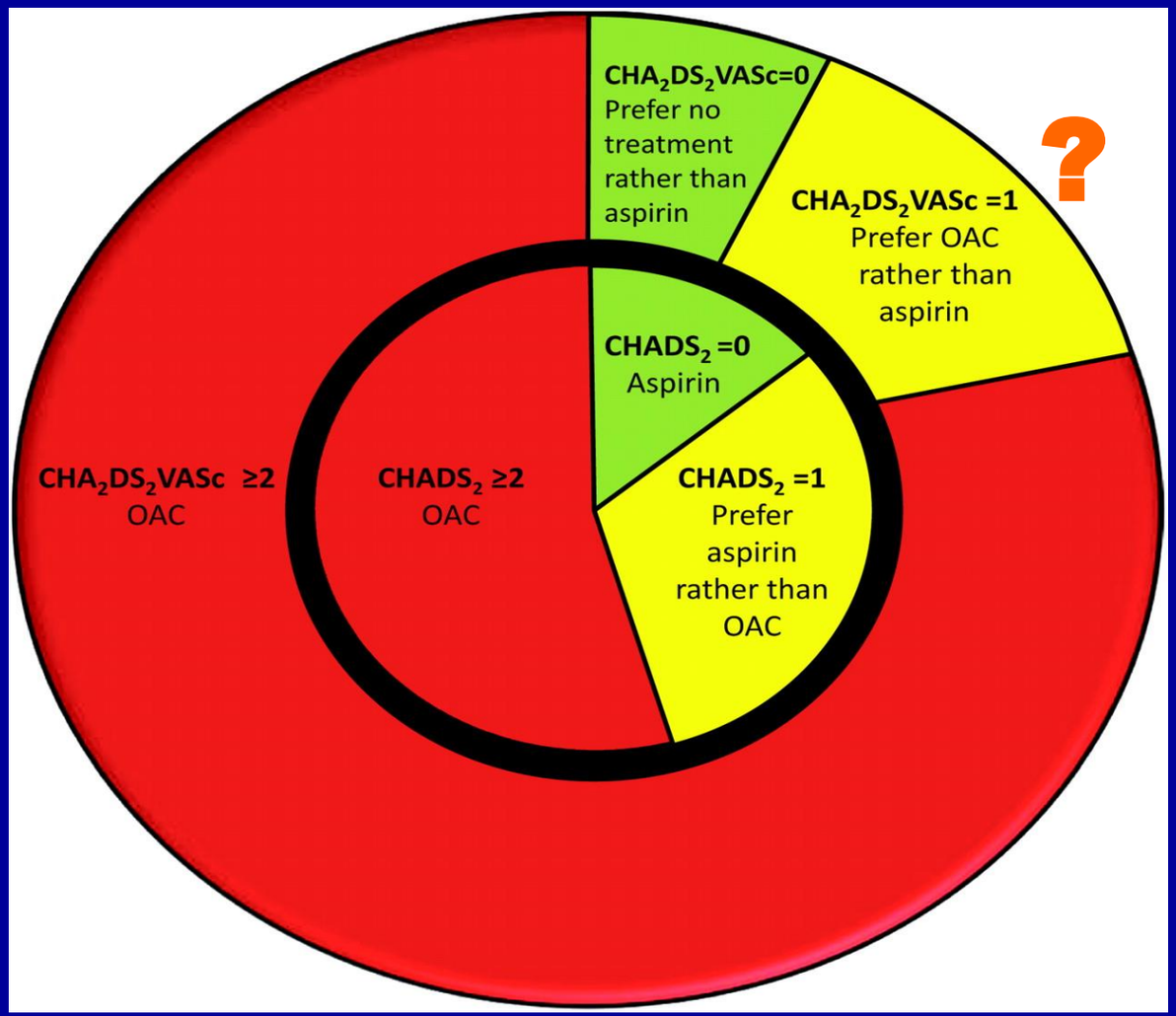
Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vascular disease (MI, PAD, aortic atherosclerosis)	1
Age 65-74 y	1
Sex category (female)	1

CHA_2DS_2-VASc Score	Annual Risk of Stroke (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

G Frendl et. al. J Thorac Cardiovasc Surg 2014;148:772

***ATRIA** - HA van den Ham et.al. J Am Coll Cardiol 2015;66:1851– Points by Age*

AC When ?- The Prevention Of Stroke .



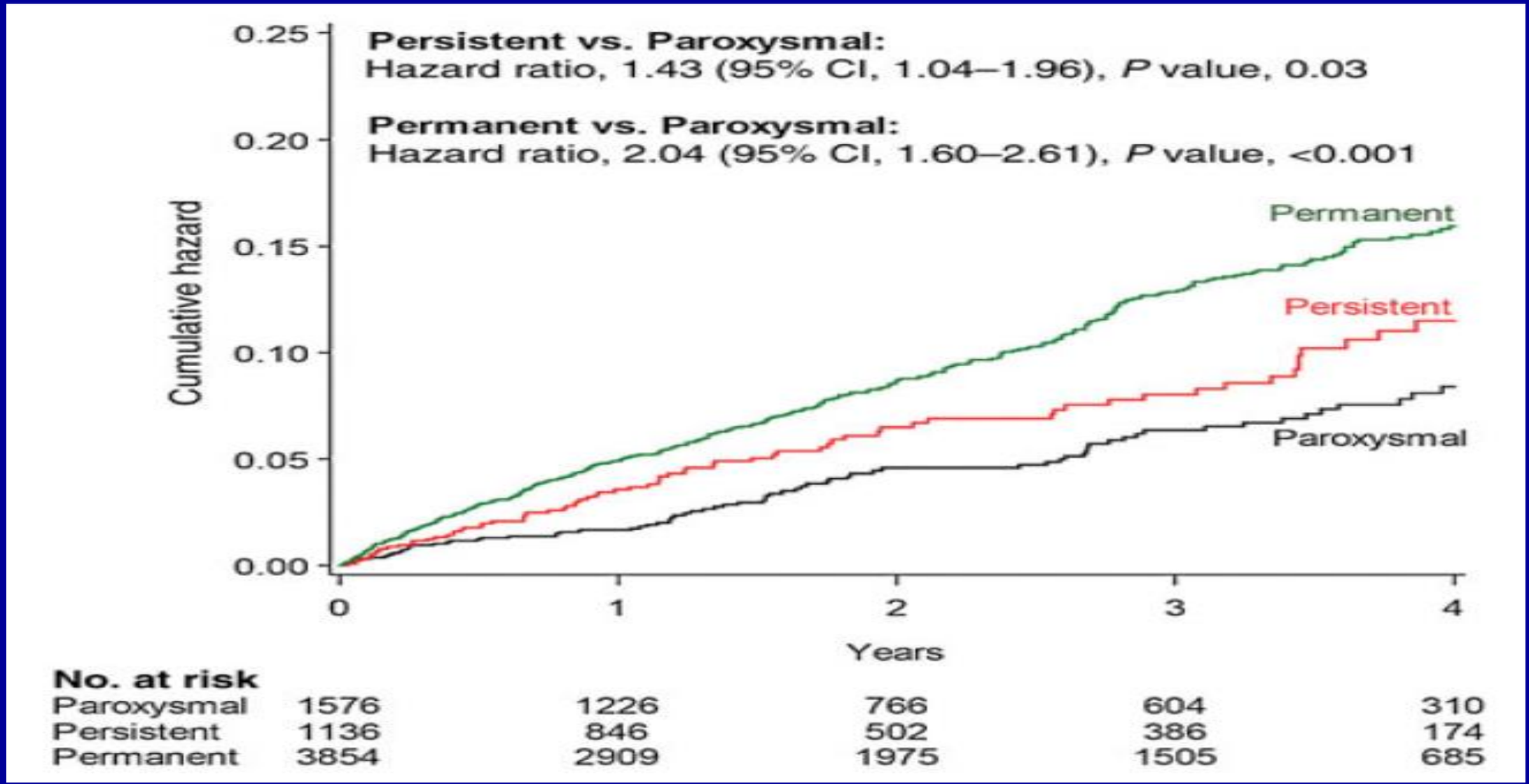
V Fuster, JS Chinitz, Circ. 2012 ; 125: 2285

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

Cumulative Hazard Rates Of Embolic Events According To The Pattern Of AF Occurrence



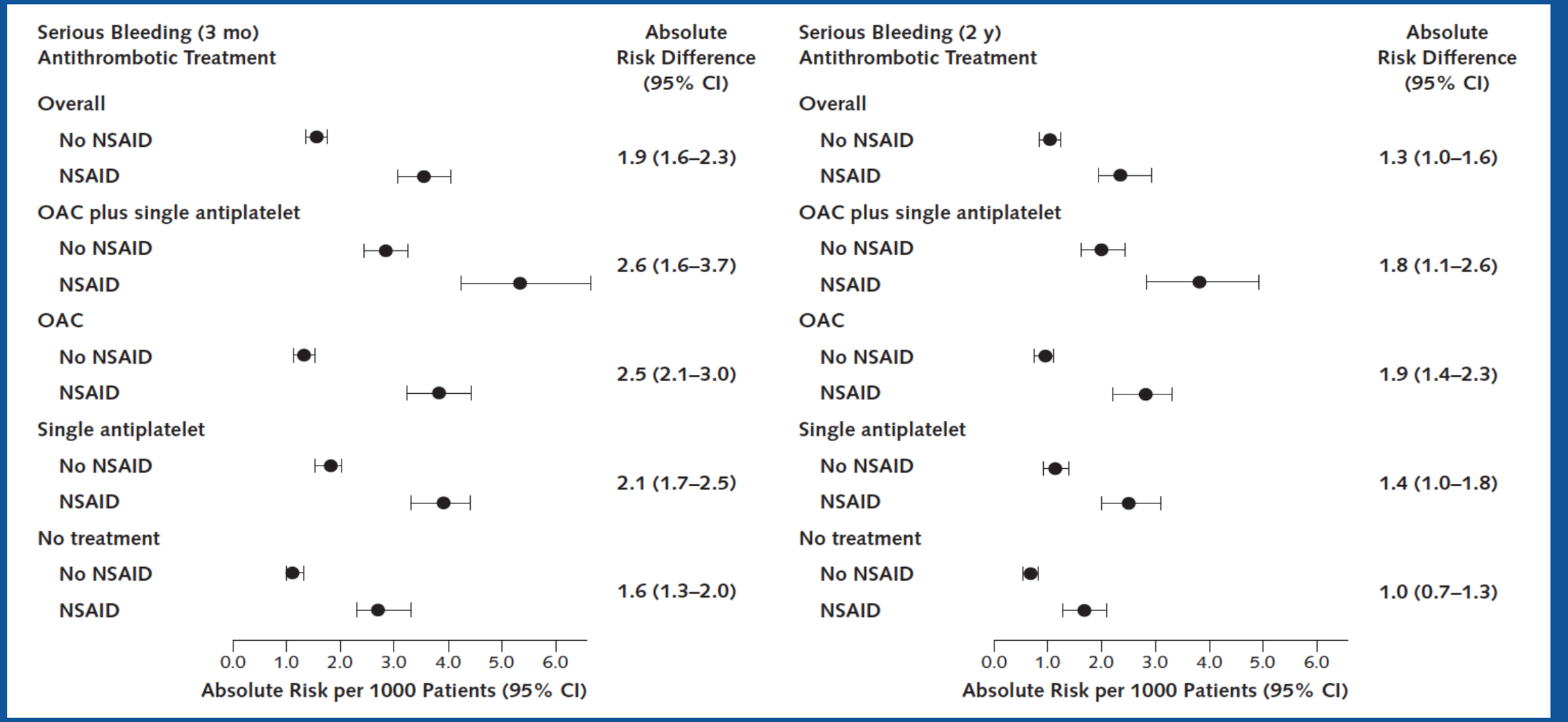
T Vanassche, SJ Connolly et. al. Eur Heart J. 2015;36:281

1b) Bridging AC and Associated Outcomes During AC Interruption in Patients With AF

The ORBIT-AF is a prospective, observational registry study of US outpatients with AF. Of 7372 patients treated with oral A/C, 2803 overall interruption events occurred in 2200 patients or 30% at a median follow-up of 2 years. Bridging A/C were used in 24% (n=665), predominantly LMW heparin (73%, n=487) and unfractionated heparin (15%, n=97). Bridged patients were more likely to have had prior cerebrovascular events (22% versus 15%; *P*=0.0003) and mechanical valve replacements (9.6% versus 2.4%; *P*<0.0001); however, there was no difference in CHA_2DS_2-VASc scores (scores ≥2 in 94% versus 95%; *P*=0.5). Bleeding events were more common in bridged than nonbridged patients (5.0% versus 1.3%; *P*<0.0001). The incidence of MI, stroke or systemic embolism, major bleeding, hospitalization, or death within 30 days was also significantly higher in patients receiving bridging (13% versus 6.3%). These data do not support the use of routine bridging, and additional data are needed to identify best practices concerning A/C interruptions.

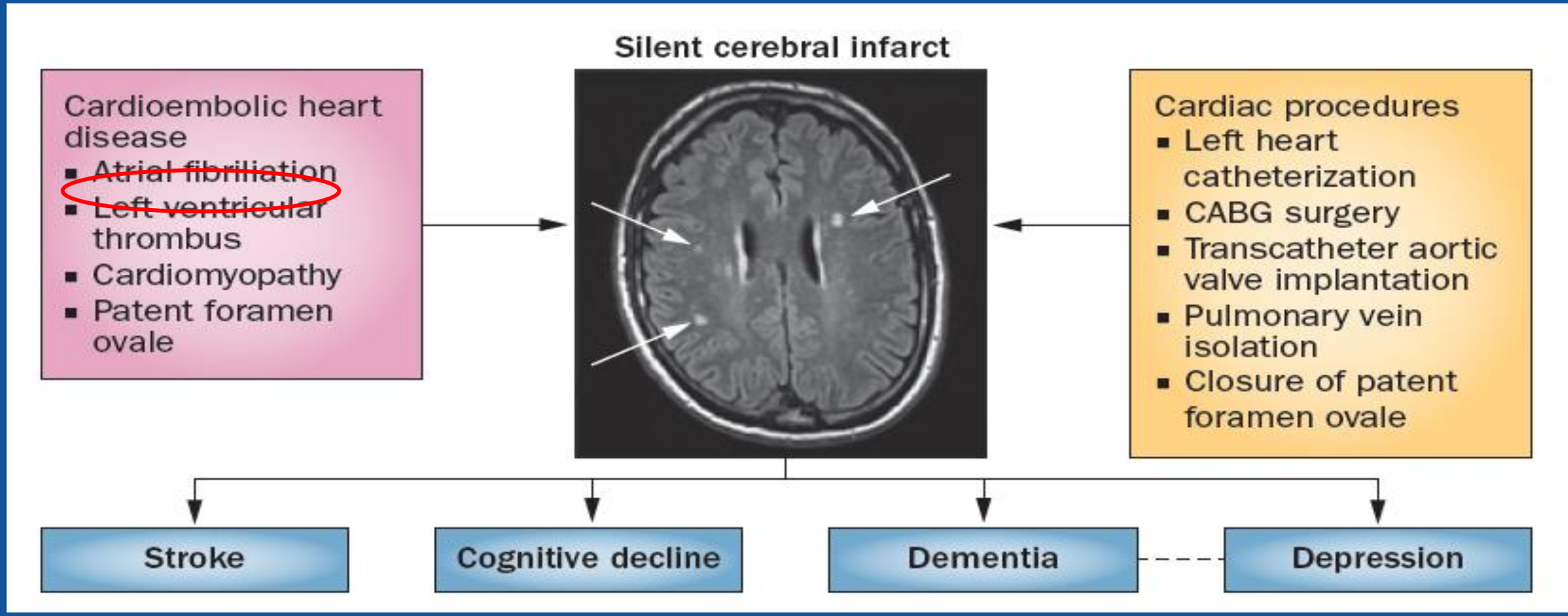
ORBIT=AF (BA Steinberg et al.), Circulation 2015; 131:488

1c) NSAID Exposure in Patients on Antithrombotic Rx Risks For Serious Bleeding At 3 Mo & 2 Yrs,



M Lamberts et. al. Ann Intern Med. 2014;161:690

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

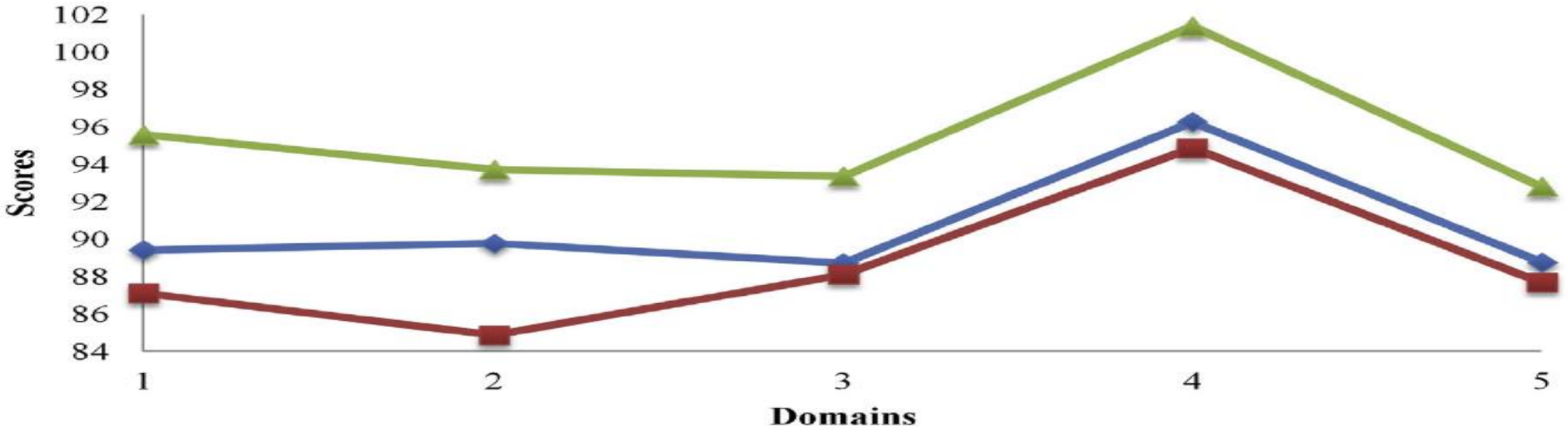


ME Hassell et. al. Nat. Rev. Cardiol. 2013;10:696

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

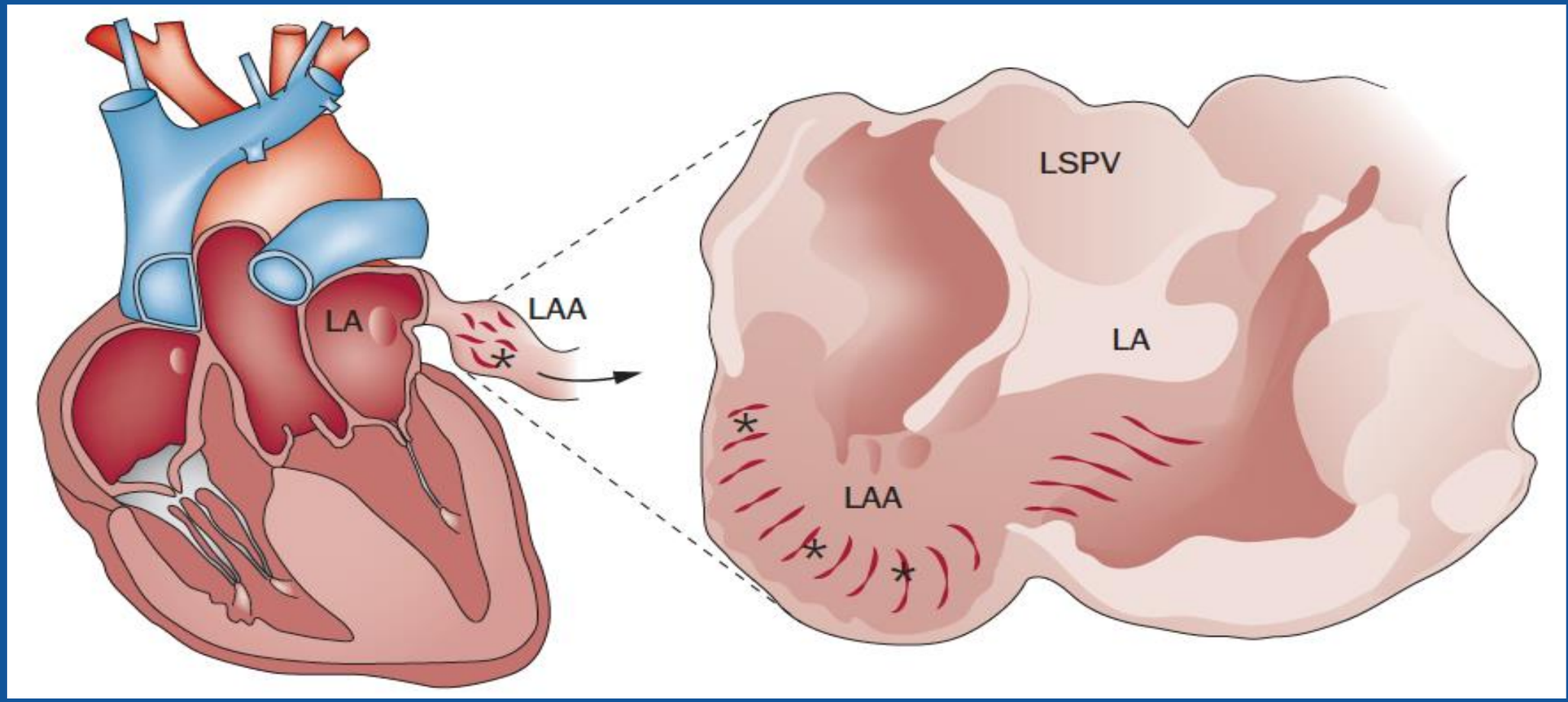
Silent Cerebral Ischemia in AF
Correlation With Cognitive Function



	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

2b). 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 ?

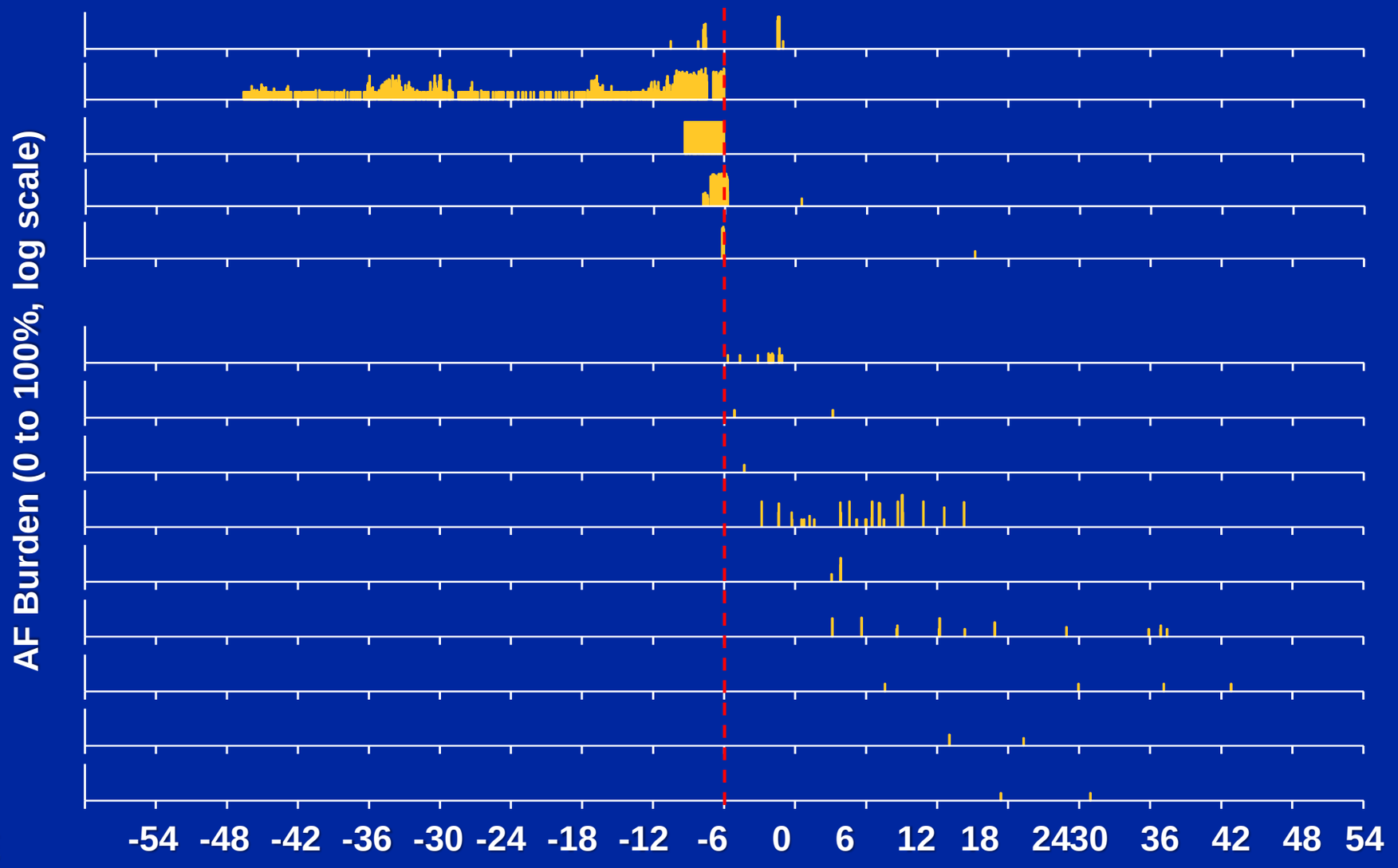
Randomized Trial of Atrial Arrhythmia Monitoring to Guide AC in Pts with Implanted Defibrillator & CRD

ATs detected by implanted devices are often AF/AFl associated with stroke. We randomized 2718 patients with dual-chamber and biventricular defibrillators to start and stop AC based on remote rhythm monitoring vs. usual office-based follow-up with AC determined by standard clinical criteria. Although AT burden was associated with thromboembolism, there was no temporal relationship between AT and stroke. In other words, in patients with implanted defibrillators, the strategy of early initiation and interruption of anticoagulation based on remotely detected AT did not prevent thromboembolism and bleeding.

IMPACT *(DT Martin et al.) Eur Heart J 2015; 36:1660*

Temporal Relationship of AF & Thromboembolism

IMPACT Trial



IMPACT (DT Martin et. al.) EHJ J. 2015;36:1660

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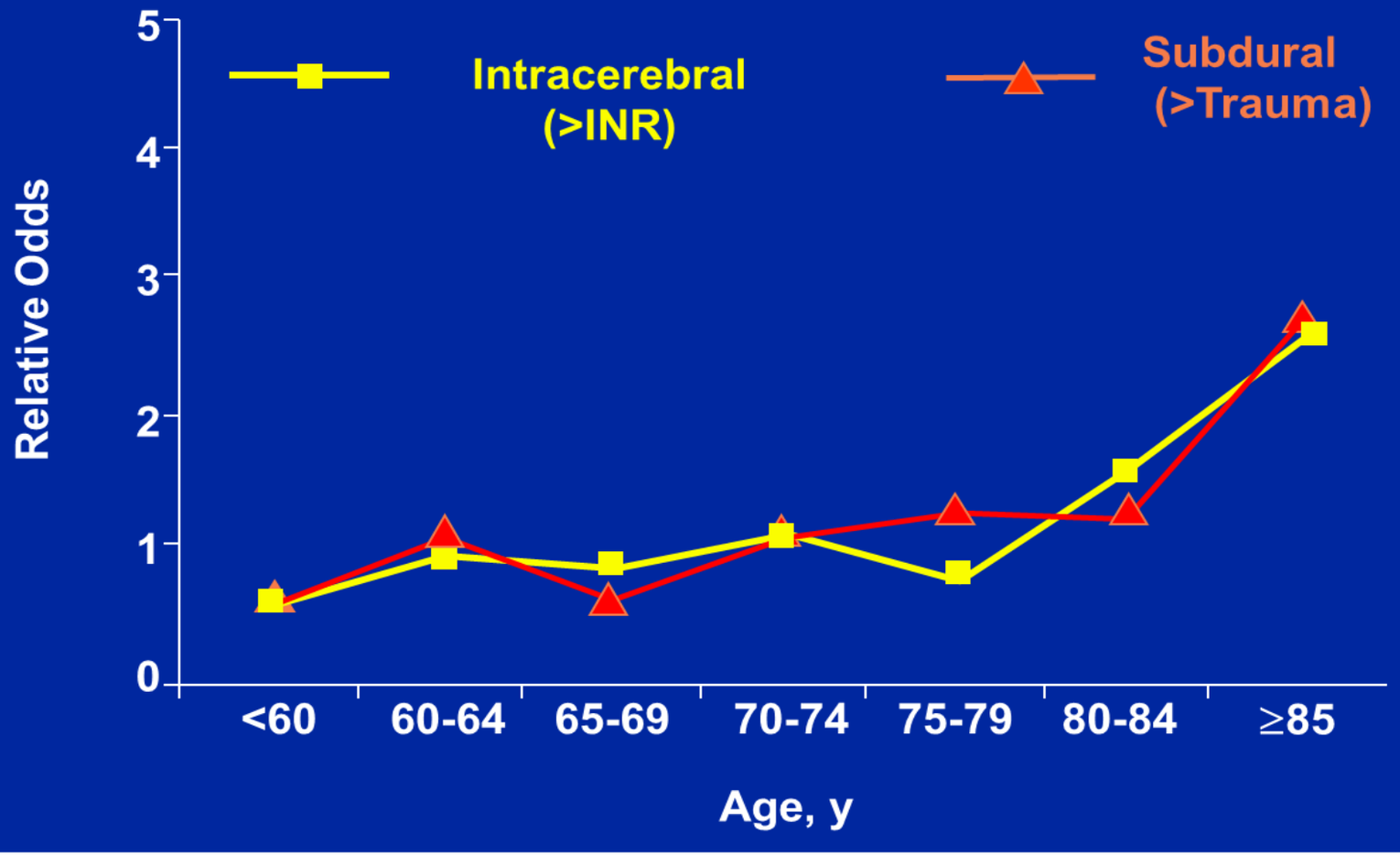
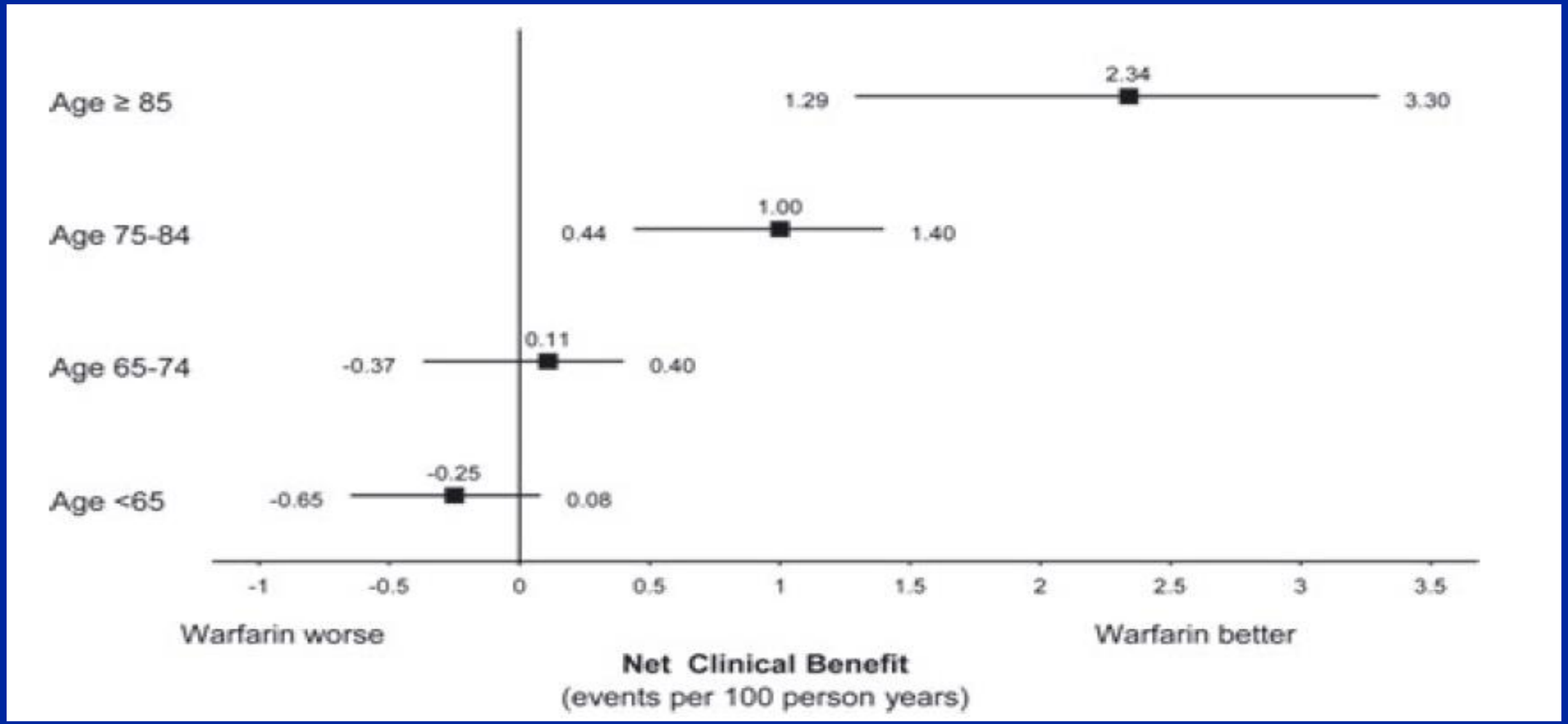
ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471

1) NVAF - ODDS OF INTRACRANIAL HEMORRHAGE & AGE IN 145 CASE-PATIENTS (INR 2.0-3.0) AND 870 CONTROLS



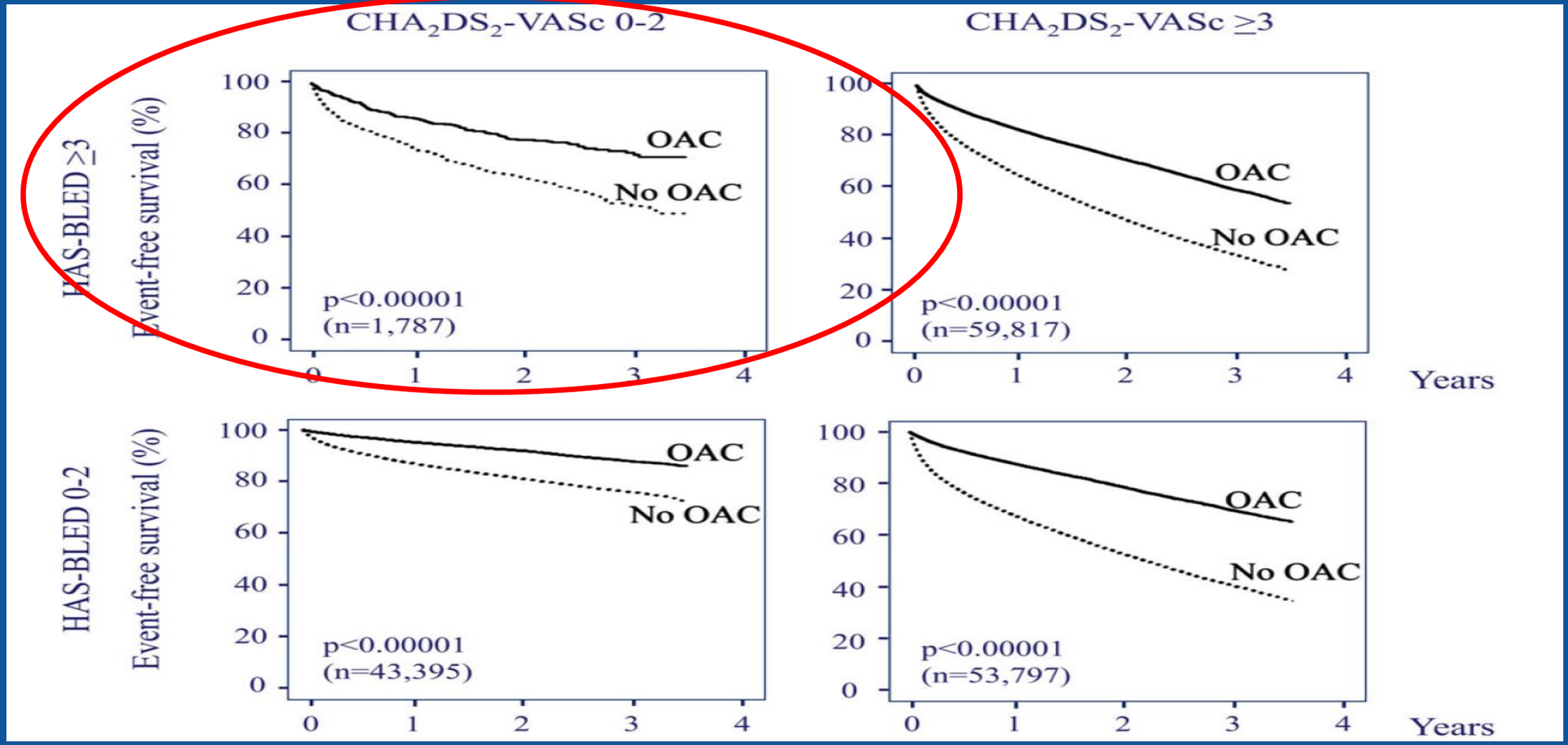
MC Fang et al., Ann Intern Med 2004; 141:745 (UCSF, Boston, Oakland)

2) The Net Clinical Benefit Of Warfarin By Age Group



JS Chinitz, V Fuster et. al. Ann. N.Y. Acad. Sci. 2012;1254:140
DE Singer et. al. Ann. Intern. Med. 2009;151:297

Relative Benefits Of Oral AC Vs. No Oral AC (Antiplatelet Therapies Or No) With CHA_2DS_2-VASC And HAS-BLED Scores



ESC Thrombosis Working Group (F Andreotti et. al.) Eur Heart J. 2015;36:3238

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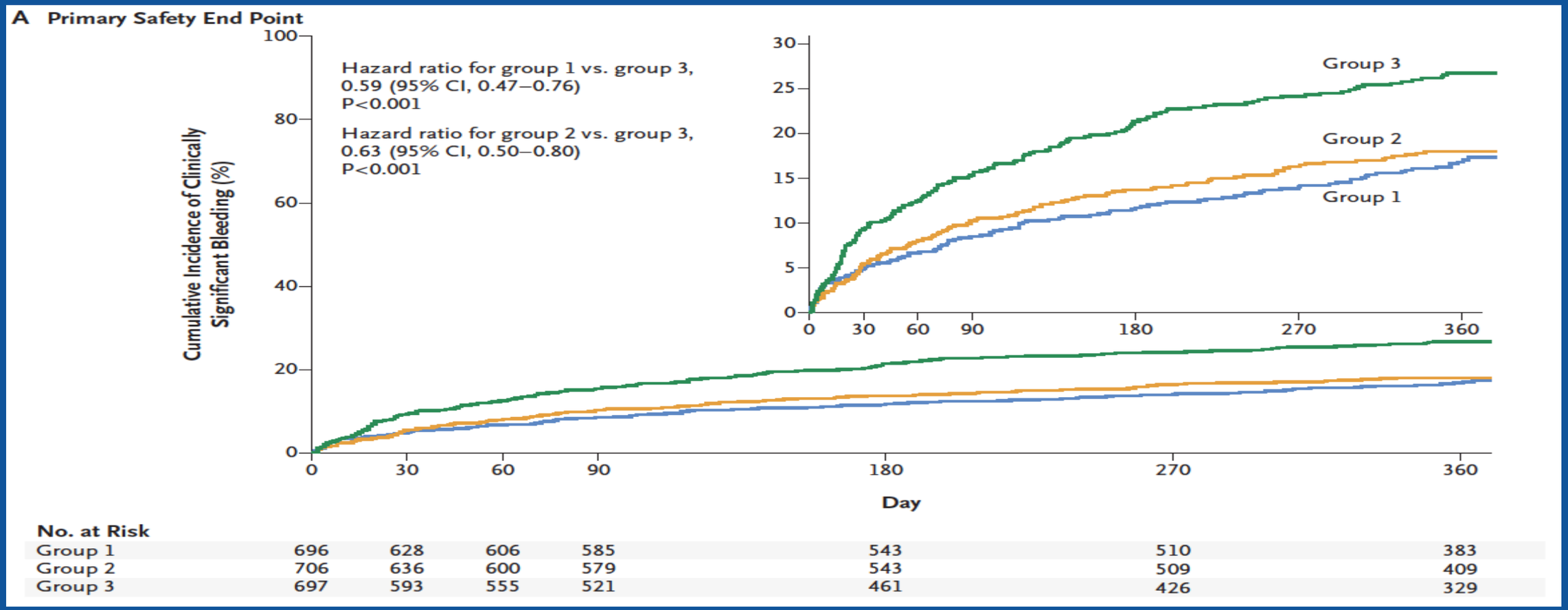
1) Drop Early Aspirin & Drop Late Clopidogrel In Stent Patients with AF

In the WOEST trial, 573 patients were randomized to dual therapy with oral anticoagulation and clopidogrel (75 mg daily) or to triple therapy with oral anticoagulation, clopidogrel and aspirin 80 mg daily. Treatment was continued for one month after bare metal stenting and one year after drug eluting stent placement.

Bleeding events (TIMI criteria)				
	Dual therapy (%)	Triple therapy (%)	HR (95% CI)	P value
All bleeding Events	19.5	44.9	0.36 (0.26-0.50)	<0.001
Significant reduction in minor bleeding, < Major bleeding (NS)				
Stent thrombosis	1.5	3.2		NS

WOEST (W DeWilde et al.) NEJM 2012

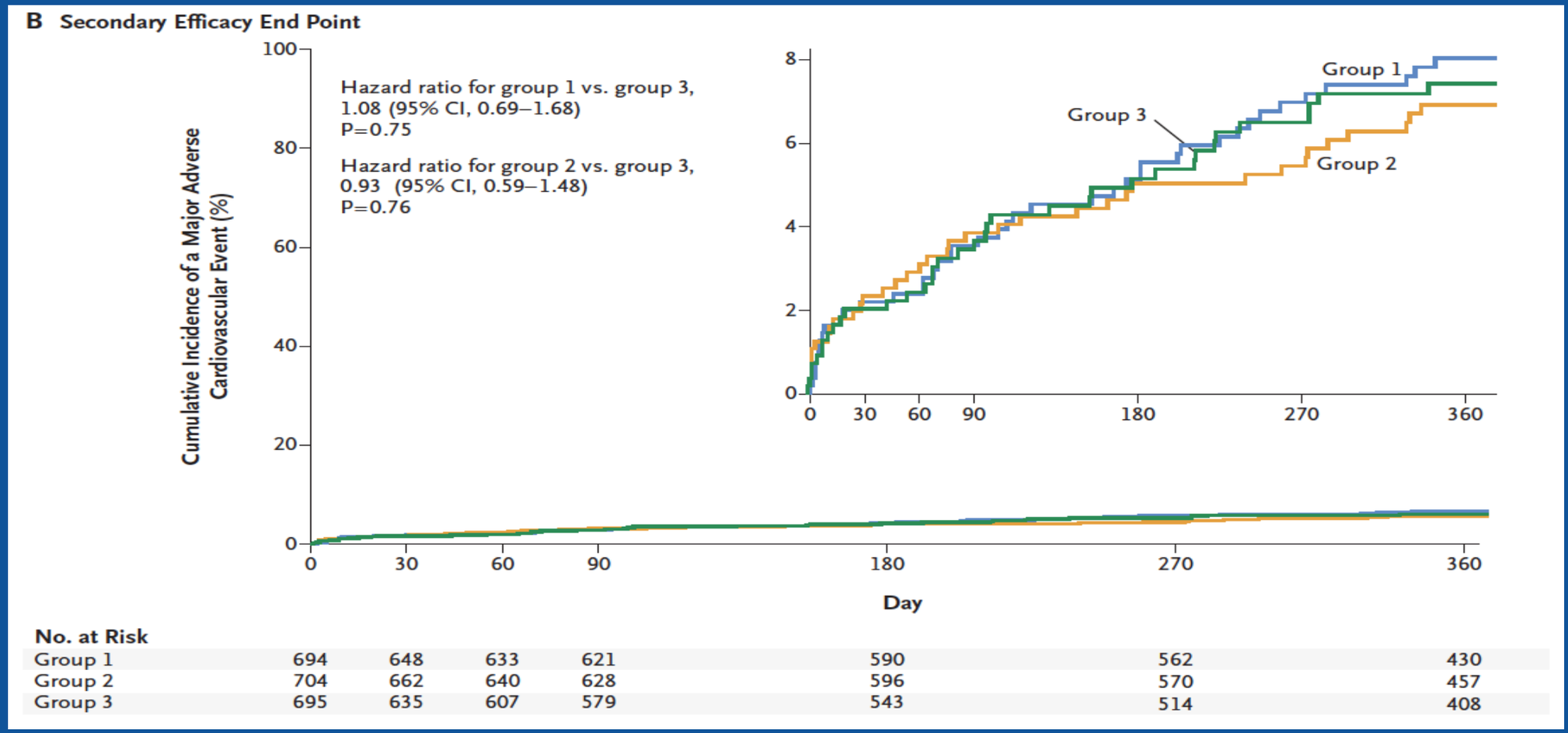
2). Preventing Bleeding in Pts with AF-PCI



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

PIONEER AF-PCI (CM Gibson et. al.) NEJM 2016 (In Press)

Prevention of CV Events in Pts with AF-PCI



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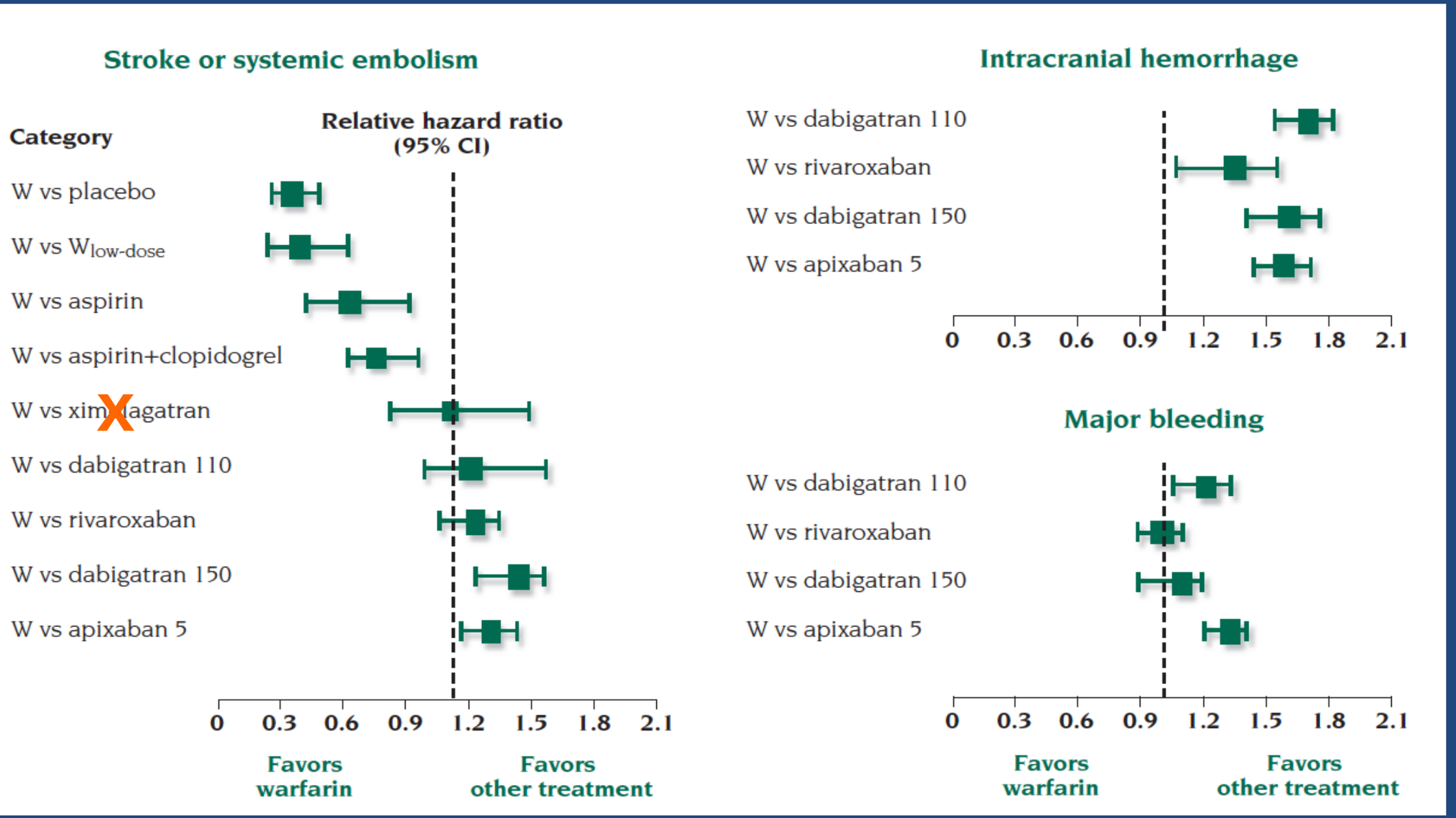
New Oral Anticoagulants - 1) Efficacy & 2).Safety



Dialogues in Cardiovascular Medicine 2012;17:189

2a). NOACs - Kidney & Prosthetic Heart Valves

Recommendations	COR
CHA_2DS_2-VASc score recommended to assess stroke risk	I
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:	
Warfarin	I
Dabigatran, rivaroxaban, or apixaban	I
Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually	I
Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits	III: No Benefit
Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve	III: Harm

CT January et. al. J. Am. Coll. Card. 2014; 64: e1

J. Am. Coll. Card. 2016 Sept 27 - VKA 75% - Apixaban 2.5-5mg bid

Major Bleeding Rates for Patients on Warfarin by Creatinine Clearance

Kidney Function	Major Bleeding (Events per 100 Patient-Years)
CrCl ≥60 ml/min	6.2 (4.1-8.9)
CrCl 30-59 ml/min	8.3 (5.1-12.8)
CrCl <30 ml/min	30.5 (17.0-50.3)
Dialysis	54-100

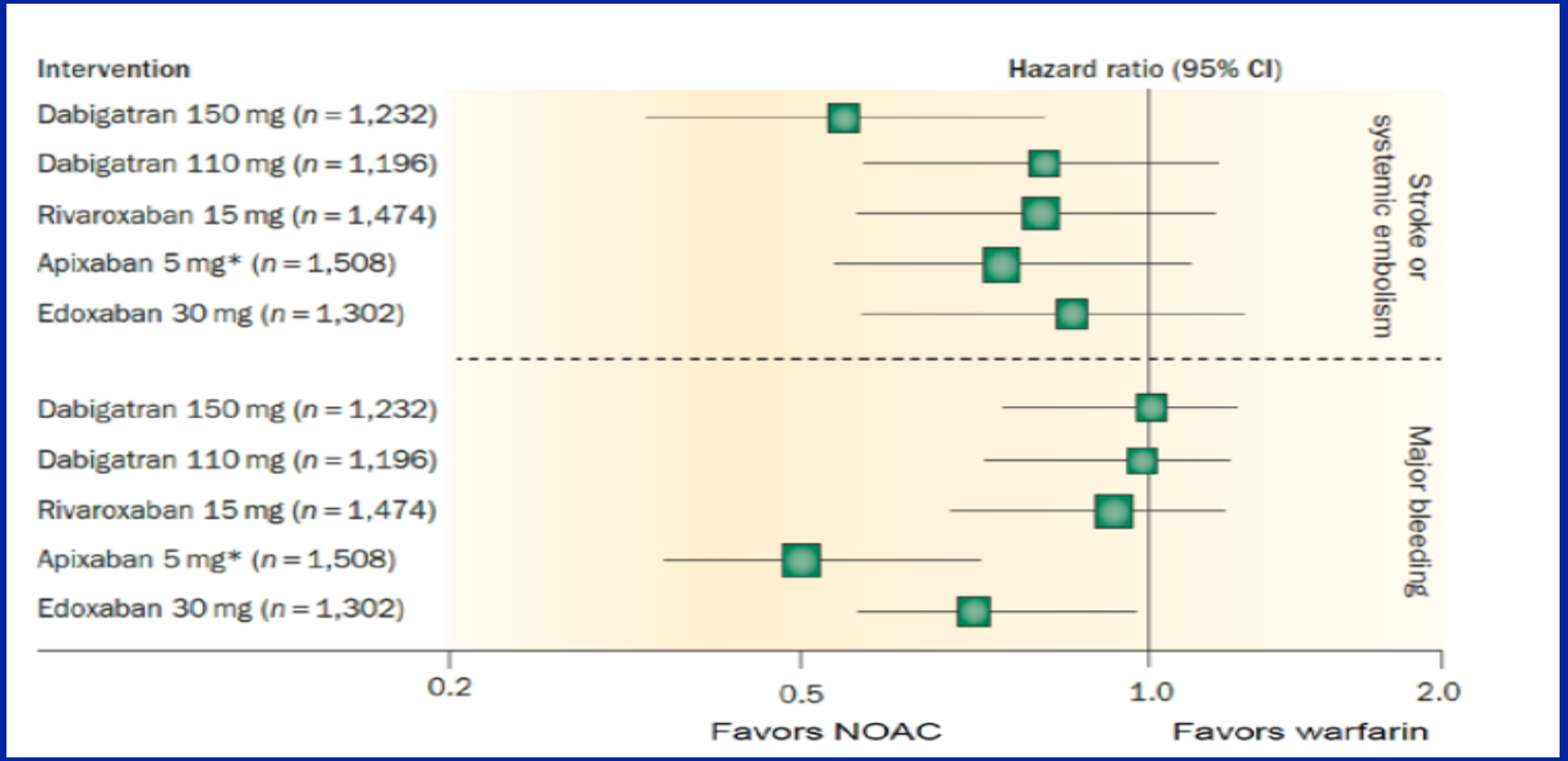
KE Chan et. al. J Am Coll Cardiol 2016;67:2888

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

Efficacy And Safety Of NOAC Vs Warfarin In Moderate CKD From RCT In AF



A Qamar et. al. Circulation. 2016;133:1512

F Del-Carpio Munoz et al., Am J Cardiol 2016; 117:69

2b). 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

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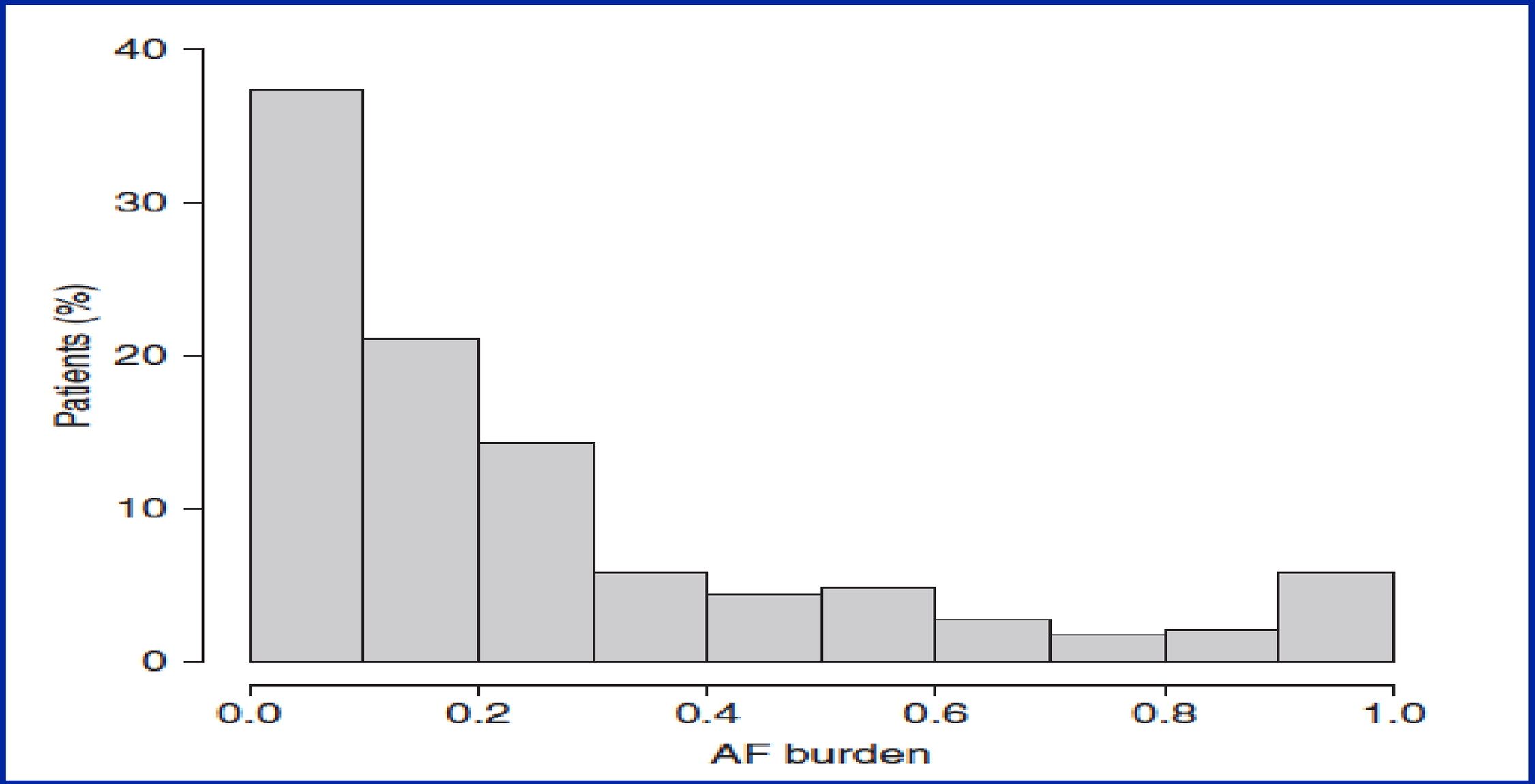
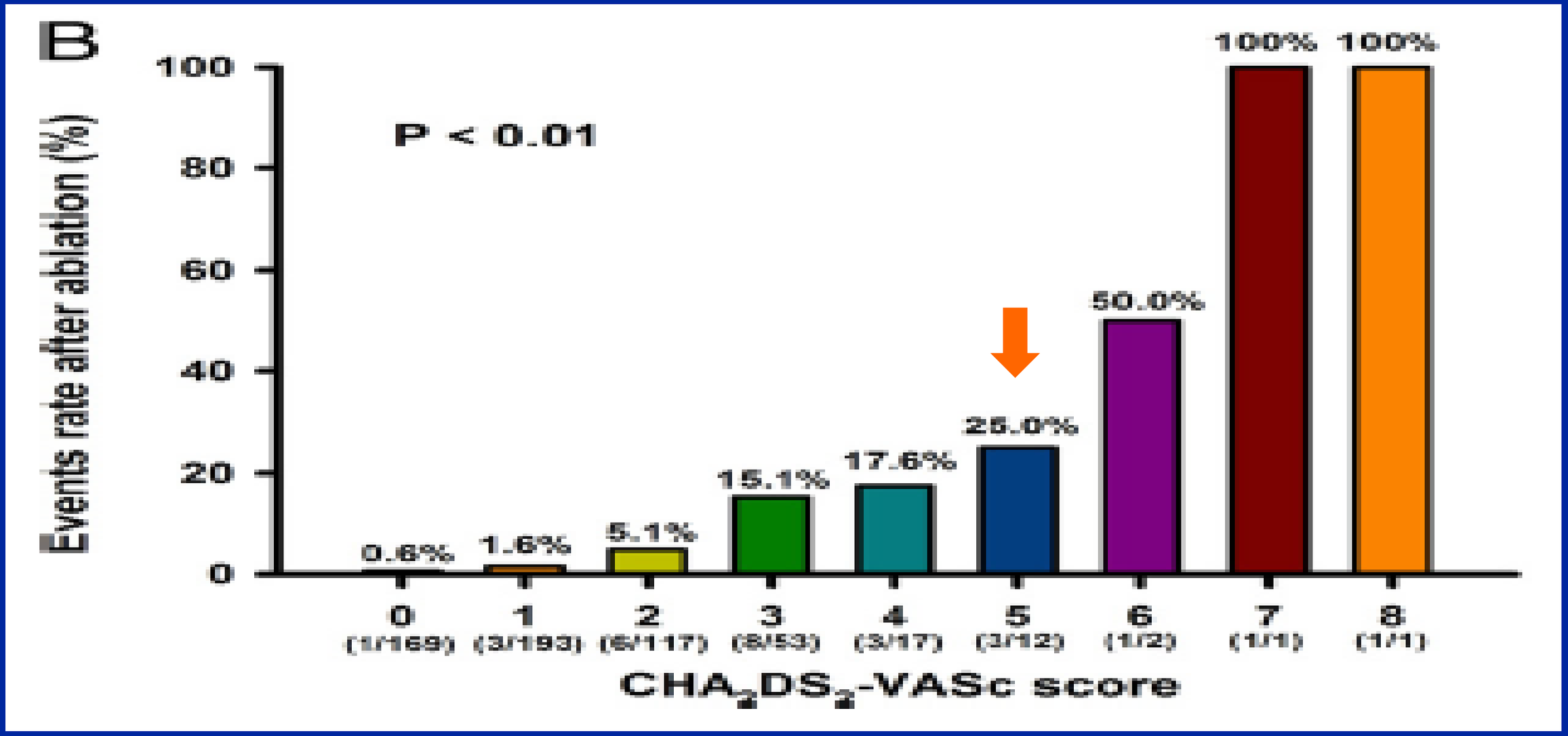
1a). AF Burden - After Catheter Ablation
Several Strategies (Linq Recorder etc)



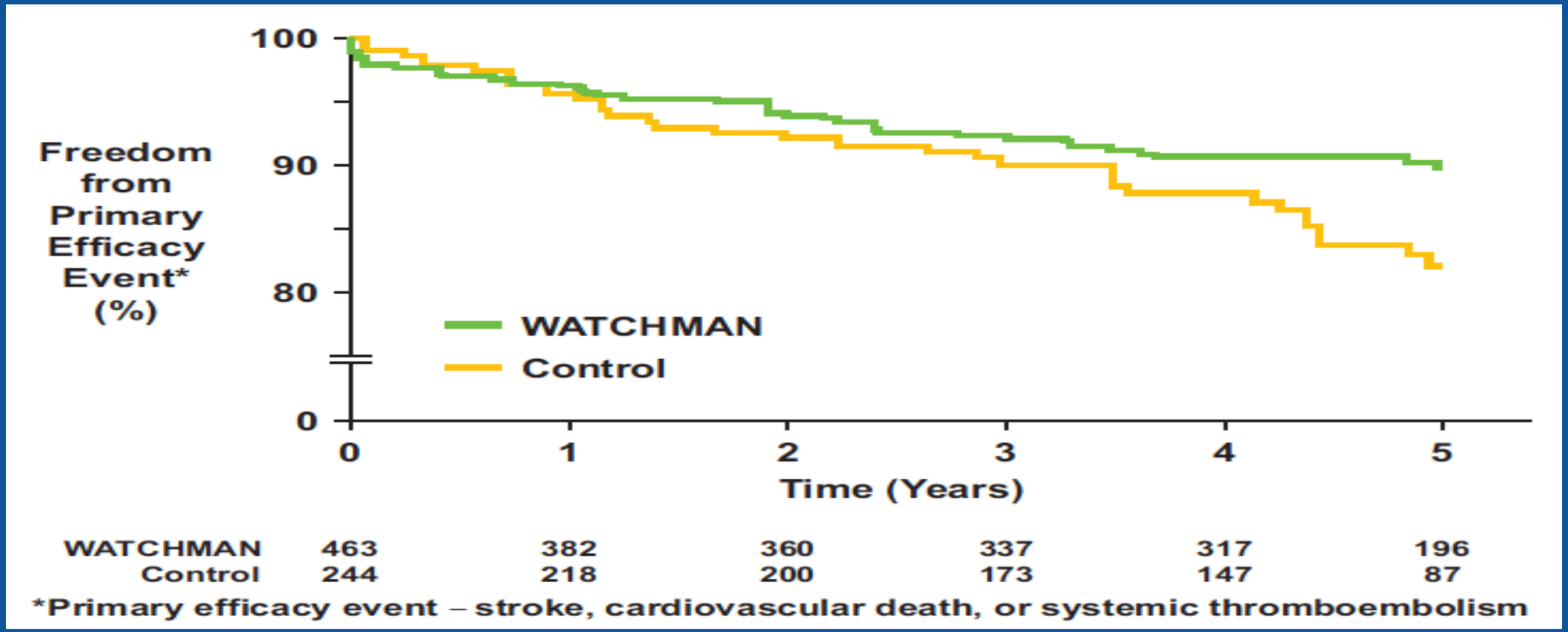
El Charitos et. al. Circulation. 2012;126:806 (Luebeck, Germ.)

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



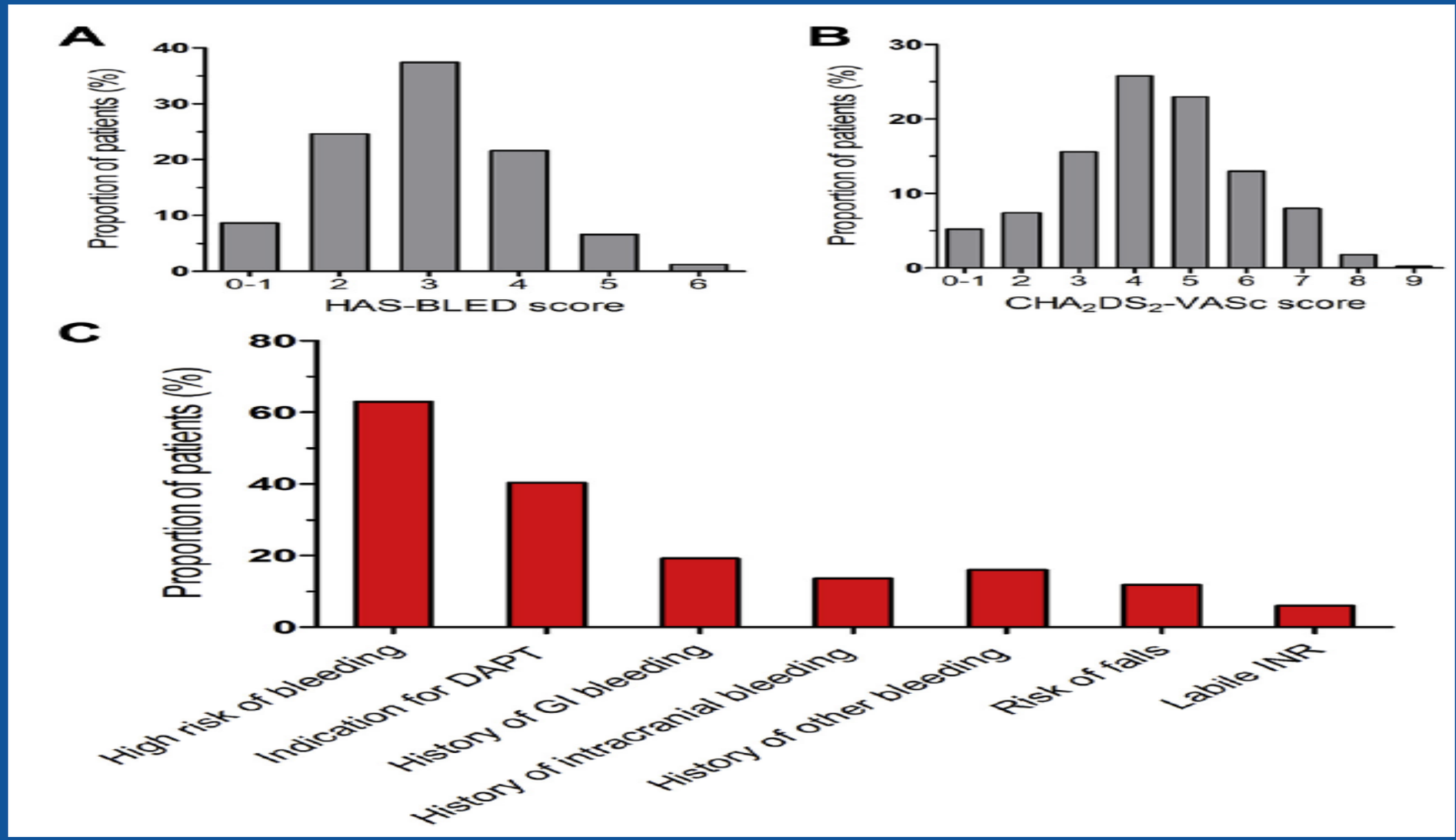
T-F Chao et al., JACC 2011; 58:2380 (Japan) – 565 Pts

2). 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

Bleeding Risk, Ischemic Stroke Risk, Indications for Left Atrial Appendage Closure



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

AF - CLINICAL CHALLENGES (14) - 2016

1.	Presentation:	Complexity vs Symplicity (ESC)		(2)
2.	Etiology:	General vs Specific		(2)
3.	AC Rx:	When / Bridge / NSAID vs	SCI / NSR	(2)
4.	Aging:	TE & Bleeding vs	Warfarin	(2)
5.	AF / Stent:	Triple Rx vs	Double Rx	(2)
6.	Warf. / NOACs:	Efficacy vs	Safety	(2)
7.	Ablat. Yes / No	AC vs	LAA Closure	(2)

ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471

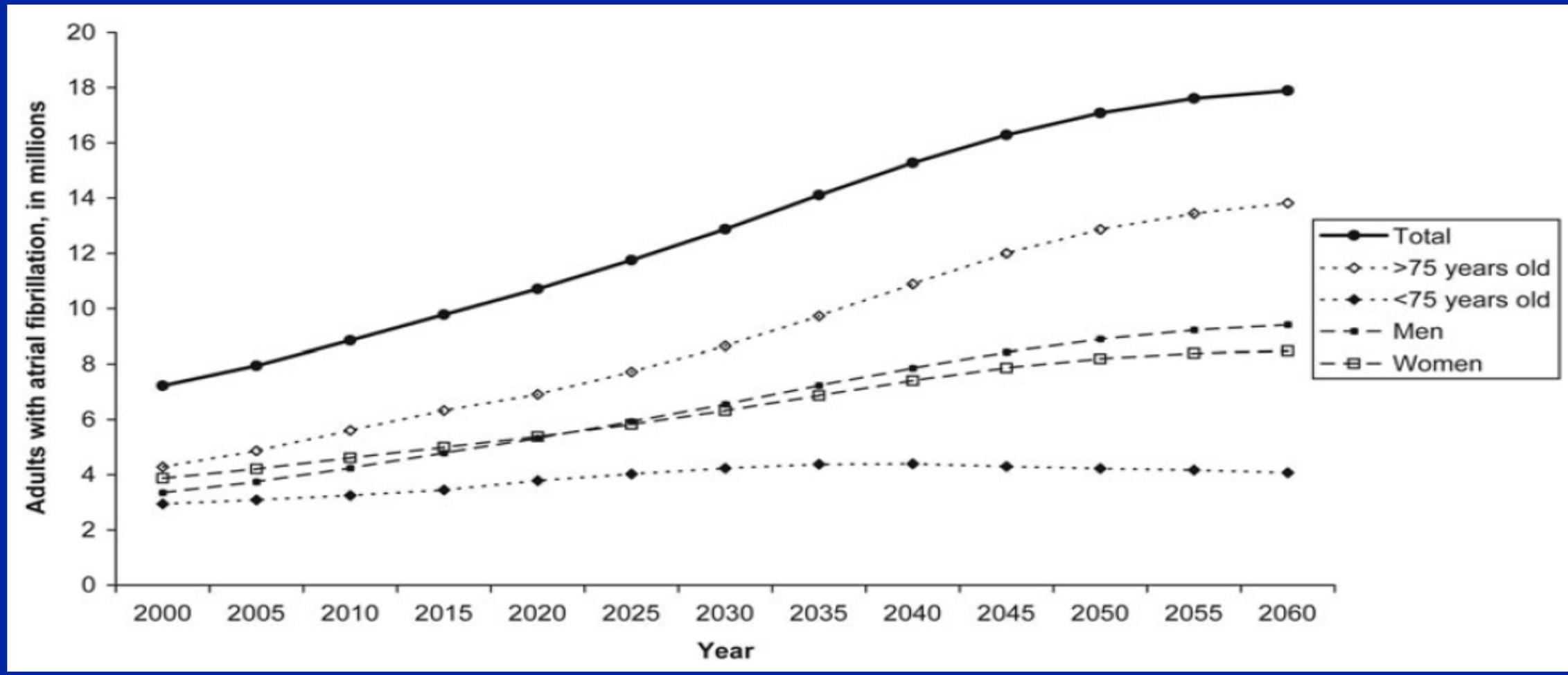
Atrial Fibrillation 2016
Quality of Life and Preventing Stroke

The 14 Clinical Challenges

New York, Dec10, 2016

No Disclosures

1a). Prevalence of Adults With AF The European Union Between 2000 And 2060



BP Krijthe et. al. Eur Heart J. 2013;34:2746

Over Age 50 yr.- AF: 1/2 1st yr of Age, -

Isq. Stroke: 1st yr of Age, Hem. Stroke: 1-2%

1b). Stroke: A Significant Cause Of Poor Health

- Stroke accounts for nearly 10% of all deaths worldwide.
- The number of strokes per year is predicted to rise dramatically as the population ages.
- About 30% strokes are cardioembolic & 15% relate to AF
- Strokes in patients with AF are more severe and have worse outcomes than strokes in people without AF.
- AF almost doubles the death rate from stroke. AF increases the risk of remaining disabled following stroke by almost 50%.

ESC Guidelines EHJ 2010;31:2369 - Working Group Report, EU 2010

Predictors of Early (1-Week) Outcomes Following Left Atrial Appendage Closure With Amplatzer Devices

The aim of this study was to assess predictors of **adverse 1-week outcomes** and determine the effect of LAA) morphology following LAA closure (LAAC) with Amplatzer devices. Between 2009 and 2014, **500 consecutive patients** with AF ineligible or at high risk for oral AC underwent LAAC using Amplatzer devices. **Procedure-and device-related major adverse events (MAEs)** were defined as the composite of death, stroke, major or life-threatening bleeding, serious pericardial effusion, device embolization, major access-site vascular complication, or need for CV surgery within 7 days following the intervention. **Early procedural success was 97.8%, and MAEs occurred in 29 patients (5.8%).** Independent predictors of MAEs included **device repositioning and LVEF<30%,** with no effect of device type & size or LAA morphology

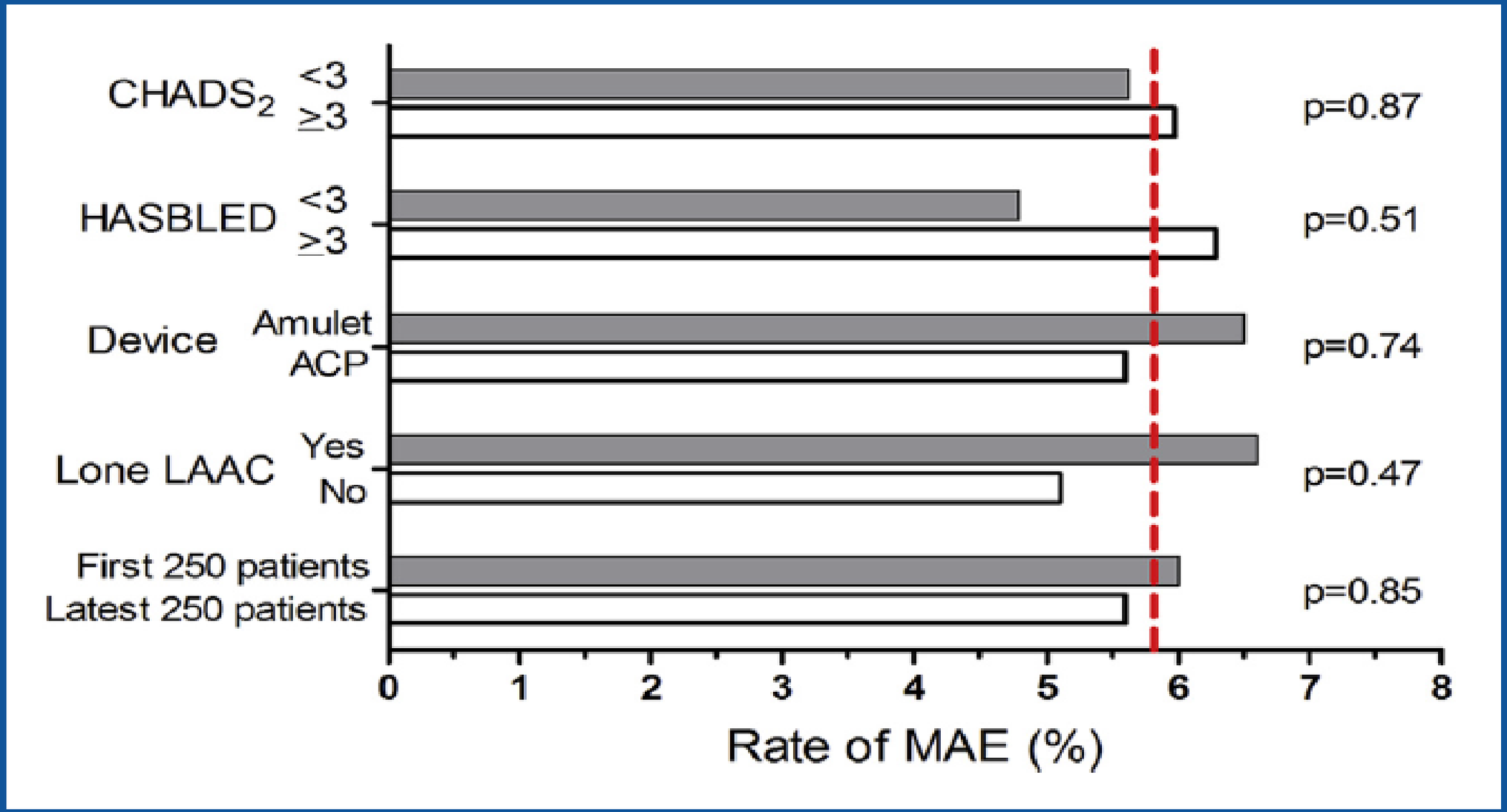
KC Koskinas et al., J Am Coll Cardiol Intv 2016; 9:1374

Baseline Predictors of Device- and Procedure-Related Major Adverse Events Within 7 Days

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Device repositioning	6.82	2.62-17.74	<0.001	9.13	2.85-33.54	0.001
LVEF <30%	3.97	1.49-10.52	0.005	4.08	1.49-11.20	0.006
Change of device size	2.53	0.82-7.77	0.105			
OAC at baseline	2.19	0.95-5.03	0.066			

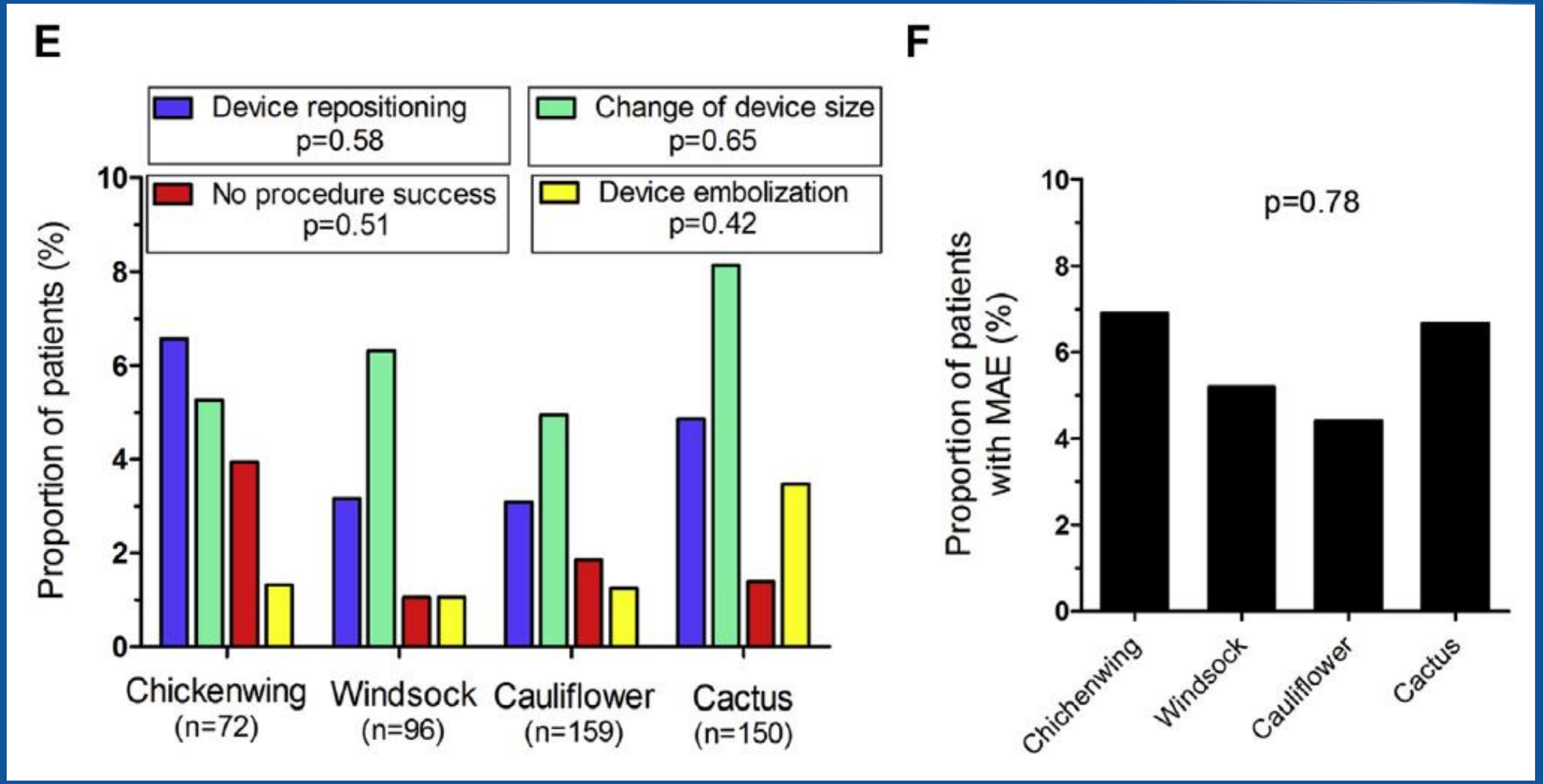
KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374

Rates of Major Adverse Events Within 7 Days Stratified on Patient & Device-Related Characteristics



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

Baseline Predictors of Patients-Related Major Adverse Events Within 7 Days



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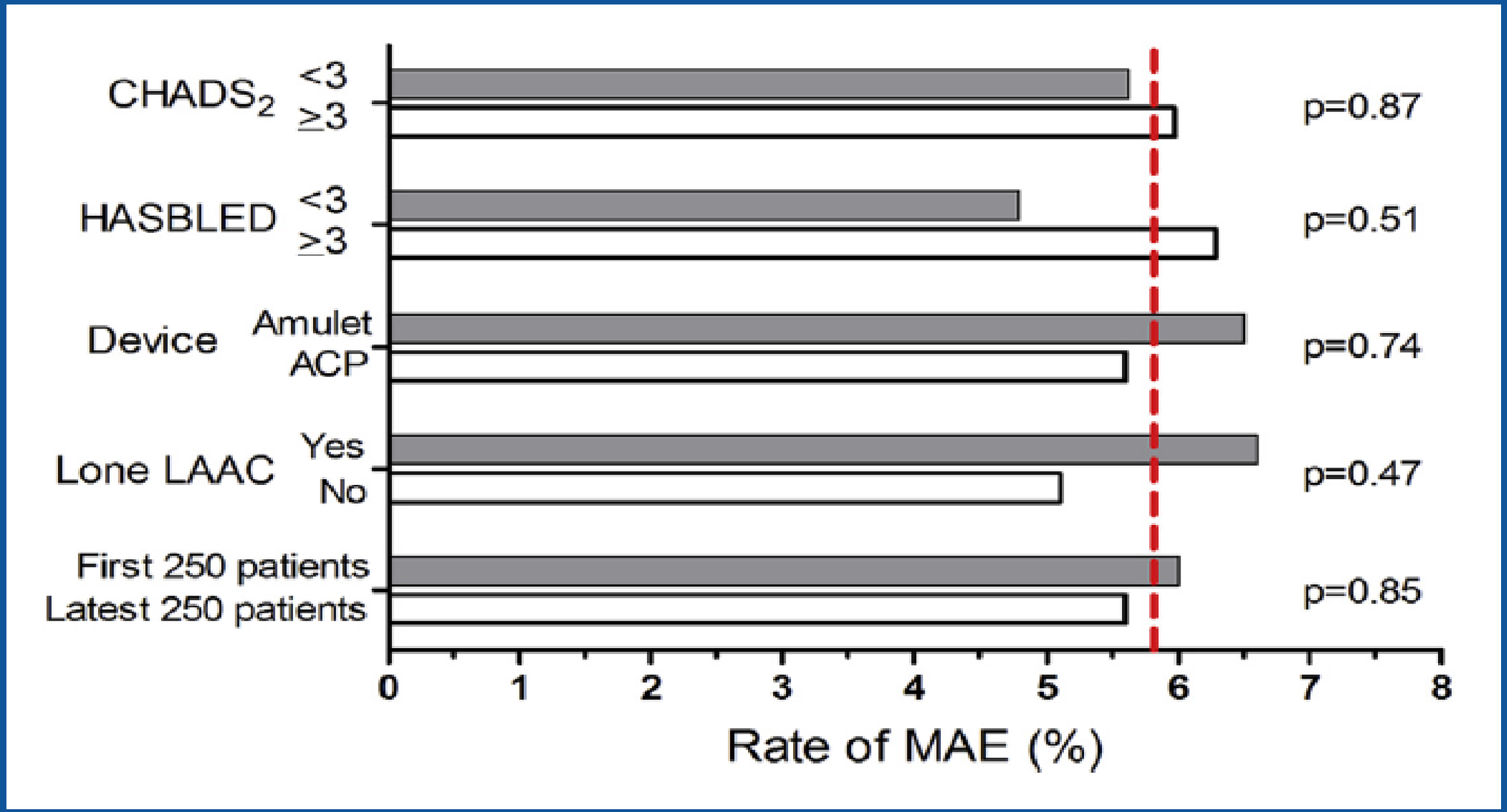

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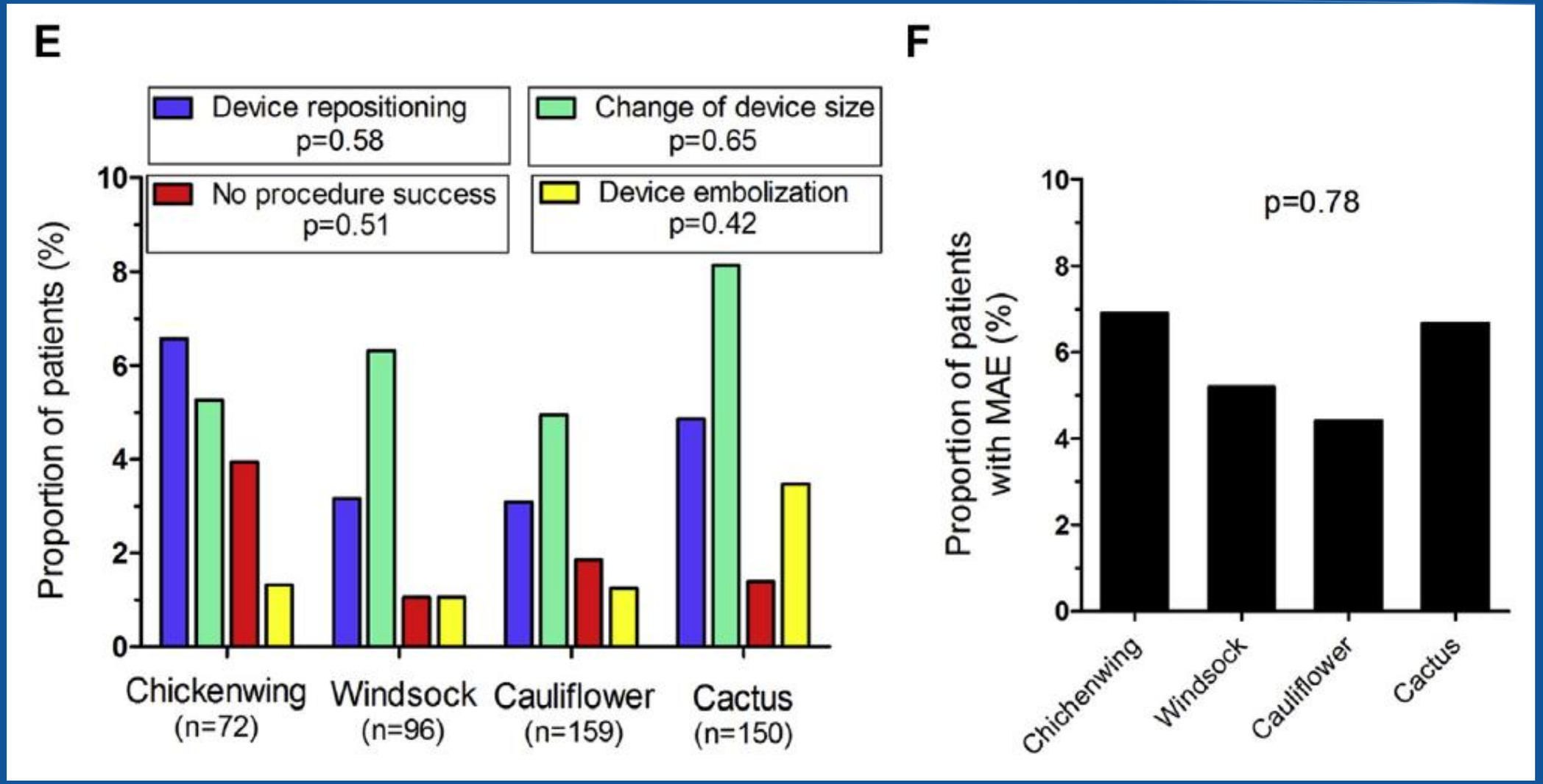


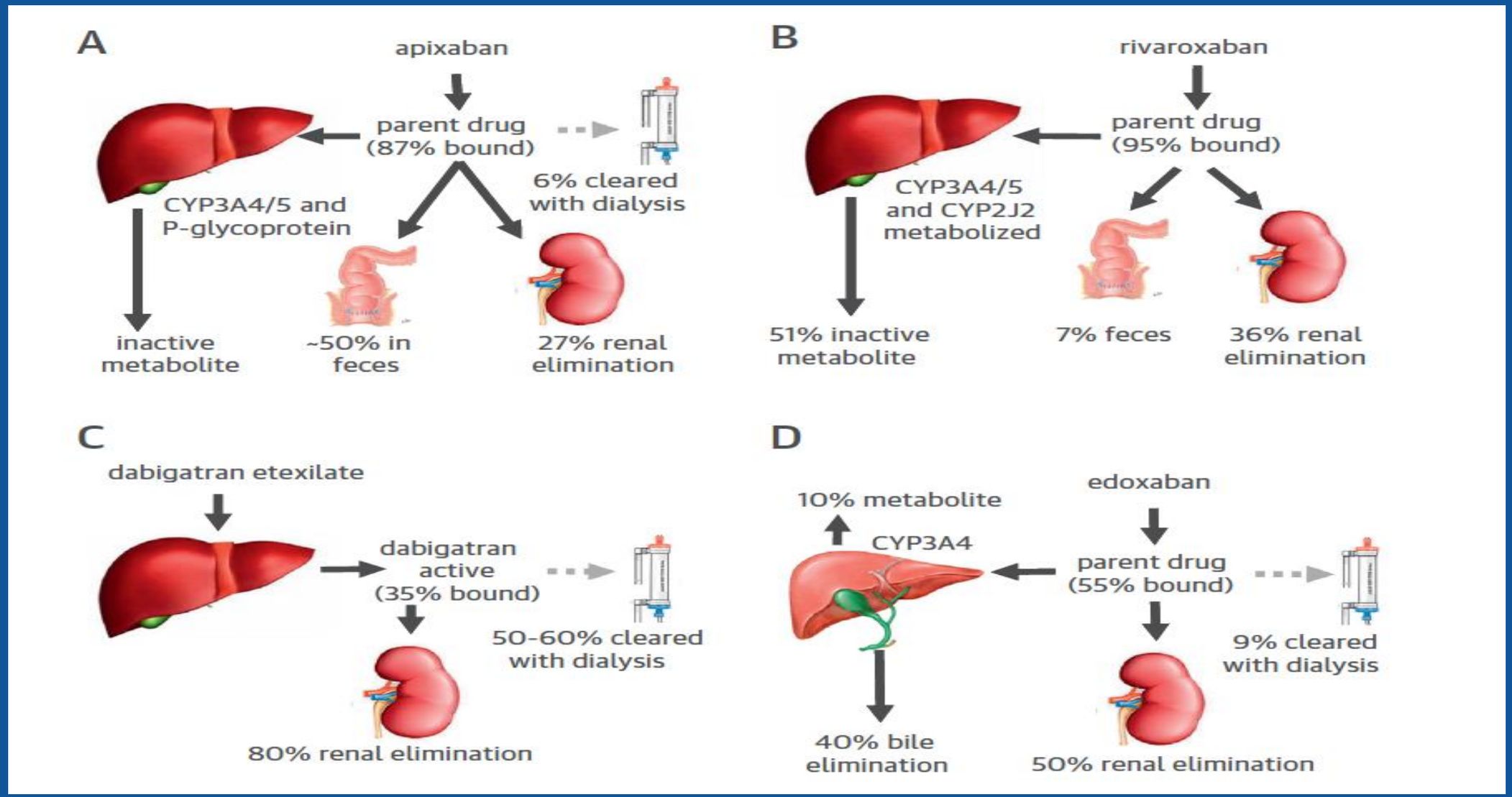
KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374

Characteristics of Warfarin & NOAC Agents

	Warfarin	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Renal clearance of parent drug	<1%	27%	36%	80%	50%
Removal with 4 h of hemodialysis	<1%	7%	<1%	50%-60%	9%
Volume of distribution, l (66)	8	21	50	50-10	107
Reversal agent	Vitamin K, FFP, 4F-PCC	4F-PCC	4F-PCC	Idarucizumab	4F-PCC
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)†

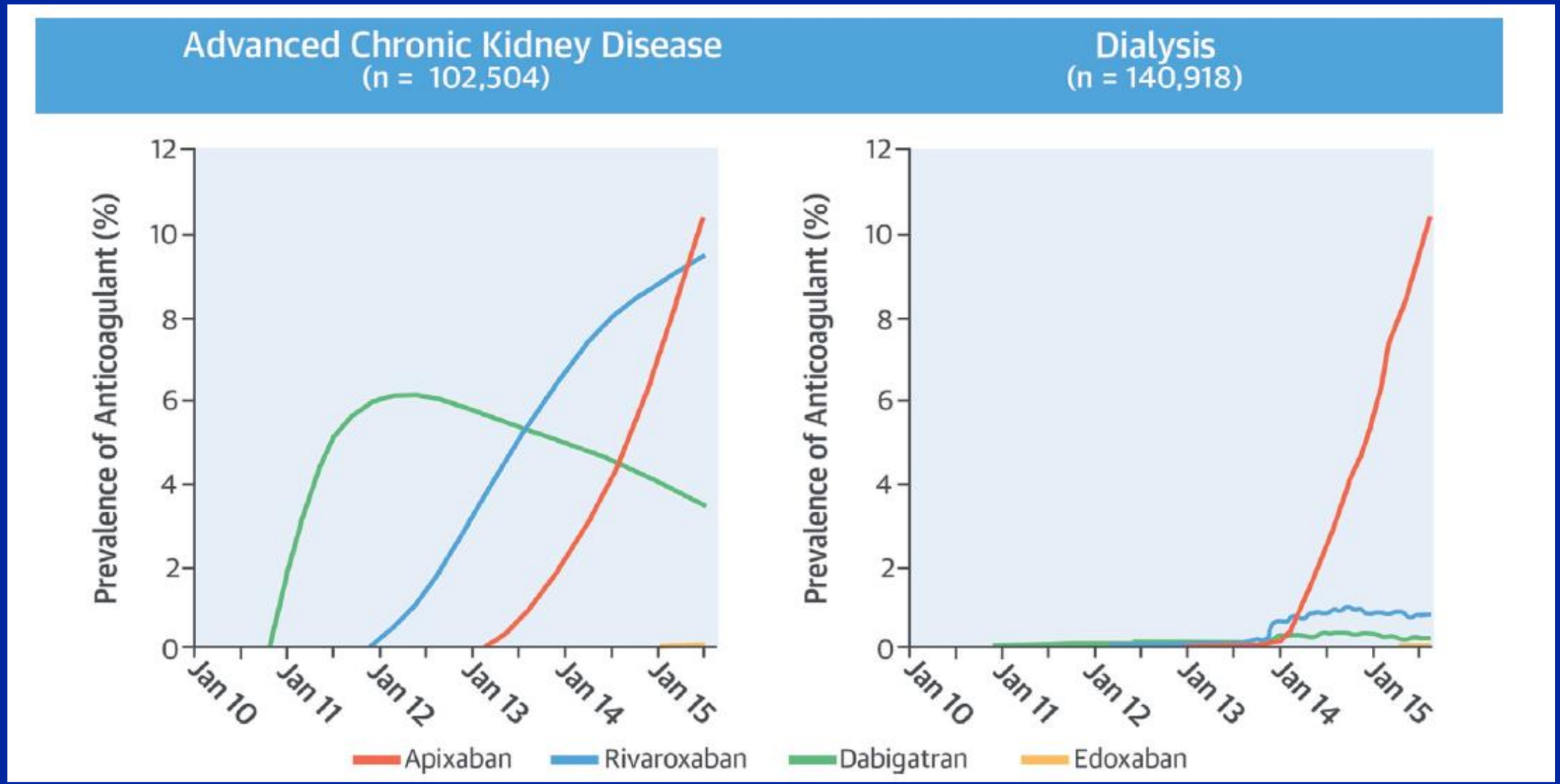
KE Chan et. al. J Am Coll Cardiol 2016;67:2888

Pharmacokinetics of NOAC Agents



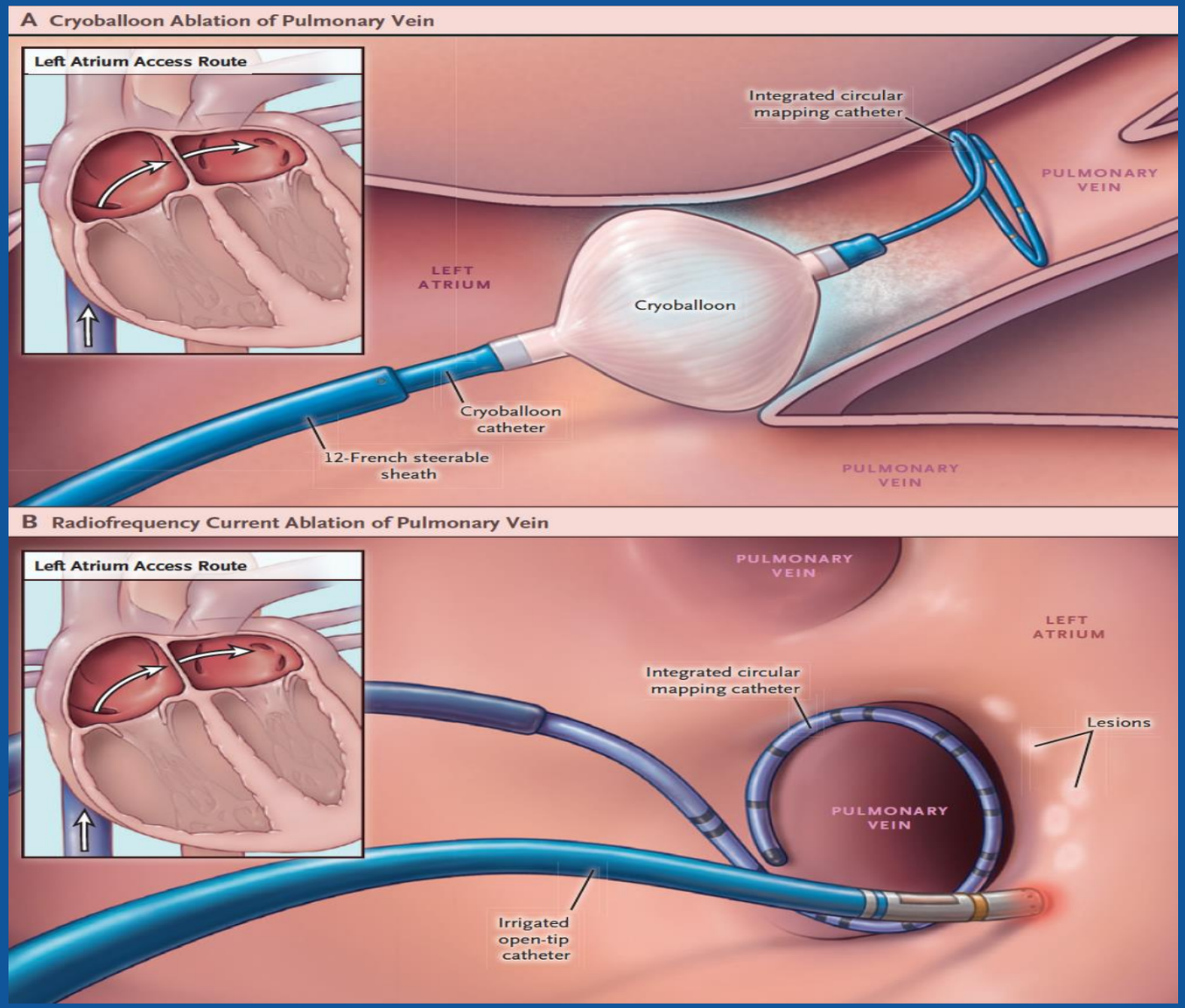
KE Chan et. al. J Am Coll Cardiol 2016;67:2888

Use of NOAC Agents in Patients With Advanced CKD and on Dialysis: Substantial and Growing



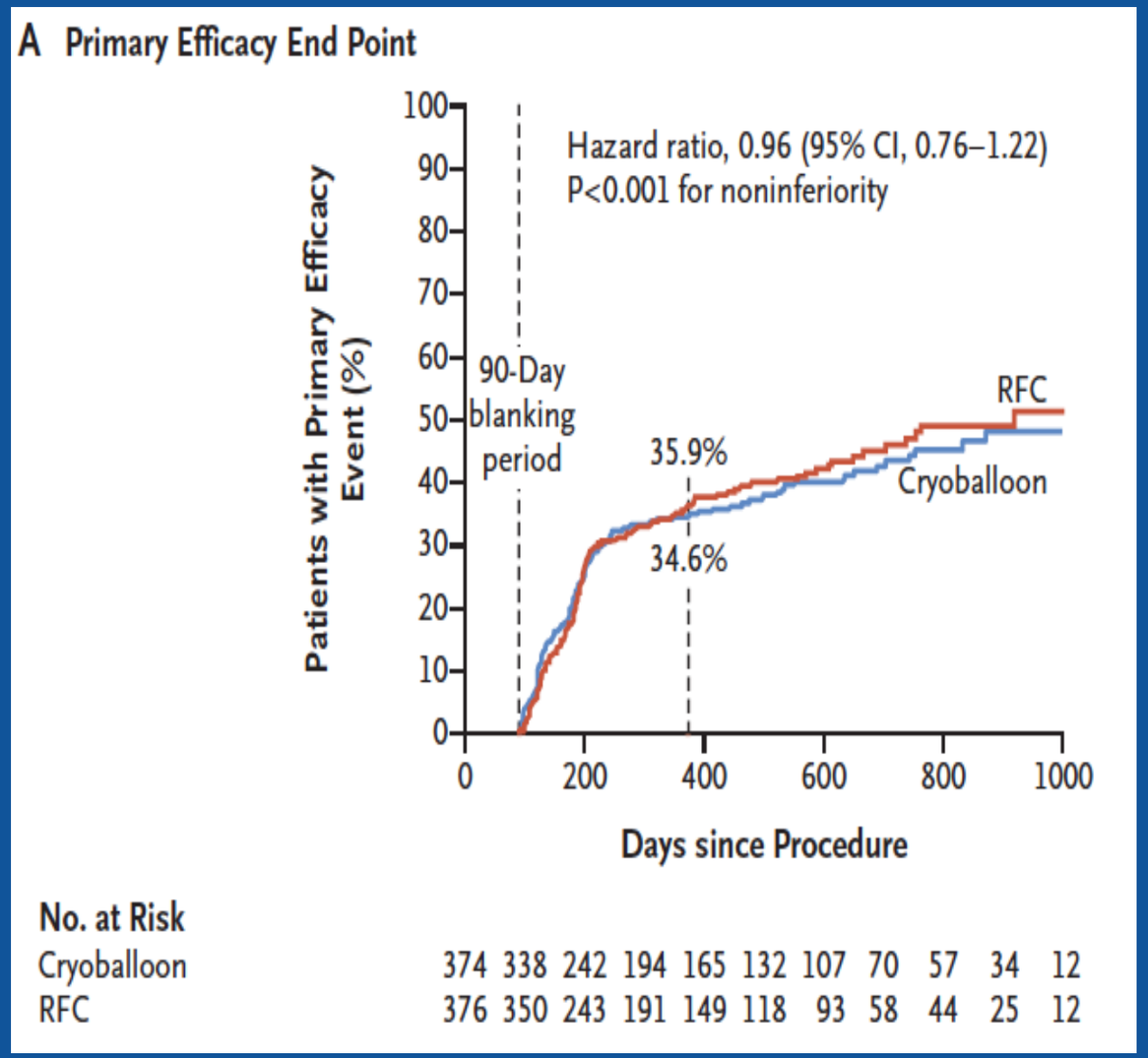
KE Chan et. al. J Am Coll Cardiol 2016;67:2888

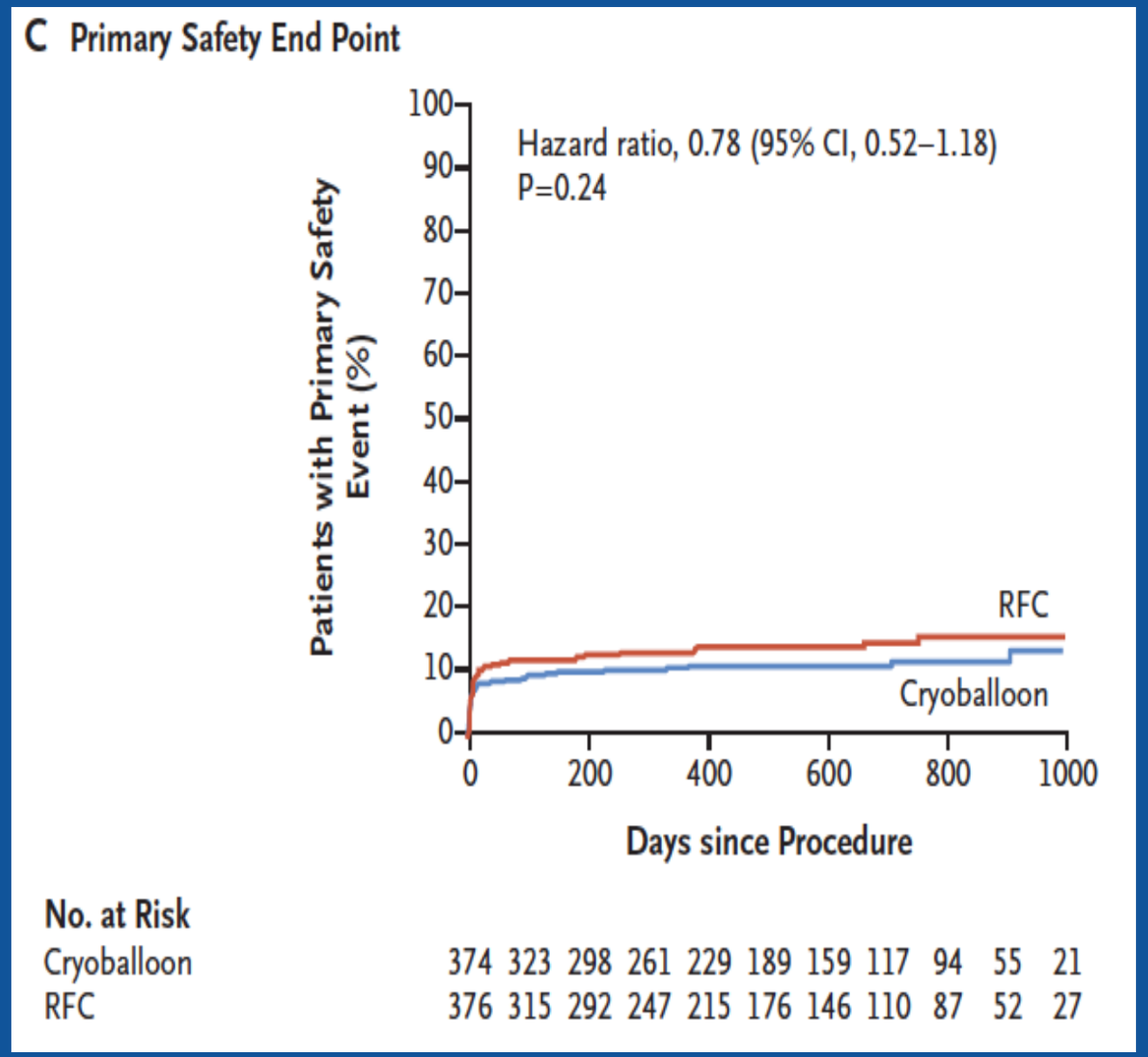
Catheter Ablation Methods



FIRE AND ICE (K-H Kuck et. al.) N Engl J Med 2016;374:2235.

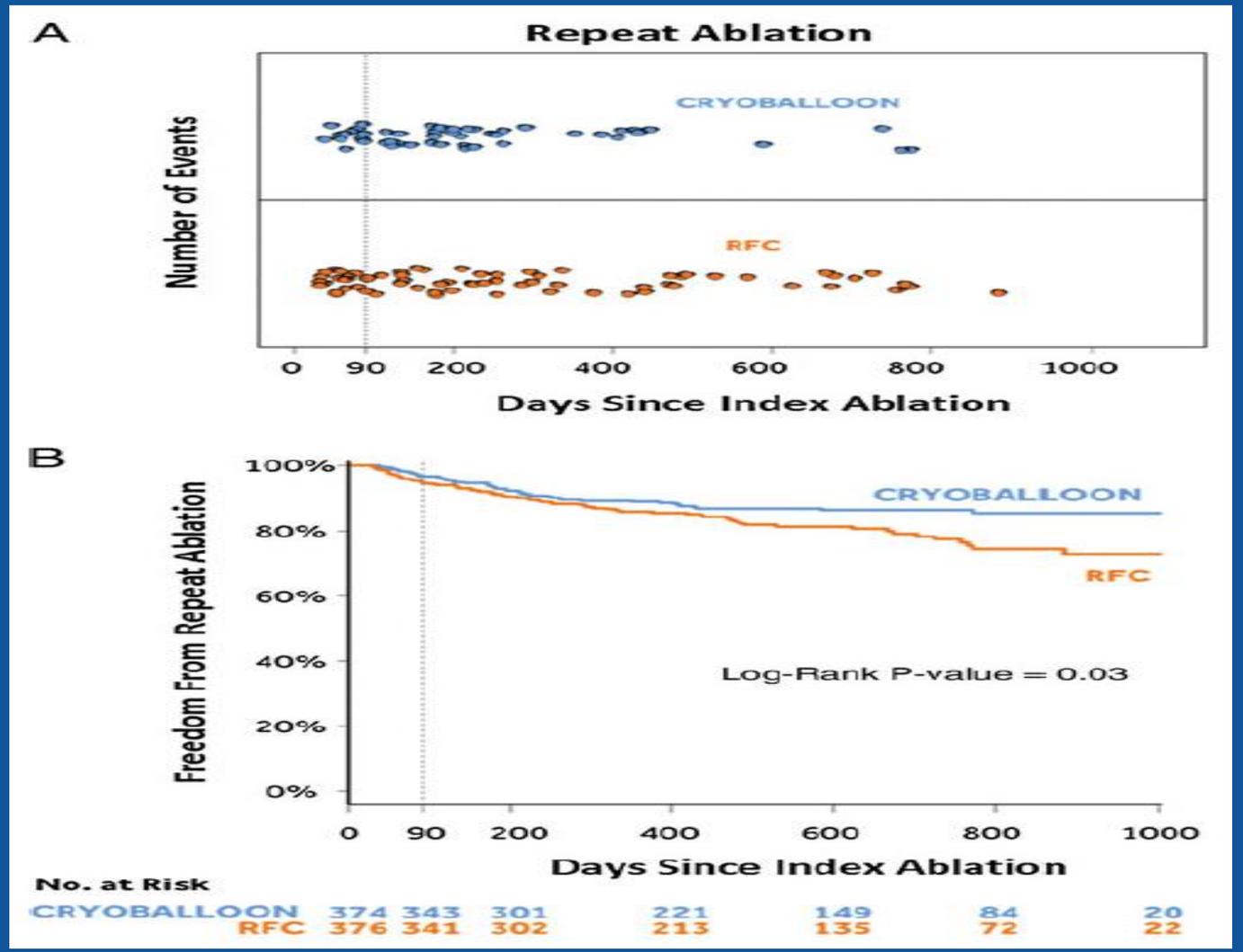
Event-free Survival for the Primary Efficacy and Safety End Points in the Intention-to-Treat Cohort





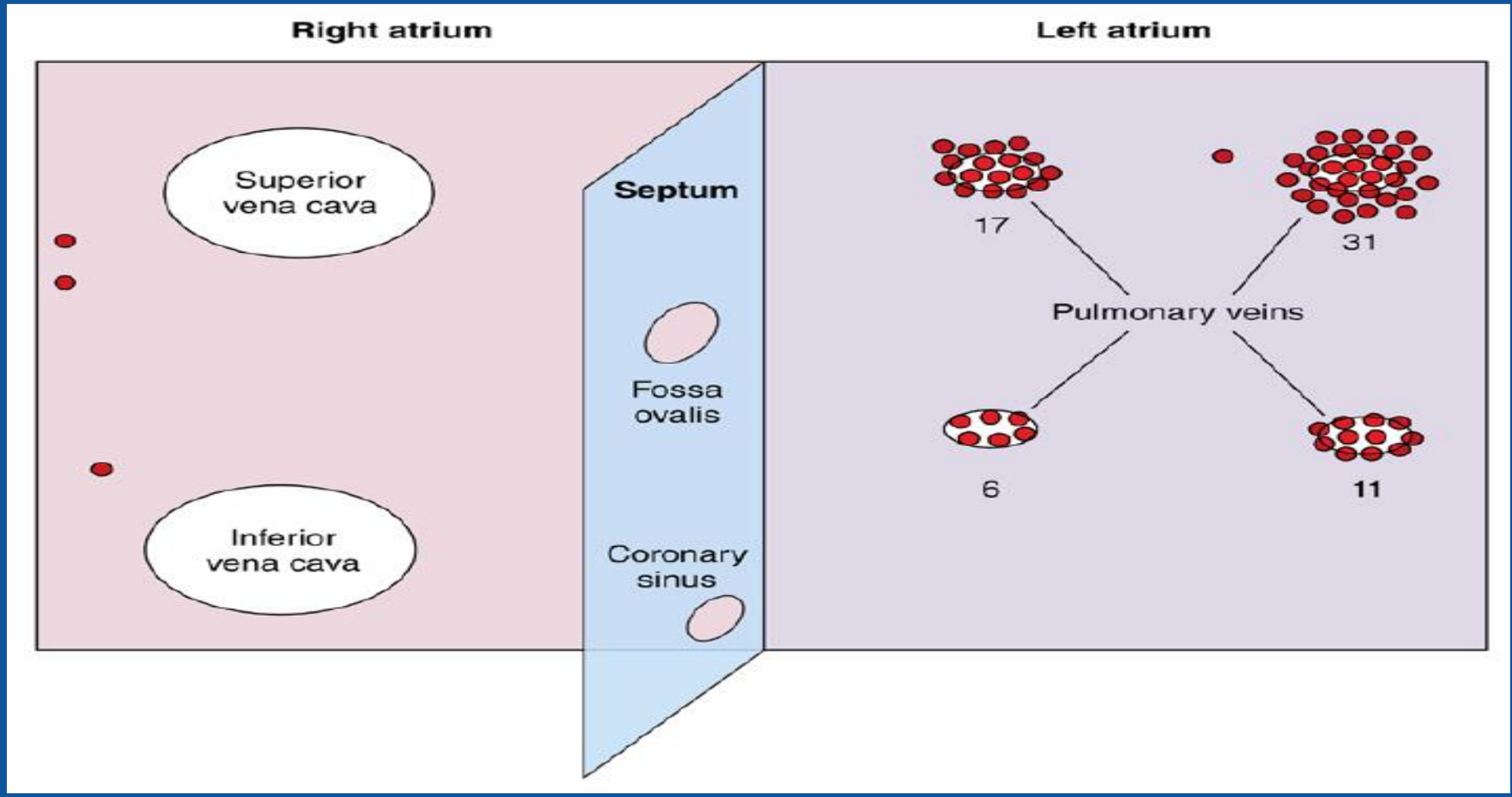
FIRE AND ICE (K-H Kuck et. al.) N Engl J Med 2016;374:2235

Catheter Ablation Methods
Repeat Ablations



FIRE AND ICE (K-H Kuck et. al.) N Engl J Med 2016;374:2235

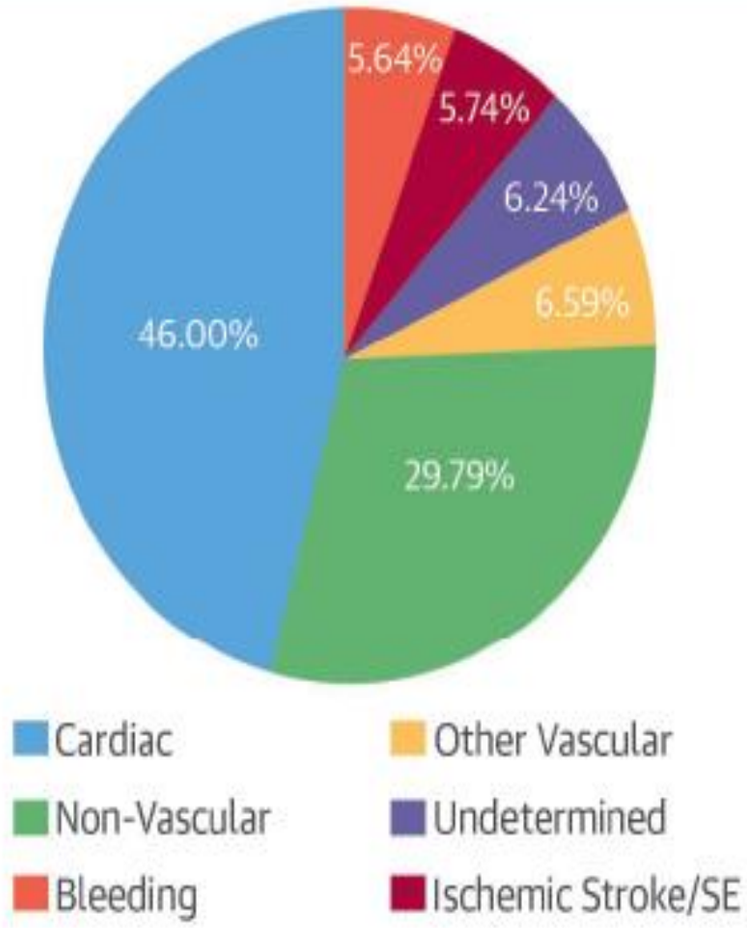
Locations Of Atrial Tachycardia That Initiated AF In 45 Patients Reported In 1998



MS Link et. al. Circulation 2016;134:339.

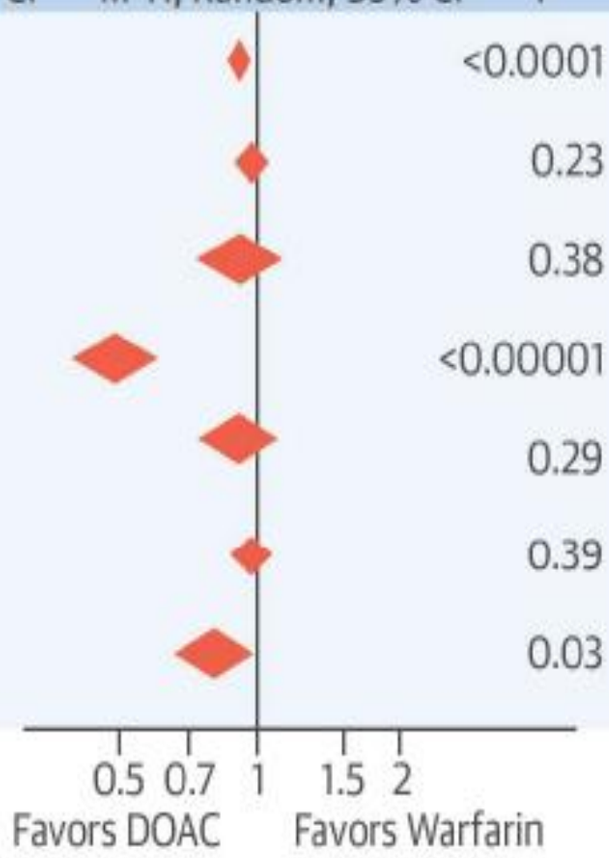
Meta-analysis Of Causes Of Death In Patients Receiving NOACs For Prevention Of Stroke And Systemic Embolism In AF

Causes of Death (n = 6,206)

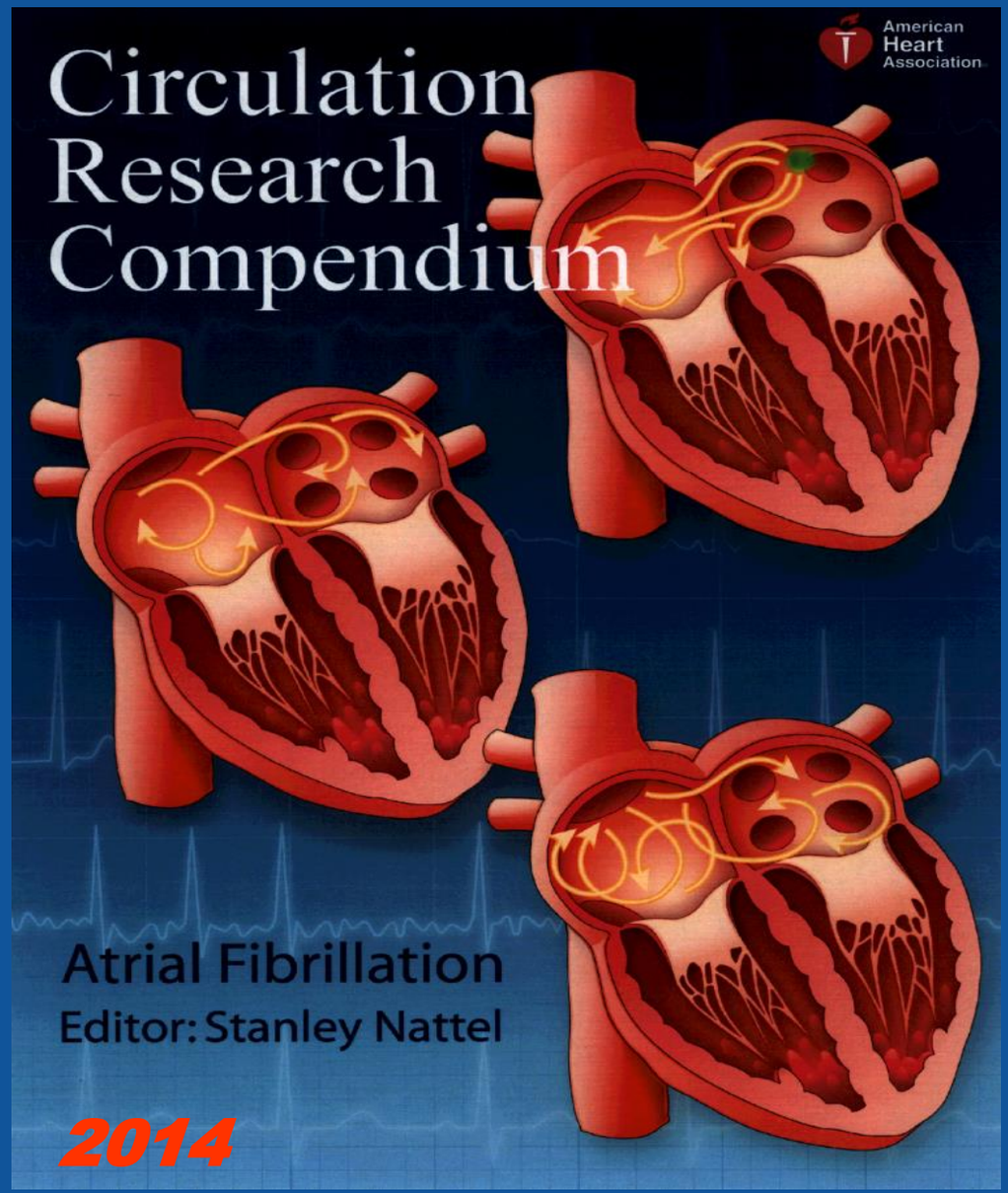


Comparison Between DOACs and Warfarin for Causes of Death

Study or Subgroup	Risk Ratio M-H, Random, 95% CI	P
All-Cause Death	0.90	<0.0001
Cardiac Death	0.96	0.23
Ischemic Stroke/SE	0.91	0.38
Fatal Bleeding	0.49	<0.00001
Other Vascular Death	0.90	0.29
Non-Vascular Death	0.96	0.39
Undetermined Death	0.80	0.03



A Gomez-Outes et. al. 2016.



ACC / AHA / HRS - JACC 2014; 64: 2246

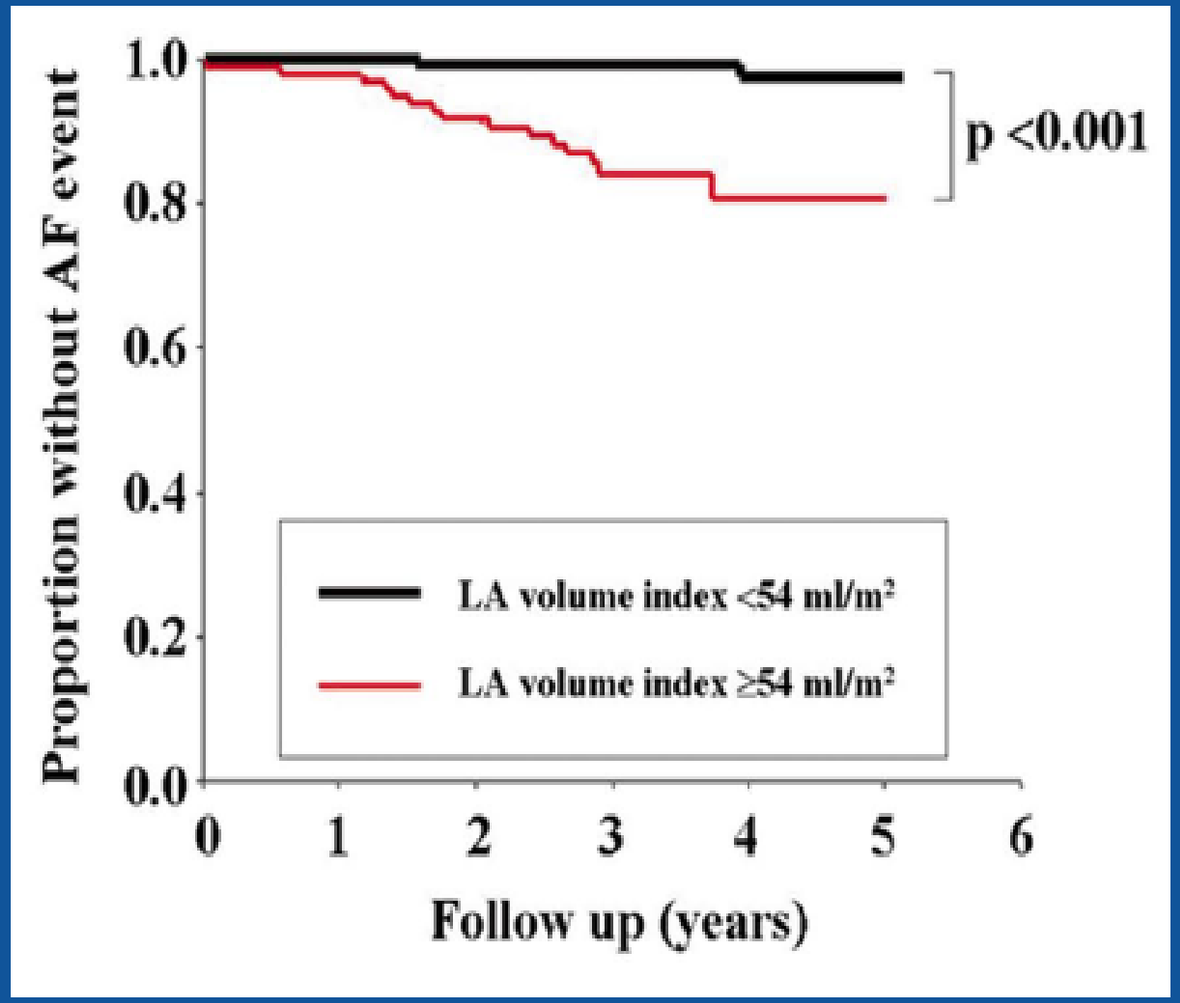
ESC - EHJ 2013; 34:1471

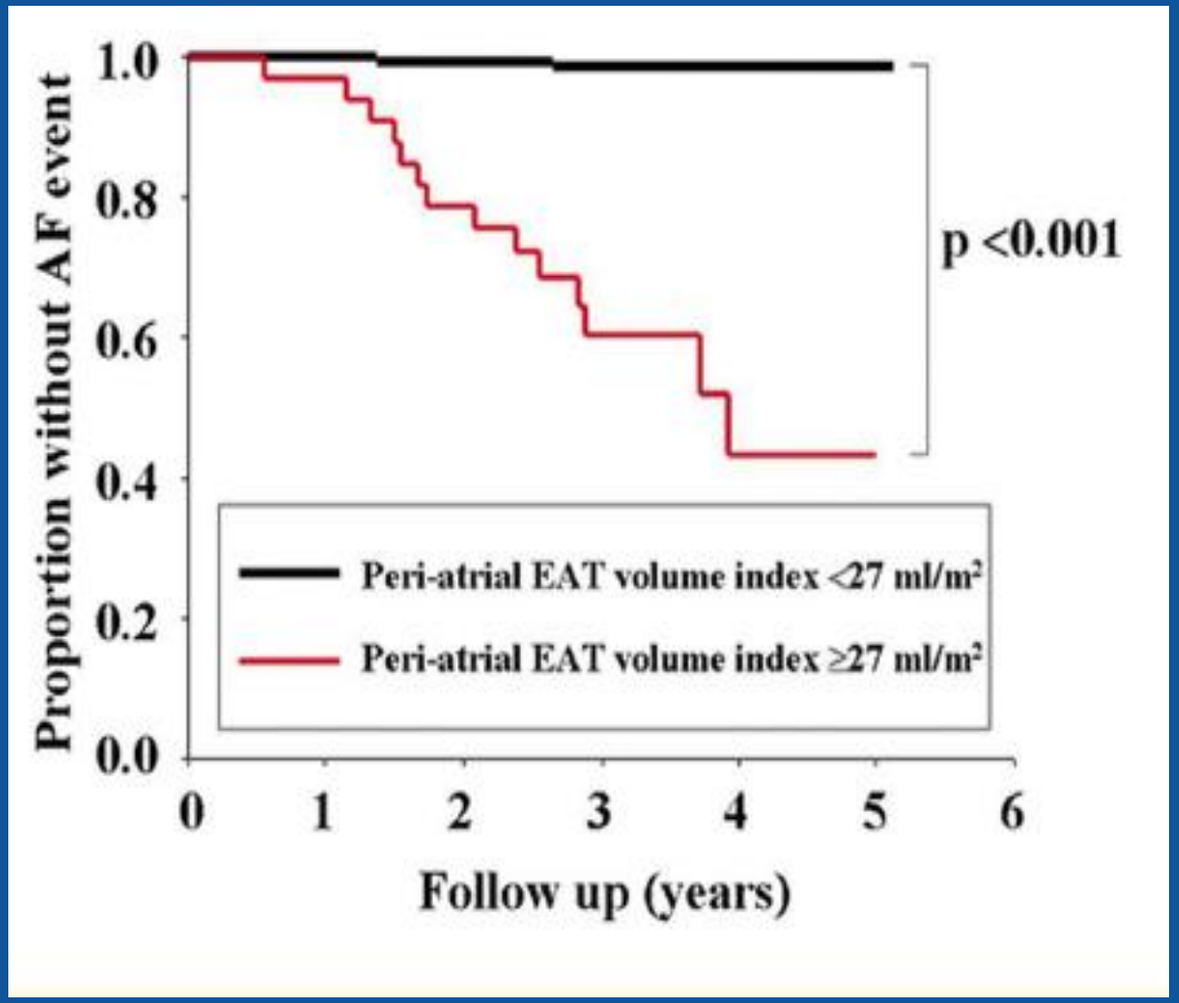
2) AF Symptoms / EtiologyEHRA Score

Classification of AF-related symptoms (EHRA score)	
EHRA class	**Explanation**
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

ESC Guidelines (P Kirchhof, AJ Camm et al) EHJ 2013;34:1471 – ANSD !!!.

2a). Obesity - Peri-atrial EAT Volume Indexes (CT)
AF Events According To LA Volume Index





K Nakanishi et. al. Circ J 2012;76:2748 (Osaka)- Adipocytokines

HS Abed et. al. JAMA. 2013;310:2050 - < Weight, < AF-Australia 2015

Clinical Studies Showing An Association Of Obesity With AF

Clinical studies

Study name	Study design	Clinical endpoints	Outcomes
Abed et al.[43]	150 obese AF patients randomized to risk factor management (RFM) vs. conventional therapy	Primary: AF symptom burden and severity Secondary: AF burden and echocardiographic parameters	RFM results in more marked decrease in body weight and improved cardio-metabolic profile. This was associated with improved AF symptom burden, symptom severity, AF burden, and echocardiographic structural parameters
ARREST-AF cohort *Pathak et al.*[44]	149 obese AF patients with $\geq$1 cardiac risk factor having ablation were offered RFM. Patients were followed prospectively for	Primary: Recurrent AF Secondary: AF frequency, duration and symptoms	RFM in patients having ablation is associated with superior procedural success, improved AF duration, AF frequency, and AF symptom severity. This correlates with weight loss and improved cardio-metabolic risk factor profiles (control vs. RFM group: HR 2.3 (95% CI 1.5–3.6) $P < 0.001$).
LEGACY cohort *Pathak et al.*[45]	825 obese AF patients were offered RFM and followed for 34 $\pm$ 15 months. Outcomes were assessed in relation to categories of weight loss and weight-fluctuation	Primary: AF burden Secondary: Echocardiographic structural parameters	AF burden and symptom severity was most improved in patients with the greatest weight loss (>10%). Greatest benefit was observed in patients with stable weights following weight loss. The benefit of weight loss was off-set by weight-fluctuation. Weight loss was associated with favourable cardiac structural changes

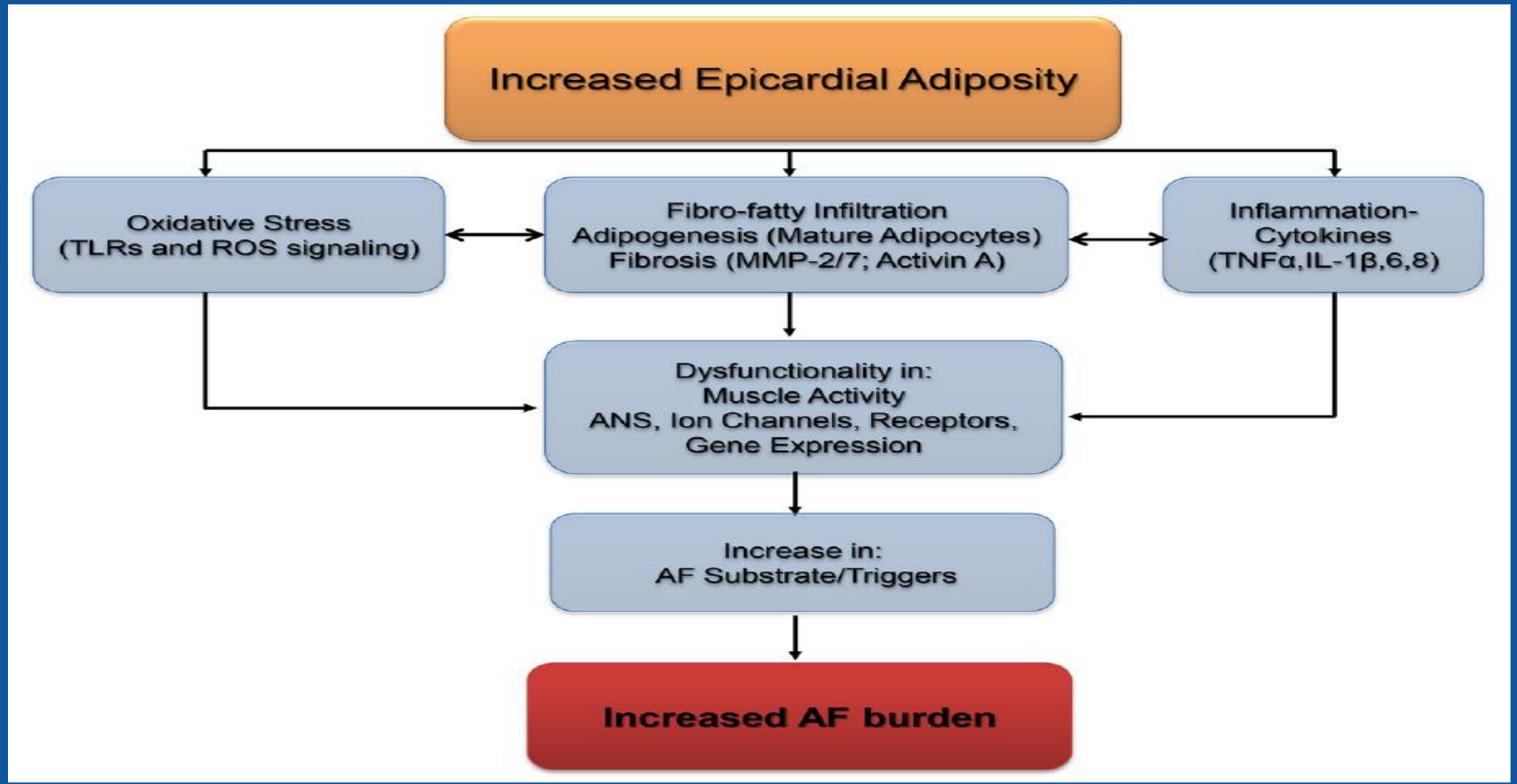
CJ Nalliah et. al. Eur Heart J. 2016;37:1565

HS Abed et. al. JAMA 2013;310:2050

RK Pathak et. al. JACC 2014;64:2222

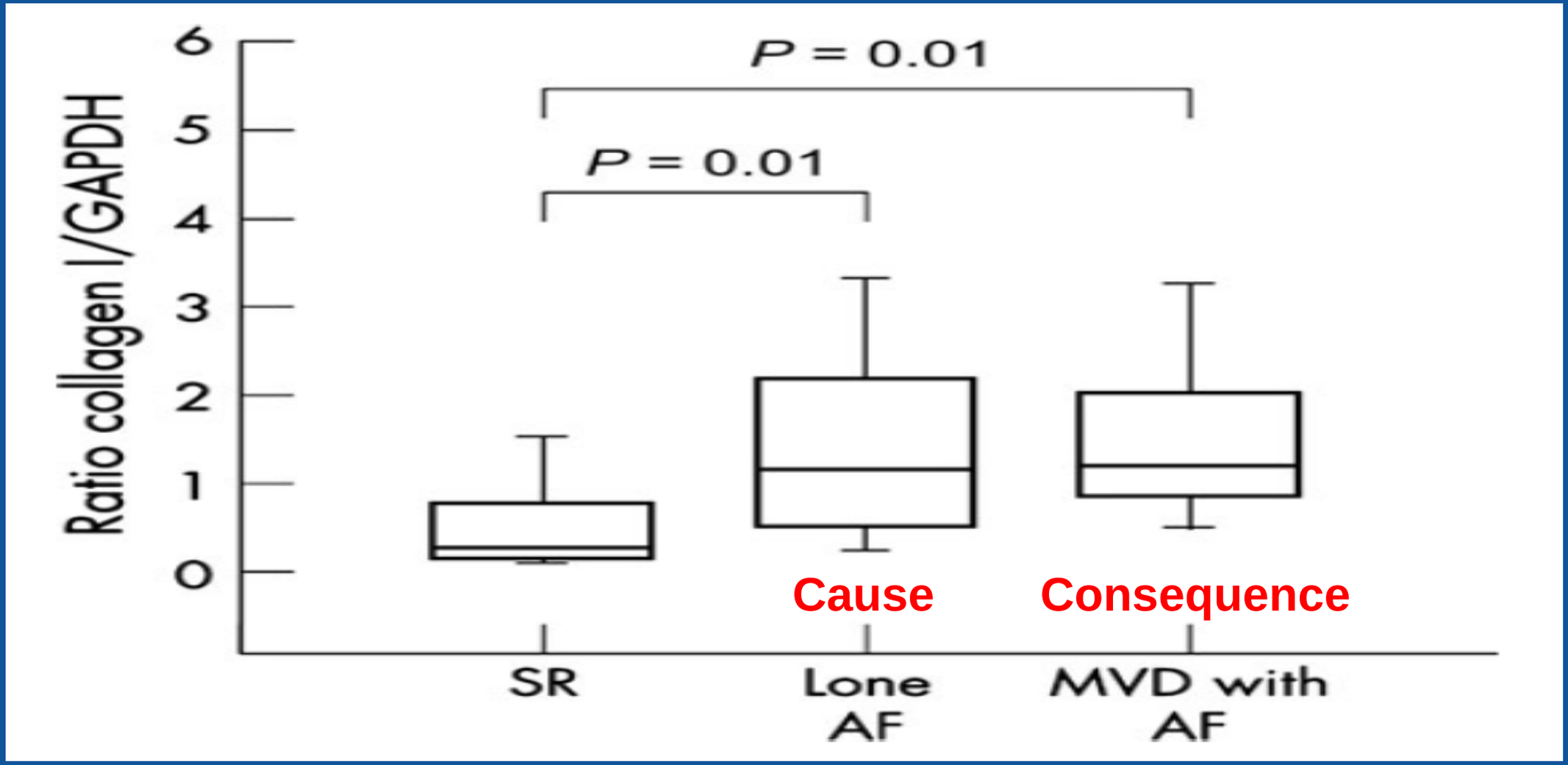
RK Pathak et. al. JACC 2015;65:2159

Mechanisms Underlying Increased AF Risk In Obesity



SV Pandit et. al. Circ Res. 2016;118:1468

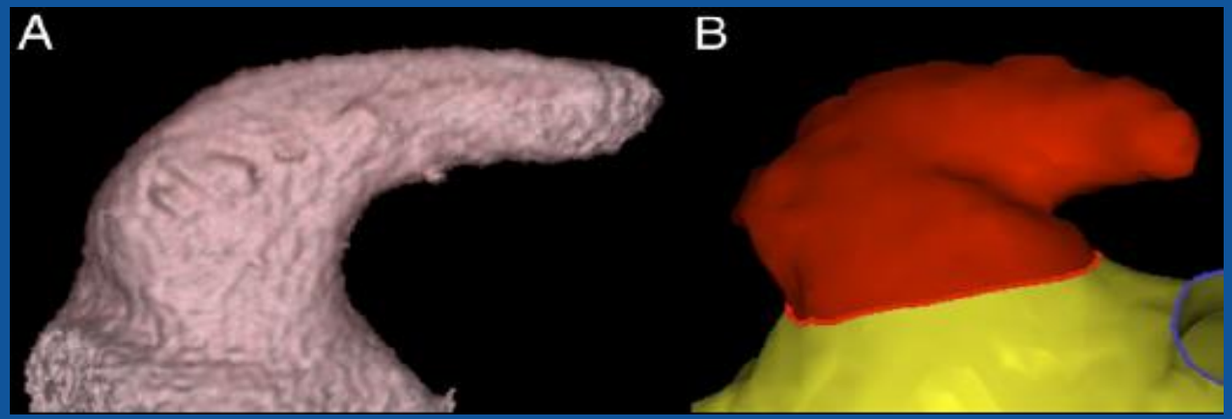
2b). AF Substrate: Towards Specific Fibrotic Atrial Cardiomyopathy



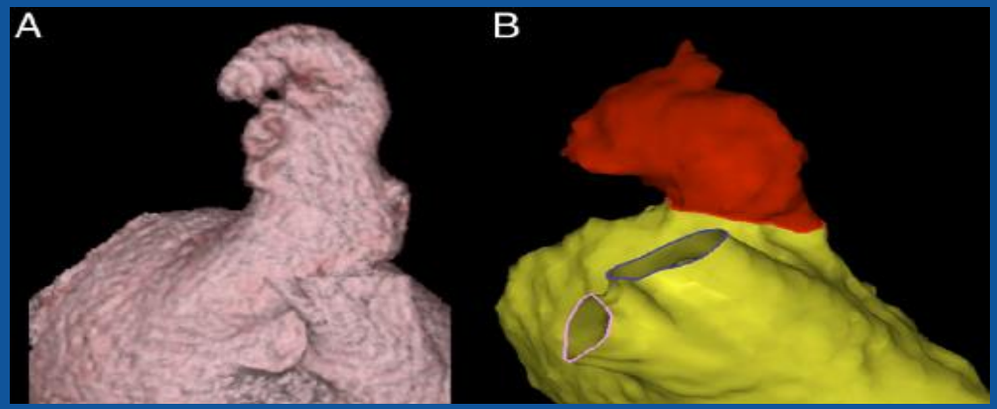
H Kottkamp Eur Heart J. 2013; 34: 2731

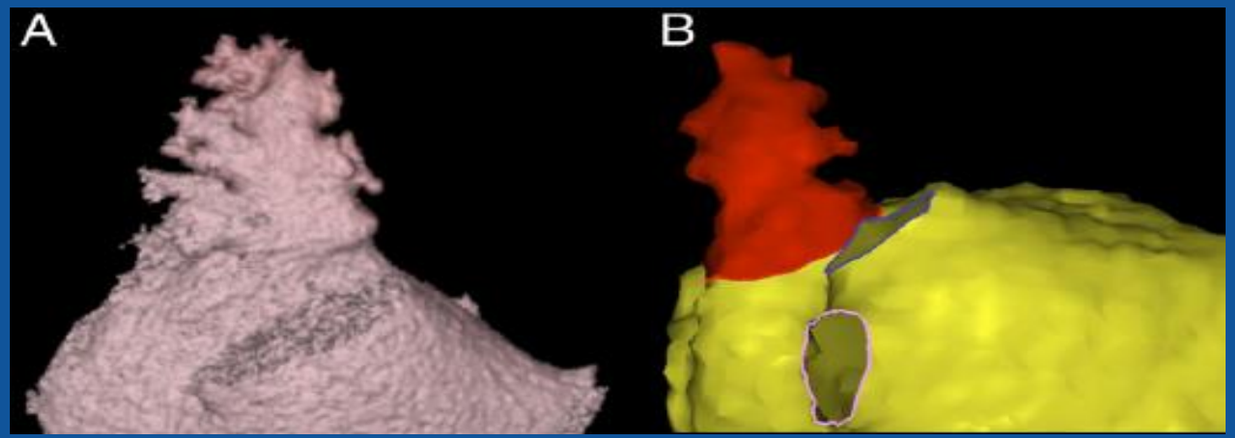
2c) AF - LAA Morphologies (CT, MRI) – N=932

Chicken Wing LAA Morphology

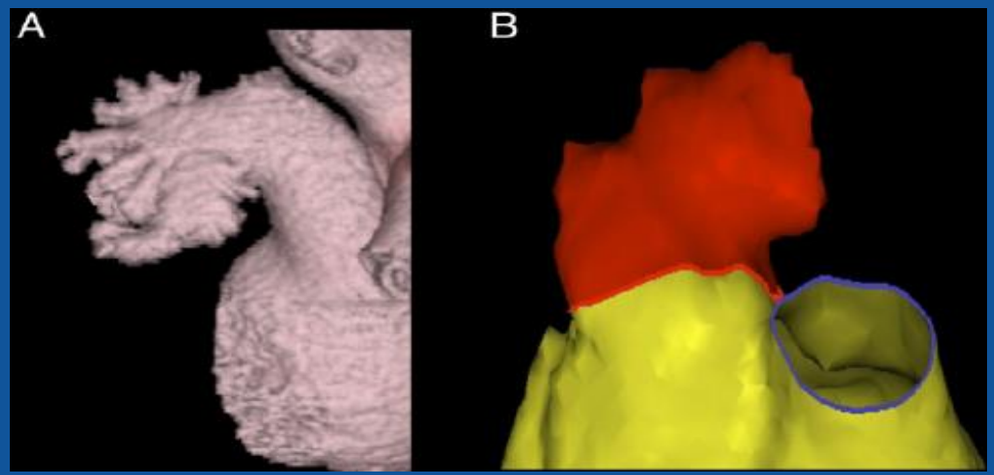


Windsock LAA Morphology





Cactus LAA Morphology



Cauliflower LAA Morphology

L Di Biase et. al. J Am Coll Cardiol 2012;60:531 (Austin, Foggia,Turin)

J H Yoon et al., Clin Cardiol 2013; 36:235 (Korea)– **LA Function>Volume**

2d). Genetics in AF – Familial 5%

Novel Genetic Markers Associate With Atrial Fibrillation Risk in Europeans and Japanese

Steven A. Lubitz, MD, MPH,[1,2] Kathryn L. Lunetta, PhD,[3,4] Honghuang Lin, PhD,[3,5] Dan E. Arking, PhD,[6] Stella Trompet, PhD,[7,8] Guo Li, MS,[9] Bouwe P. Krijthe, MSc,[10,11] Daniel I. Chasman, PhD,[12,13] John Barnard, PhD,[14] Marcus E. Kleber, PhD,[15] Marcus Dörr, MD,[16,17] Kouichi Ozaki, PhD,[18] Albert V. Smith, PhD,[19] Martina Müller-Nurasyid, MSc, PhD,[20,21,22] Stefan Walter, PhD,[23] Sunil K. Agarwal, MD, PhD,[24] Joshua C. Bis, PhD,[9] Jennifer A. Brody, BA,[9] Lin Y. Chen, MD, MS,[25] Brendan M. Everett, MD, MPH,[12,26] Ian Ford, PhD,[27] Oscar H. Franco, MD, PhD,[10,11] Tamara B. Harris, MD,[28] Albert Hofman, MD, PhD,[10,11] Stefan Kääb, MD, PhD,[20,29] Saagar Mahida, MB, ChB,[30] Sekar Kathiresan, MD, MPH,[31] Michiaki Kubo, MD, PhD,[32] Lenore J. Launer, PhD,[28] Peter W. Macfarlane, DSc,[33] Jared W. Magnani, MD, MSc,[3,34] Barbara McKnight, PhD,[35] David D. McManus, MD, ScM,[36] Annette Peters, PhD, MPH,[29,37] Bruce M. Psaty, MD, PhD,[9,38,39,40] Lynda M. Rose, MSc,[41] Jerome I. Rotter, MD,[42] Guenther Silbernagel, MD,[43] Jonathan D. Smith, PhD,[44] Nona Sotoodehnia, MD, MPH,[9,45] David J. Stott, MD,[46] Kent D. Taylor, PhD,[47] Andreas Tomaschitz, MD,[48] Tatsuhiko Tsunoda, PhD,[49] Andre G. Uitterlinden, PhD,[10,11,50] David R. Van Wagoner, PhD,[51] Uwe Völker, PhD,[17,52] Henry Völzke, MD,[17,53] Joanne M. Murabito, MD, ScM,[3,54] Moritz F. Sinner, MD, MPH,[20] Vilmundur Gudnason, MD, PhD,[19] Stephan B. Felix, MD,[16,17] Winfried März, MD,[15,55,56] Mina Chung, MD,[51,57] Christine M. Albert, MD, MPH,[12,13,26] Bruno H. Stricker, MB, PhD,[10,11,50,58] Toshihiro Tanaka, MD, PhD,[18,59] Susan R. Heckbert, MD, PhD,[9,39,40] J. Wouter Jukema, MD, PhD,[60] Alvaro Alonso, MD, PhD,[61] Emelia J. Benjamin, MD, ScM,[3,34,62,63] Patrick T. Ellinor, MD, PhD[1,2]

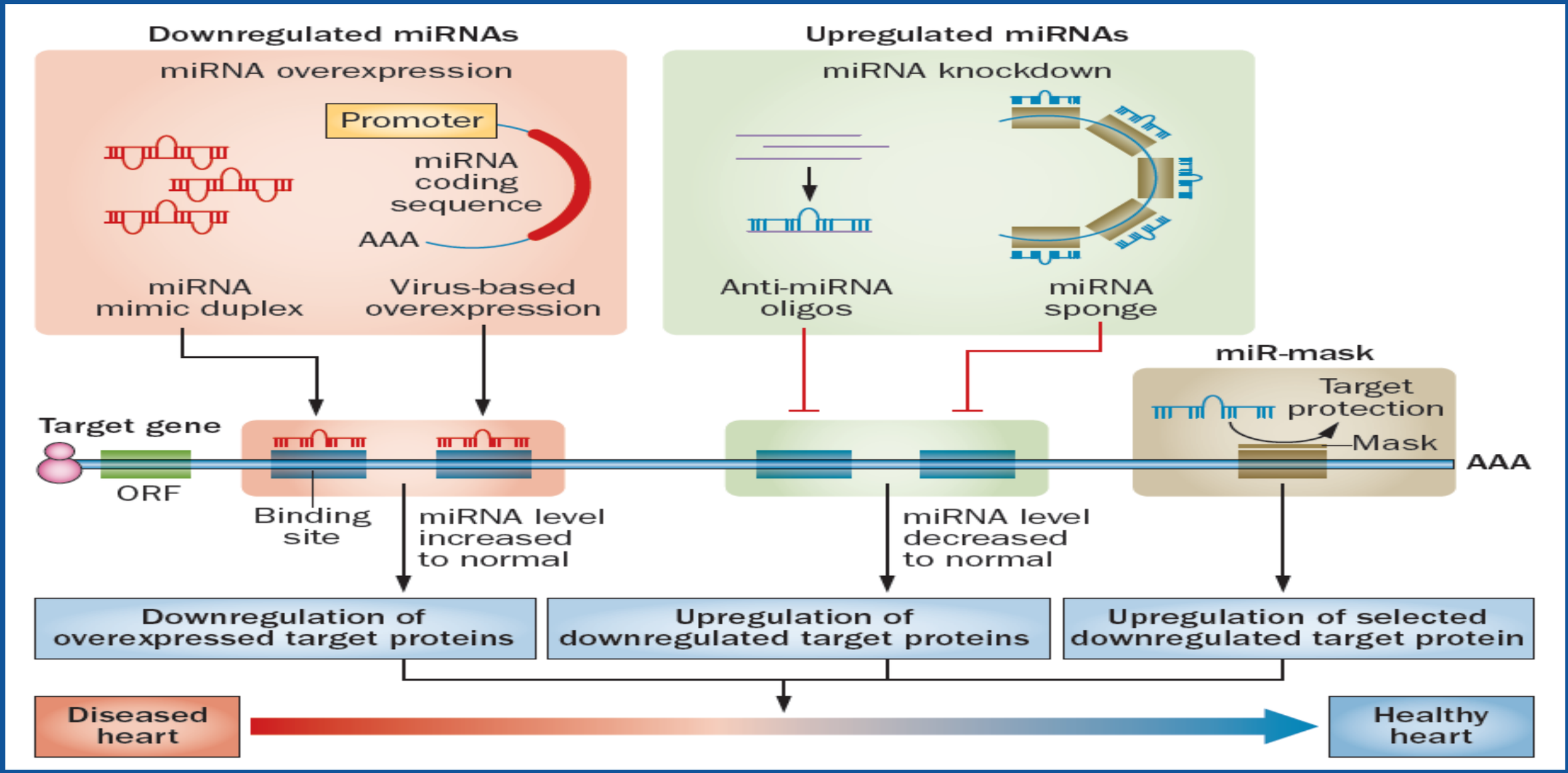
Arrhythmia/Electrophysiology

Integrating Genetic, Transcriptional, and Functional Analyses to Identify 5 Novel Genes for Atrial Fibrillation

Moritz F. Sinner, MD, MPH*; Nathan R. Tucker, PhD*; Kathryn L. Lunetta, PhD*; Kouichi Ozaki, PhD*; J. Gustav Smith, MD, PhD*; Stella Trompet, PhD*; Joshua C. Bis, PhD*; Honghuang Lin, PhD*; Mina K. Chung, MD*; Jonas B. Nielsen, MD*; Steven A. Lubitz, MD, MPH*; Bouwe P. Krijthe, PhD*; Jared W. Magnani, MD, MSc*; Jiangchuan Ye, MD, PhD; Michael H. Gollob, MD; Tatsuhiko Tsunoda, PhD; Martina Müller-Nurasyid, PhD; Peter Lichtner, PhD; Annette Peters, PhD; Elena Dolmatova, MD; Michiaki Kubo, MD, PhD; Jonathan D. Smith, PhD; Bruce M. Psaty, MD, PhD; Nicholas L. Smith, PhD; J. Wouter Jukema, MD, PhD; Daniel I. Chasman, PhD; Christine M. Albert, MD, MPH; Yusuke Ebana, MD, PhD; Tetsushi Furukawa, MD, PhD; Peter W. Macfarlane, DSc; Tamara B. Harris, MD, MS; Dawood Darbar, MD; Marcus Dörr, MD; Anders G. Holst, MD, PhD; Jesper H. Svendsen, MD, DMSc; Albert Hofman, MD, PhD; Andre G. Uitterlinden, MD, PhD; Vilmundur Gudnason, MD; Mitsuaki Isobe, MD, PhD; Rainer Malik, PhD; Martin Dichgans, MD; Jonathan Rosand, MD, MSc; David R. Van Wagoner, PhD; METASTROKE Consortium; AFGen Consortium; Emelia J. Benjamin, MD, ScM†; David J. Milan, MD†; Olle Melander, MD, PhD†; Susan R. Heckbert, MD, PhD†; Ian Ford, PhD†; Yongmei Liu, MD, PhD†; John Barnard, PhD†; Morten S. Olesen, MSc, PhD†; Bruno H.C. Stricker, MB, PhD†; Toshihiro Tanaka, MD, PhD†; Stefan Kääb, MD, PhD†; Patrick T. Ellinor, MD, PhD†

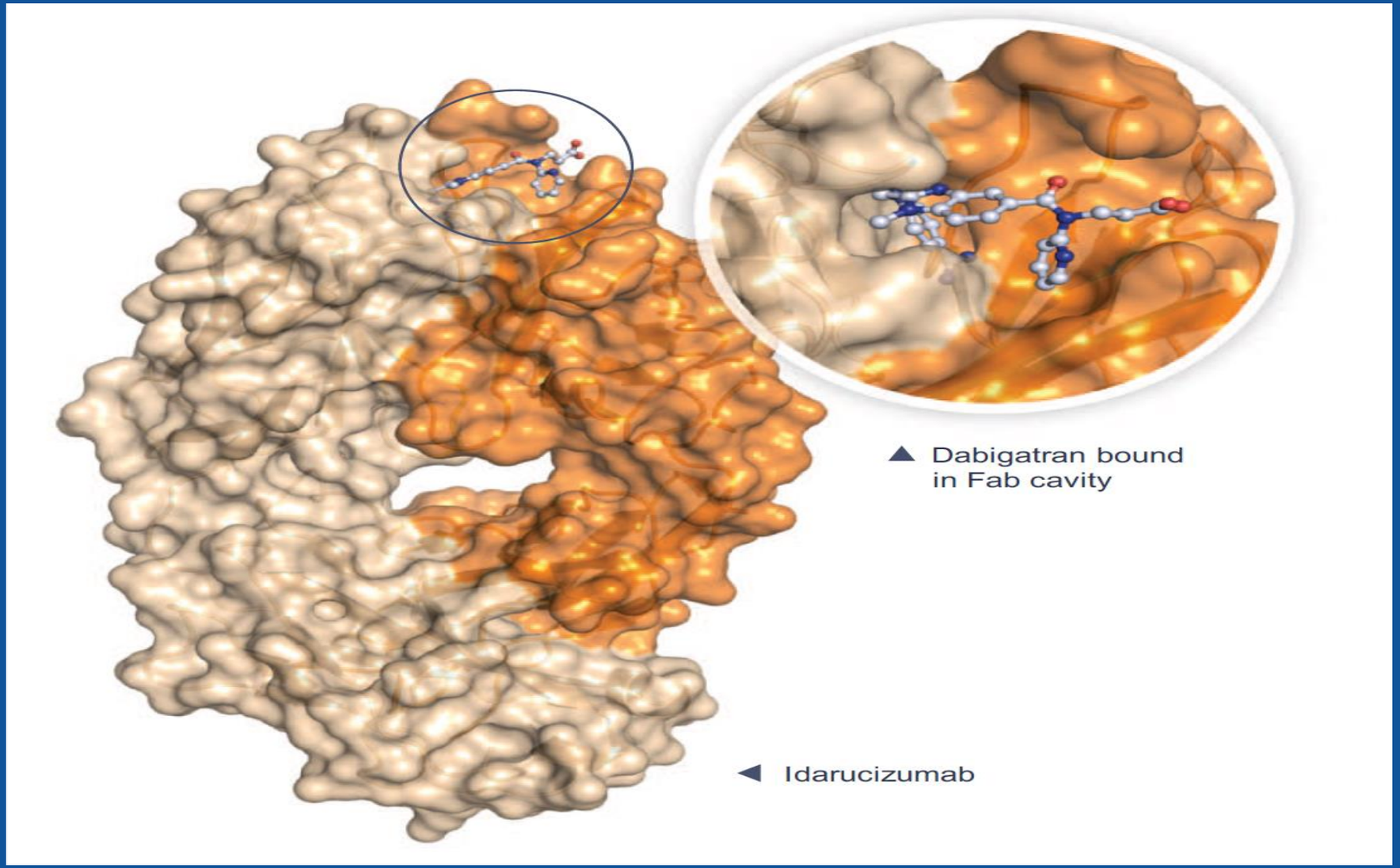
J Am Coll Cardiol 2014;63:1200 - Circulation 2014;130:1225

Strategies For miRNA-Based Therapies



X Luo et al. Nat. Rev. Cardiol. 2015;12:80 – Regulate Gene Expression

Dabigatran Bound To Idarucizumab



JW Eikelboom et. al. Circulation 2015;132:2412

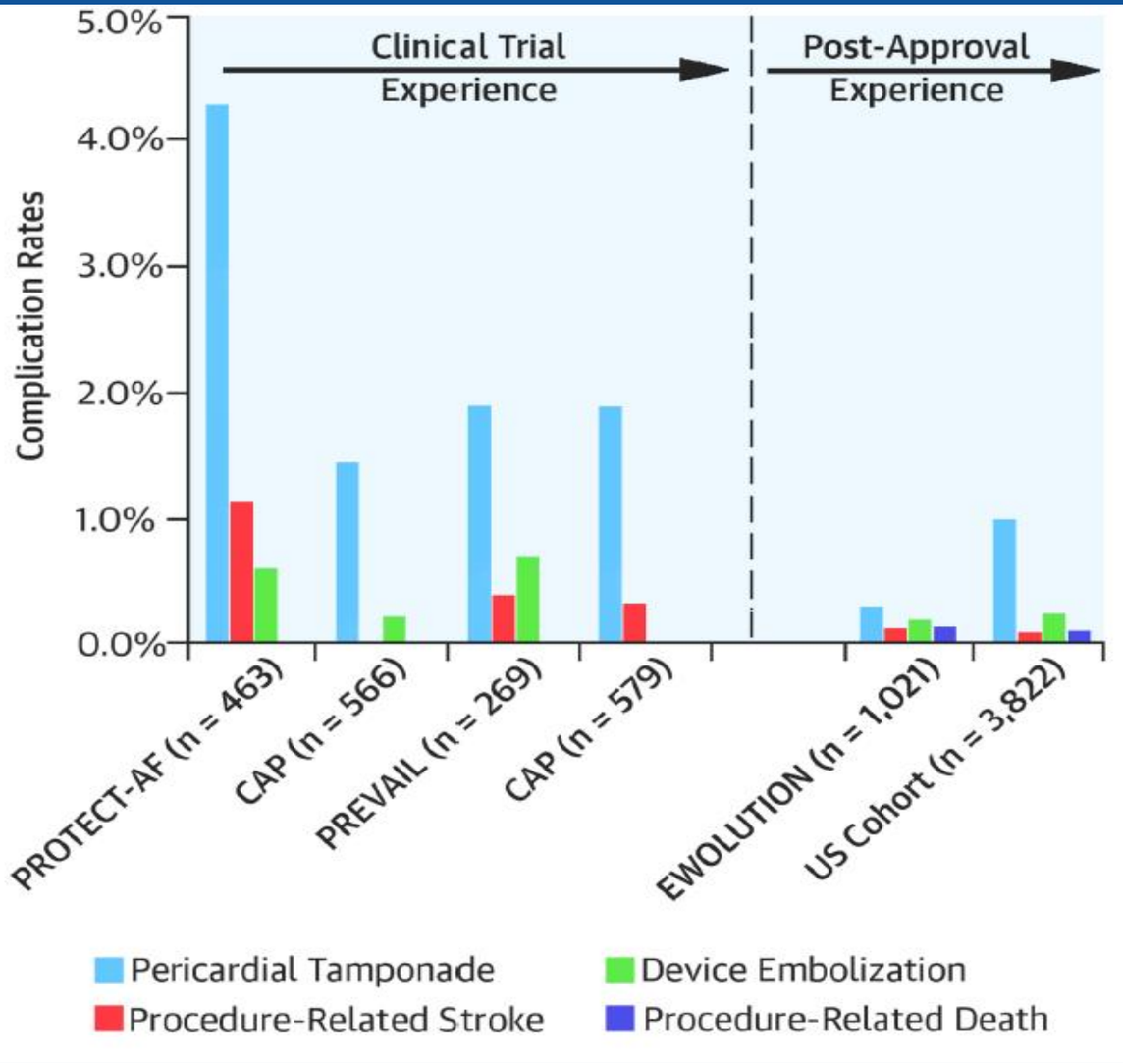
Meta-Analysis of Renal Function on the Safety and Efficacy of NOAC for Atrial Fibrillation

We performed a meta-analysis of the randomized clinical trials that compared efficacy and safety (major bleeding) outcomes of NOACs compared to W. for the treatment of NVAF and had available data on renal function. Renal function was assessed by baseline estimated GF rate divided in 3 groups: normal [estimated GF rate >80 ml/min], mildly impaired [50 to 80 ml/min], and moderate impairment [<50 ml/min]). We included 4 randomized clinical trials enrolling a total of 58,338 subjects. The use of NOACs was associated with a reduced risk of S/SE and reduced risk of major bleeding compared to Warfarin in subjects with mild or moderate renal impairment suggesting a favorable risk profile of these agents in patients

F Del-Carpio Munoz et al., Am J Cardiol 2016; 117:69

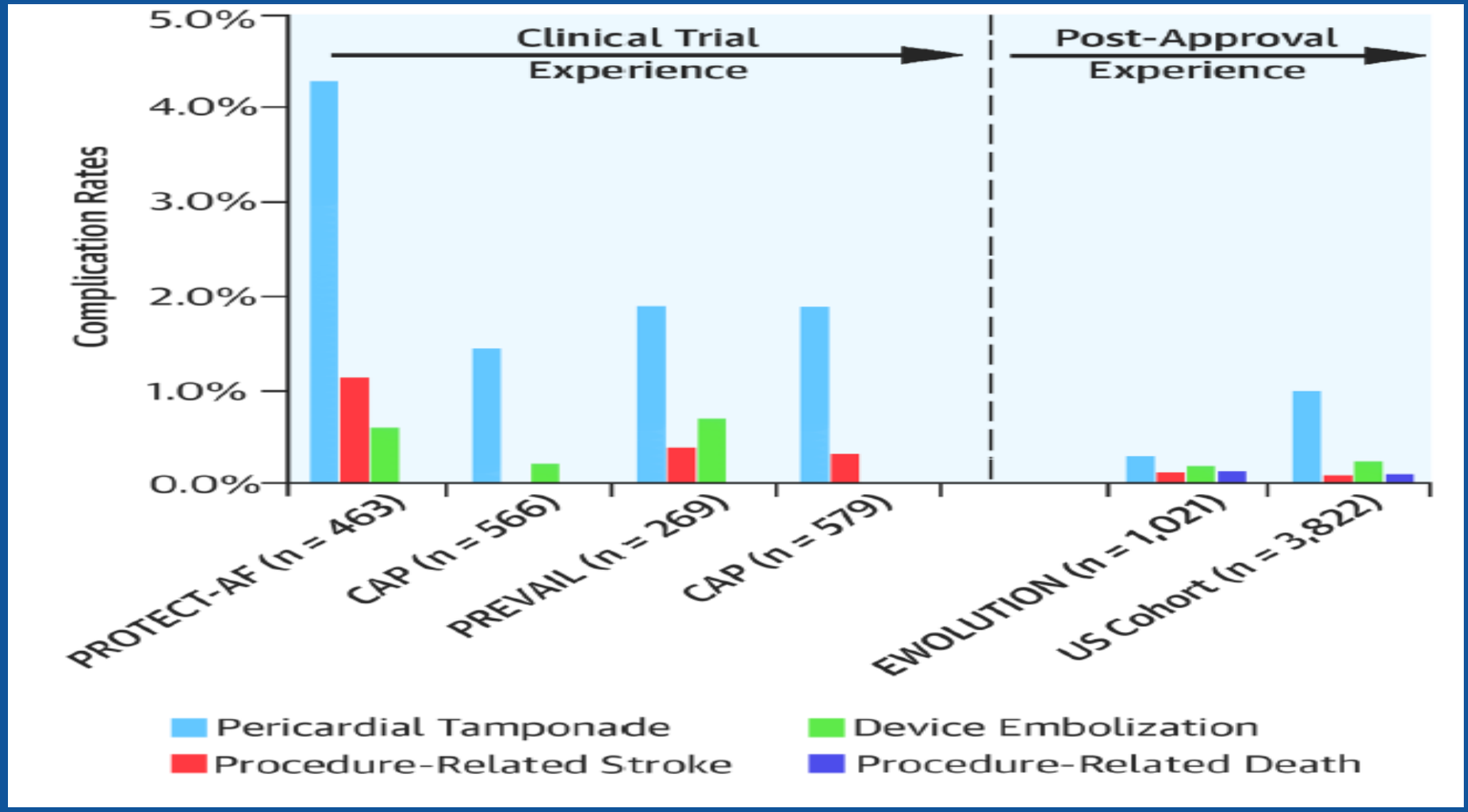
Major Complication Rates Across Watchman Clinical Studies

Procedural Parameters	Aggregate Clinical Data
Number of Procedures	6,720
Implantation Success, %	94.9%
Complication Rates	
Pericardial Tamponade	1.24%
Procedure-Related Stroke	0.18%
Device Embolization	0.25%
Procedure-Related Death	0.06%



VY Reddy et. al. 2016.

Major Complication Rates Across Watchman Clinical Studies



VY Reddy et. al. 2016.