Restoration of Sinus Rhythm: Considerations in CKD

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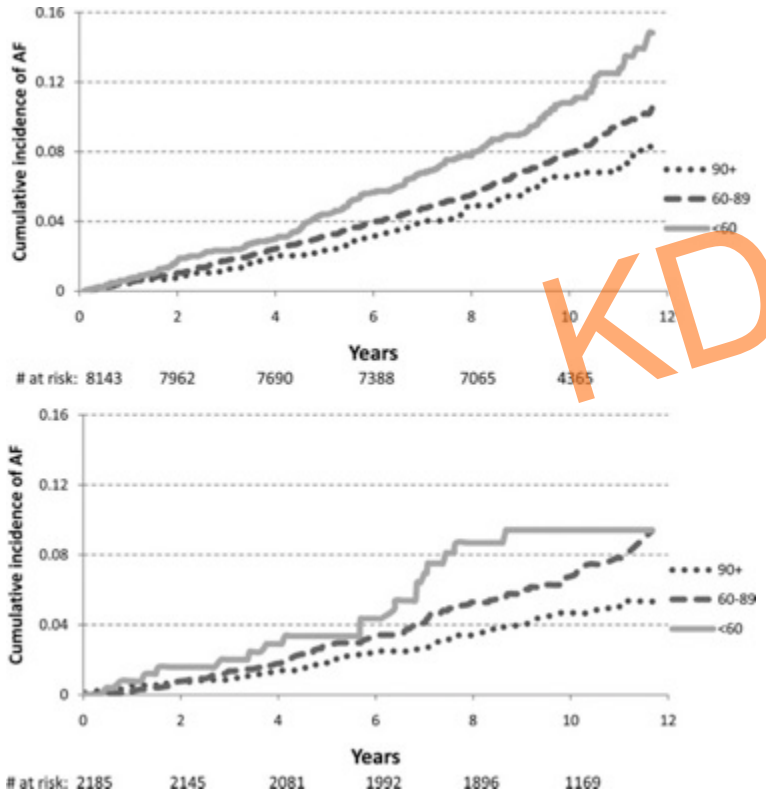
Disclosure of Interests

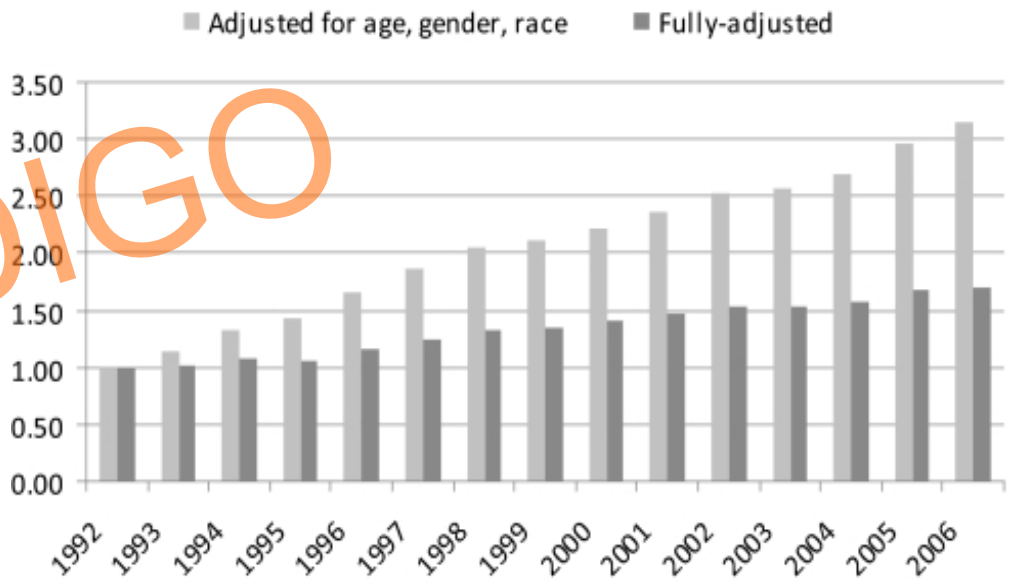
- Consultant: Medtronic, Biotronik, Janssen
- Speakers bureau: Medtronic, Pfizer, BMS
- Royalties: UpToDate
- Research support: NIH, Medtronic

Growth of AF

Incidence of AF in CKD: ARIC Study N=10328



Prevalence of AF in ESRD: USRDS 1992-2006

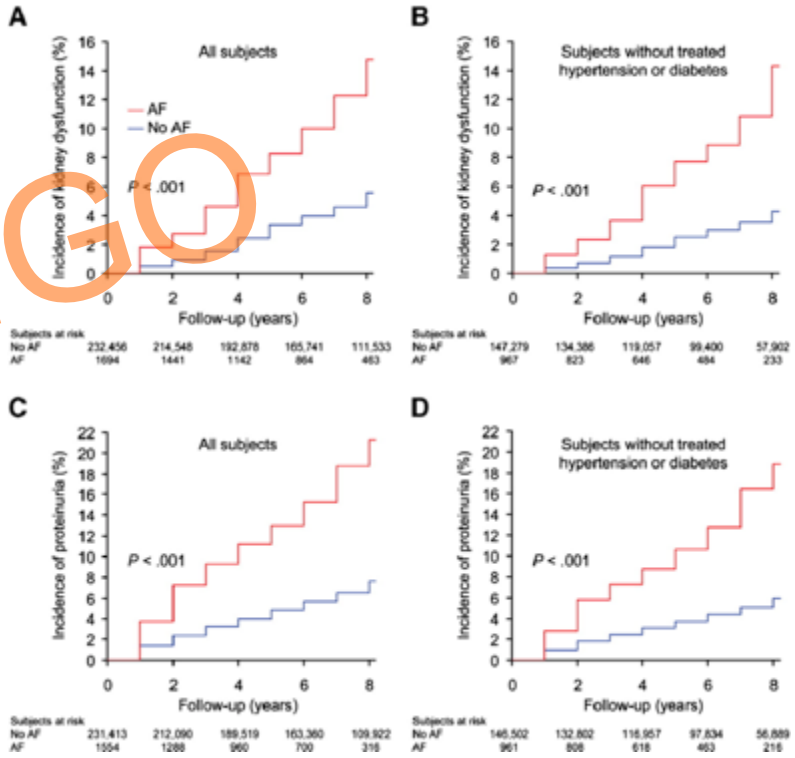


Alvaro Alonso et al. Circulation. 2011;123:2946-2953
Winkelmayer WC; J Am Soc Nephrol. 2011 Feb; 22(2): 349–357

AF Related Complications

- Mortality: adjusted 1-year increased by 45% for HD + AF compared to HD alone
- Stroke: CKD + AF = 49% increase in stroke risk
- CKD progression

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.



USRDS 2013

Olesen J; NEJM 2011;365

Watanabe; Am Heart J 2009;158:629-36

AF Management

Stroke Prevention

Rate Control

Rhythm Control

Indications for Rhythm Control

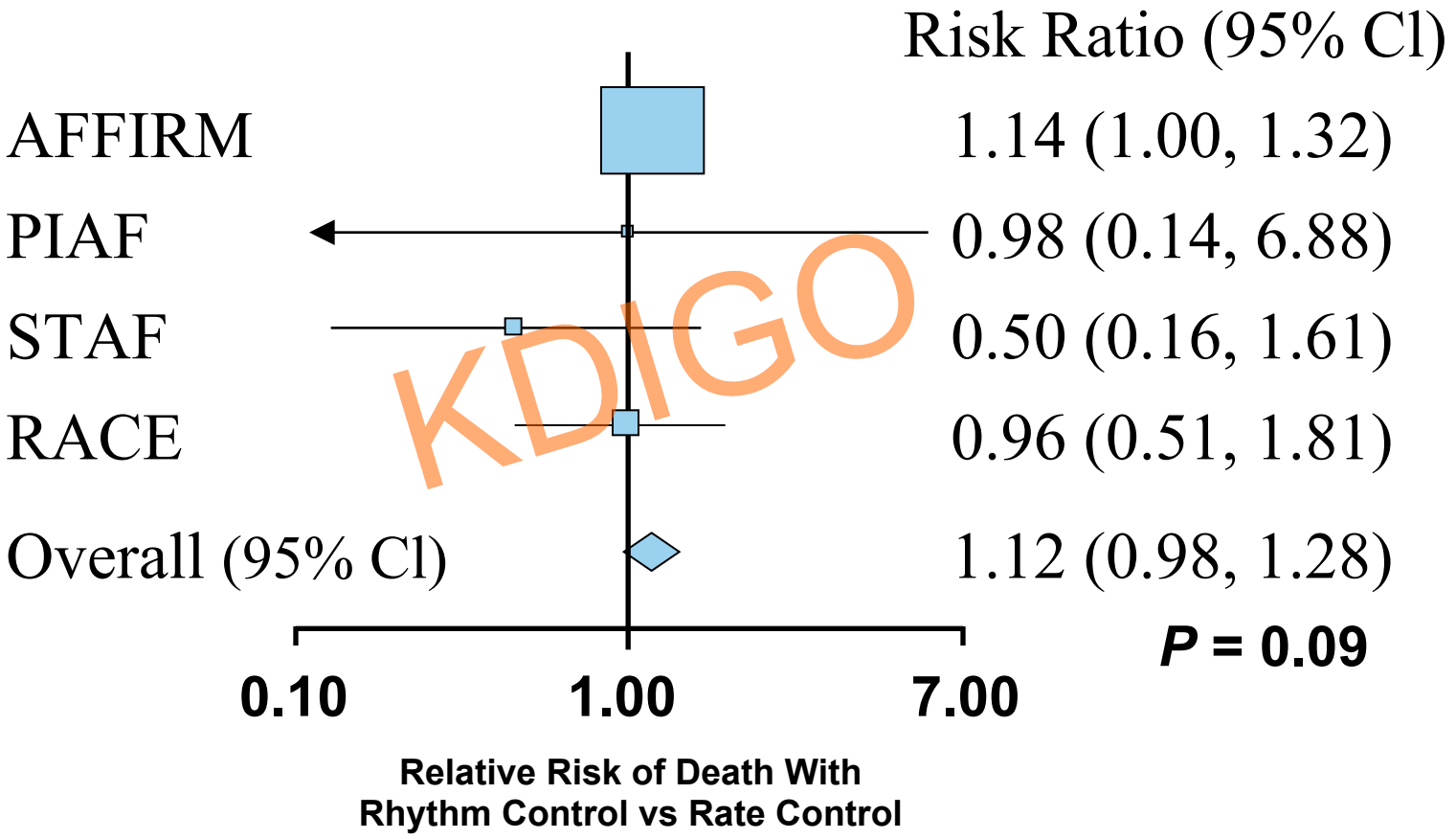
"Persistent symptoms associated with AF remain the most compelling indication for a rhythm-control strategy."

Other factors that may favor attempts at rhythm control include:

- difficulty in achieving adequate rate control
- younger patient age
- tachycardia-mediated cardiomyopathy
- first episode of AF
- AF that is precipitated by an acute illness
- patient preference

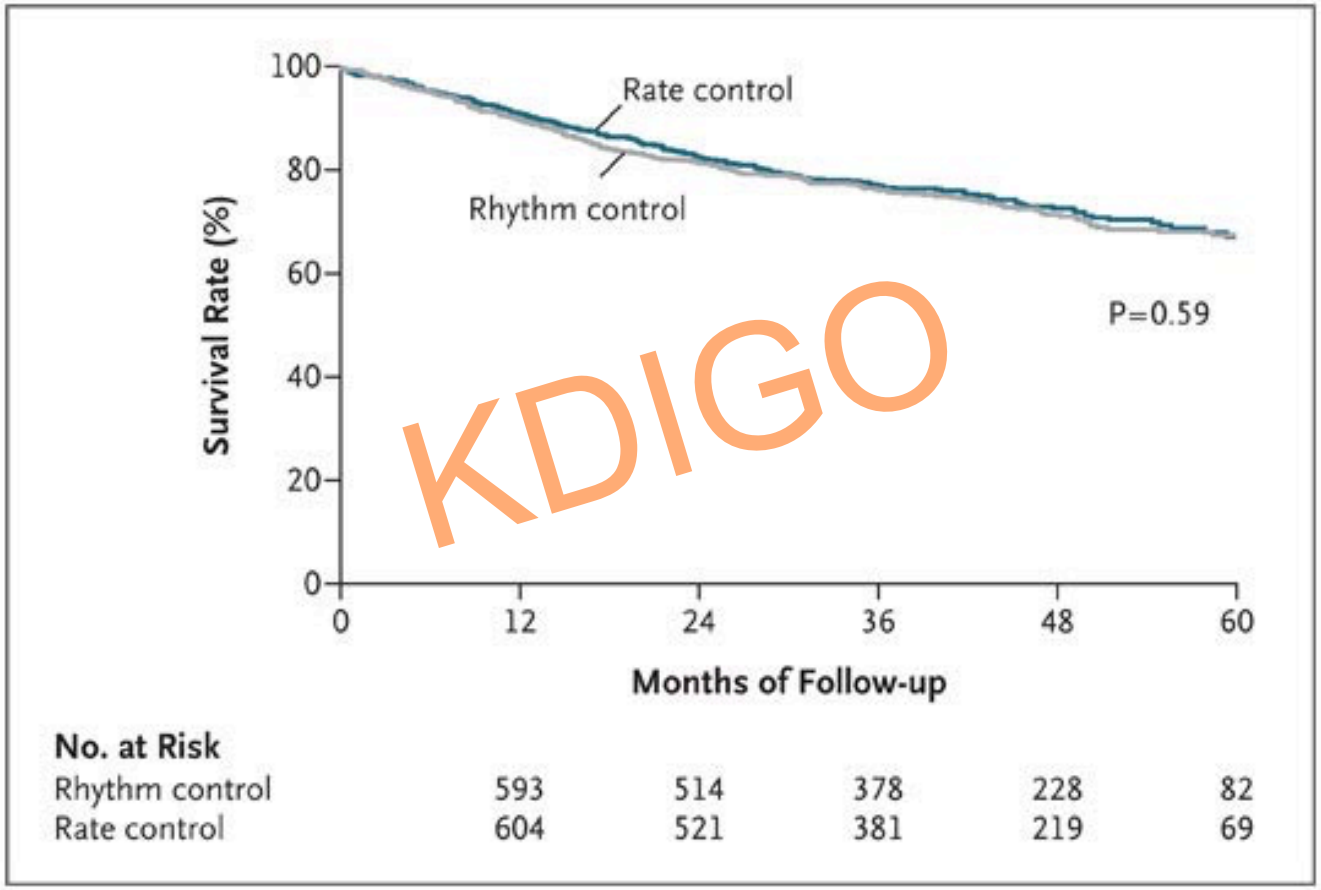
AHA/ACC/HRS AF Guidelines

Rhythm vs Rate Control on Risk of Mortality



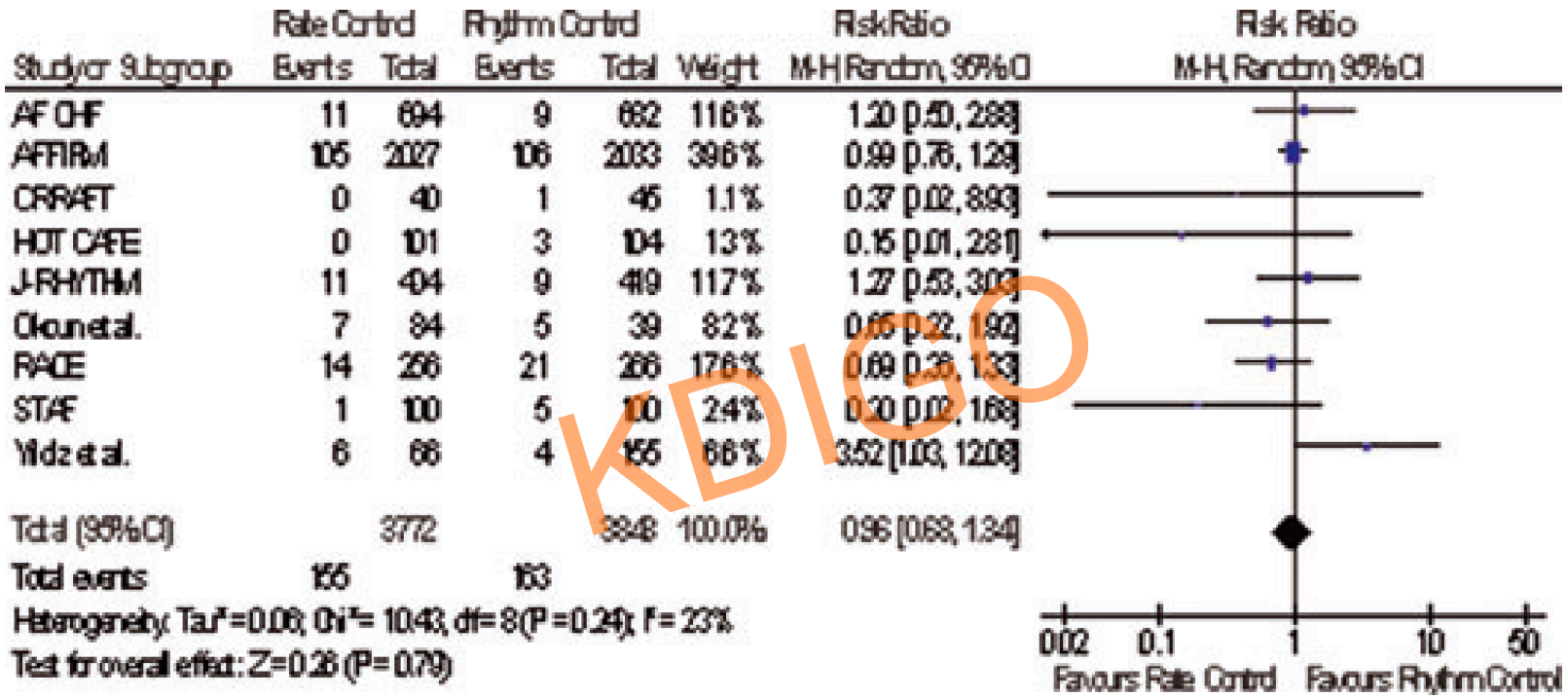
Wyse DG. *Prog Cardiovasc Dis.* 2005;48:125-138

AF-CHF: Kaplan-Meier Estimates of Death from Cardiovascular Causes



Roy D et al. N Engl J Med 2008;358:2667-2677

Rhythm vs Rate Control on Risk of Stroke /TIA



Chatterjee S; PACE 2013;36(1)

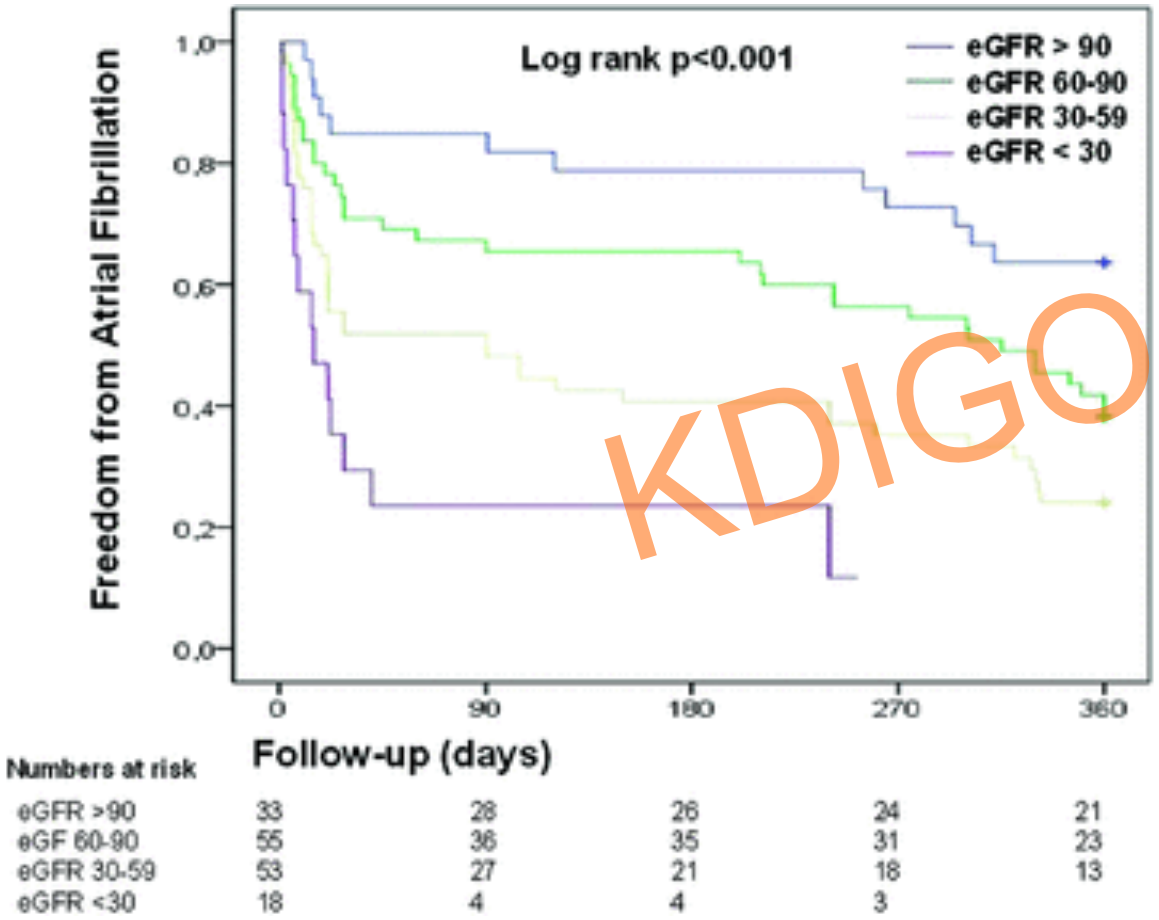
Why Isn't Rhythm Control Superior to Rate Control?

- Long term sinus rhythm hard to achieve (particularly with AAD and particularly with persistent AF)
- Side effects / toxicity of AAD

Challenges of Rhythm Control in CKD Patients

- DCCV
- Antiarrhythmic drugs
- Ablation

Renal Dysfunction and Atrial Fibrillation Recurrence Following Cardioversion



"In patients with maintained sinus rhythm after 12-month follow-up eGFR was increased (8.46 ± 9.49 mL/min [range −7 to 43]), whereas patients with atrial fibrillation recurrence showed a decrease in eGFR over time (−5.75 ± 9.4 [range −32 to 25], P < 0.001)"

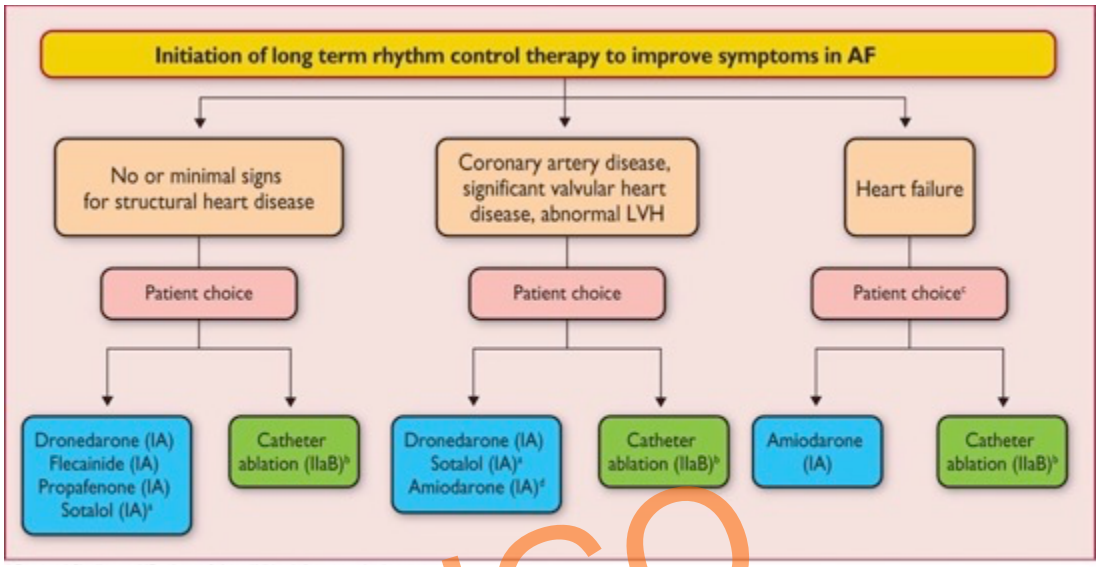
N = 159

Schmidt M; J Cardiovasc Electrophysiol, Vol. 22, pp. 1092-1098, October 2011)

Challenges of Rhythm Control in CKD Patients

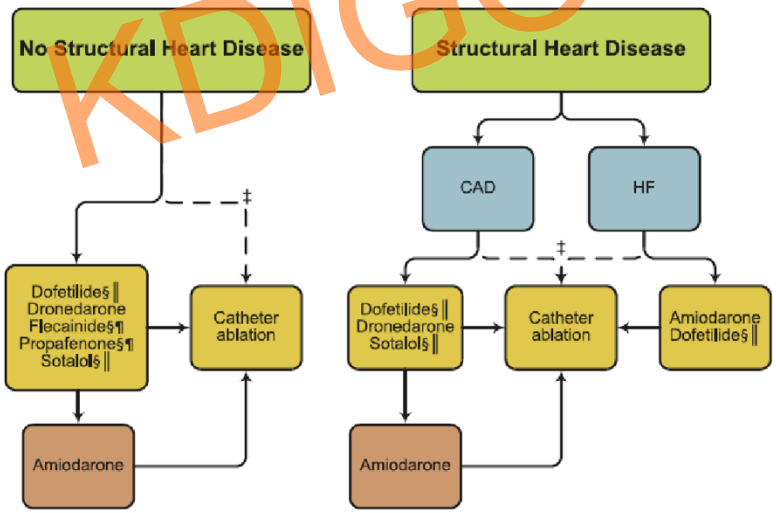
- DCCV
- Antiarrhythmic drugs
- Ablation

ESC 2016
AF
Guidelines



AHA/ACC/
HRS

AF
Guidelines



Antiarrhythmic Drugs in CKD

Drug	PK and elimination	Indications for CKD
Flecainide	Metabolized in liver and excreted unchanged in urine (35%)	Dose reduction if GFR < 35 mL/min/1.73m^2
Propafenone	95% protein bound; metabolized in liver and excreted unchanged in urine (38%)	Careful monitoring recommended (in hospital initiation for advanced CKD)
Sotalol	70% excreted unchanged in the urine	50% dose reduction in CKD; 75% in severe renal failure (relatively contraindicated)
Dofetilide	Protein binding 60-70%; 80% excreted by kidneys	Dosing by GFR; contraindicated for GFR < 20 mL/min
Dronedarone	98% protein bound; metabolized in liver; 6% excreted in urine	No dosing adjustment for mild to severe renal failure
Amiodarone	99% protein bound; no renal elimination	No dosage requirements

EHRA Position Paper; Europace 2015(17),1169

Antiarrhythmic Drugs in CKD

Drug	Indications
Flecainide	No structural heart disease
Propafenone	No structural heart disease
Sotalol	±Contraindicated if > mild CKD
Dofetilide	Contraindicated if > mild CKD
Dronedarone	EF > 35%, no recent CHF
Amiodarone*	All

* Thyroid toxicity, liver failure, pulmonary fibrosis, neuropathy, optic neuritis, skin discoloration

AFFIRM Results

Time-Dependent Covariates Associated With Survival

Covariate	*P*-Value	Hazard Ratio	99% CI
Sinus rhythm	<.0001	0.53	0.39-0.72
Warfarin use	<.0001	0.50	0.37-0.69
Digoxin use	.0007	1.42	1.09-1.86
AAD* use	.0005	1.49	1.11-2.01

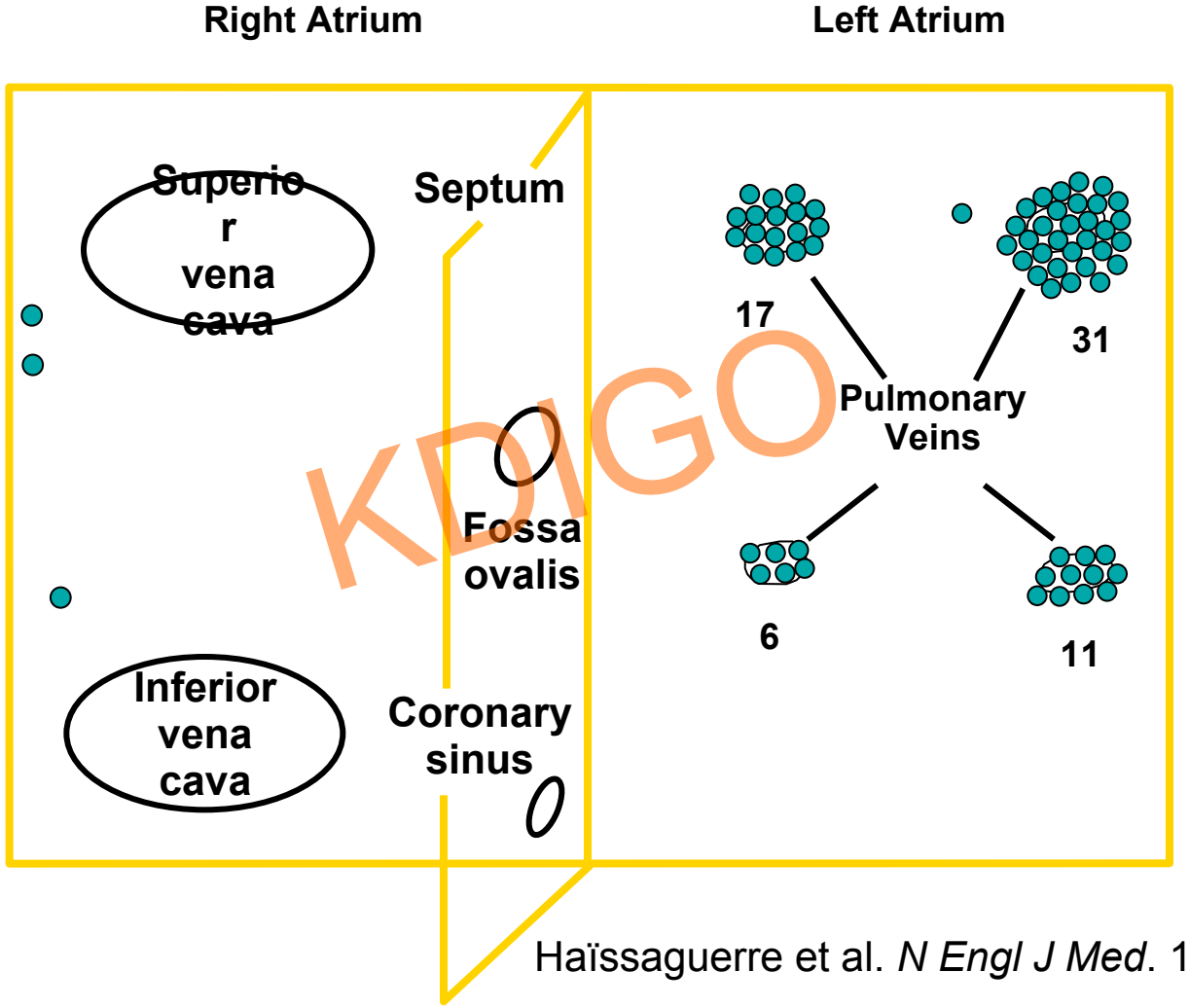
HR <1.00: decreased risk of death.
HR >1.00: increased risk of death.

*Antiarrhythmic drug.

The AFFIRM Investigators. *Circulation*. 2004;109:1509-1513.

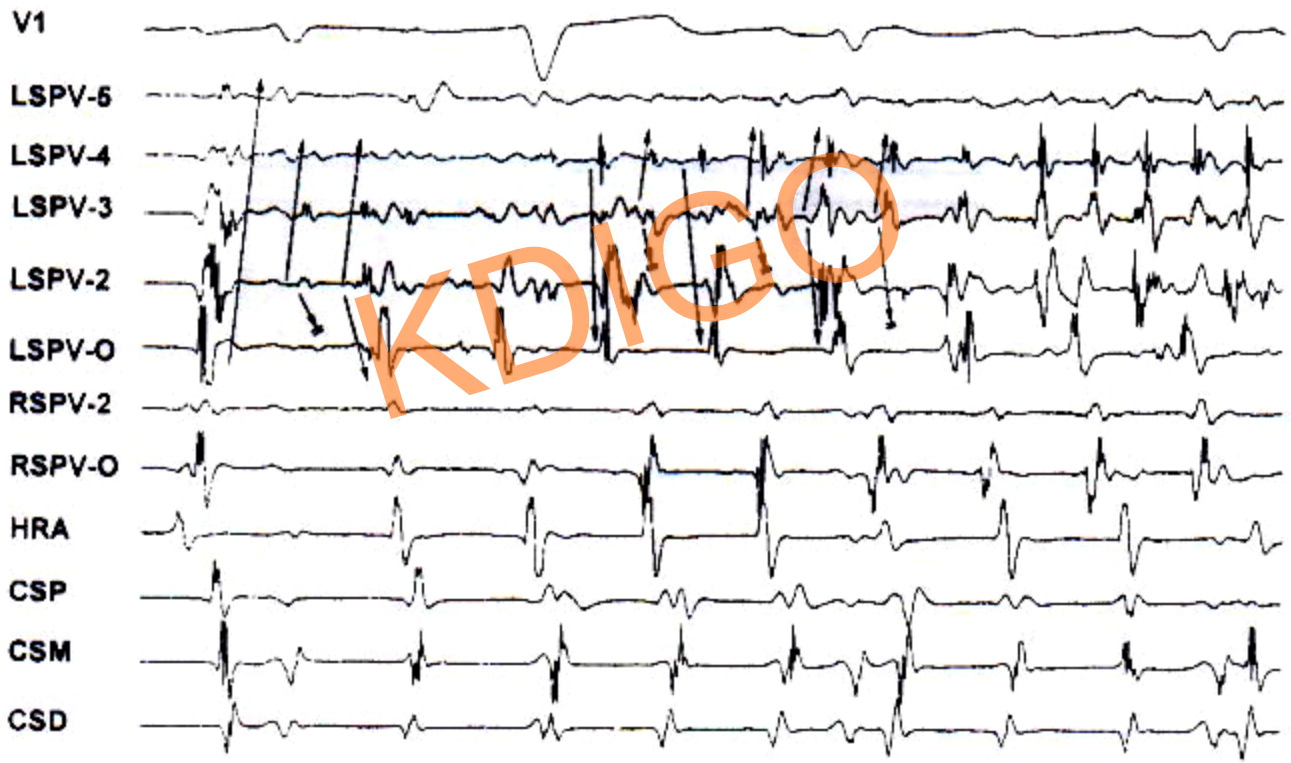
What if there were a better way of maintaining sinus rhythm?

Sites of 69 Foci Triggering AF in 45 Patients



Haïssaguerre et al. *N Engl J Med*. 1998;339:659-666

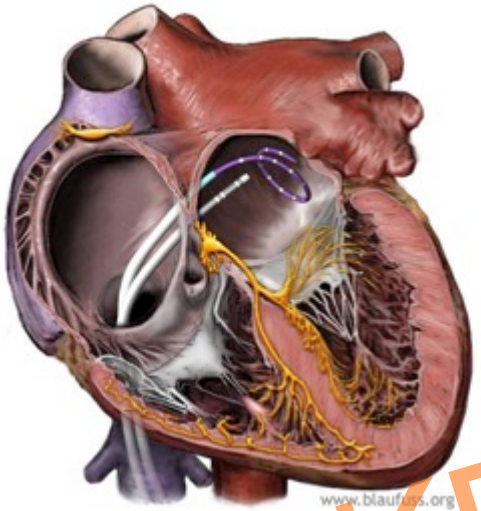
AF Onset from Pulmonary Vein

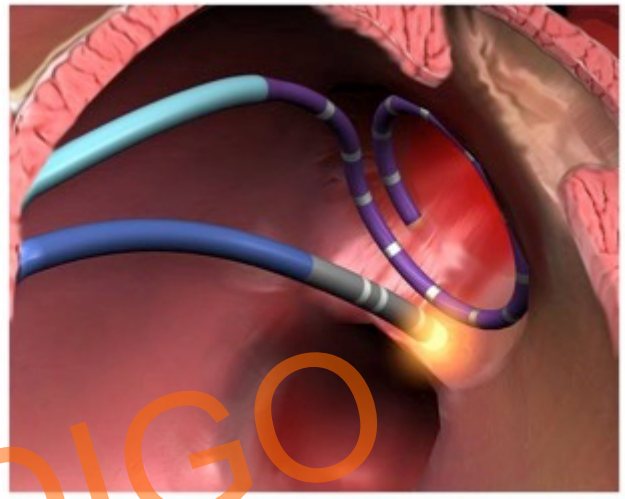


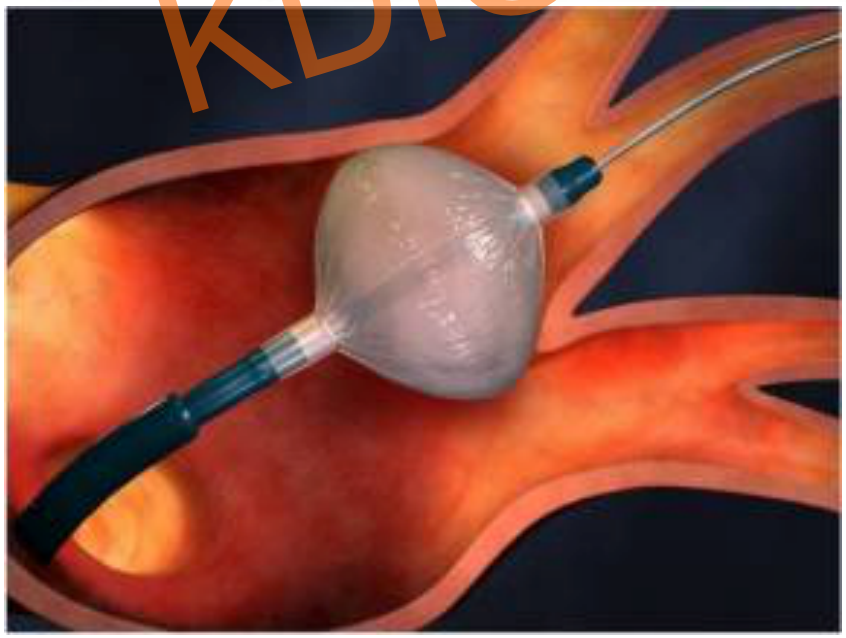
Pulmonary Veins as Triggers of AF

- Intrinsic pacemaker function
- Different EP properties
- Fewer cell-cell interactions
- More susceptible to stretch and fibrosis
- Amenable to arrhythmogenesis

AF Ablation



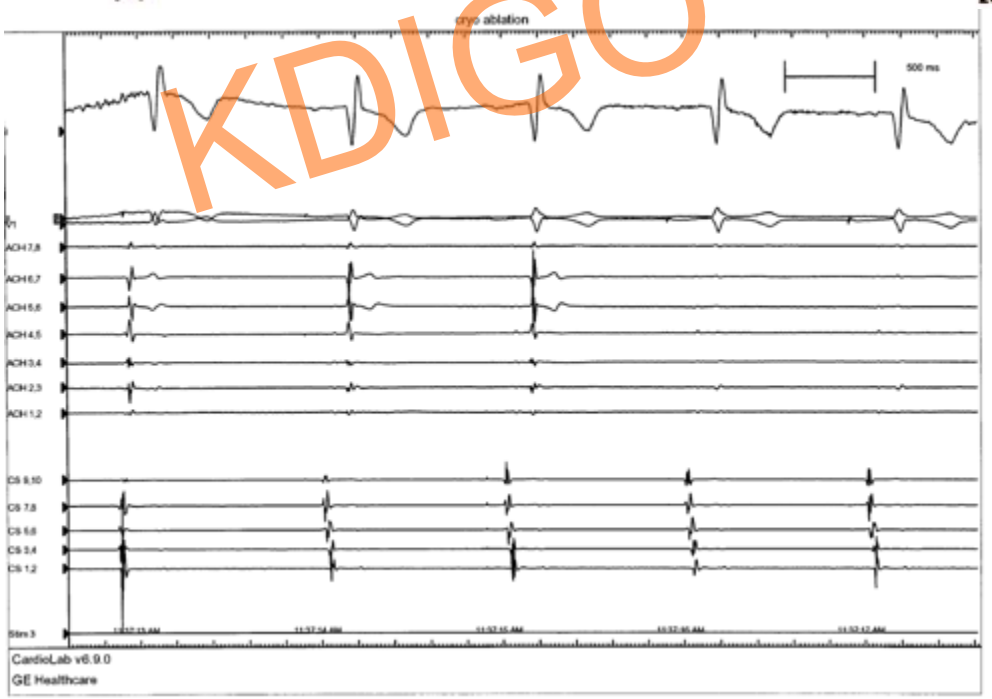




Ablation of PV Potentials

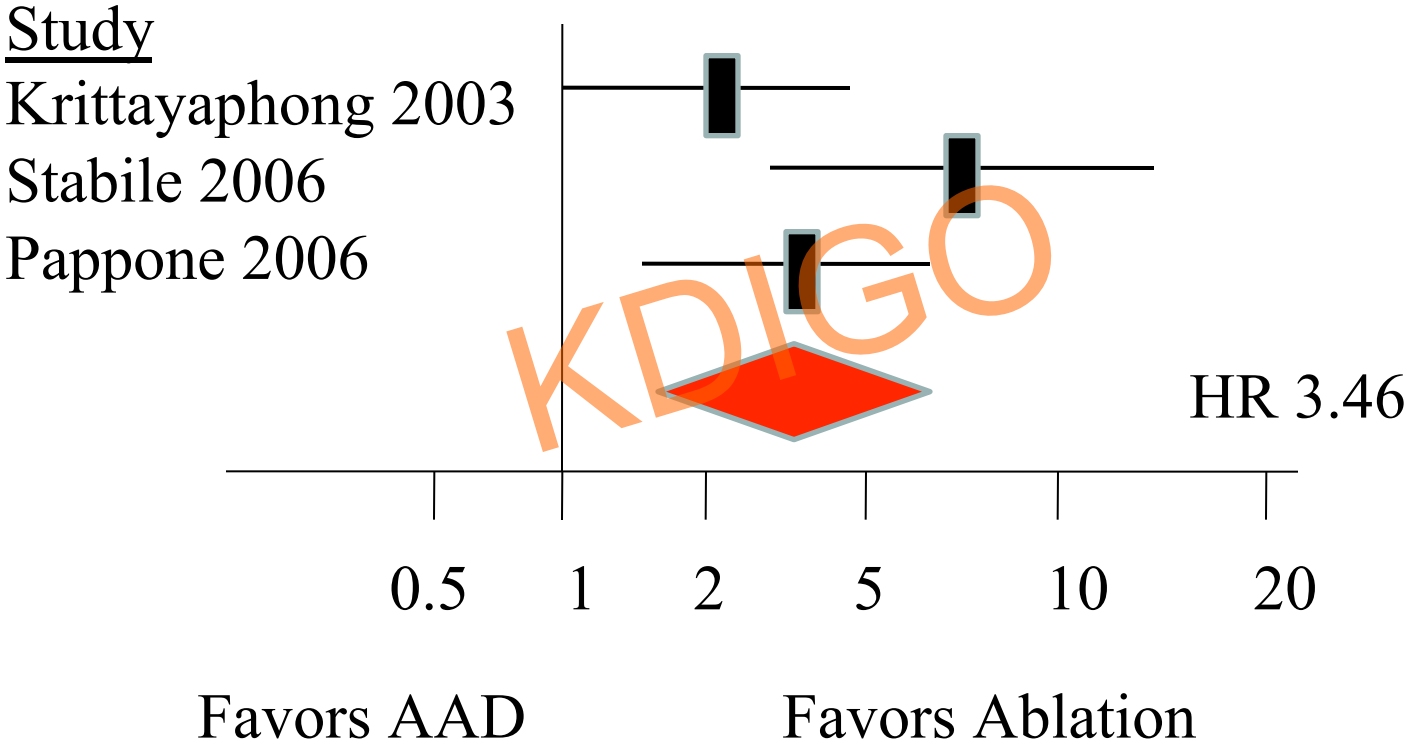
RF

CRYO



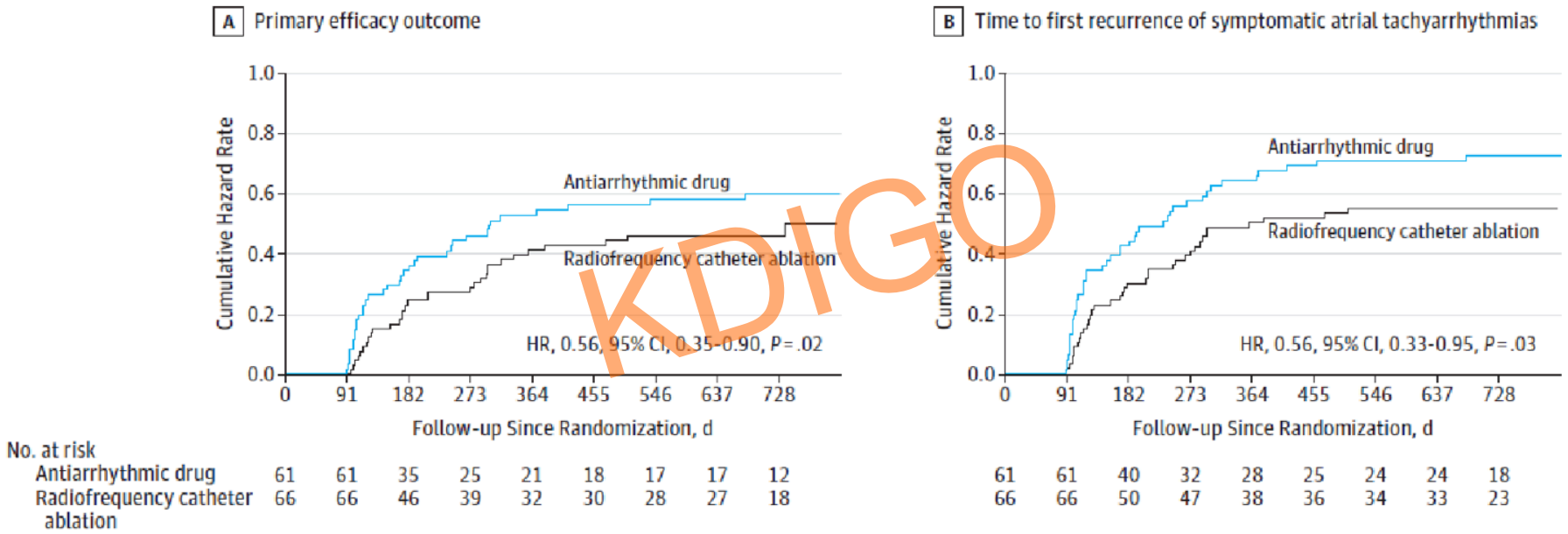
AF Termination

Meta Analysis: Ablation vs Antiarrhythmics



Terasawa T: Annals Int Med; 2009; 151:191

RCT of AAD vs RF Ablation (RAAFT2)



Morillo C, JAMA 2014; 311 (7)

Correlating clinical syndrome to pathophysiology

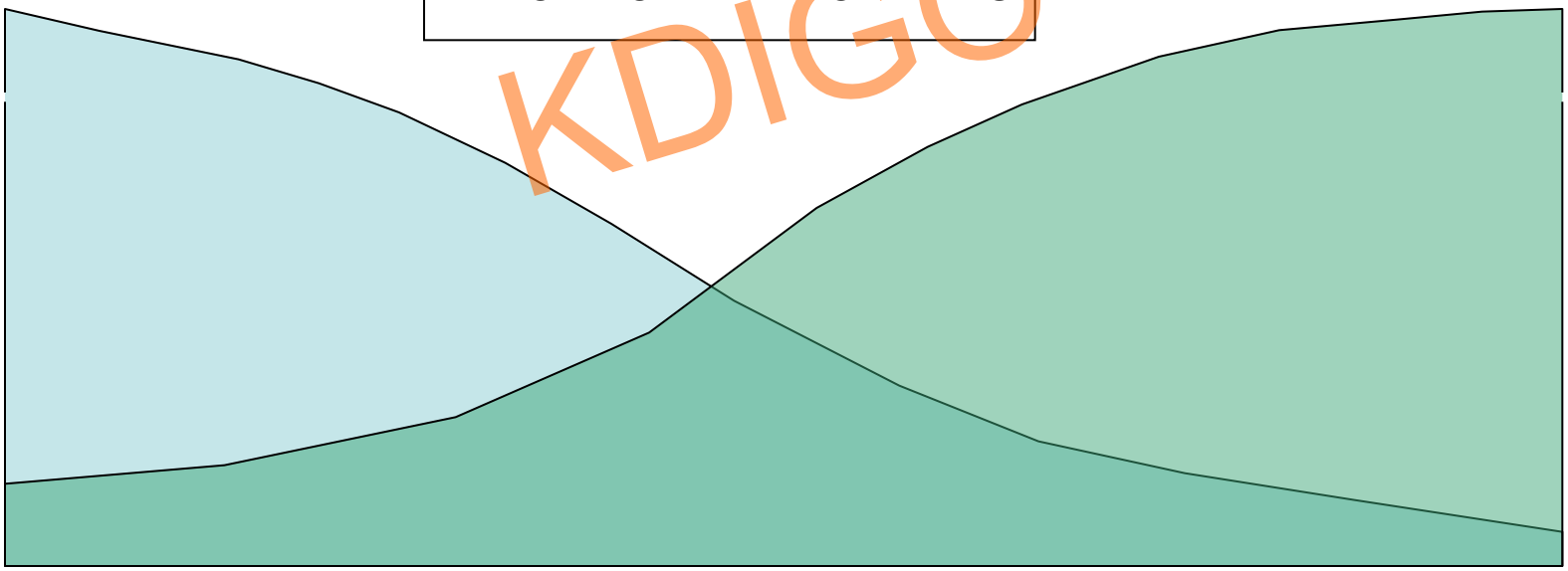
TRIGGERING

PV PACs
OTHER PACs
AT / SVT

MAINTENANCE

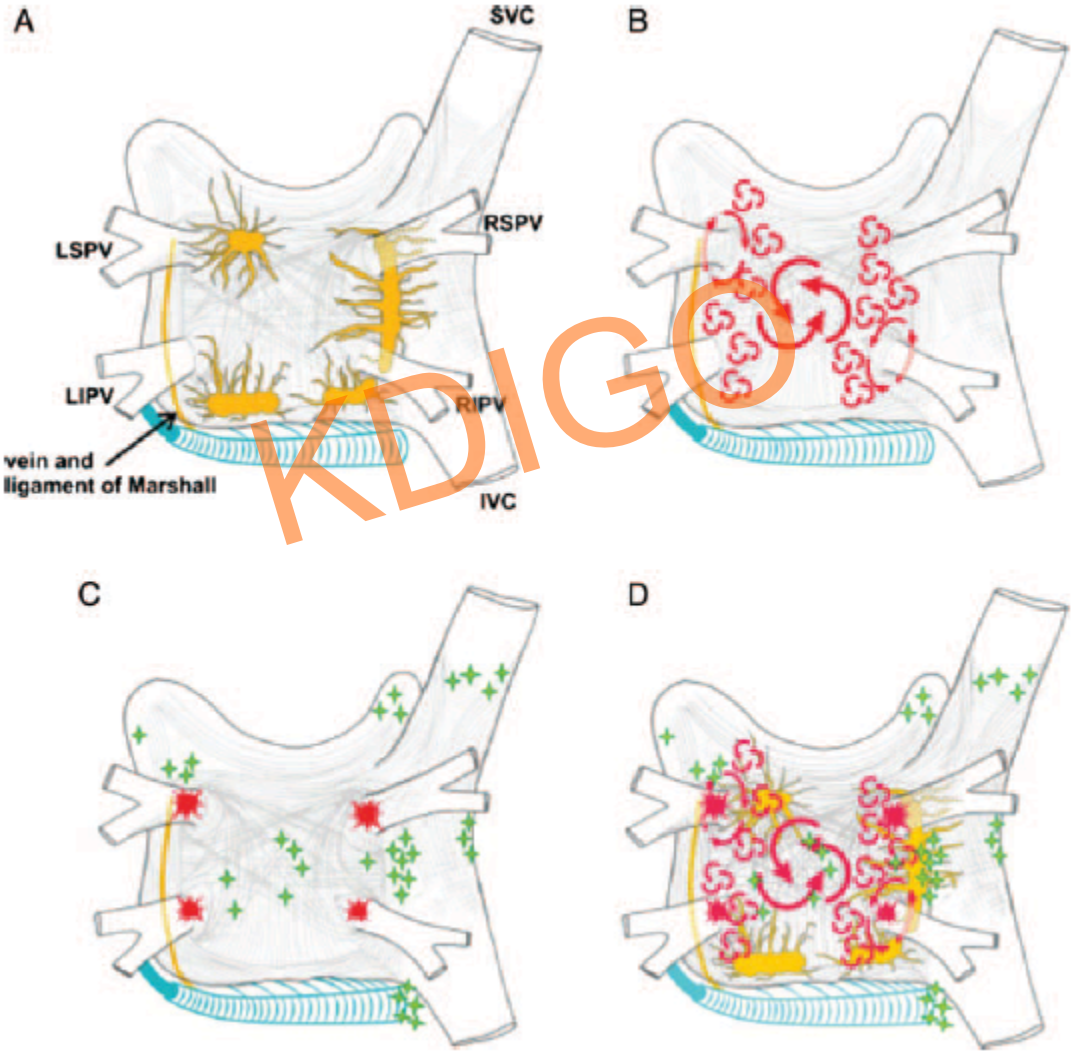
LOCAL ANISOTROPY
FIBROSIS / SCARRING
REPETITIVE TRIGGERING

MODULATORS
STRETCH
AUTONOMIC TONE
ELECTRICAL REMODELING



Paroxysmal AF **Persistent AF** **Permanent AF**

Mechanisms/Targets of AF



Indications for AF Ablation

6.3. AF Catheter Ablation to Maintain Sinus Rhythm: Recommendations

CLASS I

1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (363,392–397). *(Level of Evidence: A)*
2. Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of Evidence: C)*

CLASS IIa

1. AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (394,398–400). *(Level of Evidence: A)*
2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy (401–403). *(Level of Evidence: B)*

CLASS IIb

1. AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired (363,404). *(Level of Evidence: B)*
2. AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired. *(Level of Evidence: C)*

CLASS III: HARM

1. AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure. *(Level of Evidence: C)*

as

2014 AHA/ACC/HRS Guidelines

Challenges of Rhythm Control in CKD Patients

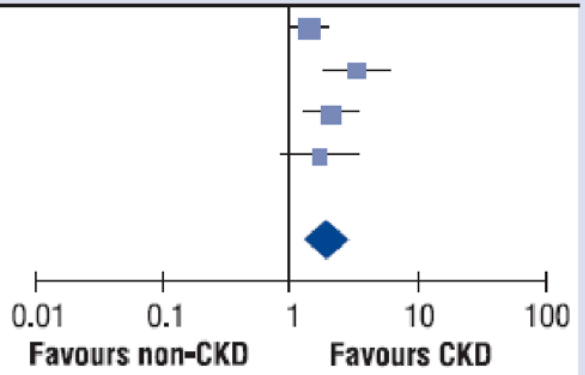
- DCCV
- Antiarrhythmic drugs
- Ablation

Catheter Ablation in CKD Patients: Meta-Analysis (RF)

Investigator	Year	Total no. of patients	Ablation strategy	Method of AF detection	Definition of CKD	Follow up period [months]	Blanking period [months]	Risk estimate	Study quality
Berkowitsch	2012	702	PVI	12-lead ECG, 24h-Holter	eGFR < 68 mL/min/1.73 m²	Median follow up time of 15.6	3	aHR	9
Chao	2011	232	PVI	Clinical symptoms, 12-lead ECG, 24h-Holter and 1 week cardiac event recordings	eGFR < 60 mL/min/1.73 m²	25.4 ± 13.3	2	HR	8
Naruse	2011	221	PVI	12-lead ECG, 24h-Holter, portable ECG	eGFR < 60 mL/min/1.73 m²	31.9 ± 7.6	3	aHR	9
Tokuda	2011	224	PVI	Patients' symptom, ECG, 24h-Holter monitor	eGFR < 60 mL/min/1.73 m²	37.4 ± 24.4	3	HR	9

Study of subgroup	log [hazard ratio]	SE	Weight	Hazard ratio IV, Random. 95% CI
Berkowitsch	0.3577	0.1576	34.3%	1.43 [1.05–1.95]
Chao	1.1982	0.2864	22.3%	3.31 [1.89–5.81]
Naruse	0.7367	0.2452	25.8%	2.09 [1.29–3.38]
Tokuda	0.5306	0.3537	17.7%	1.70 [0.85–3.40]
Total (95% CI)			**100%**	**1.96 [1.35–2.85]**

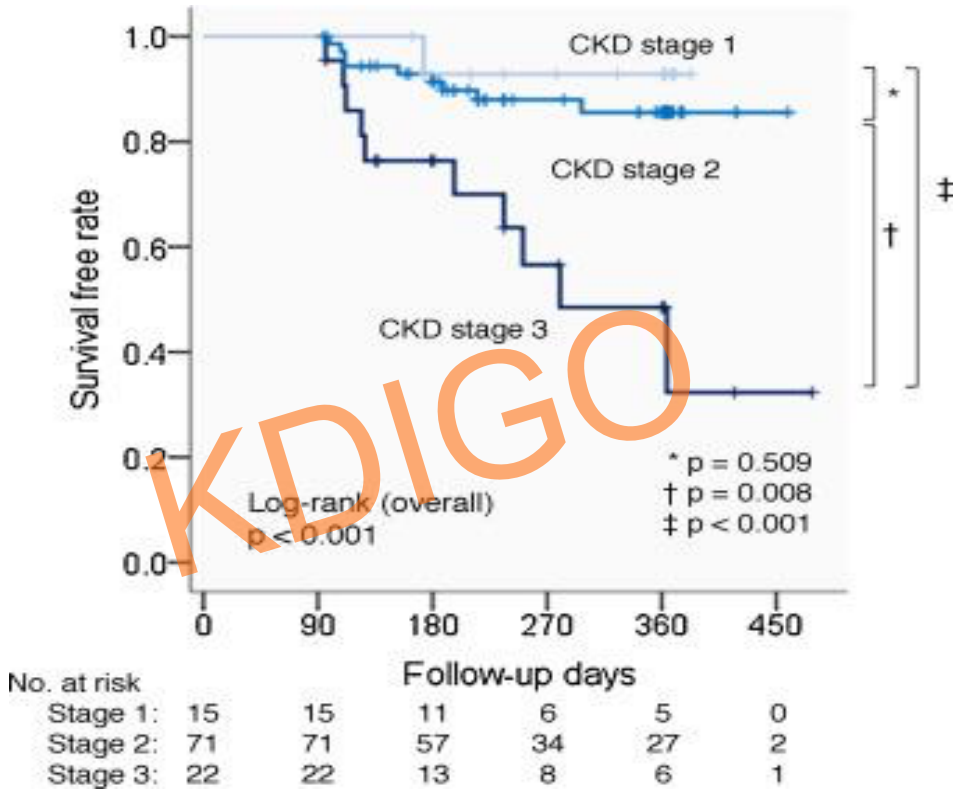
Heterogenity: $Tau^2 = 0.08$; $Chi^2 = 7.07$; df = 3 (p = 0.07); $I^2 = 58\%$
Test for overall effect: Z = 3.52 (p = 0.0004)



"CKD was associated with higher AF recurrence rate following single catheter ablation (HR = 1.96, 95% CI 1.35–2.85, p = 0.0004"

Li M, Cardiology Journal 2014, Vol. 21, No. 1, pp. 89–95

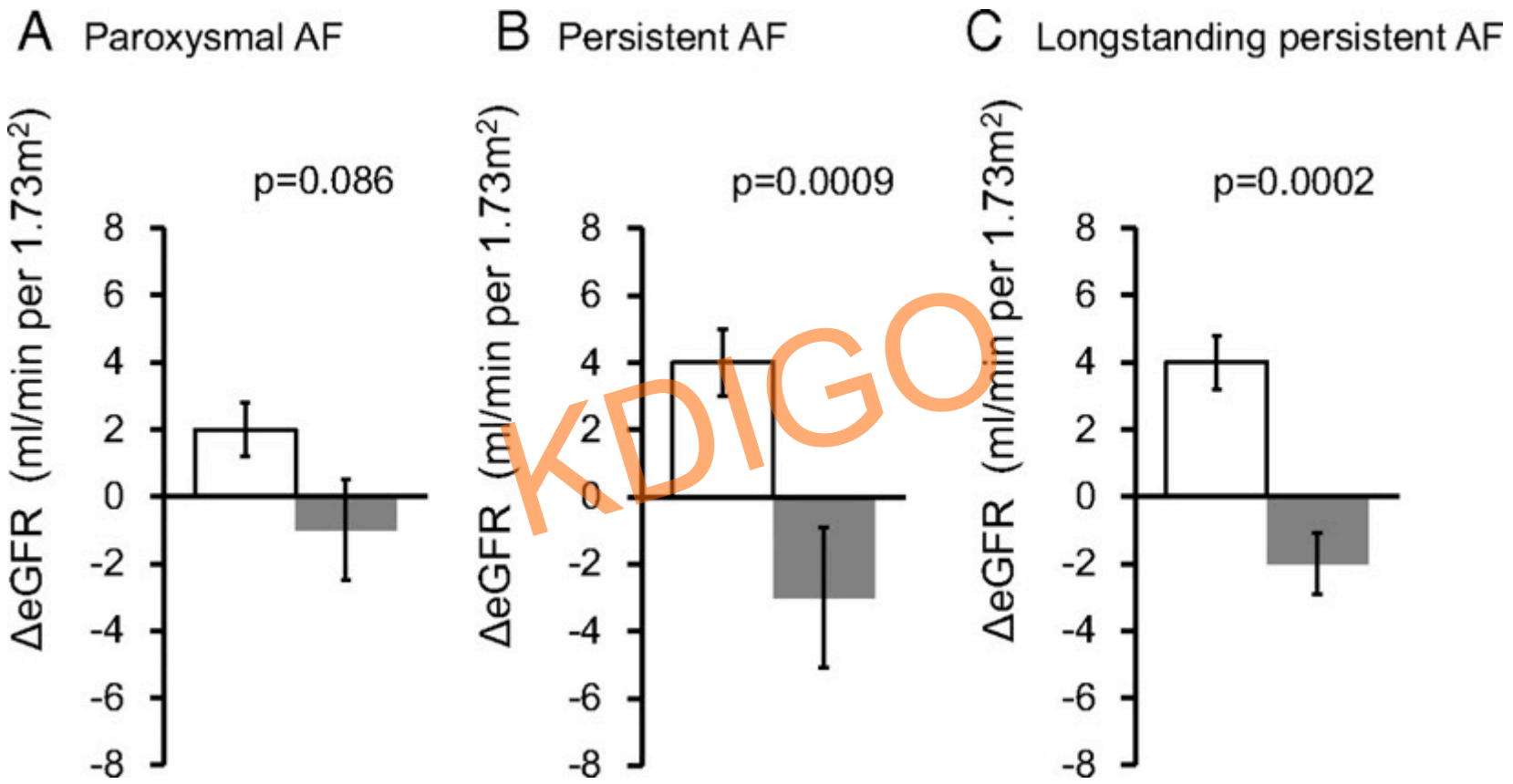
Catheter Ablation in CKD Patients: Cryoballoon



- No patients developed contrast-induced nephropathy after the catheter ablation procedure
- The presence of non-PV ectopic beats (with isoproterenol) was significantly increased in patients with impaired renal function

Yanagisawa S; Journal of Cardiology 2016 (In Press)

Mean changes in estimated glomerular filtration rate (eGFR) from baseline to 1 year after ablation of atrial fibrillation (AF)



White and black bars represent patients free from arrhythmias and patients who had recurrences of atrial tachyarrhythmia, respectively

Yoshihide Takahashi et al. Circulation. 2011;124:2380-2387

AF Ablation in CKD*

	CKD (N=1593)	No CKD (N=19498)	P
Age	64 ± 11	59 ± 11	< 0.001
Comorbidity Index	2.7	0.92	< 0.001
CHADSVASC	3.2	1.8	< 0.001
Heart Failure	57%	32%	< 0.001
Prior MI	11%	5%	< 0.001
PAD	11%	4%	< 0.001
DM	42%	20%	< 0.001
Dialysis	3.8%	0	

*Using MarketScan® Commercial Claims and Medicare Supplemental Databases,

Ullal; HRS 2016

AF Ablation in CKD: 1-Year Outcomes

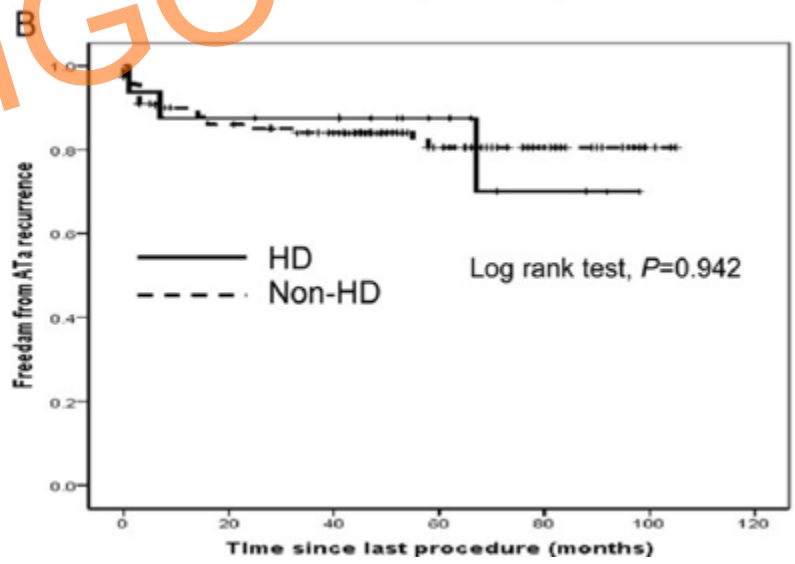
	CKD (N=1593)	No CKD (N=19498)	Adjusted P
All-cause hospitalization	42.7%	27.1%	< 0.001
AF Hospitalization	13.1%	12.4%	0.79
Cardioversion	21.5%	20.1%	0.87
Repeat AF Ablation	11.6%	14.4%	0.18

Ullal; HRS 2016

AF Ablation in Dialysis Patients

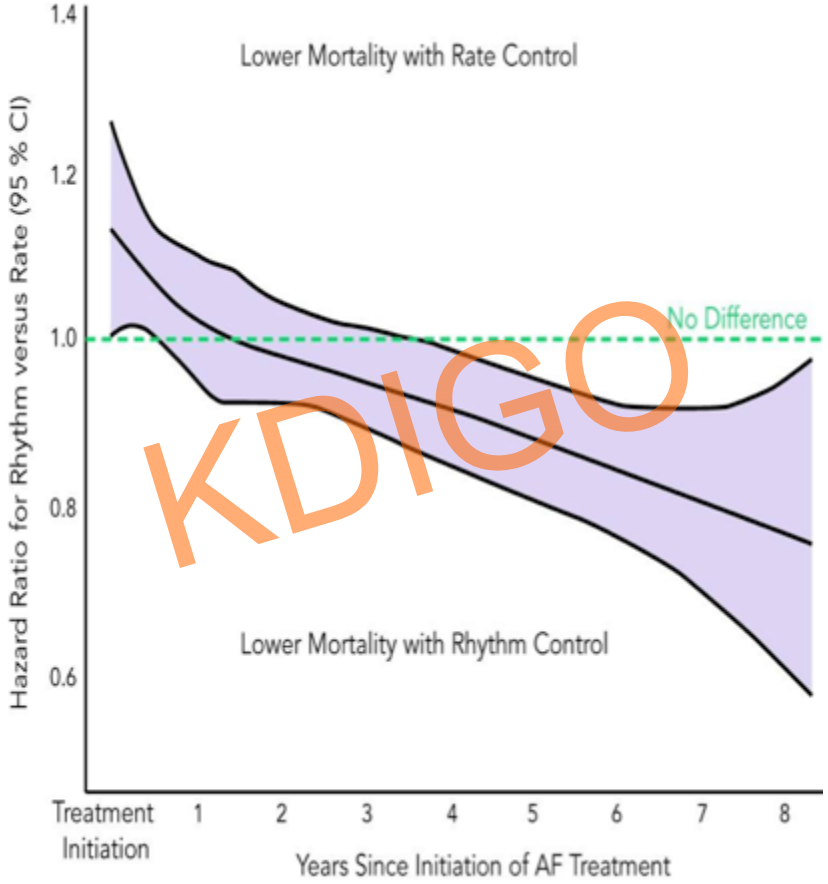
Study	HD/non-HD	Follow-Up	Success
Sairaku	30/60 (matched)	2.2 years	54% v 78%
Hayashi	16 / 111	5.5 years	25% v 41%
Takigawa	32 / 1332	5 years	20% v 62%

Panel: Multiple Procedures
81% in HD v 83 % non-HD



Sairaku A. J Cardiovasc Electrophysiology 2012; 23:1289
Hayashi M. Nephrol Dial Transplant 2014; 29:160
Takigawa M. Europace 2014; 16.327

Quebec, Canada: Population-based Study of Patients with AF; N=26,130



Ionescu-Ittu R et al. *Arch Intern Med* 2012; 172: 997

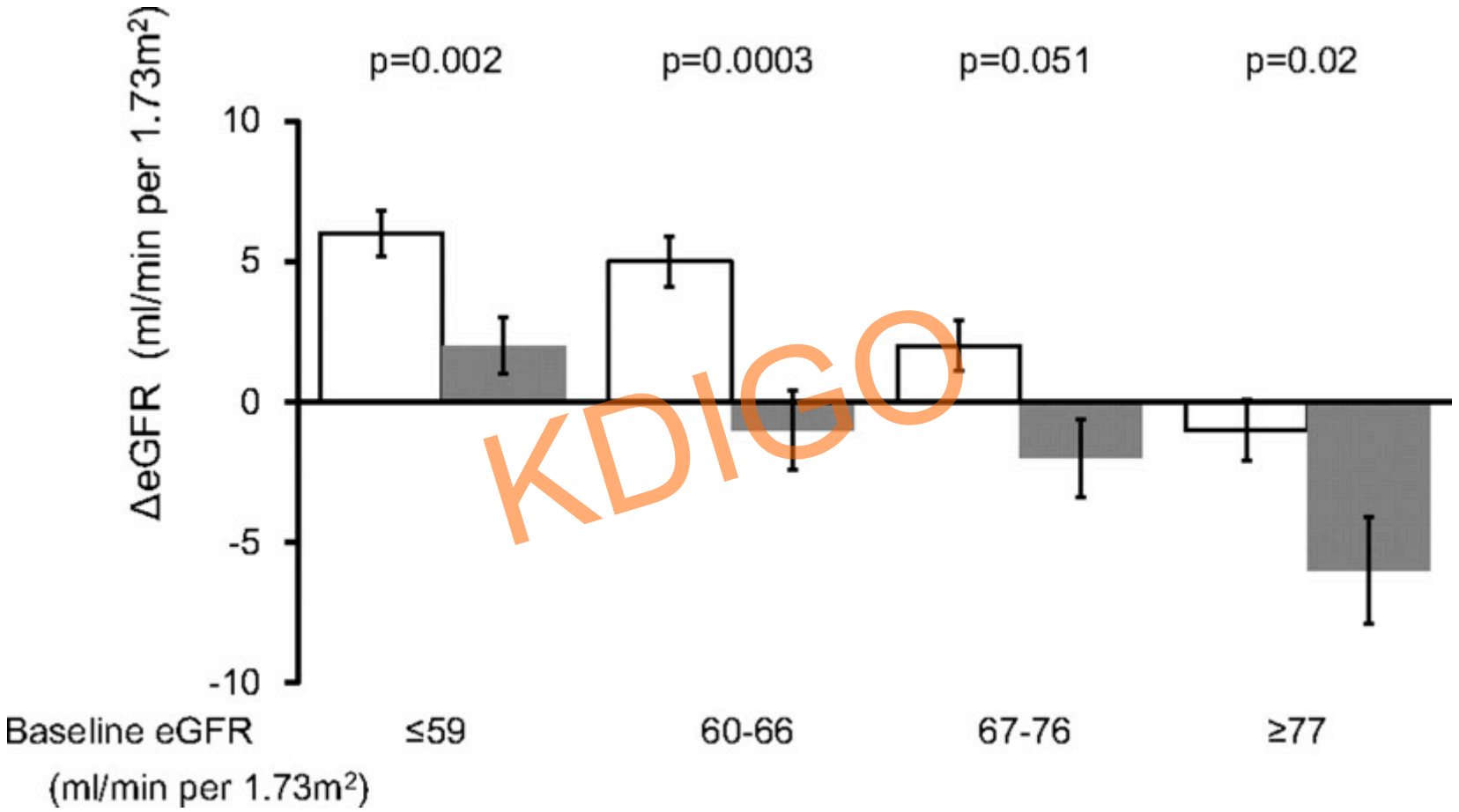
Impact of AF Ablation

Andersson, et al. EHJ 2013.
Tsadok, et al. Circ. Dec. 2012
Bunch TJ et al. Heart Rhythm 2010; 7: 433

Summary

- AF common in CKD and is associated with increased morbidity and mortality
- Scant data on benefits of rhythm control in patients with CKD (improved GFR?) and no data on ESRD
- Limited antiarrhythmic drug options
- Ablation possibly less successful based on degree of CKD
- Ideal energy (RF vs cryo) source unknown
- More study needed

Mean changes in estimated glomerular filtration rate (eGFR) from baseline to 1 year after ablation of atrial fibrillation (AF) across quartiles of baseline eGFR.

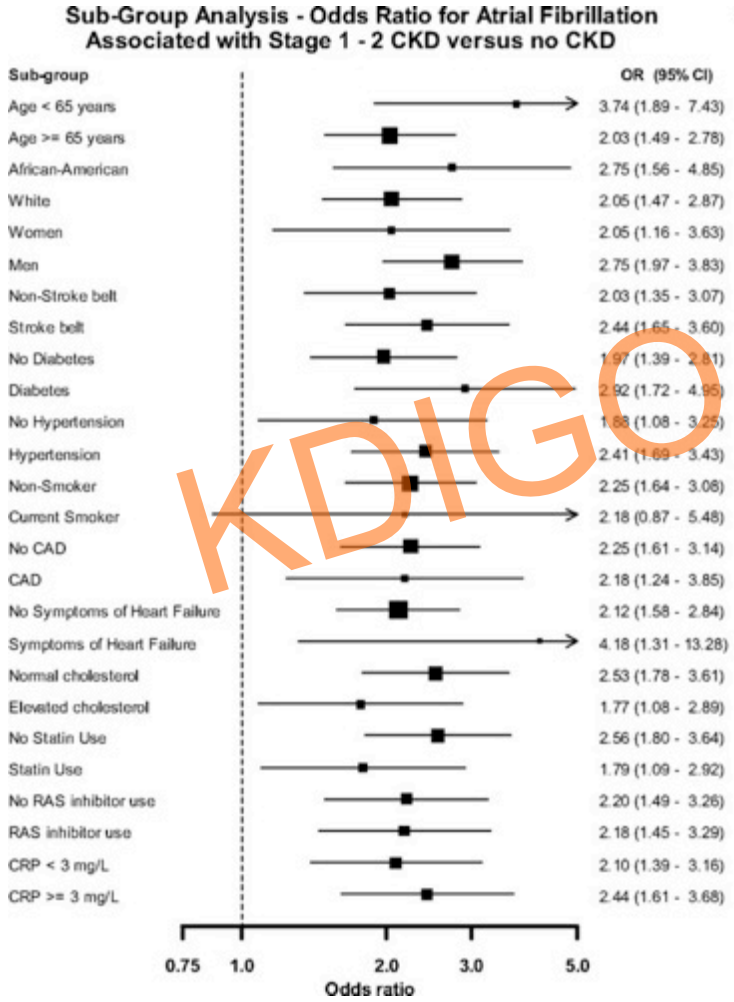


Yoshihide Takahashi et al. Circulation. 2011;124:2380-2387

ORs for AF associated with stage 1 to 2 and stage 3 to 5 versus no CKD within subgroups of REGARDS study participants (N=26917)

Prevalence of AF:
No CKD: 1.0%
stage 1 to 2: 2.8%
stage 3: 2.7%
stage 4 to 5 CKD: 4.2%

Adjusted OR for AF:
Stage 1-2: 2.7
Stage 3: 1.7
Stage 4-5: 3.5

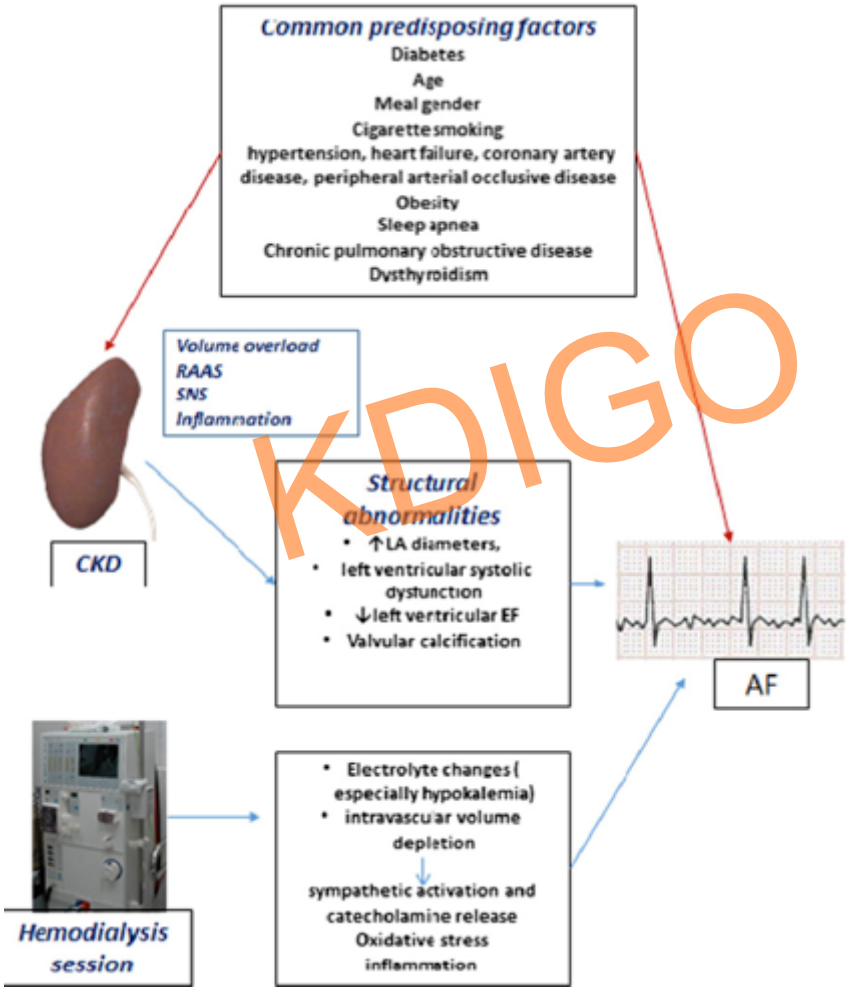


Usman Baber et al. Circ Arrhythm Electrophysiol. 2011;4:26-32

AF Risk Factors: Classical and Novel

- Age
- HTN (less so in ESRD)
- Valvular disease
- Cardiomyopathy
- DM
- CAD
- Genetic factors
- Obesity
- OSA
- LA enlargement
- Systemic inflammation (CRP, IL2, IL6, IL8, TNFα, fibrinogen)
- Low serum / dietary Mg
- Hypokalemia

Mechanisms of AF in CKD

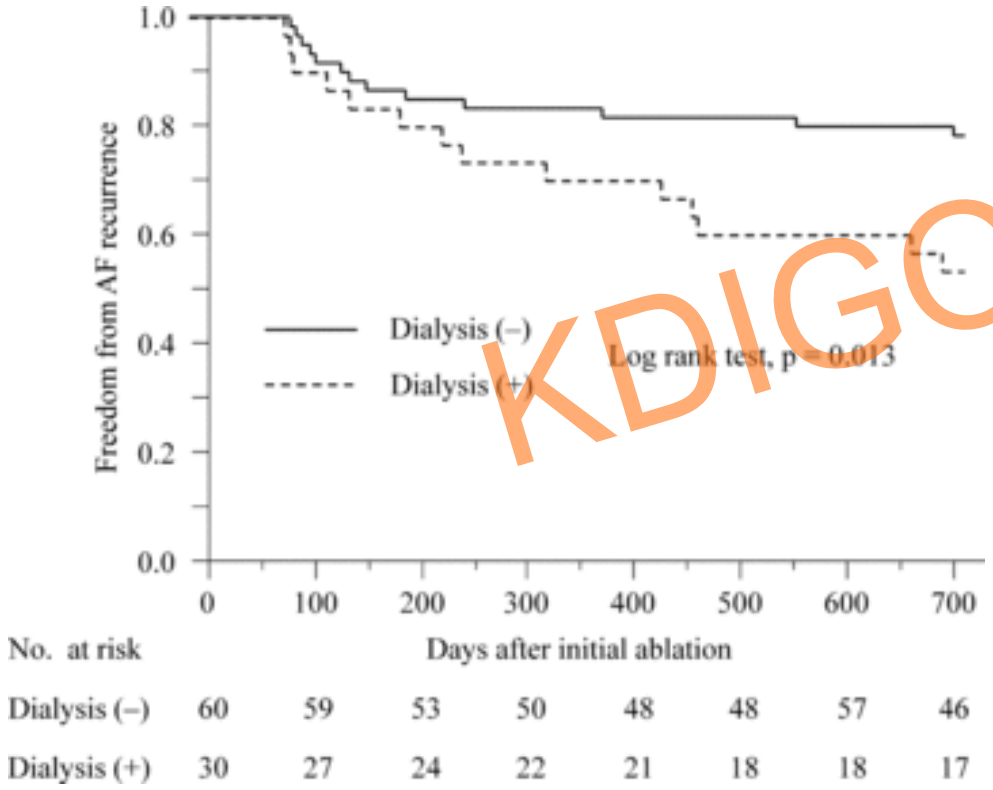


- Chronic volume overload
  - LA size
- RAAS activation
  - Fibrosis
  - Electrical remodeling
- Sympathetic activation
- Dialysis
  - More AF during HD

Voroneanu; Eu J Int Med

AF Ablation in Dialysis Patients

First Report: N = 30 HD, 60 non-HD
(matched on age/gender)



No. at risk								
Dialysis (–)	60	59	53	50	48	48	57	46
Dialysis (+)	30	27	24	22	21	18	18	17

HD Patients:

- Larger LA
- Longer procedures
- More fluoroscopy
- Long RF times

Sairaku A. J Cardiovasc

AF Prevalence by CKD Stage, Age, Race, Diabetes, HTN, CHF Status

vol 1 **Table 4.3 Prevalence of AFIB by stage of CKD, age, race, sex, diabetic status, hypertension status, and CHF status, 2013**

	Stage of CKD		
	Stages 1-2	Stage 3	Stages 4-5
AFIB (Overall)	20.8	24.5	26.6
Age:			
66-69	11.3	14.7	16.8
70-74	14.9	18.0	20.8
75-84	22.6	25.1	26.6
85+	31.3	32.9	32.9
Sex			
Male	23.0	27.3	29.3
Female	18.8	22.0	24.4
Race			
White	22.9	26.3	29.3
Black/African American	12.9	15.4	14.2
Other race	11.7	16.1	18.6
Comorbidity			
Non-diabetes	20.5	24.0	25.9
Diabetes	21.1	25.1	27.3
Non-hypertension	10.3	15.0	17.1
Hypertension	21.7	25.2	27.0
No Heart Failure (CHF)	12.5	14.2	13.5
Heart Failure (CHF)	47.8	49.8	46.7

Data Source: Special analyses, Medicare 5 percent sample. Patients aged 66 and older, alive, without end-stage renal disease, and residing in the U.S. on 12/31/2013 with fee-for-service coverage for the entire calendar year. Totals of patients for the study cohort: N=88,241; Stages 1-2=13,271; Stage 3=61,466; Stages 4-5=13,504. Abbreviations: AFIB, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease.

Risk of Stroke by AF Type: ACTIVE-A / AVERROES ASA Arms

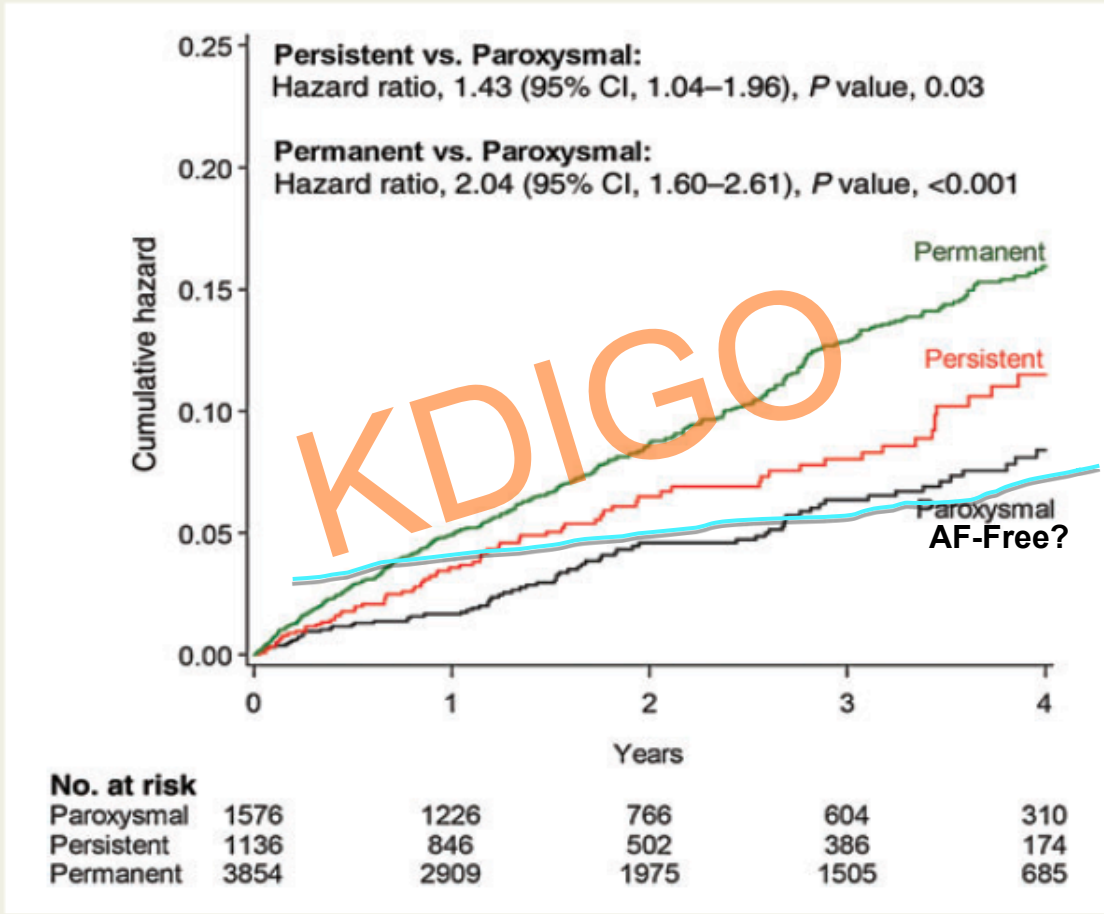
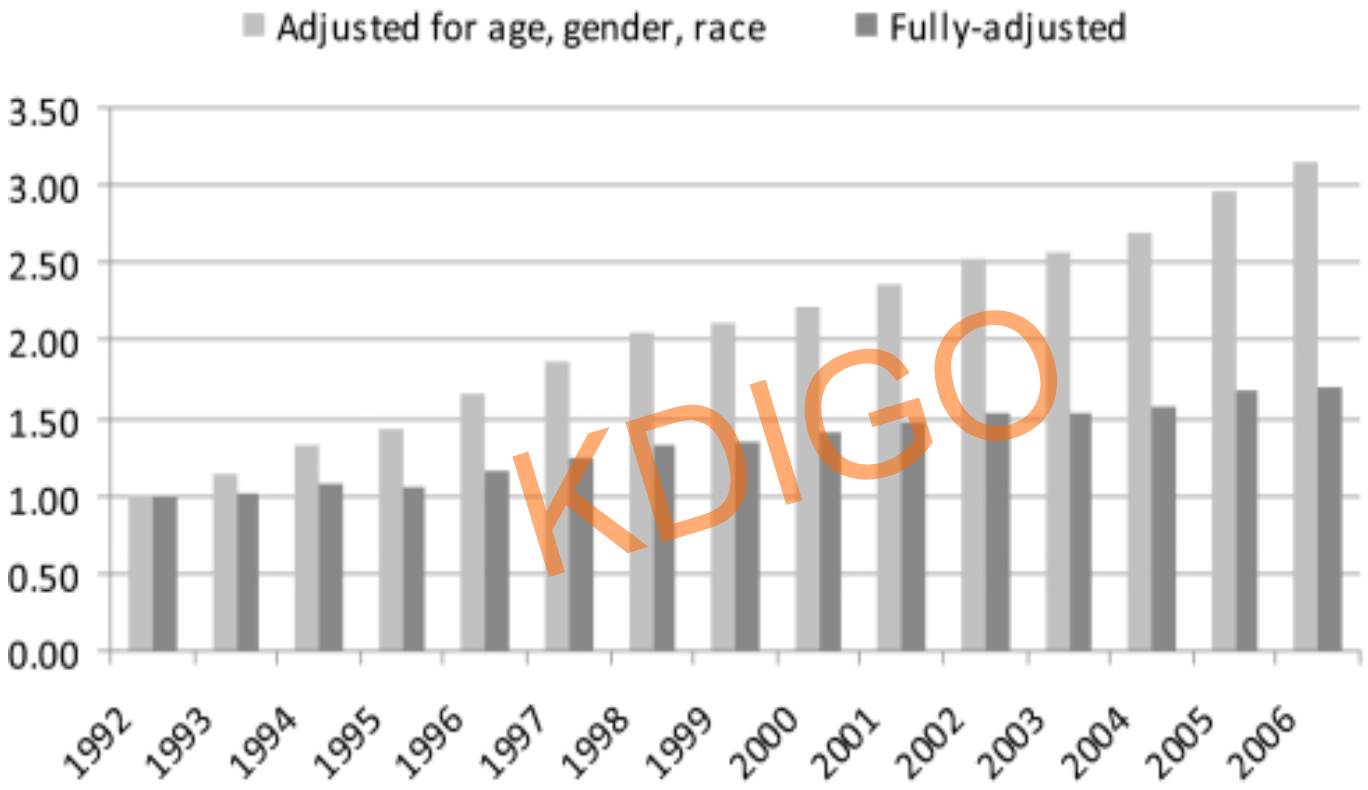


Figure 1 Kaplan–Meier cumulative hazard rates of embolic events according to the pattern of atrial fibrillation occurrence.

Vanassche et al. Eur Heart J 2014

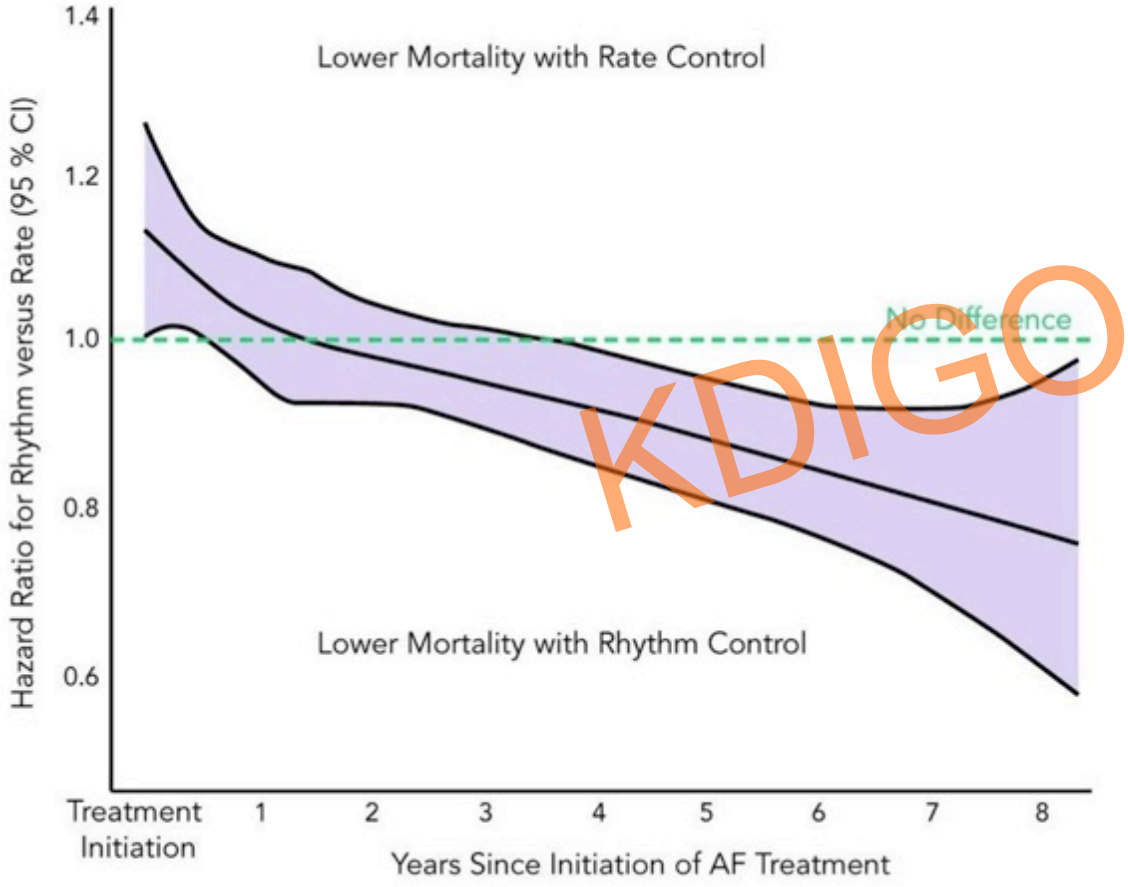
Relative



1 Year Mortality:
39% *versus* 19%

Winkelmayer WC; J Am Soc Nephrol. 2011 Feb; 22(2): 349–357

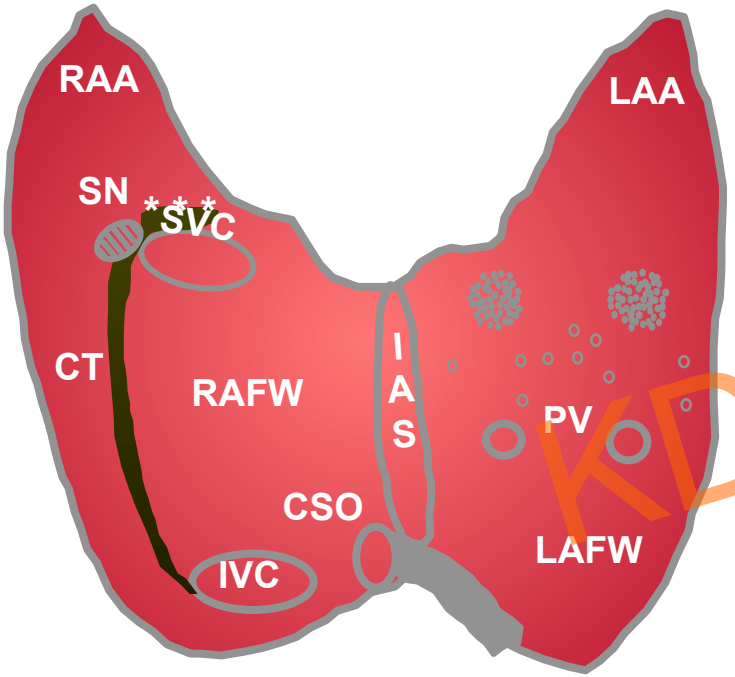
What about other neurologic sequelae of AF?



Quebec, Canada
Population-based Study
of Patients with AF

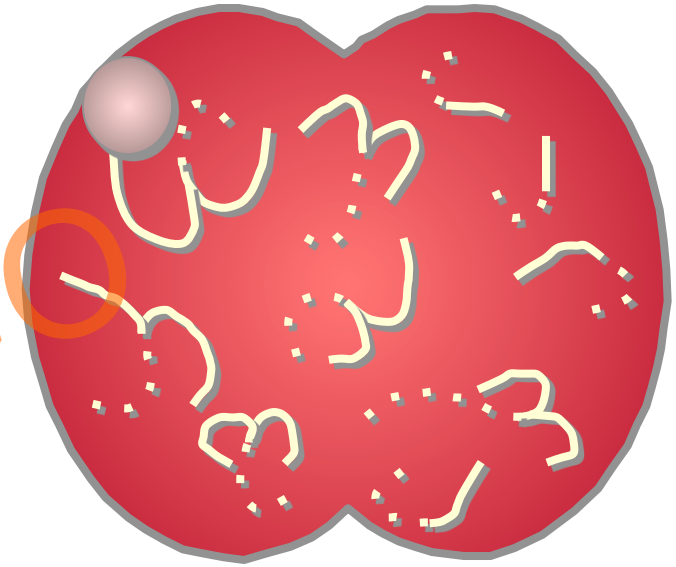
Ionescu-Ittu R et al. *Arch Intern Med* 2012; 172: 997

Mechanism of AF



Focal Triggers

1947



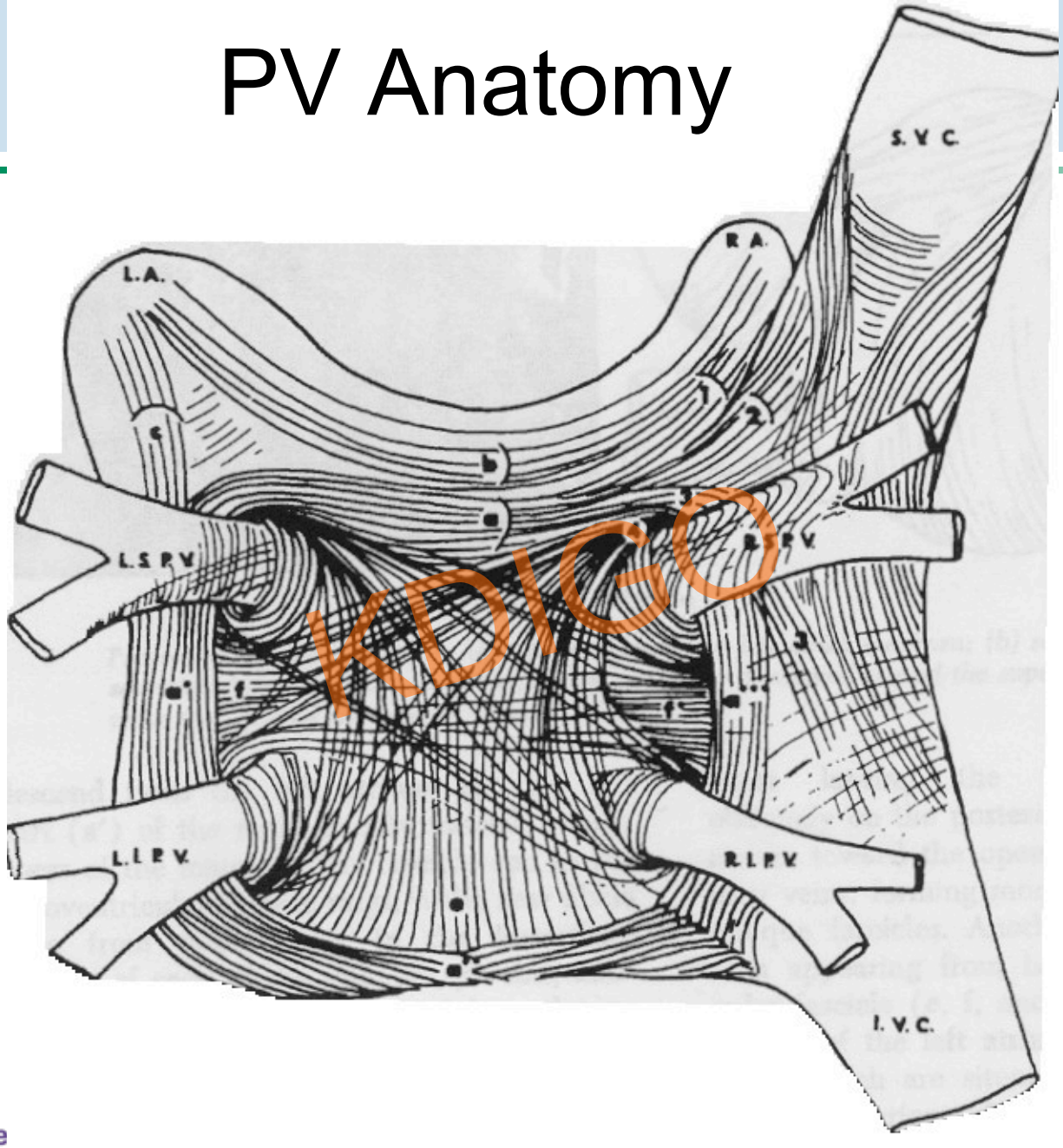
Multiple Wavelets

1959

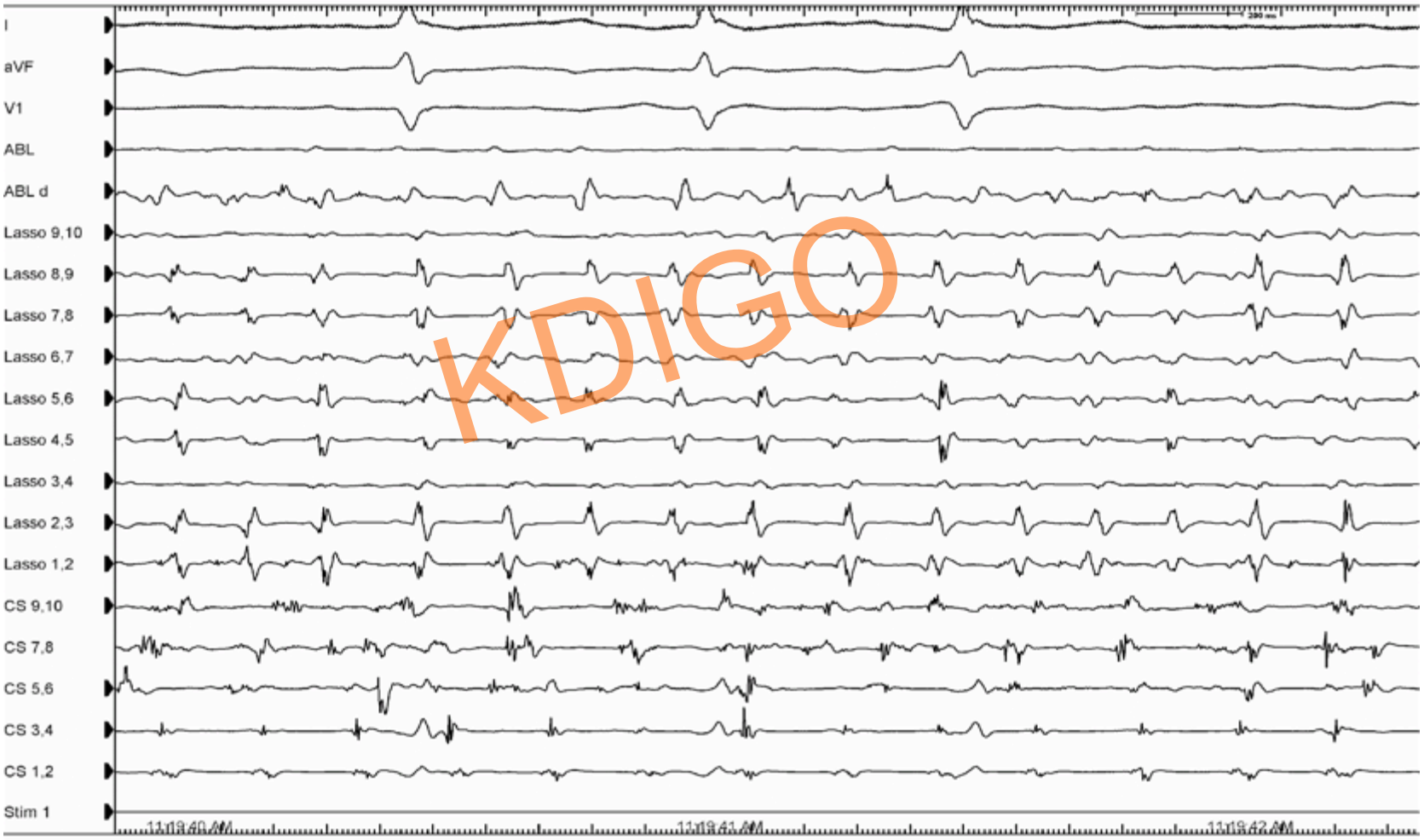
Narayan et al. *Lancet*. 1997;350:943-950.

Chen et al. *Circulation*. 1999;100:1879-1886.

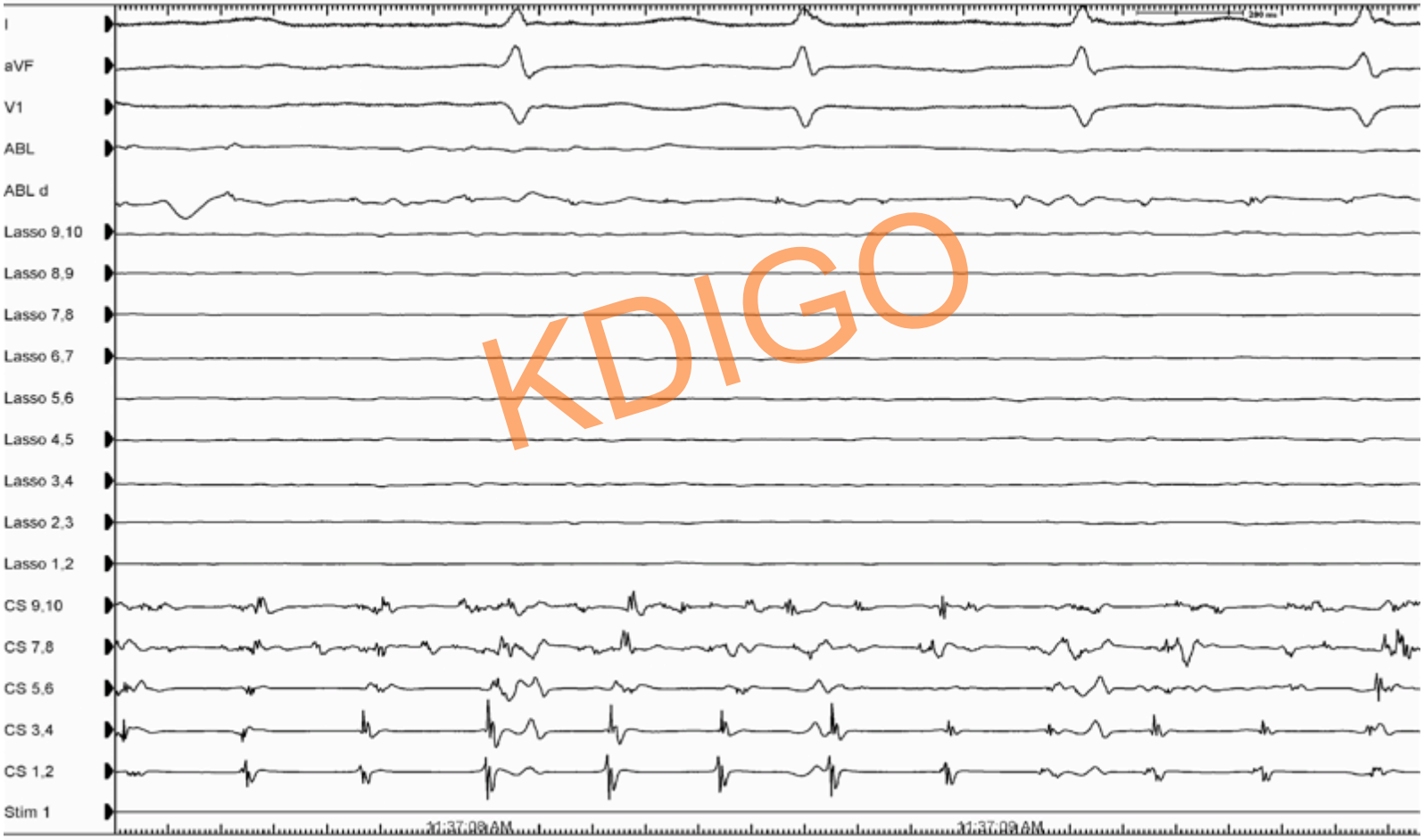
PV Anatomy

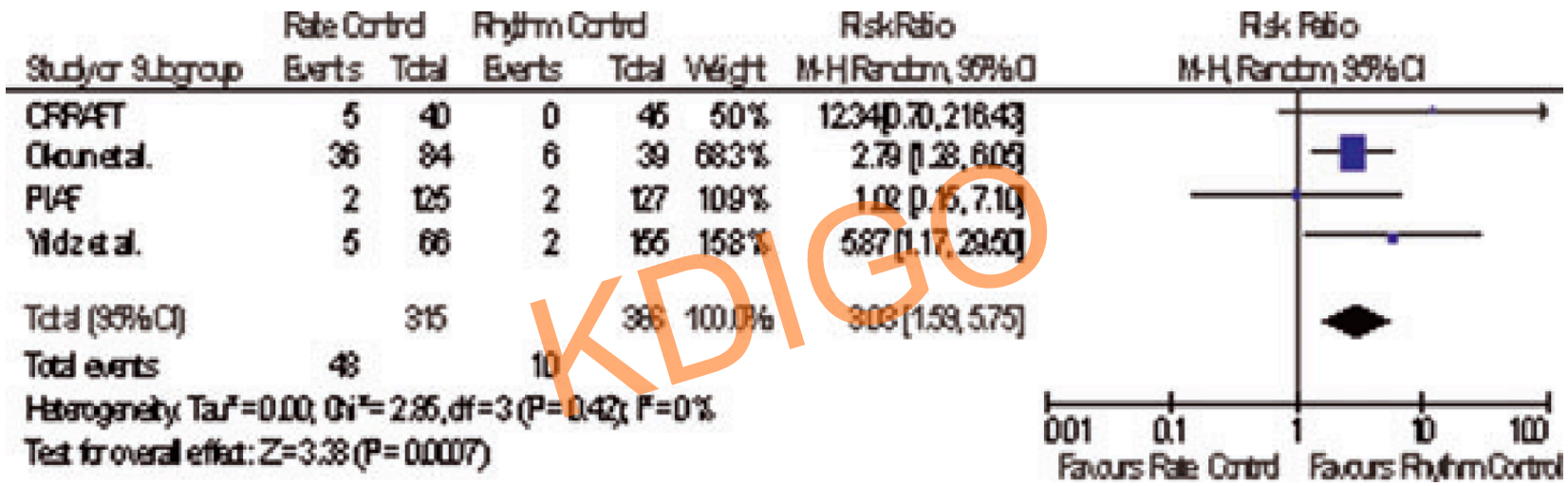


Catheter in Pulmonary Vein: Pre-Ablation



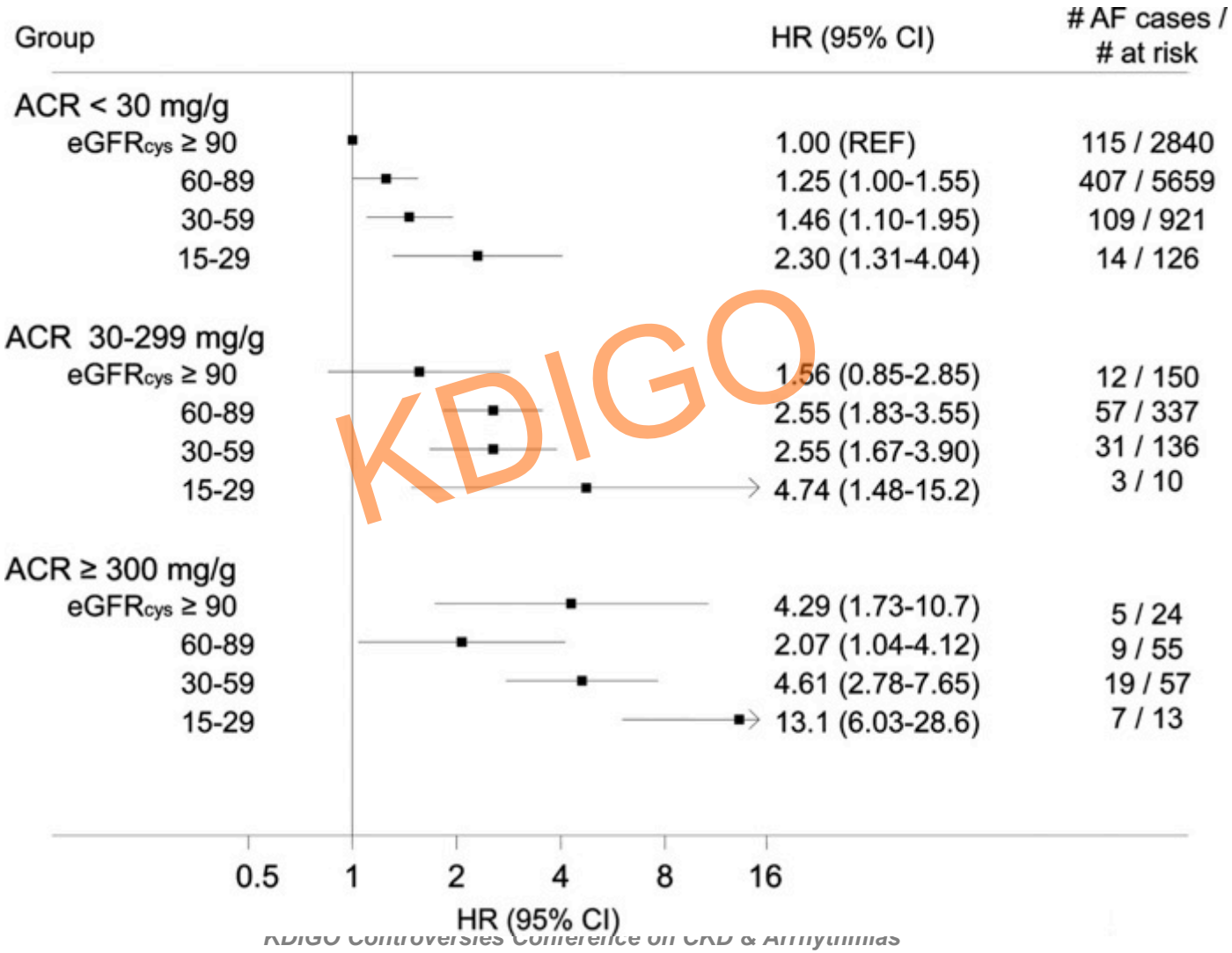
Catheter in Pulmonary Vein: Post-Ablation





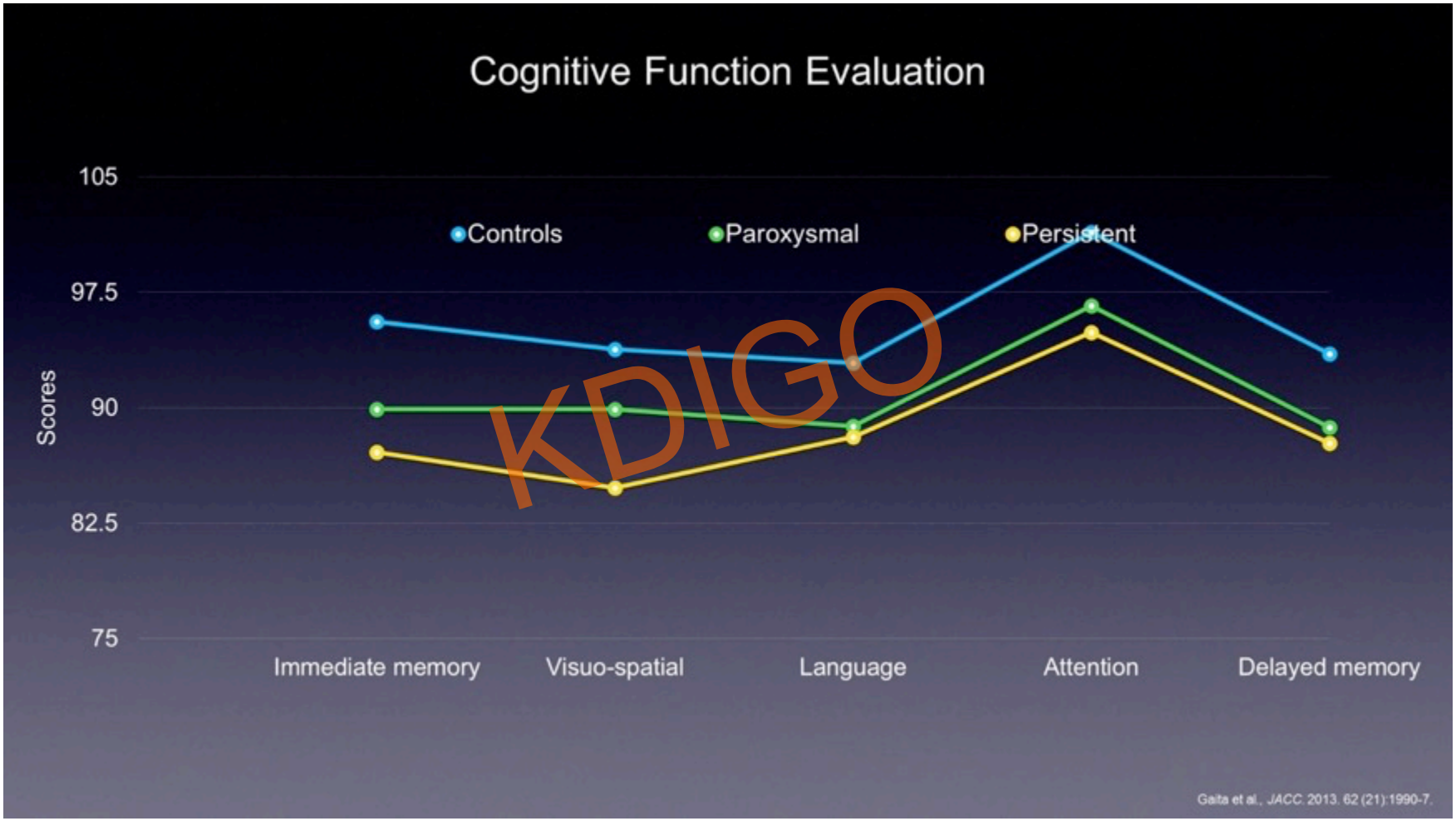
Chatterjee S; PACE

Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation (AF) according to urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate from blood cystatin C (eGFRcys), Atherosclerosis Risk in Communities (ARIC), 1996 to 2007.



Alvaro Alonso et al. Circulation. 2011;123:2946-2953

AF And Cognitive Impairment



AF And Cognitive Impairment