



EPIDEMIOLOGY OF ARRHYTHMIAS AND OUTCOMES IN CKD & DIALYSIS

Wolfgang C. Winkelmayr, MD, ScD
Baylor College of Medicine Houston,
Texas

Disclosure of Interests

AstraZeneca (scientific advisory board)

Bayer Pharma (scientific advisory board)

Bristol Myers Squibb (trial executive committee)

Daichii Sankyo (scientific advisory board)

Medtronic (event adjudication committee)

Relypsa/Vifor FMC Renal Pharma (scientific advisory boards)



General Considerations

- Epidemiological Study Designs

- Both CKD and arrhythmia remain often asymptomatic > issues with ascertainment (potential bias)

Prospective cohort studies (incl. RCTs)

- + kidney function measured [protocolized; @BL; f/u (?)];
- + ECG usually available [protocolized; @BL; f/u (?)];
- + arrhythmia from ECG (ideally centrally read) or +/- self-reported or from hospital discharge surveillance;
- + endpoints of interest may be adjudicated;
- smaller sample
- less generalizable (?)

General Considerations

- Epidemiological Study Designs

- Both CKD and arrhythmia remain often asymptomatic > issues with ascertainment (potential bias)

Insurance Claims Data (e.g., US Medicare; CAN)

- kidney function and arrhythmia usually from dx codes;
- labs/ECG usually not protocolized (routine annual?), but symptom-driven or incidental;
- CKD/arrhythmia, diagnosed or not, reported or not;
- + larger sample
- + more generalizable (?)

General Considerations

- Epidemiological Study Designs

- Both CKD and arrhythmia remain often asymptomatic > issues with ascertainment (potential bias)

Electronic health records (e.g., Kaiser; VA;)

- +/- kidney function usually from labs (but not protocolized)
- ECG usually not protocolized (routine annual?);
- +/- Arrhythmia from dx codes or look back at ECG tracing;
- If open system, may not capture all encounters
- + larger sample
- + more generalizable (?)

Atrial Fibrillation

- Most common arrhythmia
 - Affecting ~2.7-6.1 million Americans in 2010
 - May increase to 12.1 million by 2030
 - Worldwide prevalence, ~33.5 million in 2010
 - Age-adjusted incidence of AF increased by 12% from 1980-2000 (Olmstead County, MN)
 - Lifetime AF risks are (Framingham Heart Study)
 - 23% for women and 26% for men at age 40

Atrial Fibrillation and Stroke

- AF increases risk of ischemic stroke 4- to 5-fold
- Paroxysmal, persistent, and permanent AF all predispose to subsequent ischemic stroke
 - Diagnosed AF responsible for at least 15% to 20% of all ischemic strokes
 - Subclinical AF increases subsequent risk of stroke or peripheral embolism 2.5-fold
 - Subclinical (undiagnosed) AF may be responsible for another 13% of ischemic strokes

Healey JS, et al. *NEJM*
2012;366:120

Atrial Fibrillation and Other Outcomes

- While stroke is the most “recognizable” outcome of AF, analysis of RE-LY showed that:
 - 7% of deaths from stroke, but
 - 22% were from SCD
 - 15% from HF
 - 36% non-CV death

Marijon E, et al. *Circulation* 2015;128:2192

Kidney Disease and Atrial Fibrillation

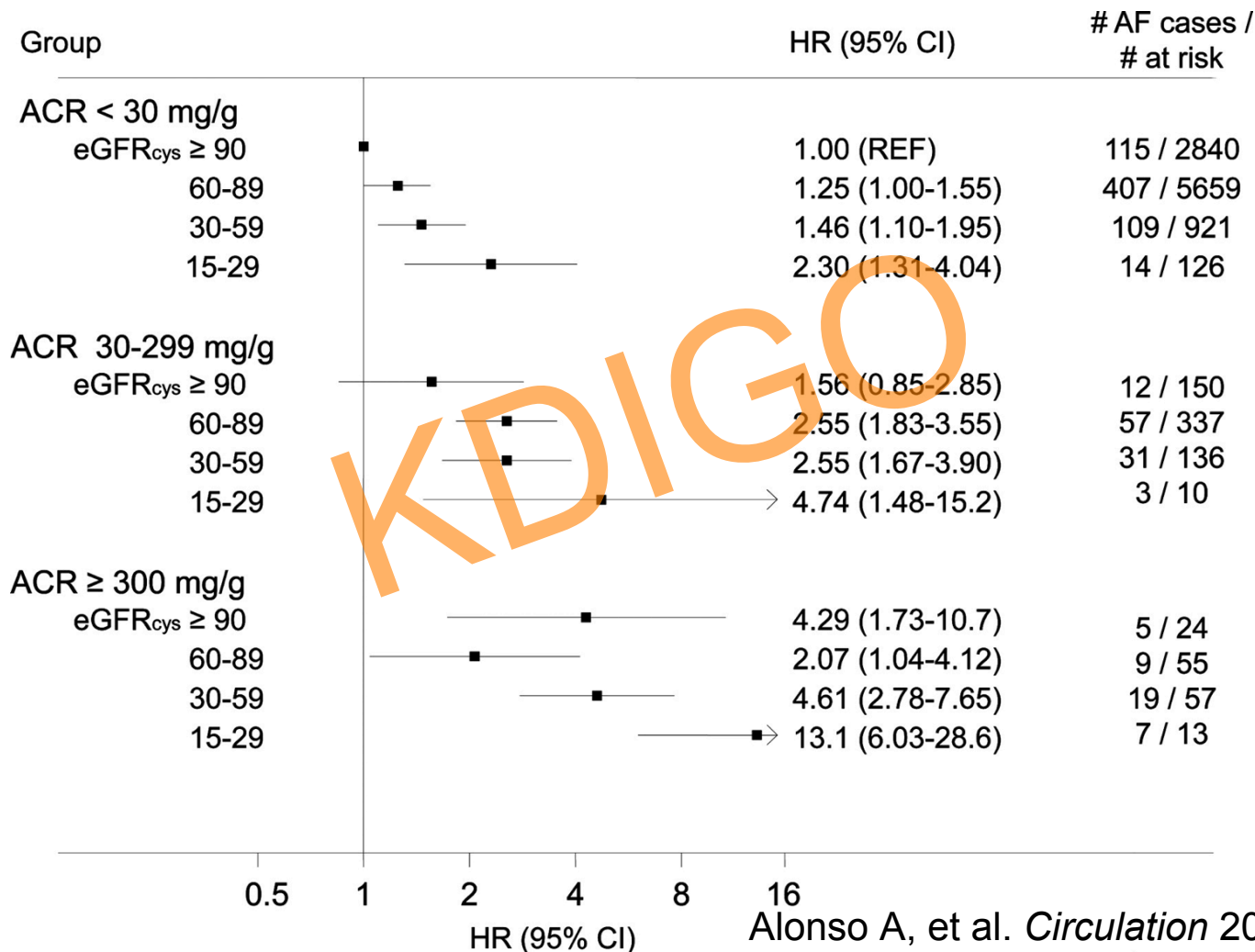
Studies linking kidney function and prevalent AF

- Heart and Soul Study: 4% AF prevalence; by eGFR_{CYS} and ACR (McManus DD, et al. *Am J Cardiol* 2009;104:1551)
- CRIC Study; 20% AF prevalence, no association w/ eGFR (Soliman EZ, et al. *Am Heart J* 2010;159:1102)
- REGARDS Study; 1.3% AF prevalence; by CKD Stage 1 to 4/5 (Baber U, et al. *Circ Arrhythm Electrophysiol* 2011;4:26)

Association of eGFR and incident AF

- Niigata Preventive Medicine Study: by eGFR_{MDRD-J}, urine dipstick (Watanabe H, et al. *Am Heart J* 2009;158:629)
- ARIC Study; by eGFR_{CYS} and ACR; no evidence of interaction (Alonso A, et al. *Circulation*. 2011;123:2946)

Kidney Disease and Atrial Fibrillation



Alonso A, et al. *Circulation* 2011;123:2946



Atrial Fibrillation and Kidney Disease

Table VI. Atrial Fibrillation and risk of chronic kidney disease and proteinuria, Multivariate Models

	HR (95% CI)	P value
Development of kidney dysfunction		
All subjects	1.80 (1.54-2.10)	<.001
Subjects w/o treated hypertension or diabetes	2.22 (1.81-2.72)	<.001
Development of proteinuria		
All subjects	2.16 (1.92-2.42)	<.001
Subjects w/o treated hypertension or diabetes	2.42 (2.06-2.83)	<.001

Models were adjusted for age, sex, body mass index, systolic and diastolic blood pressure, treated hypertension and diabetes in all subjects and were adjusted for age, gender, body mass index, and systolic and diastolic blood pressure in subjects without treated hypertension or diabetes.

Watanabe H, et al. *Am Heart J*
2009;158:629



Atrial Fibrillation and CKD Progression

Table 2. Association Between Incident Atrial Fibrillation and Subsequent Risk of End-Stage Renal Disease Among Adults With Chronic Kidney Disease

	HR (95% CI)
Unadjusted	1.18 (1.06–1.31)
Adjusted for patient characteristics, cardiovascular risk factors, and medication use*	1.67 (1.46–1.91)

Bansal N, et al. *Circulation* 2013;127:569



Atrial Fibrillation and CKD Progression

Table 2. Multivariable association of incident atrial fibrillation with risk of ESRD among participants with CKD in the Chronic Renal Insufficiency Cohort Study

Statistical Approach	N/Rate (Per 100 person-yr) of ESRD Events	Hazard Ratio (95% Confidence Interval) of AF with ESRD
Cox regression model		
No incident AF	581/3.4	Reference
Incident AF	43/11.8	3.3 (2.4 to 4.6)
Marginal structural model		
No incident AF	581/3.4	Reference
Incident AF	43/11.8	3.2 (1.9 to 5.2)

Adjusted for demographics, clinical site, proteinuria, eGFR, tobacco use, heart failure, coronary heart disease, hypertension, diabetes, systolic BP, body mass index, hemoglobin, diuretic use, and angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use. AF, atrial fibrillation.

Bansal N, et al. *CJASN* 2016;11:1189



Evidence Supports Close and Bidirectional Link Between CKD and AF

But Why?

Kidney Function and Outcomes in AF

Table 4. Multivariable Association Between Level of eGFR, Proteinuria, and Risk of Thromboembolism Off Anticoagulation in Adults With Nonvalvular AF

	Adjusted* Hazard Ratio for Thromboembolism (95% CI)
eGFR, mL · min ⁻¹ · 1.73 m ⁻²	
≥60	Referent
45–59	1.16 (0.95–1.40)
<45	1.39 (1.13–1.71)
Proteinuria	
No	Referent
Yes	1.54 (1.29–1.85)

*Model also included age, sex, race/ethnicity, educational attainment, annual income status, prior ischemic stroke, heart failure, diabetes mellitus, hypertension, and coronary heart disease.

Go AS, et al. *Circulation* 2009;119:1363



Kidney Function and Outcomes in AF

In ROCKET-AF, kidney function was associated with thromboembolism:

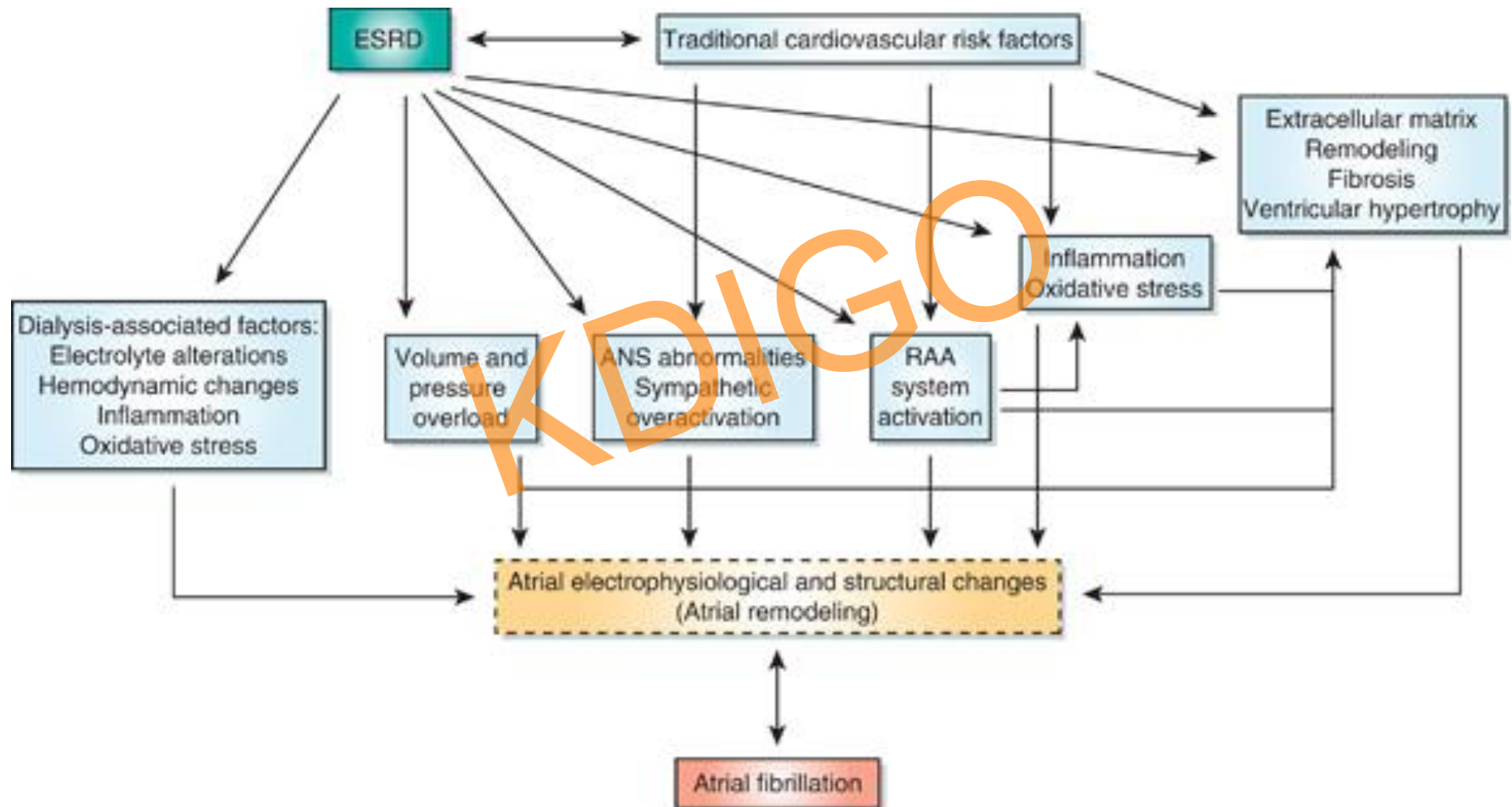
HR=1.12 (1.07-1.16) per 10 mL/min lower Cl_{Cr}

Inclusion of Cl_{Cr} in CHADS₂ score (R_2 CHADS₂) yielded a +17% reclassification for stroke/embolism in external validation cohort (ATRIA).

Piccini JP, et al. *Circulation* 2013;127:224



Atrial Fibrillation in ESRD

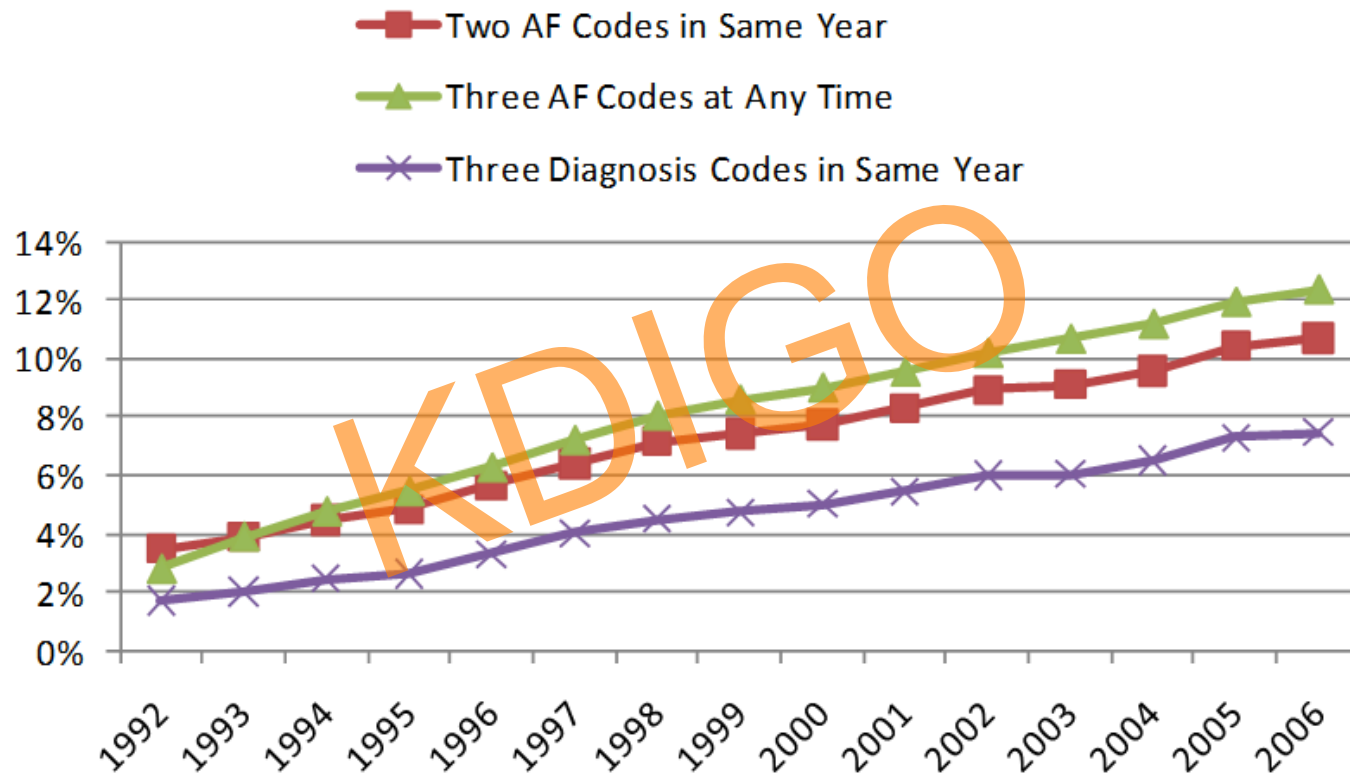


Atrial Fibrillation in ESRD

AF is a “neglected cardiovascular problem in dialysis patients”, and adds that while “AF is a common clinical problem in dialysis patients, yet it has not generated the same degree of research interest as issues relating to ischemic heart disease in ESRD patients. [...] More [needs] to be learned about the optimal treatment of AF in dialysis patients.”



Atrial Fibrillation - Prevalence in ESRD

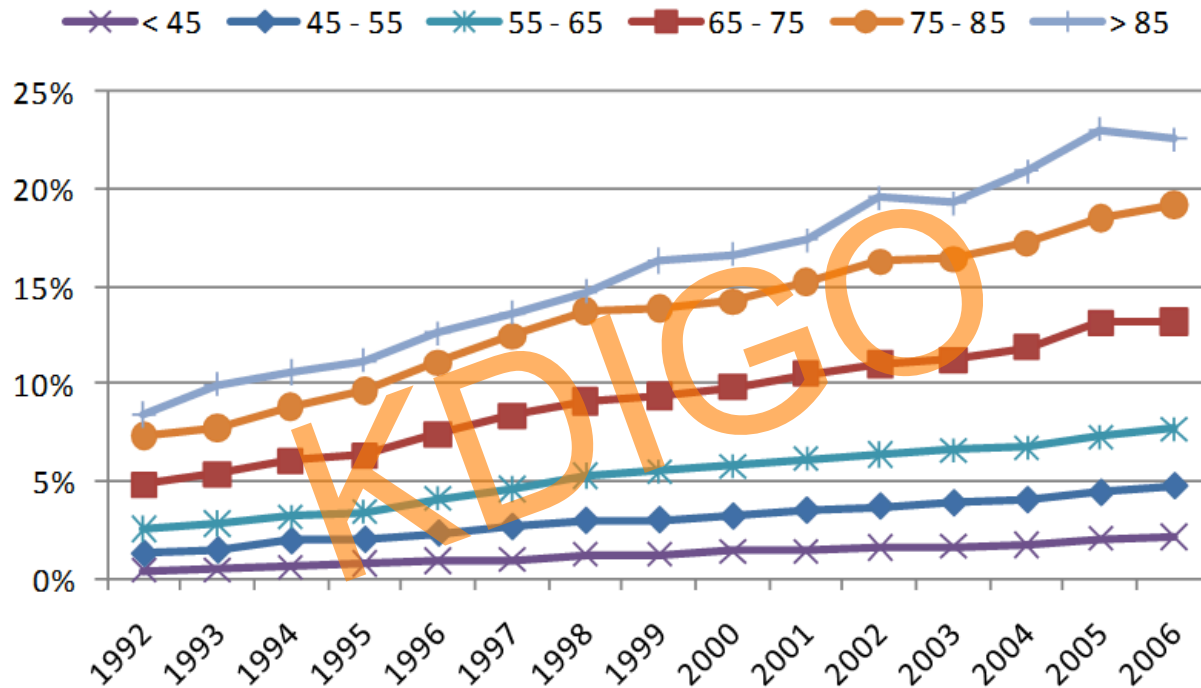


Winkelmayer WC, et al. *J Am Soc Nephrol*
2011;22:349

KDIGO Controversies Conference on CKD & Arrhythmias
October 27-30, 2016 | Berlin, Germany



Atrial Fibrillation - Prevalence in ESRD

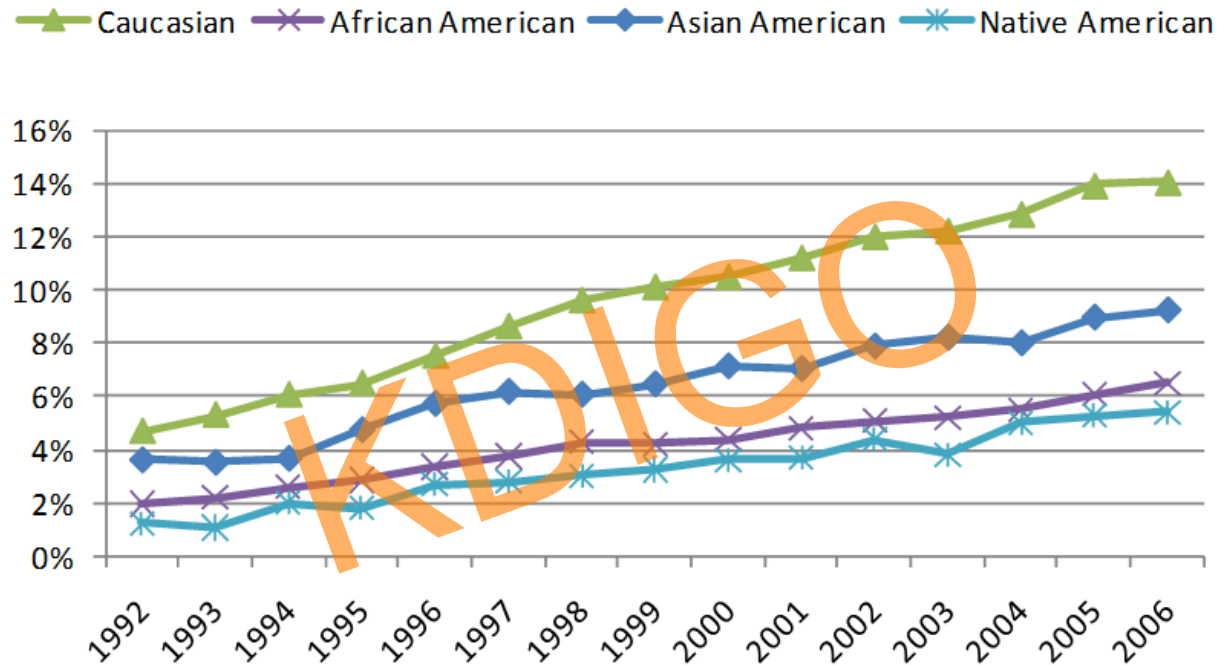


Winkelmayer WC, et al. *J Am Soc Nephrol*
2011;22:349

KDIGO Controversies Conference on CKD & Arrhythmias
October 27-30, 2016 | Berlin, Germany



Atrial Fibrillation - Prevalence in ESRD

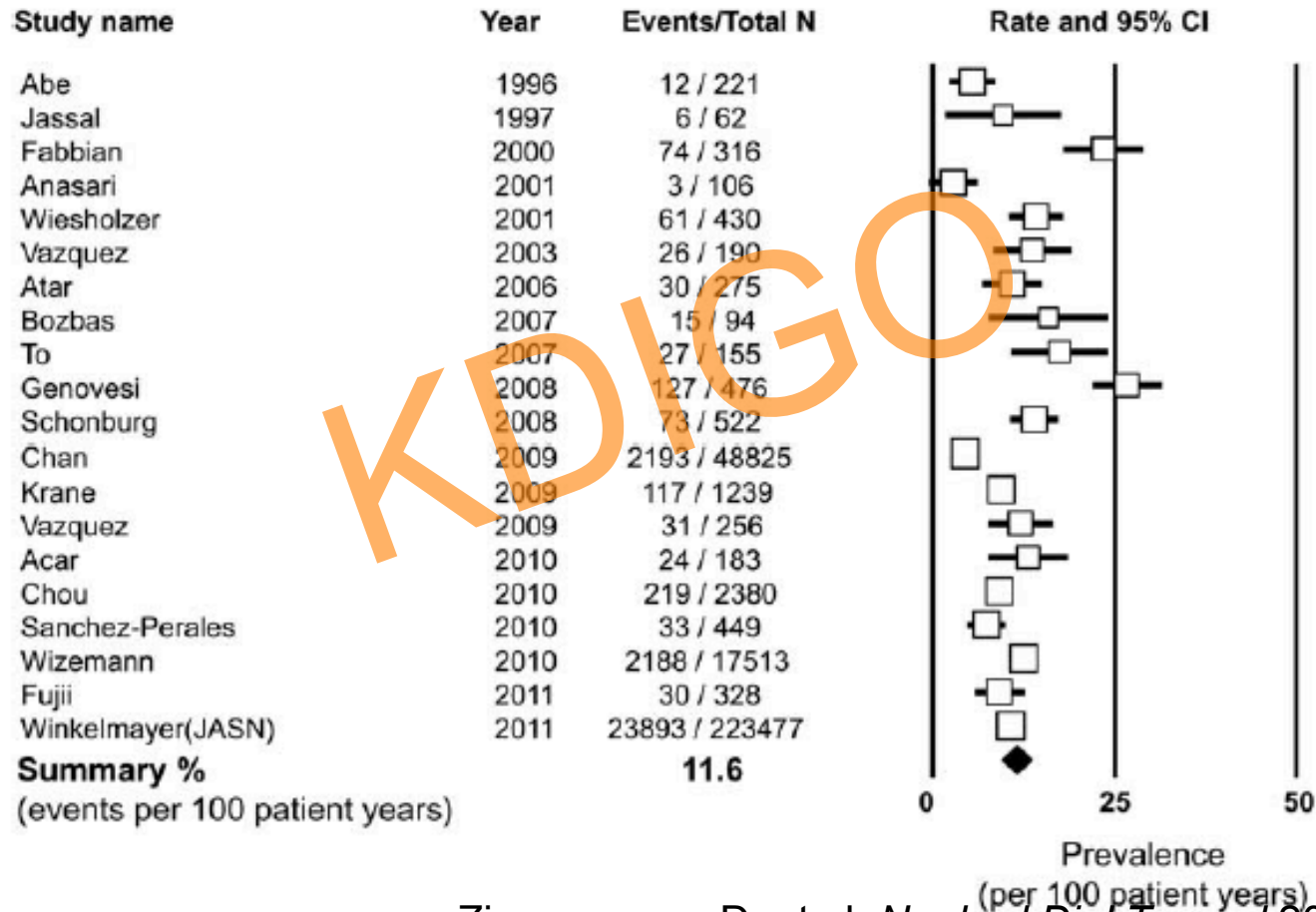


Winkelmayer WC, et al. *J Am Soc Nephrol*
2011;22:349

KDIGO Controversies Conference on CKD & Arrhythmias
October 27-30, 2016 | Berlin, Germany



Prevalence of AF in ESRD



Zimmermann D, et al. *Nephrol Dial Transpl* 2012;27:3816



Atrial Fibrillation - Prevalence in ESRD

	Prevalence Ratios		Prevalence Ratios
Age (per year)	1.04	Diabetes	0.98
Female (vs. Male)	0.89	Hypertension	1.22
<u>Race</u> (vs. Caucasian)		Heart failure	2.46
African American	0.61	Coronary artery disease	1.40
Asian American	0.82	Cerebrovascular disease	1.21
Native American	0.53	Peripheral artery disease	1.17
Years since first ESRD treatment	1.02	Chronic obstructive pulmonary disease	1.36



Atrial Fibrillation - Prevalence in ESRD

Table 3 | Prevalence of chronic atrial fibrillation in dialysis patients compared with an ambulatory patient population, by age decade and sex

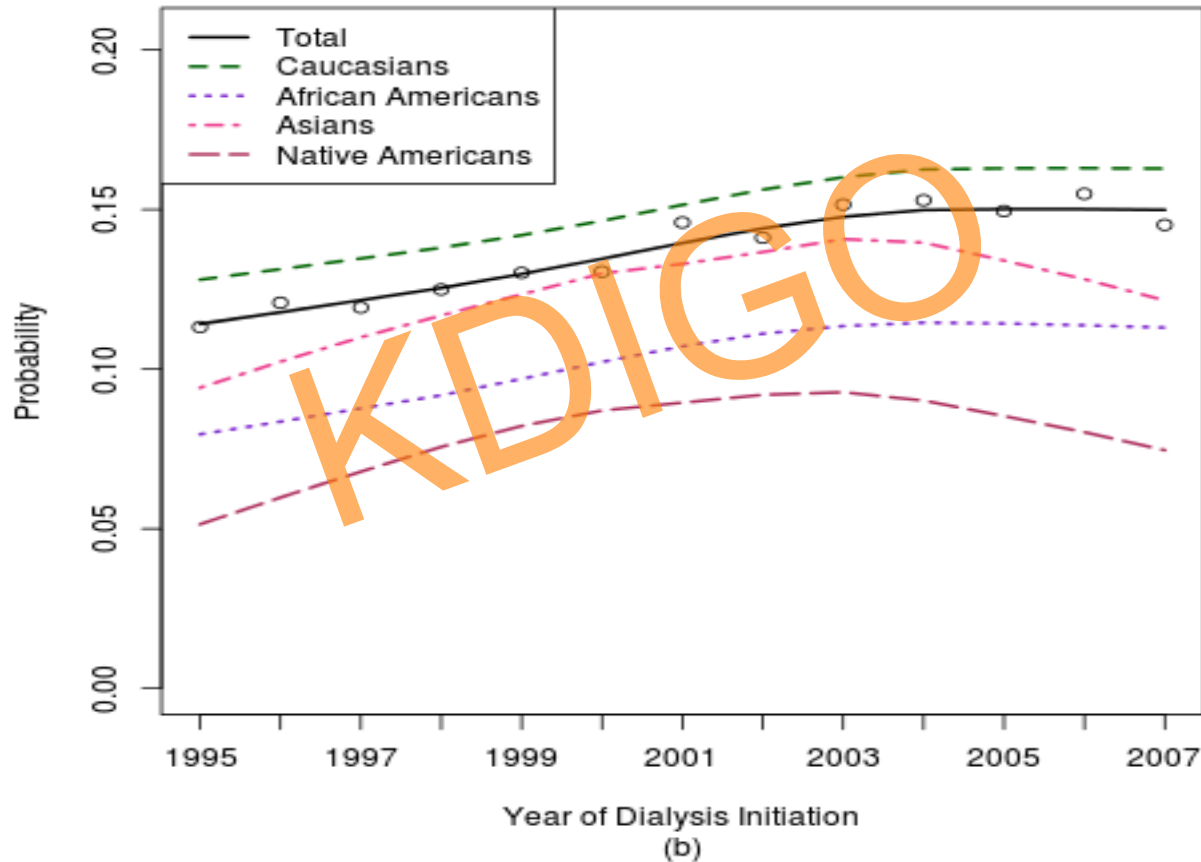
Age, years	Females		Males	
	Dialysis %	Ambulatory % ^a	Dialysis %	Ambulatory % ^a
<55	1.9 (186/9967)	0.1	2.5 (339/13,528)	0.2
55 to 60	4.7 (181/3811)	0.4	5.4 (216/3990)	0.9
60 to 65	5.7 (214/3764)	1.0	7.1 (221/3094)	1.7
65 to 70	8.0 (358/4462)	1.7	9.2 (292/3190)	3.0
70 to 75	11.6 (500/4304)	3.4	12.2 (305/2508)	5.0
75 to 80	13.0 (463/3556)	5.0	14.8 (287/1935)	7.3
80 to 85	15.1 (373/2470)	7.2	16.6 (195/1178)	10.3
>85	16.3 (244/1493)	9.1	18.0 (114/634)	11.1

^aEstimates for ambulatory patients adapted from Go et al.¹⁵

Wetmore JB, et al. *Kidney Int* 2012;81:469

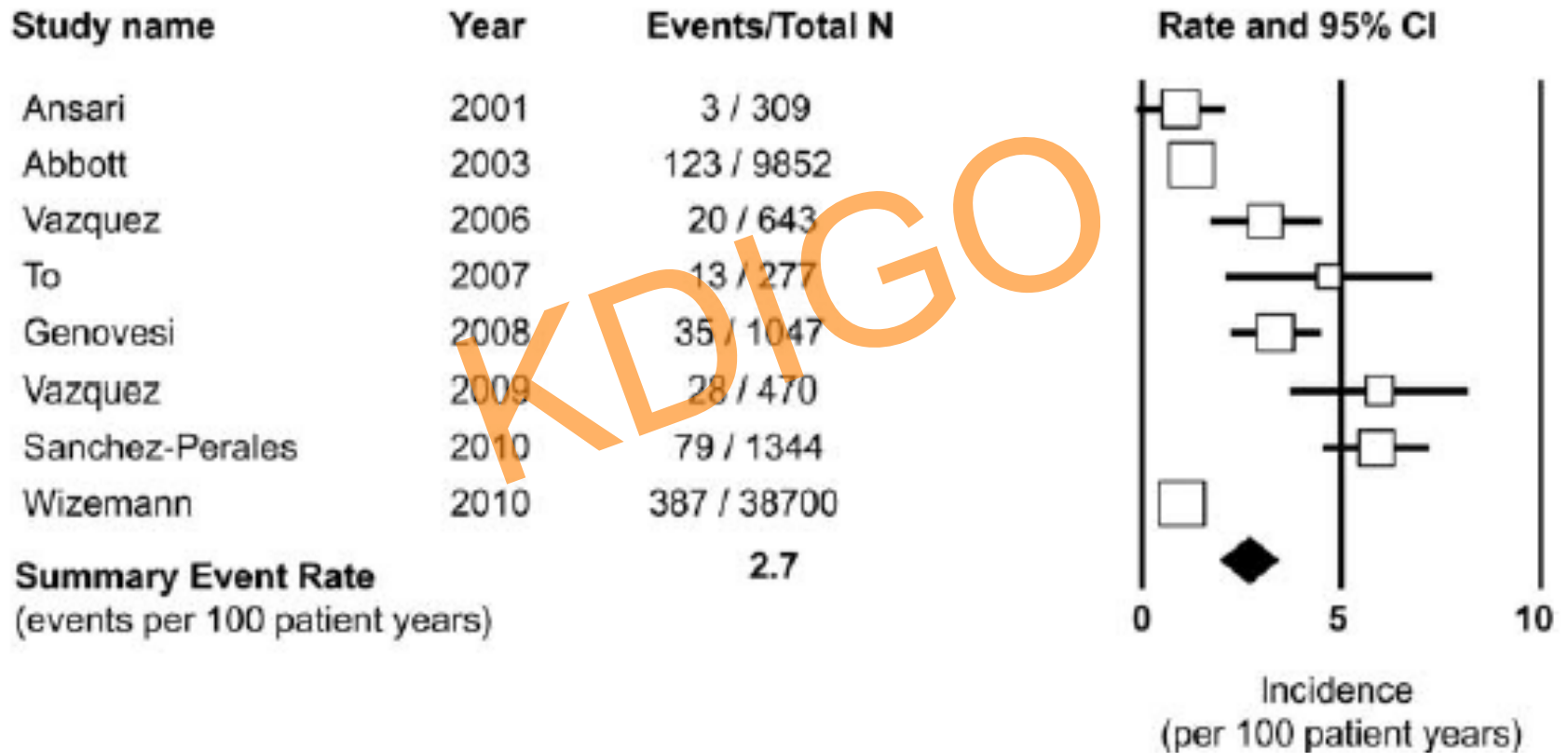


Atrial Fibrillation - Incidence in ESRD



(b)
Goldstein BA, et al. *Circulation* 2012;126:2293

Incidence of AF in ESRD



Zimmermann D, et al. *Nephrol Dial Transpl* 2012;27:3816



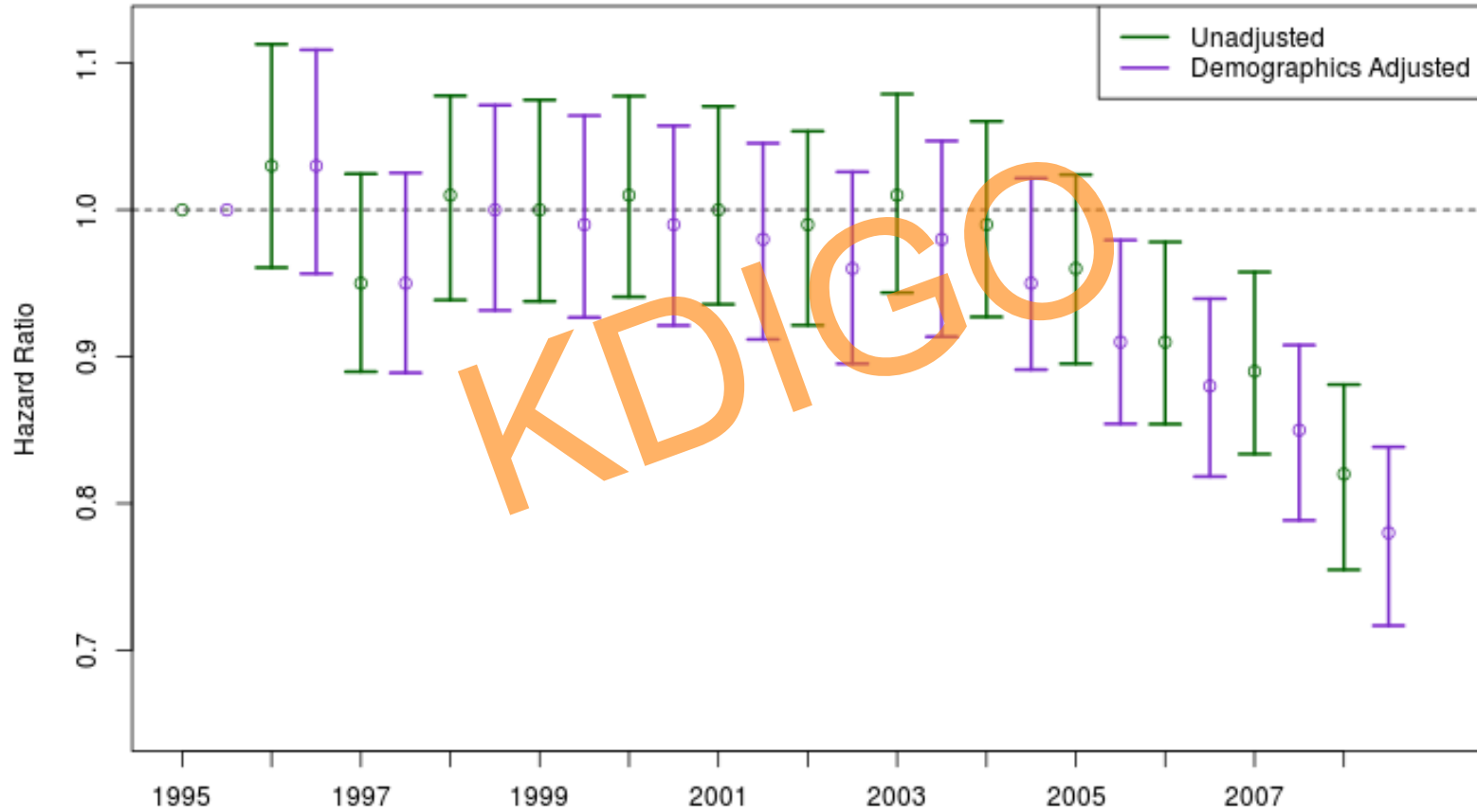
Atrial Fibrillation - Incidence in ESRD

	Demographics-Adjusted	Fully-Adjusted
Age (per 10 years)	1.33 (1.31, 1.34)	1.33 (1.32, 1.35)
Male Sex (vs. female)	0.98 (0.96, 0.99)	0.98 (0.96, 0.99)
Race (vs. white)		
African American	0.68 (0.67, 0.70)	0.70 (0.69, 0.71)
Asian	0.77 (0.74, 0.81)	0.81 (0.77, 0.85)
Native American	0.57 (0.52, 0.63)	0.58 (0.53, 0.63)
Hispanic Ethnicity (vs. non-Hispanic)	0.70 (0.68, 0.72)	0.71 (0.69, 0.73)

Goldstein BA, et al. *Circulation* 2012;126:2293



Mortality after AF Incidence in ESRD



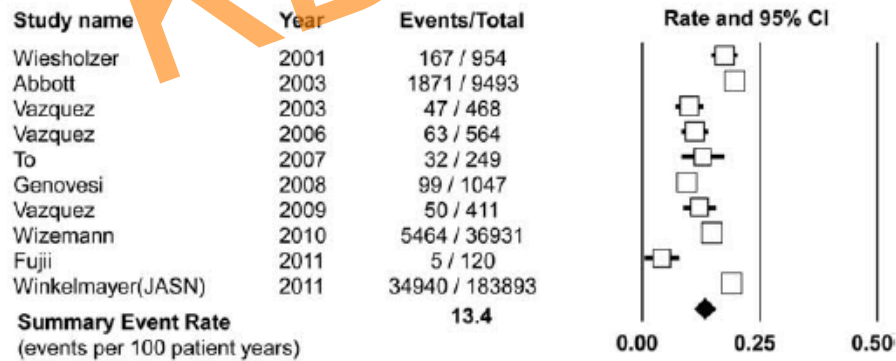
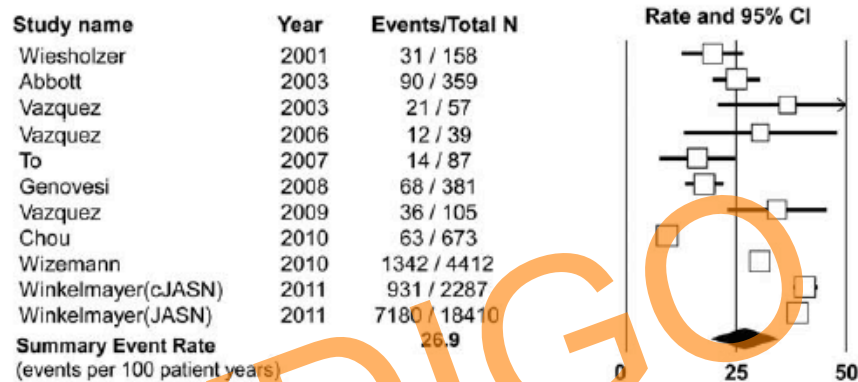
Goldstein BA, et al. *Circulation* 2012;126:2293



Reconciling Trends in Atrial Fibrillation Prevalence vs. Incidence in ESRD

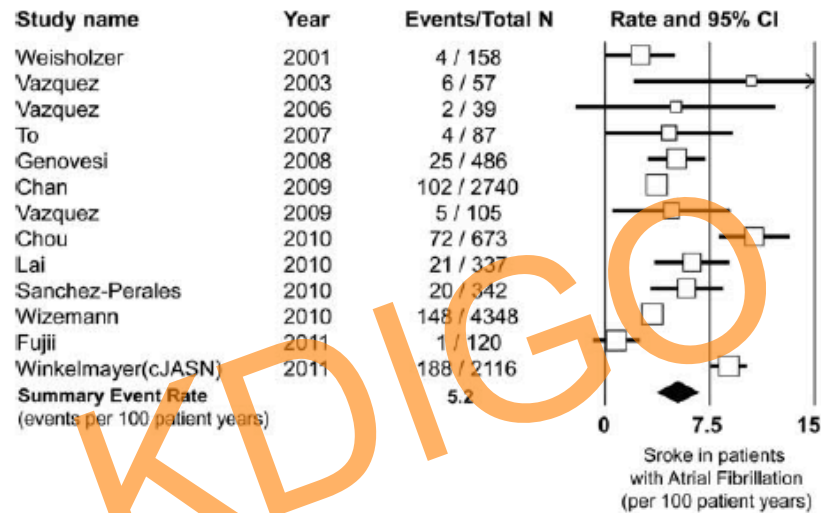
- Increasing prevalence is driven by:
 - Increasing % of patients with pre-existing AF
 - Moderate: 37% increase from 24% (1995) to 33% (2007)
 - Increasing incidence of AF
 - Modest: 15% increase between 1995 and 2007
 - Increasing survival after first AF
 - 20-25% reduced mortality from 1995 to 2008

Outcomes after AF in ESRD - Death



Zimmermann D, et al. *Nephrol Dial Transpl* 2012;27:3816

Outcomes after AF in ESRD - Stroke



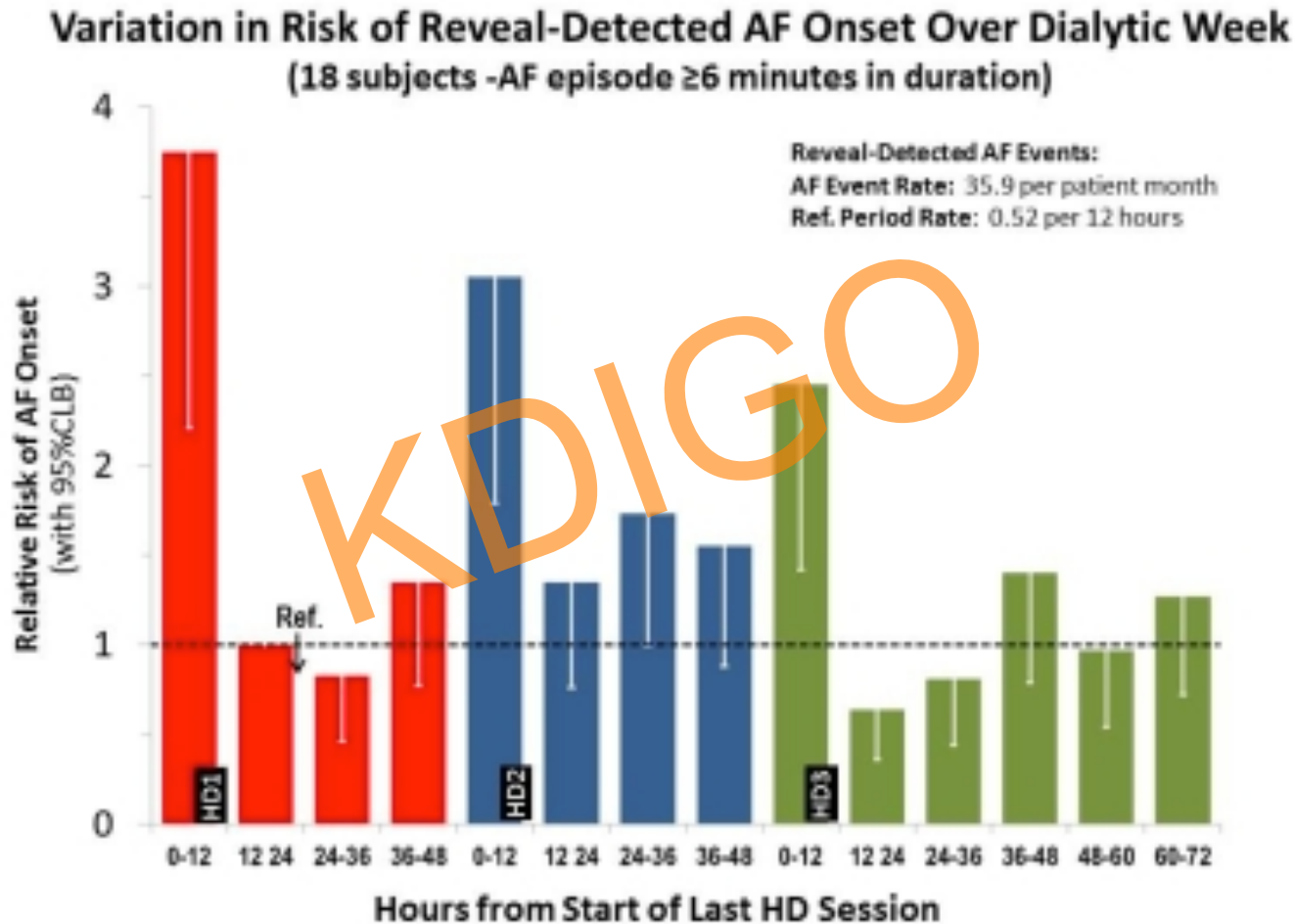
Zimmermann D, et al. *Nephrol Dial Transpl* 2012;27:3816

But What Do We Really Know?

...ask Dr. Charytan:

- 40% of HD patients in the MiD study had >1 AF episode of >6 min. duration
 - Charytan DM, et al. 2014 Kidney Week Abstract TH-OR144

But What Do We Really Know?



But What Do We Really Know?

...that's why we are having a KDIGO
Controversies Conference...

KDIGO



KDIGO Controversies Conference on CKD & Arrhythmias
October 27-30, 2016 | Berlin, Germany