KDIGO 2016 Controversies Conference

Chronic Kidney Disease and Arrhythmias

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This presentation is based on: Turakhia M. *et al.*, Submitted.

DISCLOSURES

- Salary supported from federal grants (NIDDK, NHLBI, NIAMS, AHRQ) and clinical activities.
- Advisory Boards/Consultancies (past 3 years: ACUMEN, Akebia, AMAG, Amgen, Astra-Zeneca, Bayer, Daichii Sankyo, Fibrogen, Relypsa, Vifor FMC Renal Pharma)
- Data Safety Monitoring Board (Medtronic, Zoll)
- Co-Editor, *AJKD*
- Associate Editor, *JAMA*
- Member, Public Policy Board, American Society of Nephrology
- Co-Chair, Kidney Disease: Improving Global Outcomes, KDIGO®

PART 1:

INTRODUCTION

CKD and Heart Rhythm Disorders

- Patients with CKD are predisposed to atrial fibrillation/flutter, supraventricular tachycardias, ventricular arrhythmias, and sudden cardiac death (SCD).
- Treatment options are complex and limited in CKD.
- Patients with CKD are historically underrepresented in clinical trials of treatment for heart rhythm disorders.
- Considerable gaps exist in the evidence base for treating patients with CKD and heart rhythm disorders.

KDIGO Controversies Conference

- CKD and Arrhythmias—October 27–30, 2016 in Berlin, Germany.
- International, multidisciplinary conference, divided into five breakout groups:
  - Epidemiology of Atrial Fibrillation and Stroke in Kidney Disease
  - Stroke Prevention in Atrial Fibrillation and CKD
  - Rate vs. Rhythm Control in Atrial Fibrillation in CKD
  - Risk Prediction and Prevention of SCD in CKD
  - Potassium Homeostasis and Handling in CKD and Dialysis

Conference Goals

- Assess the current state of knowledge related to the evaluation, management, and treatment of arrhythmias and CKD.
- Identify controversial topics and knowledge gaps.
- Propose a research agenda to resolve these issues.
- Determine whether there is sufficient evidence to develop a clinical practice guideline
- Help pave the way to harmonize cross-talk between the heart and the kidney communities.

PART 2:

ATRIAL FIBRILLATION (AF) AND STROKE IN CKD

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

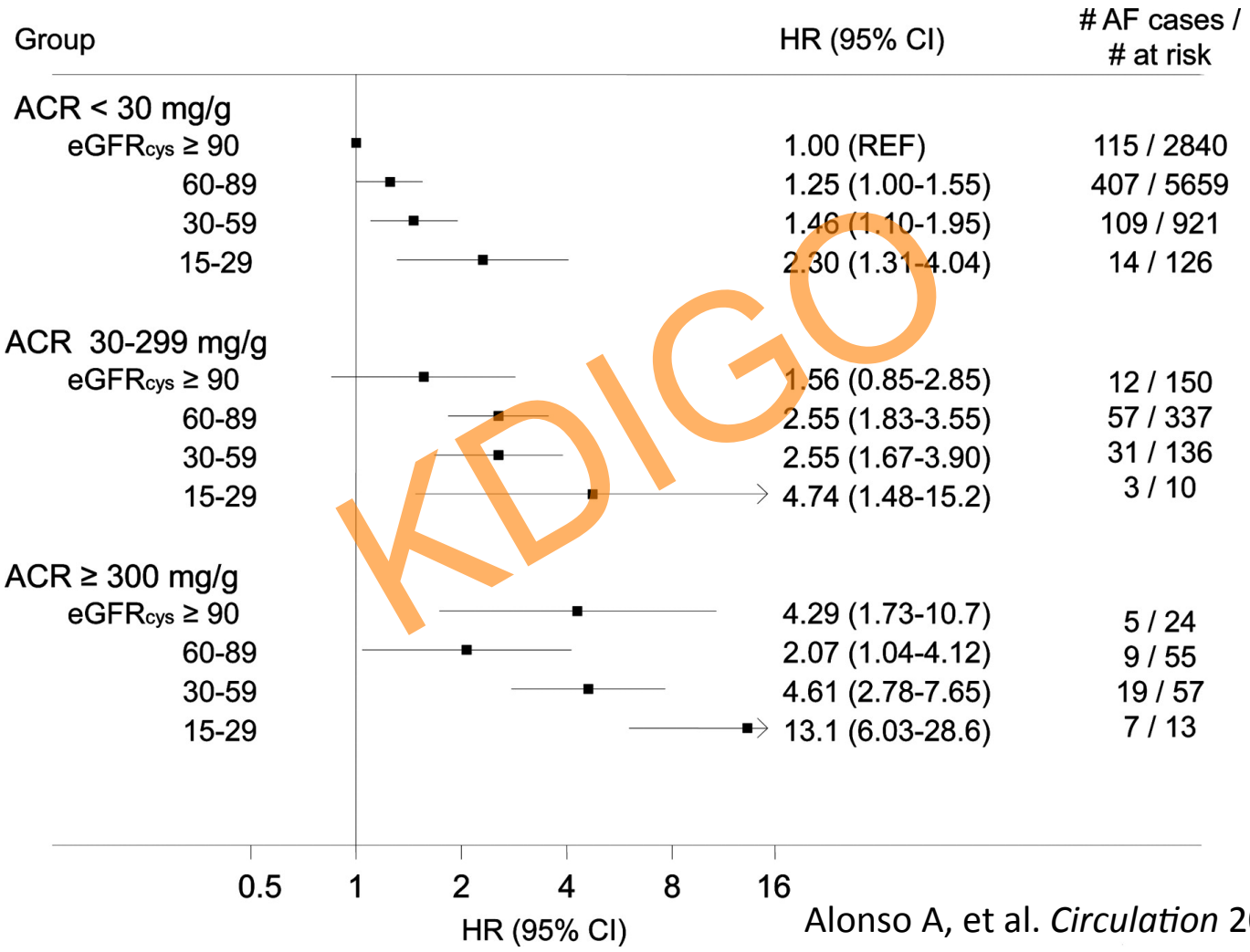
Healey JS, et al. *NEJM* 2012;366:120

Atrial Fibrillation and Other Outcomes

- While stroke is the most "recognizable" outcome of AF, analysis of the RE-LY trial showed that:
  - 7% of deaths from stroke, but
  - 22% were from sudden cardiac death
  - 15% from heart failure
  - 36% non-cardiovascular death

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

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.

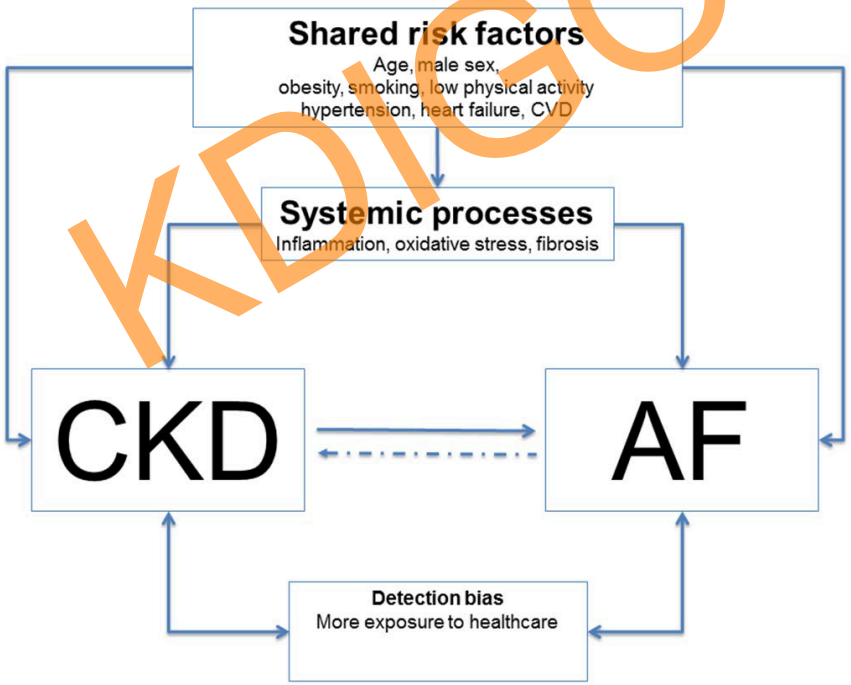
Bansal N, et al. *CJASN* 2016;11:1189

Evidence Supports Close and Bidirectional Link Between CKD and AF

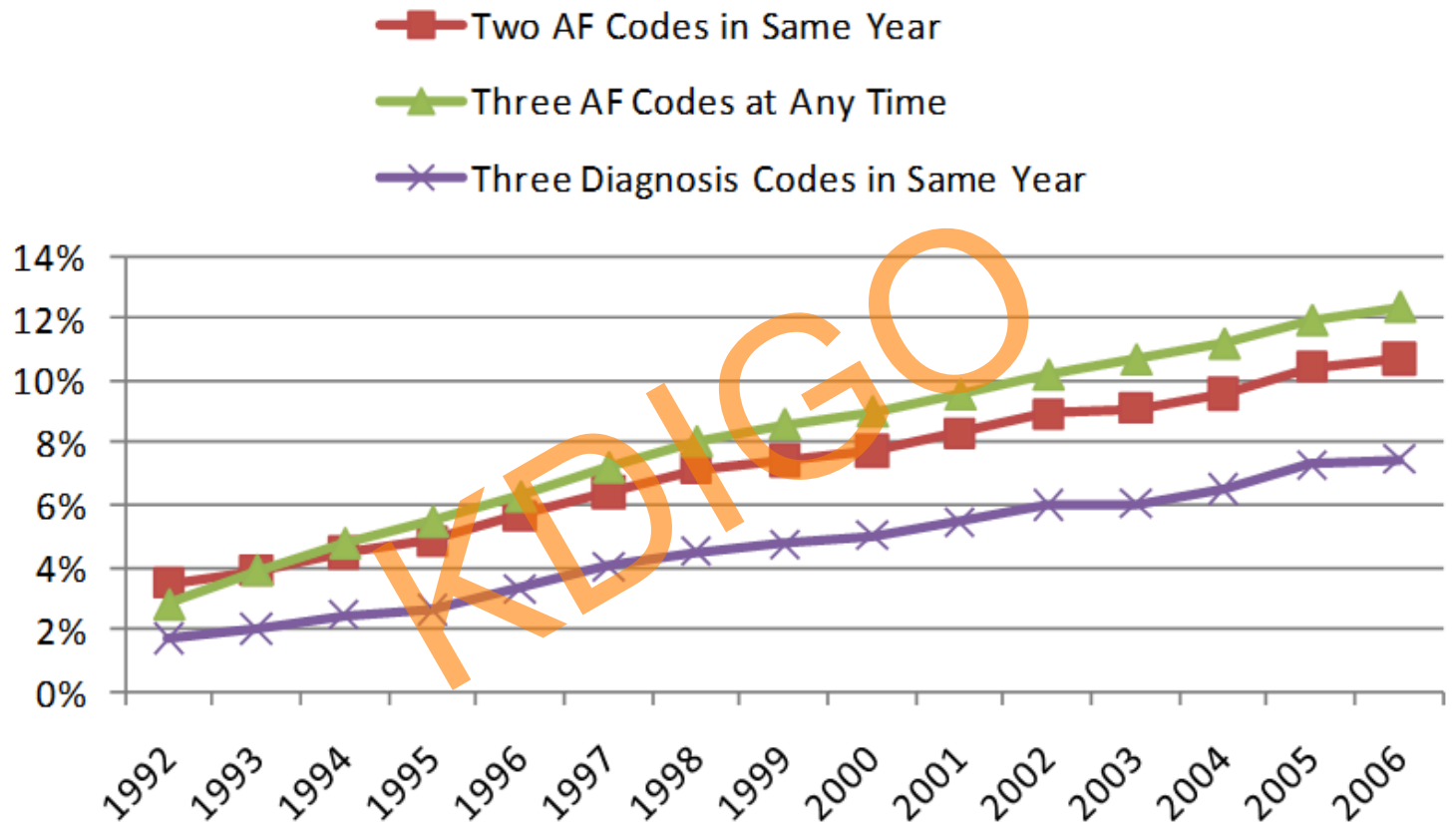
But Why?

EPIDEMIOLOGY

- Patients with CKD have an increased burden of AF compared to those without CKD.
- CKD and AF share many risk factors.

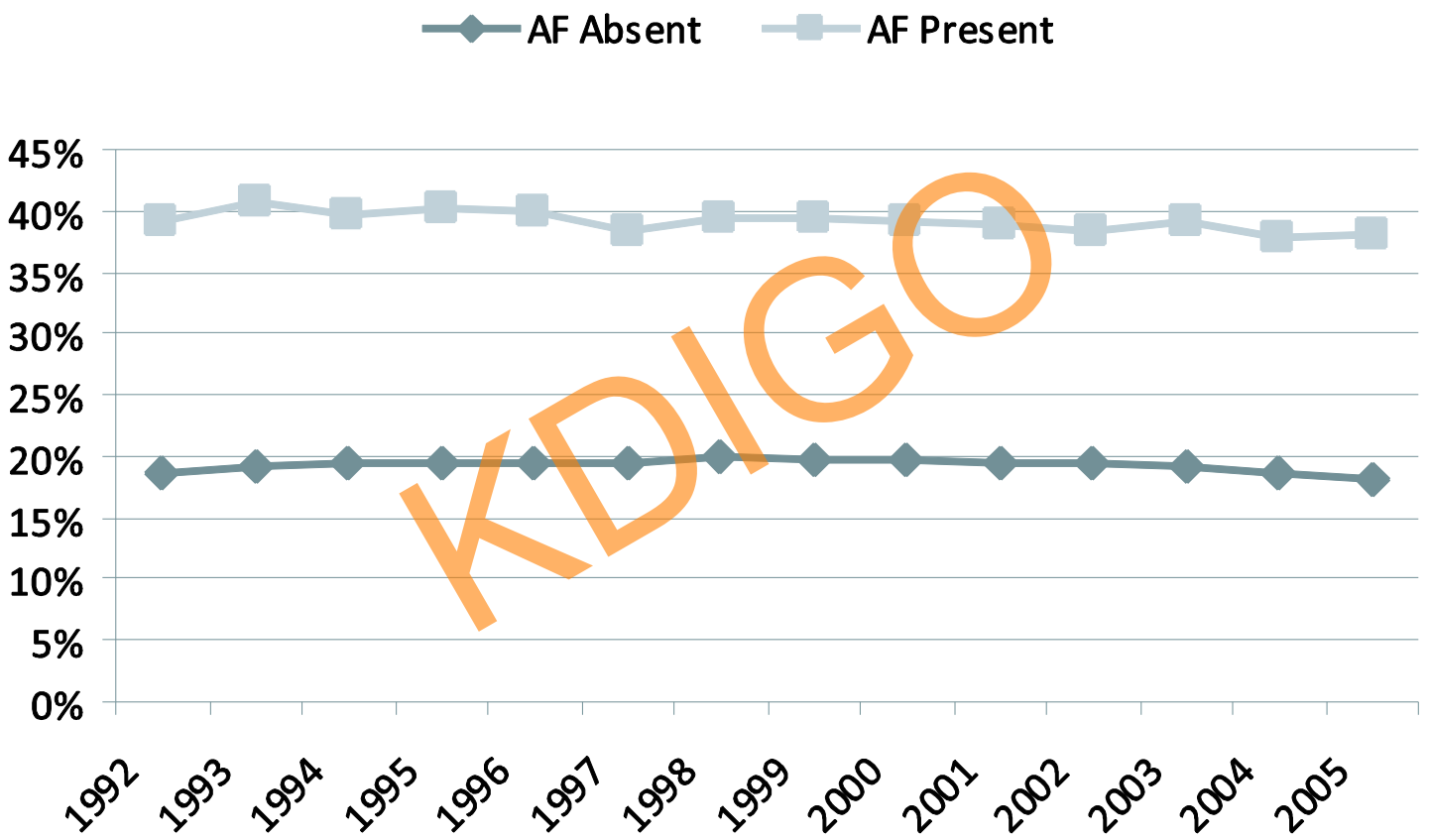


PREVALENCE OF AF IN CKD G5D



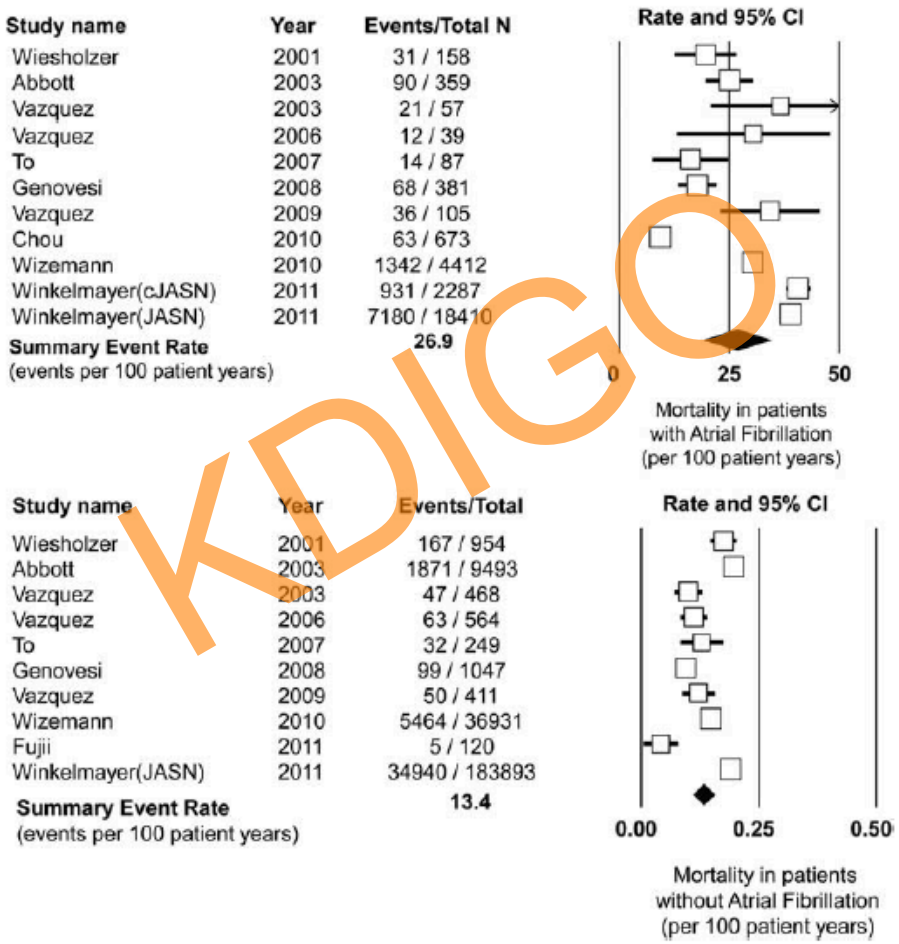
Winkelmayer WC, et al. *J Am Soc Nephrol* 2011;22:349

TRENDS IN MORTALITY IN G5D WITH AF



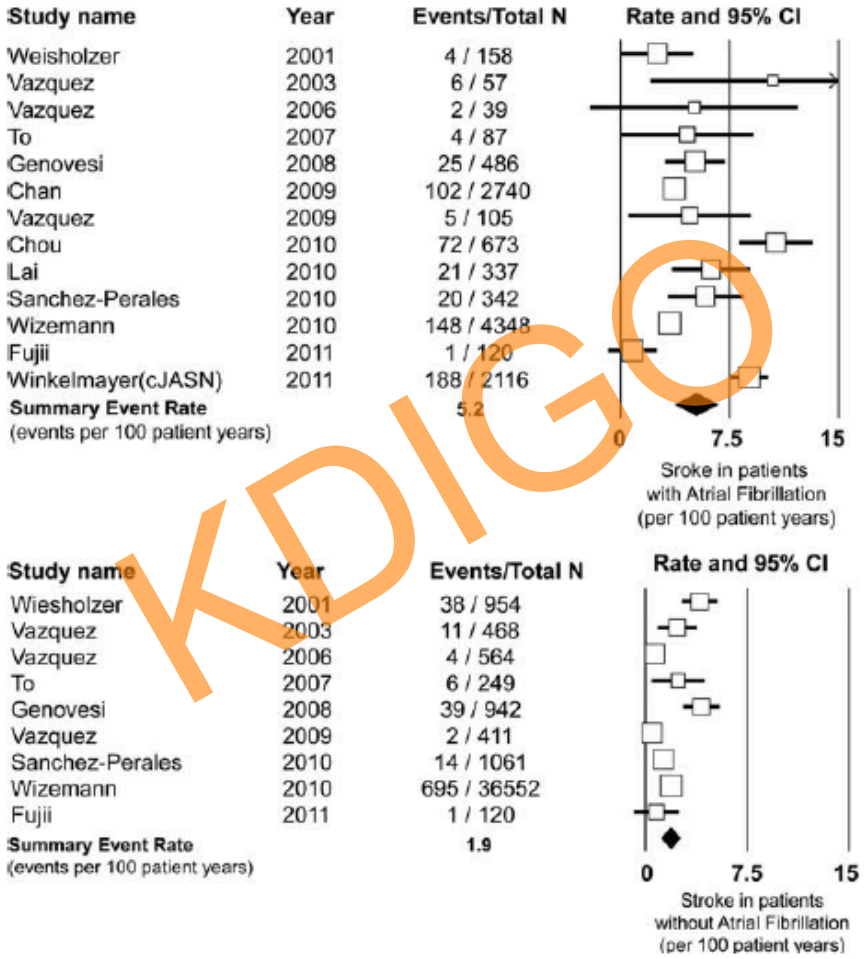
Winkelmayer WC, et al. *J Am Soc Nephrol* 2011;22:349

OUTCOMES IN G5D WITH AF - MORTALITY



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

OUTCOMES IN G5D WITH AF - STROKE



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

Consequences of AF in CKD

- Risk of stroke elevated in both dialysis and nondialysis patients with AF.
- The association between AF and CKD may be bidirectional;
  - CKD increases risk of incident AF;
  - AF may predict new-onset low GFR and proteinuria.
  - AF increases the risk of progression to end-stage kidney disease.
- AF is associated with increased mortality in CKD.

Stroke and Bleeding Risk Scores

- The predictive value of stroke risk scores ($CHADS_2$, $CHADS_2VASC$) in CKD G5D is similar to that in the general population.
- The choice of optimal stroke risk score remains controversial.
- The HAS-BLED, ORBIT, $HEMORR_2HAGES$ and ATRIA bleeding risk scores all include CKD measures.
- Although formal use of bleeding risk scores has not been recommended, the increased risk of bleeding with and without oral anticoagulants (OAC) in CKD is well described and should be considered in clinical decision making.

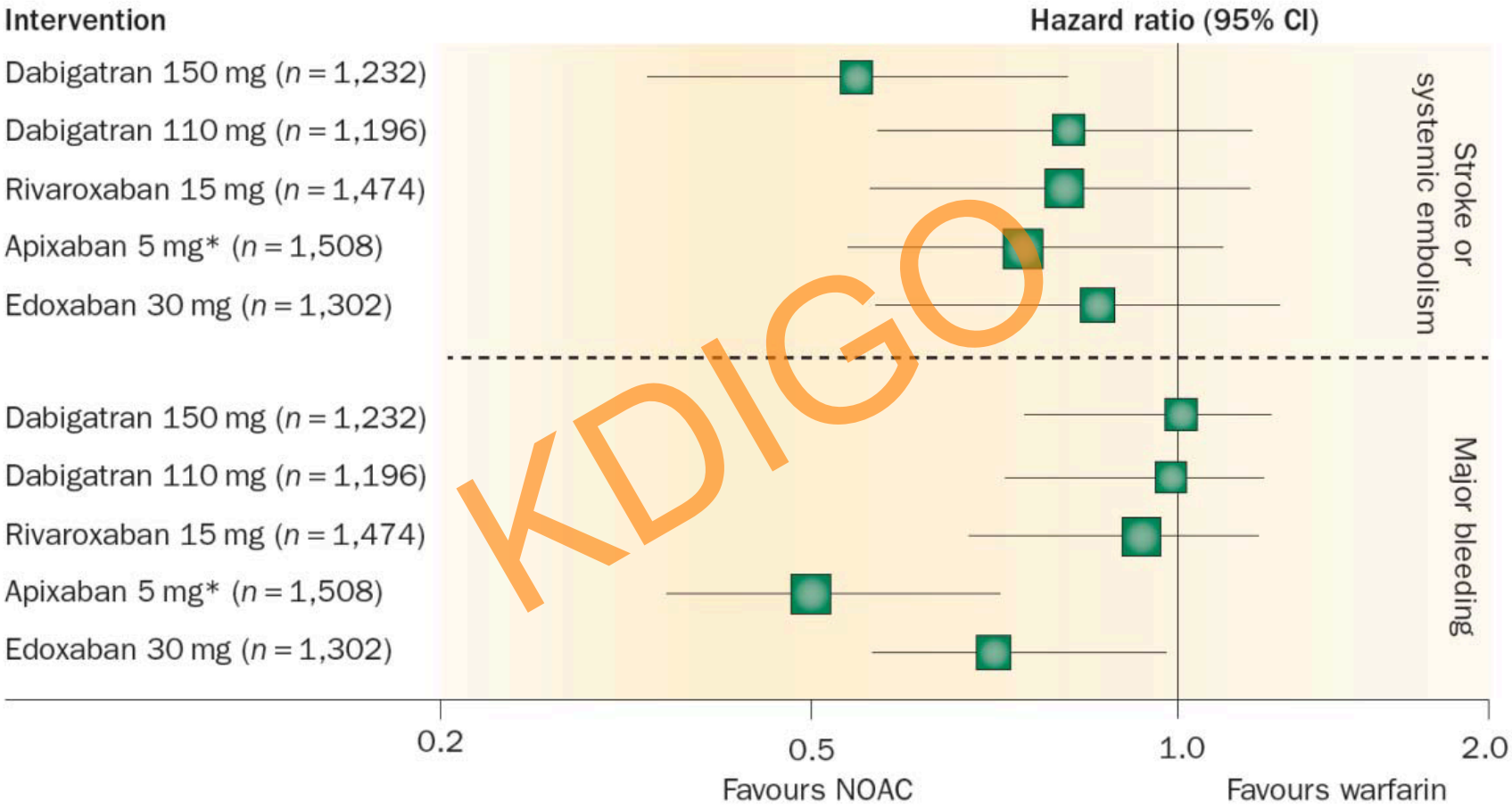
PART 3:

STROKE PREVENTION AND ORAL ANTICOAGULATION

Stroke in Patients with CKD and AF

- Multifactorial mechanisms leading to stroke that are poorly understood.
- AF may be:
  - a direct cause of cardioembolic stroke
  - a risk marker of ischemic stroke
  - in rare cases, a consequence of stroke
- Direct oral anticoagulants (DOAC) are preferred in comparison to warfarin for prevention of stroke and systemic embolism in patients with eCrCl 30–50 ml/min.

DOAC vs. Warfarin



Adapted from Qamar A and Bhatt DL. *Nat Rev Nephrol* 2015; 11: 200-202.

DOACs in Patients with CKD G4–G5D

- Observational studies provide conflicting data on the safety and efficacy of DOACs in this population.
- Therapeutic range values (TTR) are more likely to be poor in CKD and can mediate the increased stroke and bleeding risk in CKD.
- Warfarin may lead to CKD via repeated subclinical glomerular hemorrhages or through accelerated tissue or vascular calcification.
- Low-dose apixaban (2.5 mg orally twice daily) in CKD G5/G5D may be considered, to reduce bleeding risk, until clinical safety data are available.

CKD Categories Lacking RCT Data on Anticoagulation Utility

eCrCl, ml/min[1]	Warfarin	Apixaban[2]	Dabigatran	Edoxaban	Rivaroxaban
15-30	Adjusted dose for INR 2-3 could be considered	2.5 mg PO BID could be considered	Unknown (75 mg PO BID)**[4]	30 mg daily[3] could be considered	15 mg daily could be considered
<15 not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO BID)[4]	Not recommended	Not recommended	Unknown (15 mg daily)[4]
<15 on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO BID)[4]	Not recommended	Not recommended	Unknown (15 mg daily)[4]

Pragmatic Considerations for CKD Patients Treated with DOACs

- Given the imprecision in measures for estimating kidney function (eCrCl or eGFR), individualization of DOAC dosing based on either method is reasonable.
- Systemic measures focused on patient safety are needed to guide clinicians regarding the use of DOACs.
- Team-based, multidisciplinary participation in any decisions regarding DOAC therapy will be helpful.
- Ongoing, periodic monitoring of kidney function because decline over time may necessitate dose modification.
- For patients with CKD G5D on anticoagulants, strategies to reduce bleeding should be employed where feasible.

Antiplatelet Therapy for Stroke Prevention in CKD Patients with AF

- There is insufficient evidence to recommend single or dual antiplatelet therapy for prevention of stroke/ thromboembolism in AF among patients with CKD G4–G5D.
- These patients should not receive concomitant antiplatelet therapy while taking anticoagulants, unless specifically indicated (e.g., recent coronary stent).
- The duration of concomitant single or dual antiplatelet therapy in those receiving anticoagulants needs to be minimized and individualized based on clinical factors and type of stent.

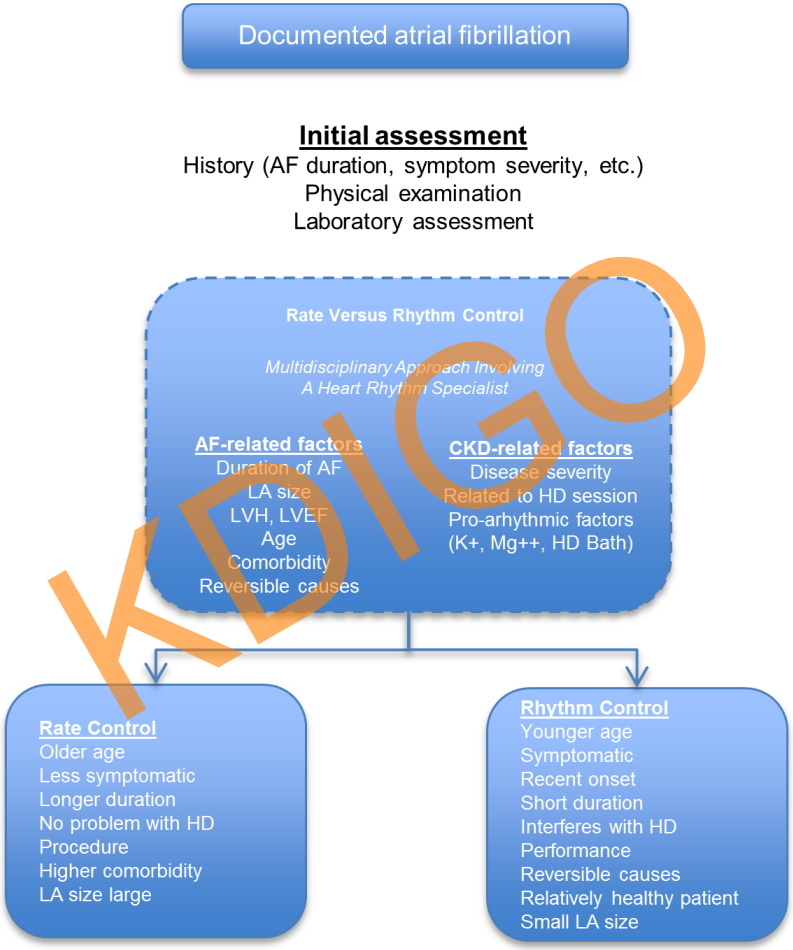
PART 4:

RATE VS. RHYTHM CONTROL

General Considerations

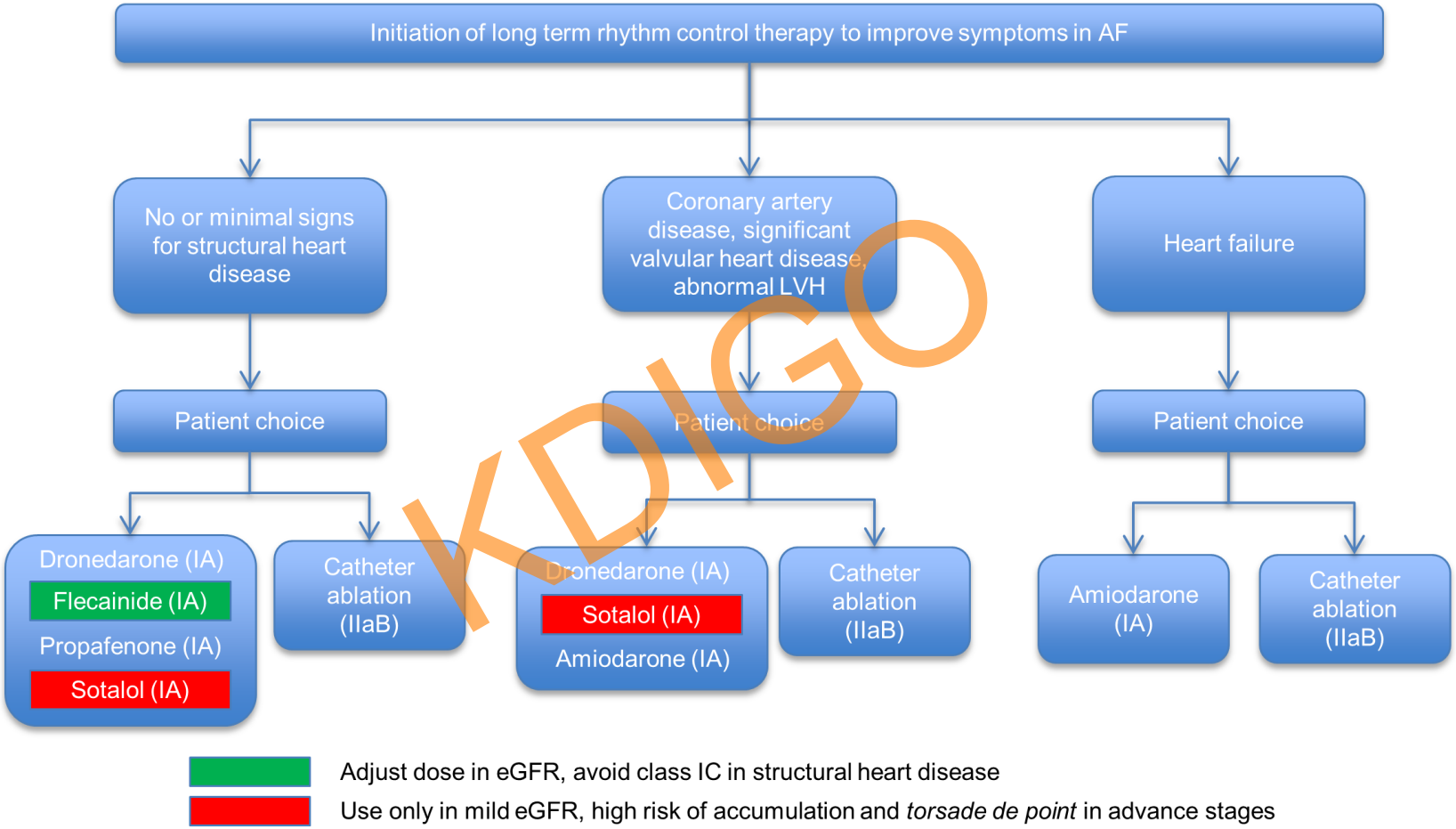
- Indications for a rhythm control strategy in CKD patients mirror those in the general population.
- Older RCTs have demonstrated that rhythm and rate-control strategies are equivalent in terms of their effects on risks of heart failure, stroke, and survival.
- Anticoagulation should also be continued based on stroke risk unless otherwise contraindicated.
- Hemodialysis patients with hemodynamic instability due to AF during dialysis sessions may benefit from rhythm control.
- Patients without clear indications for a rhythm control strategy should default to rate control.

RATE VS. RHYTHM CONTROL IN CKD



Adapted from Kirchhof P., et al. *Eur Heart J* 2016; 37: 2893–2962.

RHYTHM CONTROL IN CKD

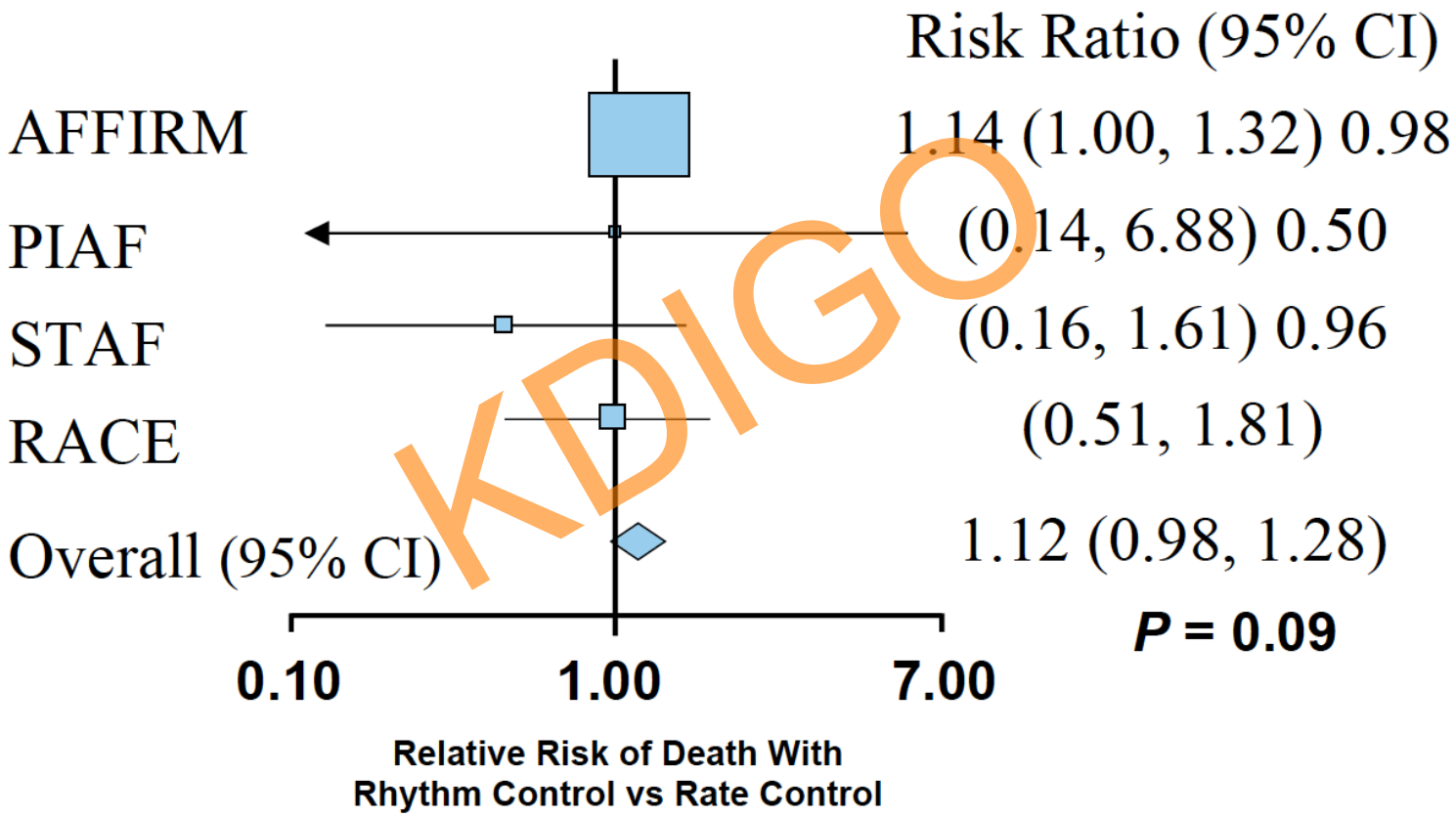


Adapted from Kirchhof P., et al. *Eur Heart J* 2016; 37: 2893–2962.

Other Considerations: Rate Control

- Alterations in symptomatology and a potentially increased propensity to develop tachycardia-mediated cardiomyopathy.
- Pharmacokinetics and dialyzability of rate-control agents.
- Atrioventricular nodal ablation and pacemaker implantation; however, transvenous devices have high rates of complications in hemodialysis patients.

RHYTHM VS. RATE CONTROL: MORTALITY



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

Other Considerations: Rhythm Control

- Direct current cardioversion (DCCV) is the most commonly used method of rhythm restoration in patients with persistent AF.
- DCCV alone is generally insufficient to maintain normal sinus rhythm.
- Long-term antiarrhythmic drugs or ablation are necessary for rhythm control.
  - The use of antiarrhythmic drugs is limited in patients with CKD because of issues with renal clearance and proarrhythmic risks in individuals with structural heart disease.
  - Catheter ablation is more effective than antiarrhythmic drugs alone for maintenance of sinus rhythm.

Other Considerations: Rhythm Control

- In general, sinus rhythm maintenance via ablation is associated with improved eGFR, while ablation failure is associated with eGFR decline.
- Radiofrequency ablation for rhythm control of atrial flutter should be considered as first-line therapy in CKD patients, given the high success and low complication rates
- Lifestyle modifications reduce the burden of AF in the general population, as does treatment for obstructive sleep apnea (OSA).

PART 5:

PREVENTION OF SUDDEN CARDIAC DEATH (SCD)

PART 6:

POTASSIUM HOMEOSTASIS AND HANDLING IN CKD AND DIALYSIS

CONCLUSIONS

- People with CKD have an increased burden from AF relative to those without CKD, and an elevated risk of stroke.
- For preventing stroke in patients with eCrCl 30-50 ml/min, DOACs are preferred to warfarin.
- For CKD G5D patients with AF, there are insufficient data to recommend warfarin routinely for preventing stroke.
- Evidence from RCTs indicates that rhythm and rate control strategies are equivalent in terms of their effects on risks of heart failure, stroke, and survival.

CONCLUSIONS

- There remain considerable knowledge gaps concerning management of AF in CKD. A multidisciplinary approach is vital for understanding the mechanisms of arrhythmias in CKD, as well as for evaluating therapies and improving clinical care.

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