A KDIGO Implementation Session

THE HEART IN CKD

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This presentation is based on:

Turakhia M. *et al.*, KDIGO Submitted.
McCullough P. *et al.*, KDIGO submitted
Wanner C. *et al*. Lancet 2016;388:276-84

The XI th Update in NEPHROLOGY

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Declaration of interests

Personal fees outside this presentation from

Amgen
Bayer
Boehringer Ingelheim
GlaxoSmithKline
Sanofi-Genzyme

Nearly four centuries ago the English physician Thomas Sydenham (1624–89) commented that

"a man is as old as his arteries".

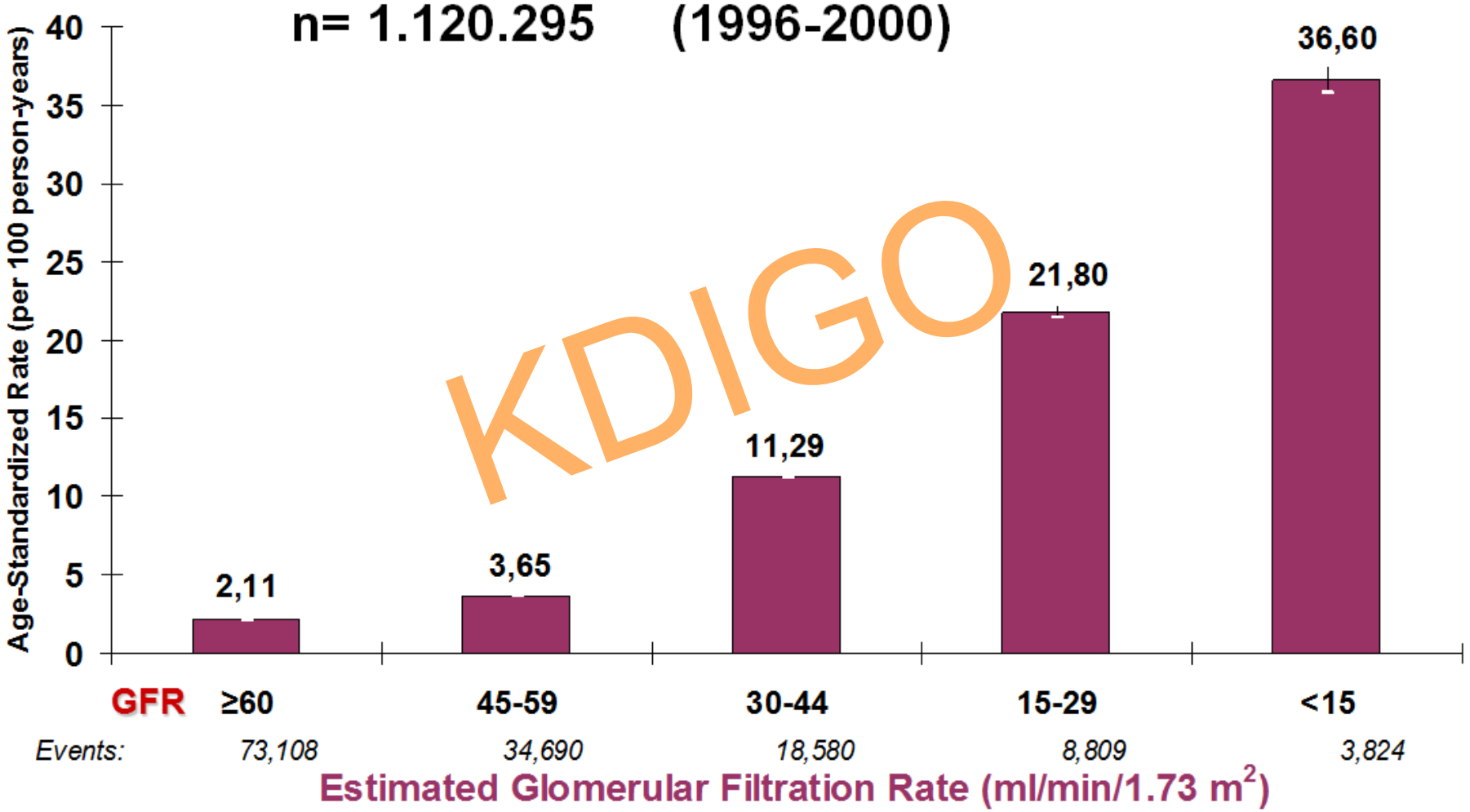
Of all the common diseases, CKD imposes the most dramatic divergence between biological age and chronological age

Declining renal function, independent of a patient's age, is the main driver of cardiovascular ageing

ControversyConferencies on :

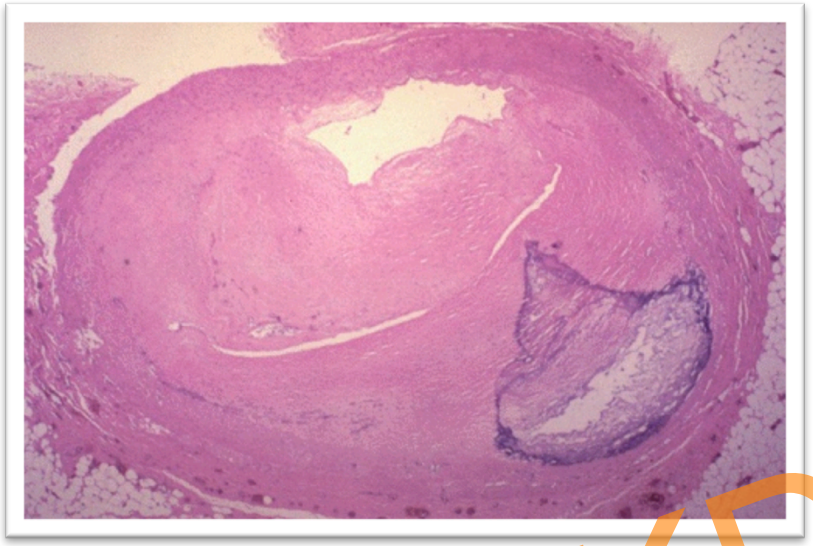
- CKD & Arrhythmias 2017
- Heart Failure in CKD 2017
- CA & Valvular Disease 2018
- Non-cardiac Vasc Dis 2019

Age-standardized rate of cardiovascular Events according to eGFR



Go AS et al. N Engl J Med 2004;351:1296-305

Atherosclerosis



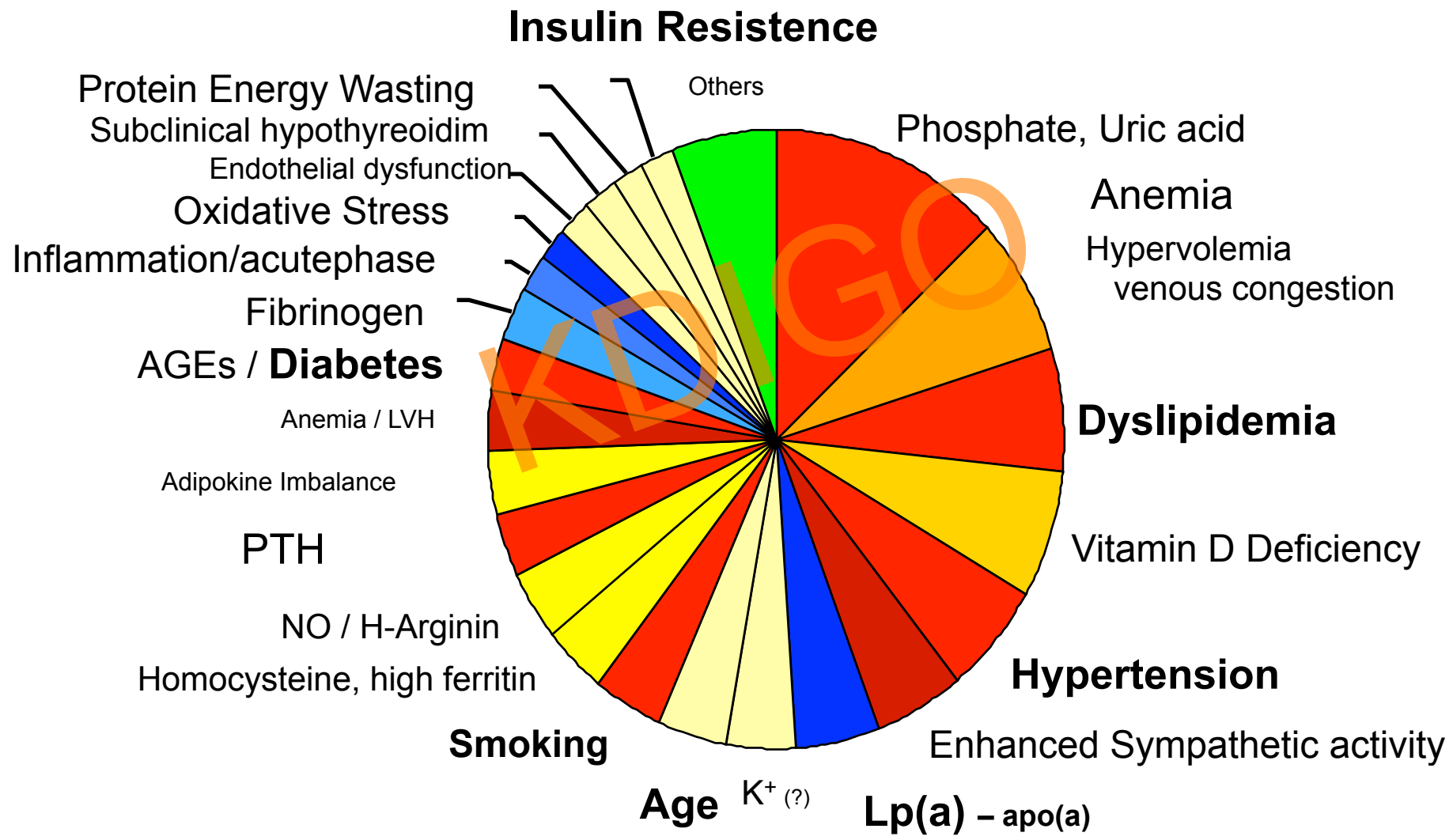
Schwartz, et al. *Nephrol Dial Transplant*. 2000.

Arteriosclerosis

Schwartz, et al. *Nephrol Dial Transplant*. 2000.

Associated with Traditional and Non-traditional cardiovascular Risk factors

Cardiovascular Risk Factors in CKD & Dialysis



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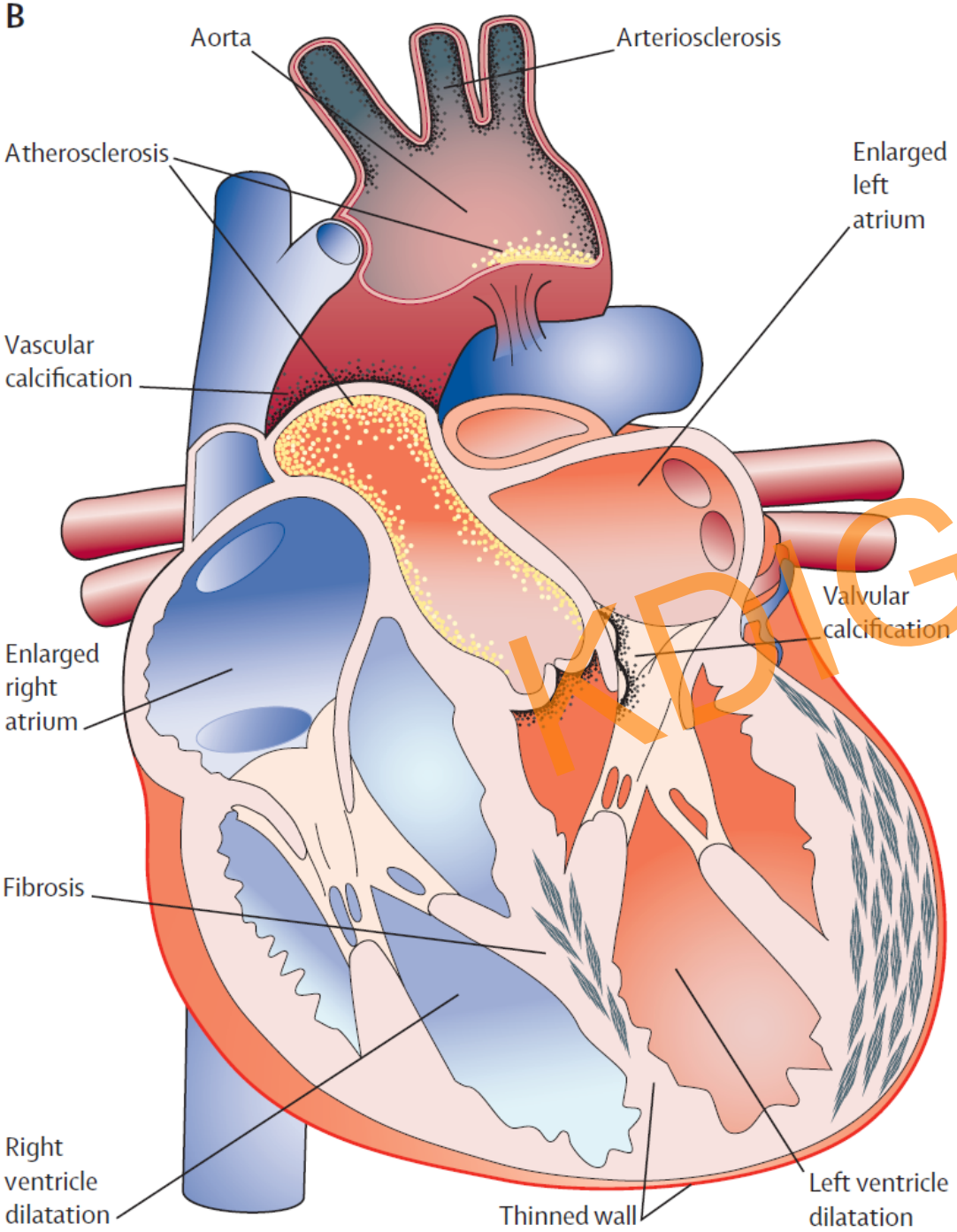
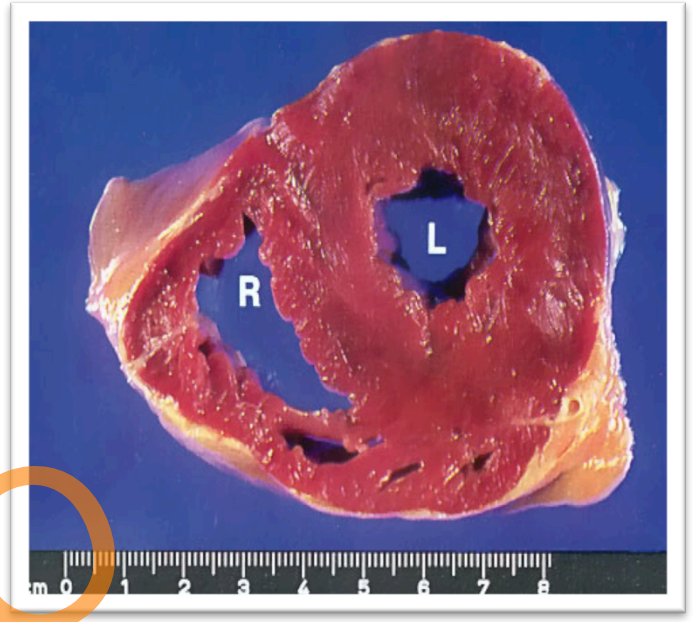
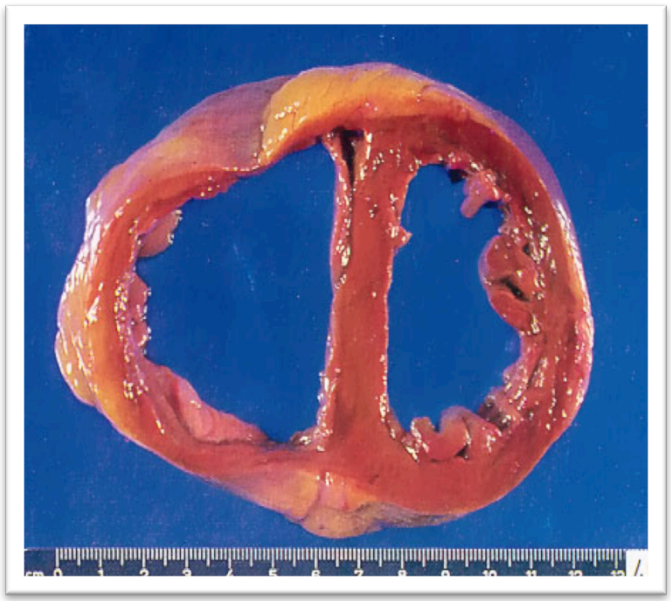
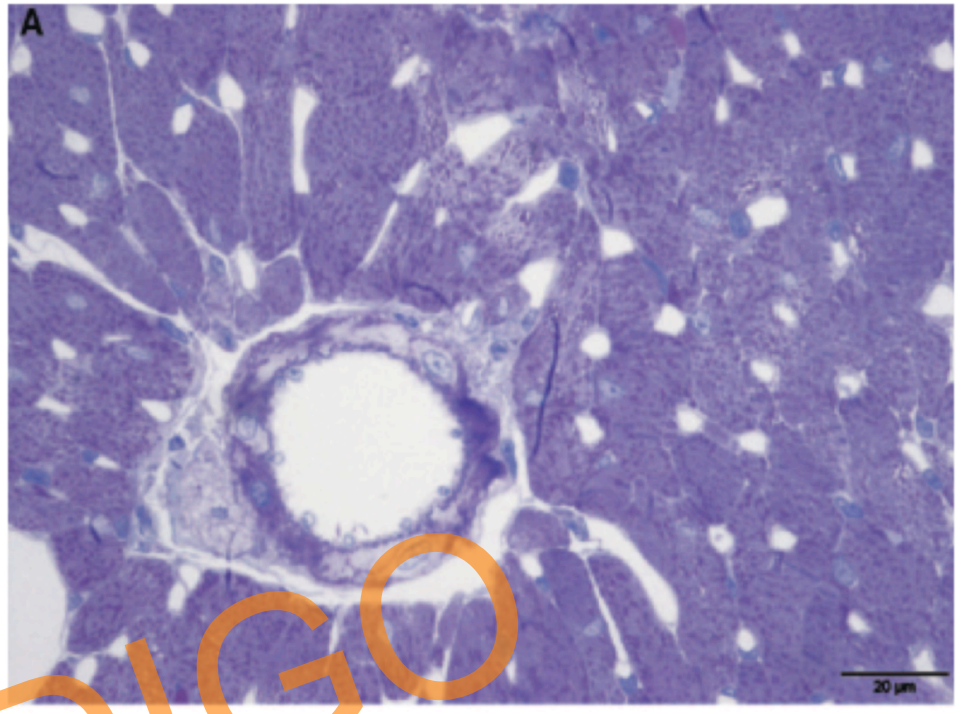

Aorta
Arteriosclerosis
Atherosclerosis
Enlarged left atrium
Vascular calcification
Valvular calcification
Enlarged right atrium
Fibrosis
Right ventricle dilatation
Thinned wall
Left ventricle dilatation

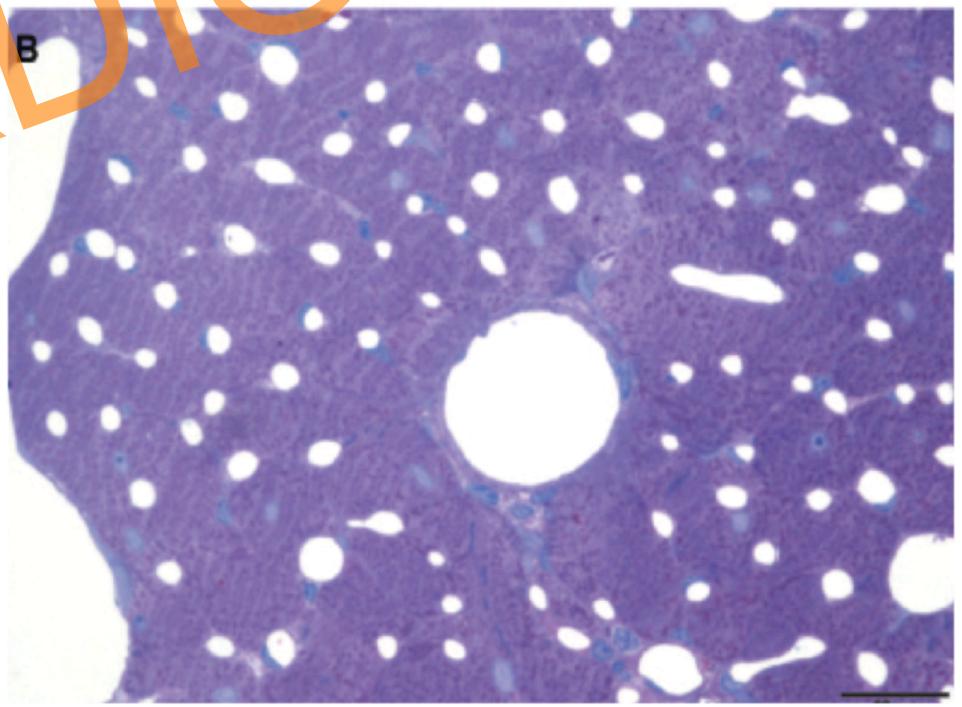

R
L



Myocardium after sub-total nephrectomy



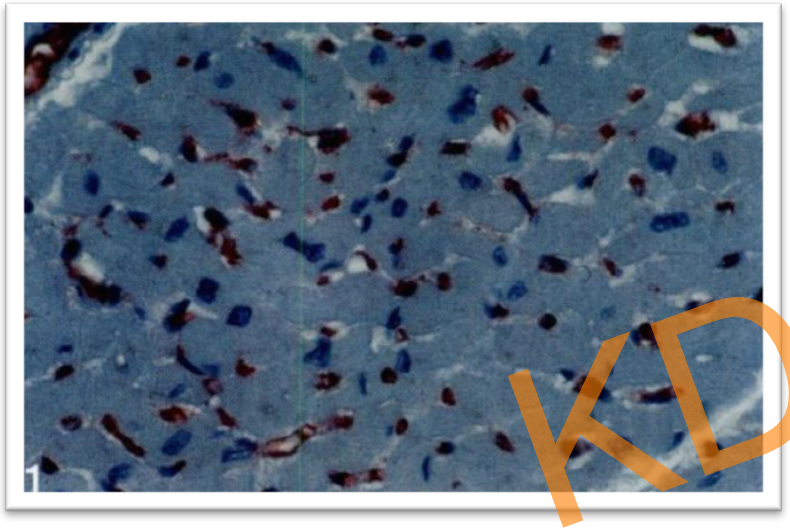
Myocardium: Control



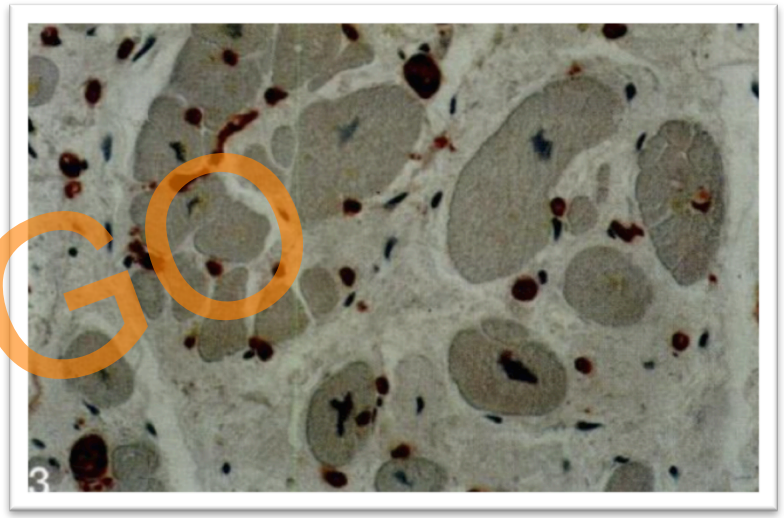
J Am Soc Nephrol 2006;17:2112-211

Morphology - human myocardium

Normal myocardium



HD patient myocardium



impaired angioadaptation

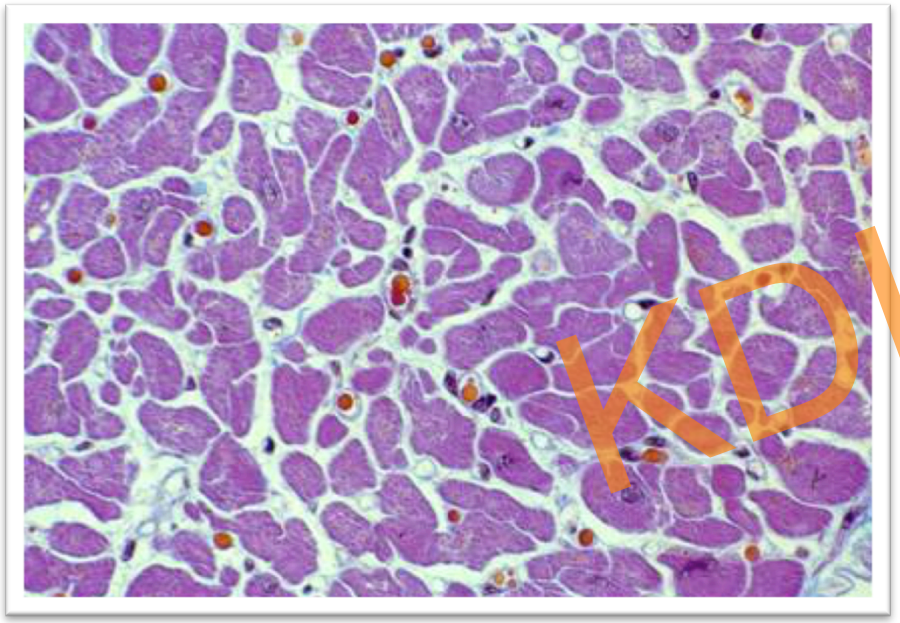
myocyte-capillary mismatch

myocardioal microarteriopathy

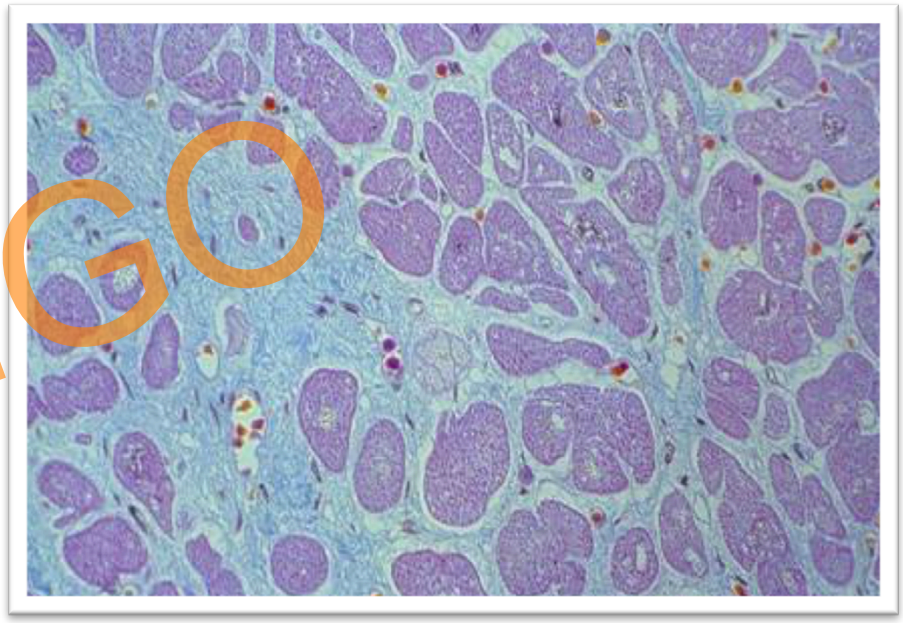
reduced capillary angiogenesis

Morphology - human myocardium

Normal myocardium



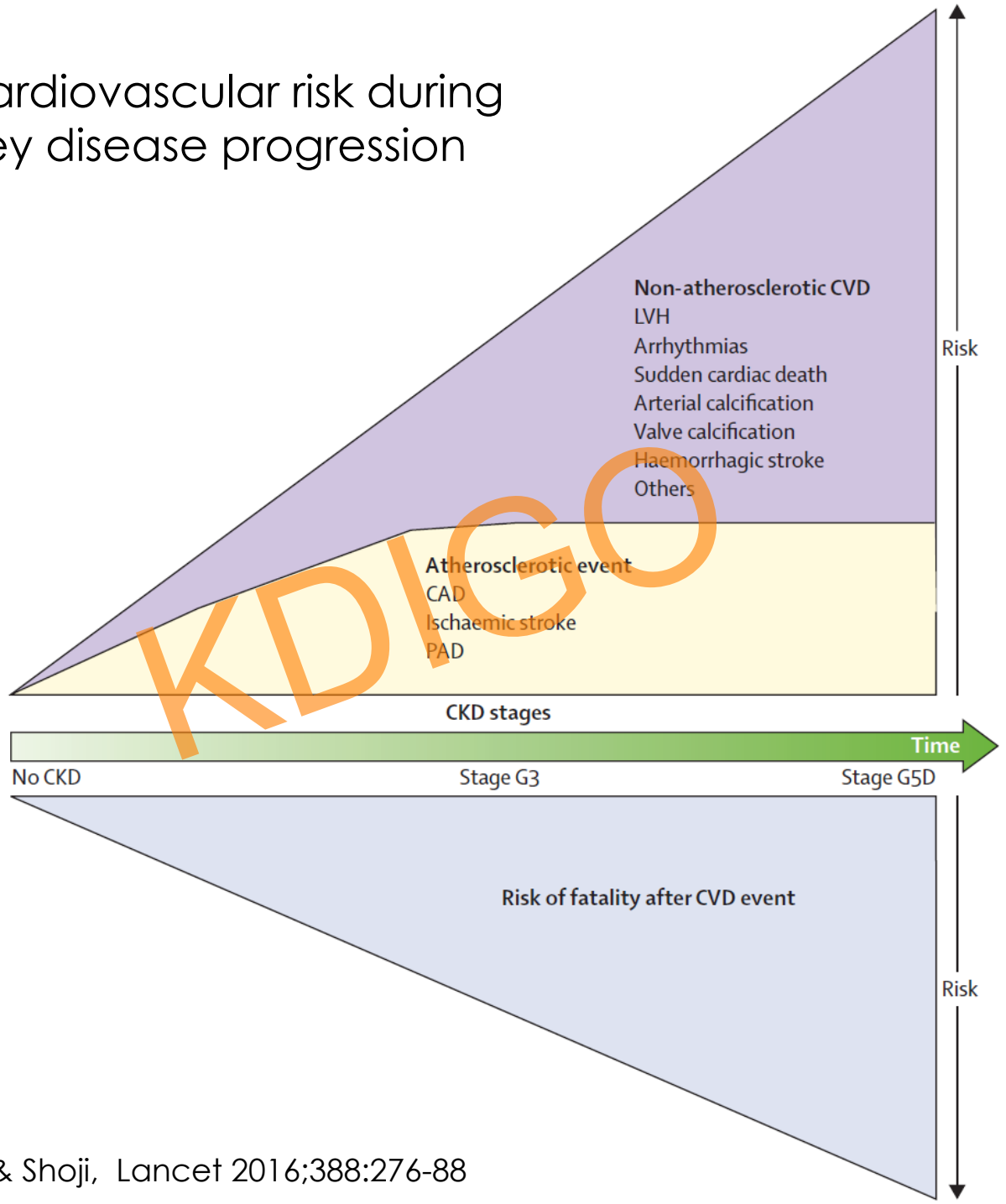
HD patient myocardium



Cardiomyocyte Dropout in Uraemia

Amann et al, Kidney Int 2003;63:1708

Change in cardiovascular risk during chronic kidney disease progression



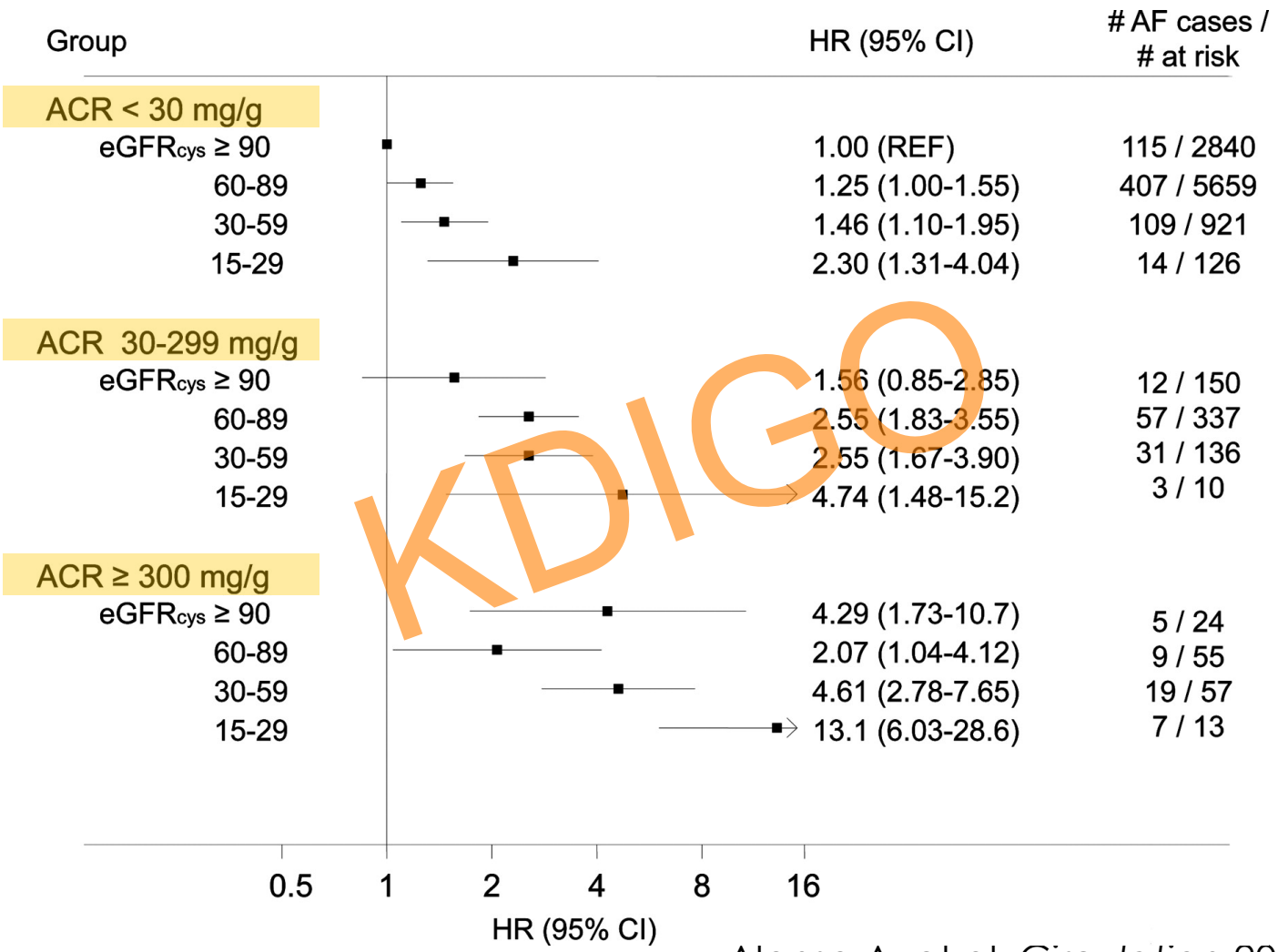
Wanner, Amman & Shoji, Lancet 2016;388:276-88

ControversyConferences on :

- **CKD & Arrhythmias** 2017
- **Heart Failure in CKD** 2017

- Coronary Artery & Valvular Disease 2018
- Non-cardiac Vascular Disease 2019

Kidney Disease and Atrial Fibrillation



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

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.

We can treat consequences such as

Heart Rhythm Disorders (atrial fibrillation/flutter, supraventricular tachycardias, ventricular arrhythmias)

….. to prevent

Stroke and sudden cardiac death

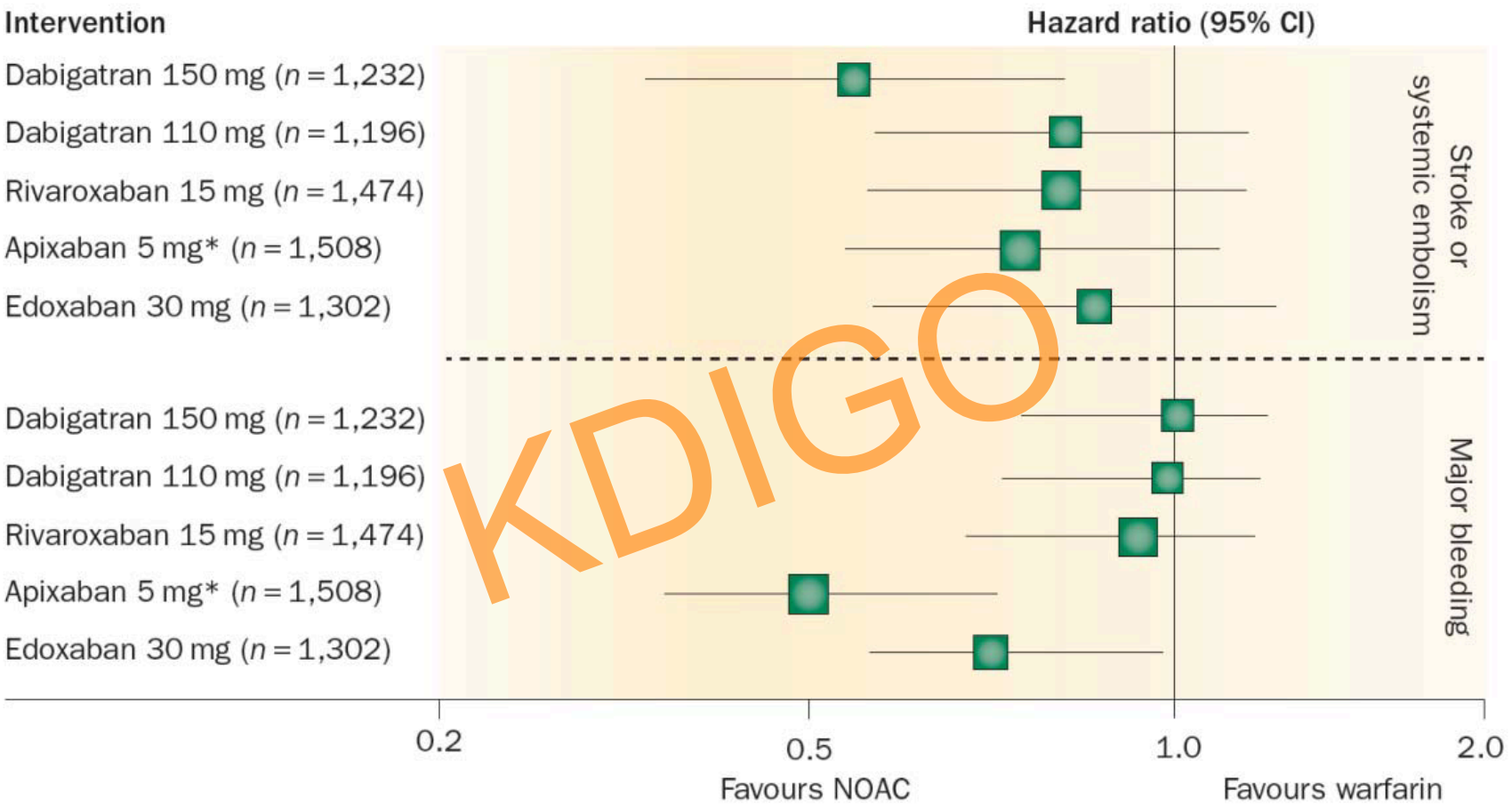
Stroke and Bleeding Risk Scores

- 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.

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 in CKD



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.

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.

General Considerations for rate vs rhythm control

- 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.

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.

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).

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.

Heart Failure

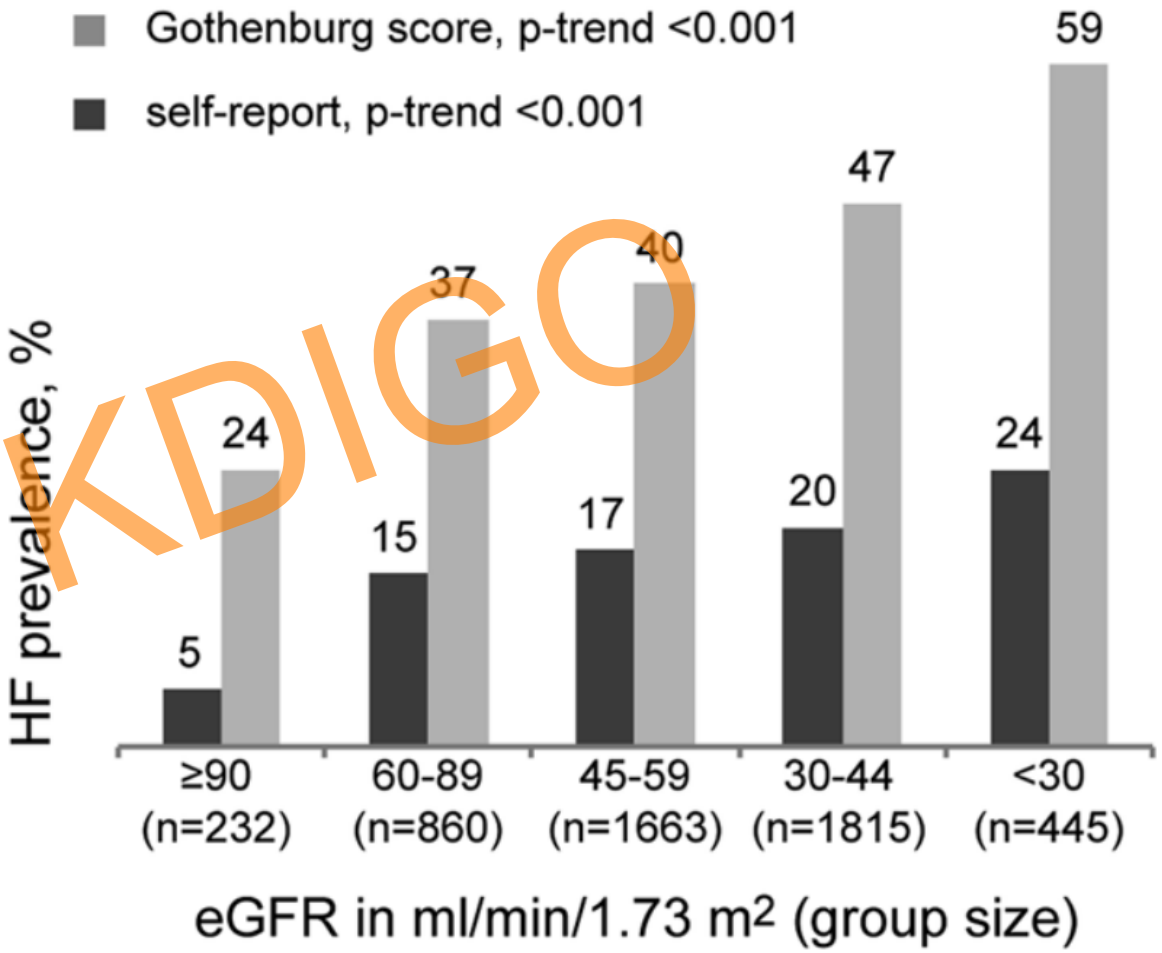
HFrEF and HFpEF – HFmREF

High-quality data are necessary for all aspects of HF (pathophysiology, epidemiology, diagnosis, prevention, and treatment) specific to the population of patients with advanced **non-dialysis CKD** as well as **dialysis** and **transplant patients**.

Prevalence of heart failure across eGFR categories in the GCKD cohort study

Volume overload
There is virtually no benign form of volume overload

Mechanisms fall into categories of
- ***hemodynamic***
- ***neurohormonal***
- ***cardiovascular***



Beck et al. PLoS ONE 2015

Table 1. Mechanisms of Heart Failure and Kidney Dysfunction

Heart failure
Systolic dysfunction
HFmrEF
Long axis
Diastolic dysfunction
Heterogeneous myocardial pathology
Hypertrophy and delayed relaxation
Myocardial fibrosis and restrictive diet
Diffuse endothelial/inflammatory conditions affecting kidney and heart
Sodium and water retention
Kidney dysfunction
Intrinsic kidney disease
Hypertension
Diabetes
Obesity
Hemodynamic effects
No overt evidence for low cardiac output
Inability to increase cardiac output following vasodilation
Chronotropic incompetence
"Fixed" left ventricular stroke volume
Elevated central venous pressure, which results from pulmonary hypertension and right ventricular dysfunction
Medications
ACE inhibitors
Angiotensin receptor blockers
Diuretics
Possibly acetylsalicylic acid
Systemic inflammation, endothelial dysfunction, and low NO bioavailability, which reduces renal blood flow and sodium excretion

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Systemic inflammation, endothelial dysfunction, and low NO bioavailability, which reduces renal blood flow and sodium excretion

Conclusions I

- A multidisciplinary approach is vital for understanding the mechanisms of HF in CKD as well as for evaluating therapies and improving clinical care.
- It is highly recommended that nephrologists and cardiologists partner to design and conduct clinical trials, and that trials be as simple and streamlined as possible.
- Because the definition of HF remains a point of debate, in clinical settings the judgement of individual practitioners matters

Conclusions II

- It is important to avoid medication toxicity, but the interpretation of changes in serum creatinine as representing true toxicity versus a dynamic change of function is one of the great challenges facing clinicians.
- In the future, it may be beneficial to include patient-centric outcomes in addition to clinical event outcomes when evaluating therapeutic strategies.

Science is global, but implementation is local

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