Cardiorenal Syndromes and their Relationship to Heart Failure

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Outline

- Heart and kidney disease trends
- Acute and chronic disease phenotypes
- Prognosis
- Intercurrent events
- Management
- Conclusions

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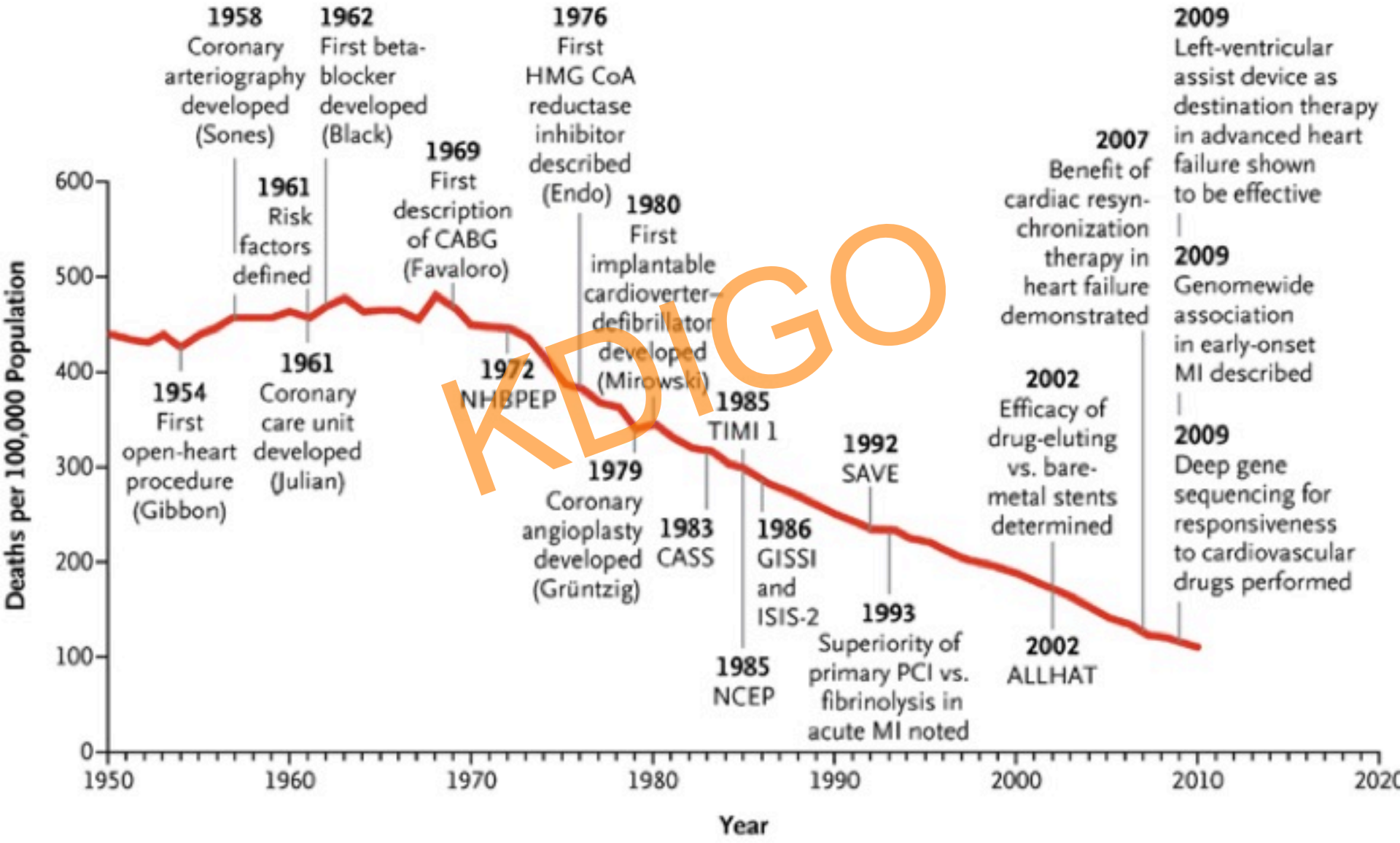
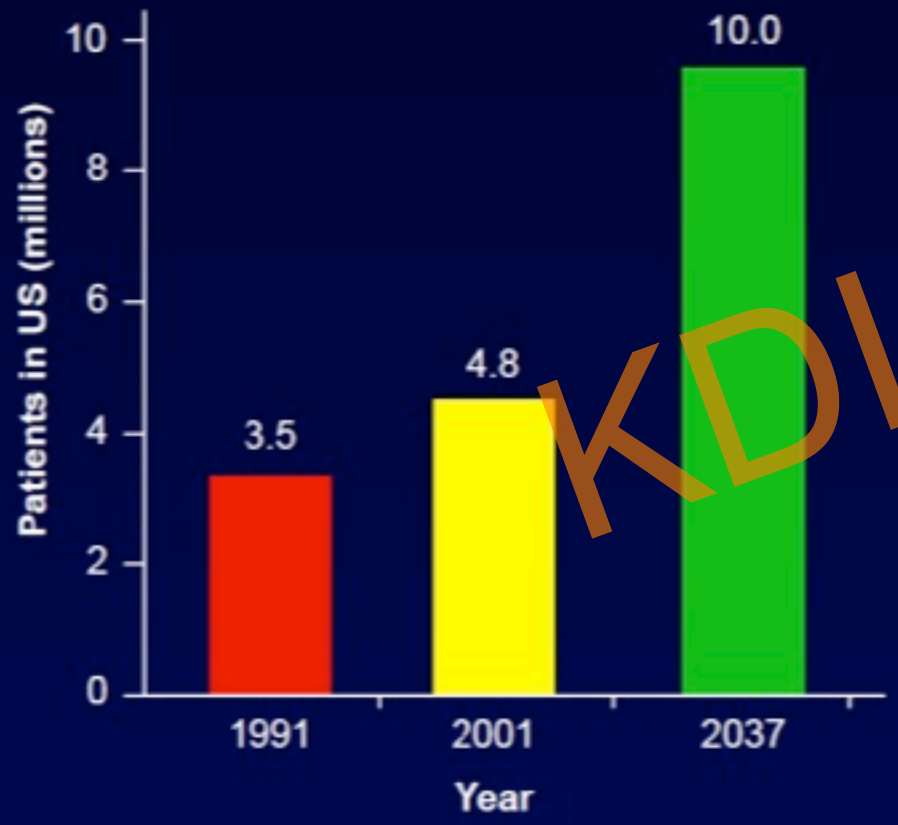
Deaths Due to Cardiovascular Disease



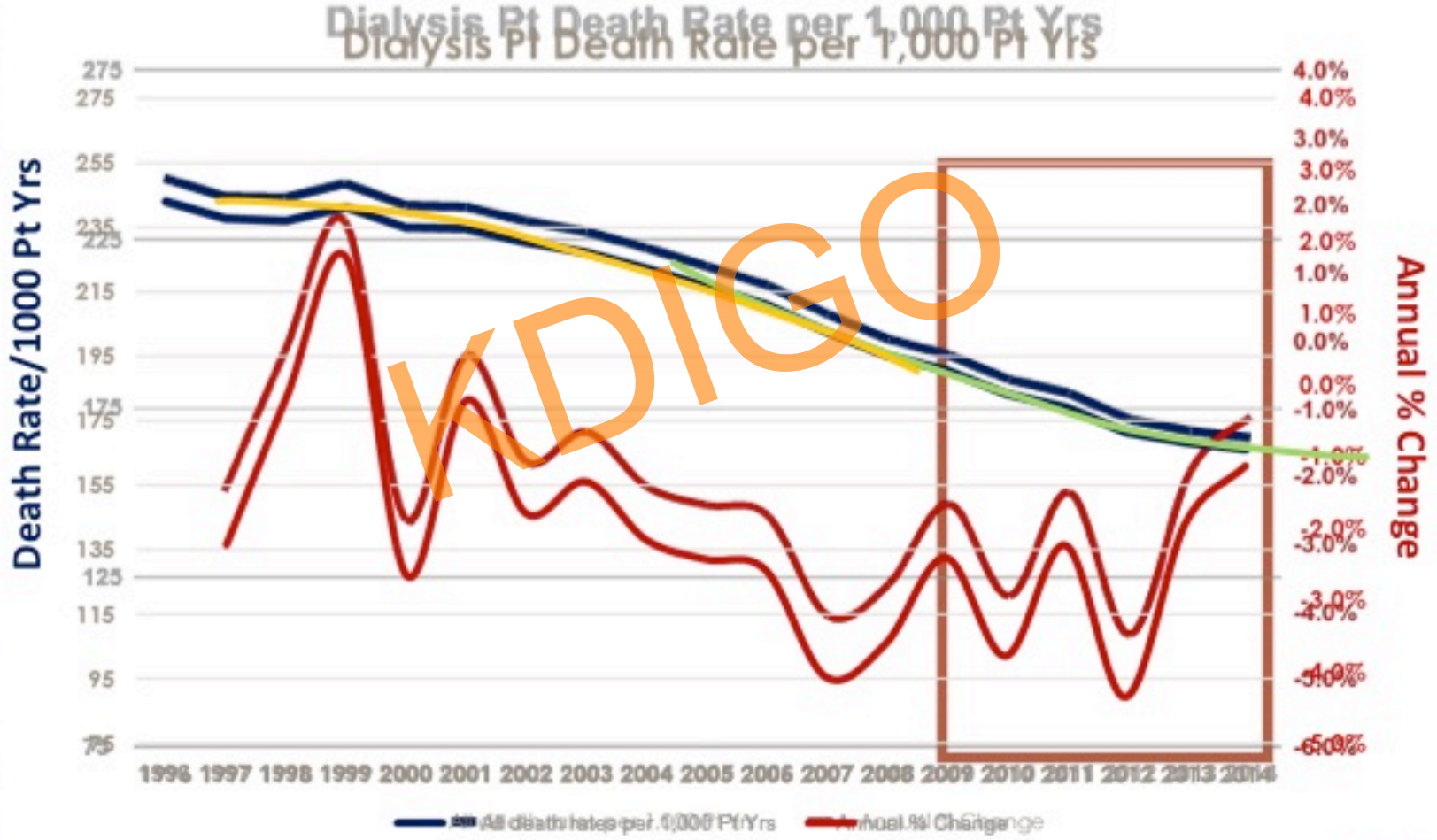
Epidemiology of Heart Failure in the United States



- 5.0 million patients[1]; estimated 10 million in 2037[2]
- Incidence: about 550,000 new cases each year[1]
- Prevalence is 2% in persons aged 40 to 59 years, progressively increasing to 10% for those aged 70 years and older[3]
- Sudden cardiac death is 6 to 9 times higher in the heart failure population[1]

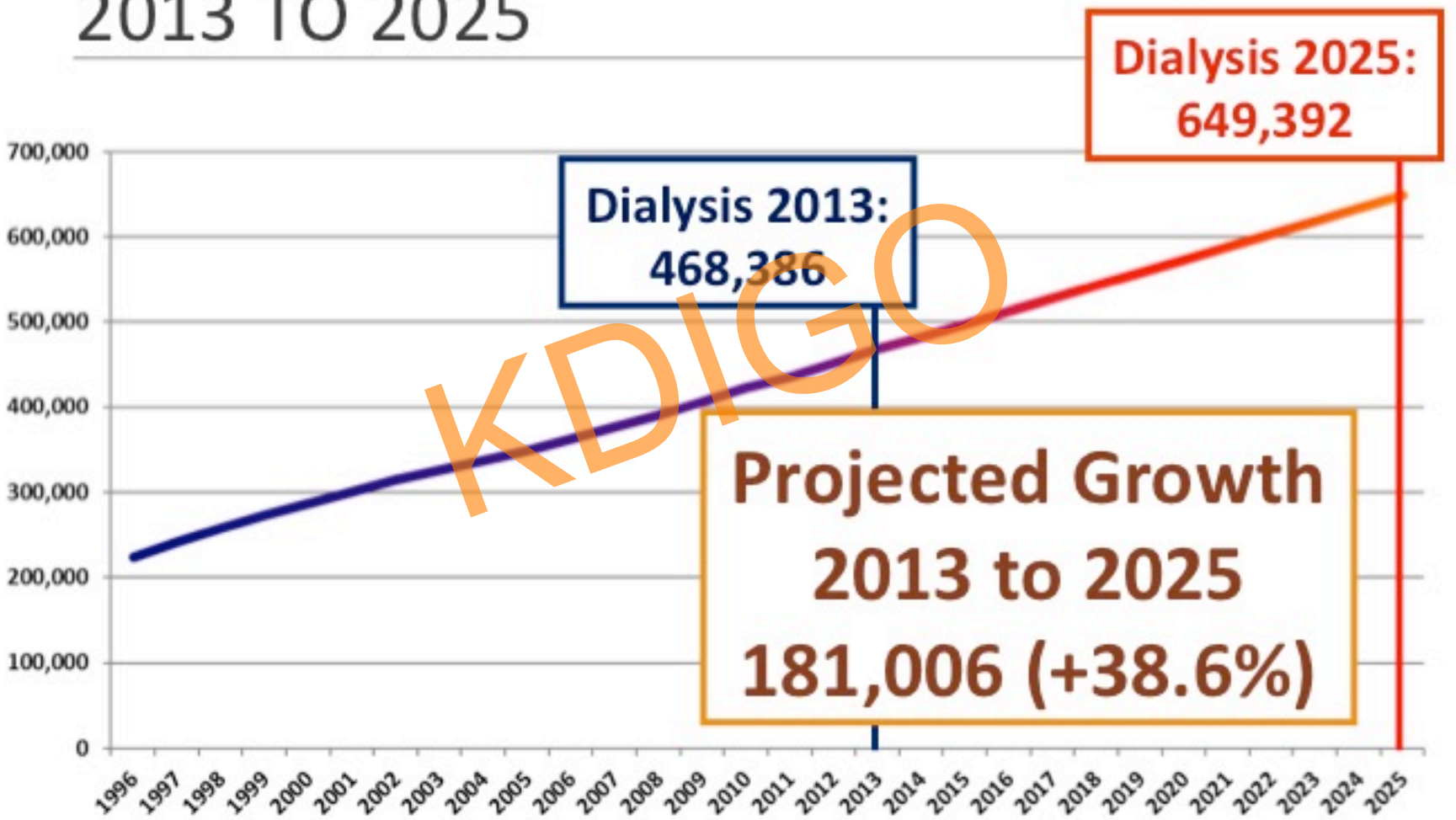
1. American Heart Association. *2004 Heart and Stroke Statistical Update*. 2001.
2. Croft JB et al. *J Am Geriatr Soc*. 1997;45:270-275.
3. National Heart, Lung, and Blood Institute. *Congestive Heart Failure Data Fact Sheet*. Available at: http://www.nhlbi.nih.gov/health/public/heart/other/CHF.htm.

Trends in Death rates per 1000 pt yrs & Annual % Change 1996 to 2014



Peer

Projected dialysis population growth
2013 TO 2025



Data source: USRDS 2015 ADR Reference table D.1; Projection simple auto regression with annual growth 2.5-3%

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Five Cardiorenal Syndromes

Cardiorenal Syndrome (CRS) General Definition:
A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (acutely decompensated congestive heart failure) leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (acute kidney ischaemia or tubular injury) causing acute cardiac disorder (new or decompensated heart failure)

CRS Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (diabetic nephropathy) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

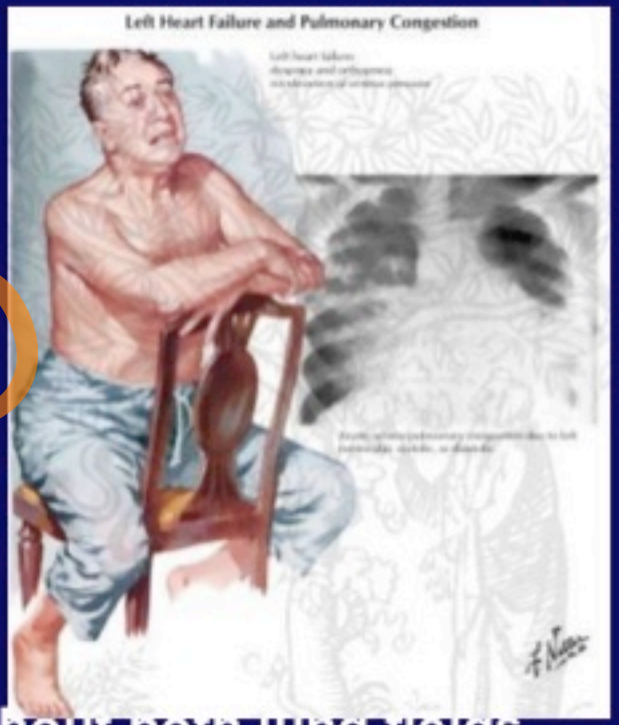
CRS Type V (Secondary Cardiorenal Syndrome)
Systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction

Ronco C, McCullough PA, Anker SD, et al; Acute Dialysis Quality Initiative (ADQI) consensus group. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2010;165:54-67.

ADQI

Common Signs and Symptoms of Heart and Kidney Failure

- Fatigue
- Effort intolerance/weakness/inanition
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Dyspnea at rest and during exertion
- Jugular vein distention
- Peripheral pitting edema
- Sinus tachycardia
- Basal rales or coarse bubbling rales throughout both lung fields
- Cardiomegaly
- S3 gallop sound
- Liver enlargement



Stevenson et al. *JAMA.* 1989;261:884-888.

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http://dx.doi.org/10.1016/j.jacc.2014.01.020

WORKGROUP REPORT

Proposal for a Functional Classification System of Heart Failure in Patients With End-Stage Renal Disease

Proceedings of the Acute Dialysis Quality Initiative (ADQI) XI Workgroup

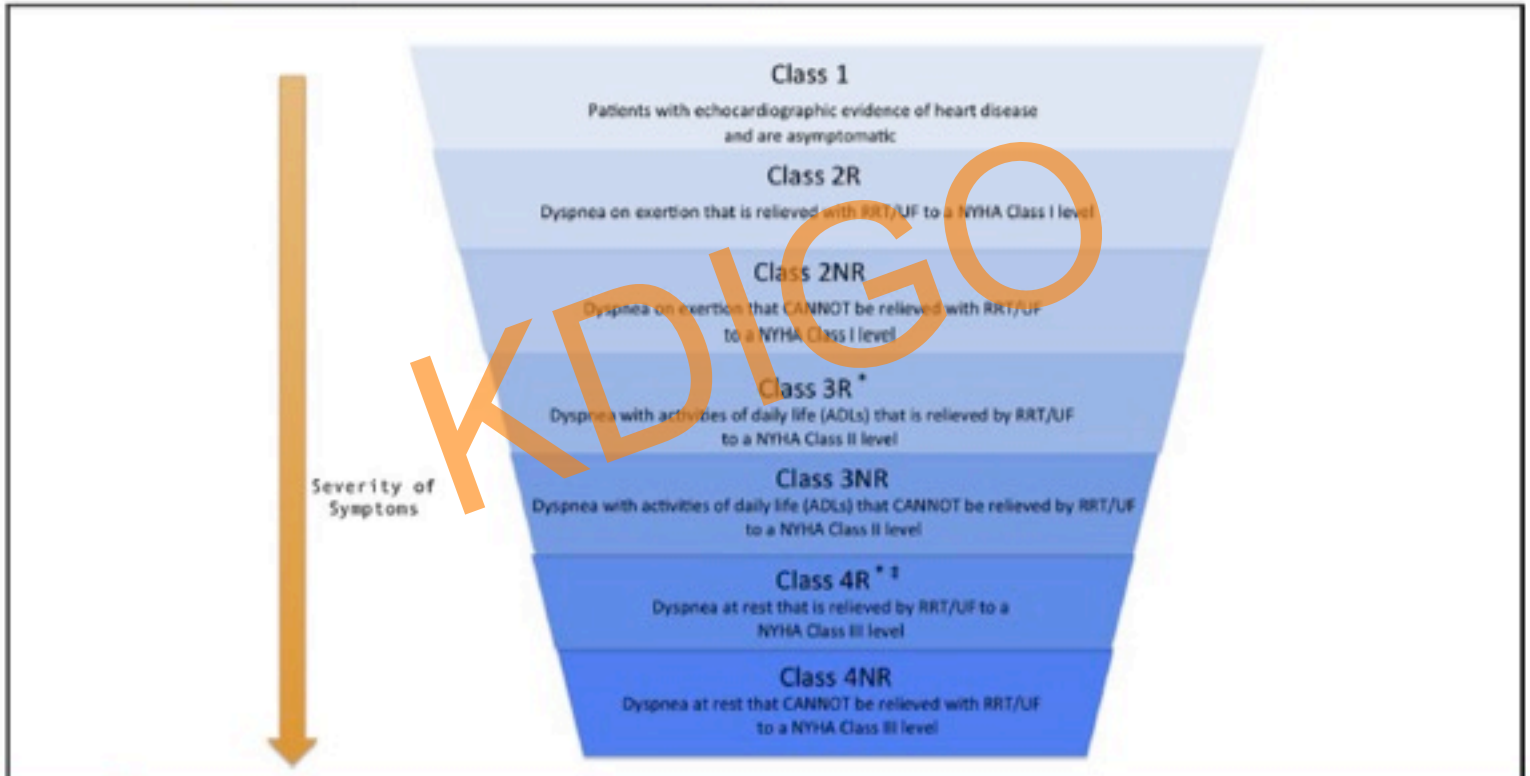
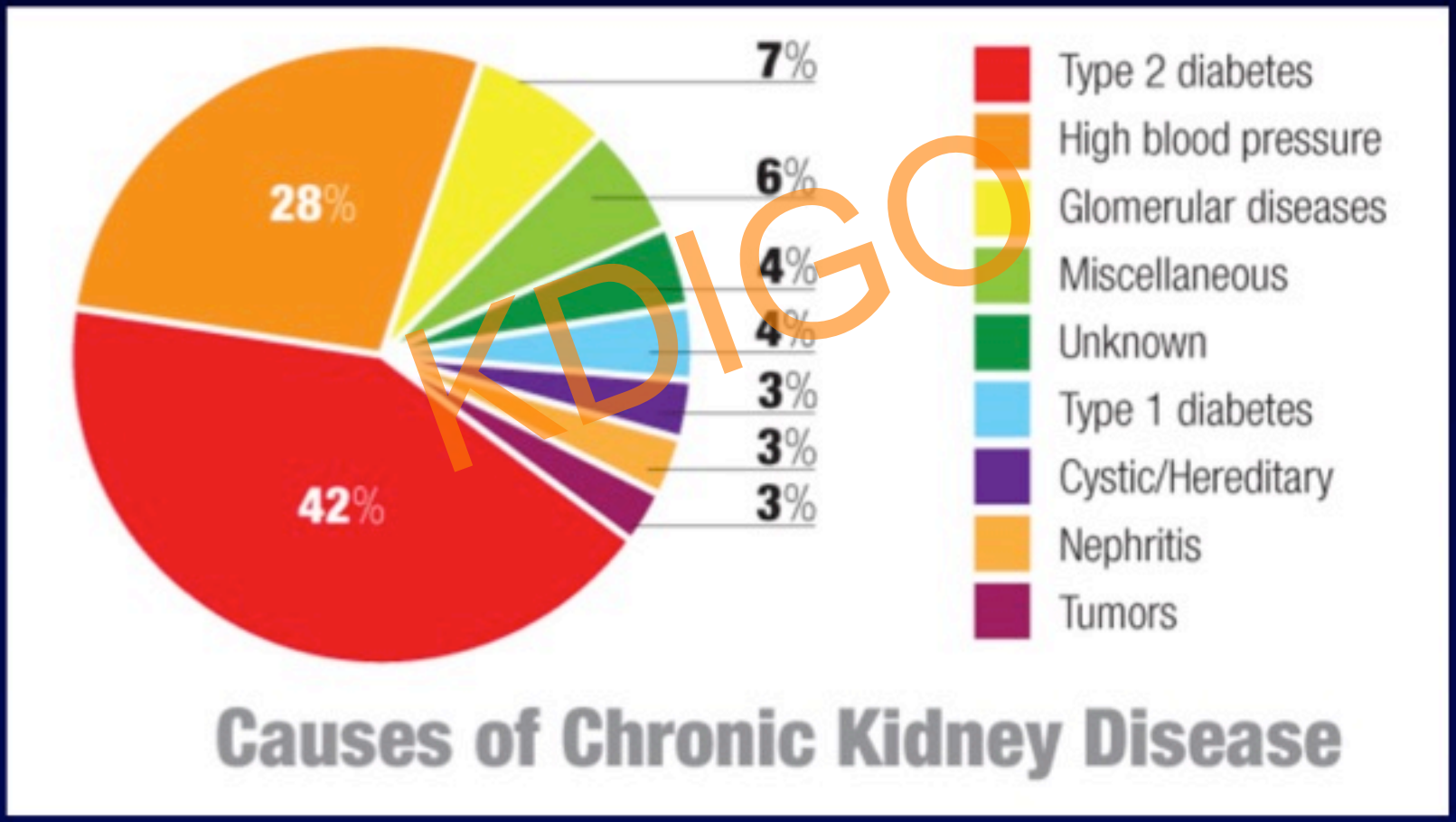


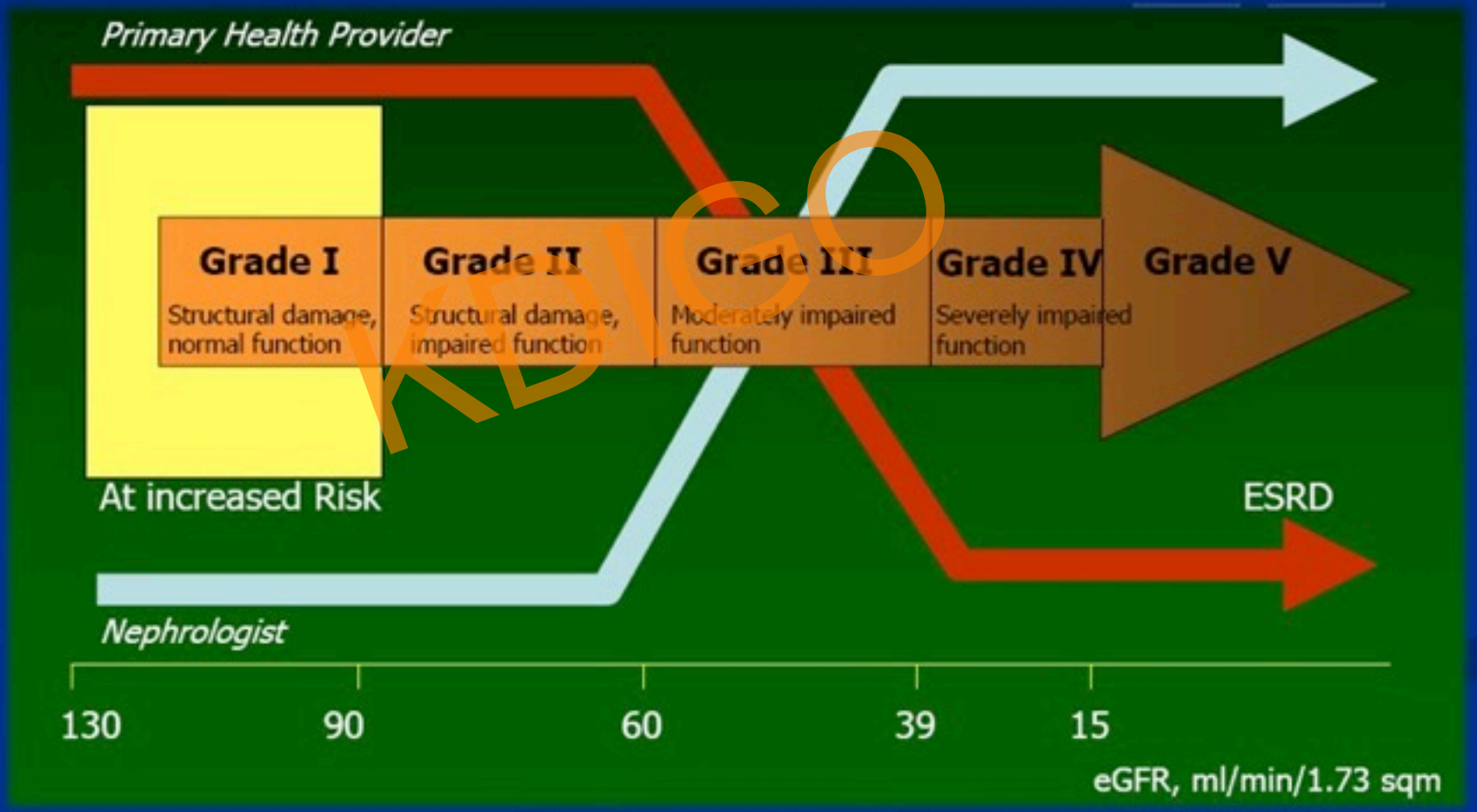
Figure 1 ADQI Heart Failure in ESRD Classification System

Classification is determined by a dyspnea assessment before and after renal replacement therapy (RRT)/ultrafiltration (UF). When patients have the same class assessment before and after RRT/UF, they are scored by their post-treatment assessment. The classification scheme assumes that the class assignment represents the patient's achievement of optimized UF and is representative of the patient's usual level of dyspnea before and after RRT/UF. *If dyspnea symptoms improve to class I levels, the patient would be classified as class 2R. ‡If dyspnea symptoms improve to class II levels, the patient would be classified as class 3R. ADQI = Acute Dialysis Quality Initiative; ESRD = end-stage renal disease; NYHA = New York Heart Association.

Etiology of Chronic Kidney Disease



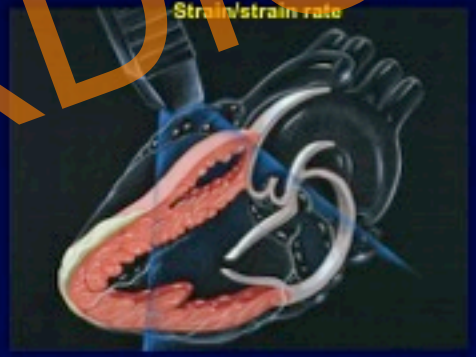
Physicians and Nephrologist in CKD



Heart Failure Phenotypes

All Heart Failure

LVEF
LV Chamber size
LVH
Other chambers
Valve function
Estimate PA pressure
Diastolic FXN
-ASE Gr 1
-ASE Gr 2
-ASE Gr 3
-ASE Gr 4
-Strain/strain rate



50%
Reduced LVEF
Systolic Dysfunction
LVEF<45%

67%
Ischemic
Etiology

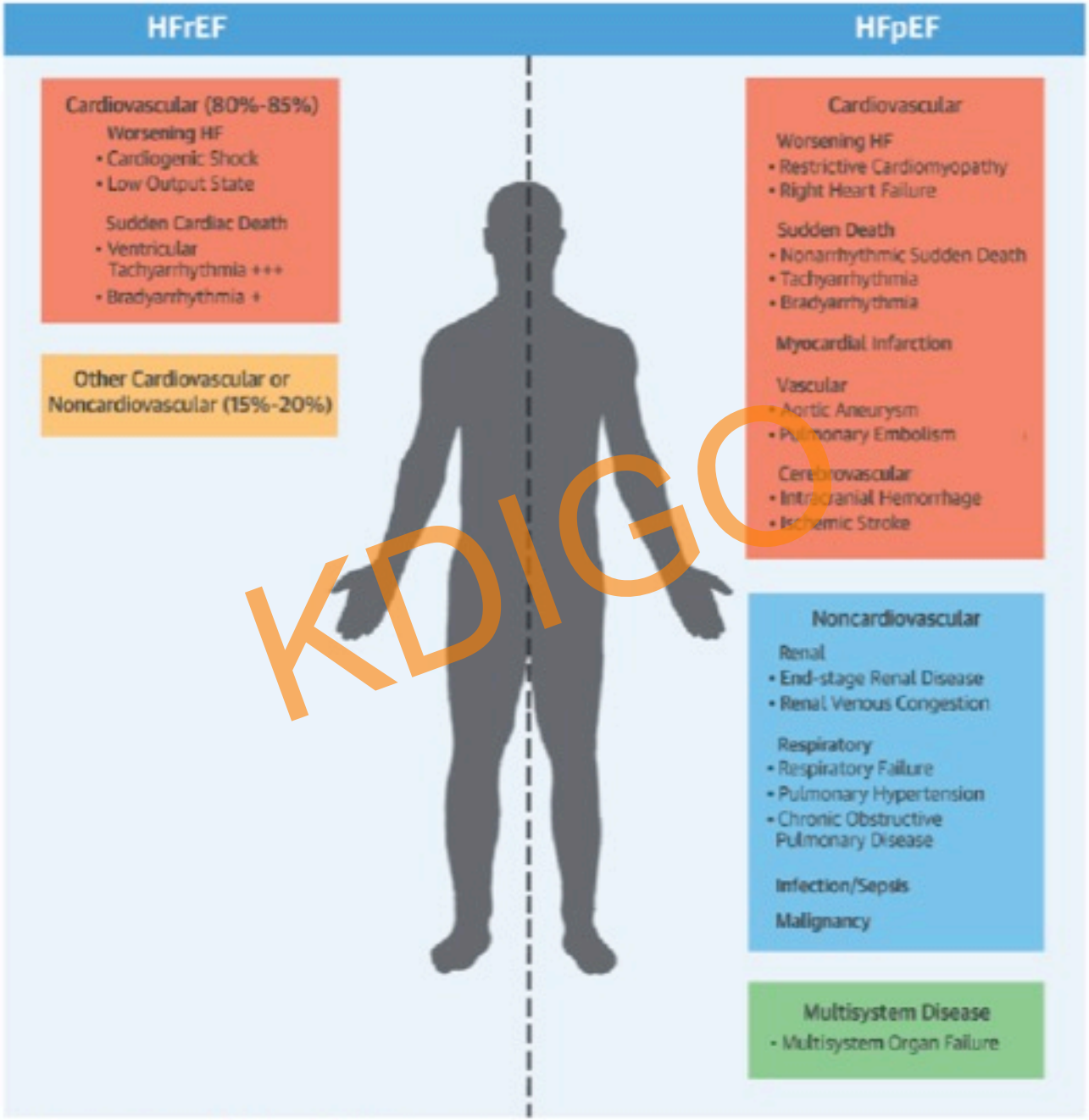
33%
Non-ischemic
Etiology

50%
Preserved LVEF
Diastolic Dysfunction
LVEF>45%

50%
No Ischemia

50%
Ischemic
Contribution
but ???importance

CENTRAL ILLUSTRATION Mode of Death Distribution in HFrEF and HFpEF



Vaduganathan, M. et al. J Am Coll Cardiol. 2017;69(5):556-69.

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Confirmation of a Heart Failure Epidemic: Findings From the Resource Utilization Among Congestive Heart Failure (REACH) Study

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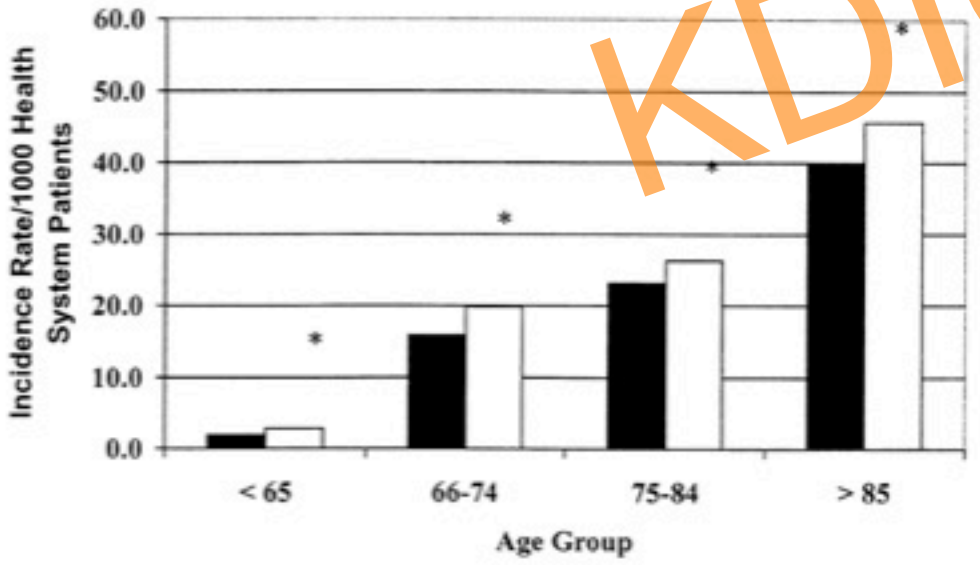
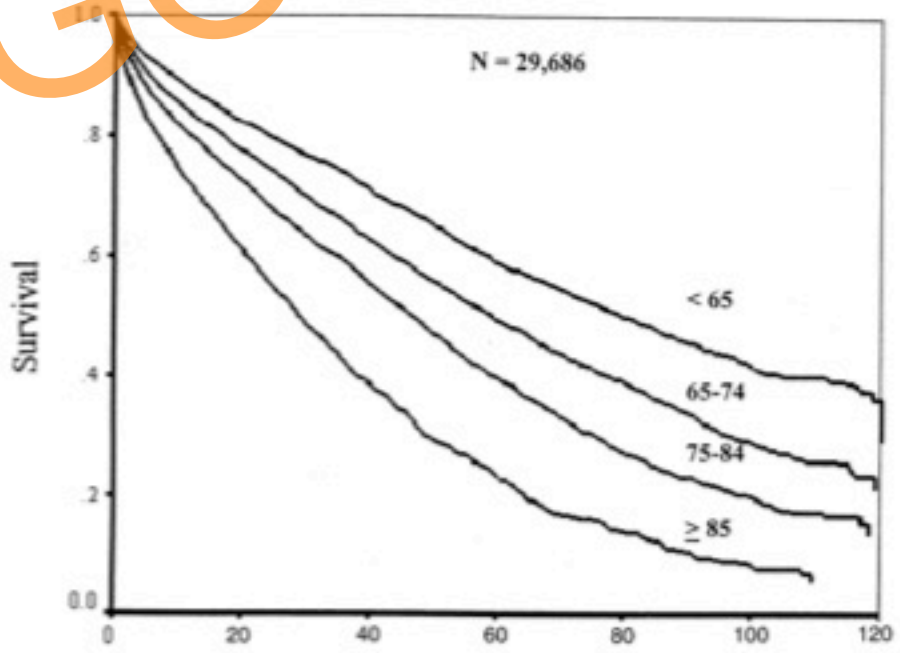
John A. Spertus, MD, MPH, FACC,‡ Scott Kaatz, DO, FACP,§ Keisha R. Sandberg, BS,‖
W. Douglas Weaver, MD, FACC‖

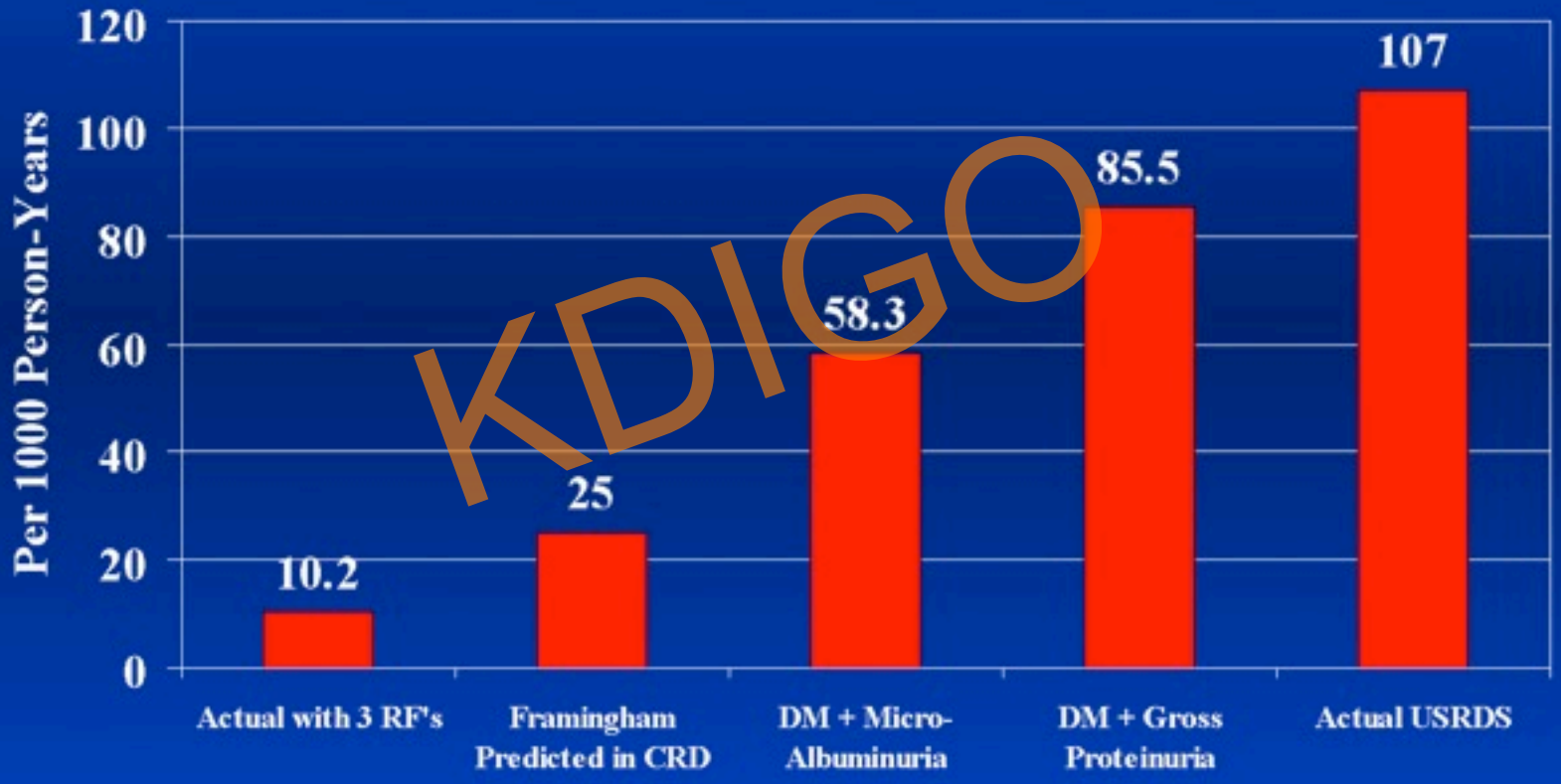
Kansas City, Missouri; Albany, New York; and Detroit, Michigan





10-year CHD Mortality

A Continuum in Risk



Chicago Heart Detection Project, Arch Int Med, 1998

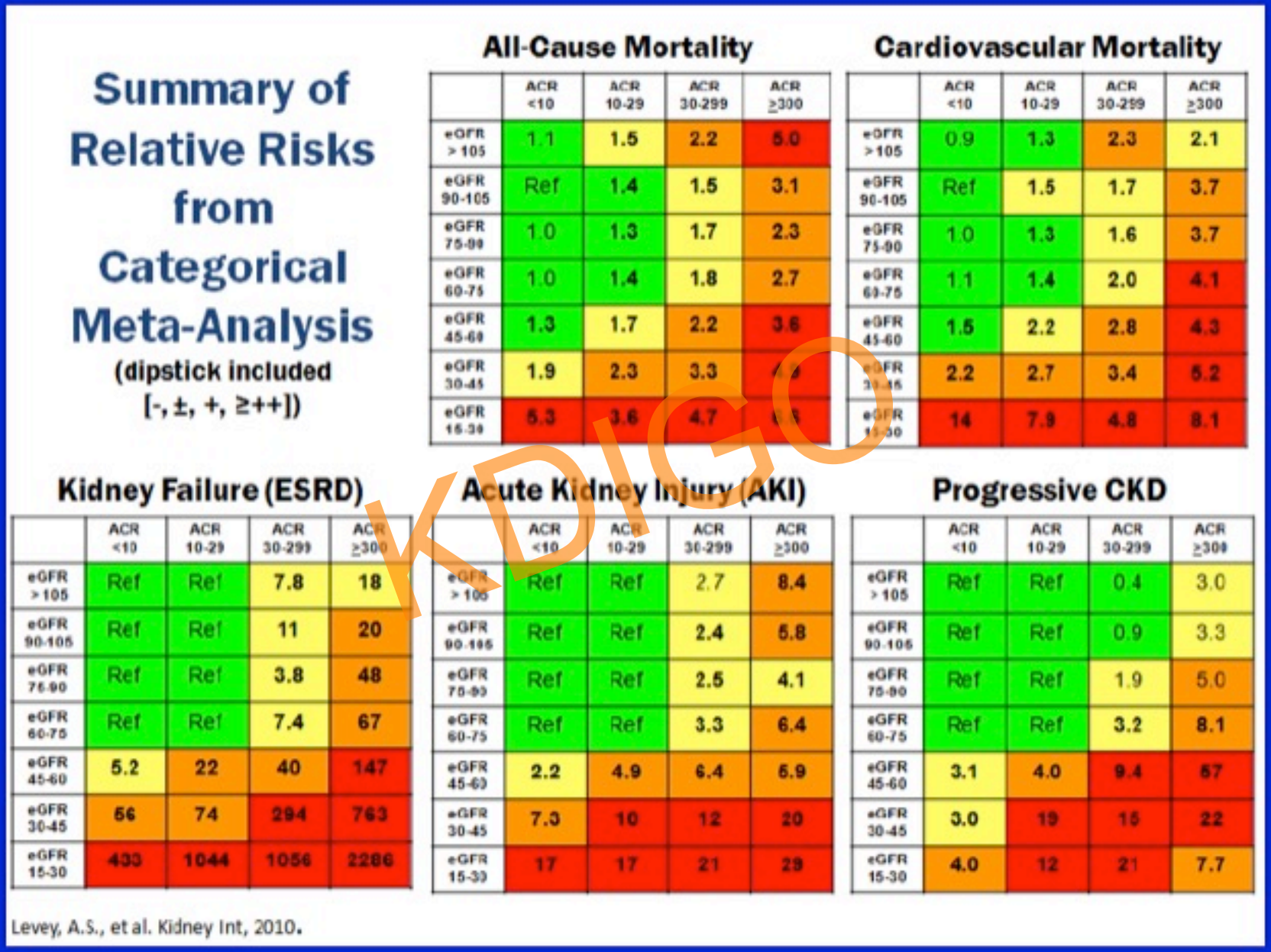
ACC/AHA Scientific Statement, Grundy et al, Circulation, 1999

Wisconsin Epidemiologic Study, Arch Intern Med. 2000;160:1093-1100

USRDS, Am J Kid Dis 1998

Levin A, Stevens L, McCullough PA. Cardiovascular disease and the kidney. Tracking a killer in chronic kidney disease. Postgrad Med. 2002 Apr;111(4):53-60.

FIGURE 88-3 Relative risks of heart and kidney outcomes in cohorts where eGFR and ACR where measured.



Levey, A.S., et al. Kidney Int, 2010.

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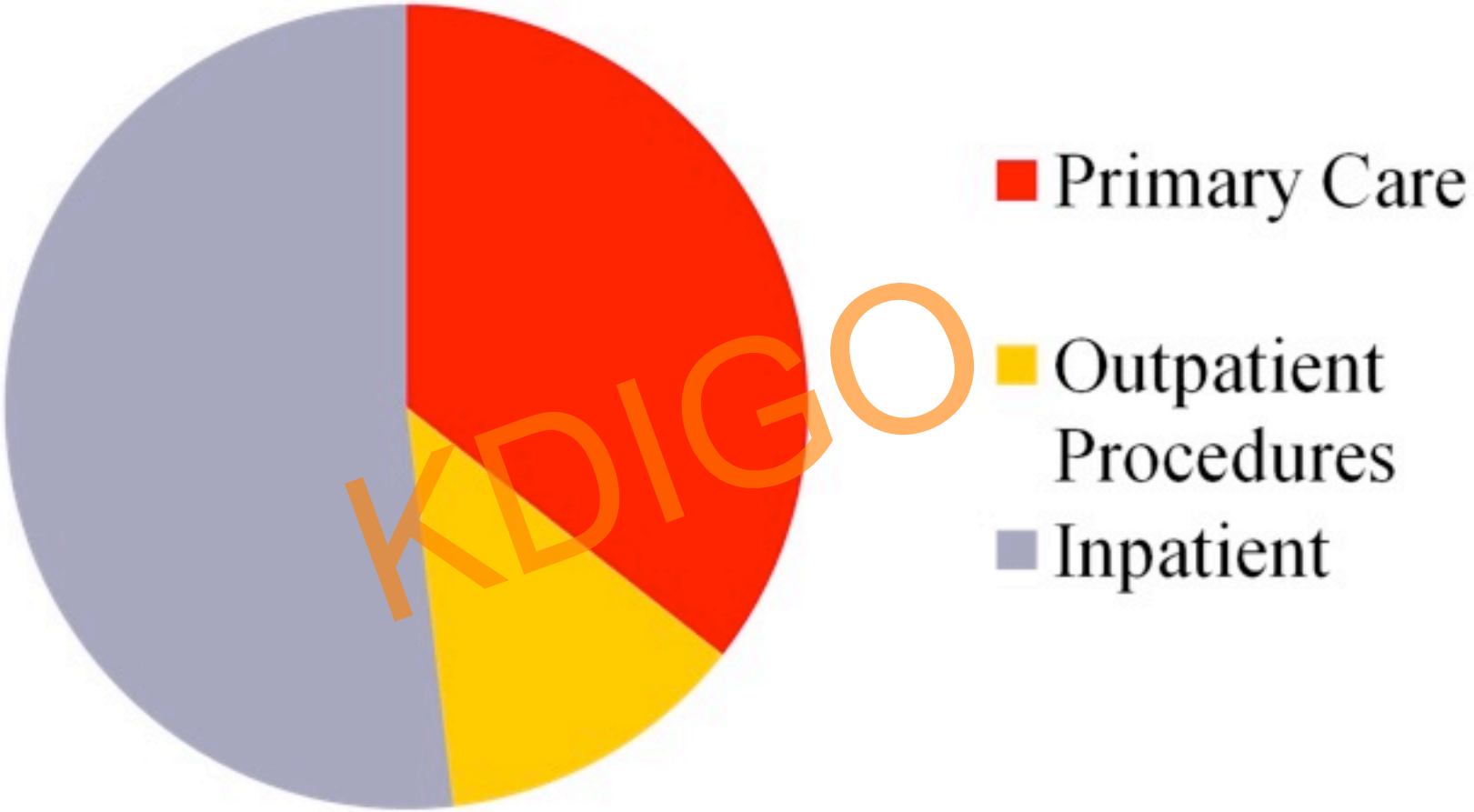
Proportion of AKI Cases



Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community–acquired acute kidney injury. *Nephrology*. 2014;19(5):282-287.

Among 11,683 qualifying AKI hospitalizations, 2954 patients (25%) were hospitalized with recurrent AKI within 12 months of discharge. Median time to recurrent AKI was 64 days.

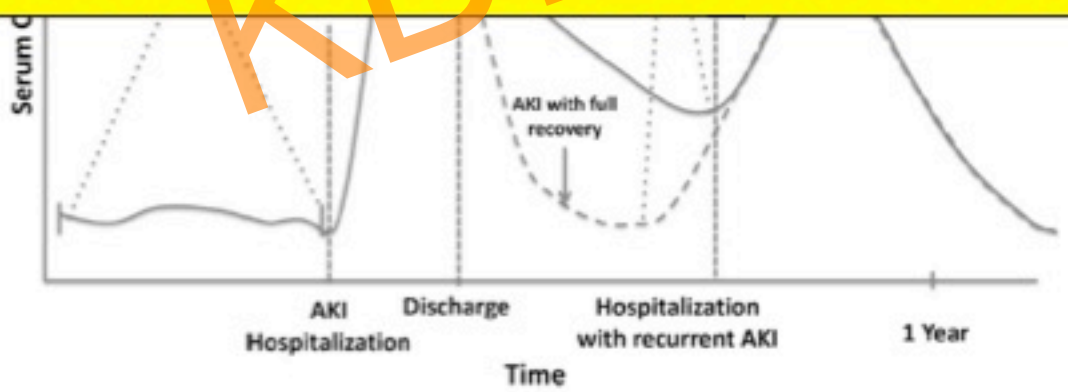
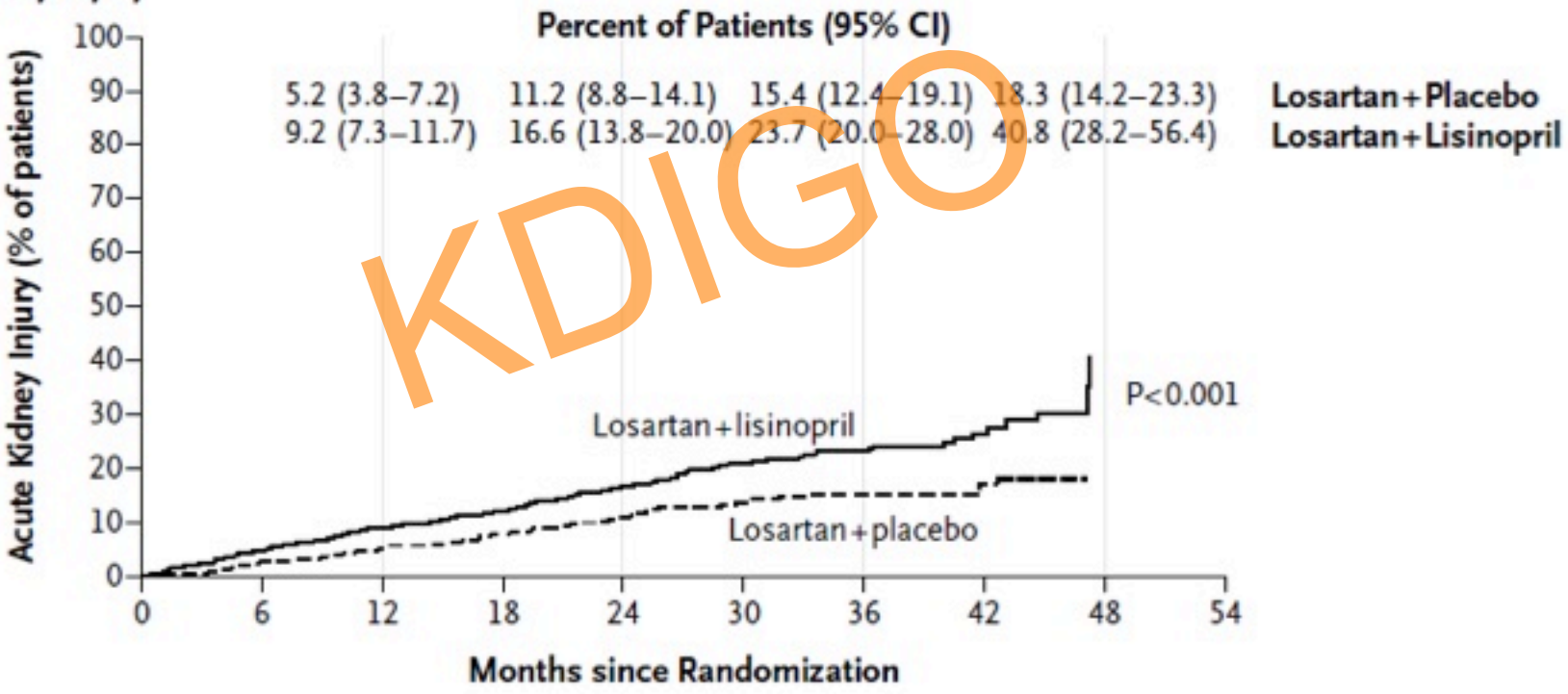


Figure 2. Choice of baseline creatinine for index and recurrent AKI. The baseline for an index AKI event was defined using the mean outpatient serum creatinine 7–365 days prior to hospitalization.[39] To account for potential trajectories of recovery, we defined the baseline for recurrent AKI as the nadir of either the most recent inpatient or outpatient serum creatinine or the admission serum creatinine of the subsequent hospitalization in which recurrent AKI occurred.

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

A Acute Kidney Injury

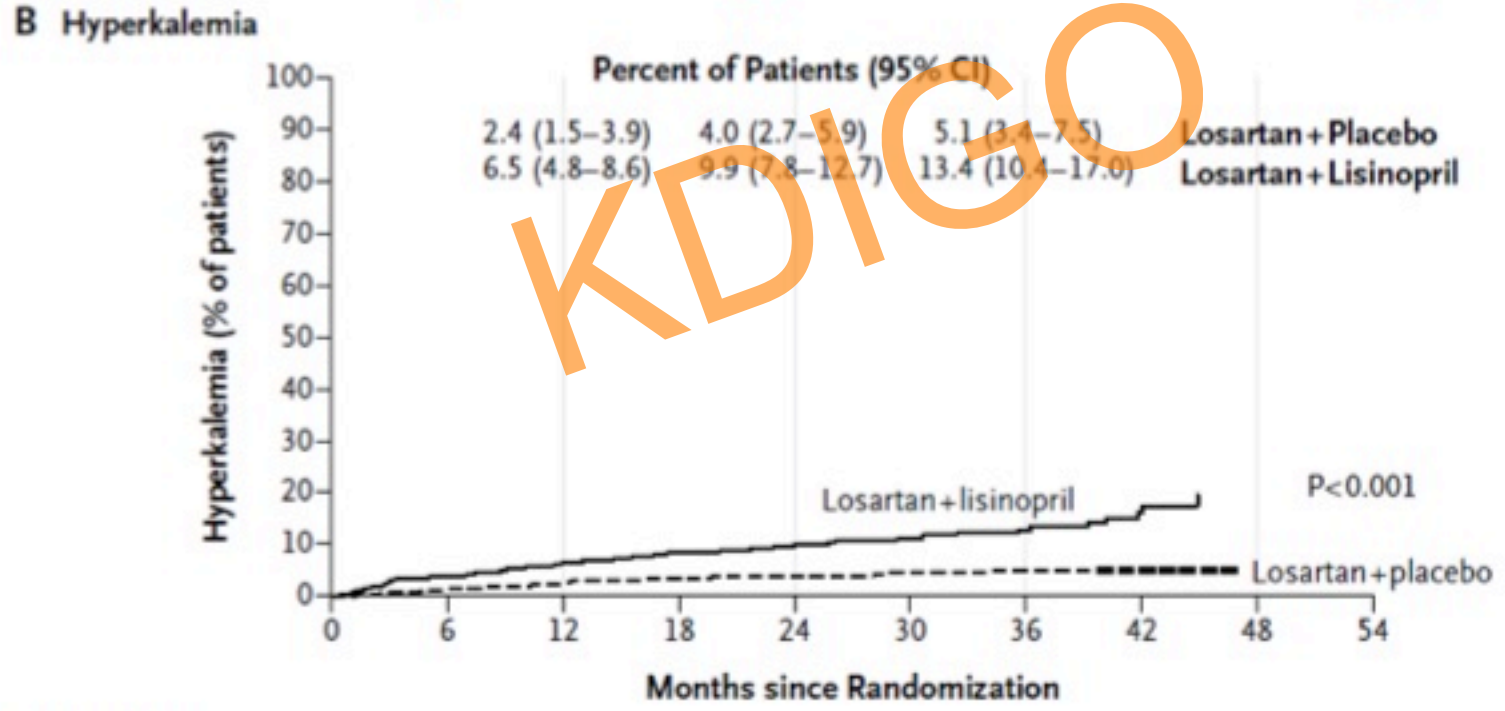


No. at Risk

Losartan+placebo	724	638	548	470	355	260	170	89	20
Losartan+lisinopril	724	630	528	453	341	251	156	78	7

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

K > 6.0 mEq/L that required ED visit or hospitalization



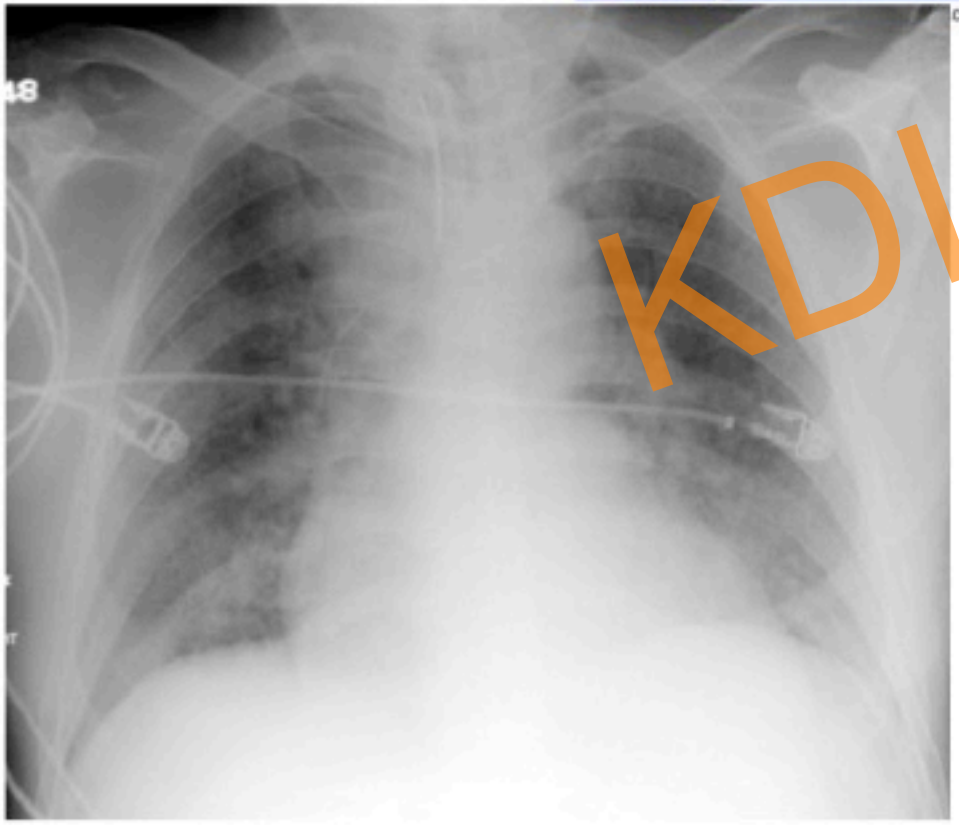
An et al. Critical Care 2012, 16:R225
http://ccforum.com/content/16/6/R225

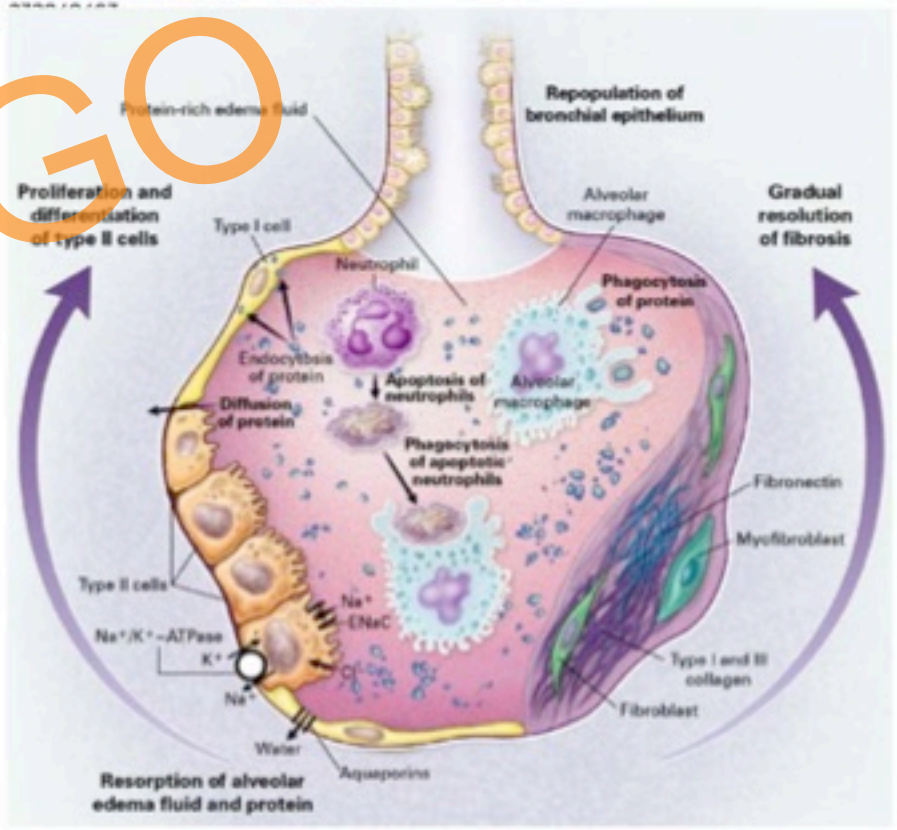
Severe Hyperkalemia (≥6.5 mEq/L)

- 36% on chronic ACE, ARB, or MRA
- 22% had AKI with baseline normal eGFR
- 52% had AKI superimposed on CKD
- 20% presented with cardiac arrest
- 31% in-hospital mortality

Acute kidney injury (AKI) in patients with normal baseline renal function was a strong predictor of mortality, compared with AKI superimposed on CKD.

Medical ward	244 (44.0)
Emergency room	28 (5.1)
Multi-organ failure at admission	108 (11.7)
Multi-organ failure at the time of diagnosis	226 (24.5)
Diagnosis at the time of cardiac arrest	187 (20.3)
Symptoms pertinent to hyperkalemia	432 (46.8)
Cardiac arrest	187 (43.3)
Arrhythmia	152 (35.2)





Azarbar S, Dupuis J. Lung capillary injury and repair in left heart disease: a new target for therapy? Clin Sci (Lond). 2014 Jul;127(2):65-76. doi: 10.1042/CS20130296. Review. PubMed PMID: 24678967.

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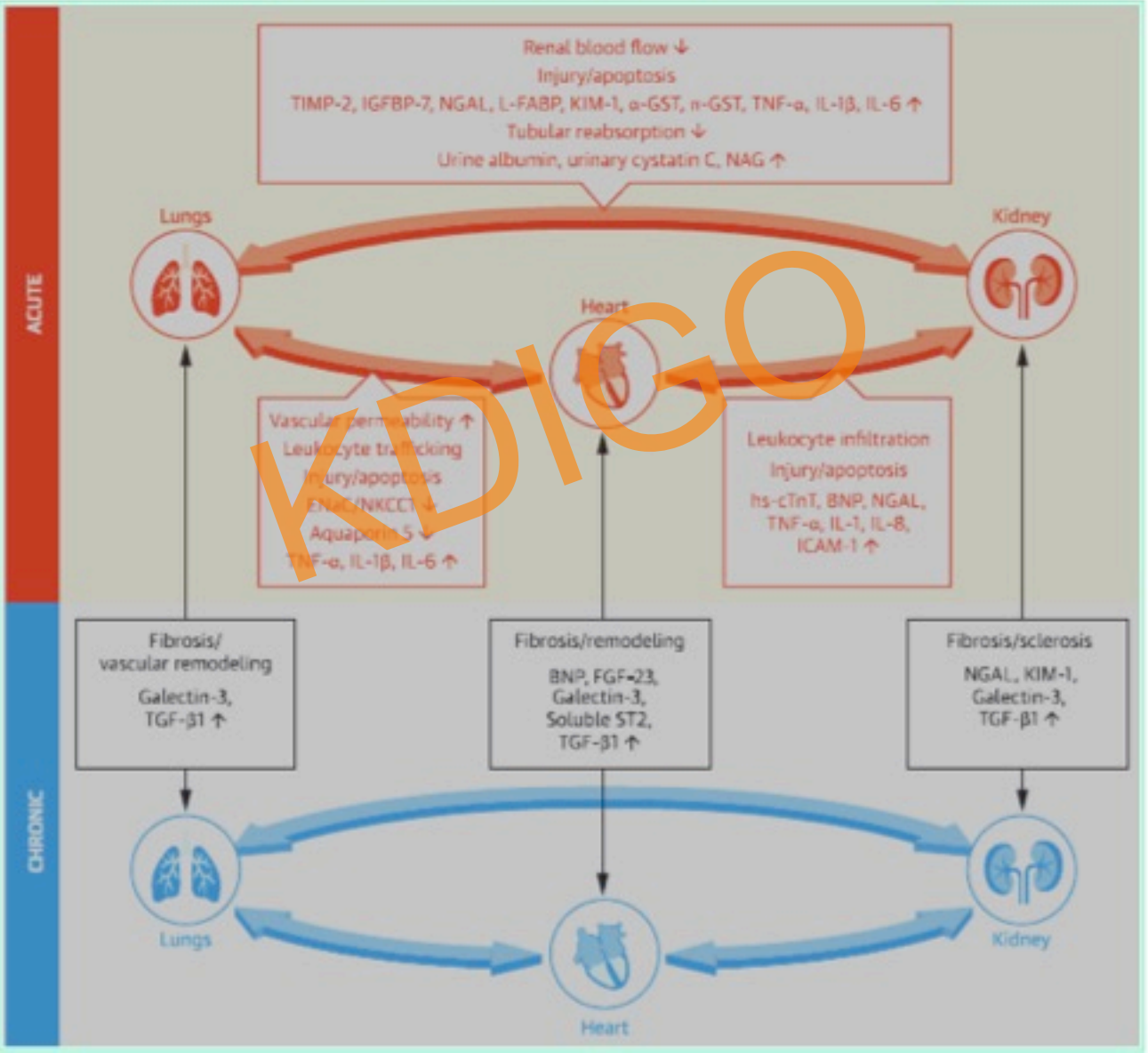
Cardio-Pulmonary-Renal Interactions

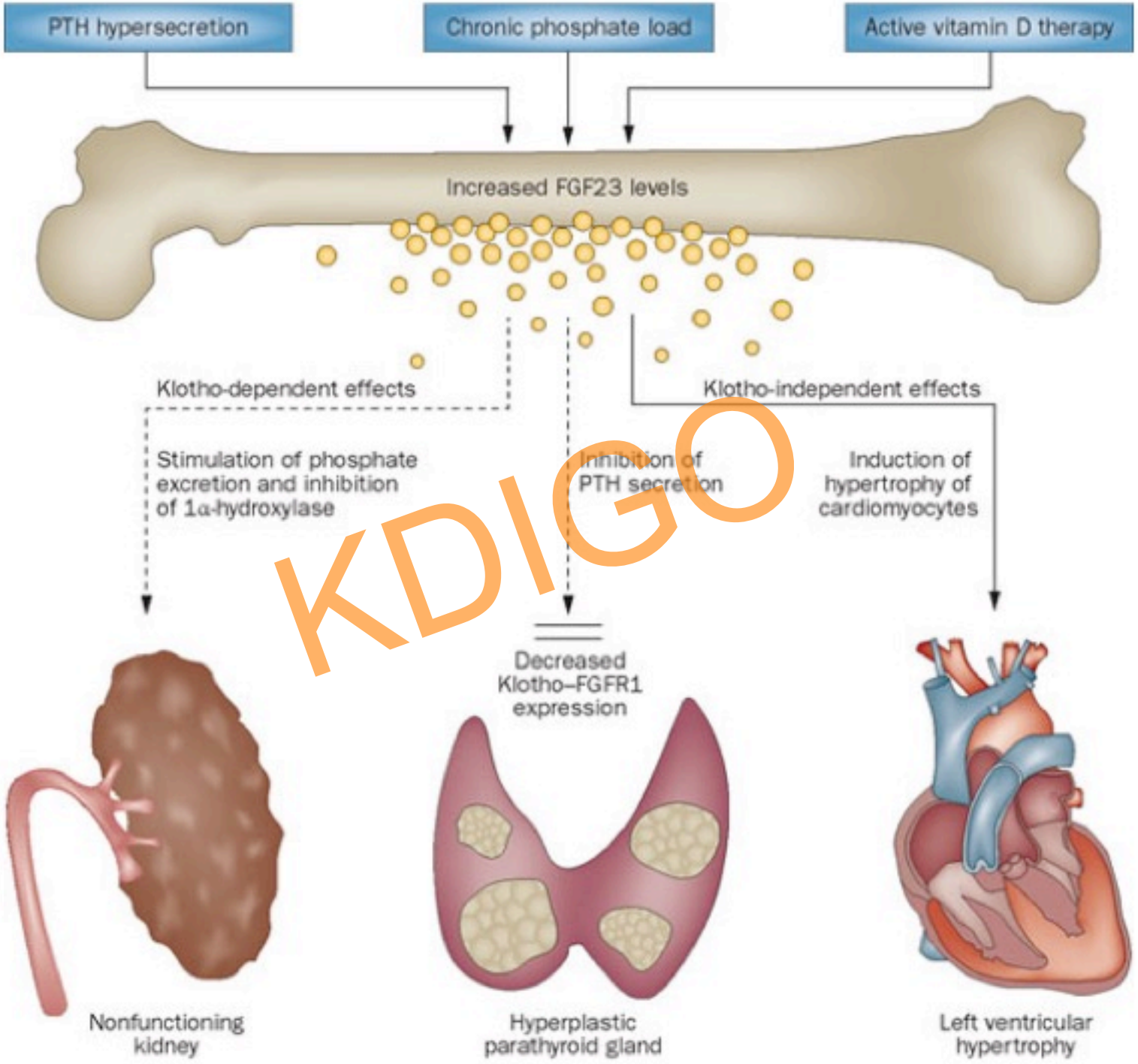
A Multidisciplinary Approach

Faeq Husain-Syed, MD,*† Peter A. McCullough, MD, MPH,‡§ Horst-Walter Birk, MD,† Matthias Renker, MD,‖ Alessandra Brocca, MSc,* Werner Seeger, MD,† Claudio Ronco, MD*

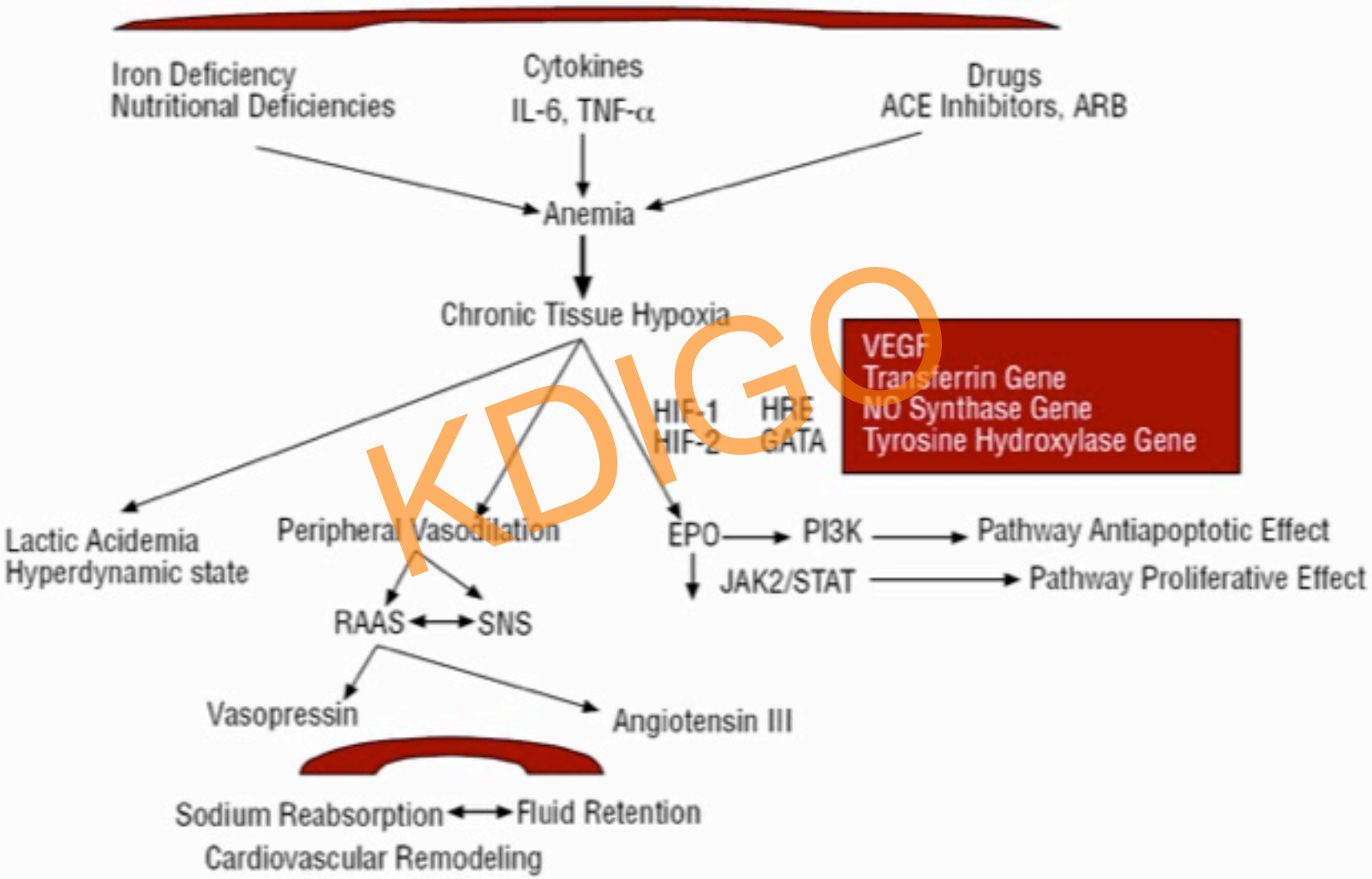


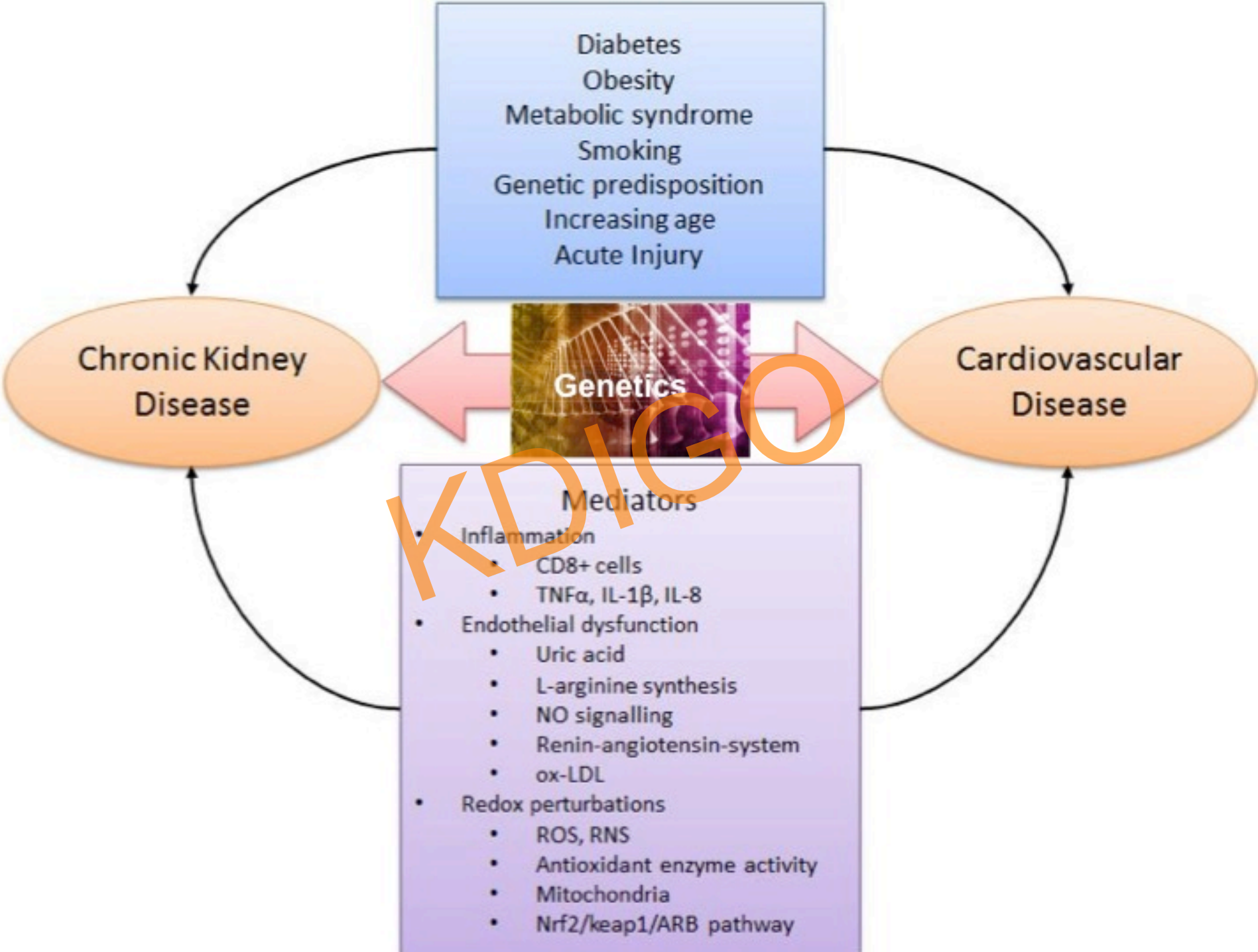
STATE-OF-THE-ART REVIEW

THE PRESENT AND FUTURE


PTH hypersecretion
Chronic phosphate load
Active vitamin D therapy
Increased FGF23 levels
Klotho-dependent effects
Klotho-independent effects
Stimulation of phosphate excretion and inhibition of 1α-hydroxylase
Inhibition of PTH secretion
Induction of hypertrophy of cardiomyocytes
Decreased Klotho–FGFR1 expression
Nonfunctioning kidney
Hyperplastic parathyroid gland
Left ventricular hypertrophy

Heart Failure, Progression of Kidney Disease




Diabetes
Obesity
Metabolic syndrome
Smoking
Genetic predisposition
Increasing age
Acute Injury
Chronic Kidney Disease
Genetics
Cardiovascular Disease
Mediators
Inflammation
CD8+ cells
TNFα, IL-1β, IL-8
Endothelial dysfunction
Uric acid
L-arginine synthesis
NO signalling
Renin-angiotensin-system
ox-LDL
Redox perturbations
ROS, RNS
Antioxidant enzyme activity
Mitochondria
Nrf2/keap1/ARB pathway
KDIGO

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Palazzuoli et al. Critical Care (2015) 19:296
DOI 10.1186/s13054-015-1017-3

CRITICAL CARE

REVIEW Open Access

Loop diuretics in acute heart failure: beyond the decongestive relief for the kidney

Alberto Palazzuoli[1*], Gaetano Ruocco[1], Claudio Ronco[2] and Peter A. McCullough[3]

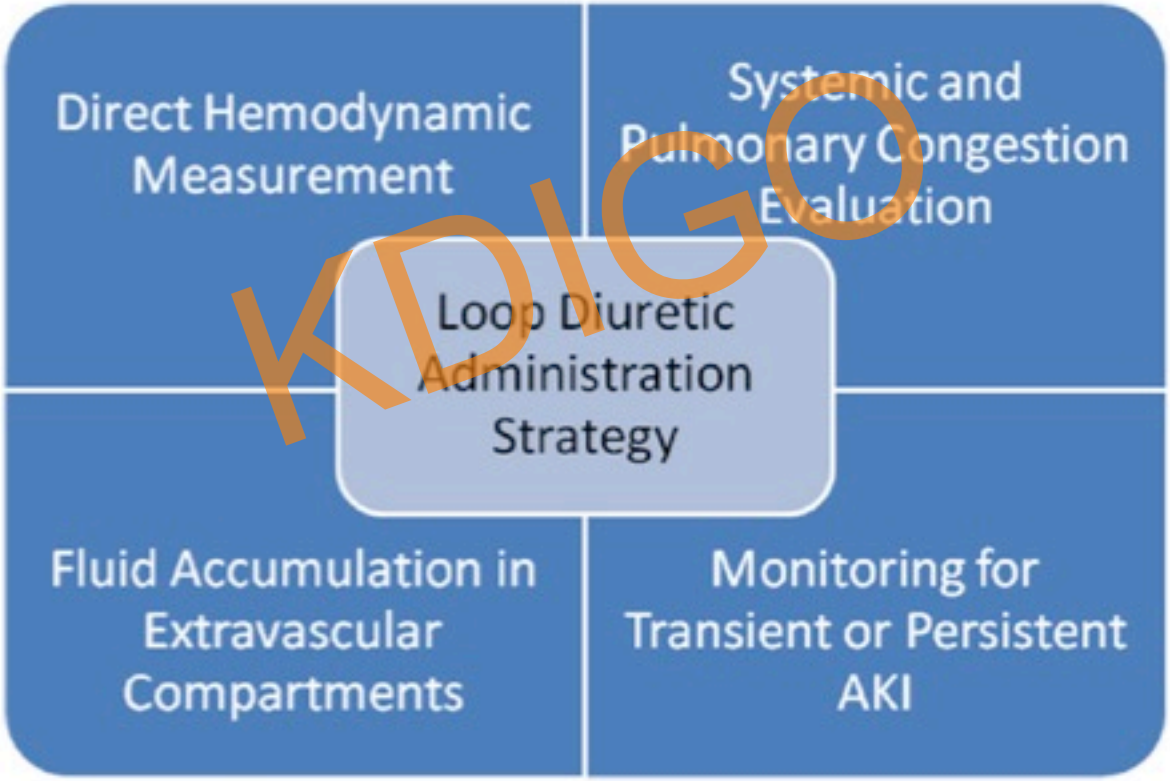


Fig. 3 Strategy for loop diuretic therapy optimization looking for renal dysfunction fluid accumulation and hemodynamic status. *AKI* acute kidney injury

Reduced GFR:

Barriers	Potential solution
Abnormal glomerular hemodynamics	Discontinue NSAIDs, consider holding ACEI/ARB
Low cardiac output	Hemodynamic support
Chronic kidney disease or functional renal hypoperfusion	

Proximal Hyperfun

Barriers
Neuro-hormonal activation
Sodium-avid states
Post-diuretic effect
Excessive daily sodium intake

Diuretic Strategy

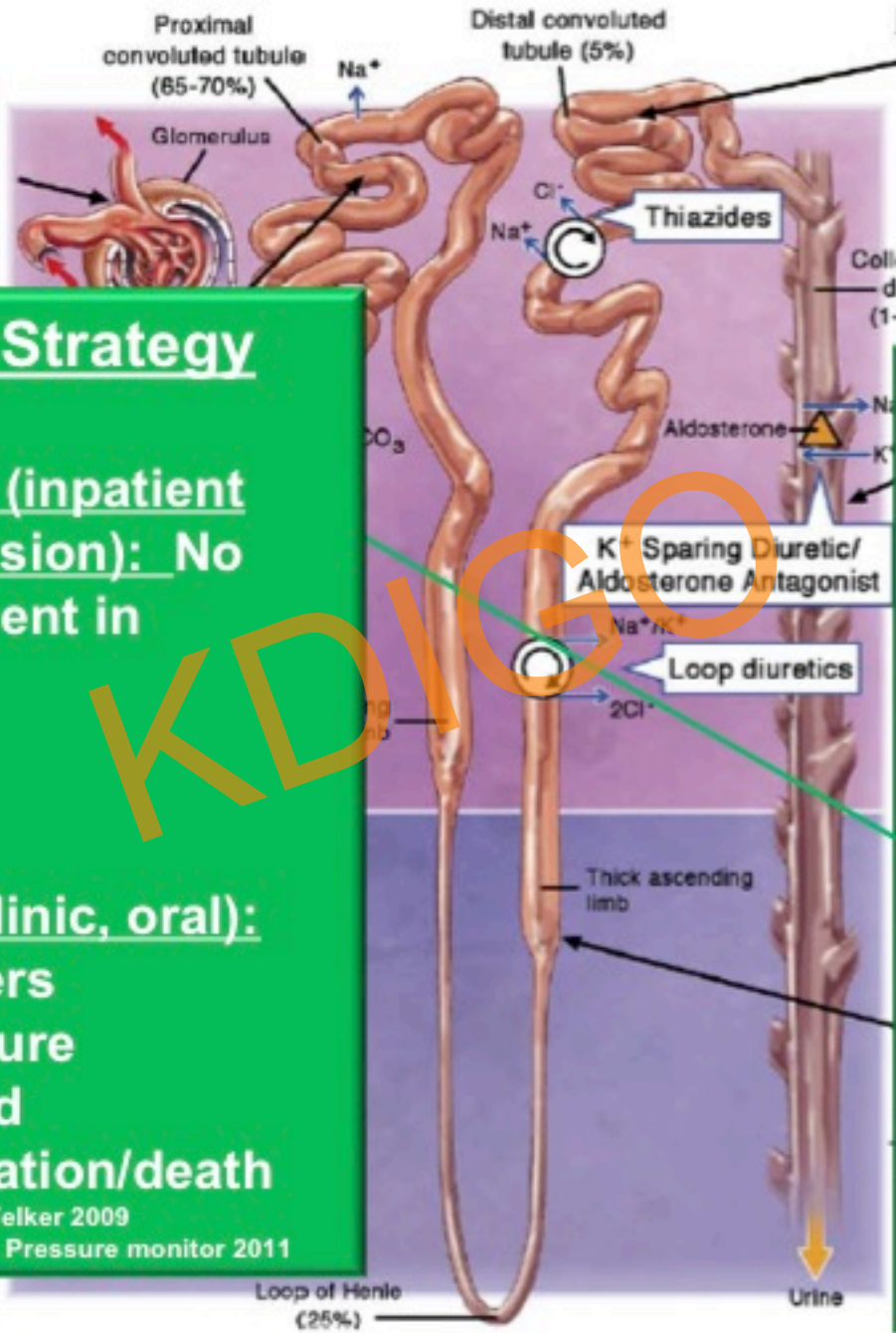
Unguided (inpatient bolus/infusion): No improvement in outcomes

DOSE HF Trial
ROSE HF Trial
DIUR-HF Trial

Guided (clinic, oral):

-Biomarkers
-PA pressure
→Reduced hospitalization/death

6 Biomarker Trials Felker 2009
CHAMPION Trial PA Pressure monitor 2011



Distal Tubule Hypertrophy:

Barriers	Potential solution
Rebound sodium retention	Sequential nephron blockade (Combination diuretic therapy)

Distal Nephron Hyperfunction:

Barriers	Potential solution
Excessive aldosterone-mediated sodium retention	Aldosterone antagonist, K+ -sparing diuretic (ENaC blocker)
Excessive vasopressin-mediated water retention	Vasopressin antagonist, free water restriction

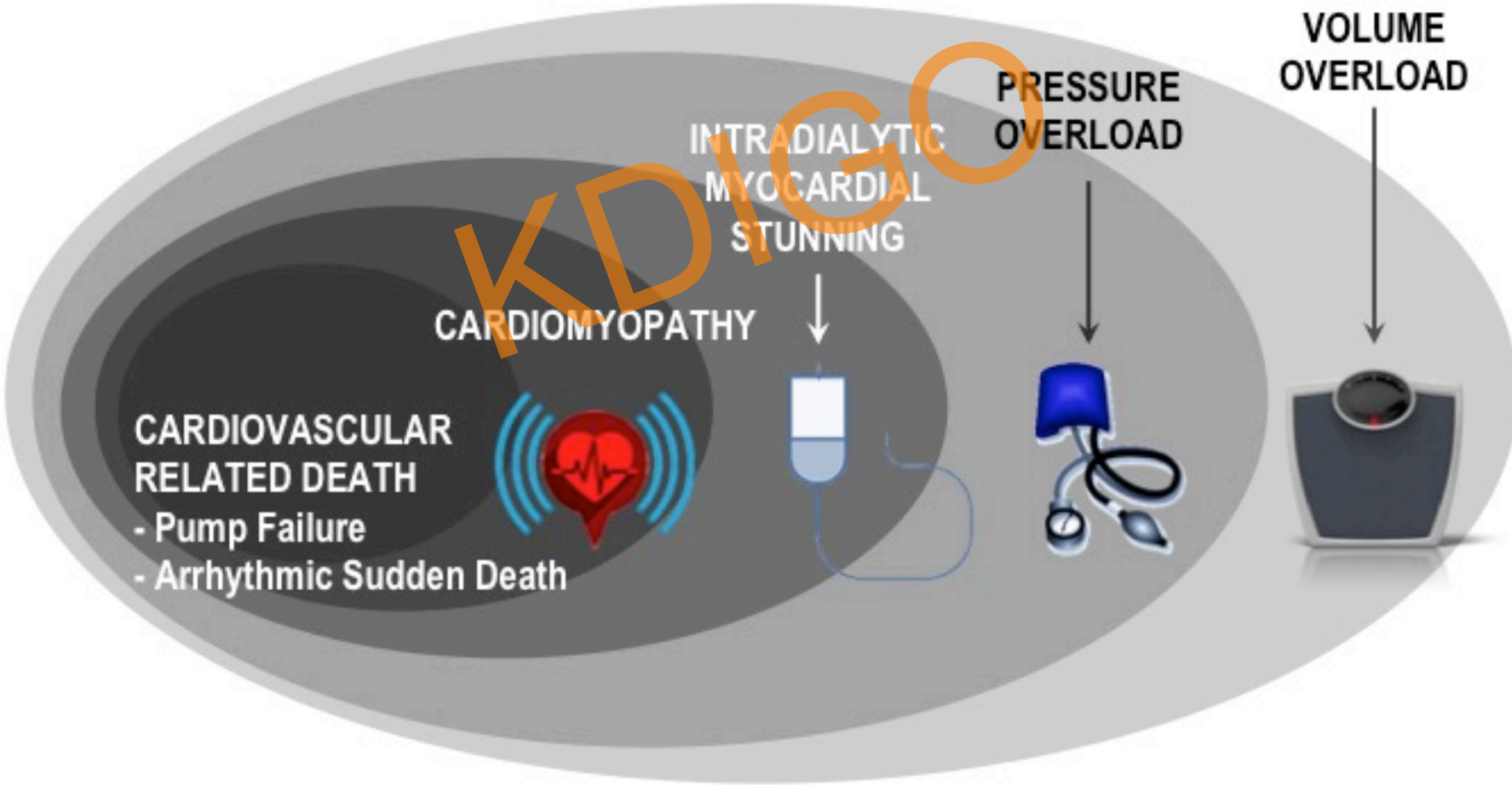
Loop of Henle Hyperfunction:

Barriers	Potential solution
Braking effect	Higher LD doses

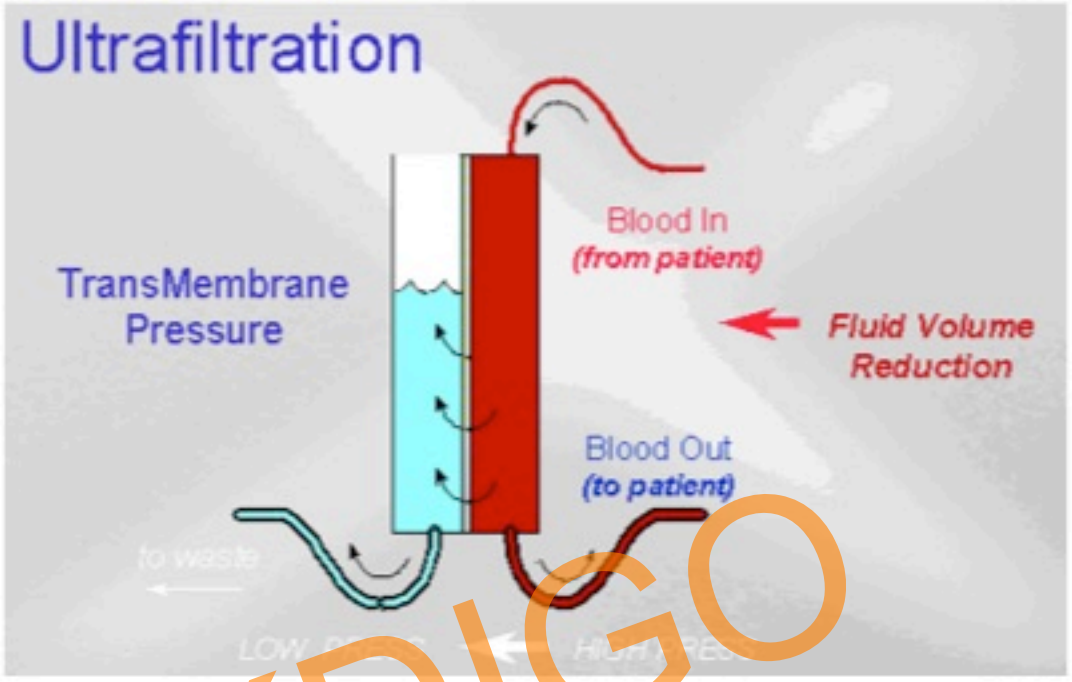
JACC Vol. 56, No. 19, 2010
November 2, 2010:1527–34

Dialysis Induced Stress on the Heart: Myocardial "Stunning"

Effective fluid management holds the promise of better cardiovascular outcomes
EFFECTIVENESS VARIES BY MODALITY: LOWER FLOW RATES, LONGER TIMES, MORE FREQUENT RUNS→LESS STUNNING



Early Benefit



Late No Benefit

KDIGO

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Heart Failure

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

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Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§
John R. Teerlink, MD, FACC,‖ Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,#
Erika D. Feller, MD, FACC,** Garrie J. Haas, MD, FACC,†† Allen S. Anderson, MD, FACC,‡‡
Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators

Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

The NEW ENGLAND JOURNAL of MEDICINE

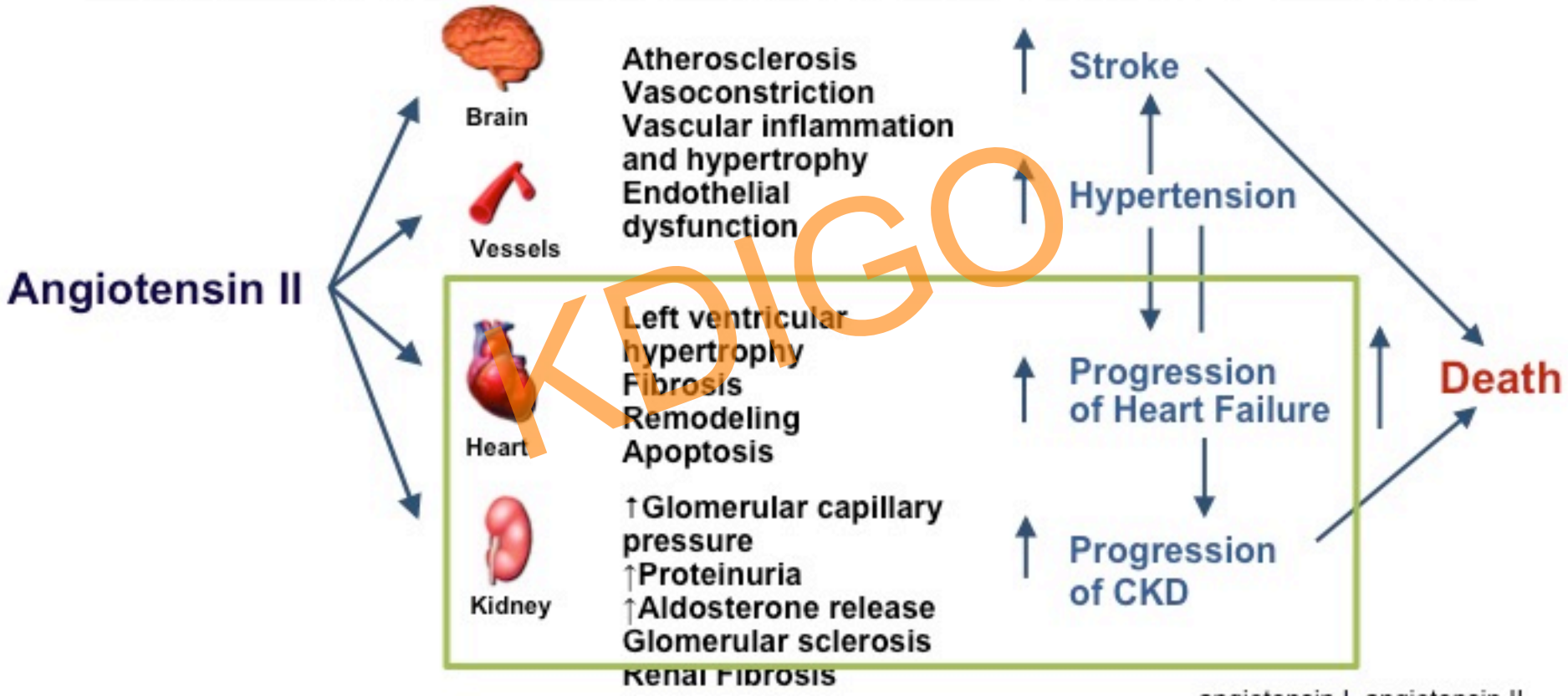
ORIGINAL ARTICLE

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O'Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., and Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

Compelling Evidence for End Organ Benefit[1-6]

Role of Angiotensin II in the Progression of Cardiovascular Disease



angiotensin I, angiotensin II

1. Adapted from Willenheimer R, Dahlöf B, Rydberg E, Erhardt L. *Eur Heart J*. 1999;20:997-1008.
2. Dahlöf B. *J Hum Hypertens*. 1995;9(suppl 5):S37-S44.
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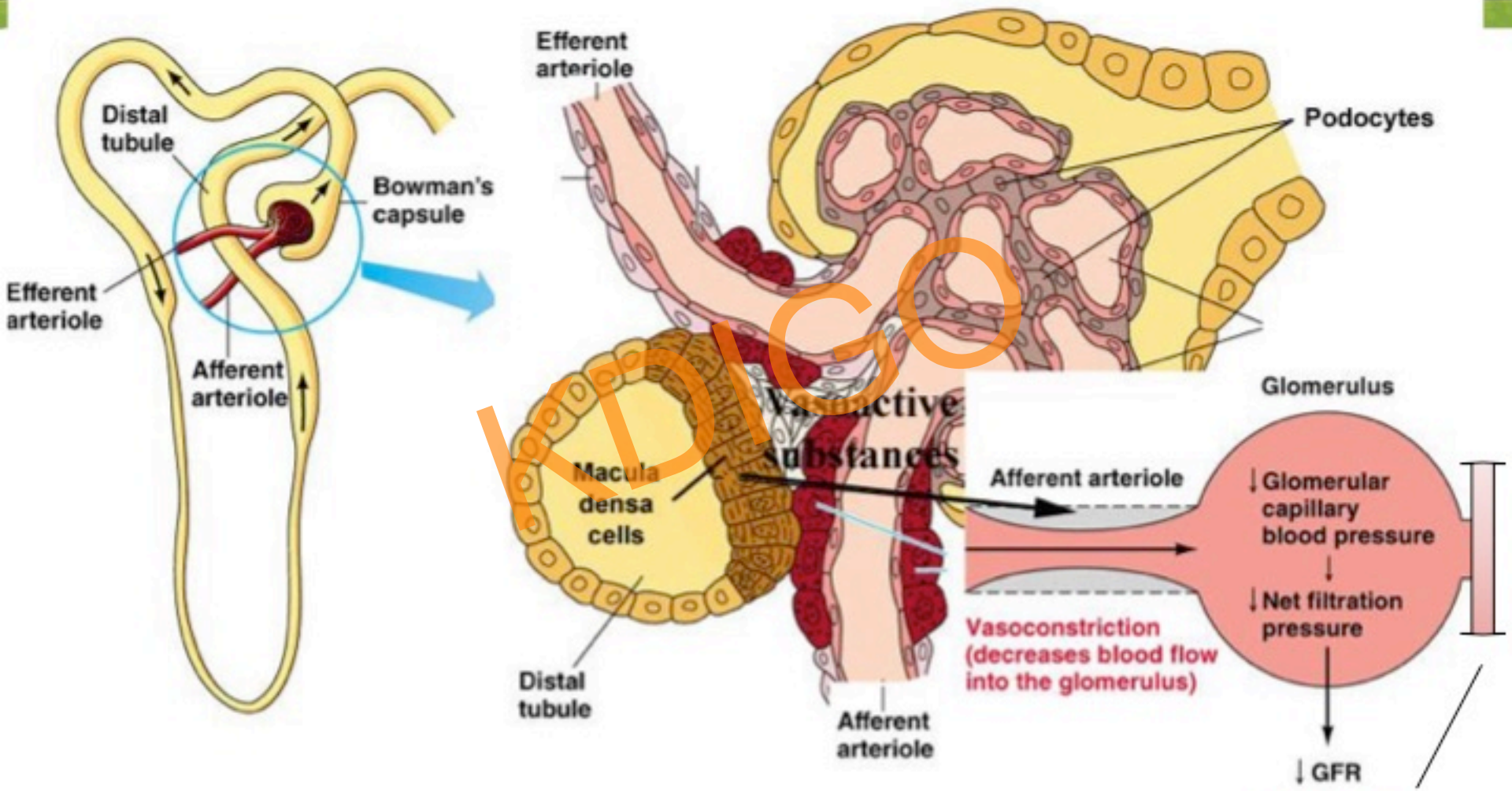
Juxtamedullary Apparatus



Campanacci L, Fabris B, Fischetti F, Bardelli M, Vran F, Carretta R. Ace inhibition in renal disease: risks and benefits.
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ACE/ARB ↓ Efferent Arterial Tone

Effects of withdrawing vs continuing renin-angiotensin blockers on incidence of acute kidney injury in patients with renal insufficiency undergoing cardiac catheterization: Results from the Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker and Contrast Induced Nephropathy in Patients Receiving Cardiac Catheterization (CAPTAIN) trial

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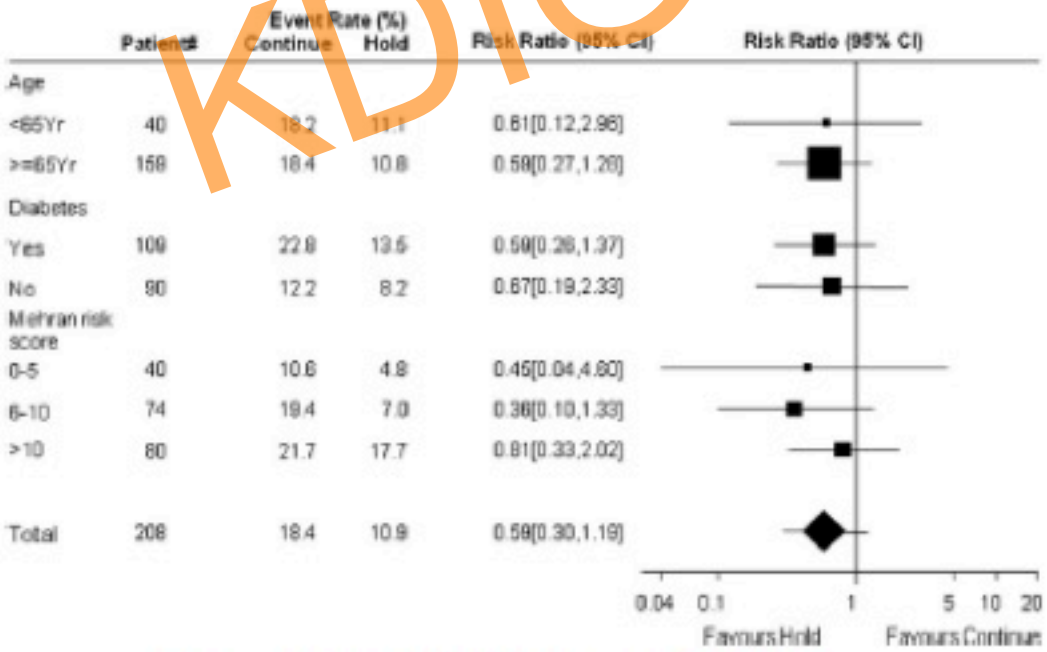
Figure 1

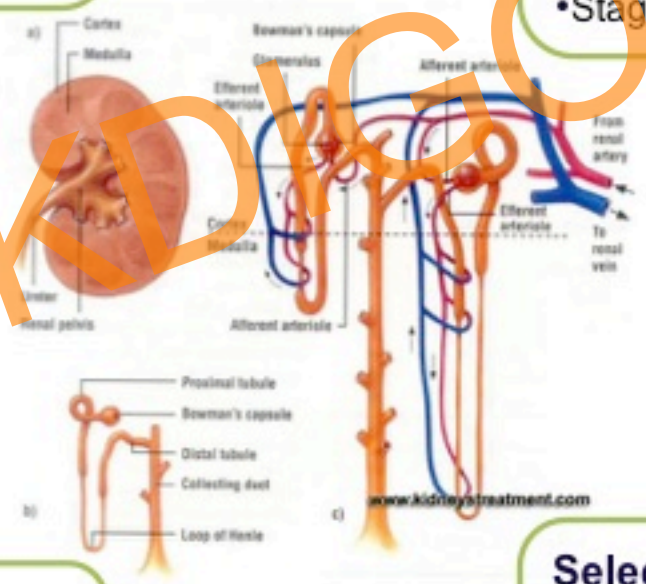


Risk ratios for the primary end point in prespecified subgroups.

RAASi: Benefit to Risk Balance

Renal Function Stable
Compelling Indication for RAASi
- Post-MI low LVEF or HF
- Progressive HF
- Progressive CKD with proteinuria

Renal Function Unstable
Risk ↑ AKI, Risk ↑ K
Less compelling Indication for RAASi
- HTN
- ASCVD
- Stage 5 CKD



Full Court Press
- Monitor carefully
- Look forward to new agents for potassium control

Select Away from RAASi
- Still have to monitor carefully
- Use fall back drugs with less efficacy
- Expect poor outcomes

Epidemiology
Pathogenesis
Diagnosis
Prognosis
Management

Questions
Discussion of Evidence
Conclusions
Research Gaps

	Heart Failure with Preserved Ejection Fraction (HFpEF)	Heart Failure with Reduced Ejection Fraction (HFrEF)
Pre-dialysis CKD	*Working Group #1*	*Working Group #2*
Dialysis CKD	*Working Group #3*	*Working Group #4*
Kidney Transplant Patients	*Working Group #5*	

Outline

- Heart and kidney disease trends
- Acute and chronic disease phenotypes
- Prognosis
- Intercurrent events
- Management
- Conclusions

Conclusions

- Both HF and CKD/ESRD prevalence pools will dramatically rise in the years to come
- Both heart and kidney disease phenotypes are important
- Prognosis is impacted by intercurrent events
- Pathophysiological targets include conventionally assessed parameters such as volume status, but also many novel ones
- KDIGO Controversies methods aim to bring bright minds together to consider evidence and arrive at conclusions and help identify gaps in knowledge for future research