Concept and General Objectives of the Conference: Prognosis Matters

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General Objectives

- Topics to discuss
  - What are the key outcomes of CKD?
  - What progress has been made in measurement of CKD with respect to estimated GFR and albuminuria?
  - What are the key factors for determining CKD prognosis, by eGFR?
  - Should the current CKD classification (based on GFR) be modified to include classification by prognosis?
  - Based on these results, should the CKD definition be modified?

Goals for the presentation

- Perspective on CKD
- Prognosis matters
  - Questions to be answered
  - Analytical plan
  - Next steps

Perspective

The debate over the definition and classification of CKD

- should be about improving outcomes for patients, not about nephrologists
- should be based on data, not on beliefs

Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes

AS Levey[1], R Atkins[2], J Coresh[3], EP Cohen[4], AJ Collins[5], K-U Eckardt[6], ME Nahas[7], BL Jaber[8], M Jadoul[9], A Levin[10], NR Powe[11], J Rossert[12], DC Wheeler[13], N Lameire[14] and G Eknoyan[15]

CKD is

- Common
- Harmful
- Treatable

Am J Kidney Dis 53:522-535. © 2009 by the National Kidney Foundation, Inc.

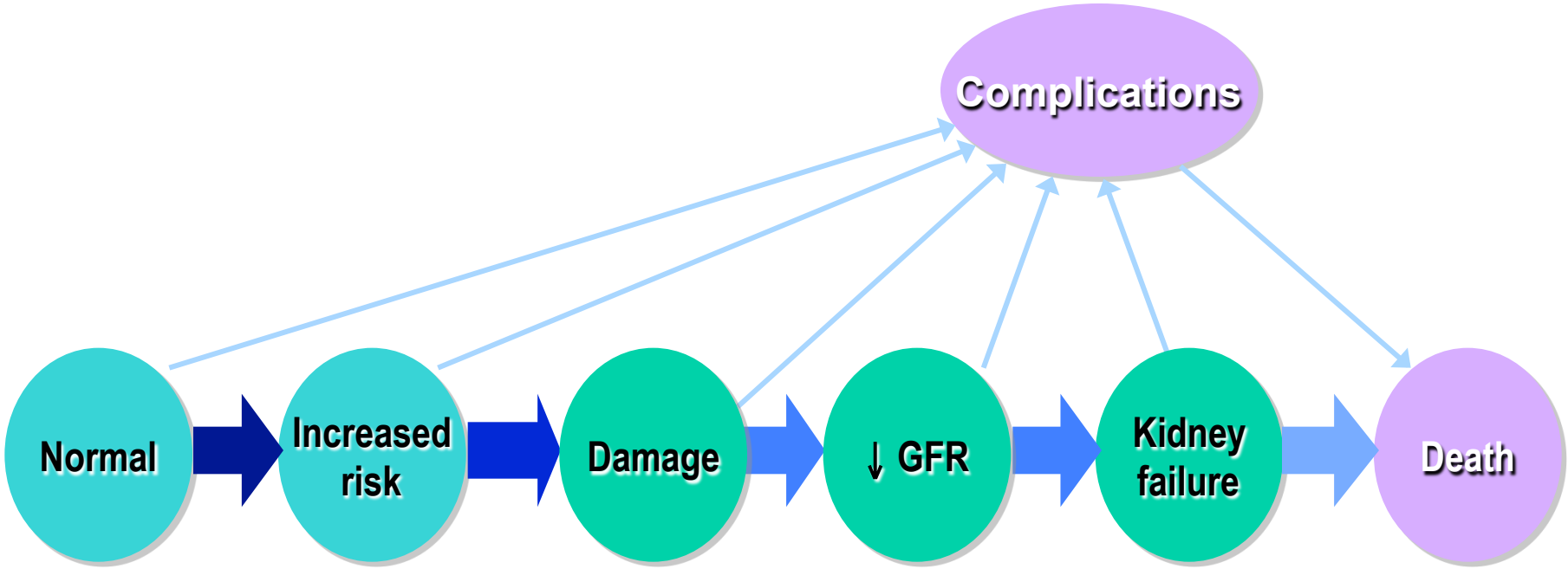
SPECIAL ARTICLE

Comprehensive Public Health Strategies for Preventing the Development, Progression, and Complications of CKD: Report of an Expert Panel Convened by the Centers for Disease Control and Prevention

Andrew S. Levey, MD,[1] Anton C. Schoolwerth, MD, MSHA,[2] Nilka Ríos Burrows, MPH, MT,[3,4] Desmond E. Williams, MD, PhD,[4] Karma Rabon Stith, PhD, CHES,[5] and William McClellan, MD, MPH[6]

"One of a number of chronic diseases … like hypertension, diabetes, and hypercholesterolemia …"

Conceptual Model for CKD

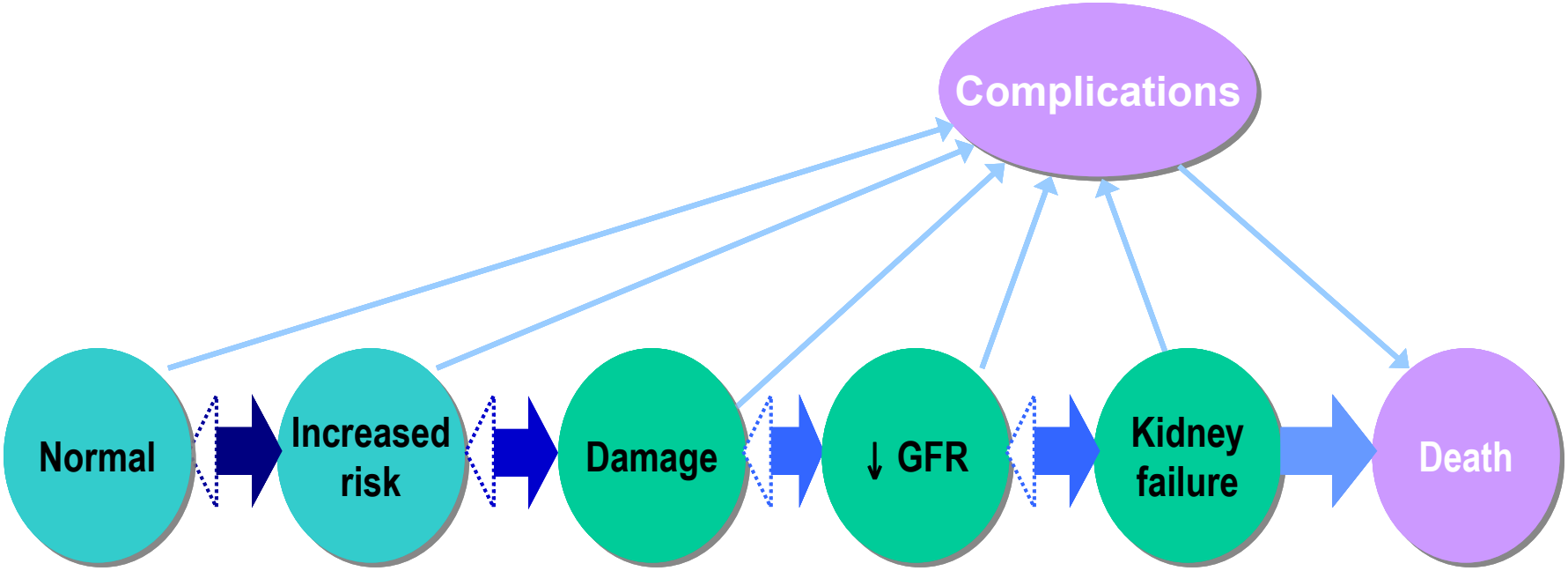


National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kid Dis 39 (suppl 1): S1-S266, 2002

Conceptual Model for CKD (revised)

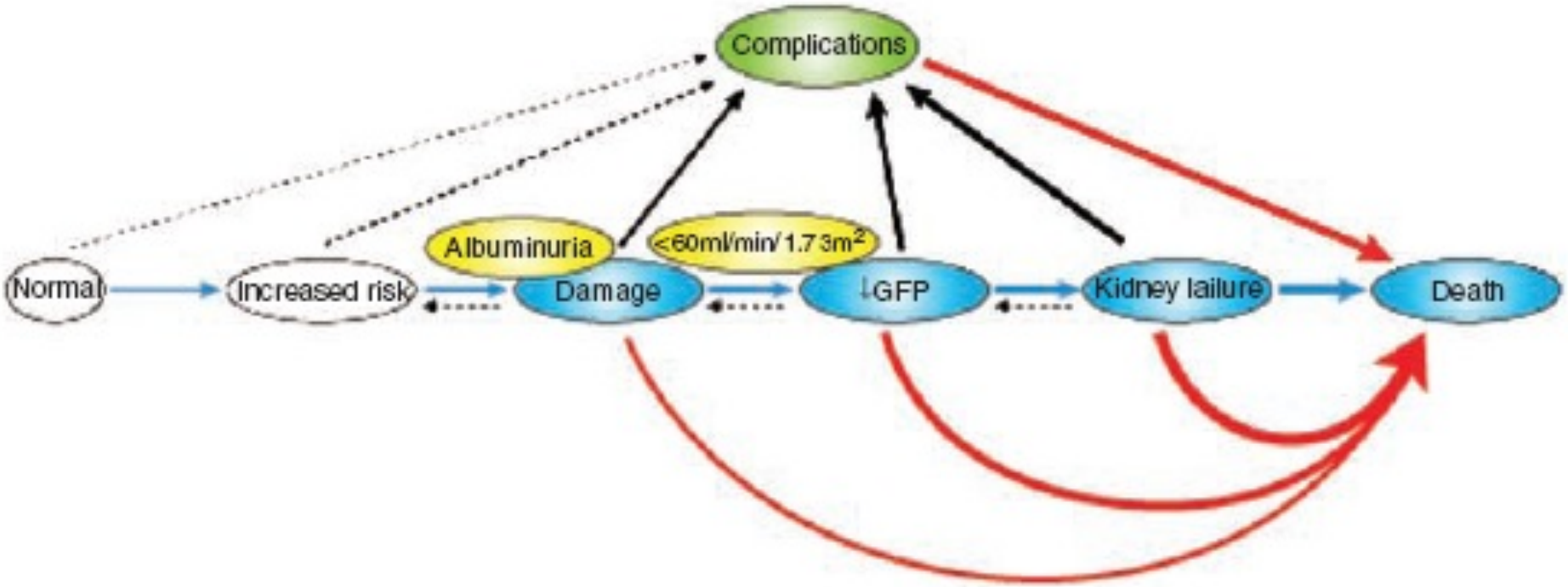
Levey, Stevens, Coresh

Am J Kidney Dis 2009; 53 S3: S4-S16



Conceptual Model for CKD (revised)

Eknoyan KI 2009



Definition and Classification of CKD

	KDOQI (2002) KDIGO (2004)	Epidemiologic Studies
Definition		
Structure	Pathology Markers (urine, blood, imaging) Transplant	Urine alb/creat >30 mg/g
Function	GFR <60 ml/min/1.73 m^2 (less than ½ the normal value in young adults)	eGFR <60 ml/min/1.73 m^2
Duration	>3 months	Single measurement
Classification		
Function	GFR >90, 60-89, 30-59, 15-29, <15	eGFR >90, 60-89, 30-59, 15-29, <15

Definition and Classification of CKD by GFR and Albuminuria (KDOQI 2002 and KDIGO 2004)

				Albuminuria (mg/g)	
				<30	>30
GFR Stages, Description and Range (mL/min/ 1.73m^2)	1	Normal or increased	>90		
	2	mild	60-89		
	3	moderate	30-59		
	4	severe	15-29		
	5	kidney failure	<15		

Definition

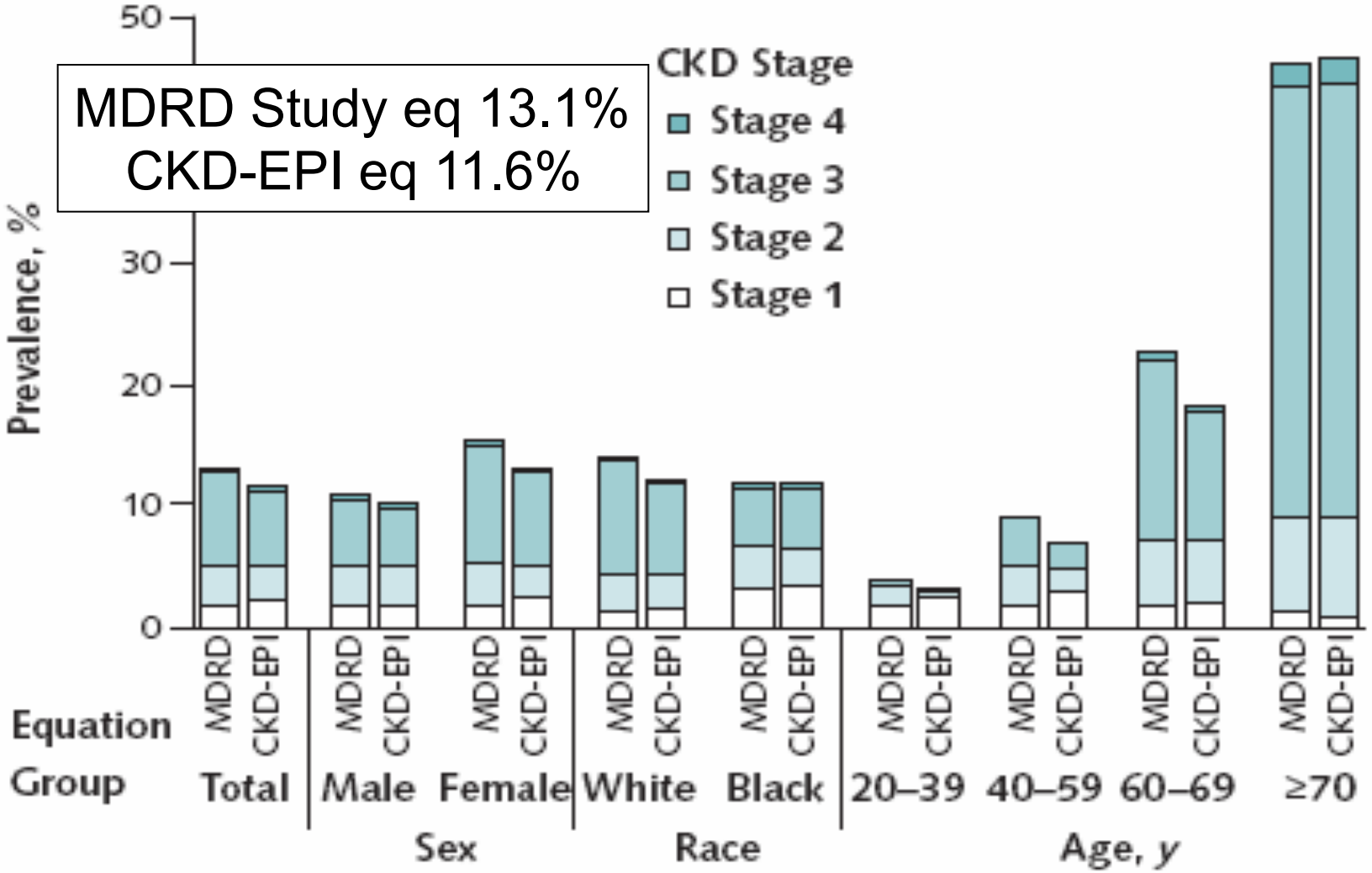
		Albuminuria	
		<30	>30
GFR	≥60		
	<60		

Classification

GFR	1	>90	
	2	60-89	
	3	30-59	
	4	15-29	
	5	<15	

Prevalence of CKD in US

NHANES 99-06 (Levey, Ann Intern Med 2009)



Winearls and Glassock
(Kidney Int 2009)

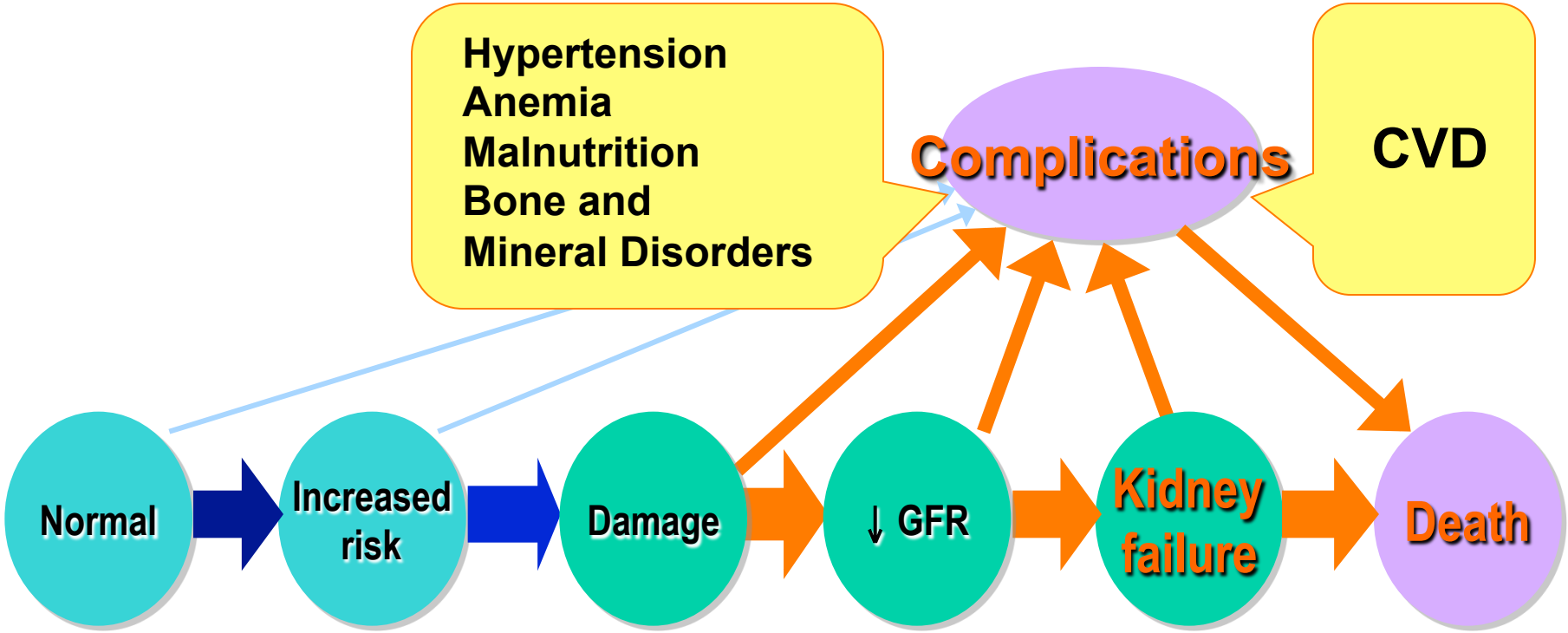
"… improbable estimates of prevalence rates."

"We believe that this decline in GFR with age is a natural and not a pathologic phenomenon."

US Prevalence of Chronic Diseases

(CDC Panel, AJKD 2009)

Diseases	US Prevalence N (%)
CKD	23,000,000 (11.6%)
Hypertension	65,000,000 (32.3%)
Diabetes	20,600,000 (9.6%)
CVD	71,300,000 (34.2%)



Outcomes of CKD

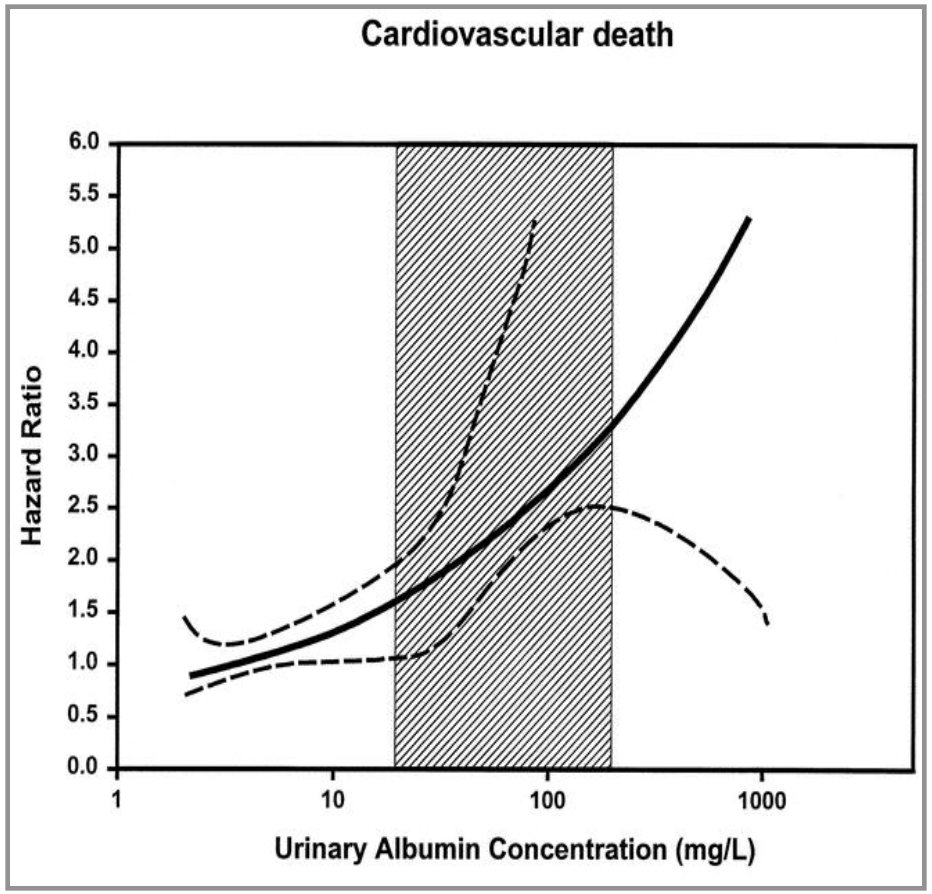
Winearls and Glassock
(Kidney Int 2009)

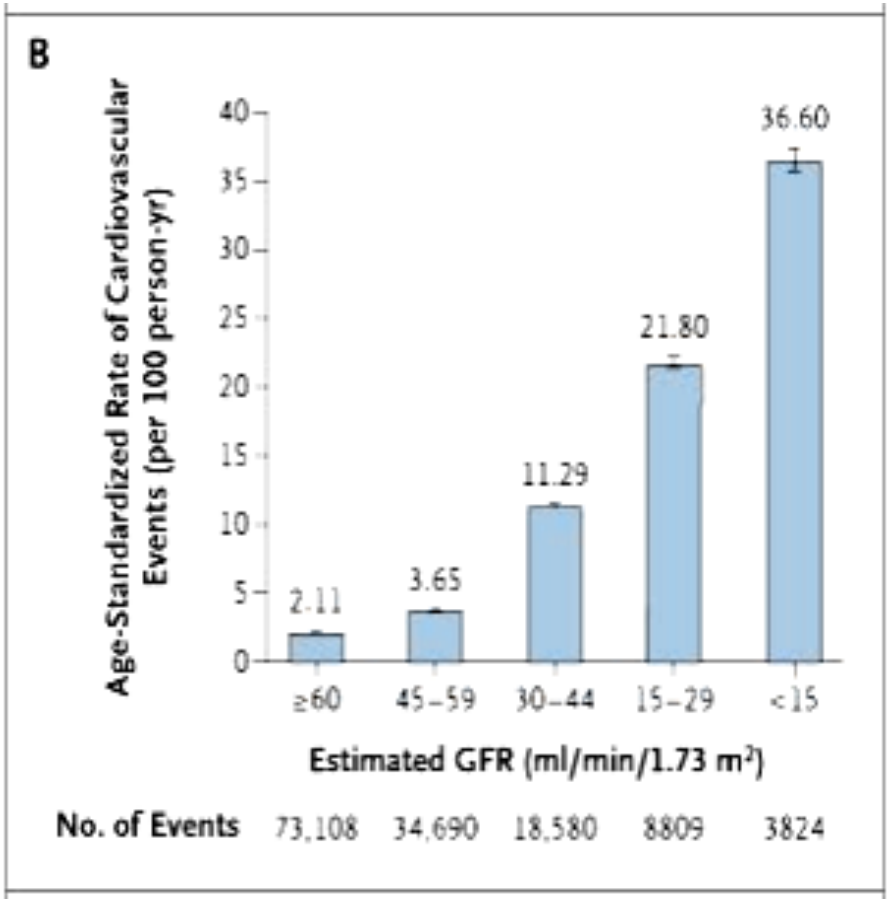
"… a reduction in kidney function causing effects attributable to functional insufficiency."

"… isolated reduced kidney function of uncertain significance."

CKD as a Risk Factor for CVD

Hillege (PREVEND), Circulation 2002
Go (Kaiser), NEJM 2004





Therapeutic Interventions in CKD

Raise GFR	None so far
Slowing Progression	Lower BP goal, ACEI, ARB
Preventing and Treating Complications	ESA, phosphate binders, vitamin D analogues, calcimimetics
Reducing CVD Risk	Lower BP goal, ACEI, ARB, statins (subgroup analyses)
Reducing Infection Risk	Immunizations
Improving Patient Safety	Accurate drug dosing; avoiding NSAID, contrast toxicity, phosphate bowel preps

Winearls and Glassock
(Kidney Int 2009)

"The nephrology community needs a revised staging system …"

- "… could distract nephrologists from their specialist role."
- "… will free nephrologists of the burden of monitoring stable patients."

CKD as a Public Health Problem: Role as Nephrologists

- Research
  - More work to define the outcomes
  - More work to define the treatments
- Patient care
  - Direct patient care – for patients with CKD stage 4 and others with high risk of complications and development of kidney failure
  - Define indications for referral and develop practice models – for patients with earlier stages of CKD
- Participate in medical education and public health efforts

Common, Harmful and Treatable

	Diabetes	**CKD**
Organ-specific disease	Yes	Yes
Symptoms	Few	Few
Functional marker	Diagnostic	Diagnostic
“Pre-stage”	Yes	Likely
Common in the elderly	Yes	Yes
Prognosis	Varies	Varies
Other outcomes (not organ specific)	Yes	Yes
CVD risk factor	Yes	Yes
Treatments to affect other outcomes	Yes	Yes

Common, Harmful and Treatable

	Diabetes	CKD
Causes	Several	Many
Structural markers	Few	Many
Treatments to improve function	Yes	No
Defined generalist role in clinical care	Yes	No
Defined subspecialist role in public health	Yes	No

Perspective

The debate over the definition and classification of CKD

- should be about improving outcomes for patients, not about nephrologists
- should be based on data, not on beliefs

Perspective

For this conference

- We have data on prognosis
  - transparent process
  - rigorous methods
- We do not have data on
  - cause of decreased GFR or albuminuria
  - “normal” aging vs. pathologic process
  - benefit of early detection
  - harm of labeling as “disease”
  - costs

Prognosis Matters

To improve patient outcomes:

- Risk for various outcomes could be better quantified.
- Treatments could be applied according to level of risk.
- Research efforts could be prioritized and conducted according to risk.

Prognosis Matters

To improve physician decisions:

- ACE inhibitors and ARB
- Intensive CVD risk reduction
- Drug dosing
- Preparation for invasive procedures
- Referral to nephrologists
- Preparation for dialysis and transplantation

Prognosis as a Tool: Questions for the Conference to Answer

Definition

1. Should the threshold value for eGFR be lower than 60 or differ by age >65?
2. Should the threshold value for albuminuria be higher than 30 or differ by age >65?

Prognosis as a Tool: Questions for the Conference to Answer

Classification

3. Should stages 1-2 be combined, separated by level of albuminuria, or both?
4. Should stage 3 be divided by eGFR <45, separated by level of albuminuria, or both?
5. Should stage 4 be separated by level of albuminuria?

Definition and Classification of CKD by GFR and Albuminuria (KDOQI 2002 and KDIGO 2005)

				Albuminuria (mg/g)	
				<30	>30
GFR Stages, Description and Range (mL/min/ 1.73m^2)	1	Normal or increased	>90		
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	4	severe	15-29		
	5	kidney failure	<15		

1. Definition: Should the threshold value for eGFR be lower than 60 or differ by age >65?

				Albuminuria (mg/g)	
				<30	>30
GFR Stages, Description and Range (mL/min/ 1.73m^2)	1	Normal or increased	>90		
	2	mild	60-89		
	3	moderate	30-59		
	4	severe	15-29		
	5	kidney failure	<15		

2. Definition: Should the threshold value for albuminuria be higher than 30 or differ by age >65?

				Albuminuria (mg/g)	
				<30	>30
GFR Stages, Description and Range (mL/min/ 1.73m^2)	1	Normal or increased	>90		
	2	mild	60-89		
	3	moderate	30-59		
	4	severe	15-29		
	5	kidney failure	<15		

3. Classification: Should stages 1-2 be combined, separated by level of albuminuria, or both?

				Albuminuria (mg/g)	
				<30	>30
GFR Stages, Description and Range (mL/min/ 1.73m^2)	1	Normal or increased	>90		
	2	mild	60-89		
	3	moderate	30-59		
	4	severe	15-29		
	5	kidney failure	<15		

4. Classification: Should stage 3 be divided by eGFR <45, separated by level of albuminuria, or both?

				Albuminuria (mg/g)	
				<30	**>30**
GFR Stages, Description and Range (mL/min/ 1.73m^2)	**1**	**Normal or increased**	**>90**		
	2	**mild**	**60-89**		
	3a	**mild-moderate**	**45-59**		
	3b	**moderate-severe**	**30-44**		
	4	**severe**	**15-29**		
	5	**kidney failure**	**<15**		

5. Classification: Should stage 4 be separated by level of albuminuria?

GFR Stages, Description and Range (mL/min/1.73m^2)				Albuminuria (mg/g)	
				<30	>30
	1	Normal or increased	>90		
	2	mild	60-89		
	3	moderate	30-59		
	4	severe	15-29		
	5	kidney failure	<15		

CKD Outcomes and Risk Factors

Outcomes (Partial List)

- Kidney Disease
  - Kidney failure (ESRD)
  - Declining eGFR
  - AKI
- Mortality and CVD
- Infections
- Fractures
- Drug side effects
- Cognition
- Physical function (frailty)
- Quality of Life
- Hospitalizations
- Cost

Risks (Parial List)

- Kidney Measures
  - eGFR
  - Albuminuria (proteinuria)
- Age, sex, race
- CVD
  - Clinical events
  - Subclinical measures
  - Risk factors
- Other comorbid conditions
- Education/ SES
- Treatments
  - Immunizations
  - Polypharmacy

Methods

- Uniform outcome definitions
- Uniform predictor definitions
- Uniform variable definitions
- Defined study populations
- Reference groups by study population
- Unadjusted and adjusted absolute and relative risks from survival analyses
- Individual studies (databook and limited presentations)
- Meta-analysis of group data (when possible)

Comments on Our Approach

Strengths

- Systematic search for general populations
- Large and varied study populations
- Uniform design and analytic approach
- Individual and group-level meta-analysis
- Best we can do at this time, and better than 10 years ago.
- Systematic and well-doumented method that can be updated as more data accrue (in 2020!).

Comments on Our Approach

Limitations

- Data driven – we only have data on the outcomes that have been studied
- Focuses primarily on risk
- Different reference ranges for different populations
- Potential selection bias for high-risk and CKD populations
- Creatinine calibration
- Estimating equations
- Spot urine samples
- Heterogeneity in meta-analysis

Next steps

- Review of data in conference
- Breakout sessions:

  Session 1. Evaluate risks

  Session 2. Decide about modifications to definition and classification
- Consensus, where possible; identification of topics for further research for ongoing controversy

Next steps

- Publication (conference report, meta-analysis as original research, data book entries as sources for reference with permission)
- Guideline update (including new data based on prognosis)
- Implementation in clinical practice and public health

Thank you