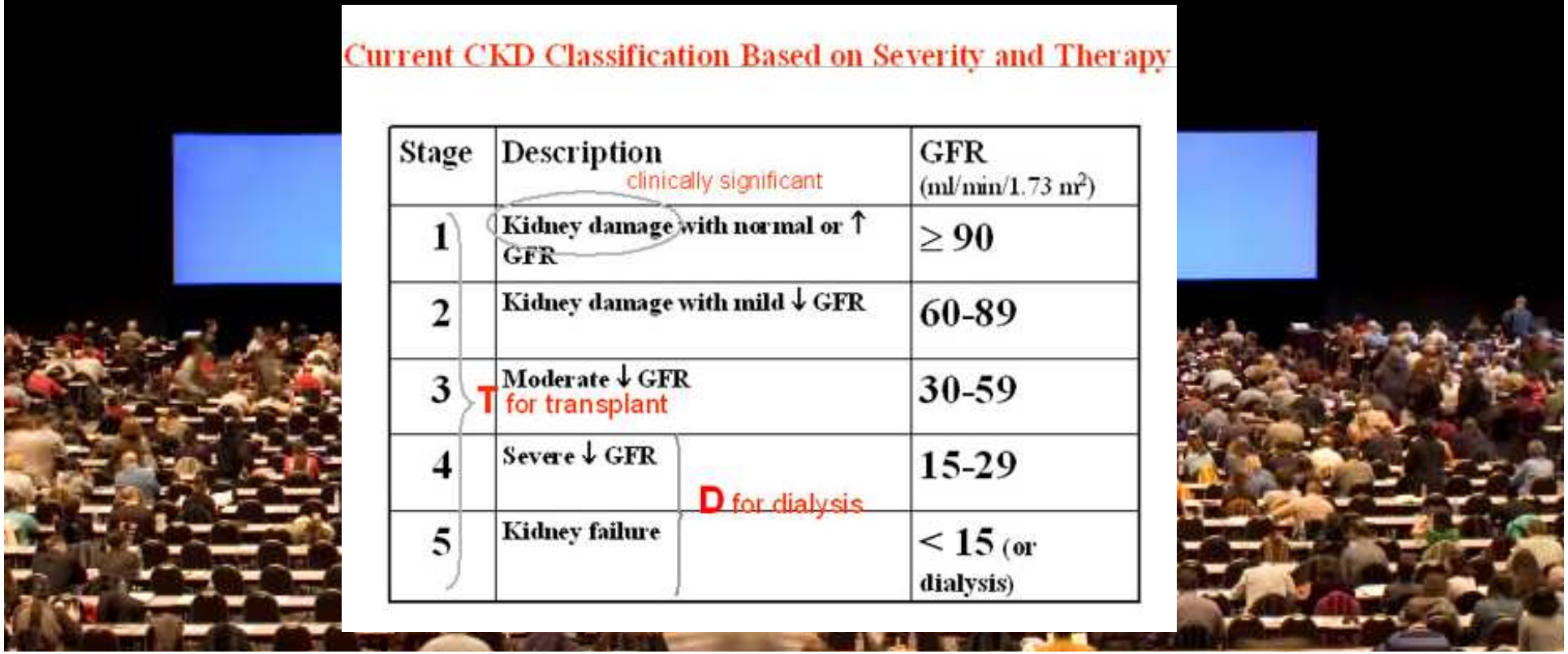

Controversies in Chronic Kidney Disease
Conall O'Seaghdha
Nephrologist, Beaumont Hospital
TUN Conference, November 29th 2013

2002 National Kidney Foundation Spring Clinical Meeting

K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification



Current CKD Classification Based on Severity and Therapy

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

clinically significant

T for transplant

D for dialysis

AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

Mark J. Sarnak, MD, Cochair; Andrew S. Levey, MD, Cochair; Anton C. Schoolwerth, MD, Cochair; Josef Coresh, MD, PhD; Bruce Culleton, MD; L. Lee Hamm, MD; Peter A. McCullough, MD, MPH; Bertram L. Kasiske, MD; Ellie Kelepouris, MD; Michael J. Klag, MD, MPH; Patrick Parfrey, MD; Marc Pfeffer, MD, PhD; Leopoldo Raij, MD; David J. Spinosa, MD; Peter W. Wilson, MD

Chronic kidney disease[1] (CKD) is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. The number of individuals with kidney failure treated by dialysis and transplantation exceeded 320 000 in 1998 and is expected to surpass 650 000 by 2010.[1,2] There is an even higher prevalence of earlier stages of CKD (Table 1).[1,3] Kidney failure requiring treatment with dialysis or transplantation is the most visible outcome of CKD. However, cardiovascular disease (CVD) is also frequently associated with CKD, which is important because individuals with CKD are more likely to die of CVD than to develop kidney failure,[4] CVD in CKD is treatable and potentially preventable, and CKD appears to be a risk factor for CVD. In 1998, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD.[5] This report showed that there was a high prevalence of CVD in CKD and that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population (Figure 1 and Table 2).[6–18] The task force recommended that patients with CKD be considered in the "highest risk group" for subsequent CVD events and that treatment recommendations based on CVD

Definition and Classification of Stages of Severity and Types of CKD

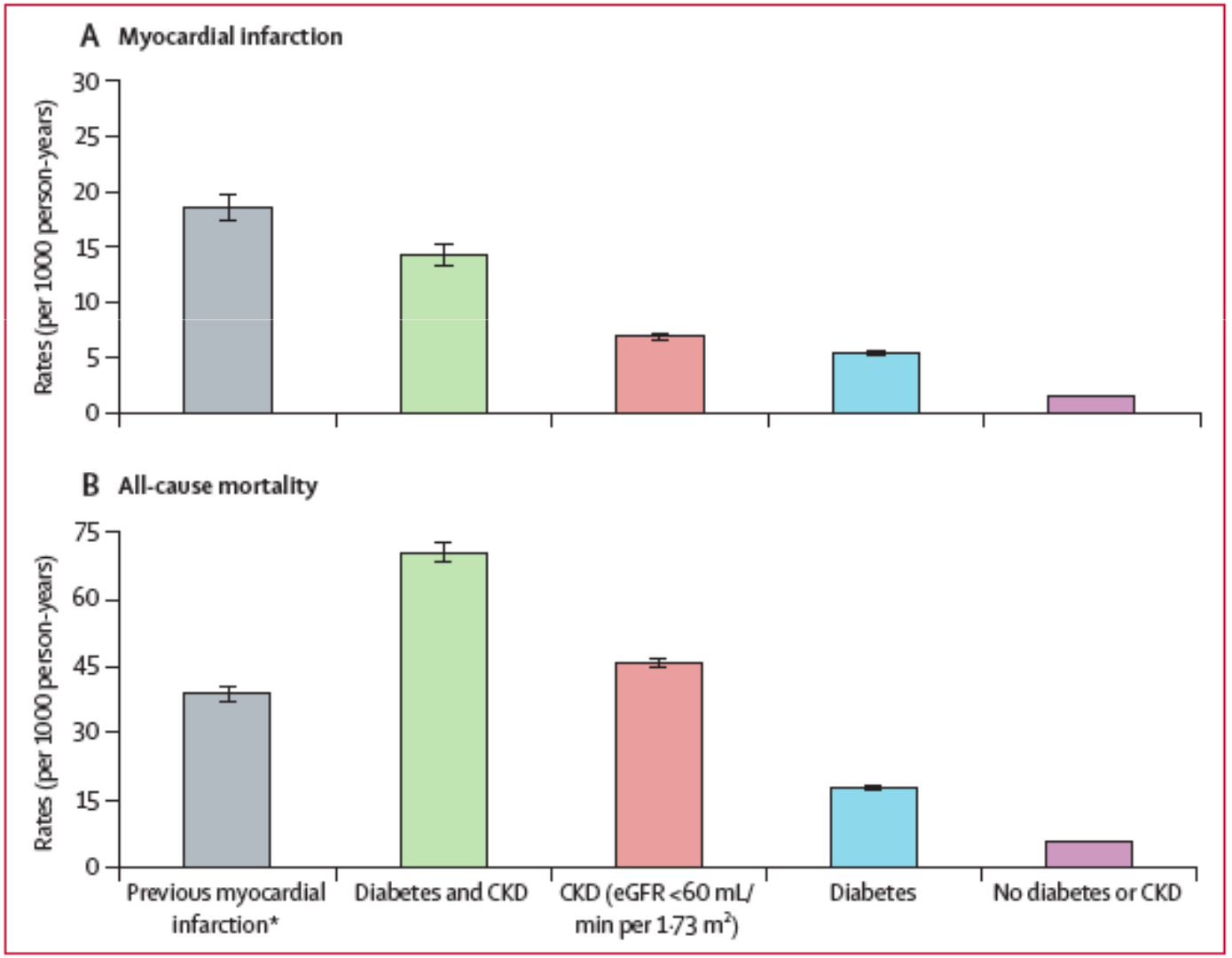
In 2002, the NKF published clinical practice guidelines on evaluation, classification, and risk stratification in CKD.[3] In these guidelines, CKD is defined as either (1) kidney damage for ≥3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR), or (2) GFR <60 mL · min^{-1} per 1.73 m^2 for ≥3 months, with or without kidney damage (Table 1).

Kidney damage is ascertained by either kidney biopsy or markers of kidney damage, such as proteinuria, abnormal urinary sediment, or abnormalities on imaging studies. The finding of proteinuria not only defines the presence of CKD but also has important implications for diagnosis of the type of kidney disease and is associated with a worse prognosis for both kidney disease progression and the development of CVD. Proteinuria is variously defined (Table 3).[3,19–21] Measurement of albumin-to-creatinine ratio or total protein-to-creatinine ratio in untimed "spot" urine samples is recommended for assessment of proteinuria.[3]

GFR <60 mL · min^{-1} per 1.73 m^2 is selected as the cutoff value for definition of CKD because it represents a reduction

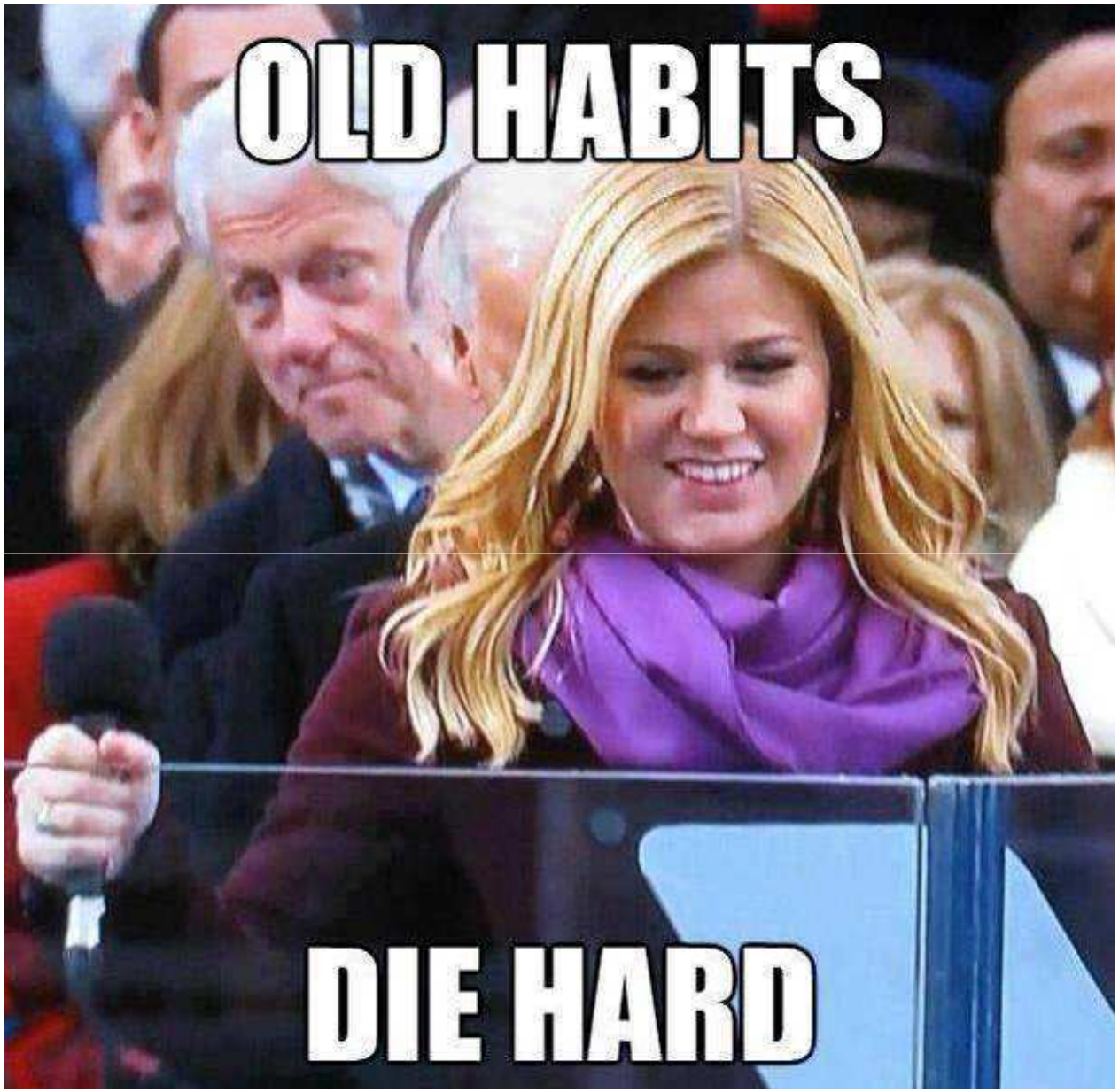
Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study

Marcello Tonelli, Paul Muntner, Anita Lloyd, Braden J Manns, Scott Klarenbach, Neesh Pannu, Matthew T James, Brenda R Hemmelgarn, for the Alberta Kidney Disease Network



Lancet 2012; 380: 807–14

chronic kidney disease was lower than for people with diabetes or previous myocardial infarction. Consequently, Tonelli and colleagues' analysis does not support classification of chronic kidney disease as a coronary heart disease risk equivalent. Much of the coronary risk in patients with chronic kidney disease is probably mediated by chronic exposure to cardiovascular risk factors.


OLD HABITS
DIE HARD

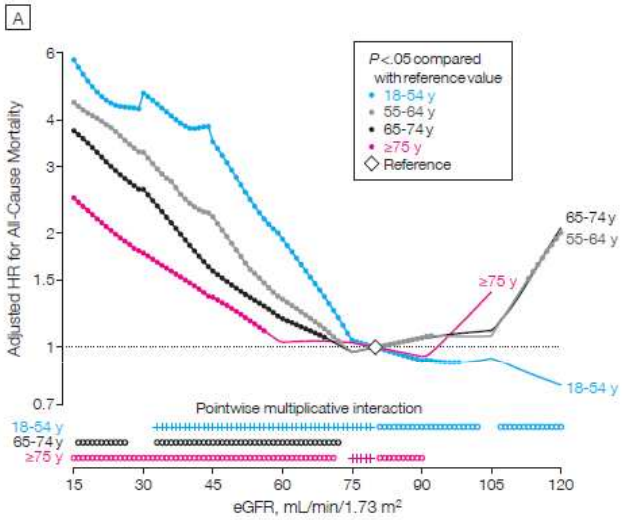
Unchallenged assumptions of the CKD era

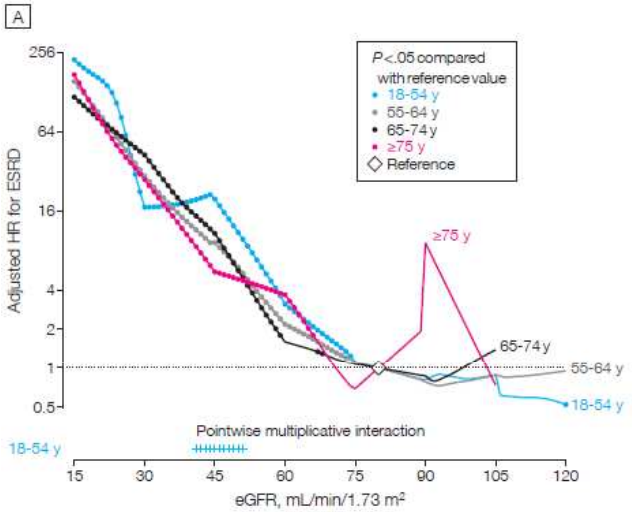
1. Much of the risk for adverse events in patients with CKD is explained by chronic exposure to risk factors such as age, hypertension and diabetes
2. Much of the risk for developing CKD is due to these same risk factors, particularly hypertension, and CKD is itself just another manifestation of vascular disease (ARVD)
3. Progression of CKD can largely be prevented by controlling cardiovascular risk factors

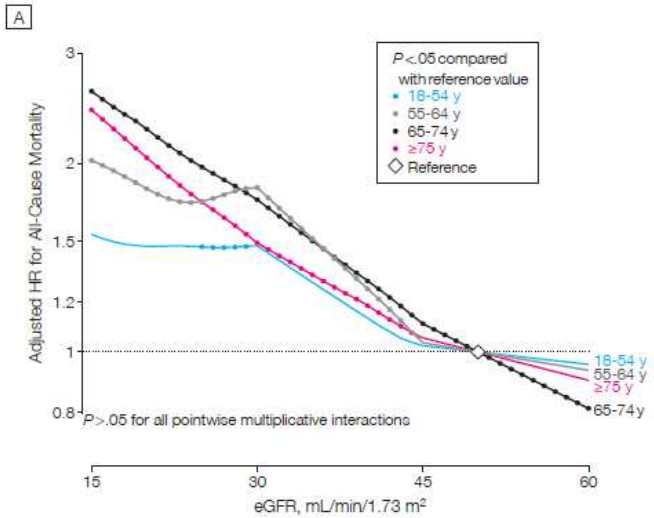
ONLINE FIRST

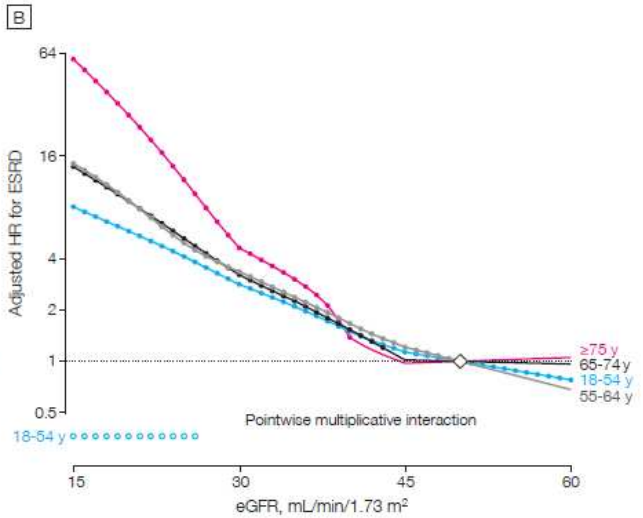
Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

Stein I. Hallan, MD, PhD
Kunihiro Matsushita, MD, PhD
Yingying Sang, MS
Bakhtawar K. Mahmoodi, MD, PhD
Corri Black, MBChB, MSc, FFPH
Areef Ishani, MD, MS
Nanne Kleefstra, MD, PhD
David Naimark, MD, MSc, FRCP(C)
Paul Roderick, MD, FRCP
Marcello Tonelli, MD, SM
Jack F. M. Wetzels, MD, PhD
Brad C. Astor, PhD, MPH
Ron T. Gansevoort, MD, PhD
Adeera Levin, MD
Chi-Pang Wen, MD, MPH, DrPH
Josef Coresh, MD, PhD
for the Chronic Kidney Disease Prognosis Consortium





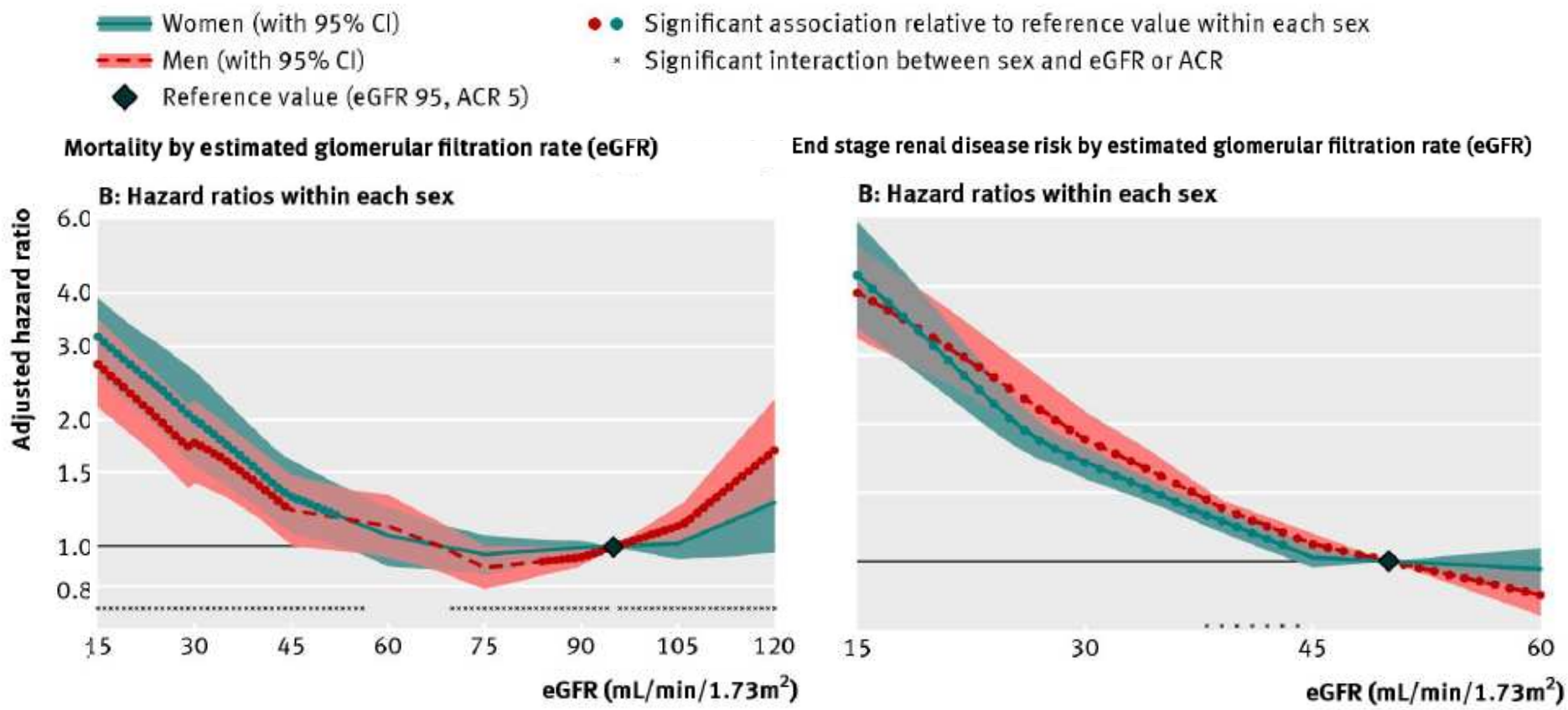




BMJ

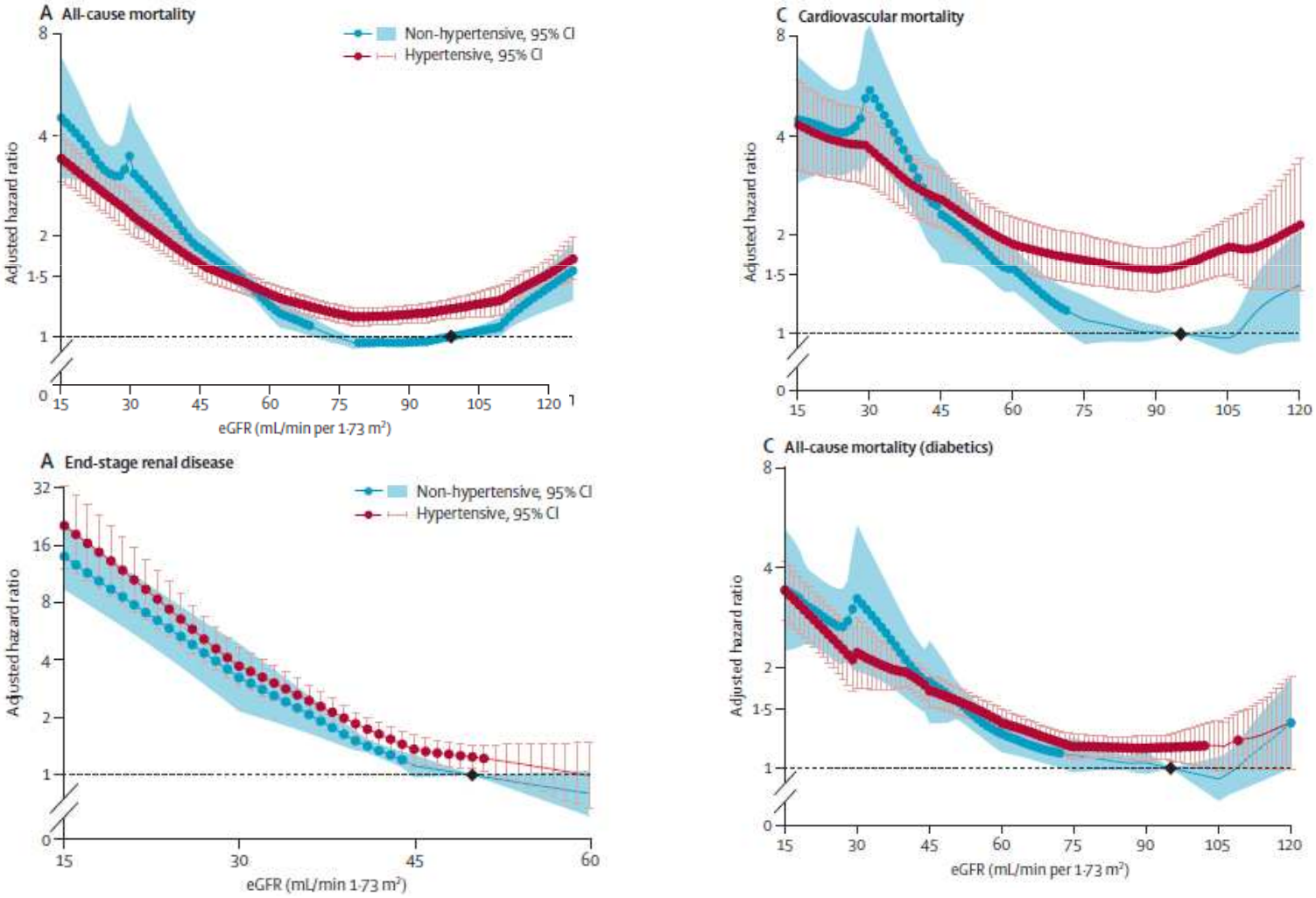
RESEARCH

Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis



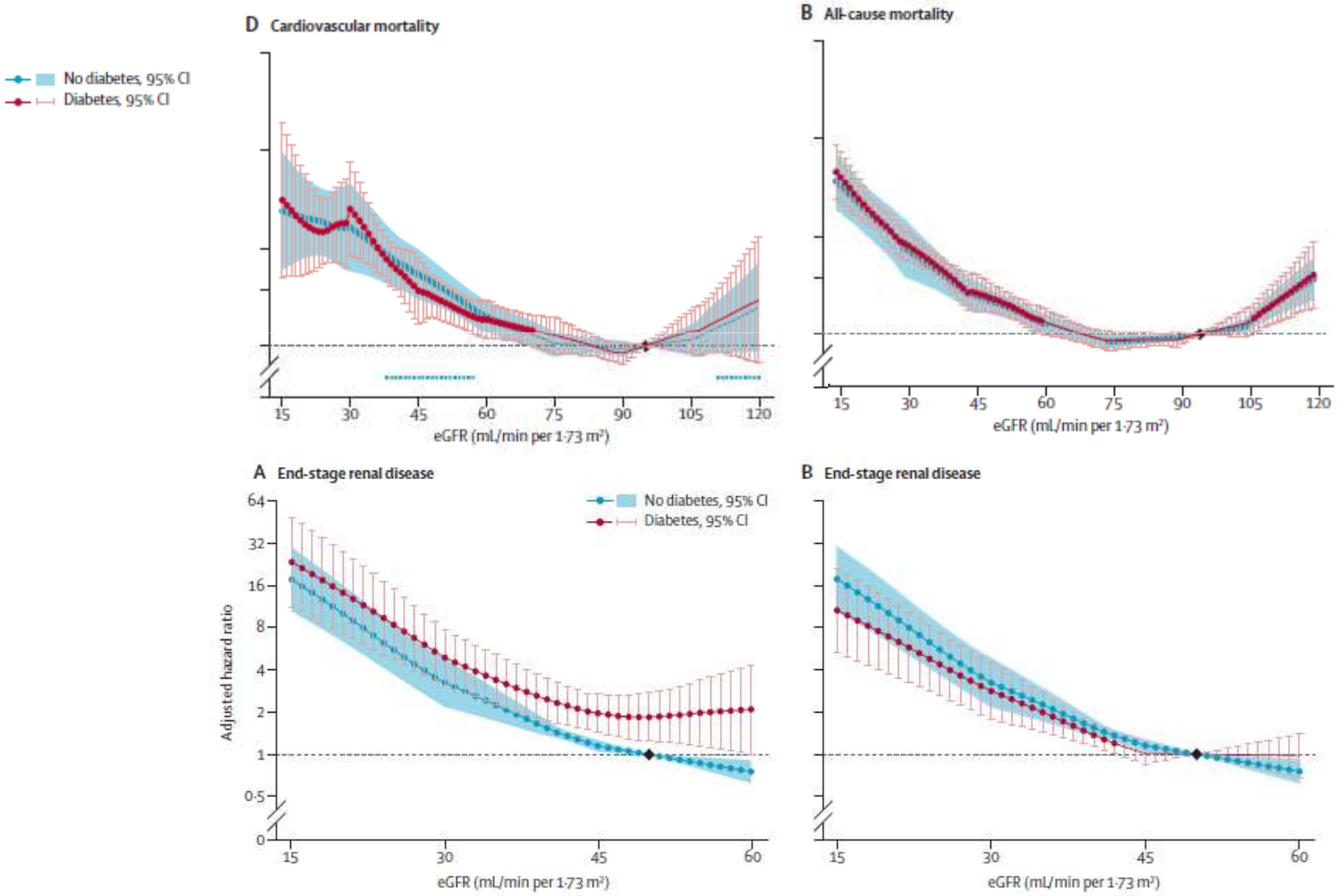
Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis

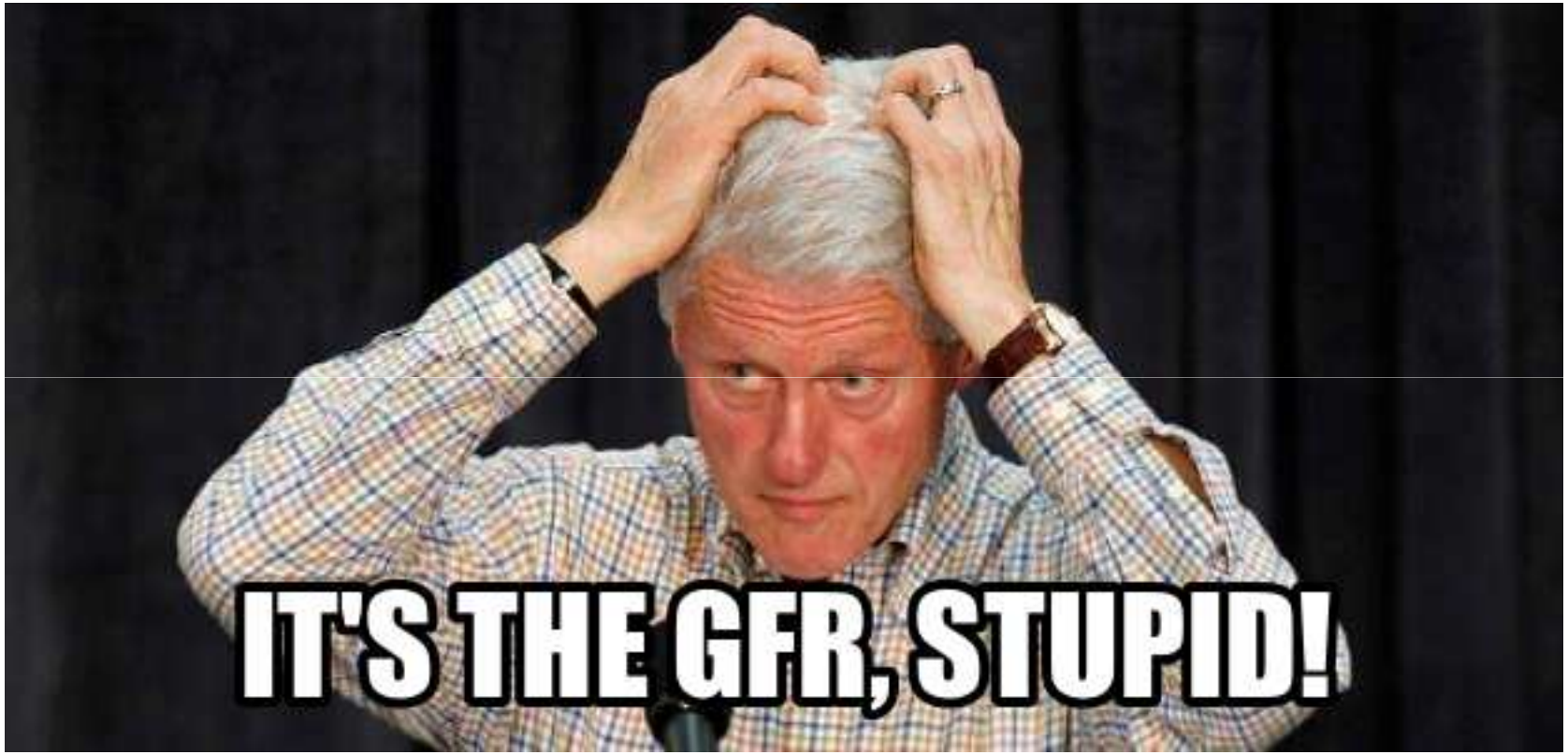
Bakhtawar K Mahmoodi, Kunihiro Matsushita, Mark Woodward, Peter J Blankestijn, Massimo Cirillo, Takayoshi Ohkubo, Peter Rossing, Mark J Sarnak, Bénédicte Stengel, Kazumasa Yamagishi, Kentaro Yamashita, Luxia Zhang, Josef Coresh, Paul E de Jong, Brad C Astor, for the Chronic Kidney Disease Prognosis Consortium



Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hiddo J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium




IT'S THE GFR, STUPID!

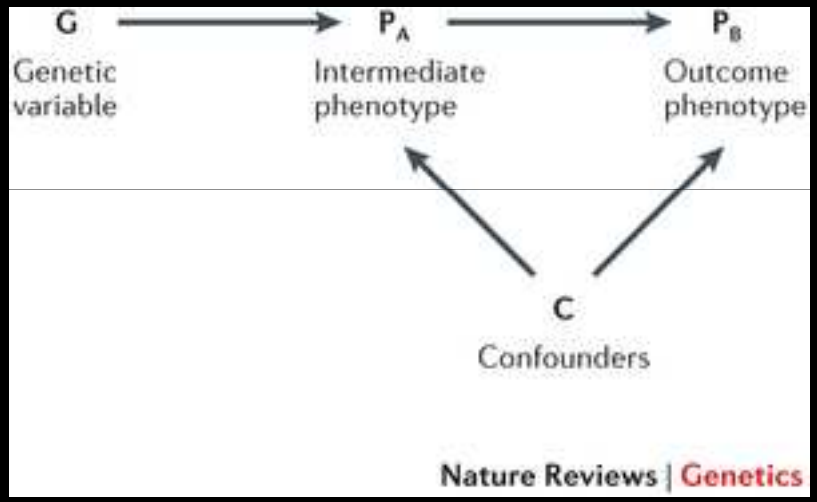
Unchallenged assumptions of the CKD era

1. Much of the risk for adverse events in patients with CKD is explained by chronic exposure to risk factors such as age, hypertension and diabetes
2. Much of the risk for developing CKD is due to these same risk factors, particularly hypertension, and CKD is itself just another manifestation of vascular disease (ARVD)
3. Progression of CKD can largely be prevented by controlling cardiovascular risk factors

Importance of Blood Pressure Control in Chronic Kidney Disease

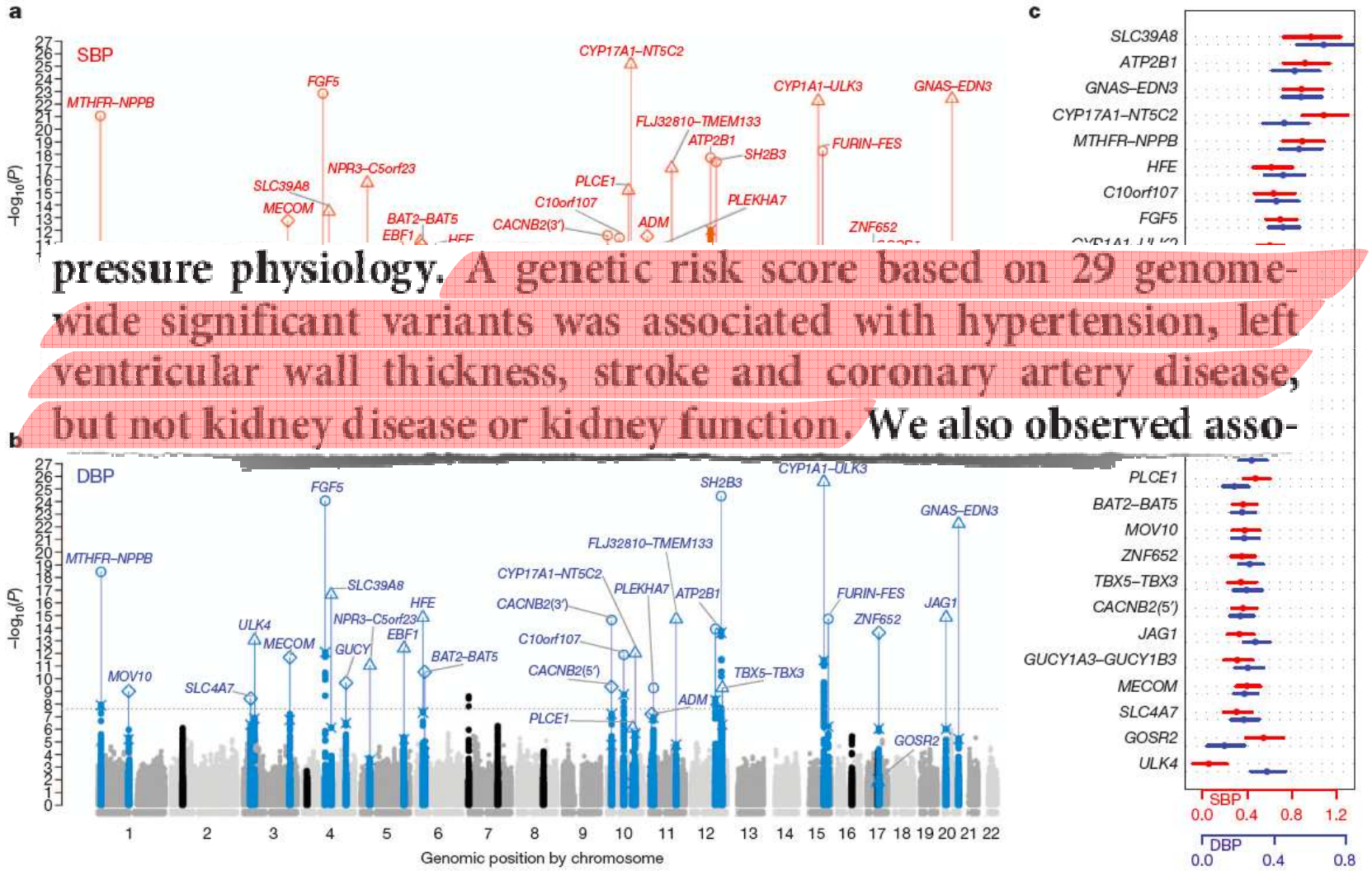
Maura Ravera, Michela Re, Luca Deferrari, Simone Vettoretti, and Giacomo Deferrari
Division of Nephrology, Dialysis and Transplantation, Department of Internal Medicine, University of Genoa
Department of Cardio-Nephrology Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

High BP can be either a cause or a consequence of CKD. High
3P may develop early in the course of CKD and can be asso-
:iated with adverse outcomes such as worsening renal function
ınd development of cardiovascular disease. Hypertension is a
najor promoter of the decline in GFR in both diabetic and


G
Genetic variable
P_A
Intermediate phenotype
P_B
Outcome phenotype
C
Confounders
Nature Reviews | Genetics

Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk

The International Consortium for Blood Pressure Genome-Wide Association Studies



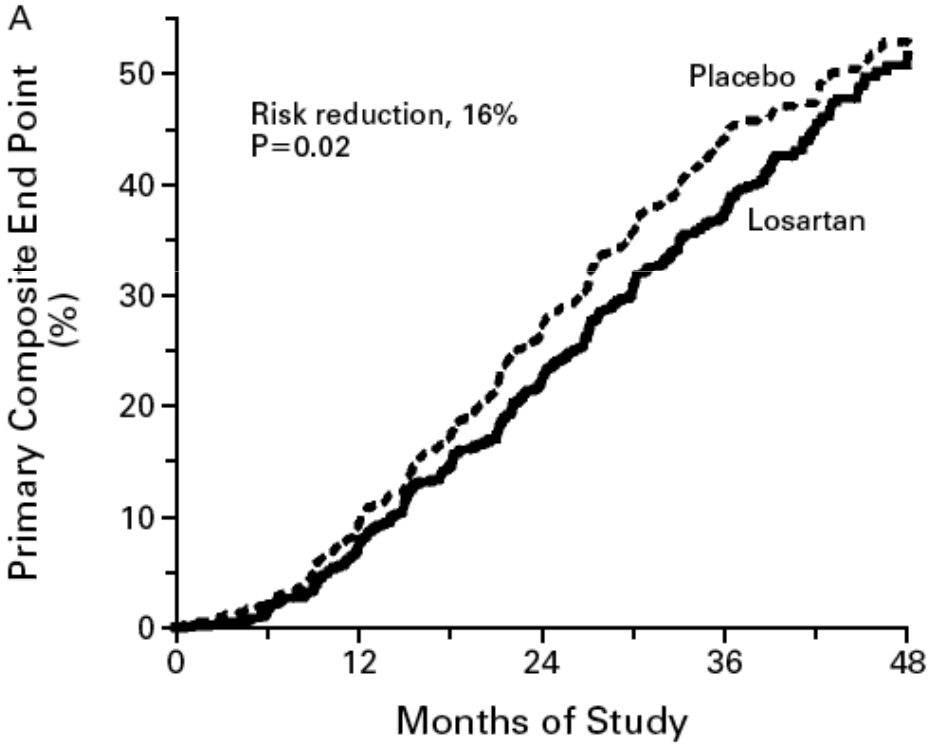
pressure physiology. A genetic risk score based on 29 genome-wide significant variants was associated with hypertension, left ventricular wall thickness, stroke and coronary artery disease, but not kidney disease or kidney function. We also observed asso-

Unchallenged assumptions of the CKD era

1. Much of the risk for adverse events in patients with CKD is explained by chronic exposure to risk factors such as age, hypertension and diabetes
2. Much of the risk for developing CKD is due to these same risk factors, particularly hypertension, and CKD is itself just another manifestation of vascular disease (ARVD)
3. Progression of CKD can largely be prevented by controlling cardiovascular risk factors

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*



NO. AT RISK

Placebo	762	689	554	295	36
Losartan	751	692	583	329	52

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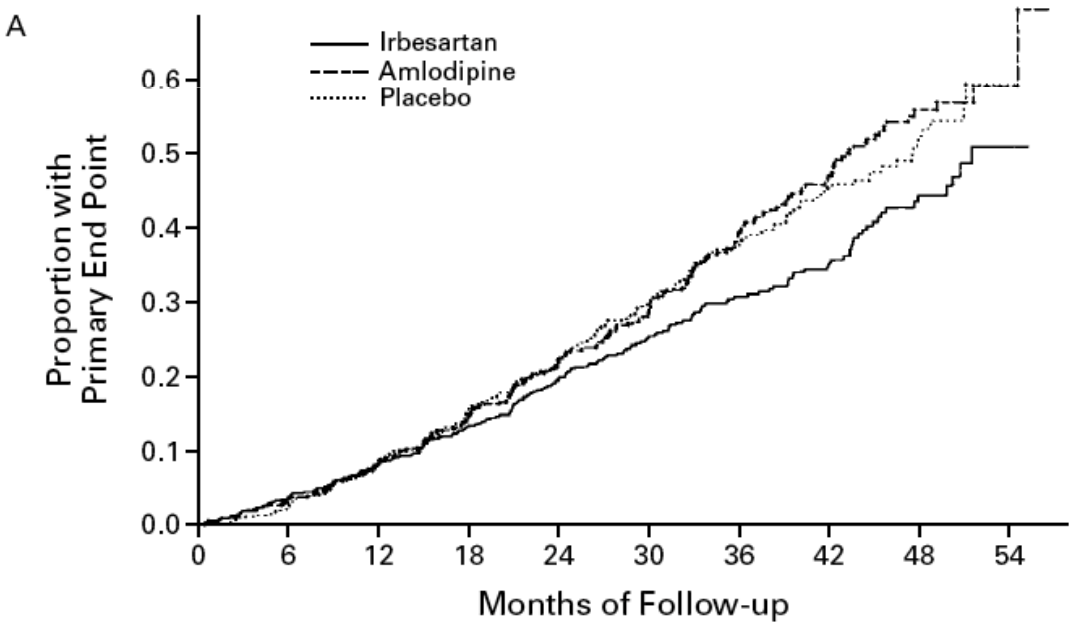
RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*

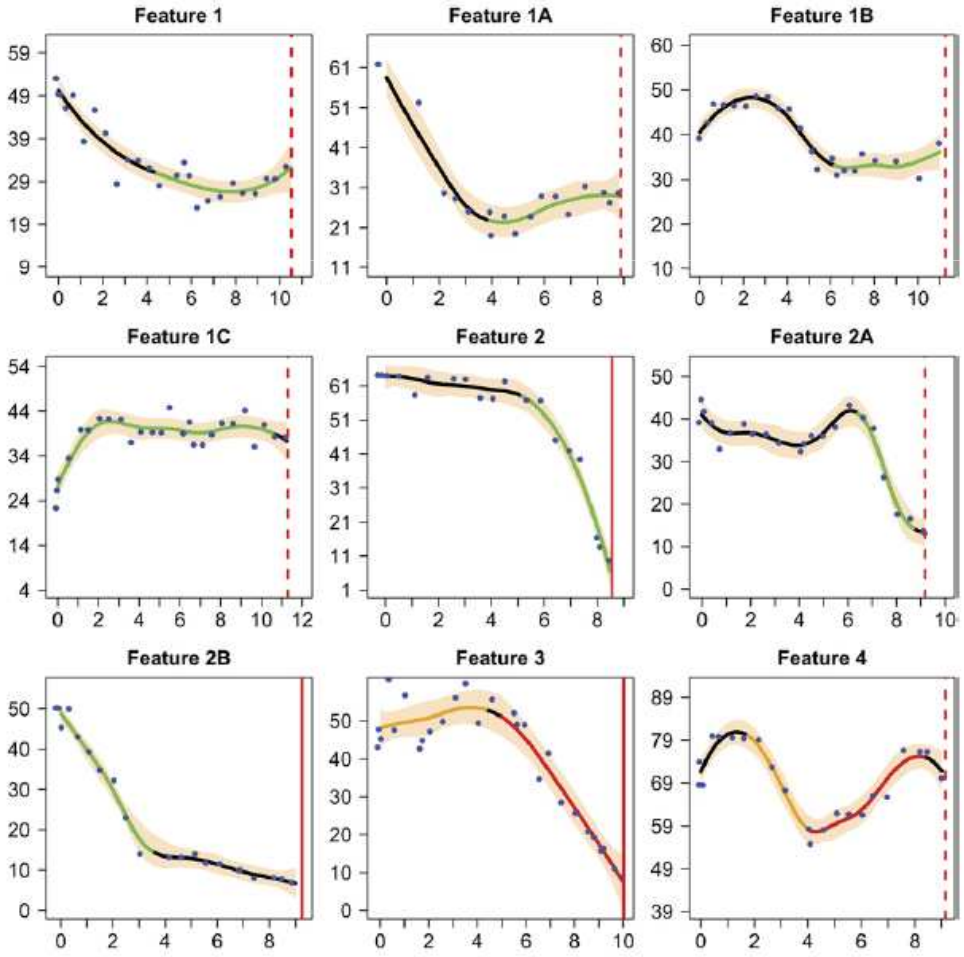


No. at Risk									
Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
Placebo	568	551	512	471	401	280	190	122	53

AJKD
Original Investigation

Longitudinal Progression Trajectory of GFR Among Patients With CKD

Liang Li, PhD,[1] Brad C. Astor, PhD,[2] Julia Lewis, MD,[3] Bo Hu, PhD,[1] Lawrence J. Appel, MD, MPH,[4] Michael S. Lipkowitz, MD,[5] Robert D. Toto, MD,[6] Xuelei Wang, MS,[7] Jackson T. Wright Jr, MD, PhD,[7] and Tom H. Greene, PhD[8]

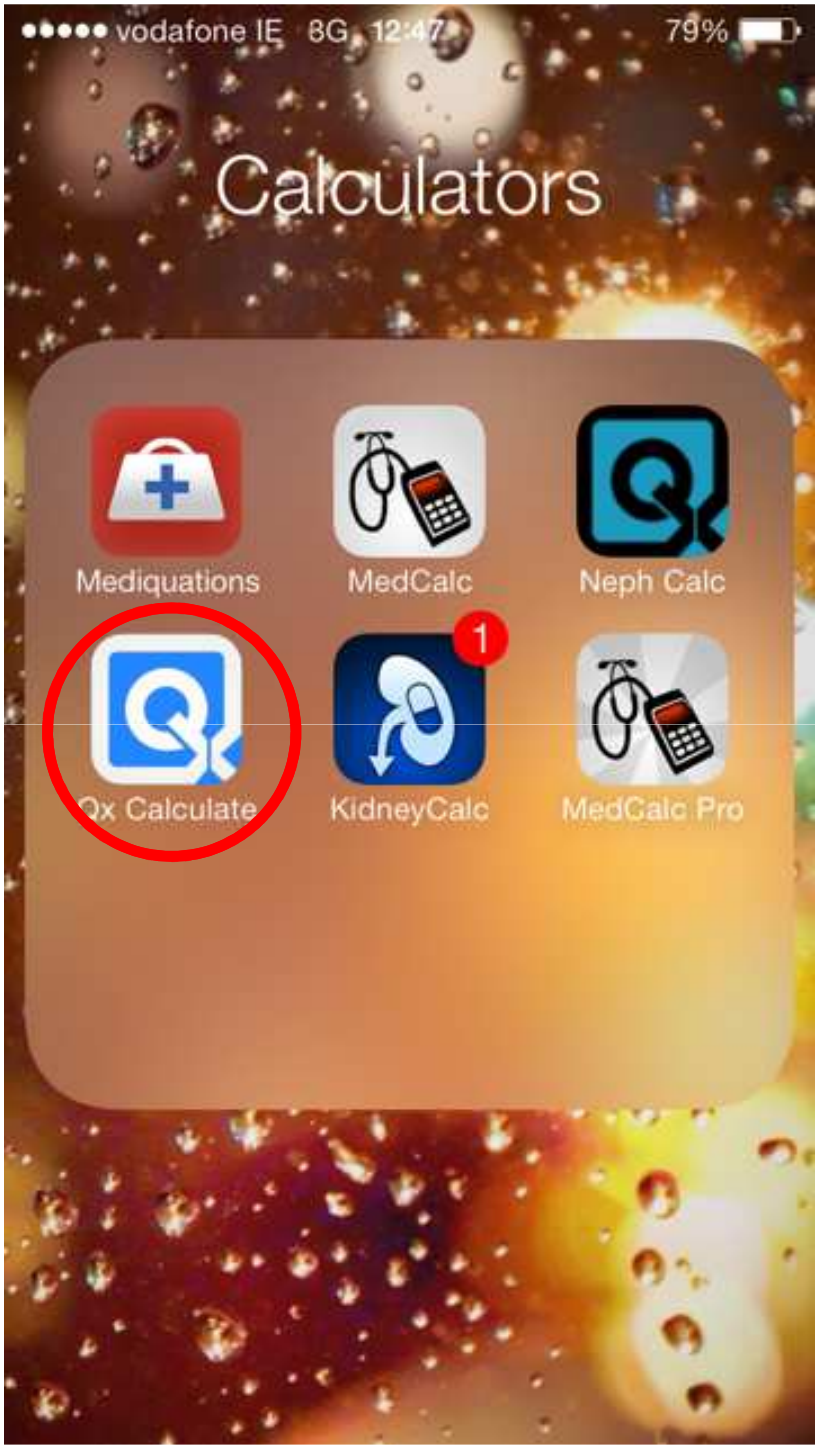


1. Stable or increasing (58%)
2. Fast decline (32%)
3. Stable or increasing followed by fast decline (5.8%)
4. Fast decline followed by stable or increasing (3.4%)

A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure

Table 2. Hazard Ratios and Goodness of Fit for Sequential Models in the Development Data Set[a]

	Models						
Variable	1	2	3	4	5	6	7
Baseline GFR, per 5 mL/min/1.73 m^2		0.54	0.57	0.58	0.60	0.61	0.64
Age, per 10 y	0.86	0.75	0.80	0.80	0.79	0.82	0.82
Male sex	1.03[b]	1.46	1.26	1.27	1.34	1.16[b]	1.26
Log spot urine ACR[c]			1.60	1.61	1.55	1.42	1.37
Diabetes				0.86[b]			0.88[b]
Hypertension				1.17[b]			0.89[b]
Systolic BP, per 10 mm Hg					1.15		1.14
Diastolic BP, per 10 mm Hg					1.10		1.15
Body weight, per 10 kg					0.91		0.91
Serum albumin, per 0.5 g/dL						0.84	0.83
Serum phosphate, per 1.0 mg/dL						1.27	1.34
Serum bicarbonate, per 1.0 mEq/L						0.92	0.93
Serum calcium, per mg/dL						0.81	0.82
C statistic[d]	0.56	0.89	0.91	0.91	0.92	0.92	0.92
Akaike Information Criterion[d]	5553	4834	4520	4521	4463	4432	4378
P value		<.001	<.001	.40	<.001	<.001	<.001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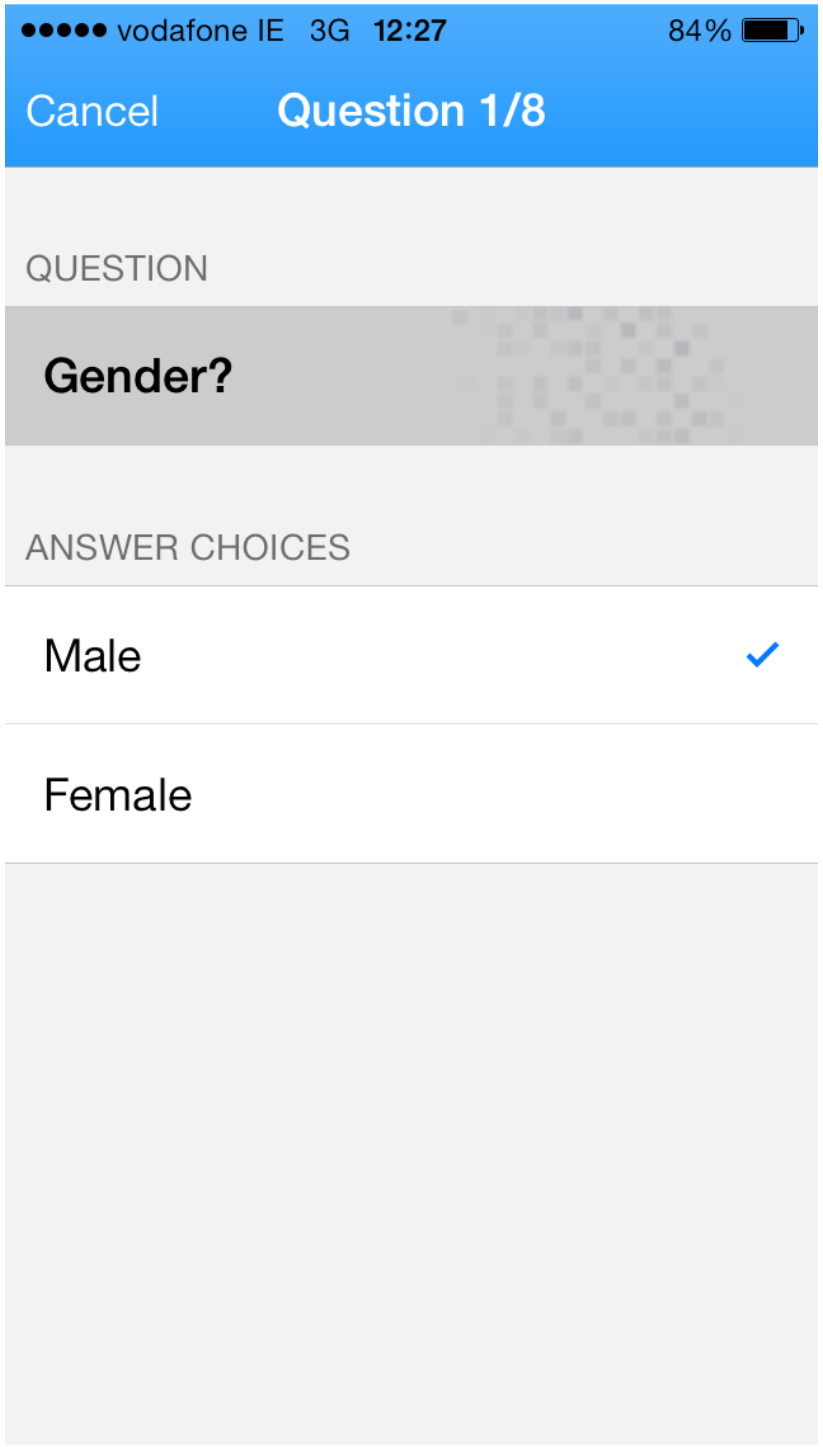
Calculators
Mediquations
MedCalc
Neph Calc
Qx Calculate
KidneyCalc
1
MedCalc Pro


vodafone IE 3G 12:27
84%
Cancel
Question 1/8
QUESTION
Gender?
ANSWER CHOICES
Male
Female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Question 2/8
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QUESTION
Age?
70
Years
1
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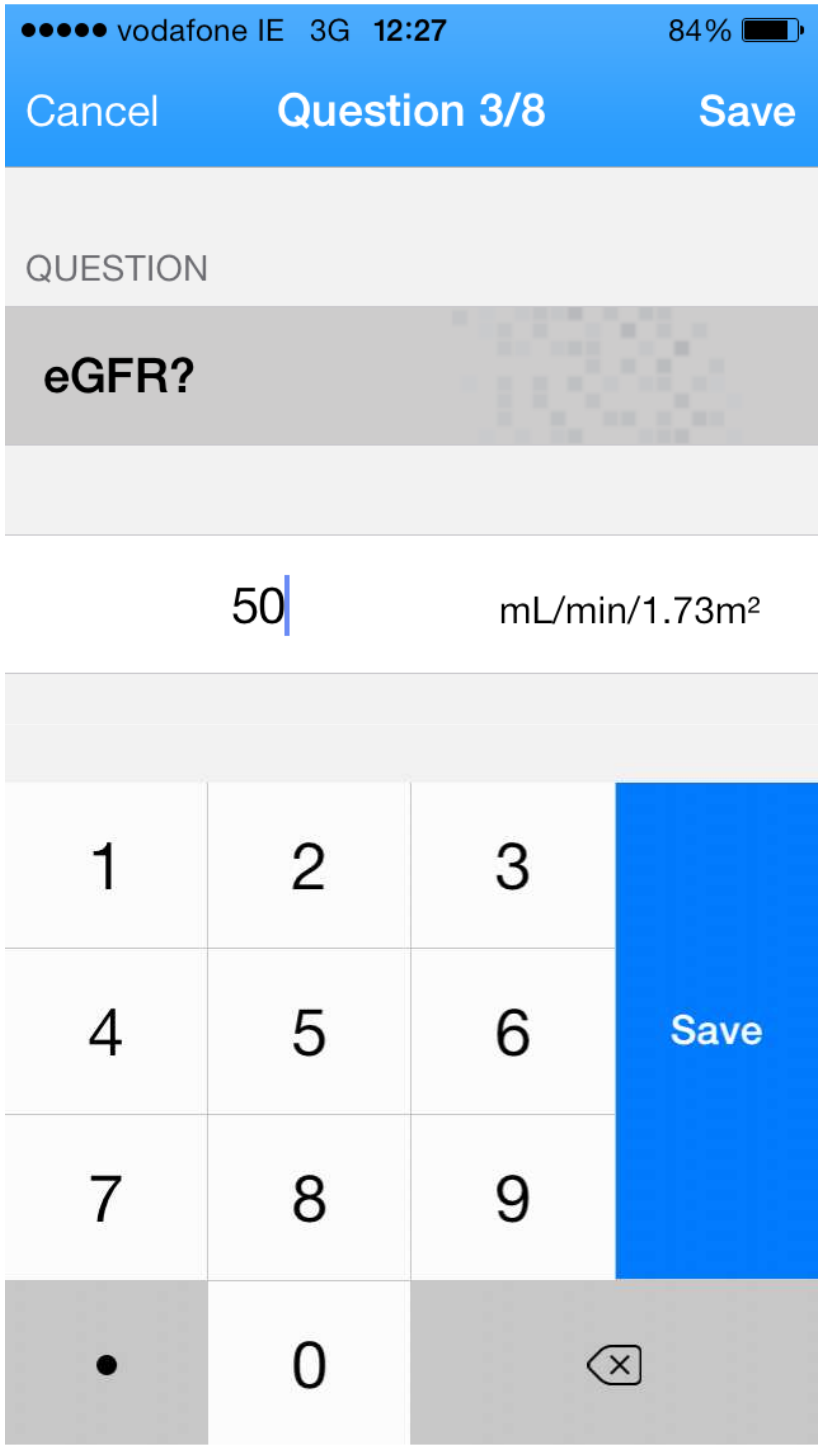
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Question 3/8
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QUESTION
eGFR?
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mL/min/1.73m²
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2
3
4
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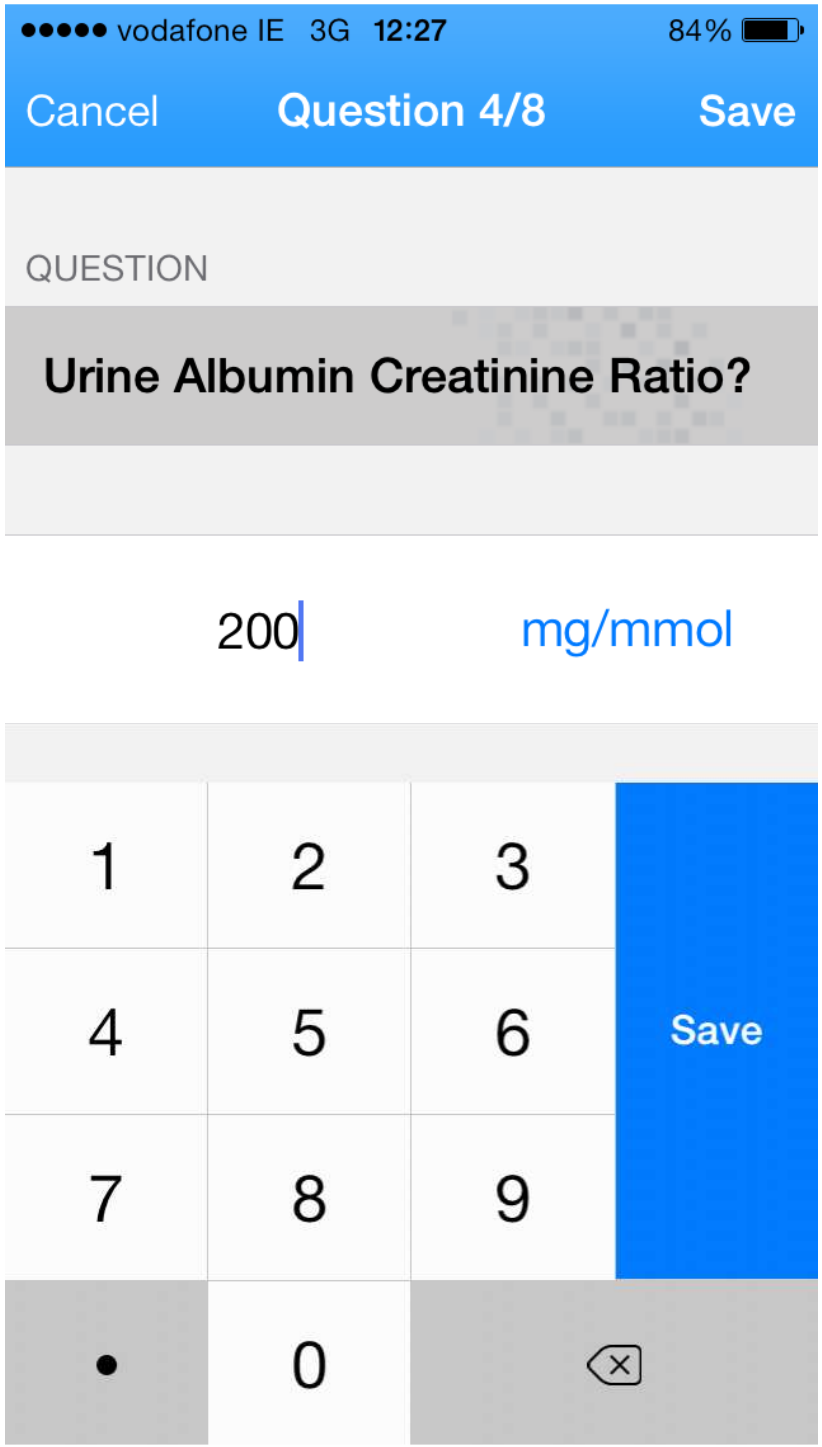
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mg/mmol
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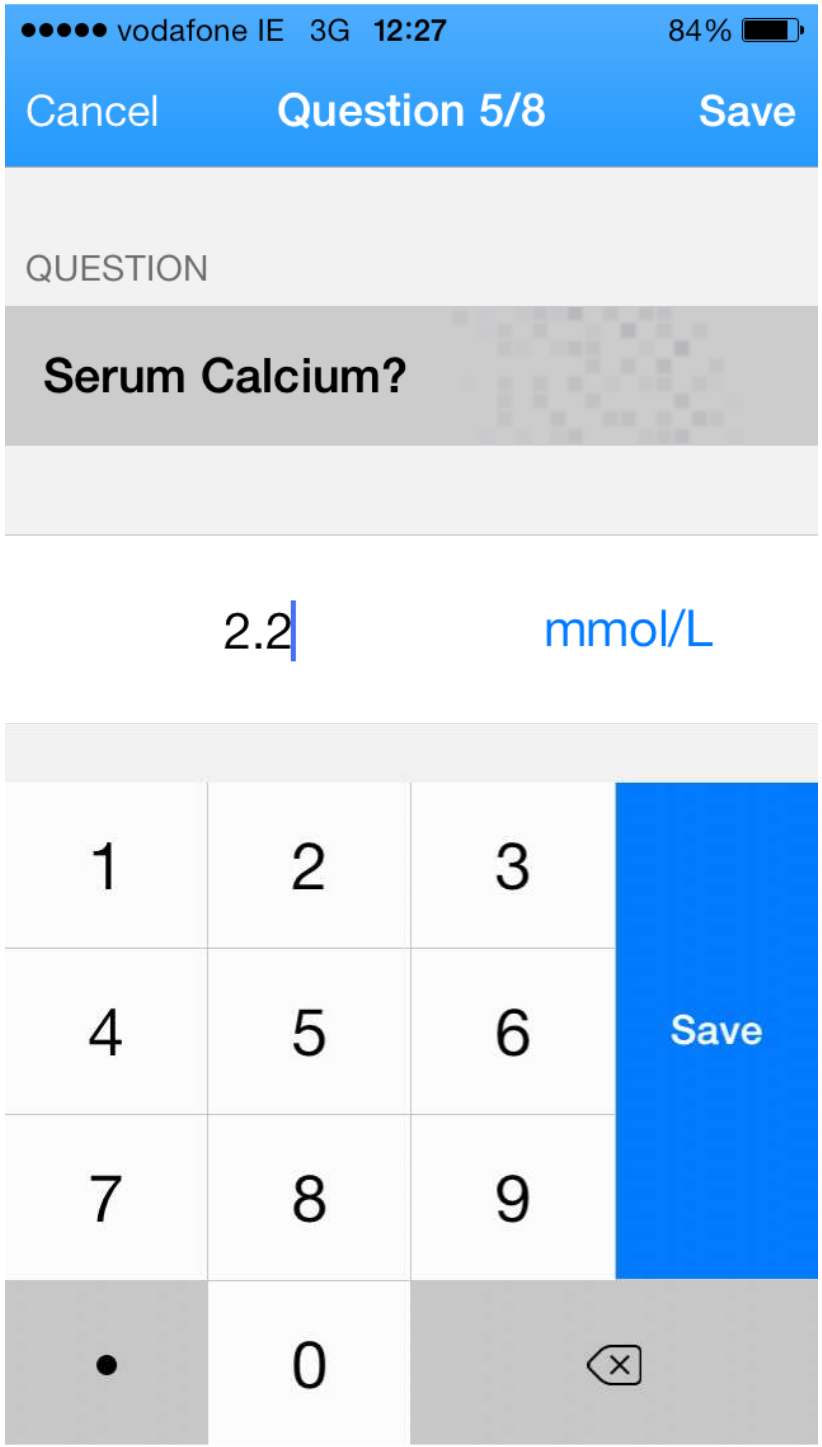
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Serum Calcium?
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mmol/L
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2
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5
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9
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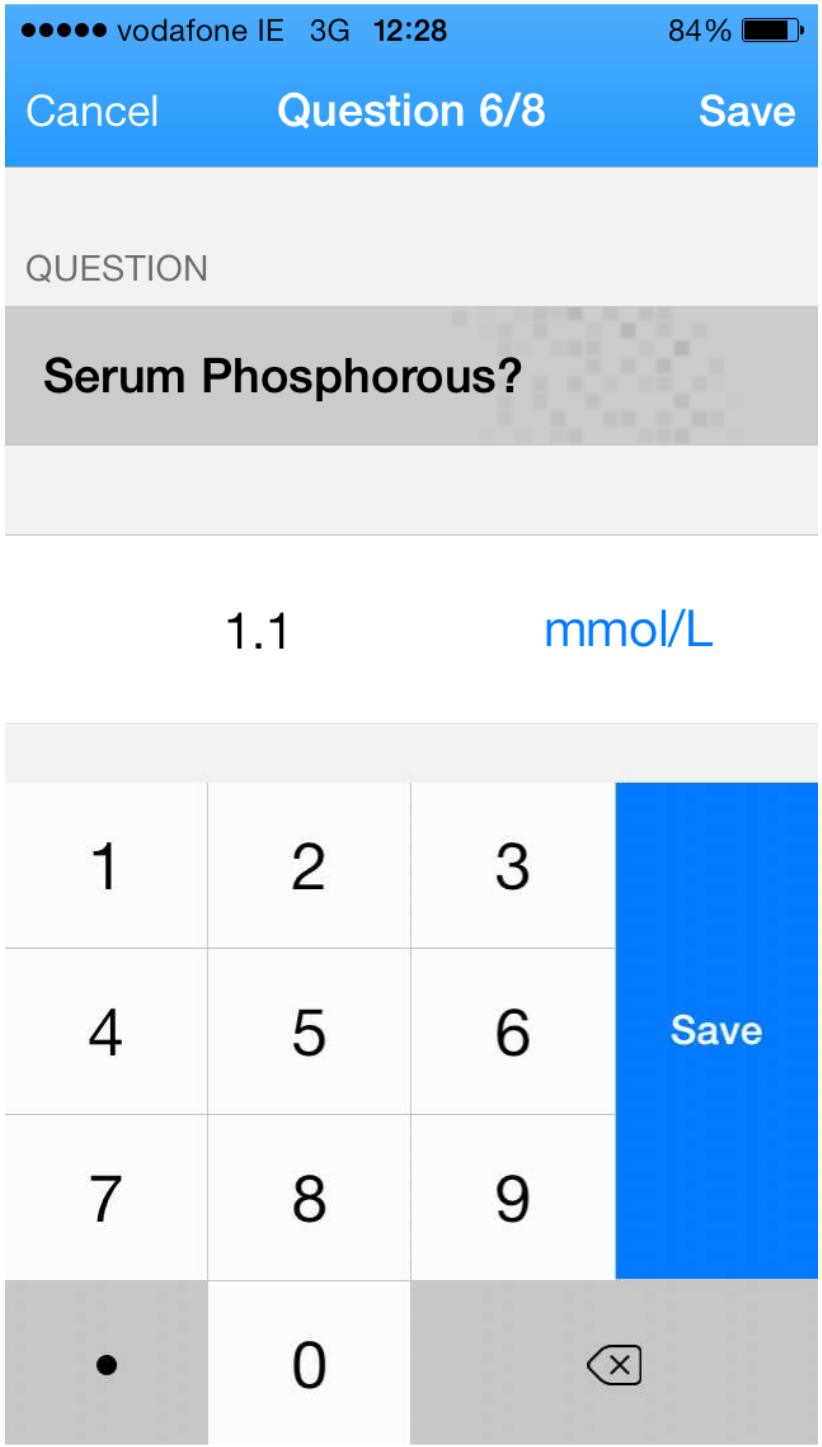
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Question 6/8
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QUESTION
Serum Phosphorous?
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mmol/L
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4
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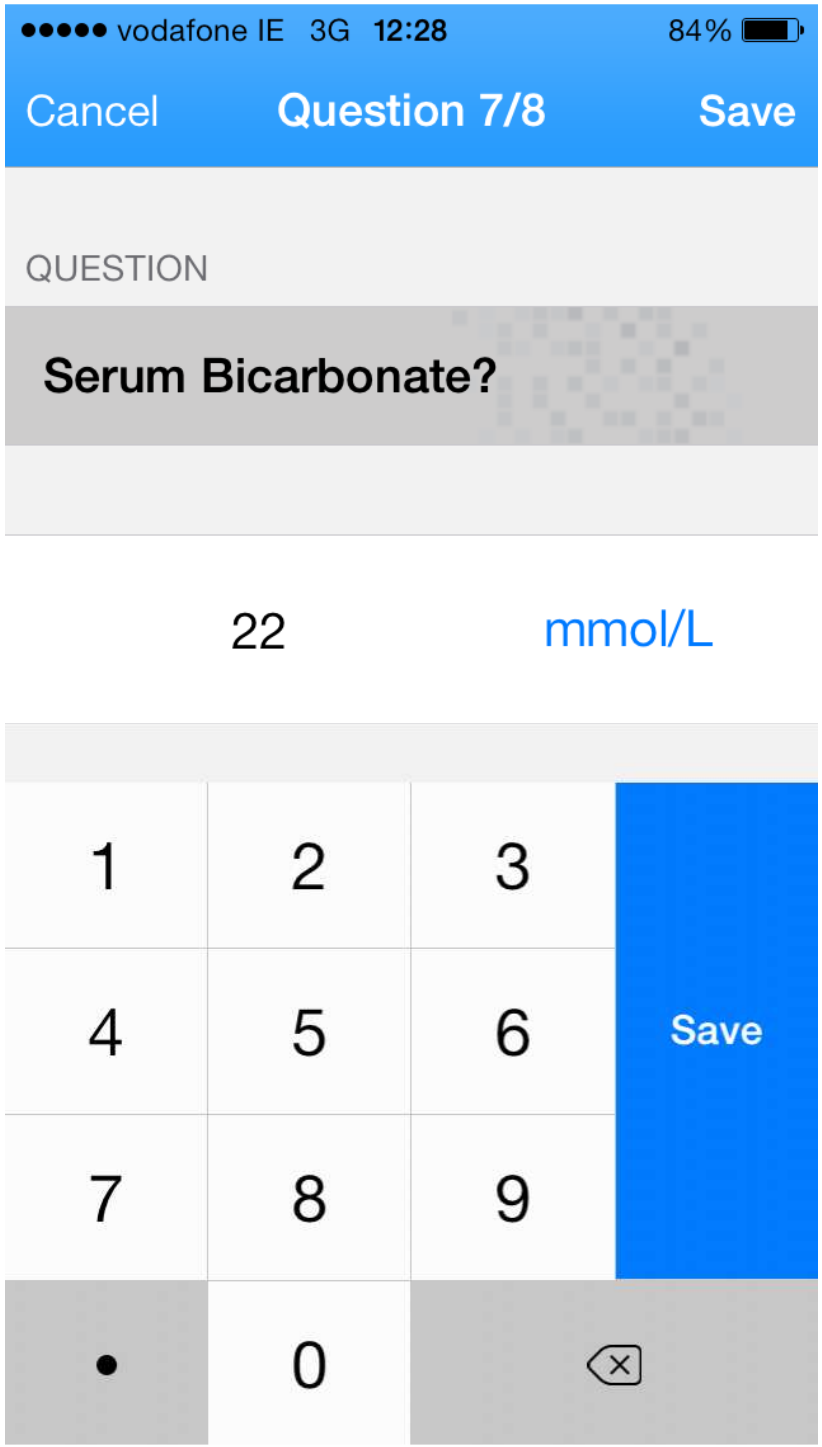
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Question 7/8
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QUESTION
Serum Bicarbonate?
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mmol/L
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2
3
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6
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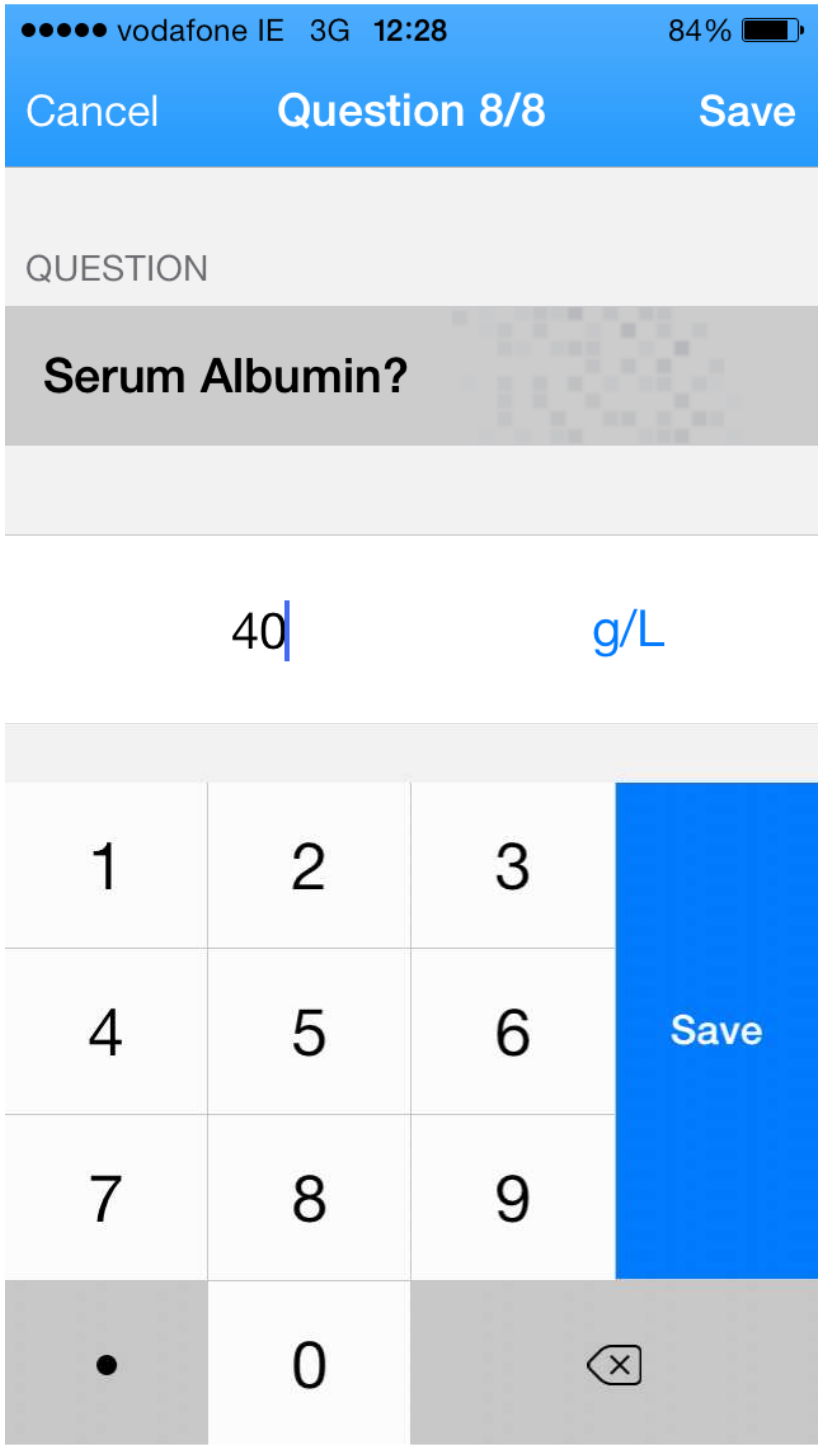
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Question 8/8
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QUESTION
Serum Albumin?
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g/L
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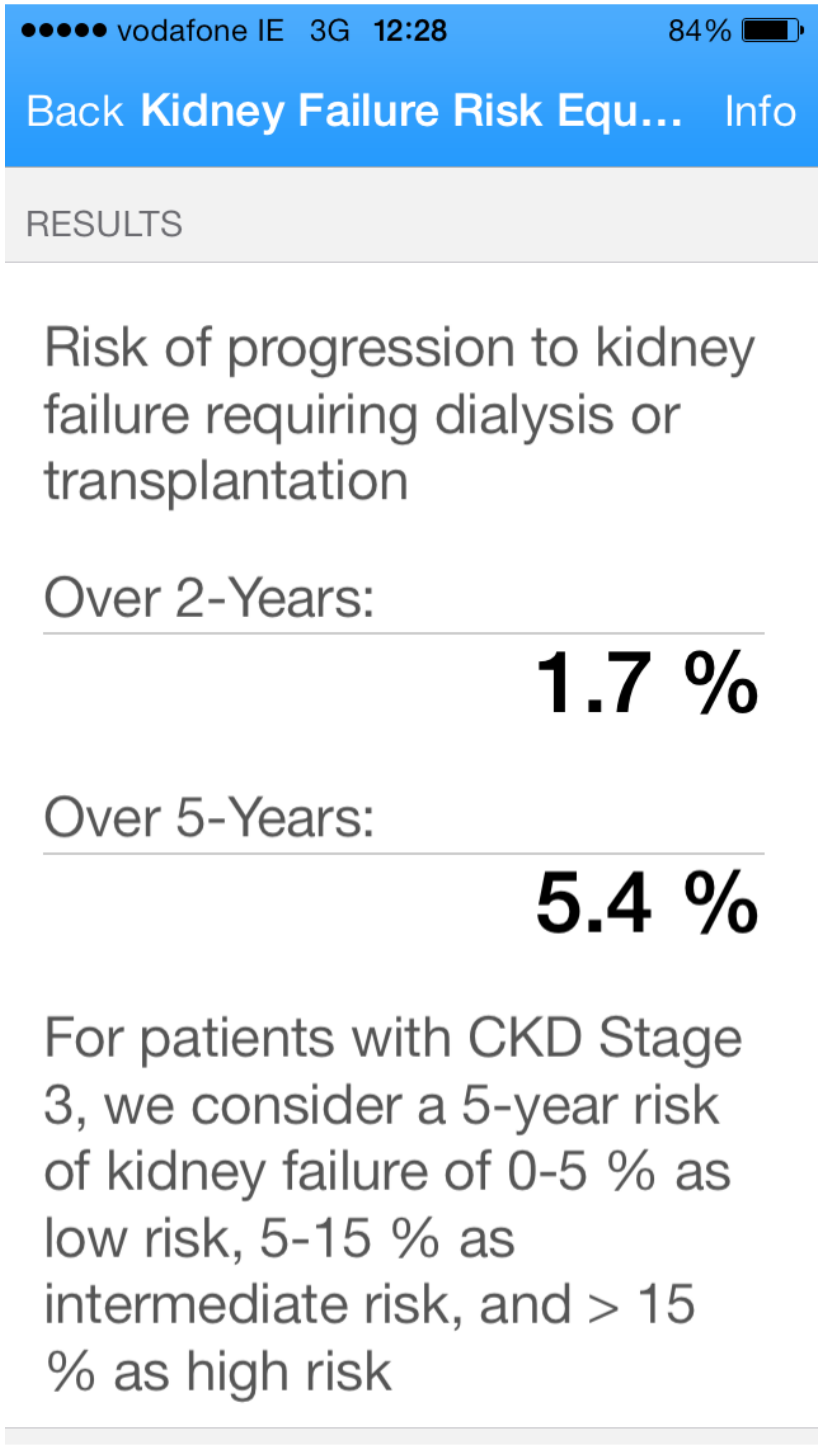

●●●●● vodafone IE 3G 12:28 84%
Back Kidney Failure Risk Equ… Info
RESULTS
Risk of progression to kidney failure requiring dialysis or transplantation
Over 2-Years:
1.7 %
Over 5-Years:
5.4 %
For patients with CKD Stage 3, we consider a 5-year risk of kidney failure of 0-5 % as low risk, 5-15 % as intermediate risk, and > 15 % as high risk

Predicting end-stage kidney disease

CAN WE DO BETTER?

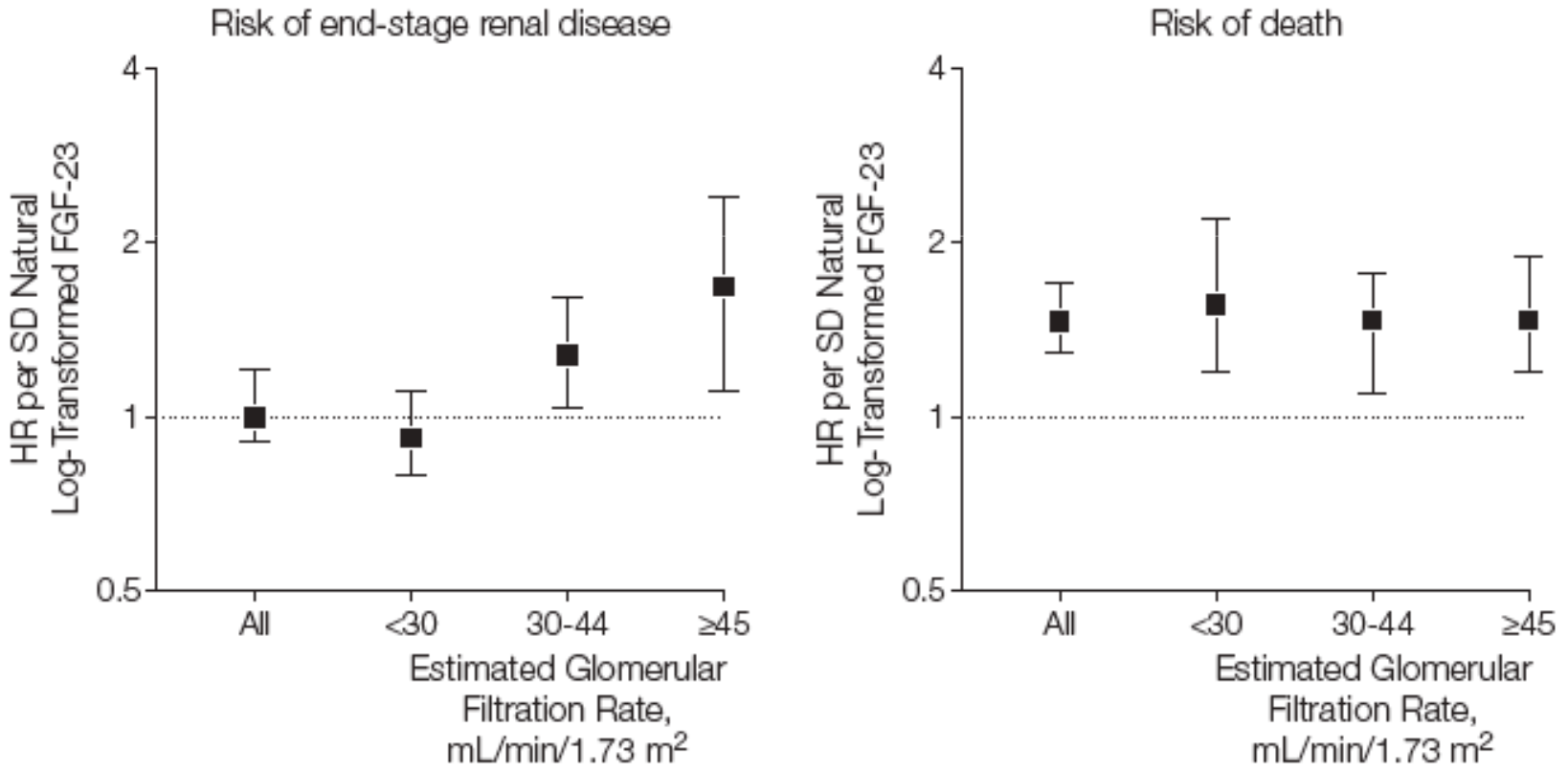
Detection of Chronic Kidney Disease With Creatinine, Cystatin C, and Urine Albumin-to-Creatinine Ratio and Association With Progression to End-Stage Renal Disease and Mortality

Table 3. Risk of Death and End-Stage Renal Disease Associated With Chronic Kidney Disease Stage 3 by Estimated Glomerular Filtration Rate Using Creatinine and Cystatin C[a]

Biomarker Measures, Estimated GFR mL/min/1.73 m^2	No. of Participants	No of Events	Rates per 1000 Person-Years	HR (95% CI) Adjusted Model 1[b]	HR (95% CI) Adjusted Model 2[c]
All-Cause Mortality Over 4.6 y					
Creatinine + Cystatin C, ≥60	22 361	1104	10.9 (10.9-11.0)	1 [Reference]	1 [Reference]
Creatinine alone, <60	849	59	15.4 (14.9-15.9)	1.0 (0.7,1.2)	0.9 (0.7-1.1)
Cystatin C alone, <60	1378	278	47.0 (45.8-48.2)	2.6 (2.2-2.9)	2.1 (1.9-2.5)
Creatinine + Cystatin C, <60	2055	799	57.8 (56.6-59.1)	2.8 (2.5-3.1)	2.1 (1.9-2.4)
End-Stage Renal Disease Over 4.6 y					
Creatinine + Cystatin C, ≥60	22 361	17	0.2 (0.1-0.3)	1 [Reference]	1 [Reference]
Creatinine alone, <60	849	2	0.5 (0.1-2.2)	3.9 (0.9-16.9)	2.5 (0.6-10.9)
Cystatin C, <60	1378	14	2.2 (1.3-3.8)	12.6 (6.2-25.9)	5.8 (2.8-12.1)
Creatinine + Cystatin C, <60	2055	144	15.8 (13.5-18.6)	90.5 (53.2-153.9)	26.1 (14.9-45.7)

ORIGINAL CONTRIBUTION

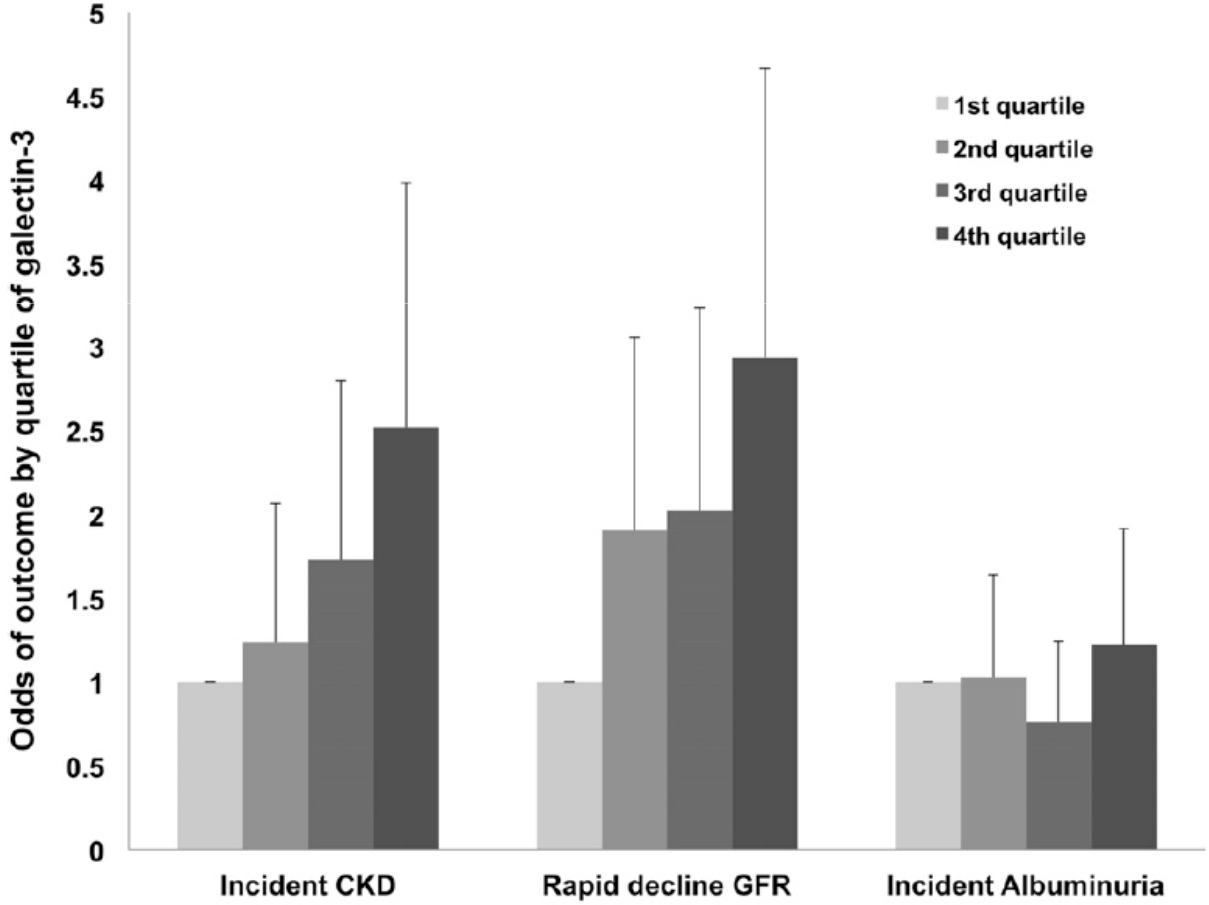
Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients With Chronic Kidney Disease



Tamara Isakova, MD, MMSc

Elevated Galectin-3 Precedes the Development of CKD

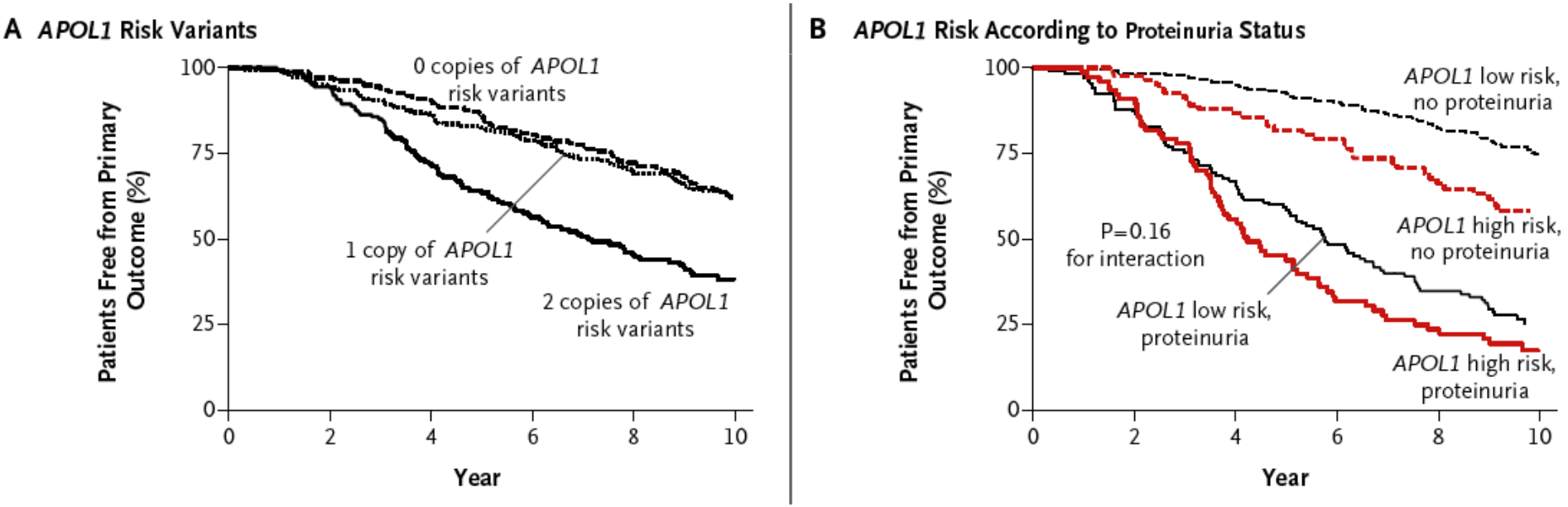
Conall M. O'Seaghdha,*†‡§ Shih-Jen Hwang,*† Jennifer E. Ho,*†‖ Ramachandran S. Vasan,*†¶ Daniel Levy,*† and Caroline S. Fox*†**



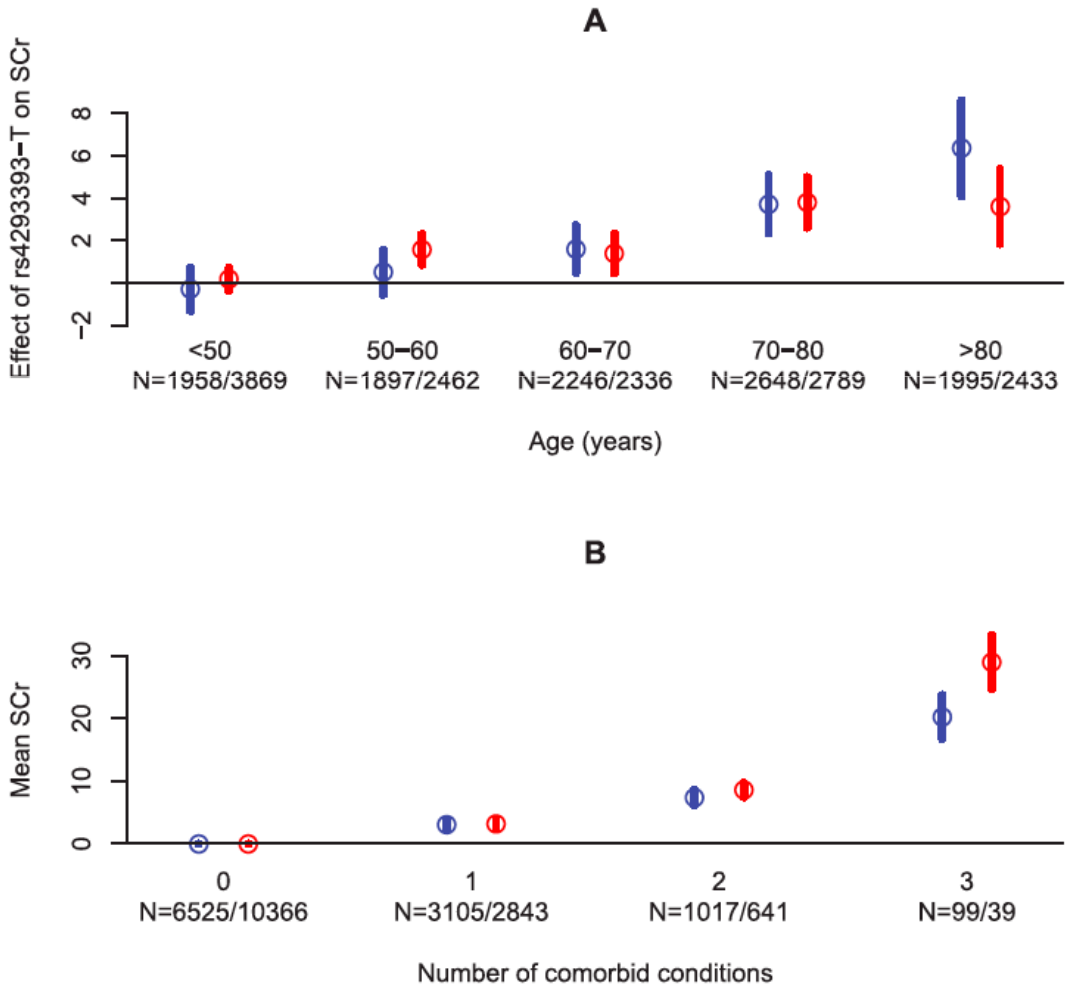
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease



Association of Variants at *UMOD* with Chronic Kidney Disease and Kidney Stones—Role of Age and Comorbid Diseases



Uromodulin Levels Associate with a Common *UMOD* Variant and Risk for Incident CKD

Anna Köttgen,* Shih-Jen Hwang,[†‡] Martin G. Larson,[§] Jennifer E. Van Eyk,[‖] Qin Fu,[‖] Emelia J. Benjamin,[†¶] Abbas Dehghan,** Nicole L. Glazer,[††] W.H. Linda Kao,* Tamara B. Harris,[‡‡] Vilmundur Gudnason,[§§‖‖] Michael G. Shlipak,[¶¶] Qiong Yang,[§] Josef Coresh,* Daniel Levy,[†‡] and Caroline S. Fox[†‡***]

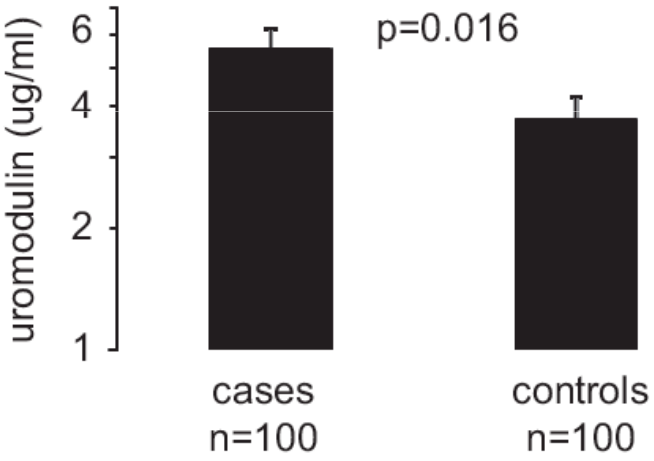


Figure 1. Geometric mean uromodulin concentrations in the case patients and control subjects at baseline are shown. Error bars represent SEs.

Table 3. Association of uromodulin concentrations at baseline and incident CKD case/control status in the FHS

Parameter	OR (95% CI)	*P*
MV[a]-adjusted model		
uromodulin concentrations	1.55 (1.06 to 2.26)	0.02
uromodulin-to-creatinine ratio	1.69 (1.02 to 2.79)	0.04
MV[a] + baseline eGFR	1.72 (1.07 to 2.77)	0.03
MV[a] + baseline eGFR + ln(UACR)	1.72 (1.06 to 2.79)	0.03
Stratified analyses		
free of diabetes (n = 184)[a]	1.76 (1.07 to 2.89)	0.03
age below median (n = 88)[a]	1.53 (0.69 to 3.36)	0.29
age above median (n = 112)[a]	1.62 (0.75 to 3.48)	0.22