Management of chronic kidney disease in older adults

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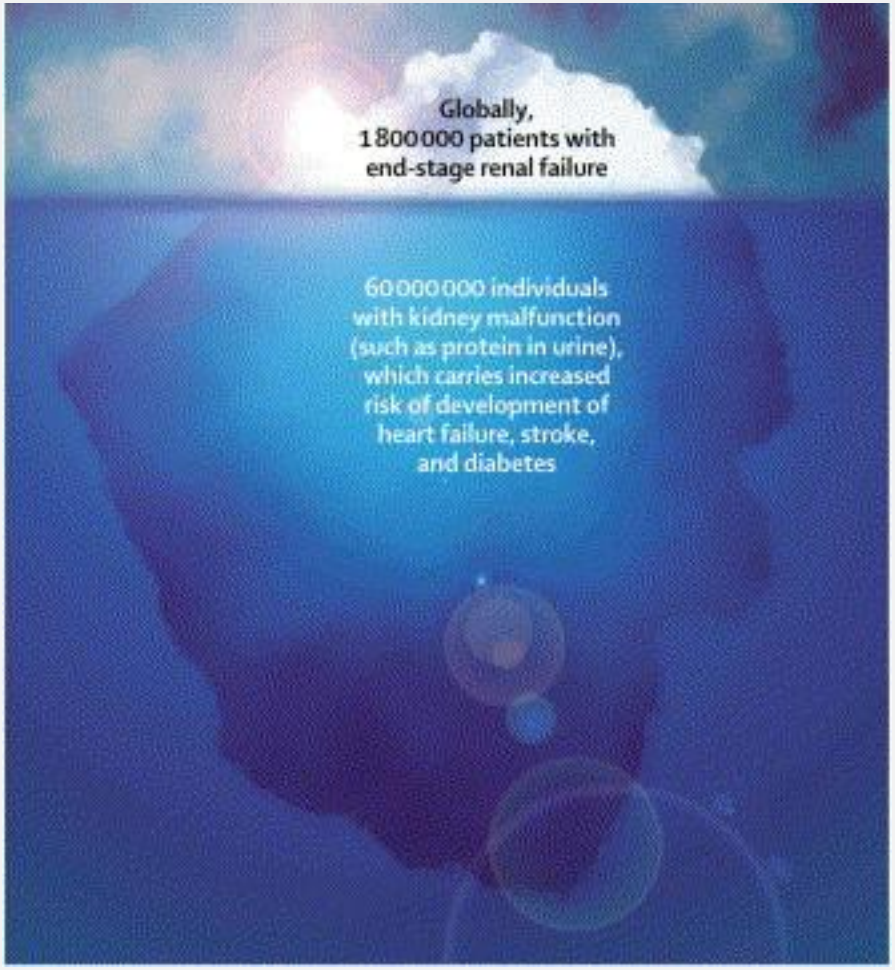
Growing interest in non-dialysis dependent CKD



Remuzzi & Weening, Lancet, 2005

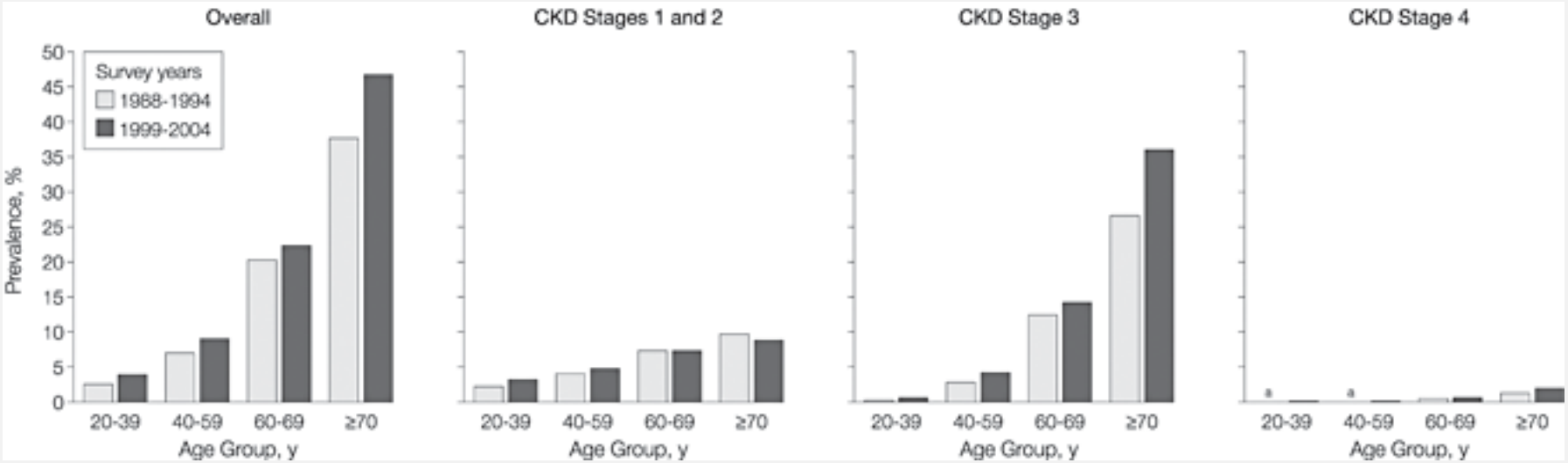
Chronic Kidney Disease

Table 139. Stages of Chronic Kidney Disease: Clinical Presentations

Stage	Description	GFR Range (mL/min/1.73 m^2)	Clinical Presentations*
	At increased risk	≥60 (without markers of damage)	CKD risk factors
1	Kidney damage with normal or ↑ GFR	≥90	Markers of damage (Nephrotic syndrome, Nephritic syndrome, Tubular syndromes, Urinary tract symptoms, Asymptomatic urinalysis abnormalities, Asymptomatic radiologic abnormalities, Hypertension due to kidney disease)
2	Kidney damage with mild ↓ GFR	60–89	Mild complications
3	Moderate ↓ GFR	30–59	Moderate complications
4	Severe ↓ GFR	15–29	Severe complications
5	Kidney Failure	<15 (or dialysis)	Uremia, Cardiovascular disease

* Includes presentations from preceding stages. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies

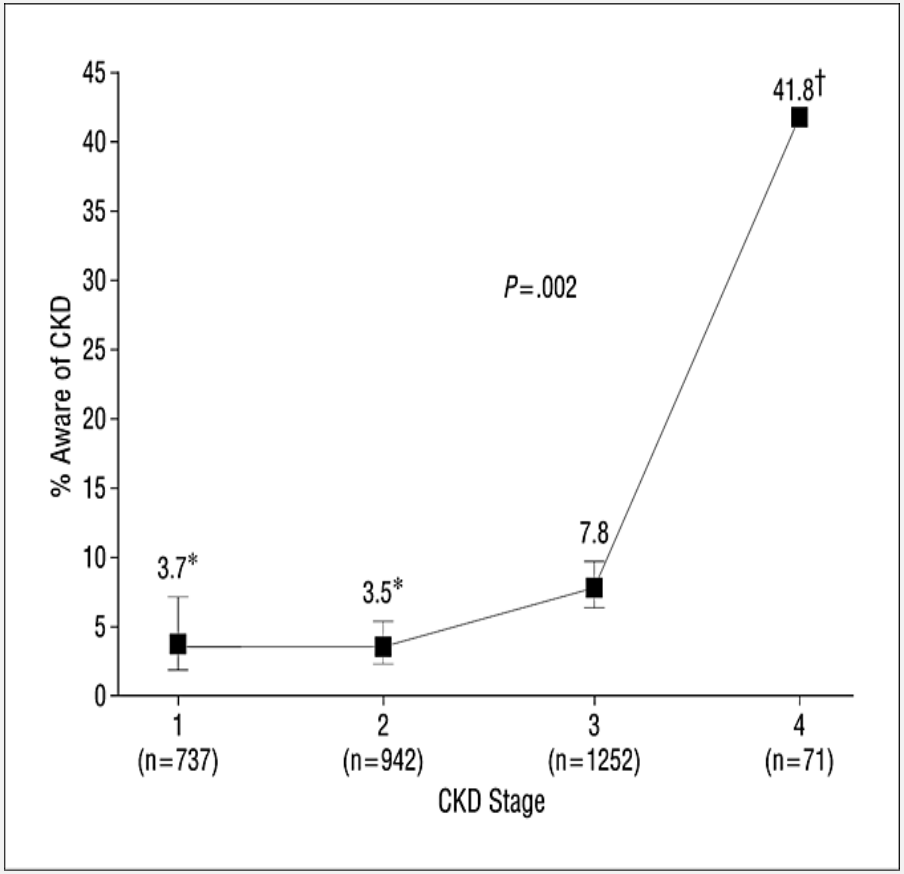
Chronic kidney disease is common and increases in prevalence with age



Coresh, J. et al. JAMA 2007;298:2038-2047.

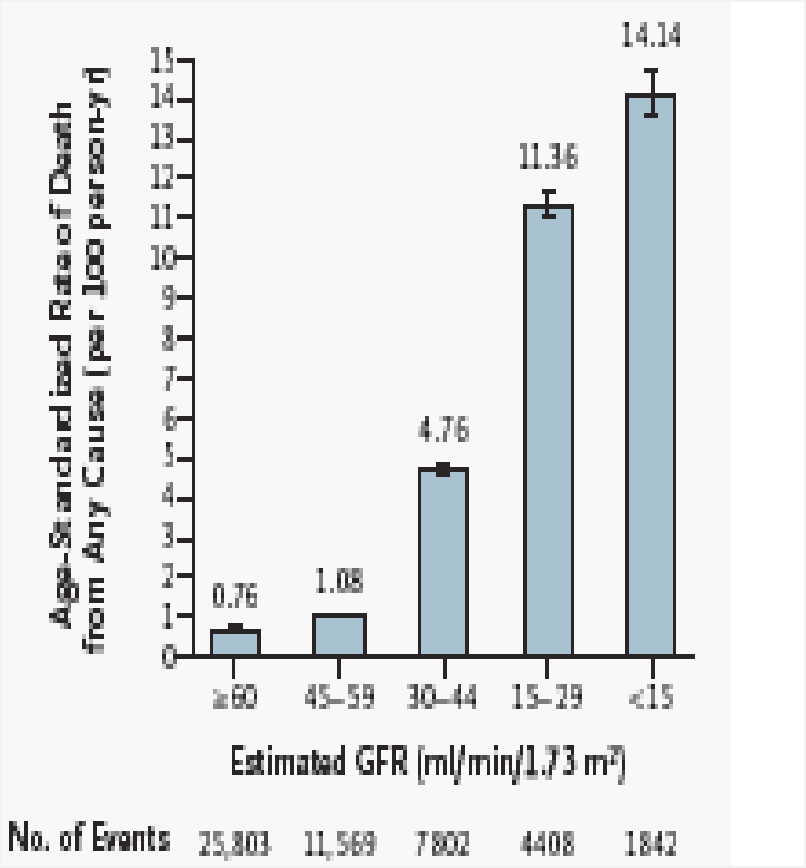
JAMA

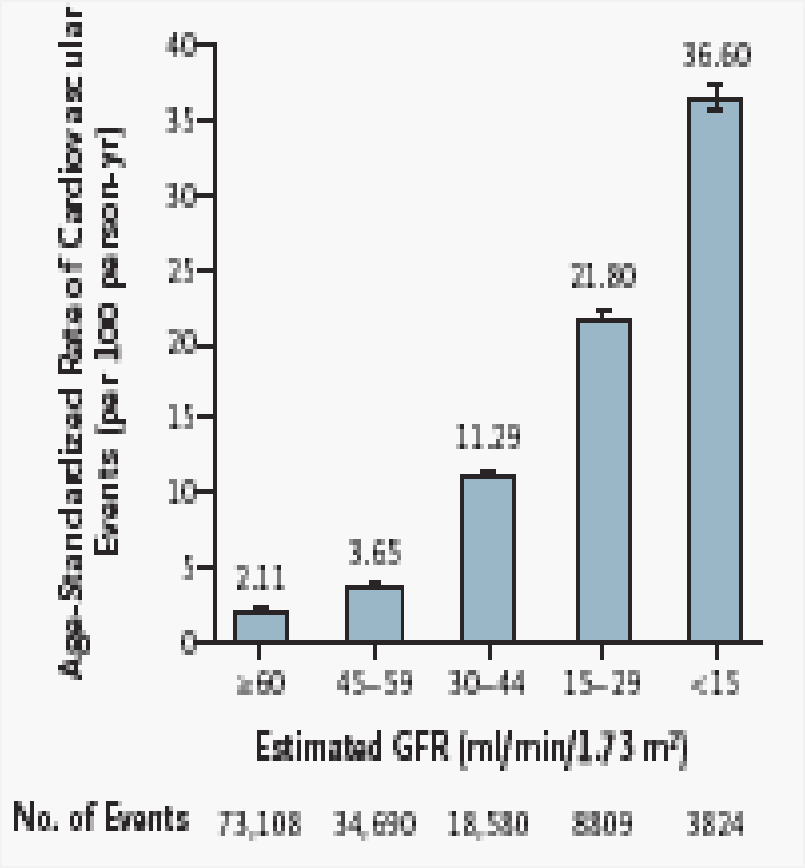
Chronic kidney disease is frequently unrecognized



Plantinga, Arch Intern Med. 2008;168(20):2268-2275.

Chronic kidney disease is associated with increased cardiovascular risk





Go, NEJM, 2004, 351:1296-1305

Progression to ESRD

Table 2. Study End points*

End Points	GFR, 60-89; No Proteinuria (n = 14 202)	Stage 2 GFR, 60-89; Proteinuria (n = 1741)	Stage 3 GFR, 30-59 (n = 11 278)	Stage 4 GFR, 15-29 (n = 777)
Disenrolled from plan	14.9	16.2	10.3	6.6
Died (prior to transplant/dialysis)	10.2	19.5	24.3	45.7
Received a transplant	0.01	0.2	0.2	2.3
Initiated dialysis	0.06	0.9	1.1	17.6
None of the above through June 30, 2001	74.8	63.3	64.2	27.8

*Glomerular filtration rates (GFRs) were estimated in milliliters per minute per 1.73 m^2. Other values are given as percentage of patients.

Keith, Arch Intern Med, 2004;164:659-663

Interventions

Table 33. Stages of Chronic Kidney Disease: A Clinical Action Plan

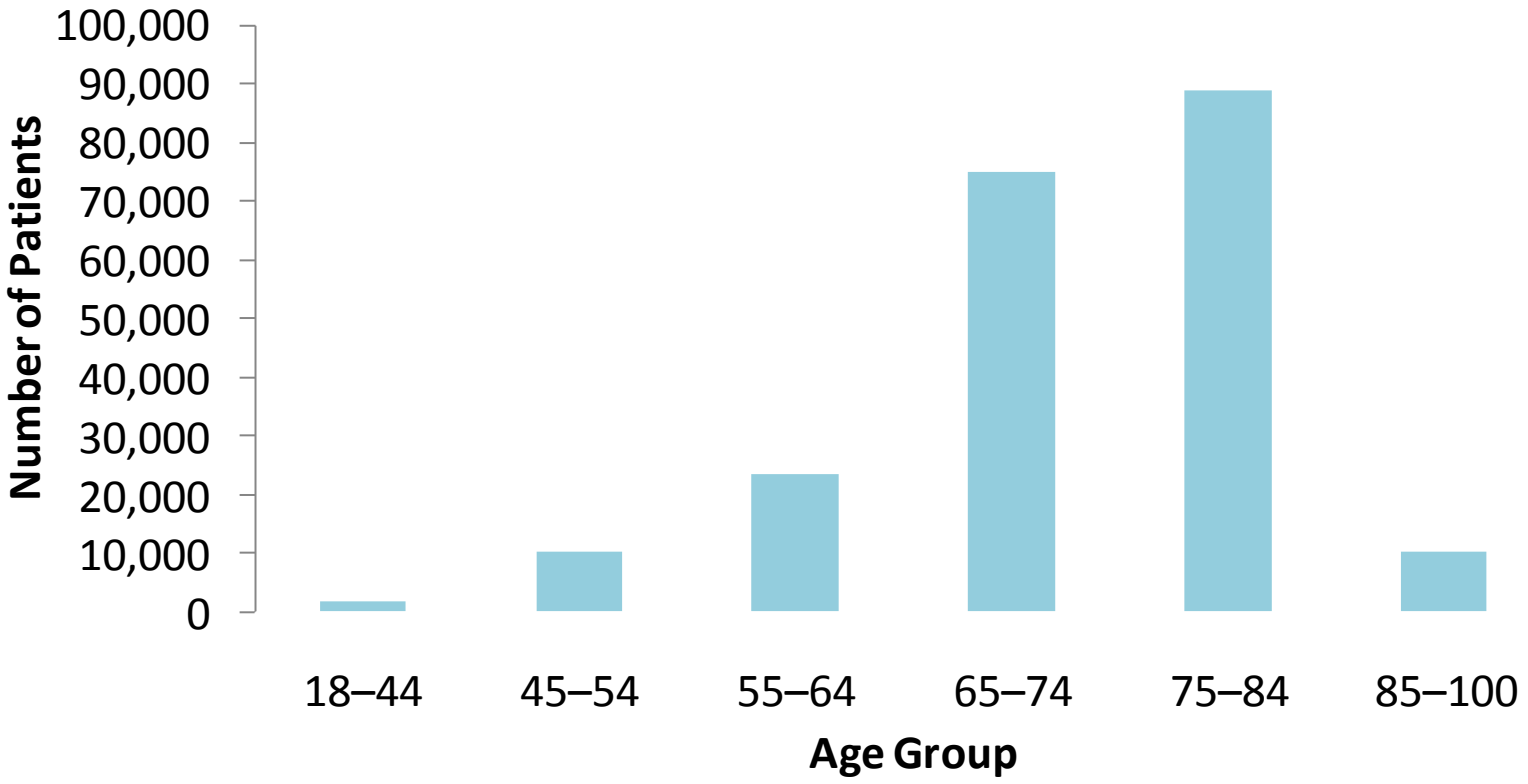
Stage	Description	GFR (mL/min/1.73 m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations: CVD, cardiovascular disease

Age Distribution of Department of Veterans Affairs (VA) Patients with CKD



Adapted from O'Hare, et al. J Am Soc Nephrol. 2007;18:2758-65.

High prevalence of comorbidity in elderly patients with CKD

Table 1. Patient characteristics by age group[a]

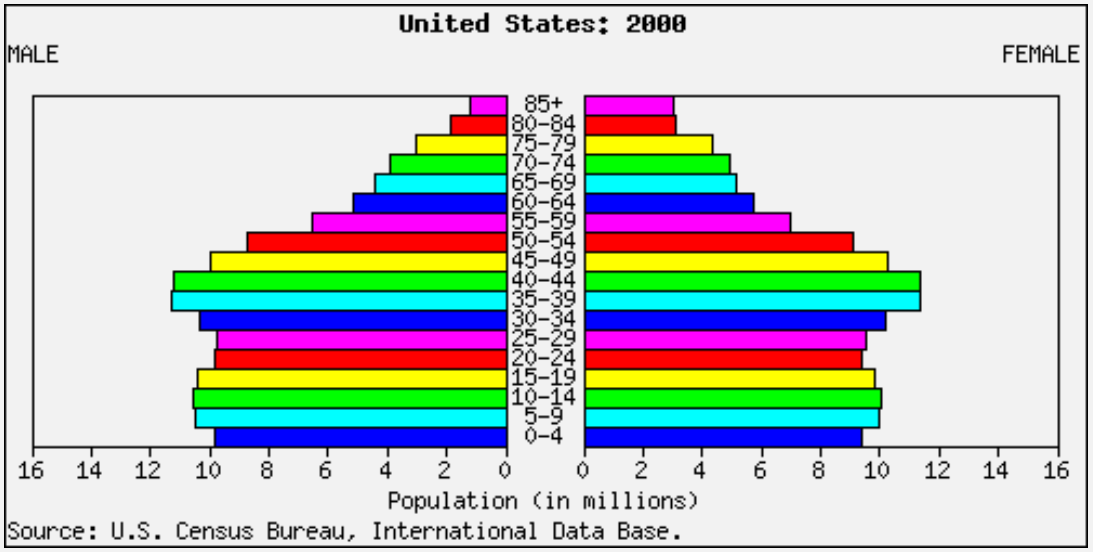
Characteristic	18 to 44 (n = 1700)	45 to 54 (n = 10,255)	55 to 64 (n = 23,559)	65 to 74 (n = 75,048)	75 to 84 (n = 88,849)	85 to 100 (n = 10,211)
Race (%)						
white	51.82	62.61	78.07	88.12	90.06	86.14
black	25.76	22.65	12.53	10.43	8.50	11.66
other	1.29	1.86	1.38	0.81	0.80	1.35
unknown	21.12	12.87	8.02	0.63	0.64	0.84
Female (%)	17.65	7.38	5.08	1.63	3.40	3.36
Diabetes (%)	25.53	41.61	47.65	47.06	40.97	31.59
Coronary artery disease (%)	18.12	35.33	49.85	60.84	65.51	63.66
Congestive heart failure (%)	11.00	19.78	27.04	33.09	38.36	43.37
Peripheral vascular disease (%)	6.24	13.18	21.37	29.84	33.68	34.28
Cerebrovascular disease (%)	6.06	12.88	19.73	26.91	32.02	32.83
Any of the listed comorbid conditions (%)	43.00	64.35	75.47	82.99	85.44	85.12
Median Charlson score (25th to 75th percentile range)	2 (0 to 4)	3 (1 to 5)	3 (1 to 5)	3 (2 to 6)	4 (2 to 6)	4 (2 to 6)

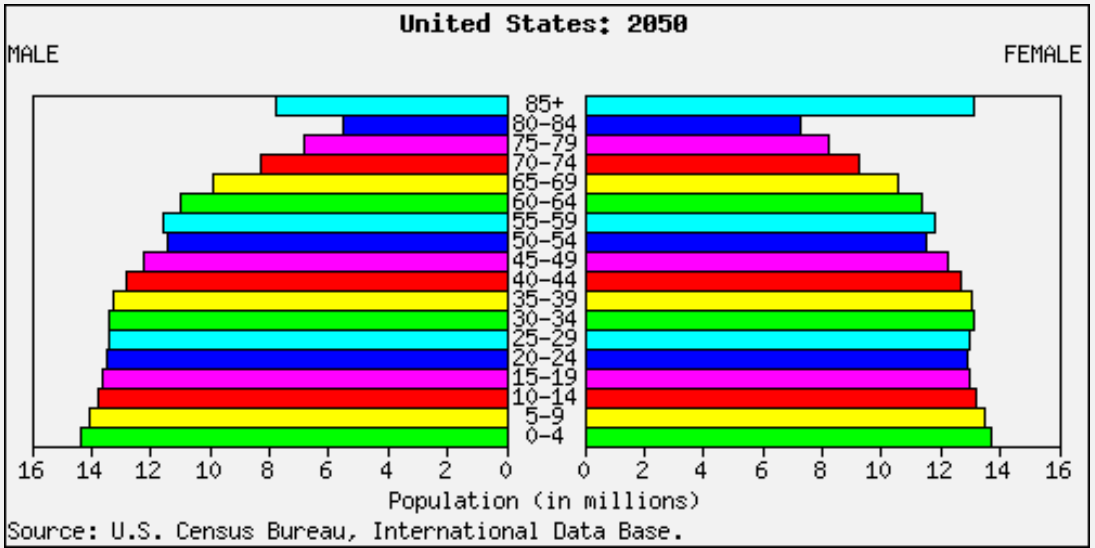
[a]Coronary artery disease was defined on the basis of the presence of either diagnostic codes for coronary artery disease, angina, or myocardial infarction or procedure codes for coronary artery bypass graft or angioplasty. Peripheral arterial disease was based on the presence of either diagnostic codes for peripheral arterial disease or procedure codes for lower extremity amputation or revascularization procedures. Cerebrovascular disease was defined on the basis of the presence of diagnostic codes for stroke or transient ischemic attack.

O'Hare et al. JASN 2007

O'Hare, et al. J Am Soc Nephrol. 2007;18:2758-65.

Population aging

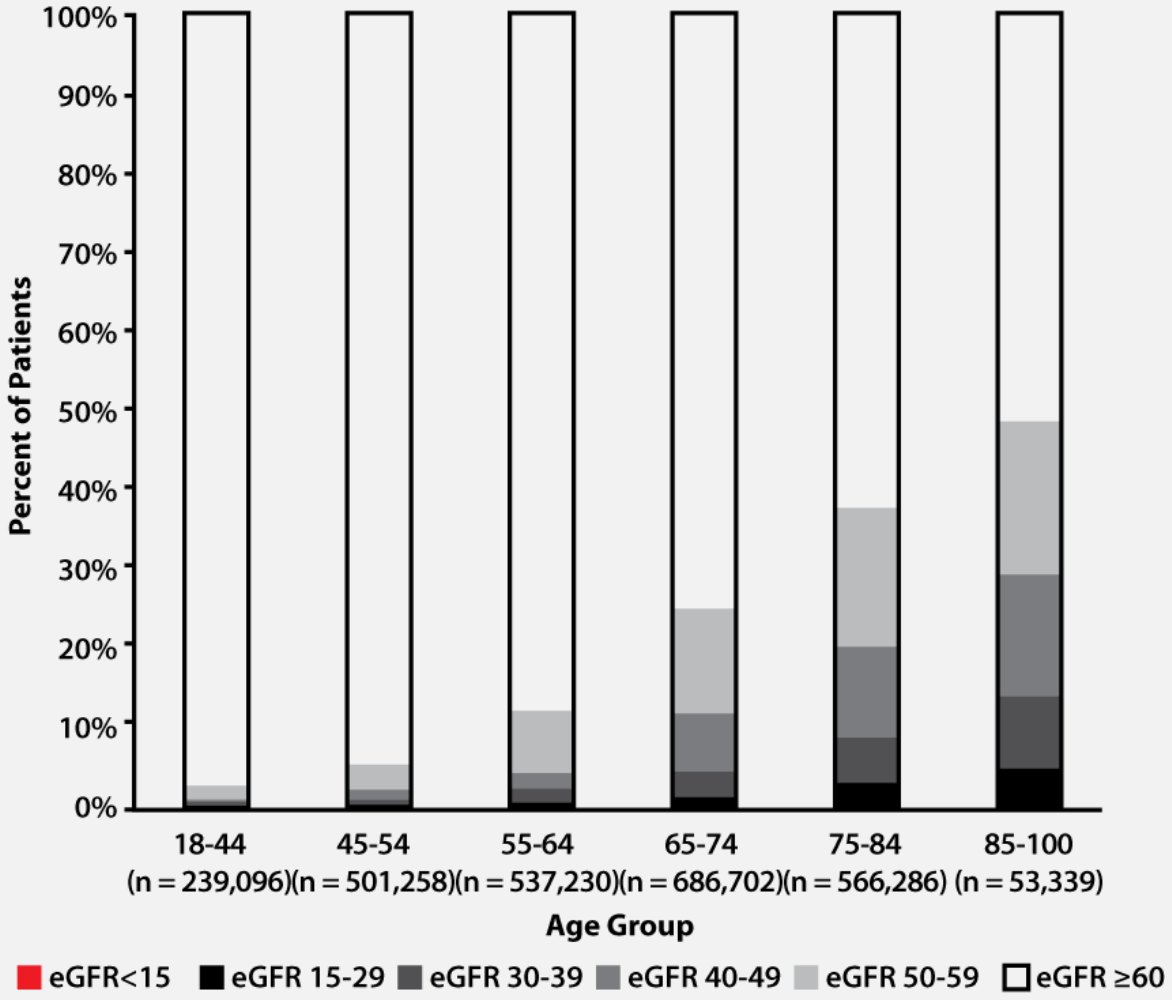




Questioning the appropriateness of this paradigm to older adults with a low eGFR

- **Are outcomes associated with a low eGFR comparable in older and younger adults?**
  - **mortality risk**
  - progression of renal disease
  - Might proteinuria contribute additional information?
- Do we know that recommended interventions are beneficial in older adults with CKD?
  - ACE/ARB
  - dialysis

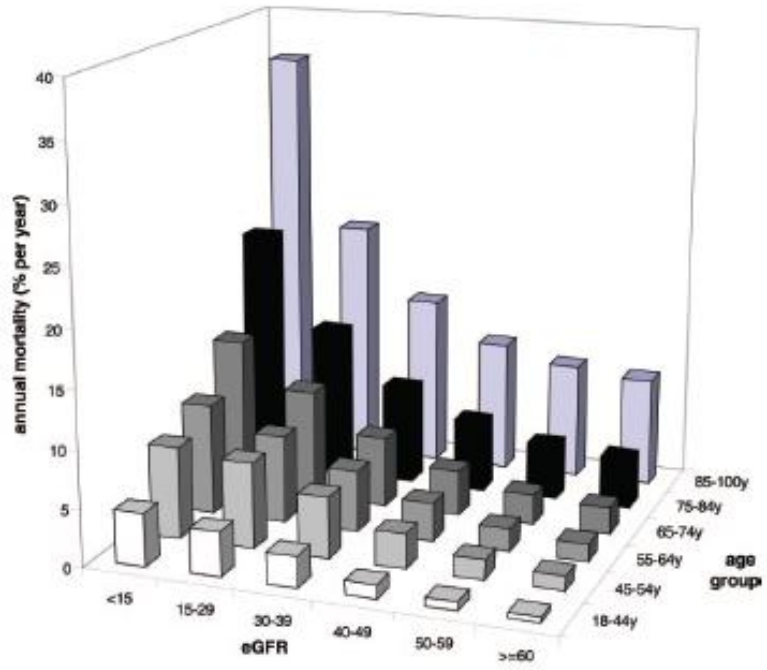
eGFR among 2,583,911 Veterans



eGFR = estimated glomerular filtration rate

O'Hare AM, et al. J Am Soc Nephrol. 2006;17:846-53.

Mortality rates extremely high in elderly patients with CKD



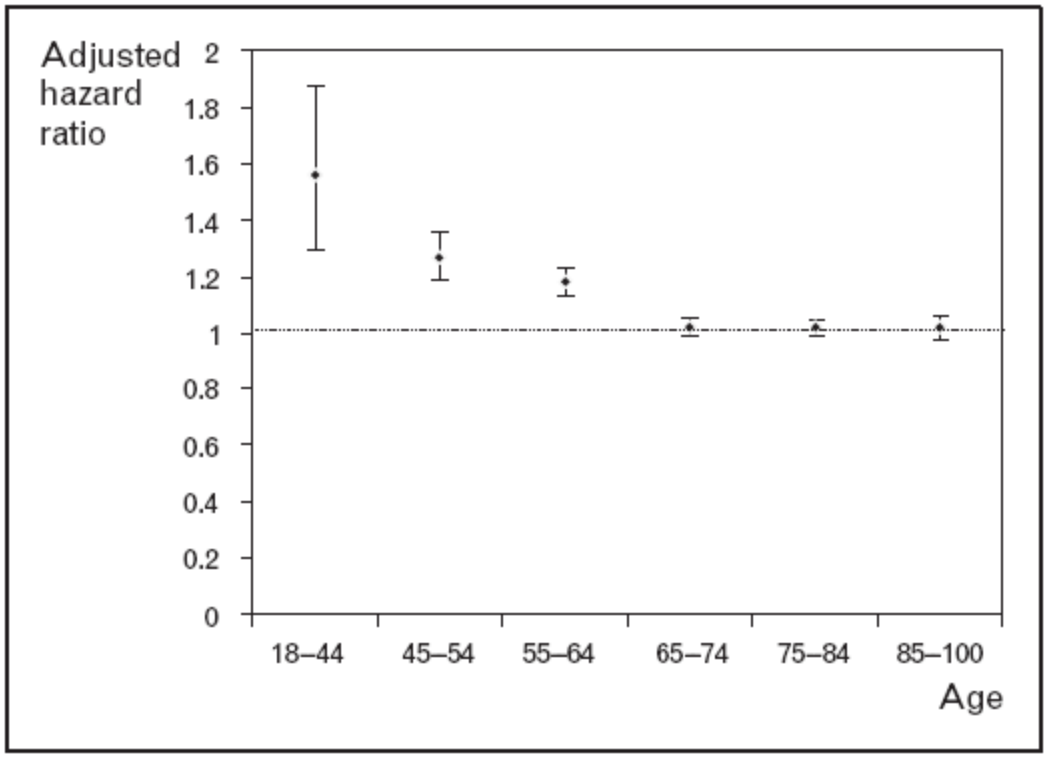
	18-44	45-54	55-64	65-74	75-84	85-100
≥60	0.42	1.25	1.48	2.31	4.40	9.47
50-59	0.76	1.73	1.95	2.62	4.78	10.07
40-49	1.20	2.99	3.33	3.92	6.19	11.40
30-39	2.68	5.30	5.33	6.08	8.60	14.74
15-29	3.81	7.42	7.54	9.50	13.16	20.95
<15	4.55	7.96	9.54	13.32	21.24	35.99

Figure 2. Annual mortality by age group and eGFR.

O'Hare AM, et al. J Am Soc Nephrol. 2006;17:846-53.

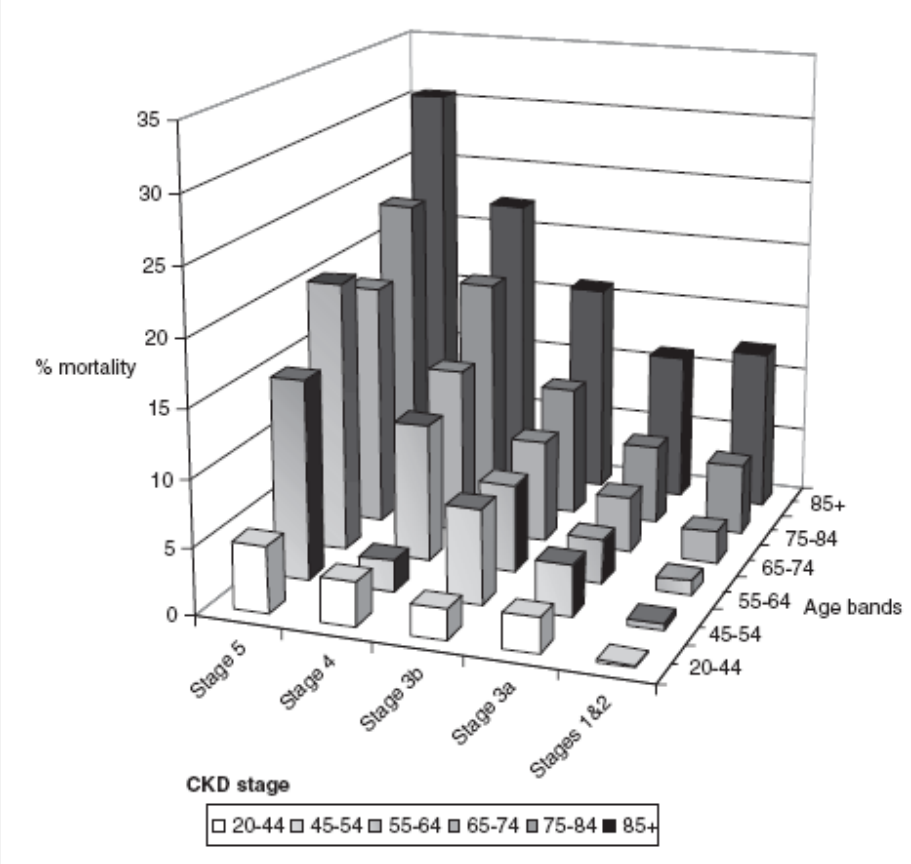
JASN 2006

Relative risk of death associated with low eGFR attenuated in the elderly



Adapted from O'Hare et al, JASN 2006

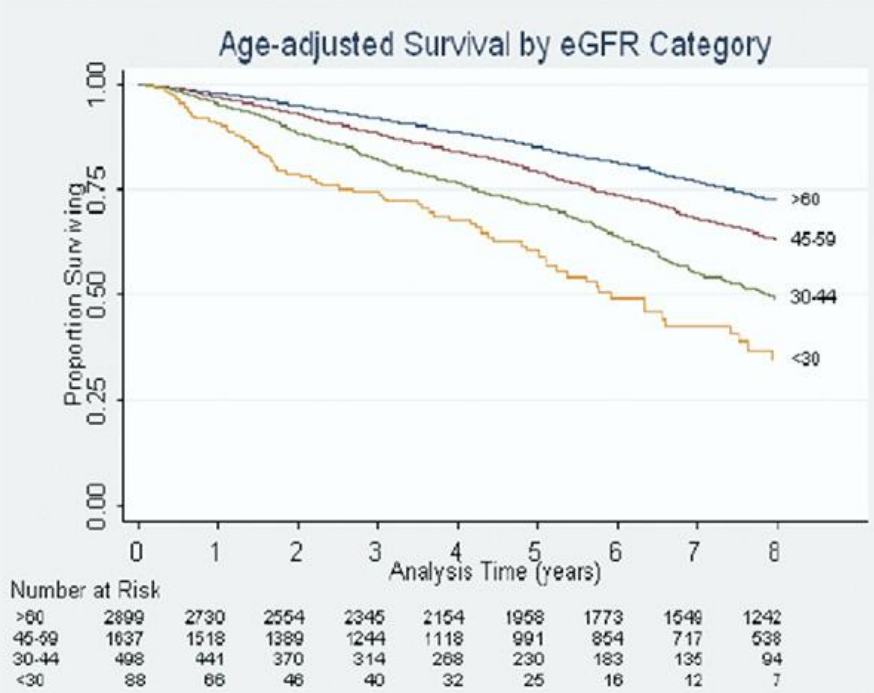
Community cohort in Coventry, England



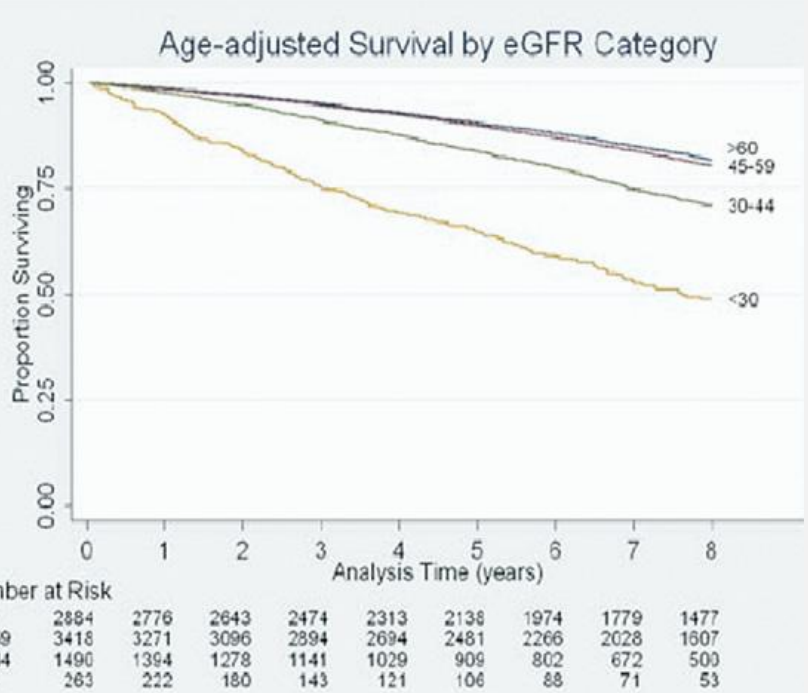
Raymond, Nephrol Dial Transplant. 2007 Nov;22(11):3214-20.

Adults aged 75 and older with an eGFR<60

Men

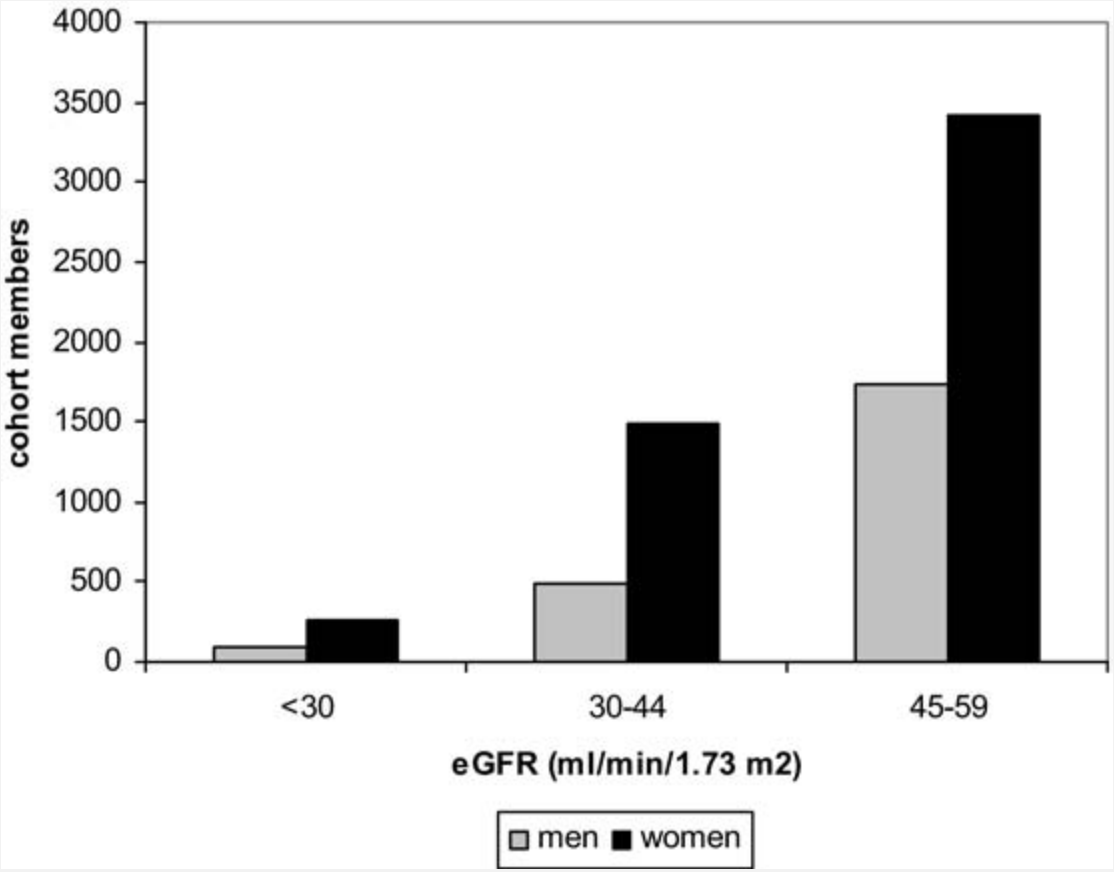


Women



Roderick et al, AJKD. 2009 Jun;53(6):950-60.

Most patients with a low eGFR have a very moderate reduction in eGFR

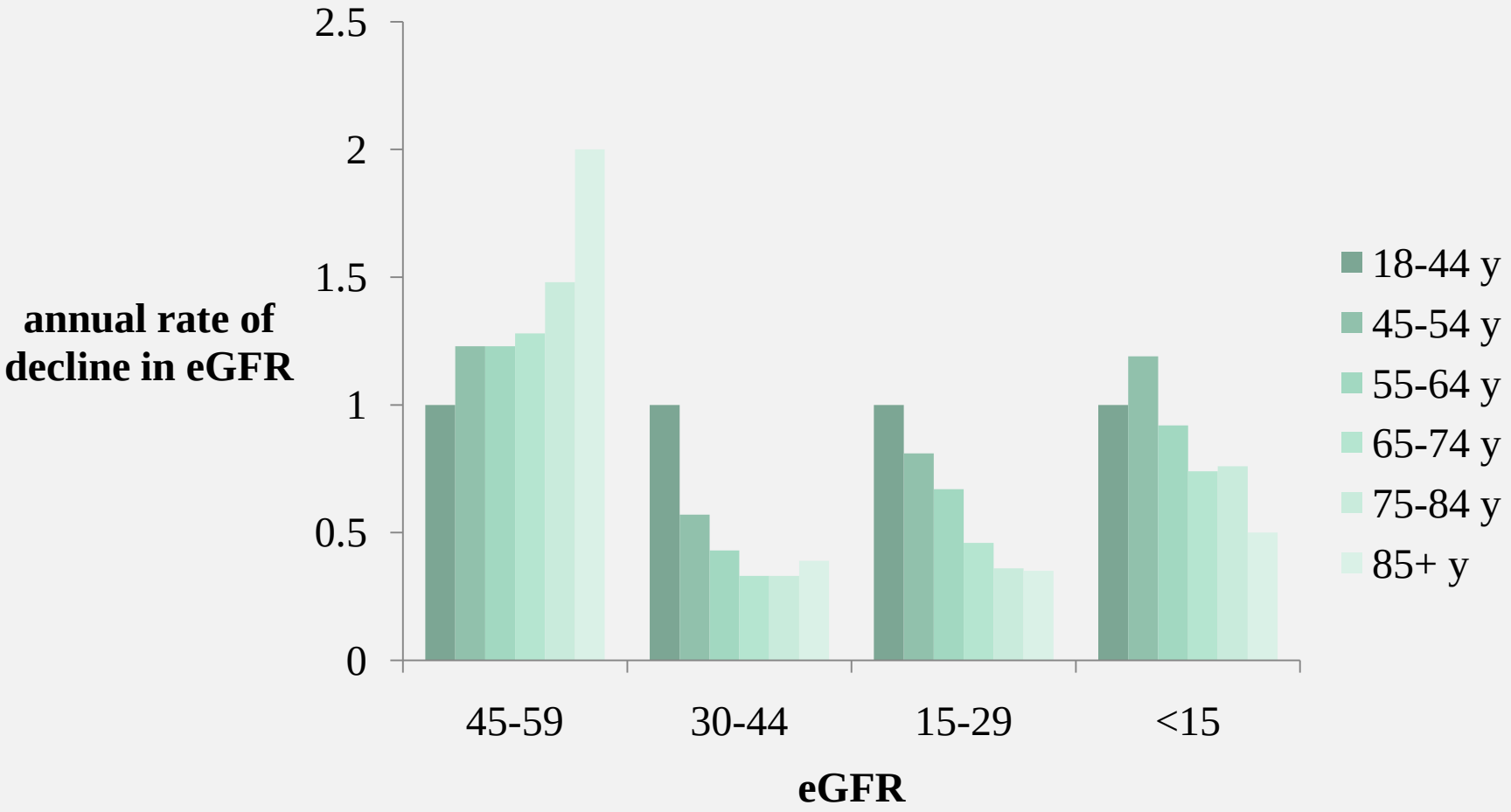


O'Hare AM, AJKD, 2009 Jun;53(6):925-7.

Questioning the appropriateness of this paradigm to older adults with a low eGFR

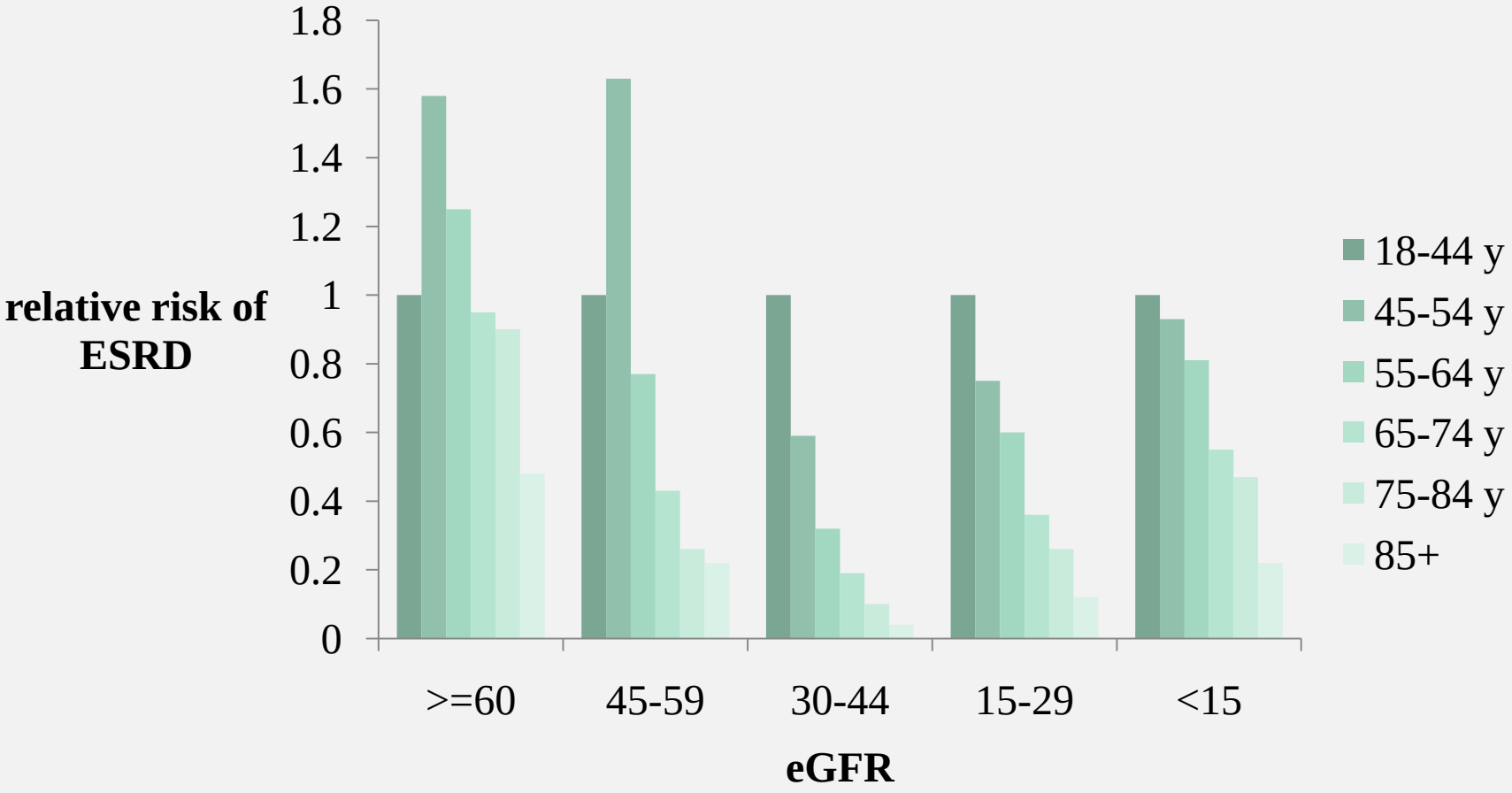
- **Are outcomes associated with a low eGFR comparable in older and younger adults?**
  - mortality risk
  - **progression of renal disease**
  - Might proteinuria contribute additional information?
- Do we know that recommended interventions are beneficial in older adults with CKD?
  - ACE/ARB
  - dialysis

Annual rate of decline in eGFR by age and eGFR at baseline



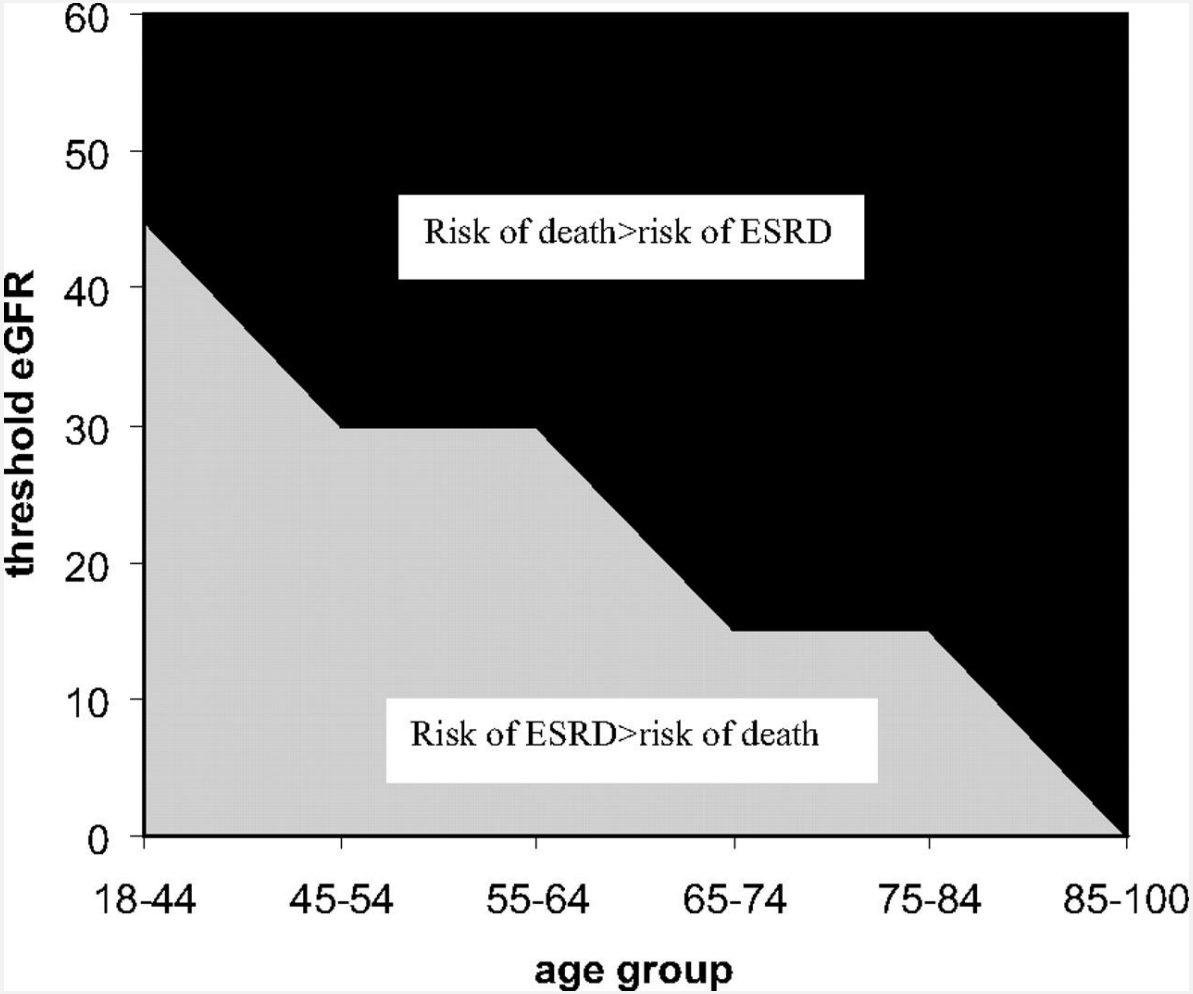
O'Hare, A. M. et al. J Am Soc Nephrol 2007;18:2758-2765

Relative hazard of ESRD by age and eGFR at baseline



O'Hare, A. M. et al. J Am Soc Nephrol 2007;18:2758-2765

Baseline eGFR threshold below which risk for ESRD exceeded risk for death for each age group

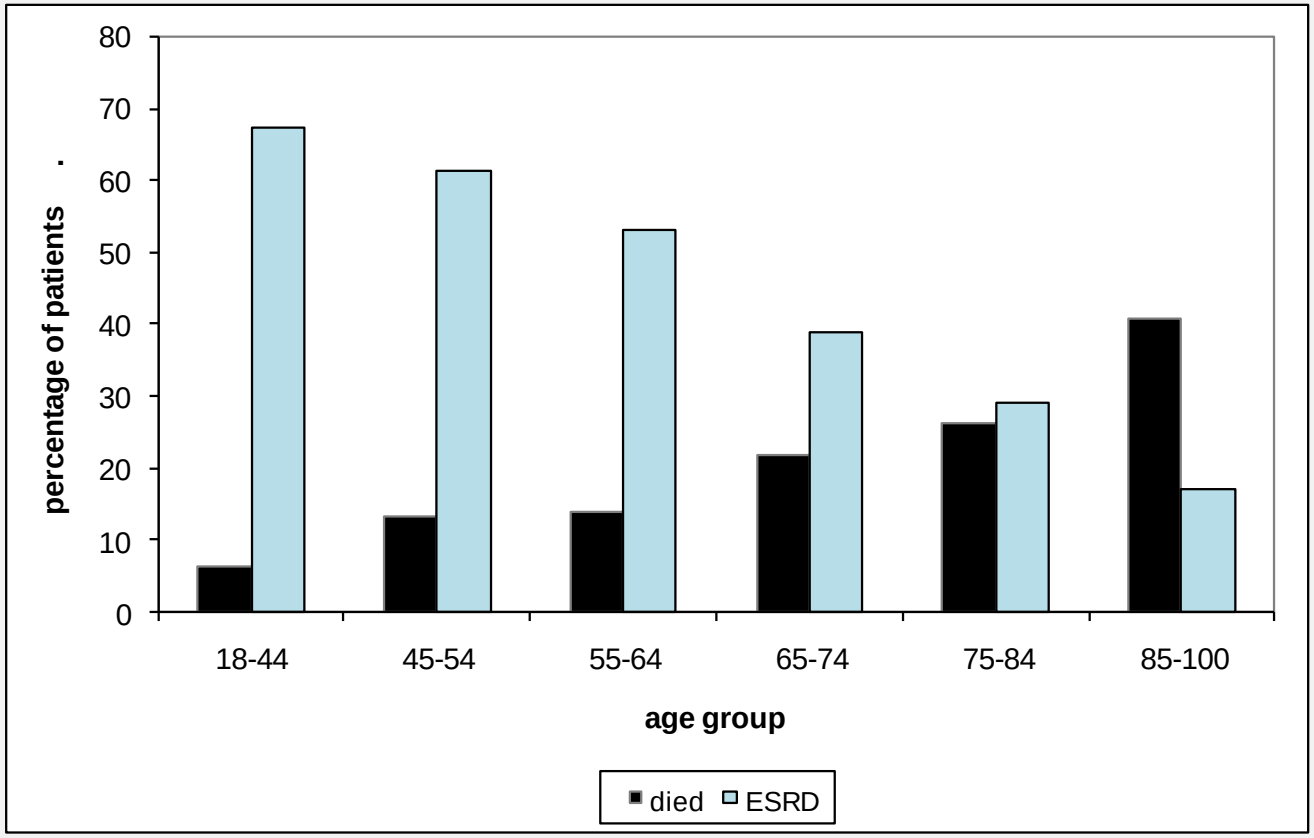


O'Hare, A. M. et al. J Am Soc Nephrol 2007;18:2758-2765

O'Hare, A. M. et al. J Am Soc Nephrol 2007;18:2758-2765

JASN

Patients with eGFR<25 treated for ESRD or who died within 2 years



O'Hare, Kidney Int. 2007 Mar;71(6):555-61

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Adjusted Rates Per 1000 Person-Years of Clinical Outcomes by Level of eGFR and Proteinuria Measured by Dipstick

Table 2. Adjusted Rates Per 1000 Person-Years of Clinical Outcomes by Level of eGFR and Proteinuria Measured by Dipstick[a]

	Proteinuria											
	All-Cause Mortality[b]			Myocardial Infarction[b]			End-stage Renal Disease[b]			Doubling of Serum Creatinine[c]		
	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy	Normal	Mild	Heavy
eGFR ≥60[d]												
Events, No.	12 157	3191	722	3171	474	103	62	11	35	739	223	146
Patients, No.	754 158	58 400	8013	754 158	58 400	8013	754 158	58 400	8013	487 335	39 835	5867
Rate (95% CI)	2.7 (2.6-2.8)	5.8 (5.5-6.0)	7.2 (6.6-7.8)	0.9 (0.9-1.0)	1.3 (1.2-1.5)	1.6 (1.3-2.0)	0.03 (0.02-0.03)	0.05 (0.03-0.09)	1.0 (0.7-1.4)	0.6 (0.5-0.6)	1.6 (1.4-1.9)	5.9 (5.0-7.0)
eGFR 45-59.9[d]												
Events, No.	4513	1598	514	1011	200	73	27	19	39	269	106	144
Patients, No.	68 768	8783	2294	68 768	8783	2294	68 768	8783	2294	58 562	7635	2011
Rate (95% CI)	2.9 (2.7-3.0)	5.2 (4.9-5.5)	7.2 (6.5-7.8)	1.2 (1.1-1.2)	1.3 (1.1-1.5)	1.8 (1.4-2.3)	0.2 (0.1-0.2)	0.7 (0.5-1.2)	4.3 (3.1-6.1)	0.9 (0.8-1.0)	2.1 (1.7-2.5)	10.0 (8.3-11.9)
eGFR 30-44.9[d]												
Events, No.	2162	1059	511	359	116	73	36	40	103	178	133	177
Patients, No.	11 823	3296	1594	11 823	3296	1594	11 823	3296	1594	10 926	3004	1462
Rate (95% CI)	4.0 (3.7-4.2)	5.8 (5.4-6.2)	7.5 (6.8-8.2)	1.4 (1.3-1.6)	1.5 (1.2-1.8)	2.1 (1.6-2.7)	1.3 (0.9-1.8)	4.2 (3.0-6.0)	16.1 (12.5-20.7)	2.0 (1.7-2.4)	4.7 (3.9-5.7)	12.8 (10.7-15.3)
eGFR 15-29.9[d]												
Events, No.	644	481	407	84	49	59	61	81	257	73	94	232
Patients, No.	1801	1078	977	1801	1078	977	1801	1078	977	1685	997	912
Rate (95% CI)	6.7 (6.2-7.3)	9.1 (8.2-10.0)	10.4 (9.3-11.6)	2.1 (1.6-2.6)	2.2 (1.6-2.9)	3.3 (2.5-4.3)	12.7 (9.3-17.3)	25.2 (18.9-33.4)	65.9 (52.3-82.9)	4.5 (3.5-5.9)	10.5 (8.3-13.3)	24.7 (20.7-29.6)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

[a] Adjusted for age; sex; diabetes; hypertension; socioeconomic status; and history of cancer, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, dementia, diabetes with end organ damage, diabetes without chronic complication, AIDS/HIV, metastatic solid tumor, myocardial infarction, mild liver disease, moderate or severe liver disease, paralysis, peptic ulcer disease, peripheral vascular disease, renal disease, and rheumatic disease. In this analysis, dipstick urinalysis was used to classify participants with respect to proteinuria: normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick ≥2+).

[b] n=920 985 for all-cause mortality, myocardial infarction, and end-stage renal disease.

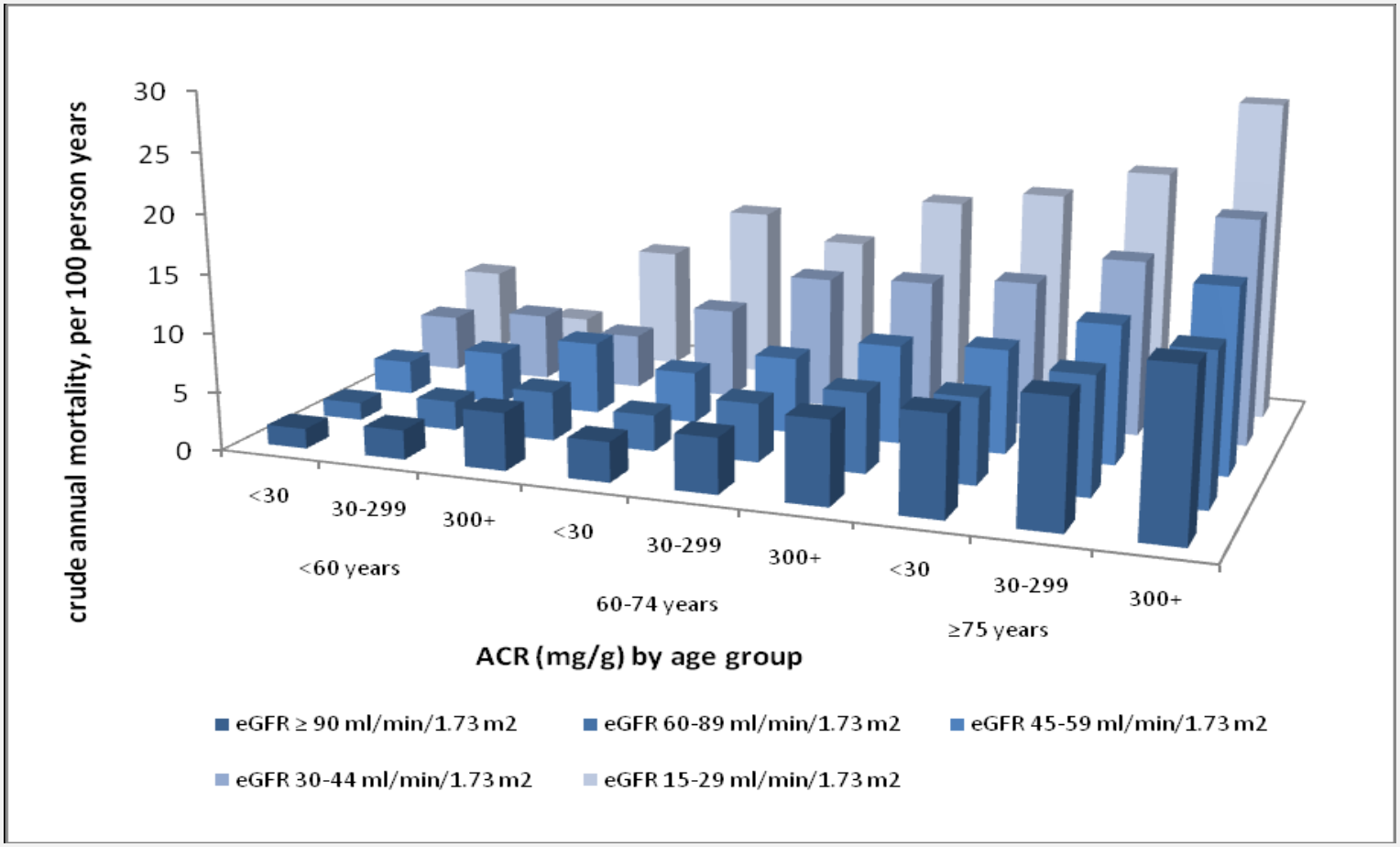
[c] n=620 231 for doubling of serum creatinine at end of follow-up.

[d] Unit of measure for eGFR is mL/min/1.73 m^2. The tests for linear trend across eGFR categories and across proteinuria categories were all significant at the $P<.001$ level.

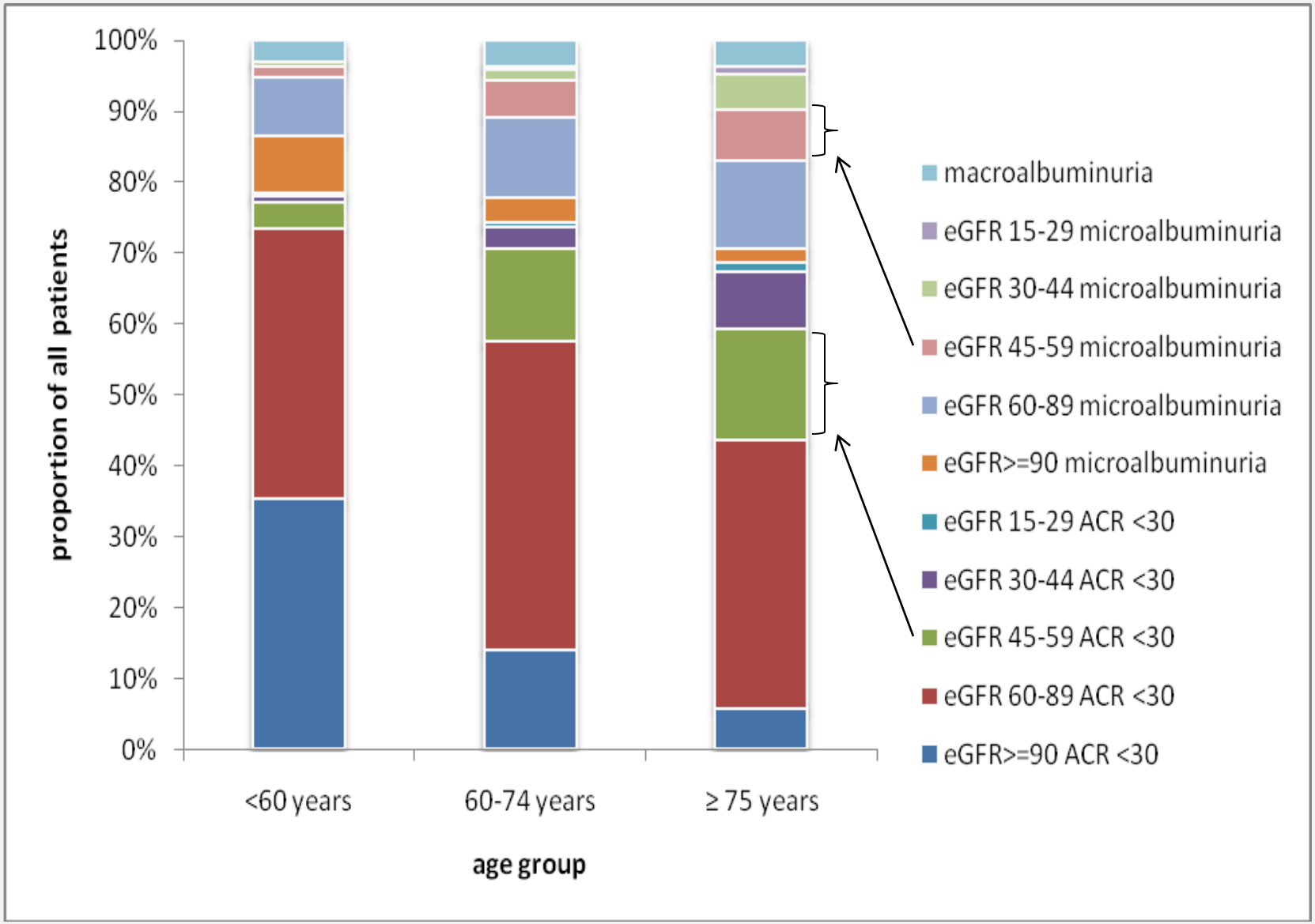
Hemmelgarn, B. R. et al. JAMA 2010;303:423-429.

JAMA

Prognostic importance of proteinuria by age group



O'Hare, A. M. et al. Archives of Internal Medicine (in press)



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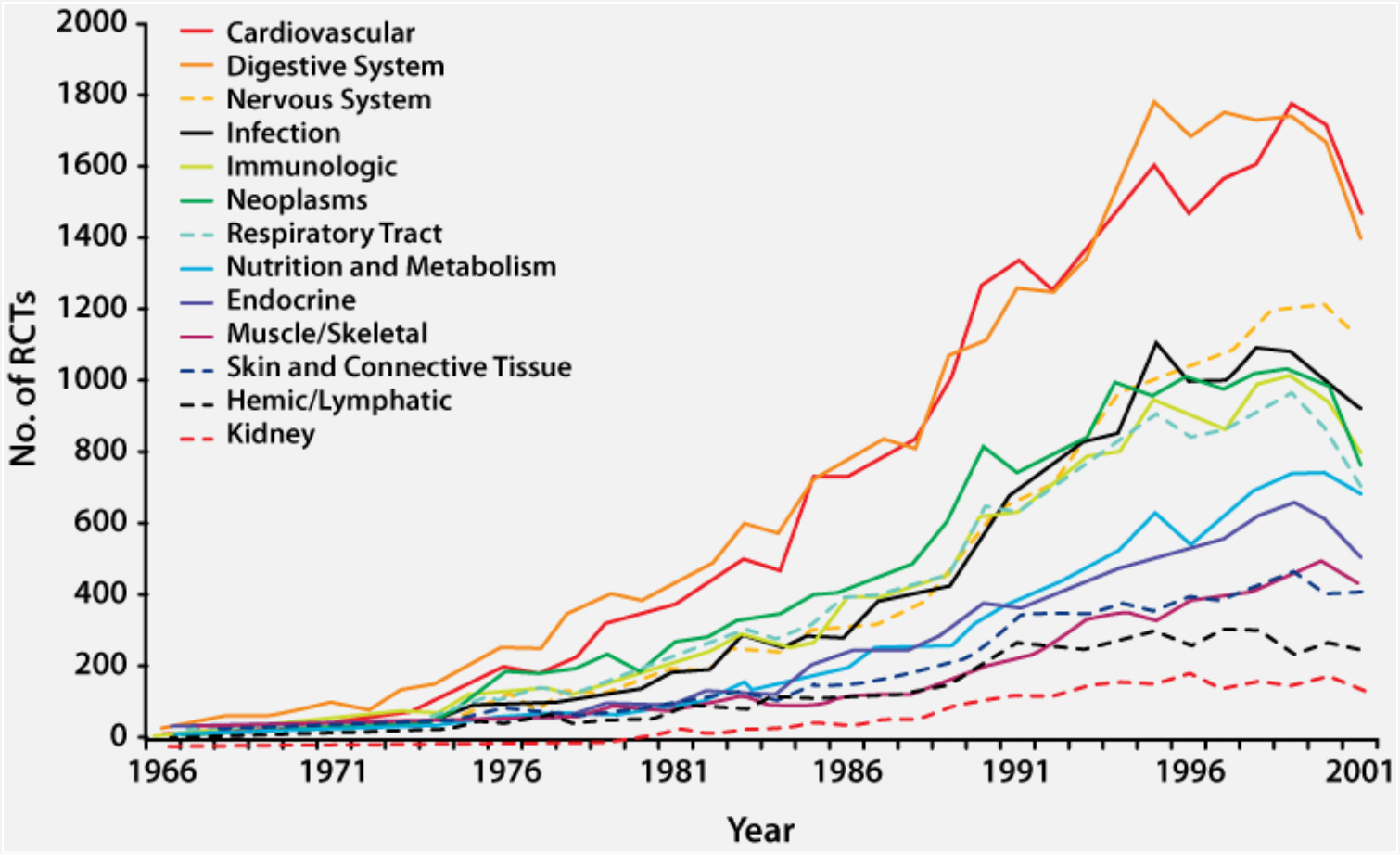
  - What information might proteinuria contribute?
- **Do we know that recommended interventions are beneficial in older adults with CKD?**
  - **ACE/ARB**
  - dialysis

Relatively Few RCTs

Number of Randomized Controlled Trials (RCTs) Published in Nephrology and 12 Other Specialties of Internal Medicine from 1966 to 2002



Strippoli GF, et al. J Am Soc Nephrol. 2004;15:411-9.

Choice of agent: Summary of Guidelines

Table 1. **Summary of Guidelines***

Source Document (Reference)	Year of Publication	Guideline Number	Search Dates for Evidence	Target Population	Trials Cited, *n*	Trials Reviewed, *n*
2004 KDOQI Clinical Practice Guidelines on Hypertension and Hypertensive Agents in Chronic Kidney Disease (8)	2004	8.2	1966 to July 2002†	Diabetes with an eGFR <60 mL/min per 1.73 m^2 or ACR ≥30 mg/g; hypertension not required	19	18
		9.2	1966 to July 2002†	No diabetes with a protein–creatinine ratio ≥200 mg/g; hypertension not required	11	8
2007 KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (10)	2007	3.1	January 1990 to August 2005	Diabetes and an eGFR <60 mL/min per 1.73 m^2 or "kidney damage"; blood pressure ≥130/80 mm Hg	18	16
JNC 7 (12)	2003		January 1997 to April 2003	eGFR <60 mL/min per 1.73 m^2 or ACR ≥200 mg/g; blood pressure ≥130/80 mm Hg	5	5
American Diabetes Association, Standards of Medical Care in Diabetes (11)	2008		1988 to October 2007	ACR ≥30 mg/g; hypertension not required	3	3
All sources					32	27

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; KDOQI = Kidney Disease Outcomes Quality Initiative.

* Some studies were cited in more than 1 guideline.

† Select studies identified by experts were added after this date.

O'Hare, A. M. et. al. Ann Intern Med 2009;150:717-724

Annals of Internal Medicine

Annals of Internal Medicine | ACADEMIA AND CLINIC

Current Guidelines for Using Angiotensin-Converting Enzyme Inhibitors and Angiotensin II–Receptor Antagonists in Chronic Kidney Disease: Is the Evidence Base Relevant to Older Adults?

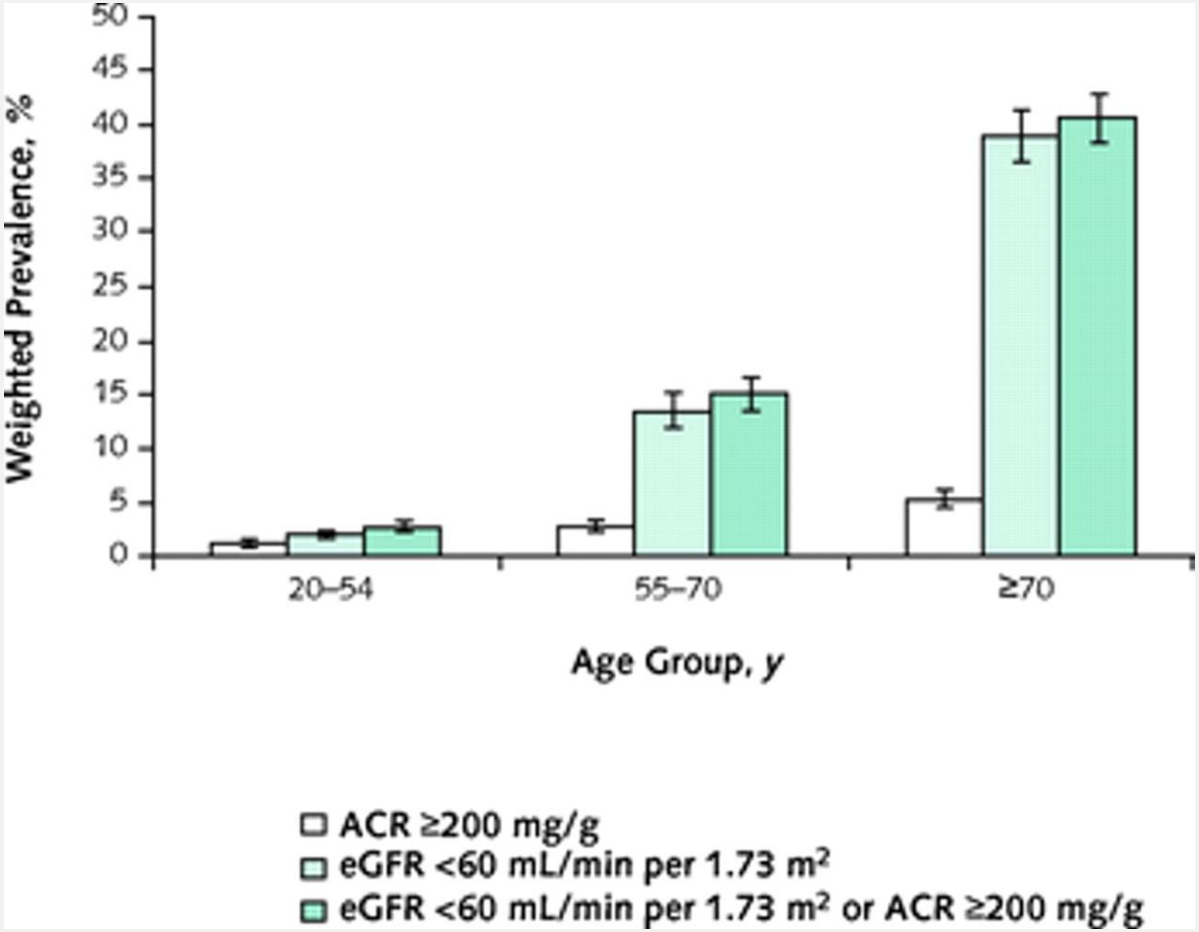
Ann M. O'Hare, MD; James S. Kaufman, MD; Kenneth E. Covinsky, MD, MPH; C. Seth Landefeld, MD; Lynne V. McFarland, PhD; and Eric B. Larson, MD, MPH

Angiotensin-converting enzyme inhibitors and angiotensin II–receptor antagonists are recommended for patients with chronic kidney disease because these drugs can slow disease progression. Older adults account for a large and growing number of patients with chronic kidney disease. The authors evaluated the relevance to adults older than 70 years of the evidence base for major U.S. practice guidelines for the use of these agents in chronic kidney disease. The authors first examined the representation of older adults in randomized trials that underpin these guidelines, then compared the characteristics of participants in these trials with those of a representative sample of older adults with chronic kidney disease in the general population. The authors found that current guidelines for the use of angiotensin-converting enzyme inhibitors and angiotensin II–receptor antagonists in chronic kidney disease are based on evidence with limited relevance to most persons older than 70 years with this condition.

Ann Intern Med. 2009;150:717-724. www.annals.org
For author affiliations, see end of text.

- Few trials have enrolled patients >70
- Most trials have selected for proteinuria

Prevalence of chronic kidney disease, by age group in the US Population



O'Hare, A. M. et. al. Ann Intern Med 2009;150:717-724

Annals of Internal Medicine

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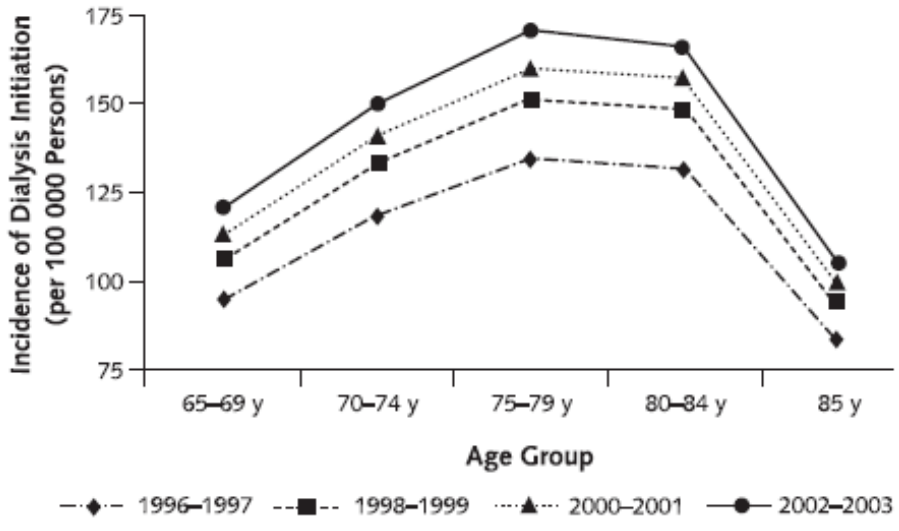
  - ACE/ARB
  - **dialysis**

Increasing numbers of older patients starting dialysis

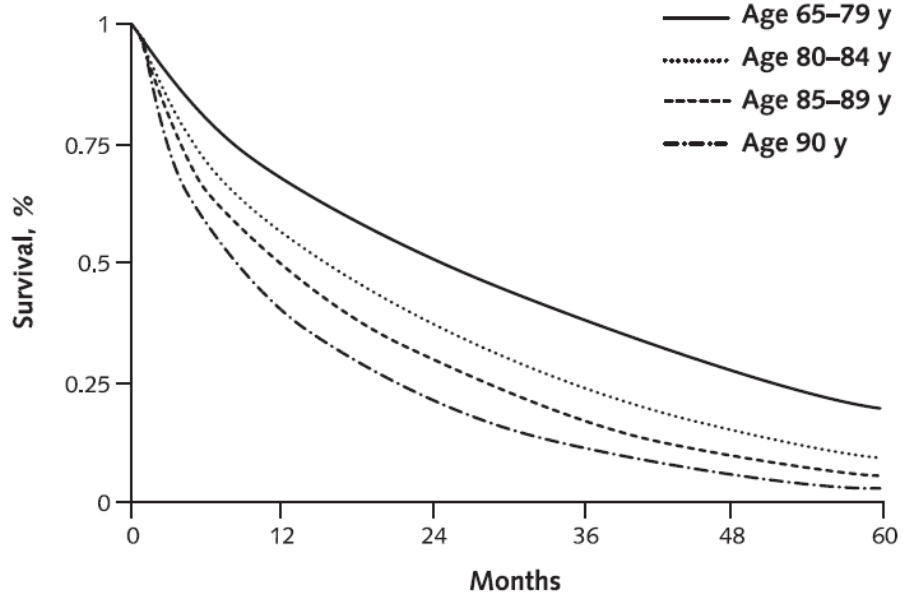
Figure 1. Incidence of dialysis initiation from 1996 to 2003 by year and age group (per 100 000 persons in U.S. population), adjusted for sex and race.



Kurella, Ann Intern Med. 2007 Feb 6;146(3):177-83.

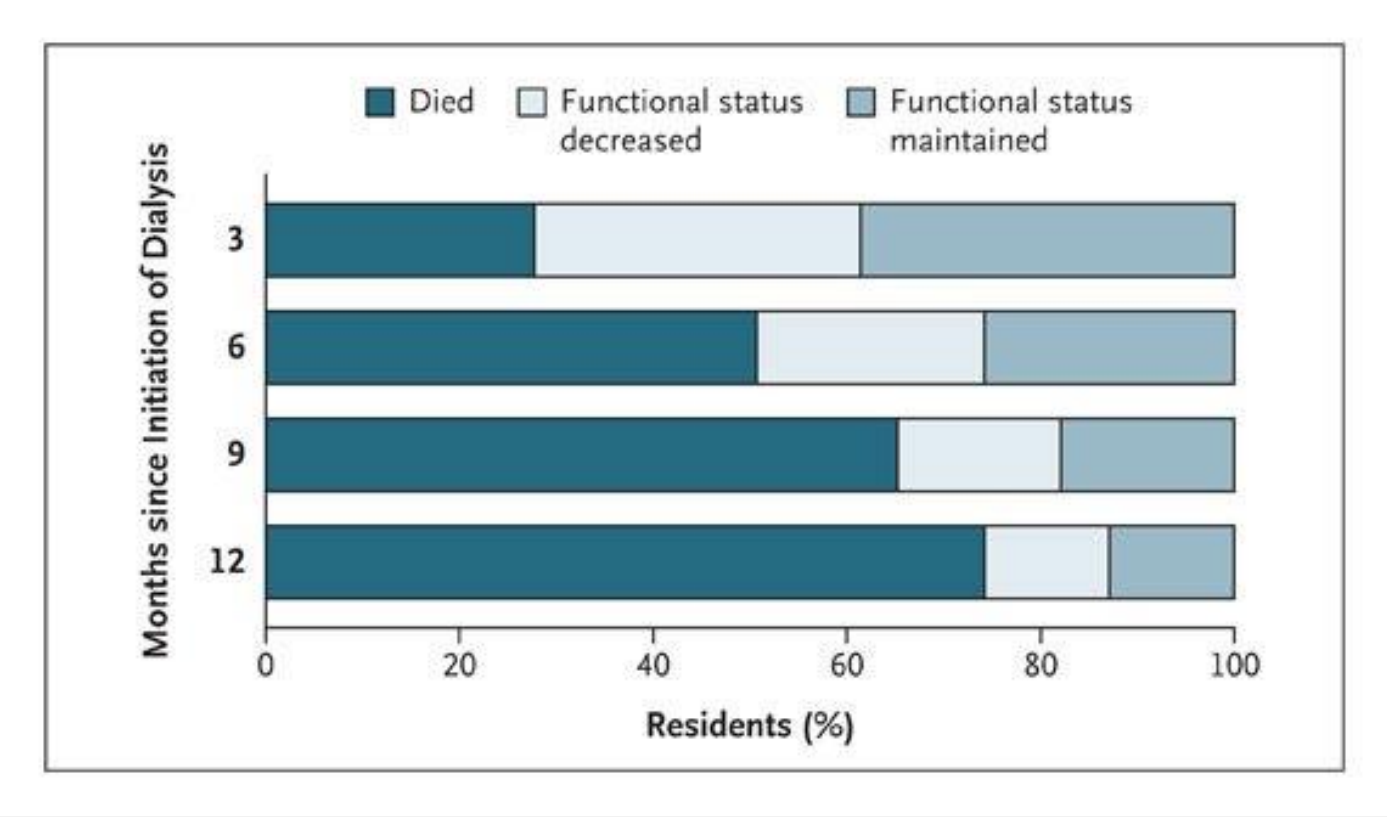
Poor survival of elderly patients beginning dialysis

Figure 2. Survival of octogenarians and nonagenarians at dialysis initiation by age group (*top*), ambulatory status (*middle*), and number of comorbid conditions (*bottom*).



Kurella, Ann Intern Med. 2007 Feb 6;146(3):177-83.

Loss of functional status among nursing home patients beginning chronic dialysis



Kurella Tamura M et al. N Engl J Med 2009;361:1539-1547

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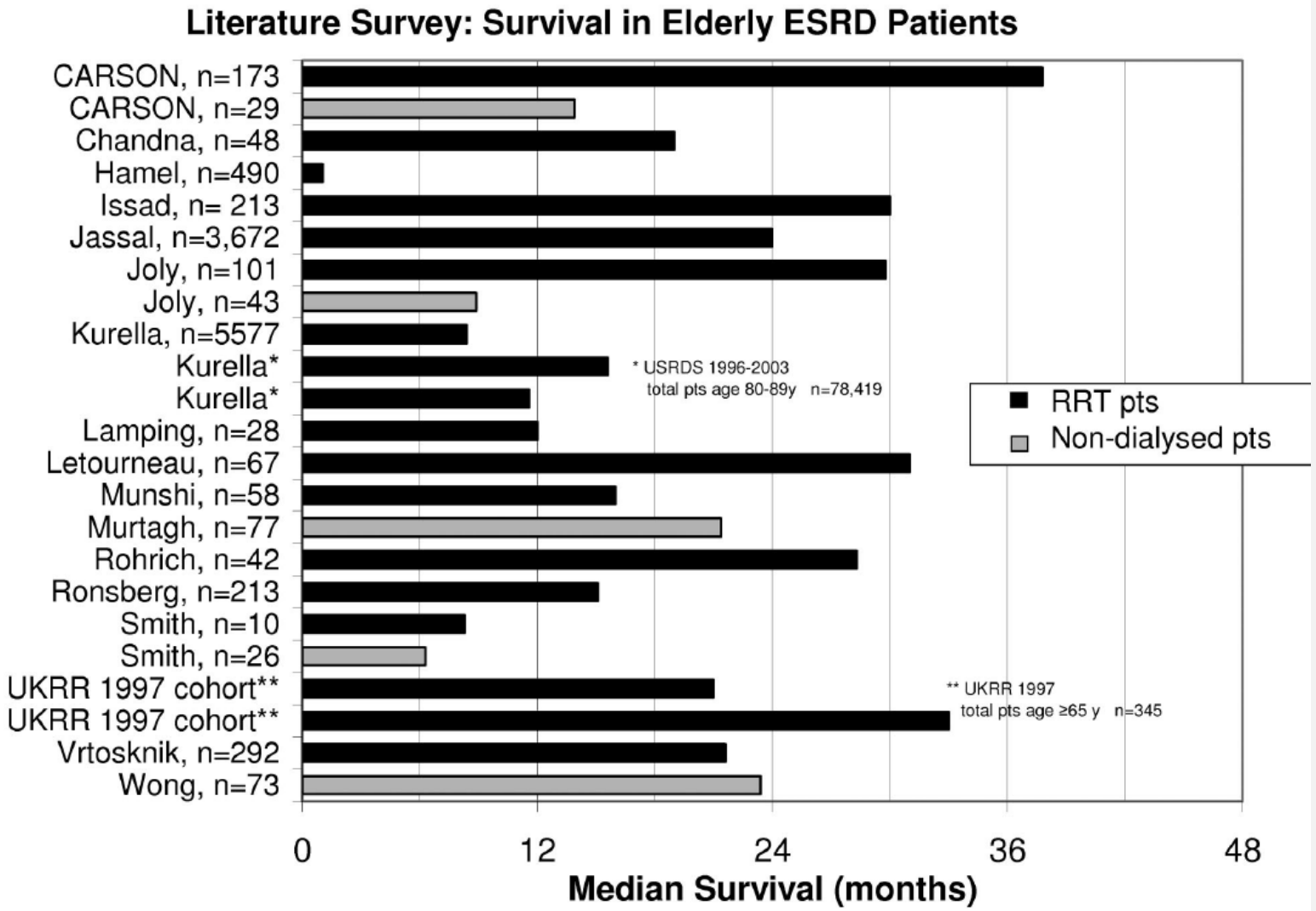
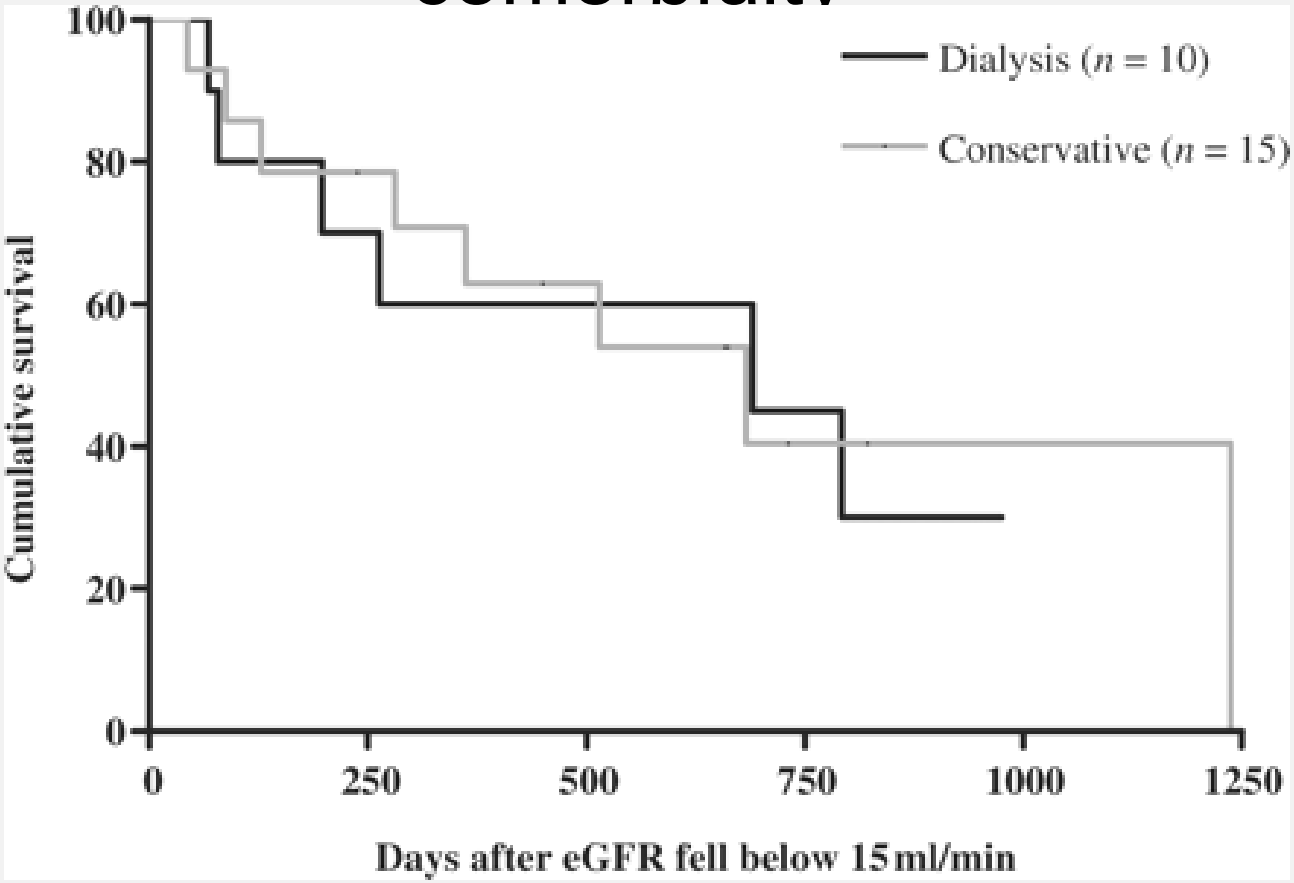


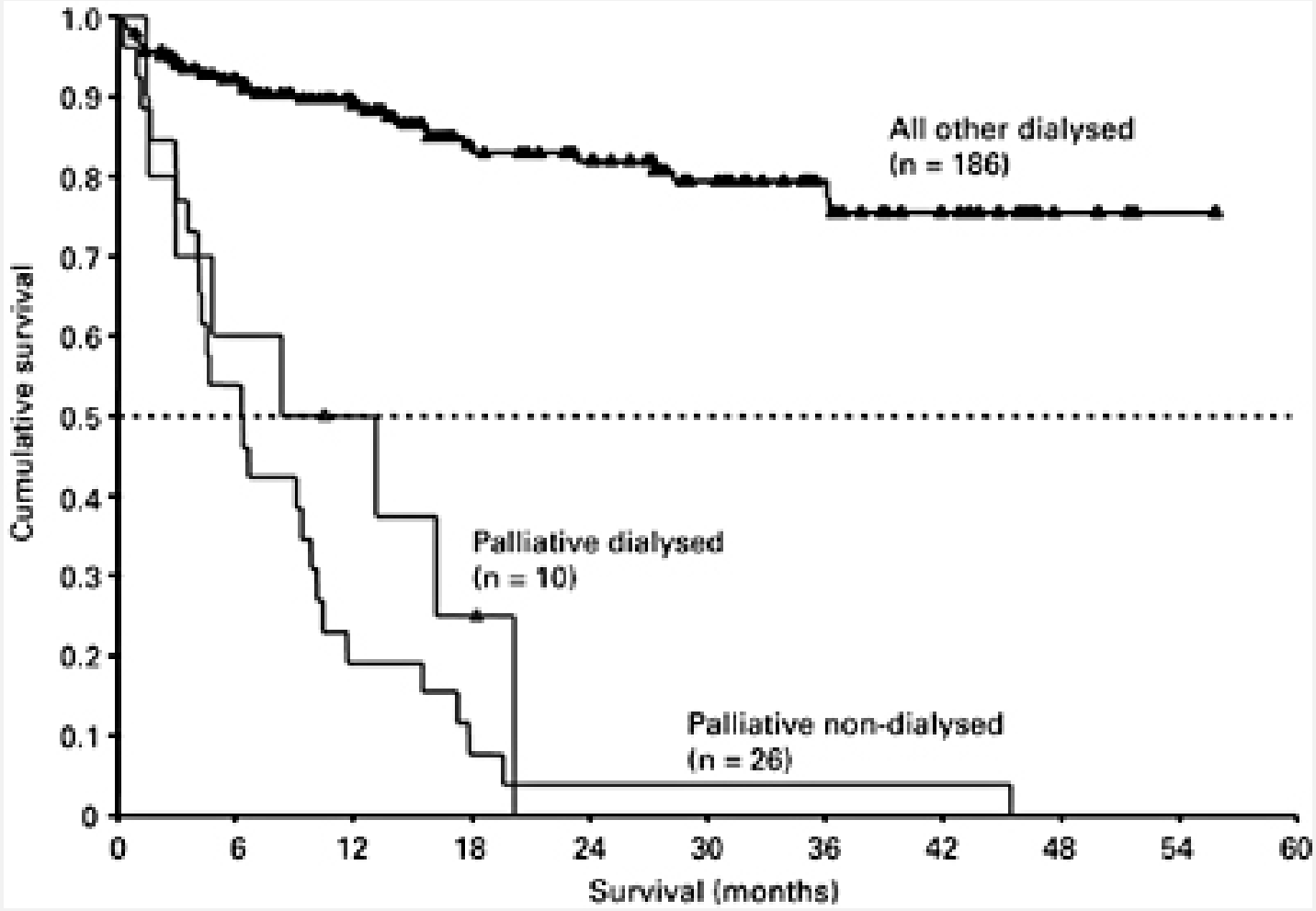
Figure 4. Literature survey: Summary graph of survival of elderly patients with ESRD in previous studies.

Carson, CJASN, 2009 Oct;4(10):1611-9.

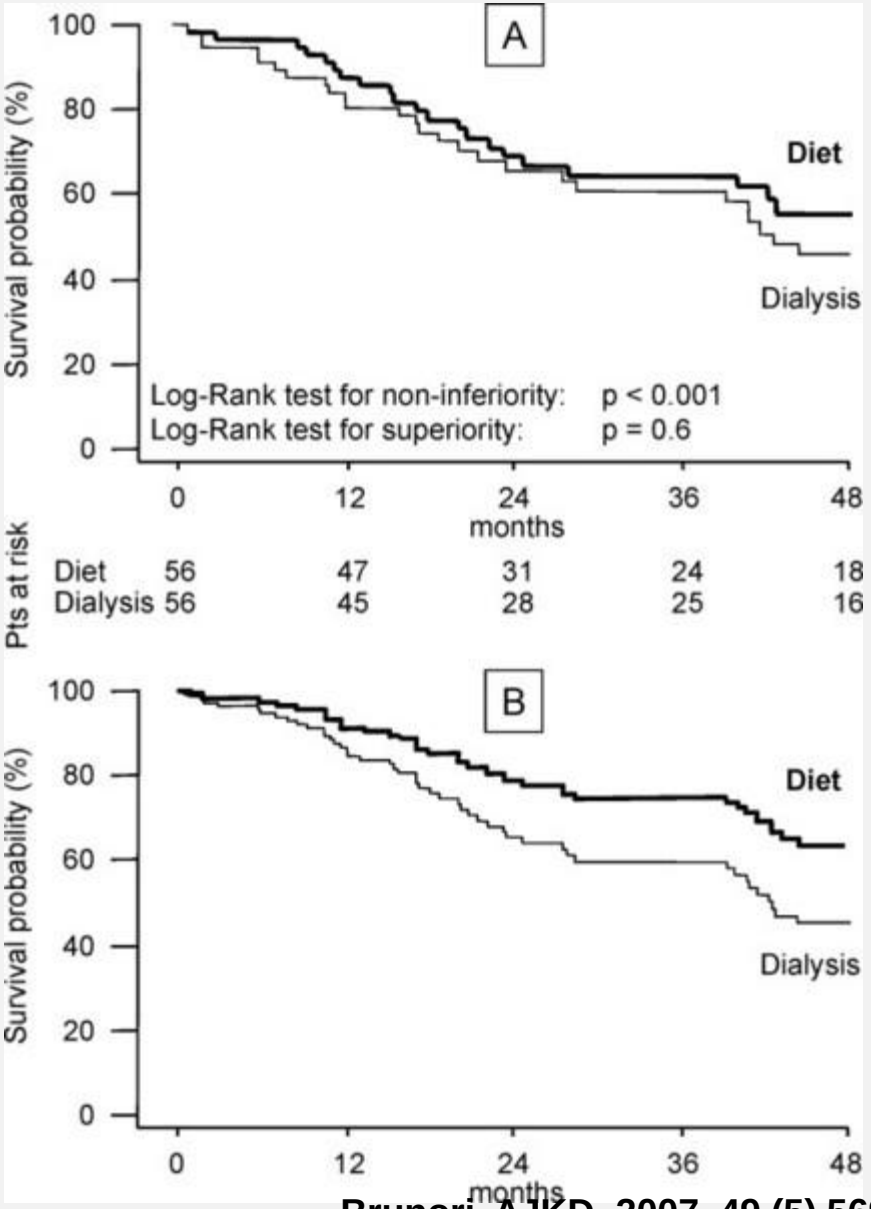
Dialysis vs. conservative therapy in adults 75 and older with high burden of comorbiditv



Murtagh, Nephrology Dialysis Transplantation 2007 22(7):1955-1962



Smith, Nephron Clinical Practice, 2003;95 (2):c40-c46.



Brunori, AJKD, 2007, 49 (5) 569-580

Interventions

Table 33. Stages of Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations: CVD, cardiovascular disease

Treatment Regimen Based on Clinical Practice Guidelines for a Hypothetical 79-Year-Old Woman With Hypertension, Diabetes Mellitus, Osteoporosis, Osteoarthritis, and COPD*

Table 3. Treatment Regimen Based on Clinical Practice Guidelines for a Hypothetical 79-Year-Old Woman With Hypertension, Diabetes Mellitus, Osteoporosis, Osteoarthritis, and COPD*

Time	Medications†	Other
7:00 AM	Ipratropium metered dose inhaler 70 mg/wk of alendronate	Check feet Sit upright for 30 min on day when alendronate is taken Check blood sugar
8:00 AM	500 mg of calcium and 200 IU of vitamin D 12.5 mg of hydrochlorothiazide 40 mg of lisinopril 10 mg of glyburide 81 mg of aspirin 850 mg of metformin 250 mg of naproxen 20 mg of omeprazole	Eat breakfast 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
12:00 PM		Eat lunch 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
1:00 PM	Ipratropium metered dose inhaler 500 mg of calcium and 200 IU of vitamin D	
7:00 PM	Ipratropium metered dose inhaler 850 mg of metformin 500 mg of calcium and 200 IU of vitamin D 40 mg of lovastatin 250 mg of naproxen	Eat dinner 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
11:00 PM	Ipratropium metered dose inhaler	
As needed	Albuterol metered dose inhaler	

Abbreviations: ADA, American Diabetes Association; COPD, chronic obstructive pulmonary disease; DASH, Dietary Approaches to Stop Hypertension.

*Clinical practice guidelines used: (1) Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII.[39] (2) ADA[19-32]; glycemic control is recommended; however, specific medicines are not described. (3) American College of Rheumatology[33-36]; recent evidence about the safety and appropriateness of cyclooxygenase inhibitors, particularly in individuals with comorbid cardiovascular disease, led us to omit them from the list of medication options, although they are discussed in the reviewed clinical practice guidelines. (4) National Osteoporosis Foundation[40]; this regimen assumes dietary intake of 200 IU of vitamin D. (5) National Heart, Lung, and Blood Institute and World Health Organization.[37,38]

†Taken orally unless otherwise indicated. The medication complexity score of the regimen for this hypothetical woman is 14, with 19 doses of medications per day, assuming 2 as needed doses of albuterol metered dose inhaler plus 70 mg/wk of alendronate.

‡DASH and ADA dietary guidelines may be synthesized, but the help of a registered dietitian is specifically recommended. Eat foods containing carbohydrate from whole grains, fruits, vegetables, and low-fat milk. Avoid protein intake of more than 20% of total daily energy; lower protein intake to about 10% of daily calories if overt nephropathy is present. Limit intake of saturated fat (<10% of total daily energy) and dietary cholesterol (<200-300 mg). Limit intake of *trans*unsaturated fatty acids. Eat 2 to 3 servings of fish per week. Intake of polyunsaturated fat should be about 10% of total daily energy.

Boyd, C. M. et al. JAMA 2005;294:716-724.

JAMA

Disease-oriented vs. individualized models of care

Table 1. Characteristics of Two Models of Medical Care

Disease-Oriented Model	Integrated, Individually Tailored Model
Clinical decision making is focused primarily on the diagnosis, prevention, and treatment of individual diseases.	Clinical decision making is focused primarily on the priorities and preferences of individual patients.
Discrete pathology is believed to cause disease; psychological, social, cultural, environmental and other factors are secondary factors, not primary determinants of disease.	Health conditions are believed to result from the complex interplay of genetic, environmental, psychological, social, and other factors.
Treatment is targeted at the pathophysiologic mechanisms thought to cause the disease(s).	Treatment is targeted at the modifiable factors contributing to the health conditions impeding the patient's health goals.
Symptoms and impairments are best addressed by diagnosing and treating "causative" disease(s).	Symptoms and impairments are the primary foci of treatment even if they cannot be ascribed to a discrete disease.
Relevant clinical outcomes are determined by the disease(s).	Relevant clinical outcomes are determined by individual patient preference.
Survival is the usual primary focus of disease prevention and treatment.	Survival is one of several competing goals.

Tinetti and Fried, Am J Med. 2004 Feb 1;116(3):179-85.

Summary

Low eGFR is very common in the elderly.

Proteinuria is also more common in older adults but prevalence increases less dramatically than eGFR with age

The relationship between eGFR and clinical outcomes such as death and ESRD varies substantially across age groups

Absence of high quality evidence to support recommended management strategies in older adults

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