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Lipids, the Heart, and the Kidney

A New Triad in the Making

Moderator

James A. Underberg, MD
Clinical Assistant Professor of Medicine
NYU School of Medicine
NYU Center for Prevention of Cardiovascular Disease
Director
Bellevue Hospital Lipid Clinic
New York, New York

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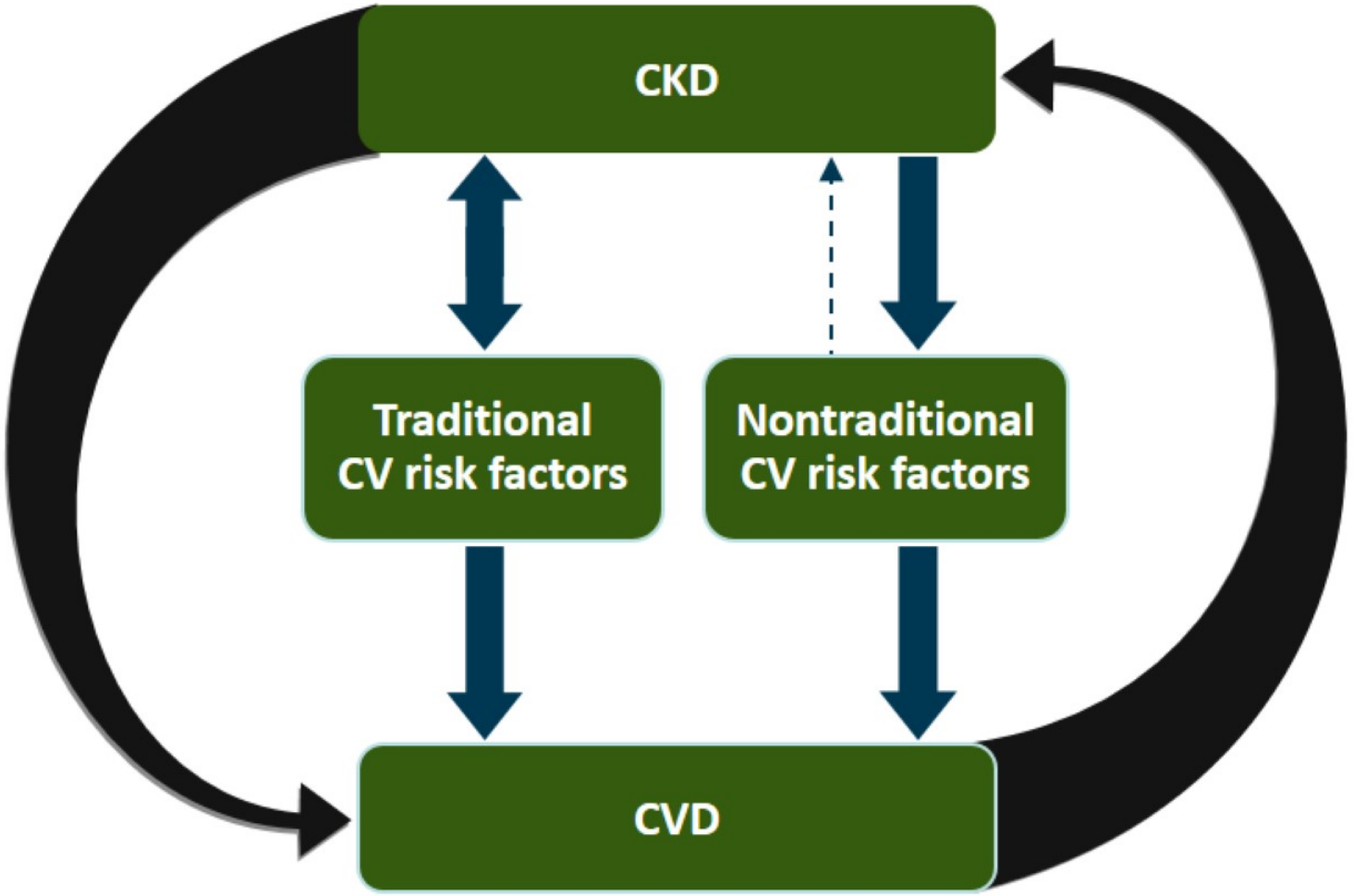
Panelists

Robert P. Giugliano, MD
Associate Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital
Cardiovascular Medicine
Boston, Massachusetts

Matthew R. Weir, MD
Professor of Medicine
Director
Division of Nephrology
University of Maryland
School of Medicine
Baltimore, Maryland

Relationship Between CKD and CVD

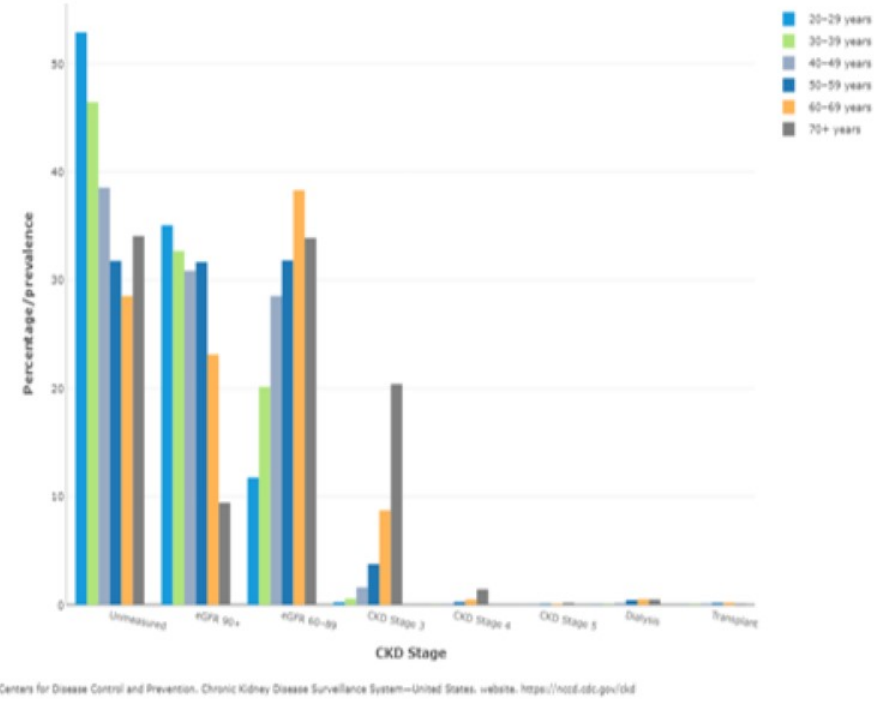


Menon V, et al. *Am J Kidney Dis*. 2005;45:223-232.

CKD Burden and Severity Increase With Age

- More than 10% of adults in the United States have CKD[a]
  - Age 20-39: 4%
  - Age ≥ 70: 47%
  - Overall prevalence of CKD ≥ prevalence of diabetes
- In the VA health system, 10% to 15% of patients have CKD stages 3-5[b]
  - Higher incidence: in patients with diabetes or hypertension, in females, and in non-Hispanic whites and Native Hawaiians/ Pacific Islanders[b]

Prevalence of CKD by Stage and Age: VA Health System, 2011[b]

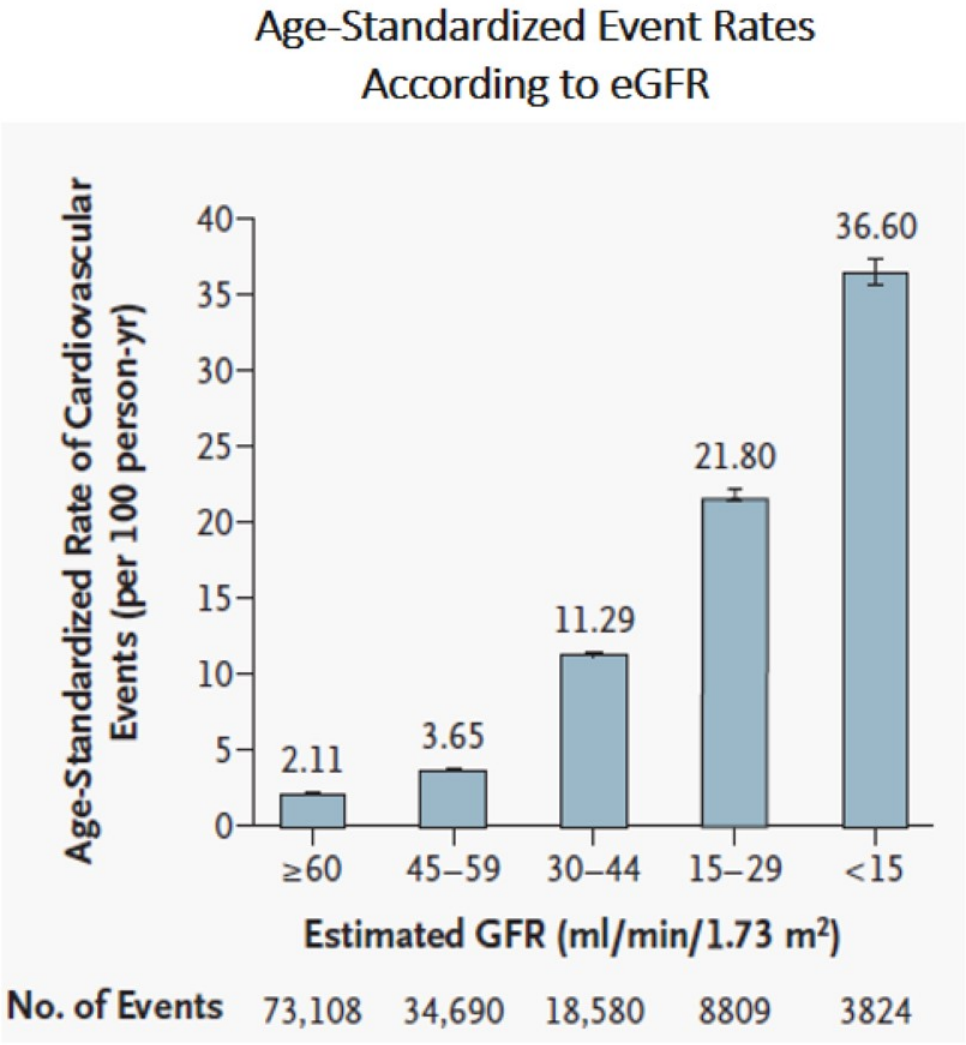


Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. website. https://nccd.cdc.gov/ckd

a. Eckardt KU, et al. *Lancet*. 2013;382:158-169.
b. CDC website. CKD surveillance system 2011.

CVD Risk Increases With Renal Impairment

- Independent, graded association between reduced eGFR and the risk for death, CV events,* and hospitalization among > 1 million ambulatory adults



*CHD, heart failure, ischemic stroke, PAD.

Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

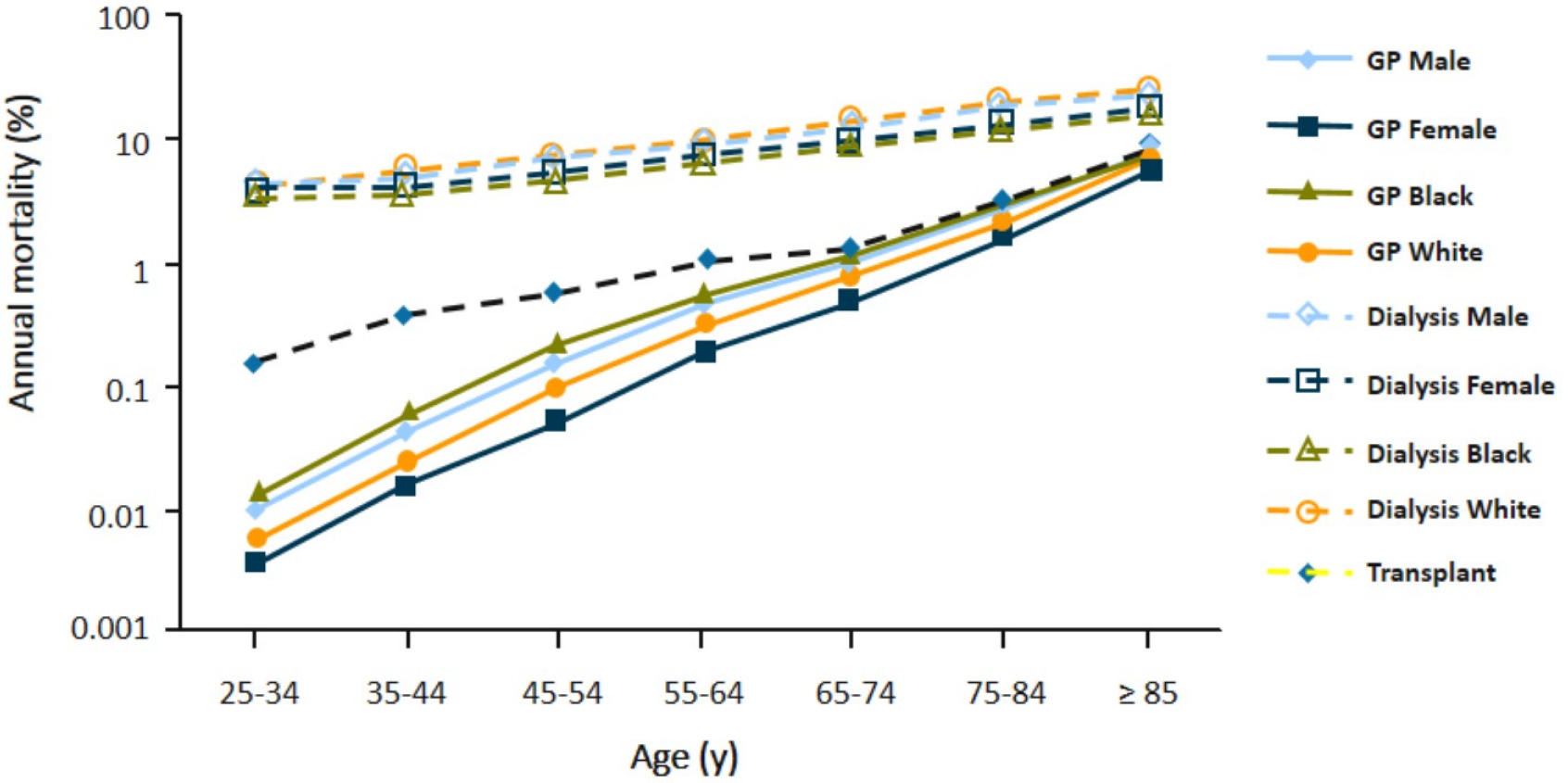
CV Mortality Is Higher in Patients With ESRD

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

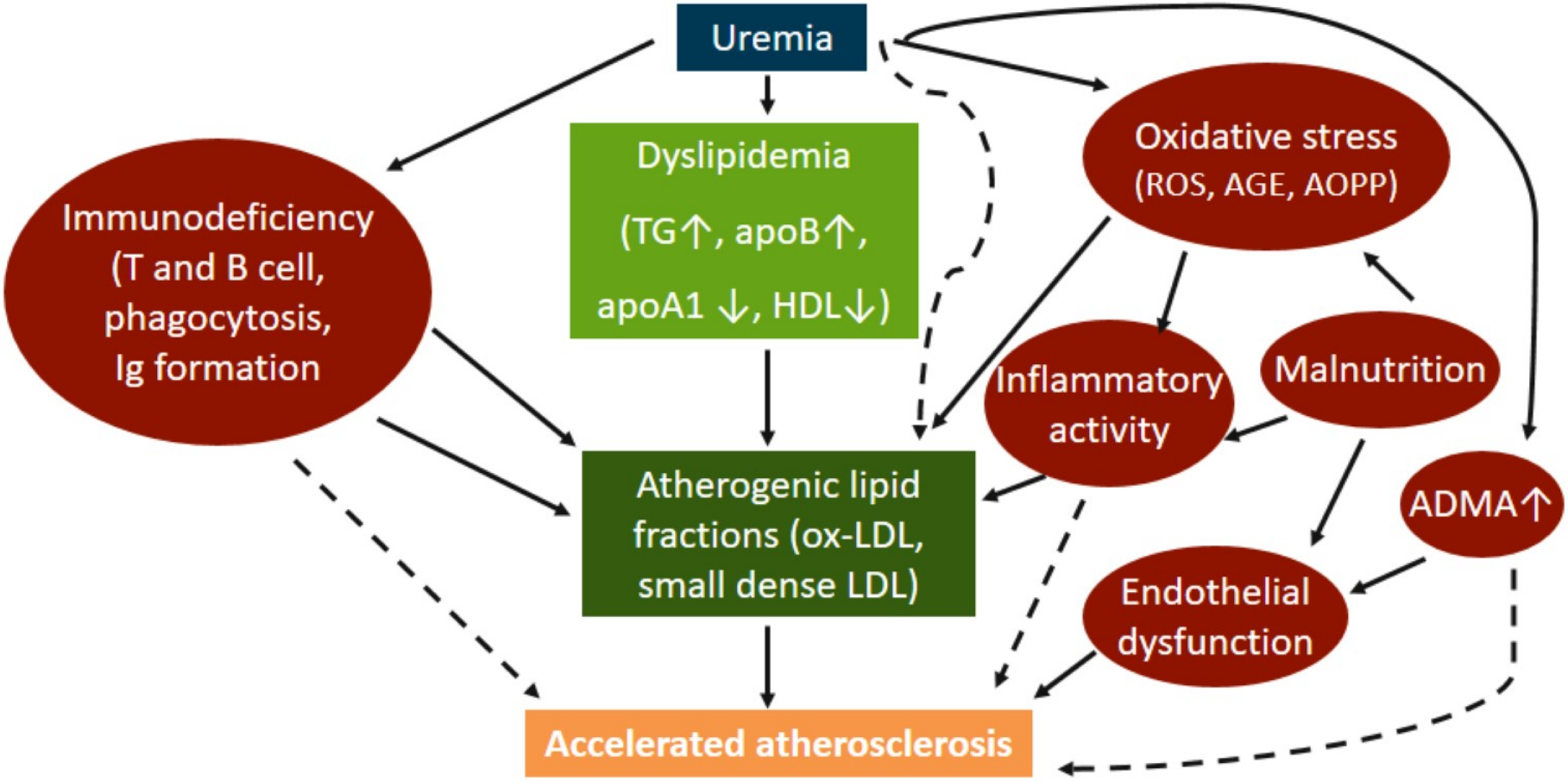
CV Mortality
General Population vs Dialysis or Transplant Patients

CV Mortality in the General Population (NCHS) and in Kidney Failure Treated by Dialysis or Transplant (USRDS)



Adapted from Foley RN, et al. *Am J Kidney Dis*. 1998;32(5 Suppl 3):S112-S119.

Mechanism of CVD Development in Patients With Uremia



Fellström BC, et al. *Kidney Int*. 2003;63(Suppl 84):S204-S206.

Lipid-Lowering Therapy Should Be Used Routinely in Patients With CKD

Rationale for Lipid-Lowering Clinical Trials in the CKD Population[a-f]

- Patients with CKD and ESRD are at increased risk for CV complications
- Patients with CKD and ESRD have abnormal lipid profiles
- Secondary analyses of lipid-lowering studies indicated statin treatment improved CV outcomes in patients with CKD
- Secondary analyses of these studies also demonstrated slowing of CKD progression
- Need for randomized placebo-controlled statin trials in patients with CKD and ESRD

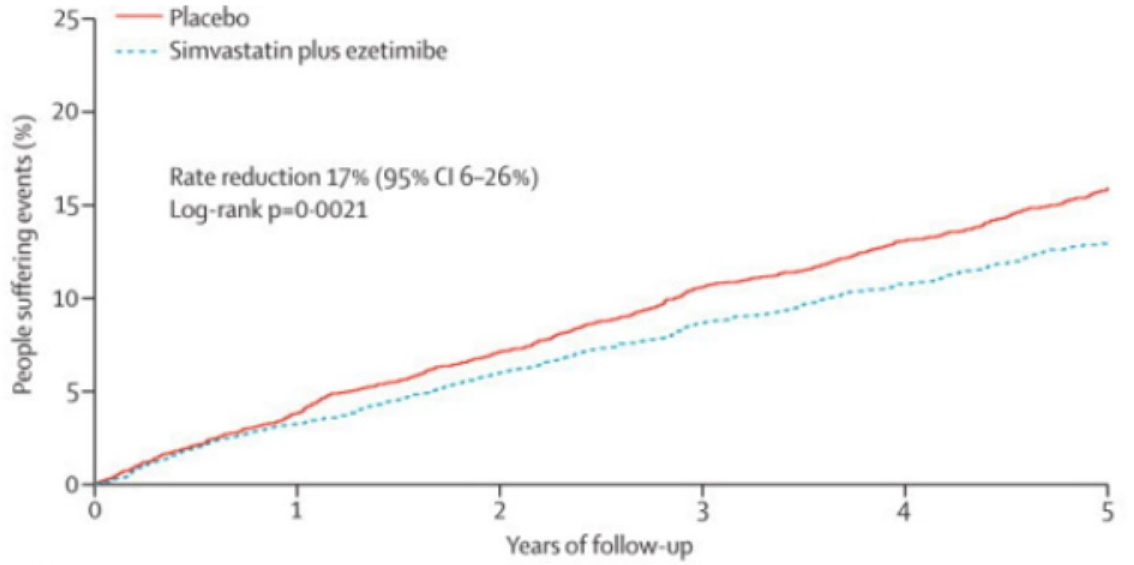
a. Pedersen T, et al. *Lancet*.1994;344:1383-1389; b. Shepherd J, et al. *N Engl J Med*. 1995;333:1301-1307; c. Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; d. Seliger SL, et al. *Kidney Int*. 2002;61:297-304; e. Liao JK. *Am J Cardiol*. 2005;96:24F-33F; f. Fellström BC, et al. *Kidney Int*. 2003;63(Suppl 84):S204-S206.

SHARP Trial

Simvastatin Plus Ezetimibe in CKD and Dialysis Patients

- Randomized, double-blind trial in 9270 patients with CKD (one-third on dialysis) randomized to simvastatin 20 mg + 10 mg ezetimibe daily or placebo

Major Atherosclerotic Events Over 5 Years*



Number at risk

Placebo	4620	4204	3849	3469	2566	1269
Simvastatin plus ezetimibe	4650	4271	3939	3546	2655	1265

Study supports LDL reduction in patients at high risk for ASCVD events

*Nonfatal MI or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure.

Baigent C, et al. *Lancet*. 2011;377:2181-2192.

NKF KDOQI Guidelines and the 2010 CVD and CKD Core Curriculum

Management of Dyslipidemia

All patients with CKD, even in the absence of known CVD, should be considered at high risk for CVD outcomes[a]

Goal lipid levels (LDL-C and non-HDL-C)

- LDL-C < 100 mg/dL (< 2.59 mmol/L) (Level B evidence)[a,b]
- LDL-C < 70 mg/dL is a therapeutic option in patients with CKD and diabetes (Level B evidence)[a-c]
- Non-HDL-C < 130 mg/dL (< 3.36 mmol/L) (Level B evidence)[a,b]

Special attention should made to patients with CKD and diabetes

- Patients with stages 1 to 4 should be treated with a statin (Level B evidence)[a,b]
- Patients with stage 5 on hemodialysis should not be initiated on a statin unless there is a specific CV indication (Level A evidence)[a,b]

a. Shastri S, et al. *Am J Kidney Dis*. 2010;56:399-417; b. NKF. *Am J Kidney Dis*. 2007;49(2 suppl 2):S12-154; c. NKF website. KDOQI™ clinical practice guidelines and recommendations for diabetes in CKD 2007.

CKD Is a Risk Enhancer for CVD
ACC/AHA 2018 Guidelines

Family history of premature ASCVD
- Males, age < 55 years
- Females, age < 65 years

Primary hypercholesteremia†
- LDL-C 160-189 mg/dL (4.1-4.8 mmol/L)
- Non-HDL-C 190-219 mg/dL (4.9-5.6 mmol/L)

Metabolic syndrome (total: 3)
- Increased waist circumference
- TGs > 175 mg/dL
- Low HDL-C (< 40 mg/dL [men], < 50 mg/dL [women])
- Elevated BP
- Elevated glucose

Conditions specific to women
- Premature menopause (before age 40 years)
- Pre-eclampsia

CKD
- eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria
- Not treated with dialysis or transplant

Chronic inflammatory conditions
- Psoriasis, rheumatoid arthritis, HIV/AIDS

High-risk race/ethnicities
- South Asian

Lipid/biomarkers
- hs-CRP ≥ 2.0 mg/L
- Lp(a) ≥ 50 mg/dL (≥ 125 nmol/L)
- apoB ≥ 130 mg/dL
- ABI < 0.9

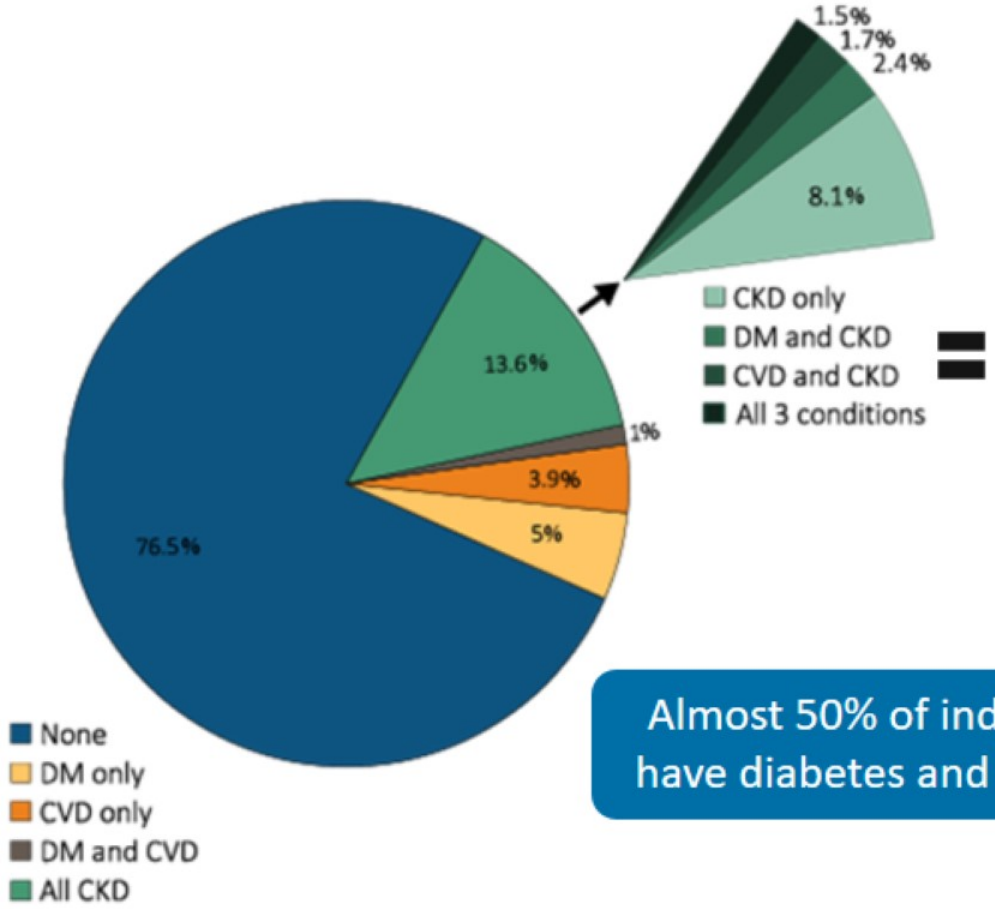
Presence of risk-enhancing factors may affect the threshold for statin initiation or intensification in primary prevention of CVD*

*Optimally, 3 determinations. †No established ASCVD or DM.

Grundy SM, et al. *J Am Coll Cardiol*. 2018;pii:S0735-1097:39034-X.

CKD Is a Disease Multiplier

Distribution of NHANES participants with diabetes, self-reported cardiovascular disease, and single-sample markers of CKD, 2007-2012

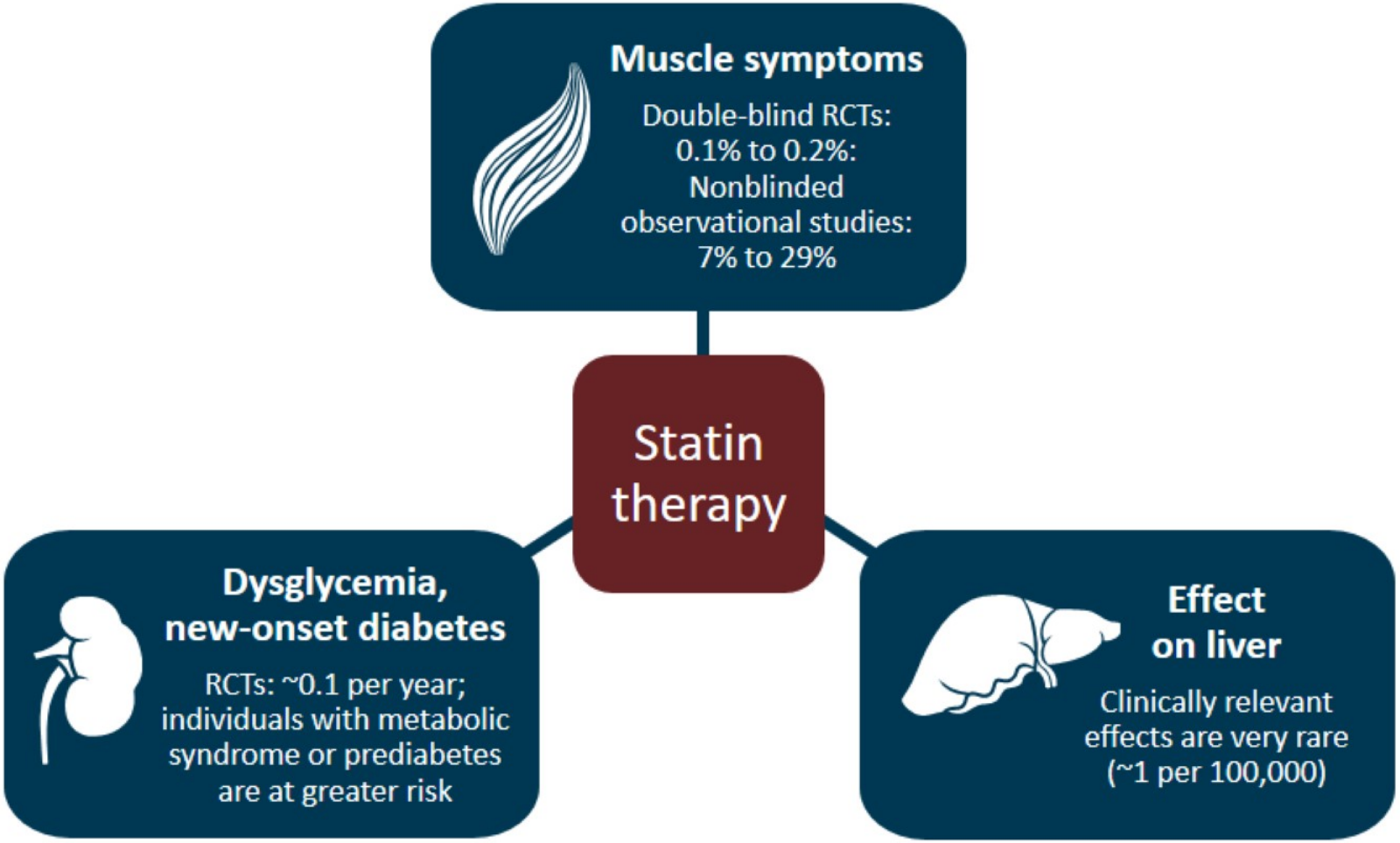


Significant risk for CV events

Almost 50% of individuals with CKD have diabetes and self-reported CVD

NIDDK website. US kidney disease statistics 2016.

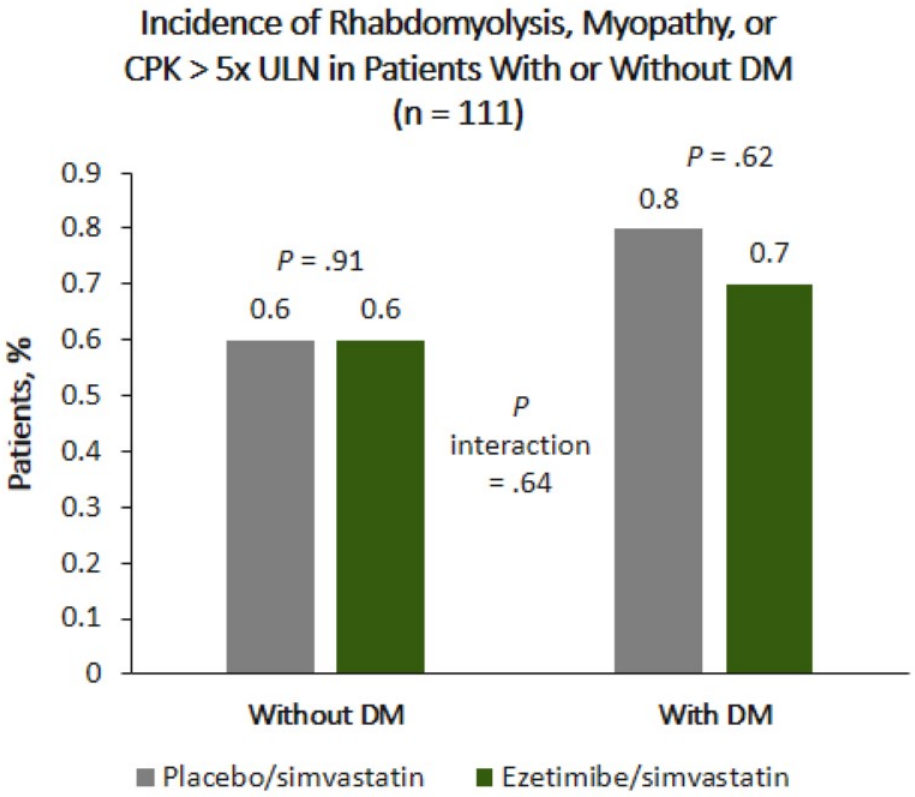
Statin AEs



Mach F, et al. *Eur Heart J*. 2018; 39:2526-2539.

IMPROVE-IT Subanalysis of Outcomes and AEs in Patients With DM

- IMPROVE-IT enrolled 18,144 patients* after ACS with LDL-C 50 to 125 mg/dL
  - Randomized to 40 mg ezetimibe/simvastatin or 40 mg placebo/simvastatin
- Primary composite endpoint: CV death, major coronary events, and stroke
- DM was a prespecified subgroup (N = 4933)



Subanalysis: Primary Endpoint in Patients With DM by Age Group (HR, CI, and *P* Value)†	
< 75 years old	0.87 (0.78, 0.96); *P* = .008
≥ 75 years old	0.80 (0.65, 0.99); *P* = .039

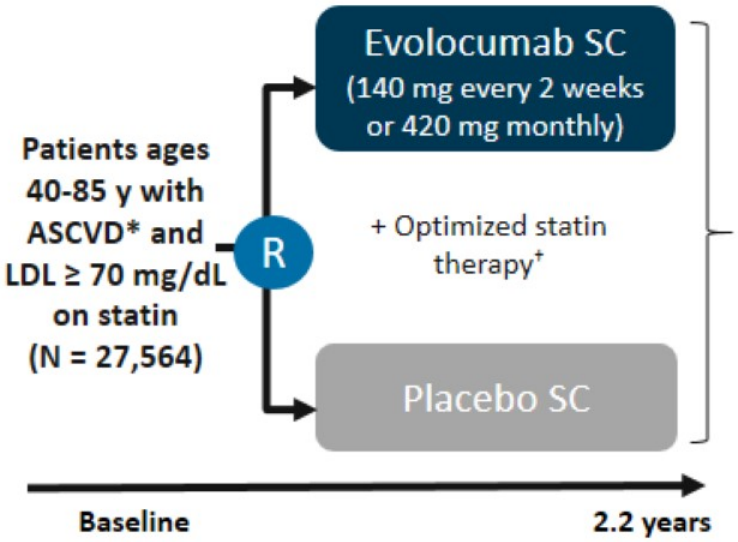
*Medical history included: hypertension, current smoker, MI, PCI, CABG, CHF, PAD. On aspirin, ACE inhibitor/ARB, and β-blocker before and at randomization. †KM event at 7 years when comparing both simvastatin treatment arms.

Giugliano RP, et al. *Circulation*. 2018;137:1571-1582.

PCSK9 Inhibitor Therapy
FOURIER CKD Subanalysis

FOURIER[a]

Randomized, double-blind, multinational study



Primary outcome: composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization

Secondary outcome: composite of CV death, MI or stroke

FOURIER CKD Subgroup Methods[b,c]

- Stratification into preserved kidney function (eGFR ≥ 90 mL/min/1.73 m^2); stage 2 or ≥ stage 3 CKD
- Time to event for binary endpoints (KM event-rate at 30 months)
- Changes in LDL-C and eGFR

Analysis Hypotheses[b]

- Reduced risk for CV outcomes with PCSK9 inhibitor is maintained with more severe CKD compared with placebo
- Safety of evolocumab is preserved across CKD stages
- Evolocumab reduces the risk for CKD progression compared with placebo

*Defined as a history of MI, nonhemorrhagic stroke, or symptomatic PAD, and additional characteristics that increased CV risk.
†Defined as preferably a high intensity statin but must have been equivalent to atorvastatin 20 mg daily, with or without ezetimibe.
a. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-22; b. Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114;
c. ClinicalTrials.gov. NCT01764633.

FOURIER CKD Subanalysis

Baseline Characteristics by CKD Stage

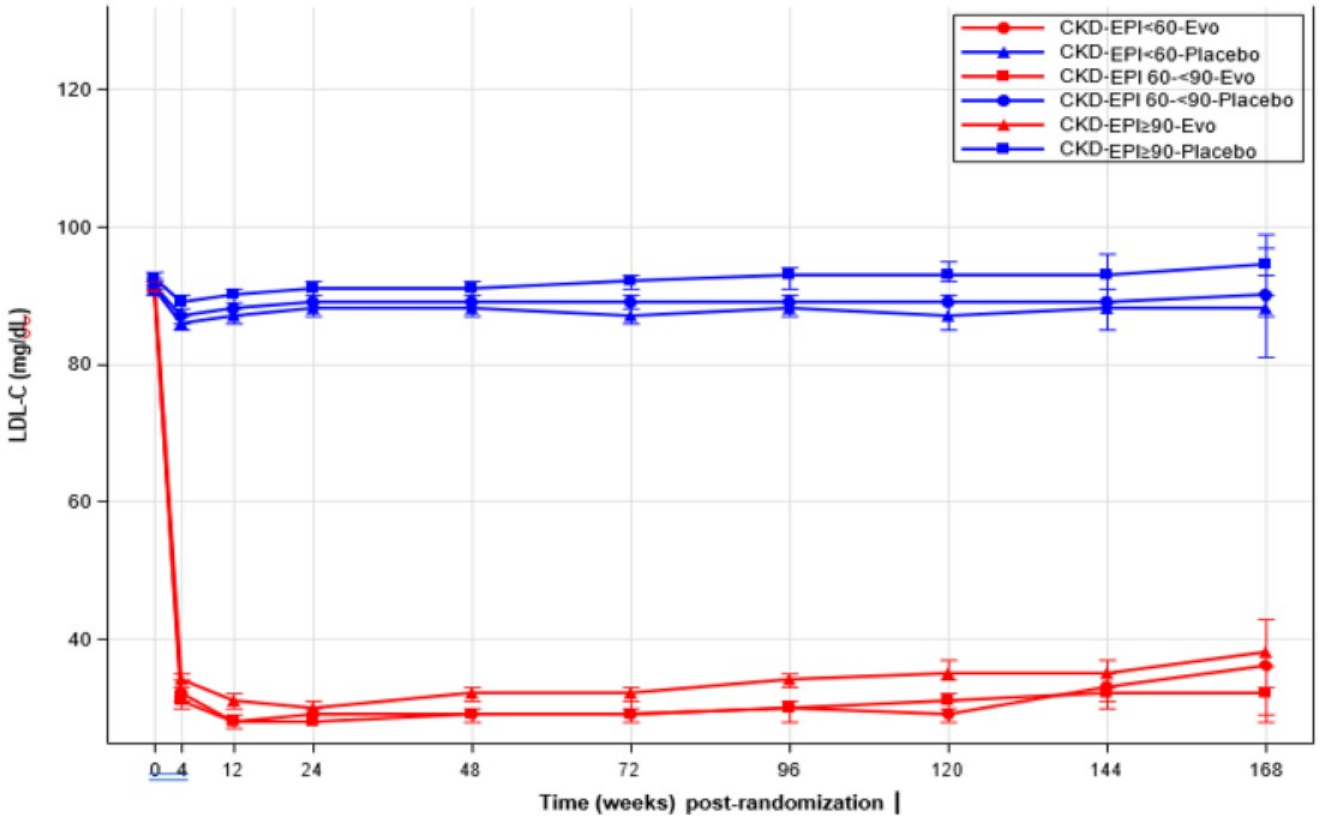
	≥ Stage3 CKD (N = 4443)	Stage 2 CKD (N = 15,034)	Preserved Kidney Function (N = 8077)
Characteristic, (%)			
Age (years)	68.7	64.0	56.3
Male	65.0	75.7	80.6
Black/African American*	3.2	2.0	2.8
CV Risk Factors			
Diabetes	46.4	33.0	37.8
Current smoker	15.8	24.5	42.0
Hypertension	89.3	79.9	75.5
MI	77.0	81.3	83.0
Ischemic stroke	25.0	19.3	16.3
Peripheral vascular disease	17.4	12.6	12.1

*P_{trend} < .001 for all comparisons across CKD groups except for race P_{trend} = .89.

Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis
Change in LDL

LDL-C at 48 Weeks: 58.2% (≥ Stage 3 CKD), 59.4% (Stage 2 CKD), and 58.7% (Preserved Kidney Function) Lower Compared With Placebo



Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis

Baseline Characteristics by CKD Stage (cont)

Median (IQR) or %	≥ Stage 3 CKD (N = 4443)	Stage 2 CKD (N = 15,034)	Preserved Kidney Function (N = 8077)	*P* Trend
CV Medications				
High-intensity statins	66.3	68.9	71.6	< .001
Ezetimibe	5.0	5.2	5.5	.23
Aspirin, P2Y12 inhibitor, or both	88.2	92.2	94.8	< .001
β-blocker	77.5	75.1	75.4	.04
ACE inhibitor, ARB, or AA	82.2	78.1	76.1	< .001
Laboratory Measures				
LDL-C - mg/Dl	91 (79-108)	92 (80-108)	93 (80-112)	< .001
Total cholesterol - mg/dL	168 (152-189)	168 (151-188)	168 (151-190)	.93
HDL-C - mg/dL	43 (36-53)	45 (38-54)	43 (36-51)	< .001
TGs - mg/dL	141.0 (107.0-195.5)	130.5 (98.5-178.0)	133.5 (99.0-183.5)	< .001
Kidney Function				
Serum creatinine - mg/dL	1.3 (1.2-1.5)	1.0 (0.9-1.1)	0.8 (0.7-0.9)	--
eGFR - mL/min/1.73m^2	51.1 (43.6-56.2)	76.6 (69.3-83.5)	97.1 (93.3-101.8)	--

Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis

Event Rates by CKD Stage

Subgroup	Evolocumab (N = 13,782) KM (%) at 30 Months	Placebo (N = 13,772) KM (%) at 30 Months	Evolocumab vs Placebo (N = 27,554) HR (95% CI)	*P* Interaction
Primary				
≥ Stage 3 CKD	14.6	16.1	0.89 (0.76, 1.05)	.77
Stage 2 CKD	10.2	12.0	0.85 (0.77, 0.94)	--
Preserved kidney function	10.0	12.2	0.82 (0.71, 0.94)	--
Key Secondary				
≥ Stage 3 CKD	10.3	12.8	0.79 (0.65, 0.95)	.75
Stage 2 CKD	6.2	7.7	0.82 (0.72, 0.93)	--
Preserved kidney function	5.4	7.1	0.75 (0.62, 0.90)	--

Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis
Additional Events by CKD Stage

Subgroup	Evolocumab (N = 13,782) KM (%) at 30 Months	Placebo (N = 13,772) KM (%) at 30 Months	Evolocumab vs Placebo (N = 27,554) HR (95% CI)	*P* Interaction
CV death				
≥ Stage 3 CKD	4.0	4.7	0.88 (0.64, 1.20)	.40
Stage 2 CKD	1.8	1.6	1.16 (0.89, 1.51)	--
Preserved kidney function	1.6	1.3	1.03 (0.70, 1.51)	--
MI				
≥ Stage 3 CKD	5.5	7.4	0.70 (0.55, 0.91)	.40
Stage 2 CKD	3.8	4.8	0.78 (0.66, 0.91)	--
Preserved kidney function	3.0	4.9	0.64 (0.50, 0.81)	--
Hospitalization for UA				
≥ Stage 3 CKD	2.2	1.8	1.20 (0.76, 1.89)	.68
Stage 2 CKD	1.7	1.9	0.96 (0.74, 1.23)	--
Preserved kidney function	2.1	2.1	0.95 (0.70, 1.31)	--

Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

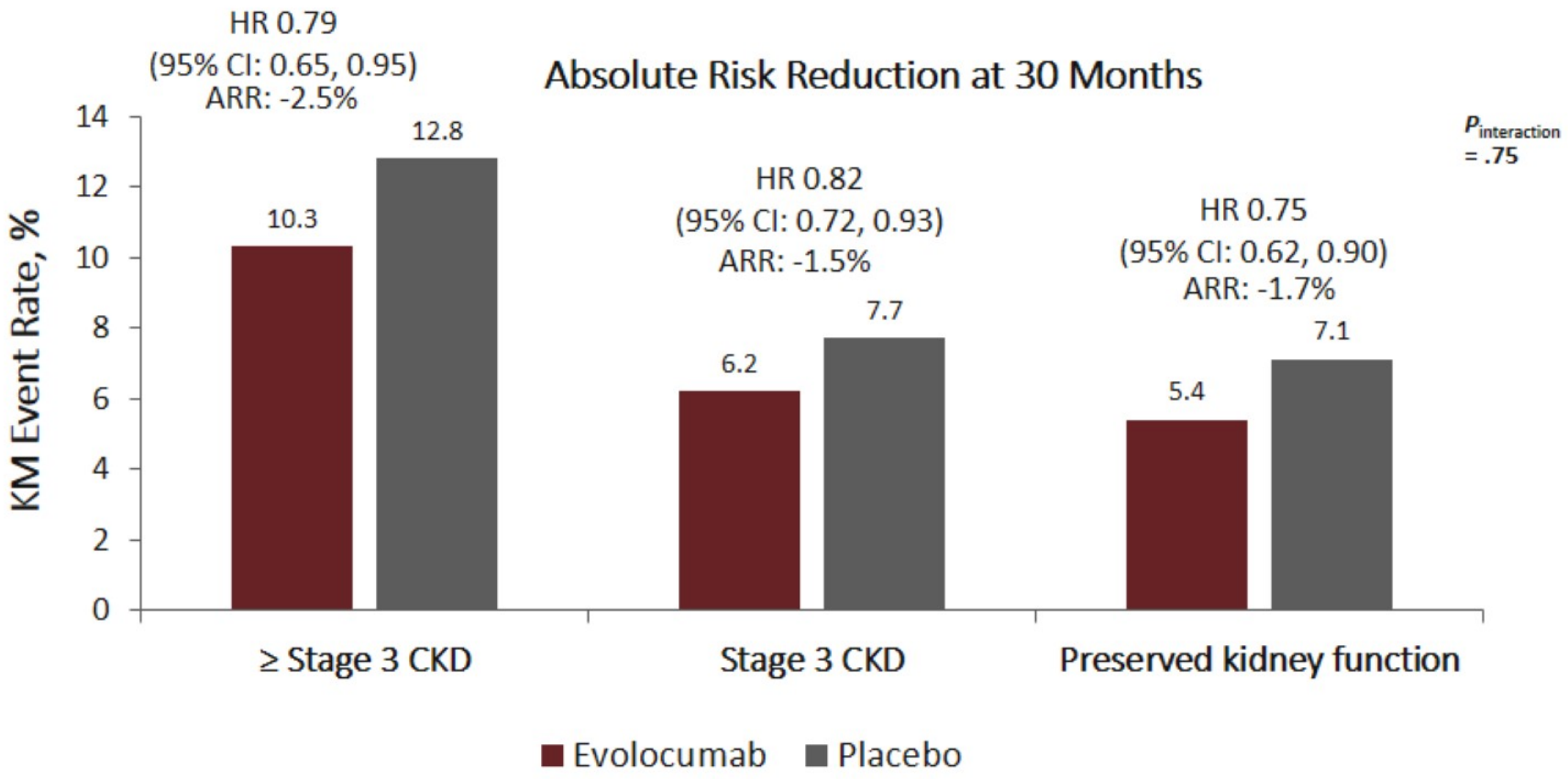
FOURIER CKD Subanalysis

Safety by CKD Stage

	≥ Stage 3 CKD (N = 4443)		Stage 2 CKD (N = 15,034)		Preserved Kidney Function (N = 8077)	
	Evolocumab (n = 2302)	Placebo (n = 2141)	Evolocumab (n = 7456)	Placebo (n =7578)	Evolocumab (n = 4024)	Placebo (n = 4053)
Event type (%)						
Any AE	82.7	81.7	77.1	76.8	75.0	76.3
Serious AE	32.6	33.3	24.2	24.0	21.4	21.6
AE leading to discontinuation	6.1	5.9	4.4	4.1	3.4	3.3
AE related to therapy AND leading to discontinuation	1.9	2.0	1.7	1.5	1.4	1.1
Allergic reaction	6.3	5.6	6.4	6.0	5.8	5.1
Muscle related	13.6	14.2	13.7	13.8	12.0	12.1
Rhabdomyolysis	0.0	0.2	0.1	0.1	0.1	0.0
Cataract	2.9	2.9	1.7	1.8	1.1	1.1
New-onset diabetes	8.8	9.1	8.3	7.8	7.4	7.0
Neurocognitive	2.5	2.7	1.9	1.7	1.5	1.3
Aminotransferase > 3x ULN	1.7	1.4	1.6	1.6	2.3	2.4
CK > 5x ULN	0.5	0.9	0.8	0.7	0.7	0.7

Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis
Key Secondary Endpoint



ARR stage 3 vs stage 2; *P* =.004
ARR stage 3 vs preserved; *P* =.01

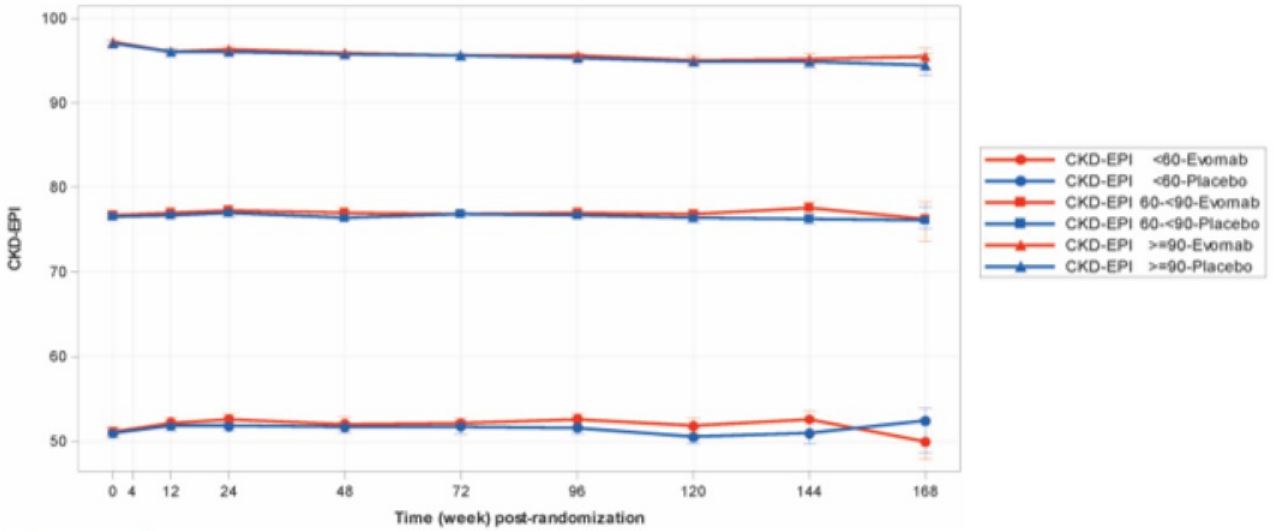
N = 27554.
Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

FOURIER CKD Subanalysis

Overall *CKD Progression and Change in eGFR*

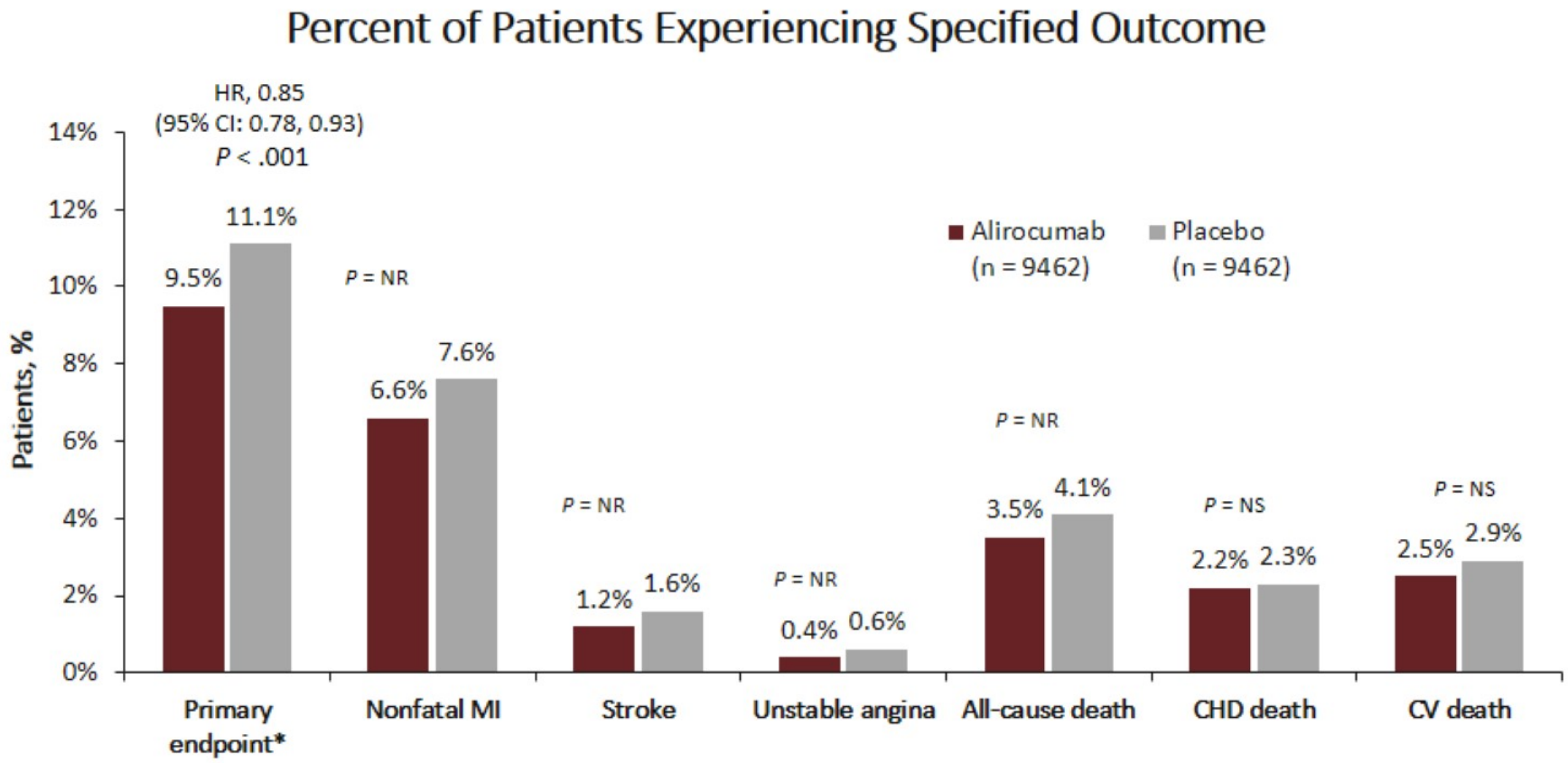
	Evolocumab (N = 13,782)	Placebo (N = 13,772)	Evolocumab vs Placebo (N = 27,554)	
	KM (%)	KM (%)	HR (95% CI)	Cox *P* Value
Overall				
≥ 30% decline in eGFR	3.2	3.3	0.99 (0.86, 1.14)	.90
≥ 40% decline in eGFR	1.4	1.4	1.05 (0.84, 1.31)	.66
≥ 50% decline in eGFR	0.5	0.6	0.97 (0.69, 1.37)	.86

Change in eGFR Over Time (Overall CKD Population)



Charytan DM, et al. Kidney Week 2018. Abstract FR-OR114.

Alirocumab
ODYSSEY Outcomes Trial Results



Results support ADA recommendation to consider PCSK9 inhibitor therapy for individuals with DM and ASCVD[b]

*Composite of CHD death, nonfatal MI, ischemic stroke, UA requiring hospitalization.

a. Schwartz GG, et al. *N Engl J Med*. 2018;379:2097-107; b. ADA. *Diabetes Care*. 2018;41(Suppl. 1):S1-S159.

CKD Stages and Associated Clinical Events

Patient Simulation Model*

Patients at CKD levels 3-5 (including dialysis and transplant) are at high risk for CV events and should be considered for lipid-lowering therapy

*Created with information from contemporary literature, UK clinical practice, and NICE guidance.
Evans M, et al. *BMC Nephrol.* 2019;20:31.

Strategies for Collaborative Patient-Centered Care in Patients With CKD

- Initiate lipid-lowering therapy in patients with CKD at highest risk for ASCVD events
  - Complex patient populations (eg, HIV, pregnancy)
- Team-based care (eg, nephrologist, internist, cardiologist, endocrinologist, diabetologist)
- Appropriate management of CV medications and comorbidities (eg, GERD, hypertension, mineral bone disease, anemia, diabetes)
  - Renal dosing of CV medications
  - Monitor for drug-drug interactions
- Patient education on risk-enhancing factors for CV events and CKD complications such as dialysis

Conclusion

- It is important to recognize CKD as a risk factor for CVD
- CV mortality remains high in CKD despite use of standard CV therapies, including statins
  - Highest in patients with ESRD
- Faculty recommends that patients with CKD (including those who are stage 5, are on dialysis, and are transplant recipients) can benefit from risk-based lipid-lowering treatment
- The ADA recommends PCSK9 inhibitor therapy for individuals with DM and ASCVD

Abbreviations

AA = aldosterone antagonist
ABI = ankle-brachial index
ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
ADA = American Diabetes Association
ADMA = asymmetric dimethylarginine
AE = adverse event
AGE = advanced glycation end product
AHA = American Heart Association
AOPP = advanced oxidation of plasma protein
ApoA1 = apolipoprotein A1
ApoB = apolipoprotein B
ARB = angiotensin receptor blocker
ASCVD = atherosclerotic cardiovascular disease
BP = blood pressure
CABG = coronary artery bypass grafting
CDC = Centers for Disease Control and Prevention
CHD = coronary heart disease

Abbreviations (cont)

CHF = congestive heart failure
CI = 95% confidence interval
CK = creatine kinase
CKD = chronic kidney disease
CPK = creatine phosphokinase
CV = cardiovascular
CVD = cardiovascular disease
DM = diabetes mellitus
ED = erectile dysfunction
eGFR = estimated glomerular filtration rate
Epi = epidemiology
ESRD = end-stage renal disease
Evo = evolocumab
GERD = gastroesophageal reflux disease
GFR = glomerular filtration rate
GP = general population
HDL = high-density lipoprotein
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio

Abbreviations (cont)

hs-CRP = high-sensitivity C-reactive protein
Ig = immunoglobulin
IQR = interquartile range
KDOQI = Kidney Disease Outcomes Quality Initiative
KM = Kaplan-Meier
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein (a)
MI = myocardial infarction
NCHS = National Center for Health Statistics
NICE = National Institute for Health and Care Excellence
NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases
NKF = National Kidney Foundation
NR = not reported
NS = not significant
Ox = oxidized
PAD = peripheral artery disease
PCI = percutaneous intervention
PCSK9 = proprotein convertase subtilisin–kexin type 9

Abbreviations (cont)

RCT = randomized controlled trial
ROS = reactive oxygen species
SAMS = statin-associated muscle symptom
SC = subcutaneous
TG = triglyceride
UA = unstable angina
ULN = upper limit of normal
USRDS = United States Renal Data System
VA = Veterans Affairs