Rischio cardiovascolare e nefropatia diabetica

Dipartimento di Medicina Clinica e Molecolare
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Disclosures

Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- ✓ Partecipazioni a Congressi: Astra-Zeneca, Laboratori Guidotti, Takeda;
- ✓ Relazioni/moderazioni/partecipazioni a board retribuite: Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novartis, Sigma-Tau, Takeda.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

In fede

Giuseppe Pugliese

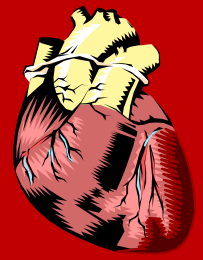
Agenda

- Impact of CKD on cardiovascular system
- CKD and cardiovascular risk
- Renal protection and cardiovascular risk

Heart-kidney interactions

Cardiorenal syndromes

Heart



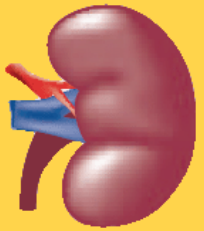
↓ renal perfusion pressure (=MAP-CVP)

Cardiorenal connectors

1. Inflammation
2. NO/ROS balance
3. SNS
4. RAAS

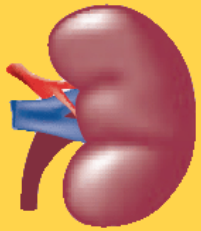
Kidney

fluid retention
electrolyte disturbances
Ca-P imbalances
protein energy wasting & malnutrition
anemia
uremic toxins

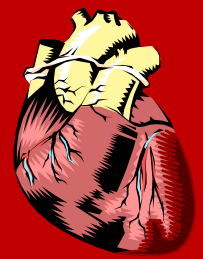


Kidney

↓ net filtration pressure
↓ GFR



Heart

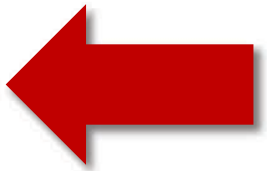


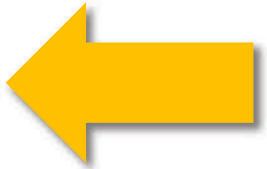
Heart failure
Arrhythmias
CVD events

Ronco C et al. Eur Heart J. 2010;31:703–711

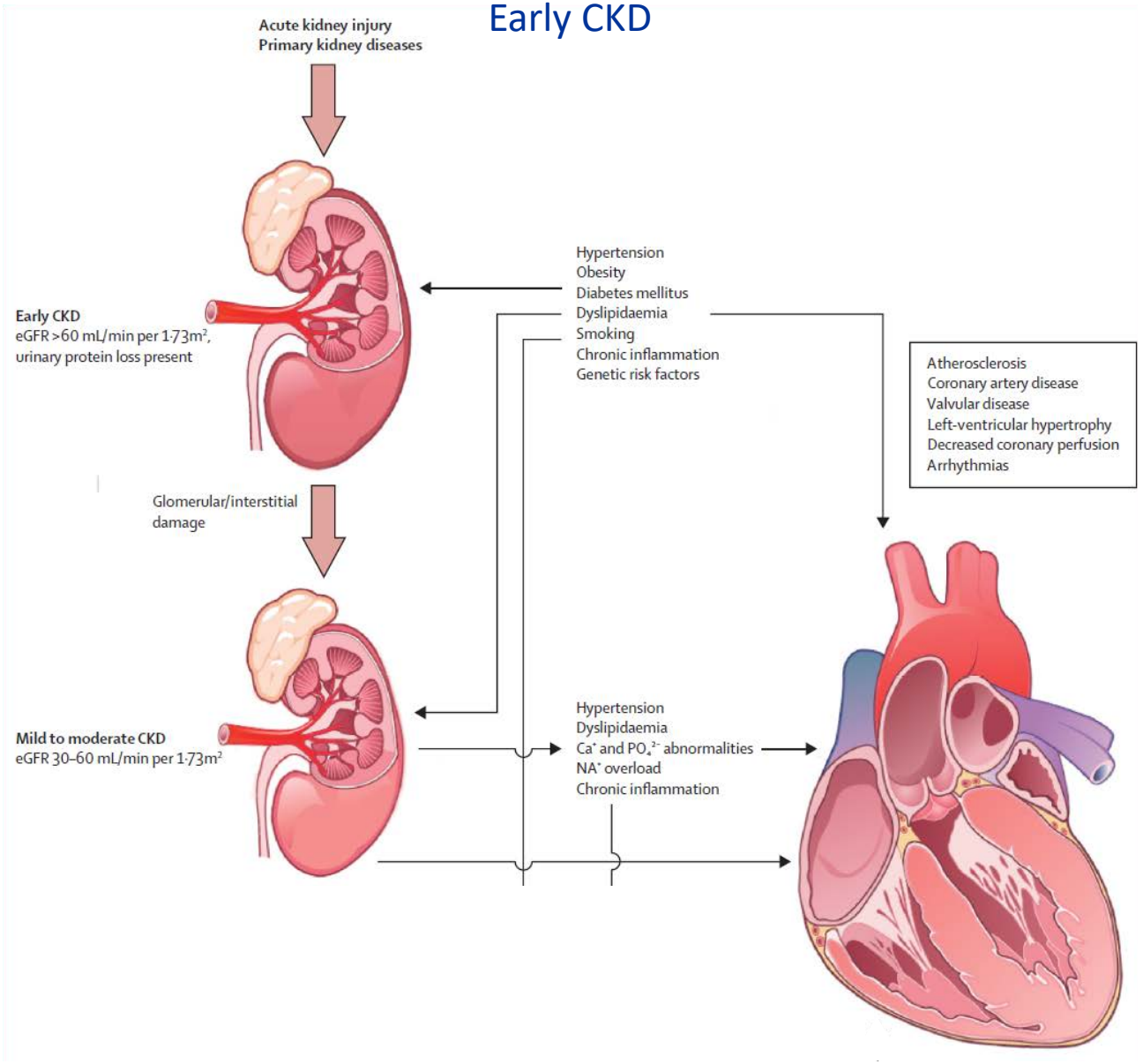
Classification of cardio-renal syndromes

1. Acute kidney injury (AKI) secondary to acute heart failure (HF)
2. Progressive chronic kidney disease (CKD) secondary to chronic HF
3. Acute HF secondary to primary AKI
4. Chronic cardiac dysfunction secondary to primary CKD
5. Combined cardiac and renal dysfunction due to acute or chronic systemic disorders



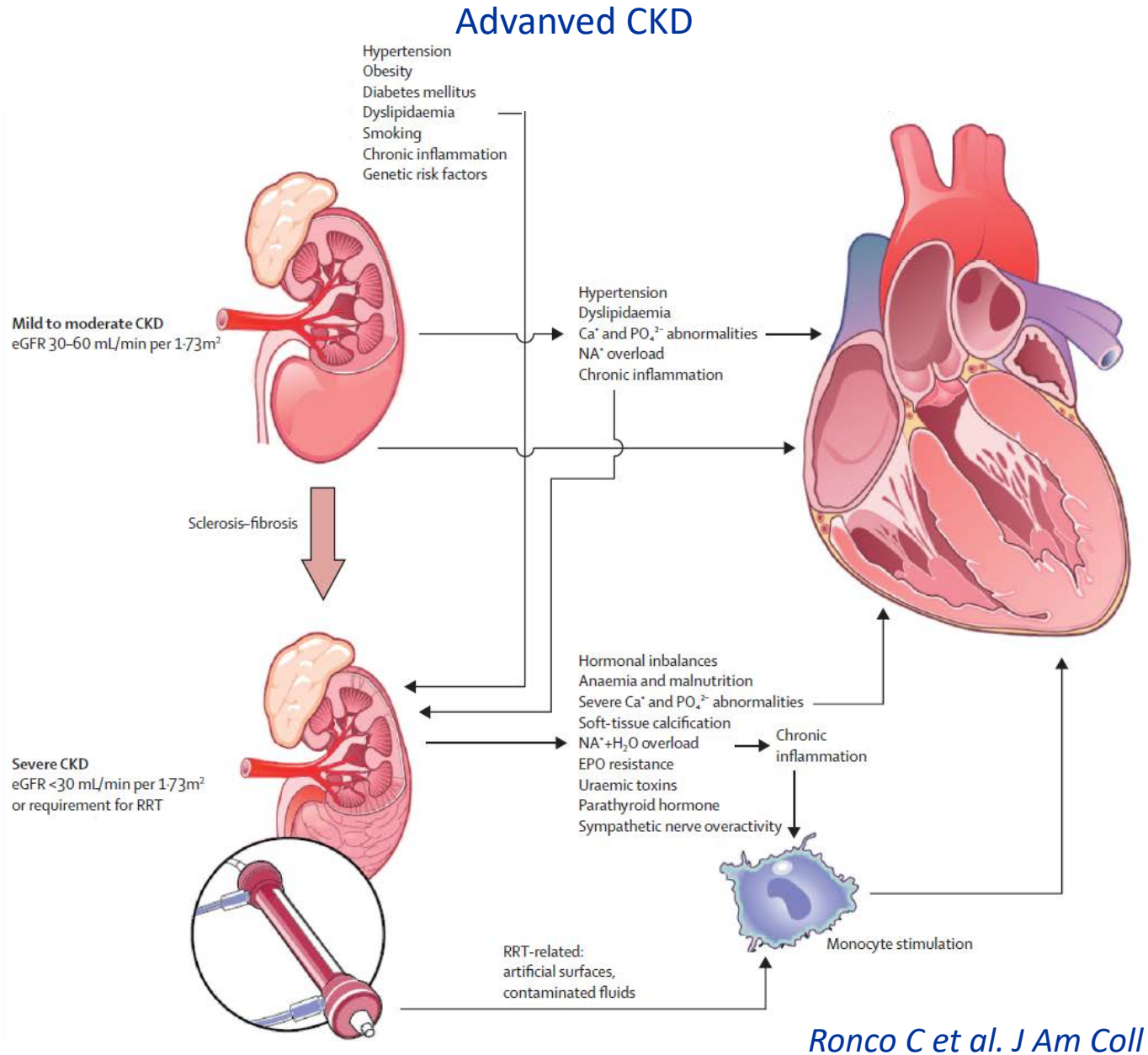


Mechanisms of cardio-renal syndrome type 4



Ronco C et al. J Am Coll Cardiol. 2008; 52: 1527–1539

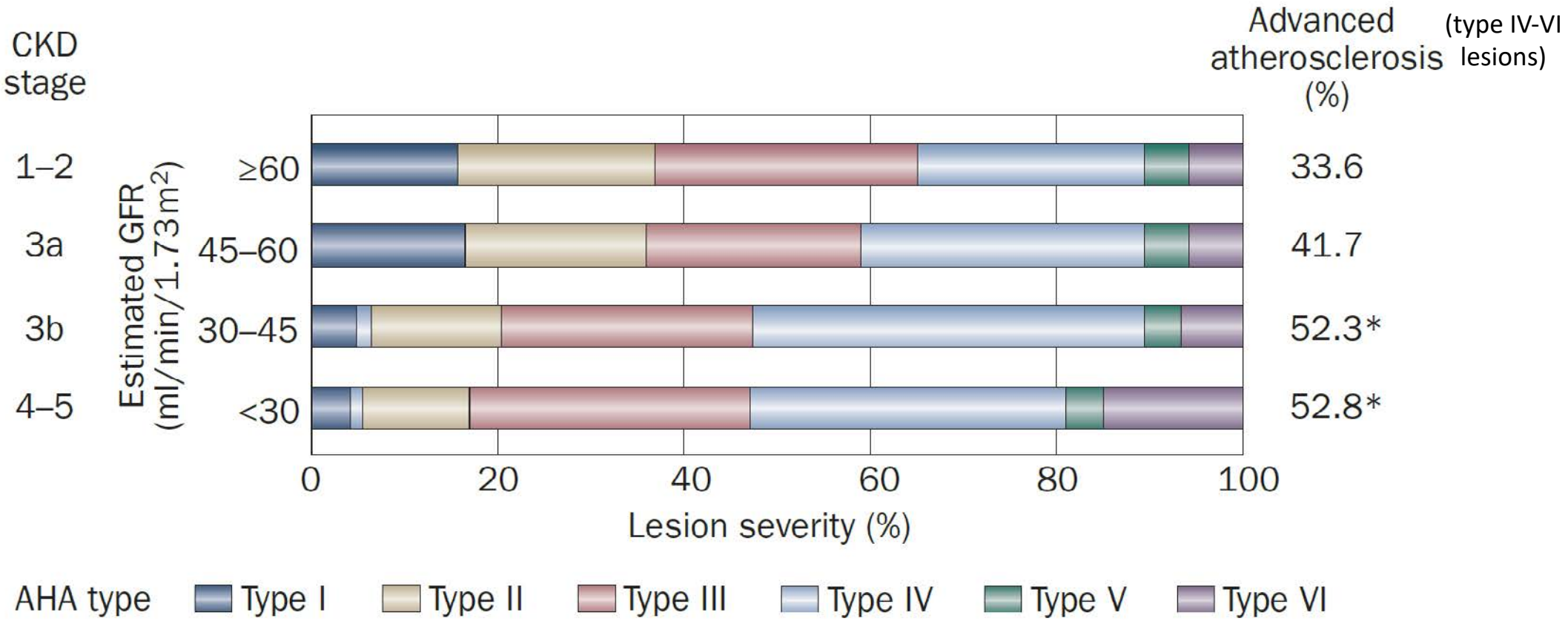
Mechanisms of cardio-renal syndrome type 4



Ronco C et al. J Am Coll Cardiol. 2008; 52: 1527–1539

Mechanisms of cardio-renal syndrome type 4

Atherosclerotic lesion types of coronary arteries as a function of CKD stage



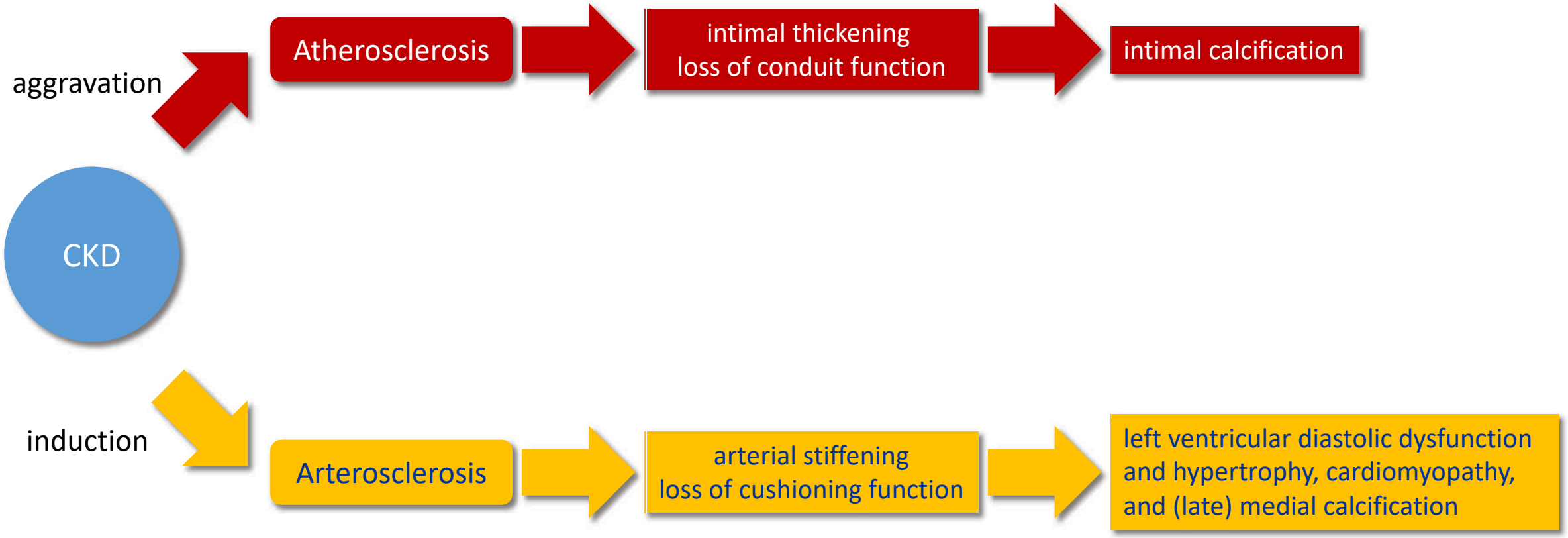
(type IV-VI lesions)

Type I (initial lesion), intimal thickening with isolated foam cells;
Type II (fatty-streak lesion), intimal thickening with intracellular lipid accumulation;
Type III (intermediate lesion): type II changes and small extracellular lipid pools;
Type IV (atheroma), type II changes and core of extracellular lipid;
Type V (fibroatheroma), lipid core and fibrotic layer to lesions, or mainly calcified, or mainly fibrotic;
Type VI (complicated lesion), disrupted lesion with hematoma or hemorrhage or thrombotic deposits.

Nakano T et al. Am J Kidney Dis. 2010;55:21–30

Mechanisms of cardio-renal syndrome type 4

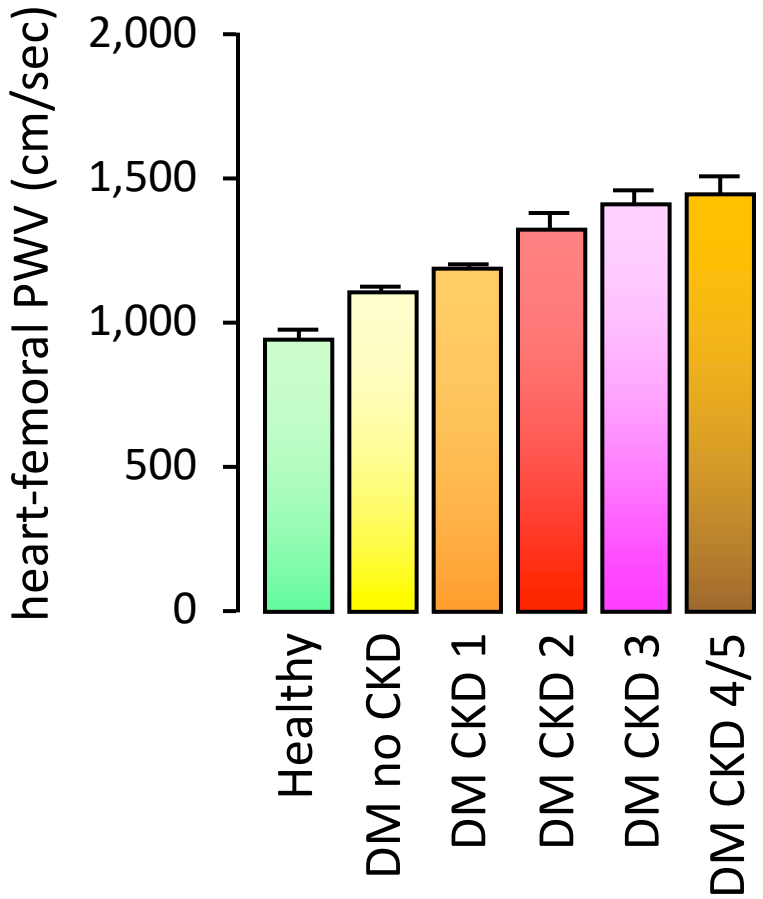
Atherosclerotic versus arteriosclerosis in CKD

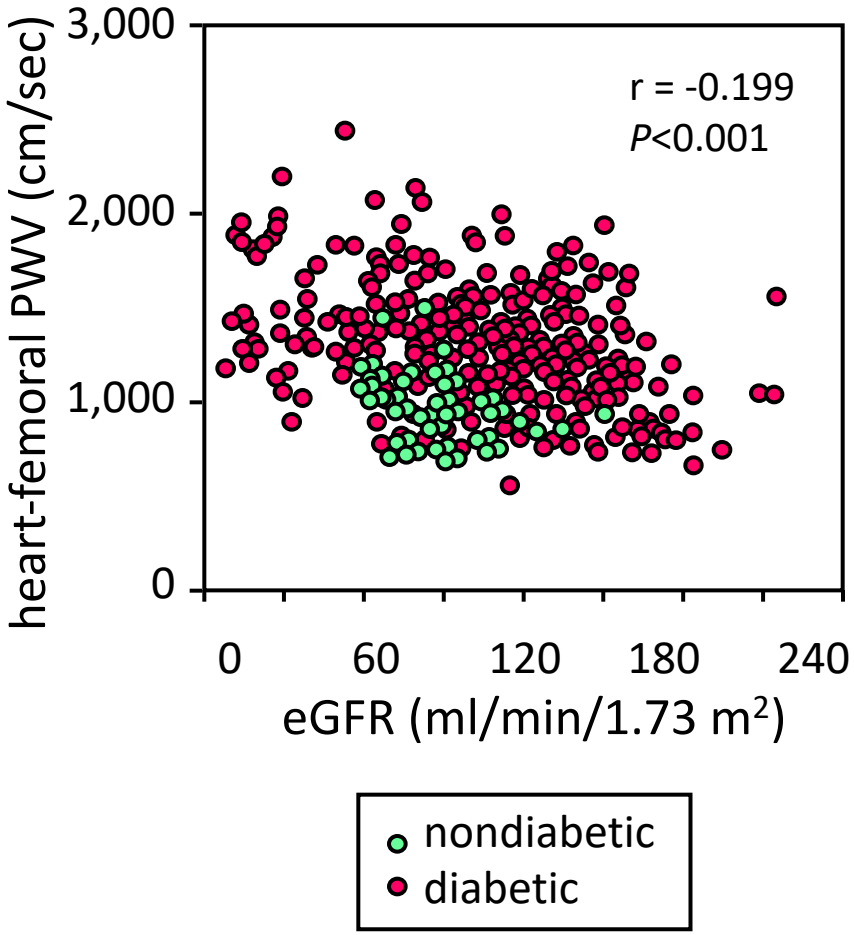


Drüeke TB & Massy ZA. Nat Rev Nephrol. 2010;6:723–735

Mechanisms of cardio-renal syndrome type 4

Arterial stiffness in CKD



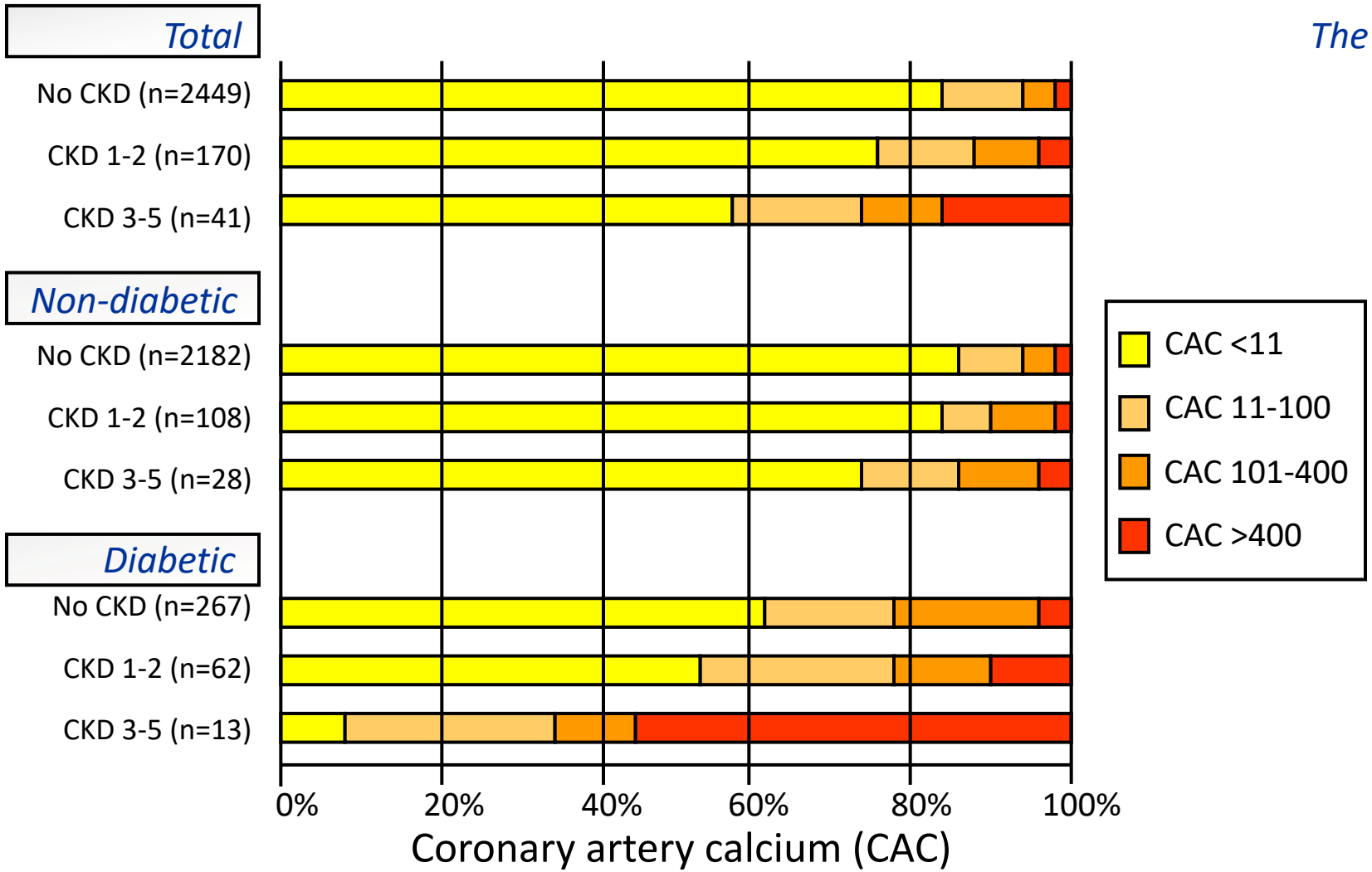


Kimoto E et al. J Am Soc Nephrol. 2006;17:2245–2252

Mechanisms of cardio-renal syndrome type 4

Vascular calcification in CKD

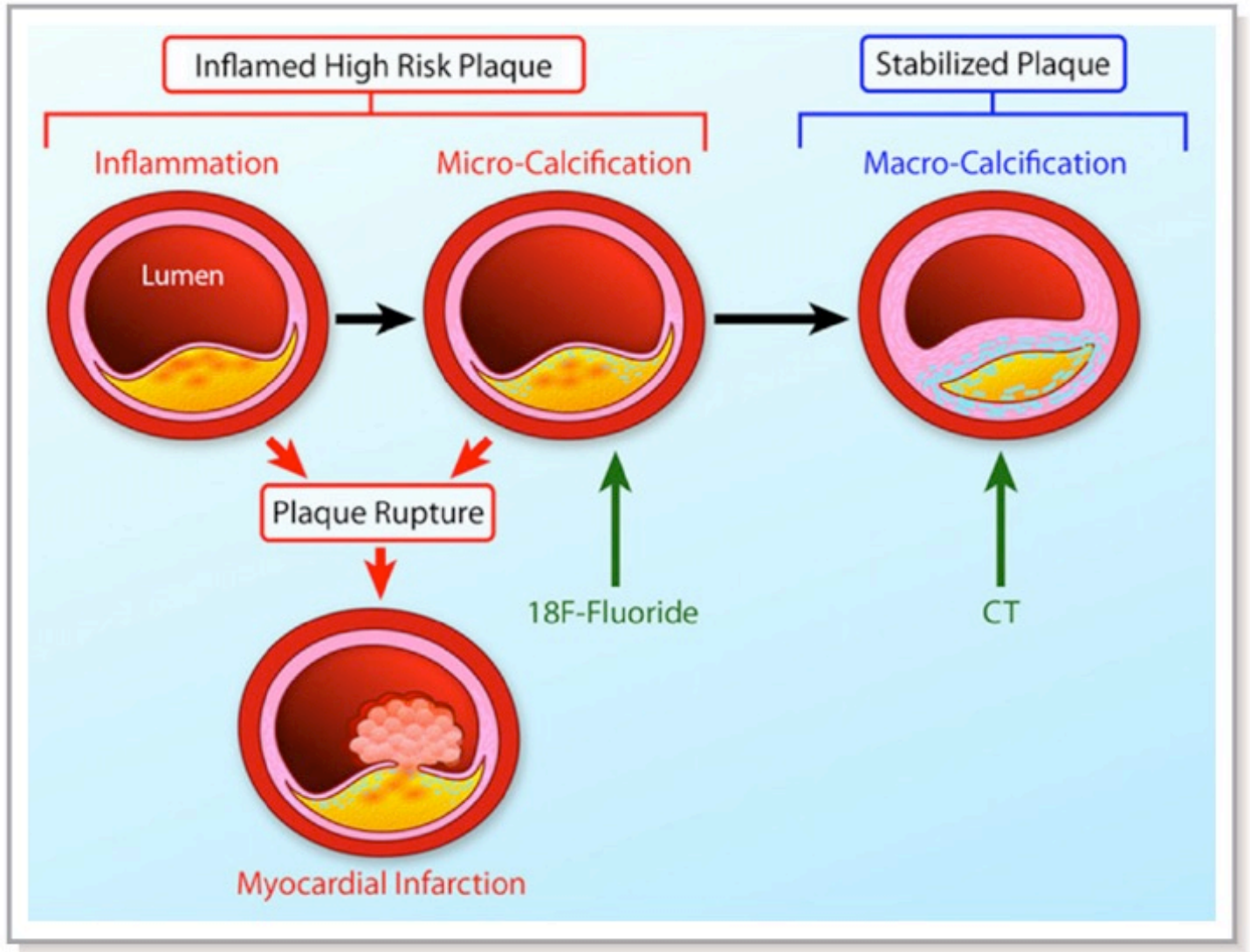
The Dallas Heart Study



Kramer H et al. J Am Soc Nephrol. 2005;16:507-513

Mechanisms of cardio-renal syndrome type 4

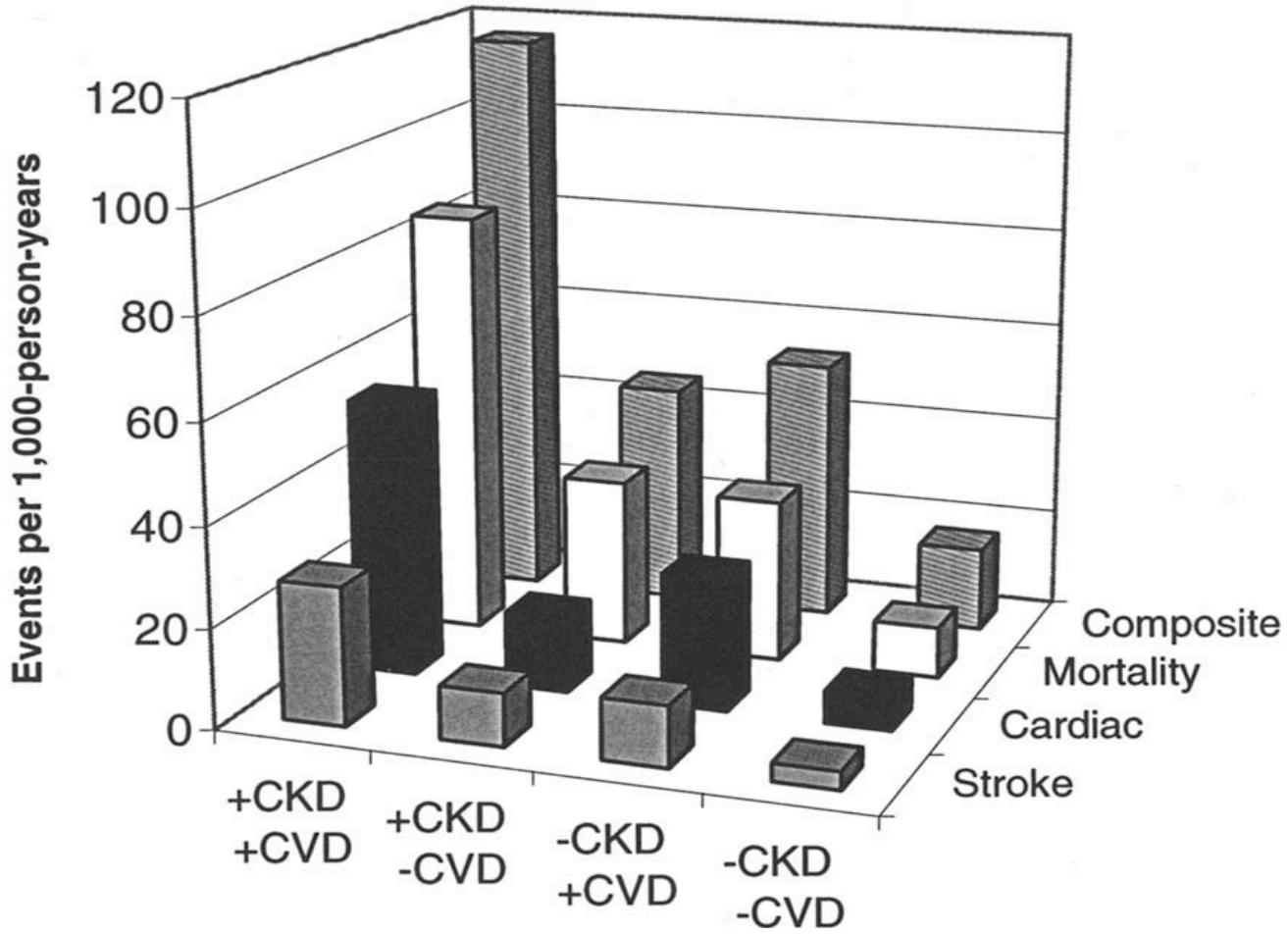
Effect of calcification on plaque stability in CKD



Wang Y et al. J Am Heart Assoc. 2018;7:e008564

Cardiovascular risk in CKD

CVD morbidity and mortality in individuals with and without CKD and CVD



Pooled analysis of 4 community-based studies: Atherosclerosis Risk in Communities, Framingham Heart, Framingham Offspring, and Cardiovascular Health Study

Weiner DE et al , Am J Kidney Dis. 2006; 48:392-401

Prevalence of CKD in the general population

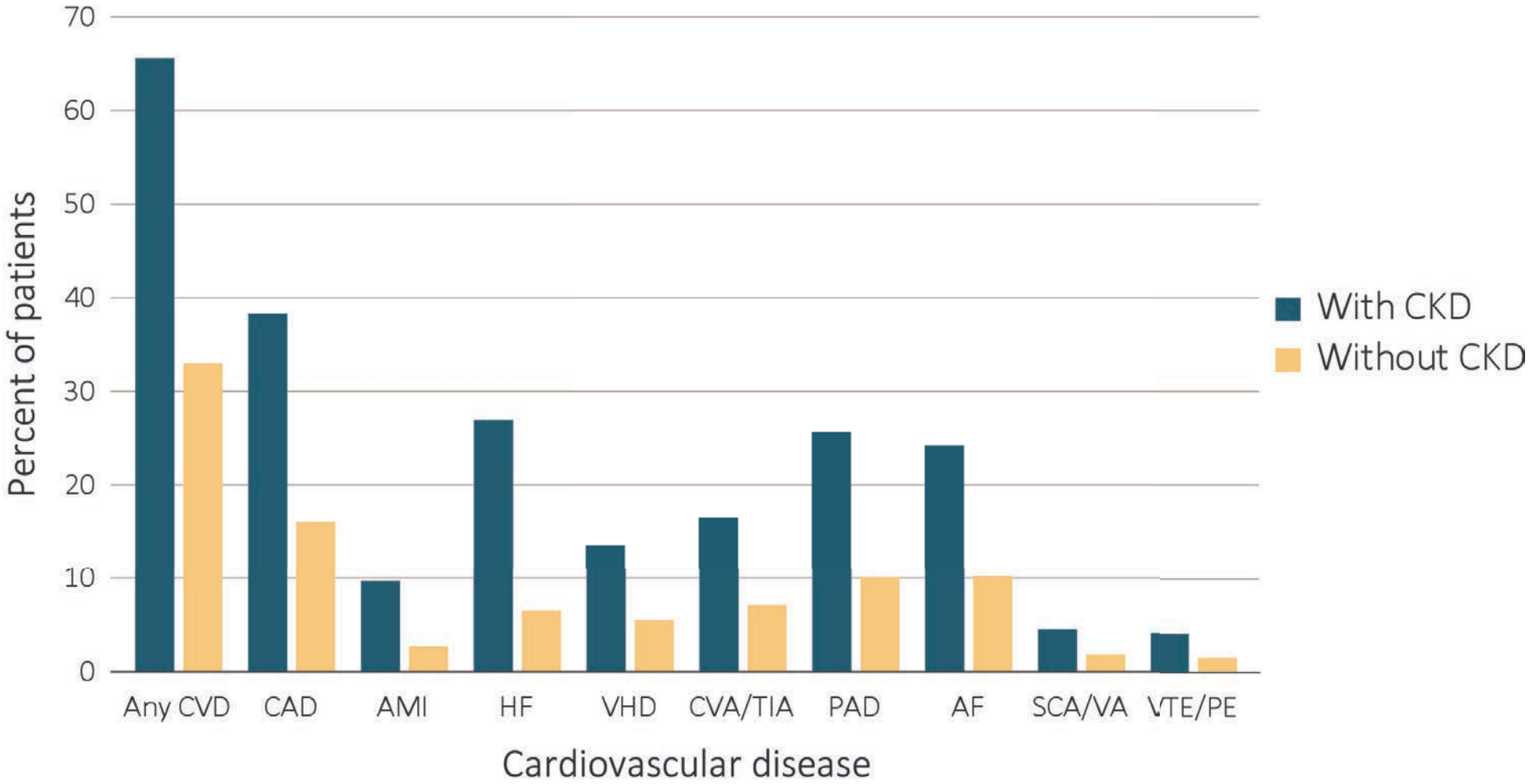
Percentage of NHANES 2013-2016 participants, in the various CKD (eGFR and albuminuria) risk categories (KDIGO 2012)

				Albuminuria categories			
				A1	**A2**	**A3**	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol	**Total**
GFR categories (ml/min/1.73 m²)	**G1**	Normal to high	≥90	54.9	4.2	0.5	59.6
	G2	Mildly decreased	60-89	30.2	2.9	0.3	33.5
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.3	4.7
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.7
	G4	Severely decreased	15-29	0.13	0.10	0.15	0.37
	G5	Kidney failure	<15	0.01	0.04	0.09	0.13
			Total	89.9 (4.74)	8.5 (1.34)	1.6 (0.74)	100

USRDS, 2018 Annual Data Report, Volume 1 CKD, Chapter 4

Prevalence of CVD in people with CKD

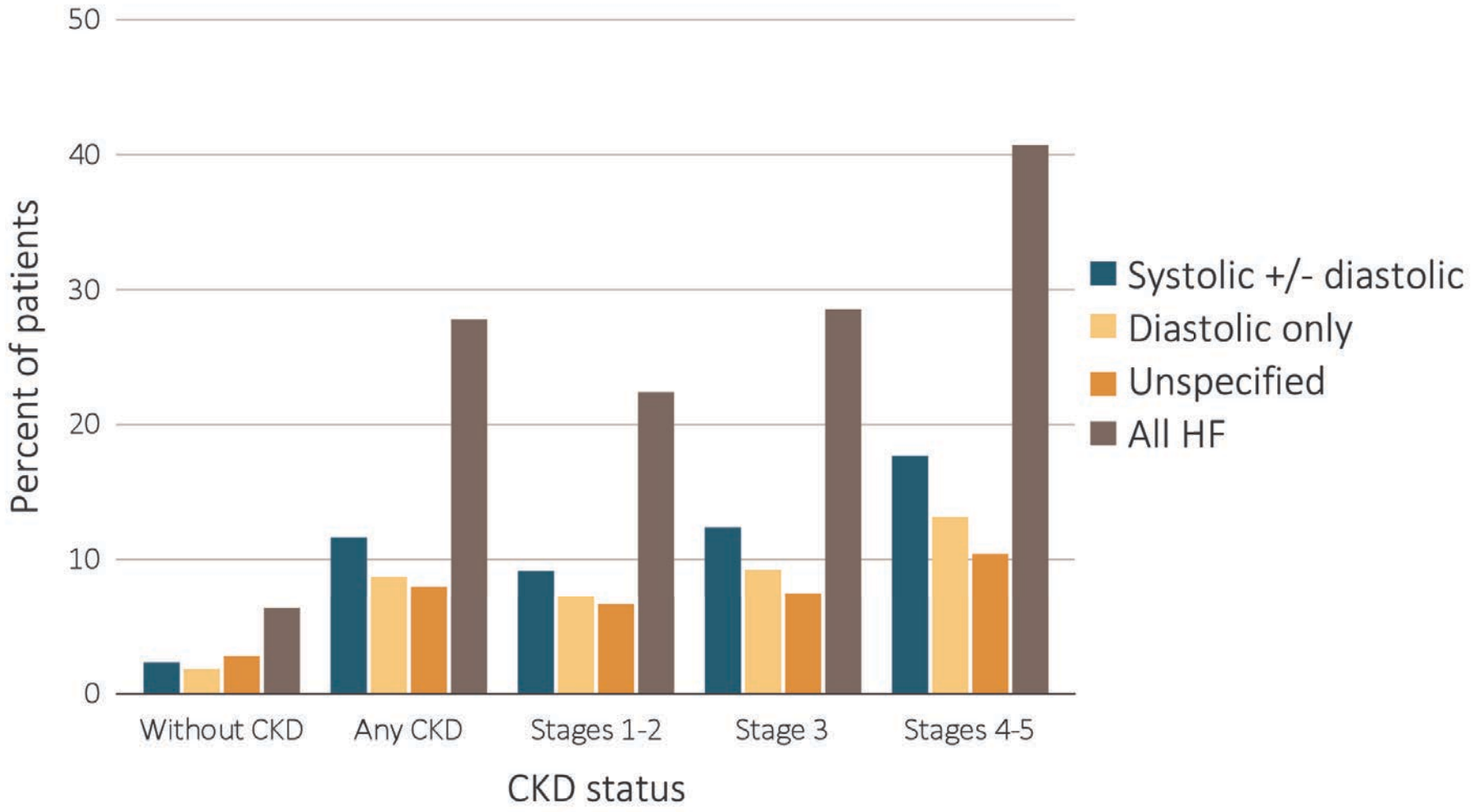
Prevalence of common CVDs in patients with or without CKD, 2016



USRDS, 2018 Annual Data Report, Volume 1 CKD, Chapter 4

Prevalence of CVD in people with CKD

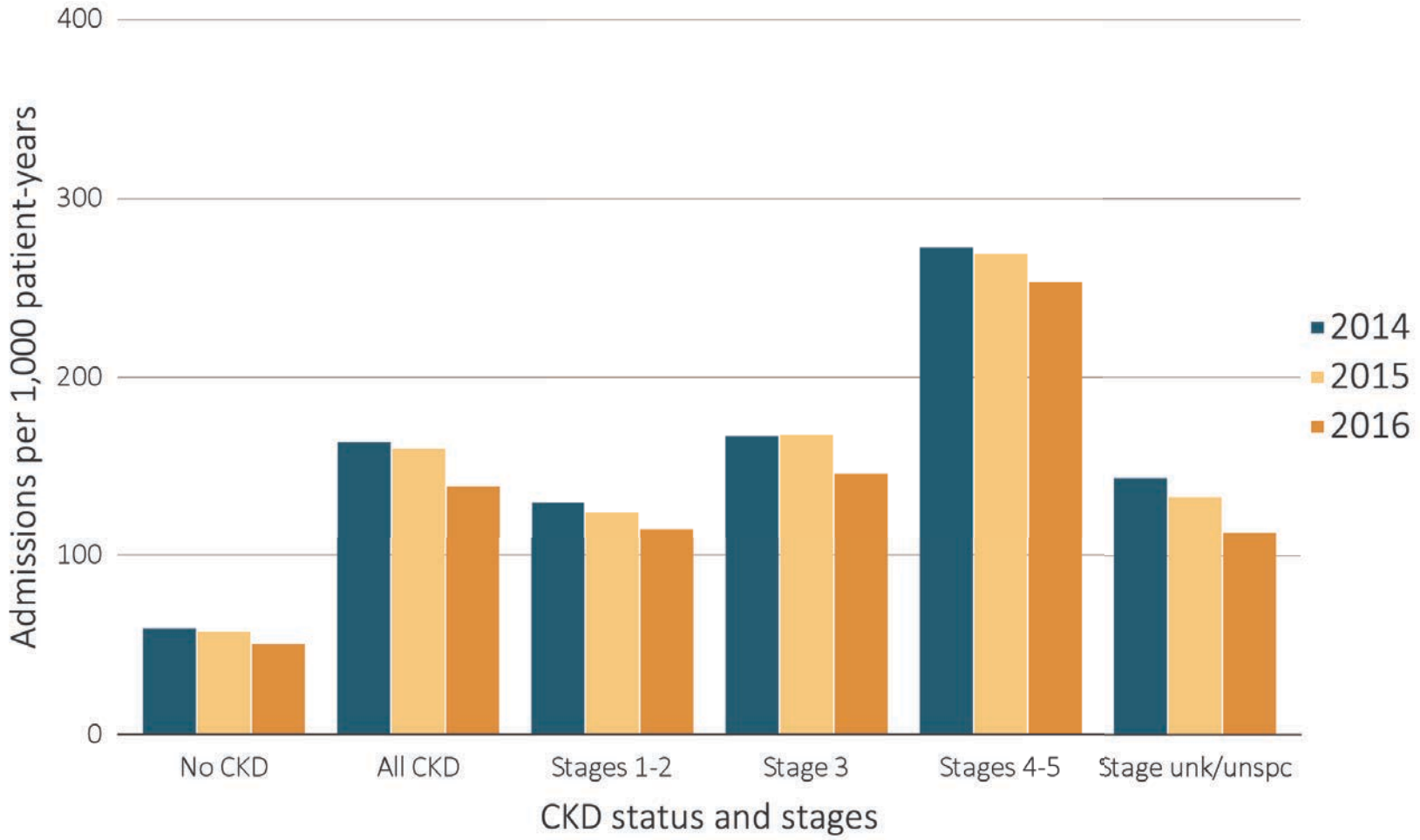
Prevalence of heart failure in patients with or without CKD, 2016



USRDS, 2018 Annual Data Report, Volume 1 CKD, Chapter 4

Prevalence of CVD in people with CKD

Adjusted rates of hospitalization for cardiovascular disease per 1,000 patient-years at risk for Medicare patients aged 66 and older, by CKD status and stage, 2014-2016



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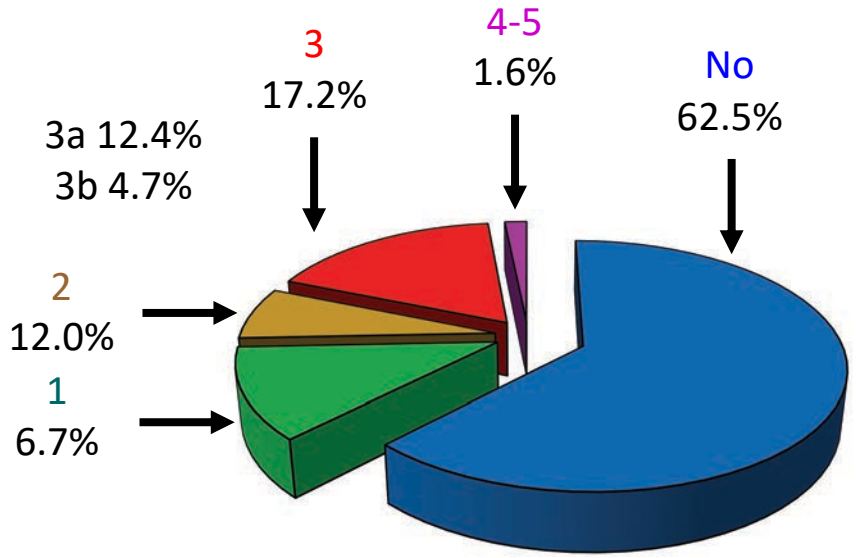
Prevalence of DKD in people with type 2 diabetes

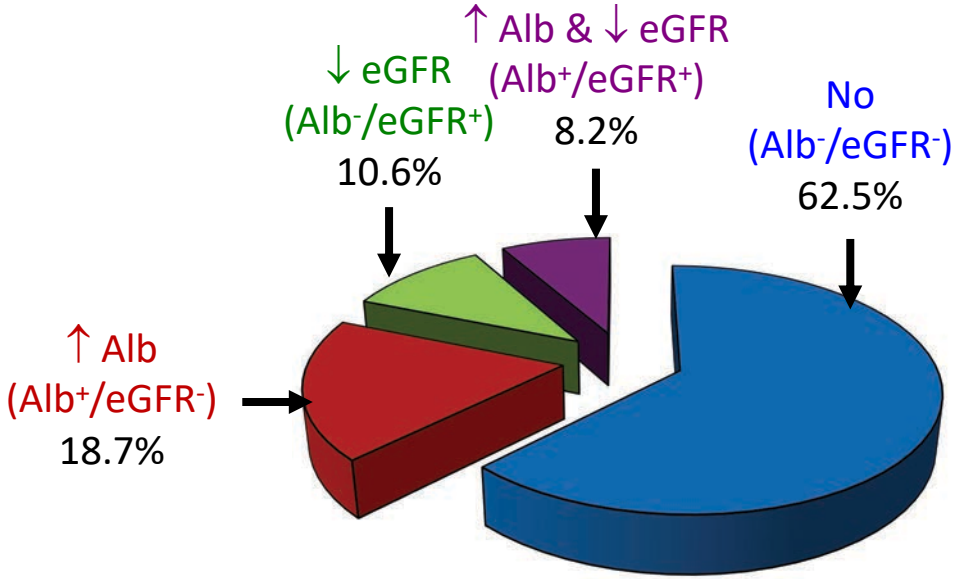
Crude prevalence of DKD in patients with type 2 diabetes from Italy

DKD stages



37.5%
1.44 millions

DKD phenotypes



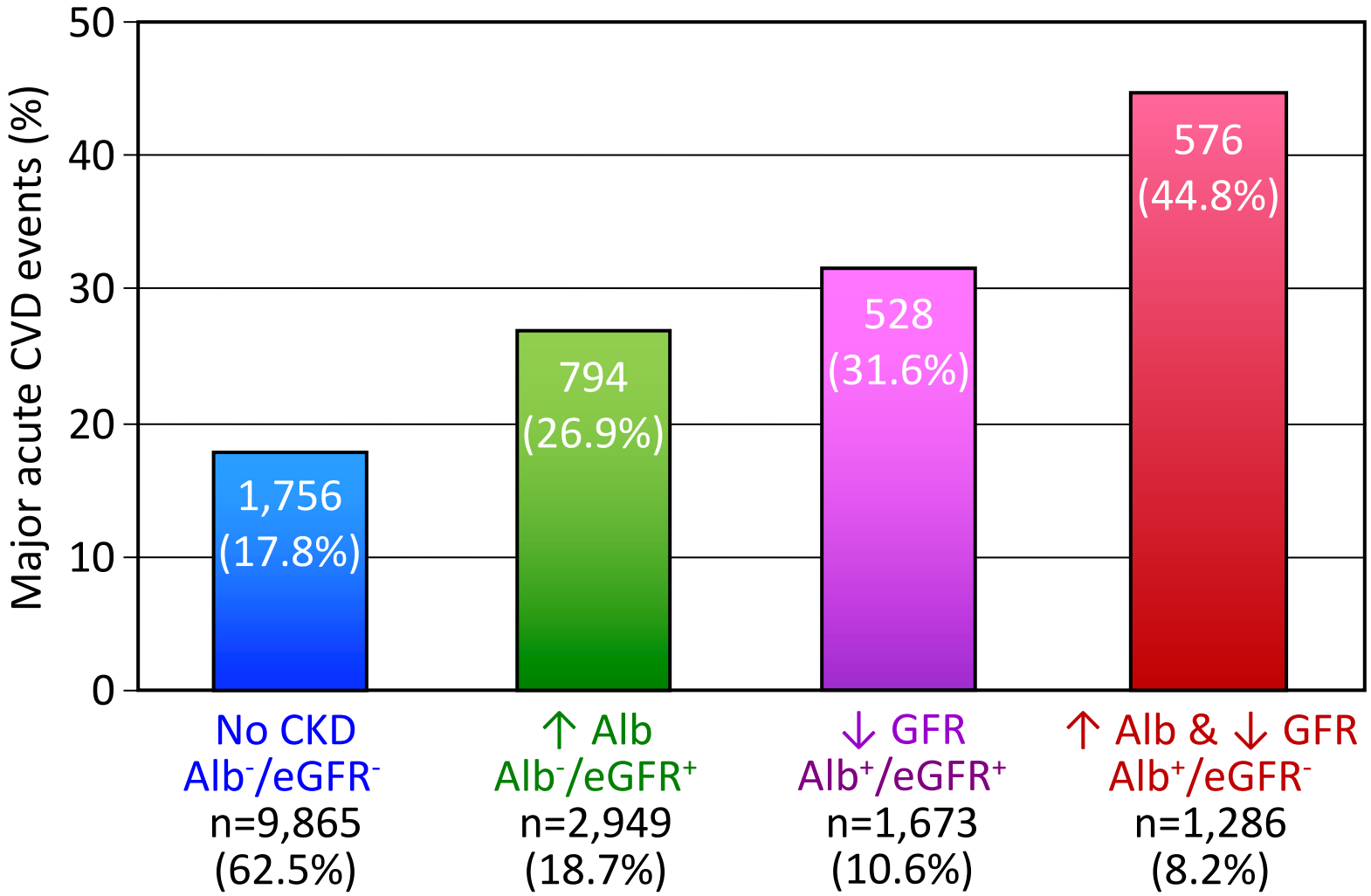
DKD phenotype	DKD stahe	Albuminuria	eGFR
No	0	-	-
↑ Alb	1-2	+	-
↓ eGFR	3-5	-	+
↑ Alb & ↓ eGFR	3-5	+	+

Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

Penno G et al. J Hypertens. 2011;29:1802-1809

Prevalence of CVD in people with type 2 diabetes

Crude prevalence of any CVD according to DKD phenotype



Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

Solini A et al, Diabetes Care. 2012;35:143-149

Risk of CVD in people with type 2 diabetes

Risk of CVD by vascular bed according to DKD phenotype

	↑ Alb Alb^{+}/eGFR^{-}		↓ GFR Alb^{-}/eGFR^{-+}		↑ Alb & ↓ GFR Alb^{+}/eGFR^{-+}	
	OR	95% CI	OR	95% CI	OR	95% CI
Total CVD events	1.20	1.08-1.33	1.52	1.34-1.73	1.90	1.66-2.19
Coronary events	0.90	0.79-1.02	1.51	1.30-1.76	1.27	1.08-1.49
Cerebrovascular events	1.41	1.20-1.65	1.22	1.01-1.48	1.69	1.40-2.00
Peripheral events	1.51	1.25-1.82	1.40	1.11-1.76	1.88	1.52-2.34

Logistic regression analysis with stepwise variable selection

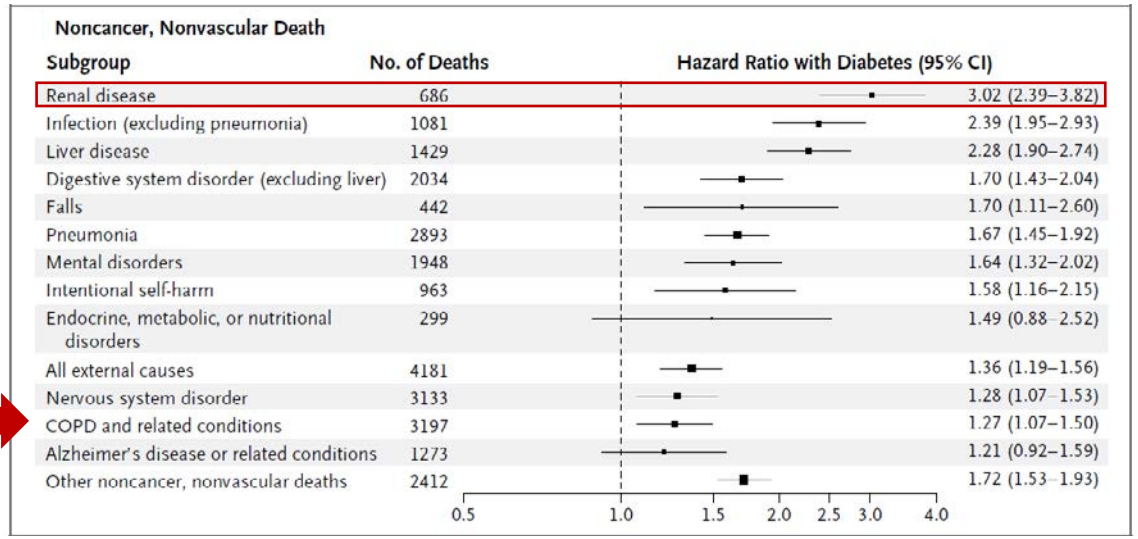
Analysis of 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

Solini A et al, Diabetes Care 2012;35:143-149

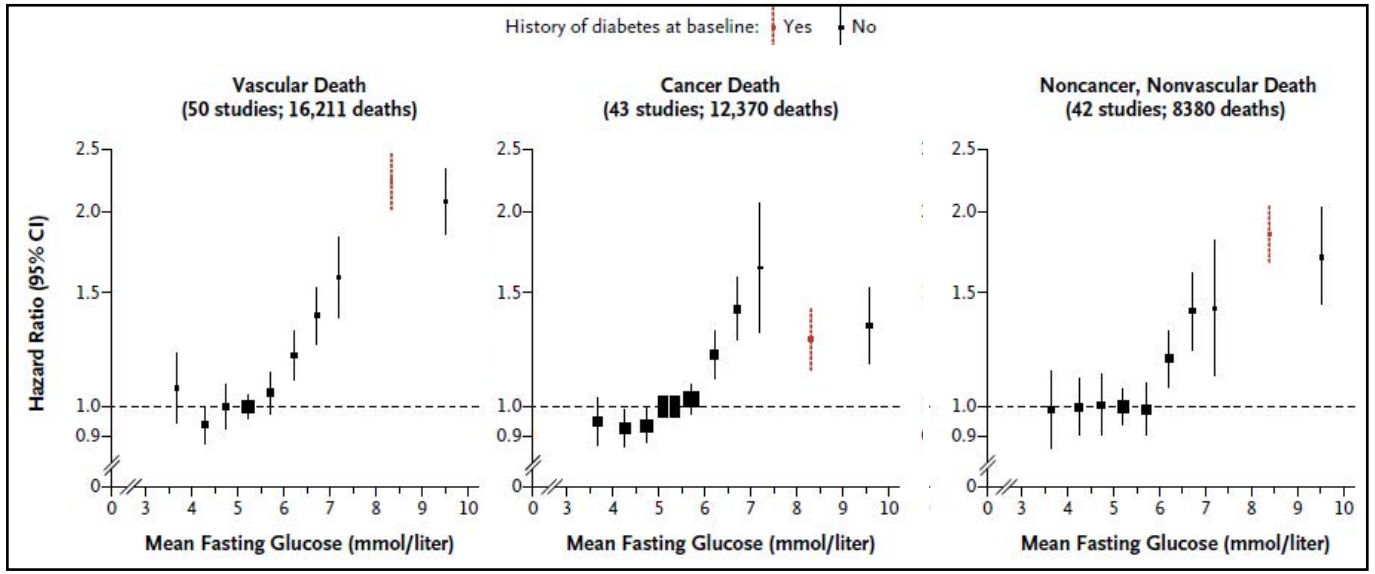
Excess mortality in people with type 2 diabetes

Hazard ratios by diabetes

Cause	HR	95% CI
All	1.80	1.71-1.90
Vascular	2.32	2.11-2.56
Cancer	1.25	1.19-1.31
Other	1.73	1.62-1.85



Hazard ratios by mean fasting glucose

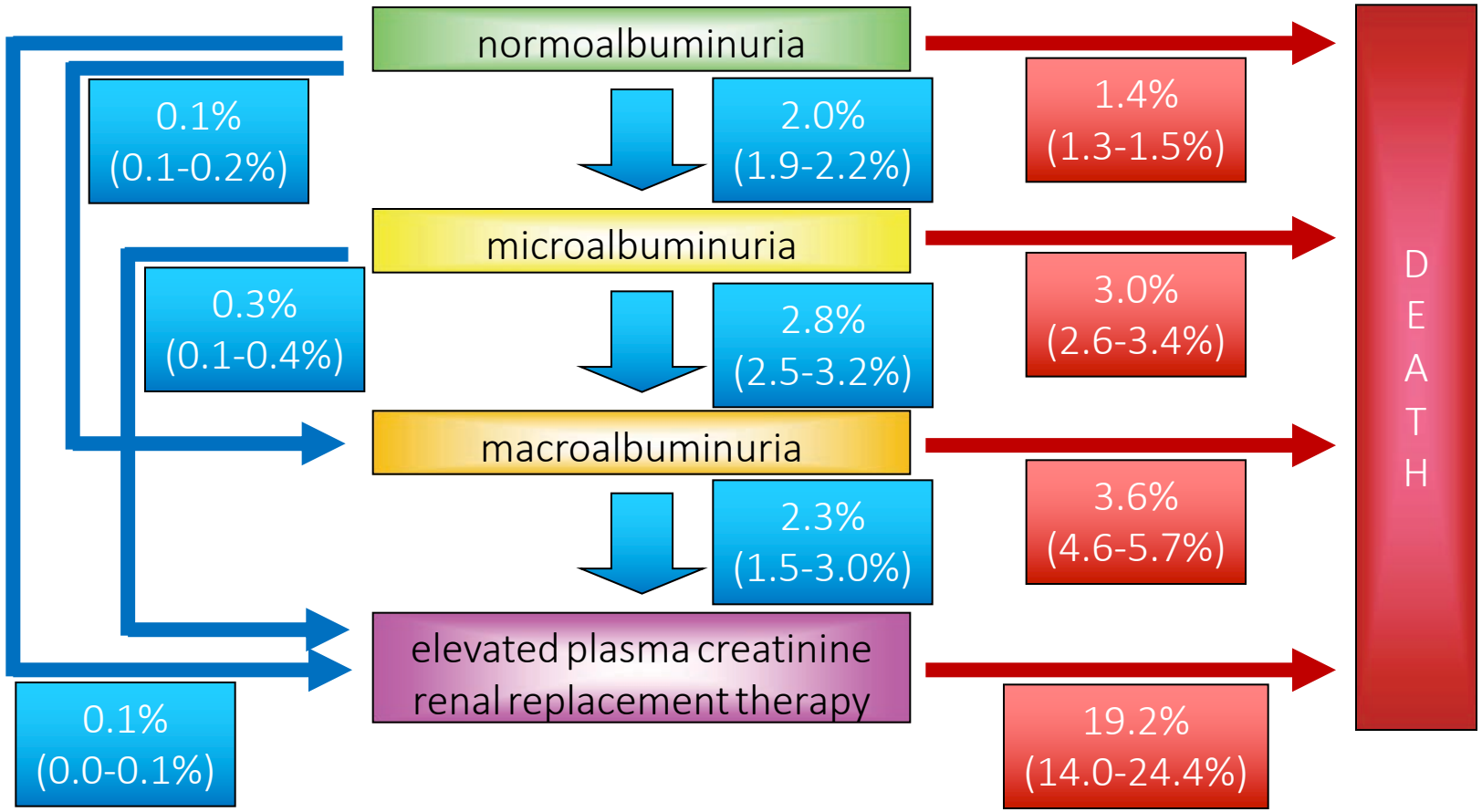


Analysis of 123,205 deaths among 820,900 people without and with (type 2) diabetes in 97 studies

The Emerging Risk Factors Collaboration. N Engl J Med. 2011;364:829-841

Progression to ESRD versus death from CVD

Annual transition rates through the stages of nephropathy and to death from any cause.

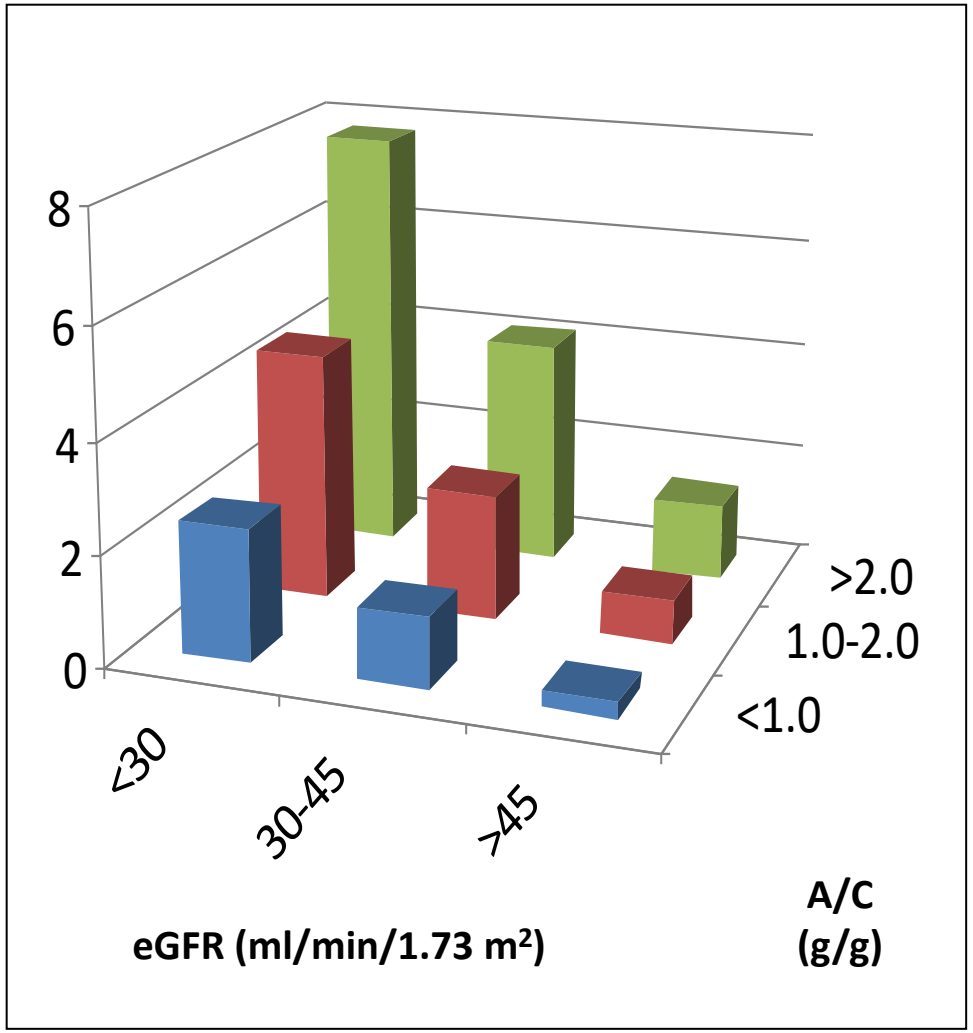


Post-hoc analysis of the United Kingdom Prospective Diabetes Study (UKPDS) 64

Adler AI et al. Kidney Int. 2003;63:225–232

Progression to ESRD versus death from CVD

Risk of ESRD for each albuminuria and eGFR category



→ 3,228 adult patients from 2 prospective randomized controlled clinical trials:

1. Irbesartan Diabetic Nephropathy Trial (IDNT);
2. Reduction of Endpoints in Non–Insulin-dependent Diabetes With the Angiotensin II Antagonist Losartan (RENAAL).

A/C (g/g)	eGFR (ml/min/1.73 m²)		
	<30	30-45	>45
>2.0	12.87 (5.97-27.74)	7.46 (3.63-15.33)	7.40 (3.32-16.47)
1.0-2.0	7.12 (3.16-16.04)	3.47 (1.63-7.40)	2.80 (1.18-6.64)
<1.0	3.61 (1.49-8.73)	1.49 (0.64-3.48)	1.00 (Ref)

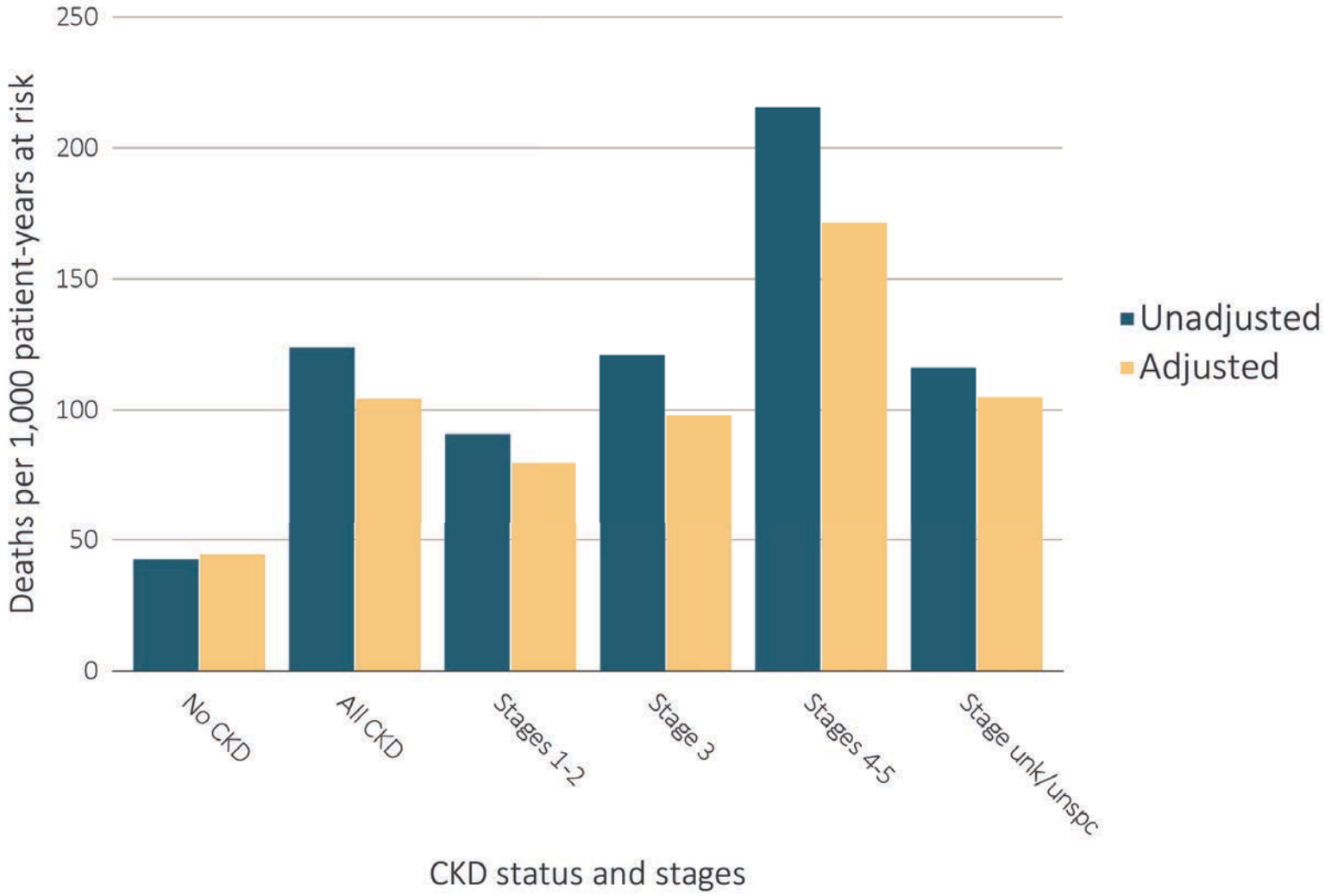
Multivariate adjusted risk of ESRD for each albuminuria and eGFR category, accounting for the possibility of competing events between ESRD and CV death

The Diabetes Mellitus Treatment for Renal Insufficiency Consortium (DIAMETRIC) Database

Packham DK et al. Am J Kidney Dis. 2011;59:75-83

All-cause mortality in people with CKD

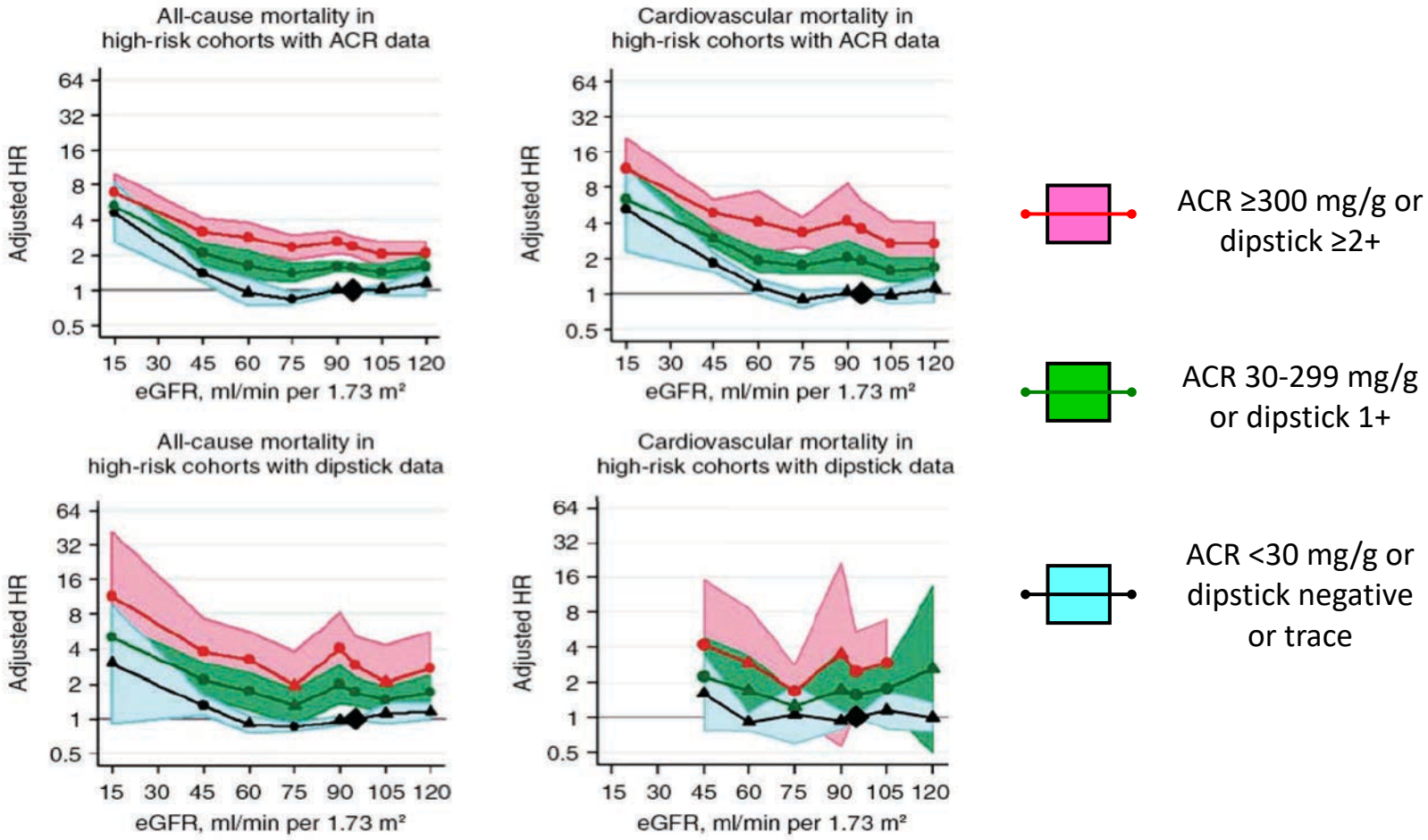
Unadjusted and adjusted all-cause mortality rates per 1,000 patient-years at risk for Medicare patients aged 66 and older, by CKD status and stage, 2016



USRDS, 2018 Annual Data Report, Volume 1 CKD, Chapter 4

Relation of albuminuria and eGFR to all-cause and CVD mortality

Risk of death by albuminuria and eGFR

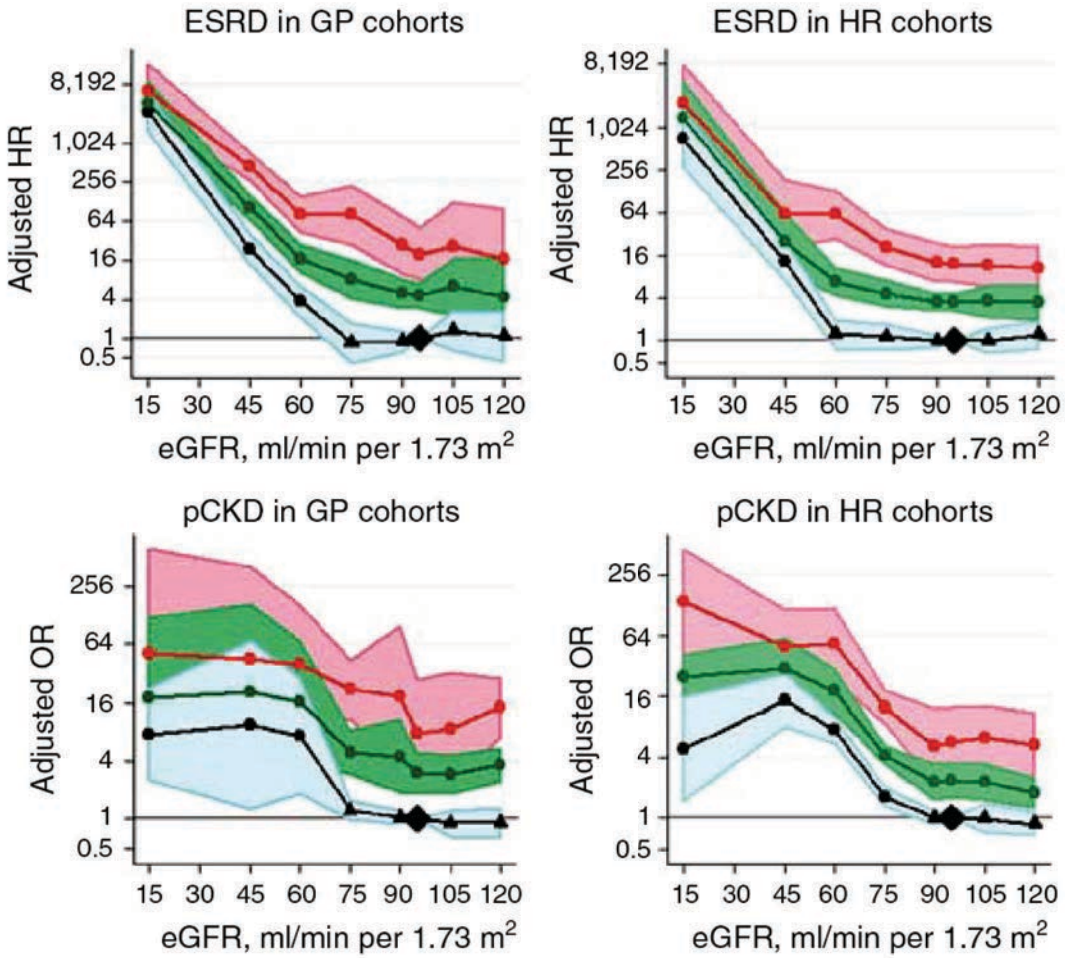


Meta-analysis of data of 105,872 participants from 10 cohorts with diabetes (49.6%), hypertension or CVD and ACR measurements or with diabetes (32.4%), hypertension or CVD and dipstick measurements

CKD Prognosis Consortium. Kidney Int. 2011;79:1341-1352

Relation of albuminuria and eGFR to adverse renal outcomes

Risk of adverse renal outcomes by albuminuria and eGFR



ACR ≥300 mg/g or dipstick ≥2+

ACR 30-299 mg/g or dipstick 1+

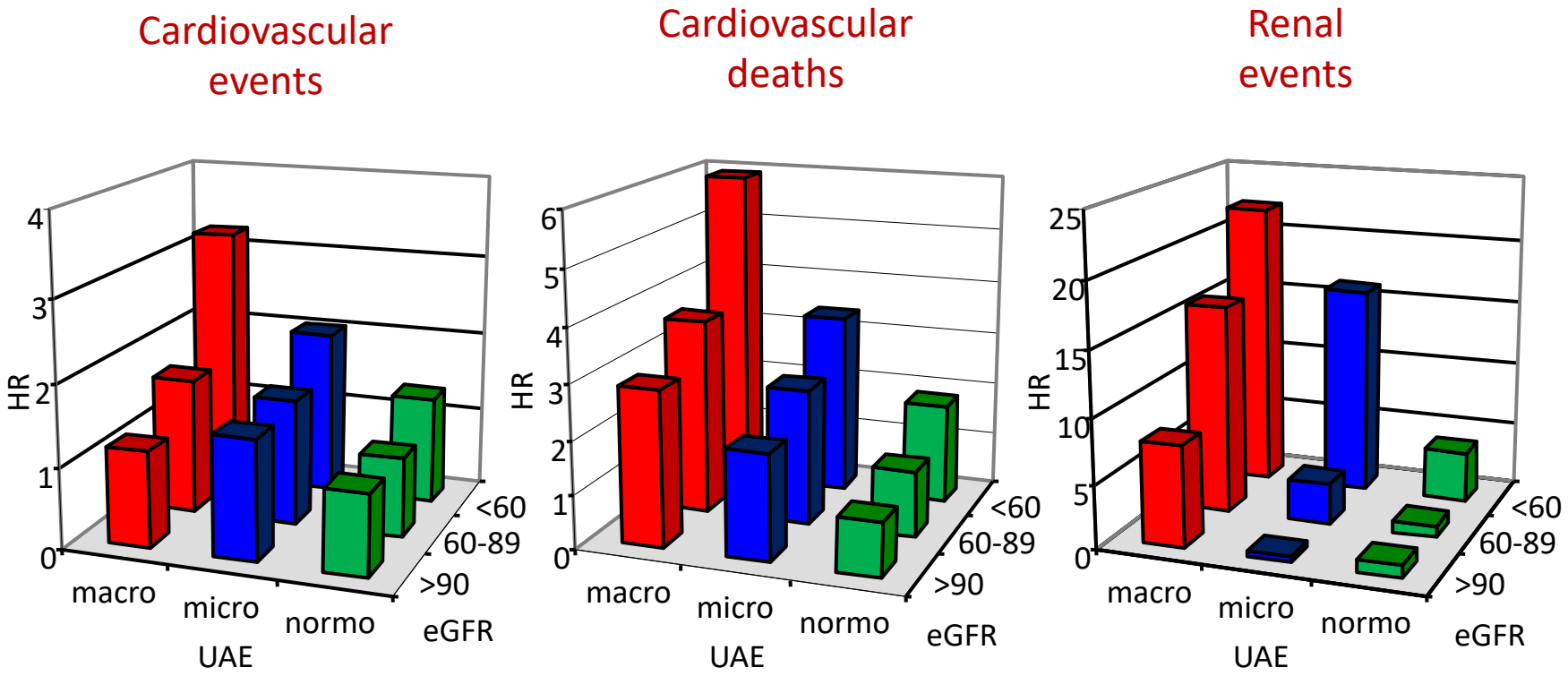
ACR <30 mg/g or dipstick negative or trace

Meta-analysis of data of 845,125 participants from 9 nine general population cohorts and 173,892 patients from 8 cohorts at high risk for CKD

CKD Prognosis Consortium. Kidney Int. 2011;80:93-104

Relation of albuminuria and eGFR to adverse renal outcomes

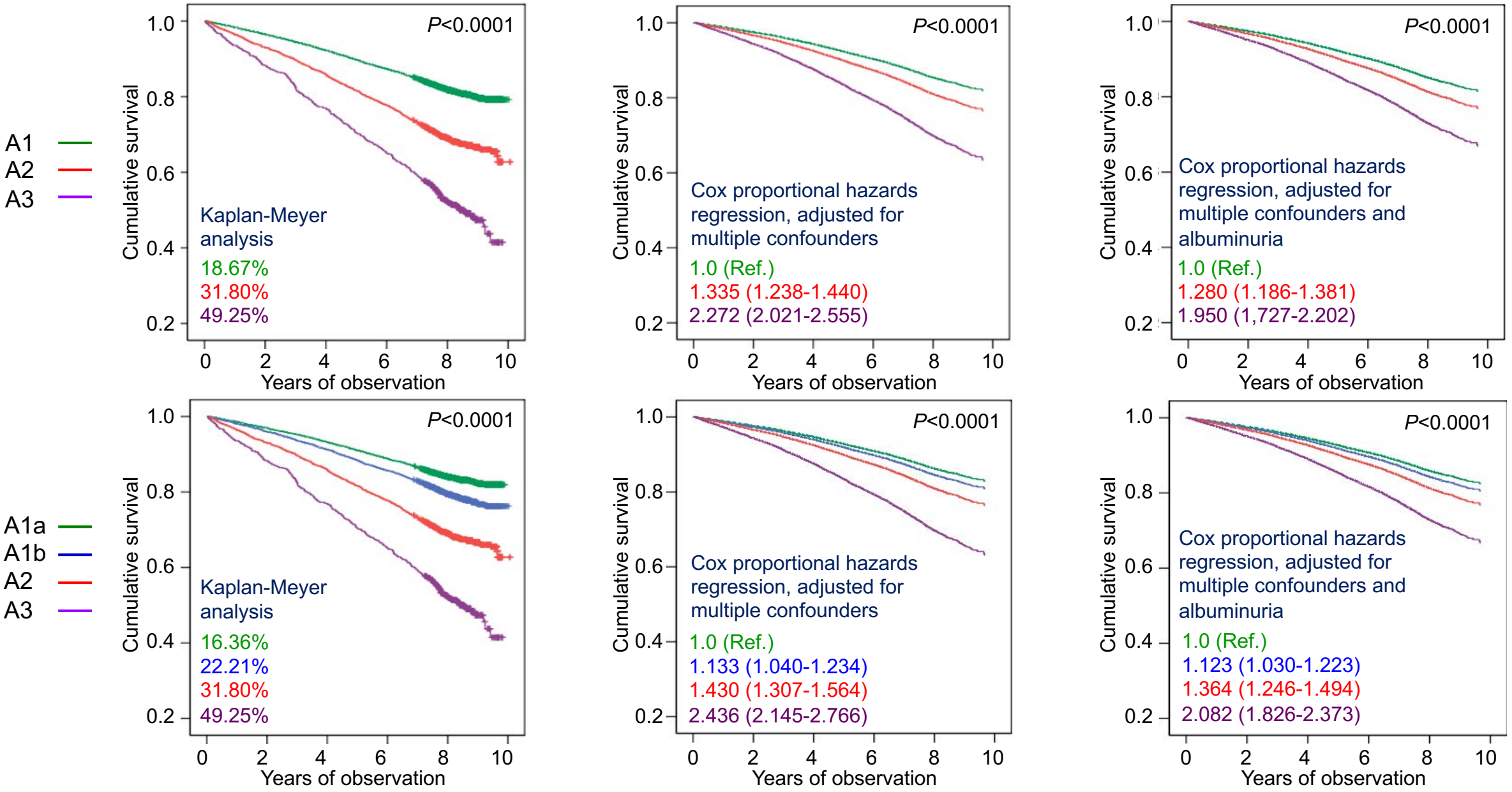
Risk of all-cause & CVD mortality and adverse renal outcomes by albuminuria and eGFR



Analysis of data of 10,640 patients with type 2 diabetes from the the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) Study over a median follow-up of 4.3 years

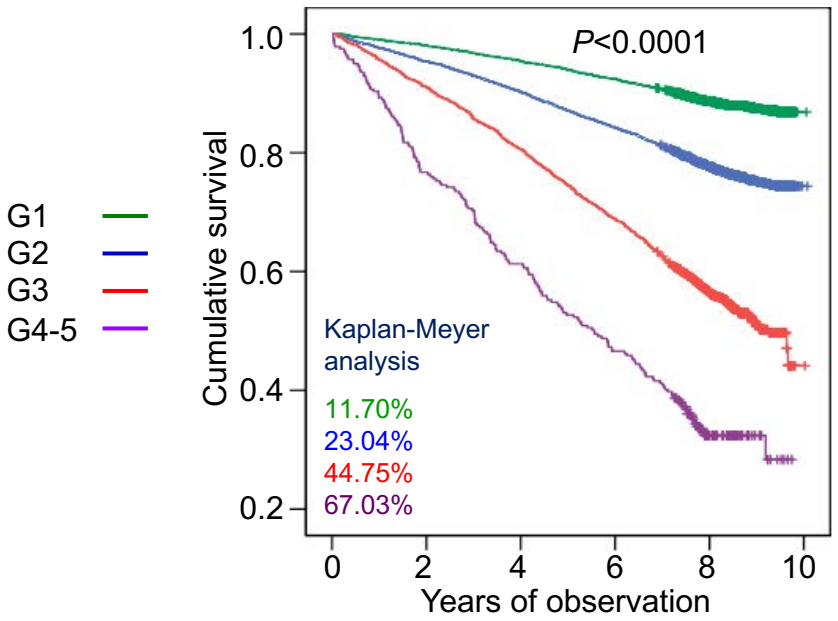
Ninomiya T et al. J Am Soc Nephrol. 2009;20:1813–1821

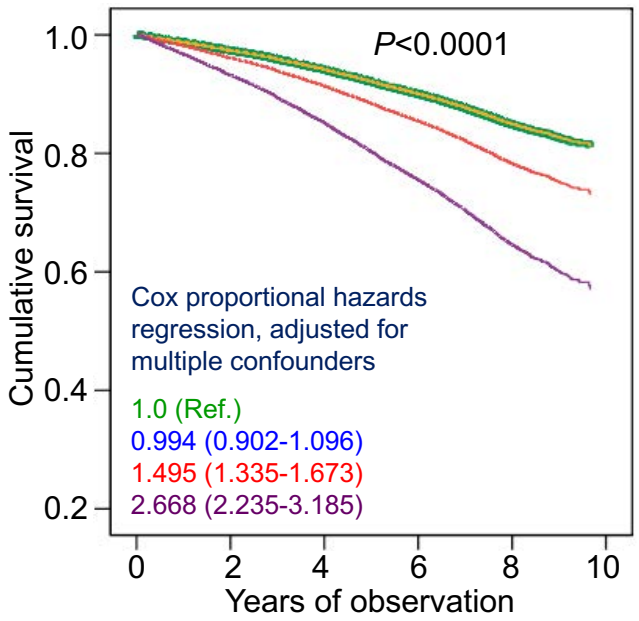
Relation of albuminuria categories to all-cause mortality

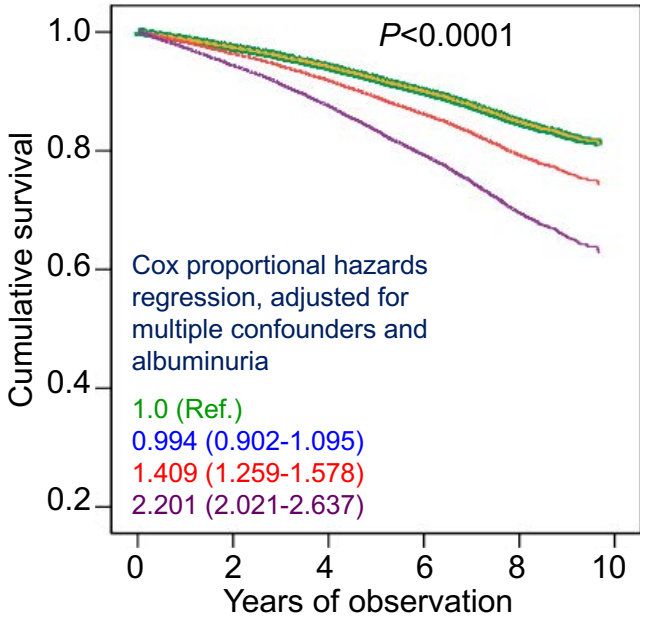


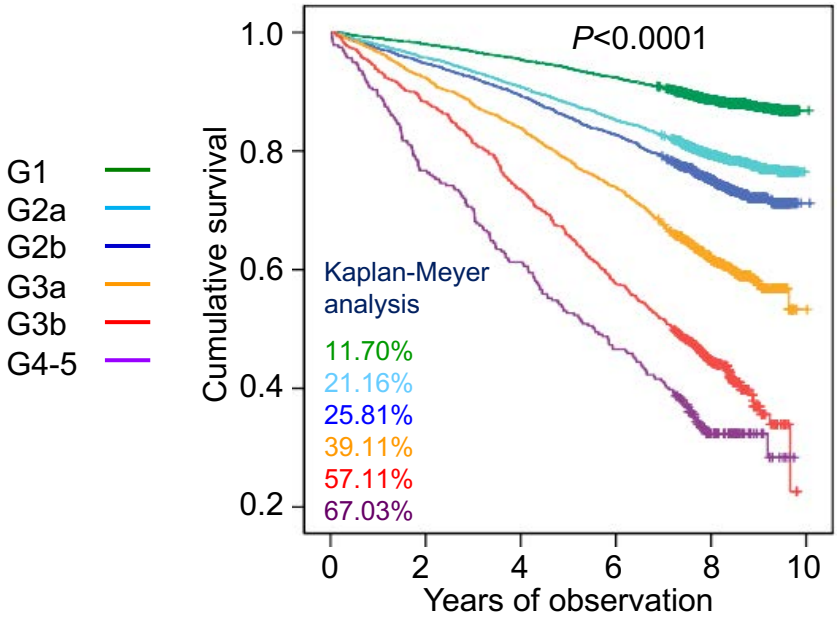
Penno G et al. Acta Diabetol. 2018; 55:603-612

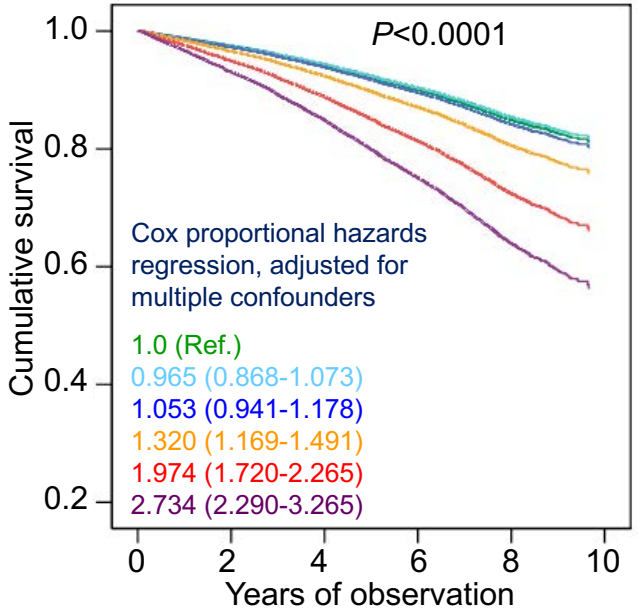
Relation of eGFR categories to all-cause mortality

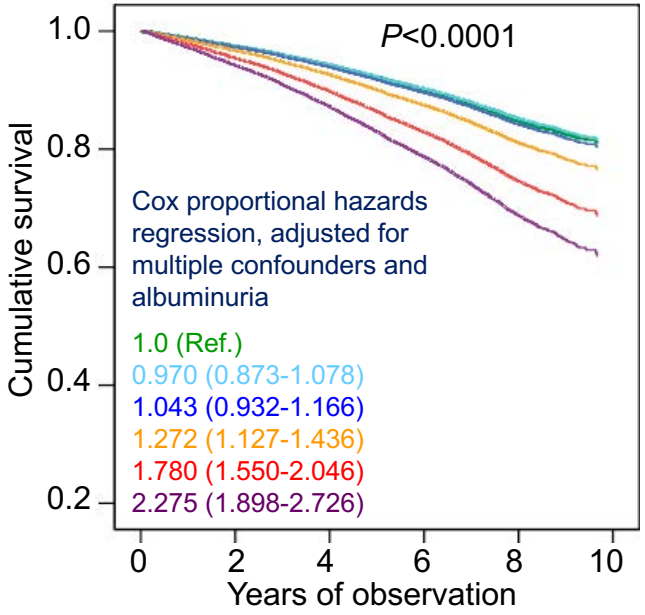






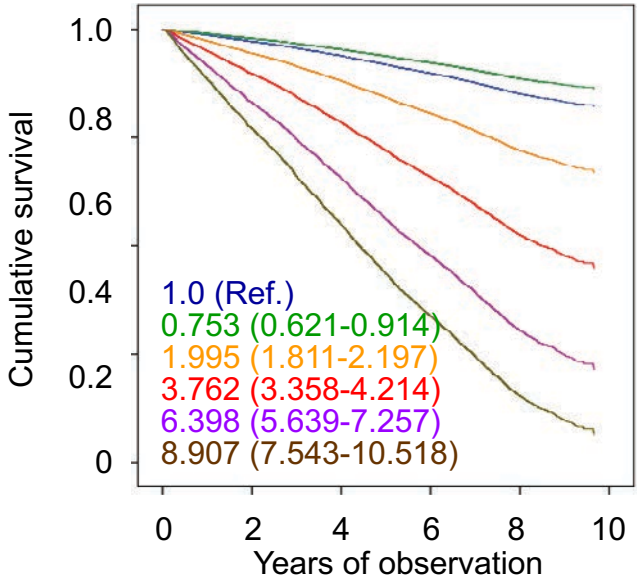


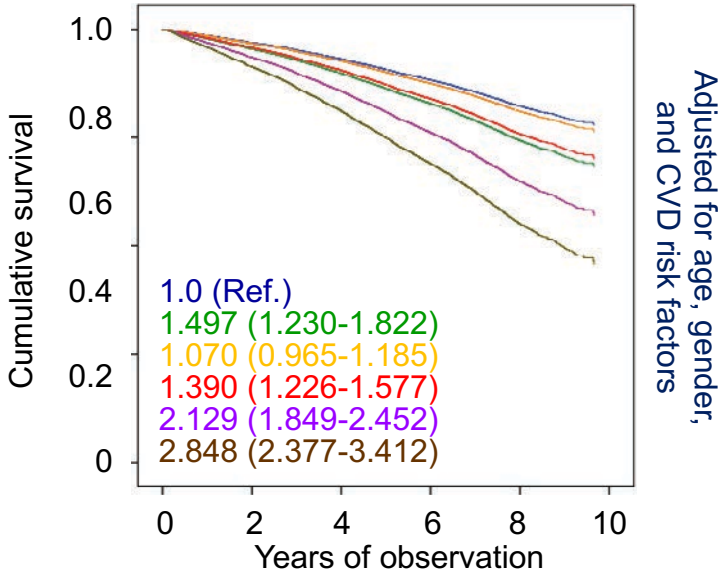


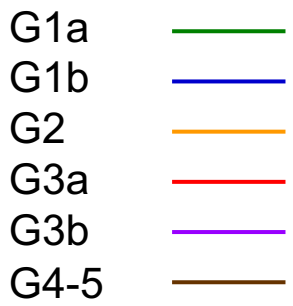


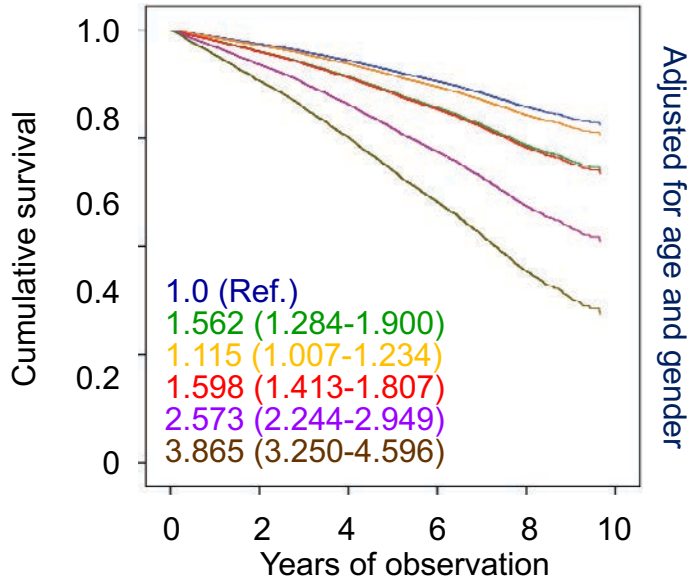
Penno G et al. Acta Diabetol. 2018; 55:603-612

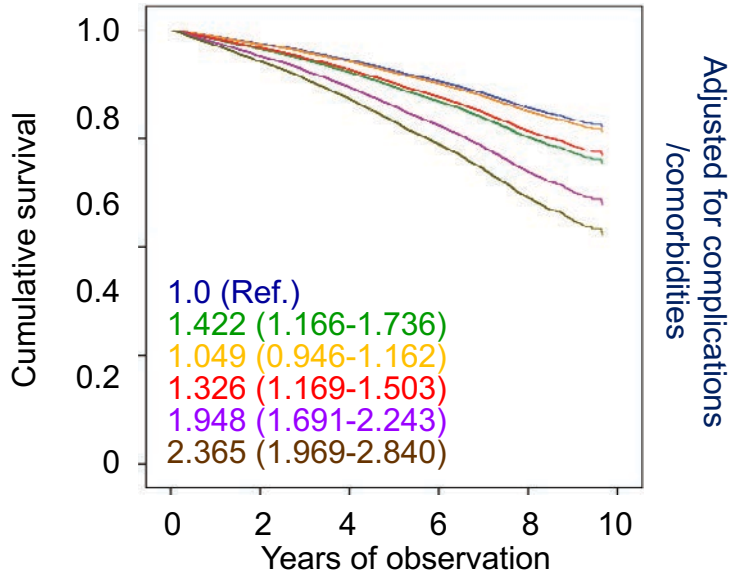
Relation of eGFR categories to all-cause mortality







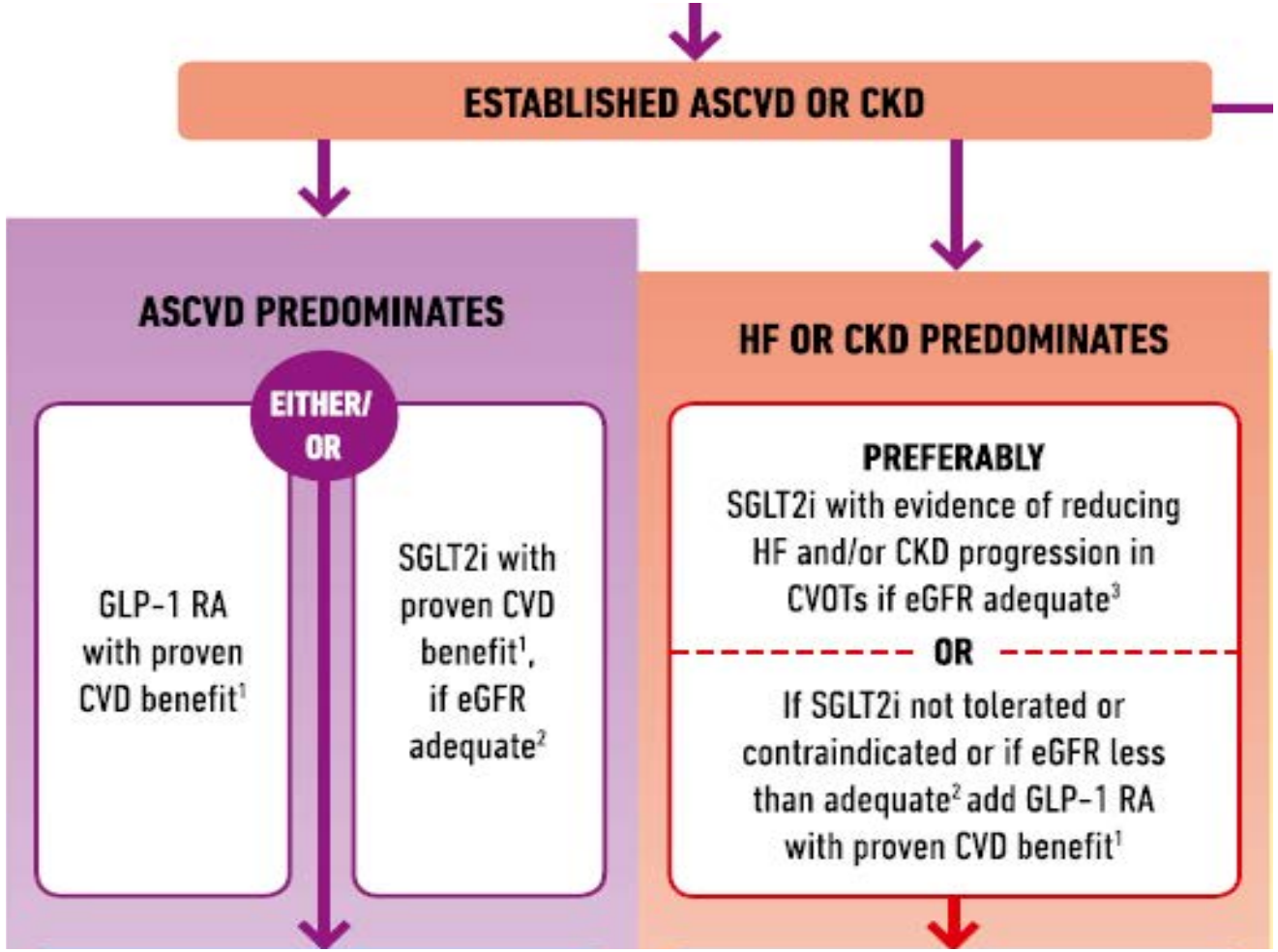




The RIACE Study Group. Unpublished data

Cardiorenal protection with anti-hyperglycemic agents

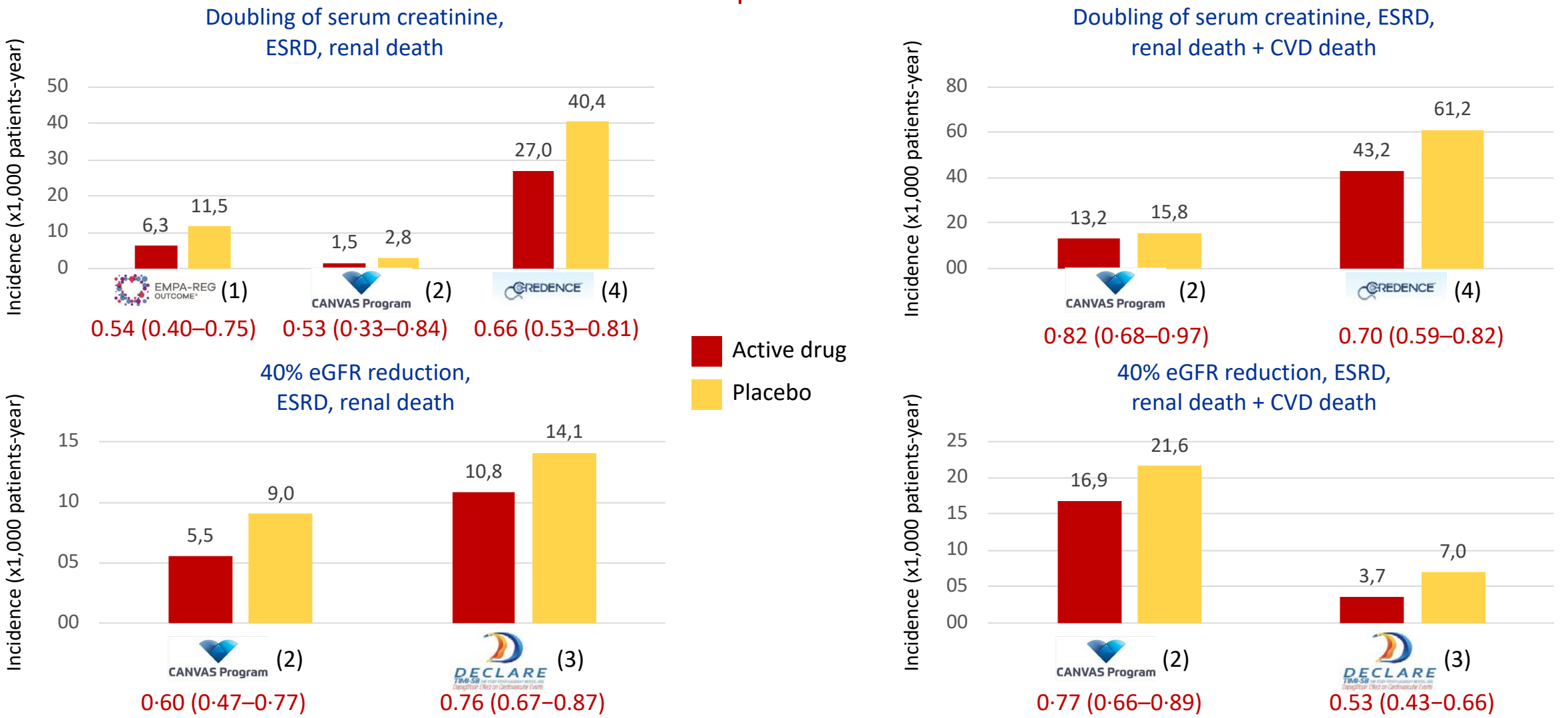
American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



Davies MJ et al. Diabetologia. 2018;61:2461-2498

Renal protection with GLP-1 receptor agonists and SGLT2 inhibitors

Renal composite outcomes

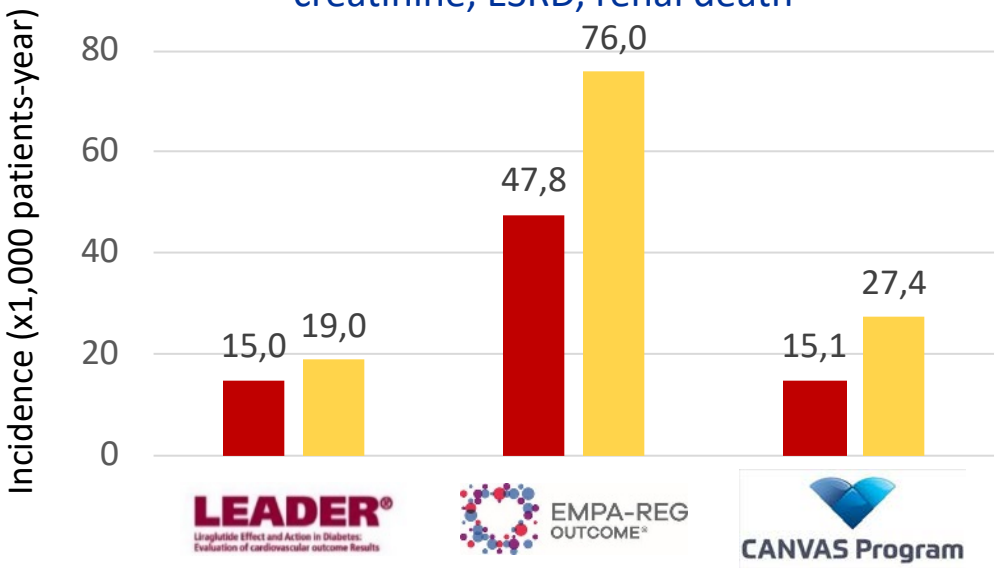


1. Wanner C et al. N Engl J Med. 2016;375:323-334; 2. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704;
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357; 4. Perkovic V et al. N Engl J Med. 2019; April 14

Renal protection with SGLT2 inhibitors

Renal composite outcomes

New-onset macro, doubling of serum creatinine, ESRD, renal death

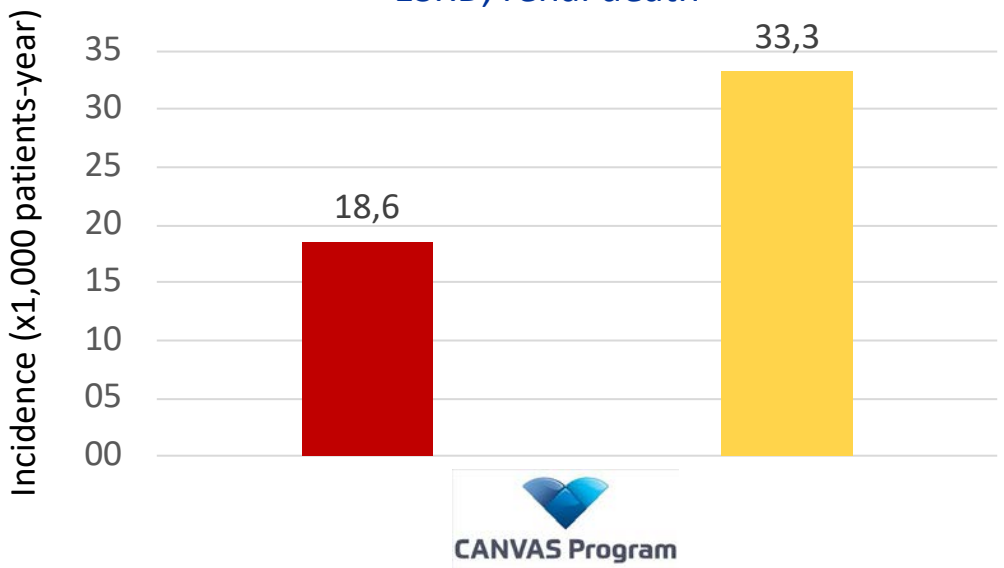


0.78 (0.67–0.92)

0.61 (0.53–0.70)

0·58 (0·50–0·67)

New-onset macro, 40% eGFR reduction, ESRD, renal death



0.57 (0.50–0.66)

Active drug Placebo

1. Marso SP et al. N Engl J Med. 2016;375;311-322
2. Wanner C et al. N Engl J Med. 2016;375:323-334
3. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704

Cardiovascular protection with GLP-1 receptor agonists

	ELIXA (1)	LEADER® (2)	SUSTAIN™ (3)	EXSCEL (4)	Harmony Outcomes (5)
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide-LAR	Albiglutide
N	6,068	9,340	3,297	14,752	9,463
Follow-up (years)	2.1	3.8	2.1	3.2	1.6
History of CVD (%)	100	81	83	73.1	100
Primary endpoint (MACE)	1.02 (0.89–1.17)* P=NS	0.87 (0.78–0.97) P=0.01	0.74 (0.58–0.95) P=0.02	0.91 (0.83–1.00) P=0.06	0·78 (0·68–0·90) P=0.0006
Fatal or nonfatal myocardial infarction	1.03 (0.87–1.22) P=NS	0.86 (0.73–1.00) P=0.046	0.74 (0.51–1.08) P=NS†	0.97 (0.85–1.10) P=NS	0.75 (0.61–0.90) P=0.003
Fatal or nonfatal stroke	1.12 (0.79–1.58) P=NS	0.86 (0.71–1.06) P=NS	0.61 (0.38–0.99) P=0.04†	0.85 (0.70–1.03) P=NS	0·86 (0·66–1·14)
Death from cardiovascular causes	0.98 (0.78–1.22) P=NS	0.78 (0.66–0.93) P=0.007	0.98 (0.65–1.48) P=NS	0.88 (0.76–1.02) P=NS	0.93 (0.73–1.19)
Death from any cause	0.94 (0.78–1.13) P=NS	0.85 (0.74–0.97) P=0.02	1.05 (0.74–1.50) P=NS	0.86 (0.77–0.97) P<0.05	0·95 (0·79–1·16)
Hospitalization for heart failure	0.96 (0.75–1.23) P=NS	0.87 (0.73–1.05) P=NS	1.11 (0.77–1.61) P=NS	0.94 (0.78–1.13) P=NS	NA
Death from cardiovascular causes or hospitalization for heart failure	NA	NA	NA	0·85 (0·70–1·04) P=NS	NA

*4-point MACE;
† only nonfatal.

1. Pfeffer MA et al. N Engl J Med. 2015;373;2247-2257; 2. Marso SP et al. N Engl J Med. 2016;375;311-322; 3. Marso SP et al. N Engl J Med. 2016;375;1834-1844; 4. Holman RR et al. N Engl J Med. 2017;377;1228-1239; 5. Hernandez HF et al. Lancet. 2018;392:1519–1529

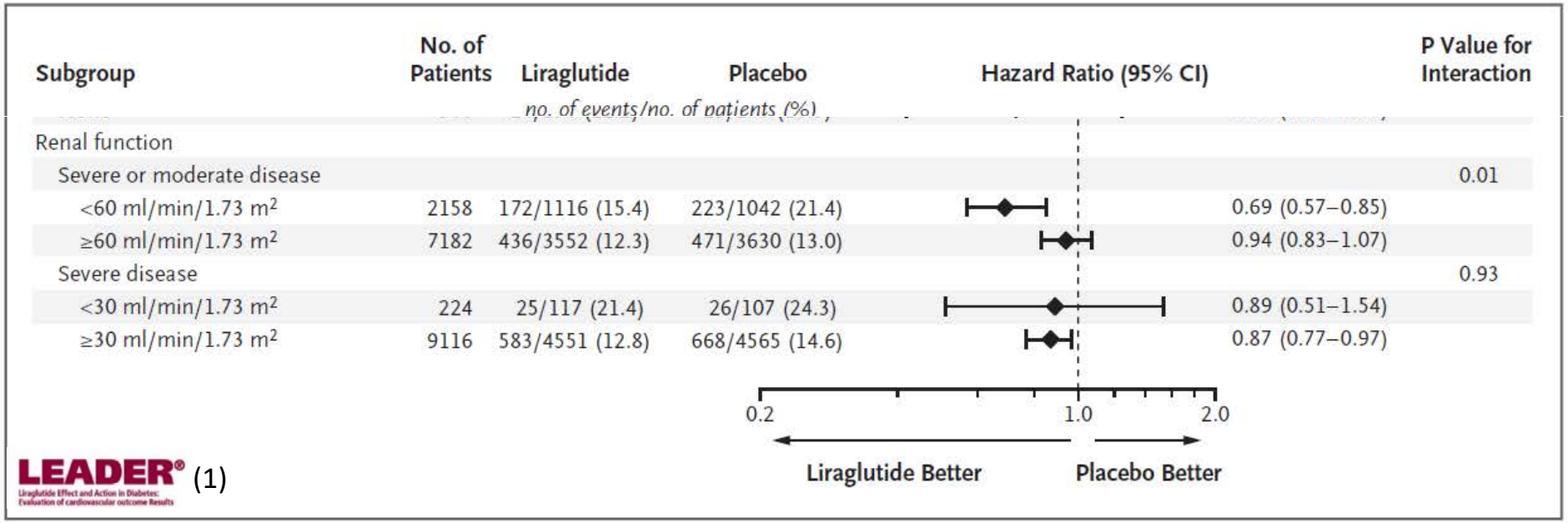
Cardiovascular protection with SGLT2 inhibitors

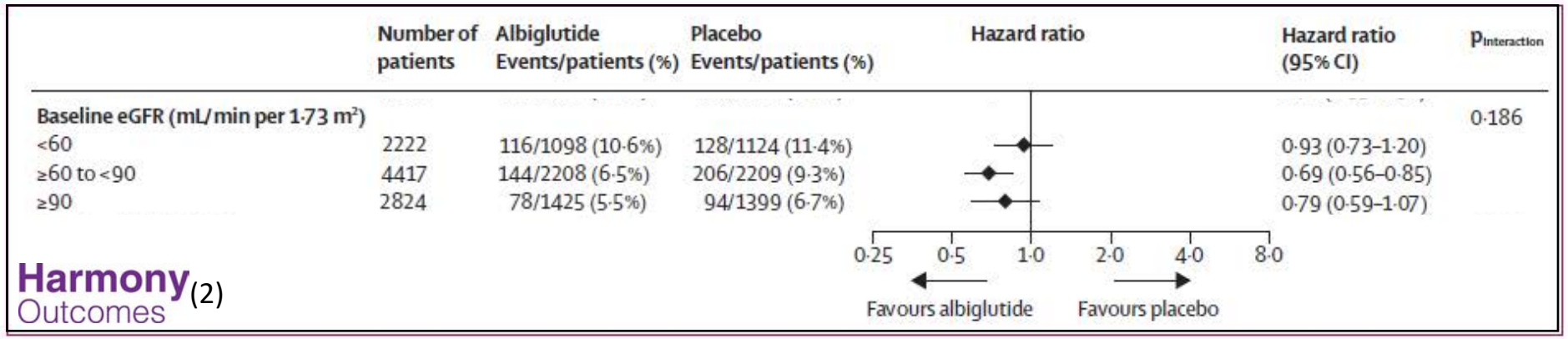
	EMPA-REG OUTCOME® (1)	CANVAS Program (2)	DECLARE TIMI-58 (3)	CREDENCE (4)
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
N	7,020	10,142	17,160	4,401
Follow-up (years)	3.1	2.4	4.2	2,6
History of CVD (%)	100	65.6	40.6	50,4
Primary endpoint (MACE)	0.86 (0.74–0.99) P=0.04	0.86 (0.75–0.97) P=0.02	0.93 (0.84–1.03) P=NS	0.80 (0.67–0.95) P=0.01†
Fatal or nonfatal myocardial infarction	0.87 (0.70–1.09) P=NS	0.89 (0.73–1.09) P=NS	0.89 (0.77–1.01) P=NS	NA
Fatal or nonfatal stroke	1.18 (0.89–1.56) P=NS	0.87 (0.69–1.09) P=NS	1.01 (0.84–1.21) P=NS	NA
Death from cardiovascular causes	0.62 (0.49–0.77) P<0.001	0.87 (0.72–1.06) P=NS	0.98 (0.82–1.17) P=NS	0.78 (0.61–1.00) P=0.05
Death from any cause	0.68 (0.57–0.82) P<0.001	0.87 (0.74–1.01) P=NS	0.93 (0.82–1.04) P=NS	0.83 (0.68–1.02) P=NS
Hospitalization for heart failure	0.65 (0.50–0.85) P=0.002	0.67 (0.52–0.87) P<0.05	0.73 (0.61–0.88) P<0-05	0.61 (0.47–0.80) P<0.001
Death from cardiovascular causes or hospitalization for heart failure	0.66 (0.55–0.79) P<0.001*	0.78 (0.67–0.91) P<0.05	0.83 (0.73–0.95) P=0.005	0.69 (0.57–0.83) P<0.001

*excluding fatal stroke; † MACE as secondary endpoint.

1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128
2. Neal B et al. N Engl J Med. 2017;377:644-657
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357
4. Perkovic V et al. N Engl J Med. 2019; April 14

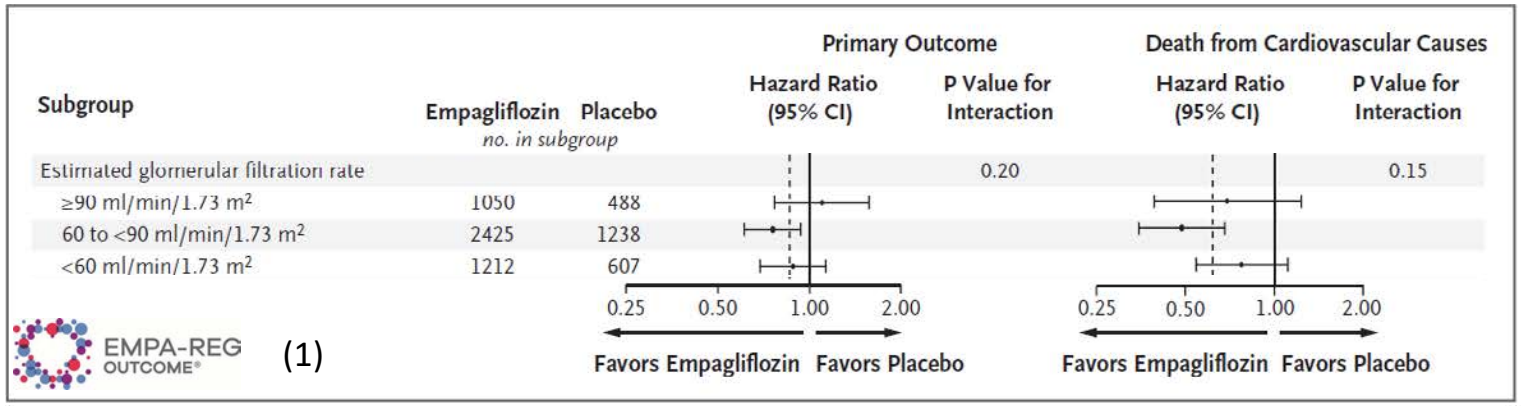
Cardiovascular protection with GLP-1 receptor agonists by eGFR

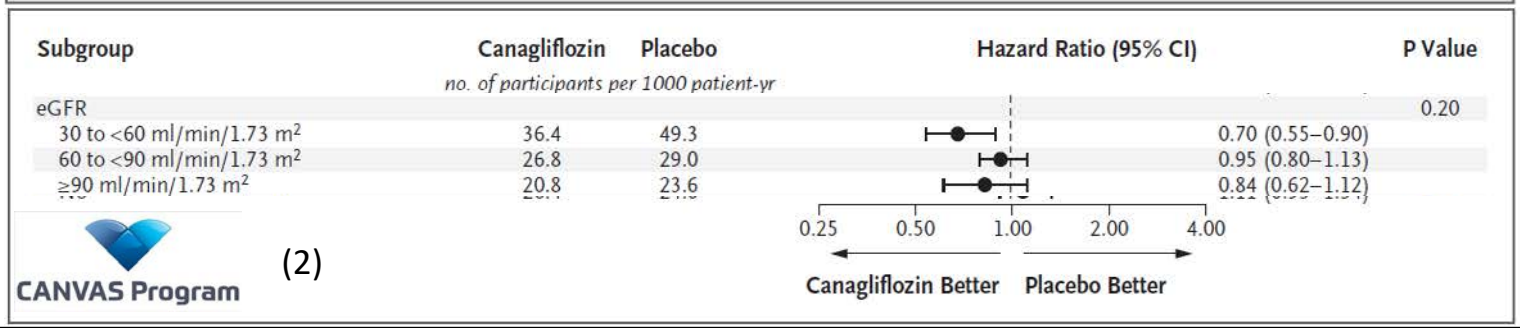


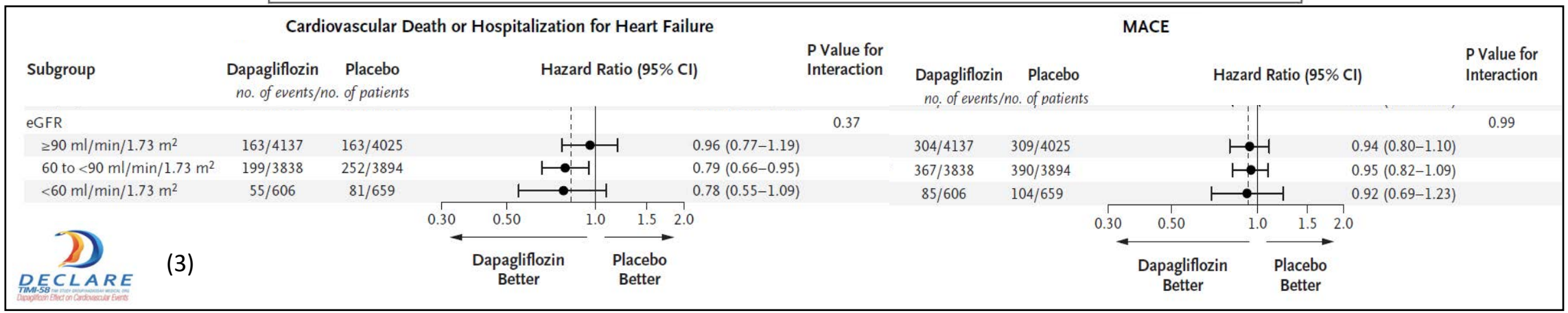


1. Marso SP et al. N Engl J Med. 2016;375;311-322; 2. Hernandez HF et al. Lancet. 2018;392:1519–1529

Cardiovascular protection with SGLT2 inhibitors by eGFR







1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128; 2. Neal B et al. N Engl J Med. 2017;377:644-657;
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357

Cardiovascular protection with SGLT2 inhibitors in DKD patients

CREDENCE

Primary	**Hazard ratio (95% CI)**	***P* value**
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001
Secondary		
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001
6. CV death	0.78 (0.61–1.00)	0.0502
7. All-cause mortality	0.83 (0.68–1.02)	NA
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	NA

Perkovic V et al. N Engl J Med. 2019; April 14

Conclusions

Impact of CKD on cardiovascular system

CVD and CKD influence each other in the context of the cardio-renal syndromes

CKD favors CVD via several mechanisms, including increased calcification

CKD and cardiovascular risk

CKD is associated with an increased CVD risk since its early phase

Both increased albuminuria and reduced eGFR are associated with an increased risk for total and CVD mortality and morbidity independent of each other and of other CVD risk factors

Renal protection and cardiovascular risk

Renal protection is associated with improved CVD outcomes (and vice versa)