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Proteinuria Primer

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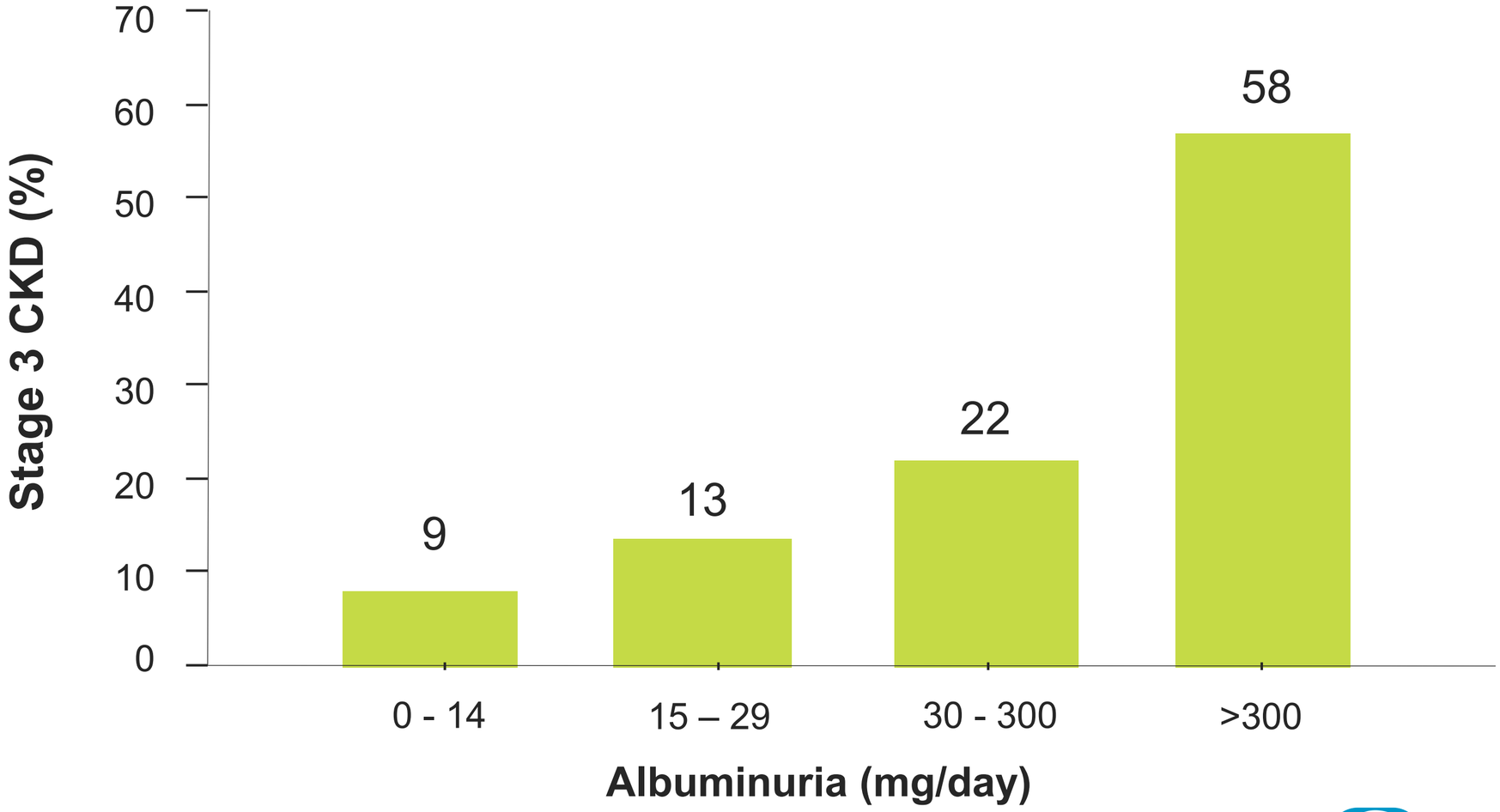
Proteinuria Predicts Renal Events

PREVEND: Albuminuria Predicts Stage 3 CKD at Year 4 (N=6894)



CKD, chronic kidney disease

Verhave JC, et al. Kidney Int Suppl. 2004 Nov;(92):S18-21.

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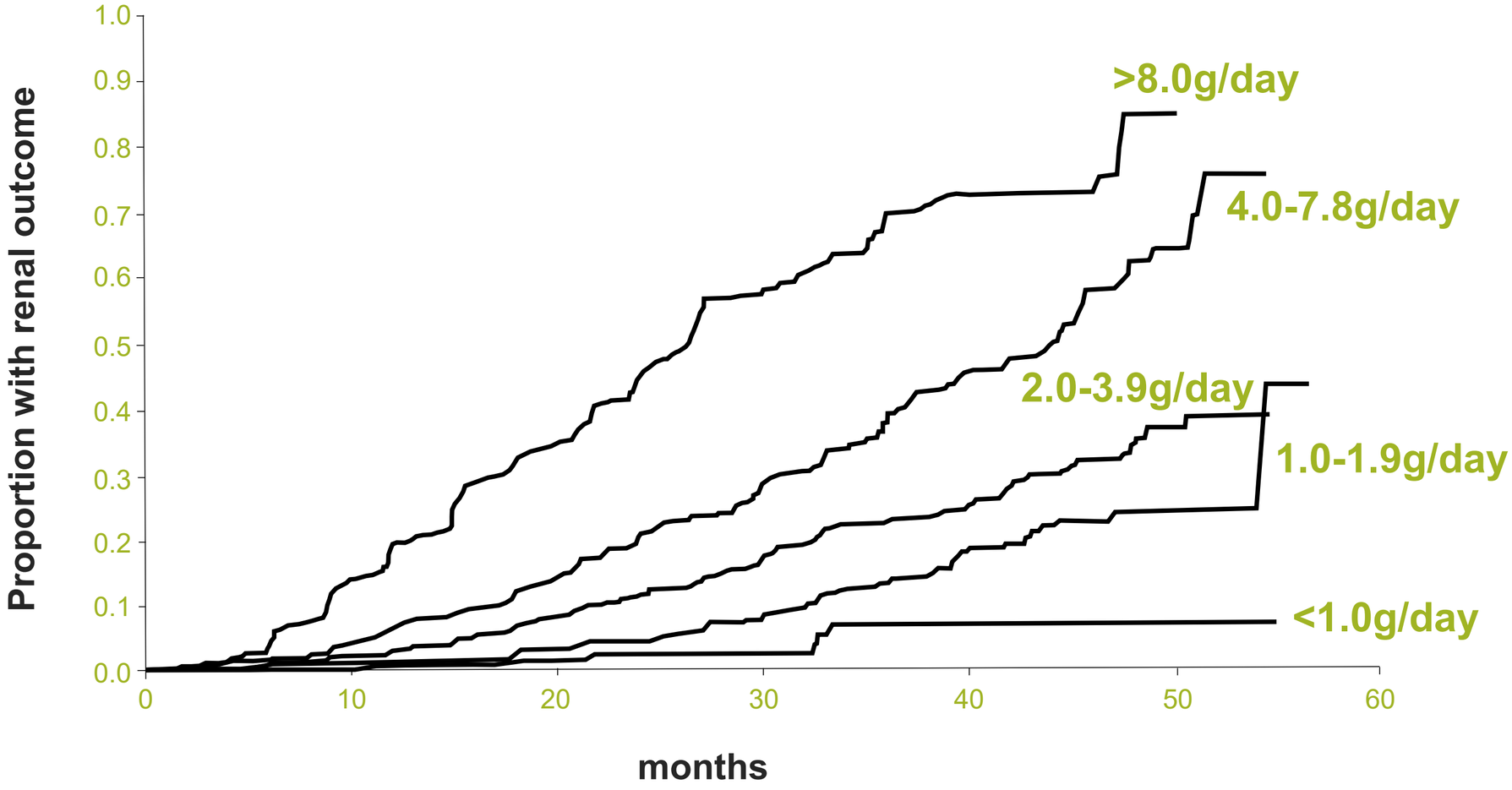
IDNT: Doubling of Scr or ESRD by Baseline Proteinuria



ESRD, end-stage renal disease; sCR, serum creatinine

Atkins RC, et al. Am J Kidney Dis. 2005 Feb;45(2):281-7.

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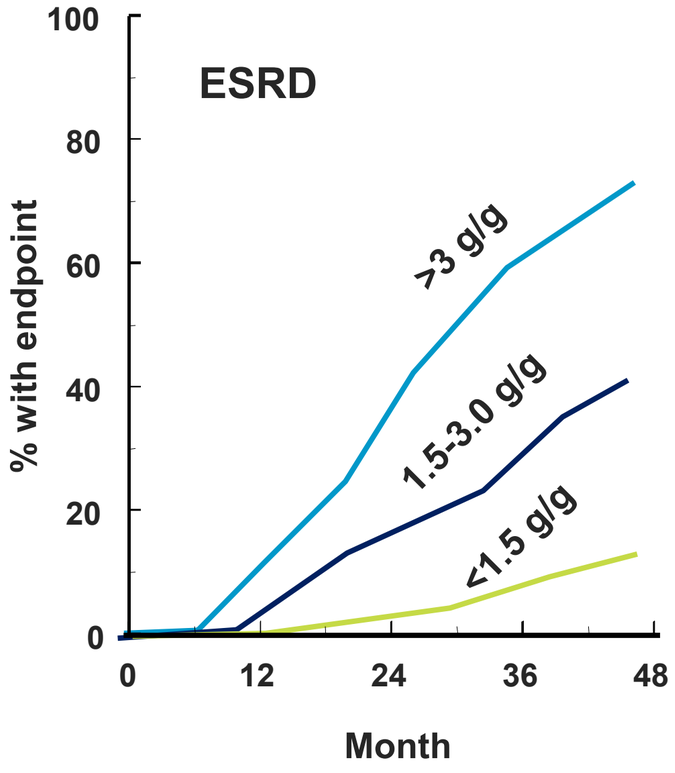
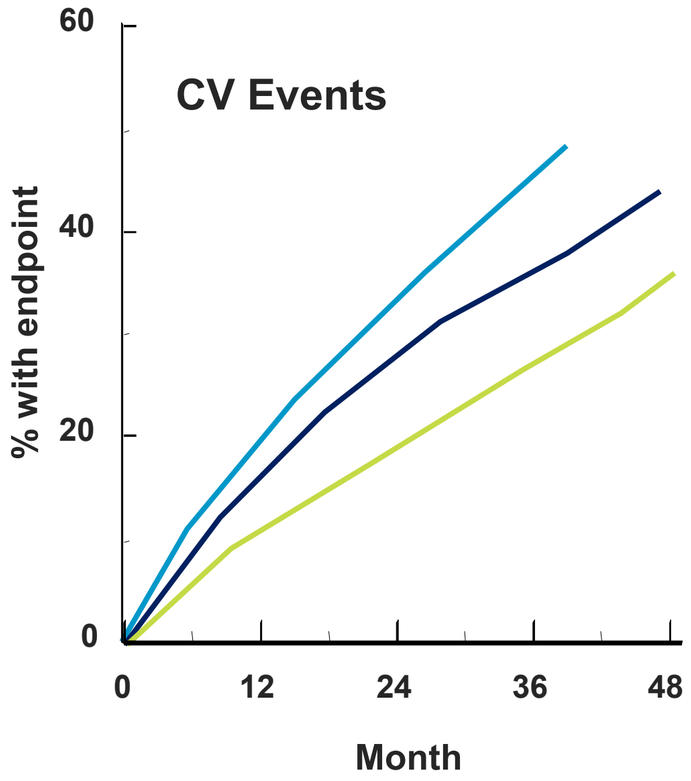
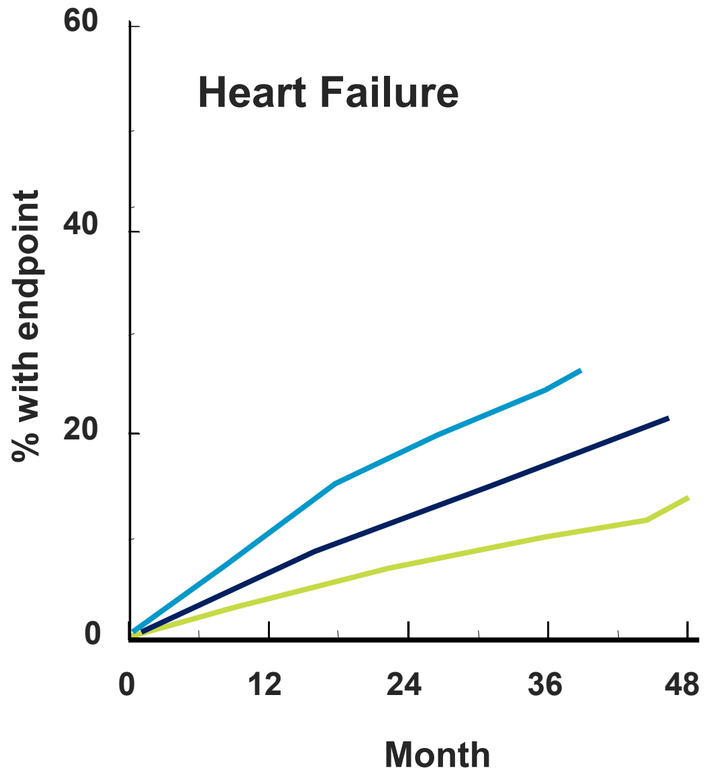
RENAAL:
Baseline Proteinuria Predicts Both Renal and CV Event Rate in T2DM







CV, cardiovascular; ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus

de Zeeuw D, et al. Kidney Int. 2004 Jun;65(6):2309-20.

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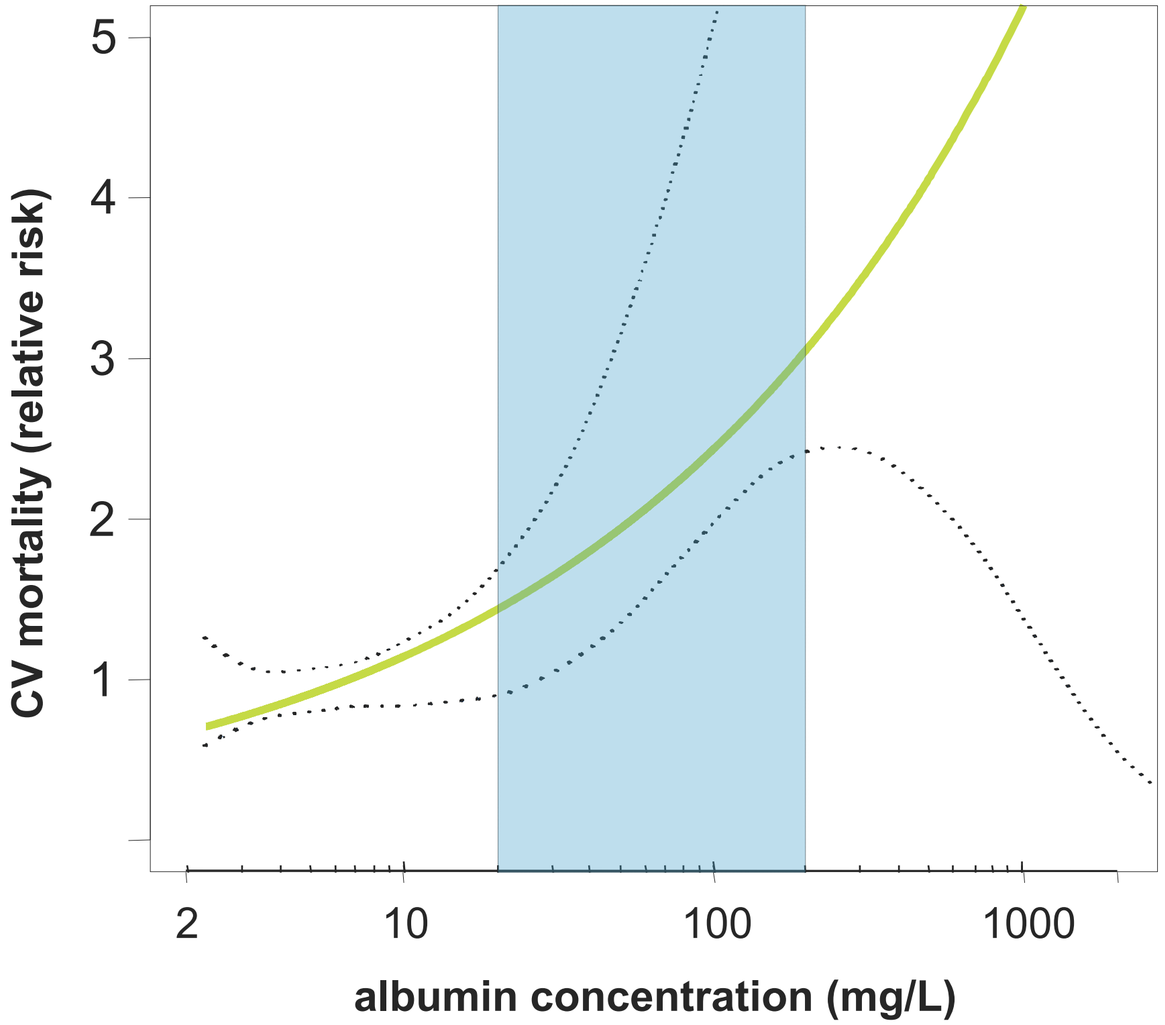
Framingham: Progressive Increase of Renal and CV Risk For Rates of Albumin Excretion within the Normal Range in T2DM

	Relative Risk	
	Progression to Microalbuminuria	**CV End-Point**
0 to 10 (mg/d)	1.0	1.0
10 to 20	2.3	1.9
20 to 30	12.4	9.8

CV, cardiovascular; T2DM, type 2 diabetes mellitus

Rachmani R, et al. Diabetes Res Clin Pract. 2000 Aug;49(2-3):187-94.

PREVEND; Albuminuria as a Predictor of CV Mortality the General Population (n=~40.000)



CV, cardiovascular

Hillege HL, et al. Circulation. 2002 Oct 1;106(14):1777-82.

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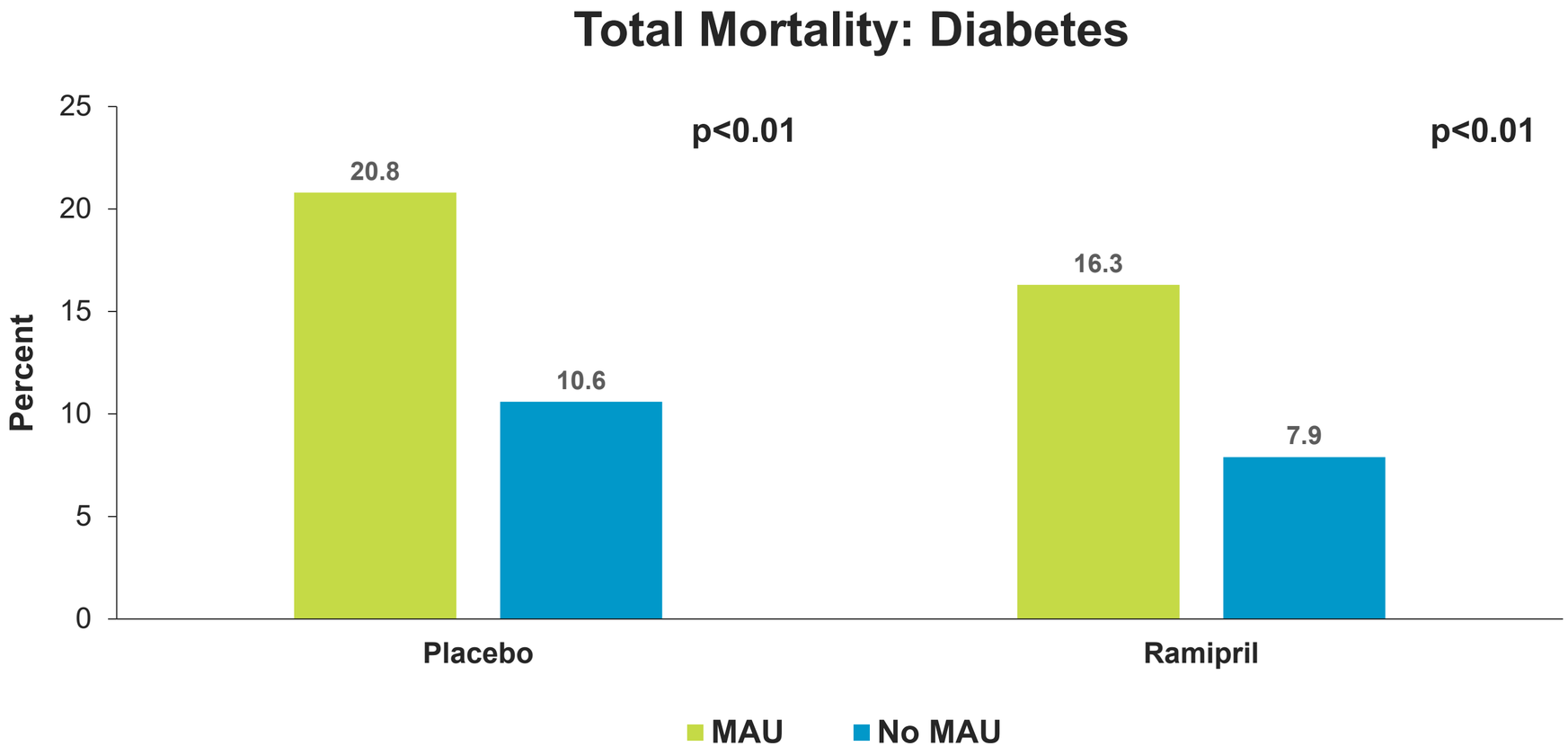
Incidence and Risk of CV Events in Participants With and Without Baseline Microalbuminuria by Randomized Group

HOPE Study



CV, cardiovascular

Gerstein HC, et al. JAMA. 2001 Jul 25;286(4):421-6.

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Percent of CKD Patients First Reaching ESRD or Death

	CKD Stage		
(N = 27,998)	2	3	4
ESRD	1.1	1.3	19.9
Death Prior to ESRD	19.5	24.3	45.7

CKD, chronic kidney disease; ESRD, end-stage renal disease
Keith DS, et al. Arch Intern Med. 2004 Mar 22;164(6):659-63.

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Summary Renal and CV Outcomes with Proteinuria and Low GFR

Low eGFR is associated with a greater risk of renal progression and greater CV risk

Albuminuria is associated with a greater risk of renal progression and greater CV risk

CV, cardiovascular; eGFR, estimated glomerular filtration rate

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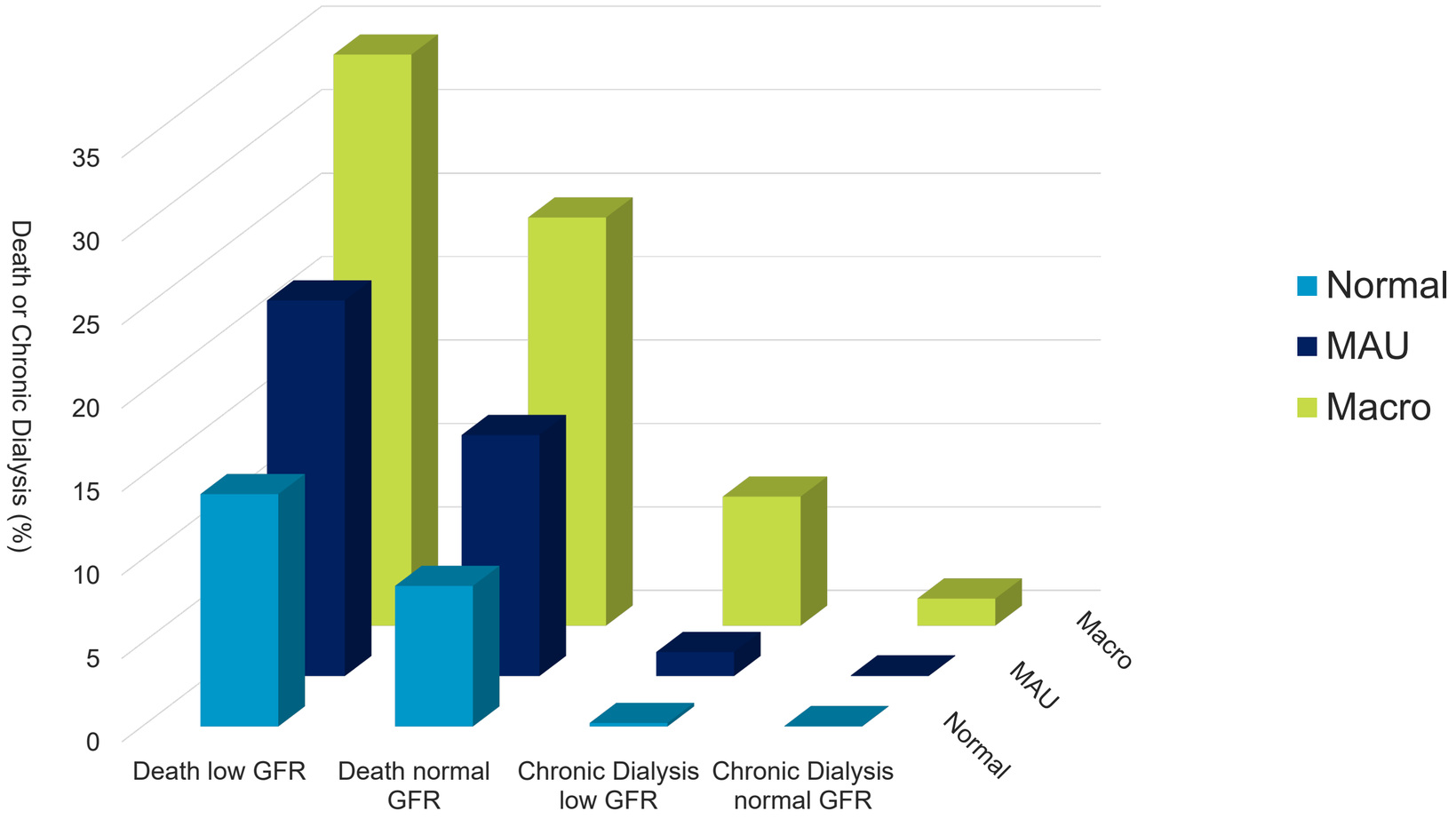
Stage of Kidney Disease	Normal		Microalbuminuria (30-300 mg/day)		Overt Nephropathy (≥ 1g/day)	
Type of Event Study	**Mortality**	**ESRD**	**Mortality**	**ESRD**	**Mortality**	**ESRD**
ONTARGET (ramipril arm N=8576, 4.7 year follow-up)	2.5	0.13				
HOPE diabetes cohort (n=1808, 4.5 year follow-up)	2.4	0.1				
ADVANCE Type 2 diabetes (n=7877, 4.3 year follow-up)	1.4	0.04	2.7	0.18		
LIFE Study (losartan arm n=4126, 4.8 year follow-up)	1.14	-	2.6	0.5		
UKPDS (64) Type 2 Diabetes* (overall n=5097, 10 year follow-up)	1.4	0.1	3.0	0.3	4.6	2.3
AASK Trial (amlodipine and metoprolol arm, n=658, 4.1 year follow-up)	**All cause mortality 0.5-5 times more likely to occur than progression to ESRD**				5.2	5.1
RENAAL** Type 2 diabetes (n=1513, 3.4 years follow-up)	**All cause mortality 5-15 times more likely to occur than progression to ESRD**				6.6	9.1
IDNT Type 2 diabetes (n=1715, 2.5 years)	**All cause mortality event 15 + times more likely to occur than progression to ESRD**				6.5	7.1

ESRD, end-stage renal disease

Tobe SW, Dai MO. Curr Hypertens Rep. 2009 Oct;11(5):345-53.

ONTARGET: CV and Renal Outcomes GFR x Albuminuria



1. Dialysis << death for all but macroalbuminuria
2. Both low GFR and albuminuria significantly increase the risk of death

CV, cardiovascular; GFR, glomerular filtration rate

Tobe SW, et al. Circulation. 2011 Mar 15;123(10):1098-107.

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Proteinuria Reduction

Is proteinuria reduction associated with improved outcomes?

Does targeted proteinuria reduction lead to improved outcomes?

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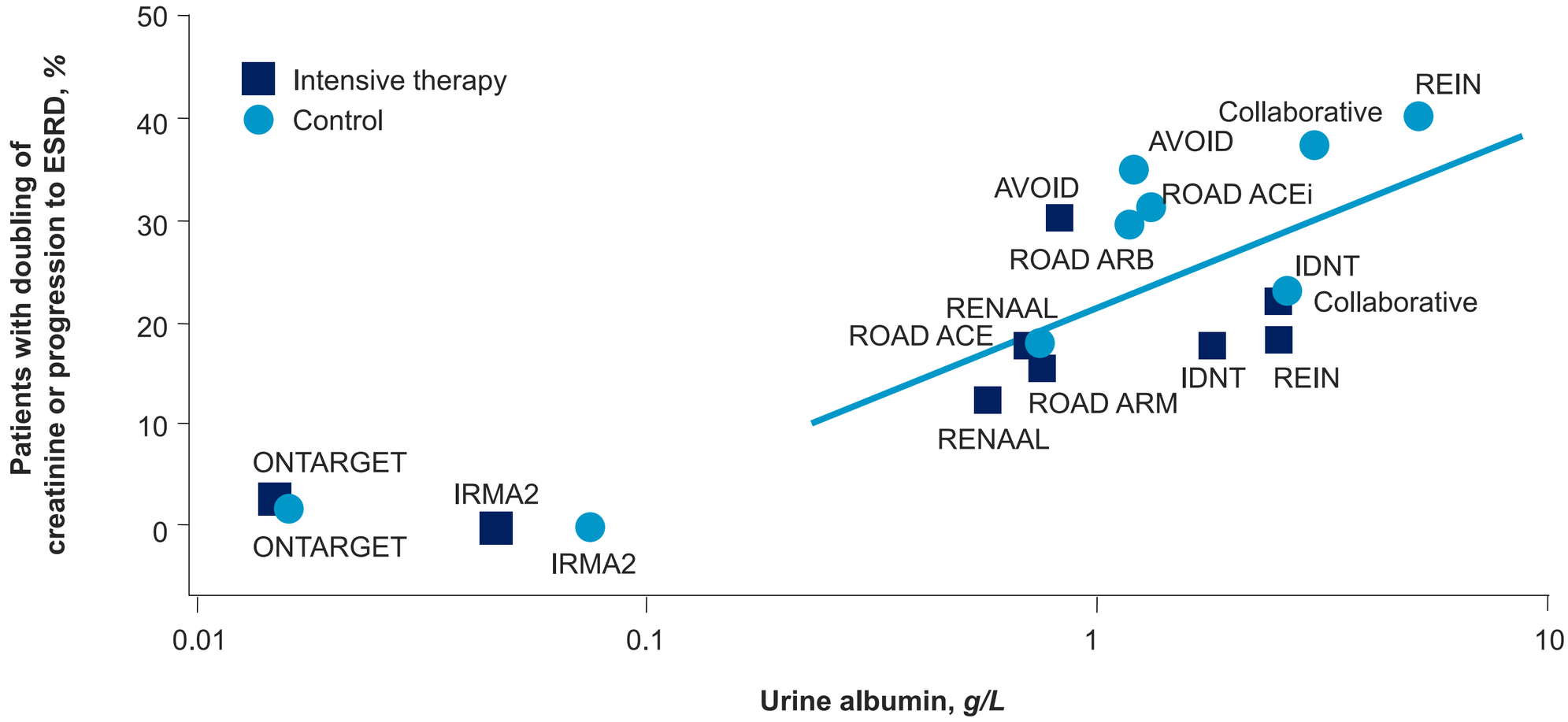
Relationship Between Achieved Urine Albumin Concentration and the Combined Renal Outcome of Doubling of Serum Creatinine and ESRD



ESRD, end-stage renal disease

Tobe SW, Dai MO. Curr Hypertens Rep. 2009 Oct;11(5):345-53.

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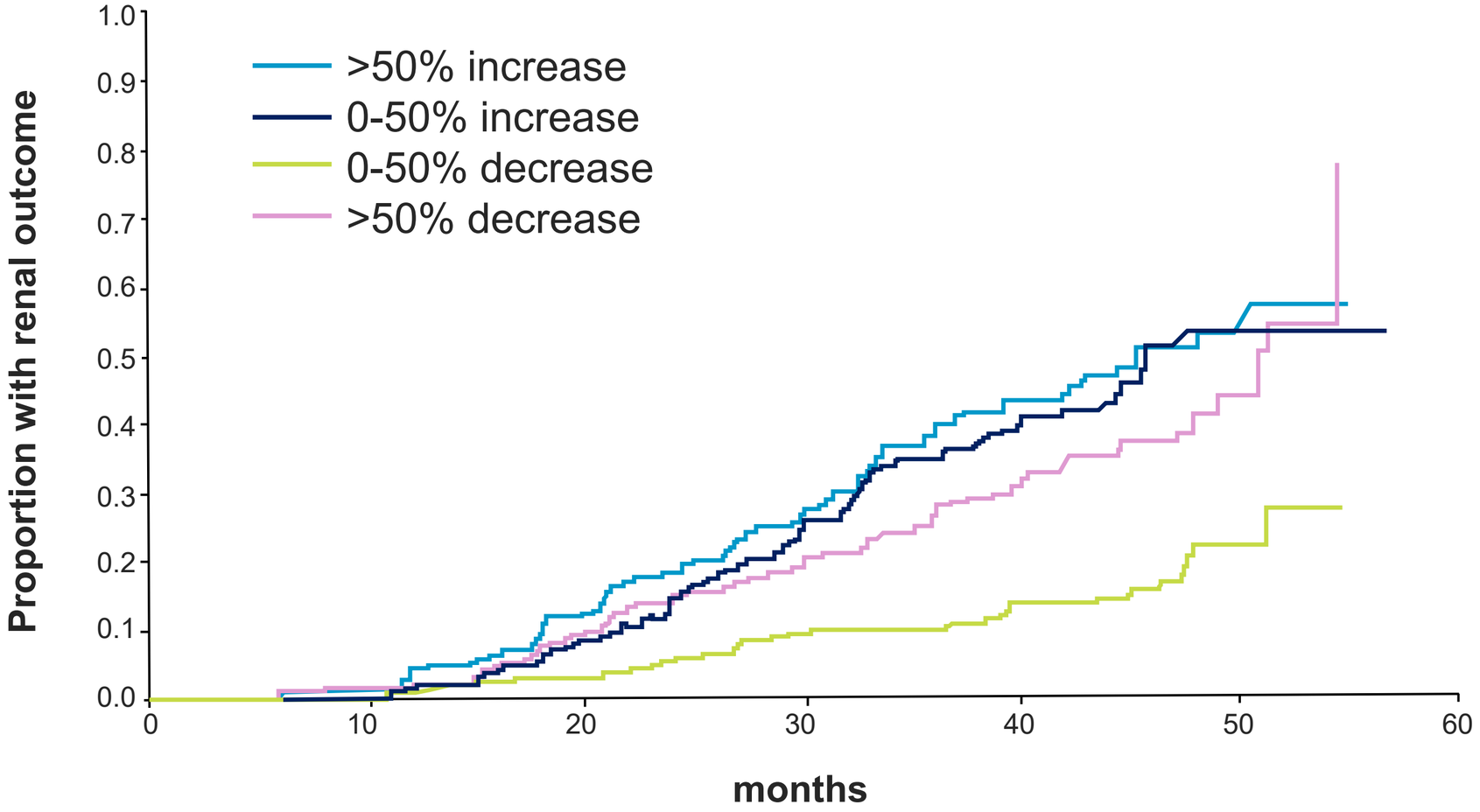
IDNT: Magnitude Of Change in Proteinuria in the First 12 Months Predicts Eventual Renal Endpoints



Atkins RC, et al. Am J Kidney Dis. 2005 Feb;45(2):281-7.

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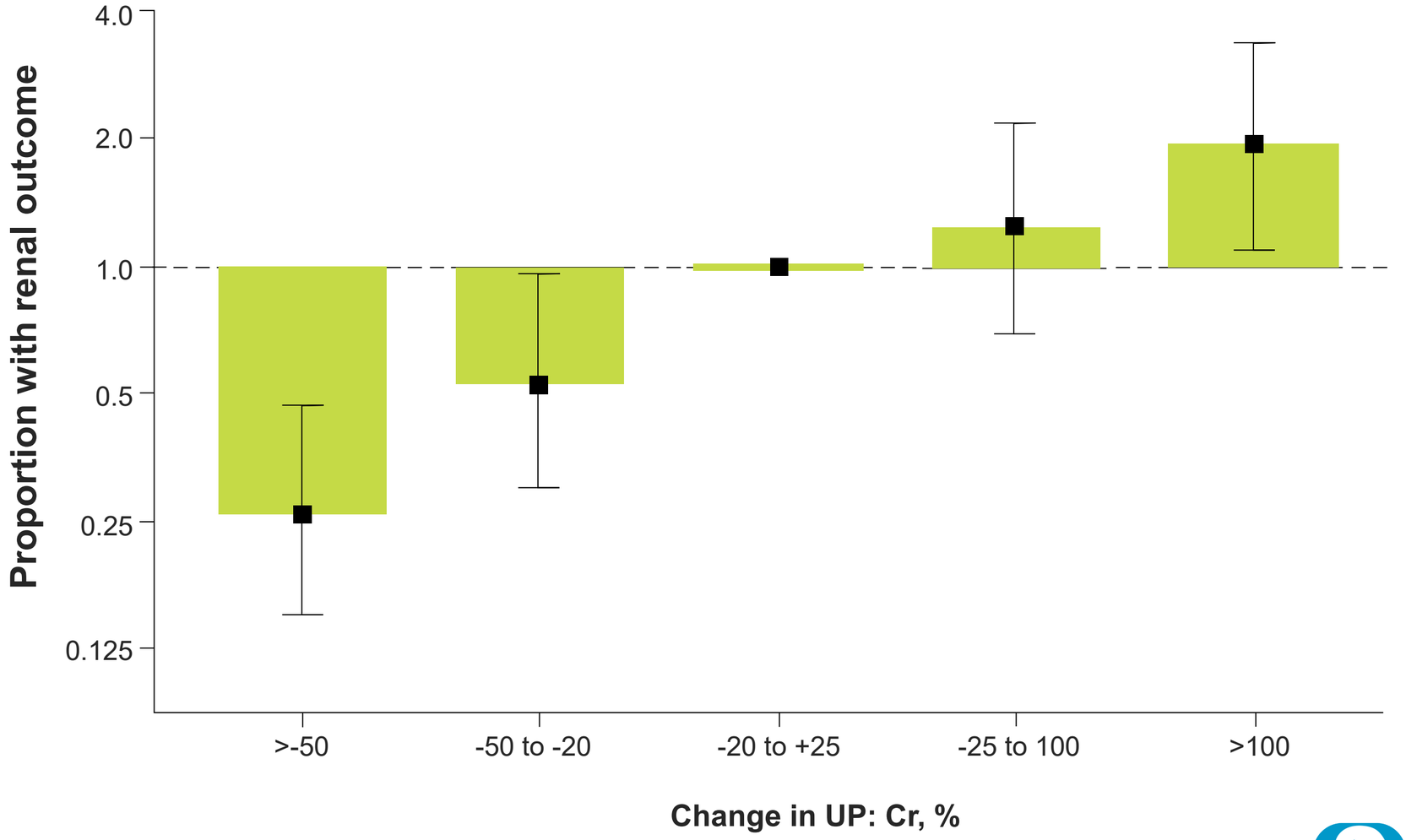
AASK: Risk of ESRD By Change In Urine Protein Across All Groups (Metoprolol, Ramipril, Amlodipine)



ESRD, end-stage renal disease

Lea J, et al. Arch Intern Med. 2005 Apr 25;165(8):947-53.

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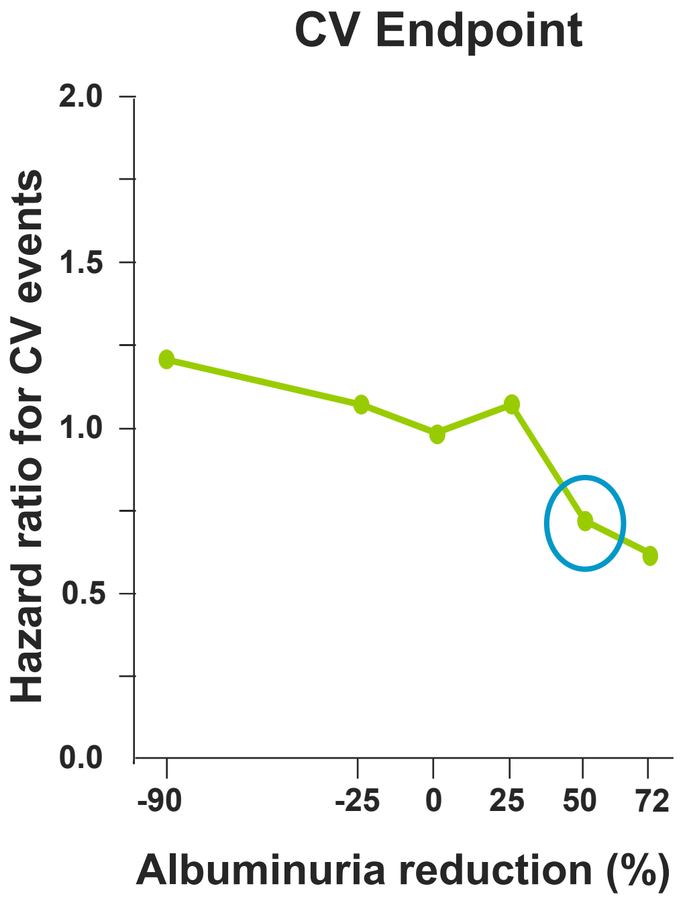
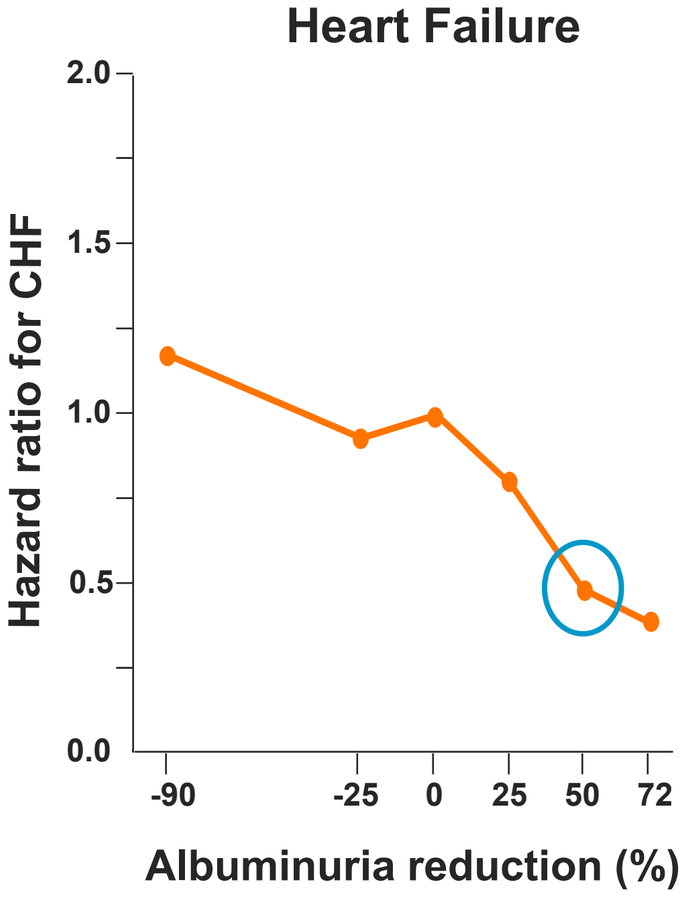
Albuminuria Reduction at 6 Months Predicts CV Endpoints and CHF

RENAAL Study





CHF, chronic heart failure; CV, cardiovascular
de Zeeuw D, et al. Circulation. 2004 Aug 24;110(8):921-7.

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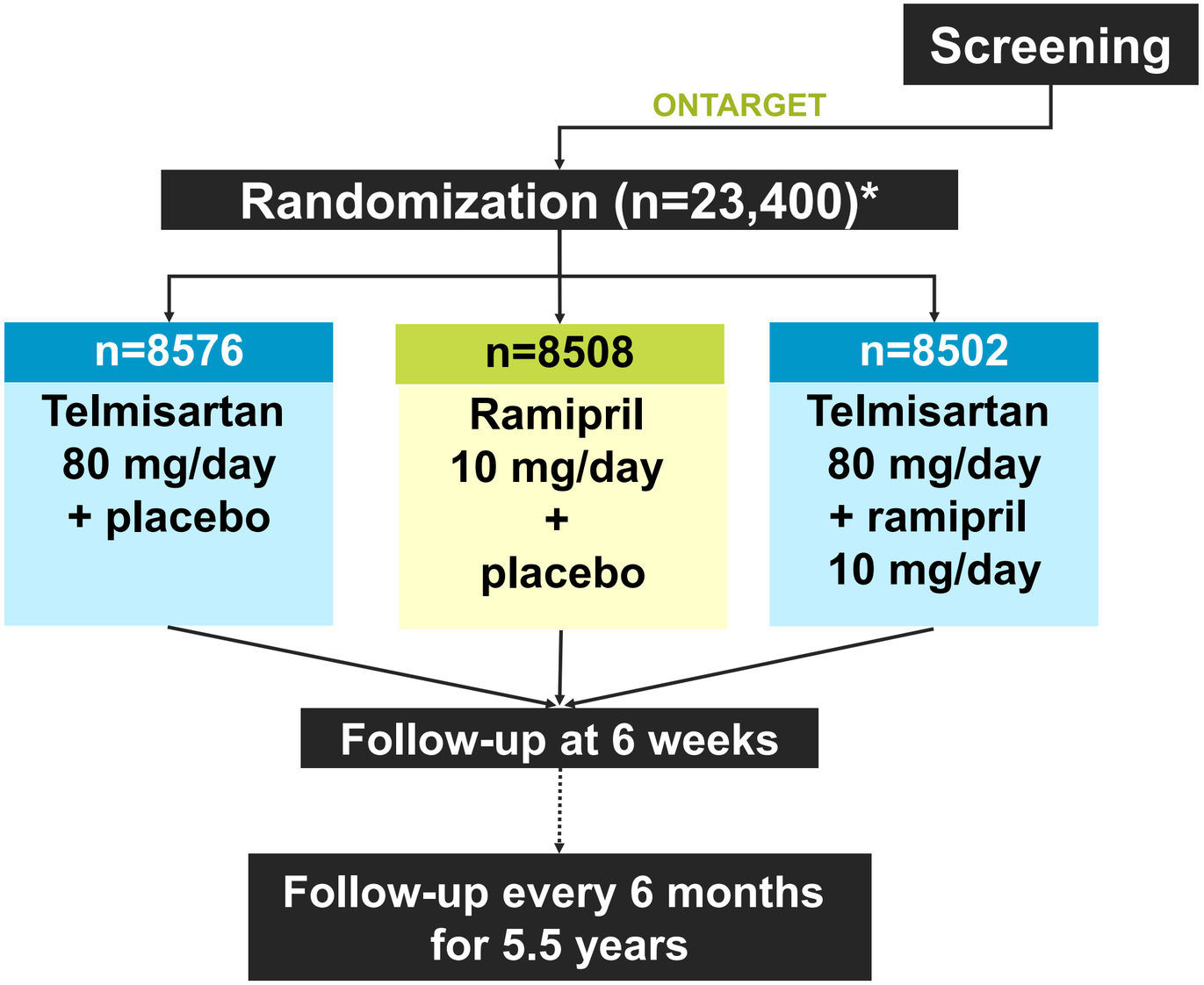
The ONTARGET Trial



5.5 years

Full doses at 2 years:

ramipril

81.7% mono
75.3% combo

telmisartan

88.6% mono

84.3% combo

*Planned. Actual=25,620; †Planned. Actual=5926.

ONTARGET/TRANSCEND Investigators. Am Heart J. 2004 Jul;148(1):52-61.

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ONTARGET: Components of the Composite Renal Outcome

	Ramipril (n = 8,576)	Telmisartan (n = 8,542)	Combined (n = 8,502)	P (combined vs ramipril)
All deaths	1014	993	1065	0.14
Doubling s.create.	140	155	166	0.11
ESRD	33	31	34	0.85
Acute dialysis*	**13**	**20**	**28**	**0.02**

*Duration < 2 months
ESRD, end-stage renal disease
Mann JF, et al. Lancet. 2008 Aug 16;372(9638):547-53.

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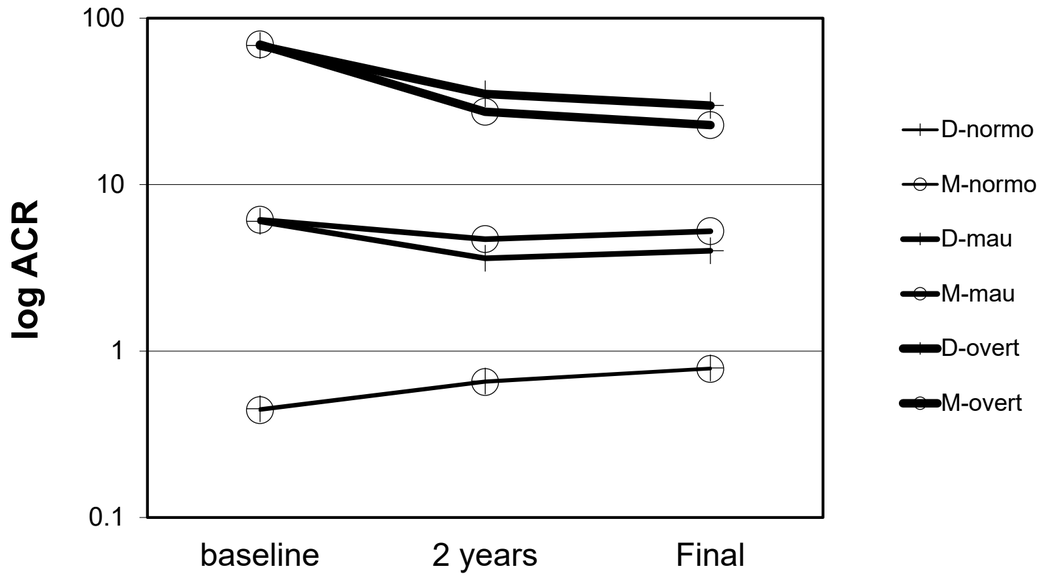
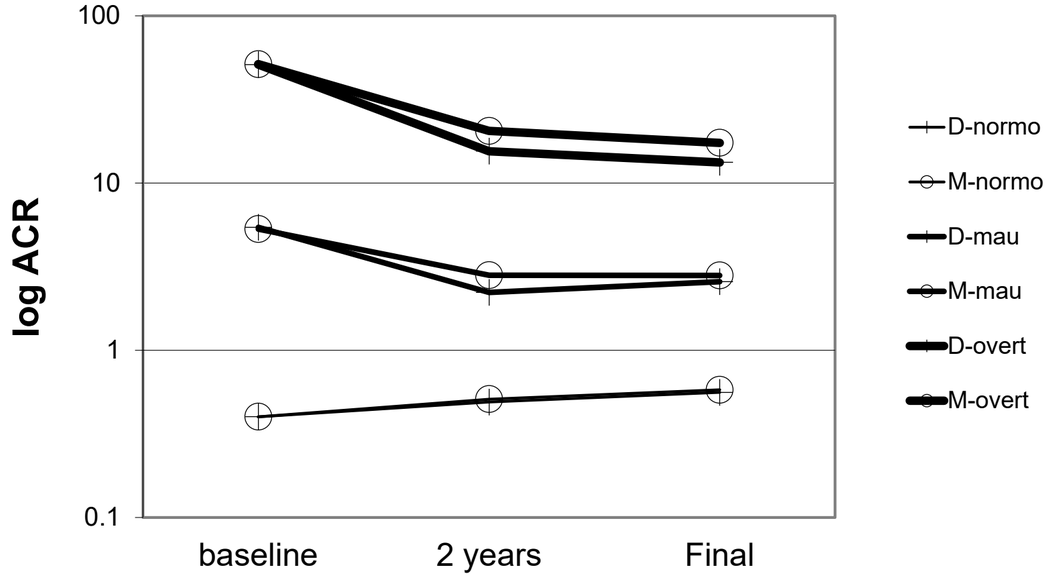
Change in ACR by Baseline Proteinuria and Dual vs Mono Therapy



eGFR < 60 at baseline



eGFR ≥ 60 at baseline

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate

Tobe SW, et al. Circulation. 2011 Mar 15;123(10):1098-107.

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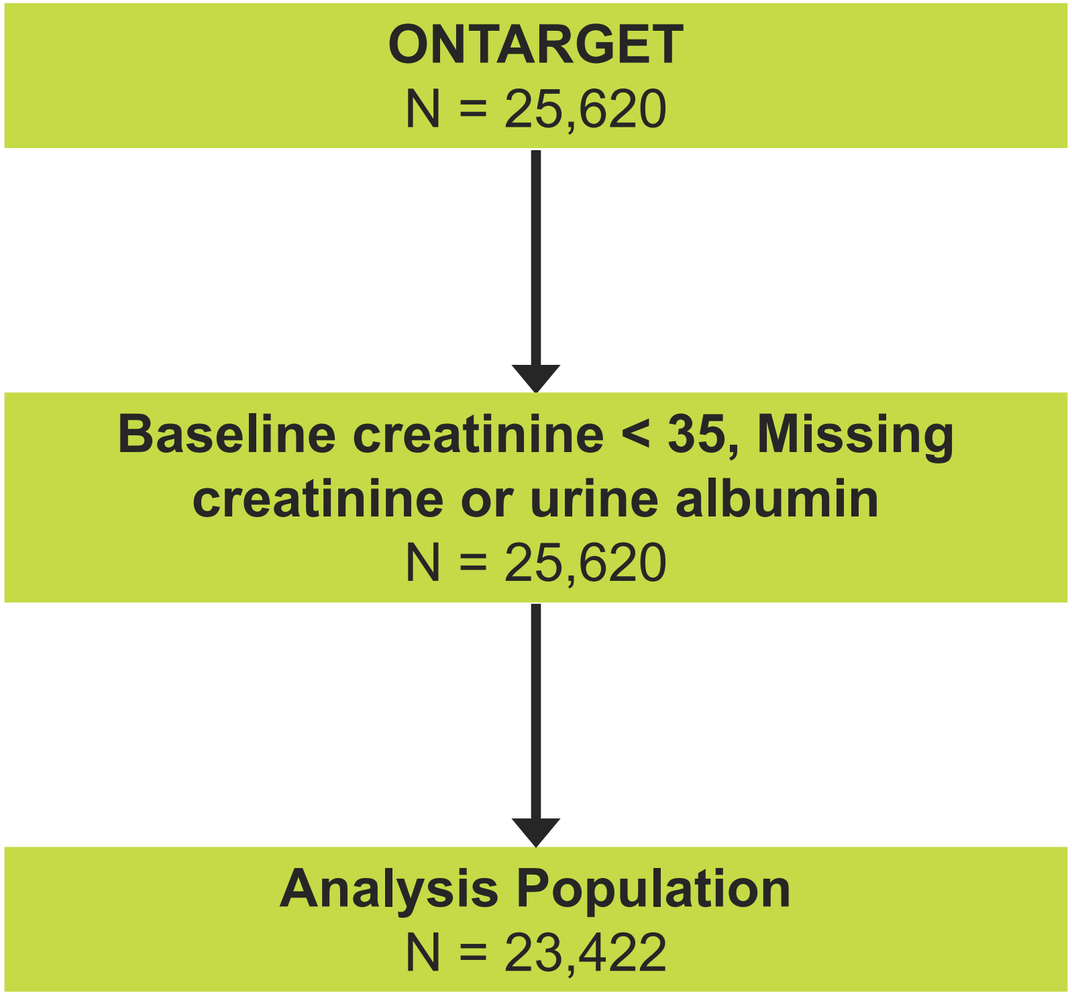
The Role of Dual RAAS Blockade with an ACEi and ARB vs Monotherapy

Purpose of sub-analysis:

Even though ONTARGET did not show an improvement in CV and renal outcomes overall, maybe dual RAASi would benefit a subgroup of patients with low GFR and macroalbuminuria

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blockers; CV, cardiovascular
eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin aldosterone system inhibitor



Tobe SW, et al. Circulation. 2011 Mar 15;123(10):1098-107.

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ONTARGET
Analysis Population
N = 23,422

→

Low GFR: 5623
GFR 60 +: 16,799
Normoalbuminuria: 18,326
Microalbuminuria: 3,809
Macroalbuminuria: 1,287
Monotherapy: 15,646
Dual Therapy: 7776

↓

GFR	Low GFR (eGFR < 60)			Normal GFR (eGFR 60+)		
U Alb	Norm	MAU	Macro	Norm	MAU	Macro
N	3837	1178	608	14489	2631	679
Mono	2568	767	417	9656	1775	463
Dual	1269	411	191	4833	856	216

eGFR, estimated glomerular filtration rate
Tobe SW, et al. Circulation. 2011 Mar 15;123(10):1098-107.

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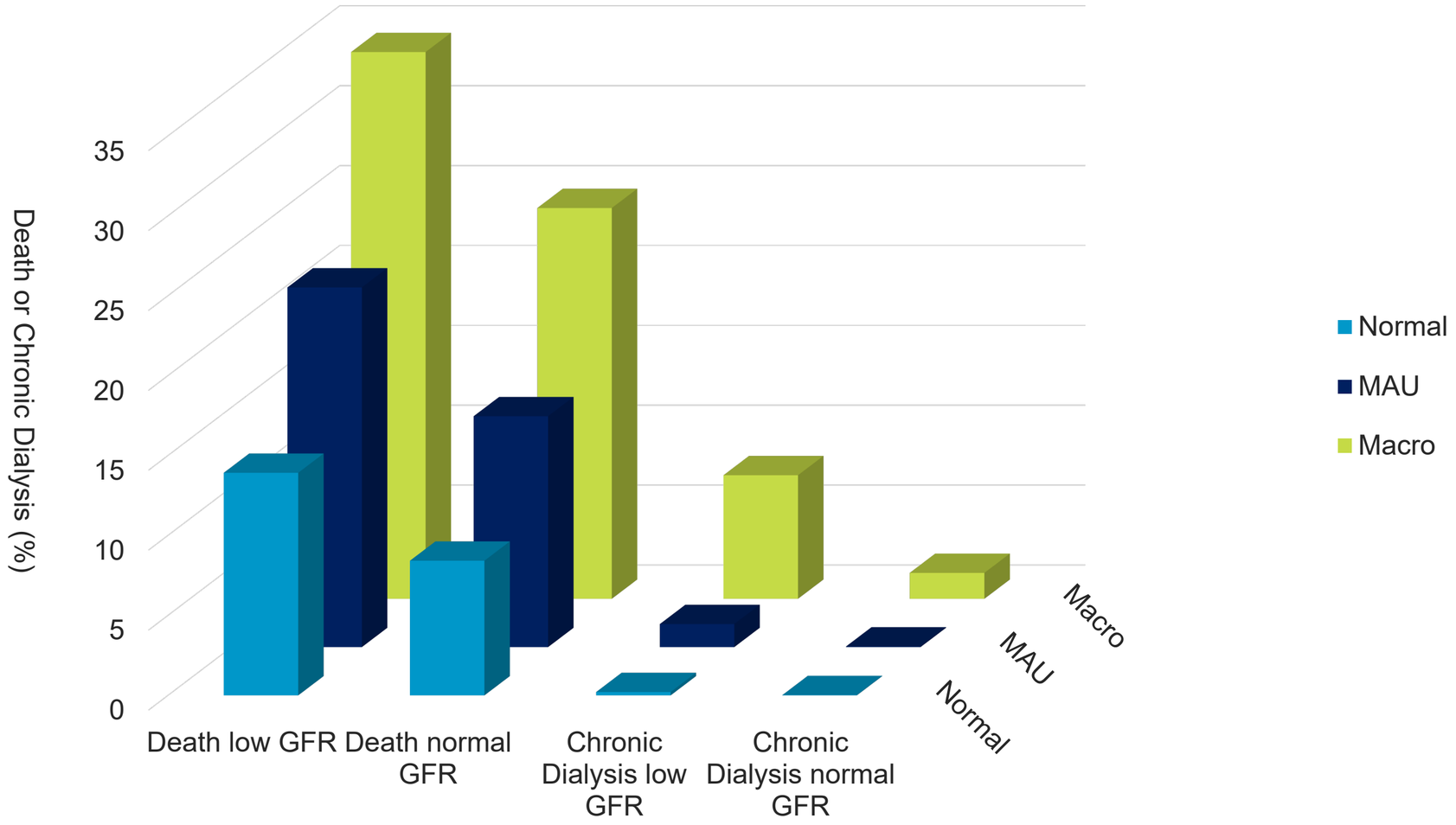
ONTARGET: CV and Renal Outcomes GFR x Albuminuria



CV, cardiovascular; GFR, glomerular filtration rate

Tobe SW, et al. Circulation. 2011 Mar 15;123(10):1098-107.

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Summary (cont.)

- Proteinuria is both a marker and a mediator of renal damage and is associated with greater CV risk.
- In normal or microalbuminuria range of proteinuria, the rate of hard renal events (dialysis and doubling of creatinine) is much lower than the mortality rate.
- At higher levels of proteinuria (overt nephropathy), the renal event rate is still lower than the mortality rate
- Patients with overt nephropathy who achieve lower proteinuria with therapy have improved hard renal outcomes
- This has not yet been demonstrated in the microalbuminuria range.

CV, cardiovascular

Summary

Dual RAAS blockade or supramaximal dosing of ACEi or ARB reduce proteinuria more than the maximum recommended doses of monotherapy

However, evidence that dual blockade provides additional benefits for hard renal and cardiovascular outcomes is still lacking

Dual therapy increases the risk for complications such as AKI and hyperkalemia

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blockers; AKI, acute kidney injury; RAAS, renin-angiotensin aldosterone system

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Conclusions: Therapy for patients with nephropathy

1. All patients should receive treatment with the maximal recommended dose of an ACEi or ARB
2. Lower blood pressure to target (<130/80 for DM, < 120 for CKD)
3. Global risk reduction
4. There is currently NO evidence to support Dual therapy with an ACEi and ARB

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blockers , CKD, chronic kidney disease

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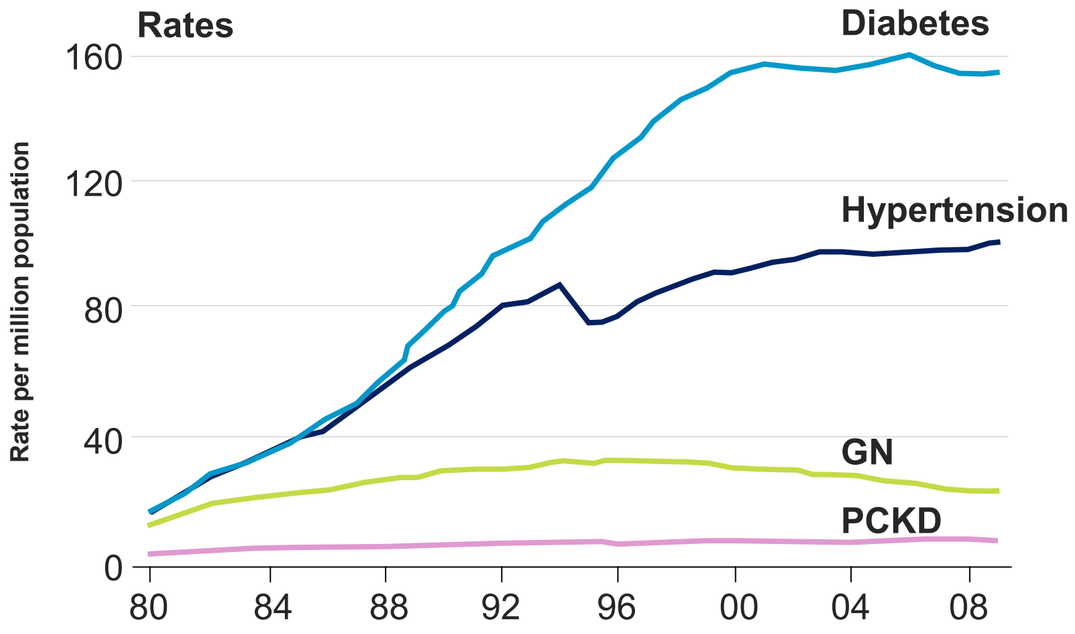
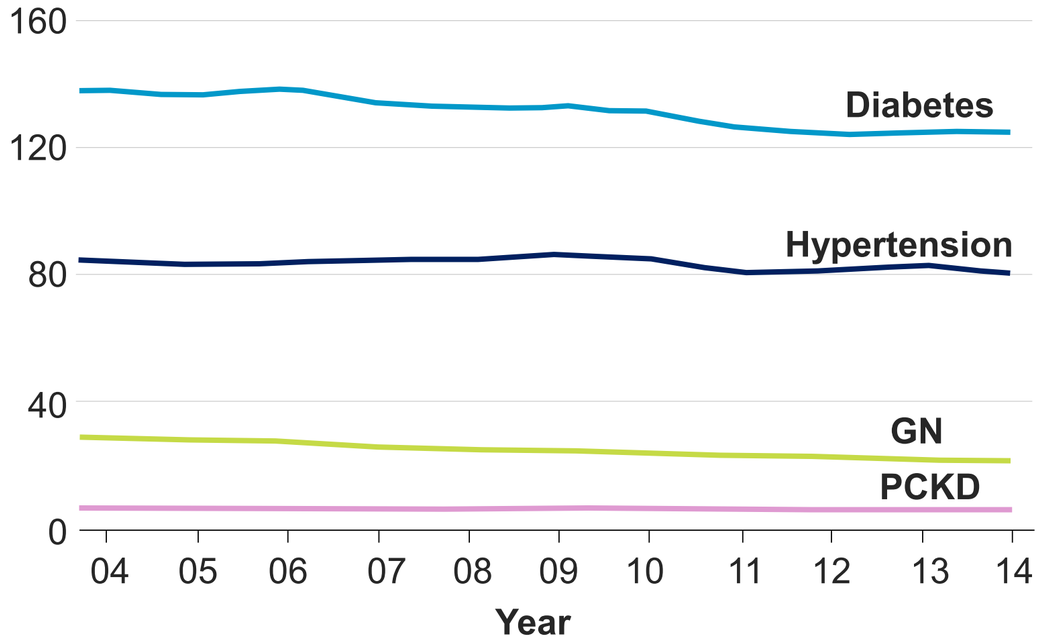
Levelling-off of ESRD from Diabetes in the US: Impact of the Clinical Practice Guideline for Diabetes Over Time

Incident counts & adjusted rates of ESRD, by primary diagnosis, data from the USRDS

United States Renal Data System 2011
Annual Data Report Figure 1.8 (Volume 2)



USRDS Annual Report Chapter 1
2016



ESRD, end-stage renal disease

https://www.usrds.org/annual-data-report/previous-adrs/

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Mogensen Demonstrates the Impact of Albuminuria as a Predictor of Risk for Progressive Renal Disease and Mortality in T2D

- Observational study based on 1082 clinic patients with T2D in 1973
- 76 patients had MAU
- After 10 years, 5.4% of those without MAU had progressed to macroalbuminuria while 22% with MAU had progressed
- Over 50% of those without MAU at baseline were alive after 10 years, compared to only 22% of those with MAU at baseline alive at 10 years
- Of interest, the mean BP was 160/90 or greater at baseline

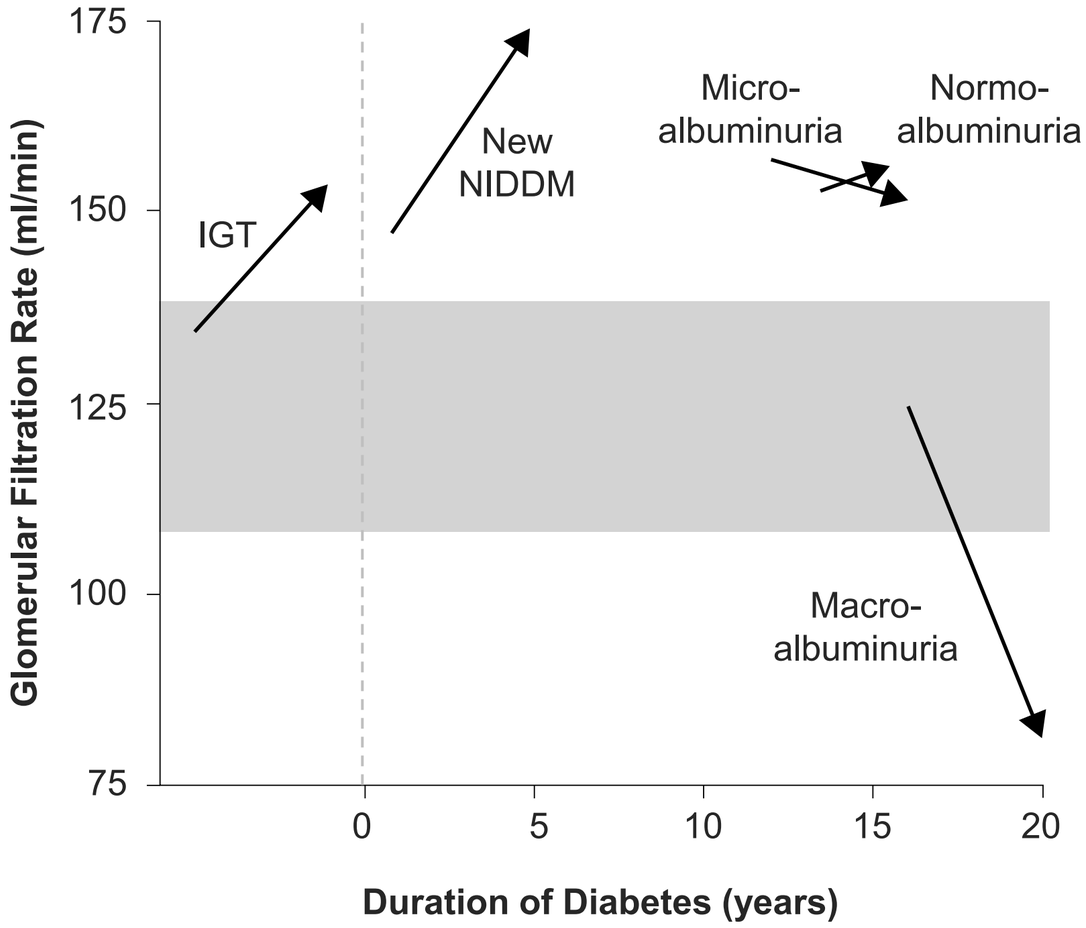
BP, blood pressure; MAU, microalbuminuria; T2D, type 2 diabetes

Mogensen CE. N Engl J Med. 1984 Feb 9;310(6):356-60.

Pima Indian (T2D) Study:
Renal Progression at Different Stages of Diabetic Nephropathy

Rate of loss of eGFR over 4 years

- **Microalbuminuria**: ~1 ml/min/year
- **Macroalbuminuria**: ~1 ml/min/month



eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes

Nelson RG, et al. N Engl J Med. 1996 Nov 28;335(22):1636-42.

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Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- Oral medication
- Mechanism of Action: eliminate glucose into the urine by reducing glucose reabsorption in the proximal tubule, leading to urinary glucose and salt excretion by osmotic diuresis
- Side effects: may include genital yeast infections, UTI, increased urination and low blood pressure
- Associated with weight loss (2-3kg) and a low risk of hypoglycemia

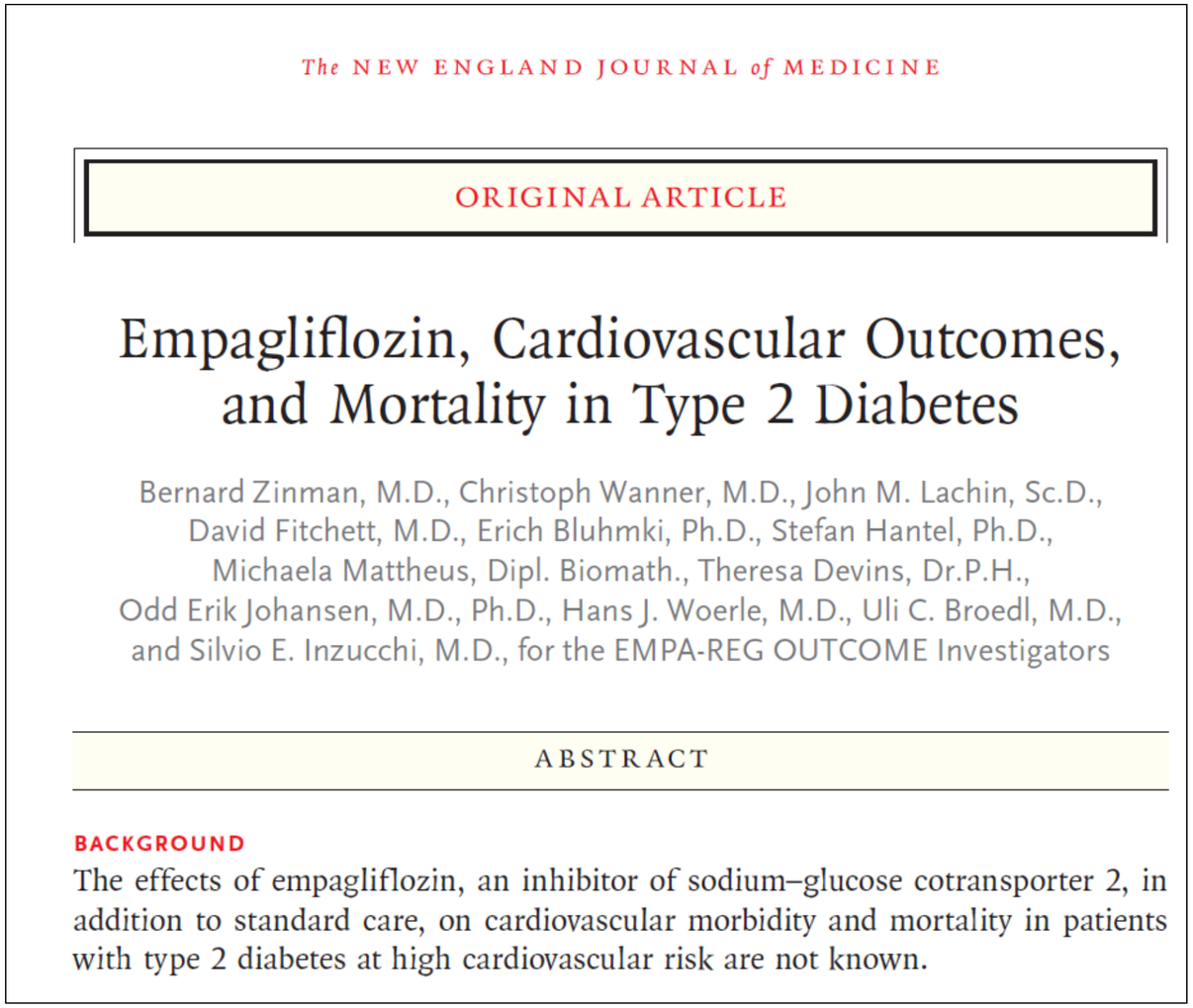
Generic Name	Brand Name
Canagliflozin (100mg, 300mg)	Invokana
Dapagliflozin (5mg, 10mg)	Forxiga
Empagliflozin (10mg, 25 mg)	Jardiance

SGLT2, Sodium-glucose Co-transporter 2 ; UTI, urinary tract infection

SGLT2 Inhibitors. https://www.diabetes.ca/DiabetesCanadaWebsite/media/Managing-My-Diabetes/Tools%20and%20Resources/Medication-Sheet-SGLT2.pdf?ext=.pdf

In 2015, the SGLT2i Class is Found to be Renal and CV Protective in T2DM in a CVOT

- Tested in a CV outcome trial the SGLT2i empagliflozin is found to be cardiac protective mostly from reduction in CHF
- Also found to be renal protective
- This benefit was additional to that
  of blood pressure control and RAASi blockade



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

CHF, chronic heart failure; CV, cardiovascular; CVOT, cardiovascular outcome; RAASi, renin-angiotensin aldosterone system inhibitor; SGLT2i, Sodium-glucose co-transporter 2 inhibitor

Zinman B, et al. N Engl J Med. 2015 Nov 26;373(22):2117-28.
Wanner C, et al. N Engl J Med. 2016 Jul 28;375(4):323-34.

Secondary Renal Outcomes from CVOTs in T2D with GLP-1, SGLT2i

Note that much of the benefit in these early studies came from preventing new onset albuminuria

CVOT Trials in Type 2 Diabetes with GLP-1 or SGLT2i Treatment: Renal Outcomes						
	LEADER	**SUSTAIN-6**	**EXSCEL**	**EMPA-REG**	**CANVAS Program**	**DECLARE**
Tx	Lira vs P	Sema v P	Exena v P	Empa v P	Cana v P	Dapa vs P
F/up yrs	3.8	2.1	3.2	3.1	5.7	4.2
eGFR	30+	30+	30+	30+	60+	60+
Secondary Outcome	**New Alb**, 2xCreat, RRT, renal death	**New Alb**, 2xCreat, RRT, renal death	**New Alb**, 40% ↓ eGFR, RRT, renal death	**New Alb**, 2xCreat, RRT, renal death	2xCreat, RRT, renal death	40% ↓ eGFR, RRT, renal/CV death
HR (± 95% CI)	**0.78 (.67-.92)**	**0.52 (.33-.80)**	**0.85 (.73-.98)**	**0.61 (.53-.70)**	**0.53 (.33-.84)**	**0.76 (0.67-0.87)**

Compare the hazard ratios for SGLT2i to the improvement of 16-28% from RAAS blockade. This is over and above RAAS blockade!

CVOT, cardiovascular outcome; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HR, hazard ratio; RAAS, renin-angiotensin aldosterone system; SGLT2i, Sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

Hu Y. Chronic Dis Transl Med. 2019 Mar 15;5(1):25-36.

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Heat Map Classification of Renal Disease with Prevalence as a Percentage of Total

Most people are normal

GFR categories (mL/min/1.73 m²)			Albuminuria categories		
			A1 Normal to mildly increased	**A2** Moderately increased	**A3** Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal to high	>90	**54.7**	**4.3**	**0.4**
G2	Mildly decreased	60–89	**30.4**	**2.6**	**0.3**
G3a	Mildly to moderately increased	45–59	**3.9**	**0.9**	**0.2**
G3b	Moderately to severely decreased	30–44	**1.0**		**0.2**
G4	Severely decreased	15–29	**0.1**	**0.1**	**0.22**
G5	Kidney failure	<15	**<0.001**	**0.001**	**0.01**

GFR, glomerular filtration rate;
USRDS Annual Report Chapter 1 2016 (based on NHANES 2011-2014).

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CREDENCE Study

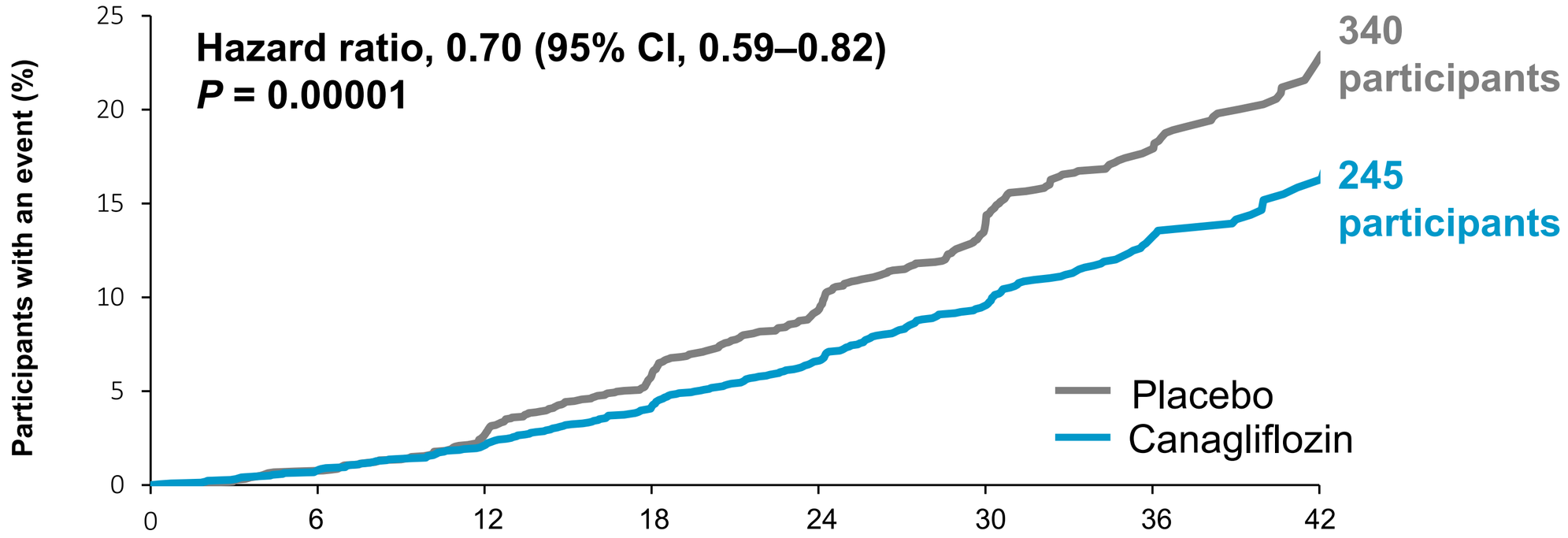
- **Patients:**
  - T2D, age 30+, A1c 6.5%-12.0%
  - eGFR 30 - 90 mL/min
  - ACR 30 to 500 mg/mmol
  - On maximum tolerated dose of ACEi or ARB
- **Purpose**: Reduce progression of renal disease and CV outcomes
- **Primary Composite outcome**: ESRD, doubling of serum creatinine, renal or CV death
- **Secondary outcomes**: CV death or hospitalization for heart failure, 3-point MACE: CV death, MI, or stroke)

Participants continued treatment if eGFR was <30 mL/min/1.73 m2 until chronic dialysis was initiated or kidney transplant occurred

ACEi, angiotensin-converting-enzyme inhibitors; ACR, albumin-creatinine ratio; ARB, angiotensin-receptor blockers; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MACE, major adverse cardiovascular event; MI, myocardial infarction

Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

Primary Outcome:
ESRD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

CV, cardiovascular; ESRD, end-stage renal disease;
Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

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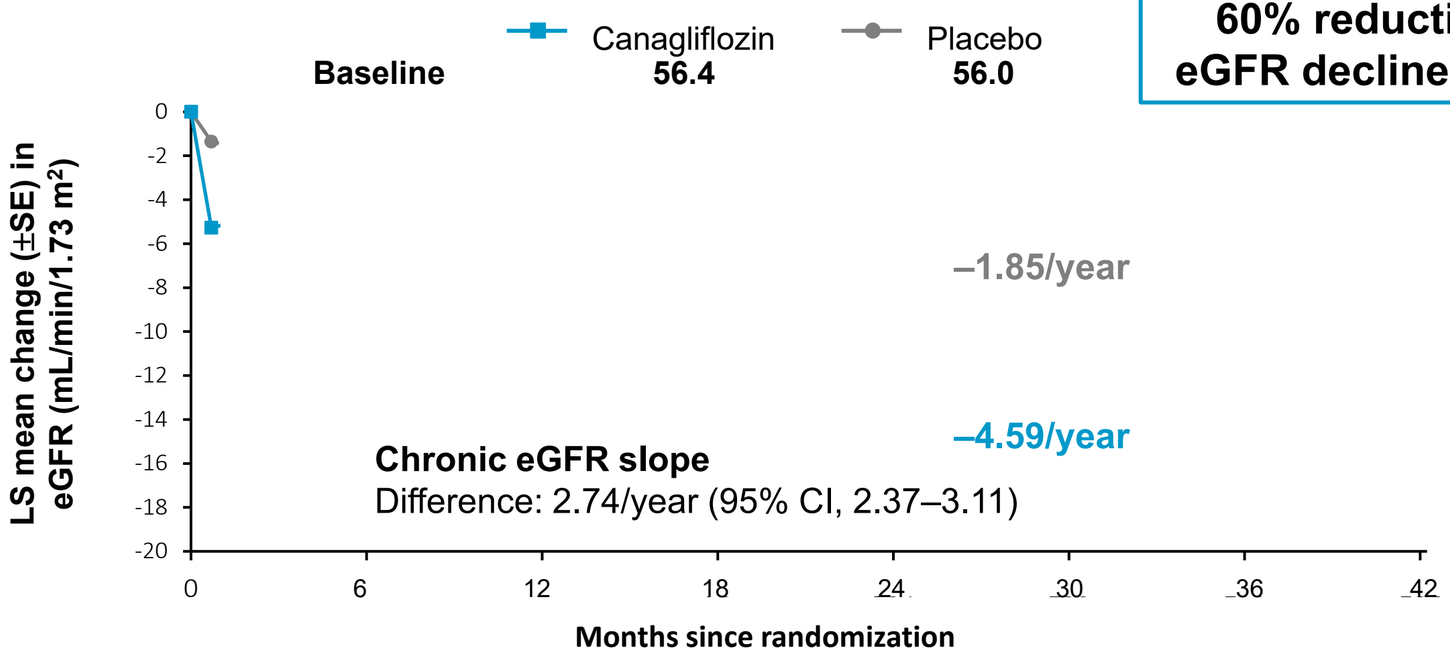
Acute and Long-term Effects on eGFR

60% reduction in the rate of eGFR decline with canagliflozin



No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

eGFR, estimated glomerular filtration rate

Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

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Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESRD, 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)	–	Not significant
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

CV, cardiovascular; ESRD, end-stage renal disease; MI, myocardial infarction

Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESRD, 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 failu			
3. CV death, MI, or stroke			✔
4. Hospitalization for heart failure			✔
5. ESKD, doubling of serum creatinine, or re			✔
6. CV death	0.78 (0.61–1.00)	0.0502	✔
7. All-cause mortality	0.83 (0.68–1.02)	–	Not significant
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

- After so many years of negative results in patients with diabetes and advanced nephropathy, this study showed a dramatic improvement in outcome.
- Note that this improvement is over and above the effect of RAAS blockade and BP control.

Perkovic V, NEJM 2019 380: 2295-2306 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).

CV, cardiovascular; ESRD, end-stage renal disease; MI, myocardial infarction
Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

RCT Protocol

Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)

Rationale and trial protocol

	Interventions	Follow-up	Primary outcome
Multicentre ~400 Target n = 4300 Patients with and without type 2 diabetes	Dapagliflozin 10 mg	~45 months	Composite renal endpoint ≥ 50% decline in eGFR
☑ ≥ 18 years 25-75 mo/min/1.73 m^2 uACR ≥ 200 mg/g			End-stage Kidney disease
☒ Polycystic kidney disease Lupus nephritis ANCA vsuculitis Type 1 diabetes	Placebo	Event-driven (681 events)	Renal or cardiovascular death

eGFR, estimated glomerular filtration rate

Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

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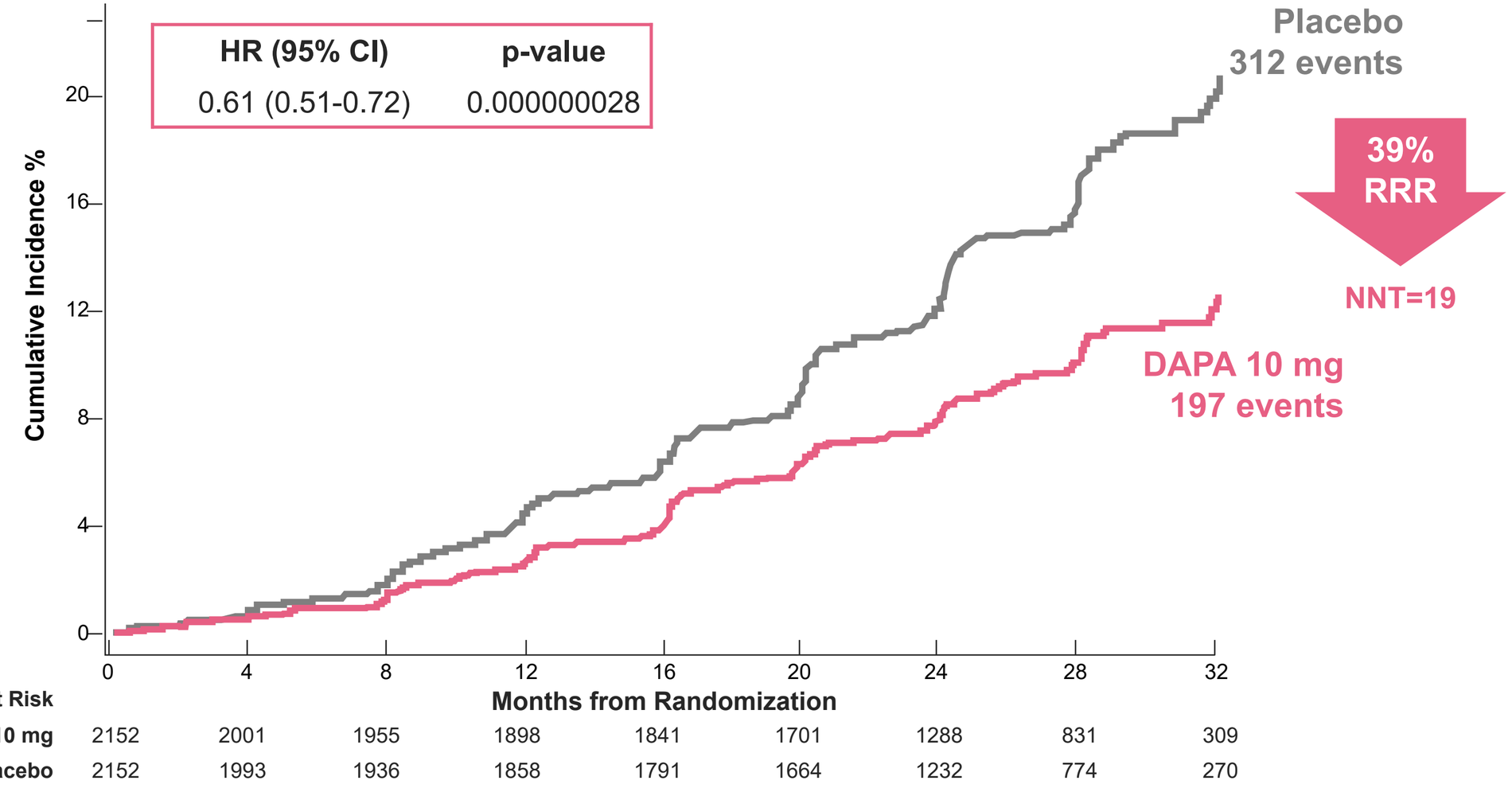
DAPA CKD
Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESRD, Renal or CV Death



CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRR, relative risk reduction

Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

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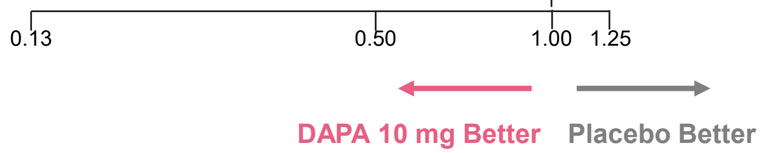
DAPA CKD
Primary Composite Outcome: Prespecified Subgroup Analyses
Diabetes and No Diabetes

	HR (95% CI)	Number of Events: DAPA 10 mg (N=2152)	Number of Events: Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death						
All Patients		197	312	0.61	(0.51, 0.72)	
T2D at Baseline						0.24
Yes		152	229	0.64	(0.52, 0.79)	
No		45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline						0.52
≤1000		44	84	0.54	(0.37, 0.77)	
>1000		153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline						0.22
<45		152	217	0.63	(0.51, 0.78)	
≥45		45	95	0.49	(0.34, 0.69)	



CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio

Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

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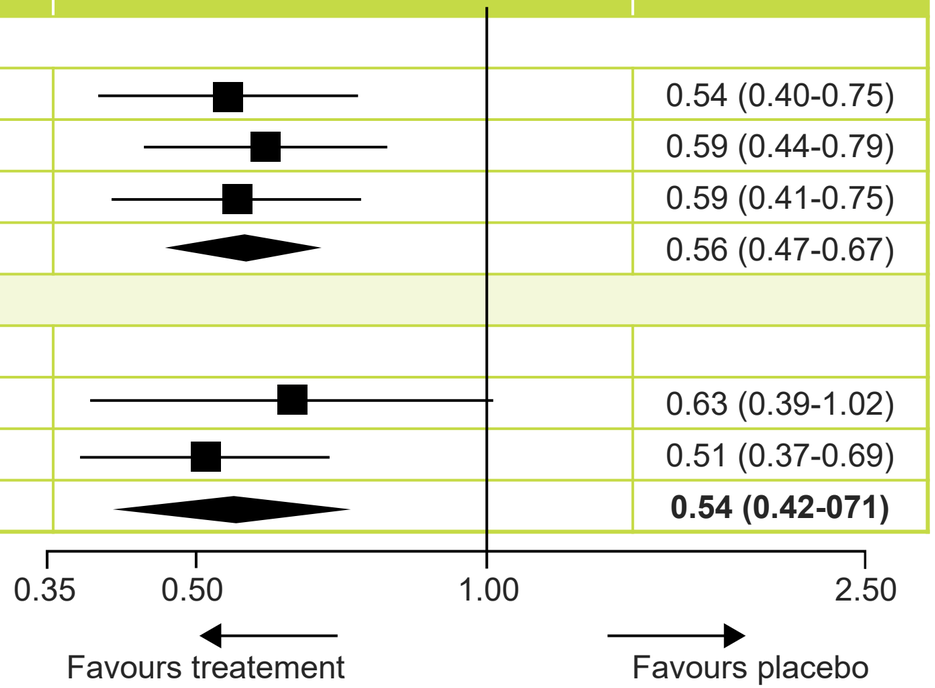
Diabetes Canada: 2020 Recommendation on the Role of SGLT2i for Prevention of Progression of Nephropathy

In adults with type 2 diabetes and CKD and an estimated eGFR >30 mL/min/1.73m^2, an SGLT2i should be used to reduce the risk of progression of nephropathy.

	Patients		Events	Events per 1000 Patients-years		Weight (%)	HR	HR(95%CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6.3.	11.5	31.0		0.54 (0.40-0.75)
CANVAS program	3756/6656	2900/6656	179	6.4	10.5	35.6		0.59 (0.44-0.79)
DECLARE-TMI 58	3474/6974	3500/6974	183	4.7	8.6	33.4		0.59 (0.41-0.75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)								0.56 (0.47-0.67)
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	70	4.1	6.6	29.5		0.63 (0.39-1.02)
DECLARE-TMI 58	5108/10186	5078/10186	182	3.0	5.9	70.5		0.51 (0.37-0.69)
Fixed effects model for multiple risk factors (p<0.0001)								**0.54 (0.42-071)**



CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2i, Sodium-glucose co-transporter 2 inhibitor

Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2020 Oct;44(7):575-591.
Zelniker TA, et al. Lancet. 2019 Jan 5;393(10166):31-39.

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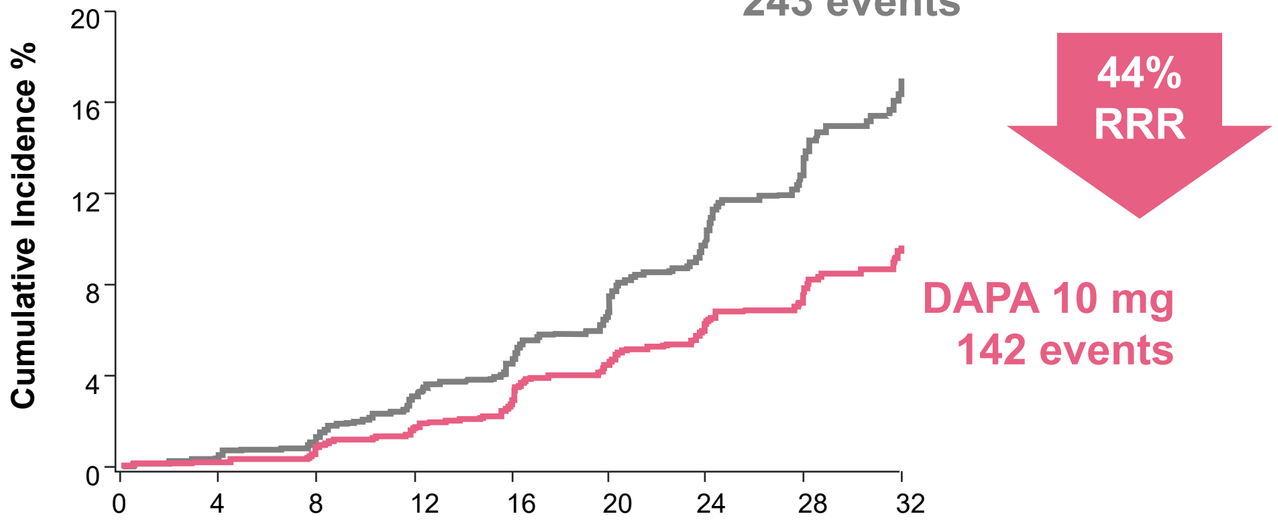
Secondary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a]

HR (95% CI)	p-value
0.56 (0.45-0.68)	0.000000018



N at Risk									
DAPA 10 mg	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

[a] ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.

DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; RRR, relative risk reduction.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
Heerspink HJL, et al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282

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SGLT2i and CKD with Proteinuria

- There is now evidence to start these agents even with an eGFR down to 30 ml/min
- No Canadian CPG yet
- Other studies pending
- Wait for data on patients without albuminuria

CPG, clinical practice guidelines; eGFR, estimated glomerular filtration rate

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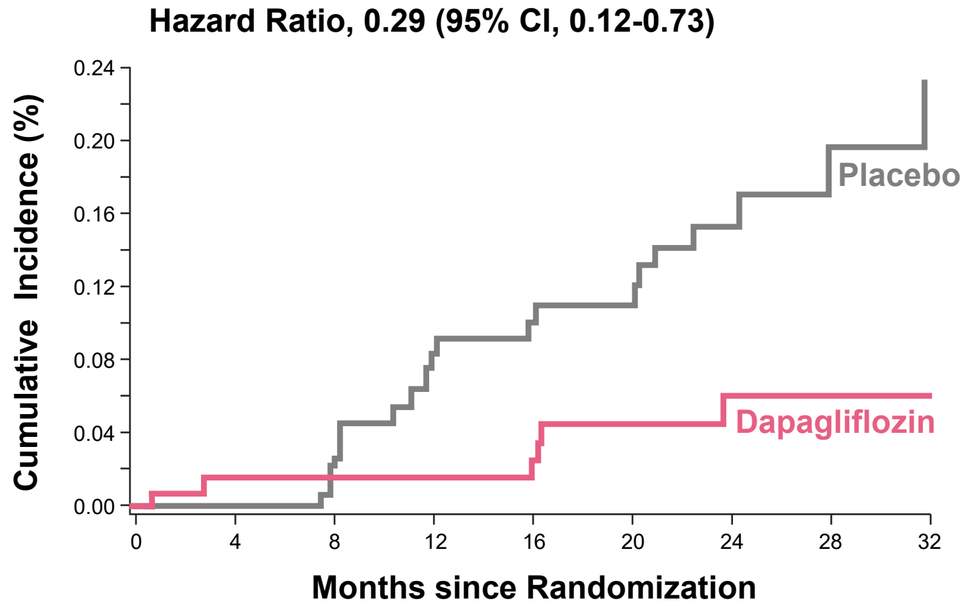
DAPA-CKD: IgA Nephropathy Subgroup

Sub-analysis of 270 patients in DAPA-CKD with IgA nephropathy

- Similar number of patients to TESTING and STOP-IgA, trials with immunosuppression[1]

Primary outcome in participants with IgA nephropathy



No at Risk									
Dapagliflozin	137	107	106	105	104	98	61	43	17
Placebo	133	113	108	101	96	92	51	32	19

Wheeler DC, et al. Nephrol Dial Transplant. 2020 Oct 1;35(10):1700-1711. doi: 10.1093/ndt/gfaa234.
Wheeler DC. FR-OR58. Oral presentation given at Kidney Week Reimagined 2020.

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Conclusions

- In this pre-specified analysis, the renal, CV and mortality beneficial effects of dapagliflozin were generally seen regardless of the underlying cause of CKD, and regardless of the presence of T2DM
- Dapagliflozin was well tolerated; the safety profile was consistent across underlying causes of kidney disease

Caveats/Limitations:

- Though the subgroup analyses, was prespecified, generally speaking results should be interpreted in this context.
- Etiology of kidney disease was determined without biopsy in the vast majority of cases (biopsy only done in 20% of patients).

CKD, chronic kidney disease; CV, cardiovascular; T2DM, type 2 diabetes mellitus

Wheeler DC. FR-OR58. Oral presentation given at Kidney Week Reimagined 2020.

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EMPEROR-Reduced Trial Specified Only Three Endpoints to be Tested in Hierarchical Manner

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)

Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

Other prespecified endpoints: Composite renal endpoint, KCCQ clinical summary score, total number of hospitalizations for any reason, all-cause mortality, new onset diabetes

- Enriched for more severe LV dysfunction and marked increases in natriuretic peptides
- >50% of patients had prevalent CKD, eGFR down to 20 ml/mg/1.73 m^2
- no inclusion criteria based on albuminuria
- Design: After screening (4-28 days), patients randomized 1:1 to empagliflozin (10 mg daily) or placebo + their usual therapy for HF

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LV, left ventricle
Zannad F. FR-OR52: Oral presentation given at Kidney Week Reimagined 2020.

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EMPEROR-Reduced Results: Effect on all three Endpoints Specified for Hierarchical Testing was Significant

Primary endpoint: Adjudicated CV death or heart failure hospitalization	**Confirmatory***	HR 0.75 (95% CI:0.65,0.86) p<0.001	✓
Key secondary endpoint: Adjudicated first and recurrent heart failure hospitalizations	**Confirmatory†**	HR 0.70 (95% CI:0.58,0.85) p<0.001	✓
Key secondary endpoint: eGFR slope	**Confirmatory‡**	Slope difference 1.73 ml/min/1.73 m^2 per year, (95% CI:1.1,2.4) p<0.001	✓

*Cox regression with a=0.0496, †Joint frailty model of adjudicated HHF and CV death with a=0.0496, ‡Random intercept random slope model with a=0.001. All models include covariates age, baseline eGFR, region, baseline diabetes status, sex and LVEF; Data on file.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure, LVEF, left ventricular ejection fraction.

Zannad F. FR-OR52. Oral presentation given at Kidney Week Reimagined 2020.

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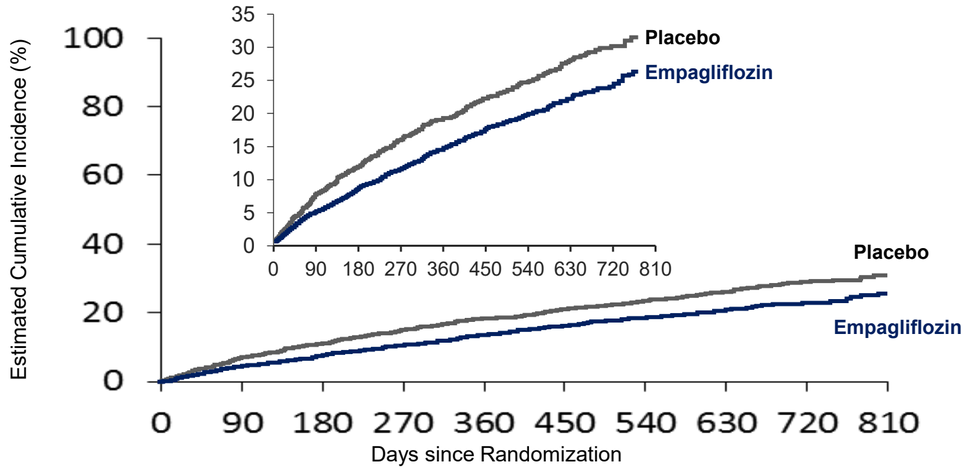
EMPEROR-Reduced: Results

Primary endpoint:
Time to first event of adjudicated hHF or CV death

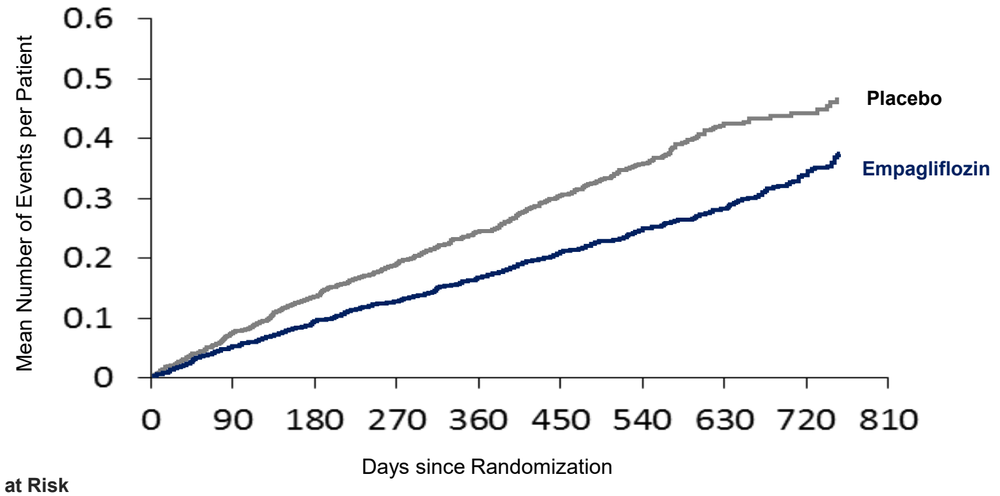
Hazard ratio, 0.75 (95% CI, 0.65-0.86)
P<0.001



No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

Key secondary endpoint:
Time to adjudicated first and recurrent hHF

Hazard ratio, 0.70 (95% CI, 0.65==58-0.85)
P<0.001



No. at Risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

CV, cardiovascular; hHF, hospitalization for heart failure; CI, confidence interval.

Packer M, et al. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190..

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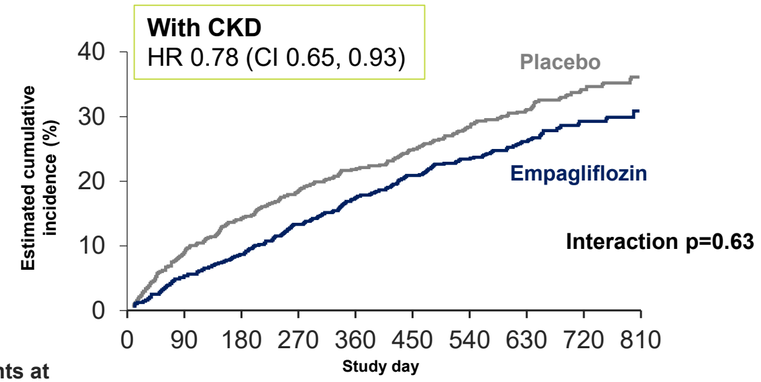
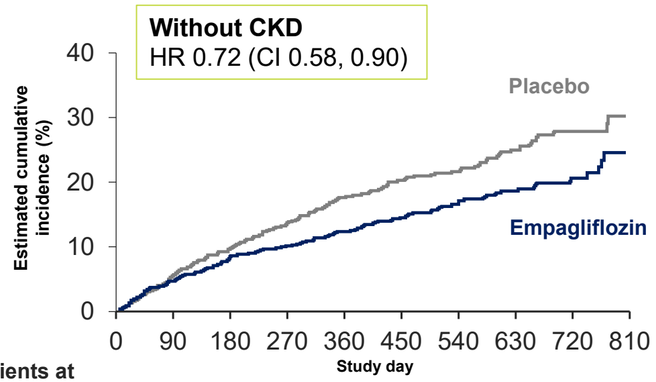
EMPEROR-Reduced: Subgroup Analysis by CKD Status
Consistent effects on the primary composite outcome

Time to first event of adjudicated HHF or CV death

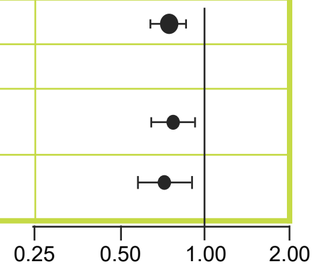




Patients at risk										
Placebo	997	900	839	685	574	450	329	223	126	64
Empa 10mg	981	927	883	725	604	461	332	218	123	58

Patients at risk										
Placebo	867	813	771	658	533	403	281	186	95	45
Empa 10mg	879	833	791	696	566	447	313	205	108	43

	Empagliflozin	Placebo		
	n with event/N analyzed		HR (95% CI)	HR (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)	
Baseline CKD status				
With CKD	219/981	273/997	0.78 (0.65, 0.93)	
Without CKD	142/879	187/867	0.72 (0.58, 0.90)	



Clinical Context

Empagliflozin treatment reverted the excessive risk of patients with CKD to the level of risk of the placebo group without CKD

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; hHF, hospitalization for heart failure

Zannad F. FR-OR52. Oral presentation given at Kidney Week Reimagined 2020.

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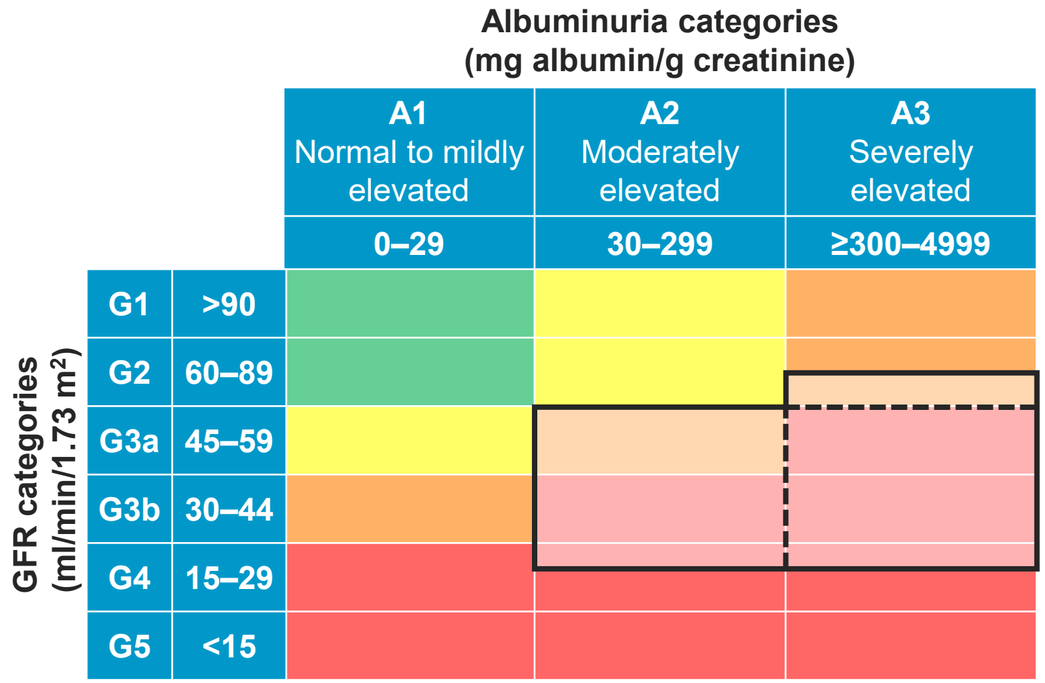
FIDELIO-DKD Study Design



Key inclusion criteria

- Aged ≥18 years with CKD and T2D
- Pretreated with optimized therapy with either an ACEi or ARB for ≥4 weeks
- Serum potassium ≤4.8 mmol/l
- Diabetic retinopathy for patients with moderately elevated albuminuria

Key exclusion criteria

- HFrEF with NYHA class II–IV
- Other kidney disease*
- HbA1c >12%
- Uncontrolled arterial hypertension#

*Known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis; #Mean sitting SBP ≥170 mm Hg or mean sitting DBP ≥110 mm Hg at the run-in visit or mean sitting SBP ≥160 mm Hg or mean sitting DBP ≥100 mm Hg at the screening visit

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus

Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

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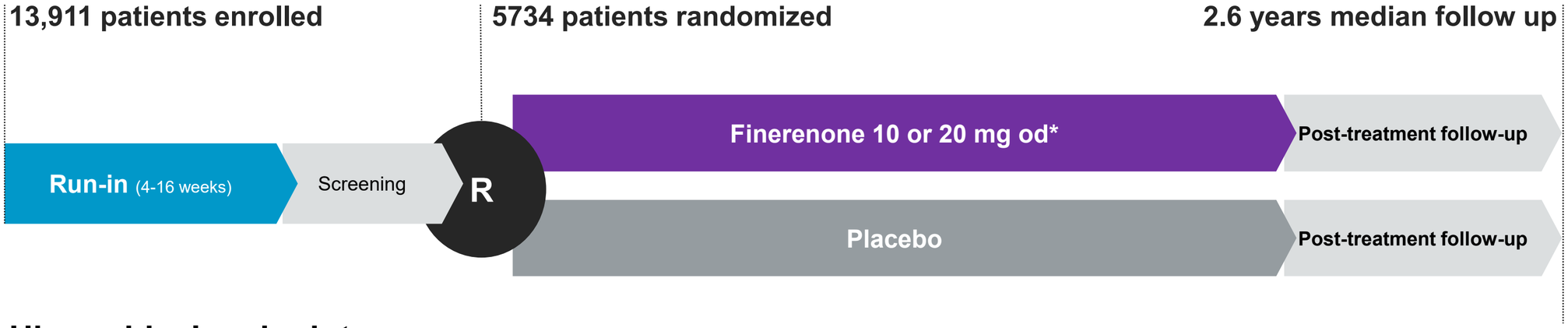
FIDELIO-DKD Study Design



Hierarchical endpoints

1. Kidney composite

Time to kidney failure sustained ≥40% decrease in eGFR from baseline, or renal death

2. CV composite

Time to CV death, non-fatal MI, non-fatal stroke or hospitalization for HF

3. Death from any cause
4. Hospitalization for any cause
5. Change in UACR
6. Second kidney composite

CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; R, randomization; UACR, urinary albumin creatinine ratio

Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

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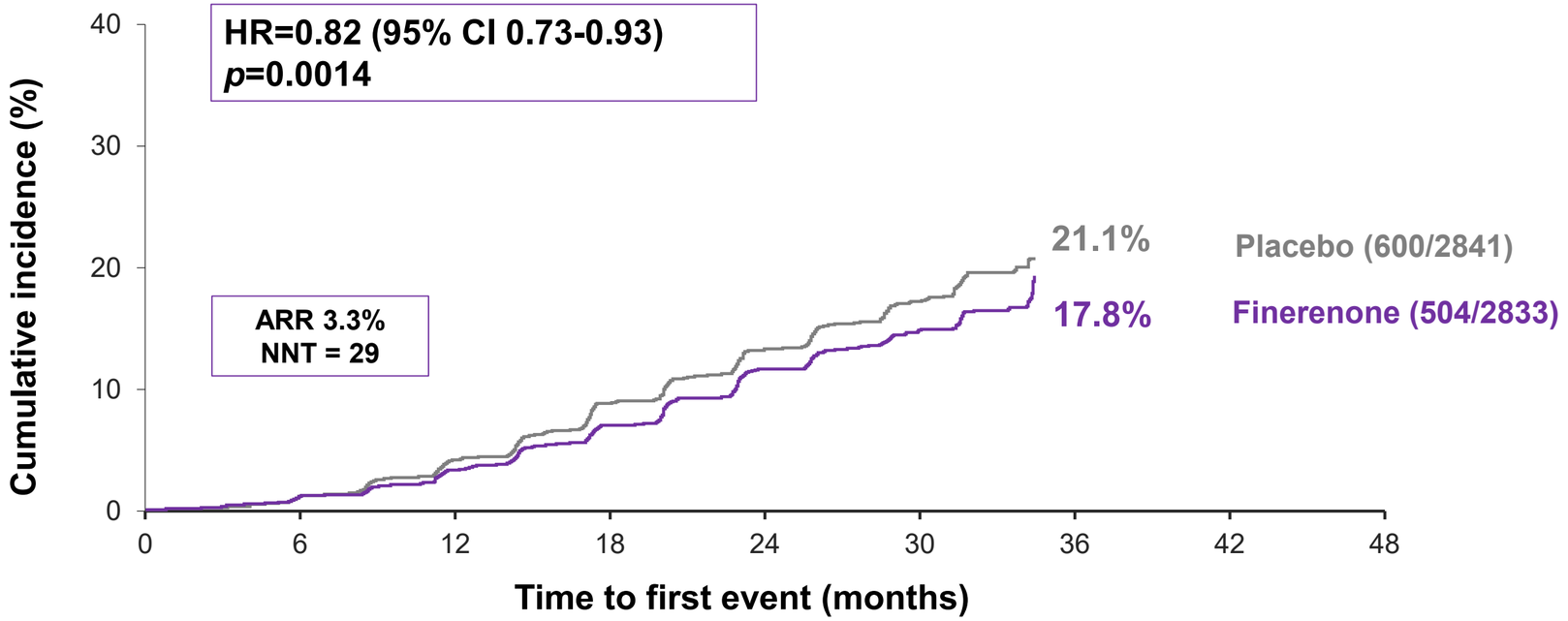
FIDELIO-DKD Study Results

Primary endpoint: Kidney failure, sustained ≥40% decreased in eGFR from baseline, or renal death. Reduced by 18%.



No. at risk									
Placebo	2841		2586		1758		792		82
Finerenone	2833		2607		1808		787		83

ARR, absolute risk reduction; CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NNT, number needed to treat

Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

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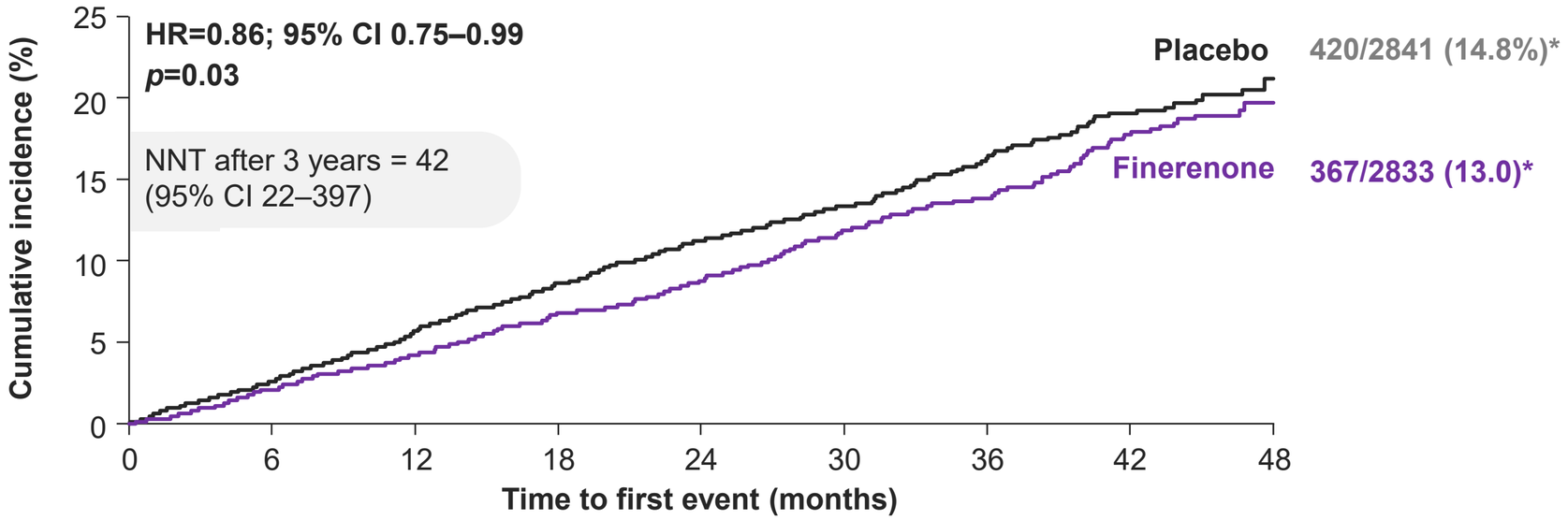
On Top of Max Tolerated RASi Therapy, Finerenone Significantly Reduced the Risk of the Key Secondary CV Outcome by 14%

Time to CV death, non-fatal MI, non-fatal stroke or HHF



No. at risk					
Finerenone	2833	2688	2017	984	111
Placebo	2841	2653	1969	951	115

*Number of patients with an event over a median of 2.6 years of follow-up
CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; RASi, renin–angiotensin system inhibition
Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

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Overall Summary

In a patient population with advanced CKD in T2D, well-controlled blood pressure and HbA1c, and treated with a maximally tolerated dose of an ACEi or ARB, finerenone significantly reduced:

The risk of CKD progression by 18%

The risk of CV morbidity and mortality by 14%

Finerenone was effective for both kidney and CV protection in patients with CKD and T2D

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; HbA1c, glycated haemoglobin; SAE, serious adverse event; T2D, type 2 diabetes

Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

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FIDELIO-DKD Study Results

Secondary Endpoints:

- **CV** (death from CV causes, nonfatal MI, nonfatal stroke, or HHF):
  - 14% relative risk reduction (13.0% with finerenone vs. 14.8% with placebo; HR, 0.86; 95% CI, 0.75 to 0.99; p=0.0339)
- **All cause mortality:** No significant reduction
- Because of hierarchical analysis, no other endpoints formally tested

Adverse events: Similar in the two groups

- Hyperkalemia-related permanent drug discontinuation was higher with finerenone than with placebo (2.3% vs 0.9%)

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; DKD, diabetic kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; NNT, number needed to treat.

Bakris GL, et al. Am J Nephrol. 2019;50(5):333-344. doi: 10.1159/000503713.

Conclusions

1. Magnitude of renal benefit similar to that seen in IDNT/RENAAL

2. While hyperkalemia risk wasn’t striking in the trial, it may be more problematic if applied in usual clinical practice

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor

Implications for Canadian Clinical Practice

Finerenone is another novel therapy that meaningfully impacts CKD progression and cardiovascular risk in patients with diabetic kidney disease

It remains unknown the degree to which finerenone may be additive to a strategy of ACEi/ARB + SGLT2i

CKD, chronic kidney disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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