

# Primary Care role in Chronic Kidney Disease (CKD)

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4 Things to know about CKD and SGLT2i



# **Primary Care role in Chronic Kidney Disease (CKD)**

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# Competing Interests

Speaker or sponsorship disclosures in past 3 years:

AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Novartis, Pfizer

# Management of patients with chronic kidney disease

- Definition, classification and prevalence
- Burden of CKD - risk of CV and renal events
- Management
  - ◆ Lipids
  - ◆ Blood pressure & RAS Blockade
  - ◆ SGLT2

# **CKD definition & classifications**

# Diagnosis of Chronic Kidney Disease

Criteria for CKD (either of the following **present for 3 months**)

- eGFR  $<60$  mL/min/1.73 m<sup>2</sup>
- Markers of kidney damage (one or more of the following)
  - ◆ Albuminuria (albumin excretion rate  $\geq 30$  mg/24 h; albumin-creatinine ratio  $\geq 30$  mg/g)
  - ◆ Electrolyte and other abnormalities due to tubular disorders
  - ◆ Abnormalities detected by histology
  - ◆ Structural abnormalities detected by imaging
  - ◆ History of kidney transplantation

# Classification of CKD: GFR

GFR Category	eGFR (mL/min/1.73 m <sup>2</sup> )	Terms	Prevalence US population
<b>G1</b>	≥90	Normal or high	2.3
<b>G2</b>	60-89	Mildly decreased*	2.5
<b>G3a</b>	45-59	Mildly to moderately decreased	4.6
<b>G3b</b>	30-44	Moderately to severely decreased	1.6
<b>G4</b>	15-29	Severely decreased	0.4
<b>G5</b>	<15	Kidney failure	0.4

\*Relative to young adult level; in the absence of kidney damage, GFR categories G1 and G2 do not fulfill the criteria for CKD. CKD, chronic kidney disease; GFR, glomerular filtration rate.

Global prevalence of CKD: 12%

# Albuminuria Categories in CKD

Category	AER (mg/24 hr)	ACR (Approximate Equivalent)		Terms
		(mg/mmol)	(mg/g)	
<b>A1</b>	<30	<3	<30	Normal to mildly increased
<b>A2</b>	30-300	3-30	30-300	Moderately decreased*
<b>A3</b>	>300	>30	>300	Severely decreased**

AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.  
 \*Relative to young adult level; \*\*including nephrotic syndrome.



# Prevalence of CKD

# CKD prevalence by age

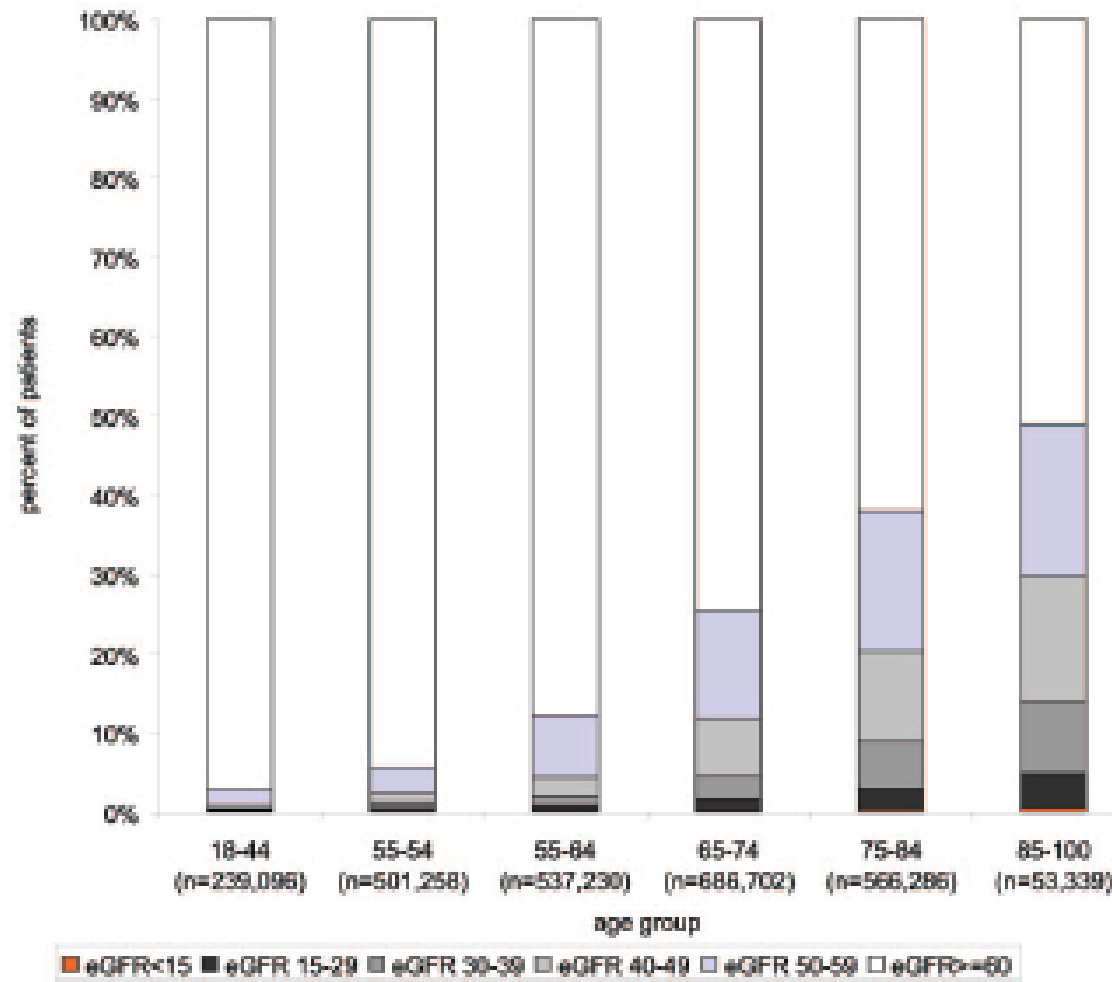


Figure 1. Prevalence of low estimated GFR (eGFR) by age group.

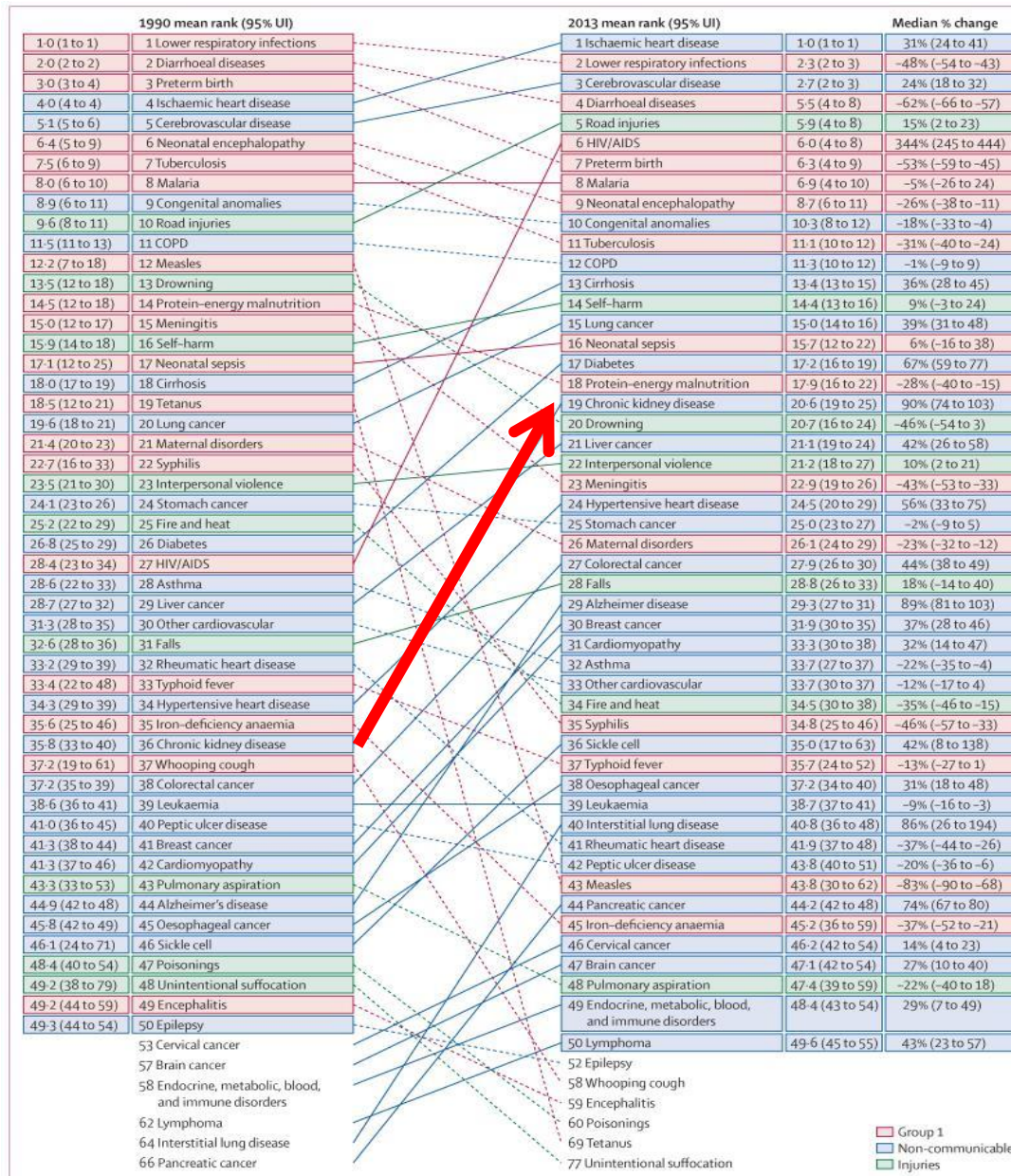
# Risk Factors for Chronic Kidney Disease

Risk Factors	Odds Ratio (95% CI)	P Value
Current smoking	1.13 (1.06-1.21)	<0.001
Obesity*	1.07 (1.02-1.11)	0.003
Diabetes <sup>†</sup>	1.45 (1.39-1.52)	<0.001
Hypertension <sup>†</sup>	1.71 (1.63-1.79)	<0.001
Cardiovascular disease <sup>†</sup>	1.31 (1.25-1.37)	<0.001

\*Body mass index >30 kg/m<sup>2</sup> or greater. <sup>†</sup>Self-reported. Data based on a survey of participants in the Kidney Early Evaluation Program (KEEP).

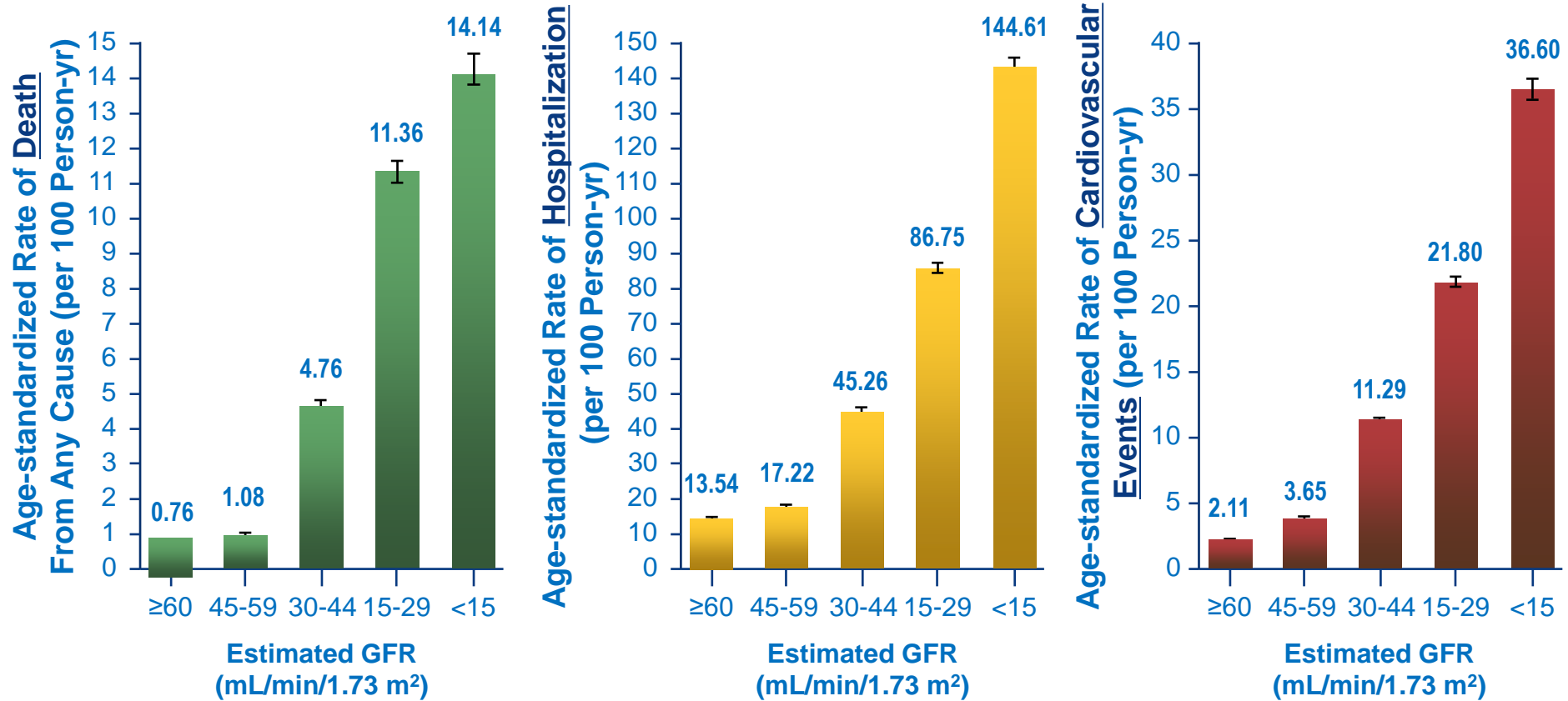
# Importance of CKD

# CKD is becoming a more important cause of death



GBD 2013 Mortality and Causes of Death Collaborators.. Lancet 2015; 385: 117-171

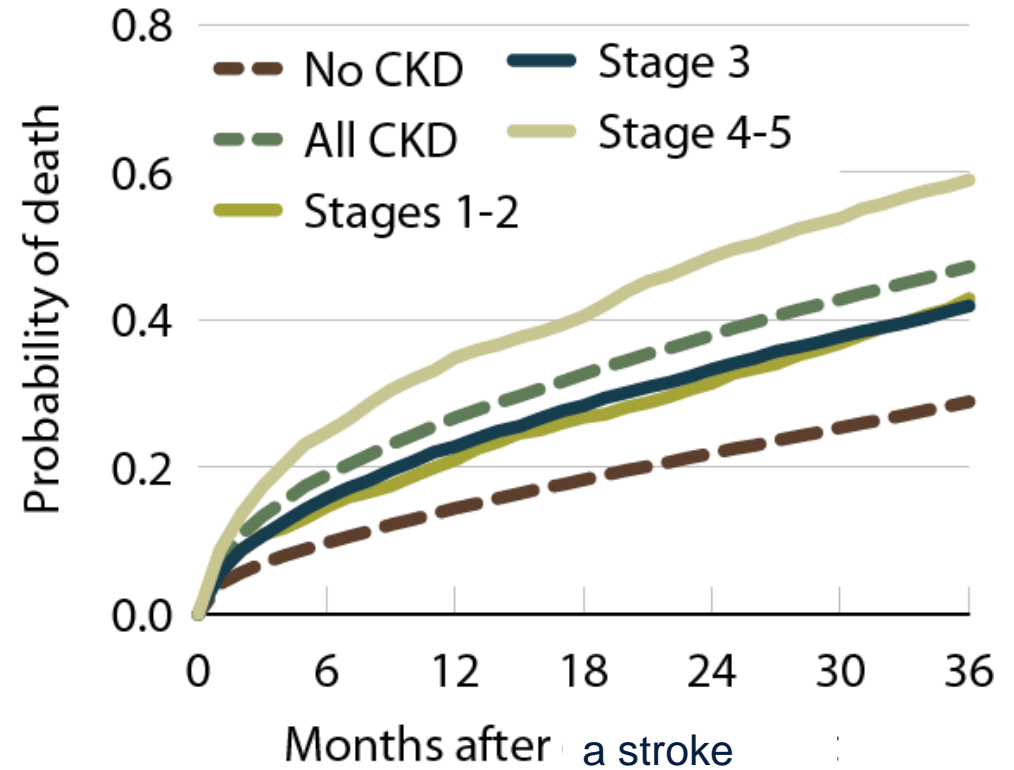
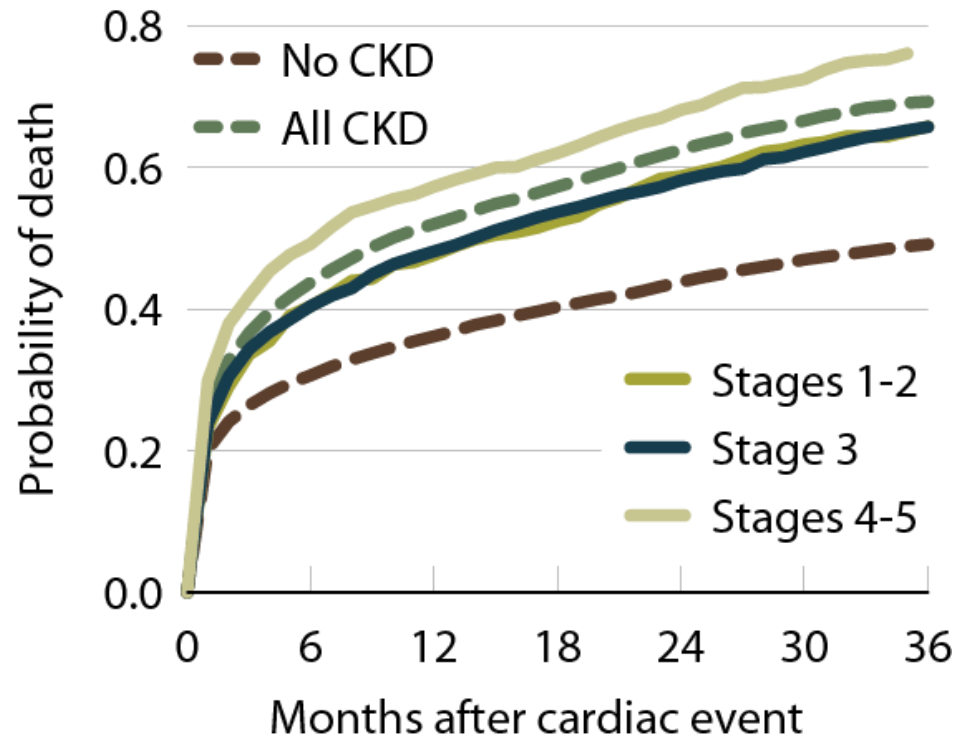
# Reduced eGFR Increases Deaths, Hospitalizations, and CV Events



No. of Events 25,801 11,569 7802 4408 1842    No. of Events 366,757 106,543 49,177 20,581 11,593    No. of Events 73,108 34,690 18,580 8809 3824

Age-standardized rates of death from any cause (left), hospitalization (middle), and cardiovascular events (right) and as a function of eGFR; N=1,120,295.

# All-cause mortality after a MI and stroke, depending on eGFR



# **Diagnosis & Management of CKD**



# Diagnosing CKD

Patient with hypertension, diabetes, CVD, FH of stage 5 CKD, multisystem disease

↓  
Measure eGFR  
(ml/min/1.73m<sup>2</sup>)

↓  
GFR>60 and risk factors for CKD;  
repeat in 1 yr  
  
GFR<60 -> repeat eGFR within 2 weeks

↓  
Measure urine  
ACR (mg/mmol)

↓  
•ACR<2.5(men)  
<3.5(women) – normal in diabetes  
•ACR<30 – normal  
•ACR 30-70 – renal damage  
•ACR>70 – consider referral

↓  
Urine dipstick

↓  
Proteinuria and haematuria -> consider referral

# Risk categories for kidney and mortality outcomes by GFR and albuminuria or proteinuria stage (KDIGO chart)

		<b>UAE</b>	<b>A1</b>	<b>A2</b>	<b>A3</b>
		mg/g mg/mmol	<30 <3	30-300 3-30	>300 >30
<b>GFR stage</b>	<b>Description</b>	(ml/min/ 1.73 m <sup>2</sup> )			
<b>G1</b>	<b>Normal or high</b>	<b>&gt; 90</b>			
<b>G2</b>	<b>Mild</b>	<b>60-89</b>			
<b>G3a</b>	<b>Mild to moderate</b>	<b>45-59</b>			
<b>G3b</b>	<b>Moderate to severe</b>	<b>30-44</b>			
<b>G4</b>	<b>Severe</b>	<b>15-29</b>			
<b>G5</b>	<b>Kidney failure</b>	<b>&lt;15</b>			

# When to refer from primary care

Consider referral if:

- Stage 4 & 5 CKD
- Higher levels of Proteinuria (ACR >70 mg/g) unless known to be due to diabetes and being treated
- Proteinuria (ACR >30 mg/g) & haematuria
- Rapidly declining eGFR (>5ml/min in 1 yr or 10ml/min in 5 yrs)
- Poorly controlled hypertension after using at least 4 agents
- Suspected renal artery stenosis

# Cardiovascular risk management in patients with CKD

- Definition, classification and prevalence
- Risk of cardiovascular events. Impact of reduced GFR and albuminuria
- **Management**

# Cardiovascular risk management in patients with CKD

## ■ Main aims of treatment

- ◆ Reno-protection: delaying progression of CKD
  - especially avoiding ESRD
  - reducing proteinuria (measure of renal damage)
  - slowing eGRF decline (measure of renal impairment)
- ◆ Cardio-protection: CKD accelerates major CVD events
  - Especially in Stage CKD 3b and 4

## ■ Evidence-based treatments

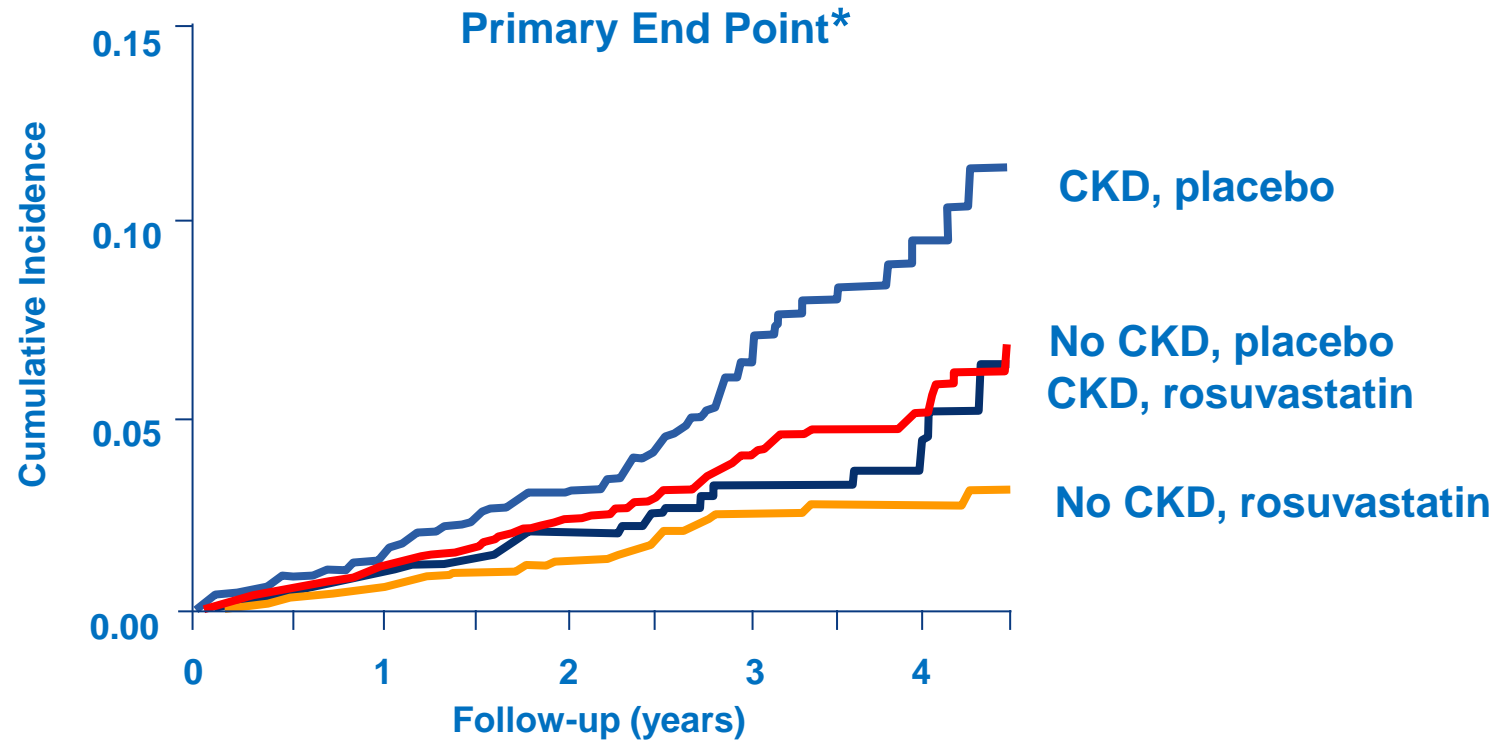
- ◆ **Lipids**
- ◆ Blood pressure and RAS Blockade
- ◆ SGLT2i

# Statins Are Beneficial in Patients With CKD Not Receiving Dialysis

Category	Number of Studies	Relative Risk (95% CI)
All-cause mortality	11	0.81 (0.74-0.88)
Cardiovascular mortality	8	0.78 (0.68-0.89)
Major cardiovascular events	14	0.76 (0.73-0.80)
Fatal or nonfatal MI	8	0.55 (0.42-0.72)
Fatal or nonfatal stroke	5	0.61 (0.38-0.98)

In a meta-analysis that included 12 trials of statins in patients with CKD who were not receiving dialysis (n=36,325), there was moderate- to high-quality evidence that statins reduced all-cause mortality, cardiovascular mortality, and cardiovascular events.

# Incidence of endpoints in JUPITER trial based on CKD



\*Primary end point: non-fatal MI, nonfatal stroke, hospital stay for unstable angina, arterial revascularization, or CV death

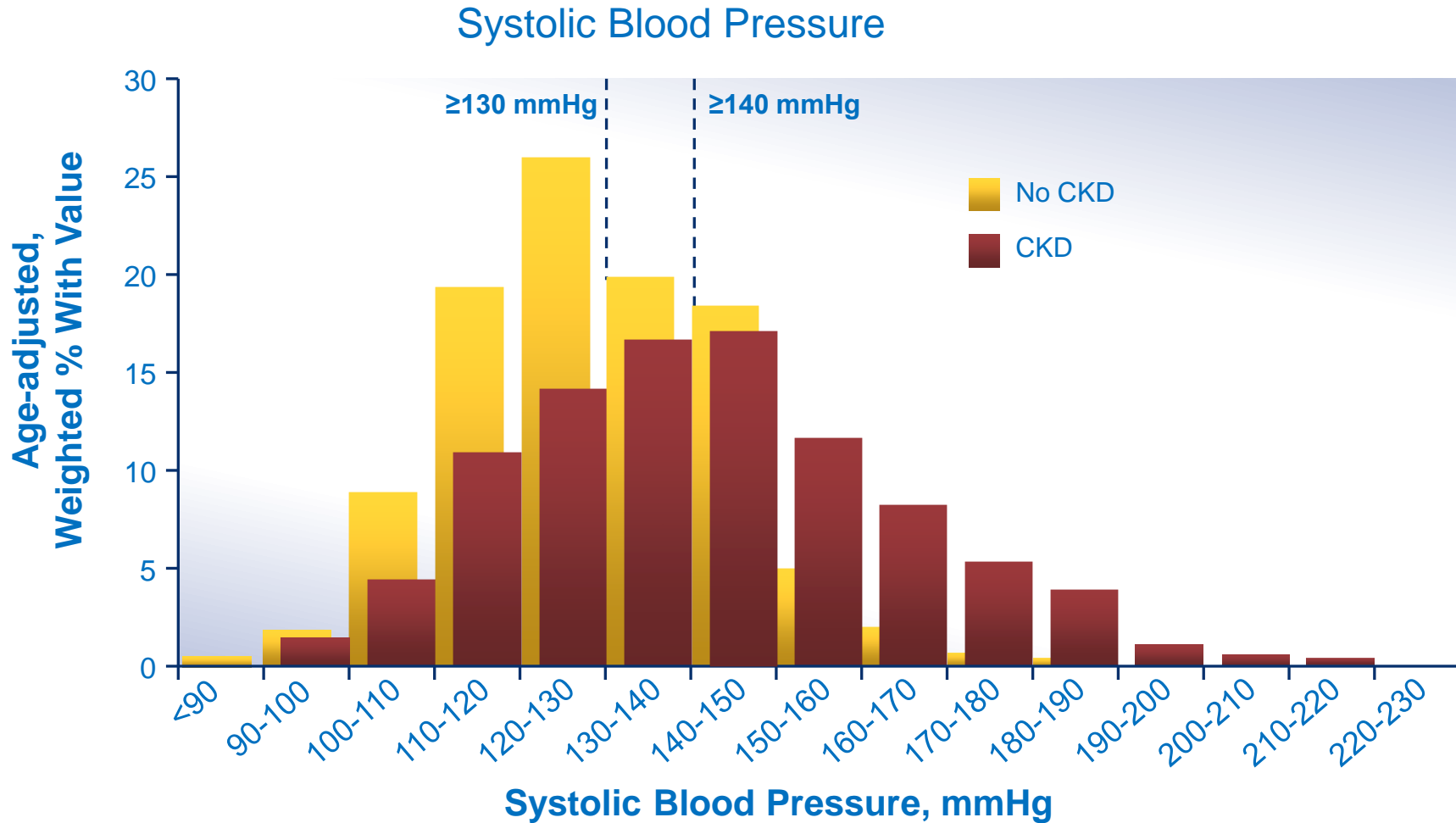
# Cardiovascular risk management in patients with CKD

## ■ Management

- ◆ Lipids
- ◆ **Blood pressure & RAS Blockade**
- ◆ SGLT2i

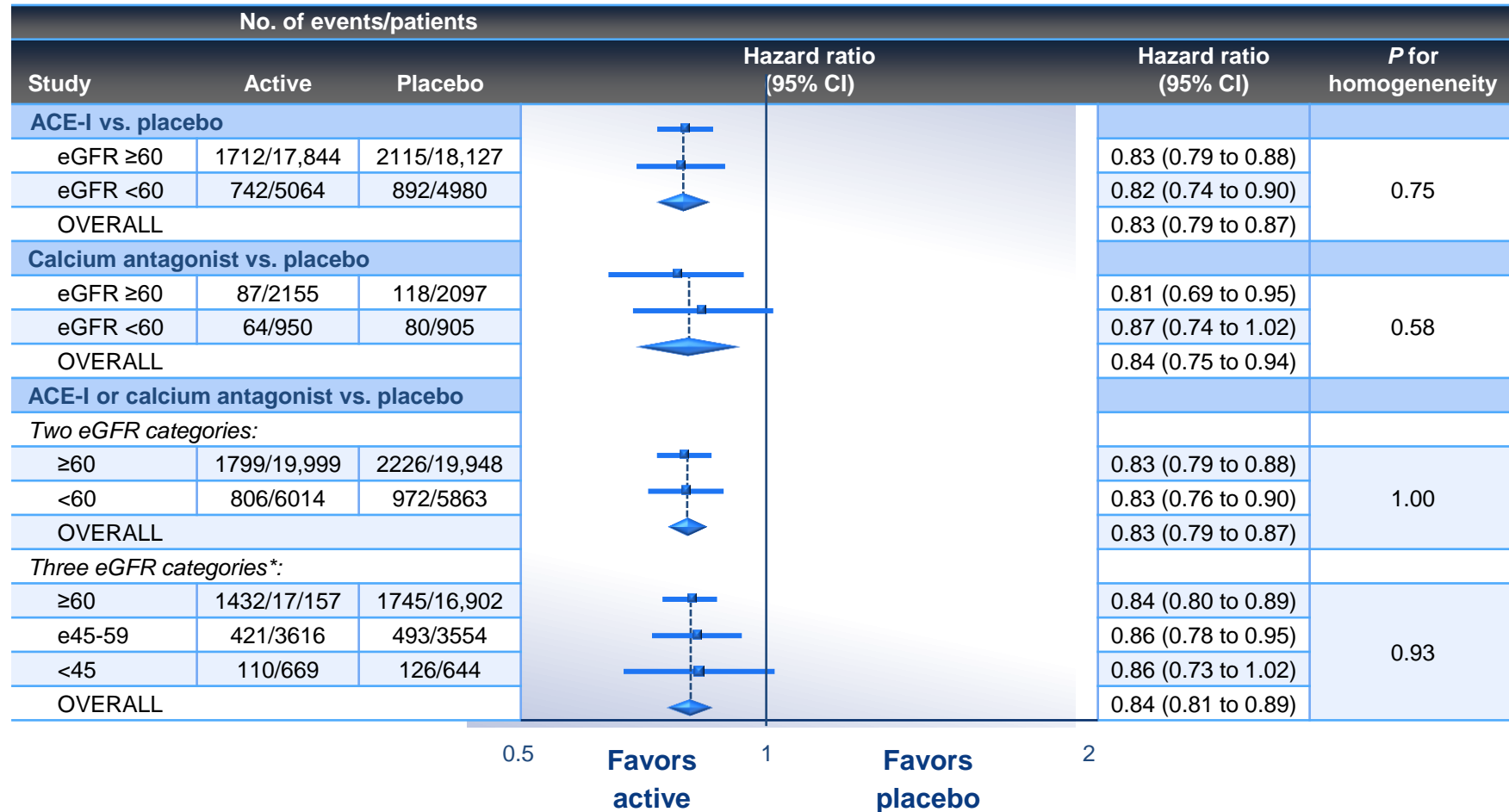


# Subjects With CKD Are More Likely to Have Uncontrolled Systolic Blood Pressure



Weighted, age-adjusted distributions of SBP among NHANES 1999-2006 participants with hypertension and with (n=1651) and without (n=7178) CKD.

# BP Reduction Reduces the Risk of Major Cardiovascular Events in Subjects With CKD



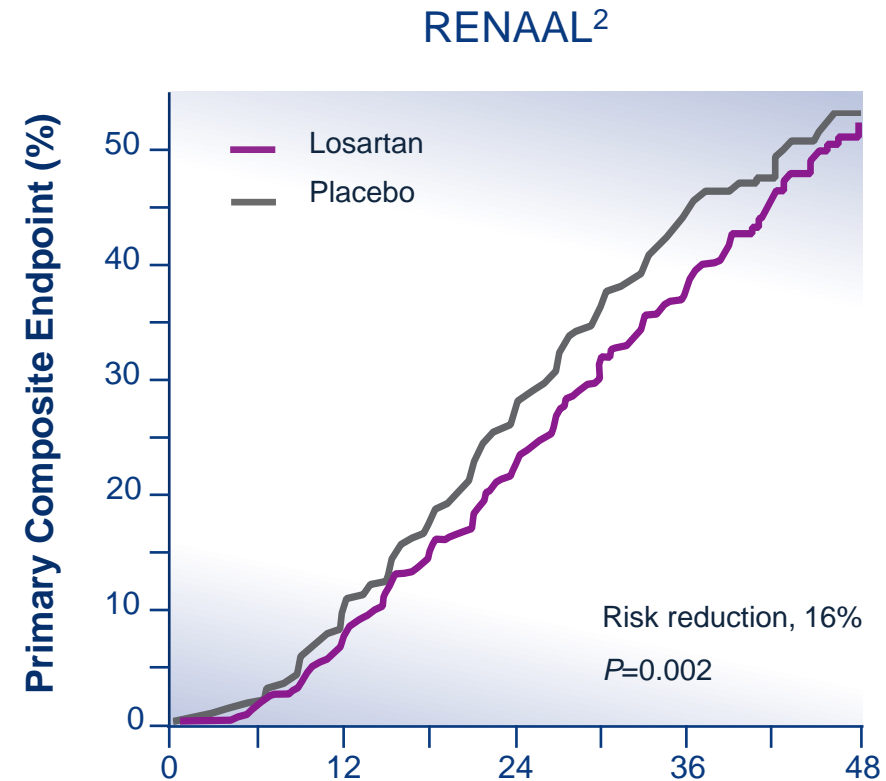
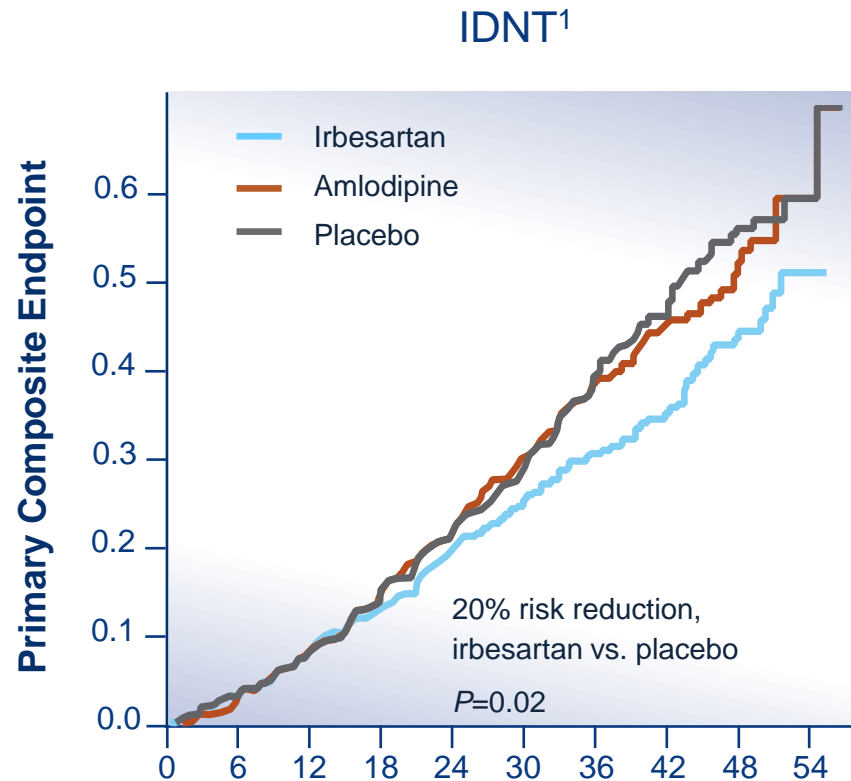
Values are relative risk per 5-mmHg reduction in SBP over time.

# Cardiovascular risk management in patients with CKD

## ■ Management

- ◆ Lipids
- ◆ Blood pressure & **RAS Blockade**
- ◆ SGLT2i

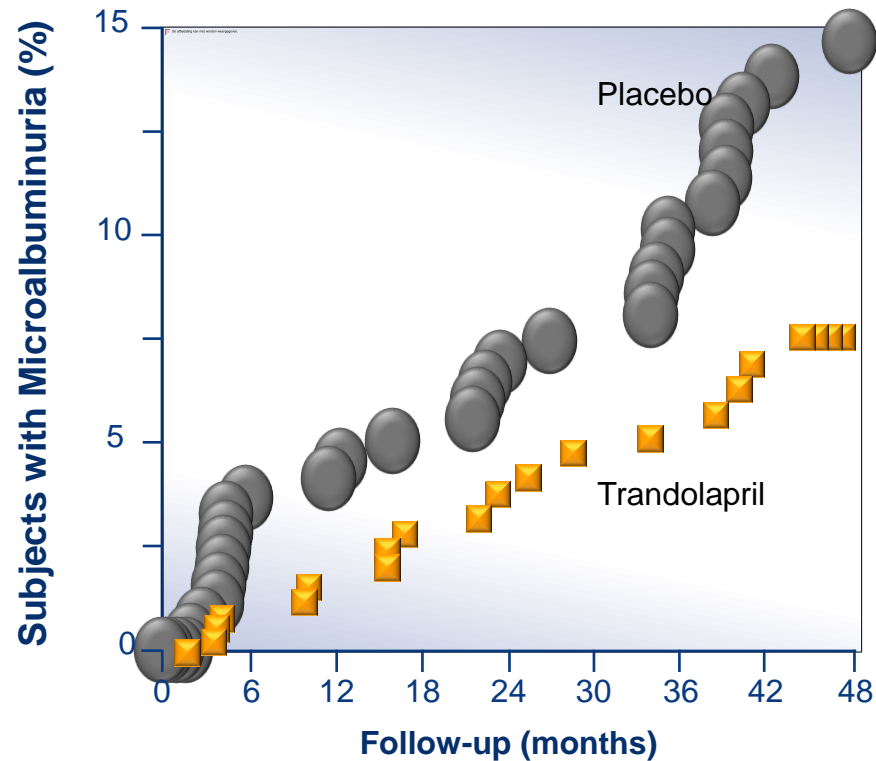
# ARBs Are Effective for Slowing Progression of Diabetic Nephropathy



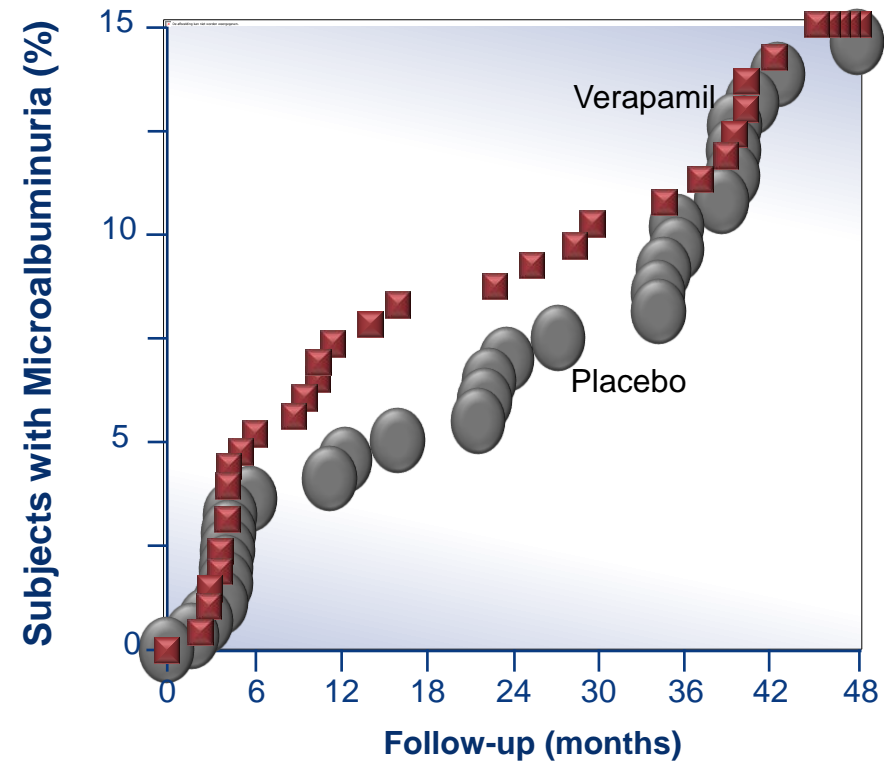
Primary endpoint (composite of doubling of serum creatinine, ESRD, or death) in the IDNT trial, which compared treatment with irbesartan, amlodipine, and placebo, and RENAAL, which compared losartan and placebo. Both ARBs significantly reduced the primary endpoint.

1. Lewis EJ et al. *N Engl J Med.* 2001;345:851-860. 2. Brenner BM et al. *N Engl J Med.* 2001;354:861-869.

# Treatment With ACEI Limits the Development of Microalbuminuria in Subjects With Diabetes



No. at Risk	0	6	12	18	24	30	36	42	48
Trandolapril	301	254	237	224	207	198	188	149	104
Placebo	300	229	214	203	187	176	164	136	89



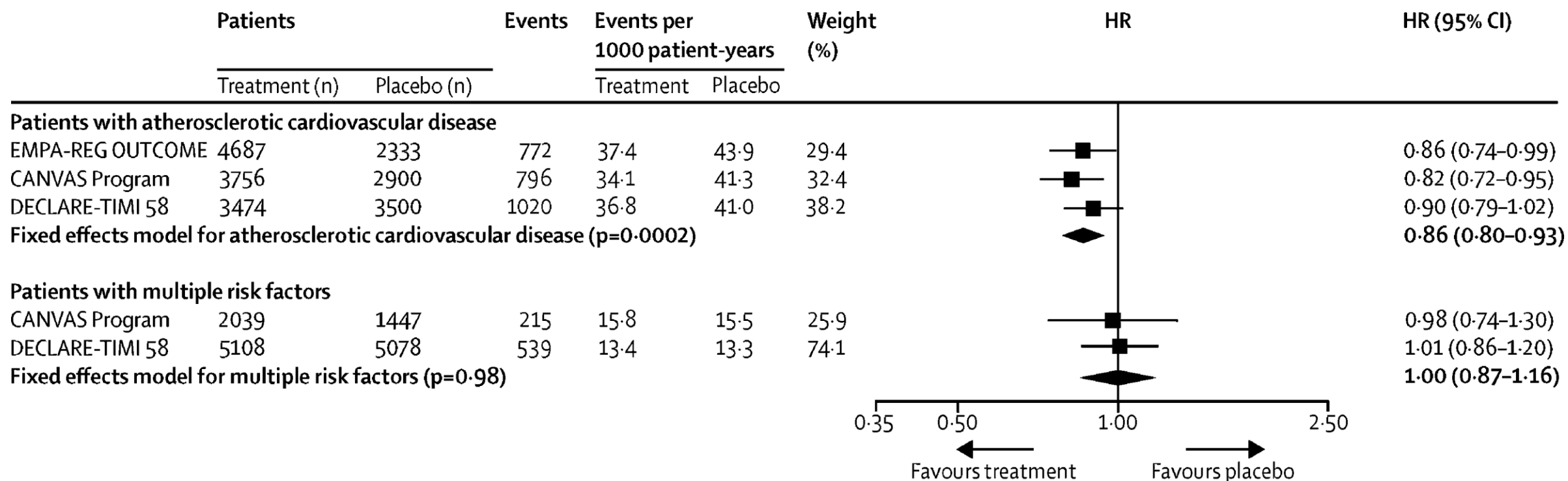
No. at Risk	0	6	12	18	24	30	36	42	48
Verapamil	303	234	210	202	189	181	174	134	98
Placebo	300	229	214	203	187	176	164	136	89

# Cardiovascular risk management in patients with CKD

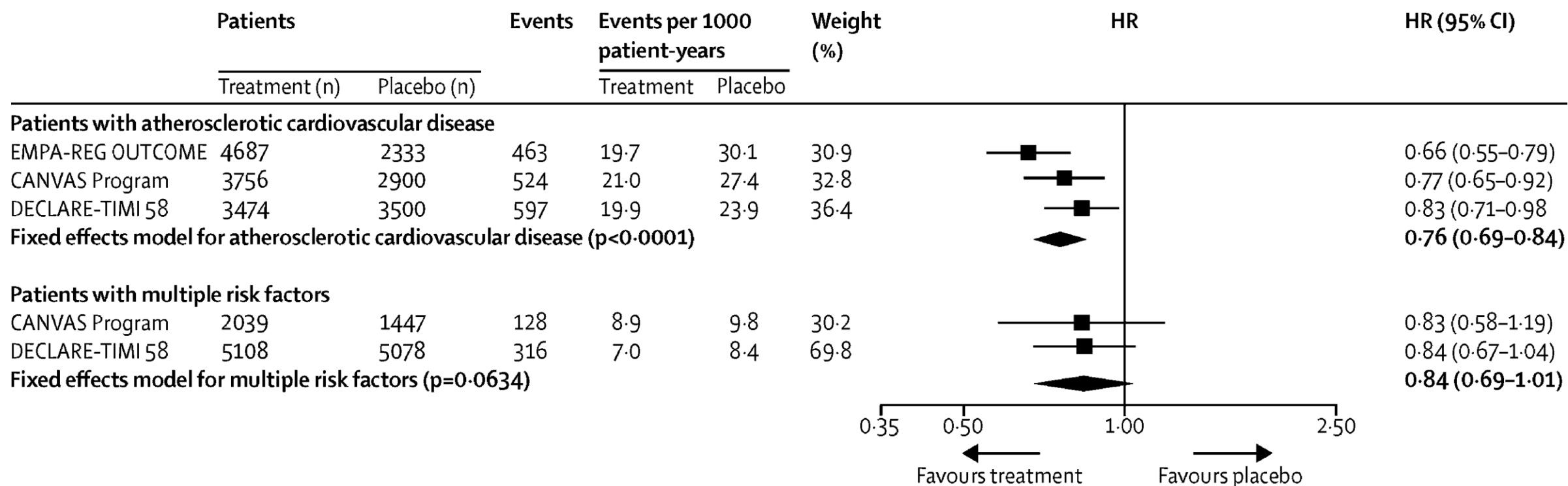
## ■ Management

- ◆ Lipids
- ◆ Blood pressure & RAS Blockade
- ◆ **SGLT2i**

# SGLT2 Inhibitors effects on MI, stroke and CV death

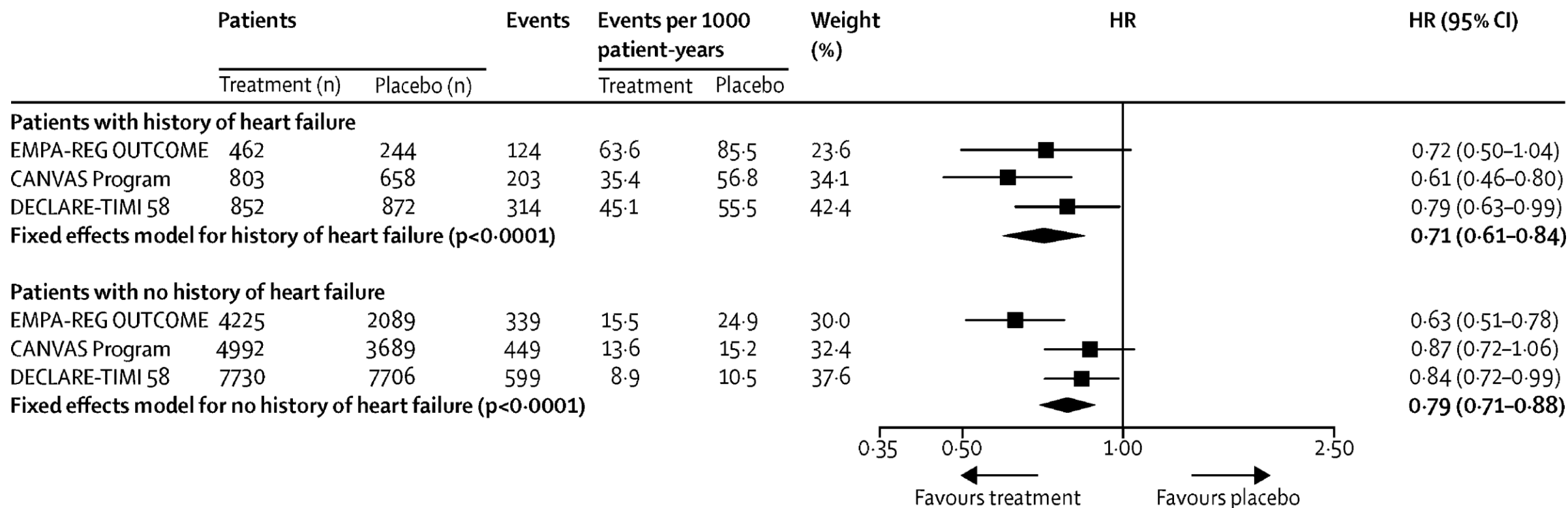


# SGLT2 Inhibitors effects on hospitalisation for heart failure or cardiovascular death

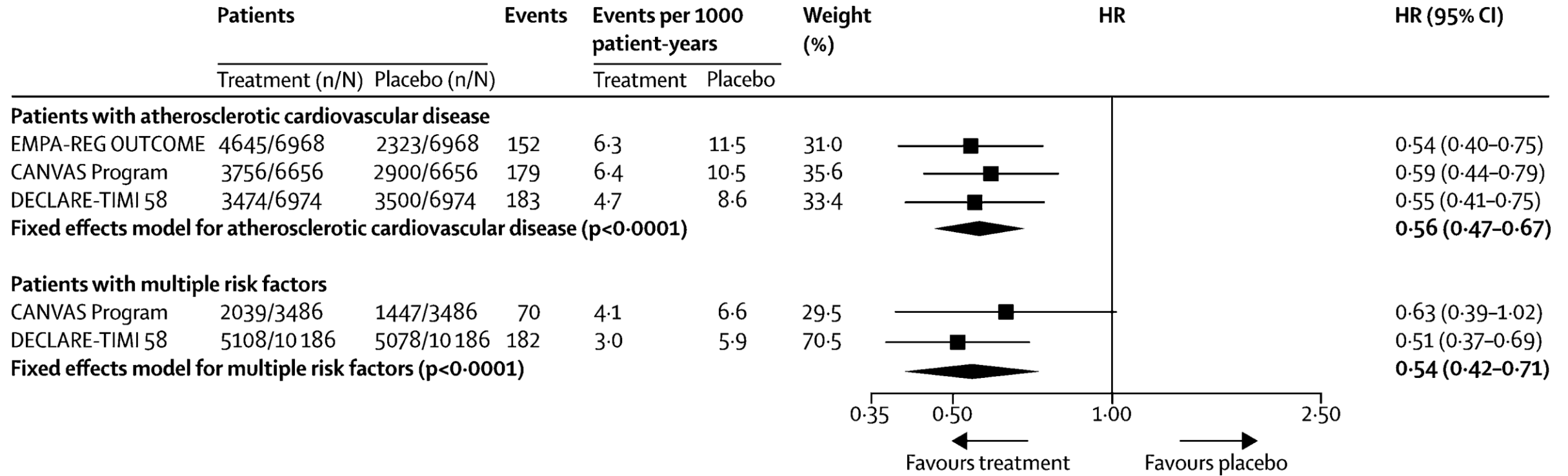




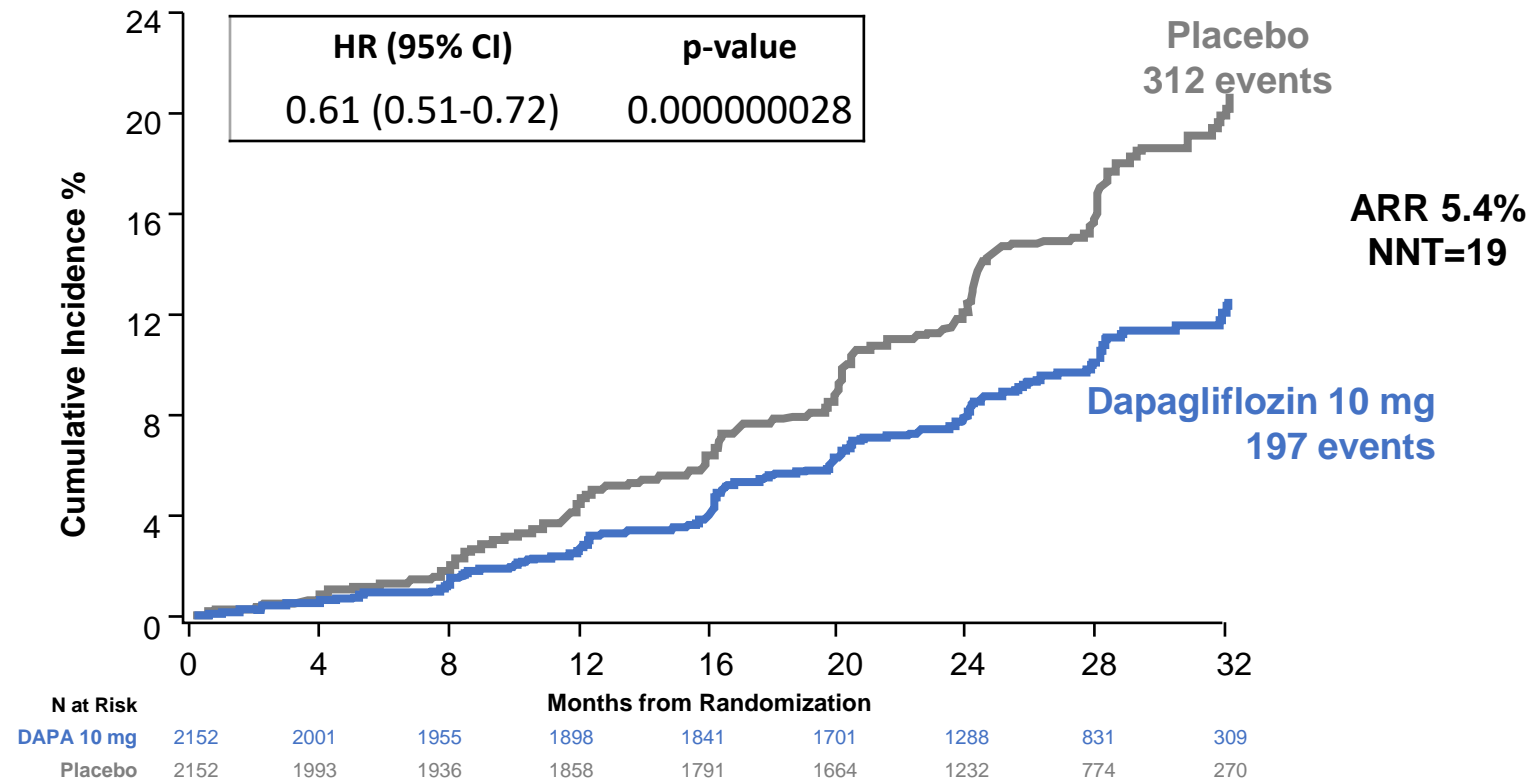
# SGLT2 Inhibitors effects on hospitalisation for heart failure or cardiovascular death by history of heart failure



# SGLT2 Inhibitors effects on renal worsening, ESRD, or renal death

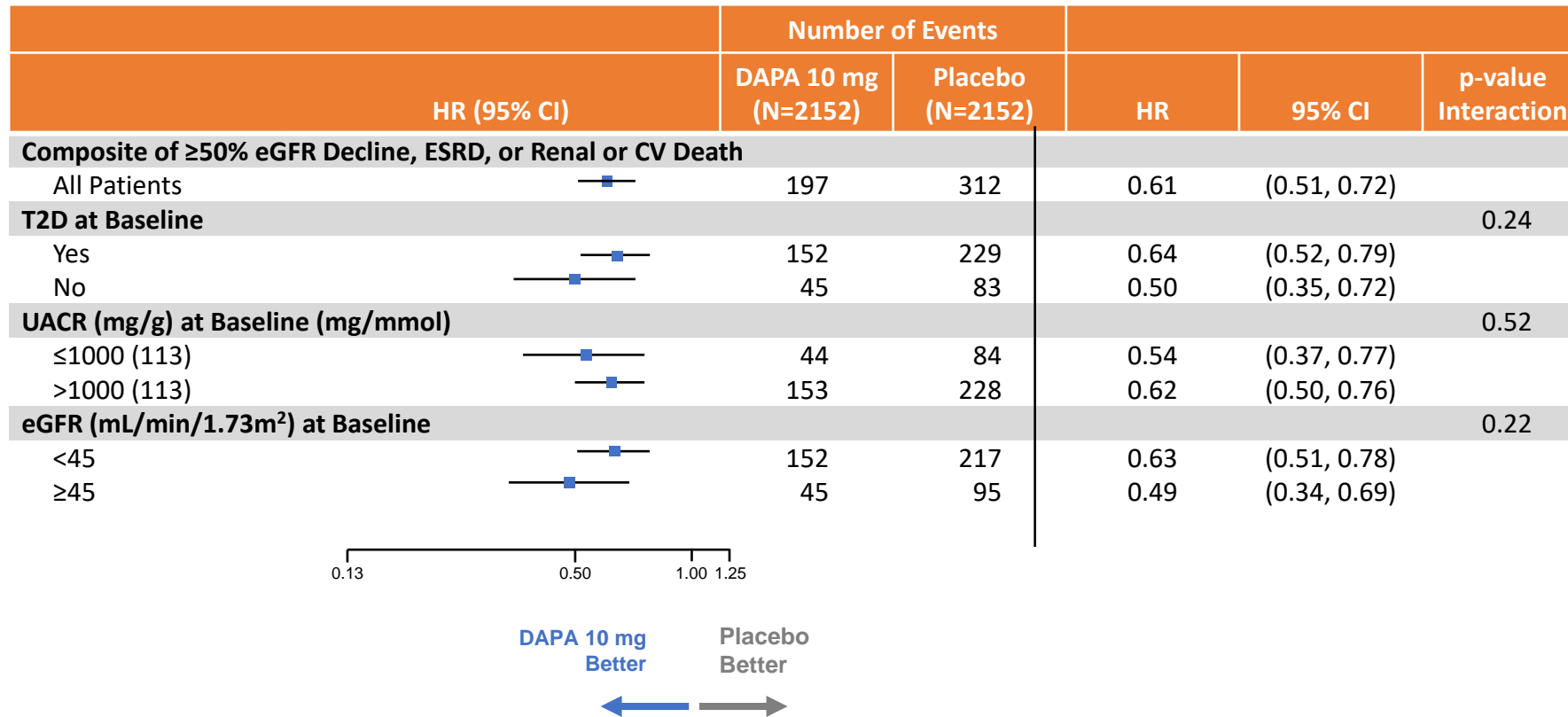


# Renal and CV protection in patients with CKD with/without diabetes (DAPA-CKD): Primary Composite Outcome (sustained $\geq 50\%$ eGFR Decline, ESRD, Renal or CV Death)<sup>a</sup>



- <sup>a</sup>ESRD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m<sup>2</sup> for at least 28 days. Renal death was defined as death due to ESRD when dialysis treatment was deliberately withheld for any reason.<sup>2</sup> CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease;
- 1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446

# Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups



- CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.
- Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

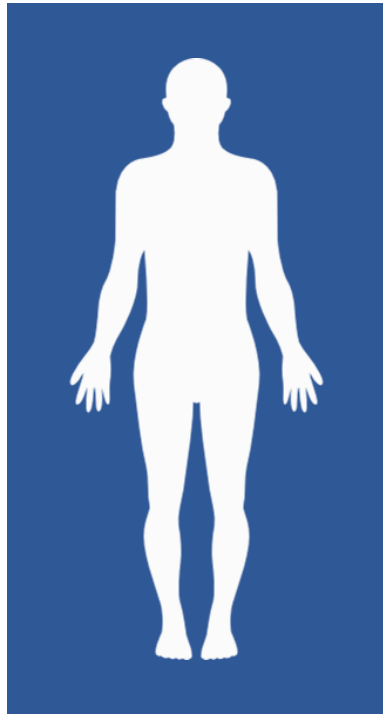
# Safety Outcomes

Safety Outcomes <sup>a</sup> , n (%)	Dapagliflozin 10 mg (N=2149)	Placebo (N=2149)
<b>Discontinuation of study drug</b>	274 (12.8)	309 (14.4)
<b>Discontinuation due to adverse event</b>	118 (5.5)	123 (5.7)
<b>Any serious adverse event</b>	633 (29.5)	729 (33.9)
<b>Adverse events of interest</b>		
Amputation <sup>b</sup>	35 (1.6)	39 (1.8)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)
Fracture <sup>c</sup>	85 (4.0)	69 (3.2)
Renal-related adverse event <sup>c</sup>	155 (7.2)	188 (8.7)
Major hypoglycemia <sup>d</sup>	14 (0.7)	28 (1.3)
Volume depletion <sup>c</sup>	127 (5.9)	90 (4.2)
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)

- <sup>a</sup>Safety outcomes reported in participants on and off treatment; <sup>b</sup>Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; <sup>c</sup>Based on pre-defined list of preferred terms; <sup>d</sup>Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention
- Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

# Genital infections with SGLT2 inhibitors are common and typically mild to moderate in severity<sup>1-4</sup>

## Management



**Raise awareness** at the start of SGLT2 inhibitor treatment to manage expectations and **promote early intervention**<sup>1</sup>



**Provide practical hygiene advice** to patients with T2D and their partners to **prevent** genital infections<sup>1</sup>



Topical treatments or appropriate oral treatments can be used for **mild to moderate infections**<sup>1</sup>

————— **Usually occur early during treatment exposure and are typically self-limiting**<sup>1</sup> —————

T2D, type 2 diabetes

1. Wilding J *et al. Diabetes Ther* 2018;9:1757; 2. Boehringer Ingelheim Pharmaceuticals, Inc. empagliflozin summary of product characteristics. Feb 2020; 3. Janssen International. canagliflozin summary of product characteristics. 2019; 4. AstraZeneca. dapagliflozin summary of product characteristics. Nov 2019

# Conclusions

- CKD is highly prevalent (globally >10% of the adult population) and carries a substantial risk of cardiovascular disease.
- Important to screen for CKD in primary care
  - ◆ eGFR and ACR
- Consider early treatment to prevent progression of CKD (decline in eGFR and worsening proteinuria) AND reduce CV events
  - ◆ Statins for cardio-protection
  - ◆ Antihypertensive agents for cardio-protection, plus reno-protection with RAS blockers
  - ◆ SGLT2 inhibitors for reno-protection and cardio-protection, additional to RAS blockade