RAASi benefits in slowing down kidney function decline

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Conflict of interest

- Clinical research: Alexion, Bayer, GSK, Otsuka
- Advisory Boards : Amgen, Baxter, Hemotech, Novartis, Otsuka, Shire, Vifor,
- Lectures : Bbraun, GE Heathcare, Novo, Novartis, Vifor, Roche, Sanofi
- Research support : Baxter, Fresenius, Meditor, Sanofi

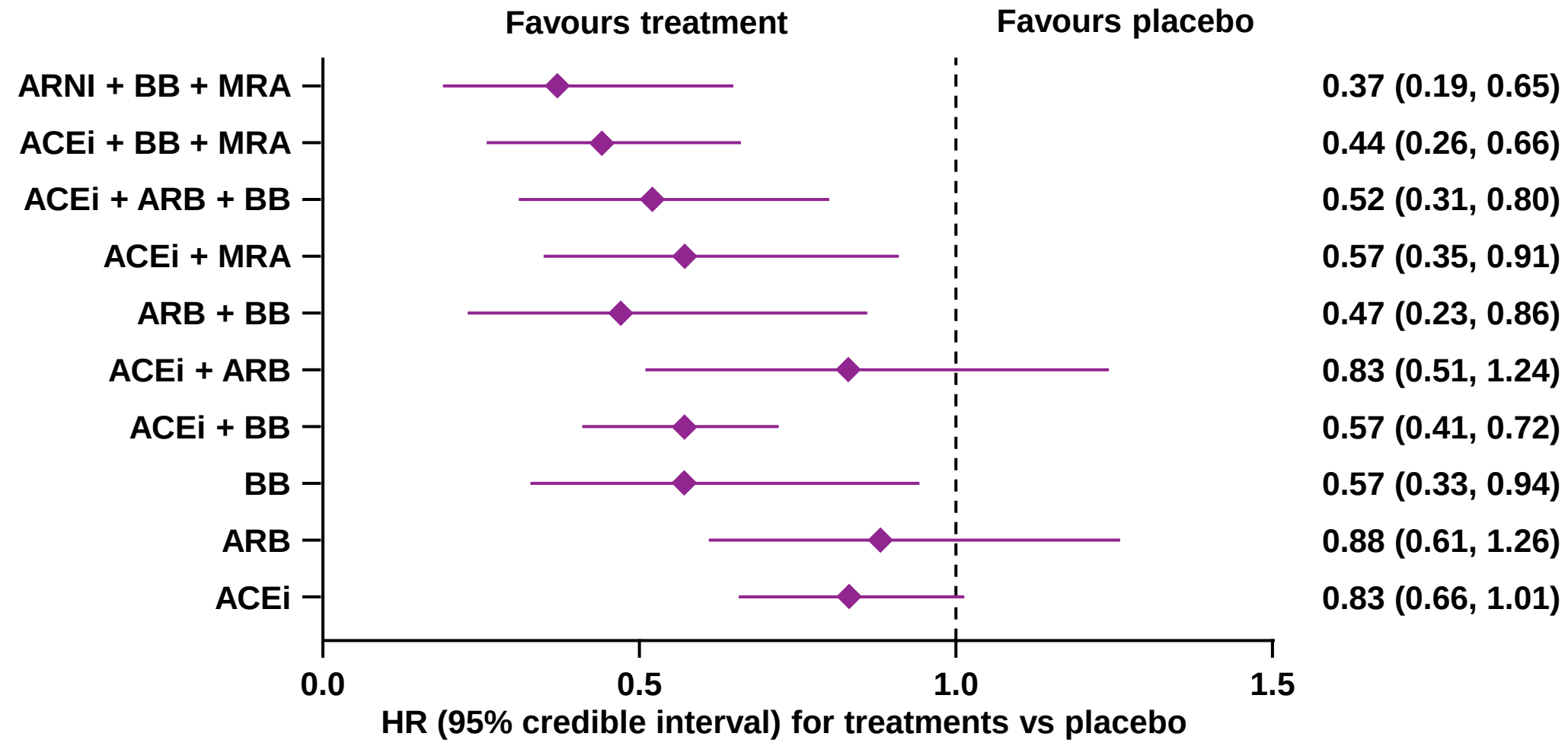
Multiple randomized trials show that RAASi confer a clear survival benefit in patients with heart failure

	CHF		Post-MI
Ejection fraction	**Low**	**Severe**	**Low**
ACEi	SOLVD[1]	CONSENSUS[2]	AIRE[3] SAVE[4]
MRA	EMPHASIS[5]	RALES[6]	EPHESUS[7]
ARB	VAL-HeFT[9] CHARM[9]	-	OPTIMAAL[10] VALIANT[11]
ARNi	PARADIGM-HF[12]	-	-

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CHF, chronic heart failure; MI, myocardial infarction; MRA, mineralocorticoid-receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

1. THE SOLVD Investigators. *N Engl J Med* 1992;325:293–302; 2. The Consensus Trial Study Group. *N Engl J Med* 1987;316:1429–35; 3. AIRE Study Investigators. *Lancet* 1993;342:821–8; 4. Pfeffer MA. *Herz*.1993;18(Suppl 1):430–5; 5. Zannad F *et al. N Engl J Med* 2011;364:11–21; 6. Pitt B *et al. N Engl J Med* 1999;341:709–17; 7. Pitt B *et al. N Engl J Med* 2003;348:1309–21; 8. Cohn JN *et al. N Engl J Med* 2001;345:1667–75; 9. McMurray JJ, *et al. Lancet* 2003;362:767–71; 10. Dickstein K and Kjekshus J. *Am J Cardiol* 1999;83:477–81; 11. Pfeffer MA *et al. N Engl J Med* 2003;349:1893–906; 12. McMurray JJV *et al*. *N Engl J Med* 2014;371:993–1004

RAASi have additive benefits for all-cause mortality: Network meta-analysis from 30 years of HFrEF studies



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

Burnett H *et al.,* Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis, *Circ Heart Fail*, 2017;10:e003529, http://circheartfailure.ahajournals.org/content/10/1/e003529.long

RAASi also demonstrate renoprotective benefits for patients with renal impairment

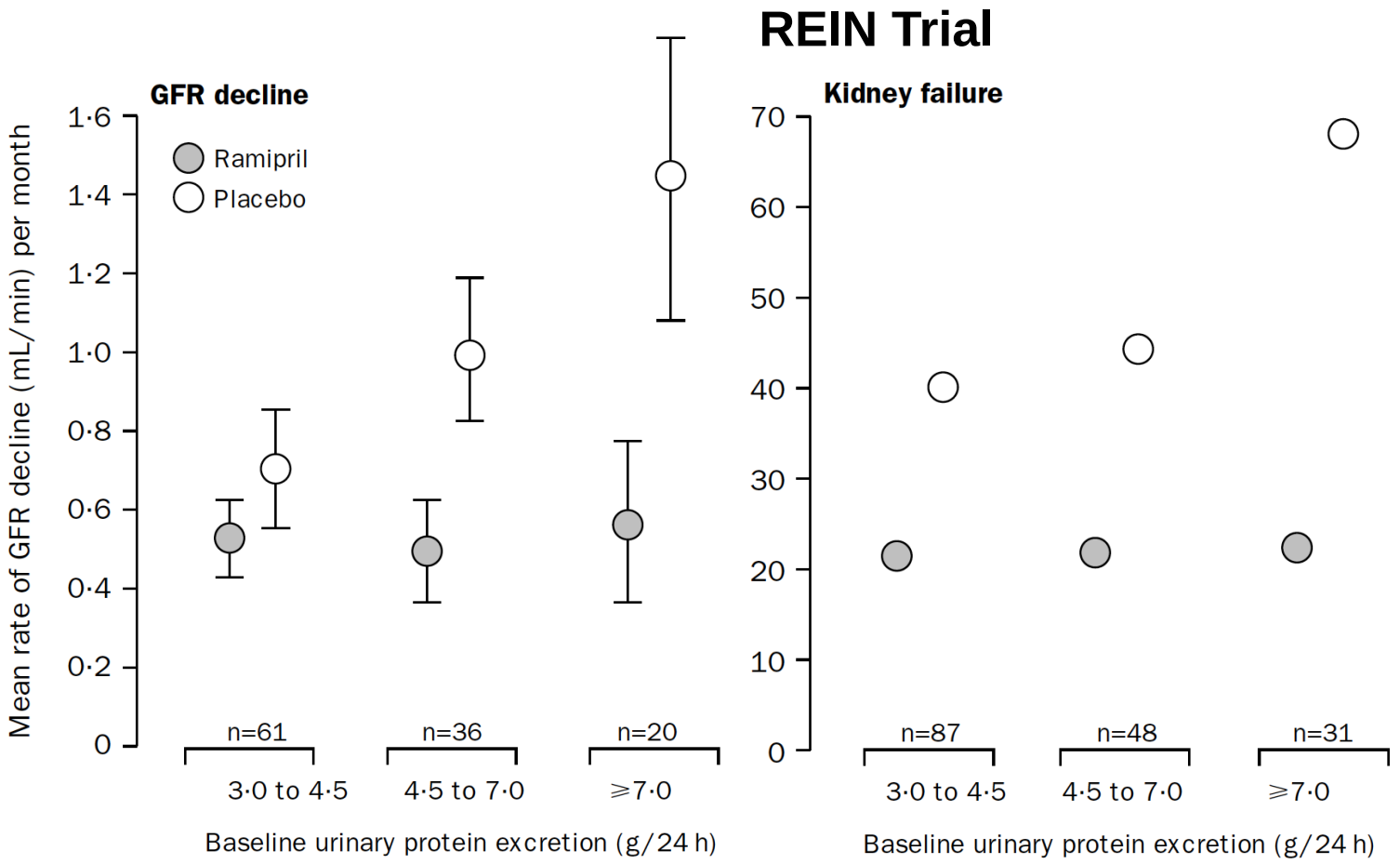
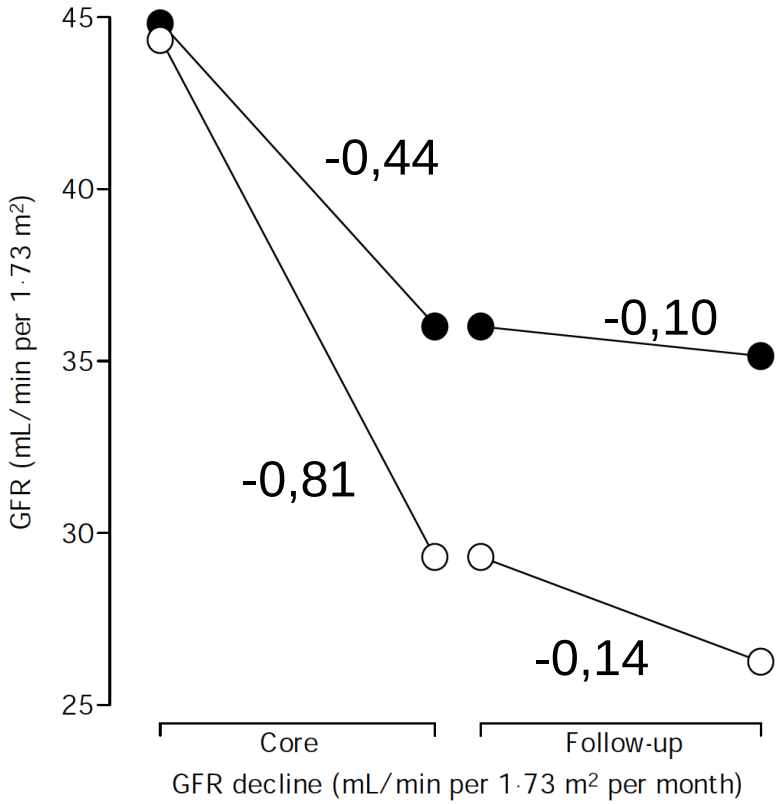


Figure 3: **Rate of decline in GFR and percentage risk of progression of nephropathy (combined endpoint=doubling of baseline serum creatinine or endstage renal failure) in two treatment groups according to baseline urinary protein excretion**

Reduction in GFR decline and renal outcomes with Ramipril in patients with heavy proteinuria

1. GISEN Group Lancet 1997

RAASi also demonstrate renoprotective benefits for patients with renal impairment



REIN Trial follow up

Group			p
● Continued ramipril	–0·44 (0·54)	–0·10 (0·50)	0·017
○ Switched to ramipril	–0·81 (1·12)	–0·14 (0·87)	0·017

Figure 2: **Mean GFR decline during the REIN core and follow-up study in patients continued on or switched to ramipril**

Mean of the differences of GFR decline between the core and follow-up study was 0·34 (95% CI 0·08–0·60) and 0·66 (95% CI 0·17–1·15) mL/min per 1·73 m² per month in patients continued on or switched to ramipril, respectively.

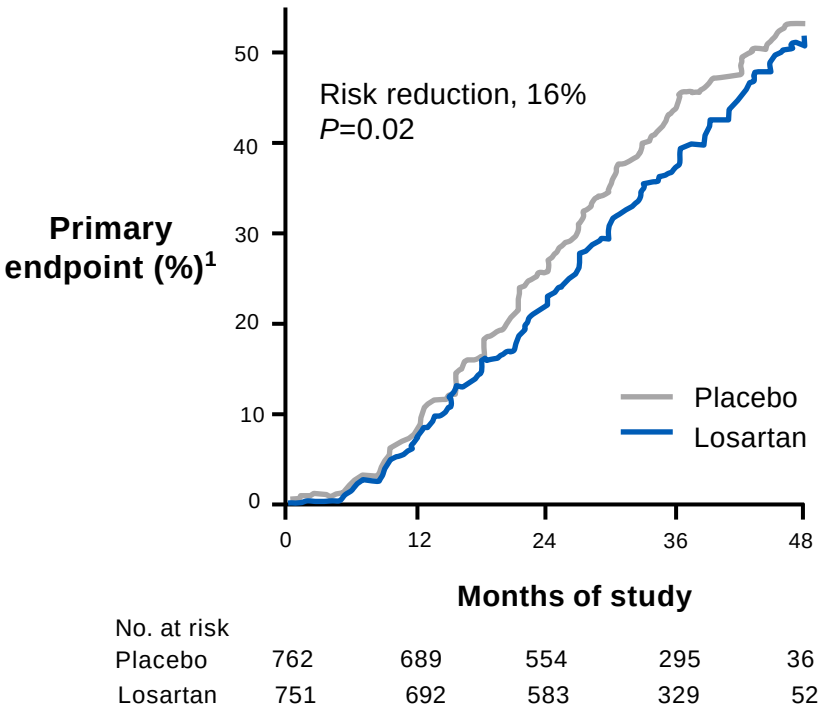
Reduction in GFR decline
with Ramipril in patients with heavy proteinuria

1. Reggunenti, Lancet 1998

RAASi also demonstrate renoprotective benefits for patients with renal impairment

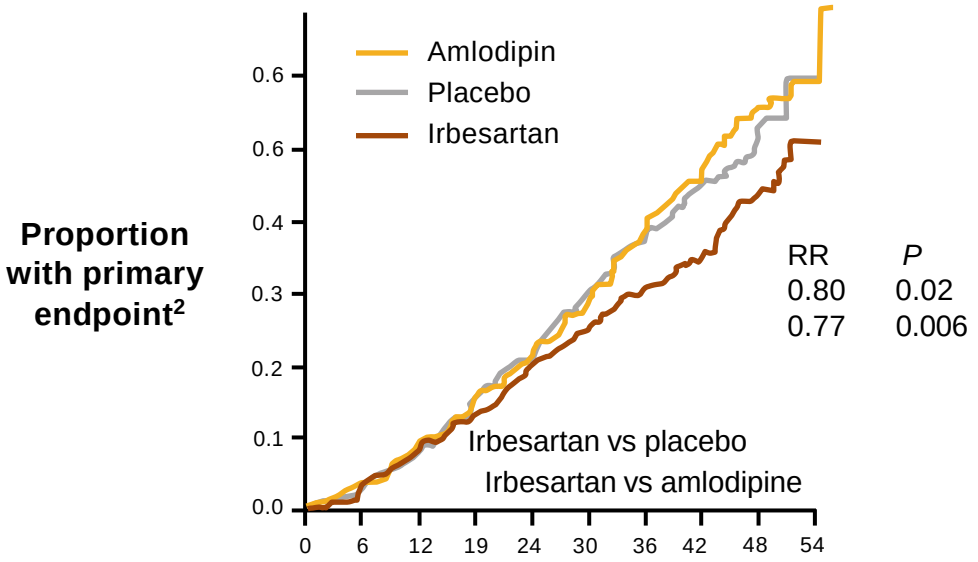
Primary endpoint: Death, progression to dialysis, or doubling of serum creatinine[1,2]

RENAAL[1]



No. at risk					
Placebo	762	689	554	295	36
Losartan	751	692	583	329	52

IDNT[2]



No. at risk									
Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
Placebo	568	551	512	471	401	280	190	122	53

Renoprotective effect of ARBs was evidenced by a 16–20% reduction in the risk of the adverse primary endpoint vs placebo[1,2]

RR, relative risk

1. Brenner BM *et al. N Engl J Med* 2001;345:861–9; 2. Lewis EJ *et al. N Engl J Med* 2001;345:851–60

Post Hoc analysis from RENAAL trial

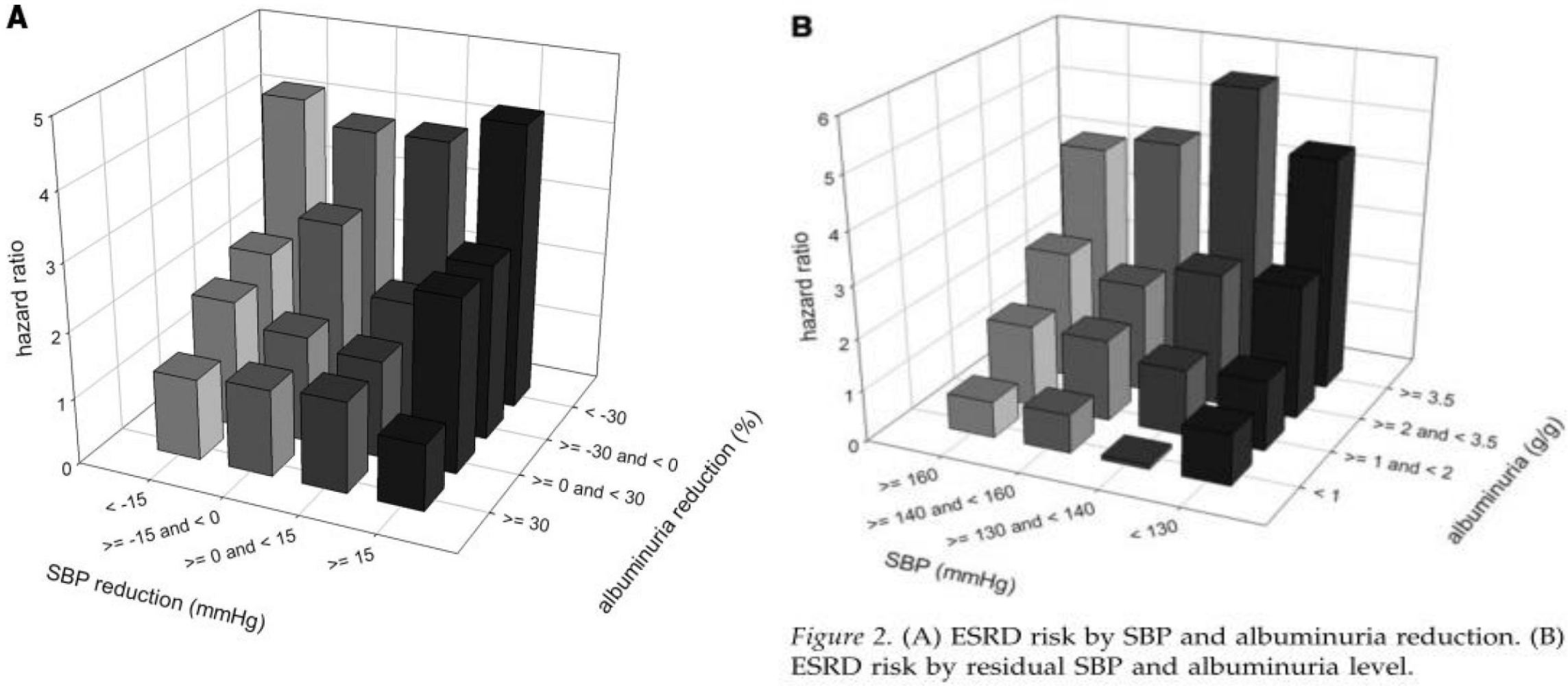
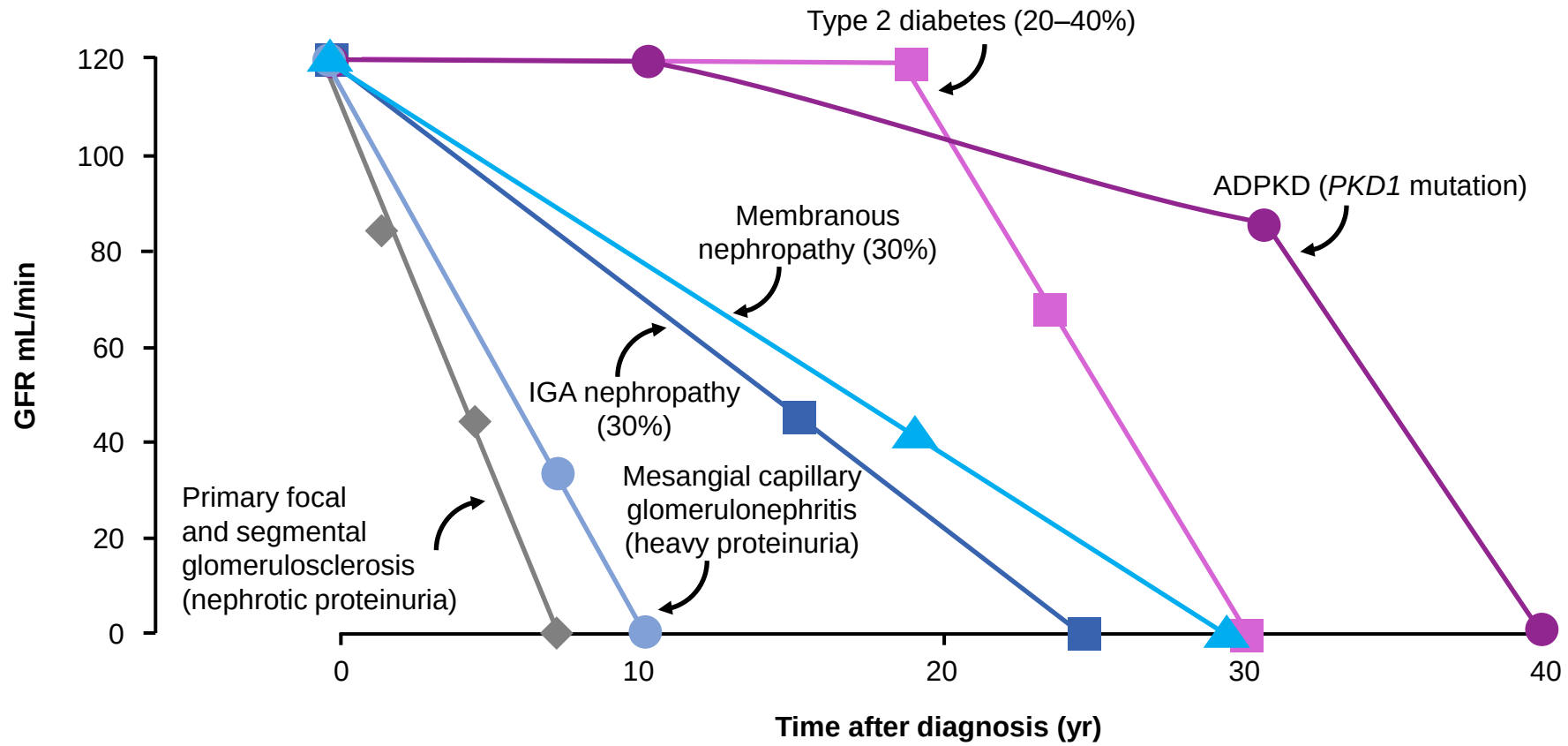


Figure 2. (A) ESRD risk by SBP and albuminuria reduction. (B) ESRD risk by residual SBP and albuminuria level.

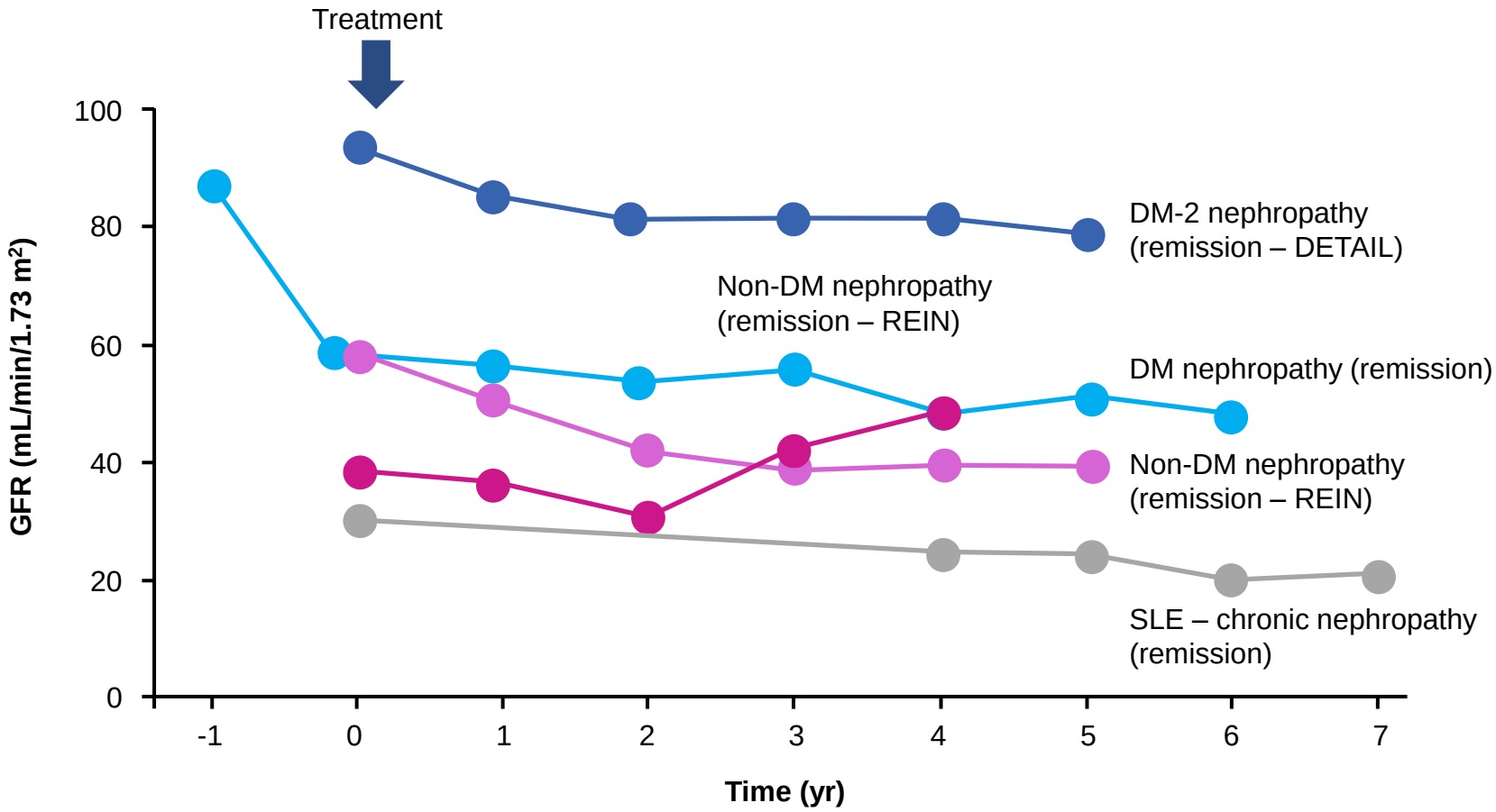
Eijkelkamp, Am Soc Nephrol 2007; 18: 1540-6

The progressive nature of chronic kidney disease



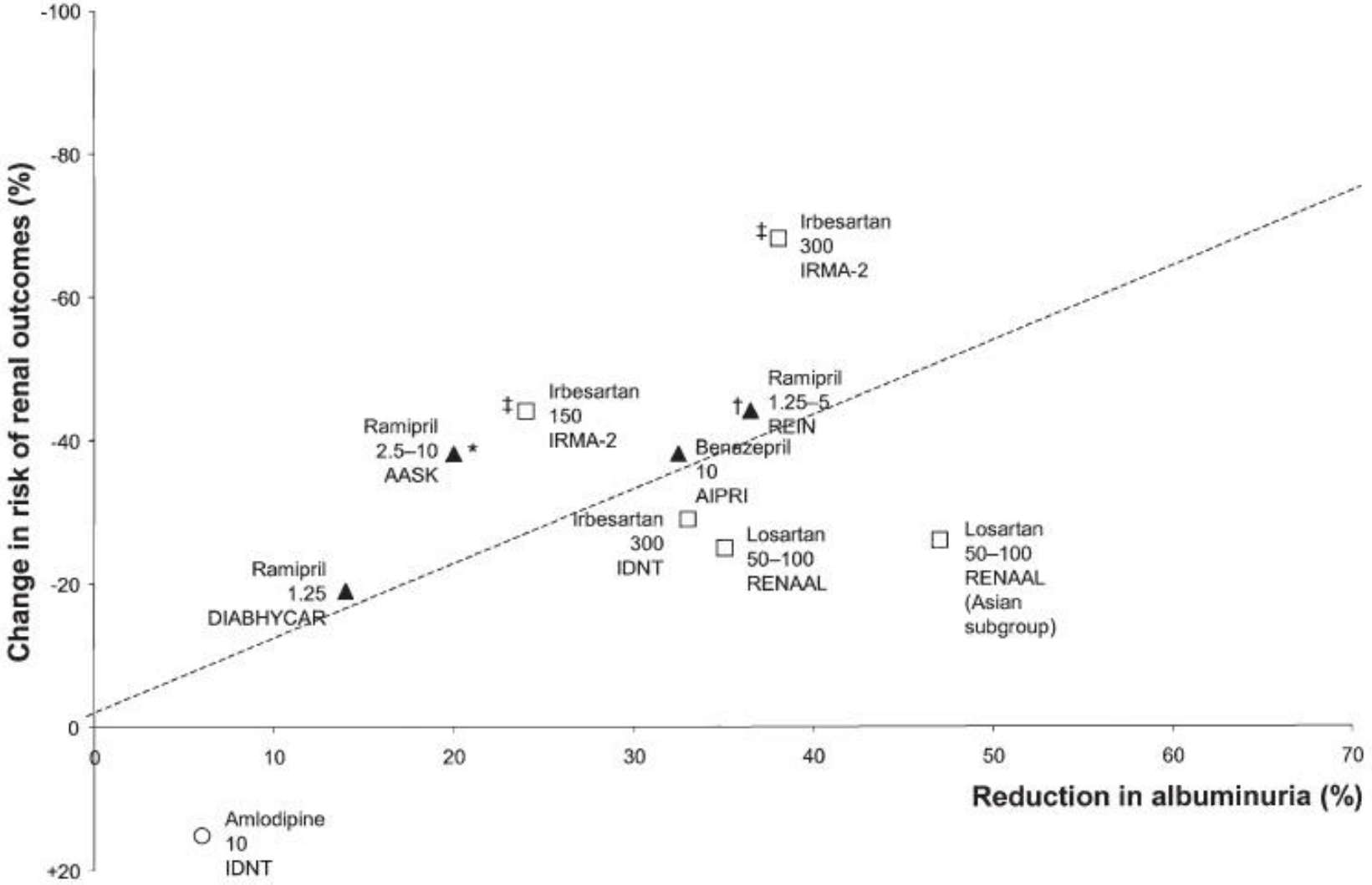
Remuzzi J, *et al.* *Clin Invest* 2006;116:288–29

Renal benefits take longer to manifest (~2 years) versus cardiac outcomes (~6 months)



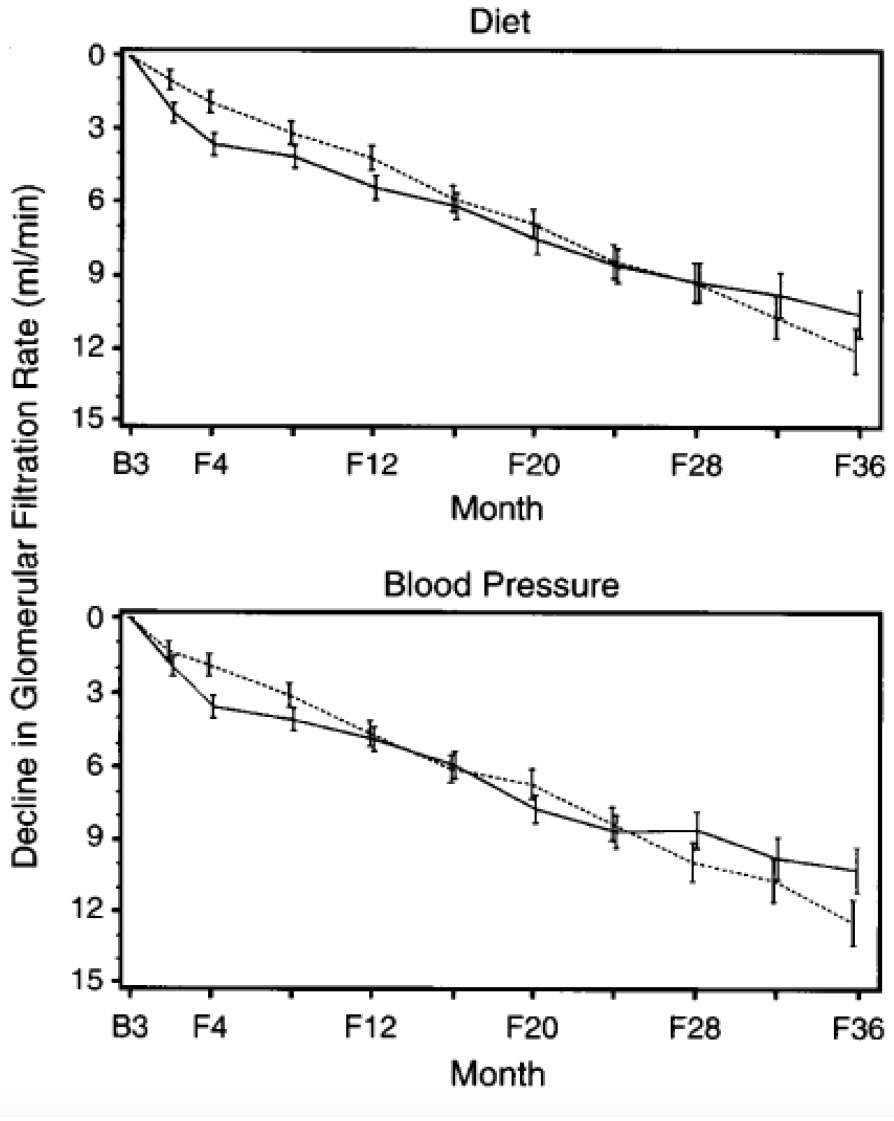
Remuzzi J, *et al.* *Clin Invest* 2006;116:288–296

Renal outcomes depends on titration of RAASi



Basi S, *et al. AJKD* 2006;47:927-946

RAASi are not nephrotoxic



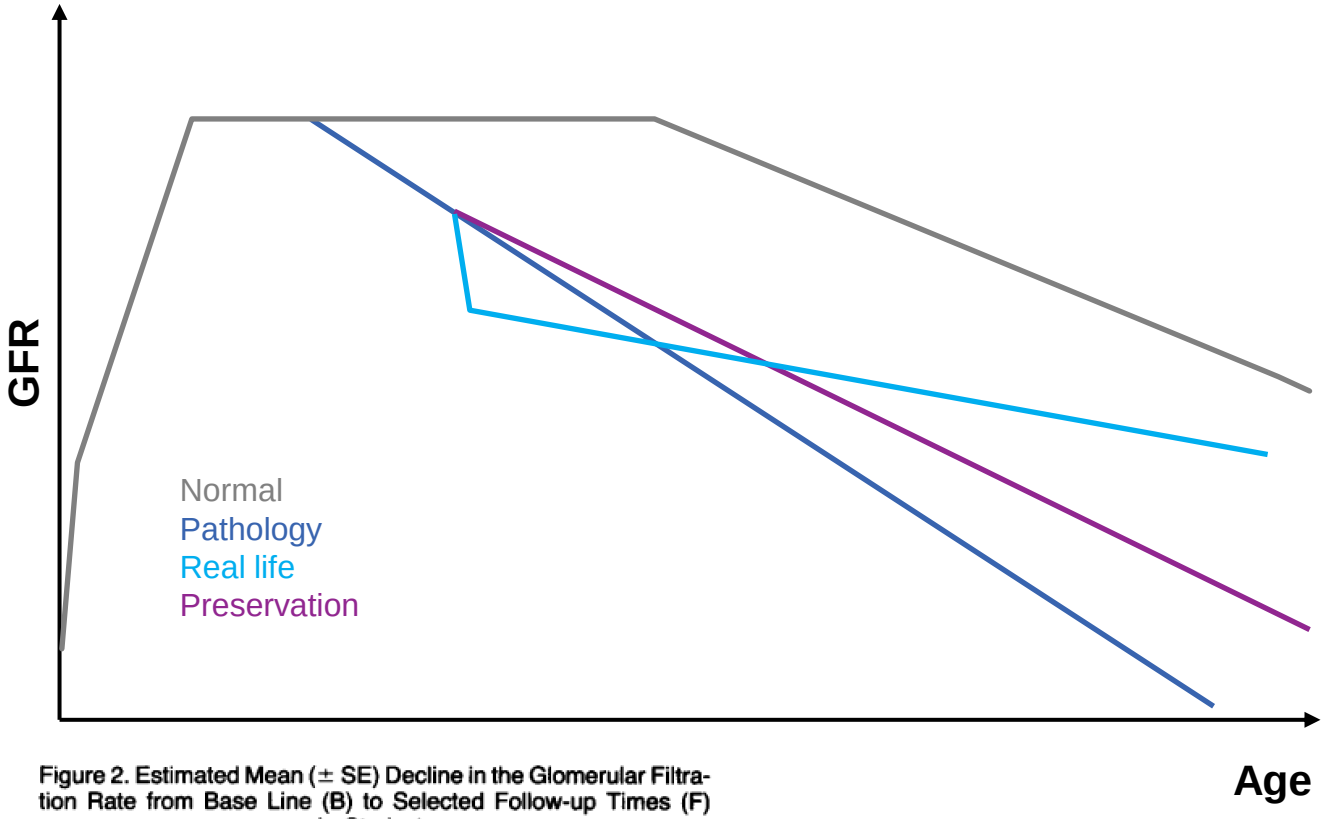


Figure 2. Estimated Mean (± SE) Decline in the Glomerular Filtration Rate from Base Line (B) to Selected Follow-up Times (F) in Study 1.

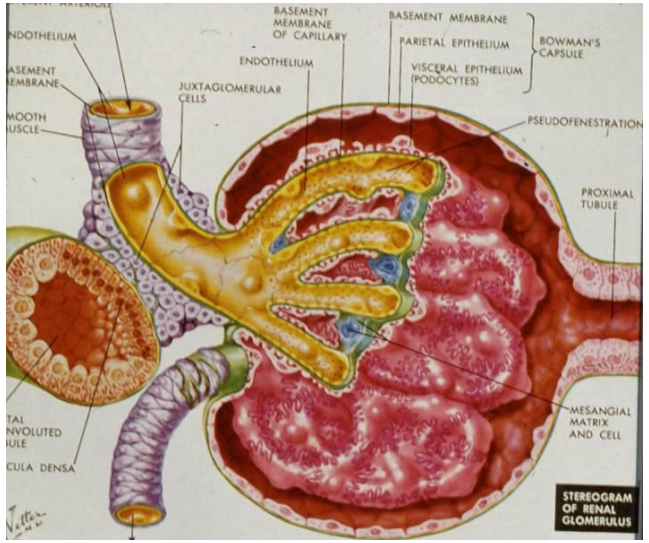
The upper panel compares the patients assigned to the usual-protein diet (dashed line) with those assigned to the low-protein diet (solid line). The lower panel compares the patients assigned to the usual-blood-pressure group (dashed line) with those assigned to the low-blood-pressure group (solid line). To correct for any bias introduced by stopping points, the mean declines were estimated by the maximum-likelihood method with a two-slope model for the covariance matrix of the serial measurements of the glomerular filtration rate.

Khlar, New England J Med 1994

What is the mental representation of CKD ?

- Irreversible loss of nephrons

- VS



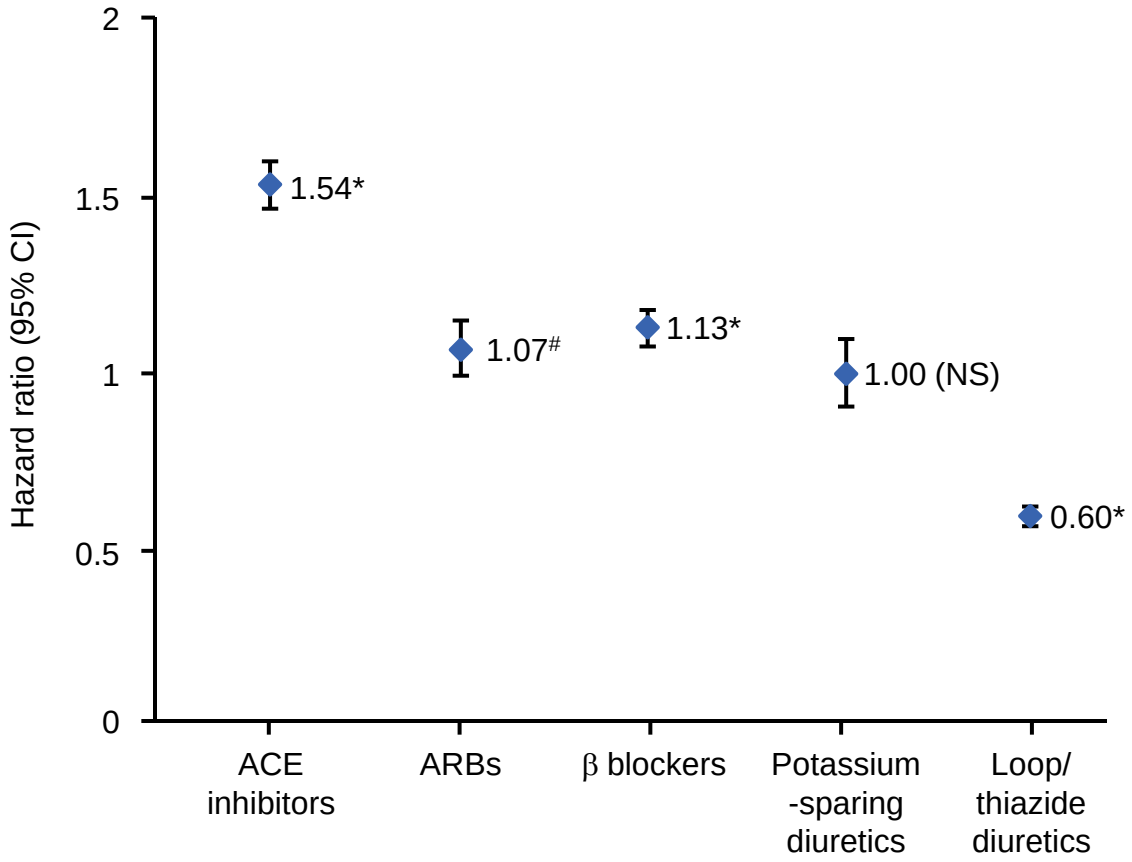
- Individual glomerular hemodynamic variation induced by RAASi

RAAS inhibition causes hyperkalaemia

In a 3-year evaluation of 194,456 patients:

Baseline use of antihypertensive medications increased the risk of hyperkalaemia*

- ACEi
  - 54% increase in risk
- ARBs
  - 7% increase in risk
- Beta-blockers
  - 13% increase in risk
- Potassium-sparing diuretics
  - No increase in risk
- Loop/thiazide diuretics
  - Decrease in risk



*Defined as K^+>5 mEq/L
CI, confidence interval

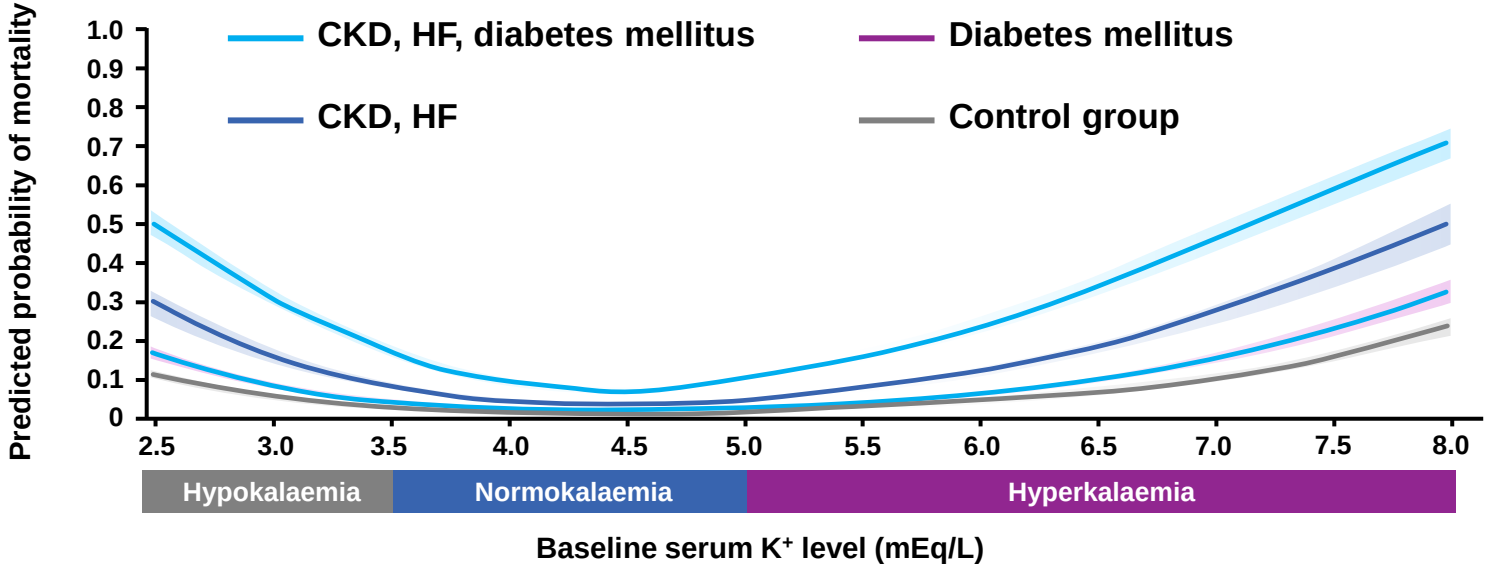
Chang AR *et al. Hypertension* 2016;67:1181–8

Hyperkalaemia is associated with an increase in all-cause mortality in at-risk populations

All-cause mortality was significantly elevated for every 0.1 mEq/L change in serum K^+ <4.0 mEq/L and ≥5.0 mEq/L[1]

- Comorbidities included CKD stages 3–5, HF and diabetes mellitus
- Definitions of hyperkalaemia vary, but it is typically defined as serum K^+ levels >5.0 mEq/L[2,3]

Adjusted mortality by serum K^+ level in patients*

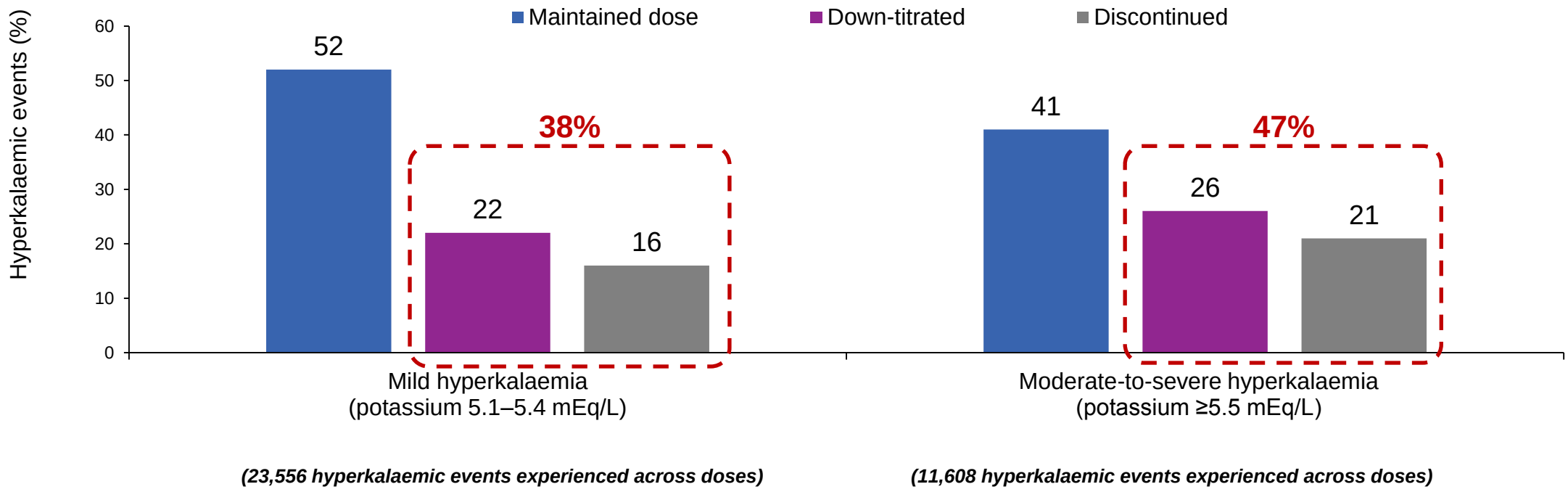


*Shading in the graph indicates 95% confidence limits

1. Collins AJ *et al. Am J Nephrol* 2017;
2. Rastegar A *et al. Postgrad Med J* 2001;77:759–64;
3. Kovesdy CP. *Am J Med* 2015;128:1281–7

Hyperkalaemia is one of the principal reasons for reducing or stopping RAASi therapy*

Patients on maximal RAASi dose had their treatment reduced or stopped after a hyperkalaemic event nearly half the time



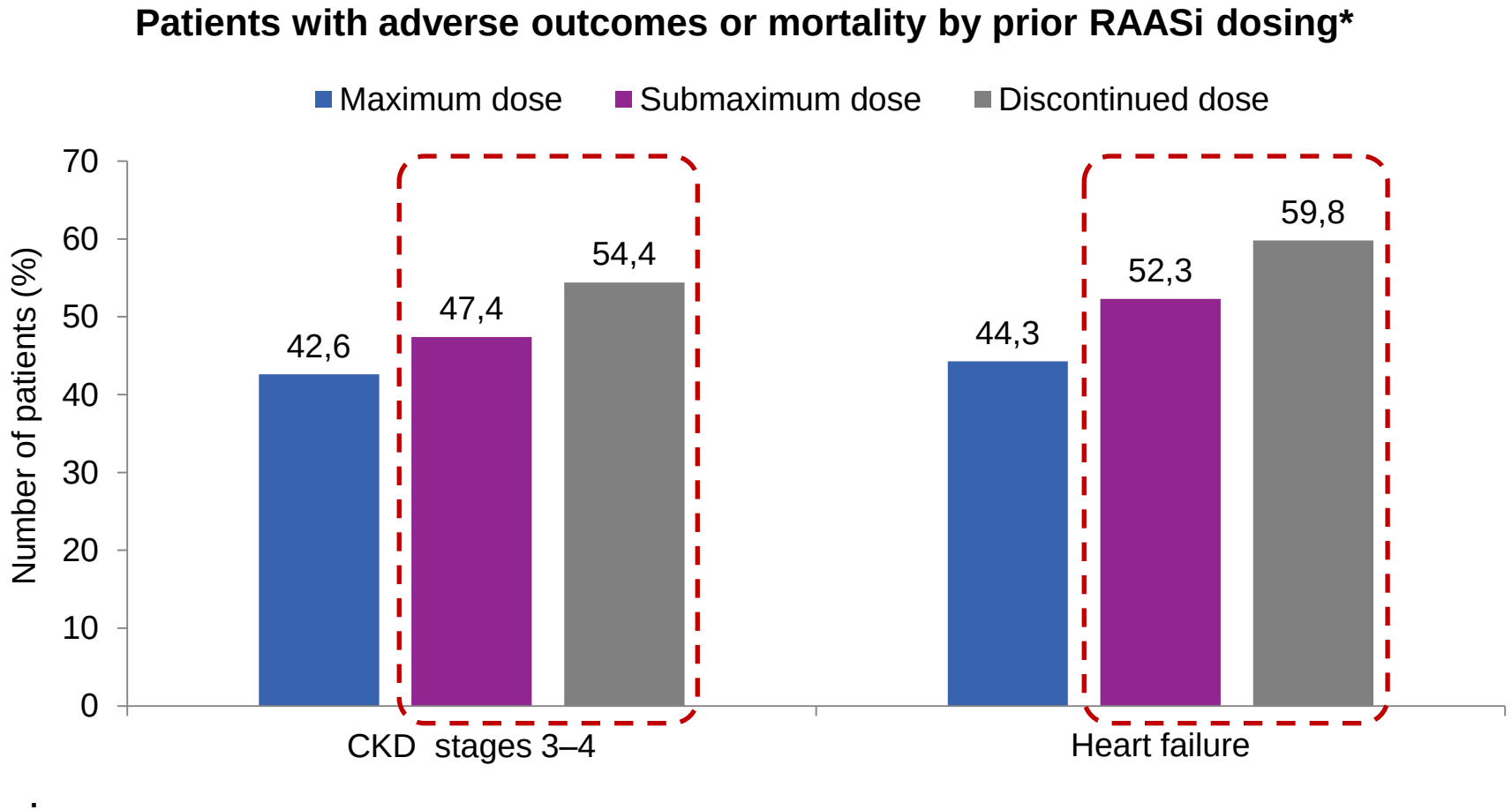
(23,556 hyperkalaemic events experienced across doses)

(11,608 hyperkalaemic events experienced across doses)

*Patients with CKD at stages 3–5 were enlisted within the study. Only those patients who were on maximum RAASi dose were included within this part of the study (which is why the total numbers do not equal 100%)

Epstein M *et al. Am J Manag Care.* 2015;21:S212–20

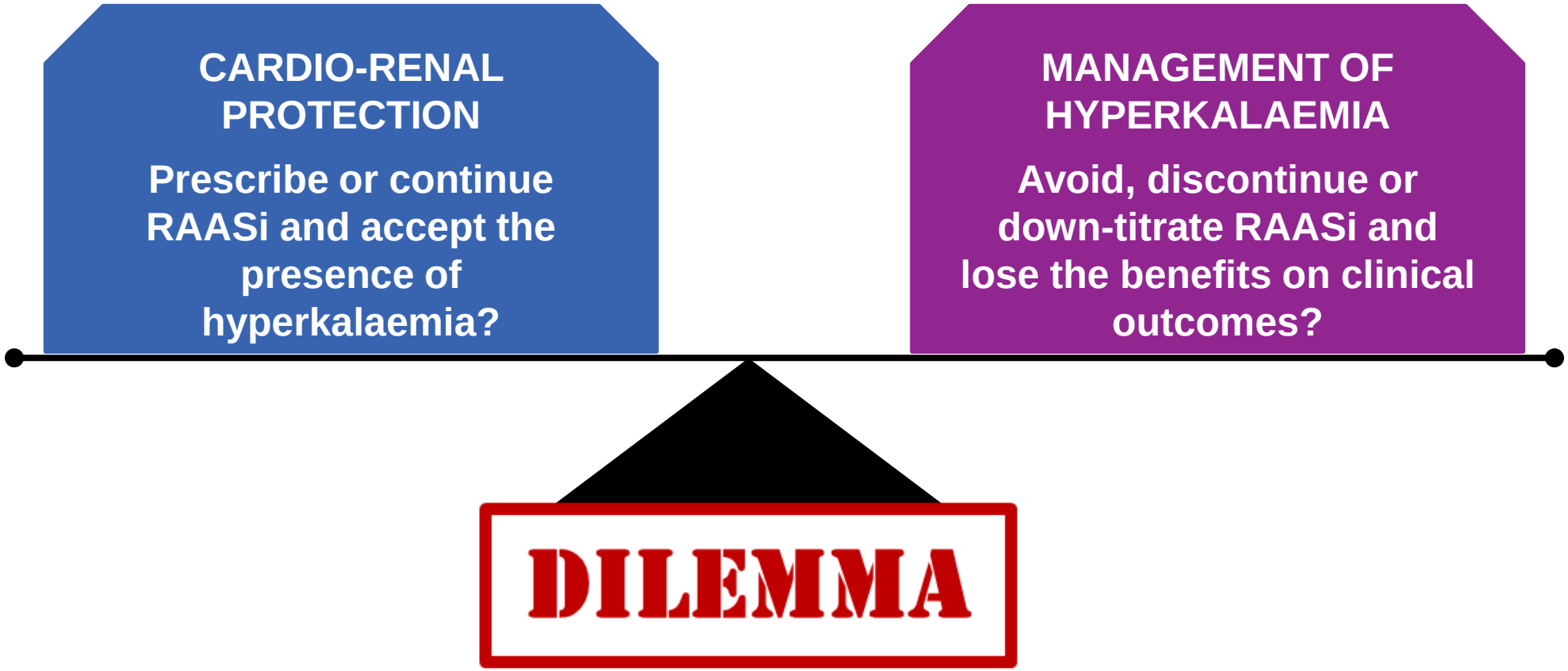
Sub-maximum dosing and early discontinuation of RAASi is associated with poor patient outcomes



*This was a retrospective database analysis, and therefore cannot detect casuality and can only provide associations in the real-world setting

Epstein M *et al. Am J Manag Care.* 2015;21:S212–20

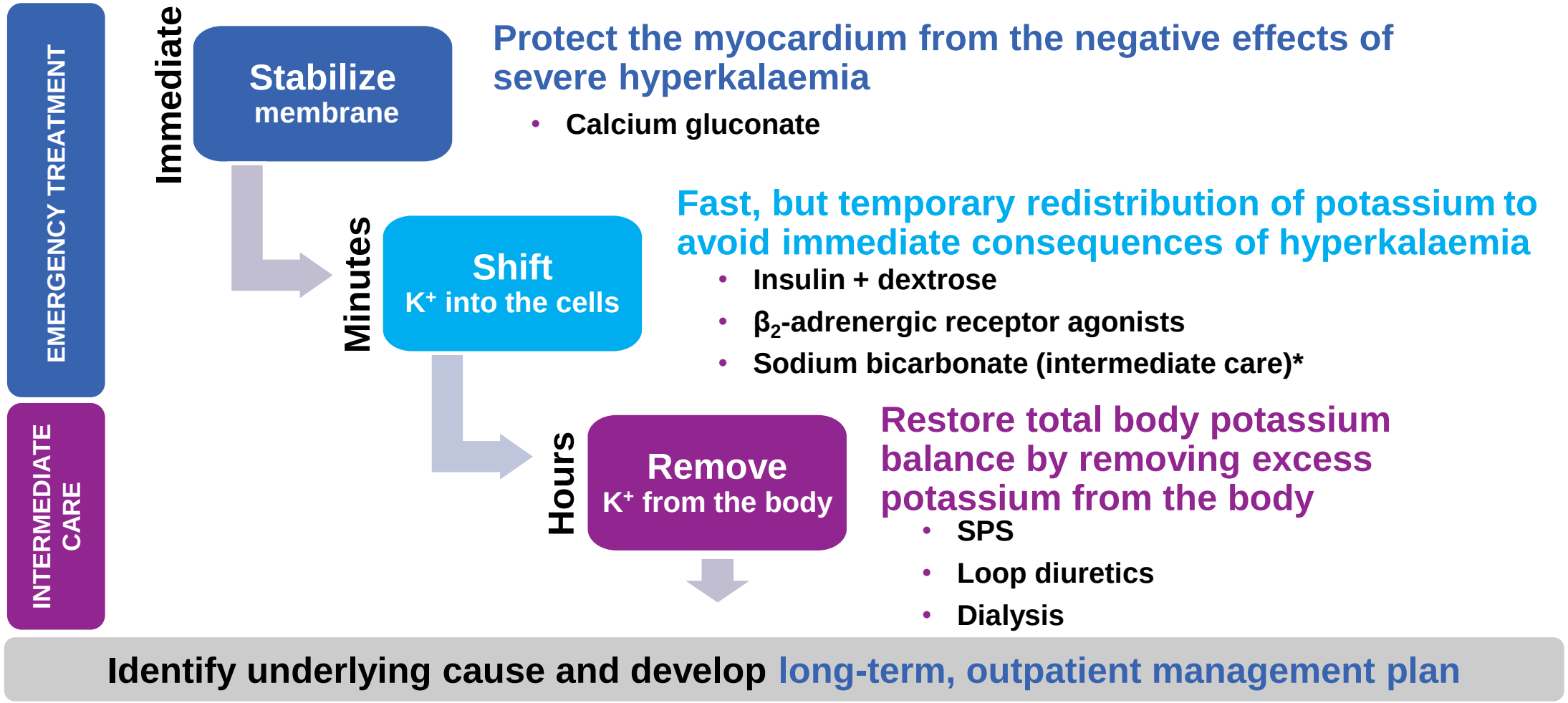
The problem: Hyperkalaemia versus RAASi benefits



RAASi, renin–angiotensin–aldosterone system inhibitor

Palmer BF *et al. N Engl J Med* 2004;351:585–92

Treatment options for hyperkalaemia: No effective long-term option



*may be used for intermediate care to shift potassium into cells when metabolic acidosis is the cause of hyperkalaemia. SPS, sodium polystyrene sulfonate

Dunn JD *et al*. *Am J Manag Care* 2015;21:S307–15

Limitations of current treatments for hyperkalaemia

Strategy	Limitation
Dietary potassium restriction[1]	• Difficult to adhere to a low-potassium diet • Contradictory to a sodium-restricted diet, which may be recommended in patients at risk for hyperkalaemia due to comorbid conditions

BP, blood pressure; CV; cardiovascular;
HFrEF, heart failure with reduced ejection fraction

1. National Kidney Foundation. https://www2.kidney.org/professionals/KDOQI/guidelines_bp/guide_11.htm;
2. Pitt B, Rossignol P. *Clin Pharmacol Ther* 2017;102:389–91;
3. Kayexalate® US prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011287s023lbl.pdf;
4. Dunn JD *et al. Am J Manag Care* 2015;21:S307–15

Long-term management of hyperkalaemia

- RAASi have demonstrated cardio-renal protective benefits
- Many patients are discontinuing or receiving suboptimal doses of RAASi therapy due to concerns over hyperkalaemia
- This has serious health and economic implications due to adverse renal and cardiovascular events
- There is an unmet need for an effective long-term treatment for hyperkalaemia that enables patients to:
  - Also receive RAASi therapy, or
  - Receive RAASi at target doses