Novità in tema di blocco del RAAS

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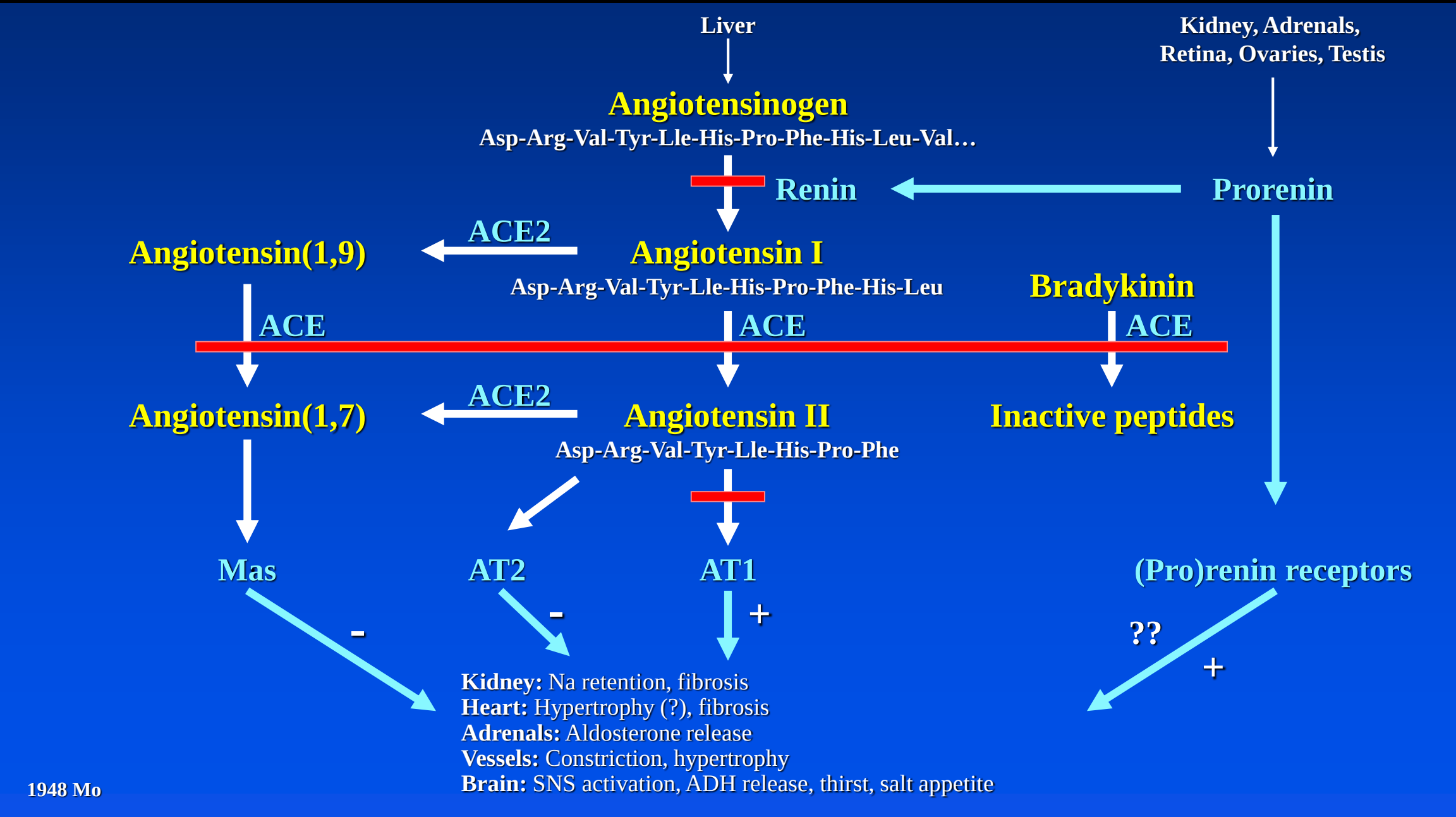
Different Levels of Pharmacological Blockade of the Renin-Angiotensin System



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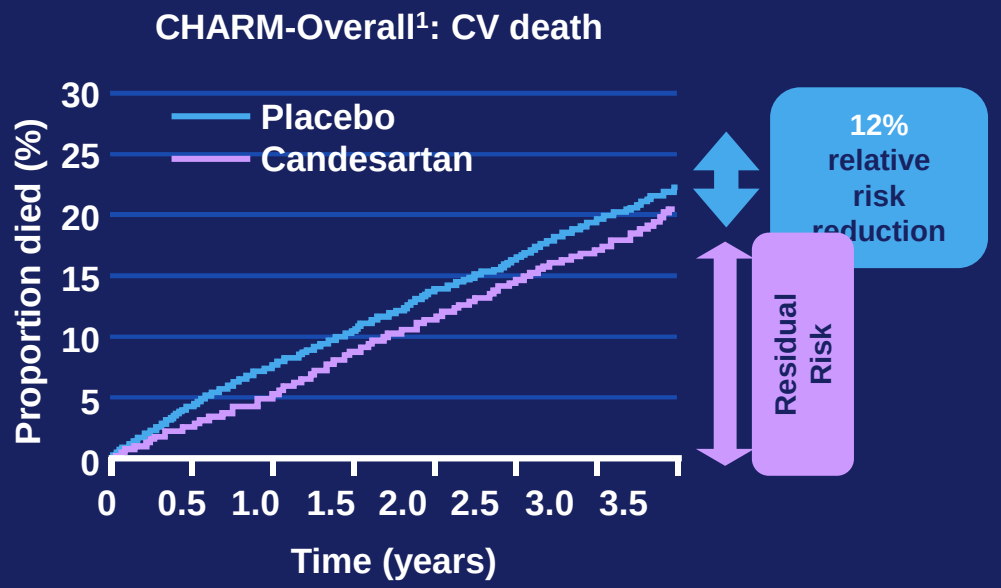
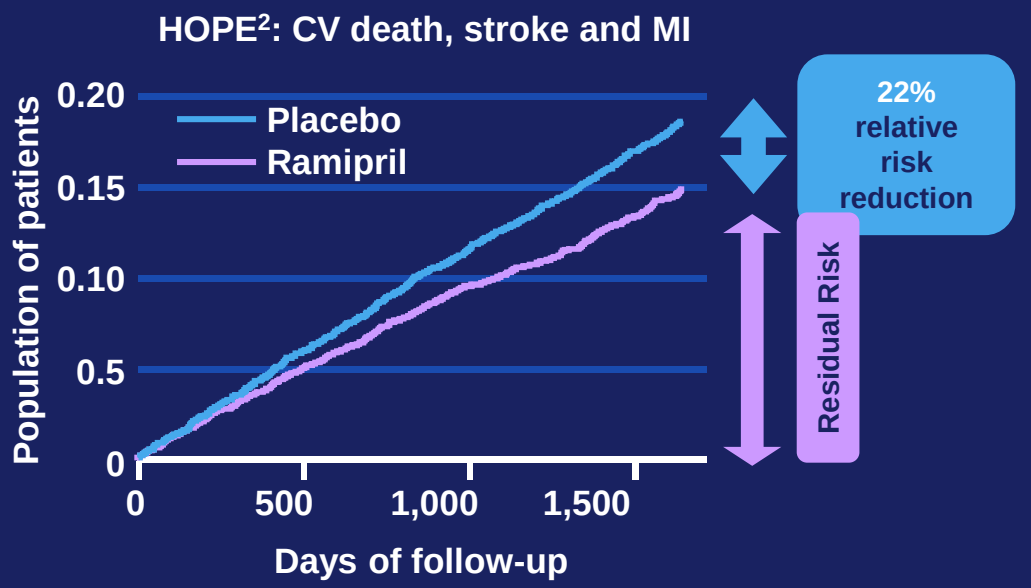
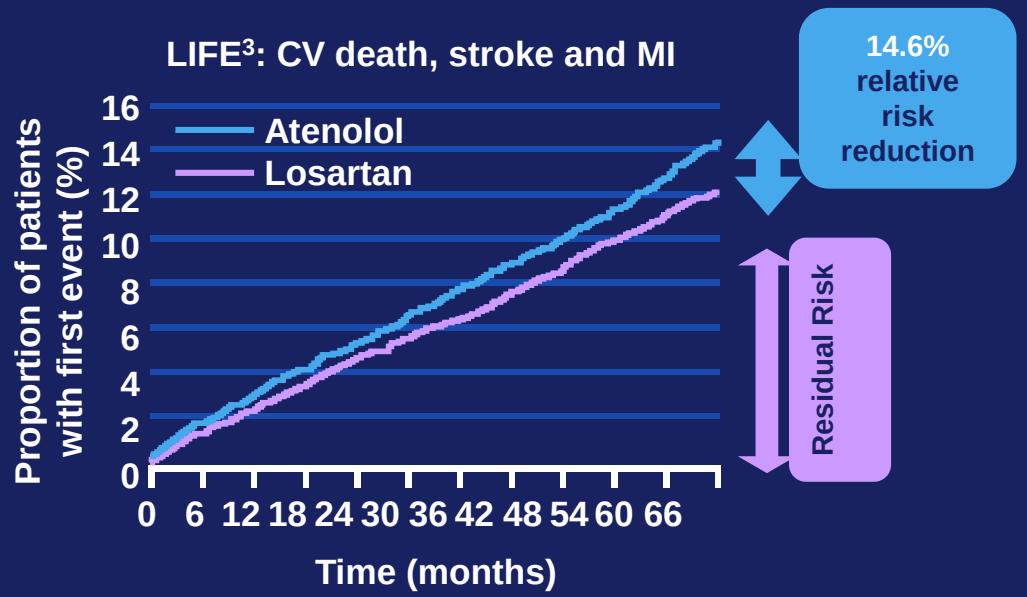
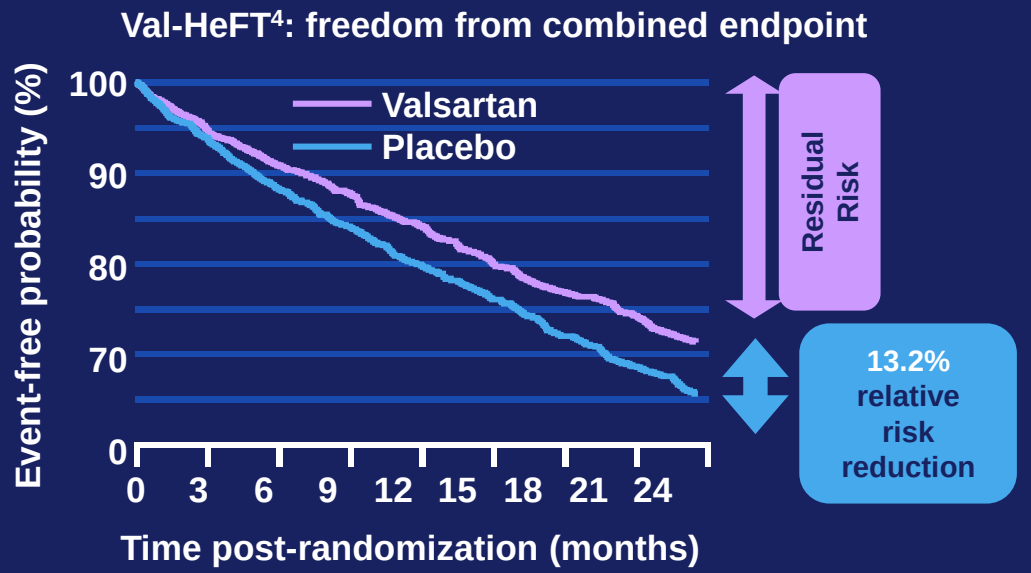
Residual risk: morbidity and mortality remains high, despite treatment with ACEIs and ARBs





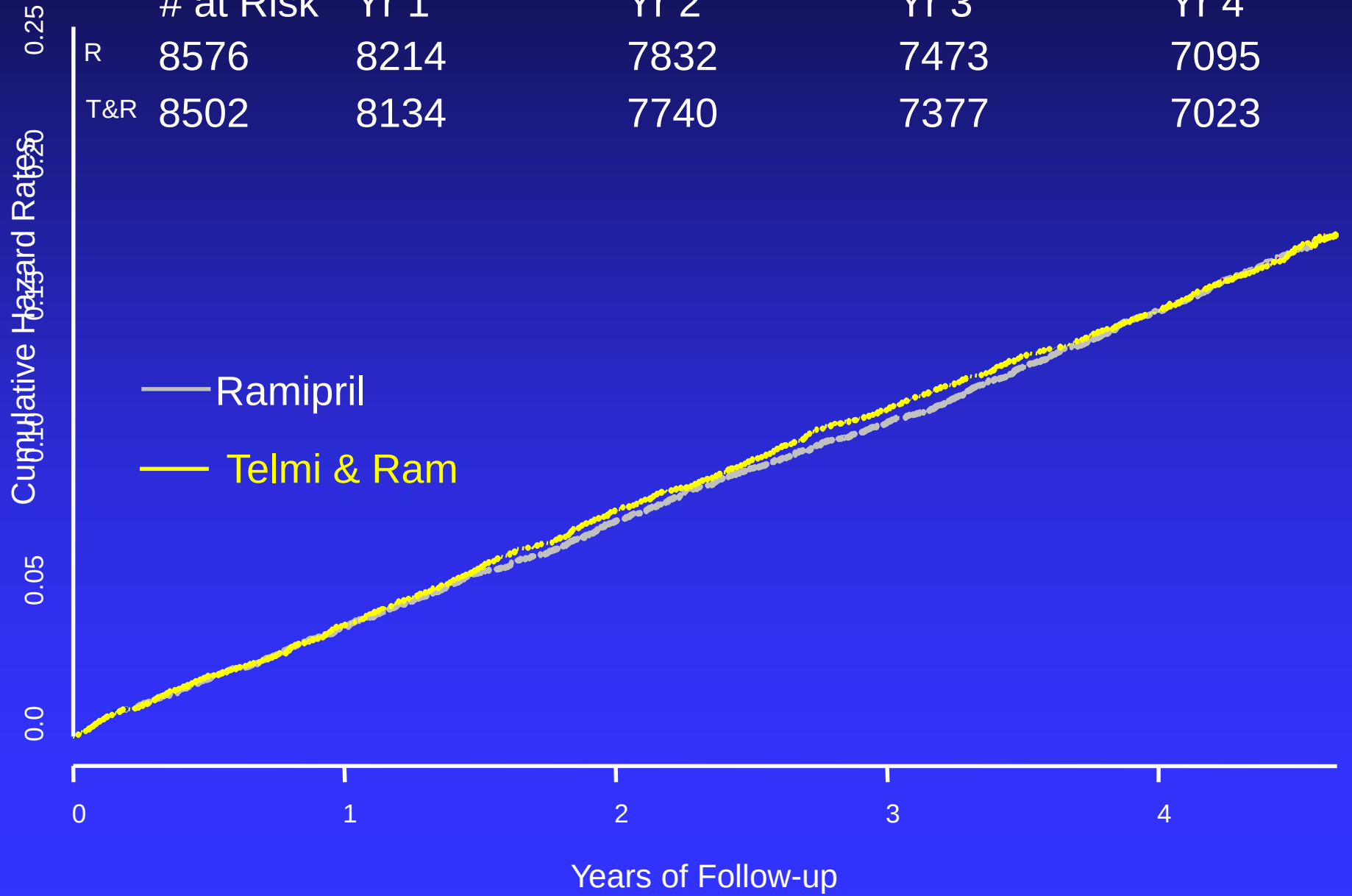




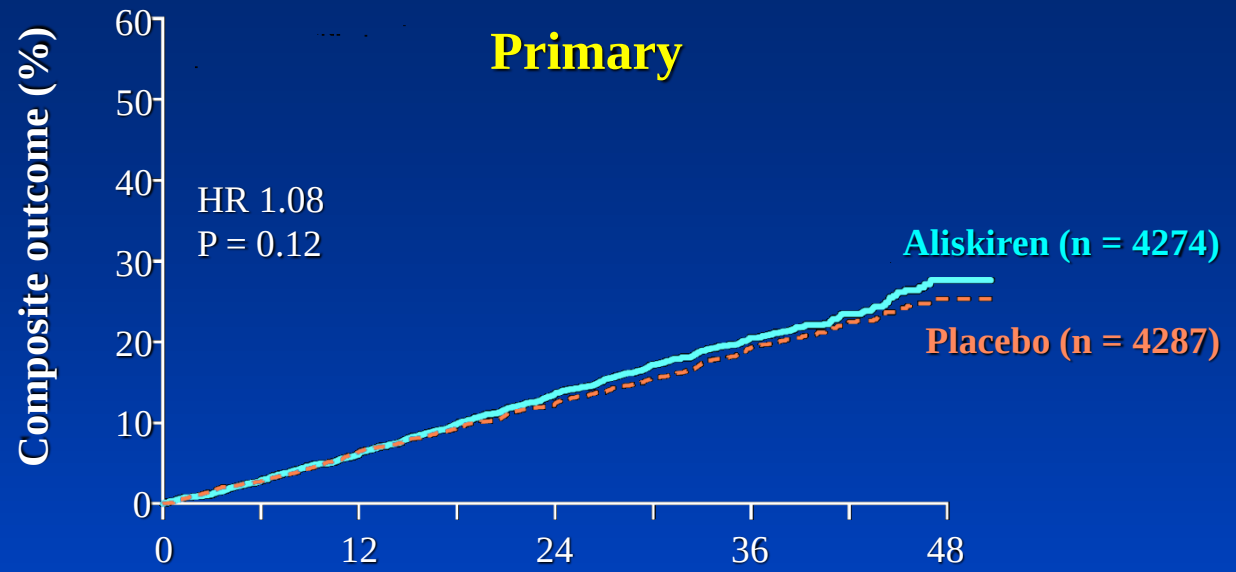
[1]Pfeffer et al. Lancet 2003;362:759–66; [2]Yusuf et al. N Engl J Med 2000;342:145–53; [3]Dahlöf et al. Lancet 2002;359:995–1003; [4]Cohn et al. N Engl J Med 2001;345:1667–75

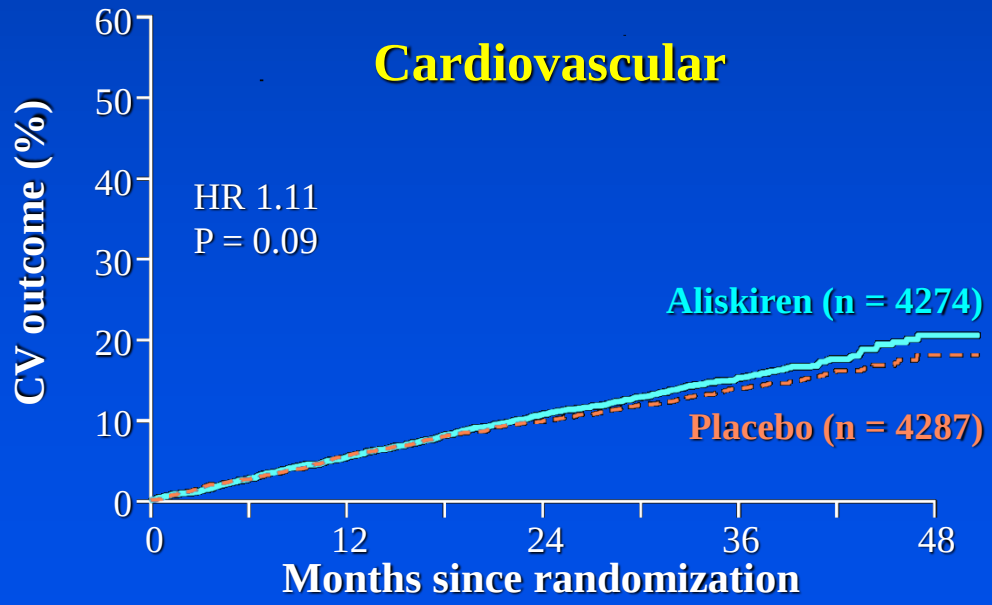
ONTARGET: Time to Primary Outcome

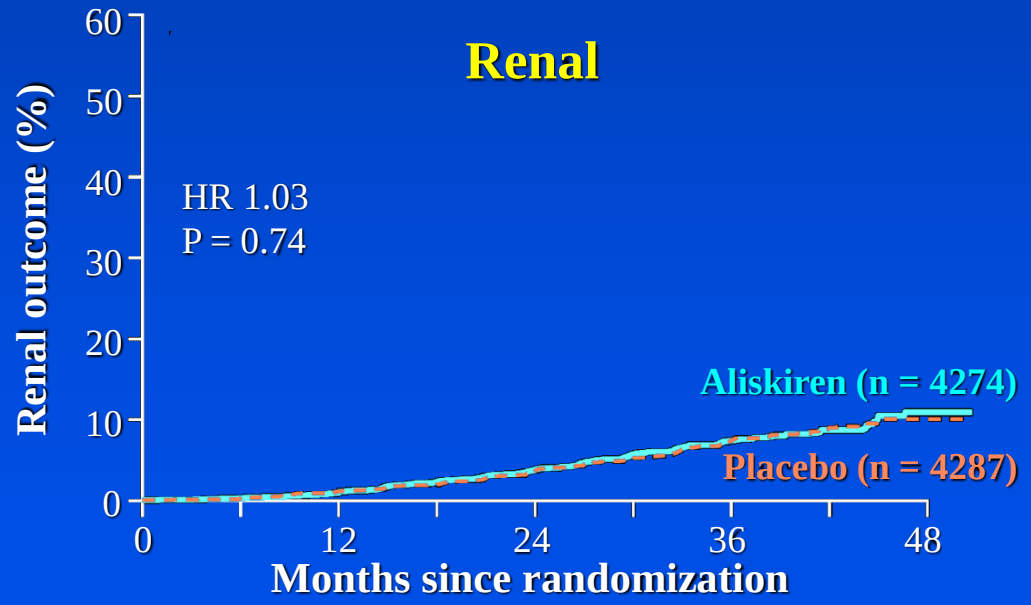
	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
R	8576	8214	7832	7473	7095
T&R	8502	8134	7740	7377	7023



Composite, cardiac and renal outcome in ALTITUDE study







Parving HH et al., NEJM 2012; 367: 2204-2213

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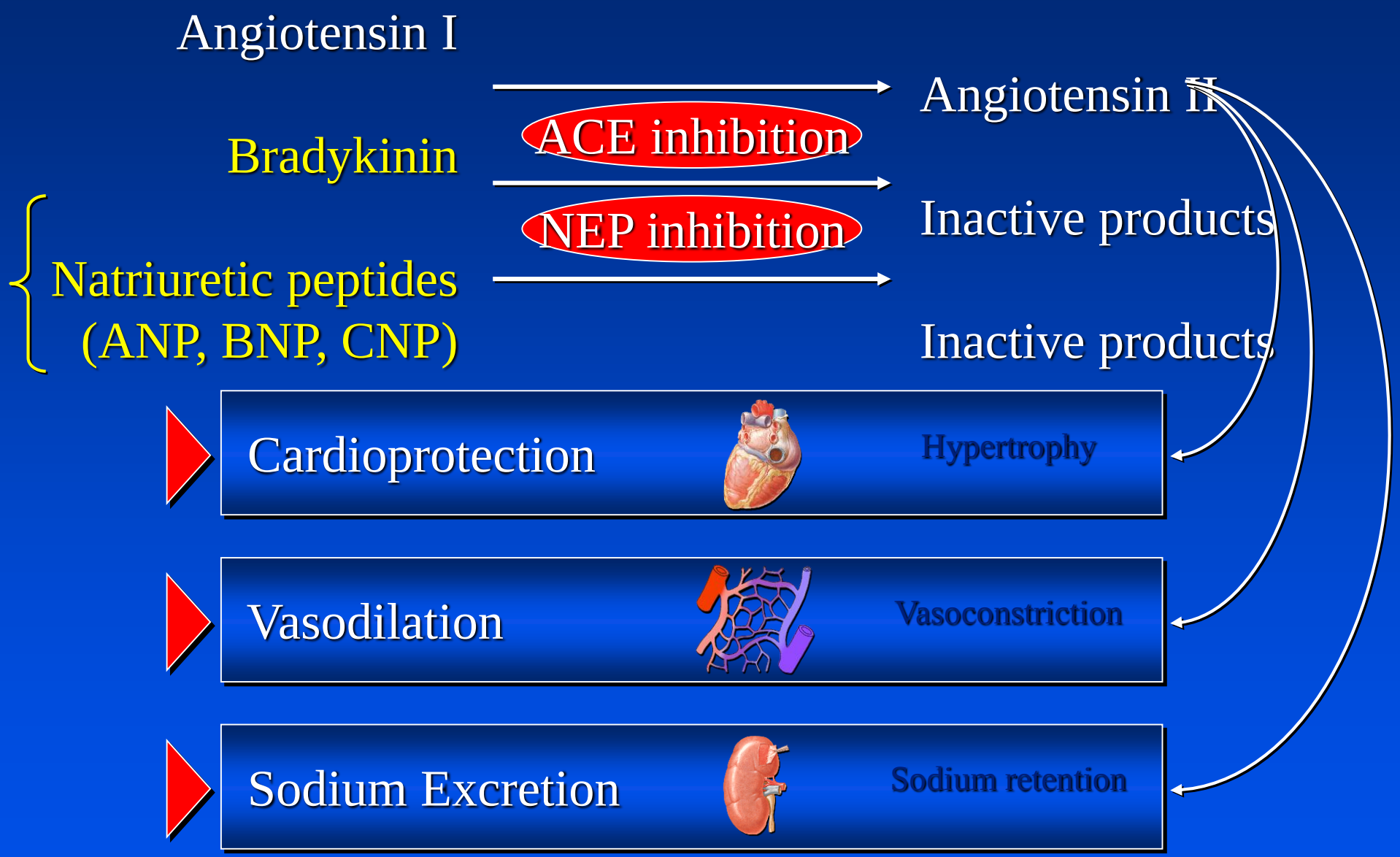
Most commonly reported adverse events in ALTITUDE study

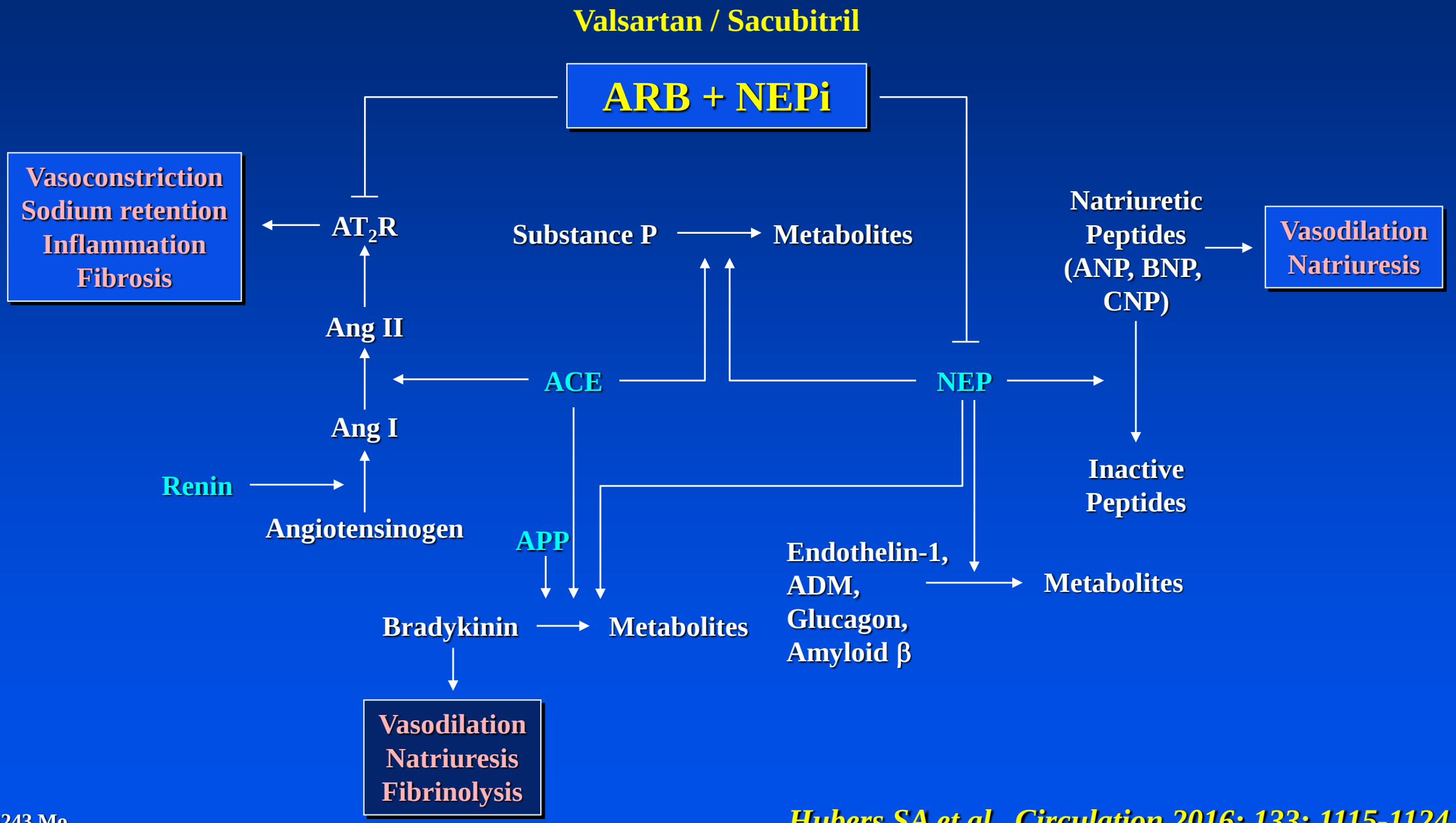
Event	Any event reported		
	Aliskiren (n = 4272)	Placebo (n = 4285)	P value
	no. of patients (%)		
Hyperkalemia	1670 (39.1)	1244 (29.0)	<0.001
Hypotension	519 (12.1)	357 (8.3)	<0.001
Diarrhea	417 (9.8)	312 (7.3)	<0.001
Renal impairment	418 (9.8)	371 (8.7)	0.07

Parving HH et al., NEJM 2012; 367: 2204-2213

Omapatrilat: Pharmacologic Actions



Mechanisms of action of ARNI



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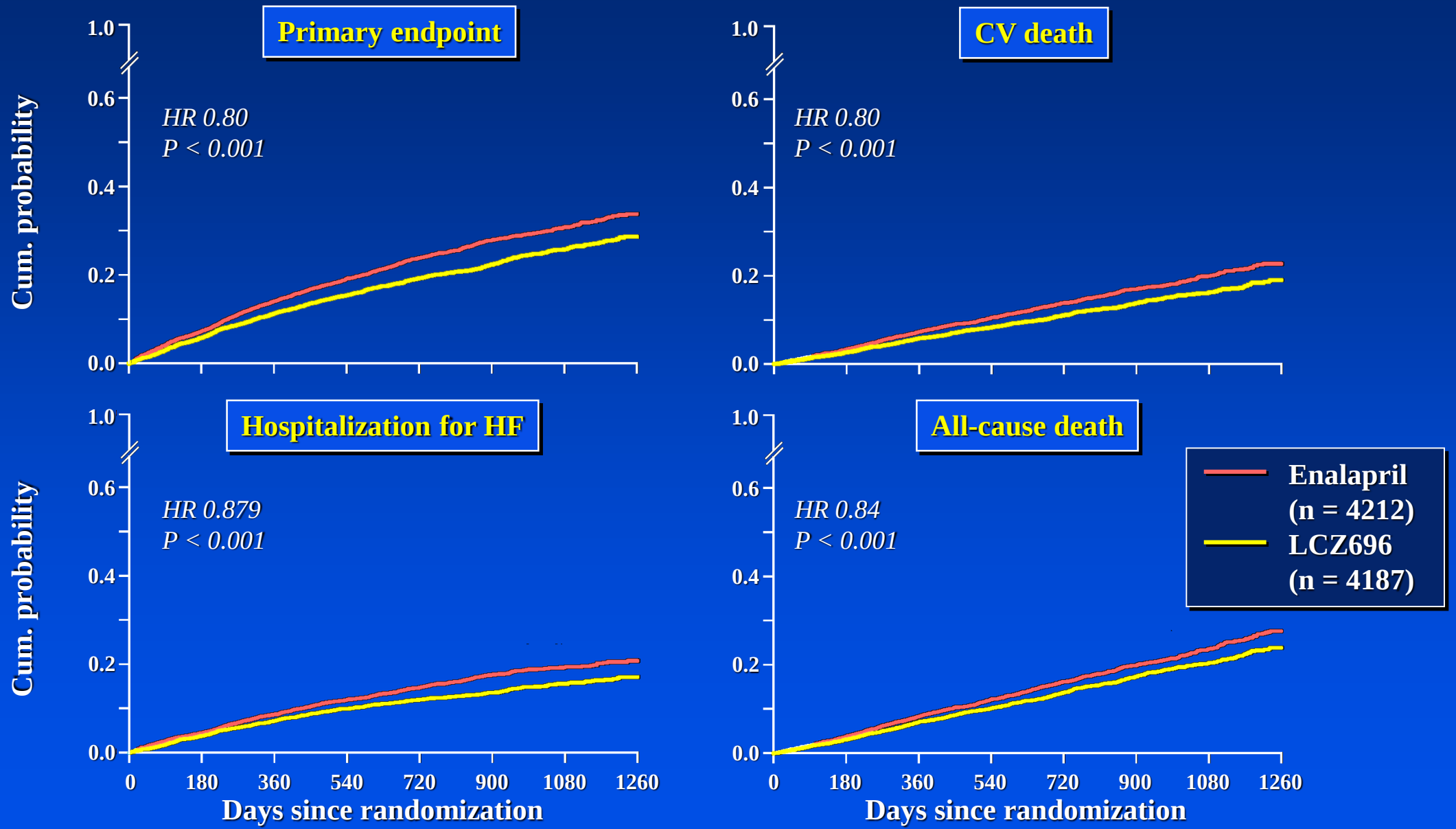
Hubers SA et al., Circulation 2016; 133: 1115-1124

Change in mean systolic and diastolic blood pressure during treatment with angiotensin-neprilysin inhibitor (LCZ696)

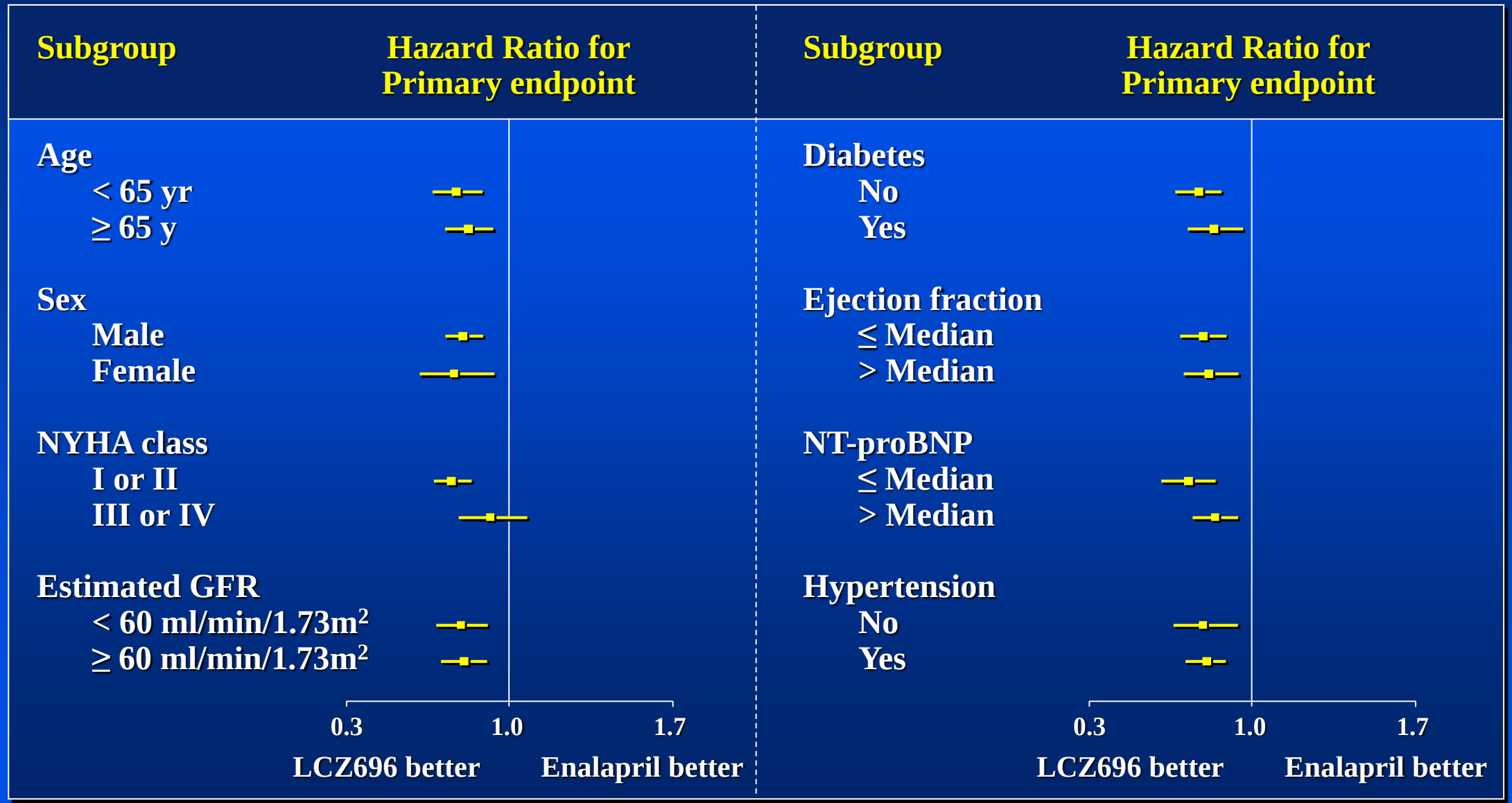
Ruilope LM et al., Lancet 2010; 375: 1255-1266

Outcome in angiotensin-neprilysin inhibitor (PARADIGM-HF) study



McMurray S et al., NEJM 2014; 371: 993-1004

Effects of ARNI in patients with HF by prespecified groups



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McMurray JJV et al., New Engl J Med 2014; 371: 993-1004

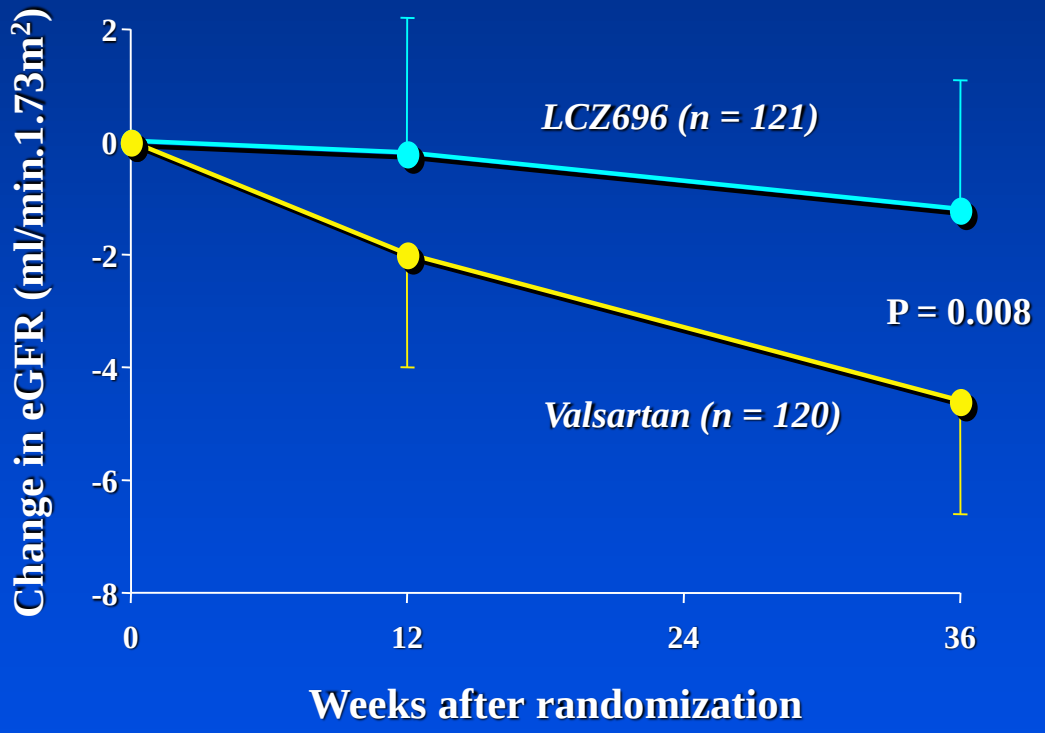
Adverse events in PARADIGM-HF study

Event	LCZ696 (n = 4187)	Enalapril (n = 4212)	P value
	no. of patients (%)		
Hypotension Symptomatic with SBP < 90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine ≥ 3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium > 6.0 mmol/	181 (4.3)	236 (5.6)	0.007
Angioedema	10 (0.2)	5 (0.1)	0.19

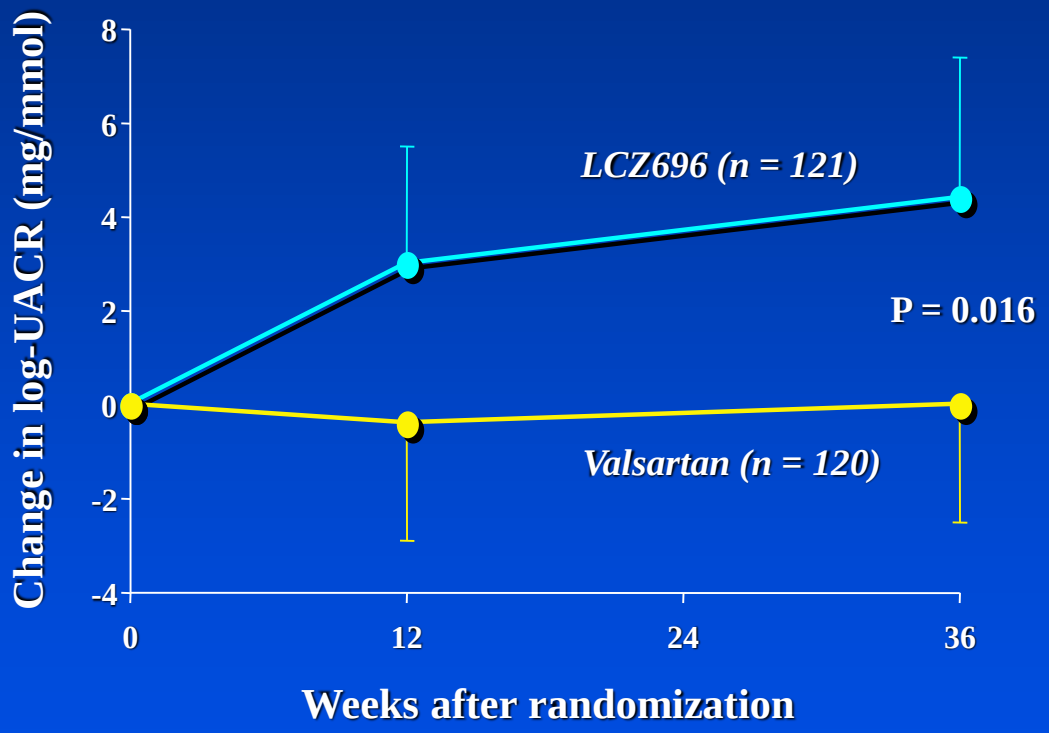
McMurray S et al., NEJM 2014; 371: 993-1004

Changes in eGFR and urinary ACR induced by ARNI treatment in patients with HF and preserved EF (Paramount Study)

Change in eGFR



Change in UACR



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Voors AA et al., Eur J Heart Fail 2015; 17: 510-517

Effects of ARNI on plasma renin and aldosterone in HT patients

		LCZ696 dose (mg/day)		
		100	200	400
Renin	n	21	46	56
	Baseline (mU/l)	11	10.2	11.3
	Mean change (%)	+72	+94	+157
	P <	0.01	0.01	0.01
Aldosterone	n	43	58	67
	Baseline (pmol/l)	238	231	227
	Mean change (%)	+14	+4	+8
	P <	n.s.	n.s.	n.s.

Ruilope L et al., Lancet 2010; 375: 1255-1266

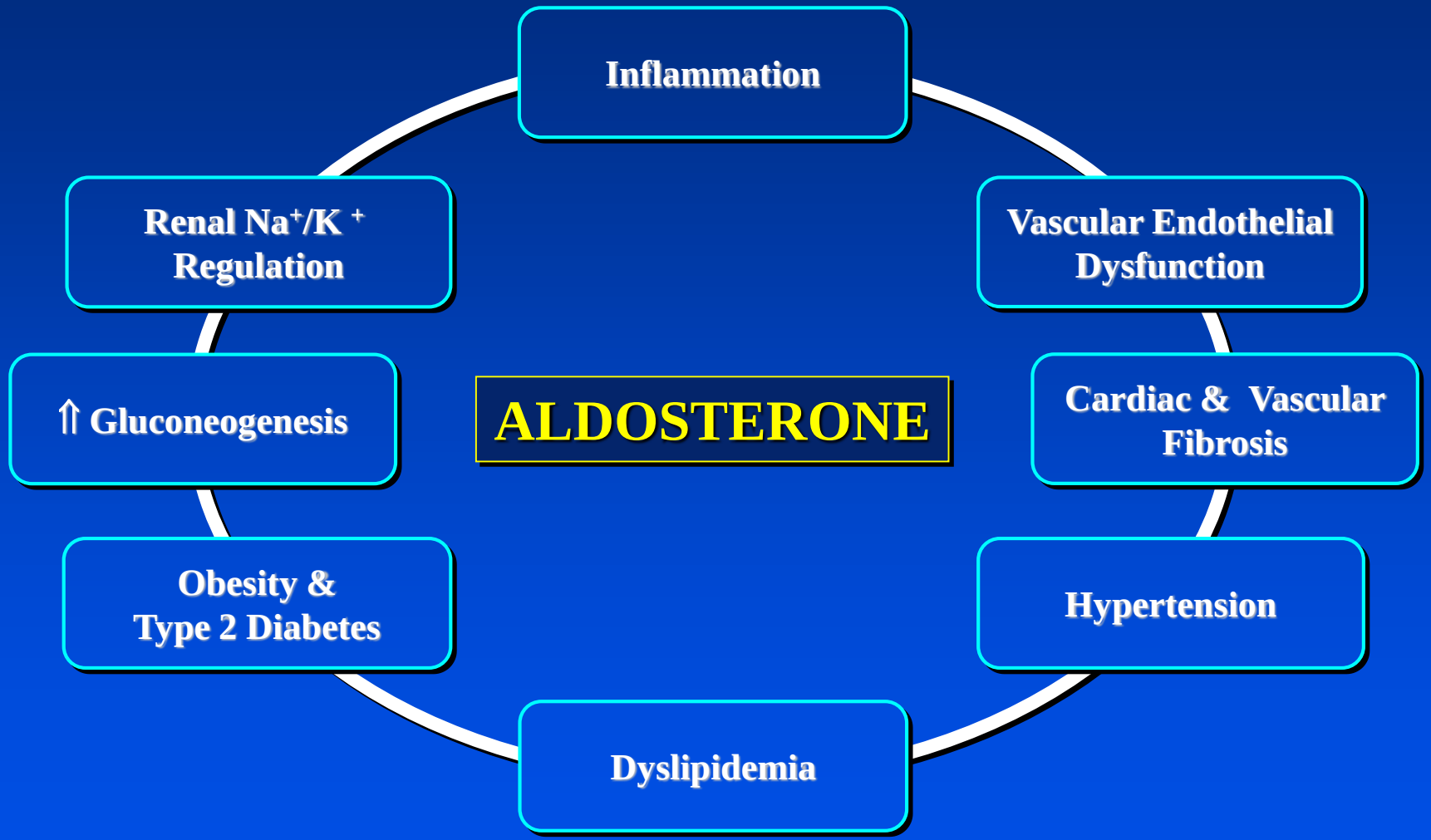
Incidence of aldosterone “escape” phenomenon during treatment with RAS inhibitors

Definition	Duration of treatment	
	6 months	12 months
Any increase from baseline	40%	53%
Aldosterone above levels in healthy subjects	10%	38%
In patients with CHF	10%	38%
In patients without CHF	40%	53%

556 patients from 8 studies

Bomback AS et al., Nat Clin Prac Nephrol 2007; 3: 486-492

Pleiotropic aldosterone actions contributing to the pathogenesis of cardiovascular diseases



Ferrario CM, Schiffrin EL, Circ Res 2015; 116:206-213

Associations between aldosterone and different comorbidities in the general community

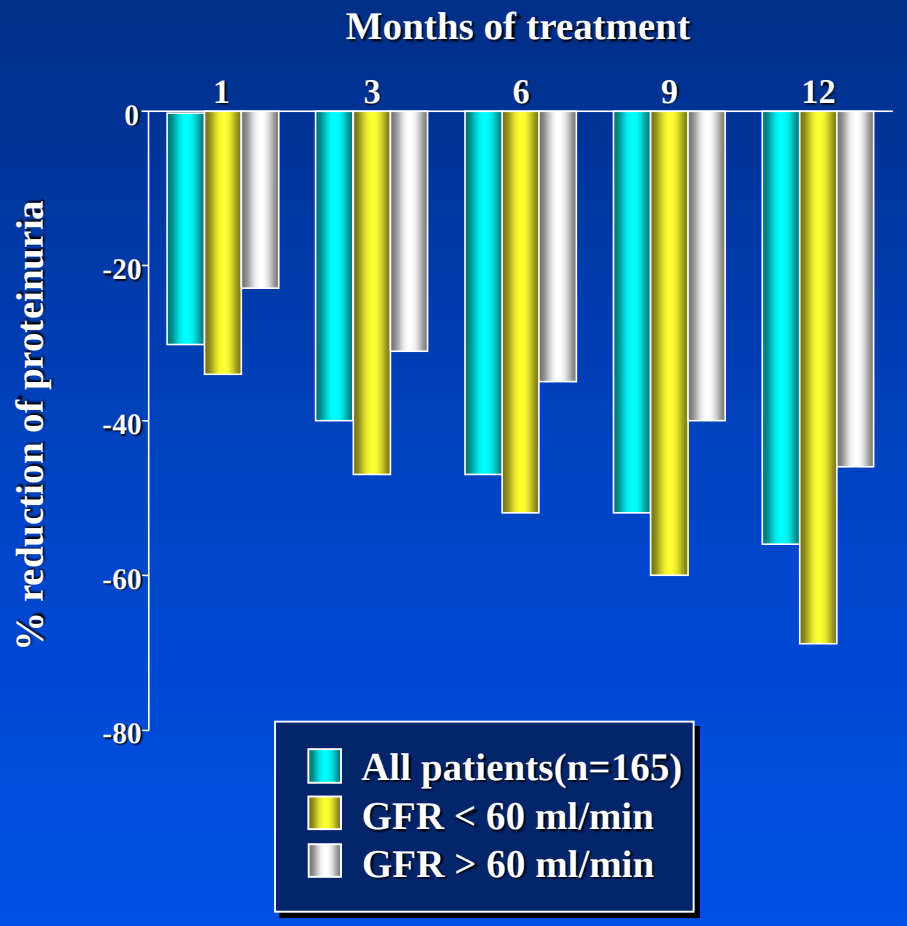
Comorbidity	OR Top tertile of aldosterone
Hypertension (n = 478)	2.45
Obesity (n = 535)	1.69
CKD (n = 243)	1.75
Central obesity (n =554)	1.61
Metabolic syndrome (n = 352)	1.53
Concentric LVH (n = 251)	1.31

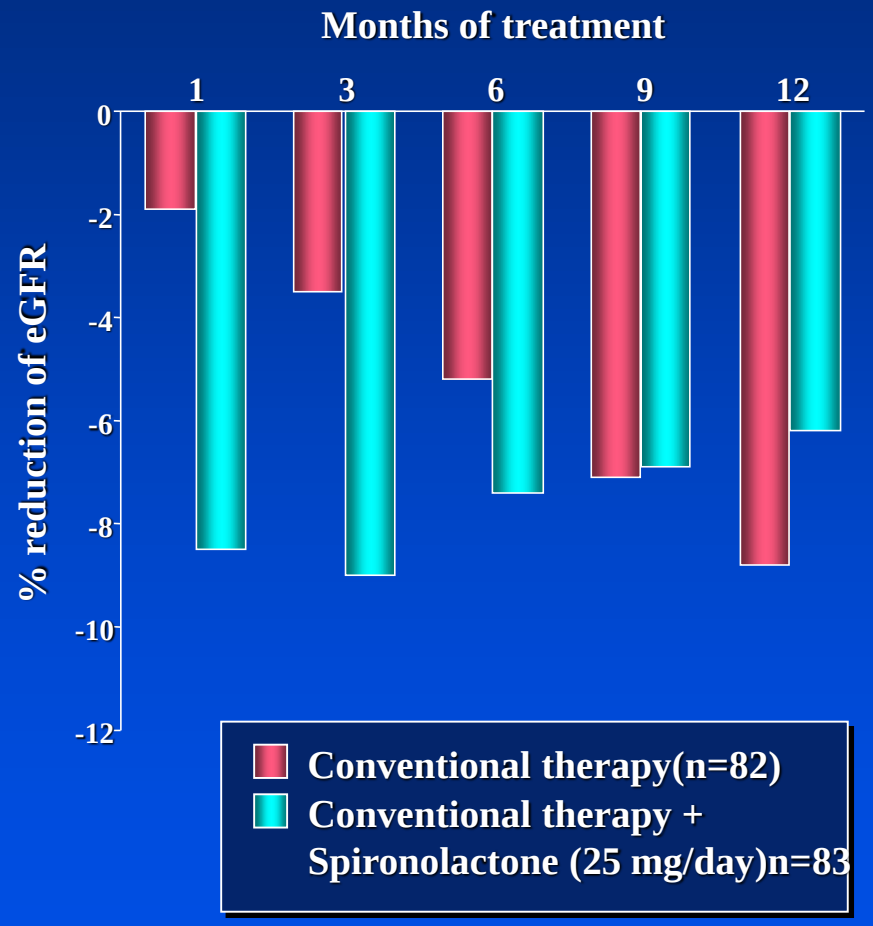
Buglioni A et al., Hypertension 2015; 65: 45-53

Anti-aldosterone medications

	Denomination	Development
Aldosterone receptor antagonist (ARA)	Spironolactone	Early 1960s
	Canrenone	1980s
	Eplerenone	2000s
Non-steroids	Some DHP CCBs (nimodipine, felodipine, nitredipine, finerenone)	2000s
Aldosterone biosynthesis inhibitor (ASI)	BR-4628, FAD 286, LCI 1699	2010s

Percent decline of proteinuria and eGFR in patients with CKD treated with spironolactone in addition to conventional therapy including RAS inhibitors





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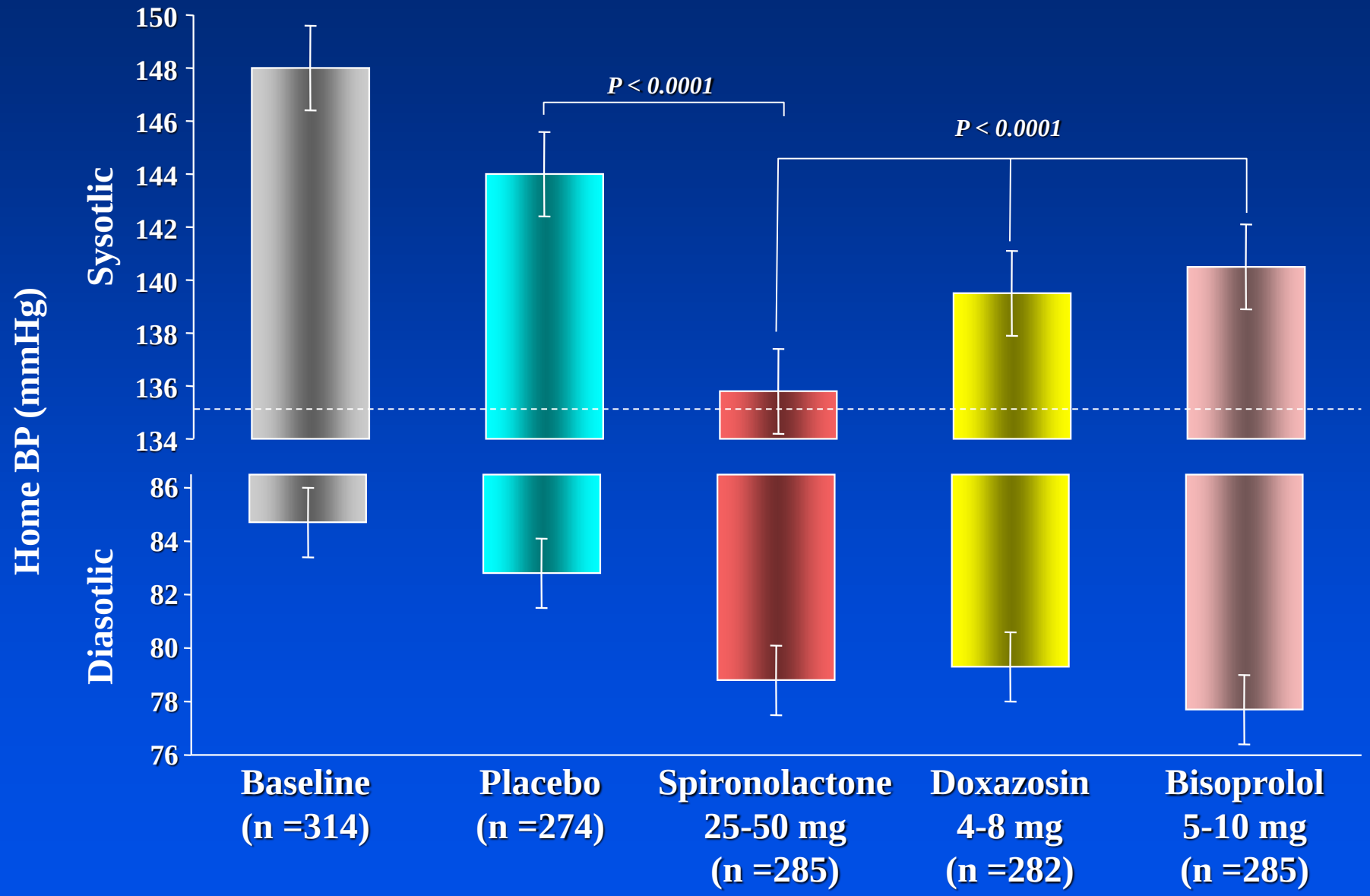
Bianchi S et al., Kidney Int 2006; 70: 2116-2123

Home blood pressure during treatment with spironolactone, doxazosin and bisoprolol in patients with resistant hypertension



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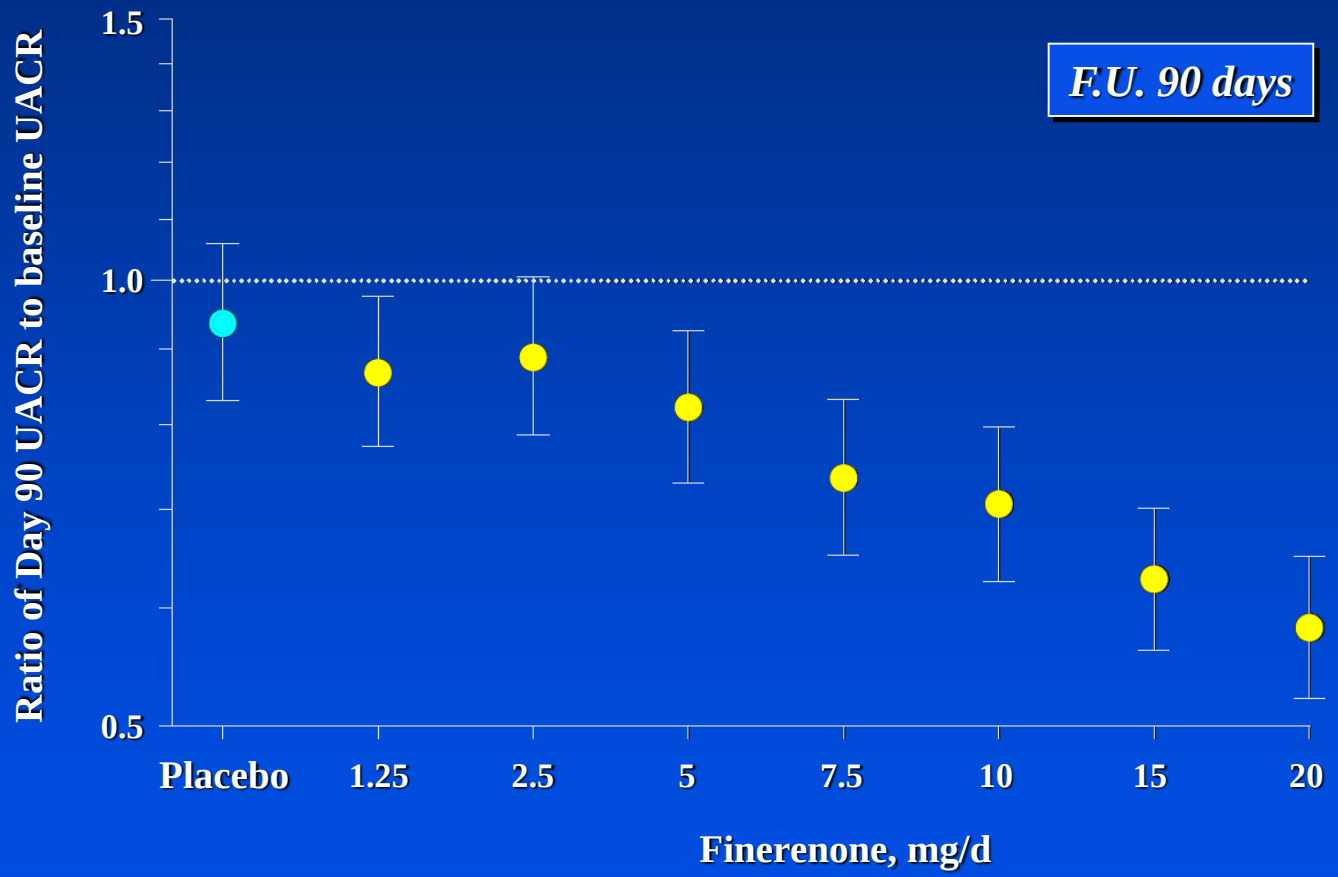
Williams B et al., Lancet 2015; 386: 2059-2068

Pharmacological characteristics of finerenone

- Non-steroidal compound
- Dihydropyridine derivative devoid of action on L-type CC
- High affinity for MR
- Long lasting binding to MR (protrusion of receptor domain critical for binding)
- Changes of MR co-activators and co-repressors
- Equal distribution in heart and kidney
- At low dose lower binding to kidney MR

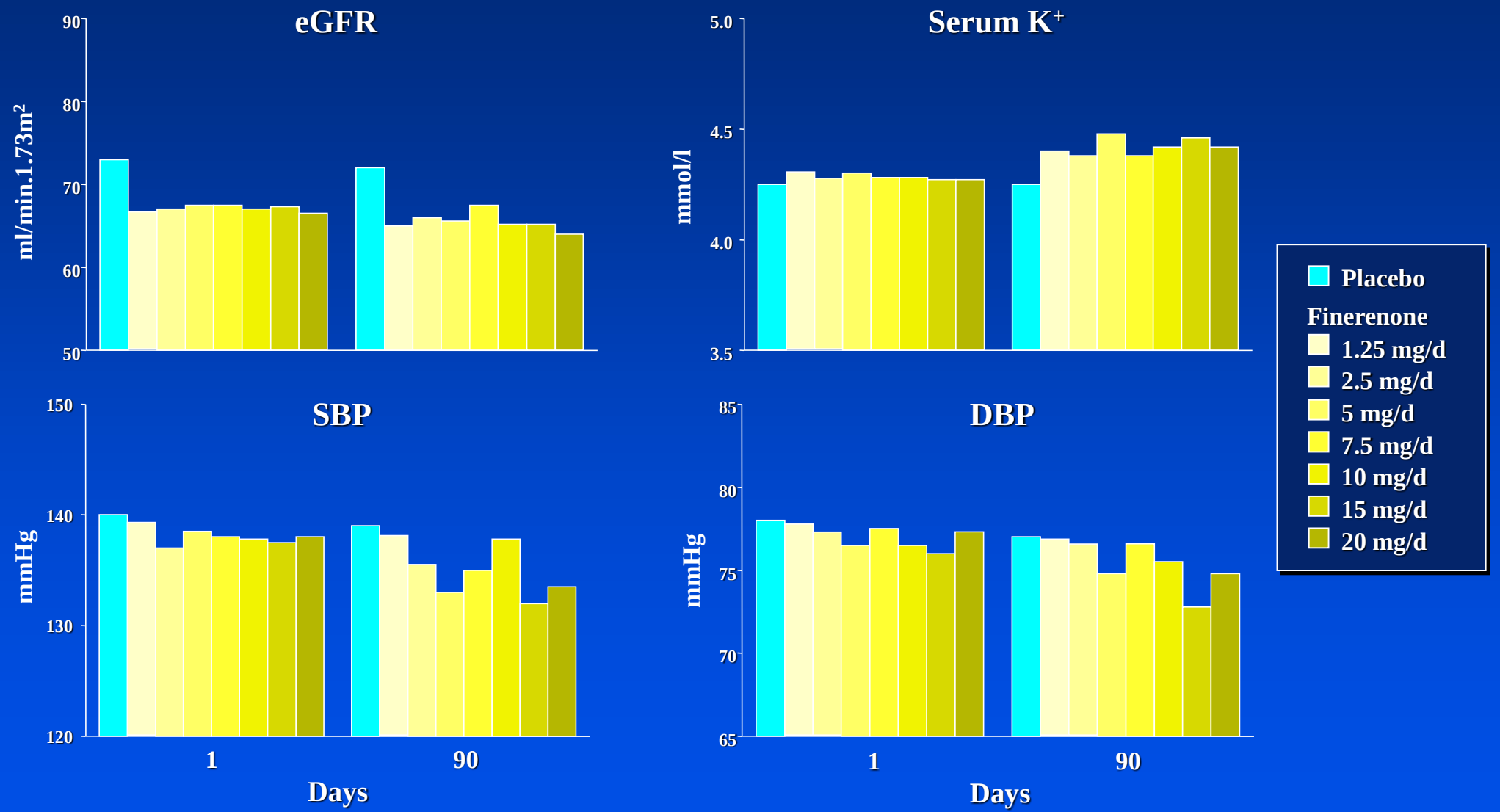
Change in UACR in patients with diabetic nephropathy treated with finerenone



3222 Mo

Bakris GL et al., JAMA 2015; 314: 884-894

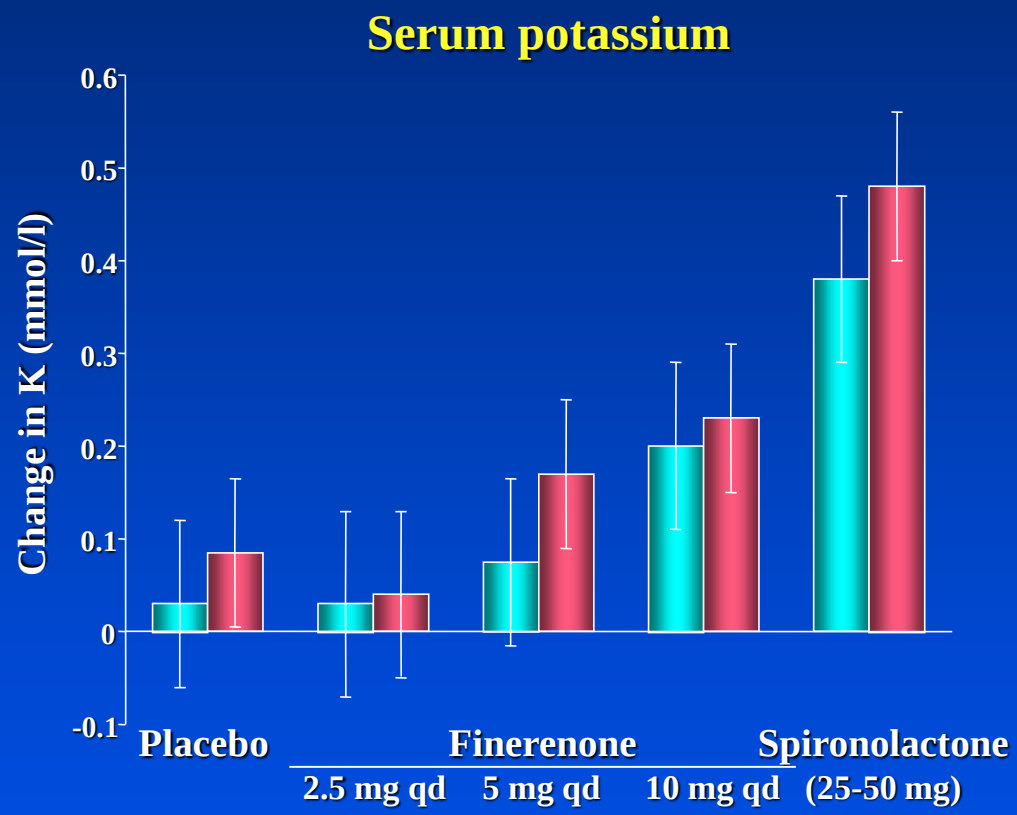
Changes in GFR, serum potassium, SBP and DBP induced by increasing doses of finerenone in patients with diabetic nephropathy

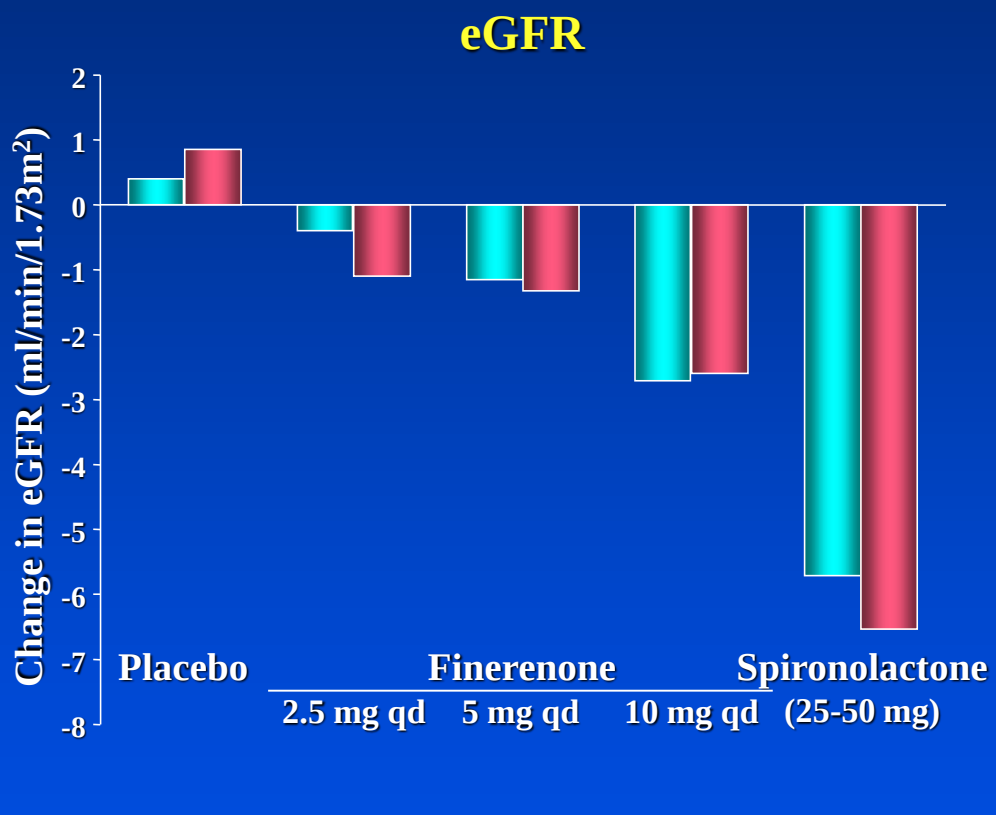


3221 Mo

Bakris GL et al., JAMA 2015; 314: 884-894

Changes in serum potassium and eGFR in patients with CHF and moderate CKD receiving finerenone or spironolactone





15 days treatment (n = 61)

29 days treatment (n = 57)

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Conclusioni

- Il nuovo antagonista del RAS agisce con un effetto combinato di blocco dei recettori dell'angiotensina II e di inibizione della neprelisina , una endopeptidasi neutra (ARNI),con conseguente aumento dei fattori natruretici con azione vasodilatante Questo farmaco ha dimostrato di ridurre efficacemente la pressione arteriosa e gli end point cardiovascolari nei pazienti con HF.
- Anche ARNI, a somiglianza degli altri antagonisti del RAS, non riduce significativamente l'aldosterone nei pazienti ipertesi. L'aldosterone , anche a livelli moderatamente elevati, può causare danni cardiovascolari e renali.
- Gli antialdosteronici convenzionali (spironolattone, eplerenone) sono efficaci antipertensivi, di prima scelta nelle ipertensioni resistenti e, come il nuovo finerenone, si sono dimostrati efficaci nella ridurre la microalbuminuria nella nefropatia diabetica.