ITALIAN CHAPTER

16° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

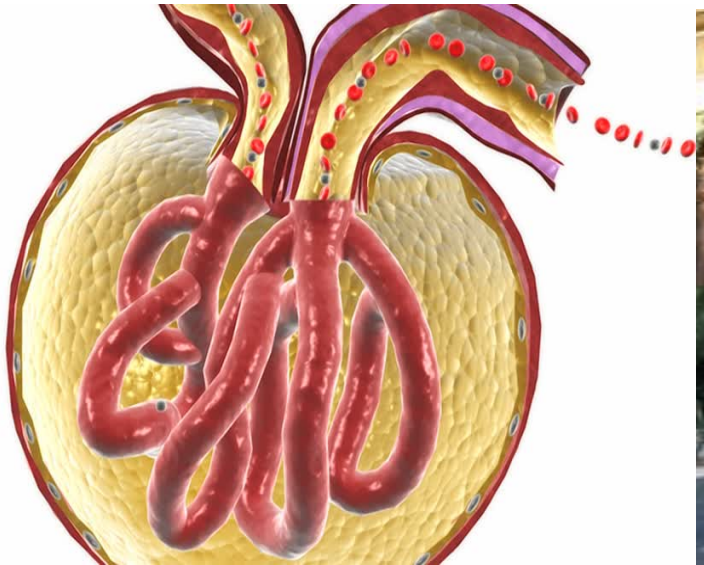
Roma, 9 - 12 novembre 2017

16° CONGRESSO NAZIONALE AME

Minicorso Nefropatia Diabetica: Le misure d'intervento

Luca Di Lullo

UOC Nefrologia – Dialisi, Ospedale "L. Parodi – Delfino", Colleferro



- Blood pressure control and renal protection in diabetic patients
- New hypoglicemic agents and cardiovascular outcomes
- New hypoglicemic drugs and renal outcomes

ESH/ESC

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs	• Lifestyle changes • BP drugs	• Lifestyle changes • Immediate BP drugs
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

CKD

SBP <140 mmHg DBP <90 mmHg

2013 ESH/ESC Guidelines. J Hypertens 2013

ESH/ESC

Type of kidney disease	Protein excretion < 0.3 g/day (normoalbuminuria, microalbuminuria, 30–150 mg/day)	Protein excretion 0.3–1 g/day (microalbuminuria 150–300 mg/day, macroalbuminuria 300–500 mg/day)	Protein excretion > 1 g/day (macroalbuminuria > 500 mg/day)
Non-diabetic kidney disease	< 140/90 mm Hg	< 130/80 mm Hg	<125/75 mm Hg*
Diabetic kidney disease	SBP < 130–140 mm Hg** DBP < 80 mm Hg**	< 130/80 mm Hg***	<130/80 mm Hg*** (<125/75 mm Hg*** for young patients with heavy proteinuria)

*As evident from MDRD study B trial phase and MDRD long-term study (see *text*); **from cardiovascular outcome trials (see *text*); ***through extrapolation from data in non-diabetic CKD and post-hoc or observational analyses in diabetic CKD (see *text*)

Sarafidis PA & Ruilope LM. ESH Newsletter 2013, No. 55

KDIGO

- **Non-diabetic adults with CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric
- **Diabetic adults with non dialysis-dependent CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric
- **Kidney transplant recipients:**
  ≤130 mmHg systolic and ≤80 mmHg diastolic
- **Elderly people with CKD:**
  probably ≤140 mmHg systolic and ≤90 mmHg diastolic, but set targets after consideration of co-morbidities

Aim for <130/80 mmHg if albuminuria is present

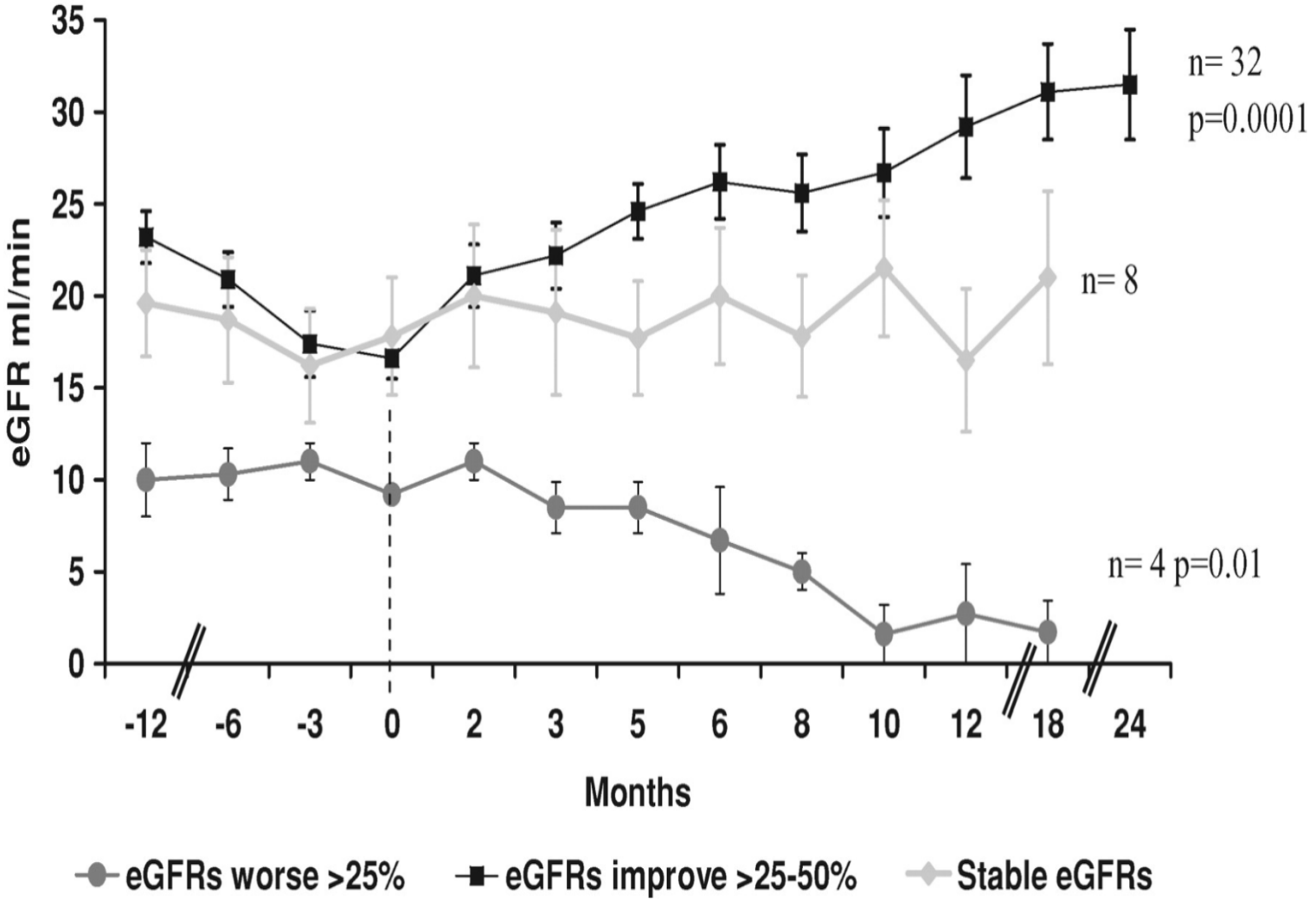
KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

ACEIs and ARBs

Indicated in all hypertensive patients with CKD, especially in proteinuric diabetic and non-diabetic CKD.

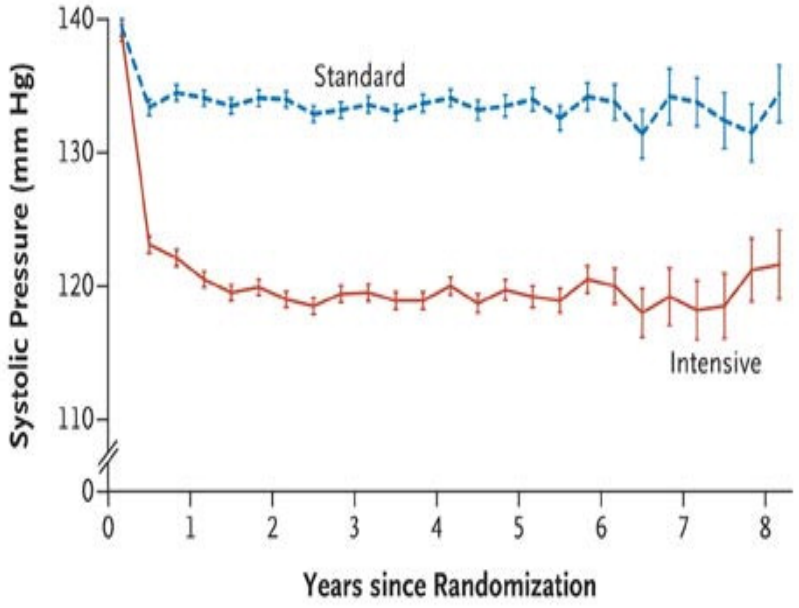
Will lead to deterioration of renal function in short term but then to slower progression of renal failure in longer term.

Stopping ACEI/ARB in Advanced CKD?



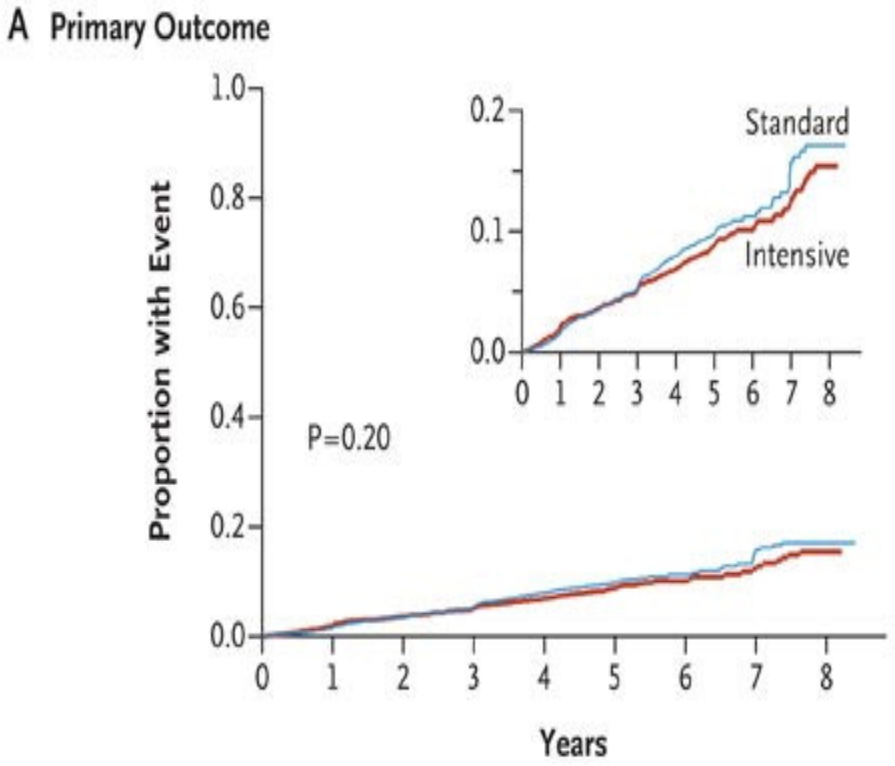
Ahmed AK et al. NDT 2010

Diabetes: ACCORD – Major CV Events



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3

No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201



No. at Risk									
Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108

ACCORD Study Group. NEJM 2010

Summary

	ESH/ESC 2013 Guidelines	AHA/ACC/CDC Scientific Advisory	JNC 8	ASH/ISH Statement
in general	<140/90	<140/90	≥ 60 years: <150/90 < 60 years: < 140/90	>140/90
Exception or special comment	Elderly > 80 years < 150/90 Elderly < 80 years < 150/90 Fit elderly < 140/90 Diabetes < 140/85 CKD+Proteinuria < 130/90	„lower“ targets for •elderly •LVH •systolic or diastolic LV dysfunction •diabetes •kidney disease	Diabetes < 140/90 CKD < 140/90	< 80 years < 150/90 CKD + Proteinuria < 130/80

RAAS inhibitors

- **Renin inhibitors**
  - **-aliskiren**

RAAS synthesis inhibitors (VDRs agonists)

- **-calcitriol**
- **-paracalcitol**

- **Angiotesin converting enzyme inhibitors (ACEis)**
- **Angiotensin receptor blockers (ARBs)**

- **Aldosterone mineralcorticoid receptor inhibitors**

-spironolactone

-eplerenone

Esiste ancora un'indicazione a terapie di combinazione con due o più farmaci RAAS-is?

Nella pratica clinica, al momento attuale

NO

In alcune selezionate condizioni cliniche

(e con uno stretto controllo specialistico)

SI (forse)

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

N ENGL J MED 358;15 WWW.NEJM.ORG APRIL 10, 2008

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N ENGL J MED 367;23 NEJM.ORG DECEMBER 6, 2012

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans-Henrik Parving, M.D., D.M.Sc., Barry M. Brenner, M.D., Ph.D., John J.V. McMurray, M.D., Dick de Zeeuw, M.D., Ph.D., Steven M. Haffner, M.D., Scott D. Solomon, M.D., Nish Chaturvedi, M.D., Frederik Persson, M.D., Akshay S. Desai, M.D., M.P.H., Maria Nicolaides, M.D., Alexia Richard, M.Sc., Zhihua Xiang, Ph.D., Patrick Brunel, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the ALTITUDE Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 369;20 NEJM.ORG NOVEMBER 14, 2013

ORIGINAL ARTICLE

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., Stuart R. Warren, J.D., Pharm.D., Suzanne Watnick, M.D., Peter Peduzzi, Ph.D., and Peter Guarino, M.P.H., Ph.D., for the VA NEPHRON-D Investigators*

Negative trials on dual RAS blockade

Study	ONTARGET	ALTITUDE	VA NEPHRON D
Study treatment	⇧ Acute HD (*Hypotension*)	⇧ Hyperkalemia, Hypotension	⇧ AKI, Hyperkalemia
Population	coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	UACR ≥200 mg/g, eGFR ≥30 mL/min or eGFR ≥30 and <60 mL/min, UACR ≥20 and <200 mg/g or Cardiovascular risk: eGFR ≥30 and <60 mL/min, UACR <20 mg/g, CVD history	mg/g, eGFR of 30-90 mL/min
N	25,620	8606	1448
Follow-up (y)	4.7	2.8	2.2
Primary endpoint	Composite outcome of CV death, MI, stroke, or hospitalization for CHF	Composite of CV death, resuscitated sudden death, MI, stroke, unplanned hospitalization for HF, ESRD, or kidney death or doubling of baseline serum creatinine concentration	Change in eGFR (a decline of ≥30 mL if the initial eGFR was ≥60 mL/min or a decline of ≥50% if the initial eGFR was <60 mL/min), ESRD, or death
Baseline blood pressure (mmHg)	134/77	135/74	137/73
Diabetes (%)	37	100	100
CVD history	49% MI 21% stroke/TIA	48%	23% CAD 16% CHF
Macroalbuminuria	N/A	58%	100%
Smoking (%)	13	13	N/A

Mann Lancet 2008 ***Parving NEJM 2012*** ***Fried NEJM 2013***

Combo RAAS-I in elderly patients: a population-based longitudinal analysis

CMAJ, Alberta Kidney Disease Network 2011

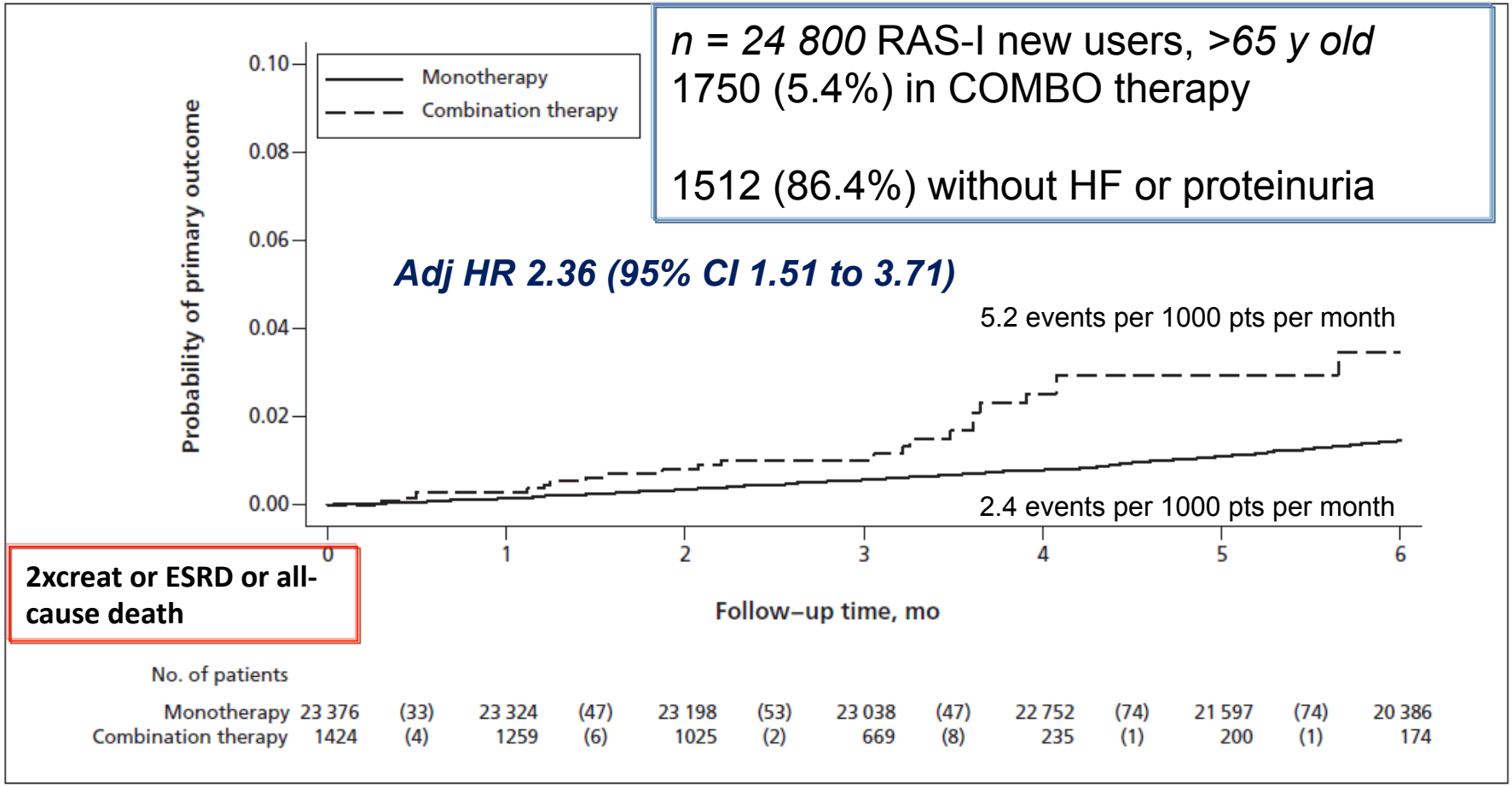
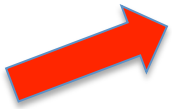


Figure 2: Kaplan–Meier curves for primary outcome (doubling of serum creatinine, development of end-stage renal failure or death from any cause) among the 24 800 patients for whom serum creatinine was measured before and after the start of treatment. Numbers in parentheses are the number of patients who had at least one of the three outcome events. Hazard ratio 2.36 (95% confidence interval 1.51 to 3.71).

Is dual RAAS blockade still a therapeutic chance in selected clinical conditions?

1. **Heart failure**
2. **Proteinuric CKD**

Table1 Summary of NICE recommendations on the use of renin-angiotensin system drugs in various indications

Heart failure 	Chronic heart failure in adults: management. NICE guideline CG108 (August 2010)	Offer both ACE inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors.	Seek specialist advice and consider adding an ARB licensed for heart failure (especially if the patient has mild to moderate heart failure) if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker. Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.

Is dual RAAS blockade still a therapeutic chance in selected clinical conditions?

1. Heart failure

2. **Proteinuric CKD**

Aldosterone antagonists for preventing the progression of chronic kidney disease (Review)

Bolignano D, Palmer SC, Navaneethan SD, Strippoli GFM

THE COCHRANE COLLABORATION®

Background

Treatment with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is increasingly used to reduce proteinuria and retard the progression of chronic kidney disease (CKD). However, resolution of proteinuria may be incomplete with these therapies and the addition of an aldosterone antagonist may be added to further prevent progression of CKD. This is an update of a review first published in 2009.

Objectives

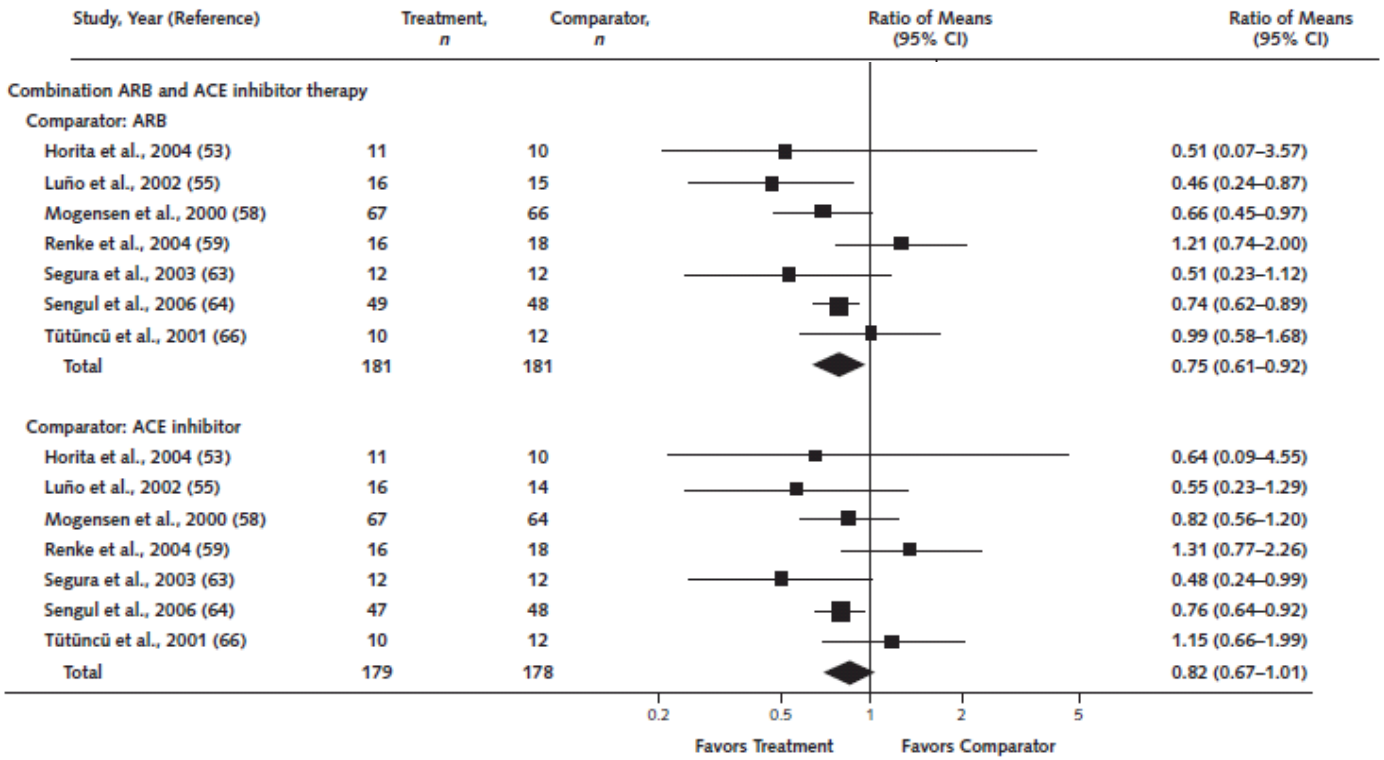
Aldosterone antagonists reduced proteinuria and blood pressure in adults with mild to moderate CKD and were treated with ACEi or ARB (or both), but increase hyperkalemia and gynaecomastia.
Wheter adding aldosterone antagonists to ACEi or ARB (or both) reduced the risk of major cardiovascular events or ESKD in this population is unknown.

REVIEW | Annals of Internal Medicine

Meta-analysis: Effect of Monotherapy and Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease

Regina Kunz, MD, MSc(Epi); Chris Friedrich, MD; Marcel Wolbers, PhD; and Johannes F.E. Mann, MD

Figure 2. **Reduction in proteinuria at 5 to 12 months.**



Kunz R et al. Ann Intern Med, 2004

Aldosterone Antagonists for Preventing the Progression of Chronic Kidney Disease: A Systematic Review and Meta-analysis

Sankar D. Navaneethan,*† Sagar U. Nigwekar,‡ Ashwini R. Sehgal,§ and Giovanni F.M. Strippoli†‖¶**

	Aldosterone antagonist			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bianchi 2006	0.89	0.54	83	2.11	0.72	82	27.8%	-1.22 [-1.41, -1.03]	
Chrysotomou 2006	2.04	1.9	11	2.97	3.7	10	3.1%	-0.93 [-3.48, 1.62]	
Furamatsu 2008	0.6	0.38	15	1.39	2.3	15	10.3%	-0.79 [-1.97, 0.39]	
Rossing 2005	1.06	0	20	1.56	0	20		Not estimable	
Schjoedt 2005	0.77	0.54	20	1.02	0.73	20	24.2%	-0.25 [-0.65, 0.15]	
Schjoedt 2006	3.06	1.74	20	4.2	1.82	20	11.2%	-1.14 [-2.24, -0.04]	
Tylicki 2008	0.51	0.42	18	1.21	0.84	18	2.4%	-0.70 [-1.13, -0.27]	
Total (95% CI)			**187**			**185**	**100.0**	**-0.80 [-1.27, -0.33]**	

Heterogeneity: Tau² = 0.20, Chi² = 20.56, df = (P=0.0010); I² = 76%

Test for overall effect Z = 3.33 (P=0.0009)

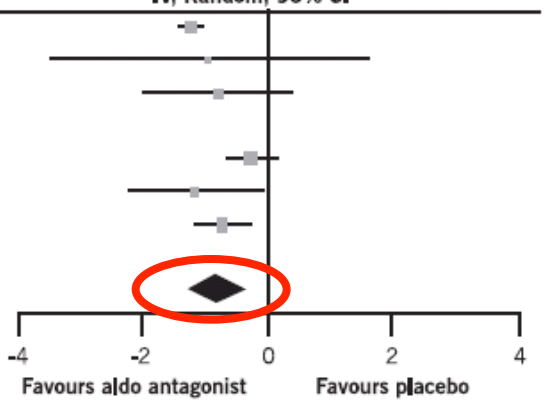
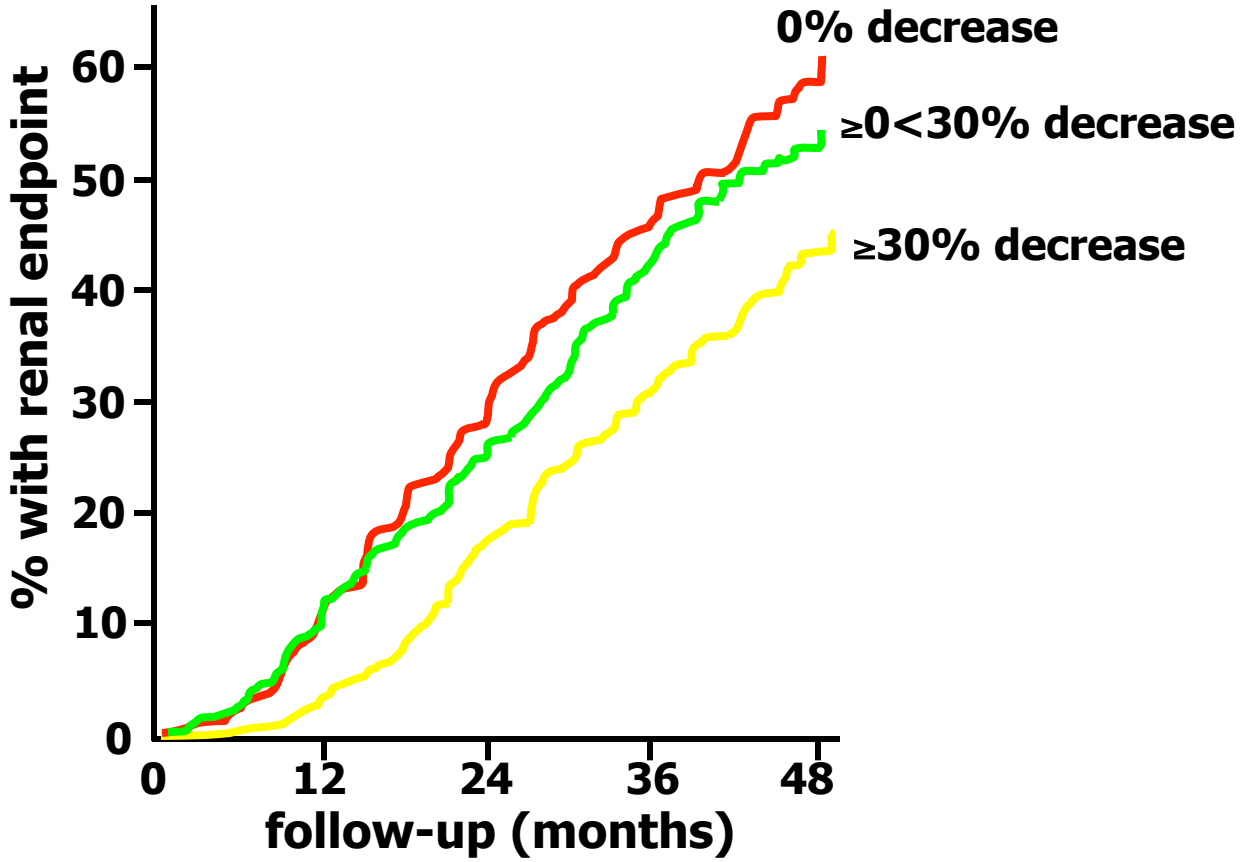


Figure 2. Effect of aldosterone antagonists plus ACEi and/or ARB compared with ACEI and/or ARB alone on the end of treatment proteinuria.

Renoprotective effect of proteinuria reduction in diabetic pts with nephropathy and hypertension: tertiary prevention (1513 pts)



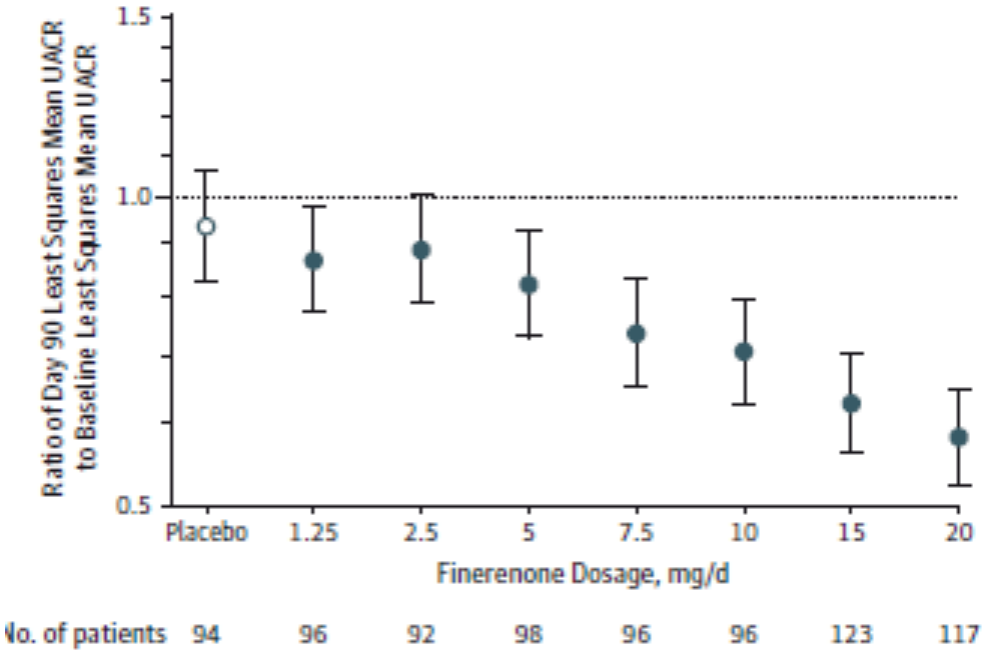
De Zeeuw et al., KI, 2004

Original Investigation

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy

A Randomized Clinical Trial

George L. Bakris, MD; Rajiv Agarwal, MD; Juliana C. Chan, MD; Mark E. Cooper, MD, PhD; Ron T. Gansevoort, MD, PhD; Hermann Haller, MD, PhD; Giuseppe Remuzzi, MD; Peter Rossing, MD; Roland E. Schmieder, MD; Christina Nowack, MD; Peter Kolkhof, PhD; Amer Joseph, MBBS; Alexander Pieper, DiplStat; Nina Kimmeskamp-Kirschbaum, PhD; Luis M. Ruilope, MD, PhD; for the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group



JAMA 2015

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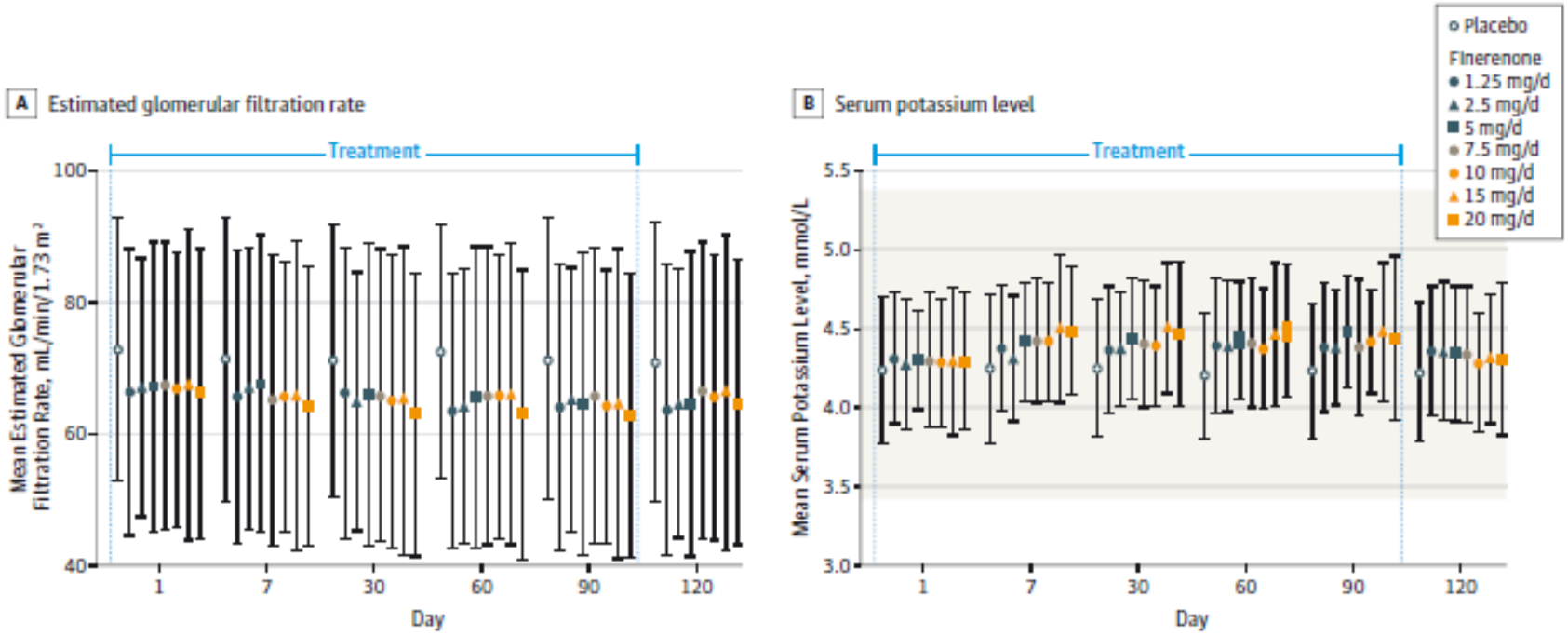
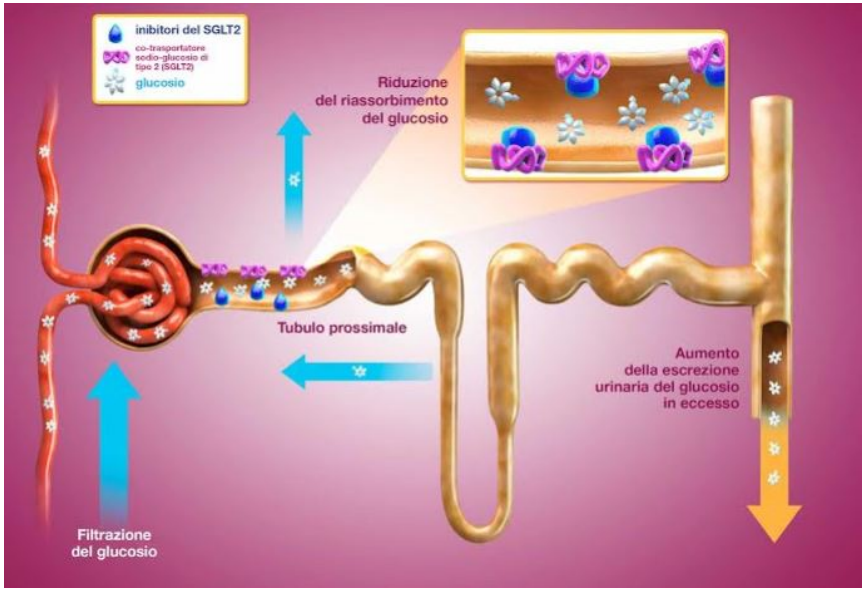
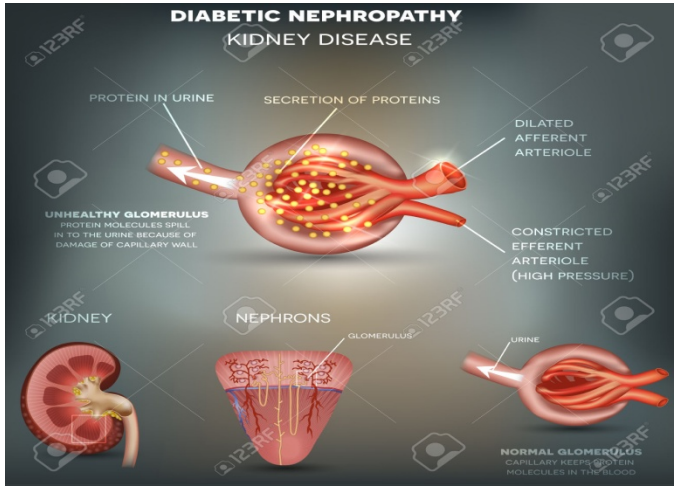
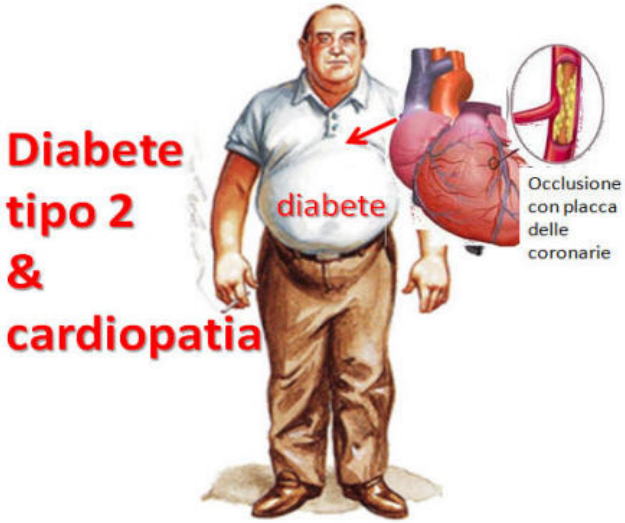


JAMA 2015

Clinical Outcomes with Newer Antihyperglycemic Agents

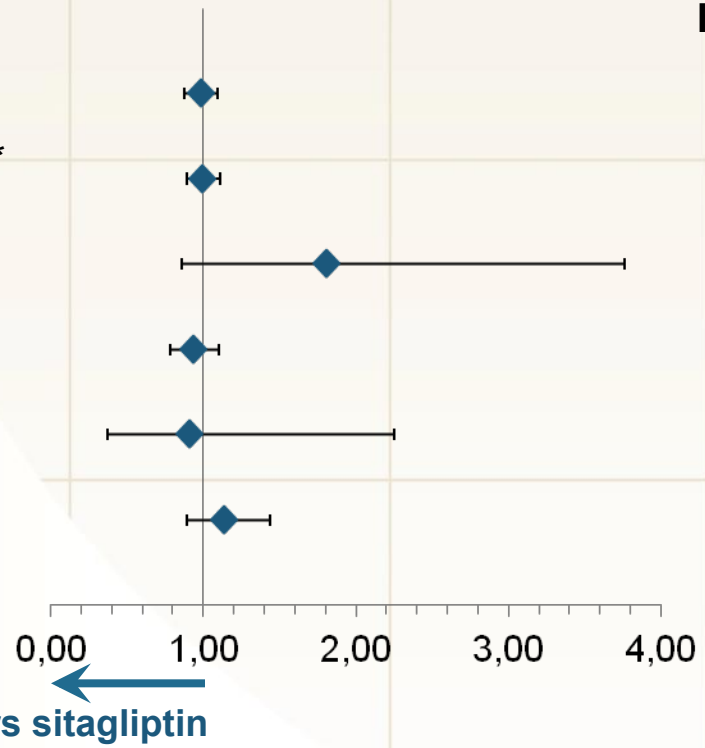






Primary and Secondary Outcomes with Sitagliptin

TECOS Per Protocol Analysis (n=14,523)



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint†	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.89-1.44)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe hypoglycemia	1.13 (0.89-1.44)	0.31

*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

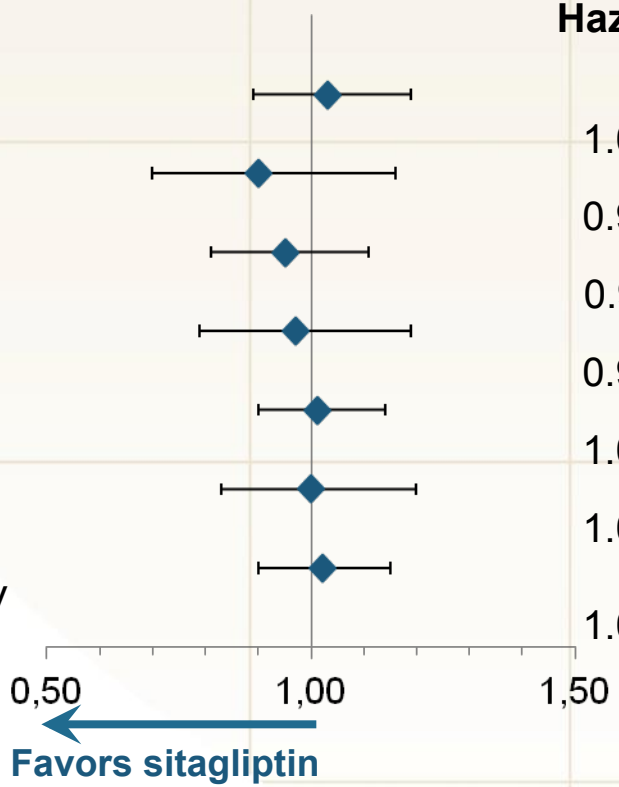
†Secondary composite: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Individual Secondary Outcomes with Sitagliptin

TECOS Intent to Treat Analysis (n=14,671)



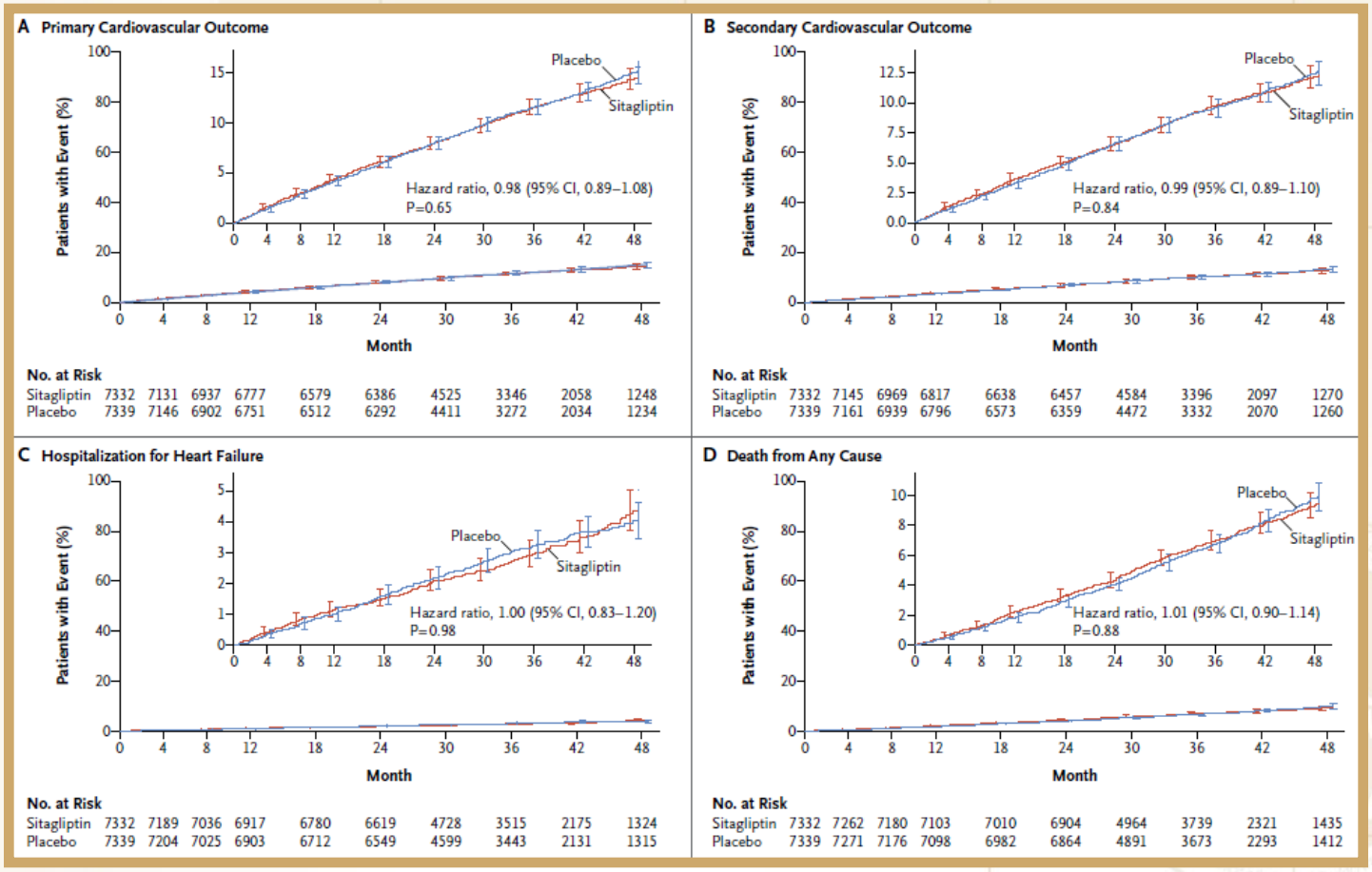
	Hazard ratio (95% CI)	*P* value
CV death	1.03 (0.89-1.19)	0.71
Hospitalization for unstable angina	0.90 (0.70-1.16)	0.42
Fatal or nonfatal MI	0.95 (0.81-1.11)	0.49
Fatal or nonfatal stroke	0.97 (0.79-1.19)	0.76
Death from any cause	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	1.09 (0.83-1.20)	0.98
Hospitalization for heart failure or CV death	1.02 (0.90-1.15)	0.74

CV, cardiovascular; MI, myocardial infarction; NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Clinical Outcomes with Sitagliptin

TECOS
(n=14,671)

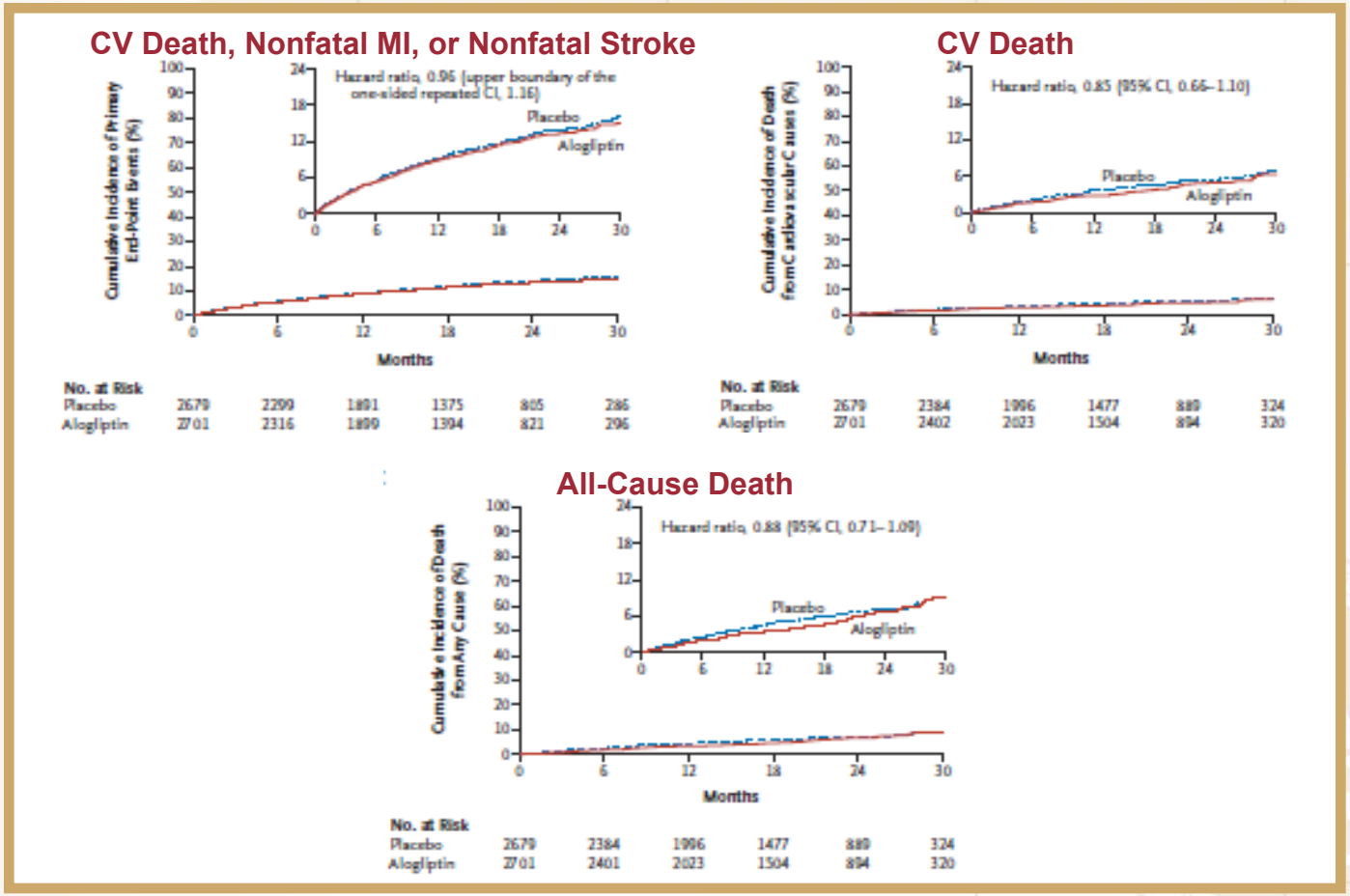


TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Alogliptin CV Outcomes and Mortality

EXAMINE

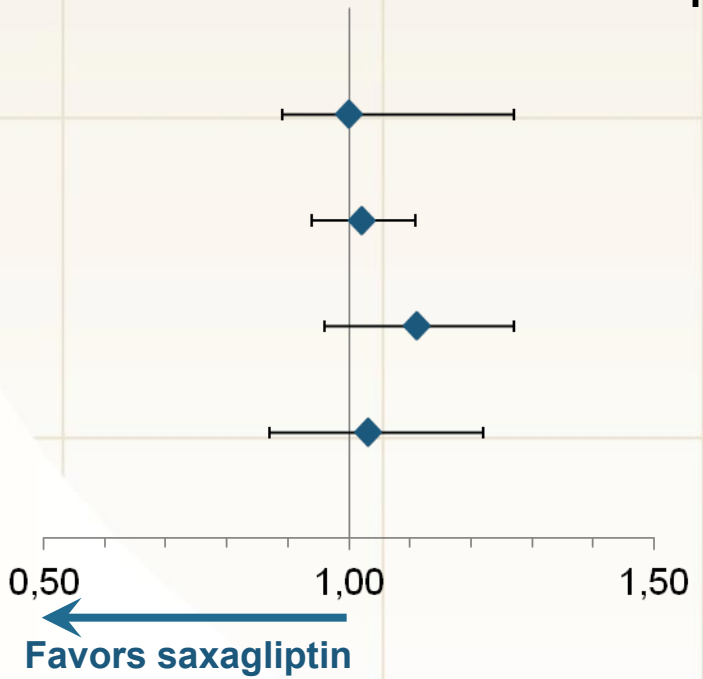


EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care.

White W, et al. *N Engl J Med*. 2013;369:1327-1335.

Clinical Outcomes with Saxagliptin

SAVOR-TIMI Prespecified Composite Endpoints and Mortality (n=16,492)



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.00 (0.89-1.27)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.52

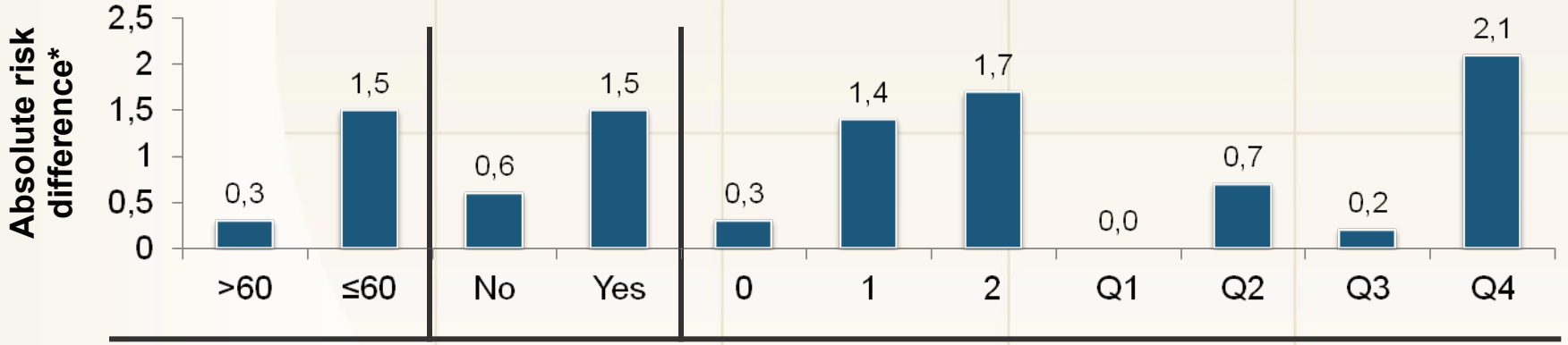
*CV death, nonfatal MI, or nonfatal ischemic stroke; †CV death, nonfatal MI, nonfatal ischemic stroke, hospitalization for HF, coronary revascularization, or unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

Scirica BM, et al. *N Engl J Med*. 2013;369,1317-1326.

Risk of HF Hospitalization with Saxagliptin vs Placebo

SAVOR-TIMI Post-hoc Analysis (n=16,492)



	eGFR (mL/min)		HF history		No. HF risk factors†			NT-proBNP quartiles (pg/mL)			
No. excess HHF events in patients treated with saxagliptin vs placebo per 1000 pt-y								(5-64)	(65-141)	(142-333)	(334-46, 647)
n =	11637	4855	14387	2105	10418	5188	866	3076	3076	3076	3073
	1	5	1	6	0	4	9	0	1	0	7

*Saxagliptin vs placebo.

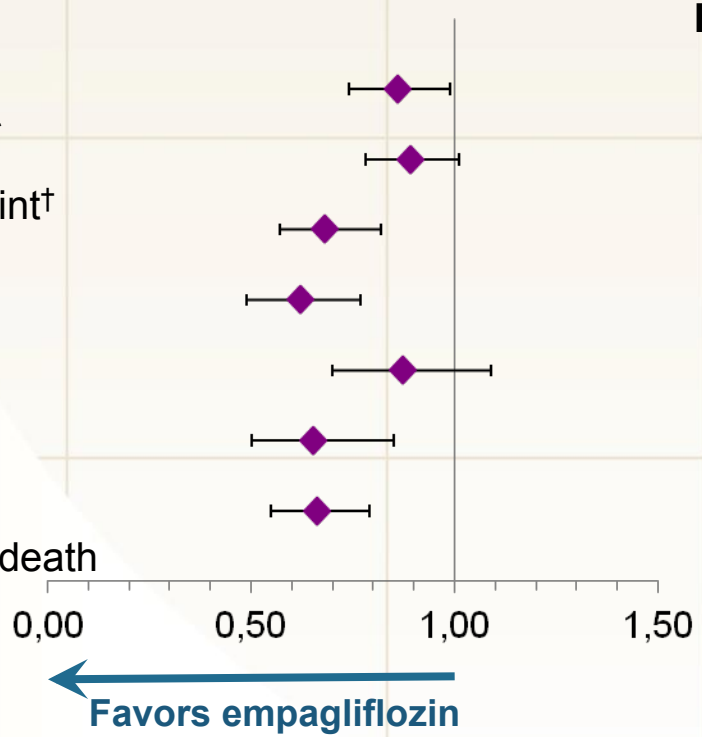
†eGFR ≤60 mL/min or history of previous HF.

HF, heart failure; HHF, hospitalizations for heart failure.

Scirica BM, et al. *Circulation*. 2014;130:1579-1588.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001

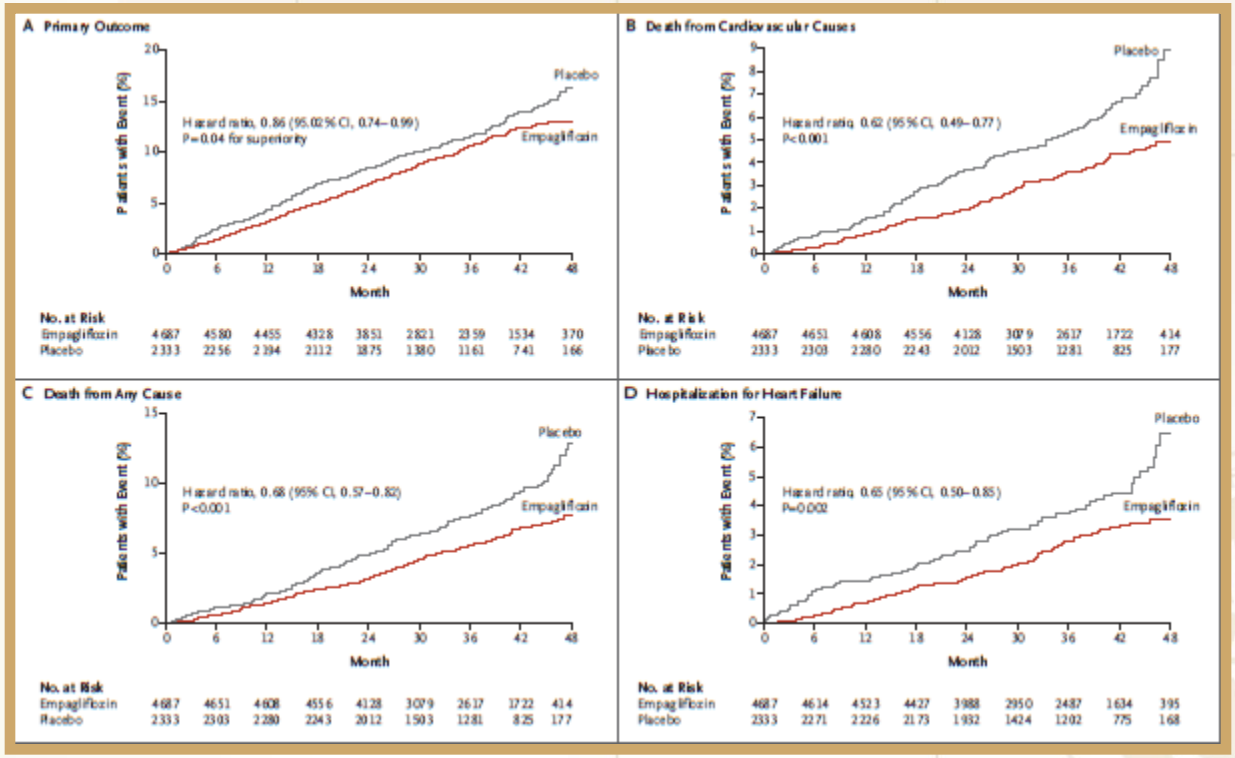
*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)



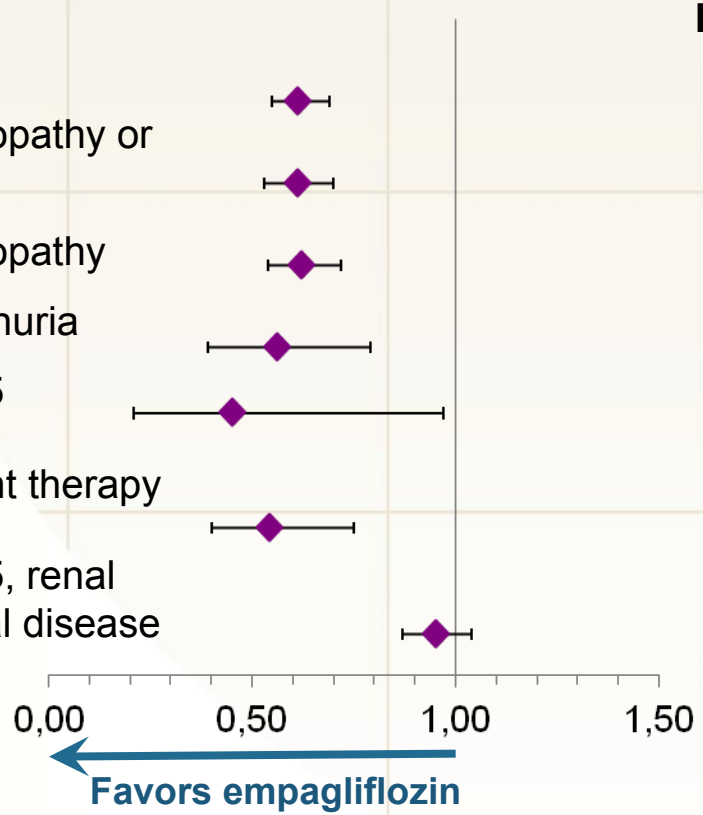
*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)



	Hazard ratio (95% CI)	*P* value
Incident or worsening nephropathy or CV death	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	0.61 (0.53-0.70)	<0.001
Progression to macroalbuminuria	0.62 (0.54-0.72)	<0.001
Doubling of SCr + eGFR ≤45	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	0.45 (0.21-0.97)	0.04
Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death	0.54 (0.40-0.75)	<0.001
Incident albuminuria*	0.95 (0.87-1.04)	0.25

*In patients with normal albuminuria at baseline.

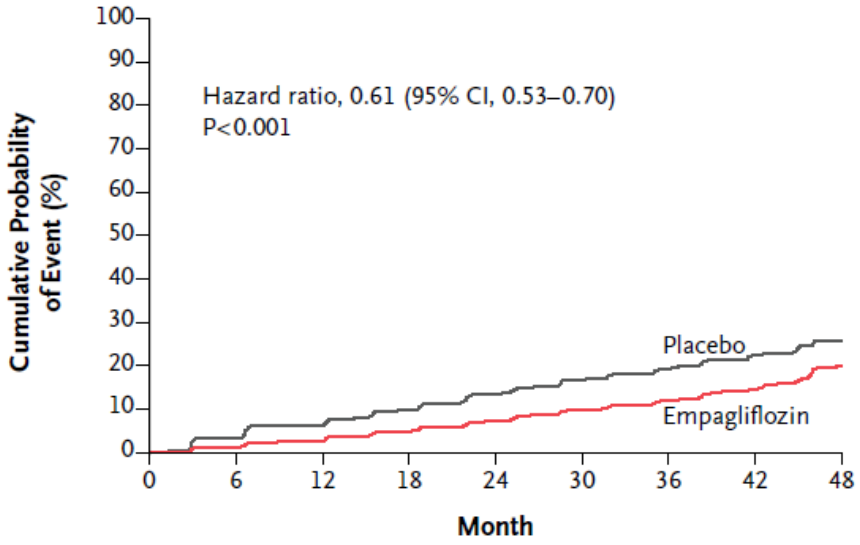
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; HR, hazard ratio; SCr, serum creatinine.

Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

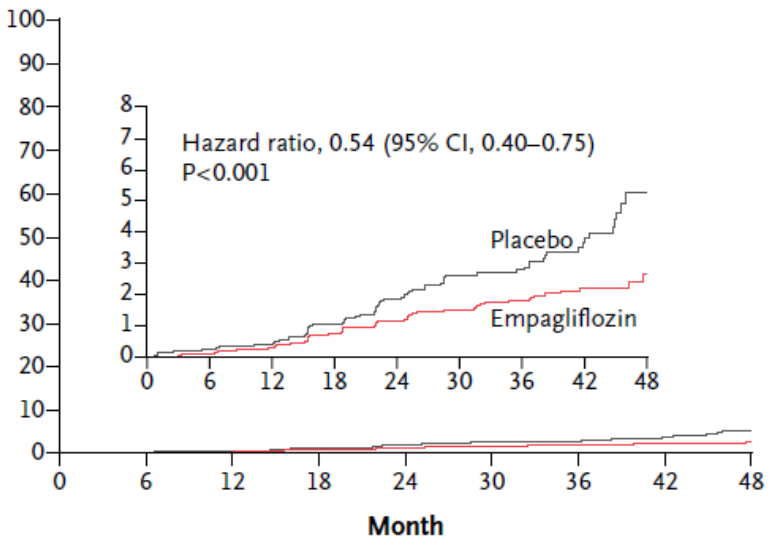
Renal Outcomes with Empagliflozin

EMPA-REG RENAL (N=7020)

Incident or Worsening Nephropathy



Post-hoc Renal Composite Outcome*



No. at Risk																		
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2061	1946	1836	1703	1433	1016	833	521	106	2323	2229	2146	2047	1771	1289	1079	680	144

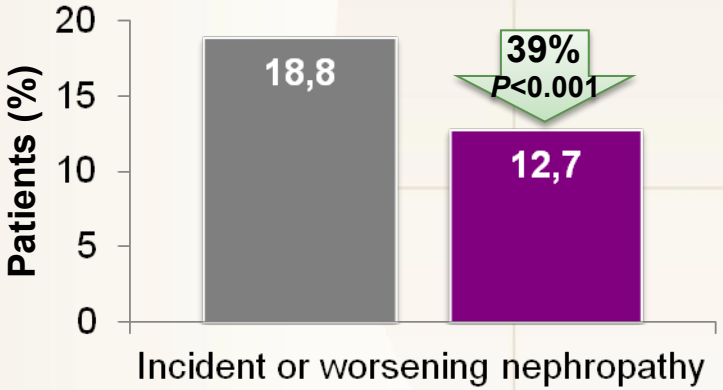
*Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

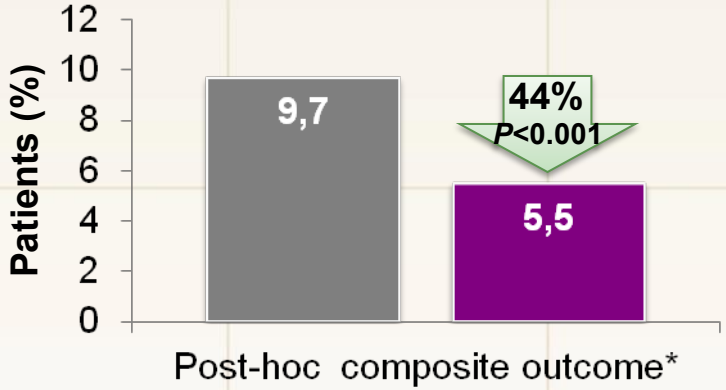
CI, confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

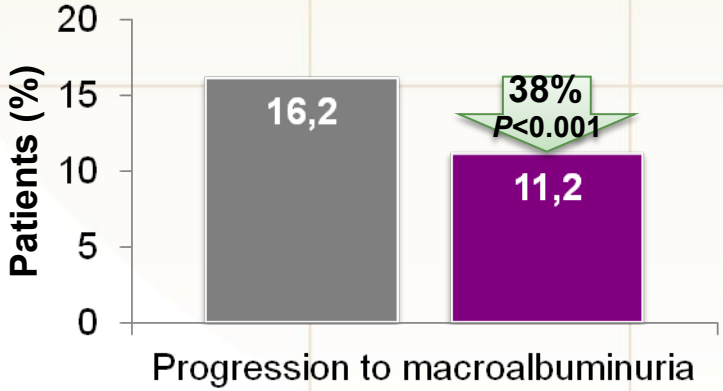
Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)







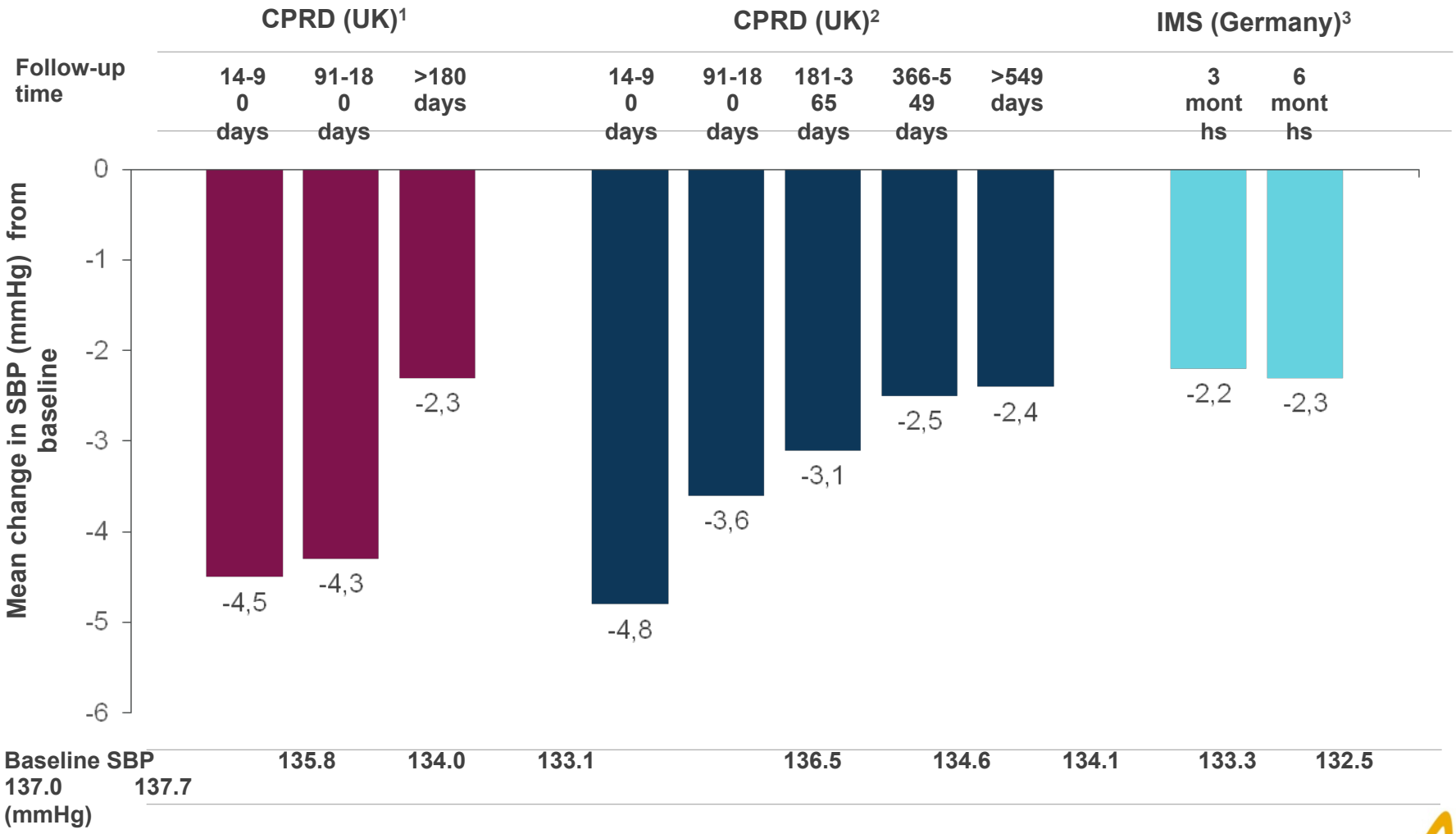
Arrows = relative risk reduction.

*Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

CI, confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

Reductions in systolic blood pressure for dapagliflozin across RWE studies



1. Wilding et al. *Diabetes Ther* 2016;7:695–711; 2. Wilding et al. Poster presented at Diabetes UK (DUK) conference 2017. Manchester, UK; 3. Scheerer et al. *Diabetes Metab Syndr Obes* 2016;9:337–45.

HbA_{1c}, glycated hemoglobin; RWE, real world evidence; SBP systolic blood pressure.

Dapagliflozin CV meta-analysis showed no increase in CV risk

- Meta-analysis of 21 Phase 2b/3 trials, n=9339 (dapagliflozin n=5936; control n=3403)

n/N	DAPA meta-analysis*				Favours DAPA ← ● → Control	DAPA HR vs Control (95% CI)[2]
	DAPA	Event rate/ 100 p–y	Control	Event rate/ 100 p–y		
MACE plus UA	95/5699	1.46	81/3240	2.15		0.79 (0.58, 1.1)
MACE	72/5418	1.15	62/3101	1.69		0.77 (0.54, 1.1)
CV death	20/3825	0.37	18/2200	0.59		0.70 (0.36, 1.36)
MI	30/5244	0.48	33/3014	0.91		0.57 (0.34, 0.95)
Stroke	25/4227	0.45	18/2412	0.57		1.00 (0.54, 1.86)
Hospitalization for heart failure	10/2576	0.15	16/1780	0.41		0.36 (0.16, 0.84)

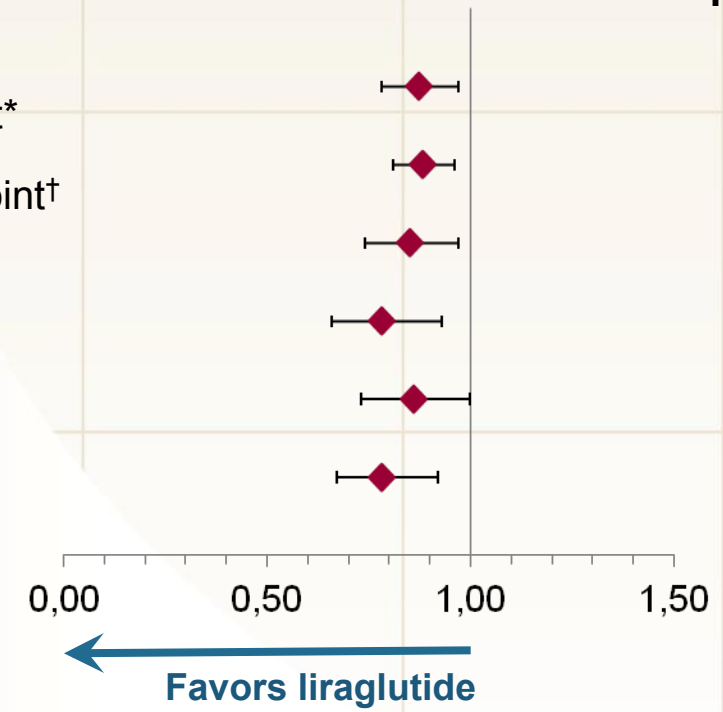
0.5 1.00

*All Phase 2b and 3 Pool, ST + LT -30MU; Stratified by study; Only trials with at least one positively adjudicated event included in analysis; Cox Proportional Hazards model.

Sonesson C et al. *Cardiovasc Diabetol*. 2016;15:37.

Clinical Outcomes with Liraglutide

LEADER (N=9340)



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74-0.97)	0.02
CV death	0.78 (0.66-0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73-1.00)	0.046
Nephropathy	0.78 (0.67-0.92)	0.003

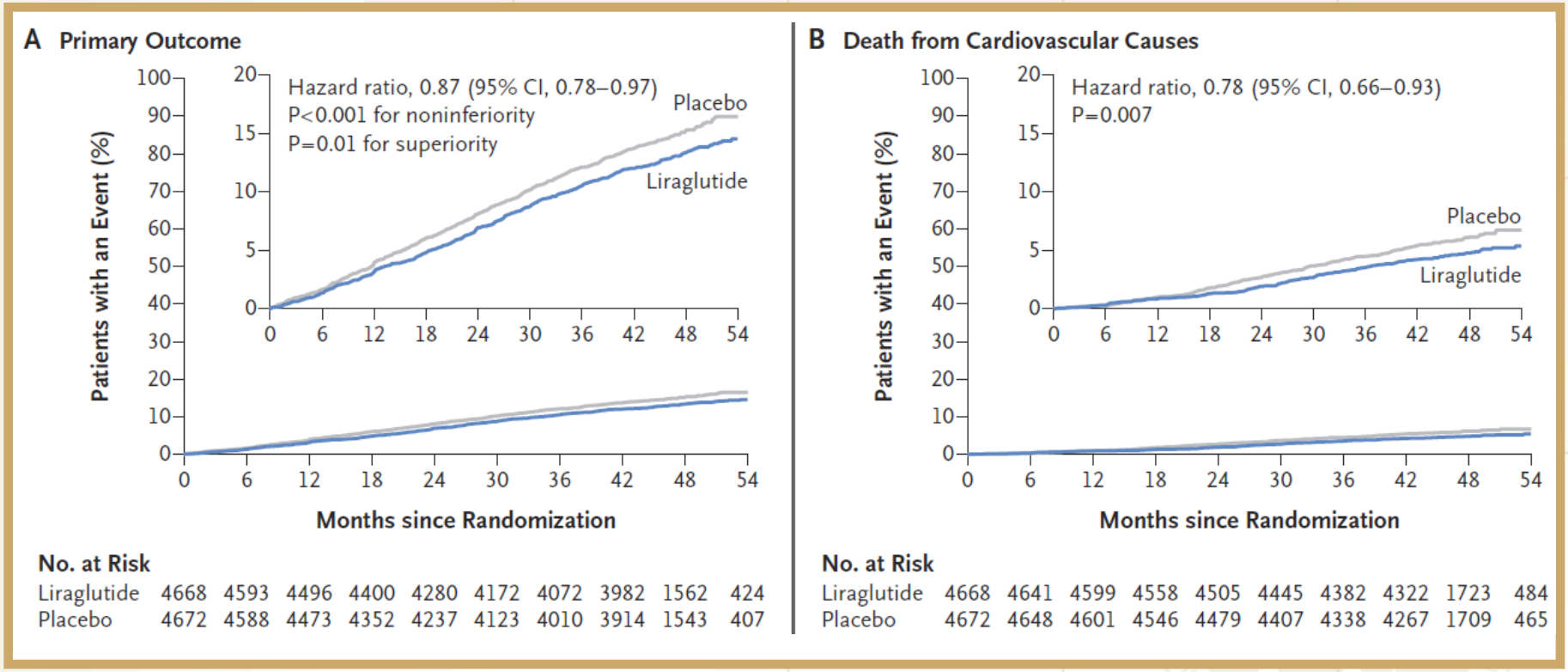
*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med*. 2016 Jun 13. [Epub ahead of print]

Clinical Outcomes with Liraglutide

LEADER
(N=9340)



*CV death, nonfatal MI (including silent MI), or nonfatal stroke.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med*. 2016 Jun 13. [Epub ahead of print].

CONCLUSIONI

- Nel paziente diabetico il trattamento delle principali comorbilità permette di migliorare gli outcome renali e cardiovascolari
- Il blocco del RAAS risulta fondamentale per ottimizzare il controllo pressorio e gli effetti nefroprotettivi
- I nuovi agenti ipoglicemizzanti risultano essere in grado di agire positivamente sui principali indicatori di esito sia a livello renale che cardiaco

fenicia-events.eu/cardionefro2017


INNOVAZIONI FARMACOLOGICHE
E TECNOLOGICHE
IN CARDIONEFROLOGIA
Roma, 15-16 Marzo 2018
A cura del GdS di Cardionefrologia
della Società Italiana di Nefrologia

Grazie per la cortese attenzione