Armi a disposizione fino all'avvento dei nuovi farmaci

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Una strategia multifattoriale *aggressiva* è raccomandata nel diabetico con MRC

HbA1c < 58 mmol/mol cercando di ridurre al massimo il rischio di ipoglicemie severe.

Obiettivo <130/80 mmHg

...per tutti?

Utilizzare ACEi and/or ARBs per ridurre la proteinuria

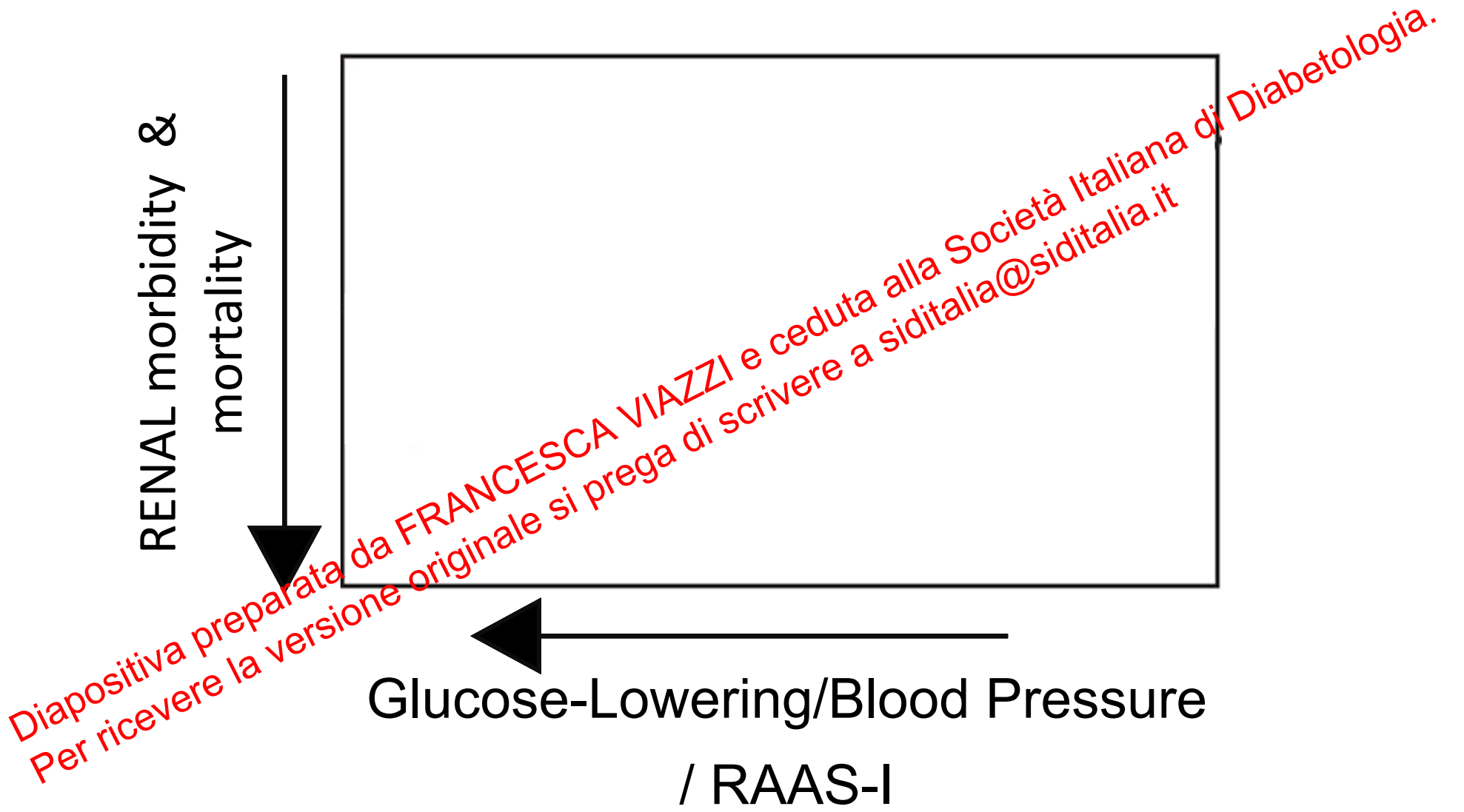
...quando presente

Terapia con farmaci ipolipemizzanti

...per ridurre il rischio cardiovascolare

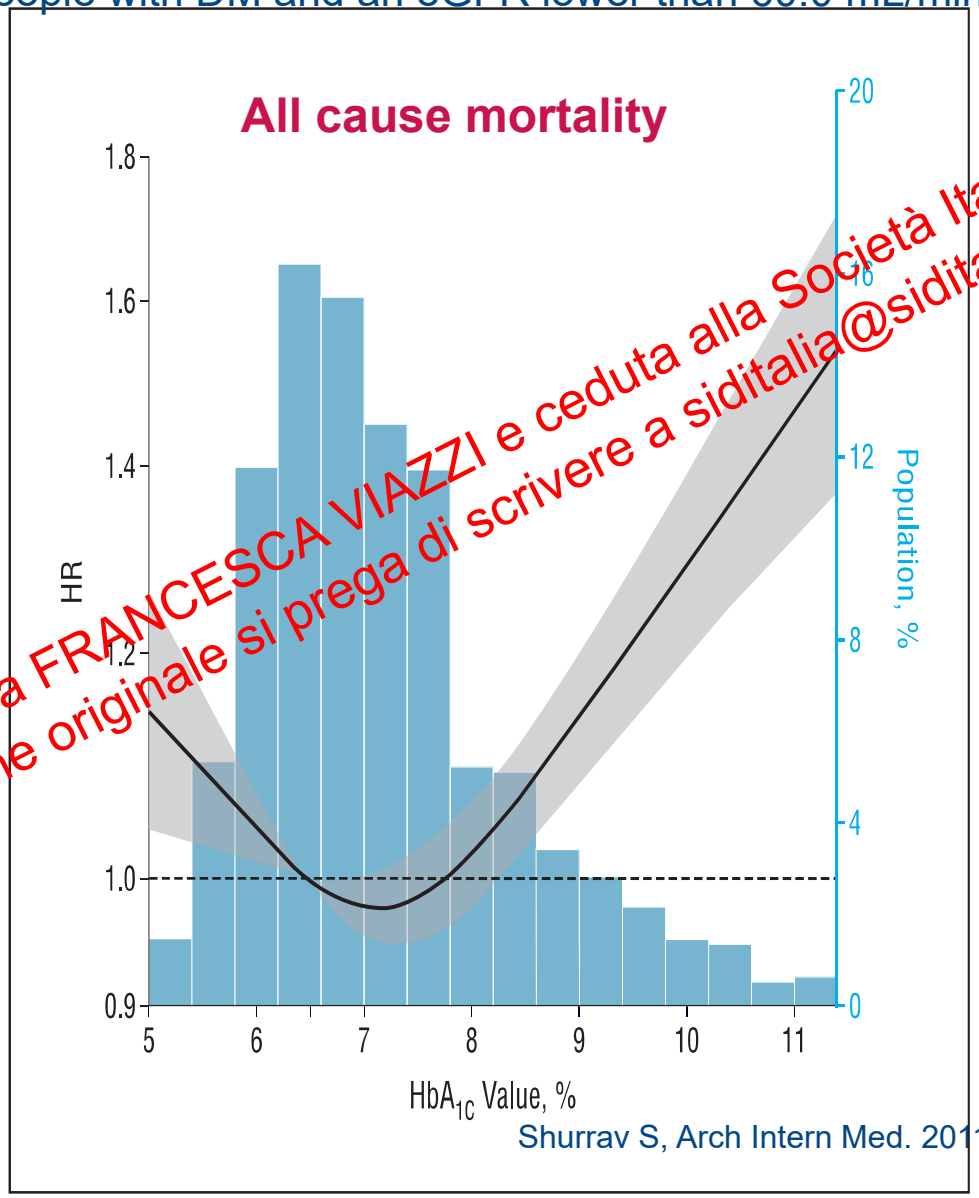
1. National Kidney Foundation. *Am J Kidney Dis* 2012;60:850; 2. NICE. Clinical guideline: Type 2 diabetes (CG87), May 2009

Despite experimental evidence supporting *super-normalization* of risk multiple factors, a J-curve phenomenon has traditionally curbed renal protection in clinical practice



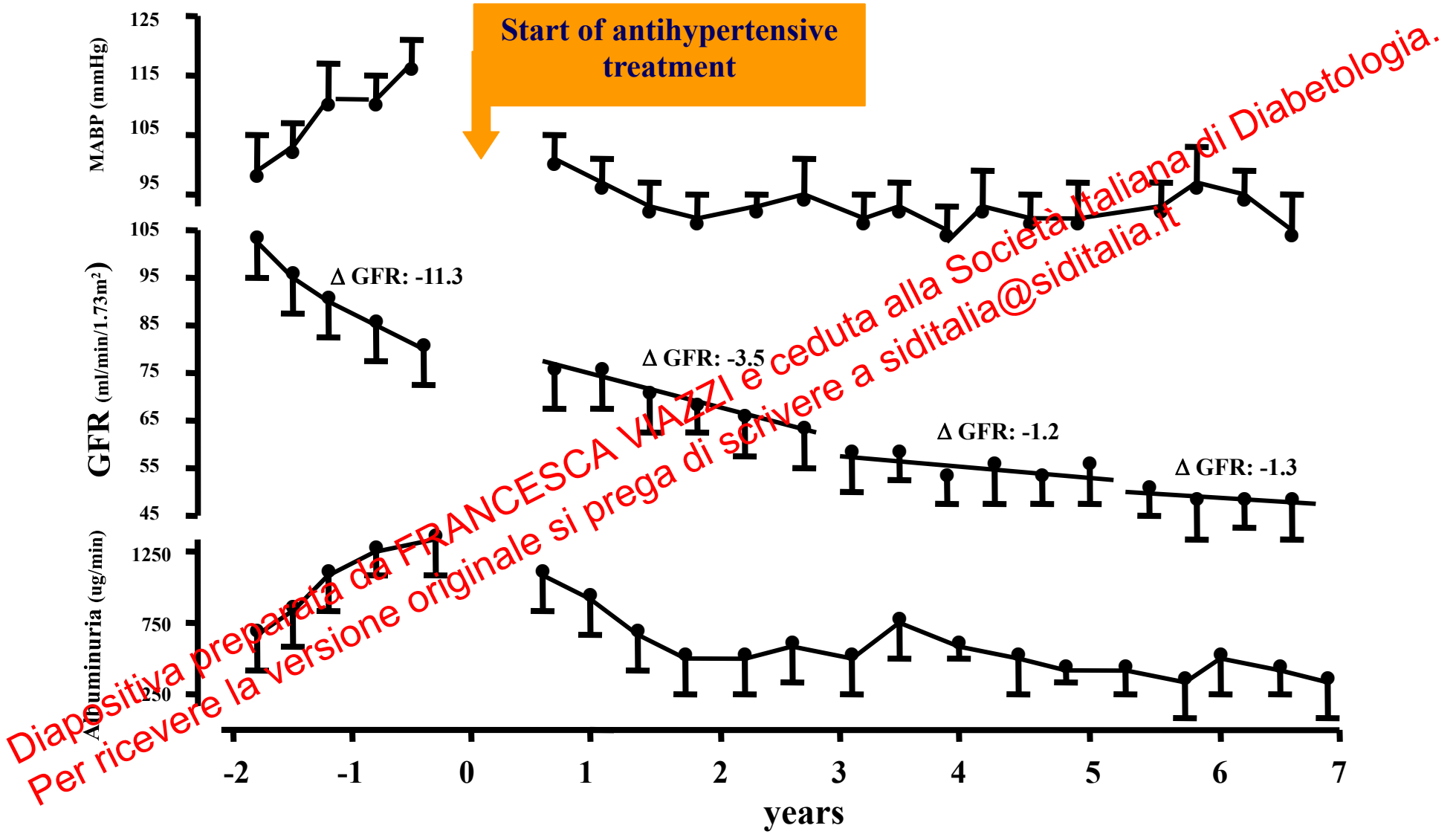
Association Between Glycemic Control and Adverse Outcomes in People With Diabetes Mellitus and Chronic Kidney Disease

23 296 people with DM and an eGFR lower than 60.0 mL/min/1.73 m^2



Shurrav S, Arch Intern Med. 2011;171(21):1920-1927

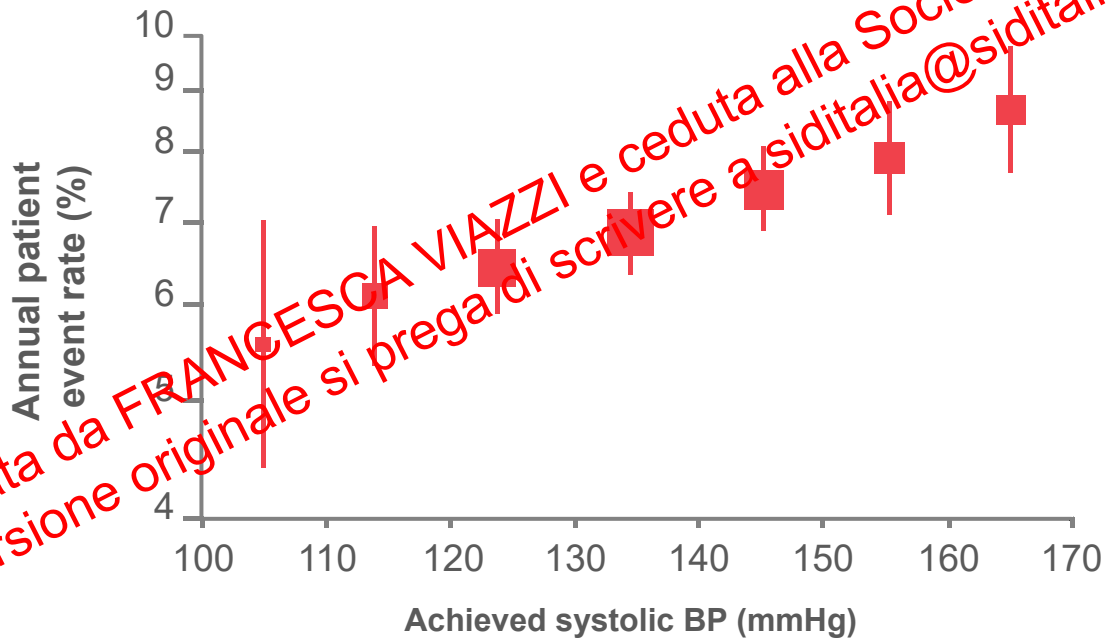
Blood Pressure reduction *conveys* renal protection



From Parving H-H, Am J Kidney Dis 1993

Lower blood pressure is associated with lower frequency of renal events in T2D

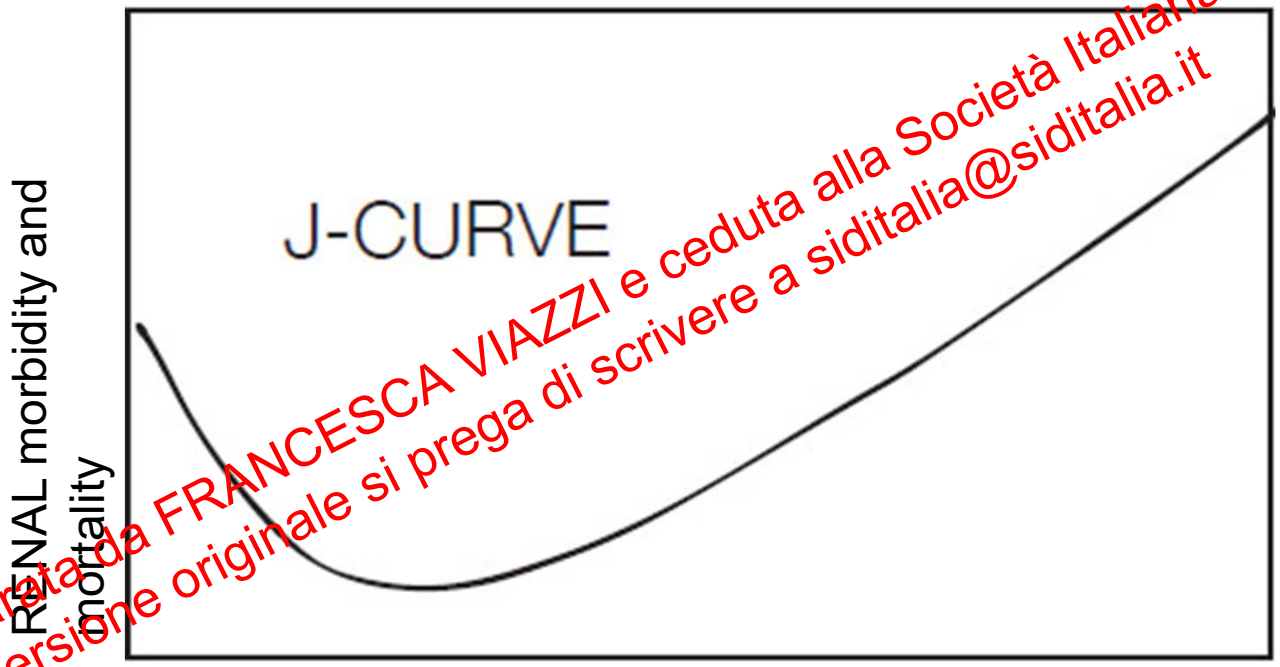
In the ADVANCE-BP study, rate of all renal events* significantly associated with achieved systolic BP levels ($p<0.0001$ for trend)



Median systolic BP (mmHg)	106	116	125	135	144	154	168
No. of person years	1431	4266	8974	11983	9138	4942	3470

*New-onset microalbuminuria or nephropathy, doubling of serum creatinine to >200 µmol/l, or ESRD
BP, blood pressure; ESRD, end-stage renal disease; T2D, type 2 diabetes
de Galan B *et al. J Am Soc Nephrol* 2009;20:883

Blood Pressure reduction and renal function: is there a J curve relationship?



Target blood pressure in chronic kidney disease

	Target BP* in CKD without albuminuria or proteinuria (mm Hg)	Target BP in CKD with albuminuria or proteinuria (mm Hg)	Target BP in diabetes (mm Hg)	Target BP in elderly people (mm Hg)	Definition of resistant hypertension
KDIGO[5]	≤140/90	≤130/80	As for non-diabetics	No specific targets	NA
CHEP[6]	<140/90 (in non-diabetic CKD) <130/80 (in diabetes)	<140/90 (in non-diabetic CKD) <130/80 (in diabetes)	<130/80	Aged ≥80 years; <150† systolic BP	NA
JNC 8[7]	<140/90	<140/90	<140/90	Aged ≥60 years; <150/90, <140/90 if in diabetes and CKD or CKD alone	NA
JNC 7[8]	<130/80	<130/80	<130/80	No specific targets	Failure to achieve goal BP in patients who adhere to full doses of an appropriate three drug regimen that includes a diuretic
ISH and ASH[9]	<140/90	<140/90‡	<140/90	Aged ≥80 years; <150/90, <140/90 if in diabetes and CKD or CKD alone	BP ≥140/90 mm Hg with use of three drugs (ACEi or ARB, CCB, and a diuretic) in full or maximally tolerated doses
NICE[10–12]	<140/90 (in non-diabetic CKD) <130/80 (in diabetes)§	<130/80	<140/80, <130/80 with kidney, eye, or cerebrovascular damage¶	Aged ≥80 years; <150/90†	BP >140/90 mm Hg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic
NHFA[13]	<130/80	<125/75	<130/80	No specific targets	NA
ESC and ESH[3]	<140, systolic BP	<130, systolic BP	<140/85	Aged ≥80 years; <150/90†	BP ≥140/90 mm Hg with appropriate lifestyle measures and three drugs (a diuretic and two other drugs belonging to different classes, not necessarily including an MRA) at adequate doses

Lancet 2015; 386: 1588–98

CMAJ RESEARCH
CMAJ, August 6, 2013

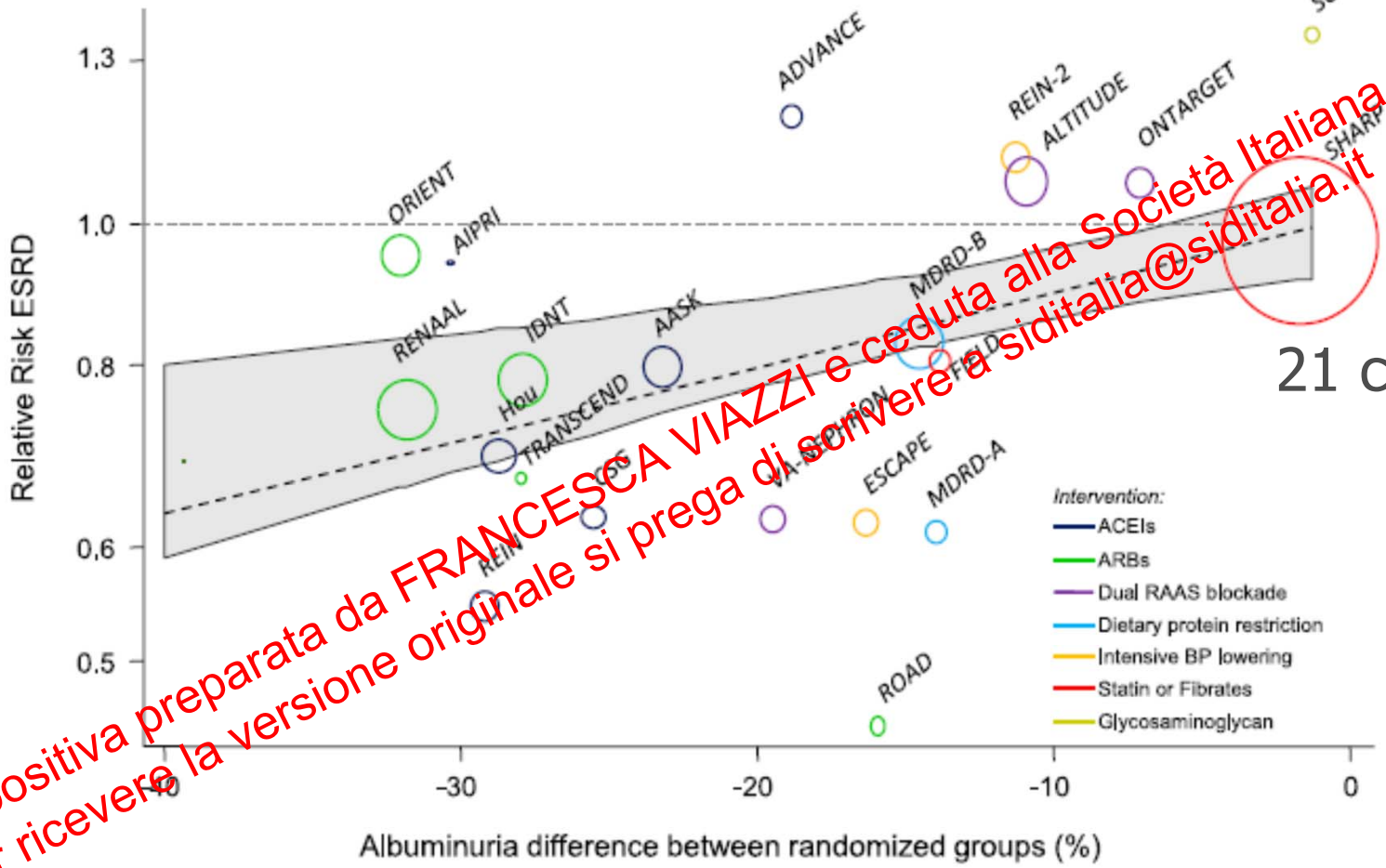
Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis

Jicheng Lv MD PhD, Parya Ehteshami BSc, Mark J. Sarnak MD, Hocine Tighiouart MS, Min Jun PhD, Toshiharu Ninomiya MD PhD, Celine Foote MD, Anthony Rodgers MD PhD, Hong Zhang MD PhD, Haiyan Wang MD, Giovanni F.M. Strippoli MD PhD, Vlado Perkovic MD PhD

Patient subgroup	Treatment, no. of events/patients: Intensive	Standard	HR (95%CI)
Without baseline proteinuria			
Wühl et al.[18]	NA/33	NA/41	1.78 (0.62–5.14)
Klahr et al.[17]	128/210	133/201	0.77 (0.58–1.02)
Appel et al.[13]	98/357	83/376	1.39 (1.04–1.86)
Overall (I^2 = 78.2%)	226/600	216/618	1.12 (0.67–1.87)
With baseline proteinuria			
Wühl et al.[18]	NA/65	NA/59	0.53 (0.33–0.87)
Ruggenenti et al.[14]	38/169	34/169	1.00 (0.61–1.64)
Klahr et al.[17]	178/221	177/207	0.71 (0.56–0.91)
Appel et al.[13]	114/181	126/176	0.76 (0.58–0.99)
Hayashi et al.[27]	2/224	4/230	0.51 (0.09–2.78)
Overall (I^2 = 0.0%)	332/862	341/841	0.73 (0.62–0.86)

Drug-Induced Reduction in Albuminuria Is Associated with Subsequent **Renoprotection**: A Meta-Analysis

REASSURE Consortium



21 clinical trials
78,342 ptz
4183 ESRD

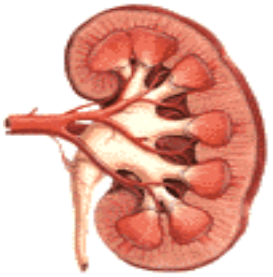
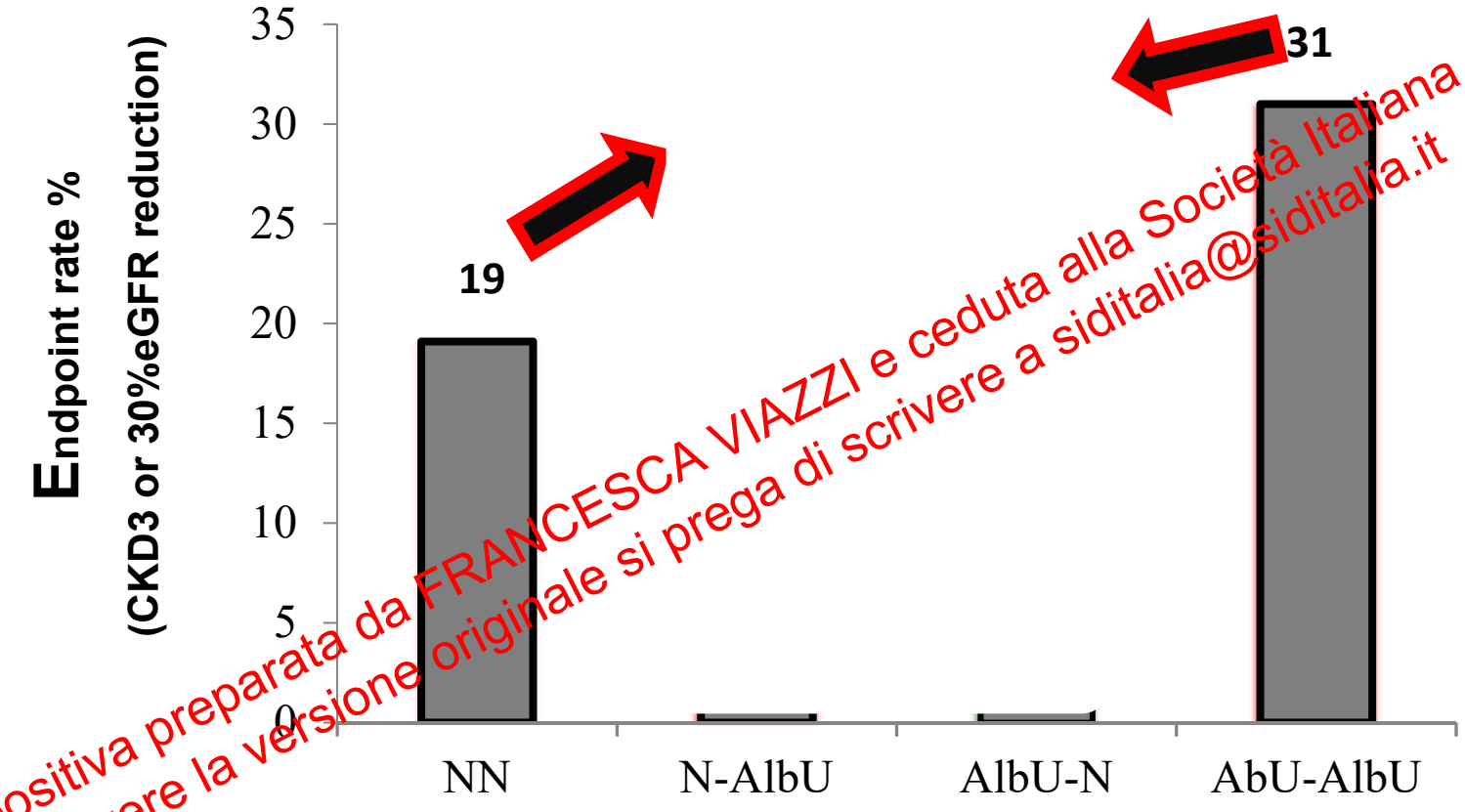


Figure 2. Univariate meta-regression exploring the association between the placebo-controlled treatment effect on albuminuria and the placebo-controlled treatment effect on ESRD events. Different types of interventions are indicated by different colors.

JASN, 2015

Changes in albuminuria and renal outcome in patients with hypertension and T2D



"[…] changes in albuminuria translate to changes in risk."

12,611 ptz with T2D and HT
eGFR >60 ml/min independently by albuminuria
4-years f-up

Viazzi F, Pontremoli R et al.
J Hypertens 2018.

Original Investigation

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

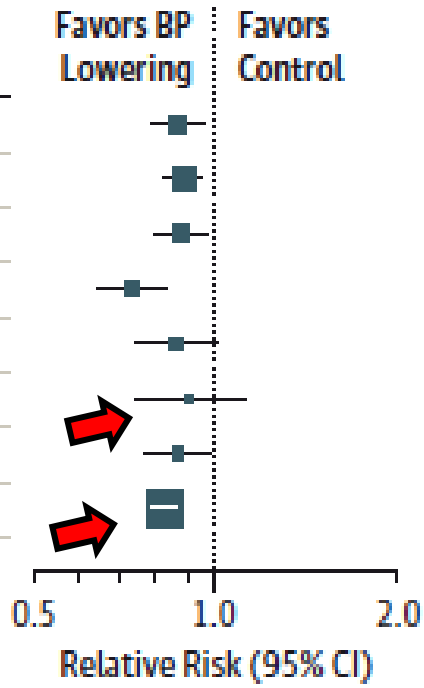
Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD

40 trials 100 354 pts
T2DM

JAMA. 2015;313(6):603-615.

Figure 2. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients

Outcome	No. of Studies	BP Lowering		Control		Relative Risk (95% CI)
		Events	Participants	Events	Participants	
Mortality	20	2334	27 609	2319	25 864	0.87 (0.78-0.96)
Cardiovascular disease	17	3230	25 756	3280	24 862	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26 150	1449	24 761	0.88 (0.80-0.98)
Stroke	19	1350	27 614	1475	26 447	0.73 (0.64-0.83)
Heart failure	13	1235	21 684	1348	20 791	0.86 (0.74-1.00)
Renal failure	9	596	19 835	560	18 912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	13 804	3163	12 821	0.83 (0.79-0.87)



Research

JAMA. 2015;313(6):603-615.

Original Investigation

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB;

Figure 3. Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes Stratified by Mean Systolic BP of Trial Participants at Entry

10 mmHg ↓ by SBP ≥140 vs <140 at entry

Outcome	No. of Studies	Baseline SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	P for Interaction
Mortality, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 51, 55, 56, 64, 65, 77-80]	13	149	1614	16418	1626	14580	0.73 (0.64-0.84)	
<140[17, 31, 36-38, 58-60, 80, 81]	7	137	720	1275	693	11284	1.07 (0.92-1.26)	P<.001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 46, 47, 51-53]	11	148	1861	14976	1918	14058	0.74 (0.65-0.85)	
<140[17, 31, 36-38, 58-60, 80, 81]	6	137	1369	10780	1362	20794	0.96 (0.88-1.05)	P=.001
Overall							0.89 (0.83-0.95)	
Coronary heart disease, mm Hg								
≥140[16, 18, 27, 29, 30, 35, 39-41, 47, 51, 64, 65]	10	148	858	14876	931	13477	0.73 (0.61-0.87)	
<140[17, 31, 36-38, 43, 58-60, 80, 81]	7	137	532	11275	518	11284	0.97 (0.86-1.10)	P=.01
Overall							0.88 (0.80-0.98)	
Stroke, mm Hg								
≥140[16, 18, 19, 27, 29, 30, 35, 39-41, 45-47, 51, 55, 56, 63-65]	14	148	1129	19066	1245	17868	0.74 (0.64-0.86)	
<140[31, 36-38, 58-60, 80, 81]	5	137	221	8548	230	8579	0.69 (0.52-0.92)	P=.70
Overall							0.73 (0.64-0.83)	
Heart failure, mm Hg								
≥140[16, 18, 29, 30, 35, 39-41, 46, 47, 64, 65]	8	146	774	13592	814	12676	0.75 (0.59-0.94)	
<140[31, 42, 43, 58-60, 80, 81]	5	137	461	8092	534	8115	0.97 (0.79-1.19)	P=.09
Overall							0.86 (0.74-1.00)	
Renal failure, mm Hg								
≥140[16, 18, 29, 30, 39, 40, 41, 64, 65]	6	147	389	12475	346	11530	0.75 (0.52-1.08)	
<140[31, 58-60]	3	138	207	7360	214	7382	1.00 (0.77-1.29)	P=.21
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥140[16, 28-30, 64, 65, 77-80]	4	146	564	7946	586	7753	0.86 (0.70-1.04)	
<140[36-38, 59, 60, 80, 81]	3	137	280	1835	319	1813	0.88 (0.74-1.05)	P=.85
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥140[16, 28-30, 64, 65]	4	146	1681	8447	1898	7647	0.71 (0.63-0.79)	
<140[17, 36-38, 59, 60]	3	137	1118	5357	1265	5174	0.86 (0.81-0.90)	P=.002
Overall							0.83 (0.79-0.87)	

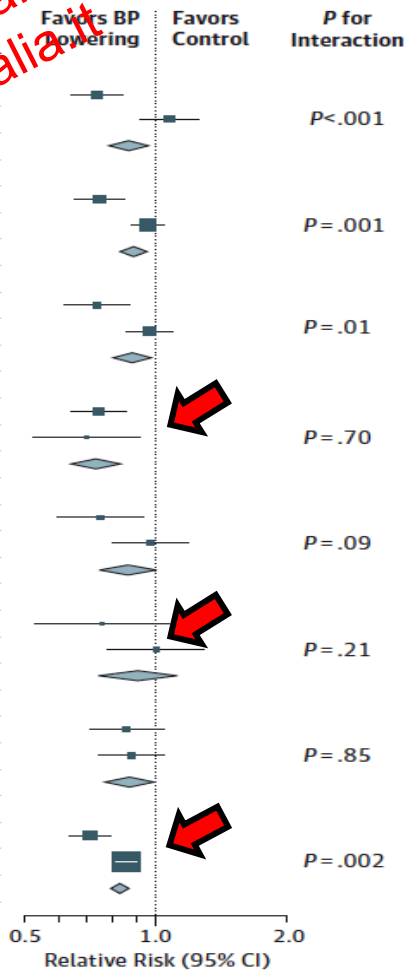
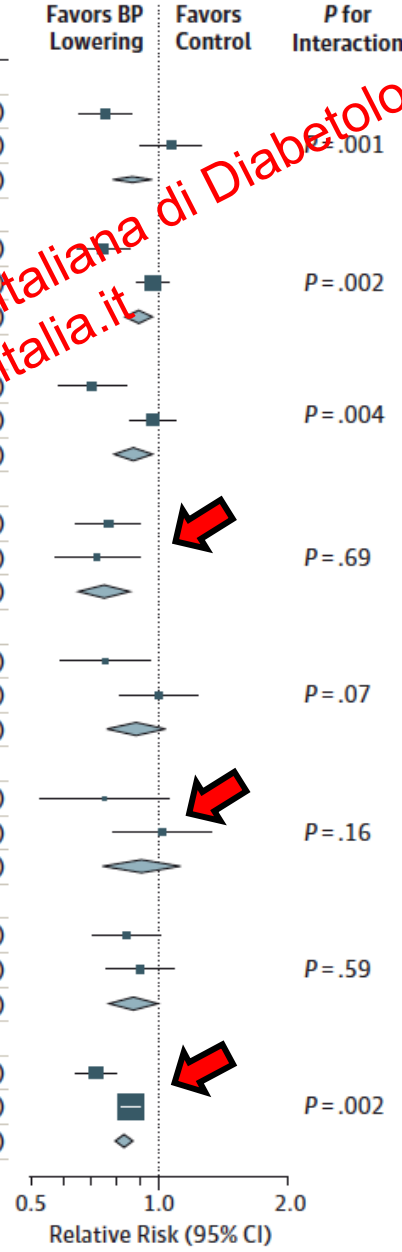


Figure 4. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes, Stratified by Mean Achieved Systolic BP in the Active Group of Each Trial

10 mmHg ↓ by achieved SBP ≥130 vs <130

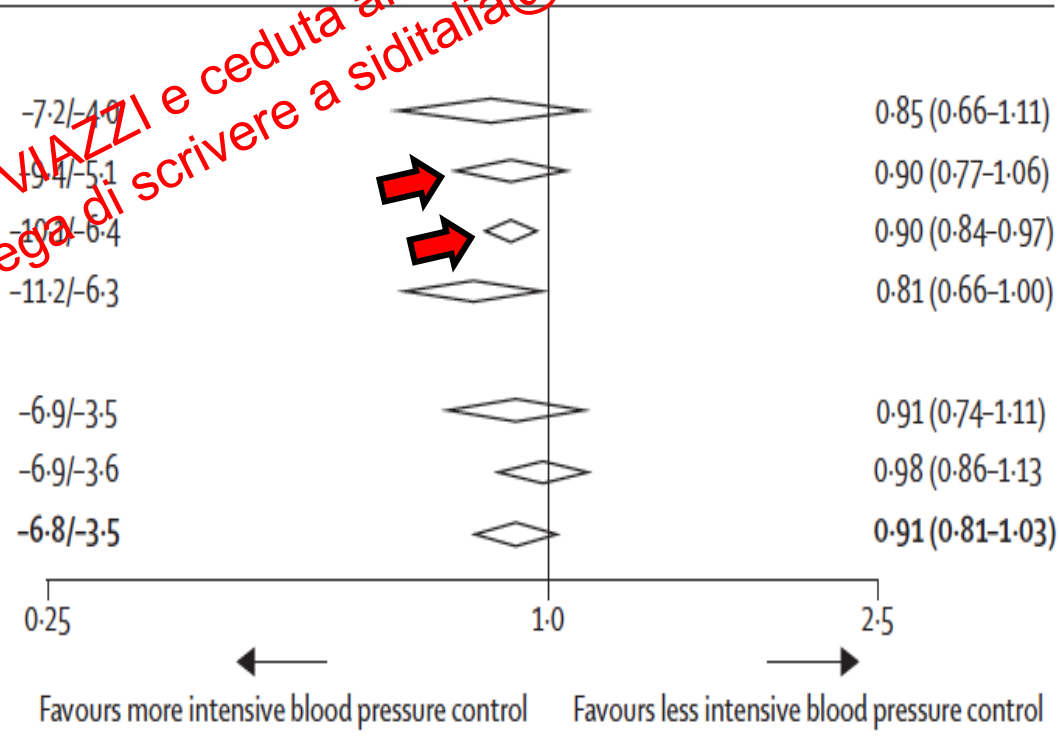
Outcome	No. of Studies	Achieved SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	*P* for Interaction
Mortality, mm Hg								
≥130[16, 18, 19, 27-31, 35-41, 51, 55, 56, 58, 64, 65, 77-80]	16	138	2090	22 367	2079	20 545	0.75 (0.65-0.86)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	244	5326	240	5319	1.06 (0.90-1.25)	*P* = .001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 51-53, 58]	13	138	2551	20 529	2558	19 668	0.74 (0.64-0.85)	
<130[17, 59, 60, 80, 81]	3	123	597	4831	631	4829	0.96 (0.88-1.05)	*P* = .002
Overall							0.89 (0.83-0.96)	
Coronary heart disease, mm Hg								
≥130[16, 18, 27, 29, 30, 32, 35-41, 51, 58, 64, 65]	12	138	1055	20 428	1126	19 077	0.70 (0.58-0.83)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	305	5326	302	5319	0.97 (0.85-1.10)	*P* = .004
Overall							0.87 (0.78-0.96)	
Stroke, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 45, 51, 55, 56, 58, 64, 65]	15	138	1196	24 066	1261	22 915	0.76 (0.64-0.90)	
<130[59, 60, 63, 80, 81]	3	121	106	3152	249	3167	0.72 (0.57-0.90)	*P* = .69
Overall							0.74 (0.65-0.85)	
Heart failure, mm Hg								
≥130[16, 18, 29, 30, 32, 35, 38-41, 58, 64, 65]	9	138	1043	18 194	1106	17 322	0.75 (0.59-0.95)	
<130[42, 43, 59, 60, 80, 81]	3	121	167	3094	209	3104	1.00 (0.81-1.23)	*P* = .07
Overall							0.88 (0.75-1.03)	
Renal failure, mm Hg								
≥130[16, 18, 29, 30, 32, 35, 40, 41, 58, 64, 65]	8	139	537	17 473	502	16 541	0.74 (0.52-1.06)	
<130[59, 60]	1	119	59	2362	58	2371	1.01 (0.78-1.32)	*P* = .16
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥130[16, 28-30, 36-38, 64, 65, 77-80]	5	137	694	8897	736	8707	0.84 (0.70-1.01)	
<130[59, 60, 80, 81]	2	120	150	884	169	859	0.90 (0.75-1.08)	*P* = .59
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥130[16, 28-30, 36-38, 64, 65]	5	137	1822	9398	2049	8601	0.71 (0.64-0.79)	
<130[17, 59, 60]	2	122	977	4406	1114	4220	0.86 (0.81-0.90)	*P* = .002
Overall							0.83 (0.79-0.87)	



Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis

Xinfang Xie, Emily Atkins, Jicheng Lv, Alexander Bennett, Bruce Neal, Toshiharu Ninomiya, Mark Woodward, Stephen MacMahon, Fiona Turnbull, Graham S Hillis, John Chalmers, Jonathan Mant, Abdul Salam, Kazem Rahimi, Vlado Perkovic, Anthony Rodgers

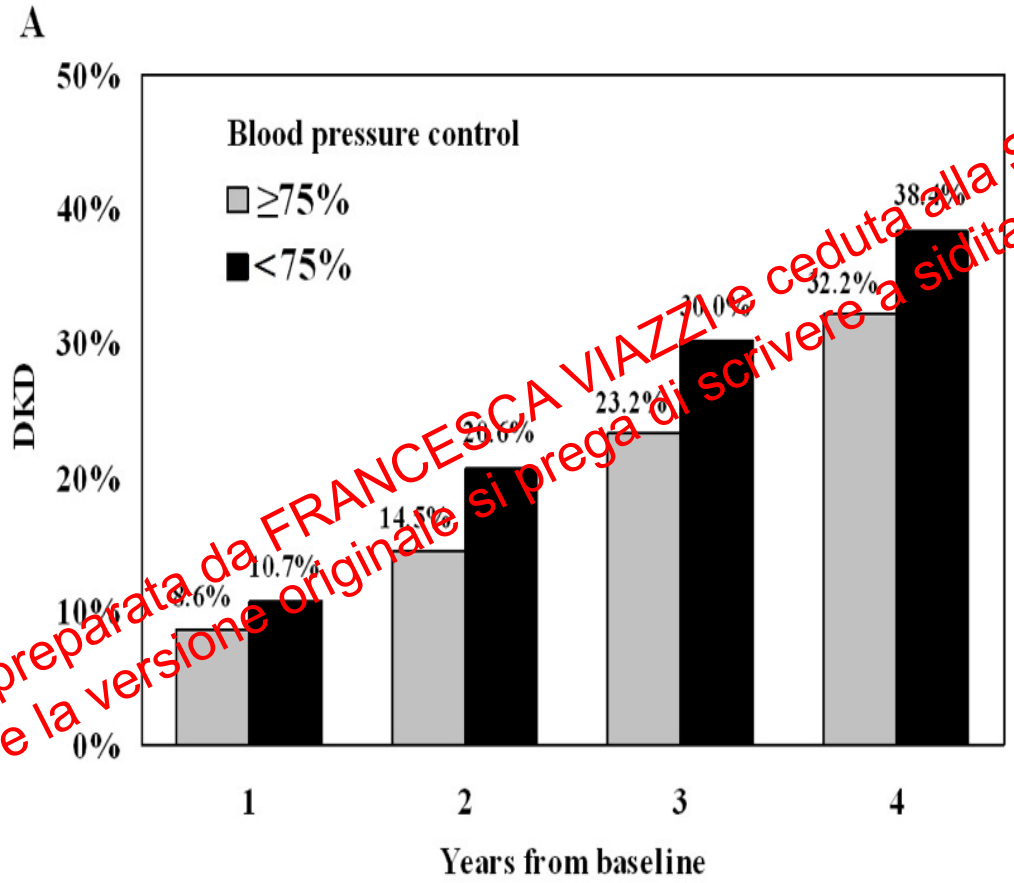
	Trials (n)	Events (n)/patients (n)	Mean blood pressure difference (mm Hg)	Relative risk (95% CI)
Other major vascular events and renal outcomes				
Heart failure	10	189/13 698 vs 221/19 608	−7·2/−4·0	0·85 (0·66–1·11)
End-stage kidney disease	8	248/4533 vs 266/4157	−5·4/−5·1	0·90 (0·77–1·06)
Albuminuria	3	926/2661 vs 988/2563	−10·4/−6·4	0·90 (0·84–0·97)
Retinopathy	4	342/1421 vs 351/1244	−11·2/−6·3	0·81 (0·66–1·00)
Mortality				
Cardiovascular death	13	354/18 209 vs 446/24 163	−6·9/−3·5	0·91 (0·74–1·11)
Non-cardiovascular death	12	385/18 027 vs 476/23 966	−6·9/−3·6	0·98 (0·86–1·13
Overall mortality	**19**	**794/19 537 vs 968/25 452**	**−6·8/−3·5**	**0·91 (0·81–1·03)**



19 trials 44 989 pts

www.thelancet.com **Published online November 6, 2015**

BP status and the incidence of CKD in patients with hypertension and T2DM: The AMD Annals initiative



- 12,995 patients
- Age: 64±9 years
- Diabetes duration: 11±8 years
- 59% male

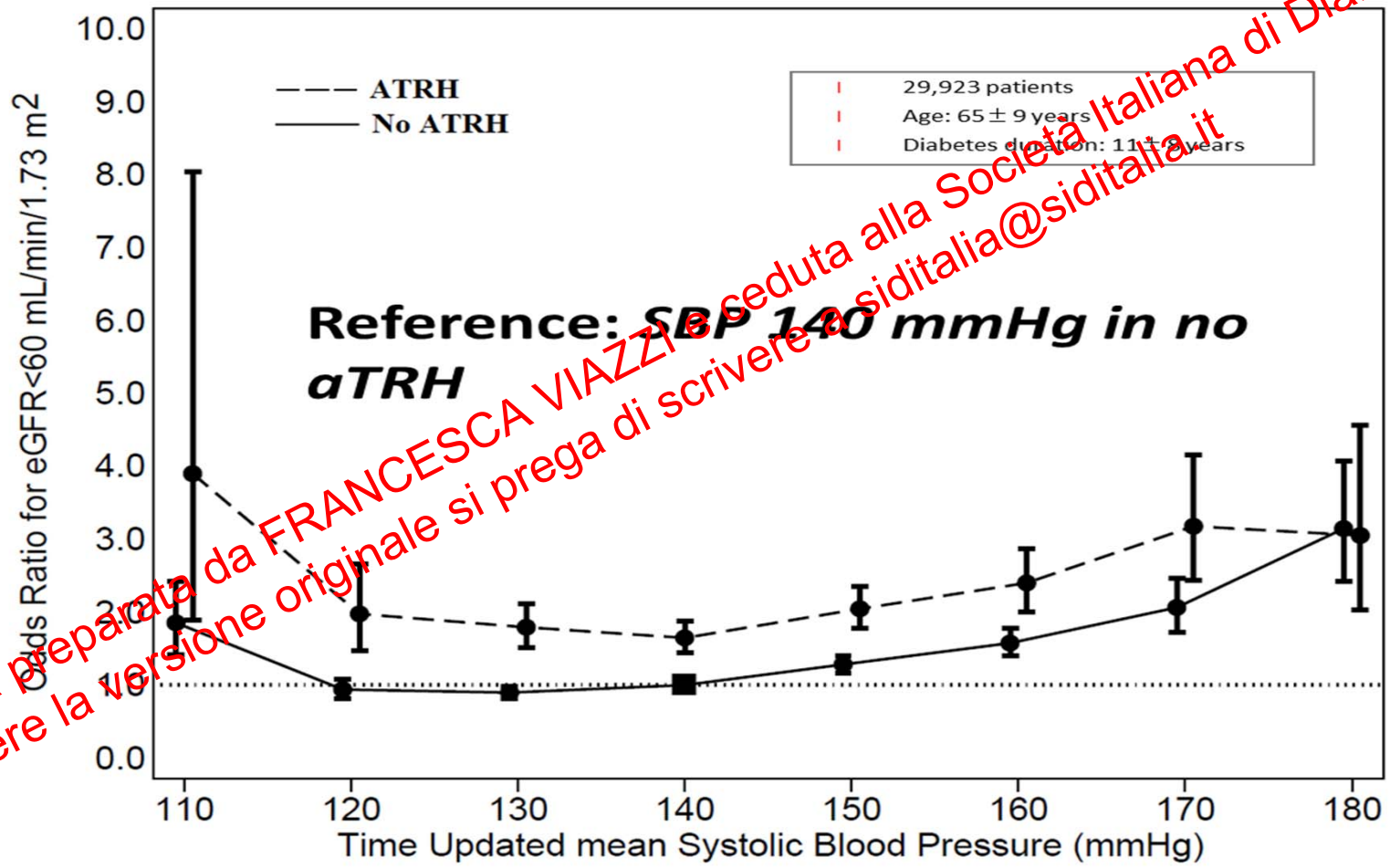
De Cosmo S, Pontremoli R et al, J Hypertens 2016

BP status and the incidence of CKD in patients wit hypertension and T2DM: The AMD Annals initiative

	Univariate		Multivariate	
	Odds Ratio	p	Odds Ratio	p
DKD				
Systolic BP (by 10 mmHg below 140)	0.84 (0.79-0.89)	<0.001	0.85 (0.80-0.91)	<0.001
Diastolic BP (by 5 mmHg below 85)	0.93 (0.89-0.97)	0.001	0.89 (0.85-0.93)	<0.001
eGFR <60 mL/min/1.73 m^2				
Systolic BP (by 10 mmHg below 140)	0.90 (0.82-0.98)	0.016	0.97 (0.88-1.06)	0.474
Diastolic BP (by 5 mmHg below 85)	1.06 (1.00-1.13)	0.057	1.00 (0.94-1.07)	0.924
Albuminuria				
Systolic BP (by 10 mmHg below 140)	0.80 (0.75-0.86)	<0.001	0.79 (0.74-0.85)	<0.001
Diastolic BP (by 5 mmHg below 85)	0.89 (0.84-0.93)	<0.001	0.85 (0.81-0.90)	<0.001

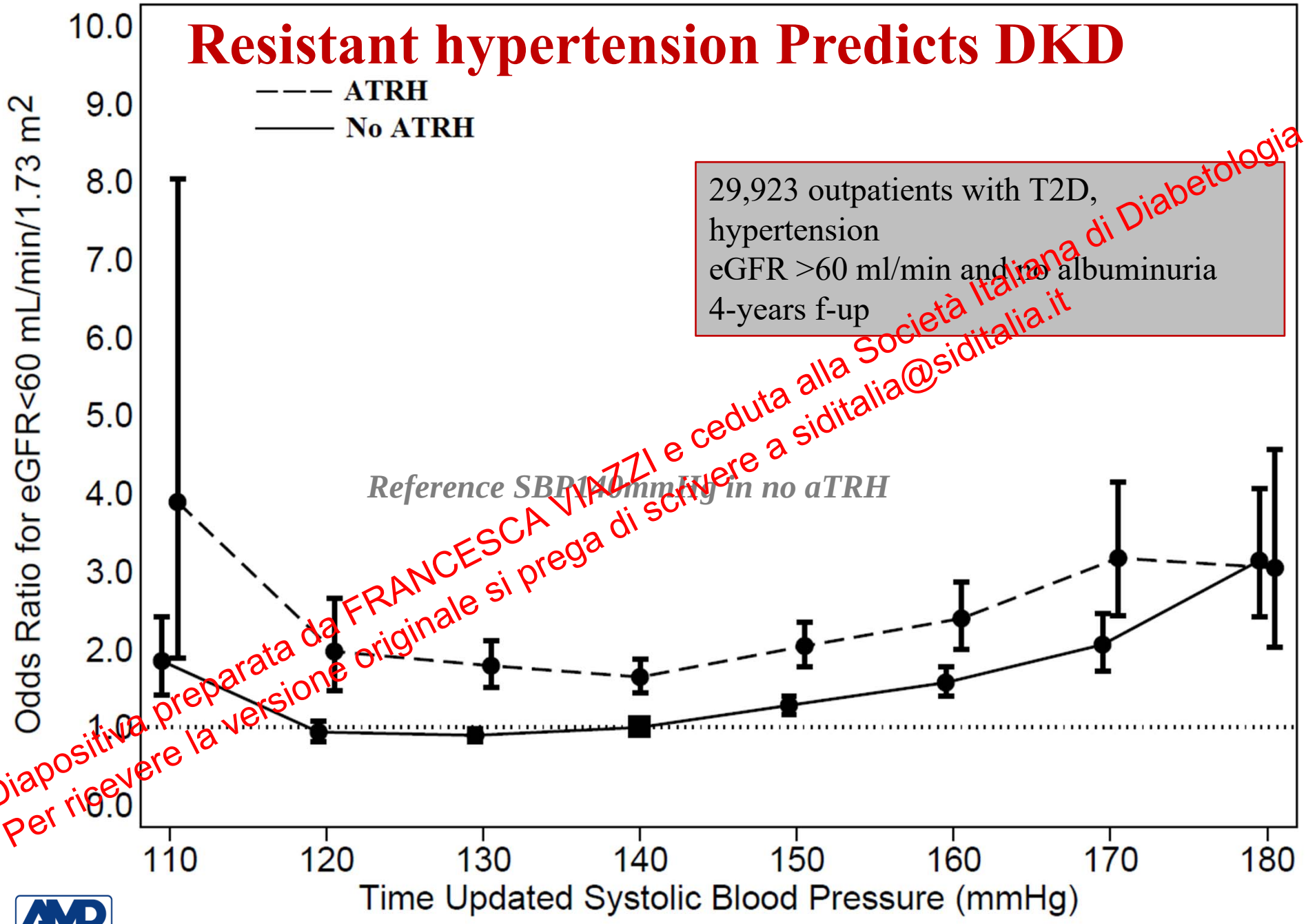
De Cosmo S, Viazzi F et al, J Hypertens 2016

Resistant hypertension and renal outcome in T2DM
The J curve relationship between BP and renal function



Viazzi F, Pontremoli R et al. J Am Heart Assoc 2017

Resistant hypertension Predicts DKD



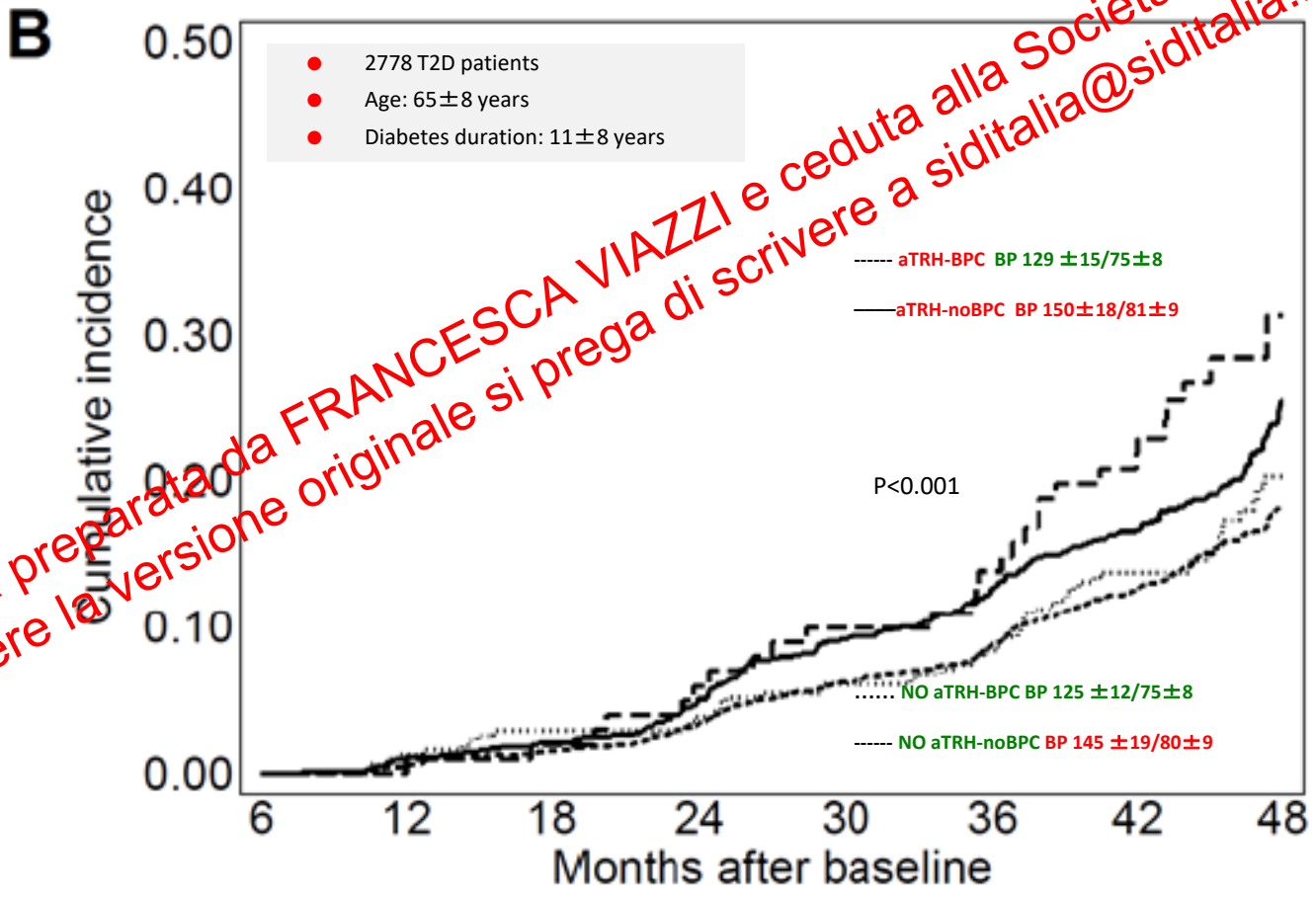
Viazzi F, et al J Am Heart Assoc. 2017

Original Paper

Apparent Treatment Resistant Hypertension, Blood Pressure Control and the Progression of Chronic Kidney Disease in Patients with Type 2 Diabetes

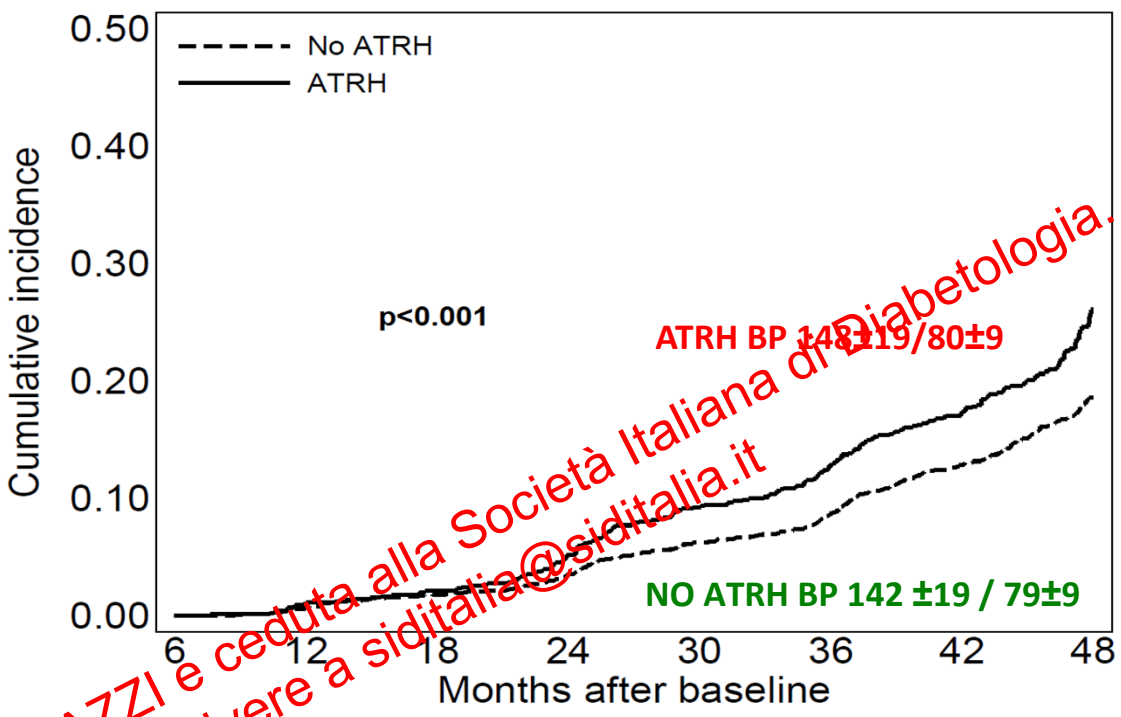
Francesca Viazzi[a] Eulalia Greco[b] Antonio Ceriello[c,d] Paola Fioretto[e]
Carlo Giorda[f] Pietro Guida[g,h] Giuseppina Russo[i] Salvatore De Cosmo[b]
Roberto Pontremoli[a] AMD-Annals Study Group[j]

Kidney & Blood Pressure Research



2018

Cumulative incidence curves by Kaplan-Meier of eGFR reduction >30% on the basis of aTRH (A) and aTRH and BPC status (B) in 2,778 T2D, HT and CKD3 (between 30 and 60 ml/min) and regular visits during a4-yrs follow-up

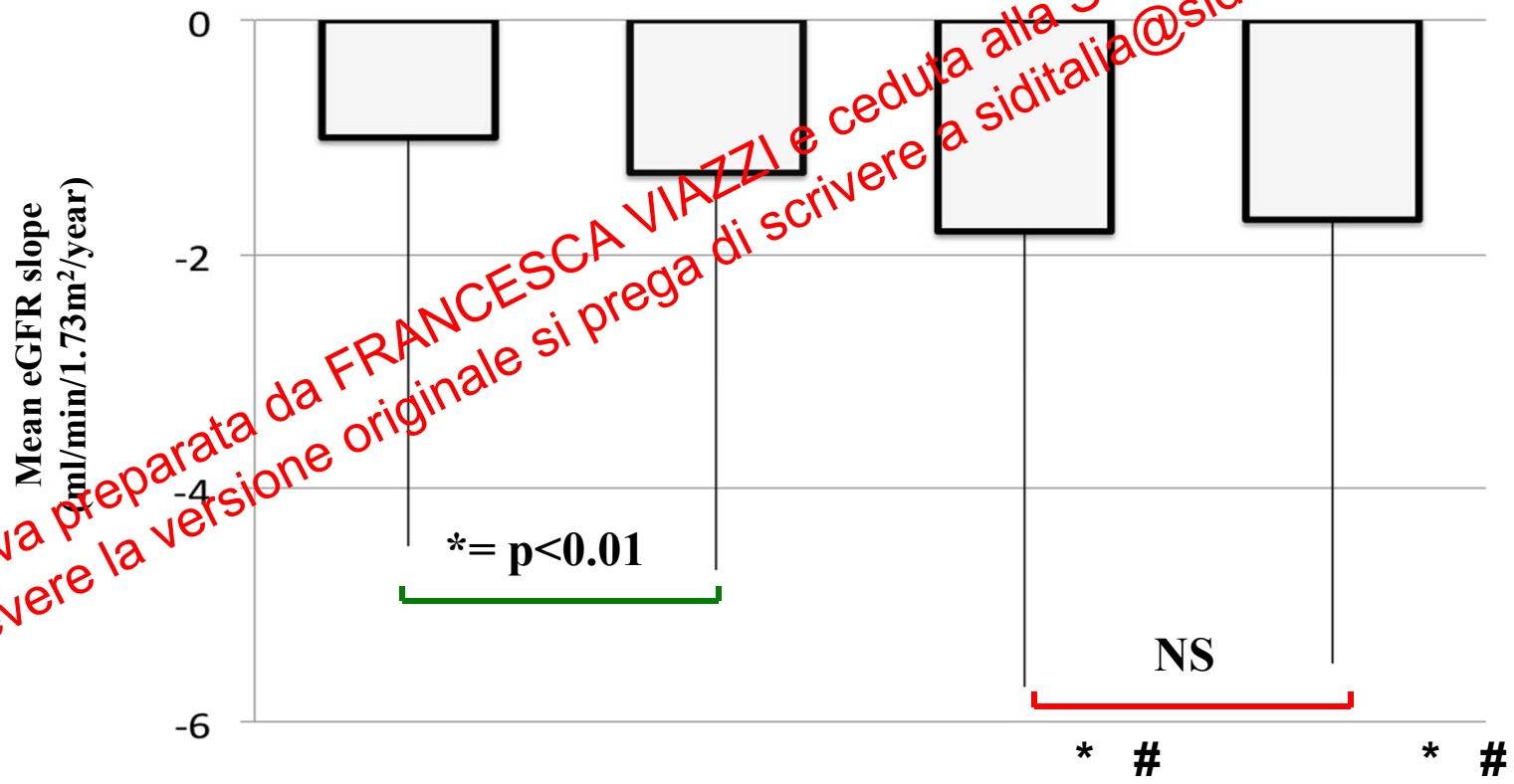


Viazzi F et al.,
Kidney Blood Press Res 2018;43:422-438

Resistant hypertension and renal outcome in T2DM

The J curve relationship between BP and renal function

	No-aTRH BPC	No- aTRH No-BPC	aTRH BPC	aTRH No- BPC
N of ptz	4198	20736	514	4475
Baseline eGFR (ml/min/1.73m^2)	86±14	86±13	83±13	83±13



*= p<0.01 vs No-aTRH with BPC; # = p<0.01 vs No-aTRH with NoBPC

The RIACE Study

Renal dysfunction is common in Italian T2DM Patients

J Hypertens 2011, 29: 1802-1809

15773 T2DM patients randomly selected in Italian outpatient clinics

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Clinical features of 120,903 patients with type 2 diabetes: whole sample and division according to the presence/absence of albuminuria or low eGFR

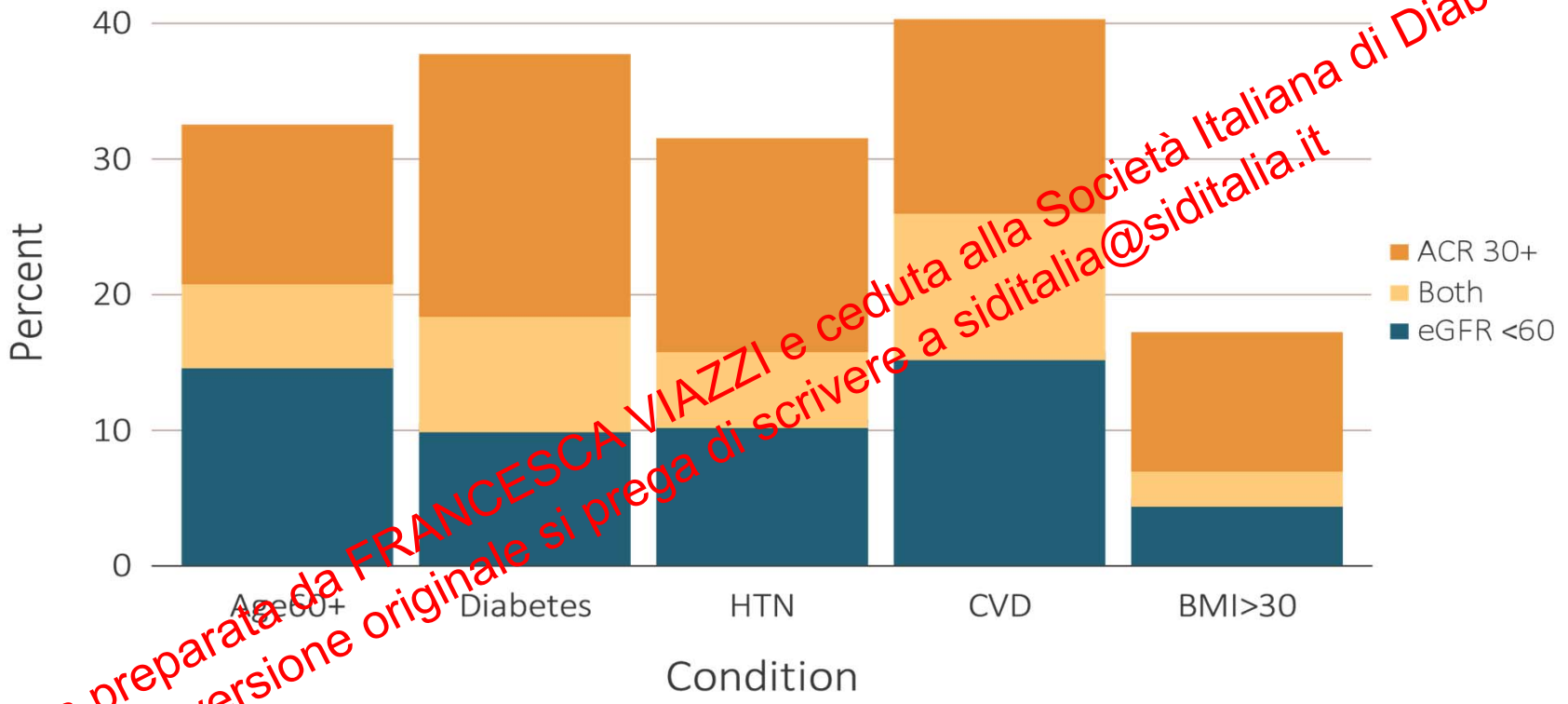
62.5%	10.6%	18.7%	8.2%

	Whole sample	Alb− and low eGFR−	Alb− and low eGFR+	Alb+ and low eGFR−	Alb+ and low eGFR+
n (%)	120 903	63 639 (52.6%)	13 660 (11.3%)	28 806 (23.8%)	14 684 (12.2%)
Male gender n (%)	70 247 (58.1)	35 822 (56.3)	5 776 (42.2)	19 874 (69.0)	8741 (59.5)
Age (years)	66.6 ± 11.0	64.1 ± 10.7	74.0 ± 8.4	65.0 ± 10.8	73.4 ± 8.5
BMI (kg/m^2)	29.7 ± 5.2	29.4 ± 5.2	28.1 ± 5.1	30.2 ± 5.3	30.0 ± 5.2
Serum creatinine (mg/dL)	1.0 ± 0.5	0.8 ± 0.2	1.3 ± 0.5	0.9 ± 0.2	1.6 ± 0.8
eGFR	75.5 ± 1.5	85.1 ± 13.9	48.0 ± 9.8	84.1 ± 14.4	42.8 ± 12.7
Known duration of diabetes (years)	11.1 ± 9.4	9.7 ± 8.6	13.3 ± 10.4	11.0 ± 9.0	15.3 ± 10.5
HbA1c (%)	7.5 ± 1.5	7.4 ± 1.5	7.4 ± 1.4	7.8 ± 1.6	7.7 ± 1.5
Total cholesterol (mg/dL)	186.4 ± 41.0	187.9 ± 40.0	185.7 ± 40.7	185.6 ± 42.3	183.4 ± 42.7
Triglycerides (mg/dL)	148.1 ± 100.2	139.4 ± 99.7	151.1 ± 87.4	157.2 ± 131.0	166.6 ± 108.1
HDL cholesterol (mg/dL)	49.3 ± 13.6	50.4 ± 13.7	49.6 ± 13.8	47.7 ± 13.2	46.5 ± 13.4
LDL cholesterol (mg/dL)	108.2 ± 34.2	110.0 ± 33.8	106.4 ± 34.1	107.1 ± 34.9	103.9 ± 34.4
SBP (mmHg)	139.6 ± 19.1	137.7 ± 18.3	139.5 ± 18.9	141.5 ± 19.5	143. 8 ± 20.5
DBP (mmHg)	79.2 ± 9.8	79.1 ± 9.5	77.3 ± 9.8	80.5 ± 10.0	78.5 ± 10.3
Pulse pressure (mmHg)	60.5 ± 16.5	58.7 ± 15.7	62.3 ± 16.6	61.1 ± 16.6	65.4 ± 18.0
Retinopathy	18.6	14.2	18.5	22.4	30.5
Smoker (%)	17.6	17.5	8.8	23.8	13.4

Alb−, normoalbuminuria; Alb+, albuminuria; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure All the between-group differences are statistically significant with $P < 0.0001$.

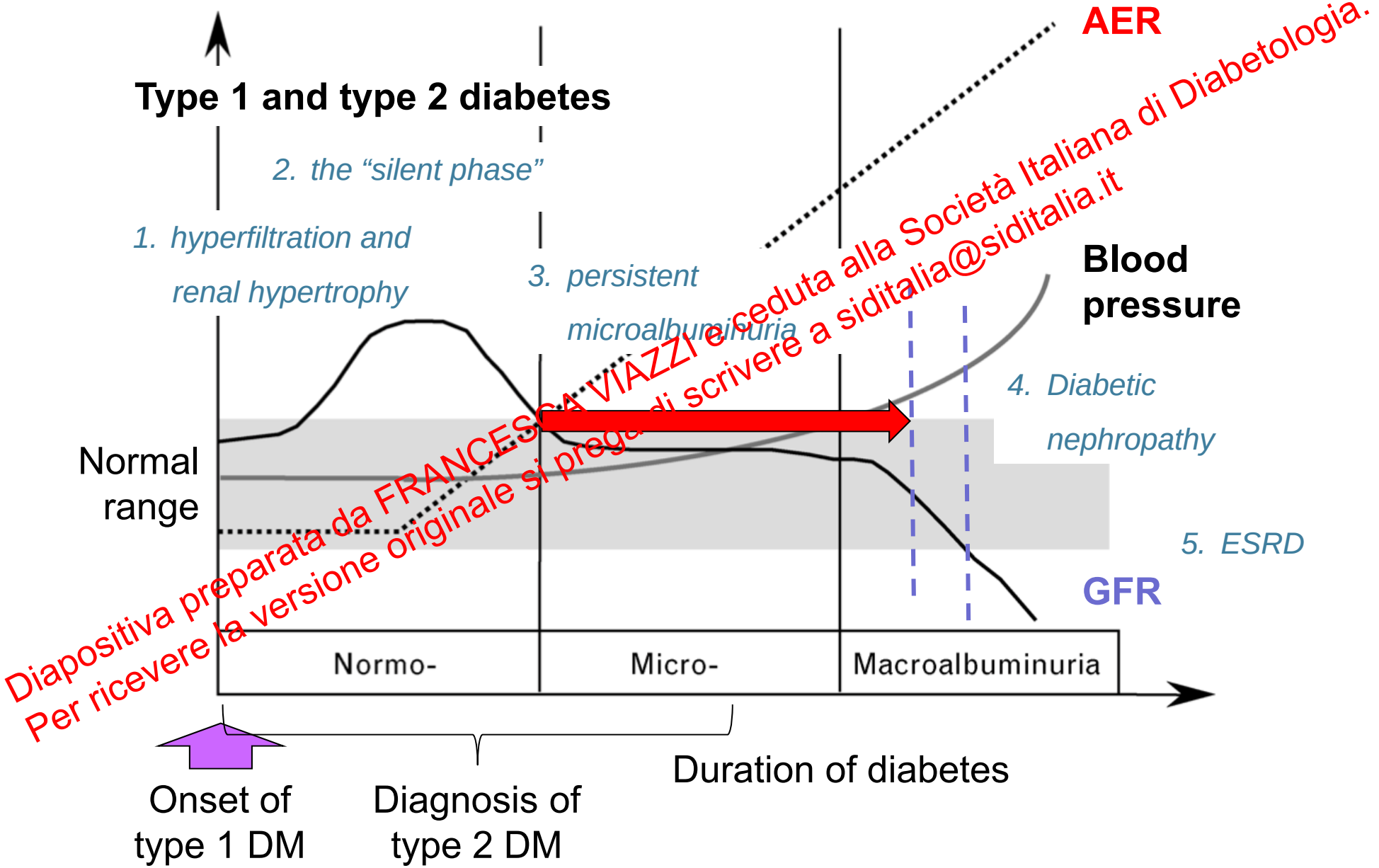
De Cosmo S, et al., The AMD-Annals Study Group. Nephrol Dial Transplant, 29: 657-662, **2014**

Distribution of markers of CKD in NHANES participants with diabetes, hypertension, CVD & obesity, 2013–2016

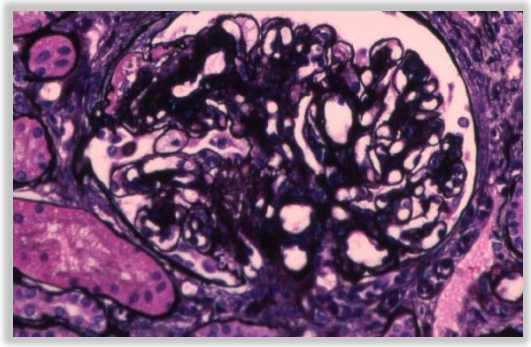


Data Source: National Health and Nutrition Examination Survey (NHANES), 2013-2016 participants age 20 & older. Single-sample estimates of eGFR & ACR; eGFR calculated using the CKD-EPI equation. Abbreviations: ACR, urine albumin/creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; SR CVD, self-reported cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension.

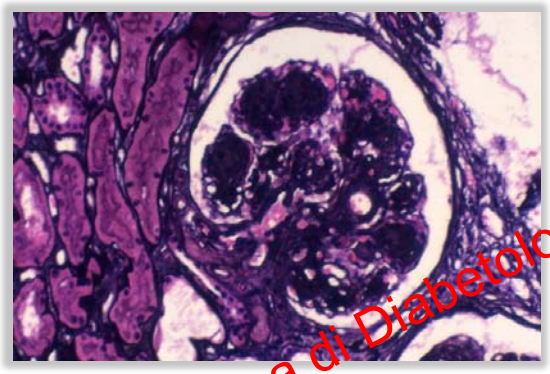
Historically, for people at risk of developing DKD, an initial increase in AER has been linked to a subsequent decline in GFR



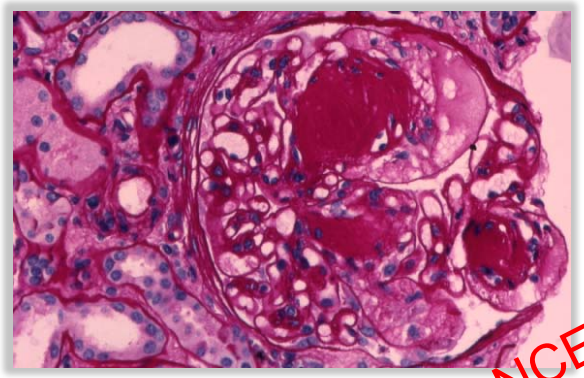
DIABETIC NEPHROPATHY



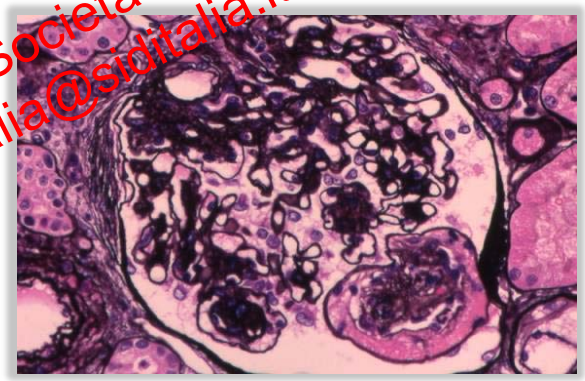
DIFFUSE
MESANGIAL INCREASE



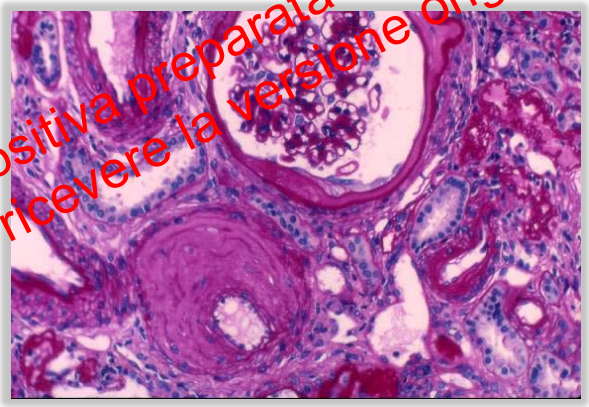
NODULAR
MESANGIAL INCREASE



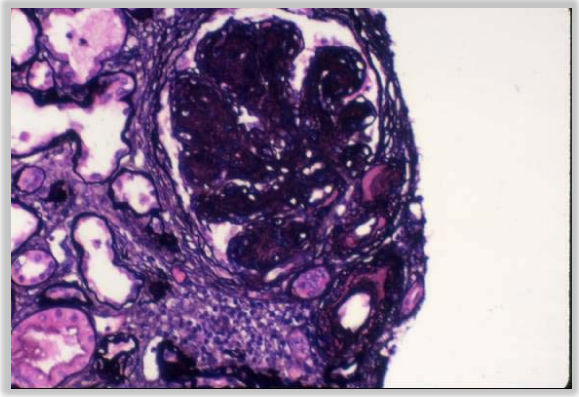
MICROANEURYSMS



MESANGIOLYSIS



AA INTIMAL FIBROSIS



Aa IALINOSIS AT VASCULAR
POLE

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Shree G. Sharma, Andrew S. Bomback,† Jai Radhakrishnan,† Leal C. Herlitz,‡ Michael B. Stokes,‡ Glen S. Markowitz,‡ and Vivette D. D'Agati‡*

2642 consecutive native renal biopsies at Columbia Renal Pathology Laboratory from (Jan- Dec 2011), 23% diabetics

Characteristics	DN Alone	DN Plus NDRD	NDRD Alone
Participants (*n*)	**(37%)** 227	**(26%)** 164	**(36%)** 220
Age (yr)	59 (49–68)	63 (55–72)[a]	63 (54–70)[b]
Male sex	129 (56.8)	100 (61.0)	142 (64.6)
Race			
Unknown	108 (47.6)	57 (34.8)[a]	104 (47.3)[c]
White	62 (27.3)	63 (38.4)[a]	70 (31.8)
African American	39 (17.2)	33 (20.1)	29 (13.2)
Hispanic	12 (5.3)	7 (4.3)	8 (3.6)
Asian	4 (1.8)	4 (2.4)	7 (3.2)
Other	2 (0.9)	0 (0.0)	2 (0.9)
DM type 1	9 (4.0)	5 (3.1)	2 (0.9)[b]
Duration of DM (yr)	13 (8–17)	10 (7–18)	5 (3–10)[b,c]
Serum creatinine (mg/dl)	2.3 (1.6–3.8)	3.1 (1.7–5.2)[a]	2.3 (1.5–4.4)[c]
eGFR (ml/min per 1.73 m^2)	31.3 (17.5–55.2)	21.4 (12.5–46.6)[a]	32.5 (14.3–60.0)[c]
Proteinuria (g/d)	5.0 (2.8–8.8)	5.0 (2.0–8.0)	2.9 (1.4–7.1)[b,c]

Clin J Am Soc Nephrol 24: 1901–1912, 2013

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

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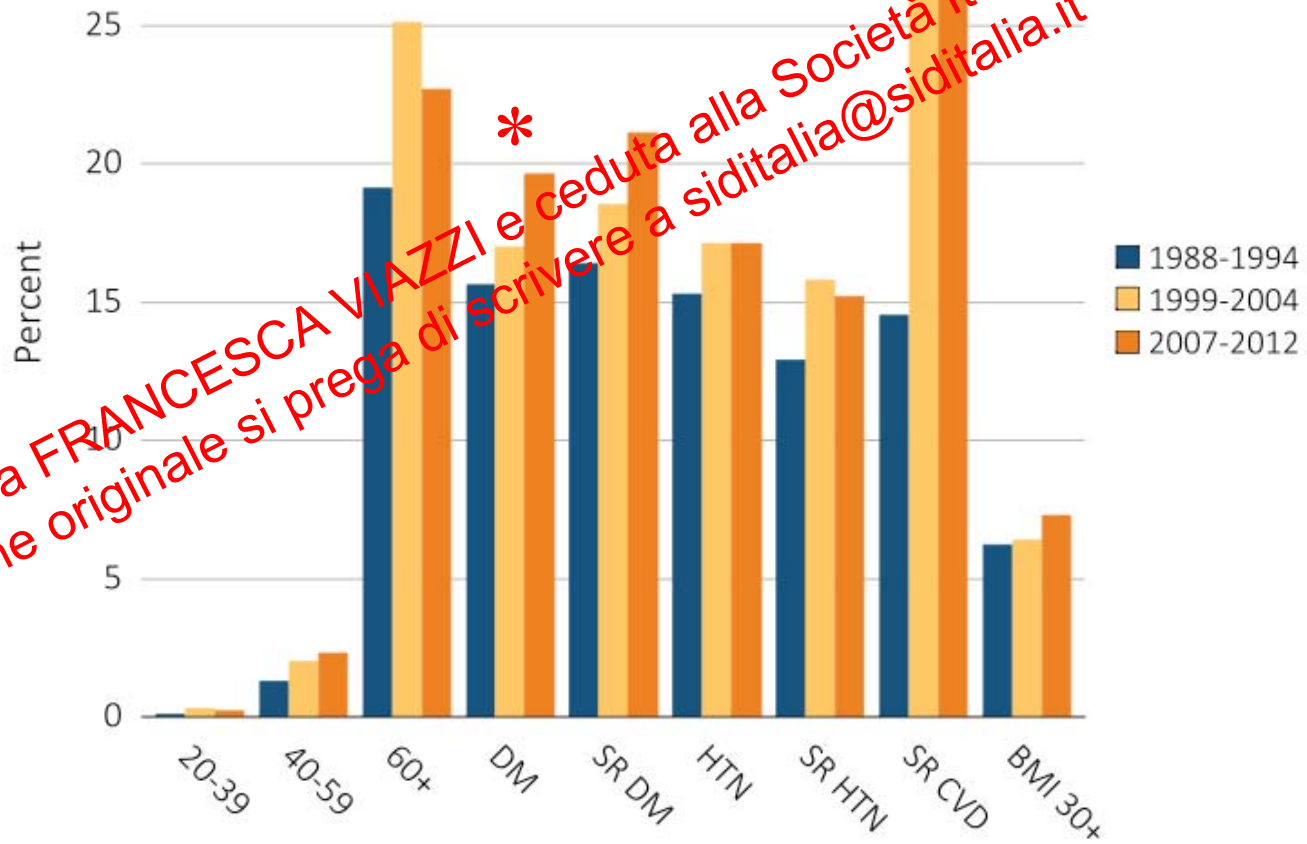
36% 63% 27%

Types of NDRD (n)	NDRD Alone (n=220)	DN Plus NDRD (n=164)	P Value[a]
Acute tubular necrosis (109)	38 (17.3)	71 (43.3)	<0.001
FSGS (69)	48 (21.8)	21 (12.8)	0.02
Primary FSGS (6)	6 (2.7)	0 (0.0)	0.03
Secondary FSGS (63)[b]			
HTN related	19 (8.6)	10 (6.1)	0.35
HTN plus obesity related	16 (7.3)	10 (6.1)	0.65
Obesity related	4 (1.8)	1 (0.6)	0.30
Other[c]	3 (1.4)	0 (0.0)	0.13
Hypertensive nephrosclerosis (70)[b]	39 (17.7)	31 (18.9)	0.77
IgA nephropathy (35)	23 (10.5)	12 (7.3)	0.29
Membranous GN (23)	18 (8.2)	5 (3.0)	0.04
Pauci-immune crescentic GN (19)	15 (6.8)	4 (2.4)	0.05
Acute interstitial nephritis (18)	11 (5.0)	7 (4.3)	0.73
Amyloidosis (10)	10 (4.5)	0 (0)	0.01
Myeloma cast nephropathy (10)	8 (3.6)	2 (1.2)	0.14
Acute postinfectious GN (6)	3 (1.4)	3 (1.8)	0.72
Atheroembolic disease (5)	2 (0.9)	3 (1.8)	0.43
Others (10)	5 (2.3)	5 (3.0)	0.64

Clin J Am Soc Nephrol 24: 1901–1912, 2013

Chronic Kidney Disease (CKD) in the general population: US Renal Data System 2014

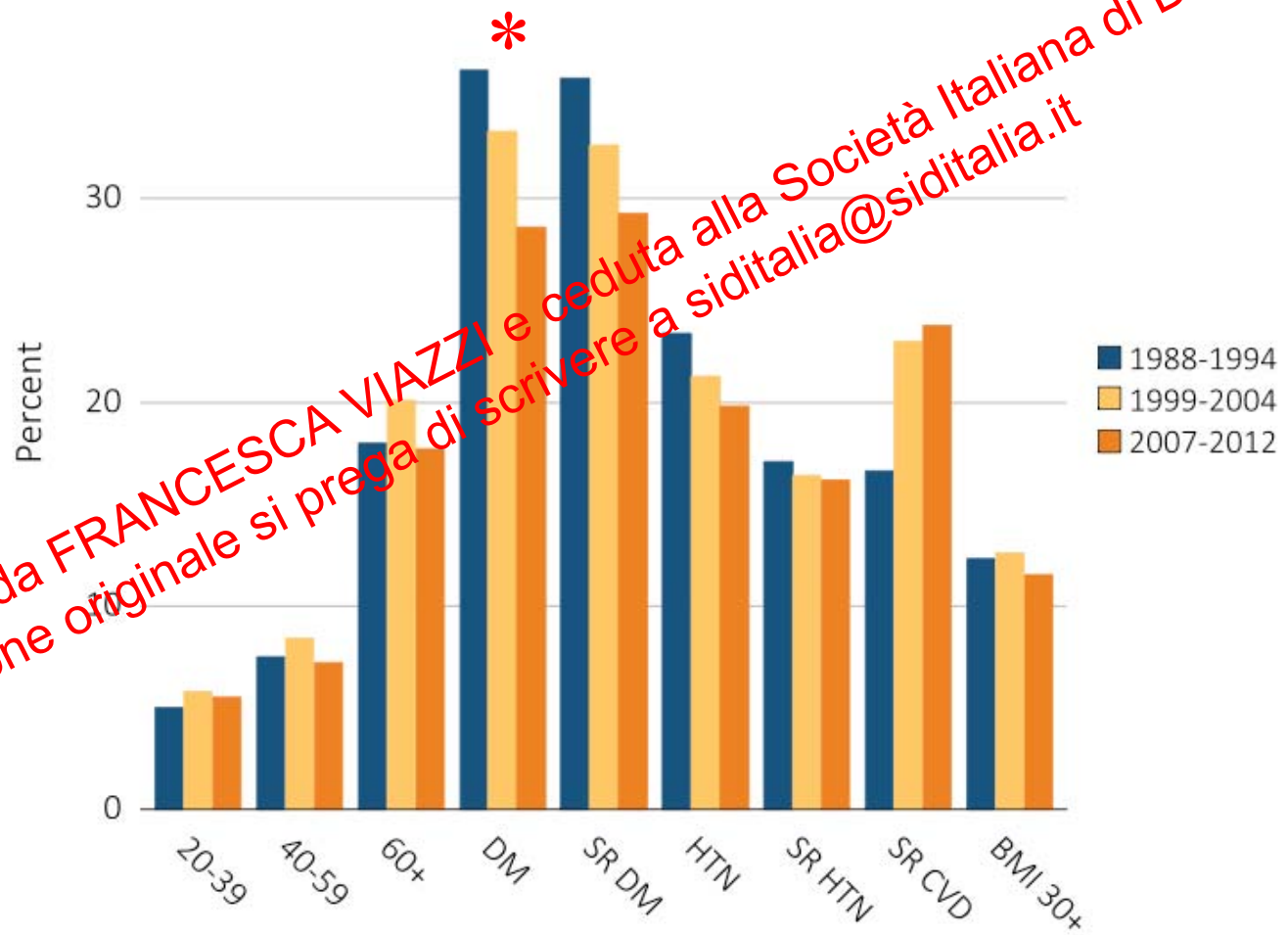
Prevalence (%) of eGFR <60 in the NHANES population by age & risk factors



2014 USRDS Annual Data Report - accessed at http://www.usrds.org/adr.aspx

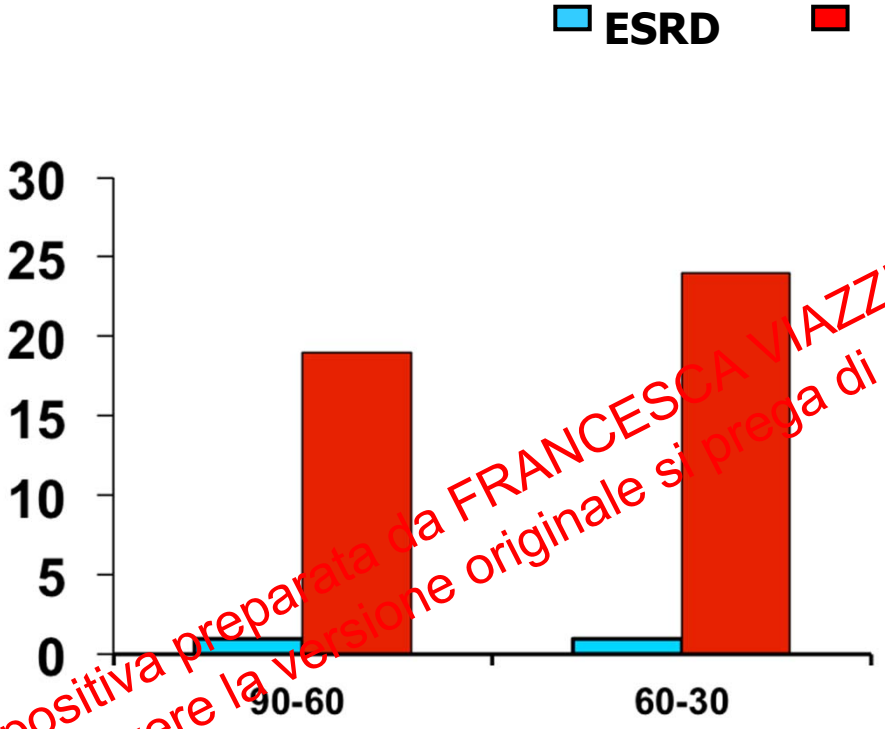
Chronic Kidney Disease (CKD) in the general population: US Renal Data System 2014

Prevalence (%) of ACR ≥30 in the NHANES population by age & risk factors

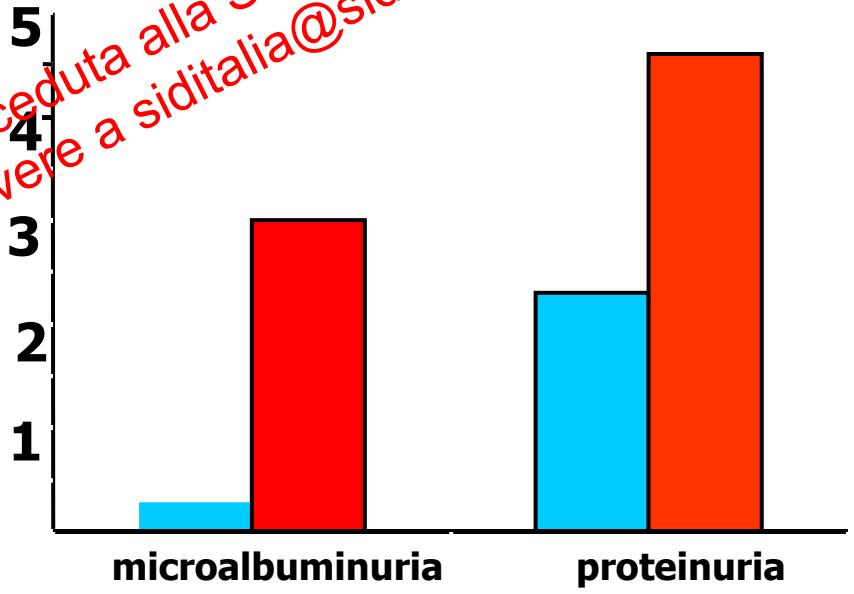


2014 USRDS Annual Data Report - accessed at http://www.usrds.org/adr.aspx

Incidence of either ESRD or death in 28,000 patients with baseline GFR < 90 ml/min and 3,402 patients with type 2 DM and CKD (UKPDS Study)



modified from Keith DS, JAMA 2004



Modified from Adler et al., 2003

Is albuminuria a prerequisite for DKD ?

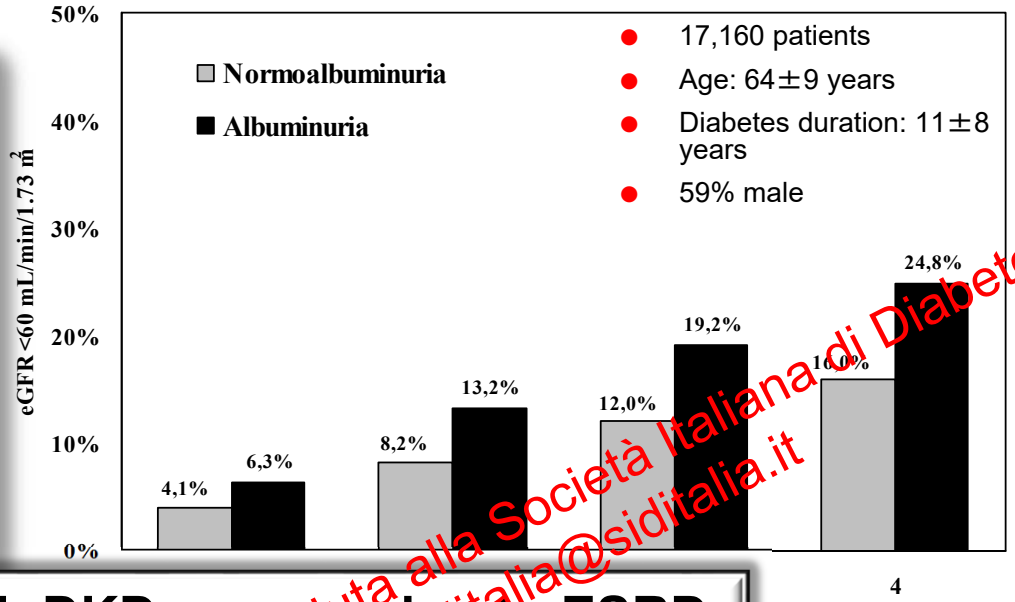
	Patients n.	DM %	Follow-up years	Renal impairment	Non-albuminuric renal impairment
UKPDS *Diabetes 55: 1832-1839, 2006*	4,006	100	15	28%	67% (51%)
DCCT/EDIC *Diabetes Care 33: 1536-1543, 2010*	1,439	100 (type 1)	19	6.2%	24%
AMD Annals **Diabetes Metab Res Rev 2017**	**20,464**	100 (T1DM)	19	23.5%	**49%**
MacIsaac RJ et al., *Diabetes Care 27: 195-200, 2004*	301	100	---	36%	39%
Kramer HJ et al., NHANES III *JAMA 289: 3273-3277, 2003*	1,197	100	---	13%	36%
Thomas MC et al., NEFRON *Diabetes Care 32: 1497-1502, 2009*	3,893	100	---	23%	55%
Ninomiya T et al., ADVANCE *J Am Soc Nephrol 20: 1813-1821, 2009*	10,640	100	---	19%	62%
Bakris GL et al., ACCOMPLISH *Lancet 375: 1173-1181, 2010*	11,482	60	---	9.5%	47%
Tube SW et al., ONTARGET/ TRASCEND *Circulation 123: 1098-1107, 2011*	23,422	37	---	24%	68%
Drury PL et al., FIELD *Diabetologia 54: 32-43, 2011*	9,765	100	---	5.3%	59%
RIACE Study Group, RIACE *J Hypertens 29: 1802-1809, 2011*	15,773	100	---	18.8%	57%
AMD ANNALS **NDT 2015**	**116,777**	**100**	**---**	**21%**	**48%**

Journal of Diabetes and Its Complications

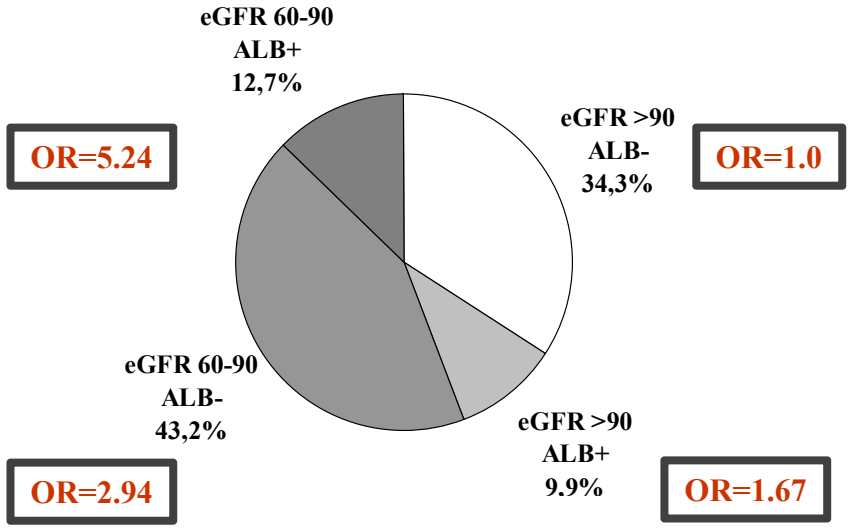
Journal homepage: WWW.JDCJOURNAL.COM

Association of kidney disease measures with risk of renal function worsening in patients with hypertension and type 2 diabetes

Francesca Viazzi [a,*], Pamela Piscitelli [b], Carlo Giorda [c], Antonio Ceriello [d,e], Stefano Genovese [e], Giuseppina T. Russo [f], Paola Fioretto [g], Pietro Guida [h], Salvatore De Cosmo [b], Roberto Pontremoli [a], the AMD-Annals Study Group

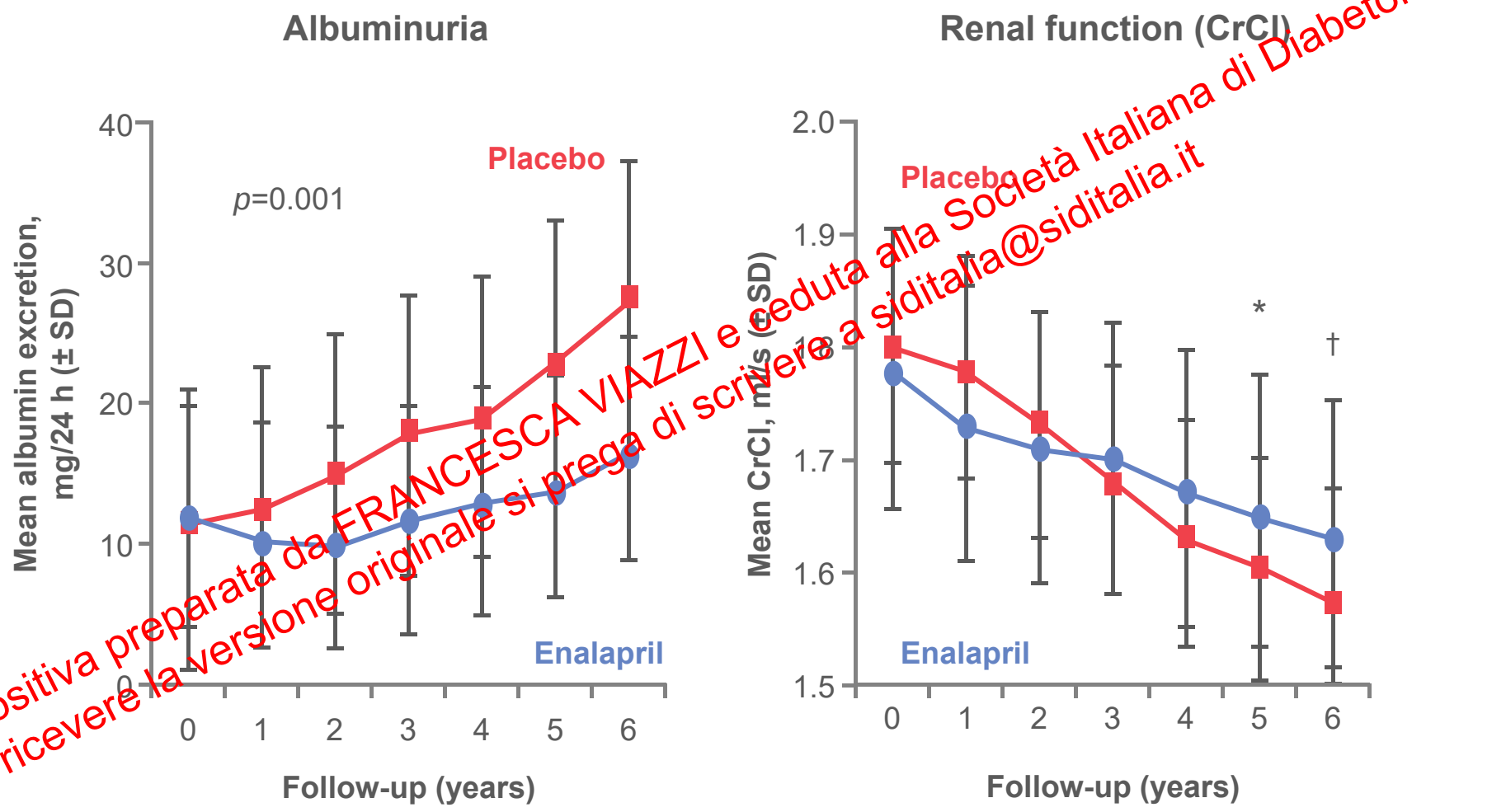


2 out of 3 pts with DKD progressing to ESRD are non-albuminuric



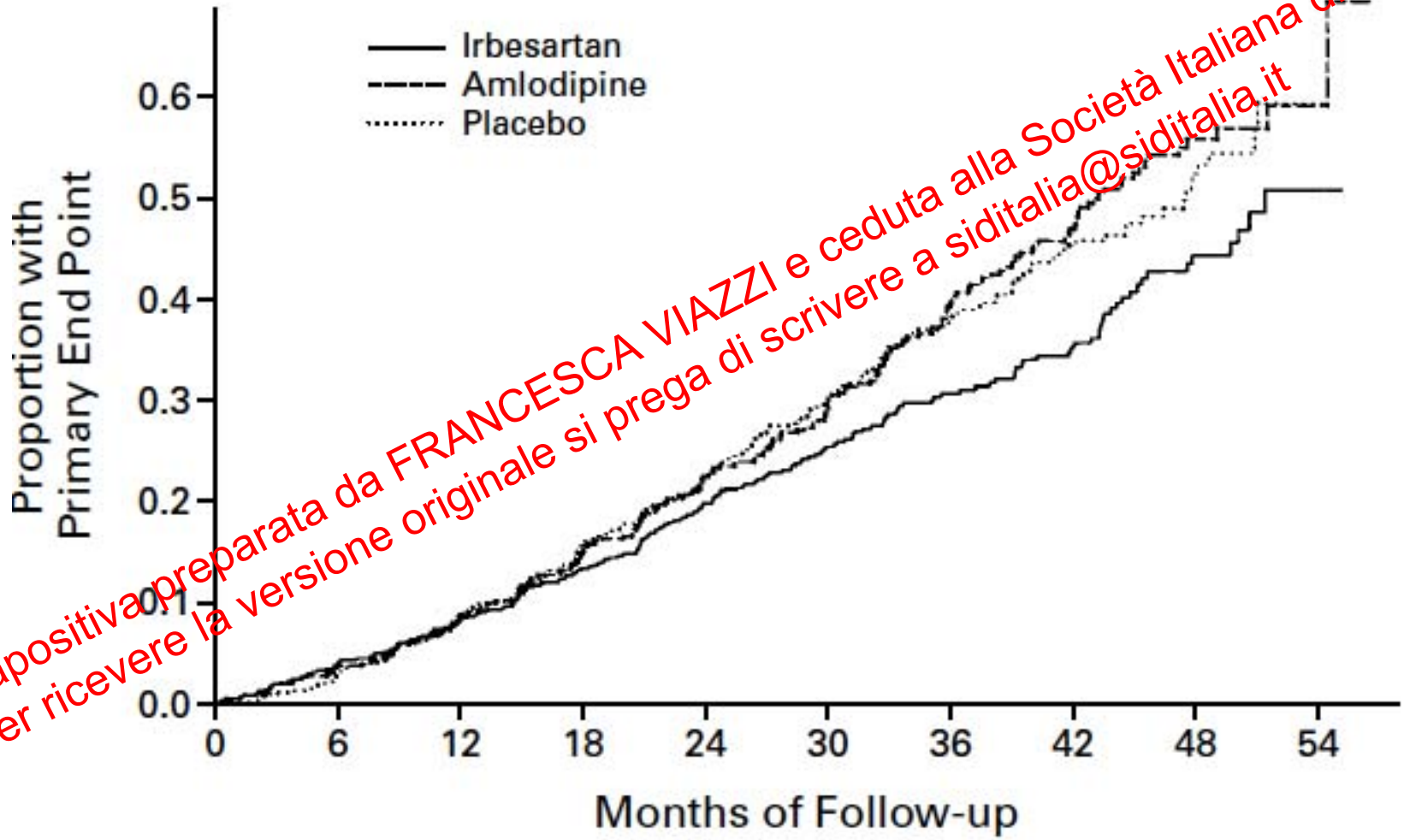
. . . The presence of albuminuria entails a greater renal risk at any given GFR value. However, due to a greater occurrence of the non-albuminuric phenotype at baseline, progression to CKD stage 3 is more likely to be observed in patients without albuminuria.

ACE inhibitors slow progression of albuminuria and renal function decline in patients with T2D



*p=0.047 vs placebo; †p=0.042 vs placebo
ACE, angiotensin-converting enzyme; CrCl, creatinine clearance; SD, standard deviation; T2D, type 2 diabetes
Ravid M *et al. Ann Intern Med* 1998;128:982

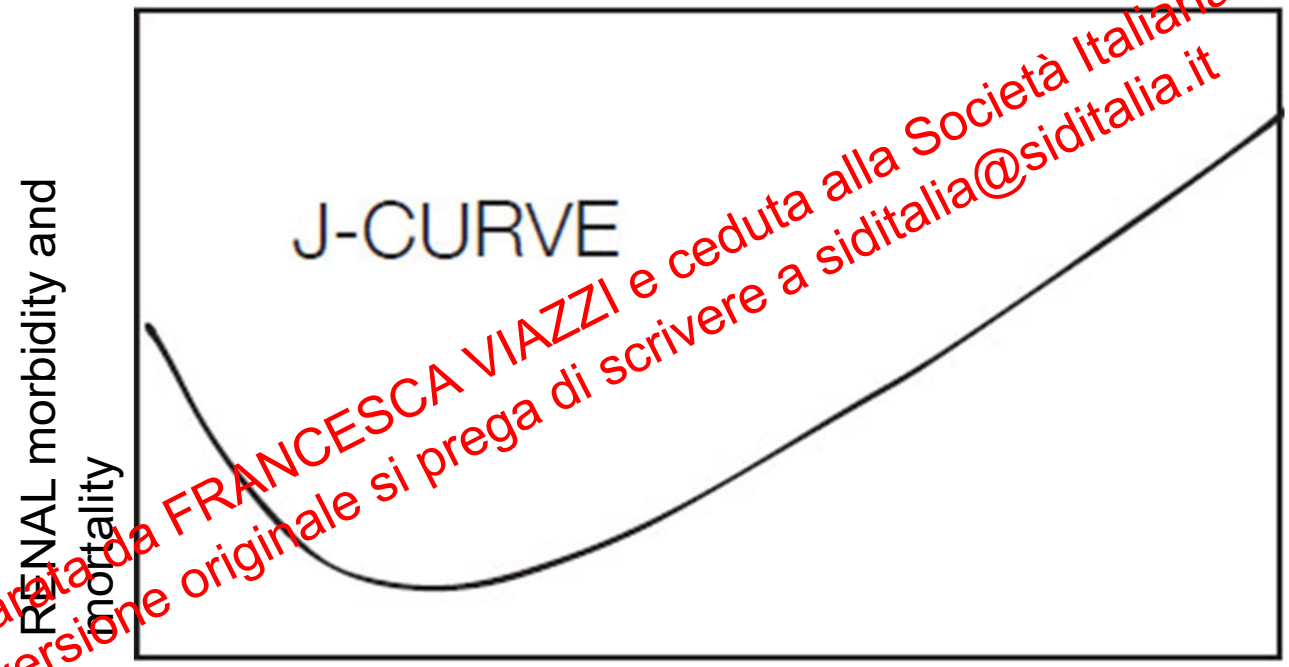
ARBs have demonstrated beneficial impact on progression to ESRD



*Exploratory *p*-value; ARB, angiotensin receptor blocker; BL SCR, baseline serum creatinine; HR, hazard ratio

1. Lewis *et al*. *N Engl J Med* 2001;345:851; 2. Menne J *et al. J Hypertens* 2012;30:811

RAAS inhibition and renal function: is there a J curve relationship?



RAAS –I

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

for the VA NEPHRON-D Investigators*

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

BACKGROUND

Combination therapy with angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain.

METHODS

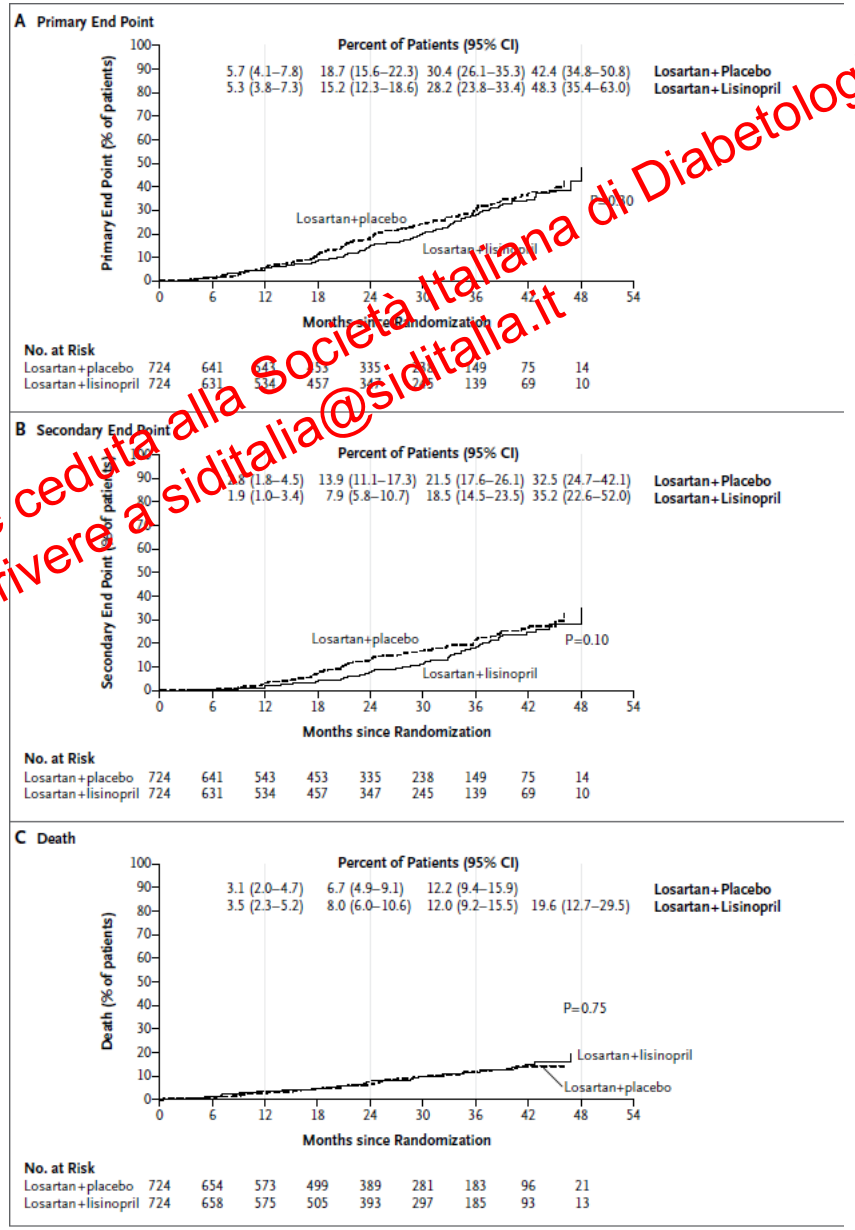
We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m² of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m² if the initial estimated GFR was ≥60 ml per minute per 1.73 m² or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m²), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

RESULTS

The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001).

CONCLUSIONS

Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.)



for the VA NEPHRON-D Investigators*

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

BACKGROUND

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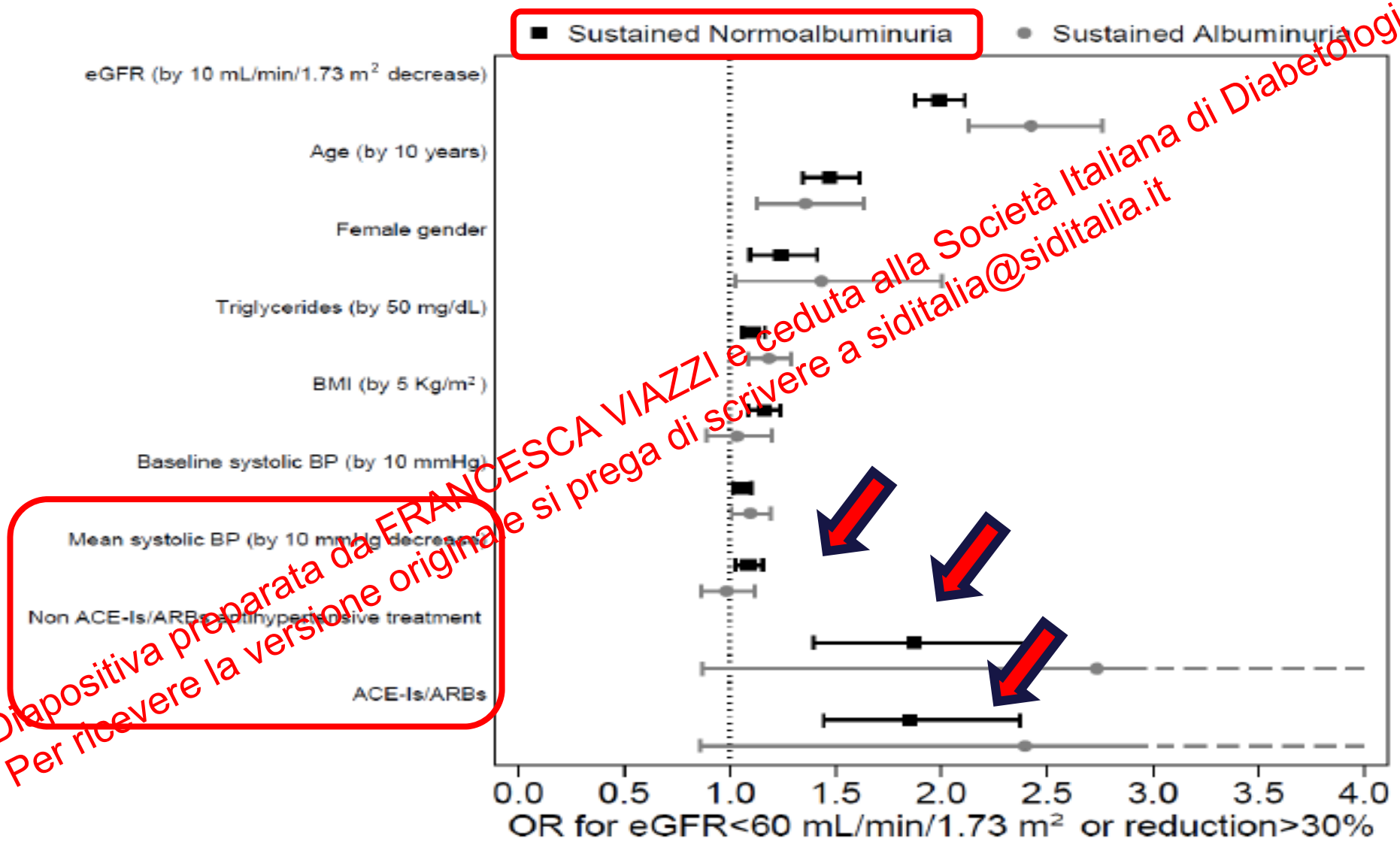
Table 3. Safety Outcomes.*

Outcome	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
Patients with serious adverse events — no. (%)	380 (52.5)	416 (57.5)	NA	0.06
No. of serious adverse events	1274	1539†	NA	
Attribution of serious adverse events to study drugs — no. of events (%)†				0.049
Not attributed	1159 (91.0)	1365 (88.7)	NA	
Possibly attributed	104 (8.2)	146 (9.5)	NA	
Attributed	11 (0.9)	27 (1.8)	NA	
Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)	1.7 (1.3–2.2)	<0.001
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)	2.8 (1.8–4.3)	<0.001

CONCLUSIONS

Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.)

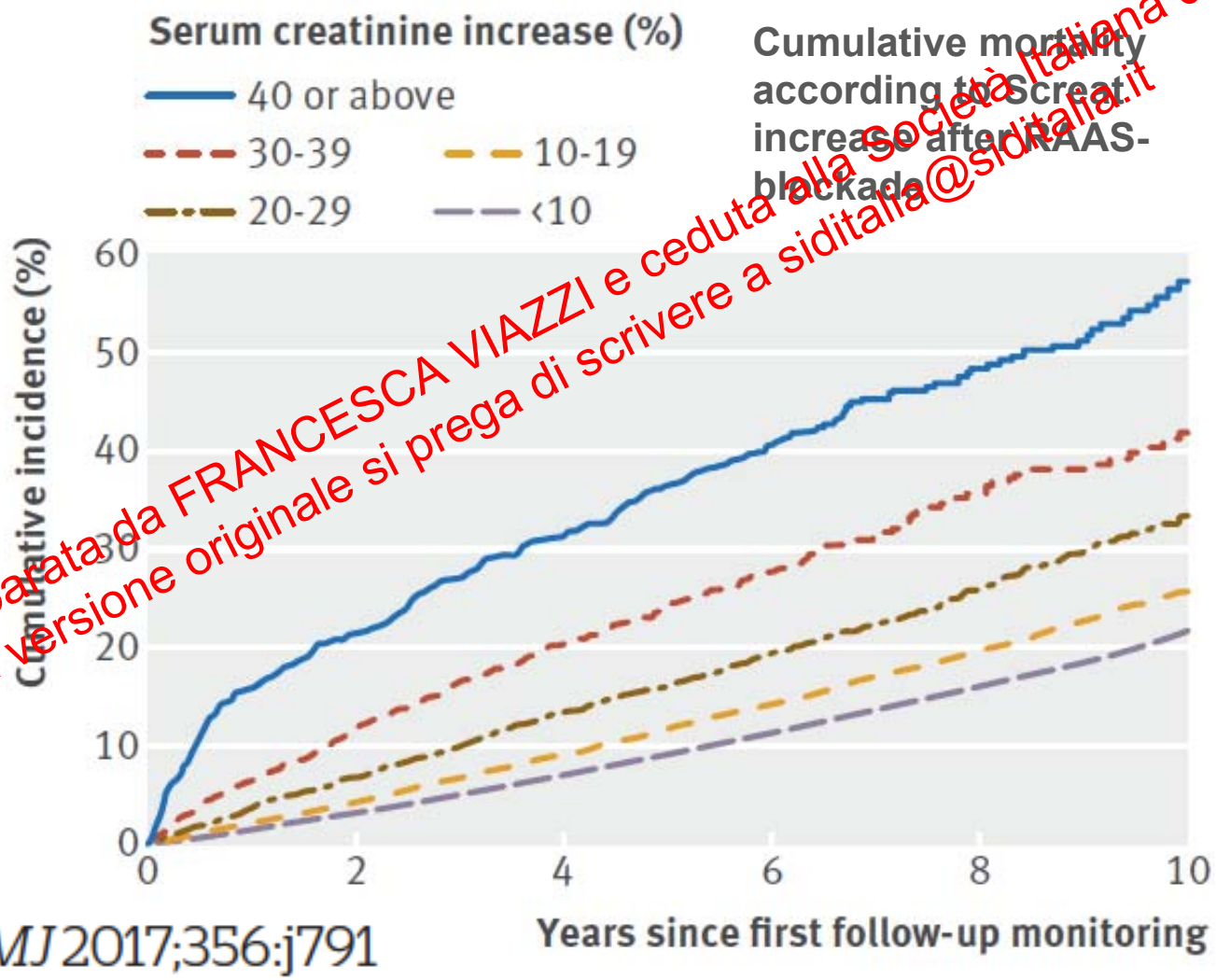
Changes in albuminuria and renal outcome in patients with hypertension and T2D



Viazzi F, Pontremoli R et al.
J Hypertens 2018

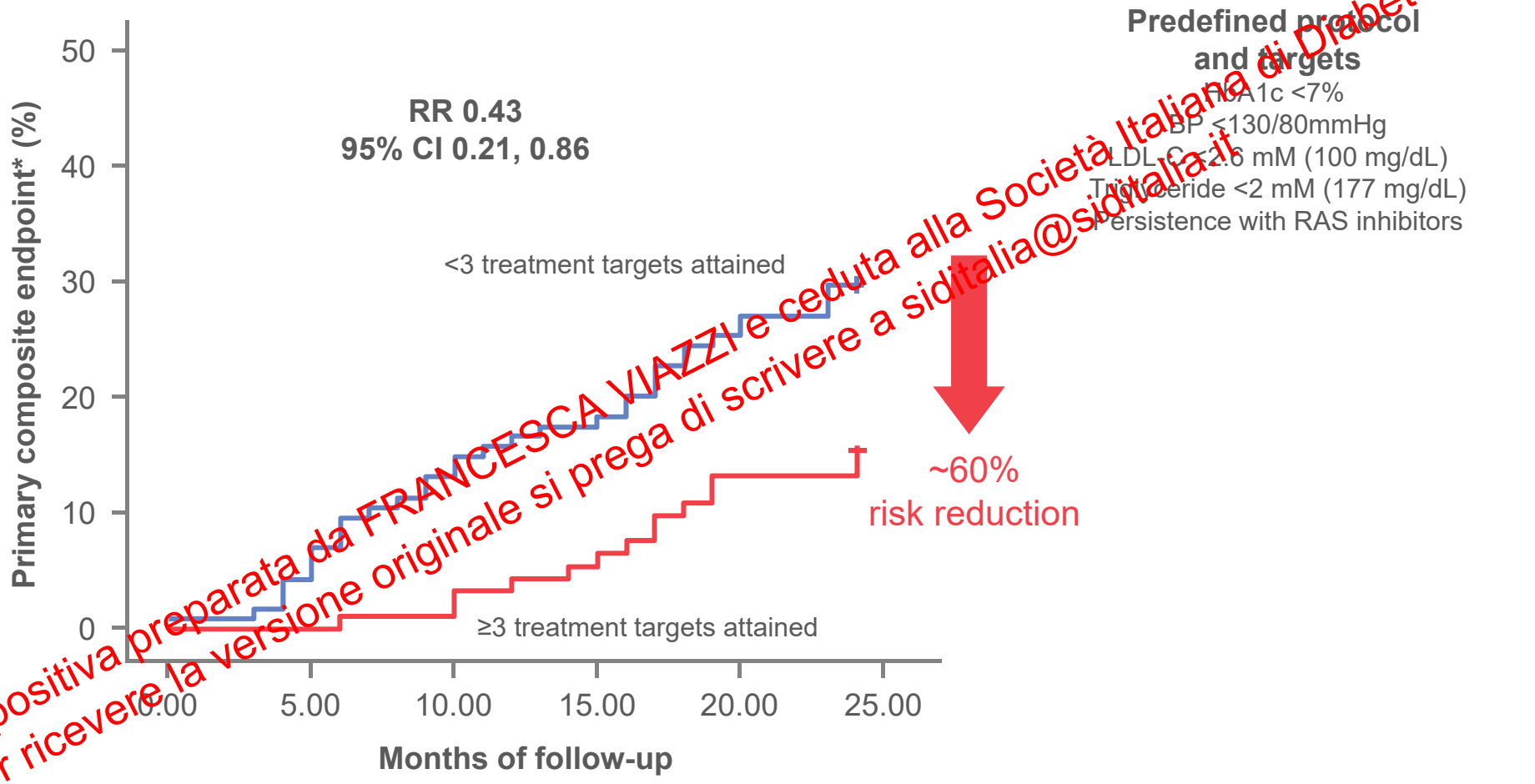
Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study

Morten Schmidt,[1,2,3] Kathryn E Mansfield,[1] Krishnan Bhaskaran,[1] Dorothea Nitsch,[1] Henrik Toft Sørensen,[4] Liam Smeeth,[1] Laurie A Tomlinson[1]



thebmj | BMJ 2017;356:j791

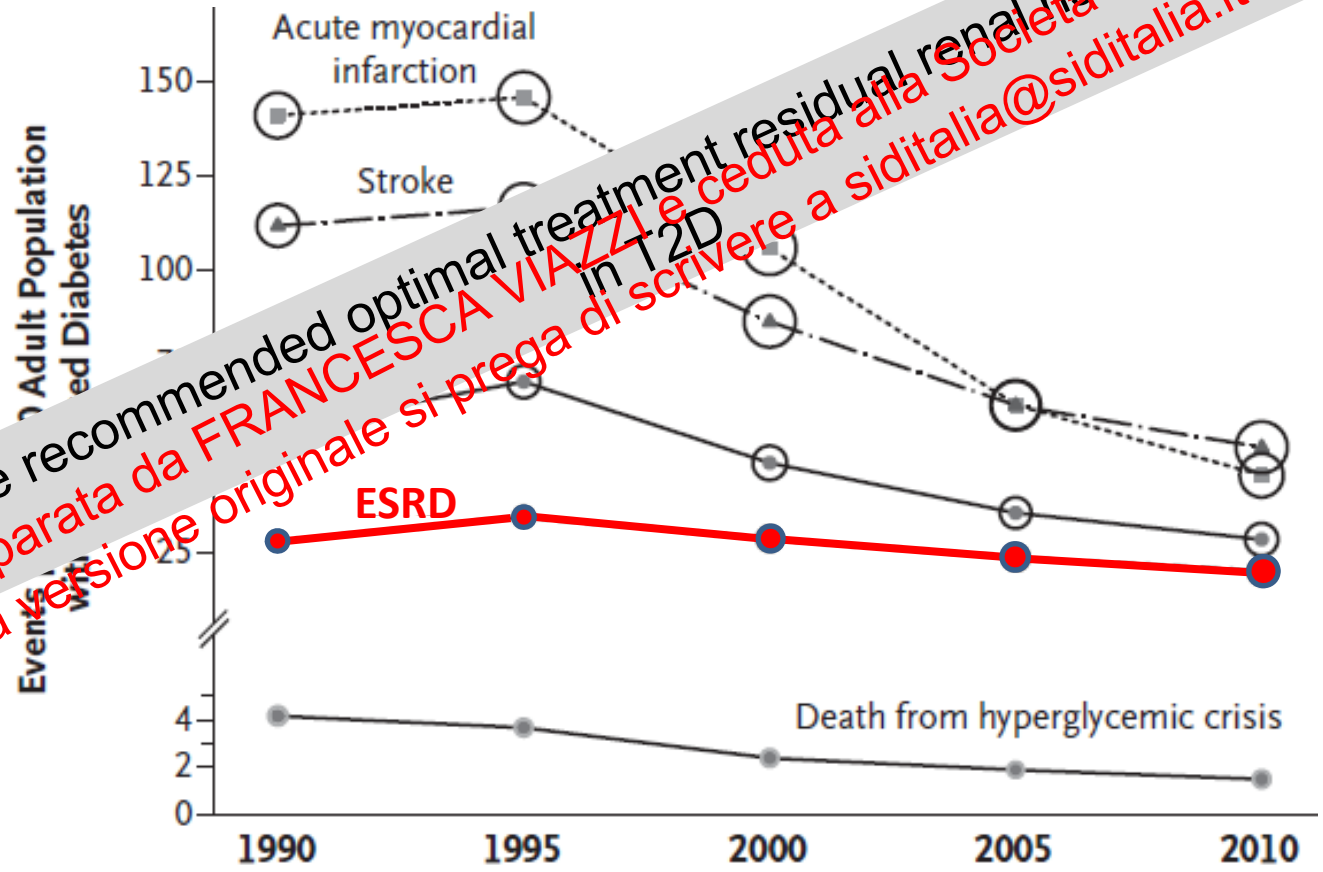
Attaining multiple treatment targets is associated with lower risk of ESRD and related death in T2D



*Death and/or ESRD, defined as the need for dialysis, or plasma creatinine level 500 µmol/l
BP, blood pressure; ESRD, end-stage renal disease; HbA1c, glycated haemoglobin; LDL-C, Low-density lipoprotein cholesterol; RAS, renin-angiotensin system; RR, risk ratio
Chan JC *et al Diabetes Care* 2009;32:977

Changes in Diabetes-Related Complications in the United States, 1990–2010

Data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System



Gregg, NEJM 2014

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Original Article

CKD and achievement of recommended therapeutic targets in T2DM

The AMD-Annals database

De Cosmo S., Pontremoli R., et al. NDT *2015*

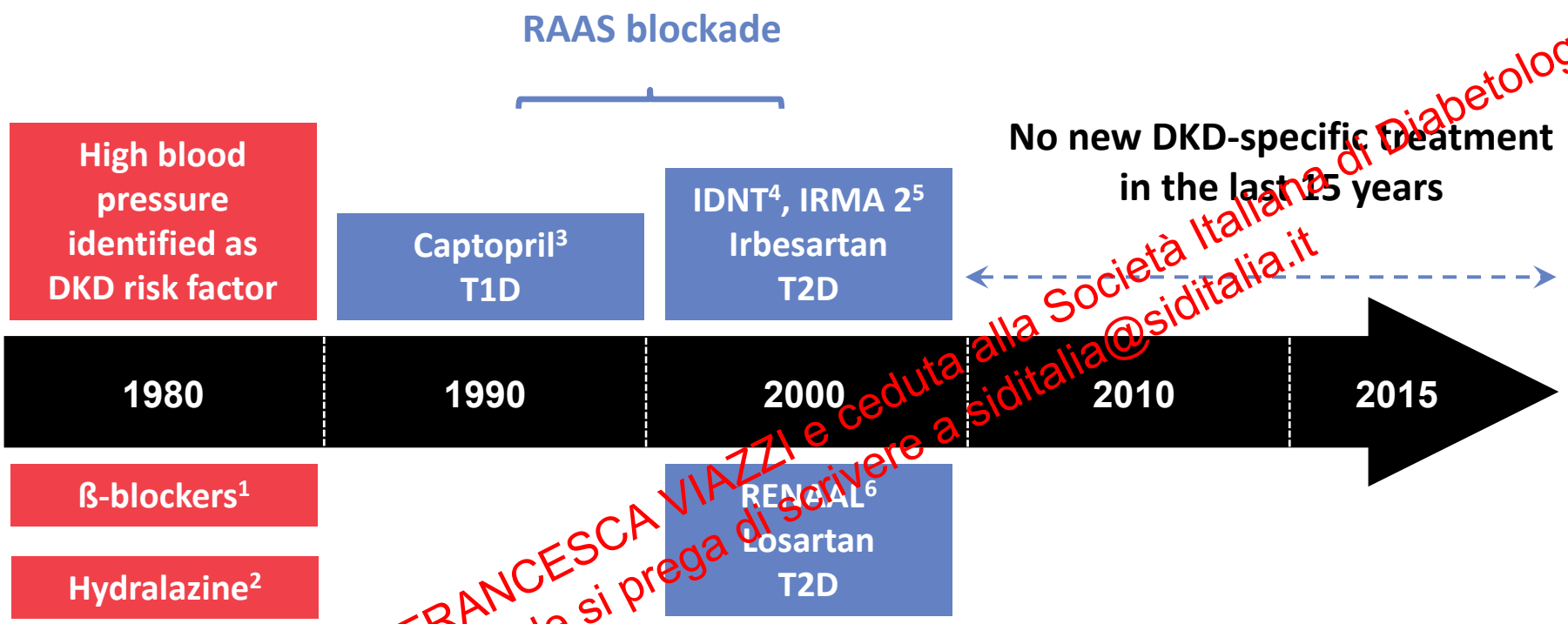
n (%)	Alb−/eGFR− 70 779 (60.6)	Alb−/eGFR+ 14 644 (12.5)	Alb+/eGFR− 21 484 (18.4)	Alb+/eGFR+ 9 870 (8.5)
HbA1c <7% (%)	53.4	48.4	43.6	42.0
LDL-c <100 mg/dL (%)	49.0	52.7	52.0	55.4
SBP/DBP <140/80 mmHg (%)	27.1	28.8	20.7	22.4
SBP/DBP <140/85 mmHg (%)	48.0	45.5	38.2	37.5
Patients with normoalbuminuria				
SBP/DBP <140/90 mmHg (%)	50.4	47.0		
Patients with high albuminuria				
SBP/DBP <130/80 mmHg (%)			13.2	13.6
Lipid-lowering treatment (%)	58.0	64.1	63.0	66.6
Treatment with statins (%)	53.7	58.0	58.8	60.5
Treatment with fibrates (%)	2.7	4.3	2.7	3.9
Anti-hypertensive treatment (%)	67.7	87.5	78.9	91.1
Treatment with ACE-Is/ARBs (%)	57.5	74.4	70.3	77.5
Aspirin (%)	30.0	41.7	35.5	45.0
AntidiabeticRx				
Diet (%)	6.2	4.9	3.3	2.6
OAD (%)	68.7	54.2	62.3	42.1
OAD + insulin (%)	14.8	17.3	22.0	20.5
Insulin (%)	10.2	23.5	12.4	34.9

Despite recommended optimal treatment residual renal risk remains high in T2D

KEY Points – Conclusions 1/2

- Optimal BP control, RAAS-i & multifactorial intervention are key for renal protection in T2D.
- Optimal BP values for CKD patients are still a matter of debate and should be tailored on individual patients (comorbidities). Lower values likely to be of greater benefit in the presence of albuminuria.
- BP reduction and RAAS-I show a paradoxycal J-curve effect (ischemic nephropathy), which may limit risk/benefit ratio of intensive treatment.

No new DKD-specific treatment in the last 15 years



DKD, diabetic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAAS, renin–angiotensin-aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

1. Mogensen CE *et al. Br Med J (Clin Res Ed)*1982;285:685; 2. Parving HH *et al. Lancet* 1983;1:1175; 3. Lewis EJ *et al. N Engl J Med* 1993;329:1456; 4. Lewis EJ *et al. N Engl J Med* 2001;345:851; 6. Brenner BM *et al. N Engl J Med* 2001;345:861

Conclusions

- Non-albuminuric renal impairment is the predominant clinical DKD phenotype in type 2 DM patients
- Non albuminuric DKD entails a significant renal and CV risk although to a lesser extent than the albuminuric phenotype
- Traditional multifactorial intervention has shown limited effcicacy in retarding progression to ESRD, especially so in non-albuminuric patients
- SGLT2i may favorably modify natural history of DKD as they confer additional renal protection independent of the presence/absence of albuminuria