Controllo glicemico, infiammazione e danno renale

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Disclosure

Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche per relazioni/moderazioni/partecipazioni a board retribuite:

- Astra-Zeneca;
- Bayer;
- Boehringer Ingelheim;
- Eli Lilly;
- Mundipharma;
- Novo Nordisk.

Dichiaro altresì il mio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

In fede

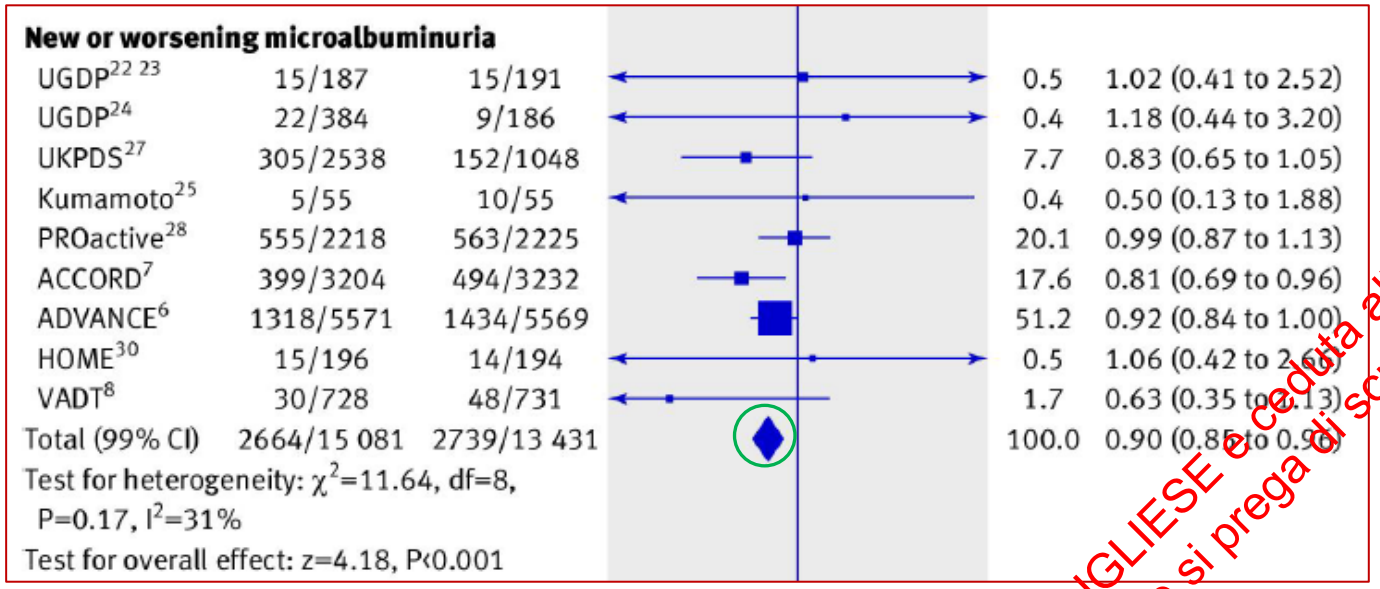
Giuseppe Pugliese

Agenda

- Impact of glycemic control on diabetic kidney disease progression
- Currently avaliable renoprotective drugs
- Search for new renoprotective strategies
- Inflammatory mechanisms in diabetic kidney disease
- Mineralocorticoid activation and blockade
- Inflammatory markers as predictors in diabetic kidney disease progression

Effect of intensive glycemic control on renal outcomes

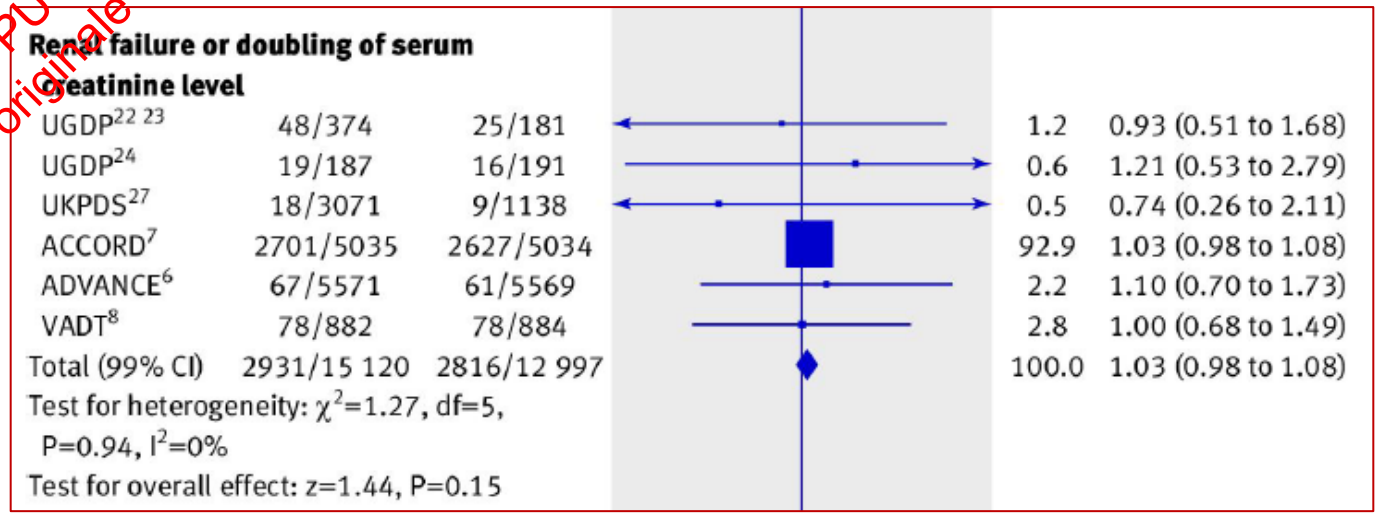
Meta-analysis of 13 randomized controlled trials



New or worsening microalbuminuria				
UGDP[22 23]	15/187	15/191	0.5	1.02 (0.41 to 2.52)
UGDP[24]	22/384	9/186	0.4	1.18 (0.44 to 3.20)
UKPDS[27]	305/2538	152/1048	7.7	0.83 (0.65 to 1.05)
Kumamoto[25]	5/55	10/55	0.4	0.50 (0.13 to 1.88)
PROactive[28]	555/2218	563/2225	20.1	0.99 (0.87 to 1.13)
ACCORD[7]	399/3204	494/3232	17.6	0.81 (0.69 to 0.96)
ADVANCE[6]	1318/5571	1434/5569	51.2	0.92 (0.84 to 1.00)
HOME[30]	15/196	14/194	0.5	1.06 (0.42 to 2.66)
VADT[8]	30/728	48/731	1.7	0.63 (0.35 to 1.13)
Total (99% CI)	2664/15 081	2739/13 431	100.0	0.90 (0.85 to 0.96)

Test for heterogeneity: χ^2=11.64, df=8, P=0.17, I^2=31%

Test for overall effect: z=4.18, P<0.001



Renal failure or doubling of serum creatinine level				
UGDP[22 23]	48/374	25/181	1.2	0.93 (0.51 to 1.68)
UGDP[24]	19/187	16/191	0.6	1.21 (0.53 to 2.79)
UKPDS[27]	18/3071	9/1138	0.5	0.74 (0.26 to 2.11)
ACCORD[7]	2701/5035	2627/5034	92.9	1.03 (0.98 to 1.08)
ADVANCE[6]	67/5571	61/5569	2.2	1.10 (0.70 to 1.73)
VADT[8]	78/882	78/884	2.8	1.00 (0.68 to 1.49)
Total (99% CI)	2931/15 120	2816/12 997	100.0	1.03 (0.98 to 1.08)

Test for heterogeneity: χ^2=1.27, df=5, P=0.94, I^2=0%

Test for overall effect: z=1.44, P=0.15

Boussageon R et al. *BMJ.* 2011;343:d4169

Effect of intensive glycemic control on renal outcomes

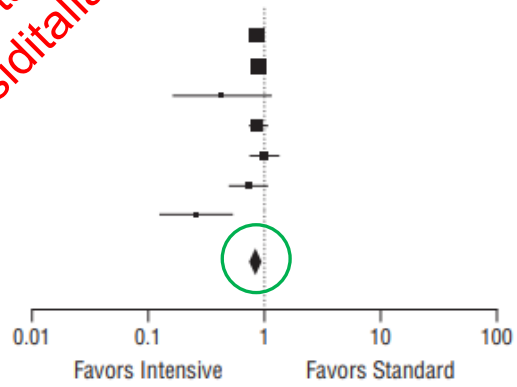
Meta-analysis of 7 randomized controlled trials

Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	720	3250	828	3273	27.3	0.88 (0.80-0.96)
ADVANCE[12]	1318	5571	1434	5569	29.3	0.92 (0.86-0.98)
Kumamoto[4,15]	5	52	11	50	1.3	0.44 (0.16-1.17)
UKPDS 33[16]	368	2277	172	938	19.6	0.88 (0.75-1.04)
UKPDS 34[17]	79	342	95	411	12.2	1.00 (0.77-1.30)
VADT[11]	43	442	61	463	7.6	0.74 (0.51-1.07)
VA Feasibility Trial[5]	7	42	30	46	2.5	0.26 (0.13-0.52)
Total (95% CI)		**11 976**		**10 750**	**100.0**	**0.86 (0.76-0.96)**
Total events	**2540**		**2631**			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2_6 = 16.71$; $P = .01$; $I^2 = 64\%$

Test for overall effect: $z = 2.60$; $P = .009$

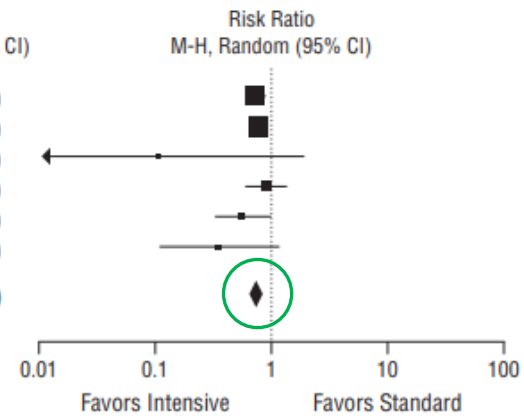


Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	195	4397	242	4424	39.3	0.72 (0.60-0.86)
ADVANCE[12]	230	5571	292	5569	42.5	0.79 (0.67-0.93)
Kumamoto[4,15]	0	52	4	50	0.2	0.11 (0.01-1.94)
UKPDS 33[16]	72	2277	33	938	10.4	0.90 (0.60-1.35)
VADT[11]	20	628	36	703	6.2	0.56 (0.33-0.96)
VA Feasibility Trial[5]	2	24	10	28	1.4	0.35 (0.11-1.13)
Total (95% CI)		**13 014**		**11 712**	**100.0**	**0.74 (0.65-0.85)**
Total events	**528**		**647**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 5.73$; $P = .33$; $I^2 = 13\%$

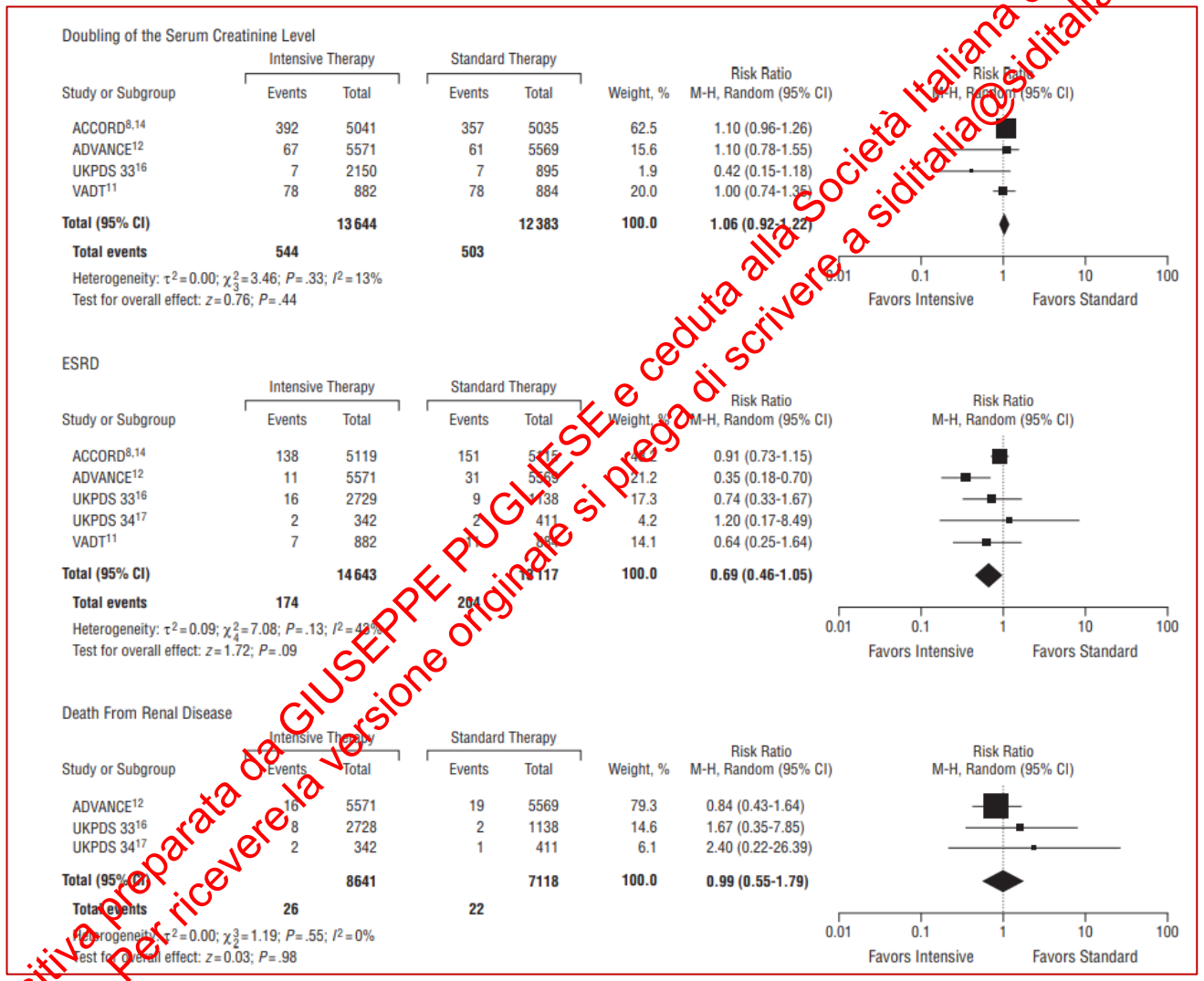
Test for overall effect: $z = 4.22$; $P = .001$



Coca SG et al. *Arch Intern Med.* 2012;172:761–769

Effect of intensive glycemic control on renal outcomes

Meta-analysis of 7 randomized controlled trials



Doubling of the Serum Creatinine Level

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	392	5041	357	5035	62.5	1.10 (0.96-1.26)
ADVANCE[12]	67	5571	61	5569	15.6	1.10 (0.78-1.55)
UKPDS 33[16]	7	2150	7	895	1.9	0.42 (0.15-1.18)
VADT[11]	78	882	78	884	20.0	1.00 (0.74-1.35)
Total (95% CI)		**13 644**		**12 383**	**100.0**	**1.06 (0.92-1.22)**
Total events	**544**		**503**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 3.46$; $P = .33$; $I^2 = 13\%$
Test for overall effect: $z = 0.76$; $P = .44$

Risk Ratio M-H, Random (95% CI)
0.01 0.1 1 10 100
Favors Intensive Favors Standard

ESRD

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	138	5119	151	5[illegible]	[illegible]	0.91 (0.73-1.15)
ADVANCE[12]	11	5571	31	5[illegible]	21.2	0.35 (0.18-0.70)
UKPDS 33[16]	16	2729	9	1138	17.3	0.74 (0.33-1.67)
UKPDS 34[17]	2	342	2	411	4.2	1.20 (0.17-8.49)
VADT[11]	7	882	[illegible]	[illegible]	14.1	0.64 (0.25-1.64)
Total (95% CI)		**14 643**		**13 117**	**100.0**	**0.69 (0.46-1.05)**
Total events	**174**		**204**			

Heterogeneity: $\tau^2 = 0.09$; $\chi^2_4 = 7.08$; $P = .13$; $I^2 = 43\%$
Test for overall effect: $z = 1.72$; $P = .09$

Risk Ratio M-H, Random (95% CI)
0.01 0.1 1 10 100
Favors Intensive Favors Standard

Death From Renal Disease

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ADVANCE[12]	16	5571	19	5569	79.3	0.84 (0.43-1.64)
UKPDS 33[16]	8	2728	2	1138	14.6	1.67 (0.35-7.85)
UKPDS 34[17]	2	342	1	411	6.1	2.40 (0.22-26.39)
Total (95% CI)		**8641**		**7118**	**100.0**	**0.99 (0.55-1.79)**
Total events	**26**		**22**			

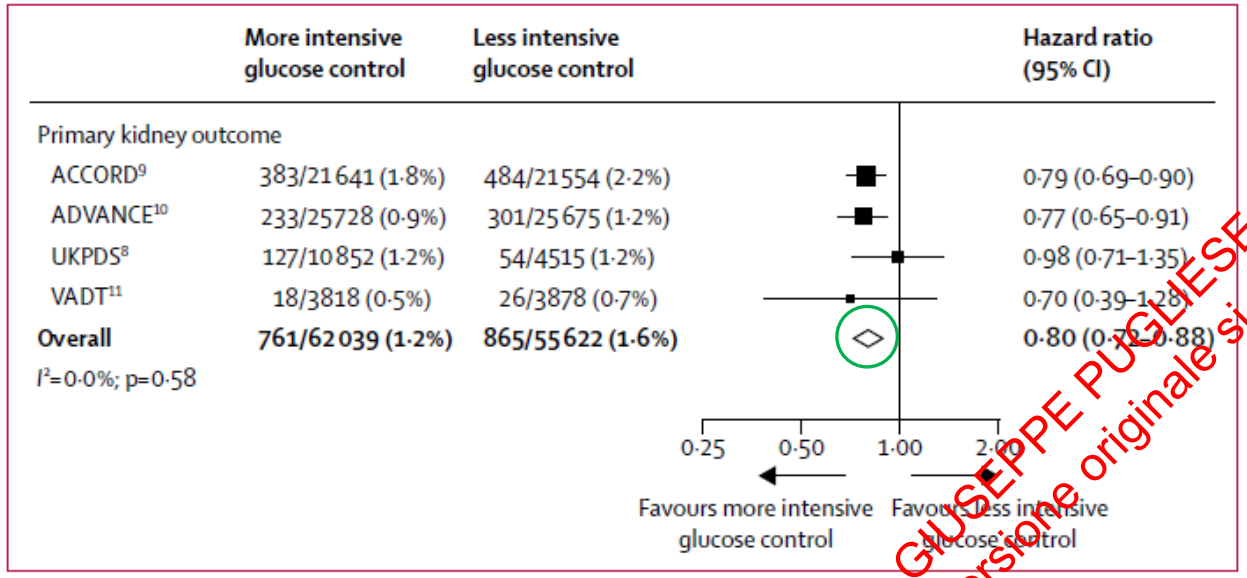
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 1.19$; $P = .55$; $I^2 = 0\%$
Test for overall effect: $z = 0.03$; $P = .98$

Risk Ratio M-H, Random (95% CI)
0.01 0.1 1 10 100
Favors Intensive Favors Standard

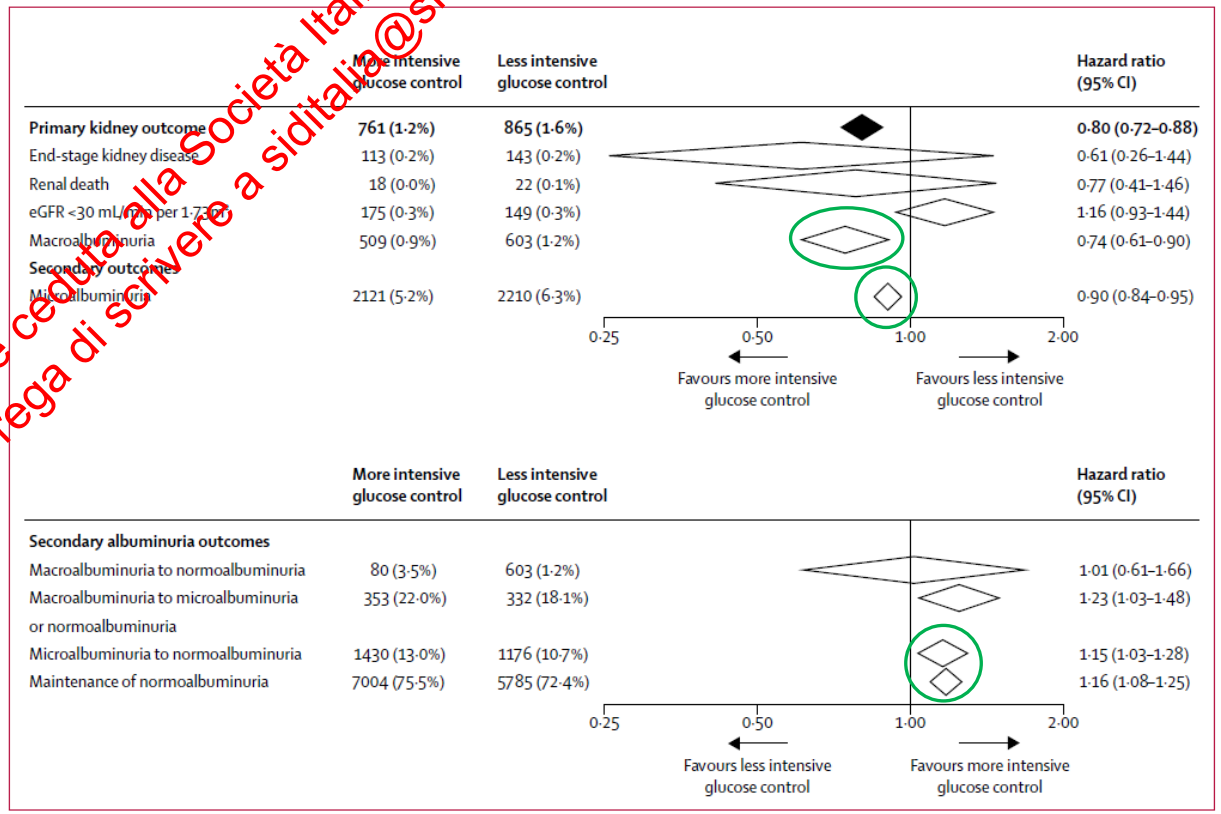
Coca SG et al. *Arch Intern Med.* 2012;172:761–769

Effect of intensive glycemic control on renal outcomes

Meta-analysis of 4 randomized controlled trials



	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Primary kidney outcome			
ACCORD[9]	383/21 641 (1·8%)	484/21554 (2·2%)	0·79 (0·69–0·90)
ADVANCE[10]	233/25728 (0·9%)	301/25 675 (1·2%)	0·77 (0·65–0·91)
UKPDS[8]	127/10 852 (1·2%)	54/4515 (1·2%)	0·98 (0·71–1·35)
VADT[11]	18/3818 (0·5%)	26/3878 (0·7%)	0·70 (0·39–1·28)
Overall	**761/62 039 (1·2%)**	**865/55 622 (1·6%)**	**0·80 (0·72–0·88)**
I^2=0·0%; p=0·58			



	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Primary kidney outcome	**761 (1·2%)**	**865 (1·6%)**	**0·80 (0·72–0·88)**
End-stage kidney disease	113 (0·2%)	143 (0·2%)	0·61 (0·26–1·44)
Renal death	18 (0·0%)	22 (0·1%)	0·77 (0·41–1·46)
eGFR <30 mL/min per 1·73 m²	175 (0·3%)	149 (0·3%)	1·16 (0·93–1·44)
Macroalbuminuria	509 (0·9%)	603 (1·2%)	0·74 (0·61–0·90)
Secondary outcomes			
Microalbuminuria	2121 (5·2%)	2210 (6·3%)	0·90 (0·84–0·95)

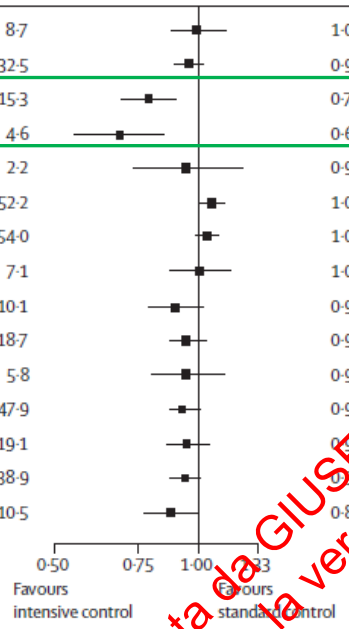
	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Secondary albuminuria outcomes			
Macroalbuminuria to normoalbuminuria	80 (3·5%)	603 (1·2%)	1·01 (0·61–1·66)
Macroalbuminuria to microalbuminuria or normoalbuminuria	353 (22·0%)	332 (18·1%)	1·23 (1·03–1·48)
Microalbuminuria to normoalbuminuria	1430 (13·0%)	1176 (10·7%)	1·15 (1·03–1·28)
Maintenance of normoalbuminuria	7004 (75·5%)	5785 (72·4%)	1·16 (1·08–1·25)

Effect of intensive glycemic control on renal outcomes

The Action to Control Cardiovascular Disease in Diabetes (ACCORD) Trial

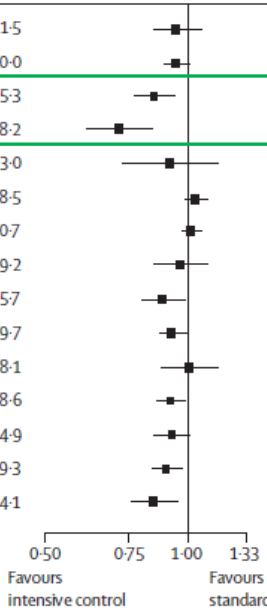
Until transition

	Glycaemia control: Intensive Events/n	%	Standard Events/n	%	Hazard ratio (95% CI)	p value	NNT
First composite	443/5107	8·7	444/5108	8·7	1·00 (0·88–1·14)	0·9969	
Second composite	1591/5107	31·2	1659/5108	32·5	0·96 (0·89–1·02)	0·1948	
Neph-1: incident microalbuminuria	399/3204	12·5	494/3232	15·3	0·79 (0·69–0·90)	0·0005	35
Neph-2: incident macroalbuminuria	138/4334	3·2	199/4361	4·6	0·69 (0·55–0·85)	0·0007	73
Neph-3: ESRD	911/5085	2·1	112/5108	2·2	0·95 (0·73–1·24)	0·7126	
Neph-4: doubling of SCr or >20 U eGFR decrease	2701/5035	53·6	2627/5034	52·2	1·07 (1·01–1·13)	0·0160	–69
Neph-5: any of Neph-2, Neph-3, or Neph-4	2788/5107	54·6	2760/5108	54·0	1·05 (0·99–1·10)	0·0958	
Eye-1: photocoagulation or vitrectomy	350/4886	7·2	347/4910	7·1	1·01 (0·87–1·17)	0·9039	
Eye-2: cataract surgery	447/4886	9·1	495/4910	10·1	0·90 (0·79–1·02)	0·1047	
Eye-3: three-line worsened visual acuity	911/5085	17·9	951/5085	18·7	0·95 (0·87–1·04)	0·3013	
Eye-4: severe loss of vision*	258/4651	5·5	273/4689	5·8	0·95 (0·80–1·13)	0·5858	
Neuro-1: neuropathy (MNSI score >2·0)	1277/2815	45·4	1338/2791	47·9	0·93 (0·87–1·01)	0·0919	
Neuro-2: loss of vibratory sensation	766/4209	18·2	805/4209	19·1	0·95 (0·86–1·05)	0·2926	
Neuro-3: loss of ankle jerk	1225/3298	37·1	1270/3265	38·9	0·94 (0·87–1·01)	0·0997	
Neuro-4: loss of sensation to light touch	424/4577	9·3	481/4564	10·5	0·88 (0·77–1·00)	0·0451	78



Until end of study

	Glycaemia control: Intensive Events/n	%	Standard Events/n	%	Hazard ratio (95% CI)	p value	NNT
First composite	556/5119	10·9	586/5115	11·5	0·95 (0·85–1·07)	0·4226	
Second composite	1956/5119	38·2	2046/5115	40·0	0·95 (0·89–1·01)	0·1172	
Neph-1: incident microalbuminuria	720/3250	22·2	828/3273	25·3	0·85 (0·77–0·94)	0·0012	32
Neph-2: incident macroalbuminuria	264/4397	6·0	362/4424	8·2	0·72 (0·61–0·84)	<0·0001	46
Neph-3: ESRD	138/5119	2·7	151/5115	3·0	0·92 (0·73–1·16)	0·4881	
Neph-4: doubling of SCr or >20 U eGFR decrease	2956/5041	58·6	2943/5035	58·5	1·04 (0·99–1·10)	0·1071	
Neph-5: any of Neph-2, Neph-3, or Neph-4	3077/5119	60·1	3107/5115	60·7	1·02 (0·97–1·07)	0·4436	
Eye-1: photocoagulation or vitrectomy	440/4915	9·0	456/4933	9·2	0·97 (0·85–1·10)	0·6176	
Eye-2: cataract surgery	696/4915	14·2	775/4933	15·7	0·89 (0·80–0·99)	0·0265	65
Eye-3: three-line worsened visual acuity	1417/5089	27·8	1510/5088	29·7	0·93 (0·87–1·00)	0·0636	
Eye-4: severe loss of vision*	384/4748	8·1	385/4774	8·1	1·01 (0·88–1·16)	0·9058	
Neuro-1: neuropathy (MNSI score >2·0)	1573/2829	55·6	1640/2797	58·6	0·92 (0·86–0·99)	0·0265	33
Neuro-2: loss of vibratory sensation	981/4227	23·2	1050/4217	24·9	0·93 (0·85–1·01)	0·0808	
Neuro-3: loss of ankle jerk	1514/3312	45·7	1612/3271	49·3	0·90 (0·84–0·97)	0·0050	28
Neuro-4: loss of sensation to light touch	554/4596	12·1	645/4573	14·1	0·85 (0·76–0·95)	0·0043	49

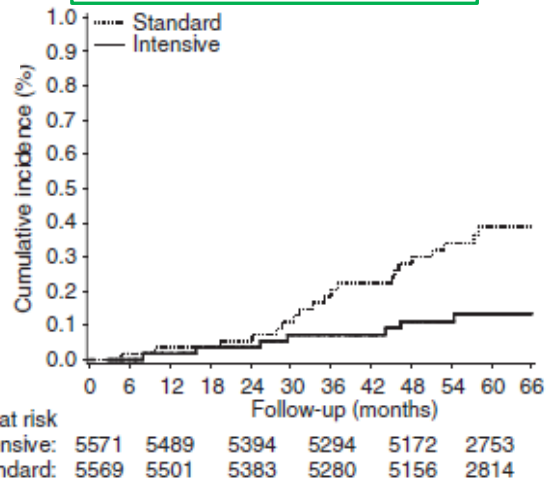


Ismail-Beigi F et al. *Lancet*.. 2010;376: 419–430

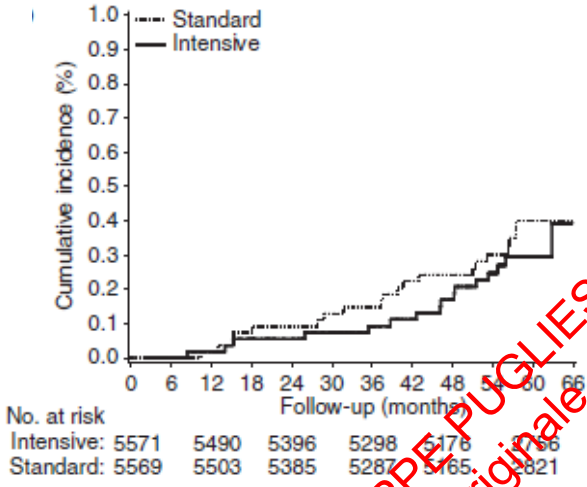
Effect of intensive glycemic control on renal outcomes

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial

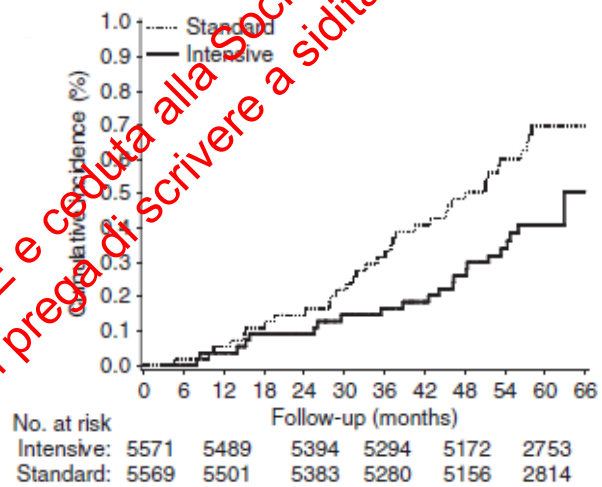
ESRD
0.35 (0.15-0.83), *p*=0.01



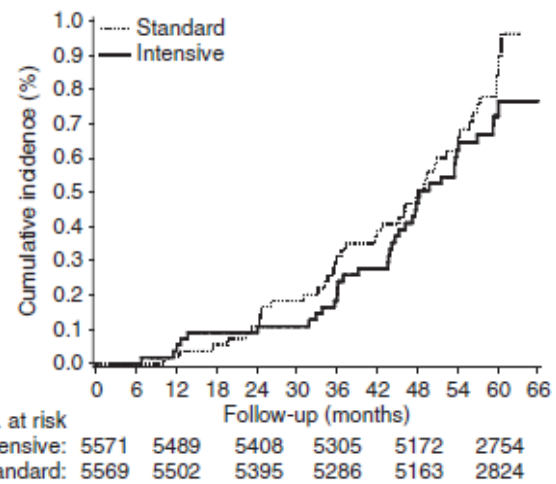
Renal death
0.85 (0.45-1.63), *p*=0.63



ESRD or renal death
0.68 (0.38-1.08), *p*=0.09



Screat doubling ≥200 µmol/L
0.83 (0.54-1.27), *p*=0.38



Outcome	Intensive, *n* (%)	Standard, *n* (%)	Hazard ratio (95% confidence interval)	*P*-value
New-onset microalbuminuria	1318 (33.5)	1434 (36.3)	0.91 (0.85–0.98)	0.012
New-onset macroalbuminuria	162 (3.0)	231 (4.3)	0.70 (0.57–0.85)	0.0004
Progression of albuminuria by ⩾1 stage[a]	1298 (23.3)	1410 (25.3)	0.90 (0.84–0.97)	0.0077
Regression of albuminuria by ⩾1 stage[b]	1003 (61.2)	914 (56.3)	1.15 (1.05–1.26)	0.0020
Regression to normoalbuminuria	922 (56.3)	814 (50.2)	1.20 (1.09–1.31)	0.0002

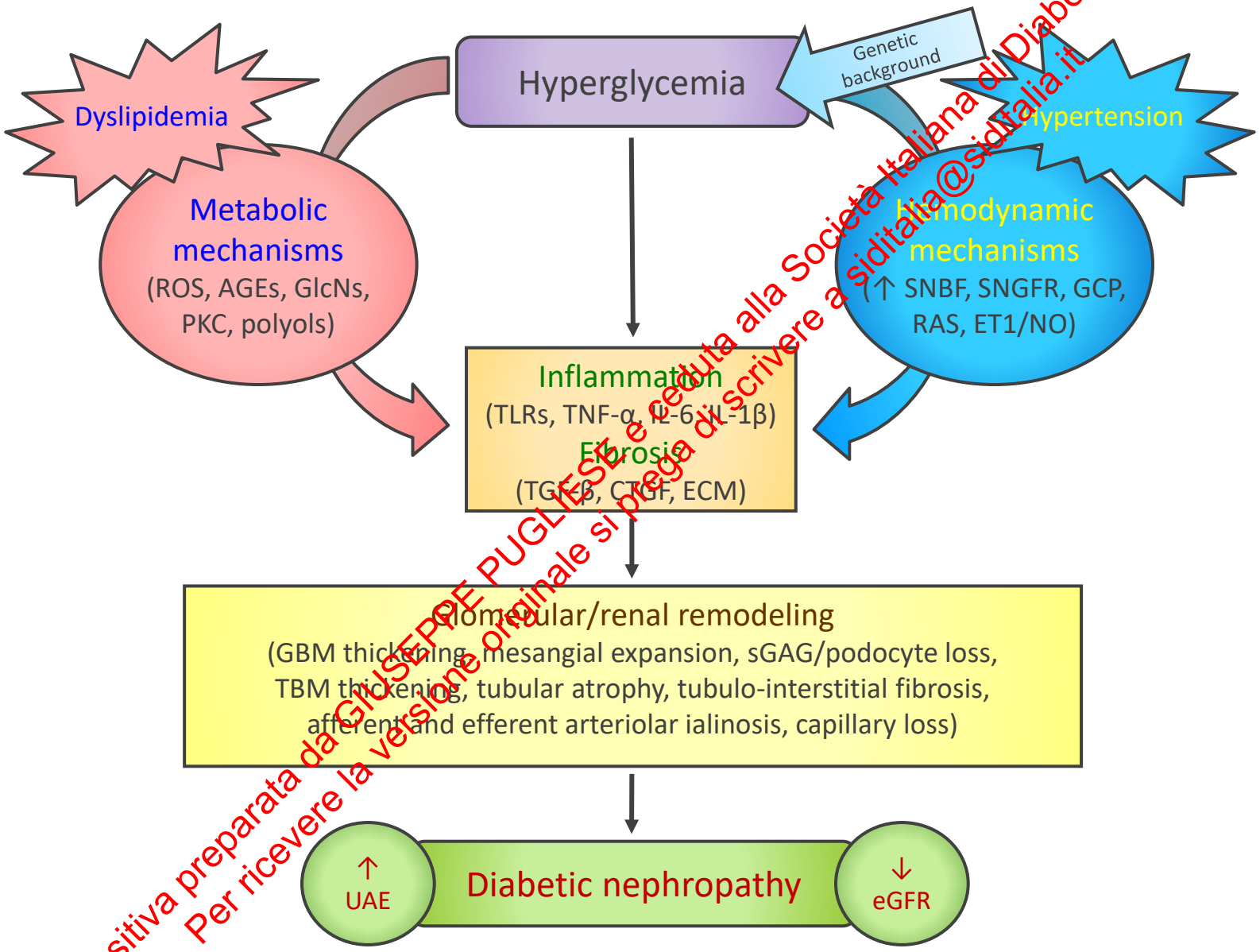
Perkovic V et al. *Kidney Int.* 2013;83:517–523

Effect of intensive glycemic control on renal outcomes

The Veterans Affairs Diabetes Trial (VADT)

Outcome	End of VADT (2000–2008) 5.6 years median follow-up			End of VADT-F[a] (2008–2013) 6 years median follow-up		
	INT	STD	*p* value	INT	STD	*p* value
eGFR >60 ml min^{-1} 1.73 m^{-2}	374/528 (70.8)	341/505 (67.5)	0.25	319/528 (60.0)	269/505 (53.3)	0.02*
15 < eGFR <30 ml min^{-1} 1.73 m^{-2}	8/528 (1.5)	5/505 (1.0)	0.45	19/528 (3.6)	30/505 (5.9)	0.08
Creatinine (μmol/l)	97 (80, 115)	97 (80, 119)	0.41	102 (82, 127)	106 (87, 139)	0.02*
Doubling of creatinine	22/527 (4.2)	15/505 (3.0)	0.30	24/515 (4.7)	24/490 (4.9)	0.86
Creatinine >265 μmol/l	6/528 (1.1)	4/505 (0.8)	0.57	24/515 (4.7)	24/490 (4.9)	0.86
ESRD[b]	2/528 (0.4)	4/505 (0.8)	0.39	22/528 (4.2)	27/505 (5.4)	0.37
Normal to micro/macroalbuminuria[c]	46/310 (14.8)	71/316 (22.5)	0.02*	34/143 (23.8)	36/131 (27.5)	0.48
Micro to macroalbuminuria[c]	19/162 (11.7)	32/141 (22.7)	0.01*	6/72 (0.1)	3/58 (0.1)	0.48

Pathogenesis of diabetic nephropathy



Effect of RAS blockers on renal outcomes

Meta-analysis of 28 studies

Dichotomous outcomes	Number of studies	Sample size	RR (95% CI)
ESRD			
ACEI/ARB vs other active drugs	6	2,147	0.82 (0.64, 1.05)
ACEI/ARB vs placebo	4	10,581	0.80 (0.69, 0.93)
Doubling of serum creatinine			
ACEI/ARB vs other active drugs	2	1,198	0.66 (0.53, 0.83)
ACEI/ARB vs placebo	4	10,594	0.76 (0.69, 0.84)
Major microvascular complications			
ACEI/ARB vs other active drugs	1	758	1.28 (0.81, 2.03)
ACEI/ARB vs placebo	4	6,489	0.85 (0.74, 0.97)
Macroalbuminuria			
ACEI/ARB vs other active drugs	8	1,211	0.71 (0.50, 1.00)
ACEI/ARB vs placebo	5	3,868	0.67 (0.54, 0.83)
Microalbuminuria			
ACEI/ARB vs other active drugs	6	1,430	0.84 (0.61, 1.15)
ACEI/ARB vs placebo	4	6,762	0.82 (0.64, 1.05)
Albuminuria regression			
ACEI/ARB vs other active drugs	9	1,286	1.16 (0.99, 1.39)
ACEI/ARB vs placebo	2	1,238	1.17 (1.00, 1.37)

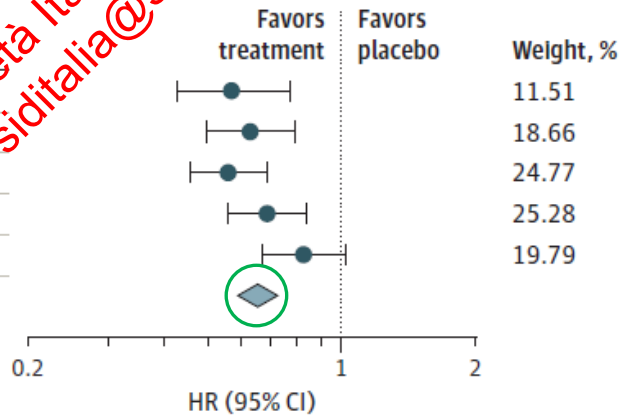
Vejakama P et al. *Diabetologia.* 2012;55:566–578

Effect of SGLT-2 inhibitors on renal outcomes

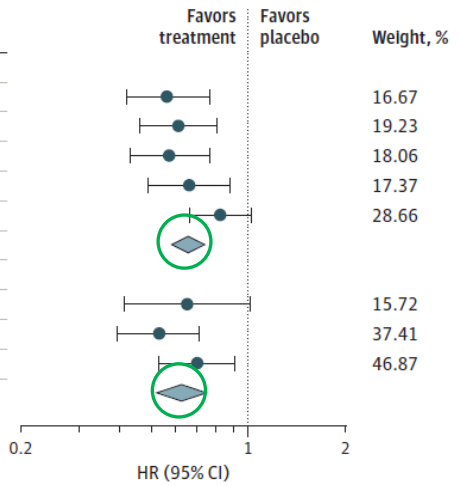
Meta-analysis of 5 randomized controlled trials

Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q=7.96; *df*=4; *P*=.09; I^2=49.7%)					0.64 (0.56-0.70)



	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2333	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q=6.09; *df*=4; *P*=.19; I^2=34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q=1.86; *df*=2; *P*=.40; I^2=0.0%)					0.60 (0.50-0.73)

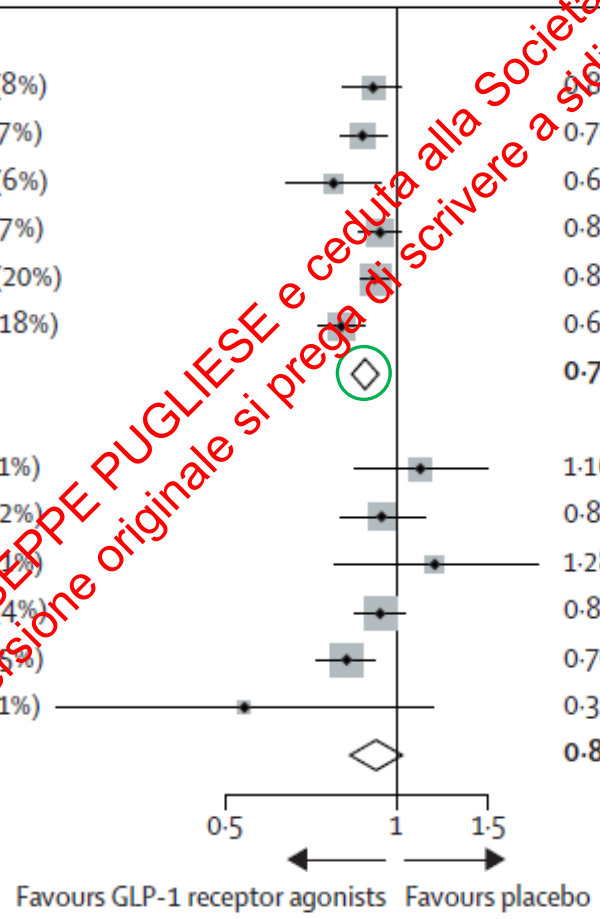


Mc Guire DK et al. *JAMA Cardiol.* 2021;6:148–158

Effect of GLP-1 receptor agonists on renal outcomes

Meta-analysis of 6 randomized controlled trials

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73 to 0·87)**	**47 (37 to 77)**	**<0·0001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·74 to 1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67 to 1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64 to 2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74 to 1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57 to 0·85)		0·0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10 to 1·27)		0·11
Subtotal (I^2=43·0%, p=0·12)			**0·86 (0·72 to 1·02)**	**241 (120 to –1694)†**	**0·089**

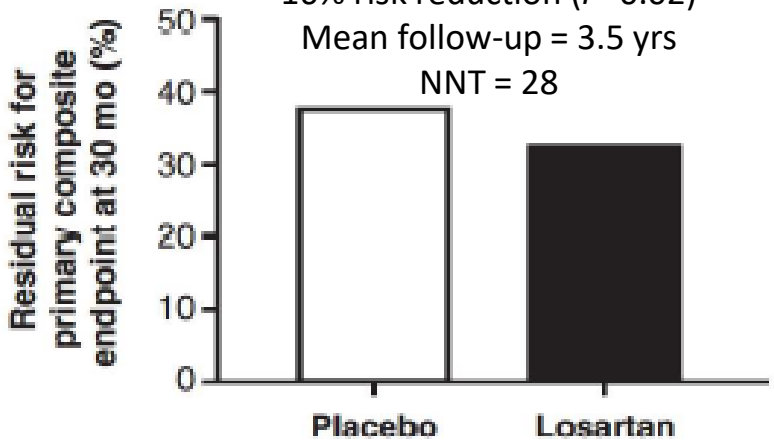


Sattar N et al. *Lancet Diabetes Endocrinol.* 2021;9:653–662

Residual renal risk after therapy with renoprotective drugs

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial

16% risk reduction (*P*=0.02)
Mean follow-up = 3.5 yrs
NNT = 28

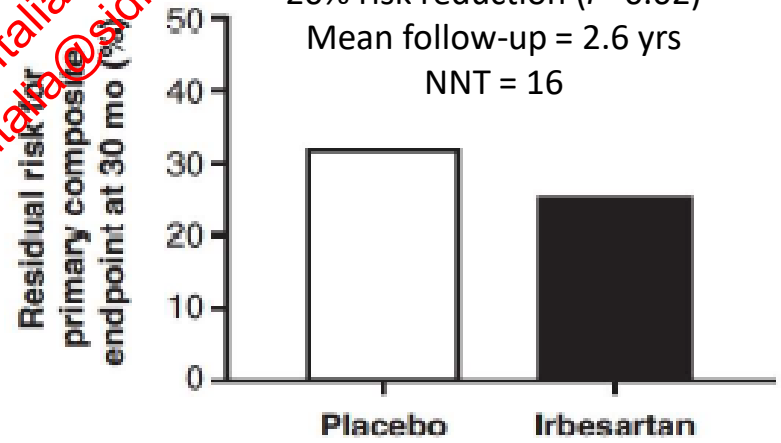


ARBs

Doubling Screat, ESKD or death

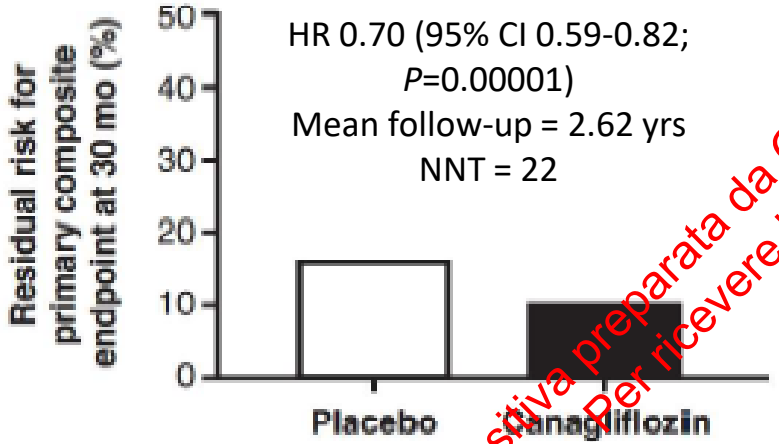
The Irbesartan Diabetic Nephropathy Trial (IDNT)

20% risk reduction (*P*=0.02)
Mean follow-up = 2.6 yrs
NNT = 16



The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial

HR 0.70 (95% CI 0.59-0.82; *P*=0.00001)
Mean follow-up = 2.62 yrs
NNT = 22

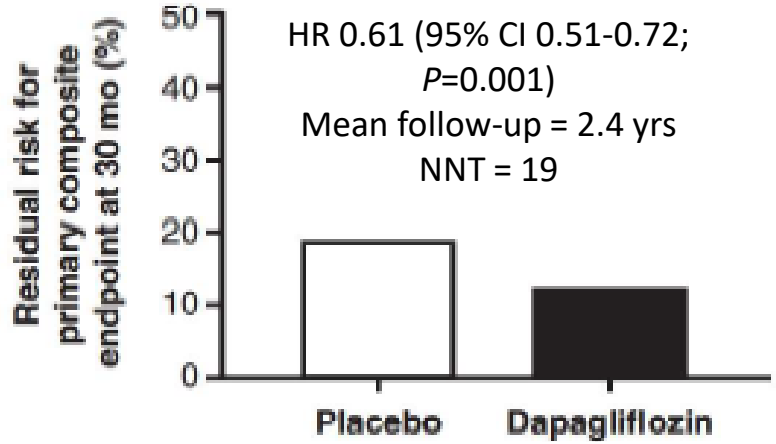


SGLT2 inhib

Doubling Screat, ESKD or CV/renal death

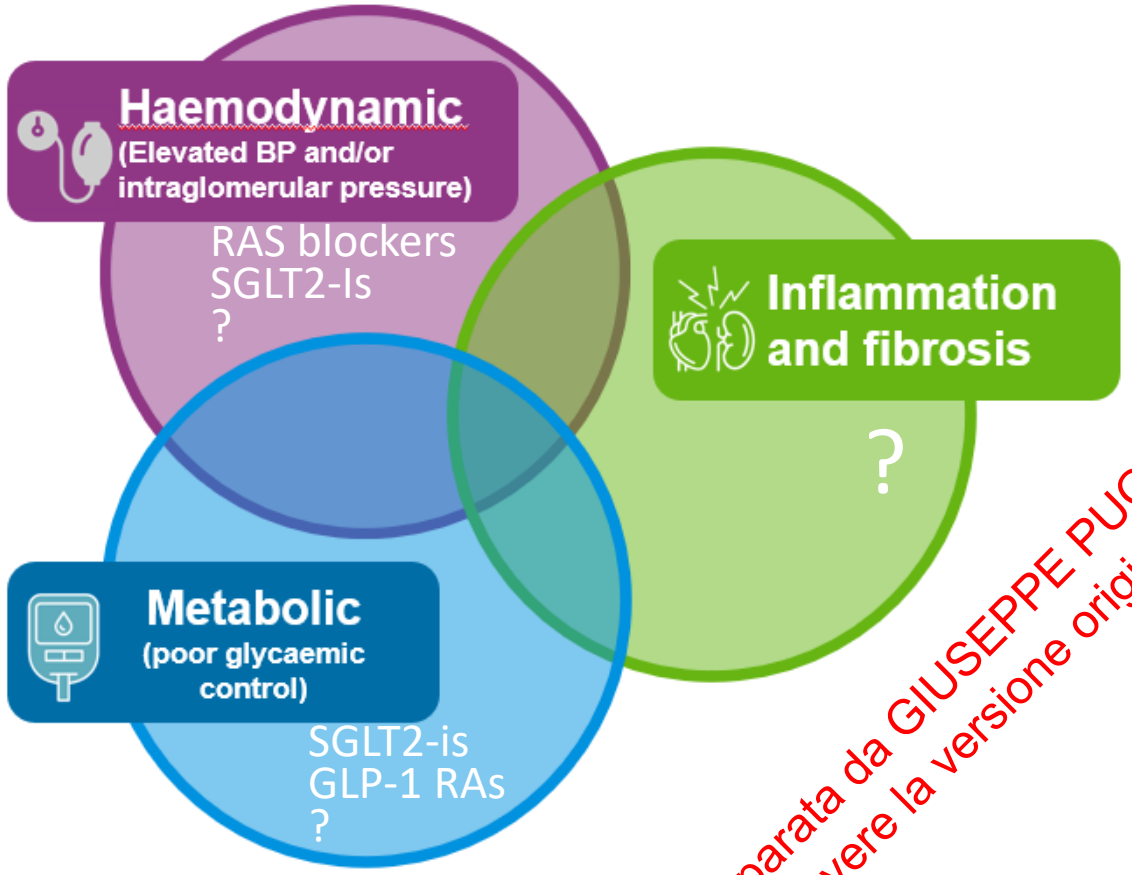
The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial

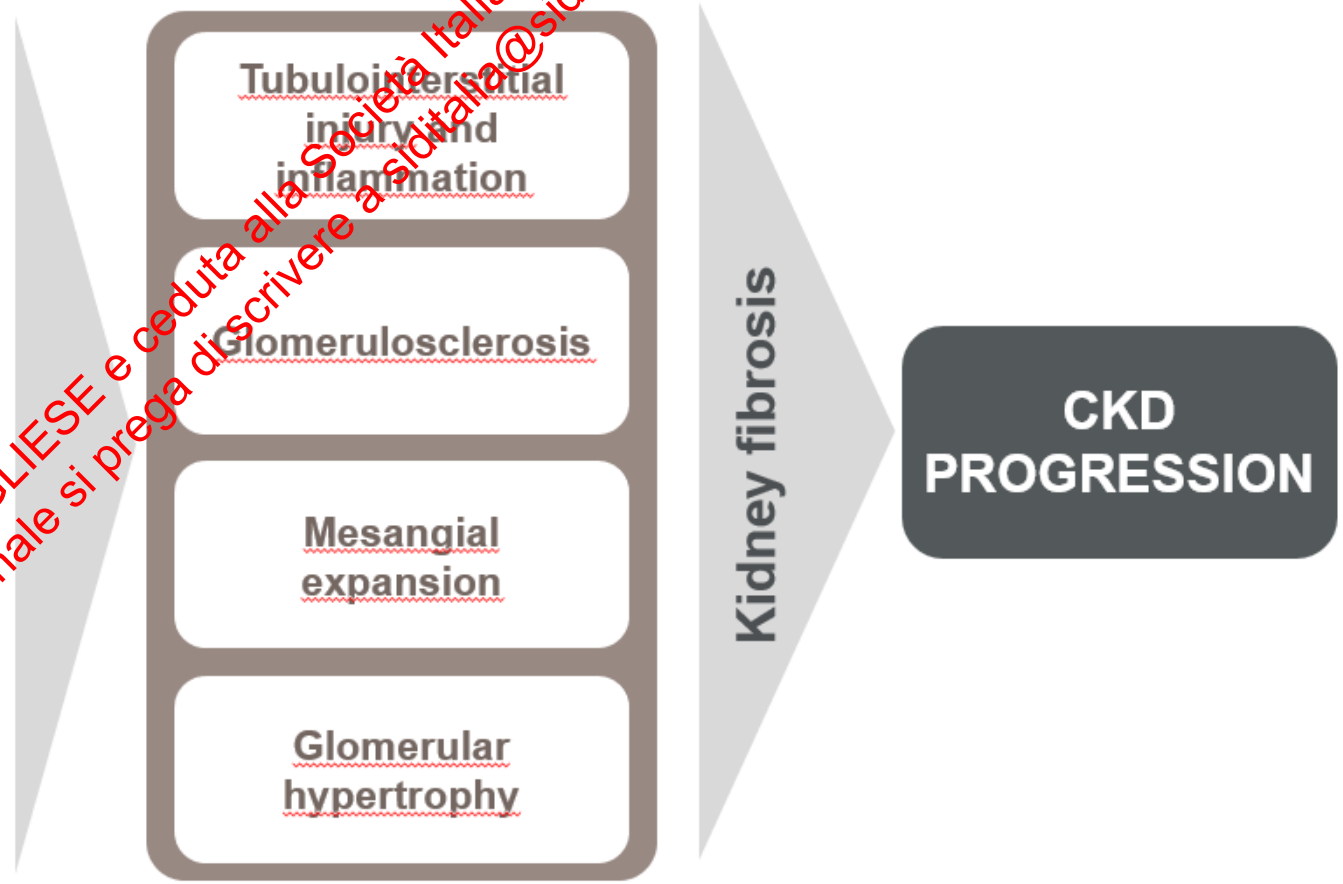
HR 0.61 (95% CI 0.51-0.72; *P*=0.001)
Mean follow-up = 2.4 yrs
NNT = 19



Chaudhuri A et al. *Diabetes Obes Metab.* 2022;24:365–376

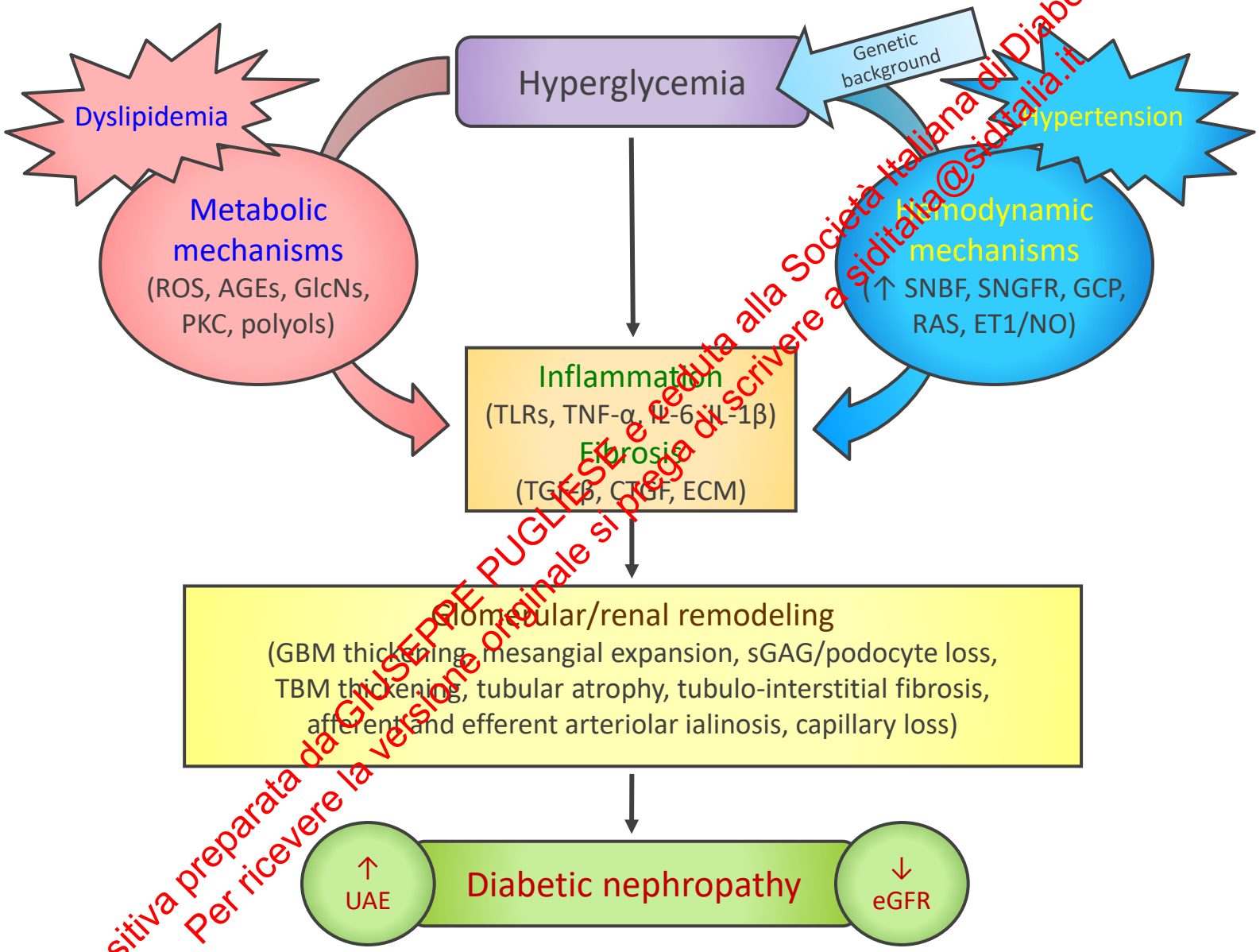
Search for new renoprotective drugs





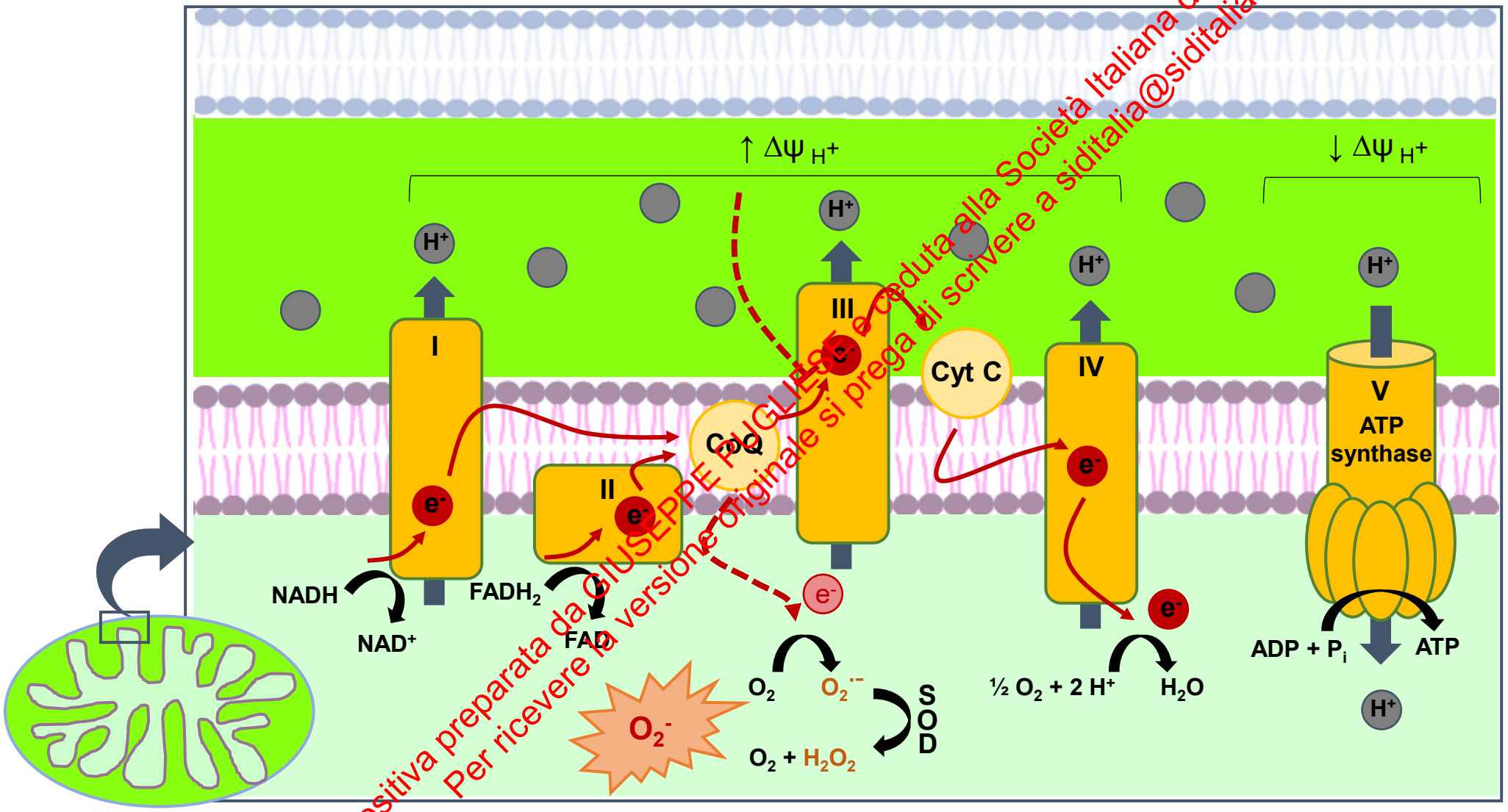
Alicic RZ et al. *Clin J Am Soc Nephrol.* 2017;12:2032–2045; Mora-Fernández C et al. *J Physiol.* 2014;18:3997

Pathogenesis of diabetic nephropathy



The unifying mechanism in diabetic complications: the Brownlee's hypothesis

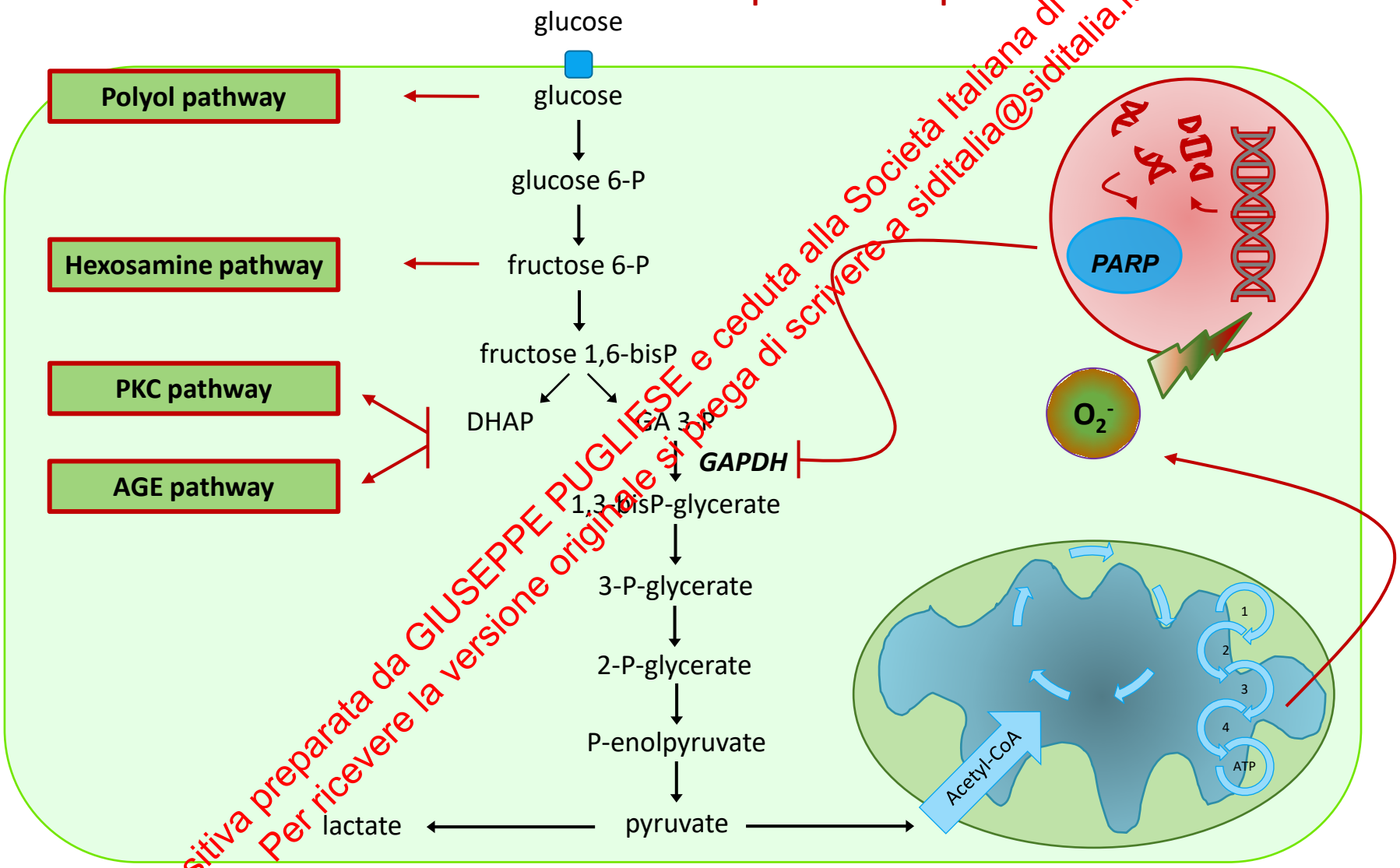
Increased mitochondrial superoxide production



Sharma K. *Diabetes.* 2015;64:663–672

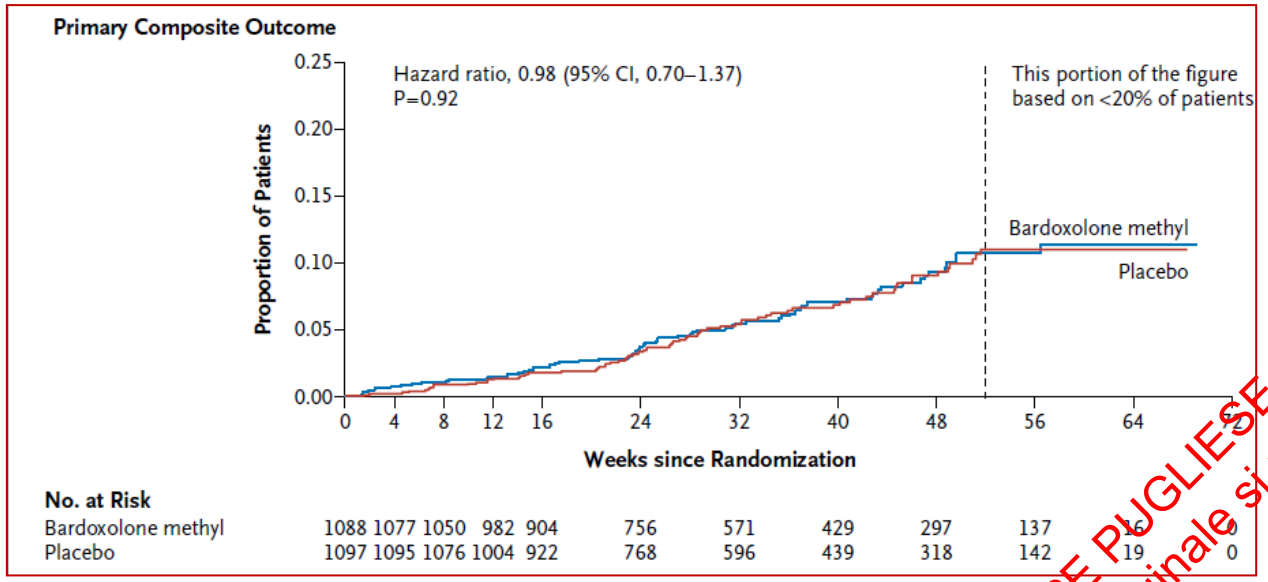
The unifying mechanism in diabetic complications: the Brownlee's hypothesis

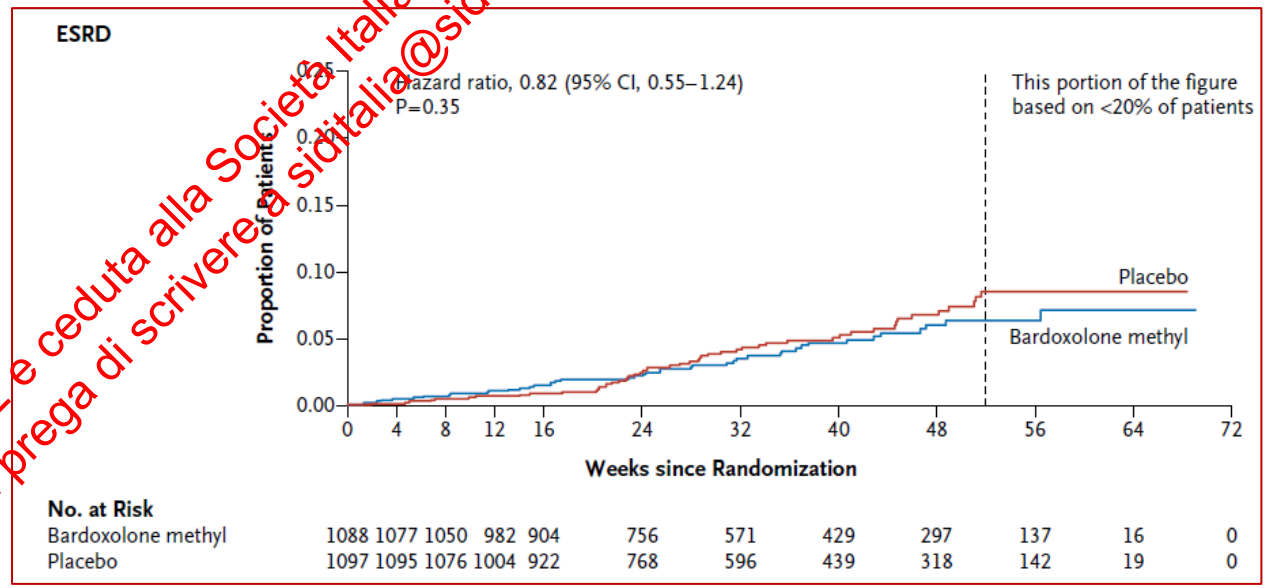
Increased mitochondrial superoxide production

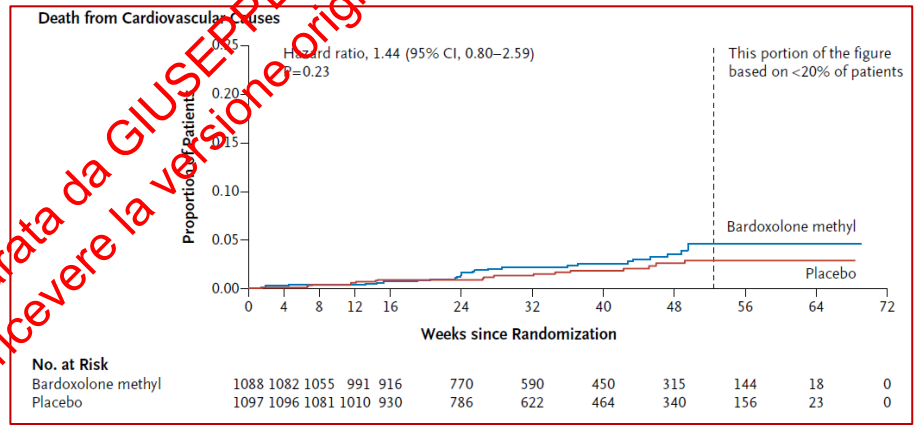


Brownlee M. *Nature*. 2001;414:813–820

The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) Trial







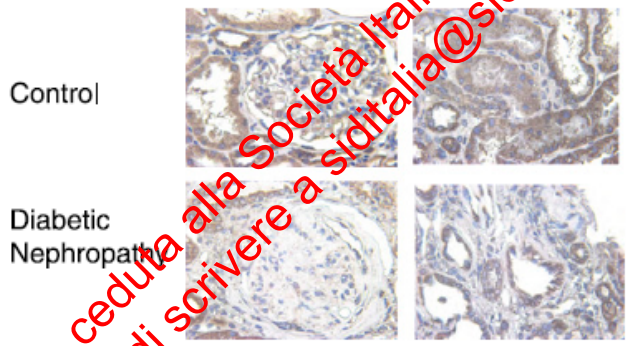
Mitochondrial dysfunction

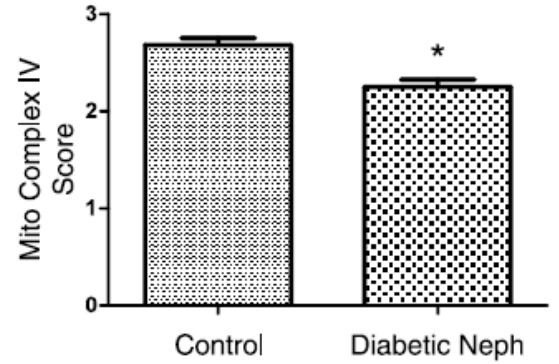
Patients with diabetes with and without nephropathy

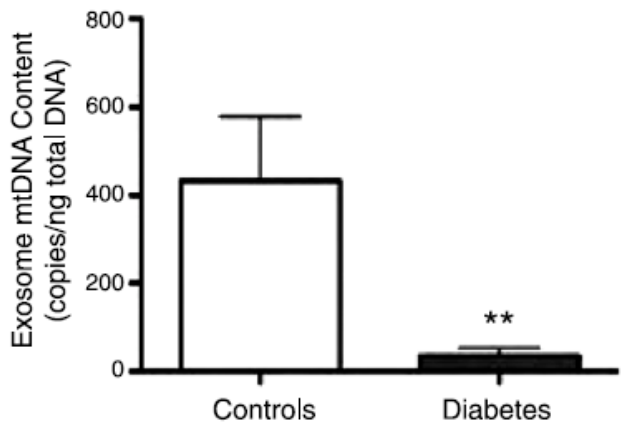
Comparison of candidate urine metabolites between patients with (n=85) and without (n=73) CKD

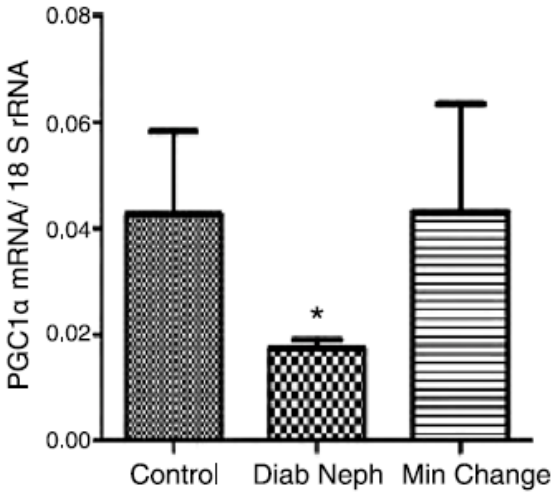
Metabolite	DM+CKD versus DM–CKD (95% CI) (%)[a]	*P* Value[b]
3-hydroxy isovalerate	−61.11 (−69.81 to −49.91)	1.11E-11
Aconitic acid	−45.4 (−54.18 to −34.93)	2.22E-10
Citric acid	−65.96 (−74.31 to −54.9)	3.82E-12
2-ethyl 3-OH propionate	−43.82 (−52.26 to −33.89)	8.80E-11
Glycolic acid	−54.19 (−62.54 to −43.99)	2.18E-12
Homovanillic acid	−38.72 (−53.04 to −20.04)	0.0003812
3-hydroxy isobutyrate	−58.35 (−68.88 to −44.25)	2.00E-08
2-methyl acetoacetate	−49.74 (−68.29 to −20.35)	0.00367
3-methyl adipic acid	−48.63 (−58.74 to −36.05)	1.42E-08
3-methyl crotonyl glycine	−41.52 (−57.72 to −19.1)	0.001349
3-hydroxy propionate	−22.54 (−42.29 to 3.97)	0.0883
Tiglylglycine	−35.71 (−50.53 to −16.44)	0.001097
Uracil	−50.1 (−63.93 to −30.97)	4.04E-05

12 of 13 were associated with mitochondria





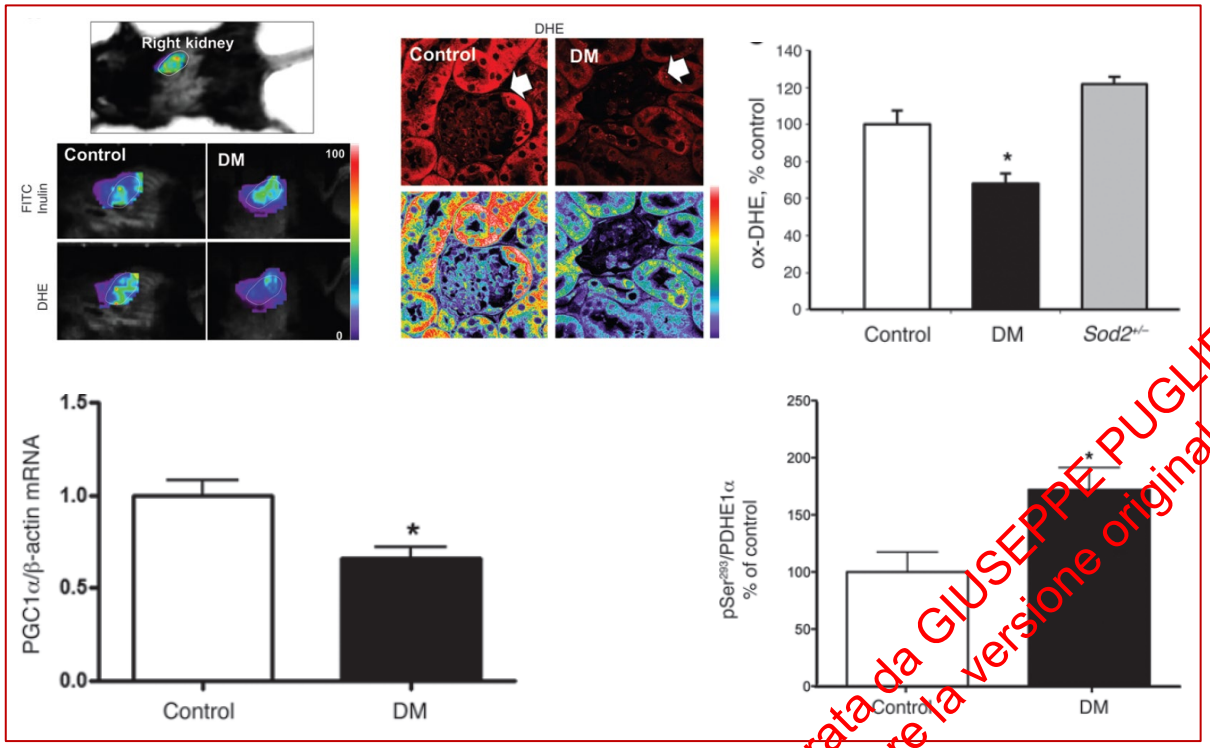


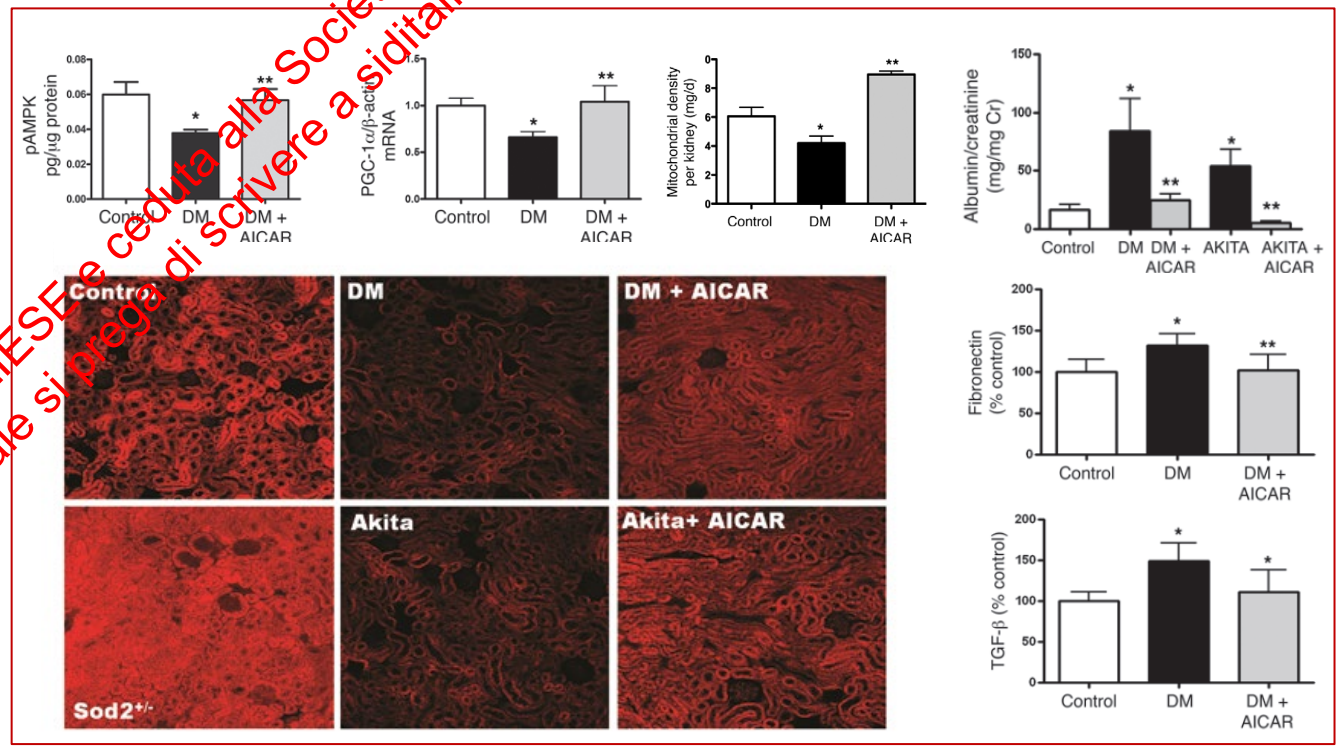


Sharma K et al. J *Am Soc Nephrol.* 2013;24:1901–1912

Mitochondrial dysfunction

Mice (diabetic, heterozygous for SOD, treated with AICAR)

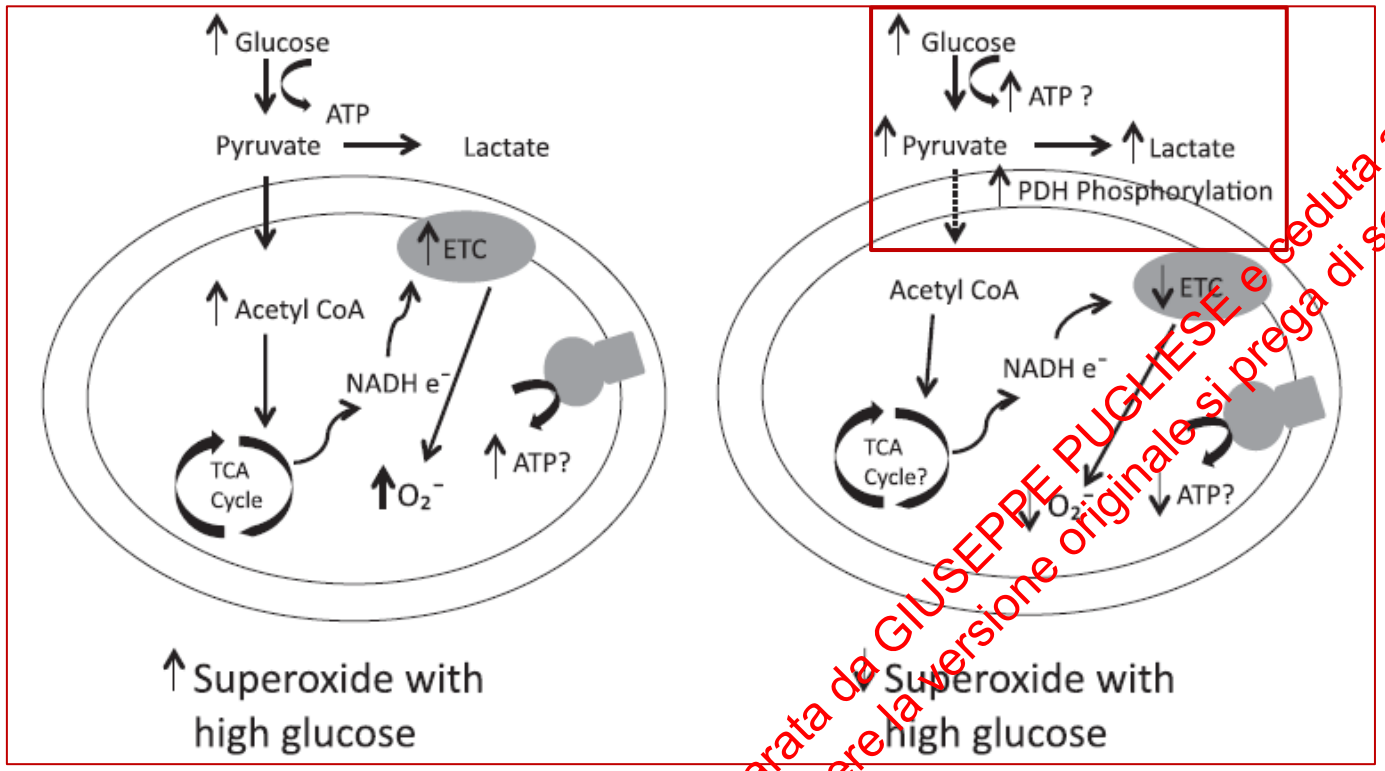


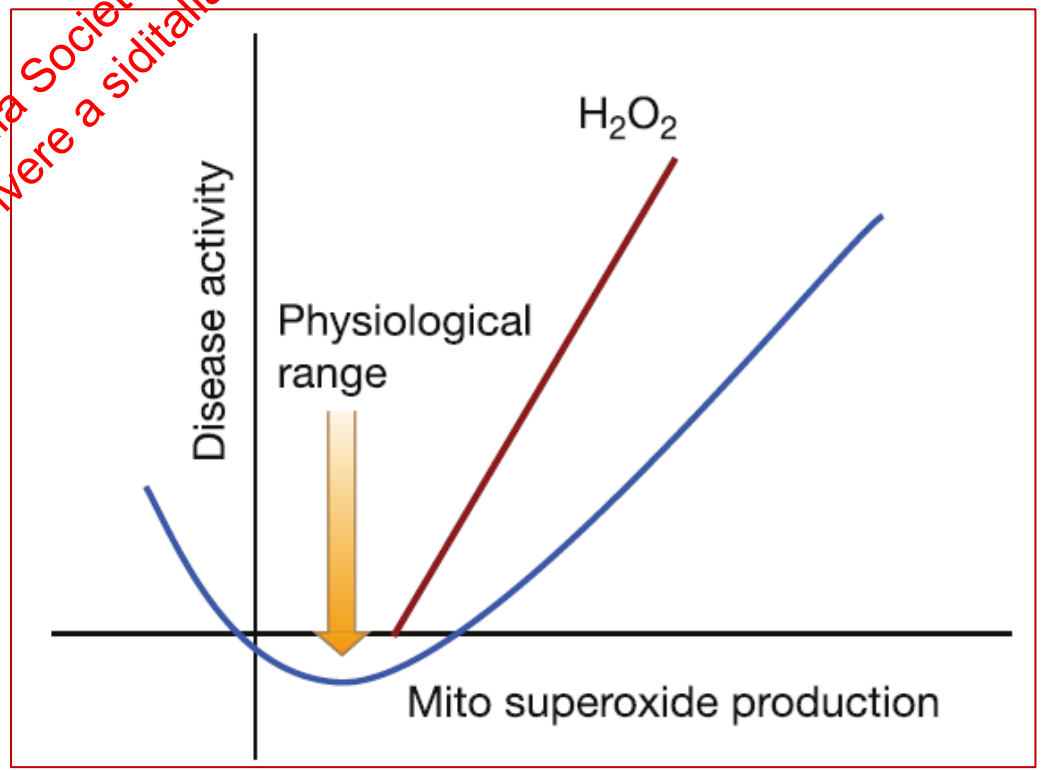


Dugan LL et al. *J Clin Invest.* 2013;123:4888–4899

Mitochondrial dysfunction

Mitochondrial hormesis



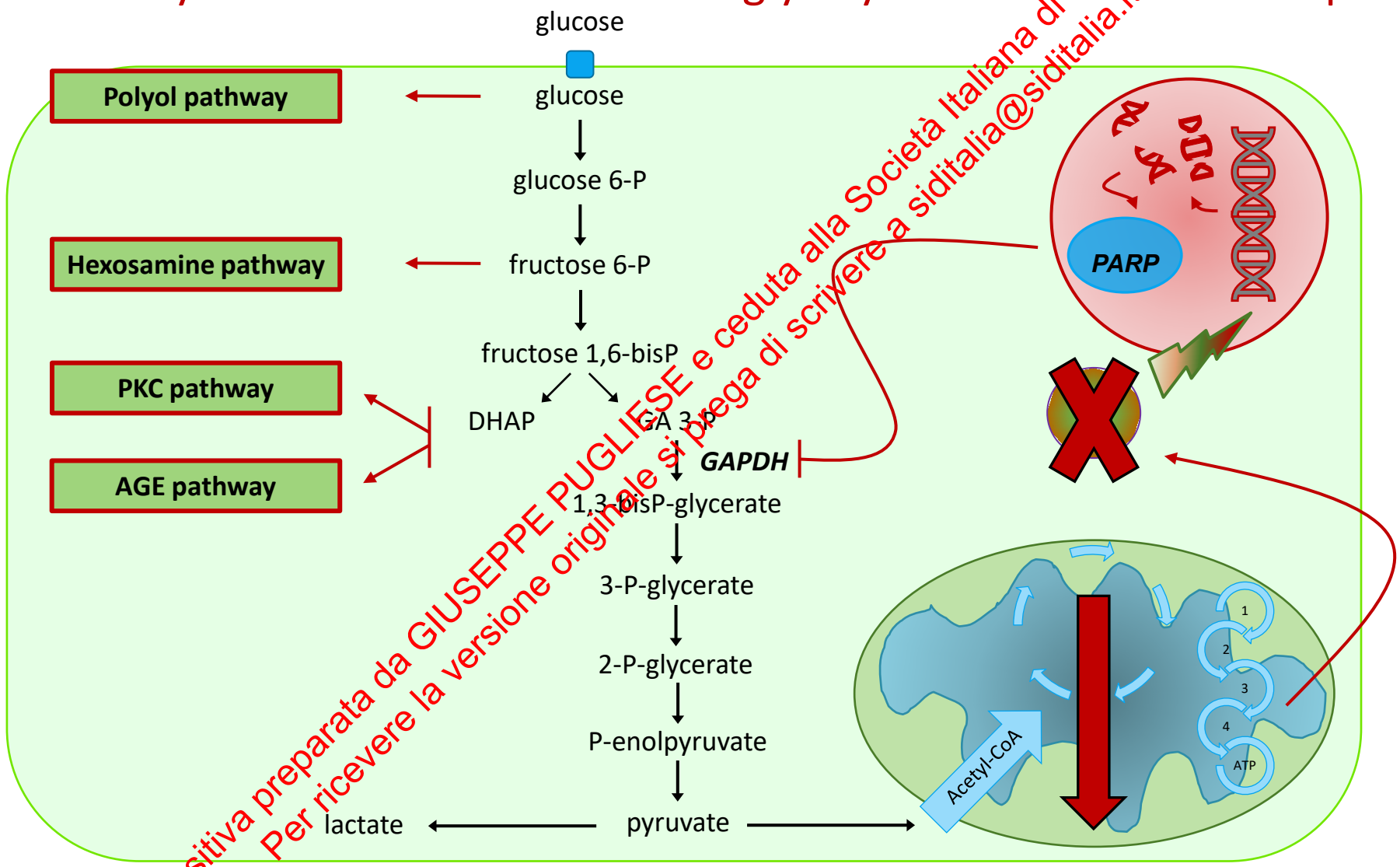


Sharma K. *Diabetes.* 2015;64:663–672

Coughlan MT et al. *Kidney Int.* 2016;90:272–279

Search for a new unifying mechanism in diabetic complications

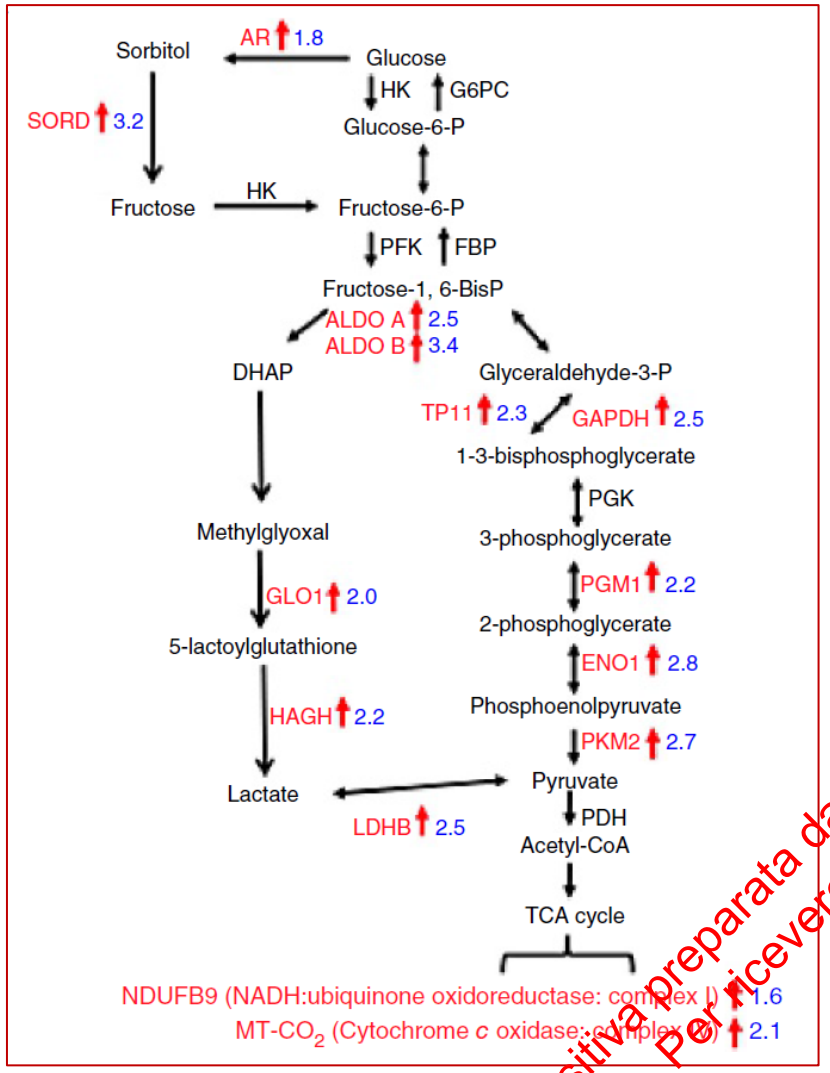
Mitochondrial dysfunction with diversion of glycolysis toward alternative pathways

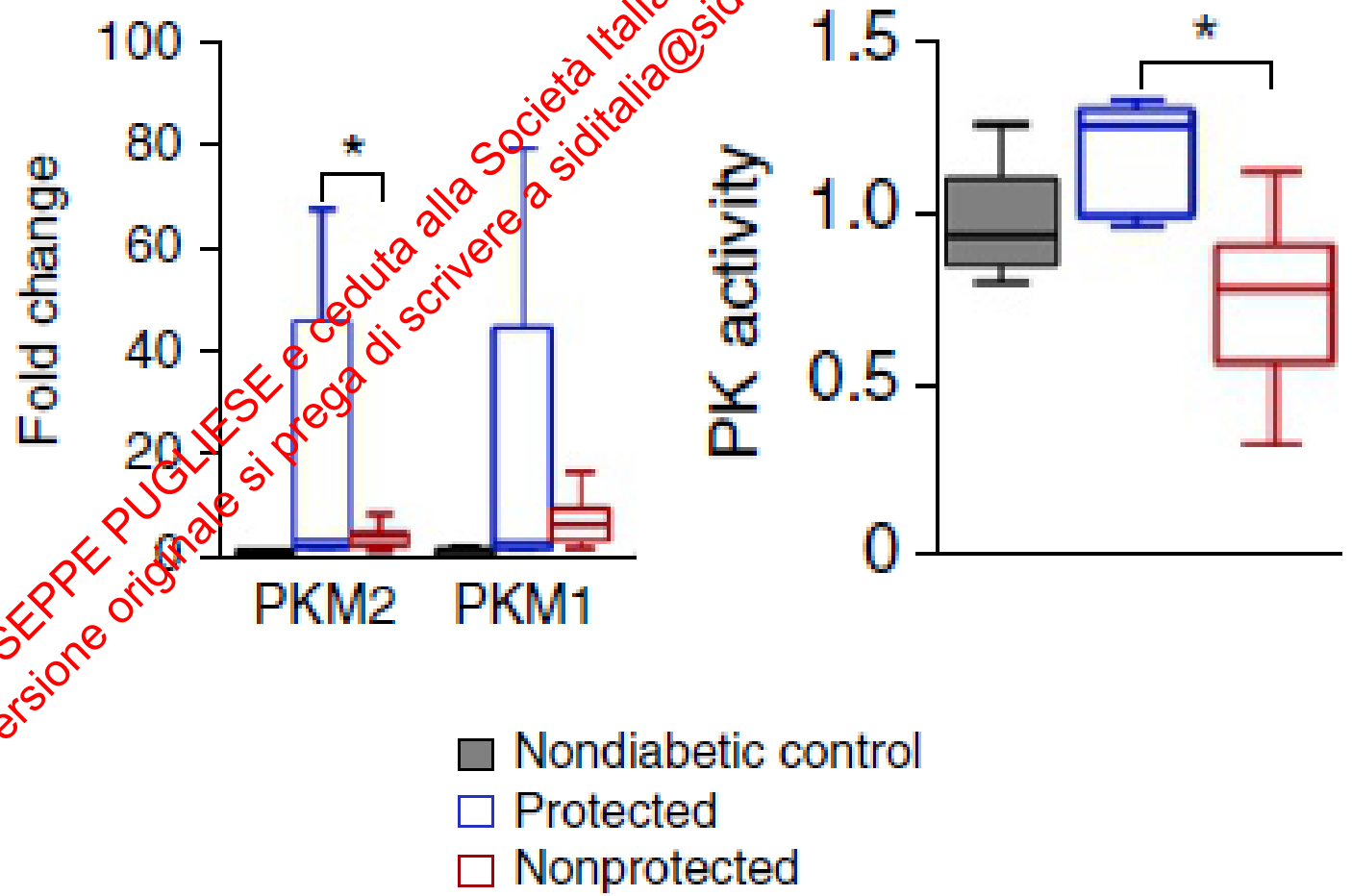


Brownlee M. *Nature.* 2001;414:813–820

Impaired pyruvate kinase M2 (PKM2) activity

Individuals with type 1 diabetes for >50 years (Medalists)

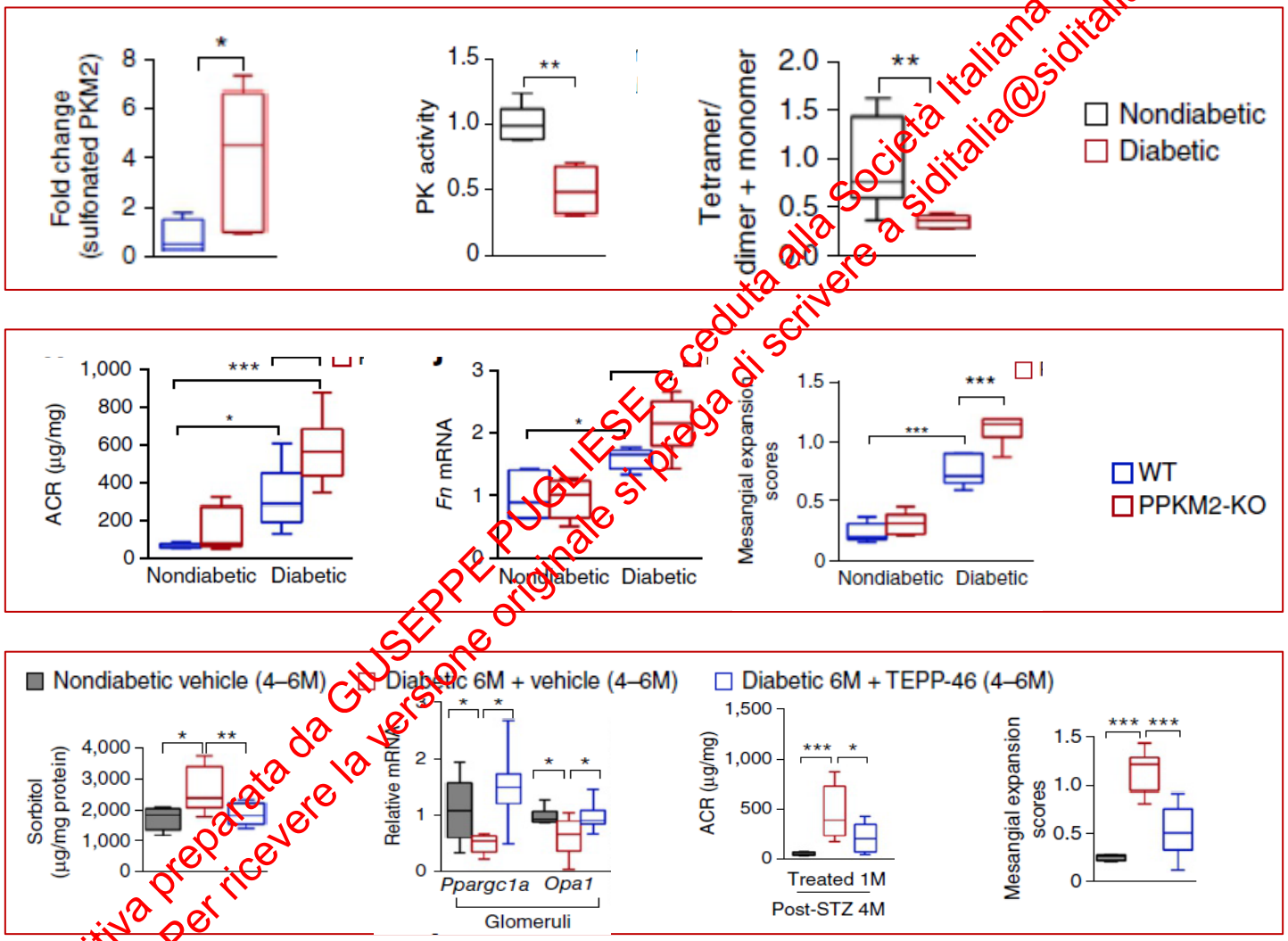




Qi W et al. *Nat Med.* 2017;23:753–762

Impaired PKM2 activity

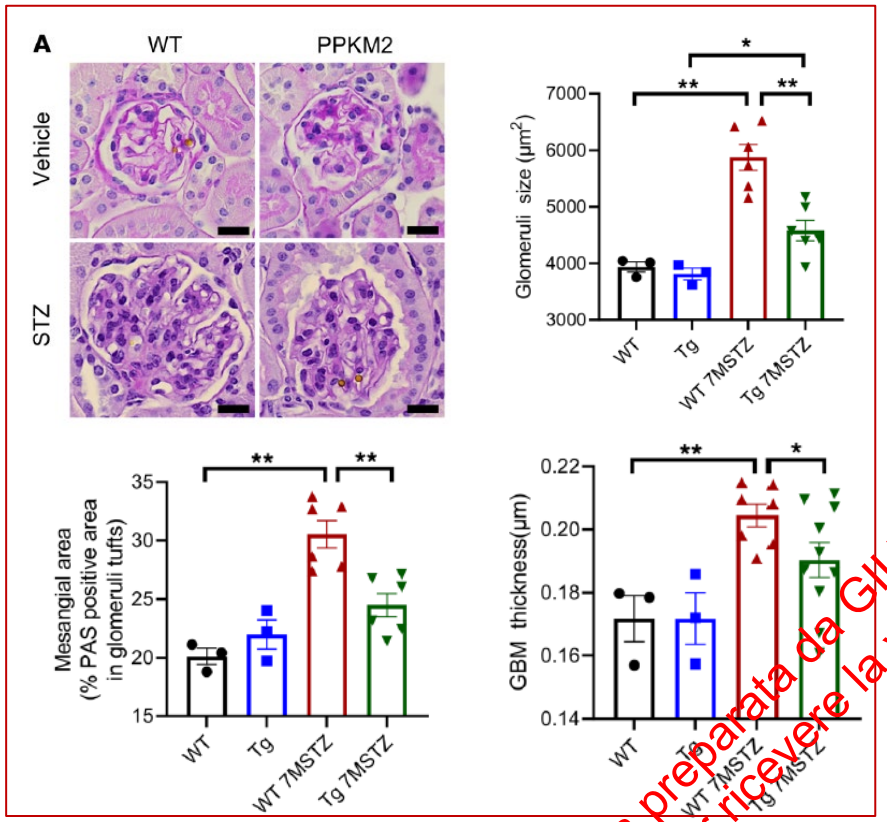
Diabetic mice (WT, KO for PKM2, treated with TEPP-46)

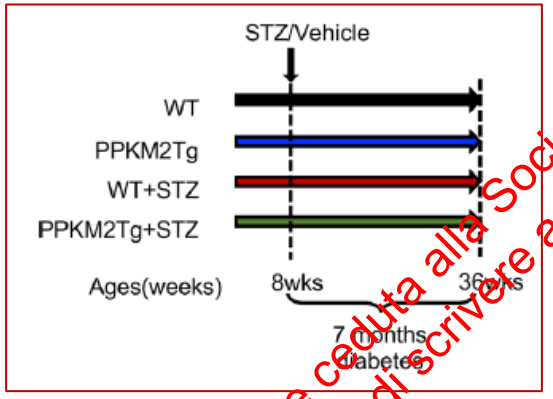


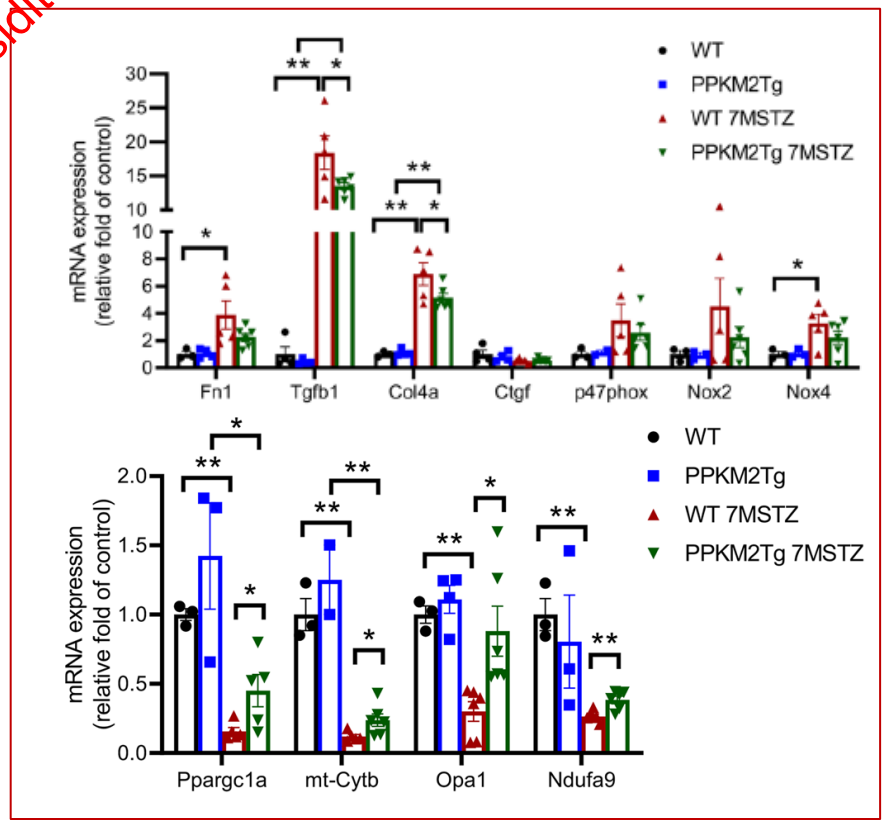
Qi W et al. *Nat Med.* 2017;23:753–762

Impaired PKM2 activity

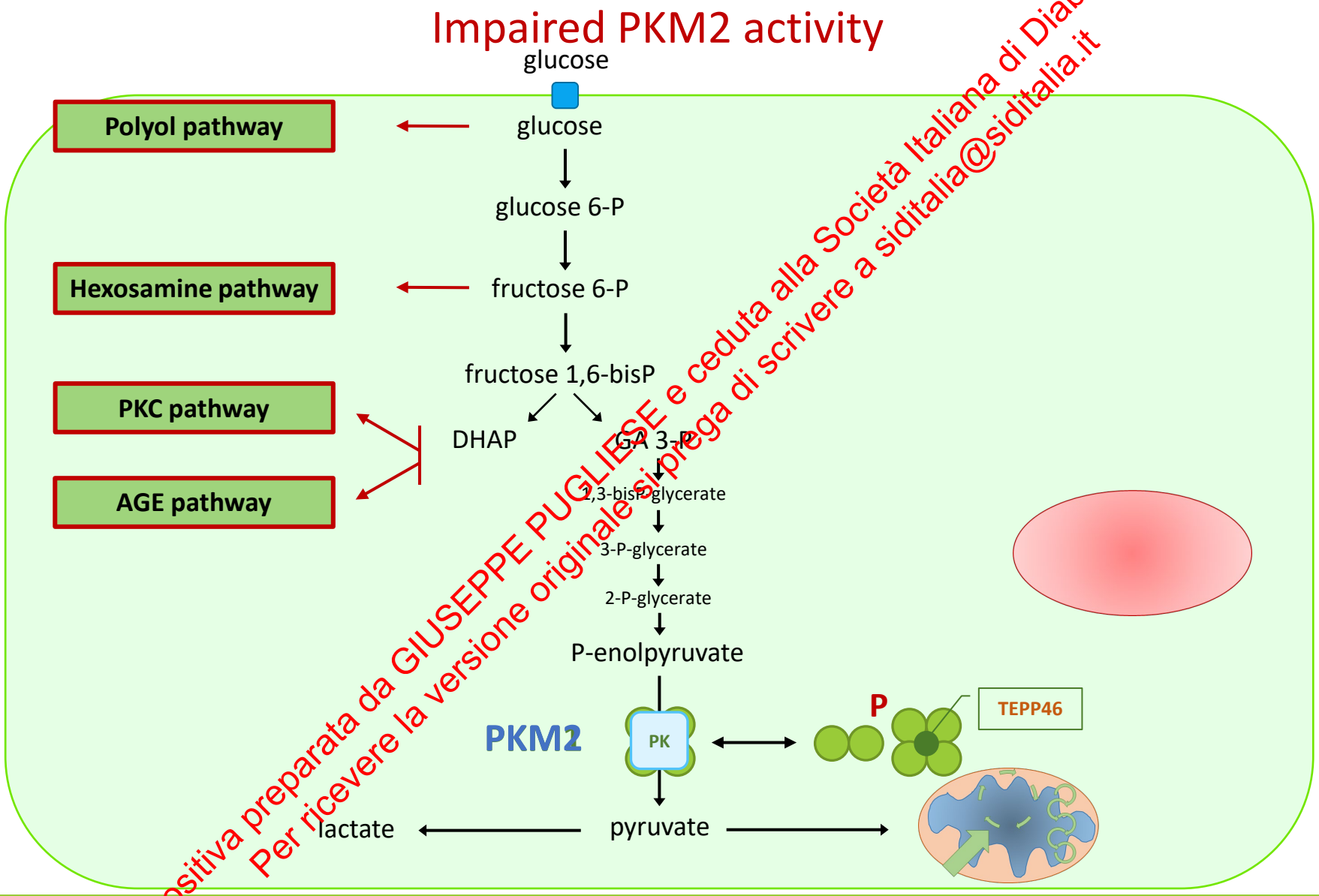
Diabetic mice (transgenic for PKM2)



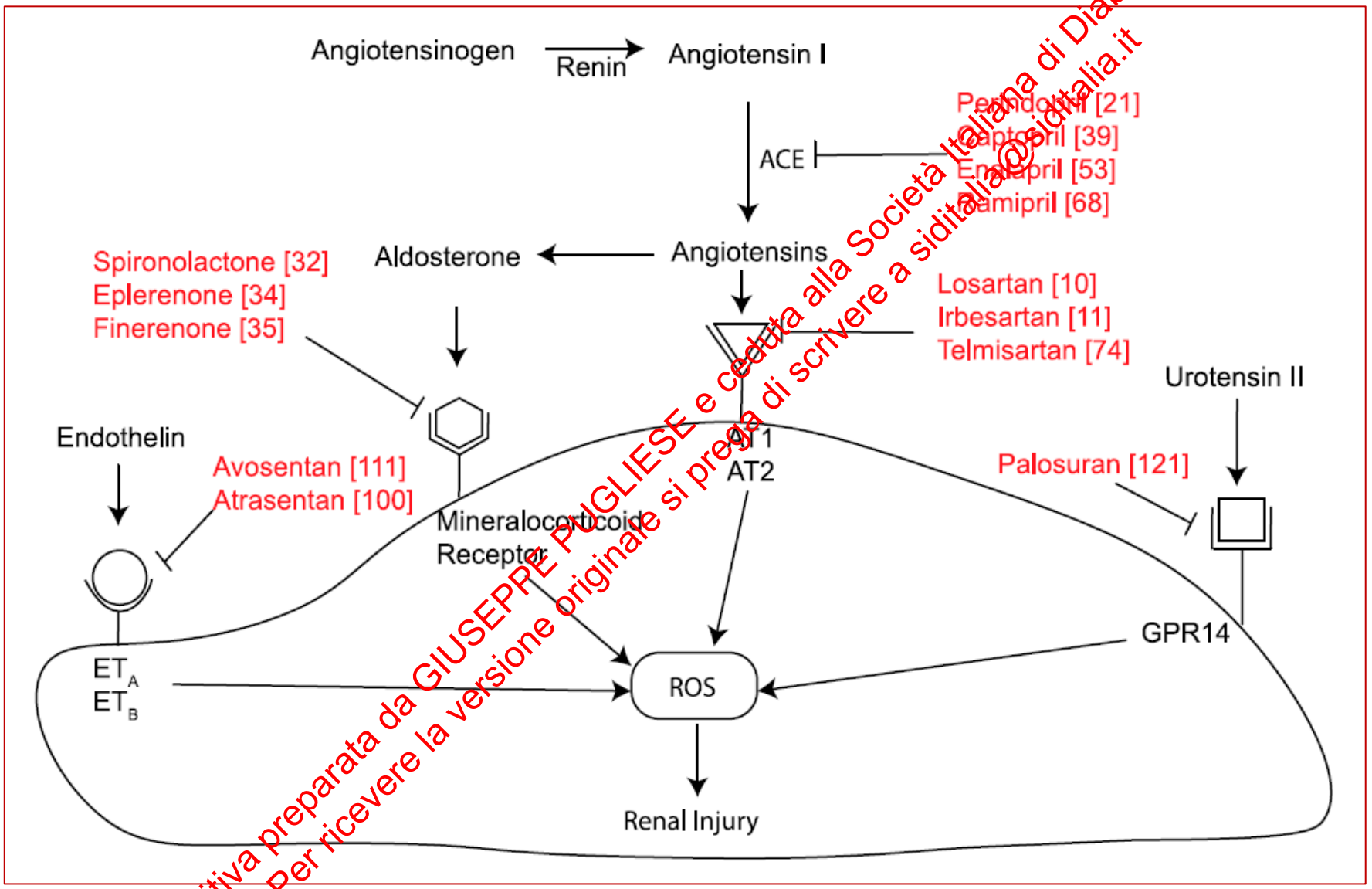




A new unifying mechanism in diabetic complications



Alterations of vasoactive hormones

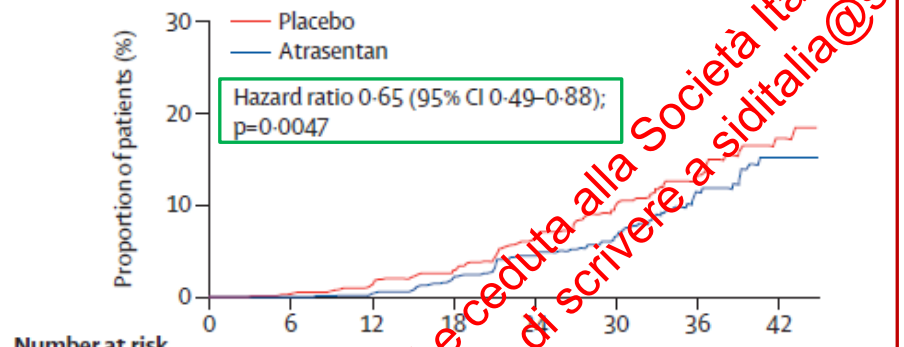


Patel DM et al. *Int J Mol Sci.* 2020;21:2218

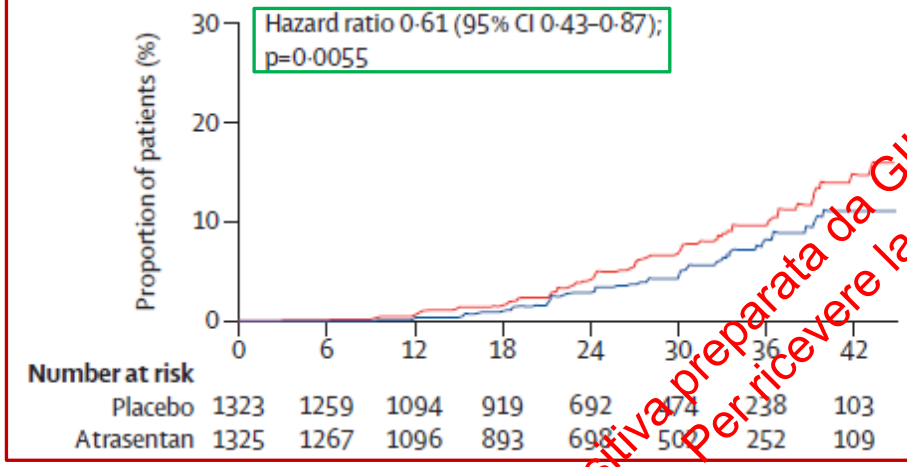
Treatment with endothelin receptor antagonist for diabetic kidney disease

The Study of Diabetic Nephropathy with Atrasentan (SONAR)

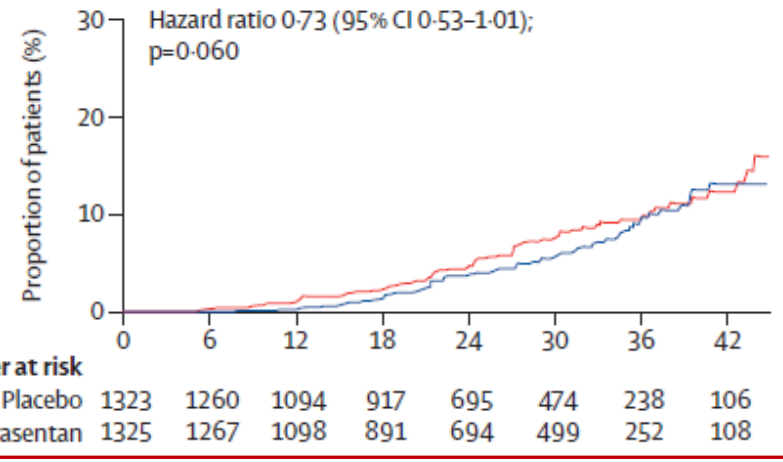
Primary composite renal outcome



Doubling of serum creatinine

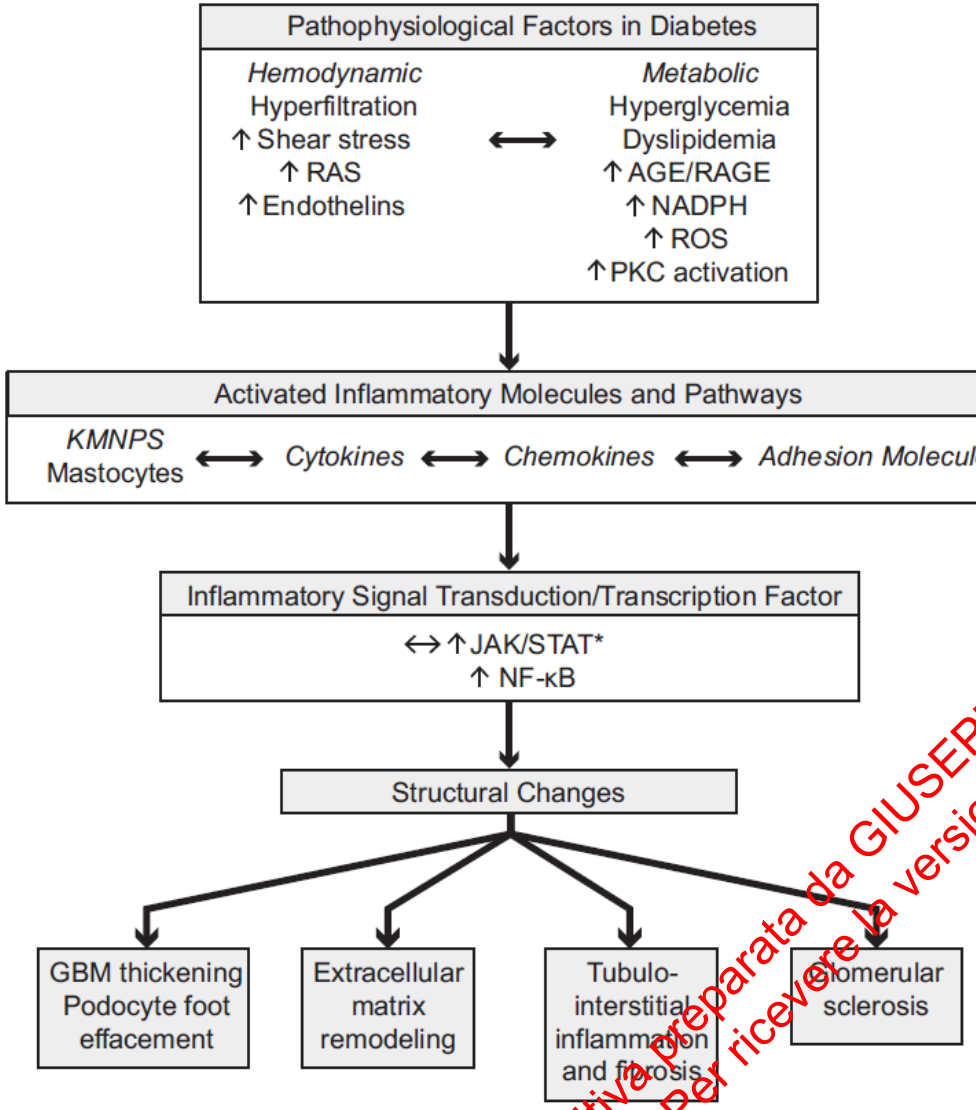


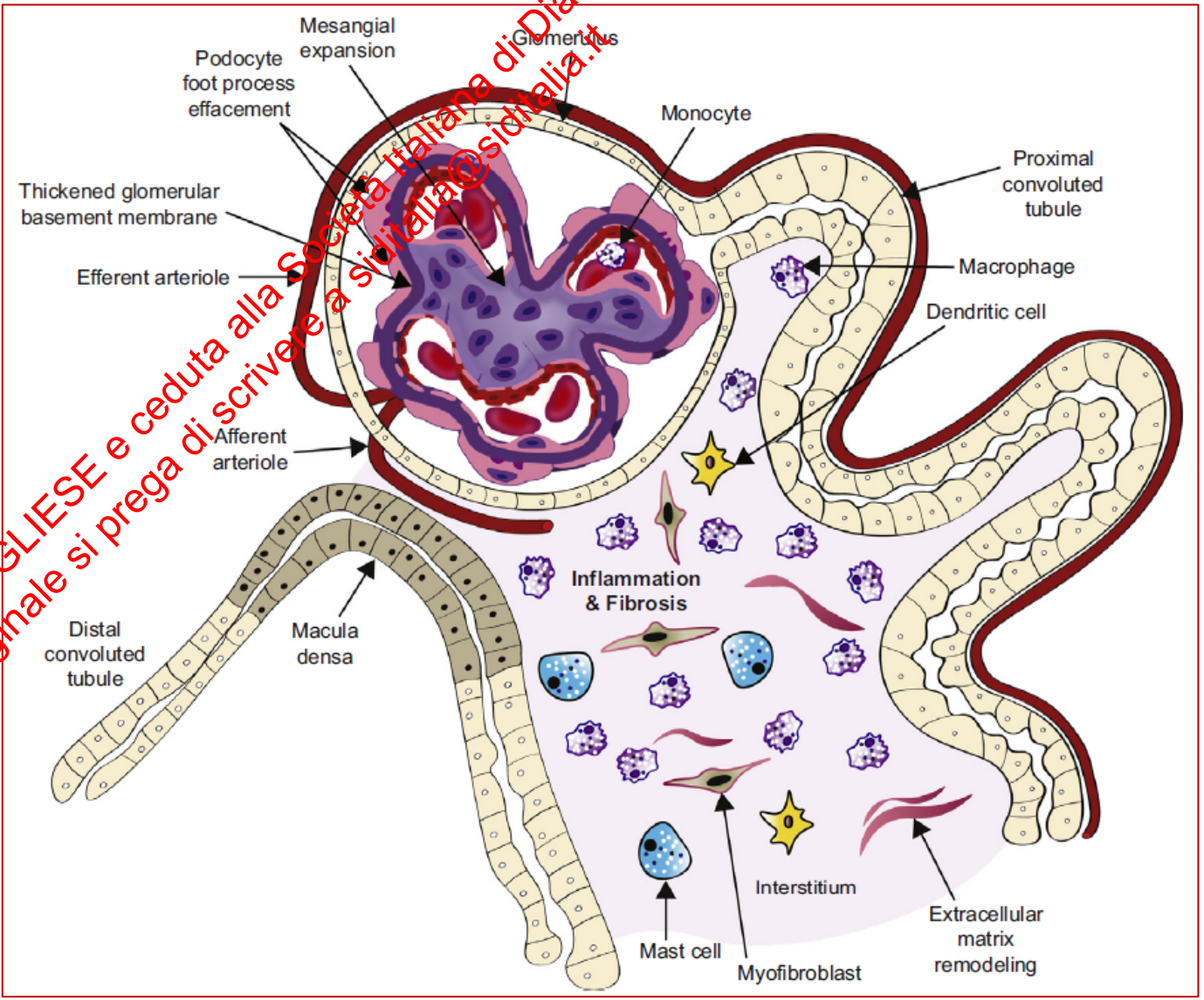
End-stage renal disease



Heespink HJL et al. *Lancet.* 2019;393:1937–1947

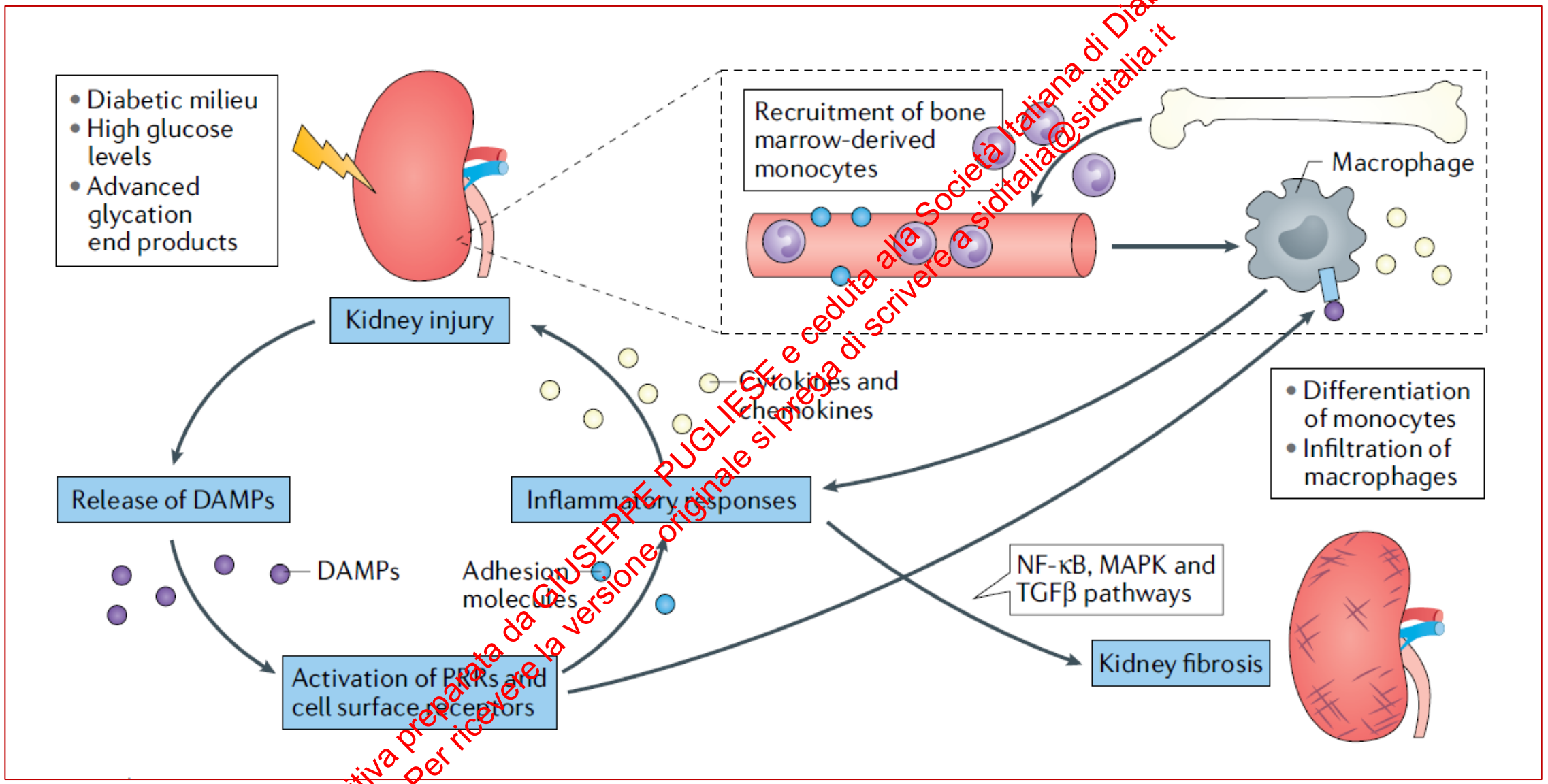
Inflammatory mechanisms in diabetic kidney disease





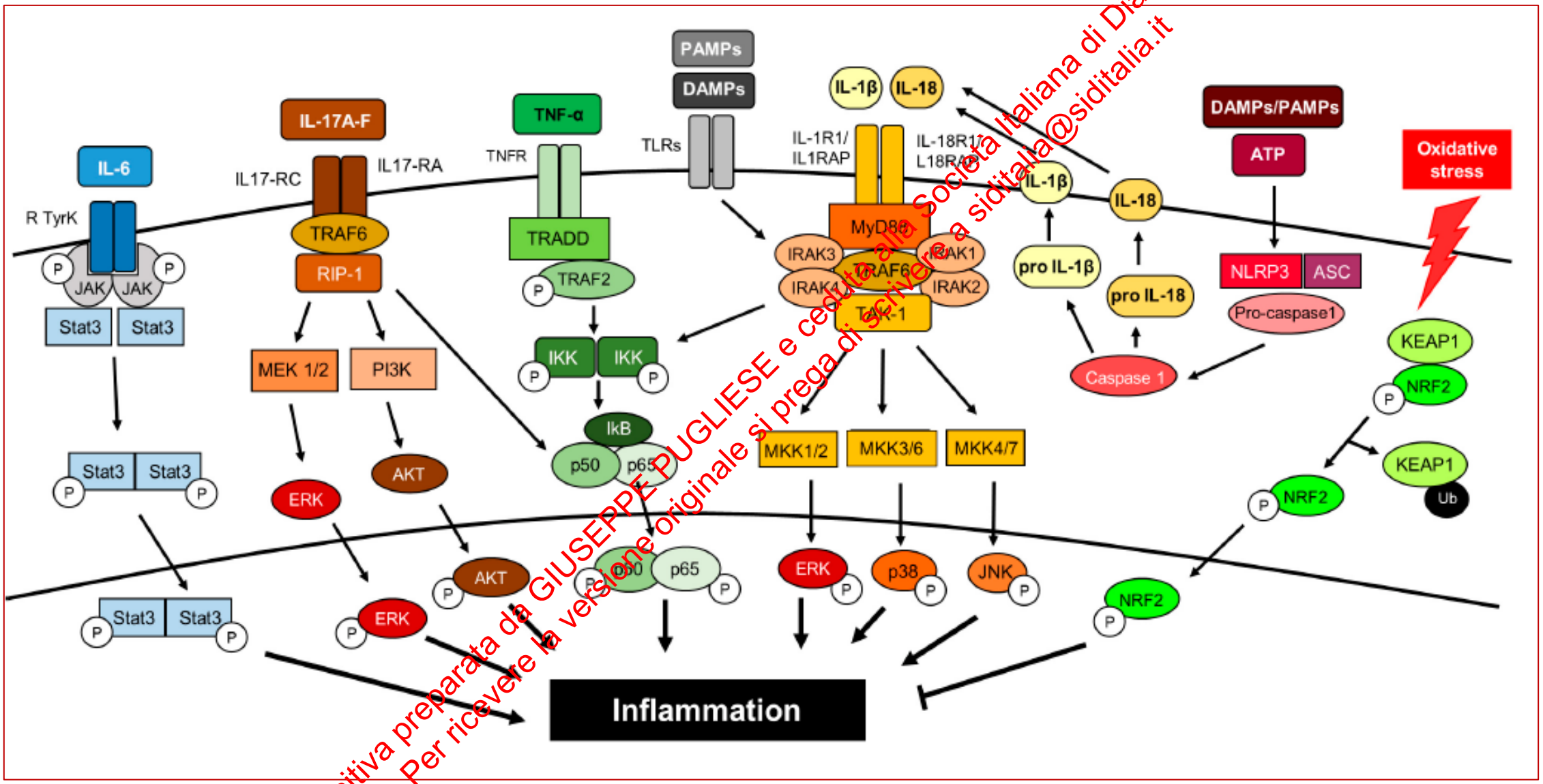
Alicic RZ et al. *Adv Chronic Kidney Dis.* 2018;25:181–191

Inflammatory mechanisms in diabetic kidney disease



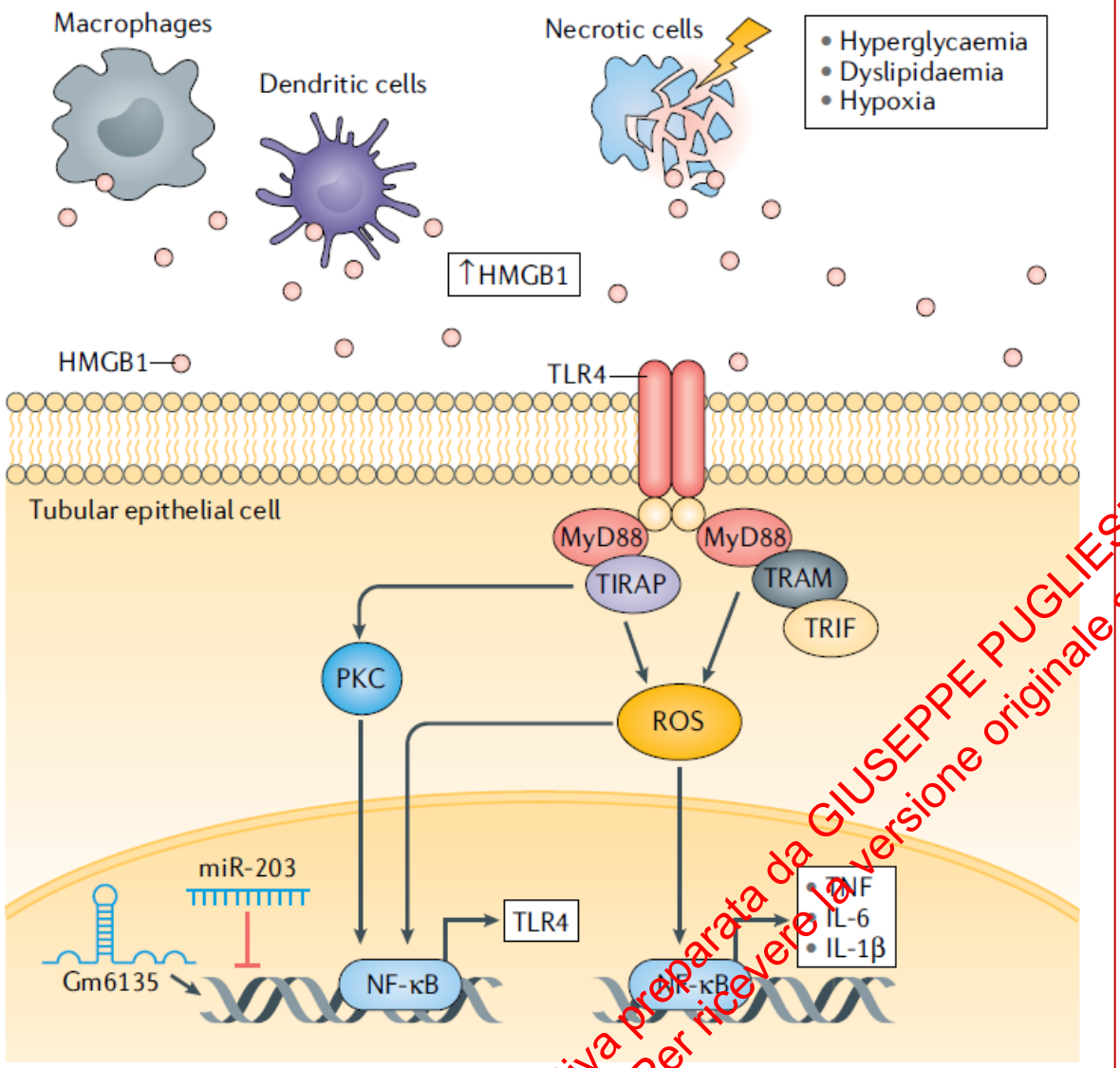
Tang SCW & Yiu WH. *Nat Rev Nephrol.* 2020;16:206–222

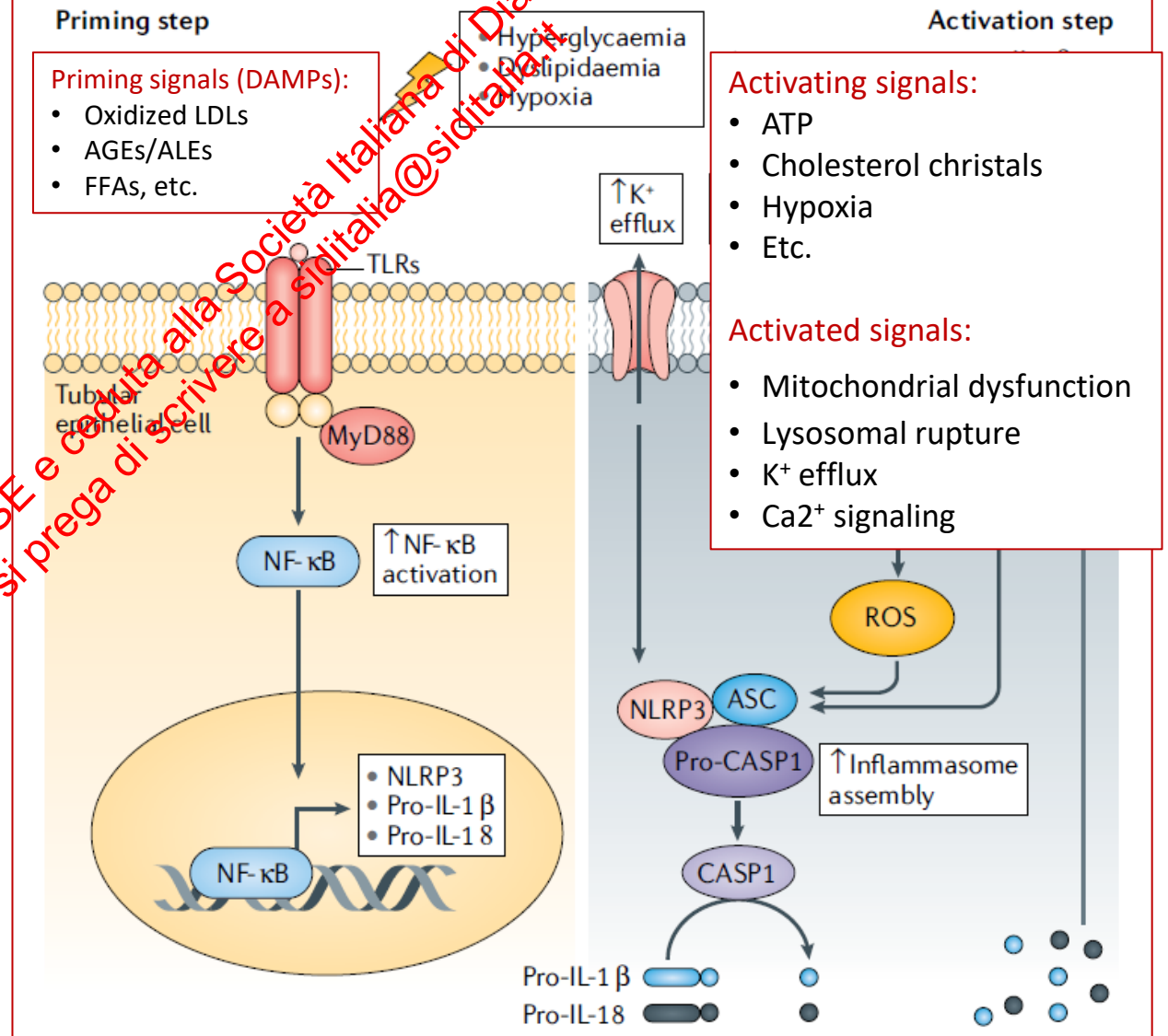
Inflammatory mechanisms in diabetic kidney disease



Rayego-Mateos S et al. *Int J Mol Sci.* 2020;31:3798

Inflammatory mechanisms in diabetic kidney disease

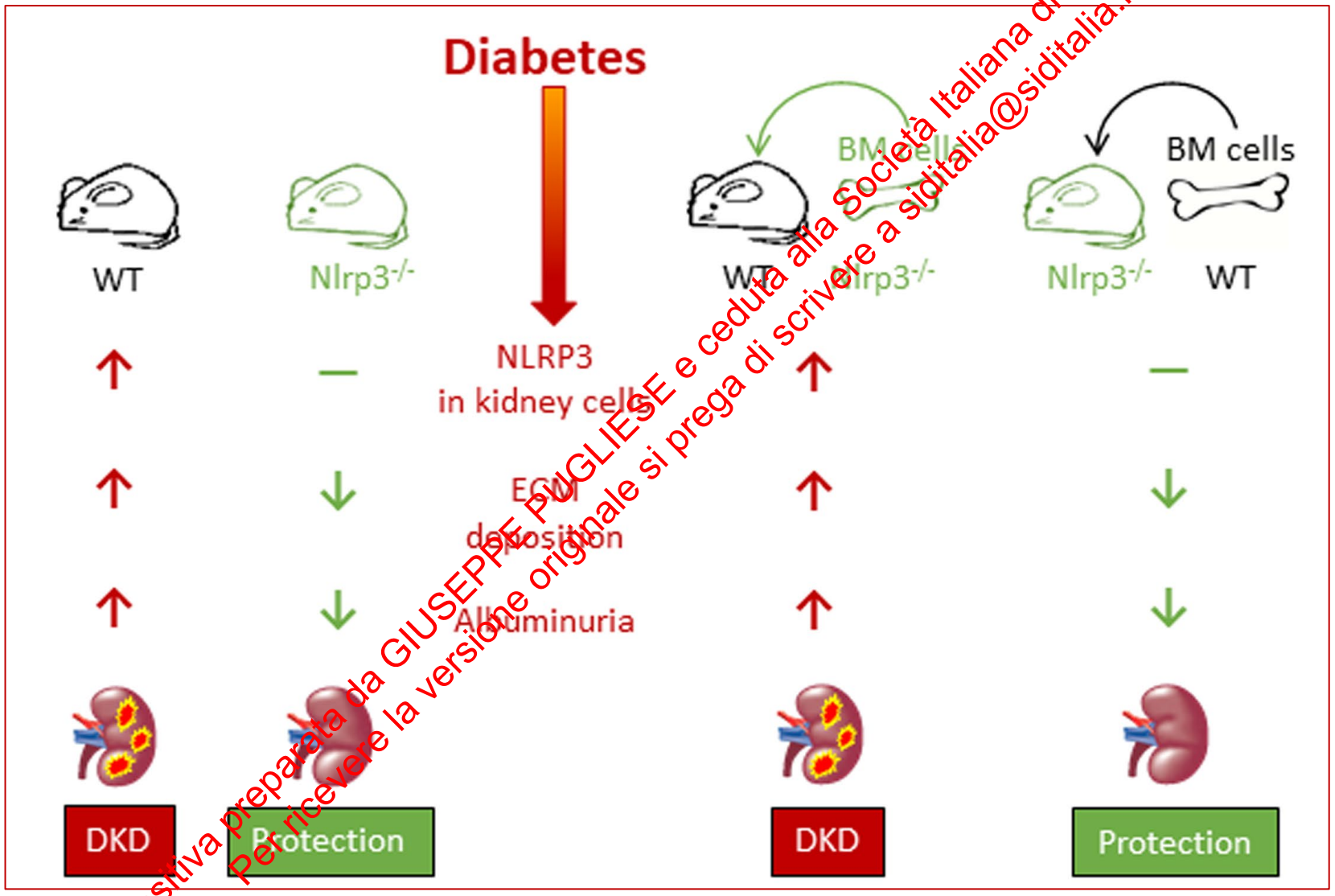




Tang SCW & Yiu WH. *Nat Rev Nephrol.* 2020;16:206–222

NLRP3 activation in diabetic kidney disease

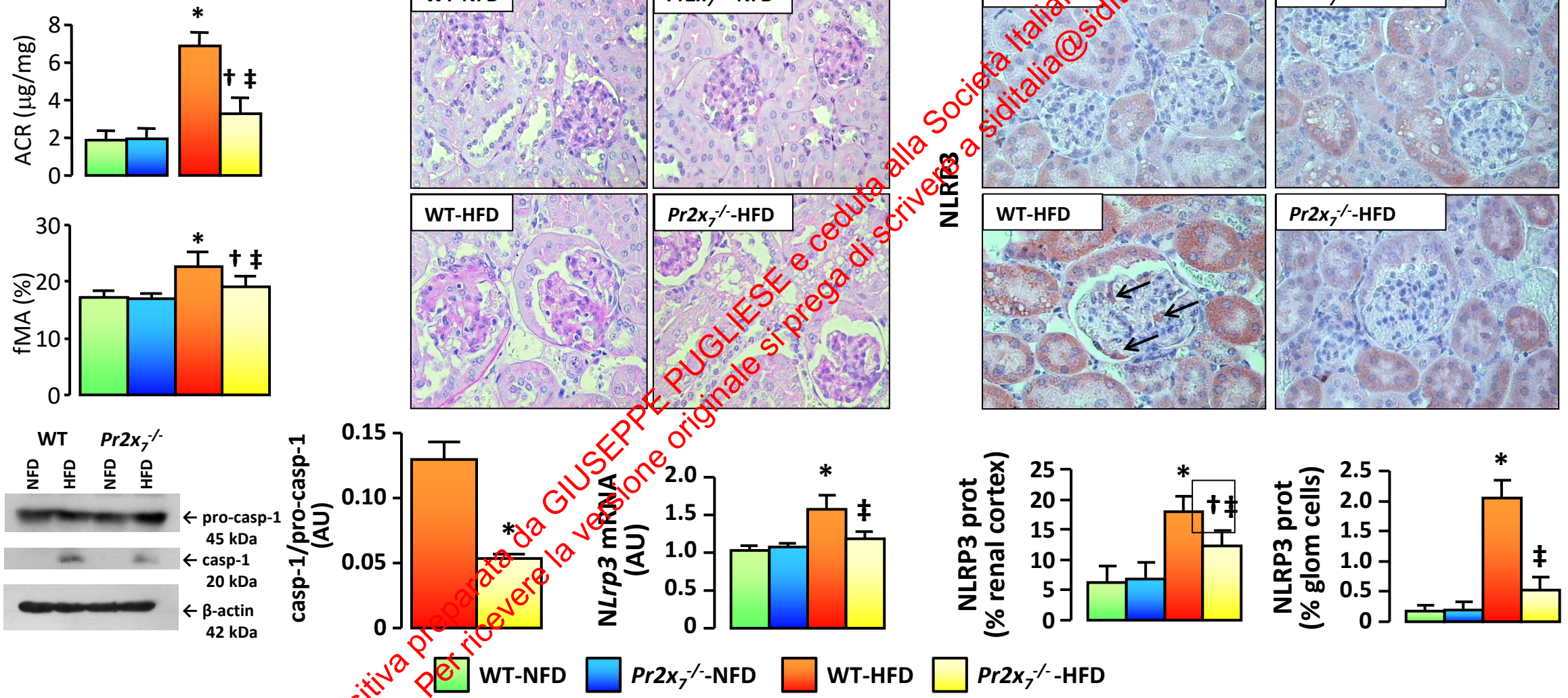
Diabetic mice (WT, KO for NLRP3, transplanted with BM cells)



Shahzad K et al. *Kidney Int.* 2015;87:74–84

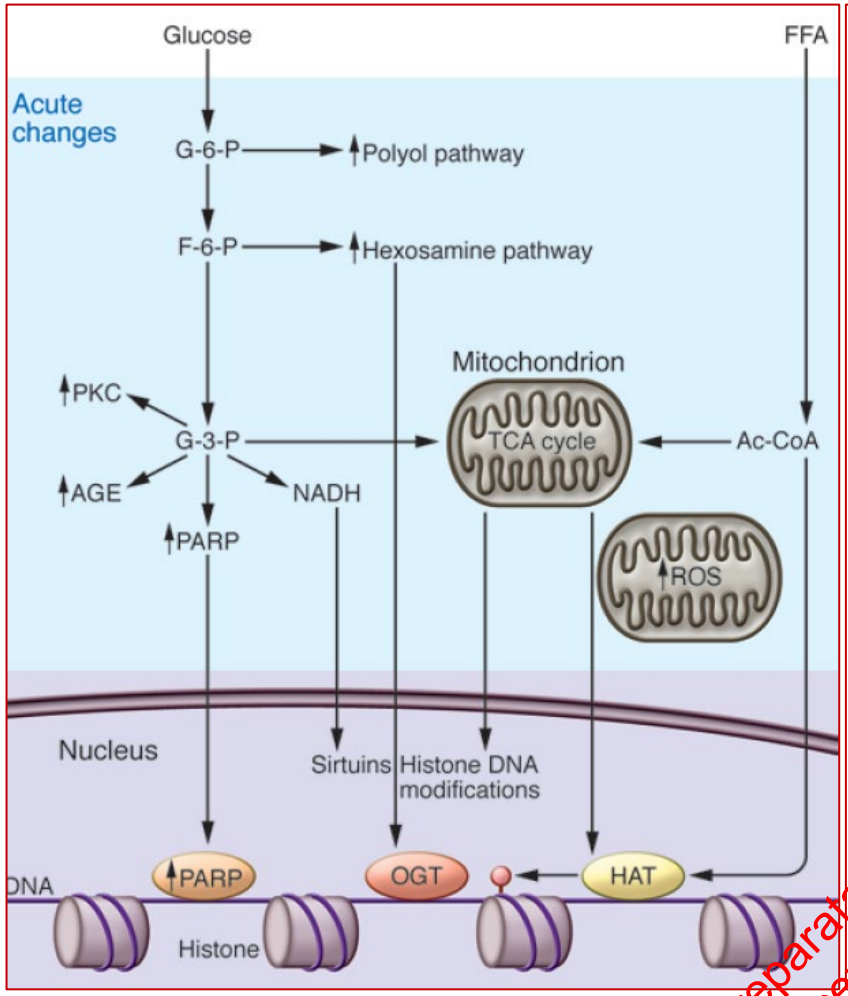
P2X7R-mediated NLRP3 activation in diabetic kidney disease

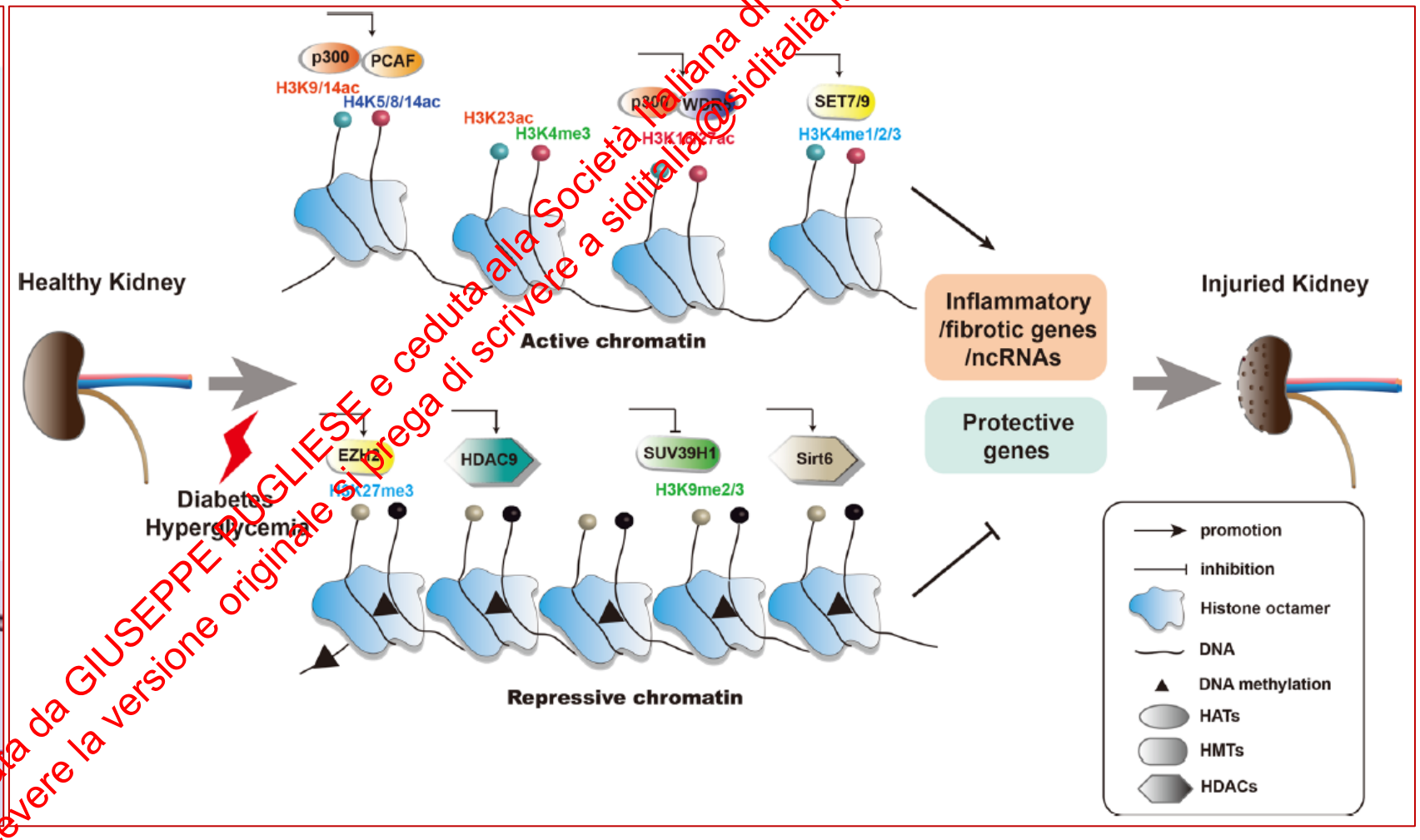
Diabetic mice (WT, KO for P2X7R)



Solini A et al. *J Pathol.* 2013;231:342–353

Role of epigenetic changes in driving renal inflammation and injury

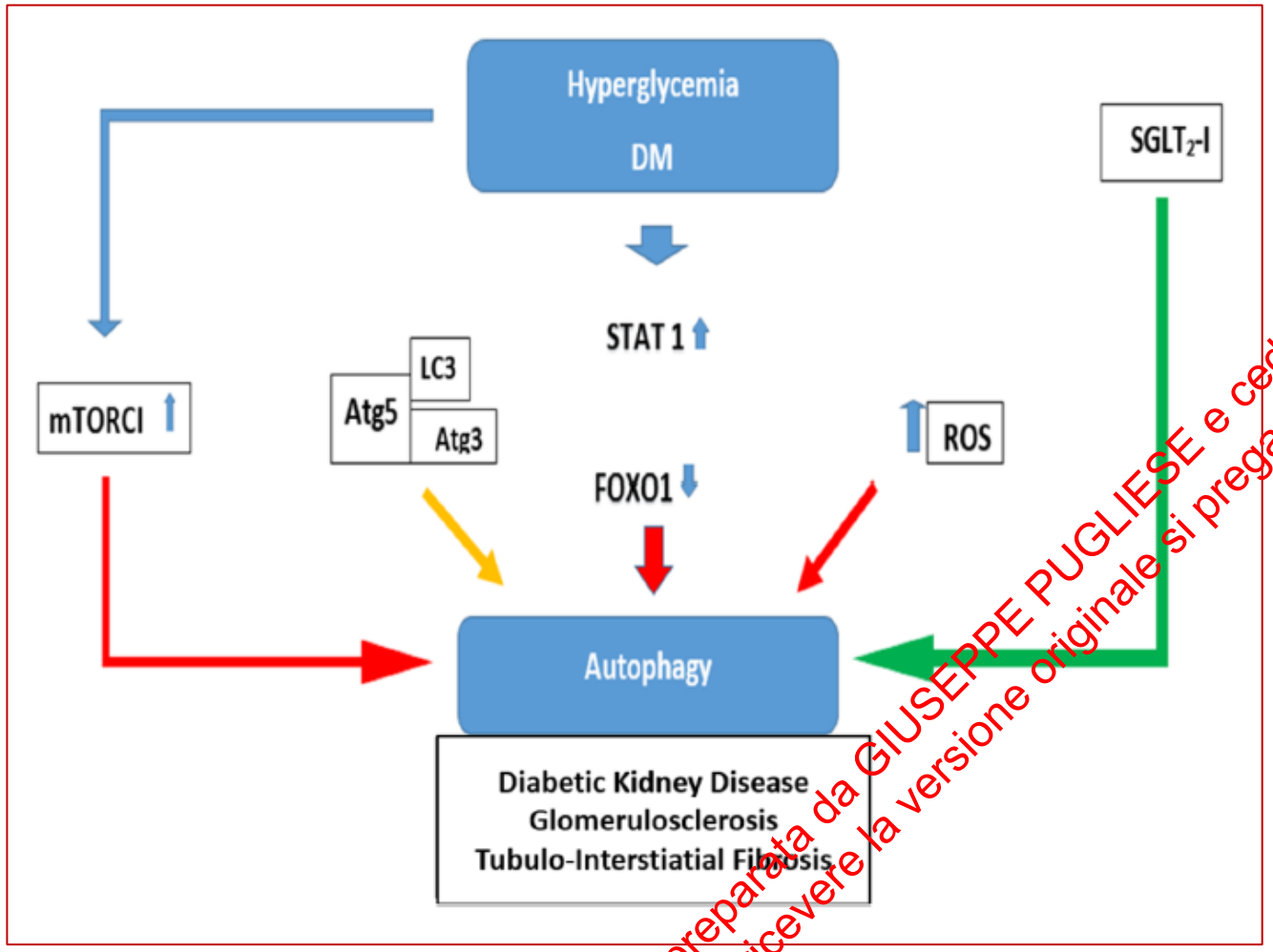


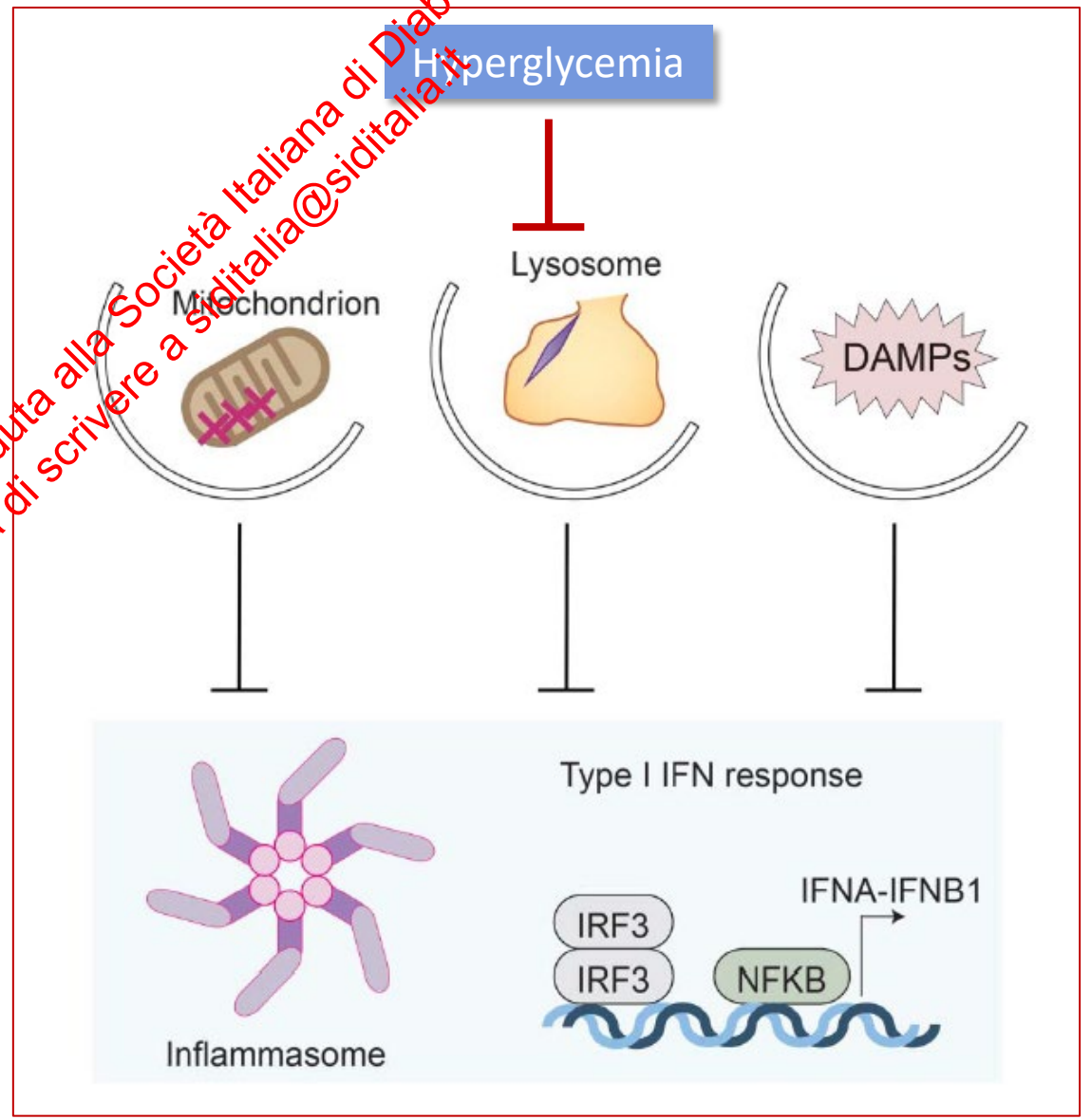


Reidy K et al. *J Clin Invest.* 2014;124:2333–2240

Zheng W et al. *Clin Epigenet.* 2021;13:87

Role of impaired autophagy in driving renal inflammation and injury

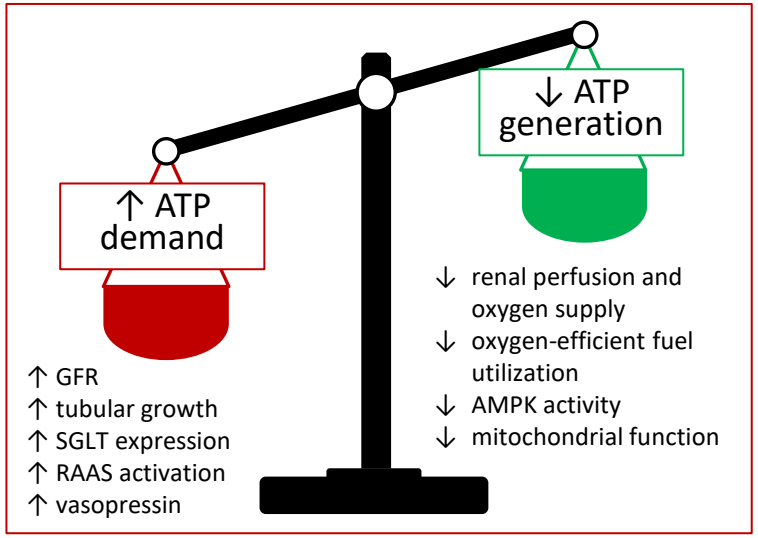


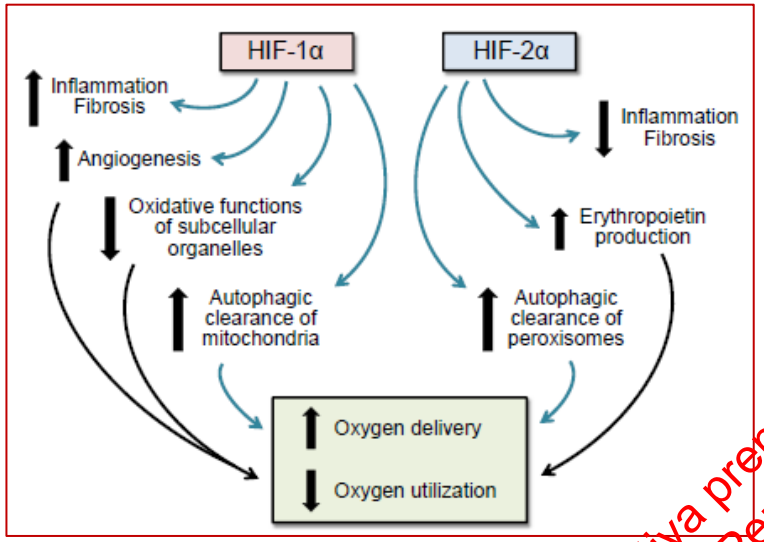


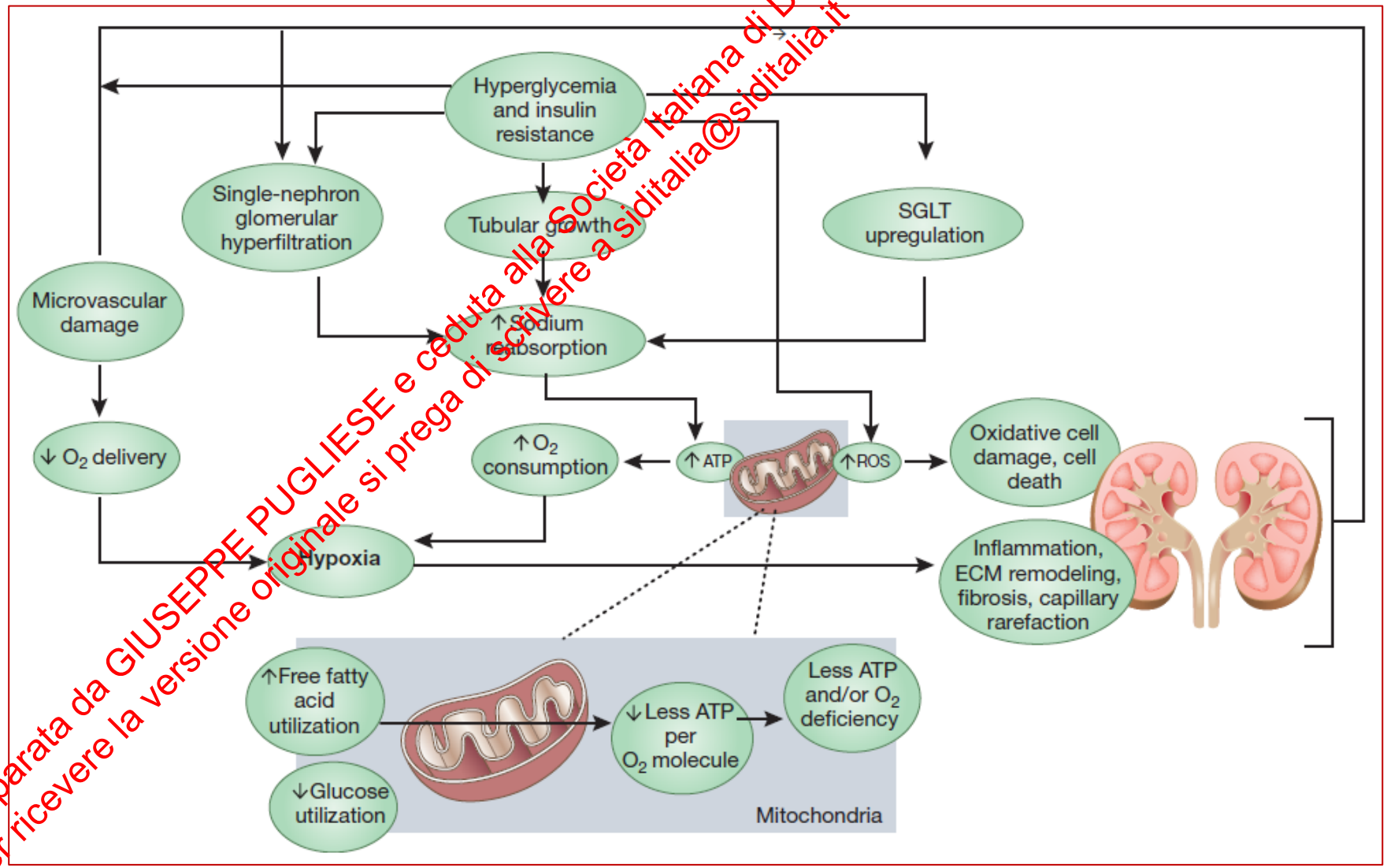
Koch EAT et al. *Int Urol Nephrol.* 2020;52:1705–1712

Kimura T et al. *Autophagy*. 2017;13:6:997–1003

Role of renal hypoxia in driving renal inflammation and injury



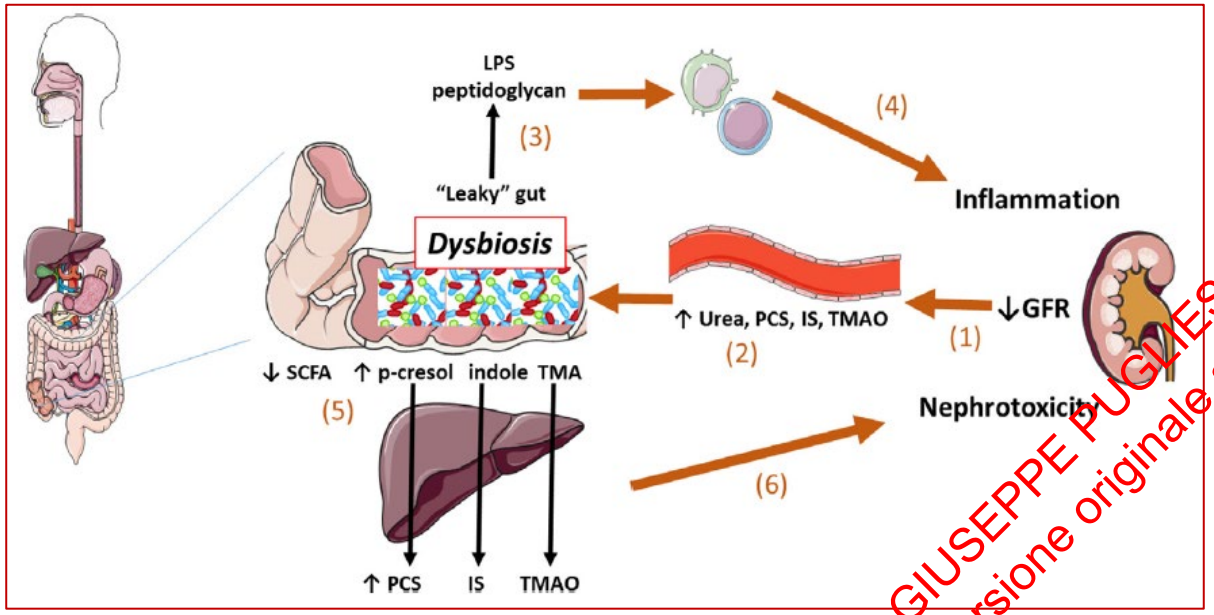


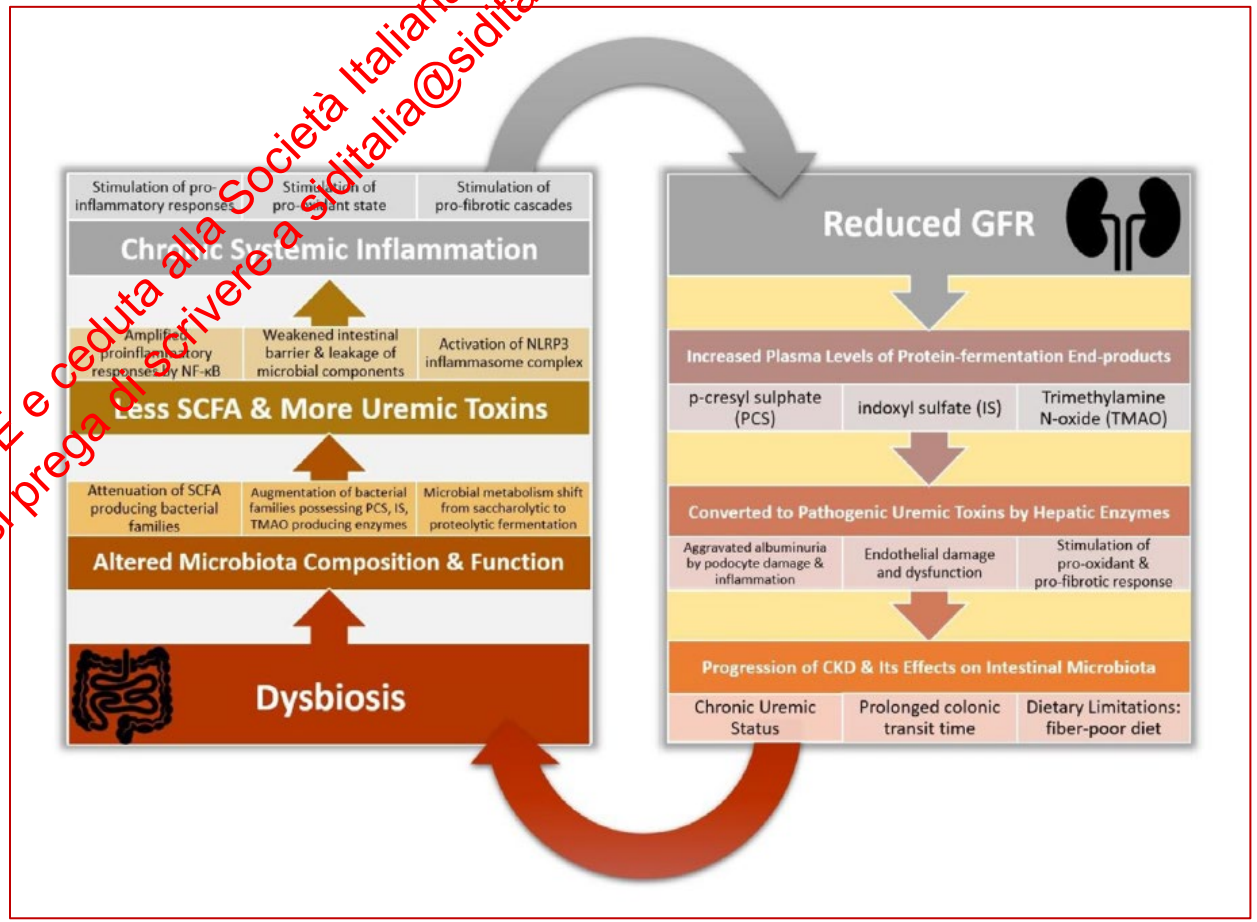


Parker M. *Am J Kidney Dis.* 2021;77:280–286

Hesp HC et al. *Kidney Int.* 2020:98:579–589

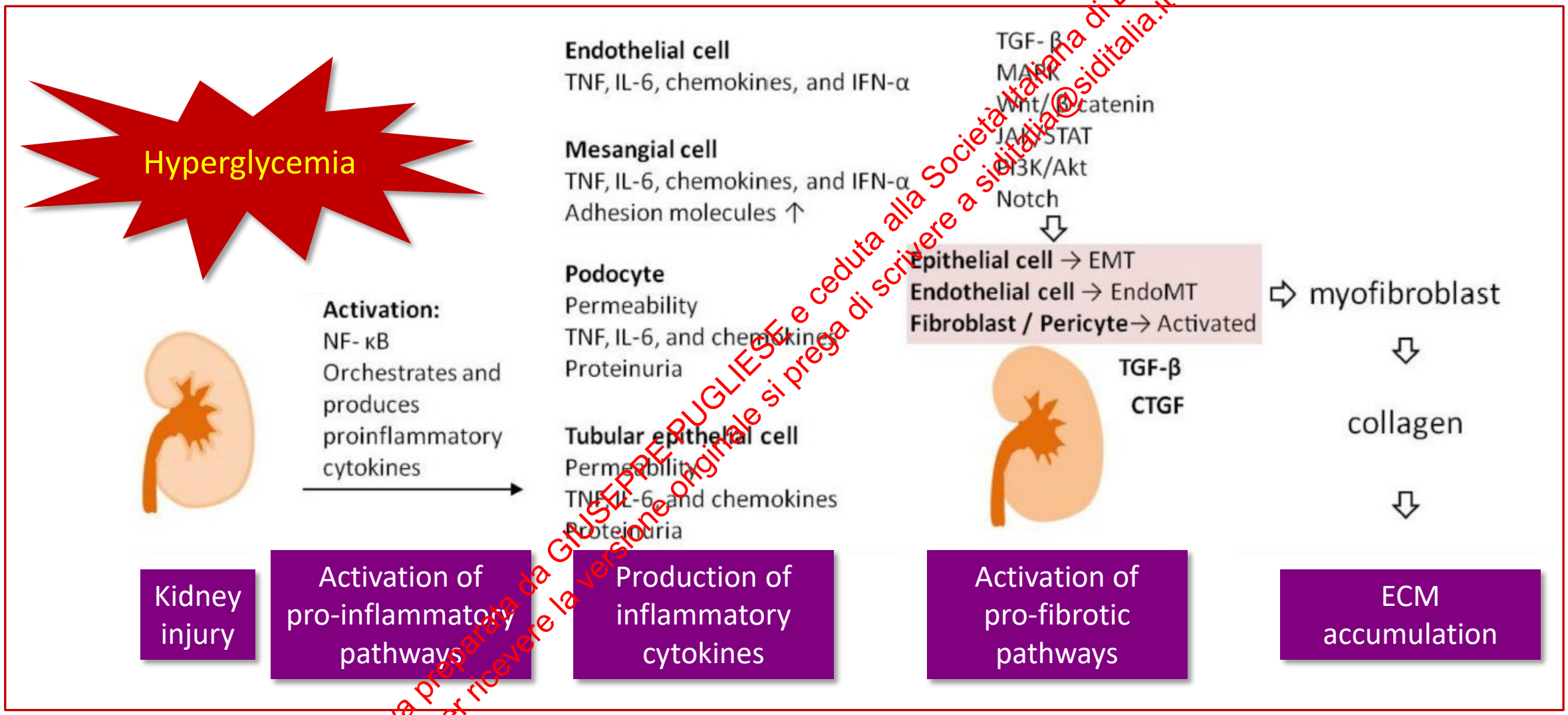
Role of intestinal dysbiosis in driving renal inflammation and injury





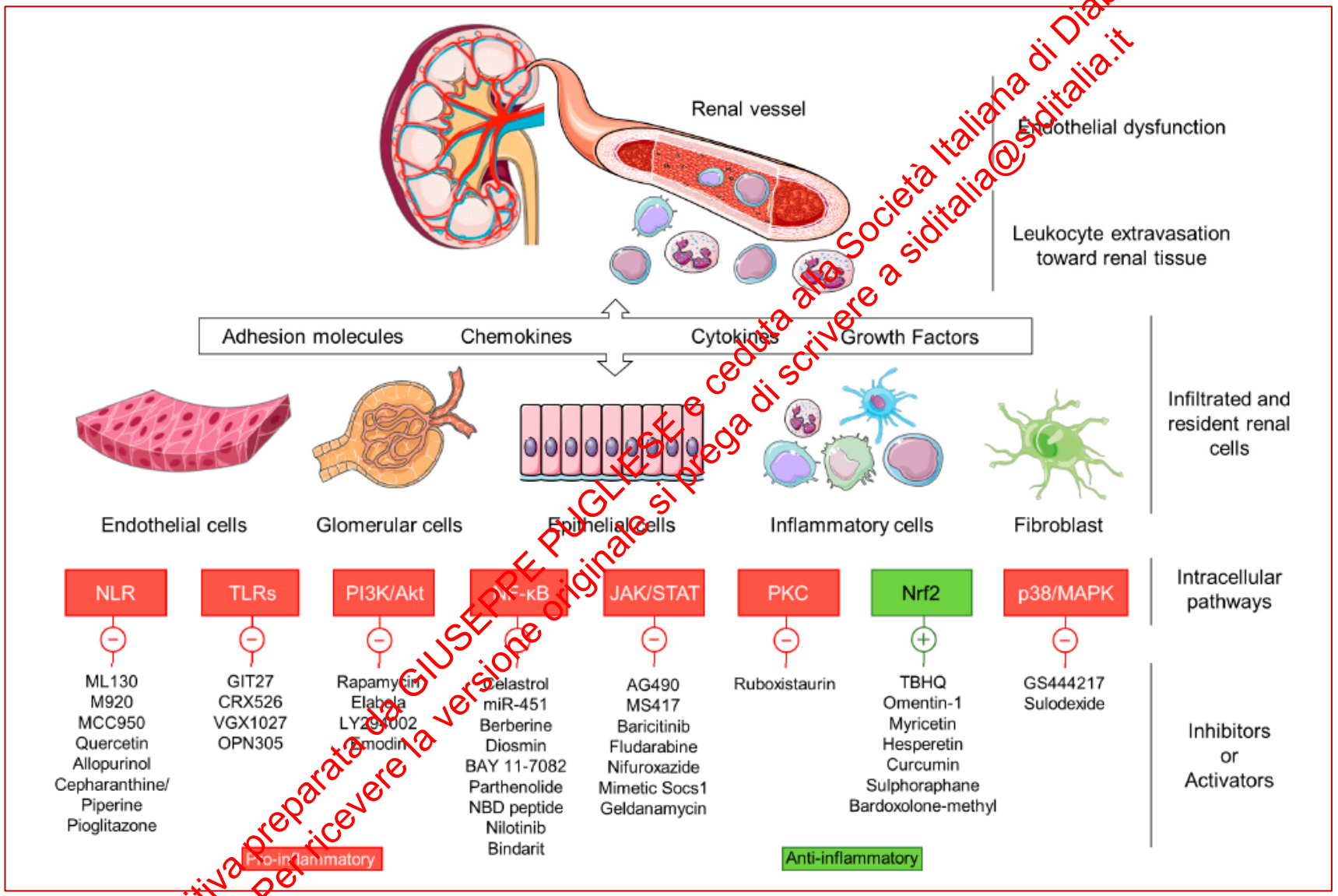
Mosterd CM et al. *Best Pract Res Clin Endocrinol Metab.* 2021;35:101484

Inflammatory mechanisms driving renal fibrosis and injury



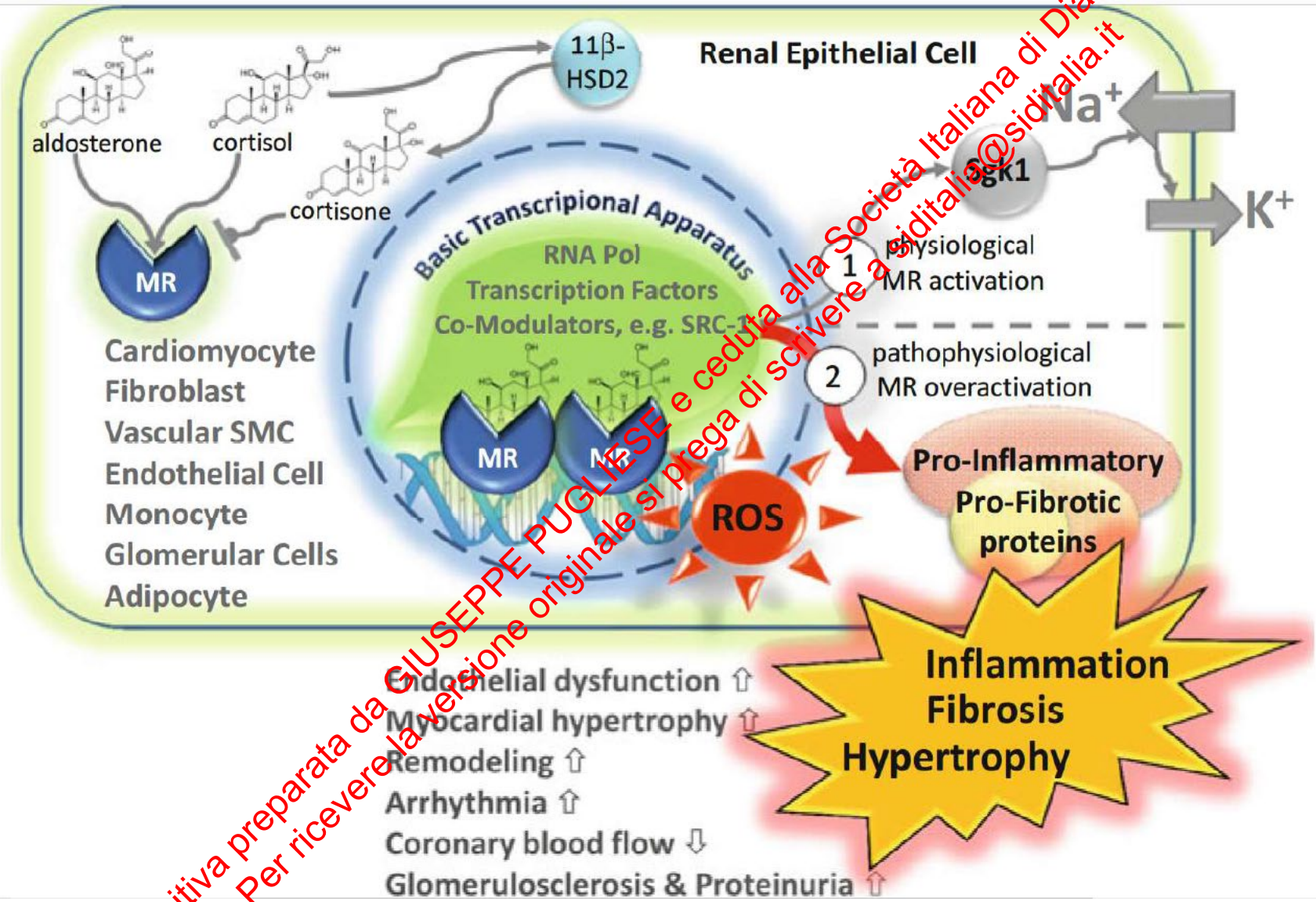
Hung PH et al. *Int J Mol Sci.* 2021;22:11857

Potential anti-inflammatory strategies for diabetic kidney disease



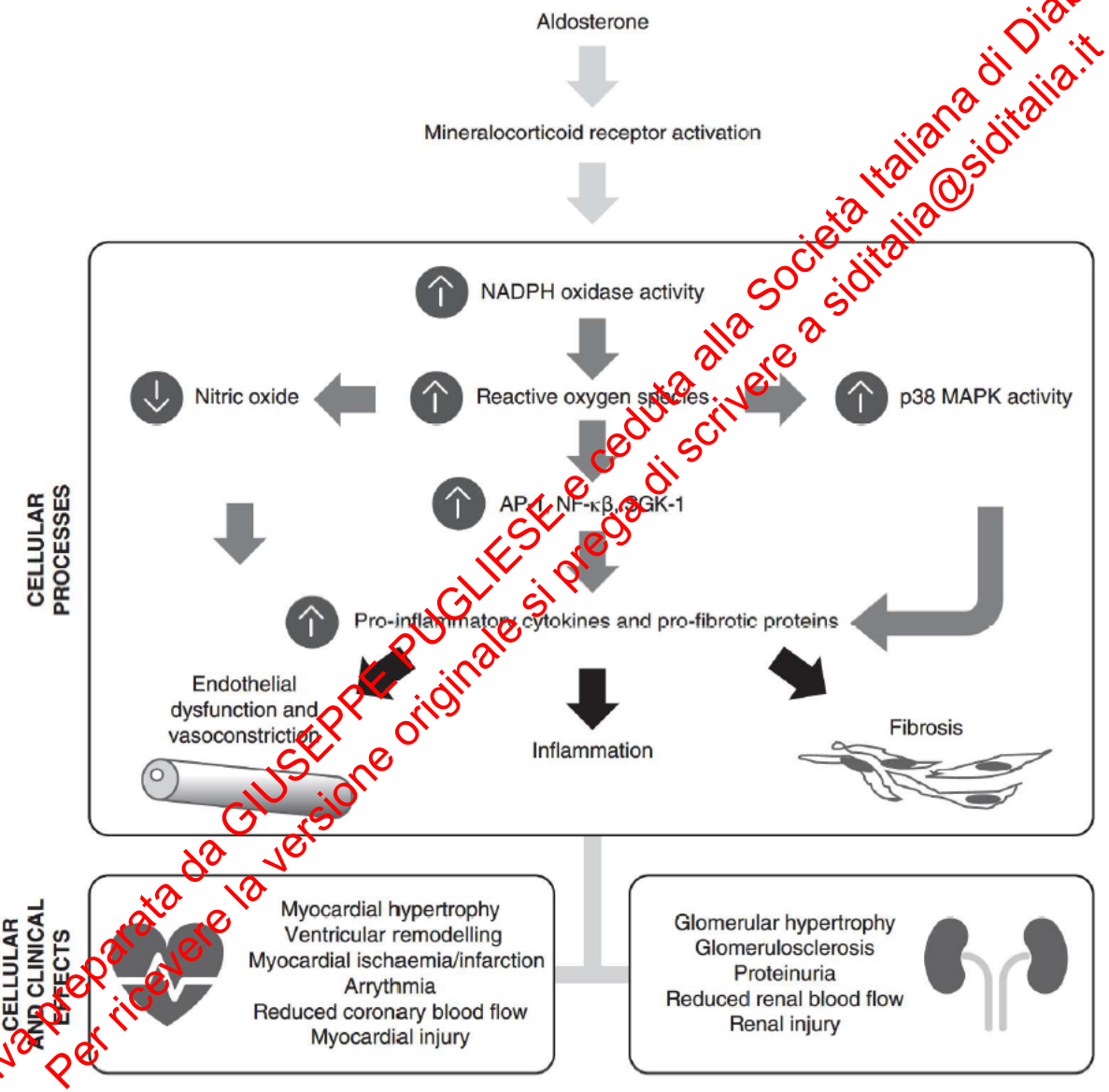
Rayego-Mateos S et al. *Int J Mol Sci.* 2020;31:3798

Mineralocorticoid receptor activation



Kolkhof P et al. *Handbook of Experimental Pharmacology 243.* 2016;271–305

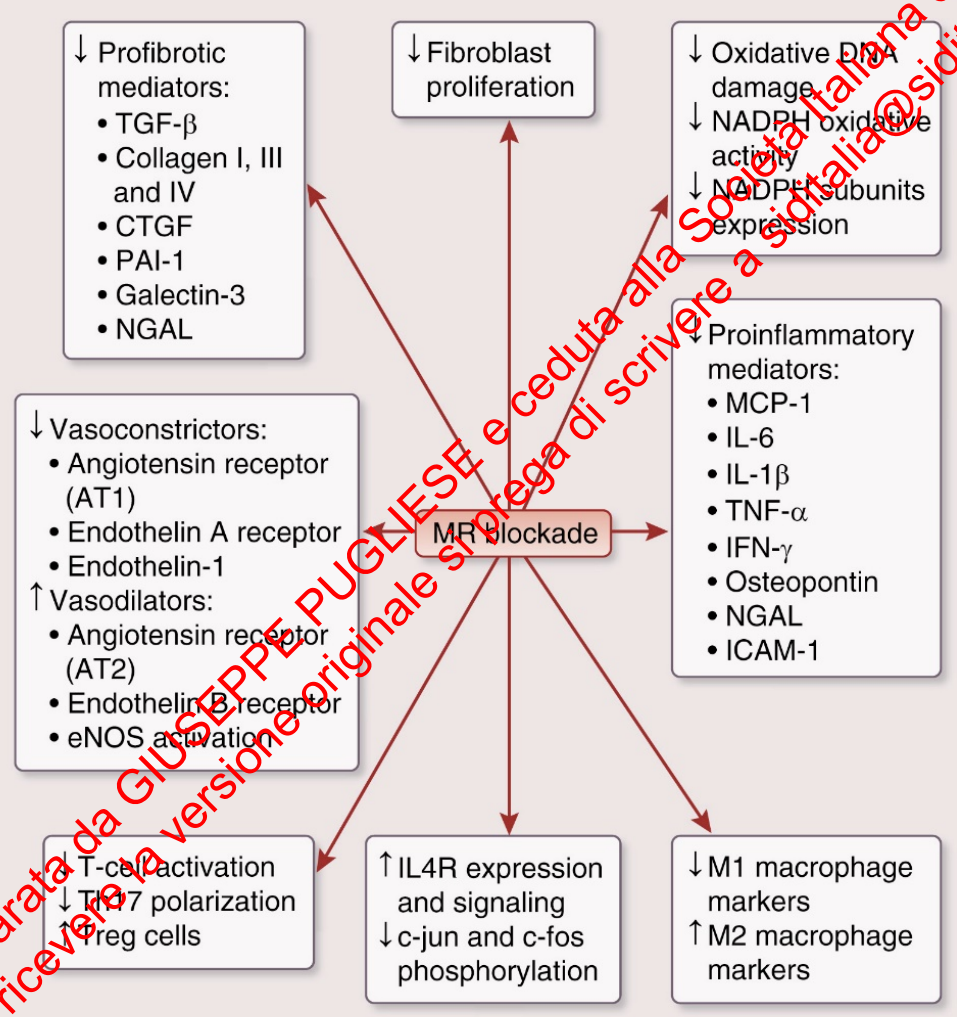
Mineralocorticoid receptor activation



Chaudhuri A et al. *Diabetes Obes Metab.* 2022;24:365–376

Blockade of mineralocorticoid receptor activation

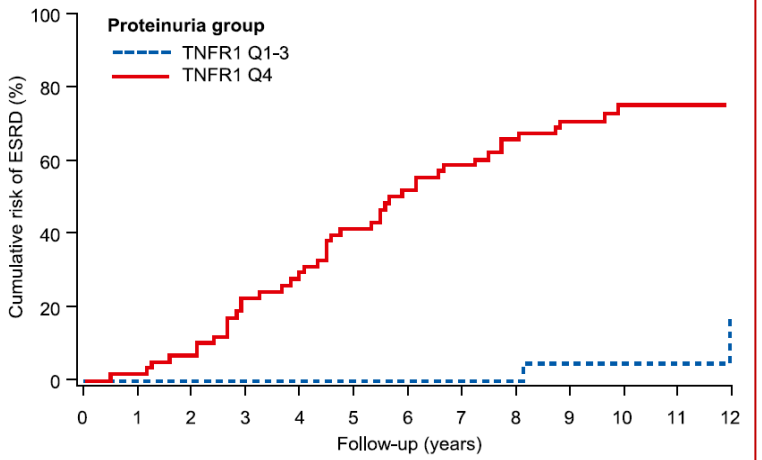
Renal cell types	Tissue effects	Mode of action of MR antagonists	Clinical settings	Clinical effects
Distal tubular cells	↓ Tubular injury		Situations with risk of IRI: • cardiac surgery • kidney transplantation • other?	IRI prevention
	↓ Fibrosis			Prevention of AKI to CKD transition
Endothelial cells SMC	↓ Glomerulosclerosis		Hypertension	Antihypertensive
	↓ Podocyte injury			
Podocytes Mesangial cells Fibroblasts	↓ Inflammation		Diabetes	Antiproteinuric
	↓ Vasoconstriction		Glomerulonephritis	Prevention of CV outcomes
Macrophages T cells	↓ Vascular injury		CKD–fibrosis	Prevention of CKD progression
	↓ Mesangium expansion		Kidney transplantation	Prevention of CNI toxicity



Barrera-Chimal J et al. Kidney Int. 2019;96:302–319

Inflammatory markers as predictors of diabetic kidney disease progression

The Joslin Kidney Studies



	Nonproteinuria		Proteinuria	
	HR[a] (95% CI)	*P* Value	HR[a] (95% CI)	*P* Value
Clinical predictor[b]				
HbA1c	1.56 (0.86, 2.82)	0.14	1.24 (0.96, 1.61)	0.10
AER	2.23 (1.11, 4.48)	0.02	2.52 (1.14, 5.56)	0.02
eGFR	1.10 (0.72, 1.67)	0.67	1.37 (1.11, 1.69)	0.004
Individual marker[c]				
free TNFα	2.22 (1.20, 4.12)	0.01	1.21 (0.81, 1.81)	0.34
total TNFα	2.53 (1.25, 5.13)	0.01	2.61 (1.42, 4.81)	0.002
TNFR1	7.11 (2.13, 23.69)	0.0004	7.05 (2.23, 22.30)	0.0018
TNFR2	3.82 (1.59, 9.20)	0.0008	5.88 (2.10, 16.43)	0.0013

410 patients with type 2 diabetes with and without proteinuria

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)

	10-Year window			3-Year window		
	Events	HR (95% CI)*	HR (95% CI)†	Events	HR (95% CI)*	HR (95% CI)†
CKD						
sTNFR-1	64	**1.29 (1.16–1.45)**	**1.36 (1.23–1.49)**	23	**1.61 (1.43–1.82)**	**1.56 (1.40–1.74)**
sTNFR-2	74	**1.55 (1.38–1.74)**	**1.63 (1.47–1.82)**	25	**1.77 (1.52–2.06)**	**1.97 (1.70–2.29)**
sE-selectin	61	**1.31 (1.14–1.50)**	**1.23 (1.08–1.40)**	23	**1.42 (1.19–1.70)**	**1.38 (1.18–1.61)**
PAI-1 active	74	**1.23 (1.06–1.43)**	1.15 (0.95–1.39)	25	**1.30 (1.03–1.65)**	1.18 (0.87–1.61)
PAI-1 total	74	**1.23 (1.02–1.49)**	1.14 (0.94–1.39)	25	**1.55 (1.23–1.94)**	**1.52 (1.24–1.87)**
sICAM-1	74	1.09 (0.86–1.37)	1.02 (0.79–1.31)	25	0.84 (0.53–1.32)	0.88 (0.56–1.38)
sVCAM-1	63	0.82 (0.60–1.12)	0.88 (0.65–1.17)	23	0.74 (0.42–1.30)	0.76 (0.41–1.40)
IL-6	61	0.85 (0.66–1.09)	0.91 (0.75–1.10)	21	1.11 (0.90–1.37)	1.13 (0.96–1.33)
Fibrinogen	46	**1.96 (1.36–2.83)**	**1.74 (1.24–2.45)**	18	**2.59 (1.50–4.47)**	**2.13 (1.29–3.51)**
CRP	64	0.93 (0.76–1.13)	0.88 (0.67–1.15)	23	1.06 (0.77–1.47)	0.99 (0.63–1.56)
Composite scores‡						
Acute-phase reagents	46	**1.34 (1.05–1.72)**	1.25 (0.99–1.57)	18	**1.51 (1.09–2.10)**	**1.56 (1.19–2.04)**
Cytokines/adipokines	61	**1.53 (1.27–1.85)**	**1.70 (1.34–2.15)**	21	**3.58 (2.45–5.23)**	**3.25 (2.20–4.81)**
Thrombosis	46	**1.92 (1.37–2.70)**	**1.77 (1.20–2.61)**	18	**2.91 (1.86–4.54)**	**2.45 (1.50–4.01)**
Endothelial dysfunction	60	1.82 (0.78–4.24)	**1.59 (1.06–2.38)**	23	**2.28 (1.21–4.28)**	**2.16 (1.27–3.68)**

1,346 (DCCT) and 816 (EDIC) patients with type 1 diabetes

Baker NL et al. *Diabetes Care.* 2018;41:128–135

Inflammatory markers as predictors of diabetic kidney disease progression

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)

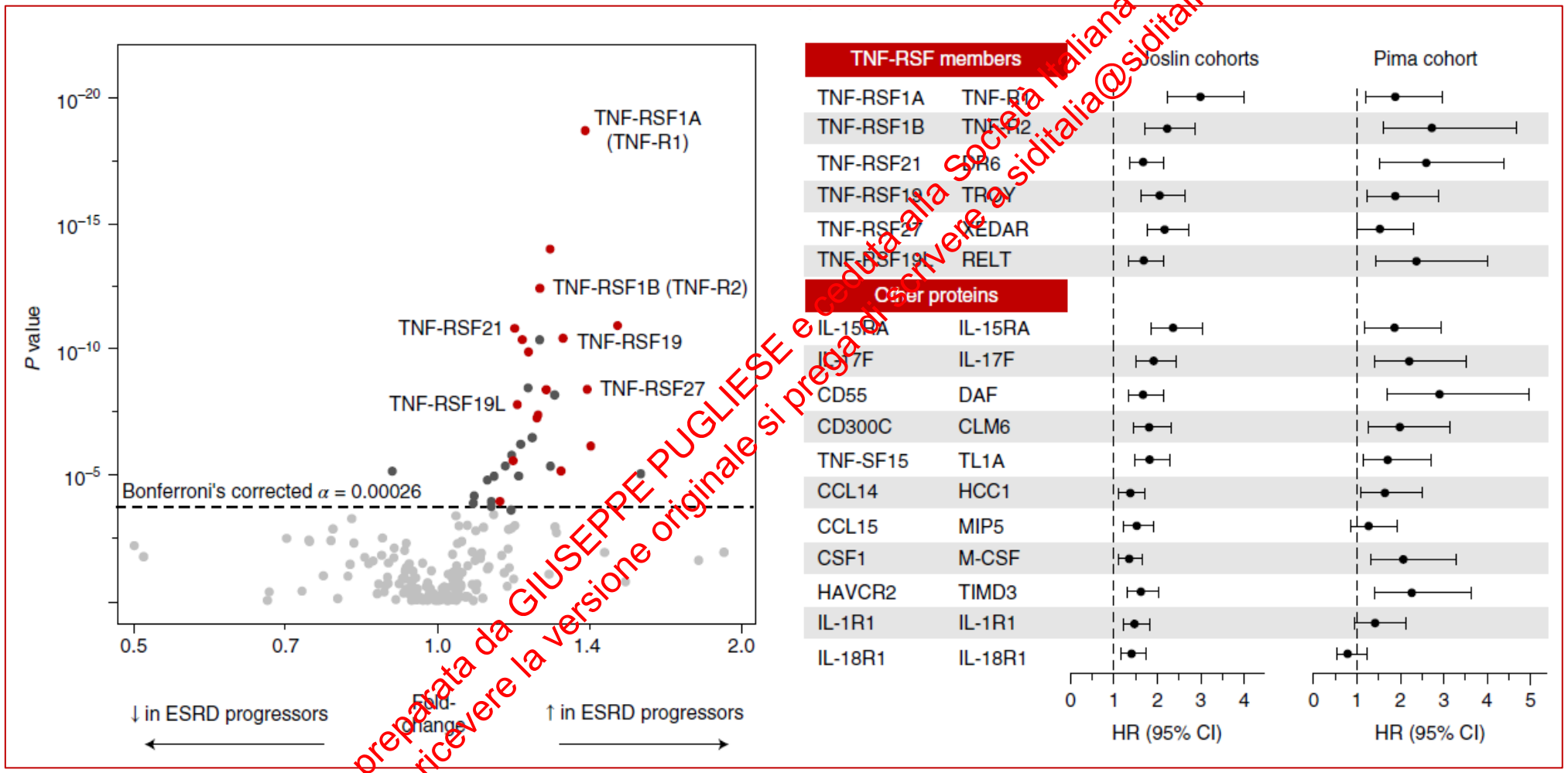
	10-Year window			3-Year window		
	Events	HR (95% CI)*	HR (95% CI)†	Events	HR (95% CI)*	HR (95% CI)†
MA						
sTNFR-1	116	1.09 (0.97–1.23)	1.08 (0.97–1.20)	39	1.19 (1.02–1.38)	1.10 (0.83–1.44)
sTNFR-2	143	**1.31 (1.18–1.46)**	**1.25 (1.10–1.42)**	44	**1.32 (1.15–1.52)**	1.19 (0.97–1.46)
sE-selectin	117	**1.20 (1.07–1.35)**	**1.17 (1.04–1.33)**	40	1.10 (0.92–1.33)	0.96 (0.70–1.32)
PAI-1 active	141	**1.22 (1.07–1.38)**	1.10 (0.96–1.27)	43	1.13 (0.90–1.42)	0.97 (0.70–1.34)
PAI-1 total	143	**1.22 (1.06–1.41)**	**1.17 (1.00–1.36)**	44	1.27 (0.99–1.63)	1.22 (0.93–1.61)
sICAM-1	143	1.16 (0.97–1.40)	1.19 (0.99–1.42)	44	1.02 (0.71–1.46)	1.07 (0.78–1.47)
sVCAM-1	100	0.85 (0.67–1.09)	0.93 (0.76–1.15)	36	1.03 (0.70–1.53)	1.11 (0.85–1.45)
IL-6	113	0.96 (0.84–1.08)	1.02 (0.93–1.13)	38	0.97 (0.72–1.30)	1.05 (0.84–1.32)
Fibrinogen	70	1.01 (0.80–1.27)	1.01 (0.79–1.30)	26	0.72 (0.46–1.12)	0.62 (0.38–1.03)
CRP	115	0.95 (0.79–1.14)	0.95 (0.77–1.18)	38	0.88 (0.63–1.23)	0.83 (0.48–1.43)
Composite scores‡						
Acute-phase reagents	70	0.84 (0.63–1.11)	0.86 (0.60–1.24)	26	0.57 (0.31–1.05)	**0.41 (0.18–0.92)**
Cytokines/adipokines	113	**1.26 (1.06–1.50)**	**1.30 (1.04–1.63)**	38	1.47 (0.99–2.16)	1.28 (0.75–2.20)
Thrombosis	70	**1.53 (1.12–2.08)**	1.26 (0.89–1.78)	26	0.96 (0.57–1.62)	0.87 (0.41–1.86)
Endothelial dysfunction	99	**1.61 (1.19–2.19)**	**1.47 (1.06–2.04)**	36	1.08 (0.60–1.95)	0.83 (0.48–1.45)

1,346 (DCCT) and 816 (EDIC) patients with type 1 diabetes

Baker NL et al. *Diabetes Care*. 2018;41:128–135

Inflammatory markers as predictors of diabetic kidney disease progression

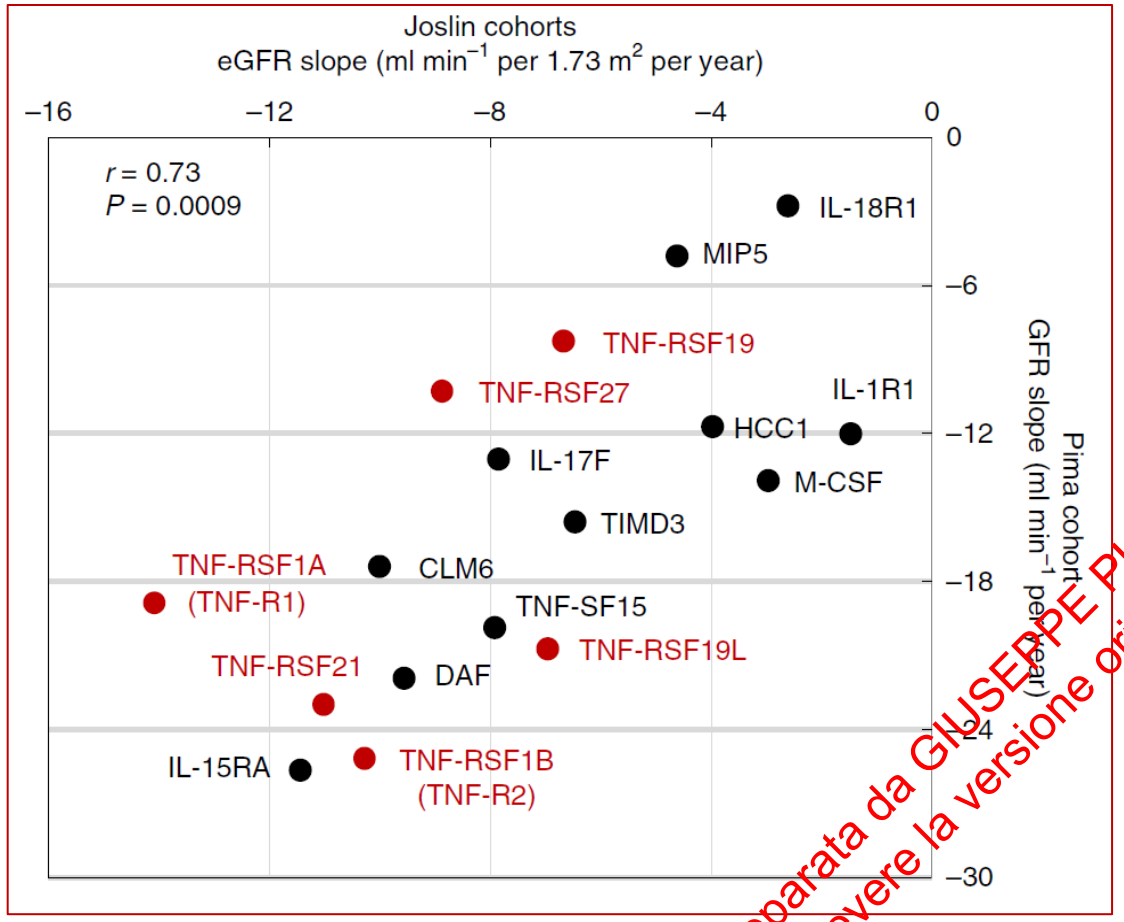
The Joslin Kidney Studies and the Pima Indian Study

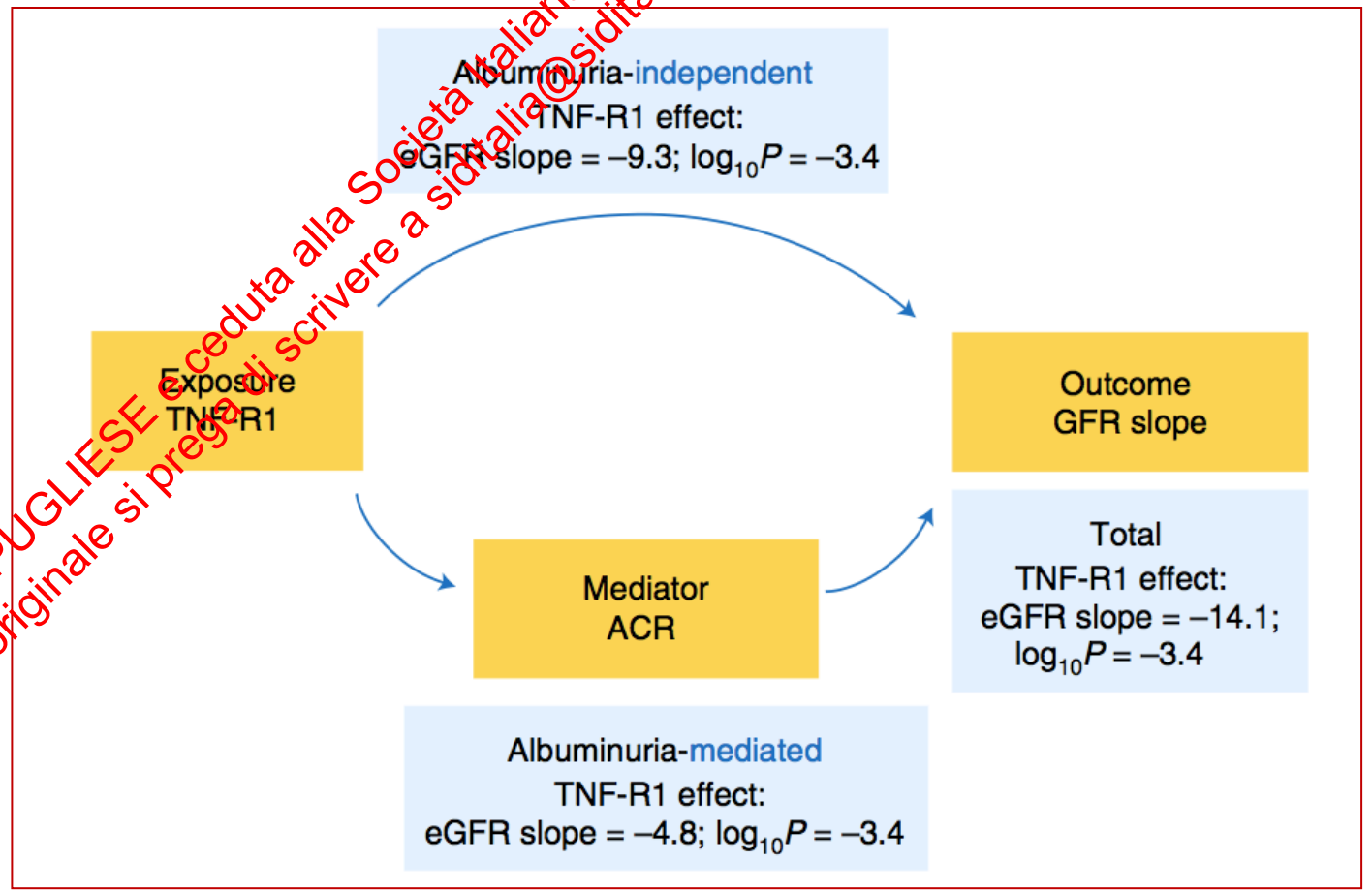


Discovery cohort of 219 and validation cohort of 144 patients with type 1 and 2 diabetes

Inflammatory markers as predictors of diabetic kidney disease progression

The Joslin Kidney Studies and the Pima Indian Study





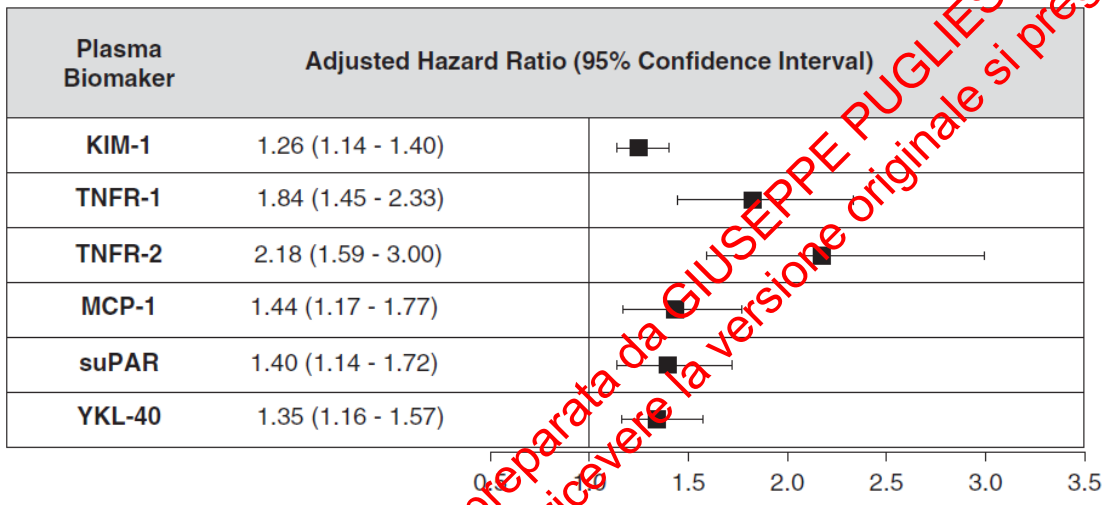
Discovery cohort of 219 and validation cohort of 144 patients with type 1 and 2 diabetes

Inflammatory markers as predictors of diabetic kidney disease progression

The Chronic Renal Insufficiency Cohort (CRIC) Study

Biomarker	MCP-1	TNFR-1	TNFR-2	suPAR	YKL-40	eGFR	UPCR
KIM-1	0.20[a]	0.48[a]	0.47[a]	0.38[a]	0.31[a]	−0.34[a]	0.61[a]
MCP-1		0.30[a]	0.32[a]	0.28[a]	0.19[a]	−0.22[a]	0.07[b]
TNFR-1			0.82[a]	0.74[a]	0.49[a]	−0.73[a]	0.44[a]
TNFR-2				0.71[a]	0.53[a]	−0.64[a]	0.39[a]
suPAR					0.47[a]	−0.64[a]	0.29[a]
YKL-40						−0.30[a]	0.27[a]

Age- and sex-adjusted Pearson partial correlations of baseline biomarkers, eGFR, and proteinuria; [a] $p<0.01$; [b] $p<0.05$



HR (95% CI) of DKD progression as a function of each biomarker. Adjusted for age, sex, race/ethnicity, education, clinical center, systolic and diastolic BP, BMI, hsCRP, HbA_{1c}, anti-hypertensive therapy, smoking status, baseline eGFR, and UPCR.

596 patients with type 2 diabetes and an an eGFR <60ml/min per 1.73m^2

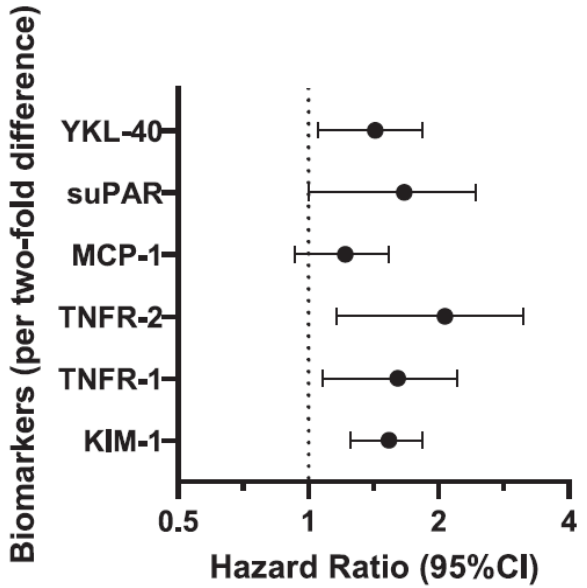
Schrauben SJ et al. *J Am Soc Nephrol.* 2021:32:115–126

Inflammatory markers as predictors of diabetic kidney disease progression

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

Marker	KIM-1	TNFR1	TNFR2	MCP-1	suPAR	YKL-40	BMP-7	UACR	eGFR
KIM-1	1.0	0.39[a]	0.41[a]	0.15[a]	0.37[a]	0.33[a]	0.23[a]	0.56[a]	−0.32[a]
TNFR1	–	1.0	0.83[a]	0.14[a]	0.79[a]	0.40[a]	0.18[a]	0.52[a]	−0.65[a]
TNFR2	–	–	1.0	0.15[a]	0.76[a]	0.39[a]	0.08	0.52[a]	−0.60[a]
MCP-1	–	–	–	1.0	0.17[a]	−0.01	−0.01	0.14[a]	−0.08
suPAR	–	–	–	–	1.0	0.37[a]	0.23[a]	0.45[a]	−0.60[a]
YKL-40	–	–	–	–	–	1.0	0.20[a]	0.26[a]	−0.23[a]
BMP-7	–	–	–	–	–	–	1.0	0.15[a]	−0.09[a]
UACR	–	–	–	–	–	–	–	1.0	−0.43[a]
eGFR	–	–	–	–	–	–	–	–	1.0

Age- and sex-adjusted Pearson partial correlations of baseline biomarkers, UACR, and eGFR; [a] $p<0.01$



HR (95% CI) of incident kidney failure with replacement therapy (KFRT) as a function of each biomarker. Adjusted for age, race, sex, education, BMI, systolic BP, antihypertensive therapy, smoking status, CHD, stroke, UACR, and eGFR.

	2-Year Risk of KFRT (22 Events)		5-Year Risk of KFRT (69 Events)	
Model	C Statistic	*P*[a]	C Statistic	*P*[a]
KFRE (4 variables)	0.832	Base model	0.859	Base model
KFRE + KIM-1	0.852	0.48	0.853	0.76
KFRE + TNFR1	0.844	0.46	0.836	0.22
KFRE + KIM1 + TNFR1	0.861	0.28	0.868	0.61

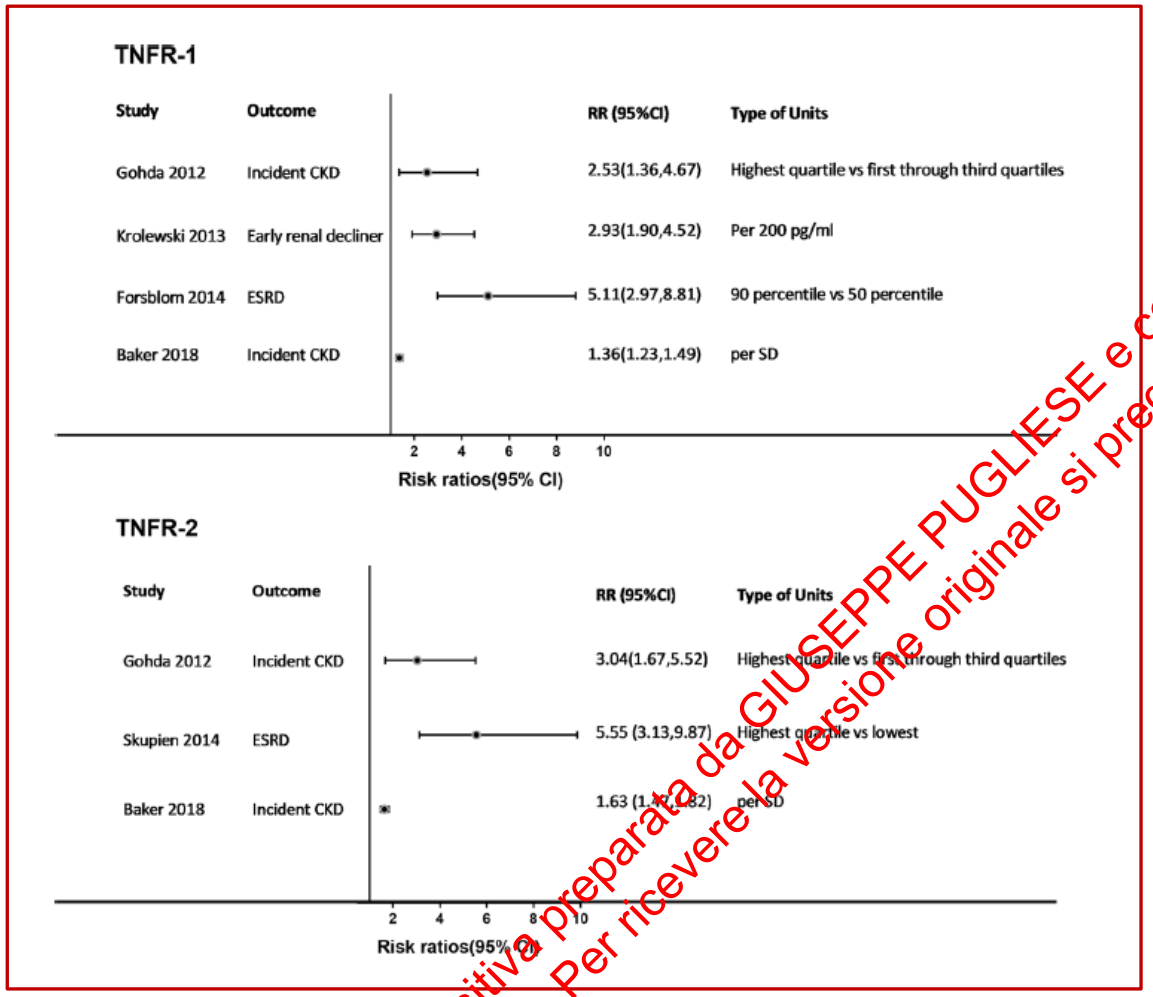
C statistic change for predicting KFRT with Kidney Failure Risk Equation (KFRE) Score KIM-1 and/or TNFR1

594 participants (mean age, 70 years; 53% women) who had diabetes and an eGFR <60 mL/min/1.73 m^2 at baseline

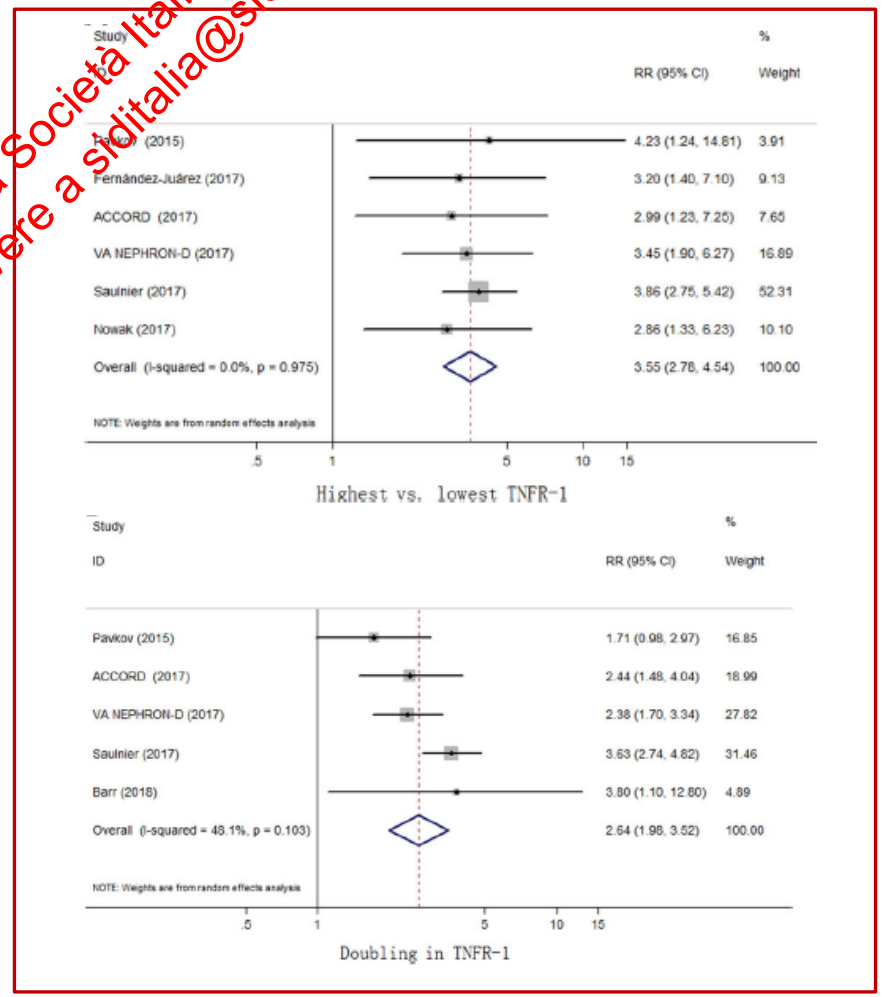
Inflammatory markers as predictors of diabetic kidney disease progression

Meta-analysis of 19 studies (5 T1D and 14 T2D)

Type 1 diabetes



Type 2 diabetes



Cheng D et al. *Endocrine.* 2020;68:32–43

Conclusions

- Intensive glycemic control reduces progression of diabetic kidney disease, acting on albuminuria more than on eGFR decline
- RAS blockers and SGLT-2 inhibitors confer renal protection beyond their anti-hypertensive and anti-hyperglycemic effects, but significant residual risk remains
- New renoprotective drugs acting on metabolic and hemodynamic mechanisms are needed to further reduce residual risk
- Pro-inflammatory and pro-fibrotic pathways are triggered by metabolic and hemodynamic mechanisms and represent another suitable target for new renoprotective drugs
- Mineralocorticoid receptor activation results in the activation of pro-inflammatory and pro-fibrotic pathways and its blockade may represent a promising therapeutic strategy
- Multiple inflammatory markers are being investigated as predictors of diabetic kidney disease progression in addition to albuminuria and eGFR