Il dr. ROBERTO TREVISAN dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- NOVO
- SANOFY
- LILLY
- NOVARTIS
- ASTRA ZENECA
- MEDTRONIC
- MERCK
- TAKEDA
- SERVIER
- JANSEN

IPERFILTRAZIONE E PROGRESSIONE DEL DANNO RENALE NEL DIABETE

Roberto Trevisan

USC Malattie Endocrine – Diabetologia

ASST Papa Giovanni XXIII - Bergamo

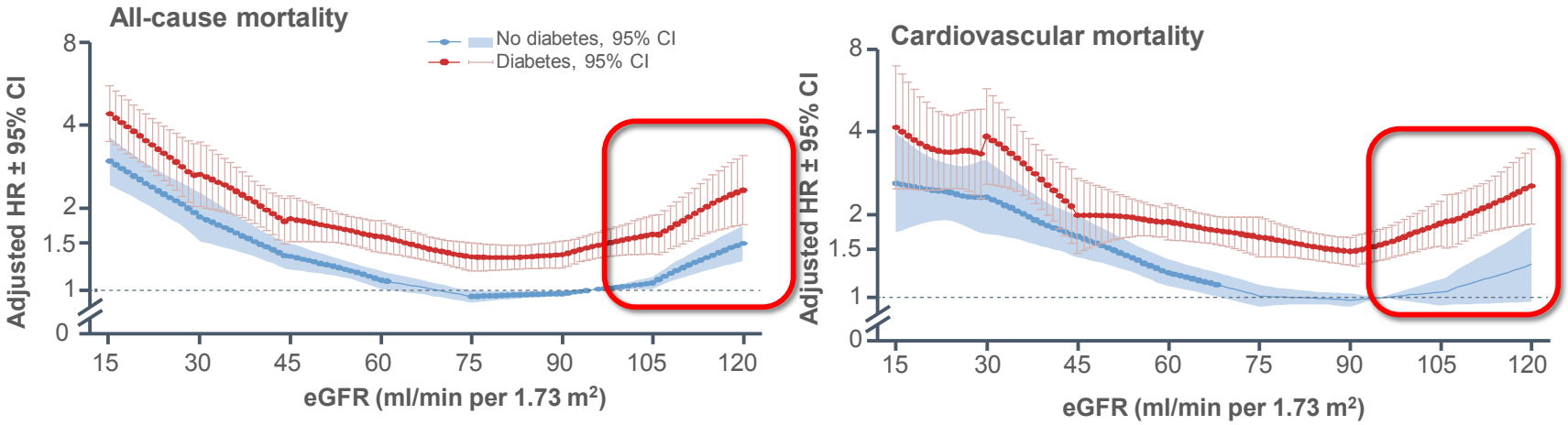
Hyperfiltration: What is it?[1–4]

- Elevated glomerular filtration rate (GFR)
  - Defined as being present when whole-kidney GFR exceeds
    125–140 mL/min/1.73m^2
- Hyperfiltration is an early compensatory mechanism to cope with metabolic stress

1. Jerums G, *et al*. *Diabetologia* 2010;53:2093–2104.
2. Dahlquist G, *et al*. *Nephrol Dial Transplant* 2001;16:1382–6.
3. Amin R, *et al*. *Kidney Int* 2005;68:1740–9.
4. Chaiken RL, *et al*. *Diabetes Care* 1998;21:2129–34.

eGFR and mortality in diabetes

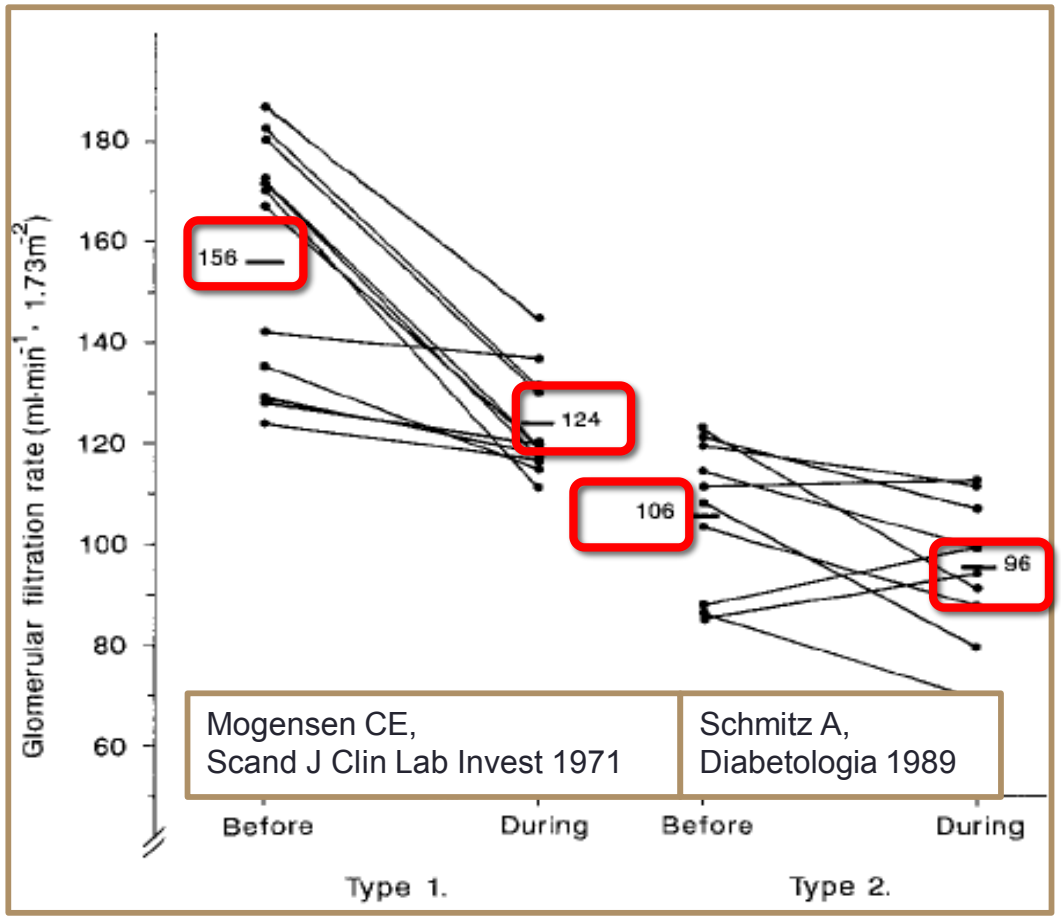
data for 1 024 977 participants (128 505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts.



HRs adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index and albuminuria

Includes data from participants with type 1 and type 2 diabetes

GFR in newly diagnosed Type 1 and Type 2 diabetic patients before and during treatment

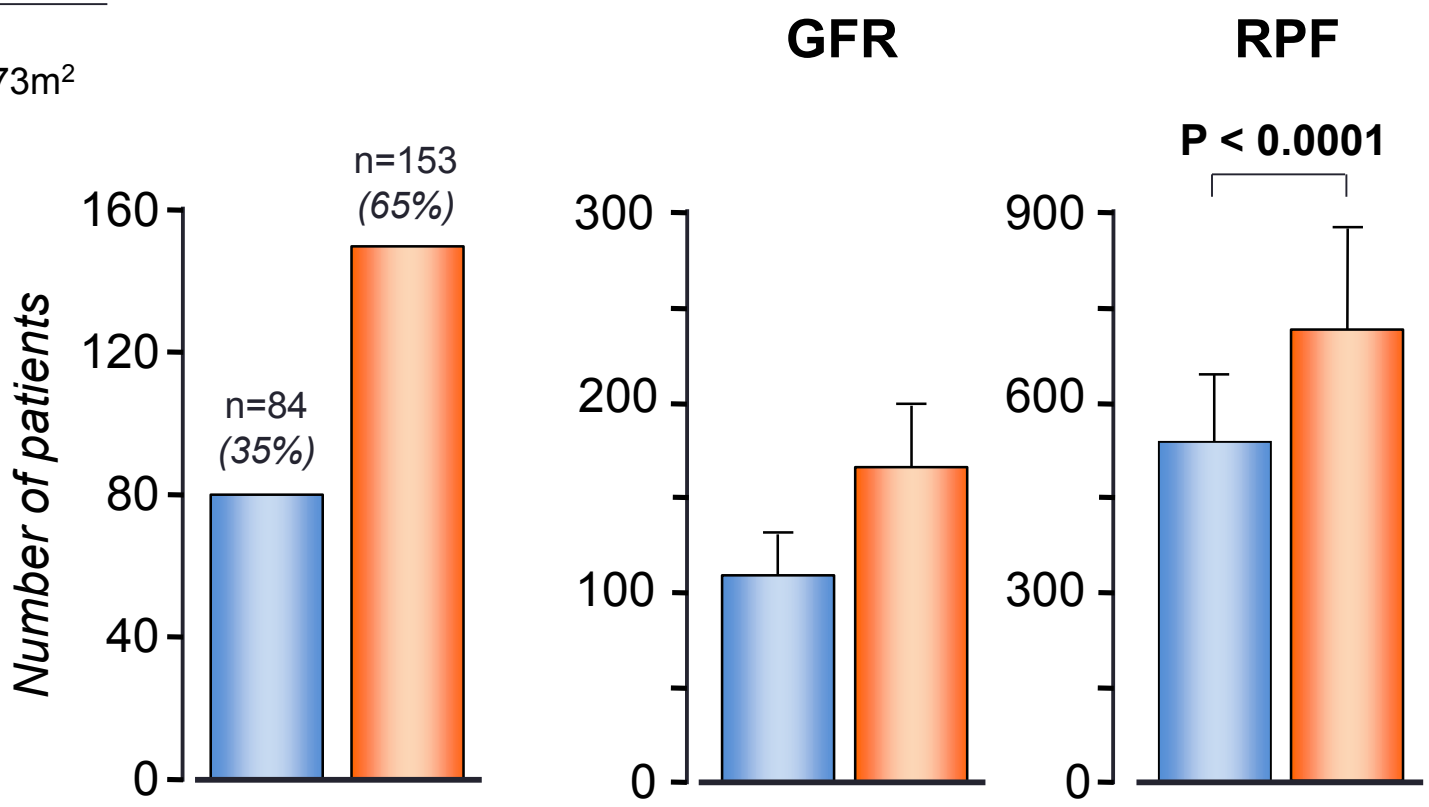


Shmitz A, *Diabetologia* 1993

BASELINE CHARACTERISTICS OF 237 TYPE 1 DIABETES SUBJECTS INCLUDED IN THE INTERNATIONAL DIABETIC NEPHROPATHY STUDY

Selection criteria

UAE ≤ 100 μg/min
eGFR>90 ml/min/1.73m^2
Normal BP



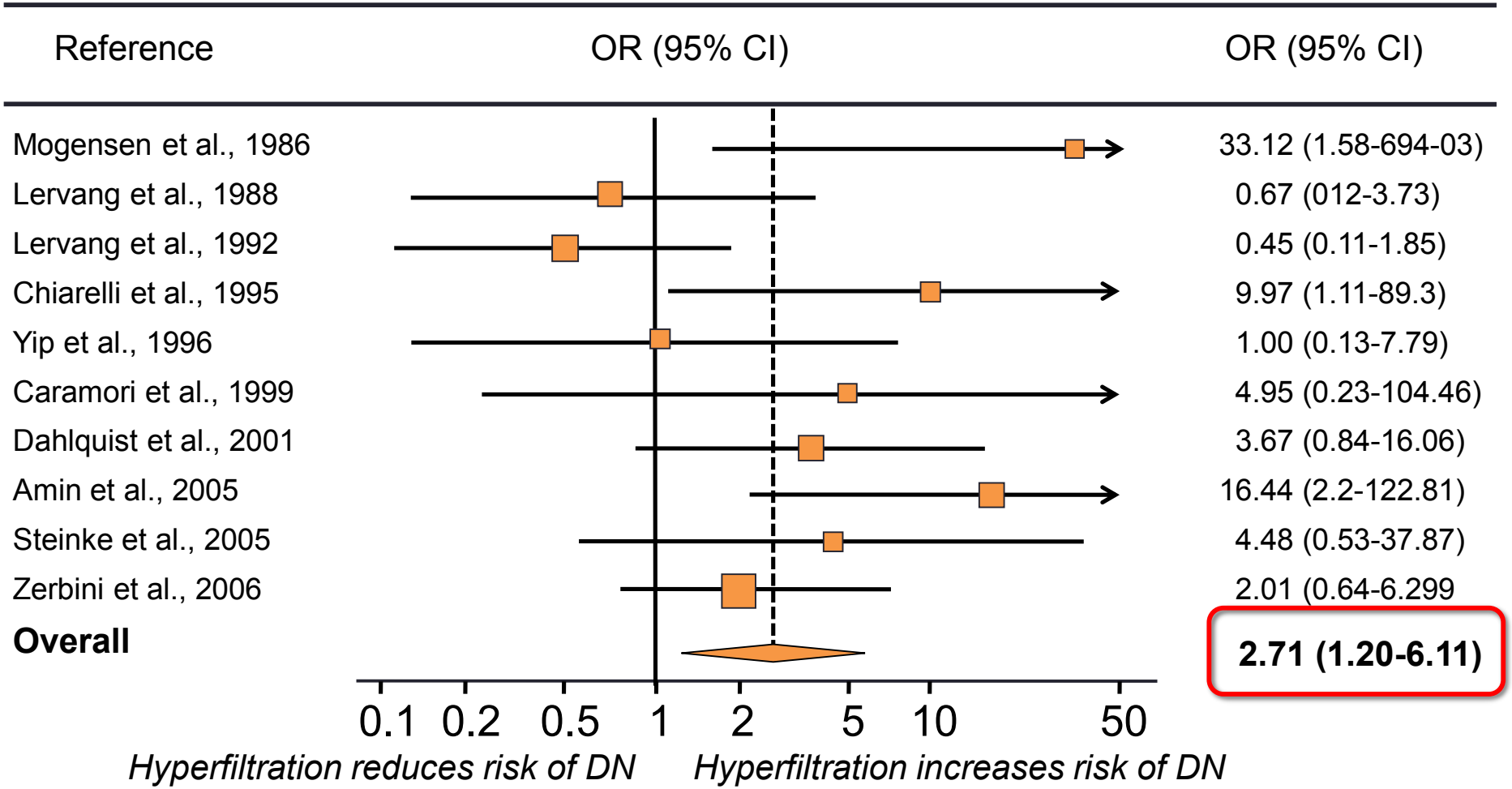
GFR ≤ 130 ml/min/1.73m^2

GFR > 130 ml/min/1.73m^2

Similar HbA1C and FF between groups

IS HYPERFILTRATION ASSOCIATED WITH THE FUTURE RISK OF DEVELOPING DIABETIC NEPHROPATHY?

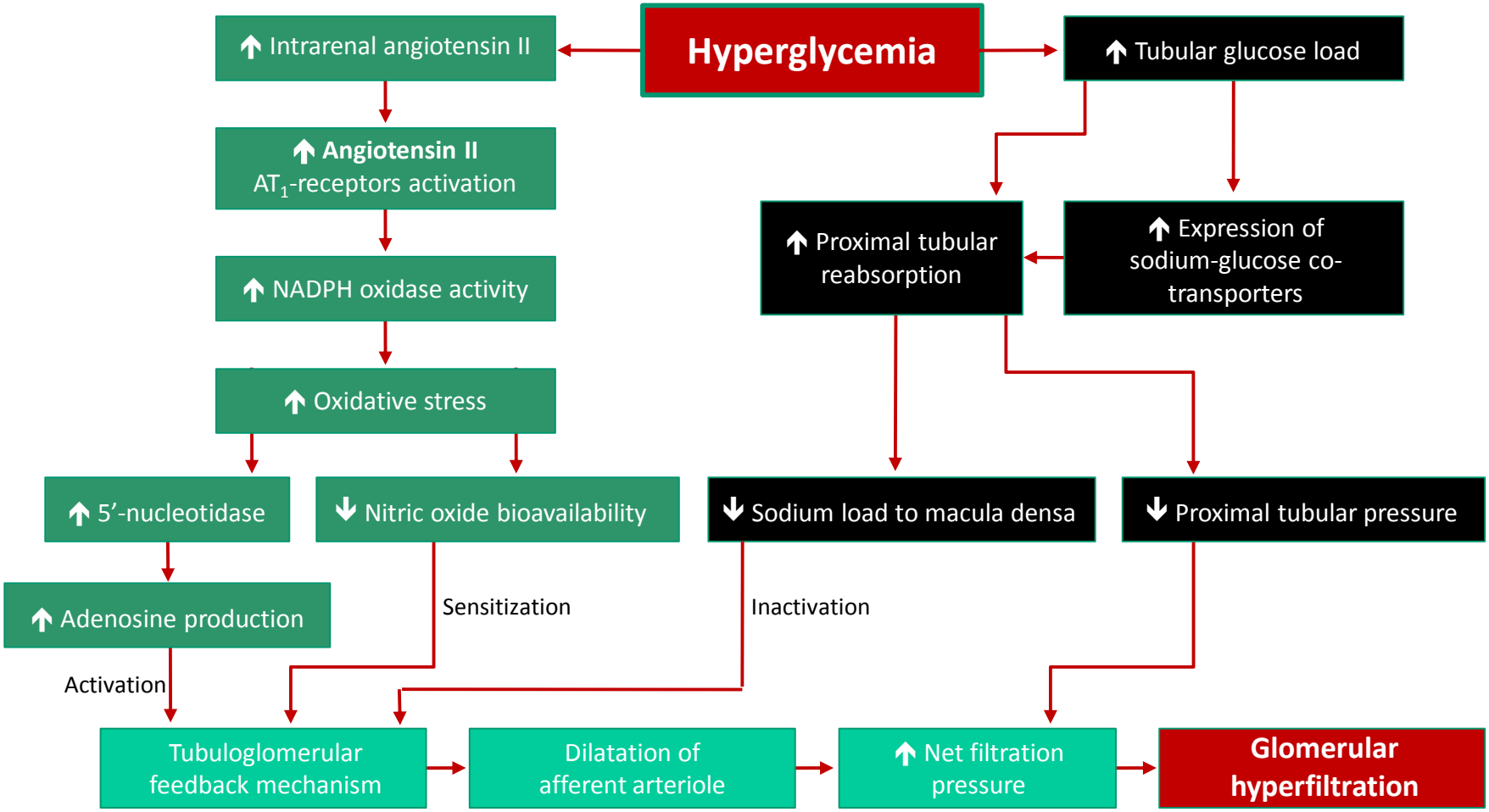
A metanalysis of 780 patients with type 1 diabetes included in 10 clinical studies and followed for a median of 11.2 years



Multivariable models predicting rapid GFR decline and incident renal impairment over 6 years

Exposure variables	Outcome variables	
	Rapid GFR decline (>3 mL/min/year) ($N = 144$)	Incident impaired GFR (<60 mL/min/1.73 m^2) ($N = 15$)
	OR (95% CI)	OR (95% CI)
HbA1c (per 1%)	1.07 (0.88–1.29) P = 0.51	1.83 (1.09–3.06) P = 0.02
SBP (per 1 mm Hg)	1.00 (0.98–1.02) P = 0.99	1.05 (0.99–1.11) P = 0.13
LDL-C (per 1 mg/dL)	0.99 (0.99–1.00) P = 0.15	1.01 (0.99, 1.04) P = 0.35
Duration (per year)	0.99 (0.96–1.02) P = 0.45	0.96 (0.86–1.08) P = 0.49
eIS (per unit)	1.02 (0.88–1.20) P = 0.83	1.40 (0.82–2.40) P = 0.22
Ln ACR (per unit)	1.23 (1.04–1.44) P = 0.01	3.04 (1.85–4.99) P < 0.0001
Renal hyperfiltration ($N = 147$)	5.00 (3.03–8.25) P < 0.0001	
Rapid GFR decline ($N = 144$)		15.99 (2.34–114.37) P = 0.006

Sustained hyperglycemia: RAAS activation and oxidative stress drive hyperfiltration[1]



1. Persson P, *et al*. *ActaPhysiol* (Oxf) 2010;200:3–10.

Brenner's concept of hyperfiltration from 1996

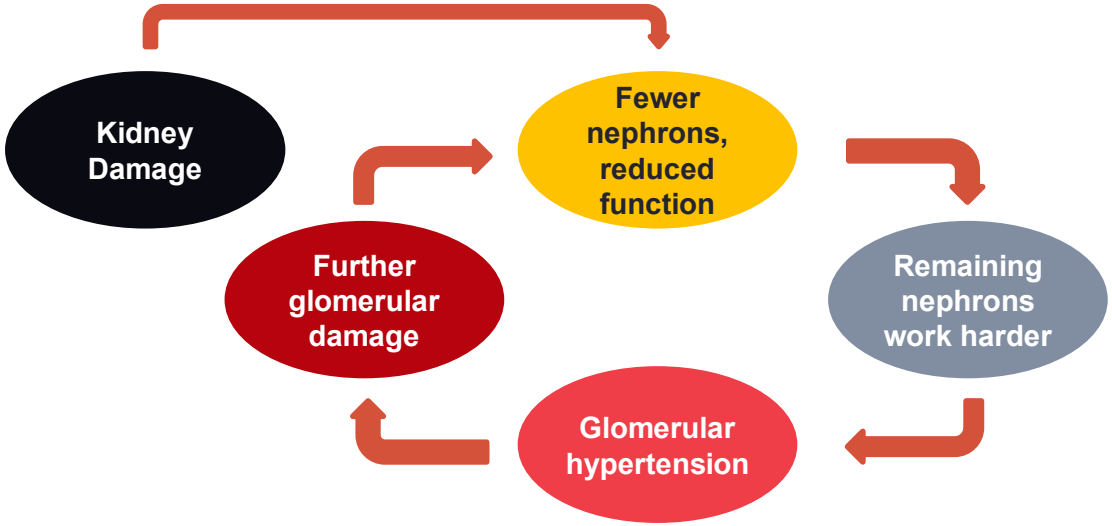
Kidney International, Vol. 49 (1996), pp. 1774–1777

STRATEGIES FOR INTERRUPTING PROGRESSIVE RENAL DISEASE

The hyperfiltration theory: A paradigm shift in nephrology

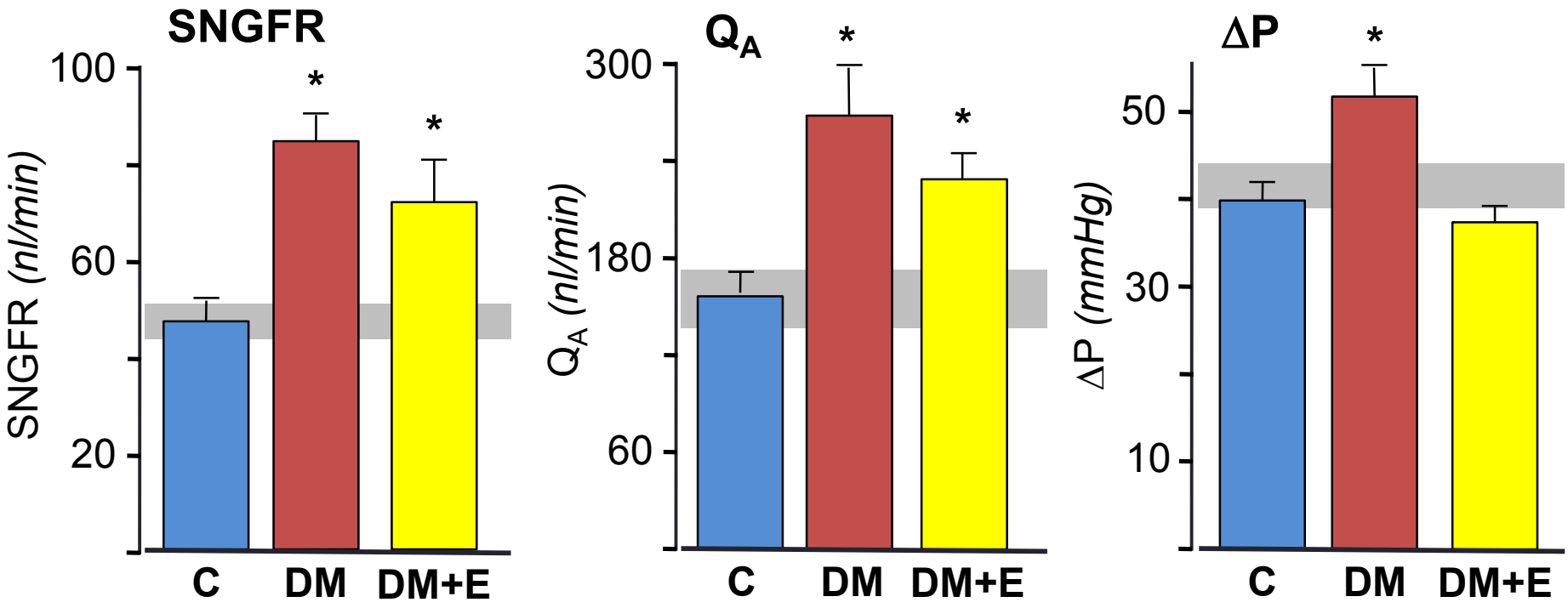
BARRY M. BRENNER, ELIZABETH V. LAWLER, and HARALD S. MACKENZIE

Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA



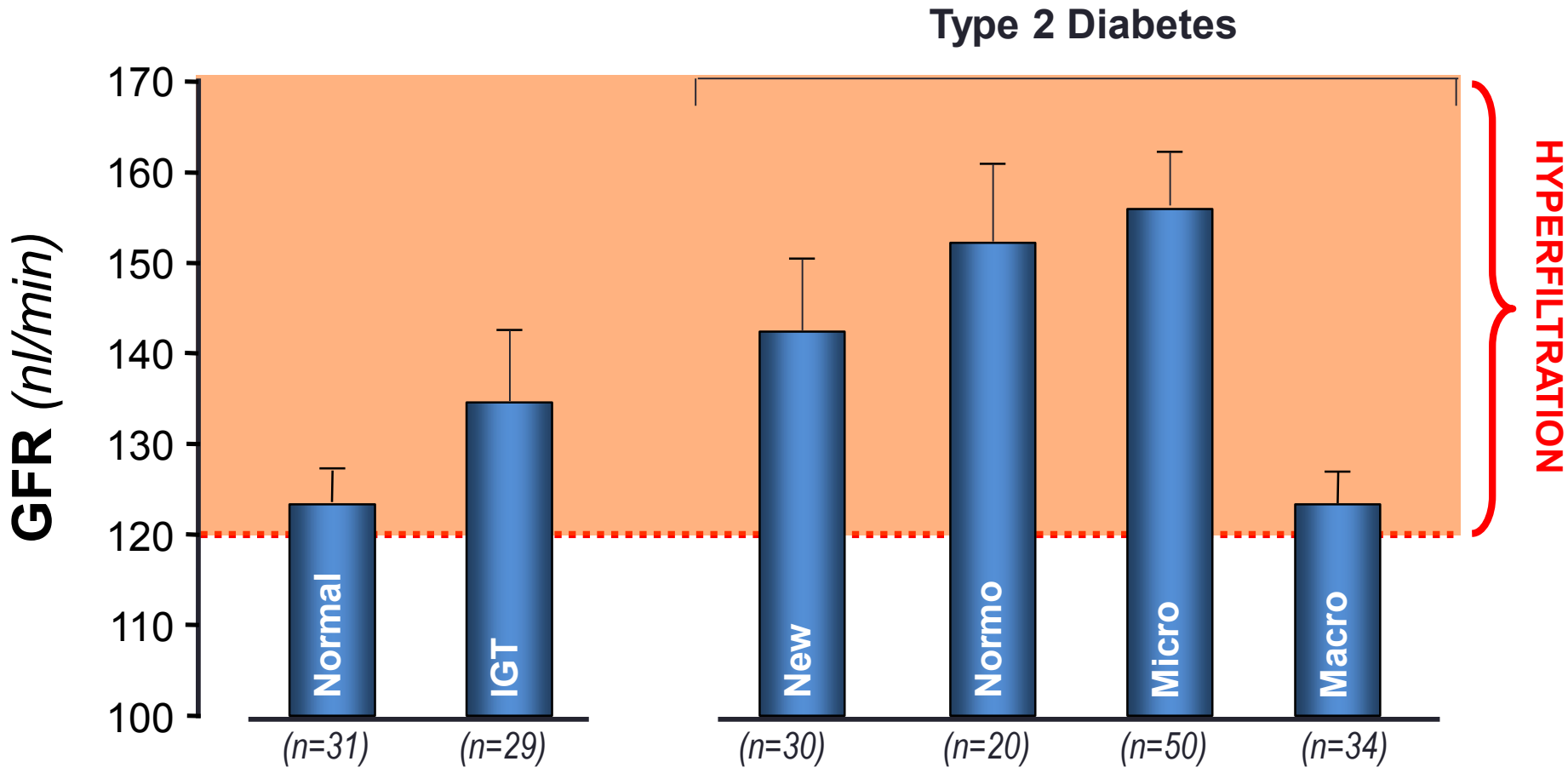
Prevention of Diabetic Glomerulopathy by Pharmacological Amelioration of Glomerular Capillary Hypertension

Roberto Zatz, B. Rentz Dunn, Timothy W. Meyer, Sharon Anderson, Helmut G. Rennke, and Barry M. Brenner
With the technical assistance of **J. L. Troy, R. L. DeGraphenried, J. L. Noddin, A. W. Nunn, and D. Sandstrom**
Laboratory of Kidney and Electrolyte Physiology and Departments of Medicine and Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115



J Clin Invest, 1986

DEVELOPMENT AND PROGRESSION OF RENAL DISEASE IN PIMA INDIANS WITH TYP 2 DIABETES

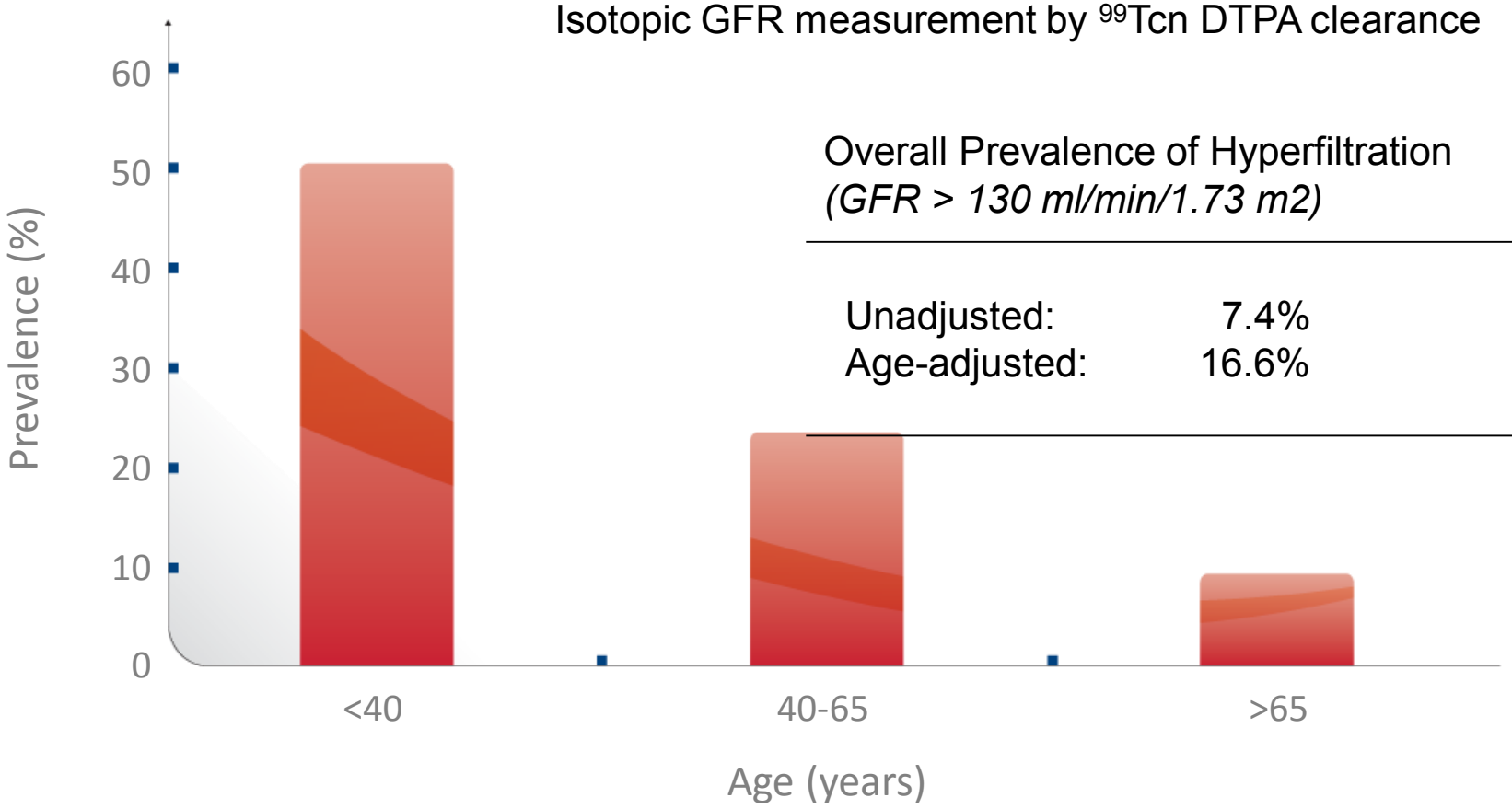


BMI *(kg/m²)*	31.8 ±1.3	39.3 ±1.7	38.1 ±1.4	34.3 ±1.9	32.7 ±1.1	31.7 ±1.1

Nelson R et al, ***NEJM*** 1996

How common is hyperfiltration in type 2 diabetes?[1]

Patients: n=662
Isotopic GFR measurement by ^{99}Tcn DTPA clearance



Overall Prevalence of Hyperfiltration
(GFR > 130 ml/min/1.73 m2)

Unadjusted:	7.4%
Age-adjusted:	16.6%

1. Jerums G, *et al*. *Diabetologia* 2010;53:2093–104.

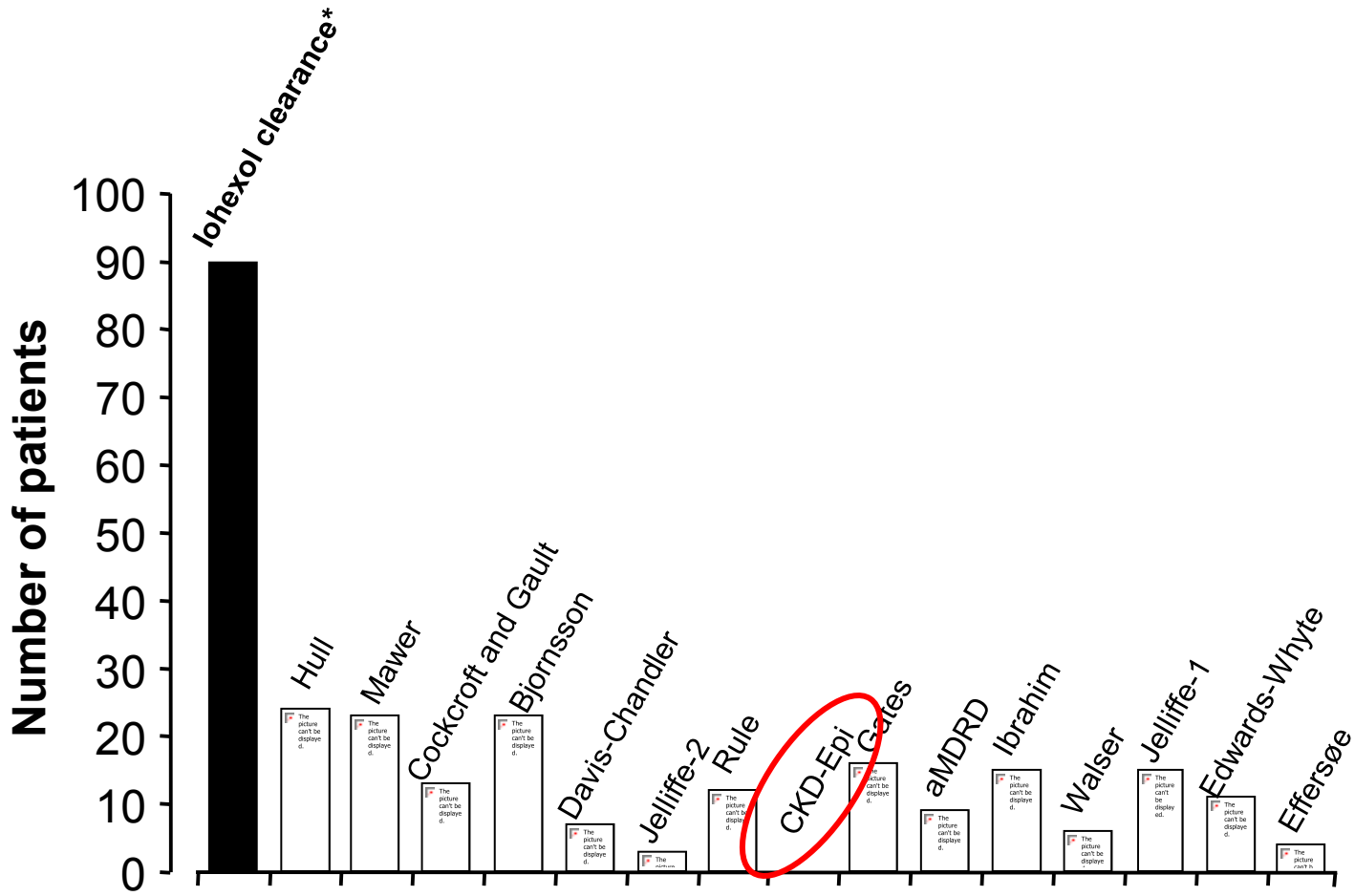
GLOMERULAR HYPERFILTRATION AND RENAL DISEASE PROGRESSION IN 600 TYPE 2 DIABETES WITH NORMO OR MICRO ALBUMINURIA

Patients	600 normo or microalbuminuric type 2 diabetics from BENEDICT B and DEMAND trials	
Outcomes	Baseline GFR* Short-term (baseline-month 6) GFR reduction Long-term GFR decline Progression to micro or macroalbuminuria	
Definitions	Hyperfiltration: GFR>120 ml/min/173m^2 Persistent Hyperfiltration:<10% GFR reduction at mo.6	
Follow-up	4.0 (1.7 – 8.1) years	
GFR measurements	Total: Median (IQR) per slope analysis:	n = 5,593 n = 9 (8 – 11)

* Iohexol Plasma clearance

Ruggenenti et al.,*Diabetes Care 35:1–8, 2012*

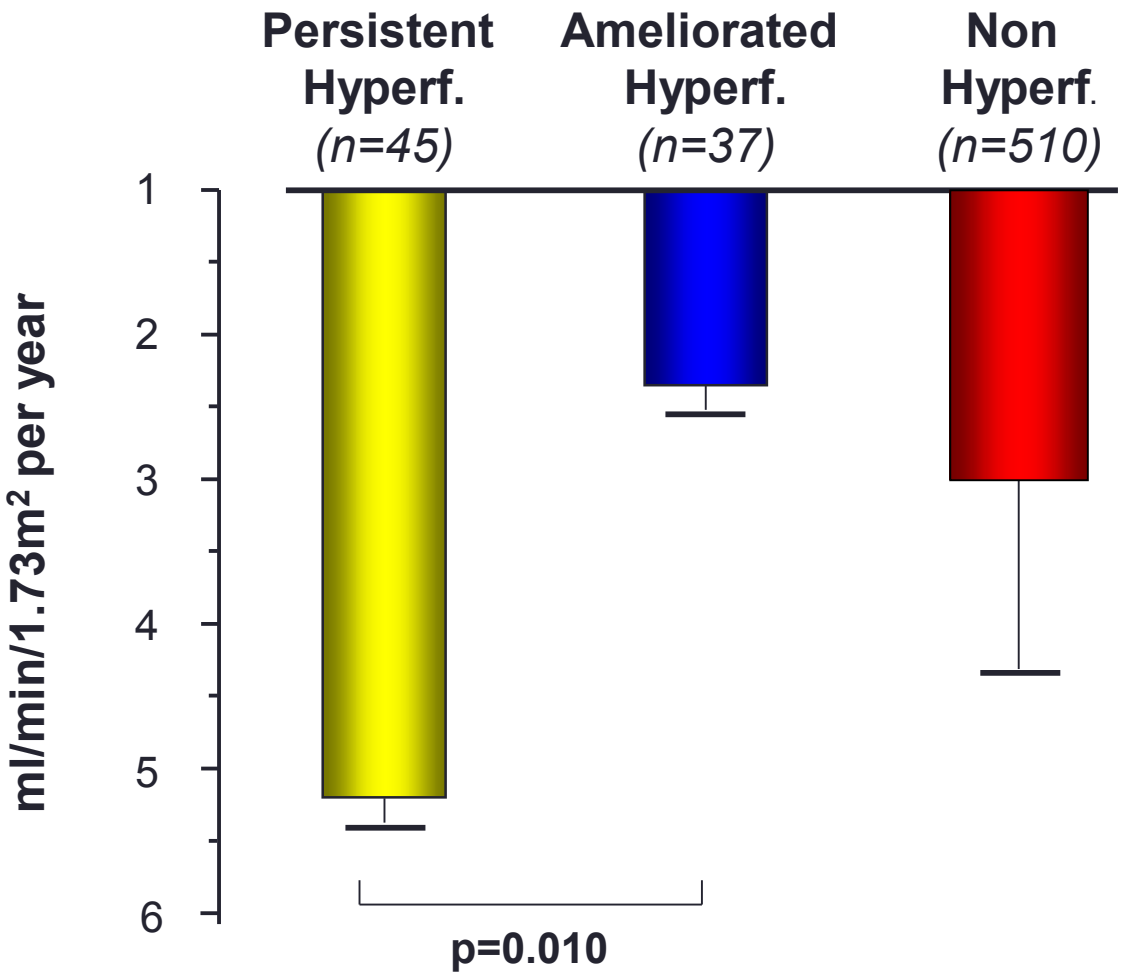
Number of patients with measured or estimated GFR > 120 ml/min/1.73 m² (*hyperfiltration*)



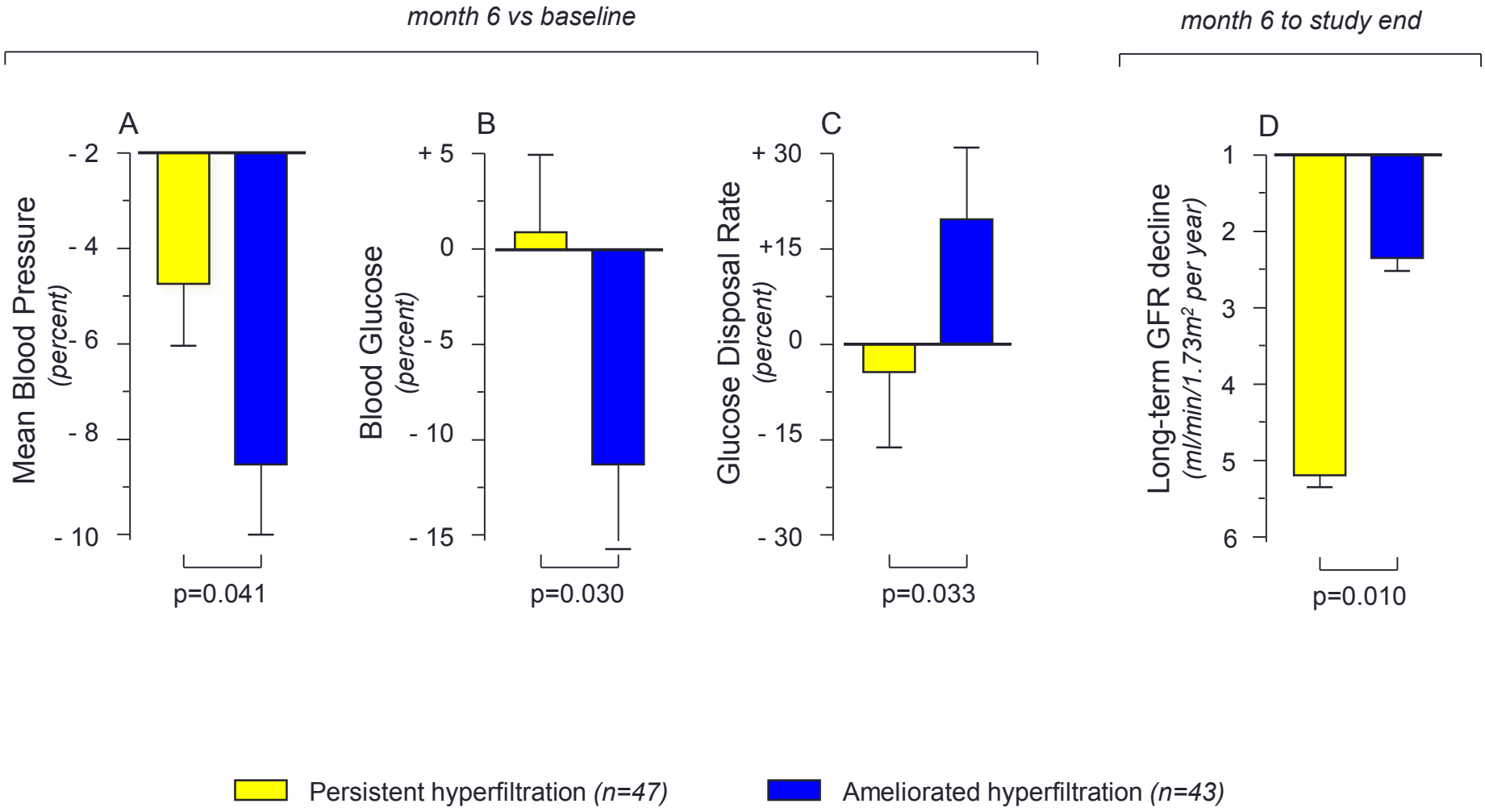
***15% hyperfiltering**

Ruggenenti et al., **Diabetes Care**, *2012*

Long-term GFR decline from mo. 6 to study end



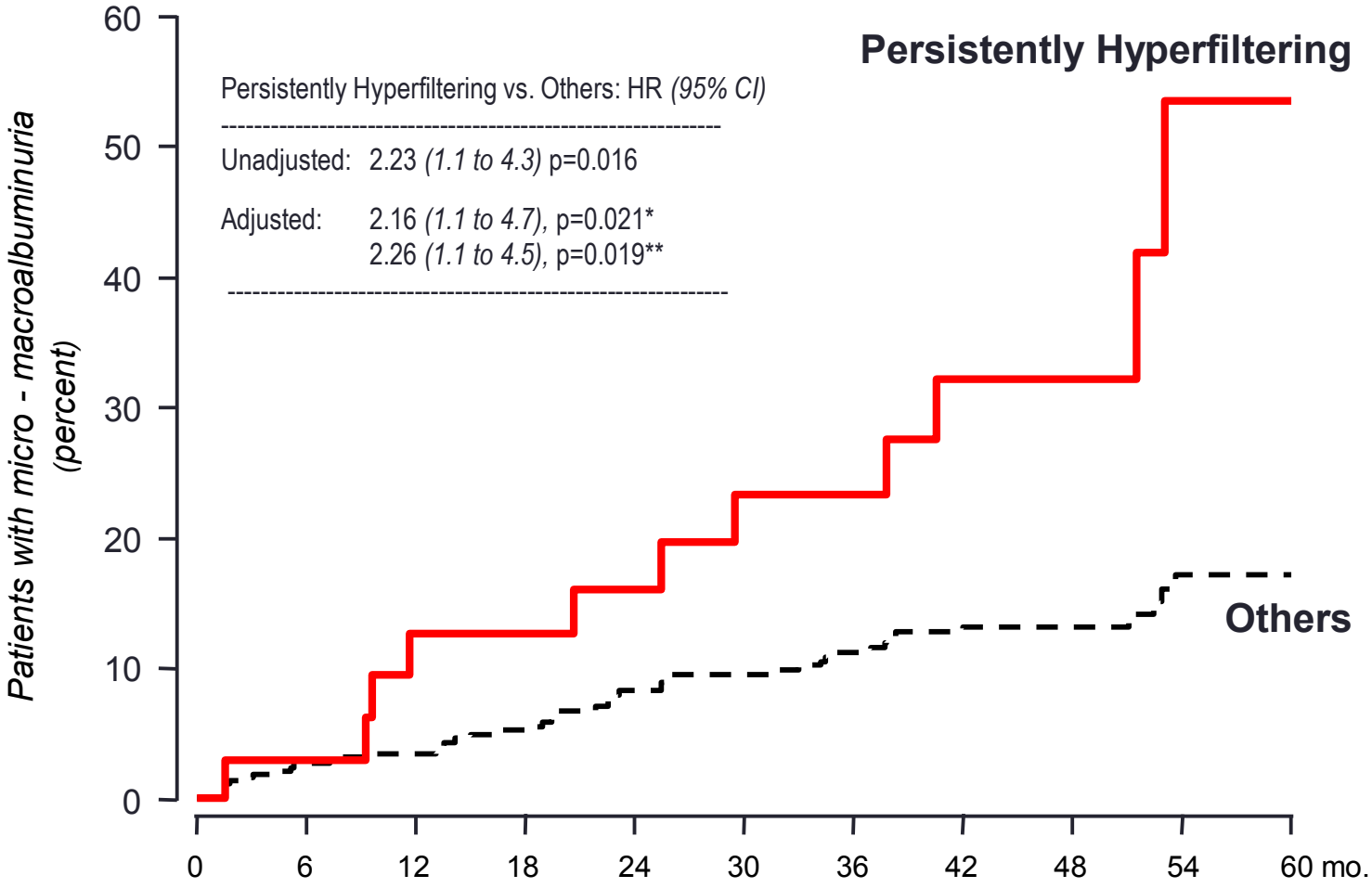
Amelioration of Hyperfiltration: Possible Determinants



PREDICTORS OF LONG-TERM GFR DECLINE (6-months – end)

Variables	*Coefficient (SE)*	*P*
Age	- 0.004 (0.002)	0.01
UAE	- 0.023 (0.002)	0.06
6-months GFR reduction	- 0.005 (0.000)	< 0.0001

Other considered variables: gender, smoking, know diabetic duration, BMI, SBP, HbA1c, triglycerides, uric acid



Patients at risk

Persistently-Hyperfiltering	47	45	40	39	38	34	33	28	21	17	15
Others	502	389	373	361	327	302	299	235	183	132	65

* Adjusted for baseline covariates

**Adjusted for baseline covariates and follow up Hba1C and MAP

CRESO

A randomized, pilot study of Caloric REstriction in Subjects with abdominal Obesity and type 2 diabetes at increased renal and cardiovascular risk

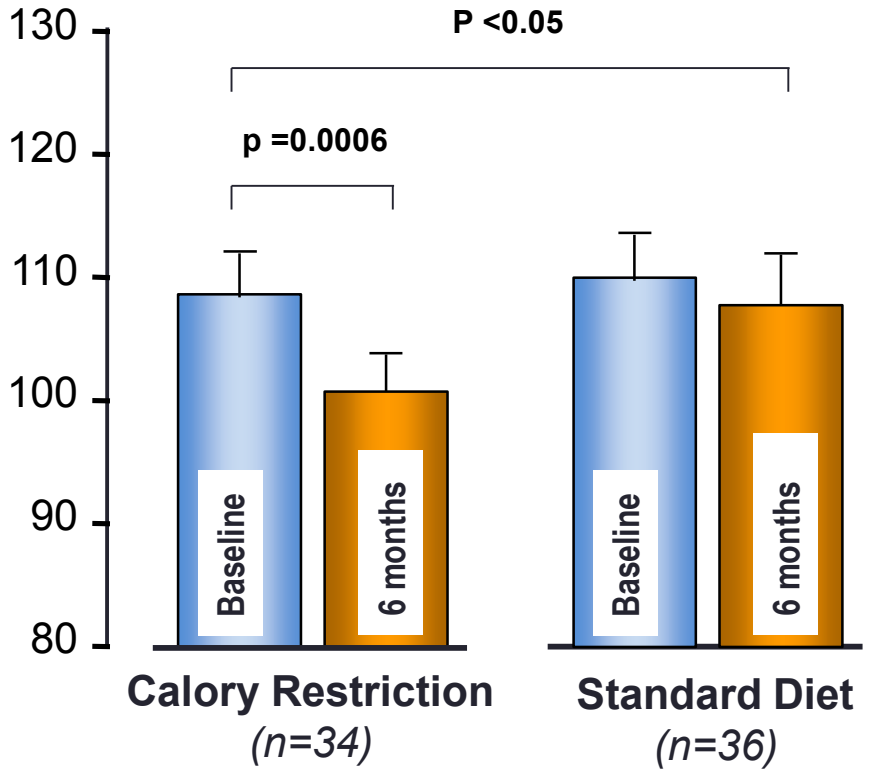
ClinicalTrials.gov Identifier: NCT01213212

Renal and Systemic Effects of Calorie Restriction in Patients With Type 2 Diabetes With Abdominal Obesity: A Randomized Controlled Trial

Diabetes 2016;65:1–12 | DOI: 10.2337/db16-0607

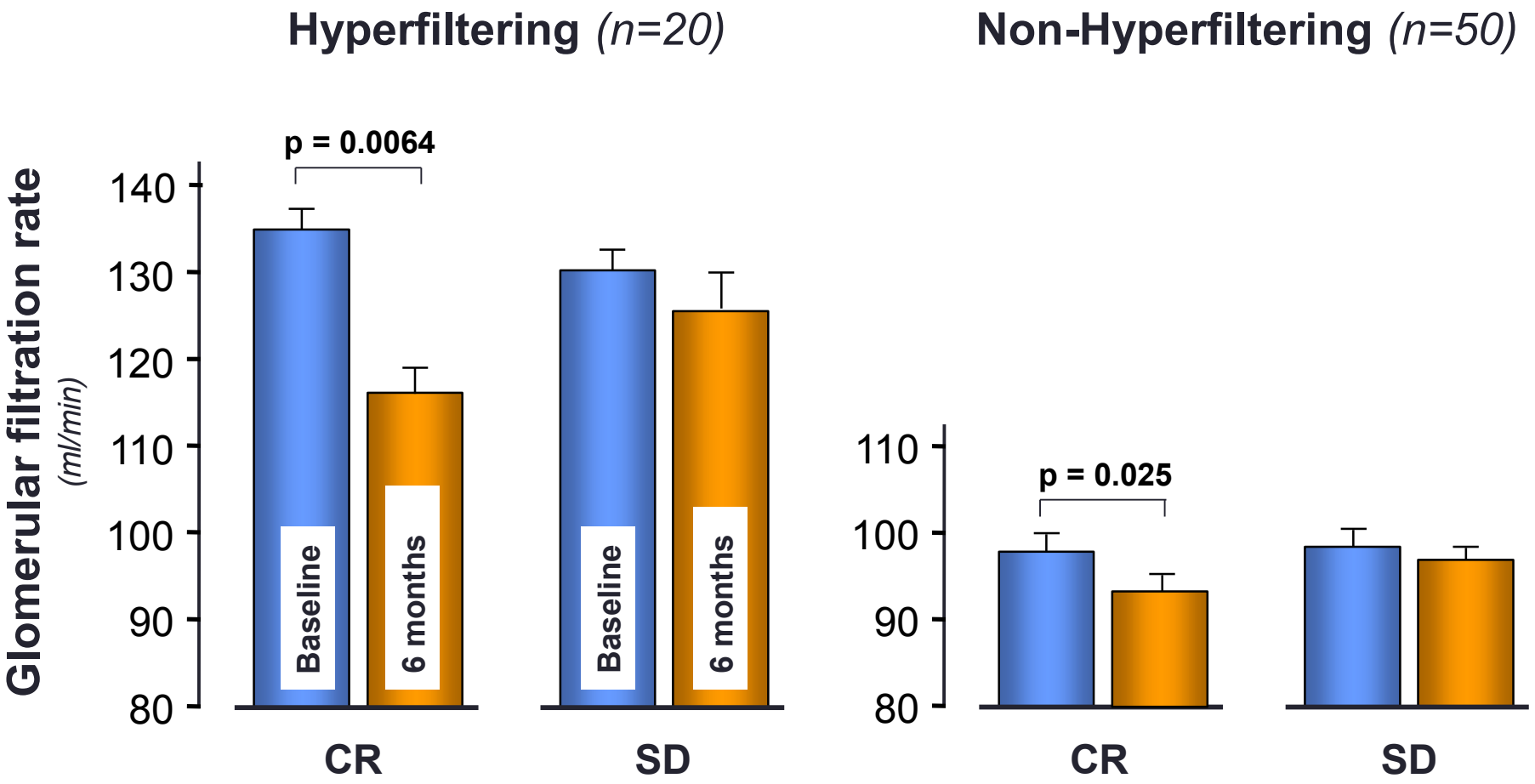
Patients:	70 Type 2 diabetics waist circumference > 94 cm (*females)* > 88 cm *females)* *s. creat. <1.2 mg/dl* *UAE<20 mg/min*
Design:	*PROBE*
Treatment:	*6-mo. 25% CR vs SD*

*ClinicalTrials.gov Identifier: **NCT01213212**



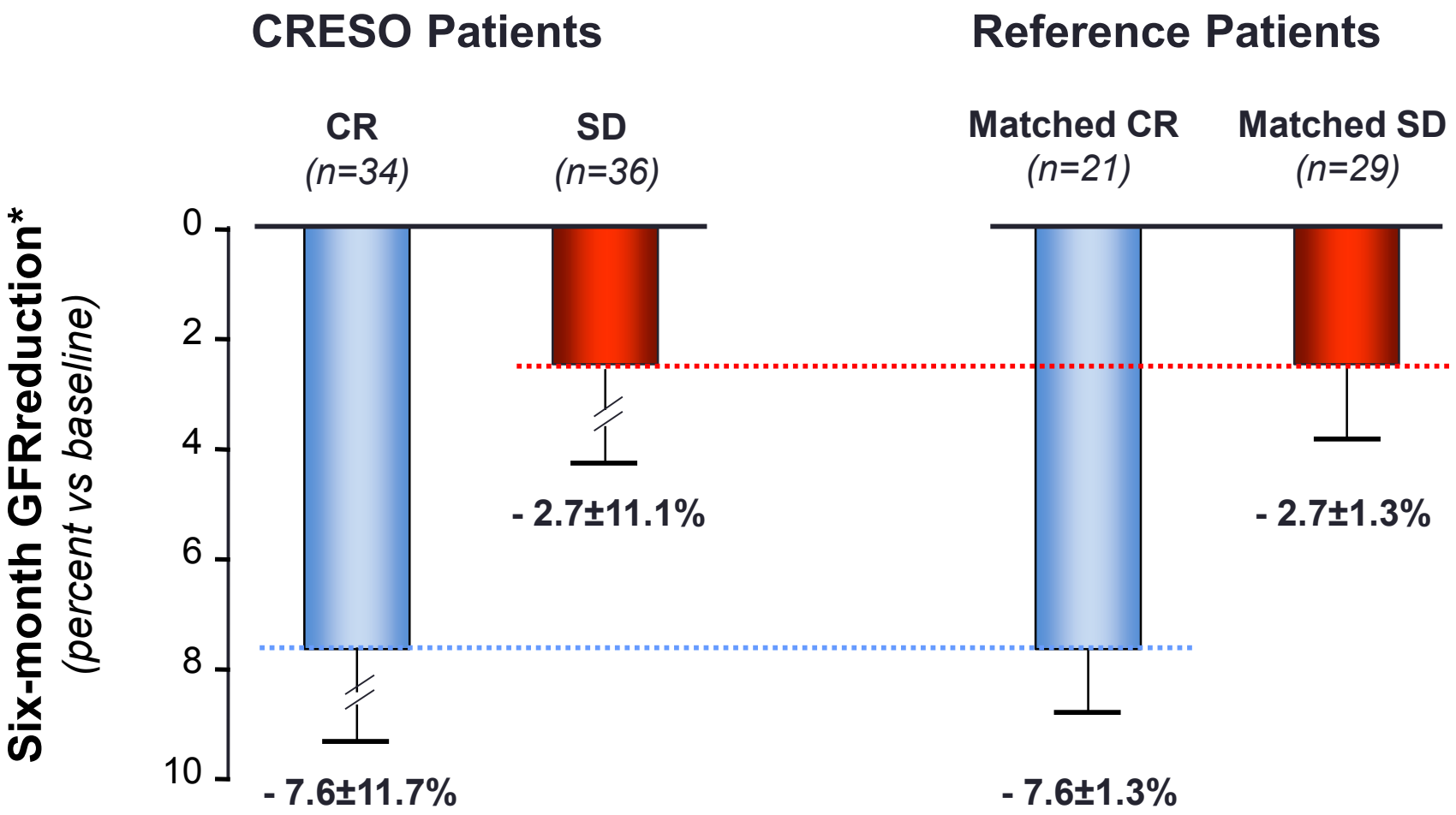
* Iohexol plasma clearance

Ruggenenti P et al, **Diabetes** 2016



Ruggenenti P et al, ***Diabetes*** 2016

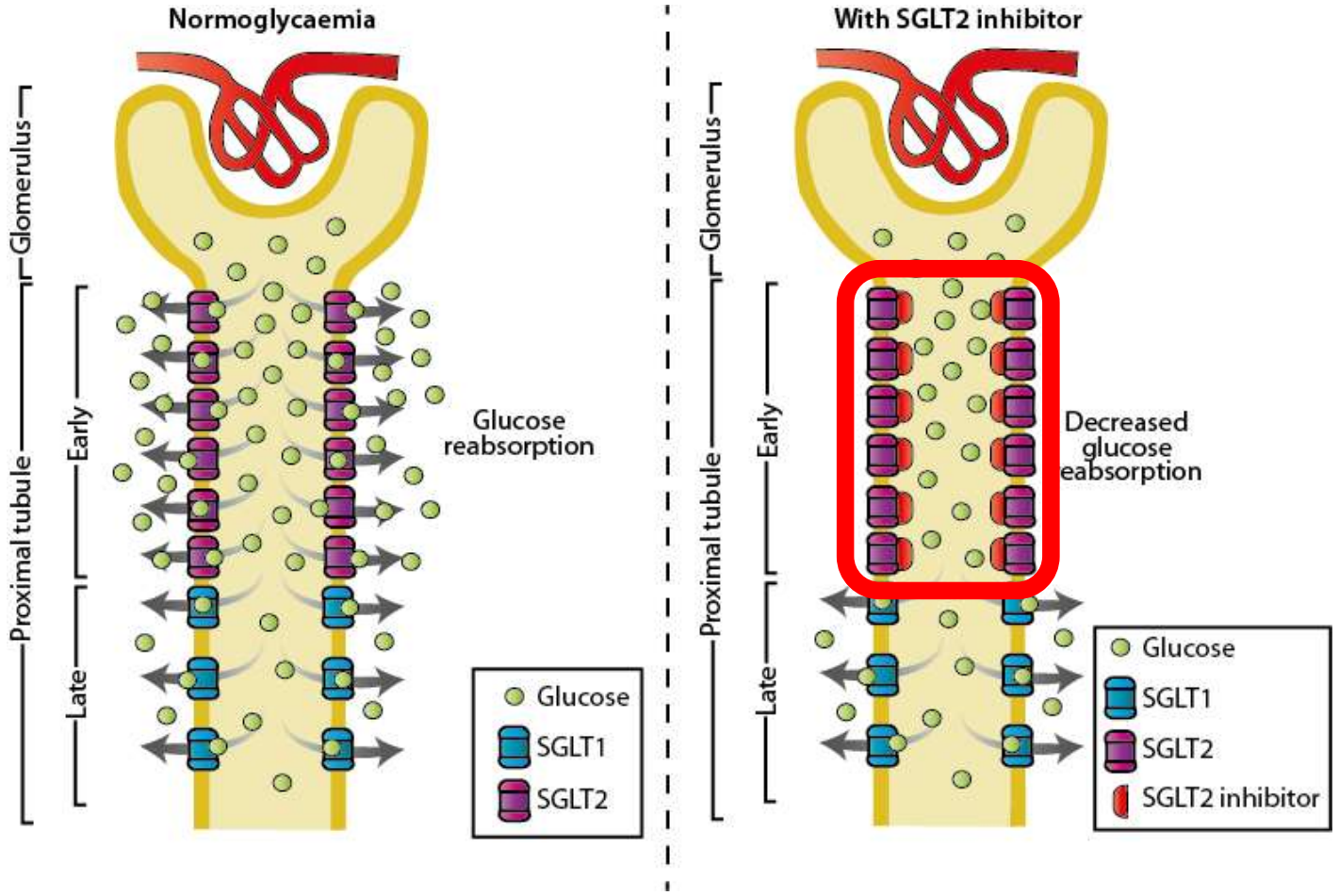
SIX-MONTH GFR REDUCTION IN CRESO PATIENTS AND MATCHED REFERENCE PATIENTS FROM BENEDICT AND DEMAND



* Iohexol plasma clearance

Ruggenenti P et al, ***Diabetes*** 2016

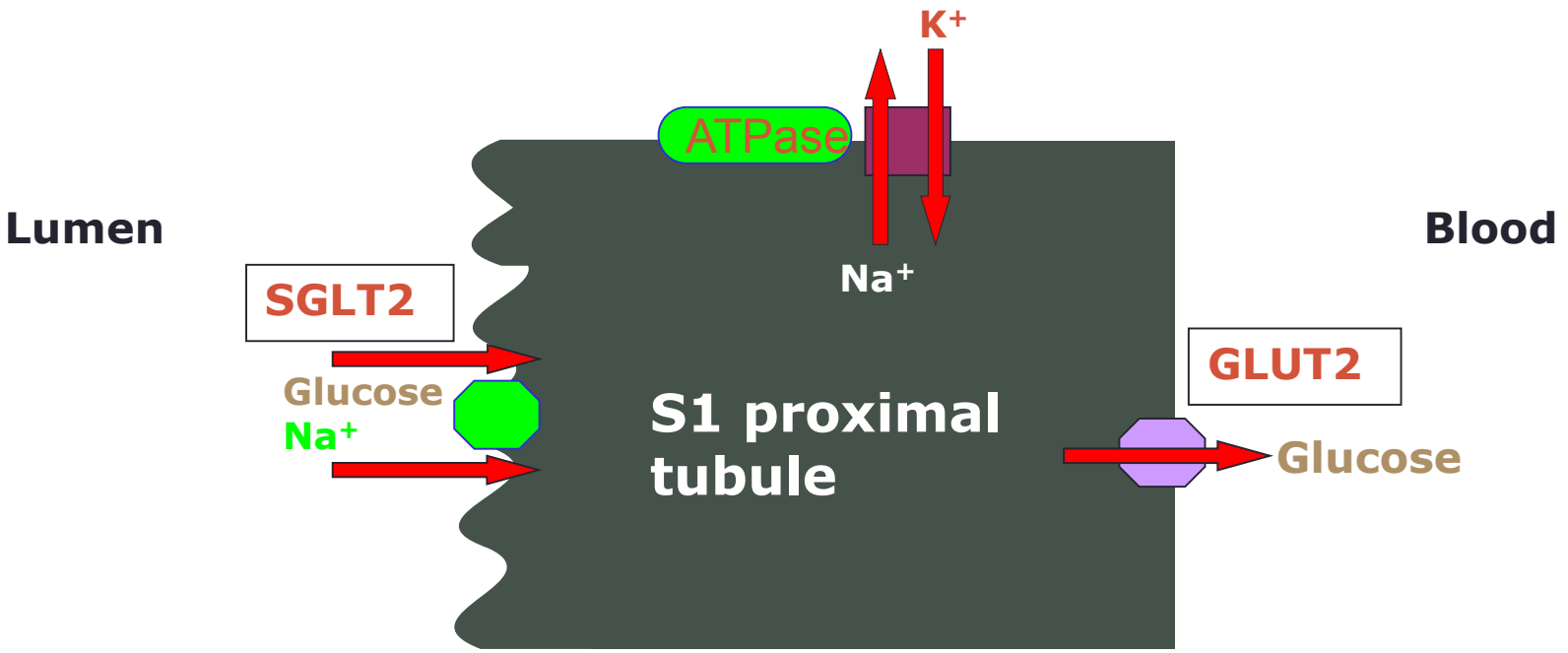
SGLT2 Inhibition:
A Novel Approach to Reduce Hyperglycaemia and HYPERFILTRATION



- SGLT2 inhibition decreases plasma glucose by increasing urinary glucose excretion

Rothenberg PL et al. Poster presented at EASD 2010; Stockholm, Sweden.

SGLT2 Mediates Glucose Reabsorption in the Kidney

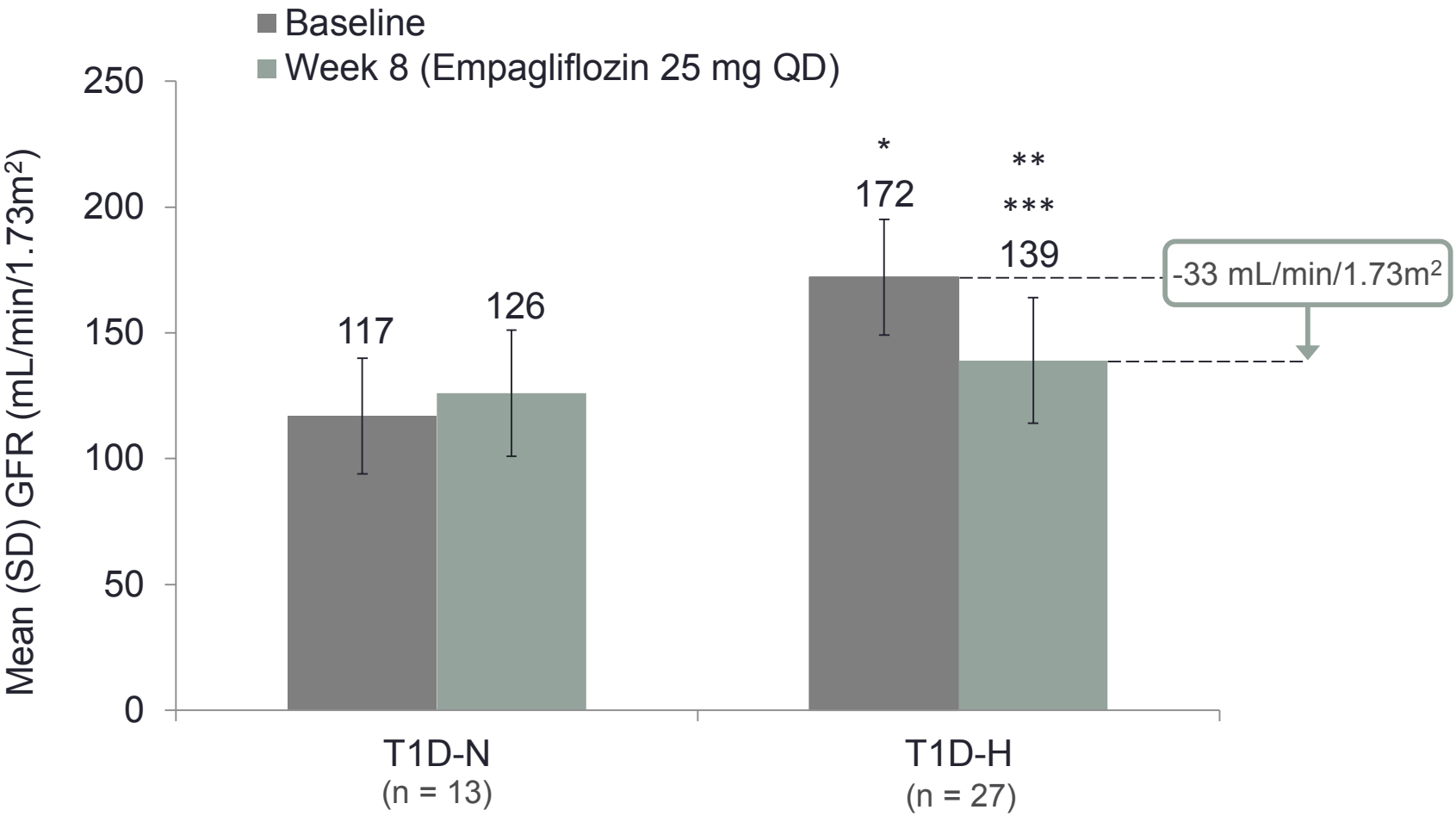


SGLT2: Major transporter of glucose in the kidney[1-3]

- Low affinity, high capacity for glucose
- Co-transports Na+ and glucose at 1:1 stoichiometry
- Nearly exclusively expressed in the S1 portion of the proximal tubule
- Responsible for majority of renal glucose reabsorption in the proximal tubule

[1]Hediger MA, Rhoads DB. *Physiol Rev* 1994;74:993-1026; [2]Magen D, et al. *Kidney Int*. 2005;67:34-41;
[3]Kanai Y, et al. *J Clin Invest* 1994;93:397-404

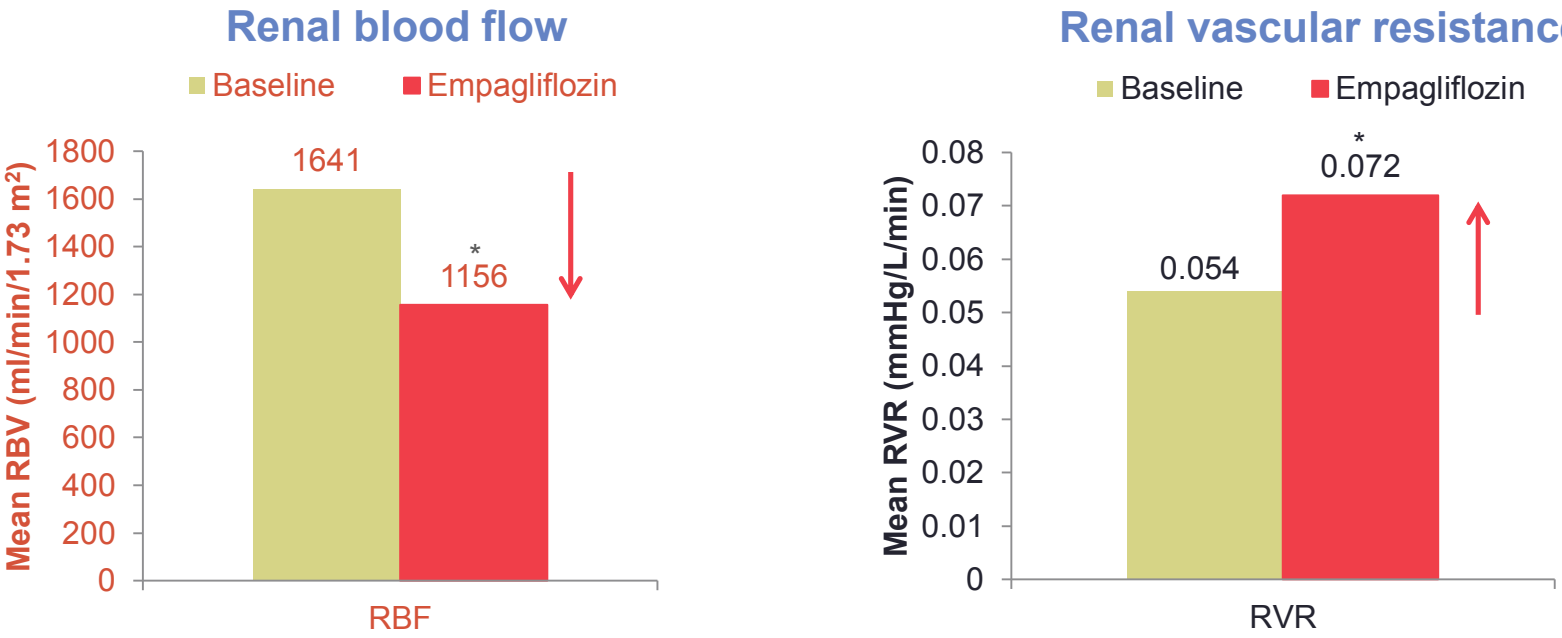
Renal hyperfiltration in patients with T1D
GFR during clamp EUGLYCAEMIA after 8 weeks of treatment



- *p < 0.01 for baseline GFR in patients with Type 1 Diabetes without (T1D-N) versus with (T1D-H) renal hyperfiltration.
- **p < 0.01 for the within group change in GFR in T1D-H. ***p < 0.01 for the between-group effect on empagliflozin on change in GFR.
- Cherney D, et al. *Circulation*. 2014;5:587–597.

Reduced hyperfiltration could be mediated by effects on renal blood flow and vascular resistance

Reduced **renal blood flow** (RBF) and increased **renal vascular resistance** (RVR) after empagliflozin treatment are consistent with **afferent arteriole vasoconstriction (narrowing)**

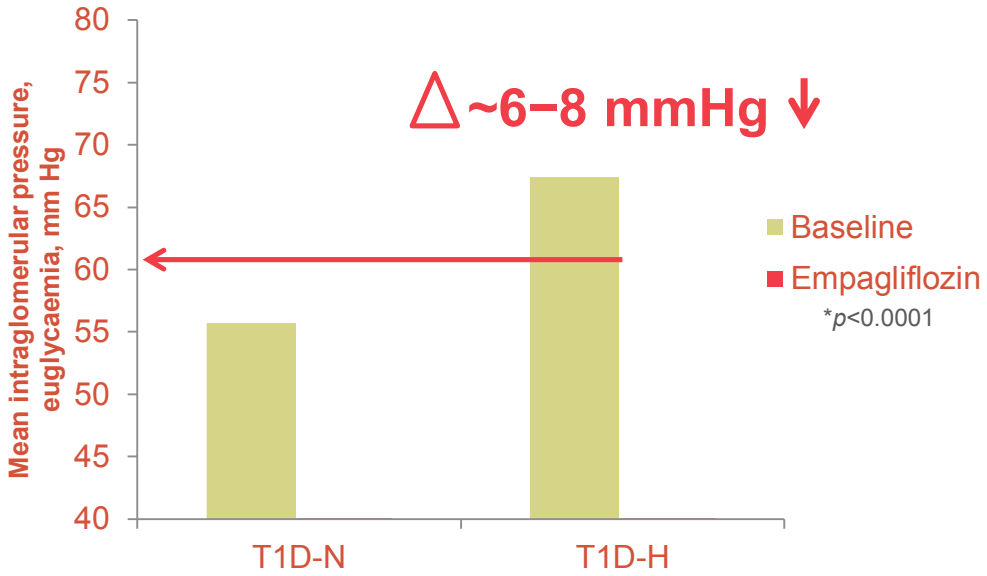


* $p<0.01$

Patients with type 1 diabetes and hyperfiltration at baseline. RBV and RVR recorded in euglycaemic state. RBF, renal blood flow; RVR, renal vascular resistance.

Cherney D *et al. Circulation* 2014;129:587-597

Empagliflozin reduces intraglomerular pressure



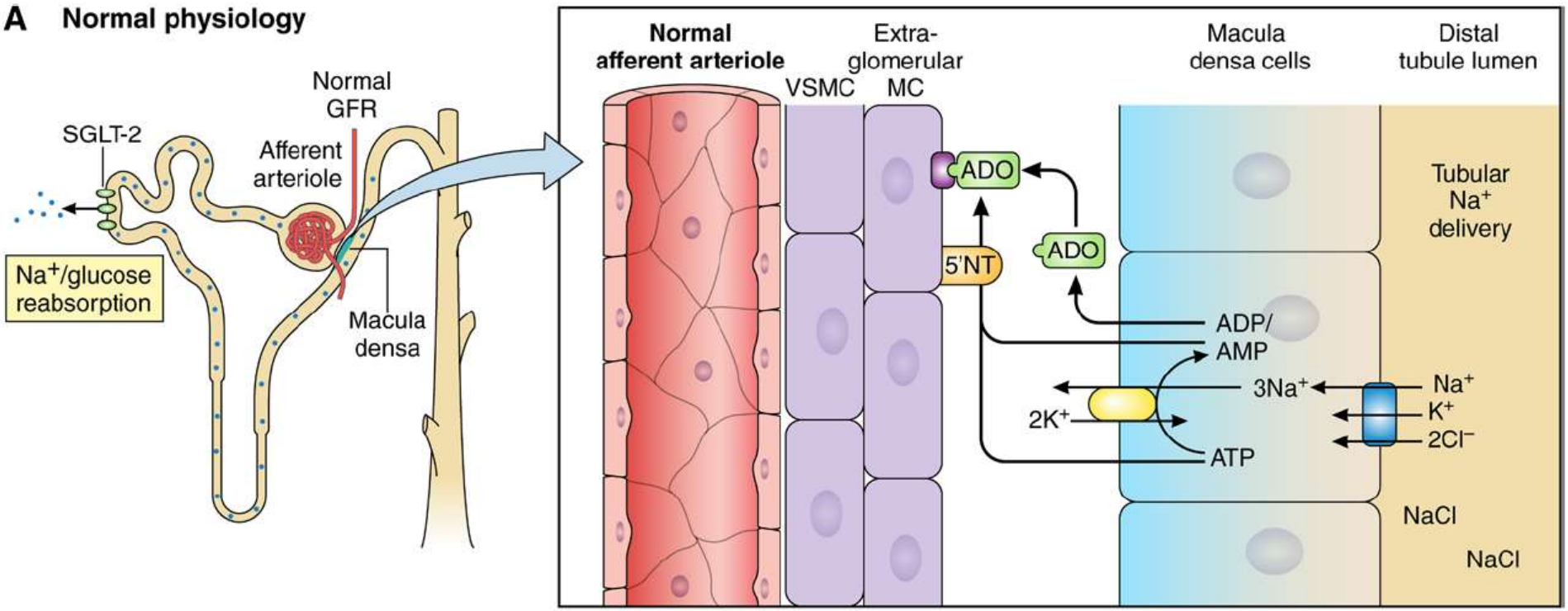
Intraglomerular pressure recorded at baseline and after 8 weeks treatment with empagliflozin

Glomerular pressure T1D-H (mmHg)	Baseline	EMPA	p value	Change from baseline
Euglycaemia (mmHg)	67.4 ± 5.4	61.0 ± 5.2	<0.0001	9.5%
Hyperglycaemia (mmHg)	69.3 ± 6.5	61.6 ± 6.3	<0.0001	11.1%

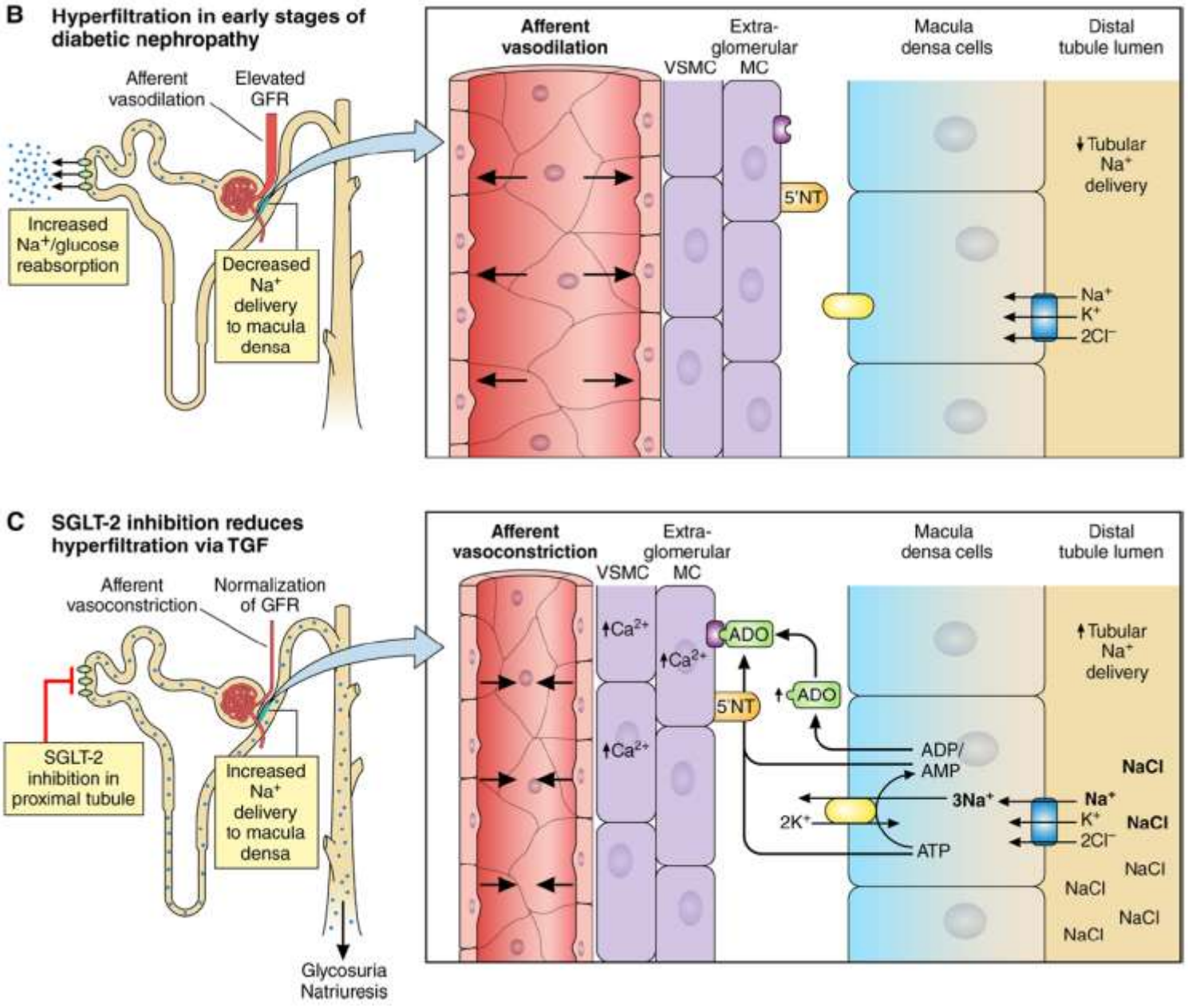
T1D-N, type 1 diabetes patients with renal normofiltration; T1D-H, type 1 diabetes patients with renal hyperfiltration; EMPA, empagliflozin.

Skrtic M *et al*. *Diabetologia* 2014;57:2599

Putative mechanism for sodium-mediated changes in adenosine bioactivity at the afferent arteriole



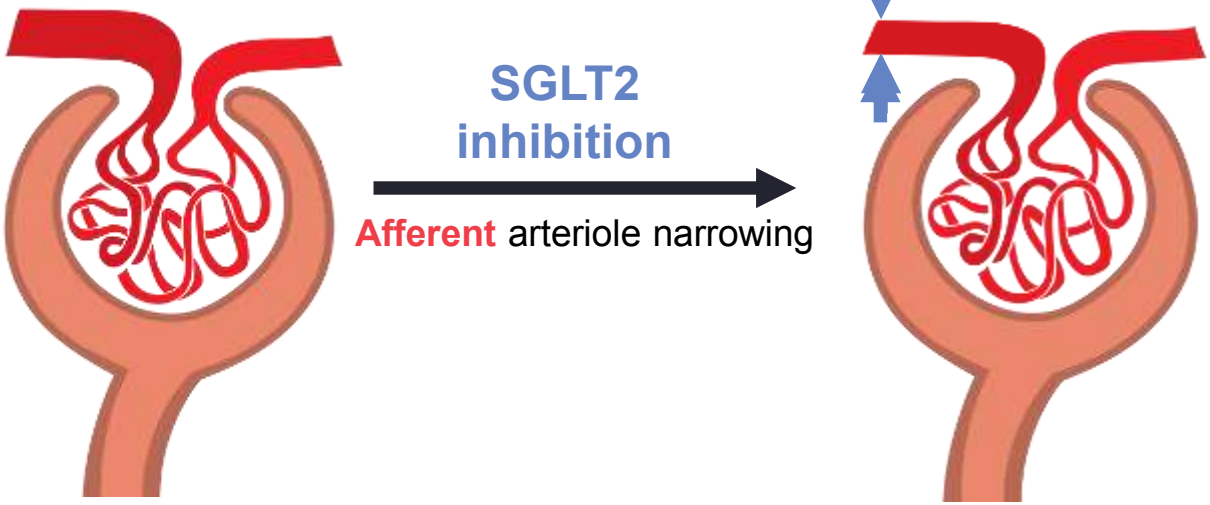
Circulation. 2016;134:752–772


B
Hyperfiltration in early stages of diabetic nephropathy
Afferent vasodilation
Elevated GFR
Increased Na+/glucose reabsorption
Decreased Na+ delivery to macula densa
Afferent vasodilation
Extra-glomerular
VSMC
MC
Macula densa cells
Distal tubule lumen
5'NT
↓Tubular Na+ delivery
Na+
K+
2Cl−
C
SGLT-2 inhibition reduces hyperfiltration via TGF
Afferent vasoconstriction
Normalization of GFR
SGLT-2 inhibition in proximal tubule
Increased Na+ delivery to macula densa
Glycosuria
Natriuresis
Afferent vasoconstriction
Extra-glomerular
VSMC
MC
Macula densa cells
Distal tubule lumen
↑Ca2+
↑Ca2+
↑Ca2+
ADO
5'NT
↑ADO
ADP/AMP
3Na+
2K+
ATP
↑Tubular Na+ delivery
Na+
K+
2Cl−
NaCl
NaCl
NaCl
NaCl
NaCl

Empagliflozin exerts a hemodynamic effect within the kidney

By restoring the Tubulo-Glomerular Feedback (TGF), empagliflozin increases the afferent arteriole tone, thereby lowering glomerular hypertension

Action:

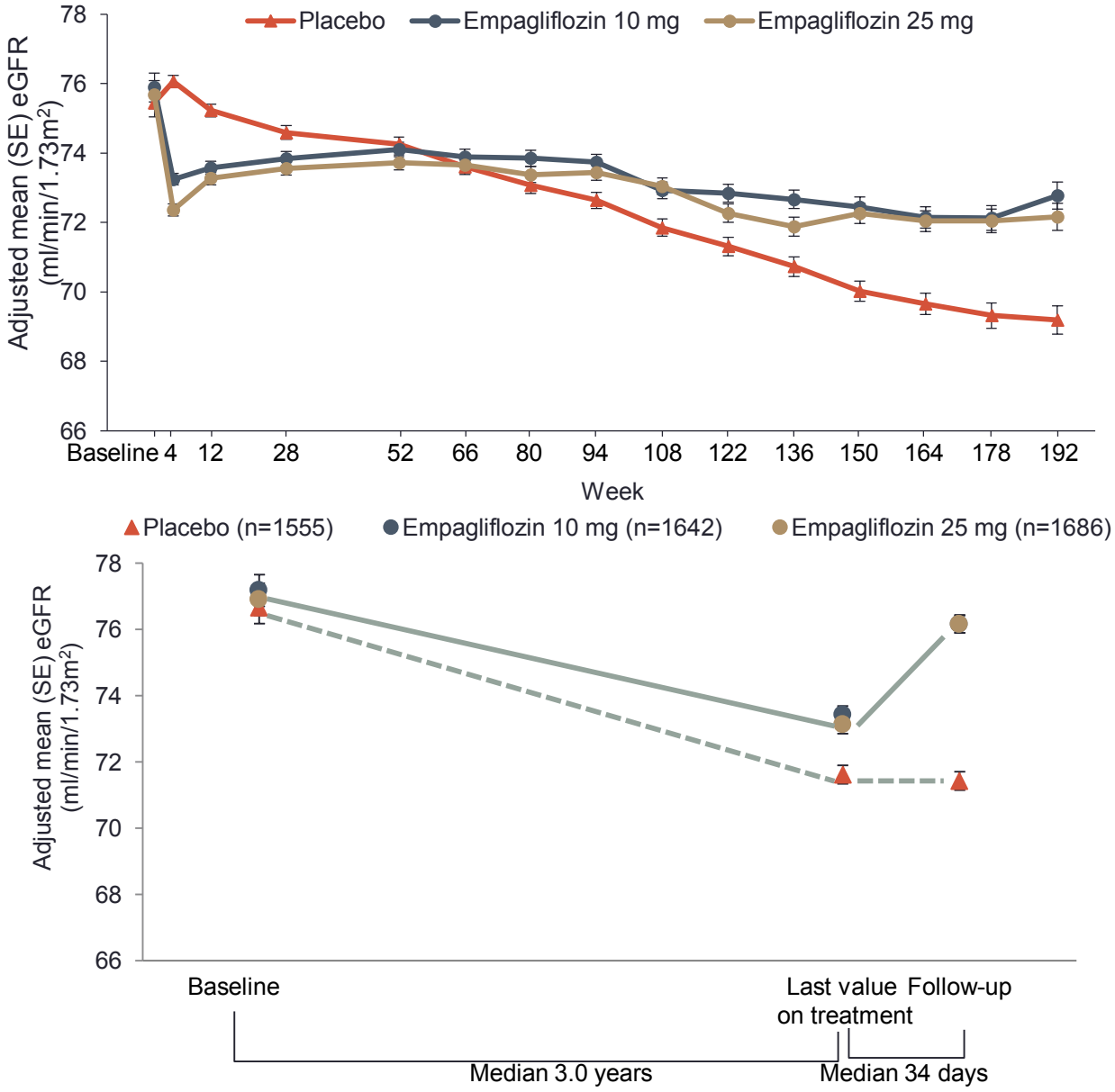


Clinical implications:

- Glomerular pressure decreases
- Early clinical marker:
  - Initial dip in GFR
  - Reduction of albuminuria

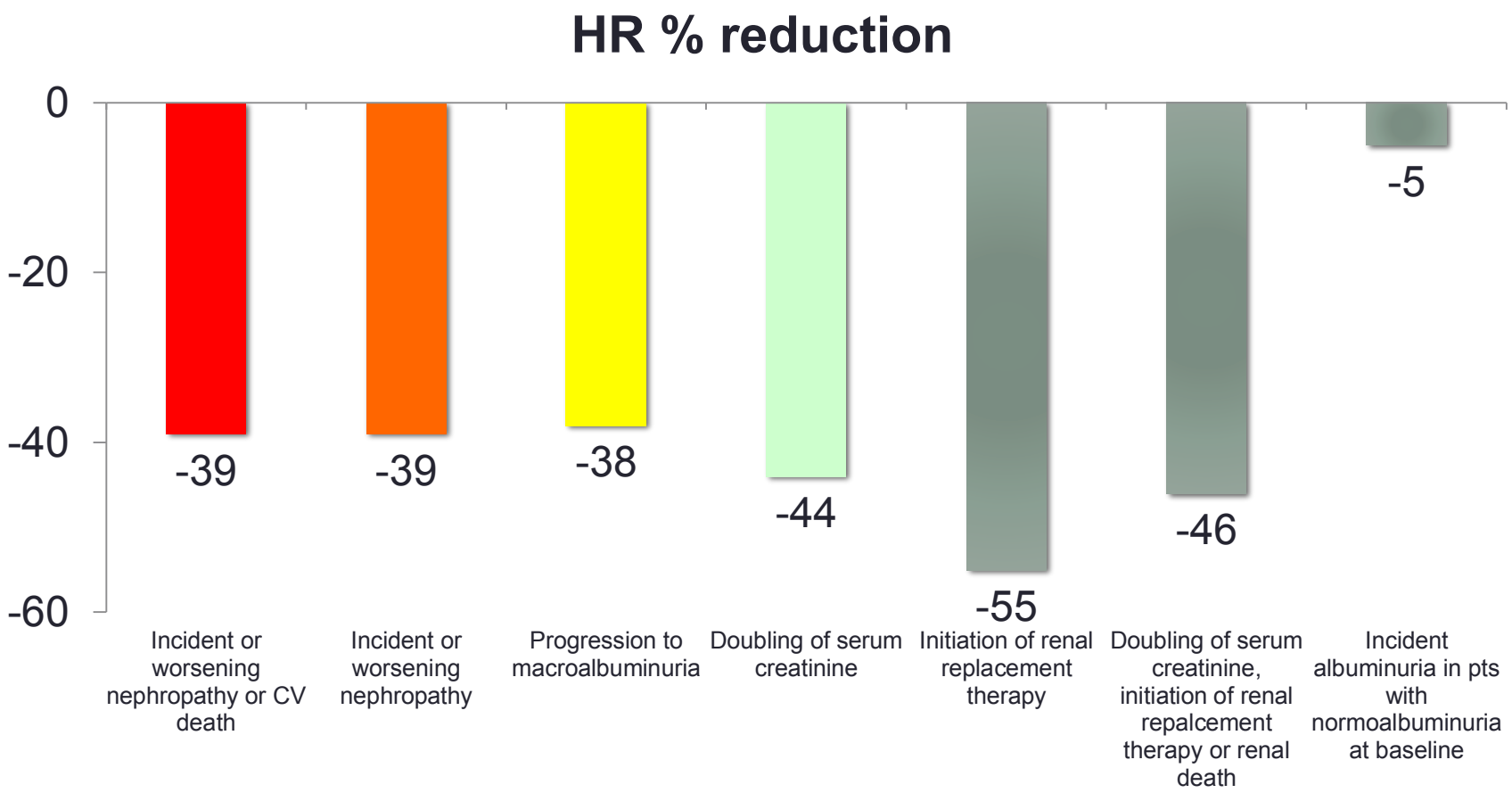
Adapted from: Cherney D *et al. Circulation* 2014;129:587
Skrtic M *et al*. *Diabetologia* 2014;57:2599

EMPAREG Study: eGFR decline during the study



Christoph Wanner et al. published online June 14, 2016, at NEJM.org

EMPAREG: Renal Outcomes



N Engl J Med 2015;373:2117-28

CONCLUSIONI

- L’iperfiltrazione è un maggiore determinante della progressione del danno renale nel diabete sia nel diabete di tipo 1 che di tipo 2.
- Controllo glicemico, riduzione calorica e della pressione con inibitori del RAS riducono l’iperfiltrazione.
- Gli inibitori del SGLT2 riducono l’iperfiltrazione e si associano a miglior “outcomes” renali nel diabete di tipo 2.
- Il miglioramento dell’iperfiltrazione risulta nefroprotettivo.