Diabetes E Rim

Manejo integral do paciente diabético com Doença Renal Crônica

CURSO ON-LINE

27 DE ABRIL A 21 DE JUNHO DE 2017

ORGANIZAM

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Sociedade Brasileira de Nefrologia

GESTÃO EDUCATIVA, INFORMÁTICA E LOGÍSTICA evimed

Fisiopatologia da hiperfiltração glomerular no diabetes mellitus

Terceira parte: Manipulação farmacológica tubular na HF
Aspectos clínicos e manejo atual da HF

Servicio de Nefrologia San Pedro

Claudio Mascheroni

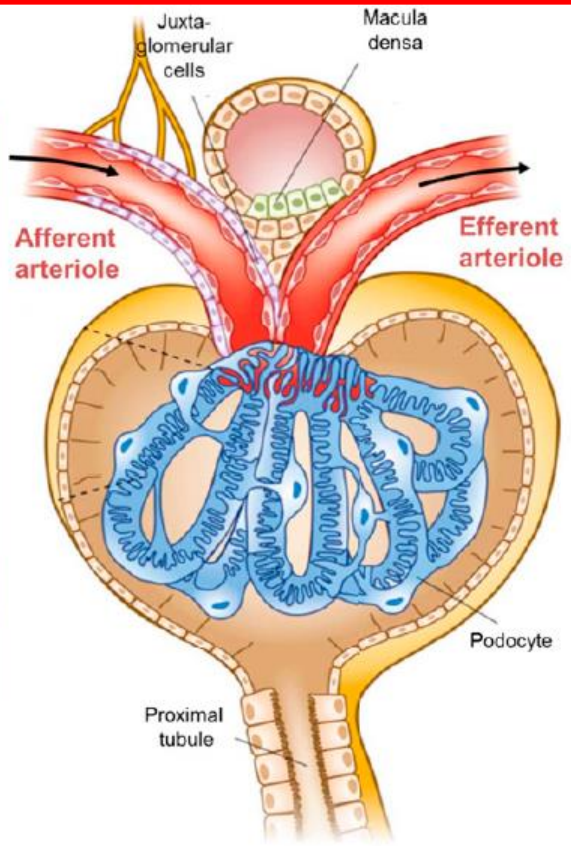
Serviço de Nefrologia e Hemodiálise San Pedro

Serviço de Nefrologia e Hemodiálise

Universidad Nacional de Rosario

Fatores que influenciam a filtração glomerular

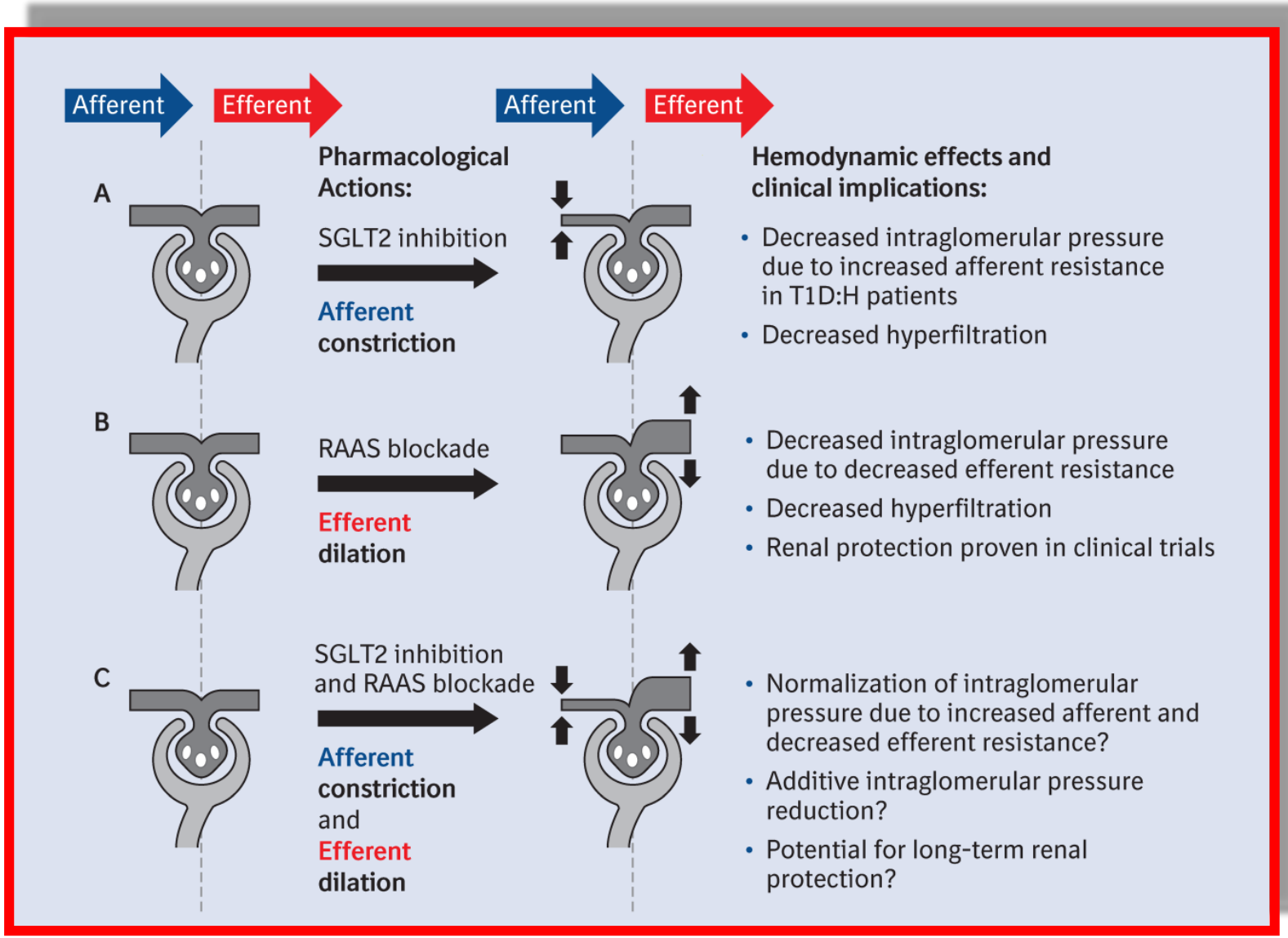
Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se* *
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals) *



Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II *
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

Tonneijck *et al. J Am Soc Nephrol* 2017 (no prelo).

HF – Manipulação farmacológica glomerular

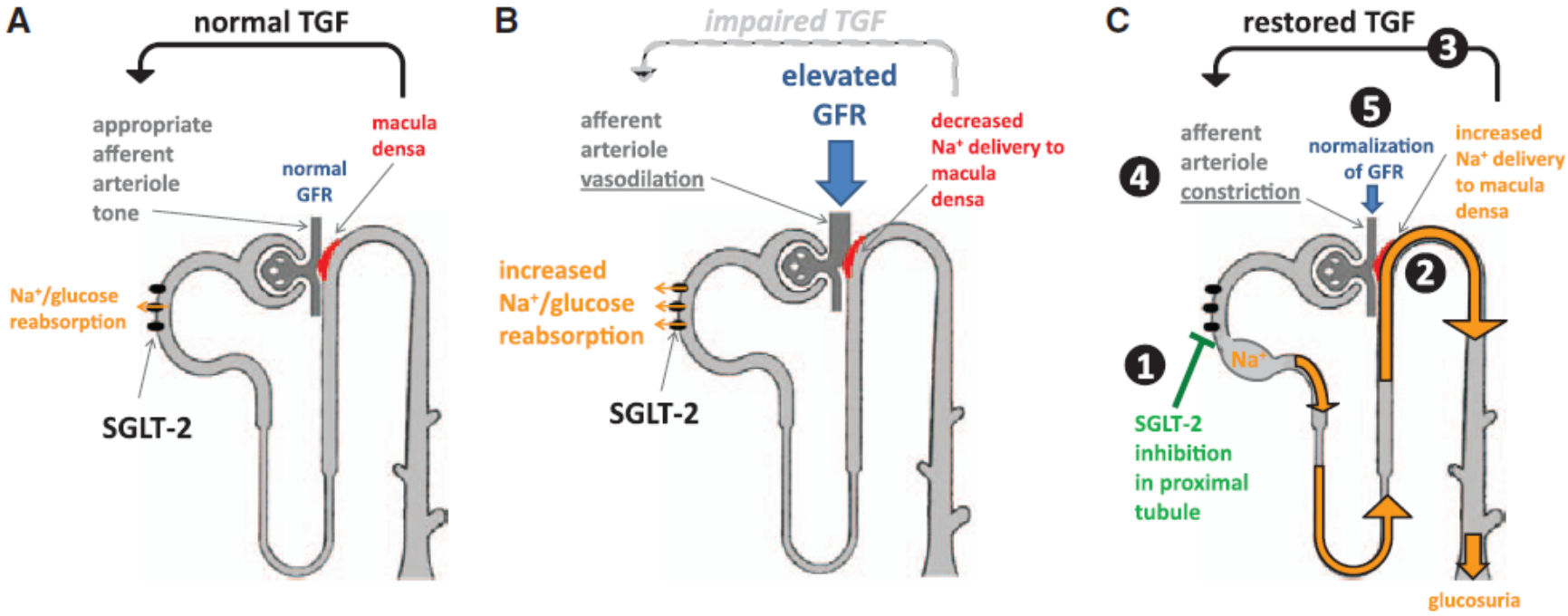


Sktic *et al. Diabetologia* 2014;57:2599.

Novas ferramentas no manejo do DBT

Inibidores de SGLT-2

Hiperfiltração no DBT



Normal physiology

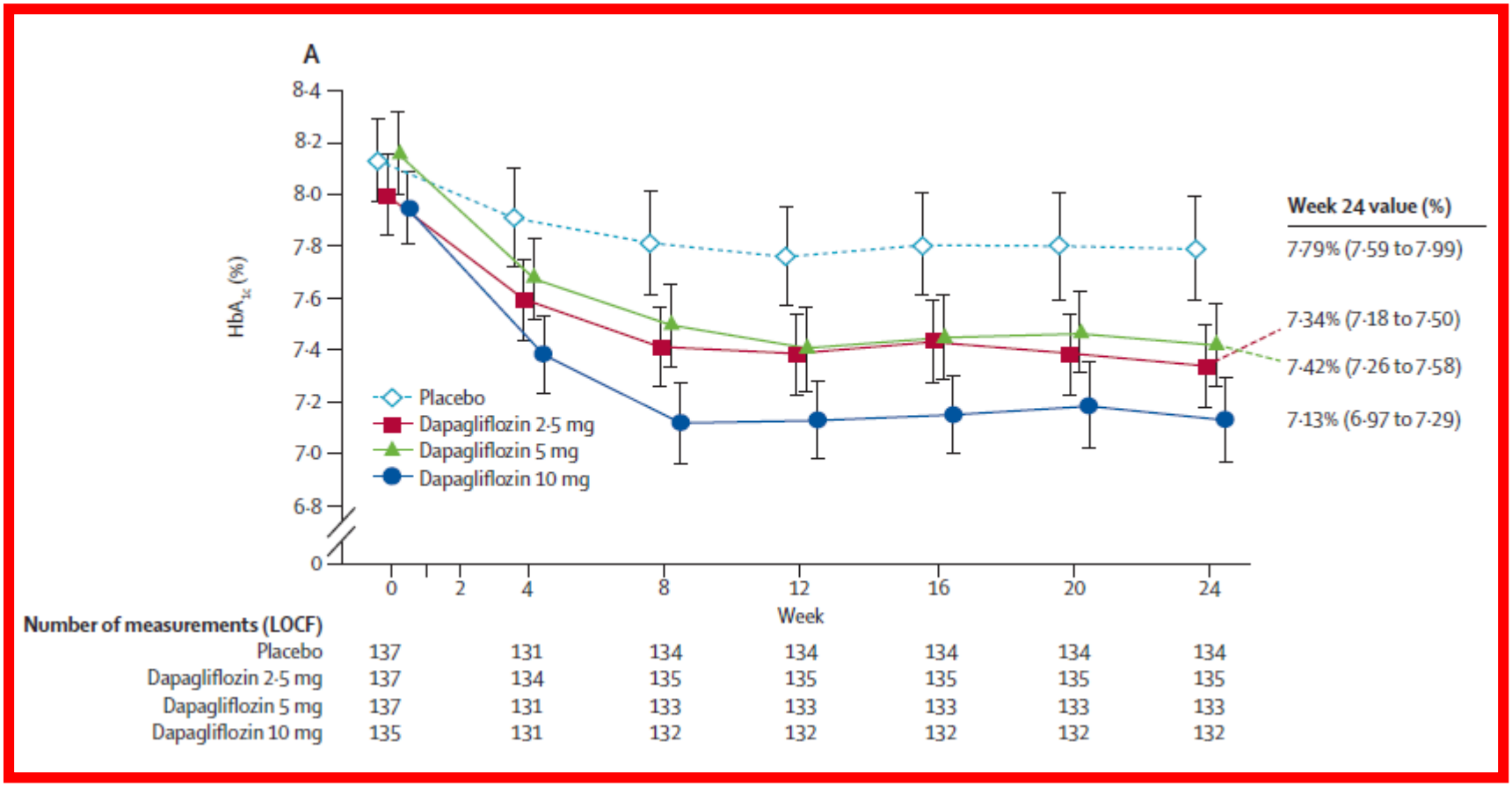
Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

Cherney *et al. Circulation* 2014 Feb 4;129:587.

Efeito da dapagliflozina (inibidor seletivo do cotransportador de Na-glicose SGLT-2) sobre os parâmetros metabólicos no DBT tipo 2

Efeito sobre os níveis de HbA1c

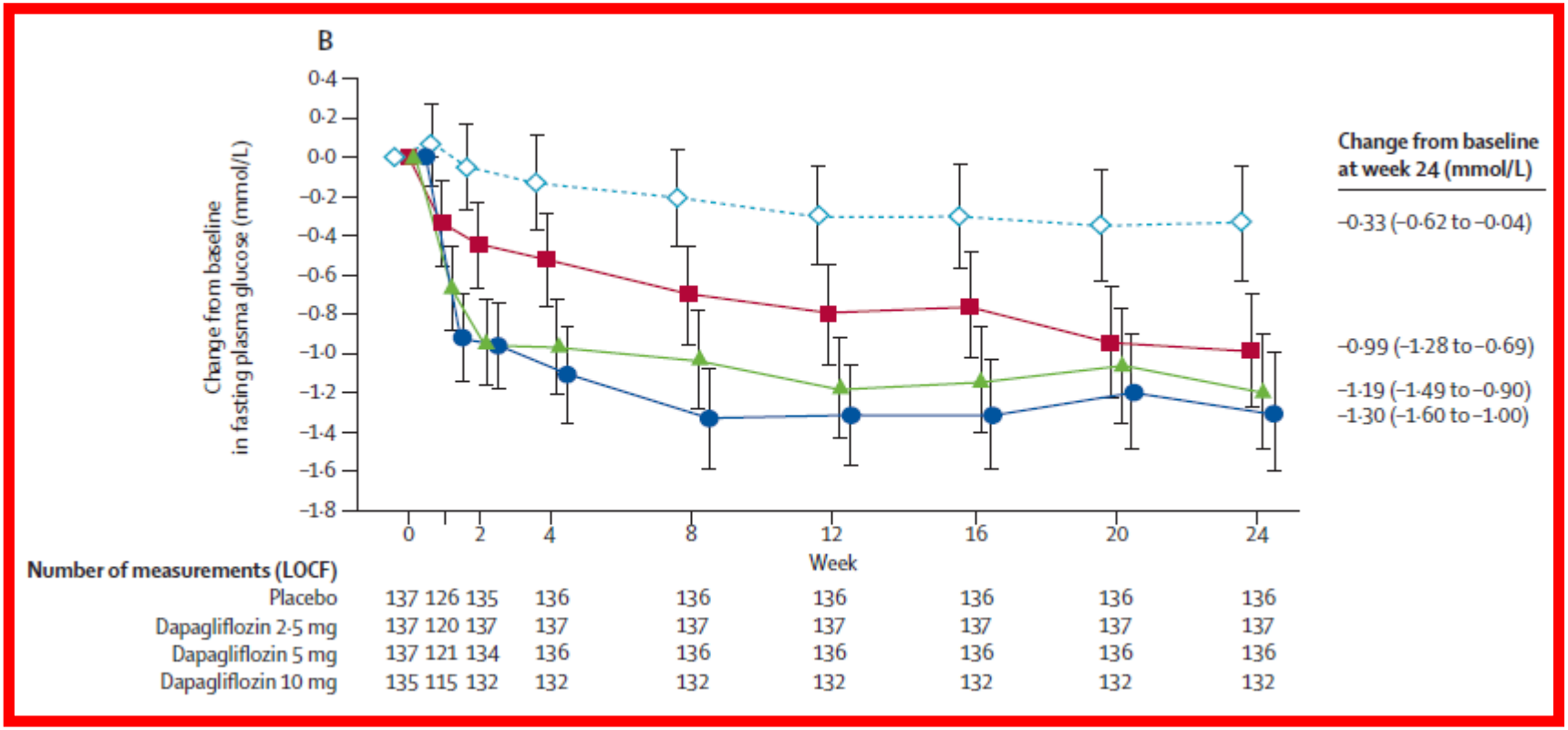


Number of measurements (LOCF)							
Placebo	137	131	134	134	134	134	134
Dapagliflozin 2·5 mg	137	134	135	135	135	135	135
Dapagliflozin 5 mg	137	131	133	133	133	133	133
Dapagliflozin 10 mg	135	131	132	132	132	132	132

Bailey *et al. Lancet* 2010;375:2223.

Efeito da dapagliflozina (inibidor seletivo do cotransportador de Na-glicose SGLT-2) sobre os parâmetros metabólicos no DBT tipo 2

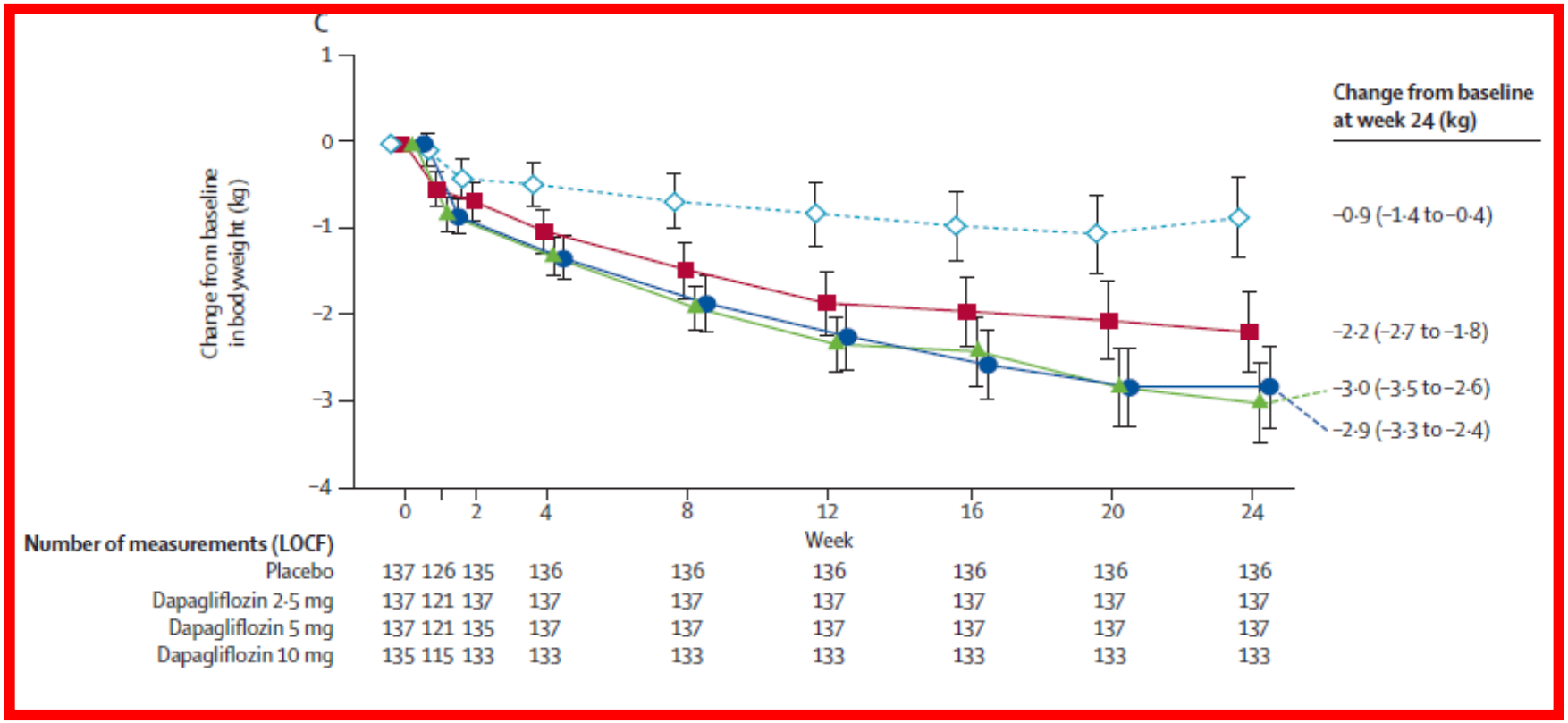
Efeito sobre os níveis da glicose em jejum



Bailey *et al. Lancet* 2010;375:2223.

Efeito da dapagliflozina (inibidor seletivo do cotransportador de Na-glicose SGLT-2) sobre os parâmetros metabólicos no DBT tipo 2

Efeito sobre o peso corporal

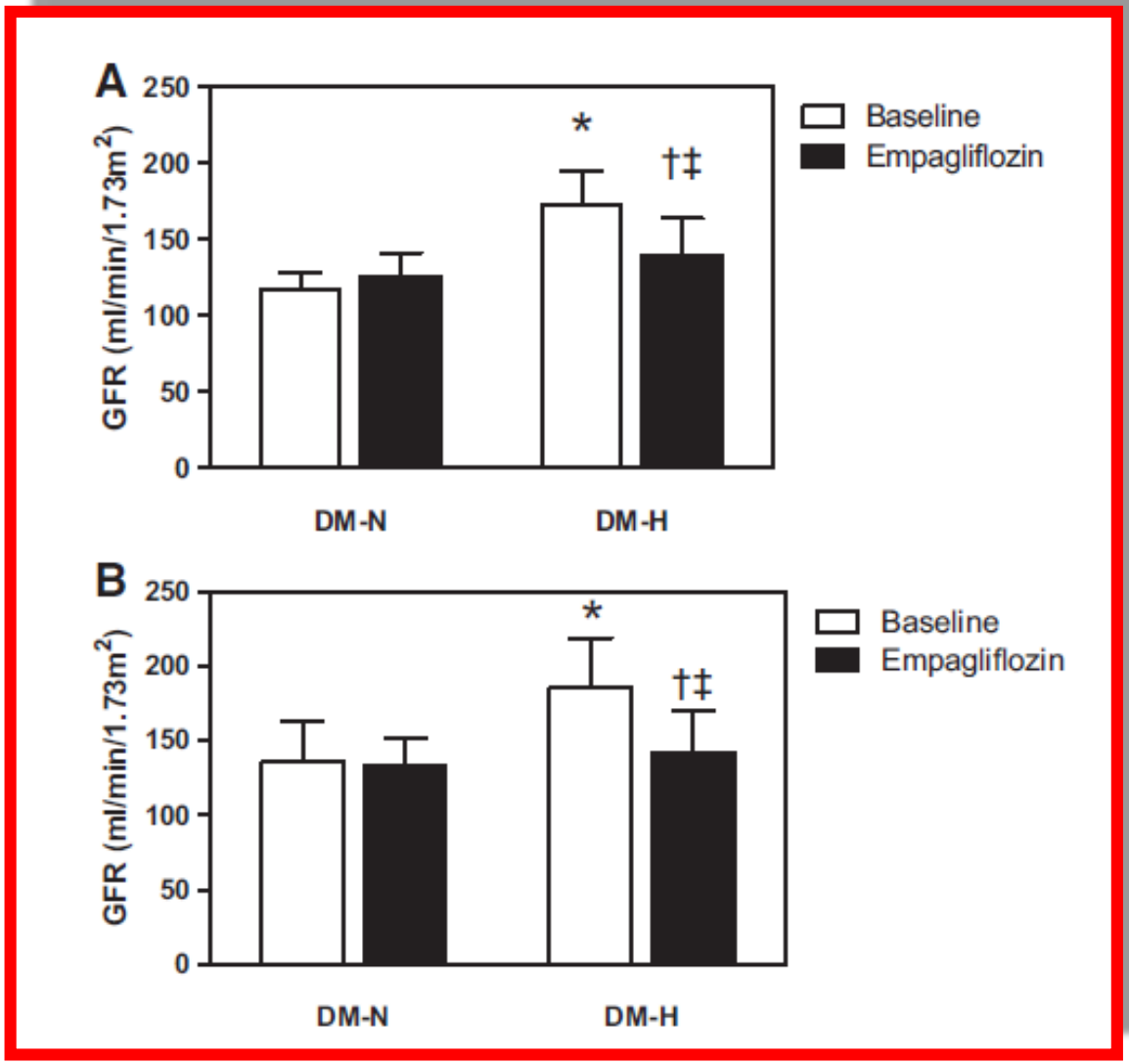


Bailey *et al.* *Lancet* 2010;375:2223.

Hiperfiltração no DBT – Uso de bloqueadores de SGLT2

40 ptes. DBT1
8 sem. empagliflozina 25 mg
Grupos c/euglicemia ou hiperG

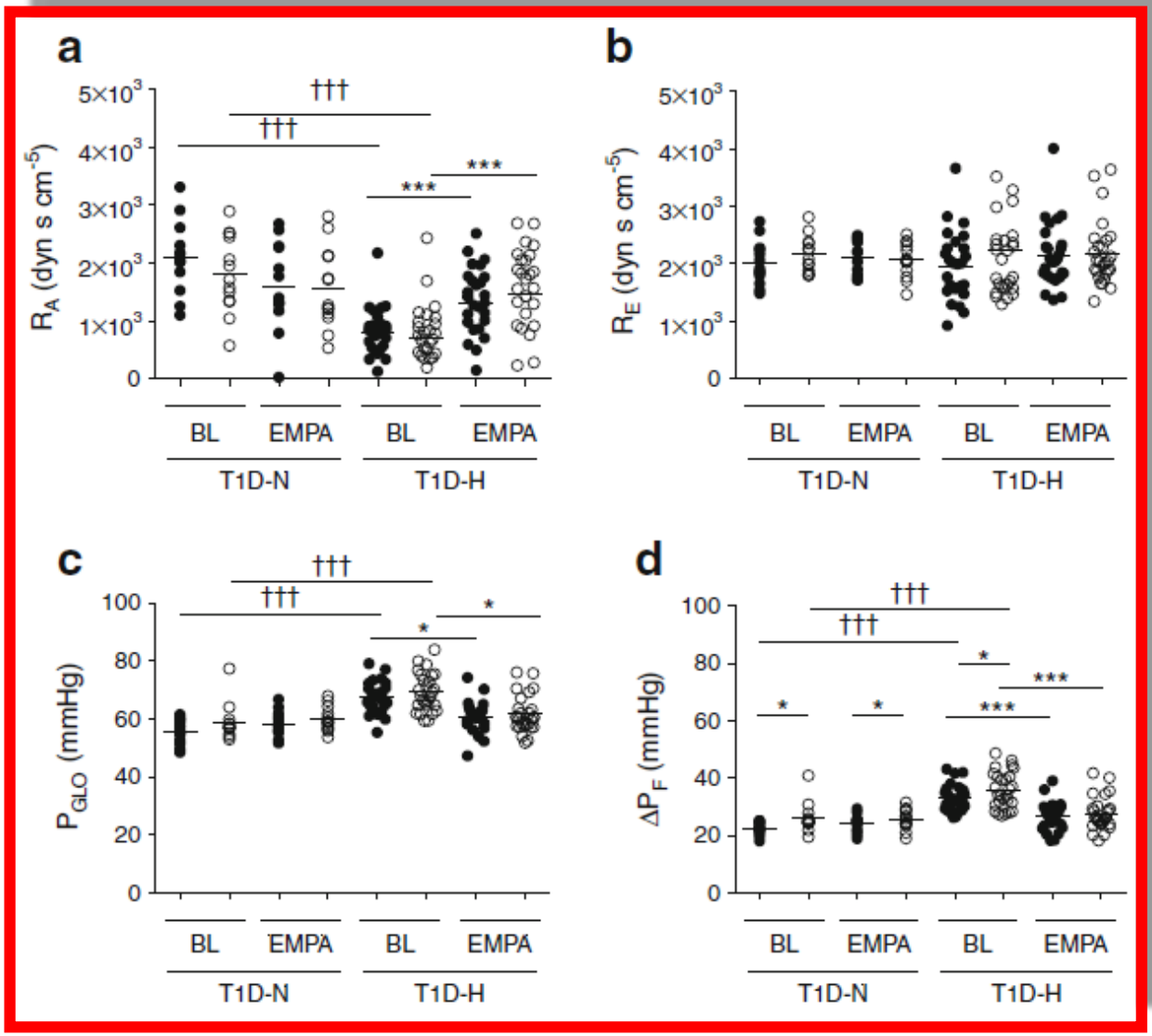
DM-N: normofiltrantes
DM-H: hiperfiltrantes



Cherney *et al. Circulation* 2014 Feb 4;129:587.

Hiperfiltração glomerular – Resposta hemodinâmica aos inibidores de SGLT2

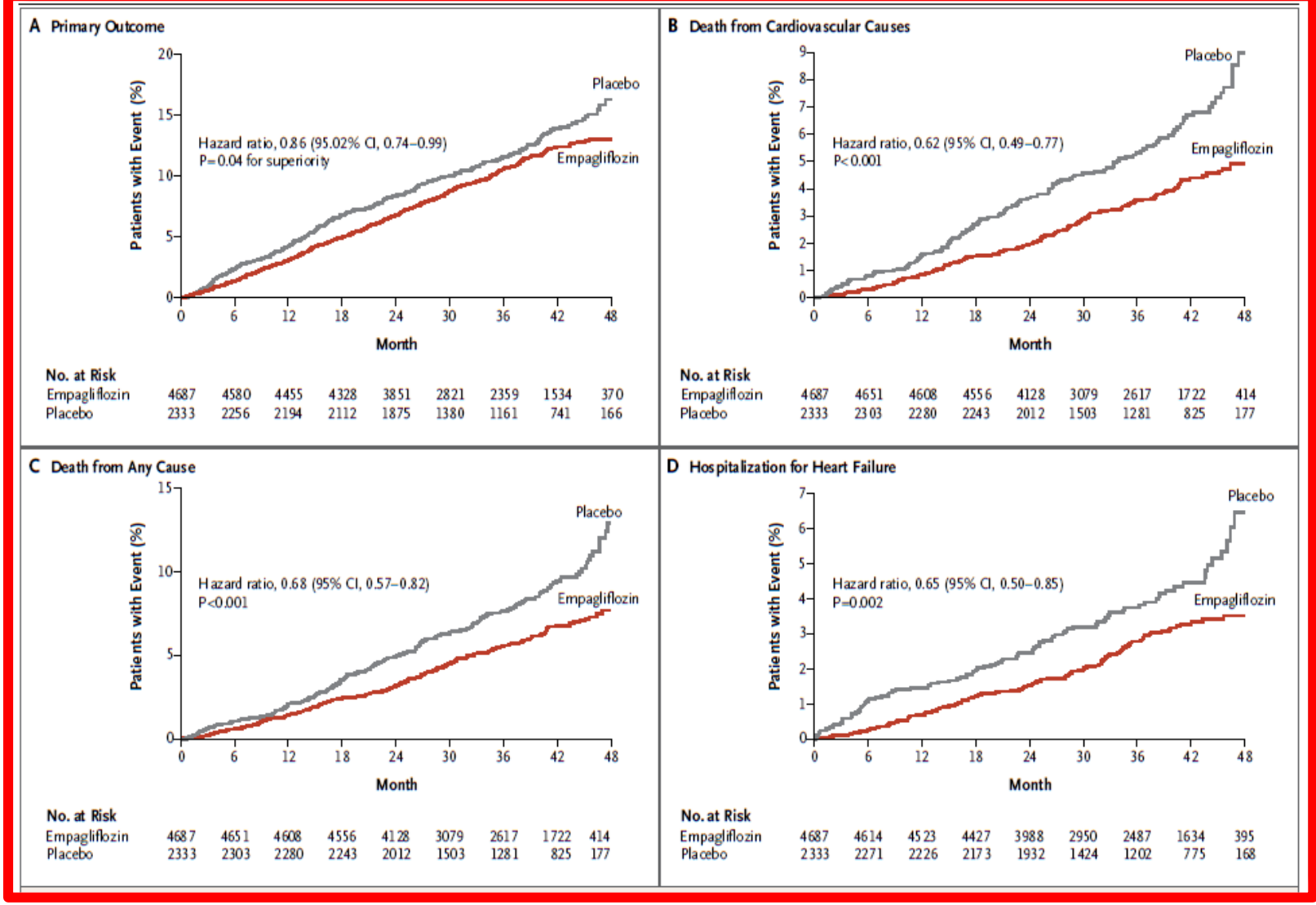
T1D-N: DBT1 NF
T1D-H: DBT1 HF
BL: basal
EMPA: empagliflozina
clampeamento EuGl
clampeamento HiperGl



Sktic *et al. Diabetologia* 2014;57:2599.

Inibidores de SGLT2 – Resultados cardiovasculares

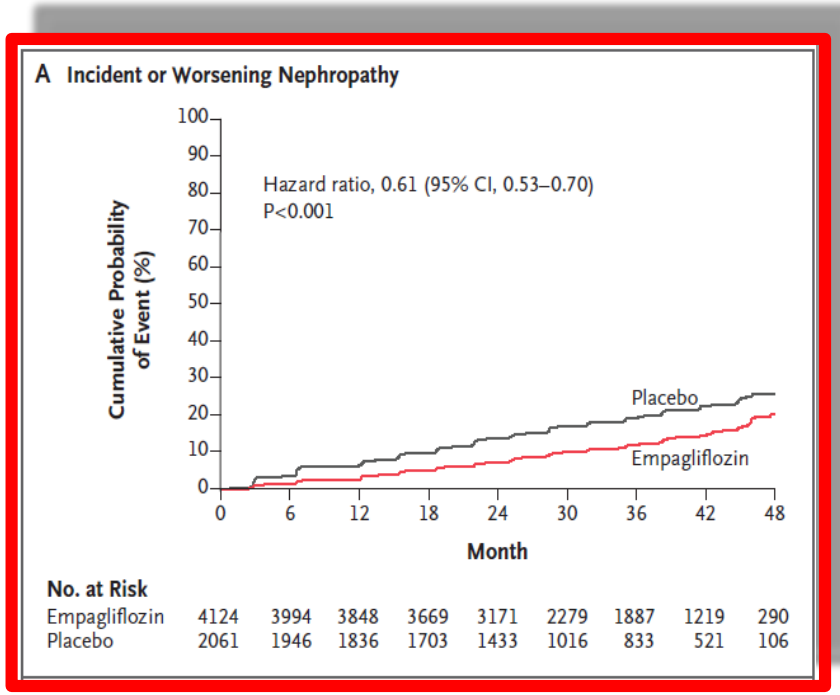
7020 ptes. DBT2

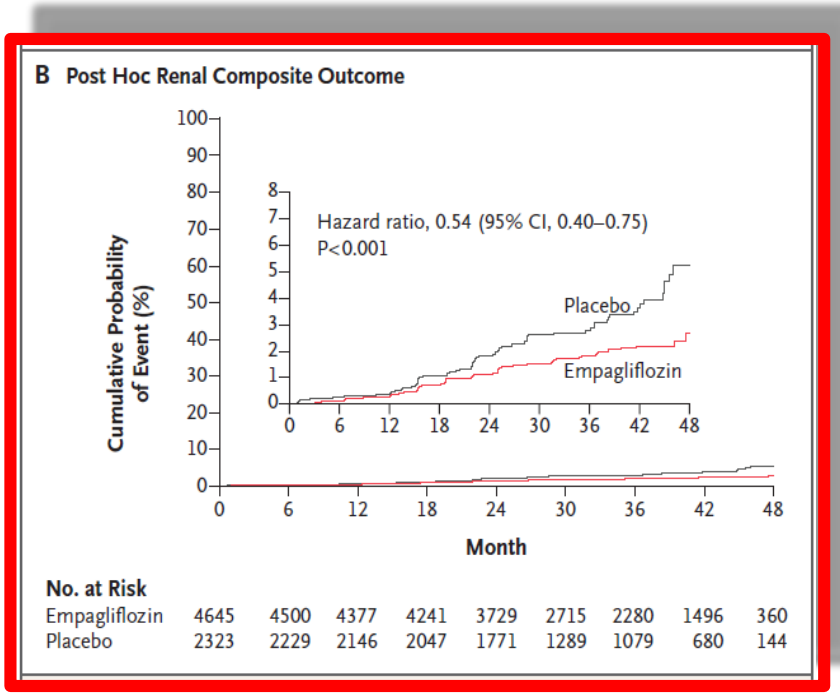


Zinman *et al.* *NEJM* 2016;373:2117.

Inibidores de SGLT2 – Evolução da nefropatia

7020 ptes. DBT2





Wanner *et al.* *NEJM* 2016;375:323.

Inibidores de SGLT2 – Evolução da nefropatia

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

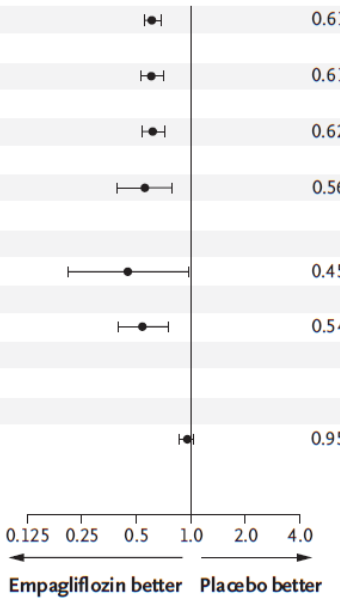


Figure 2. Risk Comparison for Seven Renal Outcomes.

All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.

Wanner *et al.* *NEJM* 2016;375:323.

Inibidores de SGLT2 – Resultados gerais

Table 3. End points of the EMPA-REG OUTCOME Trial

Outcome	Hazard Ratio Compared with Placebo (95% CI)
Prespecified	
Primary MACE (CV death, nonfatal MI, or nonfatal stroke)	0.86 (0.74 to 0.99)
CV death	0.62 (0.49 to 0.77)
All-cause mortality	0.68 (0.57 to 0.82)
Hospitalization for heart failure	0.65 (0.50 to 0.85)
Exploratory	
New onset of macroalbuminuria	0.62 (0.54 to 0.72)
New onset or worsening of DKD	0.61 (0.53 to 0.70)
Doubling of serum creatinine[a]	0.56 (0.39 to 0.79)
Initiation of RRT	0.45 (0.21 to 0.97)

Created with data from the supplemental appendix of the Randomized, Placebo-Controlled Cardiovascular Outcome Trial of Empaglifozin (EMPA-REG OUTCOME) (5,6). At baseline, the study population had an average eGFR of approximately 74 ml/min per 1.73 m^2. 95% CI, 95% confidence interval; MACE, major adverse cardiovascular event; CV, cardiovascular; MI, myocardial infarction; DKD, diabetic kidney disease.

[a]Accompanied by eGFR≤45 ml/min per 1.73 m^2.

Van Bommel *et al.* *CAJS* 2017 (no prelo).

Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis

Jason H Y Wu, Celine Foote*, Juuso Blomster, Tadashi Toyama, Vlado Perkovic, Johan Sundström, Bruce Neal*

Summary

Background In patients with type 2 diabetes, sodium-glucose cotransporter-2 (SGLT2) inhibitors are known to reduce glucose concentrations, blood pressure, and weight, but to increase LDL cholesterol and the incidence of urogenital infections. Protection against cardiovascular events has also been reported, as have possible increased risks of adverse outcomes such as ketoacidosis and bone fracture. We aimed to establish the effects of SGLT2 inhibitors on cardiovascular events, death, and safety outcomes in adults with type 2 diabetes, both overall and separately for individual drugs.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Library, and websites of US, European, and Japanese regulatory authorities from Jan 1, 1950, to Sept 30, 2015, for data from prospective randomised controlled trials assessing the effects of SGLT2 treatment compared with controls. We excluded duplicate reports, trials of compound drugs, trials that lasted 7 days or fewer, trials that did not report on outcomes of interest, and articles that presented pooled trial data for which the individual trials could not be identified. We extracted data in duplicate using a standardised approach. The primary outcome was major adverse cardiovascular events. Secondary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, admission to hospital for unstable angina, heart failure, and all-cause mortality. We estimated summary relative risks with fixed-effects meta-analysis, with the I^2 statistic used to estimate heterogeneity of results beyond chance.

Findings The analyses included data from six regulatory submissions (37 525 participants) and 57 published trials (33 385 participants), which provided data for seven different SGLT2 inhibitors. SGLT2 inhibitors protected against the risk of major adverse cardiovascular events (relative risk 0·84 [95% CI 0·75–0·95]; p=0·006), cardiovascular death (0·63 [0·51–0·77]; p<0·0001), heart failure (0·65 [0·50–0·85]; p=0·002), and death from any cause (0·71 [0·61–0·83]; p<0·0001). No clear effect was apparent for non-fatal myocardial infarction (0·88 [0·72–1·07]; p=0·18) or angina (0·95 [0·73–1·23]; p=0·70), but we noted an adverse effect for non-fatal stroke (1·30 [1·00–1·68]; p=0·049). We noted no clear evidence that the individual drugs had different effects on cardiovascular outcomes or death (all I^2<43%). Safety analyses showed consistent increased risks of genital infections (regulatory submissions 4·75 [4·00–5·63]; scientific reports 2·88 [2·48–3·34]), but findings for some safety outcomes varied depending on whether anlayses were based on data extracted from regulatory submissions or trials reported in the scientific literature.

Lancet Diabetes Endocrinol 2(

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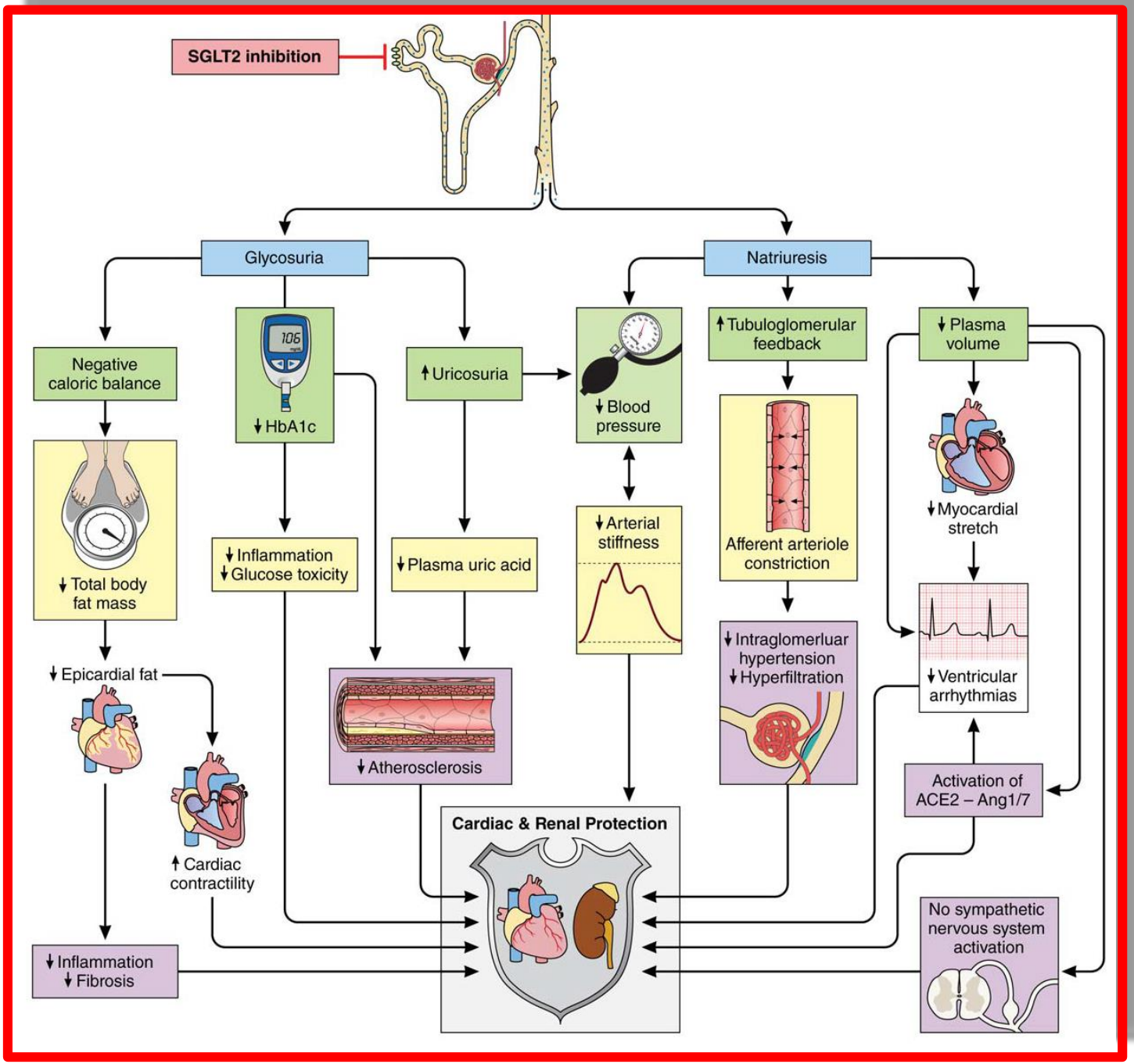
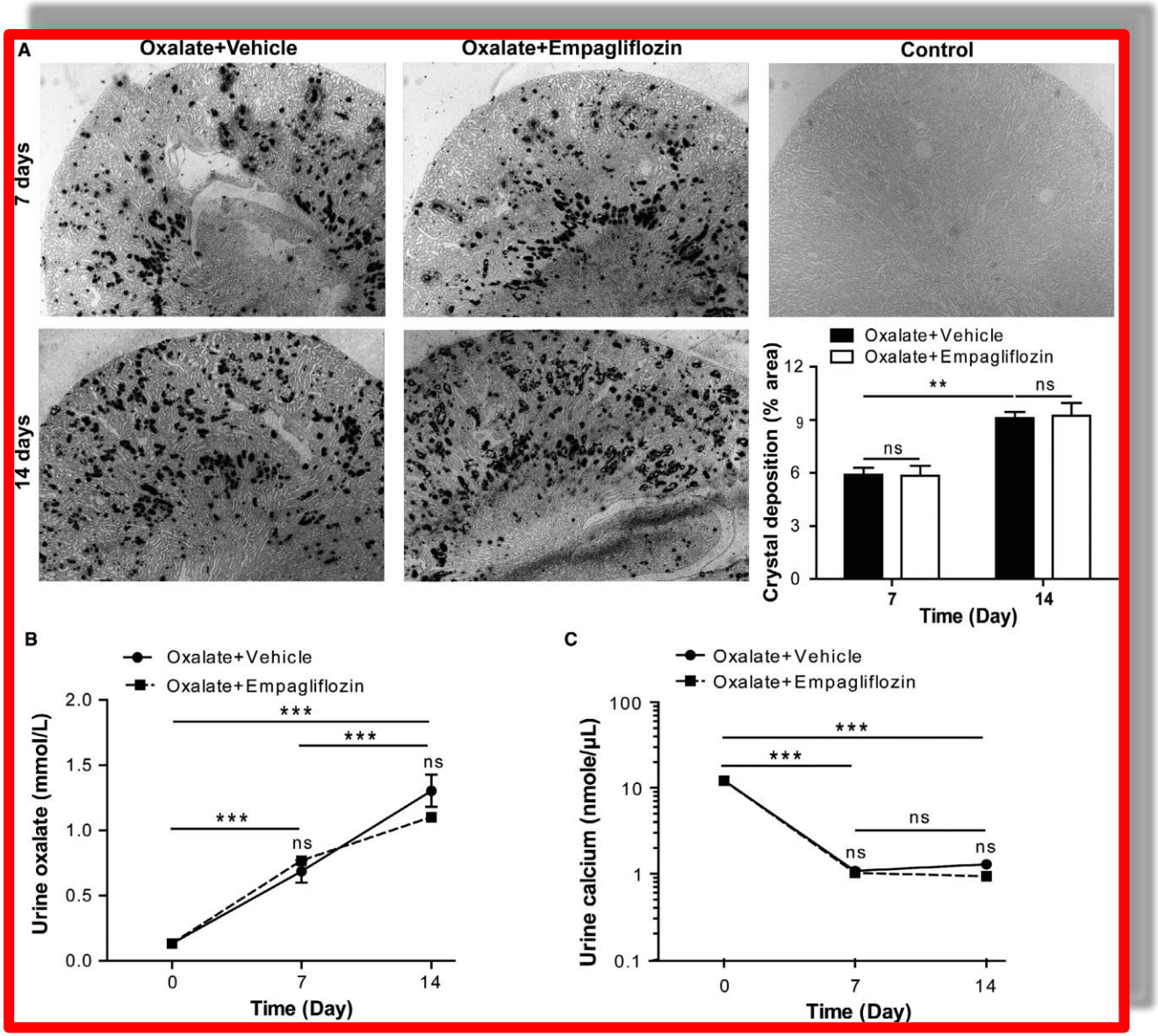
*Contributed equally

The George Institute for Glo Health, University of Sydne Camperdown, Sydney, NSW Australia (J H Y Wu PhD, C Foote PhD, J Blomster PhD, T Toyama PhD, Prof V Perkovic PhD, Prof J Sundström PhD, Prof B Neal PhD); **Concord Repatriation General Hospit Concord, Sydney, NSW, Australia** (C Foote); **Universi of Turku, Turku, Finland, an Sahlgrenska Academy at University of Gothenberg, Gothenberg, Sweden** (J Blomster); **Royal Prince Alf Hospital, Camperdown, Sydney, NSW, Australia** (V Perkovic, B Neal); **Department of Medical Sciences, Uppsala Clinical**



Heerspink *et al. Circulation* 2016;134:752.

Inibidores de SGLT2 em outras nefropatias crônicas



Ma *et al. Physiol Rep* 20170 Apr;5(7). pii: e13228

Nephrol Dial Transplant (2008) 23: 3946–3952
doi: 10.1093/ndt/gfn379
Advance Access publication 12 July 2008

Original Article

Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption

Avry Chagnac[1,2], Michal Herman[1,2], Boris Zingerman[1], Arie Erman[1,2], Benaya Rozen-Zvi[1], Judith Hirsh[1] and Uzi Gafter[1,2]

Nephrol Dial Transplant (2015) 0: 1–7
doi: 10.1093/ndt/gfv385

Original Article

Increased risk of glomerular hyperfiltration in subjects with impaired glucose tolerance and newly diagnosed diabetes

Park *et al. BMC Nephrology* (2016) 17:3
DOI 10.1186/s12882-015-0218-y

BMC Nephrology

RESEARCH ARTICLE Open Access

Association between lower serum bicarbonate and renal hyperfiltration in the general population with preserved renal function: a cross-sectional study

Minseon Park[1], Rina So[2], Kwon Wook Joo[3] and Hyung-Jin Yoon[2*]

PLOS ONE

RESEARCH ARTICLE

Abdominal Adipose Tissue was Associated with Glomerular Hyperfiltration among Non-Diabetic and Normotensive Adults with a Normal Body Mass Index

Jeonghwan Lee[1☯], Hye Jin Kim[2☯], Belong Cho[2], Jin Ho Park[2], Ho Chun Choi[2], Cheol Min Lee[3], Seung Won Oh[3], Hyuktae Kwon[3‡*], Nam Ju Heo[4‡*]

AJKD
Original Investigation

Prediabetes and Risk of Glomerular Hyperfiltration and Albuminuria in the General Nondiabetic Population: A Prospective Cohort Study

Toralf Melsom, MD, PhD,[1,2] Jørgen Schei, MD,[1,3] Vidar Tor Nyborg Stefansson, MD,[1] Marit Dahl Solbu, MD, PhD,[1,2] Trond Geir Jenssen, MD, PhD,[1,4] Ulla Dorte Mathisen, MD, PhD,[1] Tom Wilsgaard, PhD,[5] and Bjørn Odvar Eriksen, MD, PhD[1,2,3]

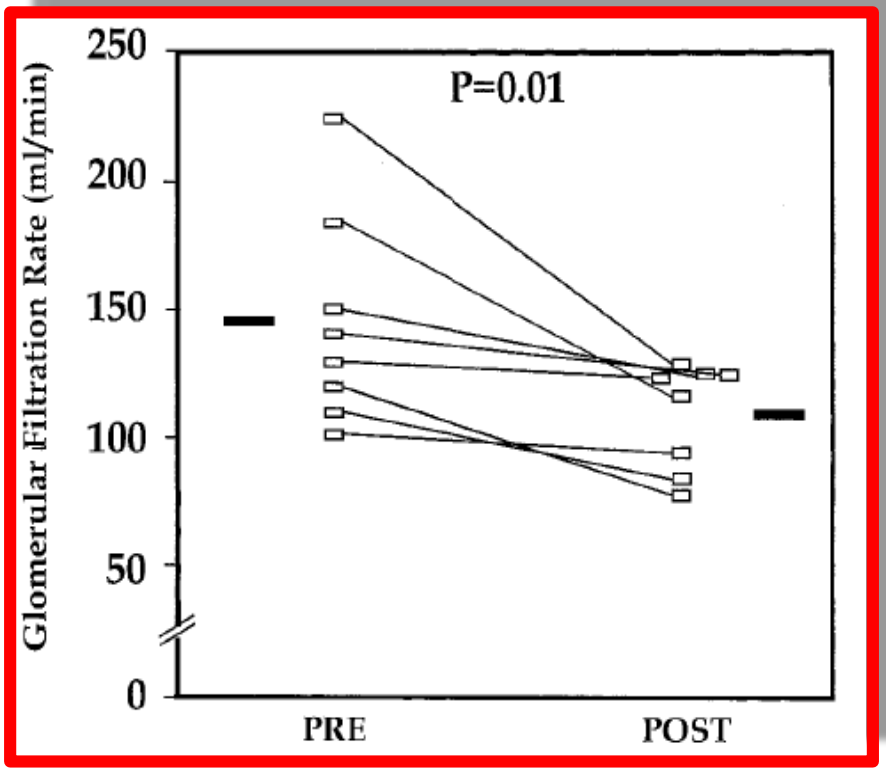
CLINICAL EPIDEMIOLOGY www.jasn.org

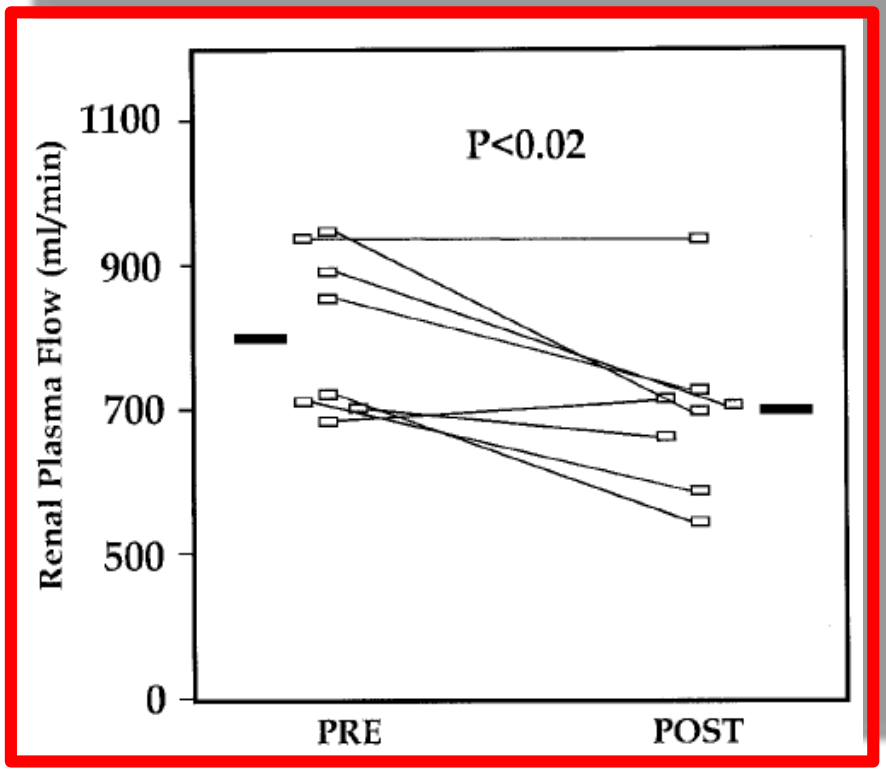
Renal Hyperfiltration as a Novel Marker of All-Cause Mortality

Minseon Park,* Eunsil Yoon,† Youn-Hee Lim,†§ Ho Kim,†§ Jinwook Choi,‖ and Hyung-Jin Yoon‖

Hemodinâmica glomerular em obesos
Efeitos da perda de peso

Perda de peso de ± 48 kg em 12 a 18 meses





Chagnac *et al. J Am Soc Nephrol* 2003;14:1480.

Hiperfiltração glomerular em obesos
Efeitos da ACZ e furosemida

	Acetazolamide		Furosemide	
	Pre	Post	Pre	Post
Serum sodium (mmol/L)	138.8±1.5	139.0±1.6	138.7±1.7	138.5±1.9
Urine sodium excretion rate (μmol/min)	216±76	521±139*	239±84	600±202*
Fractional lithium excretion	0.166±0.056	0.267±0.058*	0.167±0.050	0.212±0.062‡
Lithium clearance (ml/min)	24.6±8.3	31.9±8.9*	24.8±7.1	29.2±8.7‡

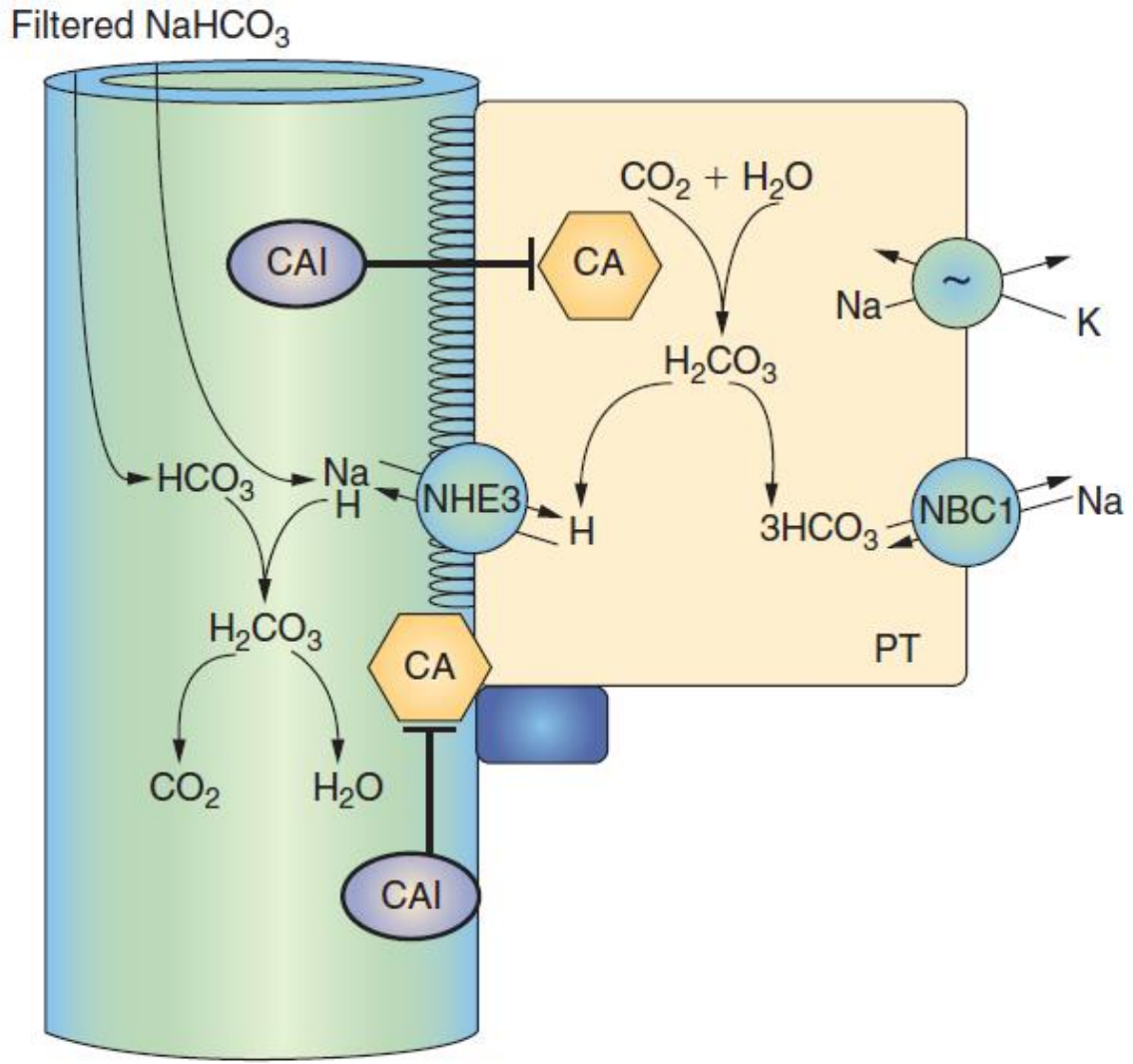
* P = 0.000
‡ P = 0.02

	Acetazolamide		Furosemide	
	Pre	Post	Pre	Post
Serum albumin (g/L)	46.3±3.1	46.1±3.0	46.2±2.9	45.9±3.2
Serum total protein (g/L)	72.3±3.1	72.2±3.6	71.6±3.9	71.4±3.9
Systolic arterial pressure (mm Hg)	127±11	128±10	127±11	130±10
Diastolic arterial pressure (mm Hg)	80±11	80±11	80±10	83±10§

§ P = 0.025

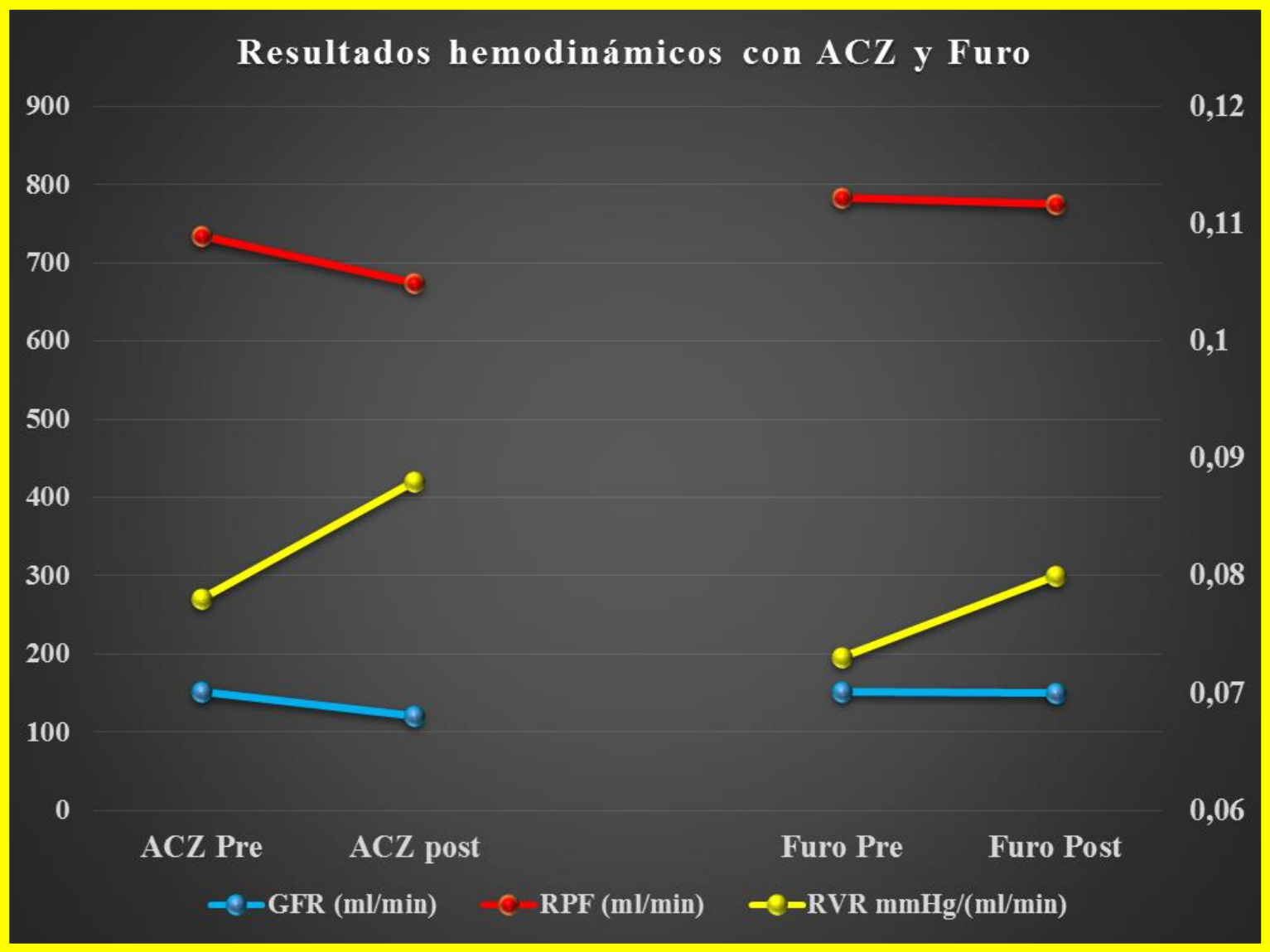
Zingerman *et al. PLoS One* 2015 Sep 14;10(9):e0137163.

Ações tubulares da acetazolamida



Brenner & Rector's The Kidney. Elsevier, 10th ed., 2016.

Hiperfiltração glomerular em obesos – Efeitos da ACZ e furosemida

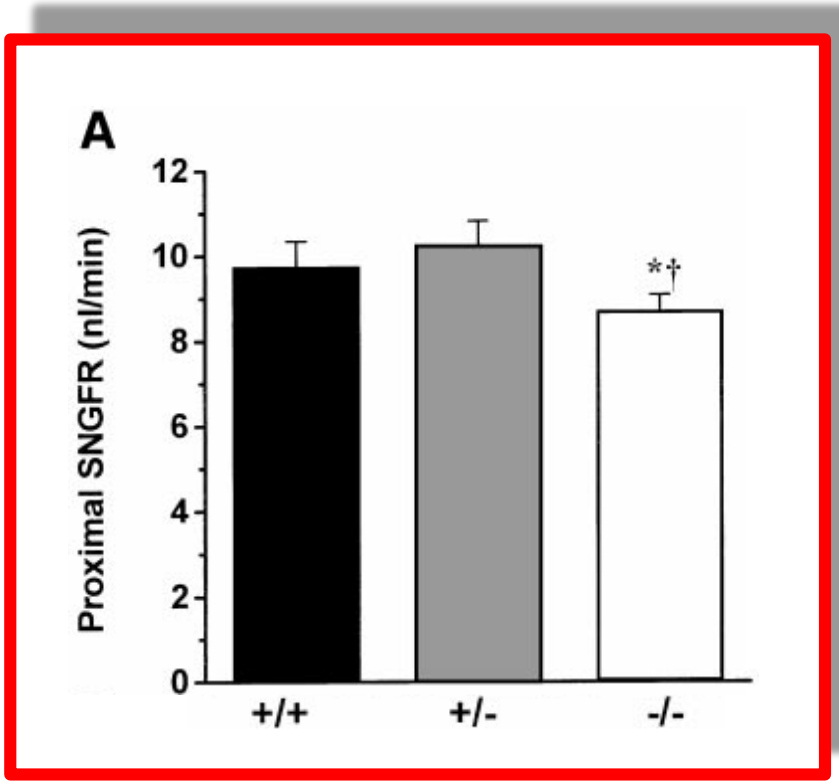


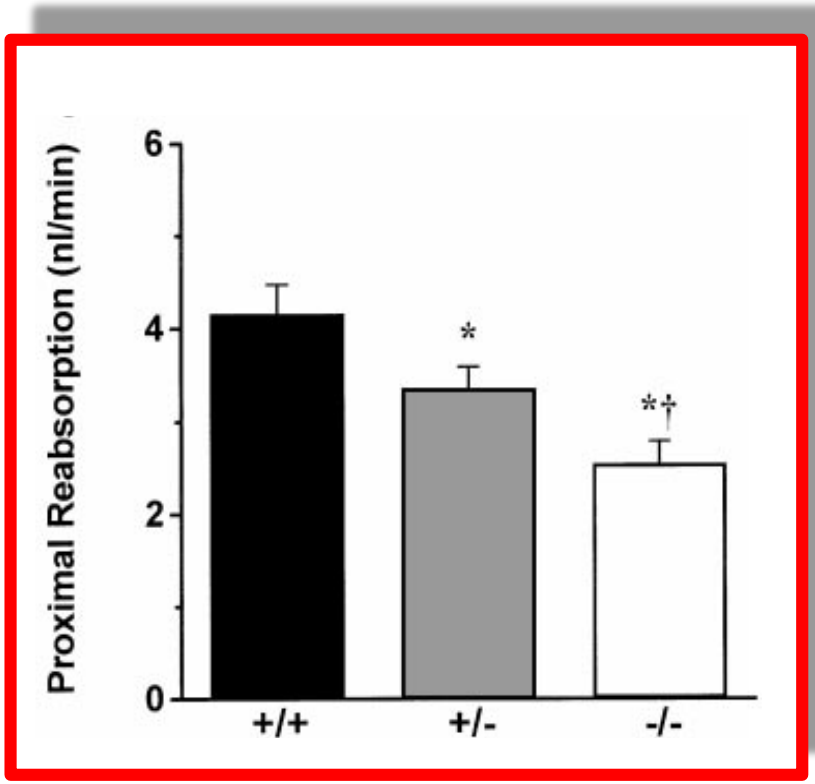
- **= < 0,05**
- **RVR: resistência vascular renal**

Zingerman *et al. PLoS One* 2015 Sep 14;10(9):e0137163.

Filtração glomerular e função tubular proximal

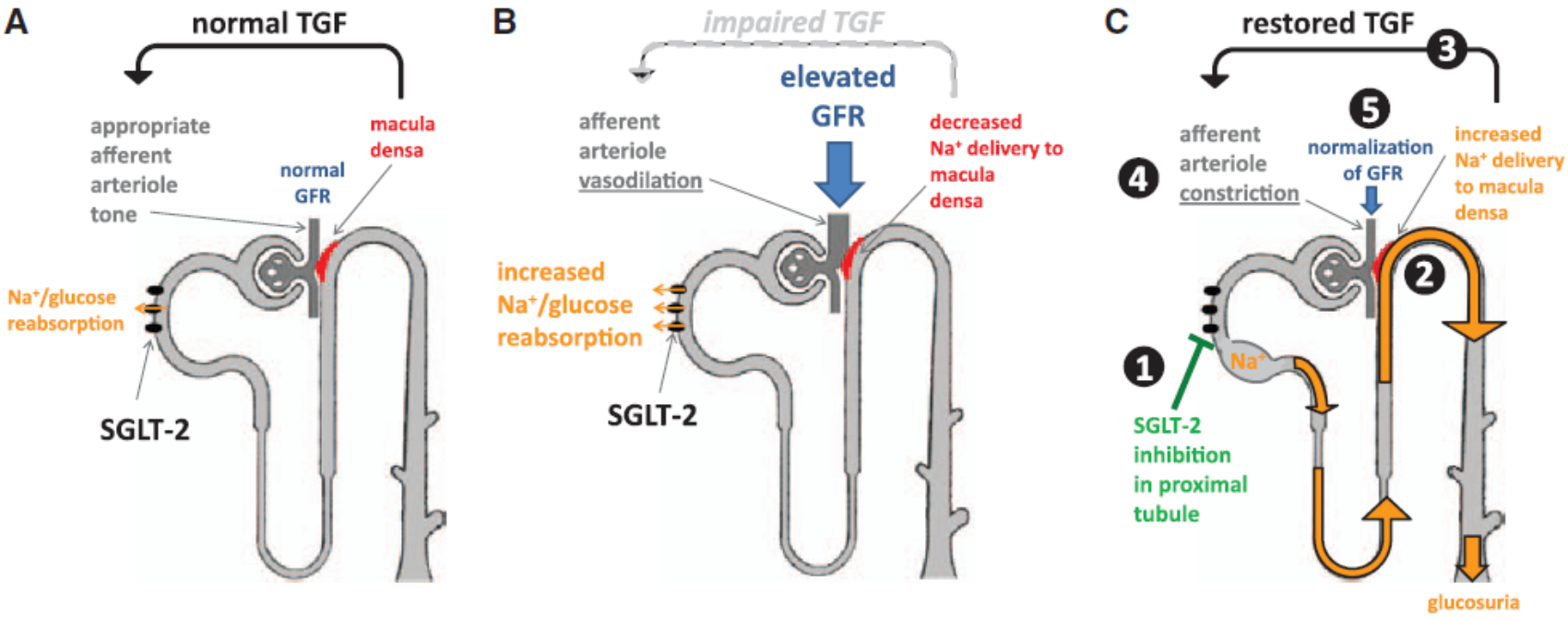
Ratos *knock-out* NHE3





Lorenz *et al. Am J Physiol* 1999;277:F447.

Hiperfiltração no DBT



Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

Cherney *et al. Circulation* 2014;4:129,587.

Pergunta aos residentes

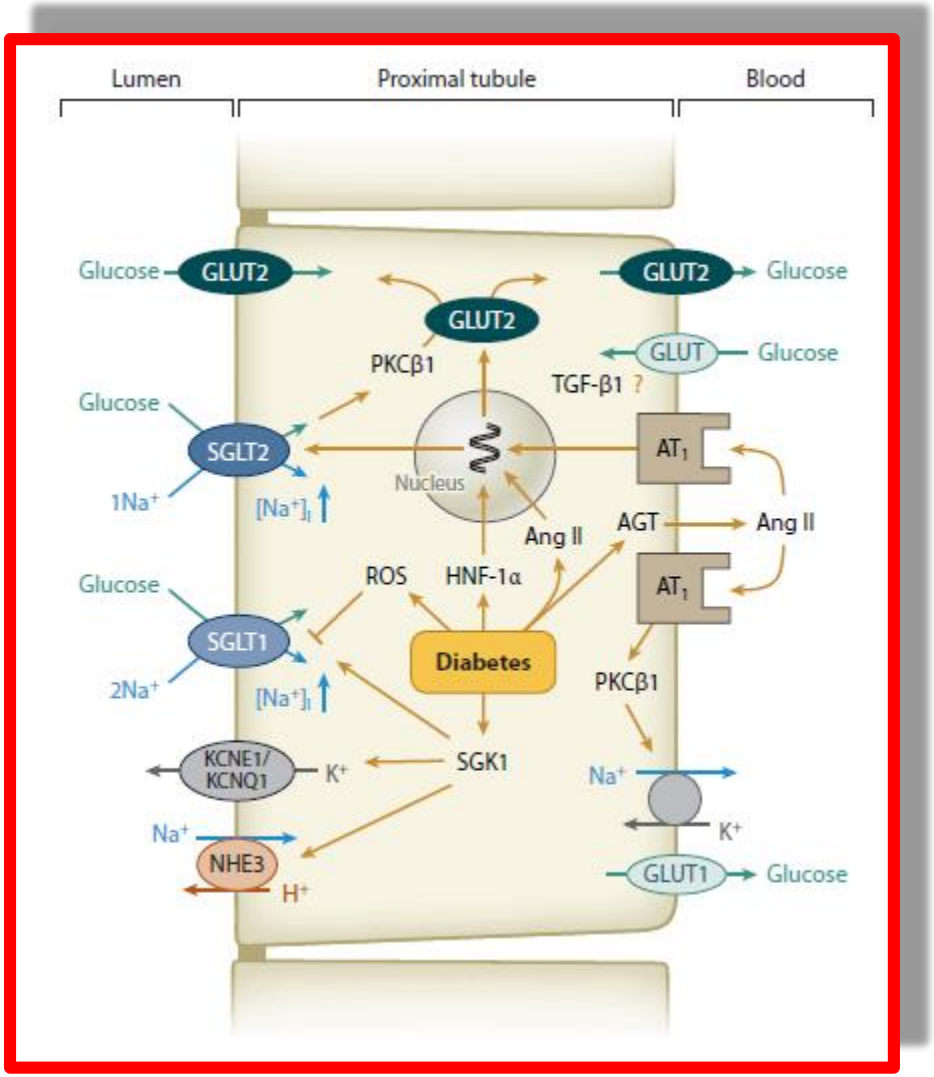
Consultado por pte. DBT1 de 22 anos, con ClCr de 169 ml/min/1,73 m^2, µalbuminúria (-), HbA1C de 7,9 % e normotenso. Após explicar a importância do cuidado do seu DBT e a repercussão que o seu estado pode gerar nos seus rins no médio e longo prazo, sua conduta seria:

1. Indicar enalapril, em dose a titular, como tratamento para sua HF. Aconselhar melhor cuidado do seu DBT.

2. Falaria com seu diabetologista, para fixar objetivos conjuntos de melhoria no cuidado do seu DBT, e controlaria o paciente em três meses, sem indicar enalapril.

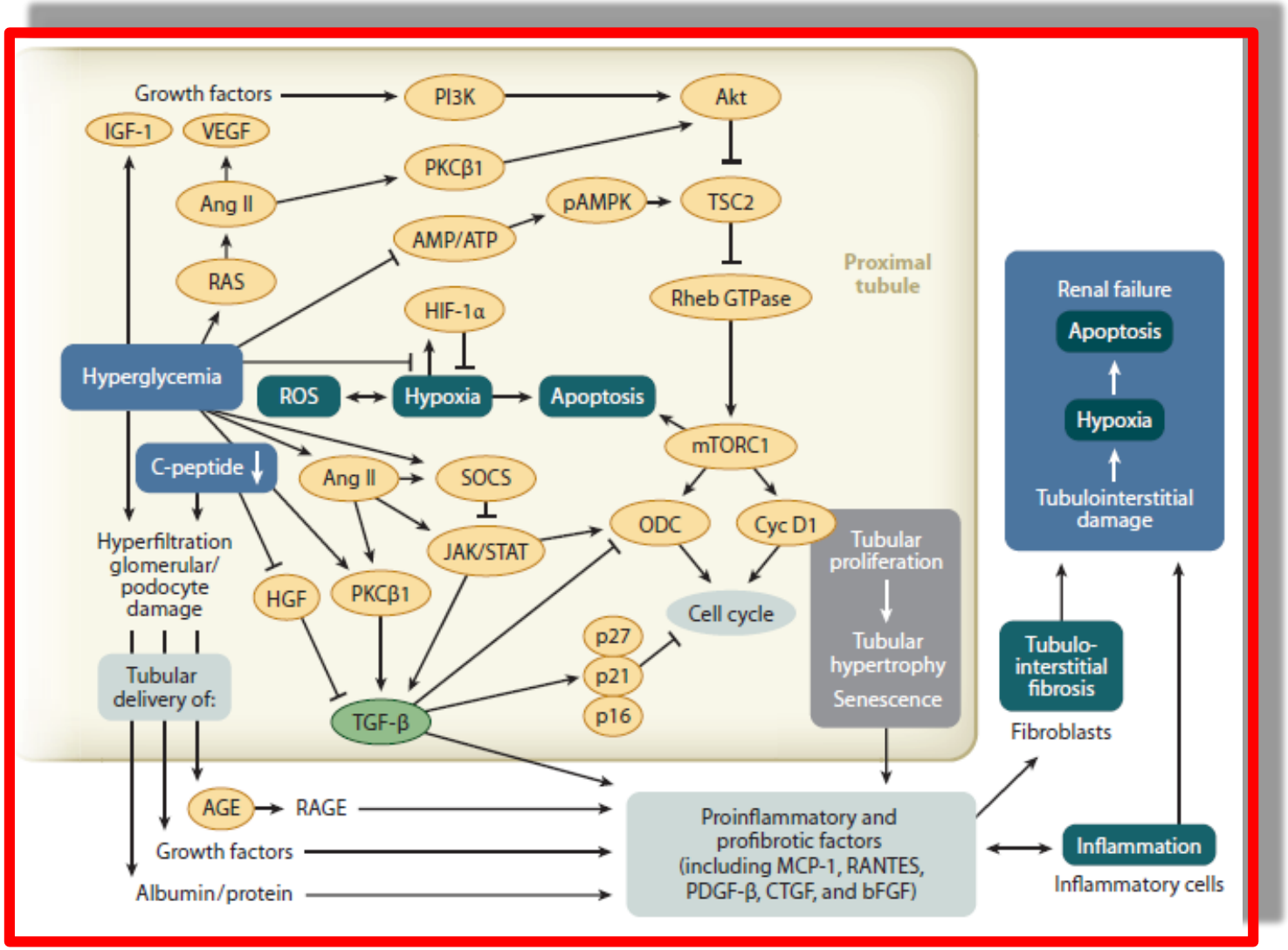
3. Indicaria empaglifozina 10 mg/d + enalapril, em dose a titular.

Reabsorção de Na+ e glicose no TCP



Vallon *et al. Annu Rev Physiol* 2012;74:351.

Mudanças fenotípicas e estruturais do TCP no DBT



Vallon *et al. Annu Rev Physiol* 2012;74:351.

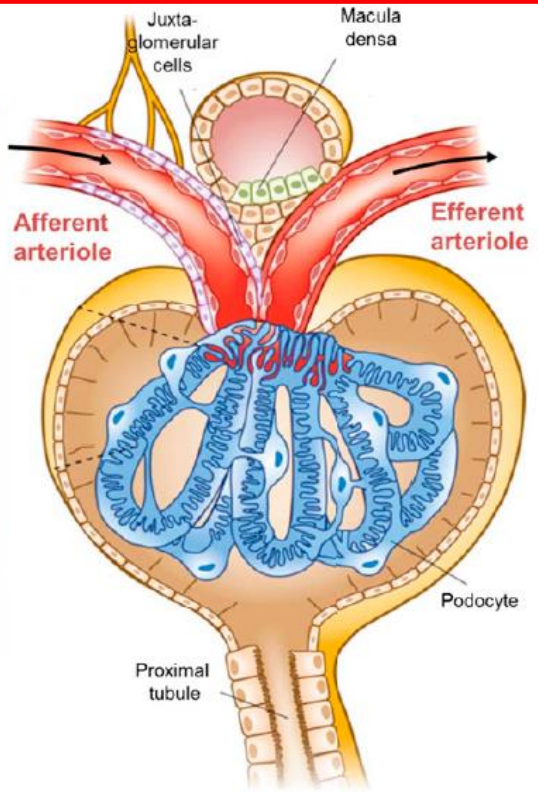
Inibidores de SGLT2 na Argentina

Dapagliflozina 10 mg (N.C.: **Forxiga**® x 28 comp.)
AstraZeneca

Empagliflozina 10 mg (N.C.: **Jardiance**® x 30 comp.)
Boehringer Ingelheim

Fatores que influenciam a filtração glomerular

Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)



Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin-II
Thromboxane A2
Endothelin-1 (ETA receptor)
Reactive oxygen species

Tonneijck *et al. J Am Soc Nephrol* 2017 (no prelo).

Hiperfiltração glomerular – Mensagens finais

- Afeta mais pacientes além dos DBT.
- Provavelmente a HF envolva um risco maior de mortalidade.
- Os aspectos hemodinâmicos variam entre as diversas patologias.
- Existem trabalhos utilizando diferentes agentes para seu tratamento fisiopatológico, como acetazolamida e bloqueadores de SGLT2.
- Essas drogas parecem conferir efeitos benéficos sobre aspectos CVC e renais, diminuindo a mortalidade e retardando a deterioração renal.
- O tempo do fim dos *pris* como monodrogas parece ter começado.

Muito obrigado