SIGG 2016
Napoli

S.B. Solerte
Università degli Studi di Pavia
bruno.solerte@unipv.it

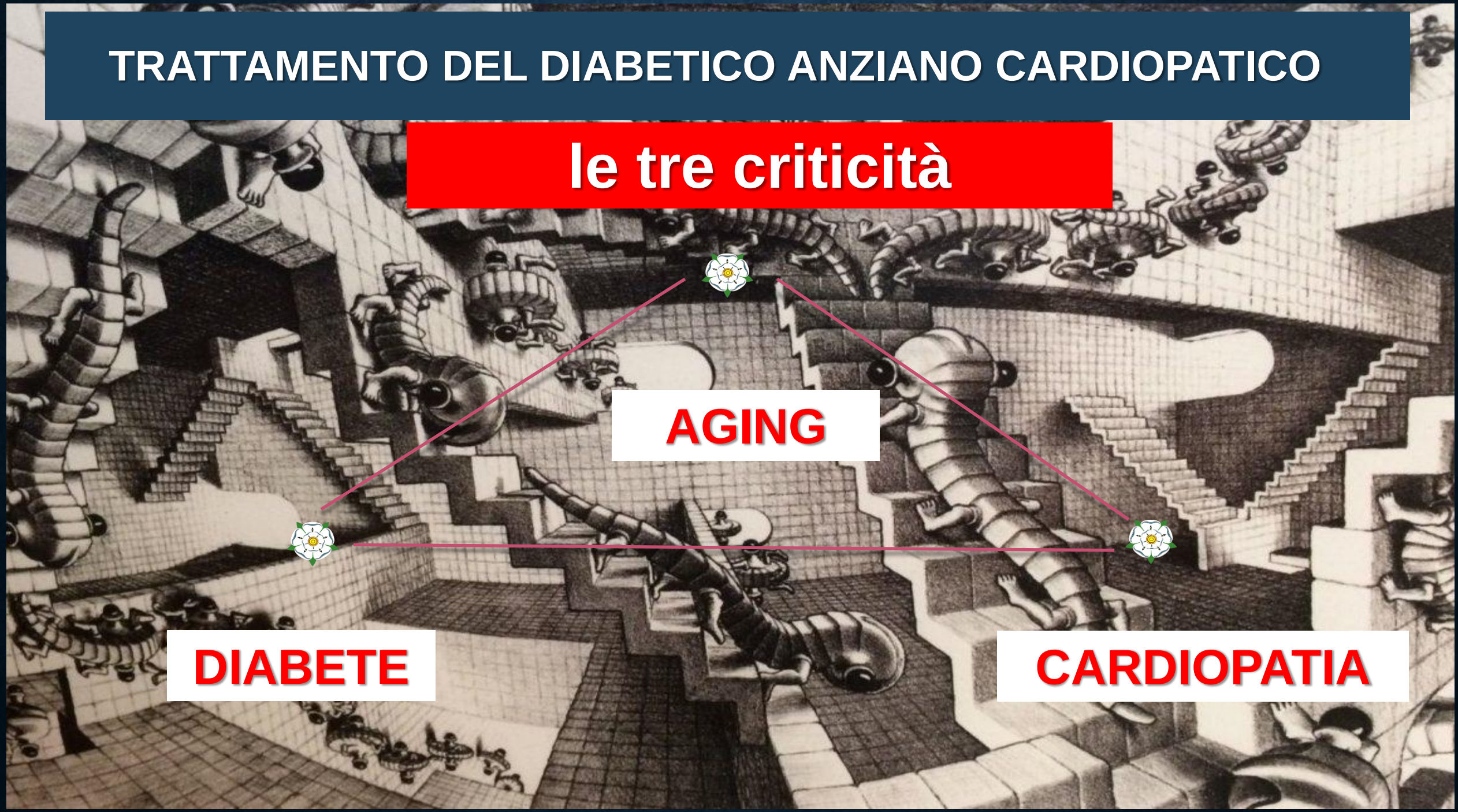
SIGG 2016
Napoli

S.B. Solerte
Università degli Studi di Pavia
bruno.solerte@unipv.it

IL CORRETTO APPROCCIO TERAPEUTICO DEL DIABETICO ANZIANO CARDIOPATICO

TRATTAMENTO DEL DIABETICO ANZIANO CARDIOPATICO

le tre criticità



i tre messaggi chiave

Essendo alta la complessità del paziente, la pre condizione clinica di partenza è la normalizzazione dell'iperglicemia evitando l'ipoglicemia, quindi: normoglicemia

Alta complessità = alta specificità del trattamento; la scelta dei farmaci cosiddetti anti diabetici si restringe quasi esclusivamente alle classi definite innovative (di ultima generazione)

I nuovi obiettivi del trattamento sono mirati alla protezione e prevenzione cardiovascolare ottenuti anche indipendentement e dagli effetti positivi sulla glicemia e sulla sua variabilità

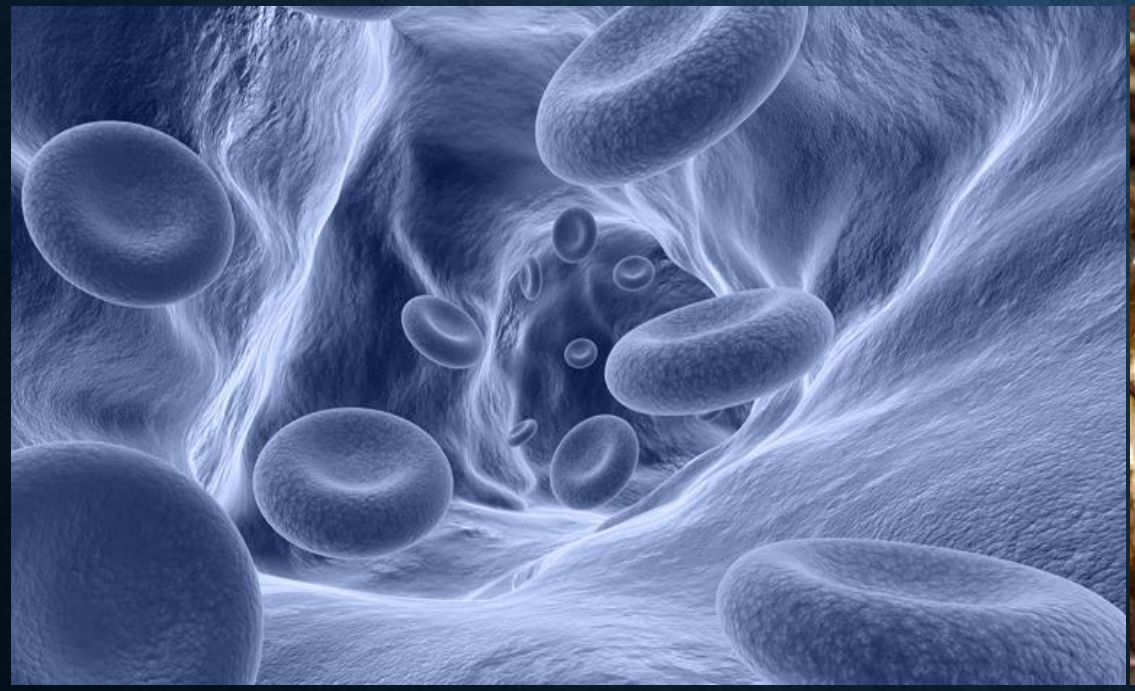
tre parole chiave

Precondizione clinica : normoglicemia

Innovazione terapeutica

Prevenzione e protezione cardiovascolare

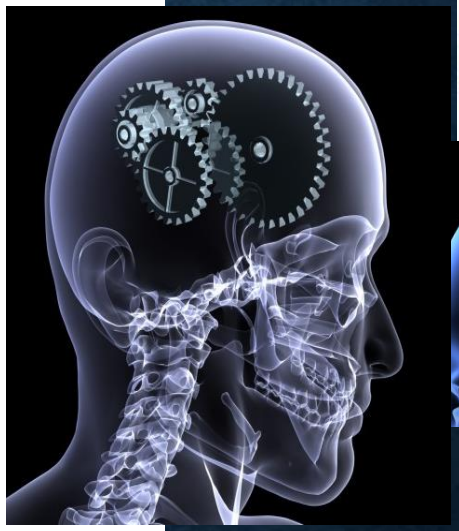
La cardiopatia del diabetico anziano……
è farmacologicamente reversibile ?

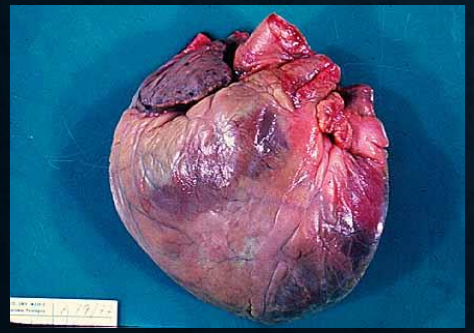
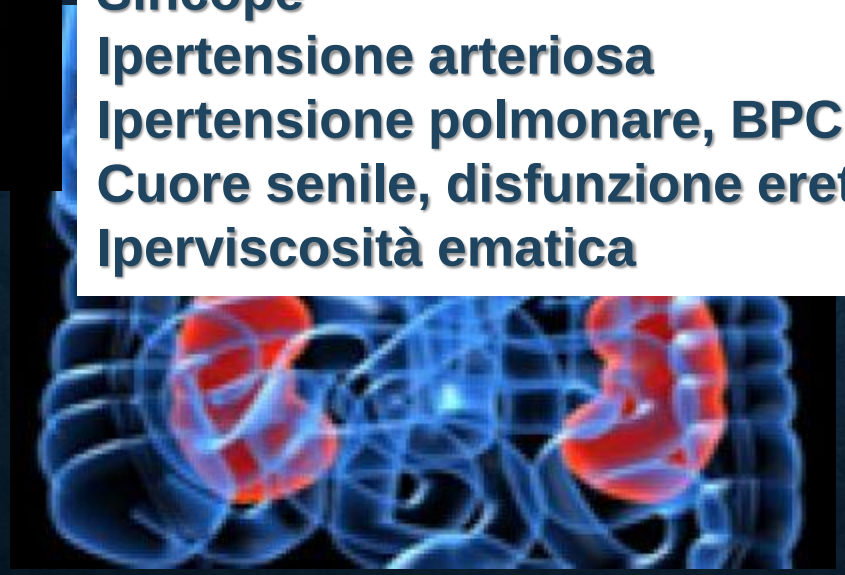
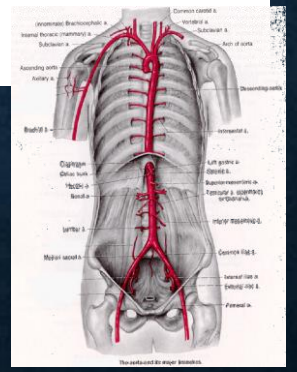
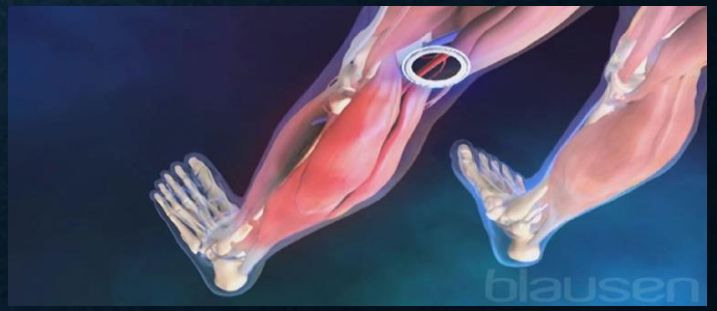


Quali sono gli ambiti nosografici di questa cardiopatia

Cardiopatia ischemica
Scompenso cardiaco
Complicanze renale IRC
Aritmie
Vasculopatie periferiche
Vasculopatia cerebrale cronica
Demenza vascolare
Cardiomiopatia ipertrofica
Sincope
Ipertensione arteriosa
Ipertensione polmonare, BPCO
Cuore senile, disfunzione erettile
Iperviscosità ematica



Quale benefici sulla riduzione dell'iperglicemia

ogni calo di 1% di HbA1c

riduce del

18% malattie cardiovascolari
13% di eventi coronarici
16% eventi coronarici fatali
17% di ictus
28% di vasculopatie periferiche
30% di esiti renali

Selvin et Al, Ann Int Med 141:421,2004

i tre messaggi chiave

Essendo alta la complessità del paziente, la pre condizione clinica di partenza è la normalizzazione dell'iperglicemia evitando l'ipoglicemia, quindi: normoglicemia

Alta complessità = alta specificità del trattamento; la scelta dei farmaci cosiddetti anti diabetici si restringe quasi esclusivamente alle classi definite innovative (di ultima generazione)

I nuovi obiettivi del trattamento sono mirati alla protezione e prevenzione cardiovascolare ottenuti anche indipendentement e dagli effetti positivi sulla glicemia e sulla sua variabilità

i tre messaggi chiave

Essendo alta la complessità del paziente, la pre condizione clinica di partenza è la normalizzazione dell'iperglicemia evitando l'ipoglicemia, quindi: normoglicemia

Alta complessità = alta specificità del trattamento; la scelta dei farmaci cosiddetti anti diabetici si restringe quasi esclusivamente alle classi definite innovative (di ultima generazione)

I nuovi obiettivi del trattamento sono mirati alla protezione e prevenzione cardiovascolare ottenuti anche indipendentement e dagli effetti positivi sulla glicemia e sulla sua variabilità

Glibenclamide
Repaglinide
Glipizide

Insulina umana

Liraglutide
Dulaglutide
Lixisenatide
Exenatide LAR

Sitagliptin
Vildagliptin
Alogliptin
Linagliptin
Saxagliptin

Add on Insulina basale
Add on Pioglitazone
Add on Metformina

Empagliflozin

Dapagliflozin

Canagliflozin

Add on Insulina basale
Add on Pioglitazone
Add on Metformina

Insulina basale degludec

Glargine 300U/mL

Normoglicemizzanti di ultima generazione

i tre messaggi chiave

Essendo alta la complessità del paziente, la pre condizione clinica di partenza è la normalizzazione dell'iperglicemia evitando l'ipoglicemia, quindi: normoglicemia

Alta complessità = alta specificità del trattamento; la scelta dei farmaci cosiddetti anti diabetici si restringe quasi esclusivamente alle classi definite innovative (di ultima generazione)

I nuovi obiettivi del trattamento sono mirati alla protezione e prevenzione cardiovascolare ottenuti anche indipendentement e dagli effetti positivi sulla glicemia e sulla sua variabilità

m e t f o r m i n a

long.-term basal insulin add-on

i n c r e t i n e

TECOS
LEADER

p i o g l i t a z o n e

PROactive

SGLT2 i. : gliflozine

EMPA-REG

emoglobina glicata, glicemia

creatinina : e GFR

cumulative end point
Peso, pressione, LDL-CT

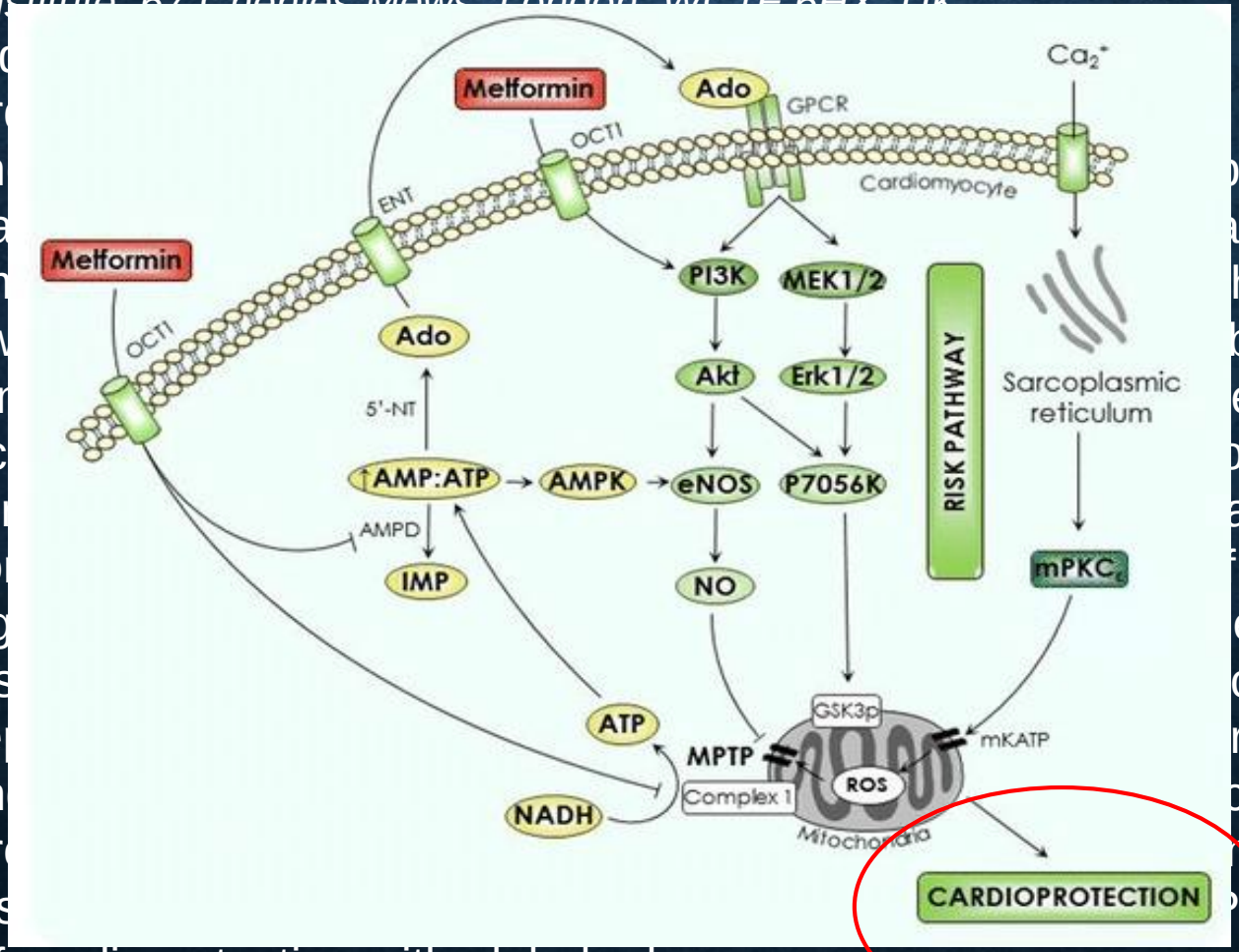
acido lattico

chetonemia

Cardiovasc Diabetol. 2015 Aug 14;14:109

THE PLEIOTROPIC EFFECTS OF METFORMIN: TIME FOR PROSPECTIVE STUDIES.

Bromage DI, Yellon DM.
The Hatter Cardiovascular Institute, 67 Chenies Mews, London, WC1E 6HX, UK

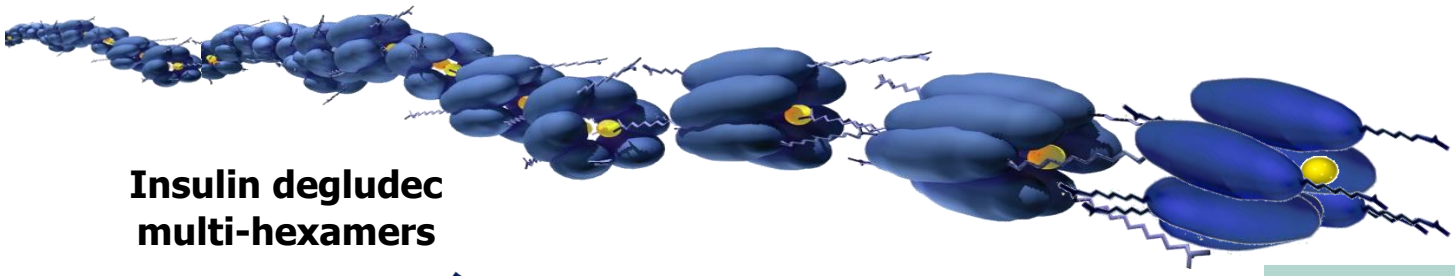


The global prevalence of c predicted to continue. The consequent burden of car concern and new treatments are required to mitigate th patients. Ischaemia-reperfusion injury is well known to exa and subsequent therapeutic reperfusion, and several n his injury have been investigated. Metformin, w betes, is one such pharmacotherapy with cor eyond its glucose-lowering effect. However, despite c on has largely been limited to studies of cardiovascular r assessment in the context of acute myocardial infarctio f metformin among patients with type 2 diabetes at hig ence, well-designed prospective cohort studies cular disease, and particularly its benefit in ischaemia-re rmin worldwide, this is particularly true in low- an cute myocardial infarction, primary percutaneous cor nts are managed with thrombolysis. As this is les PCI) could represent an effective, cheap means of cardioprotection with global relevance.

INSULIN DEGLUDEC : SLOW RELEASE FOLLOWING INJECTION

Subcutaneous depot

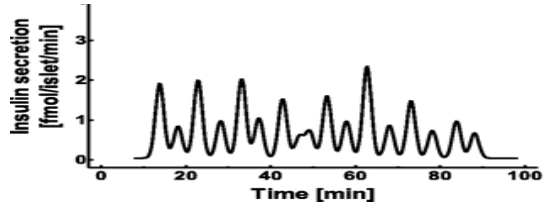
[Zn^{2+}]



Insulin degludec multi-hexamers

secrezione basale

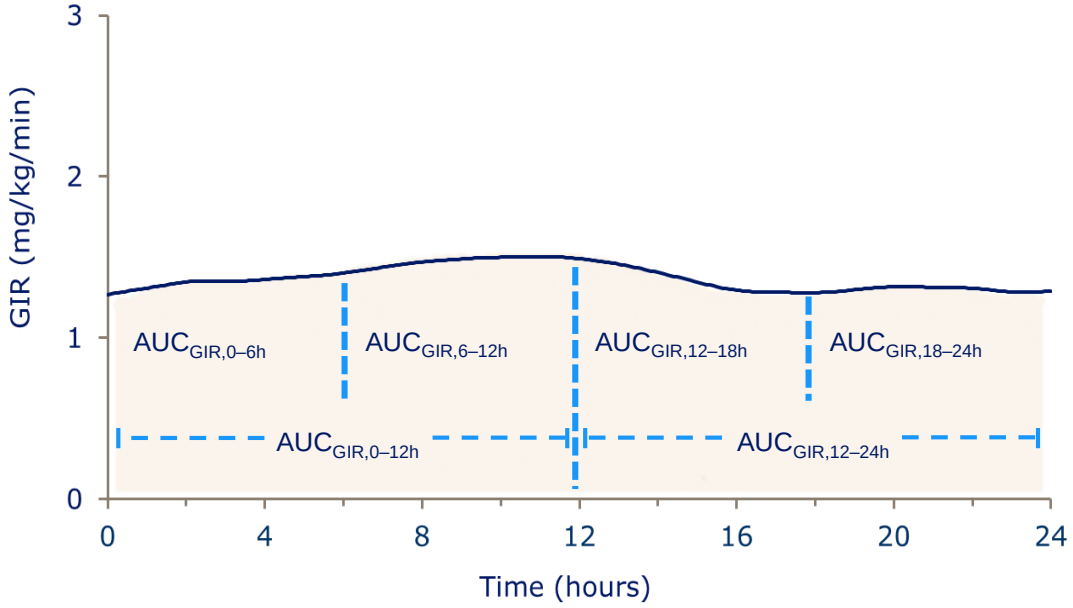
Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

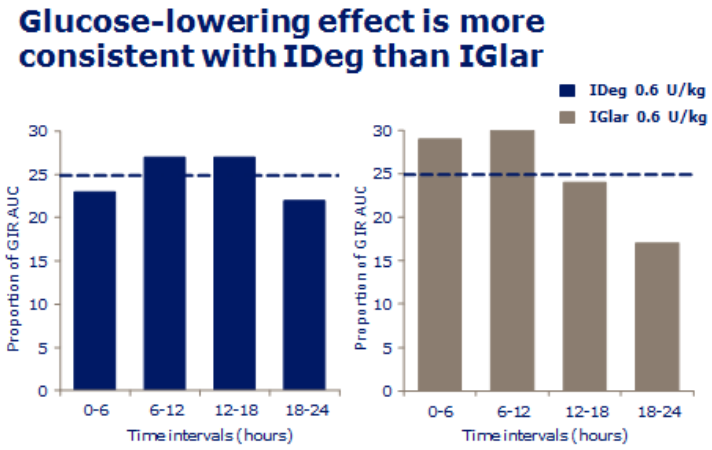


Monomers are absorbed from the depot into the circulation

Insulin degludec: PK & PD

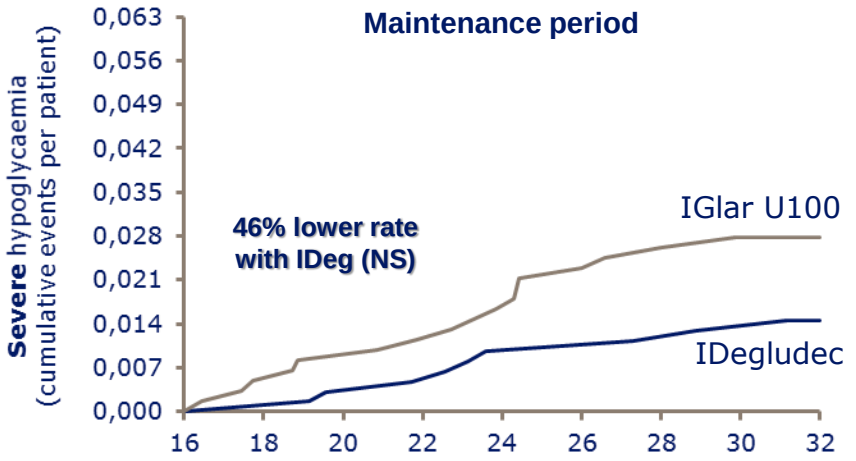
	Insulin degludec			Insulin glargine		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.6	11.5	12.9	11.9
Mean half-life		**25.4**			**12.1**	

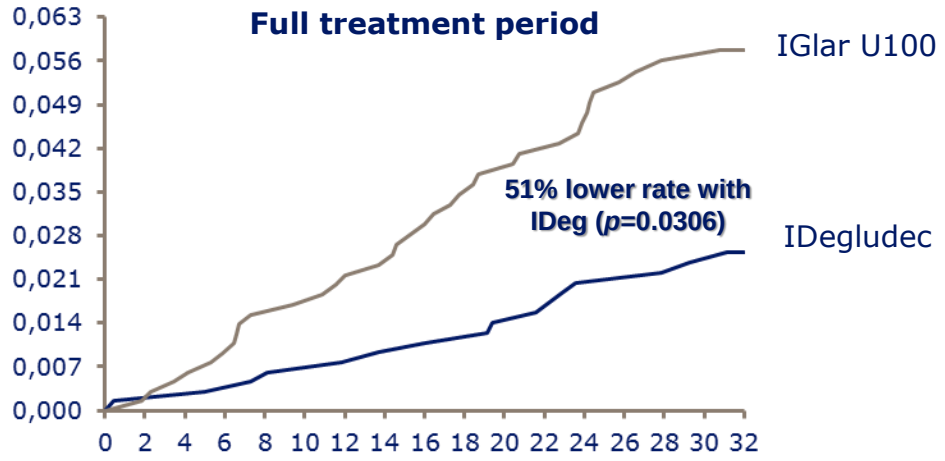




Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425

SEVERE HYPOGLYCAEMIA





IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
1.6%	5.3	2.4%	9.1

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
2.2%	4.4	3.9%	9.4

SAS
Comparisons: Estimates adjusted for multiple covariates
Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

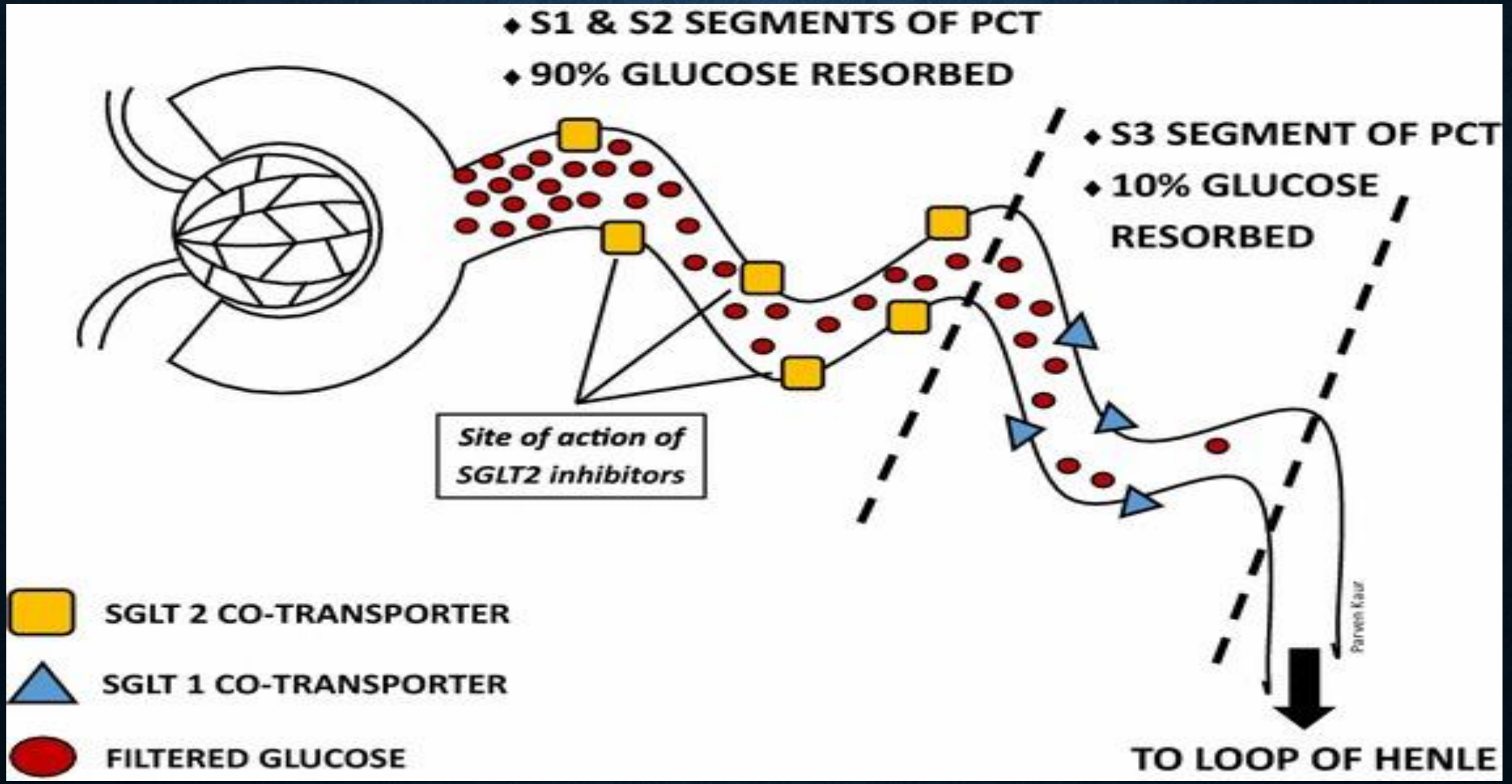
Clin Ther. 2016 Jun;38(6):1288-98.

EMPA-REG and Other Cardiovascular Outcome Trials of Glucose-lowering Agents: Implications for Future Treatment Strategies in Type 2 Diabetes Mellitus.

Schernthaner G, Schernthaner-Reiter MH, Schernthaner GH.

Rudolfstiftung Hospital, Vienna, Austria. Electronic address: guntram.schernthaner@meduniwien.ac.at.
Department of Medicine III, Division of Endocrinology and Metabolism, Medical University of Vienna,
Department of Medicine II, Division of Angiology, Medical University of Vienna,Austria

……we suggest that the addition of both empagliflozin (EMPA-REG) and pioglitazone (PROactive) to metformin might be the relative best option to reduce the high CV morbidity and mortality of patients with T2DM and already established CV complications. The very recent announcement that the CV outcome study with liraglutide (LEADER) also demonstrated a significant reduction of the composite endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) gives new hope for further beneficial treatment options for T2DM patients with established CVD.


S1 & S2 SEGMENTS OF PCT
90% GLUCOSE RESORBED
S3 SEGMENT OF PCT
10% GLUCOSE RESORBED
Site of action of SGLT2 inhibitors
SGLT 2 CO-TRANSPORTER
SGLT 1 CO-TRANSPORTER
FILTERED GLUCOSE
TO LOOP OF HENLE
Parveen Kaur

Eur Heart J. 2016 May 5. pii: ehw110. [Epub ahead of print]

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITION FOR THE REDUCTION OF CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS WITH DIABETES MELLITUS.

Marx N, McGuire DK.

Department of Internal Medicine I, University Hospital Aachen, Germany nmarx@ukaachen.de.
Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA.

……..various factors beyond glucose control such as weight loss, blood pressure lowering and sodium depletion, renal haemodynamic effects, effects on myocardial energetics, and/or neurohormonal effects, among others may contribute to these beneficial ***CV effects of SGLT2-inhibition****.*

TRATTAMENTO DEL DIABETICO ANZIANO CARDIOPATICO

SGLT2 inibitori /gliflozine
Anti HF and cardiac death risk

Caloric restriction

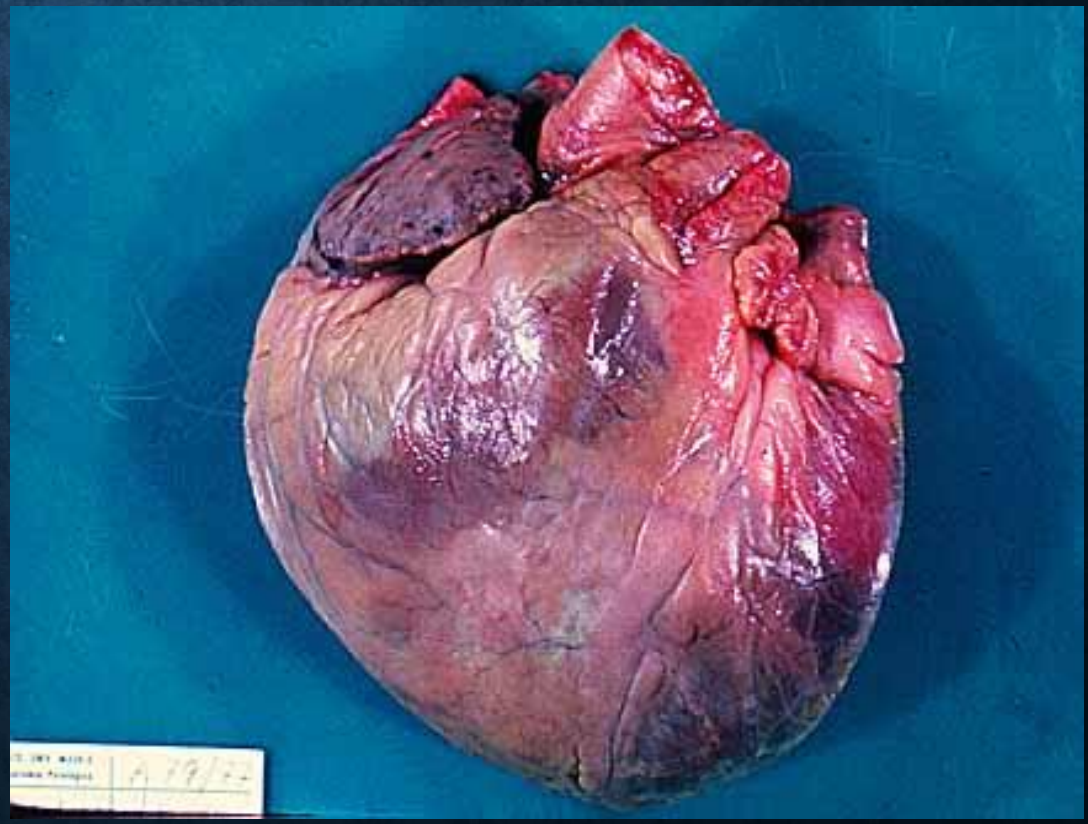
Proketogenic effect: **superfuel energy**

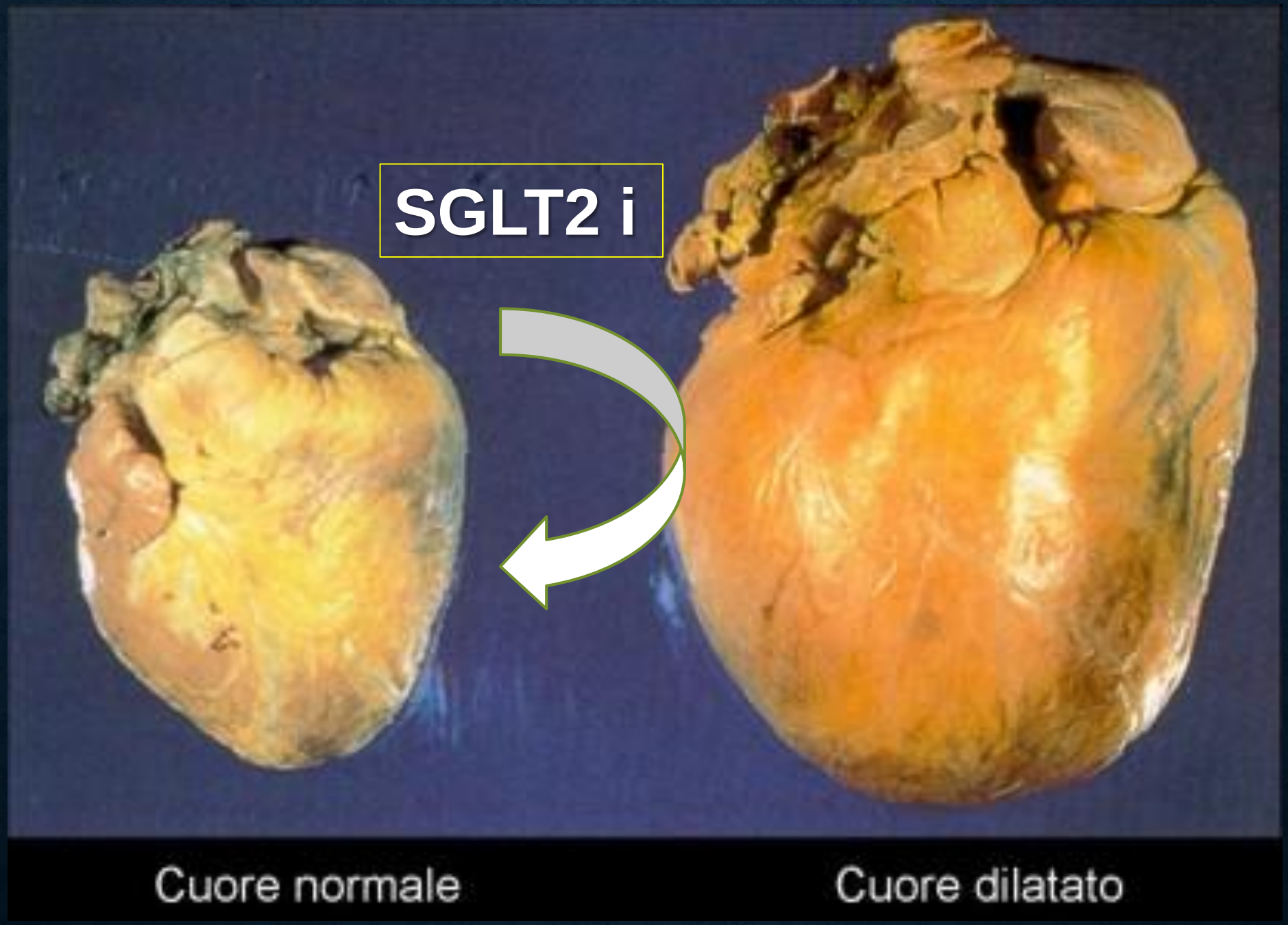
Increased mytochondrial energetics (ATP) on CV targets

Reduced cytoplasmic Na1+ and Ca2+ , and increased mitocondrial Ca2+

Increased myocardial/renal work

Hemoconcentration and **enhanced O2 extraction by CV targets**




SGLT2 i
Cuore normale
Cuore dilatato

Indian J Endocrinol Metab. 2016 Sep-Oct;20(5):725-729.

Sodium-glucose cotransporter 2 inhibition and health benefits: THE ROBIN HOOD EFFECT.

Kalra S1, Jain A2, Ved J3, Unnikrishnan AG4.

1Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India.
2Department of Medicine, Boehringer Ingelheim India Pvt, Delhi, India.
3Department of Medicine, Boehringer Ingelheim Pvt Ltd, Mumbai, India.
4Chellaram Diabetes Institute, Pune, Maharashtra, India.

Abstract
This review discusses two distinct, yet related, mechanisms of sodium-glucose cotransporter 2 (SGLT2) inhibition: Calorie restriction mimicry (CRM) and pro-ketogenic effect, which may explain their cardiovascular benefits. We term these adaptive CRM and pro-ketogenic effects of SGLT2 inhibition, the Robin Hood hypothesis. In English history, Robin Hood was a "good person," who stole from the rich and helped the poor. He supported redistribution of resources as he deemed fit for the common good. In a similar fashion, SGLT2 inhibition provides respite to the overloaded glucose metabolism while utilizing lipid stores for energy production.

KEYWORDS:
Calorie restriction mimicry canagliflozin; EMPA-REG outcome; cardiovascular outcomes; dapagliflozin; diabetes; empagliflozin; ketogenesis; ketogenic diet; liraglutide

Sodium-glucose cotransporter 2 inhibition: **Robin Hood effect** (*heart, muscle, and renal cortex. Brain utilizes ketones only in prolonged starvation. Erythrocytes do not utilize ketones as they do not have mitochondria. Liver does not utilize ketones as it does not have the enzyme thiophorase)

SGLT2 Inhibition
↓
↑Glucose excretion
↓
↓Glucose (calorie) availability
CALORIE RESTRICTION MIMICRY
↓
↑Glucagon:insulin ratio
↓

↓Glycogenolysis
↓
↓Pyruvate

↑Lipolysis
↓
↑FFA, Glycerol

Less contribution | More contribution

Acetyl CoA
↕
Acetone ← acetoacetate
↕
β-hydroxybutyrate
↓
UPTAKE IN PERIPHERAL TISSUES*
↓
↑Mitochondrial Energetics

Diabetologia. 2016 Oct 17. [Epub ahead of print]

Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits.

Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ.
Univeristy of Amsterdam and Bordeaux

Abstract

AIMS/HYPOTHESIS:
Empagliflozin (EMPA), an inhibitor of the renal sodium-glucose cotransporter (SGLT) 2, reduces the risk of cardiovascular death in patients with type 2 diabetes. The underlying mechanism of this effect is unknown. Elevated cardiac cytoplasmic Na+ ([Na+]c) and Ca2+ ([Ca2+]c) concentrations and decreased mitochondrial Ca2+ concentration ([Ca2+]m) are drivers of heart failure and cardiac death. We therefore hypothesised that EMPA would directly modify [Na+]c, [Ca2+]c and [Ca2+]m in cardiomyocytes.

METHODS:
[Na+]c, [Ca2+]c, [Ca 2+]m and Na+/H+ exchanger (NHE) activity were measured fluorometrically in isolated ventricular myocytes from rabbits and rats.

RESULTS:
An increase in extracellular glucose, from 5.5 mmol/l to 11 mm[illegible] increased [Na+]c and [Ca2+]c levels. EMPA treatment directly inhibited NHE flux, caused a reduction in [Na+]c and [Ca2[illegible]2+]m. After pretreatment with the NHE inhibitor, Cariporide, these effects of EMPA were strongly reduced. EMPA also affe[illegible]d NHE flux in the absence of extracellular glucose.

CONCLUSIONS/INTERPRETATION:
The glucose lowering kidney-targeted agent, EMPA, demonstrates direct cardiac effects by lowering myocardial [Na+]c and [Ca2+]c and enhancing [Ca2+]m, through impairment of myocardial NHE flux, independent of SGLT2 activity.

Diabetologia. 2016 Oct 17. [Epub ahead of print]

Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits.

Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ.
Univeristy of Amsterdam and Bordeaux

Abstract

AIMS/HYPOTHESIS:
Empagliflozin (EMPA), an inhibitor of the renal sodium-glucose cotransporter (SGLT) 2, reduces the risk of cardiovascular death in patients with type 2 diabetes. The underlying mechanism of this effect is unkno cardiac cytoplasmic Na+ ([Na+]c) and Ca2+ ([Ca2+]c) concentrations and decreased mitochondrial Ca2+ concentration drivers of heart failure and cardiac death. We therefore hypothesised that EMPA would directly modify [Na+]c, [Ca2+]c an cardiomyocytes.

METHODS:
[Na+]c, [Ca2+]c, [Ca 2+]m and Na+/H+ exchanger (NHE) activi luorometrically in isolated ventricular myocytes from rabbits and rats.

RESULTS:
An increase in extracellular glucose, from 5.5 mmol/l to 11 mmol/l, resulted in increased [Na+]c and [Ca2+]c levels.
EMPA treatment directly inhibited NHE flux, caused a reduction in [Na+]c and [Ca2+]c and increased [Ca2+]m. After pretreatment with the NHE inhibitor, Cariporide, these effects of EMPA were strongly reduced. EMPA also affected [Na+]c and NHE flux in the absence of extracellular glucose.

CONCLUSIONS/INTERPRETATION:
The glucose lowering kidney-targeted agent, EMPA, demonstrates direct cardiac effects by lowering myocardial [Na+]c and [Ca2+]c and enhancing [Ca2+]m, through impairment of myocardial NHE flux, independent of SGLT2 activity.

Drugs Context. 2016 Sep 2;5:212299. doi: 10.7573/dic.212299.

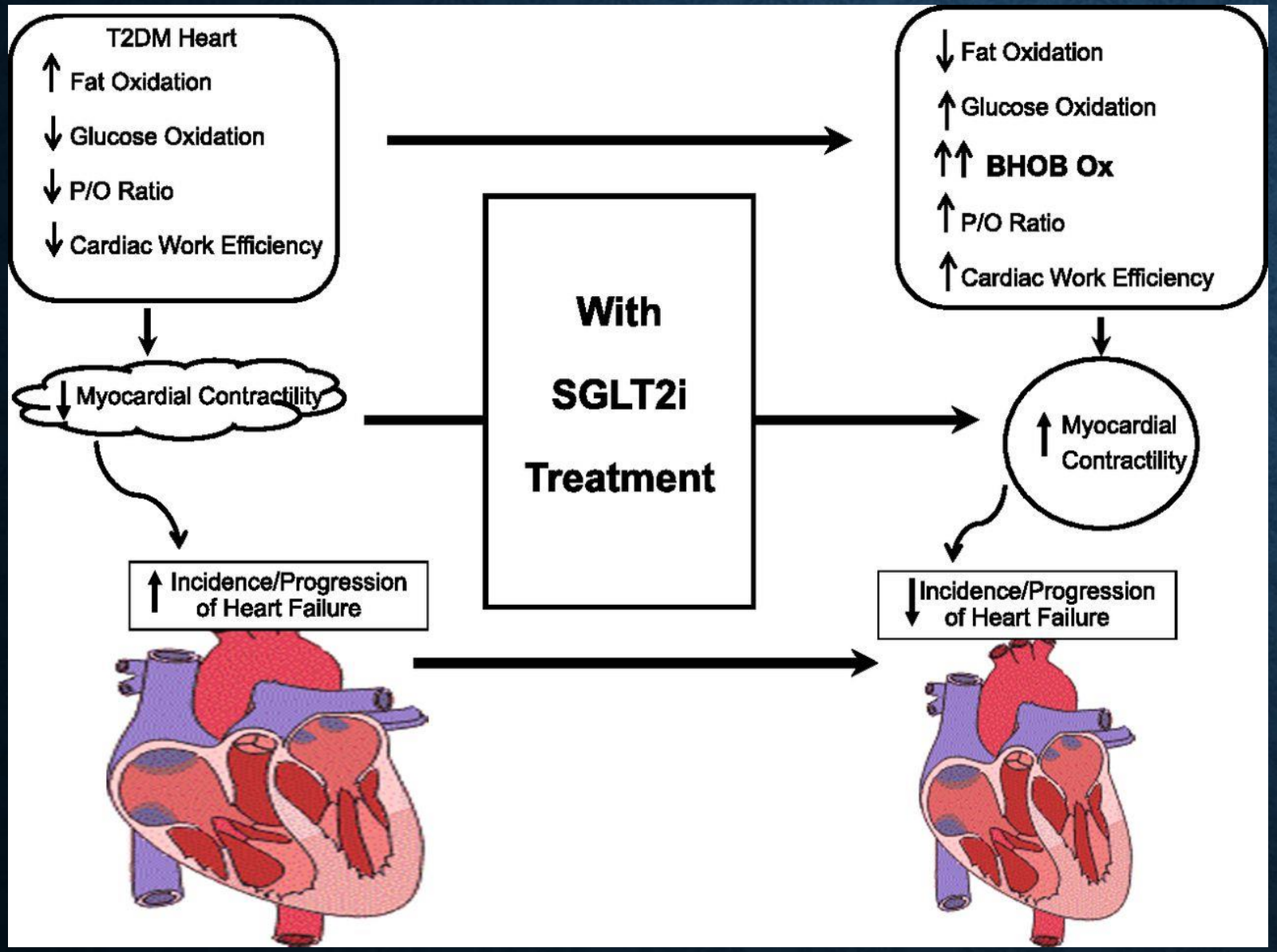
Closing the knowledge gap on cardiovascular disease in type 2 diabetes: the EMPA-REG OUTCOME trial and beyond.

Oral EA.

Division of Metabolism, Endocrinology and Diabetes (MEND), Brehm Center for Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA.

American Diabetes Association

Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy.



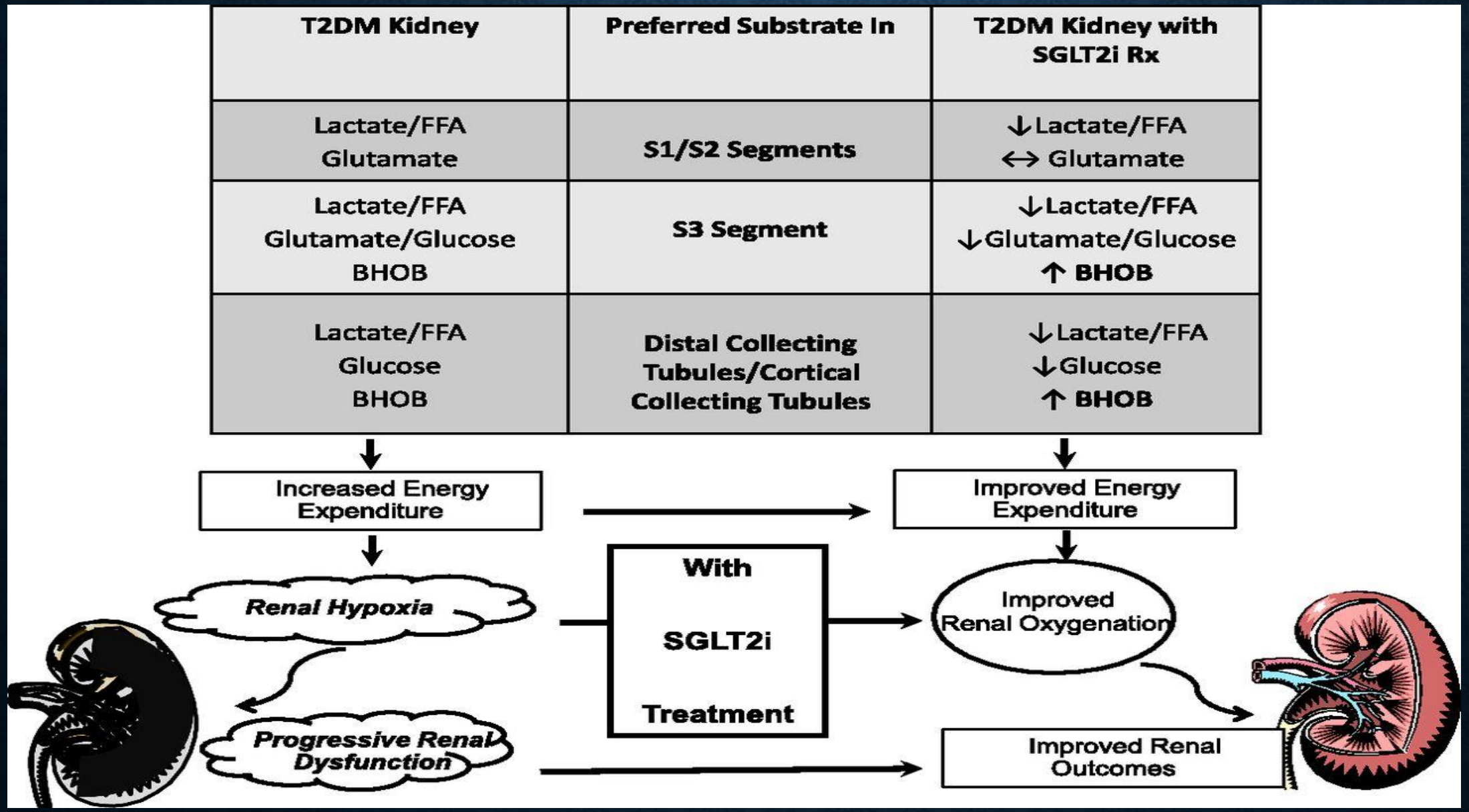
Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy.

P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain

Sunder Mudaliar et al. Diabetes Care 2016;39:1115-1122

Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy.

T2DM Kidney	Preferred Substrate In	T2DM Kidney with SGLT2i Rx
Lactate/FFA Glutamate	S1/S2 Segments	↓Lactate/FFA ↔ Glutamate
Lactate/FFA Glutamate/Glucose BHOB	S3 Segment	↓Lactate/FFA ↓Glutamate/Glucose ↑ BHOB
Lactate/FFA Glucose BHOB	Distal Collecting Tubules/Cortical Collecting Tubules	↓Lactate/FFA ↓Glucose ↑ BHOB



Sunder Mudaliar et al. Dia Care 2016;39:1115-1122

Diabetes Care. 2016 , 39:1108-1114

CV PROTECTION IN THE EMPA-REG OUTCOME TRIAL: A "THRIFTY SUBSTRATE" HYPOTHESIS.

Ferrannini E, Mark M, Mayoux E.
CNR Pisa, Italy

« *il substrato parsimonioso* »

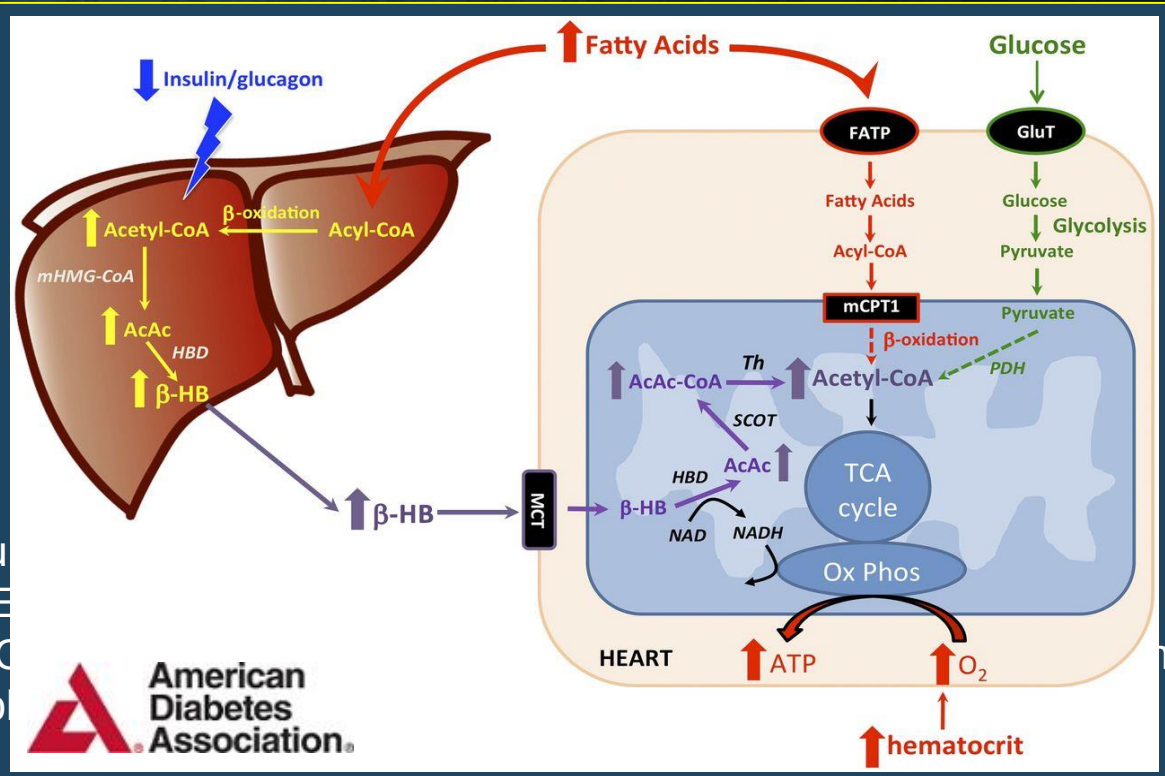
Abstract

The striking and unexpected relative risk reductions in cardiovascular (CV) mortality (38%), hospitalization for heart failure (35%), and death from any cause (32%) observed in the EMPA-REG OUTCOME trial using an inhibitor of sodium-glucose cotransporter 2 (SGLT2) in patients with type 2 diabetes and high CV risk have raised the possibility that mechanisms other than those observed in the trial-modest improvement in glycemic control, small decrease in body weight, and persistent reductions in blood pressure and uric acid level-may be at play.

Diabetes Care. 2016 , 39:1108-1114

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis.

Ferrannini E, Mark M, Mayoux E.
CNR Pisa, Italy



The striking and unexpected relative risk reductions in cardiovascu
(35%), and death from any cause (32%) observed in the EMPA-RE
cotransporter 2 (SGLT2) in patients with type 2 diabetes and high C
those observed in the trial-modest improvement in glycemic control
blood pressure and uric acid level-may be at play.

We hypothesize that under conditions of **mild, persistent hyperketonemia**, such as those that prevail during treatment with SGLT2 inhibitors, β-hydroxybutyrate is freely taken up by **the heart** (among other organs) and oxidized in preference to fatty acids. This fuel selection **improves the transduction of oxygen consumption** into work efficiency **at the mitochondrial level.** In addition, the **hemoconcentration** that typically follows SGLT2 inhibition **enhances oxygen release to the tissues**, thereby establishing a powerful synergy with the metabolic substrate shift. These mechanisms would cooperate with other SGLT2 inhibition-induced changes (chiefly, enhanced diuresis and reduced blood pressure) to achieve the degree of cardioprotection revealed in the EMPA-REG OUTCOME trial. This hypothesis opens up new lines of investigation into the pathogenesis and treatment of diabetic and nondiabetic heart disease.

Circulation. 2016 Sep 6;134(10):752-72.

Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications.

Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ.
University of Groningen, the Netherlands, University of Toronto

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, are now widely approved antihyperglycemic therapies. Because of their unique glycosuric mechanism, SGLT2 inhibitors also reduce weight. Perhaps more important are the osmotic diuretic and natriuretic effects contributing to plasma volume contraction, and decreases in systolic and diastolic blood pressures by 4 to 6 and 1 to 2 mm Hg, respectively, which may underlie cardiovascular and kidney benefits. SGLT2 inhibition also is associated with an acute, dose-dependent reduction in estimated glomerular filtration rate by ≈5 mL·min(-1)·1.73 m(-2) and ≈30% to 40% reduction in albuminuria. These effects mirror preclinical observations suggesting that proximal tubular natriuresis activates renal tubuloglomerular feedback through increased macula densa sodium and chloride delivery, leading to afferent vasoconstriction.

…… ***on the basis of reduced glomerular filtration, glycosuric and weight loss effects are attenuated in patients with chronic kidney disease (estimated glomerular filtration rate <60 mL·min(-1)·1.73 m(-2)).***

In contrast, blood pressure lowering, estimated glomerular filtration rate, and albuminuric effects are preserved, and perhaps exaggerated in chronic kidney disease.

Single pill combination (SPC)

Dual therapy
(DPPIV inhib./SGLT2 inhib.)

1. **Favorable legacy effect on cardioprotection**
2. **Weight and blood pressure control**
3. **Normoglycemia without hypoglycemia**

Zonszein J., Diabetes Ther 2016

Glyxambi®

(EMPAGLIFLOZIN/LINAGLIPTIN) TABLETS

NON INSULIN TREATMENT OF TYPE 2 DIABETES MELLITUS IN GERIATRIC PATIENTS : a Review

Wilford Germino F.
Clin Therapeut. 33:1868-1882,2011

INCRETIN THERAPIES IN THE MANAGEMENT OF ELDERLY PATIENTS WITH TYPE 2 DIABETES MELLITUS

Bourdel Marchasson I, Schweizer A, Djager S
Hosp. Pract. 39:7-21,2016

La famiglia delle incretine

Terapie incretiniche

Inibitori della DPP-4:
es. sitagliptin, vildagliptin, saxagliptin, alogliptin, dutogliptin, linagliptin, PHX1149, PF-00734200, R1579, R1583, TAK-472, AMG-222, MP-513

Agonisti del recettore del GLP-1

Terapie exendin-based:
es. exenatide, exenatide LAR, lixisenatide (AVE-0010), CJC-1134

Analogo umano del GLP-1:
es. liraglutide, dulaglutide albiglutide, taspoglutide

USE OF DPP-4 INHIBITORS IN SPECIAL POPULATIONS

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Elderly[1-5]	No restriction	≤80 years	No restriction	No restriction	No restriction
Hepatic Insufficiency[6,7]					
Mild	Yes	Yes[7]	Yes	Yes	No
Moderate	Yes	Yes[7]	Yes	Yes	No
Severe	No	Yes[7]	No	No	No
Hepatic Function Monitoring	No	No	No	No	Yes
Renal Insufficiency*[6,7]					
Mild	Yes	Yes	Yes	Yes	Yes
Moderate	Reduced dose	Yes	Reduced dose	Reduced dose	Reduced dose
Severe/ESRD	Reduced dose	Yes	Reduced dose	Reduced dose	Reduced dose
Renal Function Monitoring	Yes	No	Yes	Yes	Yes

TECOS

Green JB et Al NEJM 2015

Cornel JH et Al Diab Care 2016

***Renal insufficiency: Mild: CrCl ≥50 mL/min, Moderate: CrCl ≥30–<50 mL/min, Severe/ESRD: CrCl <30 mL/min**
CrCl=creatinine clearance; ESRD=end-stage renal disease; EU=Europe; min=minute; NR=not recommended

1. Vipidia (alogliptin) Summary of Product Characteristics (SmPC) 2014. 2. Trajenta (linagliptin) SmPC 2013. 3. Onglyza (saxagliptin) SmPC 2014. 4. Januvia (sitagliptin) SmPC 2014. 5. Galvus (vildagliptin) SmPC 2014. 6. Deacon CF. *Diabetes Obes Metab.* 2011;13:7-18. 7. Deacon CF, et al. *Expert Opin Pharmacother.* 2013;14:2047-2058.

Assessing the Safety of Sitagliptin in Elderly Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

M. Angelyn Bethel, M.D.,[1] Samuel S. Engel, M.D.,[2] Jennifer B. Green, M.D.,[3] Zhen Huang, M.S.,[3] Keith D. Kaufman, M.D.,[2] Eberhard Standl, M.D., Ph.D.,[4] Shailaja Suryawanshi, Ph.D.,[2] Frans Van de Werf, M.D., Ph.D.,[5] Eric D. Peterson, M.D., M.P.H.[3] and Rury R. Holman, M.B., Ch.B.[1] for the TECOS Study Group

[1]Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK; [2]Merck Research Laboratories, Merck & Co., Inc., Kenilworth, New Jersey, USA; [3]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA; [4]Munich Diabetes Research Group e.V., Helmholtz Centre, Neuherberg, Germany; [5]Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

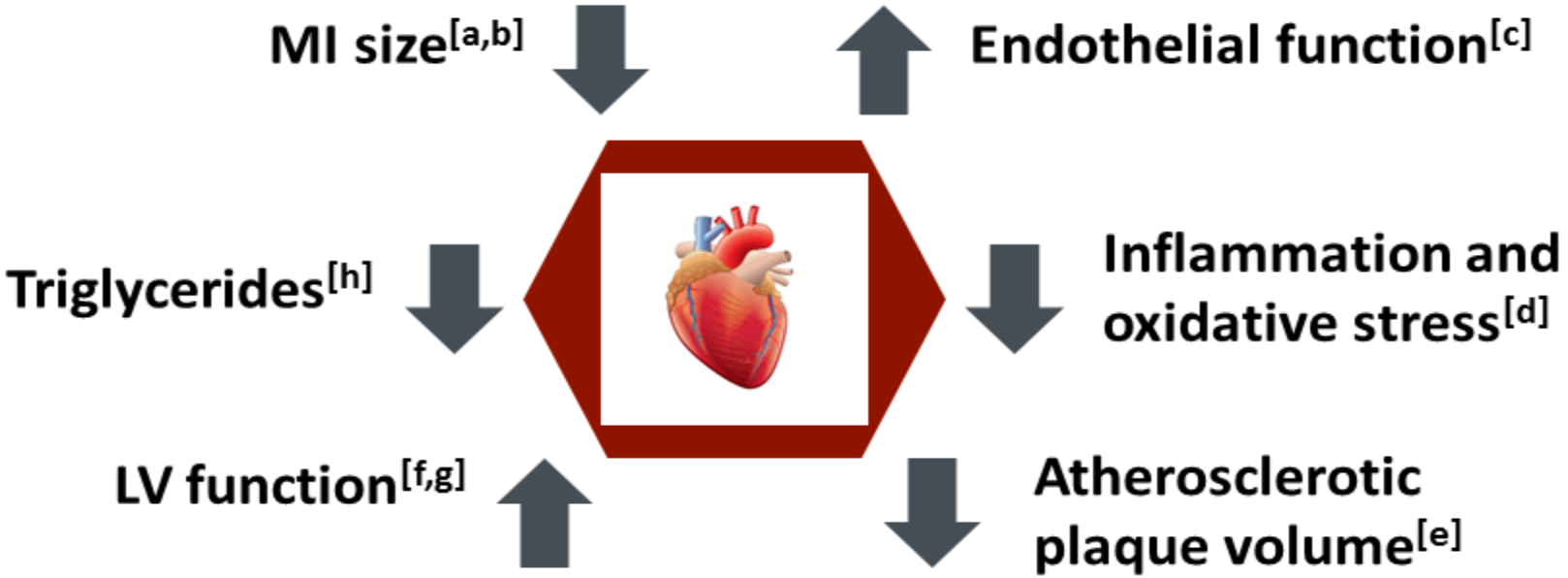
Primary and key secondary outcomes
Data are presented as hazard ratio (95% CI) and p-value

	All participants (n=14,351) Elderly *vs.* non-elderly	Elderly participants (n=2,004) Sitagliptin *vs.* placebo
3-point MACE	1.86 (1.63, 2.11) p<0.001	1.01 (0.81, 1.26) p=0.94
4-point MACE	1.72 (1.52, 1.94) p<0.001	1.10 (0.89, 1.36) p=0.39
Hospitalization for heart failure	1.48 (1.18, 1.87) p<0.001	0.99 (0.65, 1.49) p=0.94
Hospitalization for heart failure or death	2.02 (1.75, 2.34) p<0.001	1.00 (0.77, 1.29) p=0.99
All-cause mortality	2.52 (2.20, 2.89) p<0.001	1.05 (0.83, 1.32) p=0.71
Pancreatitis	1.17 (0.48, 2.83) p=0.73	2.01 (0.36, 11.04) p=0.42
Pancreatic malignancy	1.52 (0.56, 4.14) p=0.41	0.28 (0.03, 2.50) p=0.25
Overall malignancy	1.76 (1.43, 2.15) p<0.001	0.95 (0.67, 1.36) p=0.78
Severe hypoglycaemia	1.53 (1.15, 2.03) p=0.004	1.03 (0.62, 1.71) p=0.92
Bone fracture	1.84 (1.44, 2.35) p<0.0001	1.21 (0.78, 1.85) p=0.39

Conclusion

Among elderly patients with T2DM and established CV disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse CV events, hospitalization for heart failure, or other adverse events

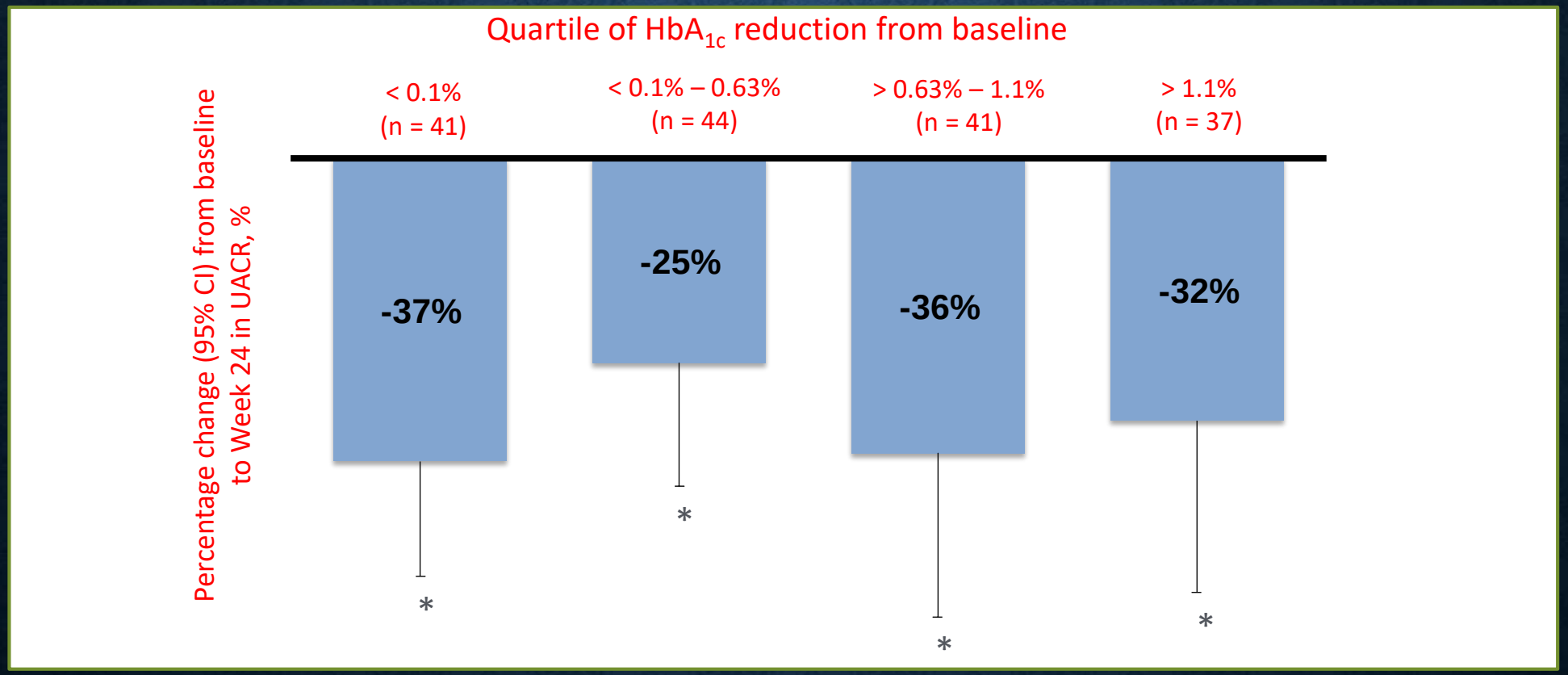
Selected Mechanistic Trials Indicate CV Effects of the DPP-4 Inhibitor Class



a. Ye Y, et al. *Am J Physiol Heart Circ Physiol.* 2010;298:H1454-1465.
b. Hocher B, et al. *Int J Cardiol.* 2013;167:87-93.
c. van Poppel PC, et al. *Diabetes Care.* 2011;34:2072-2077.
d. Kröller-Schön S, et al. *Cardiovasc Res.* 2012;96:140-149.
e. Ta NN, et al. *J Cardiovasc Pharmacol.* 2011;58:157-166.
f. Sauvé M, et al. *Diabetes.* 2010;59:1063-1073.
g. Read PA, et al. *Circ Cardiovasc Imaging.* 2010;3:195-201.
h. Matikainen N, et al. *Diabetologia.* 2006;49:2049-2057.

The albuminuria-lowering effects of linagliptin occurred independently of any reduction in HbA_{1c}

Adjusted mean change in UACR (%) from baseline at Week 24 by quartiles of HbA_{1c} change



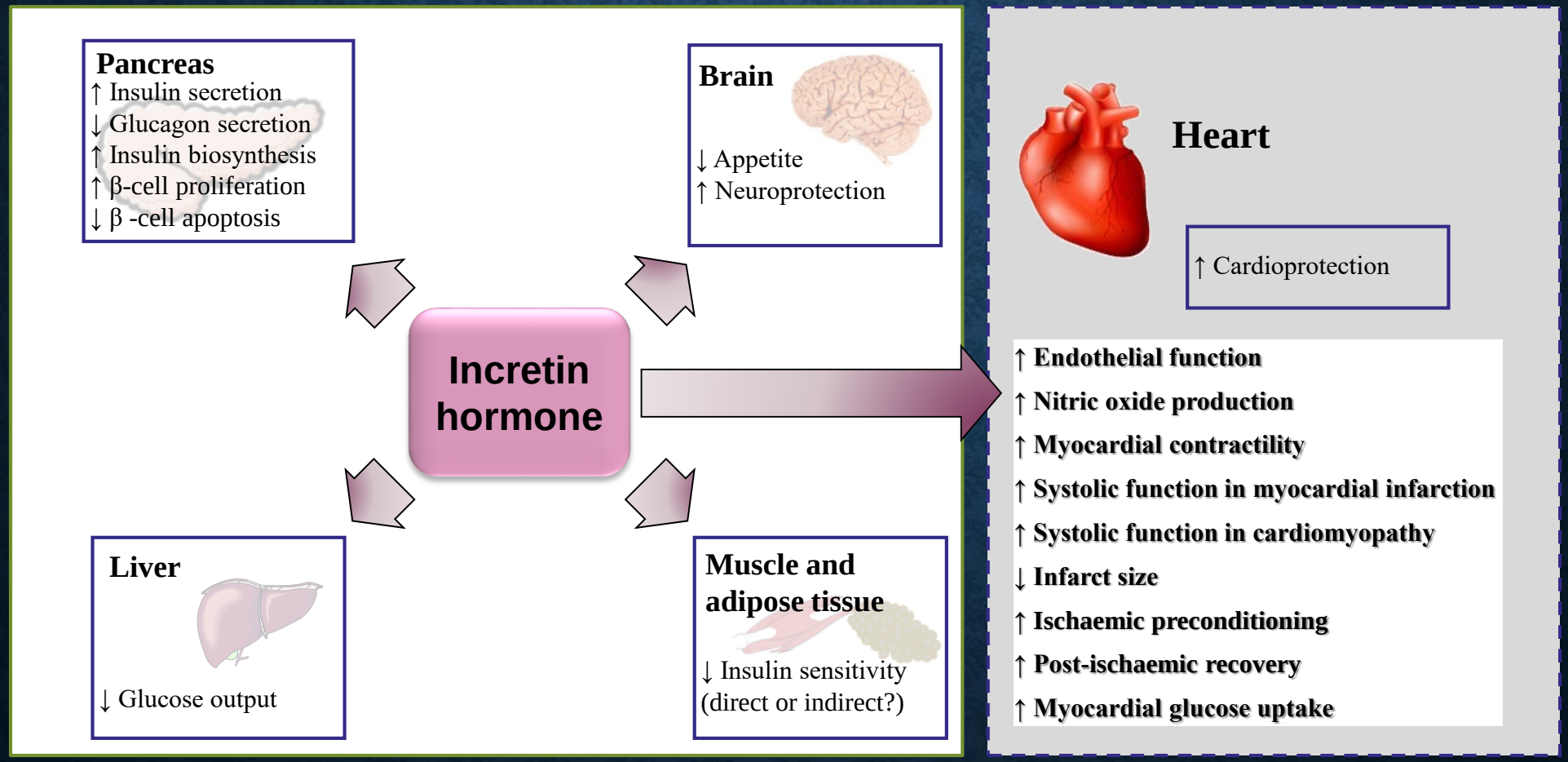
Overall, kidney function and blood pressure were unchanged

* Significant change in UACR (%) versus baseline after 24 weeks.

Source: Groop PH et al. ADA 2012, 953-P.

GLP-1 HAS VARIOUS POTENTIAL EFFECTS ON THE CV SYSTEM

Potential impact of DPP4 inhibition and the incretin system on various organs



Source: Jax T. *Clin Res Cardiol.* 2009;98:75–79;
Grieve DJ. *Br J Pharmacol.* 2009;157:1340–1351 (modified).

Terapia incretinica nel diabete

Azione pleiotropica di protezione cardiovascolare

Analoghi recettoriale GLP1

Liraglutide

Risultati clinici dello **studio LEADER**

Protezione cardiovascolare di Liraglutide nel diabete

N Engl J Med. 2016 Jul 28;375(4):311-22.

LIRAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES. LEADER CLINICAL TRIAL

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Collaborators (2255)

BACKGROUND:
The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.
METHODS:
In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.
RESULTS:
A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.
CONCLUSIONS:
In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.
(Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.).

I VANTAGGI CON IDEGLIRA

- IDegLira permette di ottenere sia un buon controllo della glicemia a digiuno che post-prandiale
- Riduce il rischio di ipoglicemie
- Riduce l'aumento di peso legato alla terapia insulinica
- Facilita l'aderenza alla terapia (un'unica somministrazione, titolazione della sola glicemia a digiuno)
- Permette di sospendere la sulfanilurea e di garantire una adeguata secrezione endogena di insulina ai pasti con miglioramento delle glicemie postprandiali
- Alla luce di risultati del LEADER study conferisce protezione al paziente ad alto rischio CVD

« era lieto il mattino ai

giorni di giovinezza /

e la sera era pianto.

Ora son più vecchio /

apro il giorno nel dubbio

/

ma il suo finire

mi è sereno e sacro ».

Friedrich Holderlin