IL CROSS-TALK

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FISIOPATOLOGIA
ED ASPETTI CLINICI

CATANIA 4 NOVEMBRE 2019



# *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

***Antonio C. Bossi***

*ASST Bergamo Ovest – Treviglio (Bg)*

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

# Disclosures

***Nell'arco degli ultimi tre anni dichiaro di aver ricevuto onorari per conferenze, collaborazioni scientifiche, lavori di ricerca clinica e documentale dalle seguenti Aziende:***

- ***Lilly Italia Spa***
- ***Novo Nordisk Italia SpA***
- ***Johnson & Johnson SpA***
- ***Boehringer Ingelheim SpA***
- ***Artsana SpA***
- ***Takeda SpA***
- ***Bayer SA***
- ***Sanofi SpA***
- ***Astra Zeneca SpA***
- ***MSD Italia SpA***



***Se oggi sono qui in qualità di relatore è perché la SID ha contribuito alla mia formazione culturale, scientifica, clinica.***

# *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

## AGENDA

- Cenni di epidemiologia (HF & CVD) nel DMT2
- Potenziali meccanismi d'azione degli SGLT2-I
  - ripristino metabolico diurno
  - protezione cardio-vascolare
  - protezione microvascolare
  - azioni ematologiche
- Evidenze cliniche
- Conclusioni



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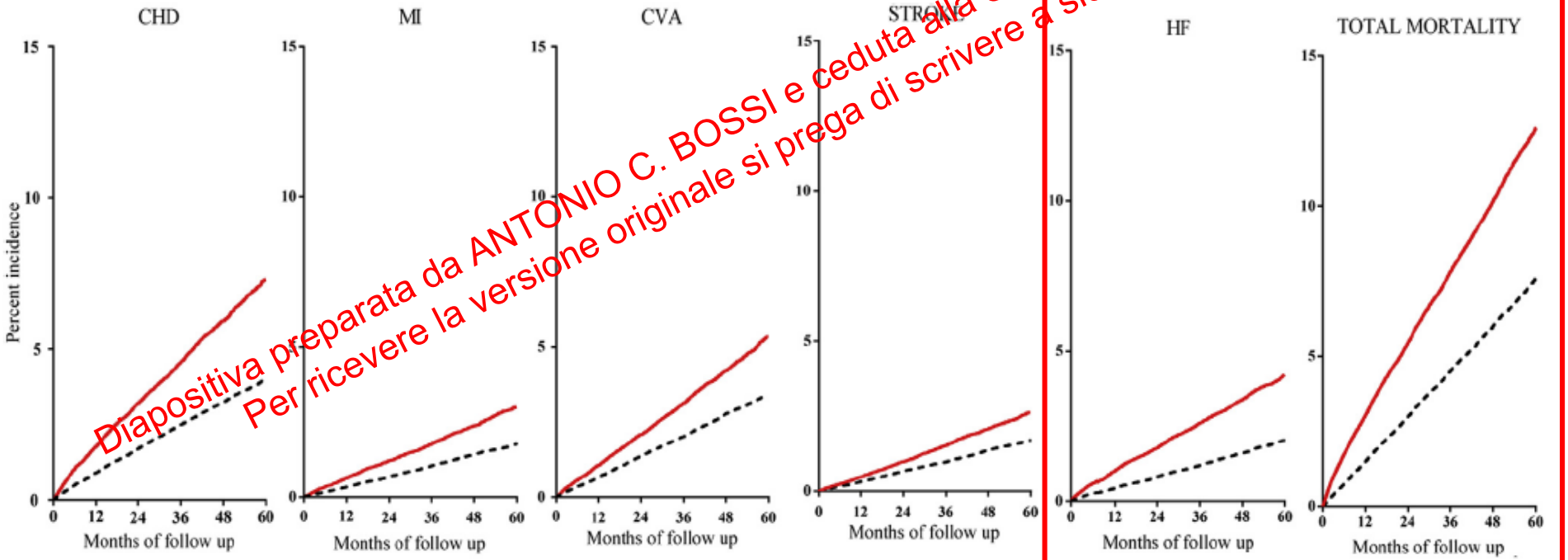
http://dx.doi.org/10.1016/j.numecd.2013.08.005
Nutrition, Metabolism & Cardiovascular Diseases
journal homepage: www.elsevier.com/locate/nmcd

# Elevated risk of death and major cardiovascular events in subjects with newly diagnosed diabetes: Findings from an administrative database

L. Monesi [a], M. Tettamanti [b], L. Cortesi [a], M. Baviera [a], I. Marzona [a], F. Avanzini [a], G. Monesi [c], A. Nobili [d], E. Riva [b], I. Fortino [e], A. Bortolotti [e], G. Fontana [e], L. Mosino [e], R. Trevisan [f], M.C. Roncaglioni [a,*]



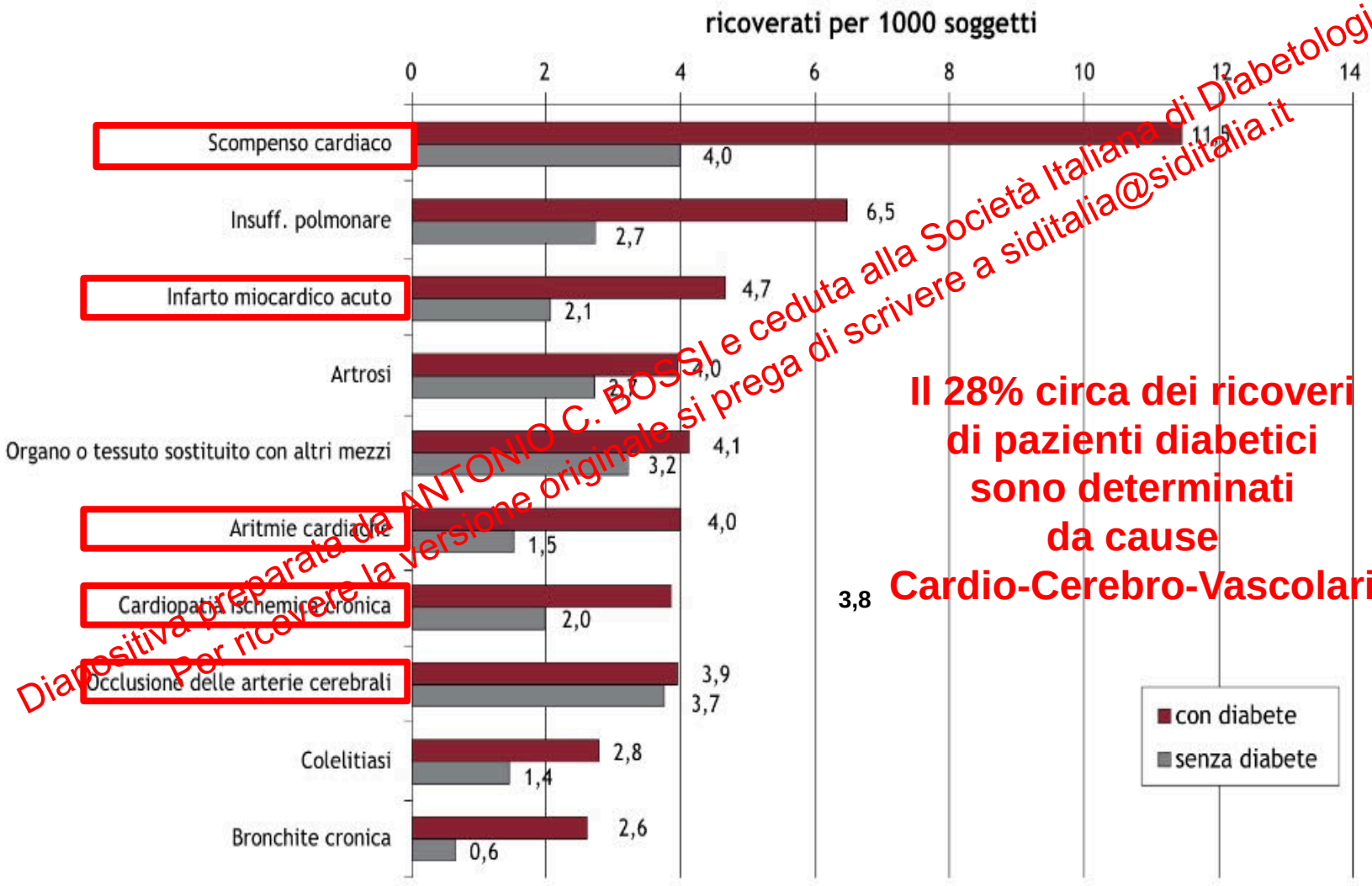



p (Long-rank test) <0.001 for all comparisons

**Incidenza %**

Patients with newly diagnosed diabetes — Subjects without diabetes

# PRIME 10 CAUSE DI RICOVERO ORDINARIO NEI PAZIENTI DIABETICI




**Il 28% circa dei ricoveri di pazienti diabetici sono determinati da cause Cardio-Cerebro-Vascolari**

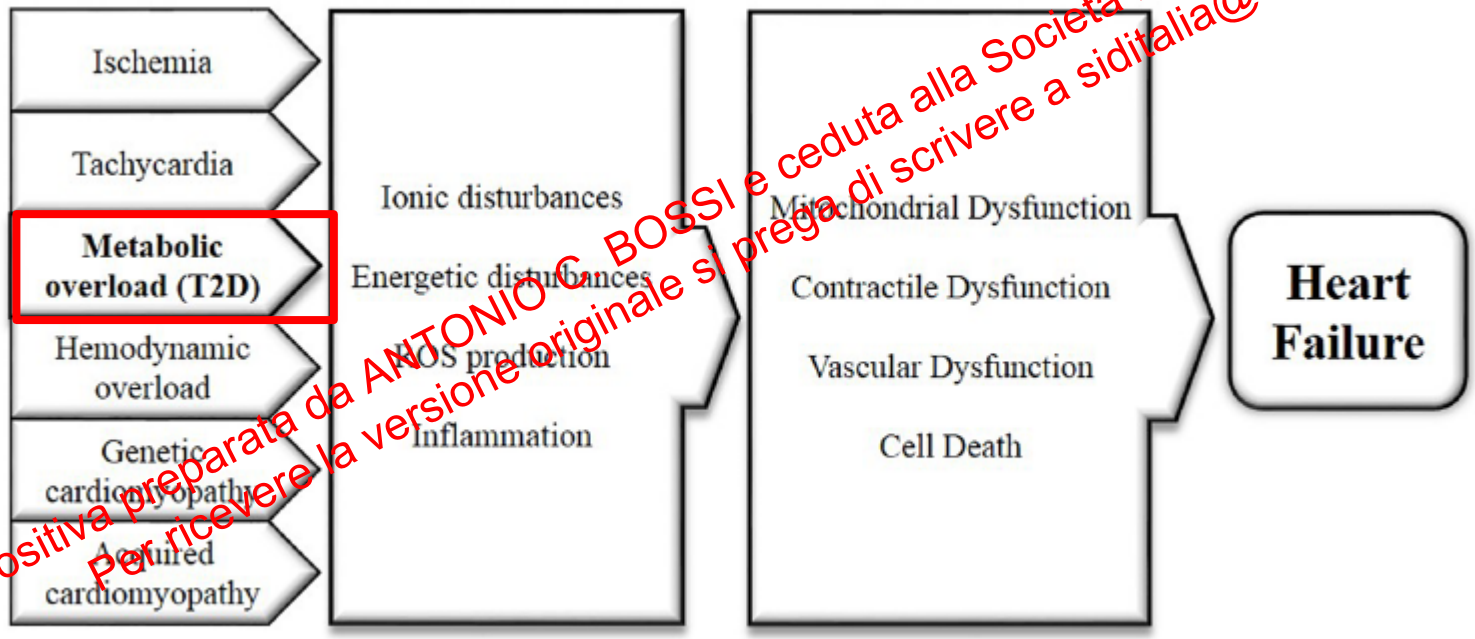
3,8



DATI ARNO 2017

# Direct Cardiac Actions of Sodium Glucose Cotransporter 2 Inhibitors Target Pathogenic Mechanisms Underlying Heart Failure in Diabetic Patients

frontiers in Physiology



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Uthman L, et Al.
Front. Physiol. 2018,9:1575.
doi: 10.3389/fphys.2018.01575

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# Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport

## From Bench to Bedside

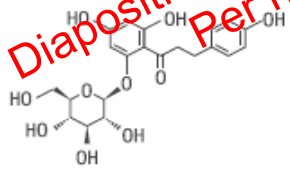
*Sunder Mudaliar,[1,2] David Polidori,[3] Brian Zambrowicz,[4] and Robert R. Henry[1,2]*

*Diabetes Care 2015;38:2344–2353*



1836

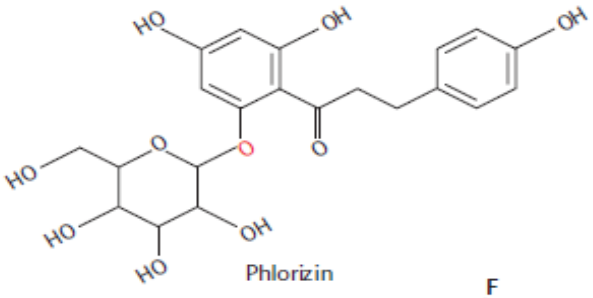
Phlorizin isolated from bark of apple tree



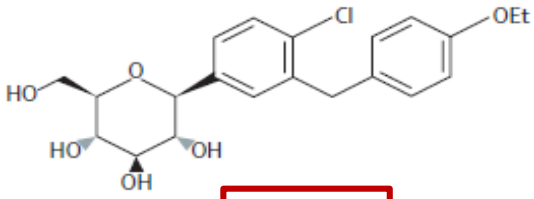
# SGLT inhibitors in management of diabetes

*Lancet Diabetes Endocrinol* 2013; 1: 140–51

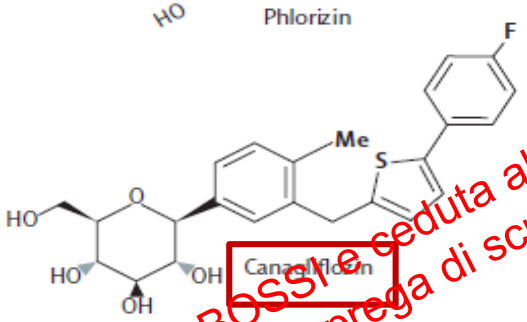
Abd A Tahrani, Anthony H Barnett, Clifford J Bailey



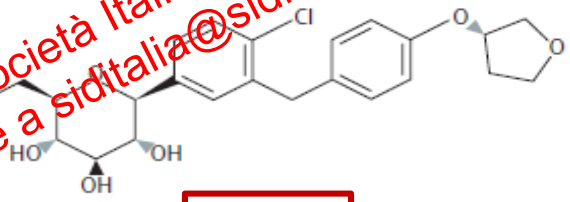
Phlorizin



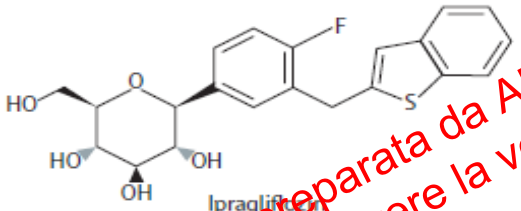
Dapagliflozin



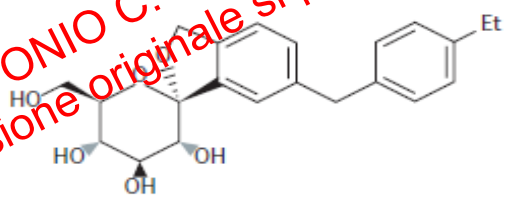
Canagliflozin



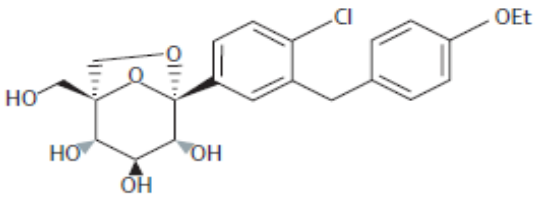
Empagliflozin



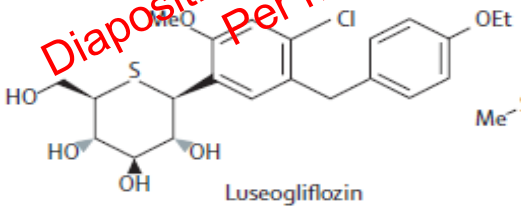
Ipragliflozin



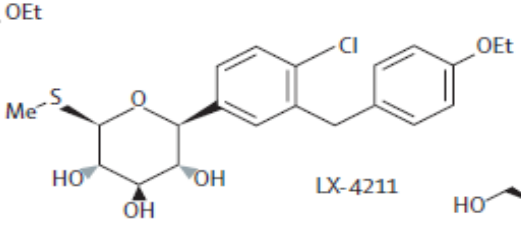
Tofogliflozin



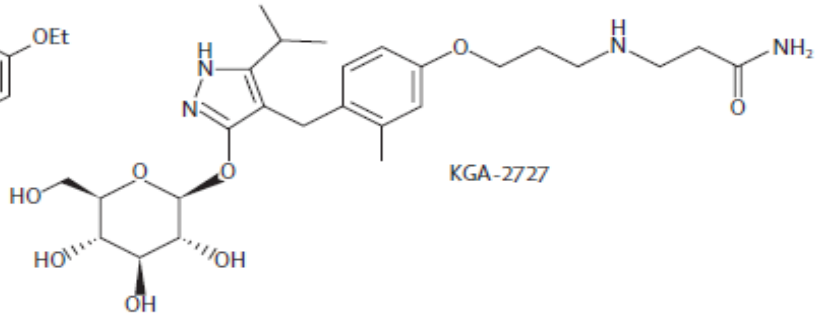
Ertugliflozin



Luseogliflozin

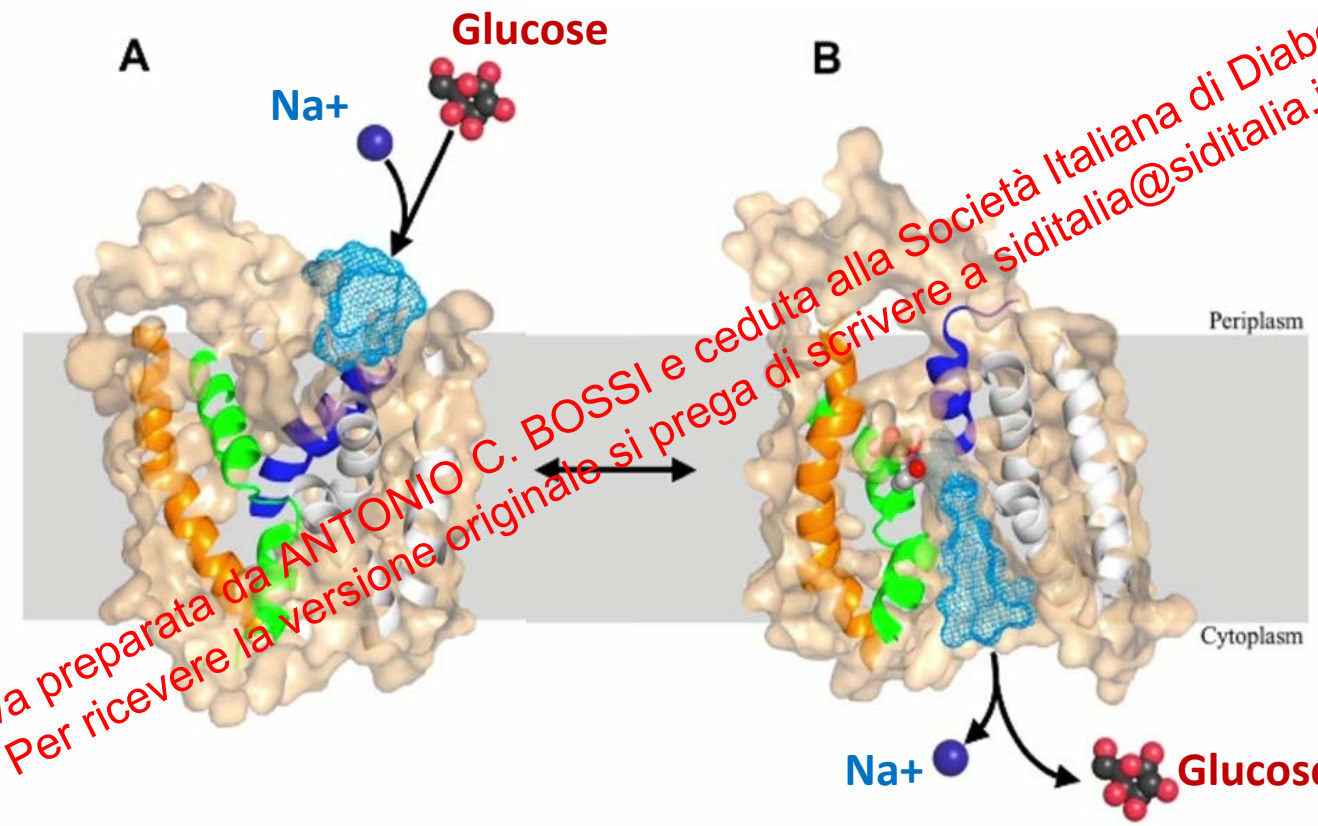


LX-4211



KGA-2727

# STRUTTURA DEL COTRASPORTATORE SODIO-GLUCOSIO



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Mod. from: Faham S, et Al.
www.sciencexpress.org, 2008 July 3, Page 1

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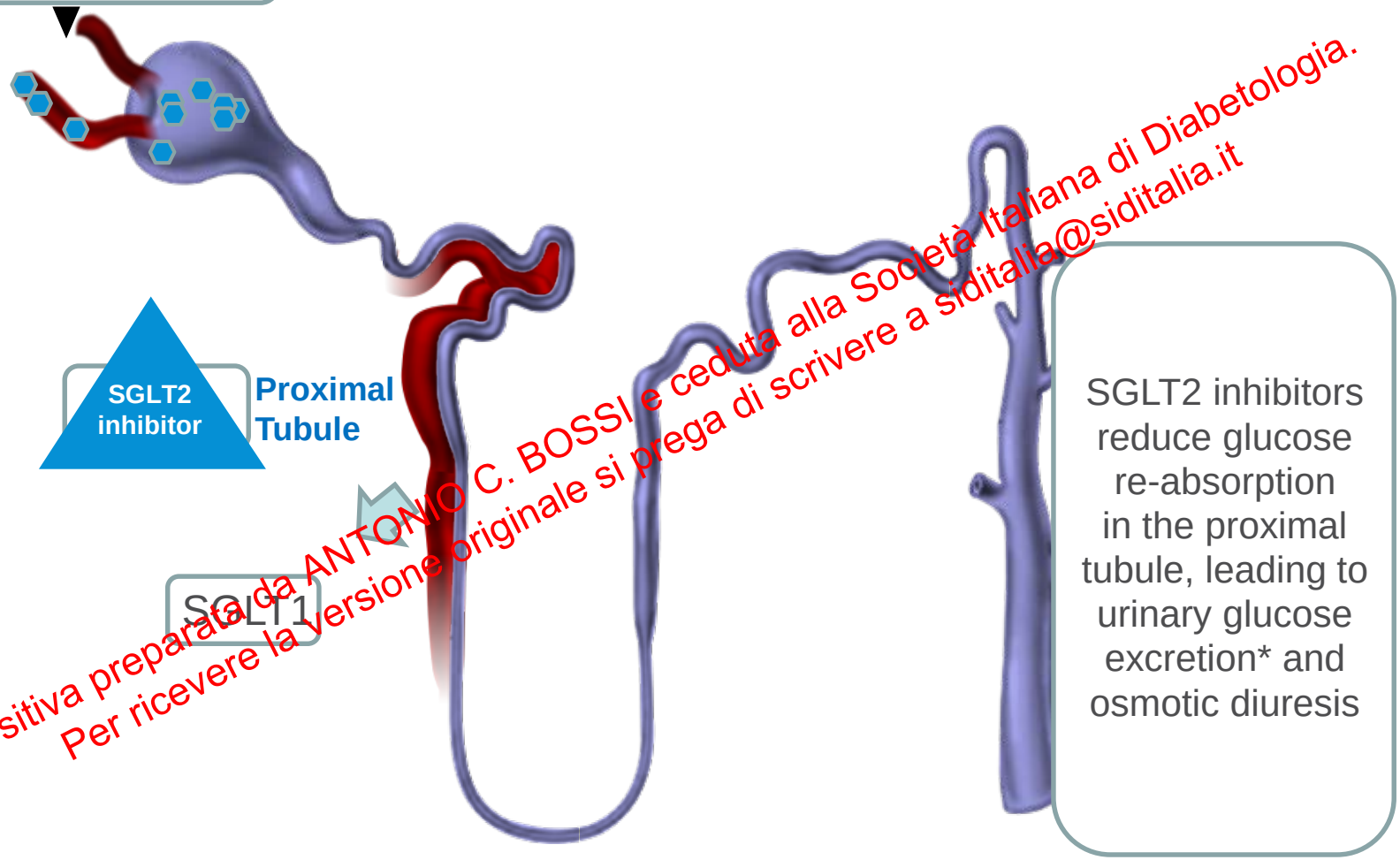
# Urinary glucose excretion via SGLT2 inhibition[1]

Filtered glucose load > 180 g/day




SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis



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SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.

1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

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# *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

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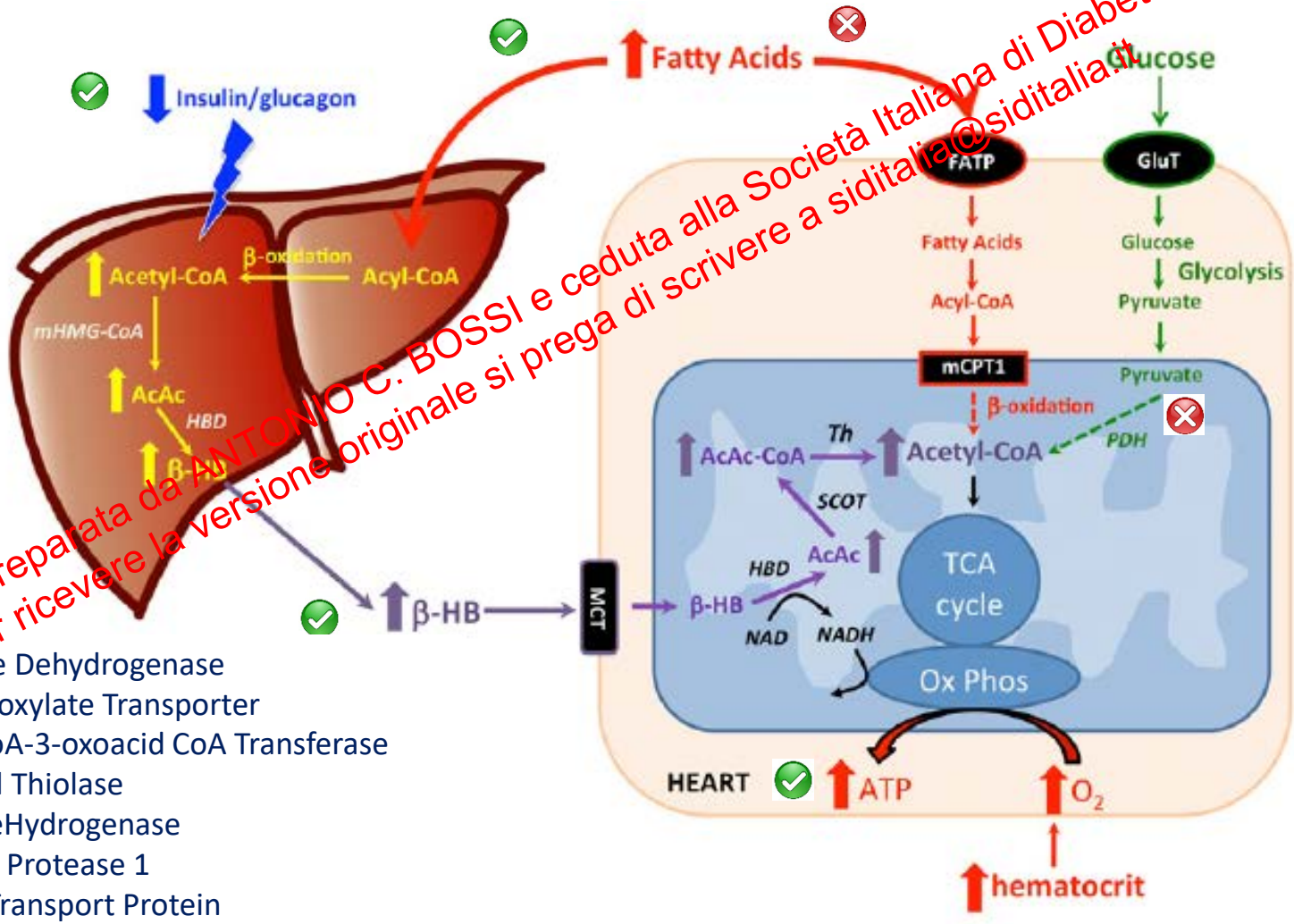
# CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

*Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]*

*Diabetes Care 2016;39:1108–1114*



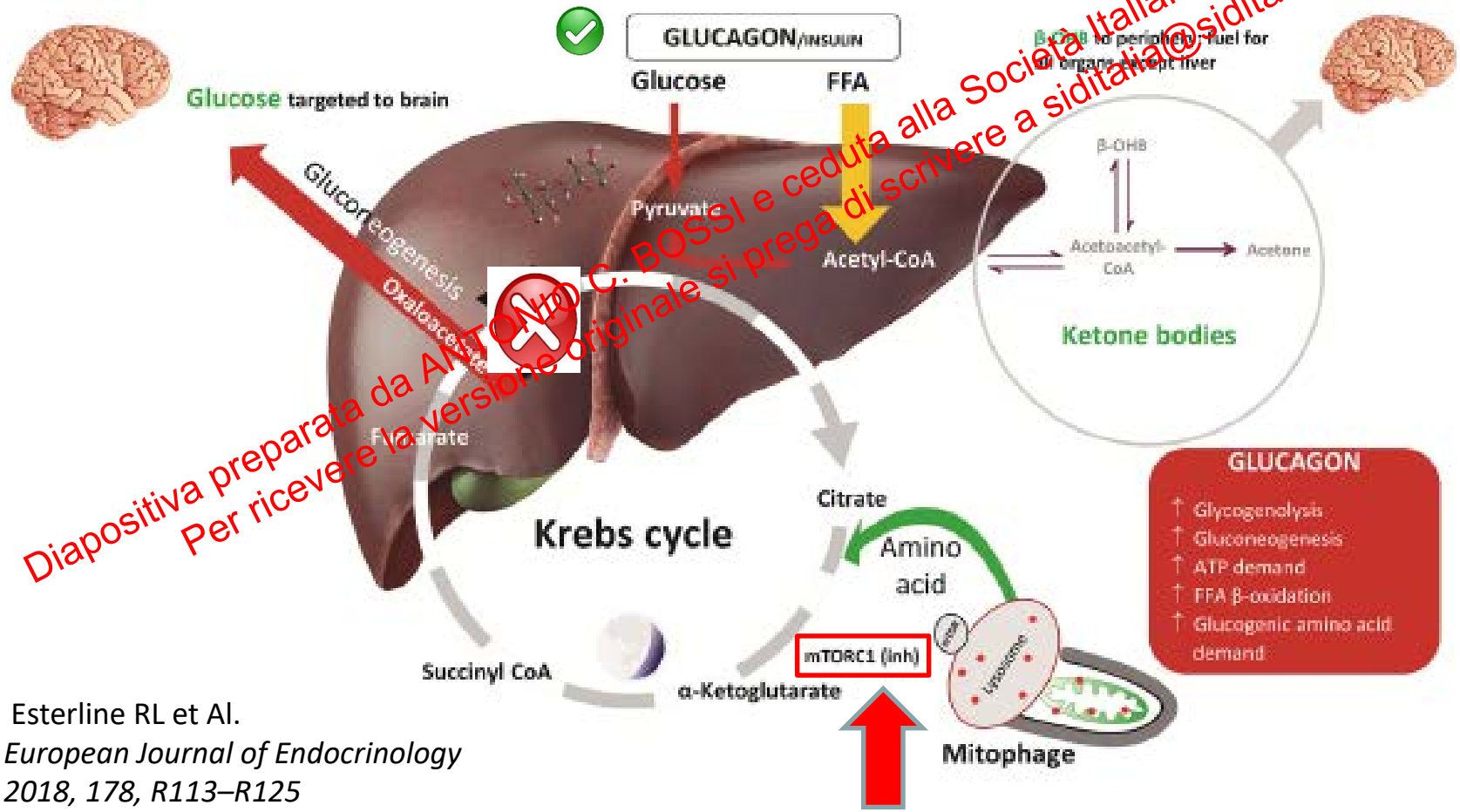



**HBD**: β-OH Butyrate Dehydrogenase
**MCT**: Mono-Carboxylate Transporter
**SCOT**: Succinyl-CoA-3-oxoacid CoA Transferase
**Th**: mitochondrial Thiolase
**PDH**: Pyruvate DeHydrogenase
**mCPT1**: mast Cell Protease 1
**FATP**: Fatty Acid Transport Protein

MECHANISMS IN ENDOCRINOLOGY

# SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

## Impact of SGLT2-i enhanced fasting on hepatic metabolism.



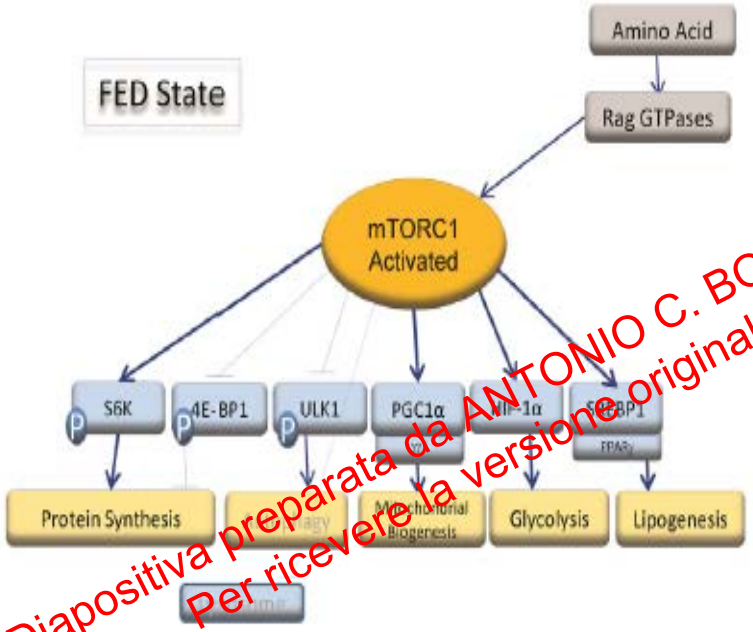



Esterline RL et Al.
*European Journal of Endocrinology*
*2018, 178, R113–R125*

MECHANISMS IN ENDOCRINOLOGY

# SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

## mTOR pathways in the fed and fasted states.



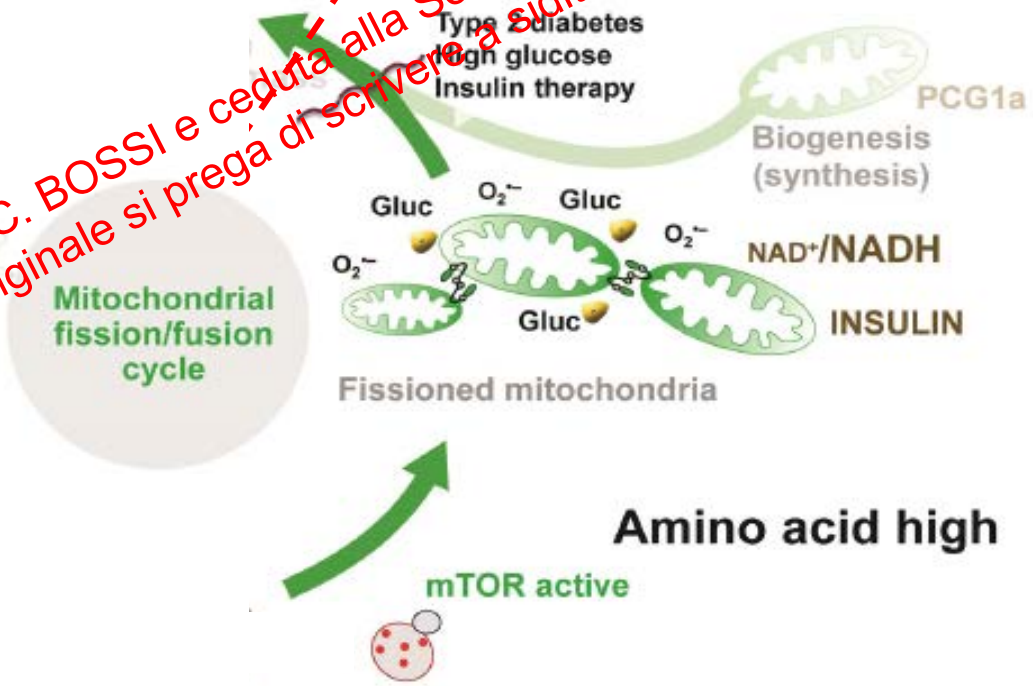



Esterline RL et Al. *European Journal of Endocrinology, 2018, 178, R113–R125*
Adapted with permission from: Maiese K. Molecules to Medicine with mTOR, 1st Edition. Translating Critical Pathways into Novel Therapeutic Strategies. Academic Press Feb 2016.

MECHANISMS IN ENDOCRINOLOGY

# SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism?

## The impact of 'insulin' and SGLT2 inhibitor treatment on the mitochondrial fission/fusion cycle






Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

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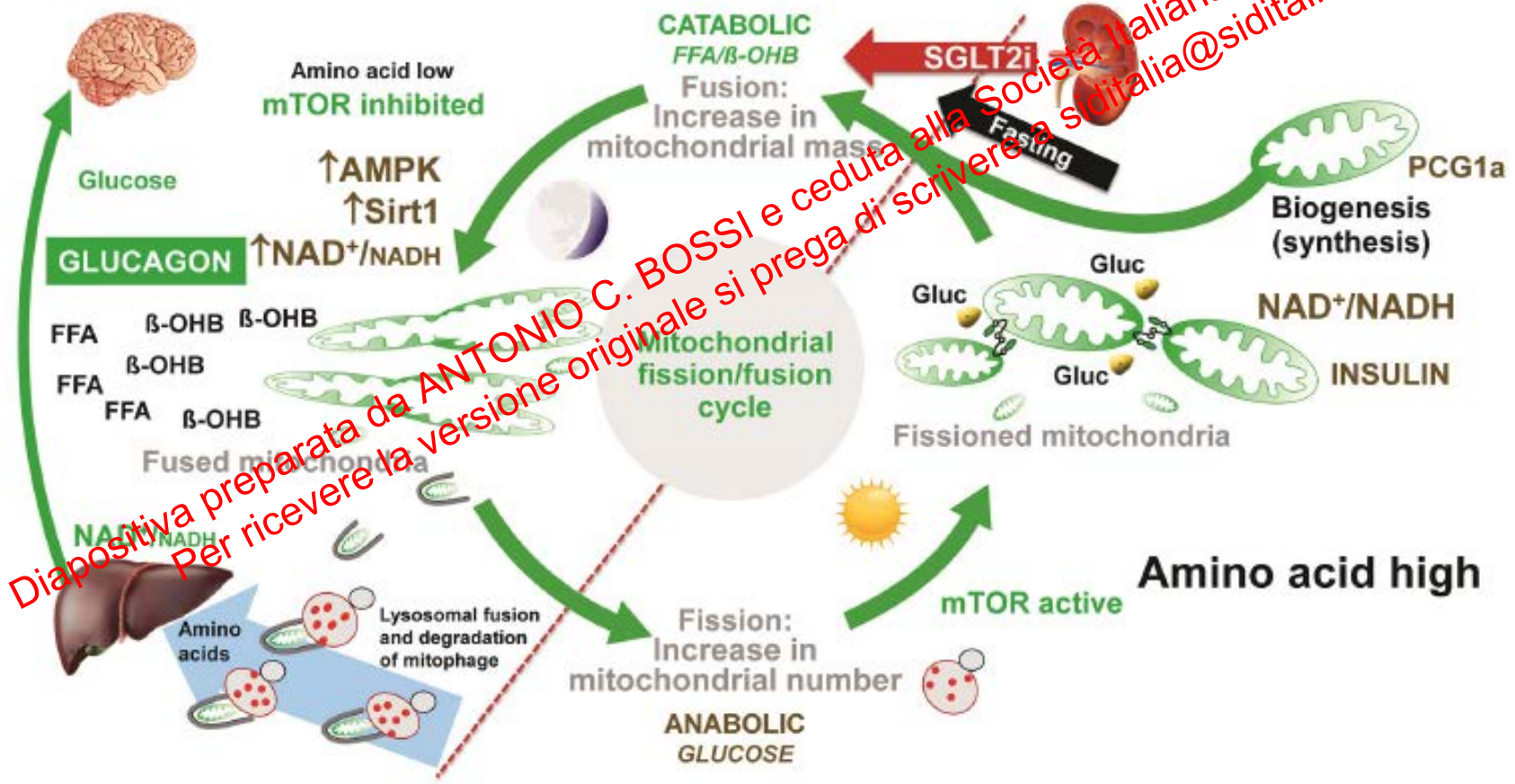




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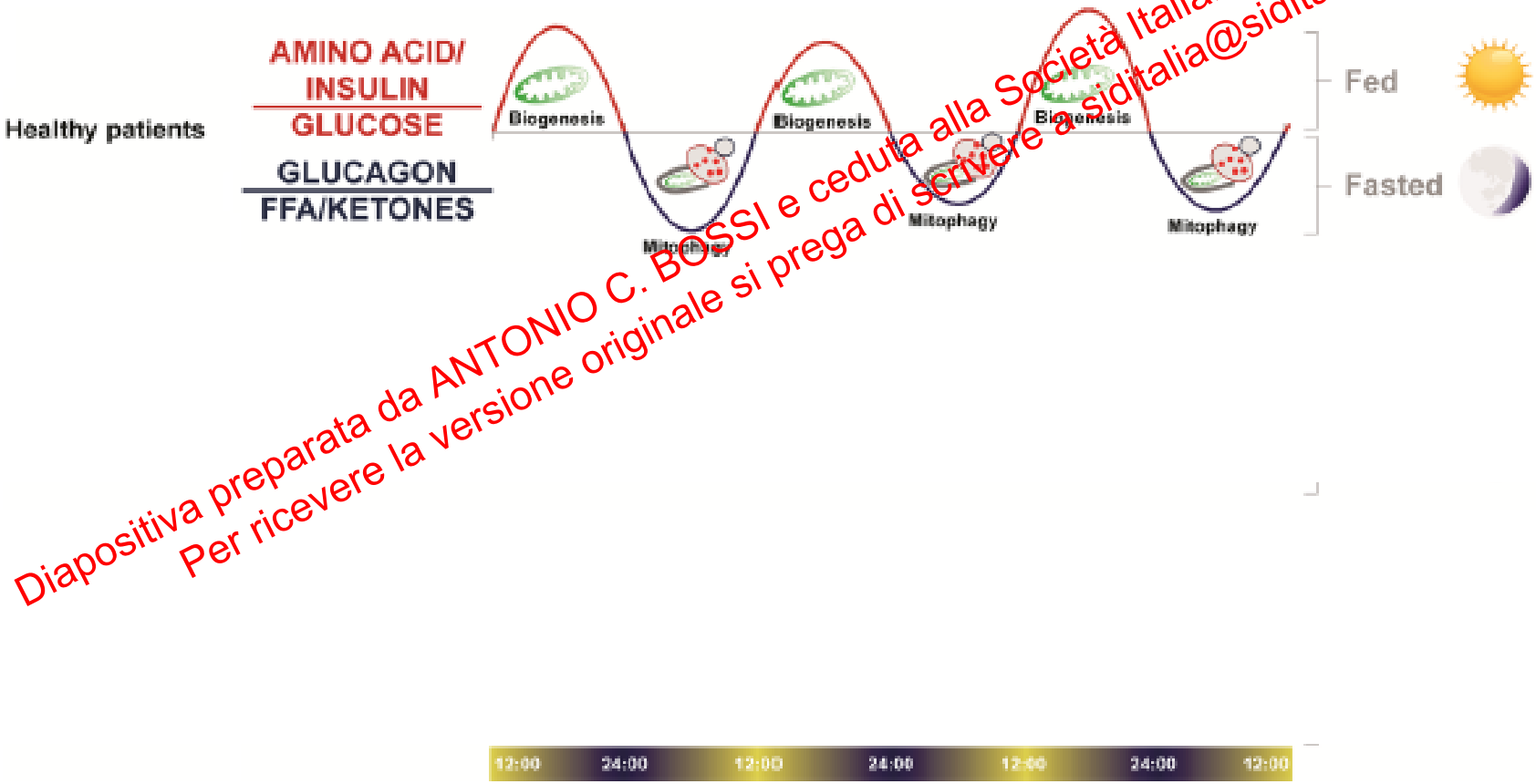




Esterline RL et Al. *European Journal of Endocrinology 2018, 178, R113–R125*

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Contents lists available at ScienceDirect

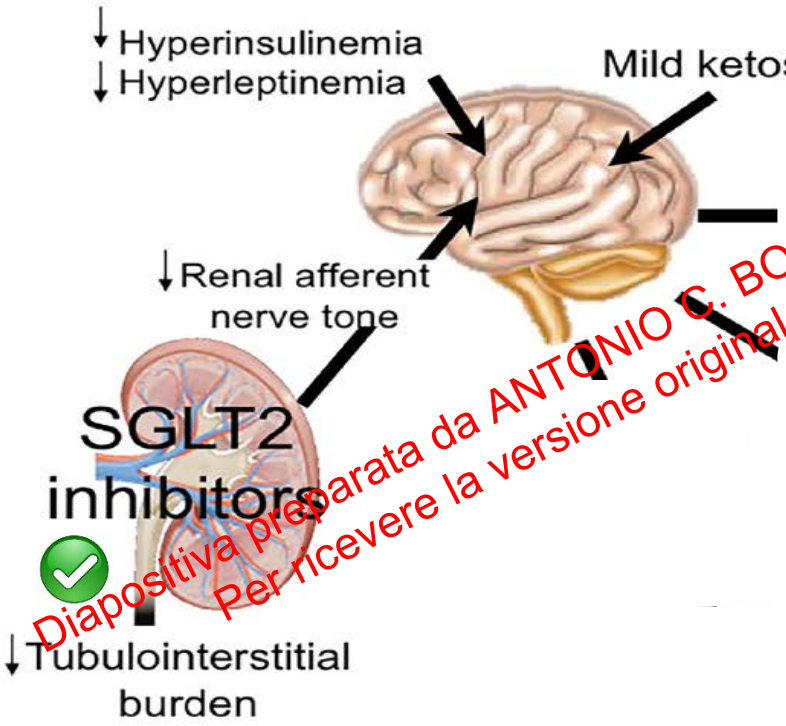
Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

# A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity

## Sympathetic Overactivity Reduction: a proposed mechanism of cardiovascular protection by SGLT2 inhibitors.

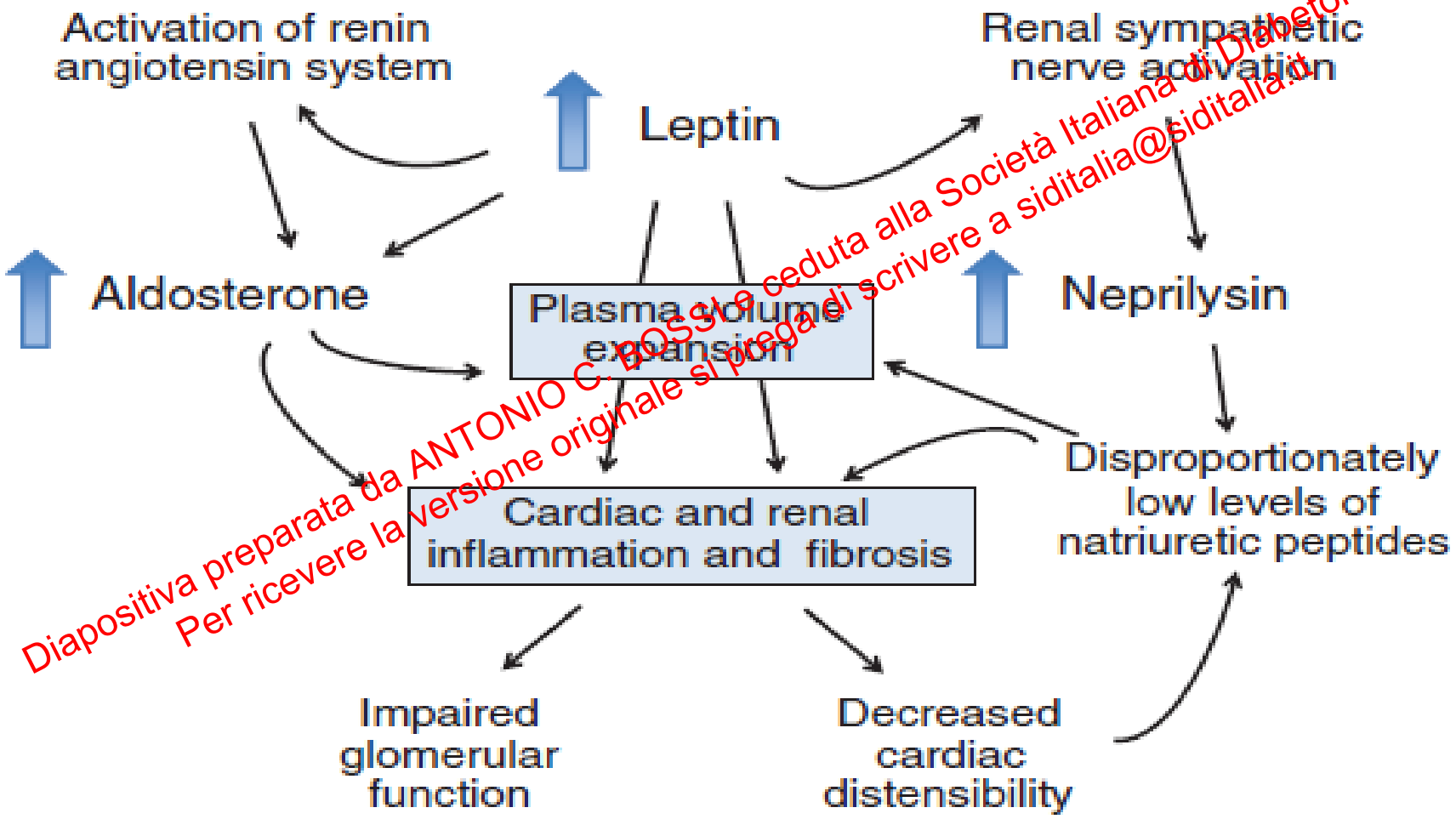





Motoaki Sano

Journal of Cardiology 71 (2018) 471–476

# Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis

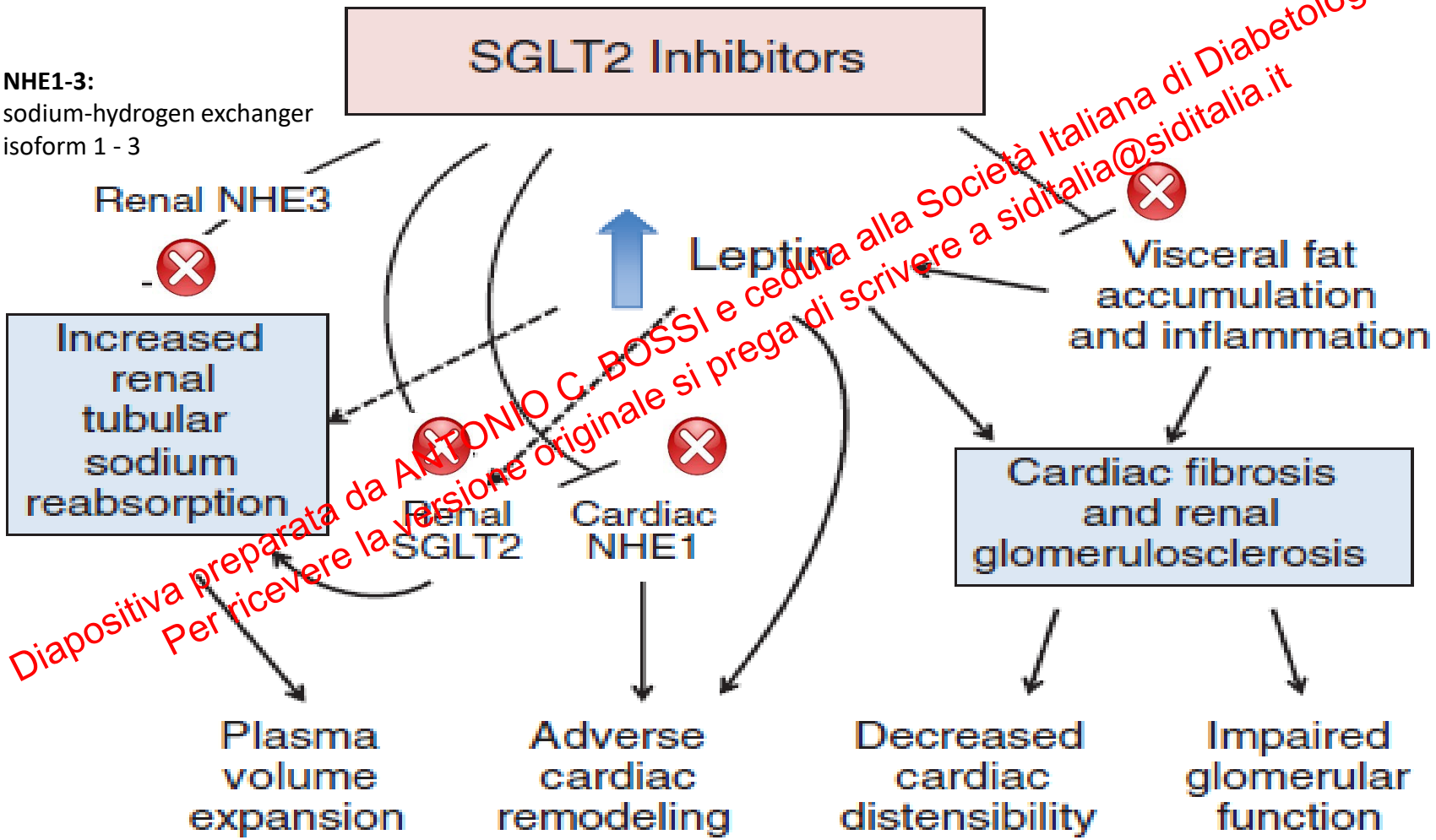





Milton Packer. Diabetes Obes Metab. 2018;1–6.

# Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis

**NHE1-3:**
sodium-hydrogen exchanger isoform 1 - 3

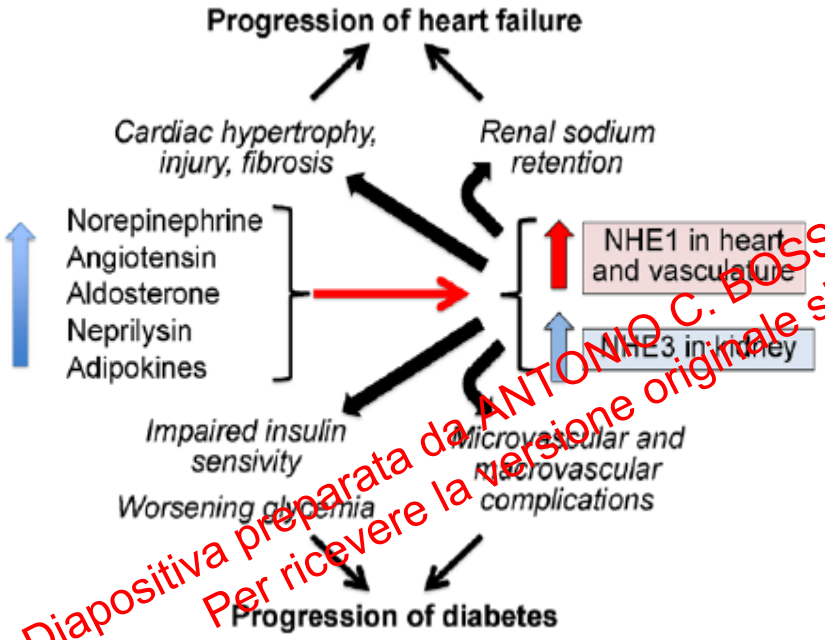





Milton Packer. Diabetes Obes Metab. 2018;1–6.

# Activation and Inhibition of Sodium-Hydrogen Exchanger Is a Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With That of Heart Failure

*Packer M. Circulation. 2017;136:1548–1559.*

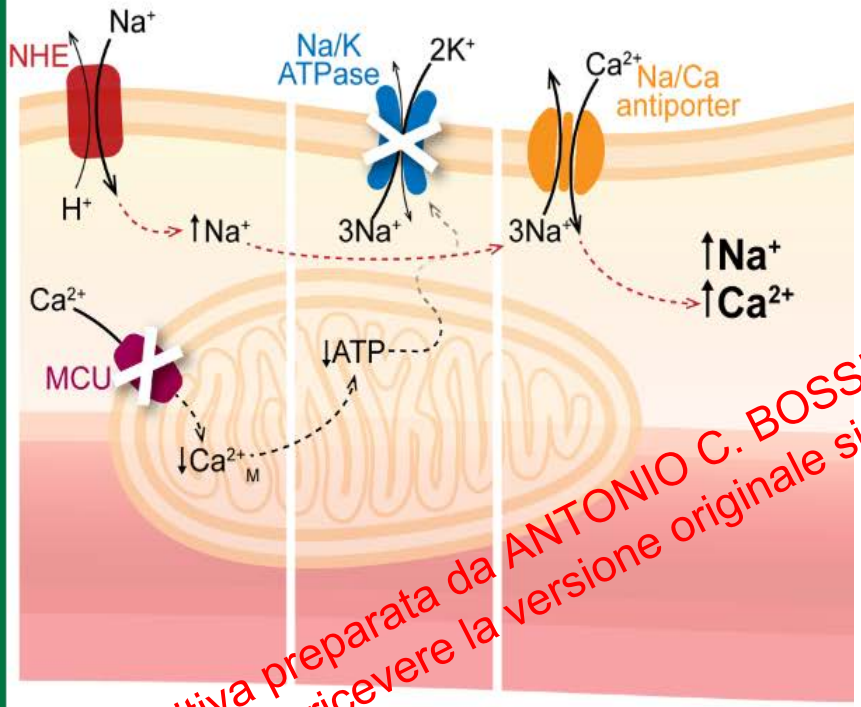





**NHE-dependent pathways that may underlie the interplay of the pathogenesis of heart failure and diabetes.**

# SGLT2 inhibition and direct effects on Na+/H+ exchange in the myocardium

Diabetologia





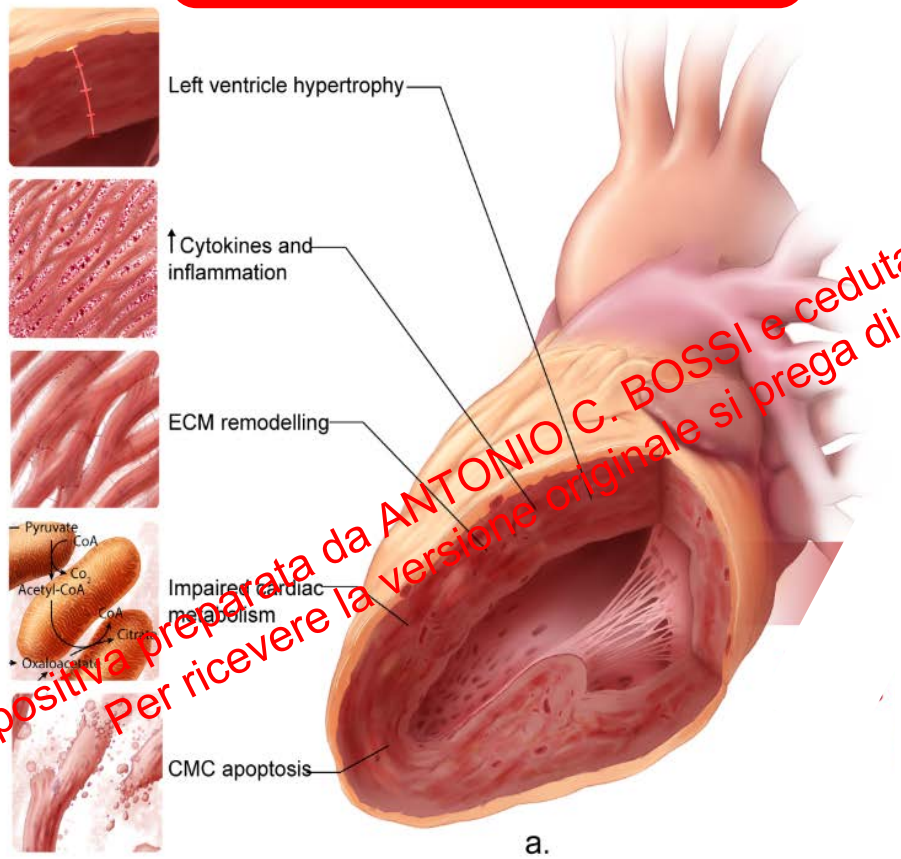

**Diabetes-associated heart failure**

Verma and McMurray (2018)
Diabetologia DOI 10.1007/s00125-018-4670-7

# Cardiovascular protection by SGLT2 inhibitors

Diabetologia

**Diabetes-associated ventricular remodelling**






Verma and McMurray (2018)
Diabetologia DOI 10.1007/s00125-018-4670-7

# Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics (porcine model)

**FIGURE 1** Empagliflozin Ameliorates Anatomical LV Remodeling

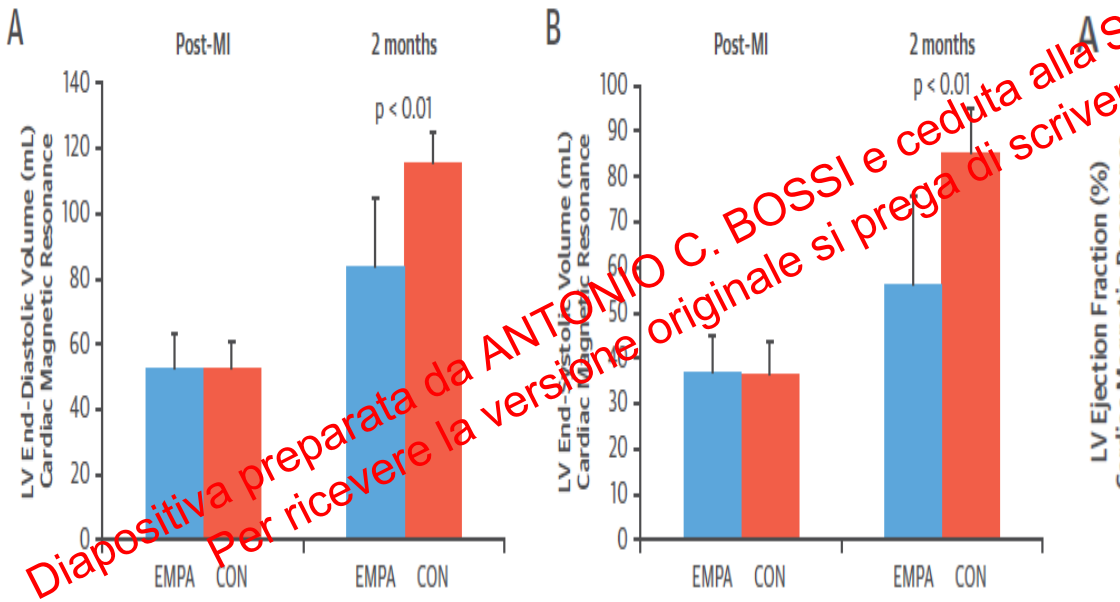
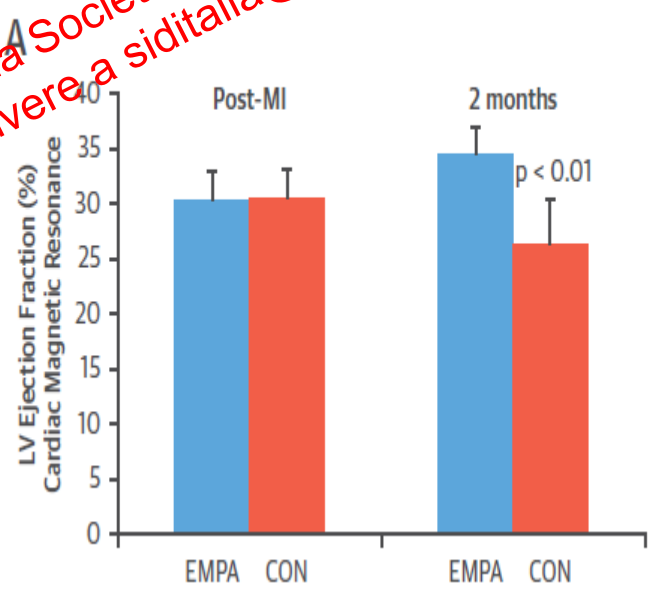



**FIGURE 2** Empagliflozin Improves LV Systolic Function Post-MI



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Santos-Gallego CG et Al.
J Am Coll Cardiol 2019;73:1931–44

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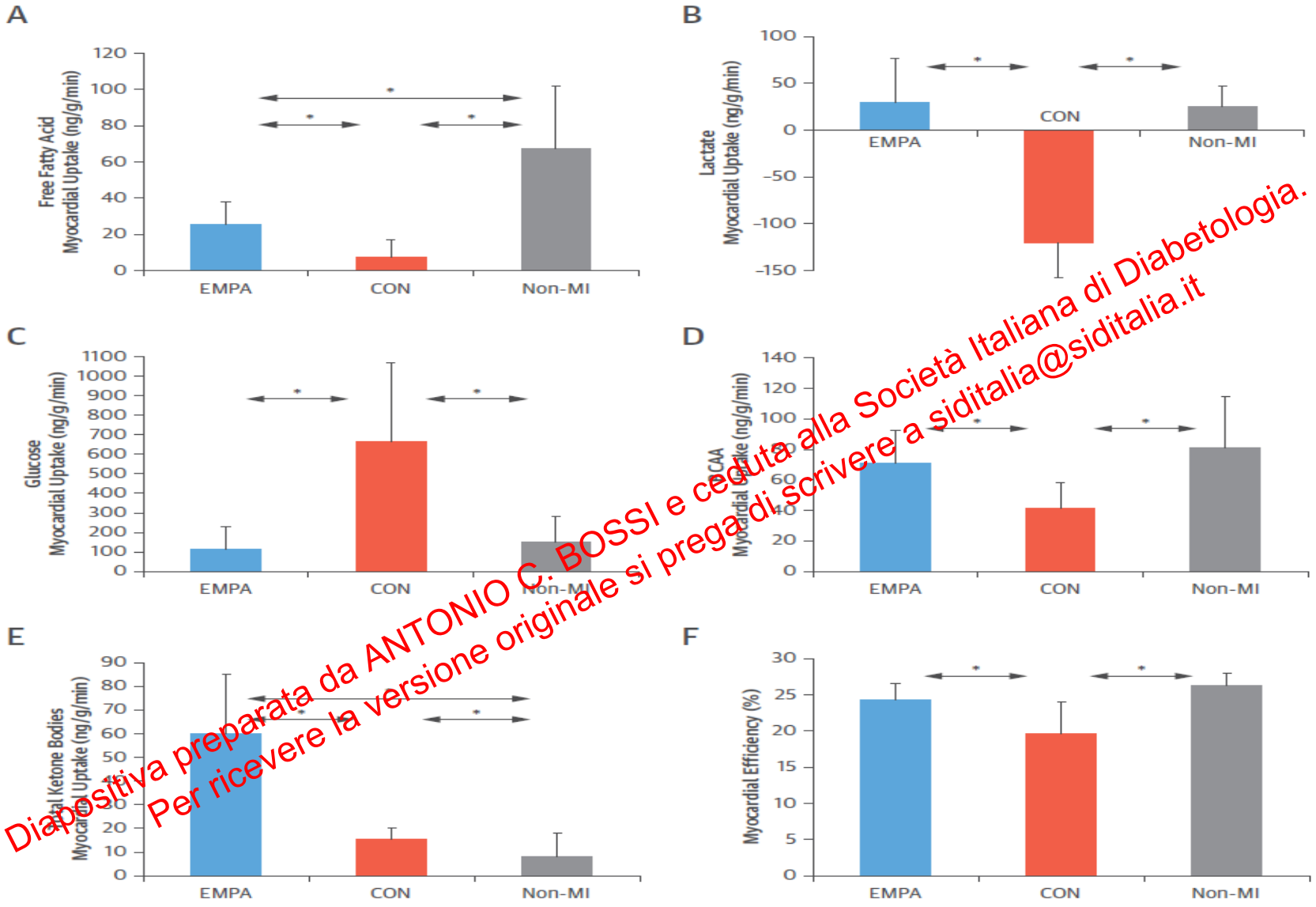




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J Am Coll Cardiol 2019;73:1931–44

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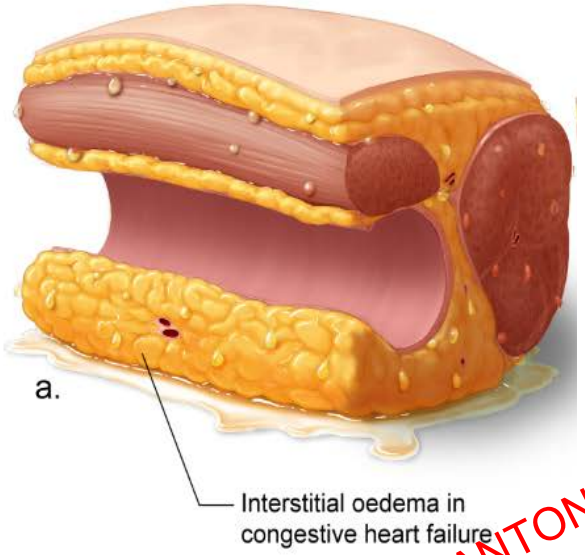
# SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics

Diabetologia






**Congestive heart failure**



**Volume regulation by SGLT2-i (interstitial > intravascular) may limit the aberrant reflex neurohumoral stimulation that occurs in the setting of intravascular depletion.**

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Verma and McMurray (2018)
Diabetologia DOI 10.1007/s00125-018-4670-7


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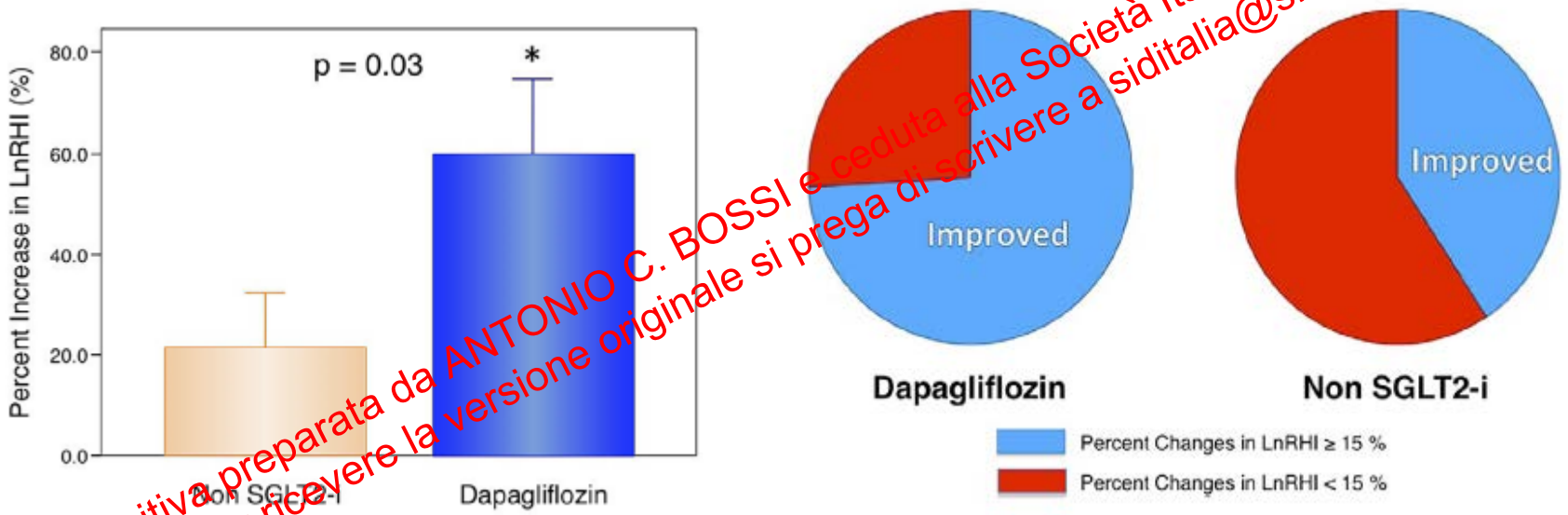
**Internal Medicine**
The Japanese Society of Internal Medicine

doi: 10.2169/internalmedicine.0701-17
Intern Med Advance Publication
http://internmed.jp

# The SGLT2 Inhibitor Dapagliflozin Significantly Improves the Peripheral Microvascular Endothelial Function in Patients with Uncontrolled Type 2 Diabetes Mellitus






**LnRHI, natural logarithmic transformation of the reactive hyperemia index**

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

Sugiyama S et Al.
Intern Med Advance Publication
DOI: 10.2169/internalmedicine.0701-17

Sistema Socio Sanitario
Regione Lombardia
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# *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

## AGENDA

- Cenni di epidemiologia (HF & CVD) nel DMT2
- Potenziali meccanismi d'azione degli SGLT2-I
  - ripristino metabolico diurno
  - protezione cardio-vascolare
  - protezione microvascolare
  - azioni ematologiche
- Evidenze cliniche
- Conclusioni



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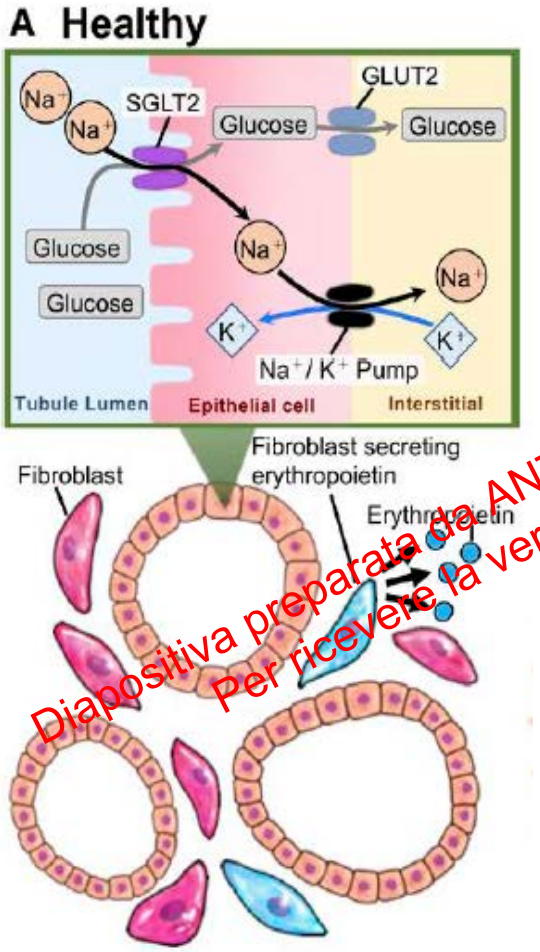
Sano M, Goto S. Circulation. 2019;139:1985–1987.

# Possible Mechanism of Hematocrit Elevation by Sodium Glucose Cotransporter 2 Inhibitors and Associated Beneficial Renal and Cardiovascular Effects

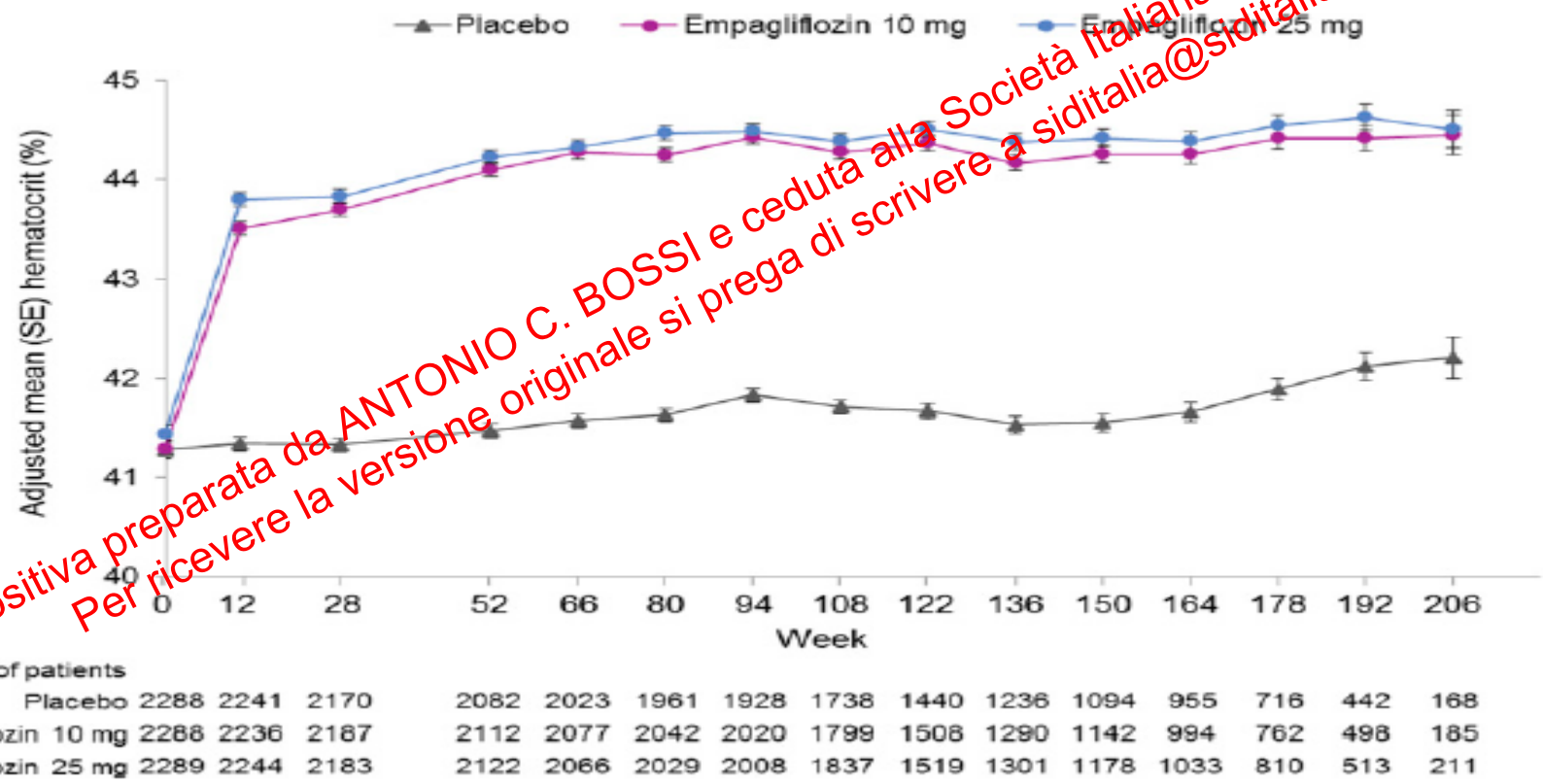


# How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial

*Silvio E. Inzucchi,[1] Bernard Zinman,[2] David Fitchett,[3] Christoph Wanner,[4] Ele Ferrannini,[5] Martin Schumacher,[6] Claudia Schmoor,[6] Kristin Ohneberg,[6] Odd Erik Johansen,[7] Jyothis T. George,[8] Stefan Hantel,[9] Erich Bluhmki,[9] and John M. Lachin[10]*

*https://doi.org/10.2337/dc17-1096*






**Hematocrit over time in patients treated with empagliflozin 10 mg, empagliflozin 25mg, and placebo.**

# How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial

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*https://doi.org/10.2337/dc17-1096*

| | HR for CV death with empagliflozin vs. placebo (95% CI) | Percentage Mediation |
|---|---|---|
| Unadjusted | 0.615 (0.491, 0.770) | |
| Adjusted for | | |
| $HbA_{1c}$ | 0.687 (0.543, 0.868) | 22.8 |
| FPG | 0.709 (0.559, 0.898) | 29.3 |
| SBP | 0.610 (0.485, 0.766) | −1.7 |
| DBP | 0.618 (0.493, 0.774) | 1.0 |
| Heart rate | 0.603 (0.497, 0.732) | 2.7 |
| LDL-C | 0.591 (0.451, 0.741) | −8.2 |
| HDL-C | 0.628 (0.500, 0.789) | 4.6 |
| logTG | 0.603 (0.481, 0.757) | −4.1 |
| FFAs | 0.587 (0.463, 0.743) | −9.6 |
| logUACR | 0.672 (0.536, 0.844) | 18.2 |
| eGFR (MDRD) | 0.601 (0.480, 0.752) | −4.7 |
| eGFR (CKD-EPI) | 0.597 (0.477, 0.748) | −6.1 |
| Weight | 0.588 (0.466, 0.741) | −9.2 |
| BMI | 0.588 (0.466, 0.742) | −9.2 |
| WC | 0.602 (0.480, 0.755) | −4.4 |
| Hematocrit | 0.791 (0.620, 1.009) | 51.8 |
| Hemoglobin | 0.768 (0.604, 0.978) | 45.7 |
| Albumin | 0.717 (0.571, 0.900) | 31.6 |
| Uric acid | 0.673 (0.536, 0.845) | 18.5 |

Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

# *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

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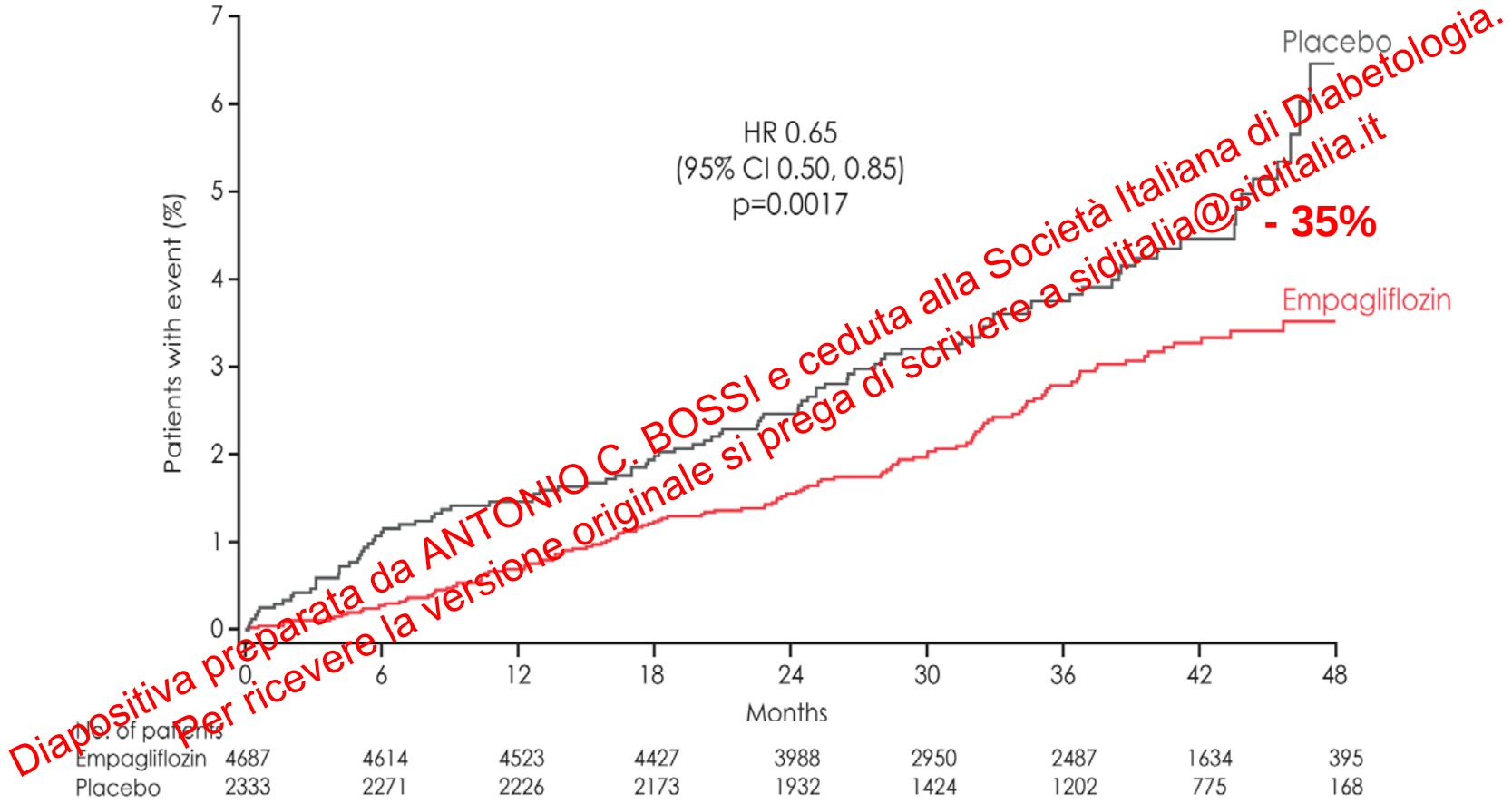
# EMPA-REG OUTCOME: Hospitalisation for HF



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Zinman B, et Al, for the EMPA-REG OUTCOME Investigators. This article was published on September 17, 2015, at NEJM.org.
DOI: 10.1056/NEJMoa1504720

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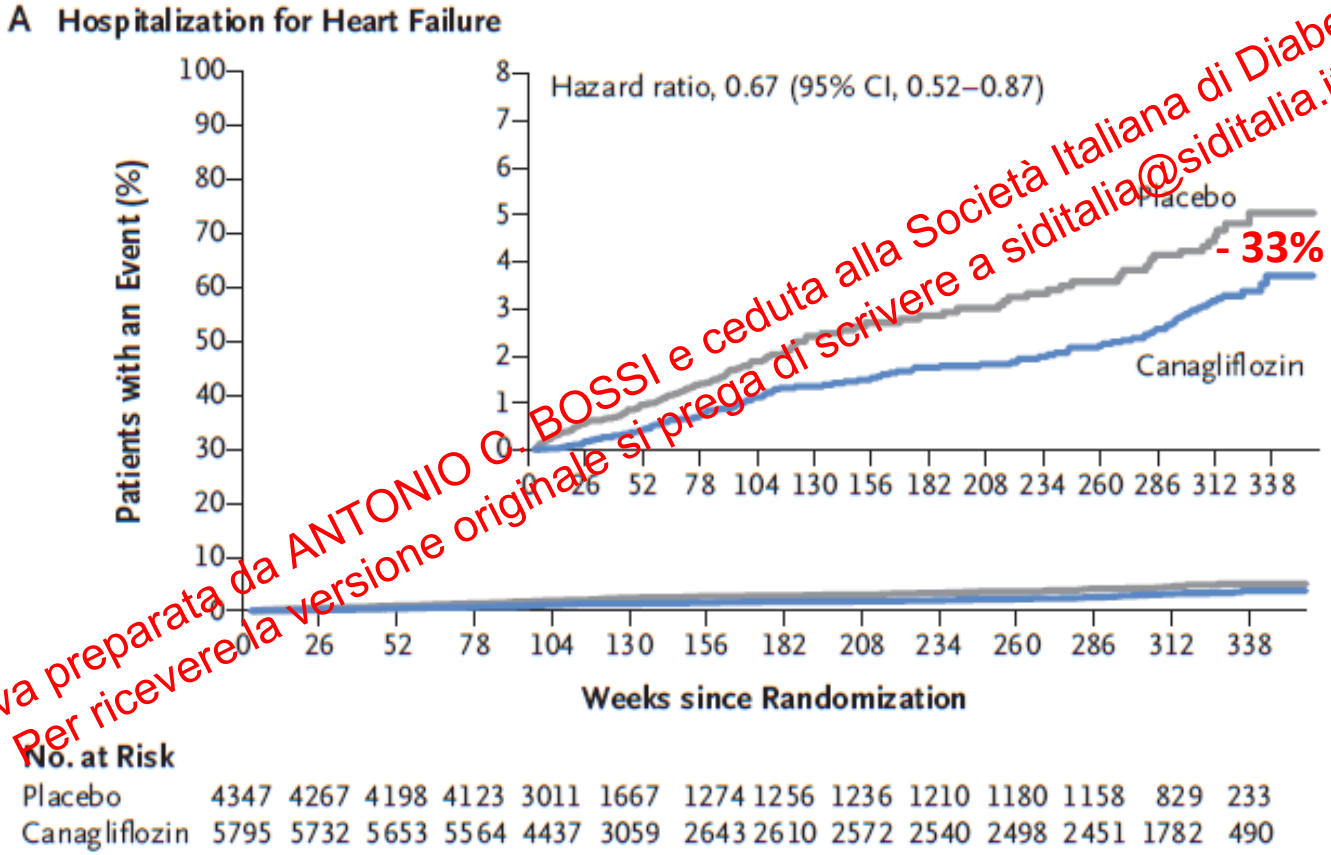
# Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



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Neal B. et Al., for the CANVAS Program Collaborative Group.
This article was published on June 12, 2017,
at NEJM.org. DOI: 10.1056/NEJMoa1611925

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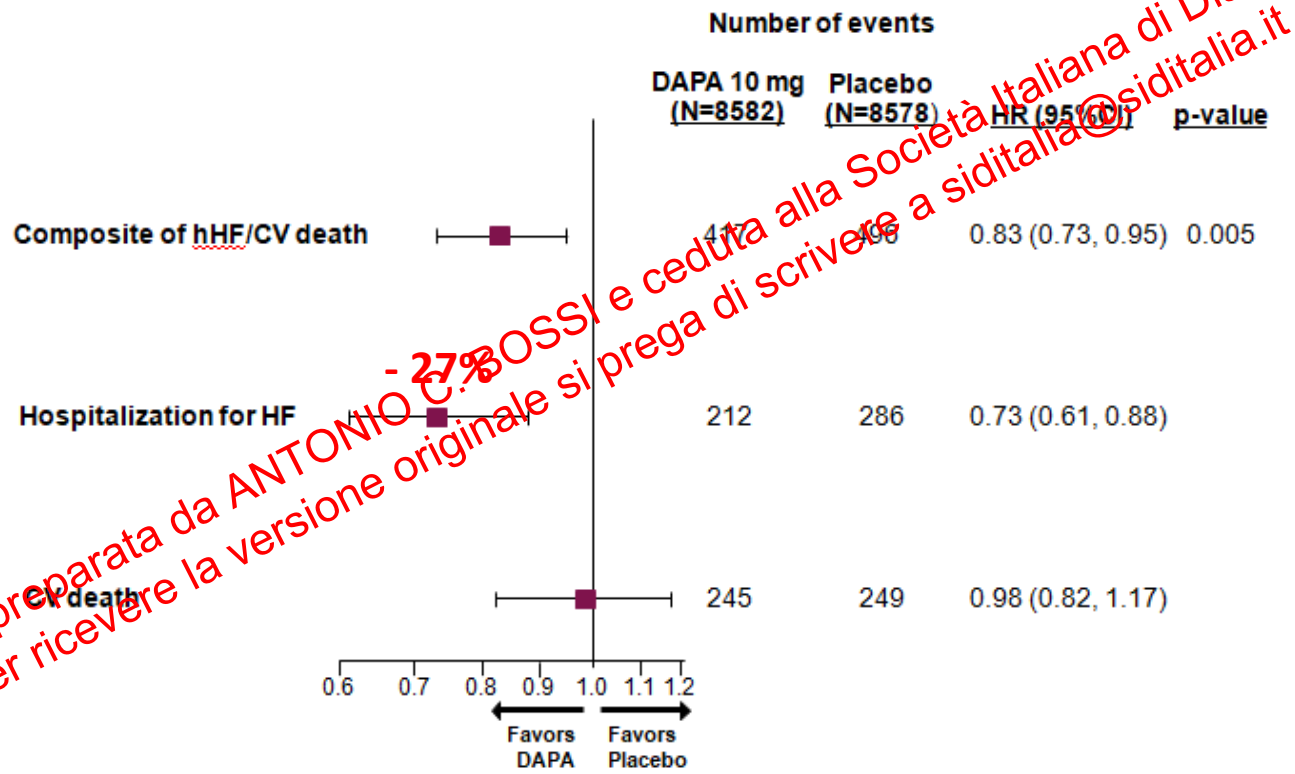
# Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes



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Centro Studi Aterosclerosi

Viviott SD, et Al, for the DECLARE-TIMI 58 Investigators.
This article was published on November 10, 2018, at
NEJM.org. DOI: 10.1056/NEJMoa1812389

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# Different representation of the T2D patients with CV risk among the of the SGLT2i CV outcomes studies

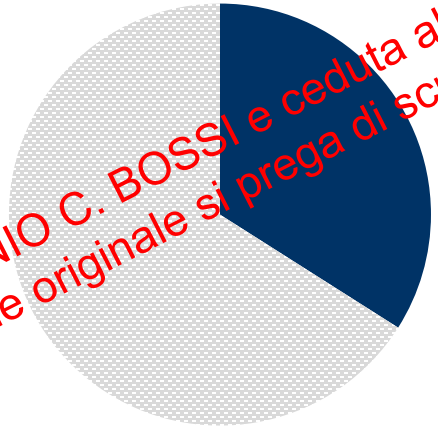
**The proportion of patients with and without established CV disease varied across the three SGLT2 CV outcome studies**



**EMPA-REG OUTCOME**
**(N=7,020)**

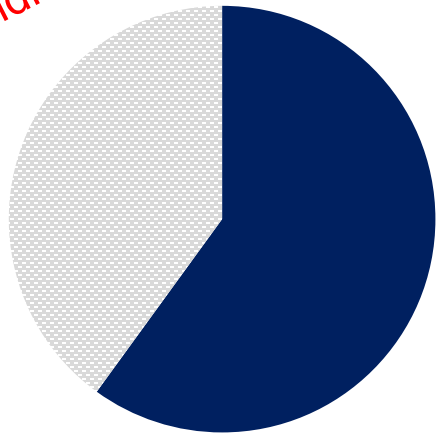
**1%**
of patients did not have eCVD

**CANVAS**
**(N=10,142)**



**34%**
of patients did not have eCVD

**DECLARE**
**(N=17,160)**



**~60%**
of patients did not have eCVD

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes; eCVD, established CV disease.

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

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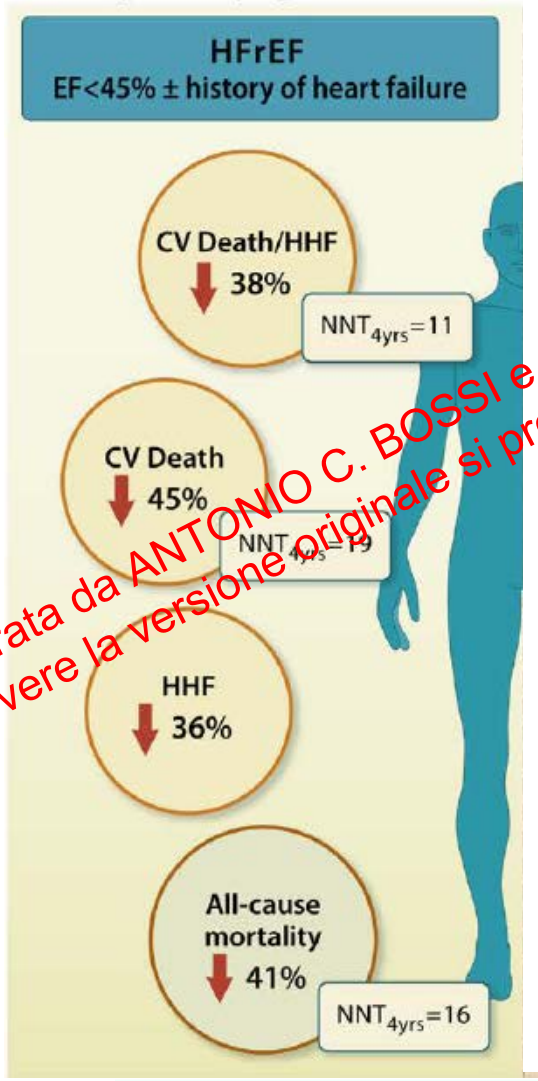
# The Serendipitous Story of SGLT2 Inhibitors in Heart Failure

## New Insights From DECLARE-TIMI 58

Verma S and McMurray JJV
Circulation. 2019;139:2537–2541.



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ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

# Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*



**N = 4744** patients with NYHA class II, III, or IV **heart failure** and an **ejection fraction ≤40%** to receive either **dapagliflozin** (10 mg daily) or placebo, in addition to recommended therapy.

The **primary outcome** was a composite of **worsening heart failure** (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or **cardiovascular death**.

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

This article was published on September 19, 2019, at NEJM.org.
DOI: 10.1056/NEJMoa1911303

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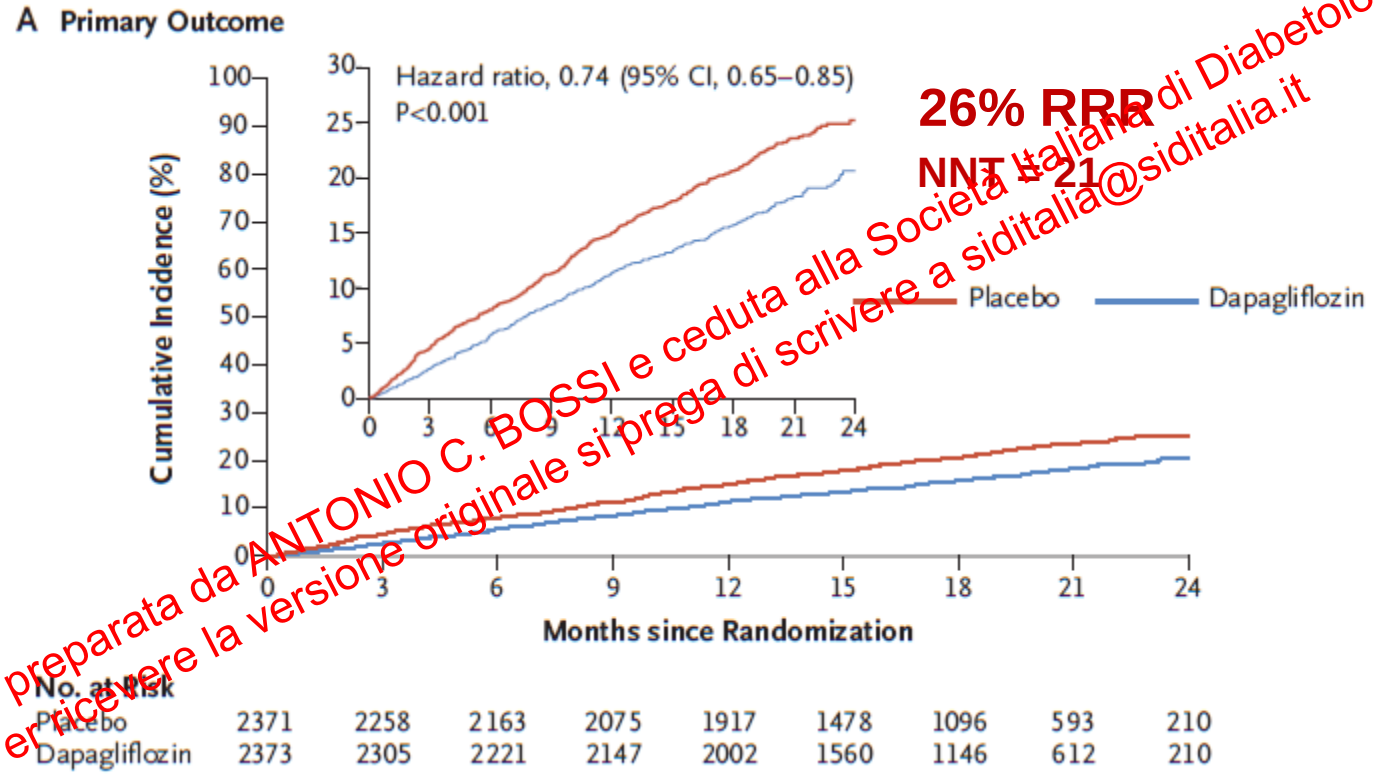
# DAPA-HF

## Primary Endpoint: CV Death or hHF or an Urgent HF Visit




**26% RRR**

**NNT = 21**



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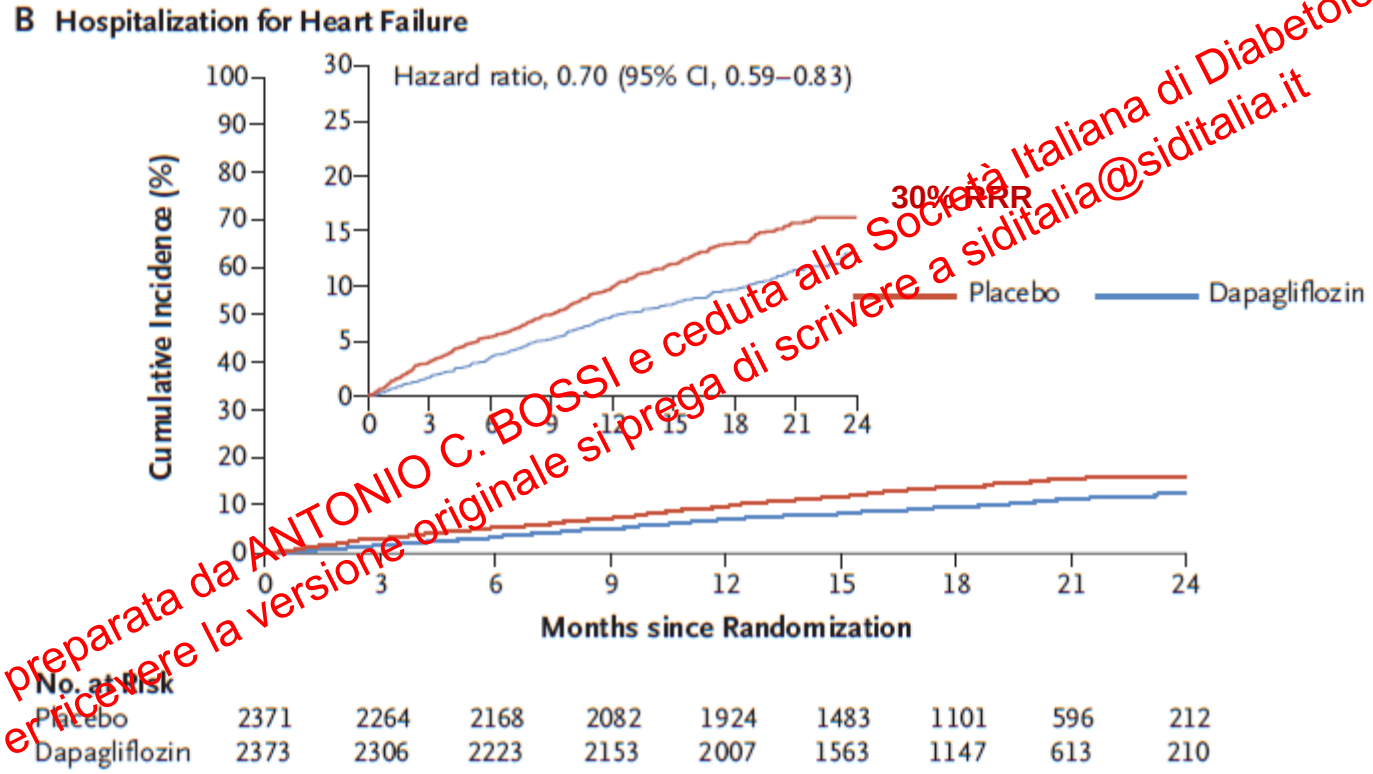
# DAPA-HF

## Hospitalization for HF



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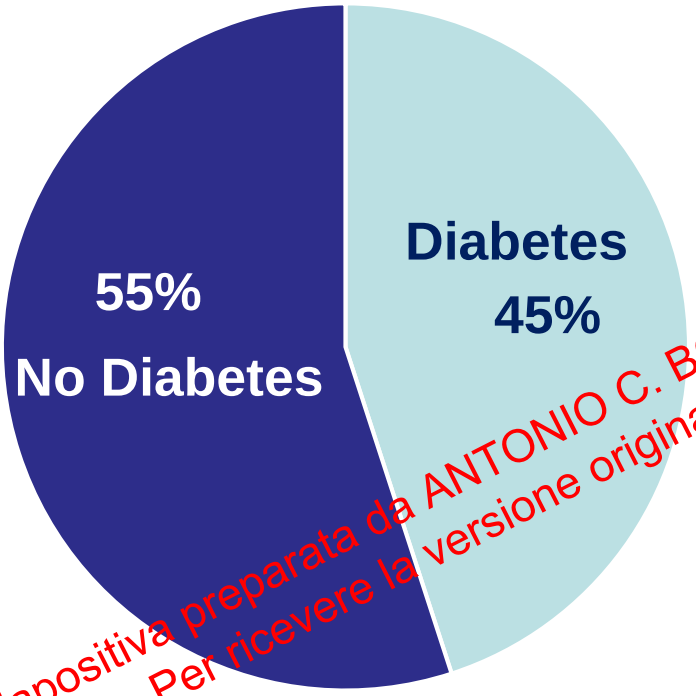
# Majority of Patients in DAPA-HF did not have Type 2 Diabetes




**N=4744**

**History of Diabetes (n=2137)**

- Pre-existing diagnosis of T2D: (42%; n=1983)
- Previously undiagnosed T2D: HbA1c ≥6.5% at Visits 1 and 2 (3%; n=154)

**No Diabetes (n=2607)**

- Prediabetes: HbA1c (≥5.7* to <6.5%) at Visits 1 and 2 (37%; n=1750)
- Euglycemic: HbA1c <5.7% at Visits 1 and 2 (18%; n=857)



- *ADA guidelines define prediabetes as A1C 5.7 to 6.4%[2]
- HbA1c = glycated hemoglobin; T2D = type 2 diabetes.


- 1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail*. 2019;doi: 10.1002/ejhf.1548. Accessed August 21, 2019. 2. ADA Standards of Care. *Diabetes Care*. 2019; 42(Supplement 1):S1-S193.

IL CROSS TALK

# cuore-rene

FISIOPATOLOGIA
ED ASPETTI CLINICI

CATANIA 4 NOVEMBRE 2019

**GRAZIE**
**per la Vostra**
**Attenzione!**



## *Effetto degli SGLT2 inibitori sullo scompenso cardiaco: meccanismi ed evidenze cliniche*

***Antonio C. Bossi***
*ASST Bergamo Ovest – Treviglio (Bg)*

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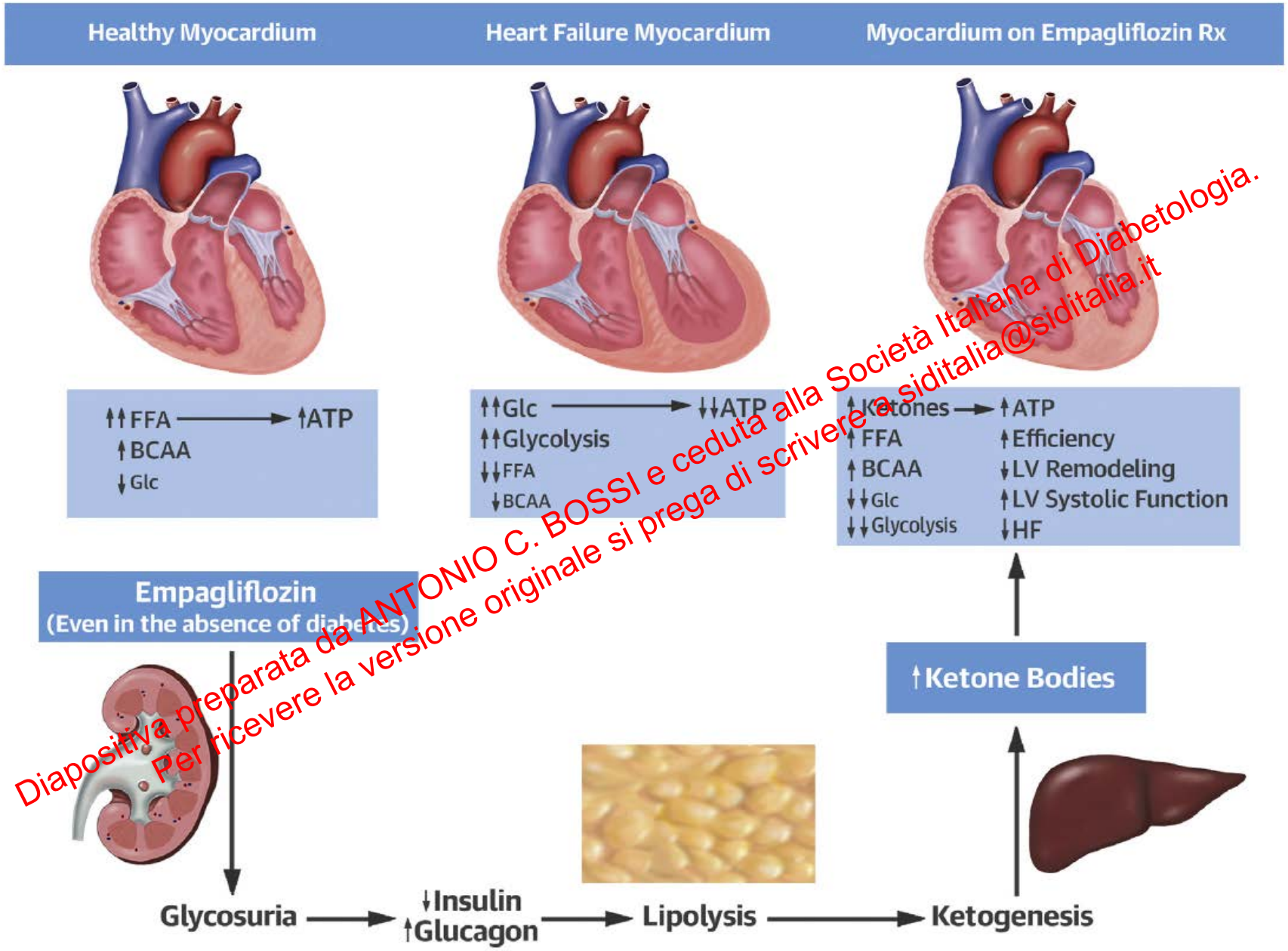
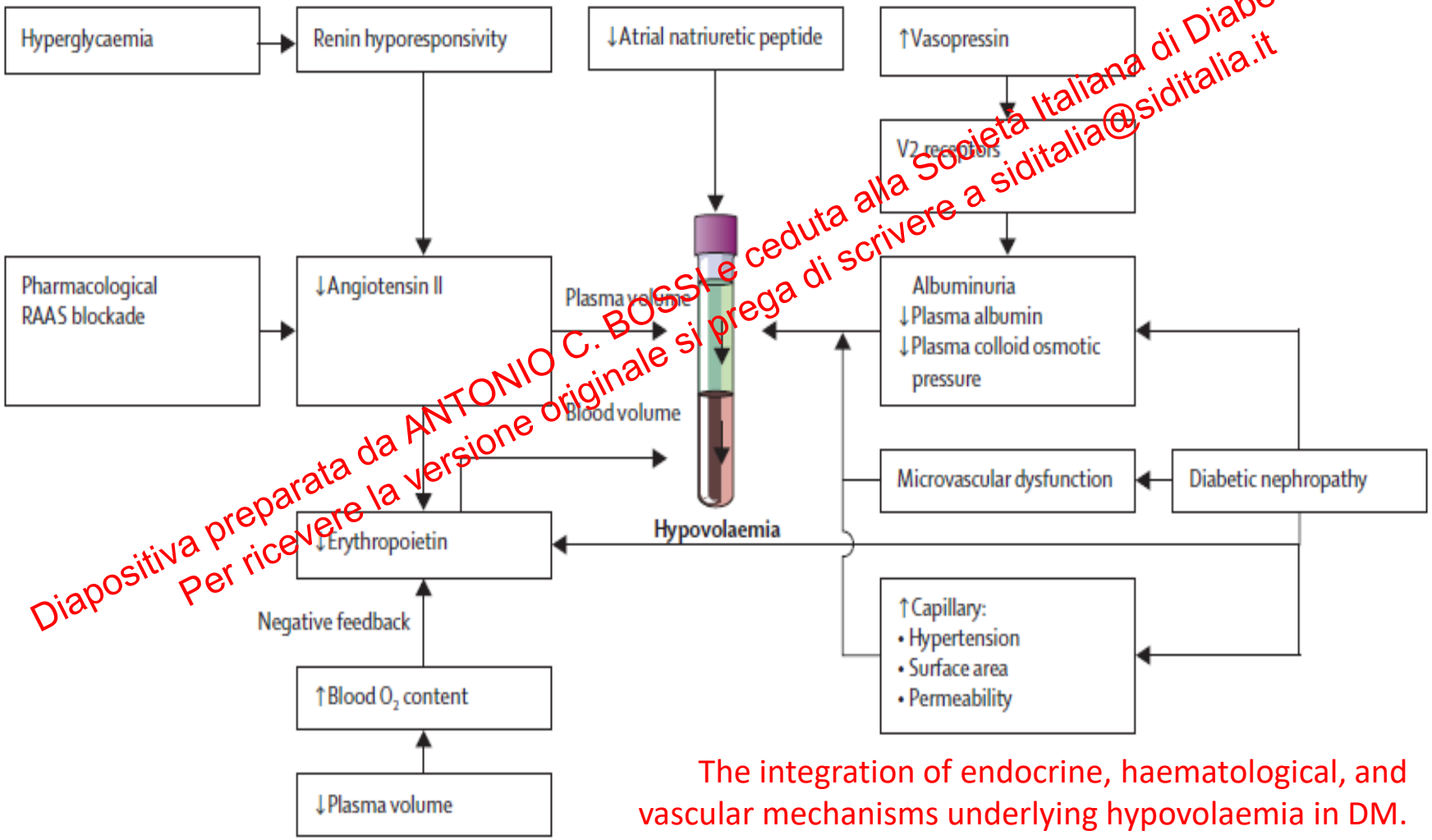



Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2019;73(15):1931–44.

# The role of blood volume in cardiac dysfunction and reduced exercise tolerance in patients with diabetes

David Montero, Candela Diaz-Canestro, Laura Oberholzer, Carsten Lundby

Lancet Diabetes Endocrinol
2019; 7: 807–16




The integration of endocrine, haematological, and vascular mechanisms underlying hypovolaemia in DM.