Effetti Nefroprotettivi degli SGLT2 Inibitori: Meccanismi ed Evidenze Cliniche

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ANDROLOGY AND METABOLIC DISEASES

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Disclosures

- Advisory Boards: AstraZeneca; Eli Lilly; Novo Nordisk; Roche Diabetes Care, Sanofi
- Consultant: Boehringer Ingelheim; Lifescan; Merck Sharp & Dohme; Sanofi, AstraZeneca, Medimmune, Roche Diabetes Care, Sanofi
- Research Support: Eli Lilly; Lifescan, Takeda

Effetti Nefroprotettivi degli SGLT2 Inhibitori:
Meccanismi

SGLT2 mediates majority of renal glucose reabsorption

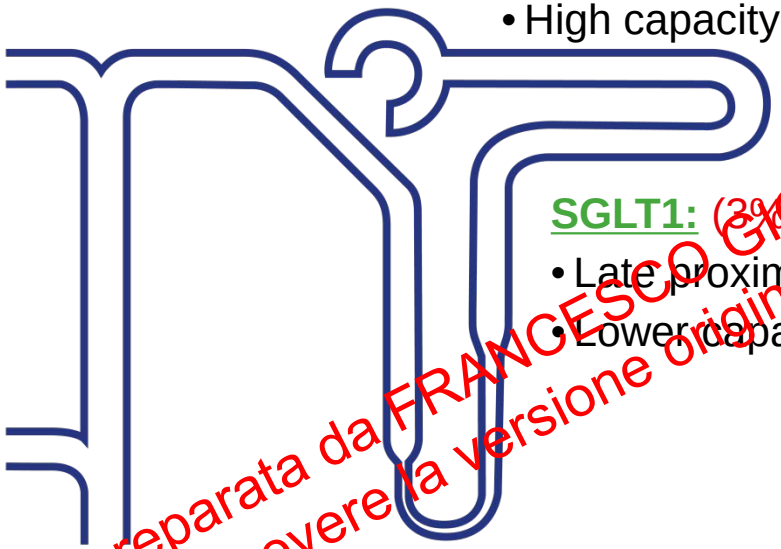
In euglycemia

Glucose filtered/reabsorbed:
180 g/day

Maximum reabsorption:
~600 g/day

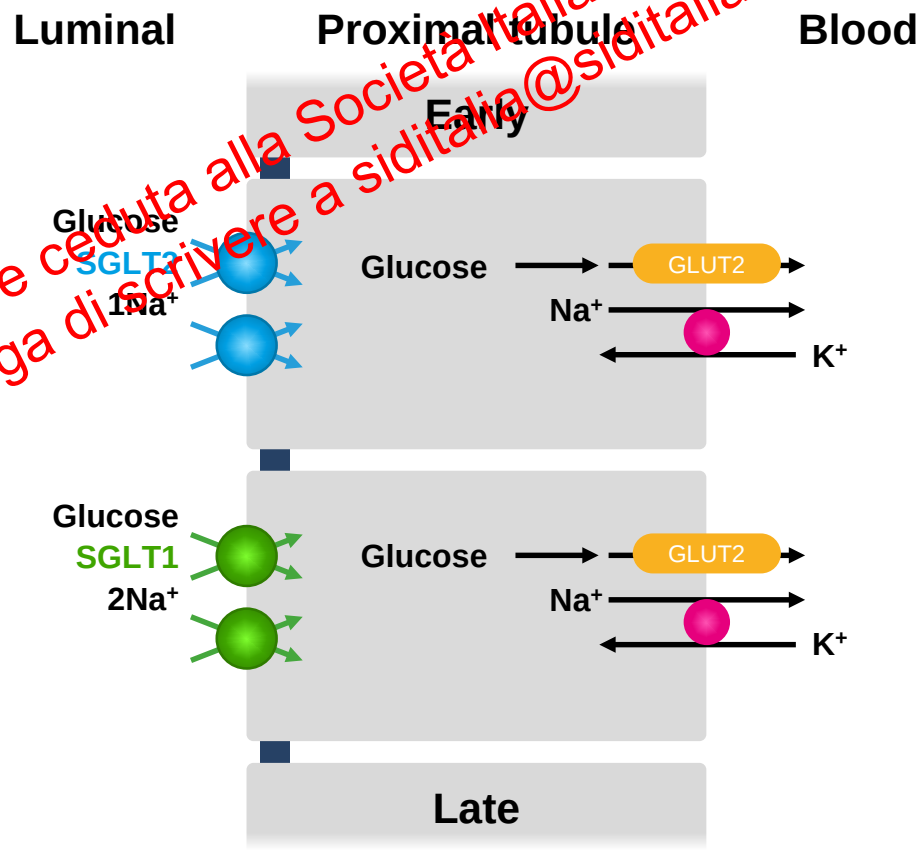
SGLT2: (97%)
- Early proximal
- High capacity

SGLT1: (3%)
- Late proximal
- Lower capacity



Urine glucose
(0%)

Fractional glucose
reabsorption in euglycemia



GLUT1/2, glucose transporter 1/2; SGLT1/2, sodium–glucose co-transporter 1/2

1. Barfuss DW, Schafer JA. *Am J Physiol* 1981;241:F322–F332; 2. Turner RJ, Moran A. *Am J Physiol* 1982;242:F406–F414; 3. Hediger MA, Rhoads DB. *Physiol Rev* 1994;74:993–1026; 4. Wright M, et al. *Physiol Rev* 2011;91:733–794; 5. Vallon V, et al. *J Am Soc Nephrol* 2011;22:104–112; 6. Gorboulev V, et al. *Diabetes* 2012;61:187–196; 7. Powell DR, et al. *Am J Physiol Endocrinol Metab* 2013;304:E117–E130; 8. Rieg T, et al. *Am J Physiol Renal Physiol* 2014;306:F188–F193

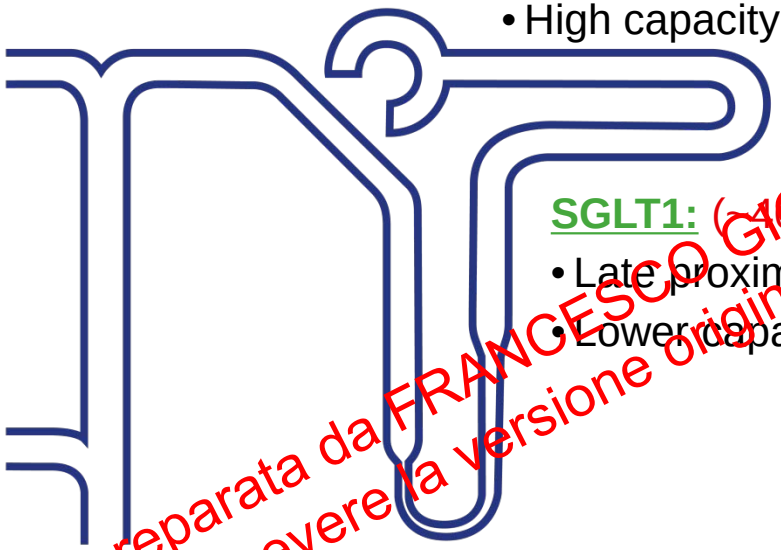
SGLT2 mediates majority of renal glucose reabsorption

In euglycemia

Glucose filtered/reabsorbed:
180 g/day

Maximum reabsorption:
~600 g/day

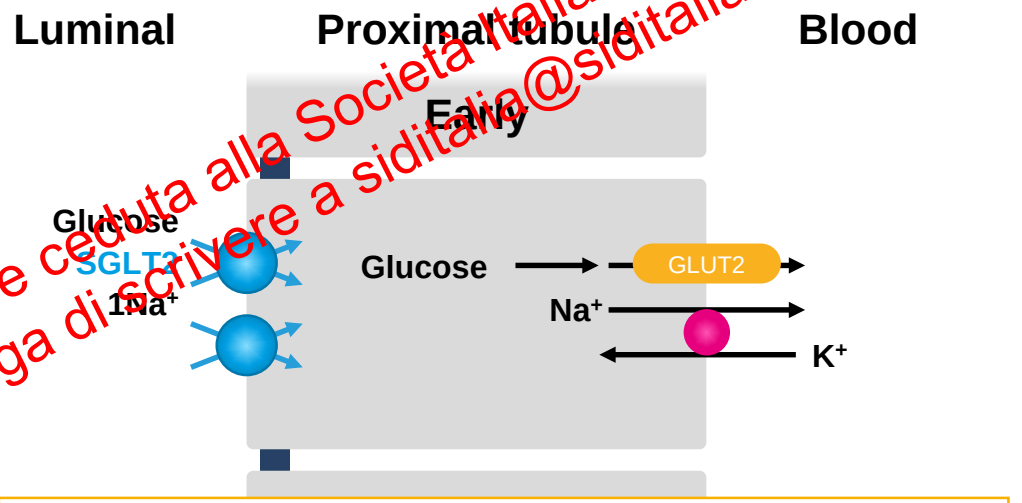
~~SGLT2:~~ (0%)
- Early proximal
- High capacity



SGLT1: (~10%)
- Late proximal
- Lower capacity

Urine glucose
(~60%)

Fractional glucose reabsorption in euglycemia



SGLT2 inhibition is protective against kidney and heart failure in patients with T2D (EMPA-REG OUTCOME, CANVAS, CREDENCE, DECLARE-TIMI 58)

Zinman, et al. *N Engl J Med* (2015)
Wanner, et al. *N Engl J Med* (2016)
Neal, et al. *N Engl J Med (*2017)
Wiviott, et al. *N Engl J Med* (2019)
Perkovic, et al. *N Engl J Med* (2019)

GLUT1/2, glucose transporter 1/2; SGLT1/2, sodium–glucose co-transporter 1/2

1. Barfuss DW, Schafer JA. *Am J Physiol* 1981;241:F322–F332; 2. Turner RJ, Moran A. *Am J Physiol* 1982;242:F406–F414; 3. Hediger MA, Rhoads DB. *Physiol Rev* 1994;74:993–1026; 4. Wright M, et al. *Physiol Rev* 2011;91:733–794; 5. Vallon V, et al. *J Am Soc Nephrol* 2011;22:104–112; 6. Gorboulev V, et al. *Diabetes* 2012;61:187–196; 7. Powell DR, et al. *Am J Physiol Endocrinol Metab* 2013;304:E117–E130; 8. Rieg T, et al. *Am J Physiol Renal Physiol* 2014;306:F188–F193

Potential Effects By Which SGLT-2 Inhibition Improves Renal Outcomes

SGLT-2 INHIBITION

Reduce Glomerular Pressure[1]
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity[3]
↓SNS activity[4]

Inflammation/Fibrosis Reductions[1,2]
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal Workload and Hypoxia[1,2]
↓Solute transport
↓Oxygen demand

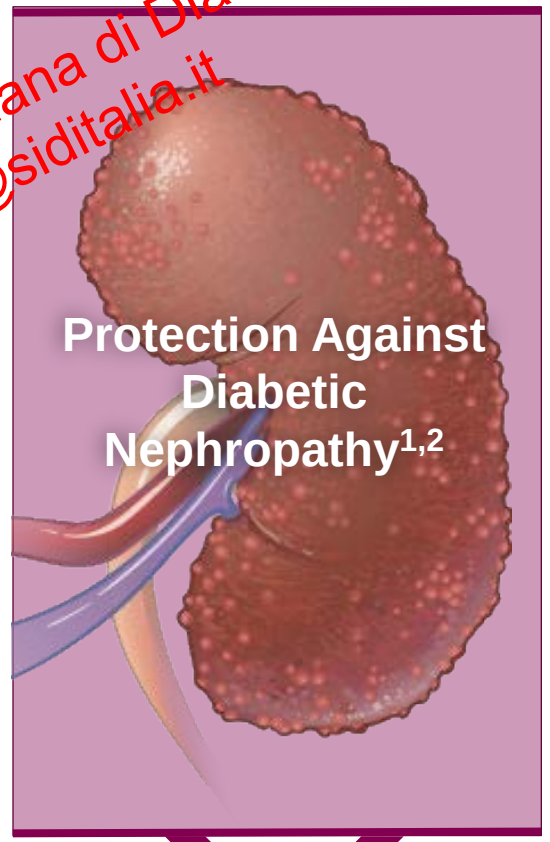
CLINICAL EFFECTS

Stabilization of eGFR[2]

↓Blood Pressure[1]

↓Tubular/Glomerular Injury[1,2]
↓Albuminuria

↓Renal Ischemic Injury[1]
↑Hb/hematocrit[2]



Preserved Renal Function[2]

eGFR=estimated glomerular filtration rate; Hb=hemoglobin; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 4. Sano M. *J Cardiol*. 2018;71(5):471-476.

SGLT-2 Inhibition Restores Tubuloglomerular Feedback and Reduces Glomerular Hypertension

SGLT-2 INHIBITION

Reduce Glomerular Pressure
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity
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Inflammation/Fibrosis Reductions
↓Inflammatory markers
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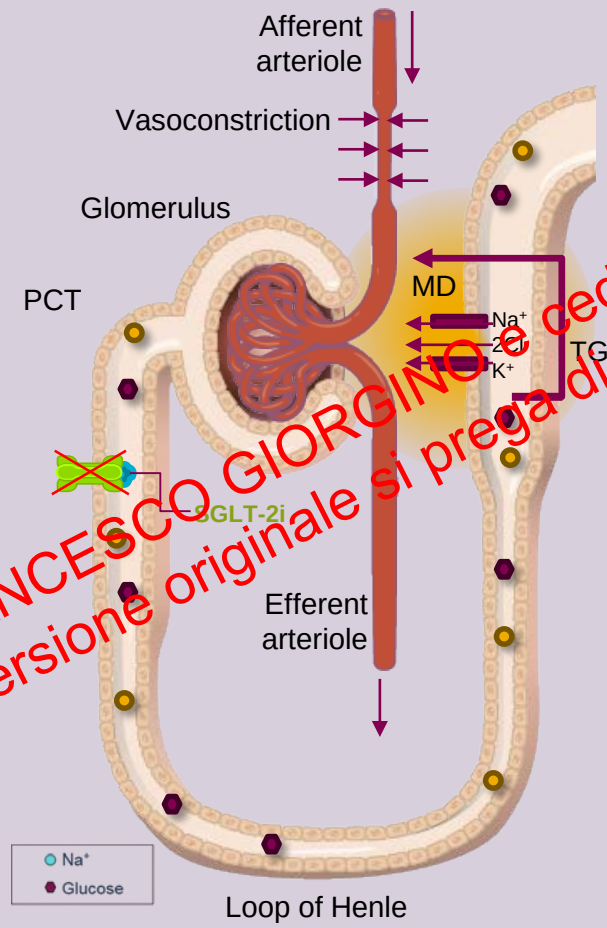
Decreased Renal [illegible] and Hypoxia
↓Solute [illegible]
↓Oxygen demand

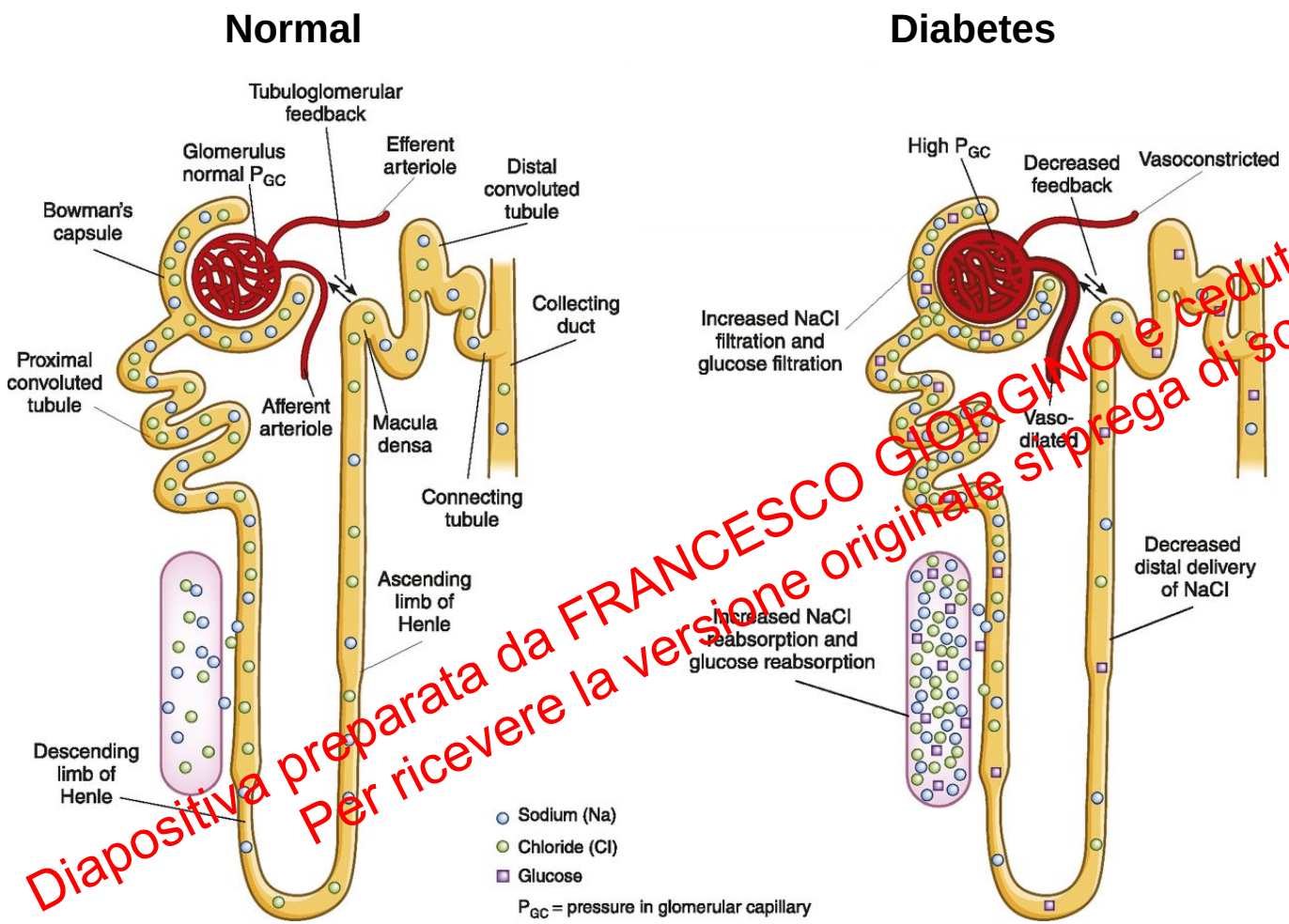


- In patients with diabetes, increased glucose and Na^+ reabsorption in the proximal tubule via SGLT-2, decreases Na^+ delivery to the macula densa, causing afferent arteriolar vasodilation and hyperfiltration[1,2]
- SGLT-2i **reduce Na^+ reabsorption in the proximal tubule and increase its distal delivery to the macula densa** (natriuresis)[1-3]
- This **restores tubuloglomerular feedback**, **producing afferent arteriolar vasoconstriction and reducing intraglomerular pressure/hyperfiltration**[1-3]
- These effects are clinically manifested as acute reductions in eGFR, followed by stabilization in eGFR in the longer term[3,4]
- SGLT-2i are complementary to ACE inhibitors which reduce intraglomerular pressure and hyperfiltration by inducing vasodilation of efferent renal arterioles[5]

ACE=angiotensin-converting enzyme; K^+=potassium; MD=macula densa; Na^+=sodium; PCT=proximal convoluted tubule; TGF=tubuloglomerular feedback.

1. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39. 2. Thomas MC, et al. *Diabetologia*. 2018;61:2098–2107. 3. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67.
4. Heerspink HJL, et al. *J Am Soc Nephrol*. 2017;28(1):368-375. 5. DeFronzo RA et al. *Nat Rev Neprhol*. 2016;13:11-26.

Glomerular Hyperfiltration Is Well Characterized in Early Diabetes



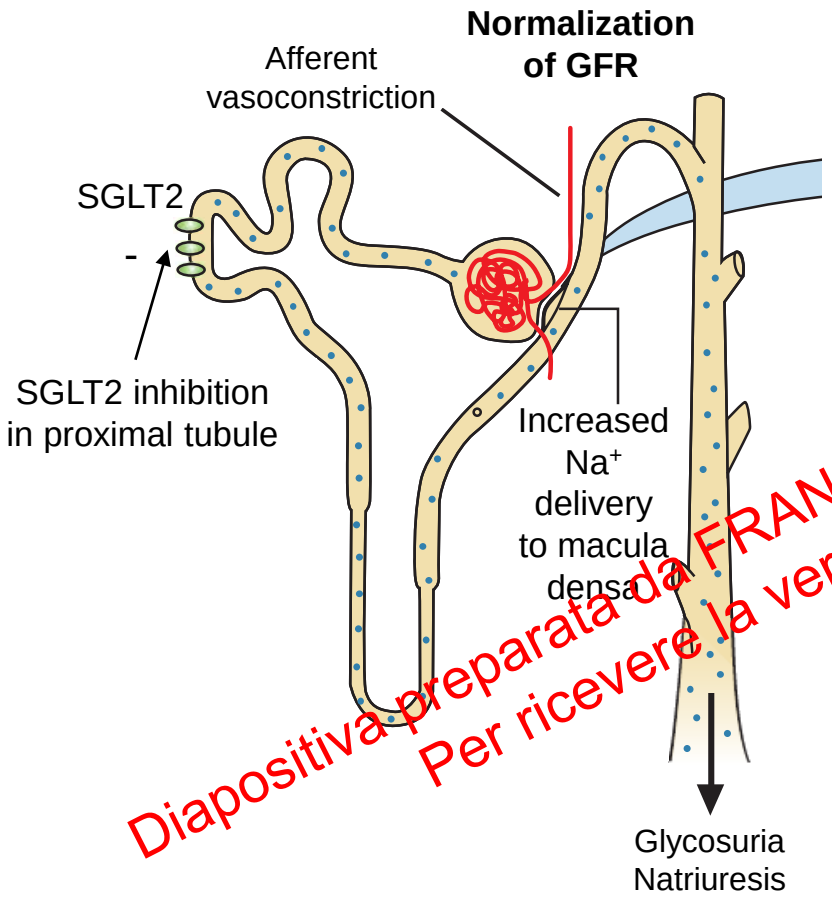
- Glomerular hyperfiltration, a consequence of early diabetes, leads to glomerular hypertension
- It is observed in up to 40% of patients with T2D
- Decreased distal delivery of sodium to the macula densa leads to a decrease in TGF and dilates the afferent arteriole to increase glomerular pressure
- Concurrently, high local production of angiotensin II at the efferent arteriole produces vasoconstriction
- The overall effect is high intraglomerular pressure and glomerular hyperfiltration

T1D, type 1 diabetes; T2D, type 2 diabetes; TGF, tubuloglomerular feedback.

Alicic RZ, et al. *Clin J Am Soc Nephrol.* 2017;12:2032-2045.

Potential Mechanisms of Renal Protection with SGLT2 Inhibitors: Reduction in Hyperfiltration via Restoration of Tubuloglomerular Feedback (TGF)

SGLT2 inhibition reduces hyperfiltration via TGF

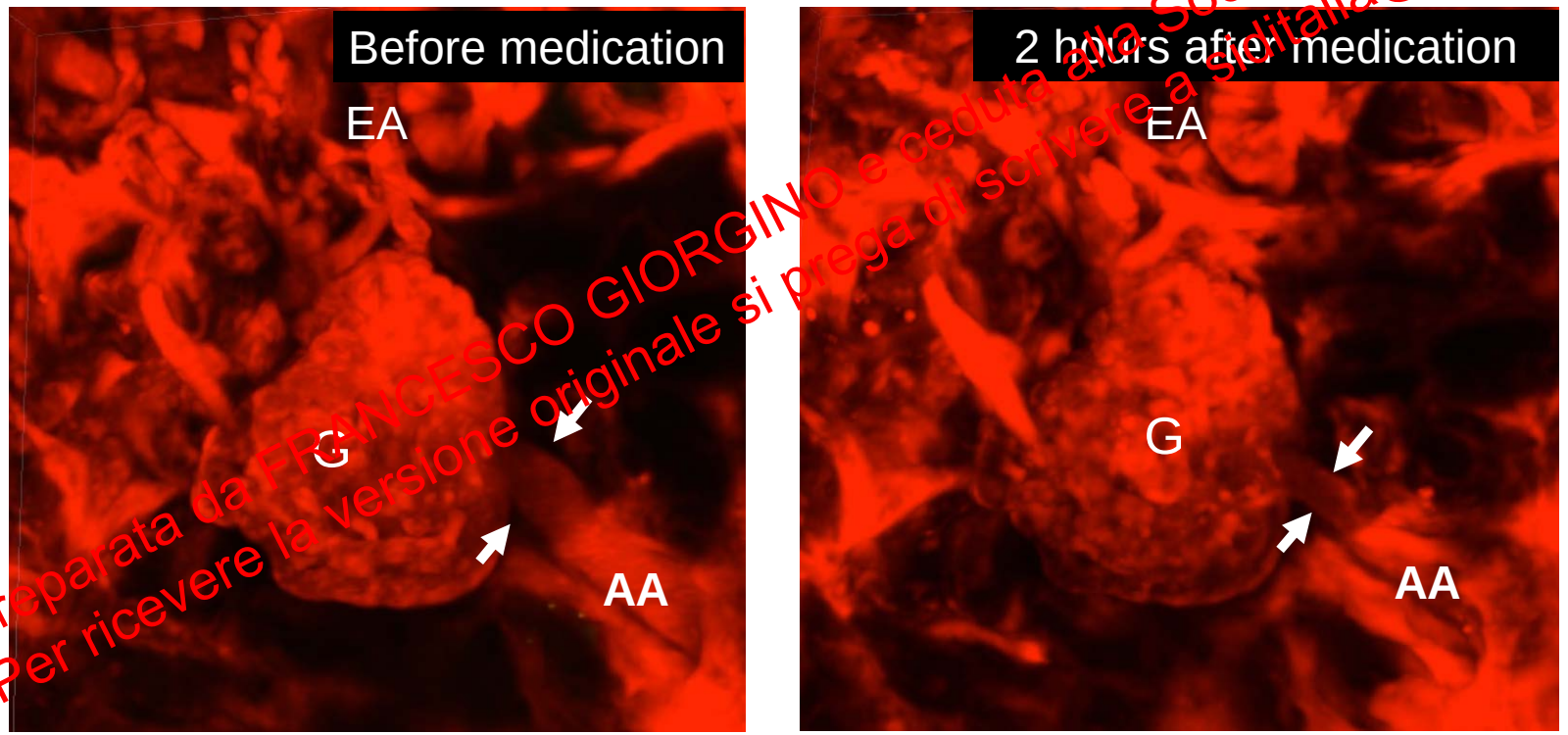


5'NT, 5'-nucleotidase; Ca^{2+}, calcium; Cl, chloride; GFR, glomerular filtration rate; K^+, potassium; MC, mesangial cells; Na^+, sodium; NaCl, sodium chloride; SGLT2, sodium–glucose co-transporter 2; TGF, tubule-glomerular feedback; VSMC, vascular smooth muscle cells

Heerspink HJ and Cherney DZ. *Circulation* 2016;134(10):752–772

In vivo Imaging Analyses Demonstrate Afferent Arteriole Constriction following SGLT2 Inhibitor Therapy

- **In vivo imaging of afferent arteriole change before and after empagliflozin**



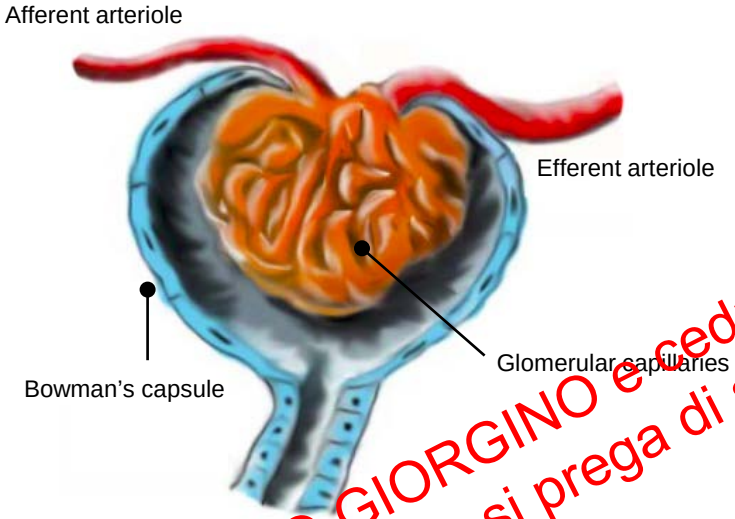
AA, afferent arteriole; EA, efferent arteriole; G, glomerulus; SGLT2, sodium–glucose co-transporter 2
Kidokoro K, et al. *Circulation* 2019;140:303–315

SGLT2 inhibition and RAAS blockade both reduce glomerular hyperfiltration by complementary mechanisms[1-3]

SGLT2 inhibitors

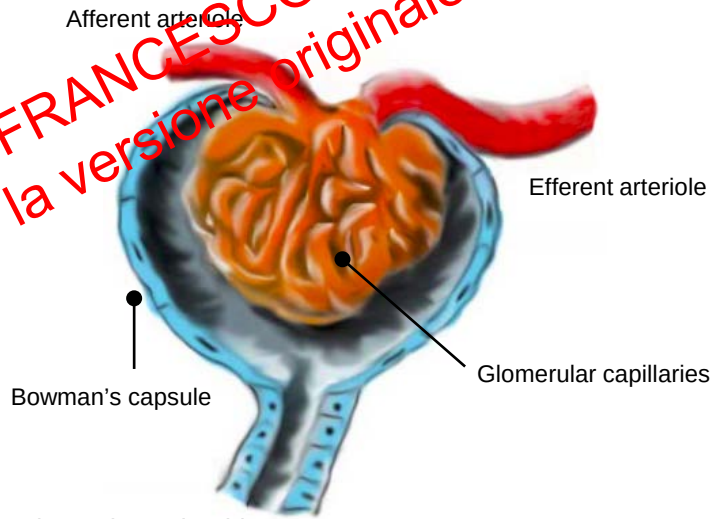
Afferent constriction[1-3]

Due to increased Na+ delivery to the macula densa[1-3]



RAAS blockade

Efferent vasodilation[1]



CLINICAL IMPLICATIONS

- Decreased glomerular pressure[1,3]
- Reduction in albuminuria[1,2]

- Decreased glomerular pressure[1,3]
- Reduction in albuminuria[4]

SGLT2, sodium-glucose cotransporter 2; Na, sodium; RAAS, renin-angiotensin-aldosterone system.

1. Van Bommel EJ, et al. *Clin J Am Soc Nephrol*. 2017;12(4):700-710. 2. Seidu S, et al. *Prim Care Diabetes*. 2018;12(3):265-283. 3. Cherney DZ, et. al. *Circulation*. 2014 Feb 4;129(5):587-97. 4. Heerspink HJ, et al. *Diabetes Care*. 2011;34 Suppl 2:S325-9. 5. Adapted from: Shiraishi M, et al. *FASEB J*. 2003;17(15):2284-6.

SGLT-2 Inhibitors May Provide Cardiorenal Benefits by Reducing Central Sympathetic Overactivity and Intrarenal RAAS Activation

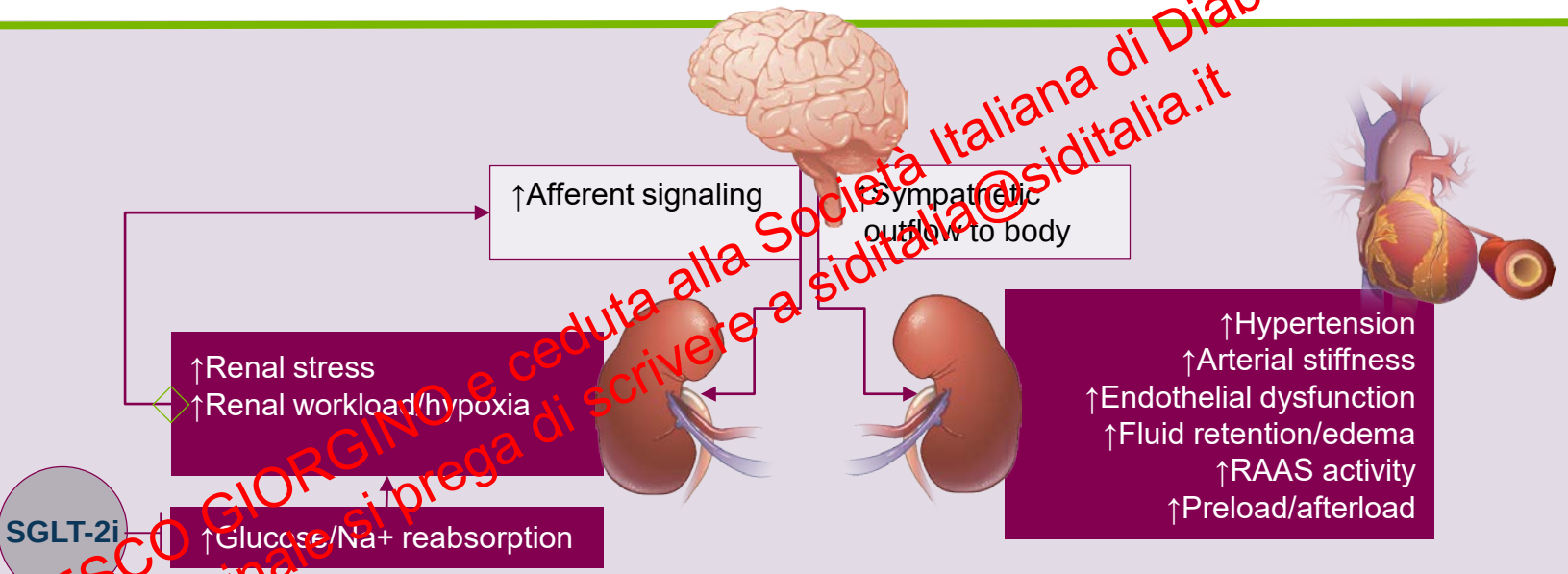
SGLT-2 INHIBITION

Reduce Glomerular Pressure
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity[2]
↓SNS activity[3]

Inflammation/Fibrosis Reductions
↓Inflammatory markers
↓Fibrotic markers

Decreased Renal [illegible] and Hypoxia
↓Solute [illegible]
↓Oxygen demand



- Chronic activation of the SNS has been identified in many conditions, including T2D, HF, and kidney disease[1]
- Sympathetic overactivity triggers the development of hypertension, increases arterial stiffness, causes endothelial dysfunction, and alters renal sodium and water homeostasis to promote fluid retention and edema[1]
- **Excess renal glucose reabsorption may contribute to renal stress, stimulating the sympathetic center in the brain and enhancing sympathetic outflow to the whole body; inhibition of SGLT-2 may reduce renal afferent nervous activity and suppress central reflex mechanisms[1,2]**
- In addition, inappropriate activation of RAAS is critical in the pathogenesis of cardiovascular and renal diseases[3]
- Evidence suggests that **intrarenal RAAS is not activated by SGLT-2i** as in rodent models of diabetes; treatment with dapagliflozin significantly lowered urinary angiotensin II and angiotensinogen levels, both regulators of RAAS activity[3,4]

HF=heart failure; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system; T2D=type 2 diabetes.

1. Sano M. J Cardiol. 2018;71(5):471-476. 2. Heerspink HJL, et al. *Kidney Int.* 2018;94(1):26-39. 3. Ansary TM, et al. *Int J Mol Sci*. 2019;20:629; doi:10.3390/ijms20030629.
4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703.

SGLT-2 Inhibitors May Protect Against Inflammatory and Fibrotic Responses[1]

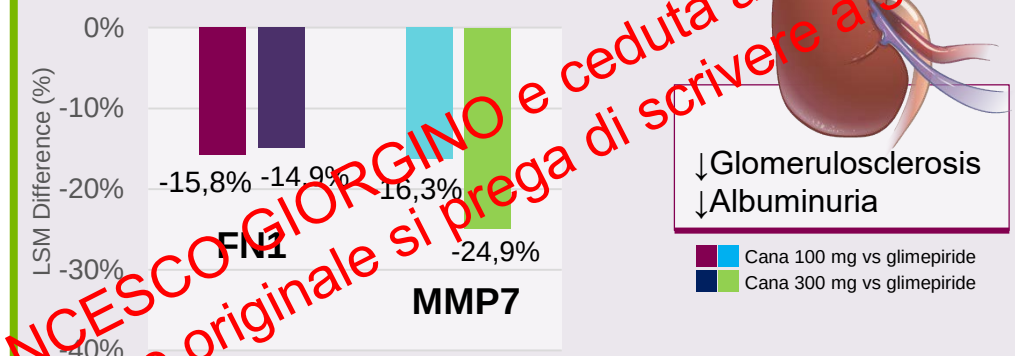
SGLT-2 INHIBITION

Inflammation/Fibrosis Reductions[2,3]
↓Inflammatory markers
↓Fibrotic markers

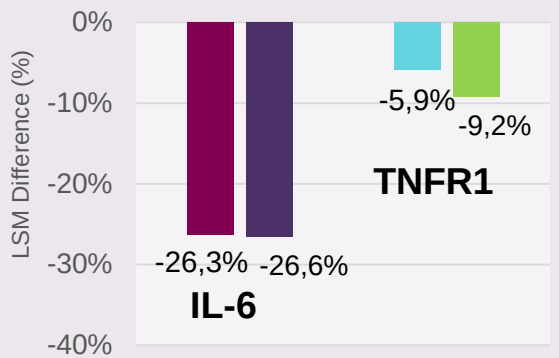
SGLT-2 Inhibition[1,4,5]

Fibrosis
↓FN1
↓MMP7

Inflammation
↓IL-6
↓TNFR1



Cana 100 mg vs glimepiride
Cana 300 mg vs glimepiride



- Patients with diabetes and/or CKD can have thickening of the tubular basement membrane, tubular atrophy, interstitial fibrosis, and chronic inflammation[6,7]
- During chronic hyperglycemia, an increase in glucose trafficking through proximal tubule cells, as well as increased secretion of inflammatory and profibrotic cytokines, can promote inflammation and fibrosis[6]
- SGLT-2i have been shown in clinical trials to have **anti-inflammatory and antifibrotic effects** as evidenced by decreases in plasma concentrations of markers of fibrosis (FN1, MMP7) and inflammation (IL-6, TNFR1)[6-8]

CKD=chronic kidney disease; FN1=fibronectin-1; IL-6=interleukin-6; LSM=least square mean; MMP7=matrix metalloproteinase-7; TNFR1=tumor necrosis factor receptor-1.

1. Heerspink HJL, et al. *Diabetologia*. 2019;62:1154-1166. 2. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 3. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 4. Kawanami D, et al. *Int J Mol Sci*. 2017;18(5):E108. 5. Ke B, et al. *Front Physiol*. 2017;8:21. doi: 10.3389/fphys.2017.00021. 6. Fioretto P, et al. *Diabetes Care*. 2016;39(suppl. 2):S165-S171. 7. Liu Y. *J Am Soc Nephrol*. 2010;21:212-222. 8. Terami N, et al. *PLoS One*. 2014;9:e100777.

SGLT-2 Inhibitors Reduce Renal Workload and Hypoxia in Patients with T2D[1,2]

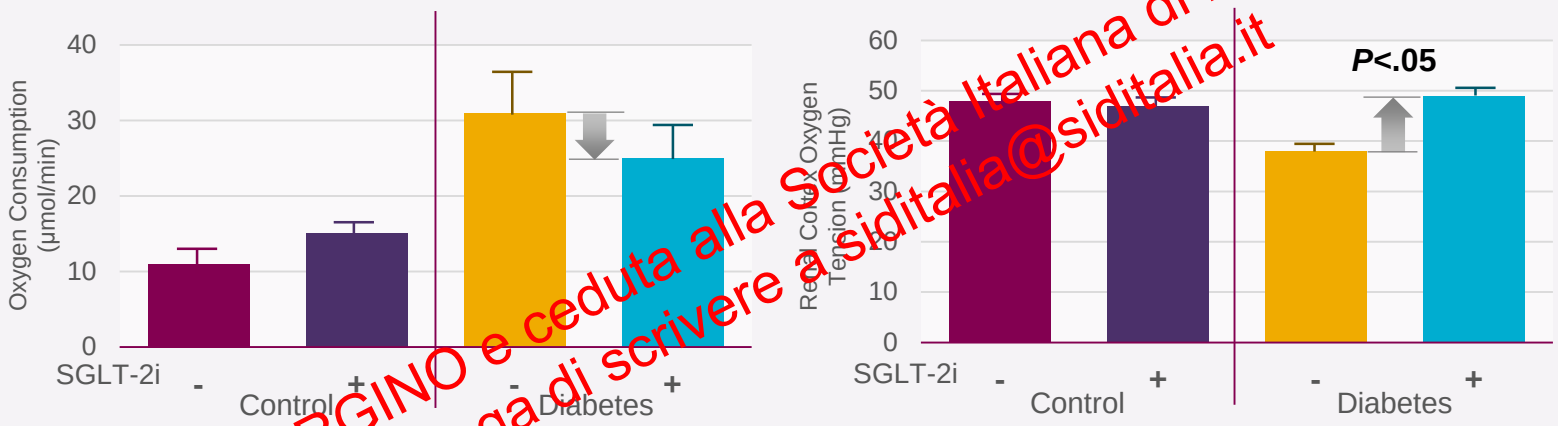
SGLT-2 INHIBITION

Reduce Glomerular Pressure
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity
↓SNS activity

Inflammation/Fibrosis Reductions
↓Inflammatory markers
↓Fibrotic markers

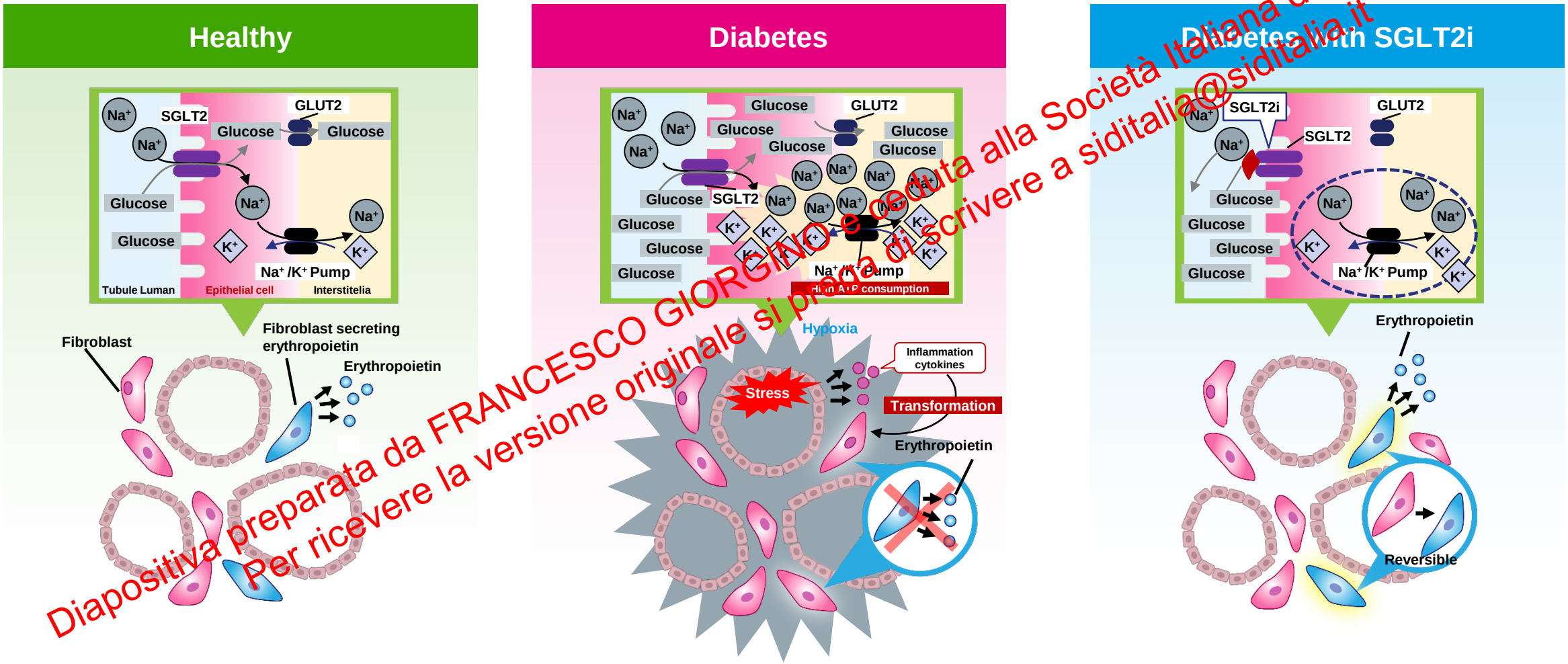
Decreased Renal Workload and Hypoxia[3,4]
↓Solute transport
↓Oxygen demand



- The reabsorption of solutes in the proximal tubule requires significant energy and accounts for the largest amount of oxygen consumption in the kidney[5]
- Increased glucose and sodium increase the oxygen demand of tubular cells, rendering them susceptible to hypoxia[5]
- SGLT-2 inhibition **reduces sodium and glucose reabsorption, thereby reducing the workload for proximal tubular cells and protecting against hypoxia-induced proximal tubular damage[2]**
- Studies have shown that SGLT-2 inhibition in rodent models of diabetes **improves oxygen concentrations in the renal cortex**, which helps to improve tubular cell integrity and reduce the risk of albumininuria[1,2]

1. O'Neill J, et al. *Am J Physiol Renal Physiol*. 2015(3);309:F227-F234. 2. Dekkers CCJ, et al. *Diabetes Obes Metab*. 2018;20(8):1988-1993. 3. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 4. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 5. Gilbert RE. *Diabetes.* 2017;66(4):791-800.

SGLT2 Inhibitors Counteract Renal Hypoxia via Increased EPO Secretion

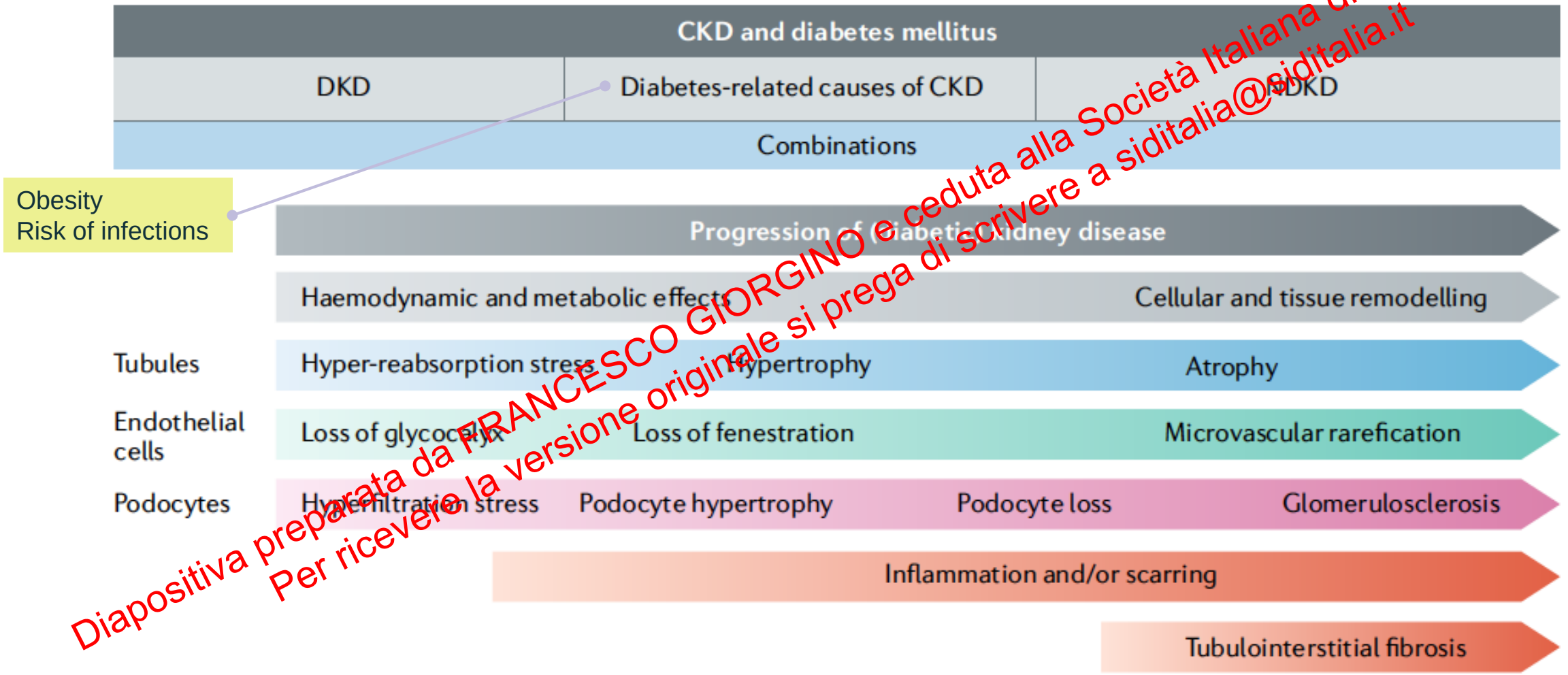


Sano and Goto, Circulation 2019

EPO, erythropoietin; SGLT2i, sodium–glucose co-transporter 2 inhibitor

Effetti Nefroprotettivi degli SGLT2 Inibitori:
Evidenze Cliniche

Causes of CKD in Patients with Diabetes and the Pathophysiology of DKD



CKD, chronic kidney disease; DKD, diabetic kidney disease; NDKD, non-diabetic kidney disease

Anders HJ et al., *Nat Rev Nephrol*. 2018 Jun;14(6):361-377.

Effects of Intensive Glucose Control (IGC) on Microvascular Outcomes in Patients with Type 2 Diabetes: a Meta-analysis of Individual Participant Data from RCTs

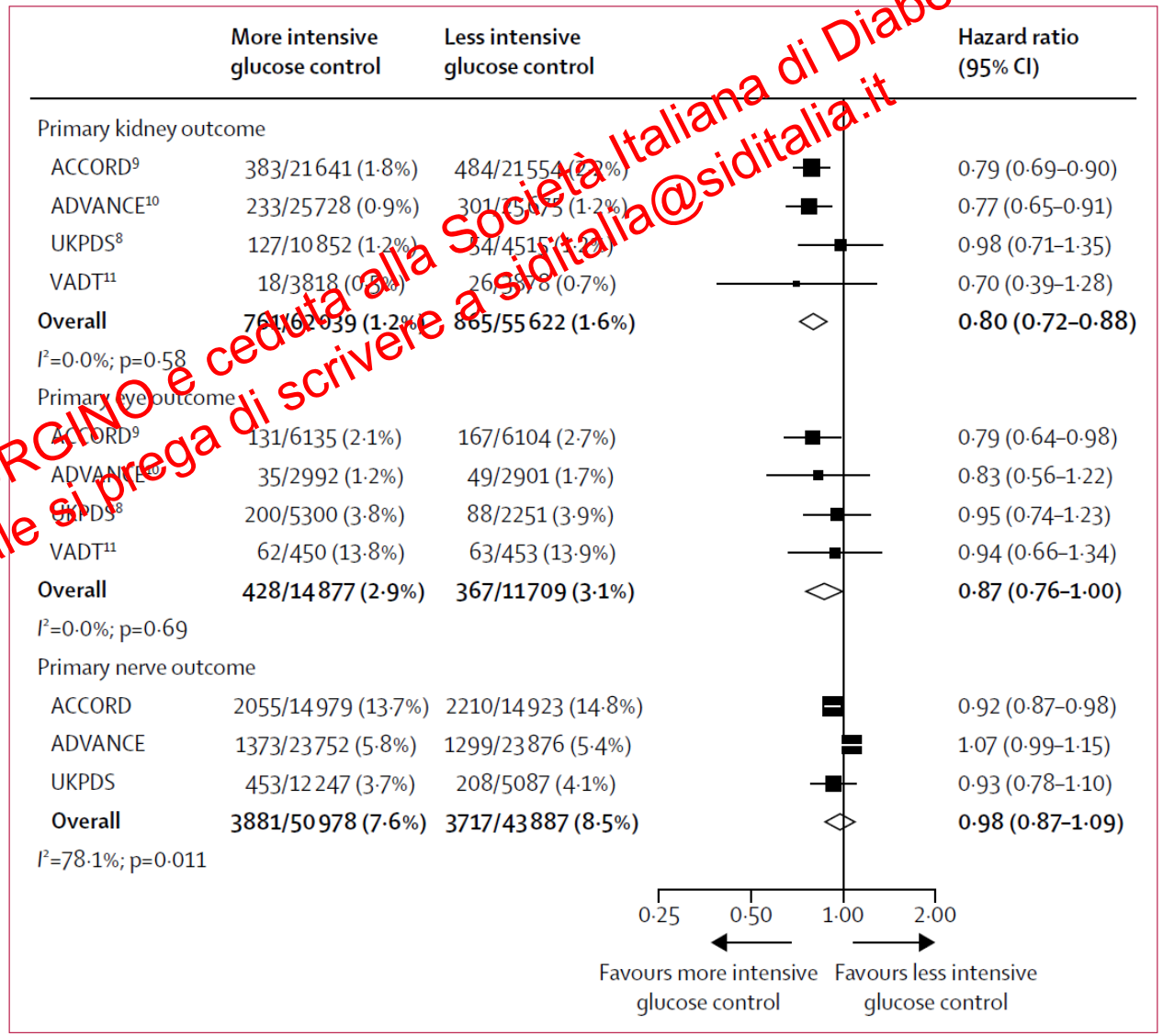
Kidney events (a composite of ESRD, renal death, development of eGFR <30 mL/min per 1·73m², or development of overt diabetic nephropathy)

Eye events (a composite of requirement for retinal photocoagulation therapy or vitrectomy, development of proliferative retinopathy, or progression of diabetic retinopathy)

Nerve events (a composite of new loss of vibratory sensation, ankle reflexes, or light touch)

IGC vs standard of care:

- -0.90% in mean HbA1c
- 20% less kidney events
- 13% less eye events
- No change in nerve events

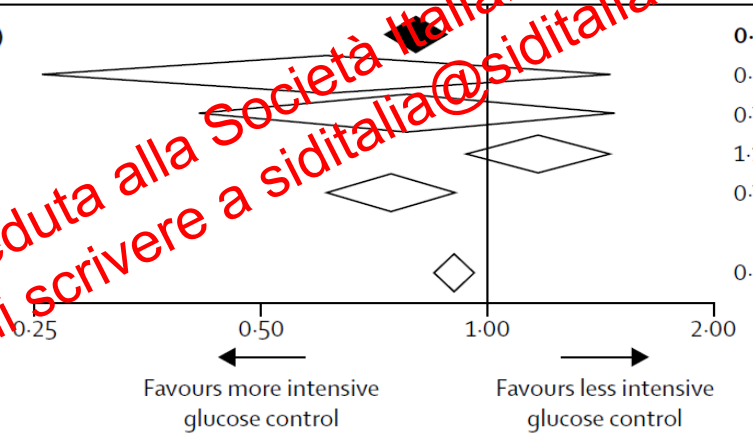


eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RCT, randomised controlled trial

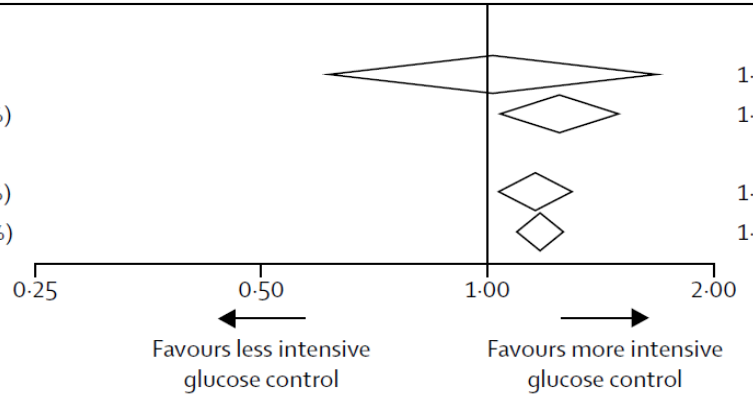
Zoungas S, et al. *Lancet Diabetes Endocrinol*. 2017;5(6):431-437

Effects of Intensive Glucose Control on Renal Outcomes in Patients with Type 2 Diabetes: a Meta-analysis of Individual Participant Data from RCTs

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



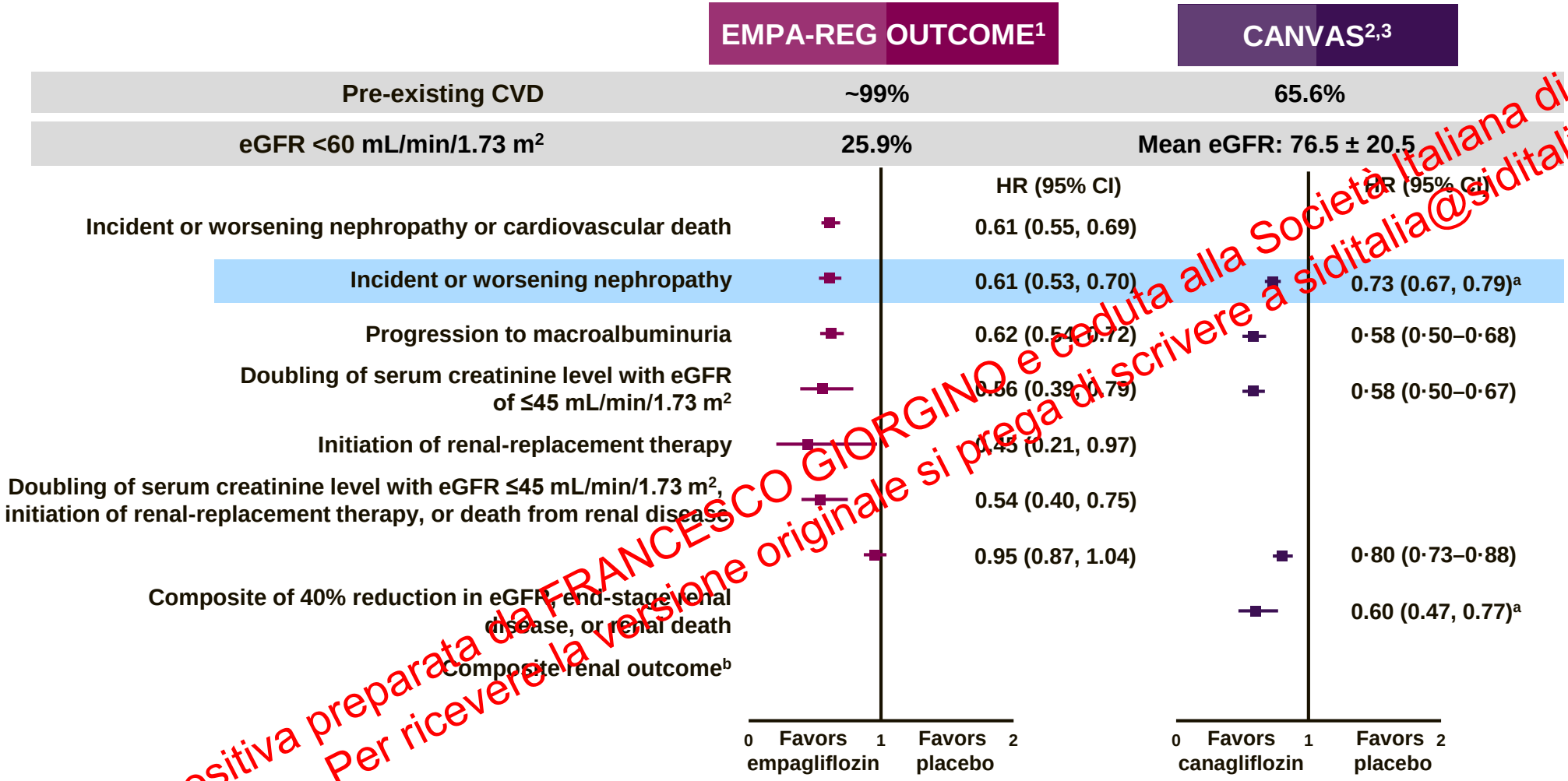
	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Secondary albuminuria outcomes			
Macroalbuminuria to normoalbuminuria	80 (3·5%)	603 (1·2%)	1·01 (0·61–1·66)
Macroalbuminuria to microalbuminuria or normoalbuminuria	353 (22·0%)	332 (18·1%)	1·23 (1·03–1·48)
Microalbuminuria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



CI, confidence interval; eGFR, estimated glomerular filtration rate; RCT, randomised controlled trial

Zoungas S, et al. *Lancet Diabetes Endocrinol*. 2017;5(6):431-437

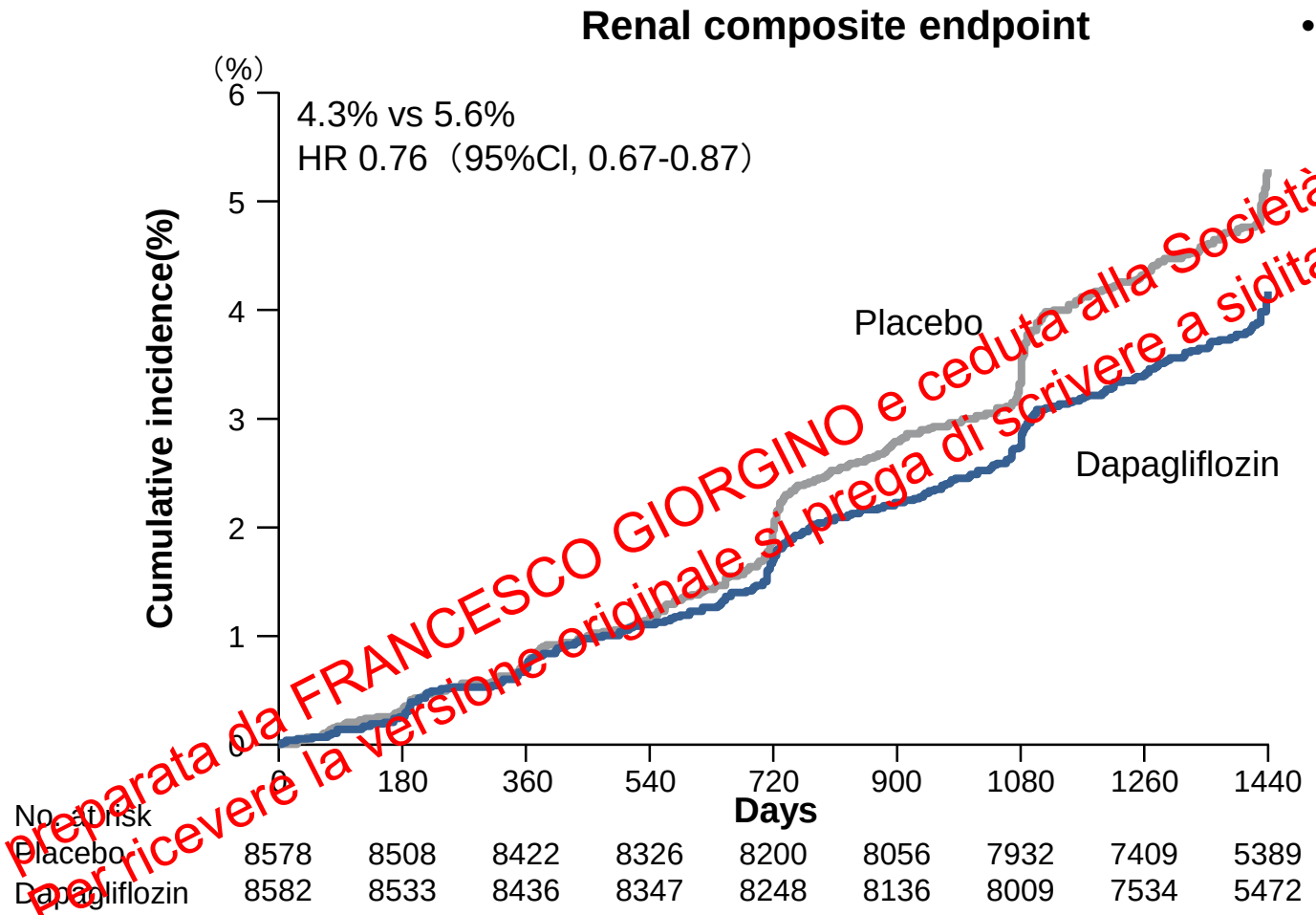
SGLT2 Inhibitors Have Shown a Protective Effect on Renal Outcomes



[a]Differences in renal endpoints vs placebo were not considered significant due to hierarchical analysis; [b]See reference for details of outcomes included in composite
[c]End-stage kidney disease (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or CV death
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT2i, sodium-glucose co-transporter 2 inhibitor

1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017; 3. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691–704.
4. https://www.jnj.com/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings (Accessed October 3, 2018)

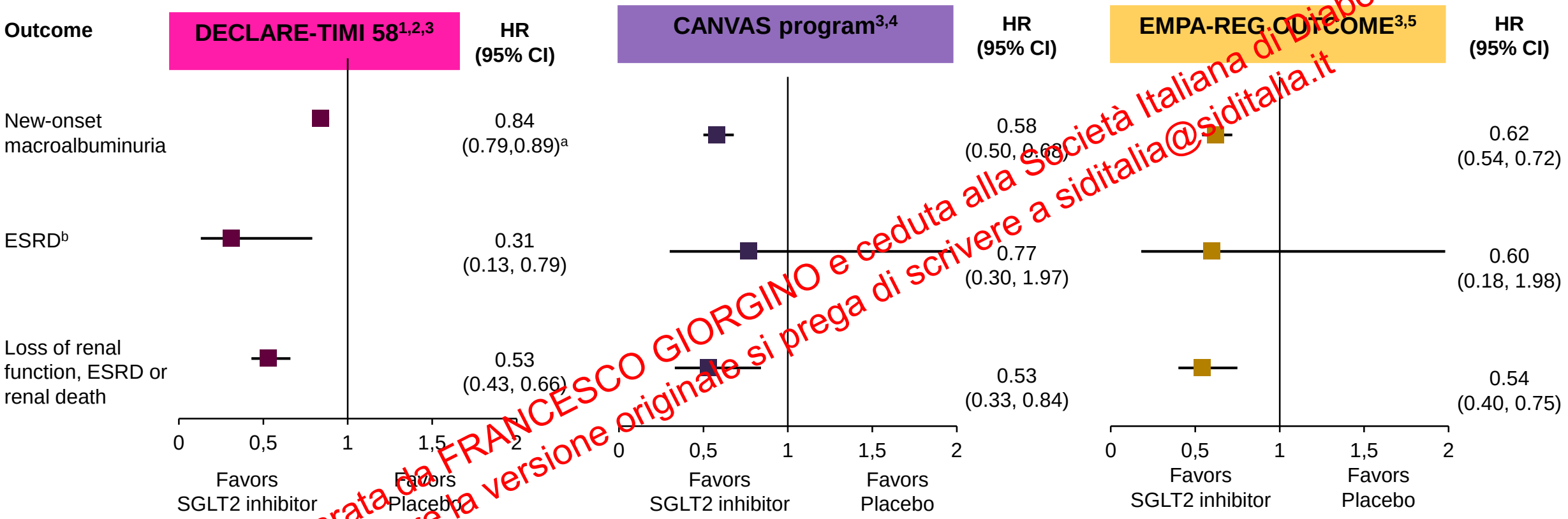
DECLARE-TIMI



- **Sustained ≥40% decrease in eGFR to<60 mL/min/1.73m² and/or ESRD (dialysis ≥90 days or kidney transplantation or confirmed sustained eGFR<15 mL/min/1.73m²) and/or death from renal or CV causes**

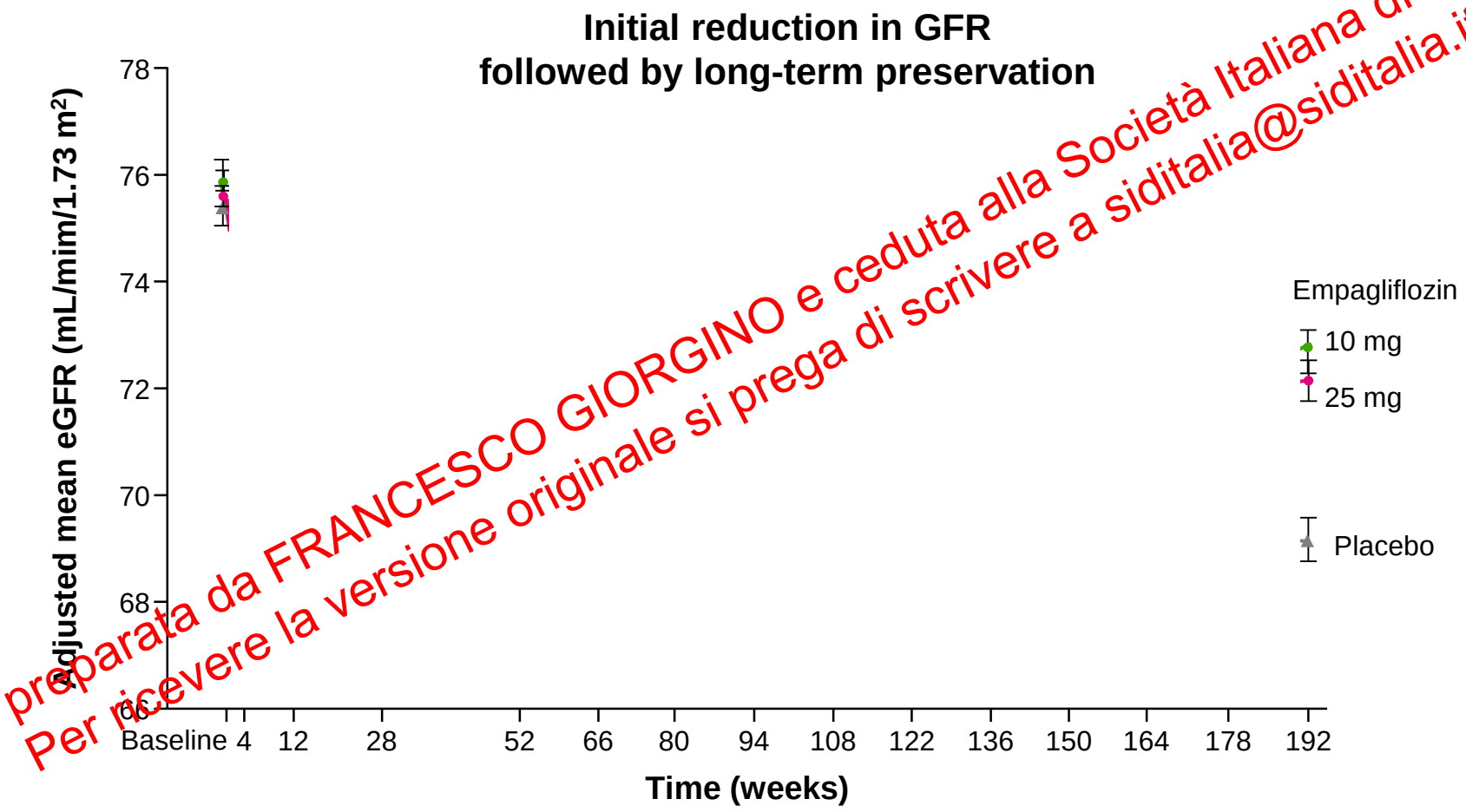
Wiviott SD. et al.: N Engl J Med. 380:347-357, 2018

SGLT2 Inhibitors Prevent New-onset Macroalbuminuria and Other End-stage Renal Events



- [a]Inclusive of new-onset micro or macroalbuminuria; [b]In DECLARE-TIMI 58, ESRD was defined as: either dialysis for 90 days or more, kidney transplantation, or sustained eGFR <15 mL/min/1.73 m^2; in the CANVAS program ESRD was defined as: a composite of maintenance dialysis for at least 30 days, renal transplantation or a sustained eGFR <15 mL/min/1.73 m^2
- CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2
- 1. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 2. Raz I, et al. Presented at ADA 79th Scientific Sessions 2019;San Francisco:CA 244-OR; 3. Neuen BL, et al. *Lancet Diabetes Endocrinol* 2019; S2213-8587: 30256–6 4. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691–704; 5. Wanner C, et al. *N Engl J Med* 2016;375:323–334

Biphasic eGFR profile in response to SGLT2 inhibition in patients with T2D and with high cardiovascular risk

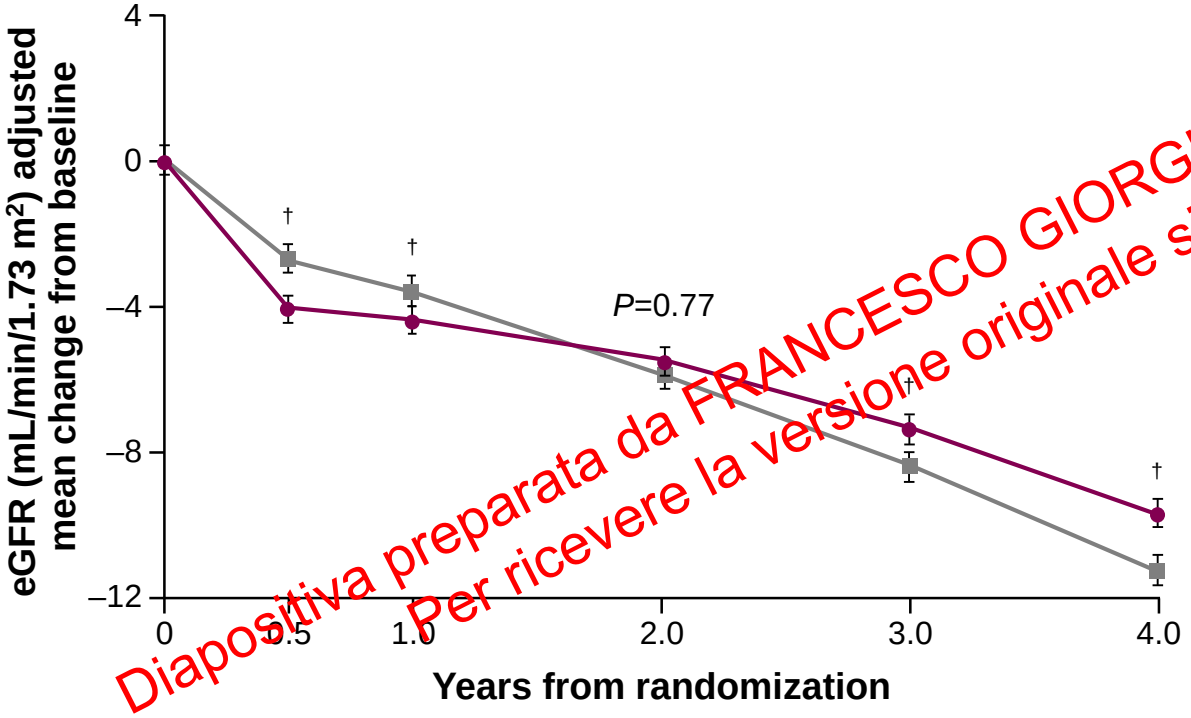


eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

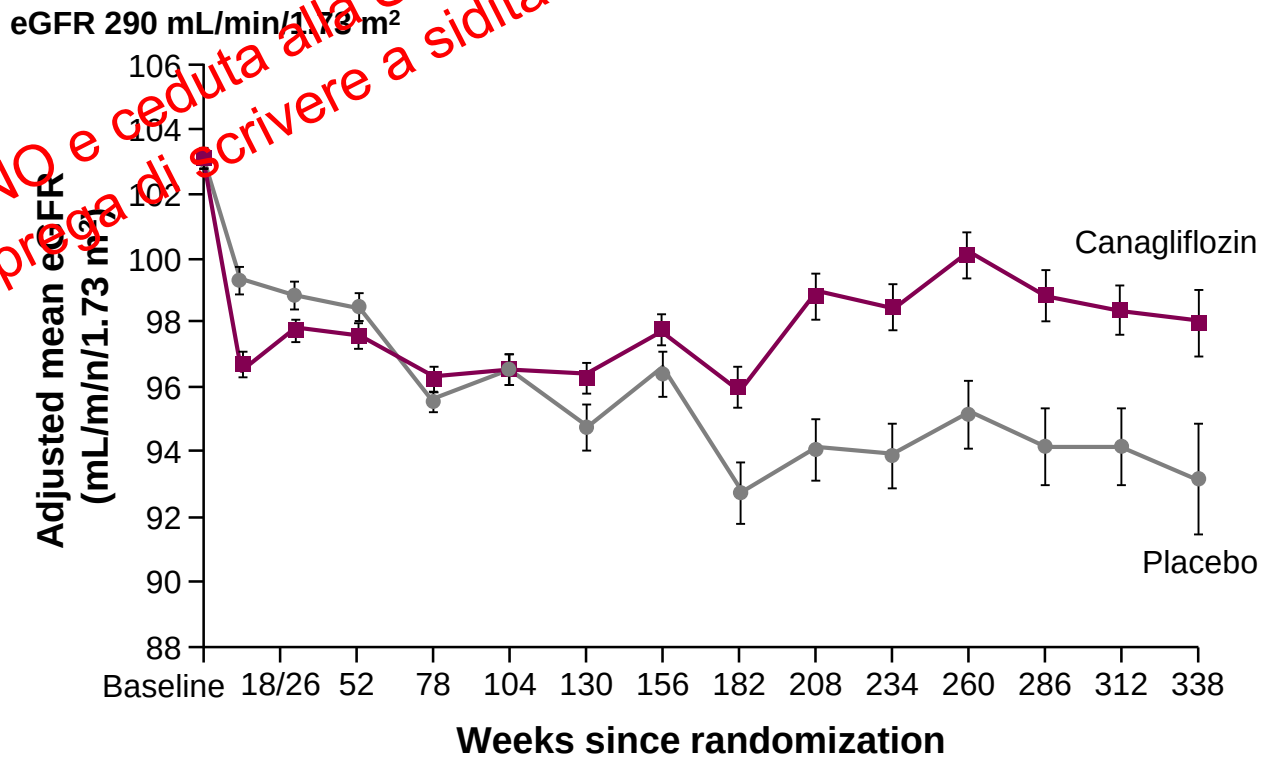
Wanner C, et al. *N Engl J Med* 2016;375:323–334

SGLT2 Inhibitors Stabilize eGFR in T2D Patients with High Baseline Renal Function (eGFR >90 mL/min/1.73m²)

Adjusted mean change from baseline in patients with eGFR ≥90 mL/min/1.73 m², from the DECLARE-TIMI 58 trial[1]



Adjusted mean eGFR in patients with eGFR ≥90 mL/min/1.73 m², from the CANVAS program[2]



†*P*<0.0001

eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

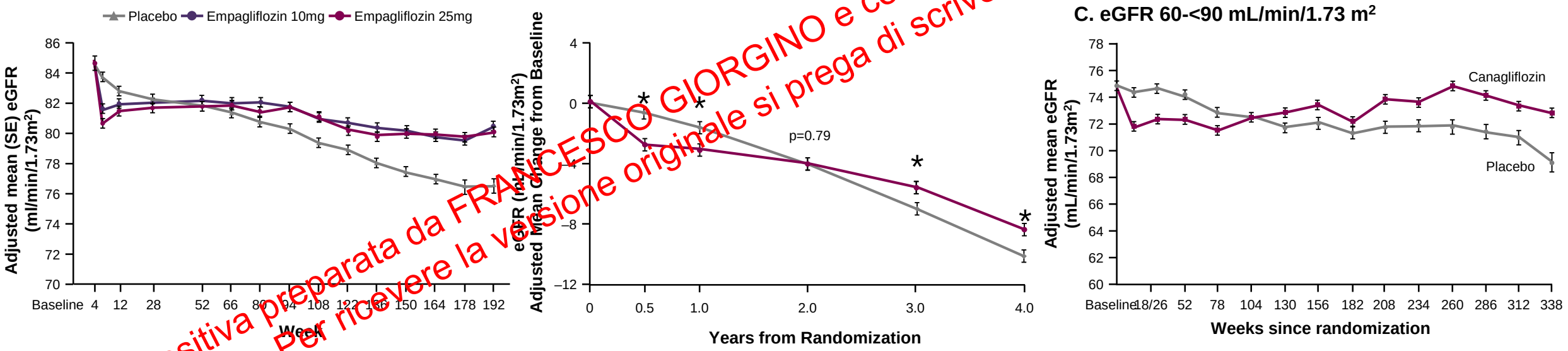
1. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 2. Neuen BL, et al. *Circulation* 2018;138:1537–1550

SGLT2 Inhibitors Stabilize eGFR in T2D Patients with Sub-optimal Renal Function (eGFR 60-90 mL/min/1.73m²)

EMPA-REG OUTCOME:[3]
Mean change in eGFR in patients with eGFR of >60mL/min/1.73m²

DECLARE-TIMI 58:[1]
Mean change in eGFR from baseline in patients with eGFR of 60–<90 mL/min/1.73m²

CANVAS:[2]
Mean change in eGFR in patients with eGFR of 60–<90 mL/min/1.73m²

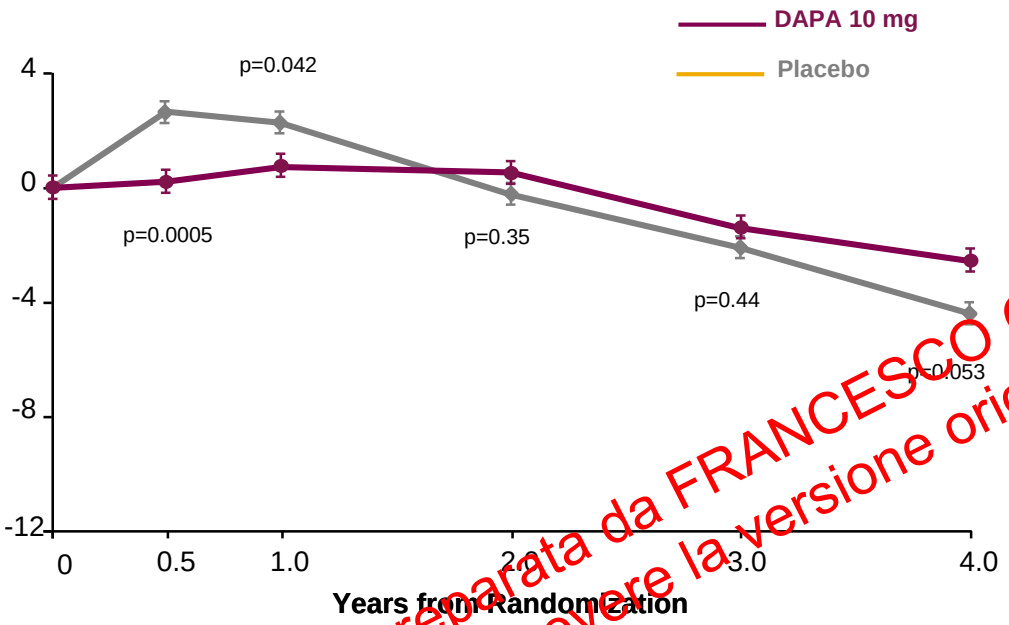


- eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

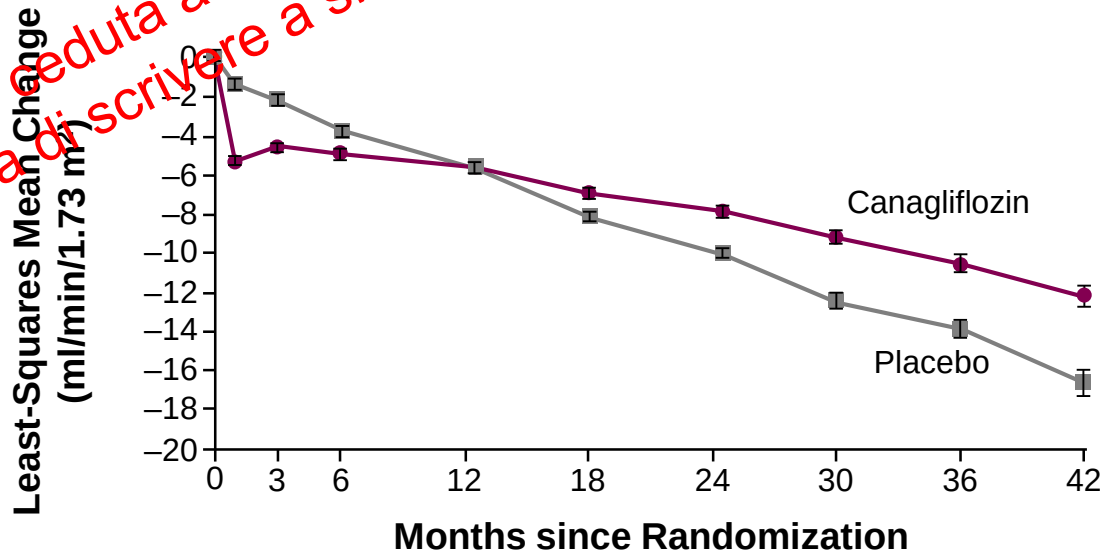
1. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 2. Neuen BL, et al. *Circulation* 2018;138;1537–1550; 3. Wanner C, et al. *N Engl J Med* 2016;375:323–334 (Supplementary Appendix)

SGLT2 Inhibitors Stabilize eGFR in Patients with Reduced Renal Function (eGFR <60 mL/min/1.73m²)

Effects of dapagliflozin[1] on eGFR in patients with a baseline eGFR<60 mL/min/1.73 m²



Effects of canagliflozin[2] on eGFR in patients with a baseline eGFR of 45–<60 mL/min/1.73 m²

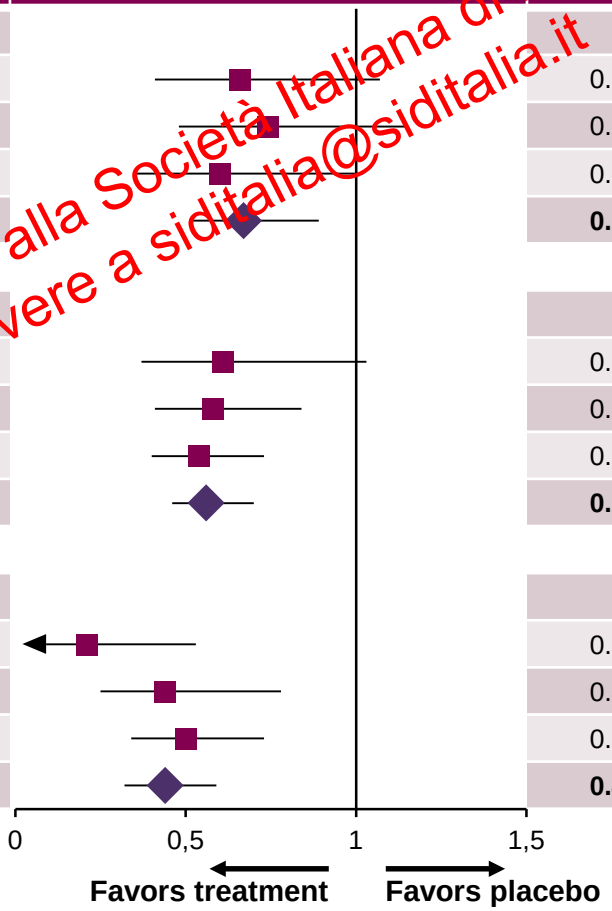


- .*p<0.0001; **p=0.005; ***p=0.42.
- DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate.

1. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 2. Neuen BL, et al. *Circulation* 2018;138:1537–1550

SGLT2 Inhibitors Reduce the Risk of Progressing to End-stage Renal Outcomes in Patients with Varying eGFR at Baseline

Renal composite[a]	Events	Treatment events per 1000 P-Y	Placebo events per 1000 P-Y	HR (95% CI)
eGFR <60 mL/min/m²				
EMPA-REG OUTCOME	N/A	N/A	N/A	0.66 (0.41, 1.07)
CANVAS program	83	11.4	15.1	0.74 (0.48, 1.15)
DECLARE-TIMI 58[c]	59	8.9	15.2	0.60 (0.35, 1.02)
FE model for eGFR <60 mL/min/m² (*P*=0.0054)				**0.67 (0.51, 0.89)**
eGFR 60 to <90 mL/min/m²				
EMPA-REG OUTCOME	N/A	N/A	N/A	0.61 (0.37, 1.03)
CANVAS program	118	4.6	7.4	0.58 (0.41, 0.84)
DECLARE-TIMI 58[c]	186	4.2	7.8	0.54 (0.40, 0.73)
FE model for eGFR <90 mL/min/m² (*P*<0.0001)				**0.56 (0.46, 0.70)**
eGFR ≥90 mL/min/m²				
EMPA-REG OUTCOME	N/A	N/A	N/A	0.21 (0.09, 0.53)
CANVAS program	48	3.8	8.1	0.44 (0.25, 0.78)
DECLARE-TIMI 58[c]	120	2.5	4.9	0.50 (0.34, 0.73)
FE model for eGFR ≥90 mL/min/m² (*P*<0.0001)				**0.44 (0.32, 0.59)**



Trend for subgroup differences *P*=0.026

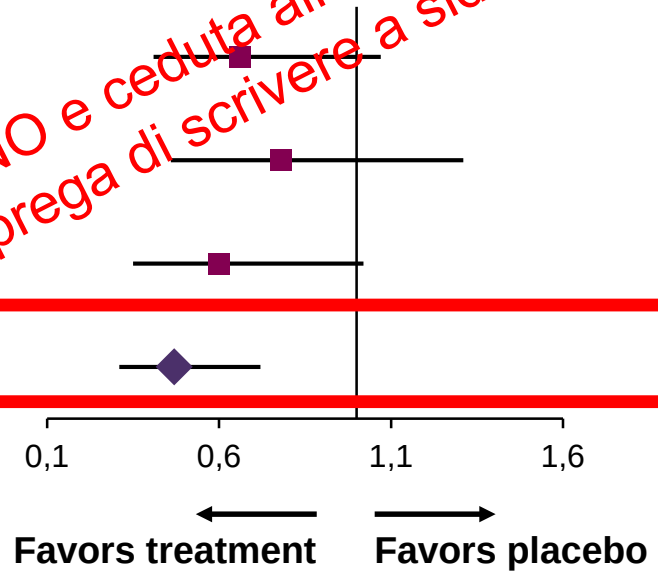
- [a]Defined as **worsening of renal function, end-stage kidney renal disease, or renal death**; [b]In the DECLARE overall population, 3-point renal endpoint was a nominally-significant exploratory endpoint: ≥40% in GFR to <60 mL/min/1.73m² of body-surface area, new end-stage renal disease, or death from renal cause (47% RRR, 1.3% ARR, HR, 0.53; 95% CI, 0.43, 0.66). CI, confidence interval; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; FE, fixed-effects; HR, hazard ratio; P-Y, patient-years;SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Zelniker TA, et al. *Lancet* 2019;393:31–39

SGLT2 Inhibitors Reduce the Risk of Progressing to End-stage Renal Outcomes in Patients with Low eGFR

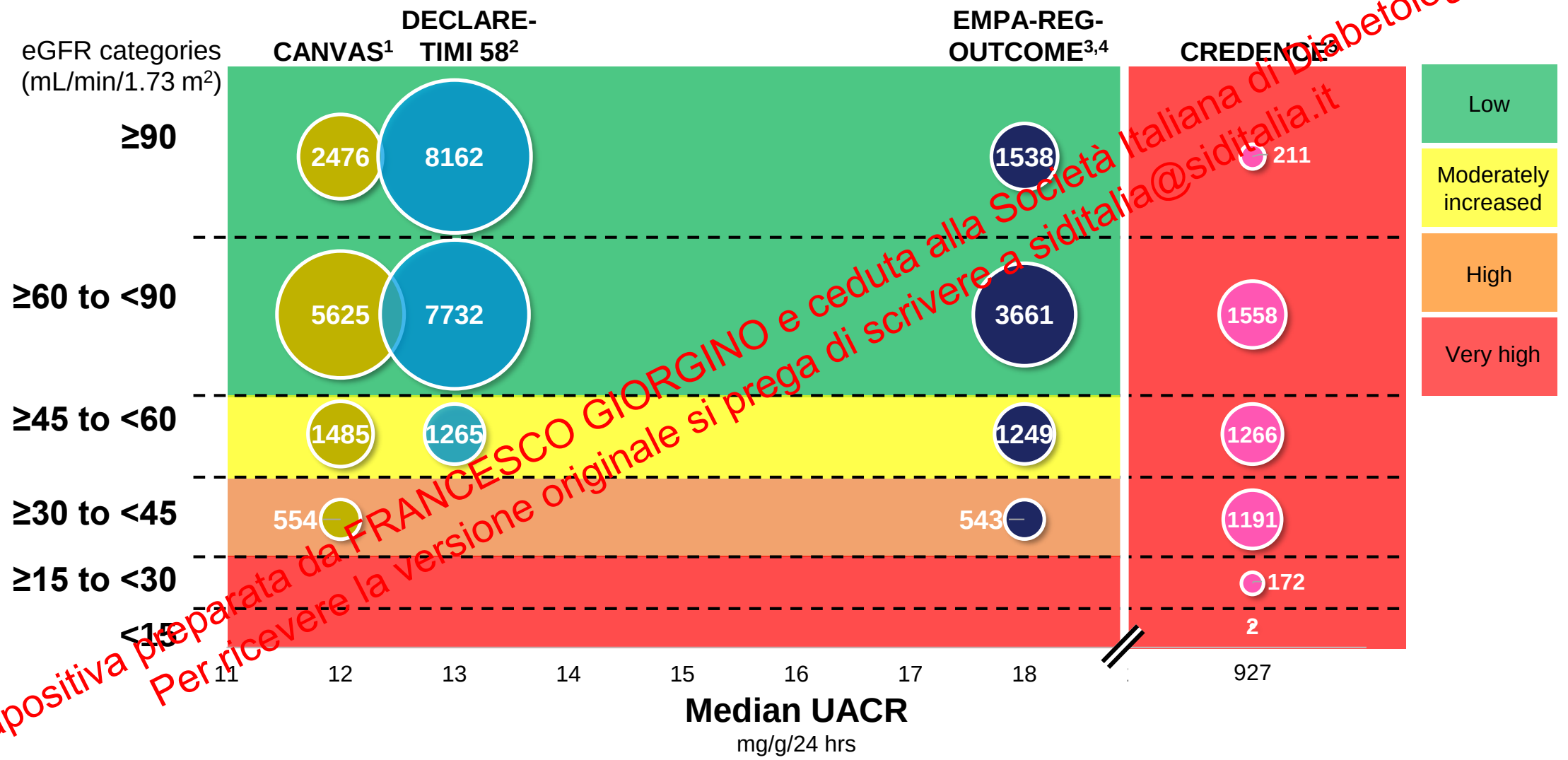
Effect of SGLT2 inhibitors on a renal composite of worsening renal function, end-stage kidney renal disease, or renal death

Trial	eGFR subgroup	HR (95% CI)
EMPA-REG OUTCOME[1]	<60 mL/min/1.73 m^2	0.66 (0.41, 1.07)
CANVAS program[2]	45–<60 mL/min/1.73 m^2	0.78 (0.46, 1.31)
DECLARE-TIMI 58[3]	<60 mL/min/1.73 m^2	0.60 (0.35, 1.02)
CREDENCE[4]	45–<60 mL/min/1.73 m^2	0.47 (0.31, 0.72)



1. Zelniker TA, et al. *Lancet* 2019;393:31–39; 2. Neuen BL, et al. Circulation 2018;138:1537–1550; 3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 4. Perkovic V, et al. *N Engl J Med* 2019; 380:2295-2306

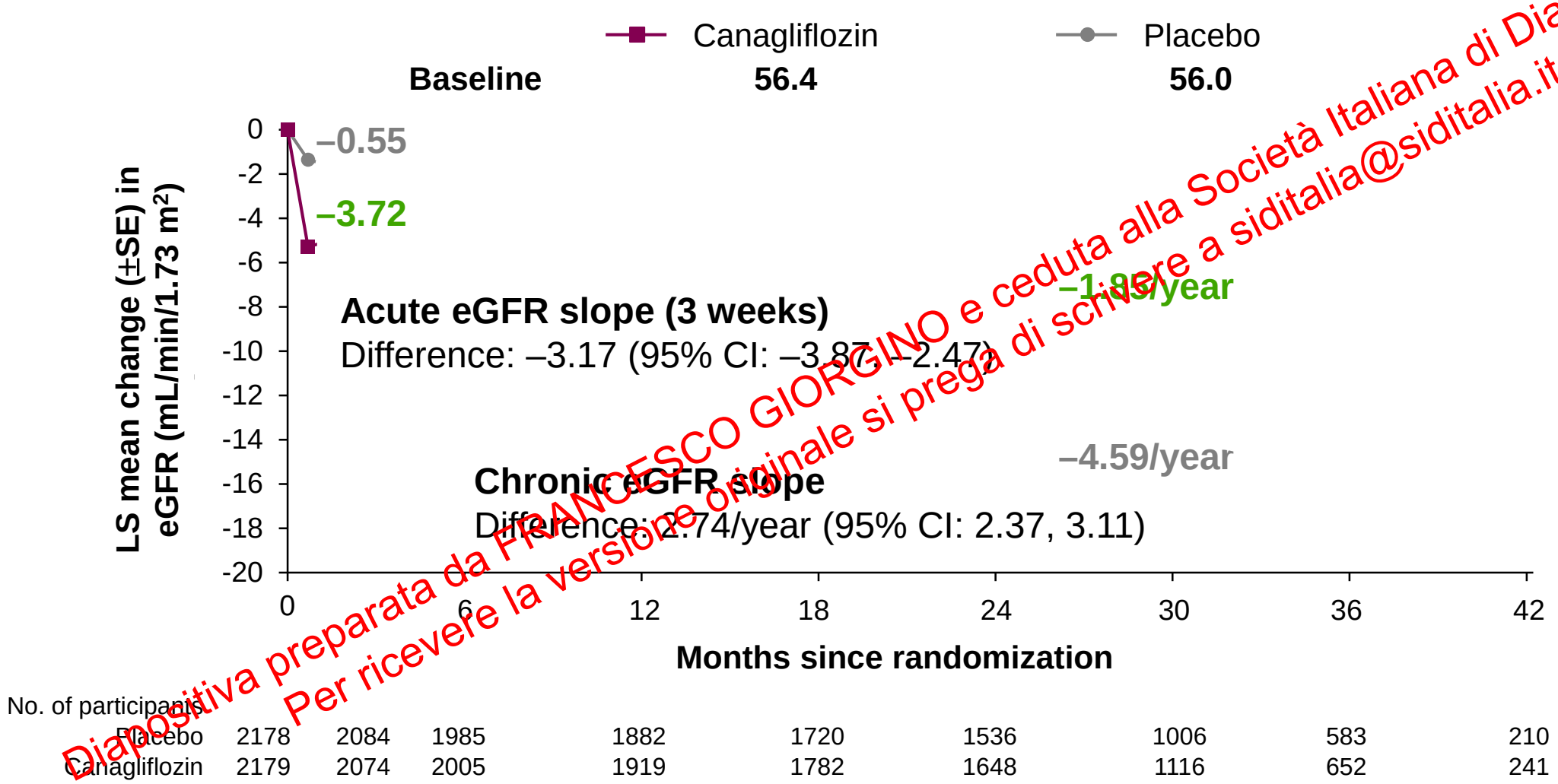
The CREDENCE Trial Population Had the Poorest Baseline Renal Function of All SGLT2 Inhibitor Trials



eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio

1. Neuen BL, et al. *Circulation* 2018;138:1537–1550; 2. Wiviott SD, et al. *N Engl J Med* 2019;380:347–357; 3. Wanner C, et al. *Circulation* 2018;137:119–129; 4. Zinman B, et al. *Cardiovasc Diabetol* 2014;13:102; 5. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

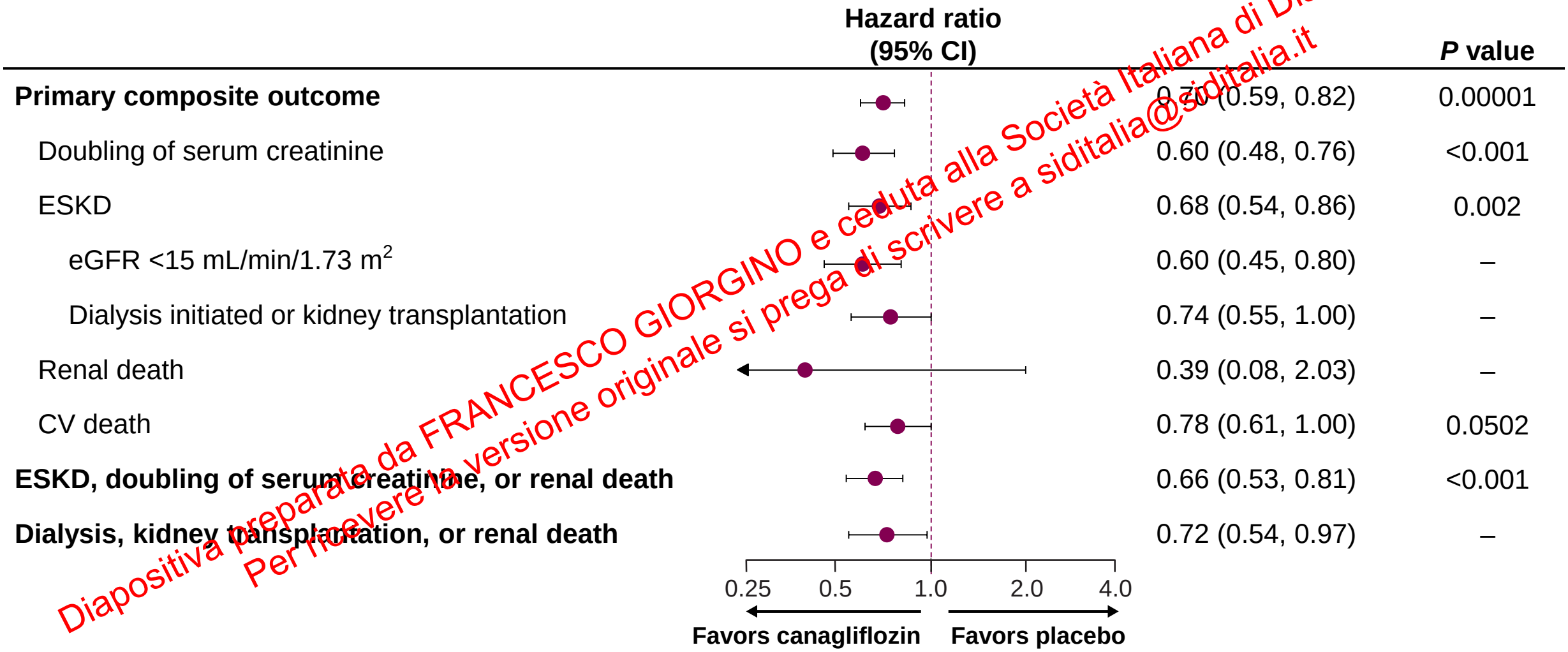
CREDENCE: Canagliflozin Was Shown to Stabilize eGFR Compared with Placebo in Patients with Poor Renal Function



eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error

Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

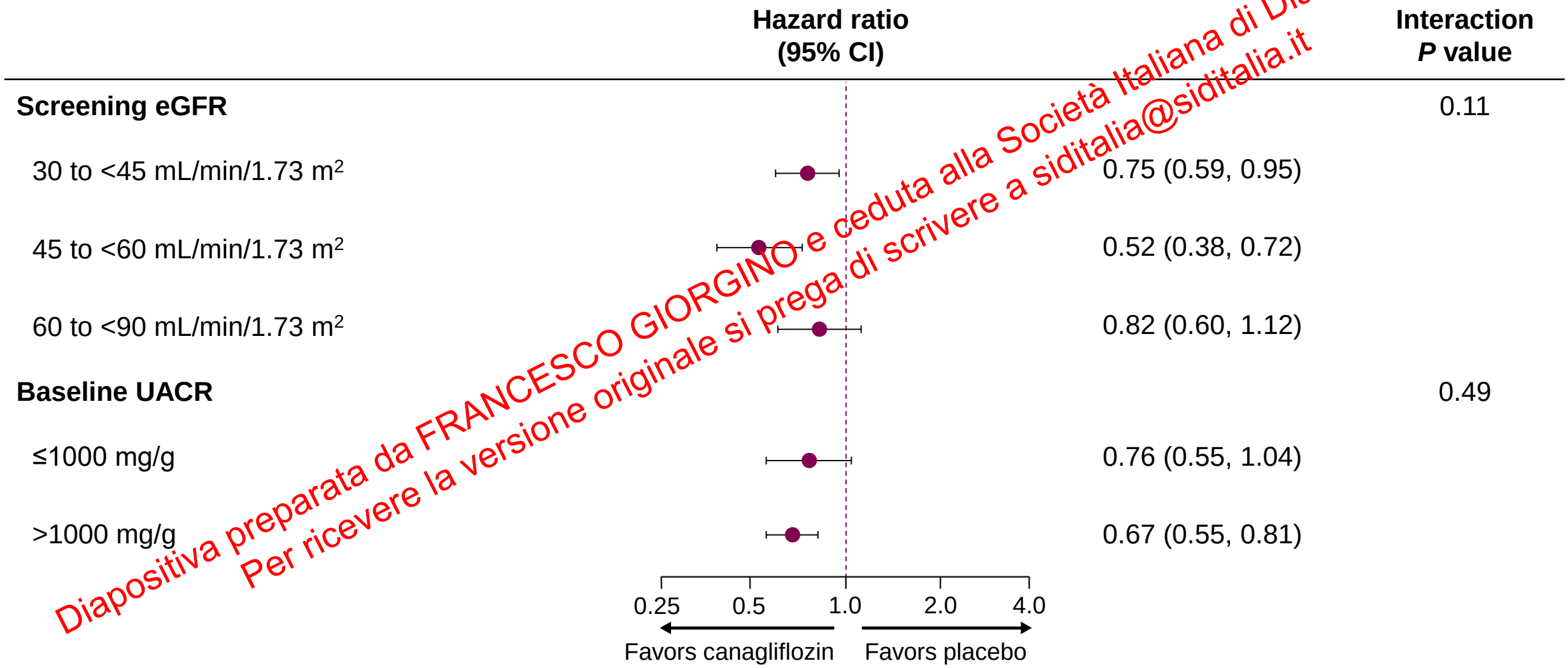
CREDENCE: Canagliflozin Prevented the Overall Renal Composite and Its Individual Components in Patients with Poor Renal Function



CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease

Perkovic V, et al. *N Engl J Med* 2019; 380:2295–2306

CREDENCE: Effects of Canagliflozin on the Renal Composite Endpoint according to Baseline eGFR and UACR

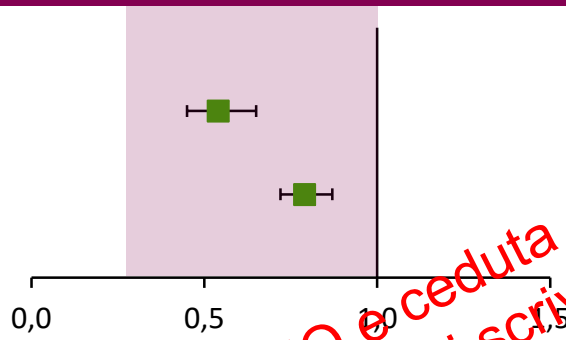


CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio

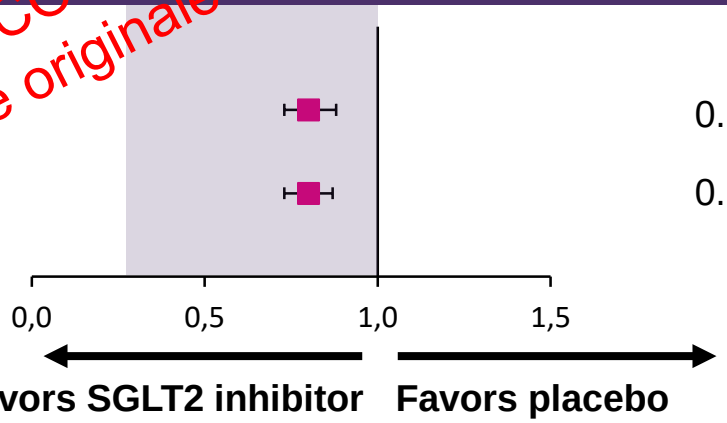
Perkovic V, et al. *N Engl J Med* 2019;380:2995–2306

SGLT2 Inhibitors Prevent Early Albuminuria Progression

Outcomes for dapagliflozin[1]	HR (95% CI)	*P* value
Deterioration from baseline		
Normo/micro to macro	0.54 (0.45, 0.65)	<0.0001
Normo to micro/macro	0.79 (0.72, 0.87)	<0.0001



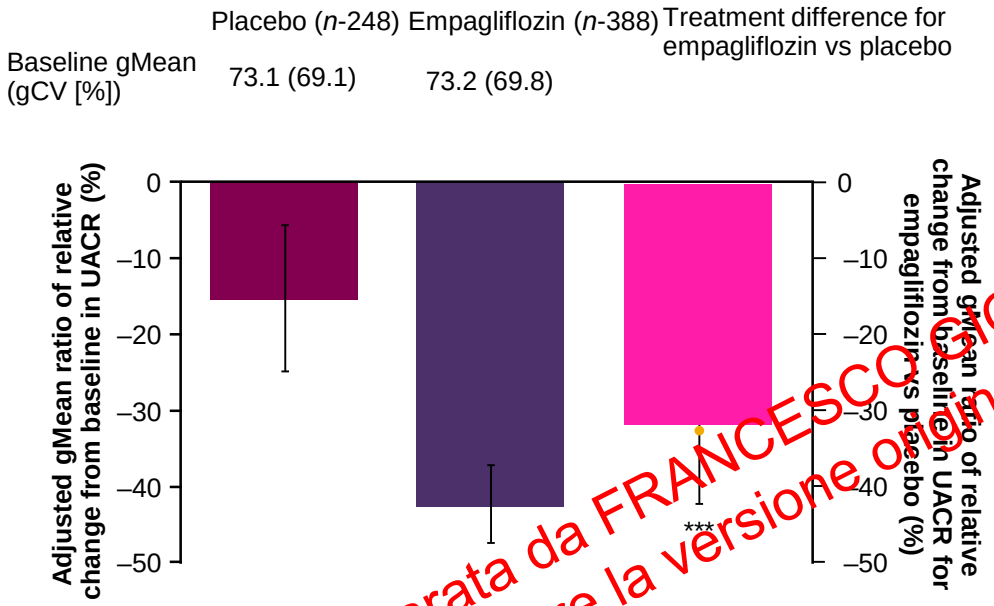
Outcome for canagliflozin[2]	HR (95% CI)	*P* value
Deterioration from baseline		
New-onset albuminuria	0.80 (0.73, 0.88)	NR
New-onset microalbuminuria	0.80 (0.73, 0.87)	NR



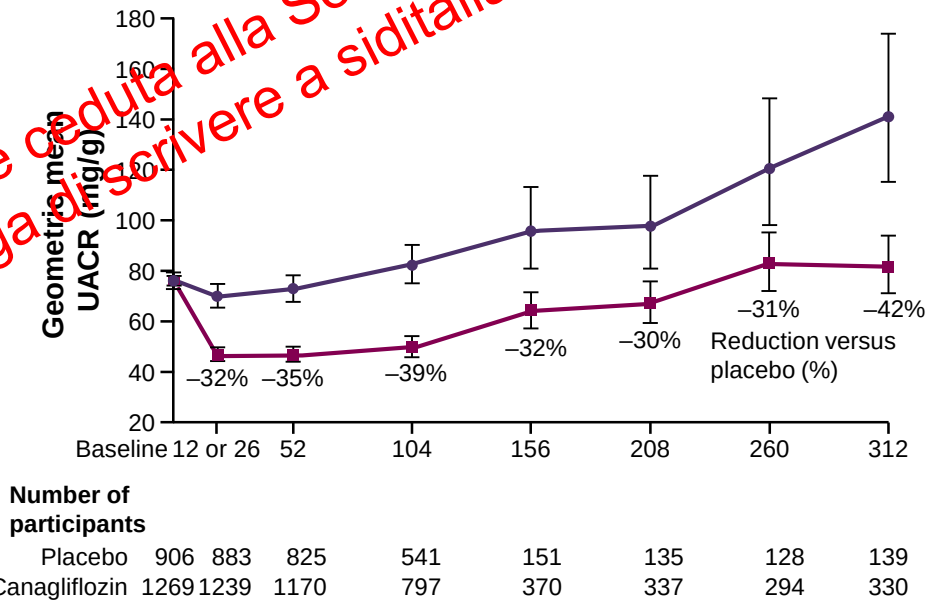
- CI, confidence interval; HR, hazard ratio; NR, not reported; SGLT2, sodium–glucose co-transporter 2
- 1. Raz I, et al. Presented at 79th Scientific Sessions of the American Diabetes Association; June 7th–11th, 2019; San Francisco, CA, USA; 244-OR; 2. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691–704

SGLT2 Inhibitors Reduce UACR in Patients with Microalbuminuria

Percentage change in UACR from baseline with empagliflozin in patients with microalbuminuria compared with placebo[1]



Effect of canagliflozin on UACR in patients with microalbuminuria[2]



Number of participants

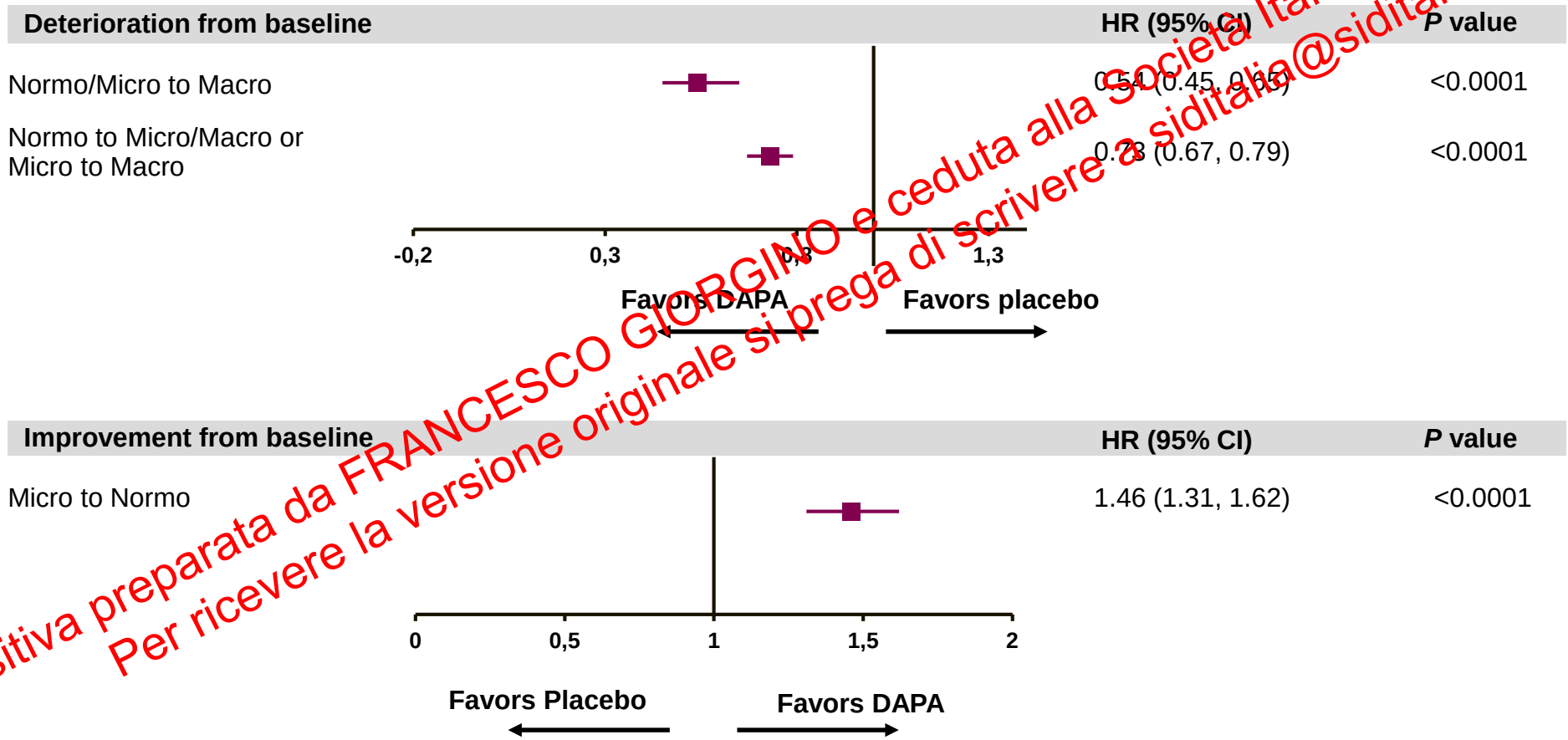
Placebo	906	883	825	541	151	135	128	139
Canagliflozin	1269	1239	1170	797	370	337	294	330

- ***$P<0.001$
- CI, confidence interval; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio

1. Cherney D, et al. *Diabetologia* 2016;59;1860–70; 2. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691–704

Dapagliflozin Prevents Progression to Macroalbuminuria and Improves UACR in Microalbuminuric Patients

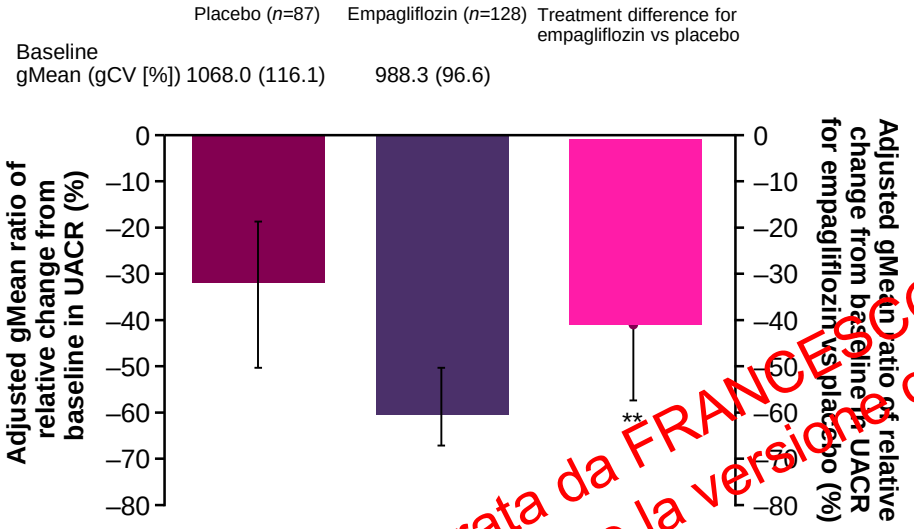
Effects of dapagliflozin in improving UACR and preventing albuminuria progression compared with placebo



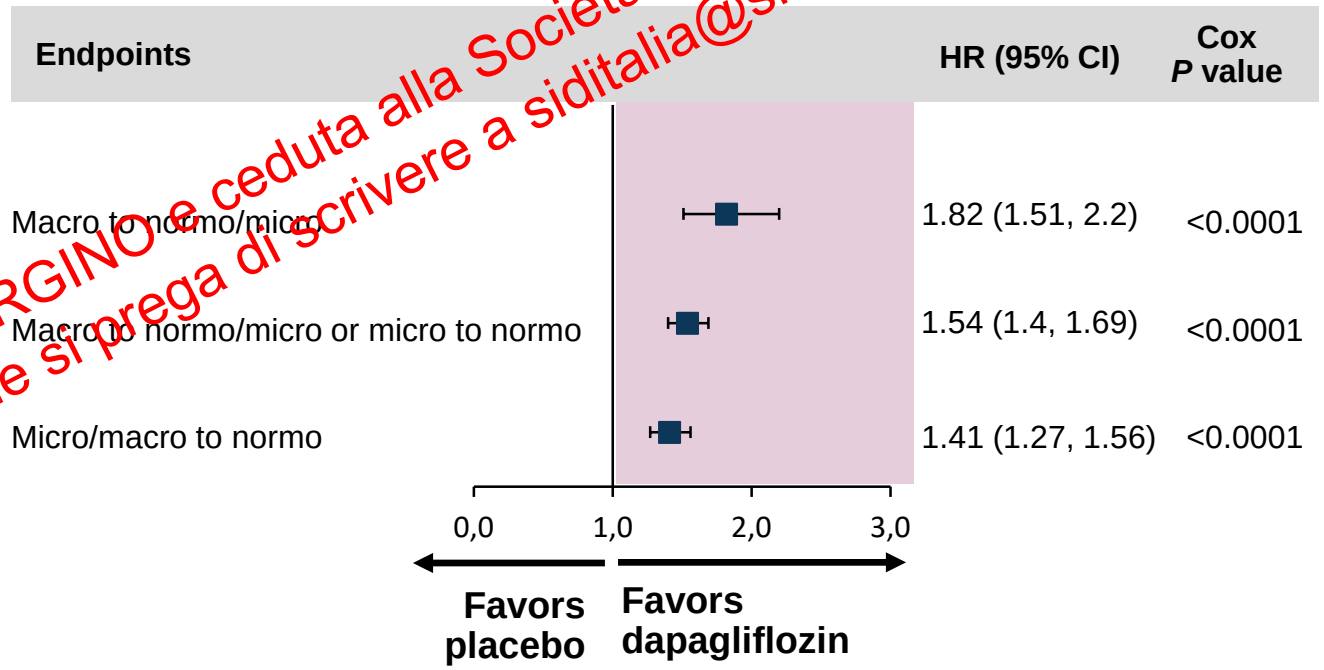
- CI, confidence interval; DAPA, dapagliflozin; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2; UACR, urine albumin:creatinine ratio
- Raz I, et al. Presented at: The American Diabetes Association 79th Scientific Sessions. San Francisco, USA; 7th June–11th June 2019;CA 244-OR.

SGLT2 Inhibitors both Reduce and Improve UACR in Macroalbuminuric Patients

Percentage change in UACR from baseline with empagliflozin in patients with macroalbuminuria compared with placebo[1]

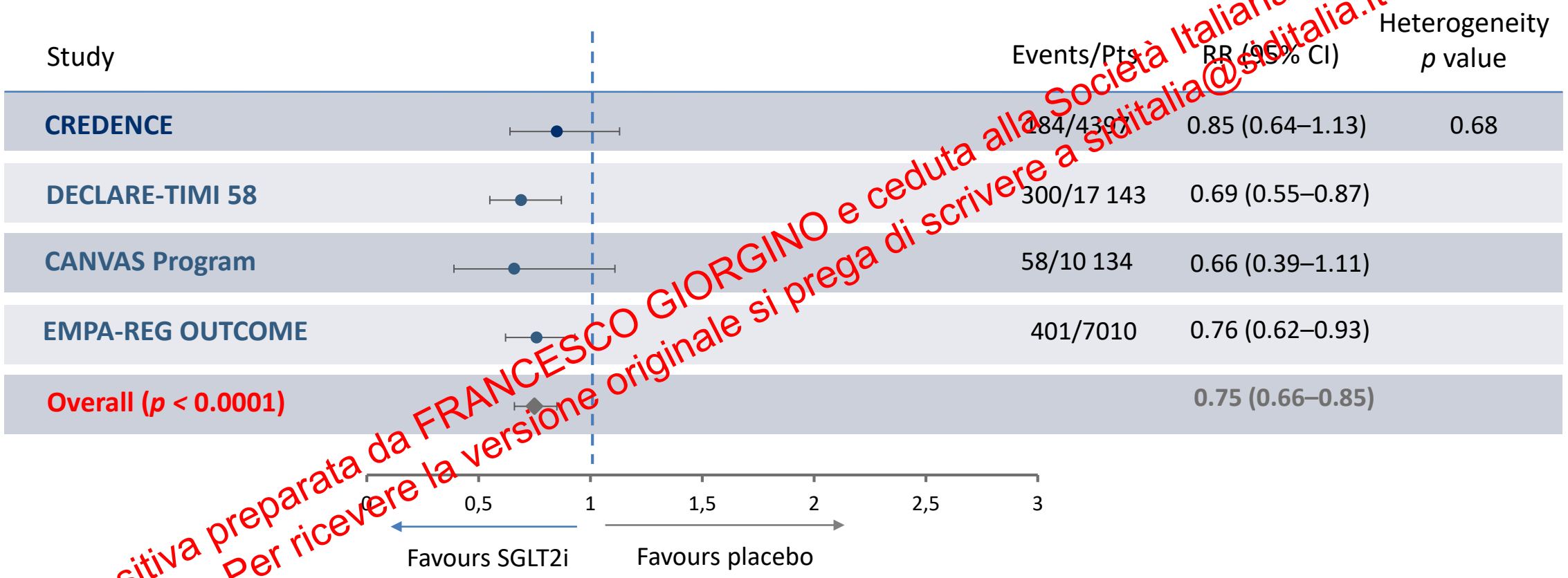


Effects of dapagliflozin in improving UACR in patients with macroalbuminuria compared with placebo[2]



- macro, macroalbuminuria; micro, microalbuminuria; normo, normoalbuminuria; UACR, urine albumin:creatinine ratio
- 1. Cherney D, et al. *Diabetologia* 2016;59;1860–70; 2. Raz I, et al. Presented at 79th Scientific Sessions of the American Diabetes Association; June 7th–11th, 2019; San Francisco, CA, USA; 244-OR

Effect of SGLT2 Inhibitors on Acute Kidney Injury



Neuen BL, ***Lancet Diabetes Endocrinol*** 2019; Sep 5. doi: 10.1016/S2213-8587(19)30256-6

Although both GLP-1 RA and SGLT2 Inhibitors Prevent Progression to a Renal Composite Endpoint[a]…

SGLT2 inhibitor trials	Treatment group events n/N (%)	Placebo group events n/N (%)	HR (95% CI)
EMPA-REG OUTCOME	525/4124 (12.7%)	388/2061 (18.8%)	0.61 (0.53, 0.70)
CANVAS Program	N/A	N/A	0.57 (0.50, 0.66)
DECLARE-TIMI 58	678/8582 (7.9%)	997/8578 (11.6%)	0.66 (0.60, 0.73)

GLP-1 RA trials	Treatment group events n/N (%)	Placebo group events n/N (%)	HR (95% CI)
ELIXA	203/2639 (7.7%)	172/2647 (6.5%)	0.84 (0.68, 1.02)
LEADER	268/4668 (5.7%)	337/4672 (7.2%)	0.78 (0.67, 0.92)
SUSTAIN-6	62/1646 (3.8%)	100/1649 (6.1%)	0.64 (0.46, 0.88)
EXSCEL	366/6256 (5.9%)	407/6222 (6.5%)	0.88 (0.76, 1.01)

[a]Defined as **new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or death of renal cause.** CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2

Zelniker TA, et al. *Circulation* 2019

…the GLP-1 RA Effect[a] Declines Once the Macroalbuminuria Component Is Removed

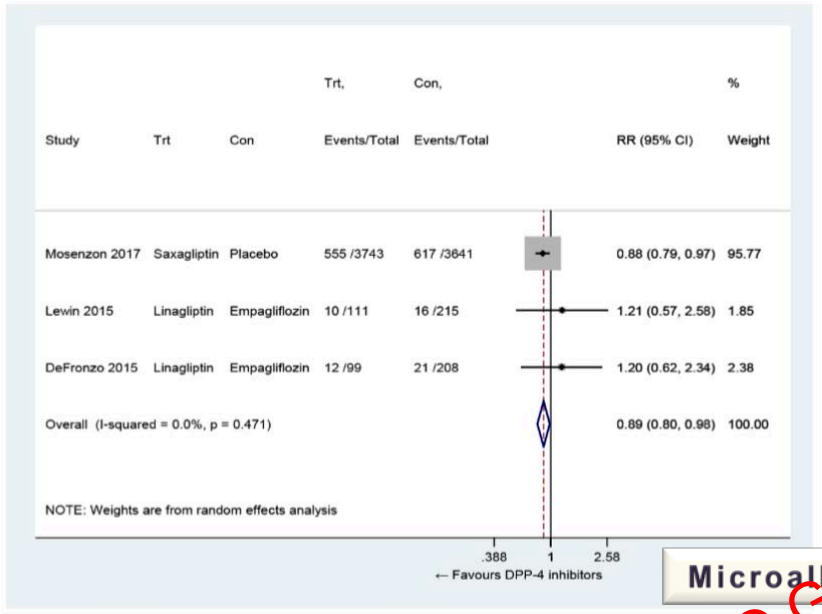
SGLT2 inhibitor trials	Treatment group events n/N (%)	Placebo group events n/N (%)	HR (95% CI)
EMPA-REG OUTCOME	81/4645 (1.7%)	71/2323 (3.1%)	0.54 (0.40, 0.75)
CANVAS Program	N/A	N/A	0.60 (0.47, 0.77)
DECLARE-TIMI 58	127/8582 (1.5)	238/8578 (2.8%)	0.53 (0.43, 0.66)

GLP-1 RA trials	Treatment group events n/N (%)	Placebo group events n/N (%)	HR (95% CI)
ELIXA	35/3032 (1.2%)	41/3031 (1.4%)	1.16 (0.74, 1.83)
LEADER	87/4668 (1.9%)	97/4672 (2.1%)	0.89 (0.67, 1.19)
SUSTAIN-6	18/1648 (1.1%)	14/1649 (0.8%)	1.28 (0.64, 2.58)
EXSCEL	246/6456 (3.8%)	273/6458 (4.2%)	0.88 (0.74, 1.05)

- [a]Defined as **sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or death of renal cause**
- CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2

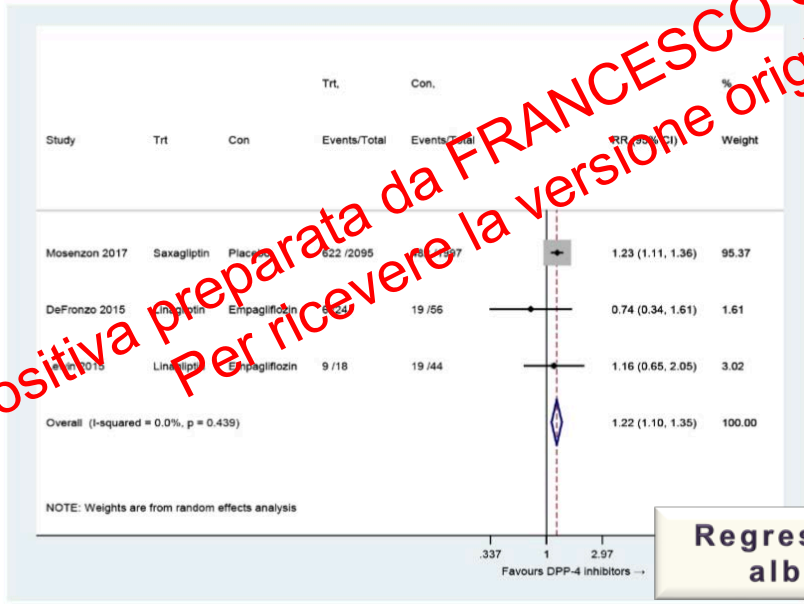
Zelniker TA, et al. *Circulation* 2019

Effects of DPP-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

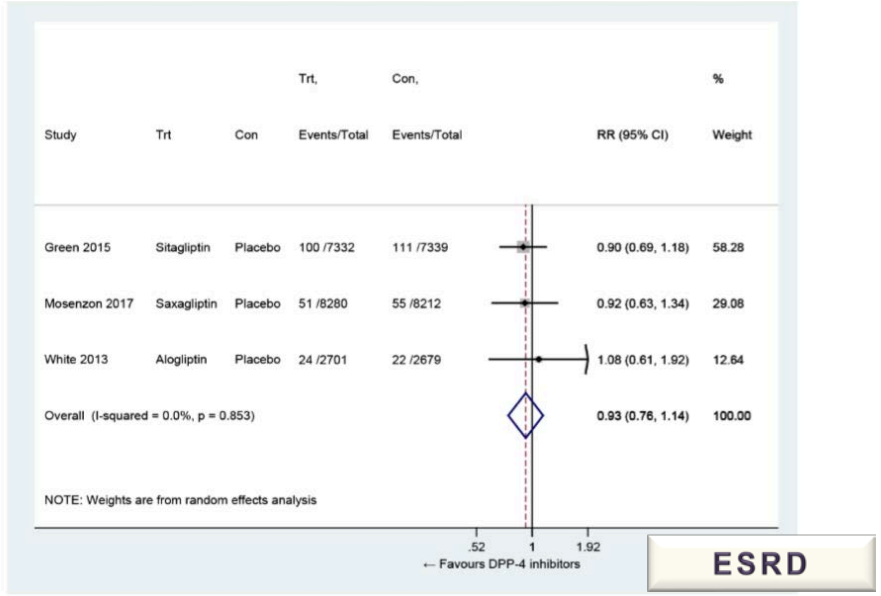


Microalbuminuria

Macroalbuminuria



Regression of albuminuria



ESRD

Bae JH et al, *Endocrinol Metab* 2019

ADA/EASD 2018 Consensus recommendation

- For patients with type 2 diabetes and CKD, with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression

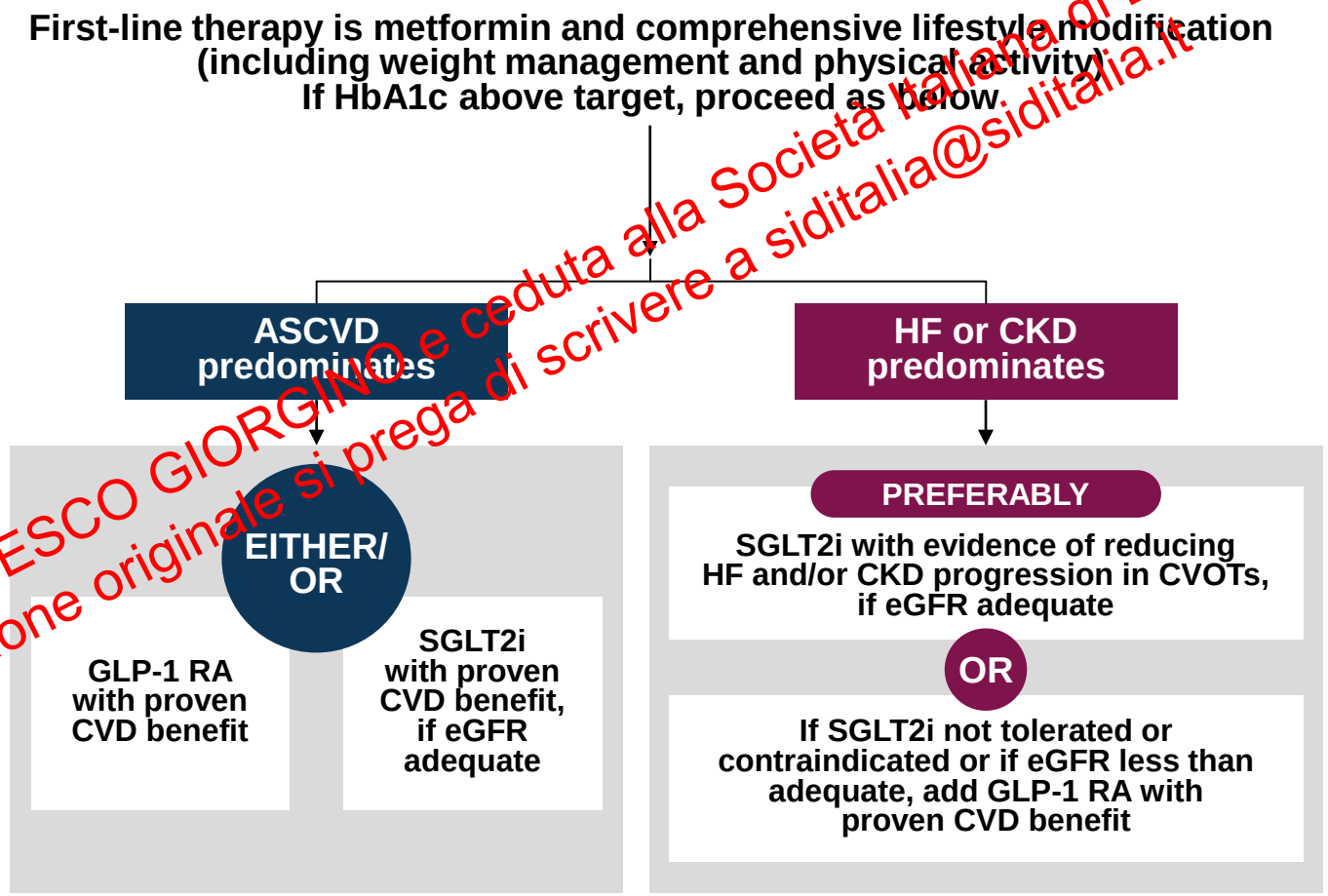
The 2018 ADA-EASD T2D Consensus Report Reflects Emerging Evidence from GLP-1 RA and SGLT2i CVOTs in Patients with Established CVD or CKD

CONSENSUS RECOMMENDATIONS

Patients with T2D who have established ASCVD:
SGLT2 inhibitors or GLP-1 RAs with proven CV benefit recommended

Patients with ASCVD in whom HF coexists or is of special concern:
SGLT2 inhibitors recommended

Patients with T2D and CKD, with or without CVD:
Consider SGLT2 inhibitor or, if contraindicated/not preferred, GLP-1 RA shown to reduce CKD progression



ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CANA, canagliflozin; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; EQW, exenatide once-weekly; ESRD, end-stage renal disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; LIRA, liraglutide; SEMA, semaglutide; SGLT2, sodium–glucose co-transporter 2; T2D, type 2 diabetes. Davies MJ, et al. Online ahead of print. *Diabetologia*. 2018;61(12):2461-2498.

DAPACKD

Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with CKD (Dapa-CKD)[1]

An international, multicentre, event-driven, randomised, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to SoC, to prevent the progression of CKD or CV/renal death.

~4,000 patients

Status: This study is currently recruiting participants

Study Design

Population

- ≥18 years of age
- eGFR ≥25 and ≤75 mL/minute/1.73 m^2*
- UACR ≥200 and ≤5000 mg/g
- Stable, maximum tolerated dose of ACEi/ARB for at least 4 weeks before visit

N=~4,000

Randomisation 1:1

- Placebo + SoC
- Dapagliflozin 10 mg or 5 mg + SoC

Duration

February 2017

46 MONTHS

Q4 2020
(estimated completion)

Primary Endpoint

- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR, or reaching ESRD, CV death or renal death

Secondary Endpoints

- Time to first occurrence of a renal composite (≥50% sustained decline in eGFR, reaching ESRD or renal death)
- Time to first occurrence of CV death or hHF
- Time to death from any cause

*Dapagliflozin is not recommended for use in patients with eGFR <60 mL/minute/1.73 m^2. The efficacy of dapagliflozin is dependent on renal function.[2] Dapagliflozin is not indicated for prevention of CV events. Please consult your local prescribing information for the approved use of dapagliflozin.

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hHF, hospitalisation for heart failure; SoC, standard of care; UACR, urine albumin:creatinine ratio.

1. https://clinicaltrials.gov/show/NCT03036150. Last accessed 22 June 2017; 2. FORXIGA. Summary of Product Characteristics, 2017.

Additional understanding of possible mechanisms behind the CV benefits seen with dapagliflozin will come from DapaMech

DapaMech is a series of mechanistic studies evaluating the impact of dapagliflozin 10 mg

PRESERVED-HF[1]
HF disease-specific biomarkers, symptoms, health status, and QoL in patients with T2D or prediabetes and chronic HFpEF

DEFINE-HF[2]
HF disease-specific biomarkers, symptoms, health status, and QoL in patients with T2D and chronic HFrEF

DAPACARD[2]
Cardiac substrate uptake, myocardial efficiency and myocardial contractile work in patients with T2D

DAPAMAAST[4]
Insulin sensitivity in skeletal muscle in patients with T2D taking no diabetes medication or metformin only

DELIGHT[5]
The impact of albuminuria in patients with T2D and CKD

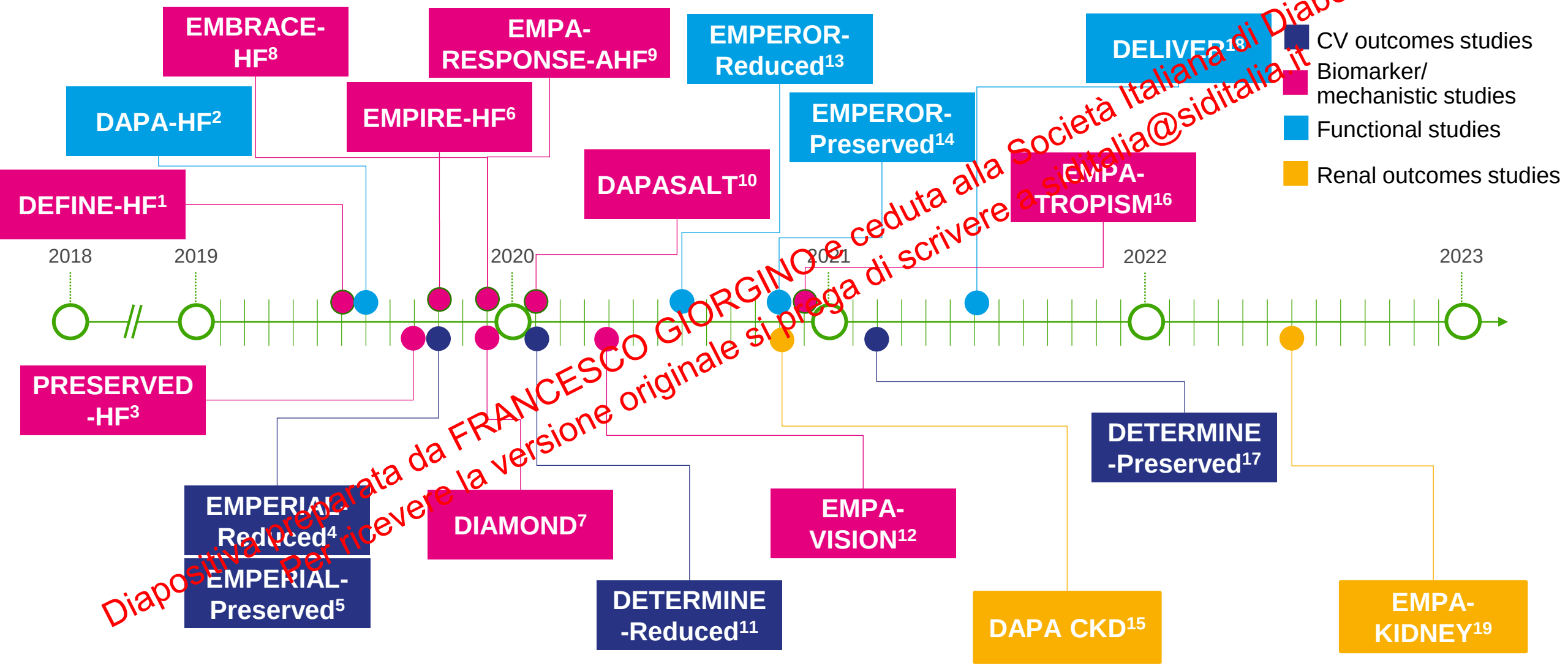
DIAMOND[6]
The renoprotective effects in ND patients with proteinuria and on stable dose of ACEi or ARB

DAPASALT[7]
The natriuretic effect in patients with T2D with preserved or impaired renal function and ND patients with impaired renal function

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ND, nondiabetic; QoL, quality of life; T2D, type 2 diabetes.

1. Saint Luke's Health System; https://clinicaltrials.gov/ct2/show/NCT03030235. **2**. AstraZeneca; https://clinicaltrials.gov/ct2/show/NCT03387683. **3.** Saint Luke's Health System; https://clinicaltrials.gov/ct2/show/NCT02653482. **4**. AstraZeneca; https://clinicaltrials.gov/ct2/show/NCT03338855. **5.** AstraZeneca; https://clinicaltrials.gov/ct2/show/NCT02547935. **6**. Hiddo Lambers Heerspink; AstraZeneca. https://clinicaltrials.gov/ct2/show/NCT03190694. **7.** AstraZeneca; https://clinicaltrials.gov/ct2/show/NCT03152084.

Ongoing SGLT2 inhibitor studies



CV, cardiovascular; SGLT2i, sodium–glucose co-transporter 2

1. clinicaltrials.gov/NCT02653482; 2. clinicaltrials.gov/NCT03036124; 3. clinicaltrials.gov/NCT03030235; 4 clinicaltrials.gov/NCT03877237; 5. clinicaltrials.gov/NCT03877224; 6. clinicaltrials.gov/NCT03198585; 7. clinicaltrials.gov/NCT03190694; 8. clinicaltrials.gov/NCT03030222; 9. clinicaltrials.gov/NCT03200860; 10. clinicaltrials.gov/NCT03152084; 11. clinicaltrials.gov/NCT03877237; 12. clinicaltrials.gov/NCT03332212; 13. clinicaltrials.gov/NCT03057977; 14. clinicaltrials.gov/NCT03057951; 15. clinicaltrials.gov/NCT03036150; 16. clinicaltrials.gov/NCT03485222; 17. clinicaltrials.gov/NCT03877224; 18. clinicaltrials.gov/NCT03619213; 19. clinicaltrials.gov/NCT03594110

Received: 4 May 2018 | Revised: 31 May 2018 | Accepted: 8 June 2018

DOI: 10.1111/dom.13413

WILEY

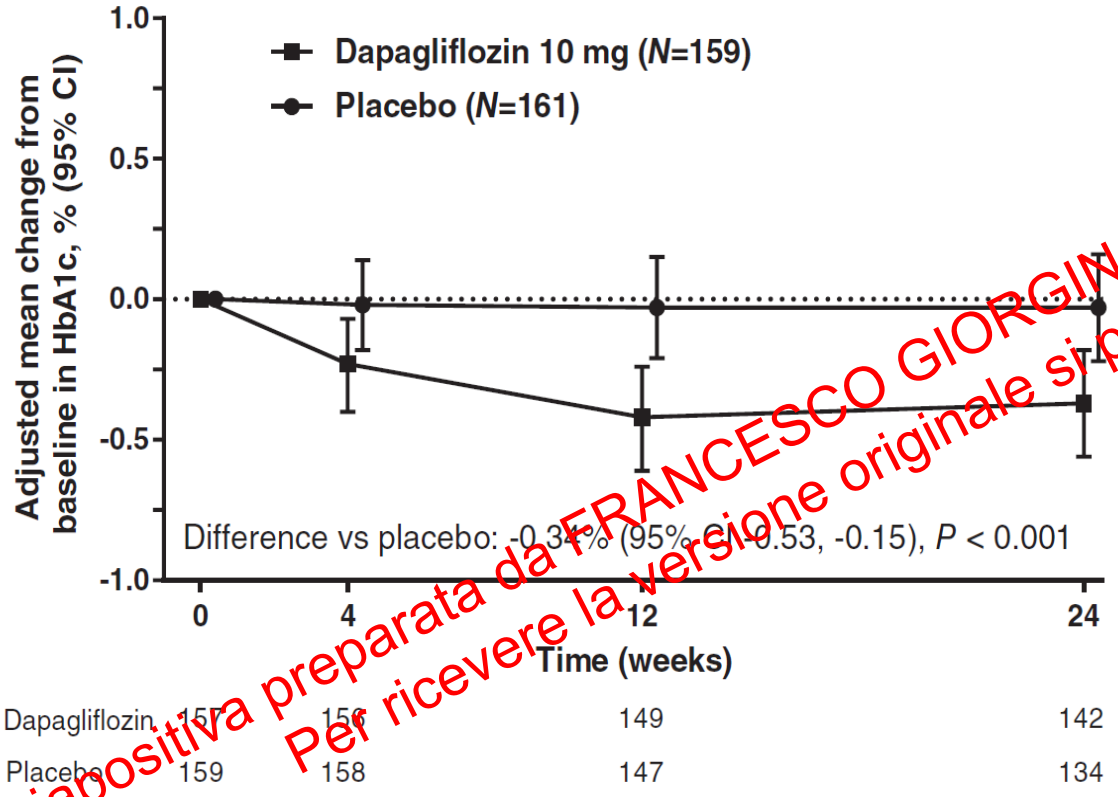
ORIGINAL ARTICLE

Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study

Paola Fioretto MD[1] | Stefano Del Prato MD[2] | John B. Buse MD[3] | Ronald Goldenberg MD[4] | Francesco Giorgino MD[5] | Daniel Reyner DrPH[6] | Anna Maria Langkilde MD[7] | C. David Sjöström MD[7] | Peter Sartipy PhD[7,8] | On Behalf of the DERIVE Study Investigators*

60% ≥65 yrs	**HbA1c 8.3%**
BMI 32 eGFR 53	**50% on insulin**

Efficacy and Safety of Dapagliflozin in CKD3a



Fioretto P et al., *DOM* 2018

	Dapagliflozin 10 mg (*N* = 160)	Placebo (*N* = 161)
AEs		
Any AE	67 (41.9)	77 (47.8)
Any related AE	17 (10.6)	10 (6.2)
Any AE leading to discontinuation	3 (1.9)	3 (1.9)
Death	0	0
Serious AEs		
Any serious AE	9 (5.6)	14 (8.7)
Any related serious AE	1 (0.6)	0
Any serious AE leading to discontinuation	2 (1.3)	2 (1.2)
AEs of interest		
Genital infection	3 (1.9)	2 (1.2)
Urinary tract infection	4 (2.5)	6 (3.7)
Hypotension/dehydration/ hypovolaemia	3 (1.9)	0
Renal impairment/failure	1 (0.6)	2 (1.2)
Bone fractures	0	0
DKA	0	0

Non-serious AEs were included up to the last day of double-blind treatment plus 4 days. Serious AEs were included up to the last day of double-blind treatment plus 30 days. Includes data after rescue. Abbreviations: AE, adverse event; DKA, diabetic ketoacidosis.

Adverse events	EMPA-REG OUTCOME Empagliflozin vs placebo Event rate %	CANVAS Canagliflozin vs placebo Event rate per 1000 patient years	DECLARE-TIMI 58 Dapagliflozin vs placebo Event rate %	CREDENCE Canagliflozin vs placebo Event rate per 1000 patient years
Severe hypoglycemia	1.3 vs 1.5	N/A (All: 50.0 vs 46.4)	0.7 vs 1.0	
Ketoacidosis	0.1 vs < 0.1	0.6 vs 0.3	0.3 vs 0.1	2.2 vs 0.2 HR 10.80 (1.39-83.65)
Urinary tract infections	18.0 vs 18.1	40.0 vs 37.0	1.5 vs 1.6	
Mycotic genital infections	6.4 vs 1.8	Women: 68.8 vs 17.5 (P<0.001) Men: 34.9 vs 10.8 (P<0.001)	0.9 vs 0.1 (P<0.001) (**)	
Volume depletion	5.1 vs 4.9	26.0 vs 18.5 (P=0.009)	2.5 vs 2.4	
Acute kidney injury	1.0 vs 1.6	3.0 vs 4.1	1.5 vs 2.0	16.9 vs 20.0
Cancer	No difference	No difference	5.6 vs 5.7	No difference
Bone fractures	3.8 vs 3.9	15.4 vs 11.9 (P=0.02)	5.3 vs 5.1	11.8 vs 12.1
Lower limb amputations	1.9 vs 1.8 IRR 1.01 (0.70-1.44)	6.3 vs 3.4 (p<0.001) HR = 1.97 (1.41-2.75)	1.4 vs 1.3	12.3 vs 11.2
Fournier gangrene	N/A	N/A	1 case vs 5 cases	

Adapted from Scheen AJ, *Exp Opinion Drug Safety* 2019

SGLT2 inhibitors

Scheen AJ, *Exp Opinion Drug Safety* 2019

SGLT-2 Inhibitors Improve Proximal Tubular Oxygen Delivery and May Also Reduce Renal Ischemic Injury

CLINICAL EFFECTS

Reduce Glomerular Pressure
↑Afferent vasoconstriction
↓Glomerular hyperfiltration

Neurohormonal Improvement
↓Intrarenal RAAS activity
↓SNS activity

Inflammation/Fibrosis Reductions
↓Inflammatory markers
↓Fibrotic markers

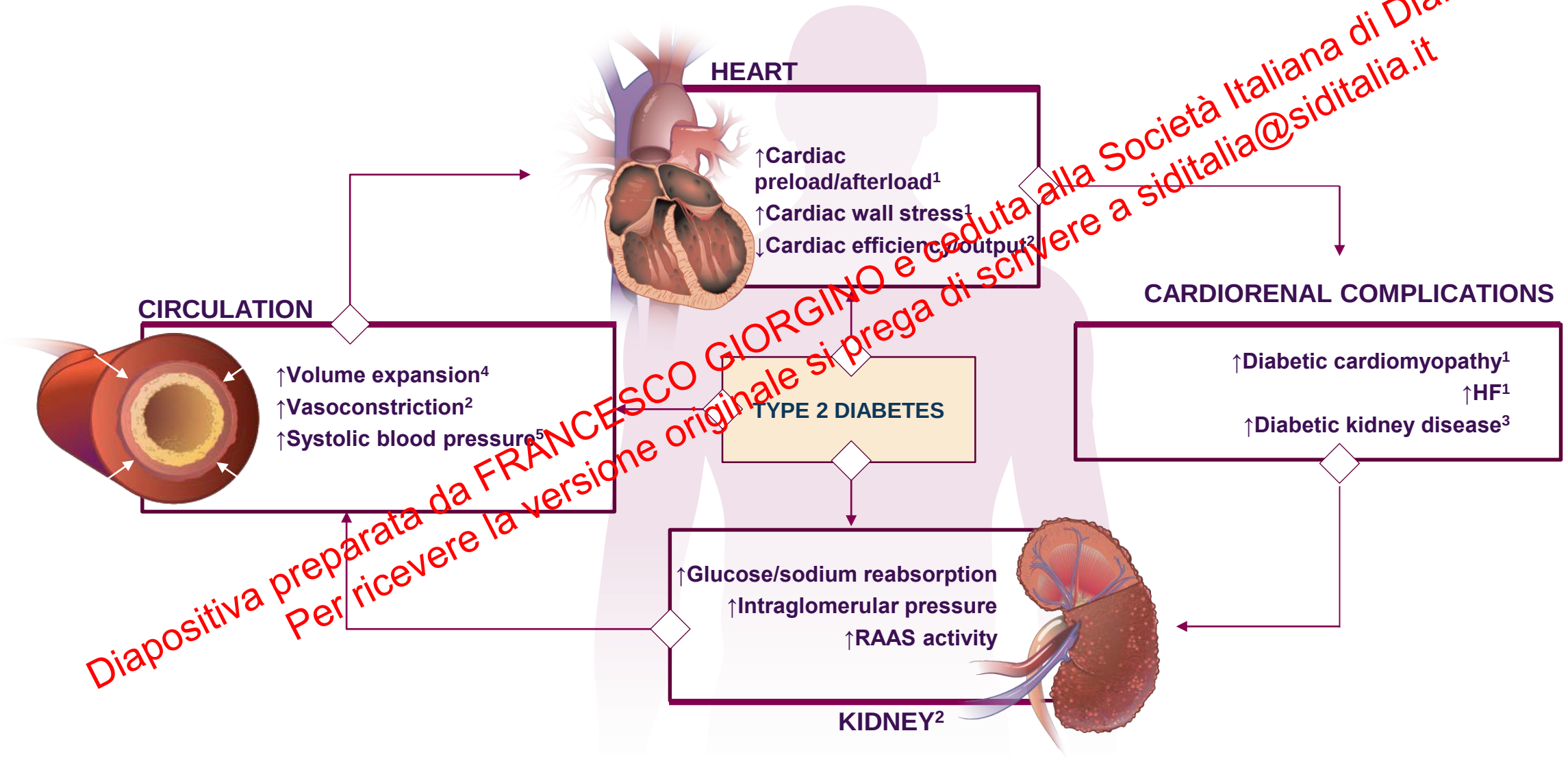
↓Renal Ischemic Injury
↑Hb/Hematocrit

- Elevated expression of HIF-1, which mediates the synthesis of erythropoietin, may play a major role in the protection of renal tubule cells under hypoxic conditions[1]
  - Recent *in vitro* studies reported that dapagliflozin induces HIF-1 in murine ischemic renal tissue and human ischemic cultured renal tubular cells, improves renal function[1], and reduces apoptotic cell death (Bax/Bcl2 ratio)[2]
- Hematocrit and erythropoietin levels have also been shown to increase following treatment with an SGLT-2i and may help to improve tubular oxygenation[3-5]

HIF-1=hypoxia inducible factor-1; IR=ischemia-reperfusion; S=sham.

1. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67. 2. Chang YK, et al. *PLoS One*. 2016;11(7):e0158810. 3. Sano M, et al. *J Clin Med Res*. 2016;8(12):844-847. 4. Sano M, et al. *Circulation*. 2019;139(17):1985-1987. 5. Inzucchi SE, et al. *Diabetes Care*. 2018;41(12):356-363.

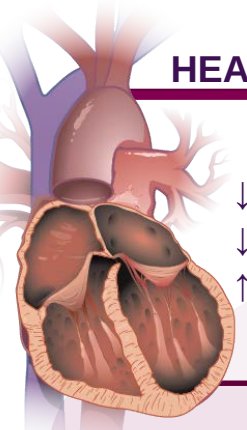
Bidirectional, Pathophysiological Interaction Between Kidney and Heart in Type 2 Diabetes



1. Muralidaran Y, et al. *J Diabetes Metab.* 2015, 6:10. 2. Sattar N, et al. *Diabetologia*. 2016;59(7):1333-1339. 3. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67. 4. Sattar N, et al. *Circulation*. 2018;138:7–9. 5. Mazidi M, et al. *J Am Heart Assoc*. 2017;6(6):e004007.

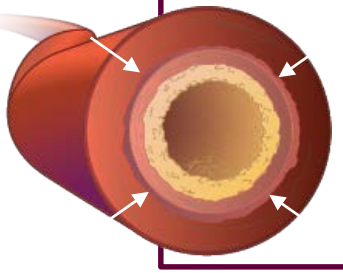
SGLT-2 Inhibition Improves Hemodynamic Parameters in Patients With Type 2 Diabetes Leading to Cardiorenal Protection

Back to Summary Slide



HEART[2]

↓Cardiac preload/afterload
↓Cardiac wall stress
↑Cardiac efficiency/output



CIRCULATION[1,2]

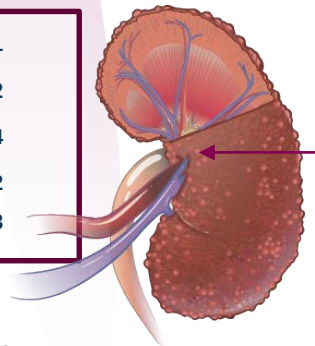
↓Plasma volume
↓Arterial stiffness
↓Systolic blood pressure
↑Hematocrit

SGLT-2 INHIBITION

Glycosuria[2]
Diuresis[3]
Natriuresis[2,3]

KIDNEY

↓Glucose/sodium reabsorption[1]
↓Intraglomerular pressure[2]
↓Intrarenal RAAS activity[4]
↓Hyperfiltration[2]
↓Inflammation/hypoxia[3]



CARDIORENAL PROTECTION[2,3]

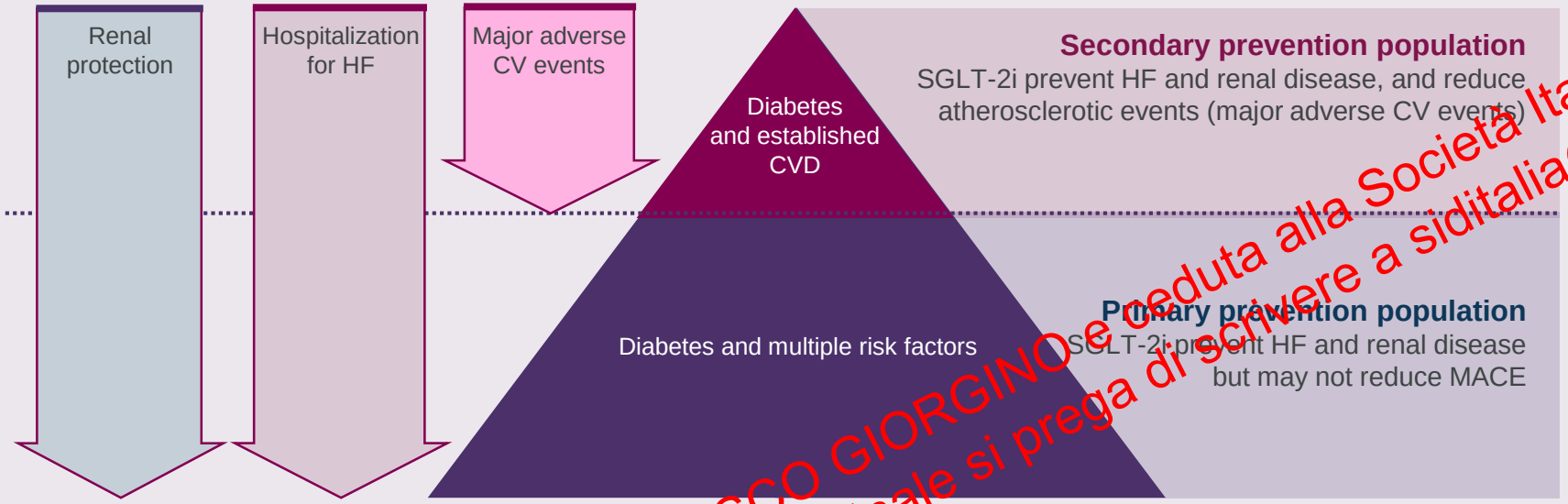
↑Cardiac function
↑Renal function

IMPROVED CLINICAL OUTCOMES[3,5]

↓CV outcomes
↓HF hospitalization
Stabilization of eGFR
↓Albuminuria

1. Sattar N et al. *Diabetologia*. 2016;59(7):1333-1339. 2. Verma S et al. *JAMA Cardiol*. 2017;2(9):939-940. 3. Scheen RJ. *Circ Res*. 2018;122:1439-1459. 4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 5. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

SGLT-2 Inhibition Leads to Benefits in Cardiorenal Outcomes in Several Patient Populations



- According to a recent meta-analysis of three randomized CVOTs in patients with T2D with either established CVD or multiple risk factors (~60% with established CVD), SGLT-2i reduced the risk of[1,2]:
  - Hospitalization for HF by 31% (HR=0.69; 95% CI, 0.61-0.79; *P*<.0001)
  - CV death or hospitalization for HF by 23% (HR=0.77; 95% CI, 0.71-0.84; *P*<.0001)
  - Major MACE by 11% (HR=0.89; 95% CI, 0.83-0.96; *P*=.0014)
  - Progression of renal disease by 45% (HR=0.55; 95% CI, 0.48-0.64; *P*<.0001)

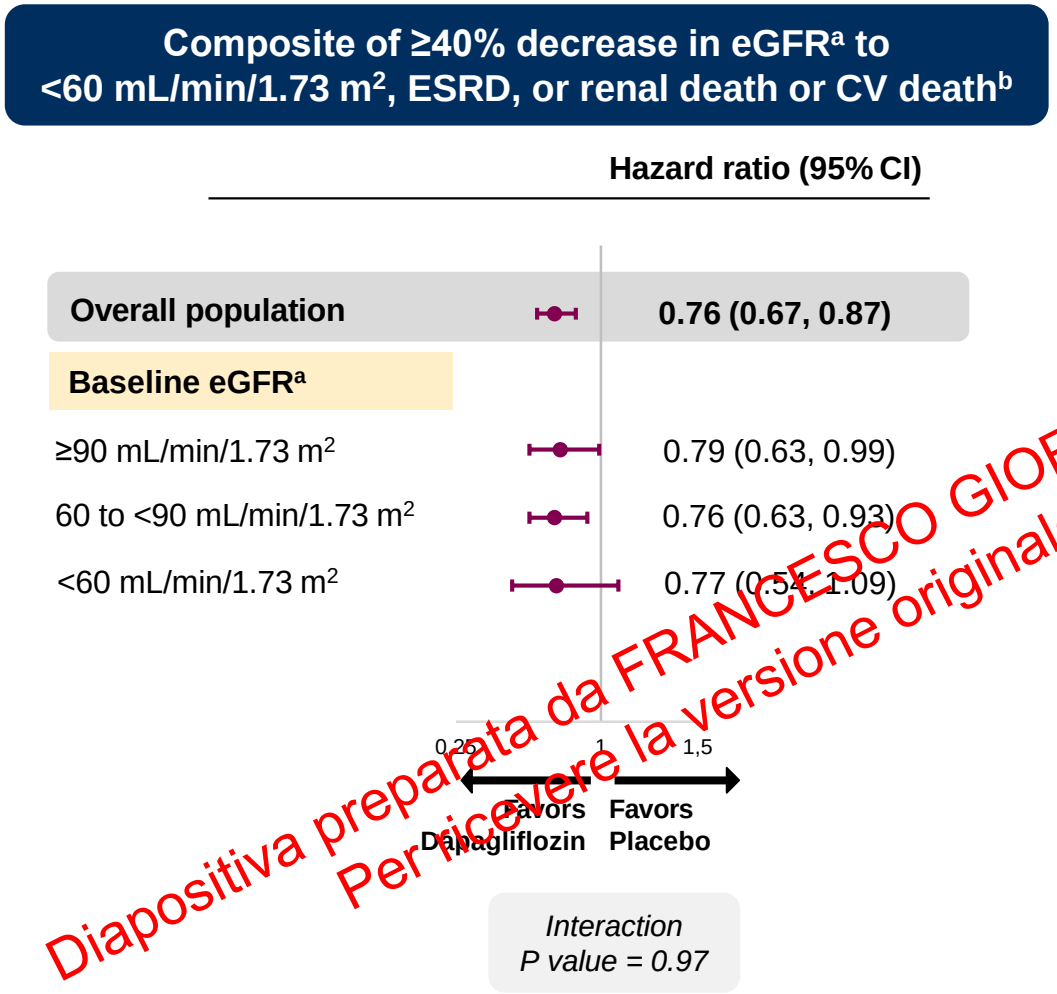
IMPROVED CLINICAL OUTCOMES

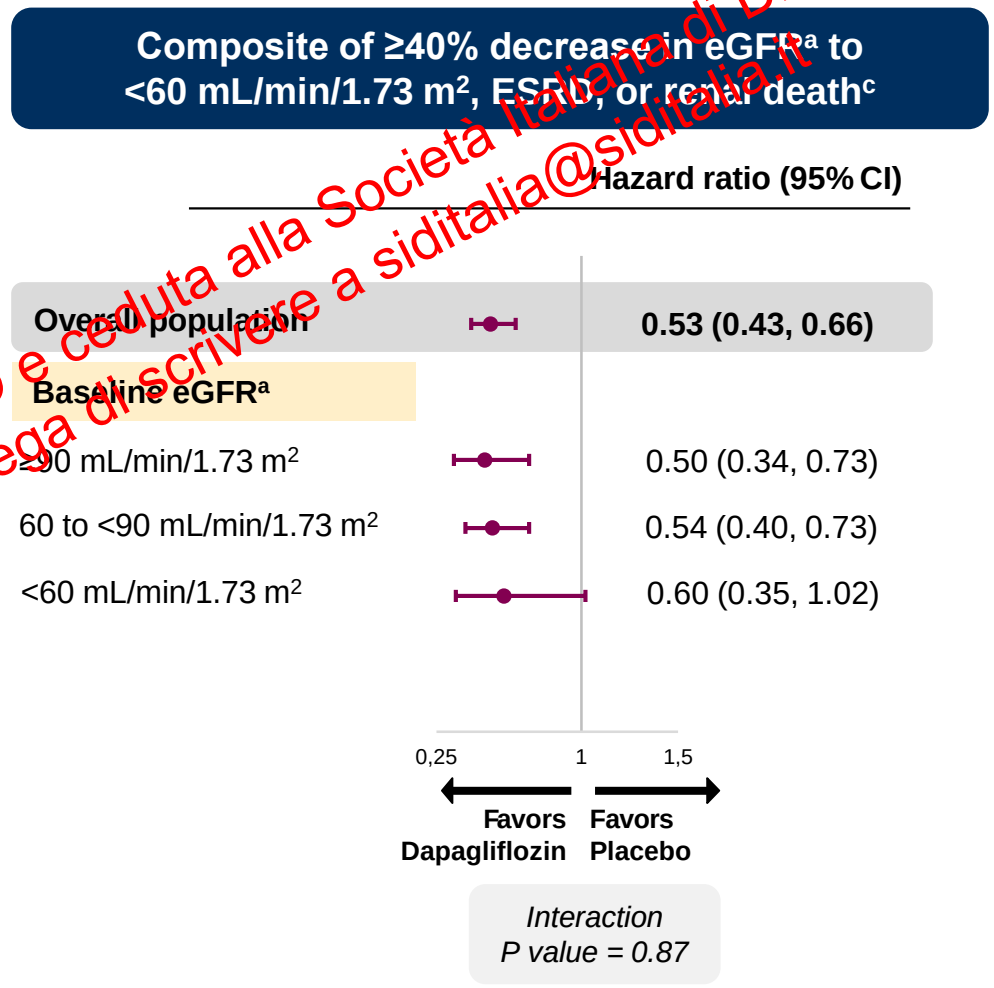
↓CV outcomes
↓HF hospitalization
Stabilization of eGFR
↓Albuminuria

CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; MACE=major adverse cardiovascular event.

1. Verma S, et al. *Lancet*. 2019;393(10166):3-5. 2. Zelniker TA, et al. *Lancet*. 2019;393(10166):31-39. 3. Scheen RJ. *Circ Res*. 2018;122:1439-1459. 4. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

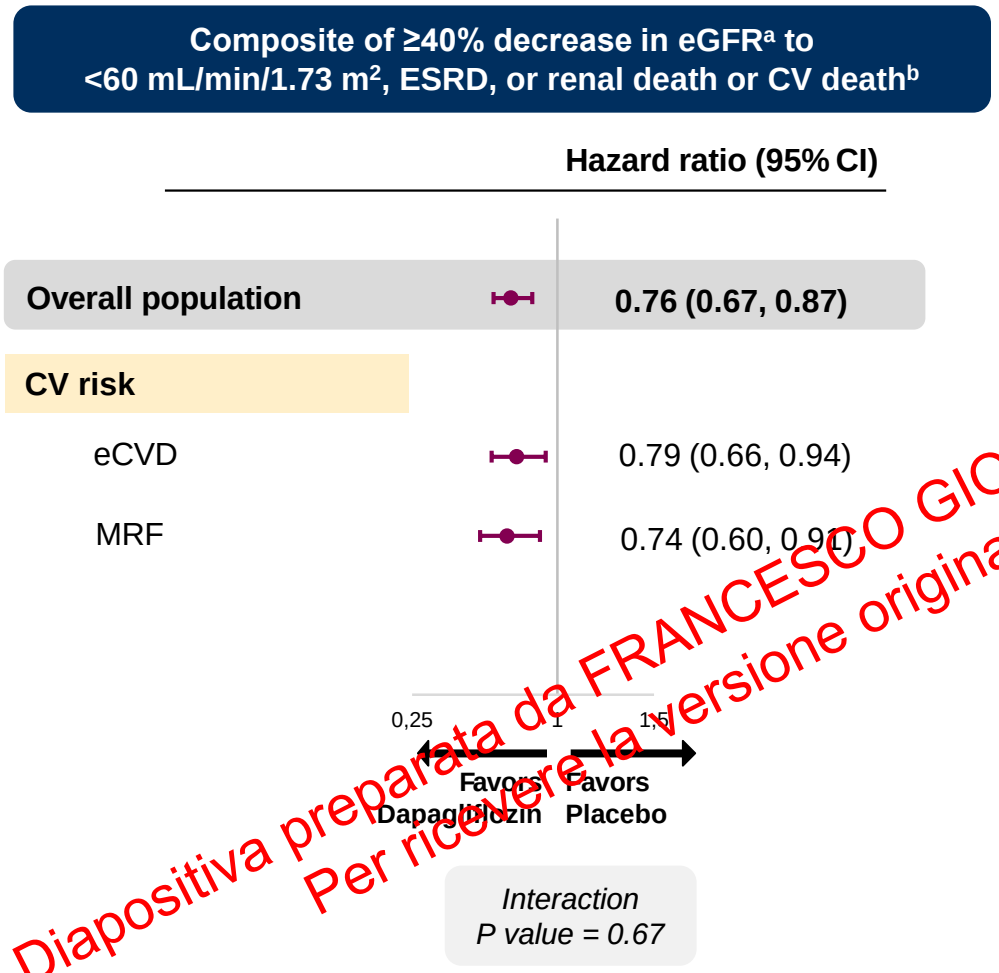
The renal protective effects of dapagliflozin were consistent across baseline eGFR subgroups

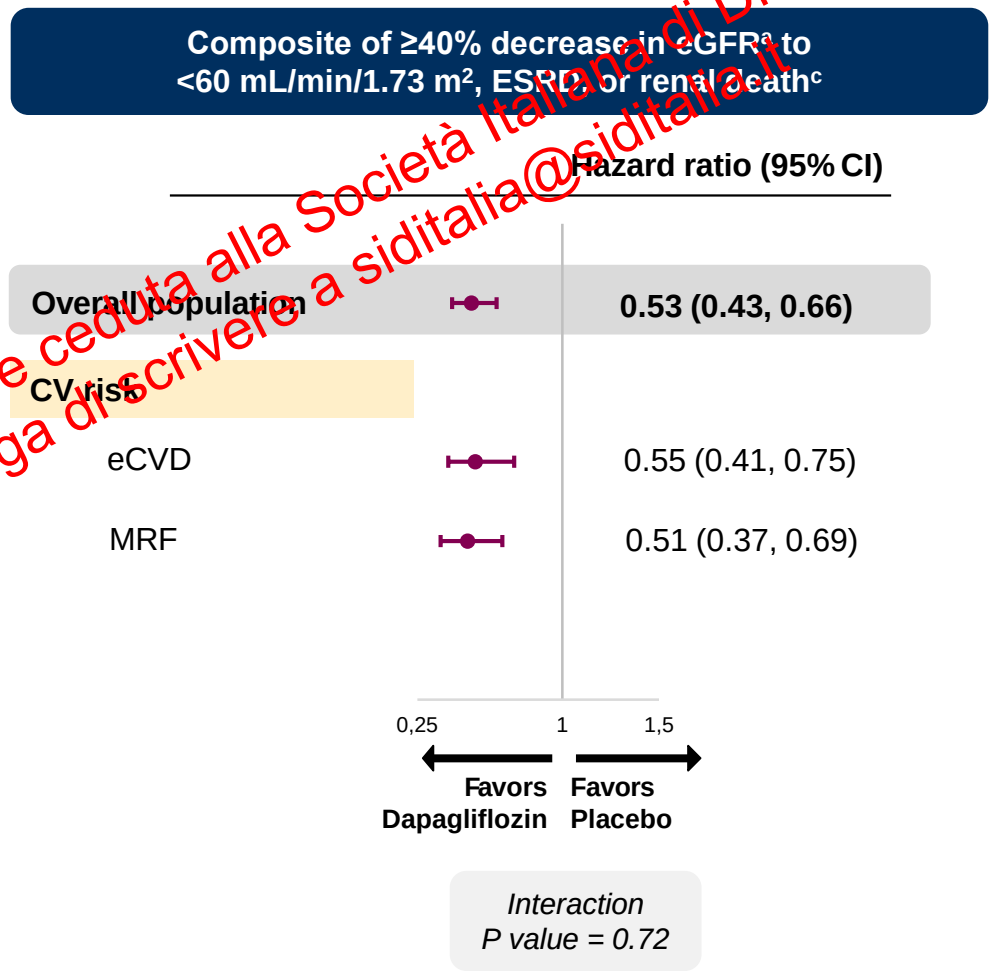




[a]Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation; [b]Secondary outcome; [c]Prespecified additional renal composite outcome.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
Wiviott SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med.* 2018.

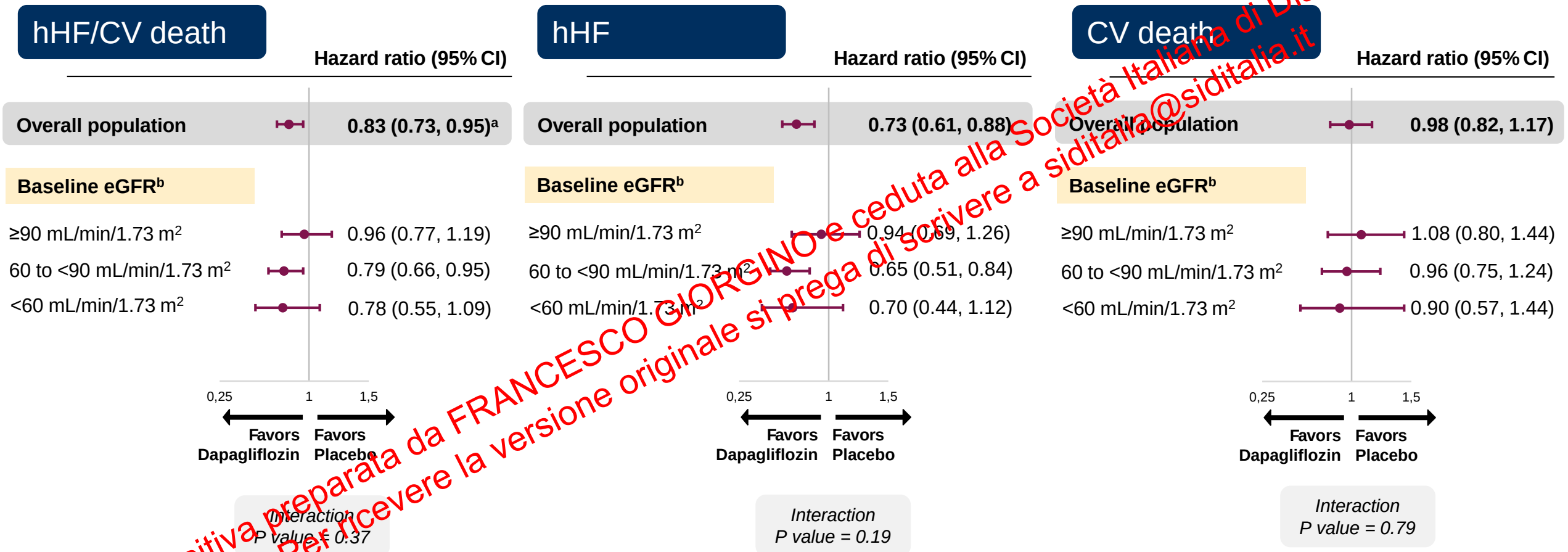
The renal protective effects of dapagliflozin were similar across baseline CV risk subgroup



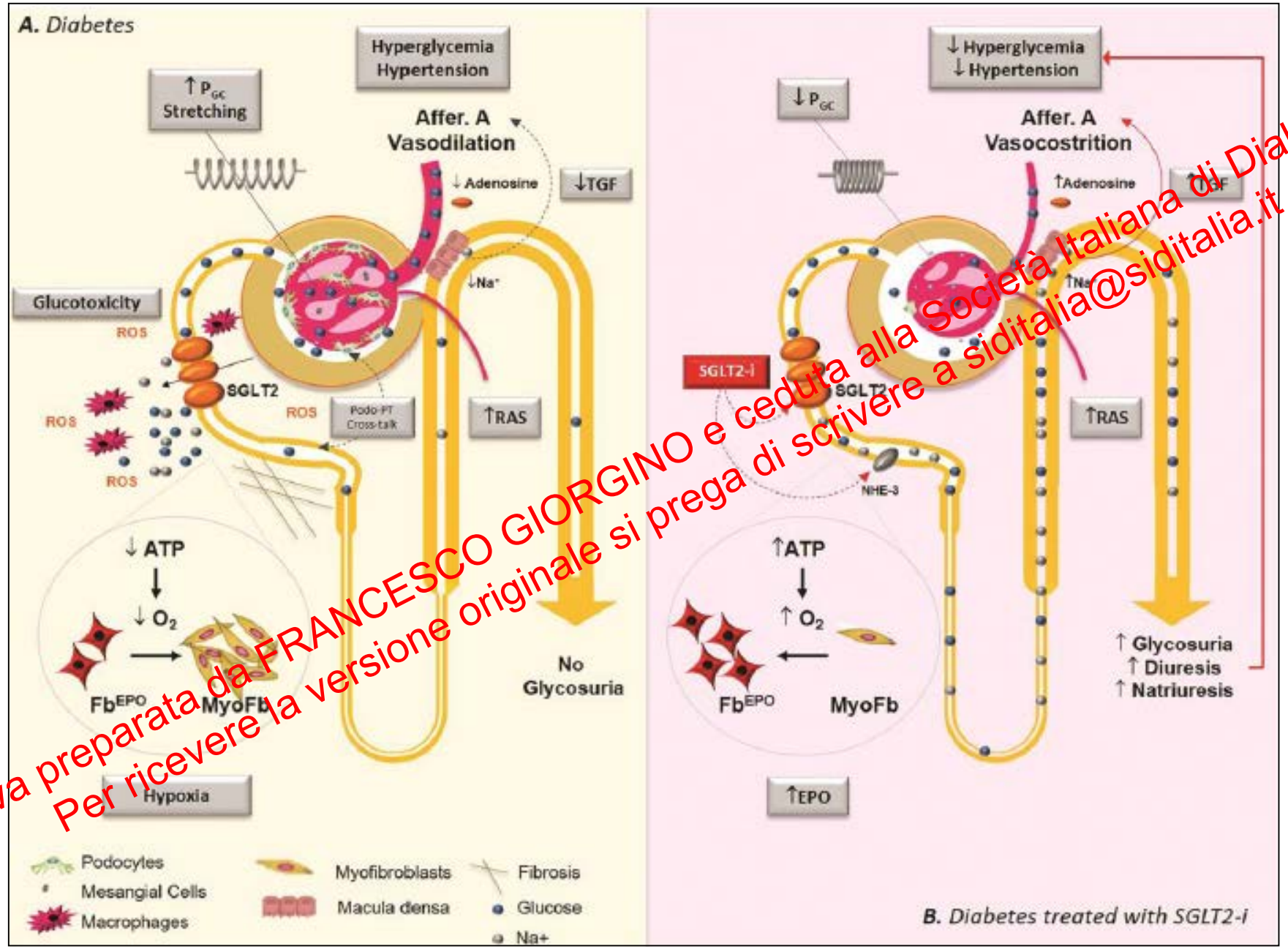


[a]Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation; [b]Secondary outcome; [c]Prespecified additional renal composite outcome.
CV, cardiovascular; eCVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MRF, multiple CV risk factors.
Wiviott SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med.* 2018.

Composite of hHF/CV death and components by renal function

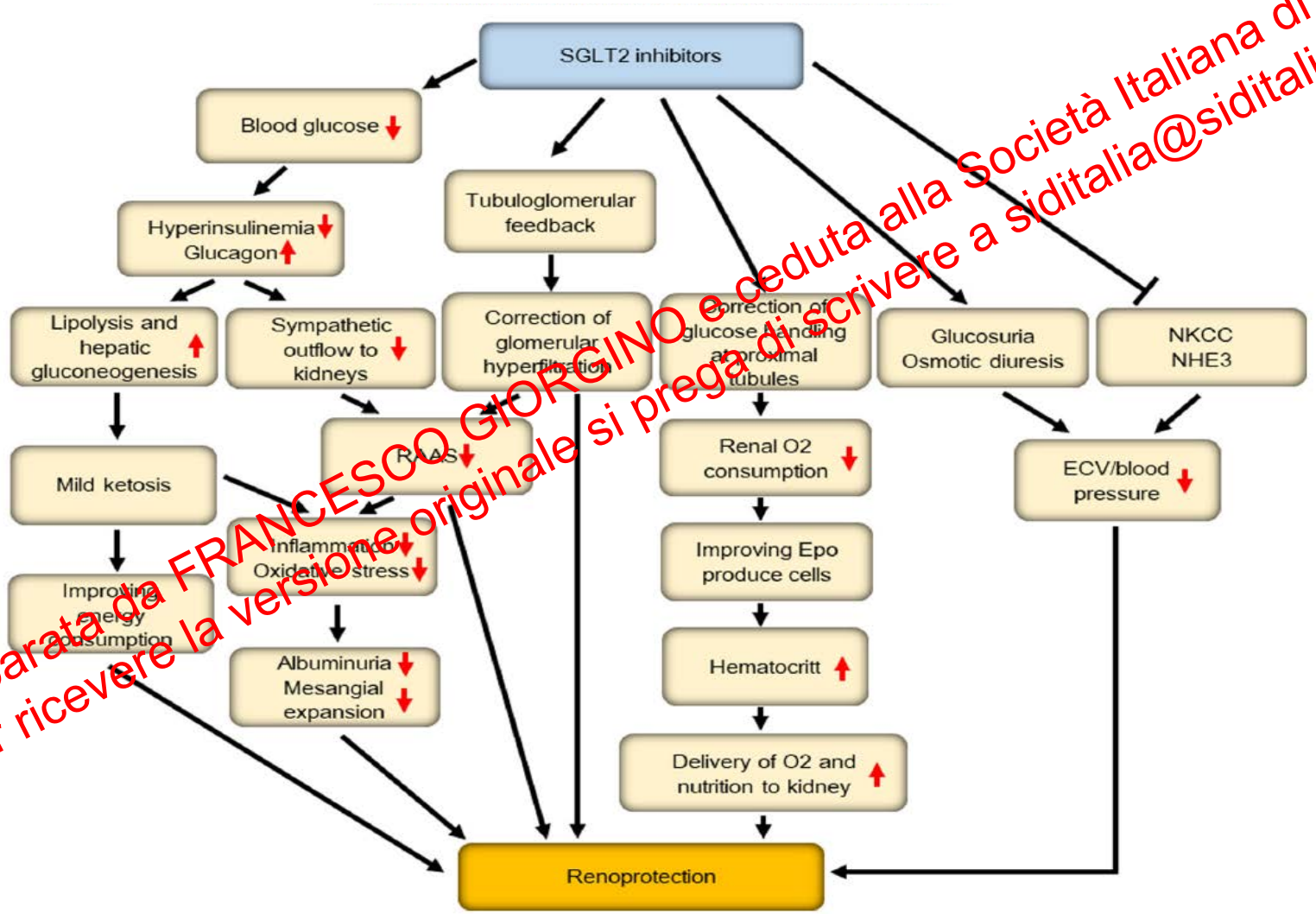


[a]*P*=0.005; [b]Calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; hHF, hospitalization for heart failure.
Wiviott SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med.* 2018.



Barutta F, ***Diabetes Metab Res Rev*** 2019 Apr 18:e3171. doi: 10.1002/dmrr.3171

Multifaceted Renoprotection of SGLT2 inhibitors



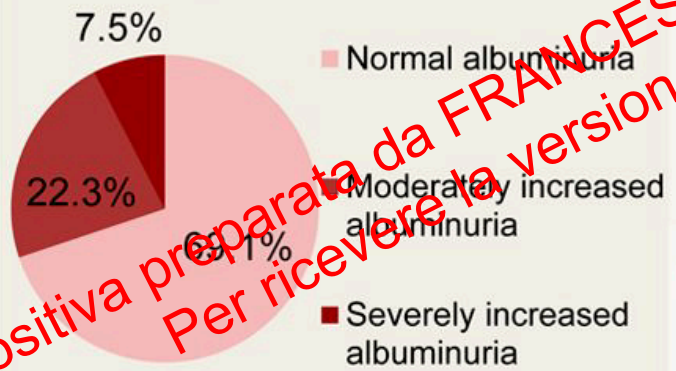
Mima A, ***J Diabetes Complications*** 2018; 32:720-725

Effect of Canagliflozin on Renal Outcomes across Different Levels of Albuminuria: Data from the CANVAS Program

METHODS

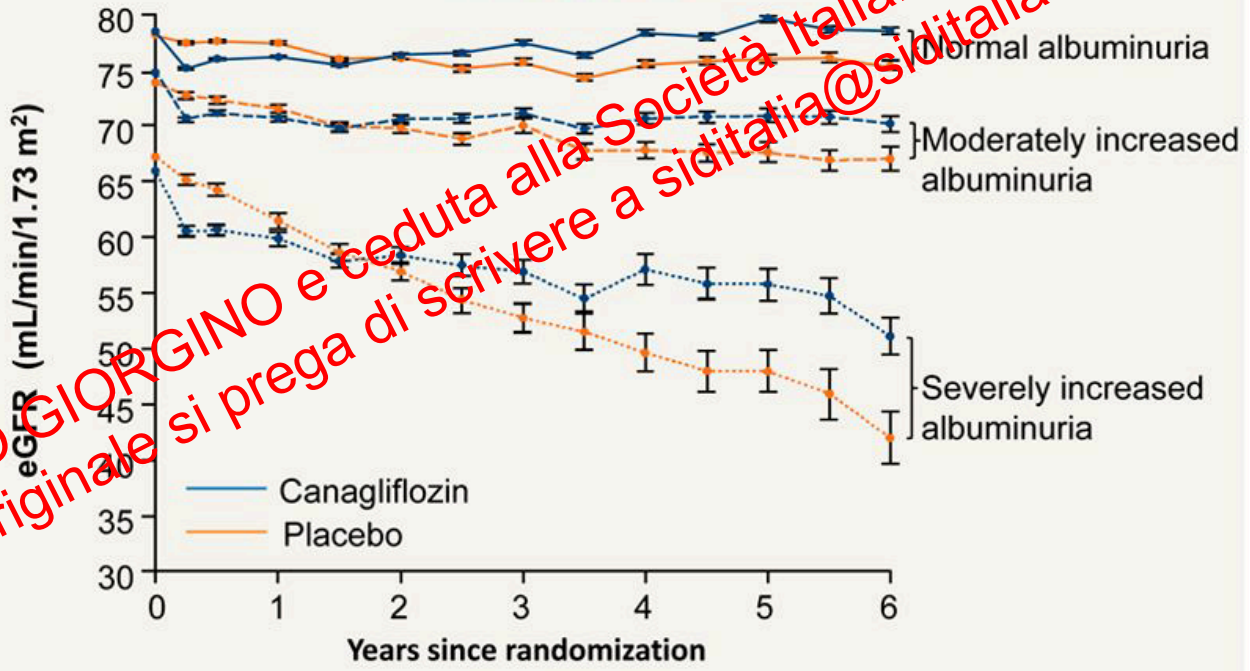
10,142 patients with T2DM

Canagliflozin | Placebo



Note: 1.1% of patients did not have a UACR measurement at baseline.

RESULTS

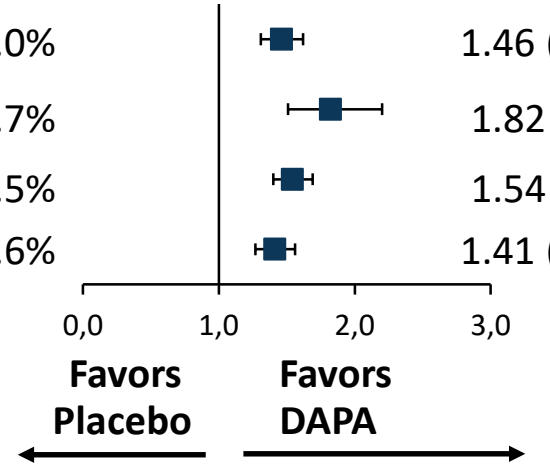


CONCLUSION The proportional effects of canagliflozin on renal and cardiovascular outcomes are mostly consistent across different levels of albuminuria, but absolute benefits are greatest in people with severely increased albuminuria.

Neuen BL, ***J Am Soc Nephrol*** 2019; Sep 17. doi: 10.1681/ASN.2019010064.

Improvement of Albuminuria Category from Baseline in the DECLARE Study

	Dapagliflozin		Placebo			
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate	Hazard Ratio (95% CI)	Cox p-value
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/575 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.00%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001

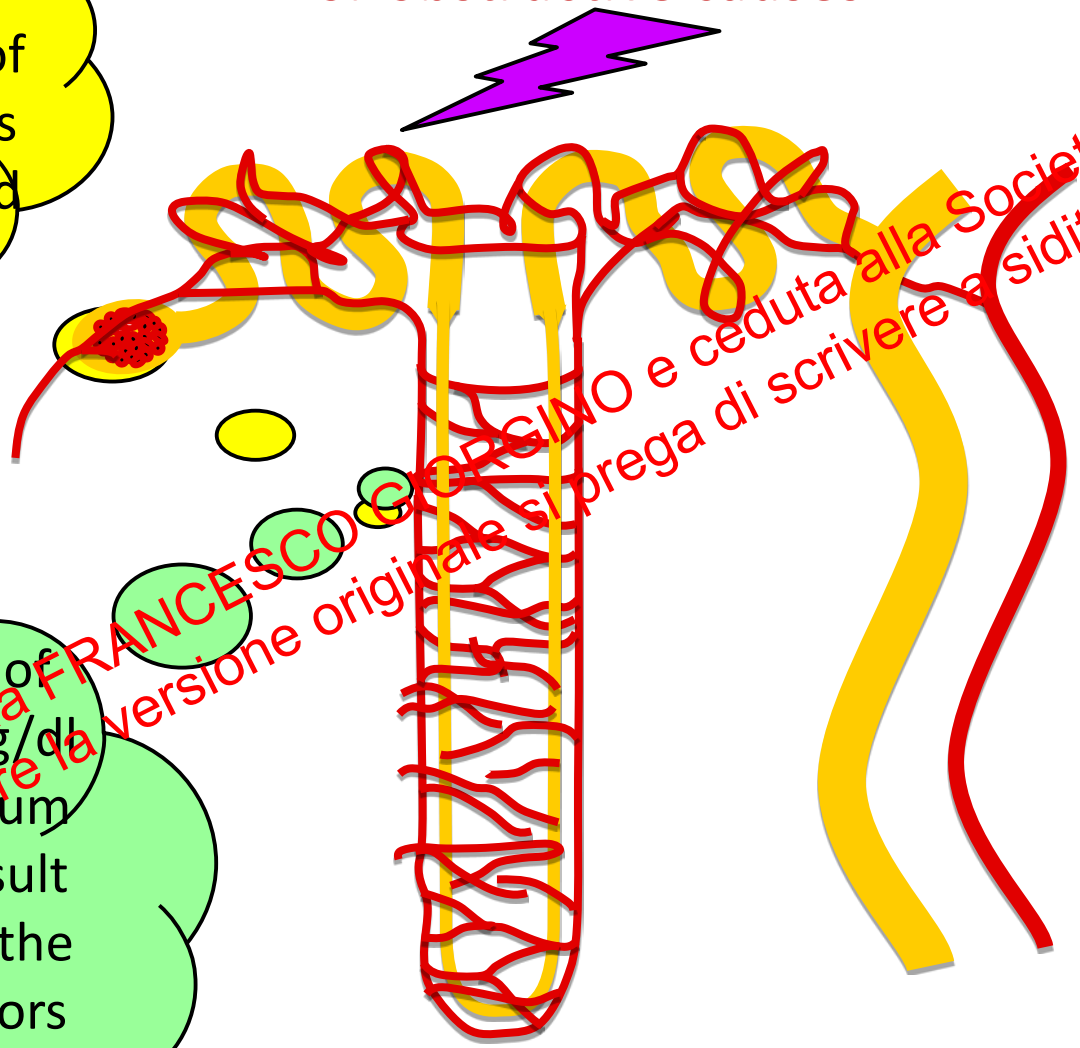


Raz I, ***ADA 79th Scientific Sessions*** 2019; 244-OR

Unresolved and/or repeated episodes of acute kidney injury (AKI)

AKI is a risk factor for future development of CKD, depending on its severity, duration, and frequency

Ischemic, infectious, toxic, or obstructive causes



The regenerative potential of tubular progenitors is limited and might be reduced in diabetes

Even mild episodes of AKI, such as a 0.3-mg/dl or no increase in serum creatinine, might result in CKD, especially in the presence of risk factors such as diabetes

Treatment with RAS blockers increases susceptibility to renal ischemia

Courtesy of G. Pugliese

AKI Outcomes in the SGLT2 Inhibitor User and Nonuser Groups in the Mount Sinai and Geisinger Propensity-Matched Cohorts

	Mount Sinai cohort			Geisinger cohort		
	User (n = 372)	Nonuser (n = 372)	P1	User (n = 1,207)	Nonuser (n = 1,207)	P2
AKI_{KDIGO}–inpatient	14 (3.8)	36 (9.7)	0.002	26 (2.2)	55 (4.6)	0.001
AKI_{ICD}	22 (5.9)	40 (10.8)	0.02	15 (1.2)	36 (3.0)	0.003
Peak creatinine in AKI_{KDIGO} events	1.6 (1.4–1.8)	1.8 (1.6–2.4)	0.02	1.7 (1.4–2.6)	1.6 (1.3–2.4)	0.91
Change in serum creatinine during AKI_{KDIGO} events	0.5 (0.4–0.7)	0.9 (0.8–1.3)	0.004	0.6 (0.5–1.0)	0.6 (0.4–1.2)	0.80
Need for acute dialysis	1 (0.3)	1 (0.3)	1.00	0 (0.0)	1 (0.1)	0.317

P1 and P2 are *P* values for primary and secondary analyses, respectively.

Nadkarni GN, ***Diabetes Care*** 2017; 40:1479-1485