

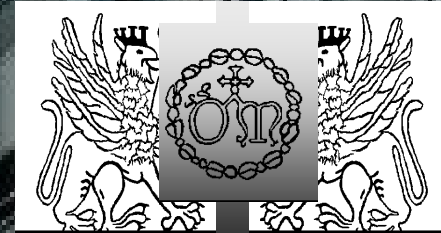
Università e Azienda Ospedaliera di Perugia



Cardiologia

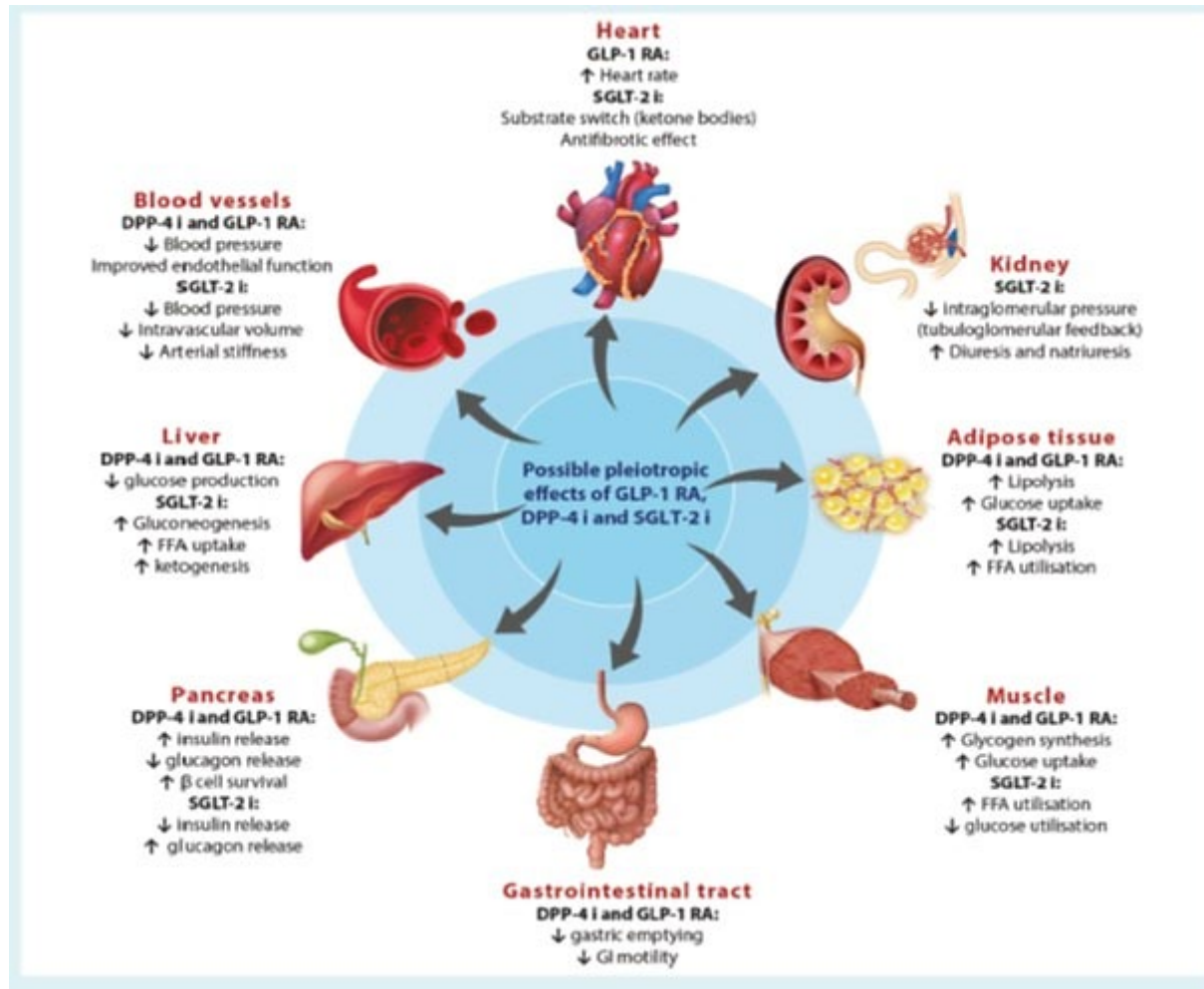
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Fisiopatologia Cardiovascolare



Nuovi Antidiabetici Orali e Scompenso: Spunti di Riflessione

Giuseppe Ambrosio



European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure

Petar M. Seferović^{1,2*}, Andrew J.S. Coats³, Piotr Ponikowski⁴, Gerasimos Filippatos^{5,6}, Martin Huelsmann⁷, Pardeep S. Jhund⁸, Marija M. Polovina^{1,9}, Michel Komajda¹⁰, Jelena Seferović^{1,11}, Ibrahim Sari¹², Francesco Cosentino¹³, Giuseppe Ambrosio¹⁴, Marco Metra¹⁵, Massimo Piepoli¹⁶, Ovidiu Chioncel^{17,18}, Lars H. Lund¹⁹, Thomas Thum²⁰, Rudolf A. De Boer²¹, Wilfried Mullens^{22,23}, Yuri Lopatin²⁴, Maurizio Volterrani²⁵, Loreena Hill²⁶, Johann Bauersachs²⁷, Alexander Lyon²⁸, Mark C. Petrie²⁹, Stefan Anker³⁰, and Giuseppe M.C. Rosano³¹



Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović^{1,2*}, Gabriele Fragasso³, Mark Petrie⁴, Wilfried Mullens^{5,6}, Roberto Ferrari⁷, Thomas Thum⁸, Johann Bauersachs⁹, Stefan D. Anker^{10,11}, Robin Ray¹², Yuksel Çavuşoğlu¹³, Marija Polovina^{1,14}, Marco Metra¹⁵, Giuseppe Ambrosio¹⁶, Krishna Prasad¹⁷, Jelena Seferović^{1,18}, Pardeep S. Jhund¹⁹, Giuseppe Dattilo²⁰, Jelena Čelutkienė²¹, Massimo Piepoli²², Brenda Moura²³, Ovidiu Chioncel^{24,25}, Tuvia Ben Gal²⁶, Stefan Heymans²⁷, Rudolf A. de Boer²⁸, Tiny Jaarsma²⁹, Loreena Hill³⁰, Yuri Lopatin³¹, Alexander R. Lyon³², Piotr Ponikowski³³, Mitja Lainščak^{34,35}, Ewa Jankowska³³, Christian Mueller³⁶, Francesco Cosentino³⁷, Lars Lund³⁸, Gerasimos S. Filippatos³⁹, Frank Ruschitzka⁴⁰, Andrew J.S. Coats⁴¹, and Giuseppe M.C. Rosano^{42†}



Heart Failure Association of the European Society of Cardiology update on sodium–glucose co-transporter 2 inhibitors in heart failure

Petar M. Seferović^{1,2*}, Gabriele Fragasso³, Mark Petrie⁴, Wilfried Mullens^{5,6}, Roberto Ferrari⁷, Thomas Thum⁸, Johann Bauersachs⁹, Stefan D. Anker^{10,11}, Robin Ray¹², Yuksel Çavuşoğlu¹³, Marija Polovina^{1,14}, Marco Metra¹⁵, Giuseppe Ambrosio¹⁶, Krishna Prasad¹⁷, Jelena Seferović^{1,18}, Pardeep S. Jhund¹⁹, Giuseppe Dattilo²⁰, Jelena Čelutkienė²¹, Massimo Piepoli²², Brenda Moura²³, Ovidiu Chioncel^{24,25}, Tuvia Ben Gal²⁶, Stephane Heymans²⁷, Tiny Jaarsma²⁸, Loreena Hill²⁹, Yuri Lopatin³⁰, Alexander R. Lyon³¹, Piotr Ponikowski³², Mitja Lainščak^{33,34}, Ewa Jankowska³³, Christian Mueller³⁵, Francesco Cosentino³⁶, Lars H. Lund³⁷, Gerasimos S. Filippatos³⁸, Frank Ruschitzka³⁹, Andrew J.S. Coats⁴⁰, and Giuseppe M.C. Rosano^{41†}

Table 1 – CVOTs results as primary endpoint (MACE) for the entire population, as HHF as secondary endpoint for the entire population (primary prevention), and as primary endpoint (MACE) for HF patients (secondary prevention) in subgroup analysis.

CLASS	TRIAL	DRUG	MACE Entire Cohort	HHF Entire Cohort Primary Prevention	MACE HF Cohort Secondary Prevention
DPP-4i	EXAMINE	Alogliptin	None (0.96)	None (1.07)	(28%) None (0.82)
	SAVOR-TIMI 53	Saxagliptin	None (1)	Increased (1.27)	(12.8) None (1.13)
	TECOS	Sitagliptin	None (0.98)	None (1)	(18.3%) None (0.99)
	CARMELINA	Linagliptin	None (1.02)	None (0.90)	(26.8%) None (1.02)
GLP-1ra	ELIXA	Lixisenatide	None (1.02)	None (0.96)	(22.4%) None (na)
	LEADER	Liraglutide	Reduced (0.87)	None (0.87)	(18.2%) None (0.94)
	SUSTAIN-6	Semaglutide	Reduced (0.74)	None (1.11)	(23.6%) None (1.03)
	EXSCEL	Exenatide	None (0.91)	None (0.94)	(16.2%) None (0.97)
	REWIND	Dulaglutide	Reduced (0.88)	None (0.93)	(8.6) None (na)
	HARMONY OUTCOMES	Albiglutide	Reduced (0.78)	None (0.85)	(20%) Reduced (0.7)
SGLT-2i	EMPA-REG OUTCOME	Empaglifozin	Reduced (0.86)	Reduced (0.65)	(10%) Reduced (0.71)
	CANVAS Program	Canaglifozin	Reduced (0.86)	Reduced (0.67)	(14.4%) None (0.80)
	DECLARE-TIMI 58	Dapaglifozin	None (0.93)	Reduced (0.73)	(10%) None (1.01)
	CREDENCE	Canaglifozin	Reduced (0.70)	Reduced (0.61)	(14.8%) None (0.89)

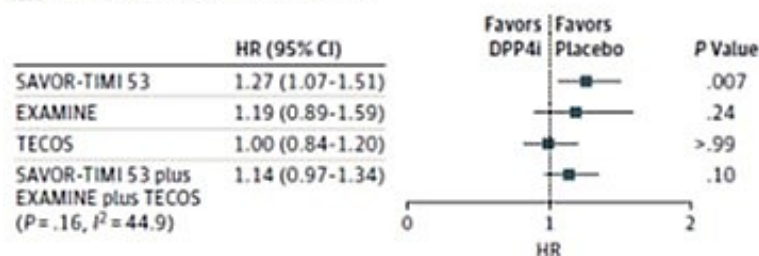
Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus

Secondary Analysis of a Randomized Clinical Trial

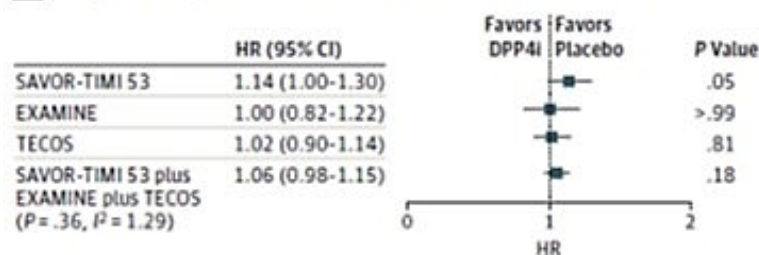
Darren K. McGuire, MD, MHSc; Frans Van de Werf, MD, PhD; Paul W. Armstrong, MD; Eberhard Standl, MD, PhD; Joerg Koglin, MD; Jennifer B. Green, MD; M. Angelyn Bethel, MD; Jan H. Cornel, MD; Renato D. Lopes, MD, MHS, PhD; Sigrun Halvorsen, MD; Giuseppe Ambrosio, MD; John B. Buse, MD; Robert G. Josse, MBBS; John M. Lachin, ScD; Michael J. Pencina, PhD; Jyotsna Garg, MS; Yuliya Lokhnygina, PhD; Rory R. Holman, MBChB; Eric D. Peterson, MD, MPH; for the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group

Figure 3. Meta-Analysis of SAVOR-TIMI 53, EXAMINE, and TECOS

A First hospitalization for heart failure



B Composite of hospitalization for heart failure or cardiovascular death



Glucose-lowering drugs and heart failure: implications of recent cardiovascular outcome trials in type 2 diabetes

Gaia Cattadori^a, Paola Pantanetti^b, Giuseppe Ambrosio^{c,*}

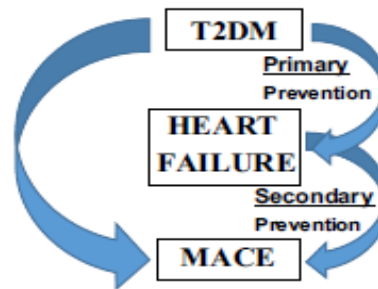


Fig. 1 – New glucose-lowering drugs effects on the interactions between heart failure (HF) and Type 2 diabetes mellitus (T2DM).

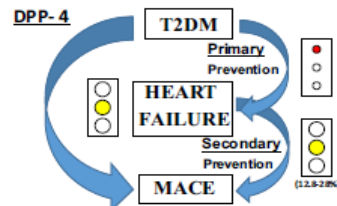


Fig. 2 – Effects of dipeptidyl-peptidase 4 inhibitors on the interactions between T2DM and HF as primary or secondary prevention, as demonstrated by CVOTs data. Traffic light is a symbol of drug effect: yellow = no effect; green = positive effect; red = negative effect. Circle size is related to the number of trial data.

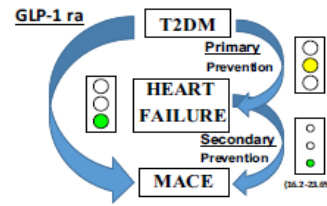


Fig. 3 – Effects of glucagon-like peptide 1 receptor agonists on the interactions between T2DM and HF as primary or secondary prevention as demonstrated by CVOTs data. Traffic light is a symbol of drug effect: yellow = no effect; green = positive effect; red = negative effect. Circle size is related to the number of trial data.

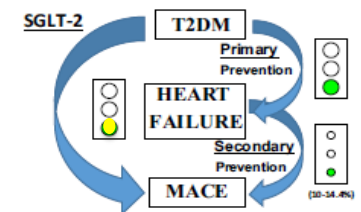


Fig. 4 – Effects of sodium-glucose co-transporter 2 inhibitors on the interactions between T2DM and HF as primary or secondary prevention as demonstrated by CVOTs data. Traffic light is a symbol of drug effect: yellow = no effect; green = positive effect; red = negative effect. Circle size is related to the number of trial data.

Table 2 Risk of heart failure hospitalisation in cardiovascular outcome trials with glucagon-like peptide-1 receptor agonists

Medication	Trial	Patients, n	Patient characteristics	HbA _{1c} (mean)	History of HF	Follow-up (mean or median)	HF hospitalisation (HR, 95% CI) ^a	P-value
Lixisenatide	ELIXA ²⁴	6068	Recent acute coronary syndrome	~7.7%	1358 (22%)	2.1 years	0.96 (0.75–1.23)	0.75
Liraglutide	LEADER ⁴¹	9340	Age ≥50 years and established CVD Age ≥60 years and CV risk factors	8.7%	1667 (18%)	3.8 years	0.87 (0.73–1.05)	0.14
Semaglutide (subcutaneous)	SUSTAIN-6 ⁴²	3297	Age ≥50 years and established CVD Age ≥60 years and CV risk factors	8.7%	777 (24%)	2.1 years	1.11 (0.77–1.61)	0.57
Semaglutide (oral)	PIONEER 6 ³⁹	3183	Age ≥50 years and established CVD; Age ≥60 years and CV risk factors	8.2%	388 (12%)	1.3 years	0.86 (0.48–1.55)	–
Exenatide	EXSCEL ⁴⁰	14 752	Established CVD (73%) CV risk factors (37%)	8.0%	2389 (16%)	3.2 years	0.94 (0.78–1.13)	–
Albiglutide	Harmony Outcome ⁴⁴	9463	Established CVD	~8.7%	1922 (20%)	1.5 years	0.85 (0.70–1.04) ^b	0.11
Dulaglutide	REWIND ⁴⁵	9901	Established CVD (31.5%) CV risk factors (68.5%)	~7.3%	853 (8.6%)	5.4 years	0.93 (0.77–1.12) ^c	0.46

Effect of new glucose lowering drugs on cardiovascular outcomes in placebo-controlled trials					
	3-point MACE	CV death	Myocardial infarction	Stroke	HF hospitalisation
DPP-4 inhibitors	Neutral effect	Neutral effect	Neutral effect	Neutral effect	↑ Risk Saxagliptin: 27%
Saxagliptin Alogliptin Sitagliptin Vildagliptin Linagliptin					Neutral effect: Alogliptin, Sitagliptin, Vildagliptin, Linagliptin
GLP-1 RA	↓ Risk Liraglutide: 13%, Semaglutide: 26% Alogliptide: 22%	↓ Risk Liraglutide: 22%	↓ Risk Alogliptide: 25%	↓ Risk Semaglutide: 20%	Neutral effect: All GLP-1 RA
Lixisenatide Liraglutide Semaglutide Alogliptide Exenatide	Neutral effect: Lixisenatide, Exenatide	Neutral effect: Alogliptide, Semaglutide, Lixisenatide, Exenatide	Neutral effect: Liraglutide, Semaglutide, Exenatide, Lixisenatide	Neutral effect: Liraglutide, Exenatide, Alogliptide, Lixisenatide	
SGLT-2 inhibitors	↓ Risk Empagliflozin: 14% Canagliflozin: 14% Dapagliflozin: 17%*	↓ Risk Empagliflozin: 32%	Neutral effect: All SGLT-2 inhibitors	Neutral effect: All SGLT-2 inhibitors	↓ Risk Empagliflozin: 35% Canagliflozin: 33% Dapagliflozin: 27%
Empagliflozin Canagliflozin Dapagliflozin		Neutral effect: Canagliflozin, Dapagliflozin			

**Mechanisms
and effects
of SGLT2
inhibitors**

**Vascular and
haemo-
dynamic effects**

- Decreased blood pressure.
- Decreased arterial stiffness.
- Improved endothelial function.
- Decreased interstitial vs. intravascular volume.
- Decreased preload and afterload.
- Increased haematocrit.
- Decreased sympathetic nervous system activity.

**Renal
effects**

- Decreased renin-angiotensin system activation.
- Reduced intraglomerular pressure.
- Increase in natriuresis, diuresis and uricosuria.
- Decreased albuminuria.
- Decreased renal oxidative stress.
- Preservation of renal function.
- Increased erythropoietin.

**Cardiac
effects**

- Decreased myocardial hypertrophy and fibrosis.
- Reverse cardiac remodeling.
- Improved myocardial energetics.
- Decreased myocardial oxidative stress.
- Inhibition of Na^+/H^+ exchanger.
- Decreased epicardial fat accumulation.

**Metabolic
effects**

- Weight loss.
- Decreased total body and visceral adiposity.
- Increased insulin sensitivity.
- Increased muscle free fatty acid uptake.
- Decreased uric acid levels.
- Decreased liver steatosis and hepatocellular injury.

SGLT-2 inhibitor	Recommended dose	Dose adjustment	Precautions and warnings
Empagliflozin	10 mg per os OD 25 mg per os OD	Impaired renal function: eGFR <30 ml/min/1.73 m²: discontinue	All SGLT-2 inhibitors - Diabetic ketoacidosis - Hepatic injury - Volume depletion - Hypotension - Critical illness - Emergency surgery - Recurrent genital mycotic infections - Lower limb amputation - Electrolyte imbalance
Canagliflozin	100 mg per os OD 300 mg per os OD	Impaired renal function: eGFR <30 ml/min/1.73 m²: discontinue	
Depagliflozin	10 mg per os OD	Impaired renal function: - eGFR <30 ml/min/1.73 m²: discontinue Hepatic impairment: - Starting dose, 5 mg	