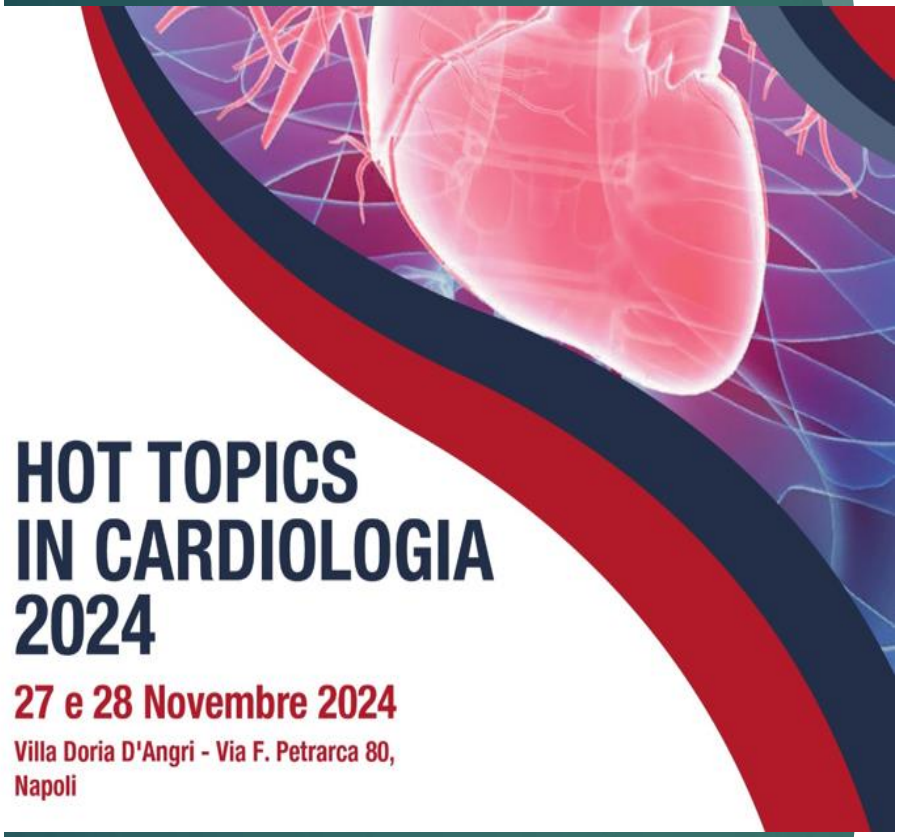
Antonio Cardarelli
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE

UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

CENTRO INTERDIPARTIMENTALE DI RICERCA IN MEDICINA DI GENERE
Genesis
Università degli Studi di Napoli Federico II



HOT TOPICS IN CARDIOLOGIA 2024

27 e 28 Novembre 2024

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

Inibitori SGLT-2: come ottimizzare il trattamento in base alla frazione di eiezione

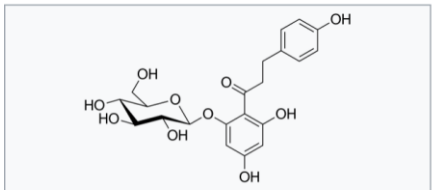
Dr Andrea Salzano,
MD, PhD, FEFIM, FHFA

Tenure Track Academic Clinical Lecturer, Dipartimento di Scienze mediche traslazionali, Università degli studi di Napoli Federico II
Dirigente Medico in Medicina Interna, Dipartimento Medicina delle complessità, AOU Federico II Napoli
Dirigente Medico in Cardiologia, Dipartimento reti tempo dipendenti, AORN A Cardarelli, Napoli, IT

Conflitti di interesse

- Nessuno impattante la presente relazione

Phlorizin



in **1835**, C. Petersen, a French chemist, isolated **phlorizin** from the root bark of the apple tree,

In **1886**, von Mering, a German professor of medicine, discovered the **glucosuric** and consequent plasma glucose lowering effects of phlorizin

1174 *Chem. Pharm. Bull.* **44**(6) 1174—1180 (1996) Vol. 44, No. 6

Na^+-Glucose Cotransporter Inhibitors as Antidiabetics. I. Synthesis and Pharmacological Properties of 4′-Dehydroxyphlorizin Derivatives Based on a New Concept

Kenji TSUJIHARA,* Mitsuya HONGU, Kunio SAITO, Masanori INAMASU, Kenji ARAKAWA, Akira OKU, and Mamoru MATSUMOTO

Lead Optimization Research Laboratory, Tanabe Seiyaku Co., Ltd., 2–2–50 Kawagishi, Toda-shi, Saitama 335, Japan.
Received October 1995; accepted February 5, 1996

Based on our new concept that inhibitors of the Na^+-glucose cotransporter (SGLT) would be useful as antidiabetics, 4′-dehydroxyphlorizin derivatives 1a—f were designed, synthesized, and examined for various pharmacological properties related to antidiabetic activity. In normal rats, 1a, e and phlorizin showed a strong SGLT-inhibitory effect and significantly increased urinary glucose on intraperitoneal administration at 10 mg/kg, though only 1a resulted in excretion of large quantities of urinary glucose on oral administration at 100 mg/kg. Compounds 1a, e, and phlorizin markedly inhibited glucose uptake in the small intestine during enteric perfusion in normal rats. Compound 1a had a significant reducing effect on blood glucose in the glucose tolerance test in mice when administered orally and also lowered blood glucose in streptozotocin-induced diabetic rats. The aglycons 2a, e of 1a, e, and 1a showed weak inhibitory effects on the facilitated glucose transporter-1 (GLUT-1) in human erythrocytes, while phloretin had a strong inhibitory effect on GLUT-1. Compound 1a caused no apparent renal damage in rats when administered orally at 1 g/kg for 4 successive weeks. Thus, 1a was considered to be a promising candidate as a lead compound for antidiabetics of a new type, and was selected for further pharmacological evaluation.

Key words antidiabetic; Na^+-glucose cotransporter inhibitor; phlorizin; 4′-dehydroxyphlorizin

In **1996**, investigators at Kyoto University and Tanuba Seiygyu Co. in Japan developed phlorizin analogs, the **first chemically engineered sodium glucose co-transporter inhibitors (SGLT2is**)

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab765

CARDIOPULSE

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

Eugene Braunwald [1,2]*

[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and [2]Department of Medicine, Harvard Medical School, Boston, MA, USA

A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the*, major pharmacological advances in cardiovascular medicine in the 21st century.

The sodium glucose co-transporter represents the (or one of the) major pharmacological advances in cardiovacular medicine in the 21th century

ESC European Society of Cardiology

European Heart Journal (2024) **45**, 2186–2196
https://doi.org/10.1093/eurheartj/ehae300

GREAT DEBATE
Heart failure and cardiomyopathies

Great Debate: SGLT2 inhibitors should be first-line treatment in heart failure with reduced ejection fraction

Milton Packer [1,2†], John G.F. Cleland [3†], and Johann Bauersachs [4*]

[1]Baylor Heart and Vascular Institute, Dallas, TX, USA; [2]Imperial College, London, UK; [3]British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; and [4]Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Online publish-ahead-of-print 28 May 2024

John G.F. Cleland: I have been asked to argue against the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors as first-line therapy for heart failure with reduced ejection fraction (HFrEF). **The idea for this debate was not mine.**

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

McDonagh T, Metra M et al EHJ 2021 & 2023

Figure 2 Tailoring of medical therapy according to clinical profiles. According to some patient characteristics – blood pressure (BP), heart rate (HR), presence of atrial fibrillation (AF), chronic kidney disease (CKD) or hypertension, some drugs may have to be reduced, discontinued, or added. Black—drugs that should be given to patients; red—drugs that should be reduced or discontinued; blue—drugs that should be added. *In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mmHg. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Rosano GMC et al EJHF 2021

Patient profiling in HFpEF and consequent therapeutic considerations

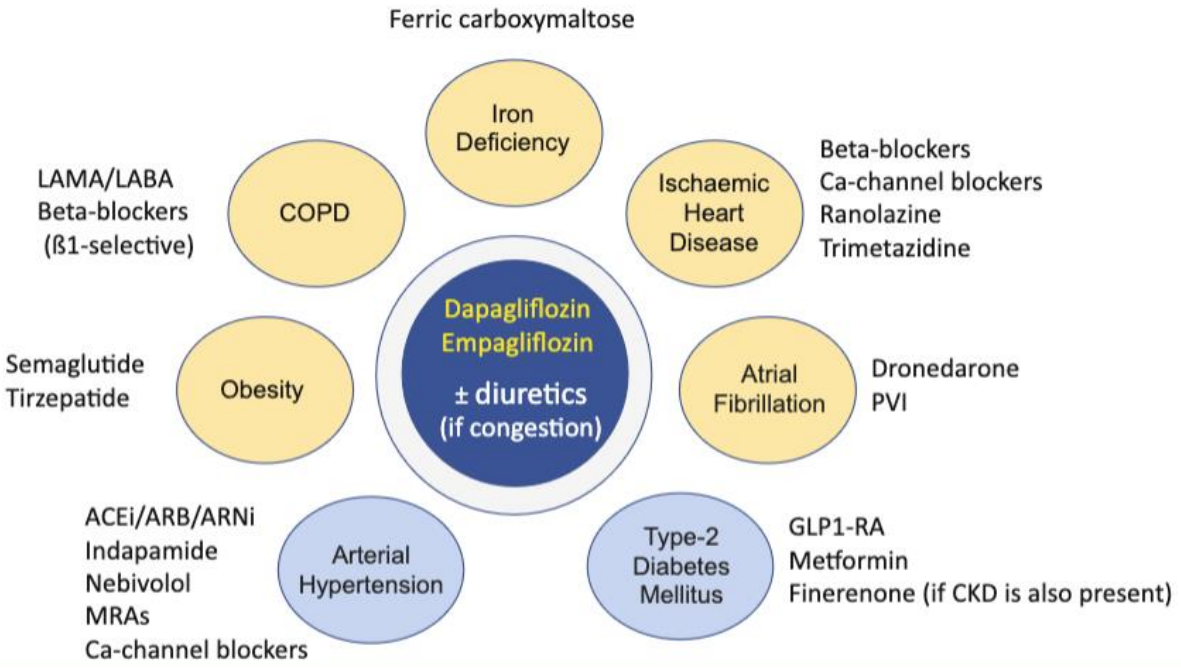
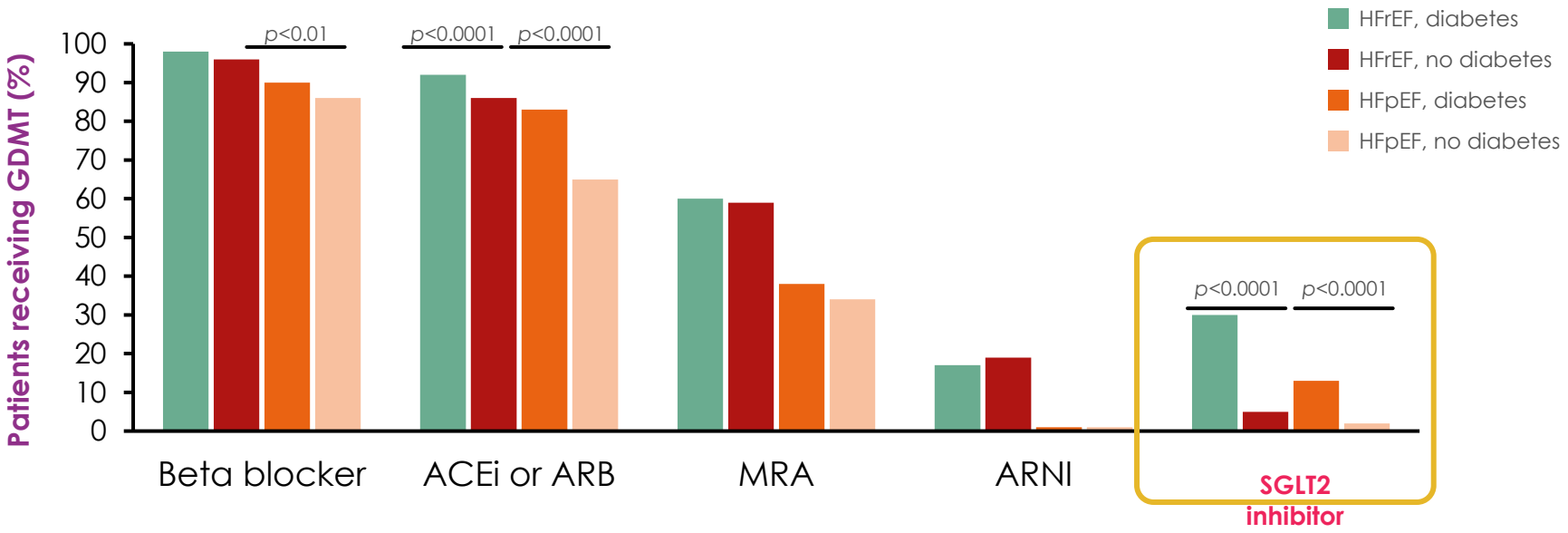


Figure 2 Patient profiling in heart failure with preserved ejection fraction (HFpEF) and its possible therapeutic consequences. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; Ca, calcium; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GLP1-RA, glucagon-line peptide-1 receptor agonist; LABA, long-acting β-agonist; LAMA, long-acting muscarinic receptor antagonist; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation.

Anker S et al EJHF 2023

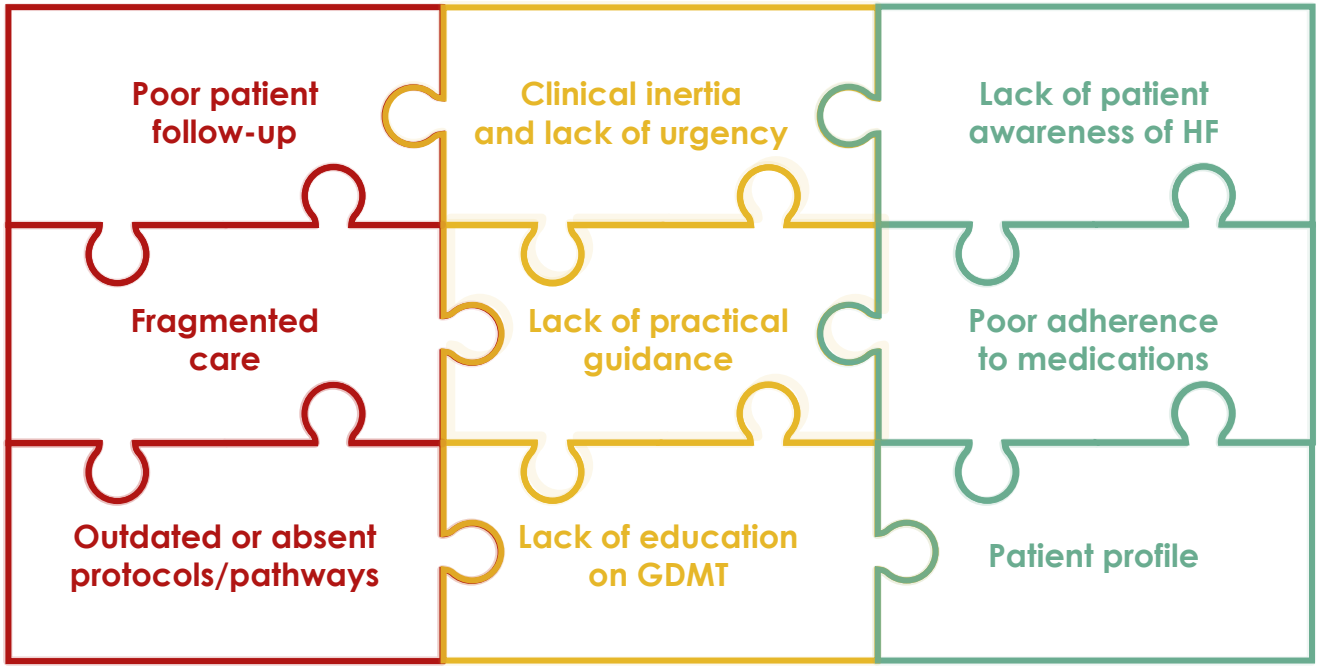
Newer GDMTs are underutilized in patients with HF



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2. Figure redrawn from data in Table 1 of Canonico ME *et al. JACC Heart Fail.* 2022;10:989.

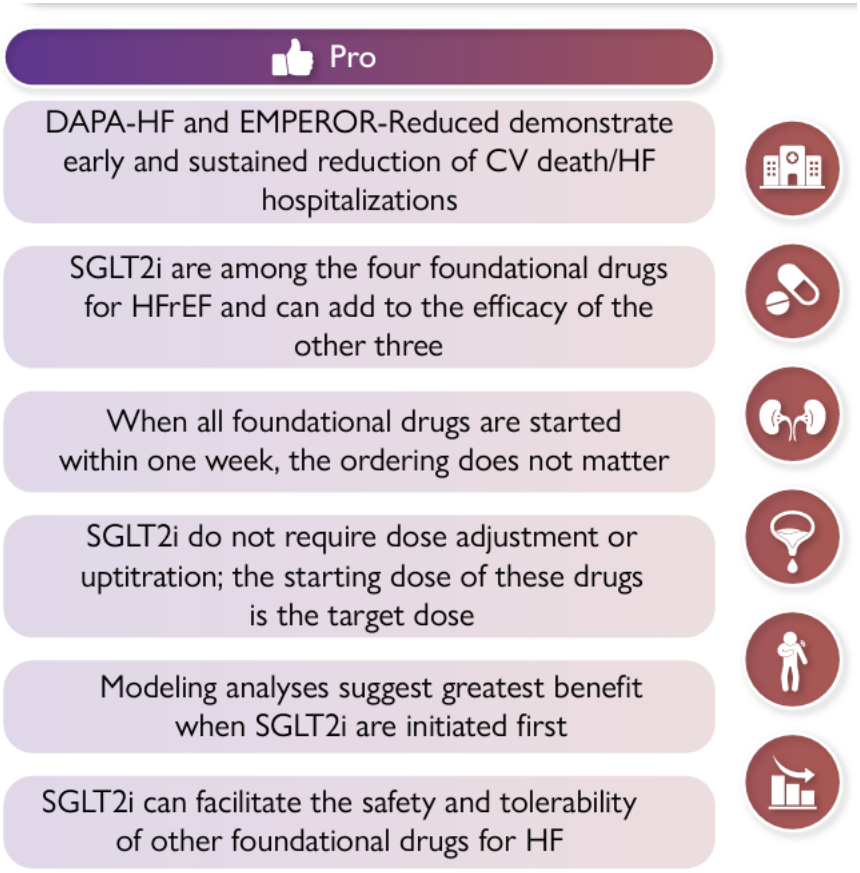
What are the main barriers for implementation of GDMT in HF?

Barriers can be system-, physician- or patient-related factors



GDMT, guideline-directed medical therapy; HF, heart failure.

SGLT2 inhibitors should be first line treatment in heart failure with reduced ejection fraction

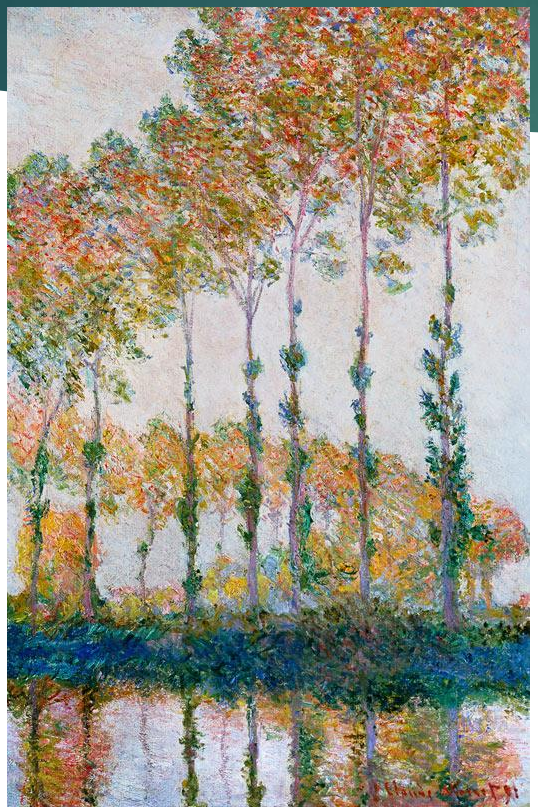


Packer M , Cleland J et al EHJ 2024

Take home message

- The sodium glucose co-transporter represents the (or one of the) **major pharmacological advances** in cardiovacular medicine in the 21th century
- SGLT2 inhibitors are recommended for patients with HF, **regardless EF** and **regardless T2DM** to reduce the risk of HF hospitalization and CV death, **class I, Level of Evidence A**
- SGLT2 inhibitors should **be first line treatment** in heart failure, and initiated as soon as possible

Acknowledgments



Monet, Pioppi sulle rive dell'Epte, autunno 1891

- Prof Antonio Cittadini
- Dr Ciro Mauro
- Prof Eduardo Bossone
- Prof Toru Suzuki
- Prof Iain B Squire
- Prof Alberto M Marra
- Dr Liam M Heaney
- Dr Michele Arcopinto
- Dr M Zubair Israr
- Dr Mariarosaria De Luca
- Dr Giulia Crisci