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Editorial

New anti-diabetic agents: major advances with unanswered questions

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During the latest European Society of Cardiology (ESC) congress, impressive results have been reported regarding the clinical benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in heart failure with reduced ejection fraction (HFrEF) in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) and Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) trials (McMurray et al., 2019; Packer et al., 2020). A meta-analysis addressing the combined 8474 patients from both trials showed a 13% relative risk reduction (RRR) of total mortality (HR [hazard ratio], 0.87; 95% CI [confidence interval], 0.77-0.98), a 14% RRR of cardiovascular death (HR, 0.86; 95% CI, 0.76-0.98), a 25% RRR of cardiovascular death or hospitalizations for heart failure (HR, 0.75; 95% CI, 0.68-0.84) and a 38% RRR of the composite renal endpoint (HR, 0.62; 95% CI, 0.63-0.90) in the treatment group compared to placebo at a median follow-up time of 16 months in EMPEROR-Reduced and 18 months in DAPA-HF (Zannad et al., 2020).

After the encouraging results from Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPAREG-OUTCOME) and Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trials in diabetic patients with HFrEF (Kato et al., 2019; Zinman et al., 2015), EMPEROR-Reduced and DAPA-HF demonstrated that the magnitude of benefits were similar in both diabetic and non-diabetic HFrEF patients, thus underlining that SGLT2i benefits are not only mediated by the anti-diabetic pharmacological properties of these drugs but other biological mechanisms are at work (McMurray et al., 2019; Packer et al., 2020). Notwithstanding, these results should not obscure the clinical efficacy of glucagone-like peptide-1 receptor agonists (GLP1-RA), which come as another emerging class of anti-diabetic drugs (Gerstein et al., 2019; Marso et al., 2016b,a).

Despite promising data from randomized controlled trials (RCT) on SGLT2i and GLP1-RA, some issues remain unresolved. Indeed, even if these drugs have proven cardioprotective effects, the underlying mechanisms of action are not yet perfectly understood Fig. 1. The class effect also remains uncertain due to the pharmacological differences among individual drugs and the heterogeneity of the results from RCTs. Moreover, it is still debated which class provides the greatest prevention against ischemic events. Indeed, only 3 RCTs, namely EMPAREG-OUTCOME, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and Peptide Innovation for Early Diabetes Treatment (PIONEER-6) demonstrated a reduction of cardiovascular mortality in the treatment group compared to optimal medical therapy, whereas all the RCTs showed no difference in non-fatal myocardial infarction rates between groups (Husain et al., 2019; Marso et al., 2016a; Zinman et al., 2015). As for stroke, only dulaglutide was proven to reduce stroke rates in the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial (Gerstein et al., 2019), but this effect was not observed in other GLP1-RA or SGLT2i trials. In REWIND, 58 (3.2%) stroke events were reported in the dulaglutide group (n = 4949) compared to 205 (4.1%) in the placebo group (n = 4952) with a hazard ratio (HR) of 0.76 (95% CI 0.62-0.94; $P = 0.010$). Ischemic stroke rates were decreased by 25% (HR 0.75, 95% CI 0.59-0.94, $P = 0.012$) with no impact on hemorrhagic stroke (HR 1.05, 95% CI 0.55-1.99; $P = 0.89$) (Gerstein et al., 2020).

Concerning the renal outcomes, RCTs on individual SGLT2i and GLP1-RA molecules demonstrated their protective role against worsening renal function, likely due to an increase of natriuresis and glycosuria, reduced proteinuria, decrease in glomerular

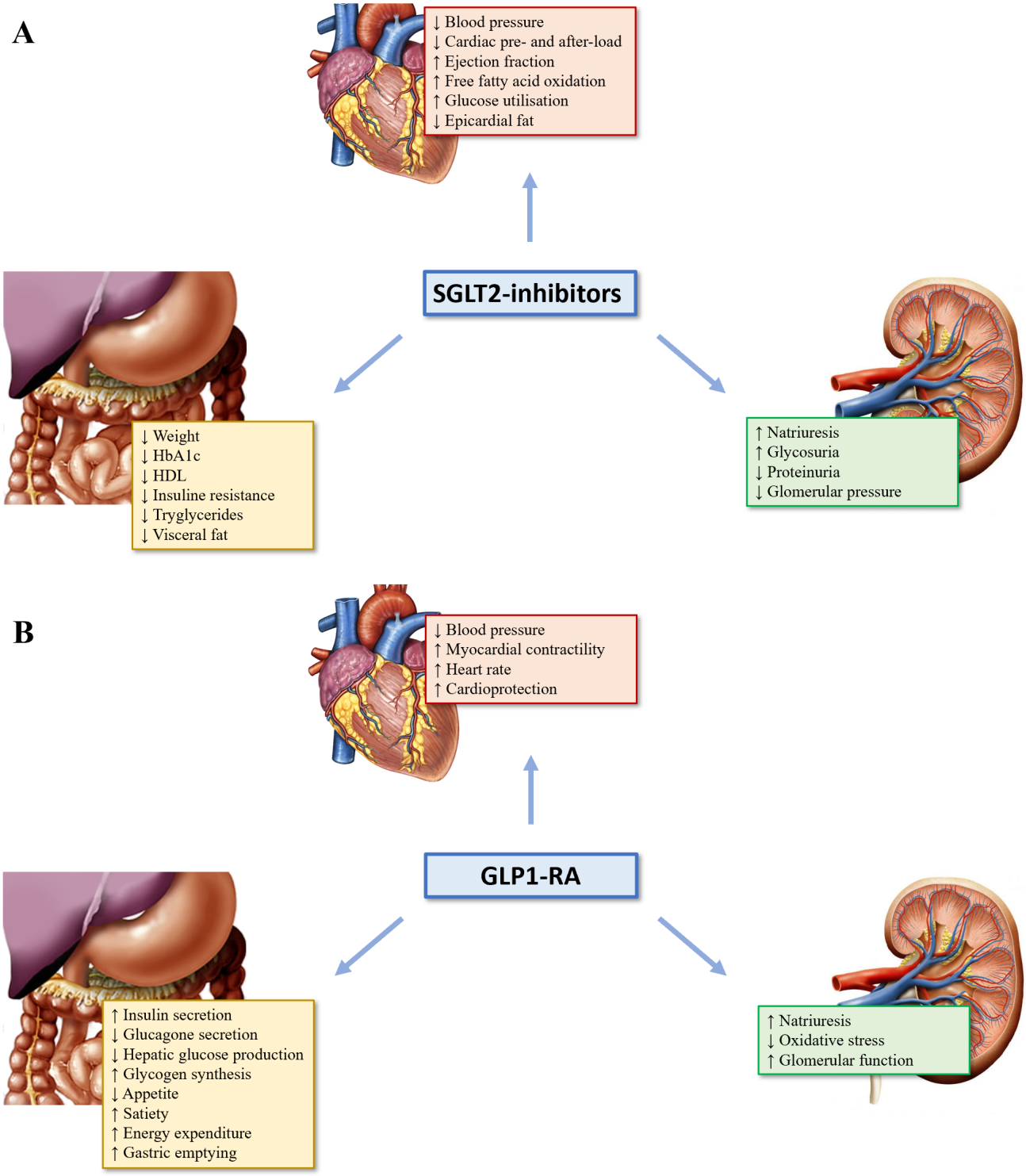

Fig. 1. Overview of the effects of SGLT2i (A) and GLP1-RA (B) on heart, kidney and metabolic pathways. GLP1-RA, glucagone-like peptide-1 receptor agonists; HBA1c, glycated haemoglobin; HDL, high-density lipoprotein; SGLT2, sodium-glucose cotransporter 2.

oxidative stress leading to an improved glomerular renal function Fig. 1 (Gerstein et al., 2019; Kato et al., 2019; Marso et al., 2016b,a; Zinman et al., 2015). However, which drug class should be considered for first-line antidiabetic therapy in patients with chronic kidney disease is still a matter of debate as the most protective agents against worsening renal function are still argued.

Lastly, whether a combination therapy with these agents is effective on cardiovascular and/or renal outcomes in diabetic and non-diabetic patients is yet to be assessed in clinical trials (Table 1) and, should it be proved true, their safety and cost-effectiveness will eventually need to be confirmed by post-marketing analyses. Of note, retinopathy complications (vitreous hemorrhage, blind-

Table 1. Trials evaluating the combination of GLP1RA with SGLT2i.

Study	DURATION 8 (Packer et al., 2020)	DECREASE (IJzerman , 2020)	EXANDA (Kautzky-Willer , 2020)	RESILIENT (Universitätsklinikum Hamburg-Eppendorf. , 2020)	NCT03018665 (Wang , 2017)
Number	2017-004709-42	NCT03361098	NCT03007329	NCT03419624	NCT03018665
Treatment group	ExenatideQW + Dapagliflozin	Exenatide BID + Dapagliflozin	ExenatideQW + Dapagliflozin	ExenatideQW + Dapagliflozin	Exenatide + Metformin
Comparator group	Placebo + Dapagliflozin	Placebo + Dapagliflozin	Placebo + Dapagliflozin	Placebo + Dapagliflozin	BIAsp30 + Metformin
Patient's Characteristics	T2 diabetes, HbA1c 8-12% BMI > 30 kg/m^2	T2 diabetes, HbA1c 7-10%, BMI 30-40 kg/m^2	T2 diabetes, HbA1c 6.5-11%, BMI ≥ 25 kg/m^2	T2 diabetes, HbA1c 8-11% BMI ≥ 30 kg/m^2	T2 diabetes, HbA1c 8-14% BMI ≥ 24-40 kg/m^2
Primary end-points	Changes in HbA1c	Differences in neuronal activity in central reward and satiety activity in response to food	Change in hepatic lipid content	Differences in weight and HbA1c	Rate of Inducing Diabetes + Change of Rate of Maintaining Diabetes Remission + Time of Maintaining Diabetes Remission
Status	Published	Recruiting	Recruiting	Ongoing	Recruiting

T2 : Type 2; HbA1c : glycosylated Hemoglobin; IR:insulin resistance.

ness or conditions requiring treatment with an intravitreal agent or photocoagulation) may be higher with GLP1-RA as reported for semaglutide compared to placebo in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) (HR 1.76, 95% CI 1.11-2.78; $P = 0.02$) (Huang and Lee, 2020; Marso et al., 2016a).

Future studies are warranted to better assess the pharmacological properties, efficacy and safety of SGLT2i and GLP1-RA in order to optimize the management of both diabetic patients and non-diabetic individuals with heart failure against a background of optimal medical treatmsent (Cosentino et al., 2020; Di Lullo et al., 2020).

Author contributions

Pierre Sabouret and Giuseppe Biondi Zoccai conceived the study. Pierre Sabouret and Pier Paolo Bocchino did the literary search and wrote the first draft of the manuscript. All authors critically reviewed the manuscript. All authors read and approved its final version.

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Conflict of Interest

Dr. Sabouret reports consulting or lecture fees from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Novartis, Pfizer, Servier, Vifor, Sanofi Regeneron, outside the submitted work. Dr. Biondi-Zoccai has consulted for InnovHeart, Milan, Meditrial, Rome, and Replycare, Rome, all in Italy, outside the submitted work. Dr. Bocchino has no conflicts of interest to declare.

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