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From pump to sink: The hydraulic connection of type 2 diabetes

Never like today, the pharmacological armamentarium against type 2 diabetes mellitus (T2DM) is so extensive. There are at least eleven different classes of drugs clinicians may use to fight the metabolic abnormalities of T2DM, namely metformin, sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl-peptidase 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), colesevelam, sodium–glucose cotransporter-2 inhibitors (SGLT-2i), the big insulin family, bromocriptine, as well as all their oral or injectable combinations. Despite this, overall glycemic control has not improved in recent years [1], which may cast some doubt about the utility of so many newer antihyperglycemic drugs. Although hyperglycemia is a hallmark of the diabetic state, the results of large interventional trials in T2DM demonstrated that the risk of both macrovascular and microvascular complications remains still high or very high after intensive and successful glycemic control; this remaining risk has been called residual vascular risk [2]. Accordingly, the paradigm of diabetes treatment has been shifting from the mere control of hyperglycemia (the mythical hemoglobin A1c value less than 7%) to a more useful compromise between the need of maintaining glucose levels within acceptable targets (to avoid metabolic decompensation) [3] and reducing the unacceptable burden of cardiovascular and renal (cardiorenal) complications of T2DM.

Beyond glycemic control

The origin of this compromise can be found in the many pleiotropic effects some newer antihyperglycemic drugs, namely DPP-4i, GLP-1RA, and SGLT-2i, have demonstrated in the last decade; this has opened the way to the slogan "beyond glycemic control" to celebrate the possibility to delay the apparently ineluctable progression of cardiorenal complications of T2DM. The starting point of this new era was the guidance issued in 2008 by the U.S. Food and Drug Administration to pharmaceutical sponsors requiring proof of cardiovascular safety as a prerequisite for the approval of new glucose-lowering drugs [4]. Cardiovascular outcome trials (CVOTs) started soon after and the first two trials were published about 5 years later [5,6]. Luckily, these newer antihyperglycemic drugs have not only demonstrated their cardiovascular safety in T2DM, but some have also showed evidence for superiority against placebo on some cardiovascular endpoints [1]. Nowadays, with 14 large-scale CVOTs already published and more than 130 000 patients evaluated [2,7,8], it is possible to drawn some conclusion about the cardiorenal efficacy of these newer diabetes drugs. The further refinement [9] of an initially suggestion [10] has led to the concept of the hydraulic connection in T2DM. To be honest, there would have been no hydraulic connection without CVOTs. The connection put together the four elements that full represents an hydraulic system: the pump, the pipes, the filter, and the sink. For analogy, these elements translate in the corresponding elements of the diabetic patient, namely the heart (pump), the blood vessels (pipes), the kidney (filter) and the whole body (sink).

MACE don't fit all cardiovascular risk

MACE (major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke and cardiovascular death) was the primary endpoint of all CVOTs. Although the classic MACE endpoint captures most of the cardiovascular morbidity/mortality burden of T2DM, it does not include hospitalization for heart failure (HF), or diabetic kidney disease (DKD). And yet, HF is a prominent early manifestation of cardiovascular disease (CVD) in T2DM, often occurs before a myocardial infarction event [11], and has a 5-year survival rate of only 12%. On the other hand, DKD still represents the main factor accounting for the substantial global increase in end stage kidney disease (ESKD) [12]. Cardioprotection in HF and nephroprotection in DKD therefore remain major unmet needs in T2DM. However, both hospitalization for HF and the occurrence of renal events were at best secondary outcomes in most CVOTs. Despite these shortcomings, which are being addressed by specific trials in both diabetic and nondiabetic people with reduced or preserved ejection fraction (EMPEROR-Reduced, NCT03057977; EMPEROR-Preserved, NCT03057951), or have already been addressed for DKD progression in diabetic patients [13], CVOTs shed some light on the clinical relevance of CVD versus HF and DKD in patients with T2DM.

The new therapeutic paradigm

Table 1 summarizes the evidence so far accumulated about the effects of DPP-4i, GLP-1RA and SGLT-2i on the cardiorenal and metabolic risk in T2DM. The pump and the filter seem to represent the best targets for the protective effects of the SGLT-2i family, at least for those so far investigated (empagliflozin, canagliflozin and dapagliflozin); in fact, they may offer cardiorenal protection by reducing hospitalization for HF, progression of DKD, and incidence of MACE. The estimates for HF hospitalization begin to separate within weeks and are maintained thereafter until the end of the trial; so,

Table 1 – Effects of newer diabetic drugs on the hydraulic connection in type 2 diabetes.

The Pump (heart failure)
- SGLT-2i reduce the risk of hospitalization for HF
- There is a class effect for SGLT-2i, as it is significant for each drug of the class
- The SGLT-2i effect is evident regardless of a history of HF or established CVD
- The SGLT-2i effect is independent of the reduction of HbA1c levels

The Pipe (major cardiovascular events)
- Both GLP-1RA and SGLT-2i reduce the risk of MACE
- There is no class effect, because it is not significant for each drug of both classes
- The effect is mainly evident in T2DM patients with established CVD
- The effect is partly dependent on the reduction of HbA1c levels

The Filter (diabetic kidney disease)
- DPP-4i, GLP-1RA and SGLT-2i reduce UACR
- SGLT-2i only reduce the progression of DKD
- There is a class effect for SGLT-2i
- The effect of SGLT-2i is independent of the reduction of HbA1c levels

The Sink (hemodynamic and metabolic effects on the body)
- Heart: reduce pre-load and after-load and increase EF (SGLT-2i); increase cardiac output (GLP-1RA); increase substrates (ketones, FFA) to the heart (SGLT-2i)
- Vessels: reduce blood pressure and vascular inflammation (SGLT-2i and GLP-1RA); reduce volume load (SGLT-2i); increase hematocrit (SGLT-2i)
- Renal: increase glycosuria (SGTL-2i), natriuresis and diuresis (SGLT-2i and GLP-1RA), and uricosuria (SGLT-2i)
- Metabolic: reduce body weight (SGLT-2i and GLP-1RAs), food intake and gastric emptying (GLP-1RA); increase negative caloric balance (SGLT-2i)

HF, heart failure; MACE, major cardiovascular events; UACR, urine albumin-to-creatinine ratio; DKD, diabetic kidney disease; EF, ejection fraction; FFA, free fatty acids.

it is highly likely that the mechanisms responsible for the reduction in HF events are beyond glucose lowering; in fact, the outstanding 31% reduction of HF hospitalization is completely independent of amelioration of HbA1c levels [2]. GLP-1RA may work as well, primarily by lessening the risk of MACE, depending on the particular drug of the class: at the present, a significant reduction of MACE has been reported for liraglutide, semaglutide, albiglutide [2] and dulaglutide [7]. Finally, the great number of pleiotropic effects may have contributed to the cardiorenal benefits of SGLT-2i and GLP-1RA. Interestingly enough, observational studies from large retrospective data that have assessed a broad population of T2DM patients yielded results consistent with those obtained in CVOTs [14], providing support for their cardiorenal benefits.

A time for precision medicine

The evidence produced by CVOTs seems to go in the direction of precision medicine, in order to address "non-glucose centric" unmet needs in T2DM patients who require amelioration of both their glycemic control and their poor cardiorenal outlook. Clinicians may dream for the ideal drug that simultaneously obtains glycemic targets and prevents the onset or slows the progression of HF, MACE and DKD. Within this context, the cardiorenal benefits exerted by SGLT-2i and some GLP-1RA are outcomes that patients ultimately value, including clinical microvascular disease (ESKD and need for dialysis), and macrovascular disease (myocardial infarction, heart failure, and ultimately death) [15]. Depending on many factors, including but not limited to availability, price, contraindications, tolerability and side effects, many T2DM patients may miss the therapeutic opportunity associated with the use of SGLT-2i and/or GLP-1RA. However, those who don't miss this opportunity may enjoy their cardiorenal benefits [16,17].

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