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Commentary

Assessment of the benefit–risk balance of SGLT2 inhibitors: Commentary on a new 'French paradox'

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In the international cardiovascular literature, the 'French paradox'—a catchphrase first introduced in the late 1980s—refers to the paradoxical epidemiological observation that French people have a relatively low incidence of coronary artery disease despite having a diet relatively rich in saturated fats. One proposed explanation was that regular moderate alcohol (red wine) consumption may be exerting cardioprotective effects [1], although other factors may also play a role [2], including in the diabetic population [3].

Patients with type 2 diabetes (T2DM) are exposed to a high risk of coronary artery disease, heart failure and premature cardiovascular (CV) death. Until recently, glucose-lowering agents have failed to demonstrate any significant positive impact on such complications, at least over the relatively short follow-up duration of 3–4 years [4]. However, since 2015, two new classes of glucose-lowering agents have succeeded in this regard [5]: sodium–glucose cotransporter type 2 inhibitors (SGLT2is) [6,7] as per the first landmark CV BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) [8]; and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [9] as per the large prospective Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [10].

However, now in 2019, the French diabetes community has to face yet another, unexpected French paradox, one that concerns assessment of the benefit–risk balance of SGLT2is. Indeed, the Transparency Committee of the French National Health Authority [Haute Autorité de santé (HAS)], which has for mission the evaluation of the clinical and added value of new medications, has recently declared that empagliflozin has insufficient medical benefit ("service médical rendu") to be made commercially available in France. It has refuted the positive CV and renoprotective effects reported with empagliflozin in the EMPA-REG OUTCOME in patients with T2DM and established CV disease [8]. Furthermore, it has considered that the glucose-lowering effect of empagliflozin was rather limited compared with placebo, thereby ignoring the fact that the objective of such a CV outcome trial (which allowed for adjustment of antidiabetic agents according to standard care in both groups) is not to evaluate the glucose-lowering effect of the SGLT2i, but to instead assess its CV effects independently of glucose-lowering effects—in other words, a search for 'glycaemic equipoise'.

Moreover, the same committee pointed out several severe adverse events reported with SGLT2is that were considered class effects, including urogenital infections, ketoacidosis episodes, lower-limb amputations and cases of Fournier gangrene. In particular, it emphasized the results of a paper published in *The British Medical Journal* (BMJ) in late 2018 [11]. This paper analyzed observational data from two national registries (Sweden and Denmark) and reported more than a doubling of the risk of amputation and diabetic ketoacidosis in users of SGLT2is compared with patients treated with GLP-1 RAs, even though the prevalences remained very low.

Thus, the somewhat provocative conclusion of the French Transparency Committee (of 27 February 2019) was that empagliflozin would have no positive impact on healthcare and that prescribing an SGLT2i (such as empagliflozin) might expose diabetes patients to "a loss of chance" compared with other glucose-lowering medications. Presumably, the comparator would be the GLP-1 RA liraglutide, which also demonstrated cardioprotection in patients with T2DM and high CV risk [10], and has been marketed and reimbursed in France since 2010.

In addition, the French Transparency Committee refuted the clinical usefulness of placebo-controlled trials—considered, by the way, as prerequisite studies by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)—and suggested a head-to-head CV outcome trial comparing an SGLT2i with another glucose-lowering agent (such as metformin, or a GLP-1 RA). Clearly, this wish is unrealistic on practical grounds: on the one hand, as far as metformin is concerned, the difficulty of recruitment would be due to the widespread real-life use of metformin as a first-line treatment, as recommended by international and national guidelines, including the HAS in France; on the other hand, with a GLP-1 RA as comparator, the excessive cost of such a trial would be because of the huge number of patients and long follow-up duration necessary to collect enough CV events to provide any meaningful direct comparison.

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The French diabetes community cannot accept the negative conclusions of the French Transparency Committee based on a biased interpretation of the available data. In March 2019, the French-Speaking Society of Diabetes [Société francophone du diabète (SFD)] published a position statement evaluating the benefit–risk balance of SGLT2is and was in support of their use in patients with T2DM and established CV disease, heart failure and progressive renal disease [12]. This SFD position statement is in agreement with other expert consensus reports, including the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) [13], European Society of Cardiology [14], American Association of Clinical Endocrinologists, American College of Endocrinology [15], American College of Cardiology and American Heart Association [16]. Its proposals were also officially endorsed by several national diabetes societies, including those of Canada, Italy and Switzerland. All of these statements declared that an SGLT2i (or GLP-1 RA as an alternative in cases of atherosclerotic CV disease) with proven efficacy in preventing CV events should be added to the treatment of patients at risk of CV disease (especially those with established atherosclerotic disease, heart failure and/or renal disease) in cases of failure with metformin monotherapy.

All of this is in complete opposition to the unique negative position of the French Transparency Commission. Now, not only may we speak of a new French paradox, but also of French exceptionalism, as SGLT2is (including empagliflozin) as of early 2019 are now commercially available in almost all European countries (with very few exceptions, such as Albania and Macedonia) and in nearly 100 other countries worldwide. It is also worth noting that empagliflozin has been marketed for many years in several other French-speaking countries (Belgium, Canada, Luxemburg, Switzerland), and was recently launched in Morocco and Tunisia too, all countries with active members of the SFD.

The EMPA-REG OUTCOME was highly criticized by the French Transparency Committee because it was primarily a safety trial with the primary goal of ruling out clinical damage (non-inferiority *vs* placebo) rather than confirming clinical benefit. However, both the FDA and EMA recognized that concluding empagliflozin superiority *vs* placebo was valid. In December 2016, the FDA added a new indication for empagliflozin, which was to reduce the risk of CV death in adults with T2DM and CV disease, while in June 2018, the EMA considered that both the improvement of glycaemic control and reduction of CV morbidity and mortality are integral parts of T2DM treatment and therefore recognized the added value of empagliflozin in this regard. Furthermore, the positive results of the EMPA-REG OUTCOME have been largely confirmed by two other CV outcomes trials with canagliflozin and dapagliflozin, thereby supporting a class effect as shown in a recent meta-analysis [6].

Finally, real-life investigations such as the two large Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) studies, which included several countries around the world (the US, Norway, Denmark, Sweden, Germany and UK, and in the Asia Pacific, Middle East and North America) [17,18], have also confirmed the reduction of CV mortality, major CV events and hospitalization for heart failure in large cohorts of patients treated with SGLT2is compared with those treated with other glucose-lowering agents. Indeed, the CVD-REAL NORDIC confirmed and extended those findings in well-documented national registries in Denmark, Norway and Sweden [19,20].

Regarding safety concerns, the SFD, in agreement with the FDA and EMA, has recognized that some adverse effects should be further screened for in dedicated post-marketing surveillance programmes. Nevertheless, adverse events, or at least the most severe ones, can be avoided or adequately managed if SGLT2i treatment is properly prescribed and adequately supervised. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA and the FDA have both confirmed the favourable benefit–risk profile of SGLT2is, despite recent warnings concerning diabetic ketoacidosis, amputation and Fournier gangrene. An updated review of the safety profile of SGLT2is revealed heterogeneous results, especially regarding the risk of amputation, when comparing randomized controlled trials, observational studies and pharmacovigilance reports [21].

Thus, even though some adverse events could not be excluded, their overall incidence is still, if anything, extremely low [21]. For example, in the above-mentioned paper published in the BMJ [11], the incidence rate averaged 2.7 vs. 1.1 events per 1000 person-years for lower-limb amputation and 1.3 vs. 0.6 events per 1000 person-years for diabetic ketoacidosis in two matched cohorts treated with SGLT2is vs. GLP-1 RAs, respectively. By comparison, in the CVD-REAL NORDIC, which also used national Scandinavian registries, the incidence rate of major CV events was 1.64 vs. 2.12 per 1000 patient-years and, for total mortality (the hardest clinical outcome), was 1.05 vs. 2.09 per 1000 patient-years in new users of SGLT2is vs. new users of other glucose-lowering agents [19]. In one large retrospective US cohort study, the relatively low incidence rate (expressed as events per 1000 person-years) of lower-limb amputation was confirmed when comparing therapy with SGLT2is vs. other comparators respectively: 2.4 vs. 1.5 in patients treated with dipeptidyl peptidase (DPP)-4 inhibitors; 2.0 vs. 1.8 in patients treated with sulphonylureas; and 1.4 vs. 1.9 in all patients not treated with metformin but with an SGLT2i [22].

Even in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, the only CV outcome trial showing a higher risk of amputation with an SGLT2i, the number needed to harm (NNH)—in other words, to see any additional lower-limb (mainly toe) amputation—was greater than the number needed to treat (NNT) to avoid a primary major CV event (MACE): CV mortality, non-fatal myocardial infarction and/or non-fatal stroke within 3 years with canagliflozin ($\approx$ 280 vs. $\approx$ 180, respectively) [23]. In addition, the safety profile of dapagliflozin was reassuring in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE–TIMI) 58, the largest and longest-running CV outcome trial involving the broadest T2DM population. In particular, it found no increased risk of amputation (1.4% vs. 1.3%) despite carefully and prospectively looking for it as an adverse event of special interest, and only a slightly increased incidence of diabetic ketoacidosis episodes, which therefore remained rare events (0.3% with dapagliflozin vs. 0.1% with placebo) [24].

The SFD, supported by the French Federation of Diabetic Patients (FFD), currently considers it a "loss of chance" for French diabetes patients who are not in a position to receive a drug that has a demonstrated ability to reduce major CV events, including CV mortality and all-cause mortality, as well as hospitalization for heart failure and progression of renal disease. Thus, this is an opposing conclusion to the enigmatic and provocative one of the HAS Transparency Committee, which considered it a "loss of chance" for patients to receive an SGLT2i instead of another glucose-lowering agent already available in France. Clearly, this particular opinion is not shared by the many diabetes patients currently obliged to travel to neighbouring countries (such as Belgium, Luxemburg, Switzerland, Germany, Spain or Italy) to buy these new medications.

Such a Kafkaesque situation may be considered a new French paradox. In contrast to the initial French paradox, which referred to better CV outcomes than expected in the French population [1–3], this new French paradox may result in poorer CV outcomes in patients with T2DM and high CV risk deprived of the protection of SGLT2is [6,13–16]. We can only hope that this situation will change soon!

Disclosure of interest

The authors declare that they have no competing interest.
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