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Abbreviations

BMI: body mass index

EGB: *échantillon généraliste de bénéficiaires* (generalist sample of beneficiaries)

GLDs: glucose-lowering drugs

GLP-1: glucagon like peptide 1

HR: hazard ratio

PE: pharmacoepidemiologic

SLGT-2: sodium-glucose co-transporter 2

SNIIRAM: *système national d'information inter-régimes de l'Assurance maladie* (French national inter-scheme health insurance information system

Summary

In the field of diabetes, pharmacoepidemiologic (PE) studies are numerous and represent an essential tool to assess the real-life effects of diabetes drugs. However, the specificity of the study of drugs used in diabetes, characterized by a high frequency of switches, interruptions and add-on, must be kept in mind by pharmacoepidemiologists in order to perform well-conducted studies and avoid several biases.

In this article, the authors discussed the specific interest of PE studies in the field of diabetes, provide a brief overview of biases that can affect those studies, and suggest pragmatic solutions for more correct results and appropriate interpretation.

KEYWORDS

Diabetes mellitus; Pharmacoepidemiology; Post-marketing surveillance; Real-world evidence; Database studies

Introduction

Type 2 diabetes is one of the most frequent chronic diseases. According to the World health organization, the global prevalence of diabetes in the adult population has increased from 4.7% in 1980 to 8.5% in 2016 [1]. Hence, in the absence of effective curative treatment, research for new glucose-lowering drugs (GLDs) has noticeably grown in the last two decades. Now, the first generation of diabetes drugs (metformin, sulfonylureas) compete with new drugs that appeared during the 1990's (α-glucosidase inhibitors and glinides), the 2000's (thiazolidinediones and incretin-based drugs) and the 2010's (sodium-glucose co-transporter 2 inhibitors).

For these reasons, a number of clinical trials were published in the last decades concerning new drugs for the management of type 2 diabetes. One of the most important events in the last years was the withdrawal of rosiglitazone for an increased risk of heart failure [2]. This had a huge impact for studies in diabetes, as patent owners need to provide proofs that their drug did not expose patients to an increased mortality compared to placebo. Up today, this is a prerequisite to allow marketing for any new drug for diabetes. If this choice has enormous regulatory implications and serves as a strong protective measure, the external validity of these comparisons to placebo is poor as prescribers need primarily information on which is the best glucose-lowering drug in their patients. Active comparators are frequently used in more advanced phase III studies, but their efficacy is frequently measured on surrogate endpoints while for mortality, cardiovascular risk, and other safety outcomes, these trials are clearly underpowered.

In real life settings, spontaneous reporting is a source of safety data, and it is known to be the best source for providing drug safety signals. It could also be used to describe the safety profile of drugs, but could not be informative on the actual risks related to drugs.

Pharmacoepidemiology (PE) studies are thus crucial for diabetes as they allow investigating real outcomes such as mortality and cardiovascular risk, but also infrequent safety outcomes such as pancreatitis or pancreatic cancer. However, the level of proof brought by this kind of studies depends on the use of the most appropriate methods in limiting the risk of bias and misinterpretation.

In this manuscript, we aimed to first study the interest of PE studies in the field of diabetes and second, review the methodological specificities, the challenges and possible solutions to the limits of PE studies in the field of diabetes.

Interest of PE studies in the field of diabetes

The interest of PE studies in the field of diabetes lies first and foremost in the limits of clinical trials and pharmacovigilance studies to assess and measure the real-world benefit/risk ratio of glucose-lowering agents. Indeed, diabetes therapy is a very dynamic field of research implying the marketing of numerous GLDs. However, these recent and new drugs such as incretin-based drugs or sodium-glucose co-transporter 2 (SGLT-2) inhibitors are, at the time of marketing, only assessed by short-term clinical trials which are both unpowered and not long enough to clearly determine the safety profile and effectiveness. In the case of diabetes drugs, the need for real-life assessment is also supported by:

i) the predominance of surrogate endpoints (such as HbA1c) to study beneficial effects (it also stands for even older drugs such as metformin or sulfonylureas for which effectiveness is still uncertain);
ii) the fact that patients with advanced age and/or multiple comorbidities, which represent the majority of the patients treated for diabetes, are under-represented in randomized controlled trials;
iii) lifelong treatment due to the chronic nature of the disease with variations over time and for which use probably differs in real-life and in the clinical trials; and
iv) the high prevalence of diabetes which then concerns a large population of patients in which even rare risks can have a significant impact.

Hence, PE studies are of great interest in the field of diabetes. Those using existing databases have shown to be very efficient to answer questions raised by authorities requiring post-registration studies [3]. They are more and more frequent also because of the increased accessibility to large medico-administrative databases where diabetic patients and diabetic drugs are easily identified and which provide substantial statistical power, less loss to follow-up, and reduced bias in ascertaining exposure and outcomes. These databases could also be used for safety signal detection and prioritization as it was found in a pilot study in France [4].

The principal interest of PE studies is to confirm or refute the safety signals raised by clinical or pharmacovigilance data functioning as a useful complementary method to pharmacovigilance studies [5]. A recent example is the confirmation by a cohort study using the United Kingdom clinical practice research datalink that glucagon like peptide 1 (GLP-1) analogs are associated with an increased risk of bile duct and gallbladder diseases; a risk that was only previously suggested by an imbalance number in gallbladder-related events in a clinical trial studying high-dose liraglutide for weight loss [6]. In certain cases, PE studies have been decisive in risk management of GLDs. For instance, in the controversy regarding the use of pioglitazone and the risk of bladder cancer, the decision of the French medicine agency to suspend the use of pioglitazone was based in June 2011 on the results of a cohort study using the French national health insurance information system, which showed an increased risk of bladder cancer with pioglitazone exposure [7].

PE studies are also an essential tool to evaluate the real impact of already known risk associated with GLDs. For example, hypoglycemia is a well-known complication in diabetic patients, because of their food restriction or because the use of hypoglycemic drugs, such as sulphonylureas, glinides or insulins both used alone or in combination [8,9]. Non-severe hypoglycemia has been considered as a mild event that has not a huge impact in health outcomes. Real-world evidences showed conversely that hypoglycemia is the second cause of hospitalisation in type II diabetic patients [10], it accounts for 20%-25% of hospital admissions for adverse drug reactions [11,12], and it might precipitate heart failure in patients at greatest risk [13]. More generally, it may impair the maintenance of euglycaemia and the full benefit of treatments [14], has a negative impact on patient quality of life [15,16], and can cause falls and fractures in the elderly [17]. A recent French PE study suggested that elderly patients treated with hypoglycemic drugs are at higher risk of hospitalization for trauma, in particular with insulins (hazard ratio [HR] 1.49, 95%CI: 1.32; 1.68) or glinides (HR 1.34, 95%CI: 1.12, 1.61) [18].

Methodological specificities, challenges and possible solutions

Exposure definition

Diabetes is associated with cardiovascular, neurological, and renal complications. It has also been related with an increased risk of cancer. The occurrence of these complications depends

on age of patients, duration of diabetes and on capacity to drugs (and patients) to optimally control the glycemic values. GLDs are intended to be used for long time periods; consequently, their benefits and their risks may vary over time.

In the study of outcomes that are associated with an early risk (*e.g.* allergic, haemorrhagic, hepatic, hypoglycaemic or gastrointestinal effects), it is crucial to exclude prevalent drug users to avoid the risk of bias due to depletion of susceptibles: the exposure group may be composed of patients who have passed through the early period of exposure, which is at higher risk, and therefore present less adverse outcomes than drug initiators. This must be taken into account when we consider all users of GLDs to avoid the risk to include a cohort of "survivors" (prevalent drug users), which could be constituted by people less susceptible of outcomes related to the first period of drug treatment. For these main reasons, studies conducted with new user designs provide a higher level of proof than others, as they increase the chances of identifying more comparable patients in term of risk of mortality, and are well suited to detect or assess outcomes that could be considered as time-dependent [19].

The profile of use of GLDs is also highly variable. If most patients begin the treatment with metformin or sulphonylureas [20], high levels of treatment discontinuation or switching could be observed with the time passing. Moreover, GLDs could be associated as double, triple, and even four different combinations. As for clinical trials, two approaches could be used: the as-treated analysis, and the intention-to-treat analysis. Both have strengths and limitations. The as-treated analysis, which ends exposure to a medication at treatment discontinuation, inform about the actual drugs to which patients were exposed, but is prone to informative censoring, in which the observation of an outcome of interest shortly after therapy discontinuation may underestimate the risk, and resulted in biased estimation of risk or benefits. Sensitivity analyses with one or more grace periods can be used to address potential informative censoring. The intention-to-treat analysis is not affected by informative censoring, but it may cause exposure misclassification (higher for longer follow-up periods), and remains open to differential loss to follow-up, thus causing selection bias. Differently from clinical trials, intention-to-treat analysis is not always considered the gold standard in PE studies. In PE studies on GLDs, higher level of proof is provided when both analyses are performed and show concordant results. From a statistical point of view, Cox models are frequently used to account for time-dependent variations in drug exposure. These models make the assumption that treatment changes are independent of the outcome(s), which is rarely the case in diabetes, a chronic disease requiring therapy adjustments directly dependent to outcomes of interest, such as cardiovascular risk. Other strategies exist to address time-

dependent confounding, such as marginal structural models or G-computation, but these methods are actually under-used in PE studies, as their interpretation could be considered complex [21–23].

Immortal time bias can occur in cohort studies when the exposure definition requires that subject must have survived for a defined period of time during which person-times are excluded or considered exposed [24,25]. With less events in the exposure group defined as such, the bias will make the drug look more beneficial. This bias can be observed in PE studies of safety or effectiveness of GLDs. For instance, a cohort study conducted on the database of Taiwanese health data showed an 88% reduction in cancer incidence in patients who had received at least two metformin prescriptions between 2000 and 2007 [26]. To be exposed, the subjects could not present a cancer before the second prescription: the period preceding this second prescription was immortal but counted for the exposed group. The bias thus contributed to the spectacular effect observed. Such effect is also particularly intense in the studies where exposure begins at the start of follow-up for subject who uses the drug at any time during follow-up. This is, for instance, the case in several cohorts studying the cardiovascular effect of diabetes drugs [27–29]. Proper definition of exposure not using events that occur during follow-up, new user design and attributing immortal person-time to the unexposed group will efficiently limit the effect of this bias.

Confounding

Diabetes is associated with higher risk for several conditions such as cardiovascular, renal, neurological, pancreatic effects or cancer. Furthermore, surveillance is higher for diabetic patients and this could introduce detection bias. Hence, in PE studies, it is not appropriate to compare diabetic to non-diabetic patients. For the same reason, comparisons between patients that are pharmacologically treated ant those who are not is not appropriate. The choice of the comparator group has to be made among other treated diabetic patients, but differential factors must be taken into account. Confounding by indication can be introduced by factors related to the indication of the drug. For instance, metformin is known to show beneficial effects on weight and is particularly indicated in obese patients. This is not the case of sulfonylureas. In a study that would compare metformin to sulfonylureas for the risk of cardiovascular disease, obesity would play a confounding role as it is associated with metformin and with the outcome. Confounding by severity or duration of diabetes can occur

when the duration of diabetes is a risk factor for the studied outcomes. For example, when studying cardiovascular effects, duration or severity of diabetes is a potential confounder since it is a risk factor that is associated with differential treatment strategies. Hence, it is crucial to control for diabetes duration and to compare drugs which share a similar position in the therapeutic strategy (*e.g.* fist-line treatments, second-line treatments, etc.). This strategy can be challenged by the inconsistent availability of diabetes duration, the difficulty of measuring diabetes severity, and the heterogeneity of treatment strategies in real-life. For example, several studies assessed the risk of pancreatitis associated incretin-based drugs. The one by Singh et al. found an increased risk when comparing incretin-based drugs users to non-users (i.e. users of any other GLD), the latter group including patients treated by various drugs from first-line monotherapy to multi-drugs combinations for advanced diabetes [30]. Other studies using a control group which represented a more comparable treatment in terms of therapeutic strategy and adjusting for diabetes duration found no association [31,32]. With no ideal comparator group, its choice is a difficult task which has significant impact on the study results. For incretin-based drugs, which are second to third-line therapies, users of sulfonylureas, switchers or initiators of two or more GLDs can all be considered as acceptable comparator groups but certainly provide different results. In the end, imperfect comparator group could result in potential residual confounding.

In PE studies performed on healthcare databases, missing data on important variables is a crucial point. Missing data can concern regular risk factors for the outcome or factors associated with exposure to diabetes drugs, both types of variable can be considered as potential confounders. For instance, tobacco consumption, which is a known risk factor for bladder cancer, is not available in the French national health insurance database. Hence, it was not possible to adequately take into account this potential confounder in the cohort study of pioglitazone-related bladder cancers [7]. History for the outcome is also an important factor which is frequently lacking in database analyses. Similarly, variables such as weight or body mass index (BMI), glycemic control values at baseline (fasting glycemia, HbA1C) or duration of diabetes which strongly influence the choice of the therapeutic strategy, are rarely recorded in claims databases. When associated with the outcome, they may act as important confounders. Rare are the efficient solutions to limit unmeasured confounding. Methods using proxies are often used (*e.g.* for smoking: hospitalization for tobacco use-related conditions and reimbursement for nicotine dependence drugs). Data imputation can also be tested, but no method has provided really convincing results.

Conversely, some PE studies have been controlled for variables that must not be used for this. Overadjustment is a bias that occurs when analyses are adjusted for variables defined as "intermediate". Intermediate variables are outcome risk factors that have been influenced by exposure to the drug. Adjusting for them weakens the effect of the drugs, resulting in a bias toward the null [33]. For instance, in the study of cardiovascular risk associated with diabetes drugs, variables such as post-treatment hypertension or hyperlipidemia, drugs used during follow-up, BMI and HbA1c measured after treatment initiation can be considered as intermediate variable and one should not adjust for them in the analyses [34].

Statistical power, duration of follow-up and long-term assessment

For the reasons presented above, new user designs must be the method of choice. However, selecting only new users will automatically reduce the sample size and, in addition to the study of rare exposure and/or outcome, statistical power issues can rise. This is for instance one of the drawback of using the *échantillon généraliste des bénéficiaires* (generalist sample of beneficiaries or EGB), a 1/97th random sample of the French national health insurance information system. Even when using large databases and studying a frequent pathology such as diabetes, there may not be enough events to allow sufficient precision of risk estimates. To limit this problem especially for rare outcomes, whole population databases or multicenter cohort studies have been developed. They combine health records from several international databases and can reach several millions of subjects. For instance, a multicenter study was set up to assess the risk pancreatic cancer associated with incretin-based drugs. Health records from four Canadian provinces, the United States, and the United Kingdom were gathered to reach 2,024,441 person years of follow-up for a total of 200 exposed cases [35]. The same methodology was used to study the association between incretin-based drugs and pancreatitis [36] or heart failure [37]. In France, the *système national d'information inter-régimes de l'Assurance maladie* (national inter-scheme health insurance information system or SNIIRAM) database, which merges information of reimbursed claims from almost the whole French health care system, linked with the hospital diagnoses, covers nearly 99% of the French population, i.e. over 66 million persons [38]. It is the world's largest claims database and provides sufficient power to study rare drug adverse reactions, such as pioglitazone-related bladder cancer [7]. Furthermore, when the link with all hospital data (labs results, in-

hospital prescriptions, etc.), it will become one of the most complete healthcare databases [39].

Another drawback of using new user design is that it also shortens the available follow-up time, and even databases studies with gigantic sample size will not be able to record outcome events if the follow-up is too short. For example, the median follow-up for the pancreatic cancer multicenter cohort study ranged from 1.3 to 2.8 years [35]. Medication stops and switches are frequent in diabetic patients and this affect follow-up time which become an important limit especially when studying long-term effects of diabetes drugs.

Other key aspects for interpretation of results

Protopathic bias (also known as reverse causality) occurs when changes in drug exposure are a consequence of a symptom or an early stage of the outcome disease (at this stage undiagnosed). In the field of diabetes, protopathic bias may be an issue for outcomes that affect the glucose levels, the course of the diabetes, or medication selection. Outcomes such as pancreatic effects, cancers or infections can typically unbalance the glycemic levels which lead to changes in pharmacologic treatments and thus reverse the causality between exposure and outcome. For example, the occurrence of a serious condition may lead to switch an oral diabetic drug to insulin before that this event is recorded in an hospital database, meaning that the patient is not exposed to the oral treatment when diagnosis occurs in the database and that insulin could be wrongly suspected. This phenomenon must be kept in mind and considering lag periods after exposure begins and latency periods after exposure stops represent an effective solution. Sensitivity analyses with varying periods can be performed to study this bias.

When studying patients with chronic disease such as diabetes, several events other than the outcome can occur (other causes of death, hospitalization, etc.). When these events and the outcome are not independent (meaning that the probability of an event is modified by the occurrence of the other) and/or they prevent each other from occurring, they are called competitive events and potentially lead to bias. For example, in a cohort studying cancer risk and metformin exposure in the Netherlands, the use of metformin was associated with a strong protective effect for cancer mortality (HR 0.43, 95%CI: 0.23-0.80). Nevertheless, the results also showed that metformin strongly increased cardiovascular mortality (HR: 2.27, 95% CI: 1.36 -3.78) [40]. A possible explanation for the strong protective effect may be that,

in this study, metformin was prescribed to the most obese patients i.e. at higher cardiovascular risk, introducing a competitive risk between cardiovascular events and cancer. If patients in the metformin group died from cardiovascular complications before developing a cancer then their cancer mortality is lower. Based on cumulative incidences, Fine-Gray models are used to limit this bias.

Because of methodological issues, PE studies may fail to confirm an existing risk but it may be even more problematic when biases generate false-positive results. Studies should always be replicable and the control of biases is a key to replicability [41].

Conclusions

In the field of diabetes, PE studies will be more and more numerous in the future. Being essential to assess the real-life risk-benefit balance of diabetes drugs, their interest is noticeable but researchers and editors must know well the many bias that can cause erroneous results and misinterpretation, in order to produce and publish well-conducted observational researches.

Disclosure of interest

Authors have no competing interest to declare

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