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Summary

The evaluation of the real-life benefits and risks of statins in population is a major pharmacoepidemiological issue, given their widespread use for cardiovascular prevention. The purpose of this review was not to be exhaustive but to show the contributions of pharmacoepidemiology for various aspects of the evaluation of statins such as real-life drug use, effectiveness and risk. Statins are among the most used drugs in the world, but recent data show a slight decrease in use. Actual statin users are older, and have more comorbidities than those studied in clinical trials, but this does not seem to compromise their effectiveness, unlike the compliance issues that are common with these drugs. Beyond the known adverse reactions of statins from the clinical trials, risks of statins can be varied and sometimes difficult to evaluate, considering the ubiquity of cholesterol throughout the body, from drug or endogenous molecule metabolism to the construction of cell membranes or cell activities.

KEYWORDS

Statin; Cardiovascular prevention; Cholesterol; Real-world evidence; Pharmacoepidemiology

ABBREVIATIONS

ACC/AHA: American College of Cardiology/American Heart Assocation

ACS: acute coronary syndrome

DUS: drug utilisation studies

EUROASPIRE IV: European Action on Secondary and Primary Prevention by Intervention to Reduce Events

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

MINAP: Myocardial Ischaemia National Audit Project

REACH: Reduction of Atherothrombosis for Continued Health (registry)

SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-bases care in Heart disease Evaluated According to Recommanded Therapies

Introduction

The real-life evaluation of statins is a major issue in pharmacoepidemiology, given their widespread use for cardiovascular prevention. These drugs inhibit the catalysis of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) in mevalonate by inhibiting HMG CoA reductase and thus reducing the hepatic synthesis of cholesterol. In addition to this effect on cholesterol lowering, statins decrease inflammation and oxidative stress by up-regulating the activity of the endothelial NO synthase, improving endothelial functions and stabilizing atheroma plaques. This drug class is one of the most prescribed in Europe or North America, with, for example, approximately 10% and 17% of adults treated per year respectively in France and in the United States [1, 2]. Although there is clear consensus on the benefit of statins in secondary cardiovascular prevention, their use in primary prevention remains debated especially for certain populations, including elderly, for whom the benefit / harm balance of such treatment is not well established [3-14].

The purpose of this literature review was not to be exhaustive but to show the contributions of pharmacoepidemiology to the evaluation of statins in real-life drug use, effectiveness and risk.

Real-life drug use

Different perspectives can be distinguished for drug utilisation studies (DUS) of statins [15]. The general objectives of these studies are to measure, explain, predict or generalize what is observed but also to examine, analyse, or interpret these observations. Utilisation studies are the first descriptive step when looking at a drug.

Foremost, DUS allow to estimate prevalence (total number of users in a population during a given period) and incidence (new users in the population during a given period) of drug usage. Many studies have estimated these indicators for statins and found substantial increases of statin use in the last decades [16-18]. For example, O'Keeffe et al. showed, in the United Kingdom, increasing prevalence of statin use from 2 per 1000 persons in 1995 to 128 per 1000 persons in 2013 [19]. In the United States, a recent study estimated that 38.6 million Americans were on a statin in 2011-2012, representing approximately 172 per 1000 persons [1]. In France, data from the health insurance system showed that 6.4 million persons received statins in 2013 [2, 20]. However, recent open data on drug utilisation provided by French health insurance system shows a slight decrease in statin reimbursements since 2015 (Fig. 1) [21].

The description of the characteristics of the user population is of particular interest in identifying potential differences between the finally treated population (also called joint population) and the target population defined as the population whose characteristics correspond to that of the population studied in clinical trials. For example, Martin et al. showed for simvastatin that women accounted for 50% of the joint population and elderly 57% but only 18% and 24%, respectively, of clinical trial populations [22]. The analysis of the user characteristics is also interesting to identify and understand the determinants of statin use. This type of study can be performed in the general population or in specific population subsets or therapeutic areas. Statins having demonstrated their efficacy in reducing cardiovascular morbi-mortality in clinical trials, two situations can be distinguished: secondary prevention (patients who have already had a myocardial ischemic event); primary prevention (patients who have not yet had an ischemic event but are more or less at risk of developing it). In secondary prevention, American and European guidelines since 2002 advocate to initiate as early as possible intensive statin therapy and continuing it indefinitely [23, 24]. However, results of recent European national registries (Myocardial Ischaemia National Audit Project [MINAP] in United Kingdom and Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies [SWEDEHEART] in Sweden) or multinational surveys conducted internationally (Reduction of Atherothrombosis for Continued Health registry [REACH] in 44 countries across 6 major regions: Latin America, North America, Europe, Asia, the Middle East, and Australia) or in Europe (European Action on Secondary and Primary Prevention by Intervention to Reduce Events [EUROASPIRE] IV) have shown that these guidelines are not entirely followed [25-27]. These findings were also confirmed by many international drug utilization studies, which showed from 2% to 19% of patients were not treated with statins after an acute coronary syndrome (ACS) [28]. Other pharmacoepidemiological studies specifically designed to assessed factors related to statin use have shown that advanced age, lower severity of the ischemic event, female gender, ethnicity disparities or lack of insurance were barriers to the use of these drugs [1, 29-31]. In primary prevention, evidence of statin effectiveness is probably less persuasive than in secondary prevention [11]. Several pharmacoepidemiological studies have shown that if statins might be underused in high cardiovascular risk patients, [32-35] a non-negligible proportion of patients with low cardiovascular risk had no indication to receive such treatment [34, 35]. As for secondary prevention, barriers to statin initiation/prescription in primary prevention were old age, social deprivation or female gender [36-38]. Conversely, the presence of cardiovascular risk factors such as diabetes or hypertension are factors favouring prescription [37, 38]. Other studies have been performed on specific populations such as the elderly [18, 39, 40]. For example, Gulliford et al.

have shown that statin use increased over the last 10 years in the elderly so that 30% of primary prevention patients were treated, 80% in secondary prevention. Statin prescription increased with the frailty index of patients [39].

Another cornerstone of the evaluation of statin treatment, as of all chronic treatments, is the compliance to treatment. This parameter is one of the most frequently studied criteria in pharmacoepidemiology and, according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), it includes the concept of adherence (day-to-day compliance with the prescription), and of persistence (continued treatment for the prescribed duration) [41, 42]. Many definitions and methods have been developed to identify and measure adherence or persistence to statins, but actually none refer to or evaluate what exactly the patient is taking. However, indirect measurement methods allow approaching it by collecting data either by interviewing health professionals or patients, or by extrapolating data from prescriptions or claims. Several pharmacoepidemiological studies have shown that estimated adherence or persistence to statin treatment is sub-optimal whether in primary or secondary prevention [25-28, 43, 44]. Moreover, although a large proportion of patients discontinue statins, many restart them [43, 45]. Reasons for adherence and persistence issues could be related to patient characteristics but also related to the patient's perception of risk or harms incurred. Indeed, women, smokers, patients with advanced age, or concomitant diseases were commonly associated with non-adherence or non-persistence to recommended drugs [28, 43, 46]. Moreover, patients who have had severe cardiovascular ischemic events or with a family history of cardiovascular deaths seem to have better compliance to treatment [47, 48]. Direct patient interviews reported that the physician's decision or the occurrence of adverse drug reactions (such as muscular reactions or fatigue) were the most common reasons for statin discontinuation [49-52]. Otherwise, switch from branded to generic statins seems to have no impact on medication compliance [53]. For elderly, although predictor factors of compliance were similar to younger population, some specific characteristics could identify those who needed better follow-up care. Older patients with high frailty levels or with anxiety disorders appeared to be more non-compliant to statins and maybe need greater assistance or follow-up care, particularly with a cardiologist [39, 54, 55]. The issue of non-compliance to statin treatment is of crucial importance as it could affect drug effectiveness.

Studies have also been performed to assess the effects of health policy on statin use. For example, in the United States, several authors have assessed the impact of the new 2013 guidelines of American College of Cardiology/American Heart Association (ACC/AHA) that abandoned cholesterol targets to focus on cardiovascular risk and showed an increase of statin initiation following the release of this guideline [56, 57].

Conversely, over the past decade, although statins are among the most studied drugs and with a broad consensus among the medical community concerning their benefit and risk, they have been confronted to a specific crisis of criticism massively relayed in the media [58]. In this context, pharmacoepidemiological studies were very helpful to evaluate and understand the population impact of this controversy. In France, for example, controversy about statins reached a wide audience by the publication of a book in February 2013 arguing that cholesterol is not linked to cardiovascular diseases and refuting the validity of all experimental studies demonstrating the efficacy of statins for cardiovascular prevention. This stance was not without consequences: a first study performed in several hospitals immediately after its publication showed that among 142 patients interviewed during medical consultation, 9% and 24% of those treated, respectively, in secondary prevention and in primary prevention planned to stop their statins [59]. A cohort study based on national data from French health insurance system and representative of the French population included several thousand chronic users of statins and showed that the rate of interruption of statin treatment had significantly increased in 2013 compared to 2012 by 26% in patients with high cardiovascular risk (secondary prevention), 40% in patients with moderate cardiovascular risk and 53% in patients with low cardiovascular risk [60]. However, the immediate causal link between this controversy and the interruptions of treatment remains difficult to prove. Similar controversies targeting statins have been described in other European countries (United Kingdom, Denmark) with identical consequences, although more moderate than in France [61, 62].

Effectiveness

Statins are one of the most studied drugs. Evidence from clinical trials is huge and several meta-analyses demonstrate the efficacy of statin in reducing mortality and cardiovascular events, mainly through lowering LDL-cholesterol, mainly during secondary prevention or in high cardiovascular risk patients [3-5, 63]. There is clear consensus on the benefit of statins in secondary cardiovascular prevention, although only simvastatin and pravastatin have demonstrated a reduction of all-cause mortality. However, the interest of statins in primary prevention remains debated, especially for patients with low cardiovascular risk [9, 11-14]. Differences exist in the definition for the cardiovascular risk eligible to initiate a statin treatment between different published guidelines and, thus, complicate the identification of patients who will actually benefit from such treatment [6, 7, 64]. In this context, pharmacoepidemiological studies allow both to verify that the efficacy

predicted by clinical trials is applicable to the treated population (so-called effectiveness), and that the real conditions of use of the drug in the population does not challenge this effectiveness.

Several studies have confirmed statin effectiveness for secondary cardiovascular prevention, and its maintenance over time. In this high-risk situation, although the joint population seems different from that included in clinical trials (older and with more co-morbidities), statins have demonstrated their effectiveness regardless of age, co-morbidities or the effectiveness of post-ACS management [28, 48, 65-70]. In primary prevention in France in patients at risk, a similar magnitude of effect was observed in real life, compared to randomised clinical trials, with a reduction of 33% of non-fatal ACS [71]. Furthermore, comparison of intra-statin effectiveness has shown that, for example, rosuvastatin was not associated with better reduction in cardiovascular risk than simvastatin at equipotent doses [72]. These results seem to be confirmed by the negative impact of poor adherence or poor persistence to treatment in these populations [44, 73-75]. For example, the review published by De Vera, et al. including 19 observational studies reported a relative risk for statin discontinuation ranging from 1.22 to 5.26 for cardiovascular disease and 1.25 to 2.54 for death [75]. Other population-based studies have also confirmed the benefit of statin therapy for stroke prevention, both in primary and secondary prevention and even for patients at higher ages [76-79].

However, the main challenge of pharmacoepidemiological studies evaluating chronic drug effectiveness is to limit indication bias and healthy user or healthy adherer bias, which particularly affects the evaluation of statins [80, 81]. For this reason, pharmacoepidemiology still remains poorly considered in the overall evidence-based data assessing the effectiveness of statins, even though there has been considerable methodological progress in the mastering of unmeasured confounding [4]. This is particularly important, given the major interest of this evaluation for certain at-risk populations poorly studied in experimental conditions [82].

Risk

The contribution of pharmacoepidemiology to the evaluation of the risk of drugs, and especially its complementarity with pharmacovigilance, is well established [83]. Given the wide use of statins, their mechanisms of action by inhibiting cholesterol synthesis, a central element involved in the metabolism of many molecules, and the controversies surrounding these drugs, their risk assessment can be considered as somewhat unusual. Indeed, one might distinguish the known and quantified adverse drug reactions, demonstrated by both experimental and

pharmacoepidemiological studies, from various reported risk signals found in the literature that still remain to be confirmed, with or without pharmacological plausibility.

Among adverse drug reactions demonstrated in clinical trials, pharmacoepidemiological studies quantified the prevalence of muscle symptoms, the most common effect associated with statin use (7 to 29 % of users), although a part of these effects could be explained by a nocebo effect [84-87]. Rhabdomyolysis, a severe form of muscle damage, is more rare, with an incidence estimated at 1.10 per 10,000 person-years [88]. Moreover, pharmacogenetic studies have also demonstrated the link between the presence of SLCO1B1 polymorphism(s) (transporter involved in the hepatobiliary excretion) and the occurrence of muscle toxicity [89]. On the risk of diabetes identified by clinical trials (about 1 per 1,000 patient-years), more substantial at the beginning of treatment, pharmacoepidemiological studies brought comparative risk information between statins, confirming a class effect [90]. Although in contrast to the results of a network meta-analysis of randomized trials showing only association with atorvastatin and rosuvastatin [91], this class effect could suggest, in addition to pharmacodynamics mechanisms, that patients receiving statin treatment do not follow strictly hygienic rules [90, 92]. The risk of diabetic complications in diabetes induced by statins seemed less frequent than in diabetes not induced by statins [93]. Concerning hepatic effects of statins, clinical trials showed transient increases in liver enzymes for 0.5 to 2% of patients taking statins but without clinically relevant consequences [84]. Population-wide studies allowed to assess risk of liver injury, which is much rarer, and showed that this risk is higher for high doses of statin and for rosuvastatin and atorvastatin compared to the other [94, 95]. Since cholesterol could be involved in the maintenance of eye lens transparency, several studies were conducted to evaluate the risk of cataract associated with statins. However, results of these studies are inconsistent, [96-102] and contrast with clinical trials that concluded to an absence of risk [103]. These discrepant results could be explained probably by residual confounding and methodological issues [104].

Apart from these known and well-studied effects, pharmacoepidemiology has enabled to highlight some signals of risk that are, for some, still to be confirmed. Replication is particularly important in this context given the possibility of false-positive results in pharmacoepidemiology [105]. Risk of cognitive dysfunction has been widely debated, although actually the evidence is in favour of an absence of risk on cognition [84]. Some observational studies have shown a possible association between statin use and increased risk of dementia suggesting that reduction in cholesterol levels with statins may be potentially detrimental for cognitive function [106, 107]. However, this risk has not been replicated in several pharmacoepidemiological studies, with both a good cognition assessment and sufficient follow-up to identify long-term effects, nor in

experimental studies [84, 108-110]. Other observational studies have investigated effects on acute memory impairment following a pharmacovigilance signal, but this risk remains unconfirmed [111, 112]. Finally, other effects could also be associated with statin use such as lupus erythematosus, rheumatoid arthritis or erectile dysfunction, but replication by other pharmacoepidemiological studies remains needed [113-115].

As pre-clinical studies of statins showed teratogenic potential at high doses and the importance of cholesterol in fetal development, this drug class was contra-indicated during pregnancy. However, large population-wide studies were able to evaluate the risk of inadvertent statin use in this specific situation [116, 117]. For example, in UK, Bateman et al. showed that <0.2% of women were exposed to statins in the first trimester and that this exposure was not associated with a higher risk of malformation than for women not exposed to statins (adjusted relative risk, 1.07; 95%CI 0.85 to 1.37) [116]. Even if these results are reassuring, this absence of risk remains to be confirmed.

One of the other strengths of pharmacoepidemiology is also the possibility to study drug-drug interactions in the population. This is the more interesting as clinical trials generally restrict concomitant diseases or treatments. Several studies have attempted to quantify known drug-drug interactions with statins [118-120]. For example, Morival et al. estimated, using a French hospital data warehouse, that 22.5% of statins users were exposed to potential drug-drug interaction with statins and, 1% to a contraindicated interaction (theoretically the most at risk). The most frequent interactions identified in these data involving influx-transporter (OATP1B1) or CYP3A4 interactions [119]. Others have studied the impact of some specific interactions with statins: statin-fibrate association was found to increase the risk of rhabdomyolysis, whereas statin-clarithromycin associations did not modify the risk of hospitalization or death [121, 122].

Finally, pharmacoepidemiology can also be useful for risk detection using data-mining approaches on large healthcare databases. For example, Korean researchers have shown that these methods, applied to rosuvastatin, can detect 60% of known, published and specific adverse reactions to this drug [123]. These preliminary results are promising and open a new potential in risk signal detection methodology, currently essentially based on pharmacovigilance signals with all the limits related to spontaneous reporting.

Conclusion

In the context of statin evaluation, pharmacoepidemiology has proven its usefulness to identify differences between target and joint populations and the impact of these differences on their effectiveness. Moreover, pharmacoepidemiology allows to quantify and study the compliance of patients with this chronic treatment, whether for daily adherence or persistence over time, required to preserve the benefits of such treatment. Even if the real-world user population is older, and has more comorbidities than that studied in clinical trials, it does not seem to question statin effectiveness, unlike the compliance issues that are common with these drugs. Pharmacoepidemiology also allows the detection and the evaluation of risks associated with statin use. Beyond the known and measured adverse drug reactions of statins found in clinical trials, cholesterol being ubiquitous and involved in the metabolism of many molecules or hormones, risks of statins can be varied and sometimes difficult to evaluate.

Disclosure of interest

Authors have no competing interest to declare

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Figure

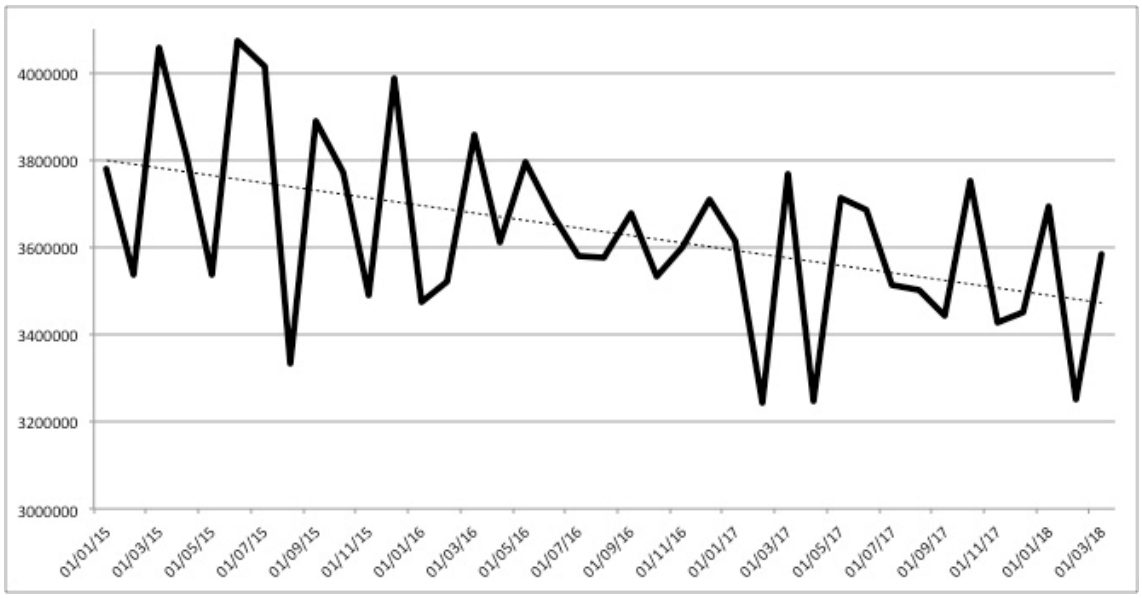

Figure 1. Monthly dispensing of statins (alone or in combination) in France from 01/01/2015 to 31/03/2018. Dotted line: trend curve obtained by linear regression.