

# Pharmacoepidemiology of statins

Julien Bezin, Nicholas Moore

## ▶ To cite this version:

Julien Bezin, Nicholas Moore. Pharmacoepidemiology of statins. Thérapie, 2019, 74 (2), pp.261-269.  $10.1016/\rm{j.therap.2019.01.004}$ . hal-03210815

## HAL Id: hal-03210815 https://hal.science/hal-03210815

Submitted on 22 Oct 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# THERAPIES HEADING: PHARMACOEPIDEMIOLOGY EPUB AHEAD OF PRINT THEN NUMBER 2 (March April) 2019

## Pharmacoepidemiology of statins

Pharmacoepidemiology of statins

### Julien Bezin<sup>a,\*</sup>, Nicholas Moore<sup>b</sup>

<sup>a</sup> Bordeaux population health research center, team pharmacoepidemiology, UMR 1219, INSERM, univ. Bordeaux, 33076 Bordeaux, France
 <sup>b</sup> Bordeaux PharmacoEpi, INSERM CIC1401, INSERM CR1219, université & CHU de Bordeaux, 33076 Bordeaux, France

Received 24 September 2018; accepted 29 September 2018

\***Corresponding author.** Service de pharmacologie médicale, université de Bordeaux, BP36, 146, rue Léo Saignat, 33076 Bordeaux cedex, France. *E-mail adress*: julien.bezin@u-bordeaux.fr

#### 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 stating 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 stating 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 metaanalyses 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 stating but without clinically relevant consequences [84]. Populationwide 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 drugdrug 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: statinfibrate 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 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

#### References

[1] Adedinsewo D, Taka N, Agasthi P, Sachdeva R, Rust G, Onwuanyi A. Prevalence and factors associated with statin use among a nationally representative sample of US adults: national health and nutrition examination survey, 2011-2012. Clin Cardiol 2016;39:491-6.

[2] Assurance maladie. Usage des statines : une structure de consommation à améliorer, un potentiel d'économies majeur pour le système de soins - Point d'information. 29 mai 2013. https://www.ameli.fr/fileadmin/user\_upload/documents/29052013\_DP\_Usage\_statines\_mai\_2013\_ vdef.pdf. [Accessed 15 January 2019 (13 pp.)].

[3] Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.

[4] Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61.

[5] Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013 jan 31(1):CD004816.

[6] US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, et al. Statin use for the primary prevention of cardiovascular disease in adults: US preventive services task force recommendation statement. JAMA 2016;316:1997-2007.

[7] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999-3058.

[8] Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009;338:b2376.

[9] Mitka M. Statin therapy in primary CVD prevention remains a hot-button topic for some. JAMA 2011;306:2077-8.

[10] Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010;170:1024-31.

[11] Redberg RF, Katz MH. Statins for primary prevention: the debate is intense, but the data are weak. JAMA 2016;316:1979-81.

[12] Godlee F. Lessons from the controversy over statins. Lancet 2017;389:1100-1.

[13] Gurwitz JH, Go AS, Fortmann SP. Statins for primary prevention in older adults: uncertainty and the need for more evidence. JAMA 2016;316:1971-2.

[14] Bonnet F, Poulizac P, Joseph JP. Safety and efficacy of statins. Lancet 2017;389:1097-8.

[15] Elseviers M, Wettermark B, Almarsdóttir AB, Andersen M, Benko R, Bennie M, et al. Drug utilization research: methods and applications. First Edition. April 2016. John Wiley & Sons Eds USA, Print ISBN:9781118949788 Online ISBN:9781118949740.

[16] DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG. Evolution of statin prescribing 1994-2001: a case of agism but not of sexism? Heart 2003;89:417-21.

[17] Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. JAMA 2013;310:2451-2.

[18] Walley T, Folino-Gallo P, Stephens P, Van Ganse E. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003. Br J Clin Pharmacol 2005;60:543-51.

[19] O'Keeffe AG, Nazareth I, Petersen I. Time trends in the prescription of statins for the primary prevention of cardiovascular disease in the United Kingdom: a cohort study using The Health Improvement Network primary care data. Clin Epidemiol 2016;8:123-32.

[20] ANSM. Analyse des ventes de médicaments en France en 2013 - Rapport. Juin 2014.Analyse des ventes de médicaments en France en 2013 - Rapport. Juin 2014.

https://ansm.sante.fr/var/ansm\_site/storage/original/application/3df7b99f8f4c9ee634a6a9b0946243 41.pdf. [Accessed 15 January 2019 (36 pp.)].

[21] Assurance maladie. Medic'AM. Données mensuelles et annuelles sur les médicaments remboursés par l'Assurance Maladie. 2018. http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/medicament/medic-am/medic-am-mensuel-2018.php. [Accessed 15 January 2019].

[22] Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004;57:86-92.

[23] Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of STelevation myocardial infarction. J Am Coll Cardiol 2016;67:1235-50.

[24] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients

presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur J Heart 2018;39:119-77.

[25] Chung SC, Sundström J, Gale CP, James S, Deanfield J, Wallentin L, et al. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. BMJ 2015;351:h3913.

[26] Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636-48.

[27] Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Hoffman E, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med 2013;126:693-700 e1.

[28] Salvo F, Bezin J, Bosco-Levy P, Letinier L, Blin P, Pariente A, et al. Pharmacological treatments of cardiovascular diseases: evidence from real-life studies. Pharmacol Res 2017;118:43-52.

[29] Sjölander M, Eriksson M, Glader EL. Few sex differences in the use of drugs for secondary prevention after stroke: a nationwide observational study. Pharmacoepidemiol Drug Saf 2012;21:911-9.

[30] Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C, et al. Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. Circ Cardiovasc Qual Outcomes 2010;3:530-7.

[31] Pereira M, Araújo C, Dias P, Lunet N, Subirana I, Marrugat J, et al. Age and sex inequalities in the prescription of evidence-based pharmacological therapy following an acute coronary syndrome in Portugal: the EURHOBOP study. Eur J Prev Cardiol 2014;21:1401-8.

[32] Gamboa CM, Safford MM, Levitan EB, Mann DM, Yun H, Glasser SP, et al. Statin underuse and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. Am J Med Sci 2014;348:108-14.

[33] Homer K, Boomla K, Hull S, Dostal I, Mathur R, Robson J. Statin prescribing for primary prevention of cardiovascular disease: a cross-sectional, observational study. Br J Gen Pract 2015;65:e538-44.

[34] van Staa TP, Smeeth L, Ng ES, Goldacre B, Gulliford M. The efficiency of cardiovascular risk assessment: do the right patients get statin treatment? Heart 2013;99:1597-602.

[35] Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study. PLoS One 2013;8:e67611.

[36] Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-sex differences in statin use and low-density lipoprotein cholesterol control among people with diabetes mellitus in the reasons for geographic and racial differences in stroke study. J Am Heart Assoc 2017 May 10;6(5). pii: e004264.

[37] Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. BMC Health Serv Res 2014;14:414.

[38] Macías Saint-Gerons D, de la Fuente Honrubia C, Montero Corominas D, Gil MJ, de Andrés-Trelles F, Catalá-López F. Standard and intensive lipid-lowering therapy with statins for the primary prevention of vascular diseases: a population-based study. Eur J Clin Pharmacol 2014;70:99-108.

[39] Gulliford M, Ravindrarajah R, Hamada S, Jackson S, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study. Age Ageing 2017;46:1001-5.

[40] Johansen ME, Green LA. Statin use in very elderly individuals, 1999-2012. JAMA Intern Med 2015;175:1715-6.

[41] Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7.

[42] Wahl C, Gregoire JP, Teo K, Beaulieu M, Labelle S, Leduc B, et al. Concordance, compliance and adherence in healthcare: closing gaps and improving outcomes. Healthc Q 2005;8:65-70.

[43] Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. BMJ 2016;353:i3305.

[44] Franklin JM, Krumme AA, Tong AY, Shrank WH, Matlin OS, Brennan TA, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. Pharmacoepidemiol Drug Saf 2015;24:1105-13.

[45] Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. Arch Intern Med 2007;167:847-52.

[46] Warren JR, Falster MO, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. Pharmacoepidemiol Drug Saf 2013;22:1298-307.

[47] Citarella A, Kieler H, Sundström A, Linder M, Wettermark B, Berglind IA, et al. Family history of cardiovascular disease and influence on statin therapy persistence. Eur J Clin Pharmacol 2014;70:701-7.

[48] Bezin J, Pariente A, Lassalle R, Dureau-Pournin C, Abouelfath A, Robinson P, et al. Use of the recommended drug combination for secondary prevention after a first occurrence of acute coronary syndrome in France. Eur J Clin Pharmacol 2014;70:429-36.

[49] Mathews R, Wang TY, Honeycutt E, Henry TD, Zettler M, Chang M, et al. Persistence with secondary prevention medications after acute myocardial infarction: Insights from the TRANSLATE-ACS study. Am Heart J 2015;170:62-9.

[50] Gencer B, Rodondi N, Auer R, Räber L, Klingenberg R, Nanchen D, et al. Reasons for discontinuation of recommended therapies according to the patients after acute coronary syndromes. Eur J Intern Med 2015;26:56-62.

[51] Turner RM, Yin P, Hanson A, FitzGerald R, Morris AP, Stables RH, et al. Investigating the prevalence, predictors, and prognosis of suboptimal statin use early after a non-ST elevation acute coronary syndrome. J Clin Lipidol 2017;11:204-14.

[52] Sessa M, Rafaniello C, Scavone C, Mascolo A, di Mauro G, Fucile A, et al. Preventable statin adverse reactions and therapy discontinuation. What can we learn from the spontaneous reporting system? Expert Opin Drug Saf 2018;17:457-65.

[53] Romanelli RJ, Jukes T, Segal JB. Compliance after switching from branded to generic statins. Pharmacoepidemiol Drug Saf 2014;23:1093-100.

[54] Wawruch M, Zatko D, Wimmer G Jr, Luha J, Hricak V Jr, Murin J, et al. Patient-related characteristics associated with non-persistence with statin therapy in elderly patients following an ischemic stroke. Pharmacoepidemiol Drug Saf 2017;26:201-07.

[55] Hickson RP, Robinson JG, Annis IE, Killeya-Jones LA, Korhonen MJ, Cole AL, et al. Changes in statin adherence following an acute myocardial infarction among older adults: patient predictors and the association with follow-up with primary care providers and/or cardiologists. J Am Heart Assoc 2017 Oct 19;6(10). pii: e007106.

[56] Markovitz AA, Holleman RG, Hofer TP, Kerr EA, Klamerus ML, Sussman JB. Effects of guideline and formulary changes on statin prescribing in the veterans affairs. Health Serv Res 2017;52:1996-2017.

[57] Olufade T, Zhou S, Anzalone D, Kern DM, Tunceli O, Cziraky MJ, et al. Initiation patterns of statins in the 2 years after release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guideline in a large US health plan. J Am Heart Assoc 2017 May 4;6(5). pii: e005205.

[58] Nissen SE. Statin denial: an internet-driven cult with deadly consequences. Ann Intern Med 2018;168:381-2.

[59] Saib A, Sabbah L, Perdrix L, Blanchard D, Danchin N, Puymirat E. Evaluation of the impact of the recent controversy over statins in France: the EVANS study. Arch Cardiovasc Dis 2013;106:511-6.

[60] Bezin J, Francis F, Nguyen NV, Robinson P, Blin P, Fourrier-Réglat A, et al. Impact of a public media event on the use of statins in the French population. Arch Cardiovasc Dis 2017;110:91-8.

[61] Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. European heart journal 2016;37:908-16.

[62] Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016;353:i3283.

[63] Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016;316:1289-97.

[64] Mortensen MB, Nordestgaard BG. Comparison of five major guidelines for statin use in primary prevention in a contemporary general population. Ann Intern Med 2018;168:85-92.

[65] Wei L, Ebrahim S, Bartlett C, Davey PD, Sullivan FM, MacDonald TM. Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials. BMJ 2005;330(7495):821.

[66] Bezin J, Klungel OH, Lassalle R, Dureau-Pournin C, Moore N, Pariente A. Medications recommended for secondary prevention after first acute coronary syndrome: effectiveness of treatment combinations in a real-life setting. Clin Pharmacol Ther 2018;103:1038-46.

[67] Smith DH, Johnson ES, Boudreau DM, Cassidy-Bushrow AE, Fortmann SP, Greenlee RT, et al. Comparative effectiveness of statin therapy in chronic kidney disease and acute myocardial infarction: a retrospective cohort study. Am J Med 2015;128:1252 e1-1252 e11.

[68] Sheng X, Murphy MJ, Macdonald TM, Wei L. Effectiveness of statins on total cholesterol and cardiovascular disease and all-cause mortality in osteoarthritis and rheumatoid arthritis. J Rheumatol 2012;39:32-40.

[69] Rannanheimo PK, Tiittanen P, Hartikainen J, Helin-Salmivaara A, Huupponen R, Vahtera J, et al. Impact of statin adherence on cardiovascular morbidity and all-cause mortality in the primary

prevention of cardiovascular disease: a population-based cohort study in Finland. Value Health 2015;18(6):896-905.

[70] Talbot D, Delaney JAC, Sandfort V, Herrington DM, McClelland RL. Importance of the lipid-related pathways in the association between statins, mortality, and cardiovascular disease risk: the multi-ethnic study of atherosclerosis. Pharmacoepidemiol Drug Saf 2018;27:365-72.

[71] Grimaldi-Bensouda L, Rossignol M, Danchin N, Dallongeville J, Bruckert E, Banayan J, et al. Real-life effectiveness of statins in the prevention of first acute coronary syndrome in France: a prospective observational study. Int J Cardiol 2013;169:271-5.

[72] Neumann A, Maura G, Weill A, Ricordeau P, Alla F, Allemand H. Comparative effectiveness of rosuvastatin versus simvastatin in primary prevention among new users: a cohort study in the French national health insurance database. Pharmacoepidemiol Drug Saf 2014;23:240-50.

[73] Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013 Oct;34(38):2940-8.

[74] Zhang H, Plutzky J, Shubina M, Turchin A. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. Ann Intern Med 2017;167(4):221-7.

[75] De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol 2014;78:684-98.

[76] Alpérovitch A, Kurth T, Bertrand M, Ancelin ML, Helmer C, Debette S, et al. Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study. BMJ 2015;350:h2335.

[77] O'Brien EC, Greiner MA, Xian Y, Fonarow GC, Olson DM, Schwamm LH, et al. Clinical Effectiveness of statin therapy after ischemic stroke: primary results from the statin therapeutic area of the patient-centered research into outcomes stroke patients prefer and effectiveness research (PROSPER) study. Circulation 2015;132:1404-13.

[78] Korhonen MJ, Ruokoniemi P, Ilomäki J, Meretoja A, Helin-Salmivaara A, Huupponen R. Adherence to statin therapy and the incidence of ischemic stroke in patients with diabetes. Pharmacoepidemiol Drug Saf 2016;25:161-9.

[79] Lee M, Saver JL, Wu YL, Tang SC, Lee JD, Rao NM, et al. Utilization of statins beyond the initial period after stroke and 1-year risk of recurrent stroke. J Am Heart Assoc 2017 Aug 2;6(8). pii: e005658.

[80] Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011;26:546-50.

[81] de Keyser CE, Leening MJ, Romio SA, Jukema JW, Hofman A, Ikram MA, et al. Comparing a marginal structural model with a Cox proportional hazard model to estimate the effect of time-dependent drug use in observational studies: statin use for primary prevention of cardiovascular disease as an example from the Rotterdam Study. Eur J Epidemiol 2014;29(11):841-50.

[82] Atar D, Ong S, Lansberg PJ. Expanding the evidence base: comparing randomized controlled trials and observational studies of statins. Am J Ther 2015;22:e141-50.

[83] Faillie JL, Montastruc F, Montastruc JL, Pariente A. Pharmacoepidemiology and its input to pharmacovigilance. Therapie 2016;71:211-6.

[84] Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018 Jul 14;39(27):2526-39.

[85] Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2017;389(10088):2473-81.

[86] Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society consensus panel statement on assessment, aetiology and management. Eur Heart J 2015;36:1012-22.

[87] Khouri C, Lepelley M, Mallaret M, Roustit M, Cracowski JL. Muscle pain and statin, pharmacological or nocebo effect? Therapie 2018 Sep;73(4):359-61.

[88] Coste J, Billionnet C, Rudnichi A, Pouchot J, Dray-Spira R, Giral P, et al. Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France. Eur J Prev Cardiol 2018:2047487318776831.

[89] Lamoureux F, Duflot T, French Network of Pharmacogenetics (RNPGX). Pharmacogenetics in cardiovascular diseases: state of the art and implementation-recommendations of the French National Network of Pharmacogenetics (RNPGx). Therapie 2017;72:257-67.

[90] Montastruc F, Benevent J, Rousseau V, Chebane L, Bondon-Guitton E, Durrieu G, et al. Statins and diabetes: is there any difference between the different statins? Pharmacoepidemiol Drug Saf 2017;26:1296-7.

[91] Thakker D, Nair S, Pagada A, Jamdade V, Malik A. Statin use and the risk of developing diabetes: a network meta-analysis. Pharmacoepidemiol Drug Saf 2016;25(10):1131-49.

[92] Betteridge DJ, Carmena R. The diabetogenic action of statins - mechanisms and clinical implications. Nat Rev Endocrinol 2016;12:99-110.

[93] Corrao G, Monzio Compagnoni M, Rea F, Merlino L, Catapano AL, Mancia G. Clinical significance of diabetes likely induced by statins: evidence from a large population-based cohort. Diabetes Res Clin Pract 2017;133:60-8.

[94] Clarke AT, Johnson PC, Hall GC, Ford I, Mills PR. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin in UK GPRD cohort. PLoS One 2016;11:e0151587.

[95] Chen GL, Hsiao FY, Dong YH, Shen LJ, Wu FL. Statins and the risk of liver injury: a population-based case-control study. Pharmacoepidemiol Drug Saf 2014;23:719-25.

[96] Erie JC, Pueringer MR, Brue SM, Chamberlain AM, Hodge DO. Statin use and incident cataract surgery: a case-control study. Ophthalmic epidemiol 2016;23:40-5.

[97] AREDS2 Research Group, Al-Holou SN, Tucker WR, Agrón E, Clemons TE, Sperduto RD, et al. The association of statin use with cataract progression and cataract surgery: the AREDS2 report number 8. Ophthalmology 2016;123(4):916-7.

[98] Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340:c2197.

[99] Klein BE, Klein R, Lee KE, Grady LM. Statin use and incident nuclear cataract. JAMA 2006;295:2752-8.

[100] Kostis JB, Dobrzynski JM. Statin use and cataract. JAMA Ophthalmol 2014;132:363-4.

[101] Lai CL, Shau WY, Chang CH, Chen MF, Lai MS. Statin use and cataract surgery: a nationwide retrospective cohort study in elderly ethnic Chinese patients. Drug Saf 2013;36:1017-24.

[102] Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I. Association of statin use with cataracts: a propensity score-matched analysis. JAMA Ophthalmol 2013;131:1427-34.

[103] Strandberg TE, Tarkkanen A. Cataracts and statin use: cause and effect not confirmed. JAMA Ophthalmol 2014;132(3):365.

[104] Bezin J, Mansiaux Y, Noize P, Salvo F, Bégaud B, Pariente A. Use of lipid-lowering drugs and the risk of cataract: a population-based nested case-control study. Clin Pharmacol Ther 2018 Jul 10. doi: 10.1002/cpt.1176.

[105] Bezin J, Bosco-Levy P, Pariente A. False-positive results in pharmacoepidemiology and pharmacovigilance. Therapie 2017;72(4):415-20.

[106] Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham heart study. Psychosom Med 2005;67:24-30.

[107] Kelley BJ, Glasser S. Cognitive effects of statin medications. CNS Drugs 2014;28:411-9.

[108] Ancelin ML, Carrière I, Barberger-Gateau P, Auriacombe S, Rouaud O, Fourlanos S, et al. Lipid lowering agents, cognitive decline, and dementia: the three-city study. J Alzheimers Dis 2012;30:629-37.

[109] Joosten H, Visser ST, van Eersel ME, Gansevoort RT, Bilo HJ, Slaets JP, et al. Statin use and cognitive function: population-based observational study with long-term follow-up. PLoS One 2014 Dec26;9(12):e115755.

[110] Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J Gen Intern Med 2015;30:348-58.

[111] Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin therapy and risk of acute memory impairment. JAMA Intern Med 2015;175:1399-405.

[112] Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-80.

[113] Moulis G, Béné J, Sommet A, Sailler L, Lapeyre-Mestre M, Montastruc JL, et al. Statininduced lupus: a case/non-case study in a nationwide pharmacovigilance database. Lupus 2012;21:885-9.

[114] de Jong HJI, Cohen Tervaert JW, Lalmohamed A, de Vries F, Vandebriel RJ, van Loveren H, et al. Pattern of risks of rheumatoid arthritis among patients using statins: A cohort study with the clinical practice research datalink. PLoS One 2018;13:e0193297.

[115] Do C, Huyghe E, Lapeyre-Mestre M, Montastruc JL, Bagheri H. Statins and erectile dysfunction: results of a case/non-case study using the French Pharmacovigilance System Database. Drug Saf 2009;32:591-7.

[116] Bateman BT, Hernandez-Diaz S, Fischer MA, Seely EW, Ecker JL, Franklin JM, et al. Statins and congenital malformations: cohort study. BMJ 2015;350:h1035.

[117] McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. Pharmacoepidemiol Drug Saf 2017;26:843-52.

[118] Bakhai A, Rigney U, Hollis S, Emmas C. Co-administration of statins with cytochrome
P450 3A4 inhibitors in a UK primary care population. Pharmacoepidemiol Drug Saf 2012;21:48593.

[119] Morival C, Westerlynck R, Bouzille G, Cuggia M, Le Corre P. Prevalence and nature of statin drug-drug interactions in a university hospital by electronic health record mining. Eur J Clin Pharmacol 2018;74:525-34.

[120] Bellosta S, Corsini A. Statin drug interactions and related adverse reactions: an update. Expert Opin Drug Saf 2018;17:25-37.

[121] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003;289:1681-90.

[122] Mesgarpour B, Gouya G, Herkner H, Reichardt B, Wolzt M. A population-based analysis of the risk of drug interaction between clarithromycin and statins for hospitalisation or death. Lipids Health Dis 2015;14:131.

[123] Choi NK, Chang Y, Choi YK, Hahn S, Park BJ. Signal detection of rosuvastatin compared to other statins: data-mining study using national health insurance claims database. Pharmacoepidemiol Drug Saf 2010;19:238-46.





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.