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ORIGINAL REPORT

Comparative effectiveness of rosuvastatin versus simvastatin in primary prevention among new users: a cohort study in the French national health insurance database

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ABSTRACT

Purpose Using the French claims database (Système National d'Information Inter-Régimes de l'Assurance Maladie) linked to the hospital discharge database (Programme de Médicalisation des Systèmes d'Information), this observational study compared the effectiveness of rosuvastatin and simvastatin prescribed at doses with close LDL-cholesterol-lowering potency on all-cause mortality and cardiovascular and cerebrovascular diseases (CCDs) in primary prevention.

Methods This historical cohort included patients with no prior CCD, aged 40–79 years, who initiated statin therapy with rosuvastatin 5 mg or simvastatin 20 mg in 2008–2009 in general practice. Follow-up started after a 1-year period used to select patients who regularly received the initial treatment.

In an intention-to-treat analysis, patients were followed up to December 2011. In a per-protocol analysis, they were censored prematurely when they discontinued their initial treatment. Adjustment for baseline covariates (age, deprivation index, comedications, comorbidities, prior hospital admissions) was carried out by a Cox proportional hazards model. In the per-protocol analysis, estimation was done by "inverse probability of censoring weighting" using additional time-dependent covariates. Analyses were gender-specific.

Results A total of 106 941 patients initiated statin therapy with rosuvastatin 5 mg and 56 860 with simvastatin 20 mg. Mean follow-up was 35.8 months. For both genders and both types of analyses, the difference in incidence rates of mortality and/or CCD between rosuvastatin 5 mg and simvastatin 20 mg users was not statistically significant after adjustment (e.g., for CCD and/or mortality in men, in intention-to-treat analysis HR = 0.94 [95% CI = 0.85–1.04], in per-protocol analysis HR = 0.98 [0.87–1.10]).

Conclusions The results of this real-life study based on medico-administrative databases do not support preferential prescription of rosuvastatin compared to simvastatin for primary prevention of CCD. © 2013 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

KEY WORDS—rosuvastatin; simvastatin; comparative effectiveness; primary prevention; inverse probability of censoring weighting; SNIIRAM (Système National d'Information Inter-Régimes de l'Assurance Maladie); pharmacoepidemiology; pharmacoepidemiology

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INTRODUCTION

With the increasing prevalence of diabetes and obesity, prevention of cardiovascular and cerebrovascular diseases (CCDs), still a leading cause of mortality and morbidity in industrialized countries, has far-reaching consequences for public health including healthcare budgets.[1–4]

There is clear-cut evidence of the benefit of statins in individuals with a clinical history of coronary heart disease.[5–12] In patients without established CCD, that is, in the context of primary prevention, placebo-controlled clinical trials and their meta-analyses have shown that statins reduce the risks of major vascular events in the short term and long term, and all-cause mortality in the long term,[13–20] in people both at high risk or low risk of cardiovascular diseases.[21,22]

Differences between individual statins have been found in their potency to reduce low density lipoprotein cholesterol (LDL-C) and achieve lipid-lowering

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goals in both randomized trials[23–25] and observational studies.[26–29] Rosuvastatin is known to induce a more marked reduction in LDL-C than other statins.[30–32] However, a meta-analysis of 14 clinical trials found that the reduction of cardiovascular events was proportional to the absolute reduction in LDL cholesterol (LDL-C) with an approximately linear relationship and this from the first year of treatment.[15]

To date, clinical trials have not provided any direct evidence of the superior efficacy of rosuvastatin compared with other statins in terms of reduction of clinical endpoints such as CCD. Observational studies comparing different statin regimens for CCD primary prevention, including rosuvastatin[33–35] or not,[36–38] have reported inconsistent results, partly depending on the endpoints examined and the methods used. Nevertheless, further benefit on clinical endpoints has been demonstrated with the use of more intensive statin therapy compared with standard therapy.[39–44]

As evidence is lacking in general practice when directly comparing, in primary prevention, rosuvastatin to older statins with generic versions such as the widely used simvastatin, we compared the effectiveness of rosuvastatin 5 mg versus simvastatin 20 mg, the most commonly prescribed dosages upon treatment initiation in France, to reduce CCD or all-cause mortality.

METHODS

Study design and data source

A historical cohort study was performed on health spending reimbursement data from the French national health insurance system (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIRAM) linked to the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information). The French national health insurance covers the entire French population (65.3 million inhabitants in 2012) and is divided into several specific schemes including the general scheme (75% of the population). In the SNIIRAM database, comprehensive data are available for all reimbursements of the general scheme, including patient demographic data such as age, gender, and vital status, as well as prescriber characteristics.[45] The medical indication for outpatient reimbursements is not available but the patient's status with respect to 100% reimbursement of care related to a severe and costly long-term disease (LTD) is recorded, in particular the LTD diagnosis encoded in the International Classification of Diseases, 10th edition (ICD-10).[46]

Study population

All patients of the French national health insurance general scheme (excluding overseas departments), aged 40–79 years, who started statin therapy with rosuvastatin 5 mg or simvastatin 20 mg (no prescriptions of any statins in the previous 24 months) during the period 2008–2009, were included (Figure 1). Patients with an initial prescription from a physician other than a self-employed general practitioner (GP) were excluded as well as patients with ischemic heart disease (hospital discharge or LTD diagnosis ICD-10 codes: I20–25), cerebrovascular disease (I60–69), intracranial and intraspinal phlebitis and thrombophlebitis (G08), or hemiplegia (G81) prior to initiation of treatment or during the first year of treatment, constituting the selection period. Patients who changed to another dose of the initial statin or who switched to another statin during this 1-year selection period and patients who did not fill at least one prescription for the initial treatment in each of the first three 4-month periods were excluded. Follow-up started after this selection period and ended at the latest in December 2011.

Definition and identification of study outcomes

The study outcomes assessed during follow-up were as follows: (1) all-cause mortality and (2) the composite of all-cause mortality and hospitalization for ischemic CDD, that is, acute ischemic heart disease (primary or secondary hospital discharge diagnosis ICD-10 codes: I21–24) or ischemic stroke (I63, I65, I66).

Covariates

Baseline covariates. Baseline covariates included age at the start of treatment, gender, the deprivation index of the patient's area of residence (calculated for 30 500 French *communes* as in Rey *et al.*[47] but with socioeconomic data from 2008), comedications (use of anticoagulants, antiplatelet agents, antihypertensive and antidiabetic drugs), hypertension LTD and heart disease LTD (i.e., severe heart failure, severe cardiac arrhythmia, valvular heart disease, severe congenital heart disease), comorbidities identified by hospital discharge/LTD diagnoses and prescriptions for specific drugs (use of antidepressants, Alzheimer's disease, chronic obstructive pulmonary disease, end-stage renal disease, recent cancer), and hospital admissions (for cardiac or vascular disease, or other reasons) observed up until the end of the selection period. All baseline covariates are listed in Table 1.

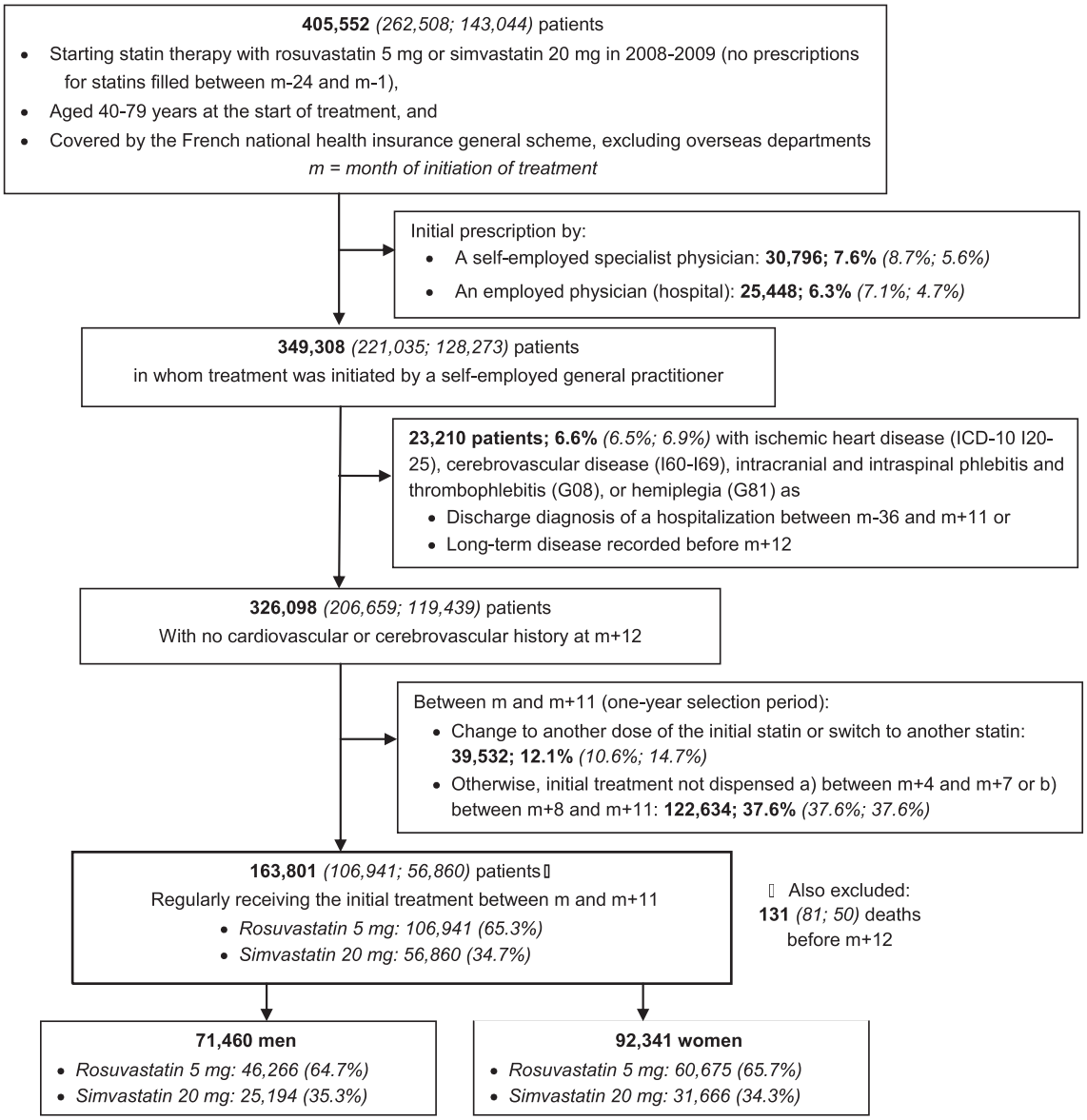

Figure 1. Study population flow chart. Values in parentheses refer to patients who initiated statin therapy with rosuvastatin 5 mg and simvastatin 20 mg, respectively

As the databases did not indicate the patient smoking status, we searched the databases for dispensing of nicotine replacement therapy and hospital discharge diagnoses related to tobacco use (ICD-10 codes F17, Z71.6 and Z72.0) during the selection period. As only a small proportion of tobacco users could be identified in this way, this variable was not used for model adjustment.

Time-dependent covariates. A time-dependent version was calculated for each of the baseline covariates Additional time-dependent covariates were lipid assessment and any statin prescription by a physician other than the initial prescriber (self-employed GPs, self-employed specialist physicians, and employed physicians, mainly hospital physicians).

Data analysis

Intention-to-treat analysis. Patients were followed until outcome, loss to follow-up (12 consecutive months without *any* drug delivery) or December 2011, whichever occurred first. This comparison was carried out by fitting a Cox proportional hazards model including the initial treatment and the baseline

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Table 1. Baseline characteristics of patients starting treatment with rosuvastatin 5 mg compared with simvastatin 20 mg (including information on the 1-year selection period following the start of treatment)

	Total ($N = 163\,801$)			Men ($N = 71\,460$)			Women ($N = 92\,341$)		
Characteristics	Rosuvastatin 5 mg ($n = 106\,941$; %)	Simvastatin 20 mg ($n = 56\,860$; %)	p-value	Rosuvastatin 5 mg ($n = 46\,266$; %)	Simvastatin 20 mg ($n = 25\,194$; %)	p-value	Rosuvastatin 5 mg ($n = 60\,675$; %)	Simvastatin 20 mg ($n = 31\,666$; %)	p-value
Period of study entry			<0.0001			<0.0001			<0.0001
1st half of 2008	24.0	25.2		24.1	25.5		24.0	25.0	
2nd half of 2008	22.4	22.8		22.7	22.7		22.2	23.0	
1st half of 2009	29.5	26.1		29.4	26.1		29.6	26.2	
2nd half of 2009	24.1	25.8		23.8	25.7		24.3	25.9	
Demographic and socioeconomic characteristics									
Male gender	43.3	44.3	<0.0001	100.0	100.0	—	0.0	0.0	—
Age at study entry (years)			<0.0001			0.8282			0.1680
40–44	5.3	5.0		4.6	4.6		7.5	7.2	
45–49	9.0	8.6		7.8	8.2		10.9	10.7	
50–54	14.8	14.4		13.6	14.6		15.0	16.4	
55–59	19.8	19.7		18.7	17.8		19.0	17.2	
60–64	19.4	19.0		19.7	19.8		16.1	14.8	
65–69	12.8	13.0		14.5	13.8		12.4	12.5	
70–74	10.9	11.4		12.4	12.5		10.5	11.1	
75–79	7.9	8.9		8.7	8.7		8.7	10.0	
Deprivation index of area of residence			<0.0001			<0.0001			<0.0001
1 (least deprived)	26.9	25.6		27.7	26.3		26.3	25.0	
2	19.5	18.8		19.2	18.7		19.7	18.9	
3	16.1	15.7		16.1	15.5		16.1	15.9	
4	17.3	17.9		17.1	17.8		17.5	18.0	
5 (most deprived)	19.0	20.8		18.8	20.6		19.2	21.0	
Area with very few inhabitants †	1.1	1.2		1.1	1.2		1.2	1.2	
Comedications and LTDs observed up to one year after the start of treatment in month m									
Anticoagulants in (m, $m+1$)	7.6	7.4	0.3251	8.1	8.0	0.6296	7.2	7.0	0.3216
Antiplatelet agents in (m, $m+11$)	16.0	18.5	<0.0001	19.9	23.3	<0.0001	13.0	14.8	<0.0001
Antihypertensive drug in (m, $m+11$)	56.6	60.1	<0.0001	56.0	59.5	<0.0001	57.1	60.6	<0.0001
Antidiabetic drug in (m, $m+11$)	18.4	23.4	<0.0001	22.0	27.2	<0.0001	15.7	20.4	<0.0001
Heart disease LTD			0.2290			0.8494			0.1462
At $m-6$	1.8	1.7		2.3	2.3		1.4	1.3	
At $m+11$, but not at $m-6$	0.6	0.7		0.8	0.8		0.5	0.6	
Hypertension LTD*			<0.0001			<0.0001			<0.0001
At $m-6$	4.1	4.9		4.3	5.2		4.0	4.8	
At $m+11$, but not at $m-6$	1.9	2.1		2.3	2.3		1.7	1.9	
Comorbidities at $m+11$									
Antidepressant drug in (m, $m+11$)	18.4	18.1	0.1507	11.5	11.7	0.5476	23.7	23.3	0.1642
Alzheimer's disease ‡	0.44	0.59	<0.0001	0.31	0.40	0.0392	0.53	0.74	0.0001
Asthma/COPD ‡	8.6	8.7	0.4884	8.8	8.8	0.9171	8.4	8.6	0.3226
End-stage renal disease ‡	0.021	0.025	0.5986	0.030	0.036	0.6973	0.013	0.016	0.7515
Cancer (not prior to $m-24$) ‡	2.2	2.0	0.1187	2.6	2.6	0.9929	1.8	1.6	0.0148

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Hospital admissions between $m-12$ and $m+11$										
In $(m-12, m-1)$ for cardiac or vascular reason[§]	2.0	2.1	0.2190	2.3	2.4	0.2691	1.7	1.8	0.6059	
In $(m, m+11)$ for cardiac or vascular reason ($\geq$1 night) [§]	1.9	2.0	0.5219	2.6	2.6	0.9400	1.4	1.5	0.5193	
In $(m, m+11)$ for a reason other than cardiac or vascular reason ($\geq$1 night) [§]	10.0	9.9	0.6307	9.8	9.8	0.8753	10.1	9.9	0.4491	

Abbreviations: LTD, long-term disease (entitled to 100% reimbursement); COPD, chronic obstructive pulmonary disease.
[*]Heart disease LTD: severe heart failure, severe arrhythmia, valvular heart disease, severe congenital heart disease.
[†]The deprivation index is not available for these areas.
[‡]These comorbidities were identified on hospital discharge and LTD diagnoses and/or prescriptions for specific drugs.
[§]Hospital admission for cardiac or vascular reason: Diagnosis-related group classified into fields of activity "cardiology (excluding vascular catheterization)," "vascular catheterization," "peripheral vascular."[47]

covariates. The proportional hazards assumption was checked by testing for correlation of the scaled Schoenfeld residuals with time.[48]

Per-protocol analysis. Patients were followed until outcome, loss to follow-up, deviation from initial treatment (change to another dose of the initial statin or switch to another statin, temporary discontinuation for more than six consecutive months or permanent discontinuation) or December 2011, whichever occurred first. More precisely, censoring occurred 3 months after treatment discontinuation. This artificial censoring must be considered informative, as patients with worsening cardiovascular or cerebrovascular disease tend to switch statin therapy and those with a poor prognosis tend to stop *all* statin therapy. Bias due to this informative censoring can be eliminated or reduced by inverse probability of censoring weighting.[49–51] Each subject's contribution to the risk set for a given month t is weighted by the inverse of the conditional probability of remaining uncensored up to t based on baseline covariates and history of time-dependent covariates. These conditional probabilities were obtained by fitting a polytomous logistic regression model with the type of deviation from initial treatment as the dependent variable (grouped into three modalities: no deviation, i.e., no artificial censoring; switches; temporary discontinuation or permanent discontinuation). The past 6-month history of time-dependent covariates was used. Separate models were built for each initial treatment. To stabilize these weights, they were multiplied by the conditional probability of remaining uncensored up to t based on baseline covariates only. Finally, these stabilized weights were used in a pooled logistic regression model, treating each person-month as an observation and explaining the outcome based on the (initial) treatment and the baseline covariates. Confidence intervals were estimated by bootstrap with 500 replications.[52] Under the assumptions of no unmeasured confounding, correct model specification, and positivity,[53] the treatment effect measured in this model has a causal interpretation: the effect that would have been observed if all patients had remained on their initial treatment.

Two-sided p-values are reported for all analyses, and results are considered statistically significant for $p < 0.05$. All statistical analyses were carried out with SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Baseline characteristics were compared between the two treatment groups using χ^2 tests, and

analyses were therefore performed separately for men and women.

RESULTS

Description of the study population

The study included 163 801 patients, 71 460 men and 92 341 women (Figure 1). Among men, 46 266 (64.7%) patients initiated on rosuvastatin 5 mg and among women, 60 675 (65.7%) patients (Table 1). Compared with simvastatin 20 mg at baseline, new users of rosuvastatin 5 mg were younger (mean age: 60.0 vs. 60.4 years), less often lived in the most deprived areas (19.0% vs. 20.8%) and were less often prescribed antidiabetic drugs (18.4% vs. 23.4%), antihypertensive drugs (56.6% vs. 60.1%), and antiplatelet agents (16.0% vs. 18.5%).

A total of 109 495 (66.8%) patients presented at least one of the following conditions at baseline: antihypertensive drug use, antiplatelet agent use, hypertension or heart disease LTD, hospitalizations for cardiac or vascular disease in the year before treatment initiation. This proportion was lower among new users of rosuvastatin 5 mg compared with simvastatin 20 mg (65.3% vs. 69.8%).

With the use of the criterion related to smoking, 2.29% of men starting treatment with rosuvastatin 5 mg were identified as smokers versus 2.42% of men starting simvastatin 20 mg (crude ratio: 0.95 [95%CI: 0.86–1.04], age-adjusted ratio: 0.93 [0.84–1.02]). These proportions for women were 1.27% and 1.14%, respectively (crude ratio: 1.12 [0.99–1.27], age-adjusted ratio: 1.10 [0.97–1.24]). Analyses were therefore gender-specific.

Deviation from initial treatment during follow-up (beyond 1 year after treatment initiation)

During follow-up, 7.4% of patients in the overall study population changed to another dose of the initial statin, 6.8% switched to another statin, 7.3% discontinued the initial statin therapy for more than 6 months before resuming treatment, and 18.7% discontinued the initial statin therapy without subsequently resuming treatment (if several types of deviation, only the first one was counted). Table 2 indicates the proportions of treatment deviations according to initial treatment and gender.

Intention-to-treat analysis

In the overall study population, the mean duration from start of treatment to end of follow-up was 35.8 months (range: 13–48 months). Among men initiating statin therapy with rosuvastatin 5 mg, the incidence rate per 1000 person-years was 8.5 for mortality and 13.0 for mortality or hospitalization for ischemic CCD (Table 3). For men initiating statin therapy with simvastatin 20 mg, these rates were 9.9 and 15.0, respectively. After adjustment, rosuvastatin 5 mg users had similar incidence rates as simvastatin 20 mg users: for men, the hazard ratio (HR) for mortality was 0.93 [0.83–1.04] and the HR for mortality or hospitalization for ischemic CCD was 0.94 [0.85–1.03]; for women, the HR was 0.99 [0.86–1.14] and 0.96 [0.86–1.08], respectively. There was no evidence against proportional hazards. In the

Table 2. Treatment deviation in patients initiated on rosuvastatin 5 mg and simvastatin 20 mg, respectively

	Total		Men		Women	
Type of first deviation from initial treatment during follow-up *	Rosuvastatin 5 mg *n* (%)	Simvastatin 20 mg *n* (%)	Rosuvastatin 5 mg *n* (%)	Simvastatin 20 mg *n* (%)	Rosuvastatin 5 mg *n* (%)	Simvastatin 20 mg *n* (%)
Change to another dose of the initial statin	7284 (6.8)	4825 (8.5)	3474 (7.5)	2129 (8.5)	3810 (6.3)	2696 (8.5)
Switch to another statin	6101 (5.7)	4962 (8.7)	2631 (5.7)	2214 (8.8)	3470 (5.7)	2748 (8.7)
Temporary discontinuation for more than 6 months †	7825 (7.3)	4107 (7.2)	3241 (7.0)	1747 (6.9)	4584 (7.6)	2360 (7.5)
Permanent discontinuation not preceded by switches or temporary discontinuation ‡	20 409 (19.1)	10 303 (18.1)	8324 (18.0)	4256 (16.9)	12 085 (19.9)	6047 (19.1)
All types	34 335 (38.9)	19 372 (42.5)	14 196 (38.2)	8217 (41.0)	20 139 (39.5)	11 155 (43.8)

*Between the end of the 1-year selection period with regular prescriptions for the initial treatment and the end of the study period.
†Followed by a new prescription for statin (i.e., an interval of more than 6 months between two consecutive prescriptions).
‡Before the end of the study period (i.e., with an interval of more than one month between (1) the month at which the last prescription for the initial treatment should have ended and (2) the end of the study period).

Table 3. Event rates in patients starting treatment with rosuvastatin 5 mg compared to simvastatin 20 mg

		Intention-to-treat analysis †					Per-protocol analysis ‡		
Study cohorts	Drug	Person-years *	Events	Incidence rate per 1000 person-years (95%CI)	Incidence rate ratio (rosuvastatin 5 mg vs simvastatin 20 mg) (95%CI)	Adjusted HR (rosuvastatin 5 mg vs simvastatin 20 mg) (95%CI)	Person-years *	Events	Adjusted HR (rosuvastatin 5 mg vs simvastatin 20 mg) (95%CI)
Men									
Mortality									
	Rosuvastatin 5 mg	91 705	775	8.5 (7.9–9.1)	0.85 (0.76–0.96)	0.93 (0.83–1.04)	74 800	530	1.04 (0.90–1.19)
	Simvastatin 20 mg	50 006	495	9.9 (9.1–10.8)			40 033	296	
Mortality and/or hospitalization for ischemic cardiovascular and cerebrovascular diseases§									
	Rosuvastatin 5 mg	91 268	1186	13.0 (12.3–13.8)	0.87 (0.79–0.95)	0.94 (0.85–1.03)	74 618	850	0.98 (0.87–1.10)
	Simvastatin 20 mg	49 721	745	15.0 (13.9–16.1)			39 926	497	
Women									
Mortality									
	Rosuvastatin 5 mg	120 344	551	4.6 (4.2–5.0)	0.93 (0.81–1.07)	0.99 (0.86–1.14)	96 874	319	0,99 (0.82–1.20)
	Simvastatin 20 mg	63 040	310	4.9 (4.4–5.5)			49 530	177	
Mortality and/or hospitalization for cardiovascular and cerebrovascular diseases§									
	Rosuvastatin 5 mg	120 122	767	6.4 (5.9–6.9)	0.91 (0.81–1.02)	0.96 (0.86–1.08)	96 773	484	0.93 (0.80–1.08)
	Simvastatin 20 mg	62 897	443	7,0 (6,4–7,7)			49 478	287	

CI, confidence interval; HR, hazard ratio.
*Excluding the 1-year selection period.
†Traditional estimation in a multivariate Cox model.
‡Inverse probability of censoring weighting (IPCW) estimation in a multivariate Cox model.
§Ischemic cardiovascular and cerebrovascular diseases: acute ischemic heart disease (primary or secondary hospital discharge diagnosis ICD-10 codes: I21–24) or ischemic stroke (I63, I65, I66)

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analysis of the composite outcome in men (1931 events), the power to detect an HR of 0.87 (or 1.15) was 83.5%.[48]

Per-protocol analysis

The mean duration of follow-up was 4.7 months shorter than for intention-to-treat analysis and fewer events were counted (Table 3). For both genders and both outcomes, none of the HRs comparing rosuvastatin 5 mg to simvastatin 20 mg was significantly different from 1.

DISCUSSION

This historical cohort study comprised a total of nearly 165 000 patients with no prior history of CCD but with potential cardiovascular risk factors. Our main findings are as follows: (1) channelling rosuvastatin 5 mg over simvastatin 20 mg toward an healthier population was observed in France for primary prevention of CCD in general practice; (2) in this context, after adjustment, performed separately for each gender, no statistically significant difference in incidence rates of hospitalization for ischemic CCD and all-cause mortality was found between rosuvastatin 5 mg users and simvastatin 20 mg users.

Regarding the observed prescribing trend, all pharmaceutical presentations of rosuvastatin and simvastatin were already available on the French market during the inclusion period of this study. The latest French guidelines for dyslipidemia management were published in 2005: rosuvastatin should be reserved for patients with an inadequate response or intolerance to other statins. In 2010, these guidelines were updated, stating that rosuvastatin 5 mg could be prescribed as an alternative to simvastatin 40 mg for patients with moderate hypercholesterolemia.[54] Scientific debate following the publication in late 2008 of JUPITER trial results may also have influenced physicians' prescribing practices.[18,55] Moreover, to confine our analysis to primary prevention, we only included patients with initial prescription from a GP but no prior history of CCD. Lastly, because rosuvastatin has been promoted as the most potent statin, we assumed it would be preferentially prescribed for high-risk patients. However, the opposite trend was observed, as rosuvastatin users presented lower levels of observable risk factors at baseline compared with simvastatin users, especially age, deprivation index and known cardiovascular risk factors such as diabetes and hypertension. Other recent studies in European countries have described a similar trend.[56–58]

When comparing the two statins, meta-analyses of clinical trials and observational studies have found a slight superiority of rosuvastatin 5 mg to lower LDL-C compared with simvastatin 20 mg. However, both are usually grouped together as "standard statin therapy" when compared with higher dosages of these two statins classified as "intensive standard therapy."[30,31,39–44] No clinical trials including rosuvastatin and simvastatin have directly compared these statins in terms of cardiovascular morbidity and mortality. In contrast, three observational studies reported conflicting results.[33–35]

In a French case–control study, Grimaldi-Bensoudal *et al.*[35] found that, compared with no statin use, rosuvastatin displayed the lowest risk (adjusted OR = 0.49 [0.35–0.68]) of first non-fatal myocardial infarction followed by simvastatin (0.62 [0.46–0.84]), for any use within 24 months. Myocardial infarction cases and controls were respectively obtained from cardiology centers and from GPs using a pharmacoepidemiological information system (PGRx).

In their historical cohort study based on the Dutch PHARMO database of 76 147 new statin users (27 752 simvastatin and 8088 rosuvastatin), Heintjes *et al.*[33] reported that rosuvastatin users had a 29% significantly lower incidence rate of a composite endpoint of CCD than simvastatin users (HR = 0.71 [0.54–0.94]). Patients with coronary and cerebrovascular events during the year prior to initiation of statin therapy were excluded and mean follow-up was 55 weeks.

In a historical cohort study of claims data, Motsko *et al.*[34] directly compared rosuvastatin new users ($n = 45\,510$) to "other statin" new users including simvastatin ($n = 73\,884$; 21.1% of the "other statin" cohort) with a mean follow-up of 180 days. Patients with non-cardiovascular life-threatening illness were excluded. No significant difference was observed between rosuvastatin and simvastatin users in terms of coronary and cerebrovascular events (HR = 0.97 [0.89–1.05]).

Ultimately, the inconclusive results provided by these observational studies may be due to methodological differences and limitations. Above all, in these two cohort studies, the statin dosage regimens compared were not equivalent,[30,31] which can be expected to impact on the observed differences.[15]

One of the strengths of our study is that it was conducted on two comprehensive and *a posteriori* linked databases providing complementary data, healthcare reimbursements and hospital discharge diagnoses, which have been prospectively and independently collected.

To our knowledge, this is the first study to compare two statins head-to-head with, notably, a close potency

to lower LDL-C, on clinical vascular endpoints and all-cause mortality in a large population of patients with no prior CCD.

The same results were obtained using both intention-to-treat analysis and per-protocol analysis. In per-protocol analysis, which is intended to remove the impact of deviation from initial treatment, the inverse probability of censoring weighting approach was used. It is clearly one of the strengths of this study, as it attempts to correct for time-varying selection bias due to artificial censoring, which depends both on treatment history and may share common causes with the outcome, i.e., censoring may be informative.[59,60]

The sample size was sufficiently large and the mean follow-up, including the selection period, was 35.8 months, which can be considered to be sufficiently long enough to capture potential differences in actual cardiovascular event rates between statins.[15]

The analyses were adjusted for the baseline characteristics to avoid overestimating the effectiveness of rosuvastatin compared with simvastatin in this study. Nevertheless, data on body mass index, smoking, family disposition, and other cardiovascular risk factors such as diet, blood pressure, physical activity, or baseline high density lipoprotein cholesterol and LDL-C levels were not available. However, the proportion of smokers seemed to be lower among men using rosuvastatin compared with men using simvastatin, according to the use of nicotine replacement therapy and a smoking-related hospital discharge diagnosis. If this trend, demonstrated for observable confounding factors and smoking, also existed for all unmeasured confounders, the calculated effectiveness of rosuvastatin would be overestimated compared with simvastatin. Potential unmeasured confounders, such as physicians' prescribing practices or LDL-C-independent mechanisms of statins,[61–63] were also not taken into account. It is likely that some measured factors, such as deprivation index or comedications, would be somewhat correlated with certain unmeasured confounders. However, because of the observational nature of our study, residual confounding therefore cannot be excluded.

As nearly one-half of all patients initially selected did not regularly use their initial treatment during the first year, we therefore only followed patients who regularly filled their initial treatment during this period, considered to be "regular users." The results of our study therefore cannot be generalized to the first year after treatment initiation or to patients who do not regularly use their initial treatment during this year. The same applies to broader populations because of the differences among countries in lifestyle, environment, genetics, and their impact on cardiovascular disease.[1,2,64] Conducting this study on patients with higher cardiovascular risk or as secondary prevention may however not have reached the same conclusions, as, in the JUPITER clinical trial, patients were at an increased risk of heart disease (nearly half had metabolic syndrome) and were also assigned to rosuvastatin 20 mg daily.[18]

Finally, as all values covered by the confidence interval could not be rejected, cost-effectiveness considerations must be taken into account to decide whether changes in medical practice should be advocated.

In conclusion, the results of this real-life study based on medico-administrative databases do not support preferential prescription of rosuvastatin compared with simvastatin for primary prevention of CCD.

CONFLICT OF INTEREST

The authors are all employees of a public institution, the French National Health Insurance, which funded this study, and have no conflicts of interest with the pharmaceutical industry.

KEY POINTS

- Channelling of rosuvastatin 5 mg over simvastatin 20 mg toward a younger and healthier population was observed in general practice in France during the period 2008–2009 for primary prevention of cardiovascular and cerebrovascular diseases.
- After adjustment, no statistically significant difference in effectiveness on mortality or mortality and/or cardiovascular and cerebrovascular diseases was observed between rosuvastatin 5 mg and simvastatin 20 mg users.
- In per-protocol analysis, informative censoring is an important and often ignored issue, but which can be adequately addressed by using inverse probability of censoring weighting.

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