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The cardiovascular safety of oral alitretinoin. A population-based cohort study involving 19,513 patients exposed to oral alitretinoin

Running head: The cardiovascular safety of oral alitretinoin

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Research ethics: The study protocol was authorized and approved by the French National Public Drug Agency (ANSM, Agence Nationale de Sécurité du Médicament) on January 24, 2019.

Data access and cleaning methods: Direct access to the whole database was granted by ANSM to our research consortium. The authors (FP, FB, EN, EO and AD) had full access to all the data that were used to generate the study population. Different metrics were used to check data completeness at population level, including the number of patients exposed (compared to the expected number) and the stability of reimbursement frequencies over time.

Data availability: The protocol and the statistical code are available on justified request. Under French law and regulations, databases extracted from the SNDS cannot be made available.

What's already known about this topic?

- Several cardiac events have been reported during alitretinoin treatment, but the risk associated with alitretinoin exposure has not been explored in a comparative study on large scale.

What does this study add?

- Among 19,513 patients exposed to oral alitretinoin in France, 64 (0.3%) experienced coronary artery disease, ischemic stroke or peripheral artery disease requiring revascularisation during their alitretinoin treatment, and 292 (1.5%) in the 2 years following initiation.
- The standardized incidence of atherothrombotic events among patients exposed to alitretinoin, compared to the general population, did not suggest an increased risk associated with oral alitretinoin.

Summary

Background: Oral alitretinoin is a retinoid used for severe chronic hand eczema. Although caution is recommended for patients with uncontrolled dyslipidaemia or cardiovascular risk factors, the actual atherothrombotic risk has not been investigated thus far.

Objectives: Our aim was to detect any excess of atherothrombotic events among patients exposed to alitretinoin, during the treatment or in the 2 years following initiation.

Methods: Using the French Health Insurance database, we compared the number of patients having had an atherothrombotic event (coronary artery disease, ischemic stroke or peripheral artery disease requiring revascularisation) in the population exposed to oral alitretinoin versus the general population of the same age, gender and baseline cardiovascular risk, using standardized morbidity ratios (SMRs).

Results: Between 2009 and 2017, 19,513 patients were exposed to oral alitretinoin in France. Sixty-four (0.3%) patients had an atherothrombotic event while on alitretinoin. Patients receiving alitretinoin experienced no more atherothrombotic events than the general population: patients without cardiovascular risk factors or previous atherothrombotic events reached a SMR of 0.65, 95%CI [0.26-1.34] during alitretinoin treatment, and 1.21, 95%CI [0.90-1.59] in the 2 years following initiation; patients with cardiovascular risk factors or previous atherothrombotic events reached a SMR of 0.82, 95%CI [0.60-1.08] during alitretinoin treatment, and 0.95, 95%CI [0.82-1.09] in the 2 years following initiation. Taken separately, SMRs for each outcome did not increase either.

Conclusions: These data from an exhaustive nationwide population-based study did not support an increase in the incidence of atherothrombotic events under alitretinoin, regardless of the baseline cardiovascular risk of the patient.

Introduction

Oral alitretinoin (Toctino®) is a retinoid used for severe chronic hand eczema. Hand eczema is a recurrent inflammatory skin condition, closely associated with atopic dermatitis, contact allergy and irritant exposure.^{1,2} The 1-year prevalence is nearly 10%, with one third of individuals reporting onset of hand eczema before the age of 20.^{1,3} Alitretinoin is the only oral drug approved for the treatment of severe chronic hand eczema unresponsive to potent topical corticosteroids among adults. Alitretinoin should be discontinued after 12 weeks of treatment among non-responding patients, and by 24 weeks in case of response. Further courses of alitretinoin can be envisaged in the event of relapse. Oral alitretinoin is marketed worldwide (Europe, Israel, Canada, Australia, South Korea...) but is not approved in the United States.

As a retinoid, alitretinoin can increase triglyceride and low-density lipoprotein (LDL)-cholesterol levels. Alitretinoin-induced dyslipidaemia is among the most frequently reported adverse events in the clinical trials, in the post-marketing surveillance, and in real-world studies.⁴⁻⁶ Thus, it theoretically entails an atherogenic risk, mostly in case of long-term dyslipidaemia.⁷ Several acute coronary syndromes have also been reported, leading to a pharmacovigilance signal from the French drug agency for major adverse cardiovascular events.^{8,9} The summary of product characteristics in all countries contra-indicates oral alitretinoin in case of non-controlled dyslipidaemia, and recommends monitoring serum cholesterol and triglycerides. Additional recommendations specific to each country have been issued for patients with cardiovascular risk factors.¹⁰⁻¹² However, no study has been conducted to evaluate the risk of atherothrombotic event among patients receiving alitretinoin.

Our primary aim, using real-world data from a large nationwide comparative cohort study, was to screen for an excess of atherothrombotic events among patients receiving oral alitretinoin in France between 2011 and 2017, during their treatment and in the 2 years following initiation, compared to the general population. Furthermore, the real-world characteristics of oral alitretinoin use, including the profiles of patients exposed and the duration of courses, were described as a secondary aim.

Methods

Data sources and study population

This study was conducted using the French National Health Insurance database (SNDS, Système National des Données de Santé, formerly SNIIRAM, Système national d'information inter-régimes de l'Assurance maladie).^{13,14} This database covers 98.8% of the population living in France (around 66 million inhabitants), and contains exhaustive data on all reimbursements for health-related expenditures, including dispensed drugs with date of dispensation, as well as any investigation (imagery, surgery, blood analysis, etc.), and individual anonymous data on sociodemographic characteristics (e.g. age, gender, area of residence, date of death). Information about all hospitalisations in a public or private hospital is also provided: dates of hospital admission and hospital discharge, diagnoses (using ICD-10 codes, International Classification of Diseases, 10th revision) and expensive drugs prescribed during hospital stays. Severe, costly, long-term diseases are recorded, with diagnoses encoded according to ICD-10, because they give entitlement to 100% health insurance coverage. All subjects who had at least one reimbursement for oral alitretinoin between November 9, 2009 (date of market release) and December 31, 2017 were included.

As a reference group, we used a sample of the general French population, named Échantillon Généraliste des Bénéficiaires (EGB). EGB is a 1/97th random, dynamic, representative sample of the SNDS database, has the same structure, and contains the same variables as the mother database. All individuals included in the EGB in the 2011-2014 period were followed from January 1, 2014 to their first atherothrombotic event, death, or until censoring on December 31, 2016 at the latest.

Drug exposure

The exposure of interest was oral alitretinoin (Anatomical, Therapeutics and Chemical classification code, D11AH04). A course of alitretinoin was considered as discontinued if no issue occurred in the 4 months following a given issue. Two time windows for exposure were considered. First, patients were followed for the whole course of alitretinoin, from initiation to 30 days after the last issue in the course, regardless of its duration. Second, the follow-up was extended to 2 years following alitretinoin initiation for patients who discontinued alitretinoin before 2 years.

Atherothrombotic events

The primary outcome was a composite endpoint for coronary artery disease (hospitalized acute coronary syndrome or angina pectoris, or myocardial revascularisation), hospitalized ischemic

stroke, and peripheral artery disease requiring limb revascularisation. These outcomes were identified from a combination of hospital discharge codes and revascularisation procedure codes. The algorithm is detailed in Table S1. Only the first atherothrombotic event occurring after inclusion was considered.

The secondary outcomes were each individual item in the composite endpoint: coronary artery disease, ischemic stroke or peripheral artery disease requiring revascularisation.

Statistical analysis

The cohort was stratified in order to contrast levels of cardiovascular risk assessed at initiation of alitretinoin, arbitrarily classified as low or high as follows: in case of a previous atherothrombotic event (those considered in the outcome), or at least one cardiovascular risk factor (dyslipidaemia, hypertension, diabetes, tobacco use or obesity, identified using a previously developed algorithm)¹⁵ recorded within the 3 years preceding alitretinoin initiation, patients were considered as having a high baseline cardiovascular risk. If not, they were considered as having a low baseline cardiovascular risk.

For the comparative analysis, the numbers of first events in the alitretinoin cohort and the reference population were compared using indirect standardization within each group of baseline cardiovascular risk. In case of a low baseline cardiovascular risk, the ratio between the number of observed events and the number of expected events was calculated in the strata defined by gender and age (1-year periods). In case of a high baseline cardiovascular risk, two additional items were used for standardization: dyslipidaemia and history of atherothrombotic events. “Observed over expected” ratios (standardized morbidity ratios [SMRs]) were calculated with their 95% confidence interval (CI). Standardized incidence was estimated for patients initiating alitretinoin from January 1, 2011, to avoid a channeling bias in the first year of marketing of the drug (*i.e.* the profiles of patients receiving a given drug can be different in the period immediately following its marketing and at a later stage). Patients receiving alitretinoin were censored on December 31, 2017.

As a sensitivity analysis for dose response, time-dependent Cox proportional hazards models were used to estimate hazards ratios (HRs) with 95% CIs for atherothrombotic events associated with the cumulative dose of alitretinoin, divided into 4 categories. A multivariate analysis was performed as attempt to minimize confounding.

P-values < .05 were considered to be statistically significant. Statistical analyses were performed with SAS Enterprise Guide Software (SAS Institute, Inc., USA) version 7.1.

This study followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guideline.

Results

Patients and treatment characteristics

Between November 9, 2009 and December 31, 2017, 19,513 patients received oral alitretinoin in France. Fifty-seven percent were men, and median age at alitretinoin initiation was 49 years (interquartile range [IQR], 36-59). Regarding cardiovascular risk at initiation, 317 (1.6%) had an atherothrombotic event in the previous 3 years, and 7140 (36.6%) had at least one cardiovascular risk factor (dyslipidaemia for 18.8% of patients). Their baseline cardiovascular risk was defined as high. In contrast, 12,373 patients had a baseline cardiovascular risk considered as low. The characteristics of the cohort exposed to alitretinoin are presented in Table 1.

The median duration of alitretinoin treatment was 3 months (IQR, 1-6). Ten percent continued alitretinoin beyond 12 months, and 2% beyond 24 months. Overall, 87% of the patients received a single course of alitretinoin. Patients having additional courses of alitretinoin observed a median time-lapse of 8.5 months before the subsequent course.

Atherothrombotic events

During alitretinoin treatment, 64 (0.3%) patients had an atherothrombotic event: 41 coronary artery disease, 10 ischemic stroke, and 13 peripheral artery disease requiring revascularisation. Seven events occurred among patients with a low baseline cardiovascular risk. In the 2 years following alitretinoin initiation, 292 (1.5%) patients had an atherothrombotic event. Coronary artery disease accounted for 66.4% of the atherothrombotic events encountered. The type of event (coronary artery disease, ischemic stroke or peripheral artery disease requiring revascularisation) according to the patients' baseline cardiovascular risk is presented in Table 2. Their distribution per trimester is presented in Figure S1. The duration of alitretinoin courses was similar among patients having experienced an atherothrombotic event and those who did not (data not shown). The baseline characteristics of the cases, including their cardiovascular risk factors, are described in Table 3.

Deaths

Twelve patients died while on alitretinoin. No atherothrombotic event was identified. Two patients had pulmonary embolism, 2 cerebral haemorrhage, 3 cancer, 1 intestinal adhesions with obstruction, 1 vehicle accident, 1 farm accident, 1 shot to death. One patient died outside hospital without identified reason (causes of deaths occurring outside hospital in 2017 were not yet recorded in the SNDS database).

Comparative atherothrombotic risk

The standardized incidence of atherothrombotic events was estimated for the 16,784 patients initiating oral alitretinoin from January 1, 2011 to December 31, 2017. The reference population was composed of 488,251 individuals, representing a total of 17,471,507 person-months, experiencing 8,259 atherothrombotic events between 2014 and 2016. Their characteristics are presented in Table S2. SMRs (Standardized Morbidity Ratios) were used to compare the incidence of atherothrombotic events between patients exposed to alitretinoin and the standardized general population.

During alitretinoin treatment, the patients had no more atherothrombotic events than the general population. Patients with a low baseline cardiovascular risk had a SMR of 0.65, 95%CI [0.26-1.34]. Patients with a high baseline cardiovascular risk had a SMR of 0.82, 95%CI [0.60-1.08].

In the 2 years following alitretinoin initiation, the patients had no more atherothrombotic events than the general population. Patients with a low baseline cardiovascular risk had a SMR of 1.21, 95%CI [0.90-1.59]. Patients with a high baseline cardiovascular risk had a SMR of 0.95, 95%CI [0.82-1.09].

SMRs for coronary artery disease, ischemic stroke and peripheral artery disease requiring revascularisation and numbers of observed versus expected events for each outcome are presented in Figure 1.

Intriguingly, fewer ischemic strokes were observed in the 2 years following alitretinoin initiation than in the general population among individuals with a high baseline cardiovascular risk (SMR=0.57, 95%CI [0.35-0.88]). However, the risk of stroke did not differ during alitretinoin treatment, nor among people with a low baseline cardiovascular risk. A supplementary standardization on the number of visits to specialist physicians (excepting dermatologists) in the previous two years, as a proxy for health-seeking tendency in the population exposed to alitretinoin, did not alter this result (Table S3).

Dose-response relationship

In univariate analysis, patients with higher cumulative dose of alitretinoin had fewer atherothrombotic events. In multivariate analysis, the risk of atherothrombotic events was not modified by the cumulative dose received (Table S4).

Discussion

These data from an exhaustive population-based study did not support an increase in the incidence of atherothrombotic events induced by alitretinoin, regardless of the baseline cardiovascular risk of the patients. A possible direct deleterious effect of alitretinoin was sought during treatment, and any delayed proatherogenic effect, which could be induced by dyslipidaemia secondary to alitretinoin, was investigated by extending the time window up to 2 years. No atherothrombotic risk resulting from alitretinoin was evidenced, whether during alitretinoin treatment or in the following 2 years. No dose-response relationship with cumulative use was evidenced either. We distinguished the risks for coronary artery disease, ischemic stroke and peripheral artery disease requiring revascularisation. We were specifically concerned about a risk of cardiac adverse events because dyslipidaemia has a prominent role in coronary artery disease,¹⁶ and because cardiac events are more frequent in the age range of patients receiving alitretinoin.¹⁷ The focus on cardiac events among patients with at least one cardiovascular risk factor or a previous atherothrombotic event did not evidence an increased risk resulting from alitretinoin: 0.5% of subjects developed coronary artery disease during alitretinoin treatment, SMR=0.83, 95%CI [0.56-1.17], and 2.2% in the two years following initiation, SMR=1.04, 95%CI [0.87-1.23].

Surprisingly, in the 2 years following alitretinoin initiation, patients had half the risk of stroke of the general population (SMR=0.57, 95%CI [0.35-0.88]). First, we searched for an underlying biological hypothesis to support this result. Alitretinoin has the particular feature of binding to the retinoid X receptors (RXRs) in addition to retinoid acid receptors (RARs), whereas other systemic retinoids, such as isotretinoin or all-trans-retinoic acid, are selective ligands for RARs. Treatment with RXR ligands has shown some efficacy in reducing the progression of atherosclerosis in apolipoprotein E knockout mice, a well-established animal model of atherosclerosis.¹⁸

Furthermore, treatment with alitretinoin increased bleeding time in mice, and inhibited platelet aggregation and thrombus formation in vitro.^{19,20} However, because the SMR did not decrease during alitretinoin treatment, an antithrombotic effect was not considered plausible. In addition, as the apparent decreased risk of stroke was not found for coronary artery disease or peripheral artery

disease, we assumed that an atheroprotective effect was not likely. Second, a healthy user effect was envisaged.²¹ Patients who consult their dermatologist to receive alitretinoin could have a higher propensity to seek consultation with other physicians, for instance for cardiovascular prevention. Therefore, we standardized the incidence of atherothrombotic events taking account of the number of visits to a specialist physician, excepting dermatologists, in the previous 2 years, as a proxy for health-seeking tendency.²¹ This additional standardization did not substantially modify the SMRs (Table S3). In particular, the SMR for stroke in the 2 years following alitretinoin initiation among patients with a high baseline cardiovascular risk was unchanged (SMR=0.54, 95%CI [0.33-0.84]). Third, alitretinoin prescription could provide an opportunity to check for cardiovascular risk factors, resulting in a decreased risk of stroke. Regarding the two main types of preventive drugs for stroke, however, we observed that the proportion of patients receiving antihypertensive drugs or antiplatelet agents rose by only 0.6 and 0.3% respectively in the year following alitretinoin initiation, compared to the previous year. Hence, we concluded to a probable false-positive inference in this context of multiple comparisons. Comparing a large number of outcomes using the usual significance threshold of .05 increases the risk of falsely concluding that a significant effect is present when none exists.²² However, whether or not to adjust for multiple comparisons in epidemiology remains controversial, since reducing the type I error for null associations increases the type II error for those associations that are not null.²³

Our study has several strengths. First, our database is comprehensive, in that it includes all issues of alitretinoin in France since its marketing, and all hospitalized atherothrombotic events and revascularisations. The absence of selection bias in the population included, and the absence of attrition bias (as there was no loss to follow-up) resulted in a reliable estimation of the cardiovascular risk of alitretinoin. Second, comparing the incidence of atherothrombotic events across 16,784 patients exposed to alitretinoin yielded maximum power to detect a risk. This enabled the study of each outcome individually, and a stratification according to the baseline cardiovascular risk of the patients. Third, we used a French reference population of 488,251 subjects as a comparator. As alitretinoin is the only systemic treatment for chronic hand eczema, and topical corticosteroids are used for a wide range of diseases, we did not choose another drug as a comparator for alitretinoin. In addition, there is no data supporting a different cardiovascular risk among people with hand eczema compared to the general population. Therefore, we chose to use the general population to compare the atherothrombotic risk in the alitretinoin cohort.

Standardization enabled the reference population to have the same distribution in terms of age, gender, dyslipidaemia and history of atherothrombotic events as the alitretinoin cohort (other cardiovascular risk factors being taken into account by the stratification). Fourth, this study fills a gap in medical knowledge, as no previous study has investigated the cardiovascular risk associated with oral alitretinoin, despite the cardiovascular events reported, and the signal issued by the pharmacovigilance system. Only one study has explored a trigger effect of isotretinoin, another oral retinoid, on cardiovascular and cerebrovascular events. But isotretinoin, approved for acne treatment, is prescribed to younger people, and the risk was evaluated only over the first 5 months under isotretinoin. No increased risk was identified, without the possibility of concluding to safety or to a lack of power.²⁴

Some limitations should be discussed. First, biological data are lacking in our database, and this could have led to a misclassification bias for dyslipidaemia. Dyslipidaemia was considered only when it involved issues of statins or fibrates, while the risk could be higher among untreated dyslipidaemic patients. If measuring the plasma lipid level before alitretinoin initiation had led to prescribe more hypolipidemic agents among patients receiving alitretinoin, the misclassification bias could have been differential between the alitretinoin cohort and the general population. In the 3 months preceding alitretinoin initiation, 11,321 (58%) patients had a measure of plasma cholesterol or triglyceride levels, but only 252 (1.3%) subsequently started statins or fibrates. In addition, patients receiving statins or fibrates had longer courses of alitretinoin (mean duration: 207 versus 174 days, $p < 10^{-3}$), which does not suggest the implementation of precautions for use among dyslipidaemic patients. Second, tobacco use and obesity are known to be under-reported in hospital discharge coding. However, this underestimation is likely to have affected the alitretinoin cohort and the reference population in similar manner. Third, the algorithms used to identify cardiovascular risk factors and atherothrombotic events in the SNDS database have not been validated. They were developed from reference coding instructions edited once a year to take new medications into account,²⁵ and algorithms developed by the French Drug Regulatory Agency which we used previously.¹⁵ Fourth, the subgroup analyses may have been underpowered because of the small number of events, in particular among patients at low baseline cardiovascular risk. However, according to the upper limit of the 95%CI for SMRs, we are confident (assuming a 5% risk of error) that the true risk of atherothrombotic events induced by alitretinoin is lower than

1.59 among low-risk patients, and lower than 1.09 among high-risk patients. Thus, our study results enabled us to rule out a major risk of atherothrombotic events induced by alitretinoin.

In summary, our population-based epidemiological study suggests that oral alitretinoin is not associated with an increased risk of atherothrombotic events, in the current context of short courses and plasma lipid monitoring. This result is reassuring and substantial, since reported cases of cardiovascular events have generated a debate in national drug agencies across Europe.

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Figure legends

Figure 1. Forest plot of the standardized morbidity ratios for atherothrombotic events in the alitretinoin cohort compared to the general population

The standardized incidence of atherothrombotic events was estimated for the 16,784 patients initiating oral alitretinoin from January 1, 2011 to December 31, 2017 in France.

CI: confidence interval ; Obs / Exp: Observed / Expected ; PAD: peripheral artery disease ; SMR: Standardized Morbidity Ratio.

^a In case of a cardiovascular risk factor or a previous atherothrombotic event within the 3 years preceding alitretinoin initiation, patients were considered as having a high baseline cardiovascular risk. If not, they were considered as having a low baseline cardiovascular risk.

Table 1. Baseline characteristics of the patients exposed to alitretinoin

Characteristics at initiation of alitretinoin, n (%)	Patients exposed to alitretinoin N=19,513
Gender, male	11,121 (57)
Age, years mean (sd)	48 (15.3)
Baseline cardiovascular risk	
Low	12,373 (63.4)
High	71,40 (36.6)
Cardiovascular risk factors ^a	
Hypertension	4,682 (24.0)
Dyslipidaemia	3,675 (18.8)
Diabetes	1,276 (6.5)
Tobacco use	1,243 (6.4)
Obesity	580 (3.0)
Number of cardiovascular risk factors ^{ab}	
0	12,373 (63.4)
1	4,059 (20.8)
2	2,084 (10.7)
3	792 (4.1)
4	172 (0.9)
5	33 (0.2)
Previous atherothrombotic events ^a	
Coronary artery disease	228 (1.2)
Ischemic stroke	46 (0.3)
Peripheral artery disease requiring revascularisation	62 (0.3)
None	19,196 (98.4)

^a in the 3 years preceding the initiation of alitretinoin

^b hypertension, dyslipidaemia, diabetes, tobacco use, obesity

Table 2. Frequency of atherothrombotic events according to the baseline cardiovascular risk

	During the courses of alitretinoin ^a , n (%)			Within 2 years following initiation of alitretinoin ^a , n (%)		
	CAD	Ischemic stroke	Revasc for PAD	CAD	Ischemic stroke	Revasc for PAD
Low baseline CV risk ^b	6 (0.05)	1 (0.01)	0	40 (0.32)	12 (0.10)	8 (0.06)
High baseline CV risk						
History of atherothrombotic event ^c	7 (2.2)	1 (0.31)	4 (1.3)	30 (9.4)	2 (0.63)	9 (2.82)
At least 1 CV risk factor ^d	28 (0.41)	8 (0.12)	9 (0.13)	124 (1.8)	25 (0.37)	42 (0.61)

CAD: coronary artery disease; CV: cardiovascular ; Revasc for PAD: peripheral artery disease requiring revascularisation.

^a only the first atherothrombotic event was considered

^b no CV risk factor and no history of atherothrombotic event in the previous 3 years

^c identified in the 3 years preceding alitretinoin initiation

^d without a history of atherothrombotic event in the previous 3 years

Table 3. Baseline characteristics of the patients experiencing an atherothrombotic event during alitretinoin treatment or in the 2 years following initiation

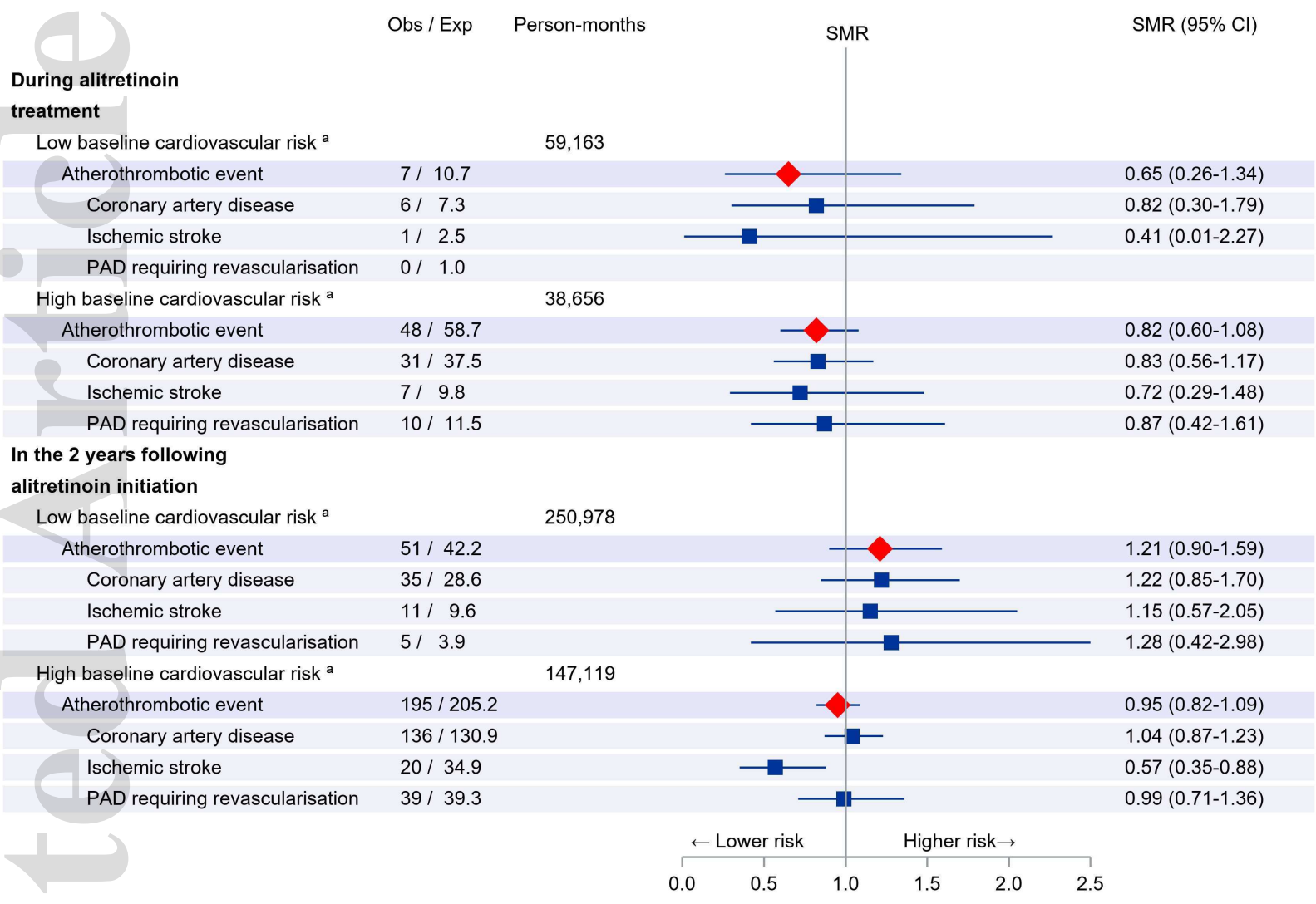
Baseline characteristics of the cases, n (%)	Atherothrombotic events ^a		
	Coronary artery disease n=194	Ischemic stroke n=39	PAD requiring revascularisation n=59
Gender, male	155 (79.9)	24 (61.5)	45 (76.2)
Age, years mean (sd)	62 (10.6)	64 (11.7)	64 (10.8)
Cardiovascular risk factors ^b			
Hypertension	121 (62.4)	22 (56.4)	41 (69.5)
Dyslipidaemia	103 (53.1)	17 (43.6)	34 (57.6)
Diabetes	54 (27.8)	8 (20.5)	12 (20.3)
Tobacco use	28 (14.4)	6 (15.4)	13 (22)
Obesity	22 (11.3)	0 (0)	3 (5.1)
Antiplatelet agent ^b	80 (41.2)	11 (28.2)	36 (61)
Number of cardiovascular risk factors ^{bc}			
0	43 (22.2)	12 (30.8)	10 (16.9)
1	53 (27.3)	9 (23.1)	17 (28.8)
2	41 (21.1)	10 (25.6)	15 (25.4)
3	39 (20.1)	8 (20.5)	14 (23.7)
4	14 (7.2)	0 (0)	1 (1.7)
5	4 (2.1)	0 (0)	2 (3.4)
Previous atherothrombotic events ^b			
All	31 (16)	2 (5.1)	9 (15.3)
Coronary artery disease	29 (14.9)	1 (2.6)	2 (3.4)
Ischemic stroke	1 (0.5)	1 (2.6)	2 (3.4)
PAD requiring revascularisation	3 (1.5)	1 (2.6)	7 (11.9)

PAD: peripheral artery disease.

^a only the first atherothrombotic event was considered

^b in the 3 years preceding the initiation of alitretinoin

^c hypertension, dyslipidaemia, diabetes, tobacco use, obesity



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Accept