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To cite this version:

Florence Poizeau, Emmanuel Nowak, Sandrine Kerbrat, Béranger Le Nautout, Catherine Droitcourt, et al.. Association Between Early Severe Cardiovascular Events and the Initiation of Treatment With the Anti-Interleukin 12/23p40 Antibody Ustekinumab. JAMA Dermatology, 2020, 156 (11), pp.1208-1215. 10.1001/jamadermatol.2020.2977 . hal-02960093

HAL Id: hal-02960093

https://hal.science/hal-02960093

Submitted on 18 Nov 2020

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Association Between Early Severe Cardiovascular Events and the Initiation of Treatment With the Anti-Interleukin 12/23p40 Antibody Ustekinumab

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Date of the first revision: May 20, 2020

Date of the second revision: June 12, 2020

Total word count: 2997

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Key points

Question: On the basis of results from previous trials and mechanistic models, concerns have been raised about the occurrence of severe cardiovascular events (SCEs) following the initiation of the anti-interleukin (IL)-12/23p40 monoclonal antibody ustekinumab.

Findings: Following a case-time-control analysis based on the French National Health Insurance database 2010-2016, we suggest that the initiation of anti-IL-12/23p40 could trigger acute coronary syndrome or stroke in patients with a high baseline cardiovascular risk.

Meaning: Ustekinumab treatment should be prescribed with caution to patients at high cardiovascular risk.

Keywords: cardiovascular, ustekinumab, biologic, case-time-control, health insurance database

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Abstract

Importance: Ustekinumab, a monoclonal antibody targeting interleukin (IL)-12/23, is effective in the treatment of moderate-to-severe psoriasis, psoriatic arthritis and Crohn's disease. In 2011, a meta-analysis of randomized trials alerted on a potential risk of severe cardiovascular event (SCE) within the first months after the initiation of anti-IL-12/23 antibodies.

Objective: To assess whether ustekinumab initiation triggers SCE.

Design: We conducted a case-time-control study. We defined the 'risk' period as the 6 months before the SCE, defined as acute coronary syndrome or stroke, and the 'reference' period as the 6 months before the risk period.

Setting: French National Health Insurance database, covering 66 million subjects.

Participants: All patients exposed to ustekinumab between 2010 and 2016, classified according to their cardiovascular risk level (high and low risk strata).

Exposure: The initiation of ustekinumab was screened in both periods.

Main outcome and measures: We assessed the odds-ratios (OR) for the risk of SCE after ustekinumab initiation.

Results: Among the 9290 patients exposed to ustekinumab, 179 experienced SCEs: 65 cases of acute coronary syndrome, 68 unstable angina and 46 stroke. Among patients with high cardiovascular risk, a significant association between ustekinumab initiation and SCE occurrence was identified (OR, 4.17; 95%CI, 1.19-14.59). Conversely, no statistically significant association was found among patients with low cardiovascular risk (OR, 0.30; 95%CI, 0.03-3.13).

Conclusions and relevance: From real-world data, we suggest that ustekinumab initiation could trigger SCE among patients with high cardiovascular risk. In line with the current mechanistic models for atherosclerotic disease, the period following anti-IL-12/23 initiation

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may be associated with atherosclerotic plaque destabilization via the Th17 inhibition. Although the study interpretation is limited by its observational design, these results should call for caution in the prescription of ustekinumab to patients with high cardiovascular risk.

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Introduction

Over the past 20 years, anti-cytokine therapies have transformed the management of many chronic immuno-inflammatory diseases including psoriasis, inflammatory rheumatic disorders, and inflammatory bowel disease. The recognition of atherosclerosis as an inflammatory process raises the question of the impact of these anti-cytokine therapies on atherosclerosis progression and cardiovascular thrombotic complications.[1–8] In psoriasis, major therapeutic successes have been obtained with antibodies blocking Tumor Necrosis Factor α (TNFα), IL-12, IL-23 and IL-17A/F.[9,10] However, their respective impact on atherosclerosis progression seems to differ.[2] A cardiovascular protective effect with long-term use of anti-TNFα drugs has been reported in several studies,[11–13] corroborating experiments in athero-prone mouse models reporting a pathogenic role of TNF-α.[14] Regarding the anti-IL12/23p40 therapies ustekinumab and briakinumab, a meta-analysis of randomized controlled trials in moderate-to-severe psoriasis in 2011 alerted on a possible excess of major adverse cardiovascular events compared to placebo-treated groups.[15–18] This warning is in line with experimental studies suggesting a protective role of the IL-23/IL-17 pathway on atherosclerotic plaque growth and vulnerability.[19–22] Following concerns about ischemic cardiovascular safety, briakinumab was withdrawn from further development, while ustekinumab was marketed.

The aim of this study, using large-scale real-world data, was to investigate whether ustekinumab can trigger severe cardiovascular events (SCE) during the 6-month period following treatment initiation.

Methods

Data source and population

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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).[23] This database covers 98% of the population living in France (around 66 million inhabitants), and includes anonymous individual sociodemographic data, exhaustive data on all reimbursements for health-related expenditures, dispensed drugs with date of issue, any investigation (imagery, surgery, blood analysis, etc.), and hospitalization discharge codes according to the International Classification of Diseases, 10th revision (ICD-10). Data from public and private practices are recorded in the same way. Severe, costly, long-term diseases are recorded, with diagnoses encoded according to ICD-10, because they give entitlement to 100% health insurance coverage.

From the entire SNDS database, we extracted all the subjects who had had at least one reimbursement for ustekinumab between April 1, 2010 (date of market release) and December 31, 2016. Thus, all patients included were incident users of ustekinumab. From this population, we selected patients who had a reported SCE.

Severe cardiovascular events

SCE cases were defined as either acute coronary syndrome (ICD-10 codes: I21 and I24) with hospitalization in intensive care unit (ICU), or ischemic stroke (ICD-10 codes: I63 and I64), whatever the hospitalization department, identified using the hospitalization discharge codes. Cardiovascular death following hospitalized acute coronary syndrome or ischemic stroke were included. The date of admission was used as the date of the event. Only SCEs occurring after April 1, 2011 were selected, in order to obtain at least one year for detecting ustekinumab initiation before the SCE. In addition, the validity criteria for the case-time-control design required the probability of observing ustekinumab initiations to be modified only by the association with a SCE.[24] We did not include the SCE if the patient had already

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experienced one in the previous two years, since it could reduce the probability of ustekinumab initiation by the physician.

Drug exposure

Since we focused on the triggering effect of ustekinumab, exposure was defined as the initiation of the treatment, i.e. the first dispensation of ustekinumab. According to the label, ustekinumab is administered subcutaneously every 12 weeks, after the first 2 injections at a 4-week interval. Ustekinumab is used as a chronic treatment, pursued until inefficacy or treatment-related toxicity is reached, or stopped after a long remission. Most patients have only one course of ustekinumab, but some can have several courses.

Covariates

The cardiovascular risk was considered high if the patient had at least 2 risk factors or a personal history of athero-thrombotic disease. Otherwise, it was considered as low. The indication for ustekinumab (psoriasis or Crohn's disease) was assessed. Algorithms used are detailed in the Supplement.

Statistical analysis

We performed a case-time-control study. This design is an extension of the case-crossover, a design used to investigate the triggering role of different factors in human acute adverse events. The rationale of these designs is to search for an excess of ustekinumab initiation immediately preceding SCE, compared to a previous time period, which could reflect a triggering effect of ustekinumab initiation on SCE. The case-crossover design is based on the principle of each individual serving as his own control in a different time period. This enables time-invariant confounders to be controlled for. The case-time-control design has the additional benefit of adjusting on time trends in the general prescribing pattern of ustekinumab by incorporating matched time-controls (figure 1).[25,26]

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Exposure to ustekinumab initiation was measured over two periods prior to the event [25]. We defined the 'risk' period as 0-6 months before the SCE and the 'reference' period as 6-12 months before the SCE (figure 1A).

Time-controls were not compared to cases. They were used to check for time trends in the general prescribing pattern for ustekinumab between 2010 and 2016. The increasing prescription of ustekinumab over time after its market authorisation could otherwise have led to a false association between ustekinumab initiation and the outcome (figure 1B).[27] For each case, 4 controls of the same sex, age (± 2 years) and cardiovascular risk were randomly sampled from the individuals exposed to ustekinumab. The OR for the case-time-control analysis was derived from the interaction coefficient between exposure and case or time-control status introduced into the conditional logistic regression models. It estimated the association between the initiation of ustekinumab and SCE, controlling for time trends. Statistical tests were two-tailed with an α-risk of 5%.

A differential effect of ustekinumab initiation according to cardiovascular risk was anticipated, on the hypothesis that patients with low cardiovascular risk were less prone to atherosclerotic plaques, or that their plaques were less prone to rupture. We planned in the protocol of the study to stratify the analyses accordingly: into the low vs. high cardiovascular risk strata. By testing a possible interaction between cardiovascular risk and ustekinumab initiation, we also evaluated the homogeneity between the ORs obtained from the 2 cardiovascular risk strata. Because interaction tests are less powerful, we planned in the protocol to consider *p*-values of less than 0.15 to be statistically significant for an interaction.[28,29]

Statistical analyses were performed with SAS Enterprise Guide Software (SAS Institute, Inc., USA) version 7.1.

Sensitivity analyses

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We tested the robustness of our study findings in sensitivity analyses using alternative assessment criteria for exposure and outcome. First, we added re-initiation and dose increase as exposure. Re-initiation was defined as a dispensation of ustekinumab without any dispensation in the previous 6 months, among patients who had previously received ustekinumab. Secondly, we added unstable angina (ICD-10 code: I200 and I200+0) and acute coronary syndrome among patients hospitalized in a unit other than ICU as SCE.

Estimation of incidence rates and risk of SCE

Incidence rates and estimated risk of SCE are provided in the Supplement.

Results

Severe cardiovascular events

Among the 66-million French inhabitants, 9290 individuals were exposed to ustekinumab between April 2010 and December 2016. Their main characteristics are presented in eTable 3 in the Supplement. Psoriasis was identified for 86% of the patients receiving ustekinumab and Crohn's disease for 12%.

In this population, between April 2011 and December 2016, 98 SCEs (52 acute coronary syndromes admitted to ICU, including 2 leading to death, and 46 strokes) met our criteria for inclusion in the main analysis. In addition, 13 cases of acute coronary syndrome hospitalized in non-ICU wards and 68 cases of unstable angina were added for the sensitivity analysis (flowchart in figure 2).

The characteristics of the patients included in the main analysis are described in table 1. Sixty-three per cent were male, the median age was 57 (IQR: 51-65), 78% had high cardiovascular risk. Ninety-one per cent had psoriasis, 4 patients had Crohn's disease and 2 had both. The characteristics of the cases and time-controls are presented in eTable 5 in the Supplement.

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Risk of SCE associated with ustekinumab initiation

Across the whole study population, the OR for the case-time-control analysis was 2.41, 95%CI [0.83-7.01]. Because of heterogeneity in the ORs obtained from patients with high vs. low cardiovascular risk (p=0.053), the main analysis was stratified according to cardiovascular risk factors, as pre-specified in our study protocol. Among patients at high cardiovascular risk, we observed a significantly increased risk of SCE in the first 6 months after ustekinumab initiation (OR, 4.17; 95%CI, 1.19-14.59) but this was not observed among patients with a low cardiovascular risk (OR, 0.30; 95%CI, 0.03-3.13). The detailed results for the overall population and for the subgroups with high and low cardiovascular risk are presented in table 2. The results for the case-crossover and the case-time-control are presented separately in eTable 6 in the Supplement.

Sensitivity analyses

Two sensitivity analyses were conducted. First, we widened the definition of triggering circumstances by adding the following to initiation: re-initiation (i.e. later initiation of at another course of ustekinumab) and dose increase. The OR for SCE in the overall population was 3.41, 95%CI [1.15-10.15]. Among patients with high cardiovascular risk, the OR was 4.62, 95%CI [1.36-15.61]. Among patients with low cardiovascular risk, the OR was 1.00, 95%CI [0.08-12.56].

Secondly, we expanded the definition of SCE by adding unstable angina and non-ICU hospitalized acute coronary syndrome to ICU-hospitalized acute coronary syndrome and stroke (n=179). The OR for SCE in the overall population was 1.75, 95%CI [0.86-3.56]. Among patients with high cardiovascular risk, the OR was 3.20, 95%CI [1.29-7.92]. Among patients with low cardiovascular risk, the OR was 0.21, 95%CI [0.02-1.69].

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The results from the main and sensitivity analyses according to cardiovascular risk are shown in figure 3. For the sub-population with low cardiovascular risk, no association between ustekinumab initiation and SCE was observed.

Discussion

In a population-based study including 9290 patients exposed to ustekinumab, we observed an excess of occurrence of early acute coronary syndrome and stroke within the 6 months following treatment initiation, among patients with high cardiovascular risk (OR, 4.17; 95%CI, 1.19-14.59; *p*=0.026). This association was not observed among patients with low cardiovascular risk (*p*-value for heterogeneity, 0.053). On account of our study design, which addresses the general question “why now?” (and not the more classic “why me?”), our results do not mean that more SCEs are observed among patients with a higher baseline cardiovascular risk (an obvious fact anyway), but that the period following ustekinumab initiation carries a higher risk for SCE in this sub-population.

We chose to focus on early events for two reasons. First, a meta-analysis of randomized controlled trials alerted on a possible excess of SCE as early as 2011 among adults exposed to anti-IL-12/23p40 (ustekinumab or briakinumab) during the first months of treatment.[15,16] The decision to stop the development of briakinumab left ustekinumab as the only anti-IL-12/23p40 on the market. Although no recommendation has been explicitly released by the European or United States Drug Agencies, the relationship between anti-IL-12/23p40 use and atherosclerotic cardiovascular disease has been a subject of controversy.[15–17,30,31] Secondly, there is an immunological substratum supporting a short-term triggering of SCE in the first weeks or months of treatment with anti-IL-12/23p40, based on the hypothesis of a therapeutically induced acute change in the immunological environment of atherosclerotic plaques.[1,2,20,21] Ustekinumab inhibits the p40 subunit shared by IL-12, a T-helper (Th)1

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inducer, and IL-23, which maintains Th17 cell homeostasis. Several experimental studies have shown that IL-12 and related-Th1 responses are pro-atherogenic.[32] In contrast, the role of the Th17 pathway, driven by IL-17A, remains ambiguous. IL-17A could have a proatherogenic effect, by promoting plaque growth, while a protective effect could also result from the stabilization of atherosclerotic plaques.[19,20,33,34] The effect of IL-17A involves 2 protective mechanisms: the stimulation of type I collagen production by smooth muscle cells in the fibrous caps, and a reduction of inflammatory cells within the vascular lesions through a decrease in the endothelial expression of vascular cell adhesion molecule (VCAM)-1.[1,20] A stabilizing effect of IL-17A on atherosclerotic plaque was again suggested by a large human study reporting that high IL-17A plasma levels following myocardial infarction were associated with a lower recurrence rate.[35] The anti-IL-12/23p40 therapy ustekinumab, by the inhibition of the Th17 pathway, could therefore induce atherosclerotic plaque rupture and athero-thrombotic events, including stroke and acute coronary syndrome.

Our study has several strengths. First, we used a design specifically suited to detecting a putative triggering impact on early events. Previous work on the cardiovascular effect of ustekinumab, based on cohort studies, did not identify increased risk in the medium or long-term.[36–38] However, our focus on a triggering effect of treatment initiation raises a new question, which required a different study design. Another major advantage of self-controlled designs over cohort studies is the absence of indication bias and of measured or unmeasured time-invariant confounders, since each individual serves as his own control.[27] Treatments such as anti-lipidemics, anti-hypertensives or anti-diabetics could act as time-dependent confounders, since discontinuing a cardiovascular treatment could have a triggering effect on SCE. We confirmed that no patient initiating ustekinumab in the risk or reference period discontinued one of these treatments in the 12 months before SCE. We selected a 6-month

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duration for the risk period, in order to include the time lapse observed for SCE in clinical trials,[15] and to allow enough time for the pathological immune changes that could promote SCEs.[39] Second, we included sensitivity analyses, in which we broadened the definition of SCE and the types of trigger (adding re-initiation and dose increase). Consistent results were observed in each stratum of cardiovascular risk. Third, our study framework comprised all the subjects exposed to ustekinumab, and every SCE was collected. Although we ended up with a relatively small number of SCEs observed within our window, the exhaustiveness of the initial 66-million population yielded maximum power. The absence of attrition bias is another major strength for our study.

Some limitations need to be discussed. First, we did not include cardiovascular death resulting from a non-atherothrombotic mechanism (n=12, mostly heart failure) in our outcome, because our hypothesis of a trigger effect was specific of a destabilization of atherosclerotic plaques. In addition, we could not identify cardiovascular deaths occurring outside the hospital, since causes of death were not yet recorded in the SNDS database. Including all-cause deaths could have resulted in a dilution of the odds-ratio because of a misclassification bias due to a majority of non-cardiovascular deaths. Second, we used dispensations as a proxy for drug intake. This approximation is widely acknowledged and used in pharmaco-epidemiological studies. Third, clinical and biological data regarding the cardiovascular risk factors could have led to a misclassification bias between the high vs low cardiovascular risk strata. Tobacco use and obesity are known to be under-reported in hospital discharge coding. Dietary factors and physical activity are not reported at all. In addition, dyslipidemia was considered only when it involved issues of statins or fibrates, and it is possible that the triggering risk is higher among untreated dyslipidemic patients.[40] However, we believe that our criteria for defining patients' cardiovascular risk profiles were sufficiently discriminant to identify two distinct sub-

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populations according to this risk. Both the triggering effect suggested among high cardiovascular risk patients, and the absence of any association among the low risk patients are in line with the immunological hypothesis, since only the first group are liable to have atherosclerotic plaques likely to be destabilized. Fourth, one may suggest that the incidence of SCEs during the 0-6 months period after ustekinumab initiation is hypothetically the same that would occur without ustekinumab; with the additional hypothesis that ustekinumab would decrease the risk of SCE during the 6-12 months period, this could lead to an OR superior to 1. However, the first hypothesis would not be compatible with the randomized trials reporting more SCEs among patients exposed to anti-IL-12/23 than placebo in the first months after the initiation, and the second one remains to be substantiated. Lastly, the observational design does not allow for proving causality.

The observation of an association between ustekinumab initiation and SCE among patients with cardiovascular risk factors calls for caution regarding the prescription of ustekinumab in this population. It seems to concern patients with psoriasis rather than Crohn's disease, probably because they are older and have a higher pre-existing cardiovascular risk. In addition to the detection of classic cardiovascular risk factors, imaging of atherosclerotic plaques could be considered when determining the individual cardiovascular risk for each patient. Novel strategies used to screen for high-risk coronary plaques, such as coronary CT angiography or 18F-FDG PET/CT, could help improve the detection of patients at higher risk.[41] Our data do not rule out the hypothesis of a dual impact of anti-IL-12/23p40 therapy on atherosclerotic disease, e.g. a destabilizing short-term effect in a subset of patients, and a beneficial or neutral impact on atherosclerosis development in the longer term.

New biologics targeting the Th17 pathway (anti-IL-17 therapies: secukinumab, ixekizumab, brodalumab; anti-IL-23p19 therapies: guselkumab, tildrakizumab, risankizumab) have already

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been marketed or are in the pre-marketing phases in psoriasis, and should be carefully monitored with respect to cardiovascular events, with a specific focus on the period following treatment initiation[34]. Physicians should be aware that randomized trials do not fully identify this risk because of the small sample sizes, and the small number of comorbidities compared to real-world settings. Thus, caution regarding patients with high cardiovascular risk should be exercised when prescribing these treatments, and should reinforce recommendations for early, active management of cardiovascular comorbidities among psoriatic patients.

In summary, our results from real-world data suggest that ustekinumab treatment could trigger acute coronary syndrome and stroke within the first 6 months of treatment initiation among patients with high cardiovascular risk. A close collaboration between cardiologists and biologic prescribers could be beneficial to evaluate the risk for a patient of receiving ustekinumab. Further investigations should help explore the underlying physio-pathological mechanisms. In an epidemiological perspective, the same systematic strategy could be used to screen for early SCE among patients exposed to other newly developed biotherapies blocking the IL-17/IL-23 pathway.

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Acknowledgements

We thank Ms. Angela Verdier and Ms. Sarah Leyshon (SARL L'Auracoise) for the English language revision. They received a compensation and gave their written permission to include their names.

Funding

This work was supported by a grant from the French National Public Drug Agency (ANSM, Agence Nationale de Sécurité du Médicament). The funding source revised the design. The funding source had no role in the conduct of the study; the management, the collection, the analysis and the interpretation of the data; the preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Competing interests

Hafid Ait-Oufella reports personal fees for medical trainings from the laboratories Abbvie, Lilly, UCB Pharma, Pfizer, outside the submitted work. **Hervé Bachelez** declares having received personal fees as a member of an advisory board for Abbvie, Almirall, Amgen, Boehringer-Ingelheim, Celgene, Janssen, Leo Pharma, Lilly, Mylan, Novartis, Pfizer, Sun Pharma, UCB; as a speaker for Abbvie, Boehringer-Ingelheim, Celgene, Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Sun Pharma, UCB Pharma; as a consultant for Abbvie, Amgen, Boehringer-Ingelheim, Celgene, Lilly, Janssen, Leo Pharma, Novartis, Pfizer, UCB Pharma. He received a grant support from Pfizer, outside the submitted work. **Other authors** have nothing to disclose.

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Contributorship

FP, EN, EO, AD developed the protocol and the statistical analysis plan. CD, MDD, ES, BG revised the protocol. FP, SK, BLN, AH extracted and prepared the database. EN conducted the statistical analysis and drafted the statistical report. All authors analyzed the data, revised the manuscript draft critically, and approved its final version for submission.

Access to data and data analysis

FP and AD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

The statistical code is available from the corresponding author. Under French law and regulations, patient-level data from SNDS cannot be made available.

Ethical approval information

The study protocol was authorized and approved by the French Drug Regulatory Agency (ANSM, Agence Nationale de Sécurité du Médicament) on July 19, 2017, by the National Institutional Review Board (INDS, Institut National des Données de Santé) and by the French data protection authority (CNIL, Commission Nationale de l'Informatique et des Libertés).

Previous meeting

This work has been presented at the Journées Dermatologiques de Paris 2018 (December 13, 2018) and at the 49th Annual European Society of Dermatological Research Meeting (September 21, 2019, Bordeaux).

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Figure 1. Study design

A. Among patients exposed to ustekinumab and having had a severe cardiovascular event (SCE), exposure to ustekinumab initiation was screened over two periods prior to SCE. The number of ustekinumab initiations in the 'risk' period was compared to the number of ustekinumab initiations during the 'reference' period, leading to assess the odds-ratio (OR) of the case-crossover.
B. Time trends in the general prescribing pattern for ustekinumab between 2010 and 2016. Because the number of ustekinumab initiations was not constant over time, time-controls were introduced in the model. The odds-ratio among time-controls estimates how much the case-crossover analysis is related to the time trends in the prescription of ustekinumab over time. The final OR of the case-time-control estimates the association between the initiation of ustekinumab and SCE (*i.e*. the OR of the case-crossover), adjusted for time trends (estimated among time-controls).

Figure 2. Study flow chart

Figure 3. Association between ustekinumab initiation and severe cardiovascular events (SCEs) according to cardiovascular risk

The figure shows odds-ratios (OR) (square) with 95% confidence interval (blue segment). The vertical grey line delineates the absence of association between ustekinumab initiation and SCE.

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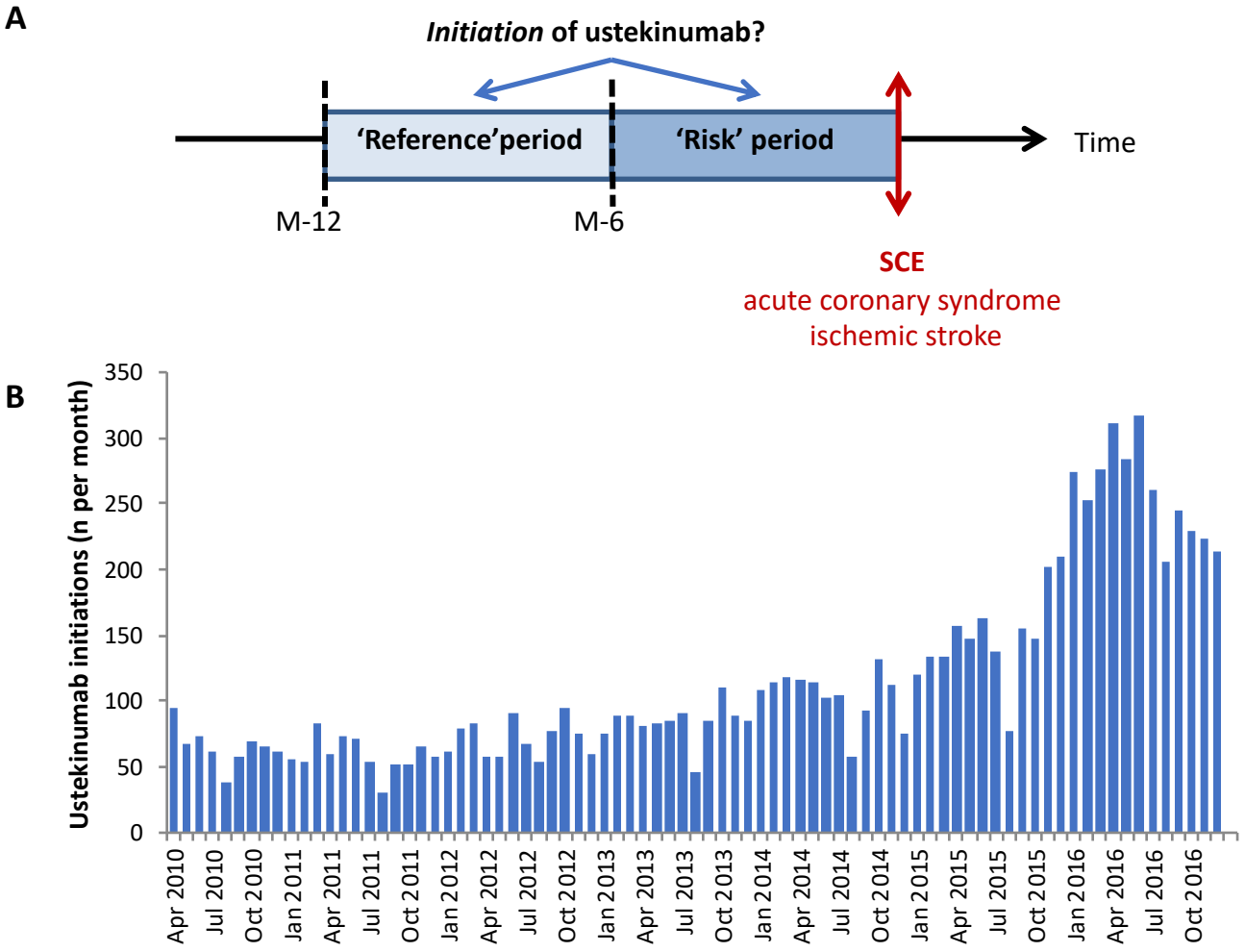
A
Initiation of ustekinumab?
'Reference'period
'Risk' period
Time
M-12
M-6
SCE
acute coronary syndrome
ischemic stroke
B
Ustekinumab initiations (n per month)
350
300
250
200
150
100
50
0
Apr 2010
Jul 2010
Oct 2010
Jan 2011
Apr 2011
Jul 2011
Oct 2011
Jan 2012
Apr 2012
Jul 2012
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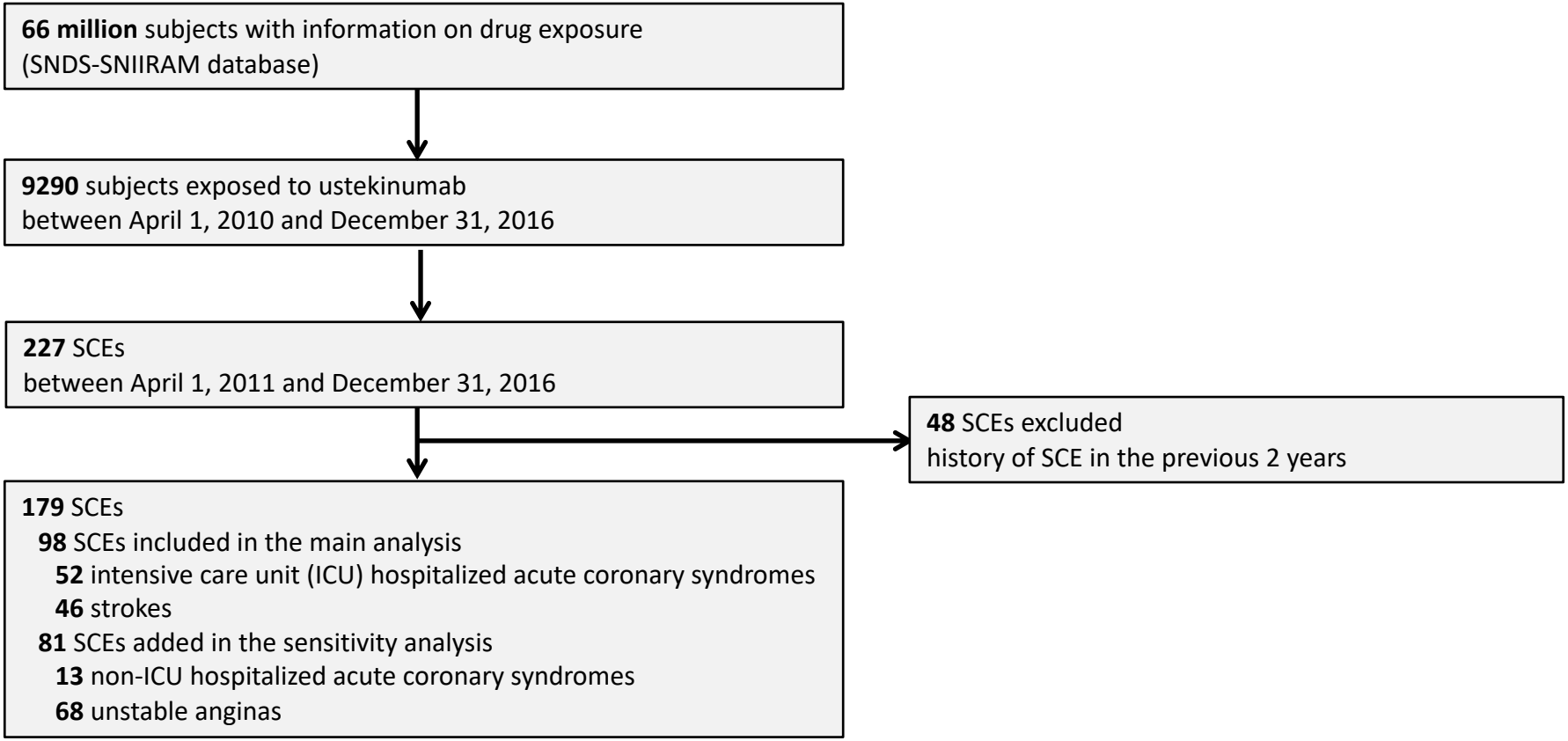
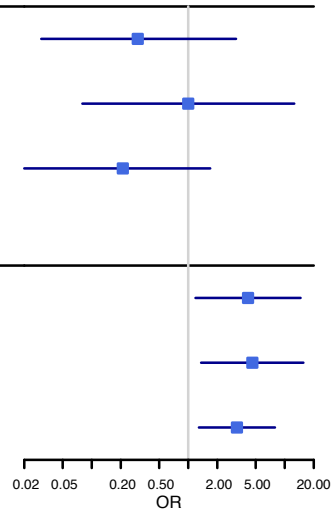


SCE: severe cardiovascular event

	OR [95% CI]
Low cardiovascular risk (n=22)[a]	
Main analysis[b]	0.30 [0.03–3.13]
Exposure including re–initiations and dose increases[c]	1.00 [0.08–12.56]
All cardiovascular events[d]	0.21 [0.02–1.69]
High cardiovascular risk (n=76)[a]	
Main analysis[b]	4.17 [1.19–14.59]
Exposure including re–initiations and dose increases[c]	4.62 [1.36–15.61]
All cardiovascular events[d]	3.20 [1.29–7.92]



[a]low risk if fewer than 2 cardiovascular risk factors and no history of SCE; high risk if more than 2 cardiovascular risk factors or a history of SCE

[b]exposure: ustekinumab initiation; event: intensive care unit (ICU)-hospitalized acute coronary syndrome and stroke; 6-month periods.

[c]exposure: ustekinumab initiation, re-initiation (after 6 months without ustekinumab prescription) and dose increases; event: intensive care unit (ICU)-hospitalized acute coronary syndrome and stroke; 6-month periods.

[d]exposure: ustekinumab initiation; event: acute coronary syndrome, stroke and unstable angina; 6-month periods.

Table 1. Characteristics of cases included in the case-time-control analysis

Characteristics	**Cases (n=98)**
Event, No. (%)	
ICU-hospitalized acute coronary syndrome	52 (53)
Stroke	46 (47)
Sex, No. (%)	
Male	62 (63)
Female	36 (37)
Age[a]	
Median (IQR)	57 (51 - 65)
Indication, No. (%)	
Psoriasis	89 (91)
Crohn's disease	4 (4)
Psoriasis and Crohn's disease	2 (2)
Undetermined	3 (3)
Cardiovascular risk[b], No. (%)	
Low risk	22 (22)
High risk	76 (78)
Previous cardiovascular event, No. (%)	0 (0)
Cardiovascular risk factors[b], No. (%)	
Age[c]	62 (63)
Hypertension	63 (64)
Dyslipidemia	45 (46)
Tobacco use	29 (30)
Diabetes	25 (26)
Obesity	16 (16)
Number of cardiovascular risk factors[b], No. (%)	
0	4 (4)
1	18 (18)
2	30 (31)
3	27 (28)
4	14 (14)
5	5 (5)
6	0 (0)

ICU: intensive care unit; IQR: interquartile range.

[a]Assessed at the date of the event

[b]Measured in the year preceding the date of the event

[c]Over 50 years for men, 60 for women

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Table 2. Risk for severe cardiovascular events (SCE) among patients exposed to ustekinumab initiation

	Ustekinumab initiation (No.)		Odds-ratio (95% confidence interval)[c]
	'Risk' period[a]	'Reference' period[b]	
Overall population (n=98)	16	6	2.41 (0.83-7.01)
Low cardiovascular risk[d] (n=22)	2	2	0.30 (0.03-3.13)
High cardiovascular risk[e] (n=76)	14	4	4.17 (1.19-14.59)

[a]-6 to 0 month period preceding the event
[b]-12 to -6 month period preceding the event
[c]Association between ustekinumab initiation and cardiovascular events, controlling for time trends in the prescribing patterns of ustekinumab. *cf* Methods section
[d]fewer than 2 cardiovascular risk factors and no history of SCE
[e]more than 2 cardiovascular risk factors or a history of SCE

The main analysis was stratified according to the cardiovascular risk (*p*-value for interaction: 0.053).

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