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

3
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31 **Key points**

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

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

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

40
41

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

44

45 **Abstract**

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

51 **Objective:** To assess whether ustekinumab initiation triggers SCE.

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

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

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

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

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

61 **Results:** Among the 9290 patients exposed to ustekinumab, 179 experienced SCEs: 65 cases
62 of acute coronary syndrome, 68 unstable angina and 46 stroke. Among patients with high
63 cardiovascular risk, a significant association between ustekinumab initiation and SCE
64 occurrence was identified (OR, 4.17; 95%CI, 1.19-14.59). Conversely, no statistically
65 significant association was found among patients with low cardiovascular risk (OR, 0.30;
66 95%CI, 0.03-3.13).

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

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

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Accepted Manuscript

75 **Introduction**

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

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

96

97 **Methods**

98 *Data source and population*

99 This study was conducted using the French National Health Insurance database (SNDS,
100 Système National des Données de Santé, formerly SNIIRAM, Système national d'information
101 inter-régimes de l'Assurance maladie).²³ This database covers 98% of the population living in
102 France (around 66 million inhabitants), and includes anonymous individual sociodemographic
103 data, exhaustive data on all reimbursements for health-related expenditures, dispensed drugs
104 with date of issue, any investigation (imagery, surgery, blood analysis, etc.), and
105 hospitalization discharge codes according to the International Classification of Diseases, 10th
106 revision (ICD-10). Data from public and private practices are recorded in the same way.
107 Severe, costly, long-term diseases are recorded, with diagnoses encoded according to ICD-10,
108 because they give entitlement to 100% health insurance coverage.
109 From the entire SNDS database, we extracted all the subjects who had had at least one
110 reimbursement for ustekinumab between April 1, 2010 (date of market release) and December
111 31, 2016. Thus, all patients included were incident users of ustekinumab. From this
112 population, we selected patients who had a reported SCE.

113 *Severe cardiovascular events*

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

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

125 *Drug exposure*

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

132 *Covariates*

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

137 *Statistical analysis*

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

147 Exposure to ustekinumab initiation was measured over two periods prior to the event²⁵. We
148 defined the ‘risk’ period as 0-6 months before the SCE and the ‘reference’ period as 6-12
149 months before the SCE (figure 1A).

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

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

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

171 *Sensitivity analyses*

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

178 *Estimation of incidence rates and risk of SCE*

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

180

181 **Results**

182 *Severe cardiovascular events*

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

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

192 The characteristics of the patients included in the main analysis are described in table 1.

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

197 *Risk of SCE associated with ustekinumab initiation*

198 Across the whole study population, the OR for the case-time-control analysis was 2.41,
199 95%CI [0.83-7.01]. Because of heterogeneity in the ORs obtained from patients with high vs.
200 low cardiovascular risk ($p=0.053$), the main analysis was stratified according to
201 cardiovascular risk factors, as pre-specified in our study protocol. Among patients at high
202 cardiovascular risk, we observed a significantly increased risk of SCE in the first 6 months
203 after ustekinumab initiation (OR, 4.17; 95%CI, 1.19-14.59) but this was not observed among
204 patients with a low cardiovascular risk (OR, 0.30; 95%CI, 0.03-3.13). The detailed results for
205 the overall population and for the subgroups with high and low cardiovascular risk are
206 presented in table 2. The results for the case-crossover and the case-time-control are presented
207 separately in eTable 6 in the Supplement.

208 *Sensitivity analyses*

209 Two sensitivity analyses were conducted. First, we widened the definition of triggering
210 circumstances by adding the following to initiation: re-initiation (i.e. later initiation of at
211 another course of ustekinumab) and dose increase. The OR for SCE in the overall population
212 was 3.41, 95%CI [1.15-10.15]. Among patients with high cardiovascular risk, the OR was
213 4.62, 95%CI [1.36-15.61]. Among patients with low cardiovascular risk, the OR was 1.00,
214 95%CI [0.08-12.56].

215 Secondly, we expanded the definition of SCE by adding unstable angina and non-ICU
216 hospitalized acute coronary syndrome to ICU-hospitalized acute coronary syndrome and
217 stroke (n=179). The OR for SCE in the overall population was 1.75, 95%CI [0.86-3.56].

218 Among patients with high cardiovascular risk, the OR was 3.20, 95%CI [1.29-7.92]. Among
219 patients with low cardiovascular risk, the OR was 0.21, 95%CI [0.02-1.69].

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

223

224 **Discussion**

225 In a population-based study including 9290 patients exposed to ustekinumab, we observed an
226 excess of occurrence of early acute coronary syndrome and stroke within the 6 months
227 following treatment initiation, among patients with high cardiovascular risk (OR, 4.17;
228 95%CI, 1.19-14.59; $p=0.026$). This association was not observed among patients with low
229 cardiovascular risk (p -value for heterogeneity, 0.053). On account of our study design, which
230 addresses the general question “why now?” (and not the more classic “why me?”), our results
231 do not mean that more SCEs are observed among patients with a higher baseline
232 cardiovascular risk (an obvious fact anyway), but that the period following ustekinumab
233 initiation carries a higher risk for SCE in this sub-population.

234 We chose to focus on early events for two reasons. First, a meta-analysis of randomized
235 controlled trials alerted on a possible excess of SCE as early as 2011 among adults exposed to
236 anti-IL-12/23p40 (ustekinumab or briakinumab) during the first months of treatment.^{15,16} The
237 decision to stop the development of briakinumab left ustekinumab as the only anti-IL-
238 12/23p40 on the market. Although no recommendation has been explicitly released by the
239 European or United States Drug Agencies, the relationship between anti-IL-12/23p40 use and
240 atherosclerotic cardiovascular disease has been a subject of controversy.^{15-17,30,31} Secondly,
241 there is an immunological substratum supporting a short-term triggering of SCE in the first
242 weeks or months of treatment with anti-IL-12/23p40, based on the hypothesis of a
243 therapeutically induced acute change in the immunological environment of atherosclerotic
244 plaques.^{1,2,20,21} Ustekinumab inhibits the p40 subunit shared by IL-12, a T-helper (Th)1

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

258

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

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

279

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

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

306
307 The observation of an association between ustekinumab initiation and SCE among patients
308 with cardiovascular risk factors calls for caution regarding the prescription of ustekinumab in
309 this population. It seems to concern patients with psoriasis rather than Crohn's disease,
310 probably because they are older and have a higher pre-existing cardiovascular risk. In addition
311 to the detection of classic cardiovascular risk factors, imaging of atherosclerotic plaques could
312 be considered when determining the individual cardiovascular risk for each patient. Novel
313 strategies used to screen for high-risk coronary plaques, such as coronary CT angiography or
314 18F-FDG PET/CT, could help improve the detection of patients at higher risk.⁴¹ Our data do
315 not rule out the hypothesis of a dual impact of anti-IL-12/23p40 therapy on atherosclerotic
316 disease, e.g. a destabilizing short-term effect in a subset of patients, and a beneficial or neutral
317 impact on atherosclerosis development in the longer term.

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

320 been marketed or are in the pre-marketing phases in psoriasis, and should be carefully
321 monitored with respect to cardiovascular events, with a specific focus on the period following
322 treatment initiation³⁴. Physicians should be aware that randomized trials do not fully identify
323 this risk because of the small sample sizes, and the small number of comorbidities compared
324 to real-world settings. Thus, caution regarding patients with high cardiovascular risk should
325 be exercised when prescribing these treatments, and should reinforce recommendations for
326 early, active management of cardiovascular comorbidities among psoriatic patients.

327

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

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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, 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.

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

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Figure 1. Study design

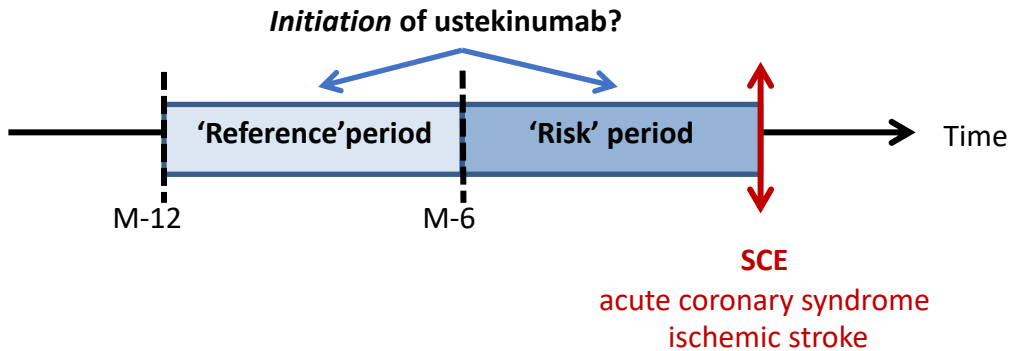
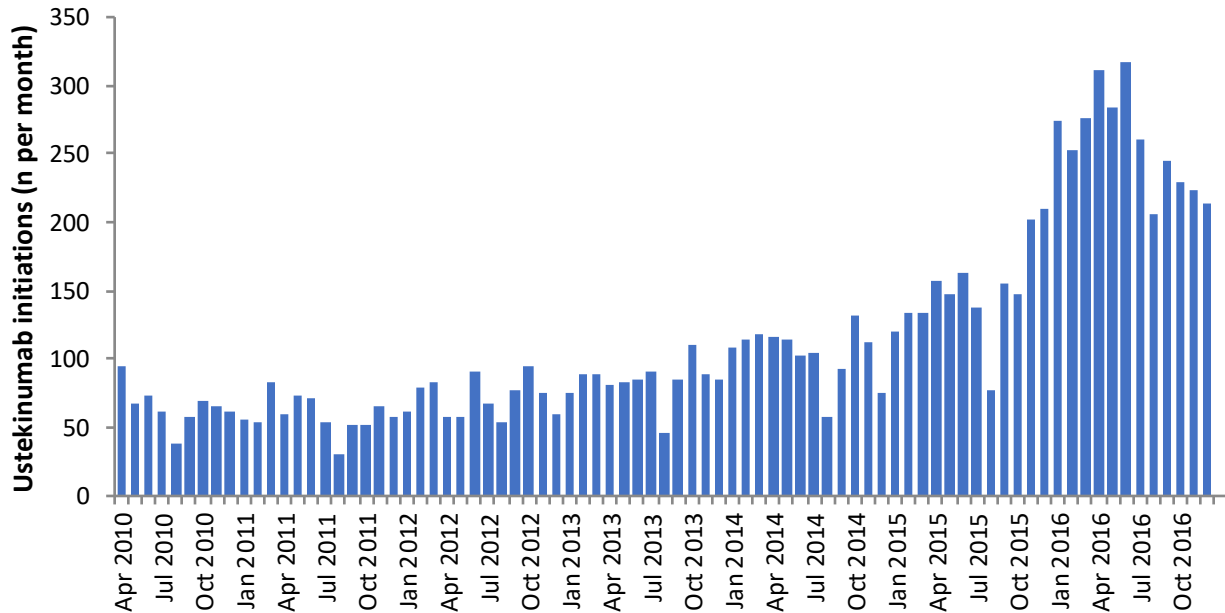
A. Among patients exposed to ustekinumab and having had a severe cardiovascular event (SCE), exposure to ustekinumab initiation was screened over two periods prior to SCE. The number of ustekinumab initiations in the ‘risk’ period was compared to the number of ustekinumab initiations during the ‘reference’ 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.

A**B**

66 million subjects with information on drug exposure
(SNDS-SNIIRAM database)



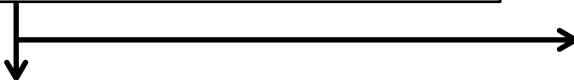
9290 subjects exposed to ustekinumab
between April 1, 2010 and December 31, 2016



227 SCEs
between April 1, 2011 and December 31, 2016



179 SCEs
98 SCEs included in the main analysis
 52 intensive care unit (ICU) hospitalized acute coronary syndromes
 46 strokes
81 SCEs added in the sensitivity analysis
 13 non-ICU hospitalized acute coronary syndromes
 68 unstable anginas

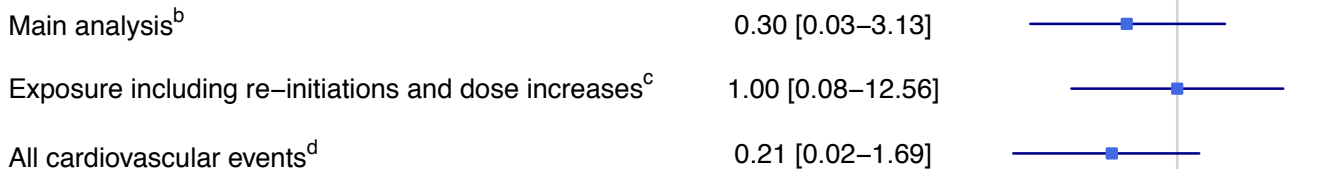


48 SCEs excluded
history of SCE in the previous 2 years

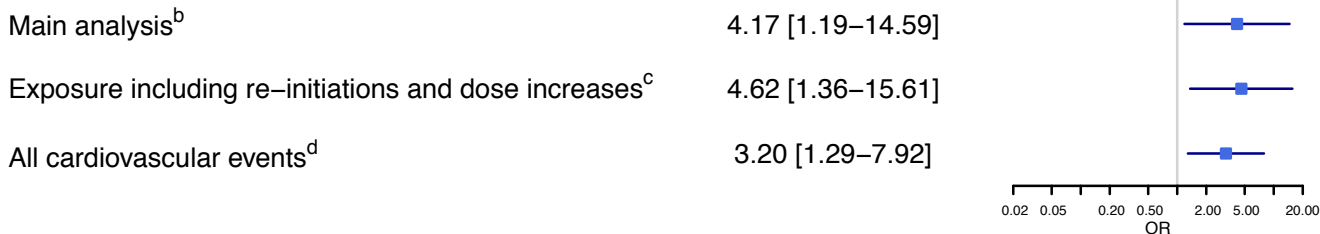
SCE: severe cardiovascular event

OR [95% CI]

Low cardiovascular risk (n=22)^a



High cardiovascular risk (n=76)^a



^alow 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

^bexposure: ustekinumab initiation; event: intensive care unit (ICU)-hospitalized acute coronary syndrome and stroke; 6-month periods.

^cexposure: 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.

^dexposure: 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.

^aAssessed at the date of the event

^bMeasured in the year preceding the date of the event

^cOver 50 years for men, 60 for women

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

^cAssociation between ustekinumab initiation and cardiovascular events, controlling for time trends in the prescribing patterns of ustekinumab. *cf* Methods section

^dfewer than 2 cardiovascular risk factors and no history of SCE

^emore 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).