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# 1 **Cardiovascular adverse effects of anti-IL5/IL5R $\alpha$ therapies: a** 2 **real-world study**

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41

42 Clinical implications: Cardiovascular events are not likely to be more reported with IL-5/IL-

43 5R $\alpha$  blocking drugs compared to omalizumab. Hypertension, ventricular arrhythmia and

44 venous thromboembolism were significantly more reported with omalizumab

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46 Word count of the text: 992

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49 Omalizumab, an antibody directed against the receptor-binding domain of IgE, was the first  
50 biological therapy marketed in severe allergic asthma. Several observational studies including  
51 long-term analyses concluded that omalizumab has showed an overall optimal safety profile<sup>1-</sup>  
52 <sup>5</sup>.Although higher incidence rate of cerebrovascular and cardiovascular adverse events  
53 emerged in some studies<sup>3, 4</sup>, confounding factors between omalizumab and non-omalizumab  
54 patients were likely to explain those results. Recently, mepolizumab, reslizumab (both anti-  
55 interleukin 5 (IL5)) and benralizumab (an anti-IL5 receptor- $\alpha$  (IL5R $\alpha$ )) have been associated  
56 with a reduction of the exacerbation rate and the dose of oral steroids in eosinophilic severe  
57 asthma. In long-term safety studies, rare cardiovascular events such as myocardial infarction,  
58 deep venous thrombosis and stroke have been described with benralizumab and mepolizumab.  
59 Nevertheless, an association between these events and these drugs is still unknow<sup>6, 7</sup>. We  
60 performed a pharmacovigilance study in order to assess the effect of anti-IL5/IL5R $\alpha$  therapies  
61 on cardiovascular events.

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63

64 Disproportionality analyses (case non-case method) were performed using Vigibase®, the  
65 World Health Organization global database of Individual Case Safety Reports (ICSRs), to  
66 assess whether anti-IL5/IL5R $\alpha$  therapies (mepolizumab, reslizumab and benralizumab) are  
67 associated with an increased risk of cardiovascular events compared to omalizumab. The  
68 study protocol was approved by the Institutional Review Board of the *Société de pneumologie*  
69 *de langue Française* (CEPRO 2019-041).

70 All reports registered between January 1, 2000 and December 1, 2019 were considered. The  
71 reports containing patients aged 12 years or older with adverse events suspected from being  
72 triggered by at least one Anti-IL5/IL5R $\alpha$  therapies or omalizumab were included herein. The  
73 outcomes of interest were cardiovascular adverse events according to the 10th revision of the

74 International Statistical Classification of Diseases. Cases were identified as having  
75 cardiovascular events defined by the Standardized MedDRA queries (SMQs) or by the  
76 MedDra dictionary using the SOC (system organ class) classification. Non-cases were  
77 patients with adverse events except cardiovascular ones for the same drugs. For all cases and  
78 non-cases, we identified patients exposed to anti-IL5/IL5R $\alpha$  therapies and those to  
79 omalizumab (reference category) according to the anatomical therapeutic chemical dictionary.  
80 ICSRs with both anti-IL5/IL5R $\alpha$  therapy and omalizumab were excluded. Using a case/non-  
81 case design, we compared anti-IL5/IL5R $\alpha$  therapies to omalizumab regarding cardiovascular  
82 events using a multivariate logistic regression. Reporting odds ratios (RORs) with 95%  
83 confidence interval (CI) were adjusted for the following covariates: age, sex, type of  
84 reporters, countries, other drugs prescribed. For the robustness of our study, several sensitivity  
85 analyses were performed. Given, oral steroids are involved in the development of  
86 cardiovascular events, we made a sensitivity analysis in patients with no oral steroids.

87

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89 We identified 22,236 adverse events associated with omalizumab, reslizumab, mepolizumab  
90 or benralizumab in Vigibase®. After using all inclusion and exclusion criteria, 21,052 reports  
91 were selected for the final analysis. Among these 21,052 adverse events, 2,955 cardiovascular  
92 events were presented including 435 reports for anti-IL5/IL5R $\alpha$  therapies (378 for  
93 mepolizumab, 48 for benralizumab and 9 for reslizumab) and 2,520 for omalizumab. In the  
94 patients treated with anti-IL5/IL5R $\alpha$  therapies and omalizumab, mean age was  $56.0 \pm 15.1$   
95 and  $47.9 \pm 17.1$  and females were 67.0% and 69.6%, respectively. Most of the reports come  
96 from America (74.3%) and Europe (18.8%). Overall cardiovascular events were significantly  
97 less reported with anti-IL5/IL5R $\alpha$  therapies compared to omalizumab (adjusted RORs 0.41  
98 [95%CI 0.36-0.46]) (Figure 1). Ischemic stroke was more reported with anti-IL5/IL5R $\alpha$

99 therapies compared to omalizumab (adjusted RORs 1.69; 95%CI 1.02-2.74). Hypertension,  
100 ventricular arrhythmia and venous thromboembolism (VTE) were significantly lower with  
101 anti-IL5/IL5R $\alpha$  therapies compared to omalizumab (adjusted RORs 0.26 [95%CI 0.22-0.30],  
102 0.55 [95%CI 0.32-0.90] and 0.68 [95%CI 0.45-0.99], respectively). A sensitivity analysis was  
103 performed on the reports restricted to the declarations made by healthcare workers or  
104 regarding patients receiving no oral steroids. Thus, these results remained the same, except  
105 ischemic stroke for which no difference was observed. If we only considered the adverse  
106 events reported during the first 4 years with omalizumab and anti-IL5/IL5R $\alpha$  therapies,  
107 cardiovascular adverse events were similar between both of them.

108

109

110 Although the safety profile of anti-IL5/IL5R $\alpha$  therapies appears to be acceptable in phase III  
111 trials, the number of patients exposed to these drugs is limited. Moreover, these patients are  
112 highly selected in clinical trials and do not fully correspond to patients treated in real life.  
113 According to the recent EAACI guidelines, anti-IL5/IL5R $\alpha$  therapies have shown an  
114 increased likelihood of drug-related adverse events (AE) compared to placebo<sup>8</sup>. Serious AE  
115 were inconclusive due to the low number of events. In phase III extension studies conducted  
116 with mepolizumab, 2% and 4% of cardiovascular events have been observed in both  
117 COSMOS and COSMEX studies, respectively<sup>6, 7</sup>. Hence, the cardiovascular safety of anti-  
118 IL5/IL5R $\alpha$  therapies remains a concern.

119 Vigibase® gathers drug-related AE all around the world and constitutes a powerful and  
120 unique tool for rare events. In our study, omalizumab was chosen as the control because of  
121 being a treatment for severe asthma like anti-IL5/IL5R $\alpha$  therapies. Indeed, the acceptable  
122 safety profile of omalizumab has been well established. Although cardiovascular adverse

123 events have been suggested by EXCELS study<sup>4</sup>, after adjustment for confounding factors, no  
124 association between omalizumab and cardiovascular events has been shown.

125 Herein, cardiovascular events were not more likely to be reported with anti-IL5/IL5R $\alpha$   
126 therapies compared to omalizumab except ischemic stroke. However, an increased risk of  
127 ischemic stroke reports was no longer observed in sensitivity analyses. This means that it is  
128 highly likely that there is no association between ischemic stroke and anti-IL5/IL5R $\alpha$   
129 therapies. Hypertension, VTE and ventricular arrhythmia had a significant higher adjusted  
130 ROR with omalizumab compared to anti-IL5/IL5R $\alpha$  therapies. However, omalizumab was  
131 commercialized 10 years before anti-IL5/IL5R $\alpha$  therapies. This duration of the administration  
132 may be associated with an increased risk of incidental events. Nevertheless, an association  
133 between a very long-term exposure to omalizumab and hypertension, VTE or ventricular  
134 arrhythmia cannot be ruled out from our study. Immune cells including mast cells seem to  
135 play a role in the pathophysiology of arteriosclerosis, cardiac disorders or venous thrombosis<sup>9</sup>.  
136 Given the interaction between IgE and the immune system, particularly mast cells, an impact  
137 of a long term use of omalizumab on these diseases cannot be excluded.

138 In conclusion, cardiovascular events were not likely to be more reported with anti-IL-5/IL5R $\alpha$   
139 therapies compared to omalizumab in the first 4 years after they became available. However,  
140 overall, hypertension, VTE or ventricular arrhythmia were more likely to be reported with  
141 omalizumab, suggesting that long-term studies are warranted for all biological therapies in  
142 severe asthma

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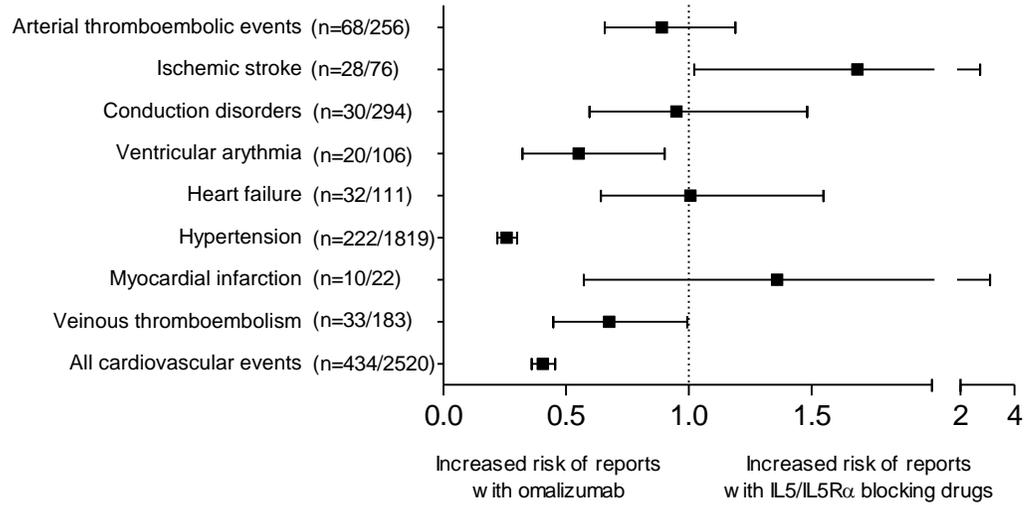
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177 **Figure 1: forest plot of adjusted reporting odd ratio (ROR) regarding cardiovascular**  
178 **events of anti-IL5/IL5R $\alpha$  therapies (benralizumab, mepolizumab and reslizumab)**  
179 **compared to omalizumab in the overall reports, in the reports restricted to the**  
180 **healthcare workers, in the reports restricted to patients with no oral steroids, in the**  
181 **reports restricted to the first 4 years of declaration. n=number of events with anti-**  
182 **IL5/IL5R $\alpha$  therapies/number of events with omalizumab**

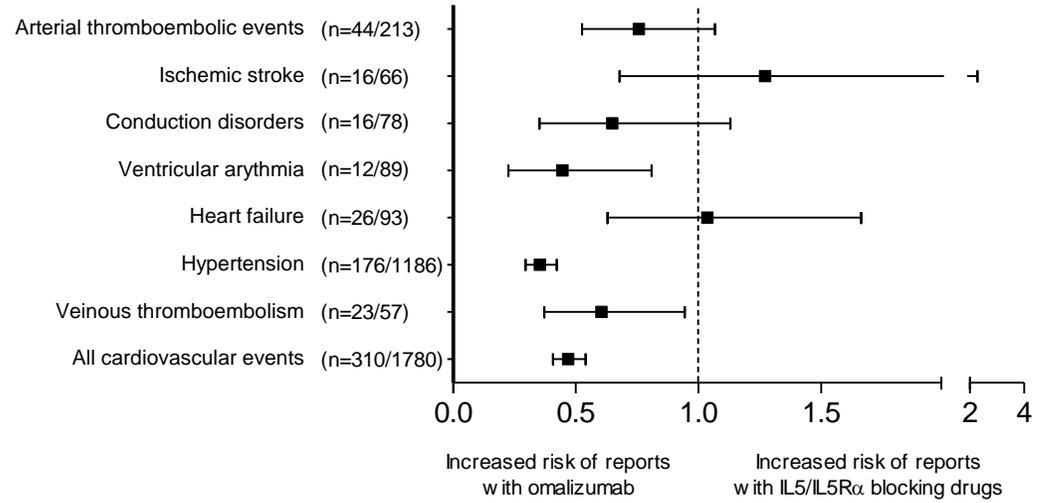
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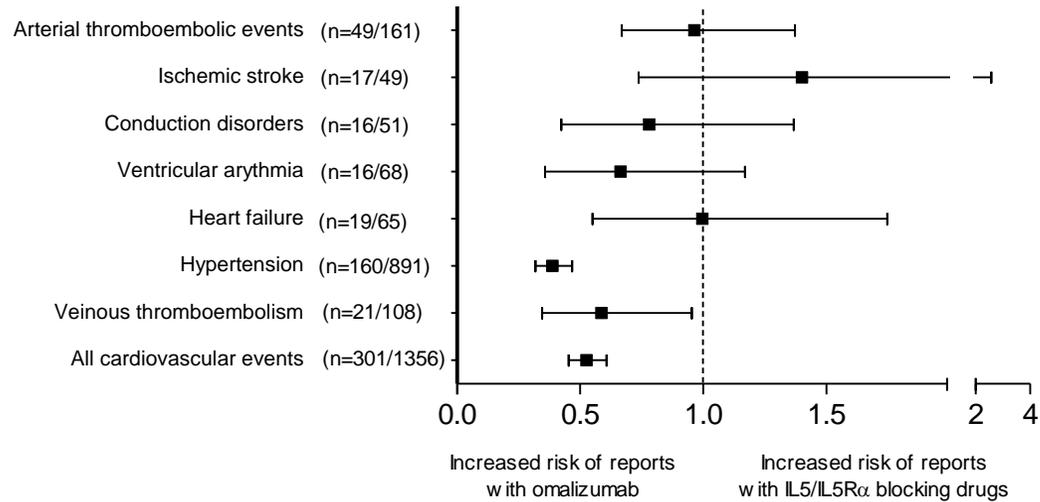
### Overall



### Healthcare professionals



### No oral steroids



### First 4 years of reporting

