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LETTER TO THE EDITOR

Hypertension and Covid-19 vaccines: are there any differences between the different vaccines? A safety signal

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Although no signal was found in clinical trials, a case series of stage III hypertension with mRNA CoV-2 vaccines (8 with tozinameran Pfizer, 1 with mRNA-1273 Moderna) was recently reported [1], suggesting that hypertension could be an adverse drug reaction (ADR) of Covid-19 vaccines. In order to validate this signal, we investigated the data registered in VigiBase®, the WHO pharmacovigilance database [2].

Reports with known age and gender in patients ≥ 18 years, reported with tozinameran, Vaxzevria® Astra Zeneca, mRNA-1273 and NRVV-Ad26 Janssen by physicians and registered between 1 January 2021 and 10 May 2021, were extracted. The study was, first, a description of hypertension and investigation of a potential signal using disproportionality analyses [3, 4]: cases were reports containing the MedDRA term "hypertension" and defined as "suspected or interacting" and non-cases all other reports. Second, we assessed the specific risk of each vaccine. Sensitivity analyses were performed, first, including only hypertension occurring after 24 h, 48 h or 72 h in order to investigate occurrence delays and, second, according to age groups (18–44, 45–64, 65–74, ≥ 75 years). Risk was calculated using the reporting odds ratio (ROR), a ratio similar to the odds ratio in case–control studies with 95% confidence intervals. RORs were adjusted on age, gender and exposure to antihypertensive and antidiabetic drugs.

Among the 175,916 reports, 91,761 involved Covid-19 vaccines with 1776 hypertension: 1325 with tozinameran (mean age 62 (18) years, 76% females, 5% in association with antihypertensives, 1% with antidiabetics), 392 with Vaxzevria® (59.1 (13.9) years, 64%, 7%, 1%), 58 with mRNA-1273 (71.9 (15.9) years, 88%, 10%, 3%) and 1 with NRVV-Ad26. The main coreported term was headache (22% for tozinameran and Vaxzevria®, 20% for mRNA-1273). Tozinameran was associated with a higher risk of hypertension compared to non-users (ROR = 2.25 (2.08–2.43)). No association was found for Vaxzevria® (ROR = 1.02 (0.92–1.14)) or mRNA-1273 (ROR = 0.88 (0.68–1.14)). A higher reporting risk was also found for tozinameran versus Vaxzevria® or mRNA-1273 in the whole population (Table 1) as well as in the different age groups (not shown). We also found increased RORs including only hypertension occurring 24, 48 or 72 h after vaccination (Table 1).

The study shows that hypertension was reported as ADRs with Covid-19 vaccines. We found a signal for tozinameran but not for Vaxzevria®. The results with mRNA-1273 should be interpreted cautiously due to the small number of reports. Mechanisms of hypertension remain unknown. One could suggest an increase in sympathetic tone for immediate hypertension and/or an interaction with the renin-angiotensin system for tardive hypertension. Involvement of vaccine excipients could be also discussed. Finally, we found that most of hypertension with tozinameran is delayed: 39% occurred after 24 h, 26% after 48 h and 20% after 72 h.

The study has some limitations. The main one is underreporting, as in any pharmacovigilance study based on spontaneous reporting. However, it was shown that underreporting does not differ within the same therapeutic group [5]. Another concern

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Table 1 Adjusted reporting odds ratios for the association between hypertension and exposure to the different Covid-19 vaccines in VigiBase®

	Cases	Non-cases	Adjusted ROR[a]	95% CI
Hypertension				
Tozinameran versus Vaxzevria®	1325/392	56,534/26,842	1.40	1.25–1.58
Tozinameran versus mRNA-1273	1325/58	56,534/3518	1.76	1.36–2.32
Hypertension after 24 h[b]				
Tozinameran versus Vaxzevria®	515/139	57,250/27,040	1.42	1.18–1.72
Tozinameran versus mRNA-1273	515/31	57,250/3540	1.40	0.99–2.07
Hypertension after 48 h[b]				
Tozinameran versus Vaxzevria®	339/92	57,426/27,087	1.39	1.10–1.77
Tozinameran versus mRNA-1273	339/23	57,426/3548	1.26	0.84–1.98
Hypertension after 72 h[b]				
Tozinameran versus Vaxzevria®	261/69	57,504/27,110	1.44	1.10–1.89
Tozinameran versus mRNA-1273	261/16	57,504/3555	1.39	0.87–2.41

ROR reporting odds ratio, *CI* confidence interval, *95% CI* 95% confidence interval, *Cases* reports of hypertension in VigiBase®, *Non-cases* all other reports in VigiBase®

[a]RORs were adjusted on age, gender and exposure to antihypertensive and antidiabetic drugs

[b]Hypertension ≥ 24 h (48 h, 72 h) means that analysis were performed with only cases of hypertension occurring 24, 48 or 72 h after vaccination

is the possibility of confounding, such as comorbidity factors or unknown data. We circumvented the difficulty associated with the absence of blood pressure values by including only reports reported by physicians, thus improving clinical validity. The main strengths are inclusion of reports collected throughout the whole world, which allows generalization of results and use of a method validated to detect rare events [3, 4] and previously found to be in accordance with meta-analyses [6].

Despite these compulsory limits, an increased risk of hypertension was found with tozinameran compared to other vaccines, requiring further studies to confirm and fully interpret this signal. These results suggest the value of measuring arterial blood pressure in vaccinated patients. Further studies are warranted to determine the incidence of new-onset hypertension following administration of different Covid-19 vaccines and its clinical implications.

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Author contribution BB, JLM, FM and FH designed the study. ST extracted the data from the database and performed the statistical analysis. All the authors analysed and discussed the data. All the authors reviewed the successive versions of the manuscript and approved the final version.

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Declarations

Competing interests The authors declare no competing interests.

References

1. Meylan S, Livio F, Foerster M, Genoud PJ, Marguet M, Wuerzner G, on behalf of the CHUV COVID Vaccination Center (2021) Stage III hypertension in patients after mRNA-based SARS-CoV-2 vaccination. Hypertension 77:e56–e57. https://doi.org/10.1161/HYPERTENSIONAHA.121.17316
2. Moore N, Berdaï D, Blin P, Droz C (2019) Pharmacovigilance - the next chapter. Therapie 74:557–567
3. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M (2011) Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 72:905–908
4. Faillie JL (2019) Case-non-case studies: principle, methods, bias and interpretation. Therapie 74:225–232
5. Pierfitte C, Bégaud B, Lagnaoui R, Moore ND (1999) Is reporting rate a good predictor of risks associated with drugs? Br J Clin Pharmacol 47:329–331
6. Khouri C, Petit C, Tod M et al (2021) Adverse drug reaction risks obtained from meta-analyses and pharmacovigilance disproportionality analyses are correlated in most cases. J Clin Epidemiol 134:14–21