Annals of Internal Medicine ORIGINAL RESEARCH

Risk for Myocardial Infarction, Stroke, and Pulmonary Embolism Following COVID-19 Vaccines in Adults Younger Than 75 Years in France

Jérémie Botton, PharmD, PhD; Marie Joelle Jabagi, PharmD, PhD; Marion Bertrand, MSc; Bérangère Baricault, MSc; Jérôme Drouin, MSc; Stéphane Le Vu, PharmD, PhD; Alain Weill, MD; Paddy Farrington, PhD; Mahmoud Zureik, MD, PhD; and Rosemary Dray-Spira, MD, PhD

Background: The BNT162b2 (Pfizer–BioNTech) vaccine has been shown to be safe with regard to risk for severe cardiovascular events (such as myocardial infarction [MI], pulmonary embolism [PE], and stroke) in persons aged 75 years or older. Less is known about the safety of other COVID-19 vaccines or outcomes in younger populations.

Objective: To assess short-term risk for severe cardiovascular events (excluding myocarditis and pericarditis) after COVID-19 vaccination in France's 46.5 million adults younger than 75 years.

Design: Self-controlled case series method adapted to event-dependent exposure and high event-related mortality.

Setting: France, 27 December 2020 to 20 July 2021.

Patients: All adults younger than 75 years hospitalized for PE, acute MI, hemorrhagic stroke, or ischemic stroke ($n = 73\,325$ total events).

Measurements: Linkage between the French National Health Data System and COVID-19 vaccine databases enabled identification of hospitalizations for cardiovascular events (MI, PE, or stroke) and receipt of a first or second dose of the Pfizer–BioNTech, mRNA-1273 (Moderna), Ad26.COV2.S (Janssen), or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine. The relative incidence (RI) of each cardiovascular event was estimated in the 3 weeks after vaccination compared with other periods, with adjustment for temporality (7-day periods).

Results: No association was found between the Pfizer–BioNTech or Moderna vaccine and severe cardiovascular events. The first dose of the Oxford–AstraZeneca vaccine was associated with acute MI and PE in the second week after vaccination (RI, 1.29 [95% CI, 1.11 to 1.51] and 1.41 [CI, 1.13 to 1.75], respectively). An association with MI in the second week after a single dose of the Janssen vaccine could not be ruled out (RI, 1.75 [CI, 1.16 to 2.62]).

Limitations: It was not possible to ascertain the relative timing of injection and cardiovascular events on the day of vaccination. Outpatient deaths related to cardiovascular events were not included.

Conclusion: In persons aged 18 to 74 years, adenoviral-based vaccines may be associated with increased incidence of MI and PE. No association between mRNA-based vaccines and the cardiovascular events studied was observed.

Primary Funding Source: None.

Ann Intern Med. doi:10.7326/M22-0988 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 23 August 2022.

The COVID-19 vaccination campaign started in France on 27 December 2020. By 20 July 2021, 37 million persons had received at least 1 vaccine dose. Four vaccines were sequentially granted authorization for emergency use: 2 mRNA-based vaccines (BNT162b2 [Pfizer–BioNTech] and mRNA-1273 [Moderna] in December and January 2021), and 2 adenoviral-based vaccines (ChAdOx1 nCoV-19 [Oxford–AstraZeneca] in February 2021 and Ad26.COV2.S [Janssen] in April 2021). An overall description of the vaccinated French population is provided in the Supplement and in Supplement Figures 1 and 2 (available at Annals.org).

Hypertension and cardiovascular, thromboembolic, and hemorrhagic events have been reported after receipt of either an mRNA-based or an adenoviral-based COVID-19 vaccine (1–3). Also, COVID-19 is known to be strongly associated with cardiovascular complications (4, 5). In a previous study, we found no increase in the rate of acute myocardial infarction (MI), stroke, or pulmonary embolism (PE) after each dose of the Pfizer–BioNTech vaccine in persons aged 75 years or older in France (6). This finding was consistent with several studies in other settings showing no association between cardiovascular outcomes (except myocarditis) and receipt of the mRNA-based vaccines (4, 7). However, some studies have reported increased risk for venous thromboembolism after receipt of the Oxford–AstraZeneca vaccine and arterial thromboembolism or hemorrhagic stroke after receipt of the Pfizer–BioNTech vaccine (8–11).

In this study, we sought to assess the short-term risk for acute MI, ischemic and hemorrhagic stroke, and PE after receipt of the Pfizer–BioNTech, Moderna, Janssen, and Oxford–AstraZeneca vaccines in the French population aged 18 to 74 years.

See also:

Web-Only
Supplement

METHODS

Databases

The French National Health Data System (Système National des Données de Santé [SNDS]) provides comprehensive health care claims and hospitalization data for 99% of the French population (8, 12, 13). This database is linked to the National COVID-19 Vaccination Database (VAC-SI), which includes the brand name of the vaccine, the dose number, and the date of injection for all people vaccinated in France. Our research group has permanent regulatory access to the SNDS data under decree no. 2016-1871 of 26 December 2016 on the processing of personal data from the SNDS and under articles Art. R. 1461-13 and 14 of French law. No informed consent was required because the data are anonymized.

Population

Vaccinated and unvaccinated persons vary by characteristics that are difficult to measure or control for (such as frailty or risk factors for cardiovascular events). Therefore, we performed within-person comparisons using an adapted self-controlled case series (SCCS) method (14, 15), as detailed in the Statistical Analysis section. This method focuses on case patients (persons who experienced a cardiovascular event of interest) such that each case patient acts as their own control, thus removing the potential confounding effect of all time-invariant covariates (for example, sex, age at the start of observation, health behaviors). The method has been conventionally used for vaccine safety evaluations (16–18).

Observation periods extended from the earliest date of vaccine availability for each manufacturer (27 December 2020 for mRNA-based vaccines, 6 February 2021 for the Oxford–AstraZeneca vaccine, and 24 April 2021 for the Janssen vaccine) until 20 July 2021. Eligible participants were all adults aged 18 to 74 years at the start of the first observation period (end of 2020) who were admitted to the hospital for acute MI, ischemic or hemorrhagic stroke, or PE during vaccine-specific observation periods (diagnoses were identified using International Classification of Diseases, 10th Revision codes) (Supplement Table 1, available at Annals.org). If a person had multiple cardiovascular events, only the first occurrence during the observation period was considered. Within every vaccine-specific observation period, all case patients who received at least 1 dose of the vaccine and all unvaccinated case patients (until 20 July 2021) were included. The inclusion of unvaccinated persons contributed directly to the assessment of baseline temporal effects and indirectly to the estimation of associations between vaccination and cardiovascular events because, as detailed in the Statistical Analysis section, vaccinations may depend on occurrence of the events (19).

Exposure Periods

The exposure period, defined as the 3 weeks after each of the first, second, and third doses of the vaccines, was subdivided into 3 subperiods of 1 week to obtain relative incidence (RI) estimates for each subperiod. A further subinterval corresponding to the day of vaccination (day 0) was also included. All other observation times were considered as baseline periods.

Comorbidities

Supplement Table 2 (available at Annals.org) shows the prevalence of several concomitant diseases among the case patients. These diseases were defined using the Cartographie des Pathologies et des Dépenses (Mapping of Diseases and Expenditures), a tool available from the Inter-Scheme Consumption Data (DCIR) database and the French Hospital National Database (PMSI) that identifies diseases in a given year using medical algorithms based on reasons for hospitalization, long-term disease diagnoses, and/or reimbursement for specific treatments for certain diseases in the previous 4 years. A detailed definition of these disease identification algorithms is publicly available in French (https://assurance-maladie.ameli.fr/sites/default/files/2020_methode-reperage-pathologies_cartographie.pdf).

Statistical Analysis

The standard SCCS method relies on 2 key assumptions: the occurrence of an event should influence neither subsequent vaccination nor the duration of observation. Here, both of these assumptions were violated owing to the possibility of postponement or cancellation of vaccination after 1 of the 4 cardiovascular events of interest and to plausible short-term mortality associated with the events of interest. Thus, the standard SCCS method had to be adapted (19, 20).

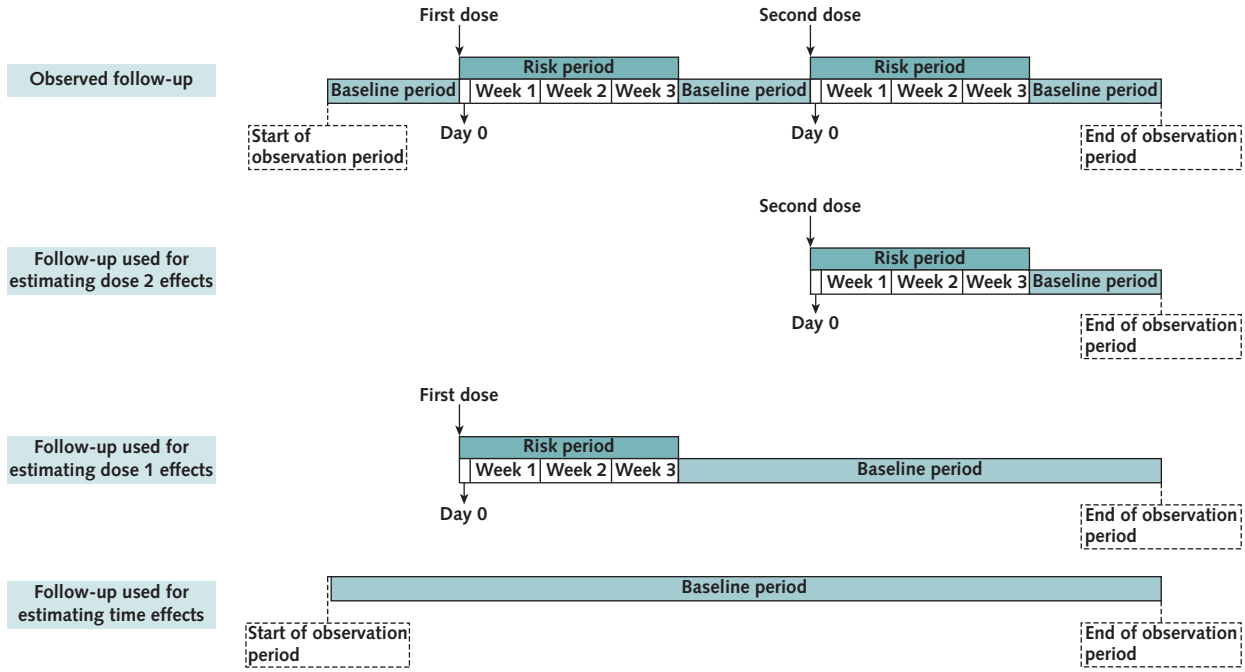
Adaptation 1: Vaccination May Vary on the Basis of Occurrence of an Event

The traditional SCCS method requires that vaccinations that preceded or followed the cardiovascular event be included to estimate the RI during exposure periods. However, it is possible that some persons may postpone or cancel subsequent vaccination because of the occurrence of an adverse event, thus leading to biased estimates. To account for this, we adapted the SCCS method, beginning with the final dose of a vaccine series (Figure). For this dose, by definition, no event can affect a subsequent vaccination because there are none. Working backward, we estimated the RI of the penultimate dose and adjusted the calculation to account for the possibility that some patients may have cancelled a dose if they had an adverse cardiovascular event. We repeated this process until the first vaccine dose. In practice, we also allow for temporal effects, and the RI is estimated simultaneously for the different vaccine doses. Because of the complexity of these adjustments, we provide a detailed (though simplified) example in the Supplement.

Adaptation 2: Cardiovascular Events May Increase Short-Term Risk for Death

A simple way to account for cardiovascular event–related mortality for some end points is to make the observation period for every case patient last until the end of the study period, regardless of the occurrence of death (6,

Figure. Conceptual diagram of the adaptation of the self-controlled case series method used.



Further details are provided in the Supplement. When the effect of the first vaccine dose is estimated, second doses (should they occur) are suppressed, but counts of cardiovascular events that occur during such second-dose exposure periods are adjusted to account for the fact that second doses were suppressed. This is done by replacing the event count *n* with *n*/RI2, where RI2 is the effect of the second dose. Second doses are suppressed when effects of the first dose are estimated because the presence and timing of such second doses may be affected by the event occurring after the first dose. See also reference 20.

19). Thus, we constructed this analysis such that observations were not censored in the event of death. This approach has recently been shown to give reliable estimates (19).

The RIs were calculated for cardiovascular events occurring during each exposure subperiod compared with the nonexposed period. The RI estimates were adjusted for temporality (in 7-day increments) to account for any temporal change in background rates of both vaccination and cardiovascular events (**Supplement Figure 3**, available at Annals.org). The numbers of case patients who received a third dose over the observation periods were insufficient to obtain reliable RI estimates for this dose; thus, the RI estimates relate to the first and second doses after the third dose was accounted for.

To limit the effect of multiple testing and hence the frequency of false-positive results, we maintained the false discovery rate at 5% (see the **Supplement**) using the method of Benjamini and Hochberg (21). We also checked the null distribution using the approach of Efron (22). To estimate the potential public health impact, we calculated the number of cardiovascular events attributable to the vaccine (the method and an example are provided in the **Supplement**) for the positive associations (23). We interpreted results both using our statistical analyses and based on consistency with estimates available in the published literature (4, 6, 7, 9).

After the emergence of risk for cerebral venous thrombosis after receipt of adenoviral-based vaccines, a substantial number of persons initially vaccinated with the Oxford–AstraZeneca vaccine received an mRNA vaccine as the second dose. Thus, for this particular vaccine, 2 analyses were performed. First, using an "initial treatment design" analysis, we did not differentiate between the types of vaccine administered as second doses after a first dose of the Oxford–AstraZeneca vaccine. Second, in an "on-treatment follow-up" analysis, the second dose was considered only when the Oxford–AstraZeneca vaccine was administered, and observation was censored otherwise. The scarcity of heterologous vaccination schedules for the other vaccines did not influence the results; therefore, for these, only the initial treatment design is presented.

To examine a possible age-related modification of the association between vaccination and adverse events, we split case patients into 2 groups at 60 years, close to the median (18 to 59 years and 60 to 74 years).

Sensitivity Analyses

To evaluate the possible effect of different follow-up time for different vaccines, we performed sensitivity analyses in which we restricted the observation period for mRNA-based vaccines to that of the Janssen vaccine. A second sensitivity analysis excluded persons with a SARS-CoV-2 infection identified during the observation period or 4 months before vaccination; this analysis was done because infection is associated with increased risk for cardiovascular events. Finally, we studied the 2

Table 1. Characteristics of Adults Aged 18 to 74 Years Who Had a Cardiovascular Event Between 27 December 2020 and 20 July 2021 in France

Characteristic	Pulmonary Embolism (*n* = 13 896)	Myocardial Infarction (*n* = 30 712)	Ischemic Stroke (*n* = 21 591)	Hemorrhagic Stroke (*n* = 7126)
Mean age (SD), *y*	59.4 (13.1)	60.7 (10.0)	62.4 (10.7)	59.9 (12.3)
Age, *n (%)*				
18–29 y	521 (3.7)	133 (0.4)	289 (1.3)	213 (3.0)
30–39 y	942 (6.8)	887 (2.9)	640 (3.0)	341 (4.8)
40–49 y	1632 (11.7)	3827 (12.5)	1891 (8.8)	868 (12.2)
50–59 y	2725 (19.6)	8486 (27.6)	4457 (20.6)	1589 (22.3)
60–69 y	4616 (33.2)	10 908 (35.5)	8043 (37.3)	2337 (32.8)
70–74 y	3462 (24.9)	6471 (21.1)	6271 (29.0)	1778 (25.0)
Women, *n (%)*	5995 (43.1)	7317 (23.8)	7633 (35.4)	2995 (42.0)
Social deprivation index* (quintiles), *n (%)*				
1 (least deprived)	2462 (17.7)	4760 (15.5)	3457 (16.0)	1204 (16.9)
2	2352 (16.9)	5496 (17.9)	3635 (16.8)	1287 (18.1)
3	2653 (19.1)	6116 (19.9)	4080 (18.9)	1274 (17.9)
4	2831 (20.4)	6280 (20.4)	4344 (20.1)	1407 (19.7)
5 (most deprived)	2901 (20.9)	6519 (21.2)	4582 (21.2)	1456 (20.4)
Missing	699 (5.0)	1541 (5.0)	1493 (6.9)	498 (7.0)
Deaths, *n (%)*	1359 (9.8)	1547 (5.0)	1770 (8.2)	1950 (27.4)
Hypertension, *n (%)*	5409 (38.9)	14 510 (47.2)	10 811 (50.1)	2966 (41.6)
Lipid-lowering treatments, *n (%)*	2862 (20.6)	9503 (30.9)	6414 (29.7)	1790 (25.1)
Diabetes, *n (%)*	1568 (11.3)	6064 (19.7)	4325 (20.0)	965 (13.5)
First vaccine, *n (%)*				
None	4338 (31.2)	7346 (23.9)	6039 (28.0)	2917 (40.9)
Oxford–AstraZeneca	1238 (8.9)	3921 (12.8)	2583 (12.0)	616 (8.6)
Janssen	77 (0.6)	282 (0.9)	196 (0.9)	38 (0.5)
Moderna	1003 (7.2)	2435 (7.9)	1491 (6.9)	414 (5.8)
Pfizer–BioNTech	7242 (52.1)	16 728 (54.5)	11 282 (52.3)	3141 (44.1)
Second vaccine, *n (%)*				
None	6946 (50.0)	12 185 (39.7)	9635 (44.6)	4181 (58.7)
Oxford–AstraZeneca	516 (3.7)	2689 (8.8)	1409 (6.5)	273 (3.8)
Janssen	2 (0.0)	3 (0.0)	3 (0.0)	1 (0.0)
Moderna	769 (5.5)	1831 (6.0)	1200 (5.6)	299 (4.2)
Pfizer–BioNTech	5665 (40.8)	14 004 (45.6)	9344 (43.3)	2372 (33.3)
Third vaccine, *n (%)*				
None	13 799 (99.3)	30 546 (99.5)	21 498 (99.6)	7109 (99.8)
Oxford–AstraZeneca	0 (0.0)	3 (0.0)	2 (0.0)	0 (0.0)
Janssen	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderna	16 (0.1)	6 (0.0)	6 (0.0)	0 (0.0)
Pfizer–BioNTech	83 (0.6)	157 (0.5)	85 (0.4)	17 (0.2)
Heterologous vaccination scheme, *n (%)*	426 (3.1)	633 (2.1)	629 (2.9)	113 (1.6)

* Social deprivation index is an indicator of socioeconomic status at the level of the city of residence, based on the median household income, the percentage of high school graduates older than 15 years in the population, the percentage of manual workers in the labor force, and the unemployment rate.

adenoviral-based vaccines in a single model, including case patients who received either the Oxford–AstraZeneca vaccine or the Janssen vaccine.

Statistical Software

The RI estimates were derived using package SCCS, version 1.0, and R software, version 3.5.2 (R Foundation for Statistical Computing). An example of annotated R code is provided in the Supplement.

Role of the Funding Source

This study received no funding.

RESULTS

General Characteristics of Patients

On average, persons with an ischemic stroke were older (mean, 62.4 years) than those with PE (mean, 59.4 years) (Table 1). Women were underrepresented, accounting for 23.8% of persons with MI and 43.1% of those with PE. All-cause mortality over the observation period was highest in patients diagnosed with hemorrhagic stroke (reaching 23% in persons receiving the Oxford–AstraZeneca vaccine, the oldest group on average) (Supplement Table 3, available at Annals.org) and lowest for those with MI (5% in the overall population of case patients and 2% in vaccinated persons). Between 39% and 50% of the included population (depending on the cardiovascular event of interest) had hypertension. Other comorbidities are summarized in Supplement Table 2. In persons who received the first dose of the Oxford–AstraZeneca vaccine, 18% to 44% received an mRNA vaccine as the second dose depending on the cardiovascular event, whereas the prevalence of a heterologous vaccine schedule was 0% to 1% when an mRNA vaccine was given as the first dose (Supplement Table 3).

Number of Persons With a Cardiovascular Event

The numbers of cardiovascular events varied by vaccine type. The numbers were greatest for persons who

received the Pfizer–BioNTech vaccine, which was most prevalent and used for the longest period (Table 1). The most frequent event was MI (30 712 overall and 16 728 among those who received the Pfizer–BioNTech vaccine). Persons receiving the Janssen vaccine had the fewest cardiovascular events, especially hemorrhagic stroke (38 among those who received the vaccine), but this vaccine was used less frequently and later. Among persons who received the Oxford–AstraZeneca vaccine, 616 hemorrhagic strokes and 3921 MIs occurred. Distributions of case patients by subperiods are shown in Table 2.

Relative Incidences

The RIs during each exposure subperiod compared with the baseline periods are reported in Table 3 for each cardiovascular event by vaccine and dose. The RIs at day 0 and during the third week after vaccination are presented in Supplement Table 4 (available at Annals.org).

The RIs quantifying the associations between cardiovascular events and the Pfizer–BioNTech vaccine after the first or second dose were close to 1 or slightly lower. Although the RIs for the Moderna vaccine were less precisely estimated than those for the Pfizer–BioNTech vaccine owing to fewer case patients, they were also generally lower than or close to 1. The highest RI was observed for PE during the first week after the second dose (36 case patients) (RI, 1.31 [95% CI, 0.90 to 1.91]).

The incidence of MI was increased during the second week after vaccination with a single dose of the Janssen vaccine compared with control periods, with an RI of 1.75 (CI, 1.16 to 2.62), which was borderline statistically significant when a false discovery rate of 5% was applied to correct for multiple testing. This association was consistent across age groups (Supplement Table 5, available at Annals.org). Other cardiovascular events were not associated with the Janssen vaccine. Under the assumption that the relationship is causal, 43% (CI, 14% to 62%) of MI events within the second week among persons who received the Janssen vaccine were attributable to vaccination, corresponding to 2.4 events per 100 000 doses.

The RI of PE during the second week after the first dose of the Oxford–AstraZeneca vaccine was 1.41 (CI, 1.13 to 1.75) in the "initial treatment design" analysis (Table 3) and 1.30 (CI, 1.04 to 1.62) in the "on-treatment follow-up" analysis (Supplement Table 6, available at Annals.org). The RI for MI during the same period was 1.29 (CI, 1.11 to 1.51) in the "initial treatment design" analysis and 1.28 (CI, 1.12 to 1.47) in the "on-treatment follow-up" analysis. These associations were consistent across age groups (Supplement Table 5). The Oxford–AstraZeneca vaccine was not associated with ischemic or hemorrhagic stroke. Under the assumption that the relationship with MI and PE is causal among persons who received the Oxford–AstraZeneca vaccine, 22% (CI, 10% to 34%) of MI events within the second week after the first dose were attributable to the vaccine, corresponding to 1.3 events per 100 000 doses. Similarly, 29% (CI, 12% to 43%) of PEs within the second week after the first dose were attributable to the vaccine, corresponding to 0.7 event per 100 000 doses.

Table 2. Number of Case Patients, by Vaccination Status and Subperiods

Vaccination Schedule	Case Patients, *n*			
	Pulmonary Embolism	Myocardial Infarction	Ischemic Stroke	Hemorrhagic Stroke
Pfizer-BioNTech*				
Unvaccinated	4336	7346	6038	2917
Before dose 1	4531	10 376	6808	1868
After dose 1†				
Total	1094	2688	1866	528
Day 0	10	20	16	4
Week 1	203	543	329	112
Week 2	200	492	366	119
Week 3	214	555	362	117
After week 3	467	1078	793	176
After dose 2†				
Total	1600	3633	2592	739
Day 0	12	20	13	5
Week 1	156	408	279	86
Week 2	178	404	307	71
Week 3	162	393	274	84
After week 3	1092	2408	1719	493
After dose 3	17	31	16	6
Moderna*				
Unvaccinated	4336	7346	6038	2917
Before dose 1	660	1679	973	265
After dose 1†				
Total	123	332	221	77
Day 0	0	2	3	0
Week 1	18	58	42	12
Week 2	26	78	40	14
Week 3	20	61	42	17
After week 3	59	133	94	34
After dose 2†				
Total	219	421	297	71
Day 0	0	0	1	0
Week 1	36	46	45	10
Week 2	23	61	41	4
Week 3	21	49	27	6
After week 3	139	265	183	51
After dose 3	1	3	0	1
Janssen‡				
Unvaccinated	1649	2926	2330	938
Before dose 1	30	109	78	10
After dose 1				
Total	47	173	118	28
Day 0	1	3	3	0
Week 1	7	33	14	6
Week 2	3	34	19	6
Week 3	6	23	9	4
After week 3	30	80	73	12
Oxford-AstraZeneca§				
Unvaccinated	3366	5757	4674	2116
Before dose 1	212	1066	529	70
After dose 1†				
Total	756	2063	1480	400
Day 0	2	7	5	1
Week 1	54	178	118	33
Week 2	94	231	154	43
Week 3	81	189	127	32
After week 3	525	1458	1076	291
After dose 2†				
Total	269	790	574	146
Day 0	0	8	7	3
Week 1	44	138	114	26
Week 2	55	129	91	34

Continued on following page

Table 2–Continued

Vaccination Schedule	Case Patients, *n*			
	Pulmonary Embolism	Myocardial Infarction	Ischemic Stroke	Hemorrhagic Stroke
Week 3	47	122	75	21
After week 3	123	393	287	62
After dose 3	1	2	1	0

* Between 27 December 2020 and 20 July 2021.
† After dose 1 = up to dose 2; after dose 2 = up to dose 3.
‡ Between 24 April 2021 and 20 July 2021.
§ Between 6 February 2021 and 20 July 2021.

Sensitivity Analyses

Restricting the observation period to that of the Janssen vaccine for the study of mRNA-based vaccines did not appreciably affect the results (**Supplement Table 7**, available at Annals.org). Exclusion of persons with a SARS-CoV-2 infection identified in the 4 months before vaccination or during the observation period yielded similar conclusions for the 4 vaccines (**Supplement Tables 8** and **9**, available at Annals.org). Finally, results from inclusion of adenoviral-based vaccines in the same model were generally similar to those for the Oxford–AstraZeneca vaccine (**Supplement Table 10**, available at Annals.org), although the RI for MI during the second week after the first dose was increased (1.40 [CI, 1.20 to 1.62]).

DISCUSSION

This nationwide study was done in a population of more than 46 million persons aged 18 to 74 years and included all who had a severe cardiovascular event. There was no evidence of a positive association between the mRNA-based vaccines and acute MI, stroke, or PE in the 3 weeks after each of the first 2 doses. There was a slight increase in risk for PE with the Oxford–AstraZeneca vaccine and for acute MI with the 2 adenoviral-based vaccines (Oxford–AstraZeneca and Janssen). The risk for PE and acute MI was increased by about 30% in the second week after the first dose of the Oxford–AstraZeneca vaccine.

Adverse cardiovascular events, including MI, stroke, and PE, were frequently reported after COVID-19 vaccination in VigiBase, the World Health Organization's pharmacovigilance database (1). Our previous analysis suggested that the Pfizer–BioNTech mRNA vaccine did not seem to be associated with increased risk for these severe cardiovascular events in persons aged 75 years or older shortly after vaccination (6). Our findings for mRNA-based vaccines in adults younger than 75 years are consistent with these earlier findings, providing further evidence that these vaccines are safe. Nevertheless, the slightly increased RI of PE in the first week after the second dose of the Moderna vaccine may warrant confirmation in other populations. We identified some positive associations with adenoviral-based vaccines, although their magnitude remained moderate compared with those related to COVID-19 itself (5).

Our findings are in line with a published Israeli study reporting that the Pfizer–BioNTech vaccine was not associated with increased risk for MI (relative risk [RR], 1.07 [CI, 0.74 to 1.60]), PE (RR, 0.56 [CI, 0.21 to 1.15]), or cerebrovascular events (RR, 0.84 [CI, 0.54 to 1.27]) at 42 days after vaccination (median age, 38 years) (4). A study in the United Kingdom that used the standard SCCS method (not the adapted method for event-dependent exposures) (20) found a slightly increased risk for arterial thromboembolism (RI, 1.06 [CI, 1.01 to 1.10]) and ischemic stroke (RI, 1.12 [CI, 1.04 to 1.20]) within 15 to 21 days after the first dose of the Pfizer–BioNTech vaccine, although these findings were sensitive to censoring due to death, with reductions in incidence ratios in sensitivity analyses (8). This study also reported increased risk for venous thromboembolism after receipt of the Oxford–AstraZeneca vaccine (RI, 1.10 [CI, 1.02 to 1.18] at 8 to 14 days). In a U.S. interim analysis that monitored 23 serious outcomes weekly using comprehensive health records from a diverse population, incidence of selected outcomes was not significantly higher 1 to 21 days after receipt of an mRNA vaccine compared with 22 to 42 days after vaccination (7). The RRs were 0.97 (CI, 0.87 to 1.08) for ischemic stroke, 0.90 (CI, 0.72 to 1.13) for hemorrhagic stroke, 1.02 (CI, 0.89 to 1.18) for acute MI, and 1.01 (CI, 0.86 to 1.19) for PE. A Scottish national prospective cohort study showed no positive associations between the Pfizer–BioNTech vaccine and thrombocytopenic, thromboembolic, and hemorrhagic events, using both a nested incident-matched case–control study and a confirmatory SCCS analysis (9). However, associations were observed between a first dose of the Oxford–AstraZeneca vaccine and arterial thromboembolic events (adjusted RR, 1.22 [CI, 1.12 to 1.34]) 0 to 27 days after vaccination, with an SCCS RR of 0.97 (CI, 0.93 to 1.02). For hemorrhagic events 0 to 27 days after vaccination, the adjusted RR was 1.48 (CI, 1.12 to 1.96), with an SCCS RR of 0.95 (CI, 0.82 to 1.11). Finally, a recent study in Hong Kong detected a possible safety signal for hemorrhagic stroke after receipt of the Pfizer–BioNTech vaccine (11); our study did not confirm this signal. To our knowledge, no study to date has assessed the association between the Janssen vaccine and risk for cardiovascular events.

Our study, which considered 4 cardiovascular events and 4 COVID-19 vaccines (including the 2 doses defining their primary schedule, when appropriate), is the most complete study on cardiovascular adverse effects of the COVID-19 vaccines to date. An inherent statistical challenge is that it required us to investigate a large number of vaccine–event pairs, thus increasing the risk for wrongly concluding that there was an association. To control this, we applied the false discovery rate method (21). A second limitation is that because the data are reported at a daily scale, we could not distinguish whether the injection or the cardiovascular event occurred first when the latter occurred on the day of vaccination (day 0). The negative associations systematically observed on day 0 are likely due to the low vaccination rate among persons who had just had a severe cardiovascular event (for whom vaccination is generally delayed). Finally, we could not include cardiovascular events occurring in an outpatient

Table 3. Relative Incidence of Severe Cardiovascular Events, by Vaccine Exposure Period*

Risk Window, by Vaccination Schedule	Relative Incidence (95% CI)			
	Pulmonary Embolism	Myocardial Infarction	Ischemic Stroke	Hemorrhagic Stroke
Pfizer-BioNTech				
Dose 1				
Week 1	0.81 (0.70–0.94)	0.91 (0.83–1.00)	0.84 (0.74–0.94)	0.97 (0.80–1.19)
Week 2	0.83 (0.71–0.96)	0.86 (0.78–0.94)†	0.95 (0.85–1.06)	1.07 (0.88–1.30)
Dose 2				
Week 1	0.83 (0.70–0.99)	0.89 (0.80–1.00)	0.93 (0.81–1.06)	0.98 (0.77–1.25)
Week 2	1.00 (0.85–1.17)	0.95 (0.85–1.06)	1.09 (0.96–1.23)	0.86 (0.67–1.11)
Moderna				
Dose 1				
Week 1	0.43 (0.26–0.71)†	0.78 (0.59–1.03)	0.76 (0.55–1.07)	0.73 (0.39–1.37)
Week 2	0.72 (0.48–1.09)	1.06 (0.83–1.37)	0.76 (0.54–1.07)	0.91 (0.51–1.61)
Dose 2				
Week 1	1.31 (0.90–1.91)	0.85 (0.61–1.18)	1.15 (0.82–1.62)	1.06 (0.56–2.00)
Week 2	0.88 (0.56–1.40)	1.21 (0.90–1.62)	1.12 (0.77–1.62)	0.45 (0.16–1.23)
Janssen				
Dose 1				
Week 1	0.94 (0.40–2.21)	1.57 (1.02–2.44)	0.78 (0.43–1.41)	1.28 (0.46–3.61)
Week 2	0.42 (0.13–1.32)	1.75 (1.16–2.62)	1.09 (0.66–1.81)	1.59 (0.60–4.21)
Oxford-AstraZeneca				
Dose 1				
Week 1	0.84 (0.63–1.10)	1.00 (0.84–1.18)	0.92 (0.76–1.11)	0.80 (0.56–1.15)
Week 2	1.41 (1.13–1.75)†	1.29 (1.11–1.51)†	1.15 (0.97–1.37)	1.06 (0.77–1.46)
Dose 2				
Week 1	0.98 (0.69–1.38)	0.86 (0.56–1.32)	1.05 (0.85–1.30)	0.96 (0.60–1.54)
Week 2	1.29 (0.94–1.78)	0.84 (0.53–1.34)	0.88 (0.69–1.12)	1.36 (0.89–2.07)

* Exposures are presented according to the vaccine administered at the first dose, by exposure subperiod after the first and second dose. Associations after a third dose are not reported because of small numbers.
† Associations considered statistically significant after controlling for the false discovery rate at 5%. Confidence intervals were not adjusted for multiple comparisons.

setting, notably sudden deaths due to such events. However, the only sudden deaths in pharmacovigilance reports were a small number associated with the adenoviral-based vaccines. The lack of outpatient data could bias the results if the associations between vaccination and the cardiovascular events were very different in patients with out-of-hospital deaths, which seems unlikely.

Several associations were negative, especially after the first dose, which is likely due either to the "well vaccinee bias," a time-varying confounding effect whereby vaccination of someone in poor health or with an infection is delayed (which is not controlled for by our SCCS models), or to a protective effect on cardiovascular outcomes, potentially through the prevention of COVID-19. Indeed, vaccination, including with adenoviral-based vaccines, could also decrease risk for a cardiovascular event by limiting the consequences of a potential SARS-CoV-2 infection.

An advantage of our study is its SCCS design, which compensates for the lack of randomization by taking into account time-invariant confounding factors, including unmeasured ones. With this method, risk comparisons are made entirely within individuals. We also adjusted for temporality to account for changes in the baseline incidence of cardiovascular events over time (**Supplement Figure 3**). Furthermore, the adaptation of the standard SCCS method for event-dependent exposures used in this study has been shown to provide valid estimates of RI when vaccination depends on the events and when the observation is highly censored due to event-related deaths (19, 20), which was the case in our study. Our study is the first to date that was able to assess the first and second doses of each of these 4 vaccines separately. This study was on a national scale and is likely to be generalizable elsewhere; we provide the analysis code to allow replication of our statistical analyses in other settings.

In conclusion, although our findings about the short-term cardiovascular safety profile of mRNA-based vaccines are reassuring overall, there is evidence of a moderate association with PE and acute MI for the Oxford–AstraZeneca vaccine and a potential risk for MI with the Janssen vaccine that would warrant confirmation in other studies.

From EPI-PHARE Scientific Interest Group in Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products – ANSM, French National Health Insurance – CNAM), Saint-Denis, France, and Faculté de Pharmacie, Université Paris-Saclay, Châtenay-Malabry, France (J.B.); EPI-PHARE Scientific Interest Group in Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products – ANSM, French National Health Insurance - CNAM), Saint-Denis, France (M.J.J., M.B., B.B., J.D., S.L.V., A.W., R.D.); School of Mathematics and Statistics, The Open University, Milton Keynes, United Kingdom (P.F.); and EPI-PHARE Scientific Interest Group in Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products - ANSM, French National Health Insurance -

CNAM), Saint-Denis, France, and University Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Anti-infective evasion and pharmacoepidemiology, CESP, Montigny le Bretonneux, France (M.Z.).

Disclosures: Authors have reported no disclosures of interest. All relevant financial relationships have been mitigated. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-0988.

Reproducible Research Statement: *Study protocol:* Our approach is fully described in the main text and in the **Supplement.** More information is available from Dr. Botton (e-mail, jeremie.botton@ansm.sante.fr). *Statistical code:* Provided in the **Supplement.** *Data set:* According to data protection and the French regulation, we cannot publicly release the data from the SNDS. However, any person or structure, public or private, for-profit or nonprofit, is able to access SNDS data upon authorization from the French Data Protection Office in order to carry out a study, research, or an evaluation of public interest (www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and www.indsante.fr).

Corresponding Author: Jérémie Botton, PharmD, PhD, EPI-PHARE, 143/147 boulevard Anatole France, F-93285 Saint-Denis, France; e-mail, jeremie.botton@ansm.sante.fr.

Author contributions are available at Annals.org.

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Author Contributions: Conception and design: J. Botton, R. Dray-Spira, M.J. Jabagi, A. Weill, M. Zureik.
Analysis and interpretation of the data: M. Bertrand, J. Botton, R. Dray-Spira, J. Drouin, P. Farrington, M.J. Jabagi, S. Le Vu, M. Zureik.
Drafting of the article: J. Botton.
Critical revision for important intellectual content: B. Baricault, R. Dray-Spira, P. Farrington, M.J. Jabagi, S. Le Vu, A. Weill, M. Zureik.
Final approval of the article: B. Baricault, M. Bertrand, J. Botton, R. Dray-Spira, J. Drouin, P. Farrington, M.J. Jabagi, S. Le Vu, A. Weill, M. Zureik.
Statistical expertise: J. Botton, P. Farrington.
Collection and assembly of data: M. Bertrand.