RESEARCH LETTER

Myocardial Infarction, Stroke, and Pulmonary Embolism After BNT162b2 mRNA COVID-19 Vaccine in People Aged 75 Years or Older

The BNT162b2 mRNA vaccine (Pfizer-BioNTech) was the first SARS-CoV-2 vaccine authorized and the most widely used in older persons in France. Although no increases in cardiovascular events were reported in phase 3 trials,[1] questions emerged once the vaccine was used on a large scale because older people were underrepresented in the trials. We evaluated the short-term risk of severe cardiovascular events among French people aged 75 years or older after the administration of the BNT162b2 mRNA vaccine.

Supplemental content

Methods | This population-based study used the French National Health Data System linked to the national COVID-19 vaccination database. Eligible participants were all persons unvaccinated or vaccinated with the BNT162b2 vaccine, aged 75 years or older, admitted to the hospital between December 15, 2020, and April 30, 2021, for acute myocardial infarction, hemorrhagic stroke, ischemic stroke, or pulmonary embolism (diagnoses identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes) (**Table 1** and eTable in the Supplement).

We undertook within-person comparisons using a self-controlled case-series method adapted to cardiovascular event-dependent exposures and high event-related mortality that can cancel or defer subsequent vaccination or increase short-term mortality[2] (eMethods in the Supplement). Only exposures preceding the event were considered. Exposure risk intervals were days 1 through 14 following each of the 2 vaccine doses. The exposure risk interval was further subdivided into days 1 through 7 and days 8 through 14. Except for the vaccination day, the remaining periods were regarded as

Table 1. Baseline Characteristics and Vaccination: Description of Cardiovascular Events That Occurred in Hospitals in France Between December 15, 2020, and April 30, 2021

	No. (%)			
	Acute myocardial infarction	Stroke		Pulmonary embolism
		Ischemic	Hemorrhagic	
Total No. of events	11 489	17 386	4891	7296
No. of persons with the event	11 113	17 014	4804	7221
No. of persons with ≥1 dose of the vaccine[a]	6510 (58.6)	9162 (54.0)	2050 (42.7)	3993 (55.3)
Month of event occurrence				
December 15, 2020-January 31, 2021	1312 (20.2)	2112 (23.0)	564 (27.5)	963 (24.1)
February 2021	1135 (17.4)	1657 (18.1)	424 (20.7)	675 (16.9)
March 2021	2640 (40.6)	3297 (36.0)	688 (33.6)	1450 (36.3)
April 2021	1423 (21.8)	2096 (22.9)	374 (18.2)	905 (22.7)
No. of persons with 2 doses of the vaccine[a]	4843 (43.6)	6531 (38.0)	1366 (28.4)	2889 (40.0)
Month of event occurrence				
December 15, 2020-January 31, 2021	20 (0.4)	44 (0.7)	9 (0.7)	18 (0.6)
February 2021	1242 (25.6)	1947 (29.8)	477 (34.9)	890 (30.8)
March 2021	1219 (25.2)	1610 (24.6)	352 (25.8)	683 (23.6)
April 2021	2362 (48.8)	2930 (44.9)	528 (38.6)	1298 (44.9)
No. of unvaccinated persons	4603 (41.4)	7852 (46.0)	2754 (57.3)	3228 (44.7)
Month of event occurrence				
December 15, 2020-January 31, 2021	2010 (43.7)	3304 (42.1)	1273 (46.2)	1347 (41.7)
February 2021	900 (19.5)	1648 (21.0)	591 (21.4)	687 (21.3)
March 2021	954 (20.7)	1720 (21.9)	569 (20.7)	669 (20.7)
April 2021	739 (16.1)	1180 (15.0)	321 (11.7)	525 (16.3)
Age at onset of the first event, y				
Mean (SD)	84 (6)	85 (6)	85 (6)	85 (6)
Median (IQR)	84 (79-88)	85 (81-90)	85 (80-89)	84 (80-89)
Women	5110 (46)	9986 (59)	2557 (53)	4534 (63)
Men	6003 (54)	7028 (41)	2247 (47)	2687 (37)
Died	2059 (19)	3971 (23)	2336 (49)	1234 (17)

[a] For vaccinated individuals between December 27, 2020 (the starting day of the vaccination campaign against SARS-CoV-2 in France), and April 30, 2021 (the end of the observation period).

Table 2. Relative Incidence of Severe Cardiovascular Events During the 14-Day Risk Periods After Exposure to the First and Second Dose of BNT162b2 Vaccine vs the Nonrisk Periods

	Acute myocardial infarction		Stroke				Pulmonary embolism	
			Ischemic		Hemorrhagic			
	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)	No. of cases	RI (95% CI)
Nonrisk periods	5233	1 [Reference]	7407	1 [Reference]	1548	1 [Reference]	3264	1 [Reference]
Mean No. of days per person	123.5		122.8		119.4		123.5	
Risk period after first dose, d								
0[a]	13	0.23 (0.13-0.40)	24	0.29 (0.20-0.44)	7	0.30 (0.14-0.64)	6	0.18 (0.08-0.41)
1-14	717	0.97 (0.88-1.06)	991	0.90 (0.84-0.98)	274	0.90 (0.78-1.04)	379	0.85 (0.75-0.96)
Subintervals								
0[a]	13	0.23 (0.13-0.40)	24	0.29 (0.20-0.44)	7	0.30 (0.14-0.64)	6	0.18 (0.08-0.41)
1-7	326	0.84 (0.75-0.95)	505	0.90 (0.82-0.99)	142	0.91 (0.75-1.09)	188	0.82 (0.70-0.96)
8-14	391	1.08 (0.97-1.21)	486	0.90 (0.82-0.99)	132	0.89 (0.73-1.07)	191	0.88 (0.75-1.02)
Risk period after second dose, d								
0[a]	9	0.22 (0.11-0.42)	22	0.37 (0.24-0.56)	8	0.45 (0.22-0.93)	12	0.51 (0.29-0.91)
1-14	538	1.04 (0.93-1.16)	718	0.92 (0.84-1.02)	213	0.97 (0.81-1.15)	332	1.10 (0.95-1.26)
Subintervals								
0[a]	9	0.22 (0.11-0.42)	22	0.37 (0.24-0.56)	8	0.45 (0.22-0.93)	12	0.51 (0.29-0.91)
1-7	269	0.97 (0.84-1.11)	363	0.87 (0.78-1.00)	113	0.95 (0.76-1.17)	167	1.04 (0.86-1.25)
8-14	269	1.11 (0.97-1.28)	355	0.96 (0.85-1.08)	100	0.99 (0.79-1.23)	165	1.15 (0.97-1.37)

Abbreviation: RI, relative incidence.

[a] Day 0 refers to the day of the vaccine injection.

nonrisk periods. Unvaccinated persons were included to account for temporal effects. Unbiased estimating equations were used to calculate the relative incidence (RI) adjusted for temporality (in 7-day increments) to consider any changes in background rates of both events and vaccination. All analyses were performed using the SCCS package in R, version 3.6.1. A 95% CI around the RI that did not include 1 defined statistical significance.

The research group has permanent regulatory access to the data from the French National Health Data System (French decree No. 2016-1871 of December 26, 2016, on the processing of personal data called National Health Data System and French law). No informed consent was required because data are anonymized.

Results | As of April 30, 2021, nearly 3.9 million persons aged 75 years or older had received at least 1 dose of the BNT162b2 vaccine and 3.2 million had received 2 doses. Over the observation period, 11 113 persons aged 75 years or older were hospitalized for an acute myocardial infarction, 17 014 for an ischemic stroke, 4804 for a hemorrhagic stroke, and 7221 for pulmonary embolism, of whom 58.6%, 54.0%, 42.7%, and 55.3%, respectively, received at least 1 dose of the vaccine (Table 1). In the 14 days following either dose, no significant increased risk was found for any outcome: the RI for myocardial infarction for the first dose was 0.97 (95% CI, 0.88-1.06) and for the second dose, 1.04 (95% CI, 0.93-1.16); for ischemic stroke for the first dose, 0.90 (95% CI, 0.84-0.98) and for the second dose, 0.92 (95% CI, 0.84-1.02); for hemorrhagic stroke for the first dose, 0.90 (95% CI, 0.78-1.04) and for the second dose, 0.97 (95% CI, 0.81-1.15); and for pulmonary embolism for the first dose, 0.85 (95% CI, 0.75-0.96) and for the second dose, 1.10 (95% CI, 0.95-1.26) (**Table 2**). No significant increase for any of the cardiovascular events was observed in the 2 subdivided exposure intervals (days 1-7 and days 8-14) (Table 2).

Discussion | In this nationwide study involving persons aged 75 years or older in France, no increase in the incidence of acute myocardial infarction, stroke, and pulmonary embolism was detected 14 days following each BNT162b2 mRNA vaccine dose.

Israeli and US studies reported that persons receiving the BNT162b2 vaccine were not at increased risk of myocardial infarction, pulmonary embolism, or cerebrovascular events in the 42 days[3] and 21 days[4] following vaccination. Based on a self-controlled case-series design that compensates for the lack of randomization by eliminating the effect of time-invariant confounding factors, this study provides further evidence regarding the risk of serious cardiovascular adverse events in older people. Limitations of the study include the possibility of residual time-dependent confounding.

Further investigations are needed to measure these risks in younger populations and for other types of vaccines against SARS-CoV-2.

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COMMENT & RESPONSE

Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation Effect on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure

To the Editor The REST trial,[1] which compared extracorporeal carbon dioxide removal ($ECCO_2R$) with lower tidal volume ventilation vs standard lung-protective ventilation for patients with acute respiratory distress syndrome (ARDS), was stopped for futility with a potential signal for harm associated with $ECCO_2R$. Previous trials[2] have suggested a clinical benefit with lower tidal volume strategies in ARDS, likely due to reduced ventilator-associated lung injury (VILI). There may be several reasons why the lower tidal volumes achieved with use of $ECCO_2R$ did not translate into better clinical outcomes in this study.[1]

First, reduction in tidal volume and drive pressure may not reduce mechanical power transmitted by the ventilator to the lung. The respiratory rate, positive end-expiratory pressure (PEEP), lung compliance, airway resistance, and inspiratory time may be other important contributors to VILI.[3] Indeed, in the $ECCO_2R$ group, higher respiratory rates and higher PEEP levels were observed (to compensate for lower ratios of the partial pressure of oxygen in arterial blood to the fractional inspired concentration of oxygen [Pao_2/Fio_2] due to lung derecruitment with lower tidal volumes). An assessment of mechanical power and VILI-associated biomarkers between groups might support this mechanism.

Second, spontaneous breathing–induced lung injury may have occurred more often in the $ECCO_2R$ group and may not have been captured in the data analysis if spontaneous tidal volumes, transpulmonary pressures, and patient-ventilator synchrony were not monitored.[4] Protocolized assessment of inspiratory occlusion pressure at 100 milliseconds, esophageal pressure, and electrical activity of the diaphragm may be useful adjuncts to mitigate these factors in future trials.

Third, extracorporeal circuits are associated with blood activation leading to systemic inflammation and circuit-induced coagulopathy. Circuit-associated biotrauma may have offset a more modest benefit of reduced tidal volumes with $ECCO_2R$.

Fourth, the threshold at which tidal volume reduction below 4 mL/kg predicted body weight achieves optimal lung protection is unknown. Preclinical data suggest that apneic ventilation may be associated with the least histologic evidence of VILI.[5]

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To the Editor The REST trial[1] targeted reductions in 90-day mortality in patients with ARDS using an $ECCO_2R$ device that is under development for treatment of patients with hypercapnic respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease. This device has been shown to be capable of removing 40% to 50% of metabolically produced carbon dioxide in a 72-hour uninjured porcine study, resulting in a reduction in minute ventilation by a similar amount while maintaining normal $Paco_2$ and pH levels.[2] Despite these data in animal studies and several