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Stroke Risk After COVID-19 Bivalent Vaccination Among US Older Adults

Yun Lu, PhD; Kathryn Matuska, BA; Gita Nadimpalli, PhD; Yuxin Ma, MS; Nathan Duma, PhD; Henry T. Zhang, PhD; Yiyun Chiang, MPH; Hai Lyu, MS; Yoganand Chillarige, MPA; Jeffrey A. Kelman, MD; Richard A. Forshee, PhD; Steven A. Anderson, PhD

IMPORTANCE In January 2023, the US Centers for Disease Control and Prevention and the US Food and Drug Administration noted a safety concern for ischemic stroke among adults aged 65 years or older who received the Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine.

OBJECTIVE To evaluate stroke risk after administration of (1) either brand of the COVID-19 bivalent vaccine, (2) either brand of the COVID-19 bivalent plus a high-dose or adjuvanted influenza vaccine on the same day (concomitant administration), and (3) a high-dose or adjuvanted influenza vaccine.

DESIGN, SETTING, AND PARTICIPANTS Self-controlled case series including 11 001 Medicare beneficiaries aged 65 years or older who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine (among 5 397 278 vaccinated individuals). The study period was August 31, 2022, through February 4, 2023.

EXPOSURES Receipt of (1) either brand of the COVID-19 bivalent vaccine (primary) or (2) a high-dose or adjuvanted influenza vaccine (secondary).

MAIN OUTCOMES AND MEASURES Stroke risk (nonhemorrhagic stroke, transient ischemic attack, combined outcome of nonhemorrhagic stroke or transient ischemic attack, or hemorrhagic stroke) during the 1- to 21-day or 22- to 42-day risk window after vaccination vs the 43- to 90-day control window.

RESULTS There were 5 397 278 Medicare beneficiaries who received either brand of the COVID-19 bivalent vaccine (median age, 74 years [IQR, 70-80 years]; 56% were women). Among the 11 001 beneficiaries who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine, there were no statistically significant associations between either brand of the COVID-19 bivalent vaccine and the outcomes of nonhemorrhagic stroke, transient ischemic attack, nonhemorrhagic stroke or transient ischemic attack, or hemorrhagic stroke during the 1- to 21-day or 22- to 42-day risk window vs the 43- to 90-day control window (incidence rate ratio [IRR] range, 0.72-1.12). Among the 4596 beneficiaries who experienced stroke after concomitant administration of either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine, there was a statistically significant association between vaccination and nonhemorrhagic stroke during the 22- to 42-day risk window for the Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine (IRR, 1.20 [95% CI, 1.01-1.42]; risk difference/100 000 doses, 3.13 [95% CI, 0.05-6.22]) and a statistically significant association between vaccination and transient ischemic attack during the 1- to 21-day risk window for the Moderna mRNA-1273.222 COVID-19 bivalent vaccine (IRR, 1.35 [95% CI, 1.06-1.74]; risk difference/100 000 doses, 3.33 [95% CI, 0.46-6.20]). Among the 21 345 beneficiaries who experienced stroke after administration of a high-dose or adjuvanted influenza vaccine, there was a statistically significant association between vaccination and nonhemorrhagic stroke during the 22- to 42-day risk window (IRR, 1.09 [95% CI, 1.02-1.17]; risk difference/100 000 doses, 1.65 [95% CI, 0.43-2.87]).

CONCLUSIONS AND RELEVANCE Among Medicare beneficiaries aged 65 years or older who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine, there was no evidence of a significantly elevated risk for stroke during the days immediately after vaccination.

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Supplemental content

Author Affiliations: Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Lu, Zhang, Forshee, Anderson); Acumen LLC, Burlingame, California (Matuska, Nadimpalli, Ma, Duma, Chiang, Lyu, Chillarige); US Centers for Medicare & Medicaid Services, Washington, DC (Kelman).

Corresponding Author: Yun Lu, PhD, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (yun.lu@fda.hhs.gov).

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On August 31, 2022, the US Food and Drug Administration authorized both the Pfizer-BioNTech (BNT162b2; WT/OMI BA.4/BA.5) and Moderna (mRNA-1273.222) COVID-19 bivalent vaccines for use as boosters through emergency use authorization.[1] The COVID-19 bivalent vaccines included mRNA components of the original COVID-19 strain as well as the BA.4 and BA.5 lineages of the Omicron variant.[1] Both COVID-19 bivalent vaccines were recommended for individuals aged 6 months or older until the approval of new monovalent vaccines in September 2023.[2,3]

On January 13, 2023, the US Centers for Disease Control and Prevention and the US Food and Drug Administration issued a public communication regarding the identification of a preliminary safety signal for ischemic stroke after receipt of the BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine for persons aged 65 years or older because of reports to the Vaccine Safety Datalink (VSD) during the immediate period (1-21 days) after vaccination.[4] The VSD noted the risk of stroke in individuals who received both the BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine and a high-dose or adjuvanted influenza vaccine on the same day (concomitant) was higher than the risk of stroke after receipt of the BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine alone.[4] The VSD was designed to be sensitive but not specific. As such, the safety signals must be evaluated in additional studies.

This report summarizes the results of a self-controlled case series including Medicare fee-for-service beneficiaries aged 65 years or older. The primary objective was to estimate the risk of incident stroke after administration of either brand of COVID-19 bivalent vaccine. Additional objectives were to investigate stroke risk by age group, after receipt of the influenza vaccine, and after concomitant administration of the influenza vaccine and either brand of the COVID-19 bivalent vaccine.

Key Points

Question Among adults aged 65 years or older, is the risk of stroke elevated in a time period immediately after administration of either brand of a COVID-19 bivalent vaccine compared with a later time period?

Findings In this self-controlled case series that included 11 001 Medicare beneficiaries who experienced stroke after administration of either brand of the COVID-19 bivalent vaccine, the risk of stroke was not significantly elevated during the 1- to 21-day or 22- to 42-day risk window after vaccination compared with the 43- to 90-day control window.

Meaning In this self-controlled case series among Medicare beneficiaries aged 65 years or older, the primary analysis showed no evidence of a significantly elevated stroke risk during the days immediately after administration of either brand of the COVID-19 bivalent vaccine.

Methods

This study did not require full US Food and Drug Administration institutional review board committee review and approval because it was determined to be exempt.[5] The use of Medicare administrative data was approved by the US Centers for Medicare & Medicaid Services privacy board under a data use agreement.

The analyses used only existing records and the individual Medicare beneficiaries cannot be identified. Patient consent was not required because the study was based on US Centers for Medicare & Medicaid Services claims data and thus does not include factors necessitating patient consent.

Data Sources

Medicare is a federally funded US health insurance program that covers individuals aged 65 years or older and those who are younger than 65 years with a disability or end-stage kidney disease. The Medicare administrative files were used; these files contain comprehensive data from program enrollment, within the inpatient claims (Part A), and within the hospital outpatient and physician office visit claims (Part B). Beneficiaries' demographic and enrollment information was obtained from the US Centers for Medicare & Medicaid Services Enrollment Database and the Common Medicare Environment. Information on nursing home residency status was ascertained using Medicare Skilled Nursing Facility claims and the Minimum Data Set (version 3.0).[6]

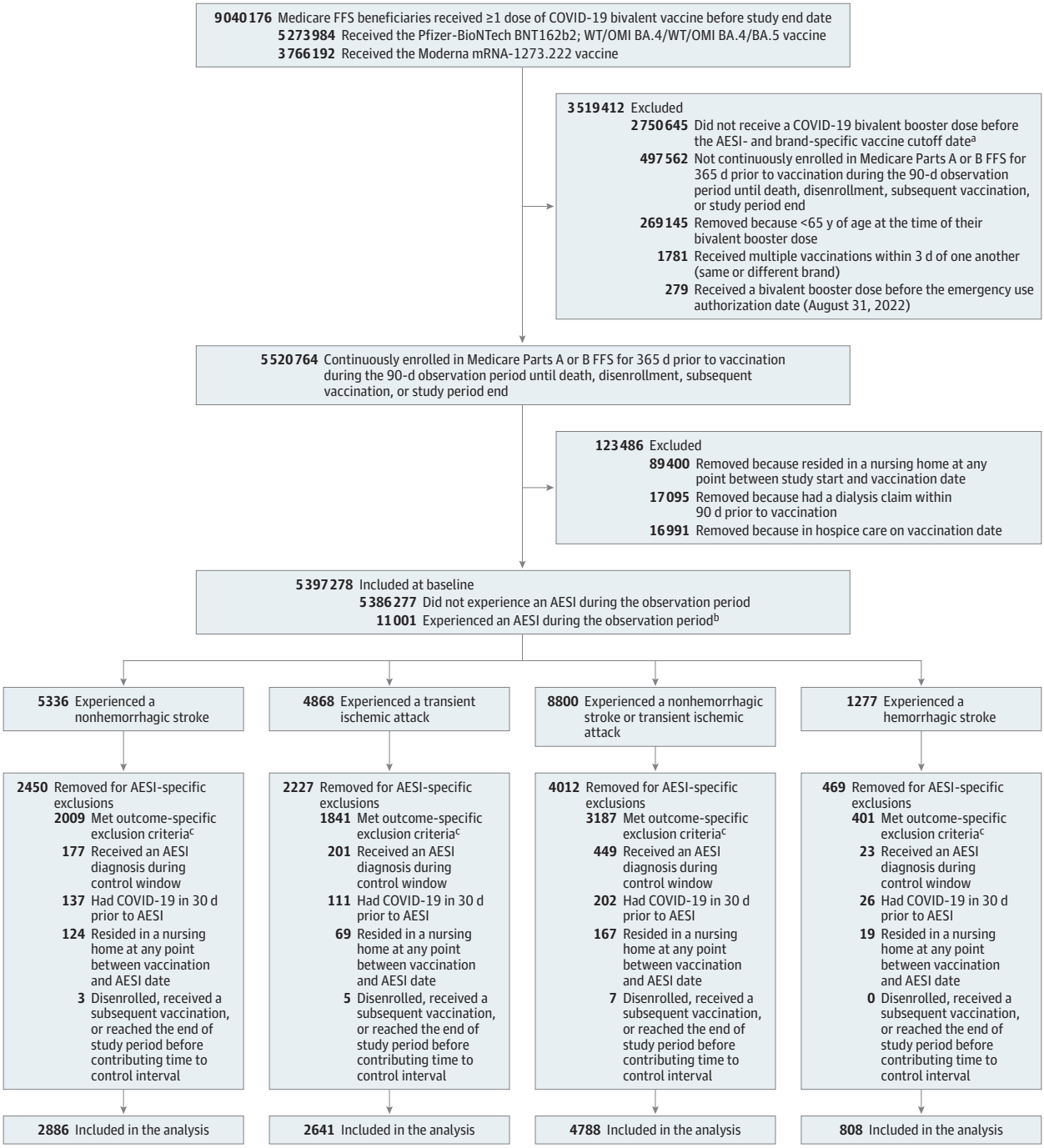
Population and Study Design

The study population for the primary analysis consisted of beneficiaries aged 65 years or older who received either brand of the COVID-19 bivalent vaccine. For the secondary analysis, the study population included those who received a high-dose or adjuvanted influenza vaccine. The case population consisted of vaccinated beneficiaries who experienced stroke after vaccination (**Figure 1**).

To be included in the study, beneficiaries could not have experienced stroke during the 365 days prior to the outcome date, lived in a long-term care facility, or received hospice care (additional exclusion criteria appear in eTable 1 in Supplement 1). Continuous Medicare fee-for-service enrollment was required from the 365 days before the relevant vaccination date. The study start date, August 31, 2022, was the emergency use authorization date for the COVID-19 bivalent vaccines. The study end date for each outcome was determined independently to ensure data completeness of at least 90% (eTable 2 in Supplement 1); the latest end date was February 4, 2023.[4]

A self-controlled case series analysis was conducted to compare the incidence of stroke outcomes after administration of (1) either brand of the COVID-19 bivalent vaccine, (2) concomitant administration of either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine, and (3) a high-dose or adjuvanted influenza vaccine within the hypothesized 1- to 21-day or 22-42-day risk window compared with the 43- to 90-day control window. The determination of the hypothesized risk windows was based on biological plausibility, prior studies, and input from subject matter experts.[7,8] Self-controlled case

Figure 1. Cohort Summary for the Primary Analysis



AESI indicates adverse event of special interest; FFS, fee-for-service.

[a] For those who experienced a nonhemorrhagic stroke, the study period spans from August 31, 2022, to January 18, 2023, and the vaccine cutoff date (90 days prior to study end) was October 20, 2022. For those who experienced a transient ischemic attack, the study period spans from August 31, 2022, to February 4, 2023, and the vaccine cutoff date was November 6, 2022. For those who experienced a nonhemorrhagic stroke or a transient ischemic attack, the study period spans from August 31, 2022, to January 18, 2023, and the vaccine cutoff date was October 20, 2022. For those who experienced a hemorrhagic stroke, the study period spans from August 31, 2022, to January 12, 2023, and the vaccine cutoff date was October 14, 2022.

[b] A beneficiary may have contributed to multiple outcome cohorts; therefore, the sum of the outcome case populations is greater than the number of unique beneficiaries who experienced an AESI during the observation period.

[c] The outcome-specific *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* exclusion codes appear in eTable 5 in Supplement 1.

series studies leverage exposed (risk) and unexposed (control) periods within the same individual, inherently adjusting for sources of time-invariant confounding in the between-individual comparisons.[9,10] The study plan appears in eTable 1 in Supplement 1. We only included vaccinated cases and limited the control period to postvaccination because of potential underreporting of vaccination status in claims data and the influence of outcomes on vaccination propensity.

Exposures

The primary exposure of interest was receipt of either brand of the COVID-19 bivalent vaccine. The secondary exposure of interest was receipt of a high-dose or adjuvanted influenza vaccine. The exposures were identified through Current Procedural Terminology Healthcare Common Procedure Coding System codes from various care settings (eTables 3-4 in Supplement 1).

Outcomes

The stroke outcomes were nonhemorrhagic stroke, transient ischemic attack, a combined outcome of nonhemorrhagic stroke or transient ischemic attack, and hemorrhagic stroke that occurred during the 1- to 21-day or 22- to 42-day risk window after vaccine administration compared with the 43- to 90-day control window.

Persons who experienced nonhemorrhagic stroke and transient ischemic attack contributed only their first stroke event to the combined outcome group of nonhemorrhagic stroke or transient ischemic attack. An incident stroke outcome was defined as the first recorded stroke event for an individual during the observation period after vaccination (eTable 4 in Supplement 1). In addition, outcome-specific exclusion criteria (eg, trauma codes; eTable 5 in Supplement 1) were applied to eliminate stroke cases determined to have causes other than COVID-19 vaccination.[4]

For the primary analysis of receipt of either brand of the COVID-19 bivalent vaccine and stroke risk, patients diagnosed with COVID-19 within 30 days prior to the stroke outcome were excluded.[11-13] The stroke outcomes were identified using *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* codes (eTable 4 in Supplement 1). All outcomes were captured in the inpatient care setting. Cases of transient ischemic attack were additionally captured in the outpatient emergency department setting.

Beneficiaries were required to accumulate time during both the risk windows (1-21 days or 22-42 days after vaccine administration) and the control window (43-90 days after vaccine administration) except when death occurred before the control window (eTable 6 in Supplement 1). For both the primary and secondary analyses, beneficiaries with the relevant vaccine exposure were followed up until the earliest occurrence of the follow-up period end, study period end, disenrollment, administration of a subsequent exposure vaccine, or death.

Medical Record Review

To validate the claims-based outcome definitions, we retrieved and adjudicated a random sample of nonhemorrhagic stroke medical records from the inpatient care settings. Using predetermined clinical definitions, cases were identified as true cases, not cases, or potentially indeterminate.[14] We calculated the positive predictive value (PPV) along with the corresponding 95% CIs and conducted a PPV-adjusted analysis to evaluate the presence and magnitude of bias in the risk estimates resulting from potential misclassification of nonhemorrhagic stroke using imputation (eTable 1 in Supplement 1).[15] In a sample of 87 nonhemorrhagic stroke cases, the PPV was 80.46% (95% CI, 70.92%-87.43%); the results of the medical record review appear in eTable 7 in Supplement 1.

Statistical Analysis

Descriptive statistics were obtained for beneficiaries' demographics, socioeconomic status, medical history, prior COVID-19 or influenza diagnosis, and concomitant vaccination. Both the primary and secondary analyses used a self-controlled case series study design with a control window of 43 to 90 days after vaccination. Conditional Poisson regression was used to estimate the incidence rate ratios (IRRs) comparing the risk and control windows for each outcome.[10,16] The IRRs were calculated separately for each brand of the COVID-19 bivalent vaccine. The risk difference per 100 000 vaccine doses, representing the excess risk of the outcome attributable to the exposure among the vaccinated population, was calculated by dividing the excess number of cases by the number of eligible vaccinations.[17]

Given the high case fatality rate associated with stroke events, and to address potential bias arising from curtailed observation time being dependent on outcome occurrence, the Farrington adjustment was used, which introduced an additional term to account for the curtailed observation time due to censoring (eTable 8 in Supplement 1).[18] A sensitivity analysis incorporated seasonal patterns and changes in stroke incidence rates to account for potential time-varying confounding. Another sensitivity analysis used the nonhemorrhagic stroke PPV to minimize outcome misclassification.

Subgroup analyses were conducted for both the primary and secondary study populations to evaluate the risk for each stroke outcome by age group (65-74, 75-84, ≥85 years) and for concomitant administration of either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine and no concomitant vaccination. We did not test for differences in the effects across subgroups.

A temporal scan was conducted to identify clusters of increased stroke risk within the 1- to 90-day period after COVID-19 bivalent and influenza vaccination. The maximum cluster size was set to 50% of the observation period (45 days), and the minimum window length was set to 3 days. The temporal scan was conducted using SaTScan.[19]

The number of tests conducted in this study may increase type I error. As such, we considered a single result as no more than tentative evidence, and looked for consistency across vaccines, outcomes, risk windows, and age groups. All tests were 2-tailed and $P < .05$ was used for statistical significance testing. All analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute Inc).

Results

Primary Analyses of COVID-19 Bivalent Vaccine

Descriptive Results

Of the 5 397 278 Medicare beneficiaries (median age, 74 years [IQR, 70-80 years]; 56% were women) who received either brand of the COVID-19 bivalent vaccine, 11 001 experienced stroke (**Table** and Figure 1). After removal of stroke cases for relevant exclusion criteria, there were 2886 cases of nonhemorrhagic stroke across both brands of the COVID-19 bivalent vaccine, 2641 cases of transient ischemic attack, 4788 cases for the combined outcome of nonhemorrhagic stroke or transient ischemic attack, and 808 cases of hemorrhagic stroke included in the primary analyses (Figure 1 and eTable 9 in Supplement 1).

The population characteristics were largely consistent between the COVID-19 vaccine brands. Cases of hemorrhagic stroke and nonhemorrhagic stroke exhibited a high case fatality rate (17%-34%), with 5% to 16% of patients dying before reaching the control window of 43 to 90 days (eTables 6 and 8 in Supplement 1). All outcomes exhibited distinct historical seasonality patterns (eFigure 1 in Supplement 1). Approximately 10% to 15% of the case population had a COVID-19 diagnosis claim in the 31 to 365 days prior to stroke outcomes, and 34% to 45% of the population had a concomitant high-dose or adjuvanted influenza vaccination (eTable 9 in Supplement 1). Patient characteristics stratified by age subgroup and concomitant influenza vaccine status appear in eTables 10-13 in Supplement 1.

Inferential Results

There were no statistically significant associations between receipt of the COVID-19 bivalent vaccines and the stroke outcomes in the primary, seasonality-adjusted, or PPV-adjusted analyses (**Figures 2**, **3**, and **4** and eTables 14-16 in Supplement 1). For the outcome of nonhemorrhagic stroke after administration of the COVID-19 bivalent BNT162b2; WT/OMI BA.4/BA.5 vaccine, the event rate was 0.83 per 100 000 person-days during the 1- to 21-day risk window after vaccination (IRR, 1.06 [95% CI, 0.94 to 1.19] vs the control window of 43-90 days; risk difference/100 000 doses, 0.99 [95% CI, −1.01 to 2.99]), 0.81 per 100 000 person-days during the 22- to 42-day risk window after vaccination (IRR, 1.05 [95% CI, 0.94 to 1.18] vs the control window of 43-90 days; risk difference/100 000 doses, 0.83 [95% CI, −1.10 to 2.76]), and 0.81 per 100 000 person-days during the 43- to 90-day control window. The temporal scan did not identify any significant stroke clusters after administration of either COVID-19 bivalent vaccine (eFigure 2 in Supplement 1).

Subgroup Analyses by Age Groups | A statistically significant association between receipt of the COVID-19 bivalent BNT162b2; WT/OMI BA.4/BA.5 vaccine and nonhemorrhagic stroke was observed in the age group of 85 years or older during the 1- to 21-day risk window after vaccination (IRR, 1.36 [95% CI, 1.09-1.69]; risk difference/100 000 doses, 11.93 [95% CI, 3.02-20.84]) and for the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 1- to 21-day risk window after BNT162b2; WT/OMI BA.4/BA.5 vaccination (IRR, 1.28 [95% CI, 1.08-1.52]; risk difference/100 000 doses, 15.35 [95% CI, 4.34-26.36]) (Figures 3 and 4 and eTables 17-18 in Supplement 1).

An association between receipt of the COVID-19 bivalent mRNA-1273.222 vaccine and the combined outcome of nonhemorrhagic stroke or transient ischemic attack was observed in the age group of 65 to 74 years during the 22- to 42-day risk window after vaccination (IRR, 1.22 [95% CI, 1.01-1.49]; risk difference/100 000 doses, 3.37 [95% CI, 0.05-6.69]). No significant association between vaccination and stroke was observed in the age subgroup analyses for hemorrhagic stroke or transient ischemic attack (Figures 3 and 4 and eTables 17-18 in Supplement 1).

Subgroup Analyses by Vaccination With Either Brand of COVID-19 Bivalent Vaccine Plus a High-Dose or Adjuvanted Influenza Vaccine | Among 4596 individuals with a stroke outcome after concomitant administration of either brand of COVID-19 bivalent vaccine and a high-dose or adjuvanted influenza vaccine, a statistically significant association between nonhemorrhagic stroke and the COVID-19 bivalent BNT162b2; WT/OMI BA.4/BA.5 vaccine was observed during the 22- to 42-day risk window after vaccination (IRR, 1.20 [95% CI, 1.01-1.42]; risk difference/100 000 doses, 3.13 [95% CI, 0.05-6.22]) and between transient ischemic attack and the COVID-19 bivalent mRNA-1273.222 vaccine was observed during the 1- to 21-day risk window after vaccination (IRR, 1.35 [95% CI, 1.06-1.74]; risk difference/100 000 doses, 3.33 [95% CI, 0.46-6.20]). No significant association between COVID-19 bivalent vaccination and stroke was observed among those who did not concomitantly receive a high-dose or adjuvanted influenza vaccine (Figure 2 and eTables 19-20 in Supplement 1).

Secondary Analyses of Influenza Vaccine

Descriptive Results

Of the 9 023 977 Medicare beneficiaries who received a high-dose or adjuvanted influenza vaccine (median age, 75 years [IQR, 70-80 years]; 58% were women), 21 345 experienced stroke (eTable 21 in Supplement 1). After removal for relevant exclusions, there were 5497 cases of nonhemorrhagic stroke, 4871 cases of transient ischemic attack, 9065 cases for the combined outcome of nonhemorrhagic stroke or transient ischemic attack, and 1498 cases of hemorrhagic stroke. The baseline characteristics of the secondary case population who received the influenza vaccine appear in eTable 22 in Supplement 1 and were similar to the primary case population who received either brand of the COVID-19 bivalent vaccine.

Inferential Results

The secondary analysis showed a small but statistically significant association between receipt of a high-dose or adjuvanted influenza vaccine and the outcome of nonhemorrhagic stroke during the 22- to 42-day risk window after vaccination. The event rate for nonhemorrhagic stroke was 0.86 per 100 000 person-days during the 1- to 21-day risk window after vaccination (IRR, 1.02 [95% CI, 0.96 to 1.10]; risk

Table. Characteristics of the Medicare Beneficiaries Included in the Primary Outcome Analysis by COVID-19 Bivalent Vaccine Brand

	Medicare beneficiaries by COVID-19 bivalent vaccine brand, No. (%)[a]	
	Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 (n = 3 173 426)	Moderna mRNA-1273.222 (n = 2 223 852)
Demographics		
Age group, y		
65-74	1 593 152 (50.2)	1 144 791 (51.5)
75-84	1 182 051 (37.2)	828 400 (37.3)
≥85	398 223 (12.5)	250 661 (11.3)
Age, median (IQR), y	74 (70-80)	74 (70-80)
Sex		
Female	1 803 666 (56.8)	1 245 259 (56.0)
Male	1 369 760 (43.2)	978 593 (44.0)
Race and ethnicity[b]		
No. with data[c]	3 066 944	2 147 863
American Indian or Alaska Native	8464 (0.3)	5746 (0.3)
Asian	57 626 (1.9)	43 421 (2.0)
Black	128 794 (4.2)	83 209 (3.9)
Hispanic	16 460 (0.5)	10 569 (0.5)
White	2 794 294 (91.1)	1 956 216 (91.1)
Other[d]	61 306 (2.0)	48 702 (2.3)
Location		
Urban or rural status[e]		
No. with data[c]	3 161 140	2 213 637
Urban[f]	2 706 679 (85.6)	1 771 493 (80.0)
Rural[g]	454 461 (14.4)	442 144 (20.0)
US Department of Health and Human Services region (included states or territories within region)		
No. with data[c]	3 171 447	2 222 036
1 (CT, MA, ME, NH, RI, VT)	251 081 (7.9)	173 813 (7.8)
2 (NJ, NY, PR, VI)	279 512 (8.8)	209 226 (9.4)
3 (DC, DE, MD, PA, VA, WV)	392 490 (12.4)	278 087 (12.5)
4 (AL, FL, GA, KY, MS, NC, SC, TN)	512 388 (16.2)	412 363 (18.6)
5 (IL, IN, MI, MN, OH, WI)	607 462 (19.2)	365 866 (16.5)
6 (AR, LA, NM, OK, TX)	239 271 (7.5)	209 893 (9.4)
7 (IA, KS, MO, NE)	202 693 (6.4)	106 691 (4.8)
8 (CO, MT, ND, SD, UT, WY)	141 033 (4.4)	62 797 (2.8)
9 (AS, AZ, CA, FM, GU, HI, MH, MP, NV)[h]	380 210 (12.0)	305 806 (13.8)
10 (AK, ID, OR, WA)	165 307 (5.2)	97 494 (4.4)
Socioeconomic status		
Area Deprivation Index[i]		
No. with data[c]	3 006 659	2 104 998
1-20 (reflects disadvantage)	1 079 773 (35.9)	762 128 (36.2)
21-40	872 736 (29.0)	551 475 (26.2)
41-60	571 833 (19.0)	392 006 (18.6)
61-80	333 060 (11.1)	271 382 (12.9)
81-100 (reflects advantage)	149 257 (5.0)	128 007 (6.1)
Insurance information		
Medicare eligibility		
Based on age	2 978 506 (93.9)	2 088 989 (93.9)
Based on age, disability, and having end-stage kidney disease	3575 (0.1)	2280 (0.1)
Based on disability without having end-stage kidney disease	191 345 (6.0)	132 583 (6.0)
Dually eligible for Medicare and Medicaid	101 471 (3.2)	65 825 (3.0)

(continued)

difference/100 000 doses, 0.44 [95% CI, −0.78 to 1.65]), 0.92 per 100 000 person-days during the 22- to 42-day risk window after vaccination (IRR, 1.09 [95% CI, 1.02 to 1.17]; risk difference/100 000 doses, 1.65 [95% CI, 0.43 to 2.87]), and 0.88

Table. Characteristics of the Medicare Beneficiaries Included in the Primary Outcome Analysis by COVID-19 Bivalent Vaccine Brand (continued)

	Medicare beneficiaries by COVID-19 bivalent vaccine brand, No. (%)[a]	
	Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 (n = 3 173 426)	Moderna mRNA-1273.222 (n = 2 223 852)
Medical information		
Modified Charlson Comorbidity Index score[j]		
0	1 090 707 (34.4)	777 662 (35.0)
1-4	1 694 715 (53.4)	1 186 093 (53.3)
≥5	388 004 (12.2)	260 097 (11.7)
Medical conditions (0-365 d prior to vaccination date)		
Hypertension	2 185 114 (68.9)	1 532 873 (68.9)
Obesity	719 695 (22.7)	511 726 (23.0)
Hypercholesterolemia	684 780 (21.6)	489 908 (22.0)
Hypothyroidism	687 271 (21.7)	481 411 (21.6)
Chronic kidney disease	624 281 (19.7)	422 211 (19.0)
Nicotine dependency	624 301 (19.7)	420 758 (18.9)
Depression	487 506 (15.4)	314 788 (14.2)
Heart failure	369 334 (11.6)	252 981 (11.4)
Chronic obstructive pulmonary disease	305 178 (9.6)	212 700 (9.6)
Asthma	252 280 (7.9)	176 696 (7.9)
Ischemic heart disease	172 590 (5.4)	123 786 (5.6)
Gout	164 656 (5.2)	116 673 (5.2)
Impaired mobility	8400 (0.3)	4934 (0.2)
Idiopathic thrombocytopenic purpura	7023 (0.2)	5033 (0.2)
Prior to stroke		
COVID-19 diagnosis within 31-365 d	866 (<0.1)	537 (<0.1)
Influenza diagnosis within 30 d	29 (<0.1)	17 (<0.1)
Influenza diagnosis within 31-365 d	37 (<0.1)	21 (<0.1)
Concomitant vaccination (same day as COVID-19 bivalent vaccine)		
High-dose influenza	837 470 (26.4)	477 284 (21.5)
Adjuvanted influenza	456 837 (14.4)	292 918 (13.2)
Recombinant influenza	11 059 (0.3)	6426 (0.3)
Live-attenuated influenza	0	0
Cell-cultured influenza	7962 (0.3)	6405 (0.3)
Standard influenza	19 587 (0.6)	13 381 (0.6)
Unknown type influenza	1 304 041 (41.1)	774 207 (34.8)
Pneumococcal vaccine[k]	94 716 (3.0)	66 738 (3.0)
Stroke outcome		
Nonhemorrhagic stroke	3352 (0.1)	1984 (0.1)
Transient ischemic attack	2973 (0.1)	1895 (0.1)
Combined outcome of nonhemorrhagic stroke or transient ischemic attack	5501 (0.2)	3299 (0.1)
Hemorrhagic stroke	831 (<0.1)	446 (<0.1)

Abbreviations: AS, American Samoa; FM, Federated States of Micronesia; GU, Guam; MH, Marshall Islands; MP, Northern Mariana Islands.

[a] Age is the only variable expressed as median (IQR) instead of No. (%). The variables with outcome counts of 10 or fewer were masked to protect the anonymity of the data.

[b] Based on a combination of self-reported, closed-category data from the Social Security Administration along with an algorithm the US Centers for Medicare & Medicaid Services uses to improve information for the Asian, Pacific Islander, and Hispanic individuals who were not captured in the original response categories. If a beneficiary did not self-report race and ethnicity, the values were classified as missing or unknown.

[c] The remainder of values were classified as missing or unknown.

[d] Self-reported as not falling under any of the categories.

[e] Determined from the core-based statistical area, which categorizes areas as metropolitan (≥1 urban area with a population of ≥50 000) or micropolitan (≥1 urban cluster with a population between 10 000 and 50 000), and was assigned based on the beneficiary's most recently available residential address.

[f] Address was classified as metropolitan.

[g] Address was classified as micropolitan or was not classified.

[h] This region also includes the Republic of Palau.

[i] Ranks neighborhoods by socioeconomic disadvantage. It includes factors for theoretical domains of income, education, employment, and housing quality. The data were collected from the Neighborhood Atlas and are based on a beneficiary's census block group, which is mapped based on their most recently available residential address in the Medicare enrollment dataset. A higher ranking corresponds to higher levels of socioeconomic advantage.

[j] Each condition was assigned a score based on its associated mortality risk. The total score ranges from 0 to 24; higher numbers indicate a greater risk of 1-year mortality.

[k] Administered during risk window (1-21 days or 22-42 days after administration of either brand of COVID-19 bivalent vaccine) or control window (43-90 days after COVID-19 vaccination).

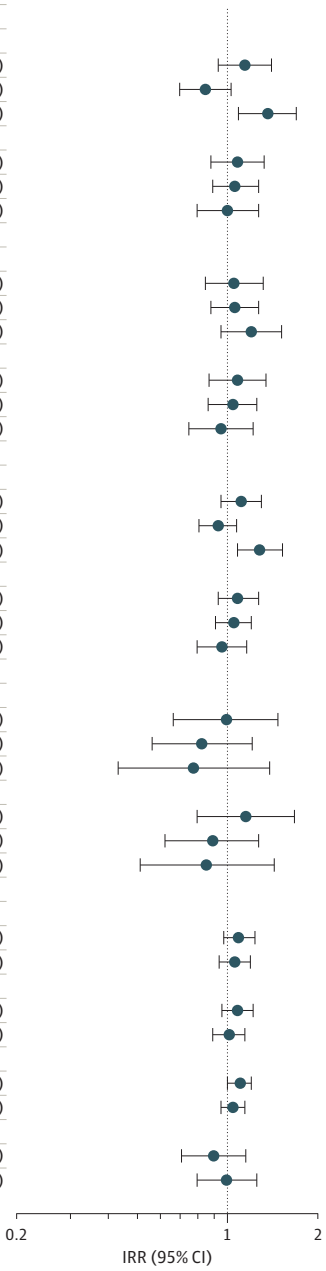
Figure 2. Risk of Stroke in the Primary Analysis and in the Subgroup Analysis by COVID-19 Bivalent Vaccine Brand

	Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 (n = 3 173 426)					Moderna mRNA-1273.222 (n = 2 223 852)				
	No. of adverse events		Event rate per 100 000 person-days			No. of adverse events		Event rate per 100 000 person-days		
	At risk	Control	At risk	Control	IRR (95% CI)	At risk	Control	At risk	Control	IRR (95% CI)
Primary analysis: COVID-19 bivalent vaccine										
Nonhemorrhagic stroke										
1- to 21-d risk window	425	953	0.83	0.81	1.06 (0.94-1.19)	215	607	0.62	0.77	0.88 (0.75-1.03)
22- to 42-d risk window	418	953	0.81	0.81	1.05 (0.94-1.18)	268	607	0.78	0.77	1.06 (0.92-1.23)
Transient ischemic attack										
1- to 21-d risk window	389	849	0.58	0.56	1.08 (0.96-1.22)	245	536	0.53	0.50	1.09 (0.94-1.27)
22- to 42-d risk window	368	849	0.55	0.56	1.02 (0.91-1.16)	254	536	0.54	0.50	1.12 (0.97-1.31)
Nonhemorrhagic stroke or transient ischemic attack										
1- to 21-d risk window	712	1579	1.39	1.34	1.07 (0.98-1.17)	394	977	1.14	1.24	0.99 (0.88-1.11)
22- to 42-d risk window	686	1579	1.34	1.34	1.04 (0.95-1.13)	440	977	1.28	1.24	1.08 (0.96-1.21)
Hemorrhagic stroke										
1- to 21-d risk window	107	295	0.24	0.29	0.88 (0.68-1.12)	50	172	0.17	0.26	0.72 (0.52-1.01)
22- to 42-d risk window	123	295	0.28	0.29	0.98 (0.78-1.23)	61	172	0.21	0.26	0.83 (0.61-1.13)
Subgroup analysis: concomitant influenza vaccine										
Nonhemorrhagic stroke										
1- to 21-d risk window										
Concomitant influenza vaccine	201	397	0.92	0.79	1.19 (1.00-1.42)	88	243	0.70	0.85	0.89 (0.69-1.14)
No concomitant influenza vaccine	215	541	0.74	0.82	0.95 (0.81-1.12)	124	354	0.58	0.72	0.88 (0.71-1.08)
22- to 42-d risk window										
Concomitant influenza vaccine	199	397	0.91	0.79	1.20 (1.01-1.42)	101	243	0.80	0.85	1.00 (0.79-1.27)
No concomitant influenza vaccine	211	541	0.73	0.82	0.94 (0.80-1.10)	165	354	0.77	0.72	1.11 (0.92-1.34)
Transient ischemic attack										
1- to 21-d risk window										
Concomitant influenza vaccine	169	379	0.62	0.61	1.06 (0.88-1.27)	98	175	0.61	0.47	1.35 (1.06-1.74)
No concomitant influenza vaccine	214	457	0.55	0.52	1.11 (0.95-1.31)	147	355	0.49	0.52	0.99 (0.82-1.20)
22- to 42-d risk window										
Concomitant influenza vaccine	156	379	0.57	0.61	0.98 (0.81-1.18)	89	175	0.55	0.47	1.21 (0.94-1.56)
No concomitant influenza vaccine	205	457	0.53	0.52	1.06 (0.90-1.25)	162	355	0.54	0.52	1.09 (0.90-1.31)
Nonhemorrhagic stroke or transient ischemic attack										
1- to 21-d risk window										
Concomitant influenza vaccine	329	688	1.50	1.38	1.13 (0.98-1.29)	165	373	1.31	1.30	1.09 (0.90-1.31)
No concomitant influenza vaccine	372	868	1.29	1.31	1.02 (0.90-1.15)	226	592	1.05	1.21	0.94 (0.80-1.09)
22- to 42-d risk window										
Concomitant influenza vaccine	312	688	1.43	1.38	1.08 (0.94-1.24)	163	373	1.30	1.30	1.06 (0.88-1.27)
No concomitant influenza vaccine	361	868	1.25	1.31	0.99 (0.87-1.12)	272	592	1.27	1.21	1.10 (0.95-1.27)
Hemorrhagic stroke										
1- to 21-d risk window										
Concomitant influenza vaccine	51	128	0.27	0.30	0.96 (0.67-1.39)	18	60	0.17	0.25	0.80 (0.45-1.43)
No concomitant influenza vaccine	56	160	0.22	0.28	0.85 (0.60-1.20)	32	108	0.17	0.26	0.70 (0.46-1.06)
22- to 42-d risk window										
Concomitant influenza vaccine	66	128	0.35	0.30	1.26 (0.92-1.74)	20	60	0.19	0.25	0.84 (0.49-1.44)
No concomitant influenza vaccine	55	160	0.22	0.28	0.76 (0.54-1.06)	41	108	0.22	0.26	0.83 (0.57-1.22)

IRR indicates incidence rate ratio. The IRRs were obtained using conditional Poisson regression. The primary analysis included Medicare beneficiaries who received either brand of the COVID-19 bivalent vaccine. The subgroup analysis included Medicare beneficiaries who received either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine on the same day (concomitant vaccination).

Figure 3. Risk of Stroke by Age Subgroup and Seasonality-Adjusted Analyses for Those Who Received the Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 COVID-19 Bivalent Vaccine

	Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 (n = 3 173 426)				
	No. of adverse events		Event rate per 100 000 person-days		
	At risk	Control	At risk	Control	IRR (95% CI)
Age subgroup analysis					
Nonhemorrhagic stroke					
1- to 21-d risk window					
Aged 65-74 y	144	305	0.56	0.52	1.14 (0.93-1.40)
Aged 75-84 y	145	405	0.75	0.92	0.84 (0.69-1.03)
Aged ≥85 y	136	243	2.17	1.69	1.36 (1.09-1.69)
22- to 42-d risk window					
Aged 65-74 y	137	305	0.53	0.52	1.08 (0.88-1.32)
Aged 75-84 y	182	405	0.95	0.92	1.06 (0.89-1.27)
Aged ≥85 y	99	243	1.58	1.69	1.00 (0.79-1.27)
Transient ischemic attack					
1- to 21-d risk window					
Aged 65-74 y	116	262	0.35	0.34	1.05 (0.84-1.31)
Aged 75-84 y	167	375	0.67	0.66	1.06 (0.88-1.27)
Aged ≥85 y	106	212	1.27	1.11	1.20 (0.95-1.51)
22- to 42-d risk window					
Aged 65-74 y	119	262	0.36	0.34	1.08 (0.87-1.34)
Aged 75-84 y	164	375	0.66	0.66	1.04 (0.86-1.25)
Aged ≥85 y	85	212	1.02	1.11	0.95 (0.74-1.22)
Nonhemorrhagic stroke or transient ischemic attack					
1- to 21-d risk window					
Aged 65-74 y	235	505	0.91	0.85	1.11 (0.95-1.30)
Aged 75-84 y	267	682	1.39	1.55	0.93 (0.80-1.07)
Aged ≥85 y	210	392	3.34	2.73	1.28 (1.08-1.52)
22- to 42-d risk window					
Aged 65-74 y	229	505	0.89	0.85	1.08 (0.93-1.27)
Aged 75-84 y	302	682	1.57	1.55	1.05 (0.91-1.20)
Aged ≥85 y	155	392	2.47	2.73	0.96 (0.79-1.16)
Hemorrhagic stroke					
1- to 21-d risk window					
Aged 65-74 y	36	98	0.16	0.19	0.99 (0.66-1.47)
Aged 75-84 y	47	124	0.28	0.33	0.82 (0.56-1.21)
Aged ≥85 y	24	73	0.45	0.60	0.77 (0.43-1.38)
22- to 42-d risk window					
Aged 65-74 y	48	98	0.21	0.19	1.15 (0.79-1.67)
Aged 75-84 y	47	124	0.28	0.33	0.89 (0.62-1.27)
Aged ≥85 y	28	73	0.53	0.60	0.85 (0.51-1.43)
Seasonality-adjusted analysis					
Nonhemorrhagic stroke					
1- to 21-d risk window	425	953	0.83	0.81	1.09 (0.97-1.23)
22- to 42-d risk window	418	953	0.81	0.81	1.06 (0.94-1.19)
Transient ischemic attack					
1- to 21-d risk window	389	849	0.58	0.56	1.08 (0.96-1.22)
22- to 42-d risk window	368	849	0.55	0.56	1.01 (0.89-1.14)
Nonhemorrhagic stroke or transient ischemic attack					
1- to 21-d risk window	712	1579	1.39	1.34	1.10 (1.00-1.20)
22- to 42-d risk window	686	1579	1.34	1.34	1.04 (0.95-1.14)
Hemorrhagic stroke					
1- to 21-d risk window	107	295	0.24	0.29	0.90 (0.70-1.15)
22- to 42-d risk window	123	295	0.28	0.29	0.99 (0.79-1.25)



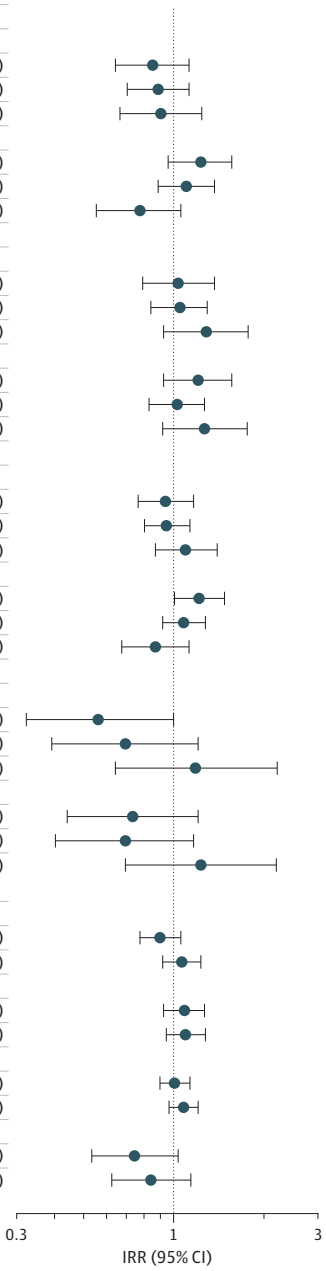
IRR indicates incidence rate ratio. The IRRs were obtained using conditional Poisson regression.

per 100 000 person-days during the 43- to 90-day control window (eFigure 3 and eTable 23 in Supplement 1).

The seasonality-adjusted results additionally showed a statistically significant association between receipt of a high-dose or adjuvanted influenza vaccine and the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 1- to 21-day risk window after vaccination (IRR, 1.06 [95% CI, 1.00-1.12]; risk difference/100 000 doses, 1.65 [95% CI, 0.11-3.20]) and during the 22- to 42-day risk window after vaccination (IRR, 1.05 [95% CI, 1.00-1.11]; risk difference/100 000 doses, 1.60 [95% CI, 0.02-3.18]) (eFigure 4 and eTable 24 in Supplement 1). The results from the PPV-adjusted analysis were

Figure 4. Risk of Stroke by Age Subgroup and Seasonality-Adjusted Analyses for Those Who Received the Moderna mRNA-1273.222 COVID-19 Bivalent Vaccine

	Moderna mRNA-1273.222 (n = 2 223 852)				
	No. of adverse events		Event rate per 100 000 person-days		
	At risk	Control	At risk	Control	IRR (95% CI)
Age subgroup analysis					
Nonhemorrhagic stroke					
1- to 21-d risk window					
Aged 65-74 y	65	189	0.36	0.46	0.85 (0.64-1.13)
Aged 75-84 y	89	265	0.69	0.90	0.89 (0.70-1.13)
Aged ≥85 y	61	153	1.63	1.79	0.91 (0.66-1.25)
22- to 42-d risk window					
Aged 65-74 y	98	189	0.55	0.46	1.24 (0.96-1.58)
Aged 75-84 y	120	265	0.93	0.90	1.11 (0.89-1.38)
Aged ≥85 y	50	153	1.34	1.79	0.77 (0.55-1.06)
Transient ischemic attack					
1- to 21-d risk window					
Aged 65-74 y	70	163	0.29	0.30	1.04 (0.79-1.38)
Aged 75-84 y	119	271	0.68	0.68	1.05 (0.84-1.30)
Aged ≥85 y	56	102	1.06	0.85	1.29 (0.93-1.79)
22- to 42-d risk window					
Aged 65-74 y	82	163	0.34	0.30	1.21 (0.93-1.58)
Aged 75-84 y	117	271	0.67	0.68	1.03 (0.83-1.27)
Aged ≥85 y	55	102	1.05	0.85	1.27 (0.92-1.77)
Nonhemorrhagic stroke or transient ischemic attack					
1- to 21-d risk window					
Aged 65-74 y	117	306	0.66	0.75	0.94 (0.76-1.17)
Aged 75-84 y	173	453	1.34	1.54	0.95 (0.80-1.14)
Aged ≥85 y	104	218	2.78	2.55	1.10 (0.87-1.41)
22- to 42-d risk window					
Aged 65-74 y	156	306	0.87	0.75	1.22 (1.01-1.49)
Aged 75-84 y	204	453	1.58	1.54	1.08 (0.92-1.28)
Aged ≥85 y	80	218	2.14	2.55	0.87 (0.67-1.13)
Hemorrhagic stroke					
1- to 21-d risk window					
Aged 65-74 y	16	67	0.11	0.19	0.56 (0.32-1.00)
Aged 75-84 y	18	66	0.16	0.26	0.69 (0.39-1.21)
Aged ≥85 y	16	39	0.51	0.55	1.19 (0.64-2.24)
22- to 42-d risk window					
Aged 65-74 y	23	67	0.15	0.19	0.73 (0.44-1.21)
Aged 75-84 y	19	66	0.17	0.26	0.69 (0.40-1.17)
Aged ≥85 y	19	39	0.61	0.55	1.24 (0.69-2.22)
Seasonality-adjusted analysis					
Nonhemorrhagic stroke					
1- to 21-d risk window	215	607	0.62	0.77	0.90 (0.77-1.06)
22- to 42-d risk window	268	607	0.78	0.77	1.07 (0.92-1.24)
Transient ischemic attack					
1- to 21-d risk window	245	536	0.53	0.50	1.09 (0.93-1.27)
22- to 42-d risk window	254	536	0.54	0.50	1.10 (0.95-1.28)
Nonhemorrhagic stroke or transient ischemic attack					
1- to 21-d risk window	394	977	1.14	1.24	1.01 (0.90-1.14)
22- to 42-d risk window	440	977	1.28	1.24	1.08 (0.97-1.21)
Hemorrhagic stroke					
1- to 21-d risk window	50	172	0.17	0.26	0.74 (0.53-1.04)
22- to 42-d risk window	61	172	0.21	0.26	0.84 (0.62-1.15)



IRR indicates incidence rate ratio. The IRRs were obtained using conditional Poisson regression.

consistent with the original analysis for nonhemorrhagic stroke (eTable 25 in Supplement 1).

Subgroup Analyses by Age Group | There were statistically significant associations between receipt of high-dose or adjuvanted influenza vaccines and all stroke outcomes in the age subgroup analyses. For individuals in the age group of 65 to 74 years, there was an observed association between receipt of a high-dose or adjuvanted influenza vaccine and hemorrhagic stroke during the 22- to 42-day risk window after vaccination (IRR, 1.31 [95% CI, 1.04-1.65]; risk difference/100 000 doses, 1.06 [95% CI, 0.13-1.98]), for nonhemorrhagic stroke during the

22- to 42-day risk window after vaccination (IRR, 1.16 [95% CI, 1.03-1.30]; risk difference/100 000 doses, 1.68 [95% CI, 0.29-3.07]), and for the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 1- to 21-day risk window after vaccination (IRR, 1.10 [95% CI, 1.00-1.21]; risk difference/100 000 doses, 1.79 [95% CI, 0.02-3.56]) and during the 22- to 42-day risk window after vaccination (IRR, 1.16 [95% CI, 1.06-1.28]; risk difference/100 000 doses, 2.88 [95% CI, 1.09-4.68]).

In the age group of 85 years or older, the association between receipt of a high-dose or adjuvanted influenza vaccine and a stroke outcome was observed for nonhemorrhagic stroke during the 22- to 42-day risk window after vaccination (IRR, 1.14 [95% CI, 1.01-1.30]; risk difference/100 000 doses, 4.95 [95% CI, 0.21-9.69]), for transient ischemic attack during the 1- to 21-day risk window after vaccination (IRR, 1.17 [95% CI, 1.02-1.34]; risk difference/100 000 doses, 3.77 [95% CI, 0.40-7.15]), and for the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 1- to 21-day risk window after vaccination (IRR, 1.12 [95% CI, 1.01-1.24]; risk difference/100 000 doses, 6.57 [95% CI, 0.49-12.66]). No significant association was observed in the age group of 75 to 84 years (eFigure 4 and eTable 26 in Supplement 1).

Subgroup Analyses by Administration of a High-Dose or Adjuvanted Influenza Vaccine Without Concomitant COVID-19 Bivalent Vaccination | Among 16 765 individuals with a stroke outcome after administration of a high-dose or adjuvanted influenza vaccine without concomitant COVID-19 bivalent vaccination, there was a statistically significant association for nonhemorrhagic stroke during the 22- to 42-day risk window after vaccination. The event rate for nonhemorrhagic stroke was 0.87 per 100 000 person-days (IRR, 1.01 [95% CI, 0.94 to 1.10]; risk difference/100 000 doses, 0.24 [95% CI, −1.16 to 1.65]) during the 1- to 22-day risk window after vaccination, 0.93 per 100 000 person-days (IRR, 1.08 [95% CI, 1.00-1.17]; risk difference/100 000 doses, 1.47 [95% CI, 0.06 to 2.88]) during the 22- to 42-day risk window after vaccination, and 0.90 per 100 000 person-days during the 43- to 90-day control window (eFigure 2 and eTable 27 in Supplement 1).

Discussion

In this large US population-based study among Medicare beneficiaries aged 65 years or older, neither brand of the COVID-19 bivalent vaccine (Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 and Moderna mRNA-1273.222) was associated with an increased risk of stroke during the 1- to 21-day or the 22- to 42-day risk window vs the 43- to 90-day control window.

The age subgroup analysis found no consistent associations across ages, outcomes, risk windows, or vaccines. Similar to the data reported to the VSD,[4] this study showed that the COVID-19 bivalent BNT162b2; WT/OMI BA.4/BA.5 vaccine was associated with an elevated rate of nonhemorrhagic stroke and the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 1- to 21-day risk window after vaccination among the oldest age group (≥85 years). However, this study also identified associations between the COVID-19 bivalent mRNA-1273.222 vaccine and the combined outcome of nonhemorrhagic stroke or transient ischemic attack during the 22- to 42-day risk window after vaccination in the youngest age group (65-74 years).

The current study showed that concomitant administration of either brand of the COVID-19 bivalent vaccine and a high-dose or adjuvanted influenza vaccine was associated with an elevated risk of stroke; however, the observed associations were inconsistent. For example, after concomitant administration of a high-dose or adjuvanted influenza vaccine and a COVID-19 bivalent vaccine, the elevated rate of nonhemorrhagic stroke was detected during the 22- to 42-day risk window with the BNT162b2; WT/OMI BA.4/BA.5 vaccine, whereas the elevated rate of transient ischemic attack was detected with the mRNA-1273.222 vaccine during the 1- to 21-day risk window. Although a recent multicenter randomized clinical trial did not report elevated risk with concomitant vaccine administration, reports to the VSD[4] did identify a small increased risk of stroke after concomitant administration of the COVID-19 bivalent vaccine and a high-dose or adjuvanted influenza vaccine.[20]

The current study additionally found an association that was small in magnitude between stroke and administration of a high-dose or adjuvanted influenza vaccine when the vaccine was administered without concomitant administration of either brand of the COVID-19 bivalent vaccine. This finding suggests that the observed association between vaccination and stroke in the concomitant subgroup was likely driven by a high-dose or adjuvanted influenza vaccination. Although a few studies[21,22] with self-reported data detail the safety profile of high-dose influenza vaccines, to our knowledge, there are no studies that report an association between receipt of a high-dose or adjuvanted influenza vaccine and risk of stroke.

The clinical significance of the risk of stroke after vaccination must be carefully considered together with the significant benefits of receiving an influenza vaccination. Because the framework of the current self-controlled case series study does not compare the populations who were vaccinated vs those who were unvaccinated, it does not account for the reduced rate of severe influenza after vaccination. More studies are needed to better understand the association between high-dose or adjuvanted influenza vaccination and stroke.

The results of this study contribute to a growing body of evidence examining the safety of COVID-19 vaccines among US older adults.[23] Our findings are consistent with a study on the French National Health Data System,[24] in which no elevation was observed in the risk of ischemic or hemorrhagic stroke within 1 to 21 days after administration of the COVID-19 bivalent BNT162b2; WT/OMI BA.4/BA.5 vaccine in adults older than 50 years of age. Consistent with the primary results of the current study, Gorenflo et al[25] found no increased risk of ischemic stroke in the BNT162b2; WT/OMI BA.4/BA.5 or mRNA-1273.222 COVID-19 bivalent vaccines among patients aged 65 years or older. In addition, Yamin et al[26] investigated the safety profile of BNT162b2; WT/OMI BA.4/BA.5 in adults aged 60 years or older and found no associated increase in the risk of ischemic stroke.

The current study has several strengths. We used the Centers for Medicare & Medicaid Services Medicare fee-for-service database, which is a large, representative database with minimal beneficiary attrition, ensuring highly generalizable findings to the older adult US population. The current study used a self-controlled study design, which inherently adjusted for time-invariant confounders such as health conditions, socioeconomic status, and health-seeking behaviors. Our study sampled vaccinated cases only and was not subject to bias due to underreporting of vaccination status in the claims data. In addition, the study minimized outcome misclassification bias by performing medical record review of the claims-based nonhemorrhagic stroke definition.

Limitations

This study has several limitations. First, stroke is a known complication after diagnosis of COVID-19. Although we excluded cases with COVID-19 during the 30 days prior to the outcome date, positive cases via home antigen tests are not documented in the claims records. This undercapture of COVID-19 diagnoses may have biased our results.[27,28]

Second, the self-controlled case series assumption that stroke events do not increase the probability of death was violated in the current study. However, we minimized this bias by using the Farrington adjustment.[18] Third, we may have missed some beneficiaries with stroke outcomes or misclassified some beneficiaries who died before the end of follow-up because of delayed reporting. However, we accounted for any claims delays in the calculation of the study end date for each outcome.

Fourth, we conducted multiple tests that may increase the likelihood of detecting statistically significant results when there was no truly elevated risk. Fifth, the current study was conducted only among the vaccinated population, which is a population considered to have health-seeking behaviors, and this may limit the generalizability of the findings.

Sixth, the current study was conducted on COVID-19 bivalent vaccines, which are no longer available. Seventh, while we accounted for seasonality in the stroke outcomes, there may be additional bias from unmeasured time-varying covariates, such as circulating COVID-19 variants and influenza virus variants that may have altered the risk of stroke.

Conclusions

Among Medicare beneficiaries aged 65 years or older who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine, there was no evidence of a significantly elevated risk for stroke during the days immediately after vaccination.

ARTICLE INFORMATION

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Author Contributions: Mr Chillarige had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lu, Matuska, Nadimpalli, Ma, Zhang, Lyu, Chillarige, Forshee, Anderson.
Acquisition, analysis, or interpretation of data: Lu, Matuska, Ma, Duma, Zhang, Chiang, Lyu, Chillarige, Kelman, Forshee, Anderson.
Drafting of the manuscript: Lu, Matuska, Nadimpalli, Zhang, Anderson.
Critical review of the manuscript for important intellectual content: Lu, Matuska, Ma, Duma, Zhang, Chiang, Lyu, Chillarige, Kelman, Forshee, Anderson.
Statistical analysis: Matuska, Ma, Duma, Chiang, Lyu, Chillarige, Forshee.
Obtained funding: Kelman, Anderson.
Administrative, technical, or material support: Matuska, Nadimpalli, Ma, Lyu, Chillarige, Kelman, Anderson.
Supervision: Matuska, Chillarige, Kelman, Forshee, Anderson.

Conflict of Interest Disclosures: Ms Matuska, Dr Nadimpalli, Ms Ma, Dr Duma, Ms Chiang, Mr Lyu, and Mr Chillarige reported being employees of Acumen LLC. No other disclosures were reported.

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Role of the Funder/Sponsor: The FDA played a role in the design and conduct of the study; interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The FDA did not play a role in the collection, management, or analysis of the data.

Data Sharing Statement: See Supplement 2.

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Additional Information: Coauthor Jeffrey A. Kelman, MD, died on February 8, 2024. He was a good friend, a brilliant collaborator, a compassionate caregiver, and an extraordinary human being. We will miss him greatly.

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