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ORIGINAL RESEARCH

BNT162b2 or CoronaVac Vaccinations Are Associated With a Lower Risk of Myocardial Infarction and Stroke After SARS-CoV-2 Infection Among Patients With Cardiovascular Disease

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BACKGROUND: COVID-19 vaccines have demonstrated effectiveness against SARS-CoV-2 infection, hospitalization, and mortality. The association between vaccination and risk of cardiovascular complications shortly after SARS-CoV-2 infection among patients with cardiovascular disease remains unknown.

METHODS AND RESULTS: A case–control study was conducted with cases defined as patients who had myocardial infarction or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022. Controls were defined as all other patients who attended any health services and were not cases. Individuals without history of cardiovascular disease were excluded. Each case was randomly matched with 10 controls according to sex, age, Charlson comorbidity index, and date of hospital admission. Adjusted odds ratio with 95% CI was estimated using conditional logistic regression. We identified 808 cases matched with 7771 controls among all patients with cardiovascular disease. Results showed that vaccination with BNT162b2 or CoronaVac was associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection with a dose–response relationship. For BNT162b2, risk decreased from 0.49 (95% CI, 0.29–0.84) to 0.30 (95% CI, 0.20–0.44) and 0.17 (95% CI, 0.08–0.34) from 1 to 3 doses, respectively. Similar trends were observed for CoronaVac, with risk decreased from 0.69 (95% CI, 0.57–0.85) to 0.42 (95% CI, 0.34–0.52) and 0.32 (95% CI, 0.21–0.49) from 1 to 3 doses, respectively.

CONCLUSIONS: Vaccination with BNT162b2 or CoronaVac is associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection among patients with cardiovascular disease.

Key Words: BNT162b2 ■ CoronaVac ■ COVID-19 vaccines ■ myocardial infarction ■ stroke

Since the outbreak of COVID-19, SARS-CoV-2 was reported to influence both the respiratory system and several other organs, including the cardiovascular system.[1] Although the initial main concern focused on the risk of pneumonia progressing to acute respiratory distress syndrome,[2] there are increasing reports of cardiovascular manifestations following COVID-19 with high risk of morbidity and mortality. Studies showed that

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CLINICAL PERSPECTIVE

What Is New?

- Vaccination with BNT162b2 or CoronaVac was associated with a lower risk of myocardial infarction or stroke after SARS-CoV-2 infection among patients with cardiovascular disease.
- A dose–response relationship between the number of doses received and the reduced risk was observed.

What Are the Clinical Implications?

- Vaccination with BNT162b2 or CoronaVac can not only prevent SARS-CoV-2 infection, hospitalization, and mortality but also prevents the severe cardiovascular complications after infection.
- It is important for patients with cardiovascular disease to receive vaccination to prevent the potential severe cardiovascular complications if infected.

Nonstandard Abbreviations and Acronyms

BNF	British National Formulary
HA	Hospital Authority

COVID-19 is a risk factor for acute myocardial infarction (MI) and stroke and can also lead to postacute COVID-19 sequelae of the cardiovascular system including cerebrovascular disorders, dysrhythmias, ischemic and nonischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease.[3,4] The acute and postacute cardiovascular complications represent a part of the clinical picture of COVID-19, and highlight the need for vaccination among patients with cardiovascular disease (CVD).

COVID-19 vaccines are shown to prevent severe outcomes after SARS-CoV-2 infection and the American College of Cardiology demonstrated the importance of vaccination, especially for patients with a high cardiovascular risk.[5] Both BNT162b2 (Comirnaty, BioNTech/Pfizer/Fosun) and CoronaVac (Sinovac Life Sciences) COVID-19 vaccines have demonstrated efficacy against SARS-CoV-2 infection with good safety and tolerability profiles in clinical trials and observational studies.[6–9] The 2 vaccines were reported to have no association with major adverse cardiovascular events in patients with CVD,[10] and a Korean study showed that vaccination can protect against MI and stroke that occurred 31 to 120 days after COVID-19 diagnosis.[11] However, previous studies also showed a high risk of MI and stroke during the first 2 to 4 weeks after SARS-CoV-2 infection,[3,12] and it remains unknown whether the 2 vaccines can prevent MI and stroke during that interval. Also, patients with CVD might be more concerned about the association between COVID-19 vaccination and MI and stroke after SARS-CoV-2 infection. Therefore, the aim of this study is to investigate the association between COVID-19 vaccinations and the risk of MI and stroke shortly after SARS-CoV-2 infection among patients with CVD.

METHODS

The data will not be made publicly available to other researchers for the purpose of reproducing the results or replicating the simulation as the data custodians have not given permission. The analysis codes support the findings are available from the corresponding author upon reasonable requests.

Study Design and Data Sources

We conducted a population-based case–control study to investigate the association between BNT162b2 or CoronaVac vaccinations and the risks of MI and stroke after SARS-CoV-2 infection in patients with CVD.

This study was conducted using electronic health records in the clinical management system from the Hong Kong Hospital Authority (HA) linked with vaccination records provided by the Department of Health, the government of Hong Kong Special Administrative Region. The HA is a statutory administrative organization in Hong Kong that manages all publicly funded acute health care facilities including 43 public hospitals, 49 specialist outpatient clinics, and 73 primary care clinics.[13] Individual patient-specific data include demographic characteristics, diagnoses, medication dispensing records, outpatient and primary care clinics, emergency department attendances, laboratory tests, and hospitalization details, all comprehensively recorded for research and auditing purposes. The Department of Health provided COVID-19 vaccination records of BNT162b2 and CoronaVac vaccines from February 23, 2021, when the mass COVID-19 vaccination program in Hong Kong was launched, until August 15, 2022. The 2 databases are linked according to a unique identifier derived from the Hong Kong Identity Card. A previous study showed high coding accuracy for cardiovascular diagnosis in HA's electronic health records, with positive predictive values estimated to be ≈85% to 91%[14] and have been used for pharmacovigilance of cardiovascular medications,[15,16] and prior COVID-19 vaccine safety studies.[17–20]

Patient Identification and Study Outcomes

We identified all patients who had a history of CVD before the outcome event. As only electronic health records on or after January 1, 2018 can be accessed, history of

CVD was defined as patients with a diagnosis of CVD between January 1, 2018 and the day before the outcome event. The definition of CVD included atherosclerotic cardiovascular disease, heart failure, and atrial fibrillation. The outcome investigated was a composite of MI and stroke within 28 days after SARS-CoV-2 infection defined as a documented diagnosis of MI and stroke made by clinicians, which were extracted from the HA's electronic health records using the *International Classification of Diseases, Ninth Revision, clinical modification* (*ICD-9-CM*) codes (Table S1). The coding accuracy of the outcomes in the HA's electronic health records had been validated in previous studies with positive predictive values 85% for MI and 91% for stroke.[14,21,22] SARS-CoV-2 infection was defined as a positive polymerase chain reaction (PCR) test using throat swab, nasopharyngeal aspirate, or deep throat sputum specimens. PCR test results are recognized as the criterion standard diagnostic criteria for SARS-CoV-2 infection and are provided by the Public Health Laboratory Services Branch of Department of Health and HA.

Definition of Vaccine Exposure

The 2 COVID-19 vaccines, BNT162b2 and CoronaVac, have been available to individuals aged 16 years old or above in Hong Kong since February 23, 2021 and were extended to individuals aged 12 years or above since June 2021 for BNT162b2 and November 2021 for CoronaVac. The third doses of BNT162b2 and CoronaVac were made available for priority groups on November 11, 2021 and the scheme was subsequently expanded to the general population from January 1, 2022.[23,24] Details of the priority groups rollout schedule of the vaccination program in Hong Kong are listed in Table S2. Individuals are not permitted to switch between vaccine types for the first 2 doses but can choose to switch vaccine types for the third dose. Therefore, COVID-19 vaccination status was classified into 8 groups based on the number of doses and vaccine type administered: (1) 1-dose-only BNT162b2, (2) 1-dose-only CoronaVac, (3) 2-doses-only BNT162b2, (4) 2-doses-only CoronaVac, (5) 3-doses (all BNT162b2), (6) 3-doses (all CoronaVac), (7) 3-doses (2-dose BNT162b2 followed by CoronaVac), and (8) 3-doses (2-dose CoronaVac followed by BNT162b2).

Definition of Cases and Controls

Cases were defined as patients with CVD who had MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022. Controls were defined as all other patients with CVD who attended any HA health services and were not cases. We excluded patients who had a history of COVID-19 before January 1, 2022, who had incomplete vaccination records and those without history of CVD. Up to 10 controls were randomly matched with the cases according to sex, age (5-year band), date of attendance (within 3 calendar days), and Charlson Comorbidity Index (categorized as 0, 1–2, 3–4, and ≥5).

Statistical Analysis

Conditional logistic regressions were applied to evaluate the association between vaccination status and risk of MI or stroke after COVID-19 diagnosis. Chronic comorbidities including cancer, chronic kidney disease, respiratory disease, diabetes, dementia, and medication use including renin-angiotensin-system agents, β-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulin, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants were adjusted to balance the baseline characteristics. The *ICD-9-CM* codes used for identification of comorbidities are presented in Table S1. The British National Formulary codes used for medication use are presented in Table S3. We also conducted subgroup analyses investigating MI or stroke after SARS-CoV-2 infection separately and their association with each dose of BNT162b2 or CoronaVac vaccination. Risk of MI or stroke was reported as adjusted odds ratio (OR) with 95% CI.

Four sensitivity analyses were conducted. First, cases were defined as patients who had MI or stroke within 28 days after a positive PCR or rapid antigen test instead of PCR-confirmed cases only since rapid antigen tests can also indicate a positive COVID-19 infection. Second, cases were defined as patients who had MI or stroke within 14 days instead of 28 days after PCR confirmed SARS-CoV-2 infection to test the sensitivity of definition of COVID-19-related MI or stroke. Third, cases were defined as only patients who had MI or stroke as the inpatient primary diagnosis within 28 days after the PCR-confirmed test to test the sensitivity of MI or stroke diagnosis in the inpatient records. Last, instead of including patients with CVD, only patients with atherosclerotic cardiovascular disease such as coronary heart disease, cerebrovascular disease, peripheral vascular disease, and cardiovascular surgery were included as cases and controls. All statistical tests were 2-sided, and P values <0.05 were considered statistically significant. Statistical analysis was conducted using R version 4.0.3 (www.R-project.org). At least 2 investigators conducted the statistical analyses independently for quality assurance (X.Y. and V.K.C.Y.). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklists were followed to guide transparent reporting of the case–control study.

Ethics Approval

This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong

(CIRB-2021-005-4) and the Department of Health Ethics Committee (LM171/2021). Informed written consent has been waived by the ethics committees as this is an observational study using deidentified electronic health records.

Role of the Funding Source

The funder has no role in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding authors had full access to all the data in the study and took final responsibility for the decision to submit for publication.

RESULTS

In total, there were 1583 patients diagnosed with MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022 and 2 687 413 patients who attended HA services and were not cases. After excluding patients with a history of COVID-19, incomplete vaccination records, or without a history of CVD, we identified 813 patients with CVD who had MI or stroke within 28 days after SARS-CoV-2 infection between January 1, 2022 and August 15, 2022 and 294 871 CVD patients without any MI or stroke at the same time as the controls. There were 5 cases that did not match with any control during the matching process and were excluded. The final cohort included 808 cases matched with 7771 controls (Figure 1). Cases and controls had a similar mean age of 81 years with ≈54% male patients in both groups. Cases generally had larger Charlson Comorbidity Index compared with the controls, and a larger proportion of cases were prescribed with renin-angiotensin system agents, β-blockers, diuretics, nitrates, insulin, antidiabetic drugs, oral anticoagulants, antiplatelets, and immunosuppressants, but more controls received calcium channel blockers (Table 1).

After adjusting the baseline characteristics in the model, the adjusted ORs for MI or stroke within 28 days after SARS-CoV-2 infection are shown in Table 2. Both BNT162b2 and CoronaVac vaccination were associated with a significantly lower risk of MI or stroke and higher effectiveness was observed with an increasing number of doses (Figure 2). For BNT162b2, risk decreased from 0.49 (95% CI, 0.29–0.84) to 0.30 (95% CI, 0.20–0.44) and 0.17 (95% CI, 0.08–0.34) from 1 to 3 doses, respectively. Similar trends were observed for CoronaVac, with risk decreased from 0.69 (95% CI, 0.57–0.85) to 0.42 (95% CI, 0.34–0.52) and 0.32 (95% CI, 0.21–0.49) from 1 to 3 doses, respectively. Patients with 2 doses of CoronaVac and a third dose of BNT162b2 also had a low risk 0.09 (95% CI, 0.02–0.40) compared with the unvaccinated. The number of patients who received 2 doses of BNT162b2 and a third dose of CoronaVac is too low to calculate the OR. The subgroup analyses identified 745 cases of MI within 28 days after SARS-CoV-2 infection matched with 6952 controls and 594 cases of stroke within 28 days after SARS-CoV-2 infection matched with 5588 controls (Table 3). The results showed that BNT162b2 had a risk of 0.47 (95% CI, 0.28–0.81) of MI within 28 days after SARS-CoV-2 infection with only 1 dose, and the risk decreased to 0.12 (95% CI, 0.06–0.24) with 3 doses. For CoronaVac, the risk of MI within 28 days after SARS-CoV-2 infection was 0.73 (95% CI, 0.58–0.92) with only 1 dose, and decreased

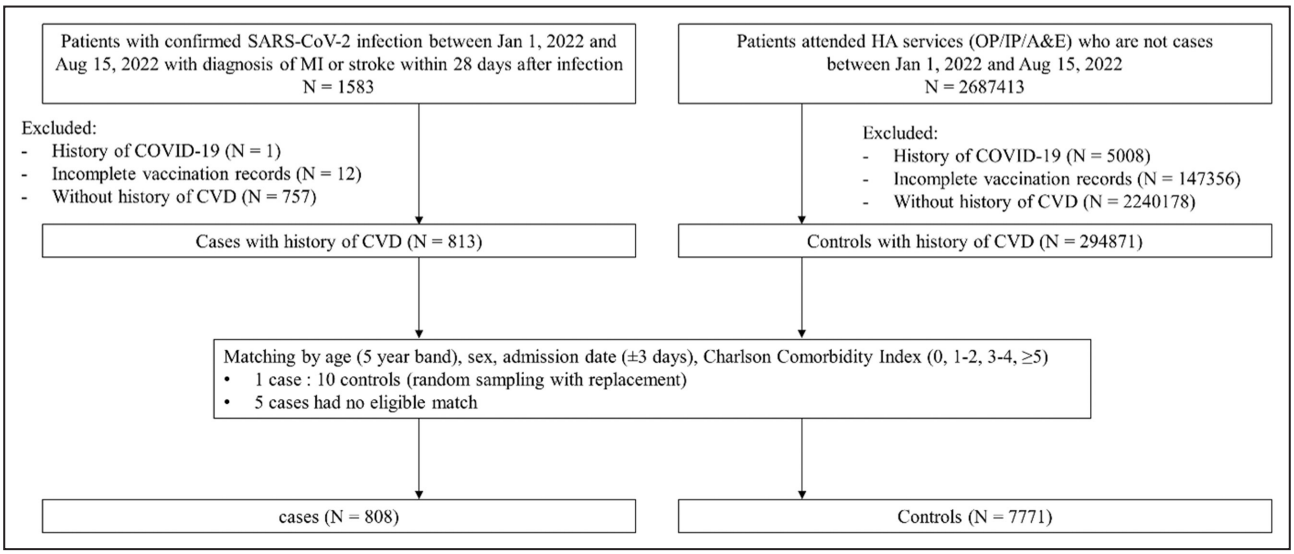

Figure 1. Inclusion and exclusion criteria of the case–control analysis.
A&E indicates accident and emergency; CVD, cardiovascular disease; HA, hospital authority; IP, inpatient; MI, myocardial infarction; N, number; and OP, outpatient

Table 1. Baseline Characteristics of Cases and Controls in the Main Analysis

Characteristics	Cases	Controls	*P* value
Number of individuals	808	7771	
Age, y, mean (SD)	81.73 (11.02)	81.68 (10.80)	0.907
Sex, male, no. (%)	439 (54.3)	4230 (54.4)	0.986
Charlson Comorbidity Index, mean (SD)	2.36 (1.78)	2.14 (1.62)	<0.001
Time since most recent dose, mean (SD)	65.21 (65.79)	55.45 (63.28)	0.004
Pre-existing comorbidities, no. (%)			
Cancer	52 (6.4)	605 (7.8)	0.192
Chronic kidney disease	134 (16.6)	998 (12.8)	0.003
Respiratory disease	82 (10.1)	821 (10.6)	0.759
Diabetes	353 (43.7)	3240 (41.7)	0.291
Dementia	54 (6.7)	408 (5.3)	0.102
Medication use within 90 d, no. (%)			
Renin-angiotensin-system agents	460 (56.9)	3884 (50.0)	<0.001
β-blockers	394 (48.8)	2822 (36.3)	<0.001
Calcium channel blockers	421 (52.1)	4307 (55.4)	0.077
Diuretics	279 (34.5)	1623 (20.9)	<0.001
Nitrates	244 (30.2)	1318 (17.0)	<0.001
Lipid-lowering agents	594 (73.5)	5742 (73.9)	0.850
Insulin	151 (18.7)	582 (7.5)	<0.001
Antidiabetic drugs	285 (35.3)	2514 (32.4)	0.100
Oral anticoagulants	129 (16.0)	1037 (13.3)	0.044
Antiplatelets	582 (72.0)	4927 (63.4)	<0.001
Immunosuppressants	19 (2.4)	42 (0.5)	<0.001

to 0.19 (95% CI, 0.12–0.30) with 3 doses. For risk of stroke within 28 days after SARS-CoV-2 infection, 1 dose of BNT162b2 or CoronaVac both had no statistically significant association with ORs 0.75 (95% CI, 0.43–1.30) and 1.01 (95% CI, 0.79–1.29). However, the risk decreased to 0.13 (95% CI, 0.07–0.25) and 0.19 (95% CI, 0.13–0.30) after 3 doses of each vaccine, respectively. Two doses of CoronaVac and a third dose of BNT162b2 also had a low risk of MI with OR 0.16 (95% CI, 0.04–0.53) and stroke with OR 0.28 (95% CI, 0.11–0.72) within 28 days after SARS-CoV-2 infection (Table 3).

The results of the sensitivity analyses were consistent with the main analysis when we defined cases as patients who had MI or stroke within 28 days after a positive PCR or rapid antigen test instead of PCR-confirmed cases only (Table S4), when we defined cases as patients who had MI or stroke within 14 days

Table 2. Results of the Main Analysis

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Unvaccinated	437	2781	(Ref)	(Ref)
1 dose only				
BNT162b2	16	207	0.47 (0.28–0.80)	0.49 (0.29–0.84)
CoronaVac	147	1361	0.68 (0.55–0.83)	0.69 (0.57–0.85)
2 doses only				
All BNT162b2	33	663	0.27 (0.18–0.39)	0.30 (0.20–0.44)
All CoronaVac	134	1889	0.39 (0.31–0.48)	0.42 (0.34–0.52)
3 doses				
All BNT162b2	9	294	0.15 (0.07–0.30)	0.17 (0.08–0.34)
All CoronaVac	30	465	0.28 (0.18–0.43)	0.32 (0.21–0.49)
B-B-C	0	7	…	…
C-C-B	2	104	0.09 (0.02–0.40)	0.09 (0.02–0.40)

B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; C-C-B, 2 doses of CoronaVac followed by BNT162b2; and OR, odds ratio.

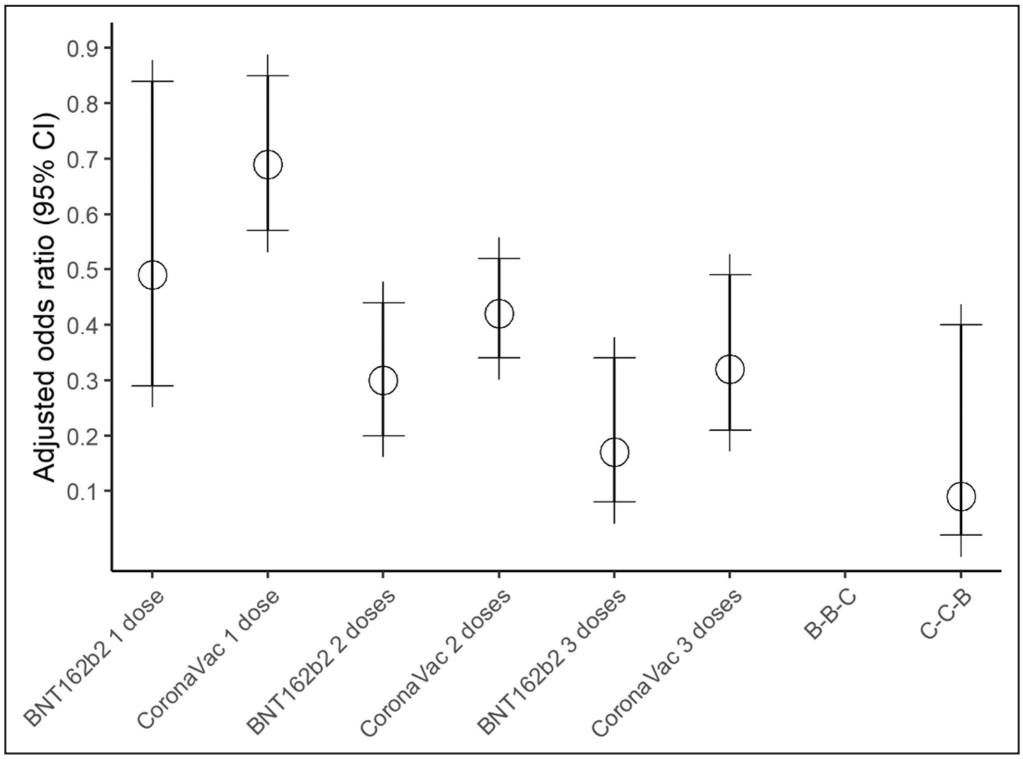

Figure 2. Adjusted odds ratios of risk of myocardial infarction or stroke after BNT162b2 or CoronaVac vaccinations.
B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; and C-C-B, 2 doses of CoronaVac followed by BNT162b2. The adjusted odds ratio in the B-B-C group cannot be estimated due to limited sample size.

instead of 28 days after PCR-confirmed SARS-CoV-2 infection (Table S5), when we only included cases of the inpatient primary diagnosis (Table S6), and when we included patients with atherosclerotic cardiovascular disease (Table S7).

DISCUSSION

This study reported a lower risk of MI or stroke after SARS-CoV-2 infection among patients with CVD after receiving BNT162b2 or CoronaVac. The results showed that both BNT162b2 and CoronaVac can significantly reduce the risk of MI or stroke after SARS-CoV-2 infection, and we observed a clear dose–response relationship between the number of doses received and the reduced risk. Results from our subgroup analyses showed that both BNT162b2 and CoronaVac can reduce the risk of MI after SARS-CoV-2 infection and at least 2 doses of either BNT162b2 or CoronaVac can reduce the risk of stroke after SARS-CoV-2 infection.

Patients infected with SARS-CoV-2 were reported to be at a higher risk of death, use of health resources and incident sequelae in the respiratory system, nervous system, neurocognitive disorders, mental health disorders, metabolic disorders, gastrointestinal disorders, and cardiovascular disorders.[1] Among all the sequelae, the cardiovascular complications can occur in both the acute and postacute phase of SARS-CoV-2 infection from the first 2 to 4 weeks up to 12 months.[3,4,12] The possible mechanism could be lingering damage from direct viral invasion of cardiomyocytes and subsequent cell death, transcriptional alteration in heart tissue, persistent hyperactivated immune response, or integration of the SARS-CoV-2 genome into DNA of infected human cells.[25,26] This was also reported by previous studies where infections with other viruses or bacteria transiently increased the risks of MI and stroke.[27,28] Recent studies reported that the risk following SARS-CoV-2 infection is higher compared with influenza.[29,30] This might be due to direct viral entry through the angiotensin-converting enzyme-2 receptor and damage to the myocardium, systemic inflammation, hypoxia, cytokine storm, interferon-mediated immune response, and plaque destabilization.[31] It was also proposed that SARS-CoV-2 had a direct effect on endothelial cells, and patients with pre-existing endothelial dysfunction and risk factors such as male sex, smoking, hypertension, diabetes, obesity, and established CVD are associated with adverse outcomes from COVID-19.[32] Therefore, patients with CVD should

Table 3. Results of the Subgroup Analysis

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Association between vaccination and risk of myocardial infarction within 28 d after SARS-CoV-2 infection				
Unvaccinated	387	2243	(Ref)	(Ref)
1 dose only				
BNT162b2	18	189	0.52 (0.31–0.86)	0.47 (0.28–0.81)
CoronaVac	136	1088	0.72 (0.58–0.89)	0.73 (0.58–0.92)
2 doses only				
All BNT162b2	40	532	0.34 (0.24–0.49)	0.38 (0.26–0.55)
All CoronaVac	124	1891	0.30 (0.24–0.38)	0.33 (0.26–0.42)
3 doses				
All BNT162b2	10	360	0.11 (0.05–0.21)	0.12 (0.06–0.24)
All CoronaVac	27	553	0.17 (0.11–0.26)	0.19 (0.12–0.30)
B-B-C	0	5	…	…
C-C-B	3	91	0.13 (0.04–0.43)	0.16 (0.04–0.53)
Association between vaccination and risk of stroke within 28 d after SARS-CoV-2 infection				
Unvaccinated	219	1384	(Ref)	(Ref)
1 dose only				
BNT162b2	17	140	0.78 (0.46–1.32)	0.75 (0.43–1.30)
CoronaVac	122	768	1.04 (0.82–1.33)	1.01 (0.79–1.29)
2 doses only				
All BNT162b2	42	442	0.50 (0.35–0.72)	0.49 (0.34–0.72)
All CoronaVac	146	1643	0.49 (0.39–0.62)	0.48 (0.38–0.61)
3 doses				
All BNT162b2	11	405	0.13 (0.07–0.25)	0.13 (0.07–0.25)
All CoronaVac	32	697	0.21 (0.14–0.31)	0.19 (0.13–0.30)
B-B-C	0	10	…	…
C-C-B	5	99	0.26 (0.10–0.65)	0.28 (0.11–0.72)

B-B-C indicates 2 doses of BNT162b2 followed by CoronaVac; C-C-B, 2 doses of CoronaVac followed by BNT162b2; and OR, odds ratio.

be more concerned about the severe outcomes following SARS-CoV-2 infection, and providing data on the effectiveness of vaccinations in protection against MI or stroke after SARS-CoV-2 infection will be important for this population.

Existing clinical trials and observational studies have thoroughly investigated the effectiveness of BNT162b2 and CoronaVac. The phase 3 clinical trial of BNT162b2 demonstrated 95% effectiveness in preventing SARS-CoV-2 infection with a favorable safety profile before the omicron wave.[6] The effectiveness of a third dose was also proved in a clinical trial and an observational study.[33,34] Although limited protection of BNT162b2 against symptomatic disease caused by the omicron variant was observed,[35] vaccination can still reduce the risk of omicron-associated hospitalization.[36] For CoronaVac, although it demonstrated effectiveness of 65.9% against infection and ≈87% against hospitalization or COVID19-related death,[8] the effectiveness dropped to 39.4% against infection and 81.3% against hospitalization or COVID19-related death during the omicron wave.[37] With the decrease in effectiveness of COVID-19 vaccines due to the omicron variant, more studies are focusing on the effectiveness of the vaccines in lowering mortality and severe complications.[9] One study from Hong Kong reported a dose–response relationship between the doses of BNT162b2 or CoronaVac and mortality and severe complications including admission to the intensive care unit and use of ventilatory support after SARS-CoV-2 infection.[9] Another Korean study reported that 2 doses of mRNA vaccines or viral vector vaccine can significantly protect against secondary complications of COVID-19, including MI and stroke that occurred 31 to 120 days after COVID-19 diagnosis.[11] Although this study showed that vaccination can prevent cardiovascular outcomes of COVID-19 during 31 to 120 days after diagnosis, whether it can prevent acute-phase MI and stroke after SARS-CoV-2 infection is unknown. Previous studies showed a high risk of MI and stroke during the first 2 to 4 weeks after SARS-CoV-2 infection,[3,12] during which whether vaccination can prevent MI and stroke is of great interest, especially for patients with a history of CVD. Our study suggested that BNT162b2 or CoronaVac can also prevent MI or stroke within 4 weeks after SARS-CoV-2 infection and the sensitivity analysis also showed a lower risk of MI or stroke

within 2 weeks after SARS-CoV-2 infection. The results confirmed the importance of patients with CVD receiving COVID-19 vaccination. Our findings also highlight the importance of receiving more than 1 dose to achieve better effectiveness in lowering the risk of MI and stroke.

In clinical practice, uncertainty about the safety of COVID-19 vaccines can lead to vaccine hesitancy, causing low vaccination rates and increasing the risk of infection and severe illness, especially for patients with a disease history.[38] Our data showed that among patients with CVD in Hong Kong by August 15, 2022, 74.9% (321 358/428 808) received at least 1 dose, 70.8% (303 758/428 808) received at least 2 doses, and 47.6% (203 910/428 808) received at least 3 doses of vaccination, compared with 93.9% who received at least 1 dose, 91.6% who received at least 2 doses, and 76.7% who received at least 3 doses of vaccination in the general population. Among patients with CVD who received the vaccination, 69.6% (223 556/321 358) chose CoronaVac, an inactivated vaccine, and 30.4% (97 802/321 358) received BNT162b2 from the mRNA platform. To lower vaccine hesitancy and the risk of complications after SARS-CoV-2 infection in patients with a disease history, not only do we need to provide vaccine safety information on this population, but we also need to provide the vaccine effectiveness data against the complications that certain patient groups are concerned about. To the best of our knowledge, this is the first postmarketing study of the association between BNT162b2 or CoronaVac COVID-19 vaccination and risk of MI or stroke after SARS-CoV-2 infection among patients with CVD. This novel finding contributes to health professionals and the general public's understanding of the vaccines' protection against CVD complications and promotes the importance of vaccination in patients with CVD to prevent potential severe CVD complications if infected.

Strength and Limitations

The main strength of this study is the focus on patients with CVD who might be more concerned about the potential severe CVD complications after SARS-CoV-2 infection such as MI and stroke. We also included all patients with CVD in Hong Kong and reported the findings on 2 COVID-19 vaccines, including an mRNA vaccine (BNT162b2) and an inactivated virus vaccine (CoronaVac). The dose-specific analysis provides a clear dose–response relationship between the number of doses received and the reduced risk of MI or stroke postinfection. The subgroup and sensitivity analyses also support the robustness of our results. Additionally, the system in Hong Kong was reported to be able to capture >98% of hospital admissions for MI during the COVID-19 pandemic compared with previous years, suggesting the solidity of the database used.[39,40]

Our study has several limitations. First, as our study focused on 2 COVID-19 vaccines, BNT162b2 and CoronaVac, studies of other vaccines are needed. Second, the majority of Hong Kong residents are of Chinese ethnicity and whether our results can be generalized to other countries and ethnicities requires further investigation. Third, the electronic health records from HA include only data from the public hospital sector and information on patients who used private medical services are not captured. However, as the service provided by the public hospitals covers >70% of all hospitalization coverage in Hong Kong, lack of private medical services data is unlikely to change our conclusion.[13] Fourth, as the case–control analysis is an observational study design, the lack of randomization can cause confounding issues and the different health status and socioeconomic conditions might introduce a potential selection bias. Therefore, we not only matched the cases and controls by sex, age, date of attendance, and Charlson Comorbidity Index, but also estimated the OR by adjusting the comorbidities and medication use in the regression model to minimize the confounding effect. Fifth, although we defined the outcome as MI or stroke within 28 days after SARS-CoV-2 infection, we cannot distinguish whether MI or stroke was directly caused by the infection or from other causes. Last, there were a limited number of patients who received a different type of vaccine as their third dose after the first 2 doses and the sample size is too small to show an association between vaccination and MI or stroke after SARS-CoV-2 infection, especially for patients who received 2 doses of BNT162b2 and a third dose of CoronaVac.

CONCLUSIONS

Vaccination of BNT162b2 or CoronaVac can reduce the risk of MI or stroke after SARS-CoV-2 infection among patients with CVD, and the risk decreased with additional vaccine doses. Therefore, it is important for patients with CVD to receive vaccination to prevent the potential severe CVD complications if infected.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7
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SUPPLEMENTAL MATERIAL

Table S1. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for disease and procedure identification.

	Medical condition	ICD-9-CM Codes
Disease history	Atherosclerotic cardiovascular disease	410-414, 430-438, 440-443, 36
	Heart failure	428
	Atrial fibrillation	427.3
	Cancer	140-209
	Chronic kidney disease	582, 585, 586, 588, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7
	Respiratory diseases	416.8, 416.9, 490-496, 500-505, 506.4, 508.1, 508.8
	Diabetes mellitus	250
	Dementia	290
Outcomes	Myocardial infarction	410
	Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, 436, 437.0, 437.1

Table S2. Details of the priority groups rollout schedule of the vaccination program in Hong Kong.

Order of expansion	Date of rollout	Vaccination group
First [41]	Feb 26, 2021	1) Healthcare workers and staff involved in anti-epidemic work 2) Persons aged 60 or above (and a maximum of 2 carers accompanying elderly people aged above 70) 3) Residents and staff of residential care homes for the elderly and persons with disabilities 4) People providing essential public services 5) People providing cross-boundary transportation or working at control points and ports
Second [42]	Mar 9, 2021	1) Staff of food and beverage premises, markets, supermarkets, convenience stores, couriers and takeaway delivery (including takeaway food delivery) 2) Staff of local public transport service operators 3) Registered construction workers 4) Staff of property management 5) Teachers and school staff 6) Staff of the tourism industry 7) Staff of scheduled premises under the Prevention and Control of Disease (Requirements and Directions) (Business and Premises) Regulation
Third [43]	Mar 16, 2021	1) People aged between 30 and 59 2) Students studying outside Hong Kong (aged 16 or above) 3) Domestic helpers
Fourth [44]	Apr 23, 2021	1) People aged 16 to 29 (≥18 for person receiving CoronaVac)
Fifth [45]	Jun 14, 2021	2) People aged 12 to 15 for BNT162b2
Sixth [23]	Nov 11, 2021	3) Eligible persons under certain groups can receive a third dose of COVID-19 vaccine free of charge
Seventh [46]	Nov 23, 2021	4) Members of the public who received two doses of the CoronaVac vaccine with the second dose received six months prior, irrespective of whether they belonged to certain groups, can reserve and receive a third dose of a COVID-19 vaccine
Eighth [47]	Dec 2, 2021	5) People aged 12 to 17 for CoronaVac
Ninth [24]	Jan 1, 2022	6) Provision of a third dose vaccination service to all eligible persons who have received two doses of the BNT162b2 vaccine with the second dose received six months prior
Tenth [48]	Jan 21, 2022	7) People aged 5 to 11 for CoronaVac

Table S3. British National Formulary (BNF) codes for medication history.

Drug	BNF
Renin-angiotensin-system agents	2.5.5
Beta blockers	2.4
Calcium channel blockers	2.6.2
Diuretics	2.2
Nitrates	2.6.1
Lipid lowering agents	2.12
Insulins	6.1.1
Antidiabetic drugs	6.1.2
Oral anticoagulants	2.8.2
Antiplatelets	2.9
Immunosuppressants	8.2

Table S4. Results of sensitivity analysis when cases were defined as patients who had MI or stroke within 28 days after a positive PCR or RAT test instead of PCR-confirmed cases only. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	**Case**	**Control**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Unvaccinated	443	2813	(Ref)	(Ref)
1 dose only				
BNT162b2	16	195	0.50 (0.30 - 0.85)	0.52 (0.30 - 0.90)
CoronaVac	152	1377	0.70 (0.57 - 0.85)	0.71 (0.58 - 0.87)
2 doses only				
All BNT162b2	33	691	0.25 (0.17 - 0.37)	0.29 (0.20 - 0.42)
All CoronaVac	138	1955	0.38 (0.31 - 0.47)	0.41 (0.33 - 0.51)
3 doses				
All BNT162b2	9	286	0.15 (0.07 - 0.30)	0.17 (0.08 - 0.34)
All CoronaVac	31	481	0.27 (0.18 - 0.41)	0.30 (0.19 - 0.45)
B-B-C	0	9	~	~
C-C-B	2	106	0.09 (0.02 - 0.39)	0.10 (0.02 - 0.41)

Table S5. Results of sensitivity analysis when cases were defined as patients who had MI or stroke within 14 days instead of 28 days after PCR confirmed SARS-CoV-2 infection. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	**Case**	**Control**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Unvaccinated	372	2419	(Ref)	(Ref)
1 dose only				
BNT162b2	15	192	0.48 (0.28 - 0.82)	0.49 (0.28 - 0.86)
CoronaVac	128	1185	0.69 (0.55 - 0.86)	0.70 (0.56 - 0.88)
2 doses only				
All BNT162b2	28	526	0.29 (0.19 - 0.44)	0.32 (0.21 - 0.48)
All CoronaVac	105	1557	0.37 (0.29 - 0.47)	0.40 (0.31 - 0.51)
3 doses				
All BNT162b2	7	231	0.15 (0.06 - 0.32)	0.16 (0.07 - 0.36)
All CoronaVac	28	370	0.33 (0.21 - 0.51)	0.35 (0.22 - 0.54)
B-B-C	0	5	~	~
C-C-B	2	83	0.12 (0.03 - 0.51)	0.11 (0.02 - 0.49)

Table S6. Results of sensitivity analysis when cases were defined as only patients who had MI or stroke as the inpatient primary diagnosis within 28 days after PCR confirmed SARS-CoV-2 infection. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Unvaccinated	164	1070	(Ref)	(Ref)
1 dose only				
BNT162b2	8	101	0.50 (0.24 - 1.06)	0.54 (0.25 - 1.16)
CoronaVac	56	571	0.65 (0.47 - 0.90)	0.66 (0.47 - 0.92)
2 doses only				
All BNT162b2	17	269	0.38 (0.22 - 0.64)	0.39 (0.22 - 0.67)
All CoronaVac	80	912	0.52 (0.39 - 0.70)	0.56 (0.41 - 0.76)
3 doses				
All BNT162b2	6	157	0.20 (0.09 - 0.48)	0.23 (0.10 - 0.55)
All CoronaVac	18	232	0.41 (0.24 - 0.71)	0.45 (0.25 - 0.79)
B-B-C	0	4	~	~
C-C-B	2	50	0.21 (0.05 - 0.93)	0.17 (0.03 - 0.78)

Table S7. Results of sensitivity analysis when patients with ASCVD were included instead of patients with CVD. OR: odds ratio; CI: confidence interval; B-B-C: two doses of BNT162b2 followed by CoronaVac; C-C-B: two doses of CoronaVac followed by BNT162b2.

Vaccination status	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)
Unvaccinated	369	2221	(Ref)	(Ref)
1 dose only				
BNT162b2	16	177	0.51 (0.30 - 0.86)	0.48 (0.28 - 0.83)
CoronaVac	122	1107	0.64 (0.51 - 0.79)	0.67 (0.53 - 0.84)
2 doses only				
All BNT162b2	26	587	0.22 (0.14 - 0.33)	0.23 (0.15 - 0.36)
All CoronaVac	106	1551	0.34 (0.27 - 0.43)	0.37 (0.29 - 0.47)
3 doses				
All BNT162b2	7	247	0.12 (0.05 - 0.26)	0.14 (0.06 - 0.31)
All CoronaVac	26	436	0.24 (0.16 - 0.38)	0.27 (0.17 - 0.42)
B-B-C	0	6	~	~
C-C-B	0	101	~	~