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ORIGINAL ARTICLE
Atrial fibrillation

Sex-based differences in risk of ischaemic stroke or systemic embolism after BNT162b2 or CoronaVac COVID-19 vaccination in patients with atrial fibrillation: a self-controlled case series and nested case-control study

Xuxiao Ye[1], Caige Huang[1], Vincent Ka Chun Yan[1], Wei Kang[1], Min Fan[1], Gigi Kwan Chi Tsang[1], Clarissa Mung Yee Ho[1], Gregory Y.H. Lip[2,3], Kai-Hang Yiu[4,5], Hung-Fat Tse[4,5], Tiantian Ma[1,6], Xiwen Qin[1,6], Celine Sze Ling Chui[6,7,8], Francisco Tsz Tsun Lai[1,6], Carlos King Ho Wong[1,6,9], Eric Yuk Fai Wan[1,6,9], Xue Li[1,6,10], Cheuk Kwong Lee[11], Ivan Fan Ngai Hung[10], Ian Chi Kei Wong[1,6,12,13,*] and Esther Wai Yin Chan[1,6,14,15,*]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [2]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK; [3]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [4]Cardiology Division, Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China; [5]Cardiac and Vascular Center, The University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China; [6]Laboratory of Data Discovery for Health (D24H), Hong Kong SAR, China; [7]School of Nursing, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [8]School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [9]Department of Family Medicine and Primary Care, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [10]Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; [11]Hong Kong Red Cross Blood Transfusion Service, Hospital Authority, Hong Kong SAR, China; [12]Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom; [13]Aston Pharmacy School, Aston University, Birmingham, UK; [14]Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China; and [15]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

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Aims Patients with atrial fibrillation (AF) have a higher risk of ischaemic stroke or systemic embolism, with a greater risk for female patients. This study aims to evaluate the risk of ischaemic stroke or systemic embolism and bleeding following COVID-19 vaccination in patients with AF and the sex differences.

Methods and results Self-controlled case series (SCCS) analysis was conducted to evaluate the risk of ischaemic stroke or systemic embolism and bleeding following BNT162b2 or CoronaVac in patients with AF, using the territory-wide electronic medical records from the Hospital Authority and vaccination records from the Department of Health in Hong Kong. Patients with a primary diagnosis of ischaemic stroke, systemic embolism, or bleeding in the inpatient setting between 23 February 2021 and 31 March 2022 were included. A nested case-control analysis was also conducted with each case randomly matched with 10 controls according to sex, age, Charlson comorbidity index, and date of hospital admission. Conditional Poisson regression was used in the SCCS analysis, and conditional logistic regression was used in the nested case-control analysis to assess the risks, and all analyses were stratified by sex and type of vaccines. Among 51 158 patients with AF, we identified an increased risk of ischaemic stroke or systemic embolism after the first dose of BNT162b2 in SCCS analysis during 0–13 days [incidence rate ratio 6.60, 95% confidence interval (CI) 1.51–28.77] and 14–27 days (6.53, 95%

* Corresponding authors. Tel: +852 2831 5110, Email: ewchan@hku.hk; Email: wongick@hku.hk

CI 1.31–32.51), and nested case-control analysis during 0–13 days (adjusted odds ratio 6.21, 95% CI 1.14–33.91) and 14–27 days (5.52, 95% CI 1.12–27.26) only in female patients. The increased risk in female patients following the first dose of CoronaVac was only detected during 0–13 days (3.88, 95% CI 1.67–9.03) in the nested case-control analysis. No increased risk of ischaemic stroke or systemic embolism was identified in male patients, and no increased risk of bleeding was detected in all patients with AF for both vaccines. An increased risk of ischaemic stroke or systemic embolism after COVID-19 was also observed in both females (17.42, 95% CI 5.08–59.73) and males (6.63, 95% CI 2.02–21.79).

Conclusions The risk of ischaemic stroke or systemic embolism after COVID-19 vaccination was only increased in female patients with AF. However, as the risk after COVID-19 was even higher, proactive uptake of COVID-19 vaccines is recommended to prevent the potential severe outcomes after infection.

Keywords BNT162b2 • CoronaVac • COVID-19 vaccine • atrial fibrillation • ischemic stroke • sex difference

Introduction

Atrial fibrillation (AF) is a global health concern with an increasing health care burden, growing prevalence, and significant morbidity and mortality.[1] Patients with AF have a higher risk of ischaemic stroke or systemic embolism,[2] and oral anticoagulants are recommended for high-risk patients as thromboprophylaxis.[3,4] Since the global rollout of coronavirus disease 2019 (COVID-19) vaccines, the safety signals have been of great concern among patients with underlying conditions,[5] and evidence from the literature on the association between vaccination and thromboembolic events has presented inconsistent results.[6–10] Studies showed that patients with AF have a higher risk of complications and mortality if infected with COVID-19.[11,12] Hence, it is important for patients with AF to be vaccinated to prevent this potential severe effect. However, cases of thromboembolic events after vaccination[13] and a case of ischaemic stroke following vaccination in patients with AF were reported.[14] Patients with AF are more likely to be concerned about the risk of ischaemic stroke or systemic embolism following vaccination because of the higher risk.[5]

Studies also reported a differential risk of ischaemic stroke or systemic embolism between male and female patients with AF.[15,16] This is reflected in the female sex being a stroke risk modifier, and incorporated into risk scores, such as the CHA_2DS_2-VASc [congestive heart failure, hypertension, age $\geq$75 years (doubled), diabetes, stroke (doubled)-vascular disease, age (65–74 years), and sex (female)] score for risk prediction of ischaemic stroke.[17] Whether there is a sex-based difference in the association between COVID-19 vaccines and the risk of ischaemic stroke or systemic embolism in patients with AF is unknown. In Hong Kong, the vaccination programme began on 23 February 2021, with two authorized COVID-19 vaccines, BNT162b2 (Comirnaty) mRNA vaccine and CoronaVac (Sinovac) inactivated vaccine. Although the two vaccines have demonstrated efficacy against infection and severe outcomes with safety and tolerability profiles in clinical trials,[18,19] their association with the risk of ischaemic stroke or systemic embolism in patients with AF is unknown. This study aimed to evaluate the risk of ischaemic stroke or systemic embolism following BNT162b2 and CoronaVac vaccination in patients with AF. As these patients are recommended to use oral anticoagulants, which are associated with the risk of bleeding,[3] and as bleeding was reported as a potential side effect of COVID-19 vaccines,[10,20] the risk of bleeding following vaccination was also investigated in this study.

Methods

Study design and data sources

We conducted a population-based study using self-controlled case series (SCCS) and nested case-control design to investigate the sex-based difference in risk of ischaemic stroke or systemic embolism and bleeding after receiving BNT162b2 or CoronaVac COVID-19 vaccines in patients with AF.

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 (DH), the government of Hong Kong Special Administrative Region. The HA serves as a statutory administrative body in Hong Kong and provides publicly funded health services to >7.4 million Hong Kong residents, managing 43 public hospitals, 49 specialist outpatient clinics, and 73 primary care clinics.[21] 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 or auditing purposes. Each patient has a unique identifier derived from their Hong Kong Identity Card Number in the clinical management system, which links up with all public hospitals, ambulatory clinics, specialist clinics, general outpatient clinics, and emergency rooms in the HA. Previous studies showed high coding accuracy for cardiovascular diagnosis in HA's electronic health records, with positive predictive values estimated at 95% for AF, 90% for ischaemic stroke, and 100% for gastrointestinal bleeding.[22–24] The DH provided COVID-19 vaccination records of BNT162b2 and CoronaVac vaccines from 23 February 2021, when the mass COVID-19 vaccination programme in Hong Kong was launched, until 31 March 2022. Individuals are not permitted to switch between vaccine types for the first two doses but can choose to switch vaccine types for the third dose. All the data were anonymized to protect patient confidentiality by using a unique identifier for each patient. These data have been used for prior COVID-19 vaccine safety studies.[25–28]

Patient identification and study outcomes

We identified all patients who had a diagnosis of AF from 1 January 2018 to 22 February 2021. AF was defined using the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM) codes of 427.3. Patients were followed up from 23 February 2021 to 31 March 2022. The primary outcome was defined as the composite of ischaemic stroke or systemic embolism. The secondary outcome was major bleeding, including intracranial haemorrhage, gastrointestinal bleeding, and other bleeding using ICD-9-CM codes (Supplementary material online, *Table S1*). Both SCCS and nested case-control analyses were conducted for the two outcomes separately.

SCCS study

The SCCS is a within-individual study design that was developed to assess vaccine-related outcomes[29] and has been widely applied in vaccine safety monitoring.[30–33] The SCCS determines the relative incidence by comparing the risks of outcome events between risk and baseline non-risk periods within the same individual (*Figure 1*). Since each patient serves as their own control, this study design can inherently minimize all time-invariant

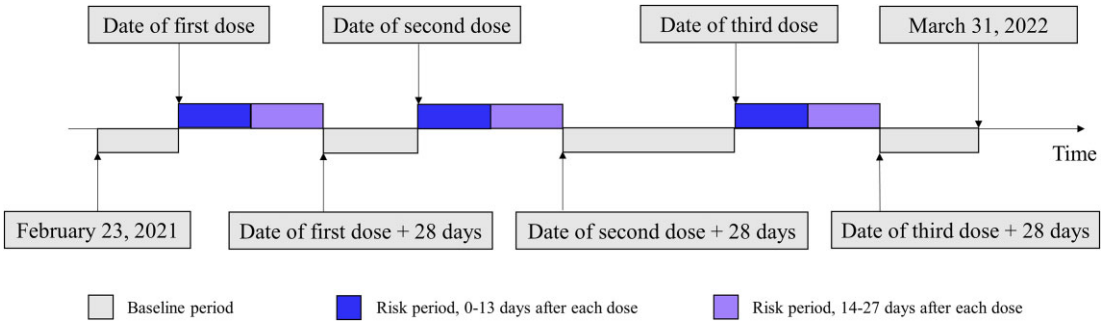

Figure 1 Visualization of the self-controlled case series observation period (23 February 2021 to 31 March 2022), baseline, and risk periods following COVID-19 vaccination. The unvaccinated who had the outcome event during the observation period were also included to adjust seasonality and the probability of receiving vaccination after the event.

confounding effects, and other time-varying covariates can be manually adjusted.[29] Patients who developed the outcome within the observation period were included in the analysis. Those who had a heterogeneous vaccine type for their third dose were excluded. The risk periods were defined as 0–13 and 14–27 days after the first three doses of vaccination, with the vaccination date considered as day 0. As the interval between the first two doses might be <27 days, the risk period was defined as day 14 to the day before the second dose in this case. The baseline non-risk period was defined as all other periods excluding the risk periods.

Three assumptions should be fulfilled to ensure the appropriate use of SCCS.[29] First, the event should be independently recurrent such that each occurrence does not affect subsequent events. To avoid the situation that the outcome events are likely to reoccur and thus increase the probability of future episodes, only the first event within the observation period was treated as the outcome of interest. Second, the occurrence of an event should not affect subsequent exposures. Patients who had the outcome events just before their vaccination appointments might postpone or even cancel their vaccine appointment. In this case, this assumption could be violated when applying the standard SCCS model, especially for the second and third dose vaccinations. Therefore, we applied a modified SCCS model, which was designed for investigating outcomes that can affect subsequent exposures.[34] The modified SCCS model required the inclusion of unvaccinated patients who also developed the outcome events during the observation period to adjust the probability of receiving vaccination after the occurrence of the events. It is important to be aware that unvaccinated patients did not act as controls, and including the unvaccinated group in the modified SCCS is essential as a lack of vaccination records may indicate cancellation of vaccination appointments, which may tend to occur more often for earlier events (before they had the opportunity to be vaccinated). Thus, the absence of vaccination can be informative regarding the timing of the event and to adjust the relative incidence. A comprehensive discussion on the use of modified SCCS for COVID-19 vaccine research can be found in a recent publication that highlights the important consideration to address event-dependent exposures.[34] The modified SCCS has been used in several high-quality studies on the association between COVID-19 vaccines and a series of outcomes;[10,30–35] thus, we also applied this method and included the unvaccinated due to similar considerations for addressing our study objectives. Finally, the occurrence of an event should not affect the subsequent period of observation, and the modified SCCS was also proved to be valid in circumstances when the outcome events could increase the risk of short-term mortality.[34]

Nested case-control study

Patients who had a diagnosis of outcome in the inpatient setting between 23 February 2021 and 31 March 2022 were selected as cases. Patients who were hospitalized during the same period but not included as cases were selected as controls. Patients who had a history of the outcome disease were excluded from the analyses. Random matching with replacement was conducted for each case to assign up to 10 controls of the same sex, age, Charlson comorbidity index (within the same group of 0, 1–2, 3–4, or ≥5), and date of admission (within five calendar days). Due to the limited number of cases diagnosed within 28 days after the second and third doses of vaccination, only cases and controls who had the first dose of vaccination within 28 days on or before the date of the first diagnosis of outcome were defined as vaccine recipients.

Statistical analysis

SCCS analysis

The R function 'eventdepenexp' in the R-package 'SCCS' was used to perform the modified SCCS for event-dependent exposure.[34] Conditional Poisson regression was used to estimate the incidence rate ratio (IRR) and its corresponding 95% confidence intervals (CIs) by comparing the incidence rates of outcomes in different risk periods with the baseline non-risk periods. We adjusted the seasonal effect in monthly categories by modelling a piecewise constant with each month set as cut points.[29] The analyses were stratified by sex and the type of vaccine, BNT162b2 or CoronaVac.

Nested case-control analysis

Conditional logistic regression was used to estimate the odds ratio (OR) and 95% CI, with adjustment for patient characteristics, including the CHA_2DS_2-VASc score, medical history (cancer, renal failure, respiratory disease, diabetes, and dementia), and medications used in the past 90 days (renin-angiotensin-system agents, beta-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, and antiplatelets). The British National Formulary (BNF) codes used to identify the history of medication prescription are presented in Supplementary material online, *Table* S2. The associations in the risk periods 0–13 days and 14–27 days on or after the first dose of vaccination were evaluated. The analyses were stratified by sex and the type of vaccines.

Sensitivity analyses were conducted excluding patients with history of COVID-19 for both outcomes in both SCCS and nested case-control analyses. Subgroup analyses regarding the risk of ischaemic stroke or systemic embolism were conducted in patients aged under 70 years or older. Additional analyses, including both sexes and vaccines, were also conducted with sex or vaccine type as an interaction term with vaccination using both SCCS and nested case-control

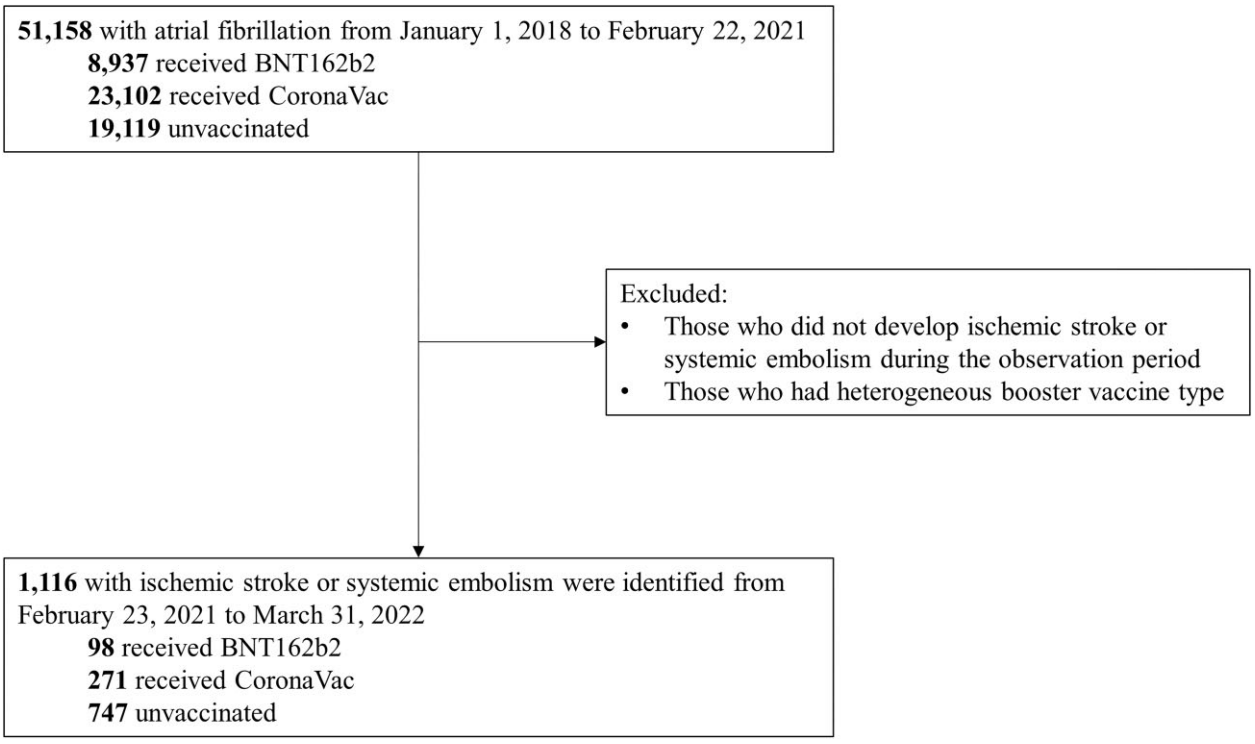

Figure 2 Inclusion and exclusion criteria of self-controlled case series analysis for ischaemic stroke or systemic embolism.

analyses. We further analysed the risk of ischaemic stroke or systemic embolism after COVID-19 in unvaccinated patients with AF. All statistical tests were two-sided, and *P*-values of <0.05 were considered significant in all statistical tests. Statistical analysis was conducted using R version 4.0.3 (http://www.R-project.org), by at least two investigators (X.Y. and C.H.) independently for quality assurance.

Ethical approval

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW21-149) and by the Department of Health Ethics Committee (LM21/2021).

Results

SCCS analysis

A total of 51 158 patients diagnosed with AF from 1 January 2018 to 22 February 2021 were identified, with 8937 receiving BNT162b2, 23 102 receiving CoronaVac and 19 119 unvaccinated. After excluding patients who did not develop the outcomes during the observation period and those who had a heterogeneous third dose of vaccine, we identified 1116 patients with ischaemic stroke or systemic embolism and 2751 patients with bleeding between 23 February 2021 and 31 March 2022 (*Figure 2*). Patients' demographics, baseline comorbidities, and medication use are reported in Supplementary material online, *Table S3*. *Table 1* shows the risk of ischaemic stroke or systemic embolism in SCCS analysis stratified by sex. We observed an increased risk of ischaemic stroke or systemic embolism during 0–13 days (IRR 6.60, 95% CI 1.51–28.77) and 14–27 days (IRR 6.53, 95% CI 1.31–32.51) after the first dose of BNT162b2 in female patients with AF. There was no significantly increased risk during 0–13 days (IRR 1.87, 95% CI 0.85–4.13) and 14–27 days (IRR 1.58, 95% CI 0.71–3.52) after the first dose of CoronaVac in female patients with AF. We did not observe an increased risk of ischaemic stroke or systemic embolism for male patients during the 0–13 days (IRR 1.50, 95% CI 0.51–4.38) and 14–27 days (IRR 2.39, 95% CI 0.63–9.08) after the first dose of BNT162b2; and during 0–13 days (IRR 0.08, 95% CI 0.01–0.85) and 14–27 days (IRR 0.88, 95% CI 0.32–2.37) after the first dose of CoronaVac. No increased risk of bleeding was observed in both males and females after vaccination (Supplementary material online, *Table S4*).

Nested case-control analysis

Figure 3 shows the selection flow of the nested case-control analysis for ischaemic stroke orsystemic embolism. After matching, we identified 813 cases and 6471 controls, and patients' demographics, baseline comorbidities, and medication use are shown in Supplementary material online, *Table S5*. *Table 2* shows similar findings as the SCCS analysis. An increased risk of ischaemic stroke or systemic embolism was observed only in female patients with AF during 0–13 days (adjusted OR 6.21, 95% CI 1.14–33.91) and 14–27 days (adjusted OR 5.52, 95% CI 1.12–27.26) after the first dose of BNT162b2; and during 0–13 days (adjusted OR 3.88, 95% CI 1.67–9.03) after the first dose of CoronaVac. No increased risk of ischaemic stroke or systemic embolism was found in male patients during 0–13 days (adjusted OR 1.13, 95% CI 0.27–4.62) and 14–27 days (adjusted OR 2.08, 95% CI 0.40–10.81) after the first dose of BNT162b2; and during 0–13 days (adjusted OR 0.68, 95% CI 0.15–3.04) and 14–27 days (adjusted OR 1.79, 95% CI 0.77–4.12) after the first dose of CoronaVac. No

Table 1 Risk of ischaemic stroke or systemic embolism in self-controlled case series (SCCS) analysis stratified by sex and type of vaccine

SCCS	Number of events	Patient-days	Crude incidence (per 1000 patient-days)	Incidence rate ratio (95% CI)	*P*-value
Ischaemic stroke or systemic embolism					
Female					
BNT162b2 ($n = 39$) + unvaccinated ($n = 445$)[a]					
Baseline	477	145 994	3.3		
First dose					
0–13 days after	3	543	5.5	6.60 (1.51–28.77)	0.01
14–27 days after	3	364	8.2	6.53 (1.31–32.51)	0.02
Second dose					
0–13 days after	1	322	3.1	2.59 (0.23–28.72)	0.44
14–27 days after	0	258	0	~	~
Third dose					
0–13 days after	0	30	0	~	~
14–27 days after	0	16	0	~	~
CoronaVac ($n = 126$) + unvaccinated ($n = 445$)[a]					
Baseline	547	177 194	3.1		
First dose					
0–13 days after	10	1715	5.8	1.87 (0.85–4.13)	0.12
14–27 days after	7	1493	4.7	1.58 (0.71–3.52)	0.26
Second dose					
0–13 days after	2	741	2.7	0.90 (0.20–4.08)	0.89
14–27 days after	5	597	8.4	2.16 (0.90–5.20)	0.08
Third dose					
0–13 days after	0	66	0	~	~
14–27 days after	0	52	0	~	~
Male					
BNT162b2 ($n = 59$) + unvaccinated ($n = 302$)[a]					
Baseline	350	109 544	3.2		
First dose					
0–13 days after	4	816	4.9	1.50 (0.51–4.38)	0.46
14–27 days after	2	495	4	2.39 (0.63–9.08)	0.2
Second dose					
0–13 days after	2	612	3.3	1.73 (0.37–8.01)	0.49
14–27 days after	0	571	0	~	~
Third dose					
0–13 days after	2	183	10.9	1.85 (0.13–27.40)	0.65
14–27 days after	1	139	7.2	1.66 (0.20–13.57)	0.64
CoronaVac ($n = 145$) + unvaccinated ($n = 302$)[a]					
Baseline	428	140 653	3		
First dose					
0–13 days after	2	1985	1	0.08 (0.01–0.85)	0.04
14–27 days after	10	1772	5.6	0.88 (0.32–2.37)	0.79
Second dose					
0–13 days after	4	954	4.2	0.69 (0.12–3.84)	0.67
14–27 days after	3	792	3.8	0.63 (0.15–2.65)	0.53
Third dose					
0–13 days after	0	125	0	~	~
14–27 days after	0	100	0	~	~

[a]The unvaccinated individuals did not act as controls but were included for adjustment of seasonality and probability of receiving vaccination after the event, which is required by the modified SCCS methodology.
CI, confidence interval.

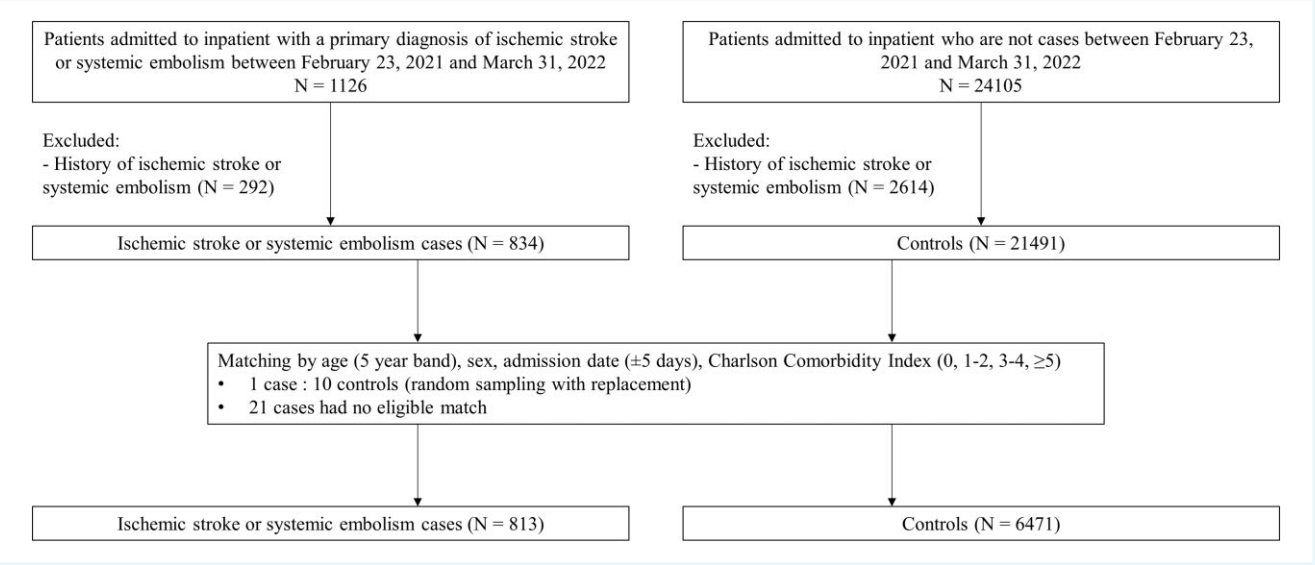

Figure 3 Inclusion and exclusion criteria of case-control analysis for ischaemic stroke or systemic embolism.

Table 2 Risk of ischaemic stroke or systemic embolism in case-control analysis, stratified by sex and type of vaccine

Case control	Case	Control	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*-value
Ischaemic stroke or systemic embolism					
Female					
BNT162b2 first dose					
0–13 days after	3	3	6.68 (1.31–34.07)	6.21 (1.14–33.91)	0.04
14–27 days after	3	4	4.75 (1.01–22.22)	5.52 (1.12–27.26)	0.04
CoronaVac first dose					
0–13 days after	10	21	3.41 (1.49–7.80)	3.88 (1.67–9.03)	<0.01
14–27 days after	7	31	1.40 (0.53–3.67)	1.45 (0.55–3.83)	0.46
Male					
BNT162b2 first dose					
0–13 days after	3	10	1.30 (0.33–5.09)	1.13 (0.27–4.62)	0.87
14–27 days after	2	6	2.09 (0.40–10.94)	2.08 (0.40–10.81)	0.38
CoronaVac first dose					
0–13 days after	2	19	0.63 (0.14–2.79)	0.68 (0.15–3.04)	0.61
14–27 days after	9	30	1.88 (0.83–4.28)	1.79 (0.77–4.12)	0.17

OR, odds ratio; CI, confidence interval.

increased risk of bleeding after vaccination was found in either male or female patients with AF (Supplementary material online, *Table S6*).

Our sensitivity analyses showed consistent results with the main SCCS analysis for the risk of ischaemic stroke or systemic embolism (Supplementary material online, *Table S7*) and risk of bleeding (Supplementary material online, *Table S8*). The results of nested case-control analyses were also consistent for the risk of ischaemic stroke or systemic embolism (Supplementary material online, *Table S9*) and risk of bleeding (Supplementary material online, *Table S10*). The subgroup analyses stratified by age showed that most cases were patients aged 70 years or older, and there was an increased risk during 14–27 days after the first dose of BNT162b2 (IRR 7.76, 95% CI 1.47–40.90) and during 14–27 days after the second dose of CoronaVac (IRR 2.66, 95% CI 1.04–6.78) in female patients with AF (Supplementary material online, *Table S11*). There was no increased risk among male patients, and the number of cases was very few among patients under 70 years (Supplementary material online, *Table S12*). When including both sexes and vaccines, 1116 patients were identified in the SCCS analysis, and the interaction tests showed a *P*-value of 0.034 for the interaction between sex and vaccination and 0.311 for the interaction between type of vaccine and vaccination during 0–13 days after the first dose of vaccination. The results of the

interaction between sex and vaccination showed an increased risk of ischaemic stroke or systemic embolism during 0–13 days (IRR 2.49, 95% CI 1.37–4.52) and 14–27 days (IRR, 2.45 95% CI 1.24–4.81) after the first dose of vaccination, and during 14–27 days after the second dose of vaccination (IRR 2.76, 95% CI 1.09–7.00) in female patients (Supplementary material online, *Table S13*). An increased risk during 14–27 days after the first dose of vaccination was also identified among male patients (IRR 2.30, 95% CI 1.25–4.23). The results of interaction between the type of vaccine and vaccination using SCCS showed an increased risk during 14–27 days after the first dose of BNT162b2 (IRR 2.55, 95% CI 1.02–6.38); during 14–27 days after the first dose (IRR 2.29, 95% CI 1.34–3.89) or second dose (IRR 2.59, 95% CI 1.24–5.40) of CoronaVac (Supplementary material online, *Table S14*). The results of interaction between sex and each type of vaccination using nested case-control design showed an increased risk only in female patients during 0–13 days (adjusted OR 5.96, 95% CI 1.12–31.73) and 14–27 days (adjusted OR 5.00, 95% CI 1.03–24.36) after the first dose of BNT162b2 and during 0–13 days after the first dose of CoronaVac (adjusted OR 3.85, 95% CI 1.67–8.90) (Supplementary material online, *Table S15*). The interaction tests in nested case-control analysis showed a *P*-value of 0.014 for the interaction between sex and vaccination during 0–13 days after the first dose of vaccination. The results of standard SCCS analysis on risk of ischaemic stroke or systemic embolism after COVID-19 in unvaccinated patients with AF showed an increased risk in female patients (IRR 17.42, 95% CI 5.08–59.73) and male patients (IRR 6.63, 95% CI 2.02–21.79) (Supplementary material online, *Table S16*).

Discussion

In this study, we conducted both SCCS and nested case-control analyses to investigate the sex difference in risk of ischaemic stroke or systemic embolism and bleeding following vaccination of BNT162b2 or CoronaVac in patients with AF. The results of SCCS and nested case-control analyses both show an increased risk of ischaemic stroke or systemic embolism after receiving the first dose of BNT162b2 only in female patients with AF but not males. The risk of ischaemic stroke or systemic embolism was also increased after receiving the first dose of CoronaVac only in females when applying a nested case-control study design, but the risk did not reach statistical significance when using the SCCS. We did not observe an increased risk of ischaemic stroke or systemic embolism in male patients with AF using both study designs but only in one risk period when analysing sex as an interaction term using SCCS, and no increased risk of bleeding was observed for both sex groups.

Ischaemic stroke and systemic embolism present a substantial burden in the management of AF. Previous studies have assessed the risk of thromboembolism, ischaemic stroke, and systemic embolism following COVID-19 vaccination, and there were inconsistent conclusions for the association between BNT162b2 and these outcomes.[6–9] One SCCS study in England reported an increased risk of thromboembolism after both ChAdOx1 and BNT162b2 vaccination,[6] but another SCCS in Scotland reported an increased risk of thromboembolism only after ChAdOx1 but not BNT162b2 vaccination.[7] Other studies showing no increased risk of ischaemic stroke or thromboembolism after receiving BNT162b2 were also reported.[8,10,31] For CoronaVac, there was a case report of ischaemic stroke following vaccination,[36] and the study found no increased risk of thromboembolism after receiving CoronaVac.[10] To date, most of the above studies were conducted in the general population, and the evidence of the safety of COVID-19 vaccines in patients with AF is limited. Patients with AF are five times more likely to have an ischaemic stroke,[2] and higher risk of ischaemic stroke or systemic embolism in women with AF has been demonstrated in previous studies,[37,38] including the Framingham Heart Study,[39] the Stroke Prevention in Atrial Fibrillation (SPAF) trials,[40] the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,[41] and the Stroke Prevention Using an Oral Thrombin Inhibitor in Patients with AF (SPORTIF) trials.[42] Female patients with AF have a higher risk of ischaemic stroke or systemic embolism,[15,16] and therefore the vaccine-related thromboembolism risks that are less apparent in the general population can be detected in this study. The possible mechanism of the relationship between ischaemic stroke or systemic embolism and COVID-19 vaccine is not completely understood, and it is hypothesized that there may be a correlation between vaccine-induced immune syndrome and cardiovascular disease.[43] The immune system is correlated with cardiac development, composition, and function, as well as an ischaemic injury, including ischaemic stroke or systemic embolism, which may impact on innate and adaptive immune cells.[43] The auto immune reactions following vaccination could trigger pathogenesis,[44] and this impact may be more prominent in patients with a complex disease history.

The sex-based difference in patients with AF is not clearly understood, and the underutilization of oral anticoagulation treatment among women has been suggested to be a contributing factor.[45] However, among the 813 matched cases with ischaemic stroke or systemic embolism in our nested case-control analysis, 318 (39.1%) had a prescription for oral anticoagulants with more female patients (182 patients) taking the prescription than males (136 patients) (Supplementary material online, *Table S5*). We cannot conclude that the increased risk only in female patients with AF is due to the underutilization of anticoagulants from our data. A previous study also reported the sex-based difference in outcomes of oral anticoagulation in patients with AF.[46] Our data show that among female patients who developed ischaemic stroke or systemic embolism within 27 days post-vaccination, 2 out of 6 patients who received BNT162b2 had a prescription for anticoagulants and 8 out of 17 patients who received CoronaVac had a prescription for anticoagulants. Yet, among the male patients who also developed the outcome, all five patients who received BNT162b2 did not have anticoagulants, and only 2 out of 11 patients who received CoronaVac had anticoagulants. It is possible that an interaction between COVID-19 vaccination and the treatment effect of anticoagulants could have led to ischaemic stroke or systemic embolism after vaccination, but this hypothesis also cannot be concluded from our data. Age and pre-existing complications might also affect the risk of ischaemic stroke or systemic embolism. The subgroup analyses stratified by age showed that most cases were 70 years of age or older, and an increased risk was only identified in female patients. Most patients had hypertension or diabetes, which might contribute to the increased risk (Supplementary material online, *Table S3*). However, as in Supplementary material online, *Table S5*, those who developed ischaemic stroke or systemic embolism after vaccination had similar disease history as the controls. However, whether a certain disease history is directly associated with an increased risk cannot be firmly established. Further, our results from including both sexes and vaccines with sex or type of vaccine as an interaction term with vaccination using SCCS showed that male patients also had an increased risk of ischaemic stroke or systemic embolism during 14–27 days after the first dose of any vaccination (IRR 2.30, 95% CI 1.25–4.23) (Supplementary material online, *Table S13*). However, as in the main analyses and the interaction analyses using nested case-control design (Supplementary material online, *Table S15*), an increased risk was observed only in female but not male patients, whether the increased risk applies to both sexes requires further investigation. The results of interaction between type of vaccine and vaccination using SCCS showed an increased risk after both BNT162b2 or CoronaVac (Supplementary material online, *Table S14*). This is consistent with our main analysis and the interaction

analyses using nested case-control design (Supplementary material online, *Table S15*) and suggests that the increased risk might be generalized to both vaccines. Importantly, results firmly indicate that the risk of ischaemic stroke or systemic embolism after COVID-19 was relatively higher (Supplementary material online, *Table S16*). As the risk was much higher than the risk after vaccination, proactive uptake of COVID-19 vaccines is advocated and recommended to prevent potential severe outcomes after COVID-19 infection. Continued surveillance is necessary to closely monitor the safety of COVID-19 vaccines, especially for patients with a certain disease history.

Patients with AF are also concerned about the potential risk of bleeding because of the use of anticoagulants. In our nested case-control study, 58.0% of patients who experienced bleeding during the observation period had a prescription for oral anticoagulants during the 3 months before admission (Supplementary material online, *Table S5*). Although two studies reported an increased risk of bleeding after BNT162b2 vaccination,[6,10] our results show no increased risk after both BNT162b2 or CoronaVac in patients with AF, suggesting the safety profile of these two vaccines regarding the risk of bleeding in this population.

Strengths and limitations

The main strength of this study is the use of two study designs to confirm the robustness of our results. The modified SCCS was developed for event-dependent exposures and outcome events with a high risk of short-term mortality and has been applied to many high-quality COVID-19 vaccine safety studies.[10,30–33] It is also the most appropriate method to study the safety of COVID-19 vaccines as vaccine coverage is increasing.[34] We also used a nested case-control study design to support our findings and the results also detected an increased risk of ischaemic stroke or systemic embolism after the first dose of CoronaVac only in female patients with AF. However, the results of SCCS analysis show an increased but not significantly increased risk. The results suggest that the increased risk might not only relate to a type of vaccine but is general for COVID-19 vaccination in female patients with AF. Another strength is that we focused on patients with AF, a population with a higher risk of ischaemic stroke or systemic embolism. Therefore, the risks that we missed in the study of the overall general population can be detected in our study.

Our study has limitations. First, only BNT162b2 and CoronaVac were investigated in our analyses, and studies of other COVID-19 vaccines are needed. Second, as the majority of Hong Kong residents are of Chinese ethnicity, the generalization of our results to other countries and different ethnicities requires further investigation. Third, the electronic health records from HA only cover the information of patients who used public healthcare services in Hong Kong; thus, the information of patients who used private medical practitioners was not captured. Finally, despite using two study designs to confirm the robustness of our results, the cases of patients who developed ischaemic stroke or systemic embolism after receiving the vaccination represent a small sample size; hence, the confidence intervals are relatively wide. Consequently, the results should be interpreted with caution, and further studies on a larger population are required to confirm our findings.

Conclusions

Our findings show an increased risk of ischaemic stroke or systemic embolism after COVID-19 vaccination only in female patients with AF but not in males. The results were consistent for BNT162b2 in both SCCS and nested case-control analyses, and the risk after CoronaVac was only increased when applying the nested case-control study design. Importantly, as the risk of ischaemic stroke or systemic embolism after COVID-19 was even higher, proactive uptake of COVID-19 vaccines is recommended to prevent potential severe outcomes after infection. No increased risk of bleeding was observed after COVID-19 vaccination in patients with AF.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Author contributions

X.Y., K.Y., I.C.K.W., and E.W.C. designed the research; X.Y. and C.H. performed the research; X.Y., C.H., and V.K.C.Y. analyzed the data; W.K., M.F., G.K.C.T., C.M.Y.H., G.Y.H.L., K.Y., H.T., T.M., X.Q., C.S.L.C., F.T.T.L., C.K.H.W., E.Y.F.W., X.L., C.K.L., and I.F.N.H. provided discussion and revision; I.C.K.W. and E.W.C. provided funding and supervision; and X.Y. prepared the manuscript with input from all co-authors.

Data availability

Data will not be available for others as the data custodians have not given permission.

Code availability

All analysis codes supporting the findings are available from the corresponding author upon reasonable request.

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