

RAPID REVIEW

Cardiovascular Outcomes and SARS-CoV-2 Infections

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Key Findings

- The results of this rapid review provide evidence to suggest an association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and increased risk of developing several cardiac clinical outcomes. Patients infected with SARS-CoV-2, compared to non-infected controls were, to varying degrees, at greater risk of cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, cardiac disorders, thrombotic disorders and composite measures such as major adverse coronary events (MACE) and mortality due to cardiovascular disorder.
- **In self-controlled case series (n=2), studies least susceptible to biases, there was evidence of increased risks of cardiovascular outcomes following SARS-CoV-2 infection, however these risks were largely transient and restricted to the acute phase of disease (≤1 month post-symptom onset or since positive SARS-CoV-2 test).** The risks of ischemic stroke (incidence rate ratio [IRR]: 6.2) and myocardial infarction (IRR: 8.4) were highest in the first week of SARS-CoV-2 infection, returning to pre-exposure risk in the 8–28 days following infection. The risks of deep vein thrombosis (IRR: 7.4) and pulmonary embolism (IRR: 46.4) were highest 8–14 days following infection, returning to pre-exposure risk at 31–180 days following infection.
- **In cohort studies (n=13), comparing patients with Coronavirus Disease 2019 (COVID-19) and matched non-SARS-CoV-2-infected controls, the risks of cardiovascular outcomes were lower in the post-acute phase of SARS-CoV-2 than in the acute period, and decreased as time since infection increased.** Few studies demonstrated a continued risk at 1–12 months post-symptom onset or since positive SARS-CoV-2 test, including risk for ischemic stroke (n=2 studies), dysrhythmias (n=3), pericarditis or myocarditis (n=4), myocardial infarction (n=2), heart failure (n=3) and deep vein thrombosis (n=2).
- Incidence of cardiovascular disorders in patients with COVID-19 during the acute phase of disease was approximately 2–7-fold higher, compared to matched non-SARS-CoV-2-infected patients; however, the incidence of outcomes was less than 0.05% in both groups.
- There was little evidence that examined the impact of vaccination status or specific variants of concern (VOC) on the associations between SARS-CoV-2 infection and cardiovascular outcomes. One study that compared vaccination status and post-COVID-19 cardiovascular outcomes noted an increase in risk of thrombotic disorders in those not vaccinated or partially vaccinated, compared to fully vaccinated patients (partial and full vaccination status not defined). A single study on VOCs and cardiovascular outcomes reported an increased 6-month risk of ischemic stroke after Delta emergence compared to before Delta emergence.

- The results of this rapid review are primarily based on studies which examined SARS-CoV-2 patients who were hospitalized, and who were of middle- to older-age groups (50 years and older). The generalizability of these results to individuals with SARS-CoV-2 infections who are younger and/or not hospitalized is uncertain.

Background

The Spike (S) protein of SARS-CoV-2 enables the virus to infect cardiovascular cells via the angiotensin-converting enzyme II (ACE2) receptor-binding protein.¹ Researchers hypothesize that infection causes a pro-inflammatory state, endothelial dysfunction, hypercoagulopathy and oxidative stress, leading to impaired microcirculation and tissue hypoxia and damage.²⁻⁶ Clinicians can diagnose myocardial injury through electrocardiograms, cardiac imaging and increased levels of cardiac biomarkers (e.g., creatine kinase, cardiac troponin) in patients presenting with chest pain accompanied by fever and respiratory symptoms.^{5,7} While cardiovascular outcomes after severe COVID-19 (hospitalized, intensive care unit [ICU]) are known, there have been reports of cardiac involvement in those with mild COVID-19 (i.e., not requiring hospitalization). In addition, cardiovascular outcomes have been reported during both the acute (≤ 1 month since symptom onset) and post-acute (> 1 month since symptom onset) stages of disease.

The primary objective of this rapid review is to identify and synthesize evidence related to the incidence and risk of cardiovascular outcomes in people with SARS-CoV-2 infections compared to people without SARS-CoV-2 infections. Secondary outcomes of interest include the impact of COVID-19 vaccination, VOCs and other risk factors (e.g., age, sex, acute illness characteristics) on the association between SARS-CoV-2 infection and risk of cardiovascular outcomes.

Methods

A rapid review is comprehensive but not exhaustive in scope.⁸ This method of knowledge synthesis omits certain steps of the systematic review process in order to be timely (e.g., quality assessment). Public Health Ontario (PHO) Library Services conducted searches for systematic review-level evidence in Medline (up to November 2, 2022; 965 records); Embase and Scopus (November 2, 2022; 168 records); and National Institutes of Health (NIH) COVID-19 Portfolio (Preprints) (November 2, 2022; 18 records). Additionally, we conducted searches for primary literature in NIH COVID-19 Portfolio (Preprints) (up to November 2, 2022; 187 records) and Medline (up to November 9, 2022; 1,972 records).

This rapid review aimed to focus on systematic review level evidence with clearly described contemporary control groups and examined the impact of SARS-CoV-2 on various cardiovascular outcomes. Primary studies were limited to those with clearly described contemporary control participants, with a sample size for SARS-CoV-2 cases $> 5,000$ (Appendix A). We used the same outcome categories as a recent large primary study by Xie et al. (2022a), which provides a comprehensive and clear outline to organize multiple cardiovascular outcomes.⁹

Results

Search Findings

Our library database searches yielded 3,319 records. After screening for eligibility, 23 records were included in this rapid review, eight were systematic reviews with meta-analyses and 15 were large primary studies. We summarized study characteristics and included cardiovascular outcomes (Appendix B). Throughout this rapid review, we report the outcome measures described in the source studies (e.g., hazard ratios [HR], odds ratios [OR], etc.), and the 95% confidence interval (CI) in the following formats: (HR: 1.2, 1.10–2.20) or HR: 1.2 (1.10–2.20).

The majority of evidence from the eight systematic reviews examined the overall risk or incidence of various cardiovascular outcomes. Most reviews included primary studies from earlier in the pandemic (two searched up to April of 2022; four searched up to February, March or April of 2021; one searched up to September of 2020; and one did not report the search date but was published in 2022). Four systematic reviews included only inpatients, two included only outpatients, and two included patients from multiple settings or the setting was not clearly described. Across all reviews that reported mean/median ages of participants, all were >50 years. The reported sex of participants was also not balanced, most systematic reviews reported <50% of participants were female. While we aimed to include only evidence where COVID-19 cases were test-confirmed, and controls were test-negative, this was found to be too limiting as most identified systematic reviews with relevant results (7 of 8) did not clearly report this same parameter in their eligibility criteria. Rather than exclude these results we have included the reviews and noted this limitation. Finally, the evidence from these systematic reviews lacked findings that are more granular such as results pertaining to vaccination status of study subjects, VOCs, or the timing of cardiovascular outcomes following SARS-CoV-2 infection. Large primary studies helped to fill these evidence gaps.

We included 15 primary studies that included large sample sizes (i.e., 12 studies had >10,000 patients with COVID-19) and with matched, contemporary, non-SARS-CoV-2-infected controls (includes those with alternative diagnoses and negative SARS-CoV-2 test). Primary studies were conducted primarily in the United States (US) (n=8), followed by European and Middle Eastern countries (n=6); one study included multiple countries. Most of the studies were performed prior to Delta circulation (9/15, wild-type to Beta), followed by wild-type to Delta (3/15) and wild-type to Omicron circulation (3/15). Ten studies included both inpatient and outpatient populations, while four included only inpatients and one study included only outpatients. In 11 of 15 studies, the mean age of participants was ≥50 years. In contrast to the systematic review evidence, most studies (12 of 15) reported that the proportion of female participants was greater than 50%.

Overall Findings

Those with documented SARS-CoV-2 infection, compared to matched, non-infected contemporary controls, had increased risks of all cardiovascular outcomes during the acute (≤ 1 month since index date) and post-acute (> 1 month) phases of the disease, decreasing as time from illness onset increases. Risk of cardiovascular outcomes was higher in patients hospitalized for COVID-19, compared to non-hospitalized patients with SARS-CoV-2. While there was a higher risk of cardiovascular disorders among patients with SARS-CoV-2, compared to contemporary controls without SARS-CoV-2, the incidence of cardiovascular disorders was relatively low in both populations (e.g., less than 0.05% of patients in both groups).

The first time we mention a study, we include sample size and comparator groups; however, for brevity, we do not repeat these details in subsequent outcome descriptions for the same study. In addition, for details on study sample sizes, control groups and patient settings, please see Appendix B.

Cerebrovascular Disorders

We identified two systematic reviews and six primary studies that examined cerebrovascular outcomes among people with and without SARS-CoV-2 infections.⁹⁻¹⁶ Cerebrovascular disorders involve occlusion in the vasculature providing blood to the brain, such as in ischemic stroke or transient ischemic attack. The incidence of cerebrovascular disorders in patients with COVID-19 and patients without COVID-19 was relatively low. For example, in the acute phase (14 days since symptom onset), the incidence of stroke was 0.04% of 83,516 in patients with COVID-19, compared to 0.01% of 340,952 matched non-SARS-CoV-2-infected patients.¹⁷

The systematic review evidence overall found evidence of increased frequency of stroke in patients with COVID-19 relative to patients without COVID-19, and described some potential risk factors. Ganesh et al. (2021) searched to March 31, 2021 and conducted a meta-analysis of four studies examining the frequency of ischemic stroke among patients with COVID-19 (n=238,501; test confirmation not reported) and among controls without COVID-19 (n=237,874; test confirmation not reported). Patients with ischemic stroke had increased odds of also having a COVID-19 infection compared to those without ischemic stroke (OR: 2.5, 1.16–5.50).¹⁰ This study did not report the exact proportion of hospitalized versus non-hospitalized patients for this result, but noted at a high level the primary studies “generally only included hospitalized patients”.¹⁰ Narrative findings from Ganesh et al. (i.e., statistical testing was not performed) suggested some clinical and socio-demographic characteristics were more common among COVID-19 stroke patients relative to non-COVID-19 stroke patients; these included involvement of large vessels in stroke (relative to other causes of stroke), increased stroke severity, younger age and Black race (in the US).

In a meta-analysis searched to September 14, 2020, Nannoni et al. (2021) examined patient and clinical characteristics in acute stroke patients with and without COVID-19 (test confirmation not reported).¹² This systematic review found stroke patients with COVID-19, relative to stroke patients without COVID-19, to be younger (pooled median age difference: 6 years, 12.3–1.4) and to experience more severe strokes (pooled median difference for NIH Stroke Scale/Score [NIHSS] score 5, 3–9). Patients with strokes due to large vessel occlusion had greater odds of COVID-19 infection prior to stroke (OR: 2.7, 1.63–4.57). Stroke patients with the following characteristics or risk factors also had greater odds of a COVID-19 infection prior to their stroke: male sex (OR: 1.4, 1.01–1.96), no history of hypertension (OR: 1.4, 1.04–2.22), and no history of a previous stroke (OR: 3.3, 1.69–5.56). This review found no significant differences between COVID-19 and non-COVID-19 patients for the following stroke risk factors (i.e., comorbidities): diabetes mellitus, dyslipidemia, smoking, coronary artery disease and atrial fibrillation.

Six primary studies demonstrated increased risks of cerebrovascular disorder outcomes in COVID-19 patients, compared to contemporary controls.^{9,11,13-16} For example, Xie et al. (2022a) examined 153,760 COVID-19 patients and 5,637,647 contemporary controls (non-SARS-CoV-2-infected patients visiting the US Veterans Health Association), and found COVID-19 patients had a greater 12 month risk of stroke (aHR: 1.5, 1.43–1.62) and transient ischemic attack (aHR: 1.5, 1.37–1.62).⁹ The risk of cerebrovascular outcomes increased with increasing COVID-19 disease severity (e.g. stroke: non-hospitalized, aHR: 1.2; admitted to hospital, aHR: 3.1; admitted to ICU, aHR: 4.4), compared to non-SARS-CoV-2 infected controls. Wang et al. (2022) examined 90,892 SARS-CoV-2-positive patients and the same number of matched test-negative controls (patients seeking medical care, but not COVID-19 related) at 12 months since testing date, and found COVID-19 patients to be at greater risk of cerebrovascular events (e.g., stroke, aHR: 1.6, 1.55–1.69).¹⁶

Katsoularis et al. (2021) included results relevant to the period shortly following infection (n=83,397 patients with COVID-19, n=340,432 non-SARS-CoV-2-infected patients).¹¹ This matched cohort study found individuals experiencing an ischemic stroke in the two weeks following their SARS-CoV-2 test date had a 3.6-fold increase in the odds of having tested positive relative to those who did not (aOR: 3.6, 1.69–7.80). In total, 0.04% of 83,516 patients with COVID-19 had a stroke, compared to 0.01% of 340,952 matched non-infected controls. In the self-controlled case series, 254 ischemic stroke events were examined, and the incidence rate ratio (IRR) for ischemic stroke were calculated for the following periods, compared to the control period: buffer period (-28 to -4 days of index date; e.g., date of symptom onset, test date) (IRR: 1.9, 1.21–2.96), -3 to -1 days pre-exposure (IRR: 4.0, 1.85–8.45), risk period 0–7 days post index (IRR: 6.2, 4.06–9.42), risk period 8–14 days post index (IRR: 2.9, 1.64–4.97) and risk period 15–28 days post index (IRR: 2.1, 1.36–3.38).

Raisi-Estabragh et al. (2022) included results related to patients' illness settings. This study examined 17,871 COVID-19 cases with positive polymerase chain reaction (PCR) or antigen test, and two matched controls for each case (n=35,742) who were patients with negative PCR or antigen test results seeking medical care. Results are stratified by cases' illness setting and diagnosis type (i.e., non-hospitalized, hospitalized with COVID-19 as primary diagnosis, or hospitalized with COVID-19 as secondary diagnosis); and reported as aHR at 30 days since index date. Across all patients and settings, COVID-19 cases were associated with an increased risk of stroke at 30 days post index date (aHR: 4.2, 2.54–6.78) compared to non-SARS-CoV-2-infected controls.¹³ There was no significant association for 30-day risk of stroke between non-hospitalized COVID-19 cases (aHR: 1.8, 0.86–3.63) and non-hospitalized non-COVID-19 controls. The risk of stroke 30 days post-index was statistically significant in patients hospitalized primarily for COVID-19 (aHR: 17.5, 5.26–57.9) compared to controls hospitalized for other conditions; there was also a significant increase in the risk of stroke among patients hospitalized with COVID-19 as a secondary diagnosis (aHR: 4.5, 1.55–13.33), compared to controls hospitalized for other conditions.

Studies that examined the risk of stroke over time from SARS-CoV-2 infection found the risk of stroke decreased over time. Rezel-Potts et al. (2022) examined outcomes of 428,650 patients with COVID-19 diagnoses and 428,650 matched controls with alternative diagnoses at 4 weeks from index date (acute), 5 to 12 weeks from index date (post-acute) and 13 to 52 weeks from index date (long-term).¹⁴ An increased risk of stroke was only observed to be statistically significant, relative to non-infected controls, in the acute follow-up period (adjusted rate ratio [aRR]: 3.3, 2.05–5.35). The post-acute (aRR: 0.9, 0.63–1.21) and long-term (aRR: 0.7, 0.59–0.89) follow up periods did not show significantly increased risks of stroke in COVID-19 patients compared to controls.

Finally, Taquet et al. (2022) is the only study that investigated SARS-CoV-2 infections from periods of the pandemic marked by the circulation of different VOCs using six cohorts: primary Alpha (n=47,675), Delta (n=44,835) and Omicron (n=39,845) cohorts, and matched control cohorts (non-COVID-19 respiratory infections) of equal size diagnosed just before the emergence of each VOC. There was no significant change in the hazards of developing ischemic stroke 6 months post-infection before versus after the circulation of Alpha; however, a higher 6-month HR was noted for ischemic stroke after Delta compared to before the circulation of Delta (aHR: 1.3, 1.01–1.6). Finally, there was no significant change in the 6-month HR of stroke before versus after the emergence of Omicron. Additionally, the 2-year cumulative incidence of ischemic stroke in patients with COVID-19 ranged from 0.1% in those <18 years to 4.1% in those ≥65 years, compared to 0.1% (<18 years) to 3.8% (≥65 years) in those with non-COVID-19-respiratory infections (overall 1,284,437 patients with COVID-19 and same number of controls).

Dysrhythmias

This rapid review did not identify any systematic reviews with relevant dysrhythmia outcomes; however, four large primary studies were identified that examined various dysrhythmias (i.e., atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias and atrial flutter) in patients with COVID-19 compared to those without COVID-19.^{9,13,14,16} The incidence of dysrhythmias in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, at 30 days since symptom onset, the incidence of atrial fibrillation was 29.9 per 1,000 person years in patients with COVID-19, compared to 5.3 per 1,000 person years in matched non-SARS-CoV-2-infected patients.¹³

Xie et al. (2022a) reported that SARS-CoV-2-infected individuals, compared to non-infected controls, had an increased 12-month risk of all assessed dysrhythmias, including atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter (aHR: 1.7, 1.64–1.75).⁹ The risk of dysrhythmia outcomes increased with increasing COVID-19 disease severity (e.g., atrial fibrillation: non-hospitalized, aHR: 1.3; admitted to hospital, aHR: 3.9; admitted to ICU, aHR: 7.7), compared to non-SARS-CoV-2 infected controls.

Two studies included results based on the illness setting of participants. Wang et al. (2022) reported an increased 12-month risk of dysrhythmia outcomes (e.g., atrial fibrillation and flutter, aHR: 2.4, 2.30–2.52), compared to controls.¹⁶ The risk of dysrhythmia outcomes increased in patients hospitalized for COVID-19 (e.g. atrial fibrillation and flutter in hospitalized patients, aHR: 1.6, 1.33–1.84 versus non-hospitalized patients, aHR: 1.2, 0.96–1.53).¹⁶ Raisi-Estabragh et al. (2022) found that, across all settings, COVID-19 was significantly associated with an increased 30-day risk of atrial fibrillation incidence (aHR: 5.3, 3.98–6.93).¹³ There was; however, no significant association of 30-day risk of atrial fibrillation between non-hospitalized COVID-19 cases (aHR: 1.0, 0.63–1.69) and non-hospitalized non-COVID-19 patients. The risk of dysrhythmia was significantly elevated in patients hospitalized for COVID-19 compared to those hospitalized for other illnesses (aHR: 14.9, 9.34–23.8), and highest for those hospitalized with COVID-19 as a secondary diagnosis (aHR: 29.3, 6.94–124).

Studies that examined the impact of time from SARS-CoV-2 infection found an increased risk of dysrhythmia in the acute infection period, relative to the post-acute period. Raisi-Estabragh et al. (2022) reported a significant interaction between SARS-CoV-2 infection and time to atrial fibrillation: increased risk was statistically significant within 30 days of COVID-19 infection (aHR: 15.5, 8.87–26.91) and significant but reduced after 30 days (aHR: 1.7, 1.11–2.67), compared to matched non-infected controls.¹³ The incidence of atrial fibrillation in patients with COVID-19 was 29.9 per 1,000 person years, compared to 5.3 in controls. Rezel-Potts et al. (2022) noted that the risk of atrial arrhythmia was significantly increased in the acute follow-up period (≤ 4 weeks, aRR: 6.4, 4.17–9.96) but was lesser, though still statistically significant, in the post-acute period (5–12 weeks, aRR: 1.6, 1.1–2.27). However, the risk of atrial arrhythmia showed no statistically significant elevation during the long-term post-infection phase (13–52 weeks, aRR: 0.9, 0.68–1.05).¹⁴

Inflammatory Heart Disease

This rapid review did not identify any systematic reviews with relevant inflammatory heart disease findings; however, we identified six primary studies that examined inflammatory heart disease (e.g., pericarditis, myocarditis) in those with and without SARS-CoV-2. The incidence of inflammatory heart disease in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, at 30 days since symptom onset, the incidence of pericarditis was 3.8 per 1,000 person years in patients with COVID-19, compared to 0.4 per 1,000 person years in matched non-SARS-CoV-2-infected patients.¹³

Six primary studies that demonstrated an overall increased risk of myocarditis and/or pericarditis outcomes in those infected with SARS-CoV-2, compared to non-SARS-CoV-2-infected controls.^{9,13,14,16,18,19} For example, Xie et al. (2022a) found that patients with COVID-19 had greater 12-month risk of pericarditis (aHR: 1.9, 1.61–2.13) and myocarditis (aHR: 5.4, 3.80–7.59) compared to non-infected controls (no significant differences in risk by age, sex, or comorbidities).⁹ The risk of inflammatory heart disease events increased with increasing COVID-19 disease severity (e.g., pericarditis: non-hospitalized aHR: 1.4; admitted to hospital, aHR: 5.3; admitted to ICU HR: 9.5). A sub-analysis was conducted to remove cohort participants who had received any COVID-19 vaccine and these results continued to show an association between COVID-19 and increased risk of pericarditis and myocarditis. Raisi-Estabragh et al. (2022) included results based on illness setting; across all settings, COVID-19 was significantly associated with an increased risk of pericarditis incidence (aHR: 8.2, 3.38–20.00), compared to those with negative COVID-19 tests.¹³ This association was not statistically significant for non-hospitalized patients with COVID-19 compared to non-hospitalized non-COVID-19 patients (aHR: 0.7, 0.07–6.48); however, the risk of pericarditis was significantly elevated in patients hospitalized for primary COVID-19 (aHR: 13.6, 4.06–45.8), compared to those hospitalized for non-COVID-19 illnesses.

Four studies reported results related to time since SARS-CoV-2 infection. Raisi-Estabragh et al. (2022) found evidence of a significant interaction with time to pericarditis. This increase in risk observed among SARS-CoV-2-infected participants remained statistically significant up to 30 days of COVID-19 infection (aHR: 24.7, 3.22–189.90). This difference remained statistically significant but was reduced 30 days post-infection (aHR: 4.6, 1.63–13.19).¹³ The incidence of pericarditis in patients with COVID-19 was 3.8 per 1,000 person years, compared to 0.4 in controls. Boehmer et al. (2021), in a study of 1,452,773 patients with a COVID-19 diagnosis and 34,552,521 matched controls without a COVID-19 diagnosis, noted an increased risk of pericarditis among older age groups with COVID-19 (16–49 years, aRR range: 7.4–10.0; >49 years, aRR range: 17.0–31.6), compared to those without COVID-19, during the acute stage of infection (≤ 1 month since index date); however, there was no differences in these risks by sex.¹⁸ In contrast, Tulvali et al. (2022), in a study of 196,992 patients with COVID-19 (SARS-CoV-2-test positive) and 590,976 matched controls (patients with negative SARS-CoV-2 test) who were followed up at a median of 4 months since test date, reported that there was an increased risk of myocarditis and pericarditis among patients with COVID-19 (e.g., myocarditis, aHR: 4.4, 1.64–11.96); however, the incidence of both outcomes were low in both study populations (e.g. incidence of myocarditis in both COVID-19 patients and controls was 0.005%).¹⁹ Rezel-Potts et al. (2022) reported an increased risk of myocarditis and cardiomyopathy only in the acute phase of disease (≤ 4 weeks) (aRR: 3.0, 1.27–6.88), compared to controls; no differences in risk were noted in the 5–12 weeks post-acute phase (aRR: 1.4, 0.70–2.68) or in the 13–52 weeks long-term phase (aRR: 1.1, 0.74–1.66).¹⁴

Ischemic Heart Disease

We included three systematic reviews and six primary studies that examined ischemic heart disease outcomes among people with and without COVID-19.^{9,11,13,14,16,20-23} Ischemic heart disease includes acute coronary disease, myocardial infarction, ischemic cardiomyopathy, cardiogenic shock and angina. The incidence of ischemic heart disease in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, in the acute phase of disease (14 days since symptom onset), the incidence of acute myocardial infarction was 0.03% of 86,737 patients with COVID-19, compared to 0.01% of 340,432 matched non-SARS-CoV-2-infected patients.¹¹

Three meta-analyses examined the risks of ischemic heart disease outcomes in patients with COVID-19, compared to non-COVID-19 patients.²⁰⁻²² Cheema et al. (2022) conducted a systematic review and meta-analysis, searched to April 2022 and included 11 studies to compare in-hospital mortality from out-of-hospital ST elevation myocardial infarction (STEMI) between COVID-19-positive (n=1,321) and COVID-19-

negative cohorts (n=30,167).²¹ Patients with cardiogenic shock were significantly more likely to be in the COVID-19 patient cohort compared to the non-COVID-19 cohort (OR: 1.4, 1.16–1.65), and length of hospital stay was longer in patients with COVID-19 (mean difference: 3.3 days, 0.34–6.23). Baral et al. (2022) searched to April 1, 2022 and included eight studies comparing hospitalized cases of acute myocardial infarction with and without PCR-confirmed COVID-19 infections (n=612 and n=9,516, respectively).²⁰ From five studies included in adjusted analysis, patients who experienced in-hospital mortality from acute myocardial infarction were more likely to have had a COVID-19 infection than those who did not (aOR: 3.5, 2.21–5.46). The total incidence of mortality in myocardial infarction patients was 42.6% (261/612) for COVID-19-positive patients and 6.4% (612/9,516) for COVID-19-negative patients. Thakker et al. (2022) did not report a search date and included a meta-analysis of five studies. This review did not find any statistically significant associations between ischemic heart disease outcomes and COVID-19 infection: left main artery disease (incidence in COVID-19 cases versus non-infected controls: 4.7% versus 2.5%; OR: 1.4, 0.68–2.90), left anterior descending artery disease (49.6% versus 44.9%; OR: 1.1, 0.83–1.43), left circumflex artery disease (15.5% versus 16%; OR: 1.2, 0.75–1.85), nor right coronary artery disease (25.2% versus 33.8%; OR: 0.6, 0.30–1.17).²²

In two studies with follow-up in the acute phase of disease, the risk of ischemic heart disease outcomes increased in patients with COVID-19, compared to control patients without COVID-19.^{11,13} Katsoularis et al. (2021) reported that individuals experiencing an ischemic stroke in the two weeks following their test date had a 3.4-fold increase in the odds of having tested positive for SARS-CoV-2 relative to those who did not (aOR: 3.6, 1.58–7.36); 0.03% of 86,737 patients with COVID-19 had a myocardial infarction, compared to 0.01% of 340,432 matched uninfected controls.¹¹ In the self-controlled case series, 186 acute myocardial infarctions were examined, and IRRs for acute myocardial infarction were calculated for the following periods, compared to the control period: buffer period (-28 to -4 days of index date; e.g., date of symptom onset, test date) (IRR: 2.1, 1.31–3.24), -3 to -1 days pre-exposure (2.5, 0.78–8.09), risk period 0–7 days post index (IRR: 8.4, 5.45–13.08), risk period 8–14 days post index (IRR: 2.6, 1.31–5.01), and risk period 15–28 days post index (IRR: 1.6, 0.85–3.09). Raisi-Estabragh et al. (2022) reported an increased risk of myocardial infarction incidence in those with COVID-19 (aHR: 1.8, 1.12–2.96), compared to non-COVID-19 patients.¹³ Risk of myocardial infarction was highest in those hospitalized with COVID-19 as a secondary diagnosis (aHR: 22.2, 2.84–173), followed by patients hospitalized for COVID-19 compared to patients hospitalized for other illnesses (aHR: 9.9, 3.36–29.1). Non-hospitalized COVID-19 cases were less likely to develop acute myocardial infarction compared to non-hospitalized non-COVID-19 patients (aHR: 0.2, 0.06–0.65). The incidence of myocardial infarction in patients with COVID-19 was 5.2 per 1,000 person years, compared to 2.7 in controls.

In three studies with follow-up in the post-acute phase of disease, the risk of ischemic heart disease outcomes increased in patients with COVID-19, compared to controls without COVID-19.^{9,16,23} For example, Xie et al. (2022a) reported that patients with COVID-19 had a greater 12-month risk of acute coronary disease (aHR: 1.7, 1.56–1.90), myocardial infarction (aHR: 1.6, 1.51–1.75), ischemic cardiomyopathy (aHR: 1.8, 1.44–2.13) and angina (aHR: 1.5, 1.42–1.64).⁹ The risk of ischemic heart disease events increased with increasing COVID-19 disease severity (e.g., myocardial infarction: non-hospitalized, aHR: 1.1; admitted to hospital, aHR: 4.4; admitted to ICU, aHR: 8.0). Similarly, Wang et al. (2022) reported a greater risk of acute coronary disease (aHR: 2.0, 1.75–2.39), myocardial infarction (aHR: 2.0, 1.83–2.14), ischemic cardiomyopathy (aHR: 2.8, 2.48–3.19) and angina (aHR: 1.7, 1.55–1.89).¹⁶ In a longitudinal study, Rezel-Potts et al. (2022) reported that the risk of myocardial infarction and inflammatory heart disease in patients with COVID-19 decreased over time since infection compared to matched non-SARS-CoV-2-infected patients, with the risk being highest in the acute phase (≤ 4 weeks, aRR: 2.0, 1.34–3.00). There was no increased risk of myocardial infarction noted during the post-acute (5–12 weeks, aRR: 1.0, 0.68–1.38) and long-term (13–52 weeks, aRR: 0.8, 0.66–0.98) phases.¹⁴

Cardiac Disorders

We included one systematic review and five primary studies that examined additional cardiac disorder outcomes (e.g., heart failure, non-ischemic cardiomyopathy, cardiac arrest, cardiogenic shock) among people with and without COVID-19.^{9,13,14,16,24,25} Cardiac disorders include heart failure, non-ischemic cardiomyopathy, cardiac arrest and cardiogenic shock. The incidence of cardiac disorders in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, at 30 days since symptom onset, the incidence of heart failure was 21.0 per 1,000 person years in patients with COVID-19, compared to 3.5 per 1,000 person years for matched non-SARS-CoV-2-infected patients.¹³

Scquizzato et al. (2021) conducted a systematic review and meta-analysis searched to April 5, 2021 and included 10 studies that examined out-of-hospital cardiac arrest in patients with SARS-CoV-2 infection compared to those without SARS-CoV-2 infection.²⁵ In patients with SARS-CoV-2, return of spontaneous circulation was less frequently achieved compared to controls (22% versus 27%; OR: 0.8, 0.65–0.86). Patients with SARS-CoV-2 infection were also more likely to suffer out-of-hospital cardiac arrest at home (OR: 1.9, 1.45–2.40) and emergency medical services response times were longer for patients with SARS-CoV-2 (mean difference: 1.6, 0.41–2.88).

All five primary studies demonstrated an increased risk of additional cardiac disorders in patients with SARS-CoV-, compared to matched controls.^{9,13,14,16,24} Xie et al. (2022a) noted a greater 12-month risk of heart failure (HR: 1.7, 1.65–1.80), non-ischemic cardiomyopathy (aHR: 1.6, 1.52–1.73), cardiac arrest (aHR: 2.5, 2.08–2.89) and cardiogenic shock (aHR: 2.4, 1.86–3.16) in patients with COVID-19.⁹ The risk of cardiac disorders increased with increasing COVID-19 disease severity (e.g., heart failure; non-hospitalized, aHR: 1.4; admitted to hospital, aHR: 3.9; admitted to ICU, aHR: 6.1). In terms of illness setting, Raisi-Estabragh et al. reported an overall increased risk of heart failure in patients across all settings with COVID-19 (aHR: 5.6, 4.05–7.87); risk of heart failure was highest in those hospitalized for COVID-19 compared to those hospitalized for other conditions (aHR: 21.6, 10.9–42.9) and those hospitalized with COVID-19 as a secondary diagnosis (aHR: 13.1, 5.06–33.8), with no significant risk in non-hospitalized patients with COVID-19 compared to non-hospitalized patients without COVID-19 (aHR: 0.9, 0.45–1.61).¹³

There was evidence to indicate an increased risk of cardiac disorders during the acute stage of SARS-CoV-2 illness. Raisi-Estabragh et al. found there was increased risk of heart failure within the first 30 days of infection (aHR: 11.0, 5.97–20.38), but decreased after 30 days (aHR: 2.8, 1.71–4.51).¹³ The incidence of heart failure in patients with COVID-19 was 21.0 per 1,000 person years, compared to 3.5 in controls. In a study of 428,650 COVID-19 patients and the same number of matched non-COVID-19 patients, Rezel-Potts et al. (2022) reported that the risk of heart failure decreased over time, in the acute (≤ 4 weeks, aRR: 5.2, 2.04–13.44), post-acute (5–12 weeks, aRR: 2.3, 1.17–4.51) and long-term (13–52 weeks, aRR: 0.7, 0.49–1.06) phases.¹⁴ The mean overall incidence of cardiovascular disease (per 100,000 patient weeks) for patients with COVID-19 in the 4 weeks prior to diagnosis was 14.1 (13.58–14.58), 76.9 (72.89–81.13) in acute phase, 22.1 (20.53–23.68) in post-acute phase and 12.6 (12.20–13.18) in the long-term phase. The incidence of cardiovascular disease in matched non-SARS-CoV-2-infected patients remained relatively stable in all four phases (pre-diagnosis, 7.6 per 100,000 patient weeks, 7.22–7.95; acute, 7.3, 6.10–8.69; post-acute, 8.4, 7.47–9.43; long-term, 9.1, 8.64–9.57).

Thrombotic Disorders

We included one systematic review and nine primary studies that examined the risks of thrombotic disorder outcomes in patients with COVID-19, compared to non-infected contemporary controls.^{9,13,14,16,17,26-30} Thrombotic outcomes were primarily venous thromboembolism, pulmonary embolism, deep vein thrombosis and superficial vein thrombosis. The incidence of thrombotic disorders in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, in the acute phase of disease, the incidence of deep vein thrombosis was 0.04% of 1,035,920 patients with COVID-19, compared to 0.007% of 3,931,211-matched non-SARS-CoV-2-infected patients.¹⁷

Mai et al. (2021) conducted a systematic review and meta-analysis searched to March 31, 2021, and included seven studies (total 41,768 patients) that examined venous thromboembolism in COVID-19 patients compared to non-COVID-19 patients.²⁸ Venous thromboembolism included pulmonary embolism and/or deep venous thrombosis. The cumulative relative risk (RR) estimate for venous thromboembolism for COVID-19 patients was 1.2 (0.79–1.77) compared to non-COVID-19 patients. Patients with COVID-19 were not at increased risk of pulmonary embolism or deep vein thrombosis. Sub-group analysis showed increased risk among COVID-19 patients when considering only those hospitalized in the ICU (RR: 3.1, 1.54–6.23), a statistically significant difference was not observed for non-ICU patients.

In three studies with follow-up only in the acute phase of disease, the risk of thrombotic disorder outcomes increased in patients with COVID-19, compared to non-COVID-19 controls.^{26,27,30} One study included results related to the vaccination status of participants. Xie et al. (2022b) examined 30-day risk of acute incident venous thromboembolism in 18,818 patients with COVID-19 (positive PCR test), compared to 93,179 non-infected control patients (negative PCR test).³⁰ The 30-day risk of venous thromboembolism in patients with COVID-19 was magnitudes higher compared to controls (aHR: 21.4, 12.63–36.31). The authors noted a differential impact for the association between SARS-CoV-2 infection and venous thromboembolism, such that individuals who were not vaccinated or partially vaccinated (not defined) were at greatest risk (aHR: 27.9, 15.11–51.65), while the risk was lesser among fully vaccinated (not defined) patients (aHR: 6.0, 1.82–19.51). The risk of venous thromboembolism in patients with COVID-19 was also greater among participants of increasing age (10-year increments, aHR: 1.9, 1.50–2.33), male sex (aHR: 1.7, 1.30–2.19) and those considered obese (body mass index ≥ 30 vs. < 30 , aHR: 1.8, 1.28–2.61). Additionally, the incidence of venous thromboembolism among patients with COVID-19 was 51.0 per 1,000 person years, compared to 2.4 in non-infected controls.

Three studies consistently demonstrated that COVID-19 patients are at continued risk of thrombotic outcomes in the post-acute phase of disease.^{9,16,29} For example, Xie et al. (2022a) reported that patients with COVID-19 had greater 12-month risk of pulmonary embolism (aHR: 2.9, 2.73–3.15), deep vein thrombosis (aHR: 2.1, 1.94–2.24) and superficial vein thrombosis (aHR: 2.0, 1.80–2.12).⁹ The risk of thrombotic events increased with increasing COVID-19 disease severity (e.g., pulmonary embolism: non-hospitalized, aHR: 2.0; admitted to hospital, aHR: 9.4; admitted to ICU, aHR: 21.7), compared to non-SARS-CoV-2 infected controls. Similarly, Wang et al. (2022) reported an increased risk of pulmonary embolism (aHR: 2.6, 2.44–2.87), deep vein thrombosis (aHR: 1.9, 1.75–2.02) and superficial vein thrombosis (aHR: 1.6, 1.44–1.76).¹⁶ Risk of venous thromboembolism increased with age (e.g., pulmonary embolism, 20–44 years aHR: 2.11 versus ≥ 65 years HR: 2.8) and disease severity (e.g. pulmonary embolism: inpatient aHR: 3.3 vs. outpatient aHR: 2.6); however, the risk of cardiovascular outcomes decreased over time (e.g., pulmonary embolism at 31–90 days HR: 3.4 versus 271–365 days aHR: 1.6). In a study of 59,893 children (< 21 years, mean standard deviation [SD] age: 8.1 years [5.7]) with COVID-19 and positive SARS-CoV-2 test (and 599,393 matched, test-negative controls), Rao et al. (2022) followed-up on COVID-19 patients at a mean (SD) of 4.6 ± 0.7 months (similar to controls).²⁹ At

follow-up, children with COVID-19 were at increased risk of thrombophlebitis and thromboembolism compared to those without COVID-19 (aHR: 1.3, 1.05–1.53).

Three studies demonstrated that the risk of venous thromboembolism was highest in the first 30 days following infection, compared to the post-acute phase.^{13,14,17} Raisi-Estabragh et al. (2022) reported that patients with COVID-19 had an increased incidence of venous thromboembolism compared to patients without COVID-19 (aHR: 13.2, 8.75–19.9). This association was statistically significant for non-hospitalized COVID-19 cases versus non-hospitalized non-COVID-19 cases (aHR: 2.7, 1.38–5.45), but was highest in patients hospitalized for COVID-19 compared to those hospitalized for other conditions (aHR: 27.6, 14.5–52.3); the risk of venous thromboembolism was also elevated for those hospitalized with COVID-19 as a secondary diagnosis (aHR: 23.1, 5.42–98.4).¹³ Venous thromboembolism was highest in the first 30 days of illness (aHR: 66.8, 24.7–180.5), compared to after 30 days (aHR: 4.0, 2.10–7.53). Similarly, study of 428,650 COVID-19 patients and the same number of matched controls, Rezel-Potts et al. (2022) noted that risk of pulmonary embolism decreased over time, highest in the acute phase (≤ 4 weeks, aRR: 11.5, 7.07–18.73), followed by the post-acute phase (5–12 weeks, aRR: 2.3, 1.47–3.57) and not significantly increased in the long-term phase (13–52 weeks, aRR: 0.7, 0.50–0.87).¹⁴ In addition, the risk of venous thrombosis decreased over time, in the acute (aRR: 5.4, 3.27–9.01), post-acute (aRR: 1.8, 1.27–2.64) and long-term (aRR: 0.9, 0.71–1.10) phases.

Similarly, in a matched cohort study of 1,057,174 patients with COVID-19 and 4,076,342 controls, Katsoularis et al. (2022) examined risks of venous thromboembolism at 30 days since episode date.¹⁷ Patients with COVID-19 were at an increased risk of deep vein thrombosis (aRR: 5.0, 4.96–5.01) and pulmonary embolism (aRR: 33.1, 32.8–33.3), compared to controls. Risk of pulmonary embolism increased as disease severity increased: mild (aRR: 6.8, 5.43–8.45), admitted to hospital (sRR: 139.2, 94.32–205.3), and admitted to ICU (aRR: 289.4, 91.55–914.7) (similar for deep vein thrombosis). In addition, 0.04% of 1,035,920 patients with COVID-19 had a deep vein thrombosis, compared to 0.007% of 3,931,211-matched, un-infected controls. In the self-controlled case series, 1,761 deep vein thrombosis events were examined, and IRRs were calculated for the following periods, compared to the control period: buffer period (-30 to -4 days of index date; e.g., date of symptom onset, test date) (IRR: 1.4, 1.12–1.73), -3 to 0 days pre-exposure (8.7, 6.92–10.97), risk period 1–7 days post index (IRR: 5.6, 4.47–6.98), risk period 8–14 days post index (IRR: 7.4, 6.06–9.14), and risk period 15–30 days post index (IRR: 5.3, 4.44–6.36). The IRRs for deep vein thrombosis events decreased in the post-acute phase, returning to the buffer period risk at 61 to 90 days post index (IRR: 1.4, 1.09–1.85). The authors reported similar risks for pulmonary embolism were highest -3 days pre-exposure to 30 days post index (IRR range: 20.2 to 46.4; n=3,267 events). The IRRs for pulmonary embolism events decreased in the post-acute phase, returning to the buffer period risk at 61 to 90 days post index (buffer, IRR: 2.8, 2.29–3.33; 61–90 days, IRR: 2.5, 1.95–3.15).

Major Adverse Coronary Events (MACE)

We included six systematic reviews that examined the risks of MACE outcomes following SARS-CoV-2 infection, compared to non-SARS-CoV-2-infected controls.^{12,20-22,25,31} We included five primary studies examining these risks.^{9,13,15,16,24} MACE includes all-cause mortality (of cardiovascular-specific death), stroke and myocardial infarction. The incidence of thrombotic disorders in patients with COVID-19 and non-SARS-CoV-2-infected patients was relatively low. For example, in the acute phase of disease, the incidence of cardiovascular disease death was 9.8 per 1,000 person years in patients with COVID-19, compared to 1.8 per 1,000 person years in matched non-SARS-CoV-2-infected patients.¹³

Six systematic reviews and meta-analyses demonstrated increased risks of acute in-hospital and out-of-hospital mortality from a major cardiac event (e.g., stroke, myocardial infarction) in patients with COVID-19, compared to matched, non-COVID-19 patients.^{12,20-22,25,31} In a meta-analysis searched to April 2022 that included 11 studies and 1,321 patients with COVID-19 and 30,167 controls, Cheema et al. (2021) reported that in-hospital STEMI-related deaths were more common among COVID-19 patients compared to non-COVID-19 patients (using adjusted studies [n=4], aOR: 3.5, 1.72–6.95; using unadjusted studies [n=7], OR: 4.5, 2.52–8.14).²¹ Similar results were reported in additional meta-analyses, with a higher risk of in-hospital death from acute myocardial infarction (aOR: 3.5, 2.21–5.45), STEMI (OR: 5.2, 3.63–7.56), cardiac arrest (OR: 2.3, 1.37–3.99) and stroke (OR: 5.2, 3.43–7.90) being observed in COVID-19 compared to non-COVID-19 patients.^{12,20,22,31} In a meta-analysis of 1,341 patients with COVID-19 and 6,204 non-infected patients (searched to April 5, 2021; n=6 studies), Scquizzato et al. (2021) reported that patients with COVID-19 had decreased rates of survival at the time of hospital discharge or at 30 days since index date (OR: 0.3, 0.17–0.65).²⁵

Four studies demonstrated a higher risk of MACE outcomes in COVID-19 patients examined in the post-acute phase.^{9,13,16,24} For example, Raisi-Estabragh et al. (2022) reported that COVID-19 was associated with an increased risk of cardiovascular disease death (aHR: 5.5, 3.24–9.29) and ischemic heart disease death (aHR: 4.2, 2.16–8.67), with highest risk in those hospitalized with COVID-19 for secondary COVID-19 (cardiovascular disease death, aHR: 14.6, 4.37–48.8; ischemic heart disease death, aHR: 23.7, 3.09–182).¹³ The risk of all-cause mortality was higher in the first 30 days of infection (aHR: 101.1, 64.9–157.3), compared to after 30 days (aHR: 9.7, 7.13–13.28). The incidence of cardiovascular disease death in patients with COVID-19 was 9.8 per 1,000 person years, compared to 1.8 in controls (ischemic heart disease death: 4.9 versus 1.1). Xie et al. (2022a) that individuals with COVID-19 had greater risk of MACE (aHR: 1.6, 1.50–1.60) and any cardiovascular outcome (aHR: 1.6, 1.59–1.68).⁹ Wang et al. (2022) noted that the 12-month risk of MACE outcomes were higher in hospitalized patients with COVID-19 (aHR: 1.3, 1.19–1.45), with no increased risk observed in non-hospitalized patients with COVID-19 (aHR: 0.9, 0.77–1.02).¹⁶

Taquet et al. (2022), examined the 6-month risk of ischemic stroke or death before and after the emergence of three VOCs (Alpha, Delta, Omicron) among 1,284,437 patients with COVID-19, compared to 1,284,437 matched controls with non-COVID-19 respiratory infections.¹⁵ The risk of ischemic stroke or death was highest after the emergence of Delta (aHR: 1.5, 1.39–1.64), compared to before emergence of Delta. Conversely, there was a lower risk of ischemic stroke or death after the emergence of Omicron (aHR: 0.7, 0.64–0.79), compared to before the emergence of Omicron.

Discussion

The results of this rapid review provide evidence suggesting that SARS-CoV-2 infections can have significant impacts on the cardiovascular system, which may present as an increased risk of developing various cardiac clinical outcomes. Patients infected with SARS-CoV-2, compared to non-infected controls, were at greater risk of cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, cardiac disorders, thrombotic disorders and composite measures such as MACE and mortality due to cardiovascular disorder. Where authors included acute illness setting, evidence was consistent that the incidence of cardiovascular outcomes was elevated in hospitalized compared to non-hospitalized patients with COVID-19. There was also evidence to suggest the risk of several outcomes decreased as time from infection increased (e.g., stroke, atrial fibrillation, pericarditis, heart failure, myocardial infarction, pulmonary embolism, venous thromboembolism, and all-cause mortality). Specifically, the risk was greatest in the 30 days following COVID-19 symptom onset or date of positive SARS-CoV-2 test. Examination of risk over time from infection was not consistently conducted across all

cardiovascular outcomes; therefore, the impact of time on the other cardiovascular outcomes cannot be determined based on this body of evidence.

STRENGTHS

A key strength of this rapid review is the focus on studies with contemporary control groups. This allows direct comparison and a clearer understanding of the increased risk of assessed outcomes than studies that examine only incidence among SARS-CoV-2 infected participants, which leave more uncertainty around what other factors influence results and do not compare to a baseline measure.

LIMITATIONS

This rapid review has several limitations to consider. Inclusion was limited to English language records; therefore, additional relevant studies may have been missed. There may be overlap of included primary studies between the systematic reviews. Additional limitations are inherent to the included systematic reviews and primary literature.

There was considerable heterogeneity between studies and outcome measures, and certain populations and demographics were overrepresented in these studies when compared to the general population, i.e., hospitalized patients and middle-age to older-age adults. Therefore, not all findings are directly applicable to the broader population of any SARS-CoV-2 infected individuals.

For the included systematic review literature, we highlight four key considerations and limitations. First, across the included systematic reviews evidence, select participant characteristics were overrepresented relative to any SARS-CoV-2 infected individual in the general population, namely, those who were male, middle- to older-age adults, and hospitalized patients. Therefore, results are not necessarily directly applicable to all individuals with a SARS-CoV-2 infection. Second, accounting for confounders and reporting of patient-level data was inconsistent across reviews. For example, while this rapid review initially intended to include only systematic reviews in which PCR-confirmed infections were studied, the lack of patient-level data from individual studies generally precluded the application of this criteria, or would have excluded the majority of relevant systematic review and meta-analysis evidence. Third, the number of included studies relevant to cardiovascular outcomes in meta-analyses were typically low (≤ 11), leading to low sample sizes and increased heterogeneity. Finally, the management of cardiovascular outcomes likely varied among studies included in meta-analyses, making it difficult to interpret results.²¹ Overall, the systematic review evidence was valuable in understanding the difference in risk of cardiovascular outcomes among SARS-CoV-2 patients relative to controls at a high level; however, more nuanced evidence around risk factors and potential confounding factors were lacking.

For the included primary literature studies, we highlight five of the common limitations noted in these studies. First, there was the lack of comparisons examining the impact of COVID-19 vaccination or different VOCs on cardiovascular outcomes. One study found increased risk of ischemic stroke in the period after Delta emergence compared to before Delta, but no significant differences before and after Alpha or Omicron.¹⁵ Another study found that increased risks of venous thromboembolism in unvaccinated and partially vaccinated participants compared to fully vaccinated participants.³⁰ More research from large, high quality studies is needed to understand the impact of these factors on cardiovascular outcomes. Second, many of the studies relied on electronic health records, which in most cases do not include confirmatory diagnostic evaluations of patients (e.g., electrocardiograms, cardiac imaging, laboratory results), potentially leading to misclassification of outcomes and overestimation of cardiac outcomes. In some cases, patients with severe or critical disease cannot undergo additional diagnostic procedures, potentially leading to an underestimate of cardiovascular outcomes.¹¹ Third, most studies did not account for administration of medications for hospitalized patients, potentially

leading to an underestimate or overestimate of the incidence of cardiovascular outcomes¹³ or potentially overestimate or increase the incidence of cardiovascular outcomes.¹⁶ Fourth, there was a potential for missing asymptomatic or non-diagnosed patients within control arms of studies, which could overestimate cardiovascular outcomes in controls.⁹ Fifth, people who tested positive for SARS-CoV-2 are more likely to seek medical care, thereby also potentially overestimating the incidence of cardiovascular outcomes.²⁹ These limitations must be taken into account since non-self-controlled studies may be biased, impacting the overall risk of cardiovascular outcomes in those with COVID-19.

Conclusions and Public Health Implications

The findings of this rapid review demonstrate increased risks for various cardiovascular outcomes among individuals with SARS-CoV-2 infections, relative to non-infected controls. These results are applicable primarily to adults over the age of 50 years and hospitalized patients; applicability to other demographics is uncertain. These results emphasize the importance of continuing to promote COVID-19 vaccination and other infection prevention measures that facilitate reductions in transmission and incidence of SARS-CoV-2 (e.g., paid sick time, masking, layering of measures). Minimizing SARS-CoV-2 infections remains an important public health goal to limit acute and long-term health impacts at the population level, and the associated burdens on both primary care and public health resources. Minimizing SARS-CoV-2 infections is especially important for populations more susceptible to severe COVID-19 disease. Based on the findings of this rapid review, early assessment and potentially increased degree of suspicion for cardiovascular disorders may be warranted following SARS-CoV-2 infection for those who are at elevated risk of cardiovascular complications (e.g., older age groups, those in the acute stage of COVID-19, those with severe COVID-19 and those with existing cardiovascular risk factors).

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Appendix A: Eligibility Criteria

Table 1a: Eligibility Criteria for Study Inclusion

Inclusion Criteria	Exclusion Criteria
<p>Systematic review-level evidence</p> <p>Primary studies with sample size of 5,000 or greater (exception for paper on pregnant women)</p>	<p>Case reports, case series, editorials, conference proceedings, abstracts, modelling studies</p> <p>Studies or reviews with no methods reported</p>
<p>Records published from January 1, 2020 onwards</p> <p>English language only</p> <p>Organisation for Economic Co-operation and Development jurisdiction (for primary studies only)</p>	<p>Not applicable</p>
<p>Population: individuals with SARS-CoV-2 infection confirmed by PCR or rapid antigen test</p>	<p>Self-reported infection, or presumed based on clinical presentation</p> <p>Epidemiologically-linked infection with no confirmatory testing</p>
<p>Control group: contemporary non-SARS-CoV-2 infected participants</p>	<p>No control population, or included only historical controls</p>
<p>Outcomes: impact of SARS-CoV-2 infection on the following cardiovascular outcome categories: cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, other cardiac disorders, thrombotic disorders, or other composite cardiovascular outcomes (e.g., MACE)</p>	<p>Non-cardiovascular outcomes (e.g. diabetes mellitus), biomarkers, autopsy results</p> <p>Molecular mechanisms of cardiovascular damage</p> <p>Cardiovascular outcomes in studies of COVID-19 vaccine adverse events</p> <p>Treatment regimens</p>

Abbreviations: MACE, major adverse cardiovascular events

Appendix B: Study Characteristics

Table 1b: Characteristics of Included Systematic Reviews with Meta-analyses (n=8)

First author, year	Last search, number of studies, relation to vaccines and VOCs	Eligible studies	Eligible COVID-19 cases	Contemporary controls	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years)	Cardiovascular outcomes assessed
Baral , ²⁰ 2022	Apr 1, 2022 8 studies No vaccine or VOC-based results	Included studies on patients hospitalized for acute myocardial infarction from Dec 1, 2019 to Dec 1, 2021 Excluded studies conducted on outpatients, case reports, case series, review articles, meta-analyses, and non-comparison studies based on COVID-19 status	N=612 Acute myocardial infarction inpatients with PCR-confirmed COVID-19	N=9,516 Acute myocardial infarction among COVID-19 test-negative inpatients	Follow up from positive test not reported. Inpatient setting suggests acute infection stage Meta-analyses adjusted for baseline differences in patient demographics and characteristics, comorbidities, and in-hospital pharmacology	Inpatient	Range from included studies: 15.4–44.8	Range of mean ages from included studies: 61.7–68	Acute myocardial infarction mortality
Cheema , ²¹ 2022	Apr 2022 11 studies No vaccine or VOC-based results	Included studies comparing in-hospital mortality between COVID-19-positive and COVID-19-negative cohorts with out-of-hospital STEMI Excluded studies that compared the COVID-19 era with the pre-pandemic era without considering the COVID-19 status of STEMI patients	N=1,321 COVID-19 positive (confirmation or test method not reported)	N=30,167 COVID-19 negative (confirmation or test method not reported)	Follow up from positive test not reported. Given the study assessed outcomes following out-of-hospital STEMI, it may be assumed that COVID-19 cases were detected upon arrival to hospital, suggesting acute stage of COVID-19 infection Subgroup analysis based on the use of unadjusted values versus adjusted values from primary studies, but items adjusted for not reported	Outpatient	Range from included studies: 15.4–35.6	Range of mean ages from included studies: 56.13–70	Primary: in hospital mortality following out-of-hospital STEMI Secondary: cardiogenic shock on presentation, door-to-balloon time and length of hospital stay

First author, year	Last search, number of studies, relation to vaccines and VOCs	Eligible studies	Eligible COVID-19 cases	Contemporary controls	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years)	Cardiovascular outcomes assessed
Ippolito , ³¹ 2022	Feb 8, 2021 10 studies No vaccine or VOC-based results	Included studies with data on mortality after in-hospital cardiac arrest in adult patients with COVID-19. Non-randomized studies, both prospective and retrospective, and case series were included. Excluded abstracts and case reports	N= 226 3 studies compared COVID-19 to non-COVID-19 controls Primary study-defined COVID-19 cases: PCR (2/3 studies); confirmed, suspected or recent (1/3)	N=989 3 studies compared COVID-19 to non-COVID-19 controls Test-negative controls (1/3); non-COVID-19 confirmation or test not reported (2/3)	Follow-up: mortality assessed at 30 days or to hospital discharge Analysis: for the outcome of mortality, performed sub-group analyses based on the level of care (i.e. ICU and non-ICU) and on the number of centres per study (i.e., multicentre, single centre)	Inpatient	Range from included studies: 13–50.8	Range of mean/median ages from included studies: 61–69	Primary: mortality of in-hospital cardiac arrest with attempted CPR Secondary: rate of in-hospital cardiac arrest, rate of non-shockable presenting rhythms, rate of return of spontaneous circulation, rate of survival with favourable neurological status
Thakker , ²² 2022	Search date not reported 5 studies No vaccine or VOC-based results	Included studies of any design that evaluated patients with acute STEMI positive for SARS-CoV-2; and reported clinical presentation, coronary involvement and outcomes of patients with vs. without SARS-CoV-2 Excluded studies that lacked details of coronary artery involvement, did not assess in hospital mortality, or compared populations that were pre-COVID-19 pandemic.	N=266 Patients with STEMI and with SARS-CoV-2 (confirmation or test method not reported)	N=2,000 Patients with STEMI without SARS-CoV-2 (confirmation or test method not reported)	Follow up from SARS-CoV-2 infection not reported No description of additional stratification or analysis adjustments	Inpatient	Range from included studies: 21.1–33.5	COV: mean, 62.4 CON: mean, 63.9	Primary: in hospital mortality from STEMI Secondary: left main artery disease, left anterior descending artery disease, left circumflex artery disease, or right coronary artery disease in STEMI

First author, year	Last search, number of studies, relation to vaccines and VOCs	Eligible studies	Eligible COVID-19 cases	Contemporary controls	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years)	Cardiovascular outcomes assessed
Ganesh , ¹⁰ 2021	Mar 31, 2021 477 studies for qualitative synthesis, 59 for meta-analysis 4 studies related to stroke No vaccine or VOC-based results	Qualitative: included studies on neurological or head/eyes/ears/nose/throat manifestations of COVID-19 in humans, including case series, case-control, cohort studies and case reports Meta-analysis: included studies with at least 100 patients with COVID-19, and used a prospective or retrospective cohort, cross-sectional, or case-control design	N= 238,501 4 studies with data on the frequency of ischemic stroke among patients with COVID-19 (confirmation or test method not reported)	N=237,874 4 studies on stroke with data on the frequency of ischemic stroke among patients without COVID-19 (confirmation or test method not reported)	Not reported Analysis: grouped studies according to their study design (prospective cohort, retrospective cohort, cross-sectional, case-control) to derive summary estimates from similarly-designed studies	Mixed: reported that the studies “generally only included hospitalized patients.”	Average of all (i.e., on all neurological or head/eyes/ears/nose/throat outcomes) study reported means: 50.4	Average of all study-reported means: 52.8	Occurrence of ischemic stroke
Maj , ²⁸ 2021	Mar 31, 2021 7 studies No vaccine or VOC-based results	Included studies with >10 patients with COVID-19, and reported on venous thromboembolism outcomes of interest	N=3,060 Positive PCR test or positive CT-scan in patients with suggestive presentation	N=38,708 Non-COVID-19 patients (confirmation or test method not reported)	Mean follow up range reported in 3 studies: 7–30 days. 4 studies did not report follow-up. Analyses to investigate heterogeneity according to hospitalization settings (cohorts of ICU patients only versus predominantly non-ICU patients), presence or absence of ventilator support, study types (prospective versus retrospective) and presence or absence of thromboprophylaxis	Inpatient	Range from included studies: 18.2–52	Range of median ages from included studies: 55.5–72	Occurrence of venous thromboembolism, pulmonary embolism, deep vein thrombosis

First author, year	Last search, number of studies, relation to vaccines and VOCs	Eligible studies	Eligible COVID-19 cases	Contemporary controls	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years)	Cardiovascular outcomes assessed
Nannoni , ¹² 2021	Sep 14, 2020 145 studies total, 61 studies in meta-analyses No vaccine or VOC-based results	Included studies on new-onset cerebrovascular events in patients with confirmed SARS-CoV-2 infection. Case reports and observational studies were included in meta-analysis if they reported at least five patients developing acute outcomes of interest Excluded studies that were abstract-only, animal studies, studies on pediatric populations, and repeat publications on the same patient cohorts	N=396 COVID-19 patients from 11 studies (confirmation or test method not reported)	N=1,670 Non-COVID-19 patients from 11 studies (confirmation or test method not reported)	Follow up not reported for all included studies. From 24 studies, delay of stroke from COVID-19 symptom onset was 8.8 days (95% CI: 6.3, 11.6). No description of additional stratification or analysis adjustments	Not reported Hospitalized for stroke: 38%	ALL: 37.6 (95% CI: 33.2, 42.2)	ALL: median: 65.3 (95% CI: 60.4, 67.6)	Incidence, risk factors, characteristics and outcomes of stroke
Scquizzato , ²⁵ 2021	Apr 5, 2021 10 studies No vaccine or VOC-based results	Included studies comparing out-of-hospital cardiac arrest patients with confirmed or suspected SARS-CoV-2 infection to those without confirmed or suspected SARS-CoV-2 infection in the same study period. Included observational cohort studies with prospective and retrospective design. Excluded systematic reviews, literature reviews and editorials	N=1,341 Suspected or confirmed SARS-CoV-2 infection; 9 studies reported lab-confirmation	N=6,204 Non-infected patients (confirmation or test method not reported)	Follow up 30 days from cardiac arrest, time from COVID-19 infection not reported. No description of additional stratification or analysis adjustments	Outpatient	COV: 38 CON: 38	COV mean: 71 (SD: 16) CON mean: 72 (SD: 16)	Incidence and outcomes of out-of-hospital cardiac arrest

Abbreviations: CI, confidence interval; CON, control; COV, COVID-19; CPR, cardio pulmonary resuscitation; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; MACE, major adverse cardiovascular events; PCR, polymerase chain reaction; SD, standard deviation; STEMI, ST elevation myocardial infarction.

Table 2b: Characteristics of Included Primary Studies (n=15)

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Boehmer , ¹⁸ 2021, US	Mar 1, 2020 to Jan 31, 2021 Vaccinated participants were excluded Wild-type to Beta	Cohort	N=1,452,773 Participants with a COVID-19 diagnoses (includes patients prior to widespread testing)	N=34,552,521 Participants without a COVID-19 diagnoses	Acute stage only Risk stratified by age group and sex	Inpatients , outpatientts	COV: 53.1 CON: 58.5	ALL: median 50 (IQR: 29-66)	Myocarditis
Go , ²⁷ 2021, US	Jan 1, 2020 to Aug 31, 2020 Pre-vaccine Wild-type to Beta	Respective cohort	N=6,319 Participants with positive COVID-19 PCR tests	N=6,319 Participants with negative COVID-19 PCR tests Matching 1:1 on age, sex, race and ethnicity, month of hospitalization, comorbidities	30-days since index date (could include after discharge) Risk factors for VTE explored Models accounted for confounders such as prior conditions, current and past treatments	Inpatients	COV: 45.9 CON: 45.9	COV: 20 (17.2) CON: 60. (17.2)	VTE: deep vein thromboembolism, pulmonary embolism Mortality
Katsoularis , ¹¹ 2021, Sweden	Feb 1 to Sept 14, 2020 Pre-vaccine Wild-type to Beta	Self-controlled case series (187 acute myocardial infarction and 254 ischemic stroke events) and matched cohort study	N=83,397 Participants with positive COVID-19 tests	N=340,432 Participants with negative COVID-19 tests Matching 1:4 on age, sex, county of residence	Follow-up 14, days after index date (positive test) 14-day risks stratified by comorbidities and country of birth, education level, income	Inpatients , outpatientts	COV: 57 CON: NR	COV: median 48 (IQR: 31-62) CON: NR	Myocardial infarction Ischemic stroke Mortality

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Tsai , ²³ 2021, US	Feb 24 to Nov 25, 2020 Pre-vaccine Wild-type to Beta	Retrospective cohort	N=8,308 Participants with positive or presumed positive COVID-19 tests	N=69,056 Participants with negative COVID-19 tests	60 days from index date (test date) Examined risk according to age, race, comorbidities, obesity, smoking status	Inpatients , outpatients	100	COV: 49 (12.7) CON: 51 (12.8)	Myocardial ischemia Any cardiovascular disease All-cause mortality
Ferrara , ²⁶ 2022, US	Mar 1, 2020 to Mar 16, 2021 Did not include vaccination as a risk factor Wild-type to Beta	Population-based cohort	N=1,332 Participants with positive COVID-19 PCR tests	N=42,554 Participants with negative COVID-19 PCR tests or not diagnosed with COVID-19	Patients followed from last menstrual period to an event of interest, except gestational hypertension Models adjusted for age, neighbourhood deprivation index, body mass index, race and ethnicity, smoking status, comorbidities	Inpatients	100	COV: 29 (5.5) CON: 31 (5.2)	Venous thromboembolism
Katsoularis , ¹⁷ 2022, Sweden	Feb 1, 2020 to May 25, 2021 Did not include vaccination as a risk factor Wild-type to Delta	Self-controlled case series (1,761 deep vein thrombosis and 3,267 pulmonary embolism events) and matched cohort study	N=1,057,174 SmiNet participants with positive COVID-19 tests	N=4,076,342 Participants with negative COVID-19 tests Matching 1:4 on age, sex, county of residence	Follow-up 30 days after index date (positive test) Models adjusted for comorbidities, surgery, medications	Inpatients Inpatients to intensive care Outpatients	COV: 51.1 CON: 50.9	COV: 40 (19) CON: 40 (19.1)	Venous thromboembolism: deep vein thromboembolism, pulmonary embolism Mortality

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Raisi-Estabragh , ¹³ 2022, UK	Mar 1, 2020 to Mar 30, 2021 Did not include vaccination as a risk factor Wild-type to Beta	Case-control	N=17,871 Participants with positive COVID-19 PCR or antigen tests	N=35,742 Participants with negative COVID-19 PCR or antigen tests Matching 1:2 on age, sex, deprivation, body mass index, ethnicity, comorbidities, smoking	Participants followed until first episode of a specific outcome, death or end of study period Mean follow-up: 141 days (range: 32–395) Study results organized by outcome events within or after 30 days from index date	Outpatient Inpatient Inpatient with COVID-19 as secondary diagnosis	COV: 53 CON: 53	COV: median 65 (IQR: 58-73) CON: median 65 (IQR: 58-73)	Stroke Myocardial infarction Heart failure Atrial fibrillation Venous thromboembolism Pericarditis Mortality: all-cause mortality, cardiovascular disease mortality, ischemic heart disease mortality
Rao , ²⁹ 2022, US	Mar 1, 2020 to Dec 31, 2021 Did not include vaccination as a risk factor Wild-type to Beta	Retrospective cohort study	N=59,893 Participants with positive COVID-19 antigen/PCR tests	N=599,393 Participants with negative COVID-19 antigen/PCR tests Matching based on date of cohort entrance	28 to 179 days after index date (test date), or Dec 31, 2021; mean 4.7 months Models adjusted for age, sex, race, ethnicity, institution, testing location, date of cohort entrance	Inpatients, outpatients	COV: 48.7 CON: 47.0	COV: 9.4 (5.9) CON: 7.9 (5.7)	Thrombophlebitis and thromboembolism

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Rezel-Potts , ¹⁴ 2022, UK	Feb 1, 2020 to Jan 31, 2022 Did not include vaccination as a risk factor Wild-type to Delta	Cohort	N=428,650 Participants with diagnoses of confirmed or suspect COVID-19; includes analyses of test-positive patients	N=428,650 Participants with alternative, non-COVID-19 diagnoses Matching 1:1 on year of birth, sex, family practice	4 weeks (acute COVID-19), 5–12 weeks (post-acute COVID-19) and 13–52 weeks (long COVID-19) Sensitivity analyses accounted for demographic, socioeconomic and comorbidities	Outpatients, inpatients	COV: 56 CON: 56	COV: median 35 (IQR: 22–50) CON: median 35 (IQR 22–50)	Cardiovascular disease Venous thromboembolism, pulmonary embolism Atrial arrhythmia Heart failure Stroke Cardiomyopathy/ myocarditis Myocardial infarction Ischemic heart disease
Salah , ²⁴ 2022, US	Mar 1, 2020 to Mar 31, 2022 Did not include vaccination as a risk factor Wild-type to Omicron	Population-based cohort	N=257,075 Participants with COVID-19 diagnoses while hospitalized and who survived to discharge	N=330,255 Participants with non-COVID-19 diagnoses while hospitalized and survived to discharge No matching; random 15% sample of non-COVID-19 patients (N=2,560,320)	Inpatients with COVID-19: median follow up 331 days Outpatients without COVID-19: median follow up 405 days Risks assessed for age, sex, race/ethnicity and use of cardiovascular medications	Inpatients with COVID-19 Inpatients without COVID-19	COV: 51 CON: 58	COV: 51 (22) CON: 46 (23)	Heart failure Mortality Composite events

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Taquet , ¹⁵ 2022, International (mostly US, Australia, UK, Spain, Bulgaria, India, Malaysia, and Taiwan)	Jan 20, 2020 to Apr 13, 2022 Did not include vaccination as a risk factor Wild-type to Omicron	Retrospective cohort	N=1,284,437 Participants with confirmed COVID-19 diagnoses	N=1,284,437 Participants diagnosed with non-COVID-19 respiratory infections Matching 1:1 on age group, sex, race, socioeconomic status, comorbidities	6 months since index date (diagnosis date) and 2 years since index date Assessed risk based on age groups and VOCs	Inpatients, outpatients	COV: 57.8 CON: 57.7	COV: 43 (21.9) CON: 43 (22.1)	Intracranial hemorrhage Ischemic stroke
Tuvalli , ¹⁹ 2022, Israel	Mar 7, 2020 to Jan 31, 2021 Vaccinated individuals excluded Wild-type to Beta	Population-based cohort	N=196,992 Participants with positive COVID-19 PCR tests	N=590,976 Participants with negative COVID-19 PCR tests Matching 1:3 on sex, age, follow-up period	18 days since index date (test date) up to 6 months or Feb 28, 2021, median follow-up of 4.1 months Assessed risk factors for cardiovascular outcomes	Inpatients	COV: 54.3 CON: 54.3	COV: 42 (17.7) CON: 42 (17.7)	Inflammatory heart disease: pericarditis, myocarditis

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Wang, ¹⁶ 2022, US	Jan 1, 2019 to Mar 31, 2022 Vaccinated individuals excluded Wild-type to Omicron	Population-based cohort	N=690,892 Participants with positive COVID-19 tests	N=690,892 Participants with negative COVID-19 tests Matching 1:1 on multiple factors, including: age at index date, race, gender, socioeconomic status, comorbidities, blood type, body mass index	12 months after index date (test date) Assessed risk factors for cardiovascular outcomes	Inpatients, outpatients	COV: 56.8 CON: 56.8	COV: 43 (16.2) CON: 43 (16.1)	Cerebrovascular: stroke, transient ischemic attack Arrhythmia: atrial fibrillation, flutter Inflammatory heart disease: pericarditis, myocarditis Ischemic heart disease: acute coronary disease, myocardial infarction, ischemic cardiomyopathy, angina Thrombosis disorders: deep vein thrombosis, pulmonary embolism, superficial vein thrombosis MACE: myocardial infarction, ischemic stroke, hemorrhagic stroke, heart failure, ventricular arrhythmia, sudden cardiac death Other: heart failure, non-ischemic cardiomyopathy, cardiac arrest, cardiogenic shock Composite outcomes: first incident of any cardiovascular complication Survival

First author, year, jurisdiction	Study period, relation to vaccines and VOCs	Study design	Eligible COVID-19 cases	Contemporary controls and matching	Follow-up period, risk stratification and model adjustments	Acute COVID-19 illness setting	Proportion female (%)	Patient age (years), means ± standard deviation, unless otherwise stated	Cardiovascular outcomes assessed
Xie, ³⁰ 2022b, UK	Mar 1, 2020 to Sept 30, 2021 Study examined vaccination status as a risk factor Wild-type to Delta	Population-based cohort	N=18,818 Participants with positive COVID-19 PCR tests	N=93,179 Participants with negative COVID-19 PCR tests Matching on index date (test date) 1:5 for several factors:: age, sex, ethnicity, socioeconomic status, BMI, comorbidities	30 days since index date (test date) Assessed risk factors for venous thrombo-embolism	Outpatients	COV: 56.0 CON: 56.2	COV: 64 (7.9) CON: 64 (8.0)	Venous thromboembolism: deep vein thrombosis, pulmonary embolism
Xie, ⁹ 2022a, US	March 2020 to January 15, 2021 Wild-type to Beta	Cohort	N=153,760 Participants with positive COVID-19 tests	N=5,637,647 Participants with no evidence of SARS-CoV-2 infection	Data collected from 30 days after a positive COVID-19 test until the end of follow up; approximate mean 350 days Median follow up: 347 days	Outpatients Inpatient Admitted to intensive care	COV: 11.0 CON: 9.7	COV: 61 (15.6) CON: 63 (16.2)	Cerebrovascular disorders Dysrhythmias Inflammatory heart disease Ischemic heart disease Cardiac disorders Thrombotic disorders Composite cardiovascular outcomes

Abbreviations: CON, control; COV, COVID-19; IQR, interquartile range; MACE, major adverse cardiovascular events; PCR, polymerase chain reaction

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