In this issue:

Abbreviations used in this issue:

ARDS = acute respiratory distress syndrome; **COVID-19** = coronavirus-19;
CVD = cardiovascular disease; **RNA** = ribonucleic acid;
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;
VTE = venous thromboembolic events.

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Welcome to issue 148 of Cardiology Research Review with a focus on COVID-19

This issue includes ten cardiology studies, all with COVID-19 focus. This review opens with a consensus study that focusses on diagnosing CVD during the COVID-19 pandemic. We also see CVD in several other studies in this review, including the impact of COVID-19 in hospital mortality in patients with CVD. Furthermore, an interesting study in this issue is the population-wide cohort study of 48 million adults in England and Wales which looks at COVID-19 and major arterial and VTEs.

We hope you enjoy these selected studies and look forward to your feedback.

Kind Regards,

Professor David Brieger
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ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up

Authors: The Task Force for the management of COVID-19 of the European Society of Cardiology.

Summary: This study provides insight to aid clinicians in the diagnosis and management of CVD in association with COVID-19. This study is split into two parts, part-one includes patients who had previously reported CVD and the manifestation in patients with COVID-19. Part-two addresses the care pathways and triage systems for patients with commonly encountered CVD symptoms and the management of COVID-19. The ESC guidance for prognosis concludes that there is a need for protective measures for healthcare personnel and patients in cardiology and triage systems, categorisation of invasive procedures, management and treatment pathways, adequate treatment for COVID-19 and adequate use of patient information.

Comment: Published in December 2021, this comprehensive consensus document is the second pair of articles on the diagnosis and management of CVD during the COVID-19 pandemic. This focusses on care and management pathways of commonly encountered cardiac conditions in the COVID-19 environment. The recommendations are consensus rather than evidence based and pertain to a time when the disease was more virulent and vaccination less widespread. Nevertheless, the recommendations around management of acute and chronic coronary syndromes, heart failure, myocarditis, valvular heart disease, hypertension, pulmonary embolus, and arrhythmias are comprehensive, sensible, and still largely relevant.

Reference: Cardiovascular Research. 2021:118;1618-66
Abstract

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Cardiology Covid Focus
Research Review™

Independent commentary by Professor David Brieger

David Brieger is an interventional cardiologist and Head of Cardiology at Concord Hospital in Sydney and Professor of Cardiology, Faculty of Medicine, University of Sydney.

He has research interests in use of antithrombotic agents and improving the quality of care in Acute Coronary Syndromes (ACS), Coronary Interventions and Atrial Fibrillation.

Impact of the COVID-19 pandemic on in-hospital mortality in cardiovascular disease

Authors: Cannata A et al.

Summary: This meta-analysis focusses on the excess hospital mortality, unrelated to COVID-19 infection and a range of CVDs. Fifteen studies including 27,421 patients with CVD were used in the analysis. The average in-hospital mortality rate was 10.4% in the COVID-19 group and 5.7% in the comparative group. Studies that included a decline in admission rate of >50% during the COVID-19 pandemic observed the greatest increase in mortality compared to those with <50% reduction. The observed mortality rates were consistent across different CVD conditions.

Comment: This systematic review compares mortality among inpatients with CVD during the COVID-19 pandemic with a comparable time-period prior to the pandemic. Admitted patients with CVD had higher mortality rates during the pandemic. While this likely reflected a sicker cohort of patients, the potential contribution of suboptimal care delivery by an overstressed healthcare system cannot be discounted. Of further interest are population-based studies of cardiovascular mortality during this timeframe, which factor in the effect of patients' reluctance to come to hospital on outcomes.

Reference: Eur J Prev Cardiol. 2022;29:1266-74
Abstract

Cardiac function in relation to functional status and fatigue in patients with post-covid syndrome

Authors: Baum P et al.

Summary: This prospective, single-centre cohort study included 227 patients with persisting symptoms after COVID-19 infection. The most frequent complaints from patients included fatigue (70%), dyspnoea (56%), neurocognitive symptoms (34%) and chest pain (28%). This fatigue severity was inversely related to age and did not correlate with CVD, echocardiographic findings, or biomarkers. There was a small subgroup of patients with a post-COVID-19-functional-scale score of 4. Patients in this category had more frequent cardiovascular comorbidities, biomarkers, and impaired global longitudinal strain.

Comment: This single-centre German study reported on 227 patients with post-COVID-19 syndrome referred for cardiologic evaluation. Fatigue severity did not correlate with CVD, echo findings or biomarker elevations. A small subgroup of patients with severe functional impairment did have cardiac abnormalities. This suggests that only a minority of post-COVID-19 patients (those with severe functional impairment) are likely to benefit from specialised cardiac care.

Reference: Sci Rep. 2022;12:19575
Abstract

Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population

Authors: Wang W et al.

Summary: This retrospective cohort study includes the results of the TriNetX US collaborative networks. The findings of this study associated COVID-19 survivors with an increased risk of cerebrovascular diseases such as a stroke and arrhythmia related disorders including atrial fibrillation, inflammatory heart disease such as myocarditis, ischaemic heart disease, ischaemic cardiomyopathy, heart failure and thromboembolic disorders. The risks of major adverse cardiovascular events (HR 1.8171) and any cardiovascular outcome (HR 1.552) were also higher in COVID-19 survivors, compared to any other controls. Therefore, the study concludes that the 12-month risk of incidental cardiovascular diseases is substantially higher in COVID-19 survivors than non-COVID-19 controls.

Comment: This enormous US database study compared cardiovascular events in non-vaccinated patients with and without COVID-19. In the 12-months following the incident COVID-19 test establishing or refuting the diagnosis, there was a higher incidence of stroke, arrhythmias, myocarditis, heart failure and thromboembolic disease among COVID-19 patients. Propensity matching was used to adjust for differences between the populations however, this does not adjust for unmeasured confounders, which may explain some of the differences in outcomes. In addition, events occurring within the first month were excluded which may distort relative event rates. Nevertheless, clinicians should be aware of these associations and perhaps incorporate a recent history of COVID-19 into the assessment when seeing patients with cardiovascular symptoms.

Reference: eClinical Medicine. 2022;53:101701
Abstract

Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different COVID-19 vaccines

Authors: Li X et al.

Summary: This international network, cohort study aims to quantify the comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with use of adenovirus-based COVID-19 vaccines versus mRNA-based COVID-19 vaccines. This matched design paired 1,332,719 ChAdOx1-S recipients to 2,124,339 BTN162b2 recipients in Germany and the UK. In the US all 628,164 Ad26.COV2.S recipients were matched with 2,230,157 mRNA-1273 recipients. The results of this study concluded that a total of 862 thrombocytopenic events were observed in the matched first dose, and a calibrated incidence rate difference of 1.18 per 1000 person-years was noted. A pooled calibrated incidence rate ratio of 2.26 for venous thrombosis with thrombocytopenia syndrome was seen with Ad26.COV2.S compared with BNT162b2.

Comment: This multinational study used routinely collected vaccination data and compared the safety of 4 different COVID-19 vaccines with a particular focus on thrombocytopenia and venous thrombosis. The analyses were complex as there was a lot of heterogeneity in the data and multiple adjustments for confounders were necessary. The take home message however is that thrombocytopenia is 30% greater following the Astra-Zeneca vaccine than Pfizer across the population. Also, for the first time, they did detect a strong trend towards an increased incidence of thrombocytopenia and thrombosis following the first injection of the Janssen/Johnson and Johnson vaccine, another adenovirus-mediated product when compared to the Pfizer. The absolute incidence rates were low, but not stratified according to high-risk groups (e.g., young women) where the differences are likely to be greater. This suggests that our strategy of preferential recommendation of the RNA-based vaccines is an appropriate one.

Reference: BMJ. 2022;379:e071594
Abstract

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References: 1. Australian Government Department of Health. Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au/medicine/item/12996B. [July 2022].
2 PAXLOVID Approved Product Information. **3.** Hammond J *et al. N Eng J Med* 2022; doi: 10.1056/NEJMoa2118542.

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Extreme obesity is a strong predictor for in-hospital mortality and the prevalence of long-COVID-19 in severe COVID-19 patients with acute respiratory distress syndrome

Authors: Heubner L et al.

Summary: ARDS is common in COVID-19 patients and is associated with high mortality rates. This study aims to describe patients' characteristics and outcome, and identify potential risk factors for in-hospital mortality and for developing long-COVID-19-symptoms. From 184 patients, 89% had severe ARDS, in 27% extracorporeal membrane oxygenation was necessary to maintain gas exchange. The median in-hospital stay was 19 days in length. ICU mortality was 51%, and hospital mortality was 59%. The study concluded that obesity was the strongest predictor for in-hospital mortality and for developing long-COVID-19-symptoms.

Comment: This German single-centre analysis of patients with COVID-19-related ARDS from March 2020 to March 2021 reported a staggering hospital mortality rate of 59%. Approximately 80% of patients who survived hospitalisation were alive at 11-months follow-up. Most of these survivors had symptoms consistent with long-COVID-19. The strongest predictor of both hospital mortality and long-COVID-19 was extreme obesity (BMI > 40kg/m^2). This study reminds us of the severity of this condition when first encountered in Europe (and of how lucky we were in Australia to be spared the worst of the pandemic before vaccines became available). The strong predictive value of extreme obesity is germane to our population however, and one expects that it will still contribute to significant morbidity in the current phase of the pandemic.

Reference: Sci Rep. 2022;12:18418
Abstract

What next for COVID-19 vaccines?

Authors: Looi MK, Mahase E.

Summary: This commentary focusses on the future for COVID-19 vaccines. There are several new vaccines included in this commentary including Valneva's vaccine which uses an inactivated form of the whole SARS-CoV-2 virus that cannot infect cells or replicate in the body but can still trigger an immune response. Sinophram, CoronaVac and Covaxin are also included in this commentary; however, they acknowledge that there is not enough publicly available data to judge the effectiveness of these vaccines against omicron.

Comment: BMJ has published a very insightful commentary on the future of COVID-19 vaccines. In brief, we should not lose sight of the fact that existing vaccines have been exceedingly effective at preventing serious disease; far more so than vaccines for influenza, which augurs well for the future. It appears that vaccination provides better protection against infection than infection with the virus, which is counterintuitive, but reflects the more reliable immune response against the spike protein generated by the former. Future vaccination strategies include pan-coronavirus vaccines (against all variants), nasal delivery (which may prevent infection altogether). Investment in newer vaccination strategies has fallen however because of our success in preventing serious disease and current policies of living with the virus. There are also going to be challenges in trialling new vaccines because of the challenges of identifying either infection or vaccine naïve individuals.

Reference: BMJ 2022;379:o2422
Abstract

Key lessons from the COVID-19 public health response in Australia

Authors: Basseal JM et al.

Summary: This report identifies the following key lessons to be learnt from the Australian COVID-19 pandemic response. The report discloses that the movement restrictions, whilst effective, would need careful consideration applied. Furthermore, disease modelling was valuable, but its limitations should have been better acknowledged. The absence of timely national data also requires reassessment of national surveillance structures. The utility of advanced pathogen genomics and novel vaccine technology was clearly demonstrated throughout the pandemic. The report includes a major system weakness in residential aged care, which they suggest requires fixing. However, the report identifies the importance of regional and global solidarity.

Comment: This is a report of an expert consultation meeting on lessons learnt from the Australian COVID-19 pandemic response. Convened by the University of Sydney, it included diverse experts from a range of disciplines and included geographic representation from around the country. A Delphi-style consensus approach was used to develop a summary of key lessons. These include: the need for critical evaluation of the lockdown measures, particularly whether they were disproportionately harsh when measured against their contribution to pandemic control, the limitations of disease modelling methodologies and how to improve these, the lack of comprehensive national data to guide decision making, weaknesses in our residential aged-care sector, and the threat to the best interests of children and young adults through closure of educational facilities, among other observations. It is gratifying to see this widely available critical evaluation, which is essential to better harmonise our political and health-care systems to better enable us to cope with future global and national health challenges.

Reference: Lancet. 2022; Published Online:100616
Abstract

No association of low-dose aspirin with severe COVID-19 in France

Authors: Botton J et al.

Summary: This cohort study featured 31.1 million people with CVD and aimed to explore whether low-dose aspirin would prevent CVD, and could be associated with a lower risk of severe COVID-19. The results of this study show that when adjusting for age and sex there was a positive association between low-dose aspirin and the risk of hospitalisation, death, and intubation. In fully adjusted models, associations were close to null. Therefore, the study concludes that there was no evidence for an effect of low-dose aspirin in primary CVD.

Comment: This enormous population-based study from France looked at the impact of low-dose aspirin provided for primary prevention on hospitalisation for severe COVID-19. There was an association observed between aspirin use and hospitalisation (aspirin protective) before adjustment and after adjustment for age and sex; however, this relationship disappeared in fully adjusted models. Although observational studies of this type can only provide information on associations not causality, this does strongly suggest that low dose aspirin does not provide protection against severe COVID-19 despite hypotheses to the contrary.

Reference: Wiley 2022;6:e12743
Abstract

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Association of COVID-19 with major arterial and venous thrombotic diseases

Authors: Knight R et al.

Summary: This study is a population-wide cohort study of 48 million adults in England and Wales. This study focusses on vascular diseases after COVID-19 diagnosis and estimated the hazard ratios comparing the incidence of arterial thromboses and VTEs. In England, there were 260,279 first arterial thromboses and 59,421 first VTEs during 51.6 million person-years of follow-up. Adjusted hazard ratios were higher for longer time after diagnosis in people hospitalised versus non-hospitalised for COVID-19. The estimated whole-population increases in risk of arterial and VTEs 49 weeks after COVID-19 diagnosis were 0.5% and 0.25% respectively.

Comment: This UK population wide analysis of electronic health records showed an early hazard of arterial and venous thrombotic events in the weeks following COVID-19. The arterial events were predominantly MI and stroke and were higher in hospitalised than non-hospitalised patients and declined rapidly but remained elevated out to 9-months of follow-up. Randomised trials evaluating the benefit of strategies such as antiplatelets for primary prevention early post-COVID-19 may be of interest in these settings. Based on current evidence, clinicians treating patients post-COVID-19 should ensure indicated primary and secondary vascular prevention strategies as appropriate are implemented.

Reference: Circulation. 2022;146:892-906
[Abstract]

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