Cardiovascular disease and cardiovascular outcomes in COVID-19

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Abstract

Patients with cardiovascular disease have an increased risk of severe COVID-19 disease and an increased mortality. Clinical observations have described cardiovascular complications of COVID-19 in patients without prior cardiovascular disease, including acute cardiac injury, myocarditis, heart failure, arrhythmias, and acute coronary syndromes. These are also associated with a worse outcome from COVID-19. Several of the potential treatments for COVID-19 may also have cardiovascular consequences. Some of the acute cardiovascular complications resolve on recovery from the infection and it is uncertain how many people will suffer permanent cardiovascular damage. During the emergency lockdown that was introduced to deal with the pandemic it has been observed that hospital admissions with other cardiovascular conditions, such as acute coronary syndromes and heart failure, have been greatly reduced.

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Key words

coronavirus; COVID-19; cardiovascular disease; troponin; myocarditis; heart failure; arrhythmia

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly diagnosed coronavirus (SARS-CoV-2). This virus and disease were unknown before an outbreak began in Wuhan, China in December 2019 and is now a global pandemic. The World Health Organization (WHO) states that most people with COVID-19 will experience a mild to moderate respiratory illness and recover without requiring special treatment, but highlights older people and those with underlying medical problems like cardiovascular disease and diabetes as people more likely to develop serious disease.[1]

Early clinical and epidemiological observations from Wuhan of 191 patients with COVID-19 showed that patients with established coronary heart disease were at a greater risk of death from COVID-19, that levels of troponin were increased in 54 patients who died from COVID-19 compared to 137 patients who survived, and that troponin levels increased as the clinical situation deteriorated.[2] Subsequent clinical observations have confirmed potentially serious cardiovascular complications of COVID-19 including acute cardiac injury, myocarditis, heart failure, arrhythmias and acute coronary syndromes.[3–6] This review describes epidemiological and clinical aspects of cardiovascular disease and COVID-19 and considers possible cardiovascular effects of some of the potential treatments for COVID-19.

Epidemiology of cardiovascular disease and COVID-19

The original small cohort observation from Wuhan was followed by a large exploratory analysis of over 44,000 COVID-19 cases recorded in China's Infectious Disease Reporting System. Overall a case fatality rate of 2.3% was observed. People who reported no comorbid medical condition had a case fatality rate of 0.9%, rising to 6% in people with hypertension, 7% in people with diabetes and 10% in people with prior cardiovascular disease.[7]

The OpenSAFELY Collaborative collated information on COVID-19 hospital deaths linked to electronic health records of 17 million adult NHS patients in the UK.[8] A total of 5683 deaths were attributed to COVID-19 and deaths were strongly associated with prior cardiovascular and cerebrovascular disease, hypertension, and diabetes, as well as other medical and social factors.

A recent systematic review and meta-analysis included information from 18 published studies of 14,558

individuals.[9] The pooled prevalence for comorbidities in patients with COVID-19 disease was 10% for cardiovascular disease, 11% for diabetes, and 23% for hypertension. Cardiovascular disease, diabetes and hypertension significantly increased the risk of severe COVID-19, and cardiovascular disease increased the risk of mortality.

To examine the interaction of diabetes and cardiovascular disease a UK population study examined mortality rates in over 61 million individuals registered with a general practice in England.[10] Of nearly 24 thousand COVID-19 deaths one third occurred in people with diabetes. People with type 1 and type 2 diabetes had 3.5 and 2.0 times the odds respectively of dying in hospital compared to those without diabetes, and this was attenuated to 2.9 and 1.8 when adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease or heart failure. A further publication looked at a smaller cohort in more detail and observed that an increased risk of COVID-19 death was observed in people with diabetes with a history of heart failure and stroke but there was no statistically significant association with hypertension or recent myocardial infarction.[11]

SARS-CoV-2 and other coronaviruses bind to the angiotensin-converting enzyme 2 (ACE2) protein which facilitates entry into cells, including lung alveolar cells. It has been hypothesised that the use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) might be harmful in patients with COVID-19 by up-regulating expression of ACE2 and facilitating increased viral entry into cells.[12] Recent cohort studies from Spain, Italy and New York have not demonstrated any association between the use of ACEIs and ARBs and worse outcomes in patients with COVID-19.[13–15] Expert opinion is that until further data are available renin-angiotensin-aldosterone system (RAAS) inhibitors should be continued in patients in otherwise stable conditions who are at risk for or being evaluated for COVID-19.[16–18] For patients who become unwell with coronavirus the usual sick day rules should apply with temporary cessation of ACE inhibitors and ARBs, as well as diuretics, NSAIDs, SGLT2 inhibitors, and other diabetes treatments except insulin.[19]

Box 1. Cardiovascular side effects of drugs that may be used to treat COVID-19

- Azithromycin: QT prolongation, ventricular arrhythmias especially when combined with hydroxychloroquine/chloroquine and/or electrolyte imbalances
- Dexamethasone: raised blood pressure, fluid retention
- Hydroxychloroquine/chloroquine: QT prolongation, ventricular arrhythmias, especially when combined with azithromycin and/or electrolyte imbalances
- Lopinavir/ritonavir: cases of AV block are reported, long-term use is associated with increased development of diabetes, lipid changes
- Remdesivir: hypotension, anaphylaxis
- Tocilizumab: no ECG changes are described, long-term use associated with increased total, LDL, and HDL cholesterol

Cardiovascular consequences of COVID-19

Acute cardiac injury, myocarditis and heart failure

Clinical observations during outbreaks with two other coronaviruses (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) identified acute cardiovascular complications so it was anticipated that COVID-19 might have similar effects. A prospective cohort study of 416 consecutive patients with confirmed COVID-19 from another hospital in Wuhan confirmed that a raised troponin occurred in 20% of hospitalised patients indicating cardiac injury and that this was associated with a higher risk of in-hospital mortality. Patients with a raised troponin had more comorbidities including hypertension, diabetes, coronary heart disease and heart failure.[20]

A recent review reported that an acutely raised troponin concentration is seen in 20–30% of hospitalised patients with COVID-19.[21] Multiple possible mechanisms for myocardial injury have been suggested, including viral ACE2 mediated direct damage, myocardial damage induced by hypoxia (type 2 myocardial infarction), microvascular damage with increased vascular permeability, and the systemic inflammatory response including the cytokine storm.[21] Troponins can also be raised by myocarditis, acute heart failure, acute coronary syndromes and pulmonary embolism, all of which are increased in patients with COVID-19. Imaging studies have demonstrated evidence of acute myocarditis in COVID-19, and post-mortem studies have shown severe myocarditis with infiltrates typical of a viral myocarditis.

Arrhythmias

An early case series of 138 patients from Wuhan reported arrhythmias in 17% of patients admitted to hospital and 44% of patients admitted to intensive care, but the actual arrhythmias were not detailed.[22] A report of four cases from New York described patients with high-grade atrioventricular block, atrial fibrillation, ventricular tachycardia, and asystole/cardiogenic shock.[23] Subsequent case series have confirmed a high incidence of sinus tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, and cardiac arrest, whereas bradyarrhythmias and heart block are less common.[24]

A large and ambitious prospective observational study from the Mount Sinai Hospital in New York will document the frequency of arrhythmias in patients with COVID-19 admitted to that institution and aims to recruit 10,000 subjects by May 2021.[25]

Factors which may predispose to arrhythmias include acute cardiac injury, hypoxia, and systemic inflammation, plus electrolyte disturbances and prolongation of the QT interval by pharmacological interventions. If an arrhythmia occurs, or the ECG shows prolongation of the QT interval, then these factors should be corrected where possible. Otherwise the treatment of individual arrhythmias is not different from when these occur in other

clinical settings. It has been suggested that routine continuous ECG monitoring may not be required in the absence of a documented arrhythmia or suspected myocardial ischaemia,[26] although in practice continuous ECG monitoring is frequently used in high-dependency and intensive-care unit settings.

Acute coronary syndromes/ thrombotic disease

Thromboembolic disease occurs in COVID-19 more frequently than would be expected for comparable hospital inpatients or intensive care patients, and thromboprophylaxis is essential. The severe systemic inflammation increases cytokines and clotting factors, which increases instability in atheromatous plaques, and type 1 myocardial infarctions have been seen as a consequence of COVID-19.[18] Clinical differentiation from the acute myocardial injury described previously can be difficult, and requires a detailed history seeking chest pain, measuring serial troponins, performing serial ECGs, and possible imaging of the heart to look for a wall motion abnormality. Even then, coronary arteriography may be required for a definitive diagnosis and so that coronary revascularisation can be performed if an acute coronary occlusion is identified.[18]

During the emergency lockdown that was introduced to deal with the pandemic it has been observed that hospital admissions with other primary cardiovascular conditions such as acute coronary syndromes and heart failure have been greatly reduced, and this is thought to be because patients do not call the emergency services for fear that they will be admitted to hospital and catch coronavirus during the admission.[27]

Therapeutic considerations

Over 100 potential treatments and 30 vaccines are under investigation for COVID-19.[28] The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial has recruited over 11,500 participants from over 175 hospitals in the UK.[29] The trial is investigating whether intervention with one of six treatments reduces mortality in patients with COVID-19 compared to usual care alone. The dexamethasone arm has been discontinued as this intervention significantly reduced deaths. The arm with the antimalarial hydroxychloroquine has also been discontinued as hydroxychloroquine had no beneficial effect. Both chloroquine and hydroxychloroquine, which is approved in India as a treatment for type 2 diabetes, can cause prolongation of the QT interval and ventricular tachycardia, including Torsade de pointes, and patients with underlying cardiovascular disease and renal disease are at an increased risk of these adverse effects.

The remaining four arms of the RECOVERY trial are the use of convalescent plasma, the antibiotic azithromycin, lopinavir/ritonavir (used to treat HIV), and the anti-inflammatory tocilizumab. Azithromycin may also increase the QT interval and cause arrhythmias, especially if used in combination with hydroxychloroquine. Tocilizumab increases total, LDL, and HDL cholesterol, and post-marketing surveillance has shown that this does not translate into an increased risk of myocardial infarction or stroke in patients with rheumatoid arthritis. Lopinavir/ritonavir increases the risk of developing diabetes and has adverse effect on lipids when used as a long-term treatment for HIV.

Solidarity is an international clinical trial, launched by the WHO and partners, comparing four treatment arms: remdesivir, lopinavir/ritonavir, lopinavir/ritonavir combined with interferon-beta, and hydroxychloroquine/chloroquine which has also been discontinued due to no benefit on an interim analysis.[30] Remdesivir, an antiviral treatment, is included in over 20 trials worldwide, and has recently been approved to speed up recovery from COVID-19. The main side effects are abnormalities in liver function tests, but hypersensitivity and anaphylaxis can also occur. The potential cardiovascular consequences of some of the drugs that are being trialled in patients with COVID-19 are listed in Box 1.

Some cardiovascular drugs like aspirin, atorvastatin, simvastatin, losartan and valsartan are being studied as possible treatments for COVID-19. DARE-19 is an interesting international study in 900 patients evaluating the safety and efficacy of dapagliflozin on the risk of all-cause mortality or disease progression and complications in adults hospitalised with COVID-19. Enrolment criteria include a history of hypertension, atherosclerotic cardiovascular disease, heart failure, type 2 diabetes or chronic kidney disease.[31]

KEY POINTS

- Prior cardiovascular disease increases the risk of death in patients with COVID-19
- COVID-19 has several documented acute cardiovascular consequences including acute cardiac injury, myocarditis, heart failure, arrhythmias and acute coronary syndromes
- Several of the potential treatments for COVID-19 can have serious cardiovascular consequences, including prolongation of the QT interval increasing the risk of arrhythmias

Conclusions

Prior cardiovascular disease increases the morbidity and mortality from COVID-19, and several cardiovascular consequences of COVID-19 have been described in hospital inpatients. Careful follow up of these patients will be required to see if these cardiovascular effects resolve completely, as was the case for most patients with SARS infection,[32] or whether some people sustain permanent cardiovascular damage from COVID-19.

Declaration of interests

Prof Fisher has received honoraria for consulting and/or speaking for Astra Zeneca.

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