The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to your question. The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate. For further information on the methodology used in the compilation of this document — including a complete list of sources consulted — please see our National Health Library and Knowledge Service Summary of Evidence Protocol.

QUESTION 68

What is the evidence on additional risk for patients >65 with cardiovascular disease?

What is the evidence on additional risk for patients >65 with cardiovascular disease?

Main Points

1. People >60 and those with underlying health conditions including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer and obesity have higher COVID–19 related morbidity and mortality.
2. COVID–19 may result in cardiovascular complications in patients without prior cardiovascular disease.
3. Several potential COVID-19 therapies may also have cardiovascular consequences or may have significant drug–drug interactions with cardiovascular medications.
4. Routine and emergency cardiac care for patients who are, may be, or are not infected with COVID-19 may be delayed.

Summary of Evidence

Patients with cardiovascular disease have an increased risk of severe COVID-19 disease and an increased mortality[16][44][36][45][9][12][14][19][38][30][31][39][25]. Cardiovascular diseases appear intricately linked with COVID-19, with cardiac complications contributing to the elevated morbidity/mortality of COVID-19[45][33][31]. People above 60 years of age and those with underlying health conditions including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer and obesity have higher COVID-19 related morbidity and mortality compared with younger individuals and those without co-morbidities[4].

Cardiovascular complications include biomarker elevations, myocarditis, heart failure and venous thromboembolism, which may be exacerbated by delays in care. Therapies under investigation for COVID-19 may have significant drug-drug interactions with cardiovascular medications[33][39].

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[16].

COVID-19 acts through the angiotensin-converting enzyme 2 (ACE2) receptor[29]. Although angiotensin-converting enzyme 2 serves as the portal for infection, the role of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers requires further investigation[32][28][30]. There is currently no evidence that use of ACE inhibitors or angiotensin-II receptor antagonists should be discontinued in these patients. Any change in medication should be based on individual patient risk assessment[13].

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[16][35].

In addition, the widespread effects of the pandemic on the global healthcare system affects the routine and emergency cardiac care for patients who are, may be, or are not infected with COVID-19[44][4][15][10].

Cardiovascular risk factors can play a crucial role in identifying patients vulnerable to developing cardiovascular manifestations of COVID-19 and thus help to save lives. Cardiac-specific biomarkers provide a useful prognostic tool in helping identify patients with the severe disease early and allowing for escalation of treatment in a timely fashion[23].

Irish and/or International Guidance

What does the World Health Organization say?

[World Health Organization (08 May 2020) Q and A: Older people and COVID-19](#)[1]
Older people and people of all ages with pre-existing medical conditions such as diabetes, high blood pressure, heart disease, lung disease or cancer appear to develop serious illness more often than others.

What does the European Centre for Disease Prevention and Control say?

[European Centre for Disease Prevention and Control (2020) Rapid Risk Assessment. Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK— ninth update 23 April 2020](#)[2]
The analysis of TESSy data shows that persons over 65 years of age and/or people with underlying health conditions when infected with SARS-CoV-2 are at increased risk of severe illness and death compared with younger individuals. These vulnerable populations account for the majority of severe disease and fatalities to date.
In summary, the impact of COVID-19 is assessed as very high for elderly and individuals with defined risk factors.

[European Centre for Disease Prevention and Control (2020) Rapid Risk Assessment: Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK — eleventh update: resurgence of cases 10 August 2020](#)[3]
Medically and socially vulnerable groups are at increased risk of severe disease and death due to the public health measures in place to reduce the spread of COVID-19. The medically vulnerable include older adults, people with underlying health conditions and the socially

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[1] WHO (2020) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-on-on-COVID-19-for-older-people [Accessed: 02/11/2020]
[2] ECDC (2020) https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-rapid-risk-assessment-coronavirus-disease-2019-ninth-update-23-april-2020.pdf [Accessed: 02/11/2020]
[3] ECDC (10 Aug 2020) [Rapid Risk Assessment: Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eleventh update: resurgence of cases 10 August 2020](#) [Accessed: 02/11/2020]

vulnerable: those with long-term physical, mental, intellectual or sensory impairments, homeless people, people living in abusive household settings, sex workers and others who face challenges due to their belonging to two or more categories of social vulnerability. Residents in long-term care facilities are also a vulnerable population group for COVID-19 and are particularly at risk when transmission rates are high within the general community.

People in prisons are another vulnerable group due to the many environmental factors that may increase risk of COVID-19 transmission such as overcrowding and unsanitary facilities and the demographic profile of the prison population, including the proportion of the population belonging to risk groups for developing severe disease. Environmental factors such as overcrowding in reception and detention centres may increase exposure to SARS-CoV-2 among the migrants and refugees living there. Outbreaks in reception and detention centres can spread quickly in the absence of adequate prevention measures.

Protection of Vulnerable Populations

For the protection of people in the community at increased risk of developing severe disease as a result of infection with SARS-CoV-2 such as the elderly or those with underlying health conditions, special measures should be considered in areas with ongoing local community transmission. These measures must include physical distancing, strict hand and respiratory hygiene and the use of personal protective equipment (PPE) by caregivers in contact with vulnerable individuals. Specifically tailored advice concerning physical distancing should also be considered, especially during periods of intense local transmission. Influenza vaccination of the vulnerable individual and their household is also advisable.

Targeted Measures

In countries seeing a resurgence in cases, it is important to prevent outbreaks in specific settings and to re-evaluate infection prevention and control measures as well as enhanced surveillance to monitor potential resurgences. The prompt and rigorous application of non-pharmaceutical interventions including physical distancing

measures, strict hand and respiratory hygiene and the appropriate use of face masks and cleaning can assist significantly in mitigating the risk of SARS-CoV-2 transmission. Cases in these settings must be promptly identified and managed and a comprehensive testing and contact tracing strategy is essential.

Healthcare Facilities

Healthcare workers and long-term care facility administrators should continue implementing the measures for COVID-19 preparedness and infection prevention and control described in ECDC's report Infection Prevention and Control for COVID-19 in Healthcare Settings, as incorporated in the national guidance. All healthcare workers should be trained properly in IPC protocols to prevent nosocomial transmission and should be provided with adequate personal protective equipment. Universal masking for all routine clinical care activities should be strongly considered for as long as there is community transmission of COVID-19. In addition, ways in which ICU and hospital treatment capacity can be increased should be clarified to accommodate a potential resurgence in cases, incorporating lessons from the response to the spring wave of COVID-19.

[European Centre for Disease Prevention and Control (2020) Guidance on the provision of support for medically and socially vulnerable populations in EU/EEA countries and the United Kingdom during the COVID-19 pandemic 3 July 2020](#)[4]
People who are medically vulnerable to COVID-19 include older adults and people who have underlying health conditions such as high blood pressure, overweight/obesity, or diabetes.
Protecting medically vulnerable populations during the pandemic is a legal obligation of EU/EEA Member States and the UK. General Comment 14 of the United Nations (UN) International Covenant on Economic, Social and Cultural Rights, which has been ratified by all EU/EEA Member States and the UK, makes explicit reference to the need to take into account and protect vulnerable groups with regard to the right to health.

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[4] ECDC (3 July 2020) https://www.ecdc.europa.eu/en/publications-data/guidance-medically-and-socially-vulnerable-populations-covid-19 [Accessed: 02/11/2020]

People above 60 years of age and those with underlying health conditions including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer and obesity have higher COVID-19 related morbidity and mortality compared with younger individuals and those without co-morbidities.

Because of their elevated risk of severe disease, physical distancing has been recommended for these populations and these recommendations are likely to remain in most settings for as long as COVID-19 remains a public health threat. However, the lack of meaningful social connection that physical distancing can bring about is associated with substantially reduced quality of life, with increases in depression, loneliness and other adverse mental health issues. While protective to minimise COVID-19 exposure, physical distancing may also negatively impact the ability of older adults and others with co-morbidities associated with higher risk for COVID-19 to seek or receive social and medical care for any existing health issues, to exercise, to shop or to run errands. Physical distancing can lead to the closure of gathering places — community centres, churches, cafes — which promote social interaction and it may also reduce opportunities for physical activity. Therefore, it is important to strike a balance between physical distancing and social contact/physical activity in order to promote overall well-being.

The experience of marginalisation may be more intense for older adults or people with co-morbidities who are also members of the other groups covered in this report: homeless, substance using, LGBTI, ethnic minorities, people with disabilities.

What do the Centers for Disease Control and Prevention (United States) say?

[Centers for Disease Control and Prevention (2020) People with Certain Medical Conditions](#)[5]

People of any age with the following conditions are at increased risk of severe illness from COVID-19:

— Cancer
— Chronic kidney disease
— Chronic obstructive pulmonary disease
— Immunocompromised state from solid organ transplant
— Obesity: body mass index of 30 or higher
— Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies
— Sickle cell disease
— Type 2 diabetes mellitus

COVID-19 is a new disease. Currently there are limited data and information about the impact of underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we know at this time, people with the following conditions might be at an increased risk for severe illness from COVID-19:

— Asthma [moderate to severe]
— Cerebrovascular disease
— Cystic fibrosis
— Hypertension or high blood pressure
— Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines
— Neurologic conditions such as dementia
— Liver disease
— Pregnancy
— Pulmonary fibrosis

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[5] CDC (2020) [https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html) [Accessed: 02/11/2020]

— Smoking
— Thalassemia
— Type 1 diabetes mellitus

[Centers for Disease Control and Prevention (2020) [Infographic] COVID-19 associated hospitalization related to underlying medical conditions: Factors that increase community spread and individual risk](#)[6]
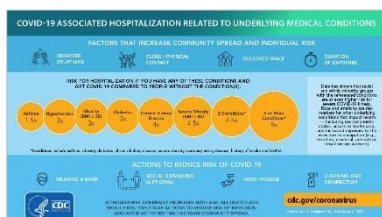
Figure: Factors that Increase Community Spread and Individual Risk
Click on image to enlarge.

[BRITISH GERIATRICS SOCIETY (2020) BGS statement on the COVID-19 pandemic](#)[7]

During the period of this pandemic, older people living with frailty and long-term conditions will continue to experience episodes of ill-health, falls or other unforeseen events, and health professionals will need to continue to respond to provide high-quality, person-centred care. While COVID-19 will be the main concern for the health system as a whole, much of the care that BGS members provide during this time may be routine care. As far as possible, efforts will need to be made to provide such care at home or in community settings, keeping older people out of hospital unless strictly necessary.

[IRISH HEART FOUNDATION (09 April 2020) FAQs. Coronavirus, Heart Disease and Stroke](#)[8]

Question: The HSE has issued a list of people who are said to be medically vulnerable and these people must cocoon. These groups include anyone with a heart transplant, pregnant women with heart

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[6] CDC (2020) https://www.cdc.gov/coronavirus/2019-ncov/downloads/covid-data/hospitalization-underlying-medical-conditions.pdf [Accessed: 02/11/2020]
[7] BRITISH GERIATRICS SOCIETY (2020) https://www.bgs.org.uk/bgs-statement-on-the-COVID-19-pandemic [Accessed: 02/11/2020]
[8] IRISH HEART FOUNDATION (2020) https://irishheart.ie/news/faq-the-coronavirus-and-heart-disease-and-stroke/ [Accessed: 02/11/2020]

disease, people with severe heart failure or severe vascular disease. Why are these people considered to be medically vulnerable?

Answer: The patients in the group above are considered to be medically vulnerable because they are immunocompromised. Being immunocompromised means that your immune system is weaker than those without these conditions and you are therefore less likely to be able to fight off infections including those caused by the coronavirus.

[EUROPEAN SOCIETY OF CARDIOLOGY (10 Jun 2020) ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic](9)[9]

— Patients with cardiovascular (CV) risk factors and established cardiovascular disease (CVD) represent a vulnerable population when suffering from COVID-19
— Patients with cardiac injury in the context of COVID-19 have an increased risk of morbidity and mortality
— CV comorbidities are common in patients with COVID-19 infection
— Presence of CVD is associated with increased mortality in COVID-19 infections
— CVD risk factors and disease correlate with increasing age

SARS-CoV-2 not only causes viral pneumonia but has major implications for the CV system. Patients with CV risk factors including male sex, advanced age, diabetes, hypertension and obesity as well as patients with established CV and cerebrovascular disease have been identified as particularly vulnerable populations with increased morbidity and mortality when suffering from COVID-19. Moreover, a considerable proportion of patients may develop cardiac injury in the context of COVID-19 which portends an increased risk of in-hospital mortality. Aside from arterial and venous thrombotic complications presenting as acute coronary syndromes and venous

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[9] EUROPEAN SOCIETY OF CARDIOLOGY (2020) https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance [Accessed: 02/11/2020]

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thromboembolism, myocarditis plays an important role in patients with acute heart failure. Moreover, a wide range of arrhythmias has been reported to complicate the course of COVID-19 including potential pro-arrhythmic effects of medical treatment targeted at COVID-19 and associated diseases. Owing to redistribution of health care resources, access to emergency treatment including reperfusion therapy may be affected depending on the severity of the epidemic at a local level. This is further aggravated by increasing concerns of delayed presentation of CV emergencies as patients are afraid to seek medical attention during the pandemic.

[EUROPEAN SOCIETY OF CARDIOLOGY (03 June 2020) The collateral damage of COVID-19: cardiovascular disease, the next pandemic wave](https://www.escardio.org/The-ESC-Advocacy/Shaping-policy-and-regulation/ESC-positions/the-collateral-damage-of-covid-19-cardiovascular-disease-the-next-pandemic-wav)[10]
Evidence and data collected during the pandemic outbreak show that COVID-19 has had a significant impact on patients with cardiovascular disease (CVD). The effects of COVID-19 on cardiovascular health are multifaceted and triggered by different factors including:

— Patient vulnerability and lack of assurance that safe in-hospital wards will be provided to non-COVID patients: CVD patients infected with COVID-19 have increased rates of complications and death.
— High risk CVD patients such as those experiencing a heart attack or stroke have been reluctant to seek help resulting in significant reduction in admission for heart attacks and stroke in Europe and elsewhere and an increase in preventable death and disability.
— Increased pressure on ambulance services resulting in late presentation to hospital of heart attacks and stroke patients, often too late to benefit from life-saving treatments.
— Re-prioritisation of hospital resources which has significantly decreased access to cardiovascular services and elective

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[10] EUROPEAN SOCIETY OF CARDIOLOGY (3 June 2020) https://www.escardio.org/The-ESC-Advocacy/Shaping-policy-and-regulation/ESC-positions/the-collateral-damage-of-covid-19-cardiovascular-disease-the-next-pandemic-wav [Accessed: 02/11/2020]

procedures as well as led to a drastic reduction in the availability of cardiac surgery.

[AMERICAN HEART ASSOCIATION (15 April 2020) Coronavirus precautions for patients and others facing higher risks](https://www.heart.org/en/coronavirus/coronavirus-COVID-19-resources/coronavirus-precautions-for-patients-and-others-facing-higher-risks)[11]
Older people with coronary heart disease or high blood pressure are more likely to develop more severe symptoms. Stroke survivors and those with heart disease including high blood pressure and congenital heart defects may be at an increased risk of complications if they become infected with the COVID-19 virus.

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[11] AMERICAN HEART ASSOCIATION (2020) https://www.heart.org/en/coronavirus/coronavirus-COVID-19-resources/coronavirus-precautions-for-patients-and-others-facing-higher-risks [Accessed: 02/11/2020]

Point-of-Care Tools

What does BMJ Best Practice say?

Coronavirus disease 2019 (COVID-19) (30 Oct 2020)[12]
Cardiovascular Complications

COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the vascular system can result in diffuse microangiopathy with thrombosis. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration and sudden death. Prevalence of cardiac disease is high among patients who are severely or critically ill and these patients usually require intensive care and have a poor prognosis and higher rate of in-hospital mortality. Patients with cardiac injury were more likely to require non-invasive or invasive ventilation compared with patients without cardiac injury. Patients with cardiac disease also have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease. Patients with underlying cardiovascular disease but without myocardial injury have a relatively favourable prognosis.

Predictors for myocardial injury include older age, presence of cardiovascular-related comorbidities and elevated C-reactive protein. Elevated myocardial markers predict risk for in-hospital mortality.

Management of coexisting conditions in the context of COVID-19 (28 Oct 2020)[13]

People with cardiovascular disease are at higher risk of severe complications and death from COVID-19; however, there is currently no evidence that use of ACE inhibitors or angiotensin-II receptor antagonists should be discontinued in these patients. Any change in medication should be based on individual patient risk assessment.

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[12] BMJ BEST PRACTICE (2020) https://bestpractice.bmj.com/topics/en-gb/3000168/complications [Accessed: 02/11/2020]
[13] BMJ BEST PRACTICE (2020) https://bestpractice.bmj.com/topics/en-gb/3000190 [Accessed: 02/11/2020]

What does UpToDate say?

Coronavirus disease 2019 (COVID-19): Myocardial infarction and other coronary artery disease issues (31 August 2020)[14]

In some patients, the heart may be affected and this can occur in individuals with or without a prior cardiovascular diagnosis. Evidence of myocardial injury, as defined as an elevated troponin level, is common among patients hospitalized with COVID-19, with putative causes including stress cardiomyopathy, hypoxic injury, ischemic injury [caused by cardiac microvascular damage or epicardial coronary artery disease] and systemic inflammatory response syndrome or cytokine storm. A minority of patients with an elevated troponin level present with symptoms and signs suggestive of an acute coronary syndrome.

Patients with cardiovascular disease, hypertension, obesity and diabetes are at increased risk of a poor prognosis. In addition, patients with myocardial injury, irrespective of cause, have a poorer prognosis.

IMPACT ON THE CARDIOVASCULAR SYSTEM

It is likely that COVID-19 directly and indirectly affects the cardiovascular system and the heart in particular. Potential mechanisms of cardiovascular injury have been identified and include direct myocardial injury from hemodynamic derangement or hypoxemia, inflammatory myocarditis, stress cardiomyopathy, microvascular dysfunction or thrombosis due to hypercoagulability, or systemic inflammation [cytokine storm], which may also destabilize coronary artery plaques. Pneumonia and influenza infections have been associated with six-fold increased risk of acute myocardial infarction (MI). Patients with severe COVID-19 disease, such as those with high fever or hypoxia due to lung disease, may need a significant increase in cardiac output. Type II myocardial ischemia, therefore, may result in patients with obstructive CAD.

The clinical impact of SARS-CoV-2 infection will, across a population, be greater in those with prior disease and increasing age.

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[14] UPTODATE (2020) https://www.uptodate.com/contents/coronavirus-disease-2019-COVID-19-myocardial-infarction-and-other-coronary-artery-disease-issues [Accessed: 02/11/2020]

ASSOCIATION BETWEEN BASELINE CVD AND COVID-19

There is substantial evidence of an association between cardiovascular disease (CVD) risk factors of hypertension, diabetes, prior CAD and the risk and severity of COVID-19 infection.

Until more data with larger numbers of patients are available, it seems reasonable to consider all patients with history of CVD, hypertension or diabetes at higher risk. Risk is likely to be highest for patients with these risk factors: older age, known history of heart failure, or clinically significant valvular disease.

Furthermore, given the association with more severe disease and increased risk for acute myocardial injury, early clinical evaluation for any suspect symptoms is advised.

International Literature

What does the international literature say?

[Centre for Evidence-Based Medicine (25 Mar 2020) Supporting people with long-term conditions (LTCs) during national emergencies](#)[15]
Disruption of care, diversion of healthcare resources and interruptions to medical supplies can all impact patients with long-term conditions (LTCs) during national emergencies. Some LTCs may be further exacerbated by increased stress and changes in diet and activity patterns. The data does not rule out any LTCs as not being at risk of neglect, but particularly highlights cardiovascular disease, diabetes, older people and people in deprived areas as being at increased risk.
During national emergencies and pandemics, health care services and supply chains may be disrupted. Health care resources may be limited and a focus on controlling a pandemic will shift focus from other areas. These may include routine care of those with LTCs such as asthma, diabetes and hypertension, among others.
Many common LTCs may put people at higher risk of COVID-19 severity and complications. Knowledge of other infections suggests that it is not just presence of these conditions but how well they are controlled that will contribute to different outcomes from infection: eg tighter glucose control is likely to be a protective factor in people living with diabetes. Stress can exacerbate some LTCs, as can inactivity, changes to diet and issues with accessing healthcare. All of these factors are likely to arise as supply chains are disrupted, food stock is temporarily depleted and people living with LTCs are asked to self-isolate.

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[15] CEBM (2020) https://www.cebm.net/COVID-19/supporting-people-with-long-term-conditions-ltcs-during-national-emergencies/ [Accessed: 02/11/2020]

FISHER, M (07 Oct 2020) Cardiovascular disease and cardiovascular outcomes in COVID- 19[16]

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.

DAMBHA–MILLER et al (14 Sept 2020) Currently prescribed drugs in the UK that could upregulate or downregulate ACE2 in COVID–19 disease: a systematic review[17]

The authors assert that the impact of currently prescribed drugs on ACE2 has been poorly studied in vivo, particularly in human lungs where the SARS-CoV-2 virus appears to enact its pathogenic effects. The authors found no convincing evidence to justify starting or stopping currently prescribed drugs to influence COVID-19 outcomes.

DEL SOLE et al (29 Aug 2020) Features of severe COVID–19: A systematic review and meta–analysis[18]

Objective: To systematically review clinical and biochemical characteristics associated with the severity of SARS-CoV-2-related disease (COVID-19).

The authors included 12 studies with 2794 patients, of whom 596

[16] FISHER, M. (07 Oct 2020) Cardiovascular disease and cardiovascular outcomes in COVID-19. https://onlinelibrary.wiley.com/doi/full/10.1002/pdi.2294 [Accessed: 02/11/2020]
[17] DAMBHA–MILLER et al (14 Sept 2020) Currently prescribed drugs in the UK that could upregulate or downregulate ACE2 in COVID-19 disease: a systematic review. https://bmjopen.bmj.com/content/10/9/e040644 [Accessed: 02/11/2020]
[18] DEL SOLE et al (29 Aug 2020) Features of severe COVID-19: A systematic review and meta-analysis. https://onlinelibrary.wiley.com/doi/full/10.1111/eci.13378 [Accessed: 02/11/2020]

(21.33%) had severe disease. A slightly higher age was found in severe vs non-severe disease. The authors found that prevalent cerebrovascular disease (odds ratio [OR] 3.66, 95% confidence interval [CI] 1.73-7.72), chronic obstructive pulmonary disease (OR: 2.39, 95% CI 1.10-5.19), prevalent cardiovascular disease (OR: 2.84, 95% CI 1.59-5.10), diabetes (OR: 2.78, 95% CI 2.09-3.72), hypertension (OR: 2.24, 95% CI 1.63-3.08), smoking (OR: 1.54, 95% CI 1.07-2.22) and male sex (OR: 1.22, 95% CI 1.01-1.49) were associated with severe disease. Furthermore, increased procalcitonin (OR: 8.21, 95% CI 4.48-15.07), increased D-Dimer (OR: 5.67, 95% CI 1.45-22.16) and thrombocytopenia (OR: 3.61, 95% CI 2.62-4.97) predicted severe infection.

Characteristics associated with the severity of SARS-CoV-2 infection may allow an early identification and management of patients with poor outcomes.

SSENTONG et al (26 Aug 2020) Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis[19]

Patients with COVID-19 with cardiovascular disease, hypertension, diabetes, congestive heart failure, chronic kidney disease and cancer have a greater risk of mortality compared to patients with COVID-19 without these comorbidities. Tailored infection prevention and treatment strategies targeting the high-risk population might improve survival.

SABATINO et al (Aug 14 2020) Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis[20]

A meta-analysis of observational studies evaluating cardiovascular complications in hospitalized COVID-19 patients and the impact of cardiovascular risk factors or comorbidities on mortality.

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[19] SSENTONG et al (26 Aug 2020) Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. [Accessed: 02/11/2020]
[20] SABATINO et al (2020). Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis. *PLoS ONE*, *15*(8), 1–12. https://doi.org/10.1371/journal.pone.0237131 [Accessed: 02/11/2020]

Cardiovascular complications are frequent among COVID-19 patients and might contribute to adverse clinical events and mortality, together with pre-existing cardiovascular comorbidities and risk factors. Clinicians should be aware of the association in order to identify patients at higher risk.

[GUZIK et al (01 Aug 2020) COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis and treatment options](#)[21]
Mortality is increased by comorbidities: cardiovascular disease, hypertension, diabetes, chronic pulmonary disease and cancer. The most common complications include arrhythmia (atrial fibrillation, ventricular tachyarrhythmia and ventricular fibrillation), cardiac injury [elevated highly sensitive troponin I (hs-cTnI) and creatine kinase (CK) levels], fulminant myocarditis, heart failure, pulmonary embolism and disseminated intravascular coagulation (DIC). Mechanistically, SARS-CoV-2, following proteolytic cleavage of its S protein by a serine protease, binds to the transmembrane angiotensin-converting enzyme 2 (ACE2) -a homologue of ACE-to enter type 2 pneumocytes, macrophages, perivascular pericytes and cardiomyocytes. This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability and myocardial infarction (MI). While ACE2 is essential for viral invasion, there is no evidence that ACE inhibitors or angiotensin receptor blockers (ARBs) worsen prognosis. Hence, patients should not discontinue use of ACE inhibitors. Moreover, renin-angiotensin-aldosterone system (RAAS) inhibitors might be beneficial in COVID-19. Initial immune and inflammatory responses induce a severe cytokine storm [interleukin (IL)-6, IL-7, IL-22, IL-17, etc.] during the rapid progression phase of COVID-19. Early evaluation and continued monitoring of cardiac damage (cTnI and NT-proBNP) and coagulation (D-dimer) after hospitalization may identify patients with cardiac injury and predict COVID-19 complications. Preventive measures such as social distancing and social isolation also increase cardiovascular risk. Cardiovascular considerations of therapies currently used, including remdesivir, chloroquine, hydroxychloroquine, tocilizumab, ribavirin, interferons and

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[21] GUZIK et al (2020) https://www.ncbi.nlm.nih.gov/pubmed/32352535 [Accessed: 02/11/2020]

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lopinavir/ritonavir as well as experimental therapies such as human recombinant ACE2 (rhACE2) are discussed.

FIGLIOZZI et al (29 July 2020) Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis[22]

Identification of reliable outcome predictors in coronavirus disease 2019 (COVID-19) is of paramount importance for improving patient management.

The authors identified 18 and 12 factors associated with the composite endpoint and death, respectively. Among those, a history of cardiovascular disease (odds ratio (OR) = 3.15, 95% confidence intervals (CIs) 2.26-4.41), acute cardiac (OR = 10.58, 5.00-22.40) or kidney (OR = 5.13, 1.78-14.83) injury, increased procalcitonin (OR = 4.8, 2.034-11.31) or D-dimer (OR = 3.7, 1.74-7.89) and thrombocytopenia (OR = 6.23, 1.031-37.67) conveyed the highest odds for the adverse composite endpoint. Advanced age, male sex, cardiovascular comorbidities, acute cardiac or kidney injury, lymphocytopenia and D-dimer conferred an increased risk of in-hospital death. With respect to the treatment of the acute phase, therapy with steroids was associated with the adverse composite endpoint (OR = 3.61, 95% CI 1.934-6.73), but not with mortality. Advanced age, comorbidities, abnormal inflammatory and organ injury circulating biomarkers captured patients with an adverse clinical outcome. Clinical history and laboratory profile may then help identify patients with a higher risk of in-hospital mortality.

SHAFI et al (11 July 2020). Cardiac manifestations in COVID-19 patients-A systematic review[23]

The authors sought to systematically review the current published literature on the different cardiac manifestations and the use of cardiac- specific biomarkers in terms of their prognostic value in determining clinical outcomes and correlation to disease severity. 61 relevant articles were identified which described risk factors for cardiovascular manifestations, cardiac manifestations (including

[22] FIGLIOZZI et al (29 July 2020) Predictors of adverse prognosis in COVID-19: A systematic review and meta-analysis. https://onlinelibrary.wiley.com/doi/full/10.1111/eci.13362 [Accessed: 02/11/2020]
[23] SHAFI et al (2020) Cardiac manifestations in COVID-19 patients-A systematic review. *Journal of Cardiac Surgery*, *35*(8), 1988–2008. https://doi.org/10.1111/jocs.14808 [Accessed: 02/11/2020]

heart failure, cardiogenic shock, arrhythmia and myocarditis among others) and cardiac- specific biomarkers (including CK- MB, CK, myoglobin, troponin and NT- proBNP). Cardiovascular risk factors can play a crucial role in identifying patients vulnerable to developing cardiovascular manifestations of COVID- 19 and thus help to save lives. A wide array of cardiac manifestations is associated with the interaction between COVID- 19 and the cardiovascular system. Cardiac- specific biomarkers provide a useful prognostic tool in helping identify patients with the severe disease early and allowing for escalation of treatment in a timely fashion.

COVID- 19 is an evolving pandemic with predominately respiratory manifestations; however, due to the interaction with the cardiovascular system, cardiac manifestations/complications feature heavily in this disease, with cardiac biomarkers providing important prognostic information.

[RAHIMI et al (06 July 2020). Challenging Issues in the Management of Cardiovascular Risk Factors in Diabetes During the COVID-19 Pandemic: A Review of Current Literature](.)[24]

Many patients with SARS-CoV-2 infection have underlying chronic medical conditions such as diabetes, cardiovascular disease (CVD) and hypertension. Patient-related outcomes are worse if there are associated comorbidities. There is insufficient evidence regarding the most appropriate management of patients with diabetes during COVID-19 infection. Insulin resistance and CVD together increase the inflammatory state of the body, which can contribute to and perhaps mediate the increase of COVID-19 severity. Hence, in addition to management of dysglycemia, other CVD risk factors should be targeted. We explore the possible pathophysiologic links between diabetes and COVID-19 and discuss various options to treat dysglycemia, hypertension and dyslipidemia in the era of COVID-19.

[24] RAHIMI et al (2020). Challenging Issues in the Management of Cardiovascular Risk Factors in Diabetes During the COVID-19 Pandemic: A Review of Current Literature. *Advances in Therapy*, *37*(8), 3450–3462.
https://doi.org/10.1007/s12325-020-01417-8 [Accessed: 02/11/2020]

GUO et al (01 July 2020) Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)[25]

Information regarding the impact of cardiovascular complications on fatal outcome is scarce.

Objective: To evaluate the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19. Among 187 patients with confirmed COVID-19, 144 patients (77%) were discharged and 43 patients (23%) died. The mean (SD) age was 58.50 (14.66) years. Overall, 66 (35.3%) had underlying CVD including hypertension, coronary heart disease and cardiomyopathy and 52 (27.8%) exhibited myocardial injury as indicated by elevated TnT levels. The mortality during hospitalization was 7.62% (8 of 105) for patients without underlying CVD and normal TnT levels, 13.33% (4 of 30) for those with underlying CVD and normal TnT levels, 37.50% (6 of 16) for those without underlying CVD but elevated TnT levels and 69.44% (25 of 36) for those with underlying CVD and elevated TnTs. Patients with underlying CVD were more likely to exhibit elevation of TnT levels compared with the patients without CVD (36 [54.5%] vs 16 [13.2%]). Myocardial injury is significantly associated with fatal outcome of COVID-19, while the prognosis of patients with underlying CVD but without myocardial injury is relatively favorable. Myocardial injury is associated with cardiac dysfunction and arrhythmias. Inflammation may be a potential mechanism for myocardial injury. Aggressive treatment may be considered for patients at high risk of myocardial injury.

CERIELLO et al (July 2020). Issues of Cardiovascular Risk Management in People with Diabetes in the COVID-19 Era[26]

People with diabetes compared with people without exhibit worse prognosis if affected by COVID-19 induced by SARS-CoV-2, particularly when compromising metabolic control and concomitant cardiovascular disorders are present. The authors explore newly occurring cardio-renal-pulmonary organ damage induced or aggravated by the disease process of COVID-19 and its implications

[25] GUO. et al (2020) https://www.ncbi.nlm.nih.gov/pubmed/32219356 [Accessed: 02/11/2020]
[26] CERIELLO et al (2020) Issues of Cardiovascular Risk Management in People With Diabetes in the COVID-19 Era. *Diabetes Care*, *43*(7), 1427–1432. https://doi.org/10.2337/dc20-0941 [Accessed: 02/11/2020]

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for the cardiovascular risk management of people with diabetes, especially taking into account potential interactions with mechanisms of cellular intrusion of SARS-CoV-2. Severe infection with SARS-CoV-2 can precipitate myocardial infarction, myocarditis, heart failure and arrhythmias as well as an acute respiratory distress syndrome and renal failure. They may evolve along with multiorgan failure directly due to SARS-CoV-2–infected endothelial cells and resulting endotheliitis. This complex pathology may bear challenges for the use of most diabetes medications in terms of emerging contraindications that need close monitoring of all people with diabetes diagnosed with SARS-CoV-2 infection. Whenever possible, continuous glucose monitoring should be implemented to ensure stable metabolic compensation. Patients in the intensive care unit requiring therapy for glycemic control should be handled solely by intravenous insulin using exact dosing with a perfusion device. Although not only ACE inhibitors and angiotensin 2 receptor blockers but also SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone and probably insulin seem to increase the number of ACE2 receptors on the cells utilized by SARS-CoV-2 for penetration, no evidence presently exists that shows this might be harmful in terms of acquiring or worsening COVID-19. In conclusion, COVID-19 and related cardio-renal-pulmonary damage can profoundly affect cardiovascular risk management of people with diabetes.

[ROY, MAZUMDER and BANIK (25 June 2020) The Association of Cardiovascular Diseases and Diabetes Mellitus with COVID-19 (SARS-CoV-2) and their possible mechanisms](#)[27]
The authors analyzed the recently published literature on CVD and DM associated with COVID-19 infections and highlight their association with potential mechanisms. The findings revealed that without any previous history of CVD, the COVID-19 patients have developed some CVD complications such as myocardial injury, cardiomyopathy and venous thromboembolism after being infected with SARS-CoV-2 and required for those patients an emergency clinical support to be aware

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[27] ROY, MAZUMDER and BANIK (2020). The Association of Cardiovascular Diseases and Diabetes Mellitus with COVID-19 (SARS-CoV-2) and Their Possible Mechanisms. *SN Comprehensive Clinical Medicine*, 1–6. https://doi.org/10.1007/s42399-020-00376-z [Accessed: 02/11/2020]

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to manage those complications. Though the association between DM and COVID-19-induced severe complications is still unclear, the limited data predict that different markers such as interleukin (IL)-1, IL-6, C-reactive protein and D-dimer linked with the severity of COVID-19 infection in diabetic individuals. Further studies on a large scale are urgently needed to explore the underlying mechanisms between CVD, DM and COVID-19 for better treatment.

MANCIA et al (18 Jun 2020) Renin-Angiotensin-Aldosterone System Blockers and the Risk of COVID-19[28]

A potential association between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (COVID-19) has not been well studied.

In this large, population-based study, the use of ACE inhibitors and ARBs was more frequent among patients with COVID-19 than among controls because of their higher prevalence of cardiovascular disease. However, there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

ASKIN, TANRIVERDI & ASKIN (01 June 2020) The Effect of Coronavirus Disease 2019 on Cardiovascular Diseases[29]

COVID-19 acts through the angiotensin-converting enzyme 2 (ACE2) receptor. Cardiovascular comorbidities are more common with COVID-19 and nearly 10% of cases develop myocarditis (22% of critical patients). Further research is needed to continue or discontinue ACE inhibitors and angiotensin receptor blockers, which are essential in hypertension and heart failure in COVID-19.

[28] MANCIA et al (2020) Renin-Angiotensin-Aldosterone System Blockers and the Risk of COVID-19. N Engl J Med. 2020 Jun 18;382(25):2431-2440. doi: 10.1056/NEJMoa2006923. Epub 2020 May 1. PMID: 32356627; PMCID: PMC7206933 [Accessed: 02/11/2020]
[29] ASKIN, TANRIVERDI & ASKIN (2020)The Effect of Coronavirus Disease 2019 on Cardiovascular Diseases. Arq Bras Cardiol. 2020 Jun 1;114(5):817-822. English, Portuguese. doi: 10.36660/abc.20200273. PMID: 32491073 [Accessed: 02/11/2020]

[CAPPUCCIO and SIANI (28 May 2020) COVID-19 and cardiovascular risk: Susceptibility to infection to SARS-CoV-2, severity and prognosis of COVID-19 and blockade of the renin-angiotensin-aldosterone system. An evidence-based viewpoint](#)[30]

The presence of cardiovascular co-morbidities and the known effects of coronaviruses on the cardiovascular system have called attention to the potential implications for patients with cardiovascular risk factors. This evidence-based viewpoint will address two questions: 1. are individuals with underlying cardiovascular risk factors such as high blood pressure or diabetes or overt disease such as coronary heart disease, heart failure or kidney disease more likely to develop severe COVID-19 and to die than those without underlying conditions? ; 2. does the regular use of angiotensin-converting enzyme inhibitors (ACE-i) or angiotensin-receptor blockers (ARB) make patients more likely to get infected and to die of COVID-19?

With a necessary cautionary note that the evidence around the links between COVID-19 and cardiovascular disease is accruing at a fast pace, to date the authors conclude that: 1. the greater susceptibility of individuals with underlying cardiovascular conditions to develop more severe COVID-19 with higher mortality rate is likely to be confounded, in part, by age and the type of co-morbidities. Patients with heart failure or chronic kidney disease might show an excess risk; 2. neither ACE-i nor ARB are associated with greater risk of SARS-Cov2 infection, or severity or risk of death in patients with COVID-19. Patients on these drugs should not stop them, unless under strict medical supervision and with the addition of a suitable replacement medicine.

[30] CAPPUCCIO & SIANI (2020). COVID-19 and cardiovascular risk: Susceptibility to infection to SARS-CoV-2, severity and prognosis of COVID-19 and blockade of the renin-angiotensin-aldosterone system. An evidence-based viewpoint. *Nutrition, Metabolism & Cardiovascular Diseases*, *30*(8), 1227–1235. https://doi.org/10.1016/j.numecd.2020.05.013 [Accessed: 02/11/2020]

MOCCIA et al (20 May 2020) COVID-19–associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches[31]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells following binding with the cell surface ACE2 receptors, thereby leading to coronavirus disease 2019 (COVID-19). SARS-CoV-2 causes viral pneumonia with additional extrapulmonary manifestations and major complications, including acute myocardial injury, arrhythmia and shock mainly in elderly patients. Furthermore, patients with existing cardiovascular comorbidities such as hypertension and coronary heart disease have a worse clinical outcome following contraction of the viral illness. A striking feature of COVID-19 pandemics is the high incidence of fatalities in advanced aged patients. This might be due to the prevalence of frailty and cardiovascular disease increase with age due to endothelial dysfunction and loss of endogenous cardioprotective mechanisms. The aim of this position paper is to hypothesize and discuss more suggestive cellular and molecular mechanisms where SARS-CoV-2 may lead to detrimental consequences to the cardiovascular system. The authors focus on aging, cytokine storm, NLRP3/inflammasome, hypoxemia and air pollution, which is an emerging cardiovascular risk factor associated with rapid urbanization and globalization. The authors finally discuss the impact of clinically available CV drugs on the clinical course of COVID-19 patients. Understanding the role played by SARS-CoV2 on the CV system is mandatory to get further insights into COVID-19 pathogenesis and to design a therapeutic strategy of cardio-protection for frail patients.

CLERKIN et al (19 May 2020) COVID-19 and Cardiovascular Disease[32]

COVID-19 is caused by SARS-CoV-2, which invades cells through the angiotensin-converting enzyme 2 receptor. Among patients with COVID-19, there is a high prevalence of cardiovascular disease and >7% of patients experience myocardial injury from the infection [22%

[31] MOCCIA et al (20 May 2020) COVID-19–associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. *GeroScience*, 42(4), 1021–1049. https://doi.org/10.1007/s11357-020-00198-w [Accessed: 02/11/2020]
[32] CLERKIN et al (2020) COVID-19 and Cardiovascular Disease. Circulation. 2020 May 19;141(20):1648-1655. doi: 10.1161/CIRCULATIONAHA.120.046941. Epub 2020 Mar 21. PMID: 32200663. [Accessed: 02/11/2020]

of critically ill patients]. Although angiotensin-converting enzyme 2 serves as the portal for infection, the role of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers requires further investigation. COVID-19 poses a challenge for heart transplantation, affecting donor selection, immunosuppression and posttransplant management. There are a number of promising therapies under active investigation to treat and prevent COVID-19.

DRIGGIN et al (12 May 2020) Cardiovascular Considerations for Patients, Health Care Workers and Health Systems During the COVID-19 Pandemic[33]

Patients with pre-existing CVD appear to have worse outcomes with COVID-19. CV complications include biomarker elevations, myocarditis, heart failure and venous thromboembolism, which may be exacerbated by delays in care. Therapies under investigation for COVID-19 may have significant drug-drug interactions with CV medications.

COVID-19 is an infectious disease caused by SARS-CoV-2 that has significant implications for the cardiovascular care of patients. First, those with COVID-19 and pre-existing cardiovascular disease have an increased risk of severe disease and death. Second, infection has been associated with multiple direct and indirect cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism. Third, therapies under investigation for COVID-19 may have cardiovascular side effects. Fourth, the response to COVID-19 can compromise the rapid triage of non-COVID-19 patients with cardiovascular conditions. Finally, the provision of cardiovascular care may place health care workers in a position of vulnerability as they become hosts or vectors of virus transmission. The authors review the peer-reviewed and pre-print reports pertaining to cardiovascular considerations related to COVID-19 and highlight gaps in knowledge that require further study pertinent to patients, health care workers and health systems.

SHI et al (11 May 2020) Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019[34]

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[33] DRIGGIN.et al (2020) http://www.onlinejacc.org/content/75/18/2352 [Accessed: 02/11/2020]

Objective: To investigate the characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019 (COVID-19).

The authors enrolled 671 eligible hospitalized patients with severe COVID-19 from 1 January to 23 February 2020, with a median age of 63 years. Clinical, laboratory and treatment data were collected and compared between patients who died and survivors. Risk factors of death and myocardial injury were analysed using multivariable regression models. A total of 62 patients (9.2%) died, who more often had myocardial injury (75.8% vs. 9.7%; $P < 0.001$) than survivors. The area under the receiver operating characteristic curve of initial cardiac troponin I (cTnI) for predicting in-hospital mortality was 0.92 [95% confidence interval (CI), 0.87−0.96; sensitivity, 0.86; specificity, 0.86; $P < 0.001$]. The single cut-off point and high level of cTnI predicted risk of in-hospital death, hazard ratio (HR) was 4.56 (95% CI, 1.28−16.28; $P = 0.019$) and 1.25 (95% CI, 1.07−1.46; $P = 0.004$), respectively. In multivariable logistic regression, senior age, comorbidities such as hypertension, coronary heart disease, chronic renal failure and chronic obstructive pulmonary disease and high level of C-reactive protein were predictors of myocardial injury.

The risk of in-hospital death among patients with severe COVID-19 can be predicted by markers of myocardial injury and was significantly associated with senior age, inflammatory response and cardiovascular comorbidities.

34 SHI et al(2020) https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa408/5835730 [Accessed: 02/11/2020]

[JANKELSON et al (11 May 2020) QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review](#)[35]

Chloroquine and hydroxychloroquine are now being widely used for treatment of COVID-19. Both medications prolong the QT interval and accordingly may put patients at increased risk for torsades de pointes and sudden death. Published guidance documents vary in their recommendations for monitoring and managing these potential adverse effects. Accordingly, the authors set out to conduct a systematic review of the arrhythmogenic effect of short courses of chloroquine or hydroxychloroquine. The authors searched MEDLINE and Embase as well as gray literature up to April 17, 2020, for the risk of QT prolongation, torsades, ventricular arrhythmia, and sudden death with short-term chloroquine and hydroxychloroquine usage. The search resulted in 390 unique records, of which 41 were ultimately selected for qualitative synthesis and which included data on 1515 COVID-19 patients. Approximately 10% of COVID-19 patients treated with these drugs developed QT prolongation. The authors found evidence of ventricular arrhythmia in 2 COVID-19 patients from a group of 28 treated with high-dose chloroquine. Limitations of these results are unclear follow-up and possible publication/reporting bias, but there is compelling evidence that chloroquine and hydroxychloroquine induce significant QT-interval prolongation and potentially increase the risk of arrhythmia. Daily electrocardiographic monitoring and other risk mitigation strategies should be considered in order to prevent possible harms from what is currently an unproven therapy.

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[35] JANKELSON et al (11 May 2020) QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review
https://www.heartrhythmjournal.com/article/S1547-5271(20)30431-8/fulltext [Accessed: 02/11/2020]

ABOUGHDIR et al (11 May 2020) Prognostic Value of Cardiovascular Biomarkers in COVID-19: A Review[36]

Among hospitalised COVID-19 patients, there is a high prevalence of established cardiovascular disease (CVD). There is evidence showing that COVID-19 may exacerbate cardiovascular risk factors and preexisting CVD or may lead to cardiovascular complications. With intensive care units operating at maximum capacity and such staggering mortality rates reported, it is imperative to identify patients with an increased risk of adverse outcomes and/or myocardial injury. Preliminary findings from COVID-19 studies have shown the association of biomarkers of acute cardiac injury and coagulation with worse prognosis. While these biomarkers are recognised for CVD, there is emerging prospect that they may aid prognosis in COVID-19, especially in patients with cardiovascular comorbidities or risk factors that predispose to worse outcomes. Consequently, the aim of this review is to identify cardiovascular prognostic factors associated with morbidity and mortality in COVID-19 and to highlight considerations for incorporating laboratory testing of biomarkers of cardiovascular performance in COVID-19 to optimise outcomes.

PALLARÉS CARRATALÁ et al (11 May 2020) [COVID-19 and cardiovascular and kidney disease: Where are we? Where are we going?][37]

Patients with cardiovascular risk and previous kidney risk have been identified as especially vulnerable for greater morbidity and mortality when they suffer from COVID-19. A considerable proportion of patients can develop a vascular lesion in the context of the disease that entails a greater lethality. Cardiovascular and renal complications represent a problem and may pose a threat to patients who have survived COVID-19.

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[36] ABOUGHDIR et al (2020). Prognostic Value of Cardiovascular Biomarkers in COVID-19: A Review. *Viruses (1999-4915)*, *12*(5), 527. https://doi.org/10.3390/v12050527 [Accessed: 02/11/2020]
[37] PALLARÉS CARRATALÁ et al (2020). [COVID-19 and cardiovascular and kidney disease: Where are we? Where are we going?]. *Semergen*, *46 Suppl 1*, 78–87. https://doi.org/10.1016/j.semerg.2020.05.005 [Accessed: 02/11/2020]

[BONANAD et al (08 May 2020) Coronavirus: the geriatric emergency of 2020. Joint document of the Section on Geriatric Cardiology of the Spanish Society of Cardiology and the Spanish Society of Geriatrics and Gerontology](#)[38]

The older population are particularly susceptible to COVID-19 infection and to developing severe disease. The higher morbidity and mortality rates in older people have been associated with comorbidity, especially cardiovascular disease and frailty, which weakens the immune response. Because Spain has one of the largest older populations in the world, COVID-19 has emerged as a geriatric emergency.

COVID-19 can cause a severe infection with serious effects in patients with heart disease. Importantly, patients with cardiovascular disease (CVD) have a higher risk of severe symptoms and death. In addition, COVID-19 infection has been associated with multiple direct and indirect complications in the cardiovascular system, such as acute myocardial damage, myocarditis, arrhythmias and thromboembolic disease. Moreover, the treatments under investigation for COVID-19 can have secondary cardiovascular effects; these interactions mean that patients' standard drug therapies are frequently discontinued during their admission, which can lead to decompensation of the underlying heart condition. Furthermore, polypharmacy involving antipsychotic drugs and other antibiotics that prolong the QT interval can contribute to cardiotoxicities related to these drug combinations in older patients.

[GUZIK et al (30 Apr 2020) COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis and treatment options](#)[39]

While COVID-19 primarily affects the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), it also affects multiple organs, particularly the cardiovascular system. Risk of severe infection and mortality increase with advancing age and

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[38] BONANAD et al (08 May 2020) Coronavirus: the geriatric emergency of 2020. Joint document of the Section on Geriatric Cardiology of the Spanish Society of Cardiology and the Spanish Society of Geriatrics and Gerontology. https://www.sciencedirect.com/science/article/pii/S18855857203017BX [Accessed: 02/11/2020]

[39] GUZIK et al (2020) COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis and treatment options. *Cardiovascular Research*, 116(10), 1666–1687. https://doi.org/10.1093/cvr/cvaa106 [Accessed: 02/11/2020]

male sex. Mortality is increased by comorbidities: cardiovascular disease, hypertension, diabetes, chronic pulmonary disease and cancer. The most common complications include arrhythmia (atrial fibrillation, ventricular tachyarrhythmia and ventricular fibrillation), cardiac injury [elevated highly sensitive troponin I (hs-cTnI) and creatine kinase (CK) levels], fulminant myocarditis, heart failure, pulmonary embolism and disseminated intravascular coagulation (DIC). Mechanistically, SARS-CoV-2, following proteolytic cleavage of its S protein by a serine protease, binds to the transmembrane angiotensin-converting enzyme 2 (ACE2) —a homologue of ACE—to enter type 2 pneumocytes, macrophages, perivascular pericytes and cardiomyocytes. This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability and myocardial infarction (MI). While ACE2 is essential for viral invasion, there is no evidence that ACE inhibitors or angiotensin receptor blockers (ARBs) worsen prognosis. Hence, patients should not discontinue their use. Moreover, renin–angiotensin–aldosterone system (RAAS) inhibitors might be beneficial in COVID-19. Initial immune and inflammatory responses induce a severe cytokine storm [interleukin (IL)-6, IL-7, IL-22, IL-17, etc.] during the rapid progression phase of COVID-19. Early evaluation and continued monitoring of cardiac damage (cTnI and NT-proBNP) and coagulation (D-dimer) after hospitalization may identify patients with cardiac injury and predict COVID-19 complications. Preventive measures such as social distancing and social isolation also increase cardiovascular risk. Cardiovascular considerations of therapies currently used, including remdesivir, chloroquine, hydroxychloroquine, tocilizumab, ribavirin, interferons and lopinavir/ritonavir, as well as experimental therapies, such as human recombinant ACE2 (rhACE2), are discussed.

GROSS et al (30 April 2020) SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: From basic science to clinical implications[40]

COVID-19 requires the collaboration of nearly 200 countries to curb the spread of SARS-CoV-2 while gaining time to explore and improve treatment options especially for cardiovascular disease (CVD) and immunocompromised patients who appear to be at high-risk to die from cardiopulmonary failure.

Currently unanswered questions are why elderly people and in particular those with pre-existing comorbidities seem to exhibit higher mortality rates after SARS-CoV-2 infection and whether intensive care becomes indispensable for these patients to prevent multi-organ failure and sudden death. The authors summarize the molecular insights into viral infection mechanisms and implications for cardiovascular disease and highlight the state-of-the-art knowledge on SARS-CoV-2-dependent mechanisms and the potential interaction with ACE2 expression and cell surface localization.

The authors aim to provide a list of potential treatment options and a better understanding of why CVD is a high-risk factor for COVID-19 susceptibility and further discuss the acute as well as long-term cardiac consequences.

Interestingly, the drastically increased mortality rate in patients with pre-existing or new cardiac injuries is associated with elevated serum levels of troponin T (TnT), a biomarker for cardiac damage. Indeed, the study of Guo et al points out that CVD patients without significantly raised TnT serum levels only represent a slightly increased mortality compared to patients without CVD. Therefore, in the case of expected cardiac damage due to distinct comorbidities or severe disease progression, TnT levels should always be strictly monitored, but also critically interpreted since some medications and interventions themselves can cause an upregulation of TnT.

KANG et al (30 April 2020) Cardiovascular manifestations and treatment considerations in COVID-19[41]

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[40]GROSS, S.(2020) https://www.ncbi.nlm.nih.gov/pubmed/32360703 [Accessed: 02/11/2020]

Pre-existing comorbidities such as hypertension, diabetes and cardiovascular disease are associated with a greater severity and higher fatality rate of COVID-19. Furthermore, COVID-19 contributes to cardiovascular complications, including acute myocardial injury as a result of acute coronary syndrome, myocarditis, stress-cardiomyopathy, arrhythmias, cardiogenic shock and cardiac arrest. The cardiovascular interactions of COVID-19 have similarities to that of severe acute respiratory syndrome, Middle East respiratory syndrome and influenza. Specific cardiovascular considerations are also necessary in supportive treatment with anticoagulation, the continued use of renin-angiotensin-aldosterone system inhibitors, arrhythmia monitoring, immunosuppression or modulation and mechanical circulatory support.

[SANKRITYAYAN, KALE and SHARMA (30 April 2020) Evidence for use or disuse of Renin-Angiotensin System Modulators in patients having COVID-19 with an underlying cardiorenal disorder](#)[42]
Cardiovascular diseases and diabetes are important risk factors for a lethal outcome of COVID-19. Extensive research ensuing the outbreak of coronavirus-related severe acute respiratory syndrome in the year 2003 and COVID-19 recently revealed a role of renin-angiotensin system (RAS) components in the entry of coronavirus wherein angiotensin-converting enzyme 2 (ACE2) had garnered the significant attention. This raises the question whether the use of RAS inhibitors, the backbone of treatment of cardiovascular, neurovascular and kidney diseases could increase the susceptibility for coronavirus infection or unfortunate outcomes of COVID-19. Thus, currently, there is a lack of consensus regarding the effects of RAS inhibitors in such patients. Moreover, expert bodies such as the American Heart Association and American College of Cardiology have now released official statements that RAS inhibitors must be continued, unless suggested otherwise by a physician. In this brief review, the authors elaborate on the role of RAS and ACE2 in pathogenesis of COVID-19 and discuss the potential effect of the use

[41] KANG et al (2020) https://heart.bmj.com/content/early/2020/04/30/heartjnl-2020-317056 [Accessed: 02/11/2020]
[42] SANKRITYAYAN, KALE & SHARMA (2020) https://journals.sagepub.com/doi/full/10.1177/1074248420921720 [Accessed: 02/11/2020]

and disuse of RAS inhibitors in patients having COVID-19 with cardiometabolic comorbidities.

WEI et al (30 Apil 2020) Acute myocardial injury is common in patients with COVID-19 and impairs their prognosis[43]

The authors sought to explore the prevalence and immediate clinical implications of acute myocardial injury in a cohort of patients with COVID-19 in a region of China where medical resources are less stressed than in Wuhan (the epicentre of the pandemic).

The authors prospectively assessed the medical records, laboratory results, chest CT images and use of medication in a cohort of patients presenting to two designated COVID-19 treatment centres in Sichuan, China. Outcomes of interest included death, admission to an intensive care unit (ICU), need for mechanical ventilation, treatment with vasoactive agents and classification of disease severity. Acute myocardial injury was defined by a value of high-sensitivity troponin T (hs-TnT) greater than the normal upper limit.

A total of 101 cases were enrolled from January to 10 March 2020 (average age 49 years, IQR 34−62 years). Acute myocardial injury was present in 15.8% of patients, nearly half of whom had a hs-TnT value fivefold greater than the normal upper limit. Patients with acute myocardial injury were older, with a higher prevalence of pre-existing cardiovascular disease and more likely to require ICU admission (62.5% vs 24.7%, p=0.003), mechanical ventilation (43.5% vs 4.7%, p<0.001) and treatment with vasoactive agents (31.2% vs 0%, p<0.001). Log hs-TnT was associated with disease severity (OR 6.63, 95% CI 2.24 to 19.65) and all of the three deaths occurred in patients with acute myocardial injury. Acute myocardial injury is common in patients with COVID-19 and is associated with adverse prognosis.

GUPTA et al (29 April 2020) Current perspectives on Coronavirus 2019 (COVID- 19) and cardiovascular disease: A white paper by the JAHA editors[44]

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[43] WEI et al (2020) https://heart.bmj.com/content/early/2020/04/30/heartjnl-2020-317007 [Accessed: 02/11/2020]
[44] AMERICAN HEART ASSOCIATION (2020) https://www.ahajournals.org/doi/10.1161/JAHA.120.017013 [Accessed: 02/11/2020]

COVID- 19 may preferentially infect individuals with cardiovascular conditions, is more severe in subjects with cardiovascular comorbidities, may directly or indirectly affect the heart and may interact with cardiovascular medications. In addition, the widespread effects of the pandemic on the global healthcare system affects the routine and emergency cardiac care for patients who are, may be, or are not infected with COVID- 19.

CHENG et al (29 April 2020) Cardiovascular Risks in Patients with COVID-19: Potential Mechanisms and Areas of Uncertainty[45]

SARS-CoV2, the virus responsible for COVID-19, enters the cell via ACE2 expressed in select organs. Emerging epidemiological evidence suggest cardiovascular risk factors are associated with increased disease severity and mortality in COVID-19 patients. Patients with a more severe form of COVID-19 are also more likely to develop cardiac complications such as myocardial injury and arrhythmia. The true incidence of and mechanism underlying these events remain elusive. Cardiovascular diseases appear intricately linked with COVID-19, with cardiac complications contributing to the elevated morbidity/mortality of COVID-19. Robust epidemiologic and biologic studies are urgently needed to better understand the mechanism underlying these associations to develop better therapies.

ZHENG et al (23 April 2020). Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis[46]

The risk factors of critical/mortal and non-critical COVID-19 patients were statistically analyzed. 13 studies were included in the meta-analysis, including a total number of 3027 patients with SARS-CoV-2 infection.
Male, older than 65 and smoking were risk factors for disease progression in patients with COVID-19. The proportion of underlying diseases such as hypertension, diabetes, cardiovascular disease and respiratory disease were statistically significant higher in

[45] CHENG et al (2020) Cardiovascular Risks in Patients with COVID-19: Potential Mechanisms and Areas of Uncertainty. Curr Cardiol Rep. 2020 Apr 29;22(5):34. doi: 10.1007/s11886-020-01293-2. PMID: 32350632; PMCID: PMC7189178 https://pubmed.ncbi.nlm.nih.gov/32350632/ [Accessed: 02/11/2020]
[46] ZHENG et al (2020) Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection*, *81*(2), e16–e25. https://doi.org/10.1016/j.jinf.2020.04.021 [Accessed: 02/11/2020]

critical/mortal patients compared to the non-critical patients. Clinical manifestation such as fever, shortness of breath or dyspnea and laboratory examination such as WBC, AST, Cr, PCT, LDH, hs-cTnI and D-dimer could imply the progression of COVID-19.

BARISON et al (15 April 2020) Cardiovascular disease and COVID-19: les liaisons dangereuses[47]

Patients with cardiovascular risk factors or established cardiovascular disease have an increased risk of developing coronavirus disease 19 and have a worse outcome when infected, but translating these insights into effective action is challenging. At present it is unclear whether cardiovascular therapies may reduce the likelihood of infection or improve the survival of infected patients. Given the crucial importance of this issue for clinical cardiologists and all specialists dealing with coronavirus disease 19, we tried to recapitulate the current evidence and provide some practical recommendations.

[47] BARISON et al (2020) https://journals.sagepub.com/doi/pdf/10.1177/2047487320924501[Accessed: 02/11/2020]

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The following PICO(T) was used as a basis for the evidence summary:

Population — person, location, condition/patient characteristic	COVID-19 patients >65 with cardiovascular disease
Intervention — length, location, type	
Comparison — another intervention, no intervention, location of the intervention	
Outcome	What is the evidence on additional risk?

The following search strategy was used:

[ABBREVIATED] COVID-19 OR CORONAVIRUS OR "CORONA VIRUS" OR (WUHAN N3 VIRUS) OR (("2019-NCOV" OR "2019 NCOV")) OR "SEVERE RESPIRATORY SYNDROME CORONAVIRUS2" OR (("2019" AND (NEW OR NOVEL) AND CORONAVIRUS)) (HCOV-19) AND (CARDIO*) AND (65 + YEARS)

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